AKI Risk Assessment, Prevention & Early Detection

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Brighton & Sussex Medical School

Western Sussex Hospitals NHS
NHS Trust

In 25 Minutes…

What Do we Mean By Risk Assessment?

HSE

Health and Safety Executive

Five steps to risk assessment

Step 1
Identify the hazards

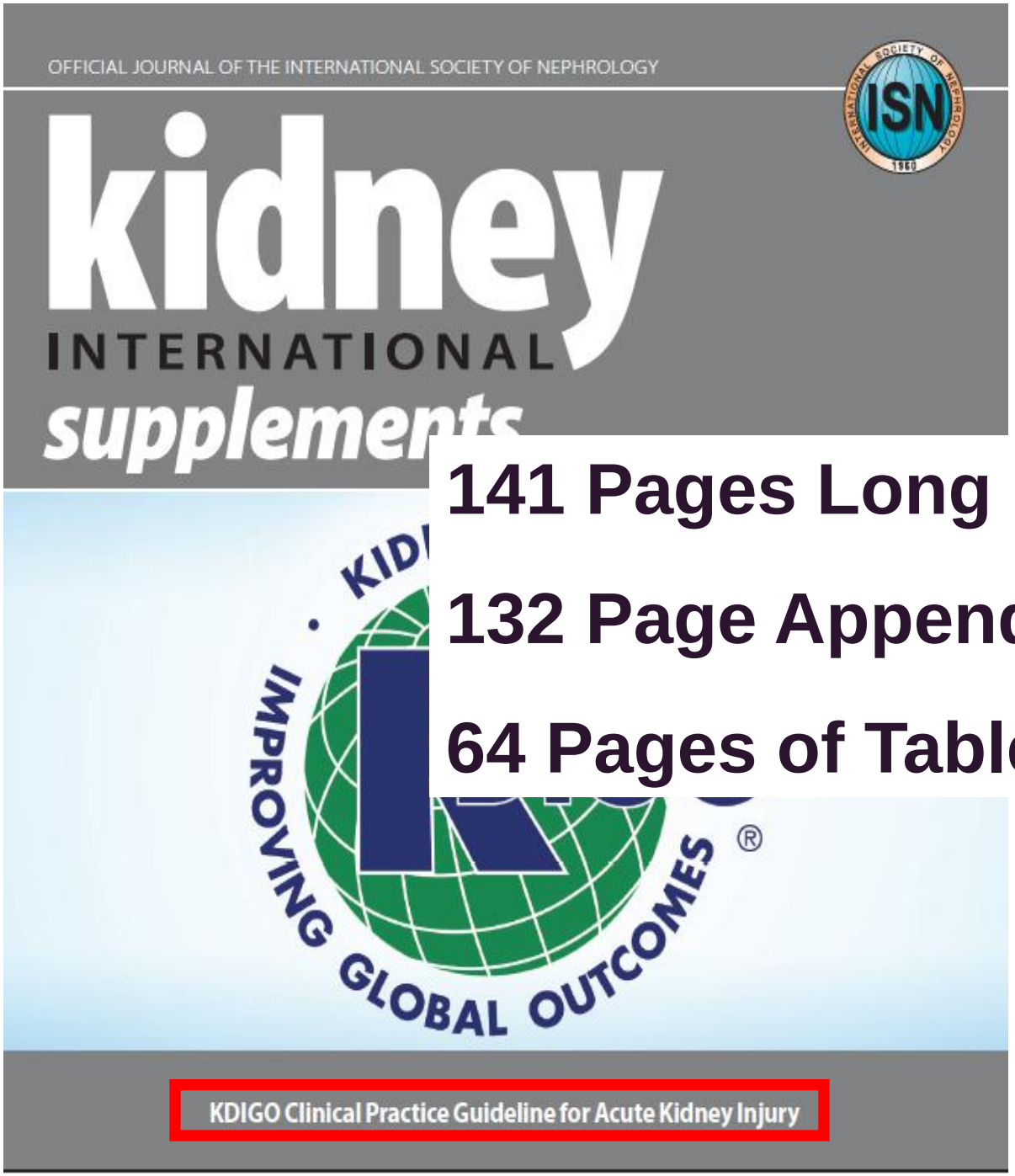

AMBULANCE

Step 1
Identify the hazards

Step 2
Decide who might be harmed and how

So Who Is At Risk?

Where Do We Go For Guidance?

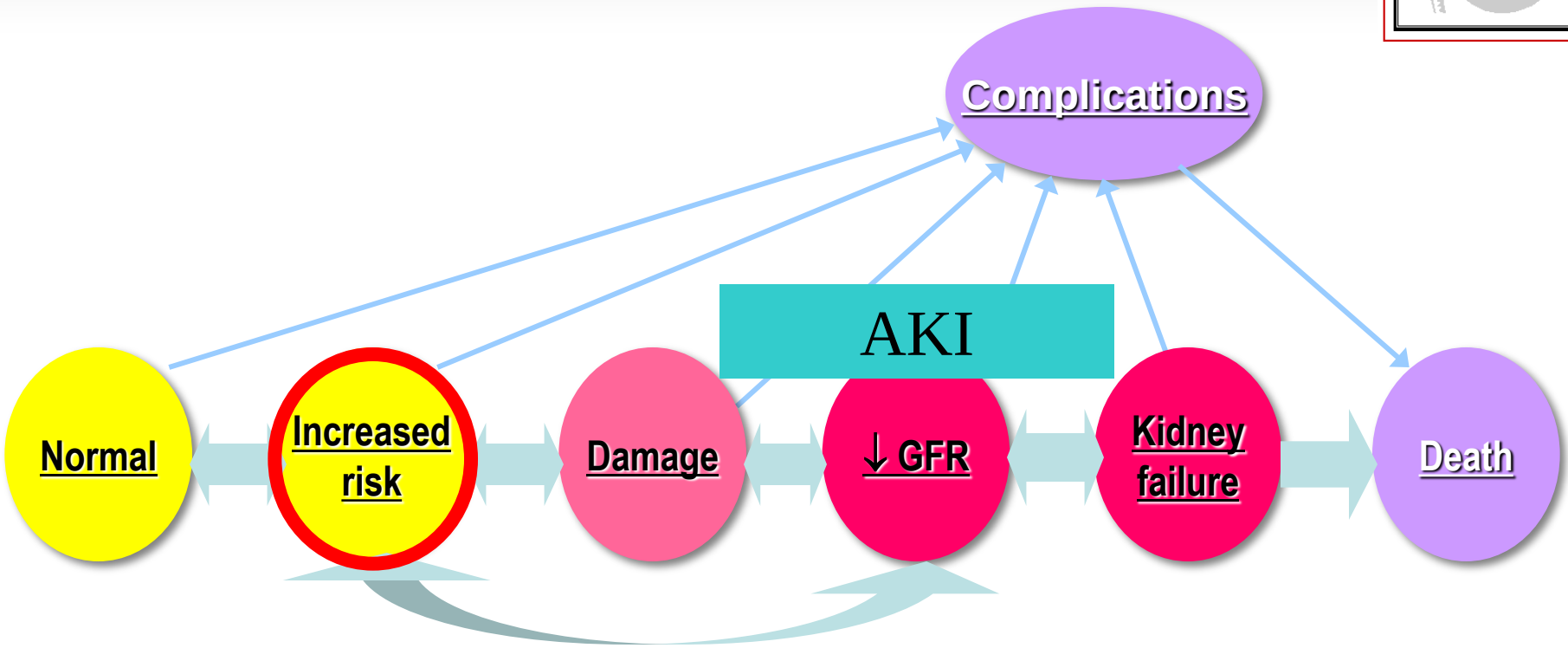


141 Pages Long

132 Page Appendix

64 Pages of Tables

Conceptual Model for Acute Kidney Injury (AKI)



Kidney Disease: Improving Global Outcomes

Vancouver meeting 2006

Risk Factors for Developing AKI

Shared (patient specific):

- Volume Depletion
- Age
- Female Gender
- CKD
- Previous AKI
- Comorbidities
  - CHF
  - COPD
  - Hypertension
  - Diabetes
- Premedication
  - ACE/ARB
  - Devil‘s Medicine

Disease specific:

- Genetics
- Pathophysiology

Intervention Specific:

- Medication
- Procedures

Revised Risk factors for AKI

Shared (patient specific):

- **Old Age**
- Female Gender
- CKD
- Previous AKI
- Comorbidities
  - **CHF**
  - **Liver Disease**
  - **Proteinuria**
- Premedication
  - ACE/ARB
  - NSAIDS

Disease specific:

- Genetics
- Pathophysiology

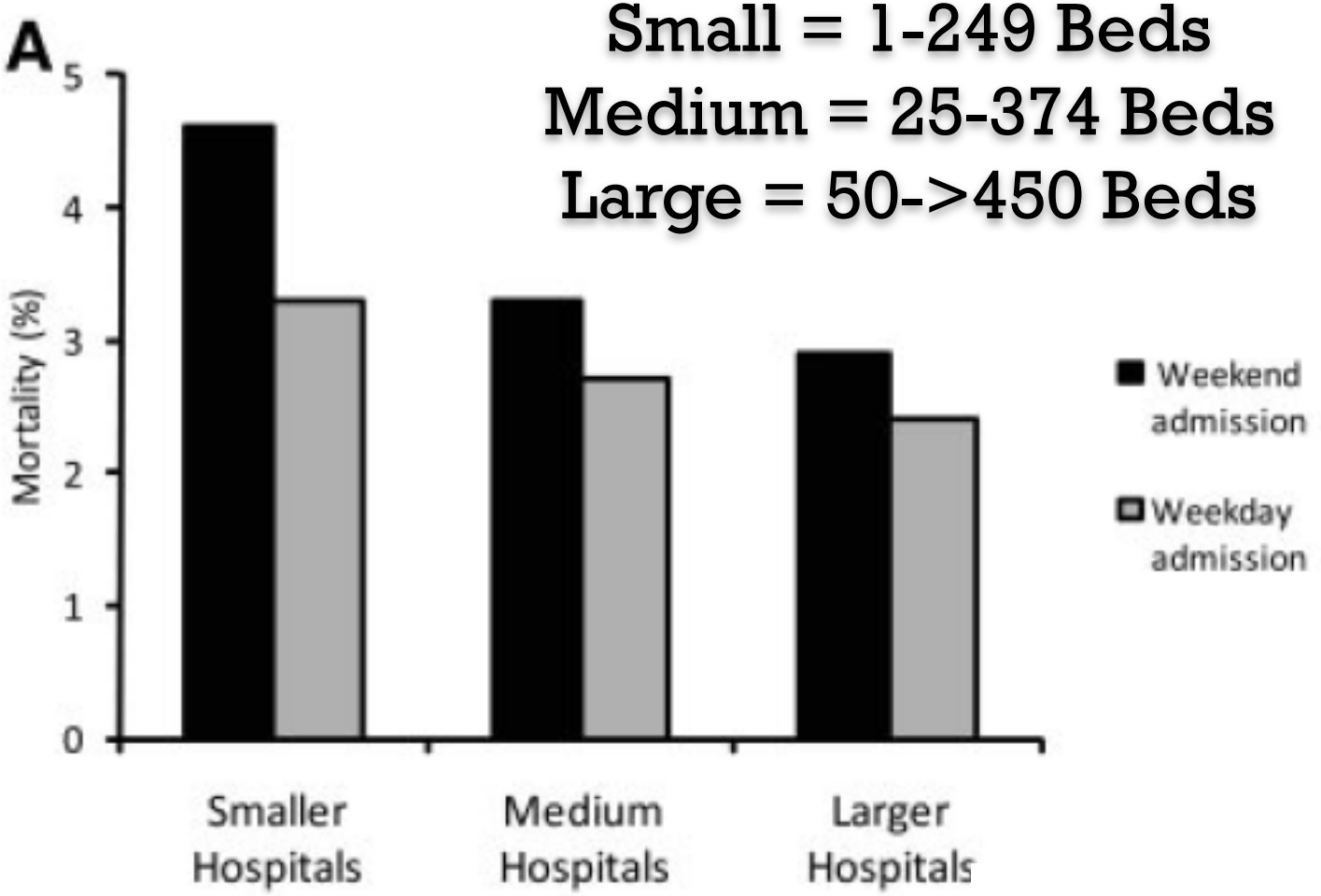
Intervention specific:

- Medication
- Procedures
- **Weekend Admission**
- **Surgery**

Examples?

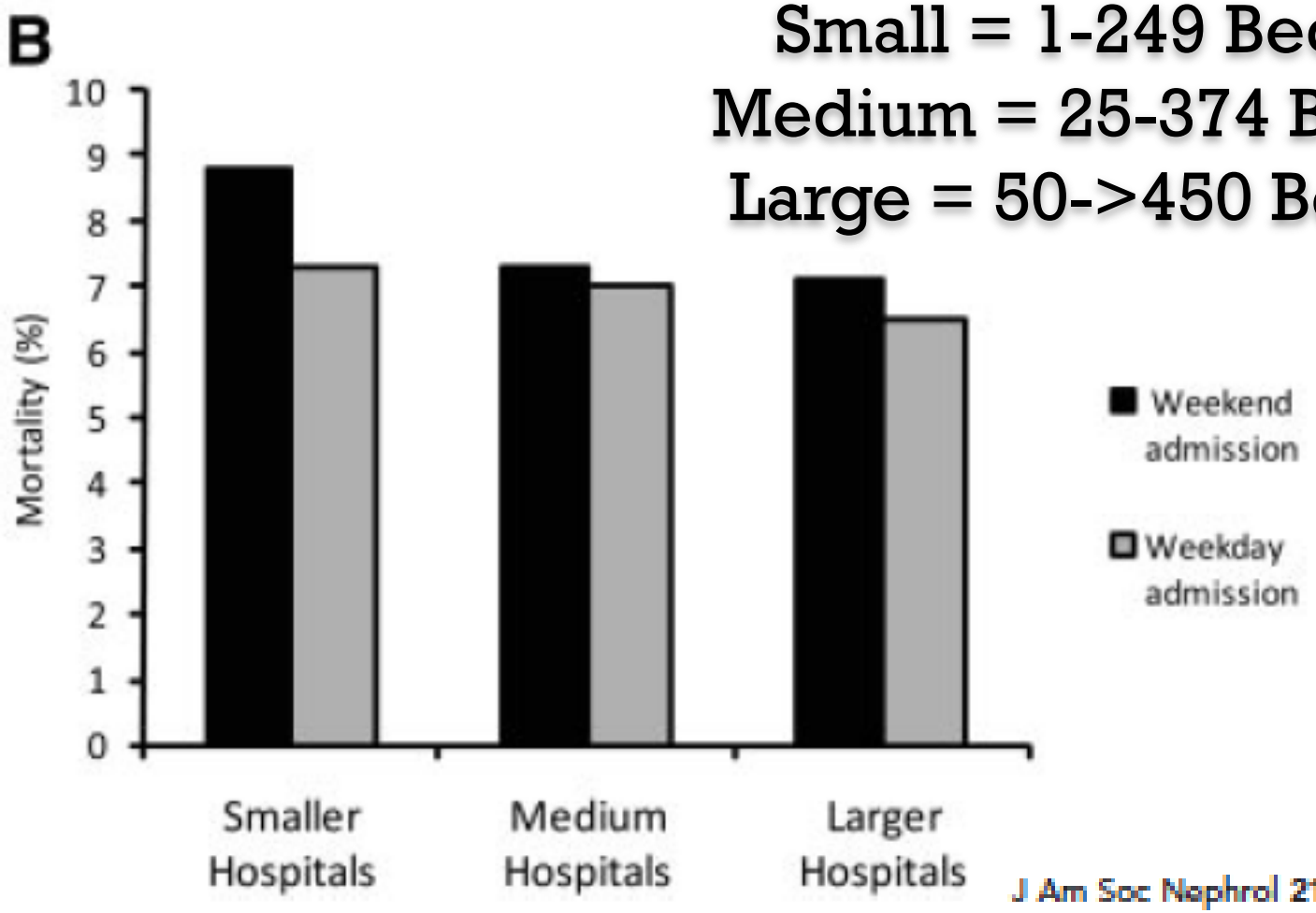
Weekends: AKI **On** Admission

Small = 1-249 Beds
Medium = 25-374 Beds
Large = 50->450 Beds



J Am Soc Nephrol 21: 845–851, 2010

Weekends: AKI **During** Admission



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Revised Risk factors for AKI

Shared (patient specific):

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  - **CHF**
  - **Liver Disease**
  - **Proteinuria**
- Premedication
  - ACE/ARB
  - NSAIDS

Disease specific:

- Genetics
- Pathophysiology

Intervention specific:

- Medication
- Procedures
- **Weekend Admission**
- **Surgery**

Why Proteinuria & Not Diabetes?

Kidney Disease: Improving Global Outcomes

Surgery & AKI : Influence of DM

Research

Determinants of postoperative acute kidney injury

Fernando José Abelha[1], Miguela Botelho[1], Vera Fernandes[1] and Henrique Barros[2]

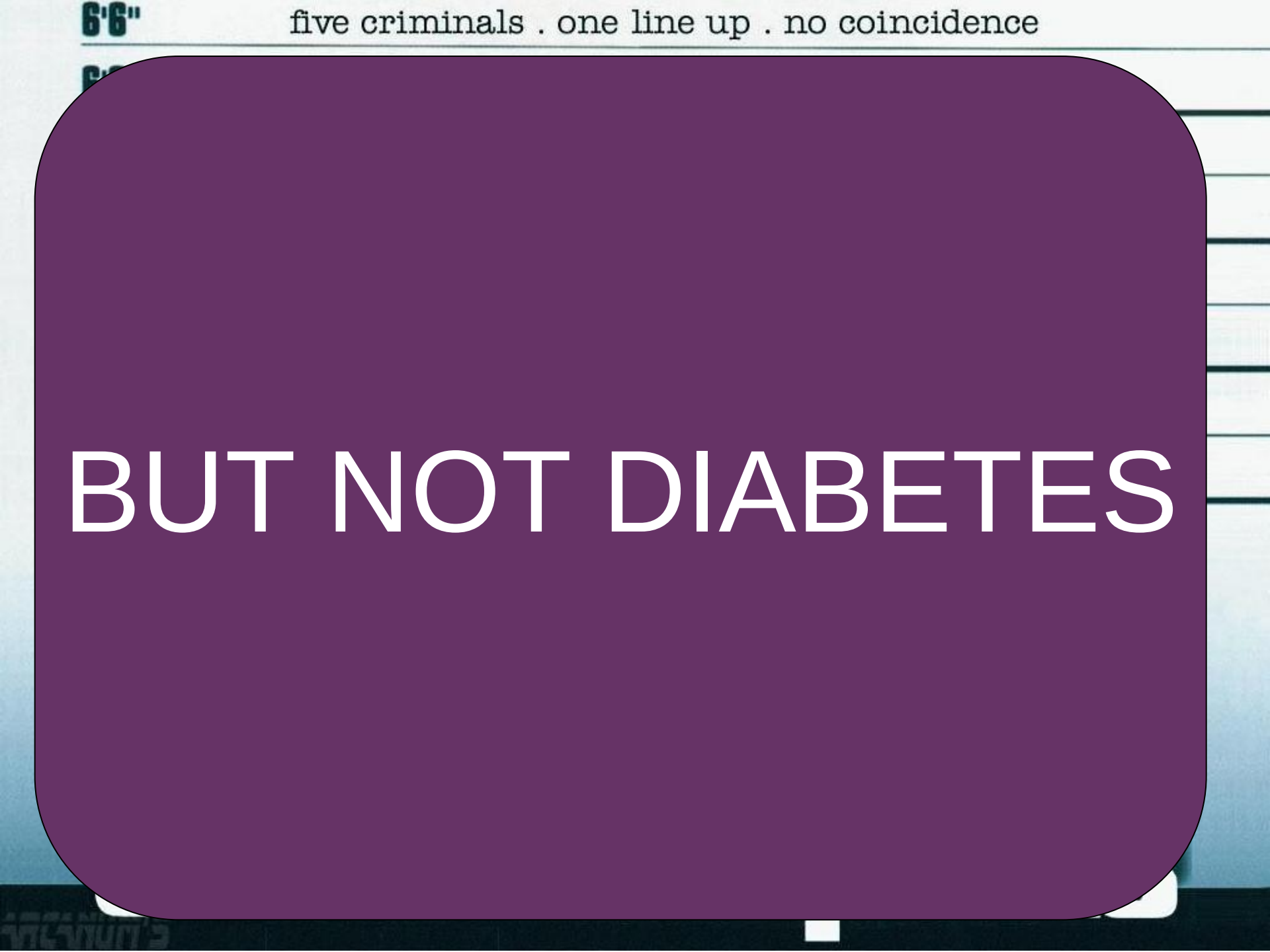
Open Access

Over 1000 Surgical Patients

AKI as defined by AKIN

Major determinants of AKI?

Critical Care 2009 **13**:R79


6'6"
five criminals . one line up . no coincidence
BUT NOT DIABETES

Diabetes & ICU Outcomes

- Is this a surprise??

- In fact conflicting results in the literature……

What We Need Is A Meta-Analysis!!!

Siegelaar *et al. Critic*
http://ccforum.com/c

TICAL CARE

RESEARCH

Open Access

The eff
patient

Sarah E Siegelaa

cally ill
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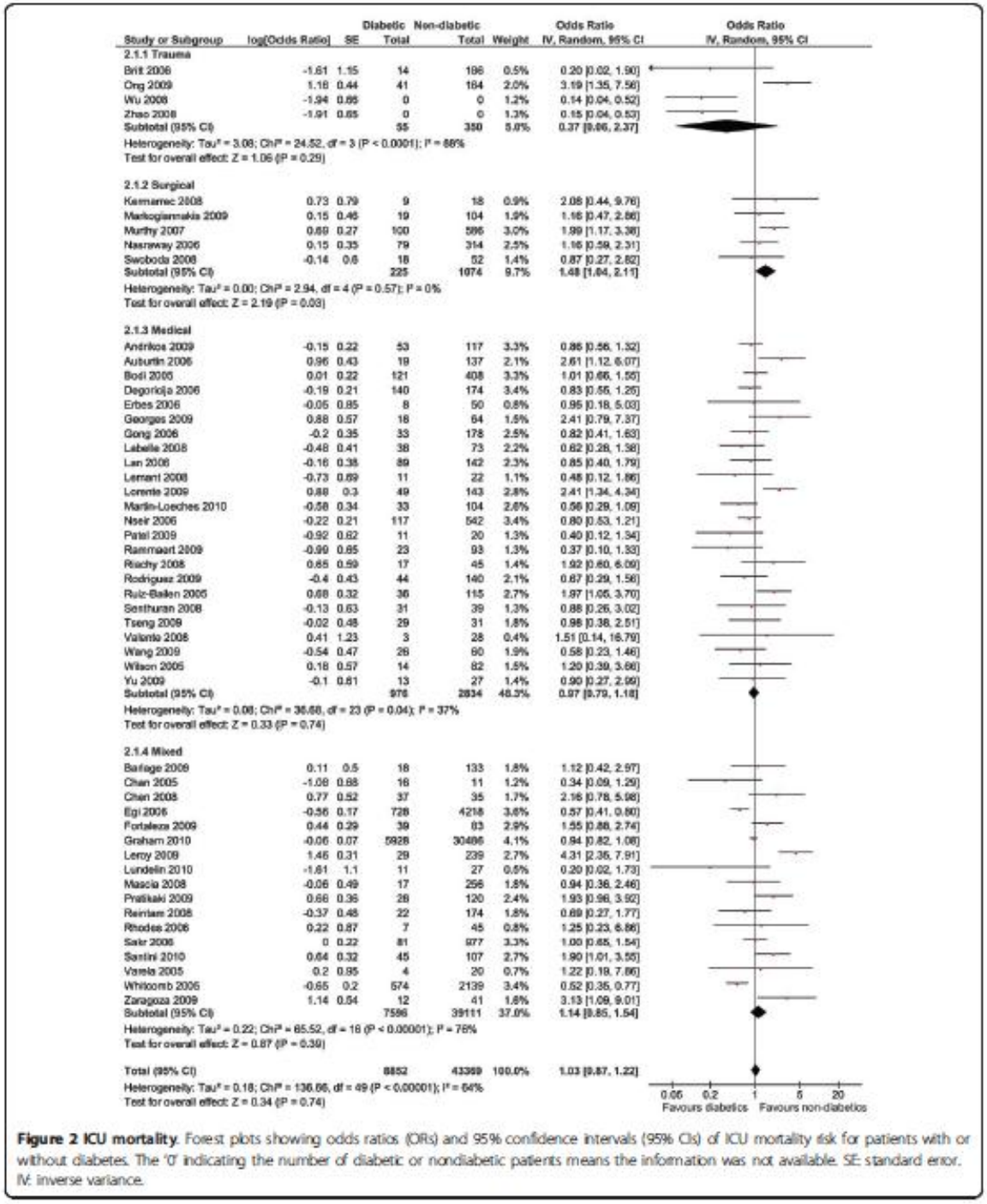


Figure 2 ICU mortality. Forest plots showing odds ratios (ORs) and 95% confidence intervals (95% CIs) of ICU mortality risk for patients with or without diabetes. The '0' indicating the number of diabetic or nondiabetic patients means the information was not available. SE: standard error. IV: inverse variance.

Summary…

Results: We included 141 studies containing 12,489,574 patients, including 2,705,624 deaths (21.7%). Of these patients at least 2,327,178 (18.6%) had diabetes. Overall no association between the presence of diabetes and mortality risk was found. Analysis for ICU type showed a significant disadvantage for patients with diabetes for all mortality definitions when admitted at the surgical ICU (ICU mortality: OR [CI] 1.48 [1.04-2.11]; hospital mortality: 1.59 [1.28-1.97]; 30-day mortality: 1.62 [1.13-2.34]). In medical and mixed ICU's no effect of diabetes was seen for all outcomes. Sensitivity analysis showed that the disadvantage in the diabetic surgical population was attributable to cardiac surgery (1.77 [1.45-2.16], $P<0.00001$) and not to general surgery patients (1.21 [0.96-1.53], $P=0.11$).

Siegelaar etal Critical Care 2011 15:R205

Summary…

Conclusions: This meta-analysis showed that diabetes was not associated with increased mortality risk in any ICU population except for those who underwent cardiac surgery.

Siegelaar etal Critical Care 2011 15:R205

Uchino etal

BEST Kidney Investigators

JAMA 2005 **294** 813-18

No obvious problem with DM here….

Table 2. Medical and Surgical Intensive Care Unit Admissions and Contributing Factors to Acute Renal Failure

	No. (%)
Medical admission (n = 1736)	1023 (58.9)
Respiratory tract	225 (13.0)
Cardiovascular	197 (11.3)
Gastrointestinal tract	175 (10.1)
Sepsis	174 (10.0)
Hematologic	77 (4.4)
Metabolic	65 (3.7)
Renal	39 (2.2)
Neurological	37 (2.1)
Trauma	34 (2.0)
Surgical admission (n = 1736)	713 (41.1)
Cardiovascular	402 (23.2)
Gastrointestinal tract	198 (11.4)
Trauma	39 (2.2)
Respiratory tract	31 (1.8)
Renal	17 (1.0)
Orthopedic	11 (0.6)
Neurological	9 (0.5)
Gynecologic	6 (0.3)
Contributing factors (n = 1726)	
Septic shock	820 (47.5)
Major surgery	592 (34.3)
Cardiogenic shock	465 (26.9)
Hypovolemia	442 (25.6)
Drug-induced	328 (19.0)
Hepatorenal syndrome	99 (5.7)
Obstructive uropathy	45 (2.6)
Other	211 (12.2)

Meta Analysis Did Tell Us That Cardiac Surgery & DM Was Bad…

Table 4. Factors associated with postoperative acute kidney injury defined by the Acute Kidney Injury Network Criteria (n = 1052)

Covariate	OR (95% CI)	P
Age (years)	1.03 (1.01 to 1.05)	0.001
DM	1.66 (1.14 to 2.44)	<0.001
Recent MI	1.78 (1.16 to 2.72)	0.009
IABP	3.56 (1.83 to 6.96)	<0.001
Nonelective surgery	3.66 (2.15 to 6.25)	<0.001
Proteinuria		
no proteinuria	1	
mild proteinuria	1.66 (1.09 to 2.52)	0.018
heavy proteinuria	2.30 (1.35 to 3.90)	0.002
CKD stage		
preserved eGFR	1	
stage 3	1.68 (1.12 to 2.52)	0.012
stage 4	3.01 (1.57 to 6.03)	0.001

Tao-Min HuangJ Am Soc Nephrol 2010 **22**:

But is it Diabetes or Proteinuria??

Table 5. Factors associated with postoperative AKI needing RRT ($n = 1052$)

Covariate	Odds Ratio (95% CI)	*P*
Age (years)	1.06 (1.02 to 1.10)	0.003
Low LVEF	3.31 (1.36 to 8.79)	0.009
ECMO	15.75 (6.01 to 41.26)	<0.001
Nonelective surgery	6.49 (2.84 to 14.86)	<0.001
Cardiopulmonary bypass	3.90 (1.86 to 8.20)	<0.001
Heavy proteinuria	7.29 (3.00 to 17.73)	<0.001

Evidence Outside the ICU?

Huge Study : 920,985 Patients

All hospital admissions between 2002-2007

Median FU 35 months

0.7% Admitted to hospital with AKI

James etal Lancet 2010 376 2096-103

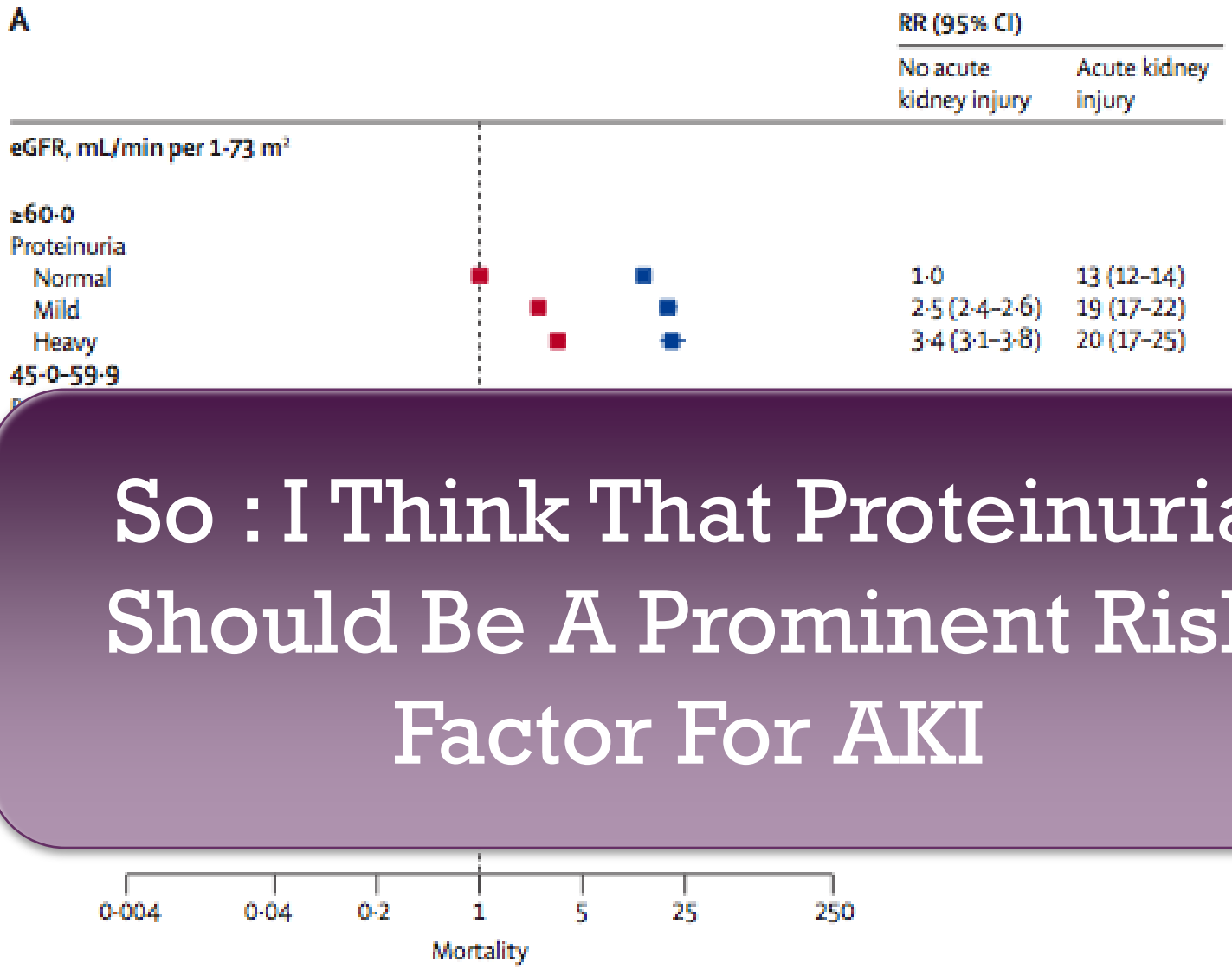
Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study

Matthew T James, Brenda R Hemmelgarn, Natasha Wiebe, Neesh Pannu, Braden J Manns, Scott W Klarenbach, Marcello Tonelli, for the Alberta Kidney Disease Network

eGFR (>60) : RR of AKI was 4.4 higher in those with proteinuria

In those with heavy proteinuria the risk of AKI and AKI requiring RRT was raised **regardless of GFR**

James etal Lancet 2010 376 2096-103



So : I Think That Proteinuria Should Be A Prominent Risk Factor For AKI

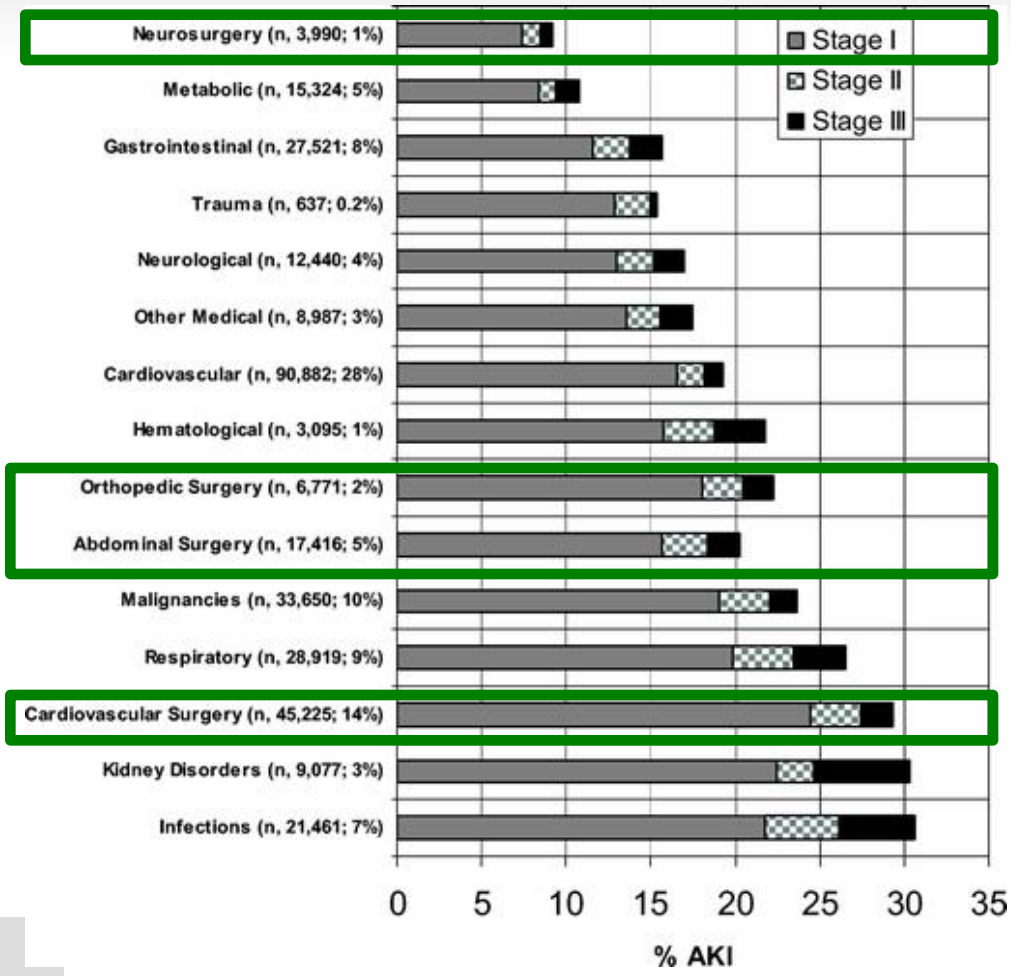
James etal Lancet 2010 376 2096-103

Step 1
Identify the hazards

Step 2
Decide who might be harmed and how

Step 3
Evaluate the risks and decide on precautions

Incidence and outcomes of acute kidney injury in intensive care units: A Veterans Administration study



Risk Dependent on Cause

CV Thakar et al, Crit Care Med 2009

Kidney Disease: Improving Global Outcomes

Step 3: Evaluating The Risk

All for Elective Procedures

Candela-Toha 2008 UI18463173 Spain	External Validation of Thakar and Wyesundera in 1780 pts with cardiac surgeries at a University Hospital in Madrid, Spain from 2002-2006	AKI	Retrospective cohort Single center
Mehran 2004 UI15464318 US	8,357 pts who underwent PCI possibly at Columbia Medical Center, New York, New York, over a period of 6 years(dates unspecified).	CIN	Retrospective cohort Presumed single center
McCullough 2007 UI 9375704 US	1,826 consecutive pts undergoing coronary intervention at William-Beaumont Hospital, Michigan from December 1993-August1994.	RRT	Retrospective cohort Single Center
Skelding 2007 UI17476039 US	External Validation of William Beaumount score in 3,213 pts from the Mayo Clinic PCI Registry who underwent PCI at the from July 1, 2000 to June 30, 2003	CIN	Retrospective cohort
Drawz 2008 UI18925522 US	540 hospitalized patients in 3 hospitals in Cleveland, Ohio since January 1, 2003	Hospital-acquired AKI	Case-controlled
Ghani 2009 UI19237811 Kuwait	247 pts undergoing PCI in Kuwait from March to May 2005	CIN	Prospective cohort Single-center

Predicting Acute Renal Failure after Cardiac Surgery: External Validation of Two Clinical Scores

Table 1. Risk factors and points in Cleveland and SRI (Toronto) scores[a]

Risk Factors	Cleveland Points	SRI Points
Female gender	1	0
History of CHF	1	0
LVEF		
<35%	1	
<40%		1
Preoperative IABP	2	1
COPD treated with bronchodilators	1	0
Diabetes that required treatment		
with insulin	1	
with any medication		1
Previous cardiac surgery	1	1
Type of surgery[b]		
valvular	1	1
combined (CABG + valvular)	2	1
other surgeries	2	1
Preoperative renal function[c]		
sCr (mg/dl)		
1.2 to 2.09	2	
≥2.1	5	
eGFR (ml/min)		
40 to 60		1
<40		2
Operative status		
emergent	1	
nonelective		1
Score range	0 to 17	0 to 8

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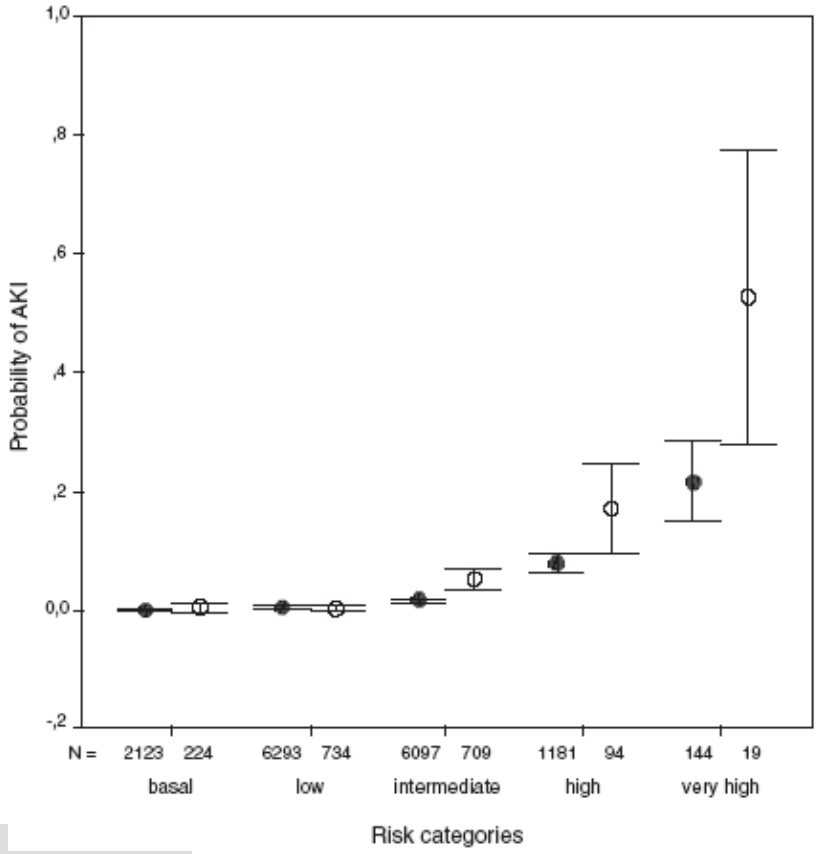
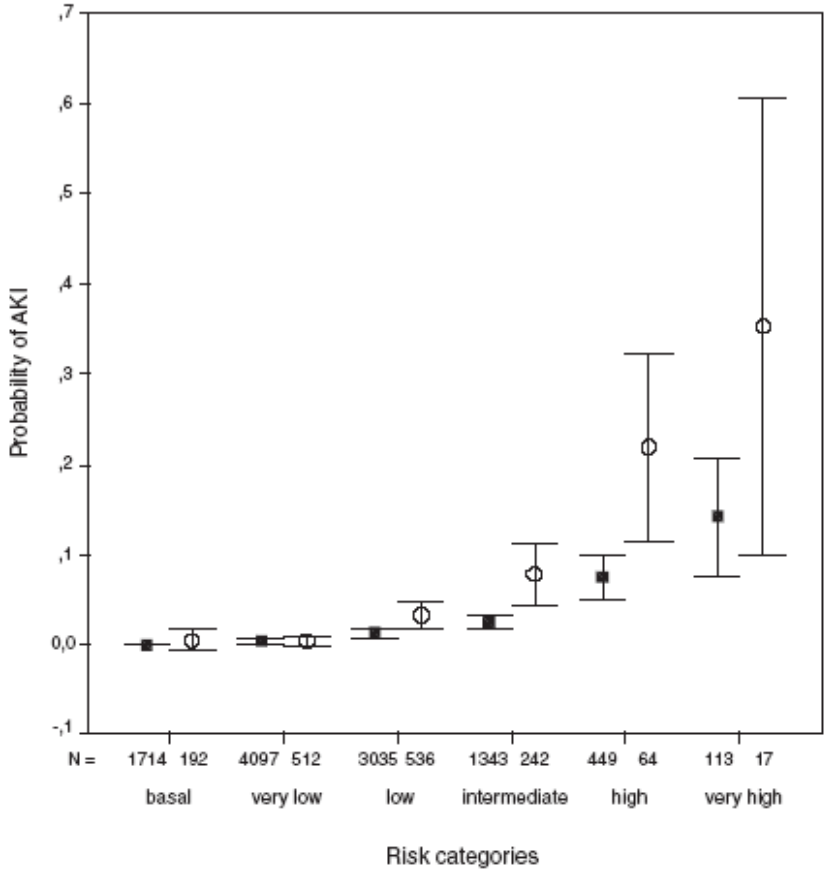
Predicting Acute Renal Failure after Cardiac Surgery: External Validation of Two New Clinical Scores

Cleveland



Toronto



Kidney Disease: Improving Global Outcomes

Candela-Toha, CJASN 2008

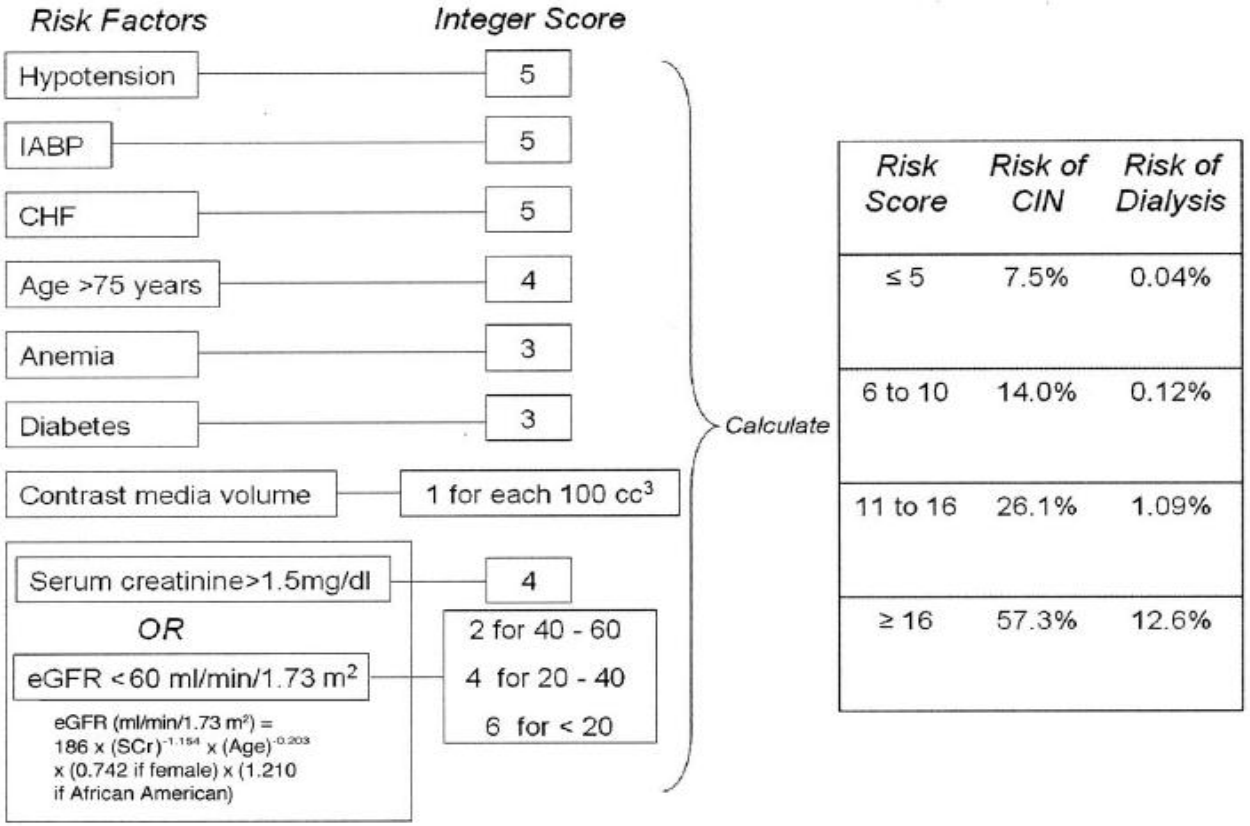
What About Non-Surgical Patients?

Risk Factors for CIN

Patient-related	Procedure-related
• CKD • Diabetes mellitus with renal insufficiency • Age • Volume depletion • Hypotension • Low cardiac output • Class IV CHF • Other nephrotoxins • Renal transplant • Hypoalbuminemia (<35 g/L)	• Multiple contrast media injection within 72 hrs • Intra-arterial injection site • High volume of contrast media • High osmolality of contrast media

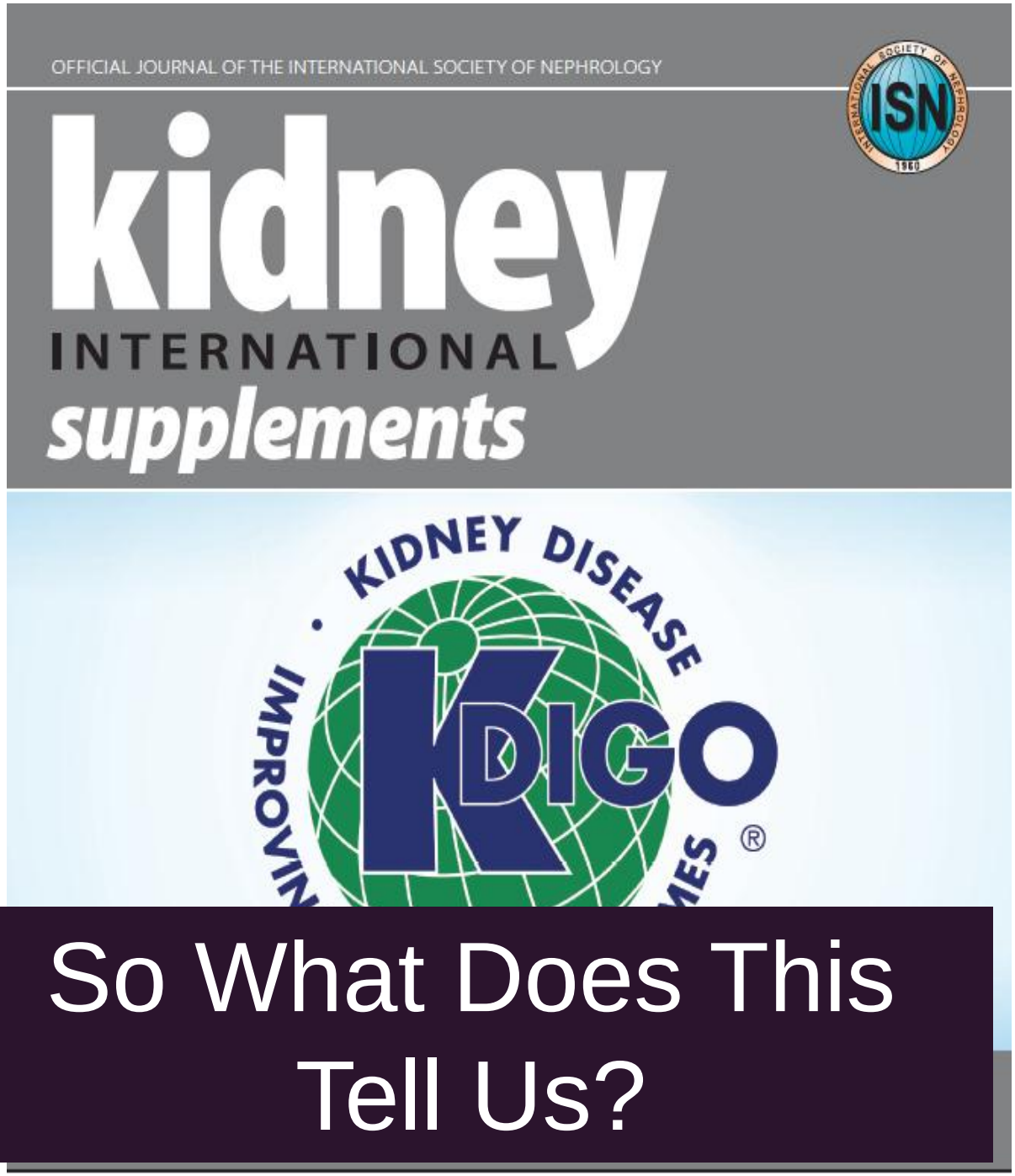
Hörl WH. Contrast induced nephropathy. *Wien Klin Wochenschr* 2009; 121: 15-32

Contrast-nephropahty Risk Score



Risk Score	Risk of CIN	Risk of Dialysis
≤ 5	7.5%	0.04%
6 to 10	14.0%	0.12%
11 to 16	26.1%	1.09%
≥ 16	57.3%	12.6%

Mehran, JACC 2004



So What Does This Tell Us?

CHAPTER 2.3: AKI RISK EVALUATION

We recommend that patients be stratified for risk of AKI according to their susceptibility and in context with the exposure whenever possible. (*1B*)

CHAPTER 2.3: AKI RISK EVALUATION

It is reasonable to manage patients according to their susceptibilities and exposures to reduce the risk of AKI.

CHAPTER 2.3: AKI RISK EVALUATION

Intensive Care Med (2010) 36:379–380
DOI 10.1007/s00134-009-1683-1

EDITORIAL

Andrew Davenport

Clinical guidelines for the protection of kidney function and prevention of acute kidney injury in the intensive care unit: common sense rather than magic bullets?

Step 1
Identify the hazards

Step 2
Decide who might be harmed and how

Step 3
Evaluate the risks and decide on precautions

Prevention?

How Do We Prevent AKI??

Don’t Get Admitted to Hospital…

UK Renal Association….

4. Acute Kidney Injury (AKI) (Guidelines AKI 4.1 – 4.5)

Guideline 4.1 – AKI : Management; General Management

We recommend that general supportive measures include optimisation of haemodynamic status by appropriate fluid therapy, administration of vasopressors and/or inotropes and treatment of any underlying sepsis. Nephrotoxic medications should be stopped. (1A)

Guideline 4.2 – AKI : Management; Pharmacological Therapy

We recommend that therapeutic drug dosing must be adapted to altered kinetics in AKI. (1B)

Guideline 4.3 – AKI : Management; Pharmacological Therapy

We recommend that there is no specific pharmacological therapy proven to effectively treat AKI secondary to hypoperfusion injury and/or sepsis. (1B)

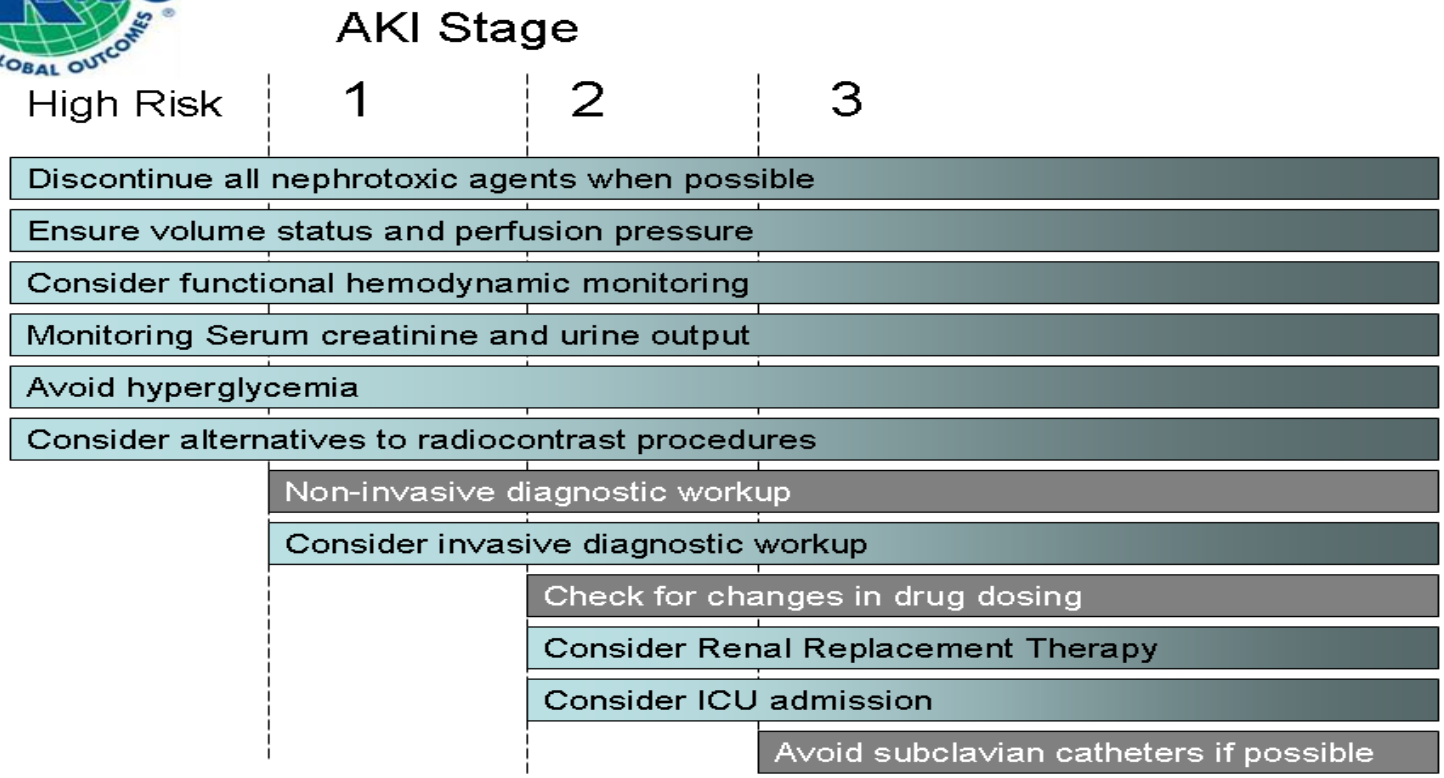
Management of Patients According to their Susceptibilities

- Hypovolemia -> Volume Expansion
- Hypotension -> Volume Expansion, Vasopressors
- CHF -> Inotropes, Inodilators (e.g. levosimendan)
- Nephrotoxins -> Stop them
- ACE/ARB -> Stop them

- Age -> ?
- Gender -> ?

WG Nephrology of ESICM (Joannidis et al , Intensive Care Med 2009)

Stage-Based Management



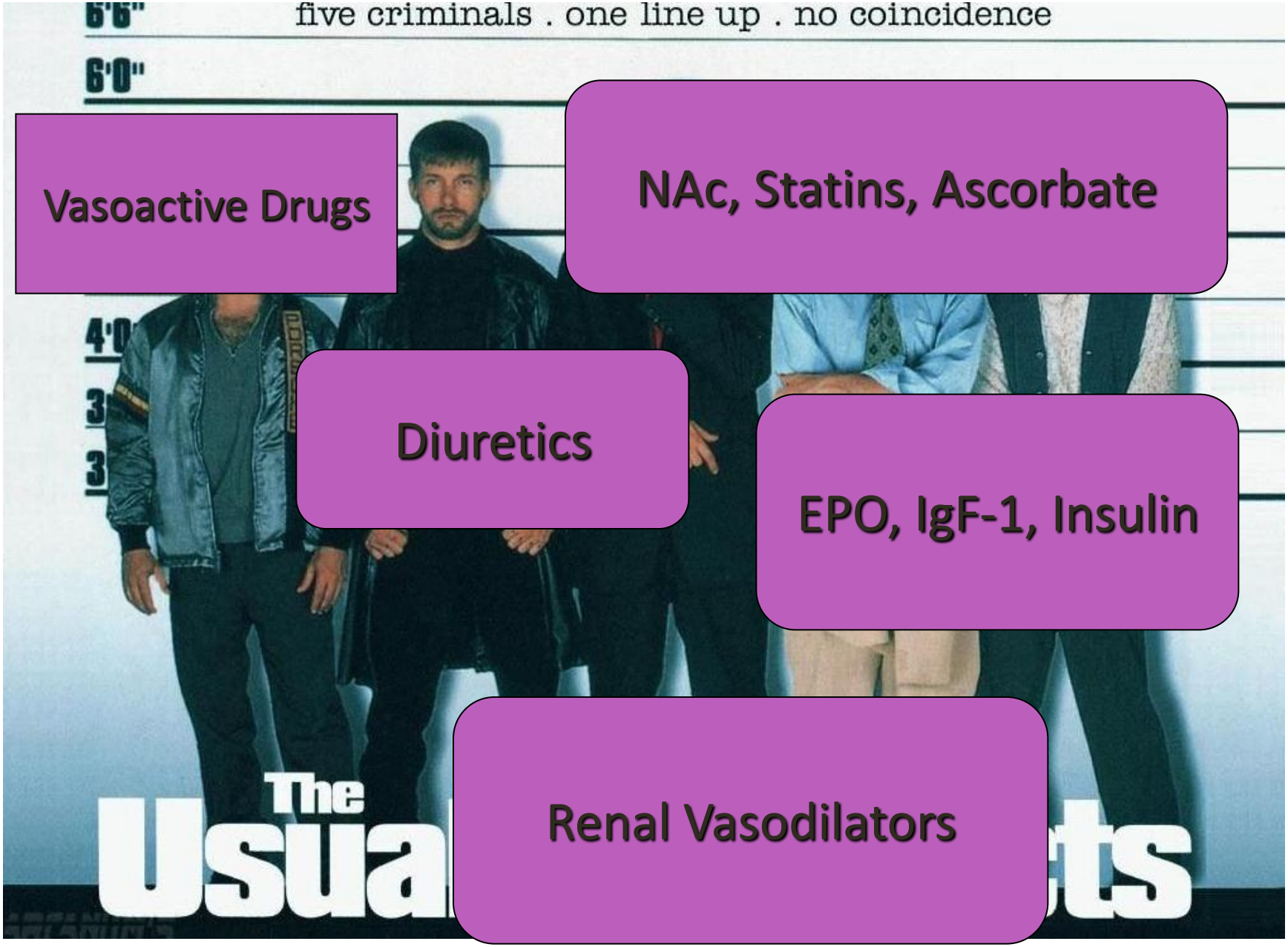
Stage-based management of AKI: Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases.

Kidney Disease: Improving Global Outcomes

Preventing AKI

- Often (always) multifactorial
- Can we expect to find a ‘cure-all’?

- What has been Tried?



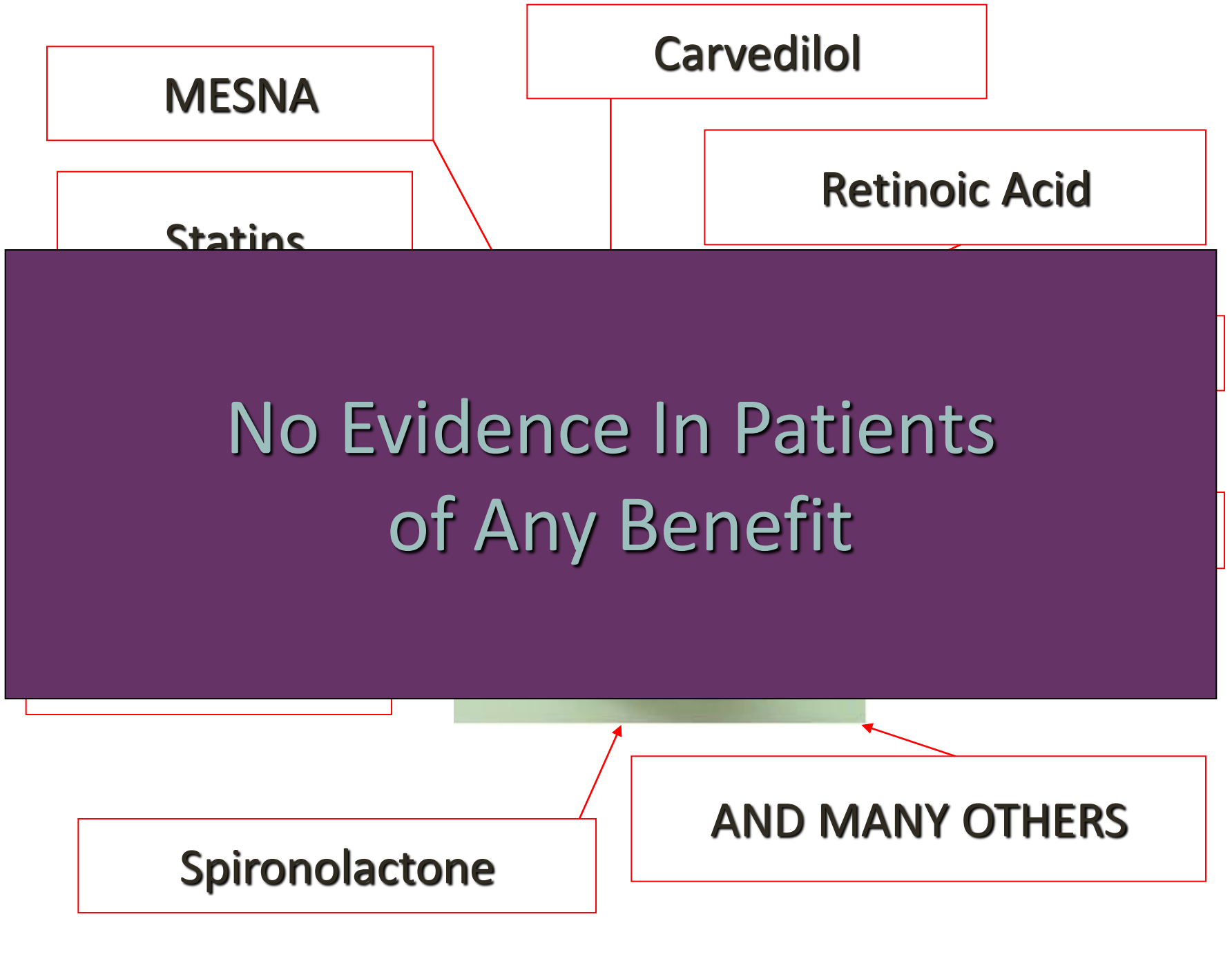
Vasoactive Drugs

NAc, Statins, Ascorbate

Diuretics

EPO, IgF-1, Insulin

Renal Vasodilators


MESNA
Carvedilol
Retinoic Acid
Statins
No Evidence In Patients of Any Benefit
Spironolactone
AND MANY OTHERS

Preventing AKI: Fluids

- Fluid replacement : Must be a good thing

Despite the recognition of volume depletion as an important risk factor for AKI, there are no randomized controlled trials (RCTs) that have directly evaluated the role of fluids vs. placebo in the prevention of AKI. However, RCTs mostly in the field of CI-AKI have

Not entirely surprising…

Preventing AKI: Colloids?

CONCLUSIONS

In patients in the ICU, there was no significant difference in 90-day mortality between patients resuscitated with 6% HES (130/0.4) or saline. However, more patients who received resuscitation with HES were treated with renal-replacement therapy. (Funded by the National Health and Medical Research Council of Australia and others; CHEST ClinicalTrials.gov number, NCT00935168.)

Evidence that colloids increase the need for RRT…

Which Fluid…..

Key messages

- It has been hypothesized that hyperoncotic colloid solutions may damage the kidney. A meta-analysis of randomized controlled trials was performed to test this hypothesis.
- Hyperoncotic albumin decreased the odds of acute kidney injury by 76% and of death by 48%.
- Hyperoncotic hydroxyethyl starch increased the odds of acute kidney injury by 92% and of death by 41%.
- Hyperoncotic colloids *per se* do not appear to be harmful to the kidney.
- Renal effects may be specific to the particular colloid molecule.

KDIGO

FLUIDS

3.1.1: In the absence of hemorrhagic shock, we suggest using isotonic crystalloids rather than colloids (albumin or starches) as initial management for expansion of intravascular volume in patients at risk for AKI or with AKI. (*2B*)

Diuretics

- Rationale
  - Reduced O_2 Consumption
  - Increased Tubular Flow
  - Increased Urea Excretion
  - Volume Management

High-dose Furosemide in patients with Established AKI

Table 2. Study End Points in the Population Assessable for Efficacy With Stratification According to SAPS

	Furosemide (n = 166)	Placebo (n = 164)	Significance (*P*)
Patients alive at the end of the study (n = 221)			
SAPS ≤15	60	67	0.36*
SAPS >15	47	47	
Total	107	114	
Deaths (n = 109)			
SAPS ≤15	16	11	
SAPS >15	43	39	
Total	59	50	
No. of RRT sessions			
SAPS ≤15	5.6 ± 5.5	5.7 ± 4.5	0.37†
SAPS >15	7.3 ± 5.3	7.9 ± 5.6	
Total	6.5 ± 5.4	6.9 ± 5.3	
Time on RRT (d)	11.4 ± 8.6	12.4 ± 8.7	0.21†
Time to achieve a serum creatinine level <2.26 mg/dL without RRT (d)	19.7 ± 40.6	21.4 ± 65.1	0.99†
Time to achieve a 2-L/d diuresis (d)	5.7 ± 5.8	7.8 ± 6.8	0.004†

Cantarovic F, Am J Kidney Dis 2004

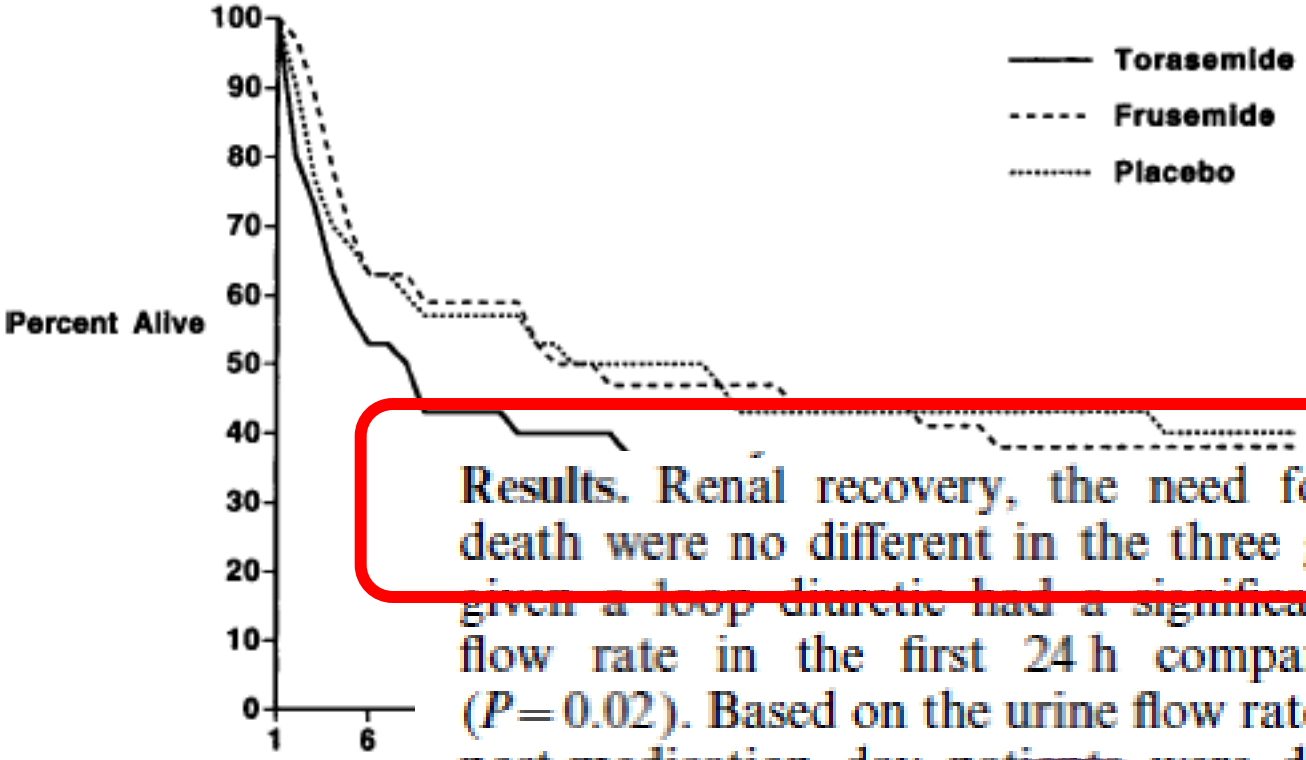


Fig. 1. Actuarial survival for the

Results. Renal recovery, the need for dialysis, and death were no different in the three groups. Patients given a loop diuretic had a significant rise in urine flow rate in the first 24 h compared to placebo ($P = 0.02$). Based on the urine flow rate during the first post-medication day patients were divided into two groups: oliguric (< 50 ml/h) and non-oliguric (≥ 50 ml/h). Non-oliguric patients had a significantly lower mortality than oliguric patients (43% *vs* 69%, $P = 0.01$). However, they were less ill (APACHE II score 17.2 *vs* 20.6, $P = 0.008$) and had less severe renal failure at entry (creatinine clearance 14 ml/min *vs* 4 ml/min, $P < 0.0001$).

Conclusion. The use of loop diuretics in oliguric patients with ARF can result in a diuresis. There is no evidence that these drugs can alter outcome.

Diuretics and AKI

- Despite Repeated Trials

STUDY PROTOCOL Open Access

The SPARK Study: a phase II randomized blinded controlled trial of the effect of furosemide in critically ill patients with early acute kidney injury

Sean M Bagshaw[1*], RT Noel Gibney[1], Finlay A McAlister[2], Rinaldo Bellomo[3]

- They must work…

KDIGO

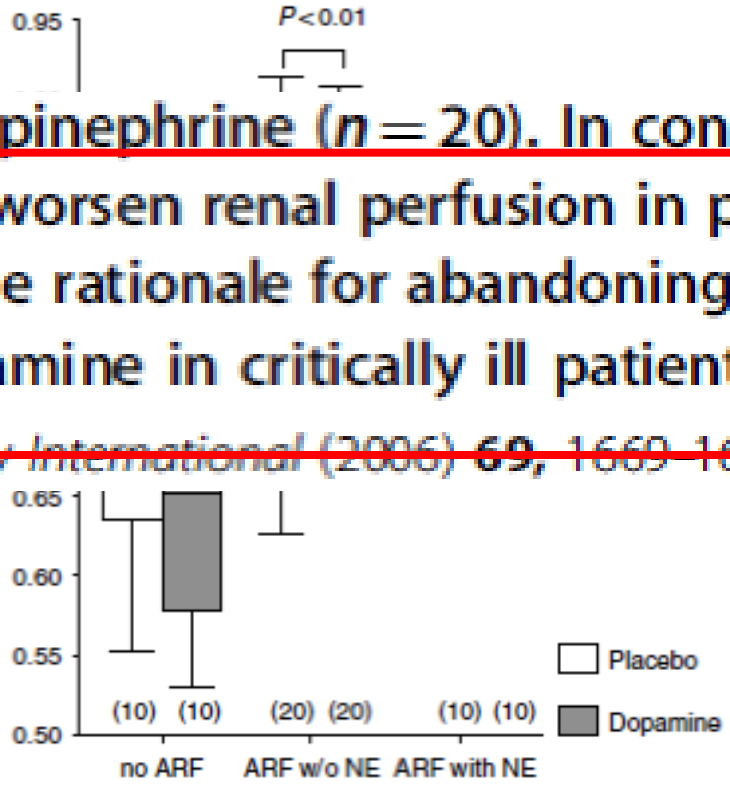
3.4.1: We recommend not using diuretics to prevent AKI. (*1B*)

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

Dopamine

- Rationale
- ? Preferential Renal Vasodilatation
- ?Evidence

Effect of ´low-dose´ dopamine on Renal Resistive Index



norepinephrine ($n = 20$). In conclusion 'low-dose' dopamine can worsen renal perfusion in patients with ARF, which adds to the rationale for abandoning the routine use of 'low-dose' dopamine in critically ill patients.

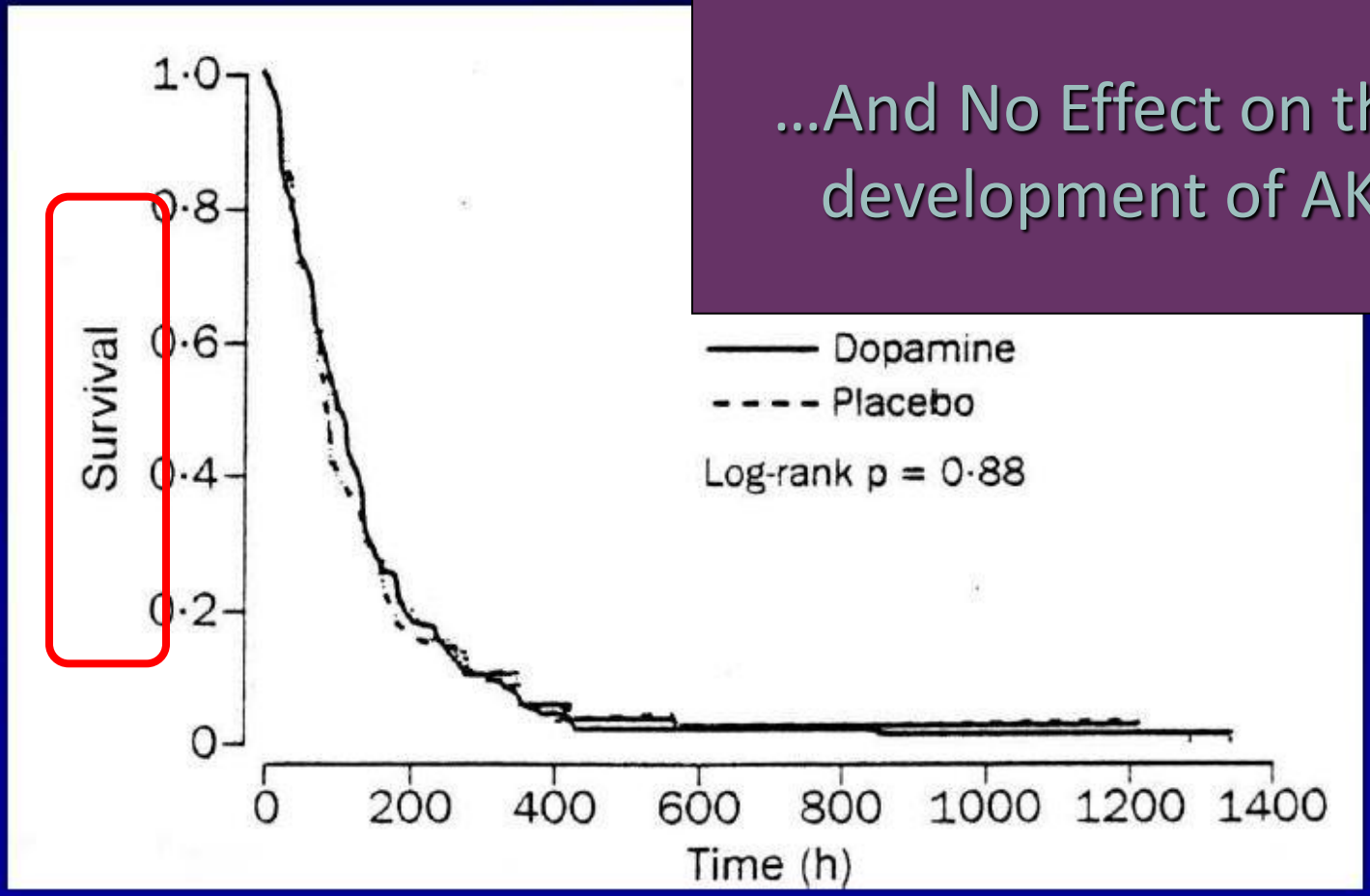
Kidney International (2006) **69**, 1669–1674. doi:10.1038/sj.ki.5000310;

Figure 5 | Effect of dopamine on RI values in patients with and without norepinephrine (NE) infusion.

Lauschke A, Kidney Int 2006

DOPAMINE DOES NOT PREVENT AKI

RCT - dopamine 2µg/kg/min throughout ITU stay



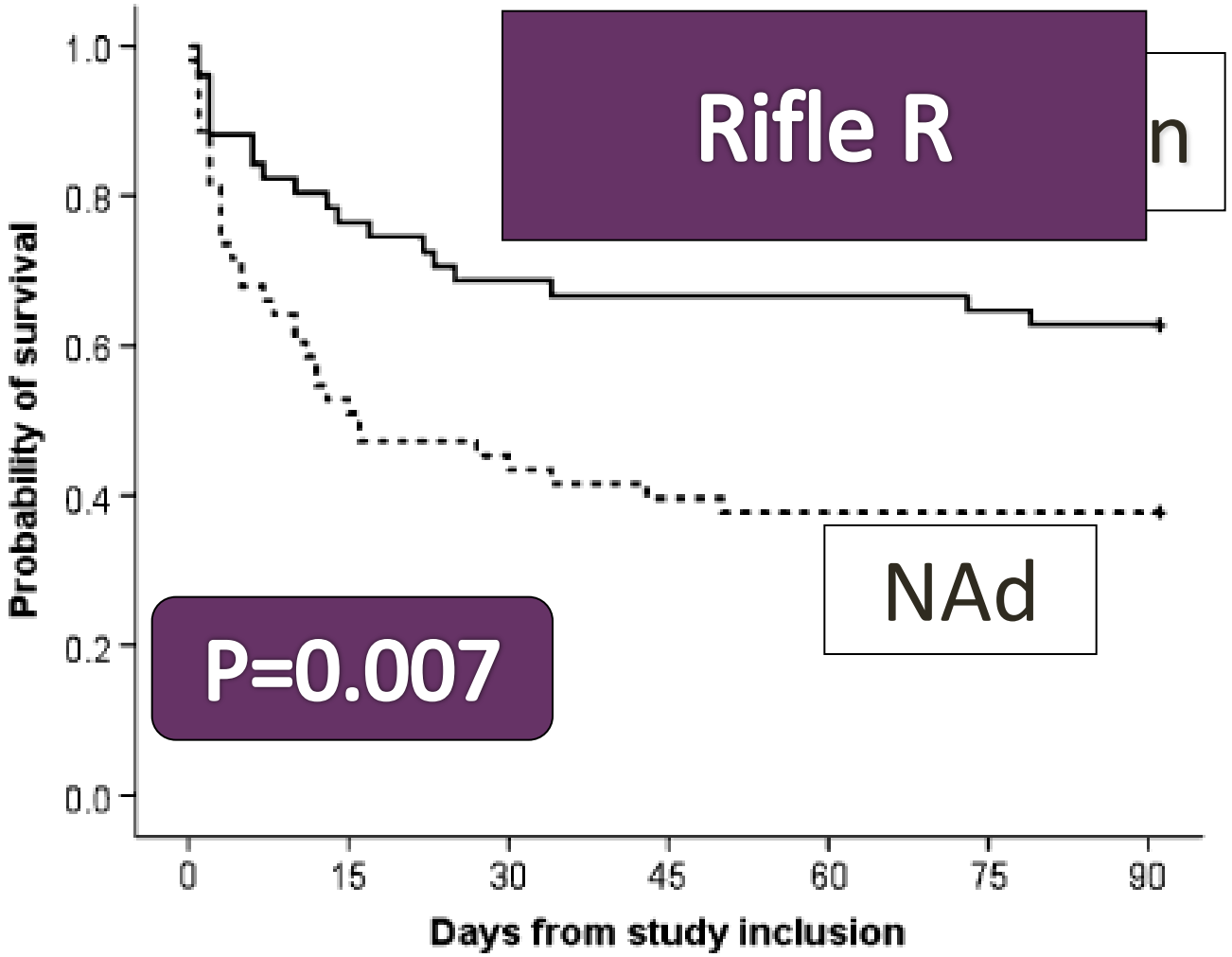
…And No Effect on the development of AKI

Lancet 2000;356:2139

KDIGO

3.5.1: We recommend not using low-dose dopamine to prevent or treat AKI. (*1A*)

What of Vasoconstrictors?



KDIGO

VASOPRESSORS

3.1.2: We recommend the use of vasopressors in conjunction with fluids in patients with vasomotor shock with, or at risk for, AKI. (*1C*)

PROTOCOLIZED HEMODYNAMIC MANAGEMENT

3.1.3: We suggest using protocol-based management of hemodynamic and oxygenation parameters to prevent development or worsening of AKI in high-risk patients in the perioperative setting (*2C*) or in patients with septic shock (*2C*).

KDIGO

• IGF-1	• Not Recommended
• ANP	• Not Recommended
• Fenoldapam	• Not Recommended
• NAc	• Not Recommended
• EPO	• Not Recommended

Insulin

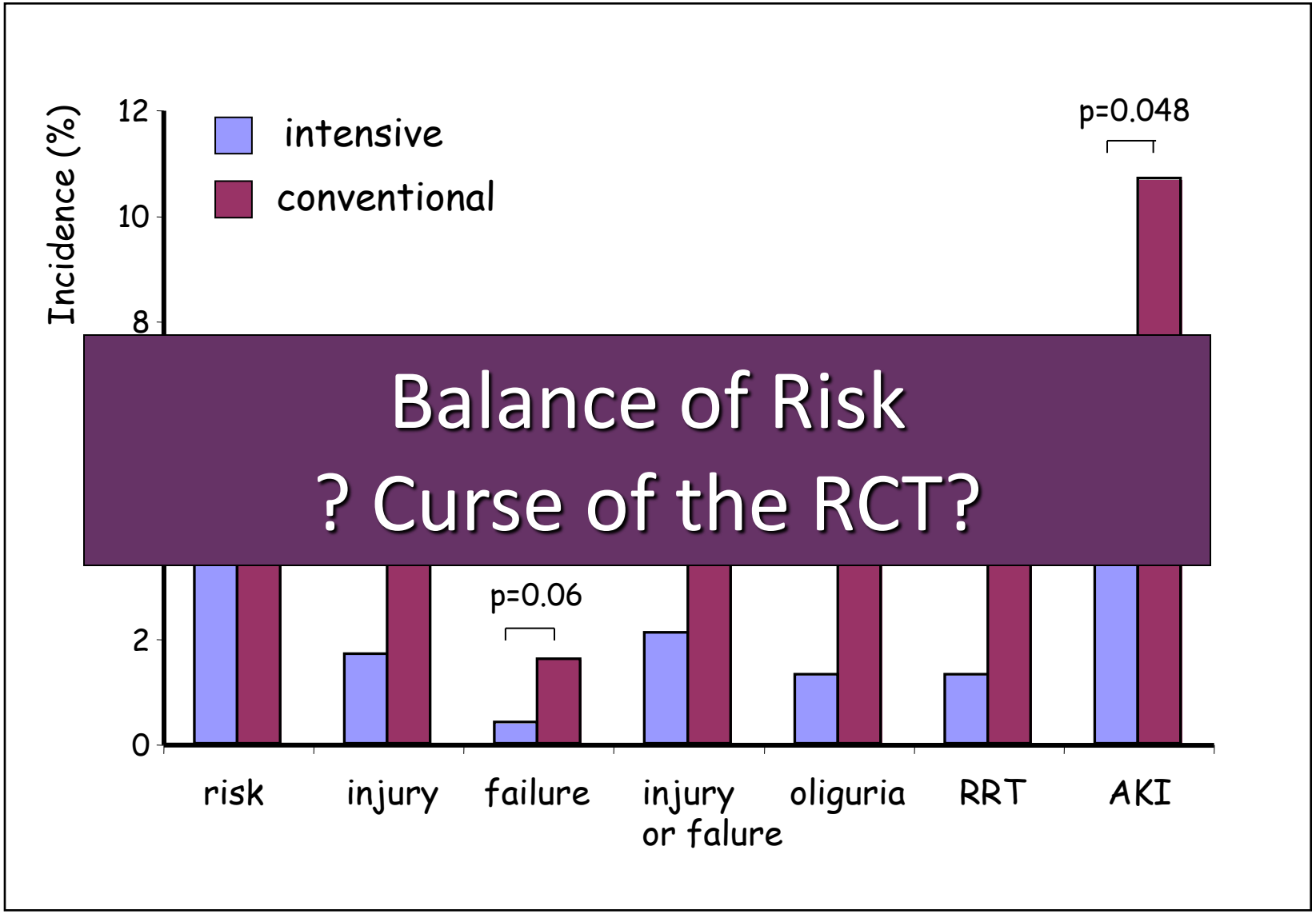
- Pooled analysis failed to confirm early beneficial effects of IIT
- NICE-Sugar the largest randomized trial to-date found that IIT increased mortality
  - BG target 4.5-6.0 higher mortality than ≤ 9.99
- The end for IIT?

Insulin

- Further analysis of the original studies on IIT
- Renal end-points combined using a modified version of RIFLE:
  - Tight glycemic control reduced the incidence of severe AKI from 7.6% to 4.5% ($P = 0.0006$)
  - Need for RRT was not decreased in overall population/ medical ICU population
  - But significantly lower in the surgical ICU patients (4% vs. 7.4%, $P = 0.008$).

M. Schetz, JASN 2008

Intensive Insulin Therapy and AKI



M. Schetz, JASN 2008

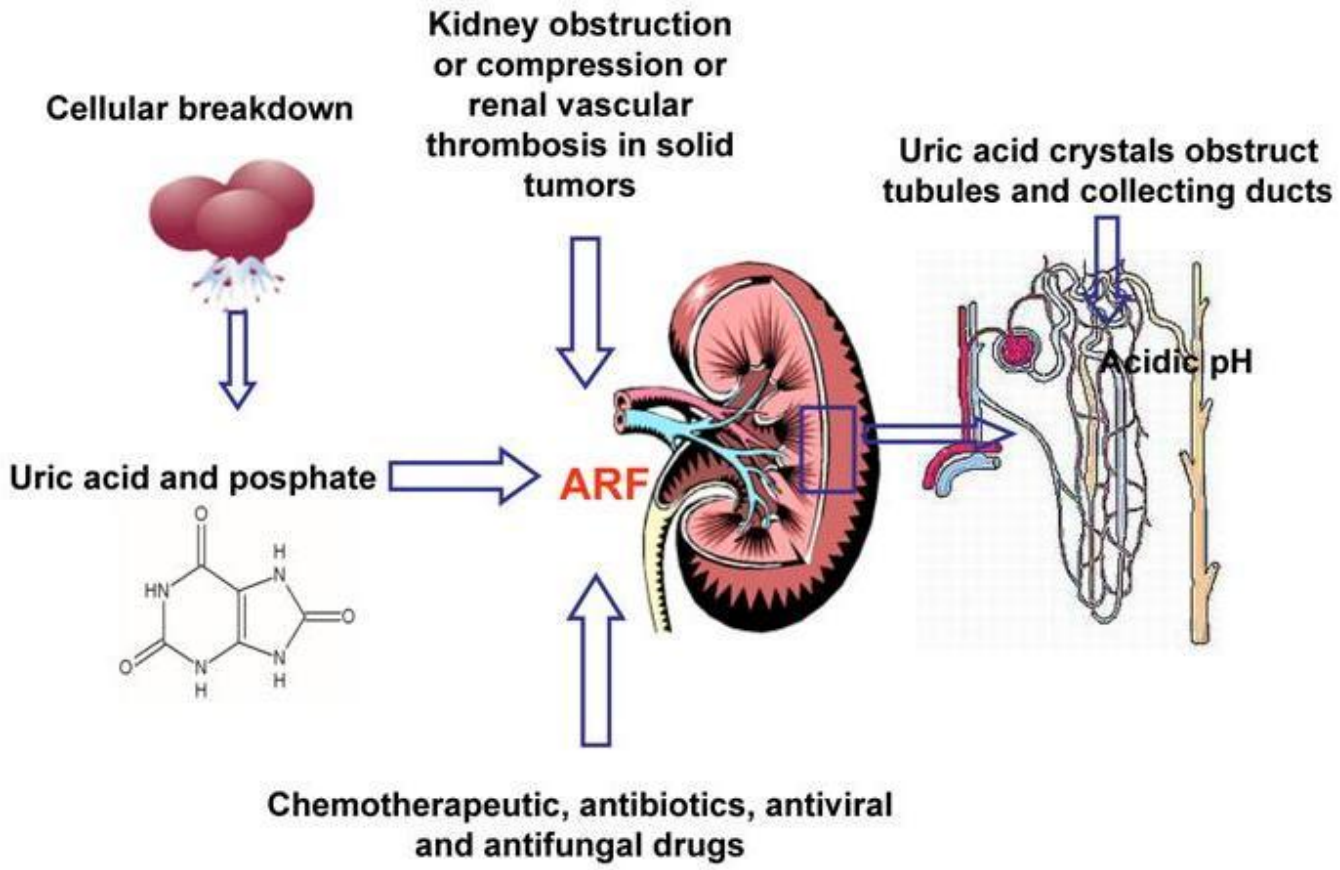
KDIGO

GLYCEMIC CONTROL IN CRITICAL ILLNESS: RENAL EFFECTS AND OUTCOMES

3.3.1: In critically ill patients, we suggest insulin therapy targeting plasma glucose 110–149 mg/dl (6.1–8.3 mmol/l). (2C)

Kidney Disease: Improving Global Outcomes

What About Well Defined Conditions?

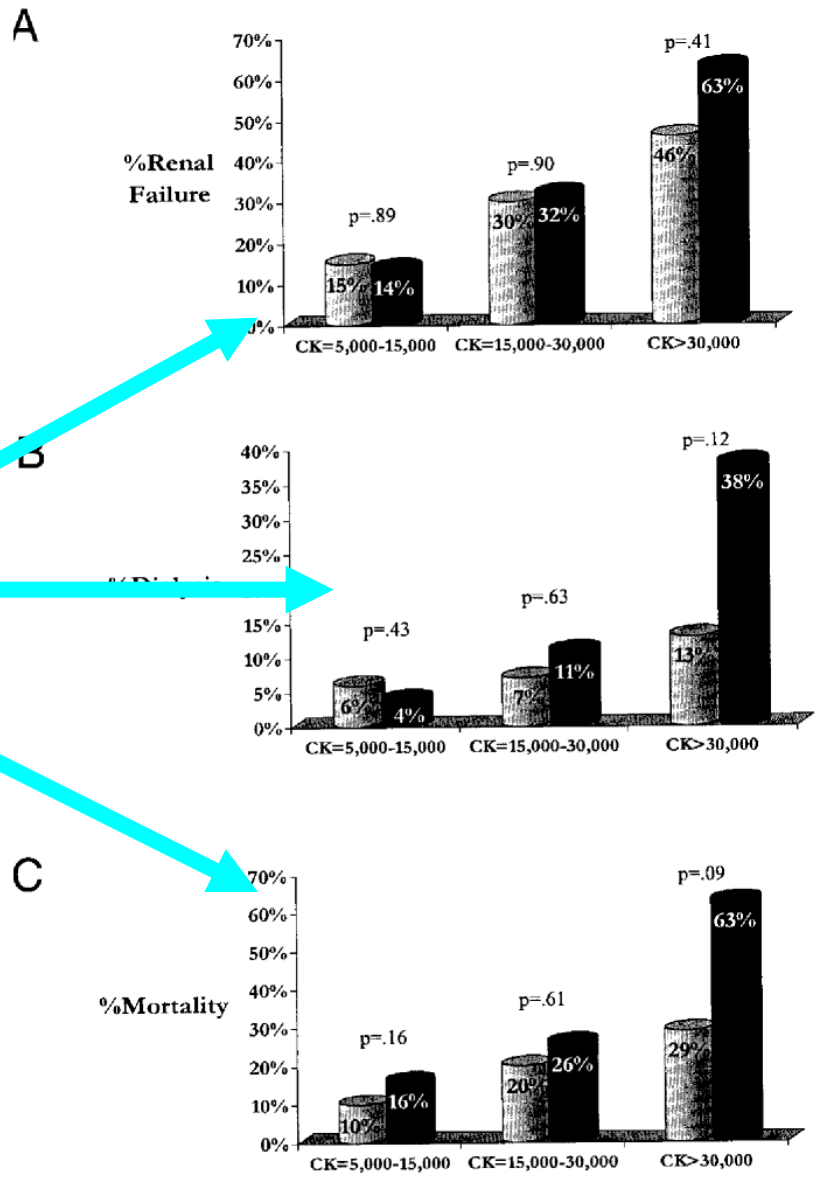


Rhabdomyolysis

- Should be easy
- Identifiable (mostly)
- Biomarker (of sorts)
- Bicarbonate/Mannitol/Frusemide
- ?Evidence

Therapy for Rhabdomyolysis

No Difference in:
% Renal Failure
% Dialysis
% Mortality



Brown C et al.
J Trauma 2004; 30 : 1191-96

Therapy for Rhabdomyolysis

Table 4. Comparative Studies on Preventive and Therapeutic Regimens in Rhabdomyolysis.

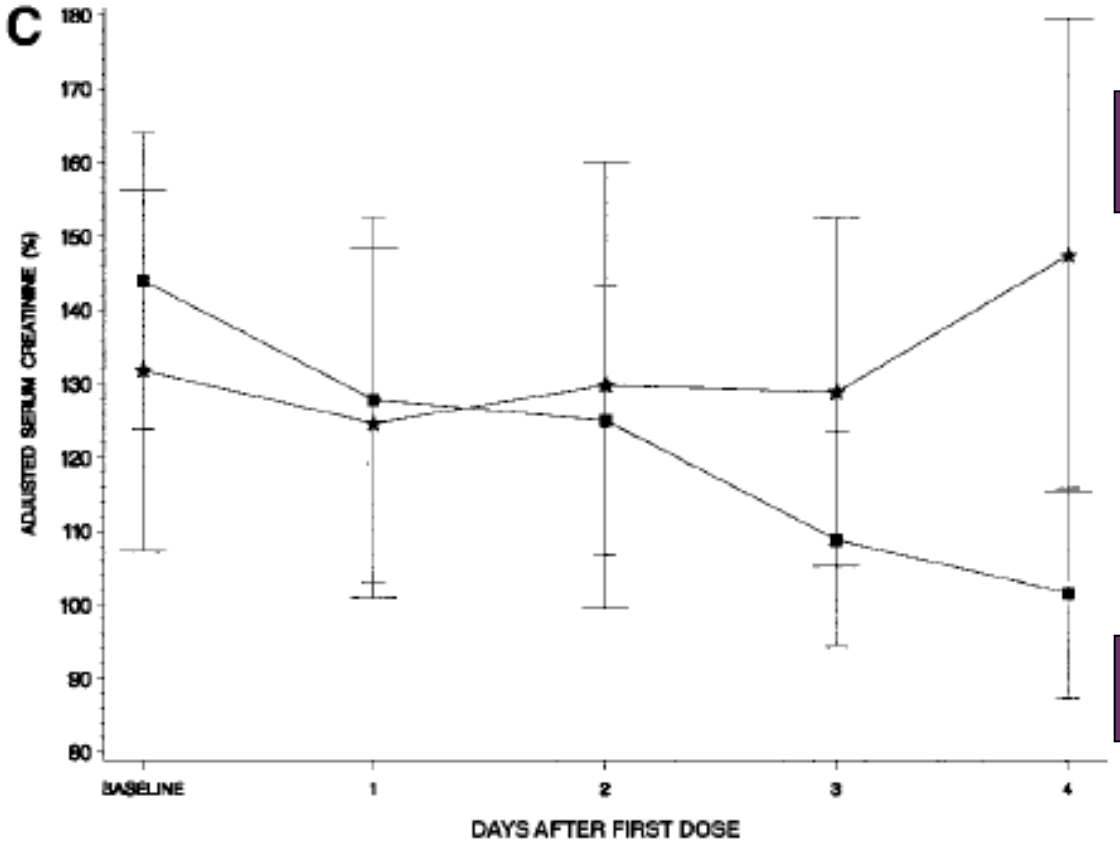
Study	Study Design	Patient Group	No. in Sample	Therapeutic Strategy	Outcome in Patients with Acute Kidney Injury
Shimazu et al.[34]	Retrospective	Patients with the crush syndrome	14	Late vs. early initiation of therapy; high (>10 liters for 48 hours) vs. low volume of hydration	Better if therapy initiated early; high volume of hydration better
Gunal et al.[35]	Retrospective	Patients with the crush syndrome	16	Early vs. late treatment with normal saline followed immediately by bicarbonate	Better if treatment initiated early
Homsi et al.[36]	Retrospective	Patients in the intensive care unit	24	Normal saline vs. normal saline plus bicarbonate and mannitol	No difference
Brown et al.[37]	Retrospective	Patients with trauma	2083	Normal saline vs. bicarbonate plus mannitol	No difference
Cho et al.[38]	Prospective, randomized	Patients with intoxication from doxylamine	28	Ringer's lactate vs. normal saline; bicarbonate if urine pH is <6.5	No effect on peak creatine kinase level or recovery with Ringer's lactate as compared with normal saline; more bicarbonate needed with normal saline than with Ringer's lactate

NEJM 2009

Tumour Lysis Syndrome

- TLS characterized by Severe
  - Hyperuricemia
  - Hyperphosphatemia
  - Hyperkalemia
  - Hypocalcemia,
  - Acute Kidney Injury

Rasburicase



Allopurinol

Rasburicase

Goldman Blood 2001 97; 2998-3003

Rasburicase

- Rasburicase Group
  - Adjusted SCr fell from 144% to 102%
- Allopurinol Group
  - Adjusted SCr rose from 132% to 147%
  - No difference in need for RRT
  - Peak Uric Acid reduced ($p<.0001$)
  - Mean Uric acid AUC less ($p<.0001$)

Goldman Blood 2001 97; 2998-3003

Preventing AKI…..

- Beset by Problems:
- An incomplete understanding of the underlying pathophysiologic mechanisms
- The lack of robust early markers for AKI, and hence an unacceptable delay in initiating therapy

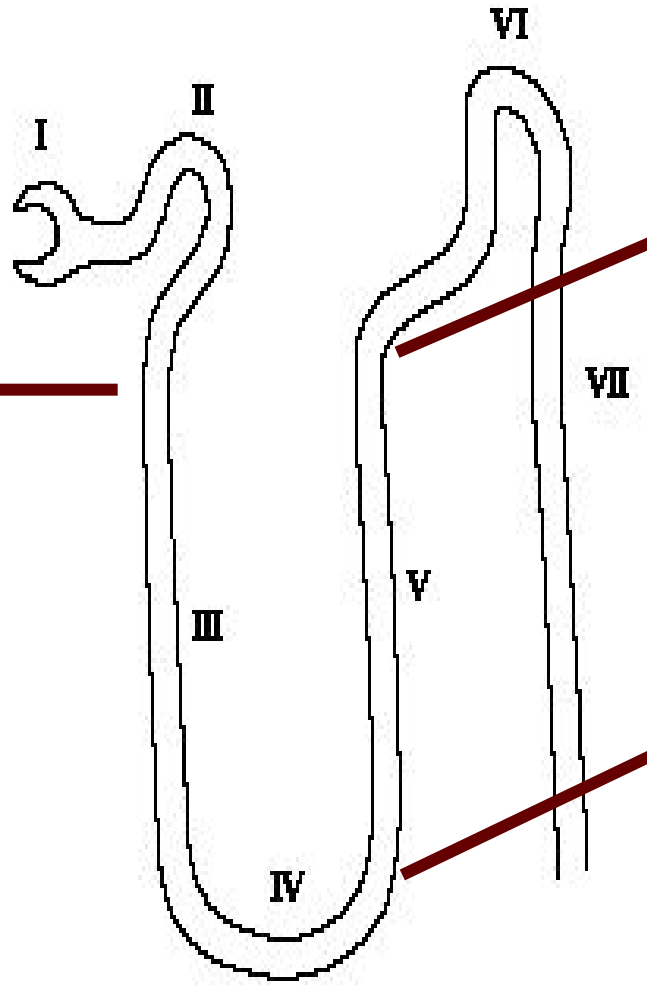

At Present….Is this the best we can hope for?
NIHILISM
Believing in nothing can be exhausting.

Early Detection?

AKI Biomarkers

Glomerular filtration:
Cystatin C
NGAL

Prox tubule:
Cystatin C
NAG
α-GST
γ-GT
NGAL
KIM–1
IL-18
RBP
L-FABP



Distal tubule:
π-GST
NAG
NGAL

Loop of Henle:
RAP (in rats)

What Is A Biomarker?

NIH Definition:

"…a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention…"

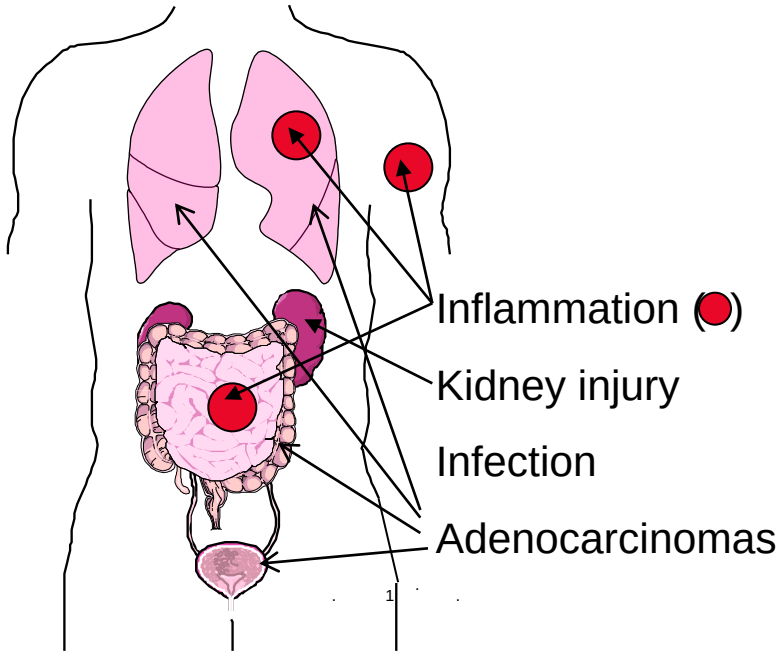
The Rise of the Biomarker

AKI biomarker	Production / origin	Handling by the kidney	Sample sources	Detection time after renal injury	Confounding factors
Neutrophil gelatinase-associated lipocalin (NGAL) also known as oncogene 24p3	25 kDa glycoprotein produced by epithelial tissues throughout the body	plasma NGAL is excreted via glomerular filtration and undergoes complete reabsorption in healthy tubular cells NGAL is also produced in distal tubular segments	plasma and urine	2-4 hours post AKI	sepsis malignancy chronic kidney disease pancreatitis COPD endometrial hyperplasia
Cystatin C	13 kDa cysteine protease inhibitor produced by all nucleated human cells and released into plasma at constant rate independent of gender, race, muscle mass and hydration level	freely filtered in glomeruli and completely reabsorbed and catabolized by proximal tubular cells; no tubular secretion (not detectable in urine in healthy subjects)	plasma and urine (plasma cystatin C may be a marker of GFR; cystatin C only detectable in urine after tubular injury)	12-24 hours post renal injury	systemic inflammation malignancy thyroid disorders glucocorticoid deficiency and excess smoking
Interleukin-18 (IL-18)	18 kDa proinflammatory cytokine	released from proximal tubular cells following injury	plasma and urine	6-24 hours after renal injury	inflammation sepsis heart failure
Kidney Injury Molecule – 1 (KIM-1)	Transmembrane glycoprotein produced by proximal tubular cells after ischaemic or nephrotoxic injury; no systemic source	present in urine after ischaemic or nephrotoxic damage of proximal tubular cells	urine	12-24 hours after renal injury	renal cell carcinoma chronic proteinuria chronic kidney disease sickle cell nephropathy
Liver-type fatty acid-binding protein (L-FABP)	14 kDa intracellular lipid chaperone produced in liver, intestine, pancreas, lung, nervous system, stomach and proximal tubular cells	freely filtered in glomeruli and reabsorbed in proximal tubular cells; increased urinary excretion after tubular cell damage	plasma and urine	1 hour after ischaemic tubular injury	chronic kidney disease polycystic kidney disease liver disease sepsis

NGAL

Neutrophil gelatinase-associated lipocalin

- Neutrophil/epithelial protein – spills into blood and urine
- Released in inflammation from several epithelia
- Released by certain adenocarcinomas
- Released in bacterial infection and sepsis
- Released at higher levels in kidney injury
- Levels increase within <2 hours of kidney injury



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N-acetyl-β-D-glucosaminidase (NAG)	>130 kDa lysosomal enzyme; produced in many cells including proximal and distal tubular cells	too large to undergo glomerular filtration; urinary elevations imply tubular origin	plasma and urine	12 hours	diabetic nephropathy
α glutathione S-transferase (α GST)	47-51 kDa cytoplasmic enzyme produced in proximal tubule	limited glomerular filtration; increased urinary levels following tubular injury	urine	12 hours	
π glutathione S-transferase (π GST)	47-51 kDa cytoplasmic enzyme produced in distal tubules	limited glomerular filtration; increased urinary levels following tubular injury	urine	12 hours	
Alanine aminopeptidase (AAP) Alkaline phosphatase (ALP) γ-glutamyl transpeptidase (γ-GT)	enzymes located on the brush border villi of the proximal tubular cells	released into urine after tubular injury	urine	?	
Hepcidin	2.78 kDa peptide hormone predominantly produced in hepatocytes; some production in kidney, heart and brain	freely filtered with significant tubular uptake and catabolism (fractional excretion 2%)	plasma and urine	?	systemic inflammation
Hepatocyte growth factor (HGF)	Marker linked to renal tubular epithelial cell regeneration				
Netrin	Laminin-related molecule, minimally expressed in proximal tubular epithelial cells of normal kidneys	highly expressed in injured proximal tubules	urine	?	
Monocyte chemoattractant peptide-1 (MCP-1)	Peptide expressed in renal mesangial cells and podocytes	detectable in urine	urine	?	variety of primary renal diseases

Calprotectin	calcium-binding complex of two proteins of the S100 group (S100A8/S100A9); derived from neutrophils and monocytes; acts as activator of the innate immune system	measure of local inflammatory activity; detectable in urine in intrinsic AKI	urine	?	inflammatory bowel disease urinary tract infection probably CKD

M Ostermann, Philips BJ & Forni LG *Crit Care* in press

And is there any evidence…

When Might We Use A Biomarker?

Pre-Renal vs Intrinsic

- Nickolas etal (J Am Coll Cardiol 2012)
- 1635 patients and evaluated
  - NGAL
  - KIM-1
  - L-FABP
  - IL-18
  - Cystatin C

All Markers Raised

Only uNGAL & uCysC able to distinguish pre renal from sustained

Addition of:

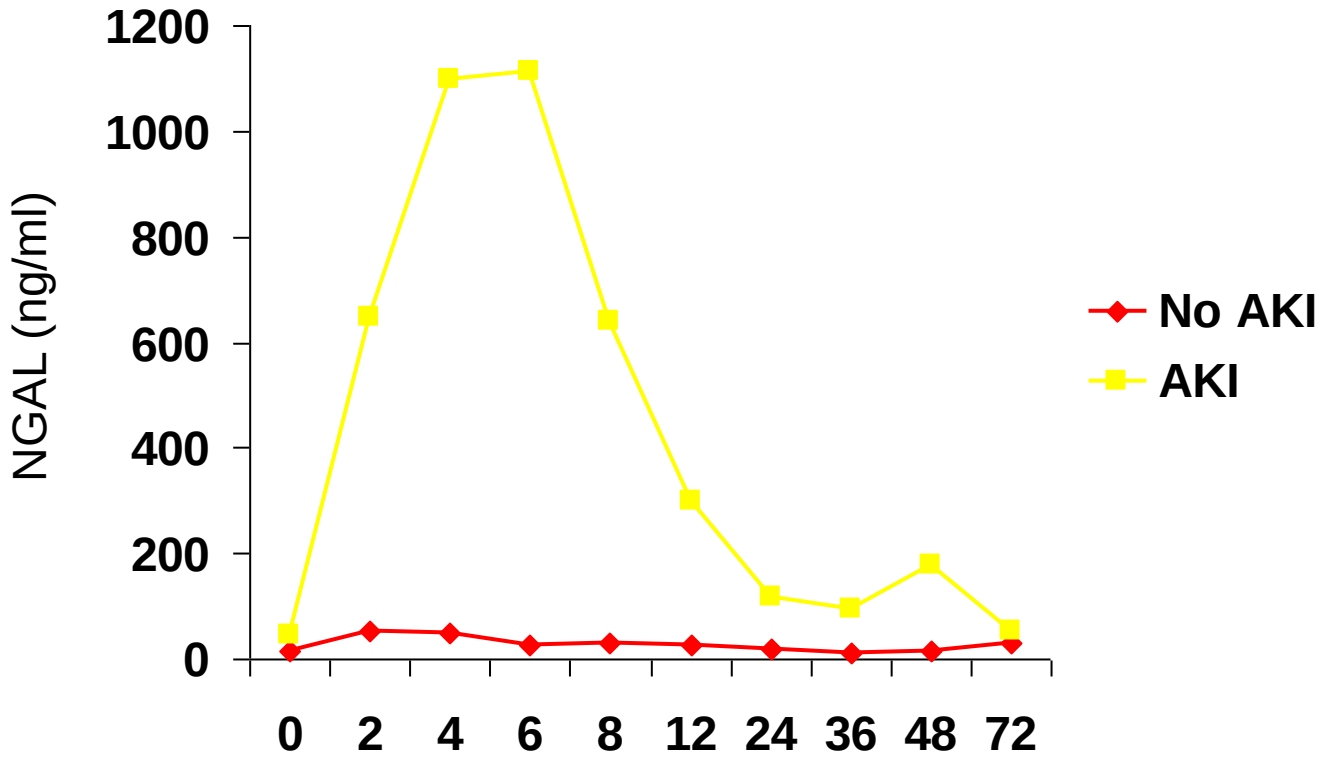
KIM-1 : 0.62 to 0.69

IL-18 : 0.62 to 0.68

uNGAL : 0.62 to 0.75

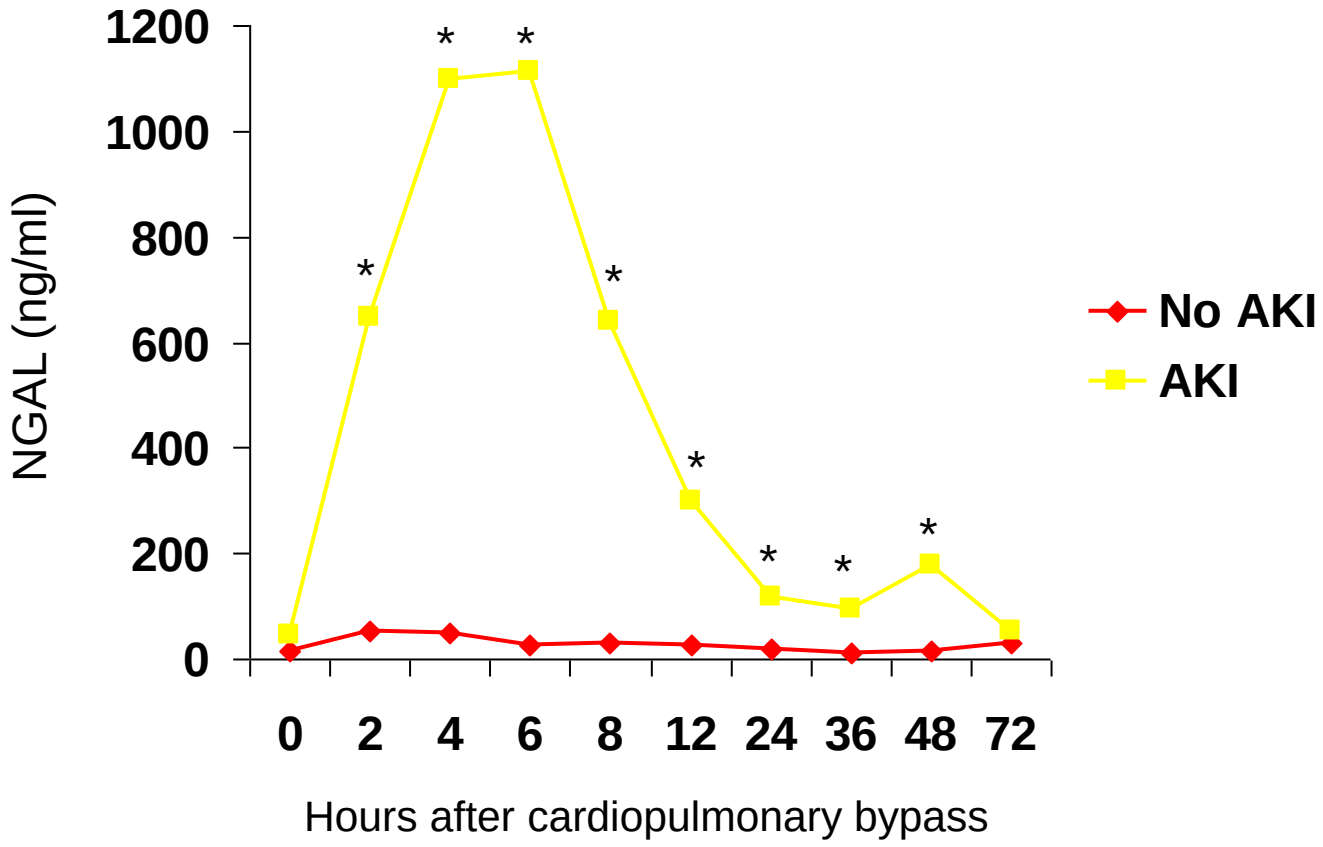
- AUC 0.62

Is NGAL Mystic meg?



Urine NGAL Levels Post- Bypass

15-fold increase in urine NGAL at 2 hours after CPB and 25-fold increase at 4 hours after CPB in children



N = 196

**P* <0.05 comparing patients with or without AKI

Bennett M, et al. *Clin J Am Soc Nephrol*. 2008;3:665-673.

Early 'diagnosis' of AKI

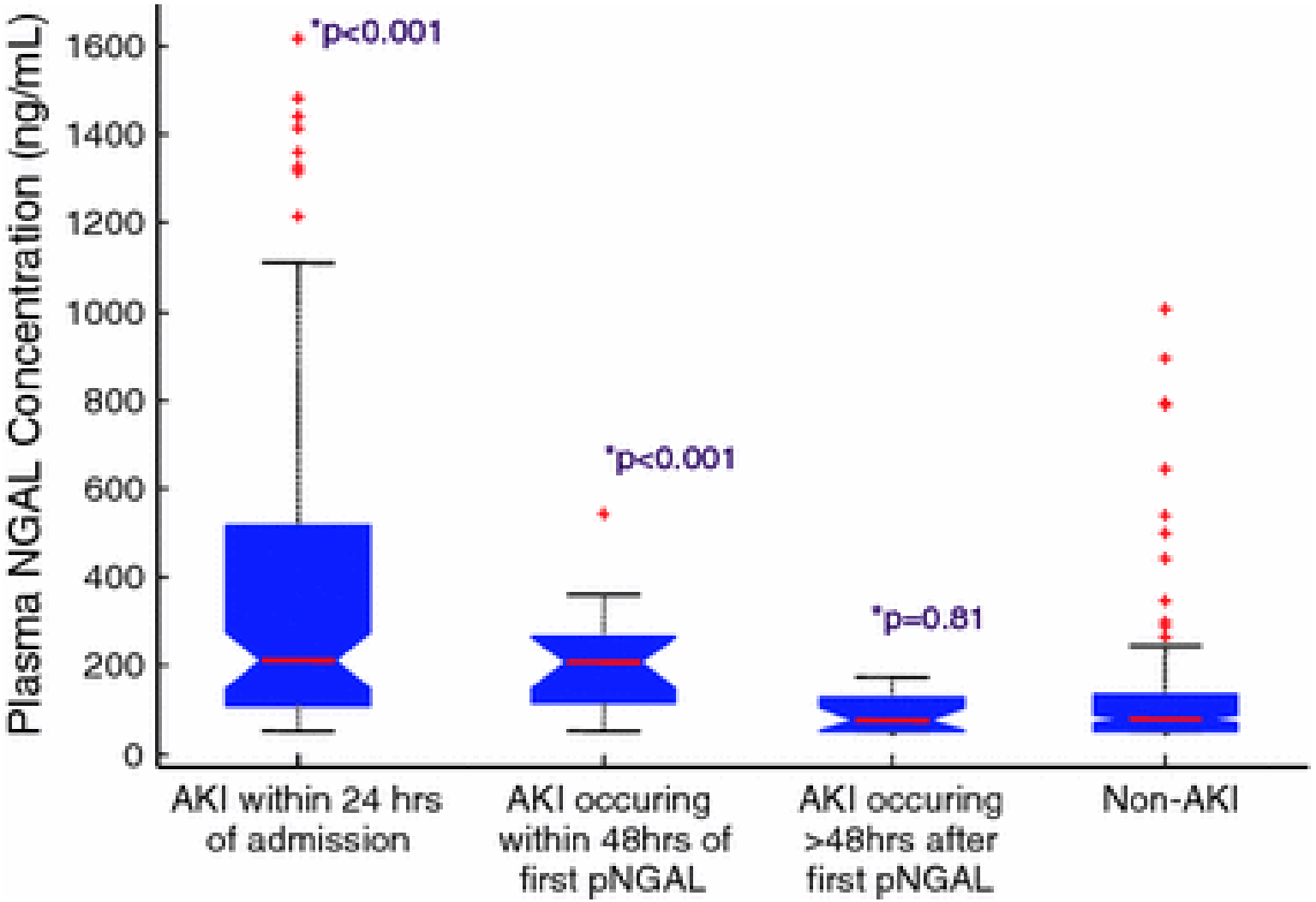
- Most studies have concentrated on the use of biomarkers to predict rises in serum creatinine…….and therefore AKI
- Despite the fact that most proponents of biomarkers for AKI tell us how bad a tool creatinine is…..

Early 'diagnosis' of AKI

Dinna N. Cruz
Massimo de Cal
Francesco Garzotto
Mark A. Perazella
Paolo Lentini
Valentina Corradi
Pasquale Piccinni
Claudio Ronco

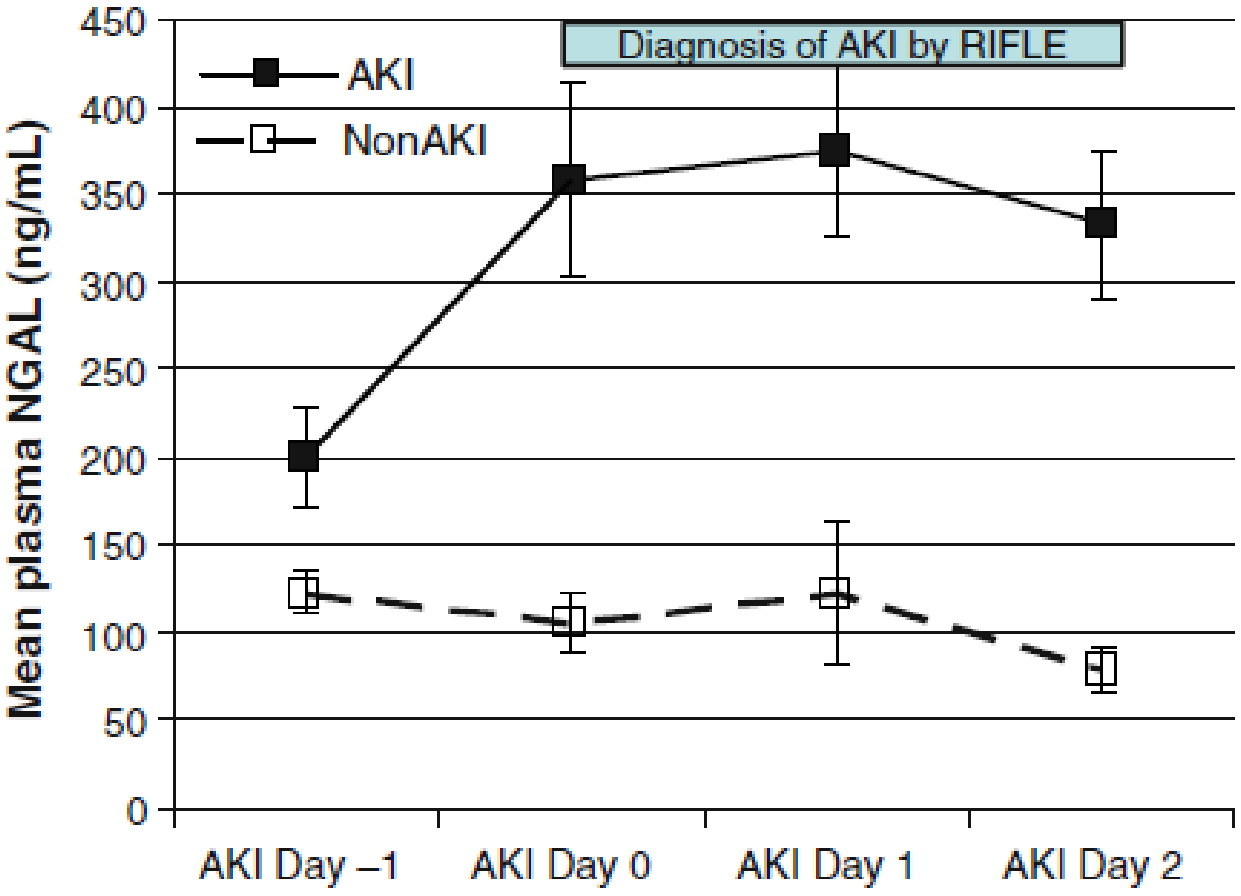
Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population

Intensive Care Med (2010) 36:444–451



Cruz et al. Intensive Care Med 2010;36

Early 'diagnosis' of AKI



Cruz et al. Intensive Care Med 2010;36

But….

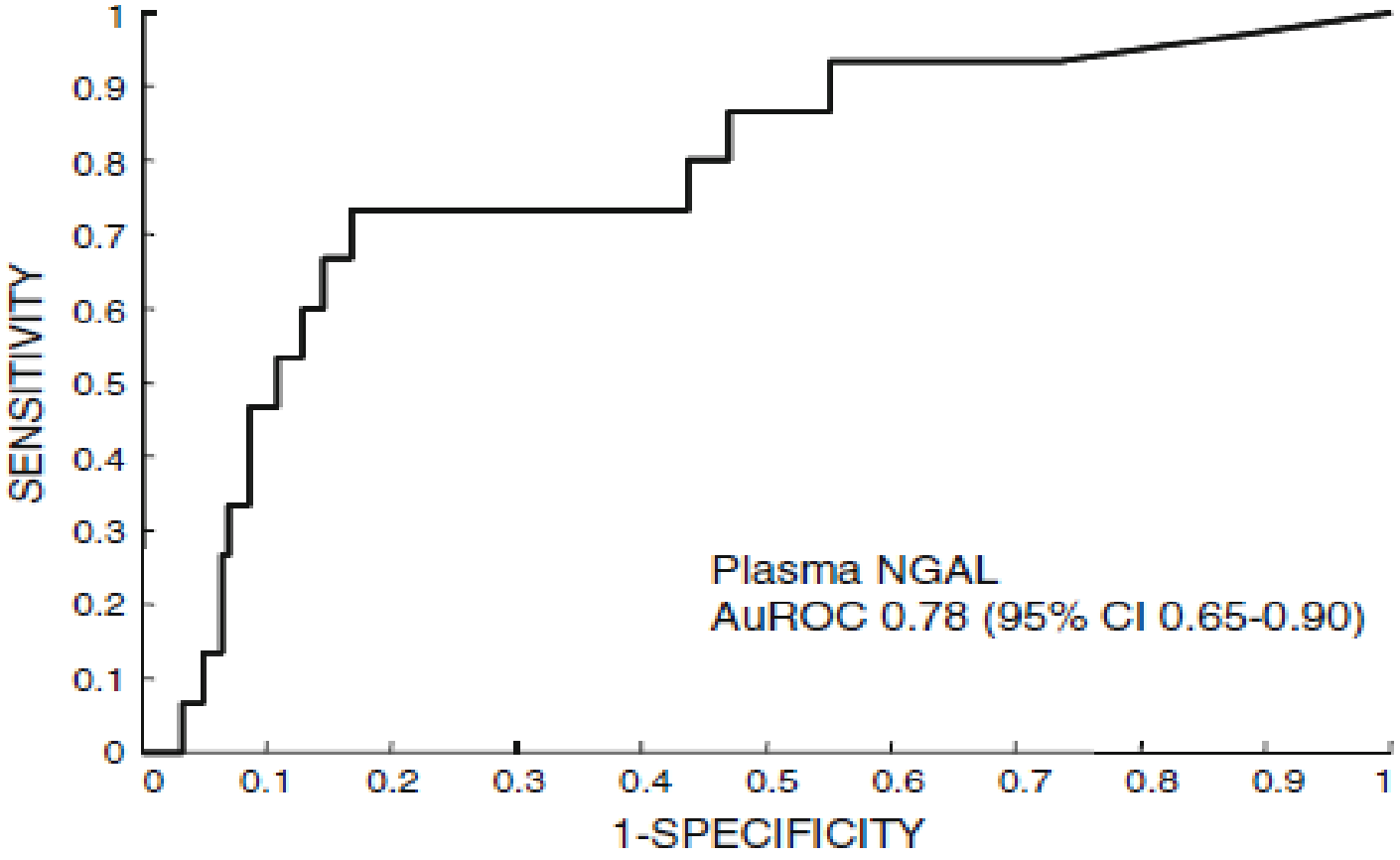


Fig. 3 Receiver operator characteristic (ROC) curve for plasma NGAL. The area under the ROC is 0.78 (95% CI 0.65–0.90), demonstrating a good performance for the diagnosis of AKI within the next 48 h

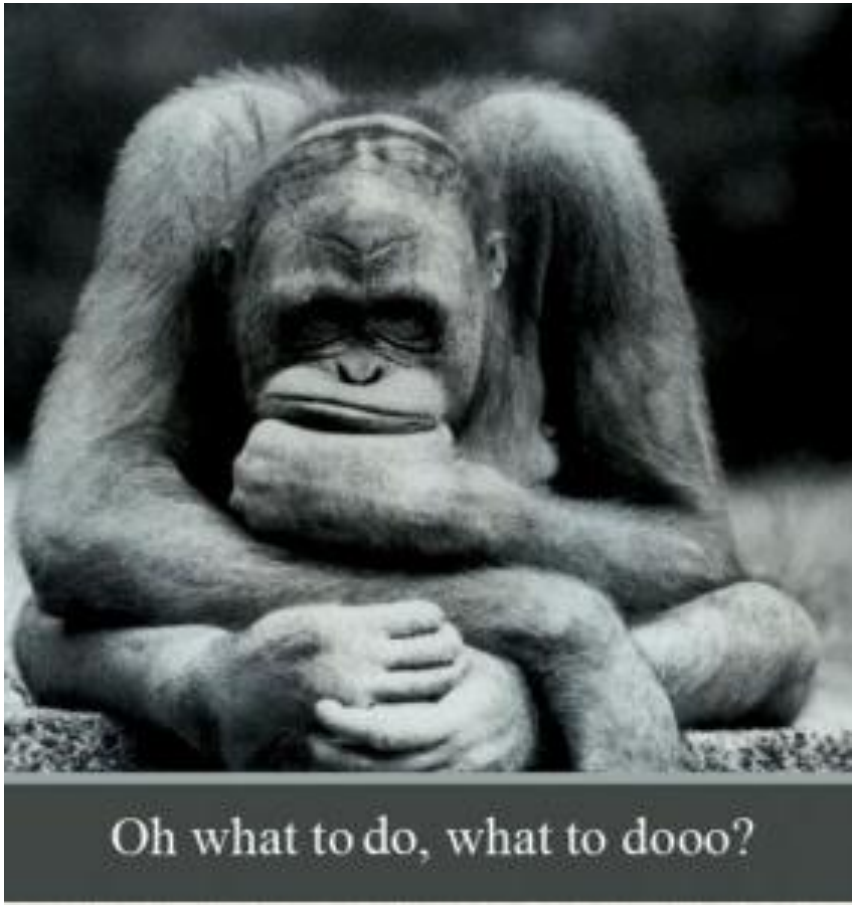
Here's the but….

301 patients : 133 developed AKI (50% septic)

- Median pNGAL AKI vs Non-AKI (p=0.13)
- 90/133: Had AKI on admission
- ? How many included in the ROC curve
- ? Are We Predicting the obvious

So Where Are We……A Troponin for the Kidney?

- The Kidney is not the heart
- AKI is not AMI
- Is the fault with the biomarkers or the concept of AKI itself?



The Future?

- A Personal View
- Little role for biomarkers in the ICU at present
- May be a role in acute medical units or the deep recesses of orthopaedics…Preferably with a risk assessment tool
- This may all change if we can work out how to treat AKI……


DUE TO
THE ACTUAL
FINANCIAL
PROBLEMS,
THE LIGHT AT
THE END
OF THE
TUNNEL
HAS BEEN
TURNED
OFF
(WE APOLOGIZE FOR THE INCONVENIENCE)


Thank You For Listening
ghost