The KDIGO AKI Guidelines: from 2011-2019

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Guangzhou, november 22, 2019

Topics of 2012 AKI guidelines and recommendations

- Section 2: AKI Definition, Staging and Risk Assessment
- Section 3: Prevention and Treatment of AKI
- Section 4: Contrast-induced AKI
- Section 5: Dialysis Interventions for Treatment of AKI

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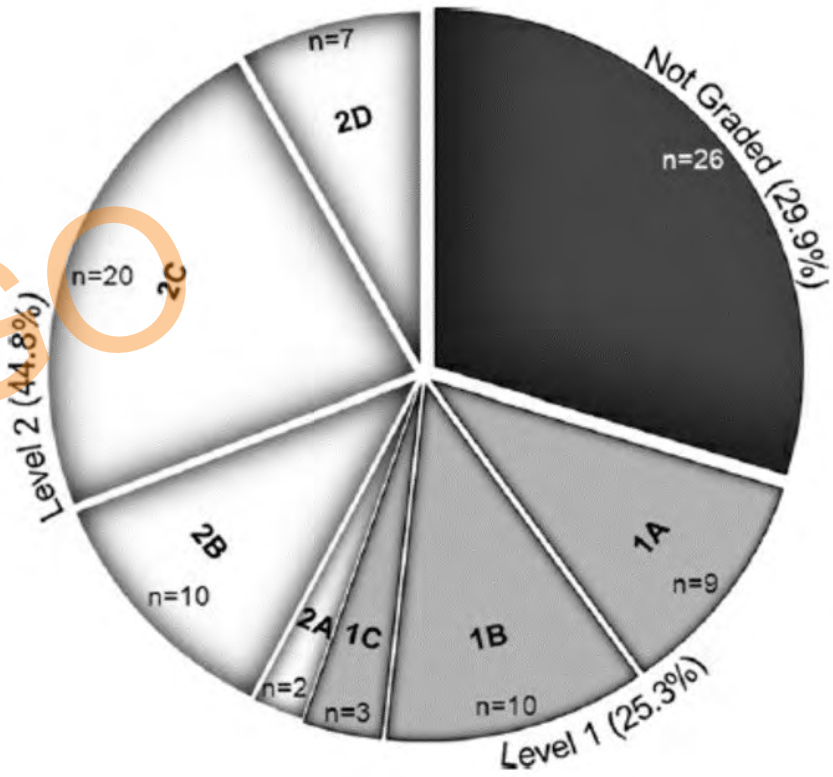
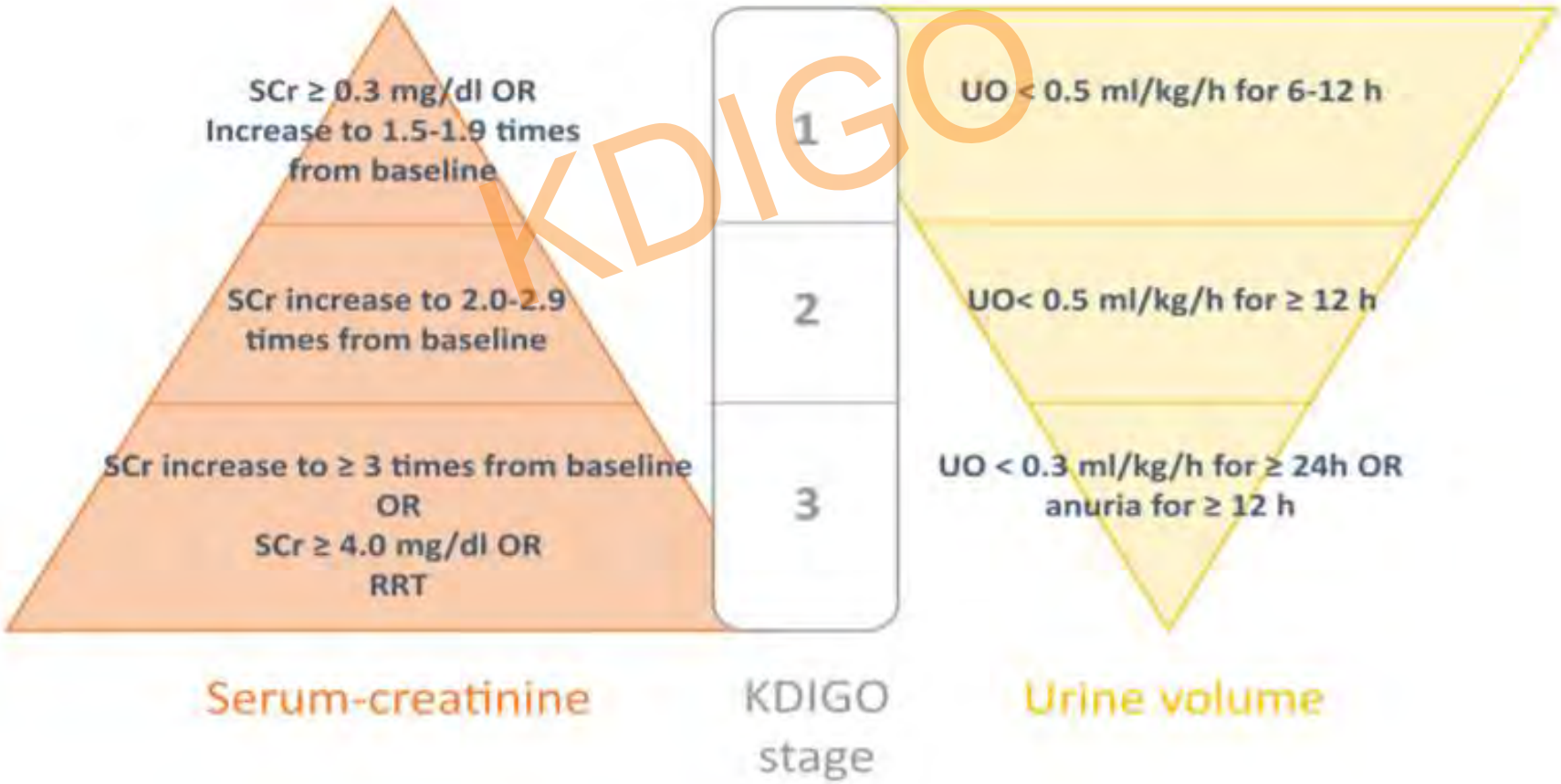


87 recommendations
22 of level 1: “we recommend”
39 of level 2: “we suggest”

KDIGO definition and classification of AKI

Diagnostic criteria for AKI:

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



Limitations of the KDIGO definitions and staging of AKI

- Many etiologies cause AKI
  - Criteria do not distinguish between the multiple etiologies that cause AKI
  - Should management be individualized on a better phenotyping of AKI by etiology, severity of injury, and ability to recover?
- Use of urine output as a sole criterium of AKI
- Problems with SCr kinetics reflecting GFR
- Determination of baseline serum creatinine
  - Should the first documented SCr at hospitalization be used as the baseline, rather than using historical values?
  - relying on small changes in SCr for the diagnosis of AKI may be associated with a high rate of misdiagnosis, especially in patients with a baseline SCr ≥1.5 mg/dL

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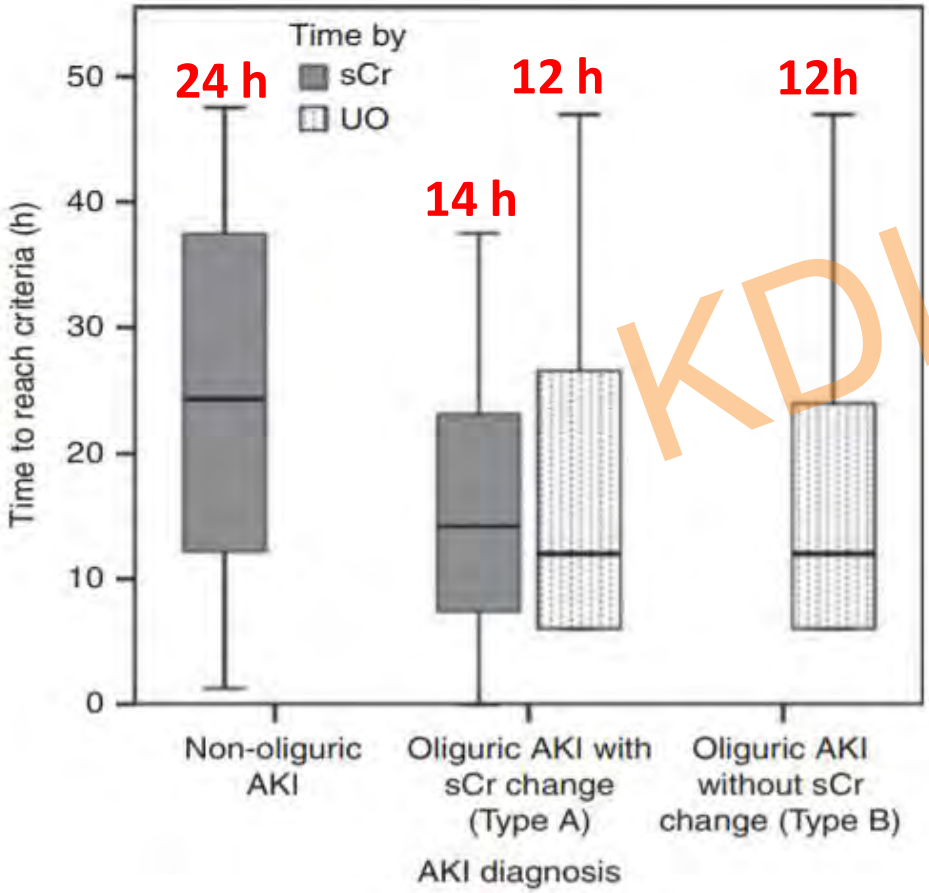
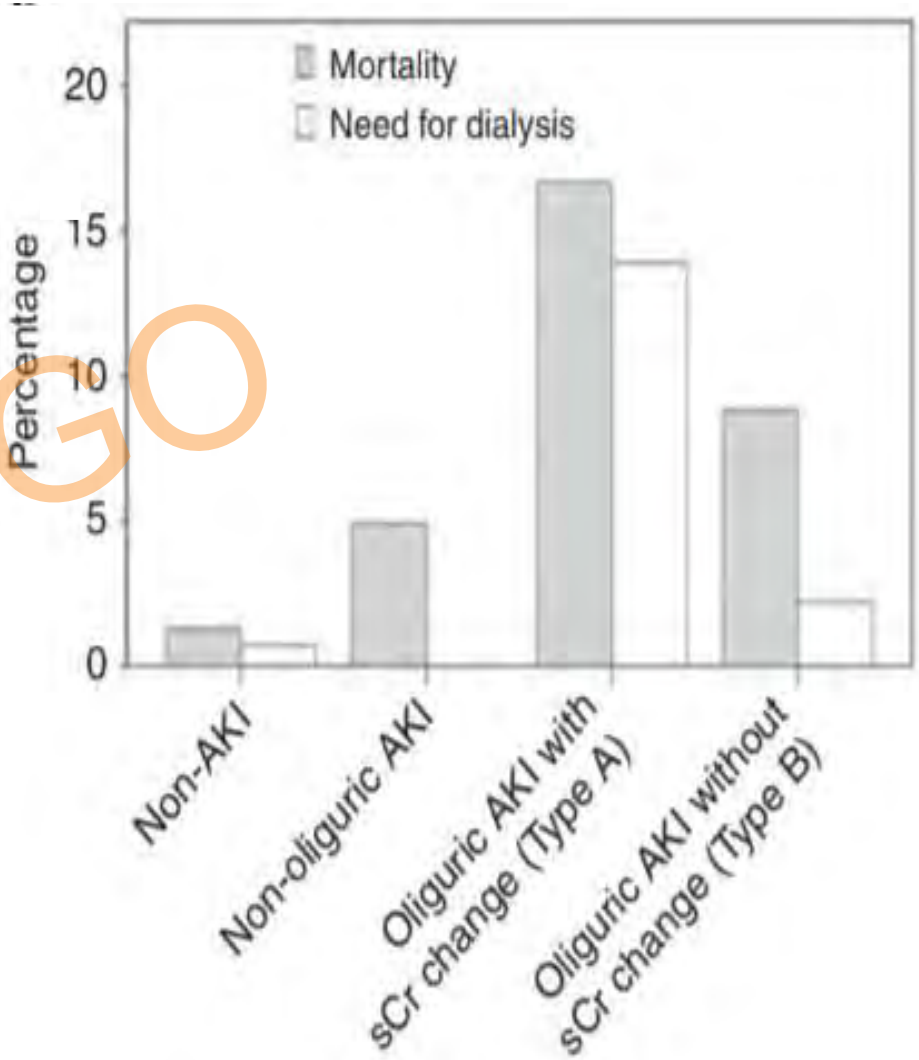
Time to reach AKI diagnosis by sCr and UO criteria in non-oliguric, and oliguric AKI with sCr and without sCr change oliguric patients



Clinical ICU outcomes by AKI diagnosis criteria



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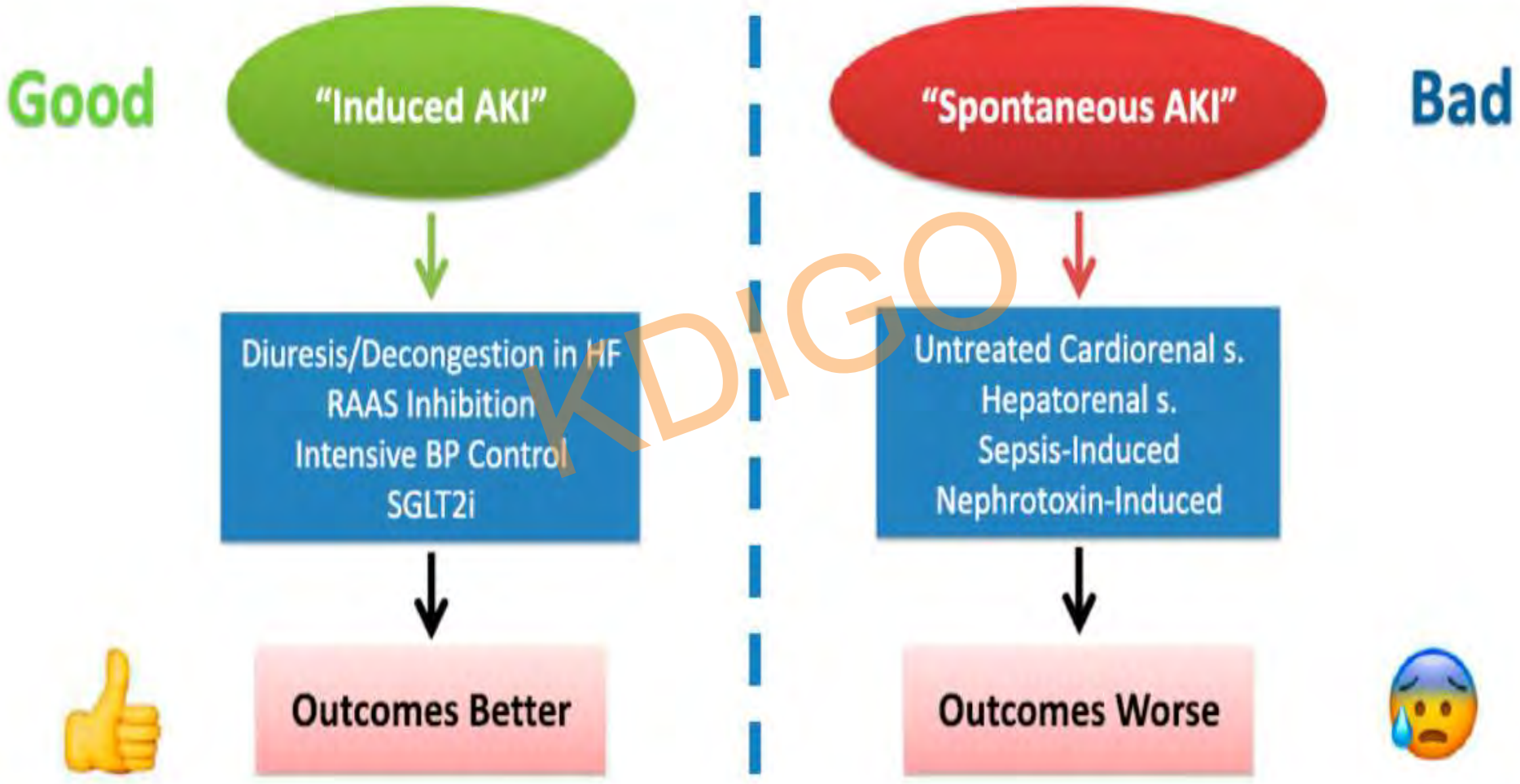
Macedo et al, Kidney International (2011) 80, 760–767

Acute elevations of serum creatinine: Implications are context-dependent



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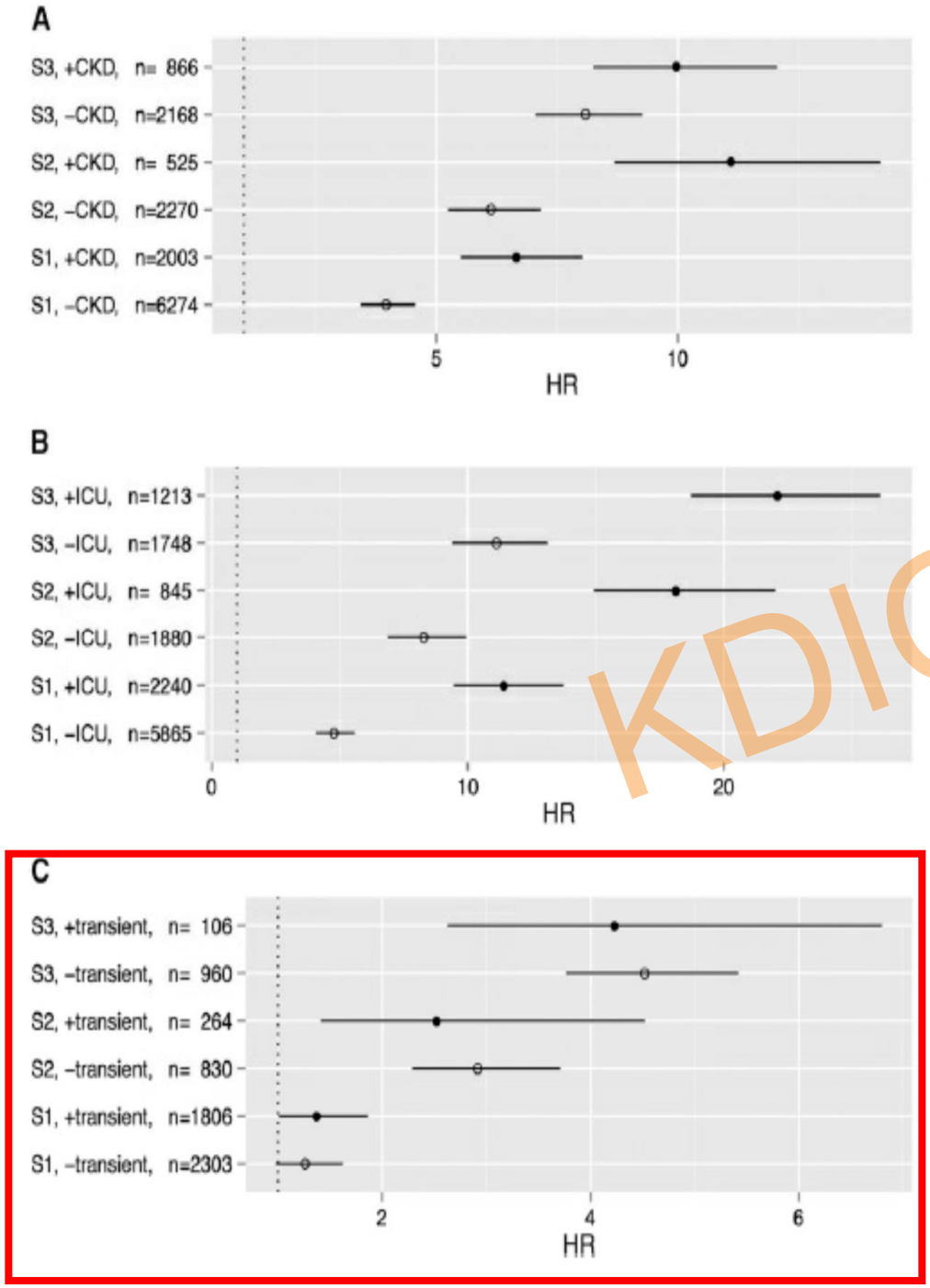
Coca S. Nephrology Self-Assessment Program - Vol 18, 49-53, 2019

Incidence of AKI in various clinical settings

9 medical centers South China



Overall incidence AKI 11,6%

CA: 2,5%

HA: 9,1%

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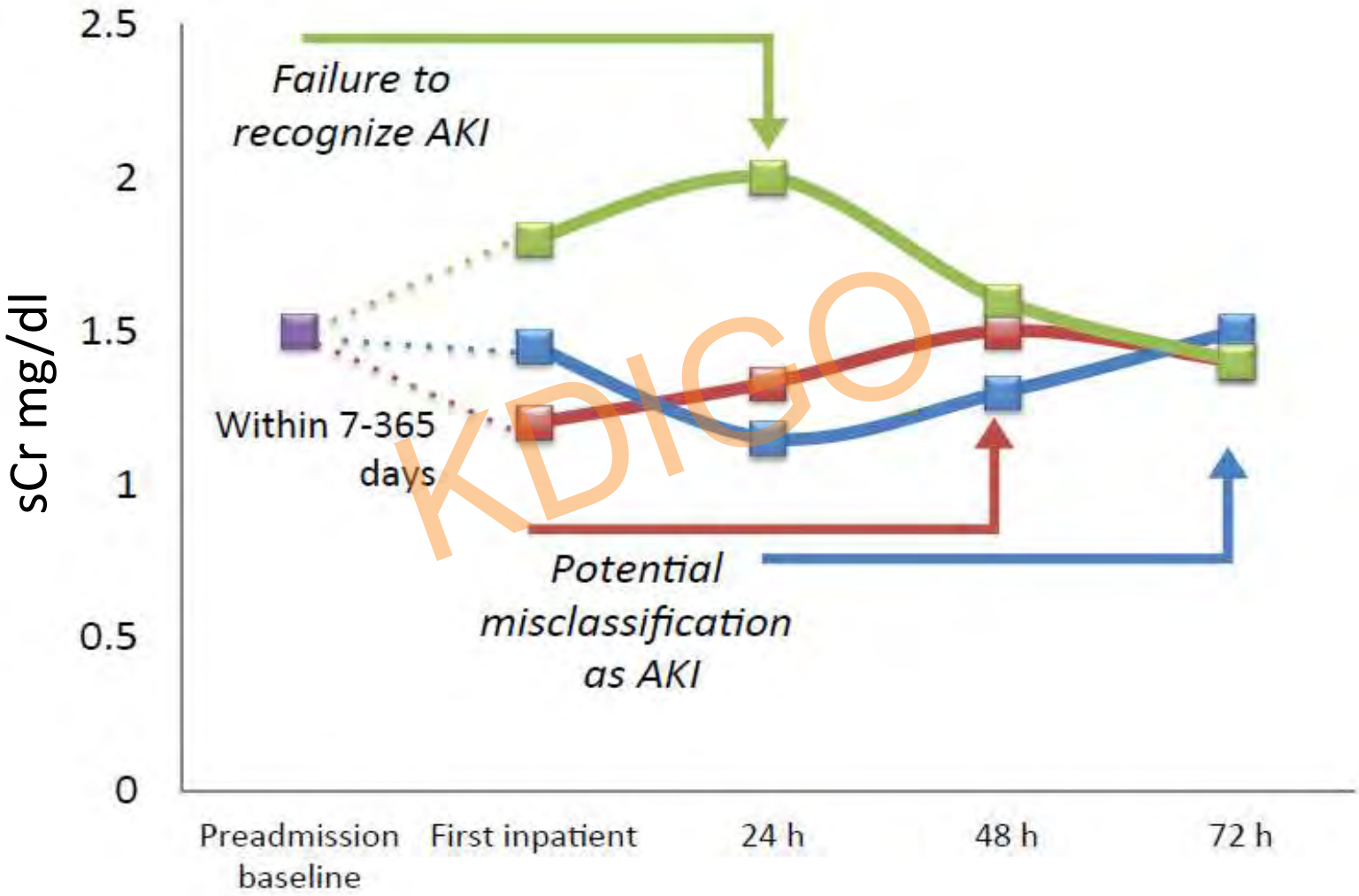
HR of in-hospital death among patients at different stages of AKI in

- **A: preexisting CKD**
- **B: ICU vs non ICU**
- **C: duration of AKI**

"Transient": AKI recovery within 3 days

XU X et al, Clin J Am Soc Nephrol 10: 1510–1518, 2015

Potential SCr trajectories and AKI misclassification



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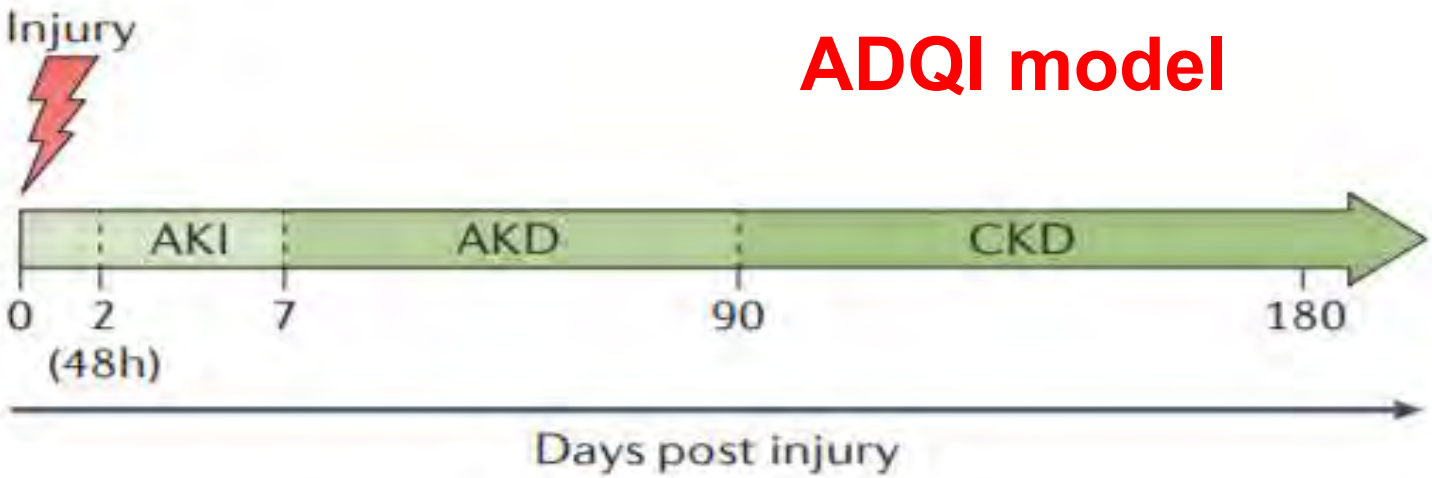
KD Liu et al, Kidney International Reports (2018) 3, 205–215

The conceptual overlap among AKI, AKD and CKD (KDIGO AKI guideline 2012)

ADQI model



Criteria for KDIGO Definitions of Kidney Diseases and Disorders

Criteria	AKI	AKD	CKD	NKD*
Duration	Within 7 days	≤3 months	>3 months	
Function Alteration	Oliguria for ≥6 hours, or Increase in Scr by ≥0.3 mg/dl in 48 hours, or Increase in Scr by ≥50% in 7 days	AKI, or GFR <60 ml/min/1.73 m^2, or Decrease in GFR by ≥35%, OR Increase in Scr by ≥50%	GFR <60 ml/min/1.73 m^2	GFR ≥60 ml/min/1.73 m^2, and Stable Scr
Structural Alteration	Not defined	Marker of kidney damage (albuminuria)	Marker of kidney damage (albuminuria)	No marker of kidney damage

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James et al, JAMA Netw Open. **2019** Apr 5;2(4):e191795

Incidence and Hazard ratio's for mortality of kidney diseases in Alberta residents, Canada

Outcome	Events, No. (%)	Total Follow-up, y	Hazard Ratio[a] (95% CI)		
			Crude[a]	Age- and Sex-Adjusted[a]	Multivariable-Adjusted[a,b]
Mortality (n = 1 109 099)					
NKD	67 655 (7.3)	7 029 114	1 [Reference]	1 [Reference]	1 [Reference]
CKD with AKD without AKI	2977 (47.2)	37 000	8.33 (8.03-8.65)	1.49 (1.46-1.52)	1.92 (1.85-2.00)
CKD with AKI	3585 (71.5)	19 574	18.75 (18.13-19.39)	4.47 (4.36-4.57)	3.30 (3.19-3.41)
AKD without AKI	10 940 (25.8)	291 157	3.90 (3.82-3.98)	2.08 (2.00-2.15)	1.42 (1.39-1.45)
AKI	7964 (50.5)	80 864	10.15 (9.91-10.39)	4.20 (4.06-4.34)	3.23 (3.16-3.31)
CKD	34 816 (29.4)	804 081	4.50 (4.44-4.55)	1.42 (1.4-1.44)	1.37 (1.35-1.39)

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Incidence

AKD without AKI: 3,8/100 adults tested

AKI: 1,4/ 100 adults tested

CKD: 10,6/100 adults tested

James et al, JAMA Netw Open. **2019** Apr 5;2(4):e1

New Tools for Risk Assessment

RISK ASSESSMENT TOOLS SINCE 2012:

- RENAL ANGINA INDEX
- RENAL FUNCTIONAL RESERVE ASSESSMENT
- NEW BIOMARKERS **-NGAL, (lipocalin-2) ,**
  -G1- Cell cycle arrest proteins
  (TIMP-2*IGFBP7)

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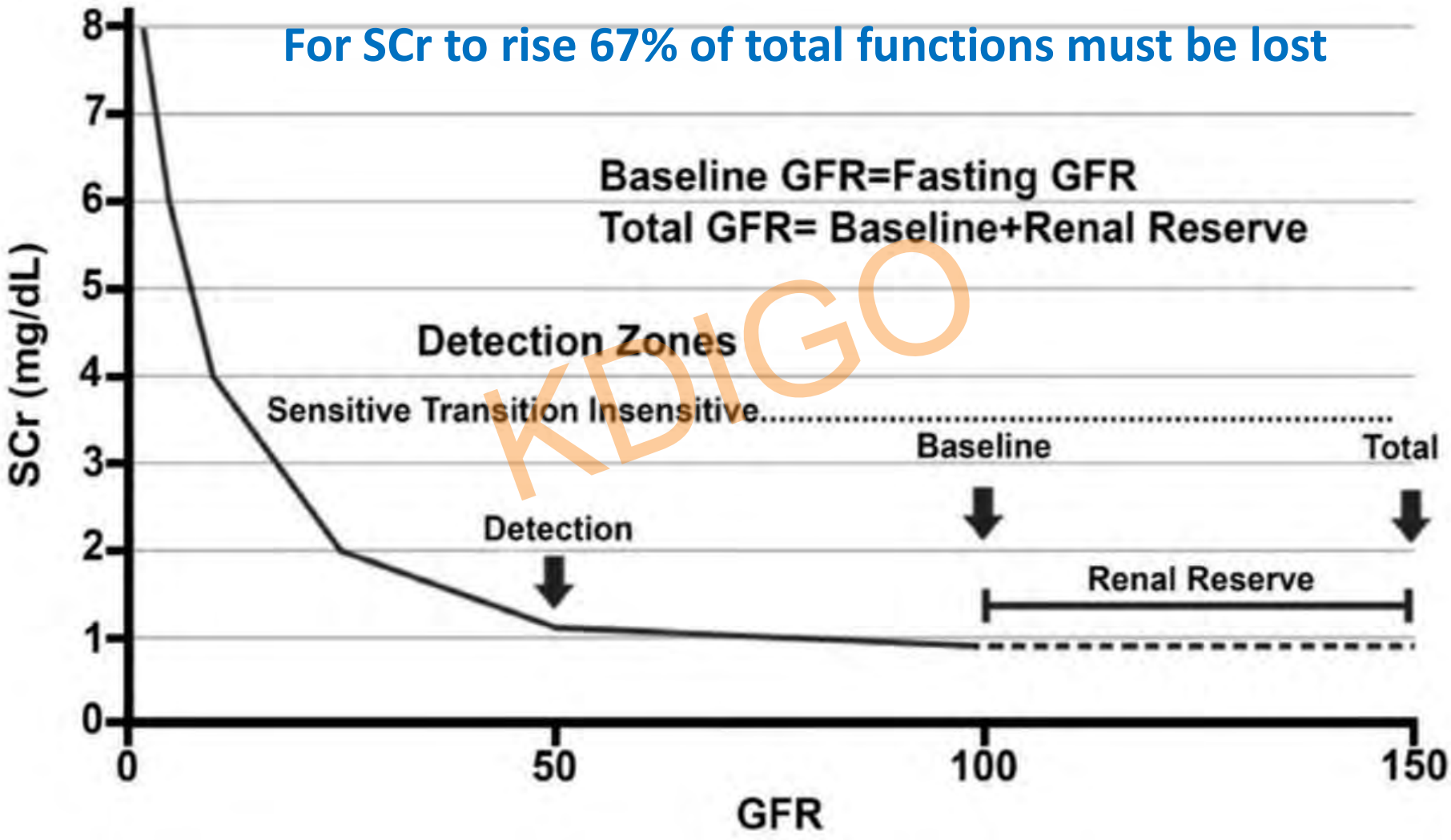
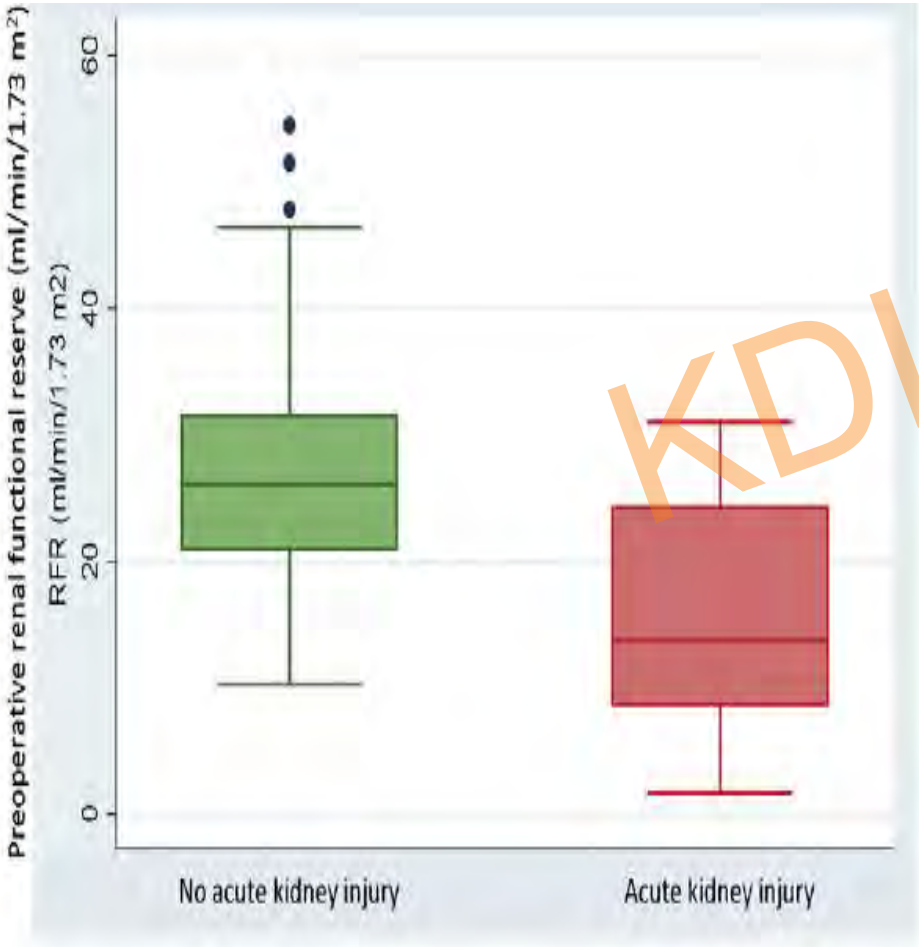
Neutrophil gelatinase-associated lipocalin
Tissue inhibitor of metalloproteinases-2- insulin-like growth factor binding protein 7

Idealized GFR vs SCr showing renal reserve in a patient with normal kidney function

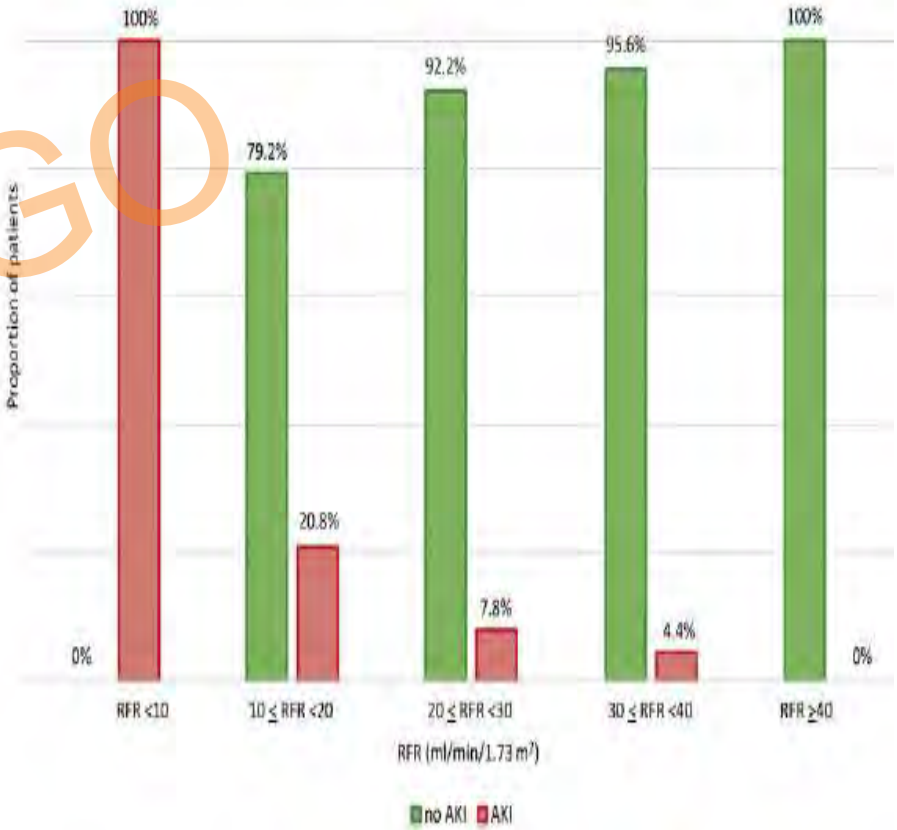


Molitoris BA, Semin Nephrol. 2016, 36(1): 31–41

Preoperative Renal Functional Reserve Predicts Risk of AKI Post Cardiac Surgery



Patiens with preoperative RFR ≤15ml/min/1.73m² were 11.8 times more likely to develop AKI



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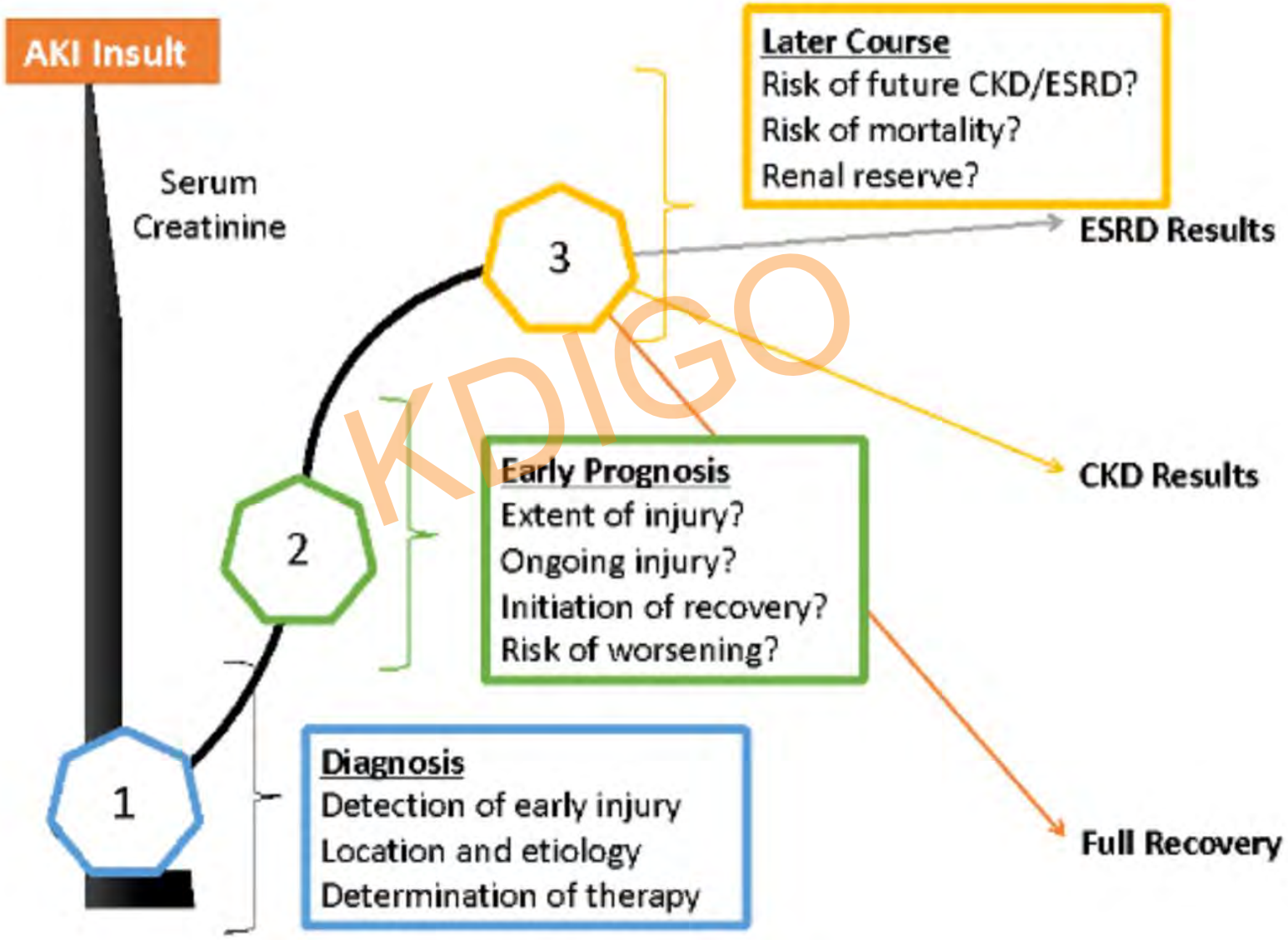
Husain-Syed F et al, Ann Thorac Surg 2018;105:1094–101

Roles of novel biomarkers



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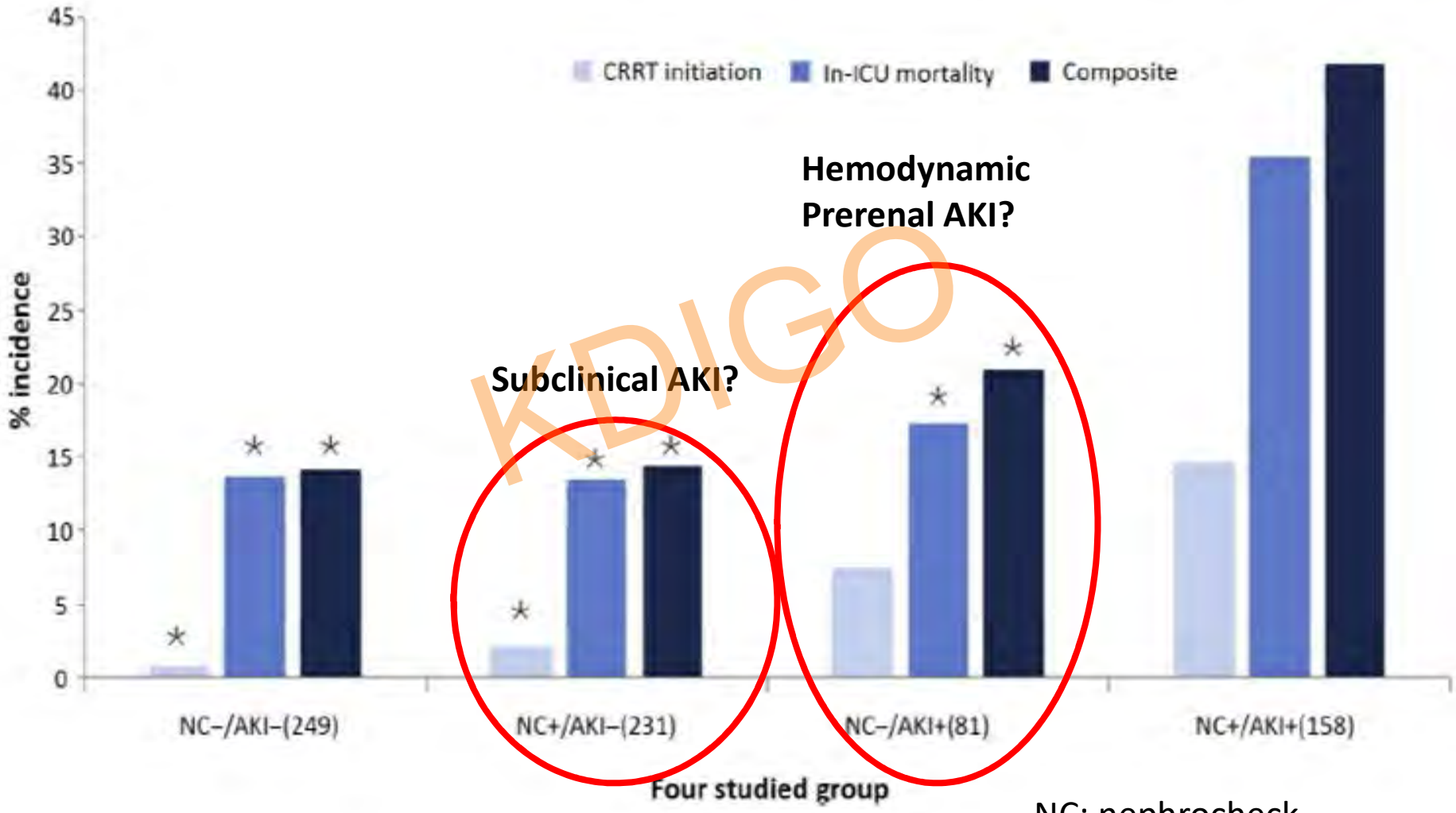
Cell cycle inhibitor marker (TIMP-2)x(IGFBP7) levels are associated with adverse outcomes in ICU with AKI

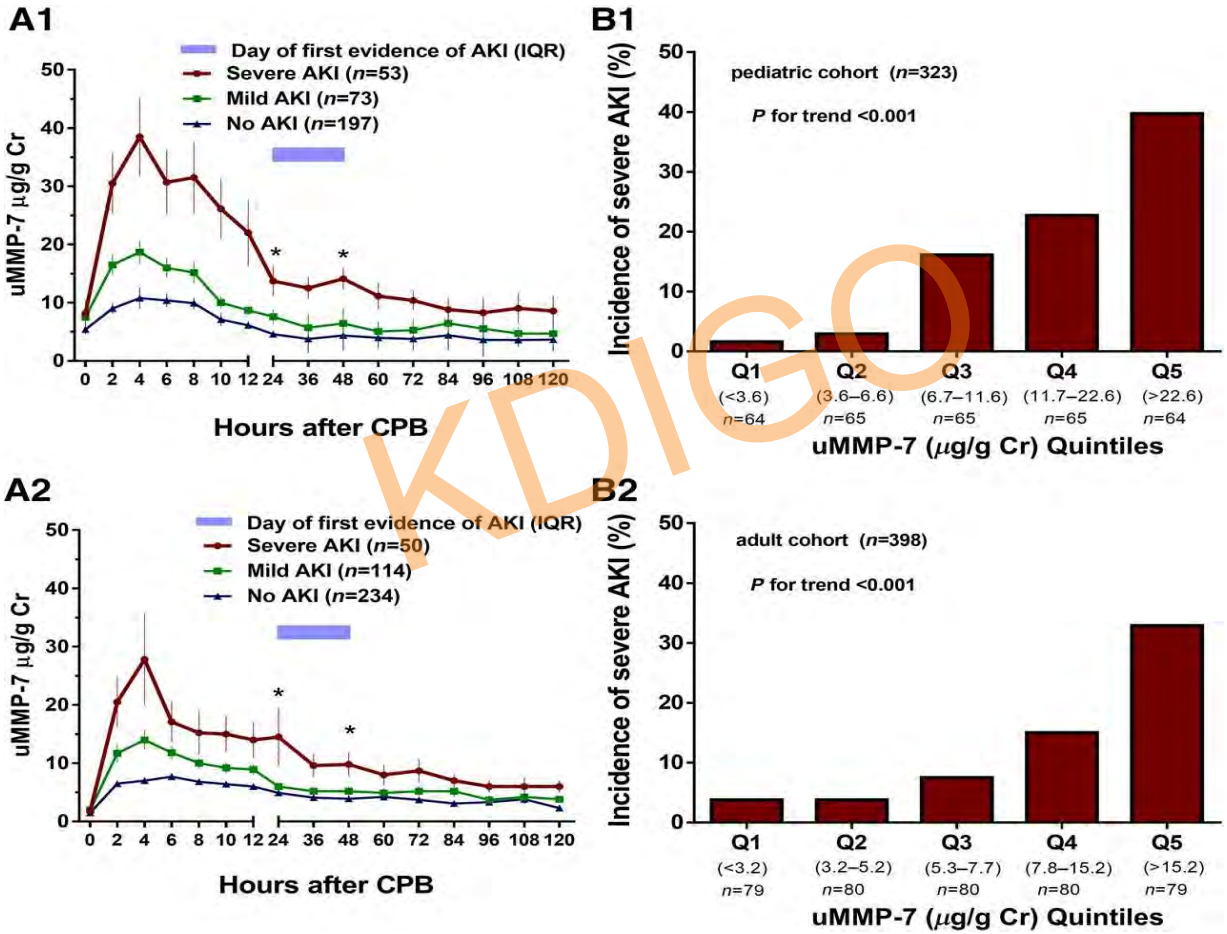


NC: nephrocheck

Xie Y et al , Kidney Int (2019) 95, 1486–1493

Urinary Matrix Metalloproteinase-7 Predicts Severe AKI and Poor Outcomes after Cardiac Surgery

uMMP-7 level peaked within 6 hours after surgery (A) and quintiles of uMMP-7 levels within the first 6 hours had a graded relationship with the incidence of severe AKI (B).



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Urinary matrix metalloproteinase-7 (uMMP-7) levels reflect the activity of intrarenal Wnt/b-catenin

Xiaobing Yang et al. JASN 2017;28:3373-3382

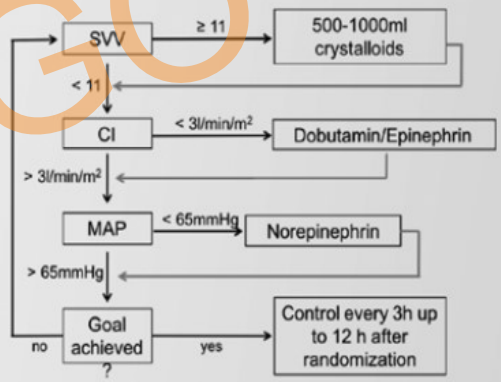
Preventive strategy performed in high risk on pump cardiac surgery patients-single center trial

High-risk

- Elevation of renal stress markers (biomarkers) **[TIMP-2]*[IGFBP7] ≥ 0.3 4h after CPB**

Intervention
(according to the KDIGO recommendation)

- Discontinuation of nephrotoxic agents (ACEi/ARBs for 48 hours)
- Optimization of volume status and perfusion pressure (according to the following algorithm for 12 hours)



- Consideration of functional hemodynamic monitoring (e.g. PICCO monitoring)
- Close monitoring of sCr and UO
- Avoidance of hyperglycemia (for 72 hours)
- Consideration of alternatives to contrast agents

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Application of the "KDIGO care bundle" **reduced overall AKI at 72 h from 71% to 55.1% and the rates of moderate-to-severe AKI from 44.9% to 29.7%.**

Meersch et al, Int Care Med 2017, 43:1551–1561

Limitations of SCr-based AKI definition

		Structural Kidney Injury	
		No Damage	Damage
SCr-based AKI	No	A No kidney injury	B "Subclinical AKI"
	Yes	C "Hemodynamic AKI"	D Clinical ATI

Pre-renal Azotemia

Hepatorenal Syndrome

Cardiorenal Syndrome

RAAS Inhibition

Renal Reserve

SCr Kinetics

Decreased Production

Lack on information on AKI Phenotypes

- Etiology
- Molecular Pathways
- Therapy
- Prognosis

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Moledina, Parikh, Semin Nephrol 38:3-11, 2017

Hemodynamic management

- 3.1.2: We recommend the use of vasopressors in conjunction with fluids in patients with vasomotor shock with, or at risk for AKI.

Recommendation:

To prevent AKI:

- target MAP range of 65–90mmHg
  (depending on age, chronic blood pressure, or other comorbidities)

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High versus Low Blood-Pressure Target in Patients with Septic Shock

Asfar et al, 2014

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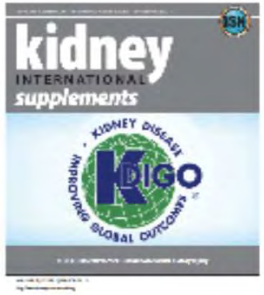
Conclusions

- **Targeting a mean arterial pressure of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days.**
- **Sub group analysis: in patients with chronic hypertension (n:340) significantly less RRT in high pressure target group (31,7 vs 42,2 %) p =0,046; but no direct relationship between AKI and mortality.**

Type of Vasopressor



It is not known which vasopressor agent is most effective for prevention or treatment of patients with AKI and septic shock. Most studies have focused on norepinephrine, dopamine, or vasopressin.

Angiotensin II for Vasodilatory Shock, resistant to high doses of vasopressors-ATHOS-3

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Table 2. Primary and Secondary End Points.*

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

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

Fluid Therapy: Unanswered Questions

When should fluids be given?

How should they be given?

What are the therapeutic targets?

How should fluid therapy be monitored?

What are the indications for fluid removal?

How should fluid removal be monitored?

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Role of Hemodynamic Optimisation

A Randomized Trial of Protocol-Based Care for Early Septic Shock- The ProCESS Investigators-The Univ of Pittsburg

Outcome	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual Care (N=456)	P Value†
Death — no./total no. (%)				
In-hospital death by 60 days: primary outcome	92/439 (21.0)	81/446 (18.2)	86/456 (18.9)	0.83‡
Death by 90 days	129/405 (31.9)	128/415 (30.8)	139/412 (33.7)	0.66
New organ failure in the first week — no./total no. (%)				
Cardiovascular	269/439 (61.3)	284/446 (63.7)	256/456 (56.1)	0.06
Respiratory	165/434 (38.0)	161/441 (36.5)	146/451 (32.4)	0.19
Renal	12/382 (3.1)	24/399 (6.0)	11/397 (2.8)	0.04
Duration of organ support — days§				
Cardiovascular	2.6±1.6	2.4±1.5	2.5±1.6	0.52
Respiratory	6.4±8.4	7.7±10.4	6.9±8.2	0.41
Renal	7.1±10.8	8.5±12	8.8±13.7	0.92

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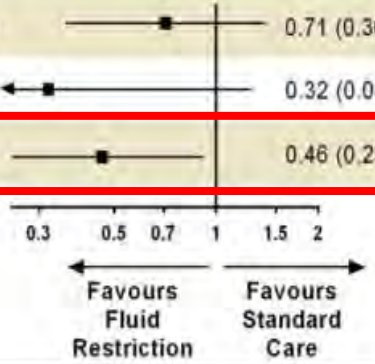
N Engl J Med 2014;370:1683-93.

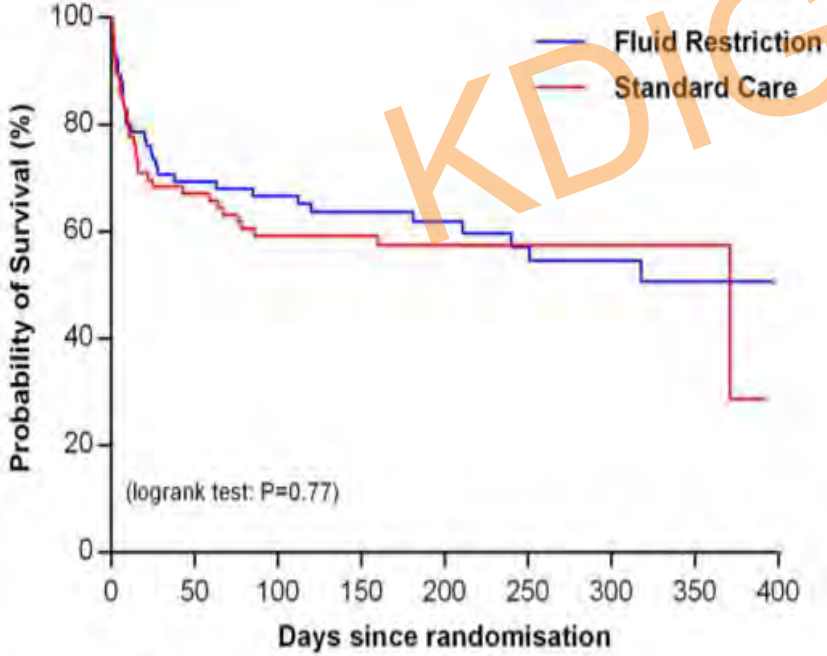
Restricting resuscitation fluid in septic shock (CLASSIC trial)

a Odds ratios of exploratory outcomes

	Fluid Restriction	Standard Care	Odds ratio (95% CI)	P value
	No. of events / No. at risk			
Death by day 90	25/75 (33%)	31/76 (41%)	0.71 (0.36-1.40)	0.32
Ischemic events in the ICU	3/75 (4%)	9/76 (12%)	0.32 (0.08-1.27)	0.11
Worsening of AKI	27/73 (37%)	39/72 (54%)	0.46 (0.23-0.92)	0.03



b Time to death



No. at risk				
Fluid Restriction	75	47	32	15
Standard Care	76	42	24	11

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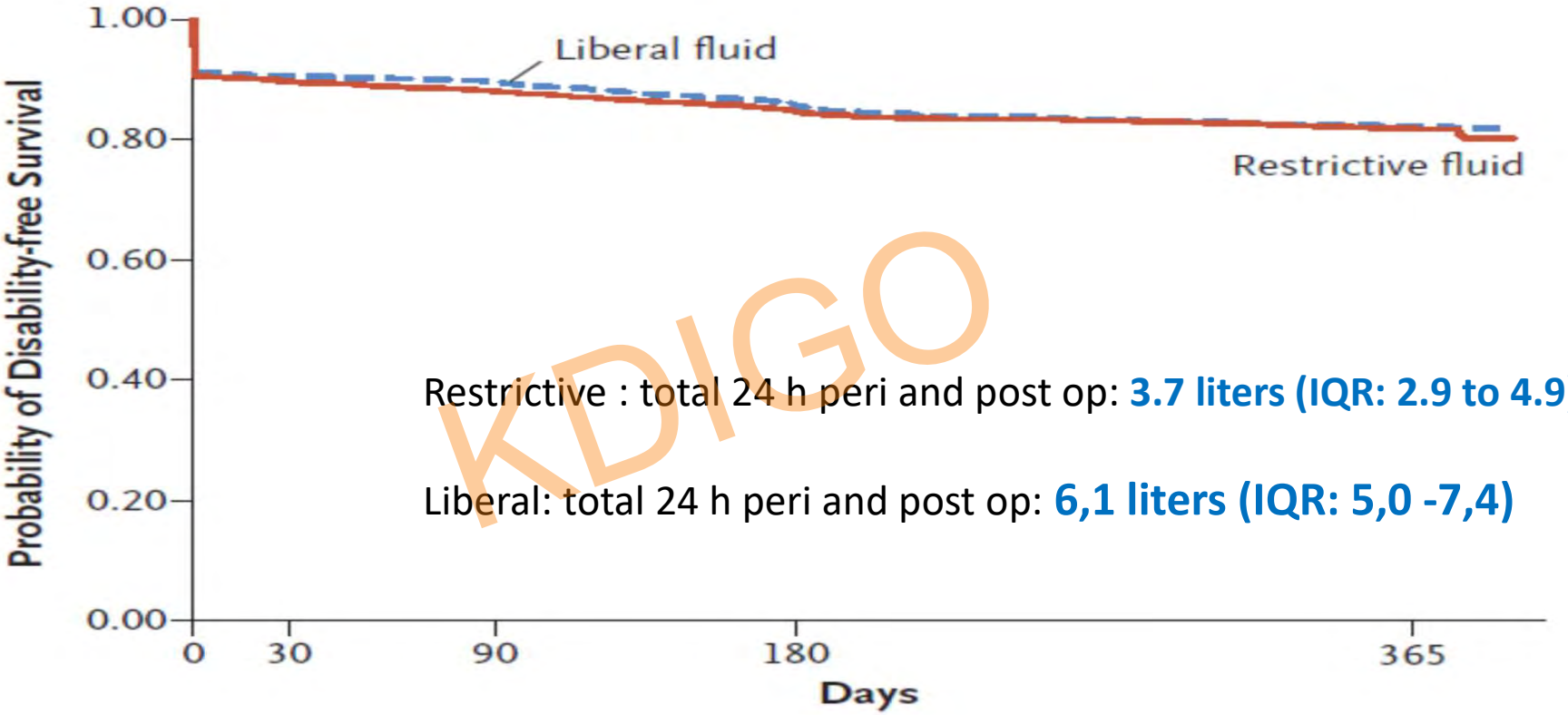
Hjortrup et al Intensive Care Med (2016) 42:1695–1705

Restrictive (n:1490) vs liberal fluid (n:1493) administration during major abdominal surgery



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Restrictive : total 24 h peri and post op: **3.7 liters (IQR: 2.9 to 4.9)**

Liberal: total 24 h peri and post op: **6,1 liters (IQR: 5,0 -7,4)**

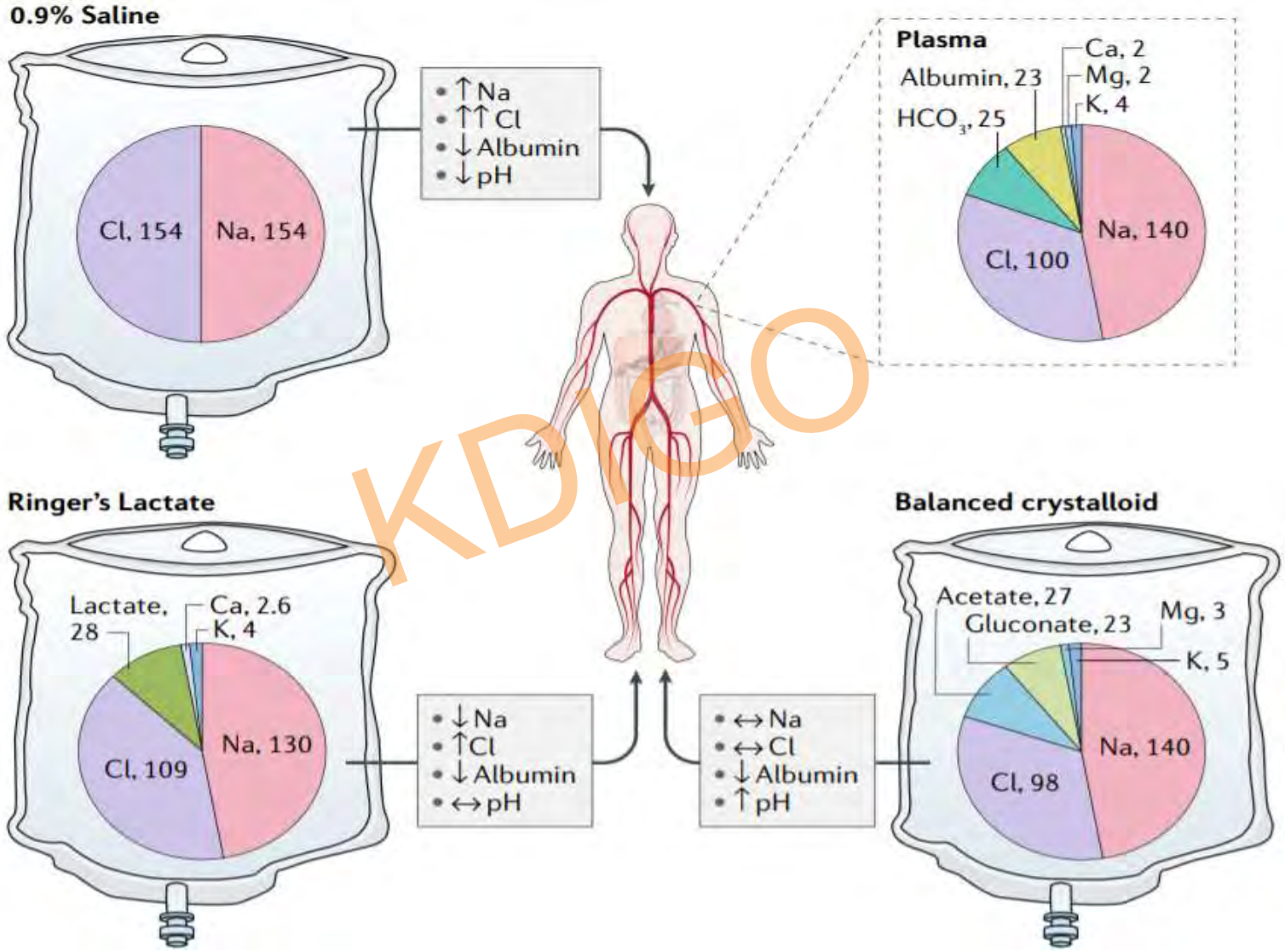
No. at Risk					
Liberal fluid	1493	1343	1320	1249	859
Restrictive fluid	1490	1323	1292	1228	835

AKI restrictive: 8.6%

AKI liberal: 5,0% (p<0,001)

Myles et al , N Engl J Med 2018;378:2263-74.

The effects of IV fluids on the plasma properties



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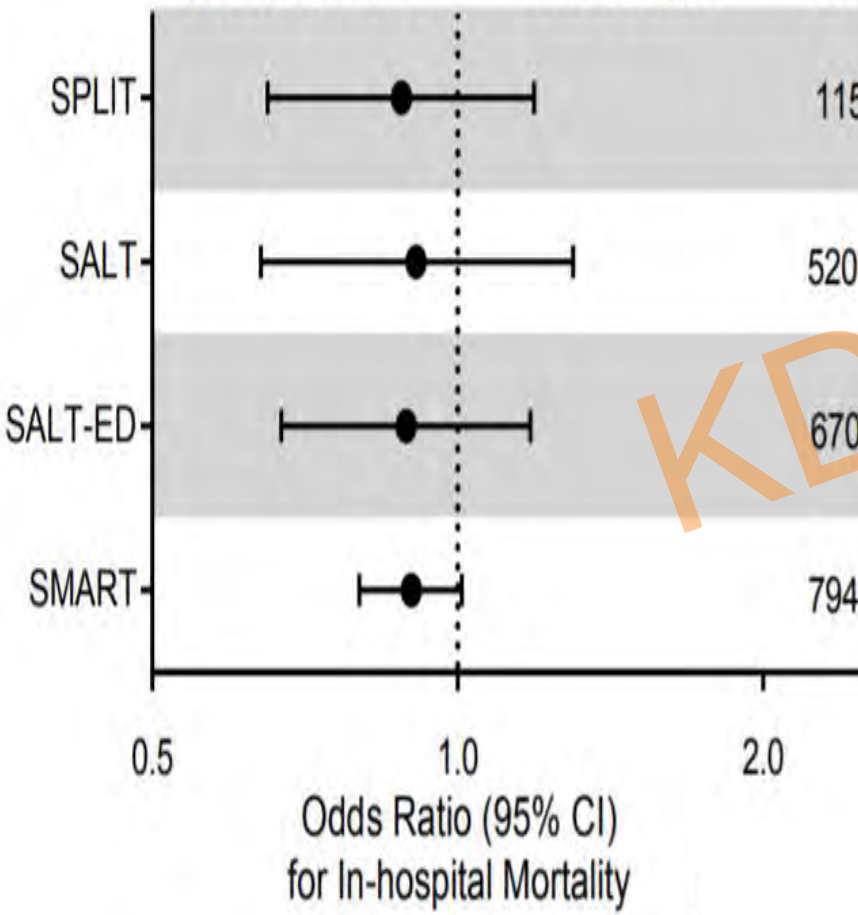
Kellum JA. Nature Rev Nephrol 2018, 14: 358-360.

Effects of balanced crystalloids compared to saline on in-hospital mortality in ICU patients



	No. of individuals		No. of events (%)		
	Balanced	Saline	Balanced	Saline	OR (95% CI)
SPLIT	1152	1110	78 (7.6)	95 (8.6)	0.88 (0.65 - 1.19)
SALT	520	454	72 (13.8)	68 (15.0)	0.91 (0.64 - 1.30)
SALT-ED	6708	6639	94 (1.4)	102 (1.5)	0.89 (0.67 - 1.18)
SMART	7942	7860	818 (10.3)	875 (11.1)	0.90 (0.80 - 1.01)

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Secondary Analysis of SMART Trial in sepsis
30 d mortality significantly lower in Balanced group
Brown et al, AJRCCM (August, 2019)

Semler, Kellum Am J Respir Crit Care Med 15;199(8):952-960, 2019

Drug Management

3.8.1: We suggest not using aminoglycosides for the treatment of infections unless no suitable, less nephrotoxic, therapeutic alternatives are available. (2A)

3.8.2: We suggest that, in patients with normal kidney function in steady state, aminoglycosides are administered as a single dose daily rather than multiple-dose daily treatment regimens. (2B)

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3.8.6: We suggest using lipid formulations of amphotericin B rather than conventional formulations of amphotericin B. (2A)

4.4.1: We recommend iv volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions rather than no iv volume, in patients at increased risk for CI-AKI. (1A)

4.4.3: We suggest using oral NAC with iv isotonic crystalloids in patients at increased risk of CI-AKI. (2D)

Controversies: contrast associated AKI in high risk patients (CKD, proteinuria, diabetes)

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ESTABLISHED IN 1812 FEBRUARY 15, 2018 VOL. 378 NO. 7

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Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine

S.D. Weisbord, M. Gallagher, H. Jneid, S. Garcia, A. Cass, S.-S. Thwin, T.A. Conner, G.M. Chertow, D.L. Bhatt, K. Shunk, C.R. Parikh, E.O. McFalls, M. Brophy, R. Ferguson, H. Wu, M. Androsenko, J. Myles, J. Kaufman, and P.M. Palevsky, for the PRESERVE Trial Group*

CONCLUSIONS

there was no benefit of intravenous sodium bicarbonate over intravenous sodium chloride or of oral acetylcysteine over placebo for the prevention of death, need for dialysis, or persistent decline in kidney function at 90 days or for the prevention of contrast-associated acute kidney injury.

Differences in design and outcomes between the ELAIN and AKIKI trials

Characteristic	ELAIN trial[7]	AKIKI trial[6]
Country	Germany	France
Number of Sites	1	31
Number of participants	231	620
ARR for sample size calculation	18%	15%
Criteria for early intervention strategy	KDIGO stage 2	KDIGO stage 3
Criteria for delayed intervention strategy	KDIGO stage 3	Specific criteria*
Mean SOFA score of enrolled patients	~16.0	~10.9
Primary end point	90 day mortality	60 day mortality
End point mortality – early intervention strategy	39.3%	48.5%
End point mortality – delayed intervention strategy	54.7%	49.7%
Proportion of patients in the delayed intervention group who received RRT	90.8%	51.0%

ARR, absolute risk reduction in primary end point; KDIGO, Kidney Disease: Improving Global Outcomes RRT, renal replacement therapy; SOFA, sepsis-related organ failure assessment. *Oliguria or anuria for >72 h, serum urea >40 mmol/l, serum potassium >6 mmol/l (or >5.5 mmol/l despite medical intervention), blood pH <7.15, or acute pulmonary oedema causing significant hypoxaemia.

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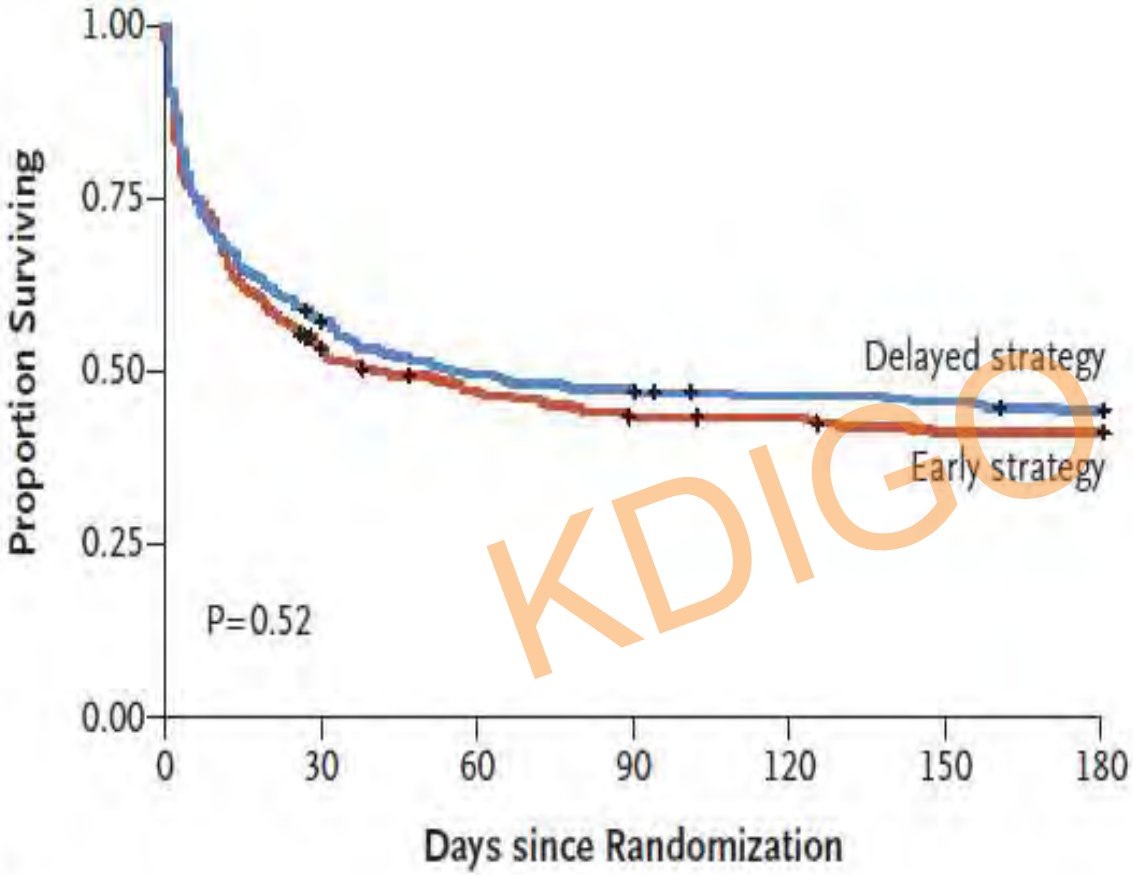
Bagshaw, Wald, Nature Reviews in Nephrol 2016

Timing of RRT in patients with AKI and sepsis



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Early start: within 12 h after diagnosis AKI N:246

Delayed start: after 48 h after diagnosis AKI N:242

No. at Risk							
Delayed strategy	242	137	117	112	107	105	101
Early strategy	246	127	109	99	98	92	92

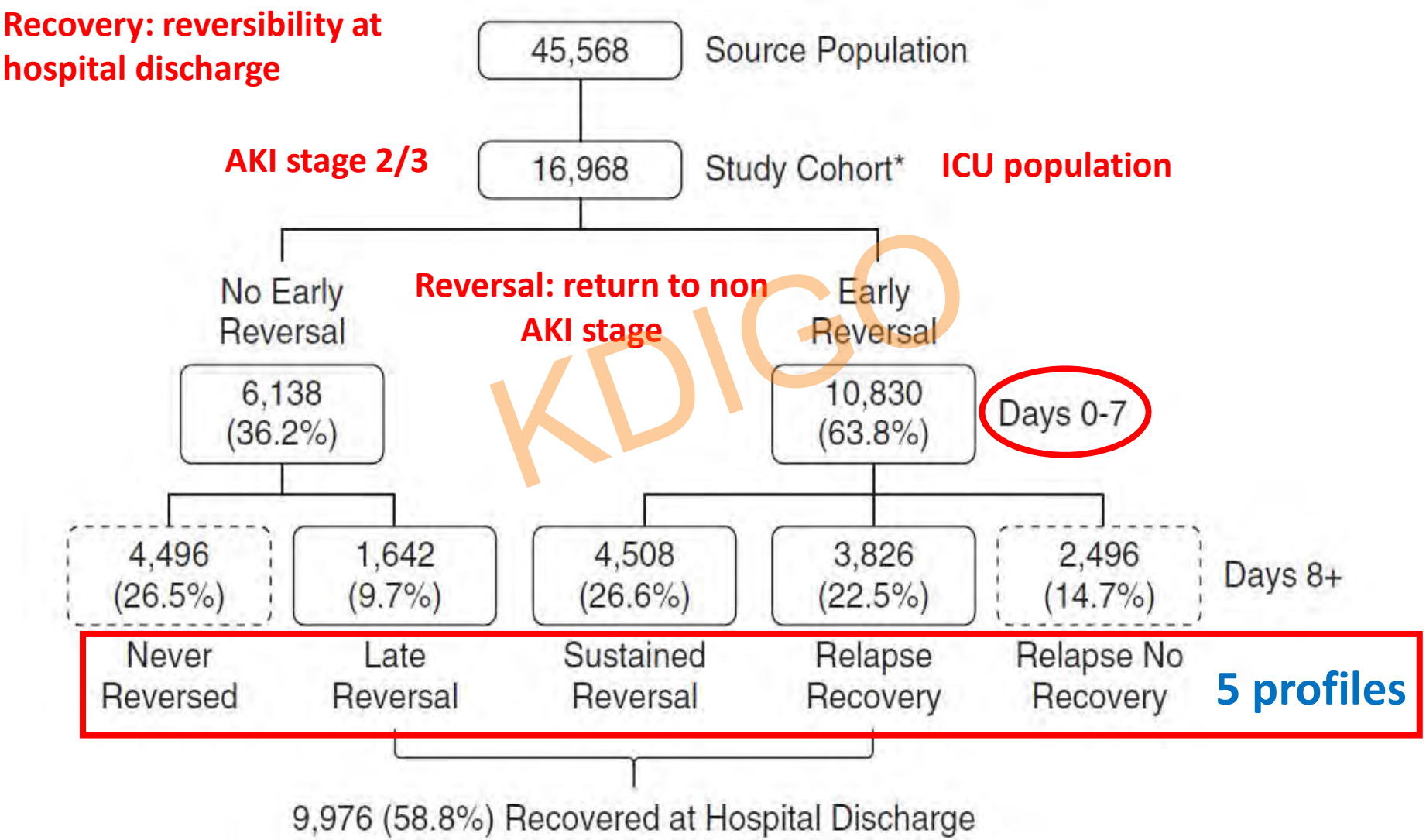
Pts receiving RRT

62 %+ 17%

97%

Barbar et al, N Engl J Med 2018;379:1431-1442.

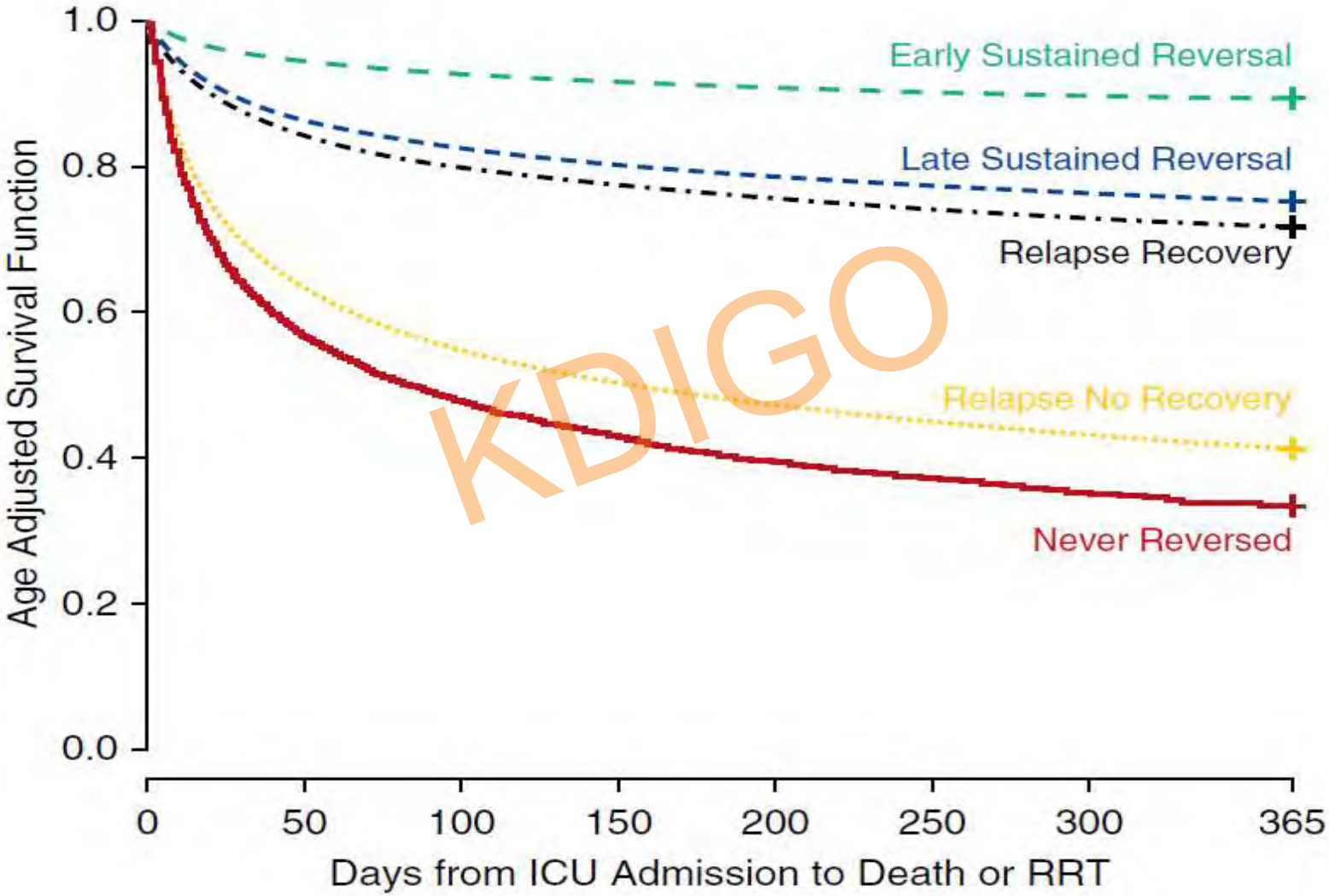
Definitions and epidemiology of early or late reversal and functional recovery of AKI in ICU



KDIGO

Kellum et al, Am J Respir Crit Care Med 195, 784–791, 2017

Different types of recovery after AKI-survival to death or RRT



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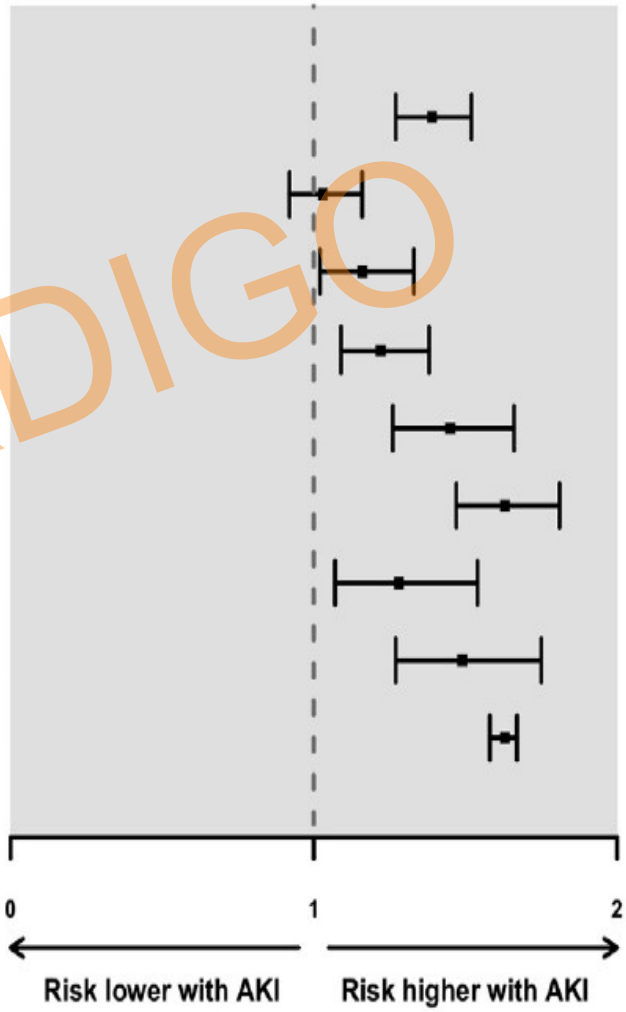
Kellum et al , Am J Respir Crit Care Med 195, 784–791, 2017

Association of AKI with 30-day hospital readmission in a propensity-matched cohort-most responsible diagnosis during index hospitalization

Diagnosis during index hospitalization	No. events (%) AKI	No. events (%) No AKI	Odds Ratio (95% CI)	Interaction p value
Congestive heart failure	1160 (21.7)	881 (16.5)	1.39 (1.27, 1.52)	<0.0001
Chronic obstructive pulmonary disease	553 (16.3)	543 (16.0)	1.03 (0.92, 1.16)	
Sepsis	446 (12.7)	389 (11.1)	1.16 (1.02, 1.33)	
Pneumonia	611 (13.3)	512 (11.1)	1.22 (1.09, 1.38)	
Urinary tract infection	489 (13.4)	344 (9.4)	1.45 (1.26, 1.66)	
Myocardial infarction	860 (21.1)	559 (13.7)	1.63 (1.47, 1.81)	
Cerebrovascular accident	262 (11.9)	210 (9.5)	1.28 (1.07, 1.54)	
Arrhythmia	367 (15.6)	256 (10.9)	1.49 (1.27, 1.75)	
Other	12,738 (15.4)	8156 (9.9)	1.63 (1.58, 1.67)	



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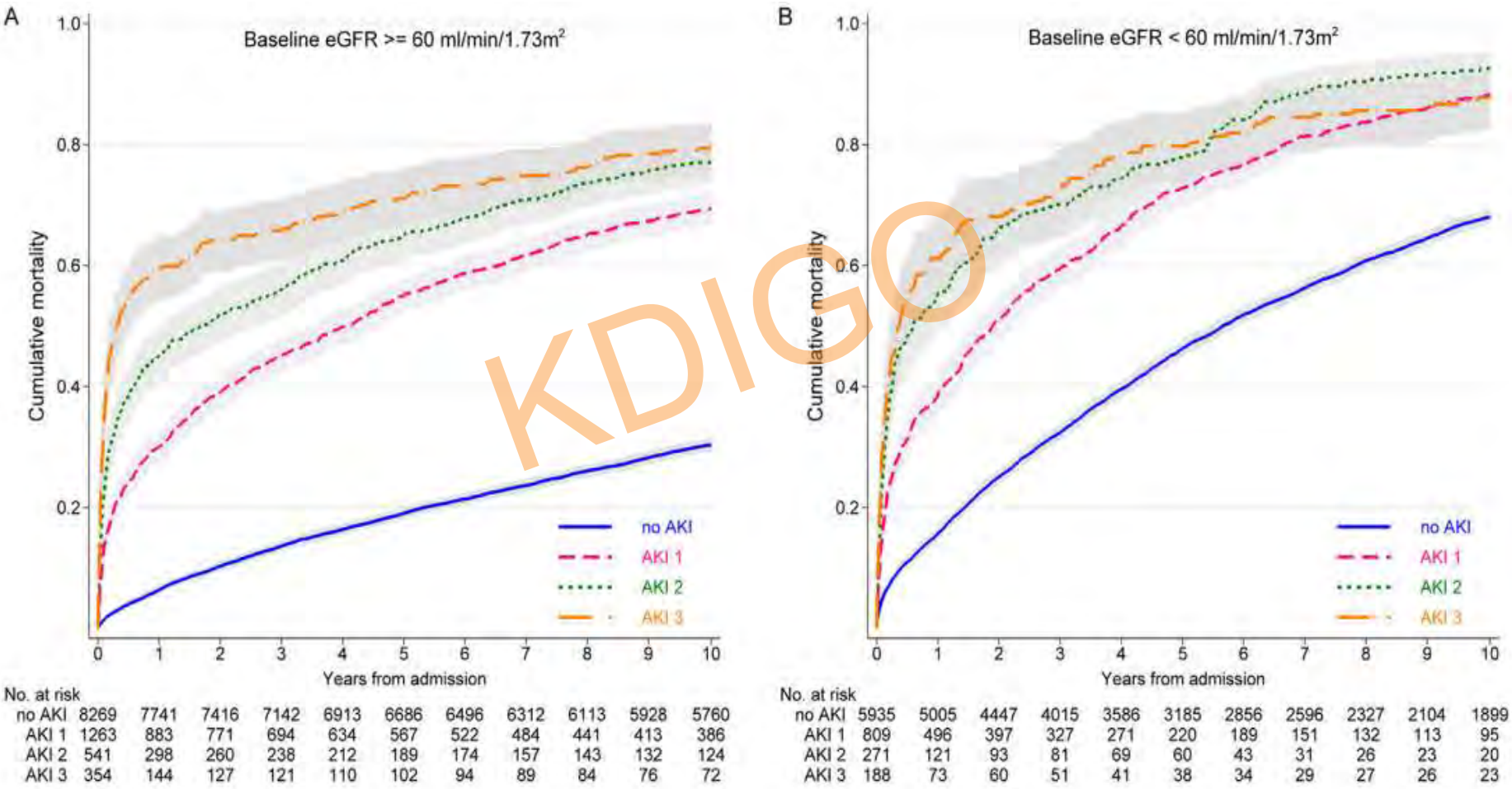
Silver et al, Am J Med (2017) 130, 163-172

Cumulative mortality by acute kidney injury (AKI) stage (1-3 denote severity stage), stratified by baseline kidney function



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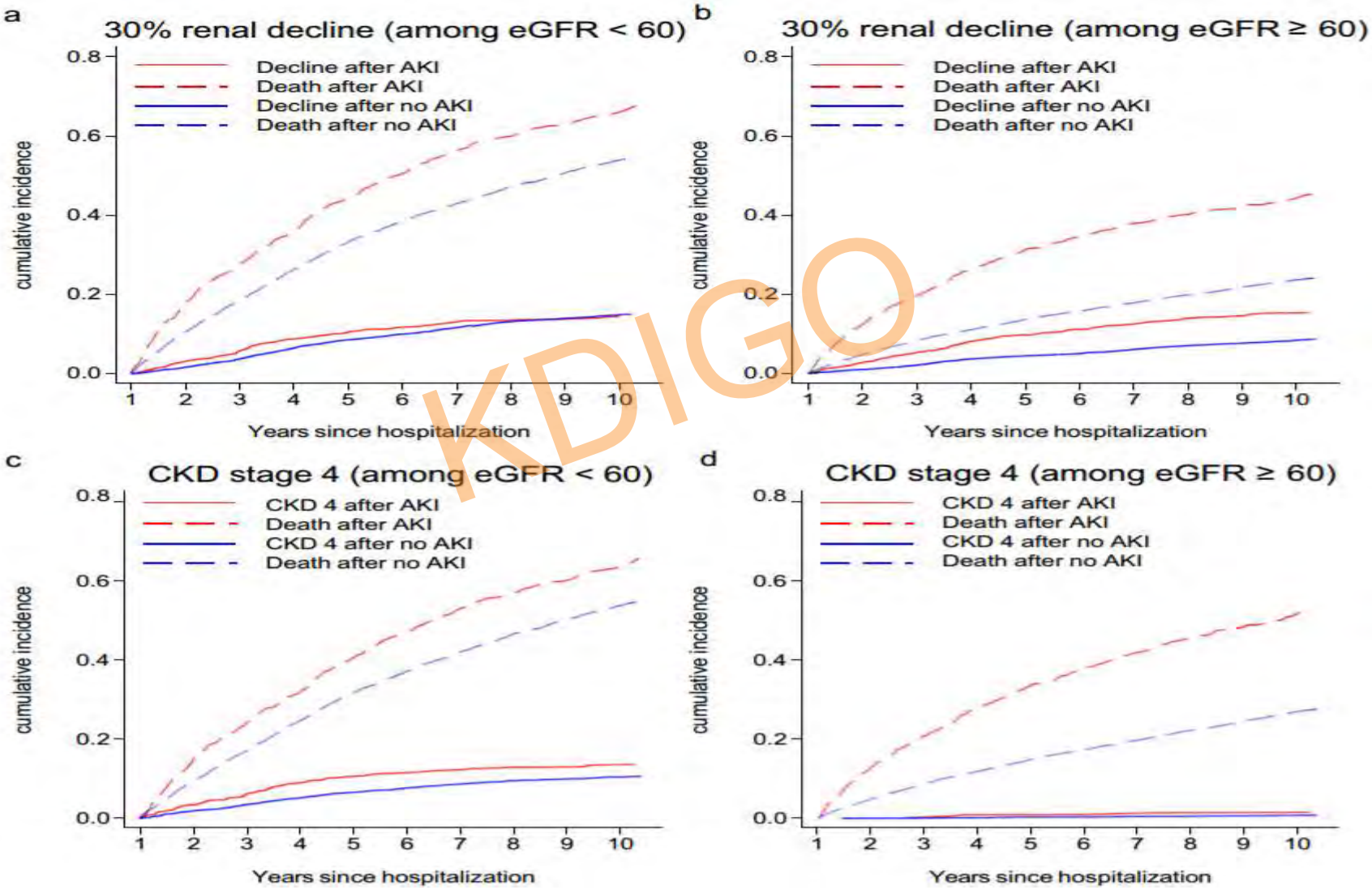
Sawhney et al Am J Kidney Dis. 2017; 69:18-28

Cumulative incidences of subsequent renal progression (solid line) for those with (red) and without (blue) an AKI admission in 2003, grouped by 1 year post-episode eGFR and accounting for the competing risk of death (dashed line) – Grampian study population



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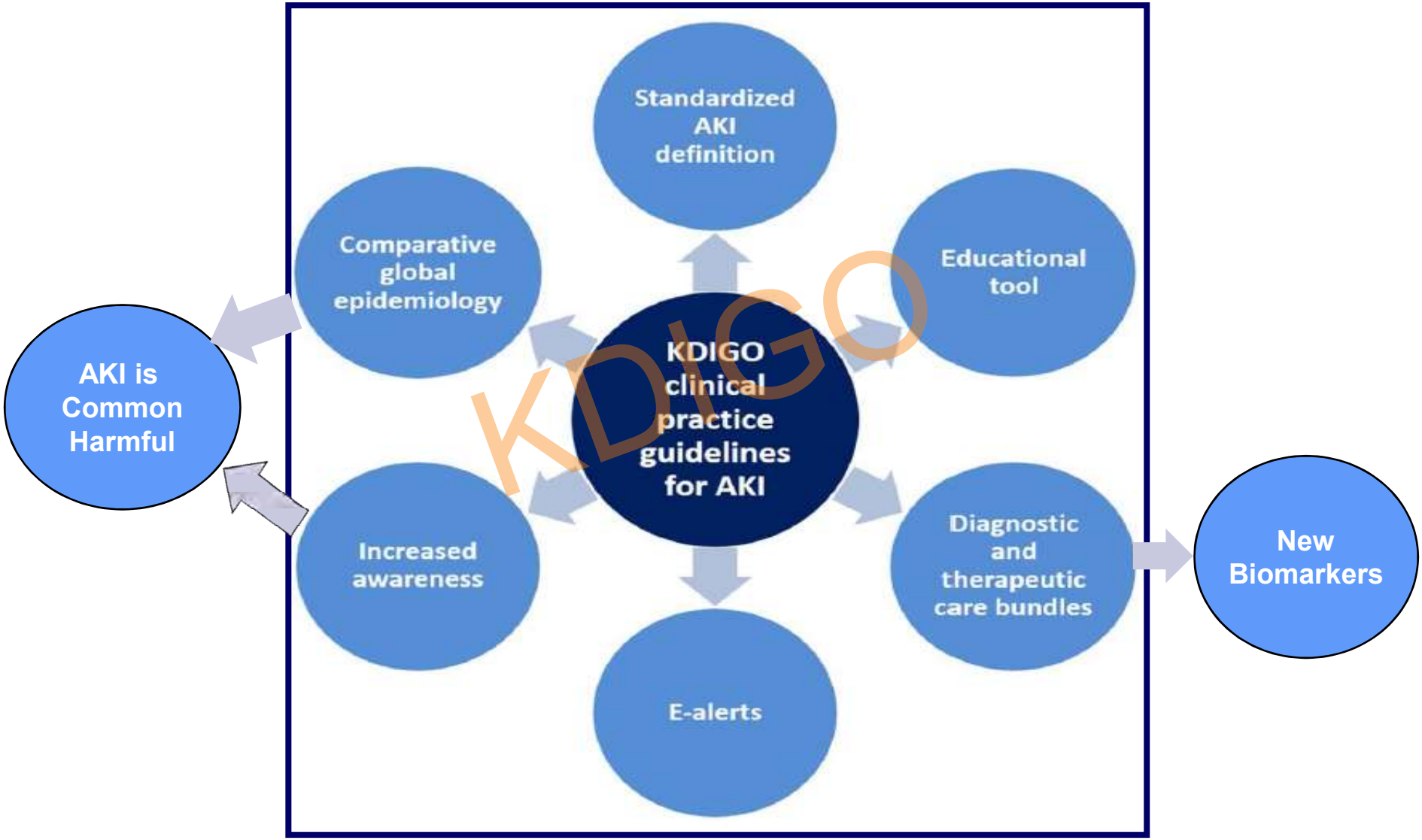
Sawhney et al Kidney Int 2017 92(2):440-452.

What the 2012 AKI KDIGO guideline has accomplished



Lameire, Vanmassenhove, Lewington, Intensive Care Med 2017, 43:921-923.

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