Acute Kidney Injury

From Galenus to KDIGO

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The Eberhard Ritz lecture
Heidelberg, April 4, 2019

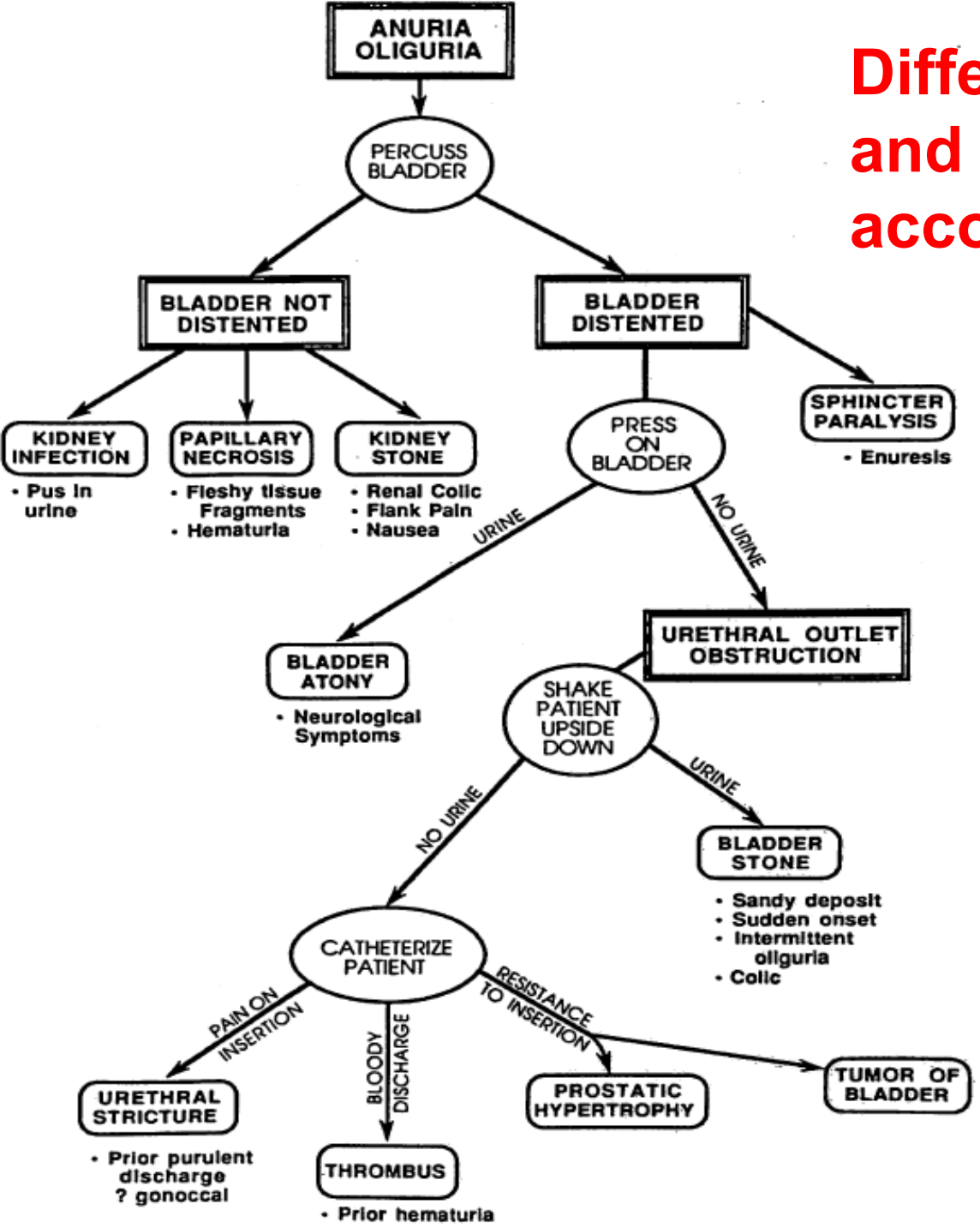
Claudius Galenus (AD 129 – Pergamon c. 200/c. 216, Pergamon

Galenus, the personal physician of 3 emperors Marcus Aurelius, Commodus, and Septimus Severus) was (according to Marcus Aurelius), the first under the physicians and the most prominent of the philosphers; he learned his skills on trauma and wound care in the sanctuary of Aesclepius, the god of cure, but mainly as physician of the gladiators of Pergamon. He continued his studies of medicine in Alexandria.

He is the most accomplished of all medical researchers of antiquity, Galenus influenced the development of various scientific disciplines, including anatomy, physiology and pathology, as well as philosophy.

He was the first to definitely demonstrate that the urine did not originate in the bladder but in the kidneys

Differential diagnosis and work- up of oliguria according to Galenus



Eknoyan G. Am J Nephrol 1989, 9:66-86.

Aphorisms

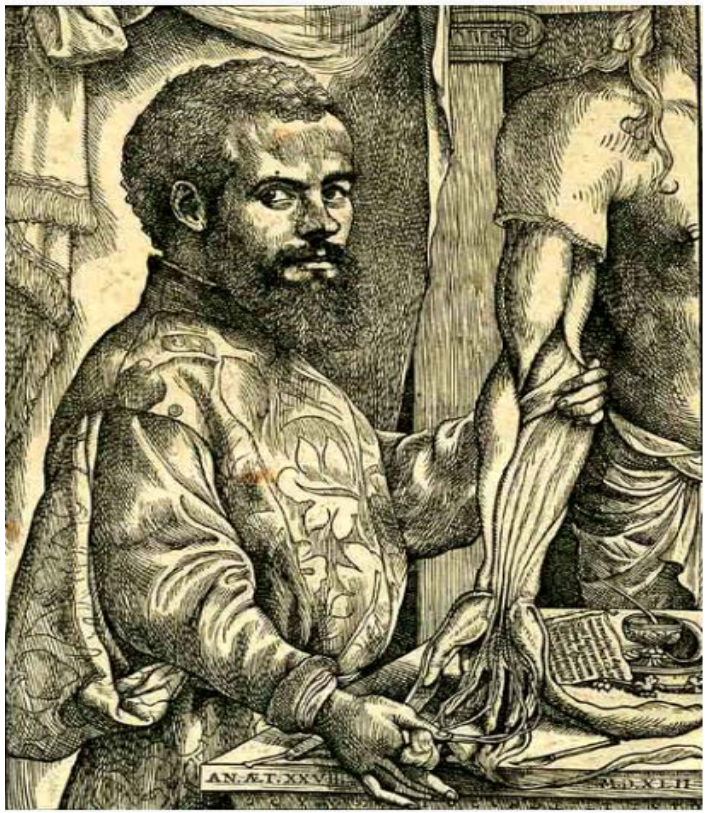
All who drink of this remedy recover in a short time, except those in whom it does not help, who all die.
Therefore, it is obvious that it fails only in incurable cases.

Galenus of Pergamon, 131-201 AD

Impact of Galenus on Medieval Medicine

- Galenus believed in the Aristotelian doctrine that, in Nature (God), form follows function. "If we want to understand the function of an organ, tissue or body part, we must first study its form".
- Galenus was a monotheist and his monotheism greatly enhanced the acceptance of his medical theories and teachings by later Muslim and Christian scholars and physicians.
- For over a 1200 years after his death, Galenus was considered to be the "gospel truth", the ultimate authority on all matters medical.
- Medieval medical authorities dogmatically agreed: If Galenus figured it all out, why look any further? It wasn't until the Renaissance that Galen was finally questioned and his errors uncovered.

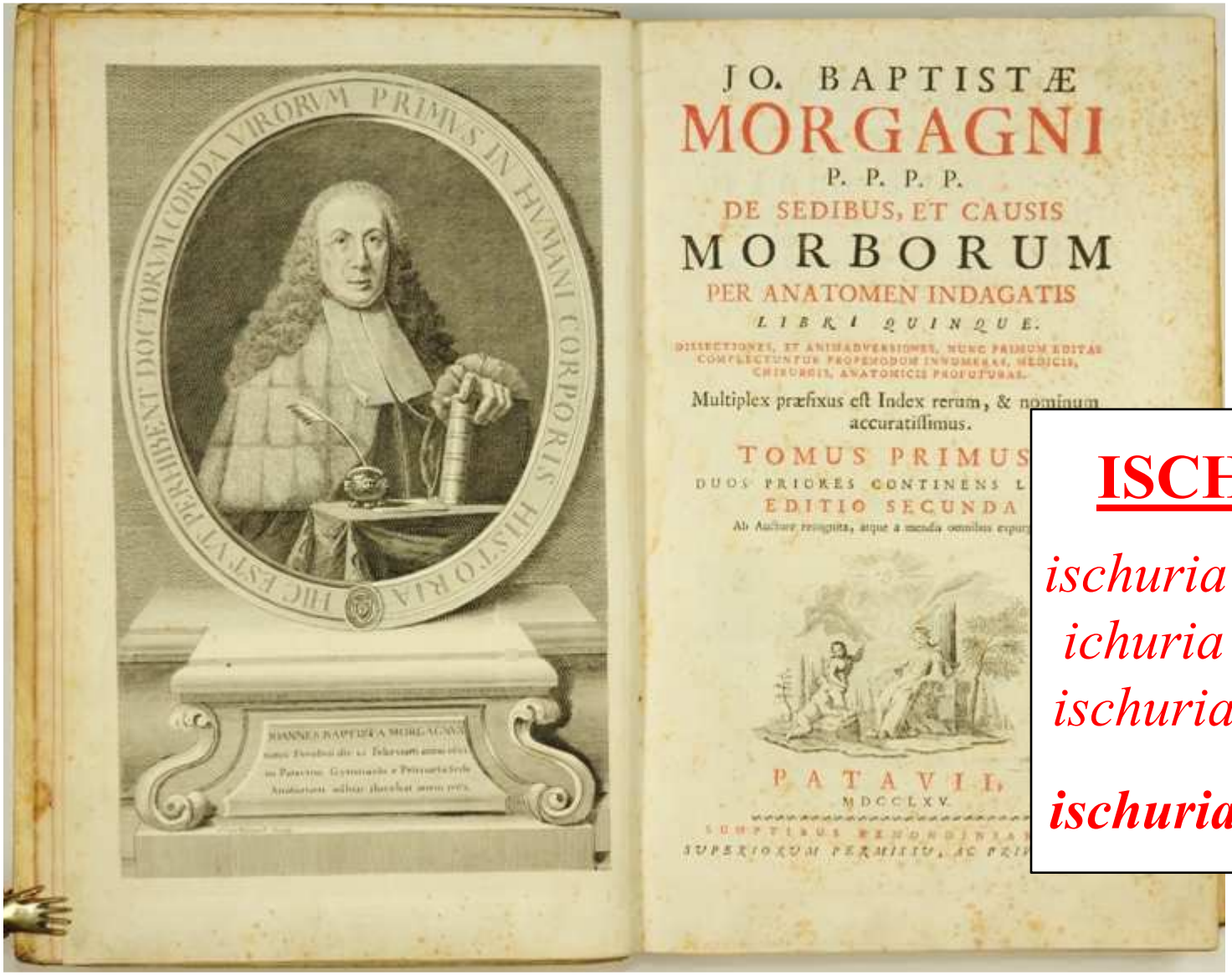
De humani corporis fabrica, Libri septem (1543) Andreas Vesalius, Basel



Brussel 31/12/1514-Zakynthos 15/10/1564

Studied in Leuven, medicine in Paris, doctorate in Padua; age: 27:prof Anatomy &Surgery in Padua.
Later personal physician of Charles V and Philips II.

Giovanni Battista **MORGAGNI** (1682-1771)



1755

ISCHURIA

ischuria urethralis

ichuria ureterica

ischuria vesicalis

ischuria renalis

Crush Syndrome History

First described in German literature in victims of Messina earthquake 28/12/ 1908

Franz Colbers-Coburg 1909 “acute muscle necrosis and oliguria”

WW I German authors noted traumatic rhabdomyolysis

-Frankenthal (army-surgeon) 1916

-Hackradt 1917 “vasomotorische nephrose” working in prof Max Borst’s systematic “war pathology” service

-Lewin student of Ludwig Pick 1919

-Siego Minami 1923 (working with Pick)

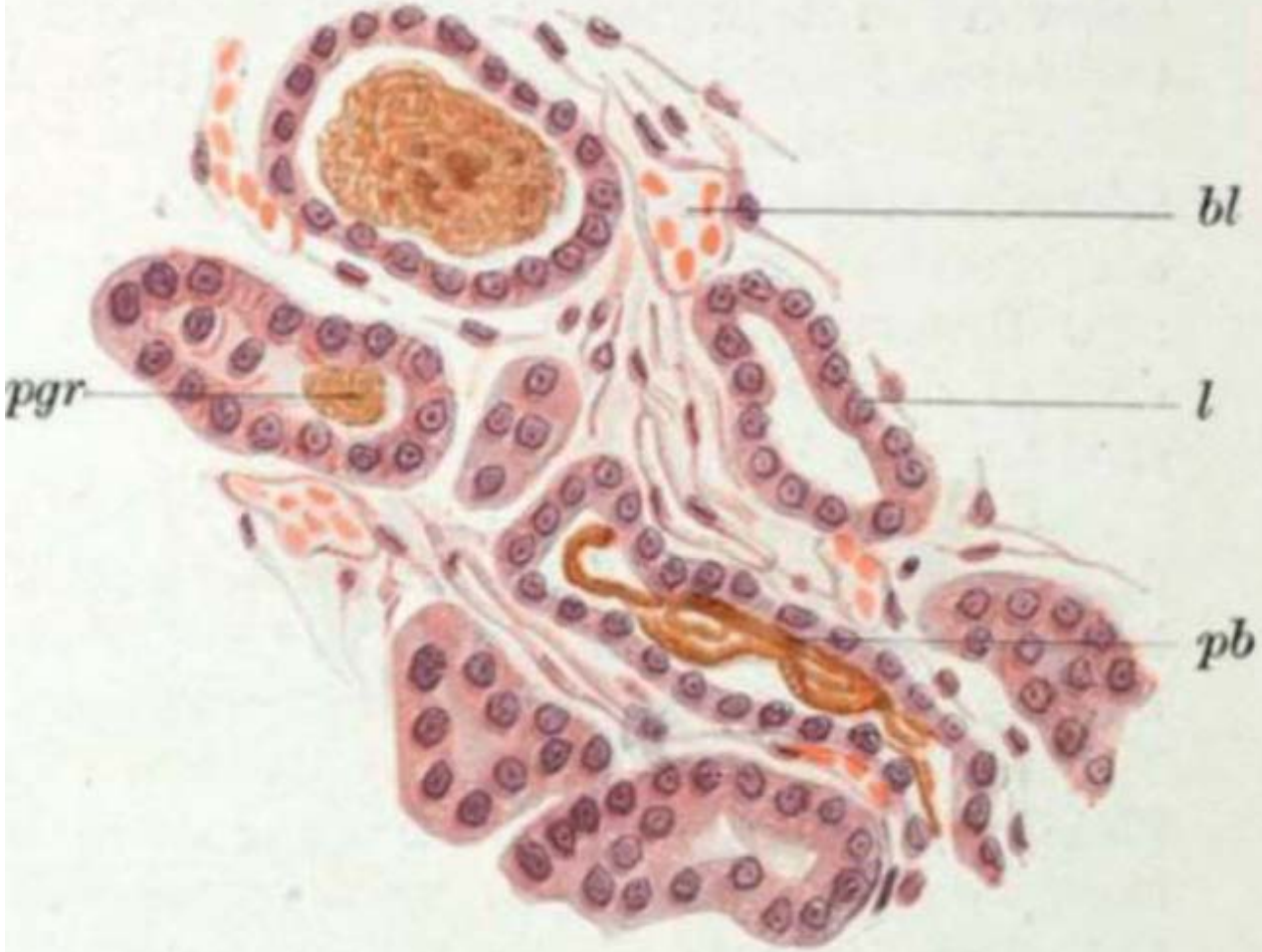
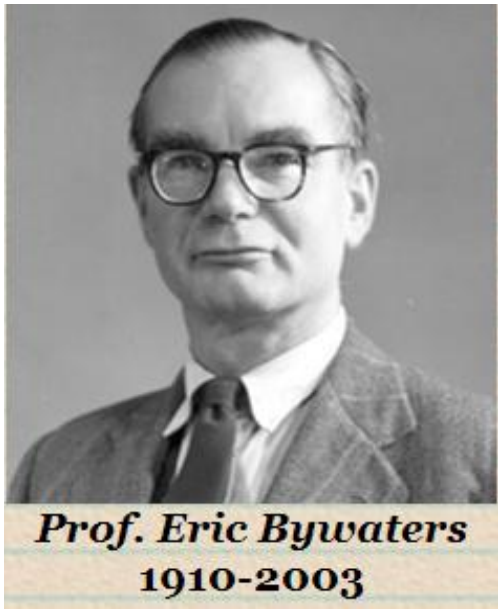


Abb. 3. Schnitt aus Nierenrinde (Fall 1159). Tod nach Verschüttung am 7. Tag. Hämalaunfärbung. Leitz, Oc. 1, Obj. 6, Tub. 155. *pgr* = Pigmentgranula in dichter Lagerung innerhalb von Tubuli contorti; *pb* = Pigmentstreifen und -bänder; *e* = Epithelien der Tubuli contorti; *bl* = geschrumpfte rote Blutkörperchen in Blutcapillaren.

Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin, Ueber Nierenveränderungen nach Verschüttung, Seigo Minami (1923) 245: 247-267.

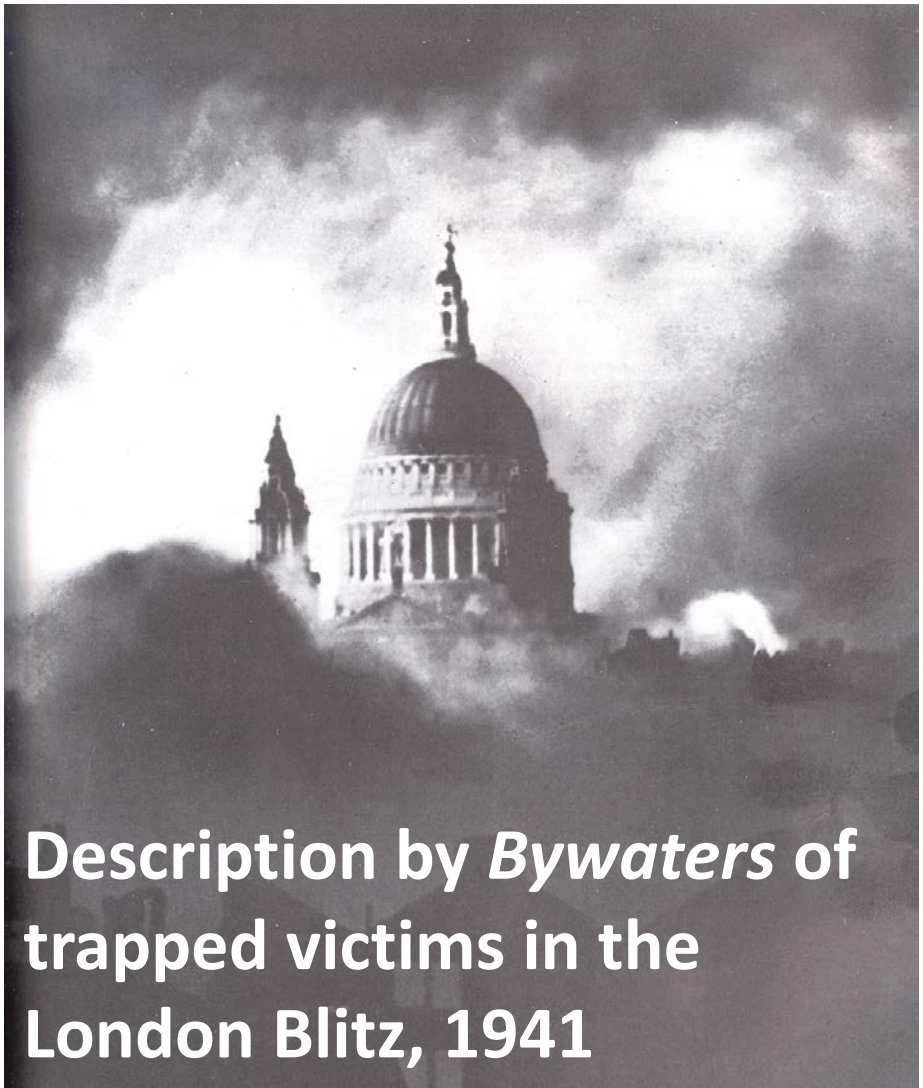
Bajema, Rotmans,NDT (2018) 33: 2113–2114



Crush Syndrome

More than one million London houses were destroyed or damaged, and more than 40,000 civilians died.

"Victim buried several hours with pressure on a limb….good condition on admission... later shock…diminution of arterial pulsations in affected limb…incipient gangrene…signs of renal damage…blood urea and potassium become progressively higher…death usually within a week."



Description by *Bywaters* of trapped victims in the London Blitz, 1941

History of dialysis

1914 1930 **1945** 1960 1970 2000 2010 2050

Willem Kolff

Kolff rotating drum kidney (1943)

The first successful hemodialysis in AKI

1914 1930 **1945** 1960 1970 2000 2010 2050

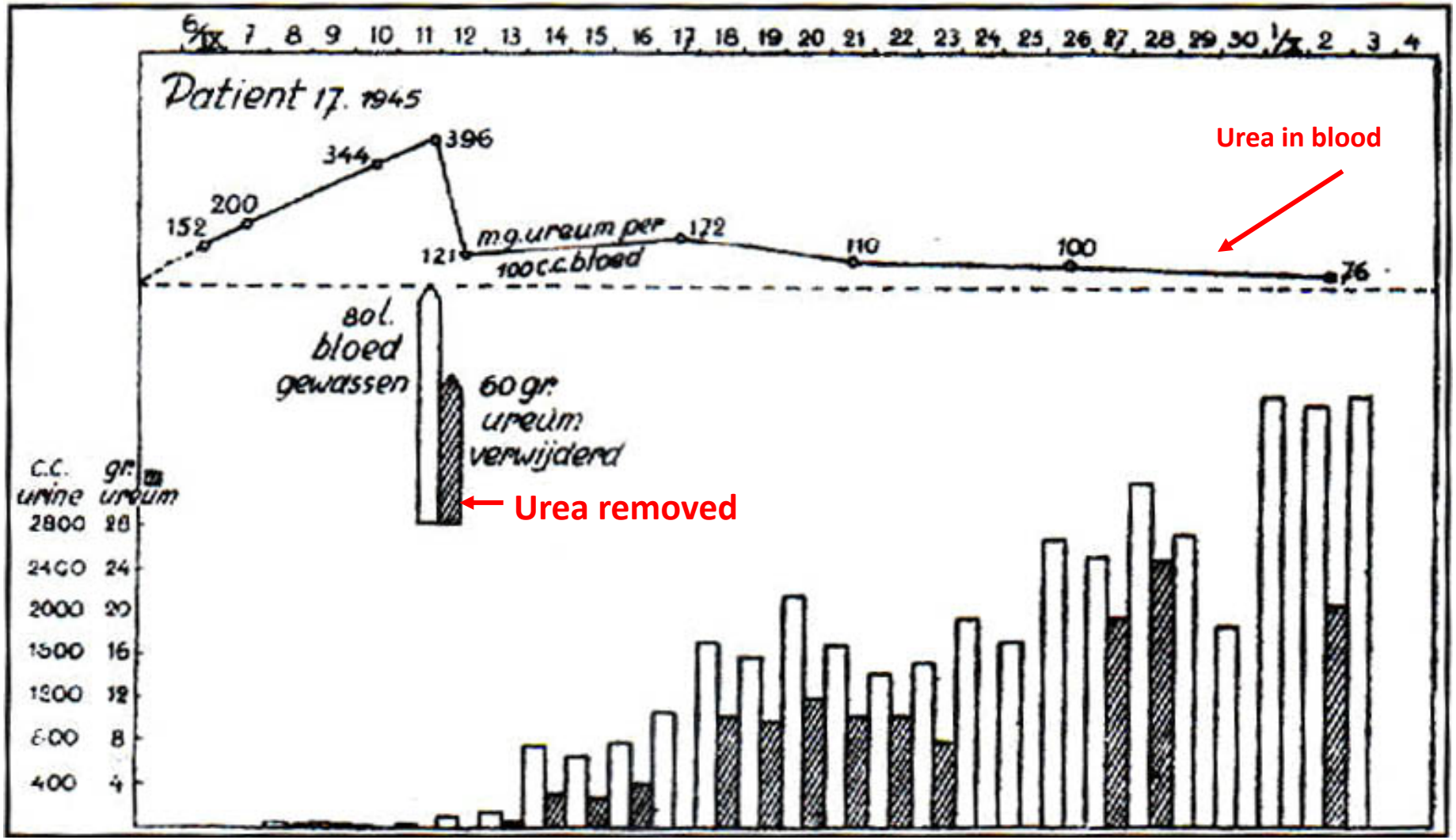
Sophia Schafstadt (1945)

The first patient, owing her life to dialysis after having suffered from ARF. She was Kolff´s patient n° 17 at age 67 yrs. Picture taken in the Kampen hospital garden 4 weeks after her „recovery“ (october 1945)

She died in 1951.

1914 1930 **1945** 1960 1971 2000 2010 2050

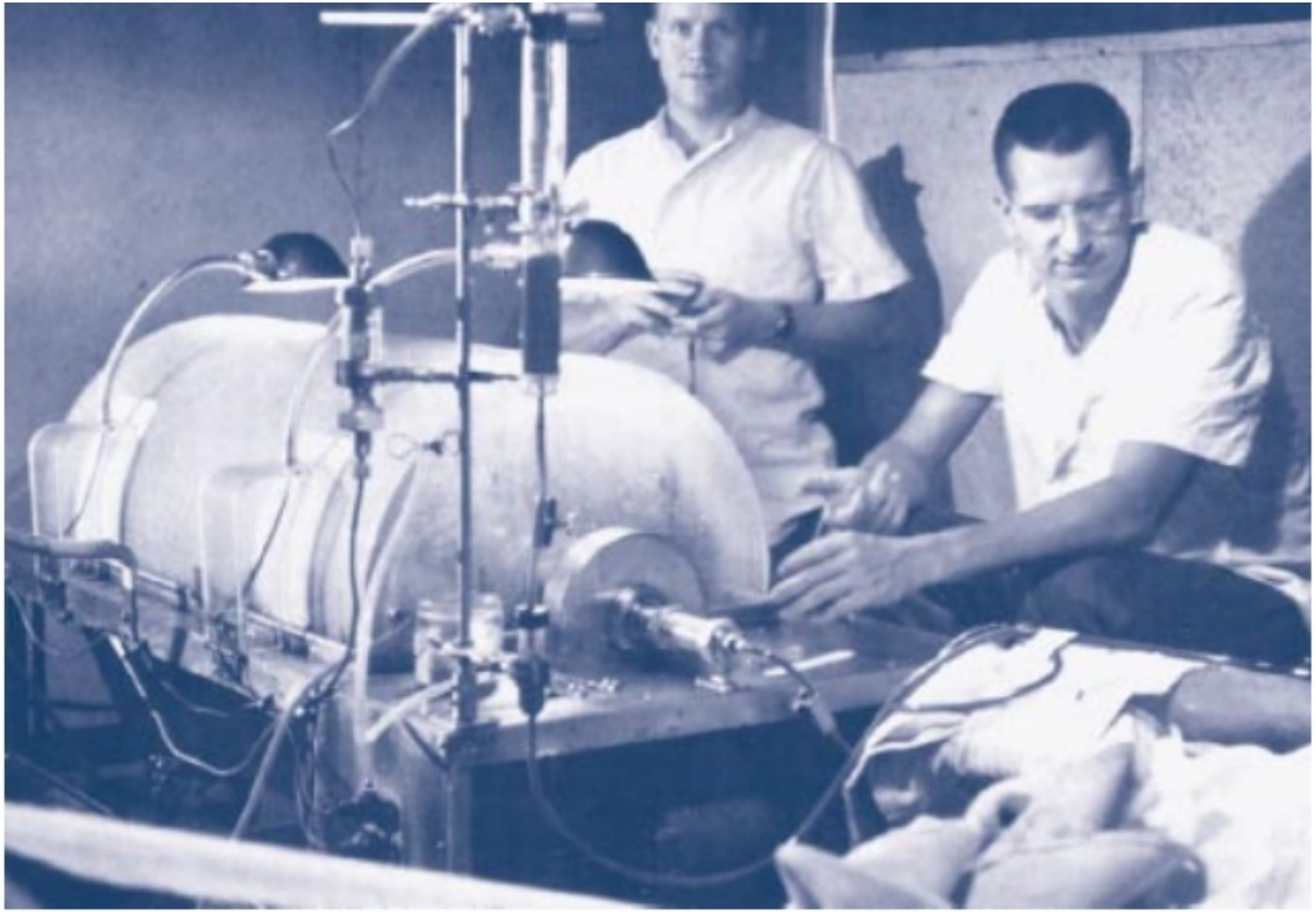
THE „ROTATING DRUM“ IN 1945 CLINICAL-BIOCHEMICAL REPORT OF PATIENT 17



: W Kolff De kunstmatige nier. PhD-Thesis, University of Groningen, 1946

A case report of patient 17……
Characteristics of the initial dialysis

Treatment time	690 min
Blood flow	116 ml/min
Urea clearance	87 ml/min
Pre-post urea	396/121 mg%
URR	69%
Kt/V	1.40
Vurea DDQ	22L



Colonel med Paul Teschan performing acute dialysis during the Korean War (1952) with the Kollf-Brigham rotating drum at the 11th Evacuation hospital, 8th US Army. The mortality rate in ARF in military casualties was 80% – 90% (like in WW2). The use of this dialyzer decreased mortality to 53%.

Developing a consensus classification system for acute renal failure

John A. Kellum, MD,* Nathan Levin, MD,† Catherine Bouman, MD,‡ and Norbert Lameire, MD§

A biochemical definition and classification system for acute renal dysfunction is long overdue. Its absence has impeded progress in clinical and even basic research concerning a syndrome associated with mortality rates of 30 to 80%. No definition of acute renal dysfunction will be perfect, but the absence of a definition or, worse, more than 35 separate definitions, as found in the literature, is unacceptable. Many of the challenges, considerations, and controversies associated with achieving consensus and developing a classification for acute renal dysfunction are addressed. Recommendations for validating a classification system are also considered. Curr Opin Crit Care 2002, 8:509–514

*Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA; †Renal Research Institute, New York, New York, USA; ‡Department of Intensive Care, Academic Medical Center, Amsterdam, the Netherlands; §Renal Division, University Hospital, Ghent, Belgium.

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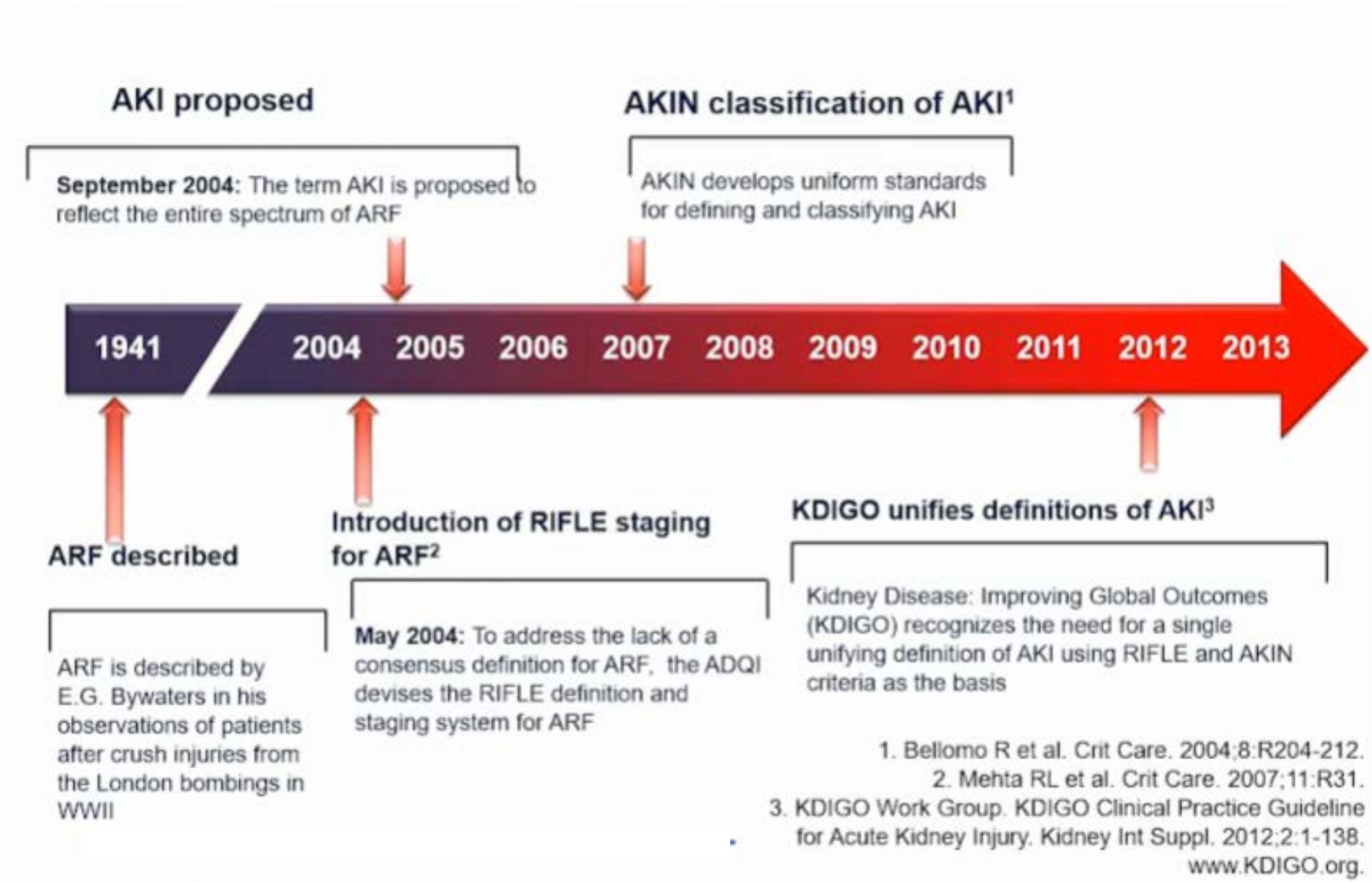
Current Opinion in Critical Care 2002, 8:509–514

Definitions are easy

Acute renal failure (ARF) is easily defined. It is an "abrupt and sustained decrease in renal function," although most might argue that *function* should be clarified because the kidney has numerous functions (*eg*, fluid and solute excretion, electrolyte and acid–base regulation, endocrine functions, and so forth). However, in clinical practice, the argument is accepted that the only functions that are routinely and easily measured and that are unique to the kidney are the production of urine and the excretion of waste products of nitrogen metabolism [1•]. This is not to say that the other functions of the kidney are less important, only that they are less verifiable, at least for now. Thus, for clinical research, ARF can be defined as an "abrupt and sustained decrease in glomerular filtration, urine output, or both."

Of course, this is only a qualitative definition and therefore is not very useful for the purposes of standardizing entry criteria or endpoints for clinical trials [1•]. To do this, a quantitative definition of ARF is needed, and there are three terms that require quantification: *abrupt*, *sustained*, and *decrease*. For ARF, *abrupt* appears to be a

Evolving definition and classification of AKI

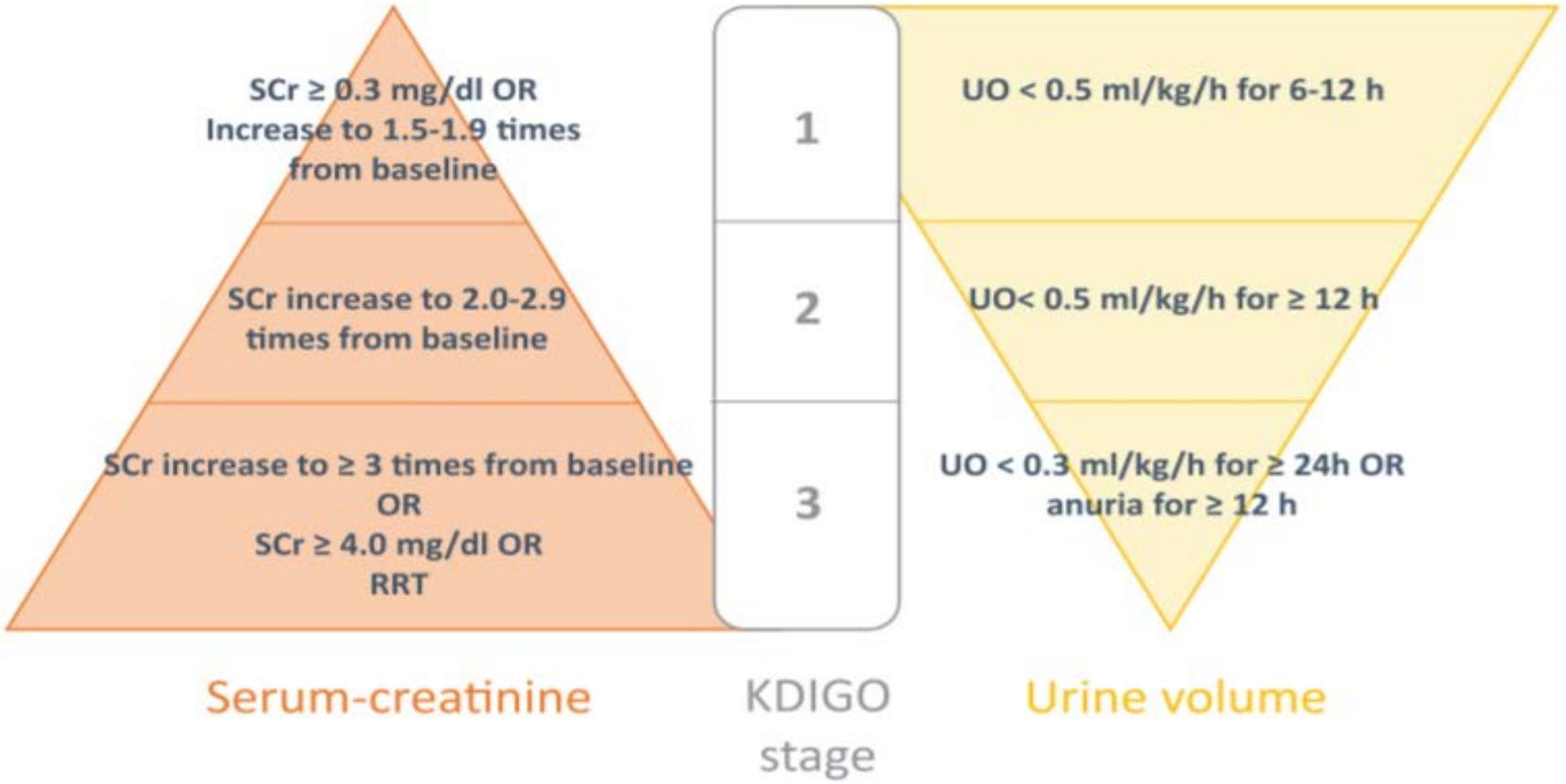


1. Bellomo R et al. Crit Care. 2004;8:R204-212.
2. Mehta RL et al. Crit Care. 2007;11:R31.
3. KDIGO Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:1-138. www.KDIGO.org.

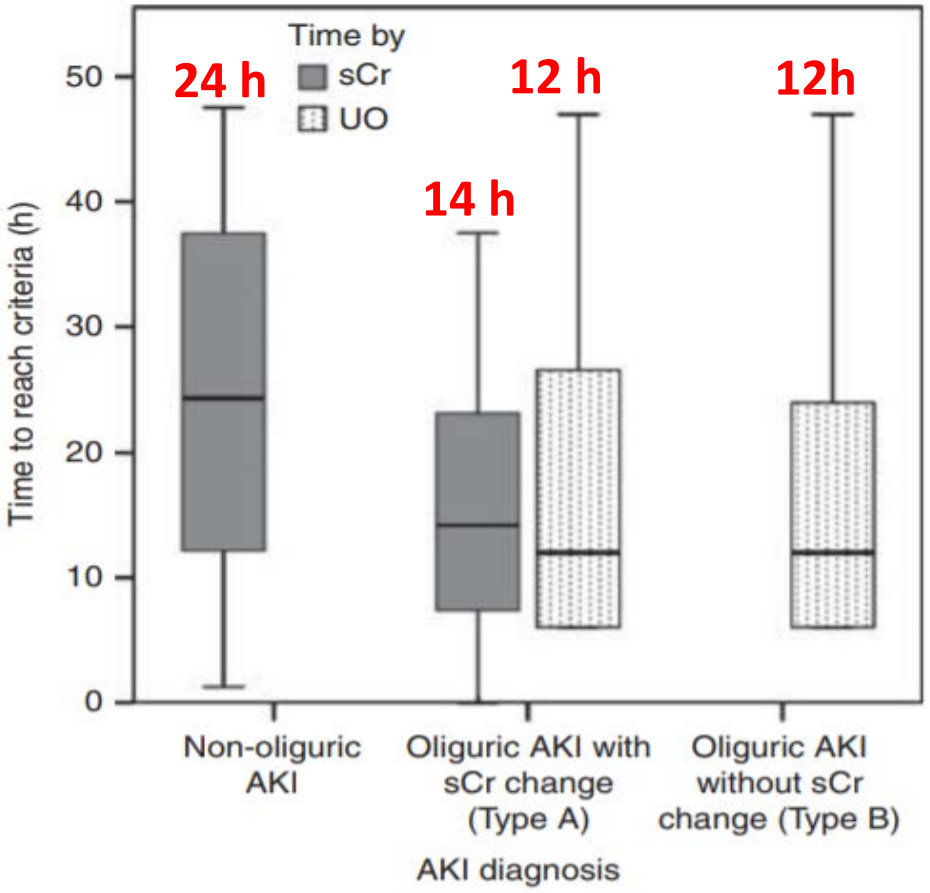
KDIGO definition and classification of AKI

Diagnostic criteria for AKI:

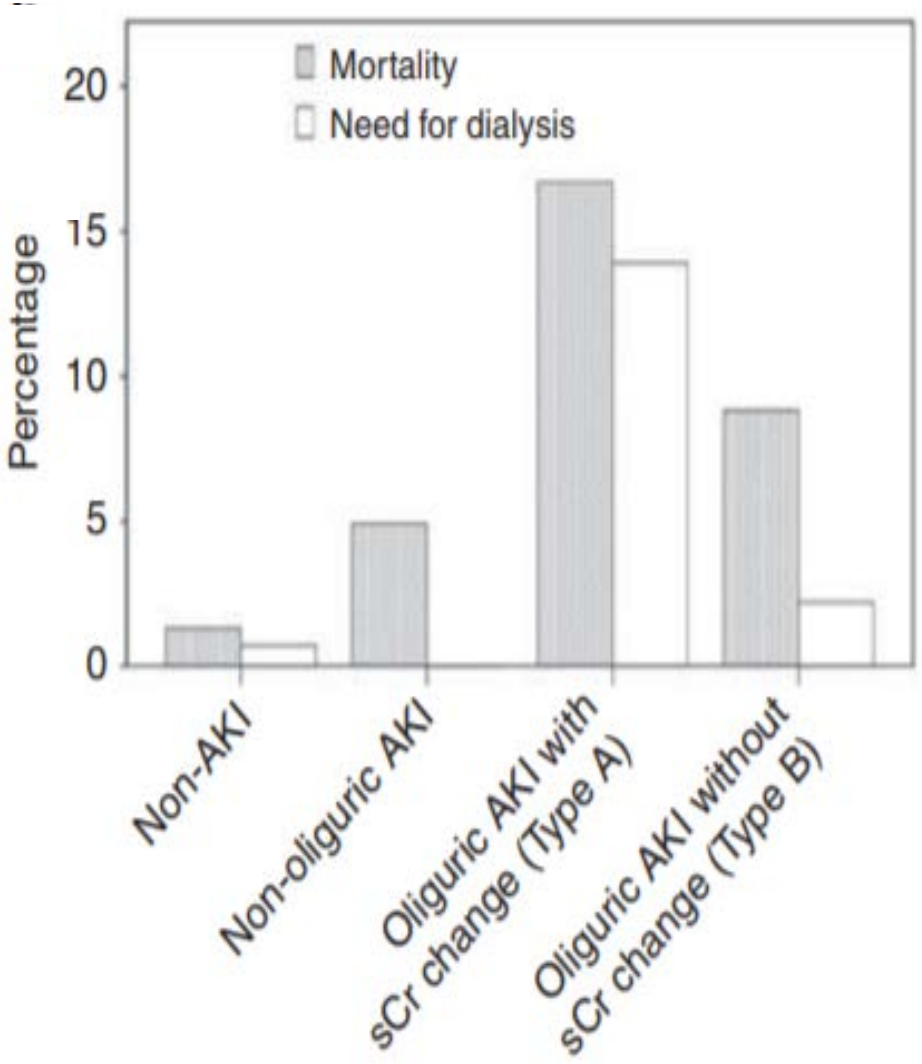
- Serum-creatinine increase ≥ 0.3 mg/dl within 48h **OR**
- Serum-creatinine increase ≥ 1.5 times baseline, which is known or presumed to have occurred within the last 7 days **OR**
- Urine volume < 0.5 ml/kg for 6 h



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



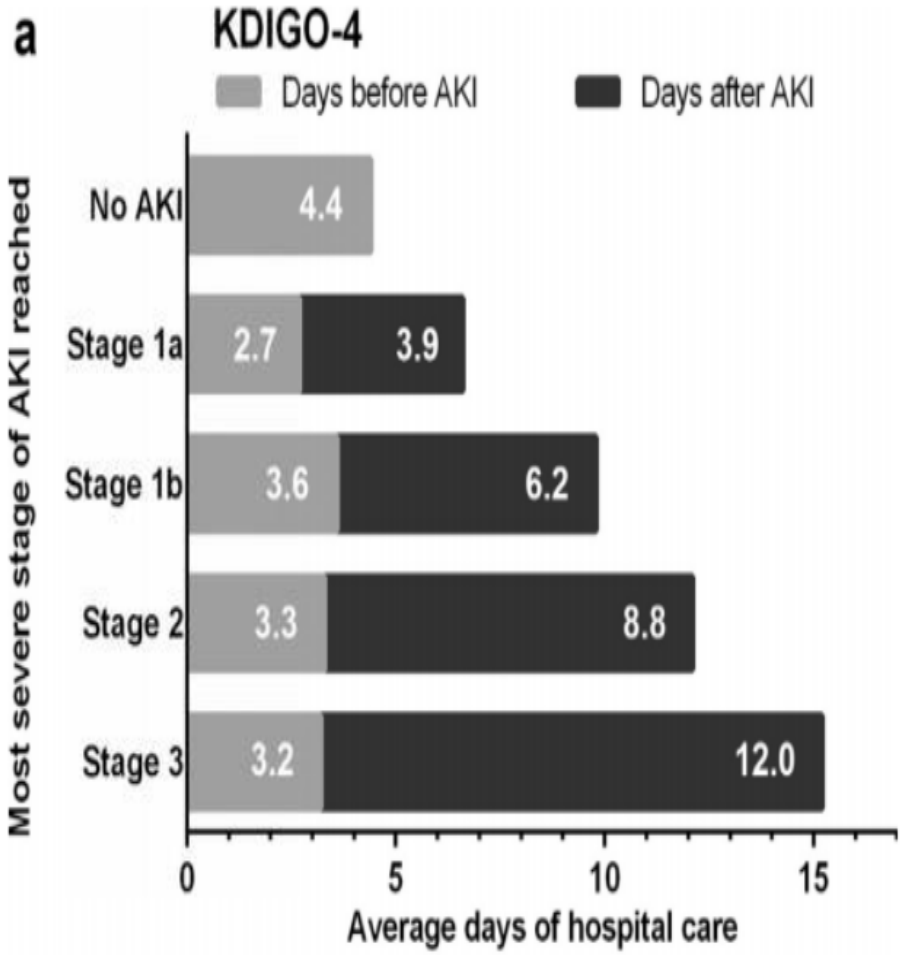
Macedo et al, Kidney International (2011) 80, 760–767

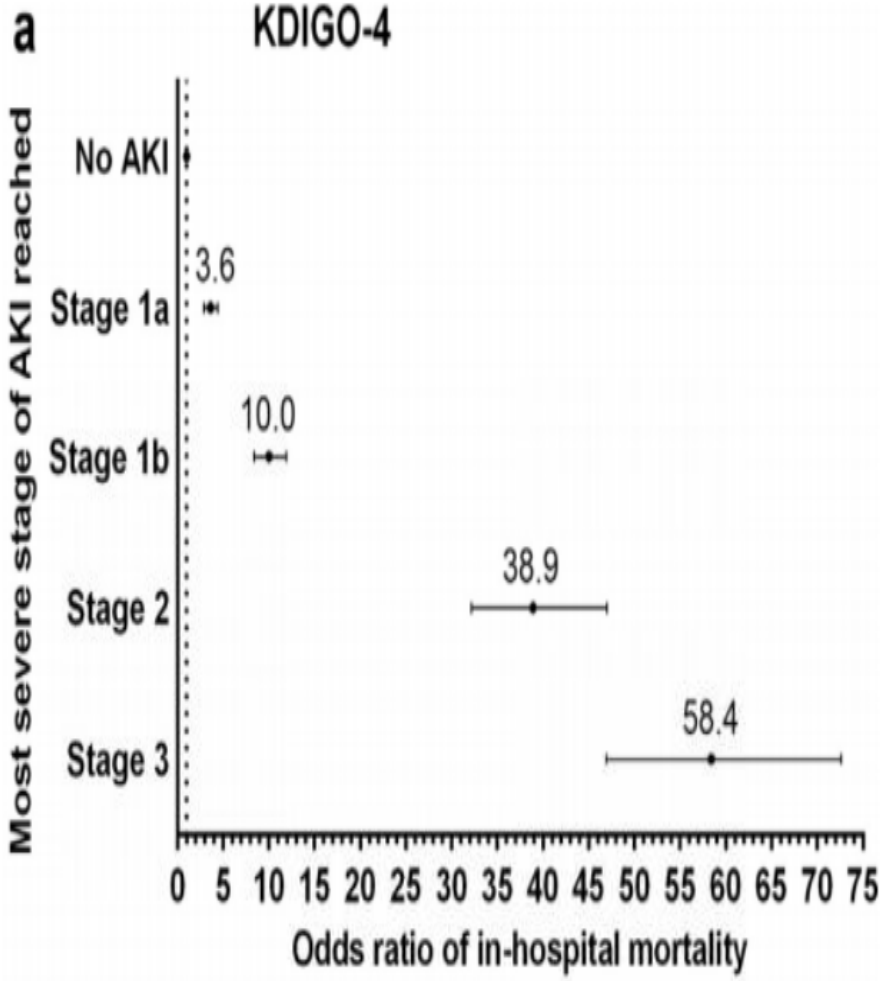
Further categorizing AKI KDIGO stage 1

	Criteria
Modification of KDIGO criteria (KDIGO-4)	
No AKI	No AKI criteria were met
Stage 1a (new)	≥0.3 absolute SCr increase over 48-hour window of observation
Stage 1b (new)	≥50% relative SCr increase over a 7-day window of observation
Stage 2	≥100% relative SCr increase over a 7-day window of observation
Stage 3	≥200% relative SCr increase over a 7-day window of observation[a]

Sparrow et al. Kidney International (2019) 95, 905–913;

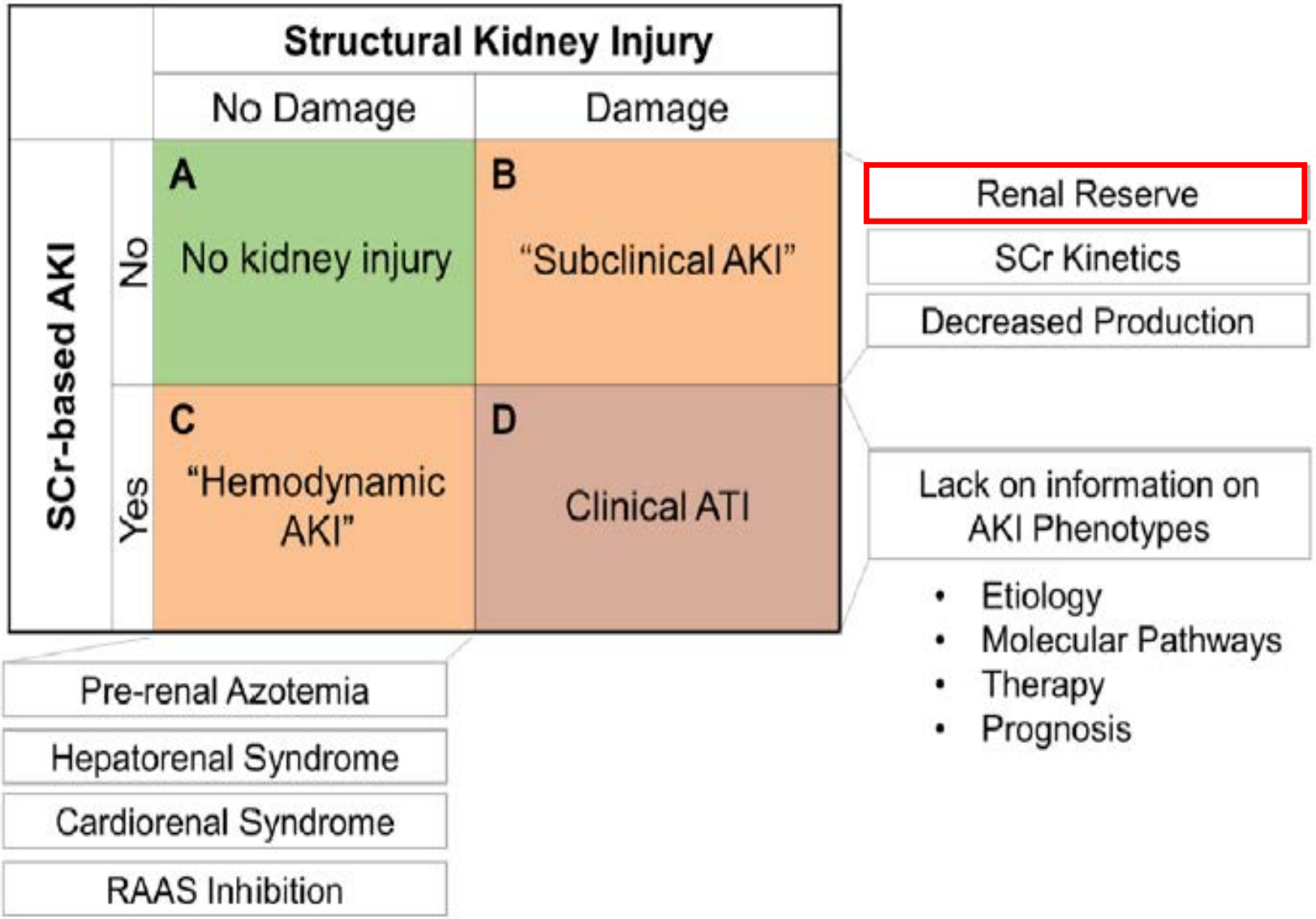
Impact of new categorization on hospital days and odds ratio of in –hospital mortality





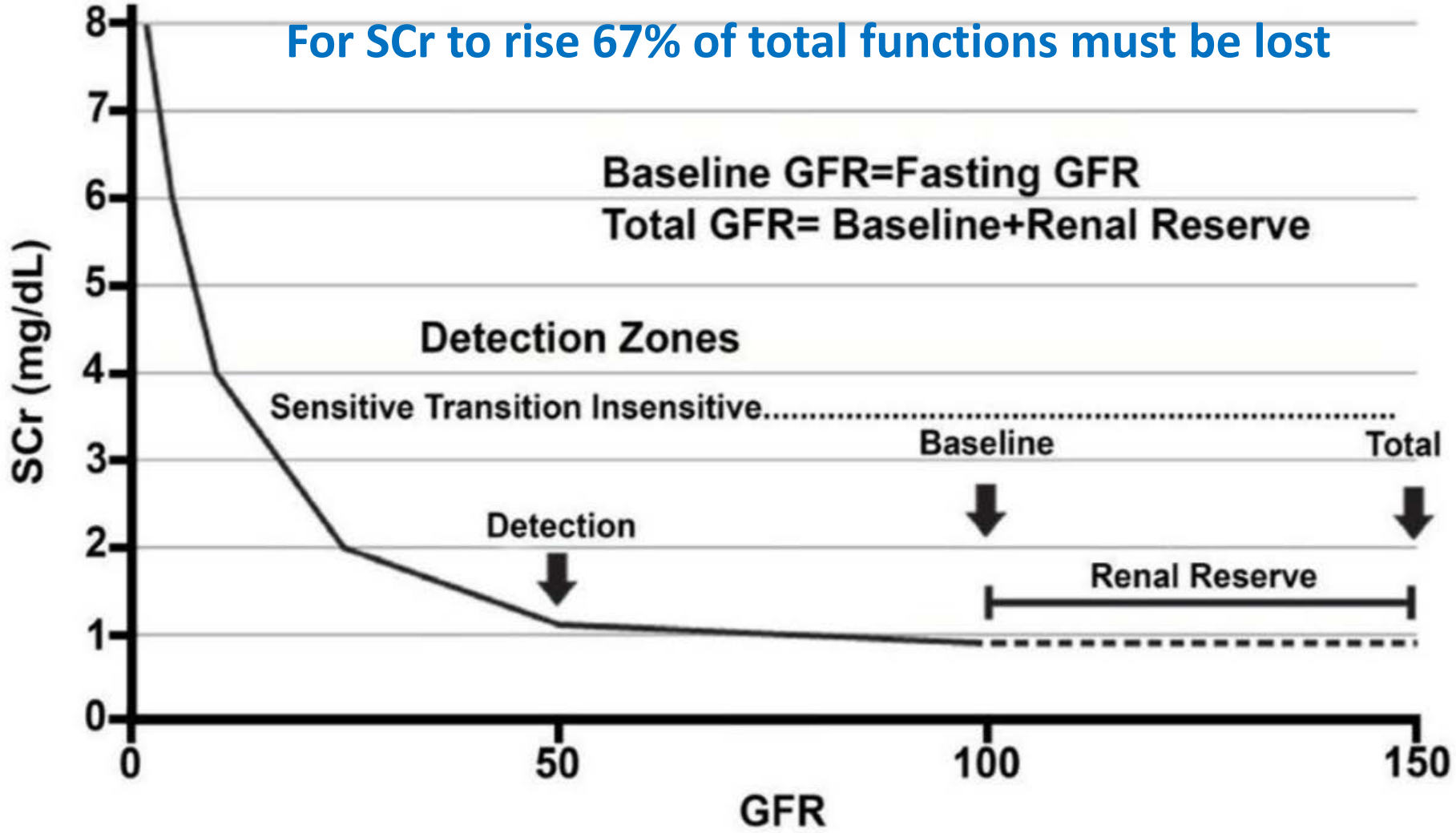
Sparrow et al. Kidney International (2019) 95, 905–913

Limitations of SCr-based AKI definition



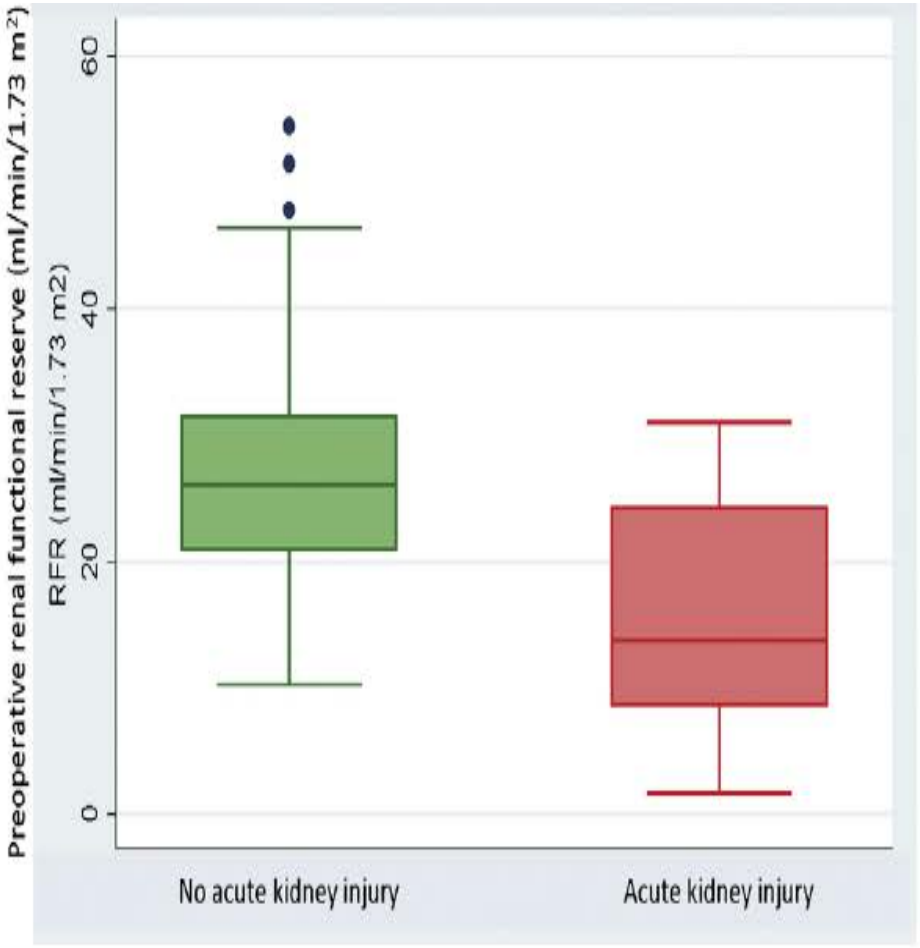
Moledina, Parikh, Semin Nephrol 38:3-11, 2017

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

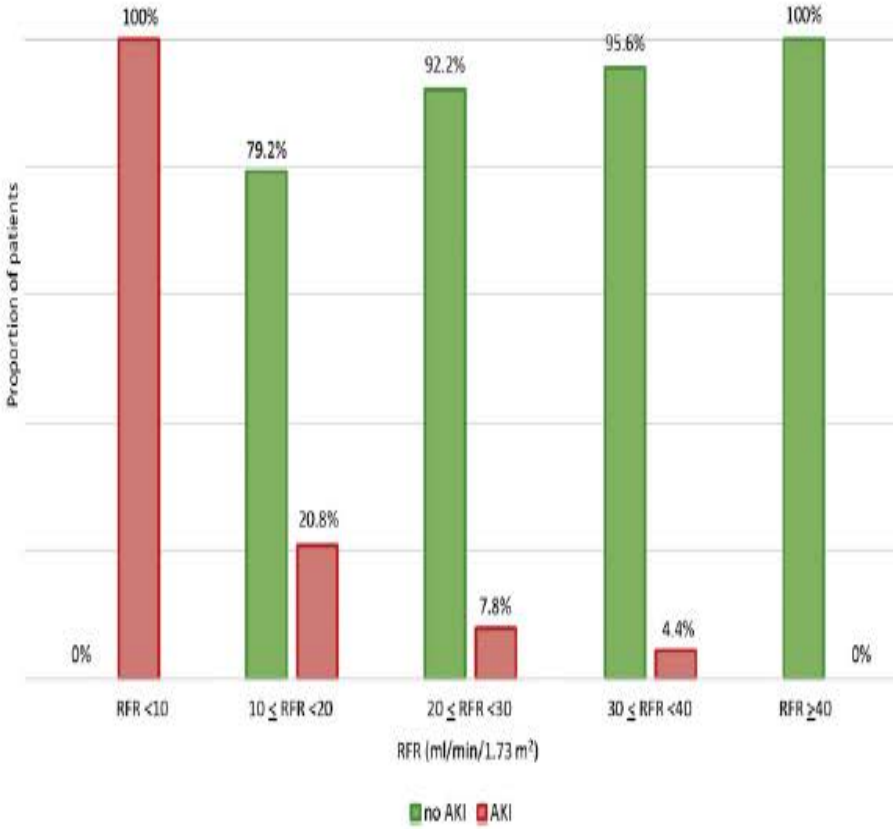


Molitoris BA, Semin Nephrol. 2016, 36(1): 31–41

Preoperative Renal Functional Reserve Predicts Risk of AKI Post Cardiac Surgery

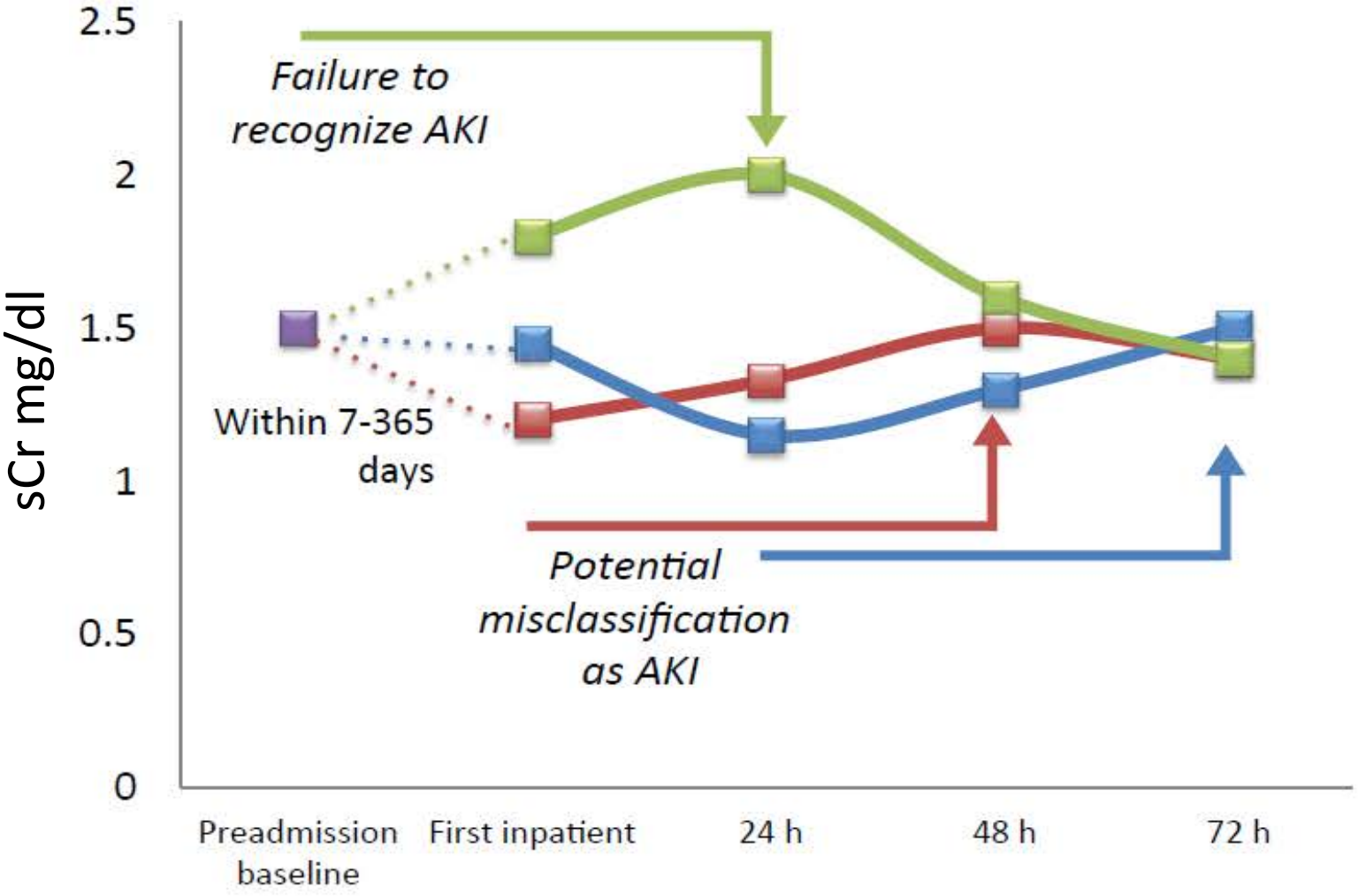


Patiens with preoperative RFR ≤15ml/min/1.73m² were 11.8 times more likely to develop AKI



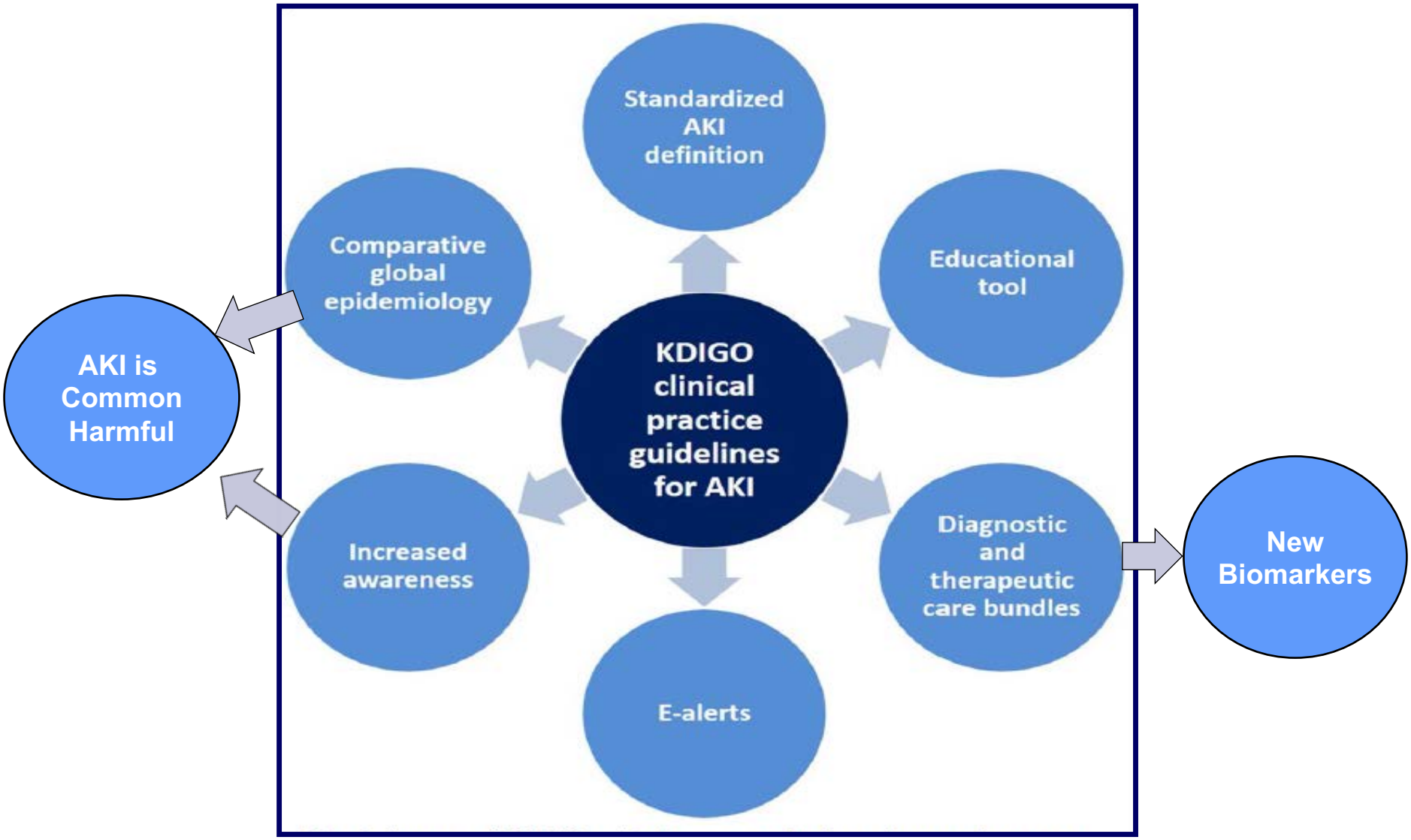
Husain-Syed F et al, Ann Thorac Surg 2018;105:1094–101

Potential SCr trajectories and AKI misclassification



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

What the AKI KDIGO guideline has accomplished



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

A selection of remaining uncertainties in AKI

- Should management be individualized on a better phenotyping of AKI by etiology, severity of injury, and ability to recover?
- Can we predict/detect AKI early enough to modify outcome?
- Should biomarkers be incorporated in the diagnosis and result in earlier intervention and improvement of prognosis?
- What determines the long-term outcome of AKI?
- How can recovery be defined and can it be optimized?
- How do we optimize RRT and what parameters can be used for correct timing for initiation and stopping RRT?
- Does RRT modality affect long-term outcome?

Rome, 25-28/04/2019

KDIGO Controversies Conference on Acute Kidney Injury

Conference Co-Chairs

John Kellum (US)

Marlies Ostermann (UK)

Nomenclature & Diagnostic Criteria		Risk Stratification		Fluid Management		Nephrotoxins		Renal Replacement Therapy	
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First they ignore, then they laugh, then they resist until they accept, and finally they use it

Mahatma Gandhi

1869-1948