Nephro Update Europe 2018

5-6 October, Budapest

Acute Kidney Injury

Patrick Murray, Ireland

Conflicts of Interest

Research Support: Abbott, Alere

Lecturing: -

Consulting activities: AM-Pharma, Sphingotec, FAST Biomedical, Genomic Medicine Ireland

AKI Diagnosis & Staging

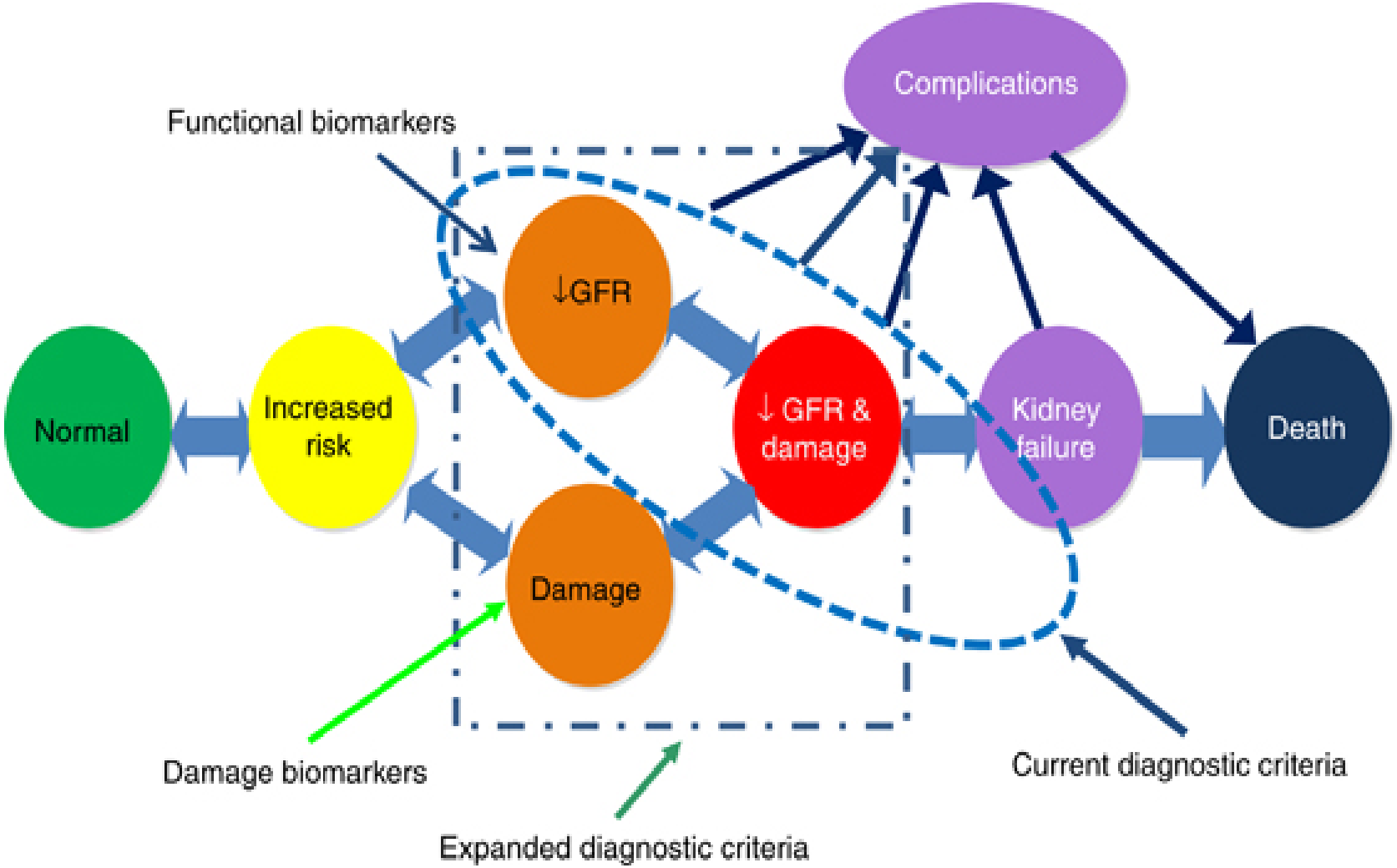
AKI Guidelines: Current Status of Criteria for Diagnosis & Staging

- *Validated Classification Systems*

	Risk/Stage 1	Injury/Stage 2	Failure/Stage 3
RIFLE[1] 2004	• Increased SCr × 1.5 **or** • GFR decrease >25%	• Increased SCr × 2 **or** • GFR decrease >50%	• Increased SCr × 3 or GFR decrease 75% **or** • SCr ≥4 mg/dL (acute rise of ≥0.5 mg/dL)
AKIN[2] 2007	• Increased SCr ≥0.3 mg/dL **or** • >1.5–2.0 × baseline	• Increased SCr >2–3 × baseline	• Increased SCr >3 × baseline **or** • SCr ≥4 mg/dL (acute increase of ≥0.5 mg/dL)
KDIGO[3] 2012	• Increased in SCr by >0.3 mg/dL (≥26.5 µmol/L) within 48 h **or** • 1.5–1.9 × baseline	• Increased in SCr by 2.0–2.9 × baseline	• Increased SCr by ≥4.0 mg/dL (≥353.6 µmol/L) **or** • 3.0 × baseline or initiation of RRT **or** • In patients <18 y, decrease in eGFR to <35 mL/min/1.73 m^2

1. Bellomo R et al. Crit Care. 2004;8:R204-212
2. Mehta RL et al. Crit Care. 2007;11:R31
3. KDIGO Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:1-138. www.KDIGO.org

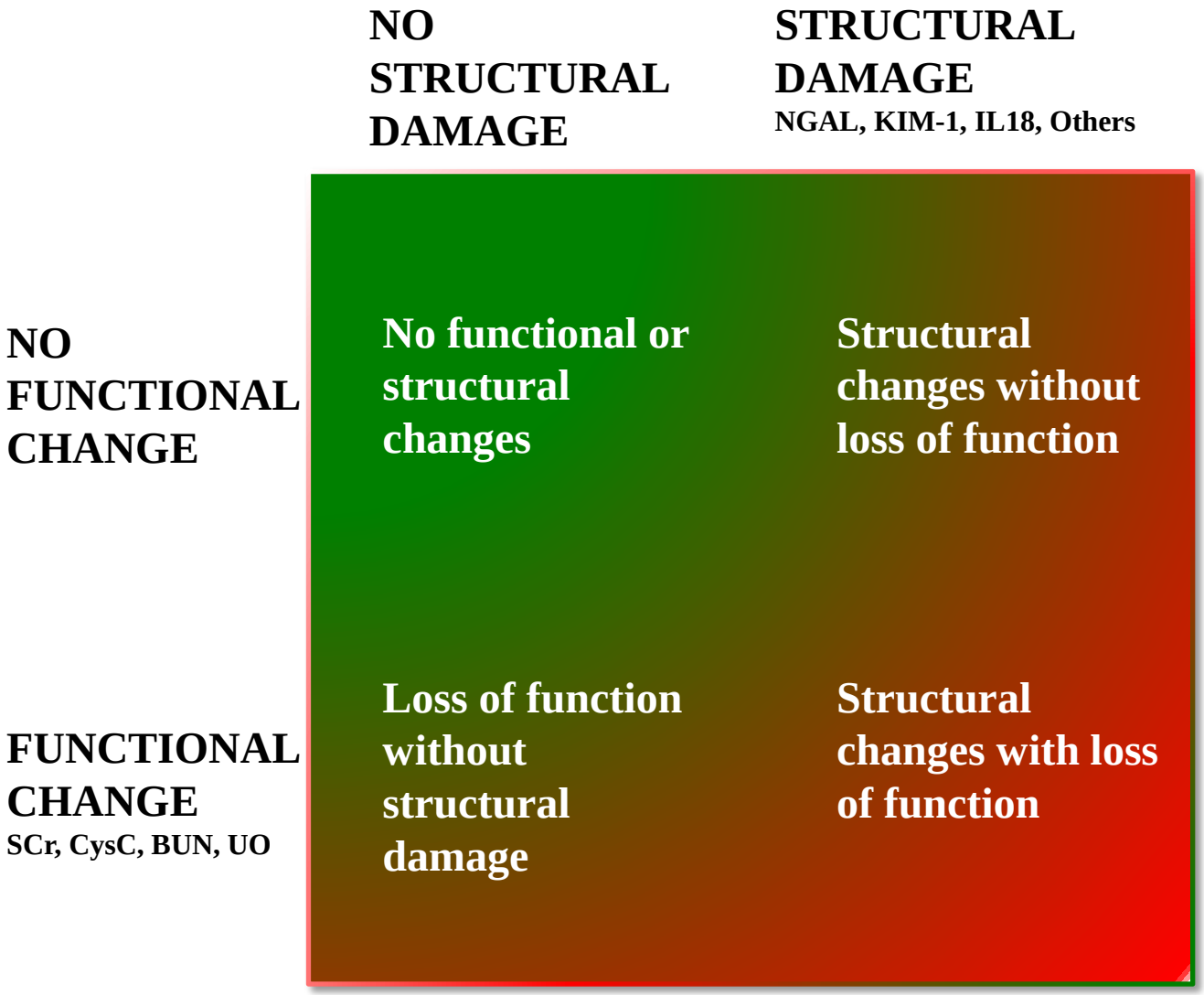
Evolution of AKI Conceptual Framework



www.ADQI.org

Murray PT, et al, for the ADQI Workgroup: 2014;85:513-521

The New Spectrum of AKI Diagnostics



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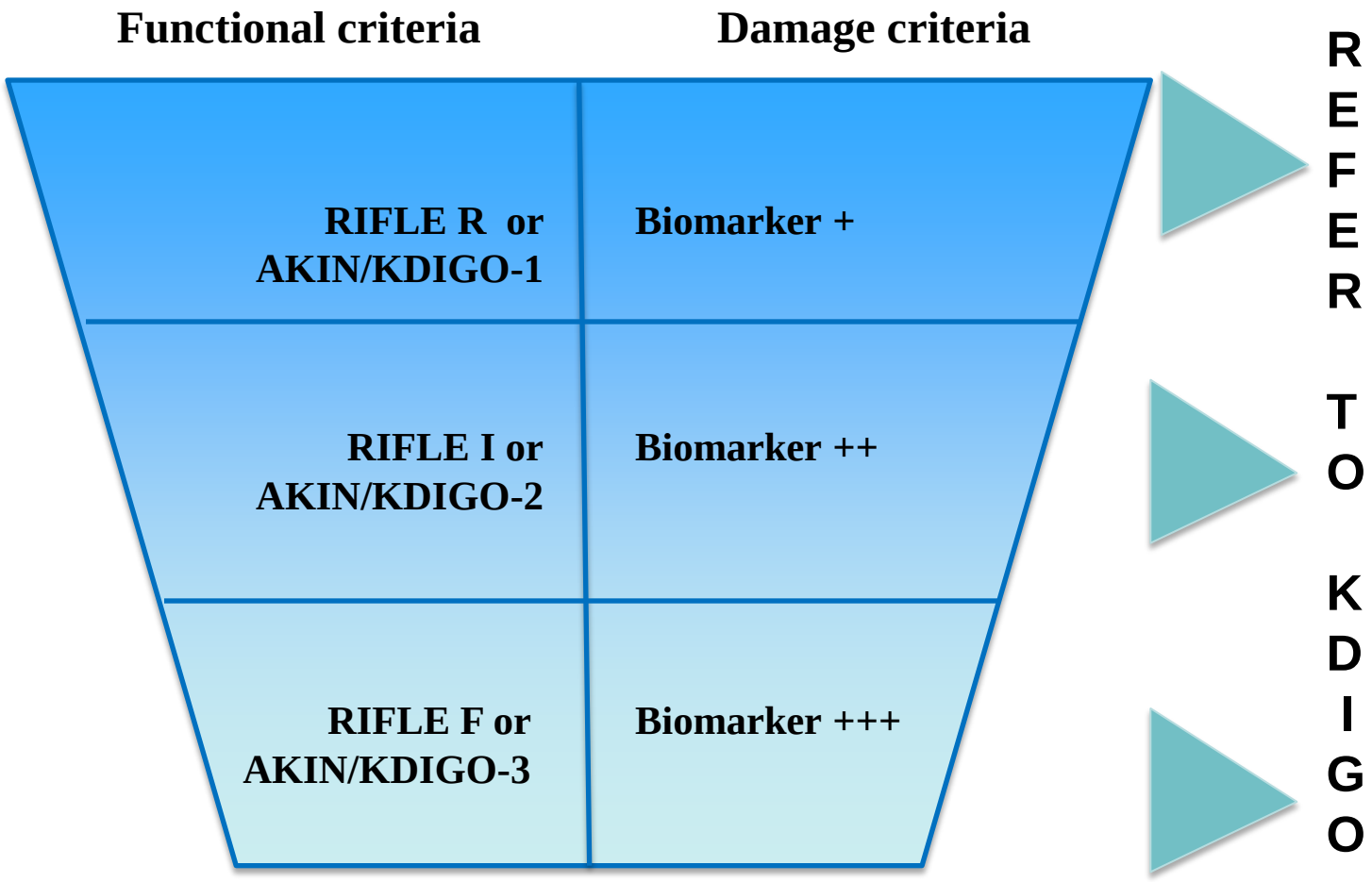

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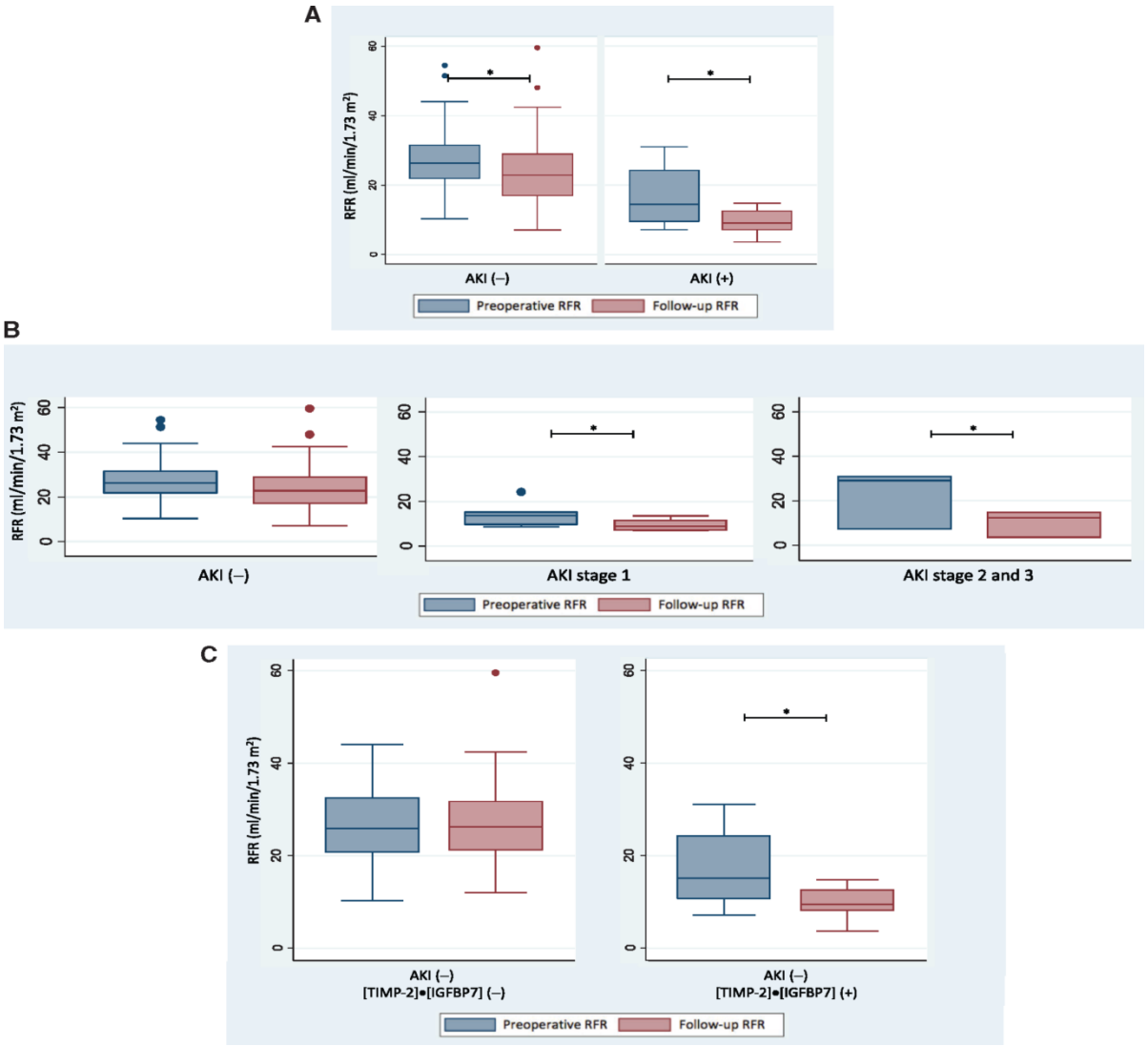
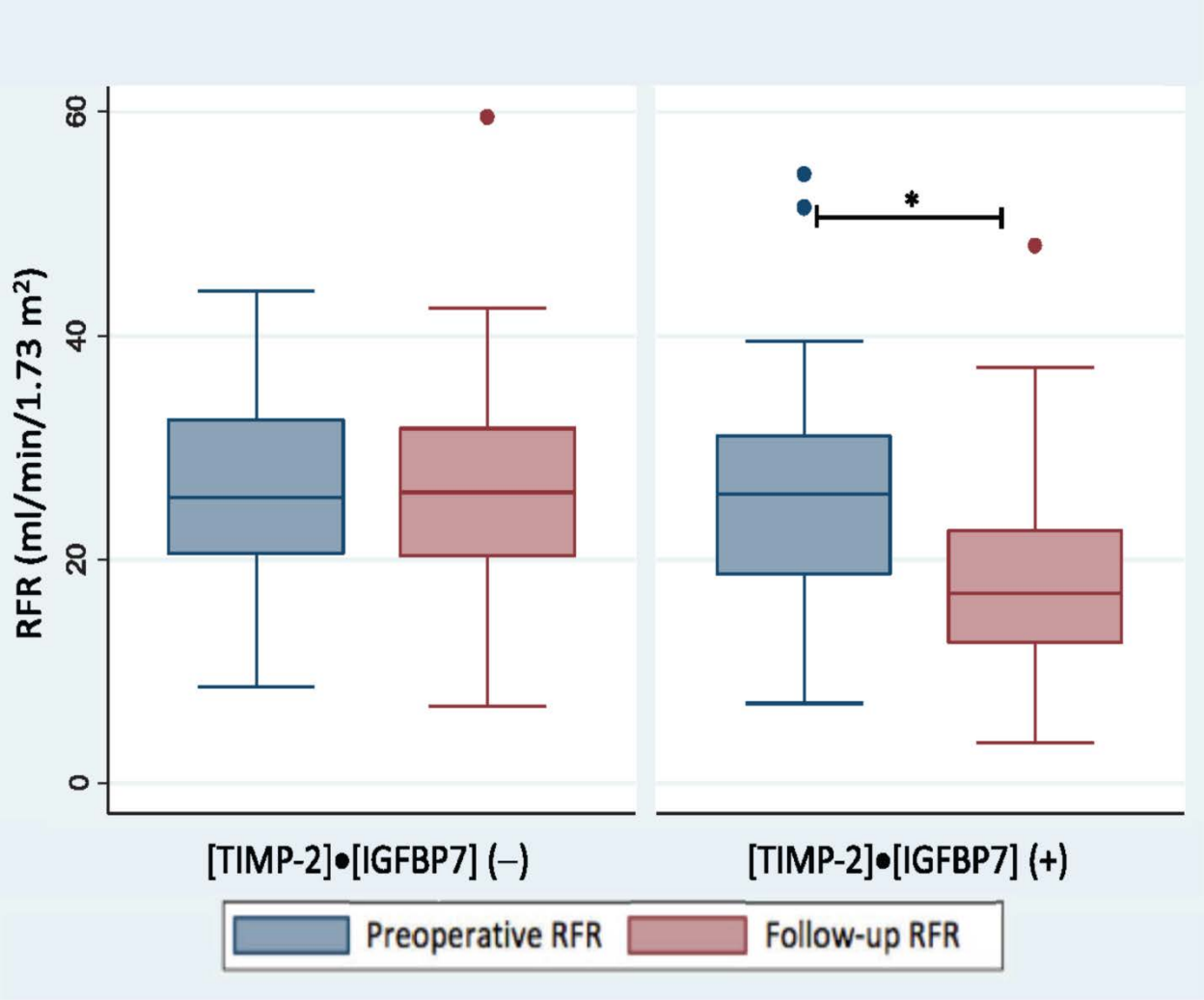
Renal Reserve & CS-A AKI Recovery



Husain-Syed F, et al: Nephrol Dial Transplant. Published online July 19, 2018. doi:10.1093/ndt/gfy227

Renal Reserve & CS-A AKI Recovery



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Take-Home Messages

Several AKI Classification Systems have been developed and validated

- Based upon functional criteria (SCr, UOP)
  - FST, real-time GFR, Renal Reserve, and other functional markers will refine these criteria
- Novel biomarkers of kidney damage or dysfunction may also improve the prediction or diagnostic/prognostic evaluation of AKI
- Combination of functional and damage biomarkers, implementation research required

AKI Prevention: Fluid Management

KDIGO Conceptual Framework for AKI Risk

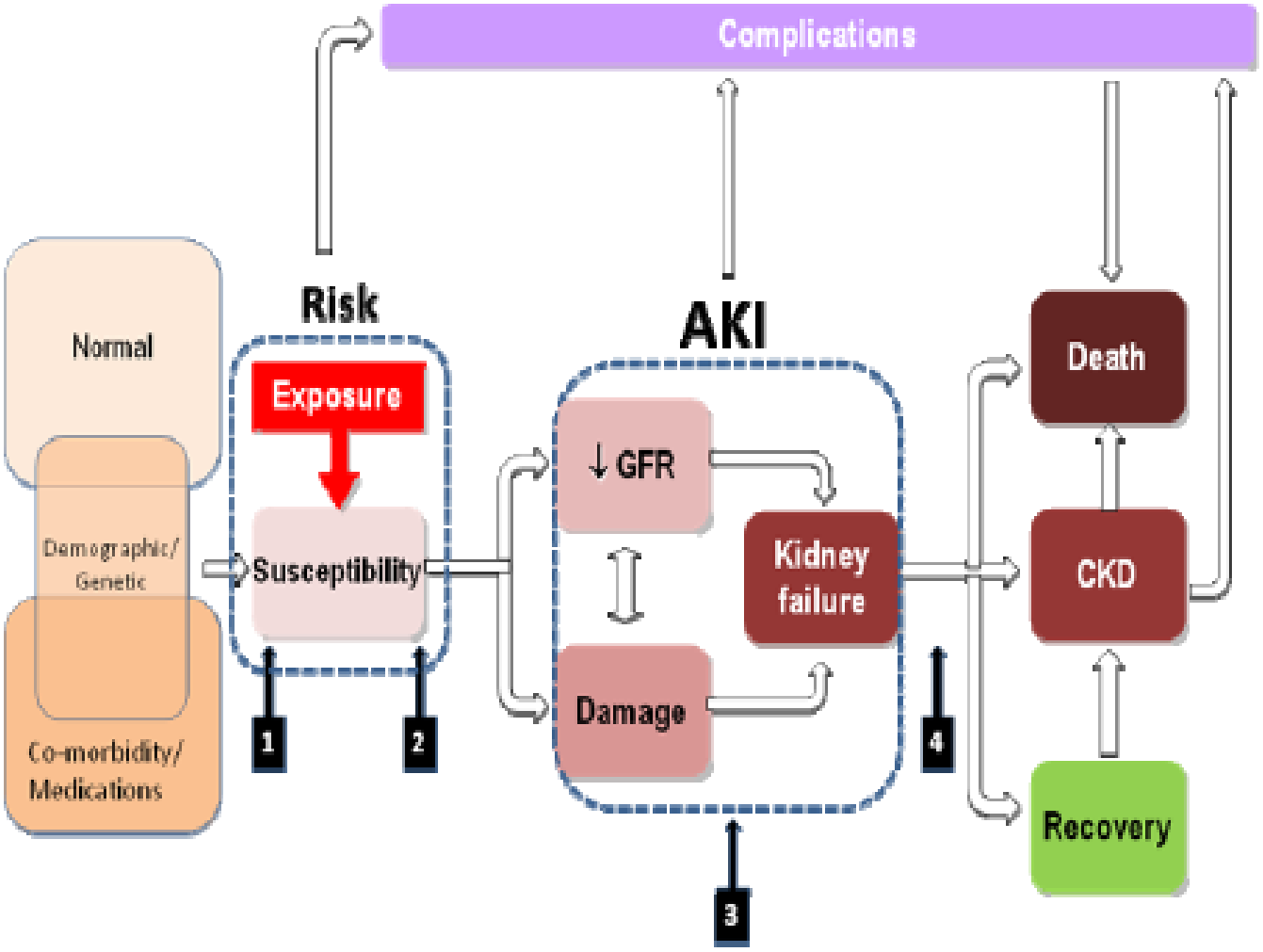


Figure 1: Suggested levels of risk assessment with relevance to AKI

KDIGO AKI Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int, Suppl*, 2012;2(1):1-138

PRESERVE TRIAL: OUTCOMES

Table 3. Primary and Secondary End Points.

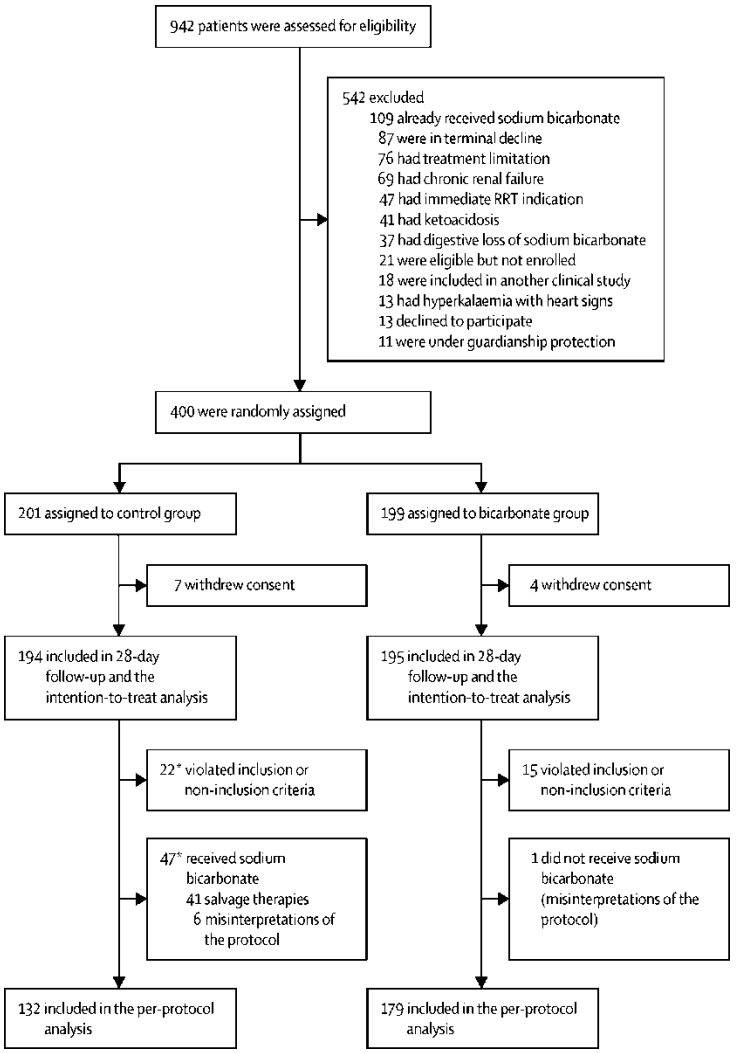
Outcome	Sodium Bicarbonate (N=2511)	Sodium Chloride (N=2482)	Odds Ratio (95% CI)	P Value	Acetylcysteine (N=2495)	Placebo (N=2498)	Odds Ratio (95% CI)	P Value
	no. of patients (%)				*no. of patients (%)*			
Primary end point*	110 (4.4)	116 (4.7)	0.93 (0.72–1.22)	0.62	114 (4.6)	112 (4.5)	1.02 (0.78–1.33)	0.88
Secondary end points								
Contrast-associated acute kidney injury†	239 (9.5)	206 (8.3)	1.16 (0.96–1.41)	0.13	228 (9.1)	217 (8.7)	1.06 (0.87–1.28)	0.58
Death by 90 days	60 (2.4)	68 (2.7)	0.87 (0.61–1.24)	0.43	67 (2.7)	61 (2.4)	1.10 (0.78–1.57)	0.59
Need for dialysis by 90 days	32 (1.3)	29 (1.2)	1.09 (0.65–1.81)	0.73	30 (1.2)	31 (1.2)	0.97 (0.58–1.60)	0.90
Persistent kidney impairment by 90 days	28 (1.1)	25 (1.0)	1.10 (0.64–1.91)	0.71	26 (1.0)	27 (1.1)	0.96 (0.56–1.66)	0.89
Hospitalization with acute coronary syndrome, heart failure, or stroke by 90 days	272 (10.8)	251 (10.1)	1.08 (0.90–1.29)	0.40	244 (9.8)	279 (11.2)	0.86 (0.71–1.04)	0.11
All-cause hospitalization by 90 days	1071 (42.7)	1052 (42.4)	1.01 (0.90–1.13)	0.85	1069 (42.8)	1054 (42.2)	1.03 (0.91–1.15)	0.64

* The primary end point was a composite of death, the need for dialysis, or a persistent increase of at least 50% from baseline in the serum creatinine level at 90 days. Data regarding 90-day creatinine levels were missing in 119 patients (4.7%) in the sodium bicarbonate group, 103 (4.1%) in the sodium chloride group, 105 (4.2%) in the acetylcysteine group, and 117 (4.7%) in the placebo group.

† Contrast-associated acute kidney injury was defined as an increase in serum creatinine of at least 25% or at least 0.5 mg per deciliter (44 μmol per liter) from baseline at 3 to 5 days after angiography. Data regarding serum creatinine levels on days 3 to 5 were missing in 212 patients (8.4%) in the sodium bicarbonate group, 229 (9.2%) in the sodium chloride group, 210 (8.4%) in the acetylcysteine group, and 231 (9.2%) in the placebo group.

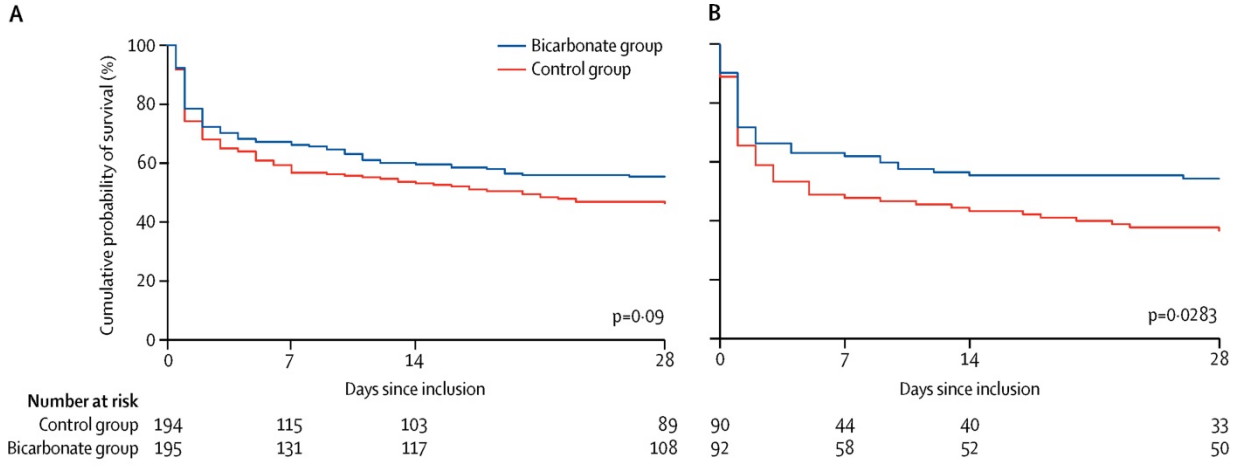
Weisbord SD, et al: N Engl J Med 2018;378(7):603-614

Sodium Bicarbonate Therapy for Metabolic Acidosis: RCT



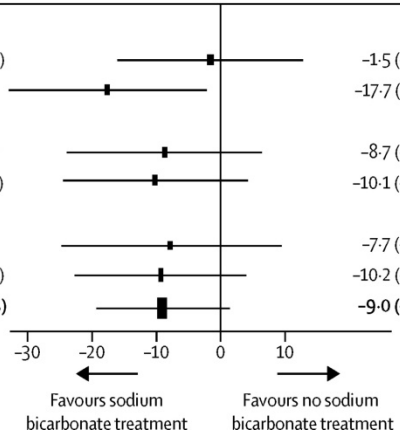
Jaber S, et al: Lancet 2018; 392: 31–40

Sodium Bicarbonate Therapy for Metabolic Acidosis: RCT Outcomes



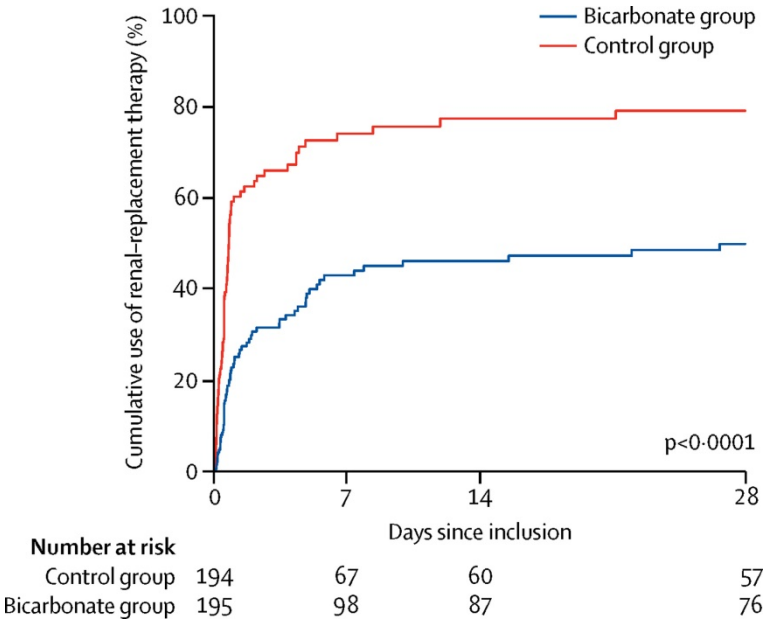
C

	Control group (n/N)	Bicarbonate group (n/N)	Absolute difference estimate (95% CI)	p value	Adjusted p value	p value for heterogeneity
AKIN score						
0–1	47/104 (45%)	45/103 (44%)	−1·5 (−16·0 to 13·0)	0·83	0·83	0·0226
2–3	57/90 (63%)	42/92 (46%)	−17·7 (−33·0 to −2·3)	0·0167	0·0334	
Age (years)						
<65	42/94 (45%)	32/89 (36%)	−8·7 (−24·0 to 6·5)	0·23	0·23	0·0031
≥65	62/100 (62%)	55/106 (52%)	−10·1 (−24·5 to 4·3)	0·14	0·28	
Sepsis status						
No	39/79 (49%)	30/72 (42%)	−7·7 (−24·9 to 9·5)	0·34	0·34	0·21
Yes	65/115 (57%)	57/123 (46%)	−10·2 (−23·7 to 3·3)	0·12	0·24	
All patients	**104/194 (54%)**	**87/195 (45%)**	**−9·0 (−19·4 to 1·4)**	**0·08**		



Jaber S, et al: Lancet 2018; 392: 31–40

Sodium Bicarbonate Therapy for Metabolic Acidosis: RRT Incidence



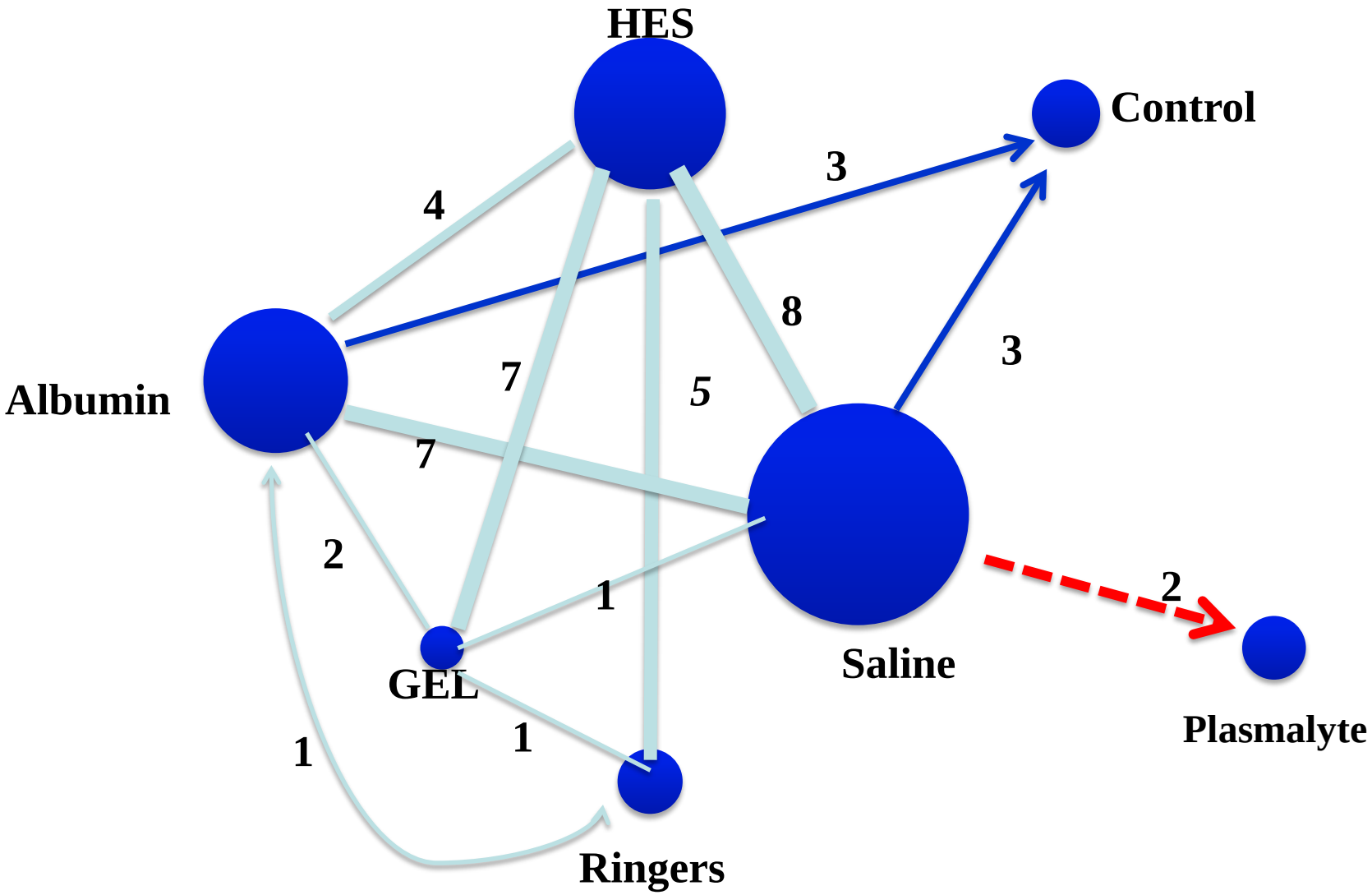
Jaber S, et al: Lancet 2018; 392: 31–40

“Adverse Effects”of IV Fluids

Type	AKI	RRT	Coag	ICP	HA	Mort.
HES	●	●	●			●
Alb				●		●
NS	●	●			●	●
BSS						

Raghunathan K, et al; Br. J. Anaesth. 2014;113(5):772-83

Network of Fluid Studies in Critical Care



Raghunathan K, et al; Br. J. Anaesth. 2014;113(5):772-83

SPLIT (Saline vs. Plasma-Lyte for ICU Fluid Therapy) Trial: Buffered Crystalloid Solution vs Normal Saline in ICU

- Blinded double-crossover RCT in critically ill patients: BSS (n=1152) vs. 0.9% saline (n=1110)
- AKI (RIFLE): 9.6% vs. 9.2%, p=0.77
- RRT: 3.3% vs. 3.4%, p=0.91
- Mortality: 7.6% vs. 8.6%, p=0.4

Young P, et al, for the SPLIT Investigators & ANZICS CTG, JAMA 2015;314(16):1701-10

Balanced Crystalloids vs. Saline in Critical Illness

Table 2. Clinical Outcomes.*

Outcome	Balanced Crystalloids (N = 7942)	Saline (N = 7860)	Adjusted Odds Ratio (95% CI)†	P Value†
Primary outcome				
Major adverse kidney event within 30 days — no. (%)‡	1139 (14.3)	1211 (15.4)	0.90 (0.82 to 0.99)	0.04
Components of primary outcome				
In-hospital death before 30 days — no. (%)	818 (10.3)	875 (11.1)	0.90 (0.80 to 1.01)	0.06
Receipt of new renal-replacement therapy — no./total no. (%)§	189/7558 (2.5)	220/7458 (2.9)	0.84 (0.68 to 1.02)	0.08
Among survivors	106/6787 (1.6)	117/6657 (1.8)		
Final creatinine level ≥200% of baseline — no./total no. (%)§	487/7558 (6.4)	494/7458 (6.6)	0.96 (0.84 to 1.11)	0.60
Among survivors	259/6787 (3.8)	273/6657 (4.1)		
Among survivors without new renal-replacement therapy	215/6681 (3.2)	219/6540 (3.3)		
Secondary outcomes				
In-hospital death — no. (%)				
Before ICU discharge	528 (6.6)	572 (7.3)	0.89 (0.78 to 1.02)	0.08
Before 60 days	928 (11.7)	975 (12.4)	0.92 (0.83 to 1.02)	0.13
ICU-free days¶				0.94
Median	25.3	25.3	1.00 (0.89 to 1.13)	
Interquartile range	22.1 to 26.6	22.2 to 26.6		
Mean	21.8±8.3	21.7±8.6		
Ventilator-free days¶			1.06 (0.97 to 1.16)	0.22
Median	28.0	28.0		
Interquartile range	26.0 to 28.0	26.0 to 28.0		
Mean	24.2±8.6	23.9±8.9		
Vasopressor-free days¶			1.05 (0.97 to 1.14)	0.26
Median	28.0	28.0		
Interquartile range	27.0 to 28.0	27.0 to 28.0		
Mean	24.7±8.5	24.4±8.8		
Renal-replacement therapy–free days¶			1.11 (1.02 to 1.20)	0.01
Median	28.0	28.0		
Interquartile range	28.0 to 28.0	28.0 to 28.0		
Mean	25.0±8.6	24.8±8.9		
Secondary renal outcomes§				
Stage 2 or higher AKI developing after enrollment — no./total no. (%)‖	807/7558 (10.7)	858/7458 (11.5)	0.91 (0.82 to 1.01)	0.09
Creatinine — mg/dl**				
Highest before discharge or day 30			1.01 (0.97 to 1.05)	0.58
Median	0.99	0.99		
Interquartile range	0.78 to 1.53	0.78 to 1.52		
Change from baseline to highest value			0.98 (0.94 to 1.02)	0.35
Median	0.04	0.04		
Interquartile range	−0.08 to 0.31	−0.08 to 0.32		
Final value before discharge or 30 days			1.02 (0.97 to 1.06)	0.51
Median	0.83	0.83		
Interquartile range	0.70 to 1.11	0.70 to 1.11		

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ICU denotes intensive care unit.

† Categorical outcomes were compared with a generalized, linear, mixed-effects model, with adjustment for the ICU to which the patient was admitted as a random effect and prespecified covariates as fixed effects.[33] Continuous outcomes were compared between groups with a proportional-odds model, with adjustment for the same variables.

‡ A major adverse kidney event within 30 days is the composite of death, receipt of new renal-replacement therapy, or final creatinine level that was at least 200% of the baseline level, with all events censored at hospital discharge or at 30 days after admission to the ICU, whichever occurred first. The effect of study group on major adverse kidney events within 30 days is the conditional effect. The marginal effect yielded an odds ratio of 0.91 and a 95% confidence interval of 0.84 to 0.99.

§ Data on receipt of new renal-replacement therapy, final creatinine level that was at least 200% of the baseline level, and secondary renal outcomes are provided for the 15,016 patients not known to have received renal-replacement therapy before ICU admission.

¶ ICU-free, ventilator-free, vasopressor-free, and renal-replacement-therapy–free days refer to the number of days on which a patient was alive and free from the specified therapy in the first 28 days after enrollment. Odds ratios of higher than 1.0 indicate a better outcome (i.e., more days alive and free from the specified therapy) with balanced crystalloids than with saline.

‖ The development of acute kidney injury (AKI) of stage 2 or higher after enrollment was defined in accordance with the Kidney Disease: Improving Global Outcomes plasma creatinine criteria[22] as any creatinine level between enrollment and discharge or 30 days that increased by at least 0.3 mg per deciliter (27 μmol per liter) from a preceding post-enrollment value and was at least 200% of the baseline value, at least 200% of a preceding post-enrollment value, or at least 4.0 mg per deciliter (350 μmol per liter) or as new receipt of renal-replacement therapy.

** Among patients who had not received previous renal-replacement therapy, the plasma creatinine level was measured a mean of 8.0 times between enrollment and the first of discharge or 30 days in each group; the plasma creatinine level was not measured between enrollment and the first of discharge or 30 days for 418 of 7558 patients (5.5%) in the balanced-crystalloids group and 443 of 7458 patients (5.9%) in the saline group.

MW Semler et al. N Engl J Med 2018;378:829-839

Balanced Cystalloids vs. Saline in Non-Critical Illness

Table 3. Clinical Outcomes According to Assigned Treatment Group in the Intention-to-Treat Analysis.

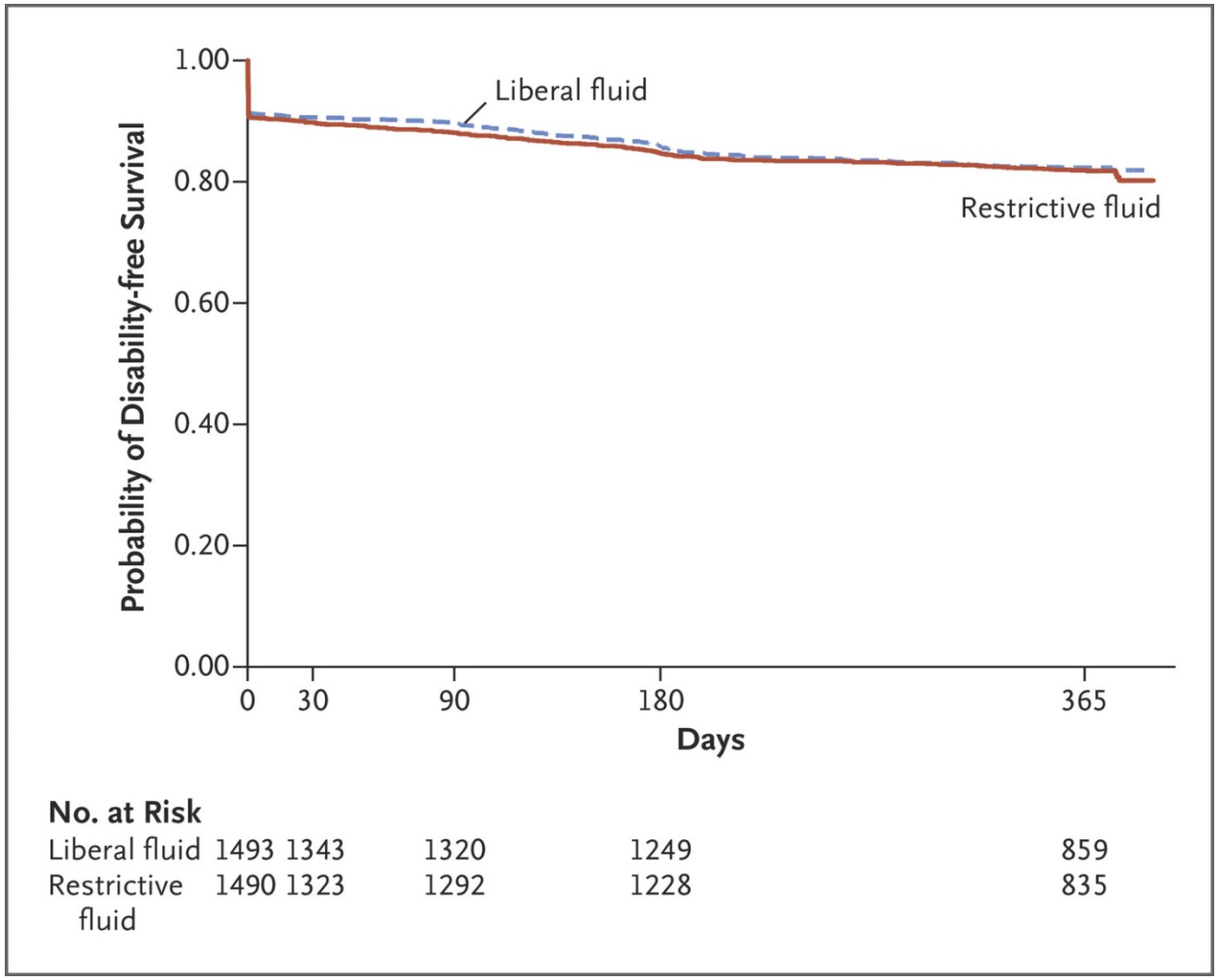
Outcome	Balanced Crystalloids (N=6708)	Saline (N=6639)	Adjusted Odds Ratio (95% CI)*	Adjusted P Value
Median hospital-free days to day 28 (IQR)	25 (22–26)	25 (22–26)	0.98 (0.92–1.04)	0.41
Major adverse kidney event within 30 days — no. (%)	315 (4.7)	370 (5.6)	0.82 (0.70–0.95)	0.01
Death — no. (%)	94 (1.4)	102 (1.5)	0.89	
New renal-replacement therapy — no./total no. (%)†	18/6582 (0.3)	31/6530 (0.5)	0.56	
Final serum creatinine ≥200% of baseline — no./total no. (%)†	253/6582 (3.8)	293/6530 (4.5)	0.84	
Stage 2 or higher acute kidney injury — no./total no. (%)†	528/6582 (8.0)	560/6530 (8.6)	0.91 (0.80–1.03)	0.14
In-hospital death — no. (%)	95 (1.4)	105 (1.6)	0.88 (0.66–1.16)	0.36

* Multivariable models were adjusted for age, sex, race, admitting service, and time (days since trial initiation).

† Patients with end-stage renal disease who were receiving long-term renal-replacement therapy at the time of emergency department arrival (126 in the balanced-crystalloids group and 109 in the saline group) were not eligible for the following outcomes: new renal-replacement therapy within 30 days, final serum creatinine concentration within 30 days at least 200% of the baseline value, and stage 2 or higher acute kidney injury.

WH Self et al. N Engl J Med 2018;378:819-828

Perioperative Fluid Management: Liberal vs. Restrictive



PS Myles et al. N Engl J Med 2018;378:2263-2274

Perioperative Fluid Management: Liberal vs. Restrictive - Primary & Secondary Outcomes

Table 3. Primary and Secondary Outcomes.*

Outcome	Restrictive Fluid (N=1490)	Liberal Fluid (N=1493)	Hazard or Risk Ratio (95% CI)†	P Value
Primary outcome				
Disability-free survival at 1 yr — no. (%)‡	1223 (81.9)	1232 (82.3)	1.05 (0.88–1.24)	0.61
Death or persistent disability — no.	267	261		
Death	95	96		
Persistent disability	172	165		
Secondary outcomes§				
Composite septic outcome or death — no./total no. (%)¶	323/1481 (21.8)	295/1487 (19.8)	1.10 (0.96–1.27)	0.19
Surgical-site infection — no./total no. (%)	245/1481 (16.5)	202/1487 (13.6)	1.22 (1.03–1.45)	0.02‖
Sepsis — no./total no. (%)	157/1481 (10.6)	129/1487 (8.7)	1.22 (0.98–1.52)	0.08
Anastomotic leak — no./total no. (%)	49/1481 (3.3)	35/1487 (2.4)	1.41 (0.92–2.16)	0.12
Pneumonia — no./total no. (%)	54/1481 (3.6)	57/1487 (3.8)	0.95 (0.66–1.37)	0.79
Acute kidney injury — no./total no. (%)**	124/1443 (8.6)	72/1439 (5.0)	1.71 (1.29–2.27)	<0.001
Renal-replacement therapy — no./total no. (%)	13/1460 (0.9)	4/1462 (0.3)	3.27 (1.01–13.8)	0.048‖
Pulmonary edema — no./total no. (%)	20/1481 (1.4)	32/1487 (2.2)	0.63 (0.36–1.09)	0.10
Unplanned admission to ICU — no./total no. (%)	161/1487 (10.8)	145/1491 (9.7)	1.11 (0.90–1.38)	0.32
Median peak serum lactate level (IQR) — mmol per liter††	1.6 (1.1–2.5)	1.6 (1.1–2.4)	NA	NA
Median C-reactive protein level on day 3 (IQR) — mg per liter‡‡	136 (82–198)	133 (80–200)	NA	0.66
Median duration of mechanical ventilation (IQR) — hr§§	17 (5–65)	14 (3–31)	NA	0.07
Median score on quality-of-recovery scale (IQR)¶¶	106 (89–121)	107 (90–122)	NA	0.31
Median duration of stay in HDU or ICU (IQR) — days‖	1.8 (1.0–3.1)	1.4 (0.9–2.9)	NA	0.13
Median duration of hospital stay (IQR) — days	6.4 (3.6–10.6)	5.6 (3.6–10.5)	NA	0.26
Death — no. (%)‡				
At 90 days	31 (2.1)	18 (1.2)	1.73 (0.97–3.10)	0.06
At 12 mo	95 (6.5)	96 (6.6)	1.03 (0.78–1.36)	0.86

* NA denotes not applicable.
† The hazard ratio or risk ratio is for the restrictive fluid group as compared with the liberal fluid group.
‡ Percentages in this category were estimated with the use of the Kaplan–Meier method. Among the patients who died, 9 in the restrictive fluid group and 12 in the liberal fluid group had persistent disability before death at 12 months. The risks of death at 90 days and at 12 months are listed in the table as predefined secondary outcomes.
§ All the secondary outcomes were assessed up to 30 days after surgery, with the exception of renal-replacement therapy and the duration of mechanical ventilation, which were assessed at 90 days.
¶ The composite septic outcome includes surgical-site infection, anastomotic leak, pneumonia, and sepsis.
‖ The P value was not significant after adjustment for multiple comparisons, with a threshold level of P=0.004 for renal-replacement therapy and P=0.003 for surgical-site infection.
** Values for acute kidney injury are the average number of events across 10 imputations in which fluid balance was imputed after adjustment for serum creatinine values on day 1 and day 3. Details regarding these analyses and sensitivity analyses are provided in the Supplementary Appendix.
†† Data regarding the peak serum lactate level were missing for 1057 patients in the restrictive fluid group and in 1086 in the liberal fluid group; the P value was not calculated.
‡‡ Data regarding the C-reactive protein level were missing for 422 patients in the restrictive fluid group and 420 in the liberal fluid group.
§§ Data regarding mechanical ventilation are for 102 patients in the restrictive fluid group and 100 in the liberal fluid group.
¶¶ Data regarding the quality of recovery on day 3 were missing for 73 patients in the restrictive fluid group and 75 in the liberal fluid group. The scores on this scale range from 0 (extremely poor) to 150 (excellent).
‖ Data regarding the duration of stay in the HDU or ICU data are for 485 patients in the restrictive fluid group and 473 in the liberal fluid group who were admitted at any time postoperatively.

PS Myles et al. N Engl J Med 2018;378:2263-2274

Take-Home Messages

Recent Developments in AKI Prevention Literature.....

- Contrast-induced AKI:
  - Sodium bicarbonate is not better than saline
  - NAC is not better than placebo
- Fluids:
  - Bicarbonate Rx may be benefical in metabolic acidosis
  - Balanced crystalloids may be beneficial in hospitalized patients
  - Perioperative fluid restrictive management may be harmful

Renal Replacement Therapy (RRT)

Indications for RRT: “State of the Art”

- Uraemia
  - Encephalopathy
  - Pericarditis
  - Bleeding diathesis
- Volume Overload
- Hyperkalemia
- Metabolic Acidosis
- Severe hyperphosphatemia
- Intoxications

- Prevention of uremic complications
- Prevention of uncontrolled positive fluid balance
- “Non-renal” indications

RRT Initiation Studies in AKI

Study	Year	Design	# of pts	Early initiation criteria	Late initiation criteria	Recovery of renal function	Survival
Conger [4]	1975	RCT	18	BUN < 70 mg/dl or SCr < 5 mg/dl	BUN ≥ 150 mg/dl or SCr ≥ 10 mg/dl or clinical indication		Early 64% Late 20%
Gillum, et al. [5]	1986	RCT	34	Treatment goal BUN < 60 mg/dl and SCr < 5 mg/dl	Treatment goal BUN < 100 mg/dl and SCr < 9 mg/dl		Early 41% Late 53%
Bouman, et al. [6]	2002	RCT	106	< 12 hrs after meeting definition for AKI requiring RRT	BUN > 112 mg/dl, K > 6.5 mmol/L or severe cardiogenic pulmonary edema		Early High-dose 74.3% Early Low-dose 68.6% Late Low-dose 75%
Gettings, et al. [7]	1999	Retrospective Observational	100	BUN < 60 mg/dl	BUN > 60 mg/dl	Early 100% Late 91.6%	Early 39% Late 20% ***
Demirkilic, et al. [8].	2004	Retrospective Observational	61	Urine output < 100 ml X 8 hours despite diuretic	SCr > 5 mg/dl or K > 5.5 meq/L		Early 76.5% Late 45.5% ***
Elahi, et al. [9]	2004	Retrospective Observational	64	Urine output 100 ml X 8 hours despite diuretic	Urea > 84 mg/dl or SCr > 3.39 mg/dl or K > 6 meq/L		Early 78% Late 57% ****
Wu, et al. [10]	2007	Retrospective Observational	80	BUN < 80 mg/dl	BUN > 80 mg/dl	Early 39.2% Late 12% ***	Early 37% Late 15.4% ***
Liu KD, et al. [11]	2006	Retrospective Observational	243	BUN ≤76mg/dl	BUN > 76 mg/dl		Early 65% Late 59%

Adapted from: Bagshaw S, et el: Crit Care 2016;20:245

RRT Initiation Studies in AKI: Update

Study	Year	Design	# of pts	Early initiation criteria	Late initiation criteria	Recovery of renal function	Mortality
Wald R, et al: STARRT-AKI/Pilot Trial	Kidney International, 2015	RCT, Canada (12 sites)	100	Two of: KDIGO Stage 2 by SCr or UOP, or PNGAL ≥400ng/ml; within 12 hours	Clinical criteria/emergent indications, > 12 hours	Early 100% Late 96%	Early 38% Late 37%
Zarbock A, et al: ELAIN Trial	JAMA, 2016	RCT, Germany (Single site)	231	KDIGO Stage 2 (within 8 hours)	KDIGO Stage 3 (within 12 hours)	Early 86.6% Late 84.9%	Early 39.3% Late 54.7%
Gaudry S, et al: AKIKI Trial	NEJM, 2016	RCT, France (31 sites)	620	KDIGO Stage 3 (within 6 hours)	Clinical criteria/emergent indications	Early 98% Late 95%	Early 48.5% Late 49.7%
Barbar SD, et al: IDEAL-ICU Trial	Trial in Progress	RCT, France (24 sites)	864	KDIGO Stage 3 (within 12 hours)	Clinical criteria (48-60 hours after eligibility, or emergent)	N/A	N/A
Wald R, et al: STARRT-AKI/Main Trial	Trial in Progress	RCT, International (>60 sites)	2866	KDIGO Stage 2 (within 12 hours)	Clinical criteria/emergent indications (>12 hours)	N/A	N/A

Adapted from: Bagshaw S, et el: Crit Care 2016;20:245

ELAIN: Key eligibility criteria

- KDIGO ***Stage 2*** AKI
- Plasma NGAL > 150 ng/mL
- One of the following:
  - Sepsis
  - Vasopressors
  - Refractory fluid overload

Zarbock et al JAMA. 2016 May 24-31;315(20):2190-9

ELAIN Interventions

Early RRT

Start RRT within 8 hours of AKI criteria being met

Delayed RRT

Start RRT when KDIGO Stage 3 is reached or in the presence of a classic indication

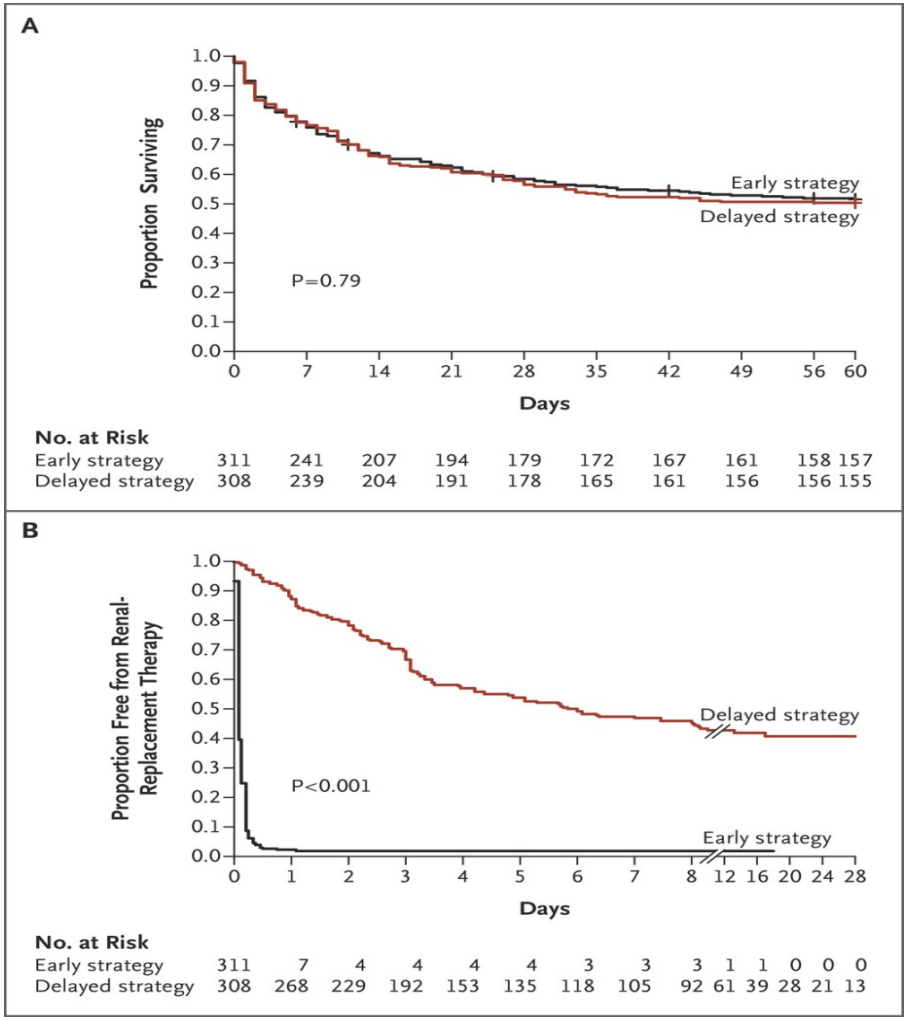
Zarbock et al JAMA. 2016 May 24-31;315(20):2190-9

Artificial Kidney Initiation in Acute Kidney Injury (AKIKI) Trial

- within 5 hours of meeting KDIGO Stage 3
- ATN as the sources of AKI
- On pressors or ventilator
- excluded if
  - [BUN] > 112 mg/dL
  - [K+] > 6 mmol/L
  - pH < 7.15
  - acute pulmonary edema → hypoxemia

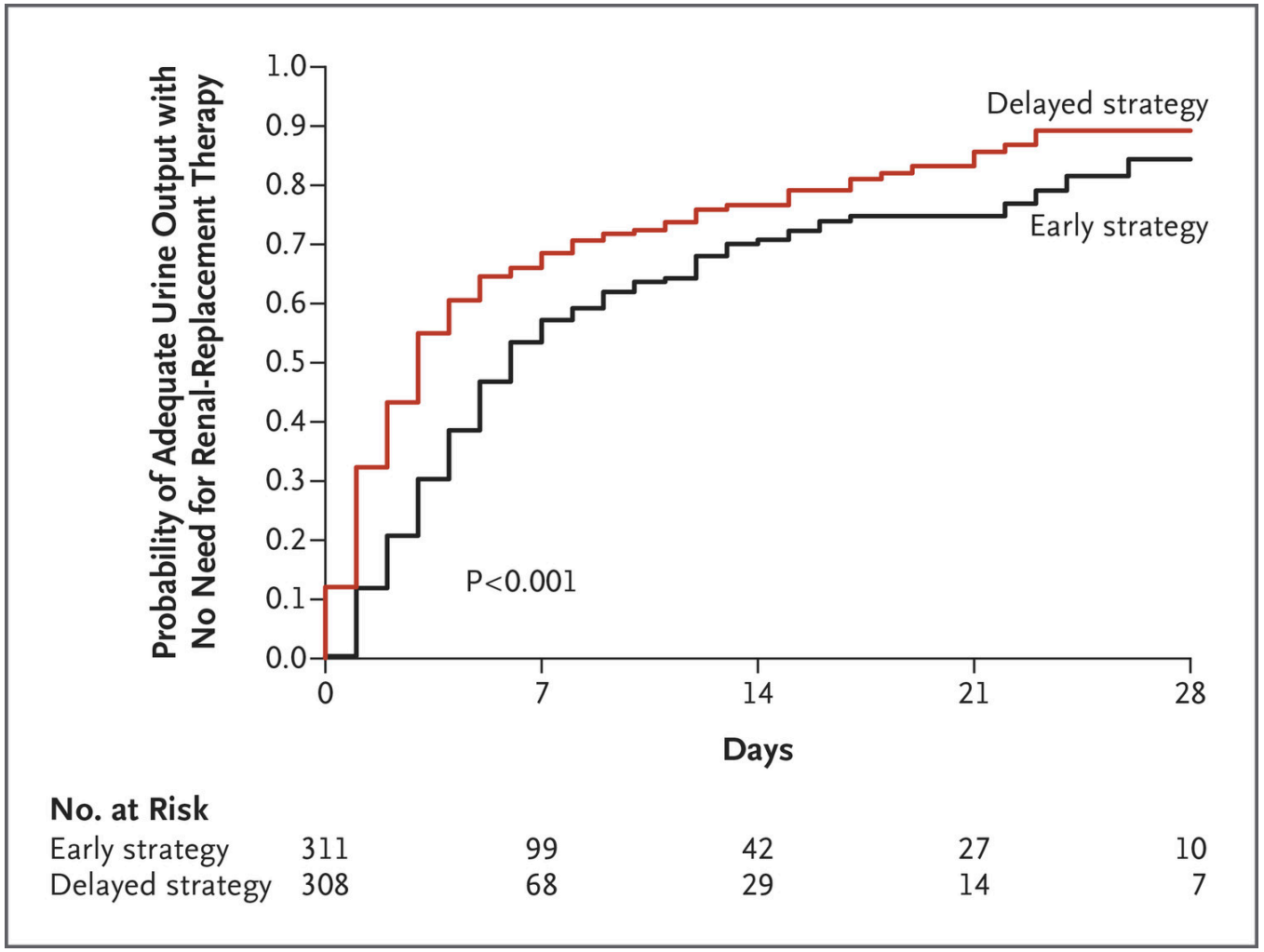
Gaudry S et al. N Engl J Med 2016;375:122-133.

AKIKI: Probability of Survival and Timing of RRT



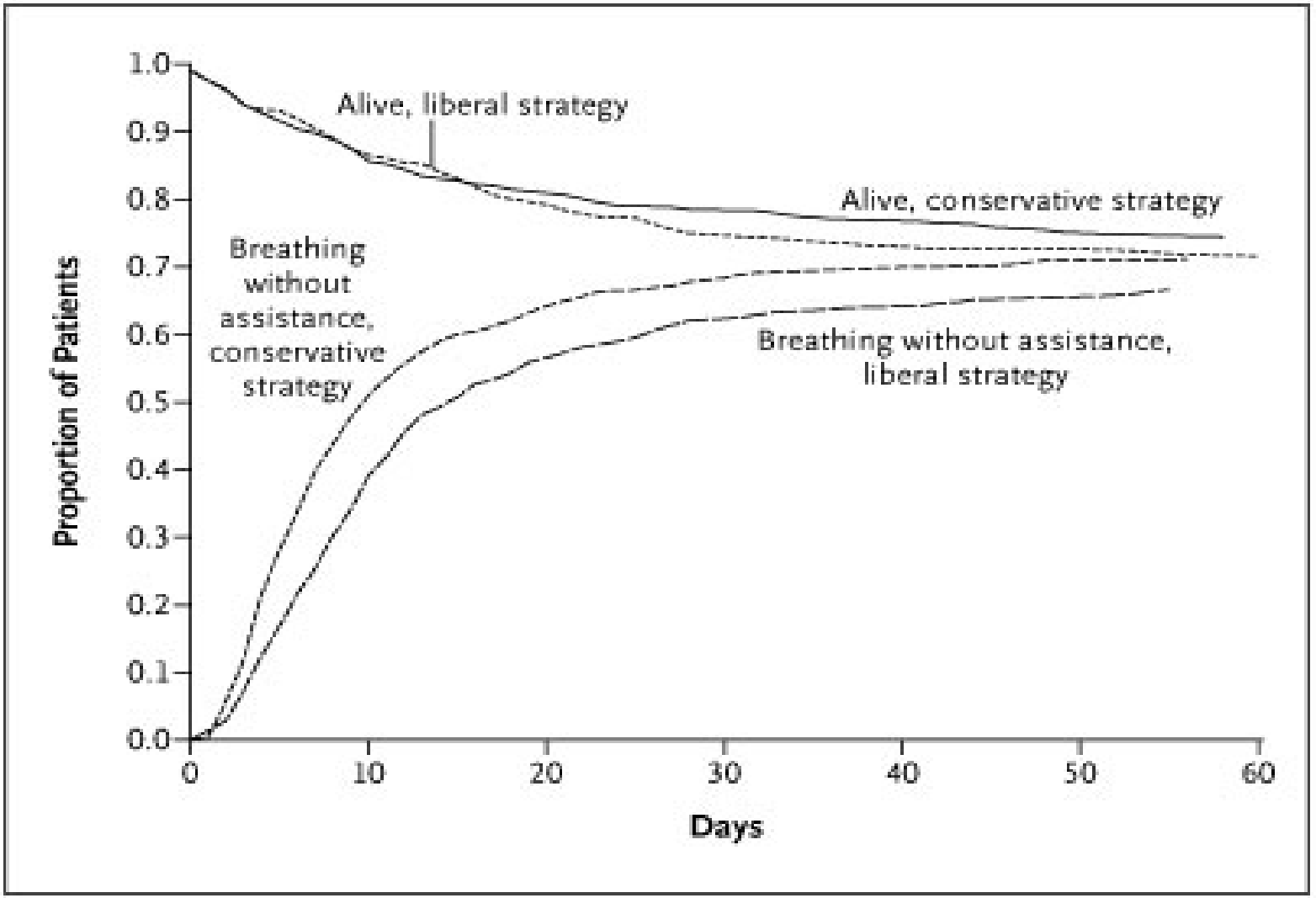
Gaudry S et al. N Engl J Med 2016;375:122-133.

AKIKI: Probability of Adequate Urine Output without Need for RRT



Gaudry S et al. N Engl J Med 2016;375:122-133.

FACTT Trial: Fluid Management in ARDS- Outcomes



NHLBI ARDS Clinical Trials Network NEJM 2006;354:2564-2575

Fluid Balance Control in AKI with AHRF

- **Diuretics (FACTT AKI Subset)**:
  - Grams ME, CJASN 2011;6:966-973
- 306/1,000 w AKI in 2 days
  - 137 in fluid liberal (+10.2L), 169 in fluid conservative (+3.7L)
    - Independently predictive of 60-d mortality: adjOR 1.61/L/d (1.29-2), p<0.001
    - Assoc. w cumulative 7-d furosemide doses 159mg vs. 562mg
    - OR 0.48/100mg/d (0.28-0.81), p=0.007; NS adjusted for fluid balance
- **RRT (AKIKI Trial- early vs late RRT in AKI)**:
  - Gaudry S, et al: NEJM 2016;375:122-133
  - No difference in ventilator-free days or survival (including ARDS subsets- 34% both arms); better UOP in late group

The STandard vs Accelerated initiation of Renal Replacement Therapy in AKI Trial **STARRT-AKI**

- Randomized, open-label trial of accelerated vs standard initiation of RRT in critically ill patients with AKI
- 2,866 patients with KDIGO Stage 2-3
- 135 centres in Canada, USA, Australia, New Zealand, China, Brazil, UK, Ireland, Belgium, France, Germany, Italy, Austria, Switzerland and Finland
- ClinicalTrials.gov Identifier: NCT02568722

Furosemide Stress Test (FST) Predicts AKI Severity

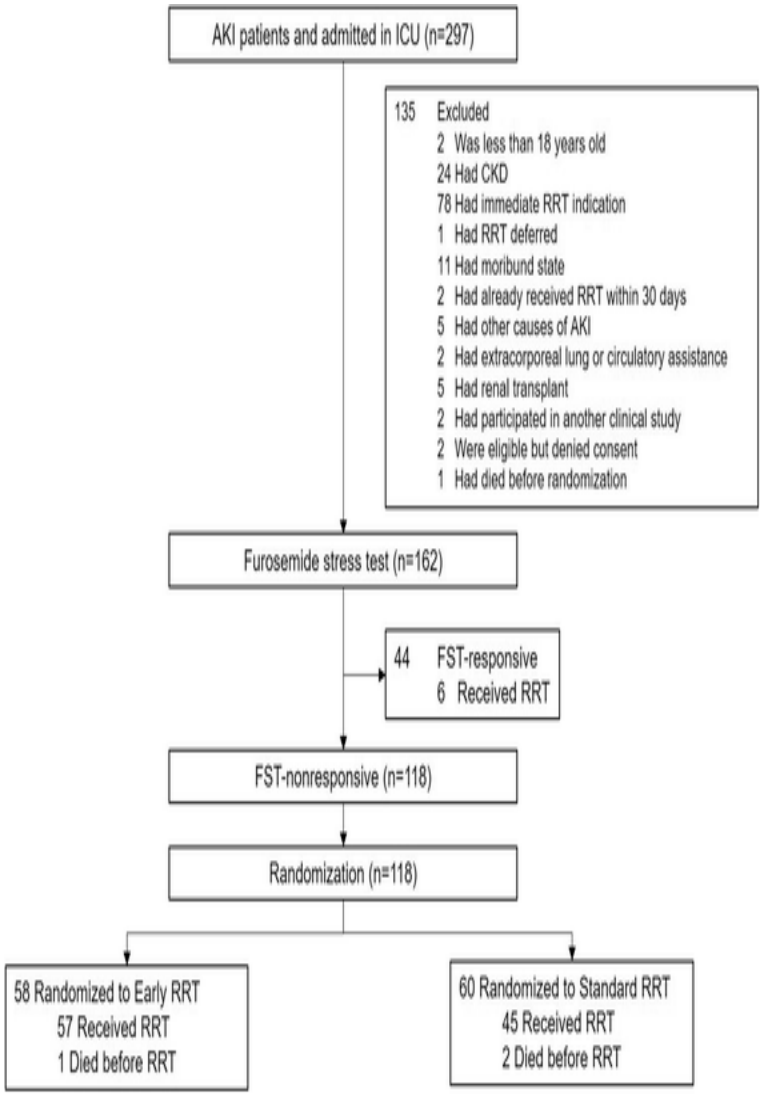
2-hour UOP following Furosemide 1-1.5mg/kg: Progression to AKIN Stage 3 (n=77)

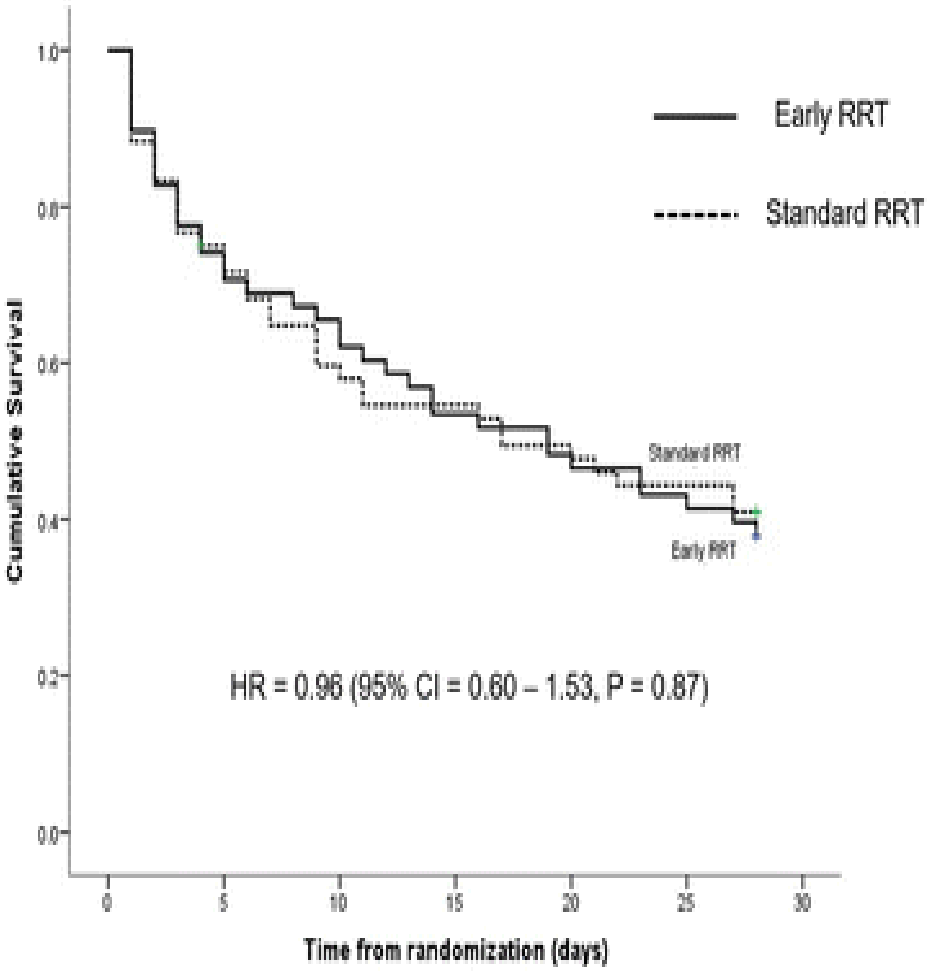
Total Urine Output over 2 hours		Sensitivity		Specificity
< 100 ml		90.2%		60.0%
< 200 ml		87.1%		84.1%
< 300 ml		85.3%		88.0%
< 400 ml		66.7%		88.0%
< 500 ml		50.5%		88.0%

AUC 0.87

Chawla LS, et al: Crit Care 2013;17(5):R207

FST & RRT Initiation





Lumlertgul F, et al: Crit Care 2018;22(1):101

Take-Home Messages

Unlike Dose and Modality guidelines, RRT initiation criteria in AKI are not yet evidence-based.....

- Results of early vs. late initiation RCTs are conflicting
- Additional secondary analyses and prospective RCTs are ongoing
- FST may help correctly triage those requiring early RRT

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