Acute kidney injury

by HP Shum
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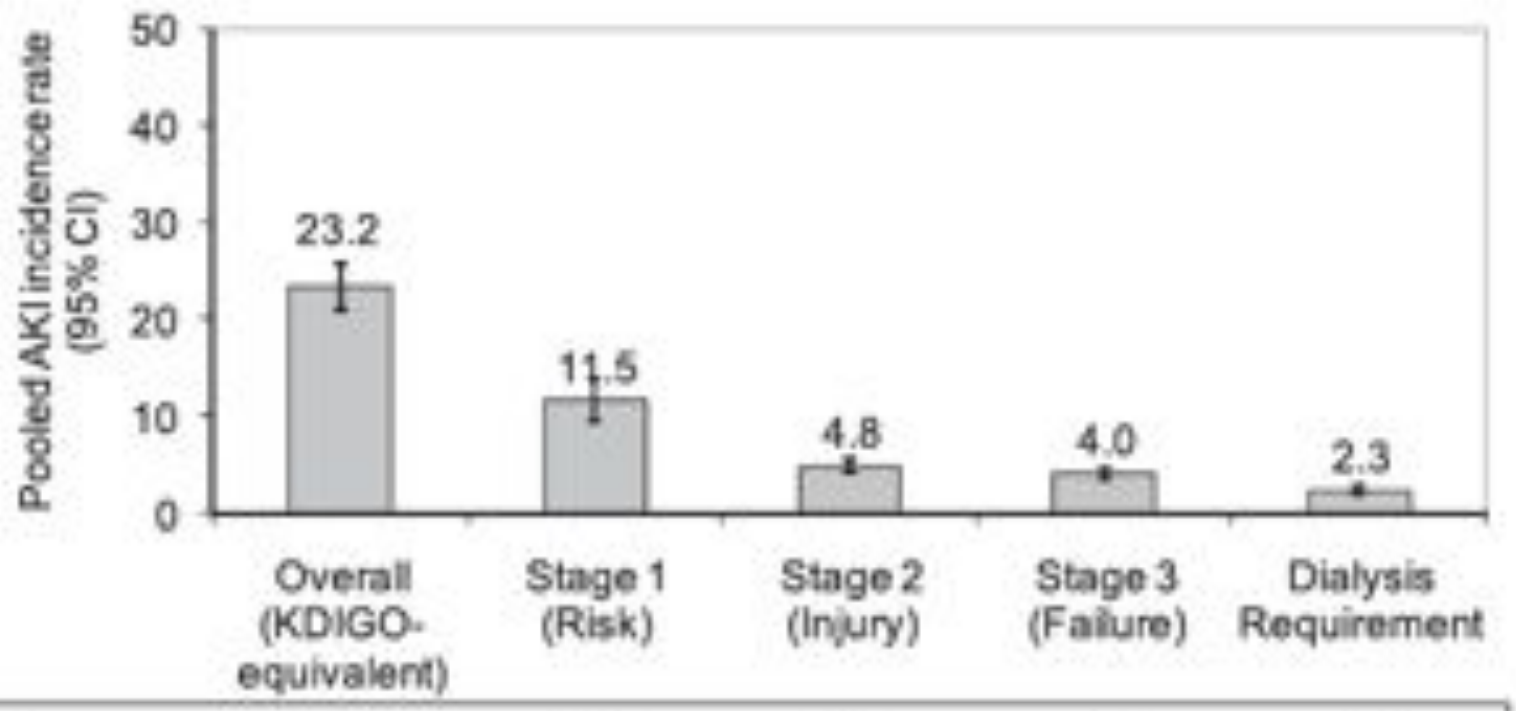
Dec 2014

Overview

- Incidence rate
- Definition and diagnosis of AKI
- Pathophysiology and varies causes of AKI
- Controversies on RRT

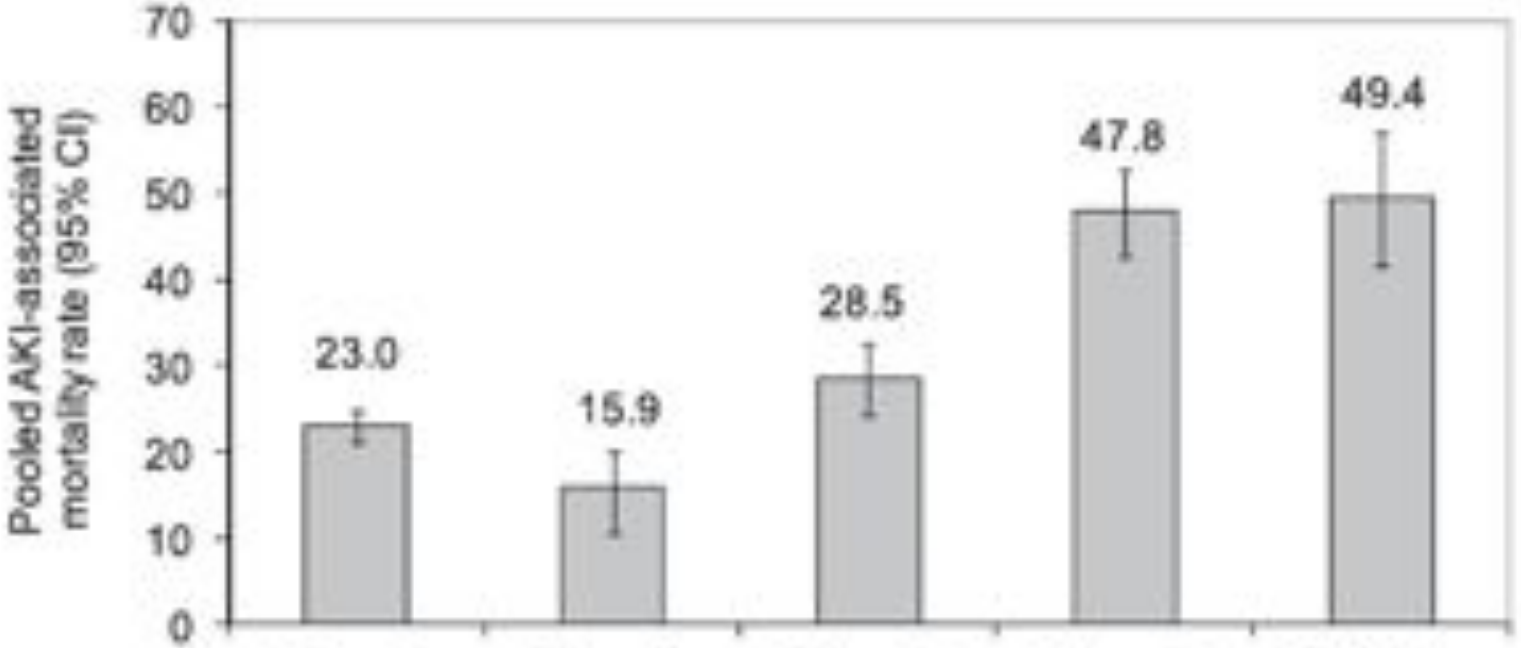
AKI incidence rate



No. studies	154	112	108	108	189
No. patients	3,585,911	3,303,992	3,281,715	3,281,715	29,400,495

Clin J Am Soc Nephrol 8: 1482–1493, 2013.

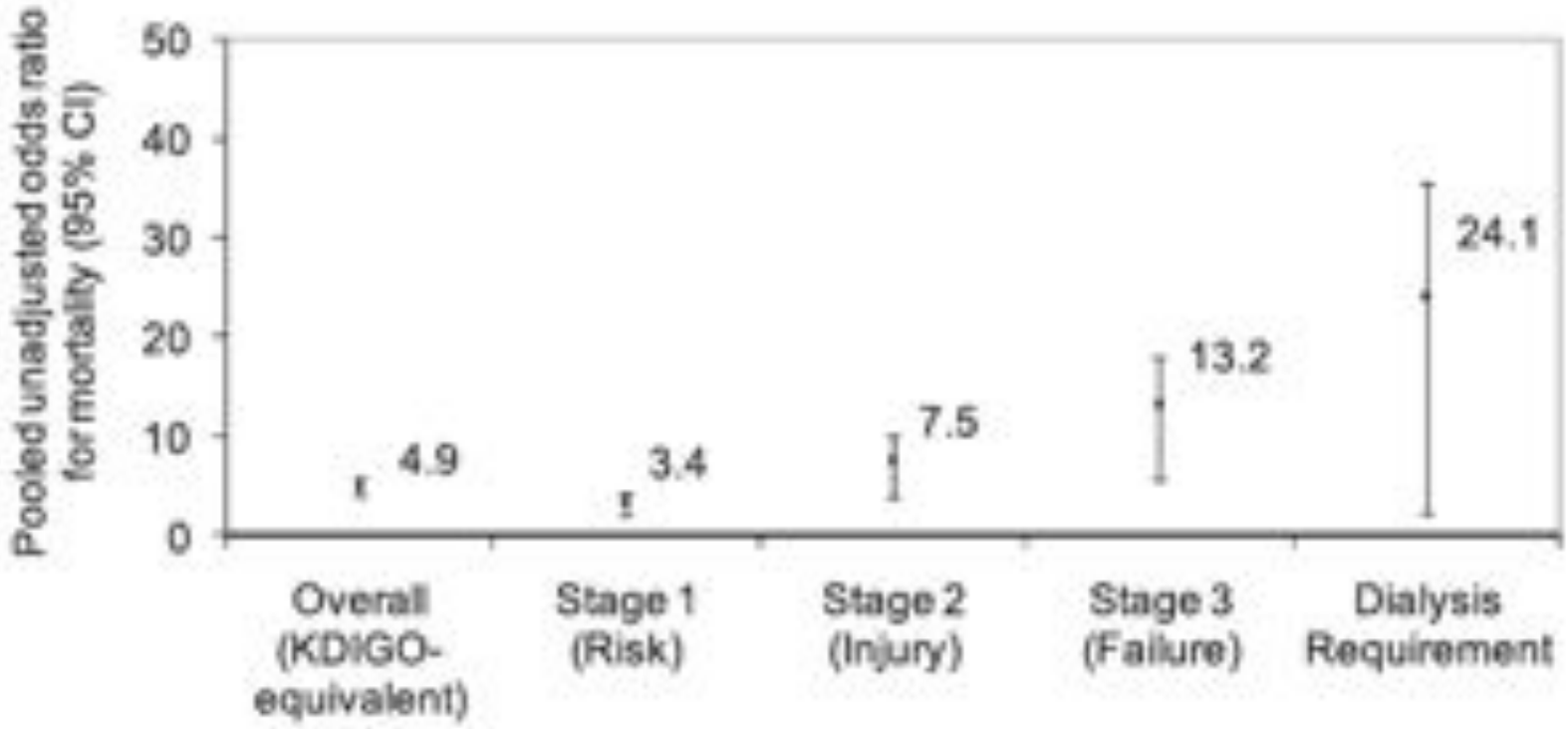
AKI mortality rate



No. studies	110	26	25	25	31
No. patients with AKI	429,535	8,226	42,354	42,354	6,534

Clin J Am Soc Nephrol 8: 1482–1493, 2013.

AKI associated OR for mortality relative to those w/o AKI



No. studies	92	21	20	20	20
No. patients with AKI	405,616	90,048	40,631	38,914	4,427
No. patients without AKI	1,765,574	127,070	1,120,523	1,120,523	127,969

Clin J Am Soc Nephrol 8: 1482–1493, 2013.

AKI definition

- Before 2004, the generic term acute renal failure (ARF) was used for an abrupt and sustained decrease in glomerular filtration rate

- At least 35 definitions in the medical literature, which gave rise to a wide variation in reported incidence and clinical significance of ARF

  Curr Opin Crit Care. 2002 Dec;8(6):509-14.

- In 2007, Acute Kidney Injury Network (AKIN) proposed to replace the term ARF by that of AKI

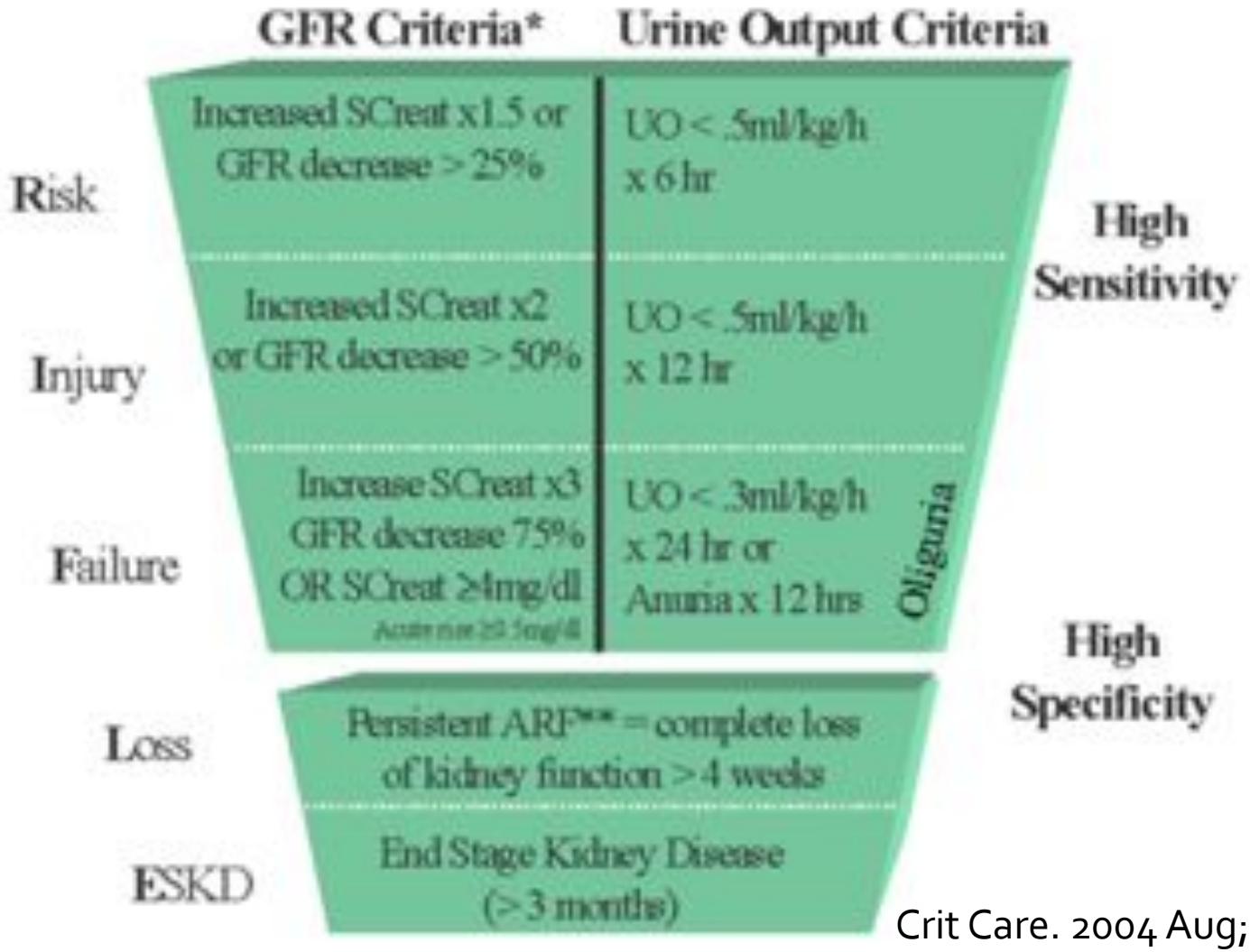
  Crit Care. 2007;11(2):R31.

RIFLE classification 2004

- In 2004, The Acute Dialysis Quality Initiative (ADQI) group developed the Risk, Injury, Failure, Loss and End-stage kidney disease (RIFLE) system

Crit Care. 2004 Aug;8(4):R204-12

RIFLE



Crit Care. 2004 Aug;8(4):R204-12

RIFLE limitations

- Use/non-use of urine output criteria
- Use of change in estimated GFR rather than change in SCr
- Choice of a baseline SCr

GFR = 175 x SerumCr-1.154 * age-0.203 * 1.212 (if patient is black) * 0.742 (if female)

GFR = 141 X min(Scr/κ,1)α X max(Scr/κ,1)-1.209 X 0.993Age X 1.018 [if female] X 1.159 [if black]

Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Ann Intern Med 150(9):604-12. (2009)

AKIN classification 2007

Table 3 | Comparison of RIFLE and AKIN criteria for diagnosis and classification of AKI

AKI staging		RIFLE	
Serum creatinine	Urine output (common to both)	Class	Serum creatinine or GFR
Stage 1 Increase of more than or equal to 0.3 mg/dl (≥ 26.5 μmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg/h for more than 6 hours	Risk	Increase in serum creatinine × 1.5 or GFR decrease > 25%
Stage 2 Increased to more than 200% to 300% (> 2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 hours	Injury	Serum creatinine × 2 or GFR decreased > 50%
Stage 3 Increased to more than 300% (> 3-fold) from baseline, or more than or equal to 4.0 mg/dl (≥ 354 μmol/l) with an acute increase of at least 0.5 mg/dl (44 μmol/l) or on RRT	Less than 0.3 ml/kg/h for 24 hours or anuria for 12 hours	Failure	Serum creatinine × 3, or serum creatinine > 4 mg/dl (> 354 μmol/l) with an acute rise > 0.5 mg/dl (> 44 μmol/l) or GFR decreased > 75%
		Loss	Persistent acute renal failure=complete loss of kidney function > 4 weeks
		End-stage kidney disease	ESRD > 3 months

inclusion of a time constraint of 48 hours

Kidney Int 2012; suppl 2(1):1-138

AKIN

- Include both an absolute and a percentage change in SCr, to accommodate variations related to age, gender, and body mass index
- reduce the need for a baseline creatinine
- do require at least two creatinine values within 48 hours

Crit Care. 2007;11(2):R31

AKIN vs. RIFLE

- 10.5% classified as having AKI by RIFLE criteria were missed by AKIN criteria; by contrast, RIFLE criteria missed only 3.5% classified as having AKI by AKIN criteria

Nat Rev Nephrol. 2010 Feb;6(2):71-3

AKIN classification 2007

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		Loss	Persistent acute renal failure=complete
		End-stage kidney disease	ESKD > 3 months

inclusion of a time constraint of 48 hours

Abrupt onset 1-7d and last for > 24hr

Kidney Int 2012; suppl 2(1):1-138

Kidney Diseases Improving Global Outcomes (KDIGO) 2012

2.1.1: AKI is defined as any of the following (*Not Graded*):

- **Increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours; or** AKIN
- **Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or** RIFLE
- **Urine volume <0.5 ml/kg/h for 6 hours.**

2.1.2: AKI is staged for severity according to the following criteria (Table 2). (*Not Graded*)

Table 2 | Staging of AKI AKIN

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

Kidney Int 2012; suppl 2(1):1-138

KIDGO

- A disease process that results in a change in SCr over many weeks is not AKI
- There is no stipulation as to when the 1-week or 48-hour time periods can occur

Baseline renal function

- Many patients do not have baseline value
  - Backward calculation based on standard GFR 75ml/min/1.73m2 (KIDGO/ RIFLE)
  - Admission SCr (European Renal Best Practice position statement)
  - Minimum SCr level (nadir value) during the hospital stay

RIFLE vs. AKIN vs. KIDGO

Results: The rates of incidence of AKI using the RIFLE, AKIN, and KDIGO criteria were 46.9%, 38.4%, and 51%, respectively. KDIGO identified more patients than did RIFLE (51% versus 46.9%, $P = 0.001$) and AKIN (51% versus 38.4%, $P < 0.001$). Compared with patients without AKI, in-hospital mortality was significantly higher for those diagnosed as AKI by using the RIFLE (27.8% versus 7%, $P < 0.001$), AKIN (32.2% versus 7.1%, $P < 0.001$), and KDIGO (27.4% versus 5.6%, $P < 0.001$) criteria, respectively. There was no difference in AKI-related mortality between RIFLE and KDIGO (27.8% versus 27.4%, $P = 0.815$), but there was significant difference between AKIN and KDIGO (32.2% versus 27.4%, $P = 0.006$). The areas under the receiver operator characteristic curve for in-hospital mortality were 0.738 ($P < 0.001$) for RIFLE, 0.746 ($P < 0.001$) for AKIN, and 0.757 ($P < 0.001$) for KDIGO. KDIGO was more predictive than RIFLE for in-hospital mortality ($P < 0.001$), but there was no difference between KDIGO and AKIN ($P = 0.12$).

RESEARCH Open Access

A comparison of different diagnostic criteria of acute kidney injury in critically ill patients

Xuying Luo[1†], Li Jiang[1†], Bin Du[2], Ying Wen[1], Meiping Wang[1], Xiuming Xi[1*] and The Beijing Acute Kidney Injury Trial (BAKIT) workgroup

Critical Care 2014, 18:R144

Problem using U/o and SCr

- RIFLE, AKIN and KDIGO all diagnose AKI according to serum creatinine and urine output
- Urine output measurement, non-automated process ->can be highly inaccurate
- Serum creatinine is neither sensitive nor specific, tending to represent a functional change rather than being a true marker of kidney injury

The BARD® CRITICORE® Monitor

SCr is affected by multiple factors

- Age
- Malnutrition
- Ethnicity
- Gender
- Muscle mass
- Medications
  - Trimethoprim, cimetidine
- Protein intake

Renal Biomarker

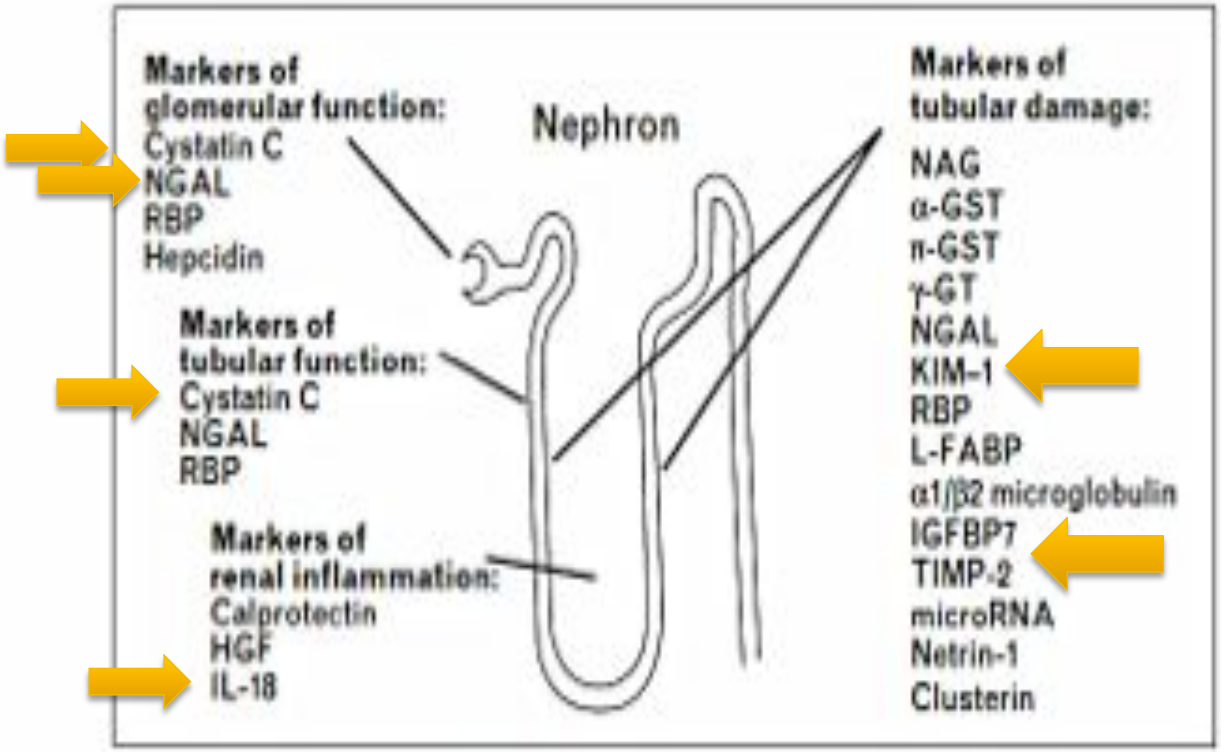


FIGURE 1. Origin and function of novel acute kidney injury biomarkers. GST, glutathione S-transferase; γ-GT, γ-glutamyl transpeptidase; HGF, hepatocyte growth factor; IGFBP-7, insulin-like growth factor-binding protein-7; IL-18, interleukin 18; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid-binding protein; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; RBP, retinol-binding protein; TIMP-2, tissue metalloproteinase-2.

Curr Opin Crit Care 2014, 20:581 – 587

Markers of kidney injury

- Neutrophil gelatinase-associated lipocalin
  - secretion from epithelial cells is induced by ischemia, inflammation and infection
  - increased several fold in both serum and urine within hours of the insult
  - accumulation was most pronounced in the most injured cells

NGAL

- Cardiac surgery
  - AuROC for AKI prediction within 48 h up to 10 days ranging from 0.50 to 0.98
  - Great variation of AKI definition among studies
- Critical care / ED
  - Difficult for several reasons
    - AKI is already present at ICU admission in the majority of cases, timing of AKI not clear
    - Etiology of AKI often multifactorial
    - ICU population displays a heterogeneous mixture of co-morbidities
    - Sepsis already induced plasma NGAL production (effect of sepsis on urinary NGAL levels is not clear)
  - AuROC between 0.78 and 0.96

British Journal of Anaesthesia 109 (6): 843–50 (2012)

Markers of kidney injury

- N-acetyl-b-D-glucosaminidase (NAG), lysosomal enzyme found in several human cells including the renal tubules
  - AuROC 0.71-0.83
- Kidney injury molecule-1 (KIM-1), type I cell membrane glycoprotein, play a role in the regeneration processes after epithelial injury.
  - AuROC 0.61
- Interleukin-18 (IL-18), proinflammatory cytokine
  - AuROC 0.53-0.7

British Journal of Anaesthesia 109 (6): 843–50 (2012)

Markers of kidney injury

IGFBP7 Insulin-like Growth Factor Binding Protein 7 (Urine)	Inducer of G1 cell cycle arrest expressed by injured tubular cells. Cell cycle stopped via its own receptor
TIMP-2 Tissue inhibitor Metalloproteinases-2 (Urine)	Inducer of G1 cell cycle arrest expressed by injured tubular cells. Cell cycle stopped via its own receptor
NGAL Neutrophil gelatinase-associated lipocalin (Blood/urine)	Protein expressed in neutrophils and prox/distal renal tubule cells; binds and traffics free iron and is upregulated in the setting of renal tubular ischaemia
IL-18 Interleukin-18 (Urine)	Inflammatory cytokine found in macrophages and proximal tubule cells that is upregulated in the setting of renal ischemic injury
Cystatin C (Blood/urine)	Cysteine protease inhibitor freely filtered at glomerulus that is normally reabsorbed by prox tubule cells and appears in the urine in the setting of tubular injury
KIM-1 (Kidney Injury Molecule) (Urine)	Type 1 cell membrane glycoprotein that is shed into the urine following proximal tubule injury

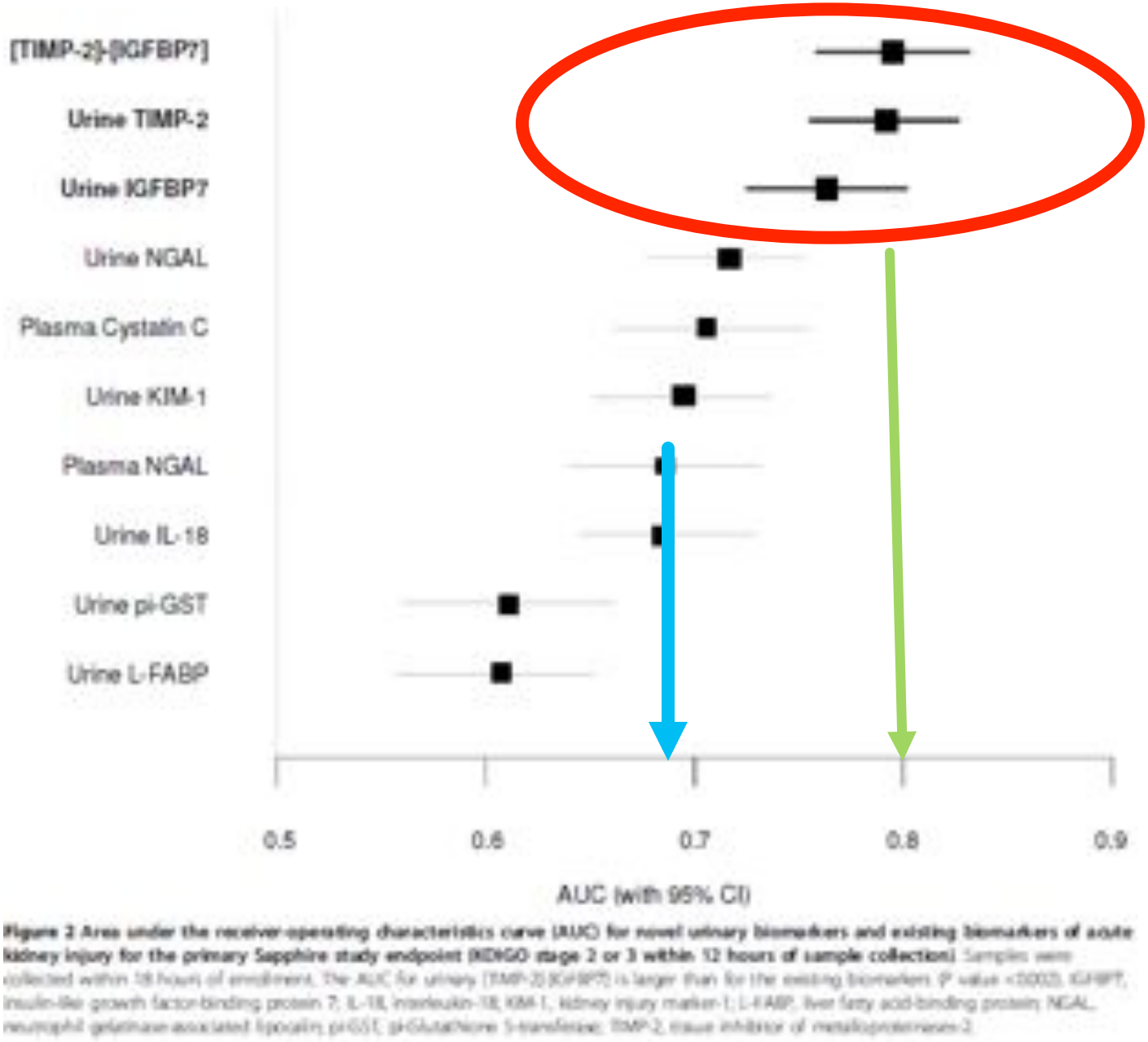


Figure 2 Area under the receiver-operating characteristics curve (AUC) for novel urinary biomarkers and existing biomarkers of acute kidney injury for the primary Sapphire study endpoint (KDIGO stage 2 or 3 within 12 hours of sample collection) Samples were collected within 18 hours of enrollment. The AUC for urinary [TIMP-2]·[IGFBP7] is larger than for the existing biomarkers (P value <0.002). IGFBP7, insulin-like growth factor-binding protein 7; IL-18, interleukin-18; KIM-1, kidney injury marker-1; L-FABP, liver fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; pi-GST, pi-Glutathione S-transferase; TIMP-2, tissue inhibitor of metalloproteinases-2.

744 Critical ill patients

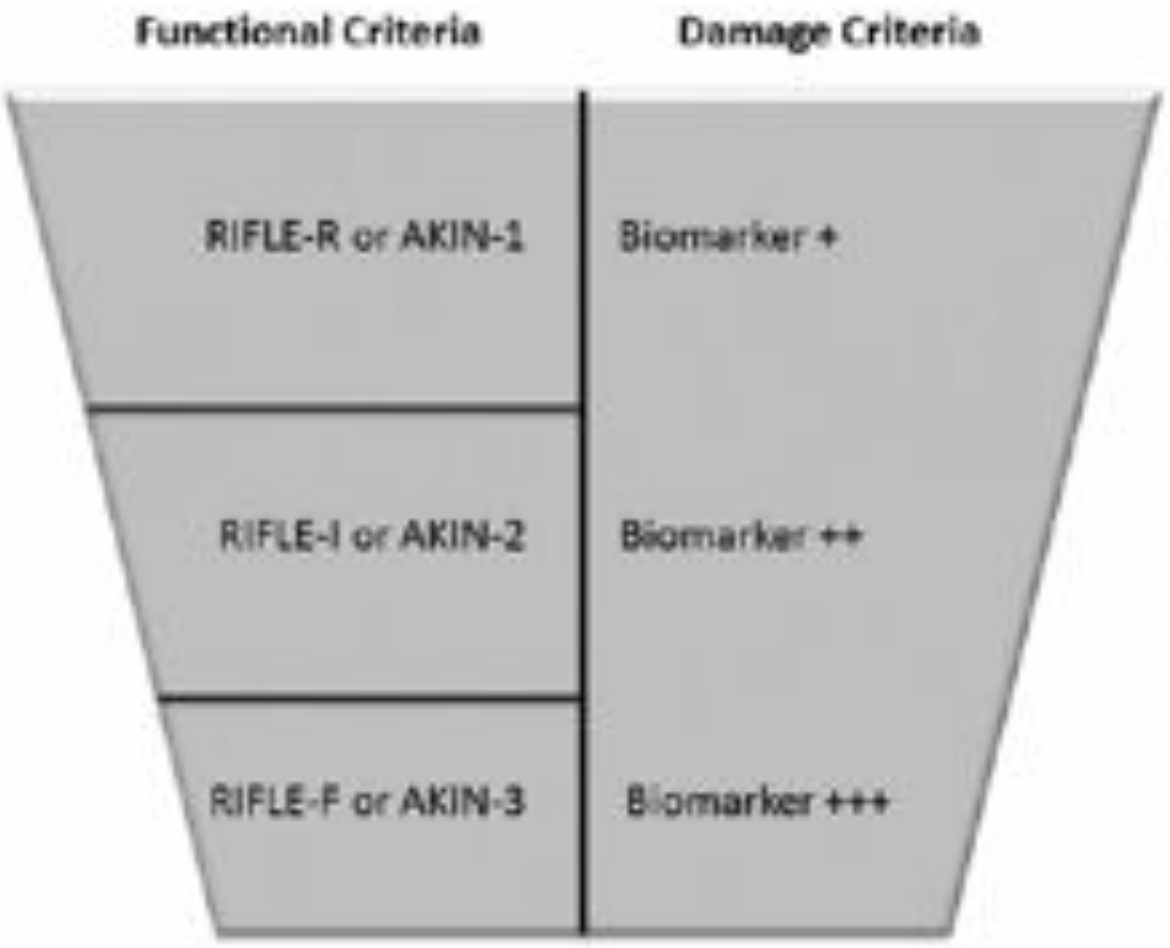
Kashaniet al. Critical Care 2013,17:R25

Markers of kidney function

- Plasma cystatin C, endogenous marker of GFR
  - produced at a constant rate by all nucleated cells , freely filtered by the glomeruli without reabsorption, also minimally bound to proteins
- AuROC 0.6-0.97

British Journal of Anaesthesia 109 (6): 843–50 (2012)

Can we use renal biomarker for staging of AKI ?



Contrib Nephrol 2013; 182: 13–29

Can we use renal biomarker for staging of AKI ?

Diagnosis of Acute Kidney Injury Using Functional and Injury Biomarkers: Workgroup Statements from the Tenth Acute Dialysis Quality Initiative Consensus Conference

Peter A. McCullough[a] · Andrew D. Shaw[b] · Michael Haase[c] · Josee Bouchard[d] · Sushrut S. Waikar[e] · Edward D. Siew[f] · Patrick T. Murray[g] · Ravindra L. Mehta[h] · Claudio Ronco[i] · for the ADQI 10 Workgroup

Contrib Nephrol. 2013;182:13-29.

Adding injury biomarkers as a criterion for AKI will complement the ability of RIFLE/AKIN to define AKI. However, there are currently insufficient data on damage biomarkers to support their use for AKI staging. Rigorous validation studies measuring the association between the novel damage biomarker(s) and clinically relevant outcomes are needed.

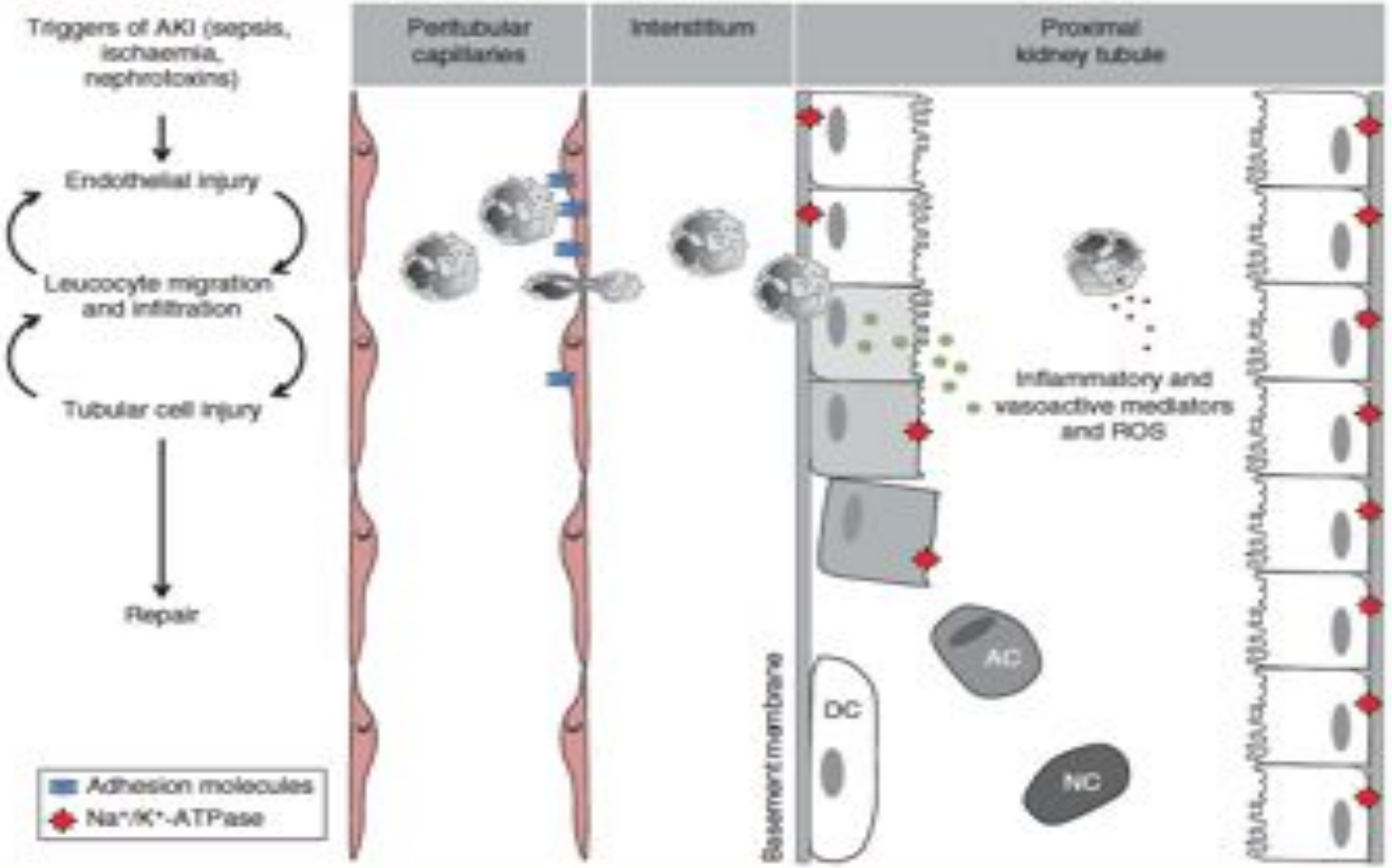


Fig 1 Pathophysiological mechanisms of AKI and repair. Adhesion molecules up-regulate on the surface of endothelial cells and facilitate migration of neutrophils into the kidney interstitium and tubular lumen. Inflammatory and vasoactive mediators and reactive oxygen species (ROS) damage the tubular cells. Shedding of the proximal tubule brush border, loss of polarity with mislocation of Na+/K+– ATPase and also apoptosis and necrosis may occur. With severe injury, viable and non-viable cells are desquamated, leaving parts of the basement membrane denuded. Inflammatory and vasoactive substances released from the injured tubular cells worsen the pathophysiological changes. If the repair process is successful, viable cells de-differentiate and spread to cover exposed areas of the basement membrane and restore the functional integrity of the nephron. AC, apoptotic cell; DC, de-differentiating cell; NC, necrotic cell.

British Journal of Anaesthesia 109 (6): 843–50 (2012)

Causes of AKI

Table 2. Causes of acute kidney injury: exposures and susceptibilities for nonspecific acute kidney injury

Exposure	Susceptibility
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	Chronic kidney disease
Cardiac surgery (especially with cardiopulmonary bypass)	Chronic diseases (heart, lung, liver)
Major noncardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anemia
Poisonous plants and animals	

Kidney Int 2012; suppl 2(1):1-138

Focus on..

- Contrast induced nephropathy
- Rhabdomyolysis
- Perioperative AKI

Contrast media-induced AKI

- Pathophysiology
  - constrict descending vasa recta -> impair blood flow to medulla -> hypoxia and increase oxidative stress
  - induce cell damage and apoptotic cell death through the activation of the intrinsic apoptotic pathway

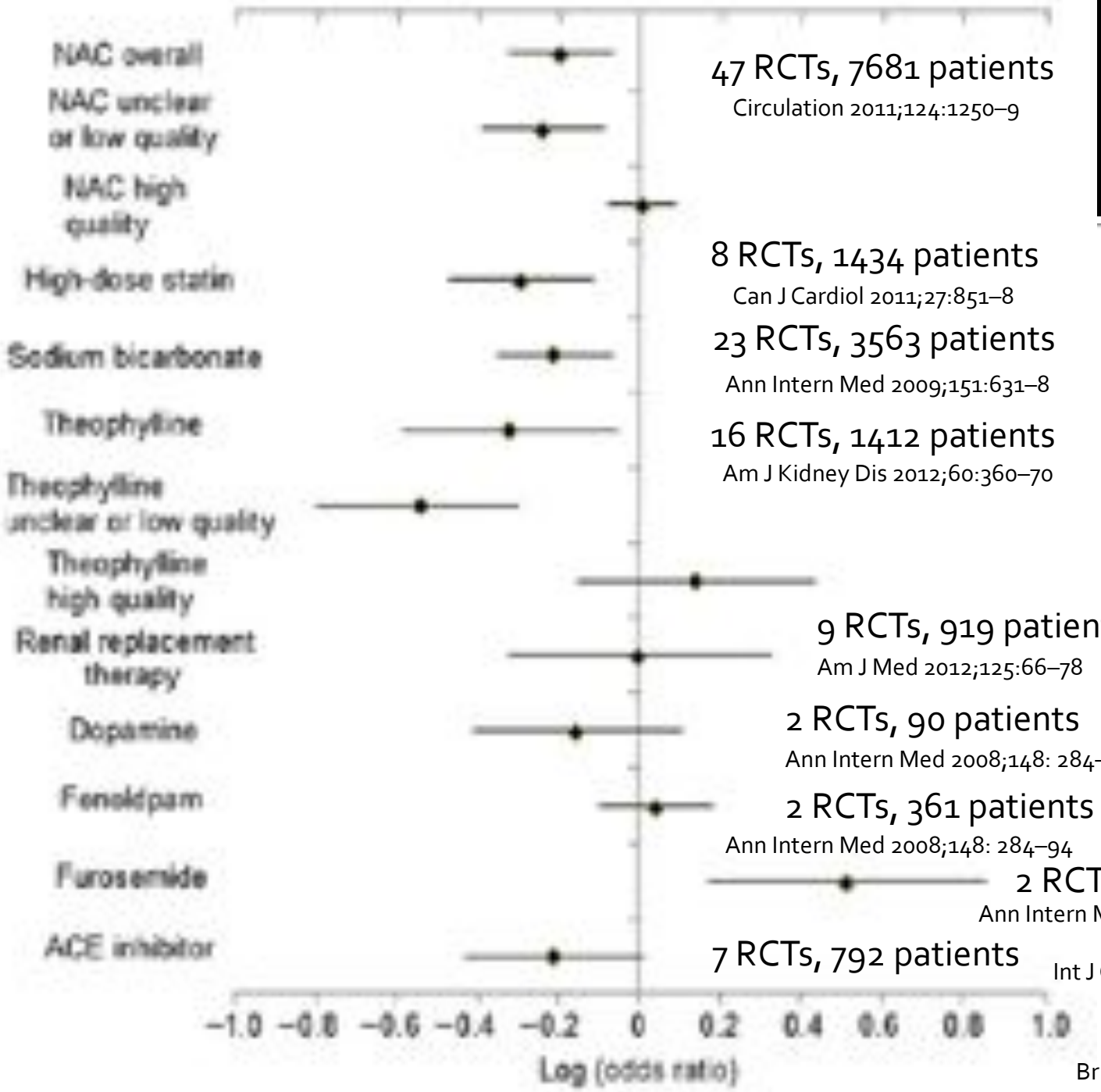
CIN – risk factors

Table 2. Risk score of contrast-induced acute kidney injury[a]

Risk factors	Integer score
Hypotension	5
IABP	5
Heart failure	5
Age >75	4
Anemia	3
Diabetes	3
CM volume	1 for each 100 cm^3
Creatinine >1.5	4
eGFR<60ml/min/1.73m^2	2 for 40–60 4 for 20–40 6 <20

Risk score	Risk of CIN	Risk of dialysis
≤ 5	7.5%	0.04%
6–10	14%	0.12%
11–16	26.1%	1.09%
≥16	57.3%	12.6%

J Am Coll Cardiol 2004; 44:1393– 1399



47 RCTs, 7681 patients
Circulation 2011;124:1250–9

8 RCTs, 1434 patients
Can J Cardiol 2011;27:851–8

23 RCTs, 3563 patients
Ann Intern Med 2009;151:631–8

16 RCTs, 1412 patients
Am J Kidney Dis 2012;60:360–70

9 RCTs, 919 patients
Am J Med 2012;125:66–78

2 RCTs, 90 patients
Ann Intern Med 2008;148: 284–94

2 RCTs, 361 patients
Ann Intern Med 2008;148: 284–94

2 RCTs, 209 patients
Ann Intern Med 2008;148: 284–94

7 RCTs, 792 patients
Int J Cardiol 2012; 486–8

Br J Radiol 2013;86:20120272

Rhabdomyolysis

- Muscle injury associated with myoglobinu- ria, electrolyte abnormalities, and often AKI
- Muscle cell membrane disruption with influx of Ca -> damage sarcoplasmic reticulum and mitochondria -> malfunction of Na/K and Na/Ca pump -> increased intracellular Ca -> lysis of cell and release of cellular contents

Chest. 2013 Sep;144(3):1058-65

AKI in Rhabdomyolysis

- Occur in 10-60% of patients
- Myoglobin – primary nephrotoxin
  - Filtered by glomeruli and ppt in acidic environment by interact with Tamm-Horsfall protein -> tubular obstruction
  - Exacerbated by intravascular depletion with renal hypoperfusion
  - Oxidative injury from iron in myoglobin
  - Induce lipid peroxidation -> produce isoprostanes -> renal vasoconstriction

Chest. 2013 Sep;144(3):1058-65

Causes of rhabdomyolysis

Hypoxic	Physical	Chemical	Biologic
External	External	External	External
Carbon monoxide exposure	Crush injury	Alcohol	Bacterial, viral, and parasitic myositis
Cyanide exposure	Trauma	Prescription medications	Organic toxins
Internal	Burns	Over-the-counter medications	Snake venom
Compartment syndrome	Electrocution	Illicit drugs	Spider bites
Vascular compression	Hypothermia	Internal	Insect stings (ants, bees, wasps)
Immobilization	Hyperthermia (heat stroke)	Hypokalemia	Internal
Bariatric surgery	Internal	Hypophosphatemia	Dermatomyositis, polymyositis
Prolonged surgery	Prolonged and/or extreme exertion	Hypocalcemia	Endocrinopathies
Sickle cell trait	Seizures	Hypo-/hypernatremia	Adrenal insufficiency
Vascular thrombosis	Status asthmaticus		Hypothyroidism
Vasculitis	Severe agitation (delirium tremens, psychosis)		Hyperaldosteronism
	Neuroleptic malignant syndrome		Diabetic ketoacidosis
	Malignant hyperthermia		Hyperosmolar state

Chest. 2013 Sep;144(3):1058-65

Drugs
Medications
Lipid-lowering agents
Statins
Fibrates
Psychiatric medications
Neuroleptics/antipsychotics (including haloperidol, atypical antipsychotics)
Selective serotonin reuptake inhibitors
Lithium
Valproic acid
Antimicrobial agents
Antiretroviral medications (protease inhibitors)
Trimethoprim-sulfamethoxazole
Daptomycin
Macrolide antibiotics
Quinolones
Amphotericin B
Anesthetics/paralytics
Succinylcholine
Propofol
Antihistamines
Doxylamine
Diphenhydramine
Appetite suppressants
Phentermine
Ephedra
Others
Sunitinib, erlotinib
Narcotics
Colchicine
Vasopressin
Amiodarone
Aminocaproic acid
Illicit drugs
Cocaine
Amphetamines/methamphetamines
Hallucinogens
Heroin
Methylenedioxypyrovalerone, mephedrone (bath salts)
Phencyclidine

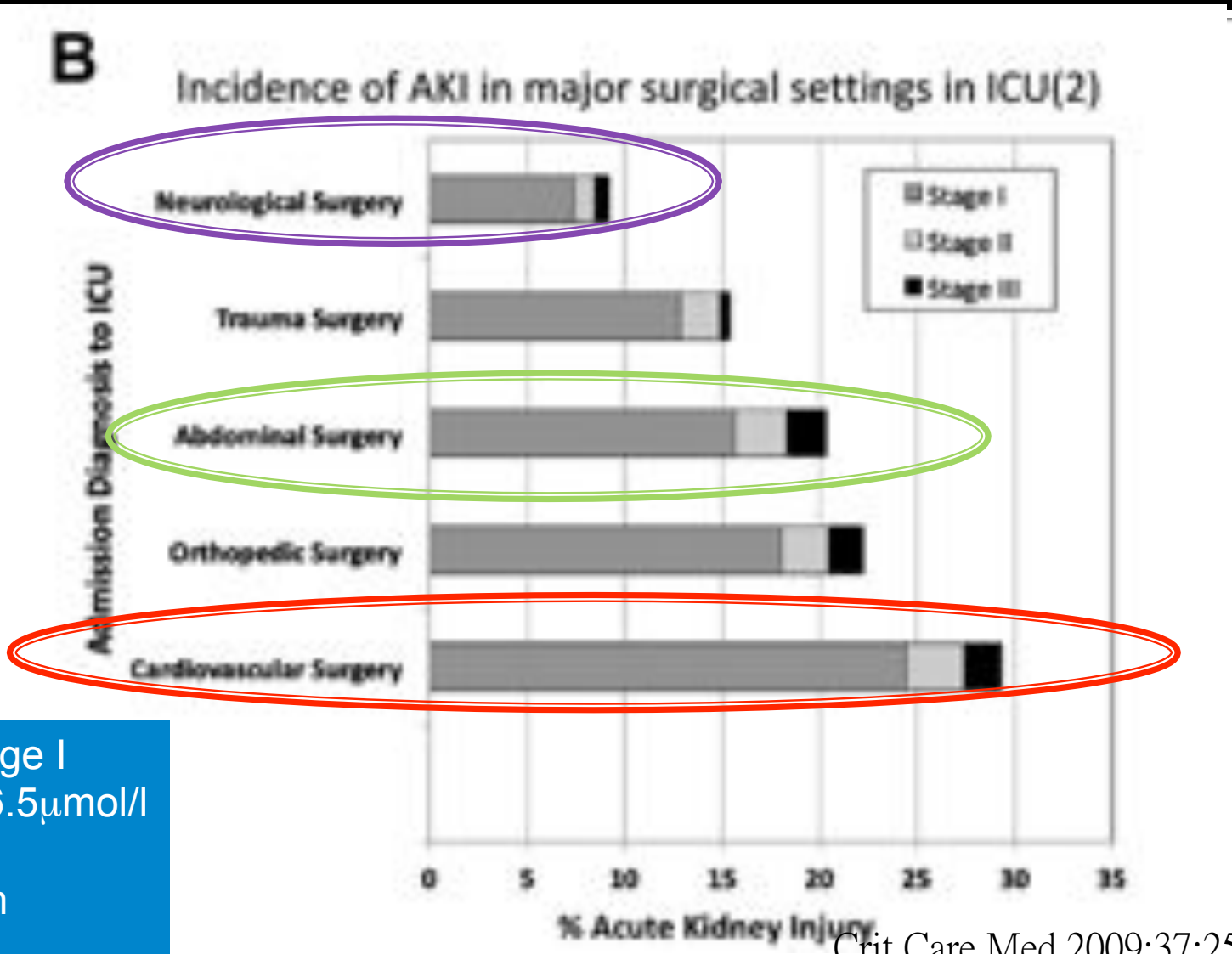
Chest. 2013 Sep;144(3):1058-65

Treatment

- No RCT that offer definitive guidance for treatment
- early and aggressive volume resuscitation
  - Volume 6-12L/d, aim u/o 300ml/hr
  - Type of fluid, LR may achieve better serum and urine pH
  - $NaHCO_3$ and mannitol -> not beneficial
  - Loop diuretic -> not clear
  - CRRT vs IHD
  - High flux vs super-high flux (HCO) hemofilter

Chest. 2013 Sep;144(3):1058-65.
Ann Pharmacother. 2013 Jan;47(1):90-105
Nat Rev Nephrol. 2011 May 17;7(7):416-22

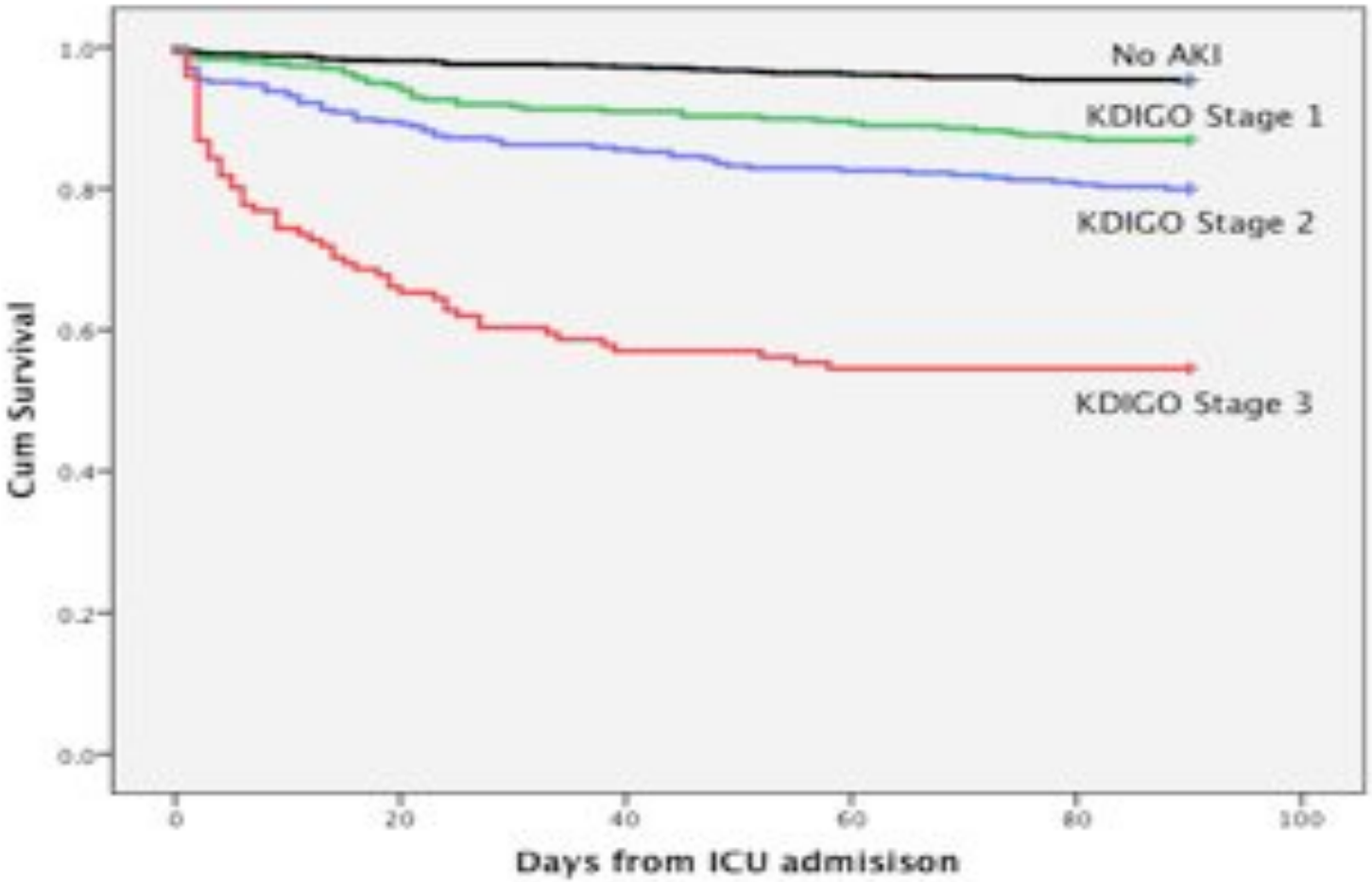
Perioperative AKI



AKIN stage I
↑ Cr > 26.5μmol/l
or
1.5x from baseline

Crit Care Med.2009;37:2552-2558

Local data



10%

18%

45%

~1540 postop patients who required ICU care
Mortality differ by 8% between those without AKI and those with Stage 1 AKI

Unpublished data from Shum HP et al

Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study

Nicola Brienza, MD, PhD; Maria Teresa Giglio, MD; Massimo Marucci, MD; Tommaso Fiore, MD

Table 2. Intervention details of analyzed studies and renal outcome definition

Author	Timing of Optimization	Goals of Optimization	Modality of Optimization	Definition of Acute Kidney Injury
Bender et al (35)	Preop from the morning of surgery for 16 hrs postop	CI ≥2.8 L·min^{-1}·m^{-2}, 8 ≤ PAOP ≥ 14 mmHg, SVR ≤1100 dyne·sec/cm^5	Fluids, blood, dopamine, NTP	Increase in baseline creatinine by >1 mg/dL
Berlauk et al (36)	Preop from 12 or 3 hrs before surgery for 18 hrs postop	CI ≥2.8 L·min^{-1}·m^{-2}, 8 ≤ PAOP ≤ 15 mm Hg, SVR ≤1100 dyne·sec/cm^5	Fluids, dopamine or dobutamine, NTP, NTG	UO <0.5 mL·kg^{-1}·hr^{-1} for 5 hrs and/or rise in baseline creatinine by >0.5 mg/dL and/or need of RRT
Bishop et al (37)	Postop within 6 hrs after surgery for at least 48 hrs	CI ≥4.5 L·min^{-1}·m^{-2}, DO_2 ≥670 mL·min^{-1}·m^{-2}, VO_2 ≥166 mL·min^{-1}·m^{-2}	Fluids, blood, dobutamine (starting at 5 μg·kg^{-1}·min^{-1})	Creatinine ≥2 mg/dL or, with preexisting renal disease, creatinine twice than admission
Bonazzi et al (38)	Preop from the day before surgery to the end of the 2nd postop da	CI >3.0 L·min^{-1}·m^{-2}, DO_2 >600 mL·min^{-1}·m^{-2}, 10 <PAOP <18 mmHg, SVR <1450 dyne·sec/cm^5	Fluids, dobutamine (starting from 2.5 μg·kg^{-1}·min^{-1}), NTG	Worsening of preop function with oliguria requiring high dose furosemide (>250 mg/die) and/or need of RRT
Boyd et al (39)	Preop from ICU admission before surgery for 24 hrs postop	DO_2 >600 mL·min^{-1}·m^{-2}	Fluids, blood, dopexamine (starting at 0.5 μg·kg^{-1}·min^{-1} to a maximum of 8 μg·kg^{-1}·min^{-1})	UO <500 ml/24 hrs despite adequate PAOP
Chytra et al (28)*	Postop from ICU admission for 12 hrs postop	SV optimization with FTc between 0.35 and 0.4 sec	Fluids, blood	Need of RRT
Donati et al (40)	Intraop up to 24 hrs postop	O_2ERe ([Sa_{O_2}–Sv_{O_2}] /Sa_{O_2}) <27%	Fluids, blood, dobutamine (starting at 3 up to 15	Creatinine >2 mg/dL or need of RRT

20 trials, 4000 surgical patients

Crit Care Med 2009; 37:2079–2090

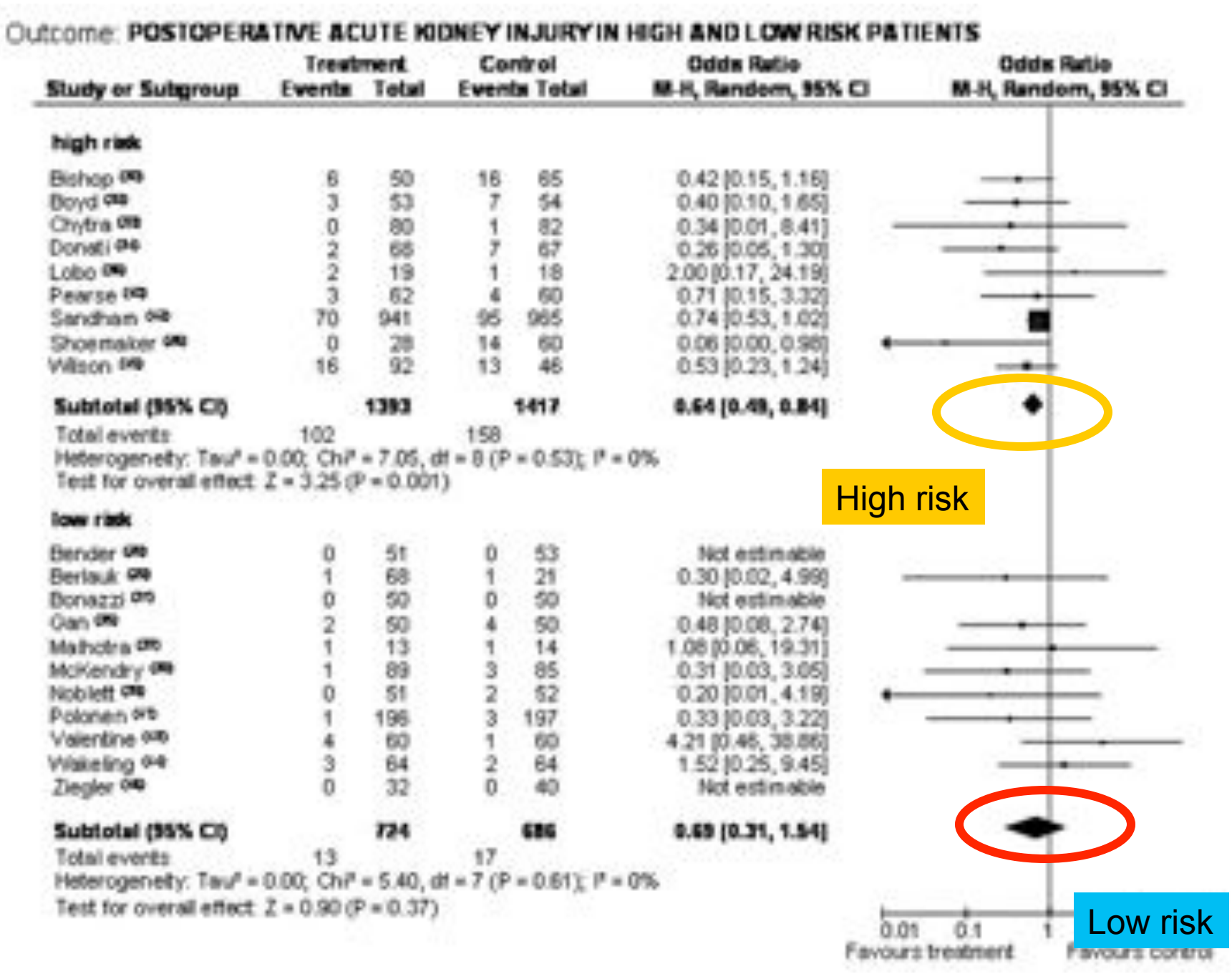
Outcome: **POSTOPERATIVE ACUTE KIDNEY INJURY**

Studies	Treatment Events	Treatment Total	Control Events	Control Total	Odds Ratio M-H, Random, 95% CI
Bender	0	51	0	53	Not estimable
Berlauk	1	68	1	21	0.30 [0.02, 4.99]
Bishop	6	50	16	65	0.42 [0.15, 1.16]
Bonazzi	0	50	0	50	Not estimable
Boyd	3	53	7	54	0.40 [0.10, 1.65]
Chytra	0	80	1	82	0.34 [0.01, 8.41]
Donati	2	68	7	67	0.26 [0.05, 1.30]
Gan	2	50	4	50	0.48 [0.08, 2.74]
Lobo	2	19	1	18	2.00 [0.17, 24.19]
Malhotra	1	13	1	14	1.08 [0.06, 19.31]
McKendry	1	89	3	85	0.31 [0.03, 3.05]
Noblett	0	51	2	52	0.20 [0.01, 4.19]
Pearse	3	62	4	60	0.71 [0.15, 3.32]
Polonen	1	196	3	197	0.33 [0.03, 3.22]
Sandham	70	941	95	965	0.74 [0.53, 1.02]
Shoemaker	0	28	14	60	0.06 [0.00, 0.98]
Valentine	4	60	1	60	4.21 [0.46, 38.86]
Wakeling	3	64	2	64	1.52 [0.25, 9.45]
Wilson	16	92	13	46	0.53 [0.23, 1.24]
Ziegler	0	32	0	40	Not estimable
Total (95% CI)		**2117**		**2103**	**0.64 [0.50, 0.83]**
Total events	115		175		

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 12.45$, $df = 16$ ($P = 0.71$); $I^2 = 0\%$

Test for overall effect: $Z = 3.37$ ($P = 0.0007$)

Crit Care Med 2009; 37:2079–2090



Crit Care Med 2009; 37:2079–2090

Patient related factors
Age
Hypertension
Diabetes Mellitus
Chronic Obstructive Pulmonary Disease
LVF, EF <40%
Chronic kidney disease
Emergency surgery
Sepsis
Peripheral vascular disease
Cerebrovascular disease
Ascites

Likely benefit from periopertive optimization

Calvert and Shaw *Perioperative Medicine* 2012, **1**:6

Anesthesiology 2011; 114:964-70

Avoid nephrotoxic agents

- NSAID - stop 3 days before OT
- ACEI/ ARB (esp. in volume depleted patients and those on diuretics) – W/H on morning of surgery (esp. in those for non-HF use)
- Antibiotics (aminoglycosides, high dose penicillin and quinolones)
- IV contrast -> use iso-osmolar and low-osmolar non-ionic contrast

Anesthesiology 2007; 106:218–225
J Hosp Med 2008; 3:319–325.

Hydroxyethyl starch

- Increase risk of AKI and requirement of RRT in critically ill patients
- ESICM recommend not to use HES with molecular weight ≥ 200 kDa and/or degree of substitution >0.4

Mutter TC, Ruth CA, Dart AB. Cochrane Database Syst Rev. 2013 Jul 23;7:CD007594.

European Society of Intensive Care Medicine. Intensive Care Med. 2012 Mar;38(3):368-83.

British Journal of Anaesthesia 112 (1): 25–34 (2014)
Advance Access publication 17 September 2013 · doi:10.1093/bja/aet303

BJA

REVIEW ARTICLES

Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis

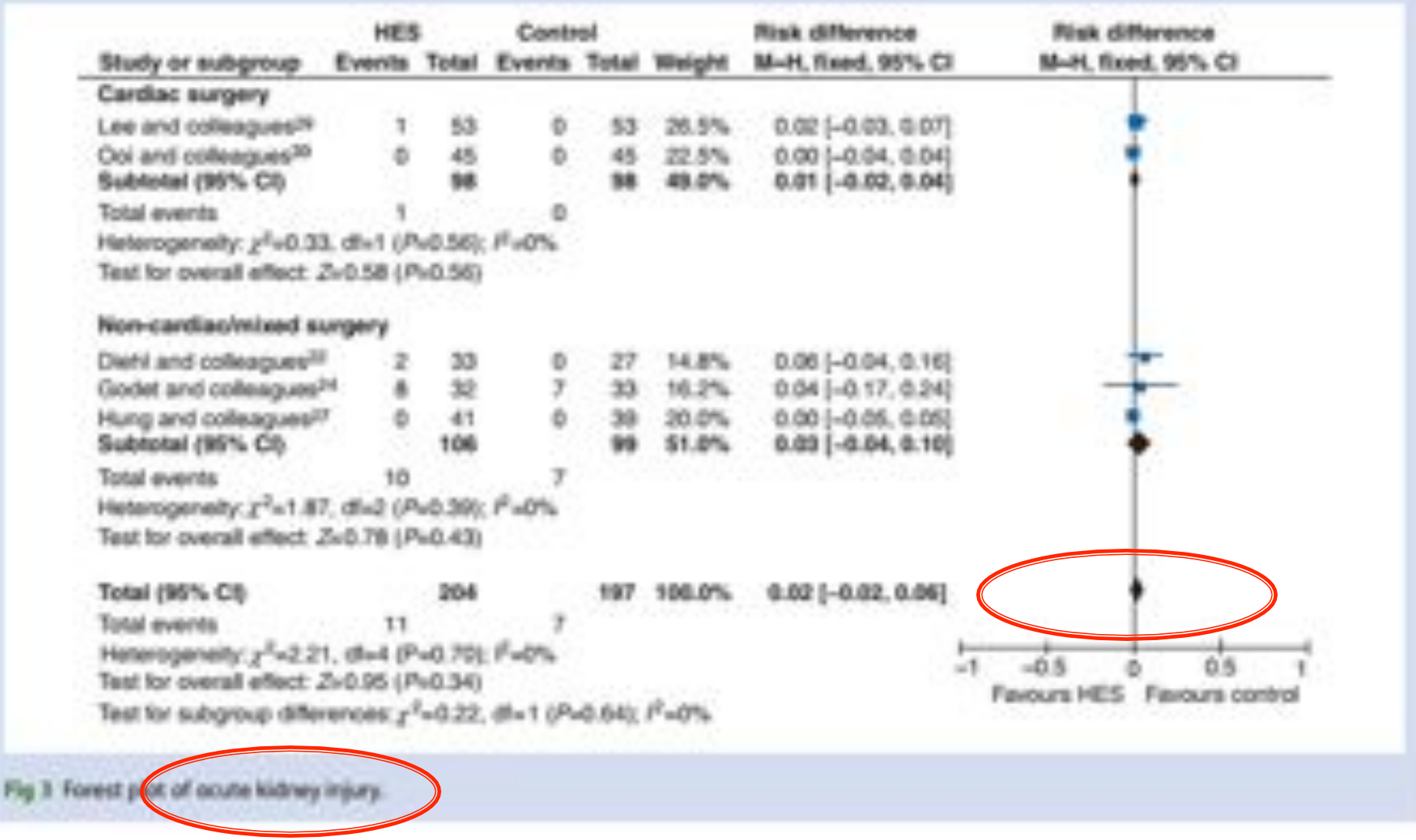


Fig 3 Forest plot of acute kidney injury.

5 studies, ~400 patients

British Journal of Anaesthesia **112** (1): 25–34 (2014)

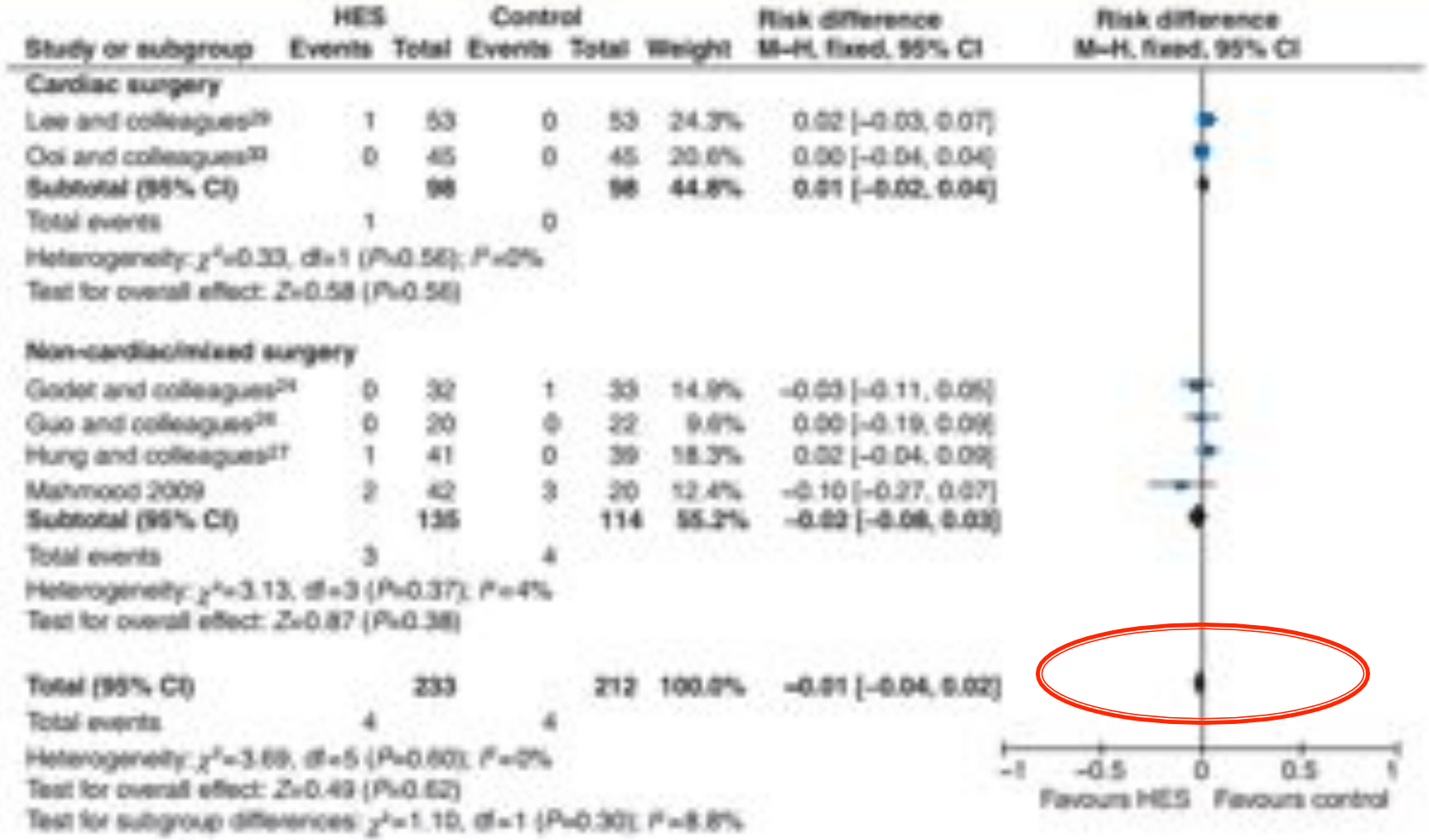
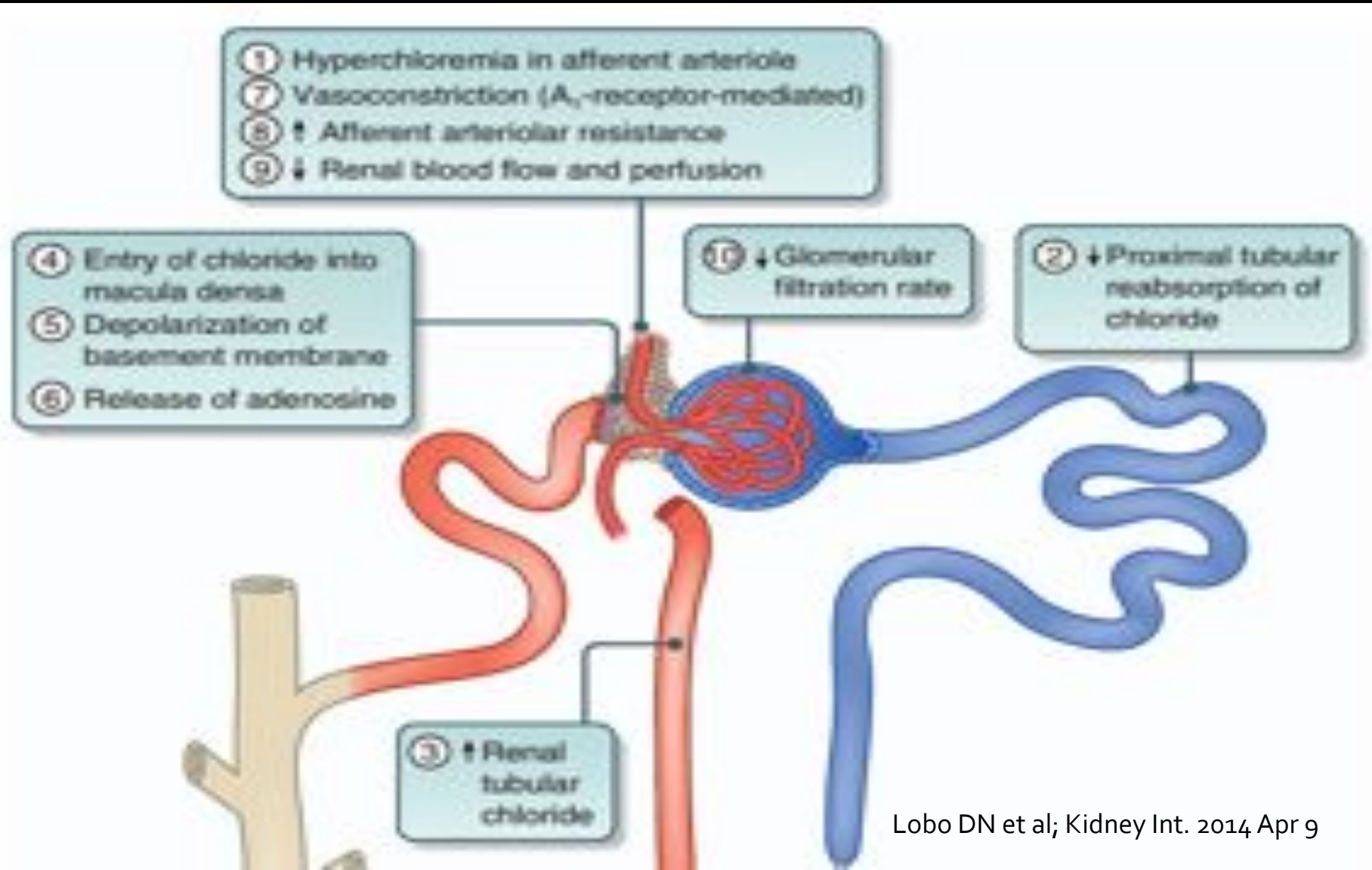


Fig 4 Forest plot of renal replacement therapy.

Is NS safe?



Lobo DN et al; Kidney Int. 2014 Apr 9

Is NS safe?

- Multiple trials (most of them observational) comparing NS with balanced crystalloid
- More likely to develop AKI and require RRT
- Also more infective complications, blood transfusion requirement
- +/- higher mortality

Anesth Analg 2013; 117: 412–421.
Ann Surg 2012;255: 821–829
JAMA 2012;308: 1566–1572
Crit Care Med2011;39: 2419–2424

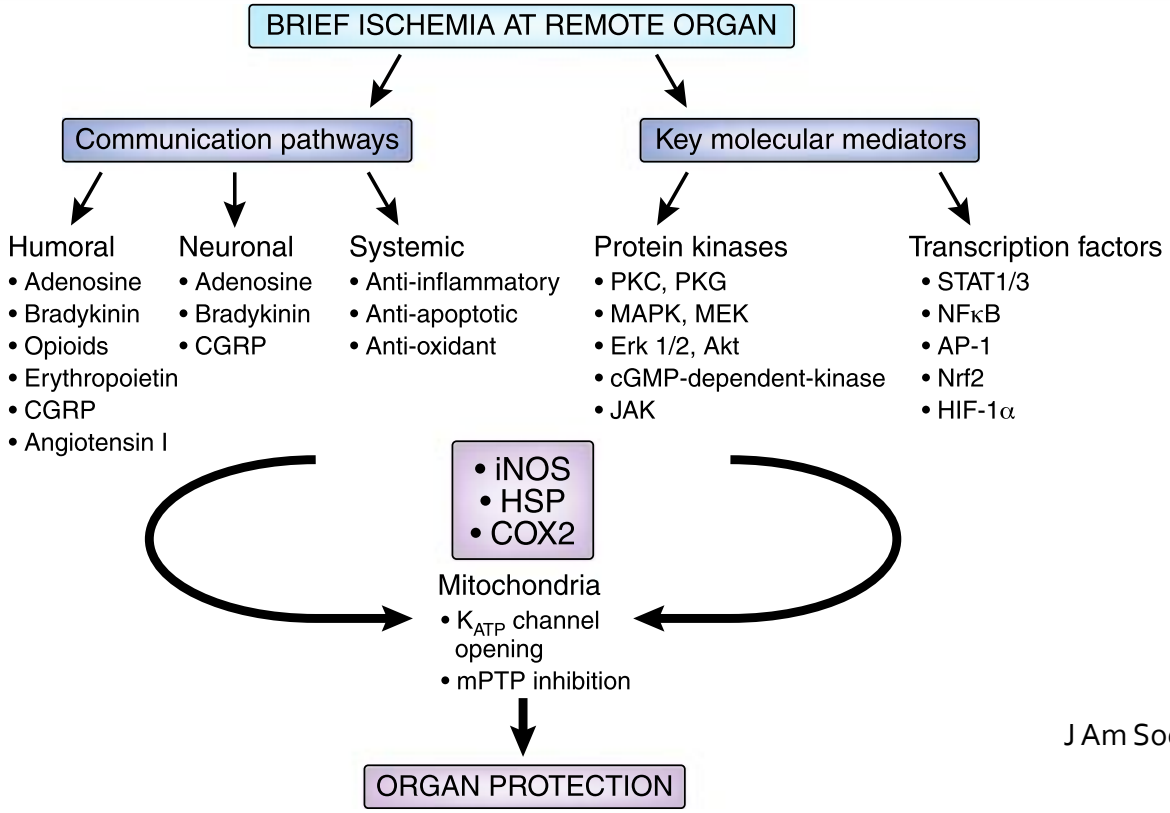
Any medications good for protecting of renal function in the perioperative period?

- Dopamine ☒
- Fenoldopam ⓘ
- Diuretics ☒
- Calcium channel blockers ☒
- Atrial natriuretic peptide ⓘ
- N-acetyl cysteine ☒
- Statin ☒
- Erythropoietin (EPO) ☒

Remote ischemic preconditioning (RIPC)

- Following ischaemic insult, tissue damage is extended after reperfusion, known as an ischaemia reperfusion injury
- Application of transient, non-lethal, episodes of ischaemia reduces the effect of a larger ischaemic insult, and limits the reperfusion injury
- Remote - preconditioning stimulus was applied to organ other than the organ of interest

Mechanism of RIPC



J Am Soc Nephrol 25: 216–224, 2014.

Figure 1. Mechanisms of rIPC. AP-1, activator protein-1; cGMP, cyclic guanosine monophosphate; CGRP, calcitonin gene-related peptide; COX2, cyclooxygenase 2; HIF-1α, hypoxia-inducible factor 1α; HSP, heat shock protein; iNOS, inducible nitric oxide synthase; JAK, Janus kinase; MEK, MAPK kinase; mPTP, mitochondrial permeability transition pore; Nrf2, nuclear factor (erythroid-derived 2)-like 2; STAT1/3, signal transducer and activator of transcription.

Table 1. Demographic Data of Included Trials

Study	No. of Patients[a]	Mean Age (y)[a]	Surgical Procedure	Contrast Dose (mL)	RIPC Procedures	Baseline Scr[a,b] (μmol/L)	AKI Definition
Ali et al[17] (2007)	41/41	74/75	Elective open AAA repair	None	Cross-clamping of iliac arteries	102/101	Peak Scr > 177 μmol/L
Walsh et al[18] (2009)	18/22	74/76	Elective endovascular AAA repair	309/286	Inflatable tourniquet around lower limbs	95/94	Decrease in eGFR ≥ 20% from baseline
Hoole et al[19] (2009)	104/98	63.2/61.8	Elective PCI	196.7/187.5	Inflatable tourniquet around upper arms	NA	Scr > 25% increase from baseline
Rahman et al[20] (2010)	80/82	63/65	CABG	None	Inflatable tourniquet around upper arms	98.1/96.4	Scr > 0.5 mg/dL increase from baseline
Thielmann et al[21] (2010)	27/26	63.4/64.1	Elective CABG	None	Inflatable tourniquet around upper arms	NA	NA
Walsh et al[22] (2010)	22/18	75/72	Elective open AAA repair	None	Cross-clamping of iliac arteries	97/88	Decrease in eGFR ≥ 20% from baseline
Zimmerman et al[23] (2011)	59/59	62/65	Elective cardiac surgery with CPB	None	Inflatable tourniquet around lower limbs	82.2/84.0	AKIN criterion
Choi et al[24] (2011)	38/38	57/60	Elective complex valvular heart surgery	None	Inflatable tourniquet around lower limbs	80.4/81.3	AKIN criterion
Er et al[25] (2012)	50/50	73.2/72.7	Elective coronary angiography	124/103	Inflatable tourniquet around upper arms	144.1/143.2	Scr ≥ 25% or ≥0.5 mg/dL increase from baseline
Young et al[26] (2012)	48/48	65.5/64.4	High-risk cardiac surgery with CPB	None	Inflatable tourniquet around upper arms	102/95	RIFLE criterion
Pedersen et al[27] (2012)	54/51	1.0/0.9	Complex congenital heart disease surgery	None	Inflatable tourniquet around lower limbs	35/32	RIFLE criterion
Lucchinetti et al[28] (2012)	27/28	59/62	Elective CABG	None	Inflatable tourniquet around lower limbs	91.7/88.0	NA
Luo et al[29] (2013)	101/104	59.2/59.3	Elective PCI	154/145	Inflatable tourniquet around upper arms	NA	Scr ≥ 25% increase from baseline

Am J Kidney Dis. 2014, 64(4):574-583

Table 3. Details of RIPC Trials Using Tourniquet Cuff Around Limb

Reference	Limb Used for RIPC	No. of Limbs Used for RIPC	Ischemia/Reperfusion Interval (min)	Total Ischemia Duration (min)
Walsh et al[18] (2009)	Lower limb	2	10	20
Hoole et al[19] (2009)	Nondominant upper arm	1	5	15
Rahman et al[20] (2010)	Left upper arm	1	5	15
Thielmann et al[21] (2010)	Left upper arm	1	5	15
Zimmerman et al[23] (2011)	Lower limb	1	5	15
Choi et al[24] (2011)	Lower limb	1	10	30
Er et al[25] (2012)	Upper arm	1	5	20
Young et al[26] (2012)	Upper arm	1	5	15
Pedersen et al[27] (2012)	Lower limb	1	5	20
Lucchinetti et al[28] (2012)	Lower limb	1	5	20
Luo et al[29] (2013)	Upper arm	1	5	15

Abbreviation: RIPC, remote ischemic preconditioning.

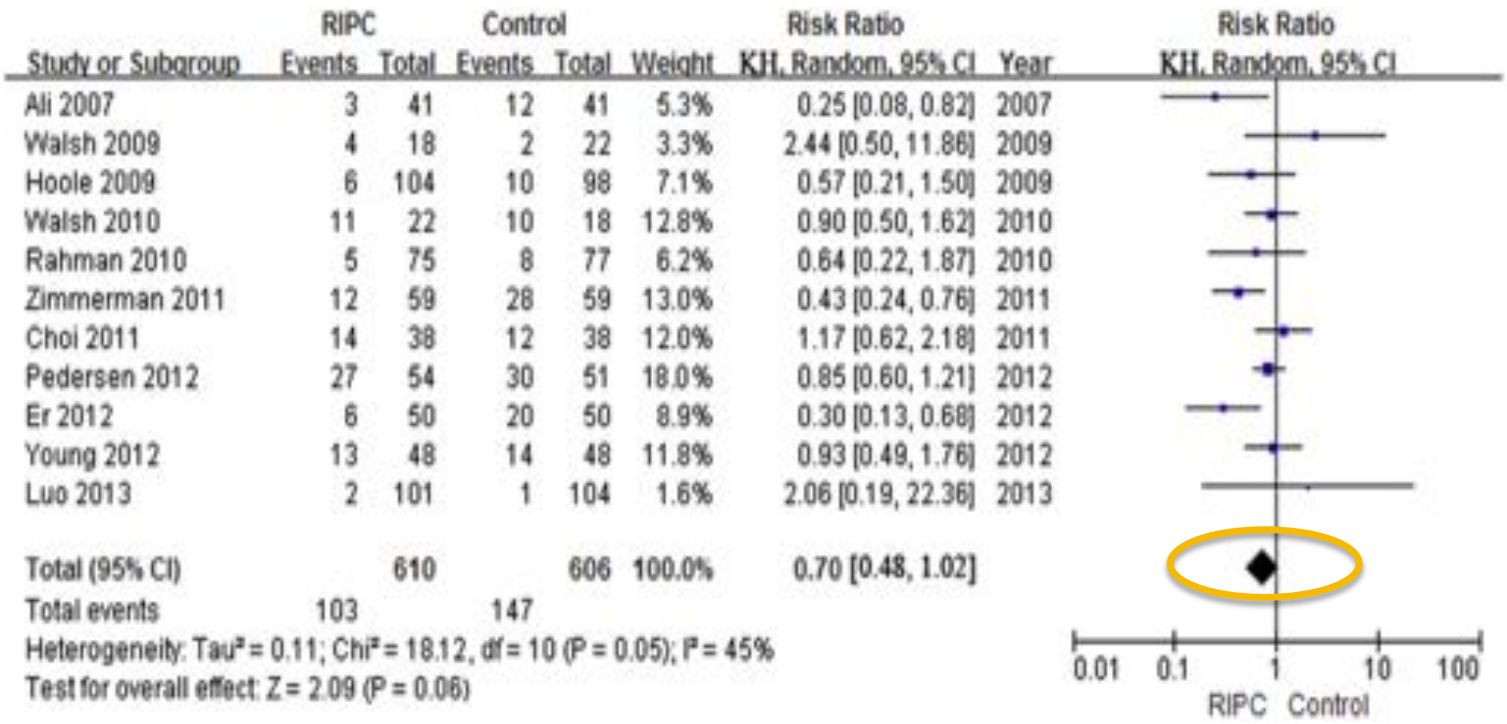


Figure 2. Comparison of remote ischemic preconditioning (RIPC) versus control group for the incidence of acute kidney injury (AKI). Abbreviations: CI, confidence interval; KH, Knapp-Hartung method.

Am J Kidney Dis. 2014 64(4):574-583

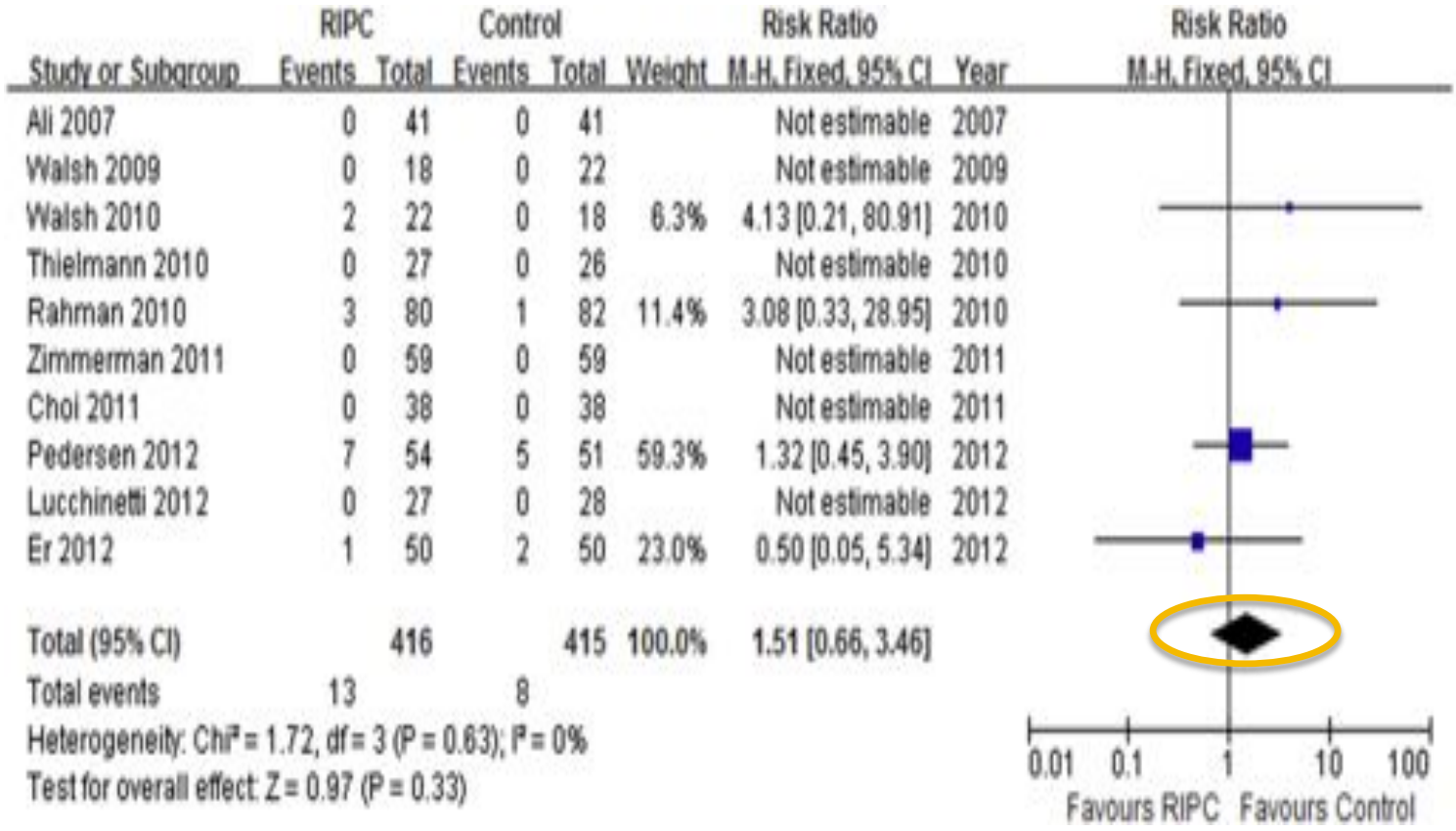


Figure 4. Comparison of remote ischemic preconditioning (RIPC) versus control group for the postoperative new initiation of renal replacement therapy (RRT). Abbreviations: CI, confidence interval, M-H, Mantel-Haenszel.

Am J Kidney Dis. 2014 64(4):574-583

AJKD
Original Investigation

Remote Ischemic Preconditioning for Prevention of Acute Kidney Injury: A Meta-analysis of Randomized Controlled Trials

Yi Yang, PhD, MD,[1,] Xia-bing Lang, BS,[1,*] Ping Zhang, MD,[1] Rong Lv, MD,[1] Yong-fei Wang, BS,[2] and Jiang-hua Chen, MD[1]*

RIPC might be beneficial for the prevention of AKI following cardiac and vascular in-terventions, but the current evidence is not robust enough to make a recommendation

Am J Kidney Dis. 2014 64(4):574-583

Treatments for AKI

- Target underlying cause of AKI
- RRT
- Novel treatment
  - α-Melanocyte–Stimulating Hormone
  - RenalGuard Therapy
  - Alkaline Phosphatase
  - Catalytic Iron

Kaushal et al; J Am Soc Nephrol 25: 877–883, 2014.

RRT issue under debate

- Dose (higher dose -> better survival?)
- Method (which method is better? CRRT vs. IRRT)
- Timing of initiation (? Early or late)

Dose

Effect of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial

Claudio Ronco etal. *Lancet 2000;356:26-30*

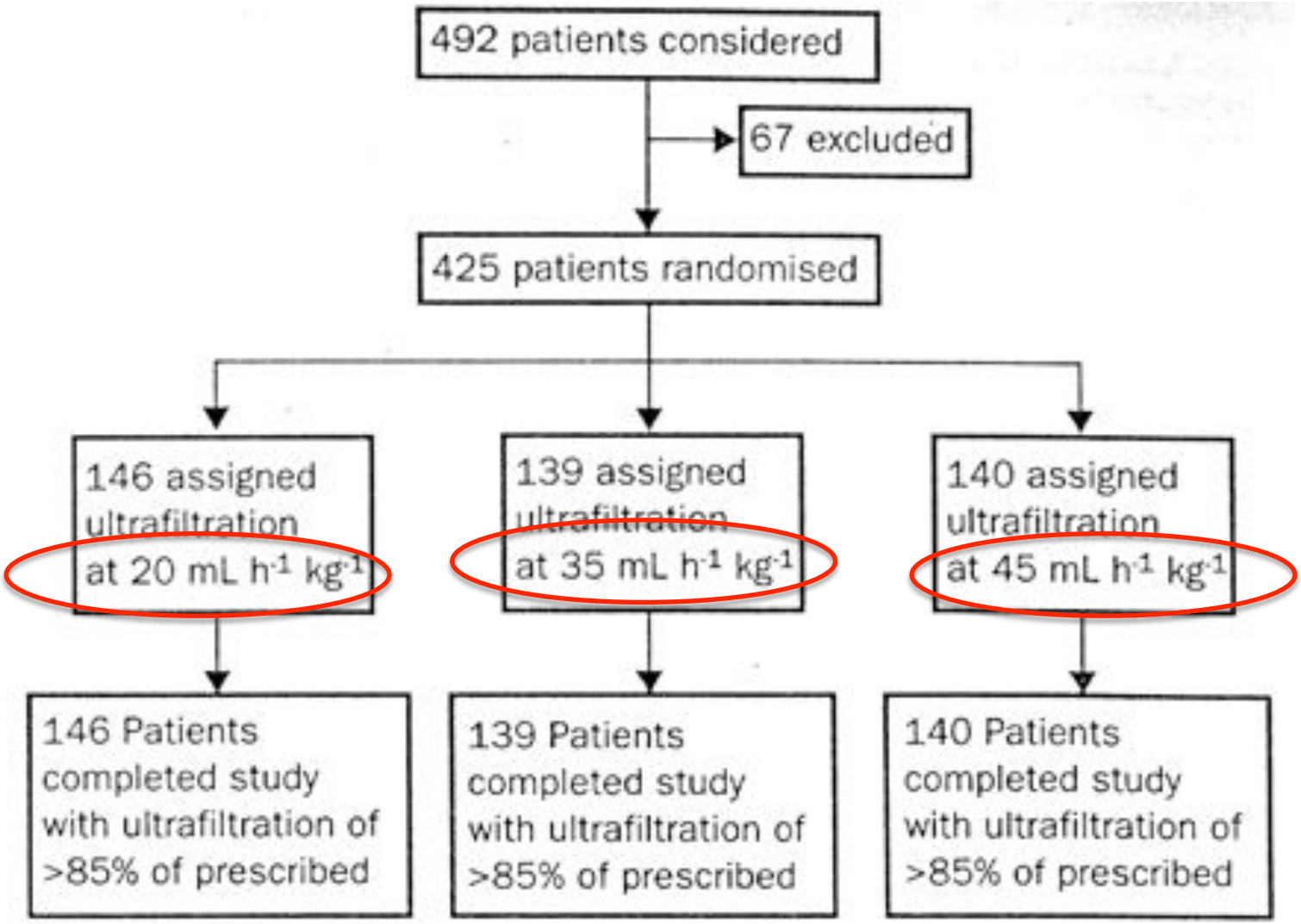


Figure 1: **Trial profile**

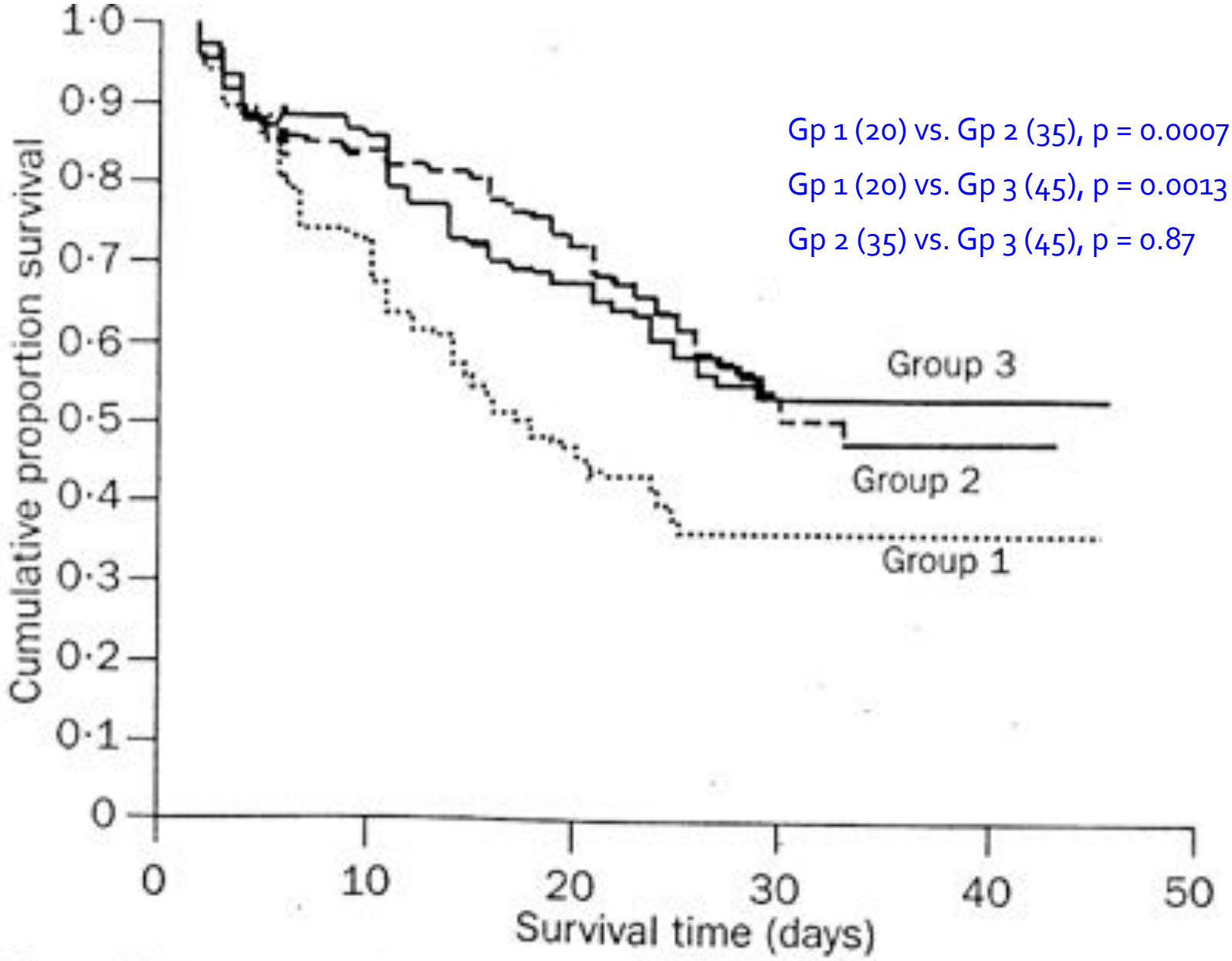
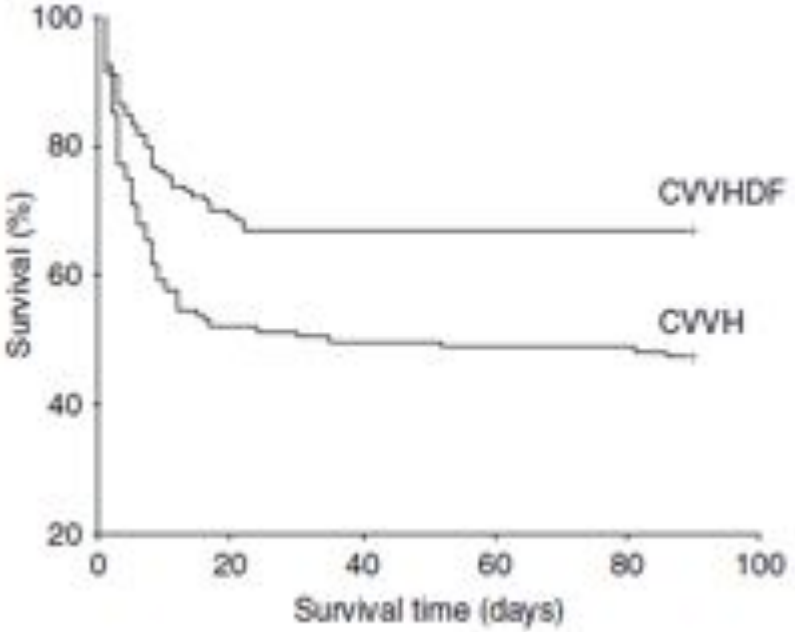


Figure 2: **Kaplan Meier estimation of survival rates in the three groups**

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

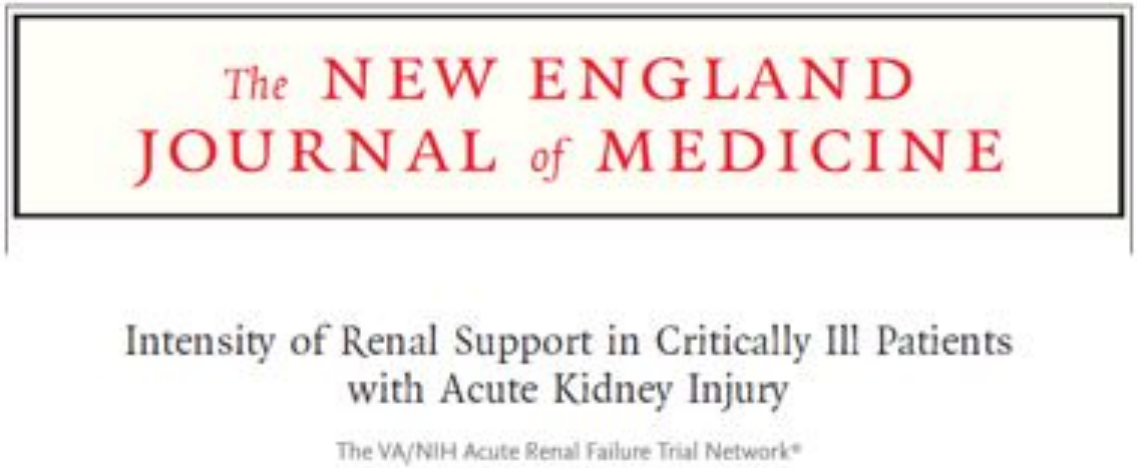
Adding a dialysis dose to CVVH increases survival in patients with ARF. *Saudan P etal, Kidney Int 2006;70:1312-7*

- Prospective RCT
  - CVVH 102 patients
  - CVVHDF 104 patients
- CVVH: 25ml/kg/h
- CVVHDF: 25ml/kg/h + 18 ml/kg/h (dialysate)
- 90-day Survival
  - CVVH: 38%
  - CVVHDF: 64%, p=0.0004



ATN Study

www.atnstudy.org



N Engl J Med 2008;359

- Prospective randomised trial
- November 2003 to November 2006
- N = 1,124 critically ill patients with AKI
- One arm CVVH 20mL/kg/h or IHD/SLED 3x/week
- Another arm CVVH 35mL/kg/h or IHD/SLED 6x/week
- Both arms employed
  - IHD if haemodynamic stable
  - SLED / CVVHDF if haemodynamic unstable
- 60-day all-cause mortality

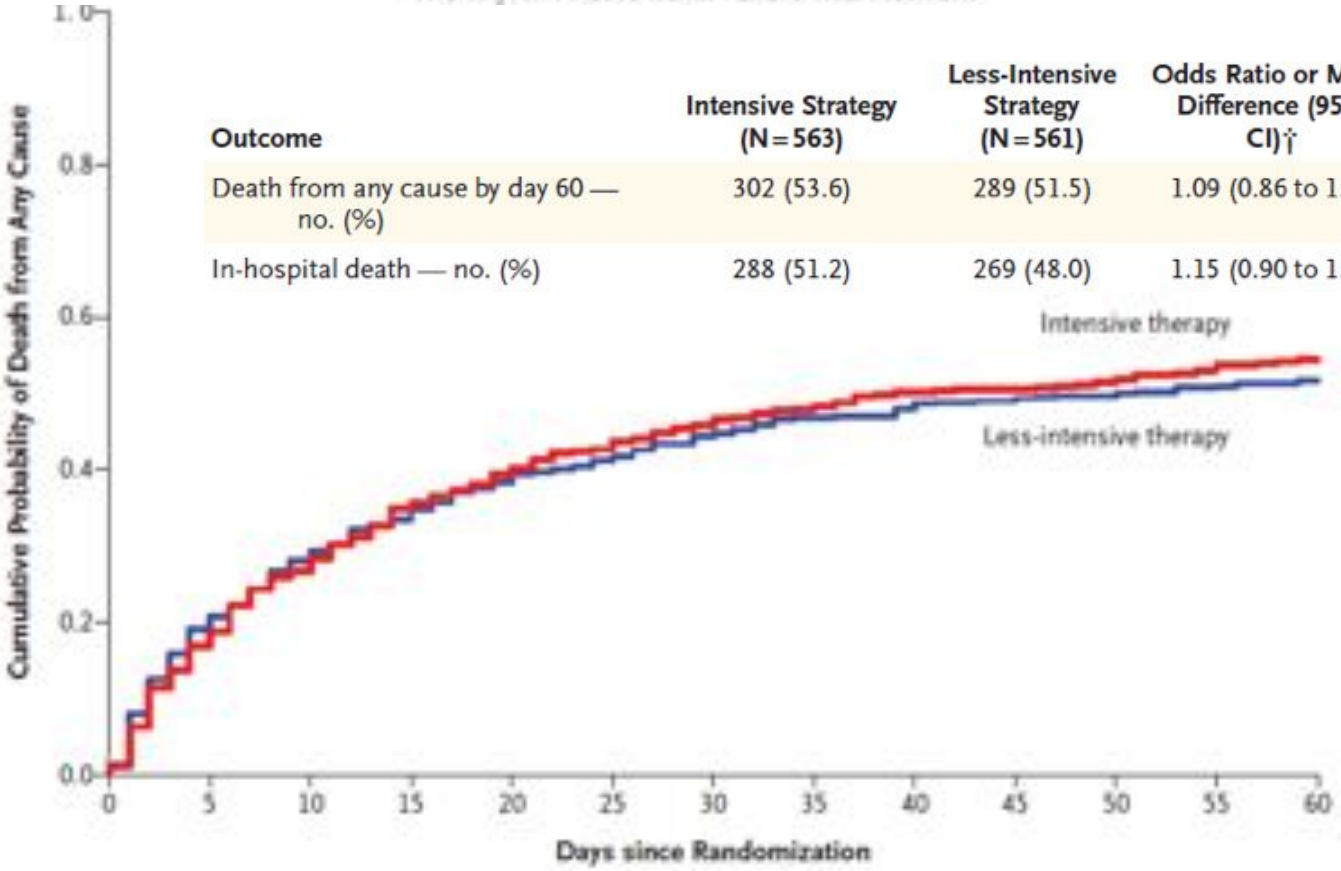
The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2008;359

Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury

The VA/NIH Acute Renal Failure Trial Network*

Outcome	Intensive Strategy (N=563)	Less-Intensive Strategy (N=561)	Odds Ratio or Mean Difference (95% CI)†	P Value
Death from any cause by day 60 — no. (%)	302 (53.6)	289 (51.5)	1.09 (0.86 to 1.40)	0.47
In-hospital death — no. (%)	288 (51.2)	269 (48.0)	1.15 (0.90 to 1.47)	0.27



Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

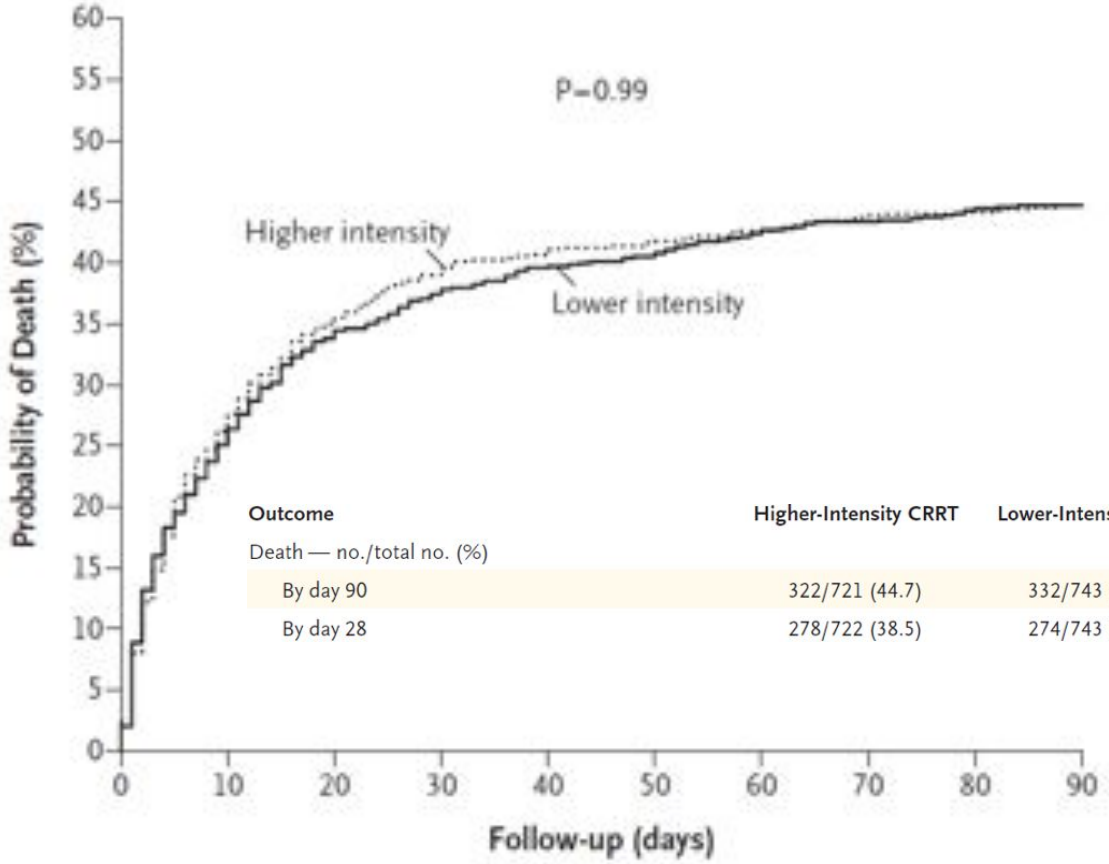
The RENAL Replacement Therapy Study Investigators*

- Randomized 1,508 patients in 35 ANZ ICUs to receive either post-dilution CVVHDF at 25ml/kg/h or at 40ml/kg/h of effluent
- 90% power to detect 8.5% absolute reduction from a 90 day mortality of 60% to 51.5% (a <5%)
- Primary outcome: Death within 90 days after randomization

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2009 VOL. 361 NO. 17

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients



Outcome	Higher-Intensity CRRT	Lower-Intensity CRRT	Odds Ratio	P Value†
Death — no./total no. (%)				
By day 90	322/721 (44.7)	332/743 (44.7)	1.00 (0.81–1.23)	0.99
By day 28	278/722 (38.5)	274/743 (36.9)	1.07 (0.87–1.32)	0.52

Summary of Studies on Continuous Renal Replacement Treatment (CRRT) Dosing and Outcomes

Study	No.	Randomisations	CRRT mode	Prescribed dose (mL/kg/h)	Delivered dose	Primary outcome	Results	
Ronco et al.,[11] 2000	425	3 Arms comparing 3 different doses (n=146 vs 139 vs 140)	Post-dilution CVVH: Q_b 120-240 mL/min	20 vs 35 vs 45	>85% prescribed dose	Survival at 15 days	41%† vs 57% vs 58%	Sig
Bouman et al.,[8] 2002	106	3 Arms comparing EHV vs ELV vs LLV (n=35 vs 35 vs 30)	Post-dilution CVVH: EHV-Q_s 200 mL/min, Q_r 72 L/day ELV-Q_s 100-150 mL/min, Q_r 24-36 L/day LLV-Q_s 150 mL/min, Q_r 24-36L/day	48.2 vs 20.1 vs 19.7	Not mentioned	Survival at 28 days; renal recovery	74.3 % vs 68.8% vs 75% (all except 1 in ELV)	NS
Saudan et al.,[12] 2006	206	2 Arms comparing 2 different doses (n=102 vs 104)	Pre-dilution: CVVH (low dose)-Q_s 100-125 mL/min, Q_r 1-2.5 L/h CVVHDF (high dose)-Q_s 100-125 mL/min, Q_r 1-2.5 L/h, Q_d 1-1.5 L/h	25 vs 44	Achieved 87 % vs 83% of the delivered dose	28 days survival; 90 days survival	39%† vs 59% 34%† vs 59%	Sig
ATN trial,[9] 2008	1124	2 Arms comparing intense vs less-intense therapy (n=563 vs 561)	CVVHDF: Intensive-Q_s 150 mL/min, Q_D 1410 mL/h, Q_r 1390 L/h Less intensive-Q_s140 mL/min, Q_D 820 mL/h, Q_r 83 mL/h For both arms: Haemodynamically unstable-CVVHF/SLED Haemodynamically stable-IHD	36.2 vs 21.5 (for IHD/SLED, 6x/wk vs 3x/wk with Kt/V of 1.2-1.4 per session)	35.8 vs 22.0	60 days mortality	51.2% vs 48.0%	NS
Tolwani et al.,[13] 2008	200	2 Arms comparing 2 different doses (n=100 vs 100)	Pre-dilution CVVHDF: Standard dose-Q_b 100-150 mL/min, Q_D 1005 mL/h, Q_r 793 mL/h High dose-Q_b 100-150 mL/min, Q_D 1831 mL/h, Q_r 1406 mL/h	20 vs 35	17 vs 29	Survival to ICU discharge or 30 days	56% vs 49%	NS
RENAL study, By ANZ group[10] 2009	1465	2 Arms comparing 2 different doses (n=743vs 722)	Post-dilution CVVHDF Qb >150 ml/min	25 vs 40	22.0 vs 33.4	90 day mortality	44.68 vs 44.66%	NS

* CVVH denotes continuous veno-venous haemofiltration; CVVHDF continuous veno-venous haemodiafiltration; EHV early high volume; ELV early low volume; ICU intensive care unit; IHD intermittent haemodialysis; LLV late low volume; Q_b blood flow; Q_D dialysate flow; Q_r replacement rate; SLED sustained low-efficiency dialysis

† Statistically significant

Trial group	No sepsis (%)	Sepsis (%)	p
Group 1	55/126 (44%)	5/20 (25%)	0-90
Group 2	76/122 (62%)	3/17 (18%)	0-001
Group 3	74/125 (59%)	7/15 (47%)	0-256

Table 3: **Survival rates stratified by trial group and presence of sepsis**

p = 0.128

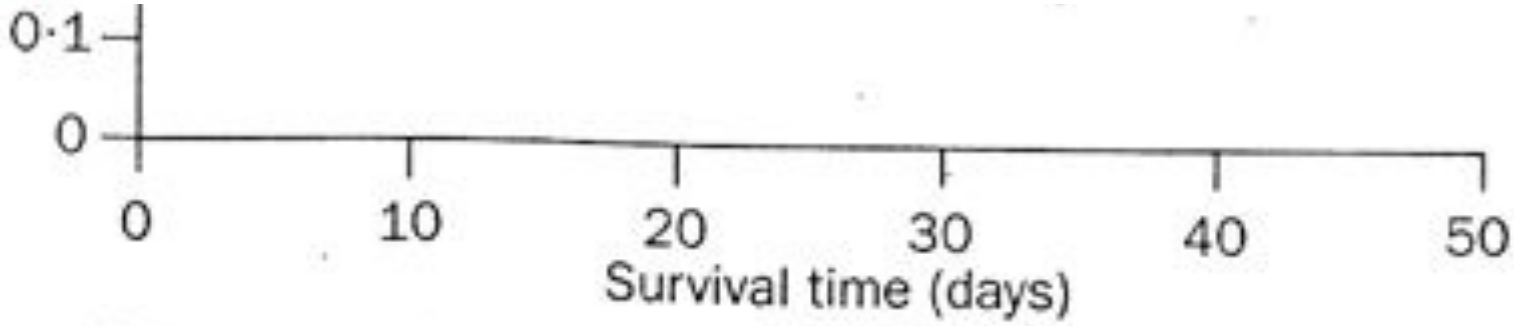


Figure 2: **Kaplan Meier estimation of survival rates in the three groups**

Table 1. Most Important Recent Human Studies that Assessed the Effects of HVHF as a Blood Purification Technique on Hemodynamics and Survival

Design	First Author, Year	Number of Patients	Clinical Setting	Dose (ml · kg^{-1} · h^{-1})	Improved Hemodynamics with HVHF	Improved Survival with HVHF	*P* Value (Survival)
Randomized, controlled trials	Laurent, 2005[79]	61	Resuscitated cardiac arrest	200	Yes	Yes; 6-mo survival: 21–45%	0.036
	Jiang, 2005[77]	37	Severe acute pancreatitis	4,000 ml/h	Yes	Yes; 14-day survival: 68.4–94.4%	<0.01
	Boussekey, 2008[14]	20	Septic shock	65	Yes	No	0.65
	IVOIRE study, on going	~150	Septic shock	70	—	—	—
Randomized, crossover trial	Cole, 2001[94]	11	Septic shock with multiorgan failure	6,000 ml/h	Yes	Not assessed	N/A
Prospective, cohort, uncontrolled trials	Honoré, 2000[78]	20	Refractory septic shock	115	Yes	Yes; 28-day survival: (Expected) 21–(Observed) 45%	<0.05
	Joannes-Boyau, 2004[71]	24	Septic shock	40–60	Yes	Yes; 28-day survival: (Expected) 30–(Observed) 54%	<0.075
	Ratanarat, 2005[74]	15	Severe sepsis	85 (pulse HVHF)	Yes	Yes; 28-day survival: (Expected) 30%–(Observed) 53%	N/A
	Cornejo, 2008[69]	20	Refractory septic shock	100	Yes	Yes; Hospital survival: (Expected) 37–(Observed) 60%	<0.03
Retrospective trials	Piccinni, 2008[73]	80	Septic shock	45	Yes	Yes; 28-day survival: 27.5–55%	0.005
	Zhu, 2009[95]	63	Severe acute pancreatitis	60–80	No	Yes; 28-day survival: 65.5–91.2%	0.014

Rimmelé T et al; Anesthesiology. 2012 Jun;116(6):1377-87.

IVOIRE Study

Intensive Care Med 2013;39:1535-46

- ~150 patients with septic shock & early acute renal failure
  - (RIFLE – injury level)
- Randomized into 2 groups
  - 35ml/kg/h for 96 hours
  - 70ml/kg/h for 96 hours
- Mortality rates at 28, 60, 90 days

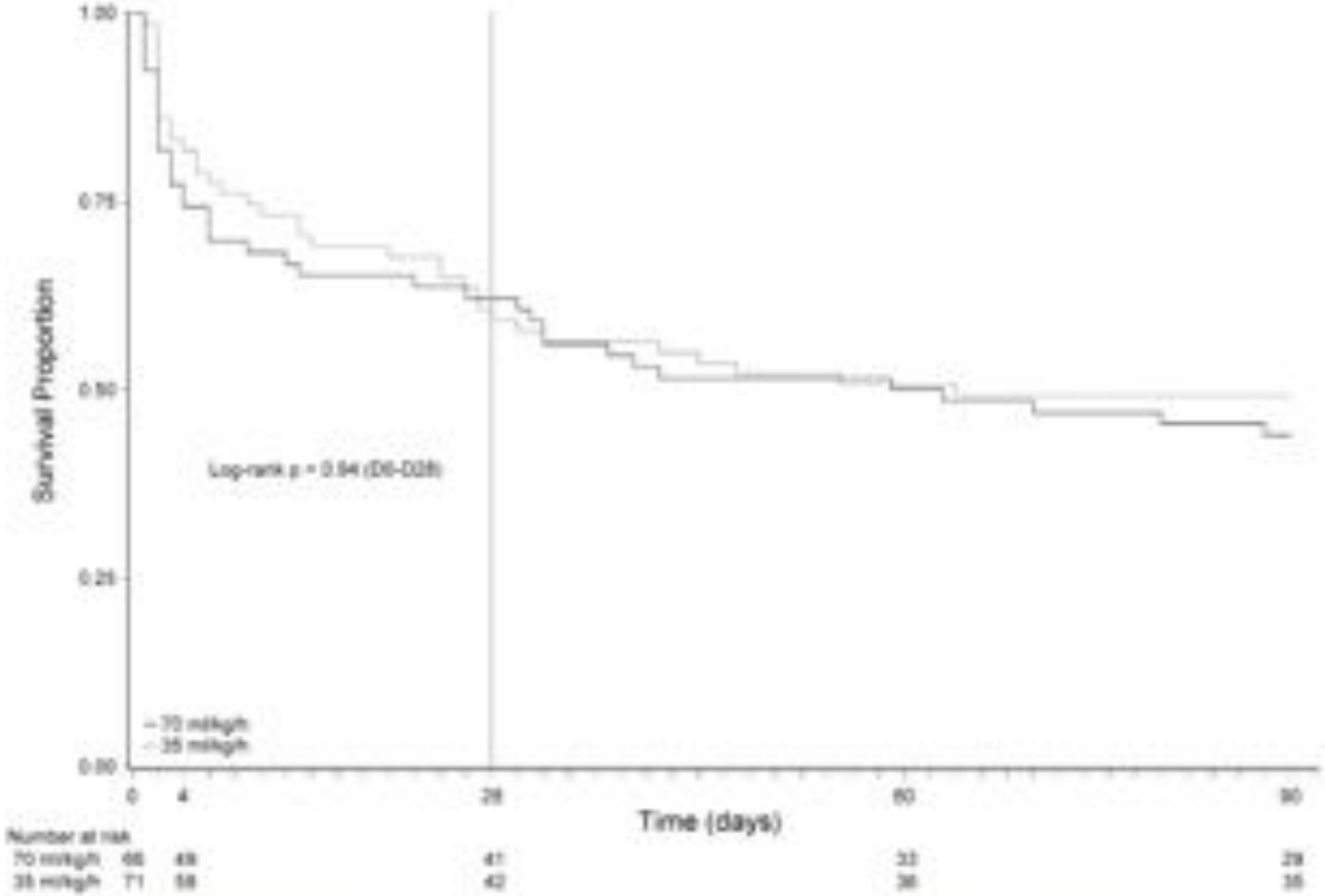


Fig. 2 Survival of participants in the IVOIRE (hIgh VOlume in Intensive caRE) trial. Participants in the HVHF group and SVHF group underwent haemofiltration at 70 mL/kg/h and 35 mL/kg/h of fluid exchange for 96 h, respectively

Intensive Care Med 2013;39:1535-46

Table 3 Comparison of patients' characteristics at different times after randomization (day 0) in the IVOIRE trial, according to randomization group

Variables	HVHF group ($n = 66$)	SVHF group ($n = 71$)	p
Prescribed dose (mL/kg/h)	70	35	
Treatment delivered (day 0–day 4 %)	93.8 (57.3–96.9)	94.8 (82.3–97.9)	0.29
Delivered dose (mL/kg/h)	65.6 (40–67.9)	33.2 (28.7–33.6)	
MAP at day 4 (mmHg)	92 (81–104) ($n = 48$)	92 (81–103) ($n = 56$)	0.76
SVRI at day 4 (dyn s^{-1} cm^{-5})	1,670 (1,200–1,980) ($n = 33$)	1,498 (1,234–2,201) ($n = 28$)	0.73
Noradrenaline at day 4 (μg/kg/min)	0.19 (0.13–0.41) ($n = 21$)	0.2 (0.10–0.64) ($n = 32$)	0.20
Inotropic score at day 4 (μg/kg/min)	3.0 (0.0–18.0) ($n = 49$)	10.0 (0.0–26.0) ($n = 57$)	0.16
VDI at day 4	0.3 (0.0–2.1) ($n = 48$)	1.1 (0.0–3.1) ($n = 56$)	0.19
PaO_2/FiO_2 at day 4	220 (159–264) ($n = 47$)	233 (168–288) ($n = 53$)	0.23

Table 4 Comparison of patients' characteristics at different times after randomization (day 0) in the IVOIRE trial, according to randomization group

Variables	HVHF group ($n = 66$)	SVHF group ($n = 71$)	p
Mortality at day 60 (n, %)	33 (50)	35 (49.3)	0.93
Mortality at day 90 (n, %)	37 (56.1)	36 (50.7)	0.53
SOFA score at day 4	9.0 (6.5–13.5) ($n = 48$)	11.0 (6.0–14.0) ($n = 57$)	0.54
SOFA score at day 28	3 (2.0–8.0) ($n = 19$)	3 (1.0–7.0) ($n = 25$)	0.47
SAPS II score at day 4	38.5 (31.5–49.0) ($n = 48$)	47.0 (35.0–56.0) ($n = 57$)	0.07
SAPS II score at day 28	36.0 (26.0–54.0) ($n = 19$)	32.0 (28.0–45.0) ($n = 25$)	0.78
Catecholamine-free days (day 28), days	23 (19–25)	22 (18–25)	0.32
RRT dependency at day 90	0	1	0.95
RRT-free days (day 90), days	84 (78–86)	83 (74–85)	0.22
MV-free days (day 90), days	82 (72–86)	79 (63–85)	0.36
ICU-free days (day 90), days	75 (59–86)	74 (59–83)	0.46
Hospital-free days (day 90), days	61 (34–86)	60 (26–81)	0.51

Intensive Care Med 2013;39:1535-46

Minerva Anestesiol. 2013 Nov 29. [Epub ahead of print]

High volume hemofiltration in critically ill Patients - a systematic review and Meta-analysis.

Lehner G, Wiedermann C, Joannidis M.

Crit Care. 2014 Jan 8;18(1):R7. [Epub ahead of print]

High-volume hemofiltration for septic acute kidney injury: a systematic review and meta-analysis.

Clark E, Molnar AO, Joannes-Boyau O, Honoré PM, Sikora L, Bagshaw SM.

- **4 RCTs, 3 with PHVHF, ~500 patients**
- **prescribed doses between 62 and 85 ml/kg/h**
- **No difference of 28d mortality,**
- **No sustained improvement in hemodynamic profile**
- **No difference of ICU or hospital LOS**

Conclusion (dose)

- CRRT
  - 25ml/kg/h is enough for AKI
- HVHF for severe sepsis or septic shock
  - No evidence to support its routine use

Method

CRRT modalities

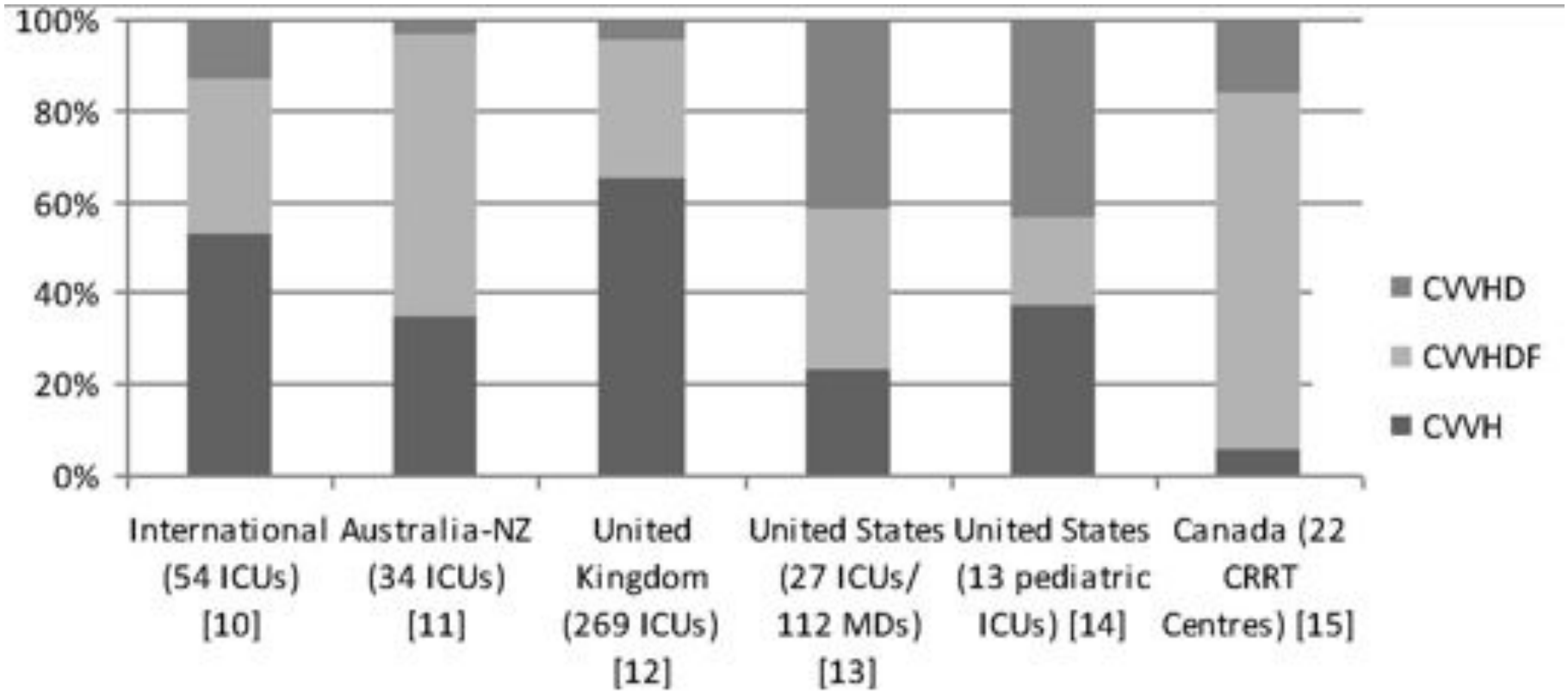


Figure 4 Distribution of mode of RRT used in different countries/regions based on practice surveys. Abbreviations: CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; ICU, intensive care unit; MD, medical doctor; NZ, New Zealand; RRT, renal replacement therapy; UK, United Kingdom; US, United States.

Friedrich et al. Critical Care 2012, 16:R146

Friedrich *et al. Critical Care* 2012, **16**:R146
http://ccforum.com/content/16/4/R146

CRITICAL CARE

RESEARCH Open Access

Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis

Jan O Friedrich[1,2,3,4,5*], Ron Wald[1,2,4], Sean M Bagshaw[6], Karen EA Burns[1,2,3,4,5] and Neill KJ Adhikari[1,5,7]

19 RCTs
737 patients
Most studies use CVVHD for HD group but some use SLED

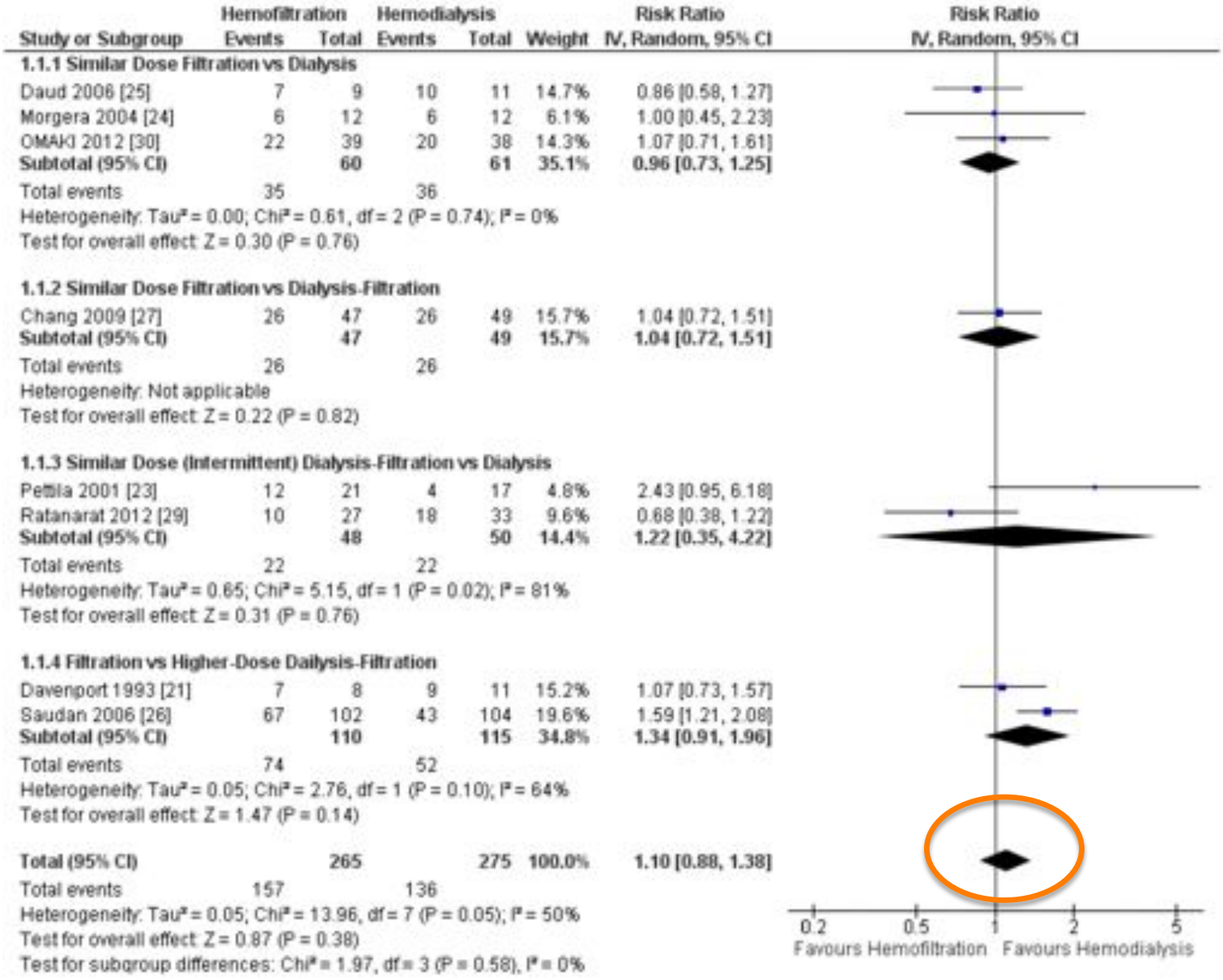


Figure 2 Effect of hemofiltration vs. hemodialysis RRT on mortality. The pooled risk ratio was calculated using a random-effects model. Weight refers to the contribution of each study to the overall estimate of treatment effect. Abbreviations: CI, confidence interval; IV, inverse variance.

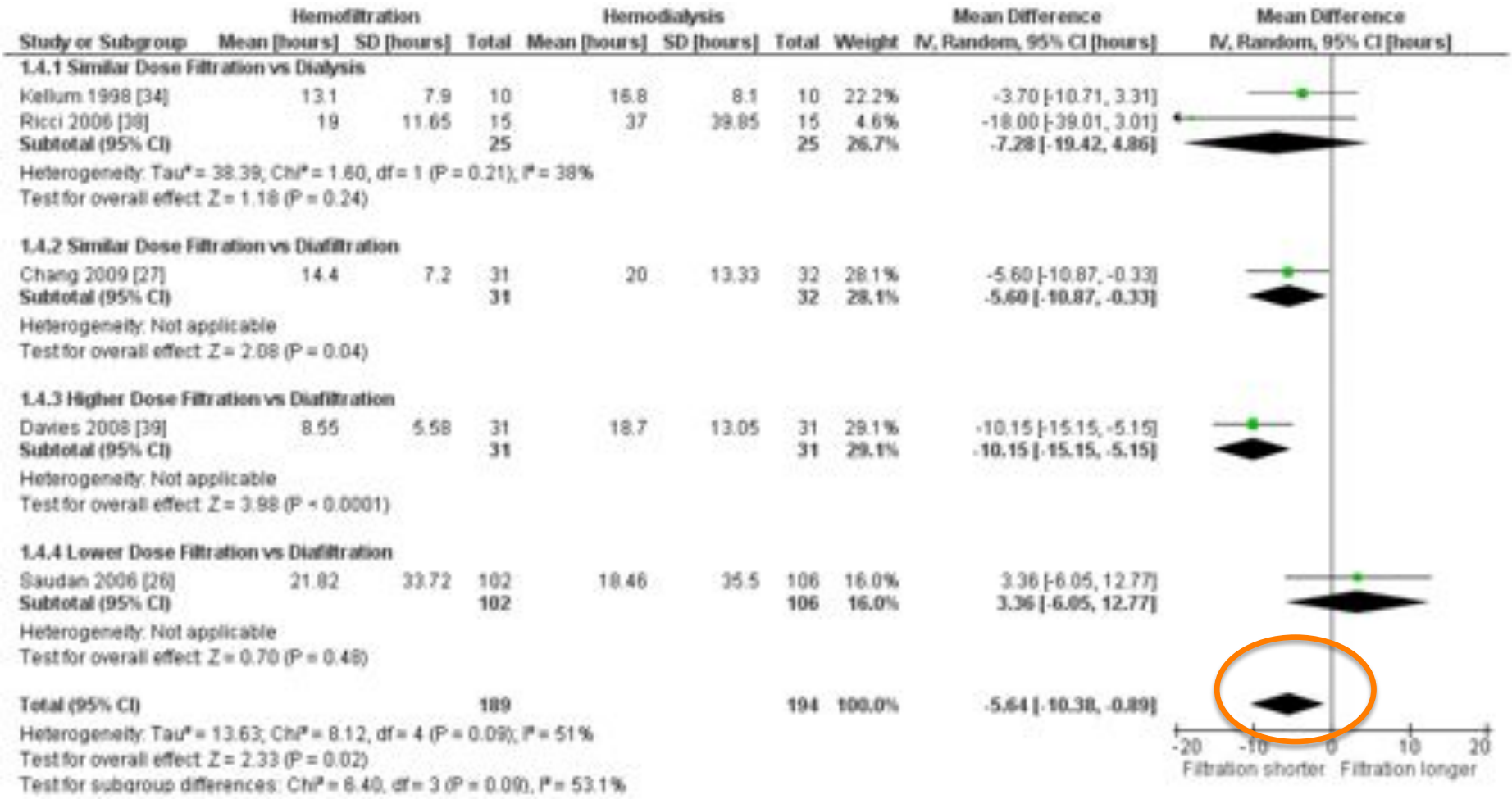


Figure 3 Effect of hemofiltration vs. hemodialysis on filter life. The pooled mean difference was calculated using a random-effects model. Weight refers to the contribution of each study to the overall estimate of treatment effect.

CRRT vs Intermittent treatment

CRRT	IRRT
Convective or diffusive or both	Diffusive
Clearance for small & middle MW	Clearance for small molecules
Pre-packed substitution fluid or online water Tx system	Online water Tx system
Slow but steady correction	Rapid and efficient correction
Labor intensive	Low work load
expensive	cheap
Required continuous anticoagulation	Anticoagulation less important
ICU trained personnel	Renal trained personnel

CRRT vs Intermittent treatment

- Claim: Better hemodynamic stability
- However, studies failed to consistently demonstrate better hemodynamic stability or other vital parameters for CRRT

Claim: Better hemodynamic stability & fluid removal

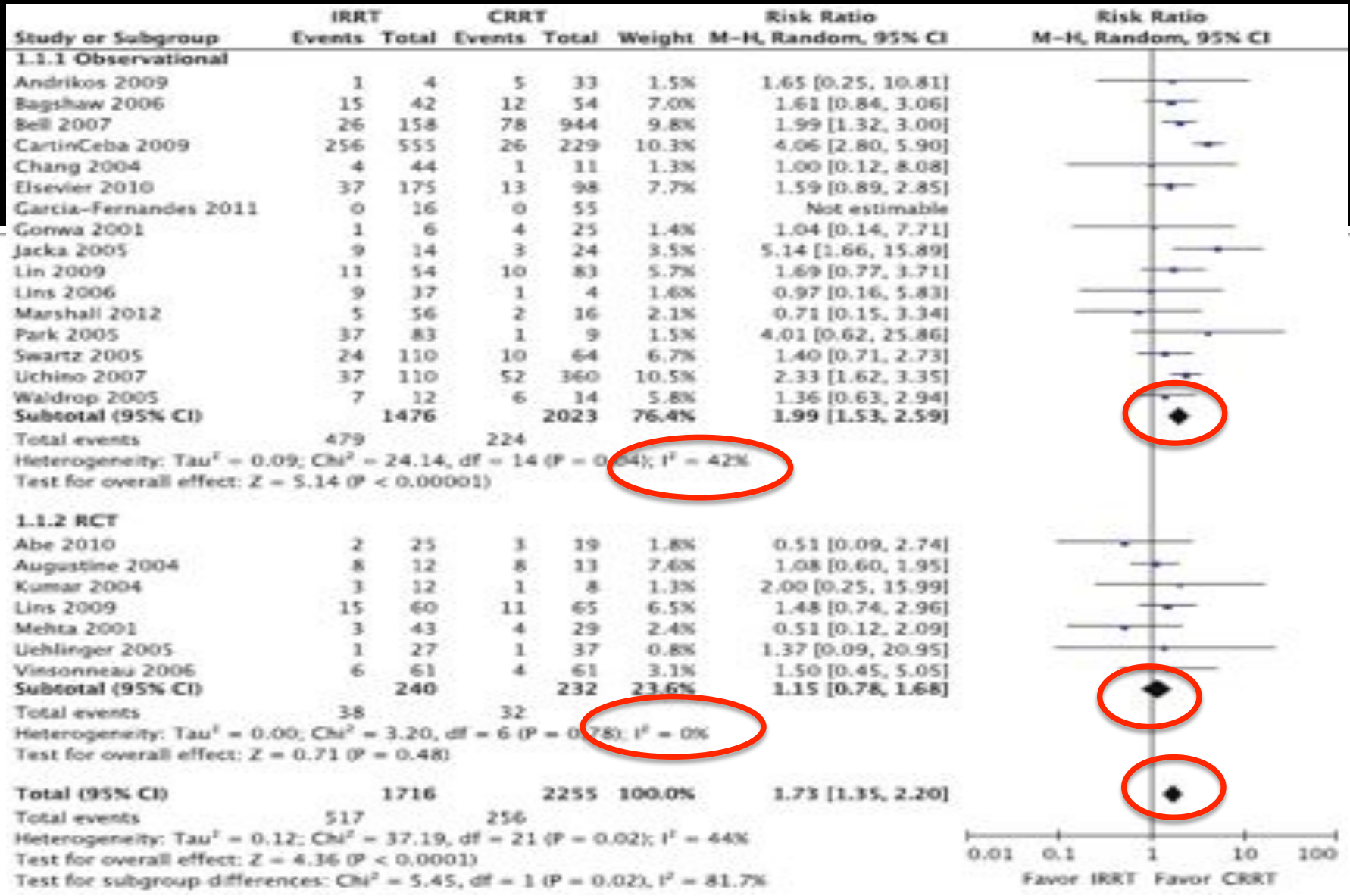
- Meta-analyses
  - Rabindranath K etal, Intermittent vs continuous RRT for ARF in adults. *Cochrane Database Syst Rev 2007;3:CD003773*
  - Pannu N etal, RRT in patients with ARF: a systemic review. *JAMA 2008;299:793-805*
  - Bagshaw SM etal, Continuous vs intermittent RRT for critically ill patients with AKI: a meta-analysis. *Crit Care Med 2008; 366:610-7*
- Failed to show significant outcome differences between 2 methods
  - A slightly higher MAP in CRRT, but not survival
- Why? Reluctance for including patients with major hemodynamic problems out of fear of instability in case of randomization to intermittent arm
  - Excluded the most unstable patients

Pro CRRT

- Claim: Better fluid removal or allow room for administration of parenteral nutrition?
  - Yes, Augustine JJ etal, A RCT comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis 2004,44:1000-7*
  - *No,* John S etal, Effects of CVVH vs IHD on systemic hemodynamics and splanchnic regional perfusion in septic shock patients: a prospective RCT. Nephrol Dial Transplant 2001;16:320-7
  - *Yes, Lameire N etal, Acute renal failure. Lancet 2005;365:417-30*
  - *No,* Uehlinger DE etal, Comparison of continuous and intermittent RRT for ARF. *Nephrol Dial Transplant 2005;20:1630-7*
- Controversial

Pro CRRT

- Claim: Better preservation of renal function?
  - Schneider AG etal, Choice of RRT modality and dialysis dependence after AKI: a systematic review and meta-analysis. *Intensive Care Med 2013;39:987-97*
    - *7 RCTs and 16 observational studies, 3971 patients*



Dialysis dependence among survivors

- Fail to consistently demonstrate superiority of CRRT

Modified IRRT

- Sustained Low Efficiency Daily Dialysis (SLEDD)
  - Extended daily dialysis / Slow continuous dialysis / Prolonged IRRT
  - Slower blood and dialysate flow
  - More prolonged duration
  - Performed daily
- Incorporate potential advantages of CRRT
  - Better suit ICU patients

CRRT vs SLED

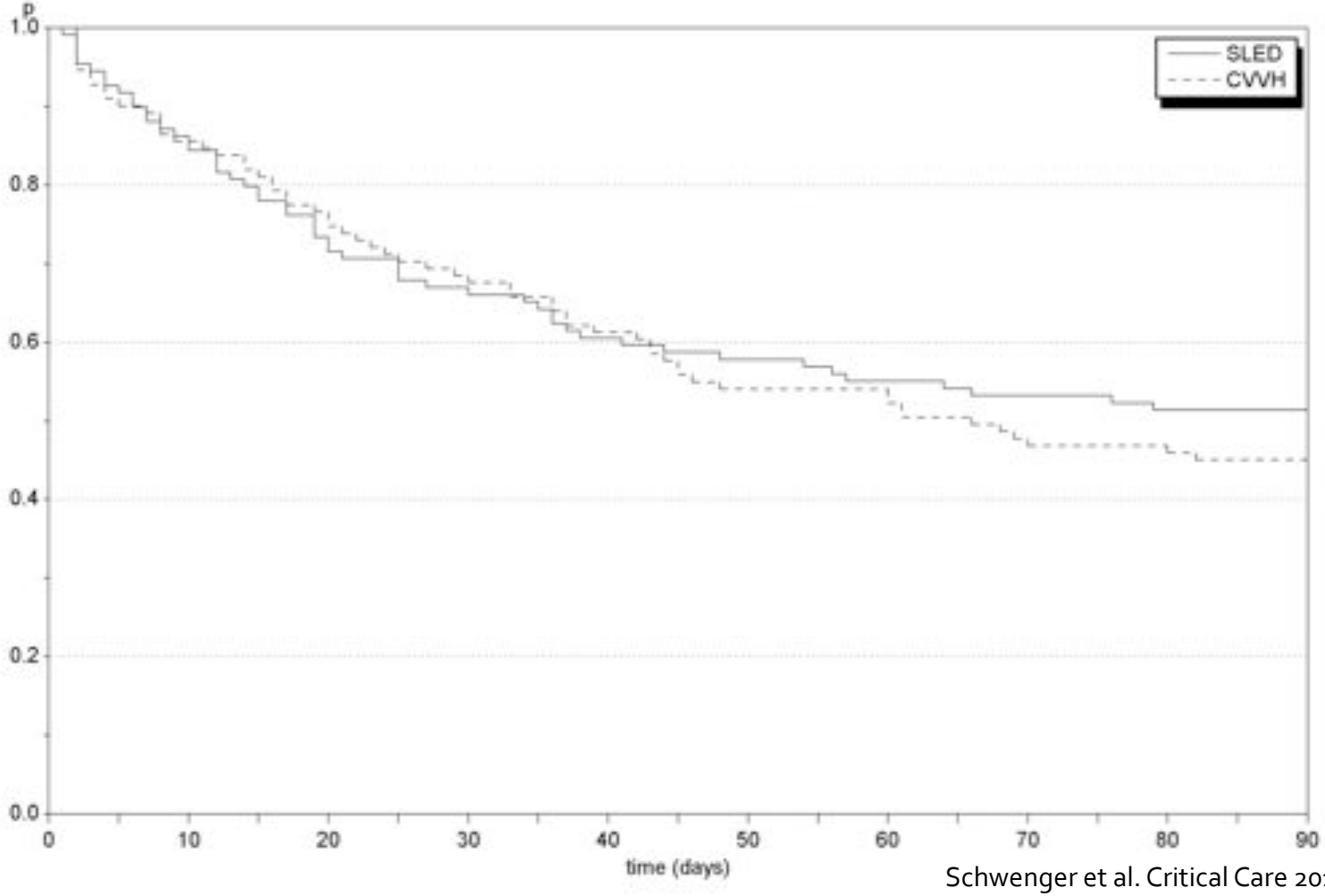
Table 3 Primary and secondary outcomes.

	All (n = 232)	SLED (n = 115)	CVVH (n = 117)	*P*
Death from any cause by day 90	122 (52.6 %)	57 (49.6 %)	65 (55.6 %)	0.434**
Death from any cause up to 30 August 2009	155 (66.8 %)	76 (66.1 %)	79 (67.5 %)	0.926**
In-hospital mortality	119 (51.3 %)	57 (49.6 %)	62 (53.0 %)	0.696**
Mortality in ICU	98 (42.2 %)	49 (42.6 %)	49 (41.9 %)	0.984**
Mechanical ventilation	205 (88.4%)	101 (87.8%)	104 (88.9%)	0.962**
Days of mechanical ventilation	1 9.4 ± 19.7	17.7 ± 19.4	20.9 ± 19.8	0.047*
Days in intensive care unit	21.7 ± 21.1	19.6 ± 20.1	23.7 ± 21.9	0.038*
Recovery of kidney function in days after RRT initiation	10.2 ± 14.5	10.0 ± 15.2	10.5 ± 14.0	0.049*
BP syst pre-treatment (mmHg)	124.8 ± 14.0	125.1 ± 14.6	124.6 ± 13.5	0.434*
BP syst after treatment (mmHg)	126.3 ± 16.4	128.3 ± 17.1	124.3 ± 15.6	0.051*
BP diast pre-treatment (mmHg)	60.7 ± 10.3	60.7 ± 10.7	60.7 ± 10.0	0.420*
BP diast after treatment (mmHg)	61.1 ± 10.7	61.8 ± 11.3	60.3 ± 10.2	0.250*
Hypotensive episodes	1.6 ± 1.5	1.5 ± 1.4	1.8 ± 1.6	0.077*

All values are expressed as number (percent) or mean ± SD; statistical analyses were performed for SLED versus CVVH. *One-tailed Wilcoxon test; **2 × 2 table Chi-Square test with Yates' correction. BP syst: systolic blood pressure; BP diast: diastolic blood pressure; SLED: sustained low efficiency dialysis; CVVH: continuous veno-venous hemofiltration.

Schwenger et al. Critical Care 2012, 16:R140

No mortality difference



Schwenger et al. Critical Care 2012, 16:R140

Economic and manpower issue

Table 4 Dialysis equipment and nursing time per patient.

	SLED (n = 115)	CVVH (n = 117)	*P**
Number of membranes used	14.3 ± 15.3	7.56 ± 8.54	< 0.001
Number of dialysis catheters used	1.74 ± 1.44	1.70 ± 1.89	0.294
Nursing time spent (minutes)			
< 1	9.36 ± 14.7	14.3 ± 41.9	0.131
1 to 5	3.64 ± 4.63	6.75 ± 13.2	0.136
> 5	7.24 ± 9.51	12.1 ± 17.0	< 0.001

*One-tailed Wilcoxon test. SLED: sustained low efficiency dialysis; CVVH: continuous veno-venous hemofiltration.

Schwenger et al. Critical Care 2012, 16:R140

Conclusion (methods)

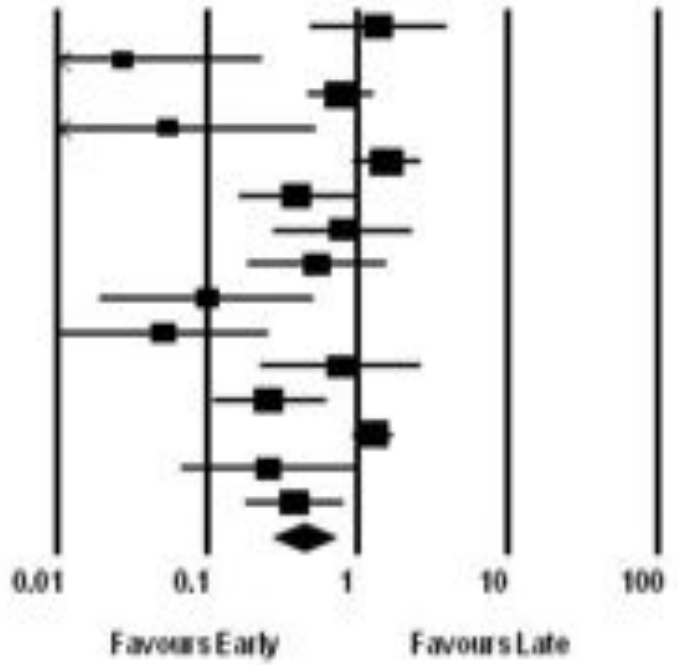
- CRRT vs. IRRT (SLEDD)
  - Complementary to each other
  - Best to have both available in the unit
- Choose the method most suitable
  - Patient's condition
  - Patient's activity
  - Nursing manpower
  - Cost consideration

Timing

Karvellas CJ etal, A comparison of early vs. late initiation of RRT in critically ill patients with AKI: a systematic review & meta-analysis. *Crit Care 2011;15:R72*

Meta Analysis: All 15 studies

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Bouman 2002	Mixed	1.375	0.487	3.884	0.601	0.548
Sugahara 2004	Surgery	0.028	0.003	0.231	-3.318	0.001
[illegible]	Mixed	0.773	0.460	1.298	-0.974	0.330
Sabater 2008	Mixed	0.055	0.006	0.524	-2.520	0.012
Bagshaw 2010*	Mixed	1.563	0.933	2.619	1.697	0.090
Gettings 1999	Surgery	0.399	0.164	0.973	-2.019	0.043
Elahi 2004	Surgery	0.800	0.273	2.341	-0.407	0.684
Demirkilic 2004	Surgery	0.533	0.183	1.552	-1.154	0.249
Andrade 2007	Mixed	0.100	0.019	0.515	-2.752	0.006
Manche 2008	Surgery	0.051	0.010	0.256	-3.623	0.000
Iyem 2009	Surgery	0.778	0.229	2.644	-0.403	0.687
Shiao 2009	Surgery	0.260	0.110	0.614	-3.075	0.002
Bagshaw 2009 adj	Mixed	1.250	0.915	1.708	1.401	0.161
Wu 2007 adj	Surgical	0.259	0.068	0.988	-1.977	0.048
Carl 2010 adj	Mixed	0.380	0.177	0.816	-2.482	0.013
		0.446	0.276	0.723	-3.279	0.001



Significant heterogeneity I^2 = 78%

Great variation of definition for "early" and "late"

Author:	Year	Study design	Population	Modality	Early (n)	Late (n)	Early criteria	Late criteria
Bouman [10]	2002	Randomised	Cardiac surgery/ medical	CWH	35	36	RRT within 12 hours if Urine Output <30 ml/hr	Urea >40 mmol/l or K >6.5 mmol/L
Sugahara [32]	2004	Randomised	Cardiac Surgery	CWH	14	14	Urine Output <20 ml/hr	Urine Output <30 cc/hr
Liu [21]	2006	Prospective Cohort	Medical,Surgery	CRRT/IHD	122	121	Urea <27.1 mmol/L	Urea >27.1 mmol/L
Sabater [33]	2008	Prospective Cohort	Medical (Septic Shock)	CWHF	9	23	Rifle Criteria (Risk, Injury)*	Rifle Criteria (Failure)**
Bagshaw [34]	2009	Prospective Cohort	Medical, Surgical	CRRT/IHD	618	619	Urea <24.2 mmol/L	Urea >24.2 mmol/L
Bagshaw [35]	2010	Prospective Cohort	Medical, Surgical	CRRT/IHD	117	117	Urea <23 mmol/L	Urea >23 mmol/L
Gettings [15]	1999	Retrospective Cohort	Trauma	CAVHD and CVVHD	41	59	Urea <21.4 mmol/L	Urea >21.4 mmol/L
Elahi [38]	2004	Retrospective Cohort	Cardiac surgery	CWH	28	36	Urine Output <100 cc in 8 hrs	K >6 mmol/L, Cr >250 mmol/L
Dermirkilic [13]	2004	Retrospective Cohort	Cardiac Surgery	CVVHDF	27	34	Cr >400 μmol/L, Potassium >5.5 mmol/L	Oliguria
Andrade [36]	2007	Retrospective Cohort	Medical (ARDS/ Sepsis)	IHD/SLED	18	15	On admission	At 24 hours
Wu [42]	2007	Retrospective Cohort	Surgical ALF	IHD/CWH	54	26	Urea < 28.6 mmol/L	Urea >28.6 mmol/L
Manche [40]	2008	Retrospective Cohort	Cardiac Surgery	IHD	56	15	Hyperkalemia	U/O <0.5 ml/kg/hour
Iyem [39]	2009	Retrospective Cohort	Cardia Surgery	CWH	95	90	RRT on admission	After 48 hours when anuric
Shiao [41]	2009	Retrospective Cohort	Surgery/Trauma	CWH	51	47	Rifle Criteria (Risk)*	Rifle Injury, Failure**
Carl [37]	2010	Retrospective Cohort	Medical (sepsis)	CRRT/IHD	85	62	Urea <35.7 mmol/l	Urea >35.7 mmol/L

Mixed cases vs surgical

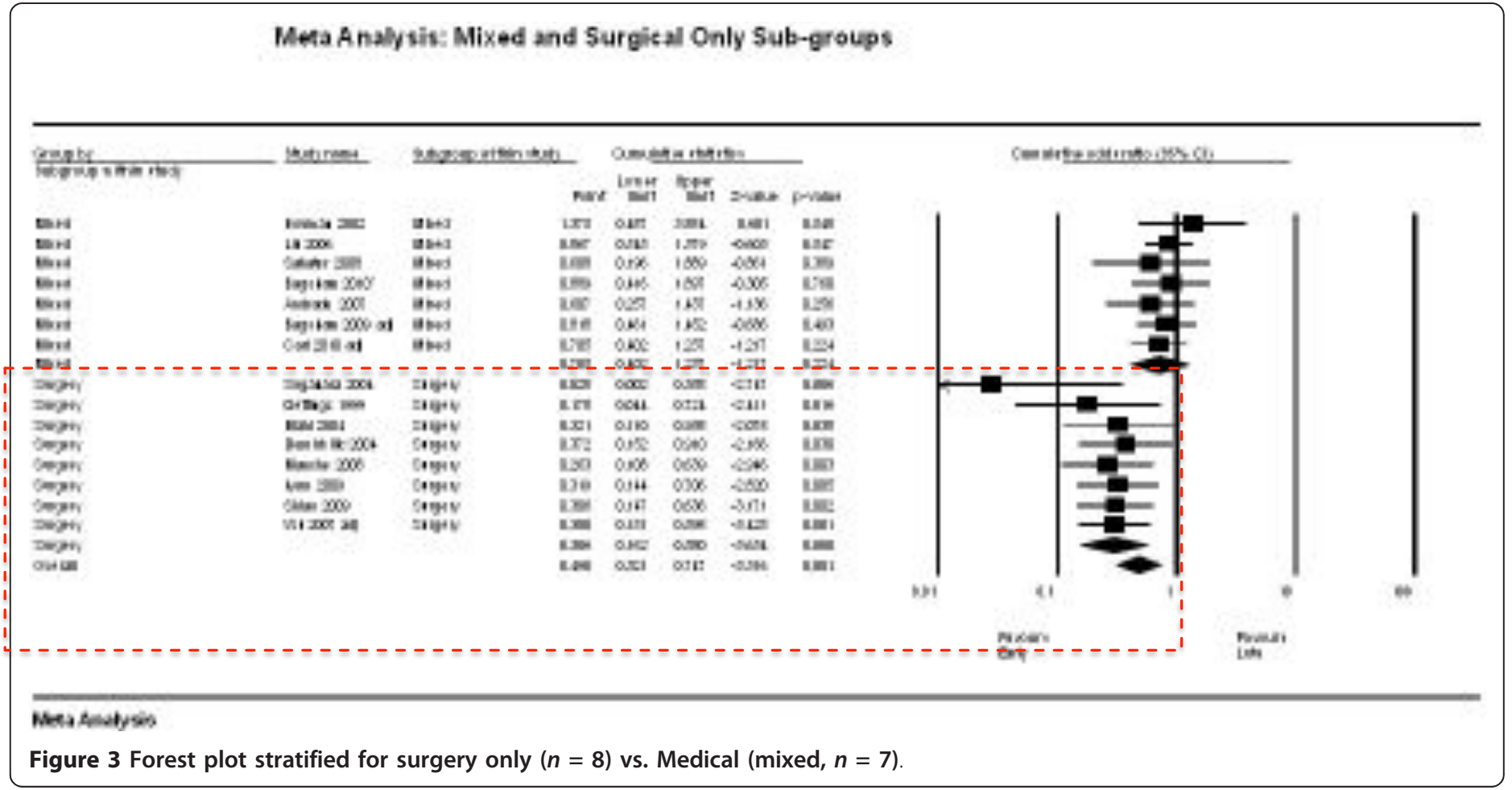


Figure 3 Forest plot stratified for surgery only (n = 8) vs. Medical (mixed, n = 7).

Wang X etal, Timing of initiation of RRT in AKI: a systematic review & meta-analysis. *Ren Fail 2012;34:396-402*

- 15 studies (3 RCTs, 2 prospective and 10 retrospective cohort studies)
- Mortality
  - "early" 772/1514 (51.0%)
  - "late" 836/1441 (58.0%)
  - Pooled RR 0.71 (0.59 – 0.86)
  - Heterogeneity existed ($p<0.00001$)

Timing of initiation of RRT in AKI

- Whole clinical scenario
  - Aetiology of AKI
  - AKI progression
  - Urine output
  - Fluid accumulation/heart function
  - Other organ failure
  - Electrolytes disturbance (hyperK+)
  - Metabolic acidosis
  - Other non-renal indications for RRT
    - Hyperthermia
    - Overdose or poisoning
- ? Other AKI biomarkers
  - NGAL, KIM-1 or Cystatin C

Conclusion (timing)

- No definitive answer yet
- Establishing a satisfactory definition for early and late initiation of RRT is urgently needed