Acute kidney injury- an update on recent data

Norbert Lameire,MD,PhD
Em Prof of Medicine and Nephrology
University Hospital
Gent, Belgium

Moskou, ISN Ambassador Program
October 2017

Topics to be covered

Lecture 1

- Definitions AKI
  - Limitations serum creatinine
  - Oliguria
  - Alert systems
  - Biomarkers
  - DD prerenal vs renal
- General approach to patient with septic AKI
  - Hemodynamic monitoring
  - Fluid therapy – pro-con
  - Diuretics
  - Vasopressors

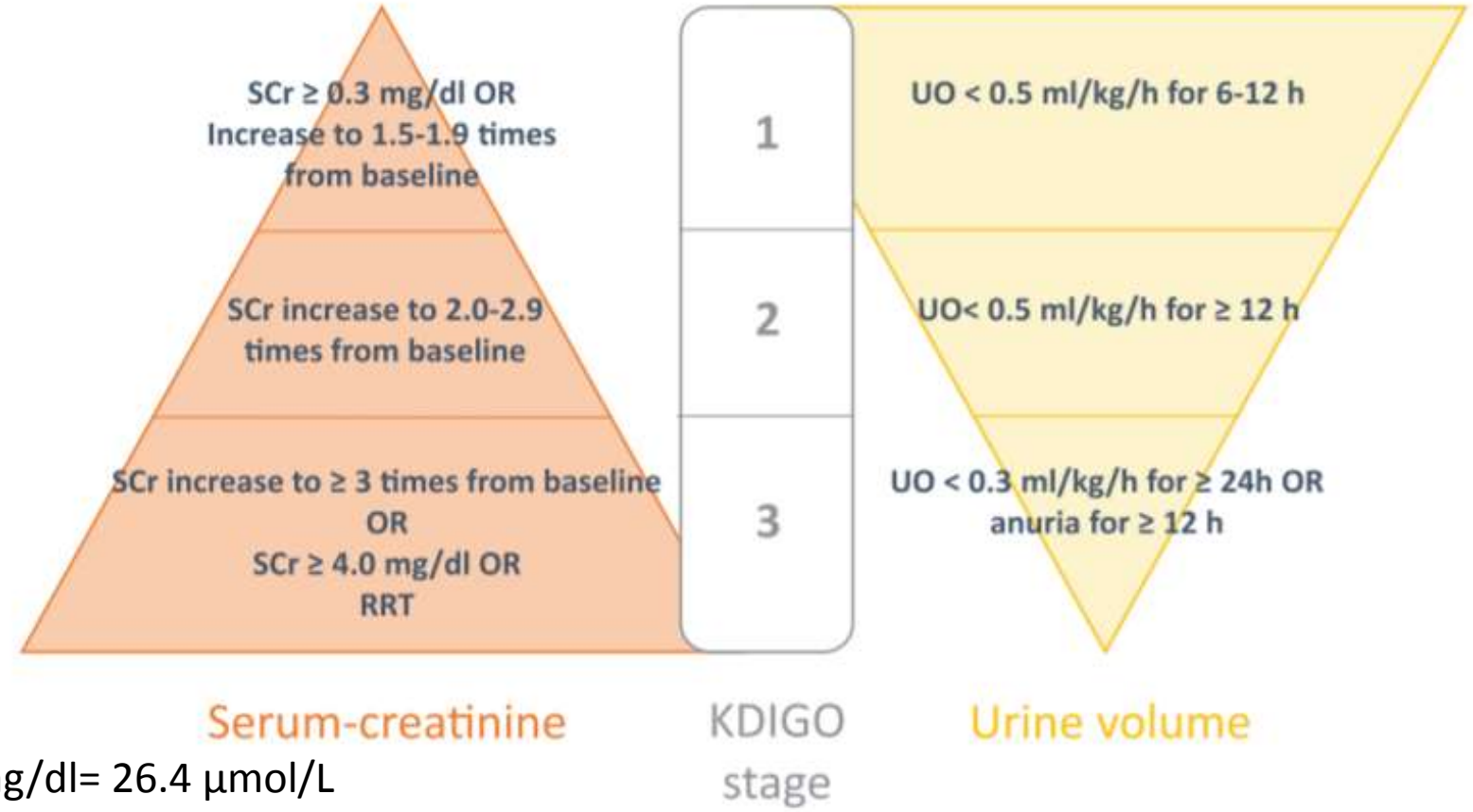
Lecture 2

- Renal replacement therapies
  - selection of dialysis strategy
  - When to start and stop
- Recovery of AKI
  - Short and longterm prognosis

KDIGO definition and classification of AKI

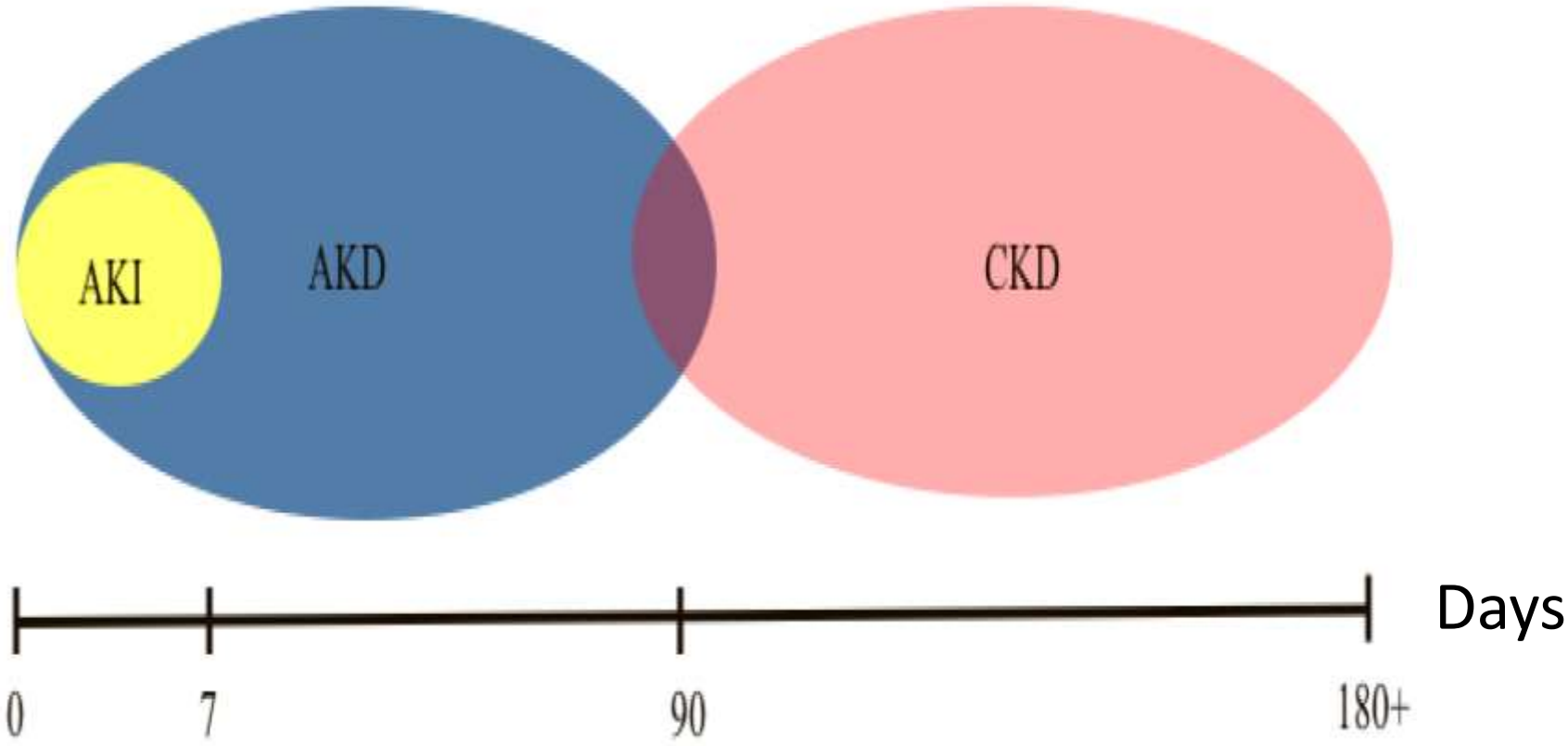
Diagnostic criteria for AKI:

- Serum-creatinine increase ≥ 0.3 mg/dl within 48h **OR**
- Serum-creatinine increase ≥ 1.5 times baseline, which is known or presumed to have occurred within the last 7 days **OR**
- Urine volume < 0.5 ml/kg for 6 h

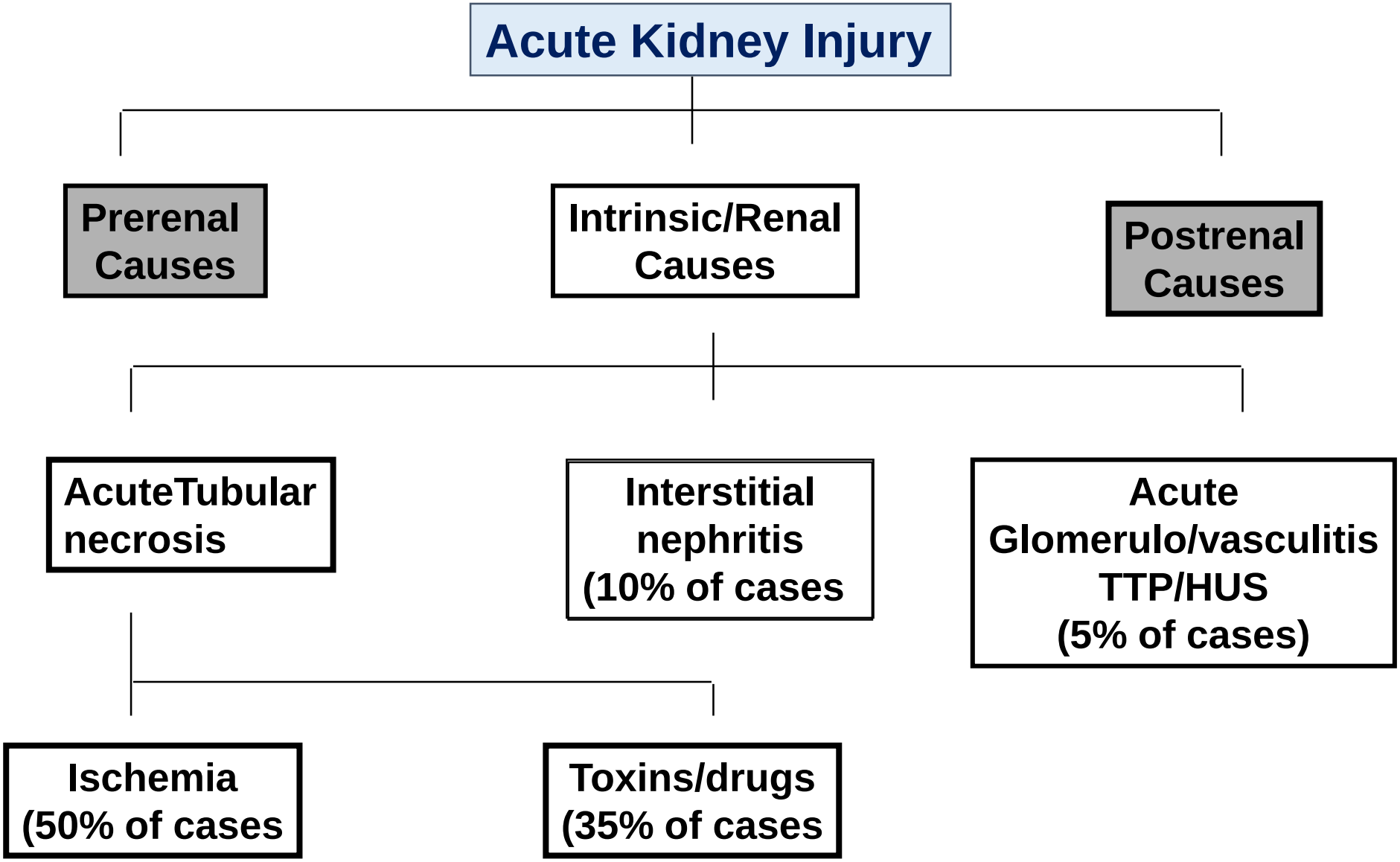


0.3 mg/dl= 26.4 µmol/L

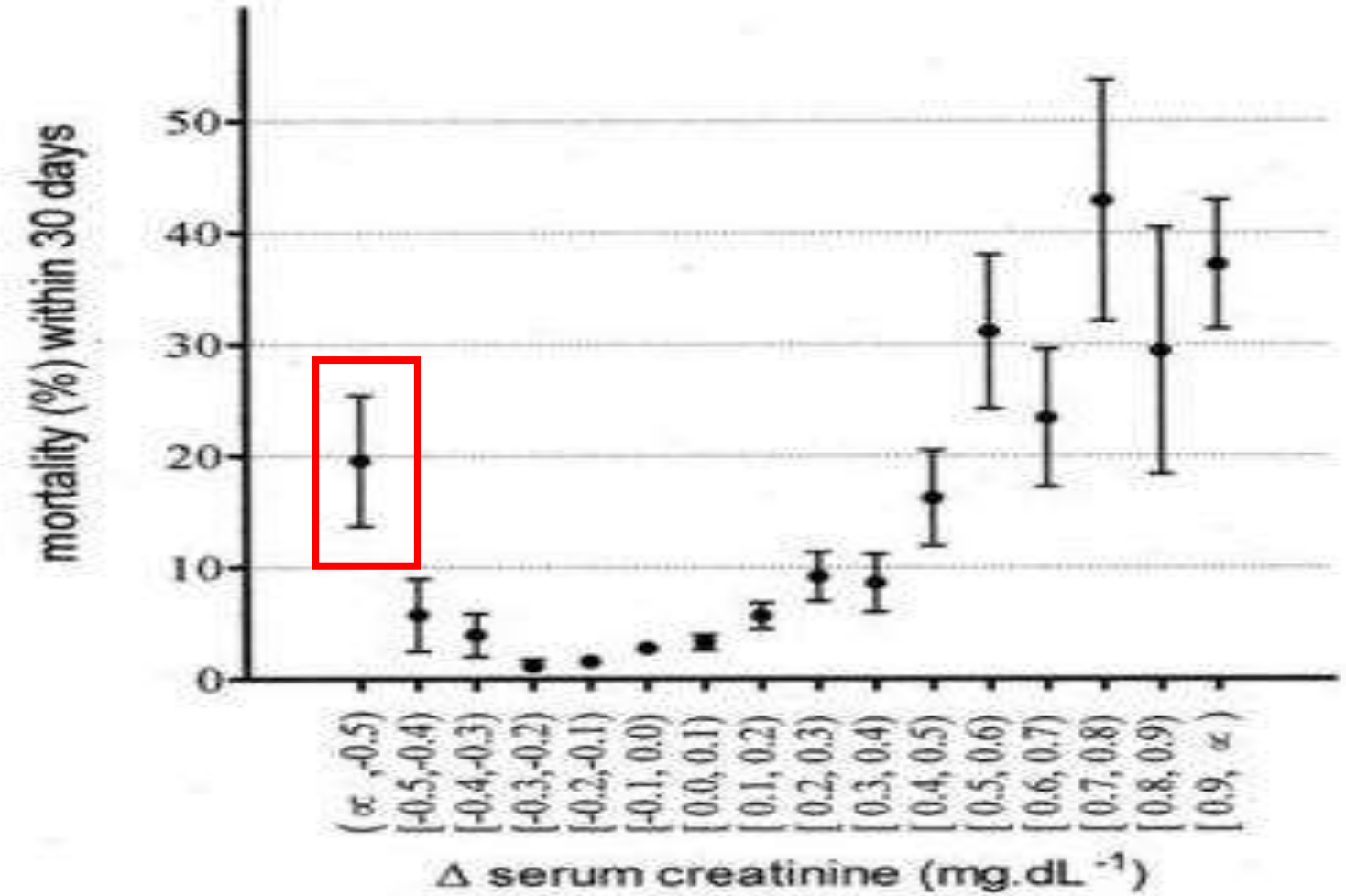
AKI-Acute Kidney Disease-CKD Continuum



Main Categories of Acute Kidney Injury

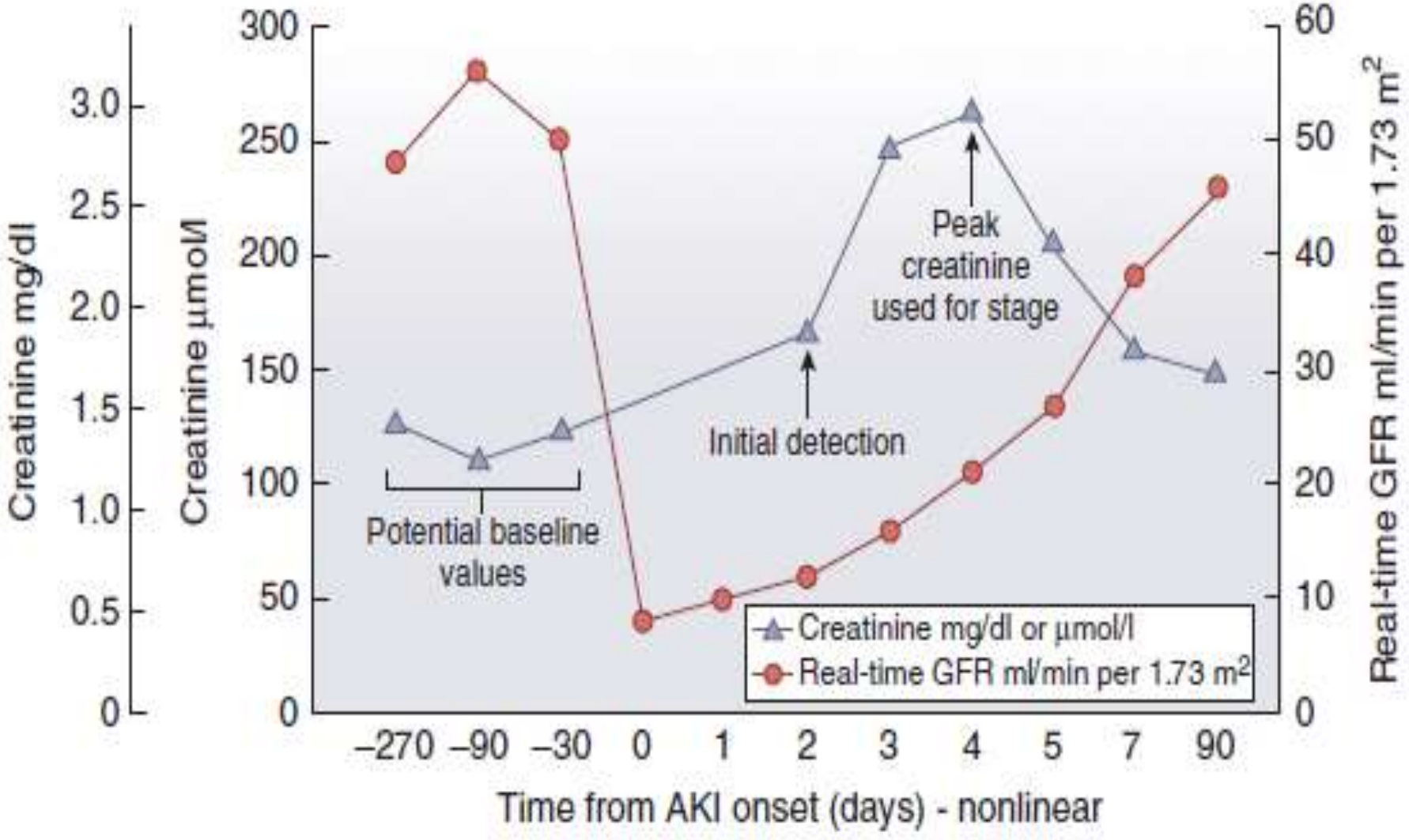


30-day Mortality and Change in SCr (ΛCrea) within 48 h after Cardiac Surgery

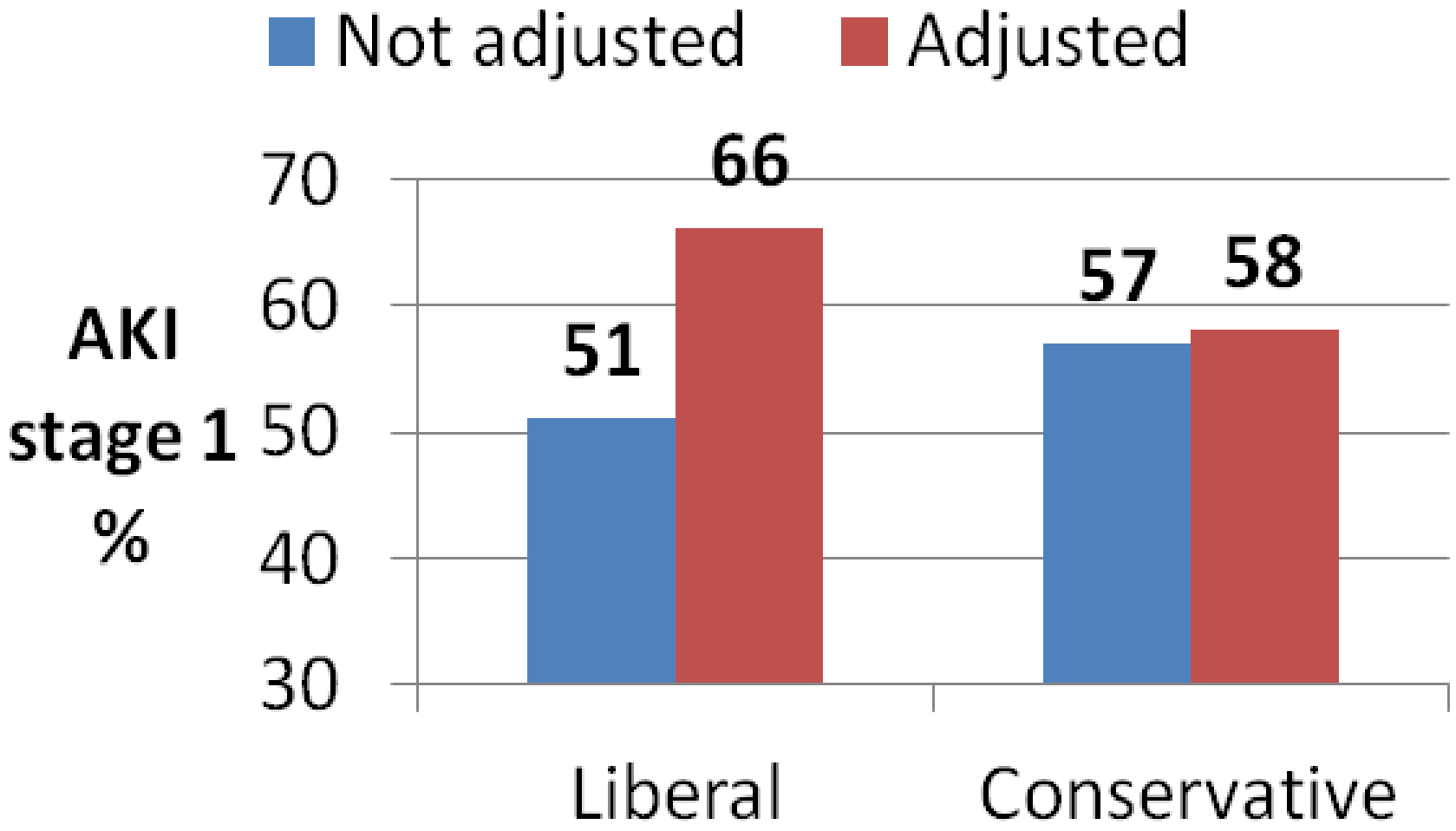


Lassnigg A, et al. J Am Soc Nephrol 2004;15:1597-1605.

A hypothetical example of real-time GFR and SCr values before and during an episode of AKI.

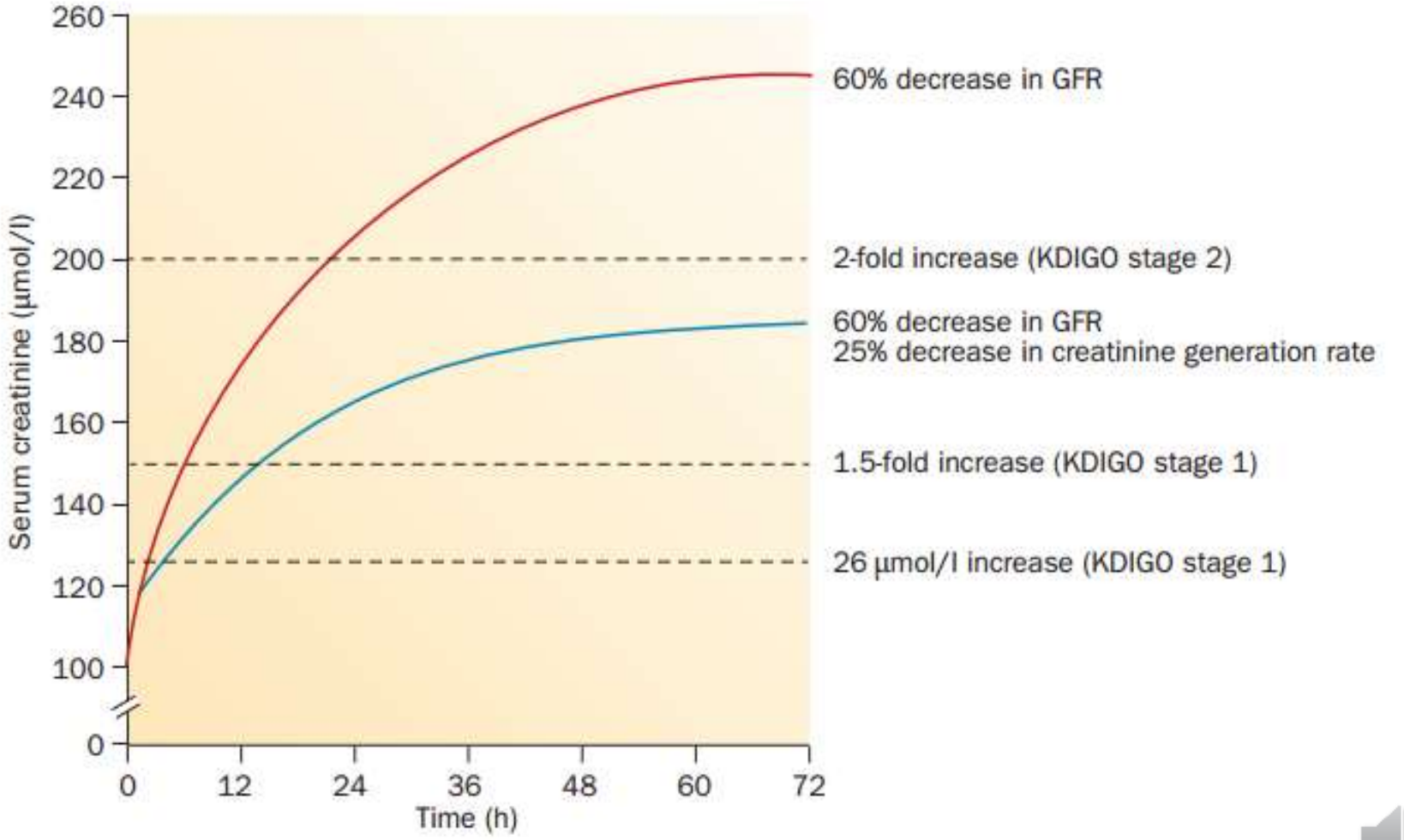


Incidence of AKI stage 1 in 2 groups of patients with ARDS and who were randomized to different fluid management strategies- adjustment of SCr.



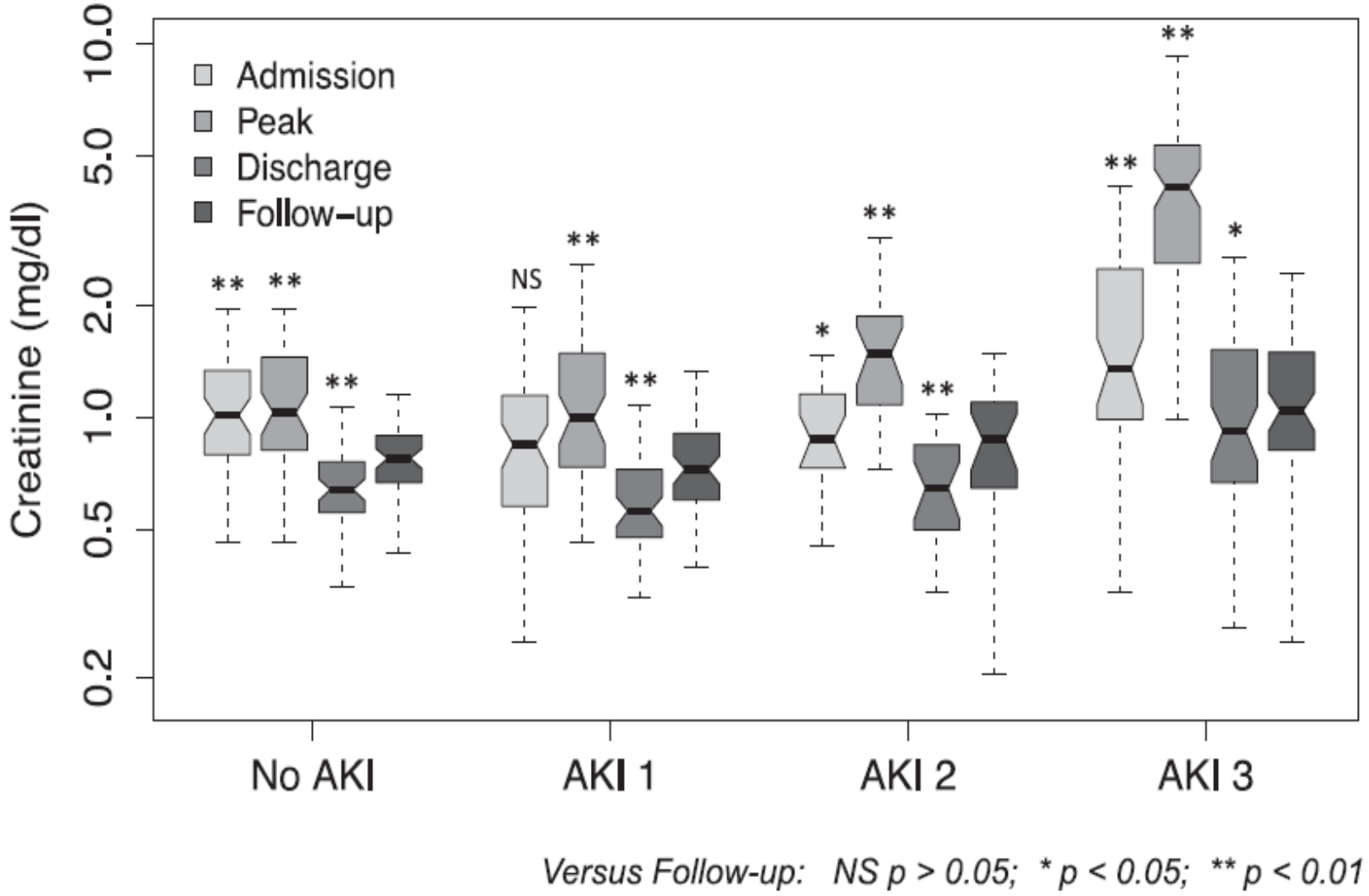
Liu et al, *Crit Care Med* 2011; 39: 2665-2671

The predicted effect of a 25% decrease in creatinine generation rate on the rate of increase of SCr and the peak SCr following a decrease in GFR with 60%



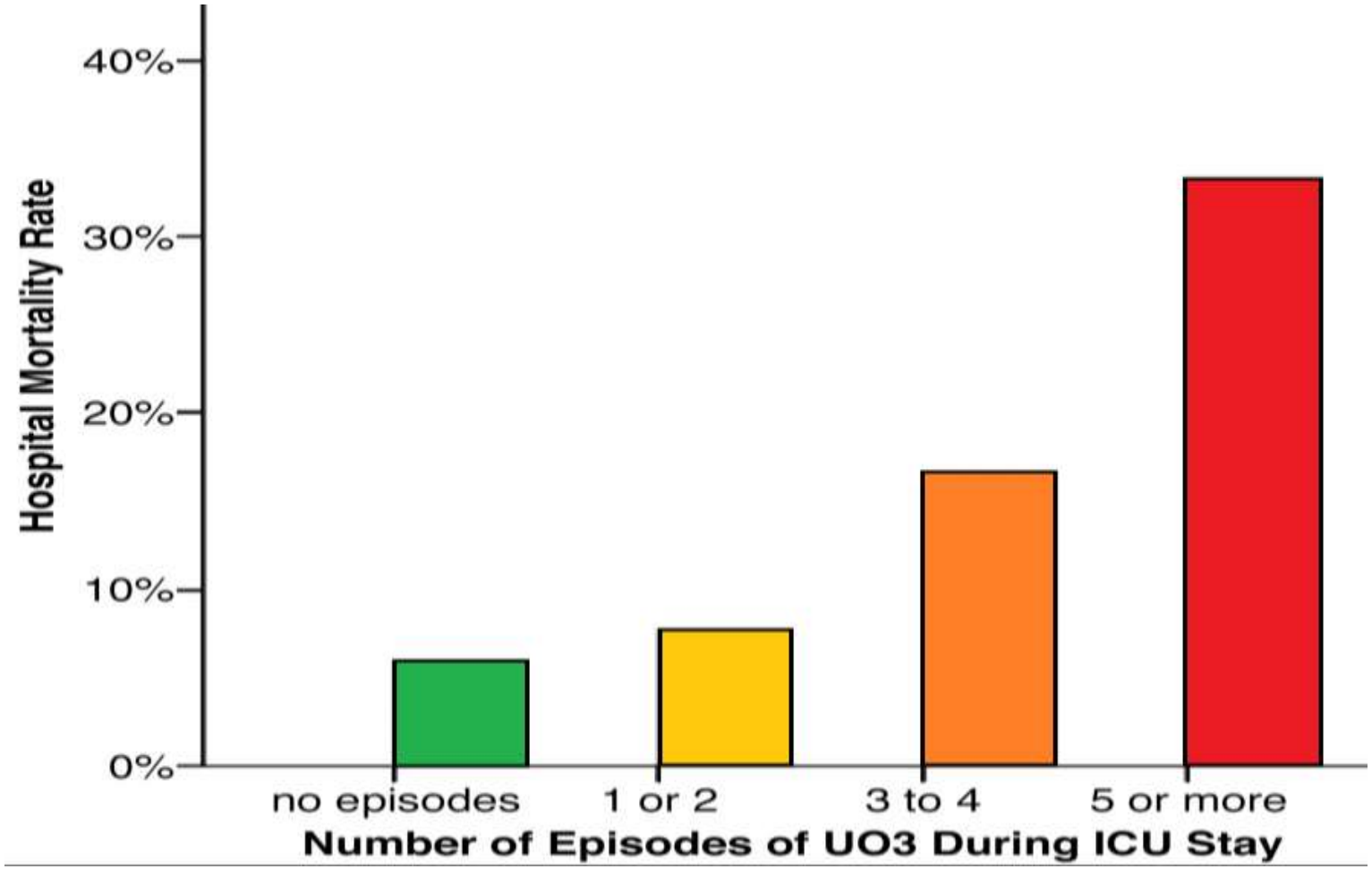
Prowle, J. R. Nat. Rev. Nephrol. 2013 ;9(4):193-195.

Difficulties to detect persistent kidney dysfunction after AKI in critically ill patients. Serum creatinine (log scale) in 221 hospitalizations with 3-12 mth FU



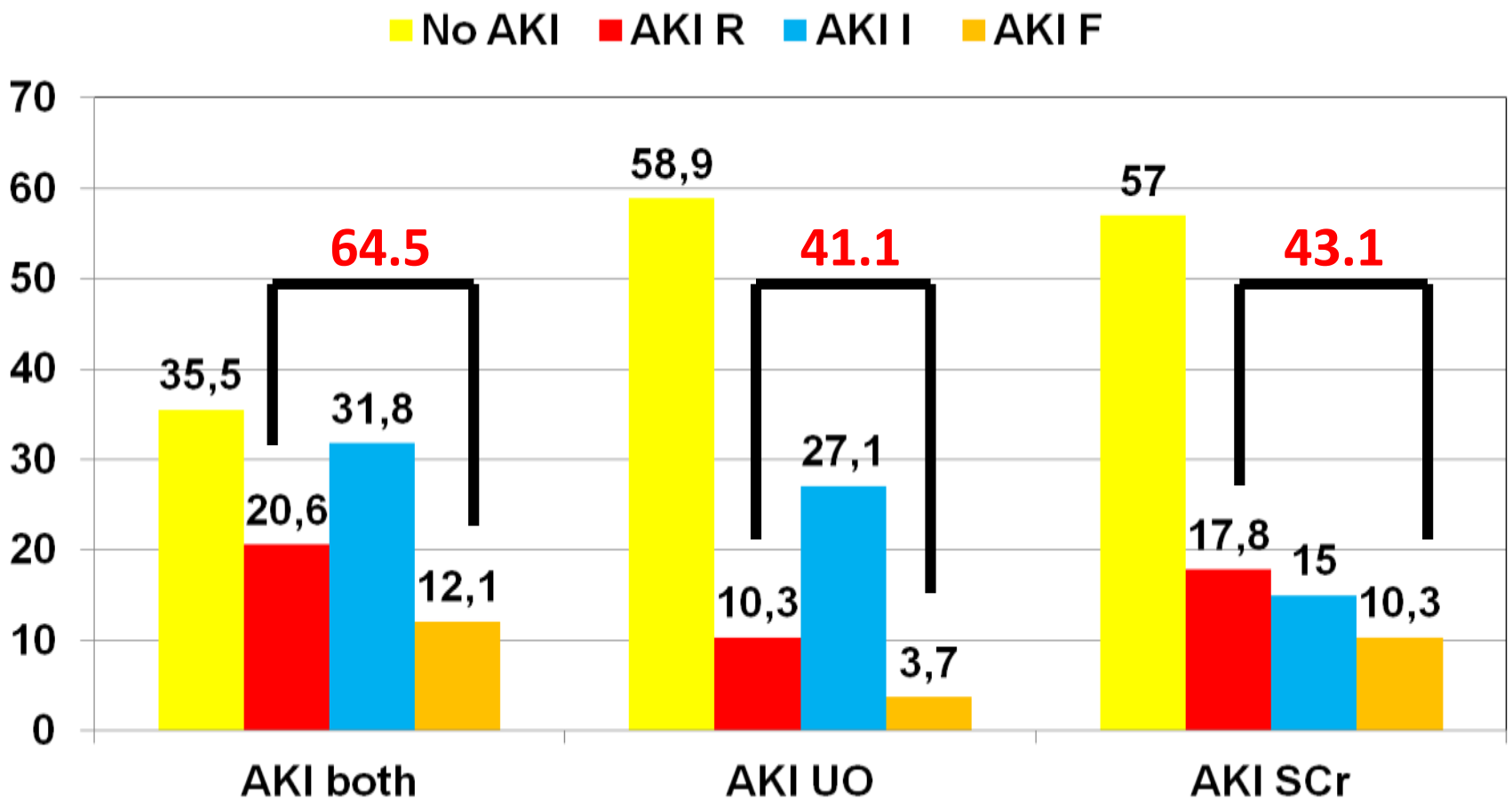
Prowle et al, Clin J Am Soc Nephrol 9: 1015–1023, 2014

Defining oliguria by 6 hour blocks identified a large number of high risk patients



Macedo et al, NDT, 26:509-515; 2011

Acute kidney injury according to RIFLE definitions – 107 septic patients admitted first day ICU



Van Massenhove et al, Crit Care. 2013,17(5):R234.

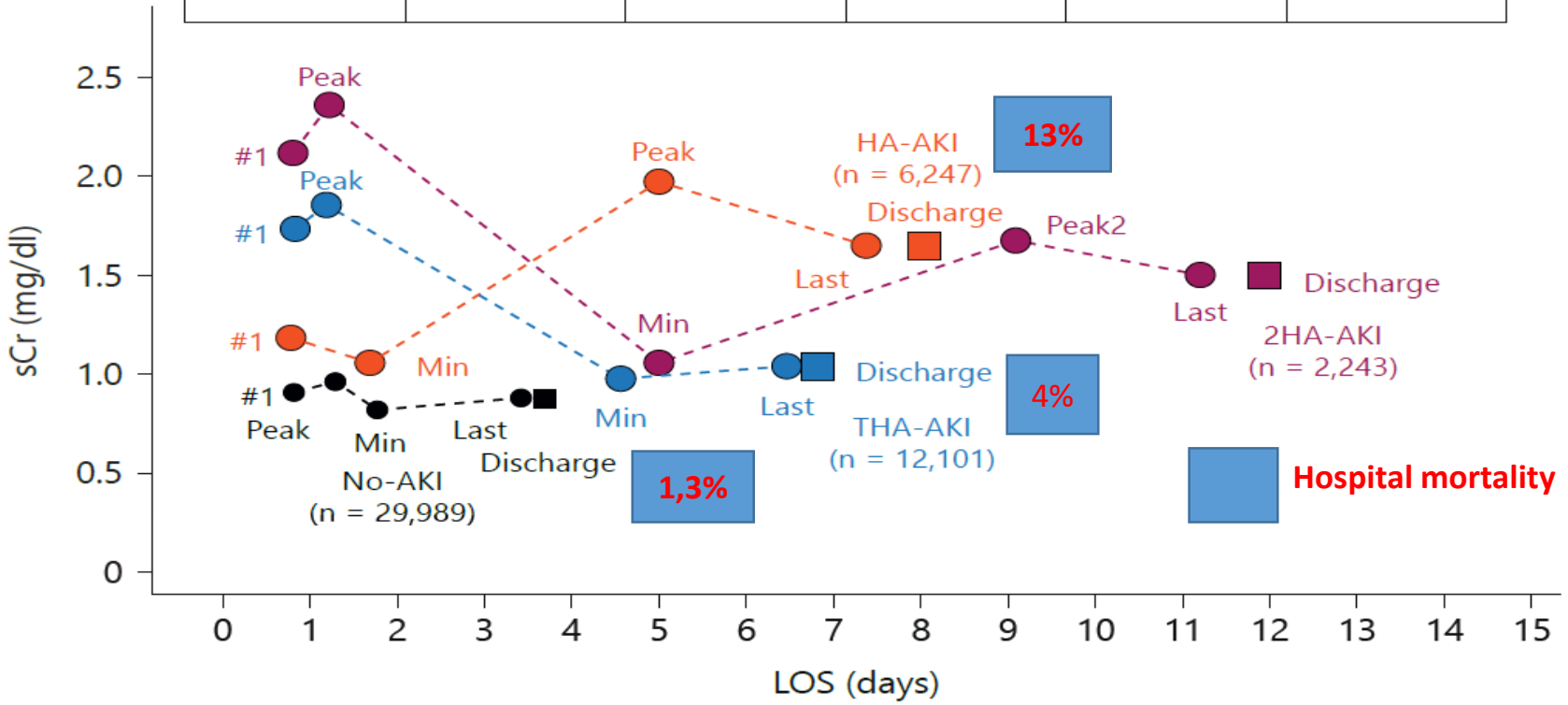
Significance of isolated oliguria in critically ill patients

- Using oliguria in isolation as a trigger for intervention in ICU might lead to some patients receiving unnecessary intervention and other patients not receiving potentially helpful intervention.
- Oliguria is relatively frequent in ICU patients and most episodes are **not** followed by AKI.
- Oliguria has only a fair predictive ability for subsequent AKI and lacks clinical utility as a test at the observed frequencies of AKI in the ICU.
- Oliguria accompanied by hemodynamic compromise or increasing vasopressor dose may represent a clinically useful trigger for other early biomarkers of renal injury with the goal of achieving a more accurate and timely identification of patients at risk of AKI.
- However, oliguric patients always need adequate assessment (hemodynamic evaluation, exclusion of obstruction, exposure to nephrotoxins)

Prowle et al. Critical Care 2011, 15:R172

Time course of sCr for different AKI types

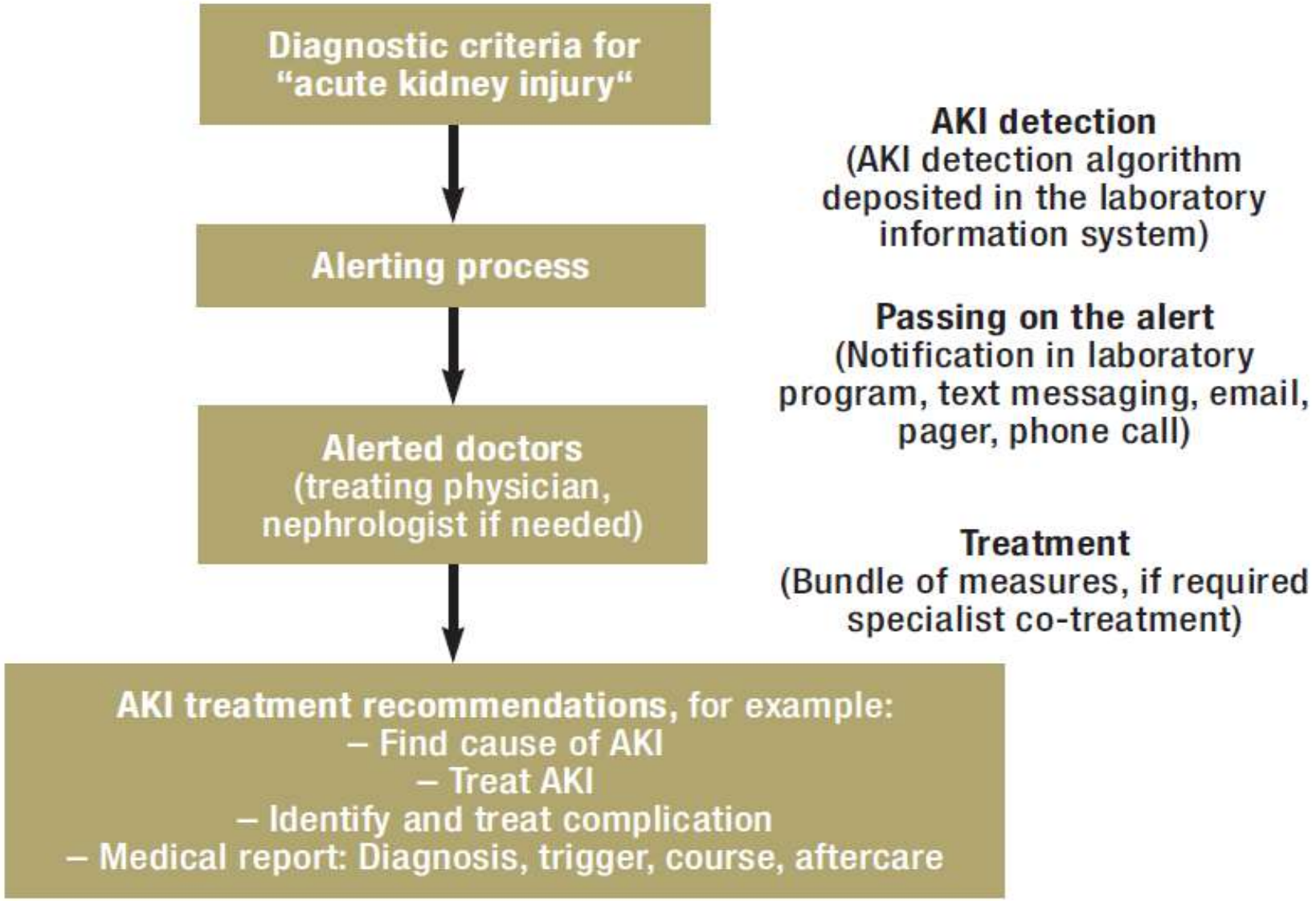
Time (h)	Min_sCr	Peak_sCr	Peak2_sCr	Last_sCr	Discharge
HA-AKI	42±59	127±105		185±135	194±146
2HA-AKI	136±97	38±47	219±126	278±143	287±157
THA-AKI	115±88	30±36		159±116	165±125
No-AKI	41±40	32±35		82±68	89±76



THA-AKI: transient hospital associated AKI; 2HA-AKI transient hospital associated AKI that resolves followed by a second episode of AKI

Warnock et al, Nephron 2015;131:227–236

Principle of an electronic early alert system for AKI



Haase M, et al, Electronic alerts for acute kidney injury—a systematic review. Dtsch Arztebl Int 2017; 114: 1–8.

Improvement in basic standard of care by implementing a care bundle (CB) with interruptive alert improved (?) outcomes in patients with AKI.

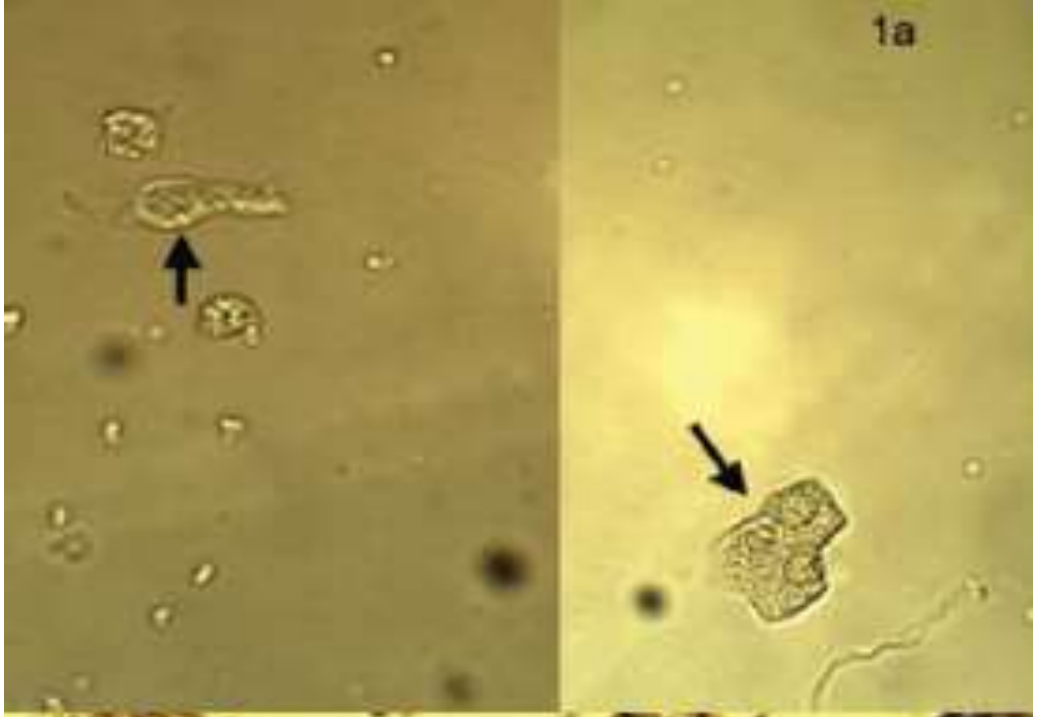
	Care Bundle completion		P value
	Within 24 hours	Not completed or completed after 24 hours	
Proportion of AKI episodes with progression to higher AKI stage	9 (3.9%)	149 (8.1%)	0.02
Length of stay in days†	11.2 (9.9, 12.4)	12.5 (11.9, 13.1)	0.098
In-hospital case fatality	55 (18%)	506 (23.1%)	0.046
30-day case fatality	77 (25.2%)	626 (28.5%)	0.219
60-day case fatality	83 (27.1%)	673 (30.7%)	0.205

Kohle et al, PLoS ONE 10(7): 2015

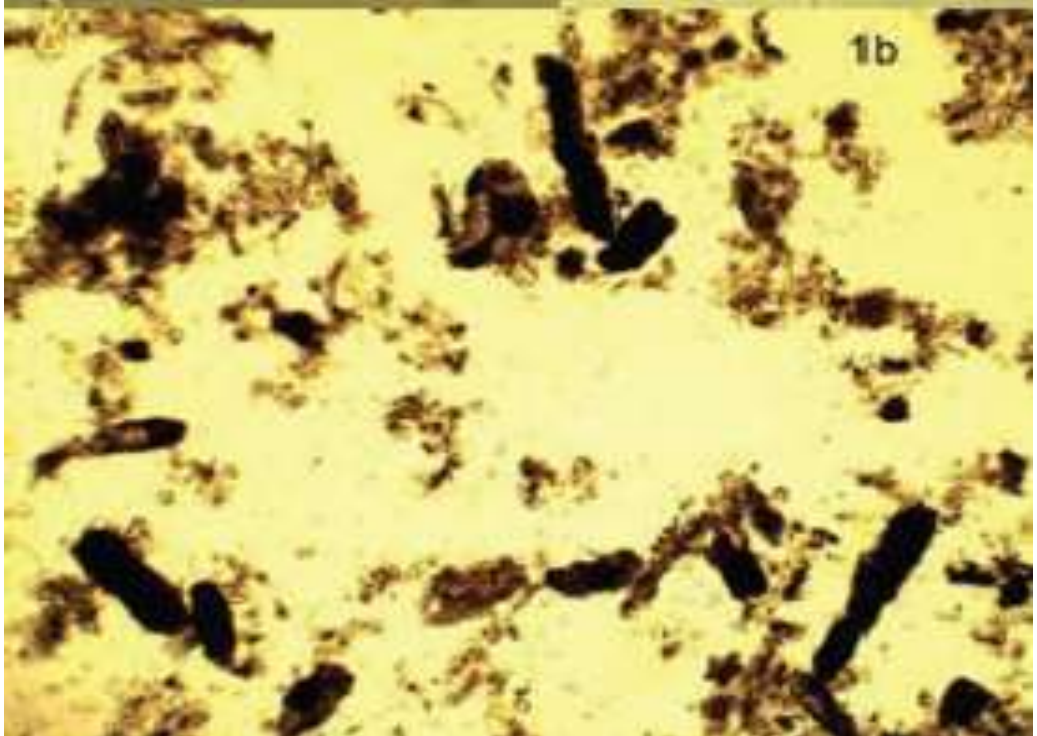
Essential biological parameters in approach patient at risk of AKI

Criterium /test	Utility	Limitations	Comments
Serum creatinine	Cheap,easily measured,readily available, well-known relationship to disease	Slow to change in response to injury, insensitive-no changes unitil > 50% loss of renal function	Increase ≥ 50% over ≤ 1 wk or ≥ 0,3 mg/dl over ≤ 48 h used as consensus criteria for AKI
Serum Cystatin C	Experience from CKD	Similar to creatinine	
Urine output	Faster to change than SCr , cheap and easy to measure	Non-specific, insensitive to certain forms of AKI, not readily measured outside ICU	Oliguria demands adequate diagnostic assessment but hardly requires any specific treatment
Urine sediment	Can help identify specific causes of AKI, glomerulo/vasculitis	Not well standardized –requires experienced and skilled investigator	May help DD between prerenal/renal AKI; has some prognostic value

Urinary microscopy in AKI



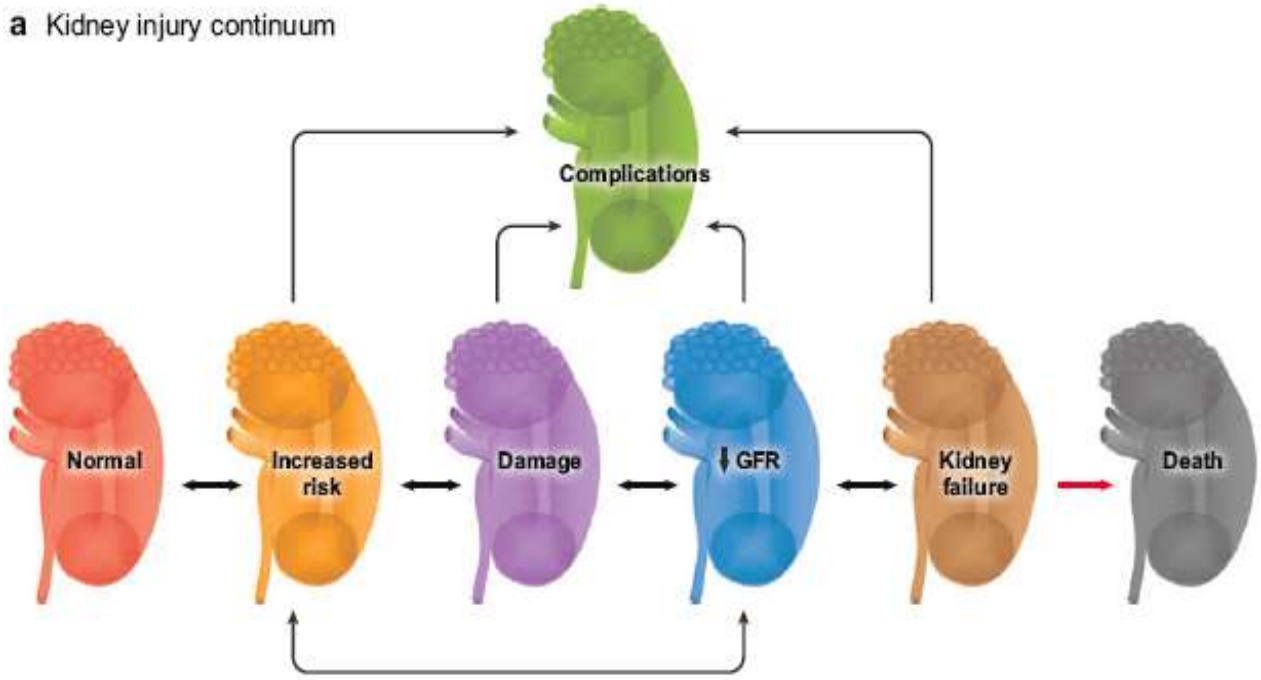
High-powered view of urinary RTE cells

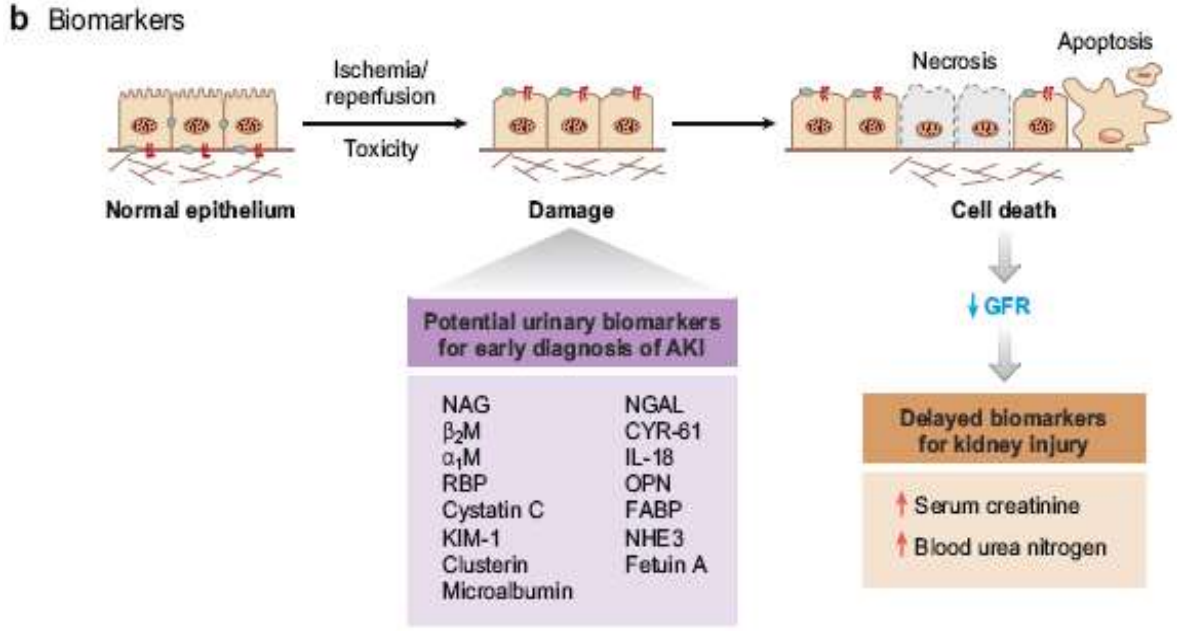


Low-powered view of urinary granular casts

Perazella et al, Clin J Am Soc Nephrol 5: 402–408, 2010

AKI- a continuum?





Vaidya et al, Annu. Rev. Pharmacol. Toxicol. 2008, 48:17.1–17.

Classes of biomarkers in AKI

Class of biomarker	Biomarker
Inflammatory	Proinflammatory cytokines (IL 6, IL 18), Neutrophil gelatinase-associated lipocalin (NGAL)
Cell injury	L-fatty acid binding protein (L-FABP), KIM-1, sodium/hydrogen exchanger-3 (NHE-3) and Netrin-1;
Cell cycle markers	urinary tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulinlike growth factor-binding protein 7 (IGFBP7)
Functional	Cystatin C

Involvement of the cell cycle biomarkers in initial tubular injury

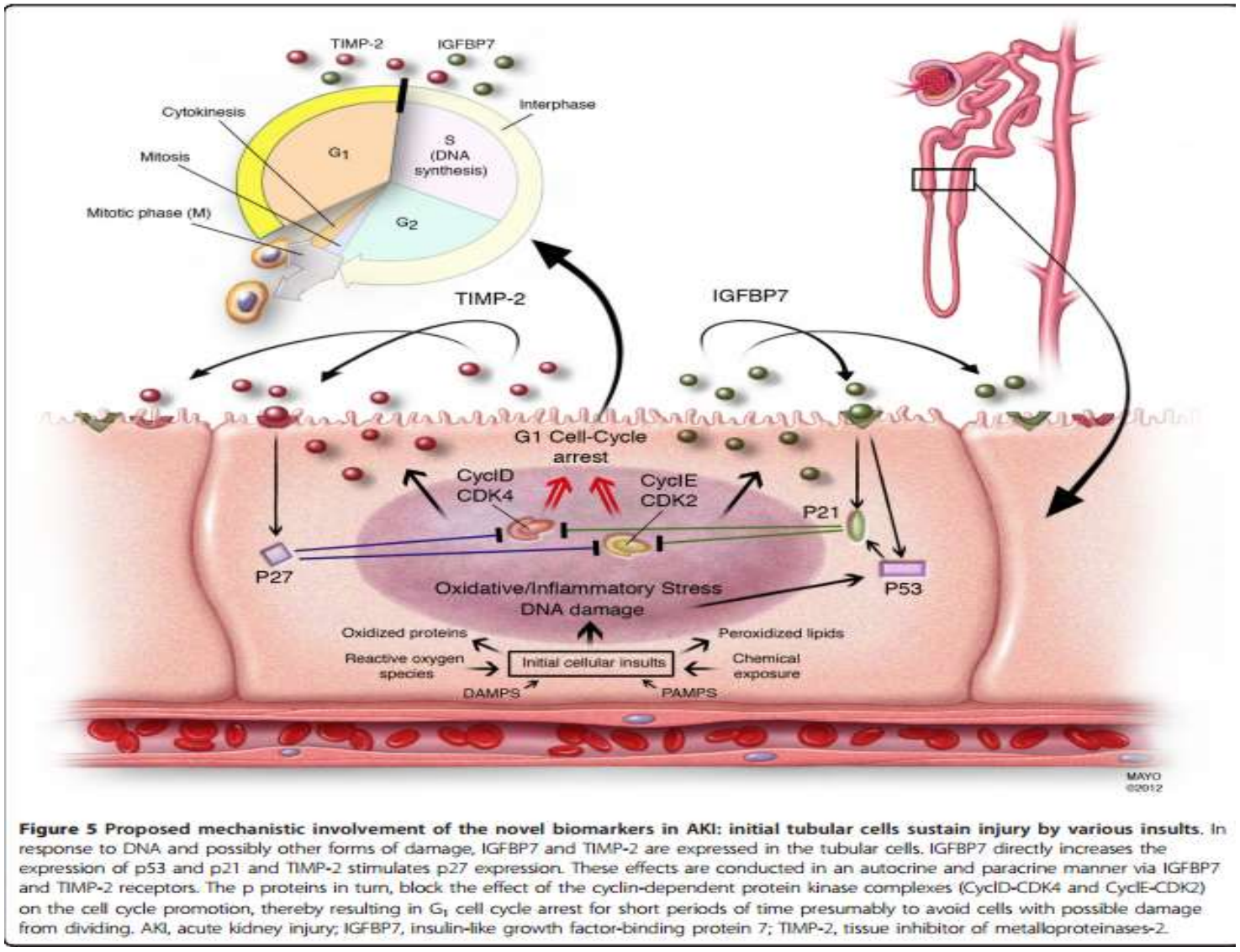
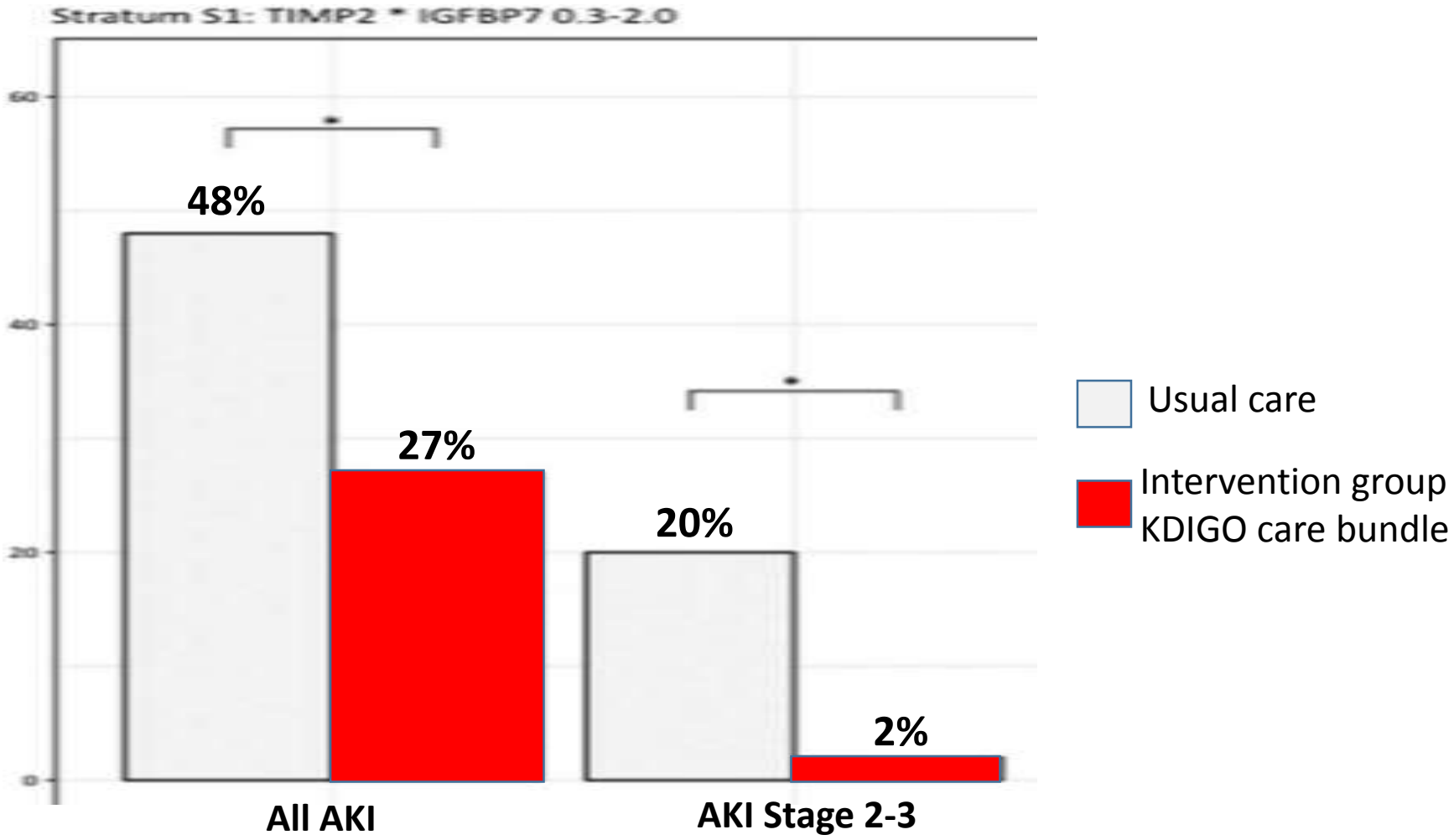


Figure 5 Proposed mechanistic involvement of the novel biomarkers in AKI: initial tubular cells sustain injury by various insults. In response to DNA and possibly other forms of damage, IGFBP7 and TIMP-2 are expressed in the tubular cells. IGFBP7 directly increases the expression of p53 and p21 and TIMP-2 stimulates p27 expression. These effects are conducted in an autocrine and paracrine manner via IGFBP7 and TIMP-2 receptors. The p proteins in turn, block the effect of the cyclin-dependent protein kinase complexes (CyclD-CDK4 and CyclE-CDK2) on the cell cycle promotion, thereby resulting in G_1 cell cycle arrest for short periods of time presumably to avoid cells with possible damage from dividing. AKI, acute kidney injury; IGFBP7, insulin-like growth factor-binding protein 7; TIMP-2, tissue inhibitor of metalloproteinases-2.

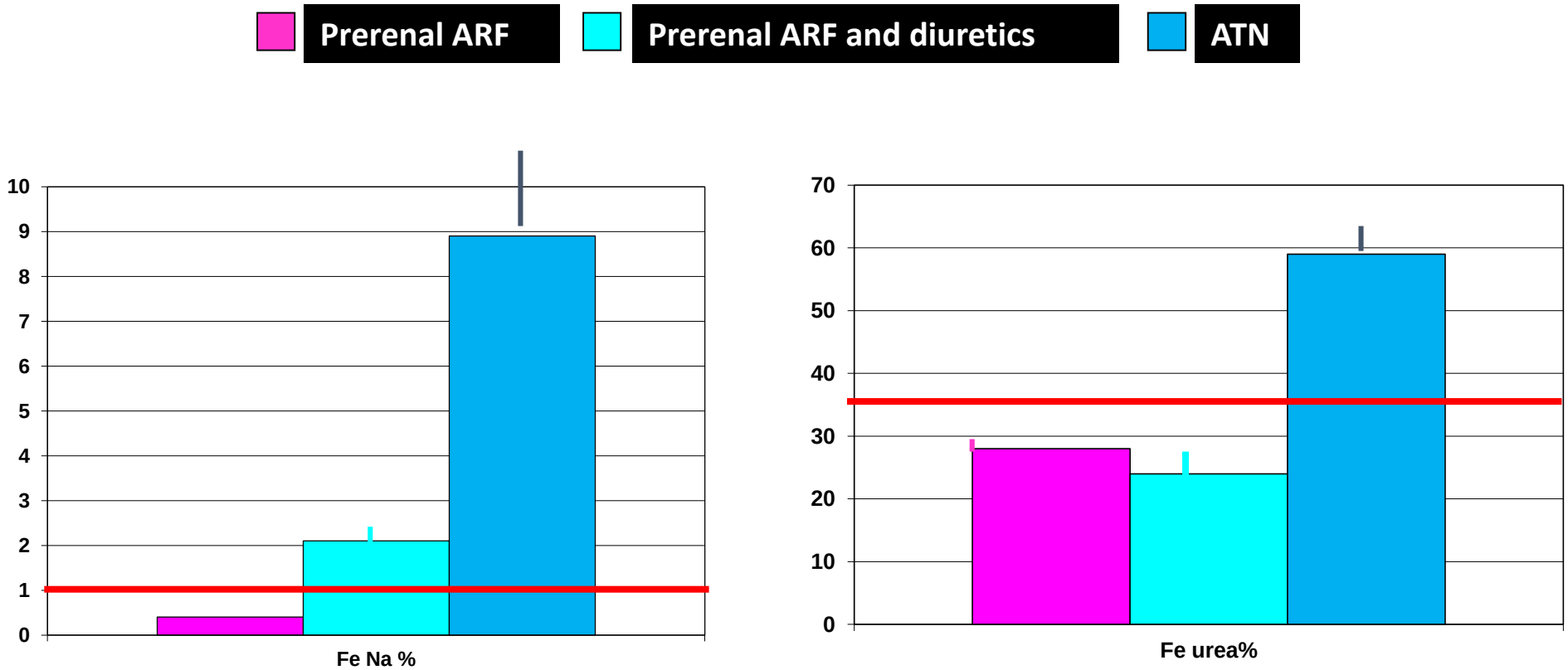
Kashani et al. Critical Care 2013, 17:R25

Biomarker-guided Intervention to Prevent AKI After Major Noncardiac Surgery



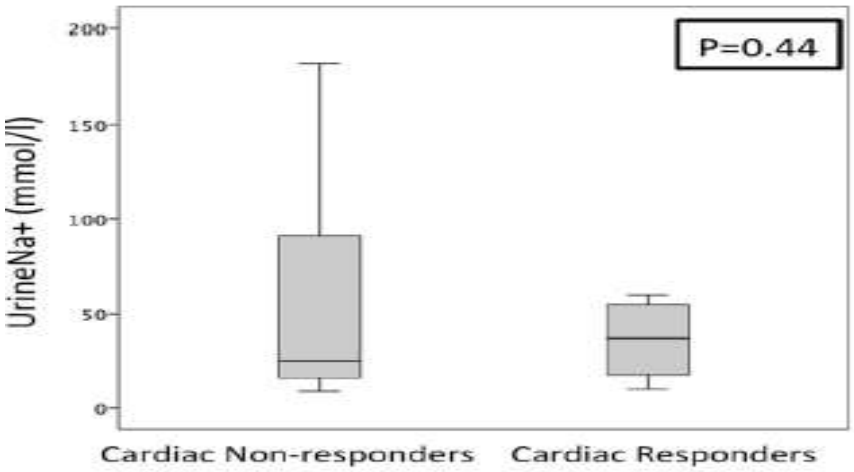
Gӧcze, et al, Annals of Surgery Volume XX, Number XX, Month 2017

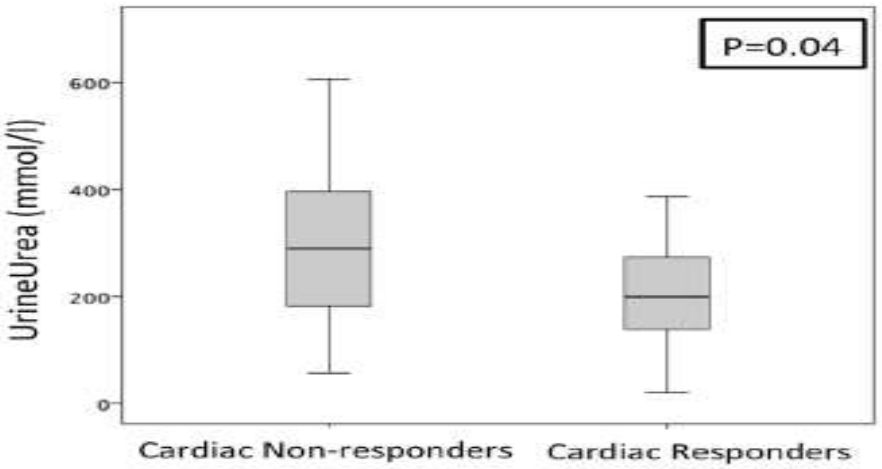
Differential diagnosis between prerenal AKI and acute tubular necrosis (ATN)

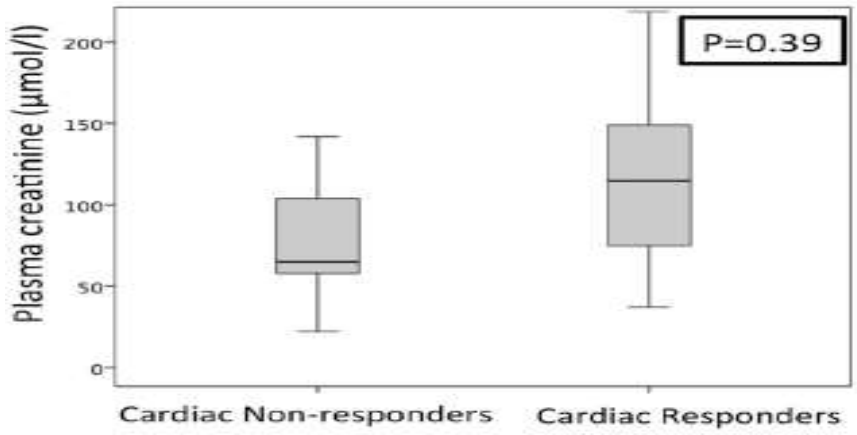


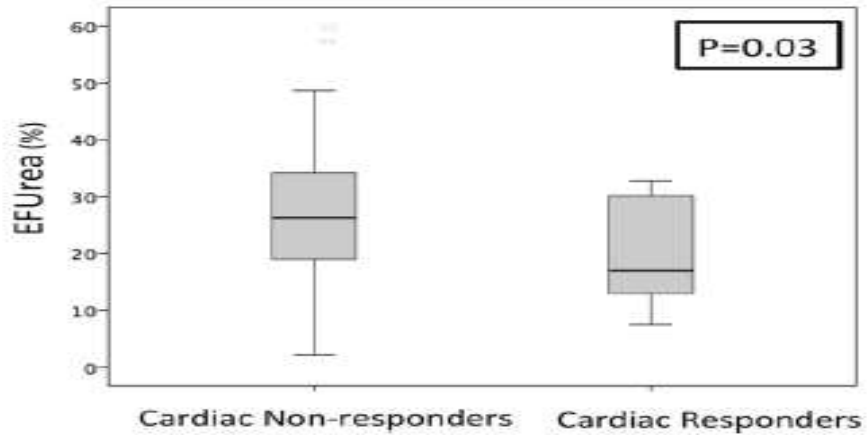
Carvounis et al, Kidney Int 2002, 62:2223-2229.

Urinary parameters as predictor of fluid responsiveness in oliguria









Cardiac responder: increase in SV >15 % at the end of the fluid challenge;
Renal responder: post-fluid challenge UO >0.5 ml/kg/h for > 3h

Legrand et al.
Critical Care (2016) 20:165

The AUROC curves for predicting renal fluid responsiveness were 0.65 for uNa+ , 0.57 for FENa+ , and 0.61 for FEUrea

Clinical DD between prerenal AKI and ATN-

Adjudication of diagnosis made by 3 experienced nephrologists

Panelists adjudications	Final adjudication result* ATN	PRA	Indeterminate	Total n (%)
3ATN	11			11 (16)
3PRA		2		2 (3)
2ATN; 1PRA	16			16 (24)
2ATN; 1IND	11			11 (16)
2PRA; 1ATN		4		4 (6)
2PRA; 1IND		6		6 (9)
2IND; 1ATN			2	2 (3)
2IND; 1PRA			5	5 (8)
1ATN; 1PRA; 1IND	3	1	6	10 (15)
Total	**41**	**13**	**13**	**67 (100)**

ATN = Acute Tubular Necrosis, PRA = Pre-Renal Azotemia.

*Final Adjudication Result was assigned if at least 2 adjudicators agreed on the AKI etiology. Adjudicators met in-person to reach a final consensus on the 10 cases where the initial adjudication differed across all 3 adjudicators.

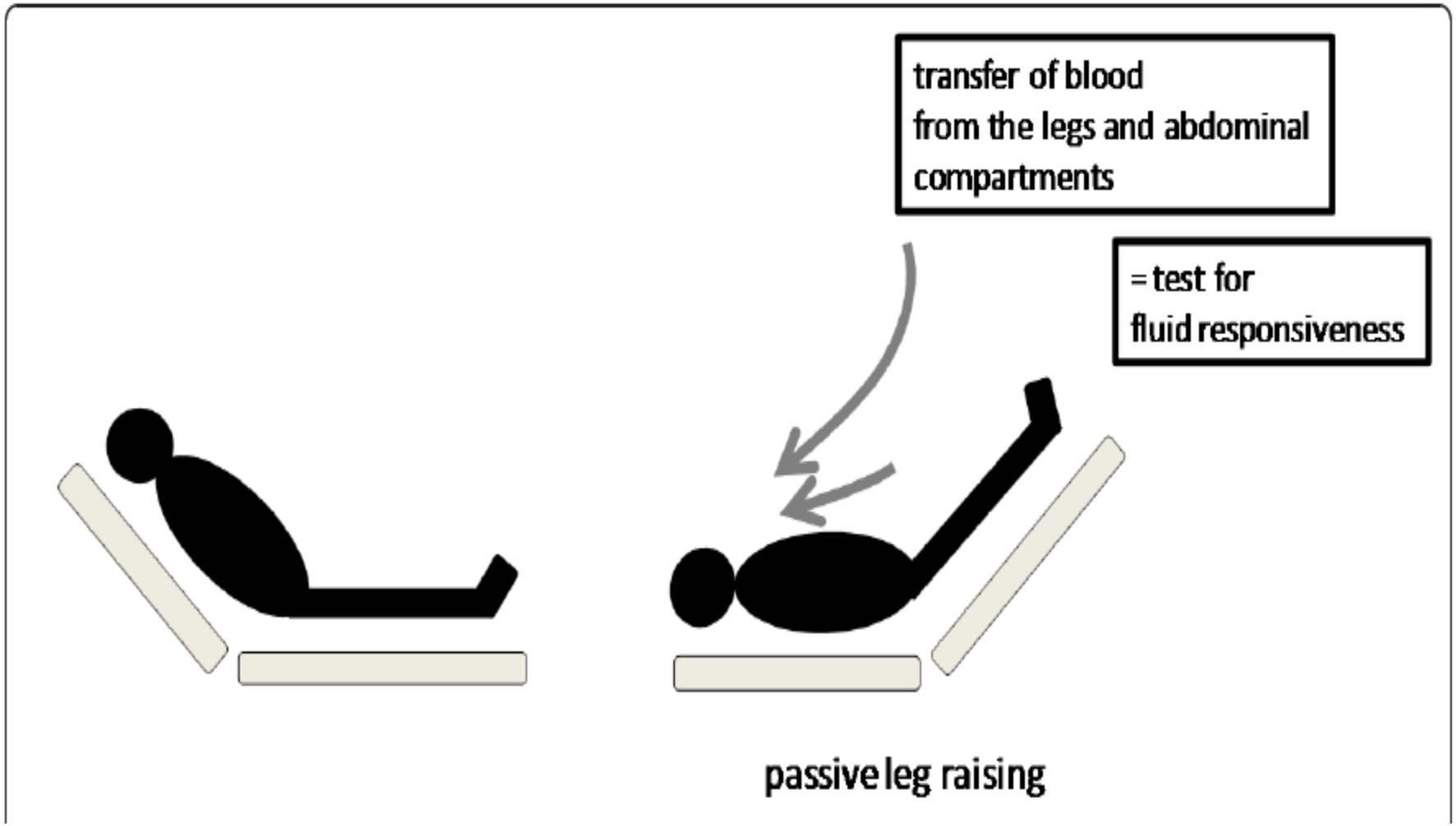
19% !

Total agreement: 13/67: 19%

2/3 agreement : 44/67: 66%

Koyner et al. BMC Nephrology 2014, 15:105

Passive leg raising



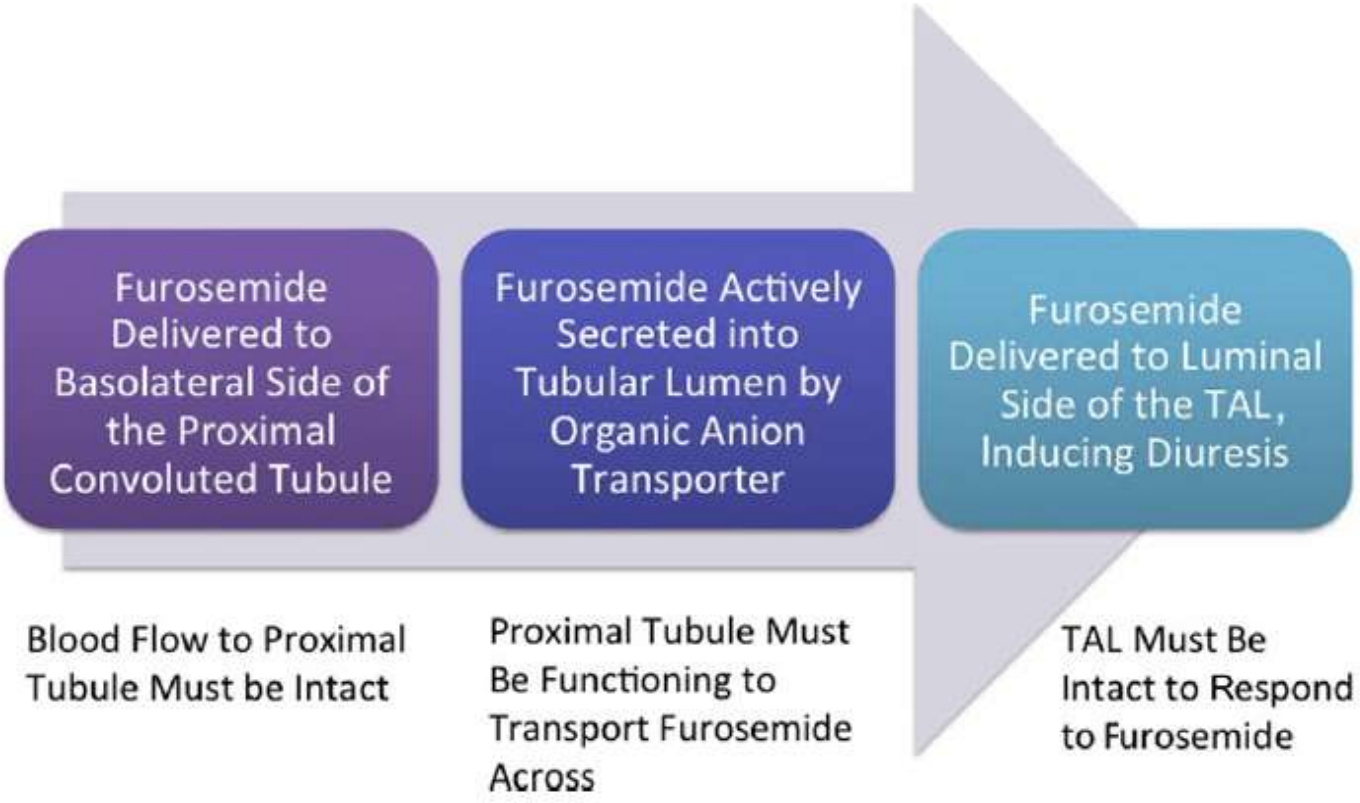
Marik et al. Annals of Intensive Care 2011, 1:1-9

Accuracy of leg-raised change in stroke volume, radial pulse pressure, and peak velocity of femoral artery flow

	Threshold Value	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
ΔSV	10%	86%	90%	86%	90%	8.6	.16
ΔPP	9%	79%	85%	79%	85%	5.2	.25
ΔVF	8%	86%	80%	75%	89%	4.3	.18

Préau et al, Crit Care Med 2010; 38:819–825

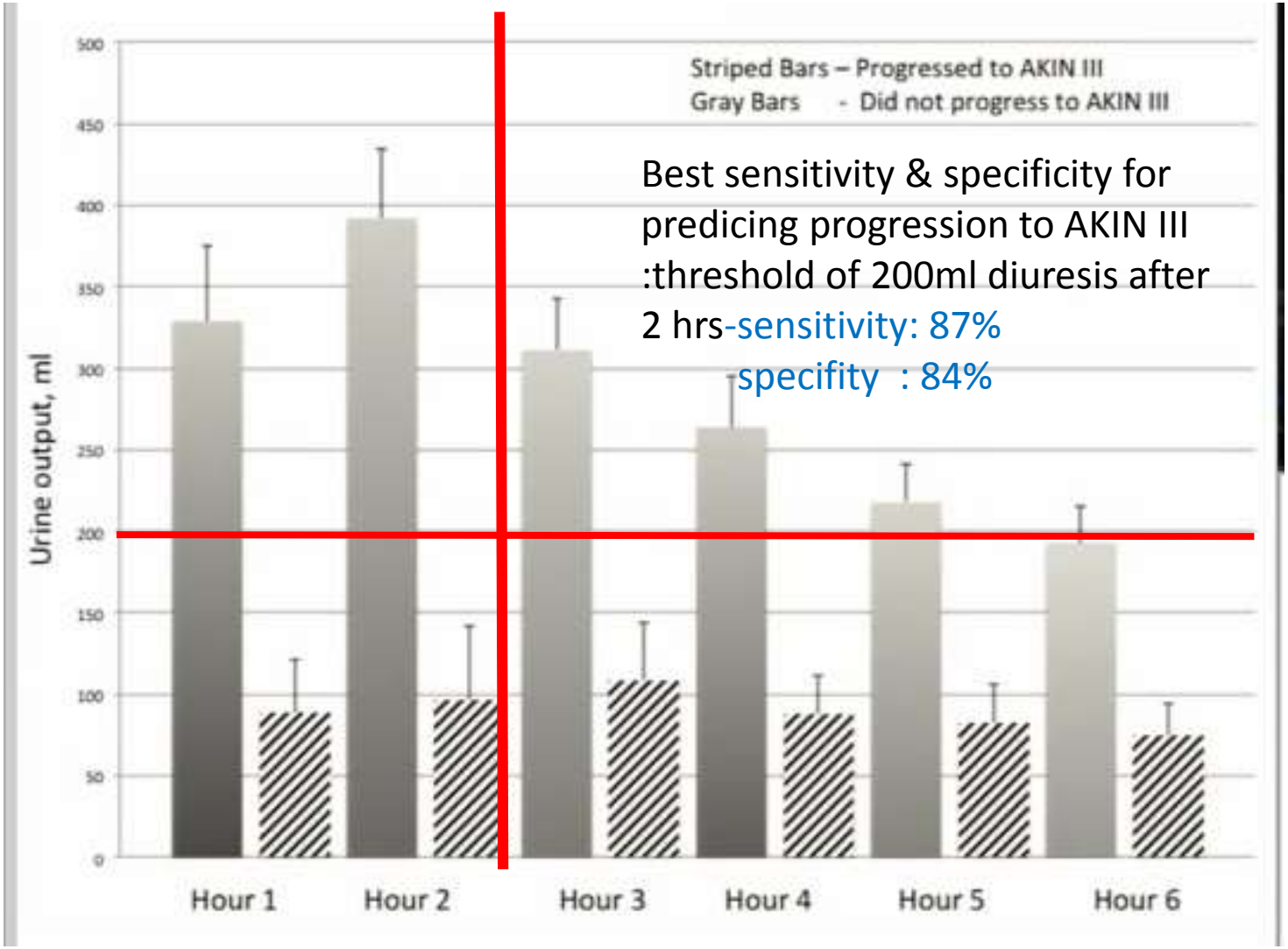
Furosemide urinary response tests tubular integrity -Chawla et al, Crit Care, 17R207, 2013



2-h urine output response to a 1.0mg/kg (in the furosemide naïve) and 1.5 mg/kg (in those with prior loop-exposure)
A cut-off of 200 ml at that same 2-h timepoint provided a sensitivity and specificity of 87.1 and 84.1% for the progression to stage III AKI.

Chawla, Ronco Kidney International Reports (2016) 1, 57–63

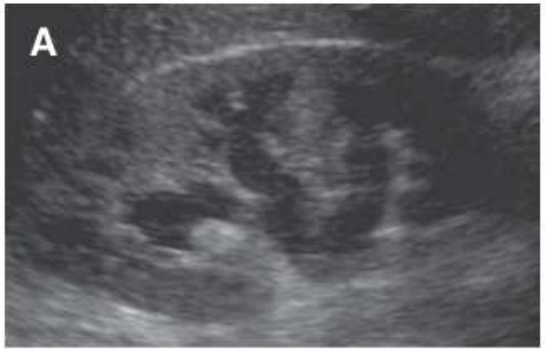
Progression to AKIN III according the diuretic response to furosemide



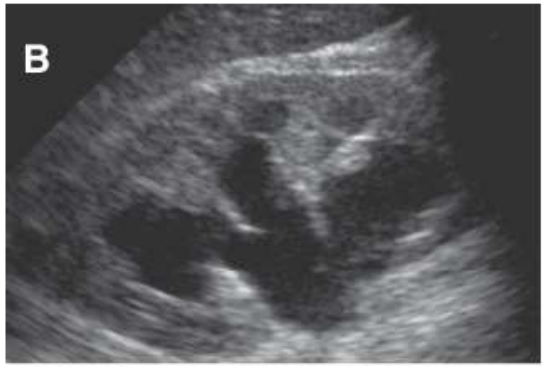
Best sensitivity & specificity for predicing progression to AKIN III :threshold of 200ml diuresis after 2 hrs-sensitivity: 87%
specifity : 84%

Chawla et al, Crit Care, 2013, R207

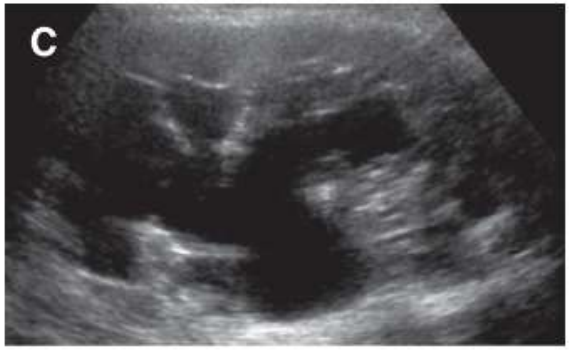
The ultrasound image in obstructive AKI



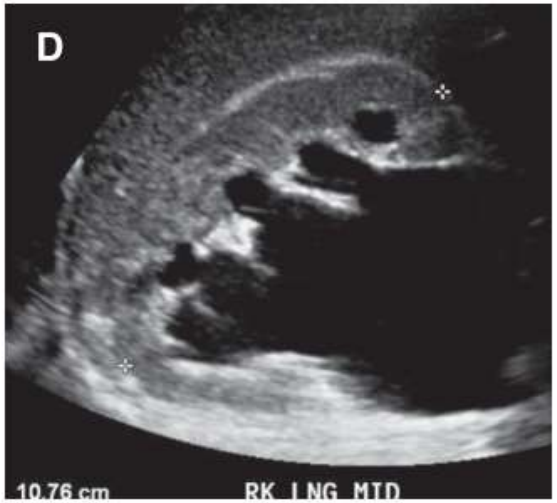
Mild hydronephrosis



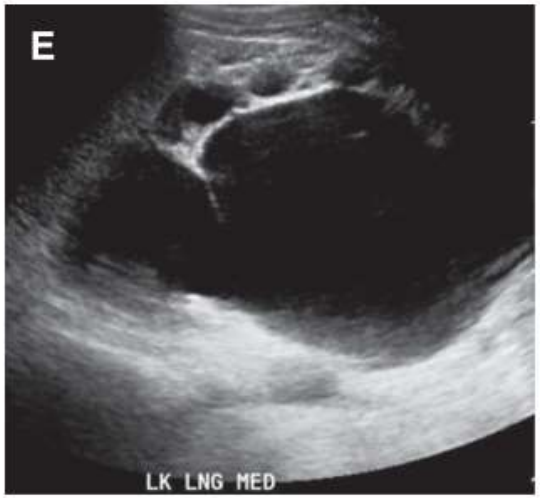
Moderate hydronephrosis



Severe hydronephrosis



Severe hydronephrosis



Severe hydronephrosis

Faubel et al, cJASN, 9: 382-394; 2014

Current terminology and clinical criteria for sepsis and septic shock - The 3th Int Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Current Guidelines and Terminology	Sepsis	Septic Shock
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis[a] and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation[13]

The quick SOFA (Sequential Organ Failure Assessment)

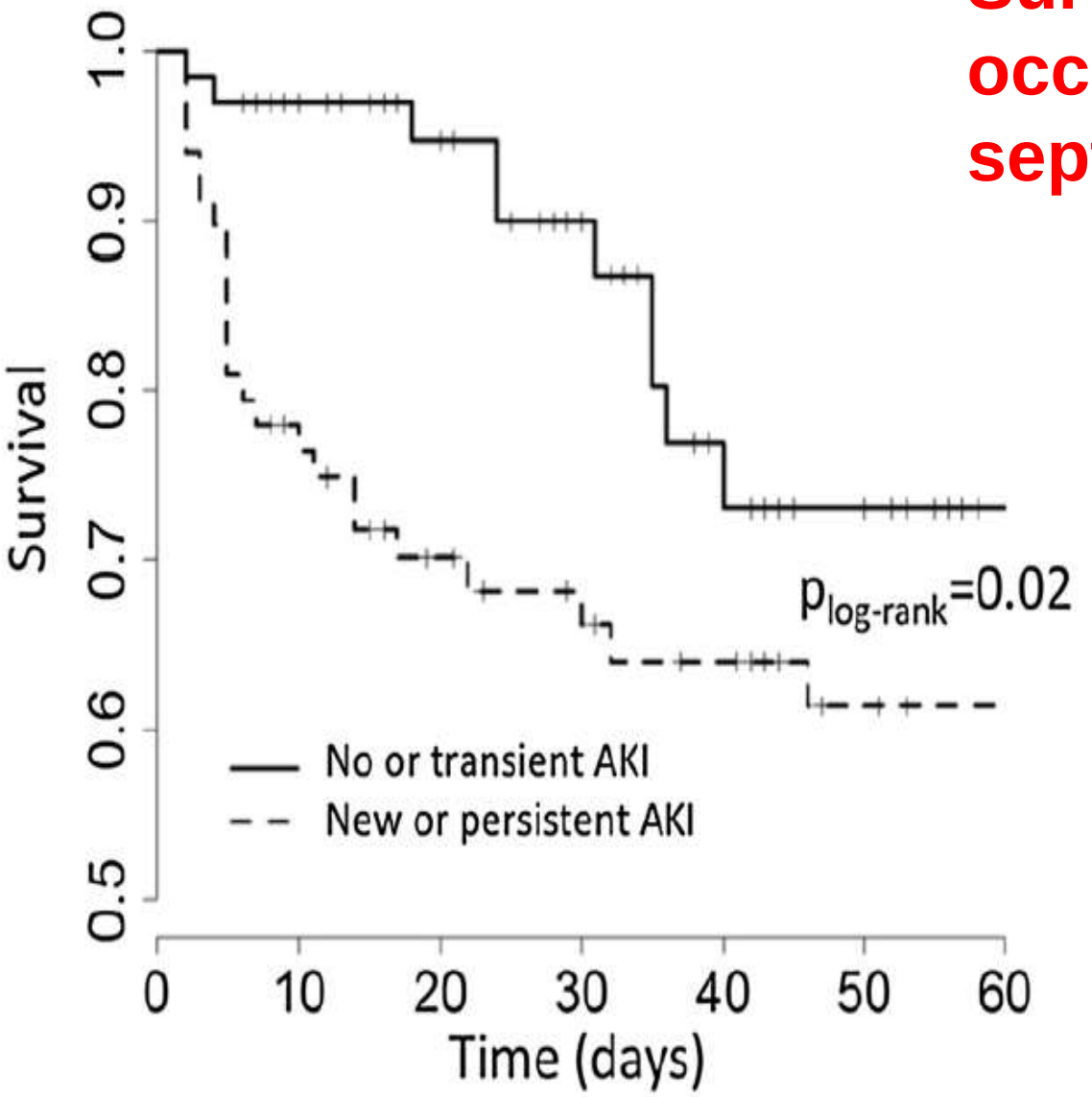
Respiratory rate ≥22/min

Altered mentation

Systolic blood pressure ≤100 mm Hg

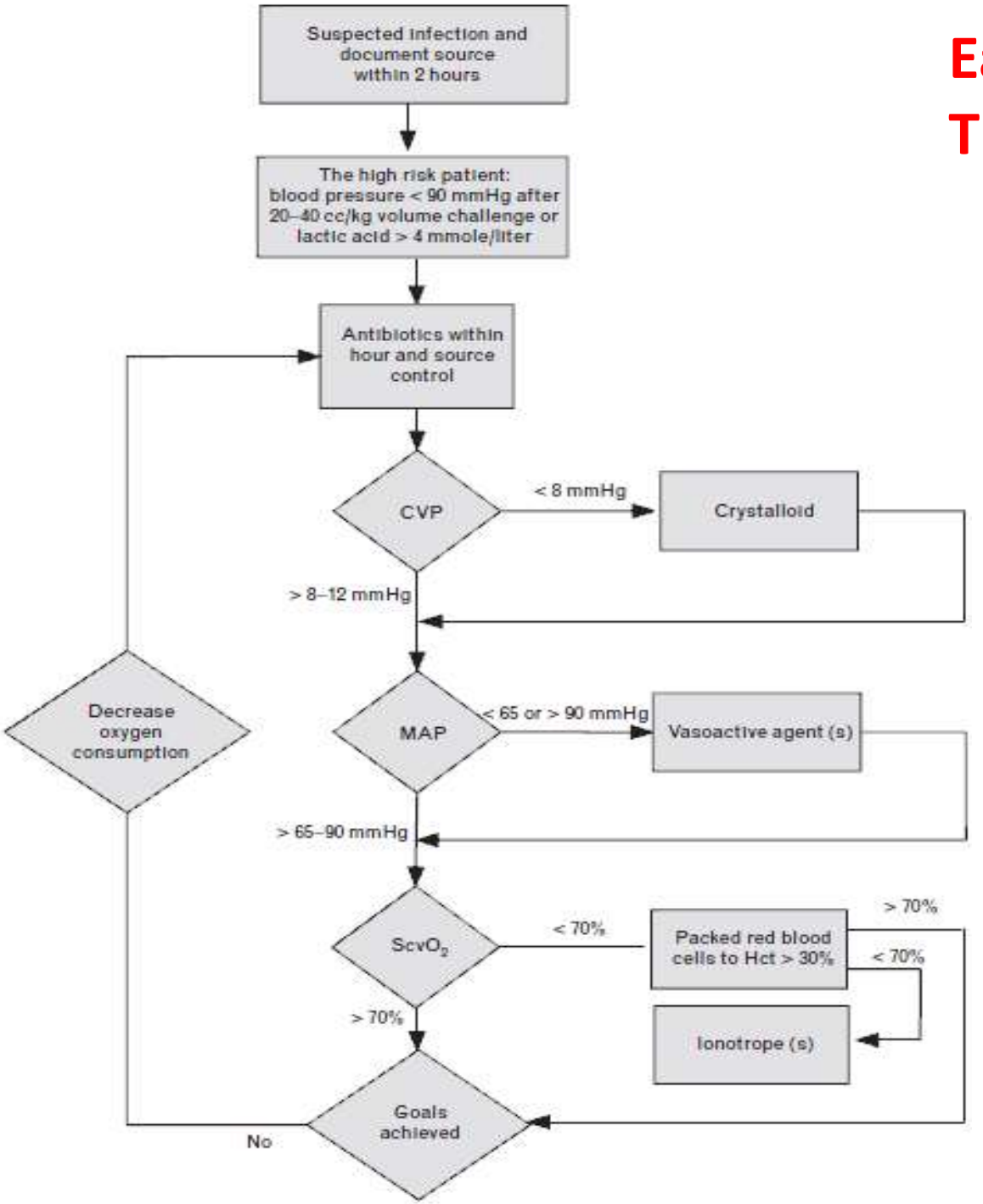
JAMA. 2016;315(8):801-810.

Survival according the occurrence of AKI in septic shock



Legrand et al. Critical Care 2013, 17:R278

Early Goal Directed Therapy in septic shock



Rivers et al, N Engl JMed 2001; 345:1368–1377.

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

SURVIVING SEPSIS CAMPAIGN CARE BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level

2) Obtain blood cultures prior to administration of antibiotics

3) Administer broad spectrum antibiotics

4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

Dellinger et al, Critical Care Med, 41: 580-637, 2013

Vasopressor therapy

- If hypotension is severe or if it persists despite adequate fluid resuscitation, use of vasopressors is indicated:
  - **Vasopressor of first choice: Norepinephrin** (0.1-2.0 µg/kg/min)
  - Dopamin not better than Norepinephrin but may induce more arrhythmias, increased mortality in cardiogenic shock*
  - Epinephrin not better than Norepinephrin**
- **Inotropic agent of first choice: Dobutamine**
- PDE-III inhibitors (Milrinone, Enoximone) combine inotropic and vasodilatory effects and may reinforce the effects of dobutamine

*De Backer D et al., NEJM 2010; 362: 779-89
**Annane D et al., Lancet 2007; 370: 676-84

Angiotensin II for the Treatment of Vasodilatory Shock- primary and seondary endpoints

End Point	Angiotensin II (N=163)	Placebo (N=158)	Odds or Hazard Ratio (95% CI)	P Value
Primary efficacy end point: MAP response at hour 3 — no. (%)†	114 (69.9)	37 (23.4)	Odds ratio, 7.95 (4.76–13.3)	<0.001
Secondary efficacy end points				
Mean change in cardiovascular SOFA score at hour 48‡	−1.75±1.77	−1.28±1.65		0.01
Mean change in total SOFA score at hour 48§	1.05±5.50	1.04±5.34		0.49
Additional end points				
Mean change in norepinephrine-equivalent dose from baseline to hour 3¶	−0.03±0.10	0.03±0.23		<0.001
All-cause mortality at day 7 — no. (%)	47 (29)	55 (35)	Hazard ratio, 0.78 (0.53–1.16)	0.22
All-cause mortality at day 28 — no. (%)	75 (46)	85 (54)	Hazard ratio, 0.78 (0.57–1.07)	0.12

Khanna et al N Engl J Med 2017, 377:419-430

What fluid to choose?

Colloids

- Less for more IV volume
- Faster effect
- Less oedema
- Albumin: its human!

- AKI
- Pruritus
- More expensive

Crystalloids

- Water and salt : its human!
- Cheap

- Volume overload
- Hyperchloremic metabolic acidosis

Surviving Sepsis Campaign Statement Regarding Hemodynamic and Oximetric Monitoring in Response to ProCESS and ARISE Trials (October 1, 2014)

- Required monitoring of CVP and $ScvO_2$ via a CVC as part of an early resuscitation strategy does not confer survival benefit in all patients with septic shock who have received timely antibiotics and fluid resuscitation compared with controls.
- Requiring measurement of CVP and $ScvO_2$ in all patients who have lactate results >4 mmol/L and/or persistent hypotension after initial fluid challenge and who have received timely antibiotics is not supported by the available scientific evidence.
- The results of the ProCESS and ARISE trials have not demonstrated any adverse outcomes in the groups that utilized CVP and $ScvO_2$ as end points for resuscitation.
- Therefore, no harm exists in keeping the current SSC bundles intact until a thorough appraisal of all available data has been performed.

http://www.survivingsepsis.org/

Association of Hydroxyethyl Starch Administration With Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation

A Systematic Review and Meta-analysis

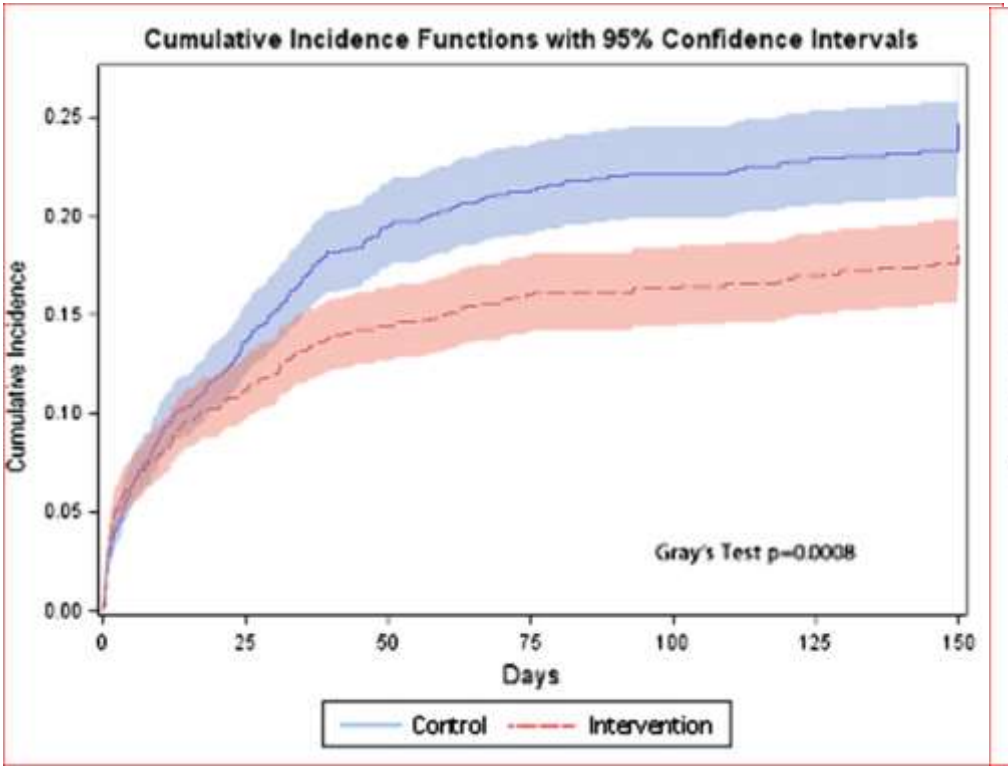
- Meta-analysis of 38 randomized controlled trials
- Hydroxyethyl starch was found to be associated with
  - increased mortality among 10,290 patients (RR 1.09; 95% CI 1.02 -1.17)
  - increased renal failure among 8,725 patients (RR, 1.27; 95% CI 1.09-1.47) and
  - increased use of renal replacement therapy among 9,258 patients (RR, 1.32; 95% CI, 1.15 to 1.50)

FDA & EMEA:

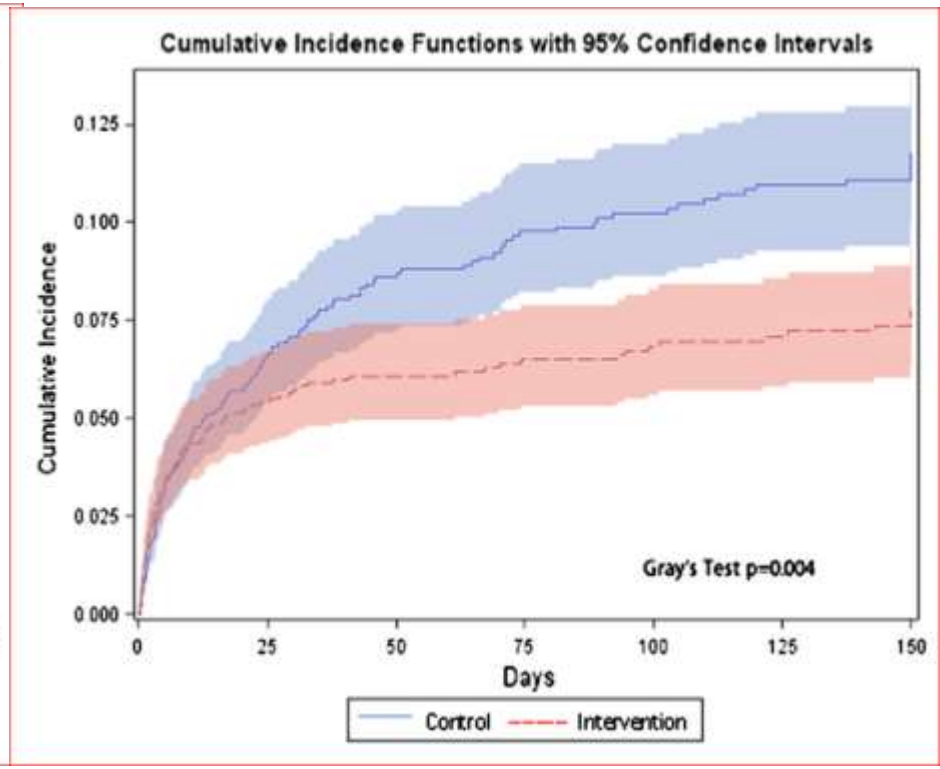
Do not use HES solutions in critically ill adult patients, including those with sepsis!

Zarychanski et al, JAMA, 309: 678-688, 2013

Chloride-liberal vs. chloride-restrictive intravenous fluid administration and AKI: an extended analysis



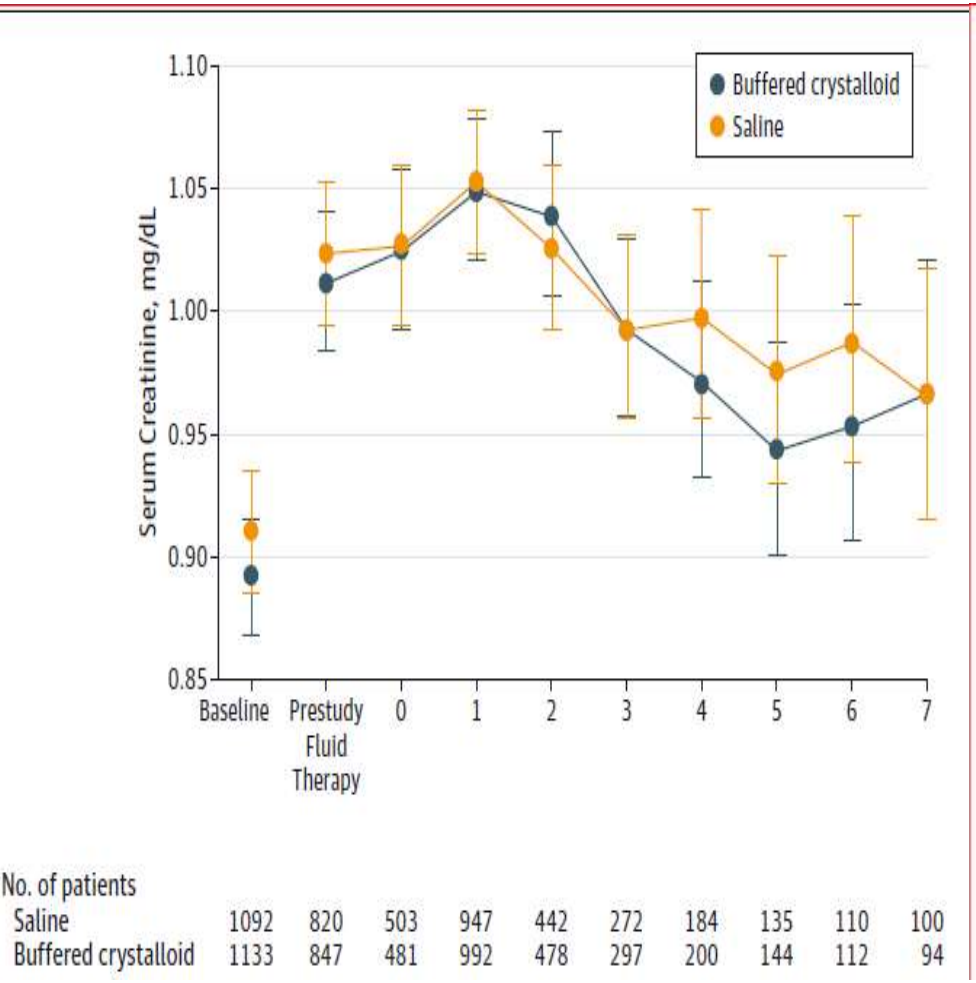
Cumulative incidence of KDIGO-defined AKI stages 2 and 3



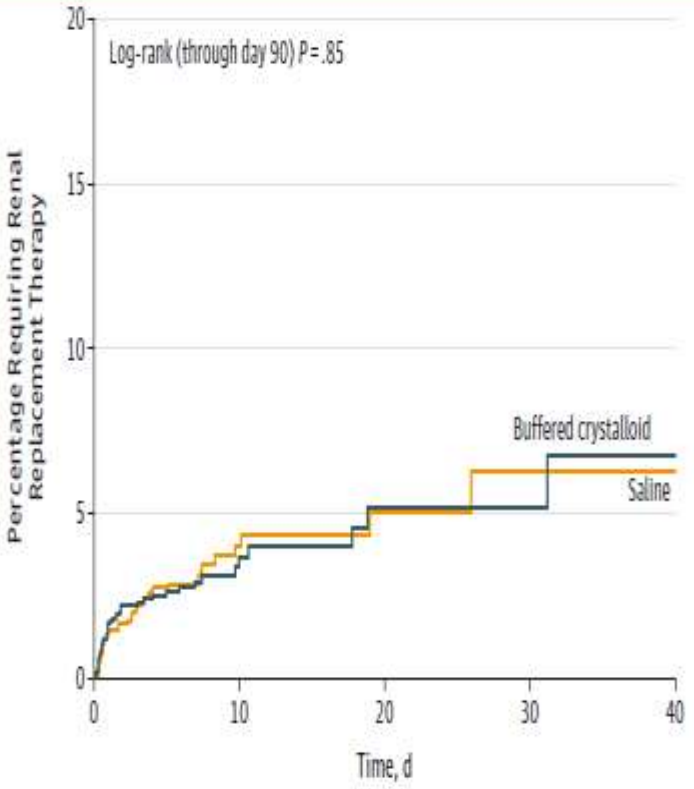
Cumulative incidence of renal replacement therapy

Yunos et al, Intensive Care Med (2015) 41:257–264

Effect of a Buffered Crystalloid Solution vs Saline on AKI Among Patients in the ICU



No. of patients										
Saline	1092	820	503	947	442	272	184	135	110	100
Buffered crystalloid	1133	847	481	992	478	297	200	144	112	94



No. at risk					
Buffered crystalloid	1152	341	134	62	36
Saline	1110	310	124	64	28

Cumulative Incidence of Patients Requiring RRT Until Day 90 After Enrollment in the SPLIT Trial

Young et al , *JAMA*. 2015;314:1701-1710

“Trial and error” fluid challenge- ”TROL”

1—Type of fluid (e.g., Ringer’s lactate or isotonic saline)

2—Rate of infusion (e.g., 500 ml in 30 min)

3—Objective (e.g., increase in arterial pressure to 75 mmHg or urine output greater than 20 ml in 30 min);

4—Limits (e.g., a maximal increase in CVP of 3mmHg from a baseline of 12mmHg).

Vincent, De Backer, Kidney Int , 2012

The NEW ENGLAND JOURNAL of MEDICINE

PRCT
N = 1000

ORIGINAL ARTICLE

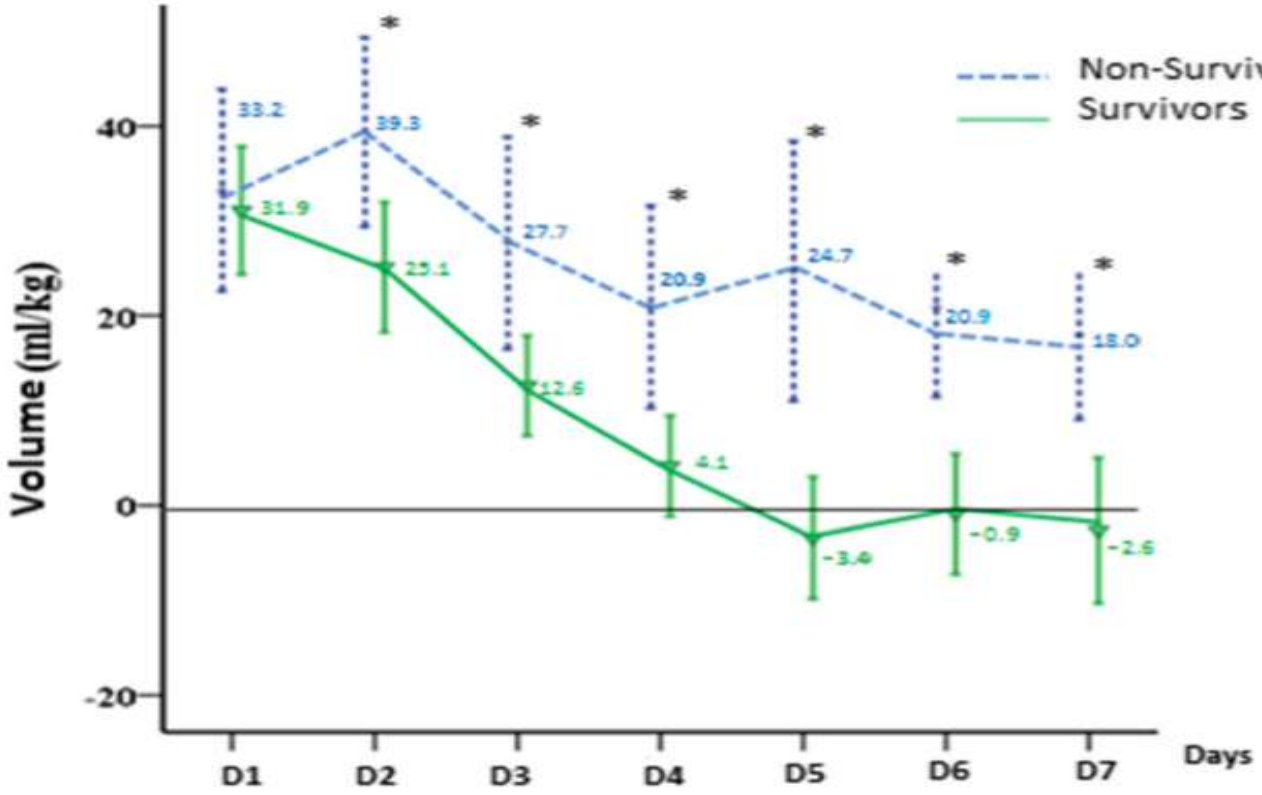
Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

	Conservative	Liberal	P
7 d volume balance (mL)	**-136 mL ± 491**	**+6992 ± 502**	**<0.001**
Death at 60 days	25.5%	28.4%	0.30
Ventilator free days	14.6 ± 0.5	12.1 ± 0.5	**<0.001**
ICU free days:			
Day 1-7	0.9 ± 0.1	0.6 ± 0.1	**<0.001**
Day 1-28	13.4 ± 0.4	11.2 ± 0.4	**<0.001**

Wiedemann, N Engl J Med 2006

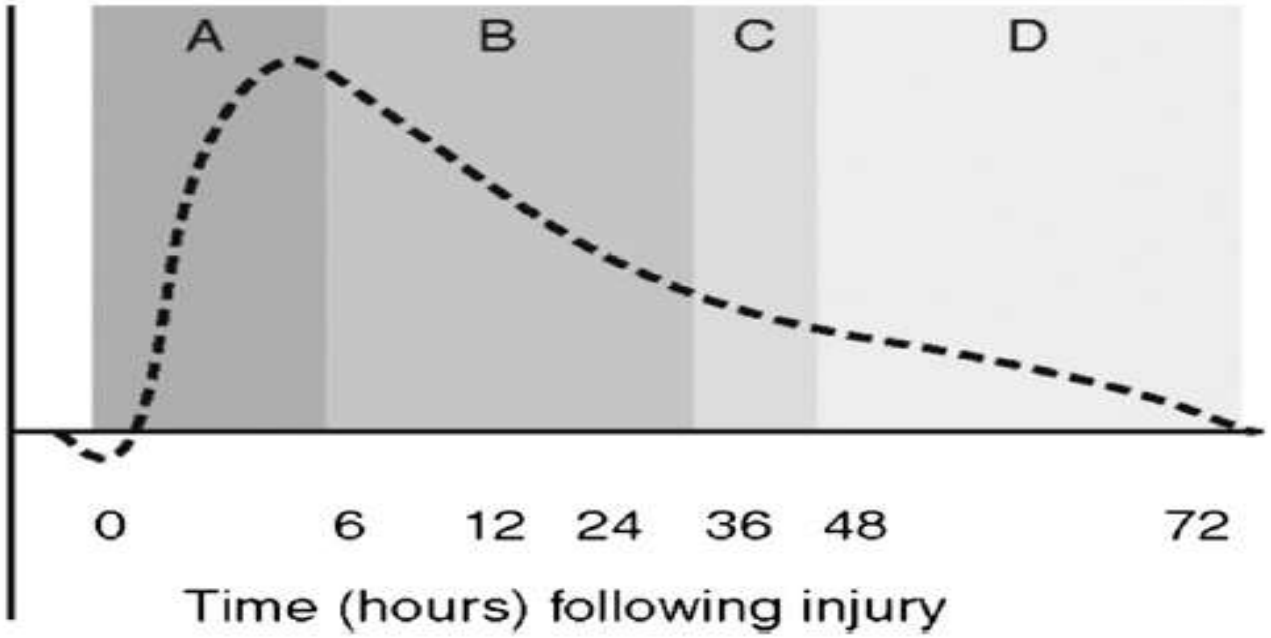
Mean fluid balance in survivors and non-survivors over 7 days after onset of sepsis



Number of patients per day							
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
NS	59	59	59	51	43	38	31
S	114	114	114	96	75	64	49

Angela Acheampong and Jean-Louis Vincent, Crit Care, Critical Care (2015) 19:251

Fluid resuscitation strategy during the stress response of sepsis



Phase A: 0 to 6 hours, indicates aggressive volume resuscitation. Phase B: 6 to 36 hours, indicates decelerating fluid resuscitation; fluid boluses should be administered to compensate for extra-vascular sequestration. Phase C: 36 to 48 hours, indicates the equilibrium phase; stop administering intravenous fluids. Phase D: 48 to 72 hours, indicates mobilization fluids; withhold fluids and allow spontaneous diuresis (or diurese if necessary).

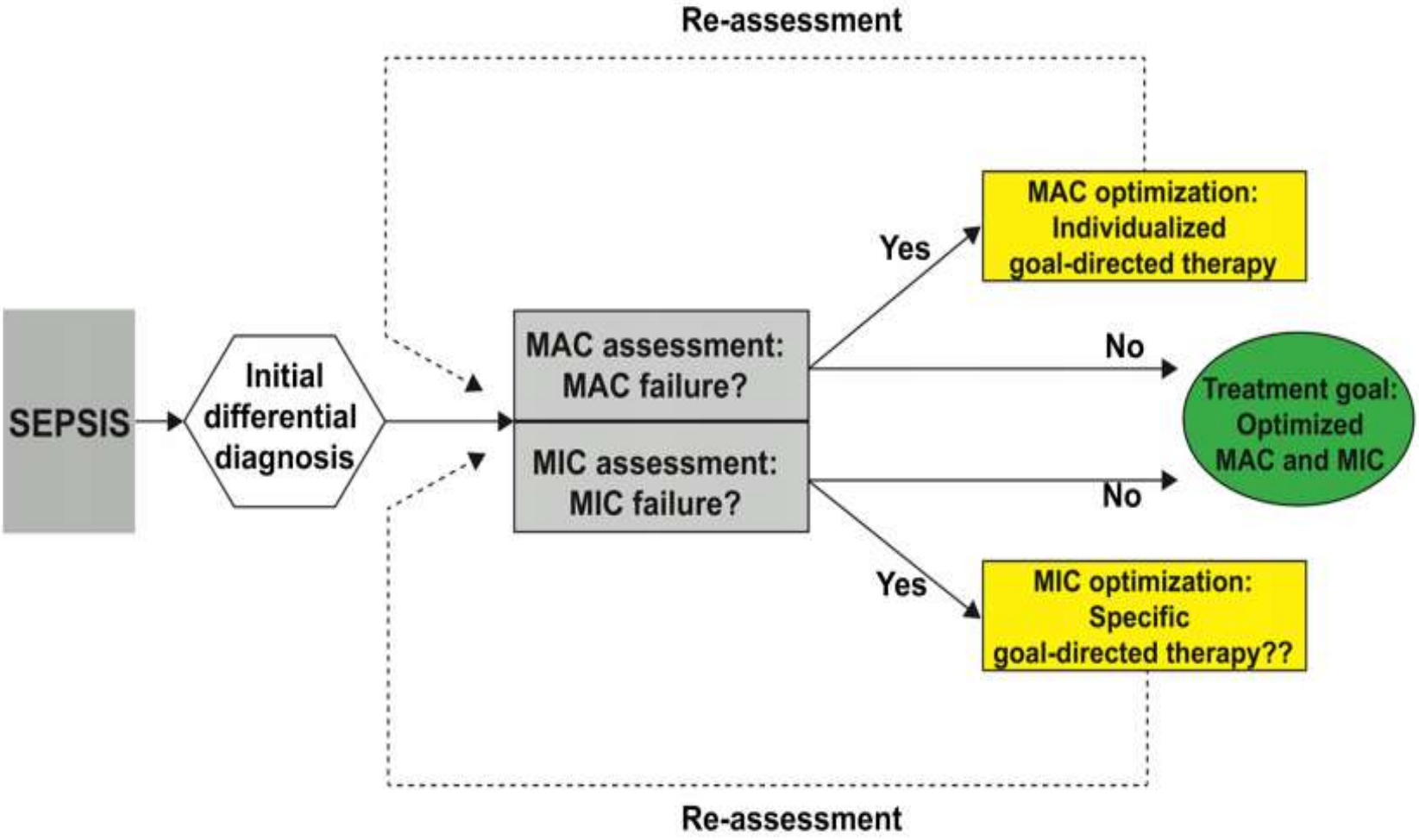
Godin, Murray, Mehta Semin Nephrol35:12-22 ,2015

CHAPTER 3.4: THE USE OF DIURETICS IN AKI

- **3.4.1: We recommend not using diuretics to prevent AKI. (*1B*)**

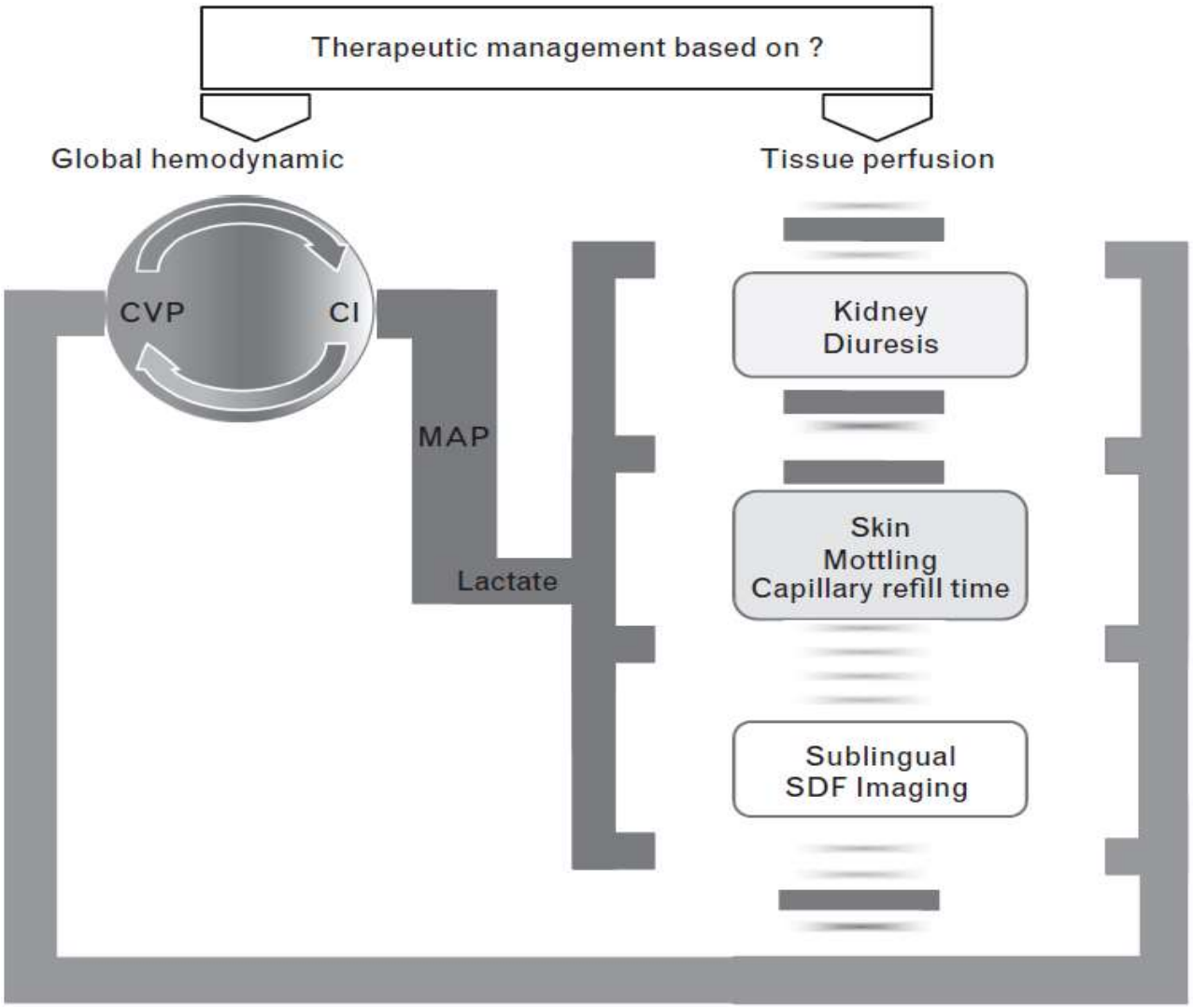
- **3.4.2: We suggest not using diuretics to treat AKI, except in the management of volume overload. (*2C*)**

Inidividualized goal-directed hemodynamic therapy of the macro-and microcirculation in sepsis



Saugel et al, SHOCK, 43 : 522-529, 2015

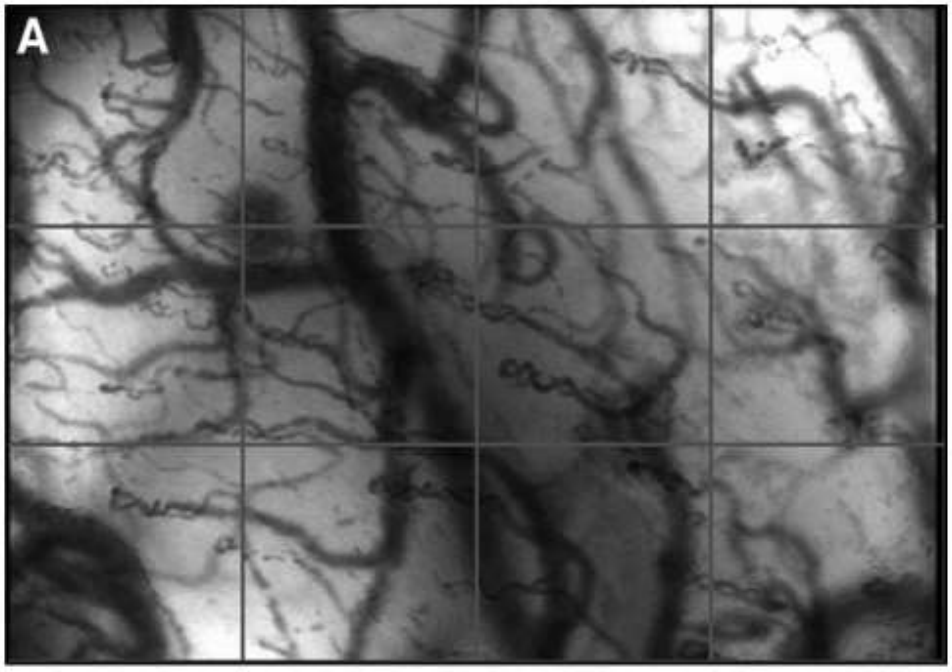
Management of septic shock should be based on both global hemodynamic parameters and tools that reflect tissue perfusion

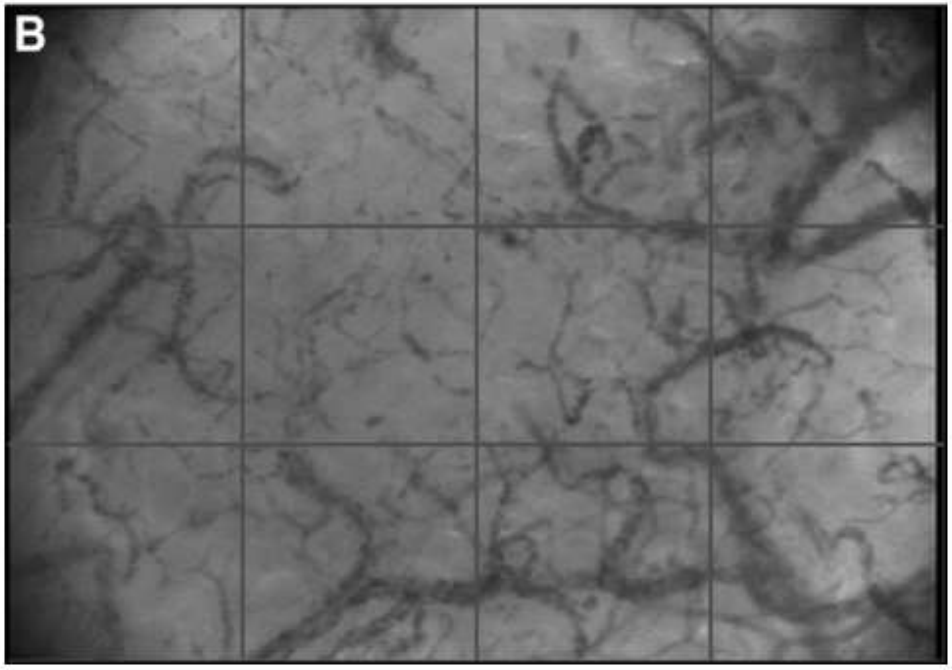


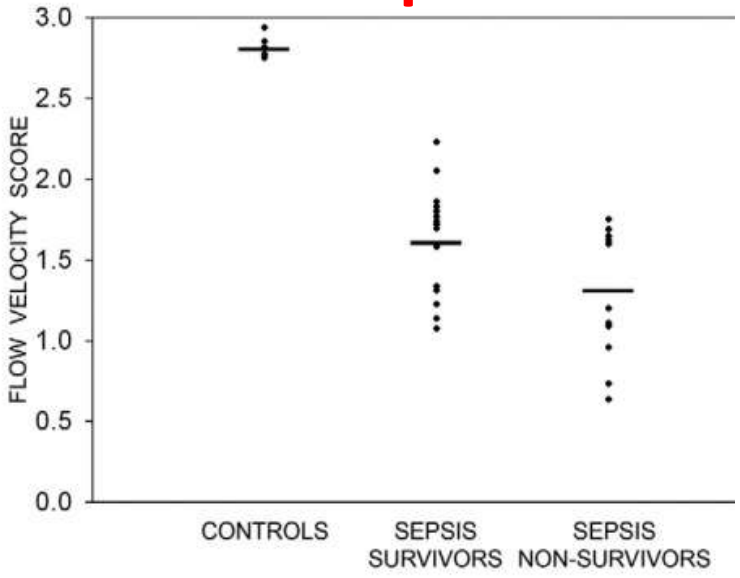
SDF: side stream dark field

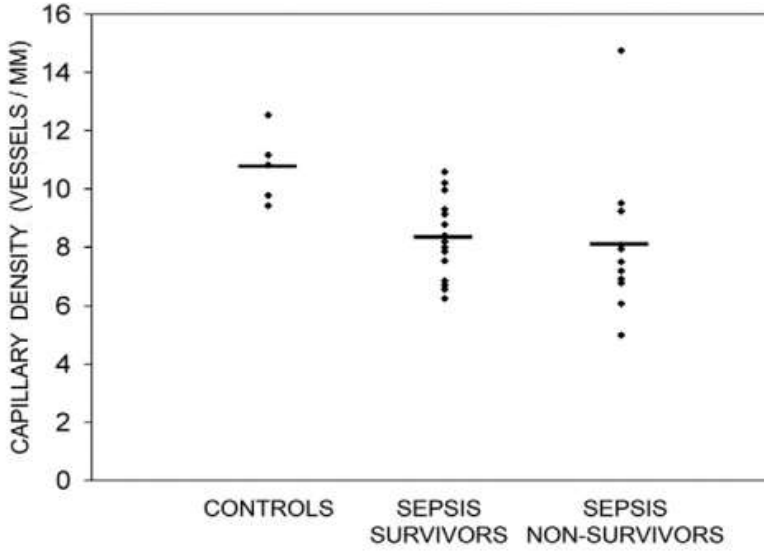
Ait-Oufella et al,
Curr Opin Crit Care 2015,
21:271–275

Sublingual microperfusion in sepsis









Trzeciak et al, Ann Emerg Med. 2007;49:88-98