



ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ  
Εθνικόν και Καποδιστριακόν  
Πανεπιστήμιον Αθηνών  
— ΙΔΡΥΘΕΝ ΤΟ 1837 —



## **Σύνδρομο ARDS (Οξείας Αναπνευστικής Δυσχέρειας) Acute Respiratory Distress Syndrome**

Αντωνία Κουτσούκου

# Happy 50th birthday ARDS!

Arthur S. Slutsky<sup>1,2\*</sup>, Jesús Villar<sup>1,3,4</sup> and Antonio Pesenti<sup>5,6</sup>

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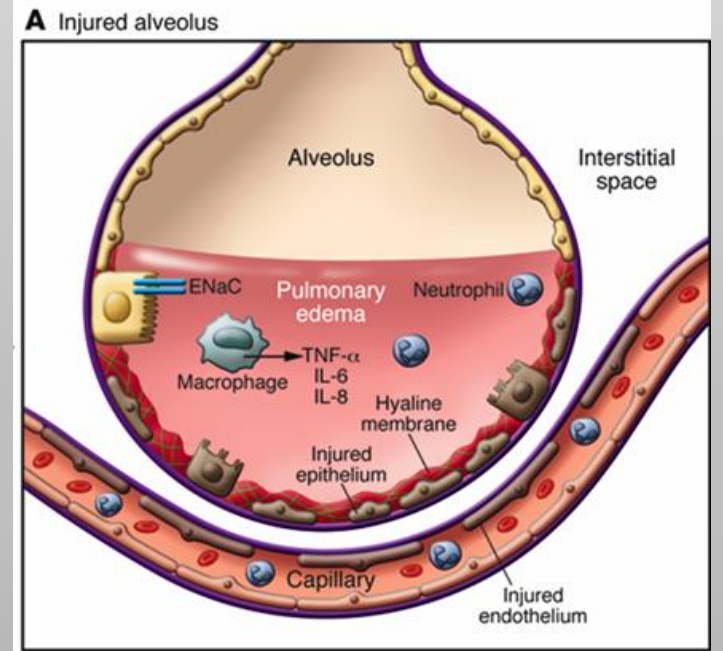
*Ashbaugh, The Lancet, 1967 290: 7511; 319 – 323*

## FIFTY YEARS OF RESEARCH IN ARDS ARDS: How It All Began

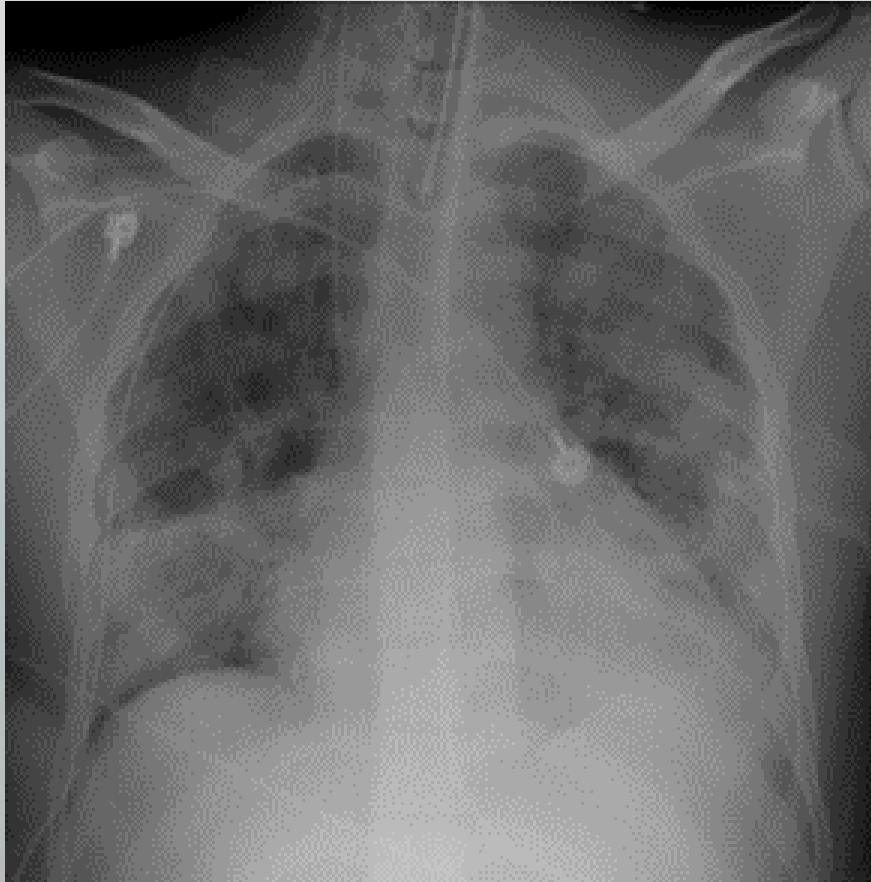
Bernard E. Levine

Clinical Professor of Internal Medicine (Retired), University of Arizona School of Medicine, Tucson, Arizona

12 (272) ασθενείς με οξεία αναπνευστική δυσχέρεια, κυάνωση, διάχυτα διηθήματα στην Ro θώρακος και μείωση της πνευμονικής ενδοτοκότητας (θνητότητα 58%)



# The Berlin Definition 2012



- ▶ Οξεία έναρξη αναπνευστικής ανεπάρκειας (εντός 7 ημερών) μετά από ένα εκκλυτικό αίτιο «καταστροφικό γεγονός»
- Αμφοτερόπλευρα διηθήματα στη Ro θώρακος (που δεν εξηγούνται από συλλογές, όζους ή ατελεκτασίες)
- Αναπνευστική ανεπάρκεια που δεν εξηγείται πλήρως από καρδιακή ανεπάρκεια
- $\text{PaO}_2/\text{FiO}_2 < 300$  ( $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$ )
- ▶  $300 > \text{PaO}_2/\text{FiO}_2 \geq 200$  Ήπιο ARDS
- ▶  $200 > \text{PaO}_2/\text{FiO}_2 \geq 100$  Μέτριο ARDS
- ▶  $\text{PaO}_2/\text{FiO}_2 < 100$  Βαρύ ARDS

# Επιδημιολογία

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

## Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

Giacomo Bellani, MD, PhD; John G. Laffey, MD, MA; Tâi Pham, MD; Eddy Fan, MD, PhD; Laurent Brochard, MD, HDR; Andres Esteban, MD, PhD; Luciano Gattinoni, MD, FRCP; Frank van Haren, MD, PhD; Anders Larsson, MD, PhD; Daniel F. McAuley, MD, PhD; Marco Ranieri, MD; Gordon Rubenfeld, MD, MSc; B. Taylor Thompson, MD, PhD; Hermann Wrigge, MD, PhD; Arthur S. Slutsky, MD, MASc; Antonio Pesenti, MD; for the LUNG SAFE Investigators and the ESICM Trials Group

459 ICUs  
50 countries, 5 continents  
29144 pts (3022, ARDS, 10.4%)

### ICU Incidence of ARDS

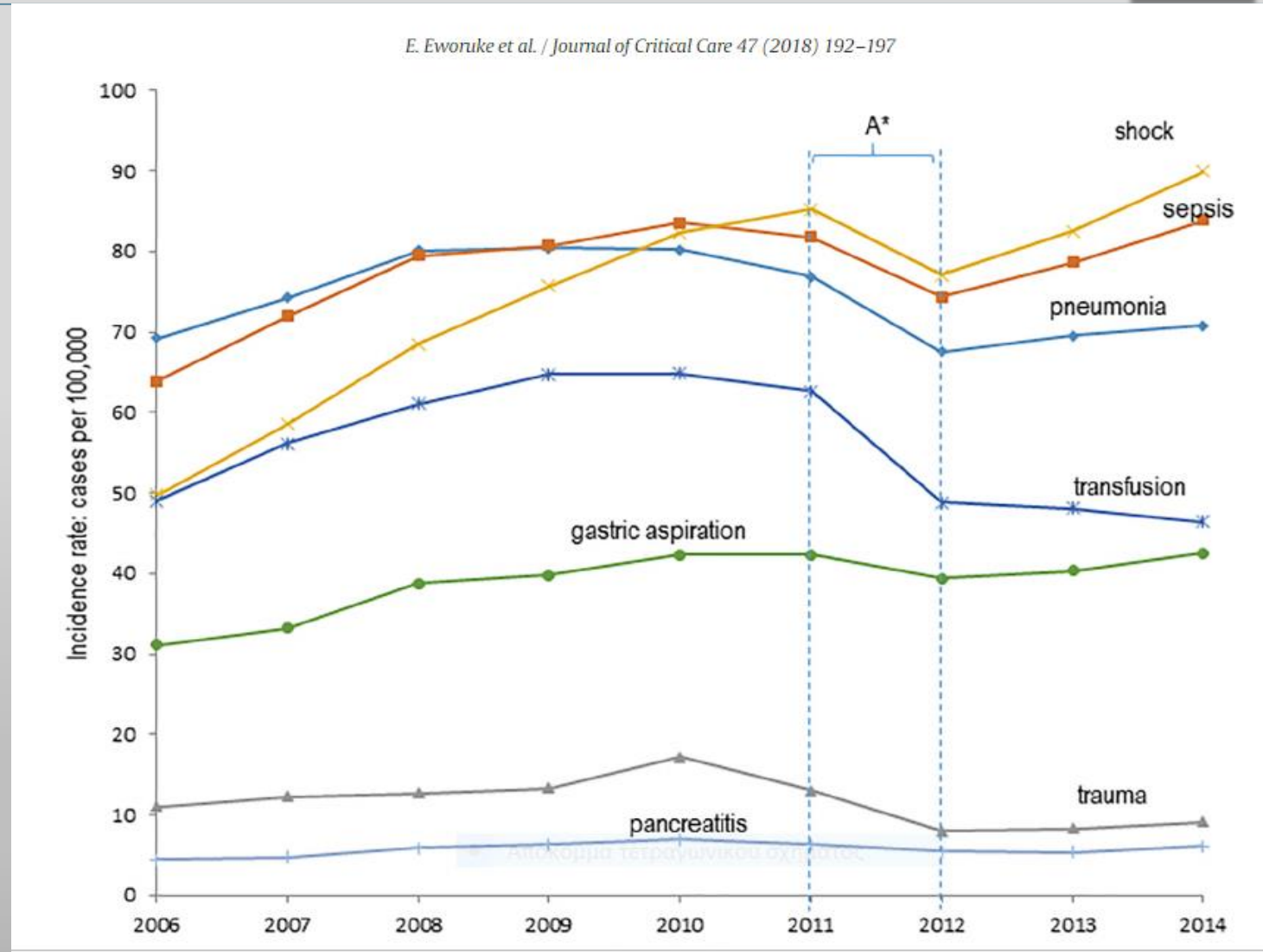
ARDS represented 10.4% (95% CI, 10.0%-10.7%) of total ICU admissions and 23.4% (95% CI, 21.7%-25.2%) of all patients requiring mechanical ventilation and constituted 0.42 cases/ICU bed over 4 weeks. There was some geographic variation,

### Recognition of ARDS

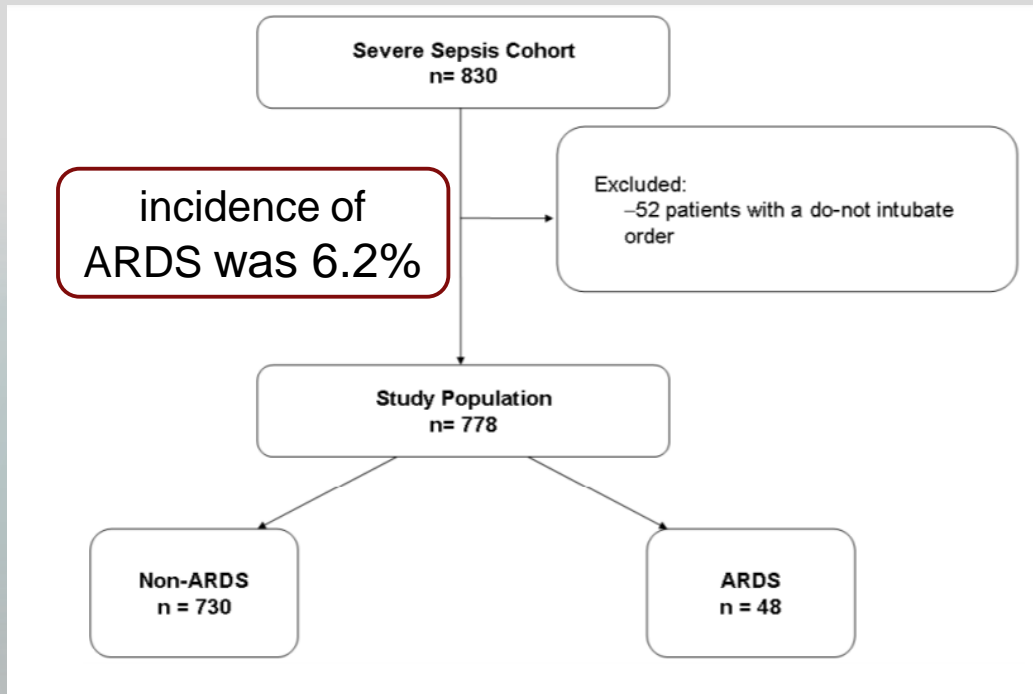
ARDS was underdiagnosed, with 60.2% of all patients with ARDS being clinician-recognized. Clinician recognition of ARDS ranged from 51.3% (95% CI, 47.5%-55.0%) for mild ARDS to 78.5% (95% CI, 74.8%-81.8%) for severe ARDS

# Κλινικές καταστάσεις που οδηγούν σε ARDS

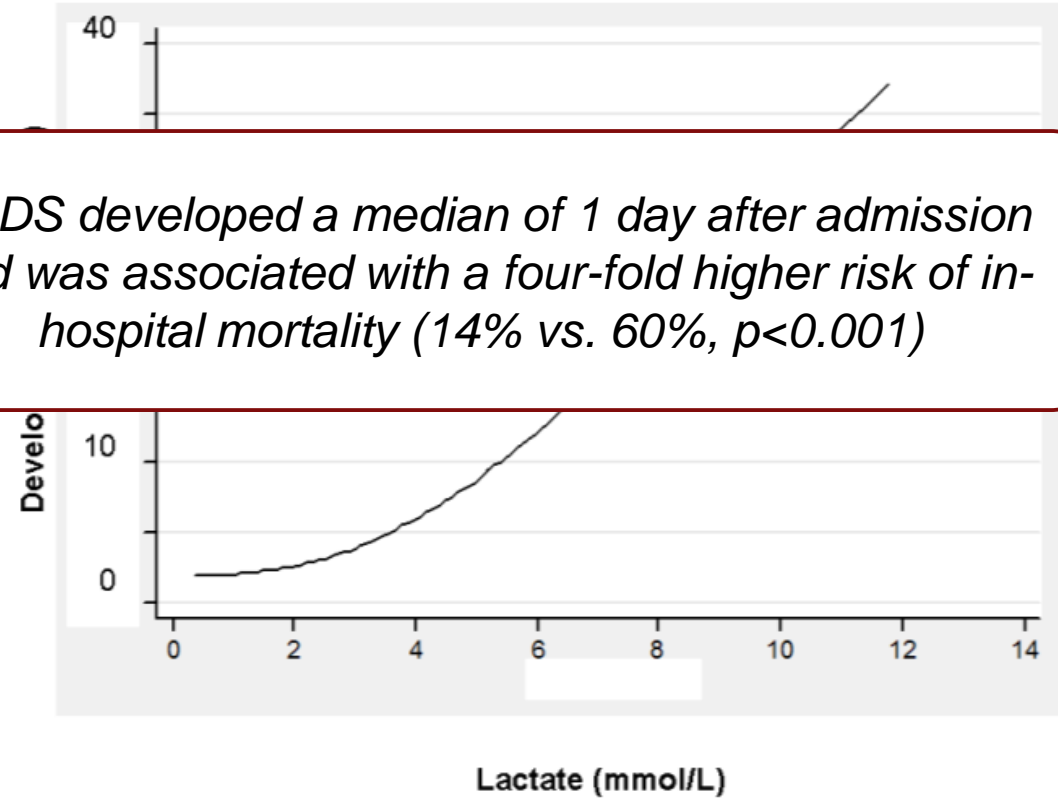
- ▶ Πνευμονία
- ▶ Σήψη
- ▶ Σοβαρό τραύμα
- ▶ Εισρόφηση
- ▶ Πνευμονική θλάση
- ▶ Μεταγγίσεις-TRALI
- ▶ Οξεία παγκρεατίτιδα
- ▶ Εισπνοή τοξικών αερίων
- ▶ Εγκαύματα
- ▶ Μη-Καρδιογενές shock
- ▶ Δηλητηριάσεις
- ▶ Παρ' ολίγον πνιγμός



# THE EPIDEMIOLOGY OF ACUTE RESPIRATORY DISTRESS SYNDROME IN PATIENTS PRESENTING TO THE EMERGENCY DEPARTMENT WITH SEVERE SEPSIS



*ARDS developed a median of 1 day after admission and was associated with a four-fold higher risk of in-hospital mortality (14% vs. 60%,  $p < 0.001$ )*



*Mikkelsen, Shock. 2013*

Independent risk factors associated with increased risk of ARDS development included: serum lactate levels ( $p=0.008$ ), lung injury prediction score (LIPS), microbiologically-proven infection

# Επιβαρυντικοί παράγοντες: Ρύπανση της ατμόσφαιρας

996 pts acute trauma. ARDS 243 pts (24%)  
daily levels from all monitors within 50 km of the geocoded location of a patient's residence.

**Table 4.** Logistic regression analysis for the association of exposure to individual air pollutants and ARDS risk

Pollutant	Three-year Average Exposure		Six-week Average Exposure		Three-day Average Exposure	
	OR <sup>#</sup> (95% CI)	P	OR <sup>#</sup> (95% CI)	P	OR <sup>#</sup> (95% CI)	P
Ozone*	1.44 (1.12, 1.86)	0.005	1.13 (0.88, 1.46)	0.248	0.90 (0.64, 1.26)	0.203
NO <sub>2</sub> *	2.39 (1.72, 3.33)	<0.001	1.77 (1.28, 2.43)	0.002	1.42 (0.99, 2.04)	0.111
SO <sub>2</sub>	3.56 (2.40, 5.28)	<0.001	2.31 (1.61, 3.31)	<0.001	1.78 (1.26, 2.50)	0.005
CO	1.92 (1.47, 2.53)	<0.001	1.23 (0.97, 1.56)	0.157	1.15 (0.90, 1.48)	0.385
PM <sub>2.5</sub>	3.58 (2.40, 5.34)	<0.001	1.59 (1.21, 2.11)	<0.001	1.05 (0.81, 1.36)	0.715

● Απόκομμα τετραγωνικού σχήματος

Reilly, AJRCCM 2018

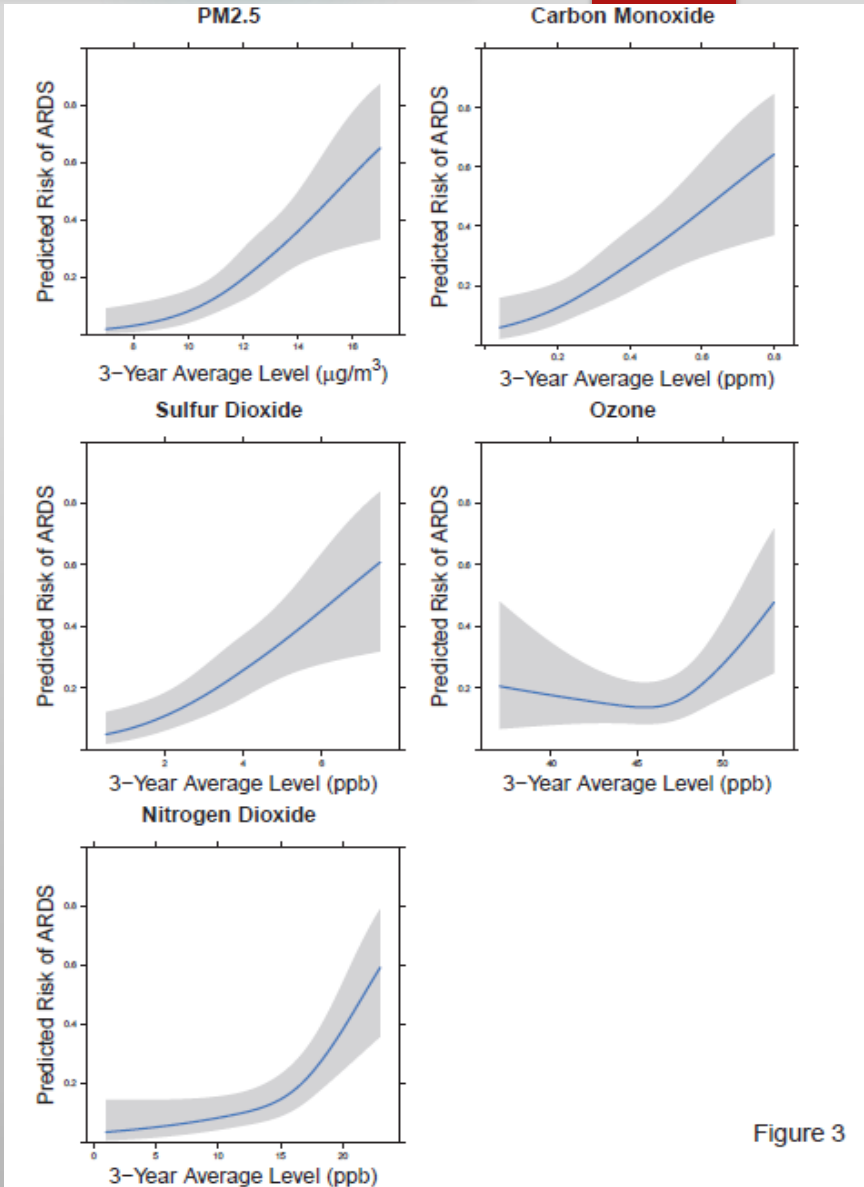


Figure 3

# Επιβαρυντικοί παράγοντες: Κατάχρηση αλκοόλ

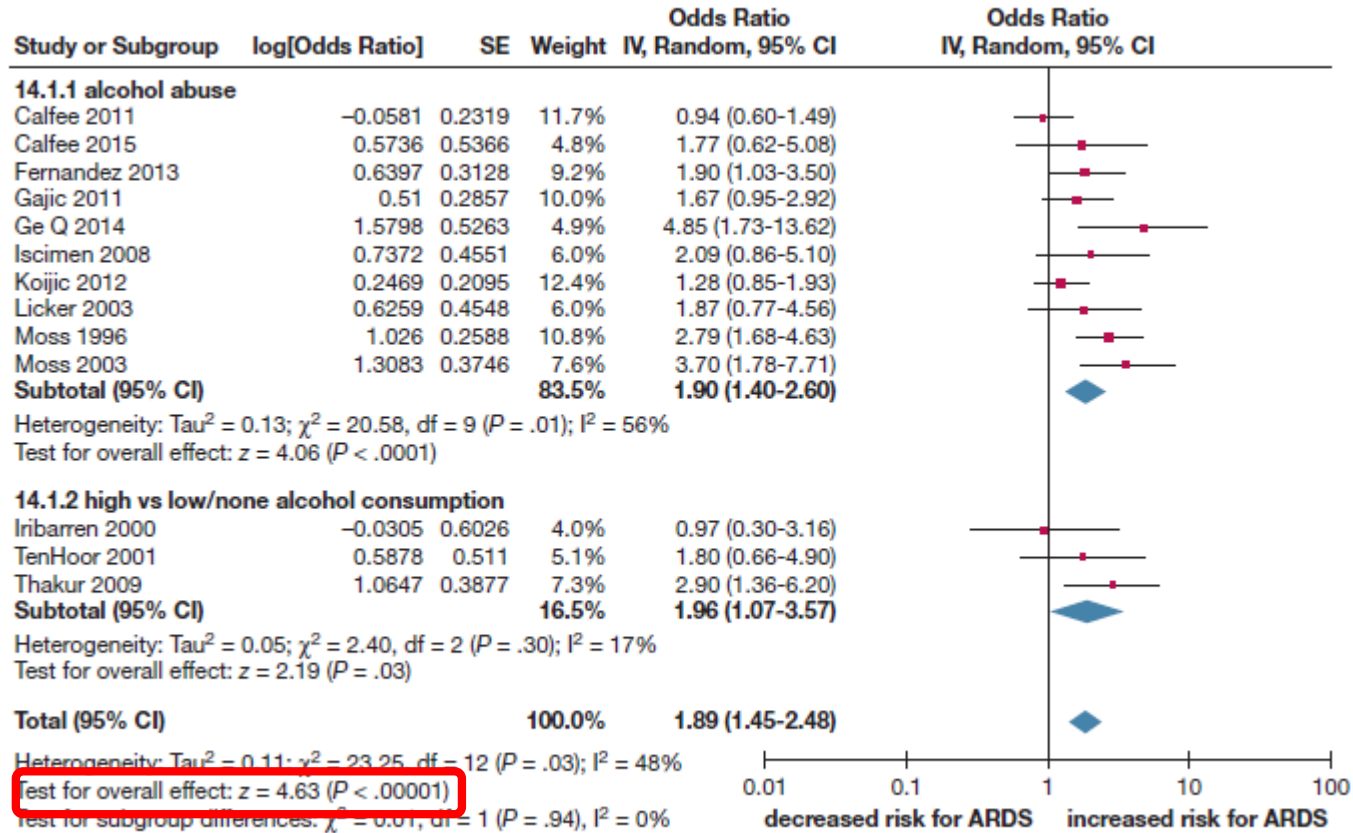


Figure 2 – Forest plot of alcohol consumption and the risk of ARDS; subgroup analysis based on alcohol abuse vs high alcohol consumption.

## Systematic Review

13 studies

any measure of high relative to low alcohol consumption

was associated with a significantly increased risk of ARDS (OR, 1.89; 95% CI, 1.45-2.48)

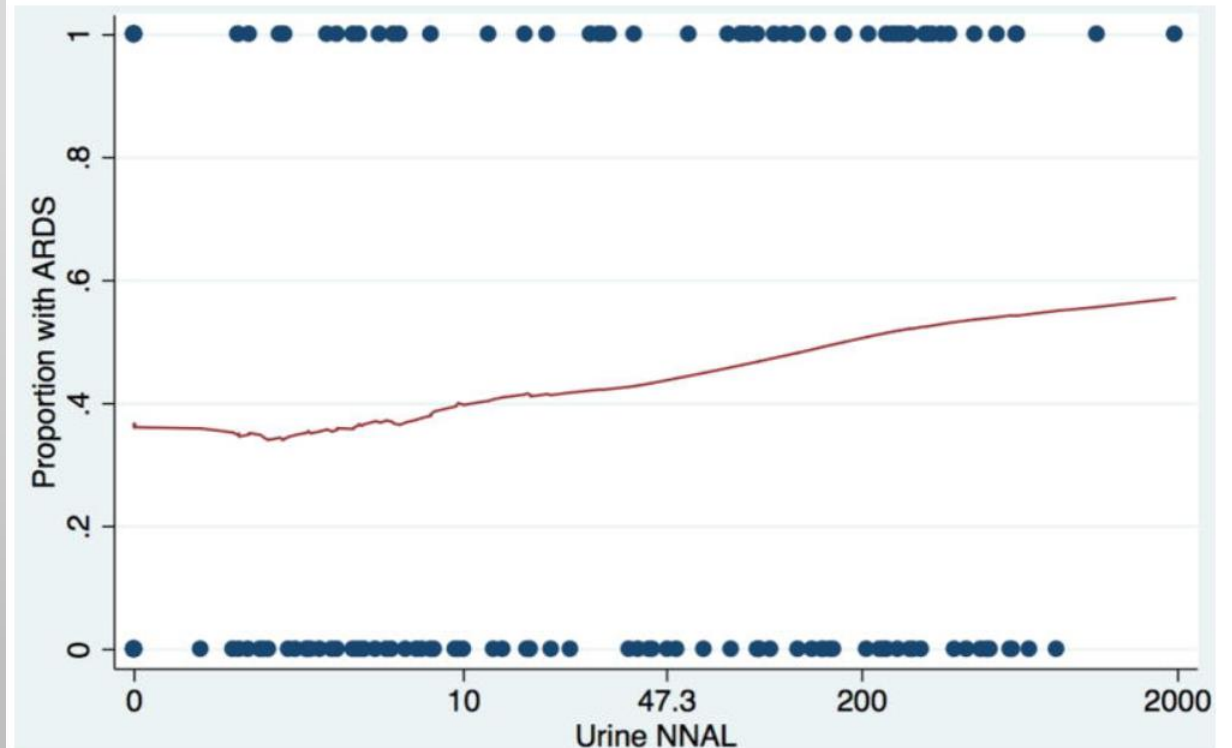


# Επιβαρυντικοί παράγοντες: Κάπνισμα

Calfee, CCM 2015

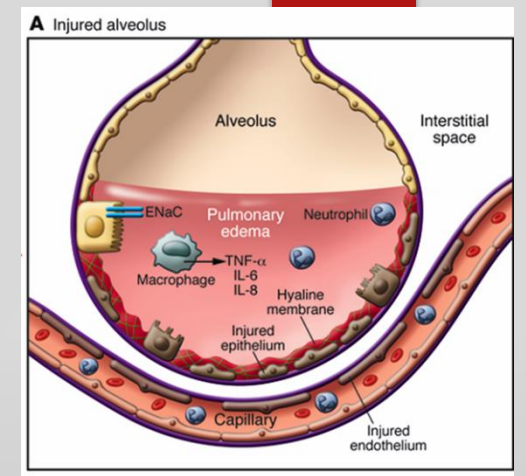
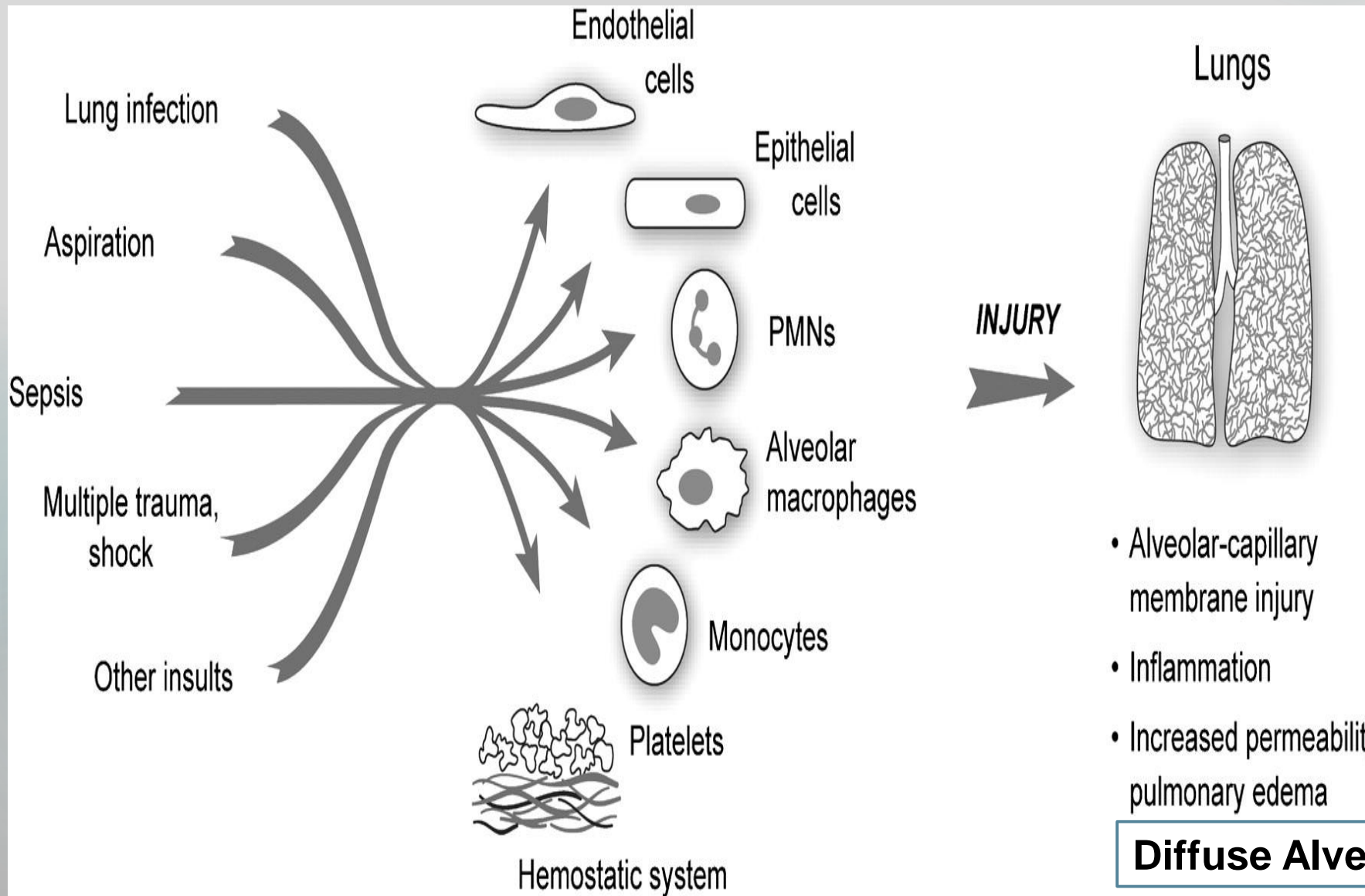
426 patients with ARDS risk factors (excluding trauma and transfusion)

Cigarette smoke exposure as assessed by either smoking history or urinary NNAL levels was associated with approximately double the odds of developing ARDS in subjects with non-pulmonary sepsis



*NNAL is a metabolite of NNK (nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, or nicotine-derived nitrosamine ketone)*

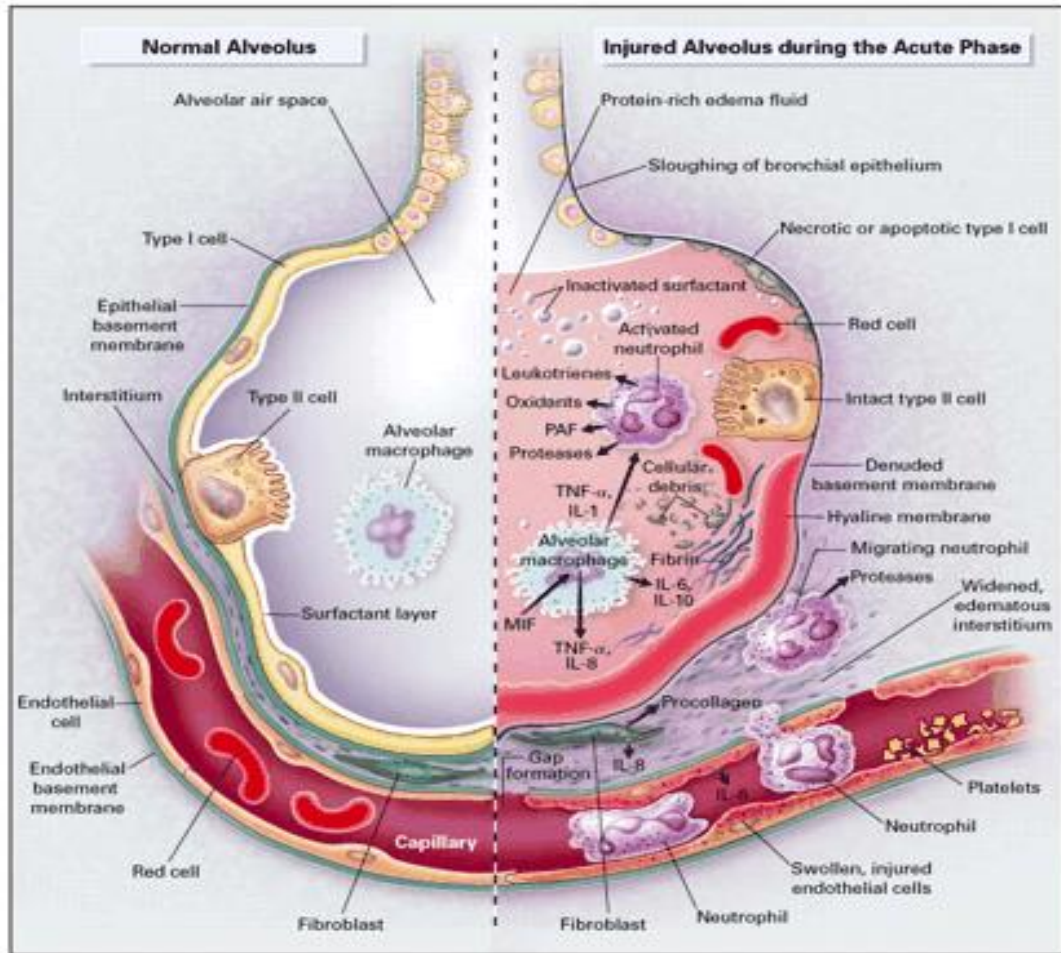
# ARDS -παθογένεια



- Alveolar-capillary membrane injury
- Inflammation
- Increased permeability pulmonary edema

**Diffuse Alveolar Damage (DAD)**

# ARDS –παθογένεια

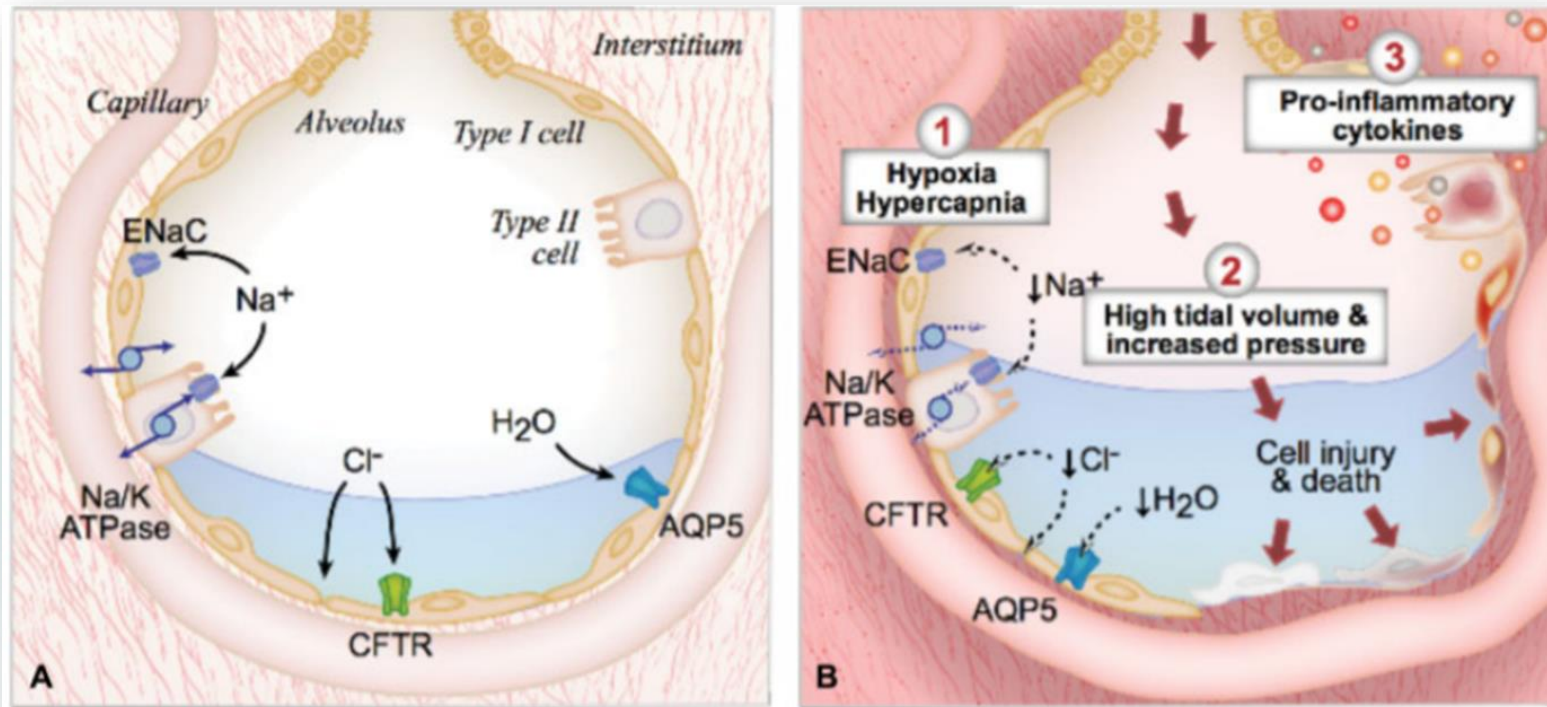


**Delicate balance between** effective immune activation to combat infection and excessive or dysregulated activation that contributes to alveolar injury

PAMPs/DAMPs bind to TLRs on ATII cells and resident macrophages, which (via chemokines) recruit circulating immune cells into the airspaces.

As neutrophils migrate across the epithelium, they release toxic mediators, including proteases, ROS, and NETs, which play an important role in host defense but **cause endothelial and epithelial injury**

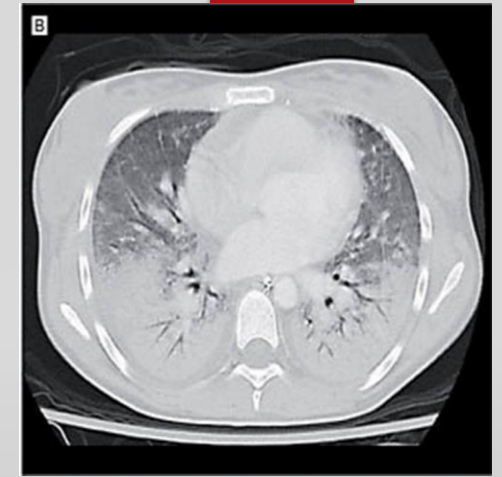
# Alveolar Fluid Clearance (AFC)



- Υποξία-υπερκαπνία AFC
- Μηχανικό stress (V<sub>T</sub>, Pressures) →
- Proinflammatory cytokines (IL1-β, IL-8, TNFα) βλάβη και νέκρωση των κυψελιδικών κυττάρων

## Οξεία εξιδρωματική Φάση (1η-3η ημέρα)

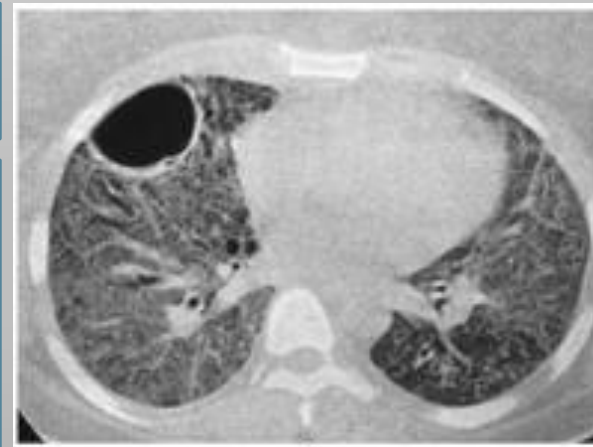
- ▶ Οξεία έναρξη αν. ανεπάρκειας (Σημαντική υποξυγοναιμία που δεν βελτιώνεται με τη χορήγηση O<sub>2</sub>)
- ▶ *Ro* θώρακος: αμφοτερόπλευρα διηθήματα συρρέοντα ή ασύμμετρα, πιθανόν πλευριτικές συλλογές
- ▶ CT θώρακος: κυψελιδικά διηθήματα και ατελεκτατικές βλάβες, ιδίως στις υποκείμενες περιοχές



## Φάση της υπερπλασίας(3-7 ημέρες)

### Ινωτική φάση (>7 ημέρες)

- Εμμένουσα υποξυγοναιμία, Υπερκαπνία (αύξηση του νεκρού χώρου)  
Πνευμονική υπέρταση  
*Ro* θώρακος: Γραμμοειδείς σκιάσεις (εξελισσόμενη ίνωση), πνευμοθώρακας  
CT θώρακος: Διάχυτες διάμεσες σκιάσεις, bullae

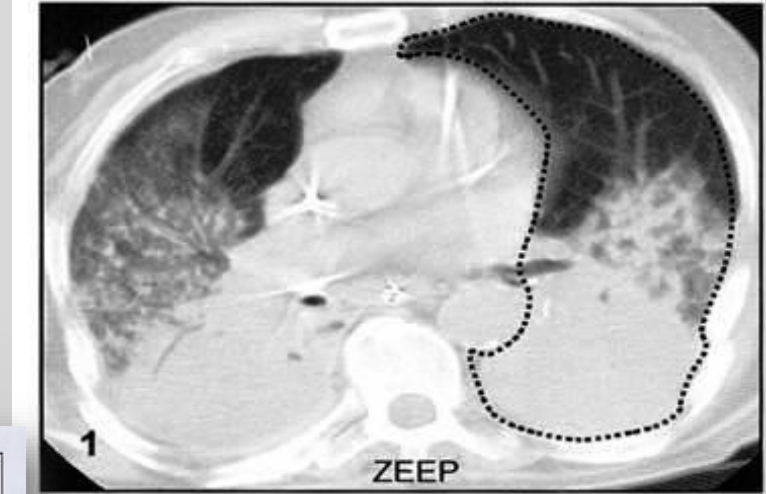


# ARDS - φυσιολογία

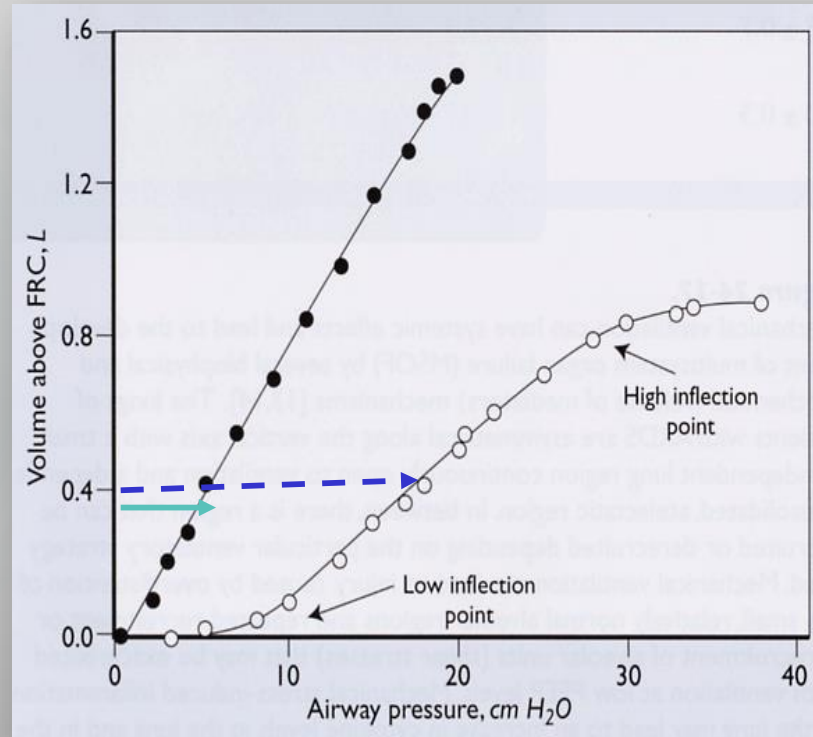
- $\downarrow$   $P_{aO_2}$ :
  - $\uparrow$  shunt
  - διαταραχές V/Q
- $\uparrow$   $P_{aCO_2}$ :
  - $\uparrow$  VD/VT
  - $\uparrow$  παραγωγή  $CO_2$



$\downarrow$  Πνευμονικού όγκου (baby lung)

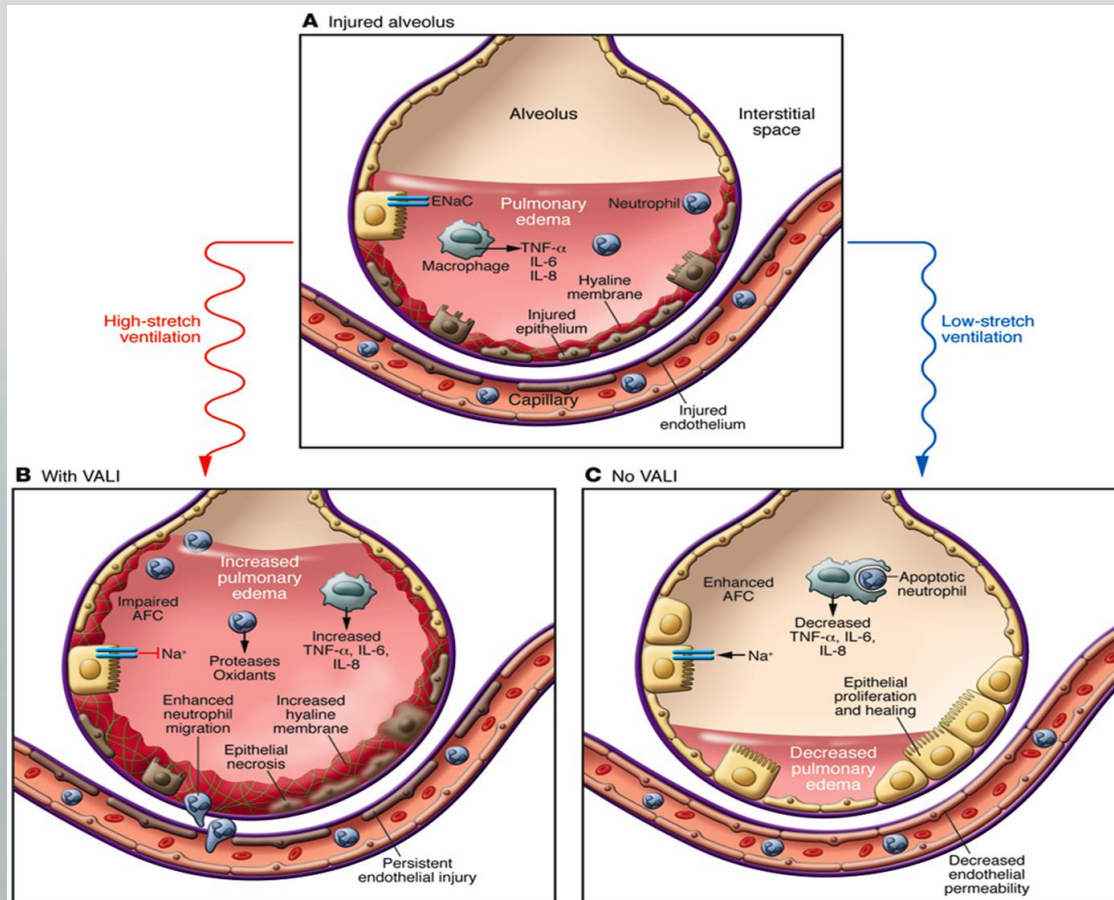


$\downarrow$  Ενδοτικότητα



# ARDS

## Θεραπεία



# ARDS- Θεραπεία

## Φάρμακα



Table 2. Major Studies and Therapeutic Advances in Acute Respiratory Distress Syndrome (ARDS) From Selected Trials

Source	Setting (Study Duration)	Study Population	No. of Patients	Intervention	Control	P	Other Outcomes	Conclusions	
<b>Pharmacologic Therapies</b>									
Gao Smith et al, <sup>20</sup> 2012	46 ICUs (2006-2010)	ARDS (AECC) with $Pao_2/Fio_2 \leq 200$ mm Hg	162	Intravenous salbutamol	Placebo	28-d mortality	RR (95% CI): 1.47 (1.03 to 2.08)	RR (95% CI): ICU mortality, 1.31 (95 to 1.80); hospital mortality, 1.18 (0.88 to 1.59)	Trial stopped due to increased mortality with intravenous salbutamol
McAuley et al, <sup>21</sup> 2017	2 ICUs (2011-2014)	ARDS (AECC) with $Pao_2/Fio_2 \leq 300$ mm Hg	60	Recombinant human keratinocyte growth factor	Placebo	Oxygenation index at day 7 <sup>c</sup>	Mean difference (95% CI): 19.2 (-5.6 to 44.0)	Median difference (95% CI): VFDs at 28 d, -8 d (-17 to -2); mechanical ventilation duration at 90-d (survivors only), 6 d (2 to 14)	No difference in oxygenation index at day 7 but fewer VFDs at 28 d, longer mechanical ventilation duration at 90 d, and higher 28-d mortality in the keratinocyte growth factor group
ARDS Network, <sup>22</sup> 2014	44 centers (2010-2013)	Sepsis-associated ARDS (AECC) with $Pao_2/Fio_2 \leq 300$ mm Hg	745	Rosuvastatin	Placebo	60-d in-hospital mortality	Absolute difference (95% CI), %: 4.0 (-2.3 to 10.2)	Absolute difference (95% CI): VFDs at 28 d, 0.0 d (-1.6 to 1.5); ICU-free days at 28 d, -0.2 (-1.6 to 1.3)	Trial stopped for futility with no difference in 60-d in-hospital mortality, VFDs at 28 d, or ICU-free d at 28 d
McAuley et al, <sup>23</sup> 2014	40 centers (2010-2014)	ARDS (AECC) with $Pao_2/Fio_2 \leq 300$ mm Hg	540	Simvastatin	Placebo	VFDs at 28 d	Mean difference (95% CI), d: 1.1 (-0.6 to 2.8)	Mean difference (95% CI): days free of nonpulmonary organ failure, 1.6 (-0.4 to 3.5); RR (95% CI): 28-d mortality, 0.80 (0.6 to 1.1)	No difference in VFDs at 28 d, d free of nonpulmonary organ failure, or 28-d mortality

(continued)



# ARDS-Θεραπεία

## Φάρμακα



G. Umberto Meduri  
Lisa Bridges  
Mei-Chiung Shih  
Paul E. Marik  
Reed A. C. Siemieniuk  
Mehmet Kocak

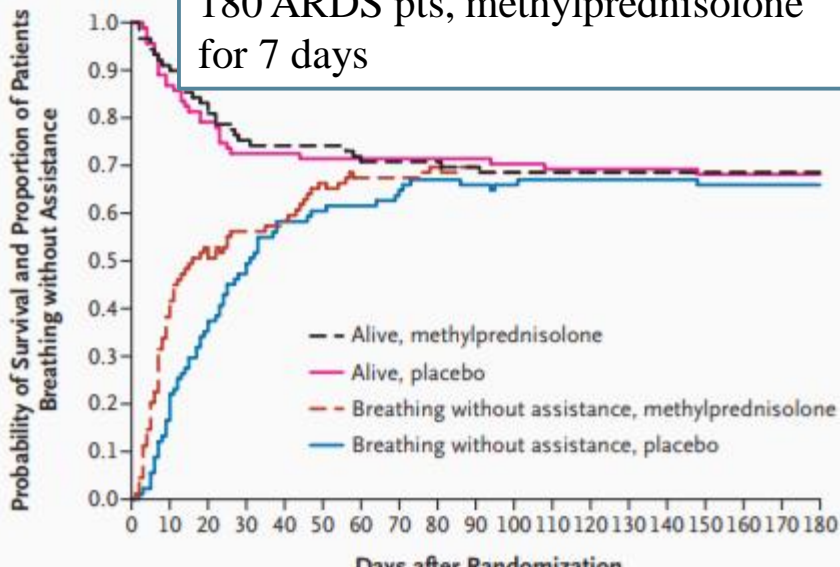
**Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature**

The NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 20, 2006 VOL. 354 NO. 16

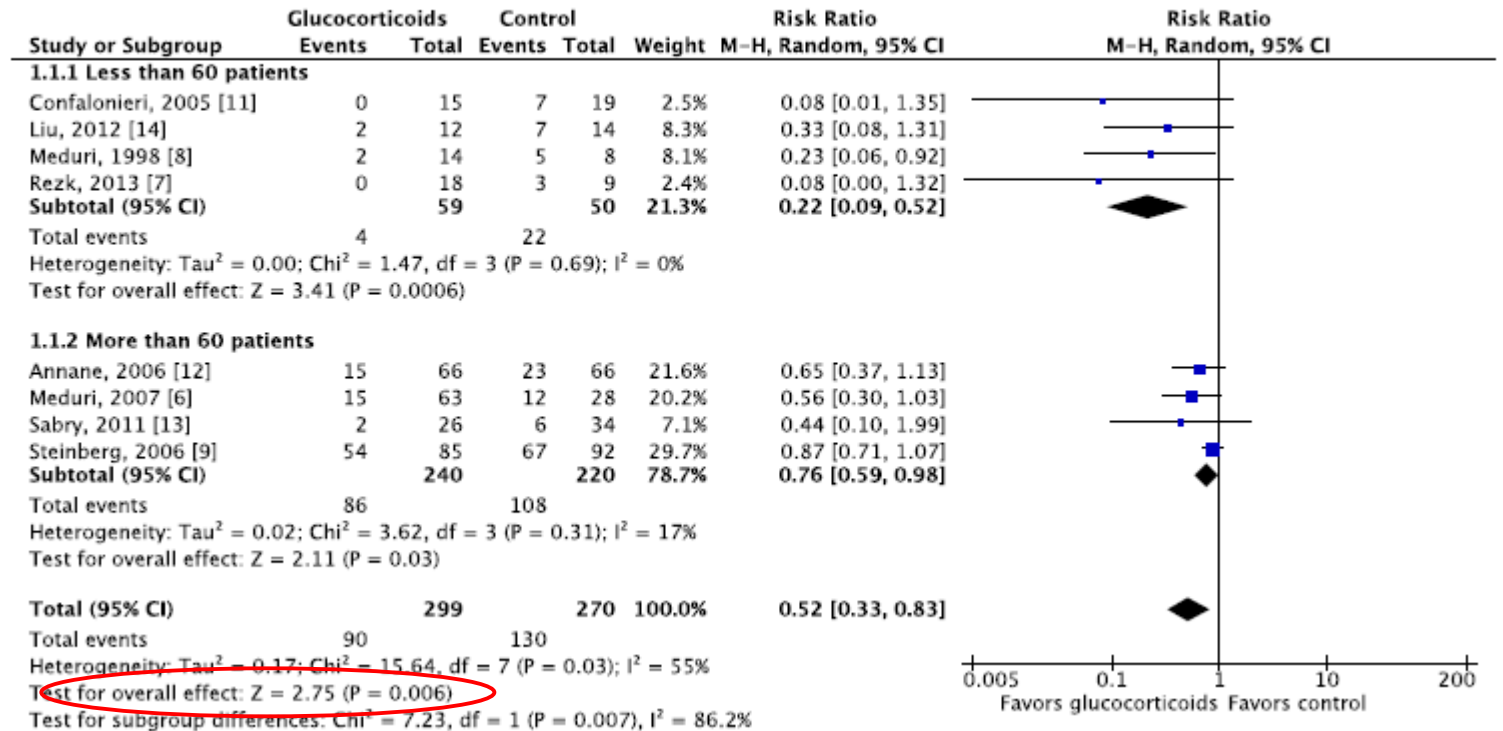
Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome

Steinberg, *NEJM* 2006  
ClinicalTrials.gov number, NCT00295269



### CONCLUSIONS

These results do not support the routine use of methylprednisolone for persistent ARDS despite the improvement in cardiopulmonary physiology. In addition, starting methylprednisolone therapy more than two weeks after the onset of ARDS may increase the risk of death. (ClinicalTrials.gov number, NCT00295269.)



Meduri, *ICM* 2016

## ARDS-Θεραπεία Φάρμακα

**277** patients with moderate to severe ARDS  
dexamethasone group 20 mg daily  
(1-5days, 10 mg (6-10 days))

The mean number of ventilator-free days was higher in the dexamethasone group than in the control group

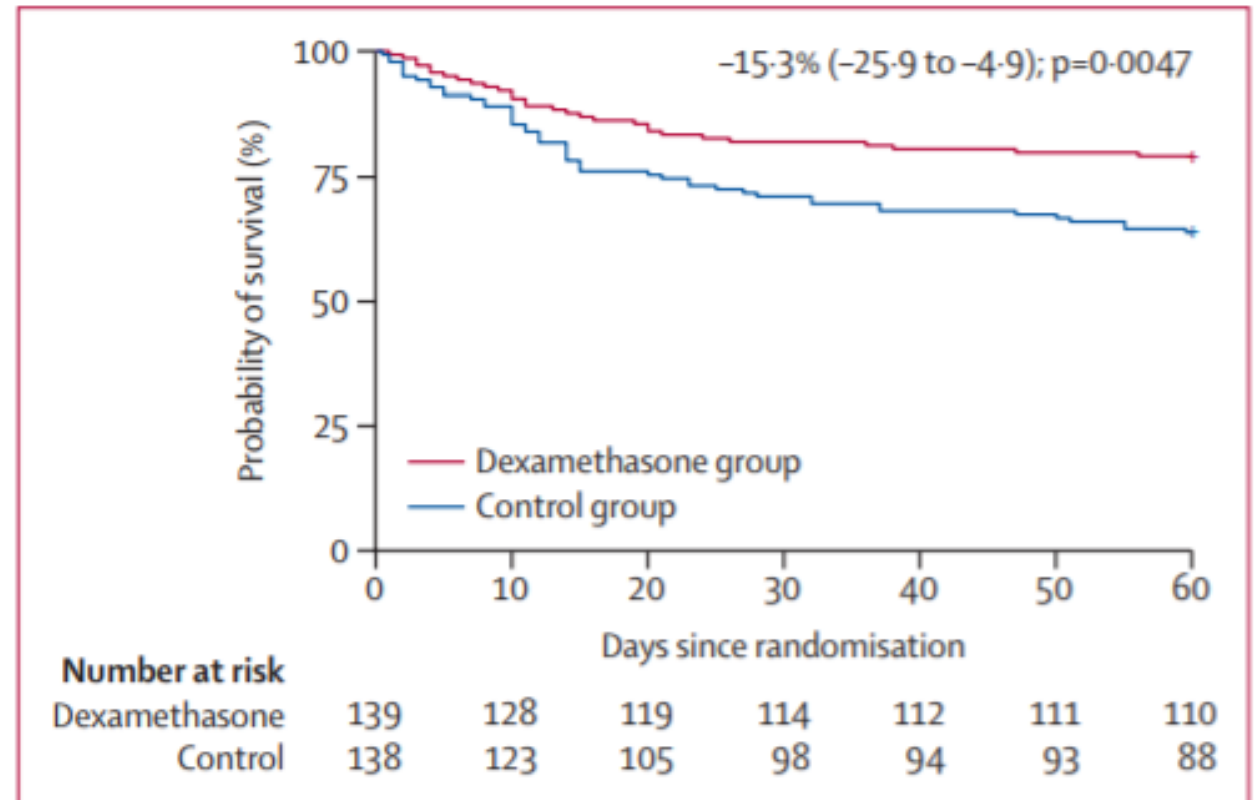
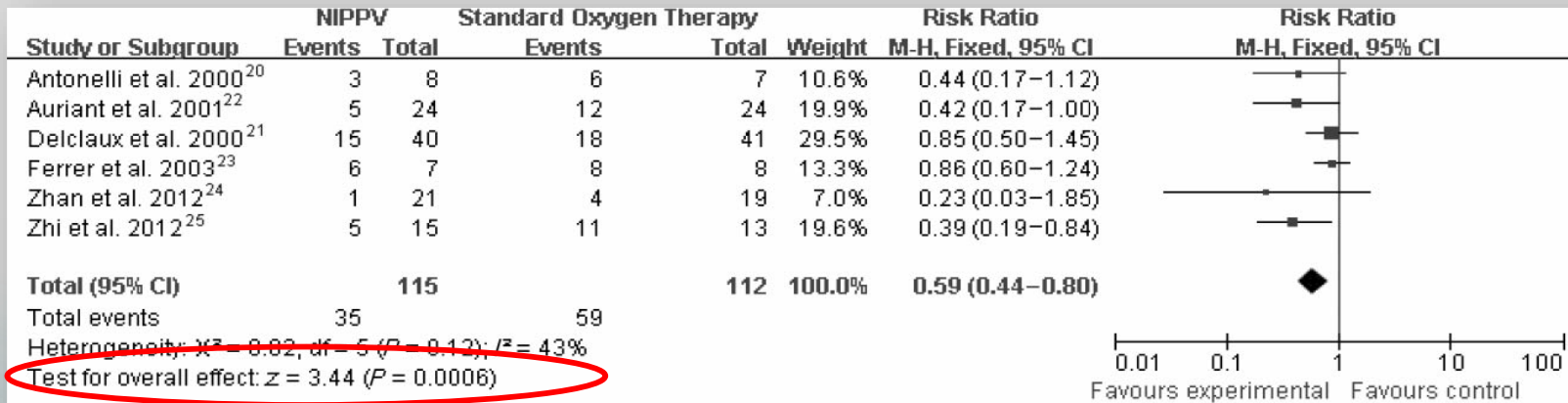


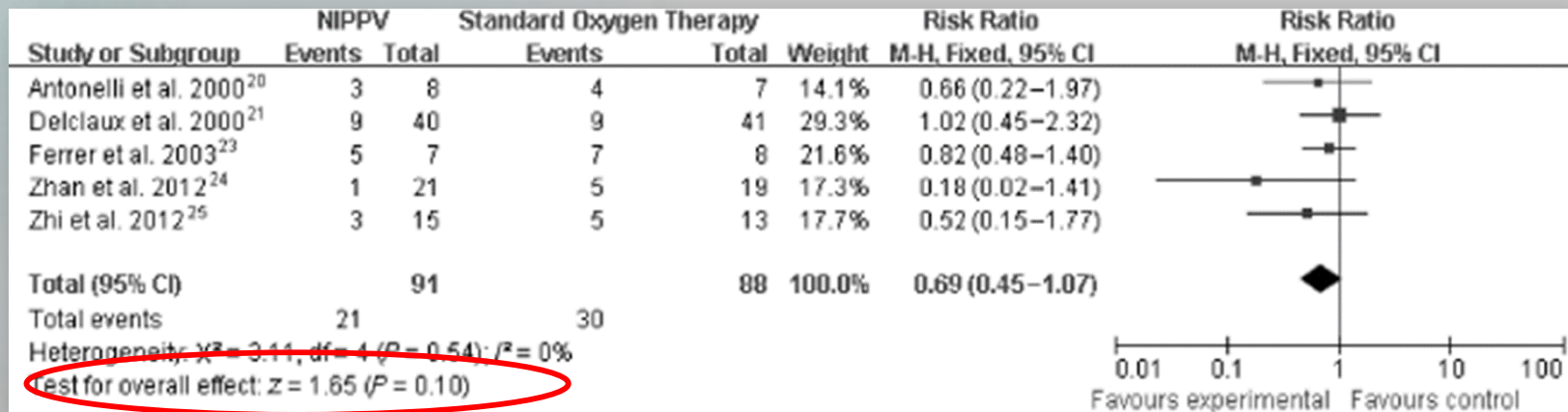
Figure 2: Kaplan-Meier survival estimates during the first 60 days of trial

# Μη επεμβατικός μηχανικός αερισμός, (NIV)

## Διασωλήνωση



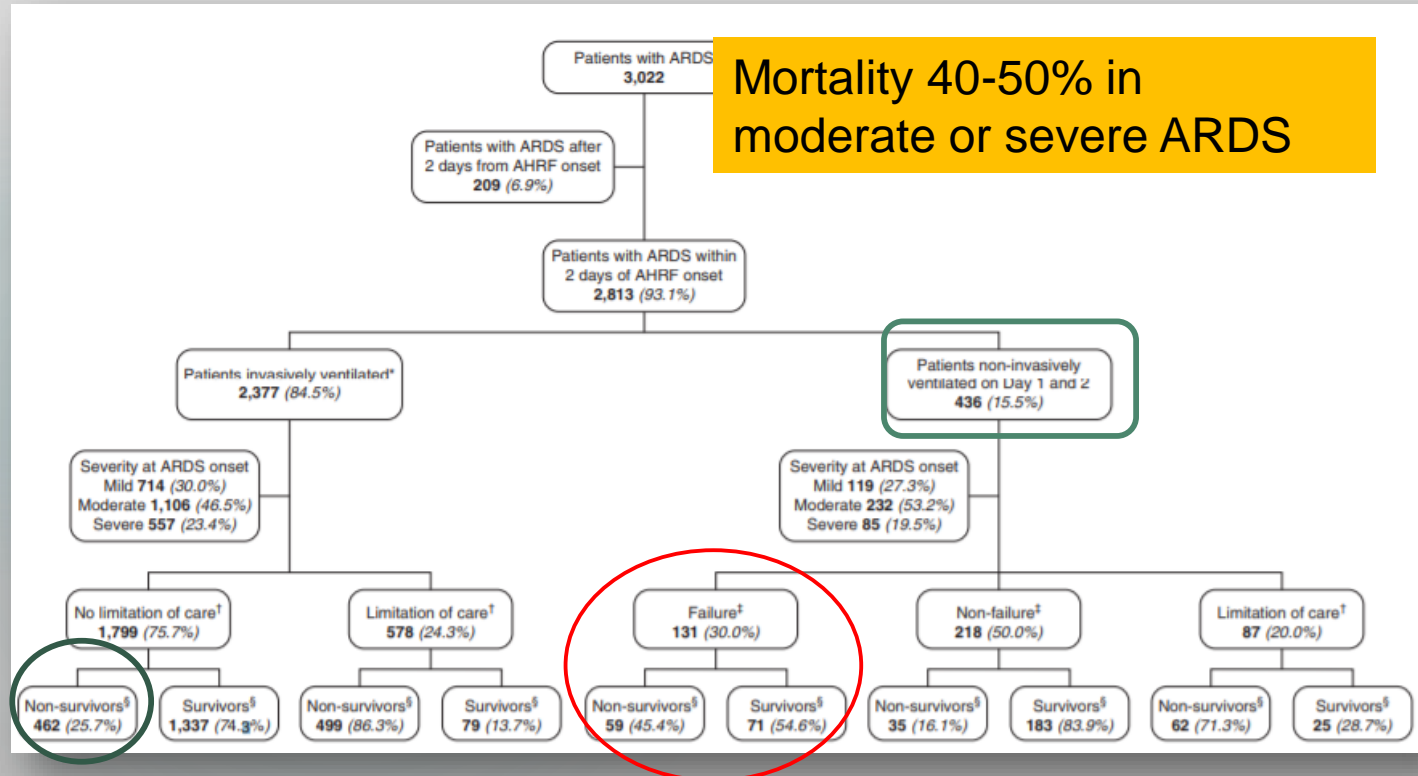
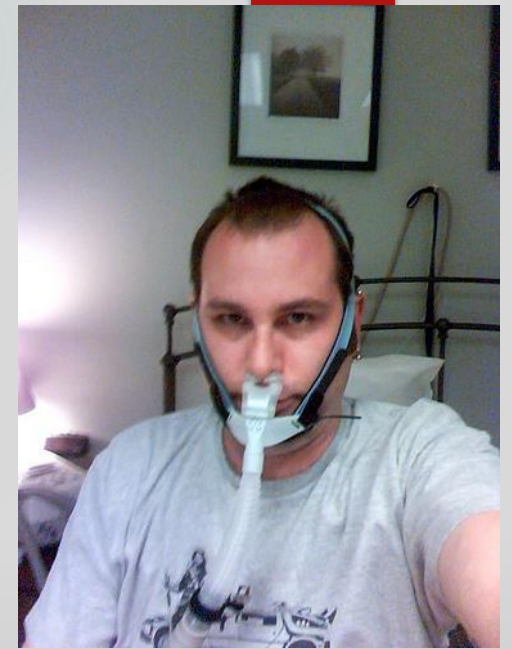
## Θνητότητα



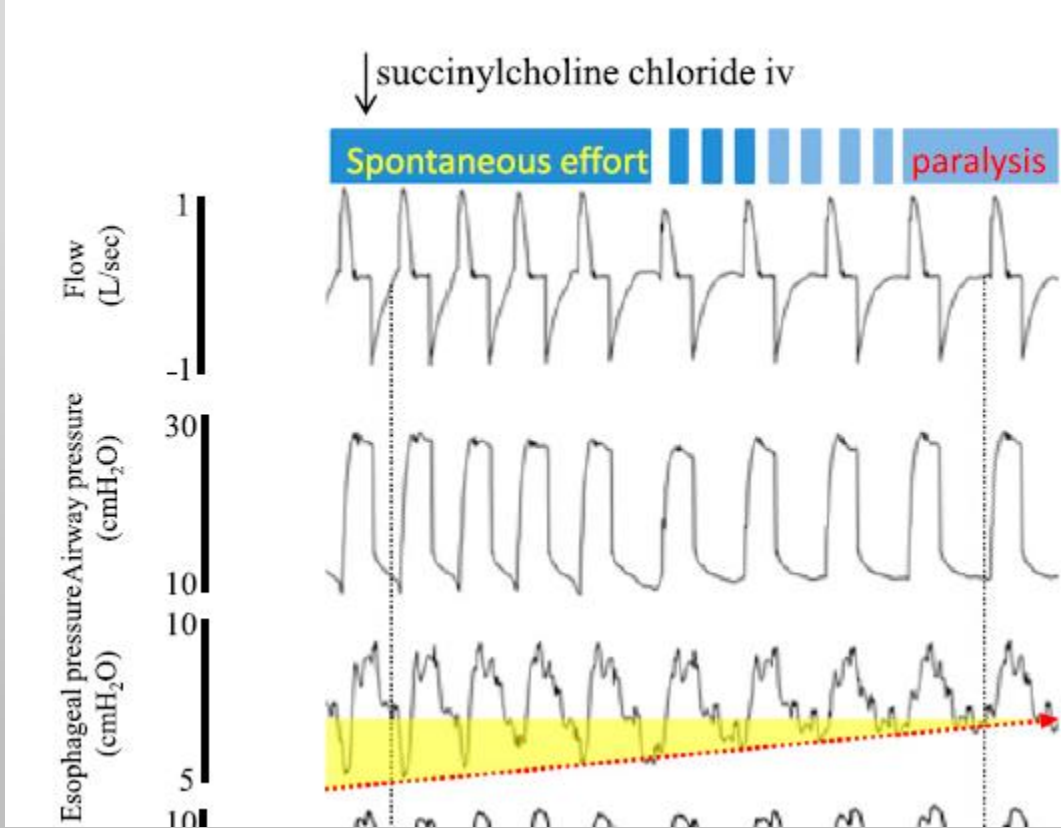
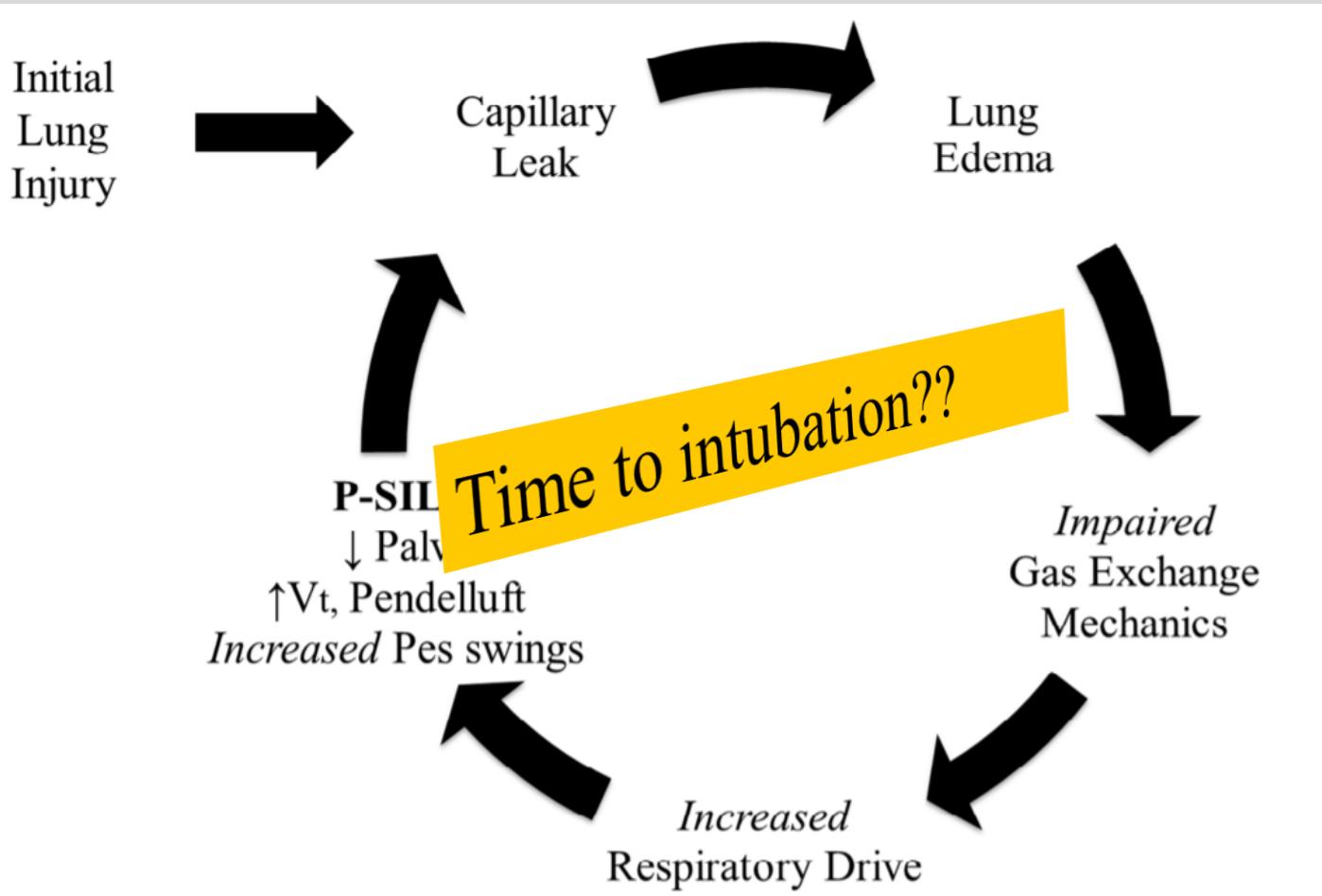
# Non Invasive mechanical ventilation

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries



# Patient-self inflicted lung injury (P-SILI)



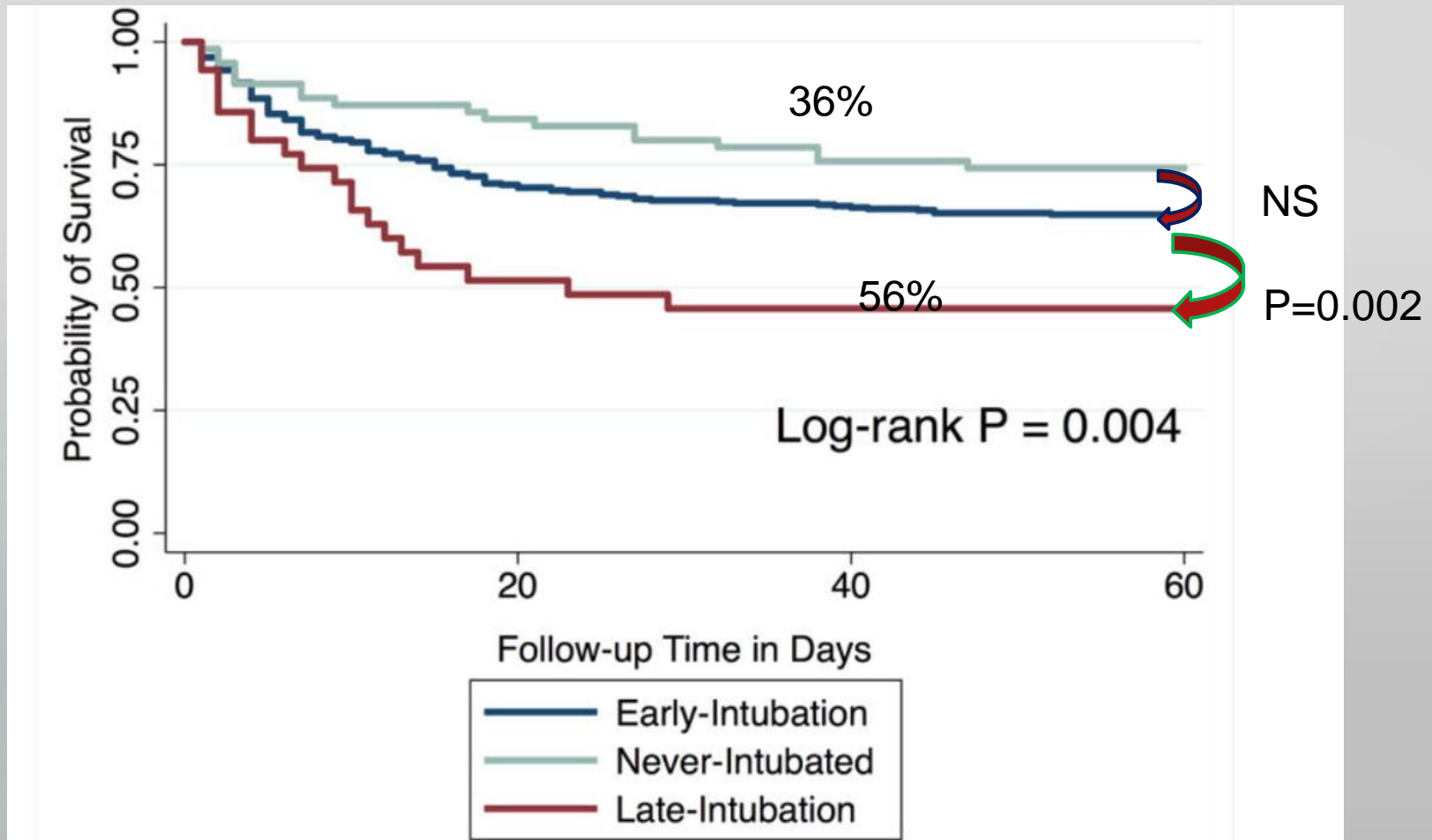
Brochard AJRCCM 2017

Yoshida, AJRCCM 2013

## Timing of Intubation and Clinical outcomes in Adults with ARDS

Kirsten Neudoerffer Kangelaris, MD MAS<sup>1</sup>, Lorraine B. Ware, MD<sup>2</sup>, Chen Yu Wang<sup>3</sup>, David

457 pts  
106 (23%) not intubated  
36 (34%) late intubation



Οι ασθενείς με ARDS χαρακτηρίζονται από βαριά υποξυγοναιμία, και χρειάζονται **μηχανική υποστήριξη** της αναπνοής

## ΑΞΟΝΕΣ ΣΤΟΧΕΥΣΗΣ ΤΟΥ ΜΗΧΑΝΙΚΟΥ ΑΕΡΙΣΜΟΥ ΣΤΟ ARDS

- **Επαρκής οξυγόνωση** ( $\text{PaO}_2$  55-80 mm Hg,  $\text{SaO}_2$ : 88-95%)
- **Ελαχιστοποίηση των βλαβών** που προκαλεί ο αναπνευστήρας (*Ventilator Induced Lung Injury-VILI*)

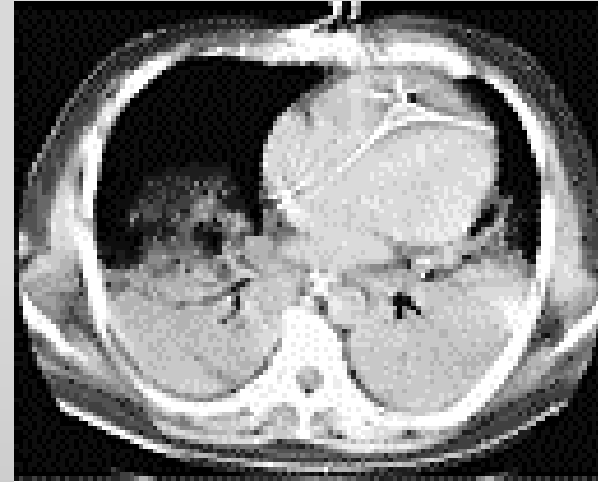


# Μηχανικός αερισμός στο ARDS

## 1. Επαρκής οξυγόνωση

↑  $\text{FiO}_2$ - Τοξικότητα

↑ Αύξηση του λειτουργικού όγκου του πνεύμονα (που συμμετέχει στην ανταλλαγή των αερίων)



**ZEEP**

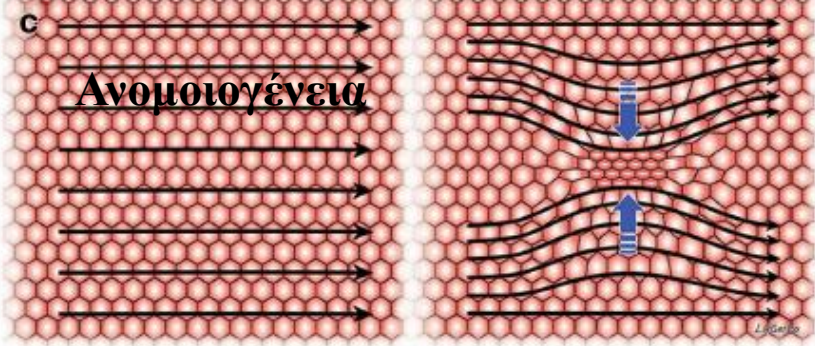
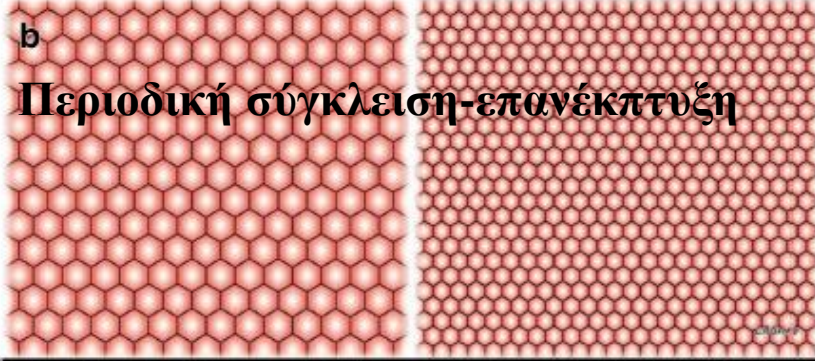
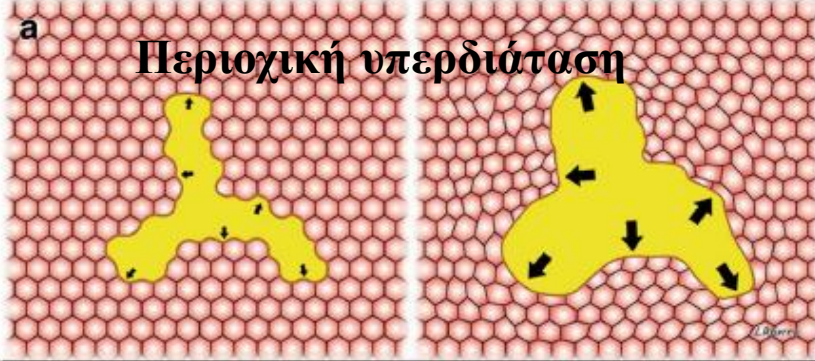


**PEEP**

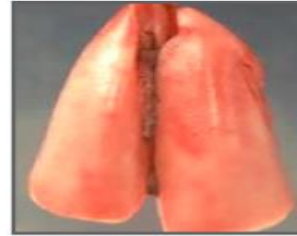
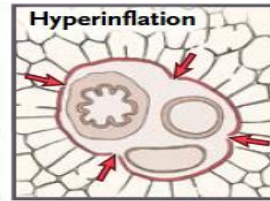
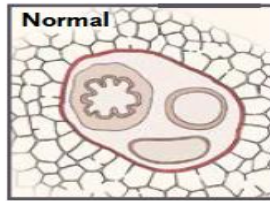




# Αποφυγή των βλαβών που προκαλεί ο αναπνευστήρας Ventilation Induced Lung Injury

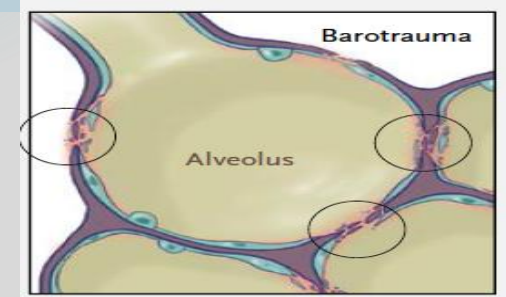


## B Ventilation at high lung volume

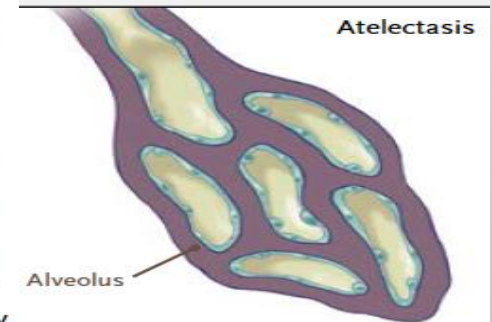
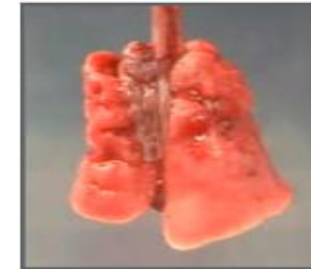
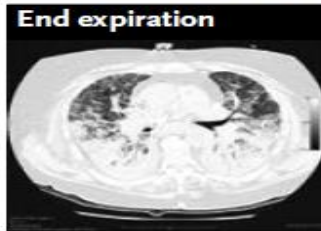


Air leaks

Overdistention

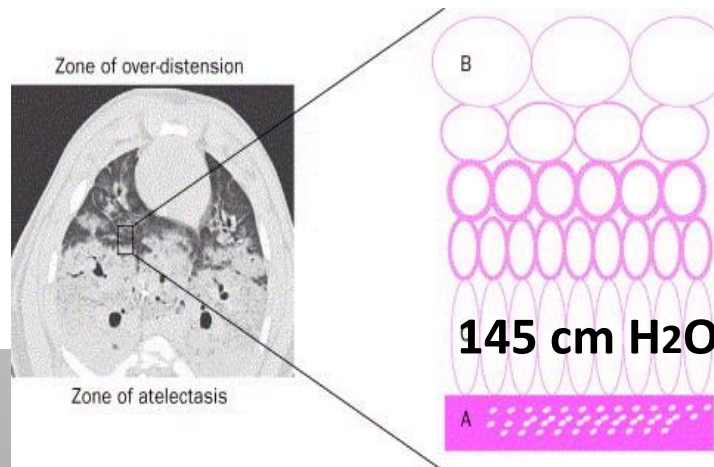


## A Ventilation at low lung volume



Atelectrauma

Lung inhomogeneity

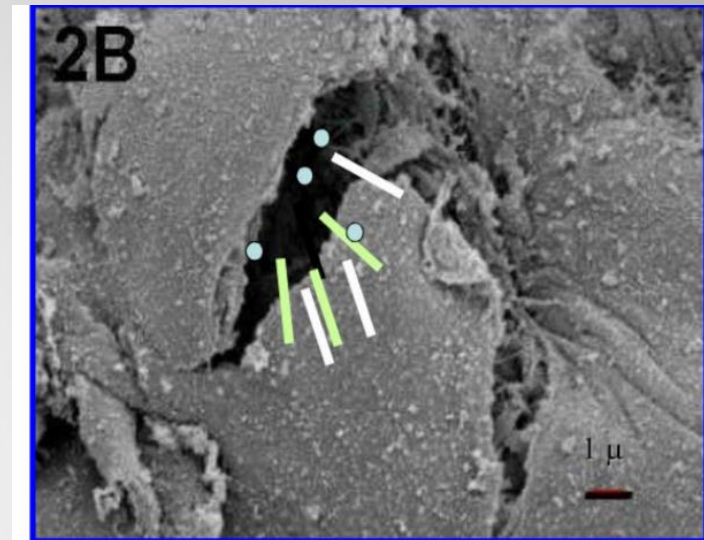
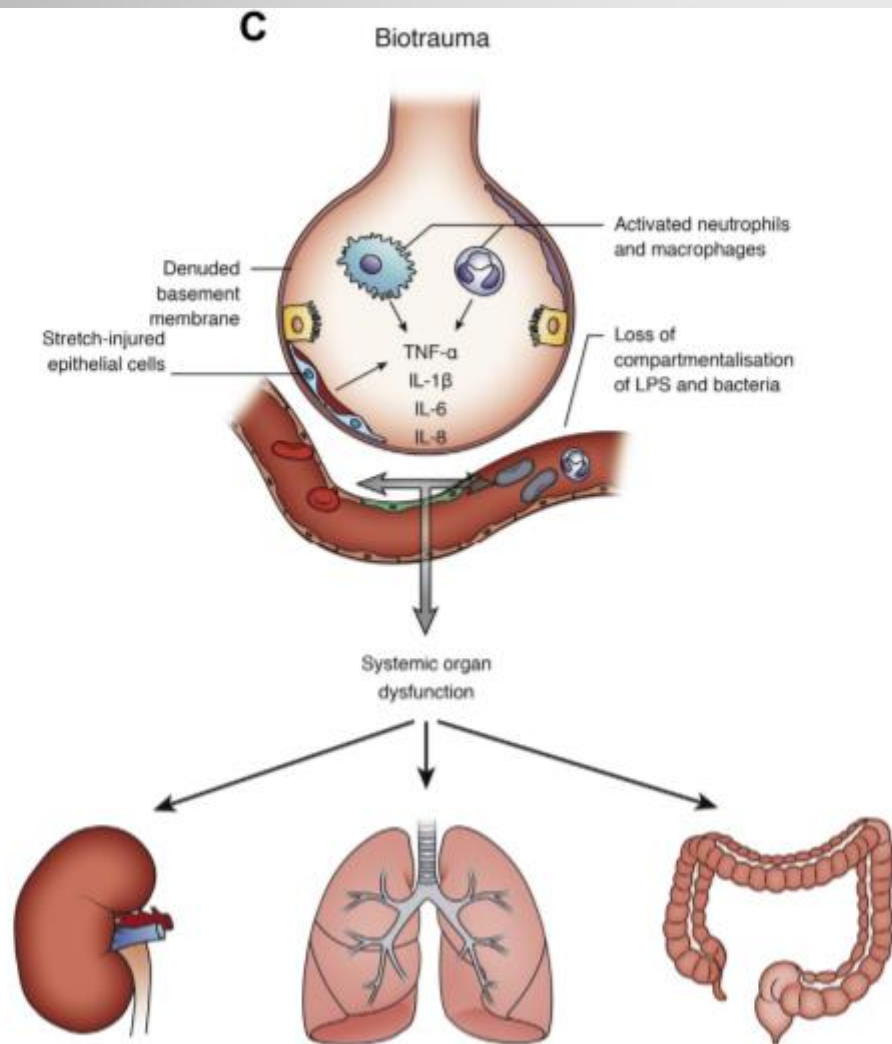


**Stress raisers or concentrators**

(Πολλαπλασιαστικές  
εφαπτόμενες δυνάμεις)

# Ventilation Induced Lung Injury

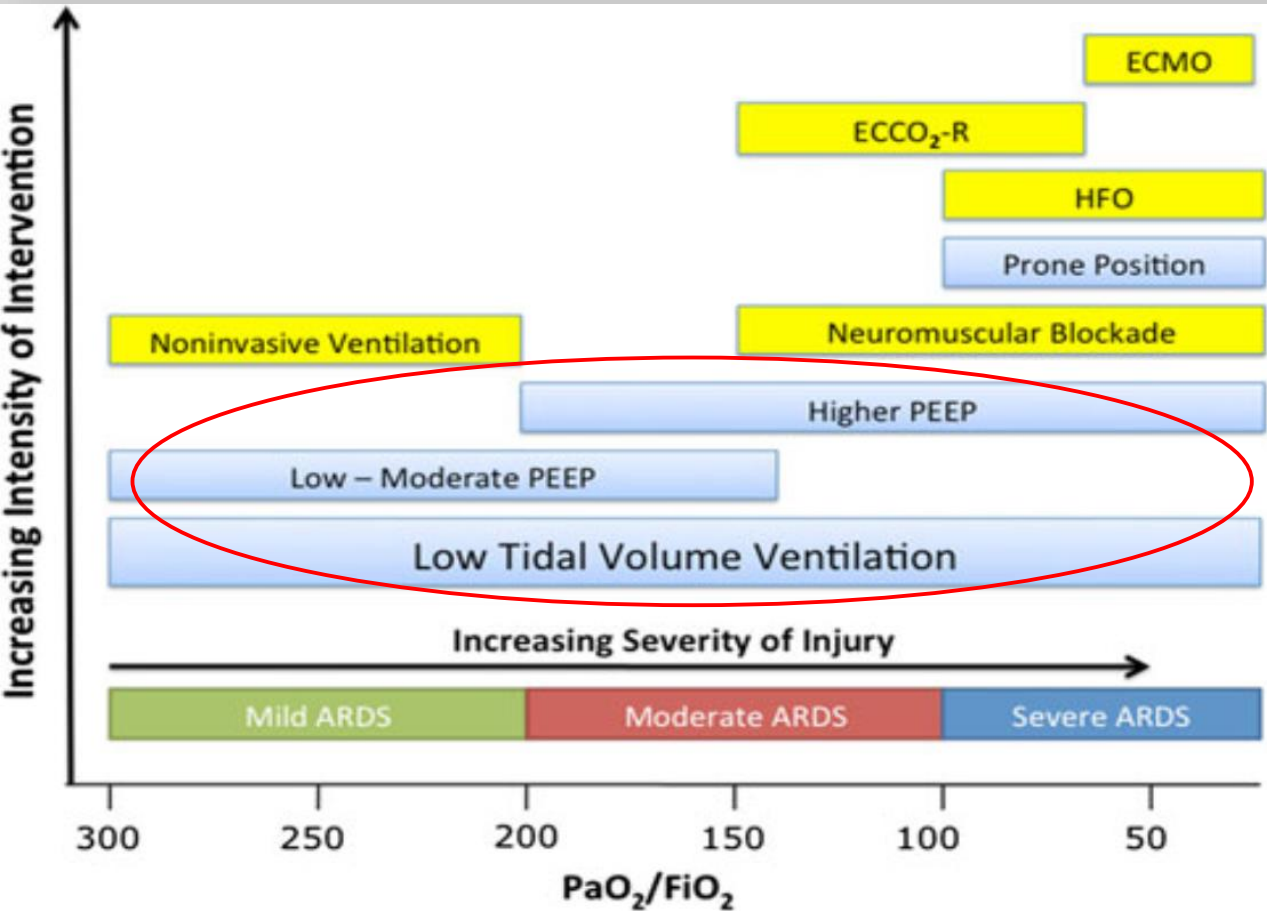
## Biotrauma



# ARDS: Lung protective ventilation



ARDSnet, *N Engl J Med* 2000



T<sub>v</sub>: 6mL/kgPBW

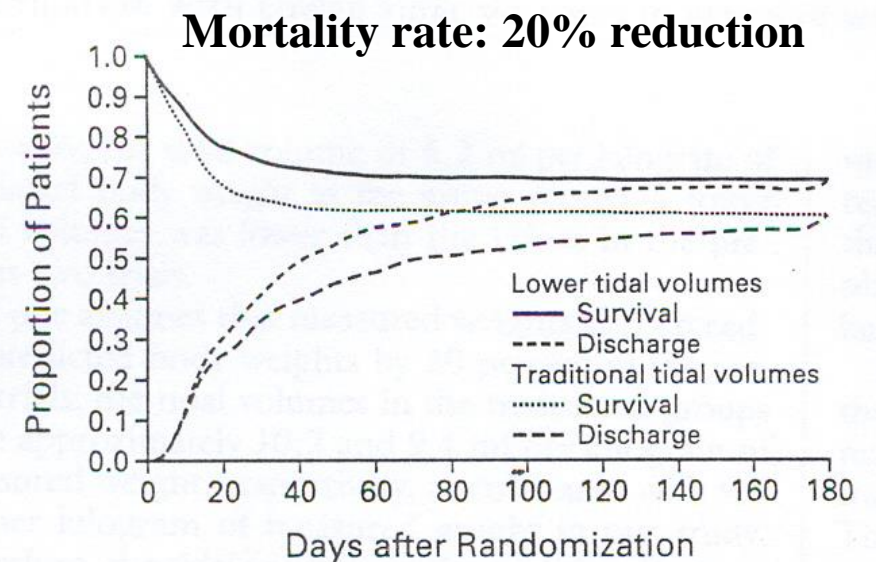
P<sub>plat</sub>: ≤30 cm H<sub>2</sub>O

RR: 6-35/min

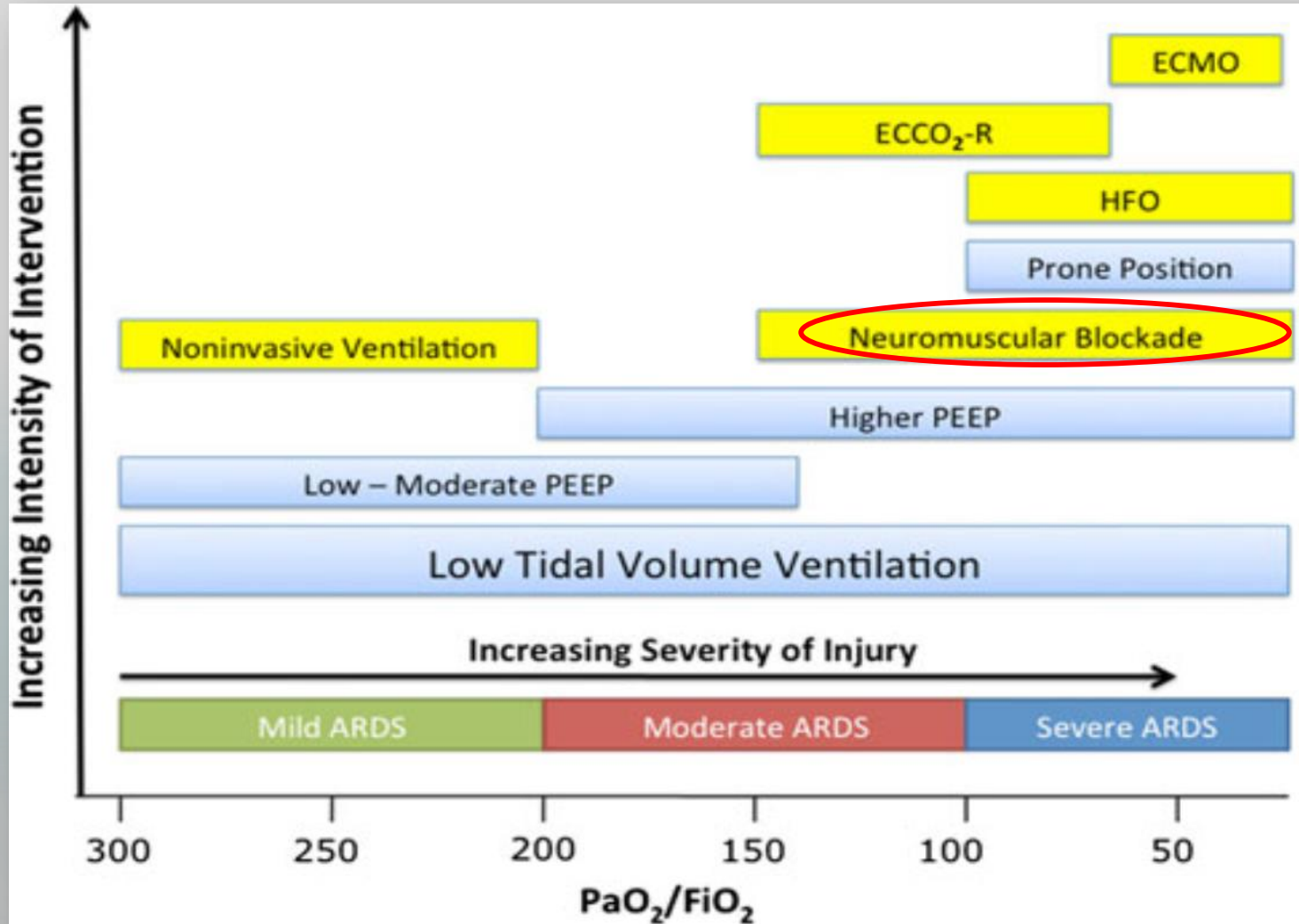
pH: 7.30-7.45

FiO<sub>2</sub>-PEEP ⇒ PaO<sub>2</sub>:55-80 mm Hg or SaO<sub>2</sub>: 88-95%

The ARDS definition Task Force: *JAMA* 2012

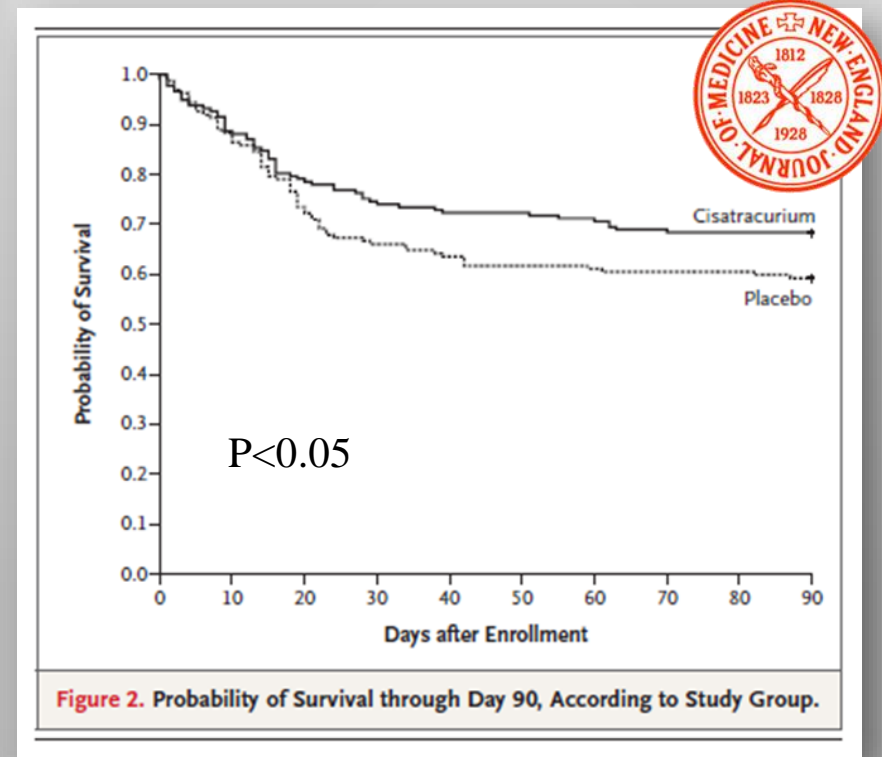


# ARDS: Lung protective ventilation



## Φάρμακα: Neuromuscular blockers in early ARDS

Πολυκεντρική, διπλή τυφλή μελέτη με 340 ασθενείς με βαρύ πρώιμο ARDS ( $\text{PaO}_2/\text{FiO}_2 < 150$  mm Hg)





## Φάρμακα: Neuromuscular blockers in early ARDS

### Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

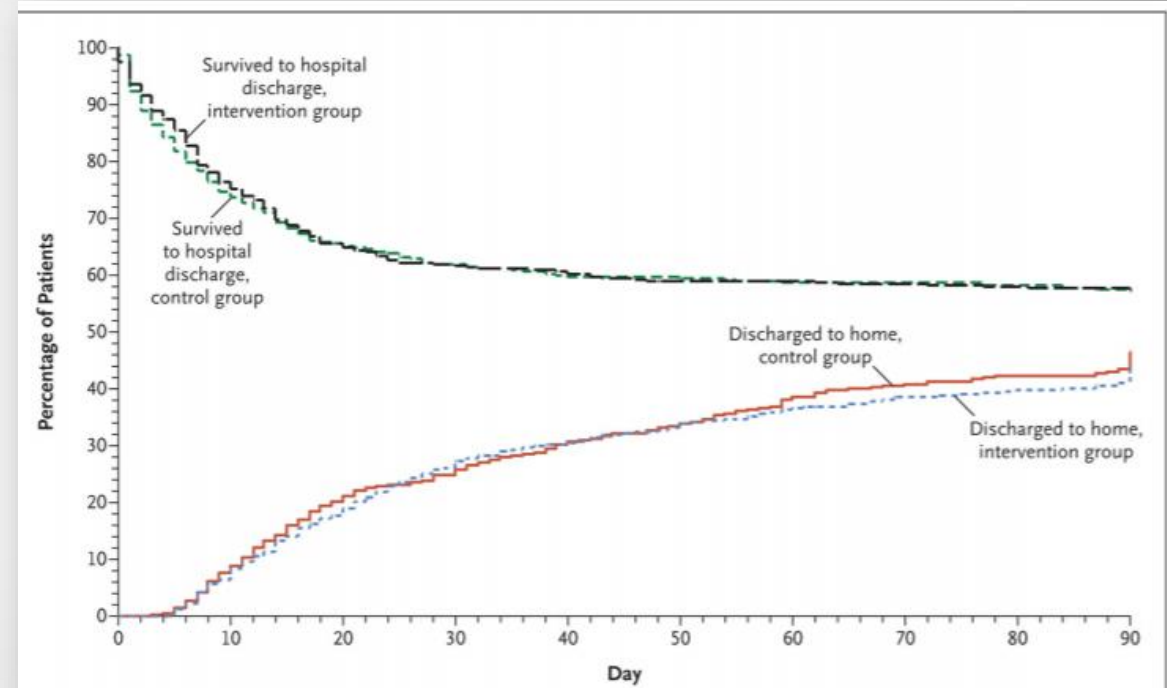
Πολυκεντρική, διπλή τυφλή μελέτη με 1006 ασθενείς με βαρύ πρωιμο ARDS ( $\text{PaO}_2/\text{FiO}_2 < 150 \text{ mm Hg}$ )

Cisatracurium besylate or placebo for 48 h

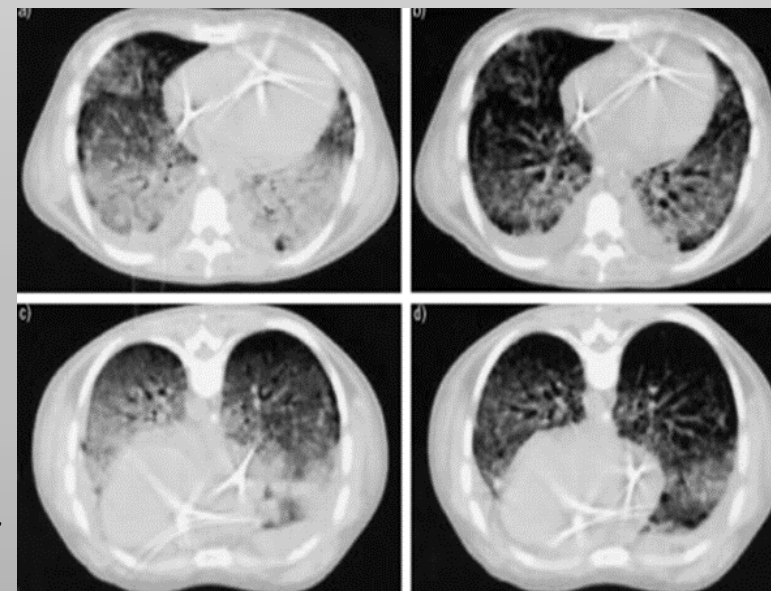
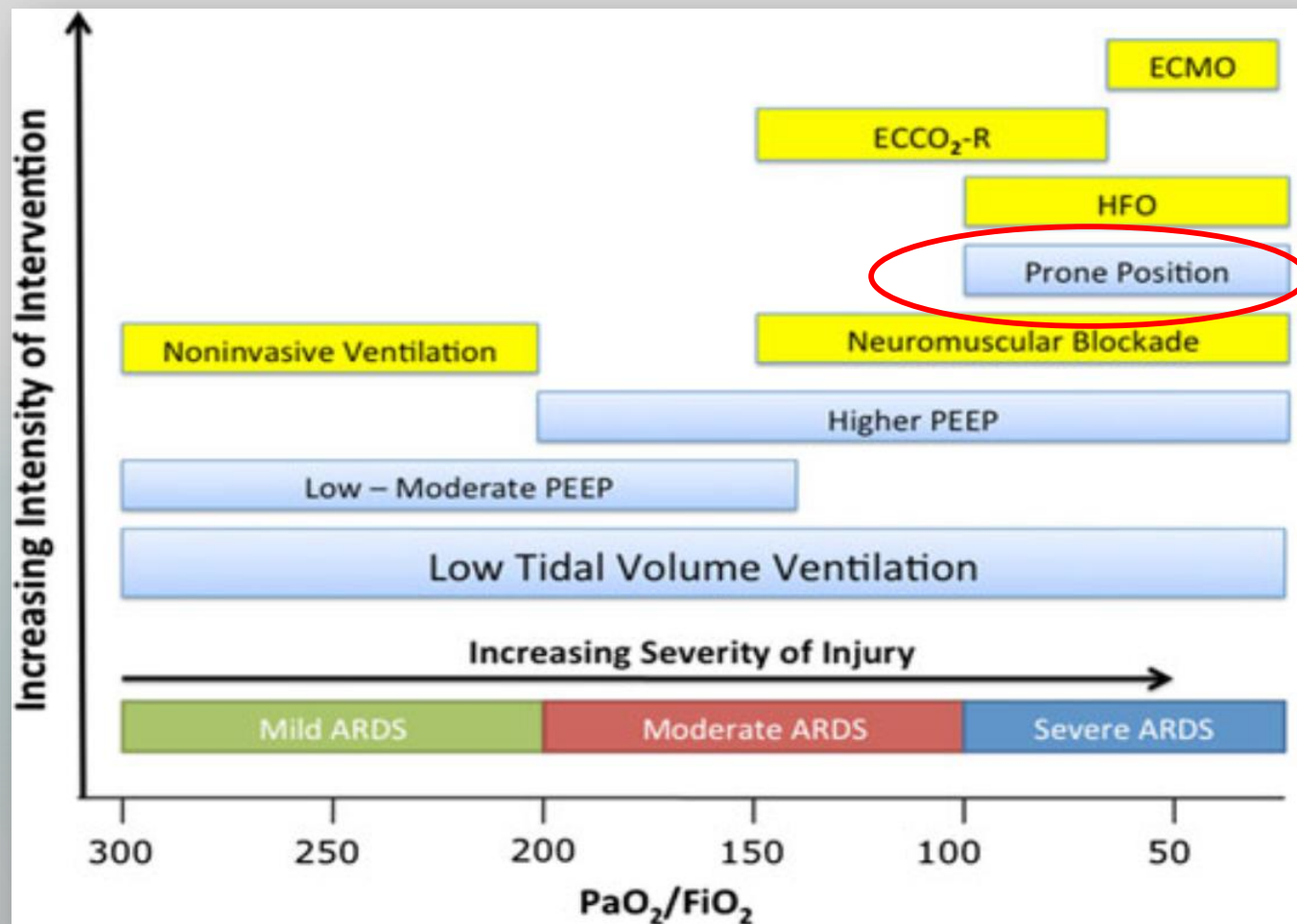
Mortality at 90 days:

The trial was stopped at the second interim analysis for futility.

N Engl J Med. 2019



# Μηχανικός αερισμός στο ARDS: Πρηνής Θέση



Petersson, JAP 2006

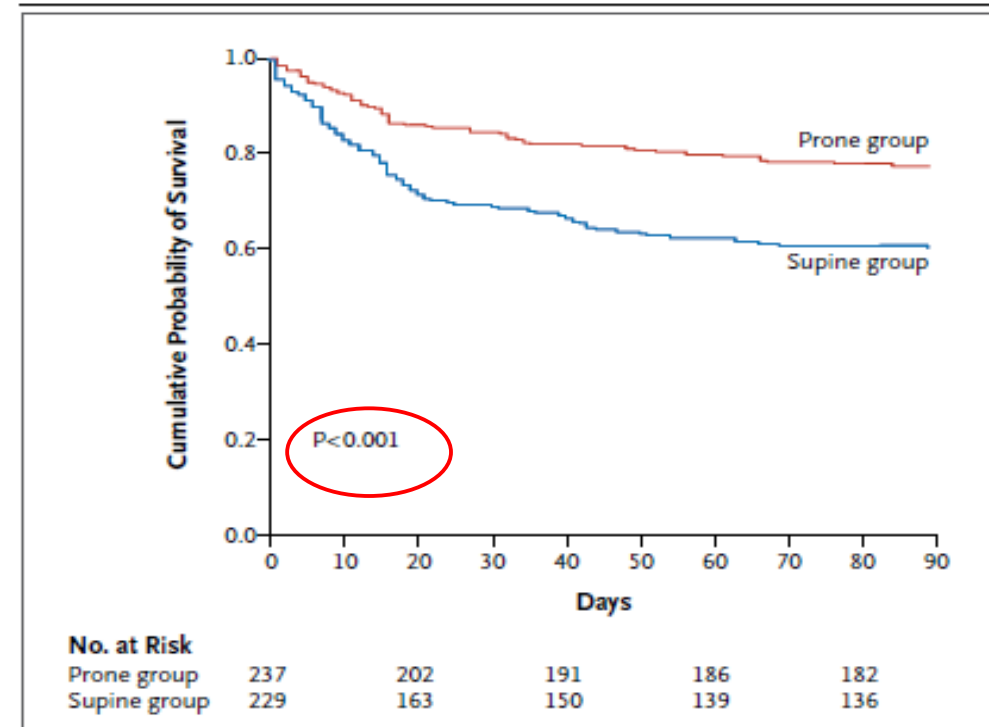
## Μηχανικός αερισμός στο ARDS: Πρηνής Θέση

65-75% βελτίωση της οξυγόνωσης λόγω:

- Ομοιογενέστερης κατανομής αερισμού-αιμάτωσης
- Μείωσης των περιοχών με πνευμονικό οίδημα και ατελεκτασία
- Αποφόρτιση από το βάρος της καρδιάς
- Παροχέτευση των εκκρίσεων

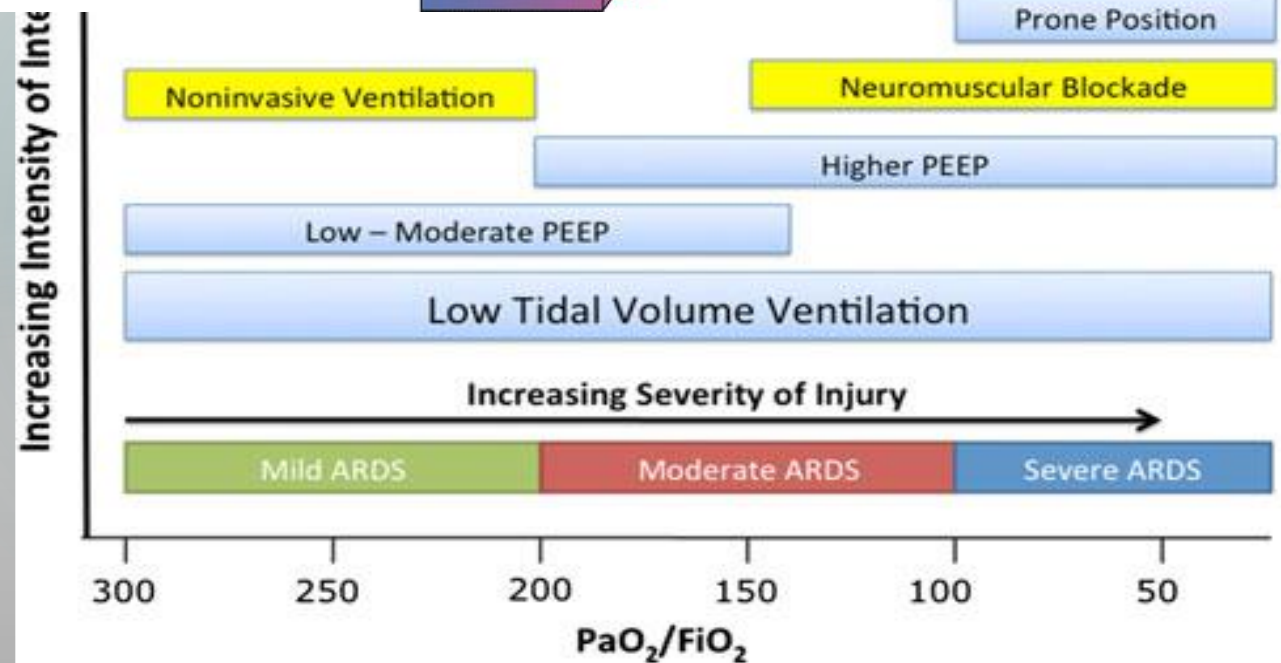
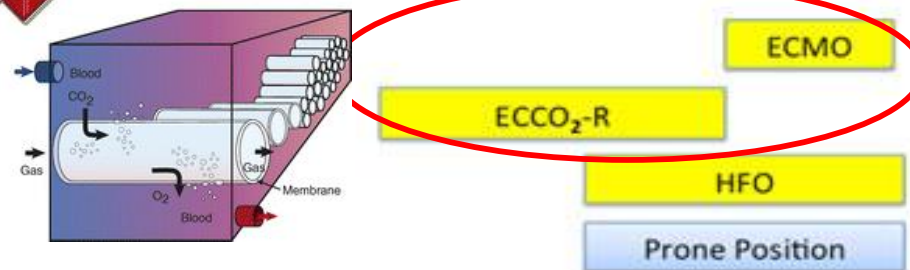
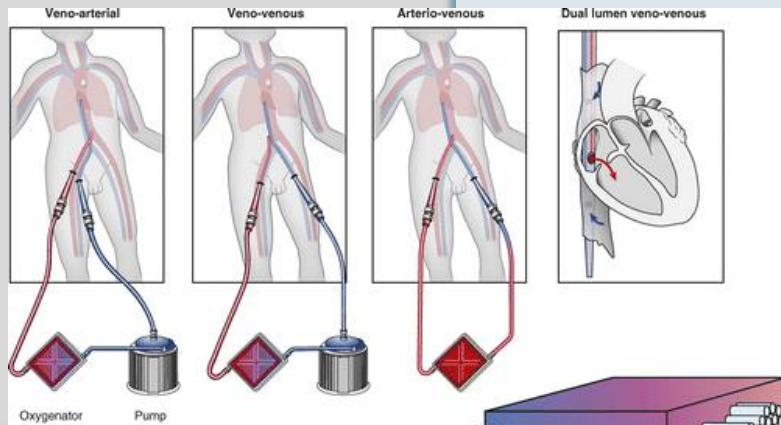
*Guerin, N Engl J Med 2013*

- 26 ICUs, 456 pts
- Μηχ. αερισμος < 36 h
- Prone positioning >17 h

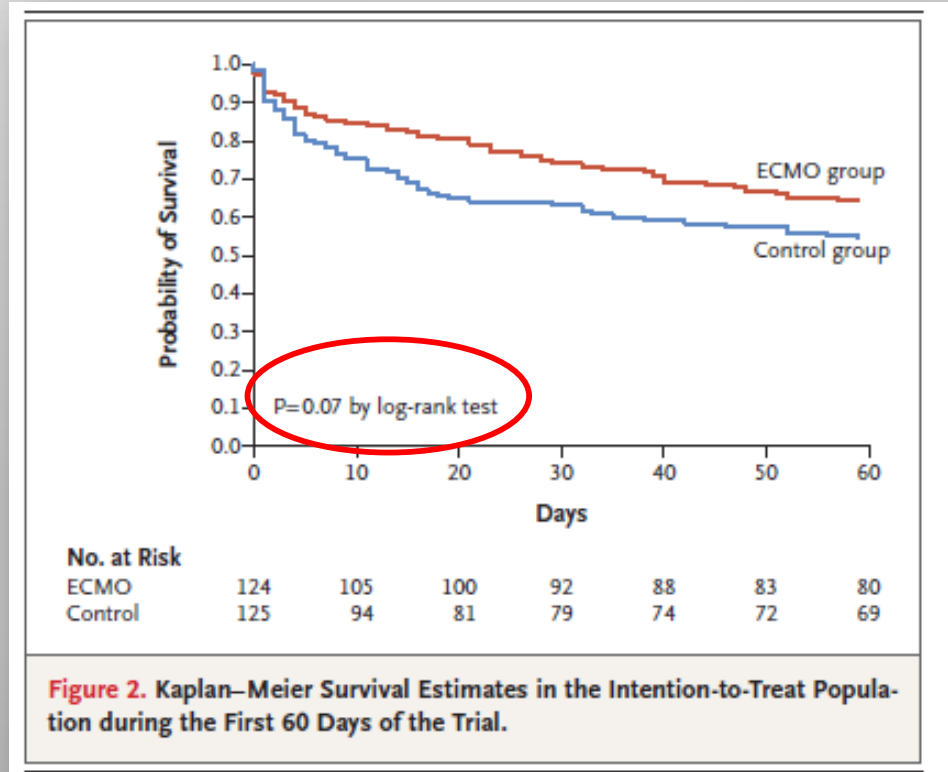


**Figure 2.** Kaplan–Meier Plot of the Probability of Survival from Randomization to Day 90.

# Extra-corporeal Membrane Oxygenation (ECMO) and/or CO2 Removal (ECCO2-R)



International Clinical Trial  
 249 ασθενείς με πολύ βαρύ ARDS  
 124: ECMO  
 125: συντηρητική αγωγή





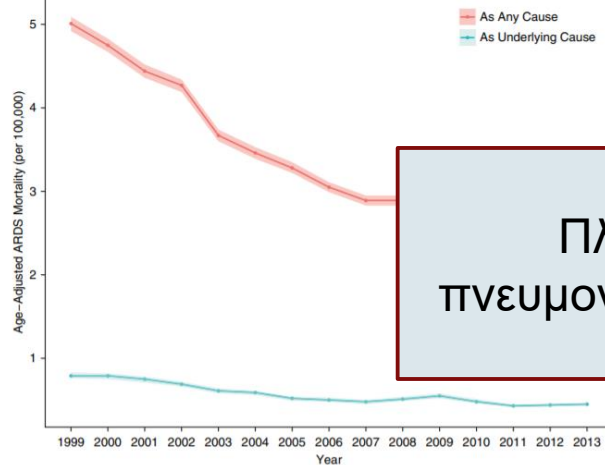
# Έκβαση

## Mortality Trends of Acute Respiratory Distress Syndrome in the United States from 1999 to 2013

Cochi Annals ATS 2016

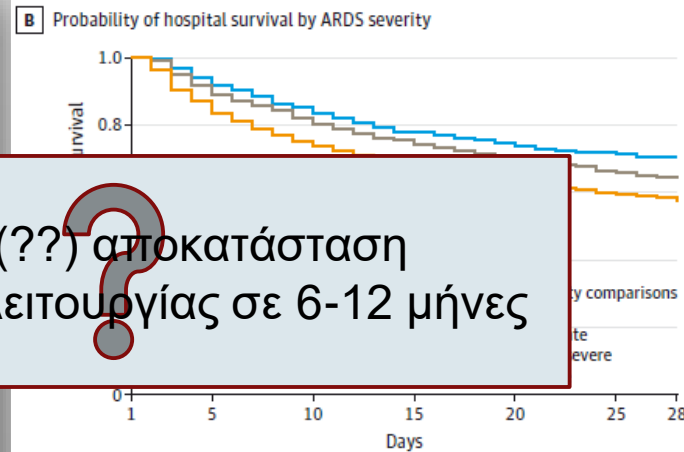
Shea E. Cochi<sup>1\*</sup>, Jordan A. Kempker<sup>2\*</sup>, Srinadh Annangi<sup>3</sup>, Michael R. Kramer<sup>4</sup>, and Greg S. Martin<sup>2</sup>

Dinglas, CCM 2017

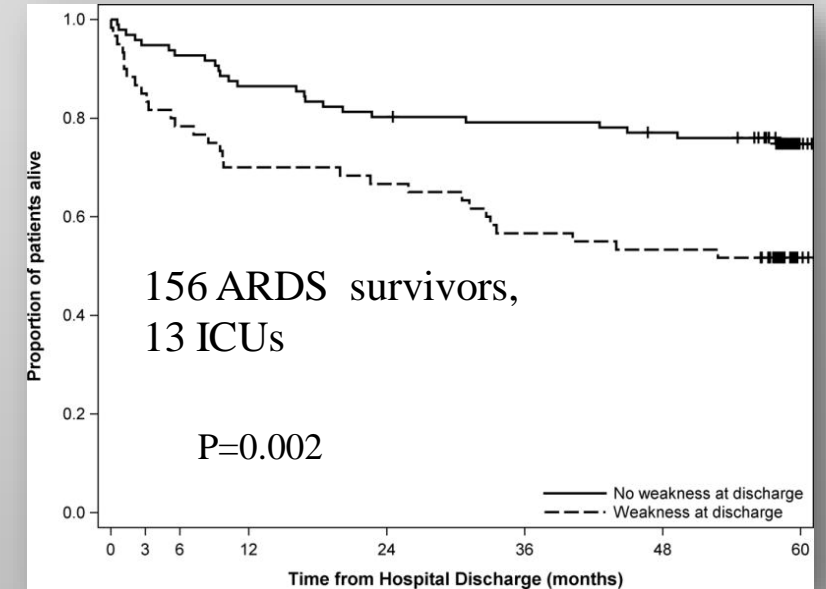


Πλήρης (??) αποκατάσταση  
πνευμονικής λειτουργίας σε 6-12 μήνες

Figure 1. Age-adjusted rates of acute respiratory distress syndrome (ARDS)-related mortality in the United States, 1999-2013. The red line displays mortality rates determined by a case definition of ARDS listed among any of the potentially 20 causes of death listed on a death record. The blue line displays mortality rates determined by ARDS listed as the principal underlying cause of death on a death record. The ribbons represent the 95% confidence limits of the estimates.



No. at risk, ARDS severity	1	5	10	15	20	25	28
Mild	708	662	599	548	522	501	489
Moderate	1101	1008	892	807	752	708	688
Severe	553	479	401	360	325	304	296



Η θνητότητα μάλλον μειώνεται τα τελευταία χρόνια λόγω:

Καλύτερων στρατηγικών μηχανικού αερισμού  
Πρωιμότερης διάγνωσης-θεραπείας της σήψης

Επιβαρυντικοί παράγοντες

Χρόνια ηπατική νόσος, Εξωπνευμονική οργανική ανεπάρκεια, Μεγάλη ηλικία

# Έκβαση

## The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

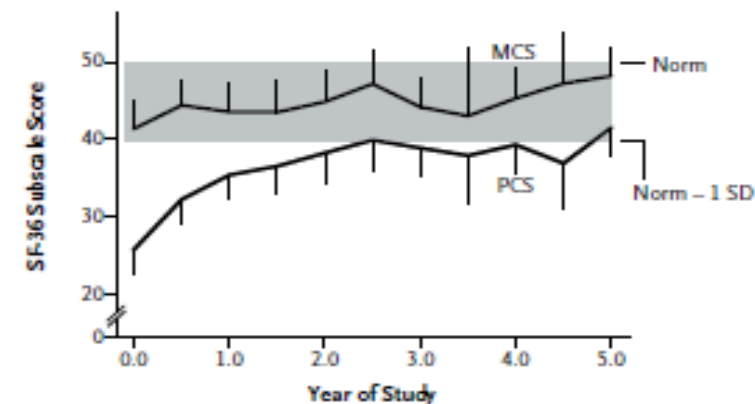
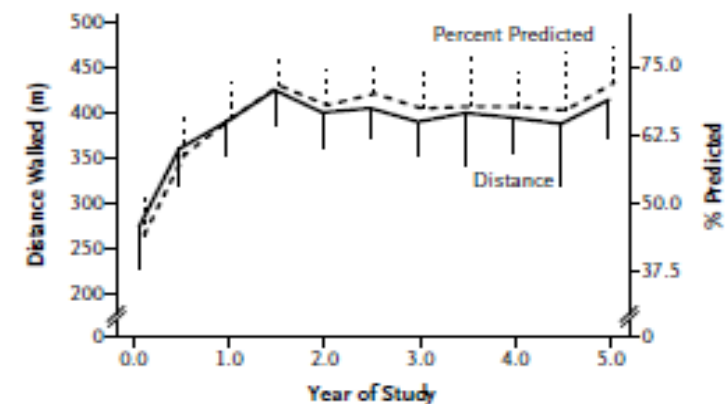
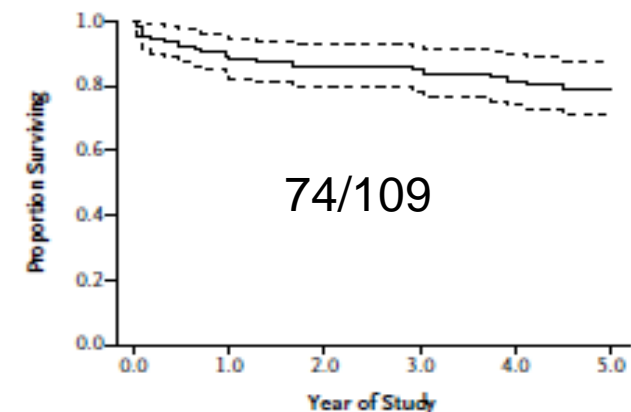
APRIL 7, 2011

VOL. 364 NO. 14

### Functional Disability 5 Years after Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Catherine M. Tansey, M.Sc., Andrea Matté, B.Sc., George Tomlinson, Ph.D.,  
Natalia Diaz-Granados, M.Sc., Andrew Cooper, M.D., Cameron B. Guest, M.D., C. David Mazer, M.D.,  
Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Paul Kudlow, B.Sc., Deborah Cook, M.D.,  
Arthur S. Slutsky, M.D., and Angela M. Cheung, M.D., Ph.D.,  
for the Canadian Critical Care Trials Group

- Toronto Study
- 4 ΜΕΘ
- 109 ασθενείς με ARDS που επεβίωσαν
- Εκτιμήθηκαν 3, 6, 12 μήνες, 2,3,4,5 έτη
- Φυσική κατάσταση: 6MWD
- Πνευματική κατάσταση
- Ποιότητα ζωής: SF-36



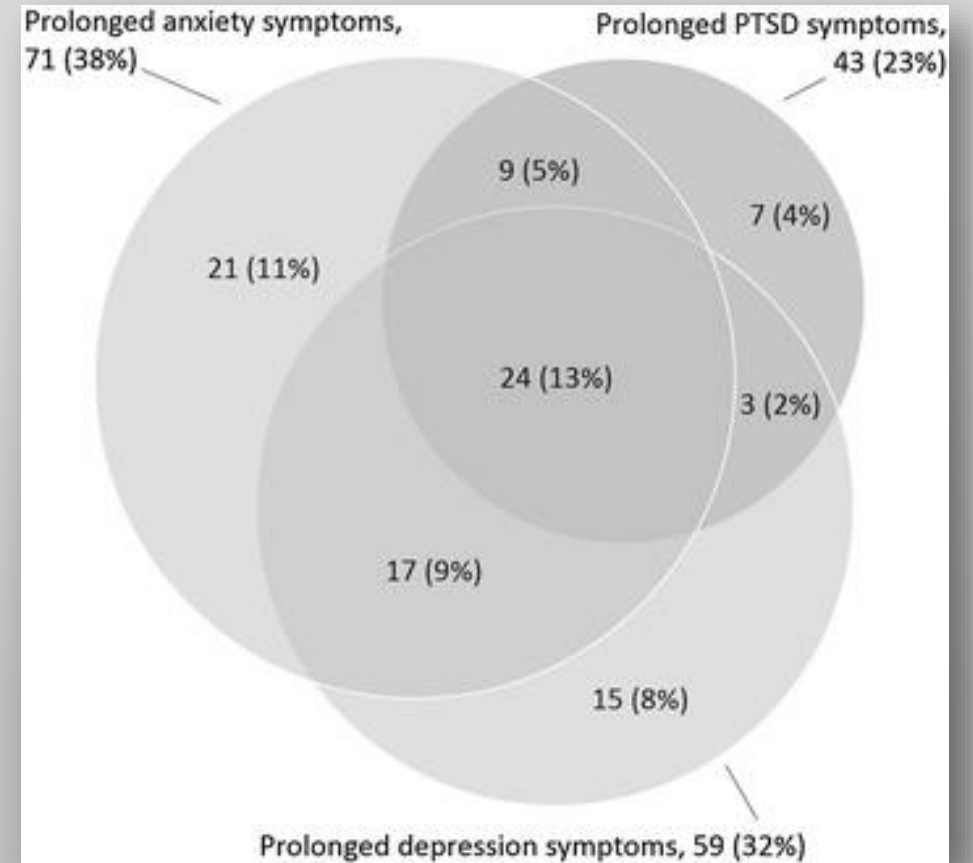
No. at Risk	109	92	86	79	77	74	69	64
No. for 6-Min Walk	80	78	81	60	64	64	57	54
No. for SF-36	67	74	74	56	57	57	49	50

# Έκβαση



*Bienvenu ICM 2018*

- 186 pts
- 13 medical and surgical intensive care units in four hospitals,
- follow-up at 3, 6, 12, 24, 36, 48, and 60 months post-ARDS
- Anxiety
- depression,
- posttraumatic stress disorder (PTSD)





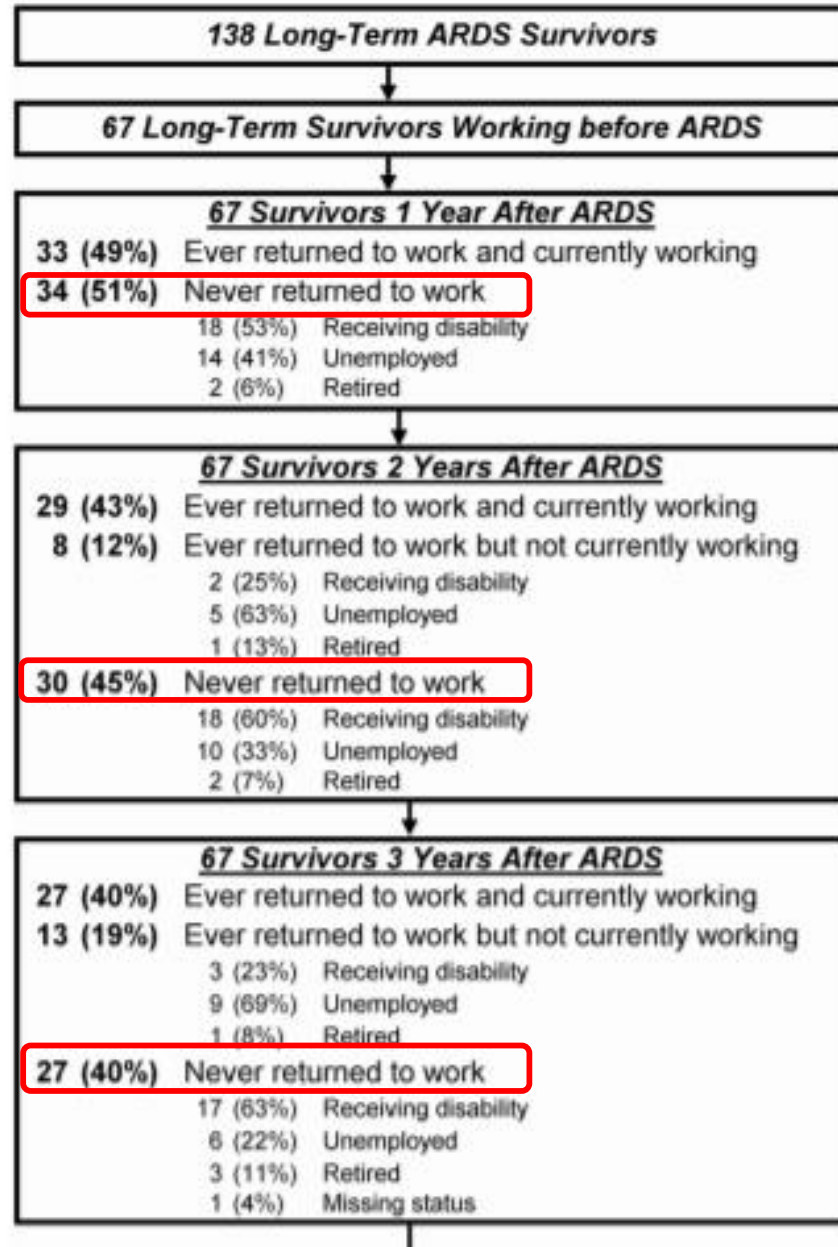
Published in final edited form as:

Thorax. 2018 February ; 73(2): 125–133. doi:10.1136/thoraxjnl-2017-210217.

## Return to work and lost earnings after acute respiratory distress syndrome: a 5-year prospective, longitudinal study of long-term survivors

### Multivariable predictors of returning to work within 5 years of ARDS\*

Characteristic	HR (95% CI)	p Value
<b>Model 1: baseline variables</b>		
Age at ARDS diagnosis, per year ≤40 years	0.99 (0.95 to 1.04)	0.79
Age at ARDS diagnosis, per year >40 years	0.97 (0.93 to 1.02)	0.28
Charlson Comorbidity Index, per point	0.75 (0.56 to 0.99)	0.05
Functional Comorbidity Index, per point	0.93 (0.72 to 1.20)	0.55
<b>Model 2: ICU and discharge variables</b>		
Mechanical ventilation, per day ≤5 days	0.66 (0.54 to 0.81)	<0.001
Mechanical ventilation, per day >5 days	1.02 (0.99 to 1.05)	0.22
Discharge to rehabilitation or other healthcare facility	0.41 (0.21 to 0.78)	0.01
<b>Model 3: final multivariable model</b>		
Charlson Comorbidity Index, per point	0.77 (0.59 to 0.99)	0.04
Mechanical ventilation, per day ≤5 days	0.67 (0.55 to 0.82)	<0.001
Mechanical ventilation, per day >5 days	1.02 (0.99 to 1.05)	0.20
Discharge to rehabilitation or other healthcare facility	0.49 (0.26 to 0.93)	0.03



EDITORIAL

## What's new in ARDS: can we prevent it?



Roy G. Brower<sup>1</sup> and Massimo Antonelli<sup>2\*</sup> 



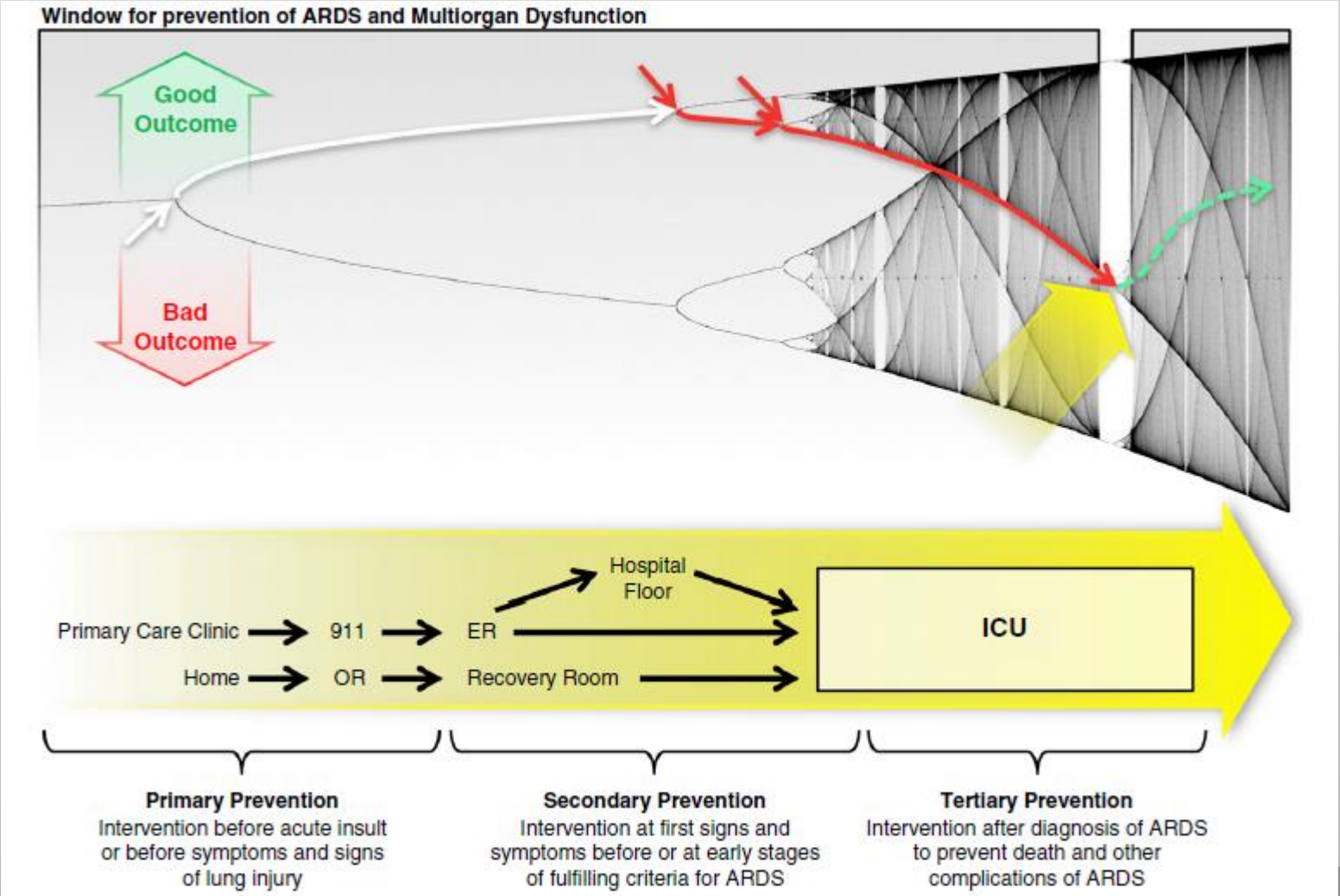
*“an ounce of prevention is  
worth a pound of cure,”*

# Πρόληψη ανάπτυξης η εξέλιξης ARDS

Η διαταραχή που προκαλεί η βαριά νόσος στη φυσιολογική ομοιόσταση έχει κοινά χαρακτηριστικά με τα πολύπλοκα φυσικά συστήματα όπως η ατμόσφαιρα, τα οικονομικά συστήματα, τα κοινωνικά κινήματα.....

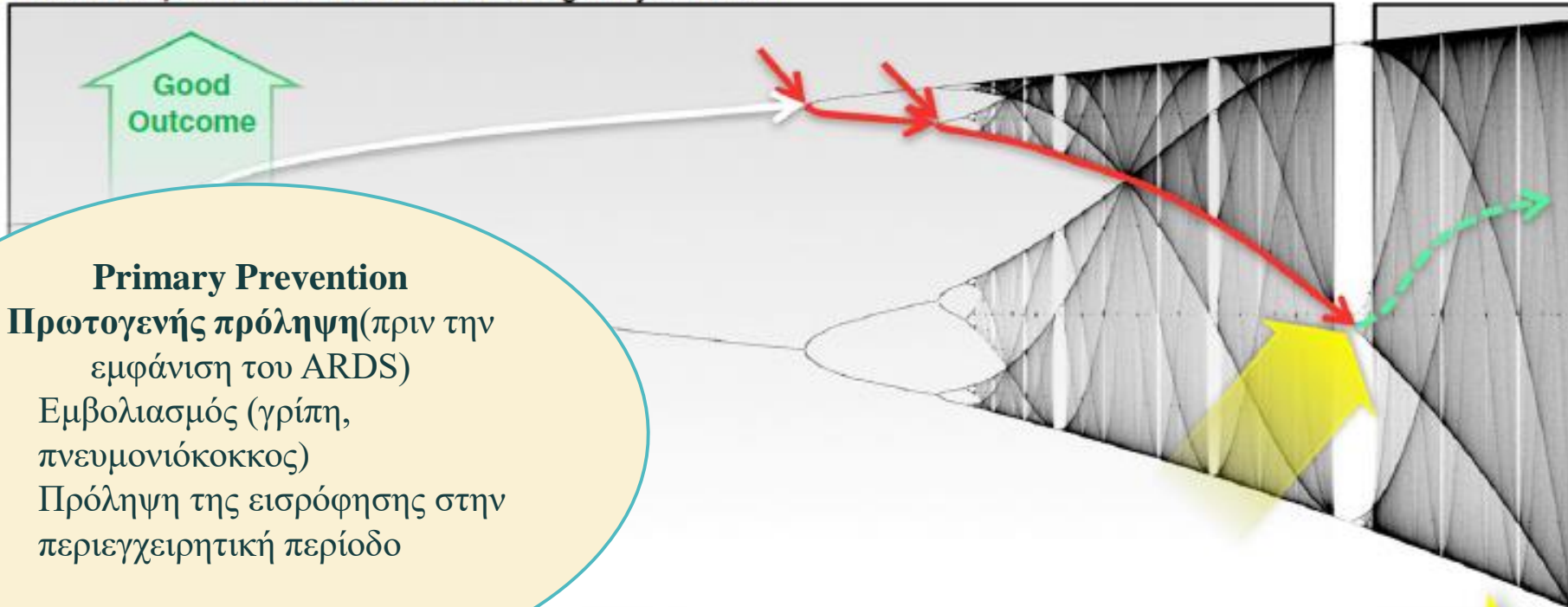


**Η θεωρία του χάους**  
Τα μη γραμμικά δυναμικά συστήματα είναι εξαιρετικά ευαίσθητα στις αρχικές μεταβολές! Μικρές διαφορές στις αρχικές συνθήκες θα αποδώσουν πολύ διαφορετικά αποτελέσματα μακροπρόθεσμα



# Πρόληψη ανάπτυξης η εξέλιξης ARDS

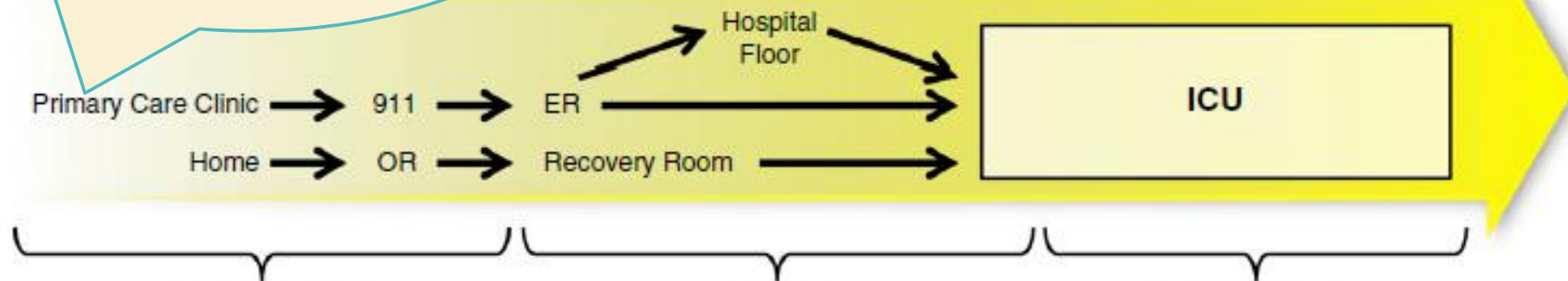
Window for prevention of ARDS and Multiorgan Dysfunction



## Primary Prevention

Πρωτογενής πρόληψη (πριν την εμφάνιση του ARDS)

- Εμβολιασμός (γρίπη, πνευμονιόκοκκος)
- Πρόληψη της εισρόφησης στην περιεγχειρητική περίοδο



## Primary Prevention

Intervention before acute insult or before symptoms and signs of lung injury

## Secondary Prevention

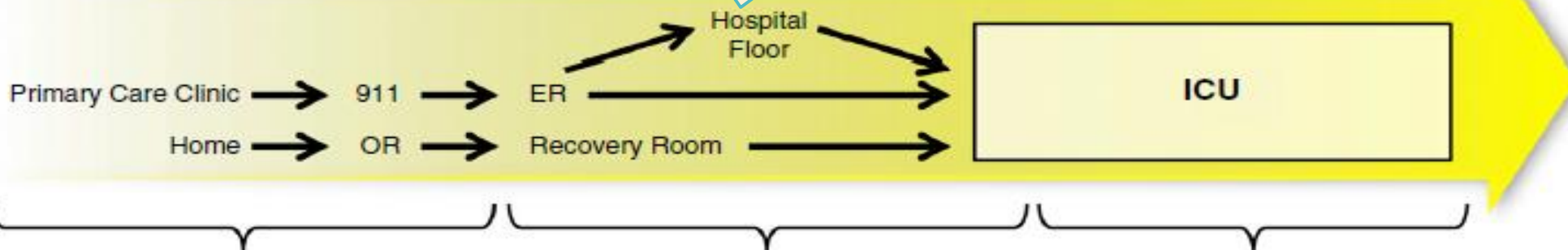
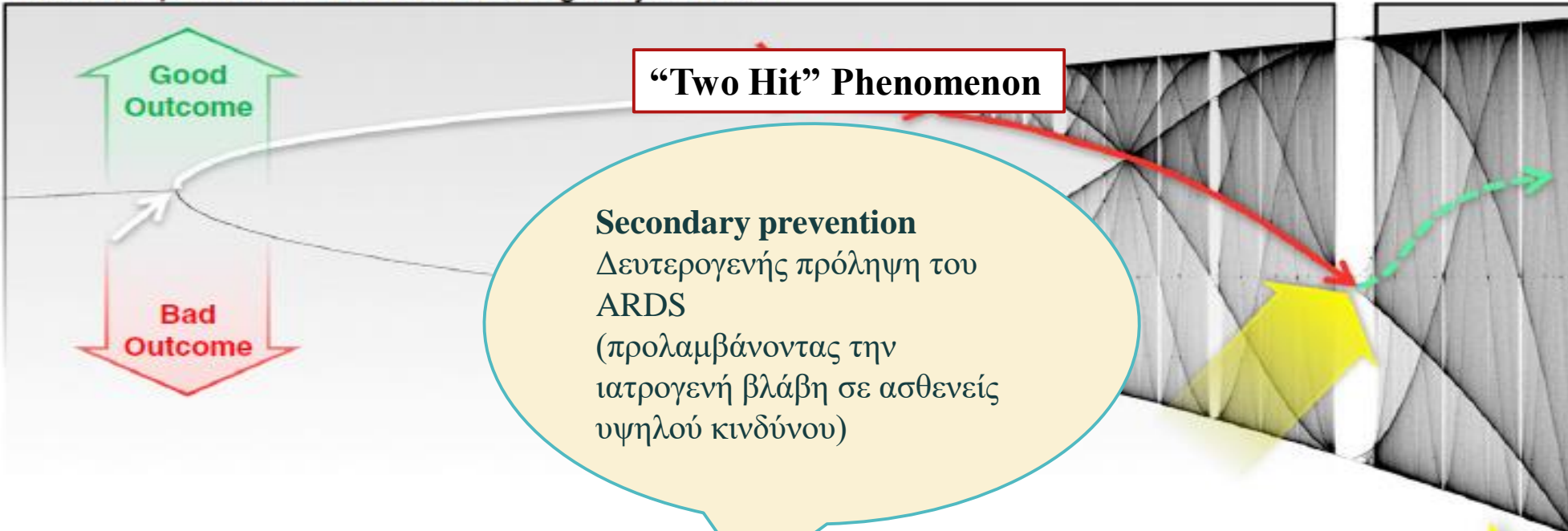
Intervention at first signs and symptoms before or at early stages of fulfilling criteria for ARDS

## Tertiary Prevention

Intervention after diagnosis of ARDS to prevent death and other complications of ARDS

# Πρόληψη ανάπτυξης η εξέλιξης ARDS

Window for prevention of ARDS and Multiorgan Dysfunction



**Primary Prevention**  
Intervention before acute insult or before symptoms and signs of lung injury

**Secondary Prevention**  
Intervention at first signs and symptoms before or at early stages of fulfilling criteria for ARDS

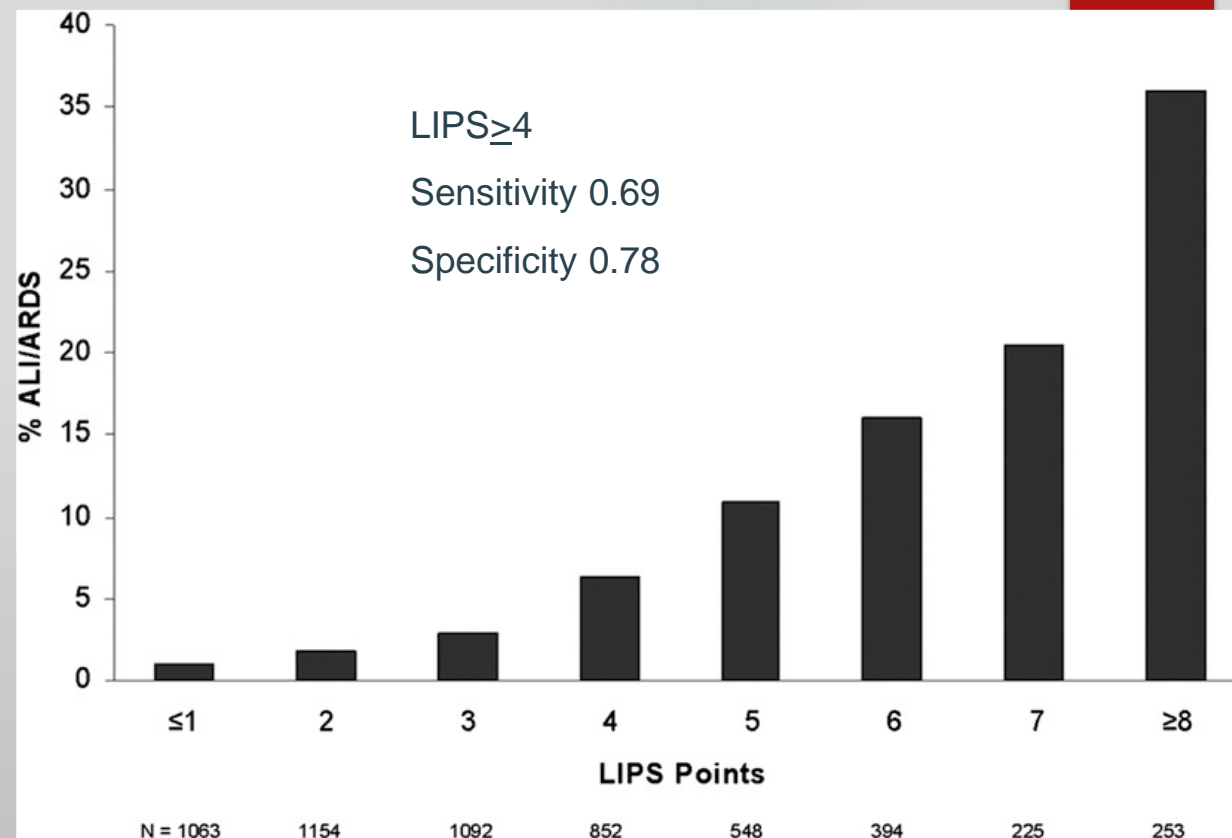
**Tertiary Prevention**  
Intervention after diagnosis of ARDS to prevent death and other complications of ARDS



# Πρόληψη-Ασθενείς υψηλού Κινδύνου

TABLE 2 ] Calculation of the Lung Injury Prediction Score (LIPS)

Characteristic	Points Awarded
<b>Predisposing conditions</b>	
Shock	2
Aspiration	2
Sepsis	1
Pneumonia	1.5
High-risk surgery <sup>a</sup>	
Orthopedic spine	1
Acute abdomen	2
Cardiac	2.5
Aortic vascular	3.5
<b>High-risk trauma</b>	
Traumatic brain injury	2
Smoke inhalation	2
Near drowning	2
Lung contusion	1.5
Multiple fractures	1.5
<b>Risk modifiers</b>	
Alcohol abuse	1
Obesity (BMI > 30 kg/m <sup>2</sup> )	1
Hypoalbuminemia (albumin < 3.5 g/dL)	1
Chemotherapy	1
Fi <sub>o2</sub> > 0.35 (> 4 L/min)	2
Tachypnea (respirations > 30/min)	1.5
Sp <sub>o2</sub> < 95%	1
Acidosis (pH < 7.35)	1.5
Diabetes mellitus with sepsis	-1



Gajic Am J Respir Crit Care Med, 2011

Adapted with permission from Gajic et al.<sup>12</sup> Sp<sub>o2</sub> = oxygen saturation as measured by pulse oximetry.

<sup>a</sup>Add 1.5 points if emergency surgery.

# Πρόληψη-Πρώιμη αναγνώριση

## Genetic predisposition

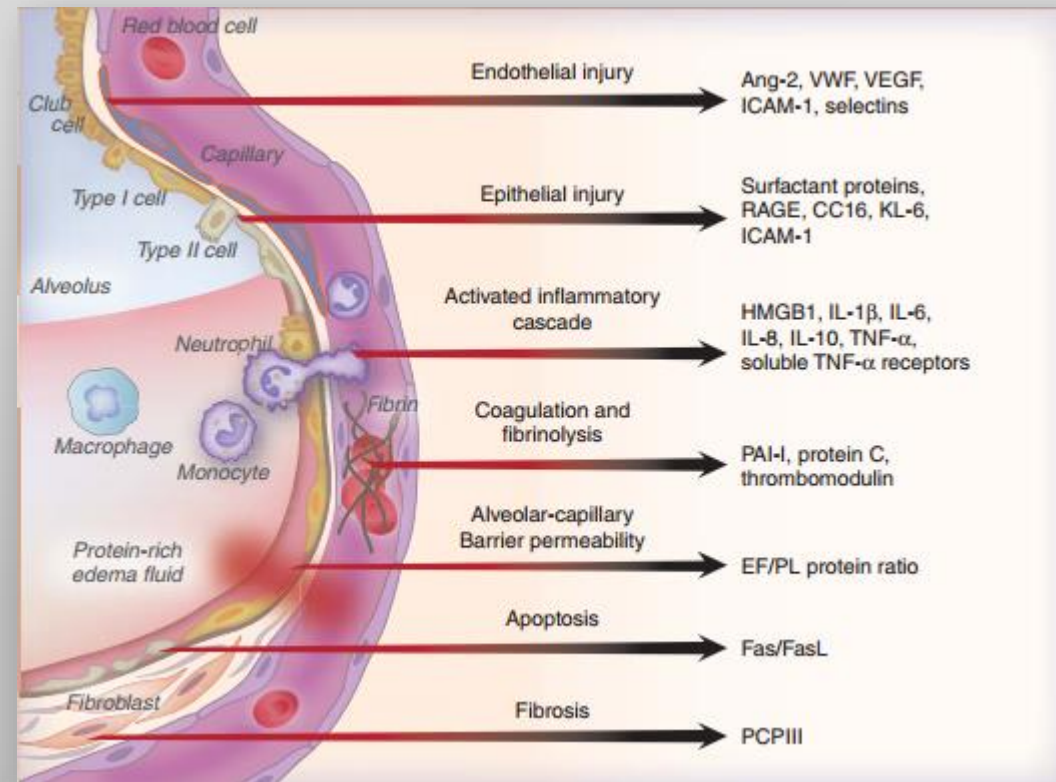
- Γενετική προδιάθεση
- Συγκεκριμένα γονίδια

## Biomarkers

- 20 βιοδείκτες διάγνωσης
- 19 βιοδείκτες πρόγνωσης

Table 1 Specific markers with a predictive value for development and/or outcome of ARDS

Biological compartment and markers	Cell injury/inflammation
Plasma	
RAGE	Epithelium
Ang-2	Endothelium
SP-D	Epithelium
IL-8	Acute inflammation
BALF	
Fas, Fas ligand	Epithelium
PCP I	Fibroproliferation
PCP III	Fibroproliferation
Exhaled air	
Octane	Lipid peroxidation
Acetaldehyde	Bacterial metabolism, inflammation
3-methylheptane	Lipid peroxidation



Walter, Expert Rev Respir Med 2014

Terpstra, Crit Care Med 2014

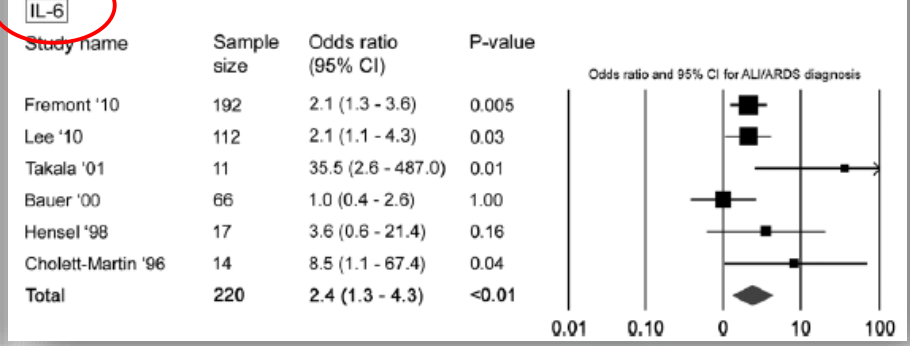
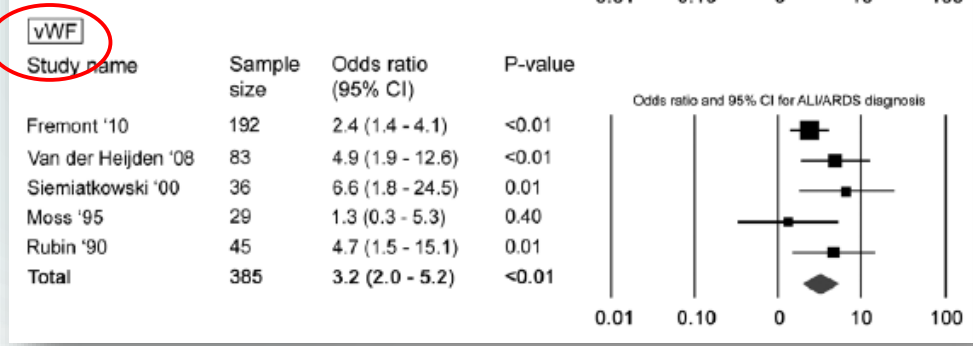
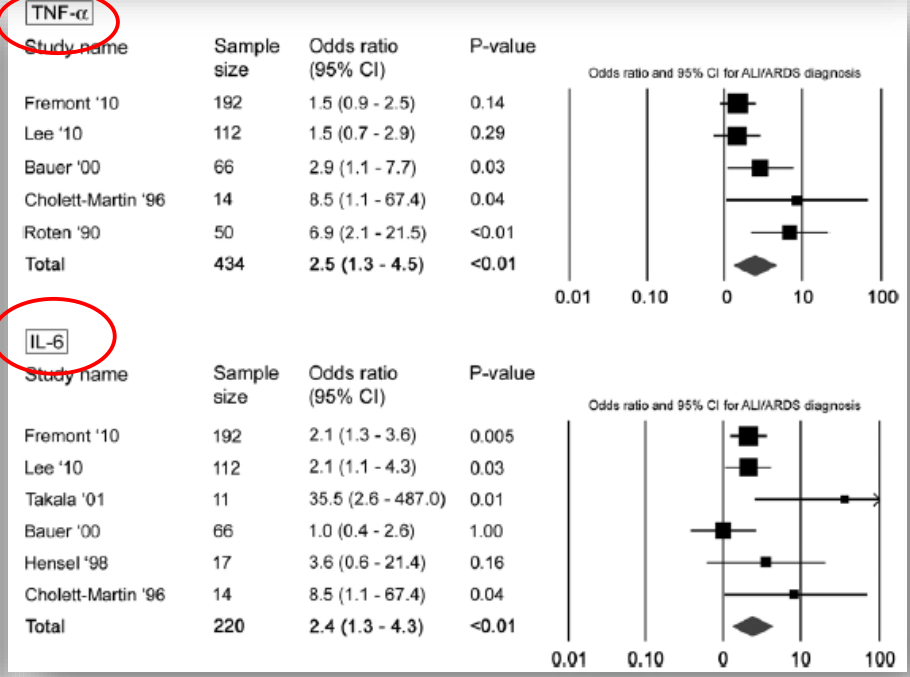
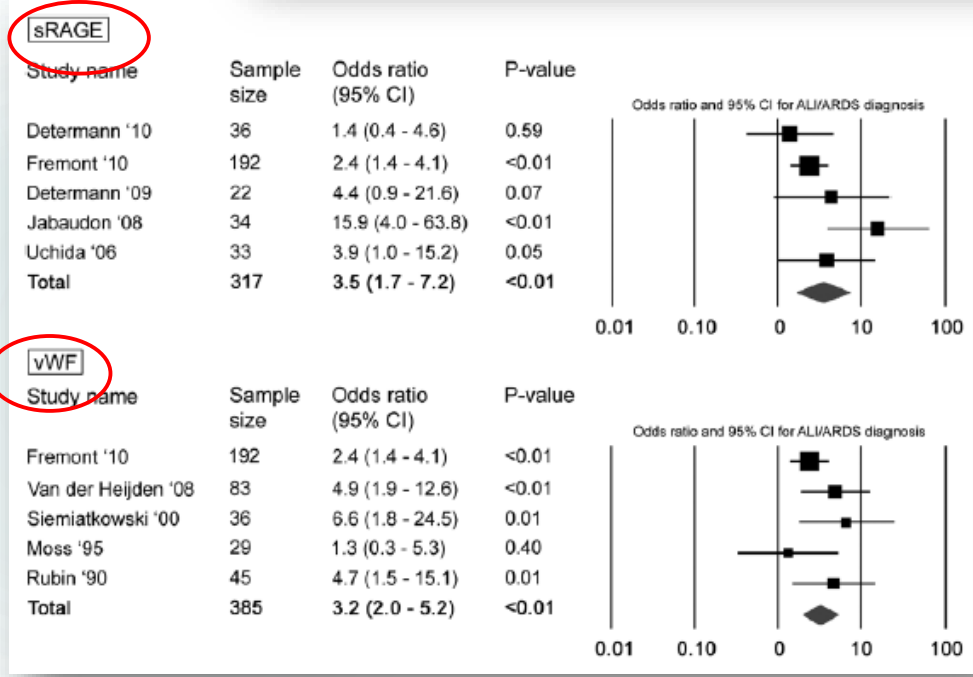
# Πρόληψη-Πρώιμη αναγνώριση Biomarkers

## Review Articles

Crit Care Med 2014

### Plasma Biomarkers for Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis\*

Matty L. Terpstra, BSc<sup>1</sup>; Jurjan Aman, MD<sup>1</sup>; Geerten P. van Nieuw Amerongen, PhD<sup>1</sup>;



# Πρόληψη – Πρώιμη θεραπεία

## “Two Hit” Phenomenon

### Patient at Risk (1<sup>st</sup> hit)

- Pneumonia
- Toxic inhalation
- Pancreatitis
- Aspiration
- Trauma
- Sepsis
- Shock
- Alcohol
- Tobacco
- High risk surgery
- Preexisting lung disease
- Radiation
- Chemotherapy

### Patients at Risk

Early recognition

~~Biomarkers~~

~~Genetic  
predisposition~~

### Preventive Measures

Low tidal volume

Restrictive  
transfusion

Sepsis  
management

Conservative fluid  
management

ARDS

EDITORIAL

# What's new in ARDS: can we prevent it?



Roy G. Brower<sup>1</sup> and Massimo Antonelli<sup>2\*</sup>

## Preventive Measures

Low tidal volume

Restrictive transfusion

Sepsis management

Conservative fluid management

## The Role of Potentially Preventable Hospital Exposures in the Development of Acute Respiratory Distress Syndrome: A Population-Based Study

Adil H. Ahmed, MBBS, John M. Litell, DO, Michael Malinchoc, MS, Rahul Kashyap, MBBS, Henry J. Schiller, MD, Sonal R Pannu, MBBS, Balwinder Singh, MBBS, Guangxi Li, MD, and Ognjen Gajic, MD, MSc

414 ασθενείς στη διάρκεια 10 ετών

Selected Exposures in ARDS Cases and Controls <sup>a</sup>

Exposures	Cases and controls after removing 2001 -2002 (N=308 pair)	Cases and controls after adjusting for baseline characteristics
	OR (95% CI) P value <sup>b</sup>	OR (95% CI) P value <sup>b</sup>
Any adverse events	4.7 (3.0-7.6) P<0.001	6.5 ( 4.1-10.4) P<0.001
Inadequate <u>empiric</u> antimicrobial	2.5 (1.3-4.7) P = 0.006	3.6 (2.0-6.7) P<0.001
Aspiration	34.0 (4.7-248.4) P <0.001	52.0 (7.1-383.2) P<0.001
Red blood cells <sup>c</sup>	1.4 (1.2-1.6) P <0.001	1.4 (1.2-1.5) P<0.001
Fresh frozen plasma <sup>c</sup>	1.4 (1.2-1.6) P <0.001	1.4 (1.2-1.6) P<0.001
TV -PBW <sup>d</sup>	1.3 (0.82-2.2) P 0.25	2.1 (1.1-4.1) P = 0.025

Abbreviations: ARDS, acute respiratory distress syndrome; OR, odds ratio; PBW, predicted body weight; TV, tidal volume

# Περιορισμός των μεταγγίσεων TRALI

Preventive Measures

Low tidal volume

**Restrictive transfusion**

Sepsis management

Conservative fluid management

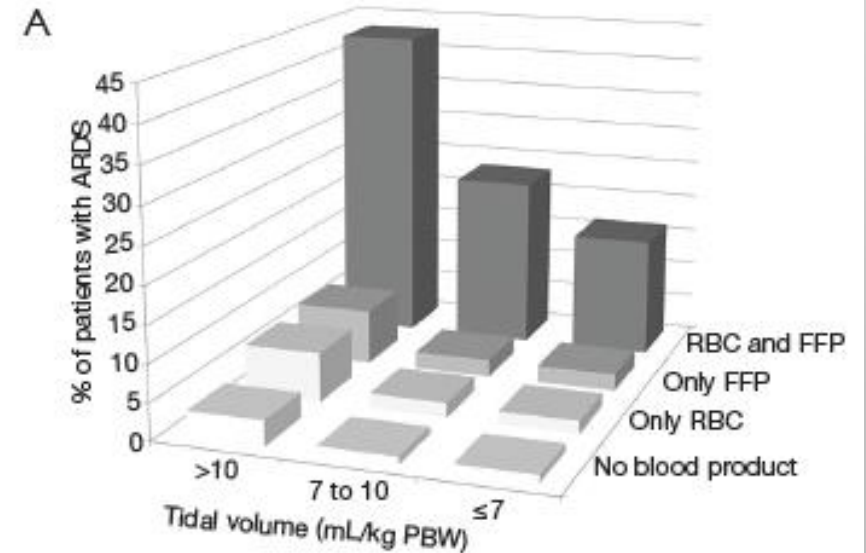


Gajic AJRCCM 2007

17 μελέτες, 3659 ασθενείς στην περιεγχειρητική περίοδο  
**ARDS: 7,2%** σε ασθενείς που έλαβαν εσω και μια μετάγγιση  
**ARDS: 2,5%** χωρίς μετάγγιση

TABLE 3. TRANSFUSION-RELATED RISK FACTORS FOR ACUTE LUNG INJURY

Variable	Unadjusted*		Adjusted <sup>†</sup>	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Any high plasma volume components (FFP or platelets)	2.55 (1.27–5.11)	0.009	2.78 (1.21–6.38)	0.016
Number of units	1.09 (0.99–1.20)	0.081	1.11 (0.99–1.25)	0.086
Number of units from female donors	1.30 (1.03–1.66)	0.029	1.51 (1.08–2.12)	0.016
Amount of plasma from male donors, L	1.55 (0.79–3.06)	0.202	1.60 (0.76–3.37)	0.215
Amount of plasma from female donors, L	3.23 (1.17–8.91)	0.024	5.09 (1.37–18.85)	0.015
Amount of plasma from female donors with at least one pregnancy, L	4.41 (1.00–19.55)	0.050	9.48 (1.38–65.35)	0.022
Number of pregnancies among donors	1.11 (1.00–1.22)	0.047	1.19 (1.05–1.34)	0.007
Number of HLA class I <sup>+</sup> units	1.81 (0.97–3.38)	0.061	1.70 (0.94–3.09)	0.098
Number of HLA class II <sup>-</sup> units	1.93 (0.88–4.28)	0.103	3.08 (1.15–8.25)	0.025
Number of GIF <sup>+</sup> units	4.19 (1.22–14.32)	0.023	4.85 (1.32–17.86)	0.018
Mean LysoPC 16:0** (per 10-mol/L increase)	1.16 (1.04–1.30)	0.011	1.16 (1.02–1.32)	0.022
Mean LysoPC 18:0** (per 10-mol/L increase)	1.58 (1.10–2.26)	0.013	1.61 (1.08–2.38)	0.018



Serpa Neto An Transl Med 2018

# Πρόληψη – Πρώιμη θεραπεία

# Έγκαιρη αντιμετώπιση της σήψης

Προοπτική μελέτη

160 ασθενείς με σηπτικό shock, χωρίς πνευμονική βλάβη

71 (44%) ανέπτυξαν ALI, 5h μετά την έναρξη του shock

## Preventive Measures

Low tidal volume

Restrictive transfusion

**Sepsis  
management**

Conservative fluid  
management

Table 2. Risk factors for development of ALI in patients with septic shock: multiple logistic regression analysis

Πρώιμη θεραπεία	Odds Ratio	95% CI	p Value
Delayed goal-directed resuscitation	3.55	1.52–8.63	.004
Delayed antibiotics	2.39	1.06–5.59	.039
Respiratory rate (per SD)	2.03	1.38–3.08	<.001
Chemotherapy	6.47	1.99–24.9	.003
Chronic alcohol use	2.09	.88–5.10	.098
Transfusion	2.75	1.22–6.37	.016
Aspiration	3.48	1.22–10.78	.024
Diabetes mellitus	.44	.17–1.07	.076

# Συντηρητική χορήγηση υγρών

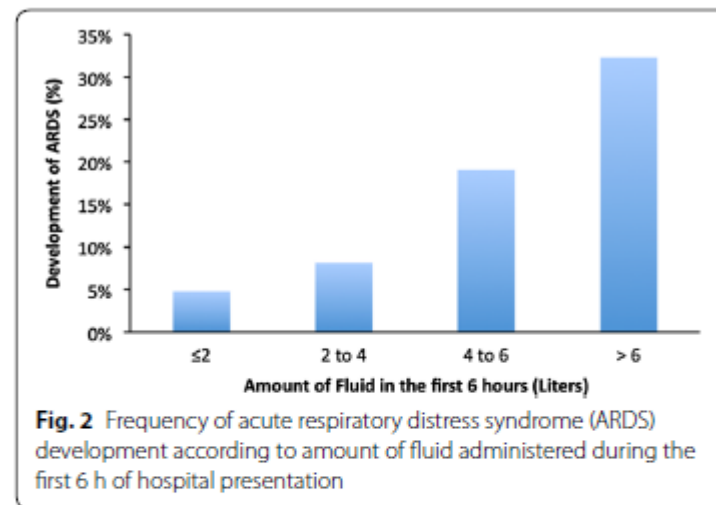
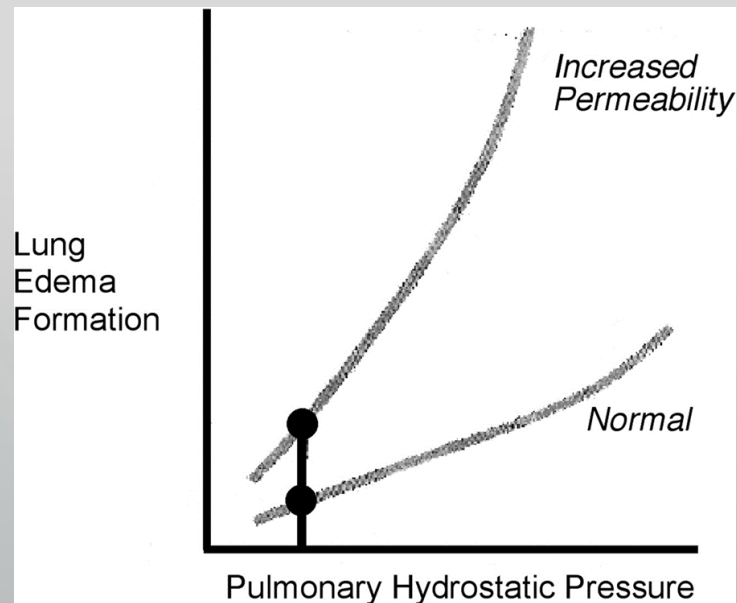
## Preventive Measures

Low tidal volume

Restrictive transfusion

Sepsis management

**Conservative fluid management**



**Table 4 Shock subgroup analysis: multivariable analysis of total volume in first 6 h and the development of ARDS**

	Odds ratio (95% CI)	p value
Shock	1.05 (0.87–1.28)	0.60
No shock	1.21 (1.05–1.38)	0.01

The odds ratio indicates the increased odds of ARDS for a 1-l increase in volume of fluids administered

*Seethala R, An Intens Care 2017*



# Πρόληψη-Φάρμακα

## Aspirin

Published in final edited form as:

*JAMA*. 2016 June 14; 315(22): 2406–2414. doi:10.1001/jama.2016.6330.

### Effect of Aspirin on Development of ARDS in At-Risk Patients Presenting to the Emergency Department:

The LIPS-A Randomized Clinical Trial

**CONCLUSIONS AND RELEVANCE** Among at-risk patients presenting to the ED, the use of aspirin compared with placebo did not reduce the risk of ARDS at 7 days. The findings of this phase 2b trial do not support continuation to a larger phase 3 trial.

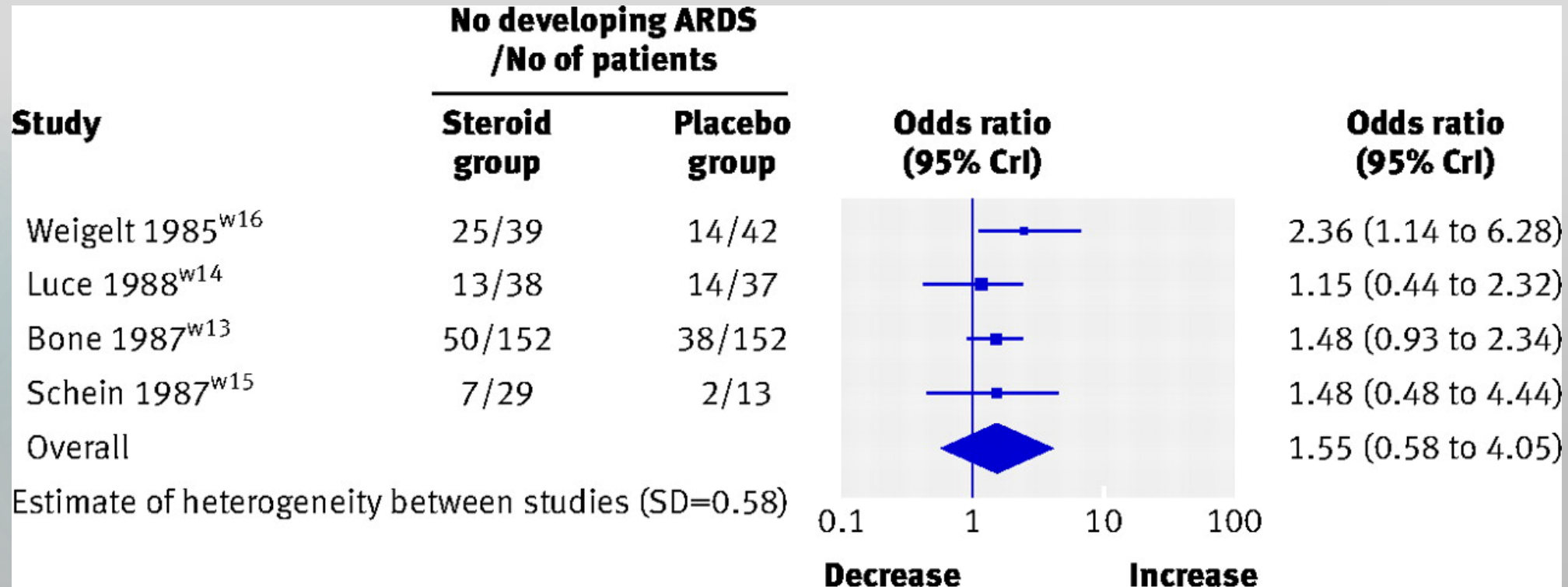
16 ΤΕΠ  
400 ασθενείς LIPS>4  
325 mg loading dose, 81 mg/d or placebo

	Aspirin (n = 195)	Placebo (n = 195)	Mean Difference (90% CI)	P Value
<b>Primary outcome</b>				
ARDS within 7 d, No. (%)	20 (10.3)	17 (8.7)	1.5 (−3.8 to 6.8)	.53
<b>Secondary outcomes</b>				
Ventilator-free days to day 28, mean (SD)	24.9 (7.4)	25.2 (7.0)	−0.26 (−1.46 to 0.94)	.72
ICU length of stay, mean (SD), d	5.2 (7.0)	5.4 (7.0)	−0.16 (−1.75 to 1.43)	.87
Hospital length of stay, mean (SD), d	8.8 (10.3)	9.0 (9.9)	−0.27 (−1.96 to 1.42)	.79
28-Day survival, % (90% CI)	90 (86 to 93)	90 (86 to 93)	HR, 1.03 (90% CI, 0.60 to 1.79)	.92
1-Year estimated survival, % (90% CI)	73 (67 to 78)	75 (69 to 80)	HR, 1.06 (90% CI, 0.75 to 1.50)	.79
Bleeding-related adverse events, No. (%)	11 (5.6)	5 (2.6)	OR, 2.27 (90% CI, 0.92 to 5.61)	.13

# Πρόληψη-Φάρμακα

## Corticosteroids

Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis



# ARDS

- Το ARDS είναι ένα σύνδρομο, όχι μια νόσος
- Συνοδεύεται από μεγάλη θνητότητα και μακροχρόνιες επιπλοκές
- Δεν είναι όλοι οι ασθενείς με ARDS ίδιοι και άρα το ίδιο πιθανό να ευνοηθούν από μια συγκεκριμένη θεραπεία

## Πρόληψη- Θεραπεία Two Hit Phenomenon

- Αναγνωρίστε εγκαίρως τους ασθενείς υψηλού κινδύνου
- Αντιμετωπίστε άμεσα και σωστά τη σήψη
- Αποφύγετε την μη απαραίτητη χορήγηση αίματος
- Στους διασωληνωμένους ασθενείς αποφύγετε τους μεγάλους αναπνεόμενους όγκους
- Σωστή ώρα διασωλήνωσης??
- Μη- επεμβατικός μηχανικός αερισμός??