Biomarcatori della funzione renale: ci sono novità?

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Firenze
25/09/2019

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BIOMARKERS - OUTLINE

The framework

Renal BIOMARKERS

CysC

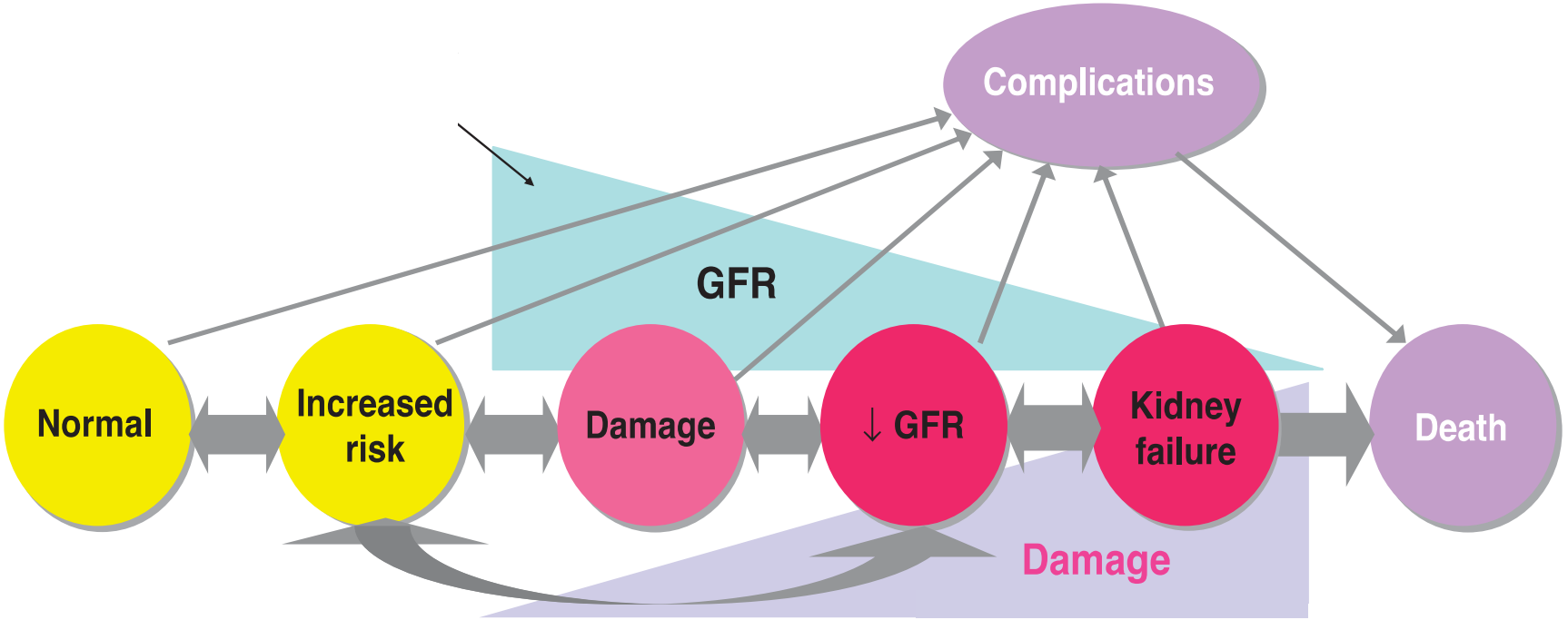
NGAL

TIMP2-IGFBP7

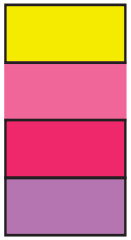
Current evidence

NO CONFLICT OF INTERESTS

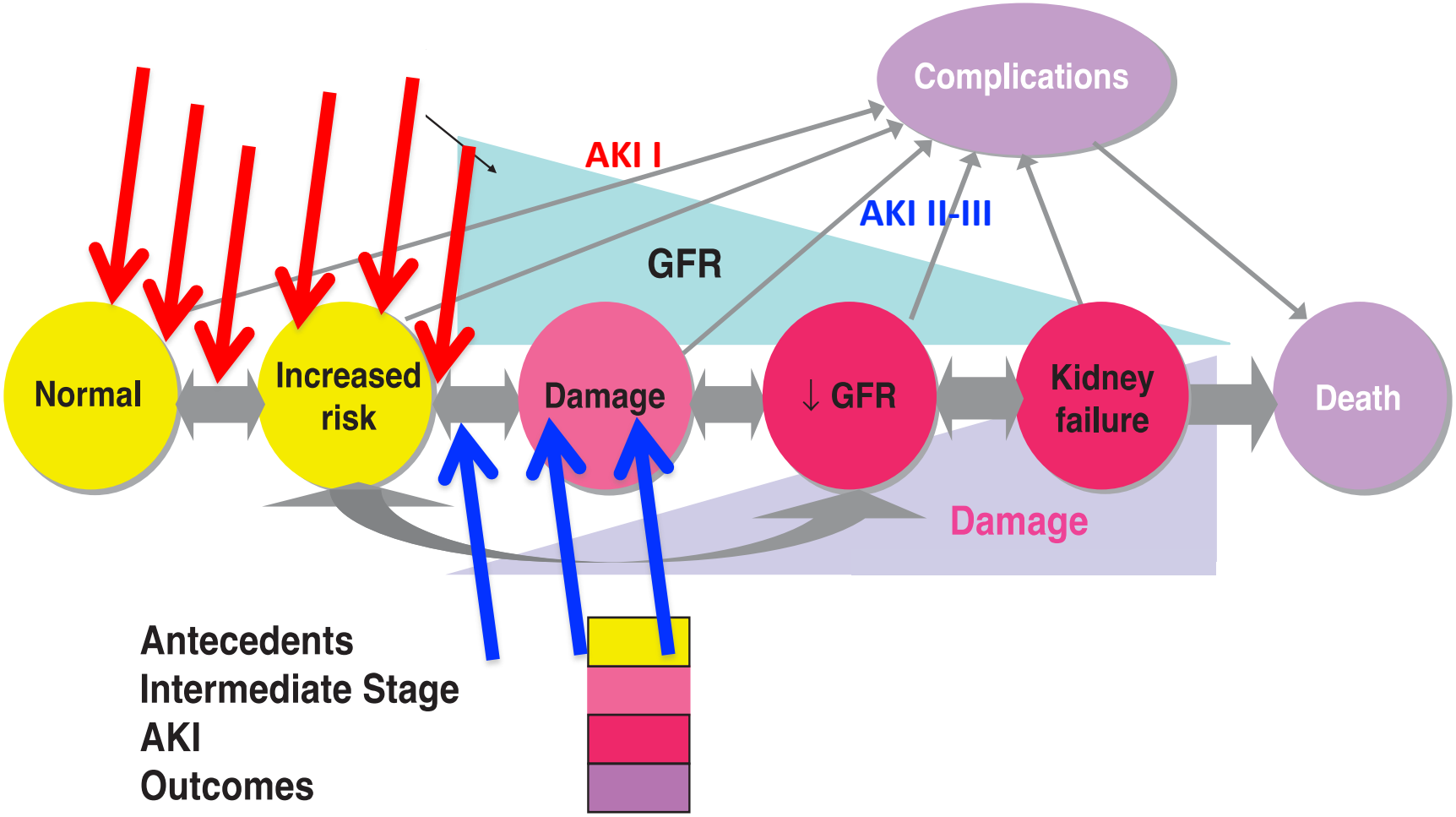
Classifications detect function not damage……



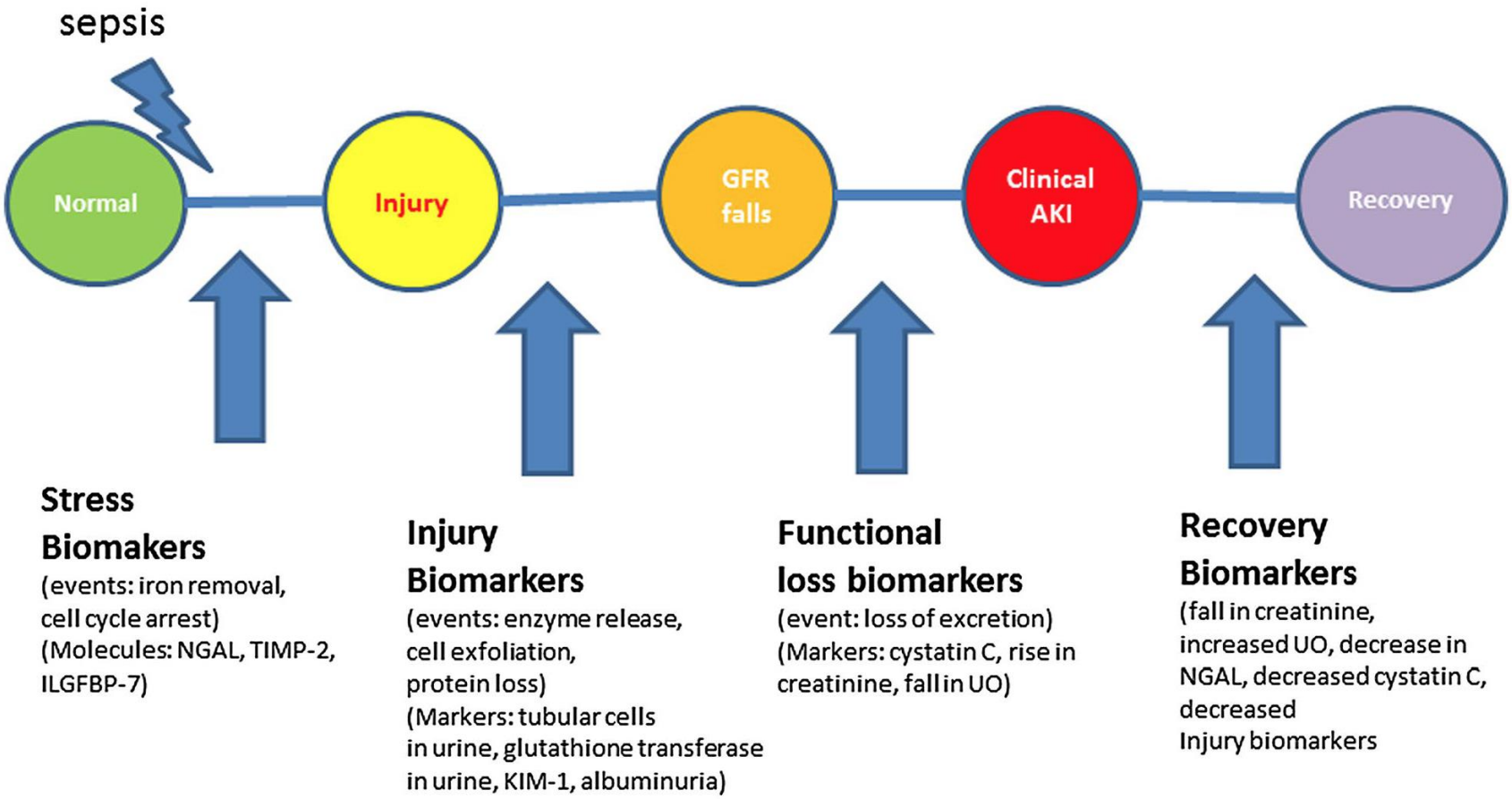
Antecedents
Intermediate Stage
AKI
Outcomes



Classifications detect function not damage……

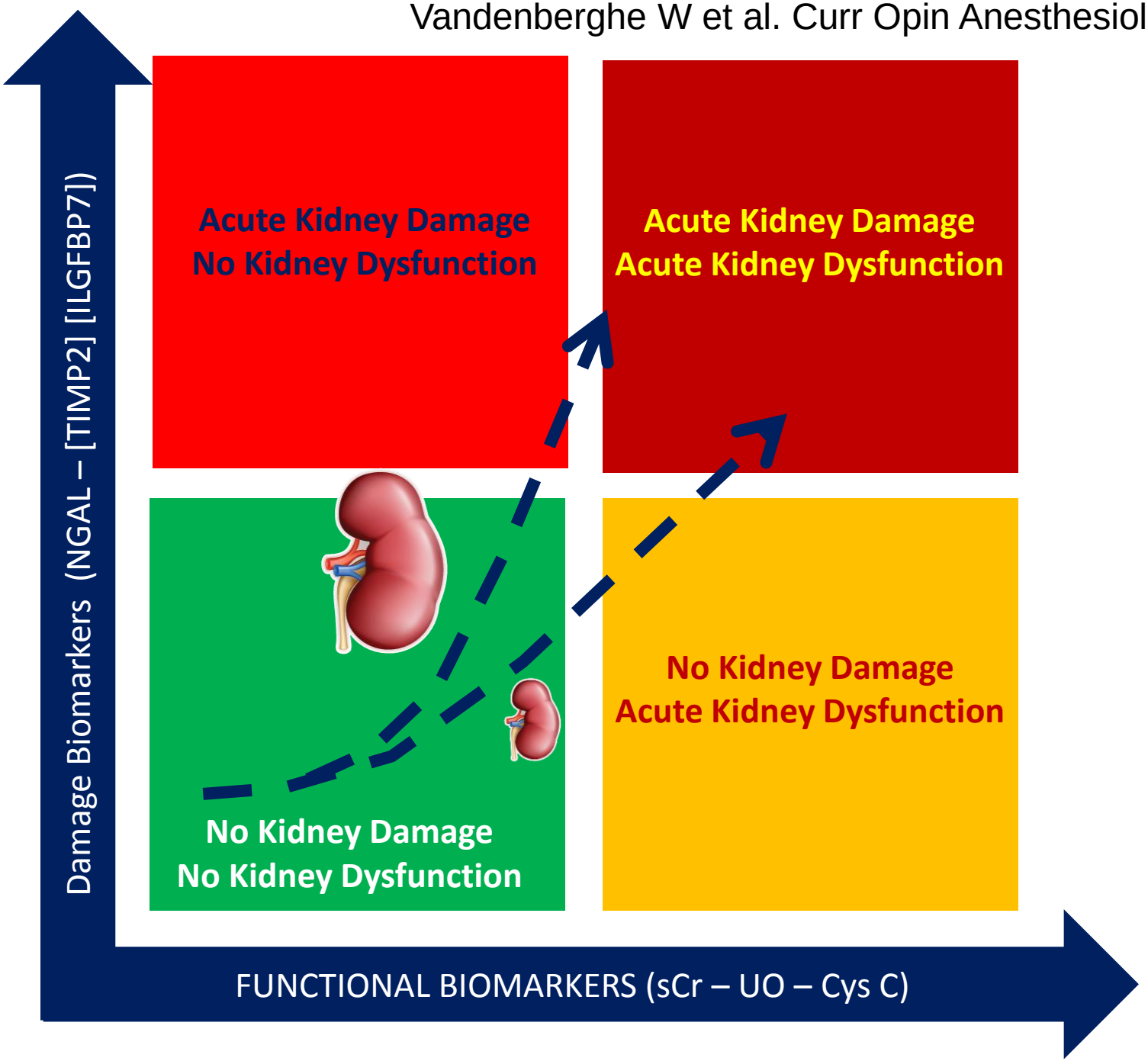


- These biomarkers may also help change the definition of AKI in the future and contribute to a better understanding, diagnosis, prevention, and treatment of septic AKI.

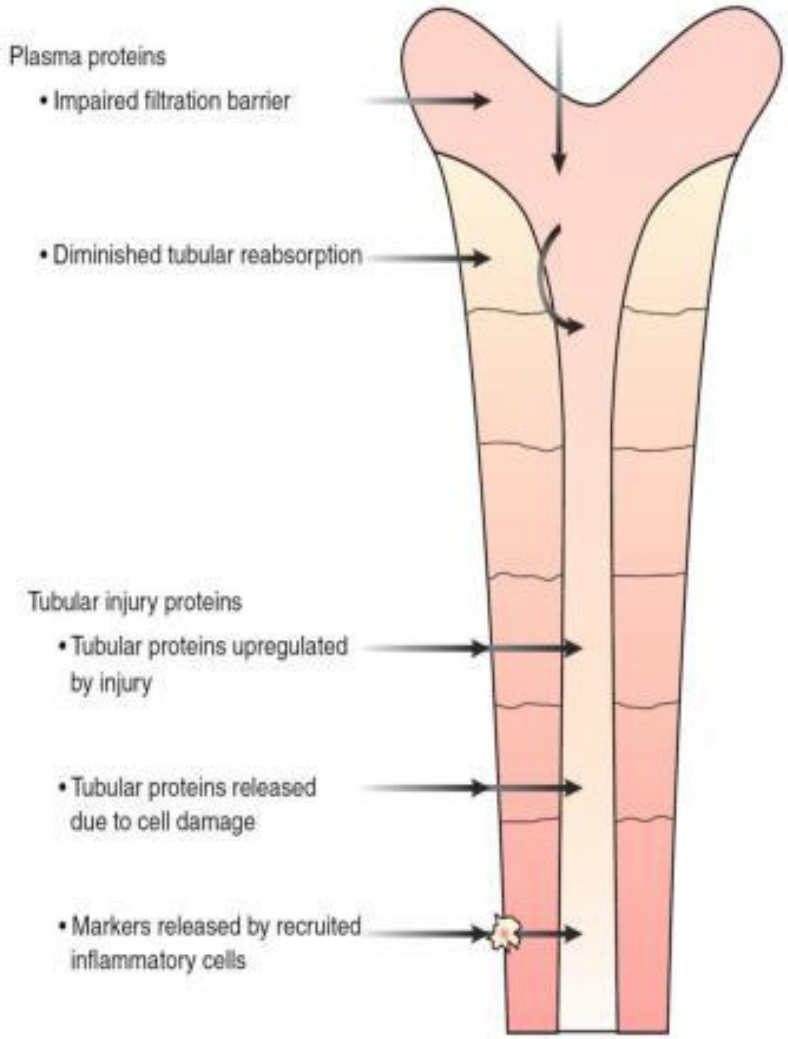


Bellomo R et al. Intensive Care Med (2017) 43:816-828

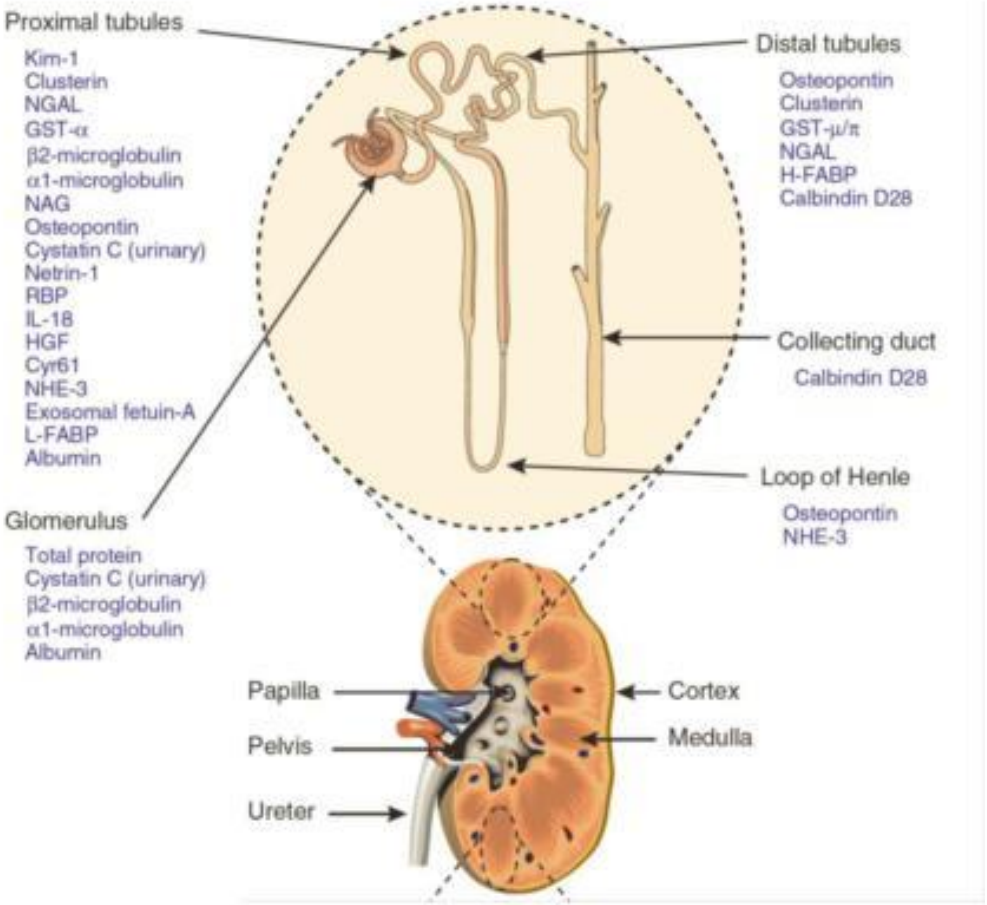
Vandenberghe W et al. Curr Opin Anesthesiol 2017, 30:66–75



A: Potential mechanisms for kidney damage biomarkers appearance in serum or urine

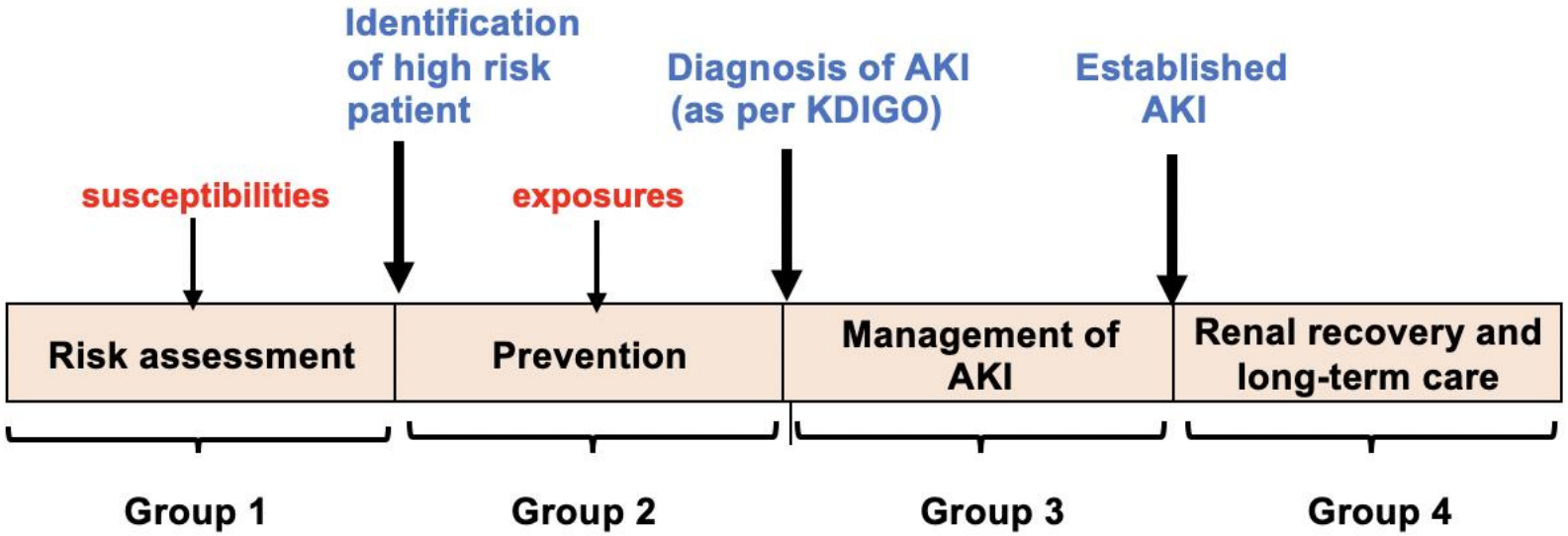


B: Source and site specificity of kidney damage biomarkers



ADQI

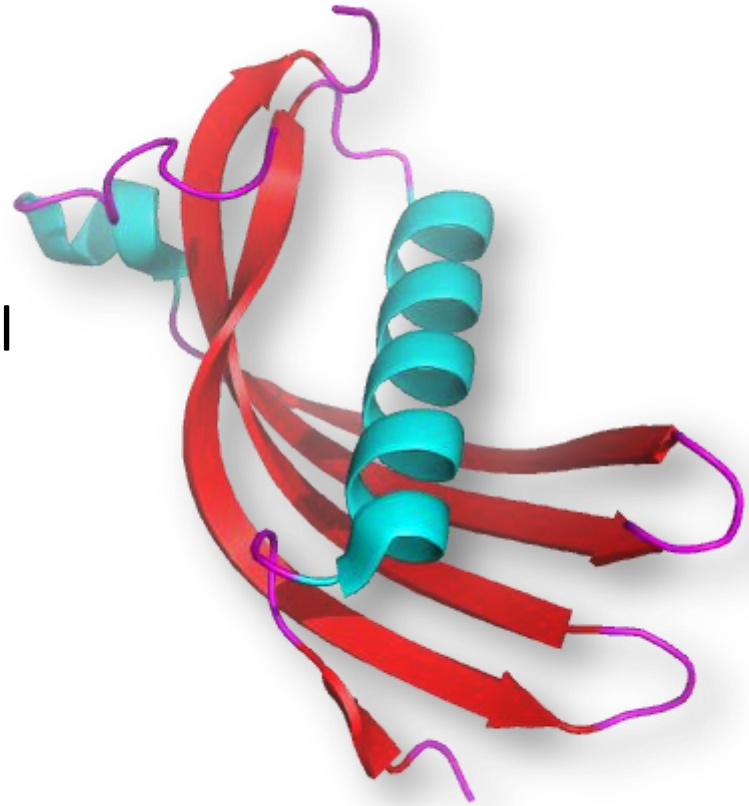
ADQI XXIII
Abano Terme
30 Maggio-2 Giugno
2019



Biomarkers in AKI: CysC

CYSTATIN C

In humans, all cells with a nucleus (cell core containing the DNA) produce cystatin C as a chain of 120 amino acids. It is found in virtually all tissues and body fluids.
It is a potent inhibitor of lysosomal proteinases and probably one of the most important extracellular inhibitors of cysteine proteases



Cystatin C levels are less dependent on age, sex, race and muscle mass compared to creatinine. It is not secreted by tubular cells

Biomarkers in AKI: NGAL

NEUTROPHIL GELATINASE ASSOCIATED LIPOCALIN

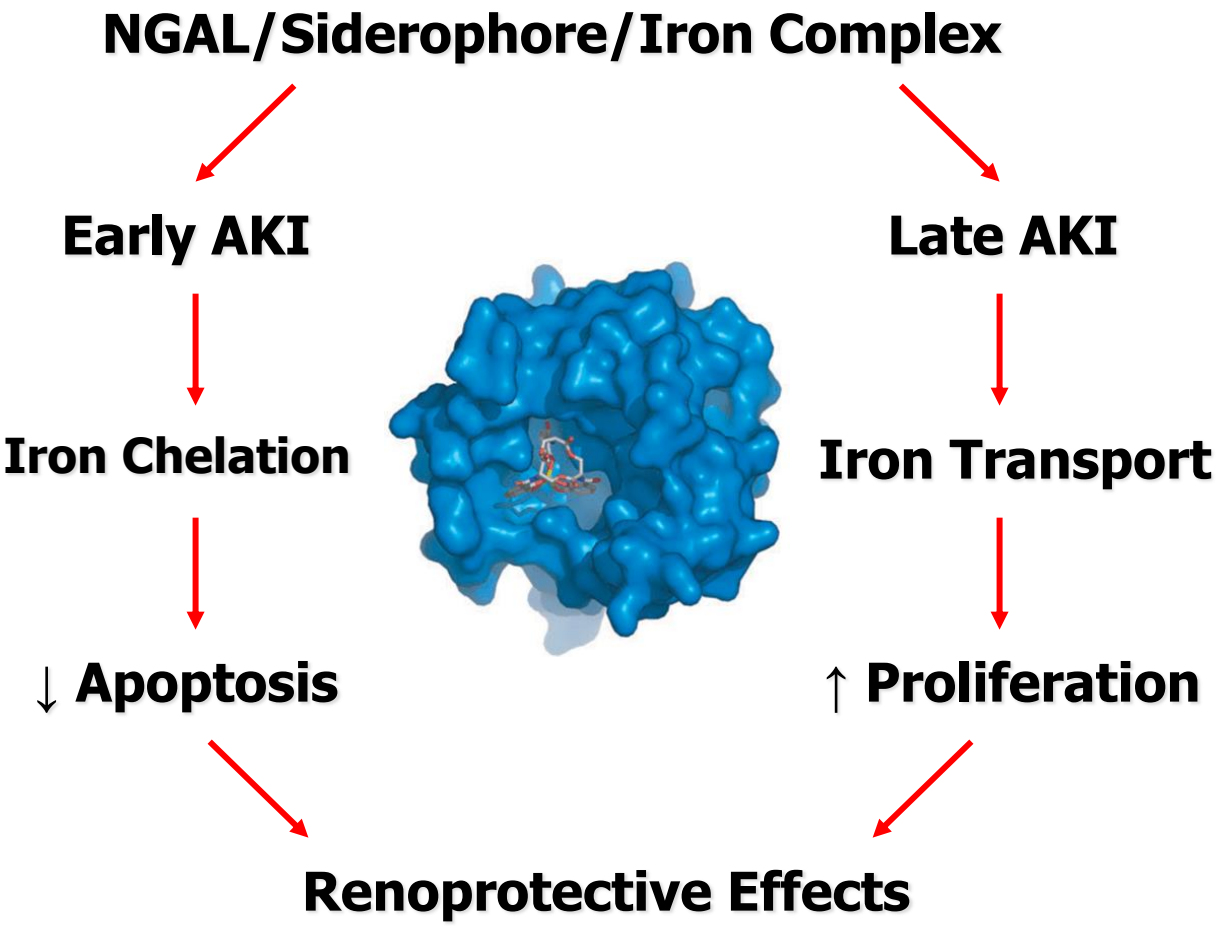
- ✓ In bloodstream as a 25-kDa monomer, as a 45-kDa disulphide-linked homodimer and as a 135-kDa heterodimer
- ✓ Produced in bone marrow, colon, trachea, lung and kidney epithelium

Activated neutrophils mainly release homodimeric NGAL and to a lesser extent the monomeric form.
In contrast, stressed kidney epithelial cells predominantly secrete monomeric NGAL apparently unable to form dimers.

Biomarkers in AKI: NGAL

Neutrophil gelatinase-assoc. lipocalin (NGAL) produced by **neutrophils** in response to specific stimuli.
Also known as lipocalin-2 and siderocalin it is known to play a role in fighting bacteria infections.

Animal studies have shown NGAL is one of the earliest proteins induced in the kidney after ischemic or nephrotoxic insult.



MISHRA J.,et al., J Am Soc Nephrol 14: 2534–2543, 2003

Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery

Jaya Mishra, Catherine Dent*, Ridwan Tarabishi*, Mark M Mitsnefes, Qing Ma, Caitlin Kelly, Stacey M Ruff, Kamyar Zahedi, Mingyuan Shao, Judy Bean, Kiyoshi Mori, Jonathan Barasch, Prasad Devarajan*

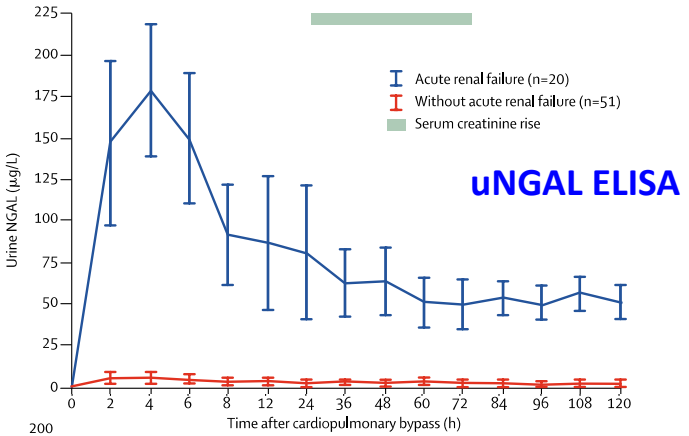
Lancet, 2005

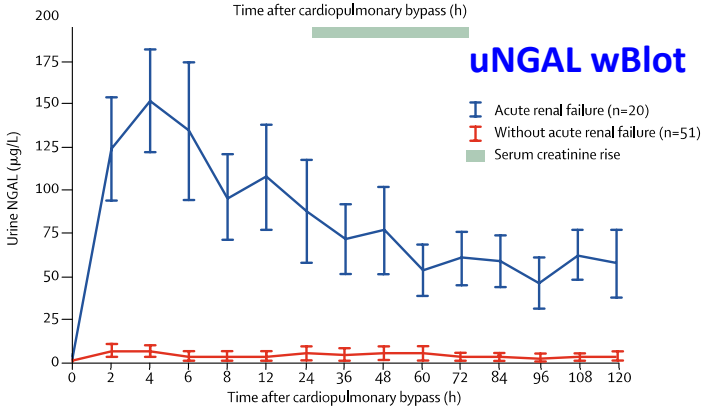
- 71 post CPB infants
- AKI incidence: 30%
- AKI definition: increase in SCr by 50% or more

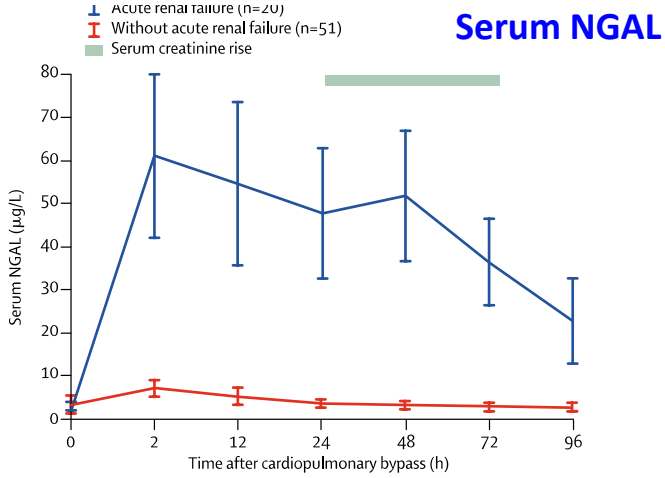
	Without acute renal injury (n=51)	Acute renal injury (n=20)	p
Demographics			
Age (years)	4·0 (0·7)	2·1 (1·2)	0·002
Boys	32	13	0·792
White ethnic origin	45	17	0·705
Clinical outcomes			
Previous heart surgery	15	5	0·778
Cardiopulmonary bypass time (min)	105 (8·6)	179 (13·6)	<0·0001
Change in serum creatinine (%)	7·7 (1·8)	99 (9·3)	<0·0001
Diagnosis			
Ventricular septal defect	9	3	
Tetralogy of Fallot	3	9	
Atrial septal defect	7	0	
Coarctation of aorta	5	1	
Aortic stenosis	6	0	
Hypoplastic left heart	2	3	
Atrioventricular canal	3	2	
Pulmonic stenosis	3	1	
Transposition of the great arteries	4	0	
Tricuspid atresia	3	0	
Double-outlet right ventricle	2	0	
Anomalous left coronary artery	1	0	
Cor triatriatum	0	1	
Left-ventricular outflow tract obstruction	1	0	
Mitral regurgitation	1	0	
Aortic regurgitation	1	0	

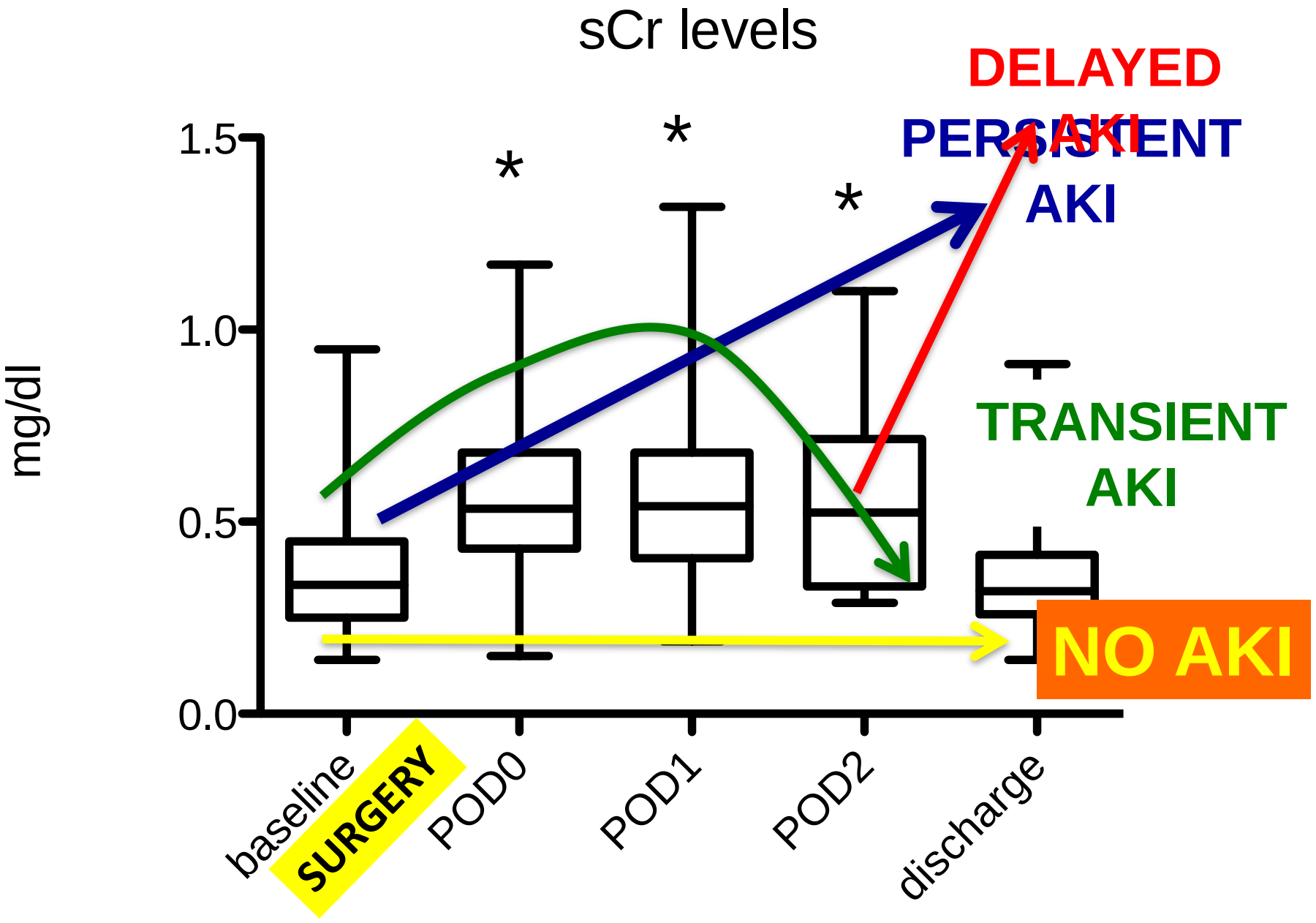
Data are mean (SE) or number of children.

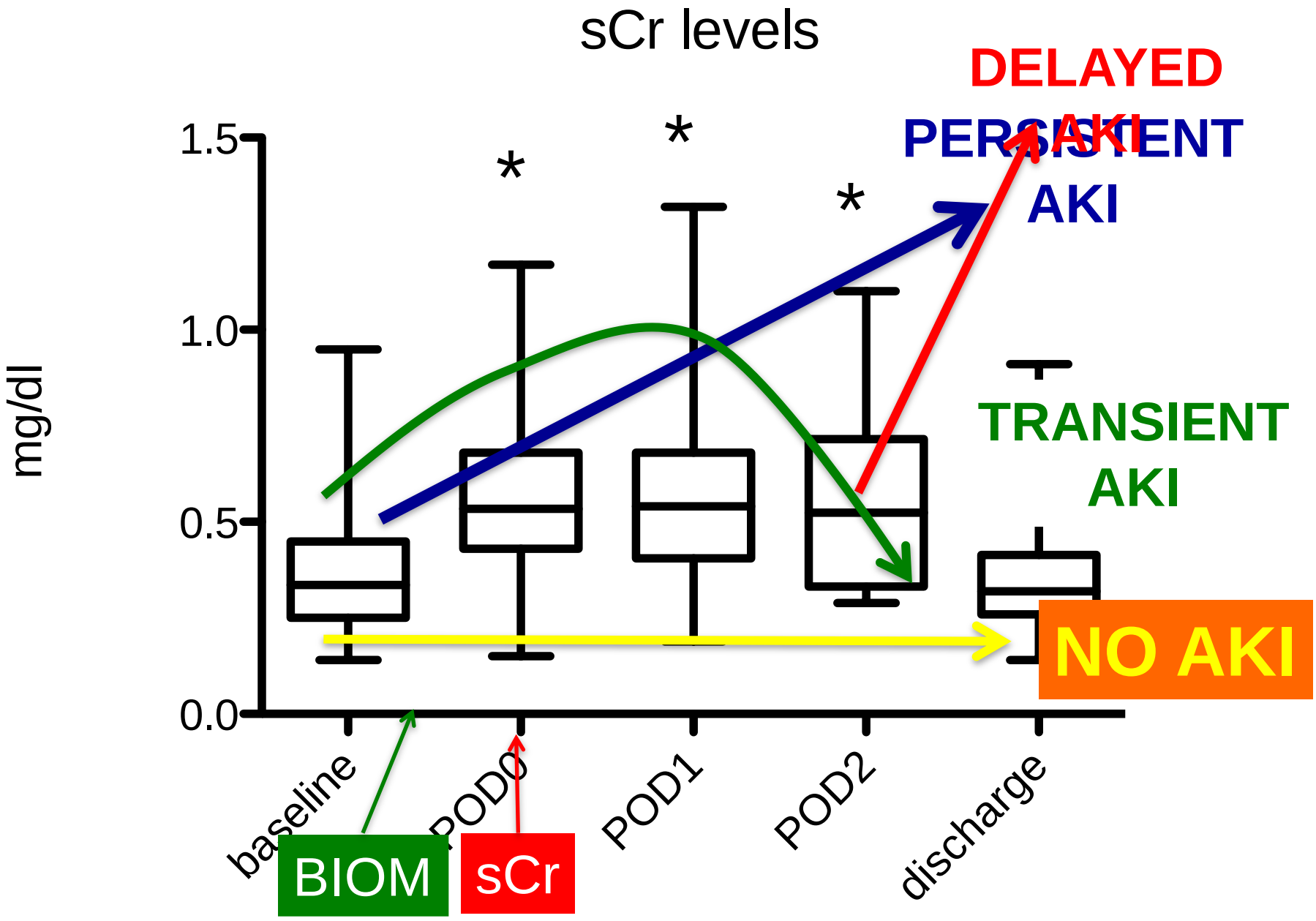
Table 1: **Patients' characteristics and clinical outcomes**








sCr levels
mg/dl
1.5
1.0
0.5
0.0
*
*
*
DELAYED AKI
PERSISTENT AKI
TRANSIENT AKI
NO AKI
baseline
SURGERY
POD0
POD1
POD2
discharge


sCr levels
mg/dl
1.5
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0.0
*
*
*
DELAYED AKI
PERSISTENT AKI
TRANSIENT AKI
NO AKI
baseline
POD0
POD1
POD2
discharge
BIOM
sCr

Combining Functional and Tubular Damage Biomarkers Improves Diagnostic Precision for Acute Kidney Injury After Cardiac Surgery

Basu et al, JACC 2014

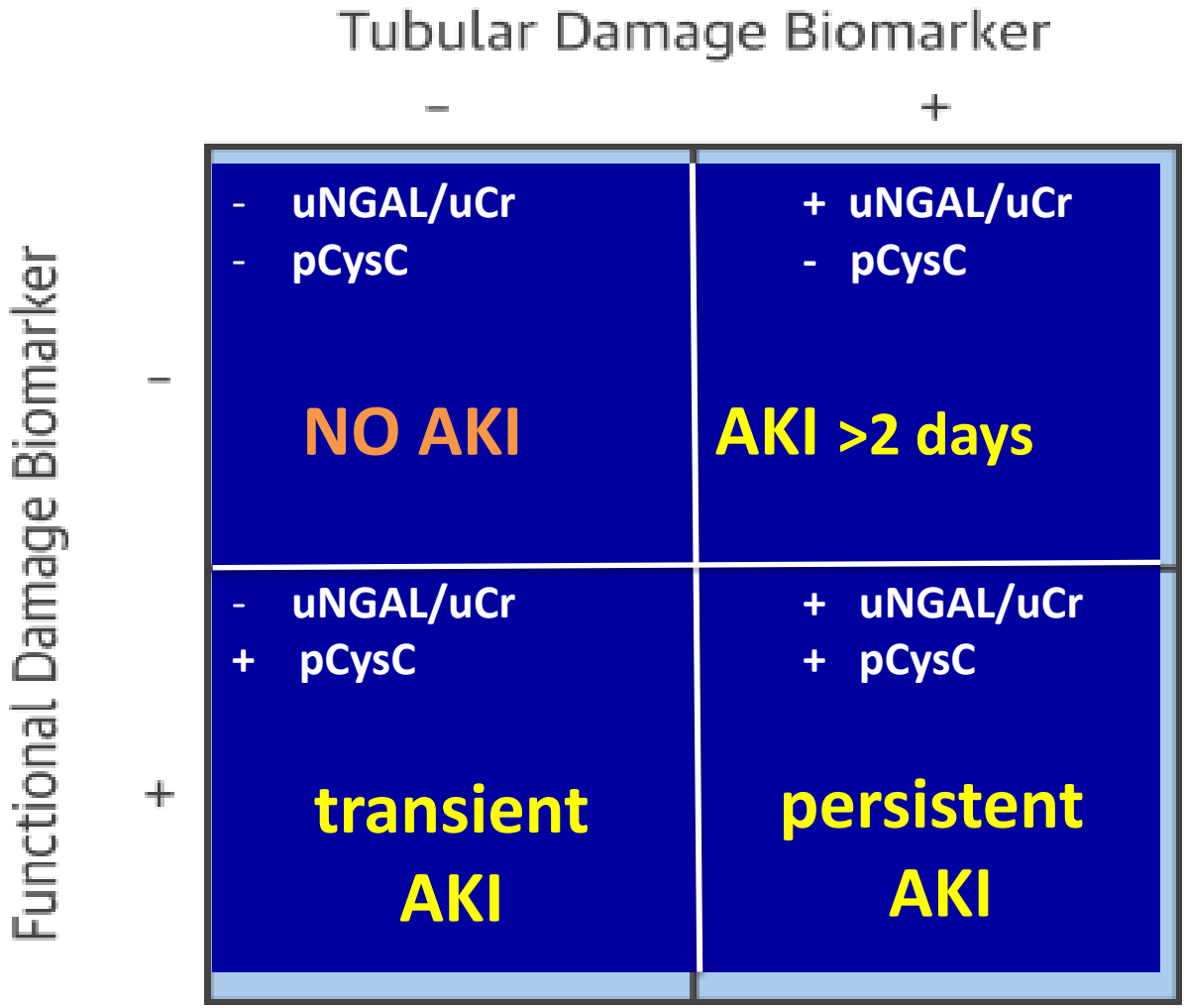
Marker	Sensitivity	Specificity	AUC
Δ SCr > 45%	38%	91%	0.65
pCysC > 0.8 uNGAL > 200	93%	92%	0.95

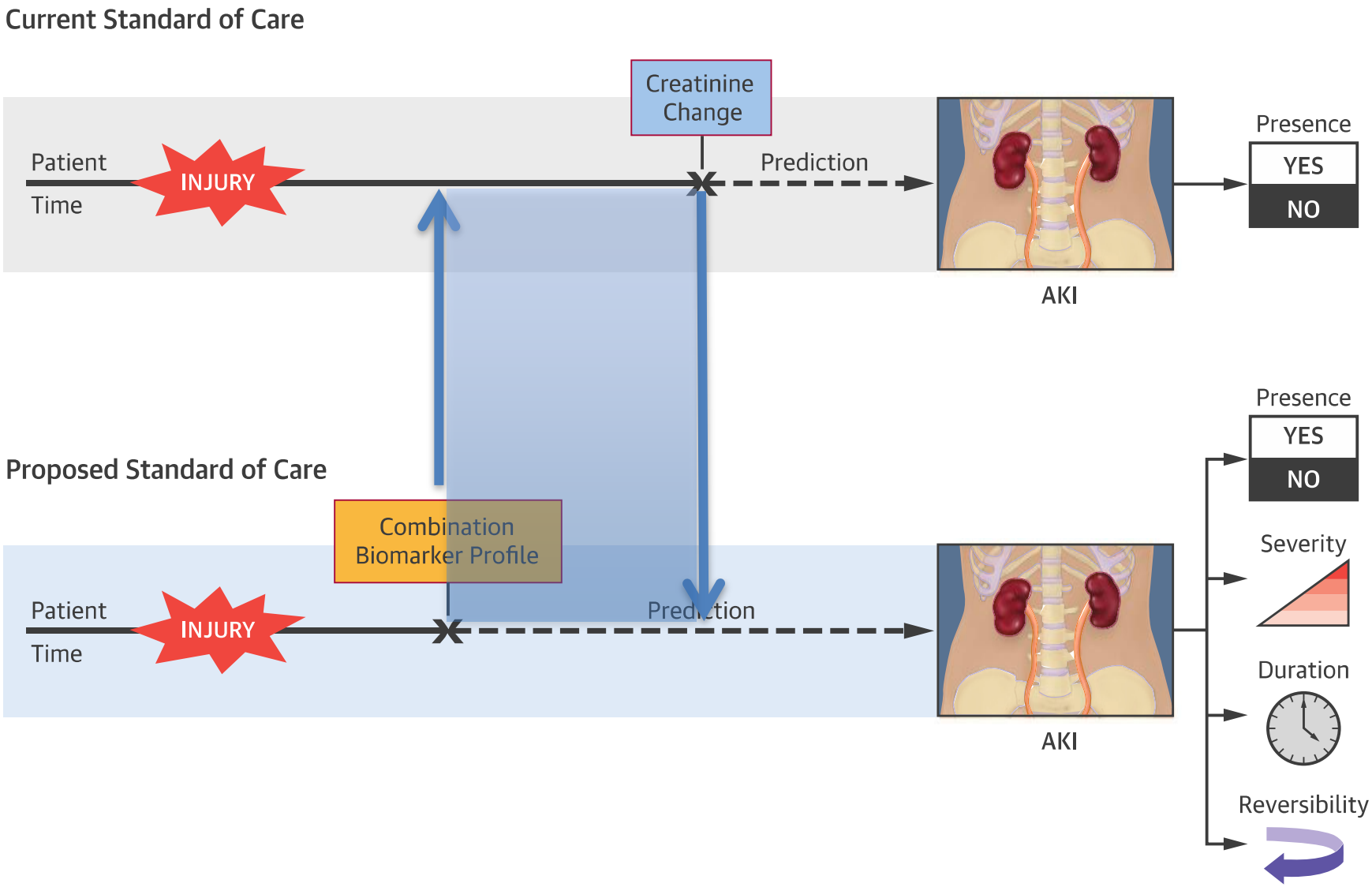
ANY AKI

DEVELOPMENT OF KDIGO stage 2 or 3 at any POD

Combining Functional and Tubular Damage Biomarkers Improves Diagnostic Precision for Acute Kidney Injury After Cardiac Surgery

Basu et al, JACC 2014



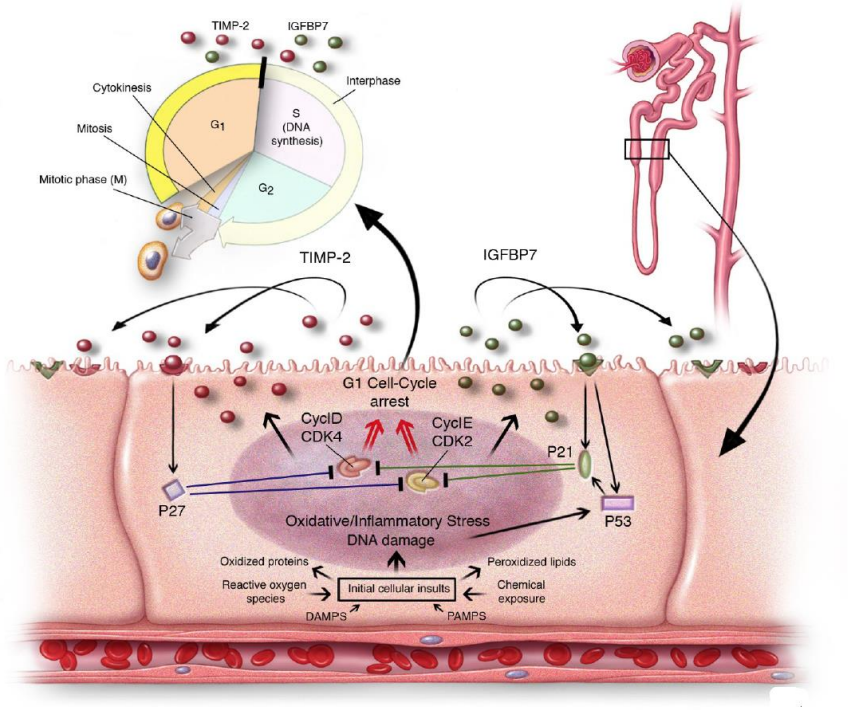

Current Standard of Care
Creatinine Change
Patient
Time
INJURY
Prediction
Presence
YES
NO
AKI
Proposed Standard of Care
Combination Biomarker Profile
Patient
Time
INJURY
Prediction
AKI
Presence
YES
NO
Severity
Duration
Reversibility

Biomarkers in AKI: TIMP2 - IGFBP7

Tissue Inhibitor of Metalloproteinases-2 (TIMP-2) and Insulin-like Growth Factor-Binding Protein 7

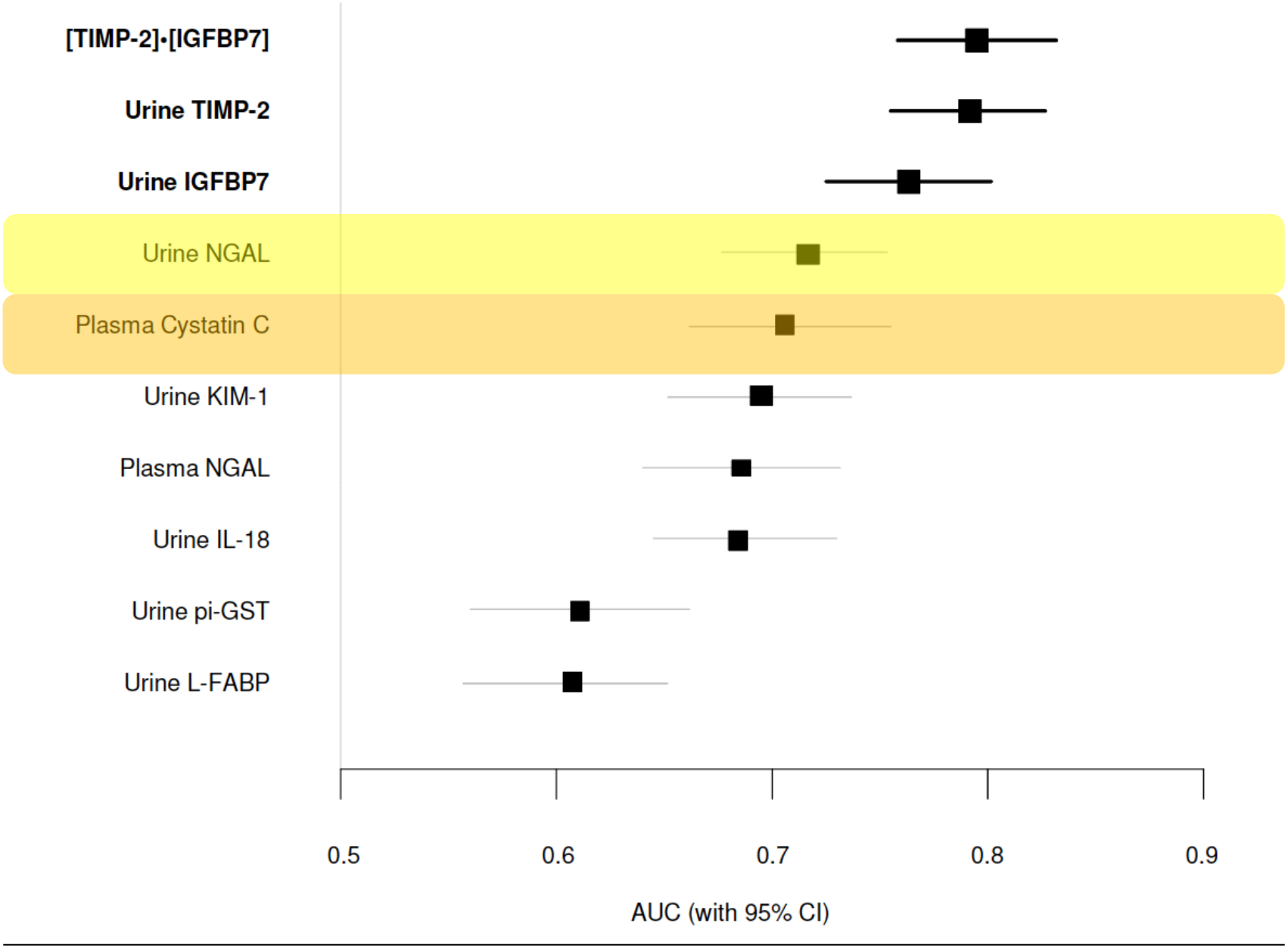
Kashani et al, CC 2013

AKI II and III after 12 hours from ICU admission

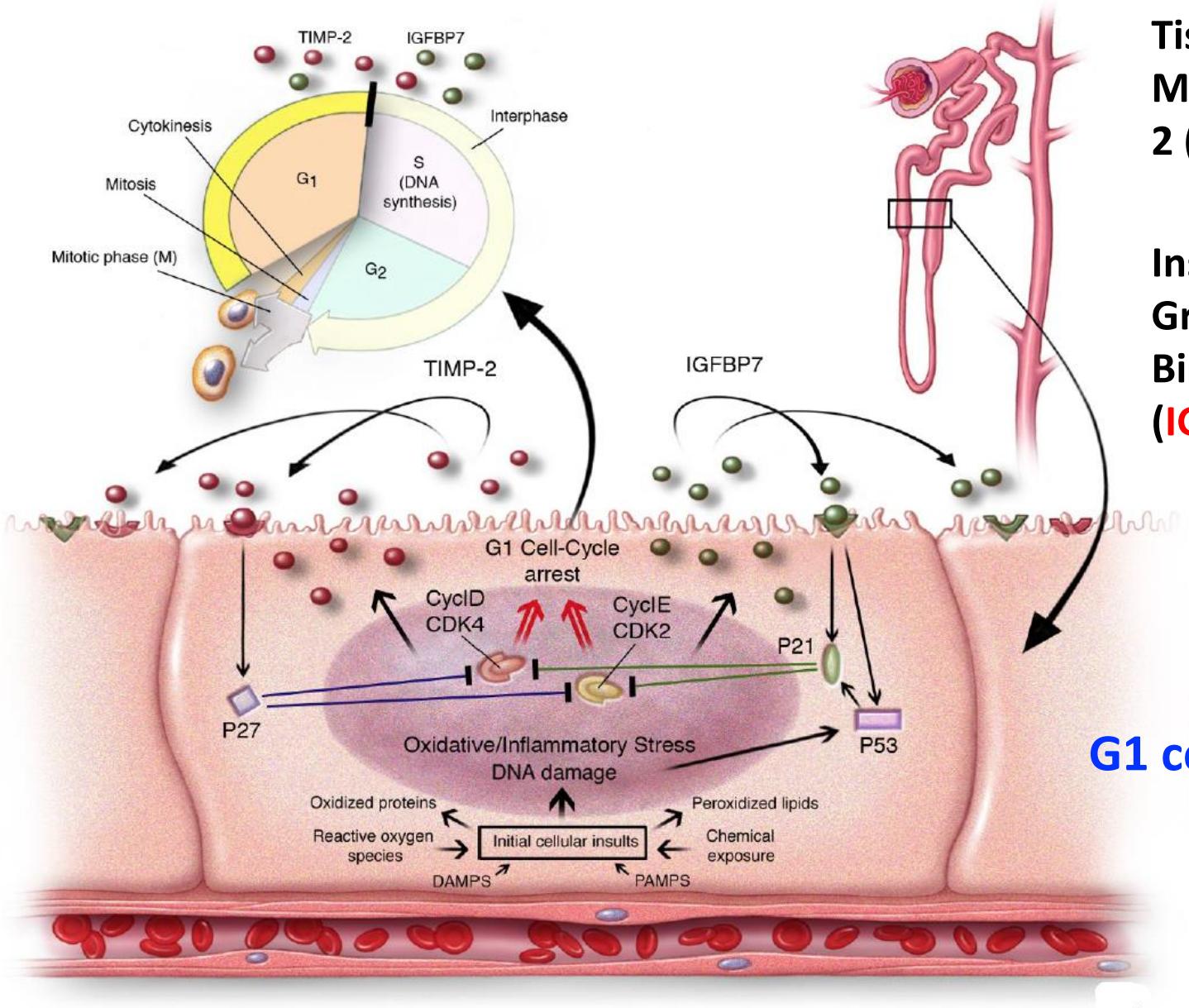


MAKE 30 or death

CELL CYCLE ARREST BIOMARKERS



Kashani et al. Critical Care (2013) 17:R25



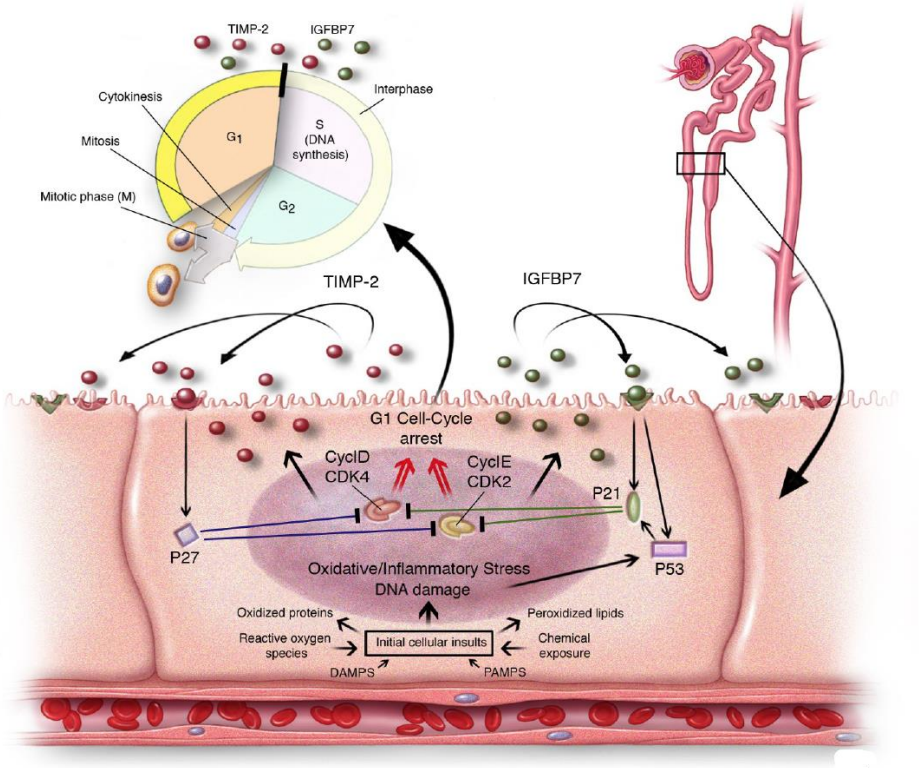
Tissue Inhibitor of Metalloproteinase 2 (TIMP-2)

+

Insulin-Like Growth Factor Binding Protein 7 (IGFBP7)

G1 cell cycle arrest

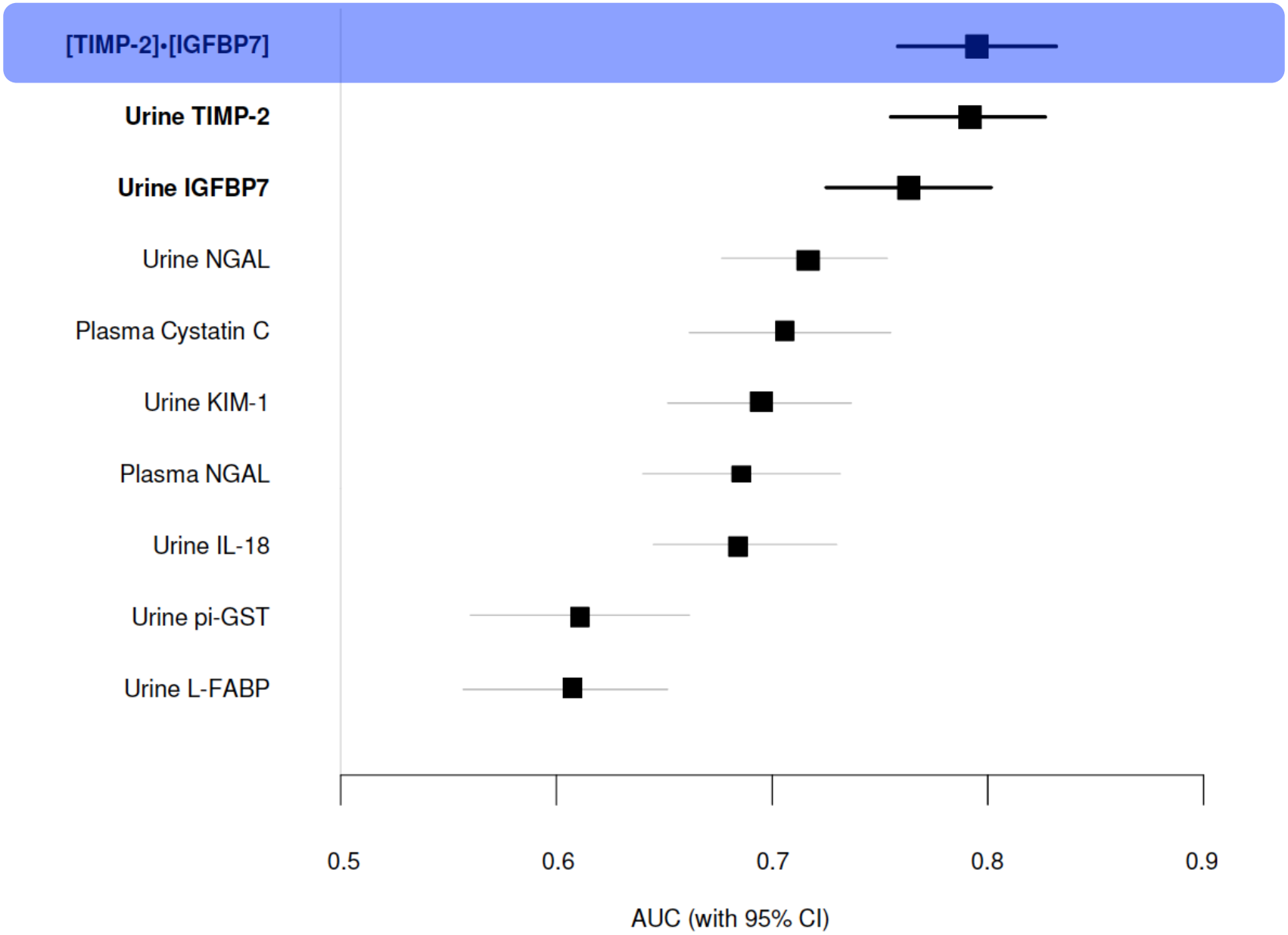
Kashani et al. Critical Care (2013) 17:R25



- Tubular cells may undergo cell cycle arrest (as demonstrated by cell cycle arrest biomarkers in the urine) to decrease energy consumption and protect themselves.

- This phenomenon may then result in activation of the **tubulo-glomerular feedback** mechanism, which would contribute to a **decrease in GFR** aimed at attenuating ultrafiltration.

Gomez H et al. Shock. (2014) 41:3-11



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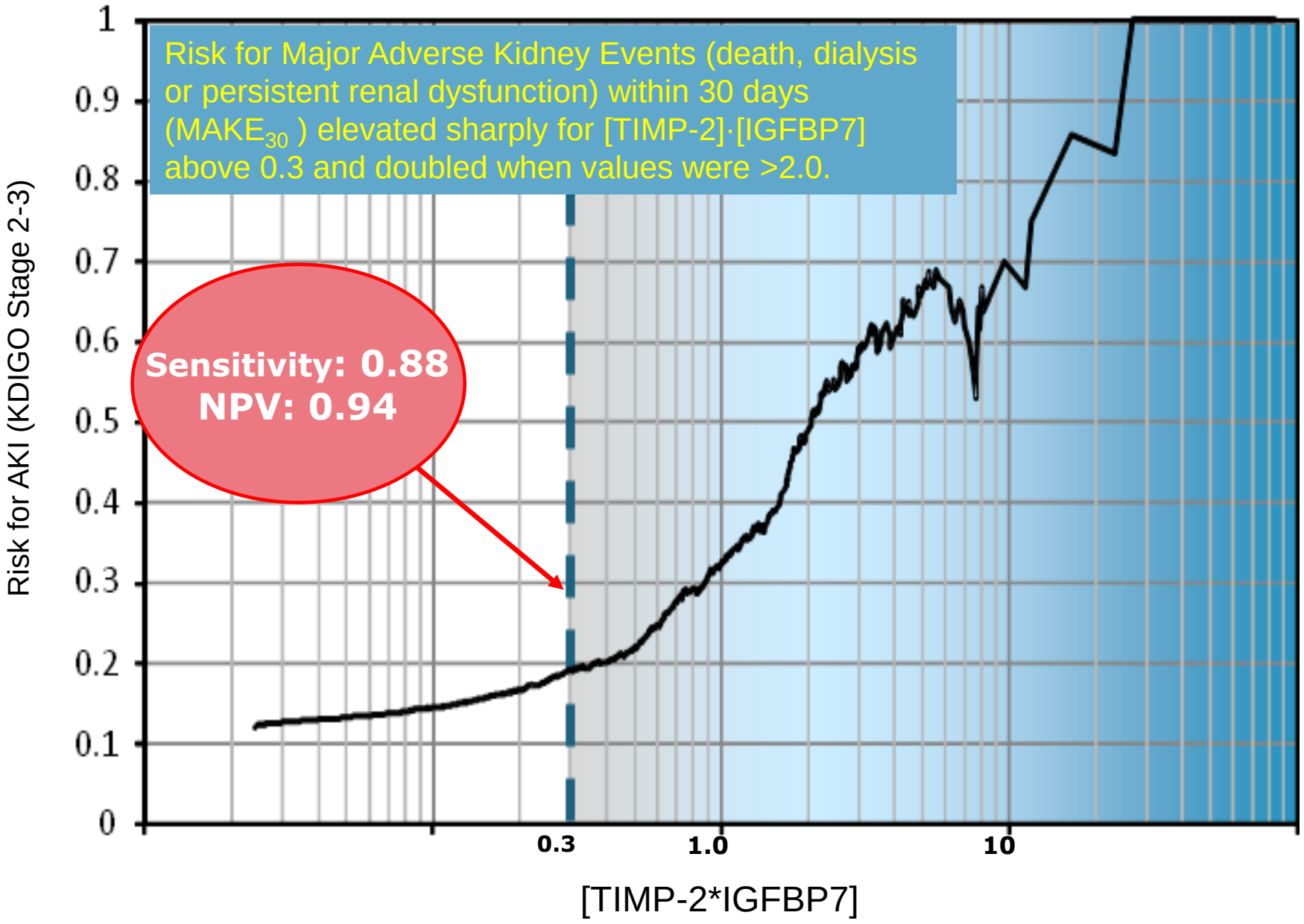
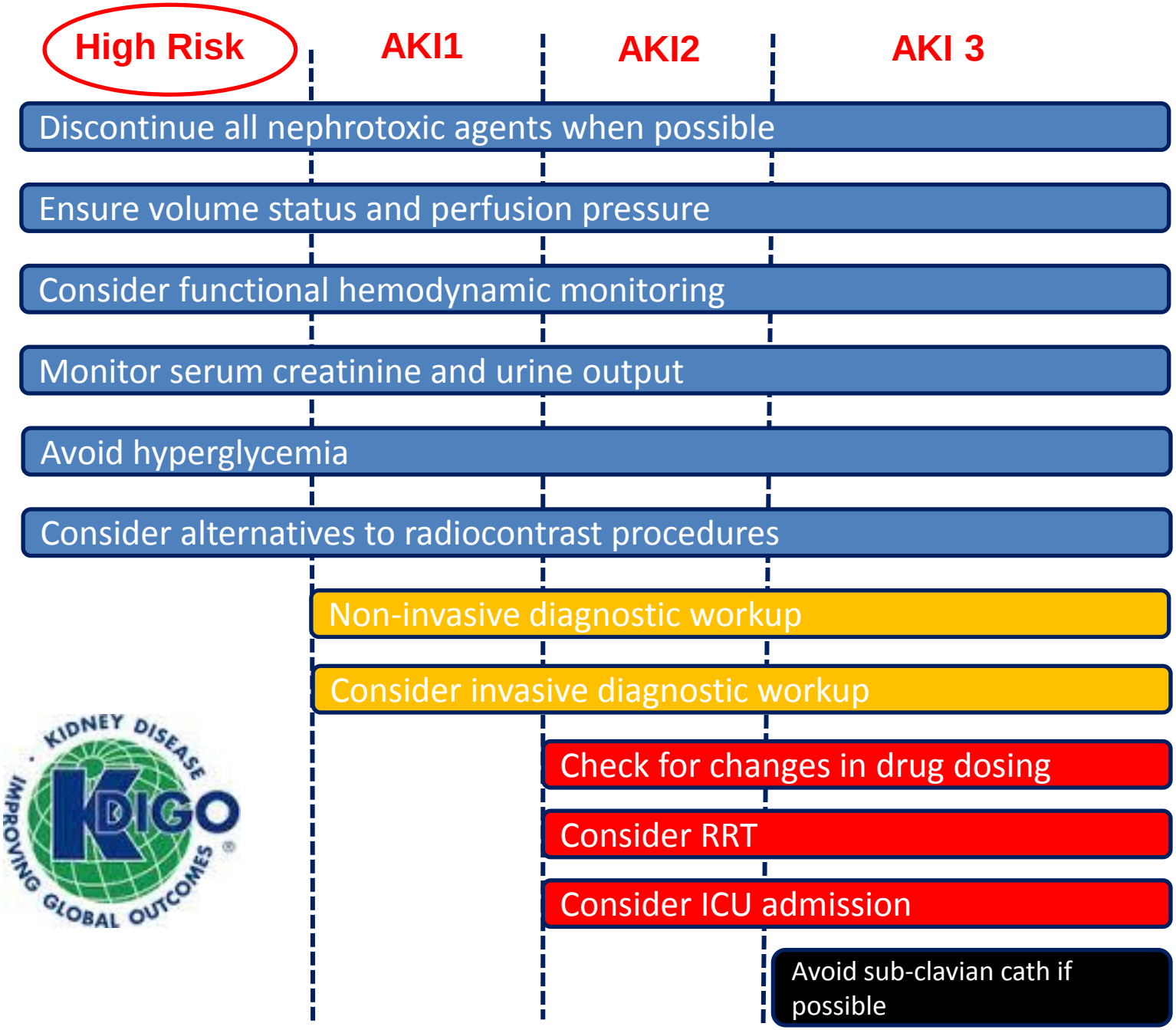

Risk for Major Adverse Kidney Events (death, dialysis or persistent renal dysfunction) within 30 days ($MAKE_{30}$) elevated sharply for [TIMP-2]·[IGFBP7] above 0.3 and doubled when values were >2.0.
Sensitivity: 0.88
NPV: 0.94
Risk for AKI (KDIGO Stage 2-3)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.3
1.0
10
[TIMP-2*IGFBP7]


High Risk
AKI1
AKI2
AKI 3
Discontinue all nephrotoxic agents when possible
Ensure volume status and perfusion pressure
Consider functional hemodynamic monitoring
Monitor serum creatinine and urine output
Avoid hyperglycemia
Consider alternatives to radiocontrast procedures
Non-invasive diagnostic workup
Consider invasive diagnostic workup
Check for changes in drug dosing
Consider RRT
Consider ICU admission
Avoid sub-clavian cath if possible
KIDNEY DISEASE
IMPROVING GLOBAL OUTCOMES
KDIGO

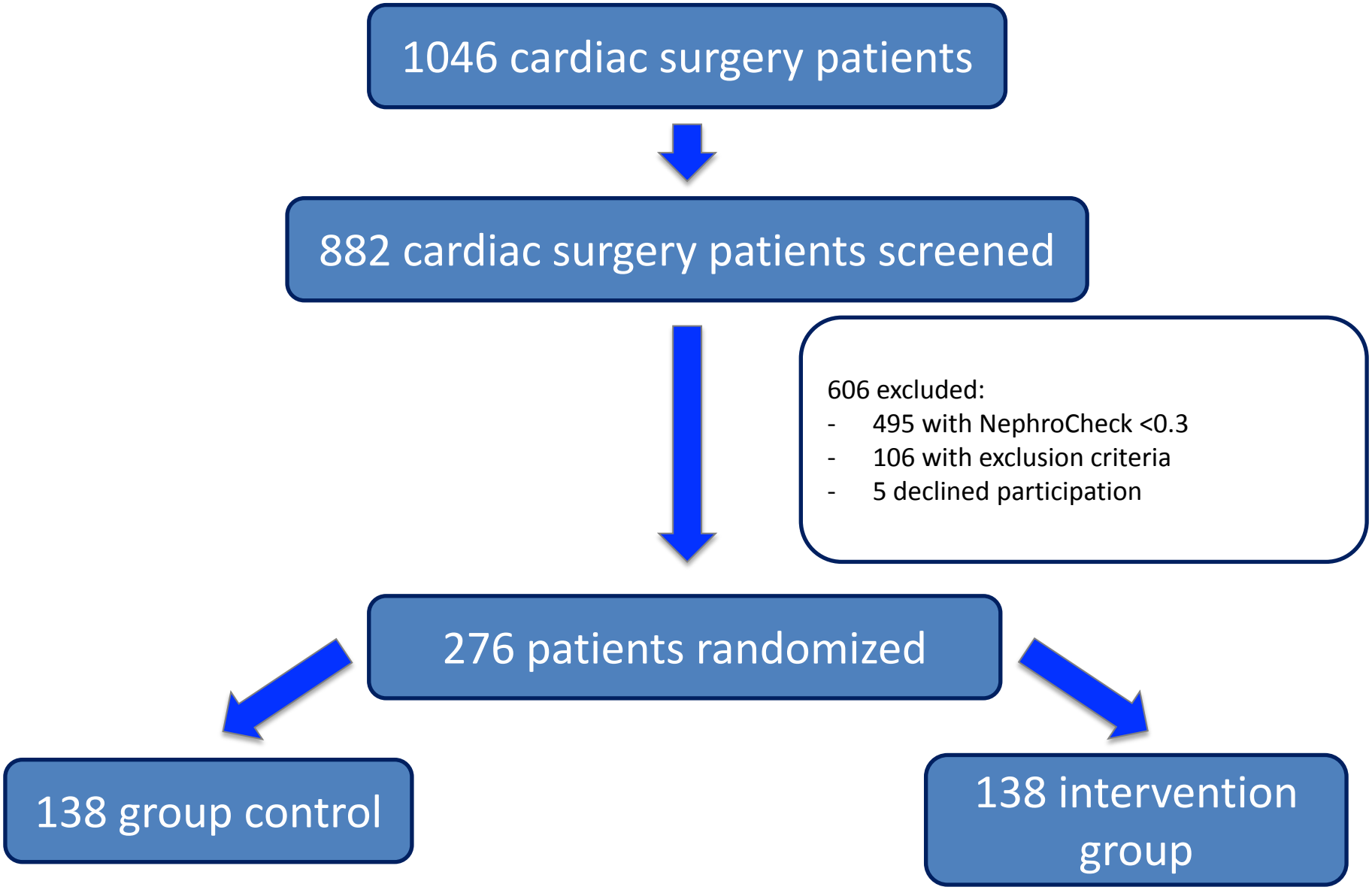
Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial

- Supportive care “bundle” in high risk patients for AKI → reduce the occurrence and severity of CSA-AKI,

- High risk for AKI was defined as urinary [TIMP-2]· [IGFBP7] ≥ 0.3 4 h after CPB.

Avoidance of nephrotoxic agents - discontinuation of ACEi and ARBs for the first 48 h after Surgery - close monitoring of Scr and UO - avoidance of hyperglycemia for the first 72 h after surgery - consideration of alternatives to radiocontrast agents - close hemodynamic monitoring (PiCCO); optimization of the volume status and hemodynamic parameters according to a prespecified algorithm

Meersch M et al. Intensive Care Med (2017)



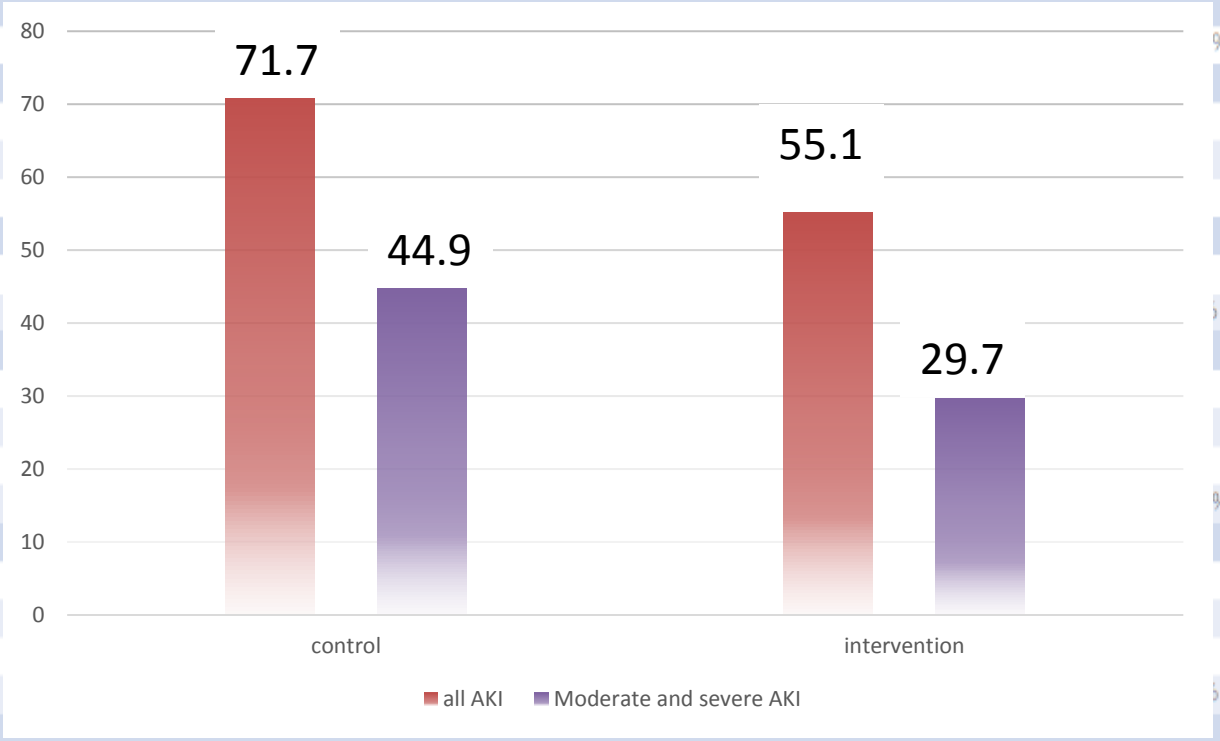
Meersch M et al. Intensive Care Med (2017)

	Control ($n = 138$)	Intervention ($n = 138$)	p value
Patients with catecholamines during intervention period, no. (%)			
Dobutamine	13 (9.4)	43 (31.2)	<0.001
Epinephrine	21 (15.2)	29 (21.2)	0.201
Norepinephrine	91 (65.9)	94 (68.1)	0.701
Catecholamines during intervention period, median (Q1, Q3), µg/kg			
Dobutamine	1107.9 (407.6, 1387.6)	1373.2 (960.7, 1700.0)	0.093
Epinephrine	31.6 (9.3, 49.0)	15.2 (5.5, 30.8)	0.191
Norepinephrine	22.7 (7.3, 49.0)	14.5 (5.2, 39.9)	0.088
Volume therapy during intervention period, median (Q1, Q3), ml			
Total volume	2745 (1968, 3625)	2575 (1965, 3518)	0.699
Crystalloids	2220 (1518, 3220)	2220 (1720, 3220)	0.470
Colloids	0 (0, 0)	0 (0, 0)	0.996
Blood products	0 (0, 0)	0 (0, 0)	0.561
H_2O	250 (0, 613)	200 (0, 400)	0.057
MAP, mean (±SD), mmHg			
At randomization	72 (11)	73 (11)	0.324
3 h	72 (9)	75 (10)	0.017
6 h	72 (9)	73 (10)	0.217
9 h	71 (10)	74 (9)	0.007
12 h	71 (11)	75 (9)	0.005
CVP, mean (±SD), mmHg			
At randomization	9 (5)	9 (4)	0.956
3 h	9 (4)	10 (4)	0.008
6 h	9 (4)	11 (5)	<0.001
9 h	9 (4)	10 (5)	0.014
12 h	10 (4)	10 (4)	0.137
S_vO_2, mean (±SD), %			
At randomization	67 (9)	67 (9)	0.872
3 h	66 (9)	68 (9)	0.180
6 h	65 (9)	69 (8)	<0.001
9 h	65 (9)	68 (10)	0.010
12 h	64 (9)	68 (8)	<0.001
Atrial fibrillation within 12 h, no. (%)	15 (10.9)	13 (9.4)	0.690
Hyperglycemia[a], no. (%)	104 (75.4)	70 (50.7)	<0.001
ACEi/ARBs[b], no. (%)	42 (30.4)	15 (10.9)	<0.001
Nephrotoxic agents[c], no. (%)	22 (15.9)	18 (13.0)	0.494
Contrast agents	19 (13.8)	11 (8.0)	0.122
Vancomycin, gentamicin	6 (4.3)	9 (6.5)	0.426
Diuretics[d], no. (%)	113 (81.9)	103 (74.6)	0.144
Infections, no./total no. (%)	11 (8.0)	9 (6.5)	0.642
Urine [TIMP-2]·[IGFBP7] at 12 h, ng/ml^2/1000, median (Q1, Q3)	0.84 (0.35, 1.57)	0.58 (0.26, 1.20)	0.045
Relative change urine [TIMP-2]·[IGFBP7] 12 h vs. baseline, ng/ml^2/1000, median (Q1, Q3)	1.13 (0.52, 2.23)	1.07 (0.38, 1.94)	0.272

	Controls	Interventions	
Dobutamine	13(9.4)	43(31.2)	<0.001
MAP (mmHg)			
3h	72(9)	75(10)	0.017
9h	71(10)	74(9)	0.007
12h	71(11)	75(9)	0.005
CVP (mmHg)			
3h	9(4)	10(4)	0.008
6h	9(4)	11(5)	<0.001
9h	9(4)	10(5)	0.014
SvO_2 (%)			
6h	65(9)	69(8)	<0.001
9h	65(9)	68(10)	0.010
12h	64(9)	68(8)	<0.001
Hyperglicemia	104(75.4)	70(50.7)	<0.001
ACEi/ARBs	42(30.4)	15(10.9)	<0.001
Urine [T2I7] 12 h	0.84(0.35,1.57)	0.58(0.26,1.20)	<0.001

	Control ($n = 138$)	Intervention ($n = 138$)	p value	OR (intervention versus control) (95% CI)	RRR[a] (95% CI)	ARR[b] (95% CI)
Primary outcome						
AKI within 72 h, no./total no. (%)	99/138 (71.7)	76/138 (55.1)	0.004	0.483 (0.293, 0.796)	23.2% (7.8, 36.1%)	16.6% (5.5, 27.9%)
Diagnosis based on, no. (%)						
Creatinine	14 (14.1)	10 (13.2)				
Urine output	81 (81.8)	62 (81.6)				
Both	4 (4.0)	4 (5.3)				
Secondary outcomes						
AKI stage, no./total no. (%)						
1	37/138 (26.8)	35/138 (25.4)	0.784	0.928 (0.542, 1.588)	5.4% (−40.7, 36.4%)	1.4% (−8.9, 11.8%)
Diagnosis based on, no. (%)						
Creatinine	12 (32.4)	9 (25.7)				
Urine output	23 (62.2)	25 (71.4)				
Both	2 (5.4)	1 (2.9)				
2	45/138 (32.6)	30/138 (21.7)	0.042	0.574 (0.335, 0.984)	33.3% (0.8, 55.2%)	10.9% (0.5, 21.3%)
Diagnosis based on, no. (%)						
Creatinine	1 (2.2)	1 (3.3)				
Urine output	42 (93.3)	28 (93.3)				
Both	2 (4.4)	1 (3.3)				
3	17/138 (12.3)	11/138 (8.0)	0.232	0.617 (0.278, 1.370)	35.3% (−33.0, 68.5%)	4.3% (−2.8, 11.5%)
Diagnosis based on, no. (%)						
Creatinine	1 (5.9)	0 (0)				
Urine output	16 (94.1)	9 (81.8)				
Both	0 (0)	2 (18.2)				
Moderate/severe AKI, no./total no. (%)	62/138 (44.9)	41/138 (29.7)	0.009	0.518 (0.316, 0.851)	33.9% (9.3, 51.8%)	15.2% (4.0, 26.5%)
Requirement of RRT within 72 h, no./total no. (%)	7/138 (5.1)	10/138 (7.2)	0.453	1.462 (0.540, 3.959)	−42.9% (−264.5, 44.0%)	−2.2% (−7.8, 3.5%)
Requirement of RRT during hospital stay, no./total no. (%)	9/138 (6.5)	14/138 (10.1)	0.276	1.618 (0.676, 3.874)	−55.6% (−247.4, 30.3%)	−3.6% (−10.1, 2.9%)
PRD on day 30, no./total no. (%)	7/126 (5.6)	14/129 (10.9)	0.124	2.070 (0.806, 5.313)	−95.3% (−367.9, 18.4%)	−5.3% (−12.0, 1.4%)
PRD on day 60, no./total no. (%)	6/125 (4.8)	11/128 (8.6)	0.228	1.865 (0.668, 5.207)	−79.0% (−369.3, 31.7%)	−3.8% (−9.9, 2.3%)
PRD on day 90, no./total no. (%)	9/125 (7.2)	9/126 (7.1)	0.986	0.992 (0.380, 2.587)	0.8% (−141.6, 59.3%)	0.1% (−6.3, 6.4%)
Requirement of RRT on day 30, no./total no. (%)	3/132 (2.3)	4/131 (3.1)	0.722	1.354 (0.297, 6.173)	−34.4% (−488.6, 69.3%)	−0.8% (−4.7, 5.4%)

The overall AKI incidence was 63.4% (175/276).



Primary outcome (AKI within 72 h after surgery):
Intervention group (55.1%) vs control (71.7%) [p = 0.004; OR, 0.483 (95% CI, 0.293–0.796).

In the intervention group significantly lower rates of moderate and severe AKI were observed compared to the control group (29.7%) vs (44.9%); p = 0.009; OR, 0.518 (95% CI, 0.316–0.851).

- The adherence to guidelines (and bundles) can reduce the occurrence of CSA-AKI

- Maybe … patients who received dobutamine … also received a better hemodynamic monitoring

- … resulting in the possibility of a more **personalized medicine**

WHO TO TEST: Post-op CT surgery patients (All cardiac surgery patients on post-op day 1 at 0530)

WHO NOT TO TEST: Pre-op creatinine >2, established stage 2/3 AKI, on RRT or in imminent need

1) MD, NP, PA orders NephroCheck on EMR
2) ICU RN collects fresh urine sample and sends to lab immediately
3) Lab reports results to ordering MD, NP, PA who will follow flow diagram below

Time of sample collection: 0530 POD1

LOW RISK <0.3 Negative AKIRisk Score	**MOD RISK 0.3-2.0** Positive AKIRisk Score - Moderately high risk of AKI in next 12 hours	**HIGH RISK >2.0** Positive AKIRisk Score - Very high risk of AKI in next 12 hours
Standard of Care	**Super Standard Management**	**Aggressive Management to Prevent AKI**
Foley out ASAP	Keep foley and hourly U.O.	Keep foley and hourly U.O.
Daily Serum Cr.	Serum Cr. Q 12	Serum Cr. Q 8-12
Remove HD Monitoring	Consider HD Monitoring	Do HD Monitoring
Average hourly U.O.	Avoid any nephrotoxin	Avoid all potential nephrotoxins
May use NSAIDS/ACE	For oliguria, may use balanced fluid IF CVP<8; Hold lasix unless pulmonary edema	May use balanced fluid IF CVP<8 AND evidence of hypovolemia (not just oliguria); hold lasix
SVO2 not monitored	No NSAIDS or ACE/ARB's	No NSAIDS or ACE/ARB's – adjust doses (narcotics)
Consider transfer out of ICU	Monitor SVO2 if h/o abnormal LV fx	Monitor SVO2, Echo or PA catheter if <55% -
Recheck markers in 12 hours if new insult occurs	Consider inotropes	Inotropes to keep CI.2.2
	Consider renal phone call	Renal consult
	Sensible fluids	Sensible fluids
	Avoid dye	Avoid dye
	Consider Colloids only approach	Dobutamine for cardiac surgery patients
	Recheck markers in 8-16 hours, if more than 1.4 or vectoring more than 0.6 presume AKI should be treated	
	Avoid multiple pressors	

***NOTE**: Record LOS, mortality, dialysis (yes/no, length of RRT), peak creatinine, KDIGO stage of AKI (nephron clin prac 2012 120 179-184), rehab (yes/no, LOS)

JAMA Surgery | Special Communication

Guidelines for Perioperative Care in Cardiac Surgery
Enhanced Recovery After Surgery Society Recommendations

Daniel T. Engelman, MD; Walid Ben Ali, MD; Judson B. Williams, MD, MHS; Louis P. Perrault, MD, PhD; V. Seenu Reddy, MD; Rakesh C. Arora, MD, PhD; Eric E. Roselli, MD; Ali Khoynezhad, MD, PhD; Marc Gerdisch, MD; Jerrold H. Levy, MD; Kevin Lobdell, MD; Nick Fletcher, MD, MBBS; Matthias Kirsch, MD; Gregg Nelson, MD; Richard M. Engelman, MD; Alexander J. Gregory, MD; Edward M. Boyle, MD

Postoperative Strategies

Kidney Stress and Acute Kidney Injury

Based on these studies, biomarkers are recommended for early identification of patients at risk and to guide an intervention strategy to reduce AKI (class IIa, level B-R).

Class (Strength) of Recommendation

I (strong): benefit many times greater than risk

IIa (moderate): benefit much greater than risk

IIb (weak): benefit greater than risk

III: no benefit (moderate): benefit equal to risk

III: harm (strong): risk greater than benefit

Level (Quality) of Evidence

A

High-quality evidence from more than 1 randomized clinical trial

Meta-analysis of high-quality randomized clinical trials

One or more randomized clinical trials corroborated by registry studies

B-R

Moderate-quality evidence from 1 or more randomized clinical trial

Meta-analysis of moderate-quality randomized clinical trials

B-NR

Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies or observational studies

C-LD

Randomized or nonrandomized observational or registry studies with limitations of design or execution

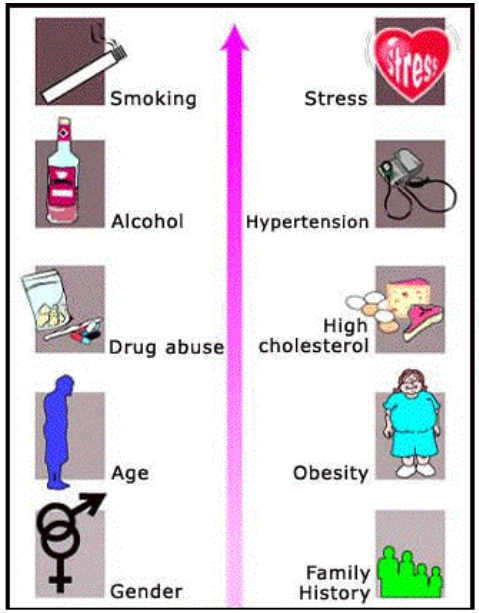
C-EO

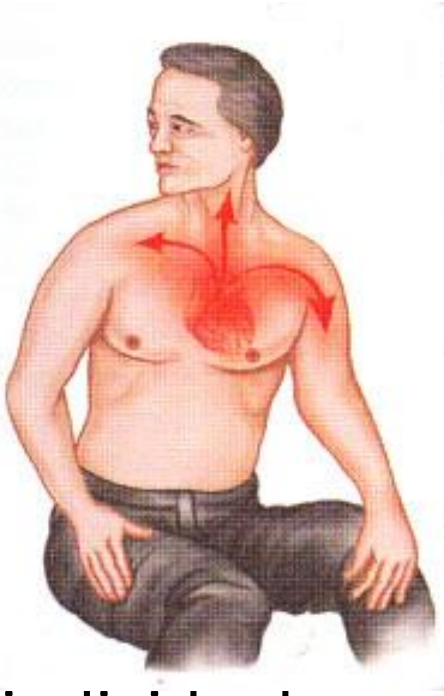
Consensus of expert opinion based on clinical experience

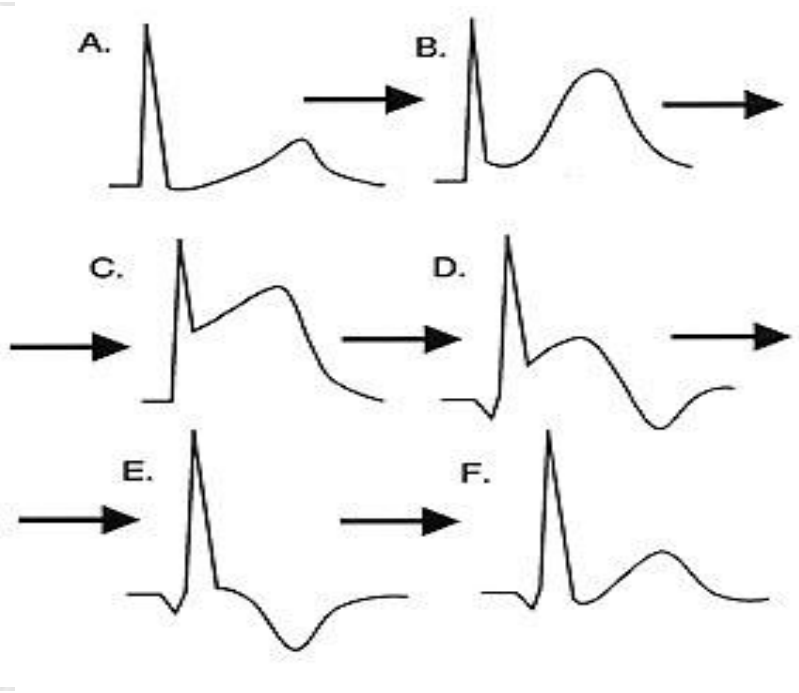
SO

WHY SHOULDN'T WE DOSE BIOMARKERS TO ALL PATIENTS ADMITTED TO THE ICU?

IS TROPONIN DOSED TO ALL PATIENTS?







  - An at-risk individual
  - Symptoms that raise suspicion for MI (angina, ST elevation)

- **Lack of the anginal equivalent should inform us to not use the marker**

Troponin, the "Gold Standard", + sick patient

Intensive
DOI 10.1(

P. Amm
T. Fehr
E. I. Min
C. Günt
O. Berte

Abstract *Objective*: To detect myocardial damage in severe systemic inflammation by cTnI measurements in patients without acute coronary syndromes.
Design: Prospective case control study.
Setting: Tertiary referral center.
Participants: Twenty patients with sepsis, septic shock, and systemic inflammatory response syndrome (SIRS) were examined and compared to controls without coronary artery disease or myocarditis.
Measurements and results: cTnI levels were assessed in patients with SIRS, sepsis, and septic shock. Eight patients (two female/six male) suffered from septic shock, nine (three female/six male) from sepsis without shock, and three (three male) from SIRS. Seventeen patients (85 %) showed elevated cTnI (median 0.57 µg/l; 0.17–15.4), whereas no patient in the control group showed elevated cTnI ($P < 0.0001$). Six patients (30 %), – three with septic shock and three with sepsis – died during hospitalization, five of them with elevated cTnI. Four out of five autopsies showed normal coronary arteries. Coronary angiography, autopsy, and stress echocardiography ruled out significant coronary artery disease in ten cTnI-positive patients (59 %). In 41 % of cTnI-positive patients, *Streptococcus pneumoniae* could be cultured, whereas no cTnI-negative or control patient showed signs of infection due to *S. pneumoniae*. *Conclusion:* Cardiac troponin I was elevated in 85 % of patients with sepsis, septic shock or SIRS in our study. A high percentage showed infection caused by *S. pneumoniae*. In what way microorganisms cause cTnI elevations is not yet understood.

Keywords Cardiac troponin I · SIRS · Sepsis · Septic shock · Myocardial cell injury

Being sick → Increased Troponin

Table 2 Reasons for acutely elevated troponins

Acute coronary syndrome
Acute heart failure
Pulmonary embolism
Stroke
Acute aortic dissection
Tachyarrhythmias
Hypotension / Shock
Sepsis
ARDS
Perimyocarditis
Endocarditis
Tako-tsubo cardiomyopathy
Radiofrequency catheter ablation
Cardiac contusion
Strenuous exercise
Sympathomimetic drugs
Chemotherapy

Frontiers in c

Tropor **oronary disease**

S. Agewall [1]*

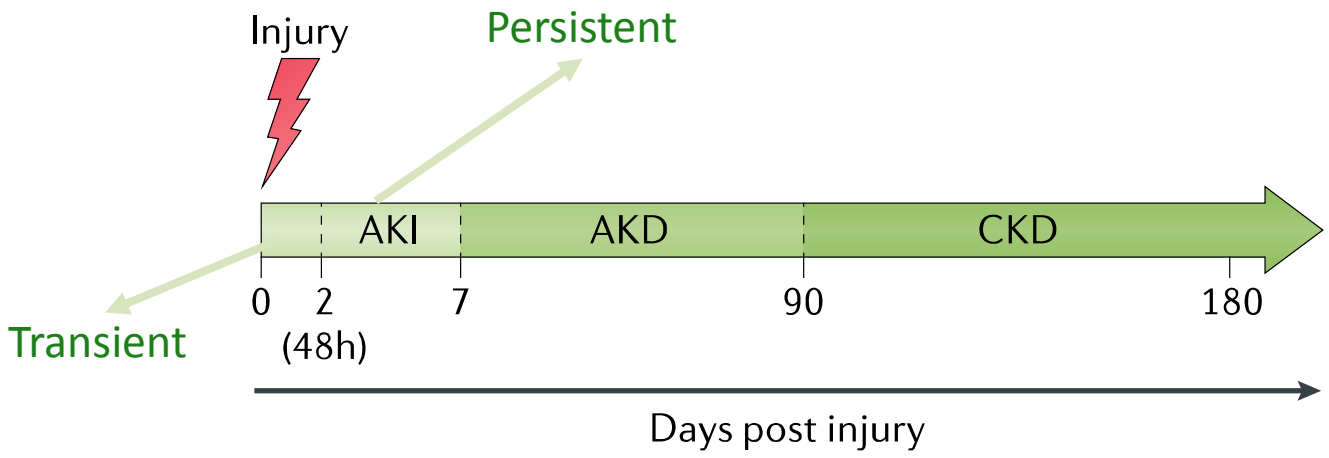
[1]Department of Medicine dinge, Karolinska Institutet, Karolinska University Ho

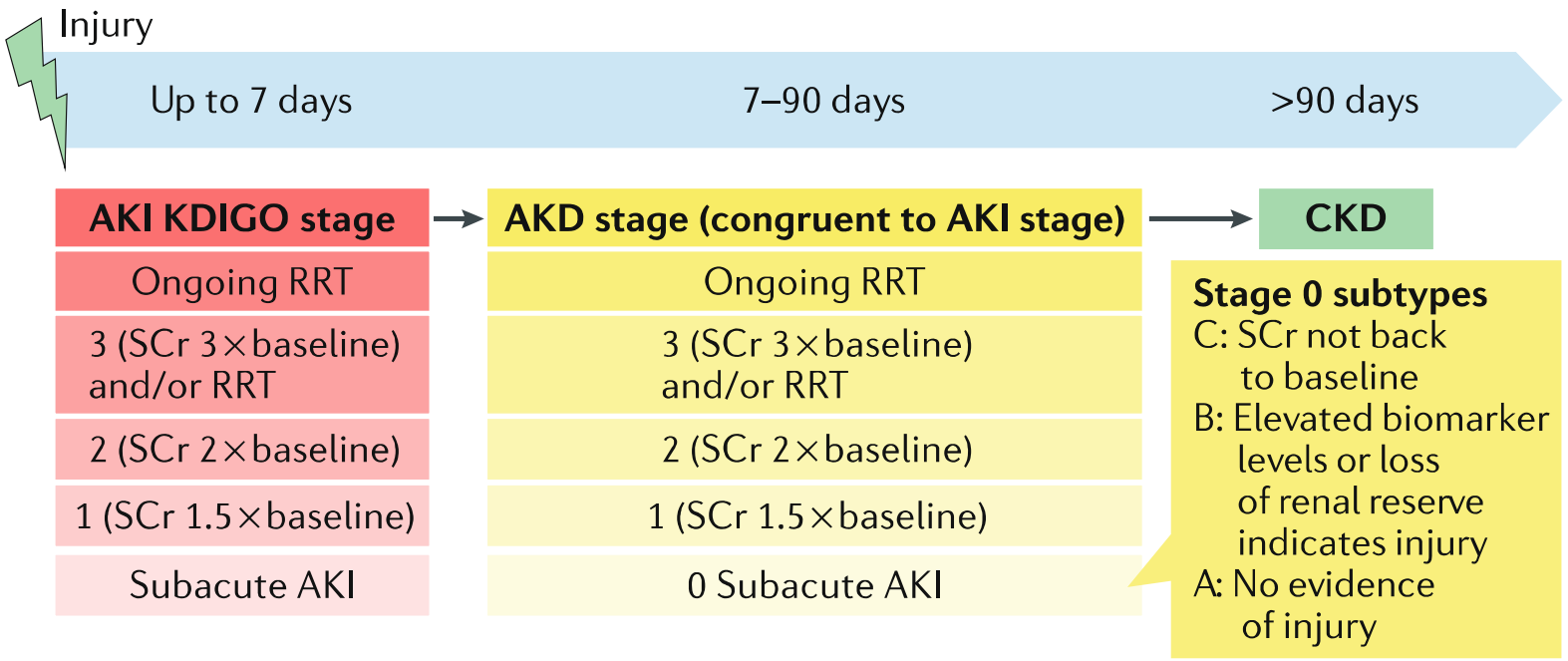
Received 23 April 2010; re

How, and In Whom, Do We Apply AKI Biomarkers?

- Medical school aphorism: “There are only three reasons that people go to a doctor”
  - Fever
  - Bleeding
  - Pain
- AKI is not specifically associated with any of these, simply put, “**AKI doesn’t hurt**”

ACUTE DIALYSIS QUALITY INITIATIVE WORKGROUP 16 (NAT REV NEPHROL 2017)





Use of Cell Cycle Arrest Biomarkers in Conjunction With Classical Markers of Acute Kidney Injury

Michael Joannidis, MD[1]; Lui G. Forni, BSc, PhD, MBBS, MRCPI, AFICM[2]; Michael Haase, MD[3]; Jay Koyner, MD[4]; Jing Shi, PhD[5]; Kianoush Kashani, MD, MSc[6,7]; Lakhmir S. Chawla, MD[8]; John A. Kellum, MD, MCCM[9]; on behalf of the Sapphire Investigators

CCM 2019

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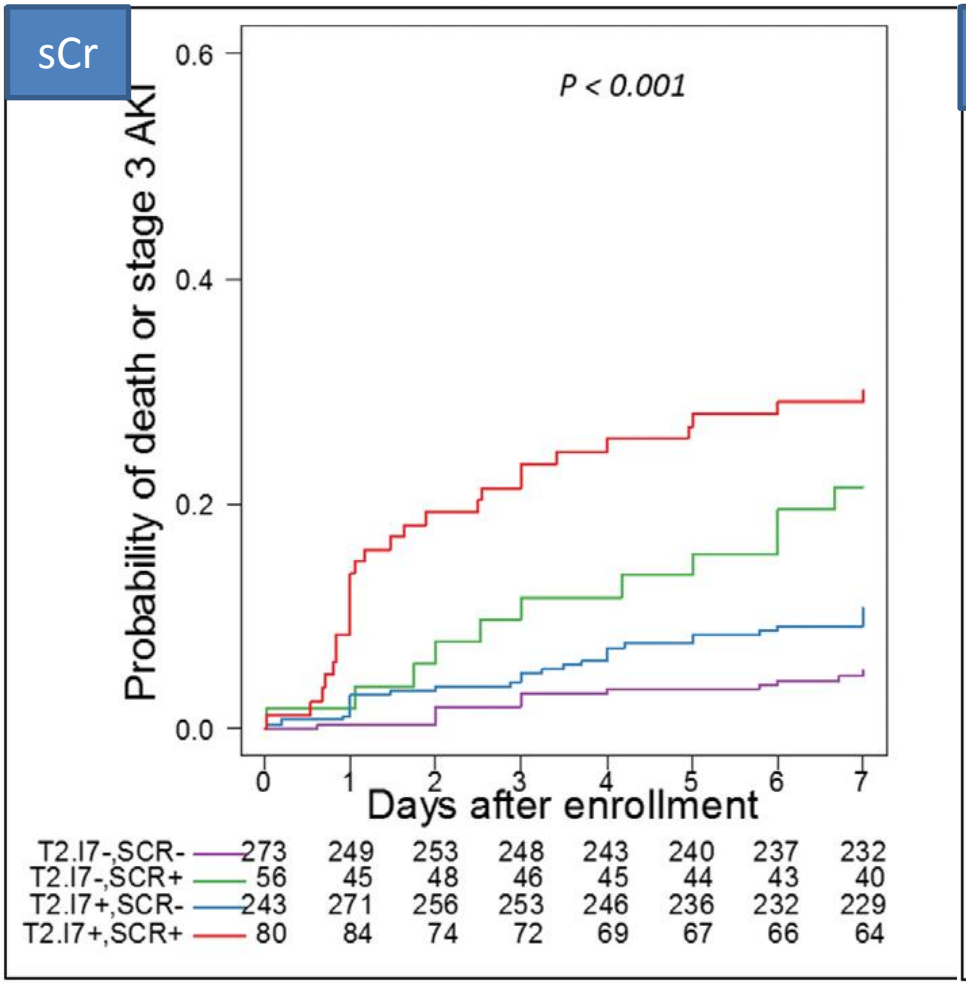

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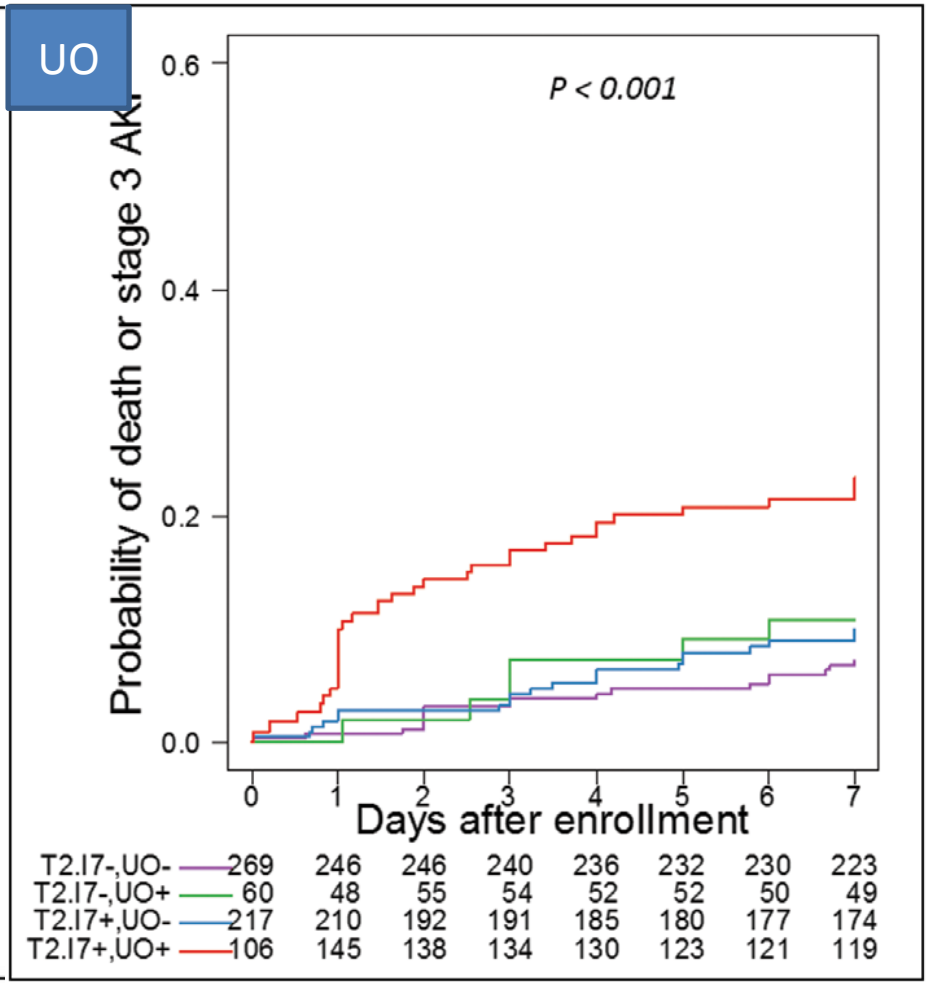

RENAL ANGINA INDEX (RAI)

Zaccaria Ricci
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zaccaria.ricci@gmail.com

Comment

A renal angina index to overcome the silence of the kidneys

RAI

Risk strata

Risk criteria	Score
Admission to intensive care unit	1
Solid organ or stem-cell transplantation	3
Mechanical ventilation or vasoactive support, or both	5

Injury strata

Serum creatinine relative to baseline	FO accumulation (%)	Score
Decreased or no change	<5	1
>1×–1·49×	5–10	2
1·5×–1·99×	11–15	4
≥2×	>15	8

Risk × injury
Scores: 1–40

Renal angina fulfilled with renal angina index score ≥8

The index calculation for the fulfilment of renal angina is assessed **12 h after a patient is admitted to an intensive care unit and used for prediction of severe acute kidney injury 72 h (3 days) later.**

Risk factors are determined as described and assigned a point value (1, 3, and 5, where 1 denotes the lowest risk and 5 denotes the highest risk). Mechanical ventilation and vasoactive support should be used within the 12-h timepoint but are not required to be simultaneous for a patient to be scored 5 points.

Injury strata are described and assigned to a patient as appropriate.

Assessment of a renal angina index for prediction of severe acute kidney injury in critically ill children: a multicentre, multinational, prospective observational study

2017

Rajit K Basu, Ahmad Kaddourah, Stuart L Goldstein on behalf of the AWARE study investigators

Day 0 renal angina status

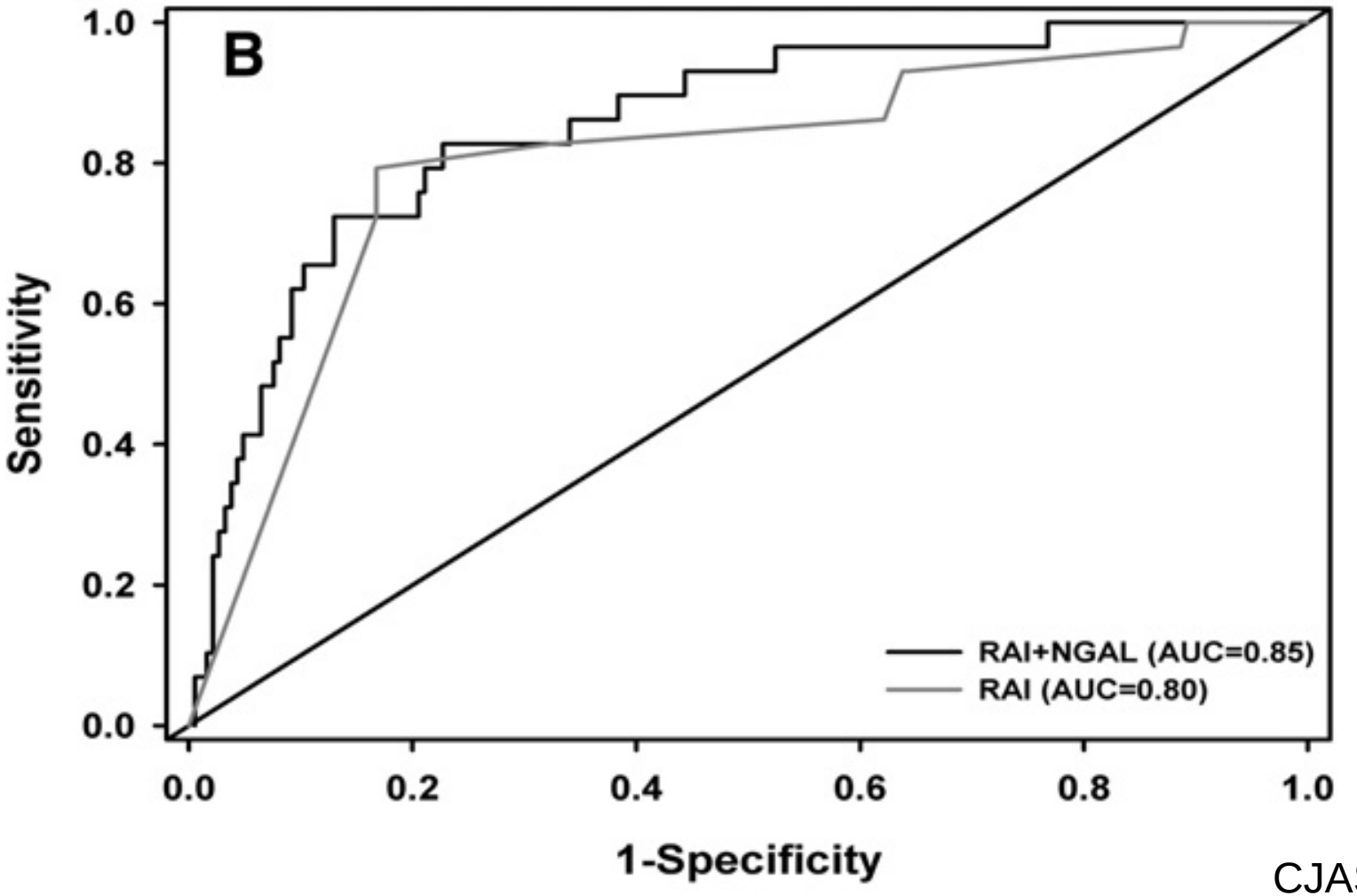
Fulfilment of renal angina: 286 (18%)
- PRISM-III: 7 (3–14)
- PIM-2: 3 (1–6)
- Severe acute kidney injury day 3: 121 (41%)
- Renal replacement therapy use: 36 (13%)
- Mortality: 32 (11%)

No renal angina: 1304 (82%)
- PRISM-III: 5 (3–8)
- PIM-2: 3 (1–4)
- Severe acute kidney injury day 3: 247 (19%)
- Renal replacement therapy use: 22 (1%)
- Mortality: 49 (4%)

- For the assessment of the renal angina index, patients from the AWARE study who had full data from the day of ICU admission, day 3, and day 28, including serum creatinine concentrations and urine output measurements were included.
- Data for 1590 patients. **286 patients (18%) had fulfilment of renal angina.**
- At day 3, severe acute kidney injury occurred in 121 (42%) patients positive for renal angina and 247 (19%) patients negative for renal angina (relative risk [RR] 2·23, 95% CI 1·87–2.66, p<0·0001).
- Fulfilment of renal angina showed better prediction for severe AKI than serum creatinine greater than baseline (RR 1.61, 95% CI 1·33–1·93; p<0·0001), which was maintained on multivariate regression (independent odds ratio for fulfilment of renal angina 3·21, 95% CI 2·20–4·67 *vs* serum creatinine greater than baseline 0·68, 0·49–4·94).

Incorporation of Biomarkers with the Renal Angina Index for Prediction of Severe AKI in Critically Ill Children

Rajit K. Basu,[*†‡§] *Yu Wang,*[†] *Hector R. Wong,*[†‡] *Lakhmir S. Chawla,*[‖] *Derek S. Wheeler,*[*†‡] *and Stuart L. Goldstein*[*†¶]



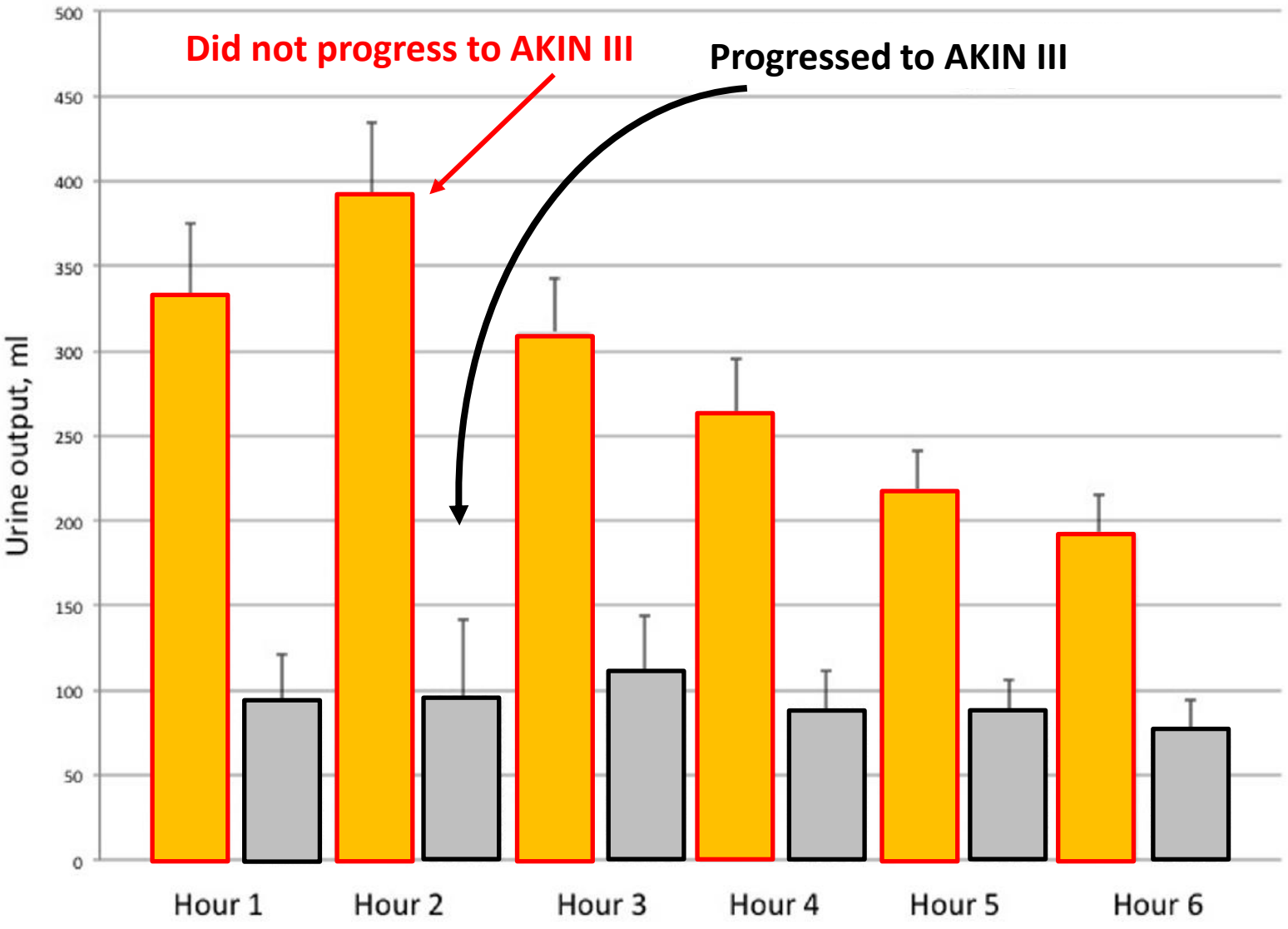
CJASN 2014

Development and Standardization of a Furosemide Stress Test to Predict the Severity of Acute Kidney Injury

- ✓ 77 patients with early AKI →
- ✓ I.V. furosemide (1 mg/kg for diuretic-naïve patients or 1.5 mg/kg for diuretic-exposed patients)
- ✓ → measured urinary volume over time

Chawla et al. Critical Care 2013, 17:R207

Furosemide stress test effect on urine flow



Chawla et al. Critical Care 2013, 17:R207

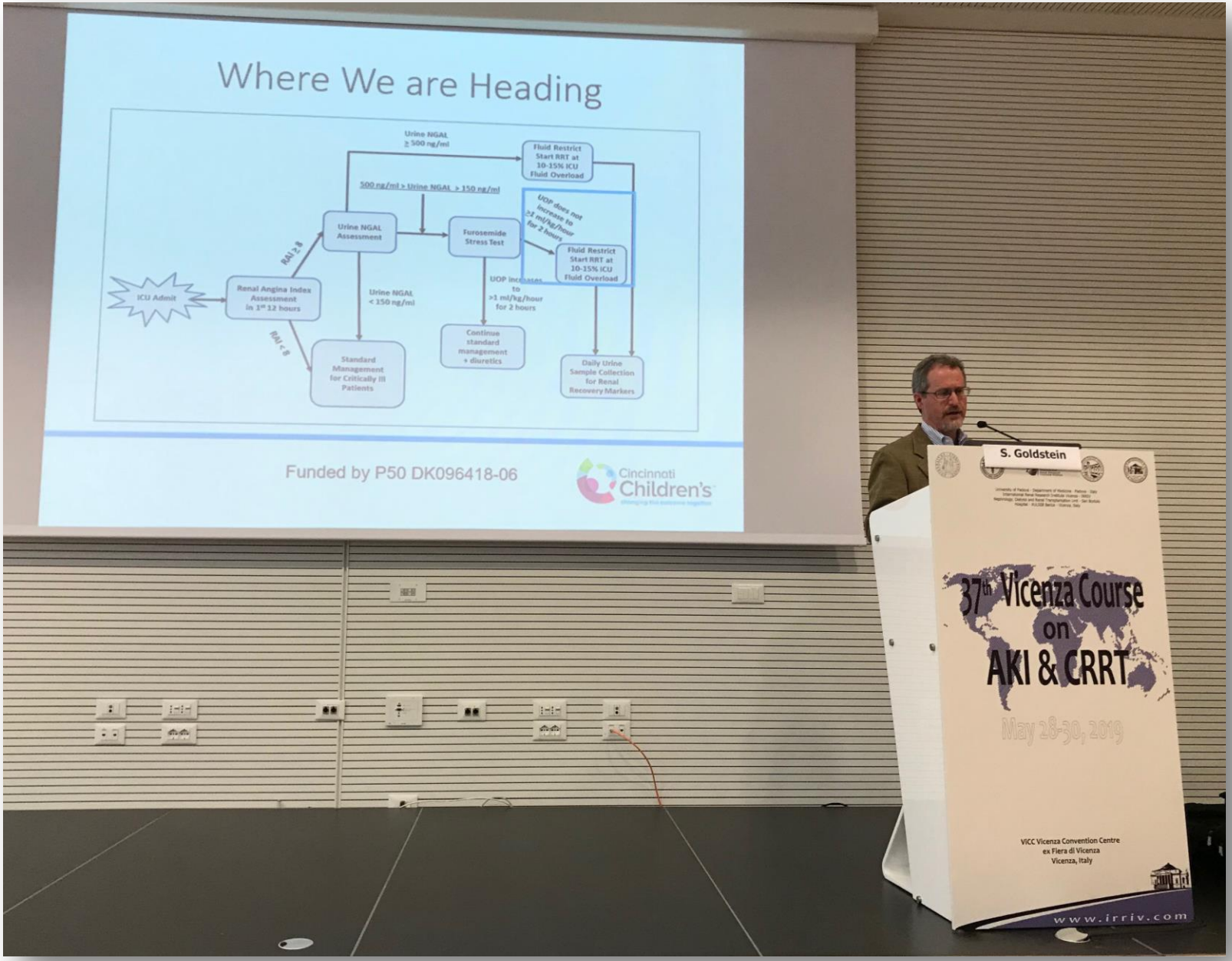
Furosemide Stress Test

Total urine output over 2 hours	Combined cohort	
	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%

- A volume less than 200 mL in 2 hours (100 ml/h) had 87% sensitivity and 84% specificity of worsening of AKI.

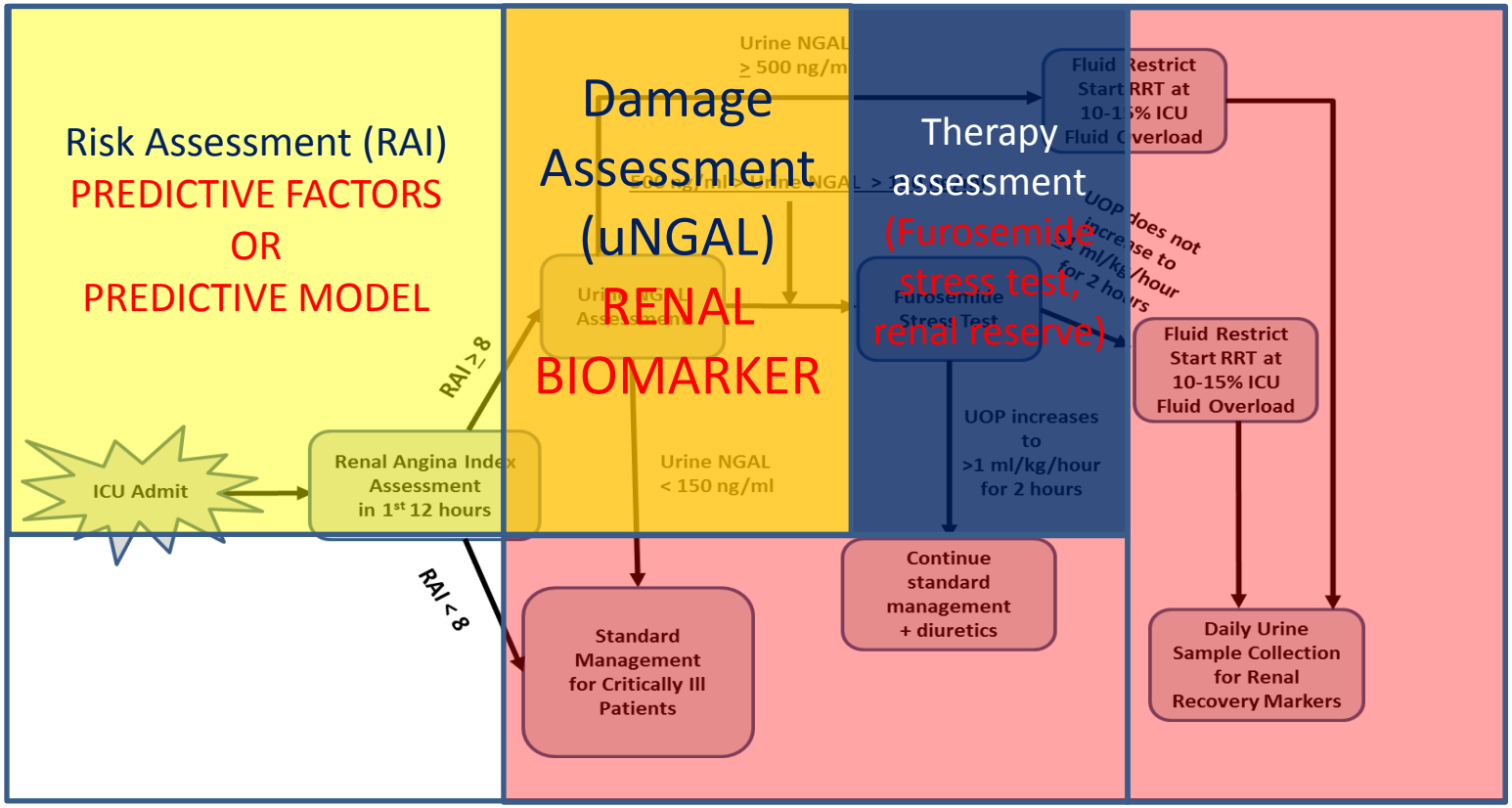
Conclusions: The FST in subjects with early AKI serves as a novel assessment of tubular function with robust predictive capacity to identify those patients with severe and progressive AKI. Future studies to validate these findings are warranted.

Chawla et al. Critical Care 2013, 17:R207



With permission, by Stu himself

Where We are Heading



Funded by P50 DK096418-06

CONCLUSIONS

- ✓ AKI is bad
- ✓ KDIGO classification (especially classes 2 and 3) highlights that function is lost
- ✓ Prevention is key
- ✓ **Renal damage/stress can now be identified and further disease evolution anticipated**
- ✓ **Adequate selection of patients screened with biomarkers (high risk surgery, AKI1, RAI, FST) is recommended**

CONCLUSIONS

✓Active **research is ongoing** on renal biomarkers and the Holy Grail is about to come

✓Further research should confirm the efficacy of therapeutic/preventive bundles in the management of AKI

Critical Care Nephrology and Renal Replacement Therapy in Children

Akash Deep
Stuart L. Goldstein
Editors

Springer