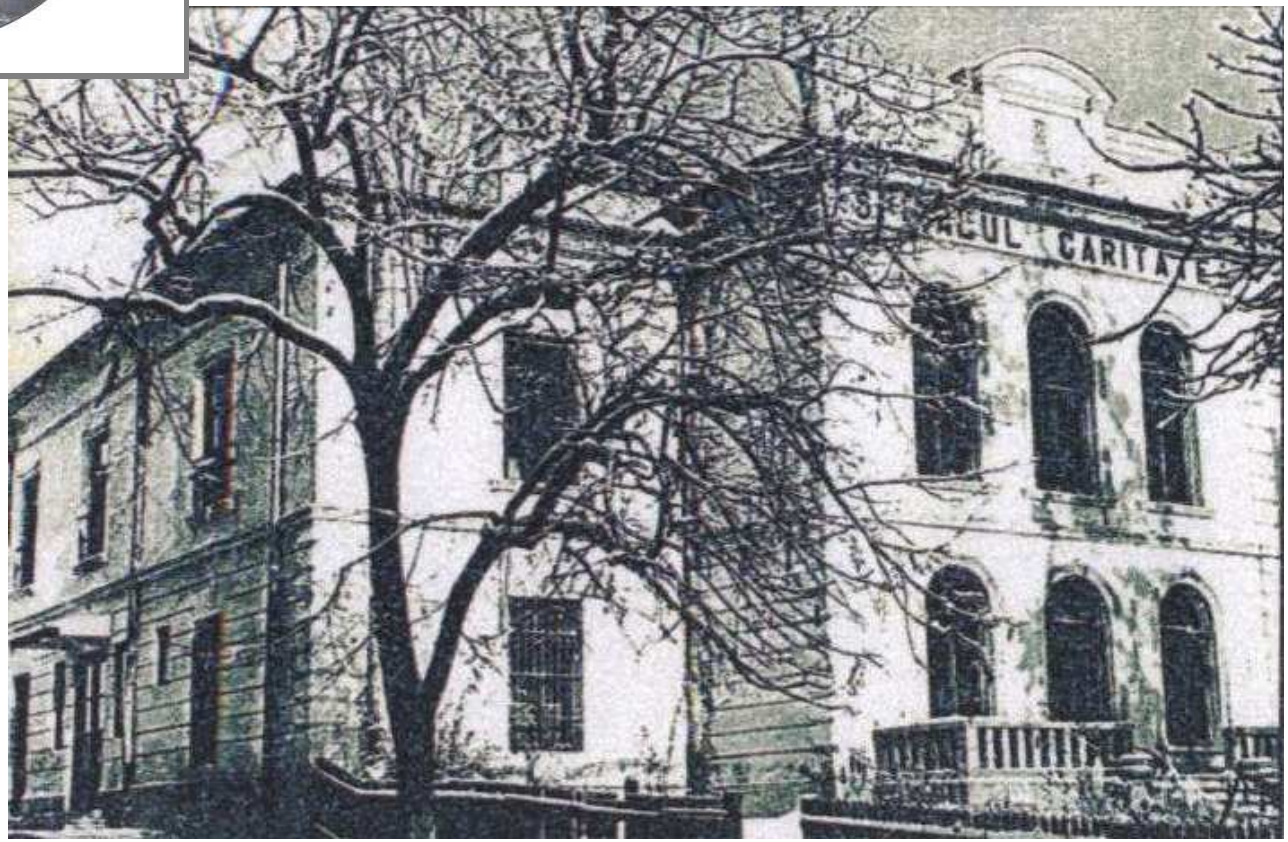
LESSONS FROM EVIDENCE BASED MEDICINEIN THE CARE OF ARF AND ESRD



Prof. Dr. Adrian Covic
University of Medicine "Gr. T. Popa", Iaşi

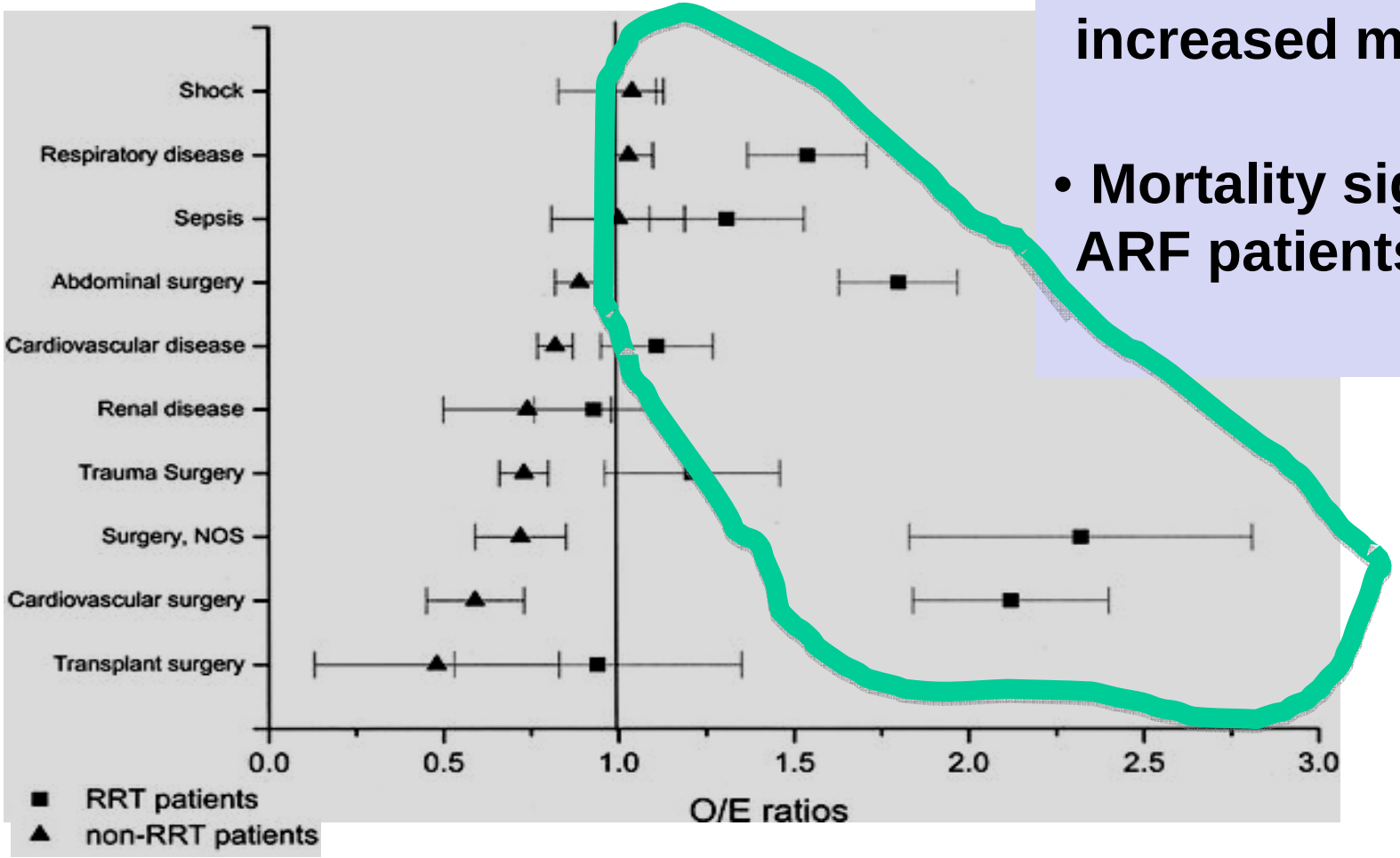
2008

Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients

Metnitz PG *et al.*

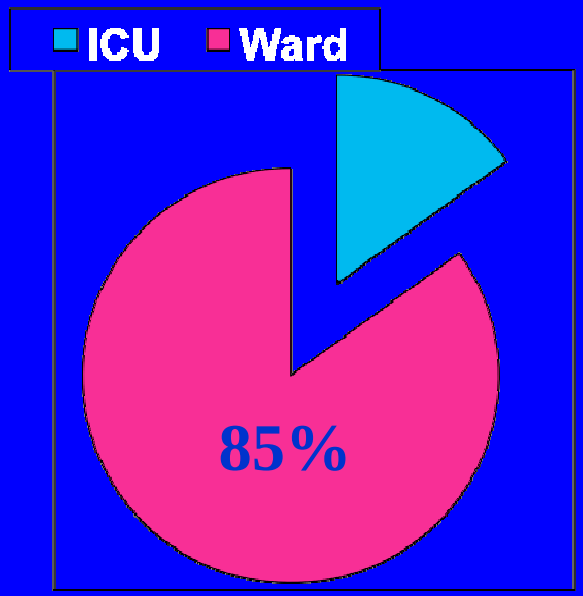
Crit Care Med. 2002 Sep;30(9):2051-8.

- **ARF associated with four-fold increased mortality**
- **Mortality significantly higher in ARF patients (62.8 *vs.* 38.5%)**



Myth 1 – mortality in ARF remains unchanged?

1974-1979

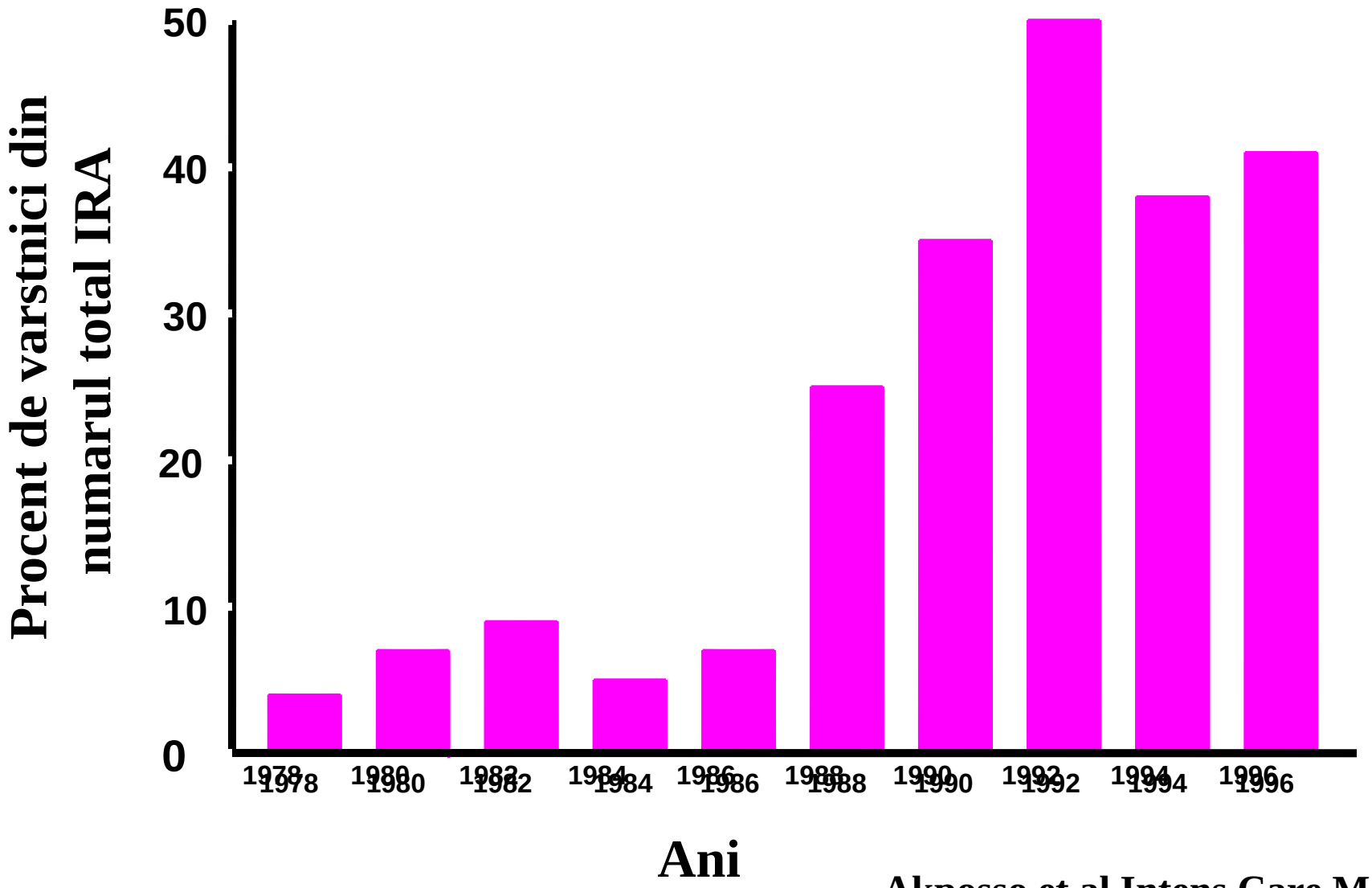


Mortality 54%

Sf Ioan BOTEZATORUL

Ricci, Ronco Crit Care Clin 21

Proportion of old pts. (> 80 yrs.) with ARF in ICU



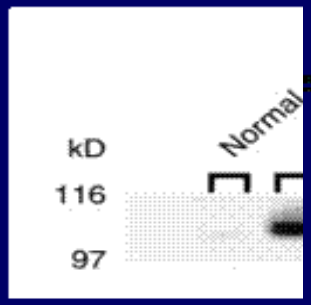
Akposso et al Intens Care Med 26:400-406,2000

Novel Markers of Renal Injury

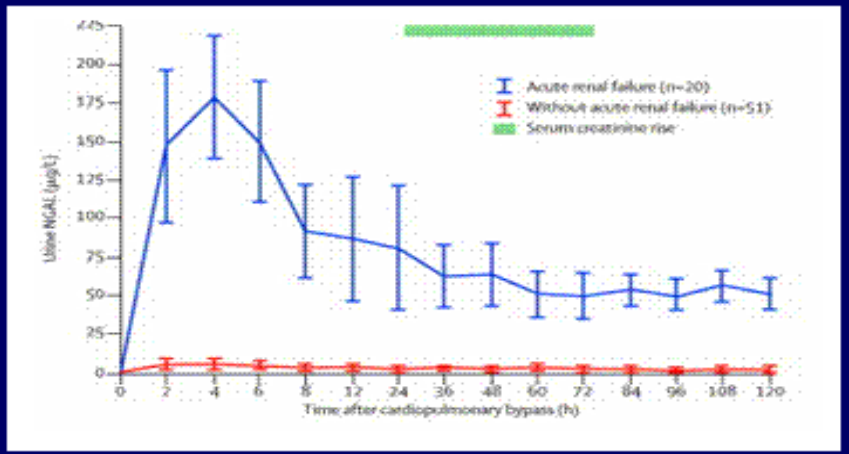
- Kidney injury molecule-1 (KIM-1)
- Neutro
- Cystei
- Na^+/H^+
- N-acet
- γ-Gluta
- α- and

KIM-1 in Ischemic ATN

Western Blot Analysis of



Urine NGAL post Cardiac Surgery



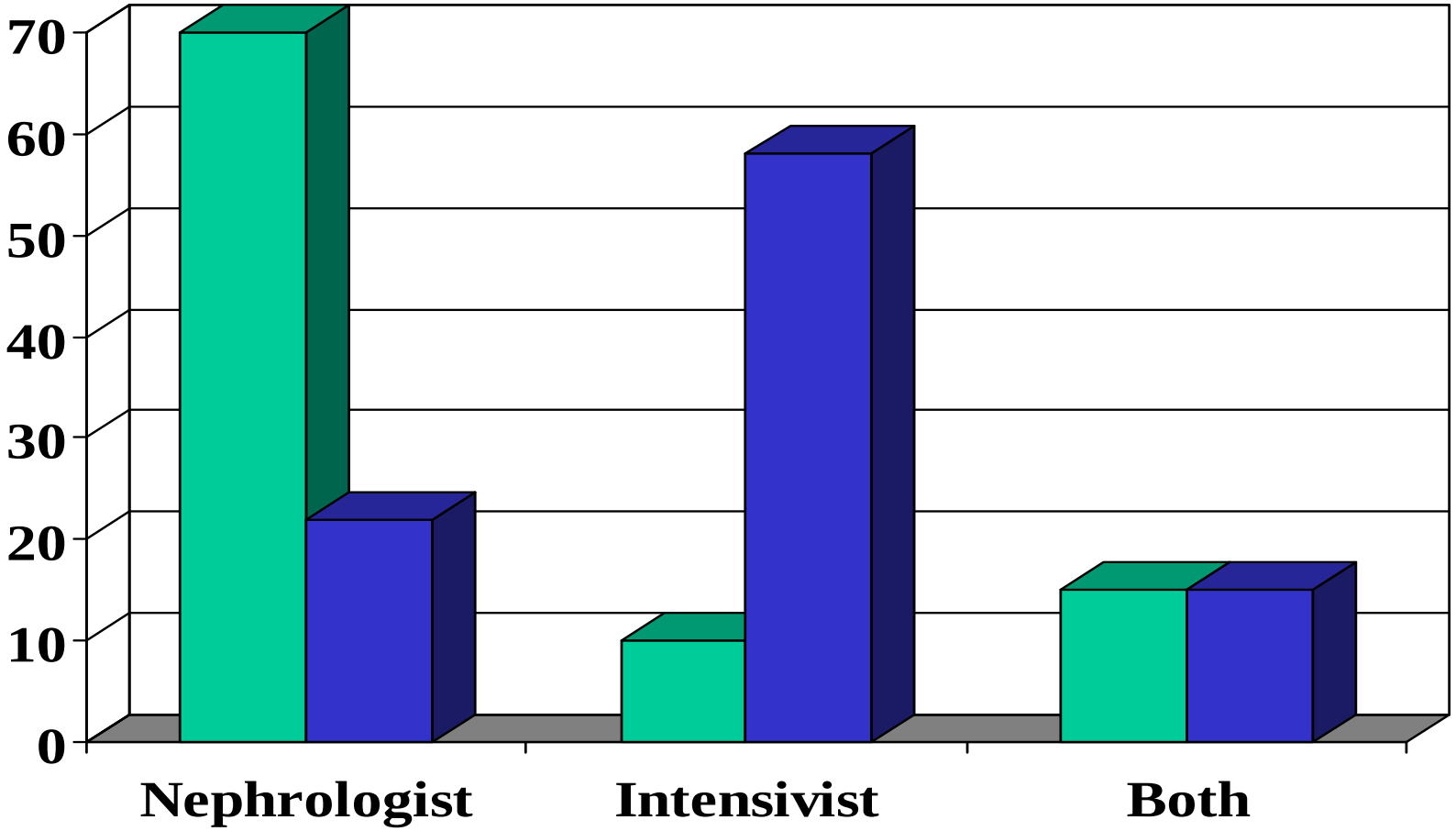
Mishra J, et al. Lancet 2005; 365:1231-1238

East and North Hertfordshire NHS Trust

FIRST “CONCLUSION”: WE TREAT BETTER

AND RESULTS WILL PROBABLY SHOW UP

MYTH 2
Who is responsible for the RRT?



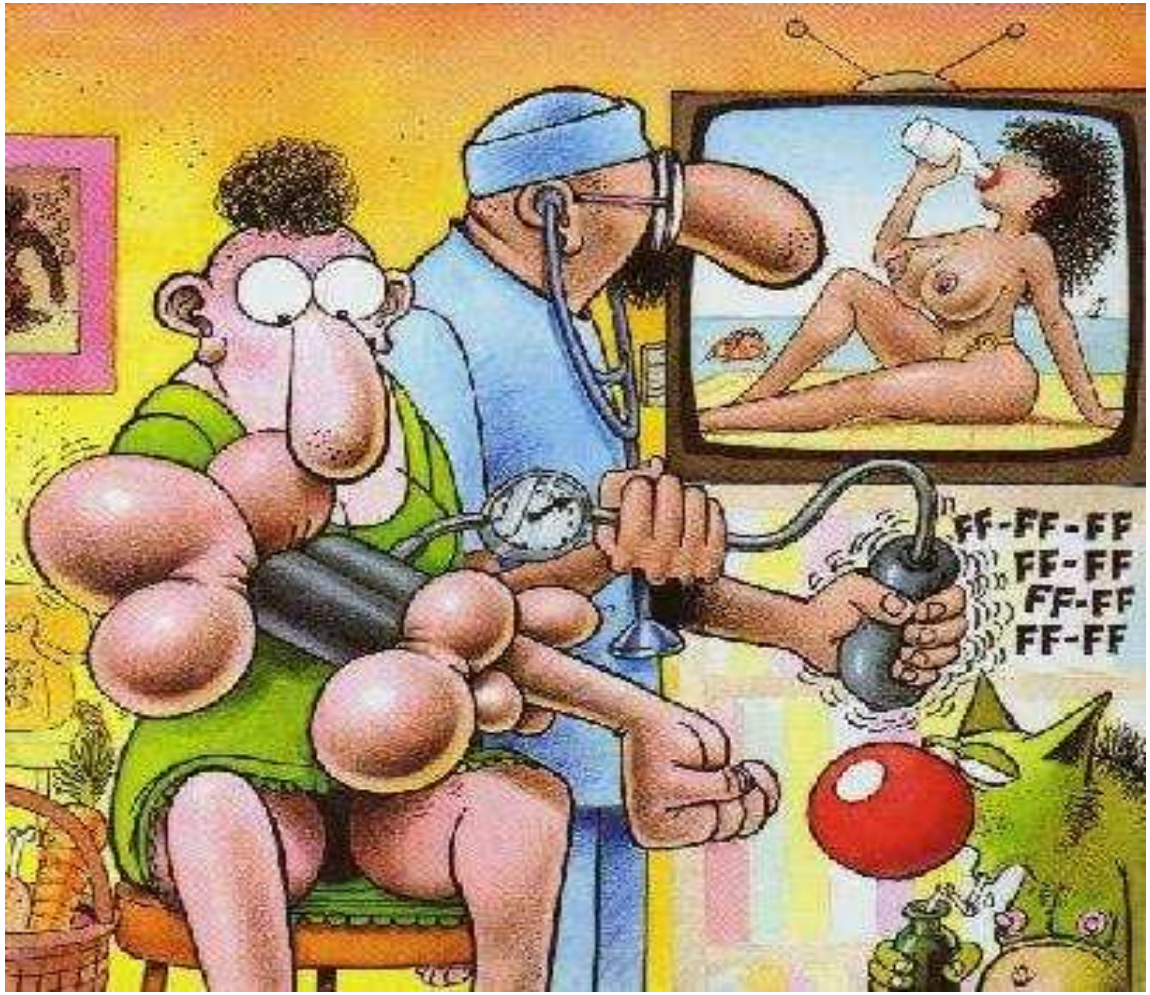
N= 5887

Nephrology
Intensivist

Gambro Dialysis Opinions 2005

A SIMPLE EXPLANATION…

…Intensivists are intensively managing many things at the time….



WHILE A NEPHROLOGIST IS THINKING…

Nephrology Consultation in ARF: Does Timing Matter ?

- 215 pat. with ARF in 4 U.S. academic centers
- In 67 pat. consultation of nephrologist only after > 48 h (median 4 days)
- In this group, ***mortality was significantly higher***:
  74% vs. 49% (p=0.006) in pat. with RRT
  53% vs. 22% (p=0.01) in pat. without RRT
- Likewise, ICU and hospital length of stay significantly longer

Mehta R et al. *Am. J. Med.* 2002; 113: 456-461

Q J Med 2005; **98**:661–666
doi:10.1093/qjmed/hci109

Advance Access publication 29 July

Severe acute renal failure in adults: place of care, incidence and outcomes

J. HEGARTY[1], R.J. MIDDLETON[1], M. KREBS[1], H. HUSSAIN[1], C. CHEUNG[1], T. LEDSON[1], A.J. HUTCHISON[2], P.A. KALRA[1], H.C. RAYNER[3], P.E. STEVENS[4] and D.J. O'DONOGHUE[1]

From the [1]Department of Renal Medicine, Hope Hospital, Salford, [2]Manchester Institute of Nephrology and Transplantation, Central Manchester and Manchester Childrens' Hospital, Manchester, [3]Department of Renal Medicine, Birmingham Heartlands Hospital, Birmingham, and [4]Department of Renal Medicine, Kent & Canterbury Hospital, Canterbury, UK

Received 21 December 2004 and in revised form 31 May 2005

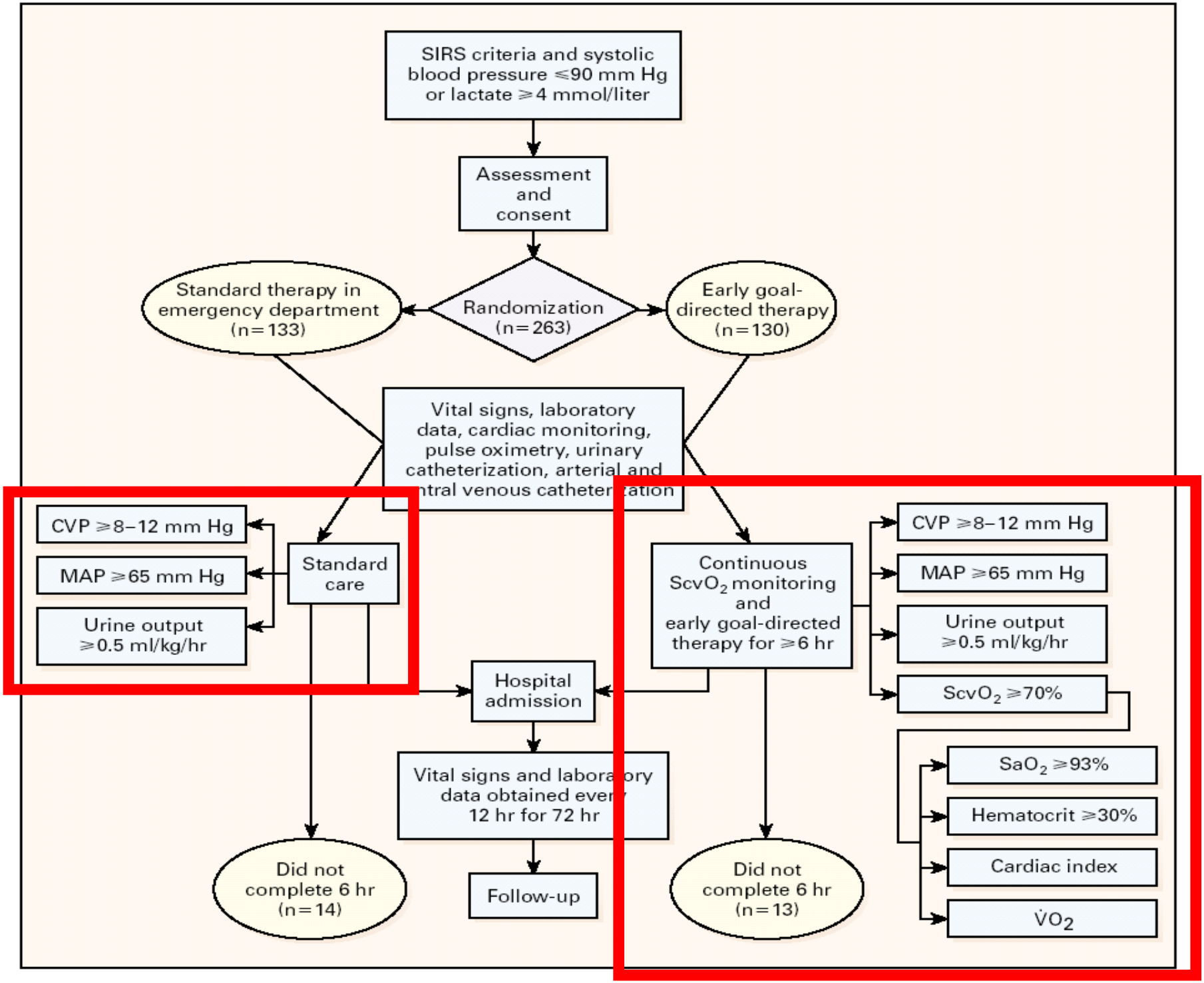
dent renal function. In 13 (46%) cases there was an unacceptable delay in patient transfer and in 7 (25%), delays in assessment or commencement of RRT may have adversely affected patient outcome.

WHY?

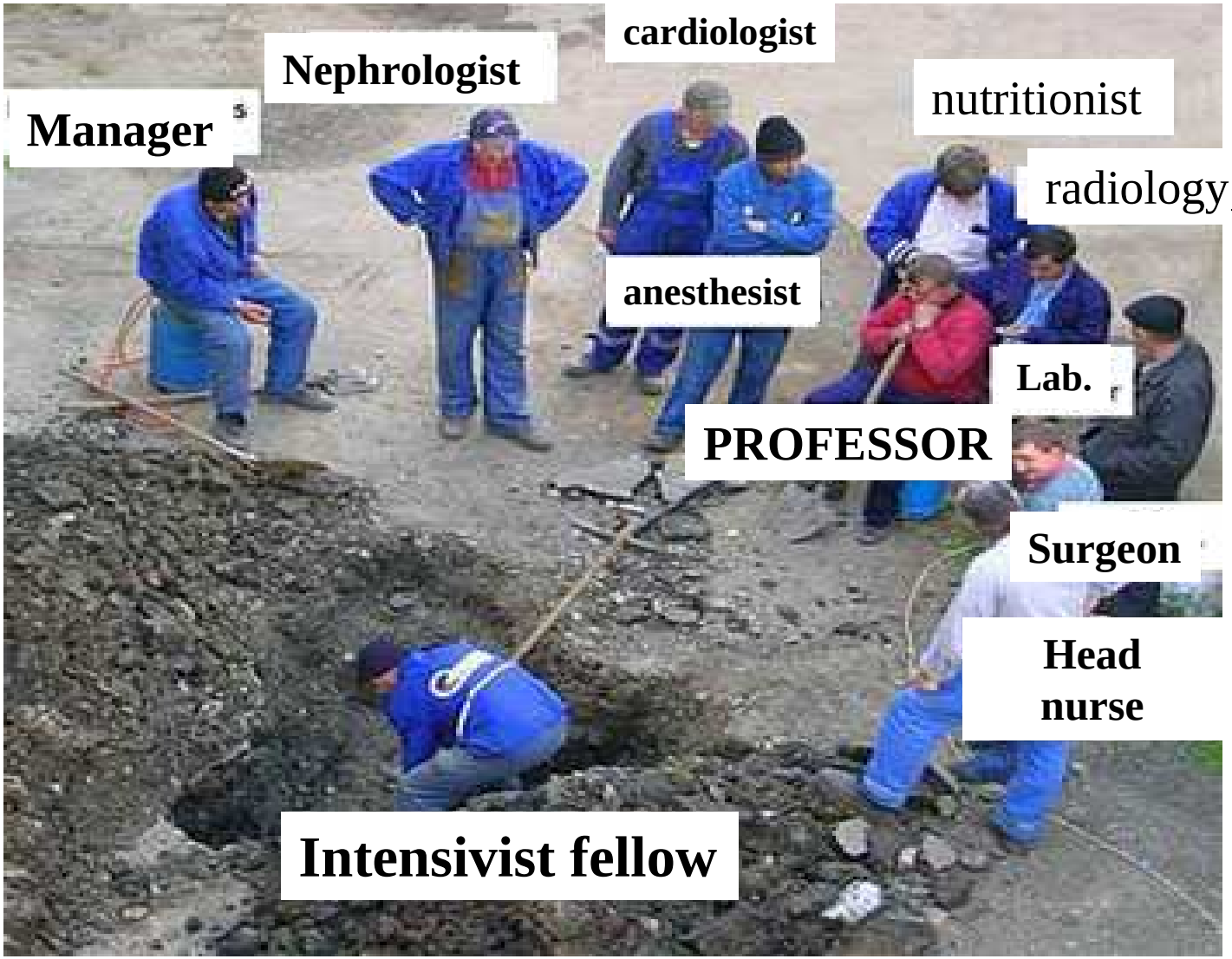
Early goal-directed therapy in the treatment of severe sepsis and septic shock

(Rivers et al. N. Eng. J. Med. 2001; 345 : 1368-1377)

	Early goal therapy (n = 130)	Standard therapy (n = 130)	
MODS*			
Baseline	**7.6 ± 3.1**	**7.3 ± 3.1**	
6 h	**5.9 ± 3.7**	**6.3 ± 3.7**	**p < 0.001**
72 h	**5.1 ± 3.9**	**6.4 ± 4**	**p < 0.001**
Mortality	**30.5 %**	**46.5 %**	**p < 0.01**


SIRS criteria and systolic blood pressure ≤90 mm Hg or lactate ≥4 mmol/liter
Assessment and consent
Randomization (n=263)
Standard therapy in emergency department (n=133)
Early goal-directed therapy (n=130)
Vital signs, laboratory data, cardiac monitoring, pulse oximetry, urinary catheterization, arterial and
ntral venous catheter tation
CVP ≥8–12 mm Hg
MAP ≥65 mm Hg
Urine output ≥0.5 ml/kg/hr
Standard care
Continuous $ScvO_2$ monitoring and early goal-directed therapy for ≥6 hr
CVP ≥8–12 mm Hg
MAP ≥65 mm Hg
Urine output ≥0.5 ml/kg/hr
$ScvO_2$ ≥70%
SaO_2 ≥93%
Hematocrit ≥30%
Cardiac index
$\dot{V}O_2$
Hospital admission
Vital signs and labora ory data obtained ever 12 hr for 72 hr
Follow-up
Did not complete 6 hr (n=14)
Did not complete 6 hr (n=13)

2-nd CONCLUSION: TEAMWORK, BUT, *NEPHROLOGIST FROM THE VERY START*



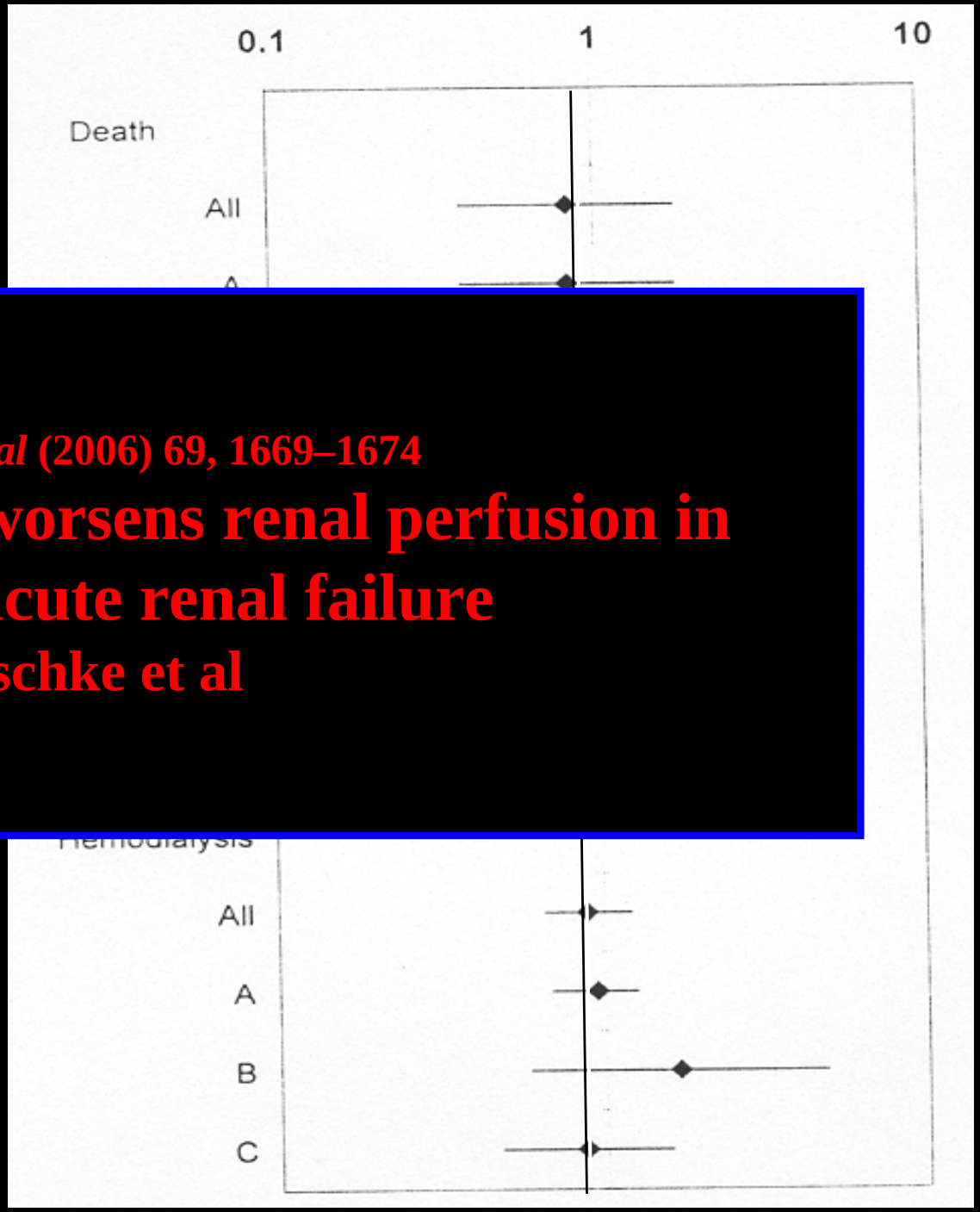
Myth 3

“Renal-dose” Dopamine

Or

“IDEAL” vssopressor agent

Use of dopamine in ARF: a meta-analysis



Plot s
(diam
interv
for su

A:exc
B: Studies limited to heart disease
C: excluded statistical outliers

Kellum and Decker Crit Care Med 29:1526-1531,2001

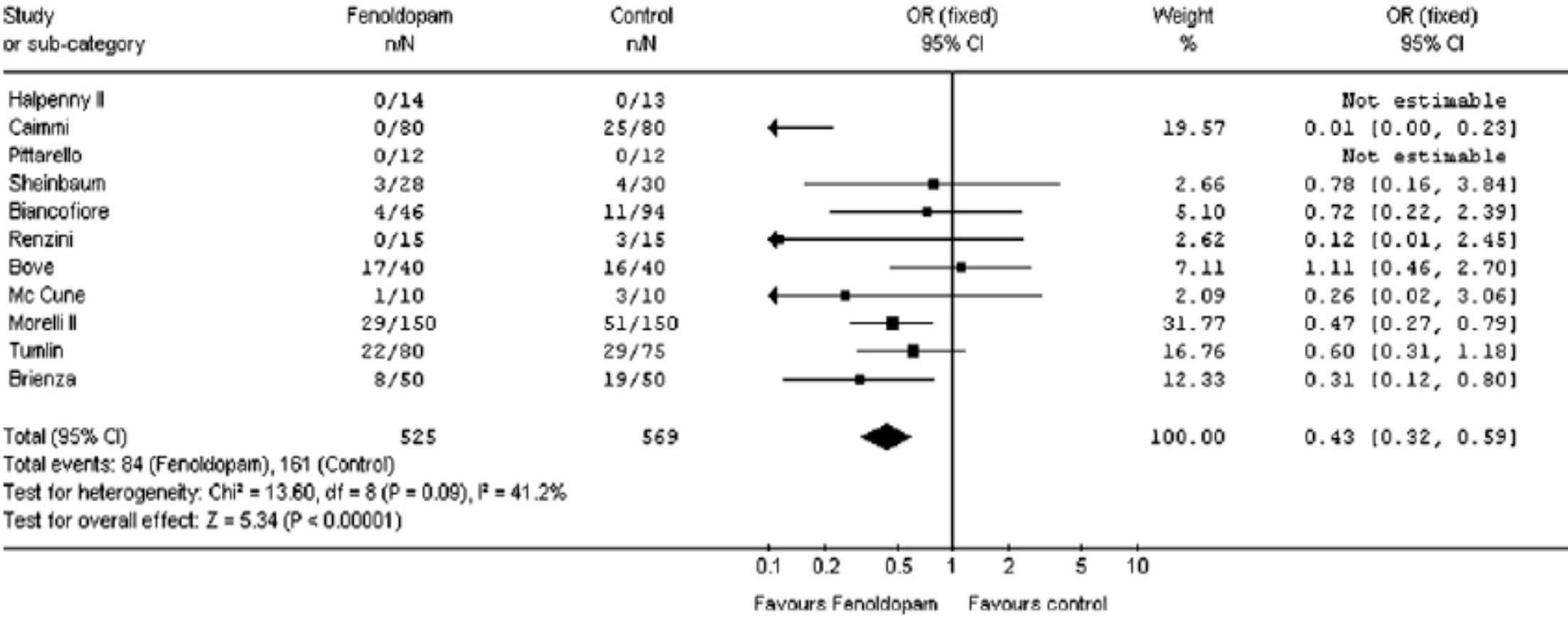
Kidney International (2006) 69, 1669–1674

'Low-dose' dopamine worsens renal perfusion in patients with acute renal failure

A Lauschke et al

Potential solutions: Fenoldopam-risk of AKI in critically ill

Review: Fenoldopam (Version 12-7-2006)
Comparison: 01 Fenoldopam vs Control Rx
Outcome: 02 Acute Renal Failure



Landoni et al, AJKD 49:56-68, 2006.

Prevention of vasoconstriction

Fenoldopam – dopamine A-1 receptor agonist

Systematic review of RCTs in ICU or major surgery
16 studies, 1290 patients

Reduced risk of acute kidney injury – OR 0.43 (0.32-0.59)
Reduced need for RRT – OR 0.54 (0.34-0.84)
Reduced in hospital death – OR 0.64 (0.45-0.91)

NOREPINEPHRINE in patients with AKI

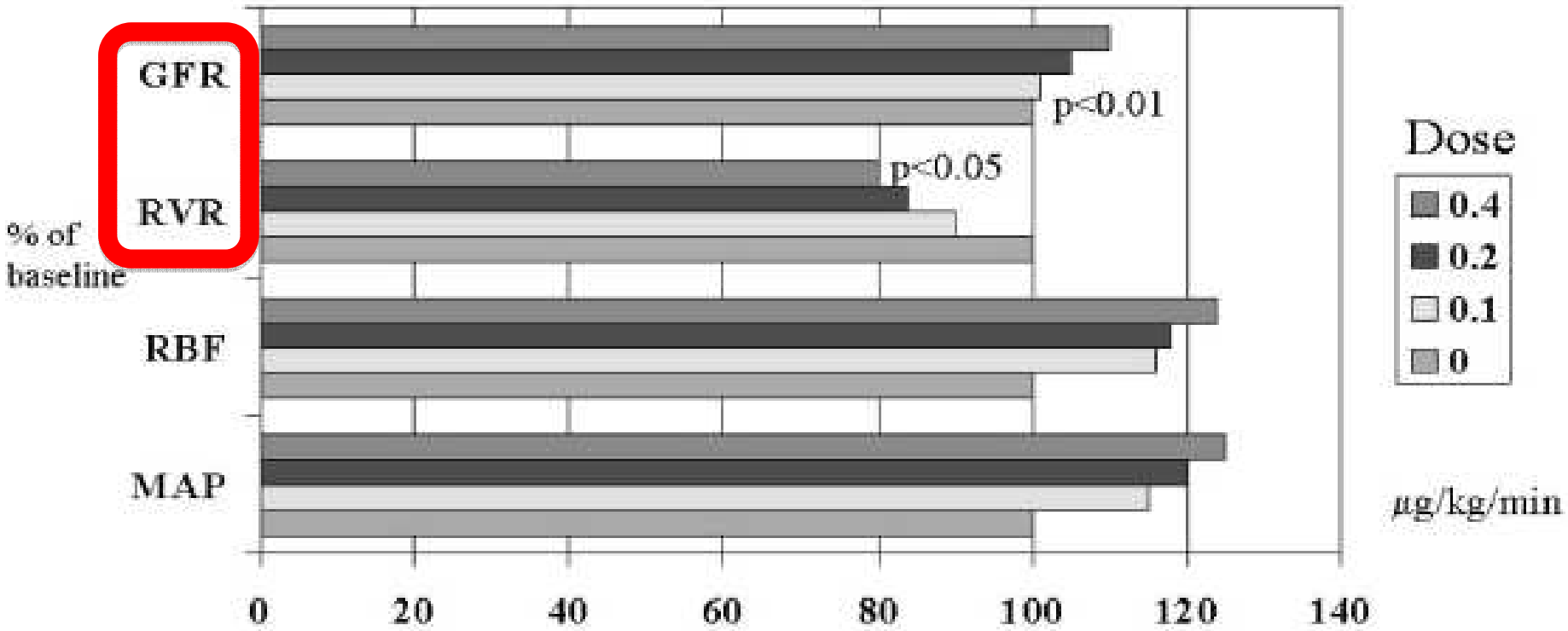


Figure 2. Histogram illustrating the effect of different doses (0–0.4 µg/kg/min) of norepinephrine on mean arterial pressure (*MAP*), renal blood flow (*RBF*), renal vascular resistance (*RVR*), and glomerular filtration rate (*GFR*) in the conscious dog. Flow is presented as a percentage, with 100% being flow in control dogs receiving placebo. Both MAP and GFR are significantly increased by norepinephrine at clinically relevant doses.

Bellomo et al, Crit Care Med, 2008

NOREPINEPHRINE in patients with AKI

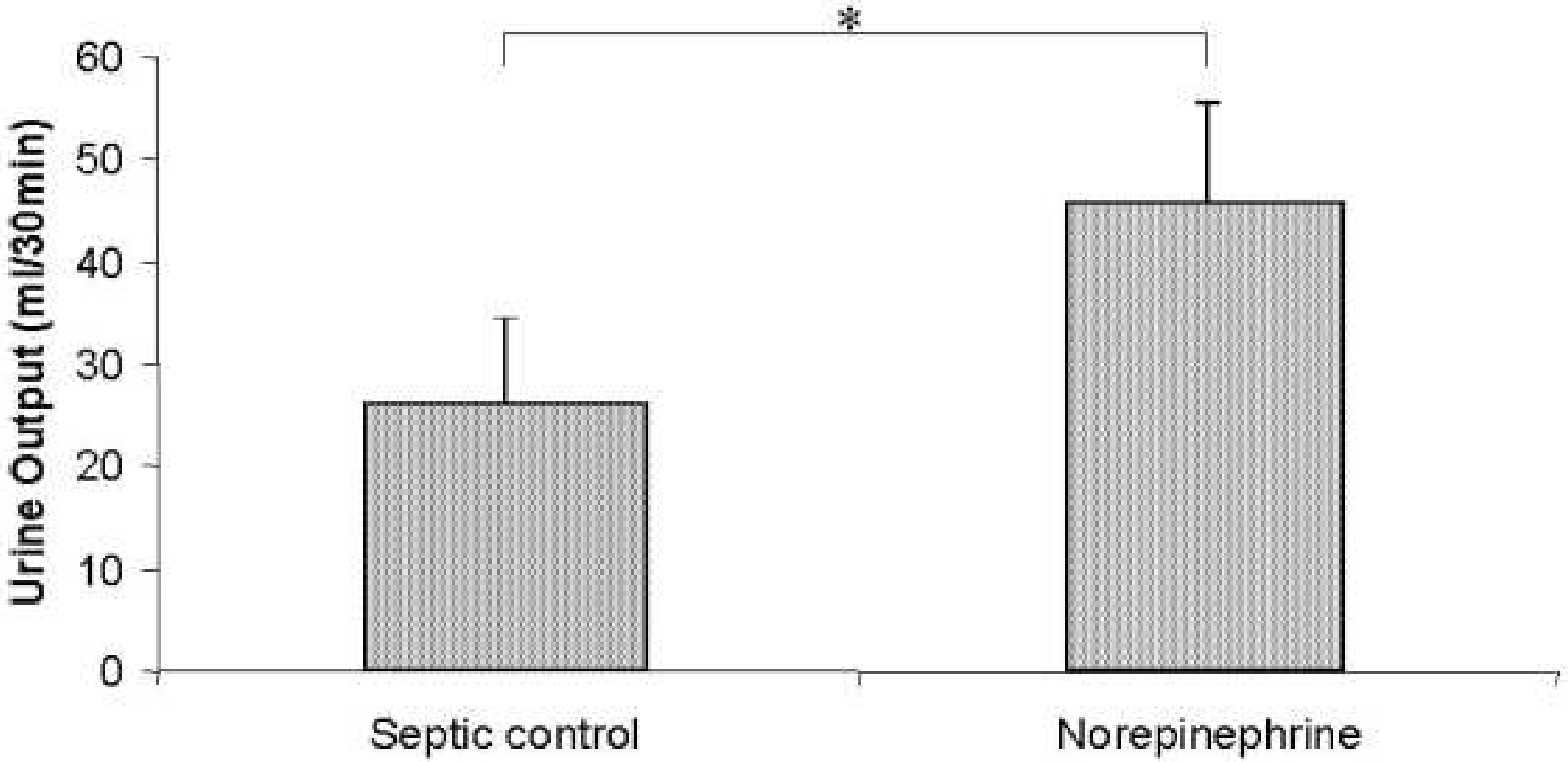
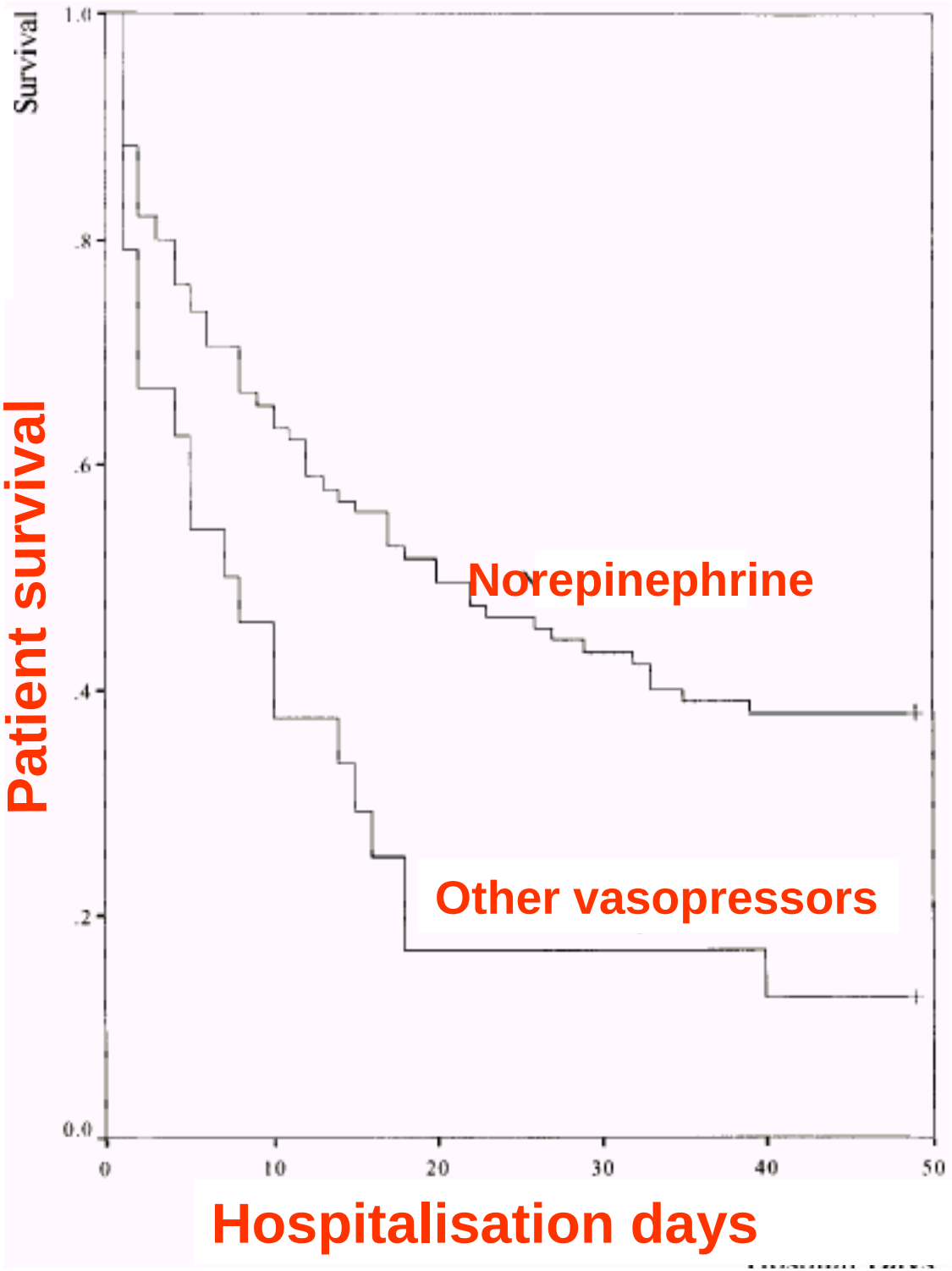


Figure 3. Histogram showing the effect of norepinephrine infusion on urine output in septic sheep compared with placebo (*septic control*). Norepinephrine infusion nearly doubled urine output.

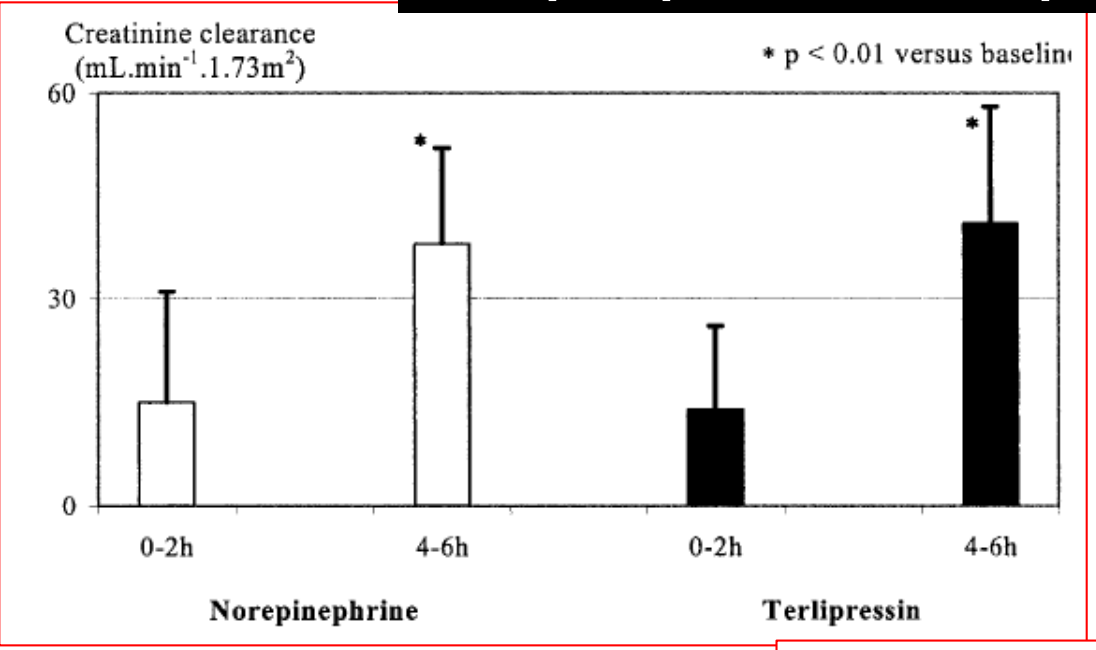
Leone et al, Current Opinion in Anesthesiology, 2008

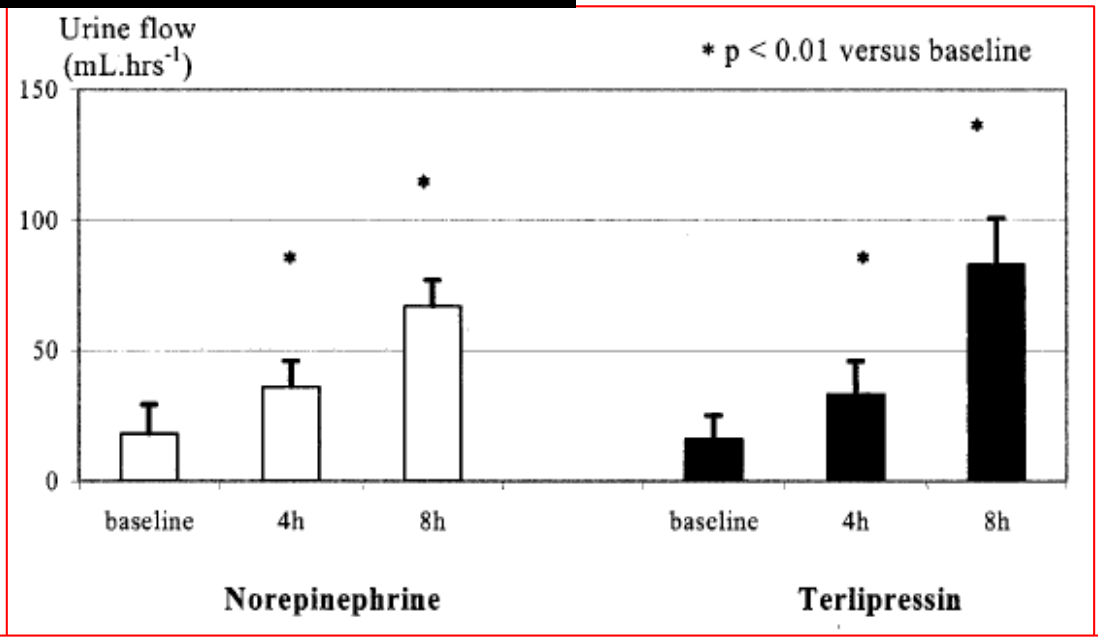
Survival of septic shock patients treated with vasopressors

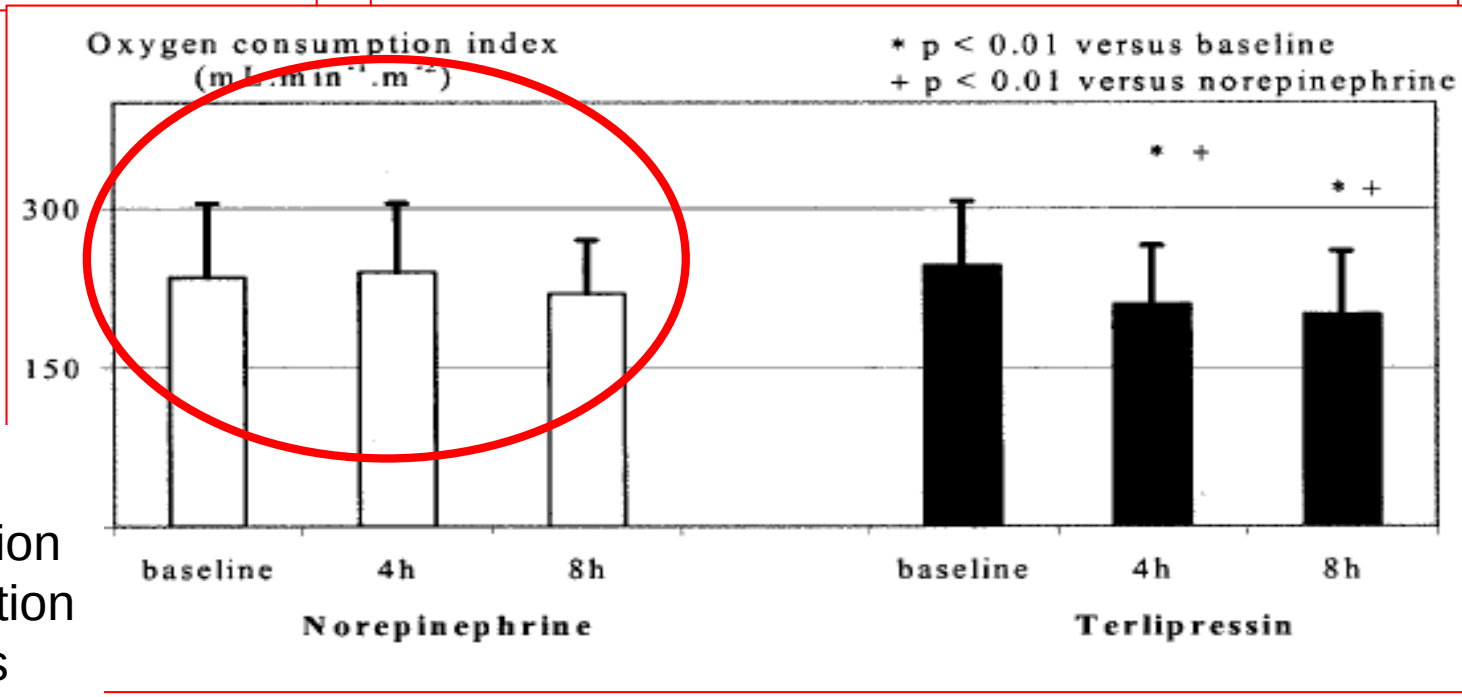


Martin et al Crit Care Med, 28: 2758-2765, 2000

Norepinephrine vs Terlipressine in septic shock





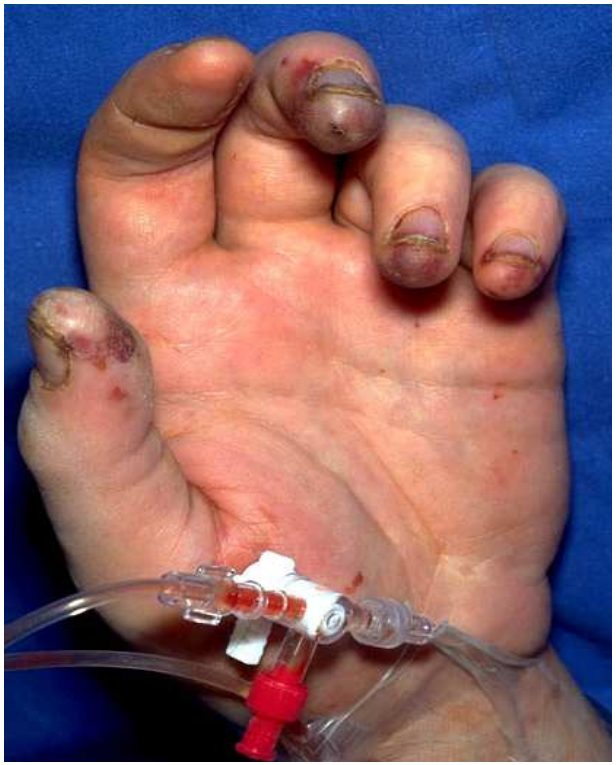


Albanese et al,
Crit Care 2005

Vasopressin:

-Strong splanchnic vasoconstriction
-Eferent glomerular vasoconstriction
-Deficient in many shock patients

3-rd CONCLUSION: NOREPINEPHRINE *AND NOT DOPAMINE*



Norepinephrine dose (mg/kg/min)	Mortality (%)
<0.1	20
0.1-0.3	24
>0.3	76

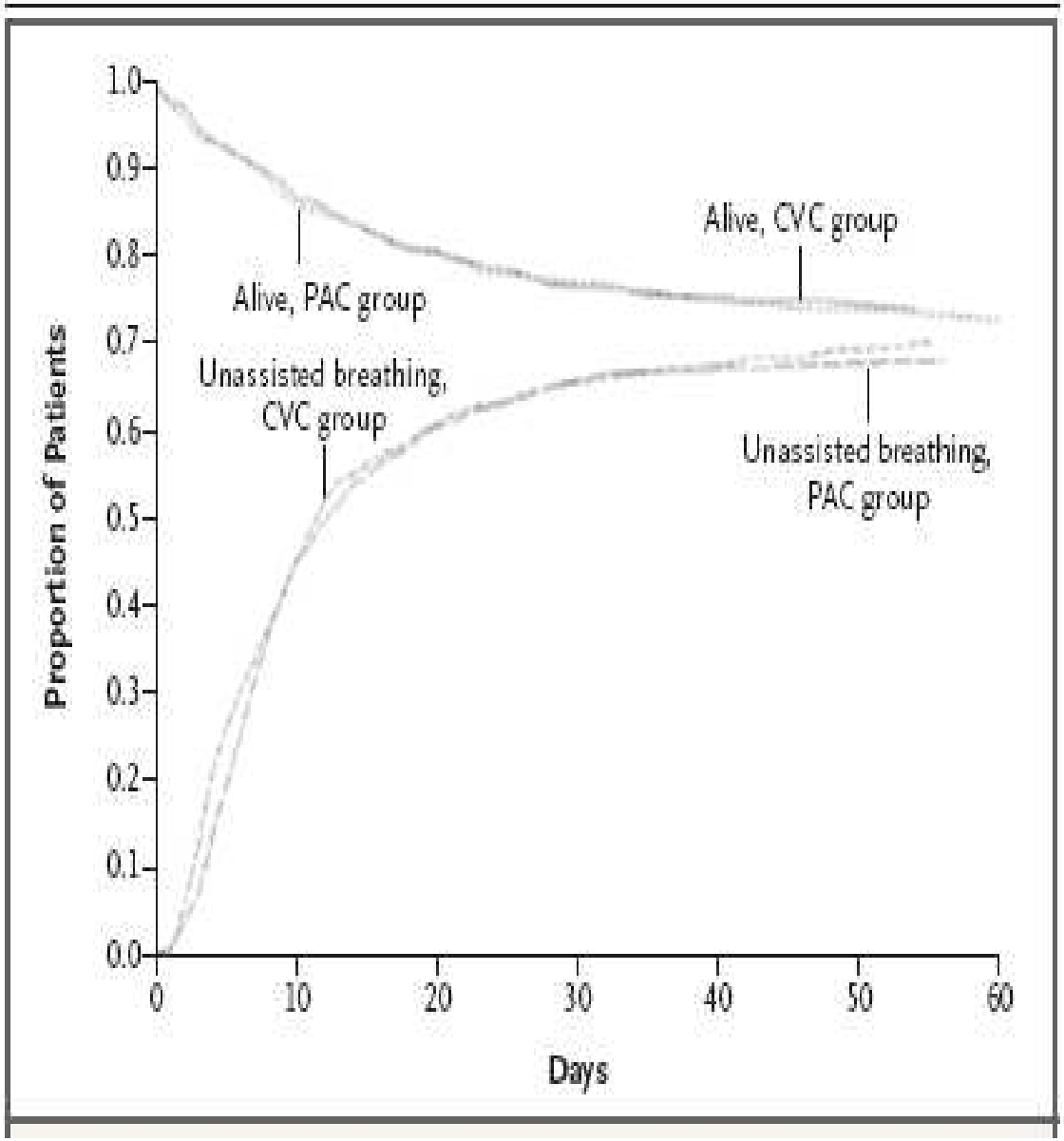
Myth 4

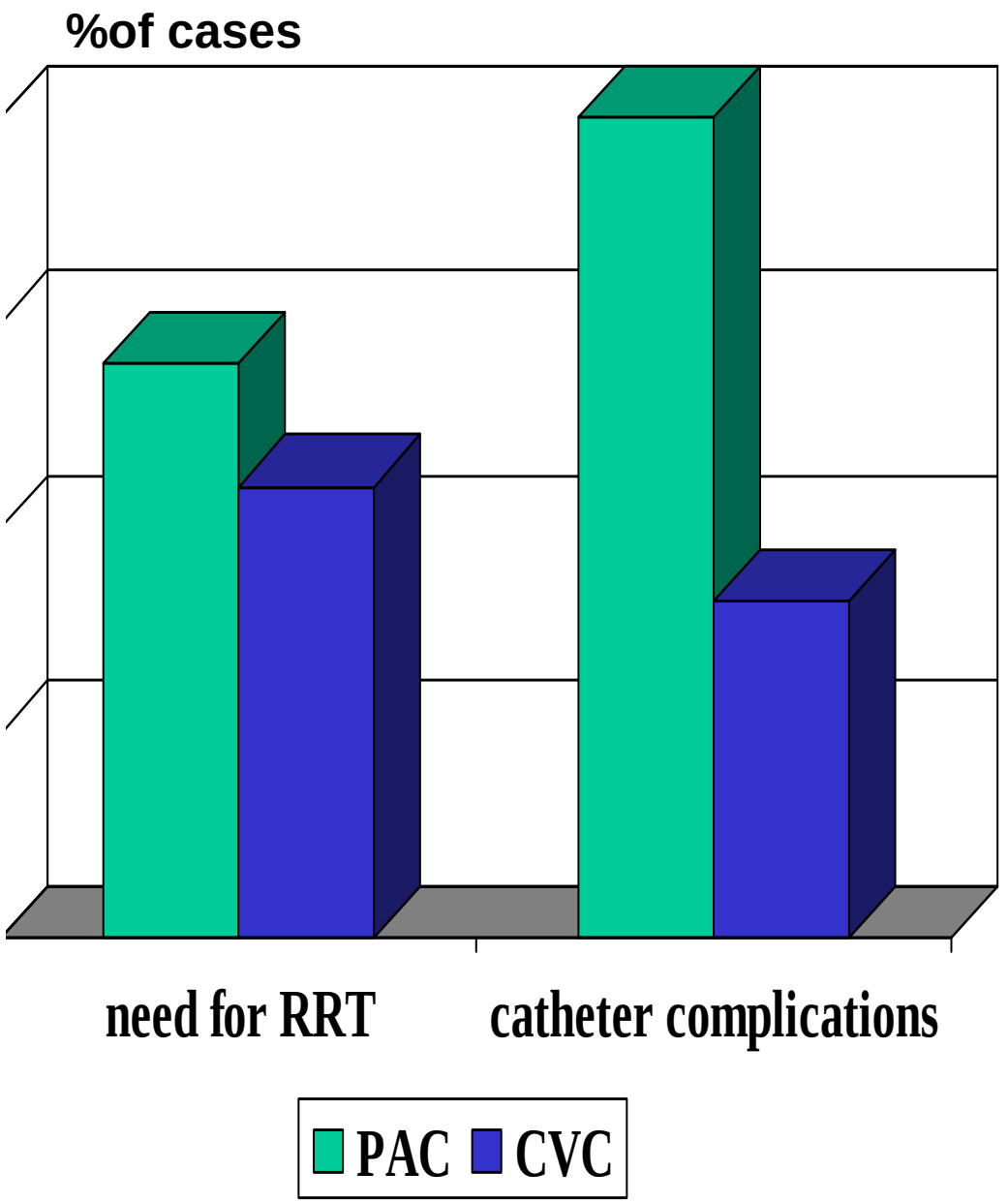
“FILLING”

MOST IMPORTANTLY

“IDEAL” SOLUTION

Use of Pulmonary artery Catheter

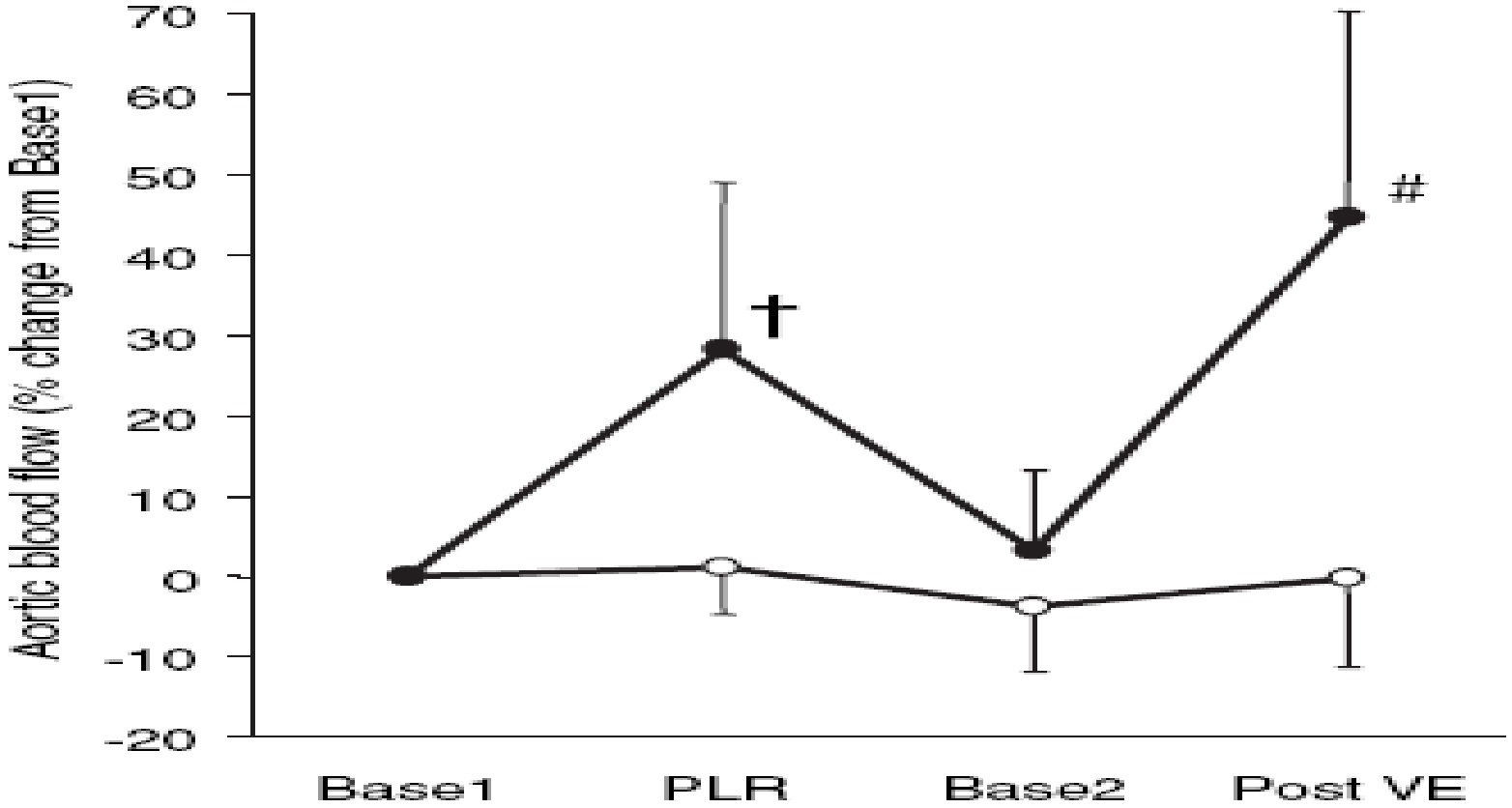




NEJM, 2006, 354, 2213

Clinical evaluation of intravascular filling status

Figure 1. Study design. *PLR*, passive leg raising; *VE*, volume expansion.



N=71, non-spontaneous breathing patients

Monnet et al, Critical Care Medicine, 2006

Conservative vs liberal fluid loading in ARDS patients – POSSIBLY BETTER FOR THE LUNGS

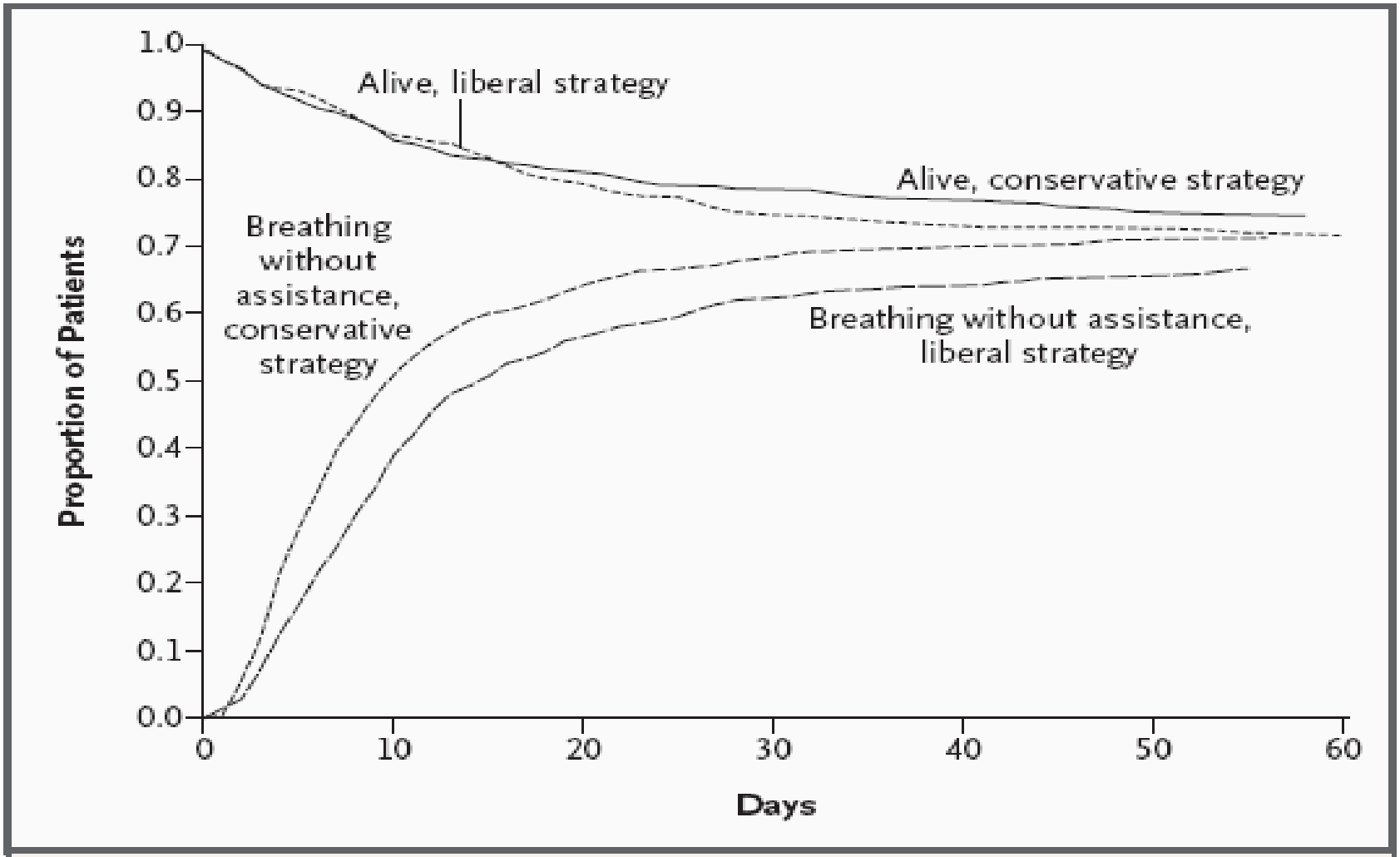
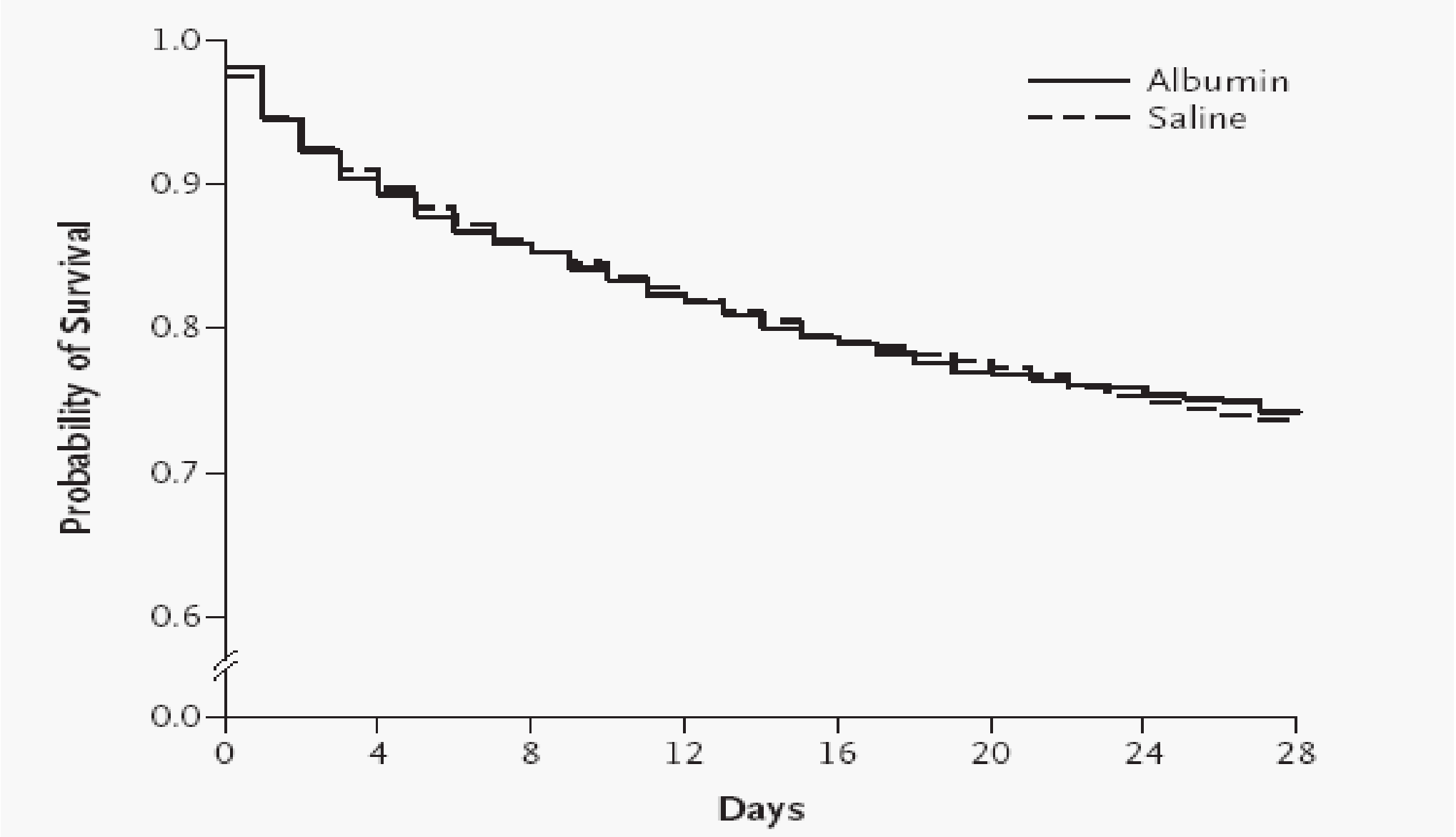


Figure 3. Probability of Survival to Hospital Discharge and of Breathing without Assistance during the First 60 Days after Randomization.

NEJM 2006, 354, 2564

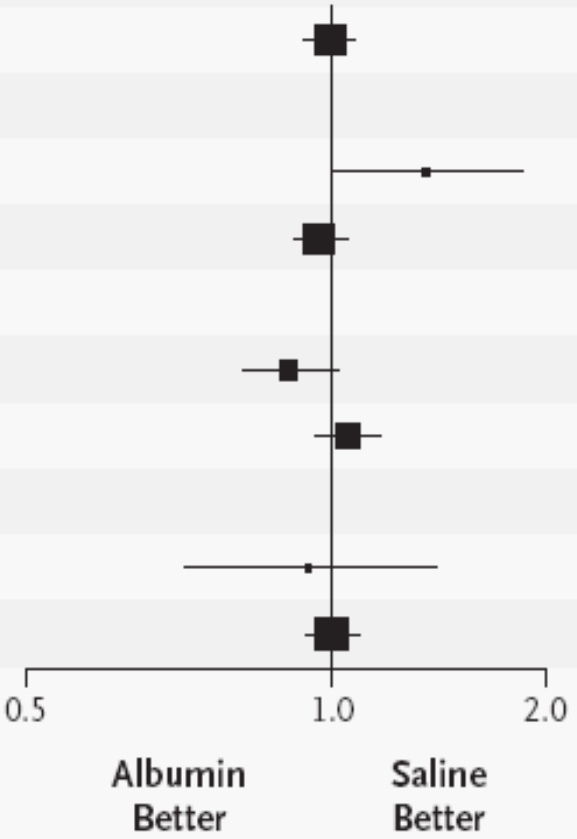
SURVIVAL:
albumin VS saline



SAFE study N Engl J Med 2004;350:2247-2256.

Global mortality risk in the « SAFE » study in critically ill patients (albumin vs isotonic saline)

Patients	Albumin Group	Saline Group	Relative Risk (95% CI)
	no. of deaths/total no.		
Overall	726/3473	729/3460	0.99 (0.91–1.09)
Trauma			
Yes	81/596	59/590	1.36 (0.99–1.86)
No	641/2831	666/2830	0.96 (0.88–1.06)
Severe sepsis			
Yes	185/603	217/615	0.87 (0.74–1.02)
No	518/2734	492/2720	1.05 (0.94–1.17)
ARDS			
Yes	24/61	28/66	0.93 (0.61–1.41)
No	697/3365	697/3354	1.00 (0.91–1.09)



SAFE study N Engl J Med 2004;350:2247-2256.

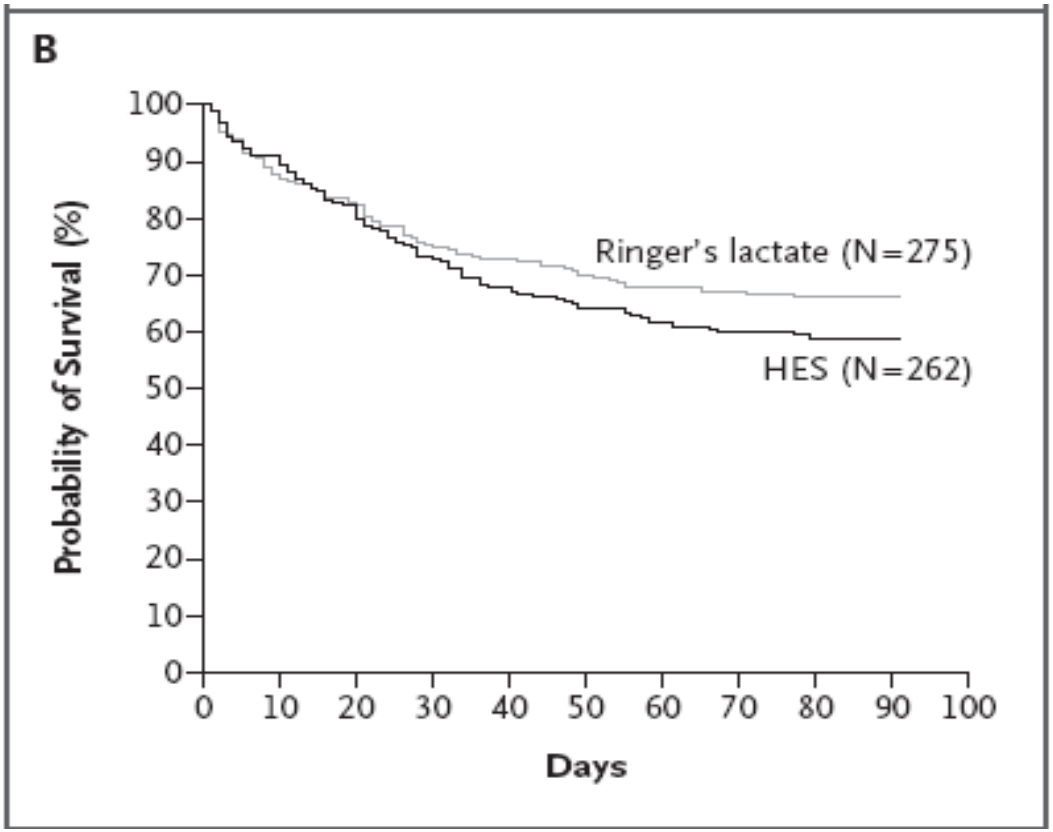
Fluids in ICU
Cochrane survey march 2007

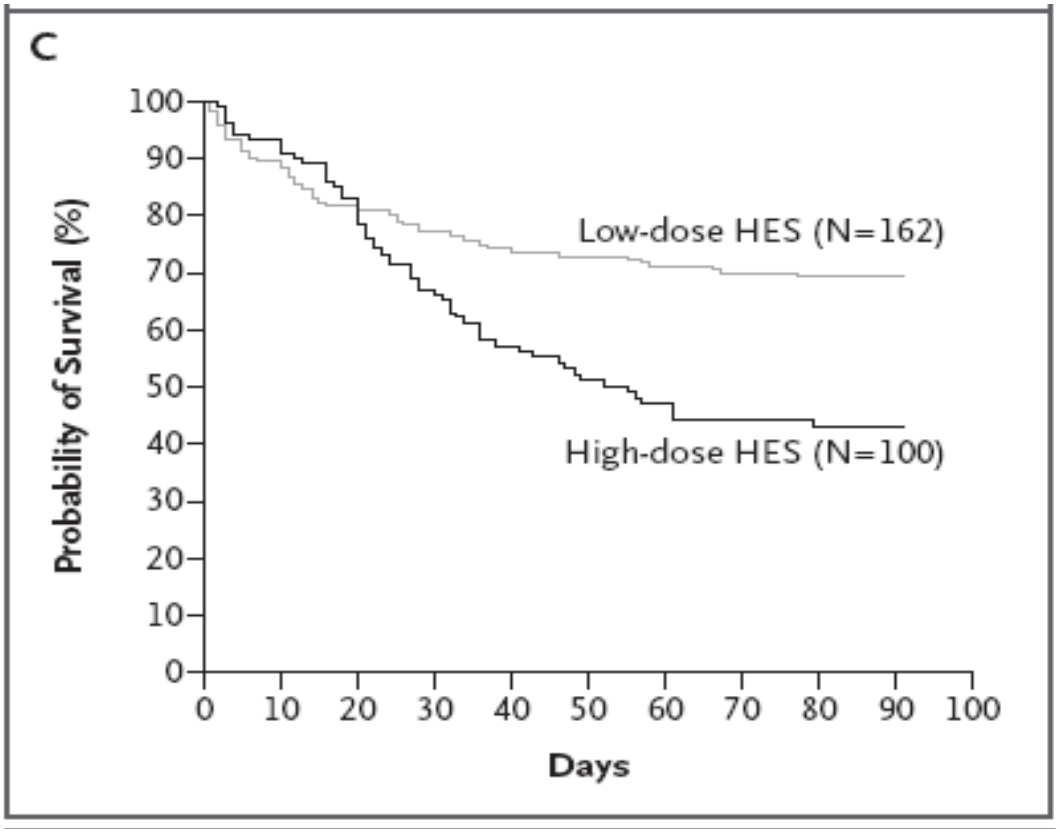
- **Albumin vs HES (24 trials): RR 1.14 (0.91-1.43)**
- **Albumin vs gelatine (7 trials): RR: 0.97 (0.68-1.39)**
- **Albumin vs Dextran (4 trials): RR.3.75 (0.4-33.4)**
- **Gelatin vs HES: (18 trials): RR: 1.0 (0.8-1.25)**

Conclusion: no difference !!

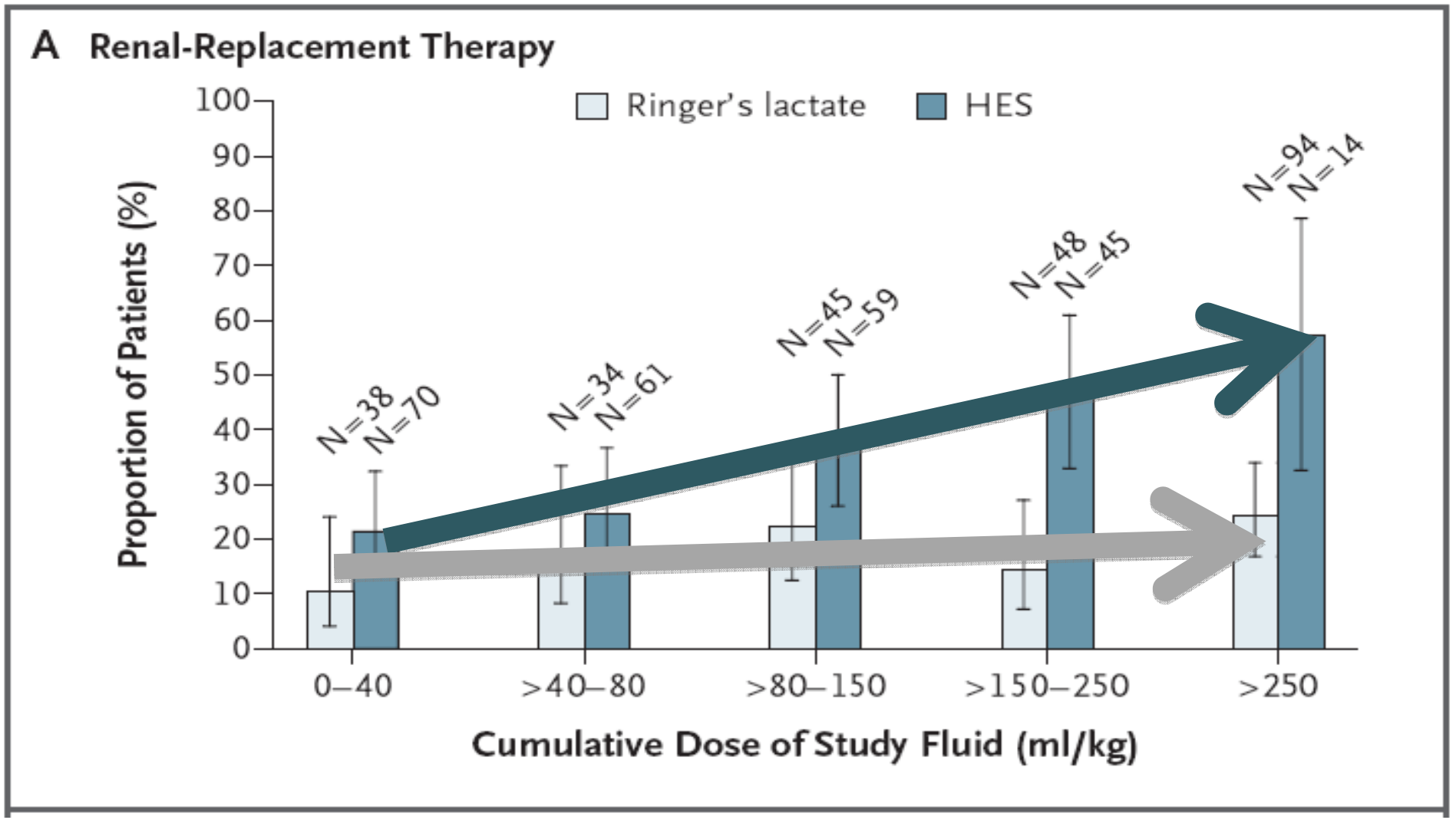
Bunn et al, Cochrane database, 2008

Fluid type and outcome

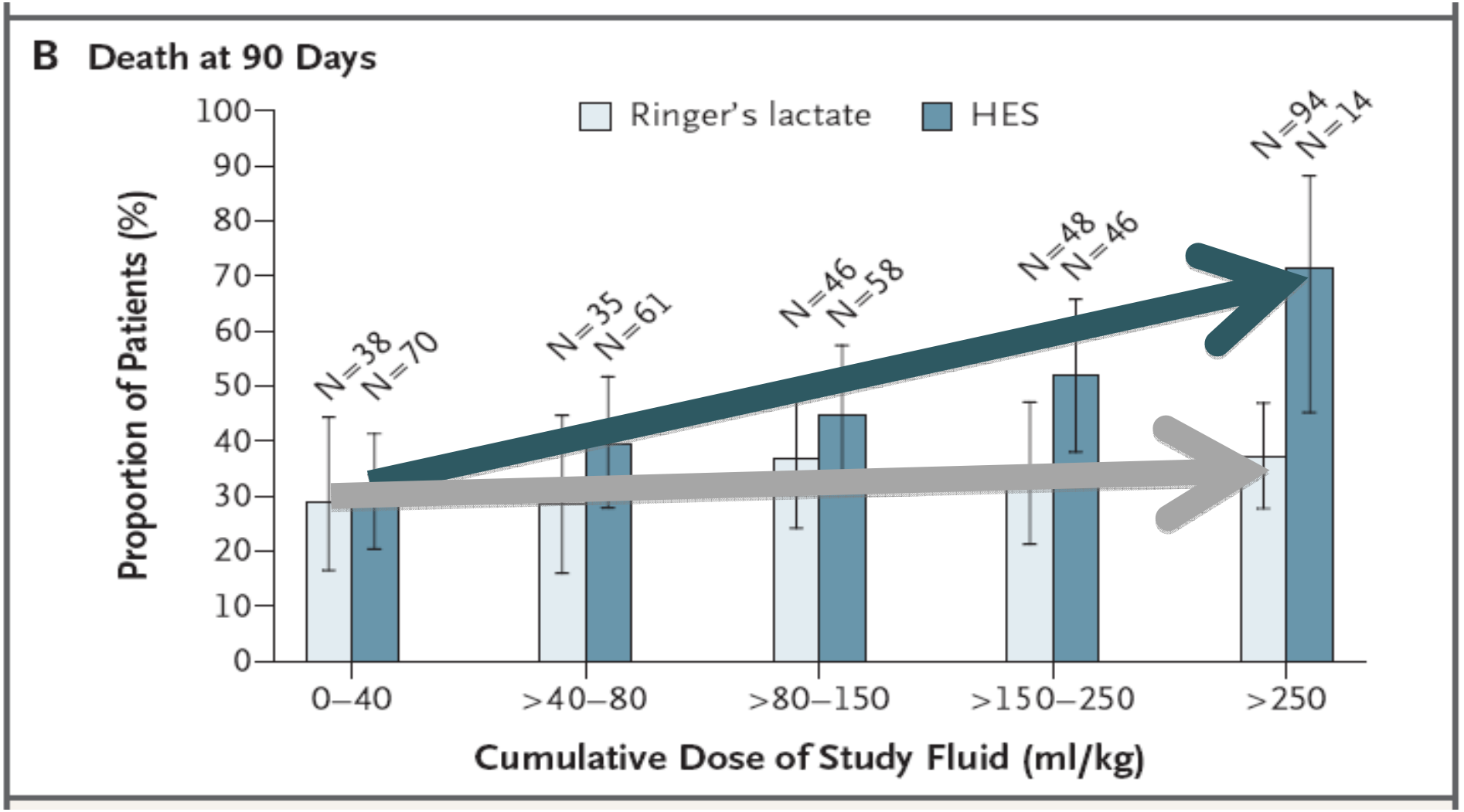




Brunkhorst et al, NEJM 2008



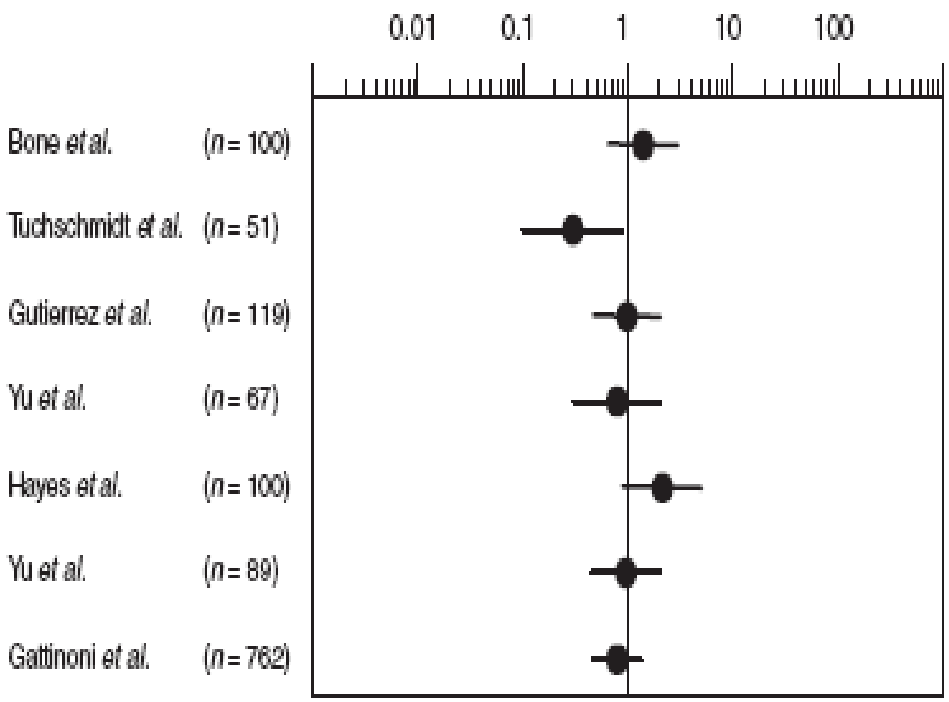
Brunkhorst et al, NEJM 2008



Brunkhorst et al, NEJM 2008

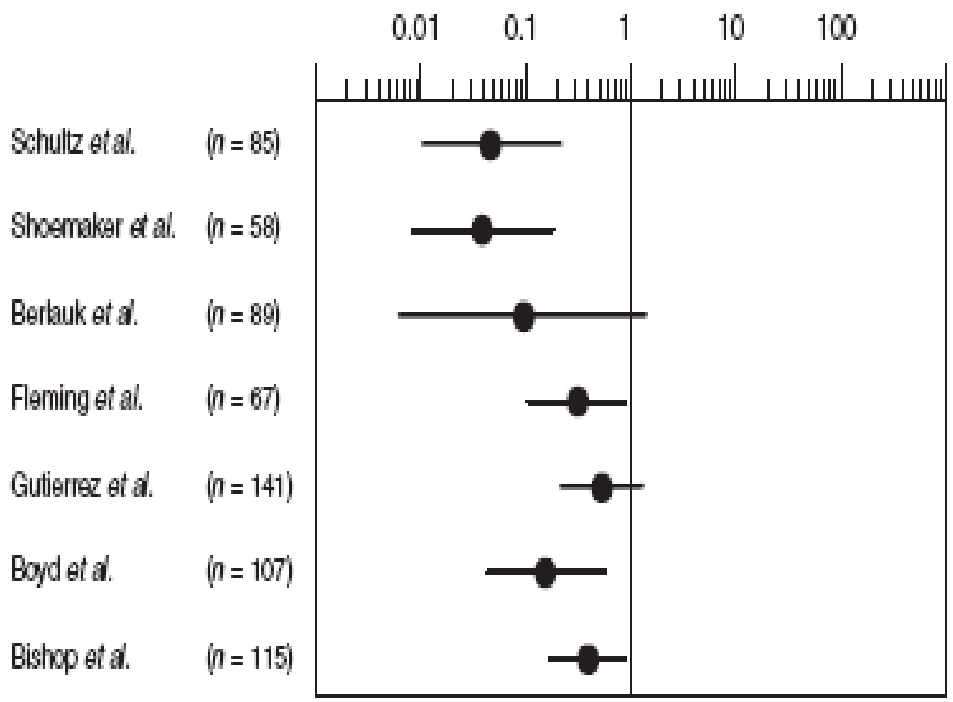
Timing of correction of tissue perfusion on outcome

Figure 1



Odds ratio and 95% confidence interval for studies (total of 1031 patients) attempting to improve tissue perfusion after onset of tissue hypoxic can be expected. No beneficial effect on mortality was seen. (Modified from [30].)

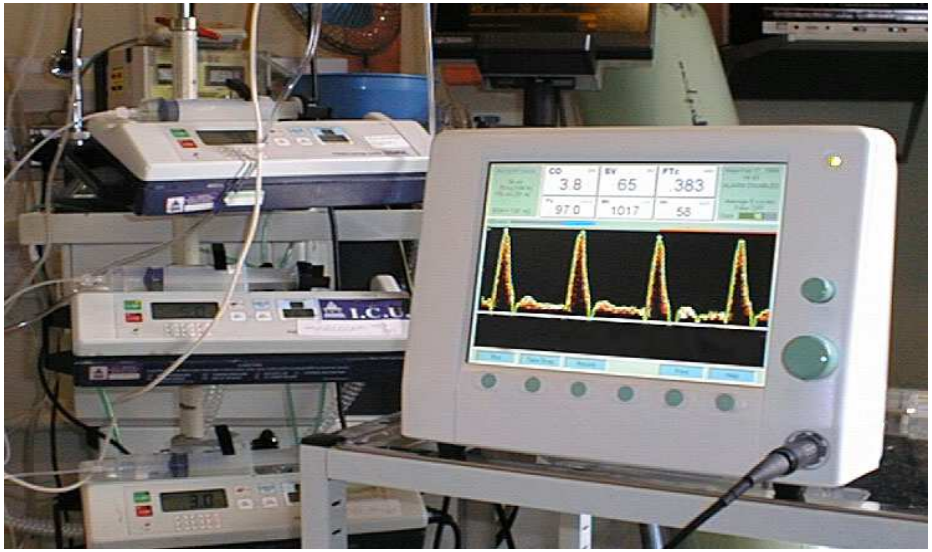
Figure 2

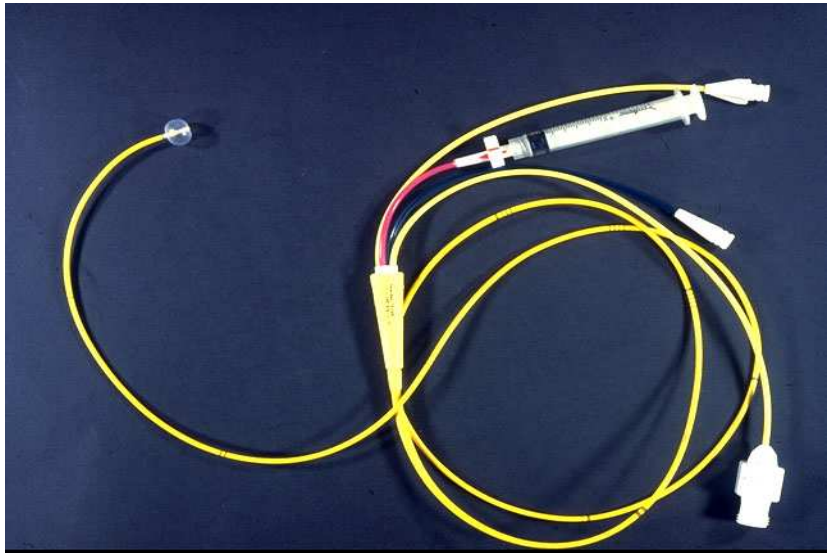


Odds ratio and 95% confidence interval for studies (total of 662 patients) attempting to improve tissue perfusion before onset of tissue hypoxic can be expected. Beneficial effect on mortality were seen. (Modified from [30].)

Boldt et al, Crit Care 2002

4-th CONCLUSION: SALINE, CVP + GOOD CLINICAL PRACTICE, POSIBIL RINGER *MACROMOLECULAR SOLUTIONS*

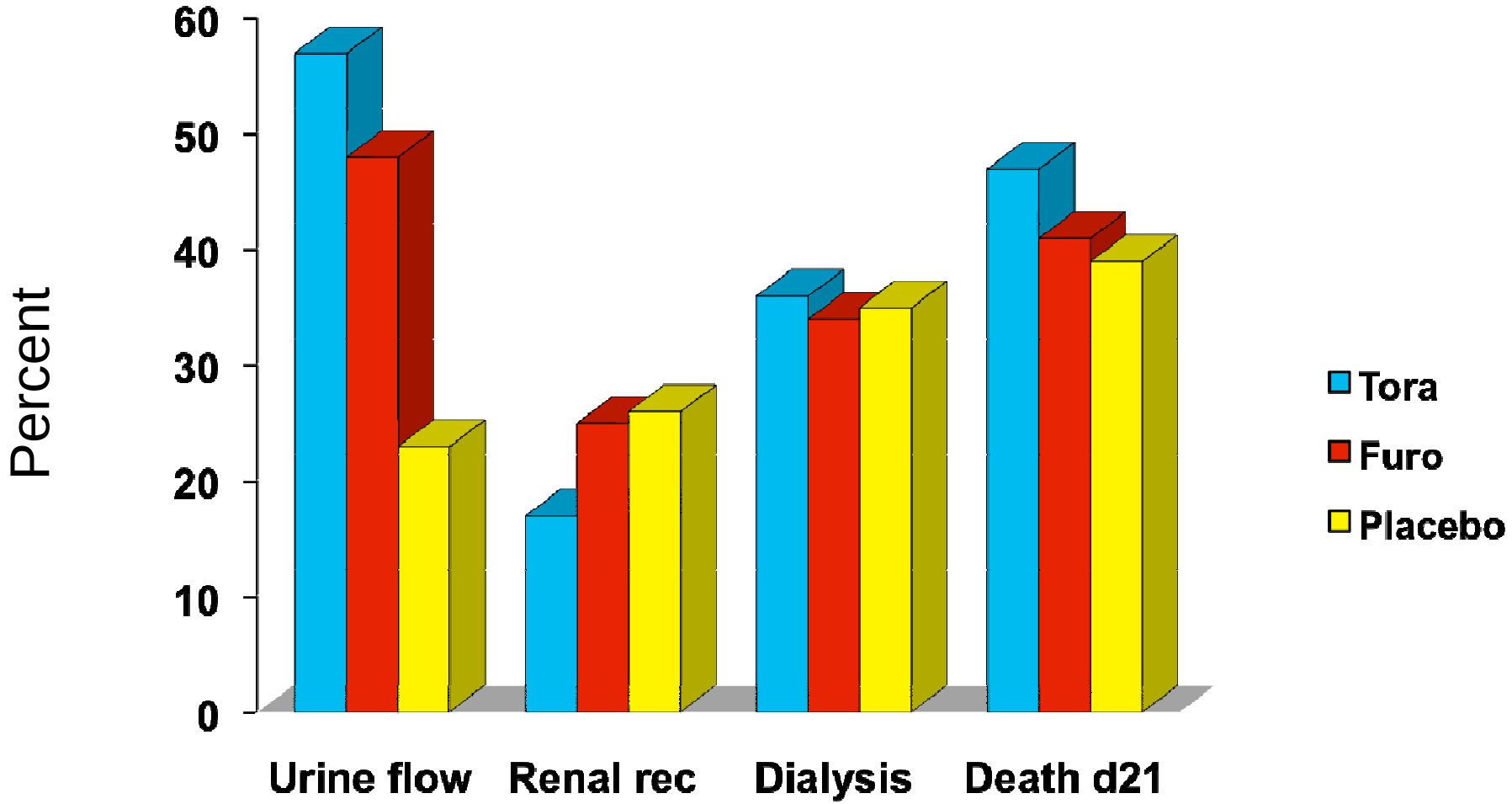




MYTH 5

FUROSEMID COMPULSORY?

Loop Diuretics and ARF: double-blind, randomized trial



Shilliday et al. Nephrol Dial Transplant 11,1684,1996.

Loop Diuretics and ARF: double-blind, randomized trial

Variable	Unadjusted	OR (95% CI) Covariate adjusted	Covariate and propensity score adjusted
In-hospital mortality	1.37 (0.97-1.92)	1.65 (1.05- 2.58)	1.68 (1.06-2.64)
Nonrecovery of renal function	1.53 (1.08-2.15)	1.70 (1.14-2.53)	1.79 (1.19-2.68)
Death or nonrecovery	1.48 (1.02-2.12)	1.74 (1.12-2.68)	1.77 (1.14-2.76)

Mehta et al JAMA 288: 2547-2553, 2002

Diuretics and outcome of AKI - metaanalysis

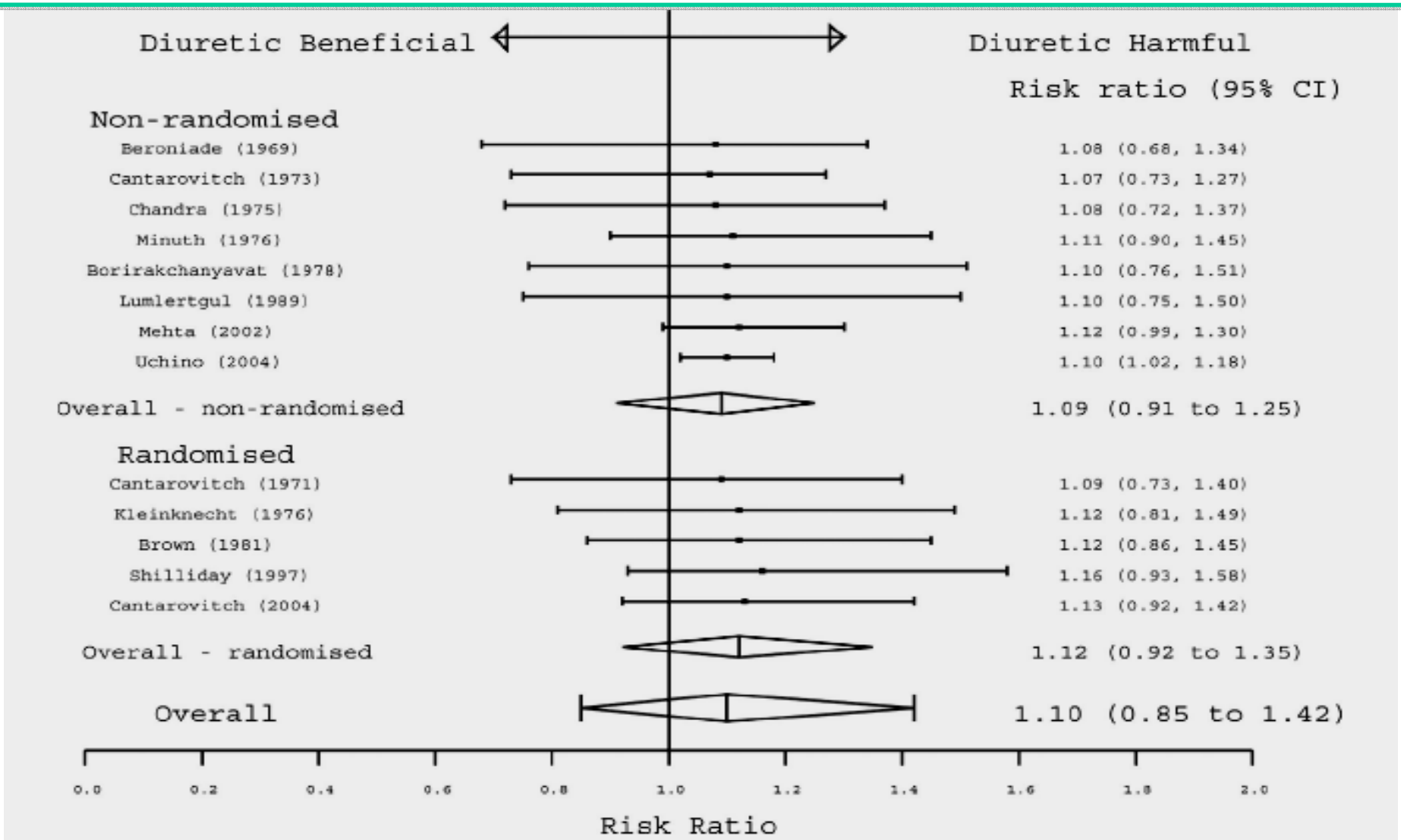


Figure 1. Forest plot showing effect of randomized and nonrandomized studies on mortality treatment effect as risk ratio. *Small solid squares*, study estimates; *vertically capped horizontal lines*, 95% credible intervals (*CI*); *vertical lines within vertically capped diamond-shaped boxes*, subgroup and overall point estimates and 95% CI; *vertical straight line*, the null effect.

Sampath et al, Crit Care Med, 2007

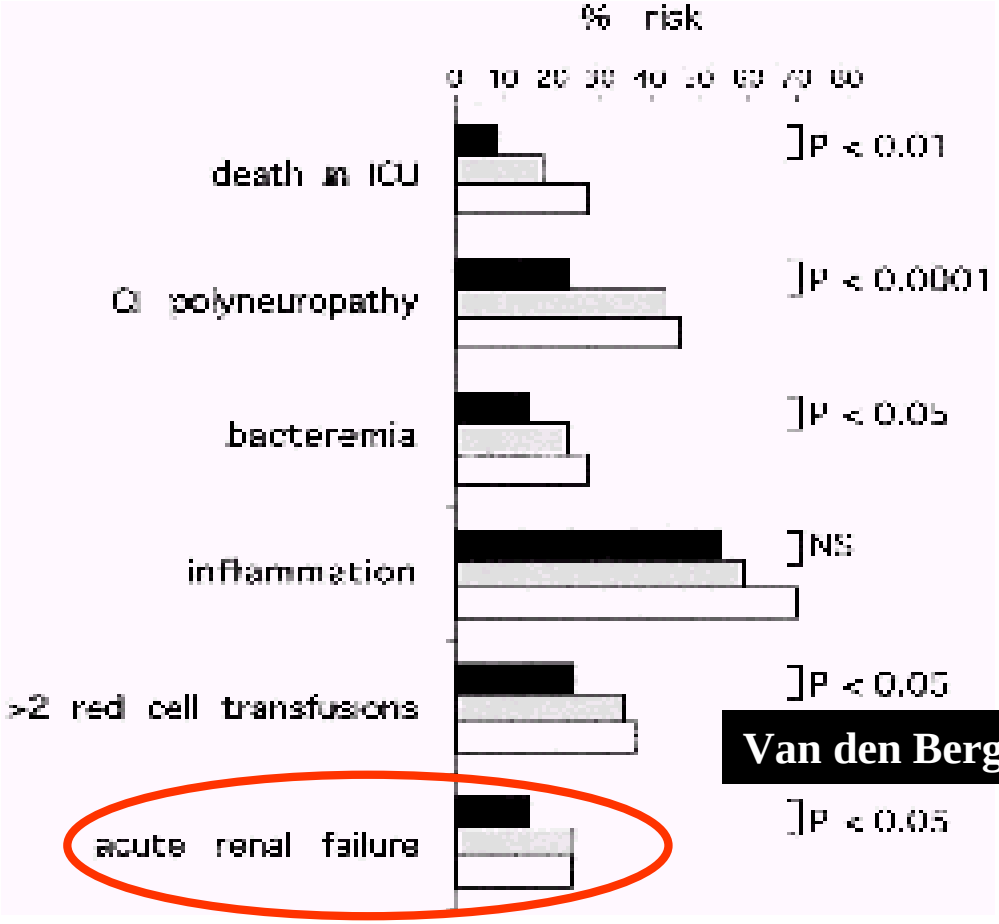
5-th CONCLUSION: FUROSEMID – PROBABLY, but
AFTER CORRECT FILLING (!)

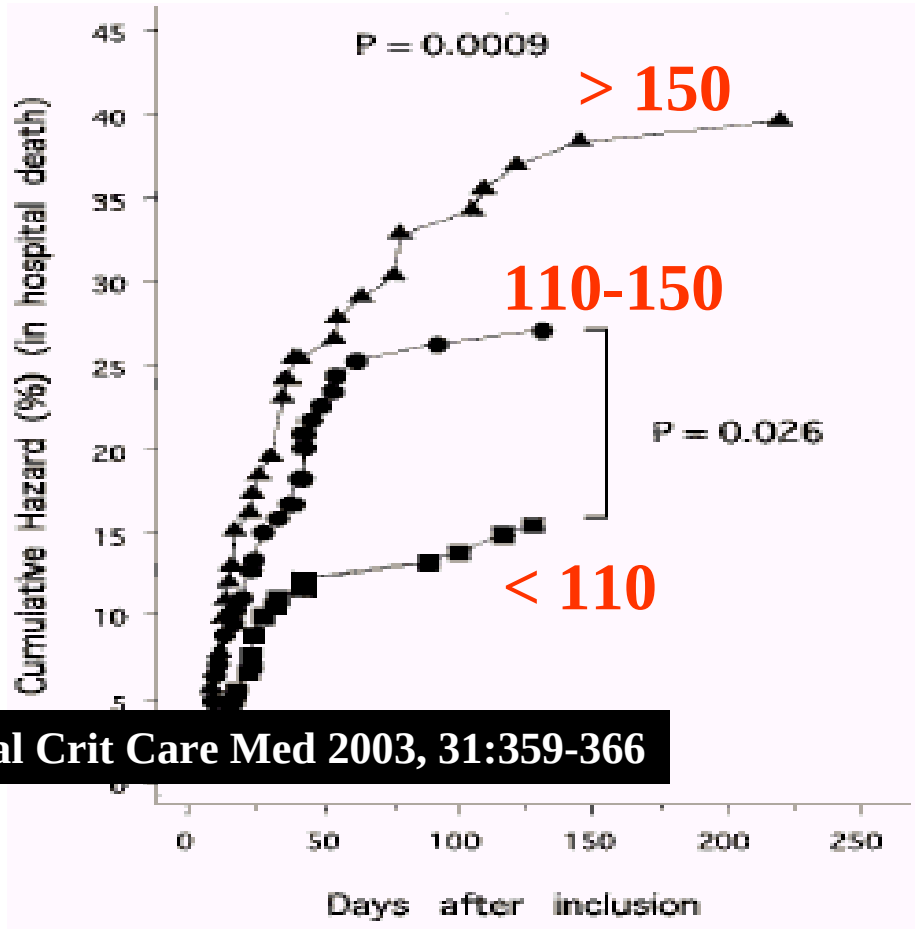
PROMISSES OR CERTITUDES?

1. **Insulin – intensive glycaemic control**
2. **EPO**
3. **Activated Protein C**
4. **Steroids**
5. **Atrial Natriuretic Factor - ANF**

6. **Growth factors - IGF I; Endothelin antagonist receptors; Tyroxin; PGE_1**

1) Effect of control of mean blood glucose in ICU patients



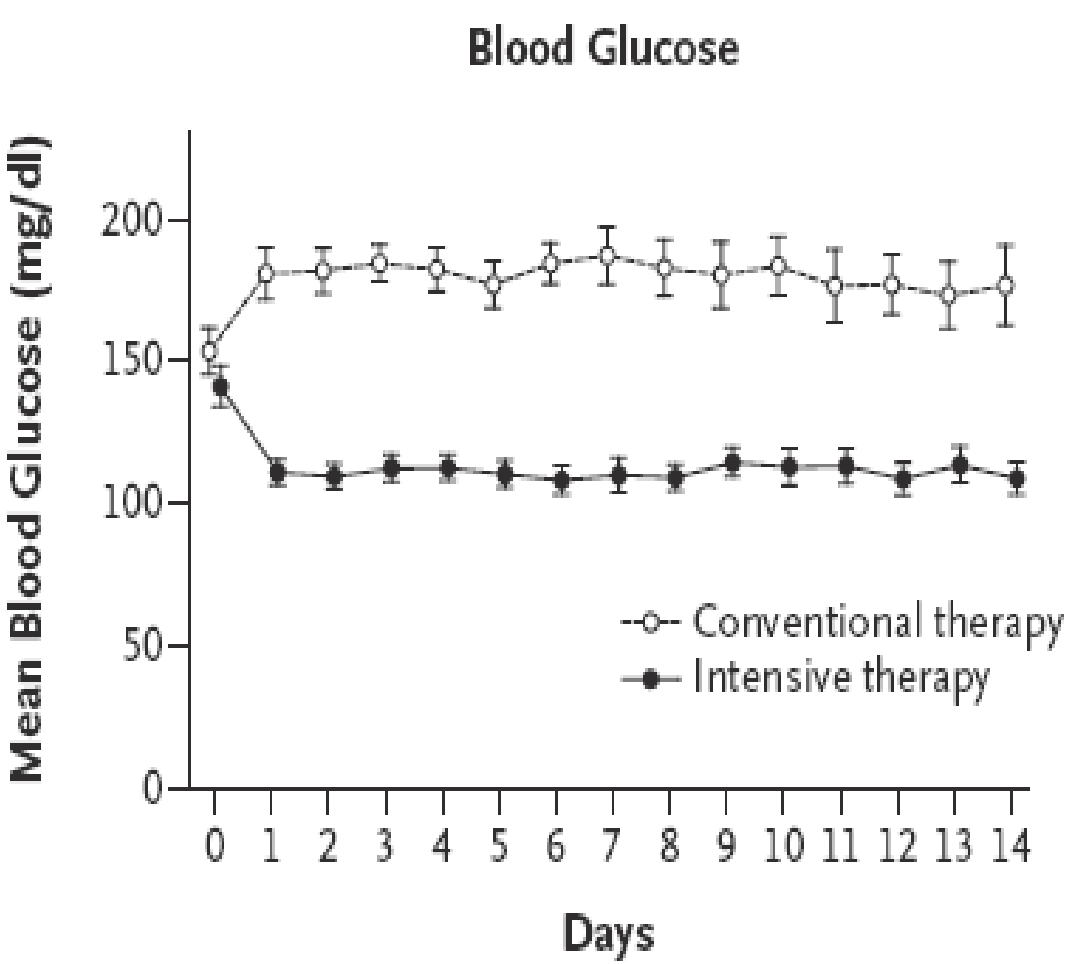


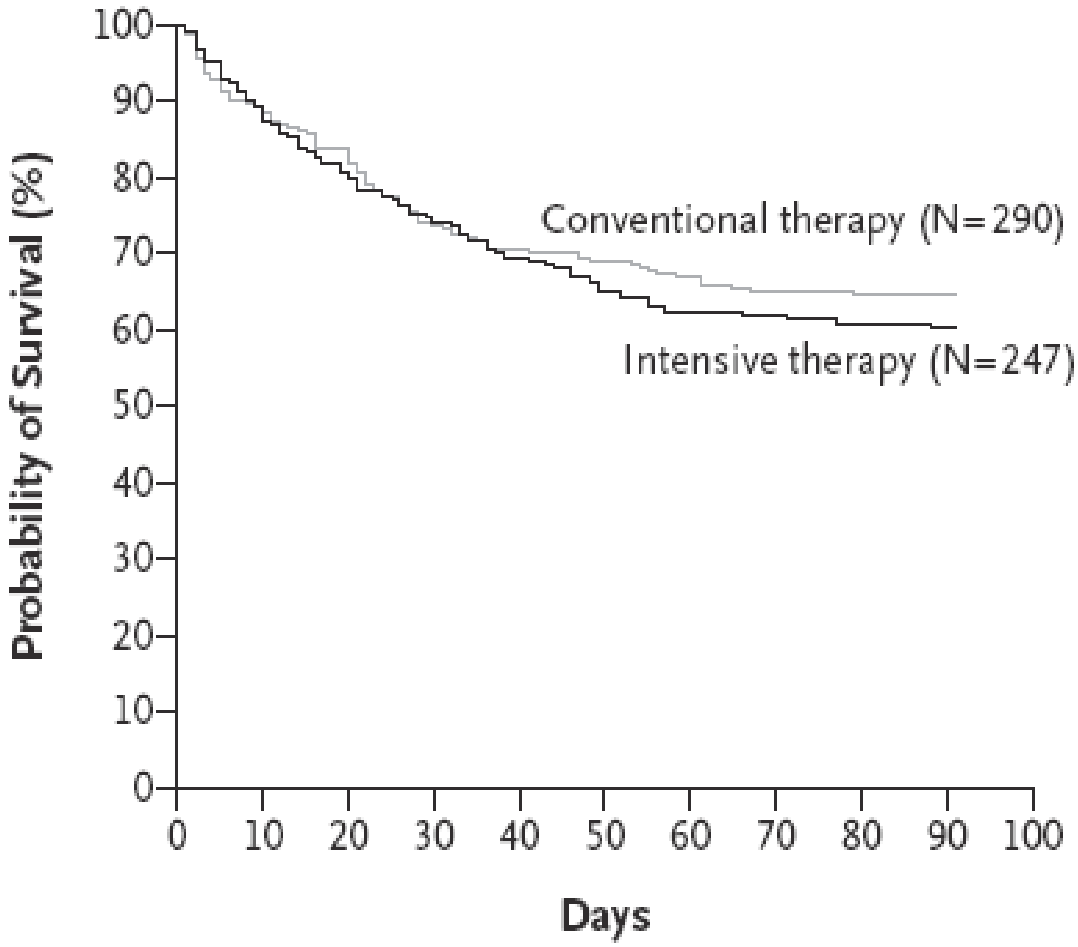
Van den Berghe et al Crit Care Med 2003, 31:359-366

Percentage of risk for several complications in ICU patients with stay > 5 days

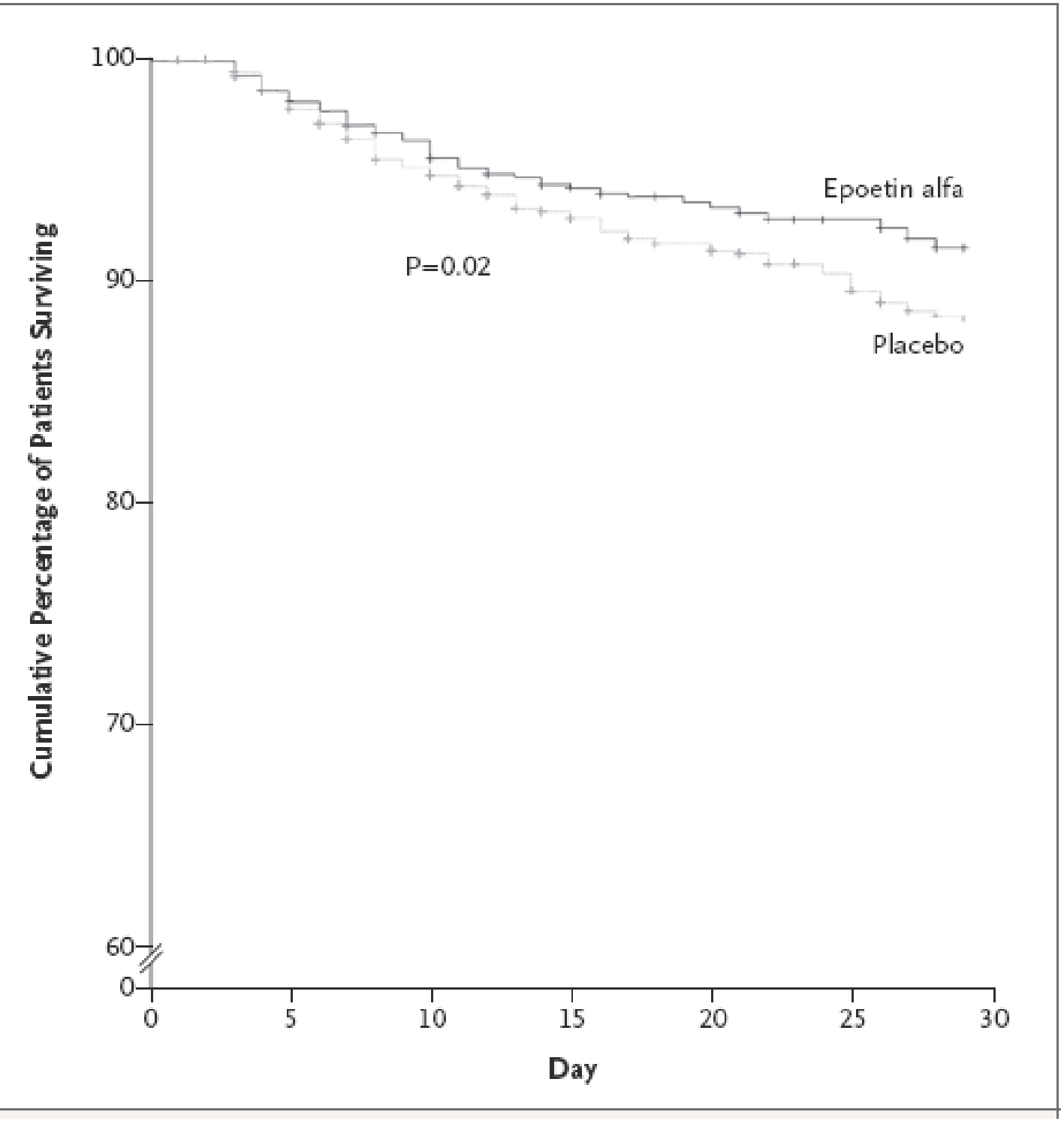
Cumulative risk of hospital death in ICU patients with stay> 5 days

Survival:
intensive insulin therapy or conventional insulin therapy in severe sepsis





Brunkhorst et al, N Engl J Med 2008;358:125-139.



2) EPO:

Cumulative patient survival in critically ill patients

EPO: n 733
Control: n 722

Corwin et al, N Engl J Med 2007; 357:965-976.

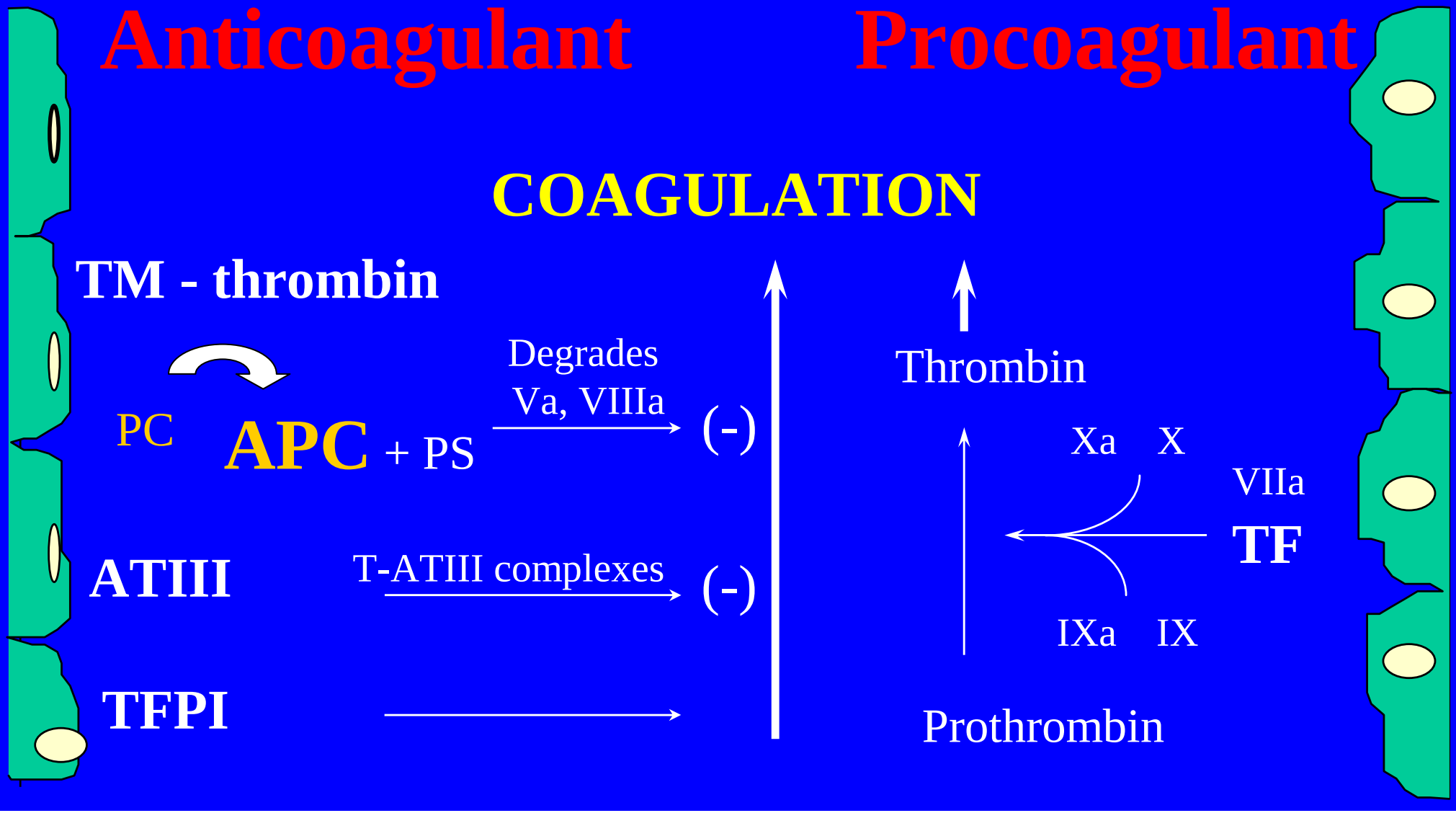
The New England
Journal of Medicine

VOLUME 344 MARCH 8, 2001 NUMBER 10

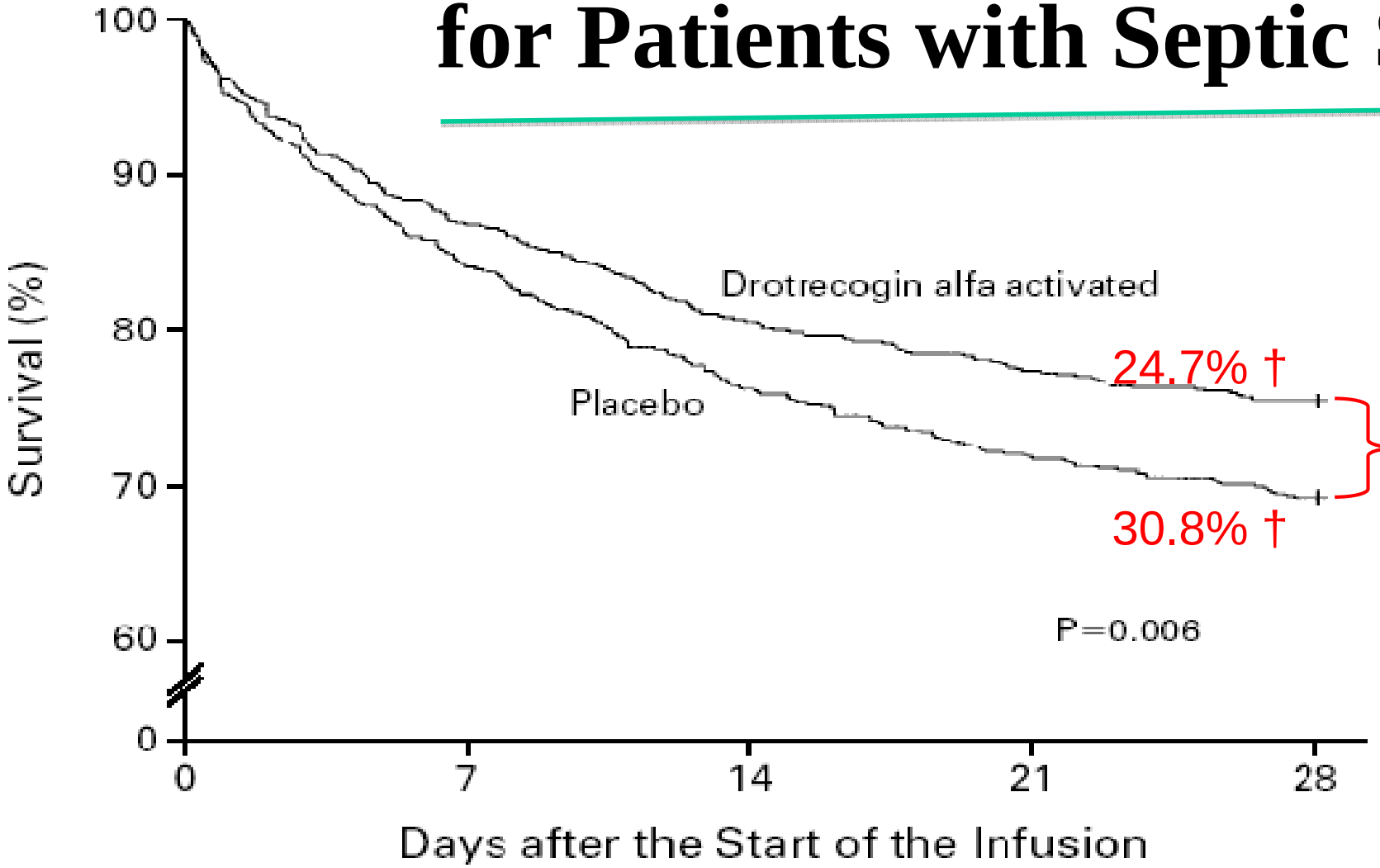
EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

GORDON R. BERNARD, M.D., JEAN-LOUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*

Coagulation

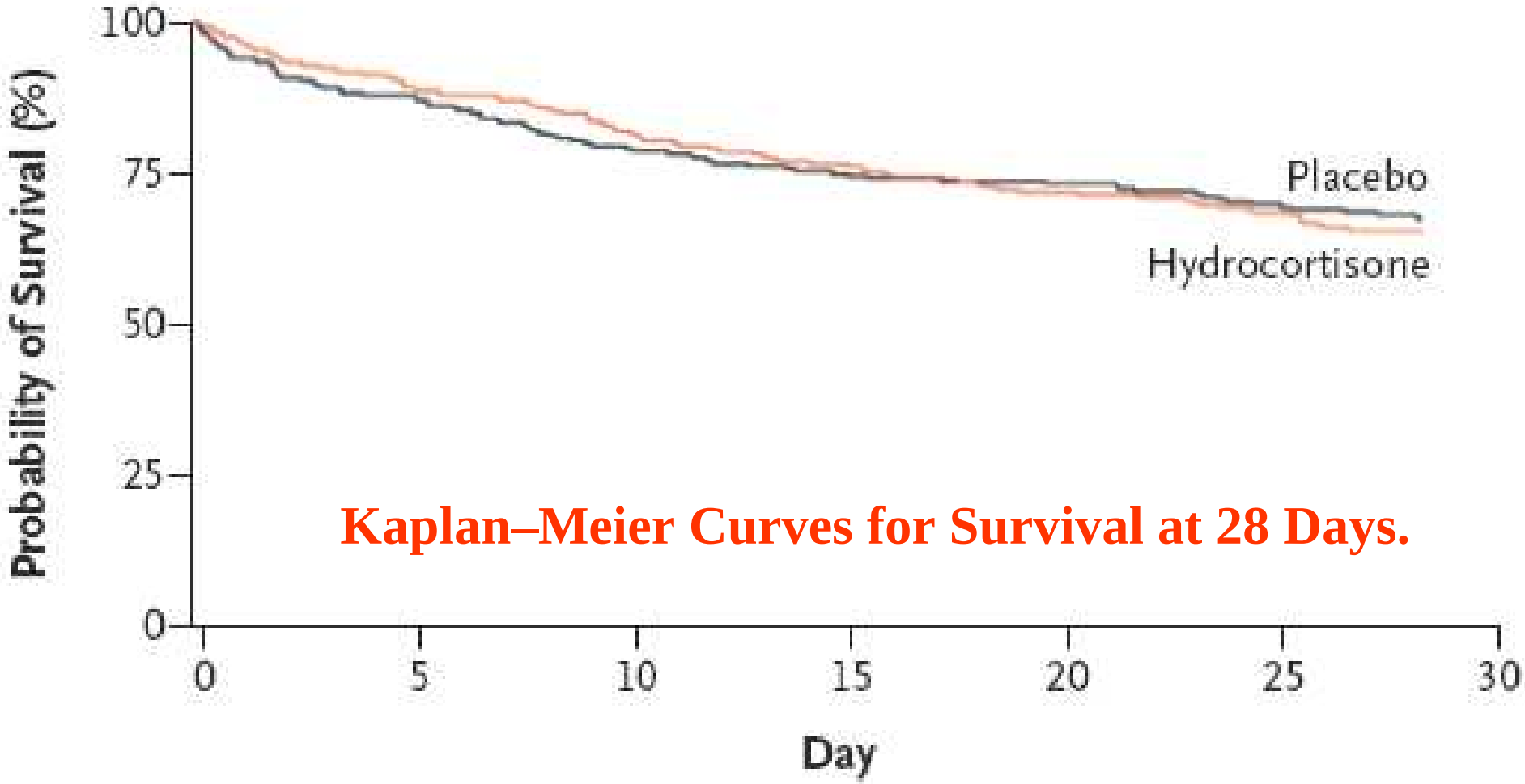


APC Therapy for Patients with Septic Shock



No. at Risk					
Drotrecogin alfa activated	850	737	684	657	640
Placebo	840	705	639	602	581

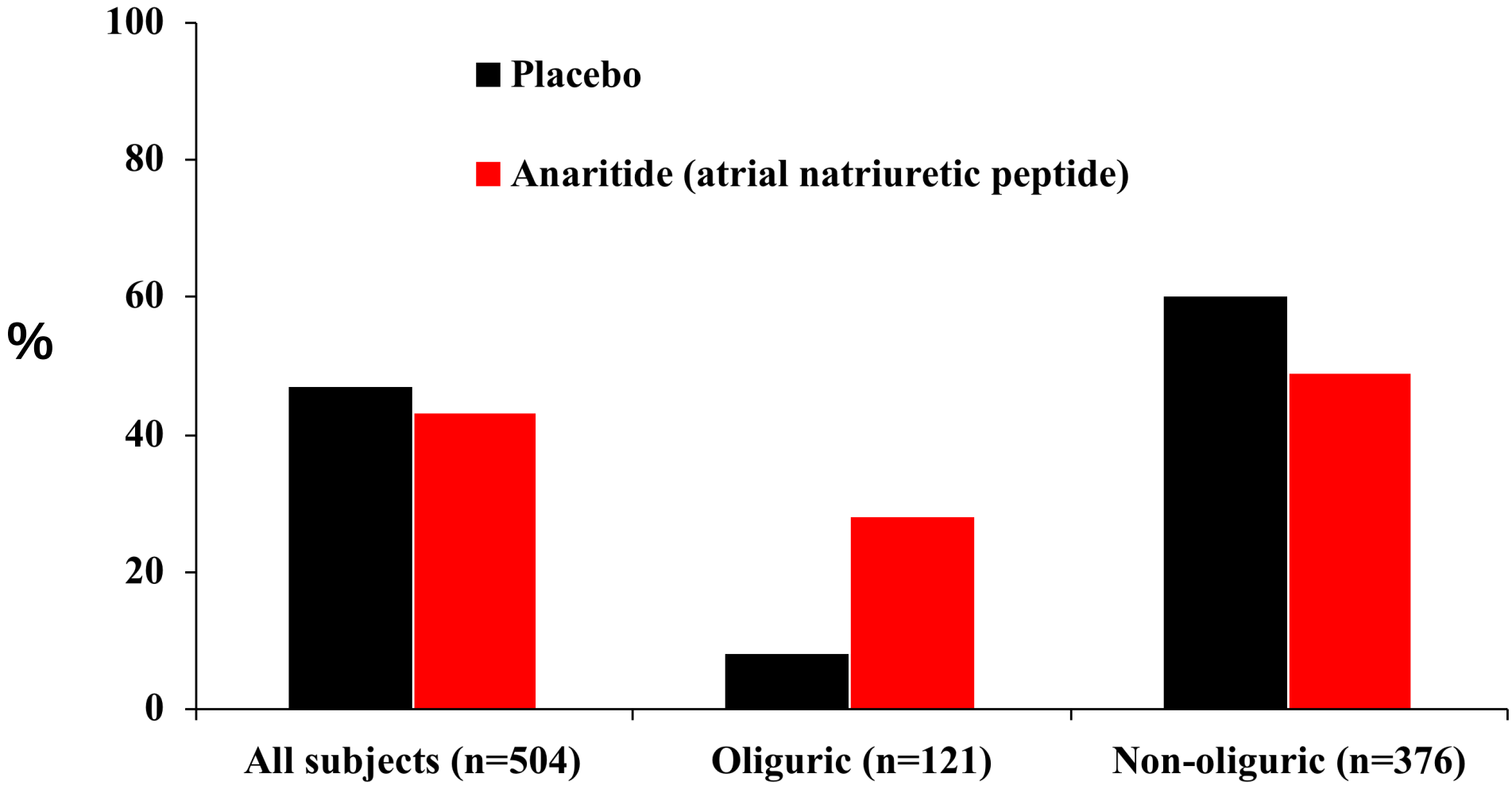
Hydrocortisone Therapy for Patients with Septic Shock



Kaplan–Meier Curves for Survival at 28 Days.

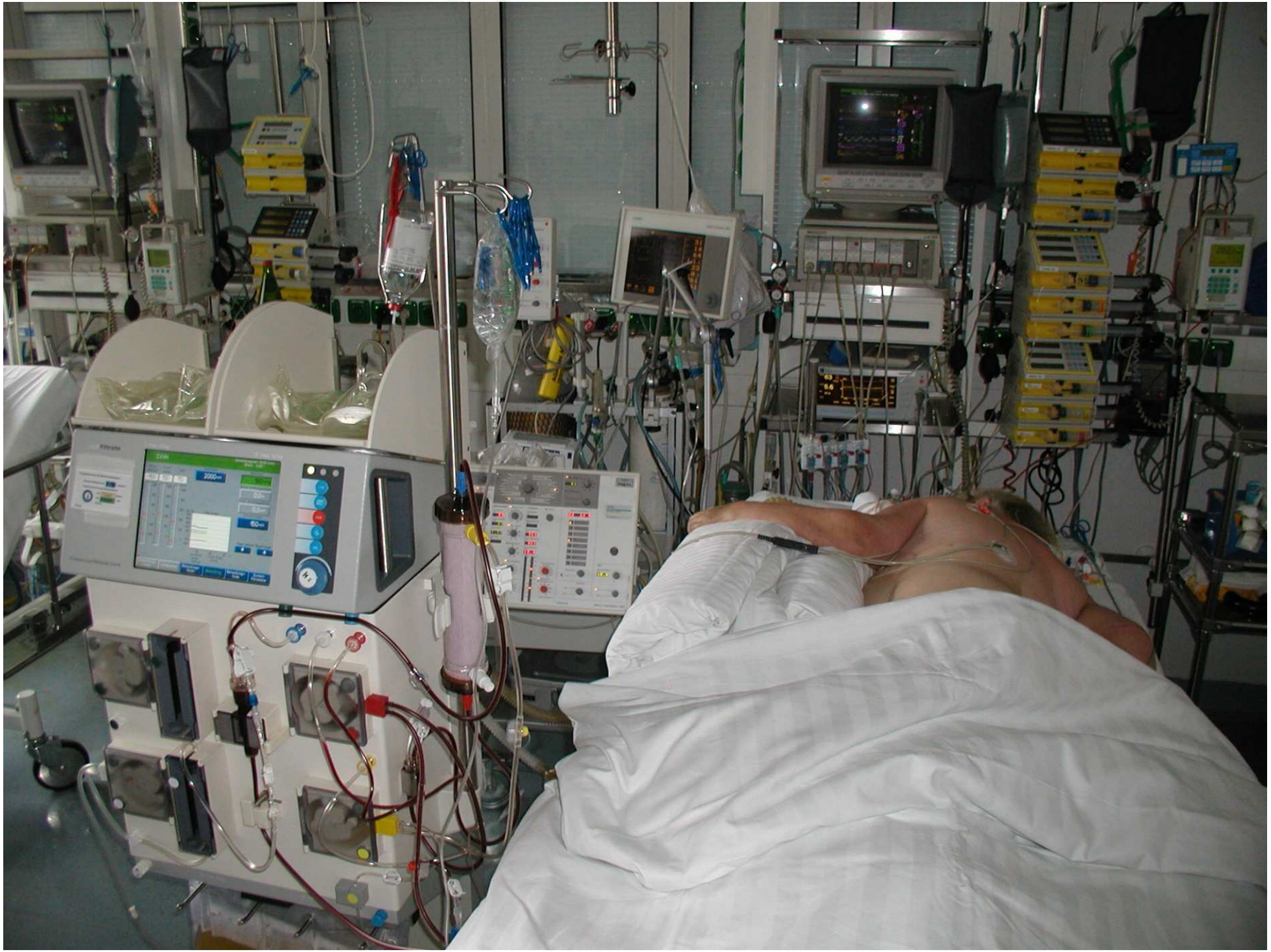
Sprung et al, N Engl J Med 2008;358:111-124.

Anaritide:
21-Day Dialysis-Free Survivorship.



* p=0.005 A vs. P

Lewis et al, AJKD 2000



When to initiate acute dialysis ?
Generally accepted indications

- Acute (life-threatening) hyperkalemia
- Severe volume overload (pulmonary edema)
- Severe metabolic acidosis
- Uremic organ complications (e.g. pericarditis)

- ‚Prophylactic‘ dialysis:
  - Creatinine clearance, e.g. 0.1-0.15 ml/kg/min ?
  - Serum urea concentrations, e.g. 150, 200, ... mg/dl ?

Intensive Care Med (1999) 25: 805–813

ORIGINAL

L. G. Gettings
H. N. Reynolds
T. Scalea

Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early vs. late

- Retrospective analysis (100 trauma patients, 1989-97)
- „Early“: BUN<60 mg/dl; „late“: BUN> 60 mg/dl
- „Early“ starters had significantly better survival compared to „late“ starters: 39% vs. 20.3% (p=0.041)

Timing of initiation of RRT and prognosis in AKI-PICARD group

	RR for death (CI)*	RR for death (CI)**	RR for death (CI)***
Low BUN at start RRT < 76 mg/dl	1.0	1.0	1.0
High BUN at start RRT > 76 mg/dl	1.85 (1.16-2.96)	2.07 (1.30-3.29)	1.97 (1.21-3.20)

•Adjusted for age, hepatic failure, sepsis,
•thrombocytopenia,and serum creatinine
•and stratified by site and initial dialysis modality,

** Adjusted for propensity score alone

*** Adjusted for co)variates and propensity score

Liu et al cJASN 1: 915–919, 2006.

Treatment practices in RRT for AKI

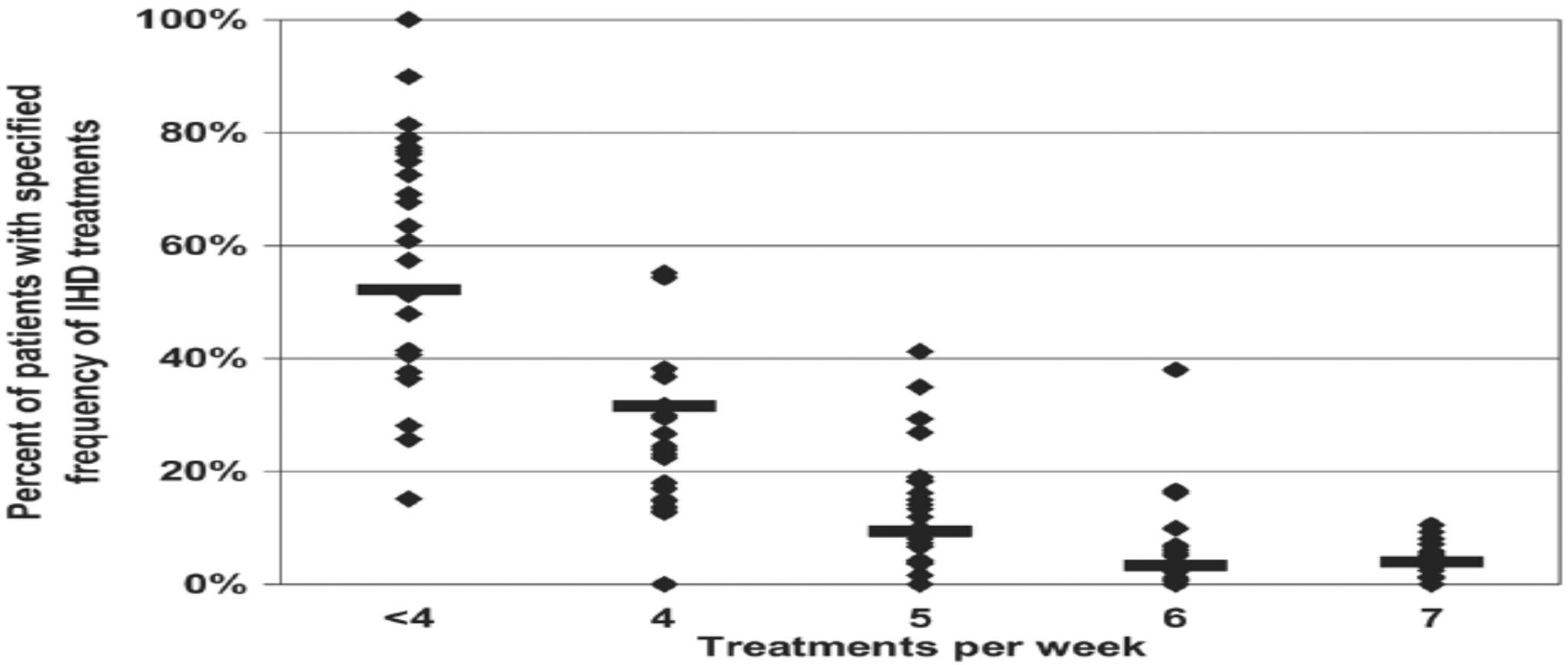


Figure 1.
Percent of patients with specified frequency of intermittent hemodialysis (IHD) treatment. Horizontal lines represent pooled data from all sites while the symbols represent data for individual sites. Data for treatment schedules less frequent than four-times per week (two-times per week, three-times per week and alternate-day treatment schedules) are pooled.

Overberger et al, cJASN,2008

Daily HD and prognosis of patients with ARF

TABLE 3. OUTCOMES ACCORDING TO TREATMENT GROUP.*

	ALTERNATE-DAY HEMODIALYSIS (N=80)	DAILY HEMODIALYSIS (N=80)	P VALUE
Mortality — no. (%)†	37 (46)	22 (28)	0.01
Resolution of acute renal failure — days	16±6	9±2	0.001

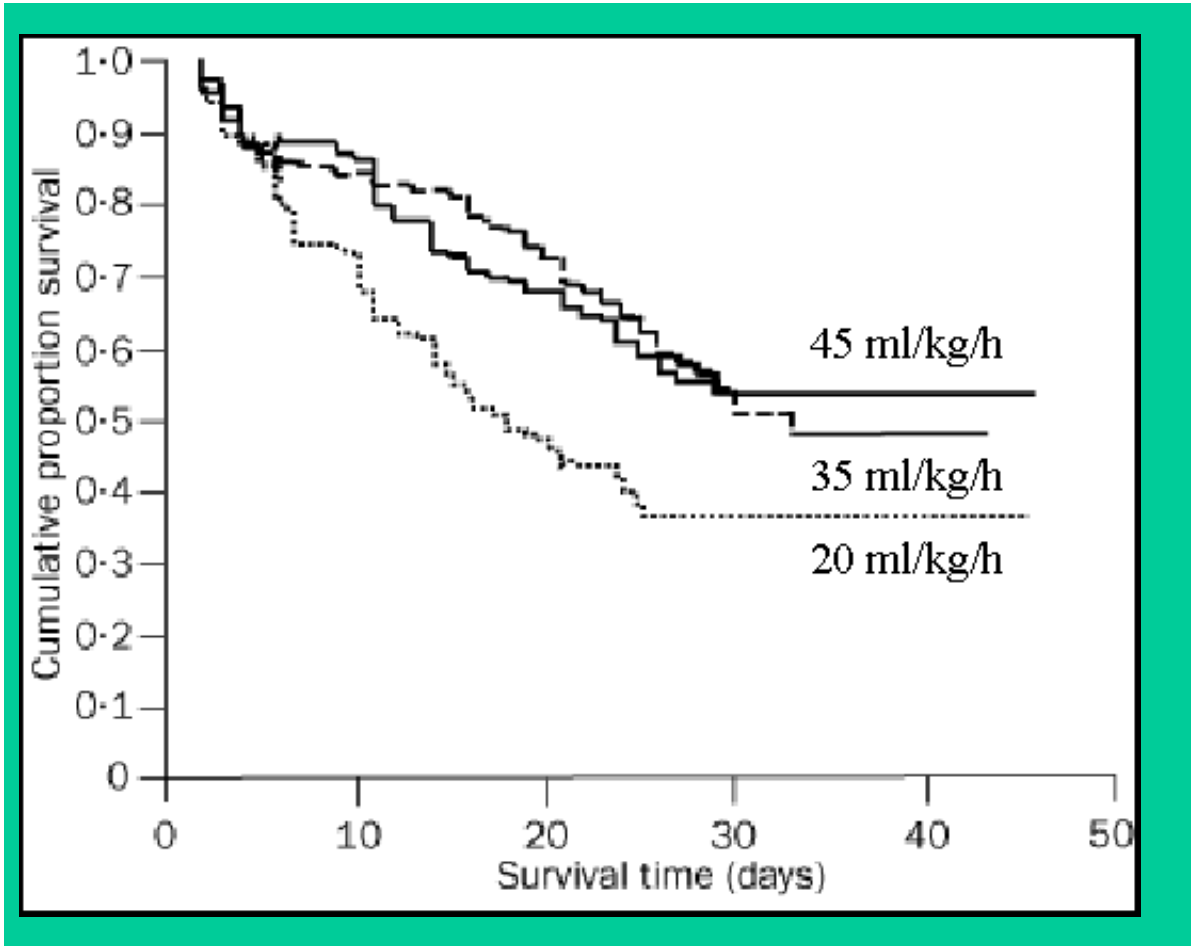
*Plus–minus values are means ±SD.

†Mortality was calculated according to the intention to treat.

Mortality in CVVH patients is related to the volume of replacement fluid

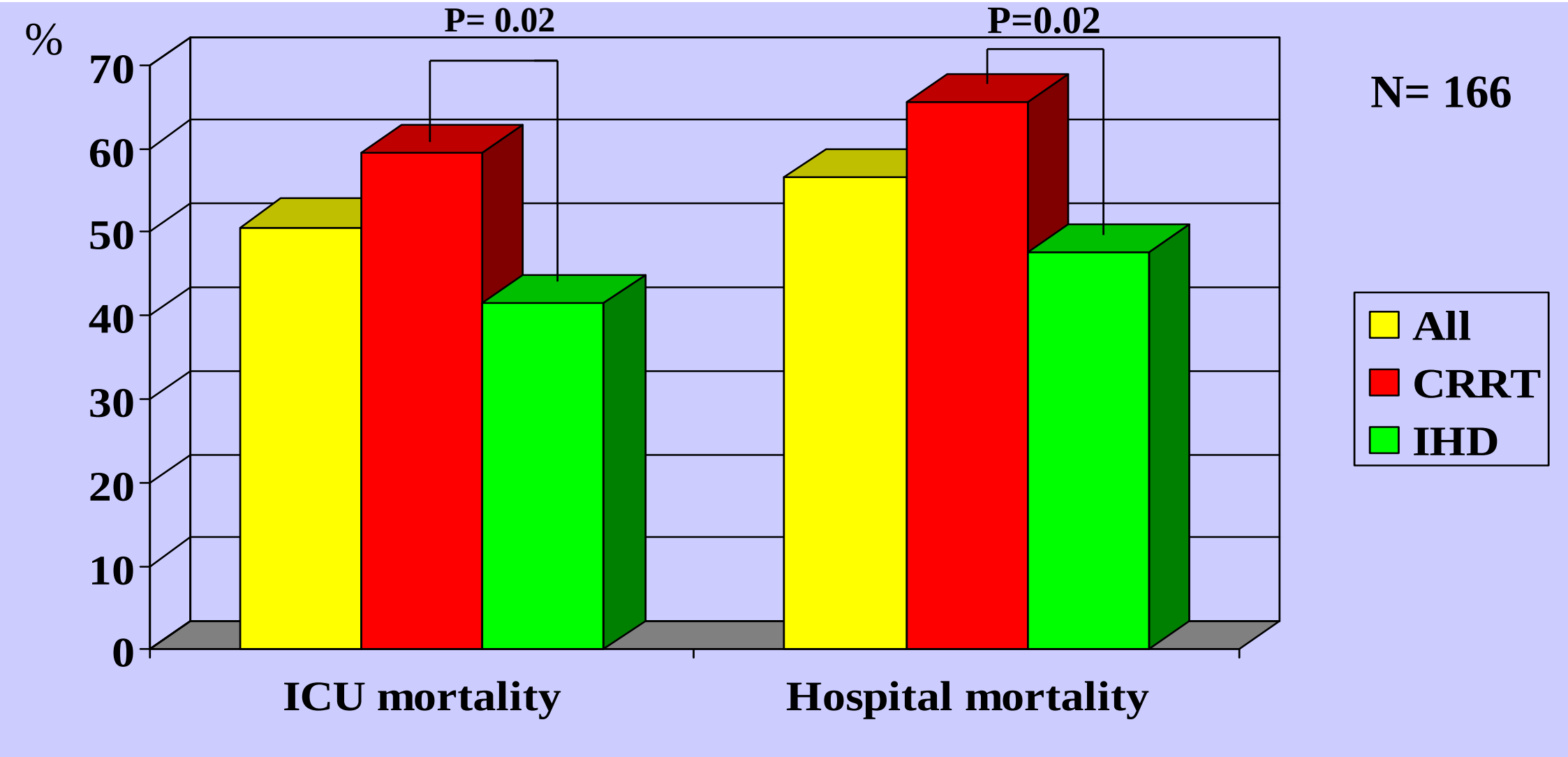
- Prospective RCT of different doses in CVVH treatment of ARF
- 425 patients
- Primary endpoint: survival @15 days after stopping CVVH

Significantly better survival with 35 or 45 ml/kg/min vs. 20 ml/kg/min



Ronco et al, *Lancet 2000*; 356: 26-30

Outcome CRRT vs IHD



Mehta et al, Kidney Int, 2001, 1154-1163

Survival IHD vs CRRT
A randomised controlled trial

DAILY TREATMENT

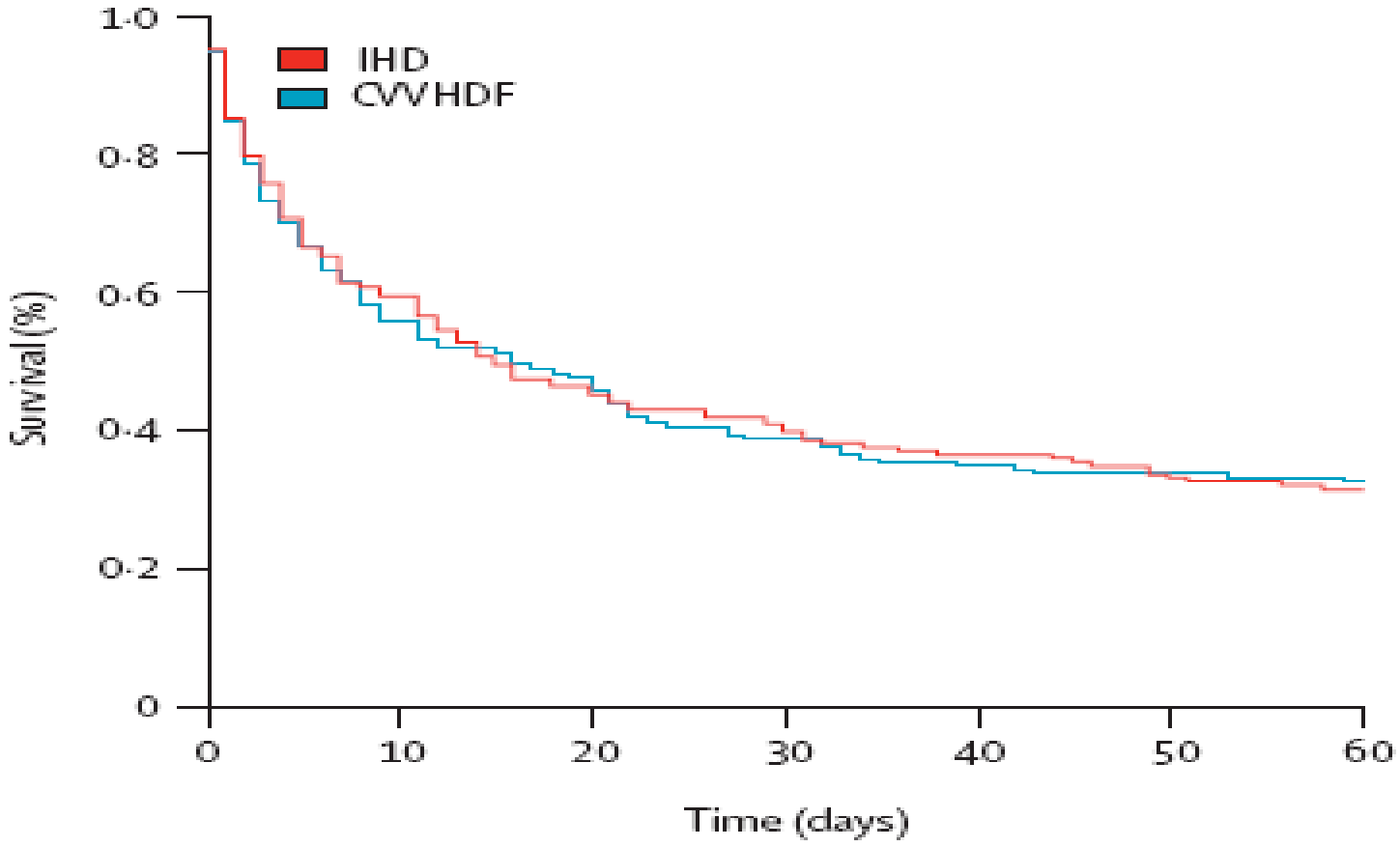
	Intermittent haemodialysis	Continuous venovenous haemodiafiltration
Duration of sessions (h)	5·2 (5·1–5·3)	continuous
Blood flow (mL per min)	278 (275–281)	146 (145–147)
Dialysate flow*	500	1099 (1068–1128)
Ultrafiltration flow (mL per h)		1278 (1255–1301)
Net ultrafiltration† (mL per day)	2213 (2141–2285)	2107 (2011–2203)
Mean urea (mmol/L)	15·7 (7·5)	14·8 (9·1)

Data are mean (95% CI) or mean (SD). *mL per min in the intermittent haemodialysis group and mL per h in the continuous venovenous haemodiafiltration group. †Mean volume loss per day of treatment.

Table 2: **Treatment modalities**

Vinsonneau et al, Lancet 2006, Hemodaife

Survival IHD vs CRRT
A randomised controlled trial



Numbers at risk

IHD	184	85	68	58
CVVHDF	175	83	62	57

Vinsonneau et al, Lancet 2006, Hemodaife

CRRT vs IHD: The PICARD experience

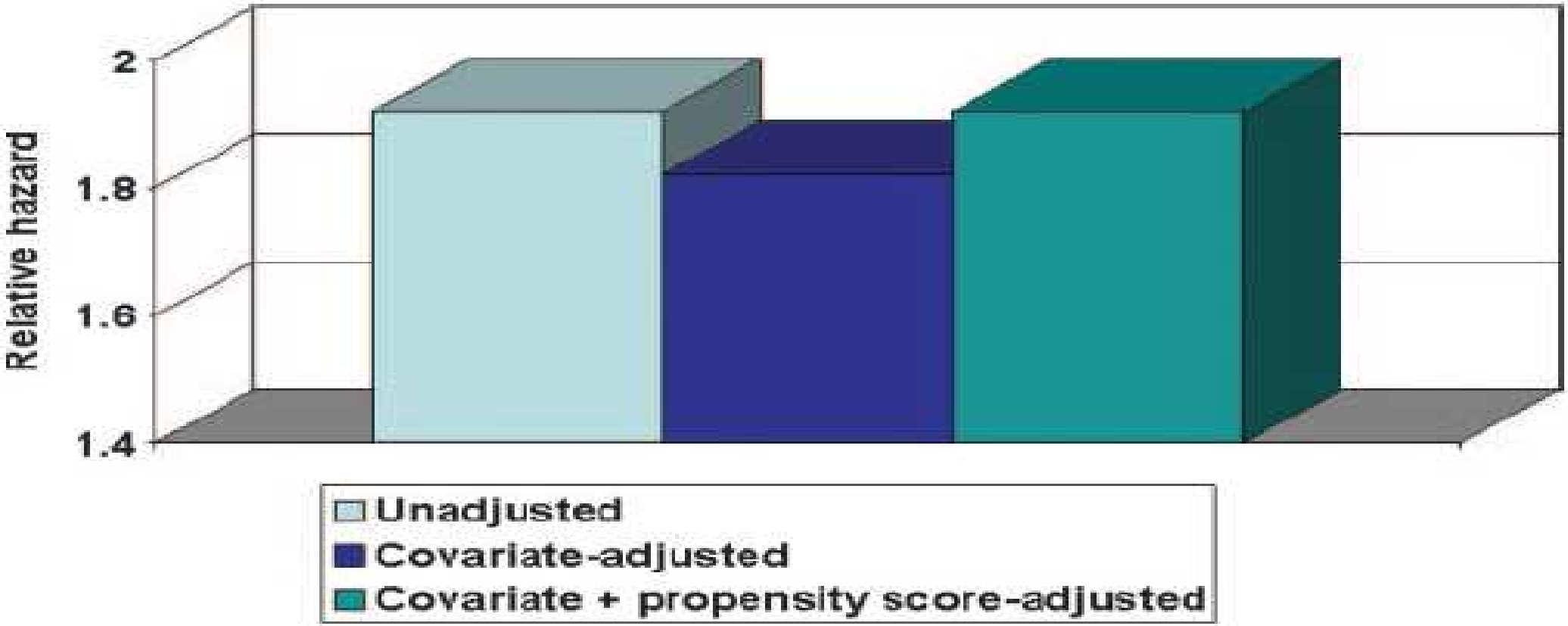
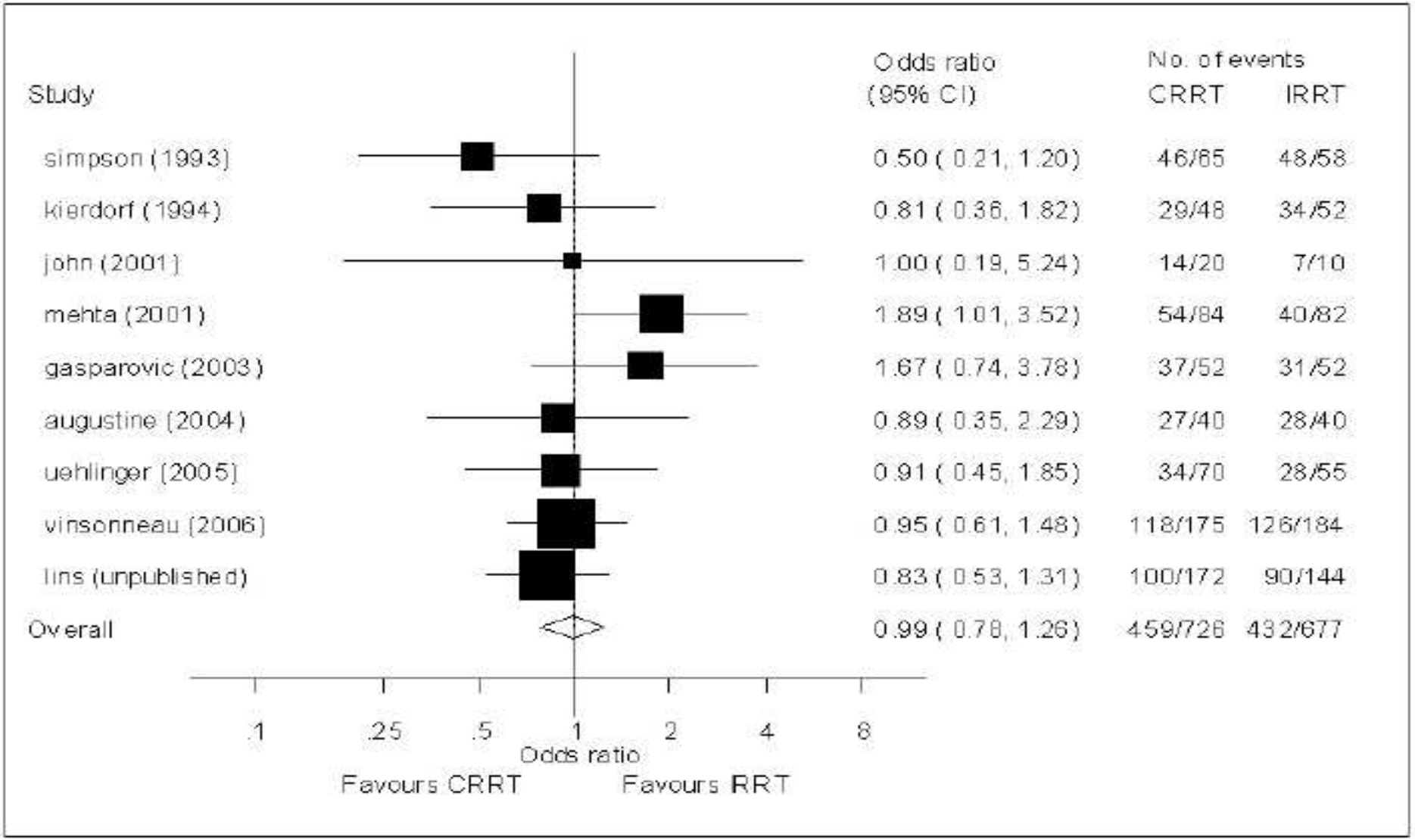


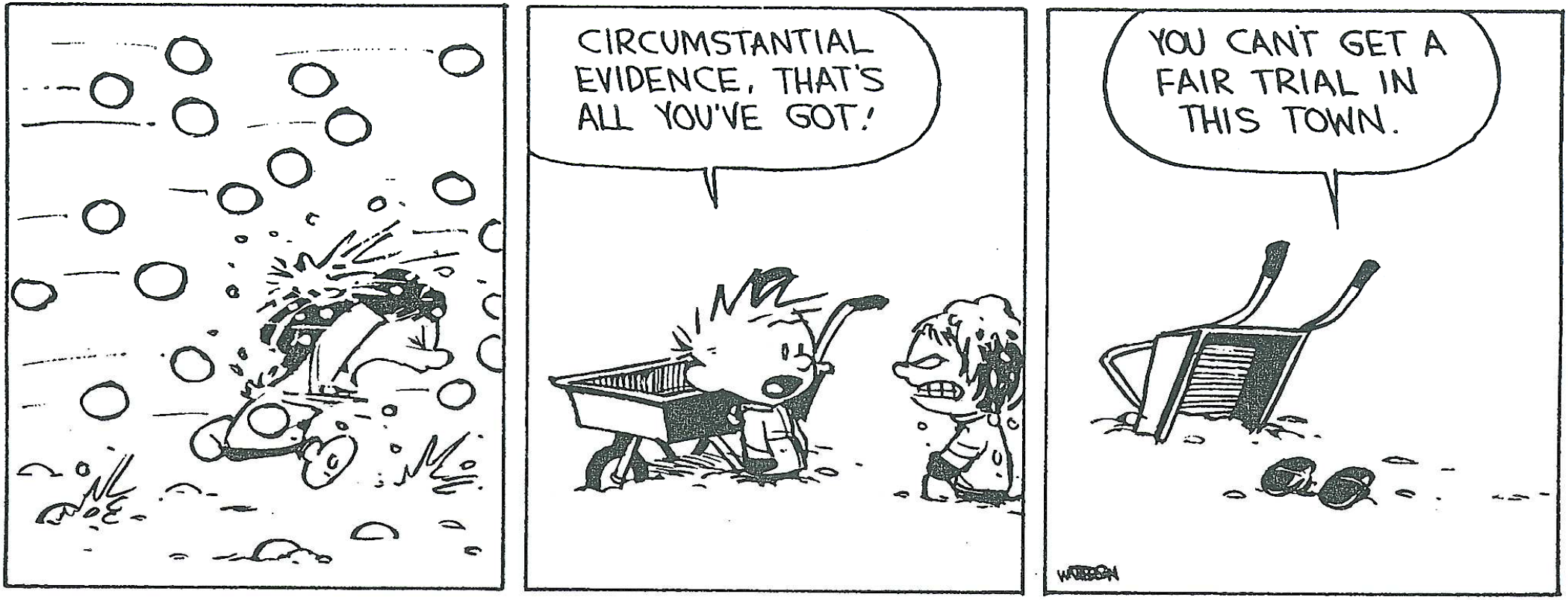
Figure 1. Mortality within 60 d after acute kidney injury requiring dialysis: Continuous renal replacement therapies *versus* intermittent hemodialysis.

Cho et al, JASN november 2006

IHD vs CRRT: a meta analysis



Bagshaw et al, Crit Care Med, 2008



Cartoon Stolen from An De Vriese

CVVHD vs. IHD for RRT in ICU

Conclusion:

„These data suggest that, provided strict guidelines to improve tolerance and metabolic control are used, almost all patients with acute renal failure as part of multiple-organ dysfunction syndrome can be treated with intermittent haemodialysis“

Vinsonneau et al, *Lancet 2006*; 368: 379-85

SLEDD vs CVVH: a randomised controlled trial

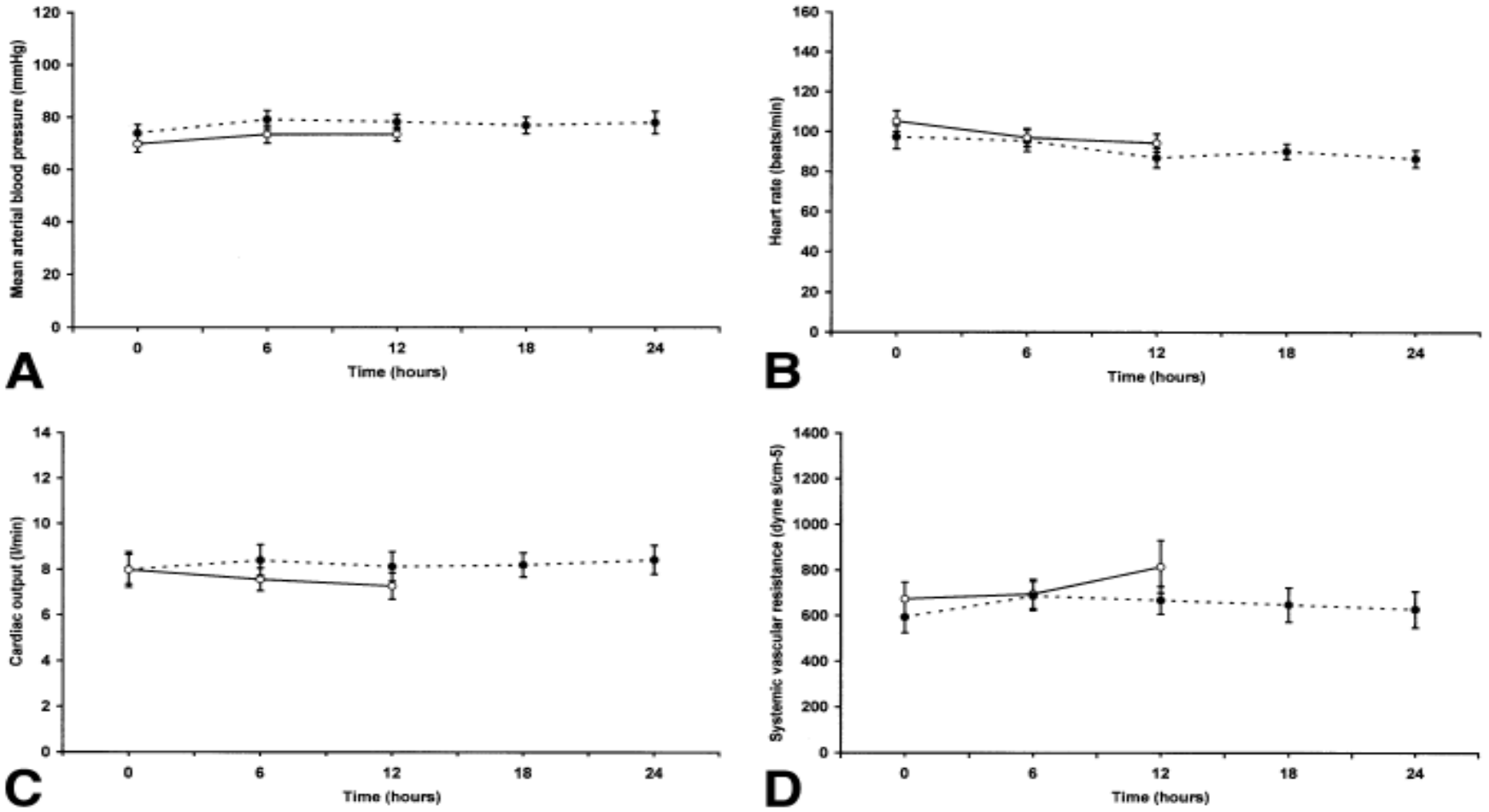
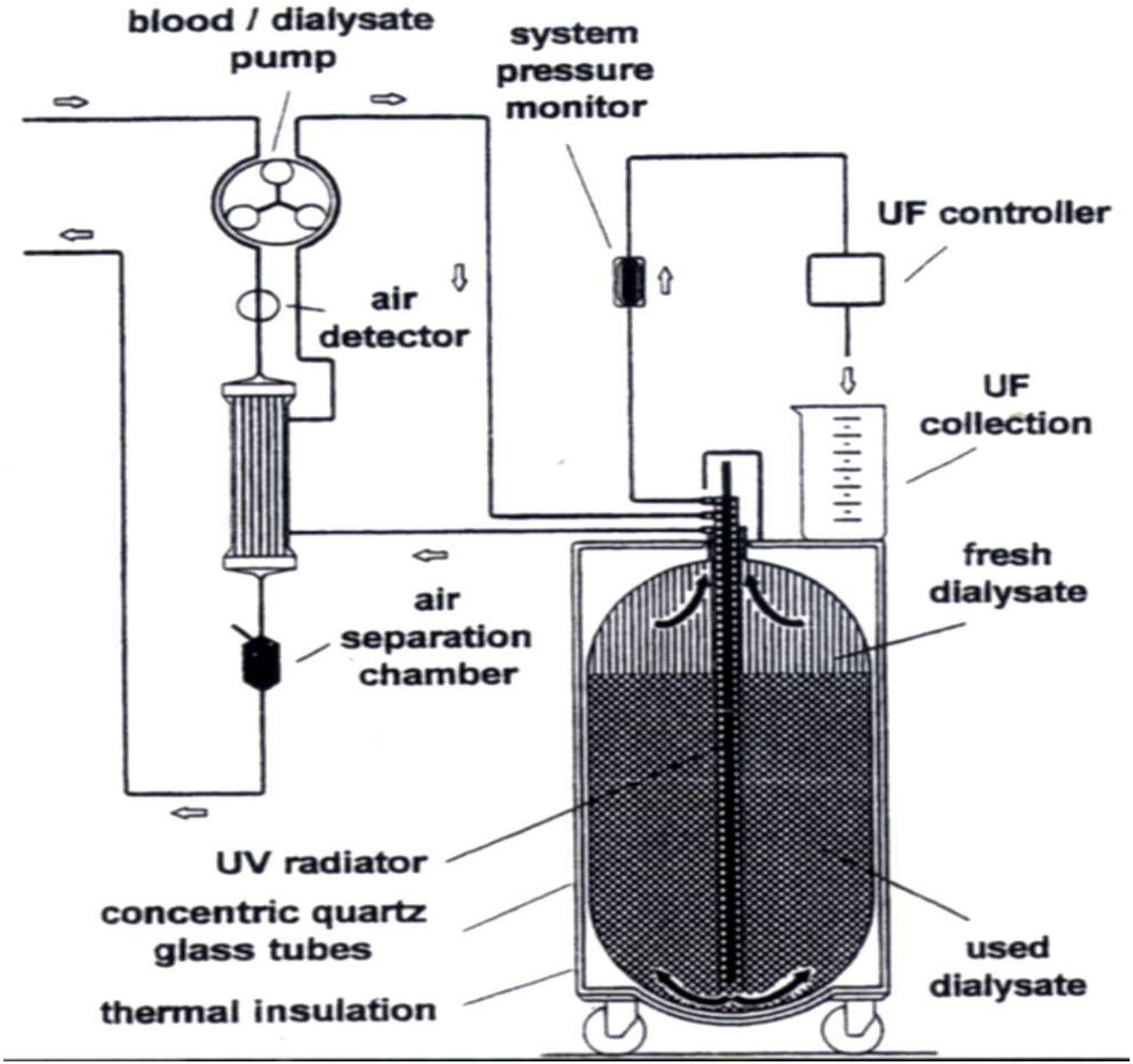


Fig 2. (A) MAP, (B) heart rate, (C) CO, and (D) SVR in 20 patients treated with extended dialysis (open circles) and 19 patients treated with CVVH (closed circles). There were no significant differences between groups with respect to hemodynamic variables.

Kielstein et al, AJKD 2004

The Genius dialysis System



… What else is important:

Dialysis dose

$$\frac{K \times t}{V}$$

$$\frac{M.D. \times t}{P}$$