



Extracorporeal Therapies in Septic Acute Kidney Injury: Current Status in 2011

1.-Rationale :How & When ?

2.- Septic Shock Without AKI:A Coming Back ?

3.- High Adsorptive Membranes:What About Endotoxin ?

4.- High Cut-Off Membranes:New Avenues in Sepsis ?



5.-Combined ECMO & CRRT in Refractory ARDS &Fluid Overload

6.-Combined CO2 Elimination & CRRT:An Alternative ?

7.- Recently Completed Trials..

8. Perspectives-Conclusions

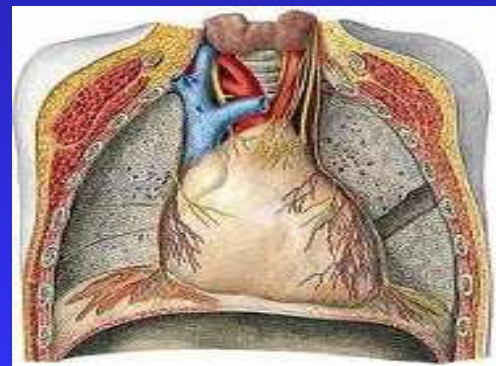
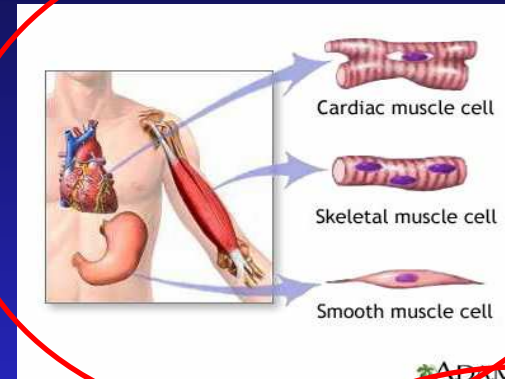
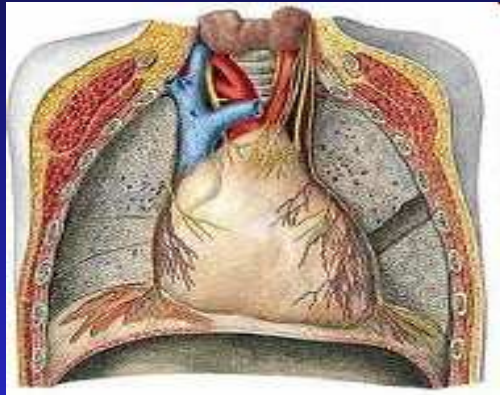
P.M. Honoré,Intensivist-Internist-Nephrologist
Head of Clinics ICU,UZ-VUB University,Bxl,Bel

University Hospital of Queen Elizabeth ,27 Oct 2011
Seminars in Hong-Kong, China, October 2011

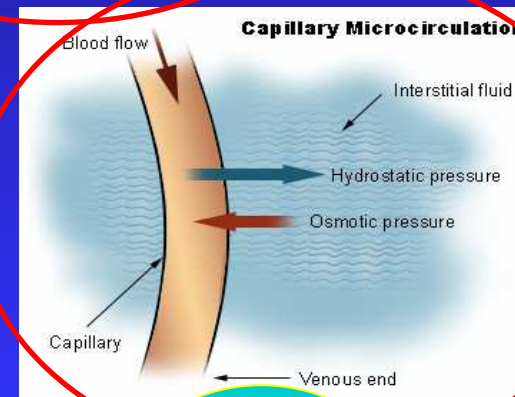


Rationale: Where to Remove ?

The « Multiple Compartments Hypothesis »



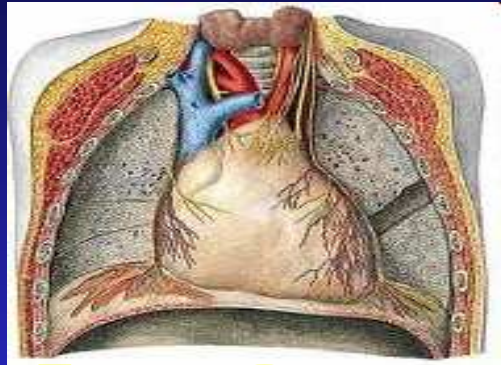
30 Sq
Meter



300 Sq
Meter

Rationale: How to Increase Removal ?

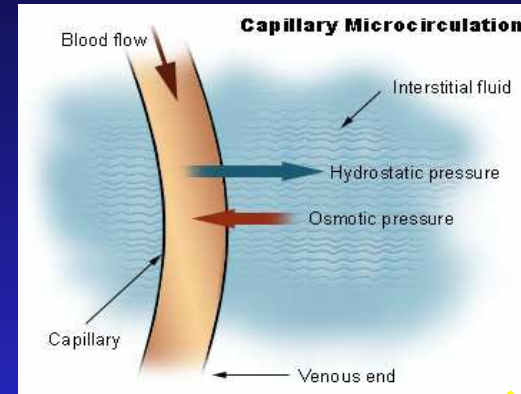
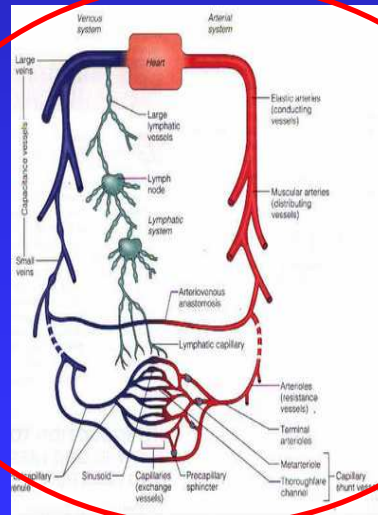
The «Active Transportation Hypothesis»



30 Sq
Meter

40 %

Exchange Volume
of 3-4 Liters/H



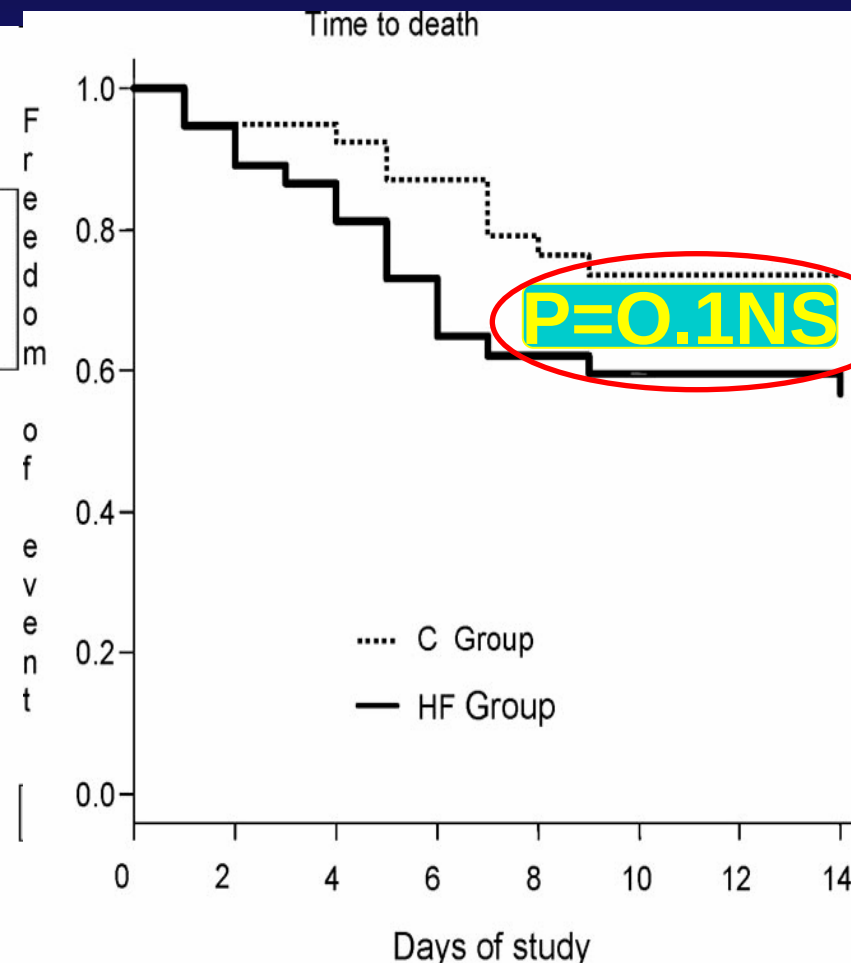
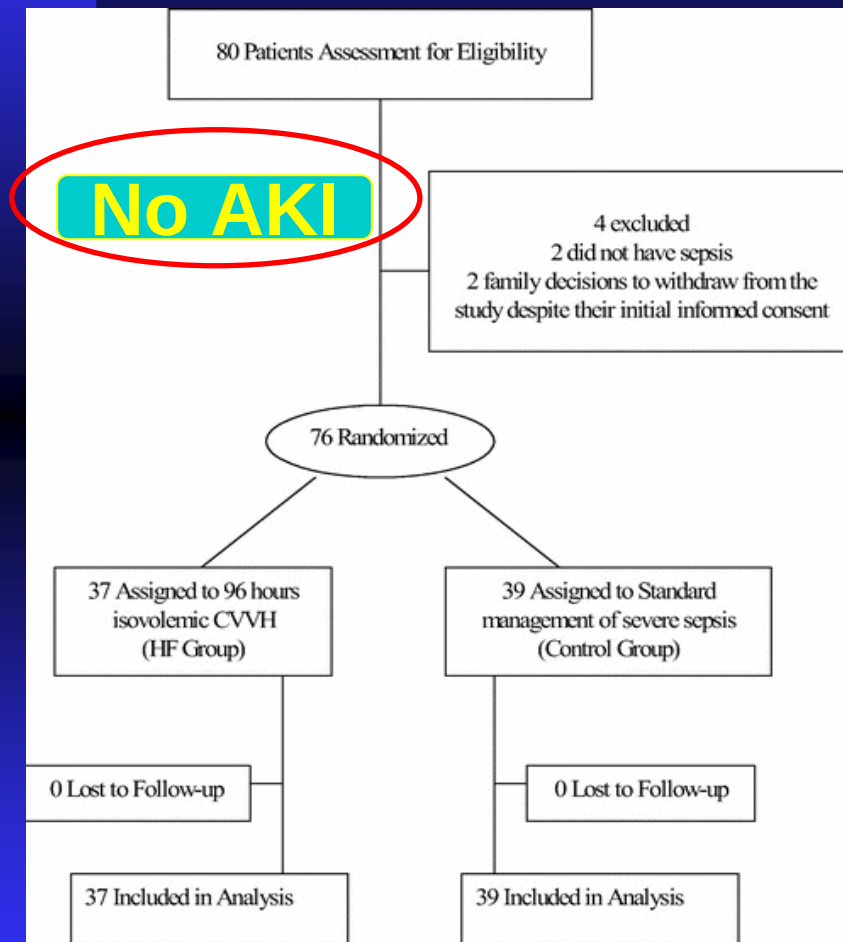
300 Sq
Meter

4 %

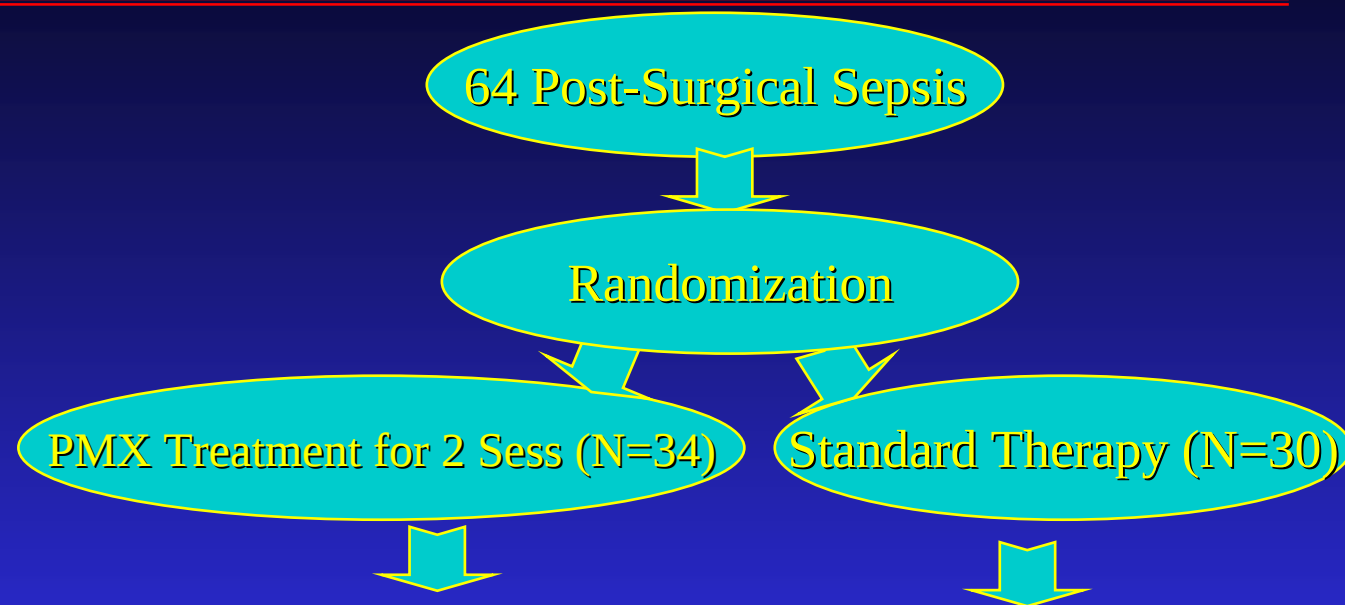
Active Transportation
80 Fold

Septic Shock Without AKI Should be the Target ?

Critical Care Medicine
OFFICIAL JOURNAL OF THE SOCIETY OF CRITICAL CARE MEDICINE



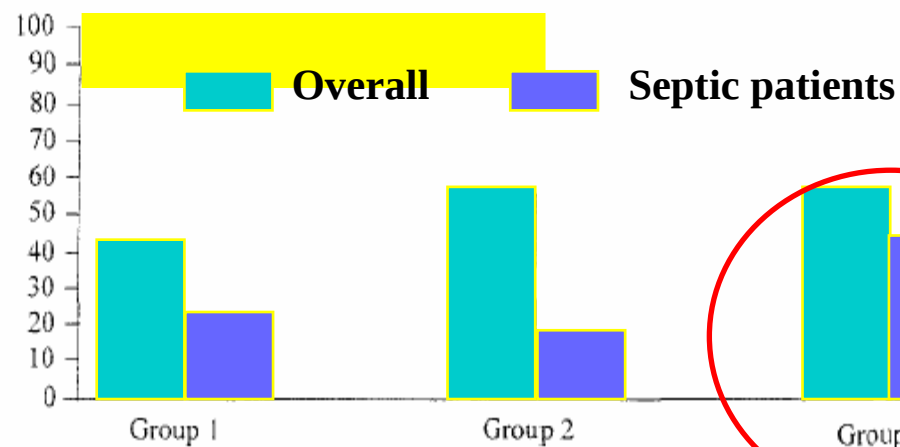
Septic Shock With AKI: A Comeback?



	34 PMX Treatment	30 Standard Therapy
SOFA Score	Improved	No Changes(P)
Hemodynamics(MAP)	Improved	No Improvement(P)
28 Days Mortality	32 %	55 % (P 0.43)
Vasopressors	Decreased	No Changes(T)

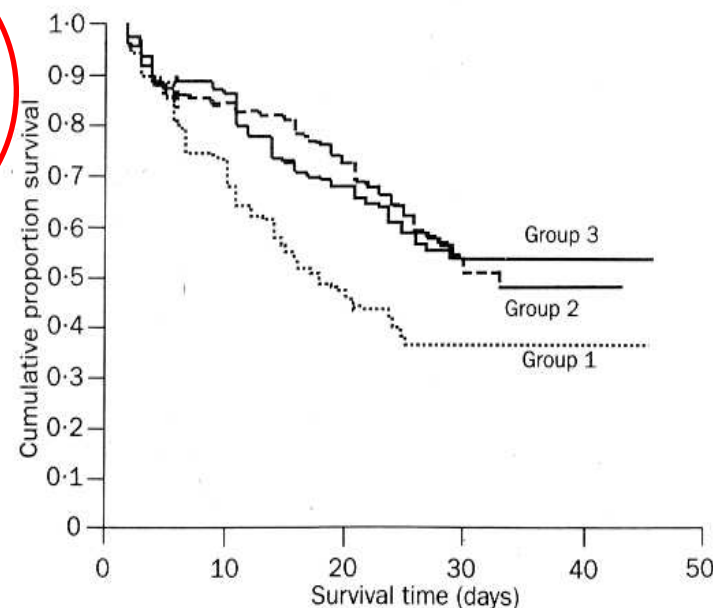
Cruz D et al JAMA 2009; 301:2445-2452

Positive Studies Regarding CRRT in ICU



The Vicenza Study

APACHE II = 23



Kaplan Meier estimation of survival rates in the three groups

Survival rates stratified by trial group and by presence of sepsis

Groups and Uf rates	No sepsis (%)	Sepsis (%)	p value
Group 1 (20 ml/h/kg)	55/126 (44%)	5/20 (25 %)	0.90
Group 2 (35 ml/h/kg)	76/122 (62 %)	3/17 (18 %)	0.001
Group 3 (45 ml/h/kg)	74/125 (59 %)	7/15 (47 %)	0.256

**Reiter et al ,
Nephron 2002 ; 92 : 251-258
Ronco et al, Lancet
2000;355:26-30**

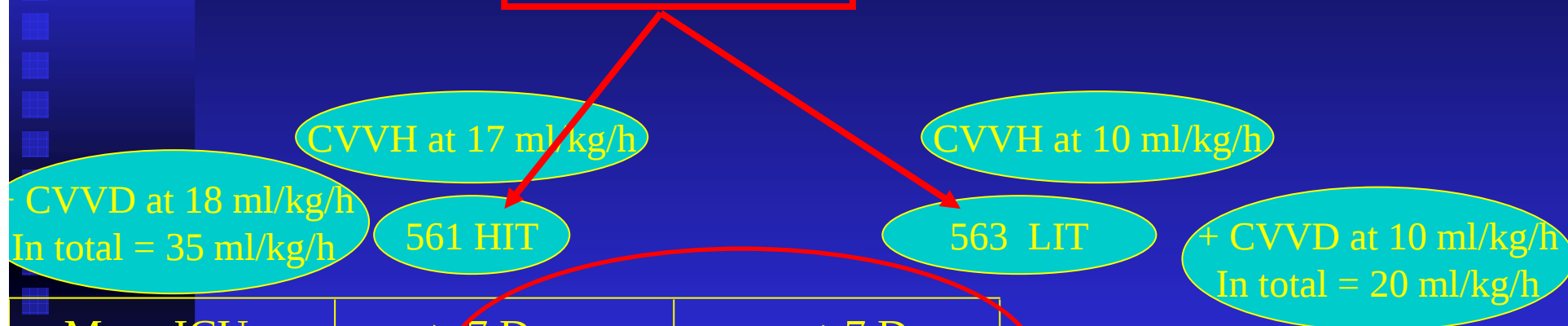
(Neg)Prospective Randomized Studies with Septic Subpopulations



The VA/NIH Study

1124 patients

Between 2003 et 2007



Mean ICU	>7 Days	>7 Days
Stay Before Randomisation		
Excluding 3216 patients		
Survival at day 60	46.4 %	48.5 %
Sepsis	43.0 %	47.4 %
Predilution	100 %	100 %

Palevsky P et al. NEJM
2008;359:7-20

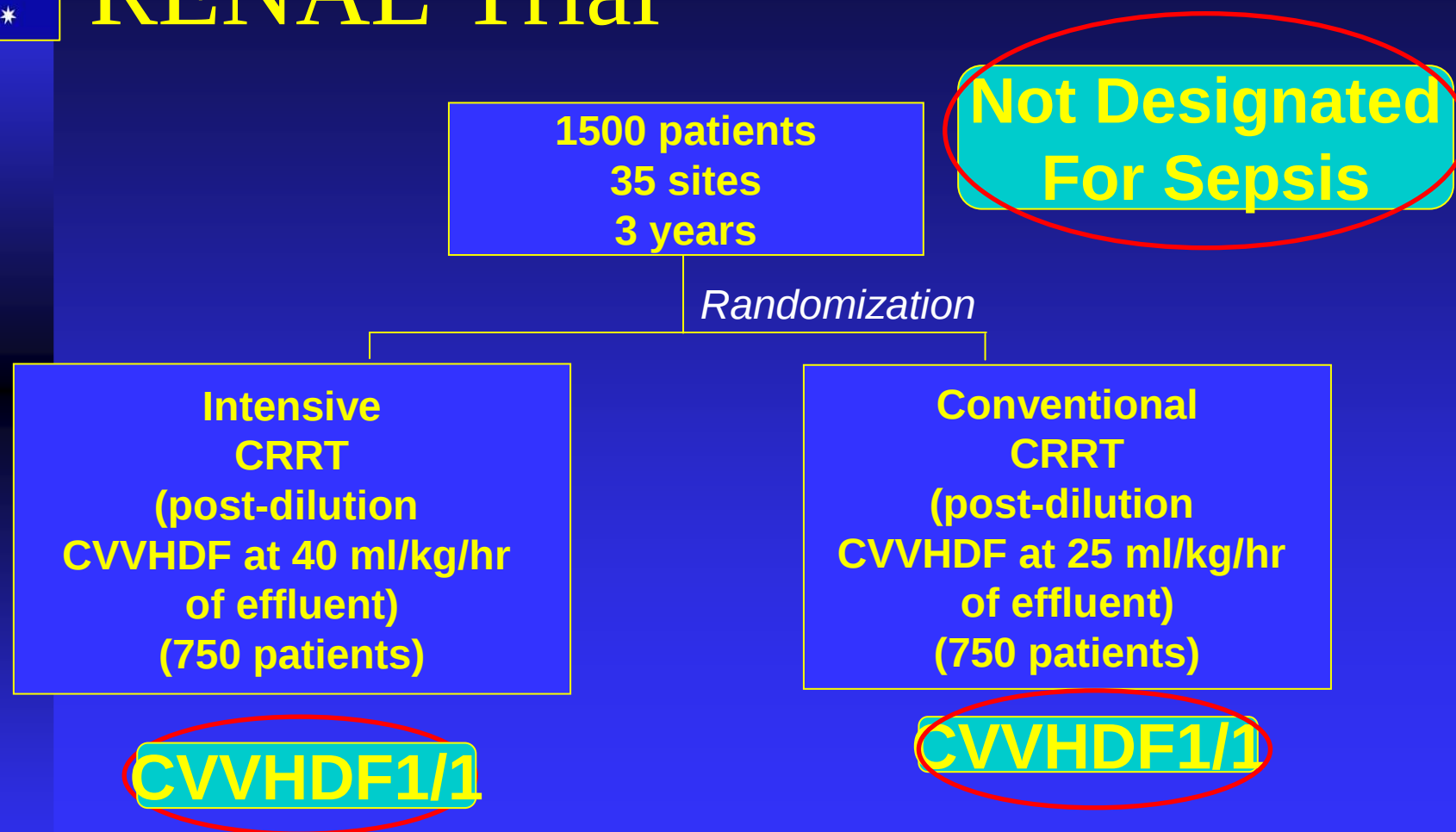
Ronco C, Honore PM.
Letter. NEJM 2008;359:1959
1962

Ronco C, Cruz D,
Oudemans HM, Honore PM
et al. Review. Crit Care
2008;308:EAP

(Neg) Prospective Randomized Studies with Septic Subpopulations

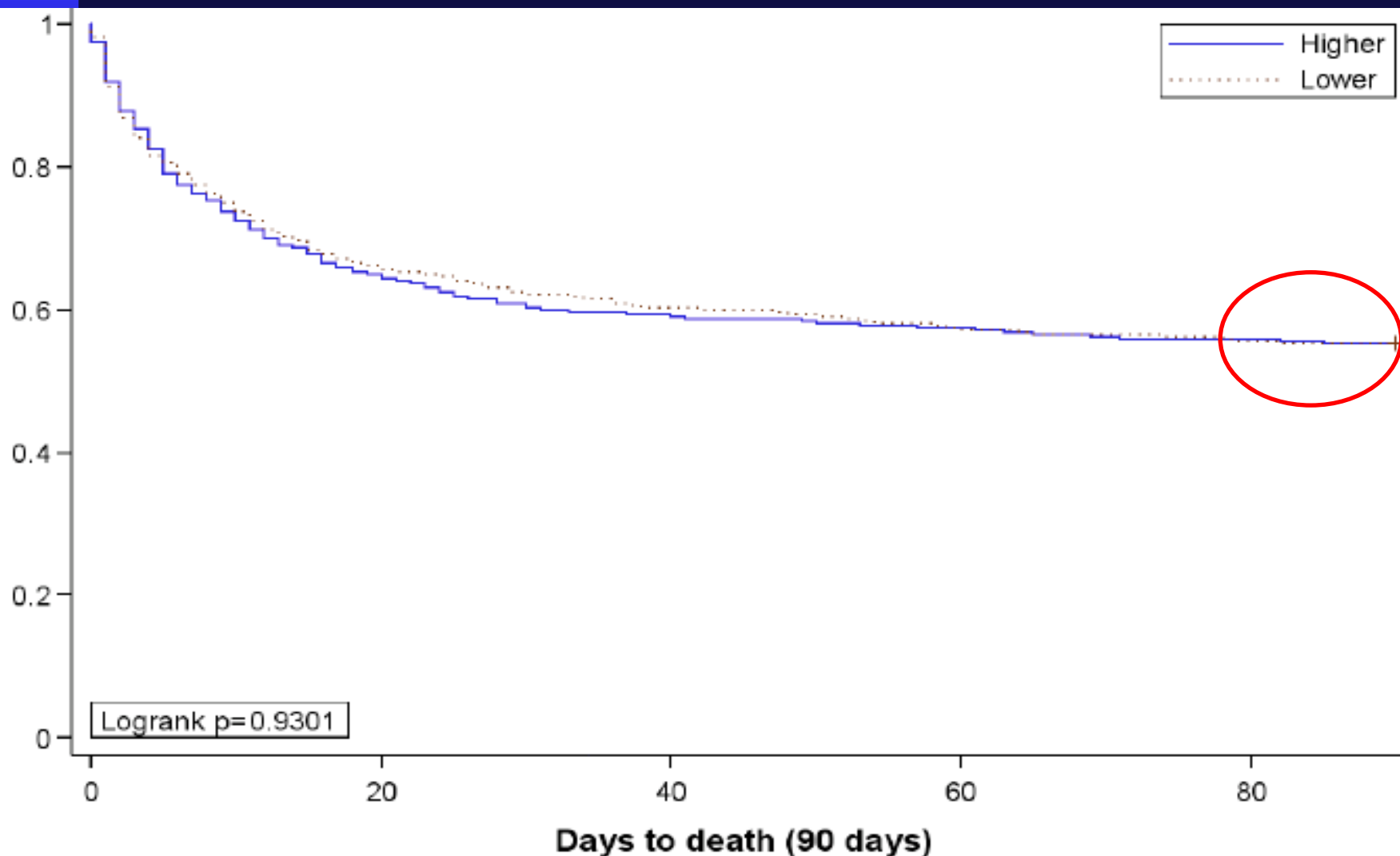


RENAL Trial



The RENAL Study

Kaplan Meier graph of survival time from randomisation to day 90



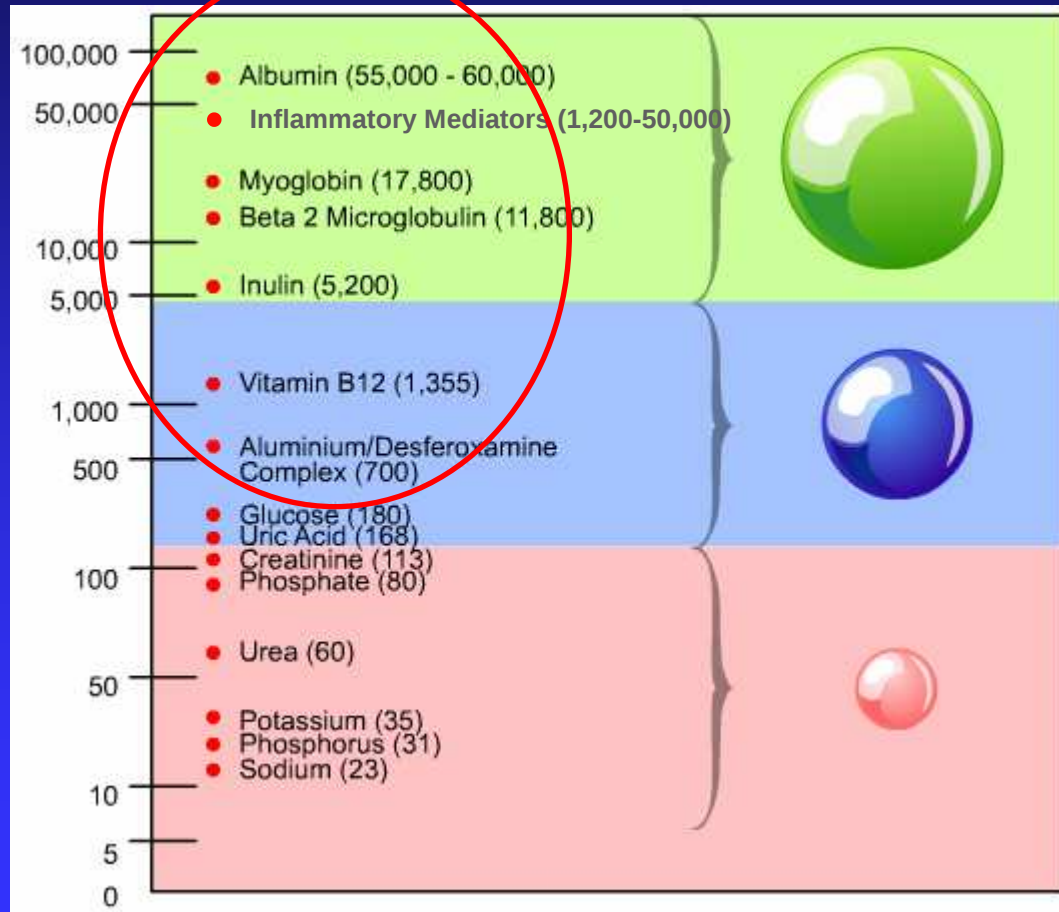
	No. of Subjects	Event	Censored	Median Survival (95% CL)
Higher	721	45% (322)	55% (399)	NA (NA NA)
Lower	743	45% (332)	55% (411)	NA (NA NA)

Agregation of RENAL & VA/NIH Databases

- CRRT is now widely accepted as the most appropriate therapy for vasopressor-dependent patients who require renal replacement therapy for AKI in the ICU

Newly Adsorptive Membranes: All in One ?

Daltons



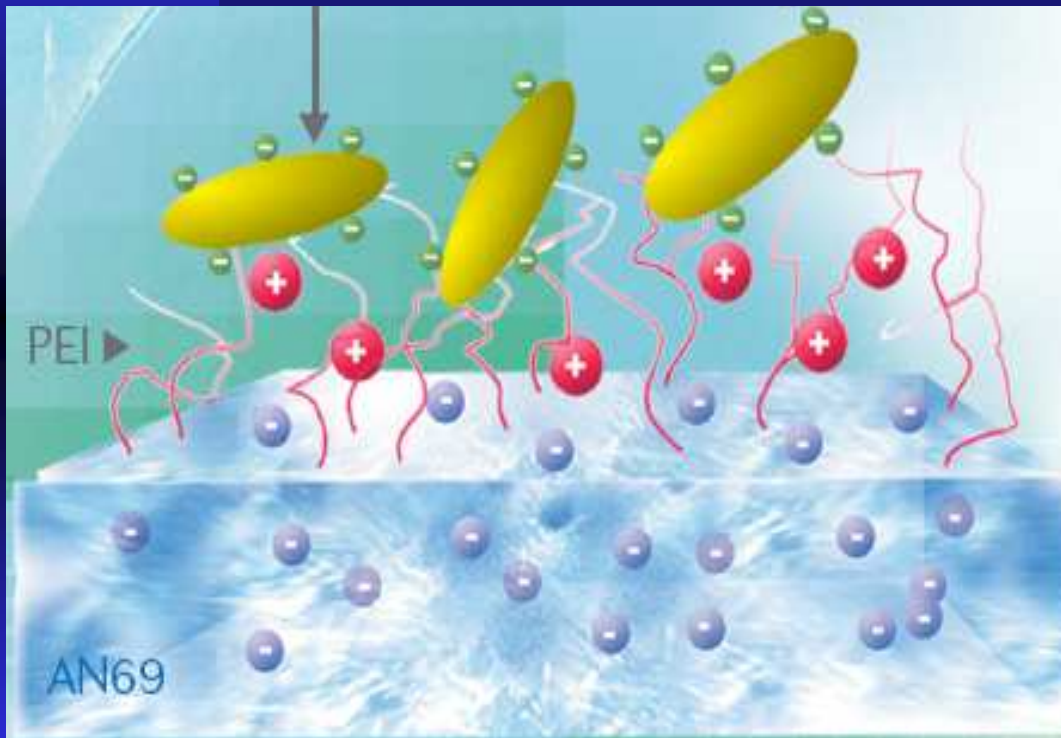
“large”

“middle”

“small”

oXiris: Unique Membrane Technology with a 3-Fold Mode of Action

heparin



➤ Pre-coating w/heparin

Heparin at surface **remains active** for Inhibition of Thrombin by formation of Thrombin – Anti –Thrombin (TAT) complex

➤ Surface treatment ➔

Absorbed on PEI:** the molecules that are negatively charged like Endotoxins & Heparin

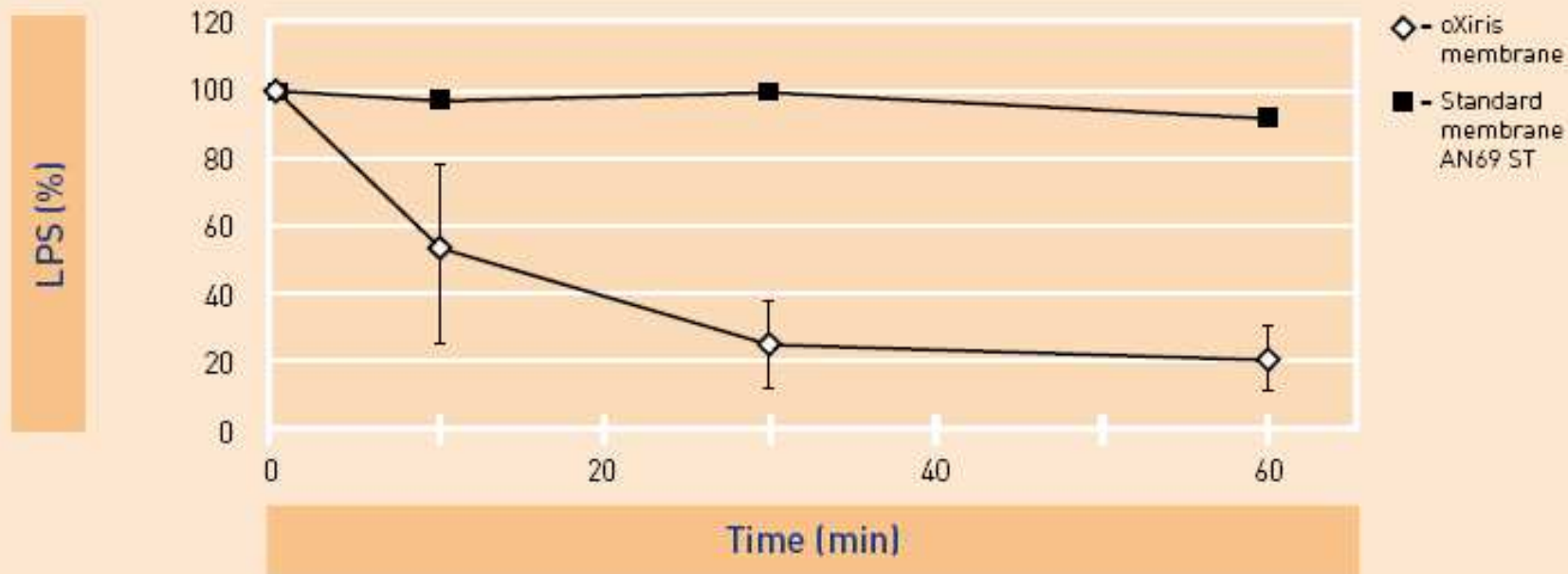
➤ AN69 core membrane

Selectively absorbed into the membrane bulk: all molecules which can access the membrane pores (MW<35kDa) and have a physico-chemical affinity w/ membrane (ionic binding for the positively charged molecules or hydrophilic interaction)

**PEI=PolyEthylene Imine

Endotoxins adsorption – in vitro

LPS adsorption on the oXiris membrane versus standard AN69 ST membranes—Endotoxin E.C. 055B5, bovine blood



LPS adsorption on oXiris closed circuit, 500 ml, bovine blood

In-vivo experiment: Animal Model of Septic Shock

Rimmele T et al., NDT 2009;24:354-357

Table 3. Mean $\pm$ SD haemodynamic and biochemical parameters after a 6-h HVHF session, at T6

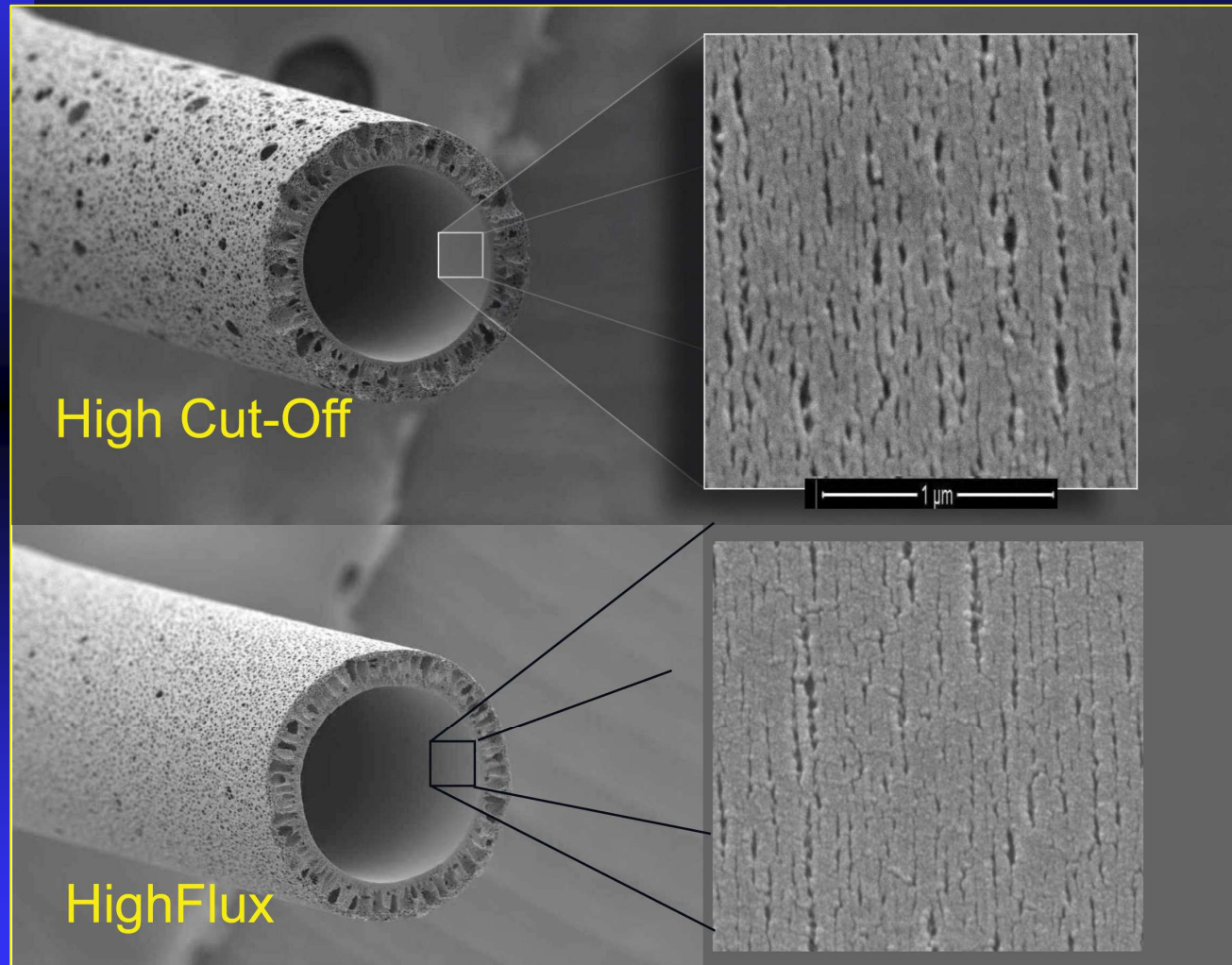
	AN69 mb (<i>n</i> = 10)	Treated mb (<i>n</i> = 10)	<i>P</i> -value
HR (beats/min)	138 $\pm$ 20	148 $\pm$ 16	0.23
MAP (mmHg)	64 $\pm$ 6	59 $\pm$ 8	0.13
SPAP (mmHg)	39 $\pm$ 9	30 $\pm$ 8	0.029
MPAP (mmHg)	34 $\pm$ 8	24 $\pm$ 7	0.008
PCWP (mmHg)	12 $\pm$ 3	11 $\pm$ 4	0.53
CO (l/min)	6.9 $\pm$ 4.8	5.5 $\pm$ 2.8	0.44
SAR (dyn/s/cm ⁵)	672 $\pm$ 205	797 $\pm$ 346	0.34
PAR (dyn/s/cm ⁵)	325 $\pm$ 186	234 $\pm$ 148	0.24
Epinephrine (mg)	3.27 $\pm$ 3.02	2.11 $\pm$ 1.05	0.27
Crystalloids (ml)	7587 $\pm$ 1456	5937 $\pm$ 1588	0.026
Hydroxyethylstarch (ml)	1912 $\pm$ 538	1437 $\pm$ 320	0.027
pH	7.10 $\pm$ 0.07	7.20 $\pm$ 0.11	0.026
Lactate (mmol/l)	14.11 $\pm$ 3.36	9.61 $\pm$ 4.47	0.02

oXiris

Table 4. Mean $\pm$ SD serum endotoxins levels (EU/ml)

	AN69 mb (<i>n</i> = 10)	Treated mb (<i>n</i> = 10)
T0	3.98 $\pm$ 3.31	4.26 $\pm$ 7.68
T1	11.07 $\pm$ 10.64	1.91 $\pm$ 1.19 ^a
T6	2.96 $\pm$ 2.75	2.26 $\pm$ 2.39

Recent HPHF Studies in Sepsis: New functional membrane with defined large pore size



HCO membrane

Recent HPHF Studies in Sepsis:

HICOSS (High Cut-Off Sepsis Study)

Multicenter study with septeX / HCO in septic AKI

PI Dr. Morgera (Berlin), Prof. Joannidis (Innsbruck), Prof. Risler (Tübingen),
Prof. Max (Marburg), Prof. Schindler (Berlin), Prof. Honoré (Bxl), Prof. Clark (Indianapolis)

Primary objective: Reduction of catecholamine requirements by High Cut off-CVVHD

Secondary objectives: clinical improvements and Safety (albumin levels), SOFA

Study design:

- Prospective, randomized, double-blinded multicenter study
- Two parallel study-arms: High Cut Off (HCO/Septex 1.1m²) compared to high flux (Polyflux 1.1m²)
- 120 pts, powered to show a 50% reduction in catecholamine use
(at interims analysis: 81 patients enrolled, 7 drop outs)
- Stratification for disease severity (APACHE score 19 to 30) and age
- 5 days treatment period (CVVHD) and follow up of catecholamine use
- 28 days follow-up period

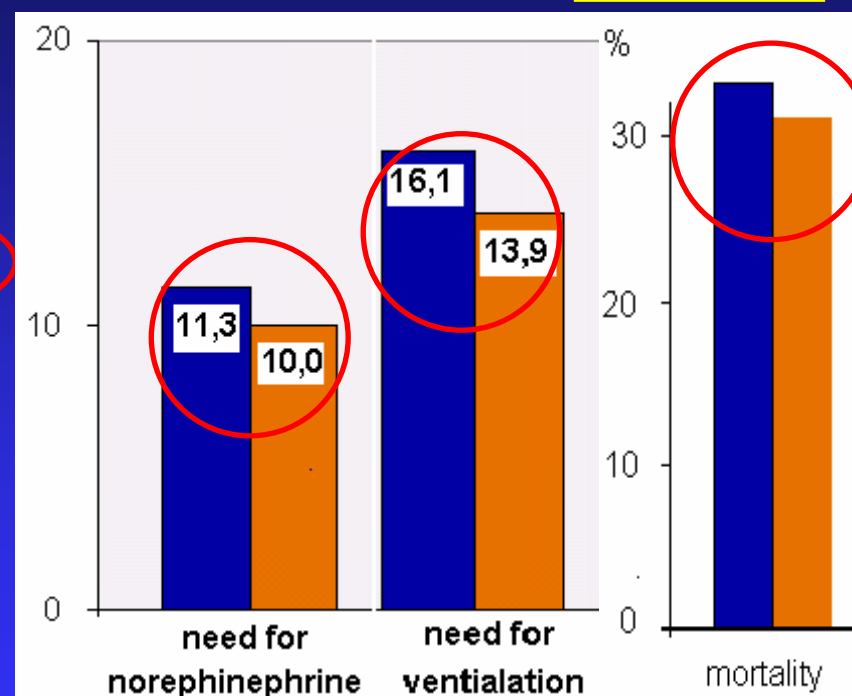
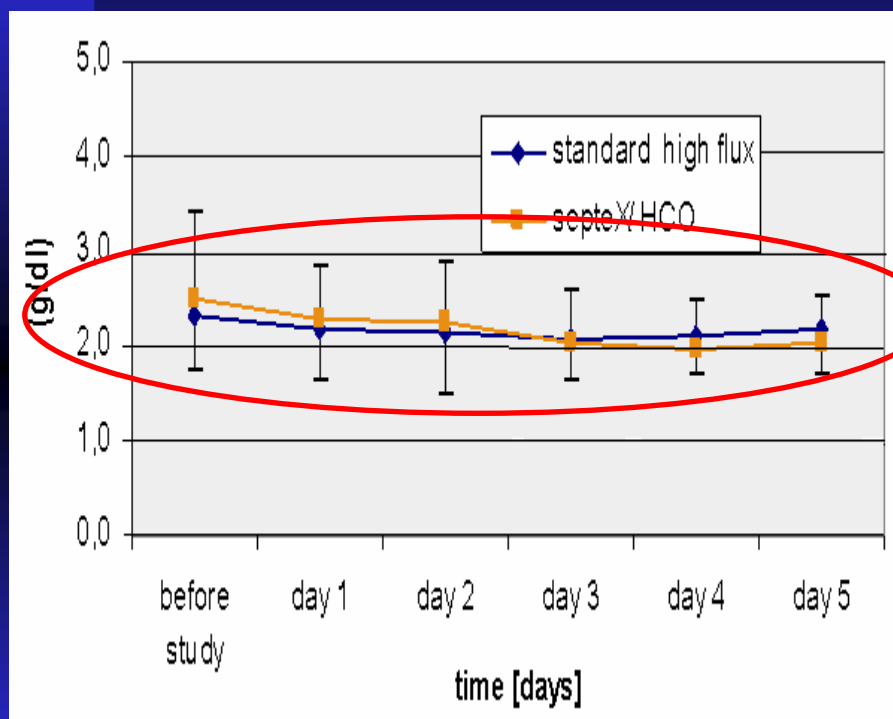
In preparation for publication

Honore PM, Clark W et al. 10th Congress of WFSICCM. Florence 2009

Recent HPHF Studies in Sepsis:

Safety: Stable plasma albumin levels
with septeX/ HCO compared to standard high flux -CVVHD

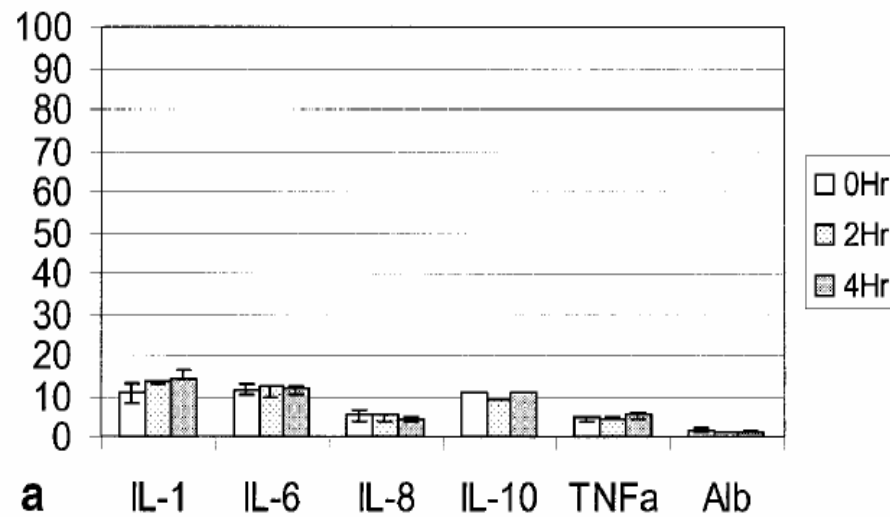
N= 81 pts
CVVHD



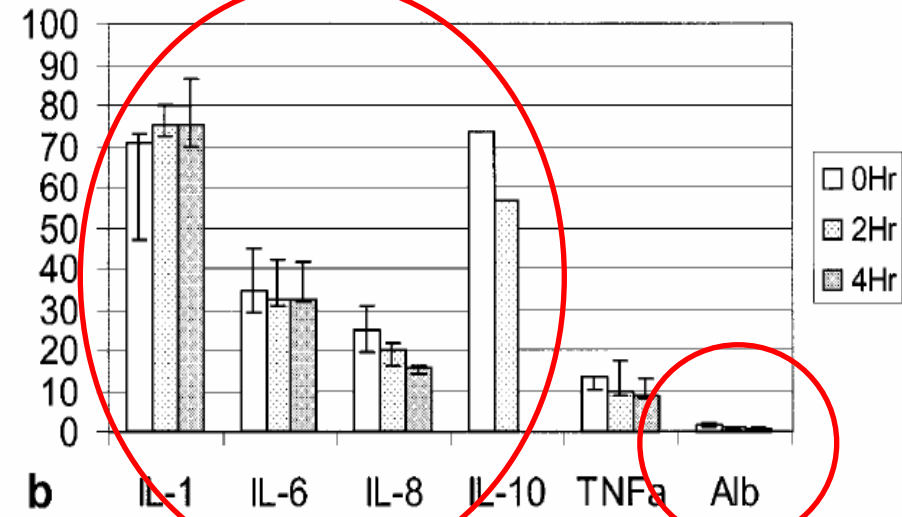
In preparation for publication



Recent HPHF Studies in Sepsis: Synergy with HVHF ?



**CVVH + HPHF = 1l/h =
16.6 ml/kg/h**



**HVHF+HPHF = 6 l/h =
80 ml/kg/h**

Uchino et al, Int Care Med 2002; 28: 651-655

■ Woman

■ ARDS

■ PaO₂

■ TOE :

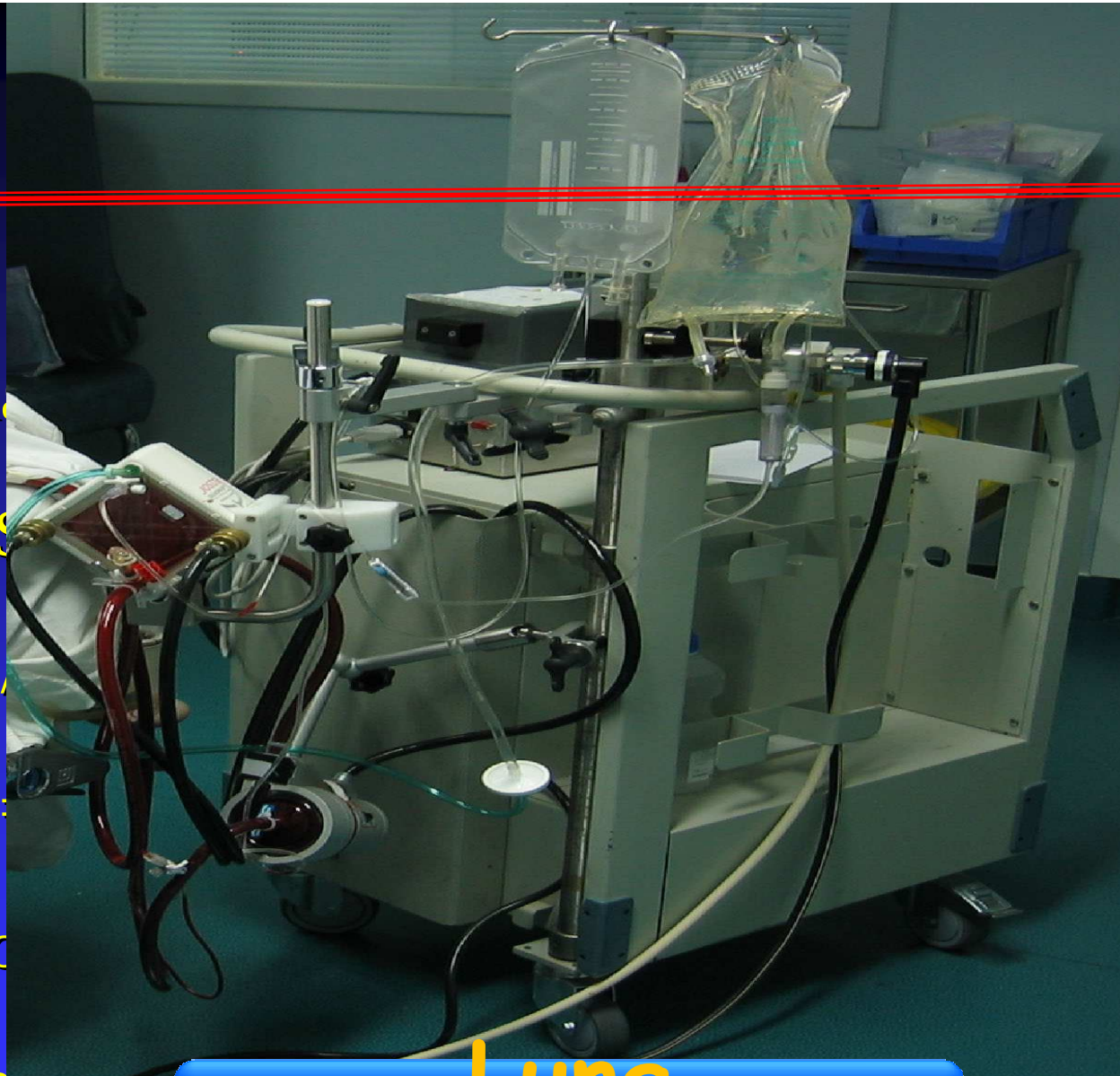
■ NA for

■ Left pneumo

■ Untreatable ARDS

umopathy

PP.



Lung
replacement

ARDS in Septic Shock

- 20 Kg of hyperhydration → pneumopathy
- ARD Without AKI → ation, NO and PP.
- PaO₂/FiO₂ = 50 → H₂O = 1/4 → H₂O.
Despite normal diuresis
- TOE = No cardiac dysfunction
- NA for PAM > 70 mmHg. Use of diuretics
- Left p **ce**
- Untreatable ARDS

HEMOFILTRATION

ECMO + CVVH: How to Couple ?



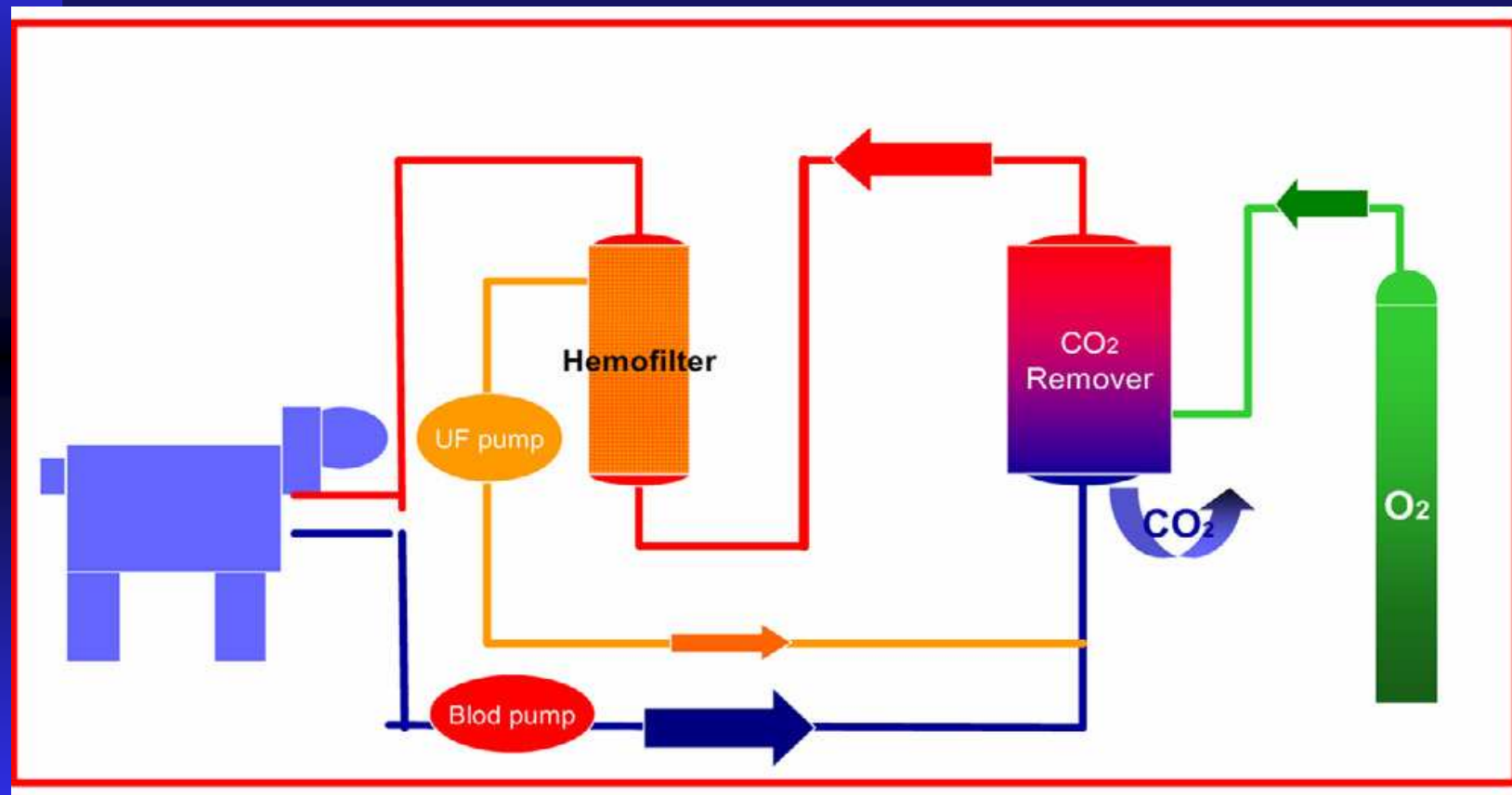
- 22 liters removed in 3 days, PAPS decreases 50%
- Extubated at Day 22
- Discharge from ICU after 1 month and 1 week
- Discharge from hospital after 2 months
 - ◆ without O₂

Problems To Overcome When Combining ECMO + CRRT

- Avoid to insert a new catheter
- Problems of Positive and Negative Pressures
- ECMO run with Heparin Coated membrane because of High Flow..
- Should be placed in the Venous Return
- CRRT do need anticoagulation..
- High range of pressure tolerated in the software
- Citrate can be given very efficiently under these conditions..where bleeding should be avoided..

Honore PM et al. Annals of Intensive Care 2011;26 EAP

Low Flow ECCO²R Technique: DECAP



Terragni, Ranieri, Contrib Nephrol 2010;165:185-196

Low Flow ECCO²R Technique: DECAP



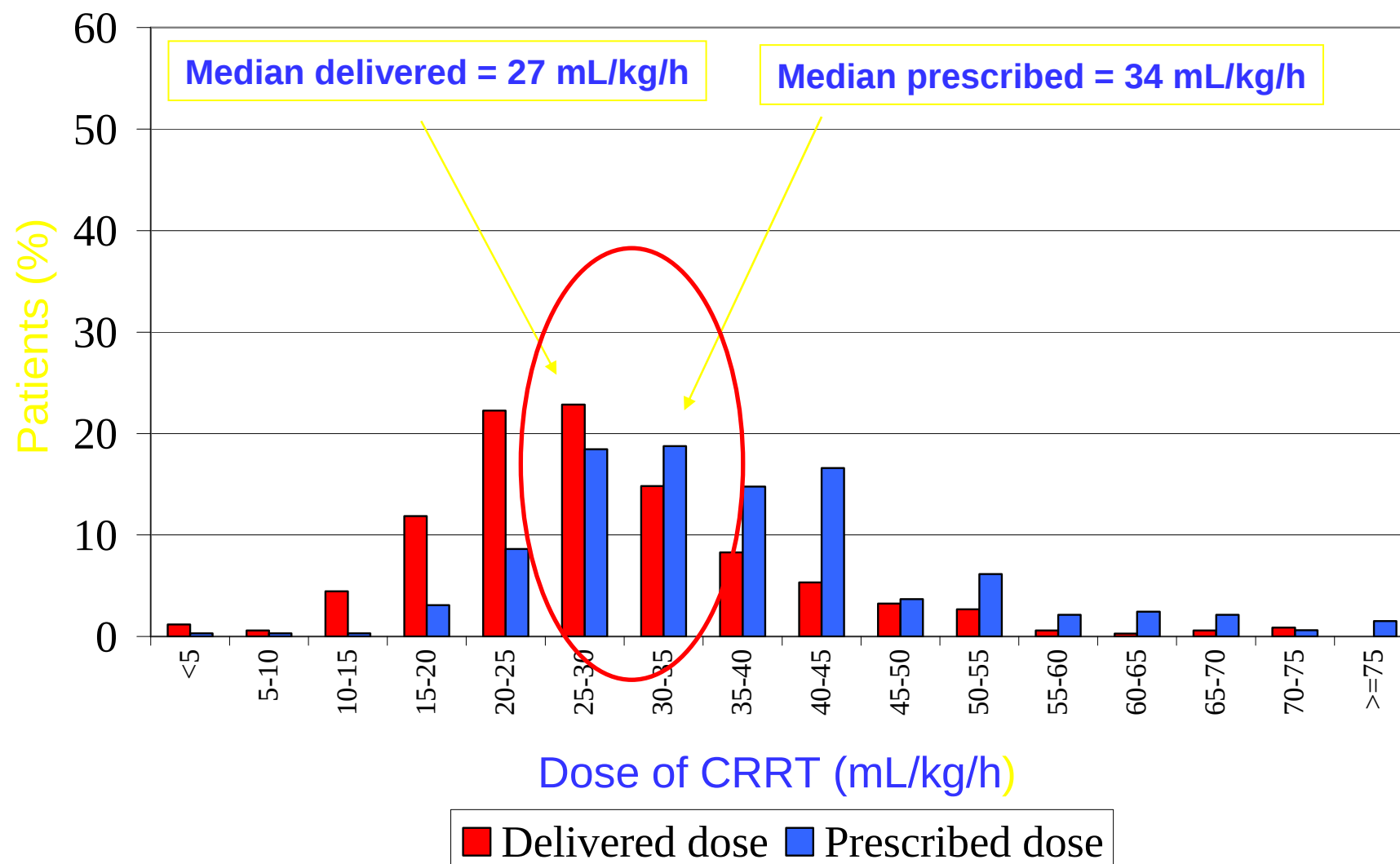
Terragni, Ranieri, Contrib Nephrol 2010;165-185-196

Problems and Potentials When Combining ECCO²R + CRRT

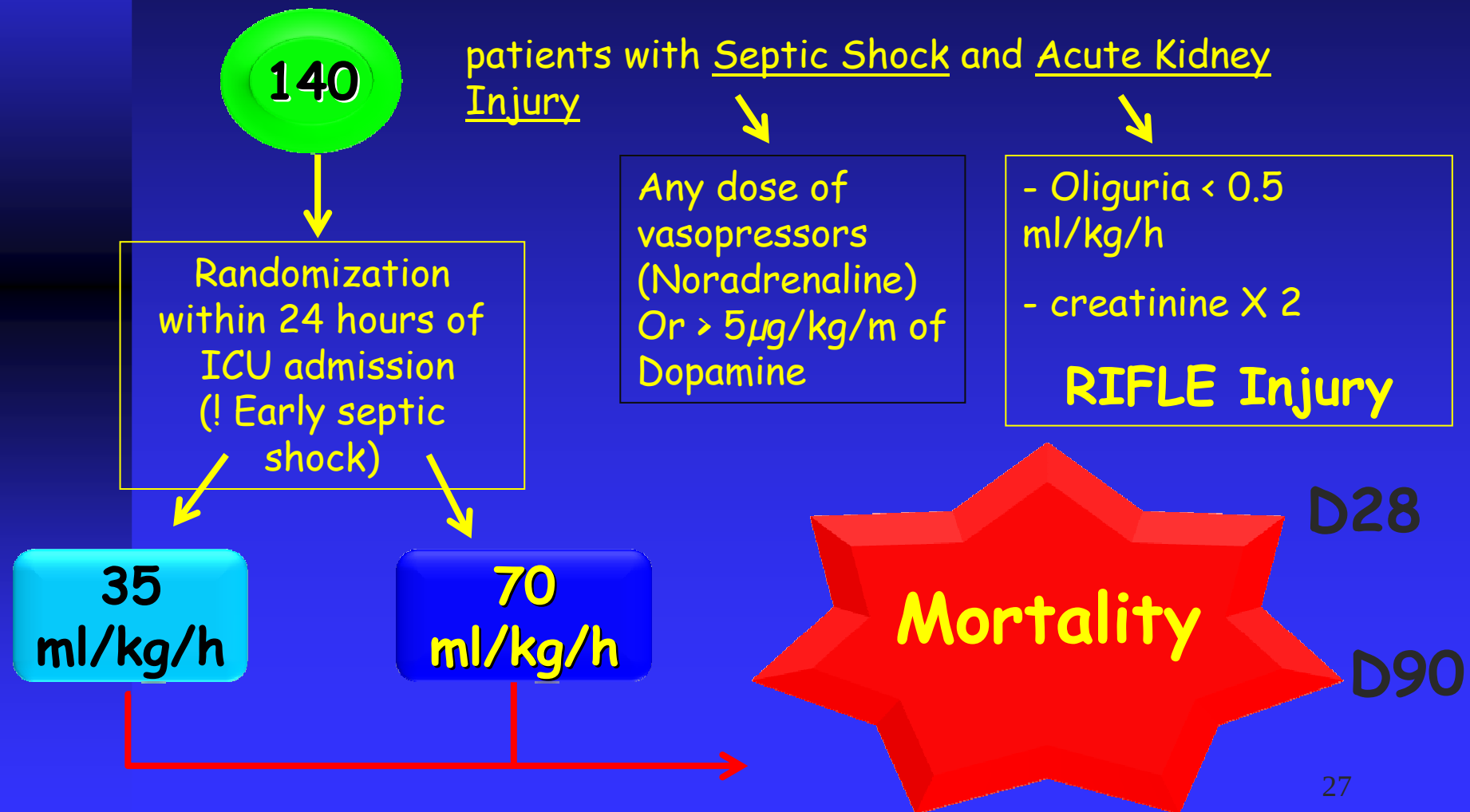
- Low Blood Flow (250 to 350 ml)
- Serie: increasing pressure and reducing bubbles
- Diluting Blood and reducing need of Anticoagulation
- Recirculating Ultrafiltrate & Enhancing Performance
- Can reduce by 20 % the PCO² & reduce Peak Press

DoReMi Database (N=865)

Ronco et al, 2009



IVOIRE STUDY



RIFLE Criteria



GFR Criteria Urine Output Criteria

Risk

Increased creatinine
 $\times 1.5$ or GFR decrease
 $> 25\%$

UO $< .5\text{ml/kg/h}$
 $\times 6\text{ hr}$

High
Sensitivity

Injury

Increased creatinine $\times 2$
or GFR decrease $> 50\%$

UO $< .5\text{ml/kg/h}$
 $\times 12\text{ hr}$

Failure

Increase creatinine
 $\times 3$
or GFR decrease
 $> 75\%$

UO $< .3\text{ml/kg/h}$
 $\times 24\text{ hr}$ or
Anuria $\times 12\text{ hrs}$

High
Specificity

Loss

Persistent ARF** = complete loss of
kidney function $> 4\text{ weeks}$

ESKD

End Stage Kidney Disease
($> 3\text{ months}$)

Patient flow diagram



167 patients assessed for eligibility

27 Excluded
14 Refuse participation
2 Obesity > 150 kg
11 Met exclusion criteria

140 Randomized

2 patients excluded
1 Withdraw consent
1 Acute leukemia

1 patient excluded
1 Withdraw consent

66 patients
analyzed

71 patients
analyzed

Hemodiafe study

ATN study www.thelancet.com Vol 368 July 29, 2006

N Engl J Med 2008

Death from any cause by day 60 — no. (%) 302 (53.6) 289 (51.5) **66**

N Engl J Med 2009

SOFA cardiovascular score

0–2	509	43.9	37.8
3–4	615	61.7	62.9

Sepsis

60 %

Patients with SOFA cardiovascular score of 3 or 4

52 %

Yes	247/510 (48.4)	254/546 (46.5)
No	74/210 (35.2)	75/194 (38.7)

Patients with criteria for sepsis

49 %

Yes	168/359 (46.8)	186/363 (51.2)
No	154/362 (42.5)	145/379 (38.3)

Conclusions & Perspectives

- **Rationale do show that Volume is needed to Displaced meditors from the Capilaries back to the Circulation..**
- **High Adsorptive Membranes including Endotoxin might be a good alternative to PMX with the Advantage of Running CRRT at the same time..**
- **High Cut-Off Filters might Represent a Good Alternative for Sepsis and Rhabdomyolysis..**
- **ARDS: A Coming Back in the Setting of Fluid Overload especially with ECMO**
- **CO2 elimination during ECCOR-CRRT might be an Intermediate Alternative for Refractory ARDS before Ful ECMO & ECCOR**

Conclusions & Perspectives (II)

- **Dose for Non-Septic AKI should be 25 ml/kg/h**
- **Dose for Septic AKI without catecholamine dependency should be 25 ml/kg/h**
- **Dose for Septic AKI with catecholamine dependency should be 35 ml/kg/h (Awaiting for IVOIRE Trial Results)**
- **Patient with Septic AKI under catecholamines should be on CRRT rather IHD**
- **Prescribed Dose should be 5 to 10 ml higher than Target Dose**