Roma, 26-4-2019

AKI
Past, Present and Future

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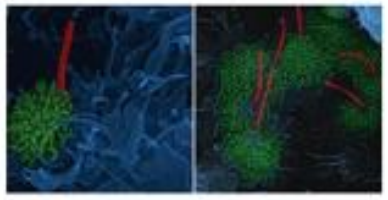
Targeting Endogenous Repair Pathways after AKI

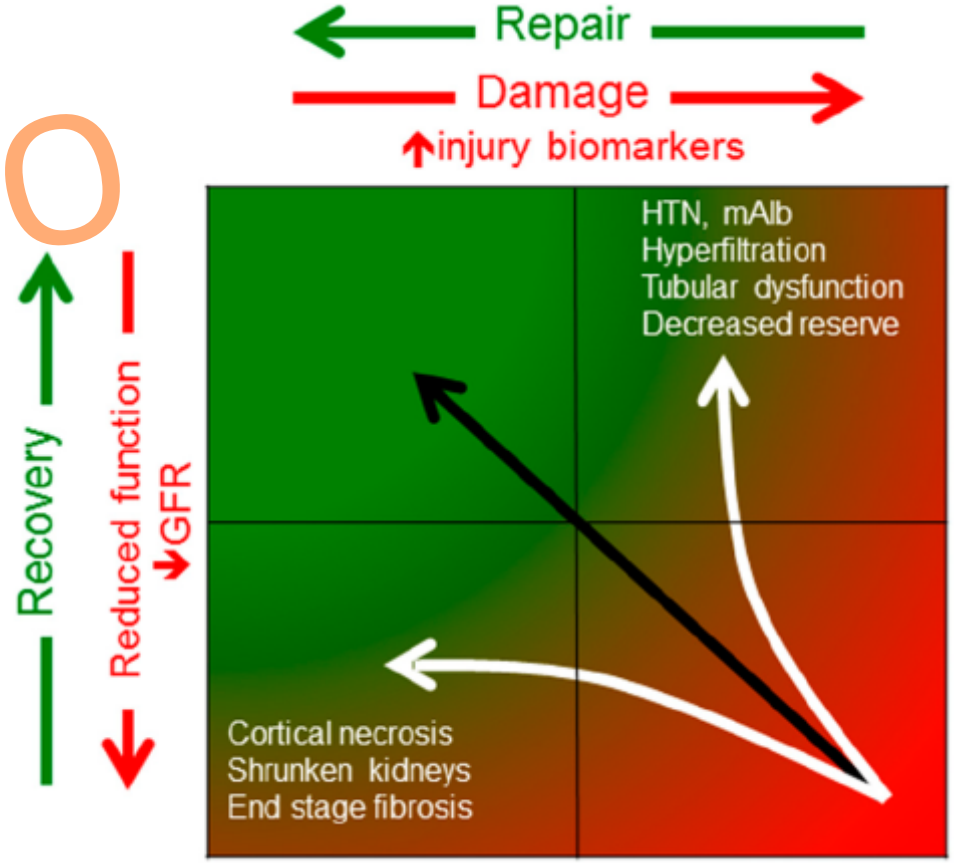
Benjamin D. Humphreys,* Vincenzo Cantaluppi,† Didier Portilla,‡ Kai Singbartl,§ Li Yang,‖ Mitchell H. Rosner,‡ John A. Kellum,§ and Claudio Ronco,¶ for the Acute Dialysis Quality Initiative (ADQI) XIII Work Group

J Am Soc Nephrol 27: 990–998, 2016. doi: 10.1681/ASN.2015030286

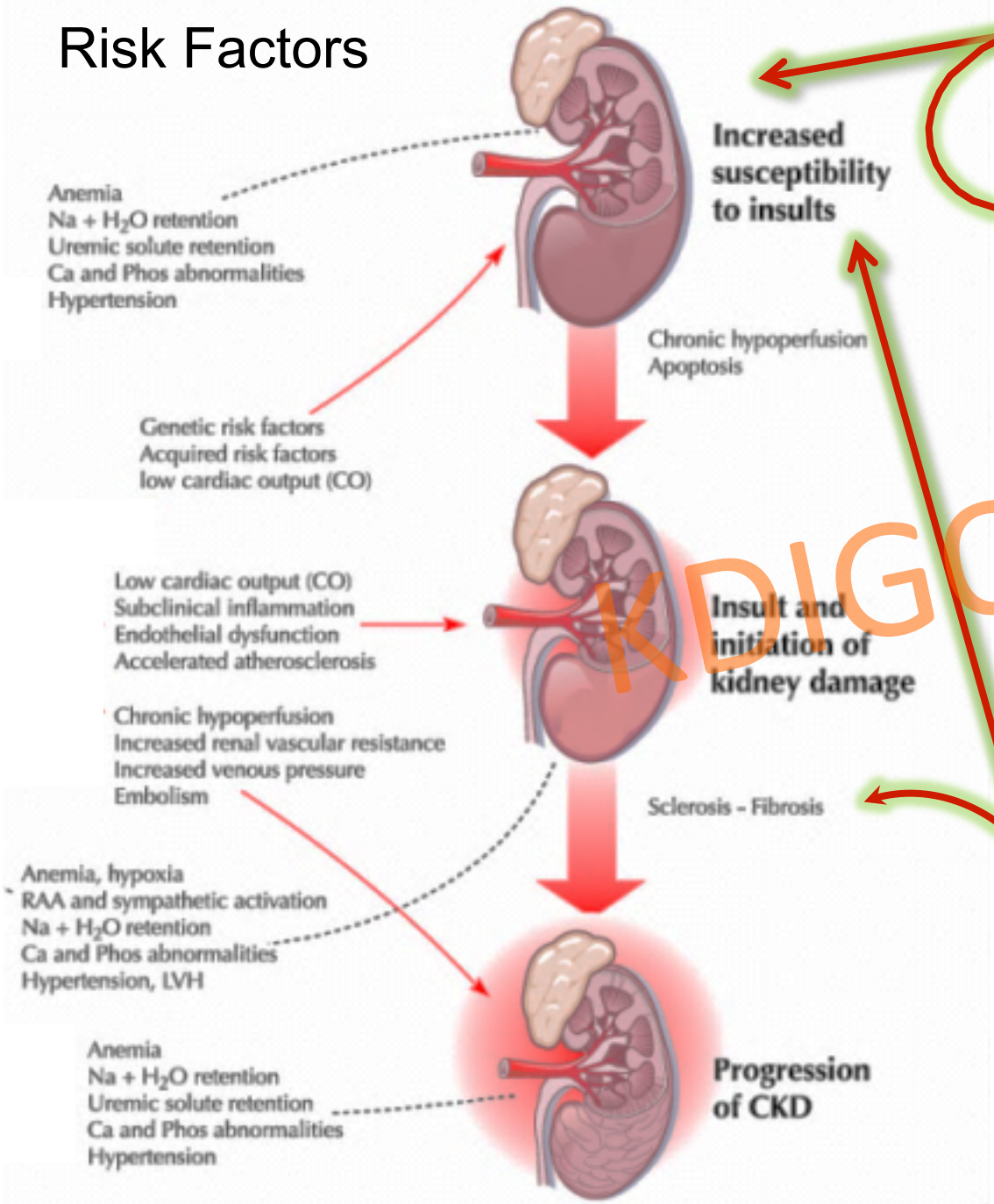
JASN Journal of the American Society of Nephrology

KDIGO

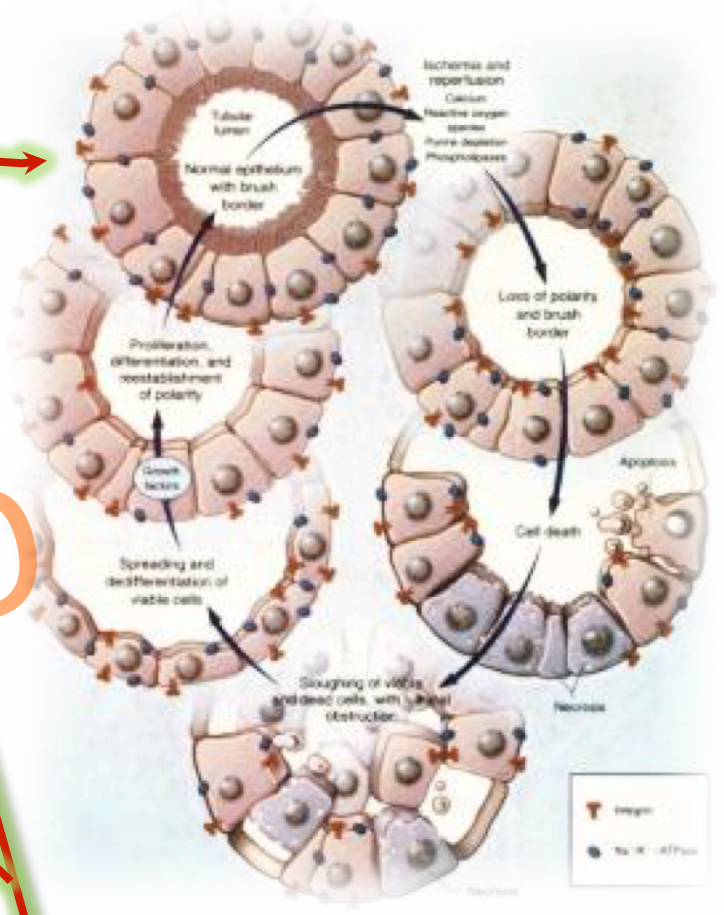




Risk Factors



Kidney Attack



Partial Recovery

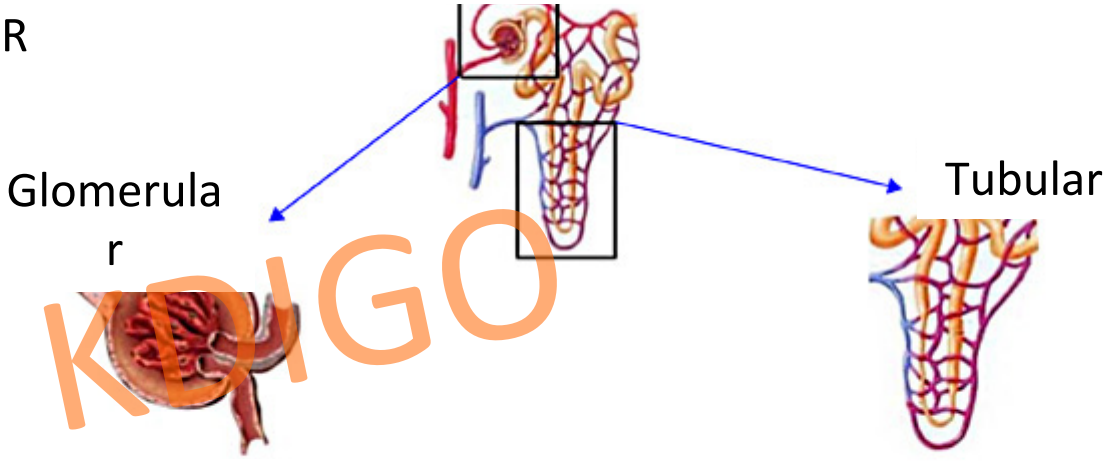
Complete Recovery

Glomerular and Tubular Kidney Stress Test: New Tools for a Deeper Evaluation of Kidney Function

Ronco C, Chawla L.

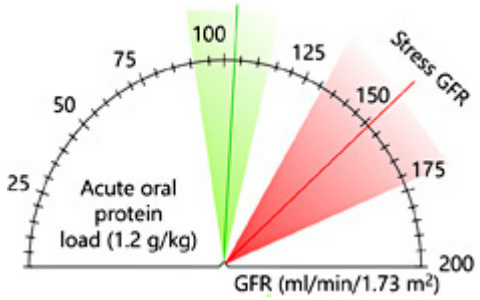
- Measure baseline GFR
- Count glomeruli
- What else?

Kidney stress test

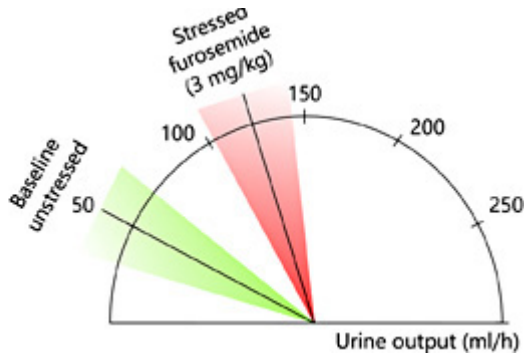


Renal Functional Reserve

Baseline GFR

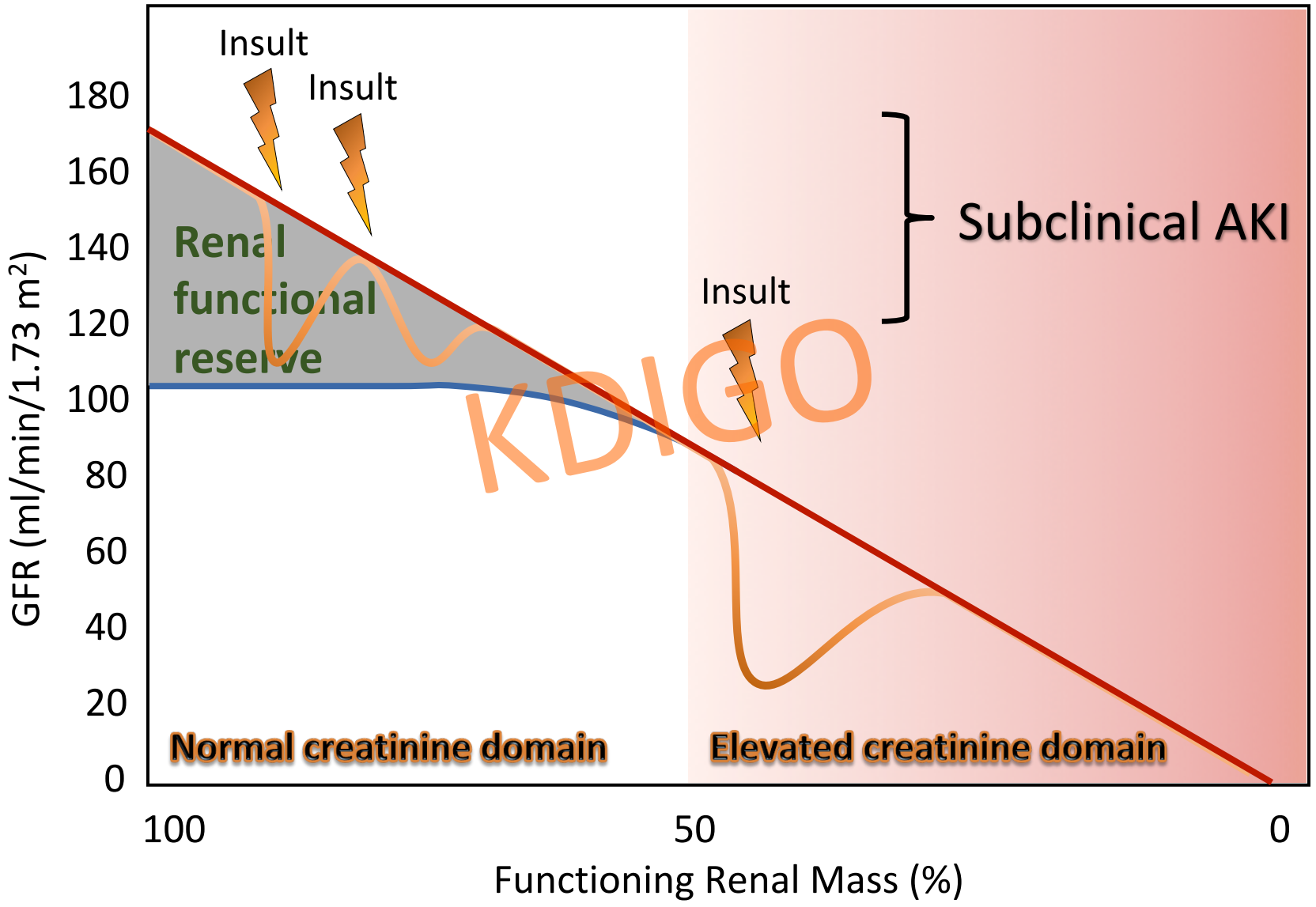


Furosemide Stress Test



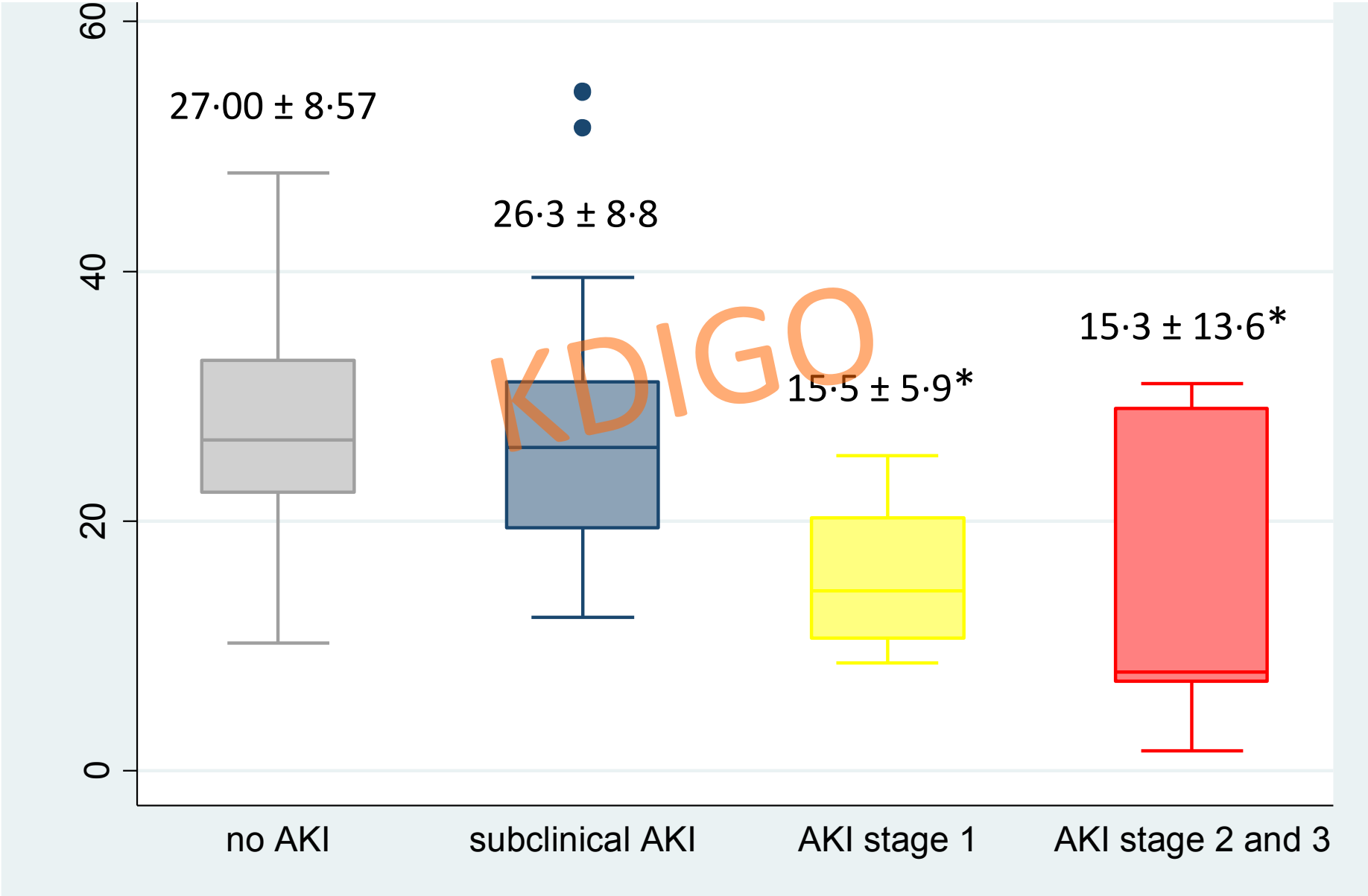
Ronco C and Chawla L. Nephron 2016

Renal Functional Reserve

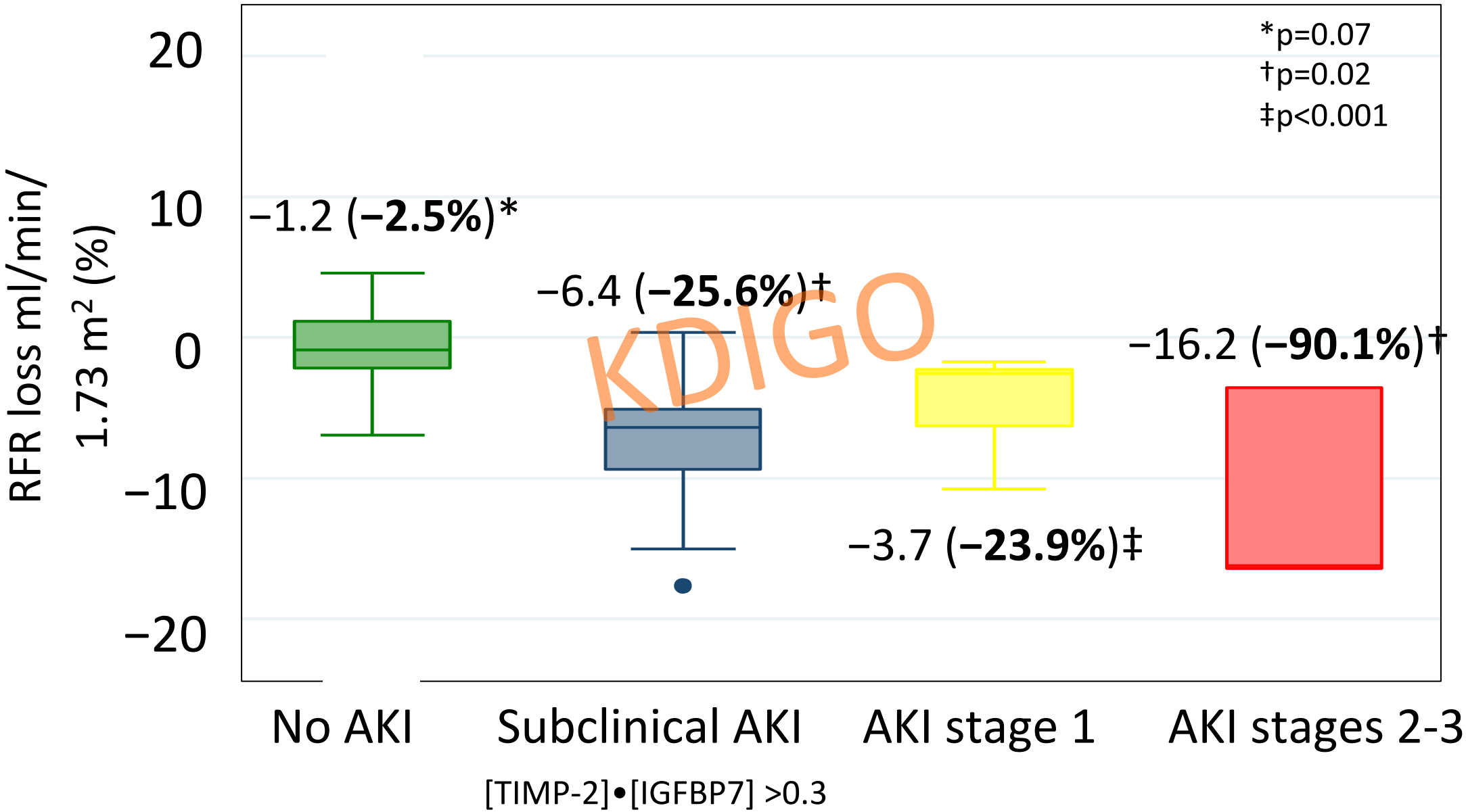


Sharma A et al. Nephron Clin Pract 2014

Pre-surgical RFR in patients with non-AKI vs. each type of AKI
Biomarkers and RFR identify kidney frailty



RFR loss in patients with AKI and subclinical AKI (3 months follow up)



Acute Kidney Disease (3 months)

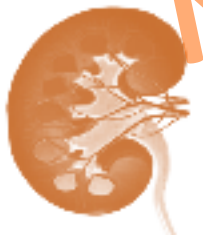
Highly Susceptible Kidney (Baseline GFR > 90 ml/ min and RFR < 30 ml/min) or **Established CKD**

Biomarker Domain (Subclinical)

Creatinine Domain (sCr KDIGO Clinical)

Increased Risk Acute Kidney Stress (AKS)

Acute Kidney Injury (AKI with Damage)



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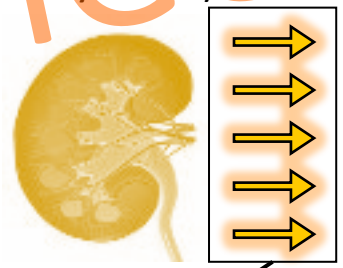
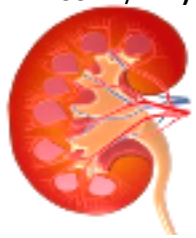
Acute Kidney Injury (AKI with dysfunction)



Adaptive Repair

Kidney Recovery (GFR > 60 ml/min**)**



Full Recovery (Baseline GFR > 90 ml/ min and RFR > 30 ml/ min

Apparent Full Recovery (Baseline GFR > 90 ml/ min and RFR < 30 ml/min

Organ Death Dialysis

Maladaptive Repair

Sclerosis Fibrosis

Partial Recovery (GFR < 60 ml/min**)**

CKD (GFR< 60 ml/min)

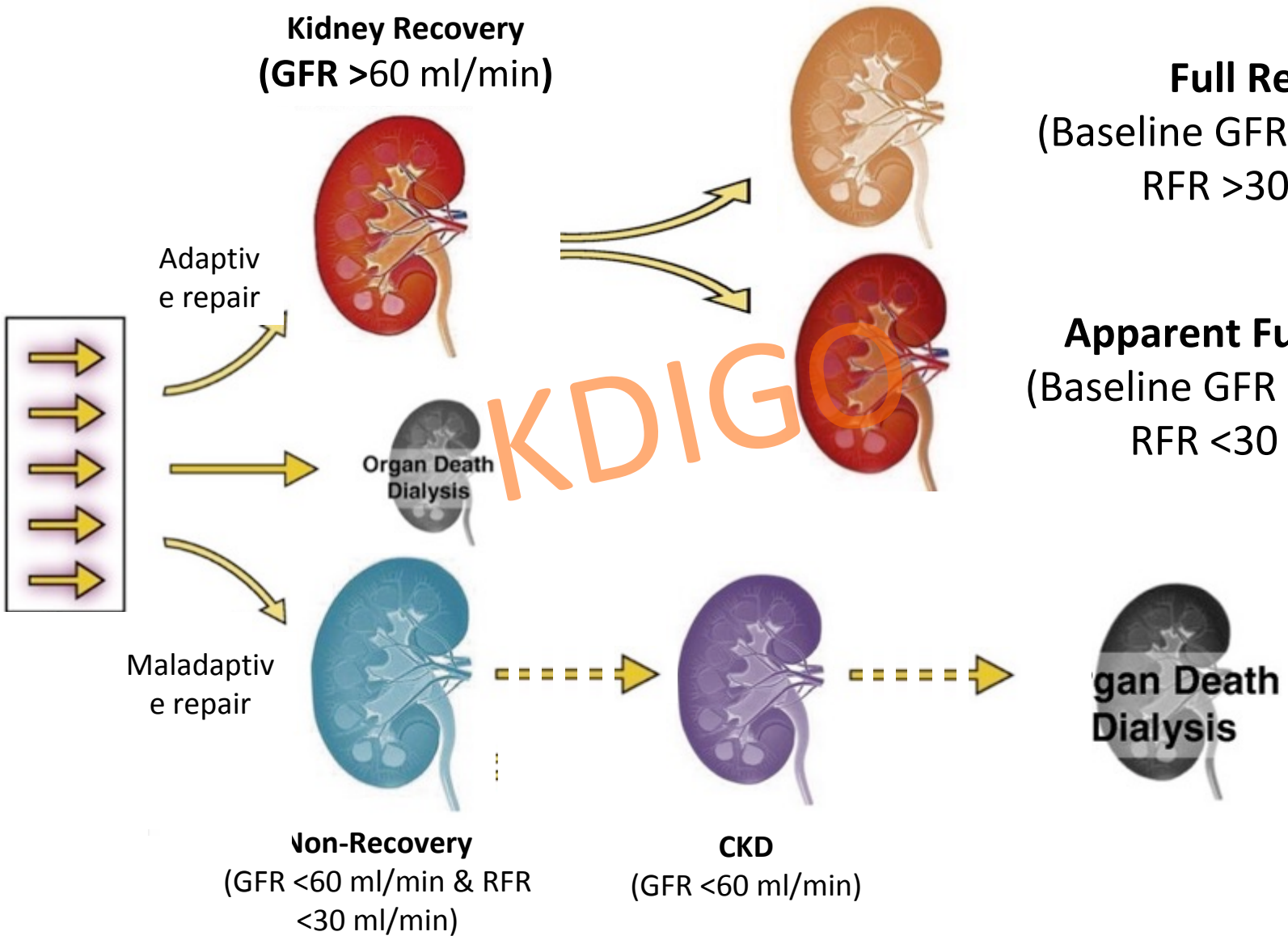
Organ Death Dialysis

Normal Kidney Normal Baseline GFR and intact RFR (>30 ml/ min)

Recovery Patterns:

a) Early sustained reversal
b) Late reversal
c) Relapsing AKI with recovery
d) Relapsing AKI without recovery
e) Non reversal

Renal Recovery

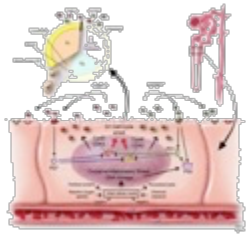


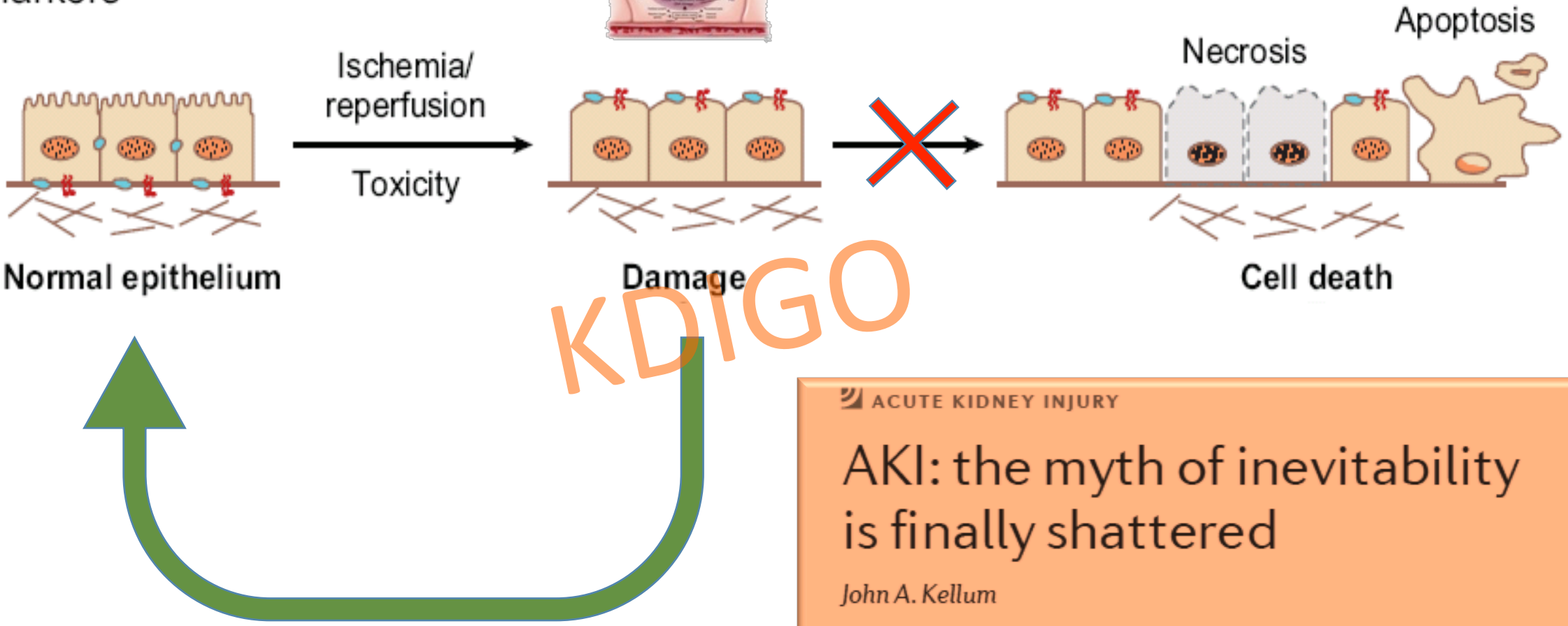
Full Recovery
(Baseline GFR >90 ml/min & RFR >30 ml/min)

Apparent Full Recovery
(Baseline GFR >90 ml/min & RFR <30 ml/min)

Ronco C et al. Am J Respir Crit Care Med 2017

Biomarkers





KDIGO

ACUTE KIDNEY INJURY

AKI: the myth of inevitability is finally shattered

John A. Kellum

Acute kidney injury continues to challenge physicians, researchers and patients. To date, there is no efficient treatment for acute kidney injury and its occurrence in many critically ill patients seems inevitable. However, a new study might just change the way we approach this seemingly intractable problem.

ACUTE KIDNEY INJURY

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KDIGO

haemodynamic monitoring), avoidance of nephrotoxic drugs, and prevention of hyperglycaemia — in patients at high risk of AKI who had undergone cardiac surgery[5] (FIG. 1). Patients at high risk were identified by assessing urine levels of IGFBP7 and TIMP-2. The investigators found that rates of AKI were significantly lower in patients who received the bundled intervention than in patients who received standard care, including the specification to keep mean arterial pressure >65 mmHg and central venous pressure 8–10 mmHg (55.1% versus 71.7%; absolute risk reduction (ARR) 16.6%; 95% CI 5.5%–27.9%; $P = 0.004$). Furthermore, implementation of the bundle resulted in

> “Now that evidence demonstrates that AKI can be prevented, it is our duty to find more ways to do it”

Using biomarker enrichment the authors were able to achieve an effect with a number needed to treat of only 6. Without biomarkers it would have been >33.

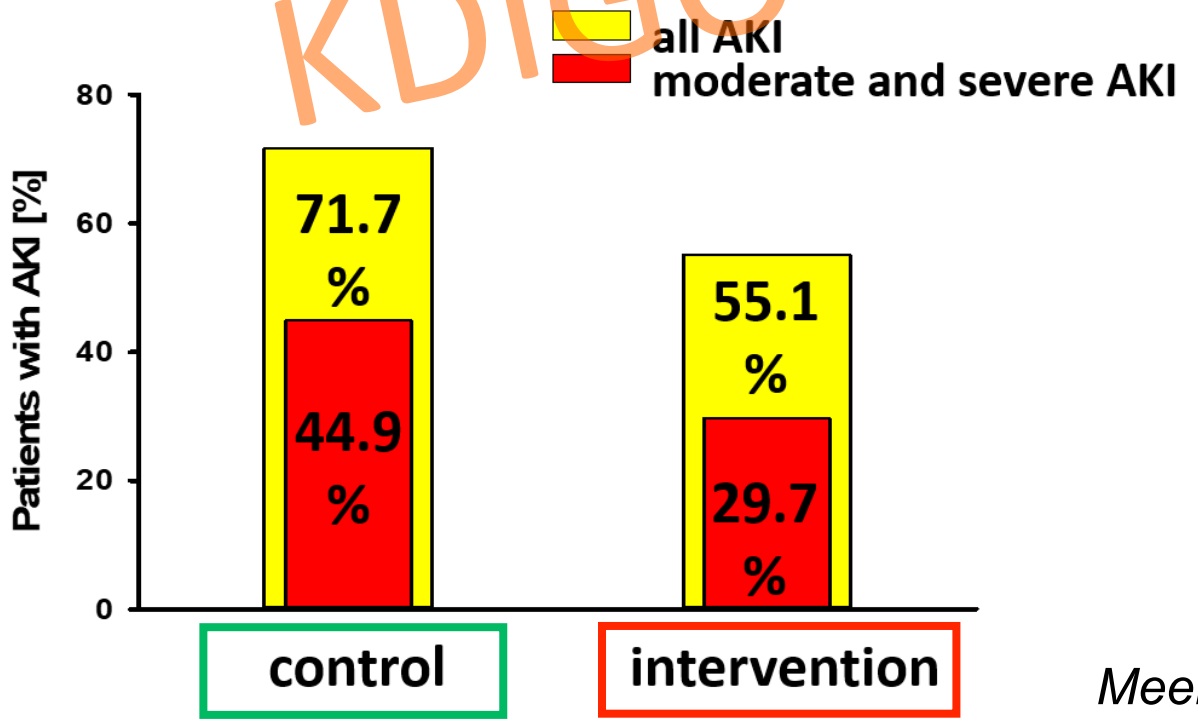
PREVAKI

Measuring [TIMP2]*[IGFBP7] 4h after cardiac surgery: if [TIMP2]*[IGFBP7] is ≥ 0.3

↓

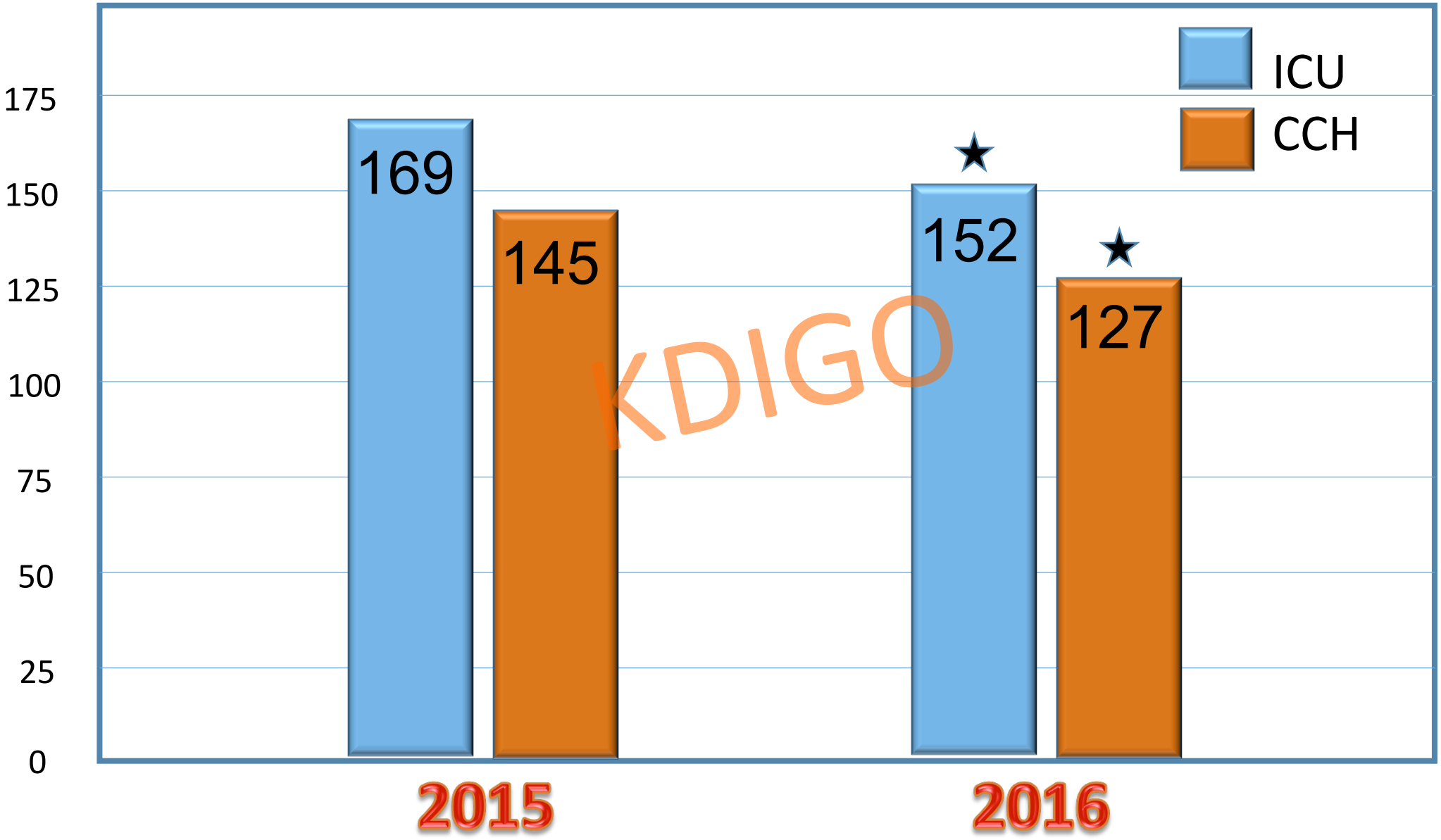
Randomization

Control group (Standard) | Intervention group (KDIGO)

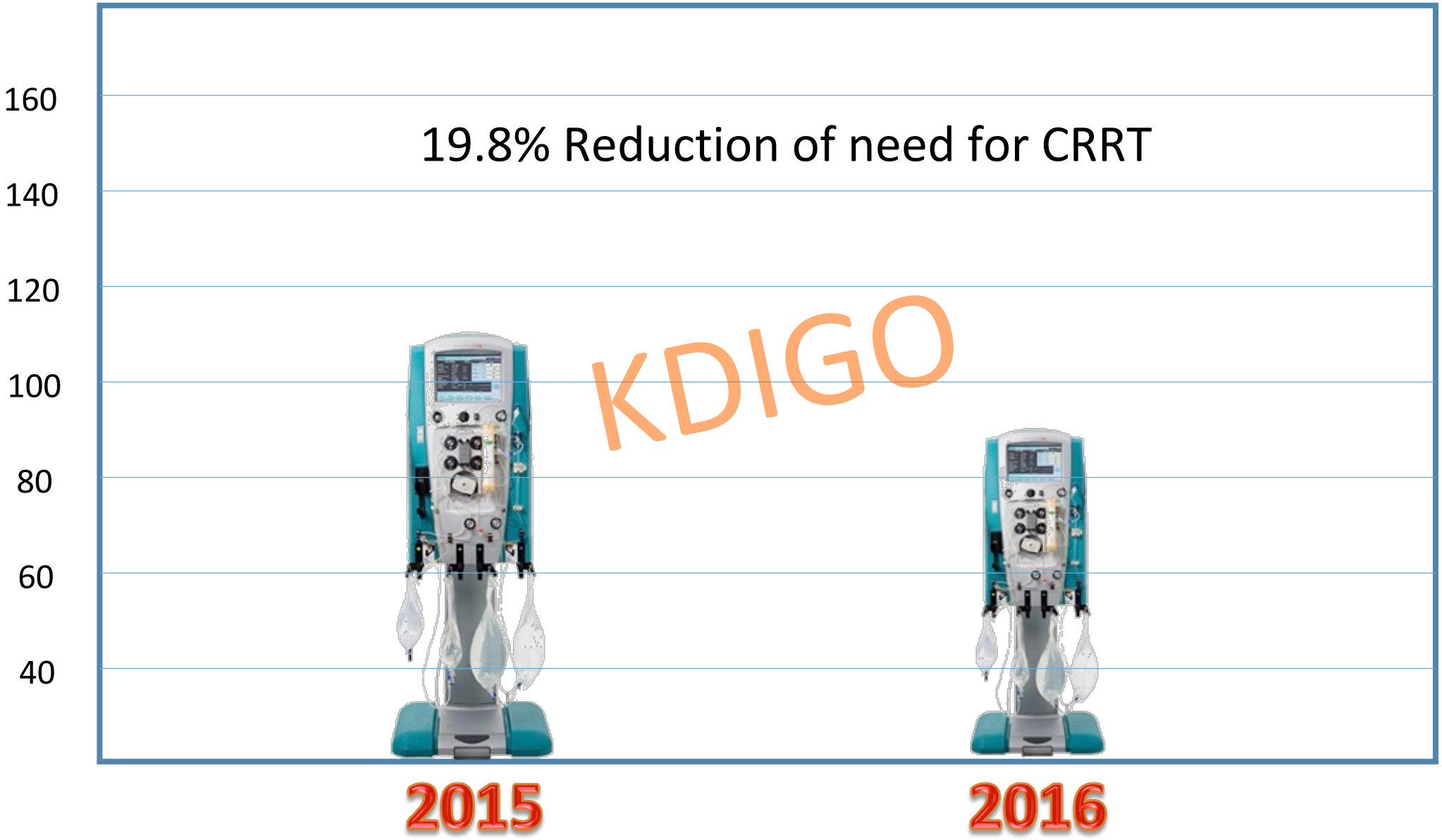


Meersch M, ICM 2017

Number of Patients with AKI



Number of Patients requiring CRRT



Contributions to Nephrology
Editor: C. Ronco
Vol. 174

Controversies in Acute Kidney Injury

Editors
J.A. Kellum
C. Ronco
J.-L. Vincent

KARGER

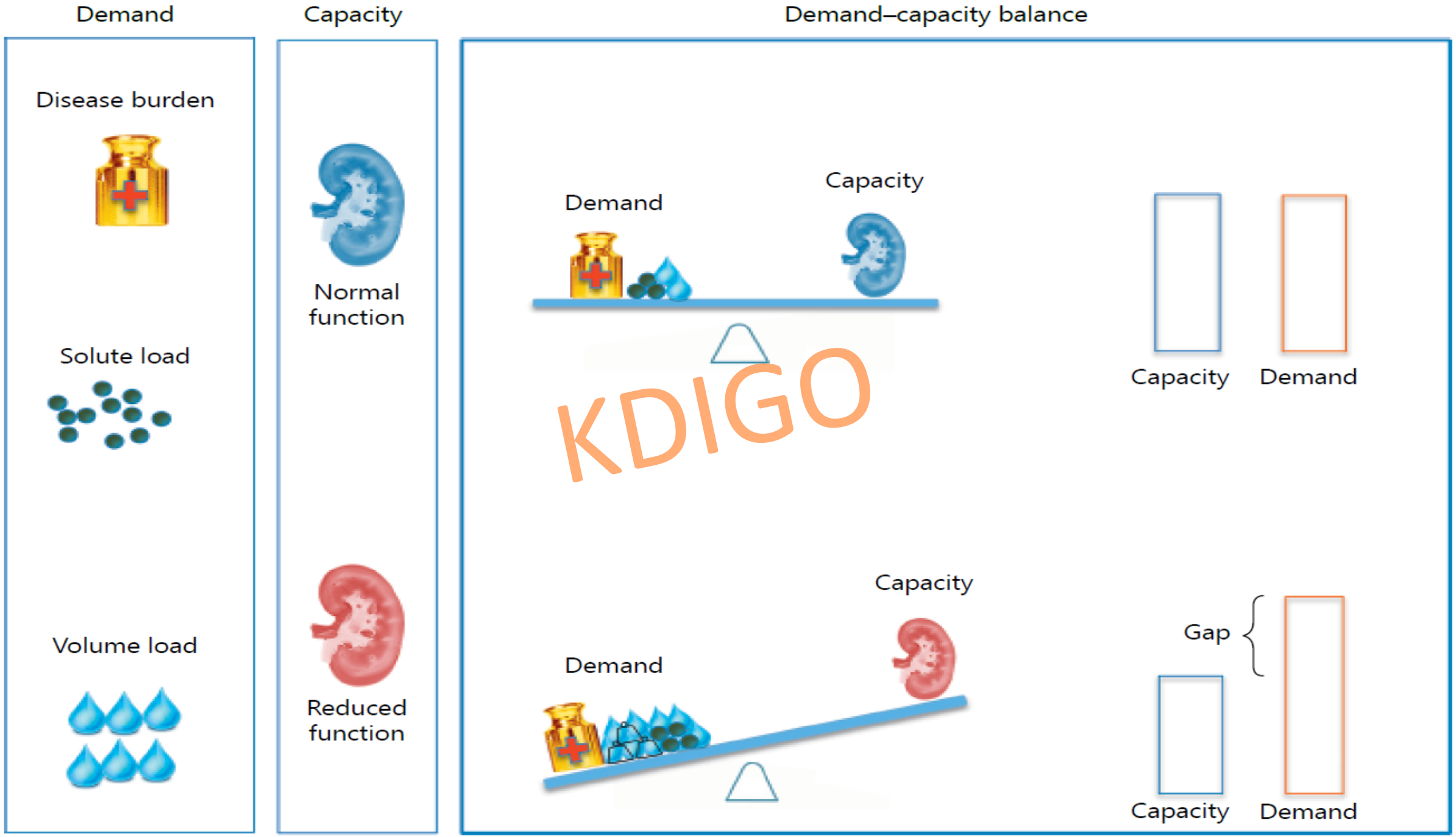
RRT Indications

Time of Initiation

Modality of RRT

Prescription, dose, Fluid Management

Quality Control


Demand
Capacity
Demand–capacity balance
Disease burden
Solute load
Volume load
Normal function
Reduced function
Demand
Capacity
KDIGO
Capacity
Demand
Demand
Capacity
Gap
Capacity
Demand

About timing

- No consensus on “When” to initiate RRT (controv. studies)
- Early initiation probably improves outcomes (but early means what? Admission? Creatinine? Other?
- RIFLE/AKIN Stage stratification may represent a surrogate of timing (severity)
- There is a rationale for early initiation
- There are draw backs for early initiation
- An objective algorithm has been proposed for RRT initiation

Do we need additional clinical studies?

About Modality

- The process of decision making is linked to indications leading to therapy initiation

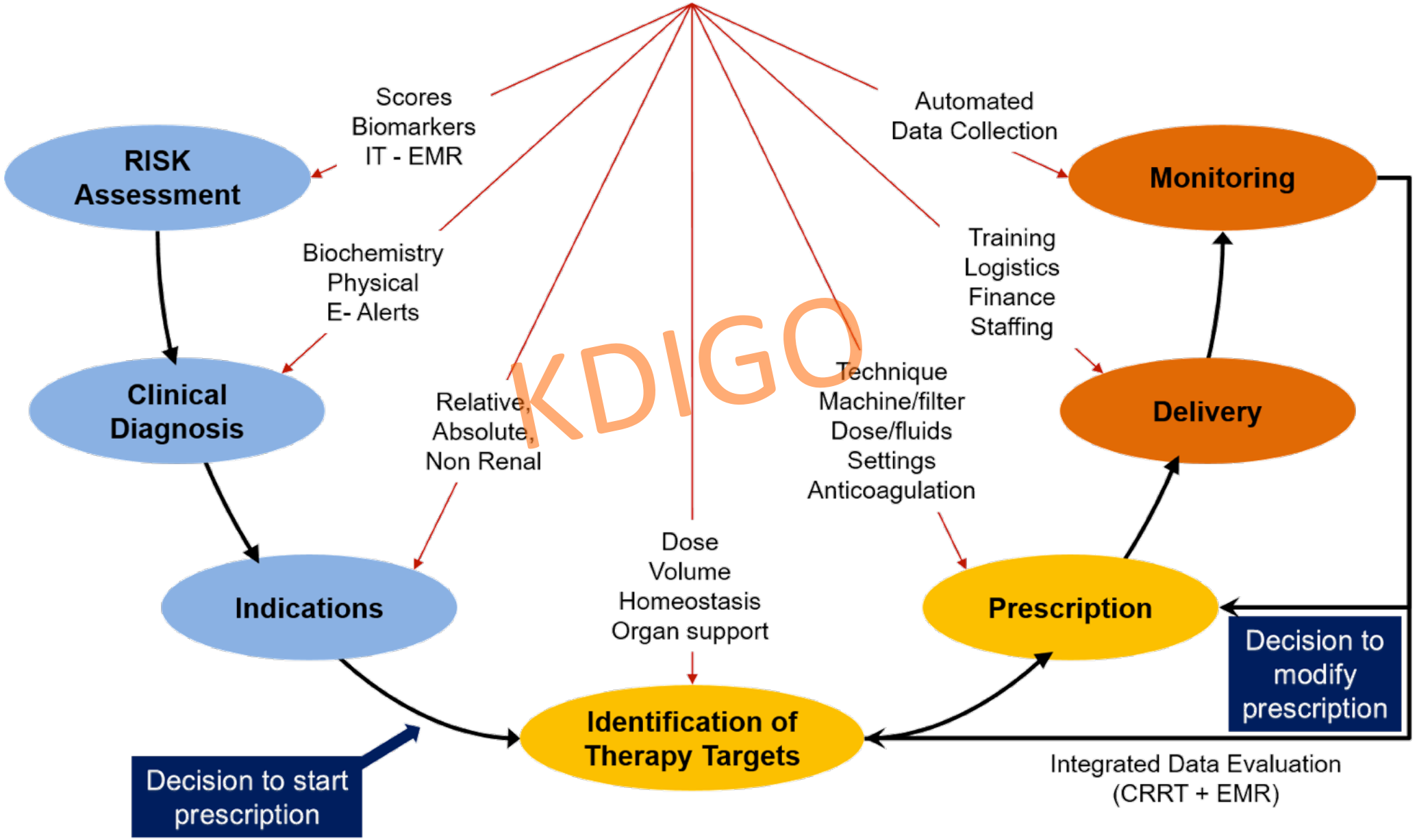
  – Classic — Blood Purification

  – Alternative
    - Fluid overload — Ultrafiltration
    - Sepsis — HVHF - CPFA

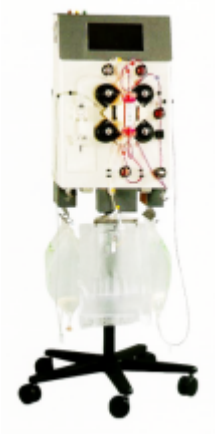
About Dose

- ✓ Recent multicenter RCTs have failed to confirm earlier trials suggesting a benefit of higher CRRT dose in critically ill patients
- ✓ Several differences (total effluent dose, convective contribution, timing of treatment initiation) exist among the various CRRT dose/outcome trials, making it difficult to establish a “standard“ dose
- ✓ Based on standard practice in chronic dialysis, routine assessment of delivered CRRT dose should be an integral aspect of AKI patient management in the future
- ✓ For the time being, 30 to 35 mL/kg/hr is a reasonable target for prescription to make sure no less than 20-25 mL/kg/hr is effectively delivered

Technology in CRRT



Evolution of CRRT



1995

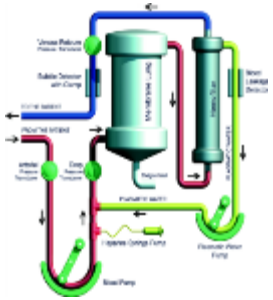
Second generation CRRT machines
CVVH
CVVHD
CVVHDF
and studies on Dose & Adequacy
35 ml/Kg/h

Third generation CRRT machines, Tr. of Sepsis
HVHF &
HCO Membr.

2002

2005

Liver support
MOST, CPFA

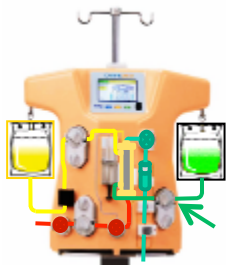


Lung support
ECCO2R
Citrate anticoagulation
Sorbents

2010

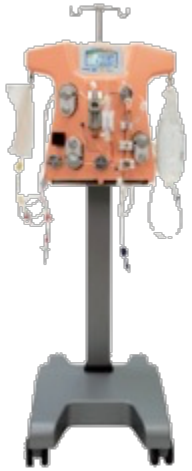
2017

New generation of CRRT machines



Pediatric CRRT

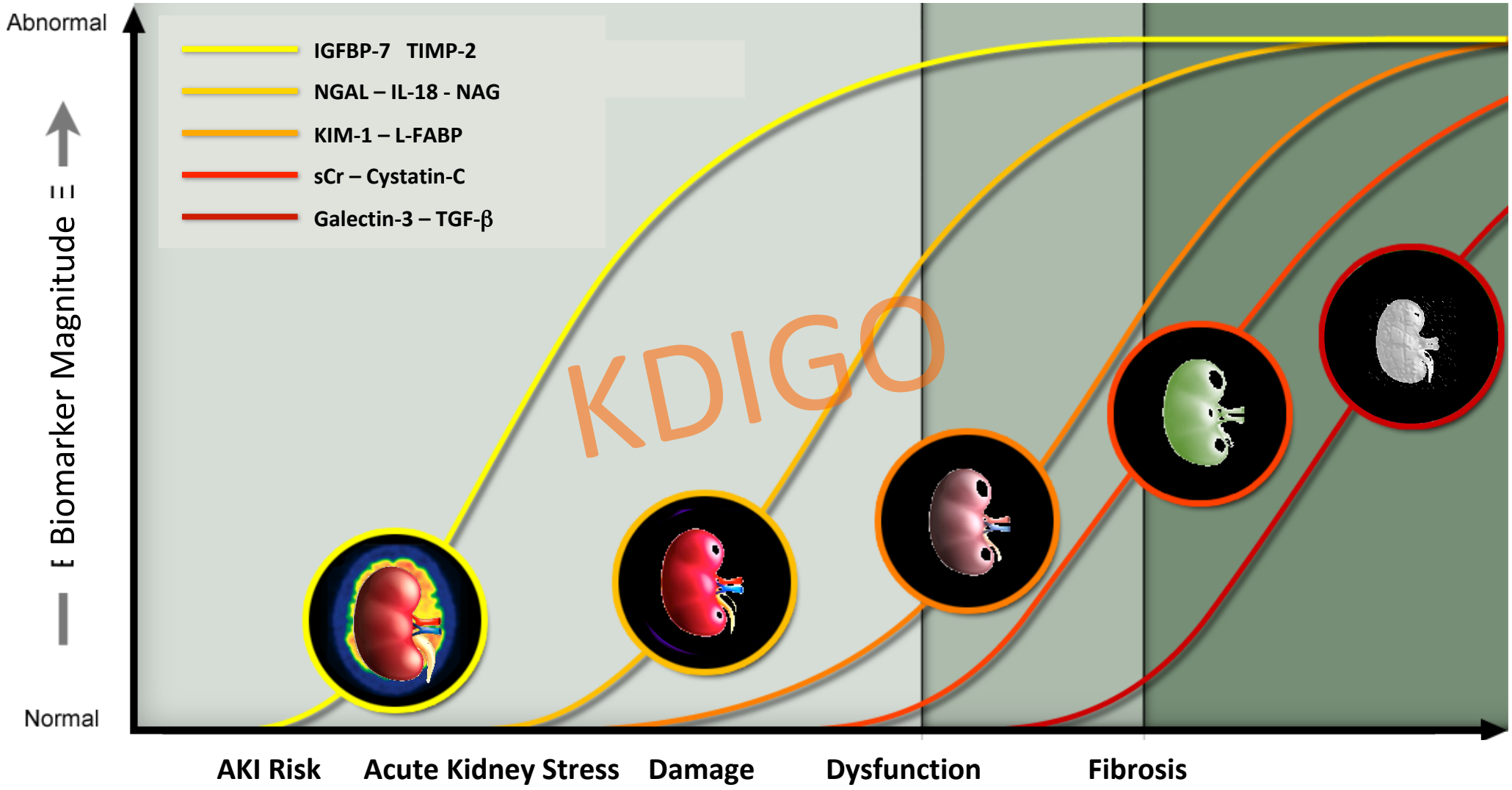
2017



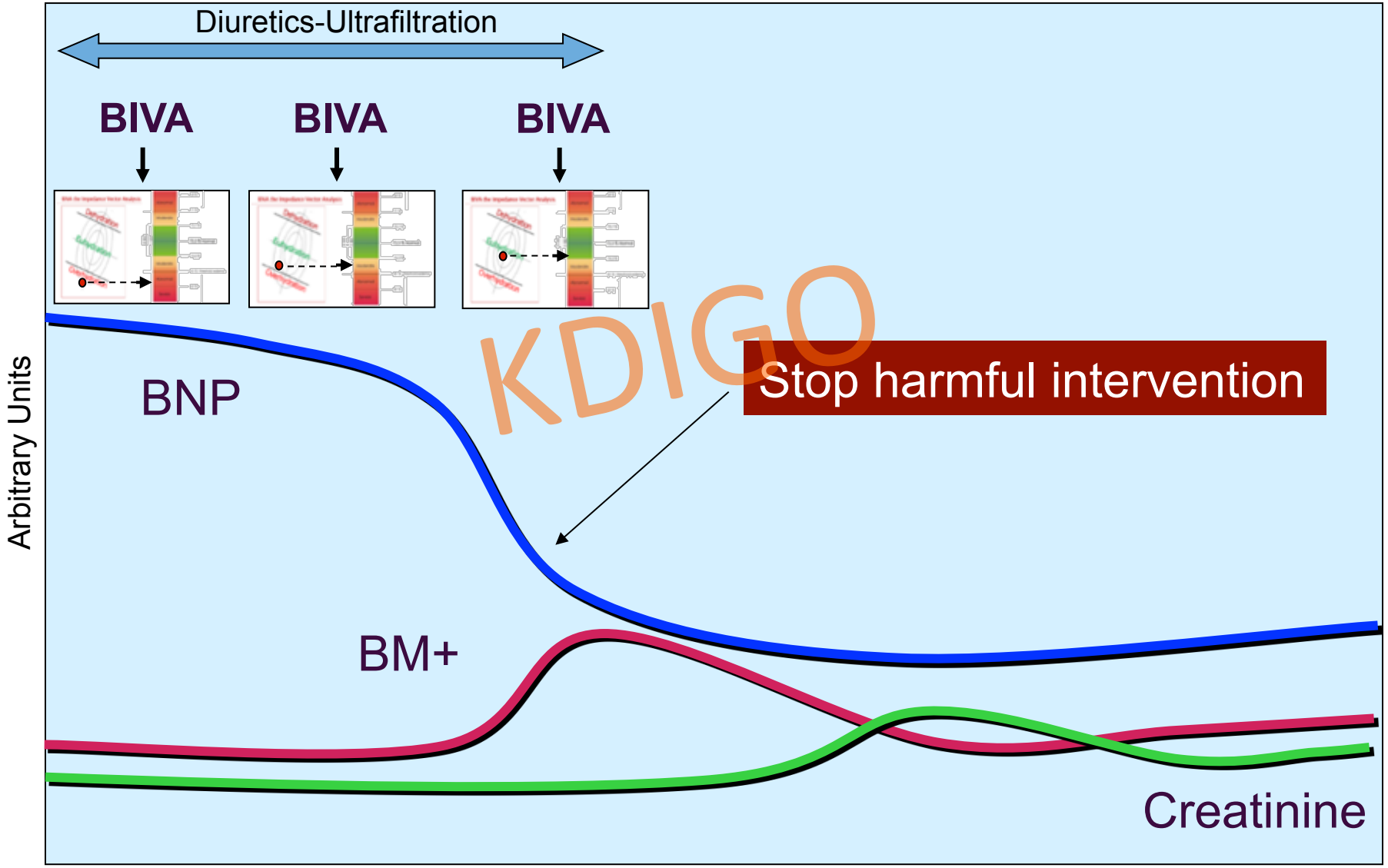
Fourth generation CRRT machines

2018-2019

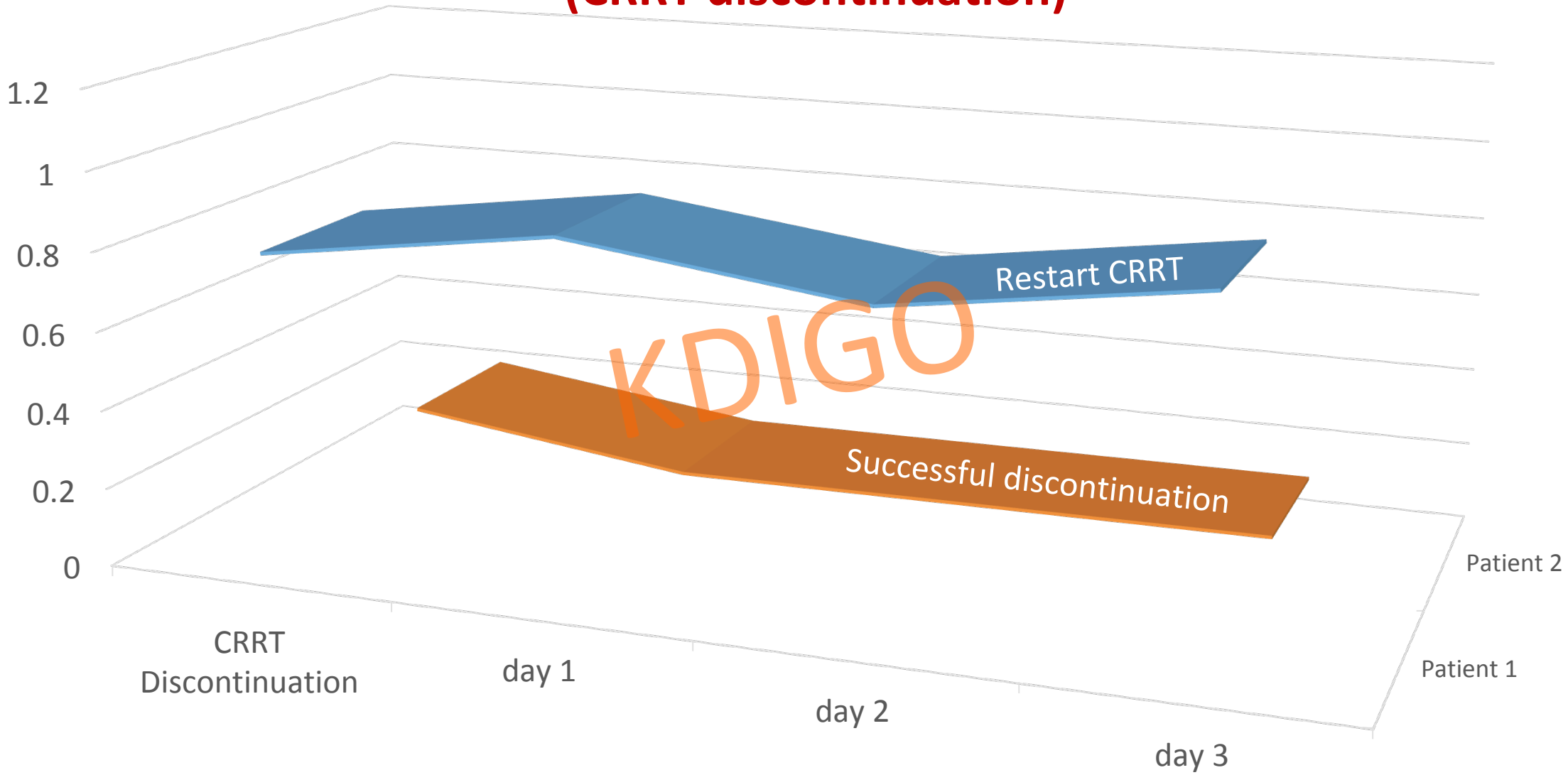
Biomarker Type & Magnitude at different AKI Stage



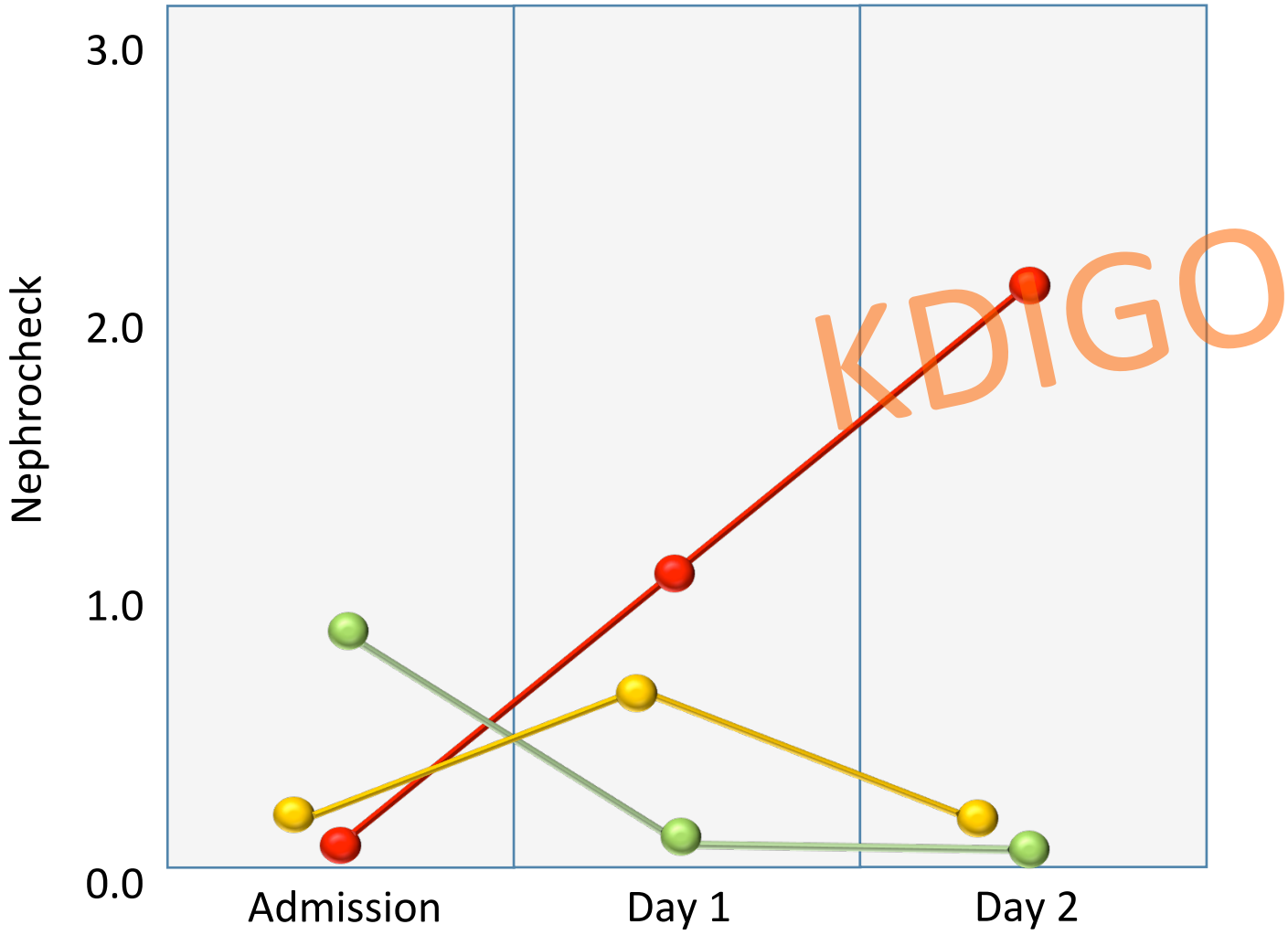
Biomarkers for CRS detection



Biomarker for Recovery (CRRT discontinuation)

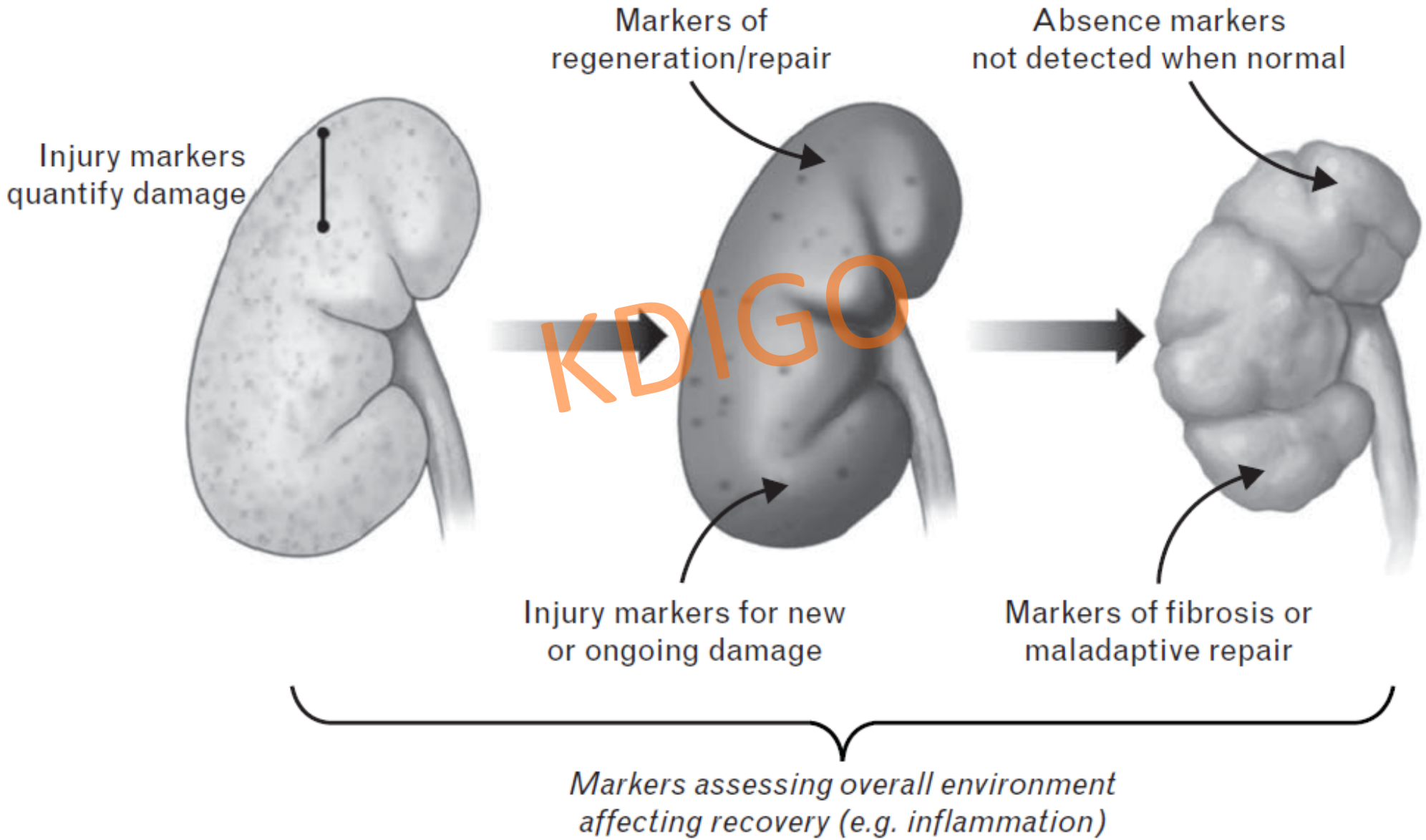


Nephrocheck Curve Study
(Vicenza 2017-2018)



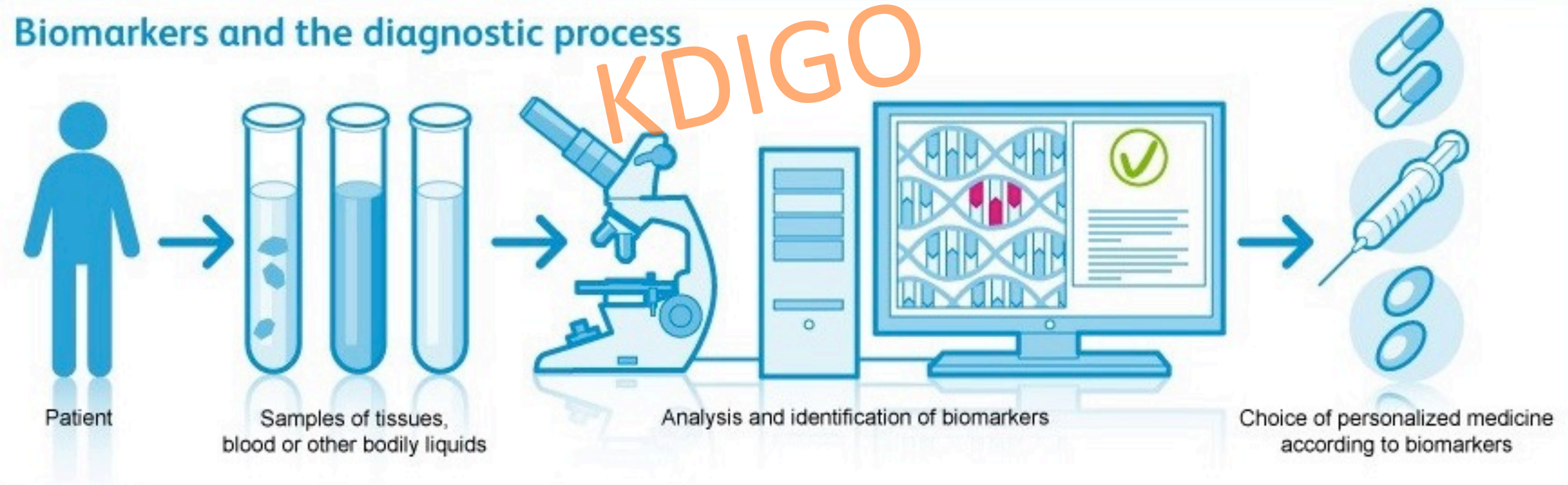
Novel Biomarkers indicating repair or progression after AKI

Kellum J, Kashani K



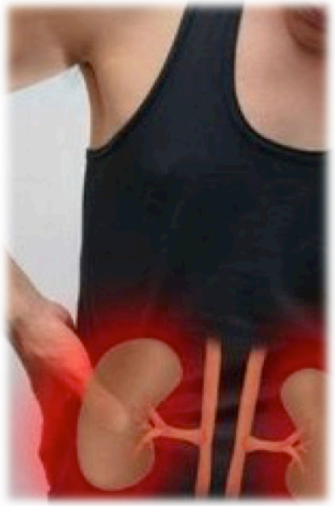
Is there a molecular signature for different types of AKI?

Translating Biomarker Research



Different types of diagnosis

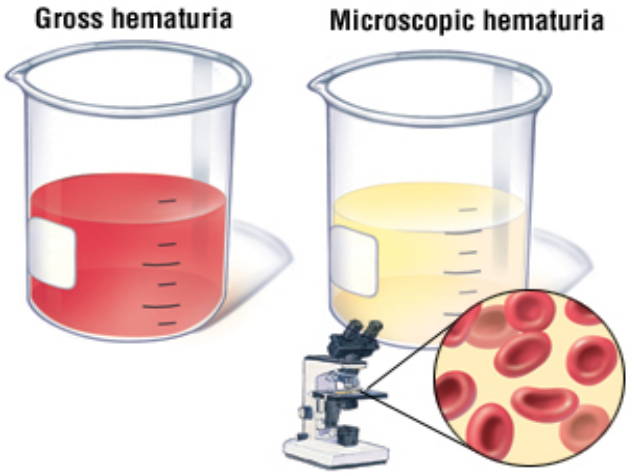
Signs



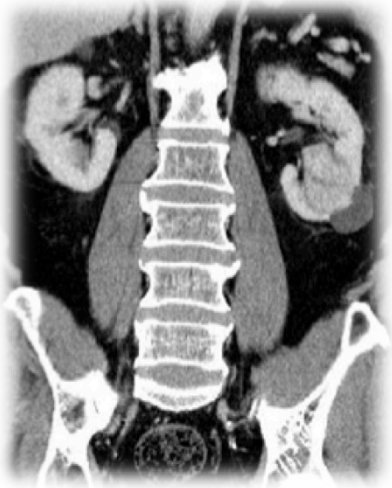
Symptoms

Physical

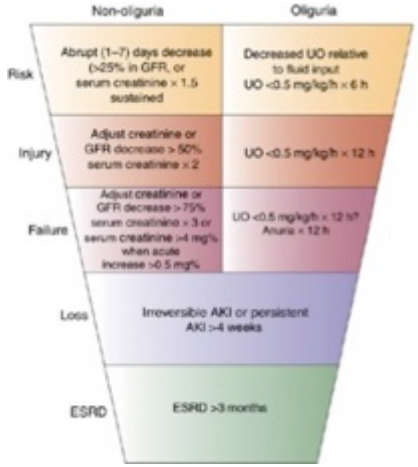
Laboratory



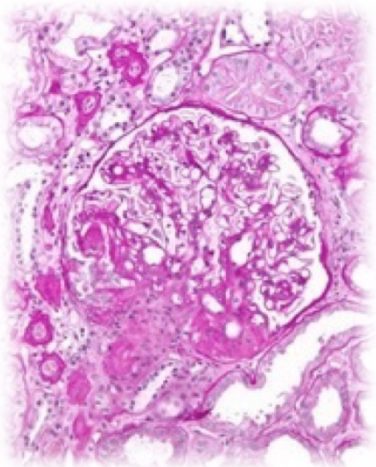
Instrumental



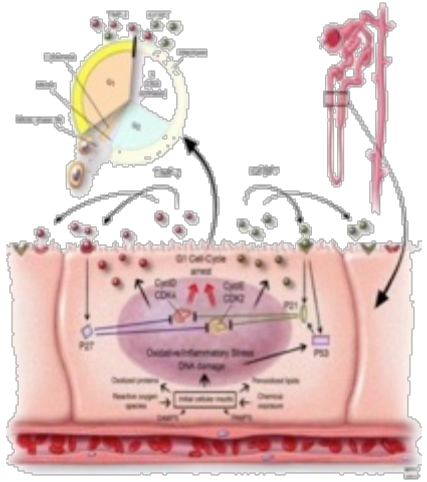
Imaging



Biochemical

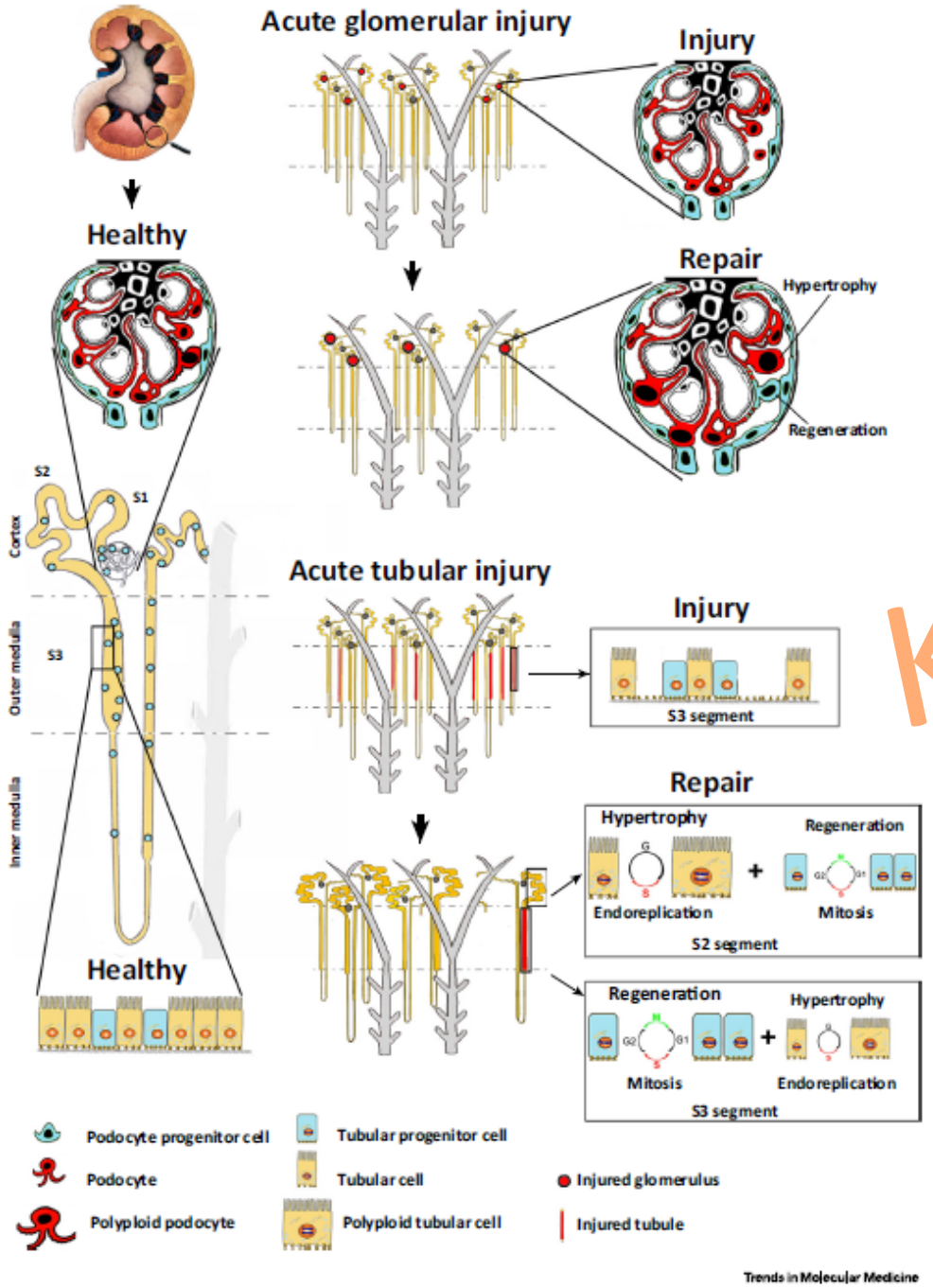


Histological



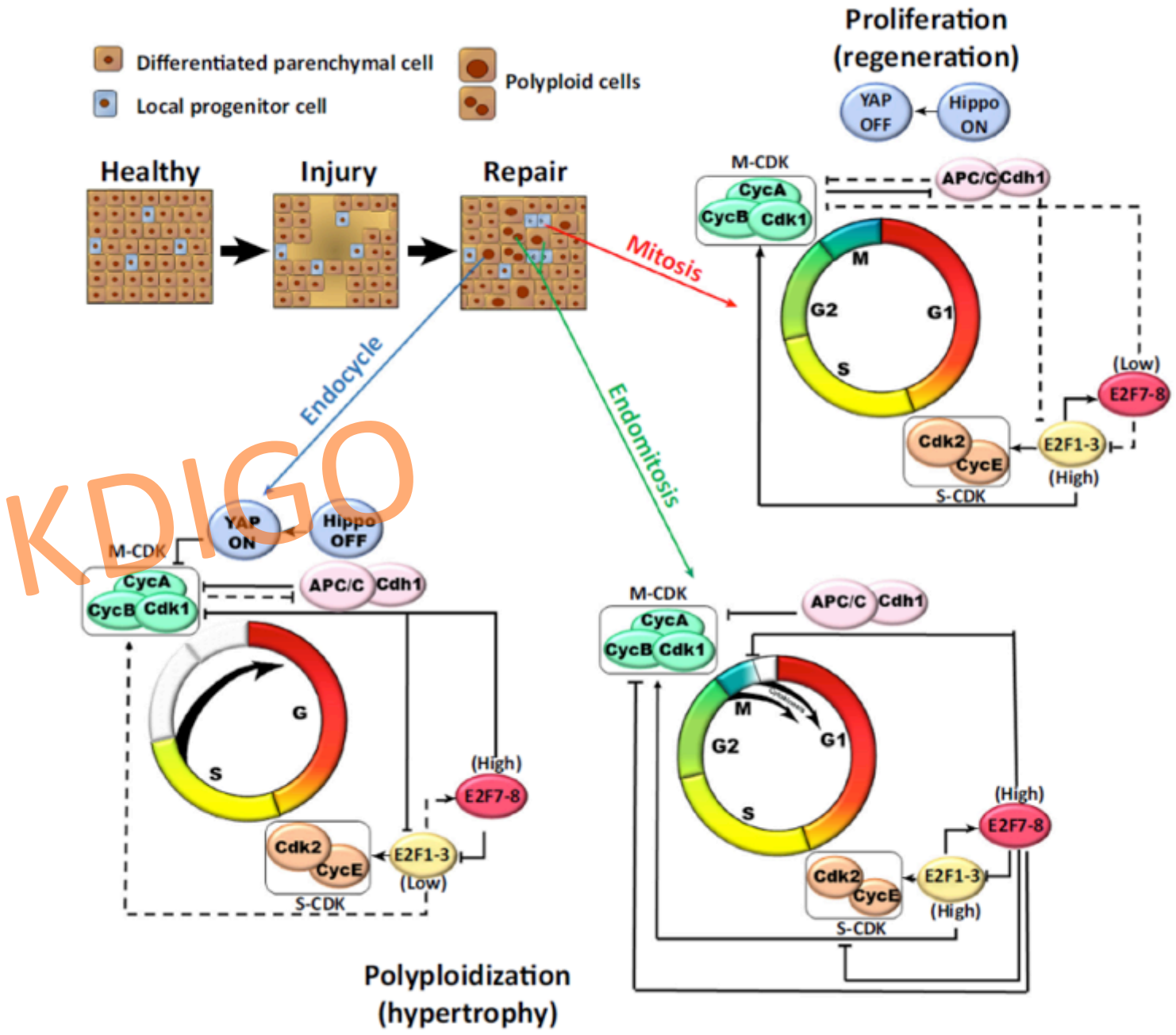
Molecular

Computer Aided



Renal Epithelial Cell Polyploidization and Progenitor Proliferation Repair of AKI. The kidney responds to AKI with two separate strategies: local progenitor cells produce new podocytes on the glomerular tuft or new tubular cells depending on the site of injury and epithelial cell loss. In the glomeruli, differentiated podocytes cannot undergo cytokinesis and increase their working capacity by entering the cell cycle to increase their DNA content and become polyploid. At the same time, podocyte progenitors localized among parietal epithelial cells of the Bowman's capsule differentiate and replace lost podocytes. Tubular epithelial cells that are already fully engaged in essential organ functions increase their working capacity without any interruption by entering the cell cycle to increase their DNA content; a form of alternative cell cycle named endoreplication. This process allows differentiated cells in uninjured S2 segments a compensatory hypertrophy to take over the filtration load of nonfunctioning injured or lost nephrons, while tubular progenitors scattered along the nephron proliferate, completing cell division and drive regeneration in necrotic S3 segments of the proximal tubule of affected nephrons.

Tubulointerstitial fibrosis is considered a hallmark of maladaptive repair processes after tubular injury leading to chronic kidney disease. Upon injury, myofibroblasts promote epithelial repair by producing retinoic acid in place of injured tubular cells. Thus, resident fibroblasts turning into myofibroblasts maintain a cross-talk that protects tubular epithelial cells from injury and can restore tissue integrity and functionality, challenging the concept that fibrosis is only detrimental in nature.



The Future of CRRT

Patients identification

CRRT optimization

MOST and ECOS technology

Integrated Equipment

Patient care and precision CRRT

The Future of AKI & CRRT

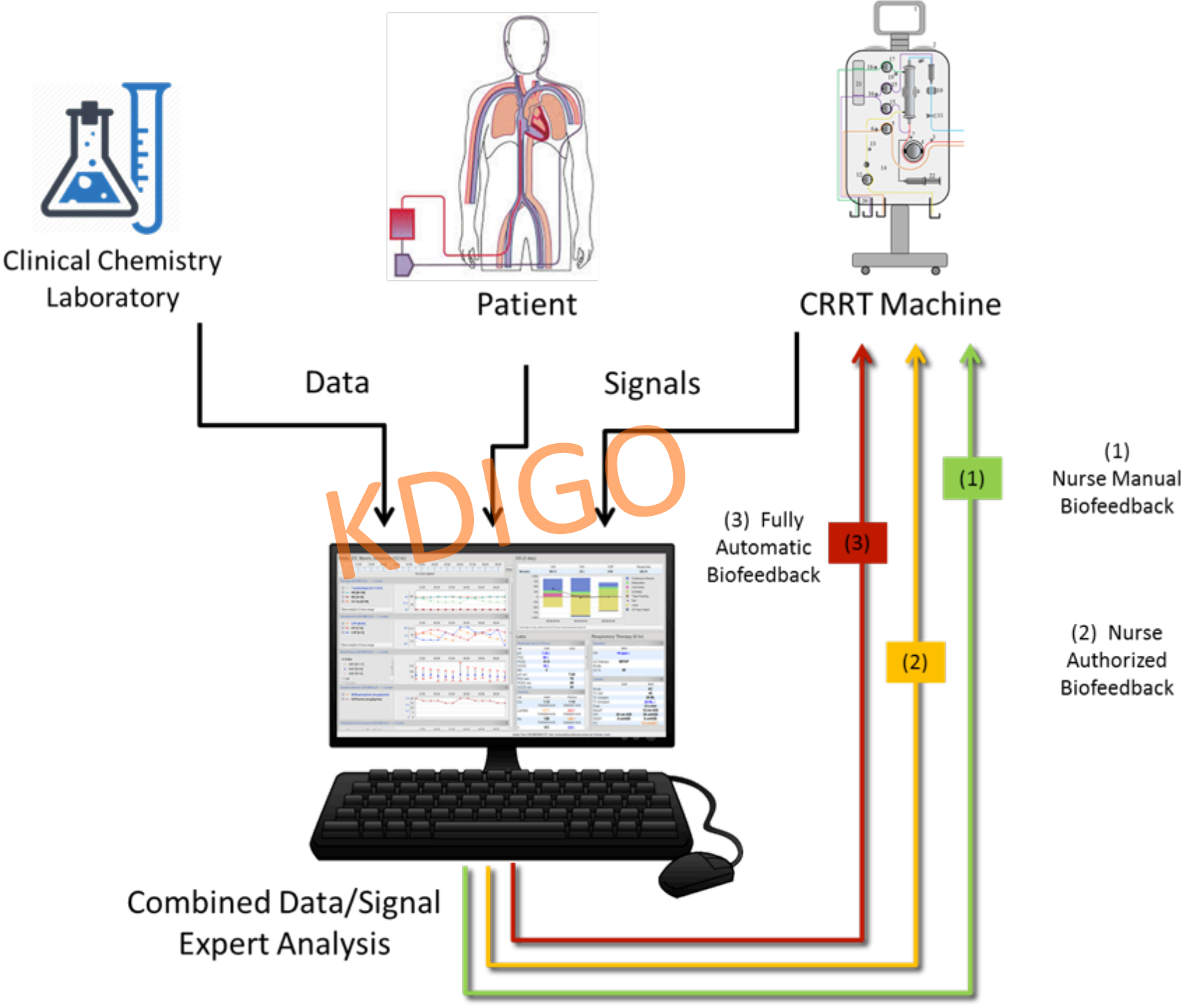
PATIENT IDENTIFICATION

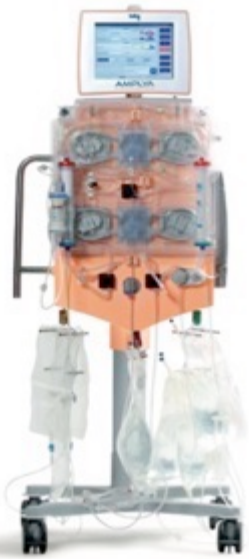
- Clear understanding of Capacity and Demand
- Genotype characterization
- Fenotype characterization
- Statistical probability of success evaluation
- Identification of patient’s needs
- Precise definition of therapy targets
- Personalized prescription of the therapy
- Dynamic follow up during and after hospital stay

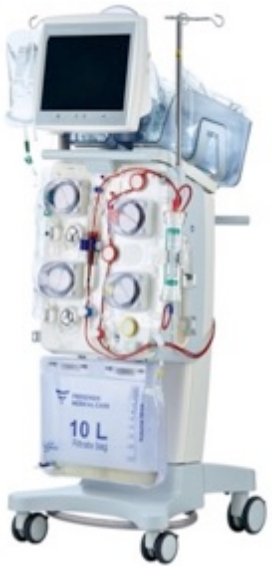
The Future of CRRT

CRRT TECHNOLOGY

- Vascular Access
- Circuitry
- Filters and membranes
- Anticoagulation
- Machines
- Monitoring
- Biofeedback


Clinical Chemistry Laboratory
Patient
CRRT Machine
Data
Signals
KDIGO
(3) Fully Automatic Biofeedback
(3)
(1)
(2)
(1) Nurse Manual Biofeedback
(2) Nurse Authorized Biofeedback
Combined Data/Signal Expert Analysis

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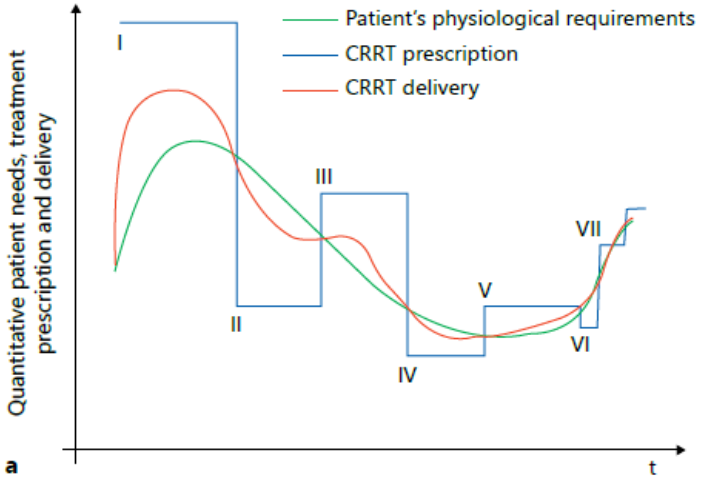
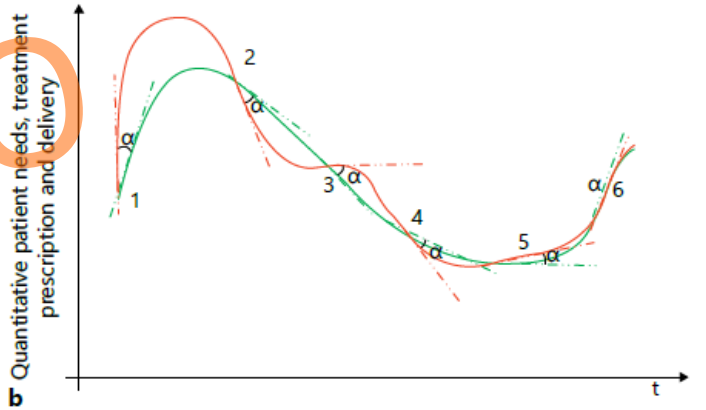

Patient's physiological requirements
CRRT prescription
CRRT delivery
Quantitative patient needs, treatment prescription and delivery
I
II
III
IV
V
VI
VII
t
a


Quantitative patient needs, treatment prescription and delivery
1
2
3
4
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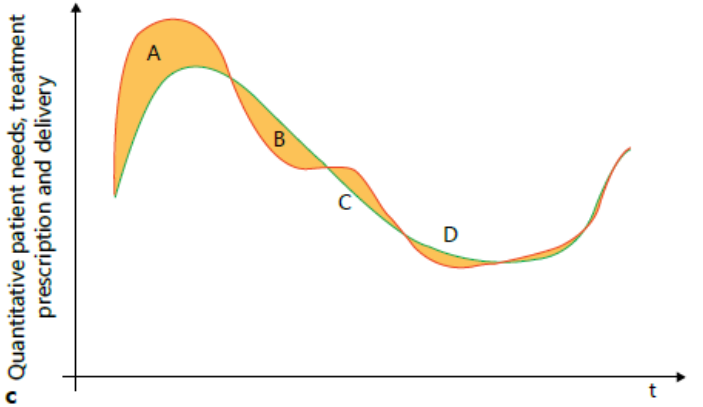

Quantitative patient needs, treatment prescription and delivery
A
B
C
D
t
c

Machine Data Only

Filter Life

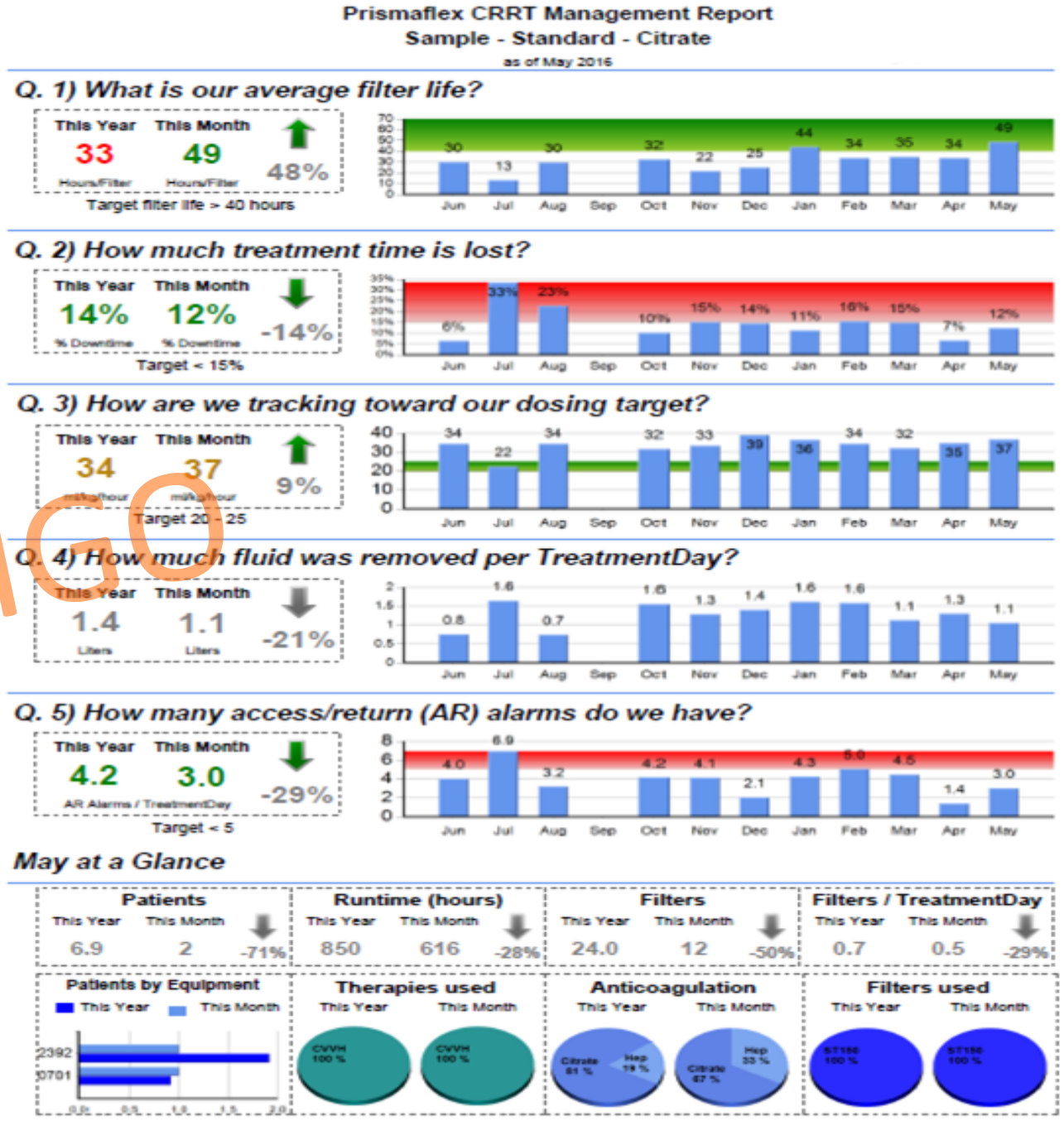
Treatment Downtime

Prescribed & Delivered Dose

Fluid Removal Parameters

Alarm Management

Summary



Machine & EMR Data

Timing of CRRT Initiation

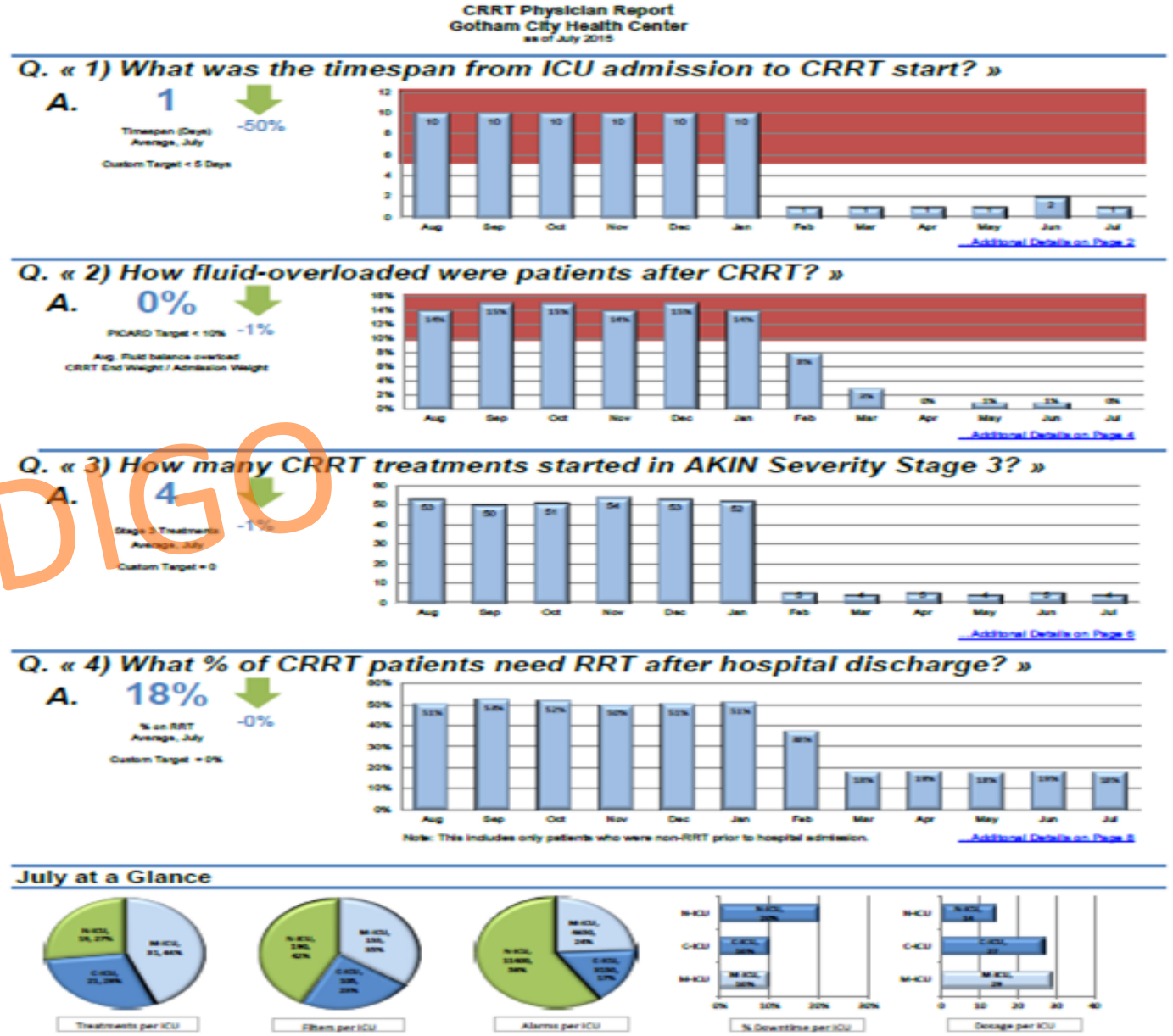
Fluid Overload and Management, Ventilator and Vasopressor Duration

CRRT Initiation versus KDIGO AKI Stage

Frequency of RRT After CRRT

Summary

Quality Control



KDIGO

Extracorporeal circuits

- Antithrombogenic
- Anti microbial properties
- Temperature self adjusting
- Collapsable (minimum storage volume)
- Biodegradable (minimum wasting)

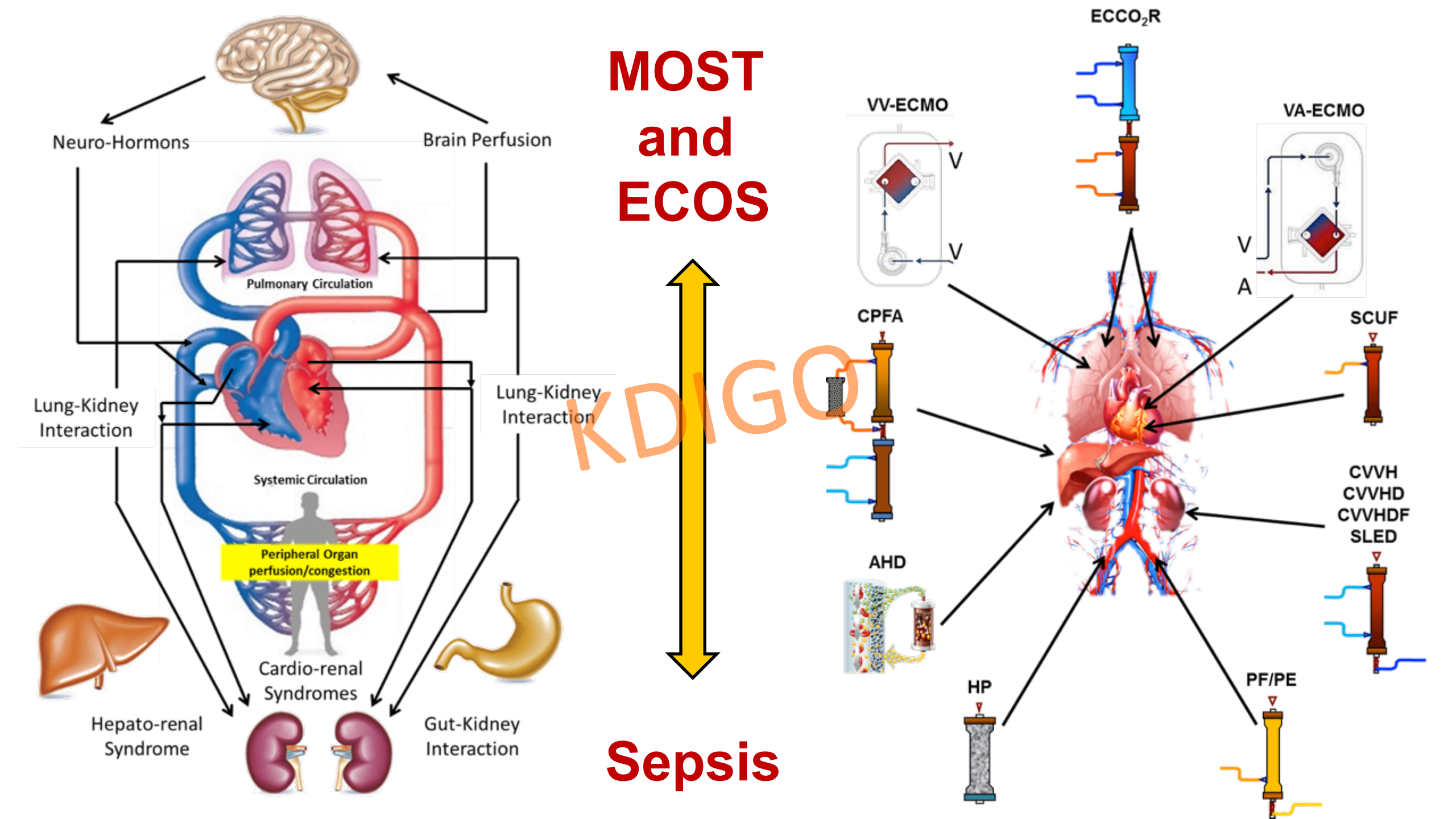
Water sparing technologies

(Blue Planet Dialysis)

1. Regeneration
2. Double filtration
3. Physical-chemical processes
4. Recirculation
5. Sorbent technologies

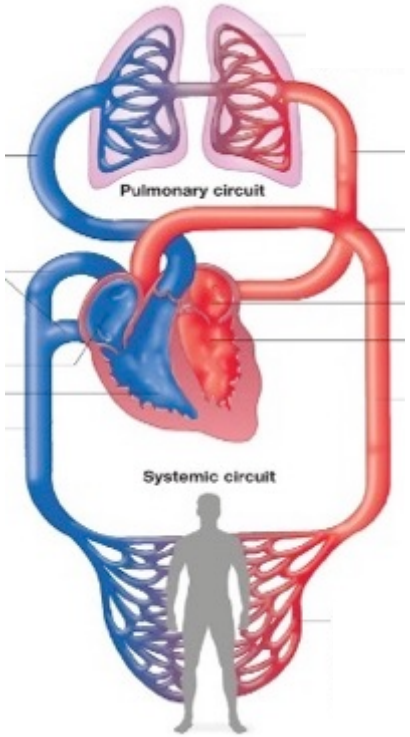
Devices, MOST and ECOS

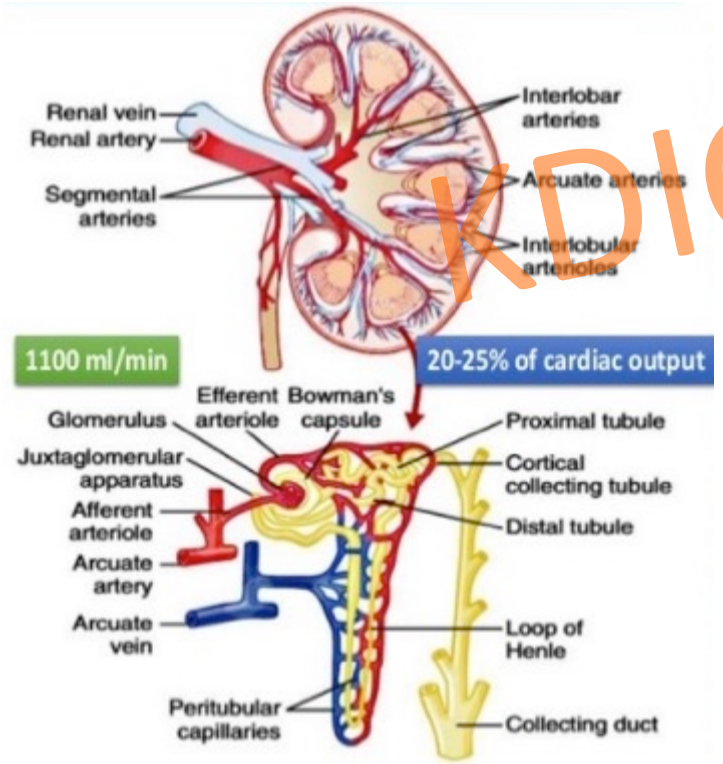
- Fluid Balance control
- New Membranes
- New sorbent devices
- Wearable devices
- Population.specific therapies

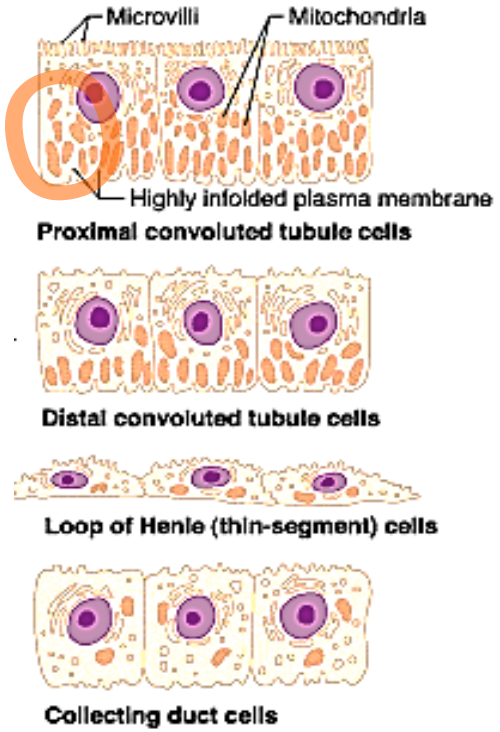

MOST
and
ECOS
Sepsis
KDIGO
Neuro-Hormons
Brain Perfusion
Pulmonary Circulation
Lung-Kidney Interaction
Lung-Kidney Interaction
Systemic Circulation
Peripheral Organ perfusion/congestion
Cardio-renal Syndromes
Hepato-renal Syndrome
Gut-Kidney Interaction
ECCO2R
VV-ECMO
V
V
VA-ECMO
V
A
CPFA
SCUF
CVVH
CVVHD
CVVHDF
SLED
AHD
HP
PF/PE

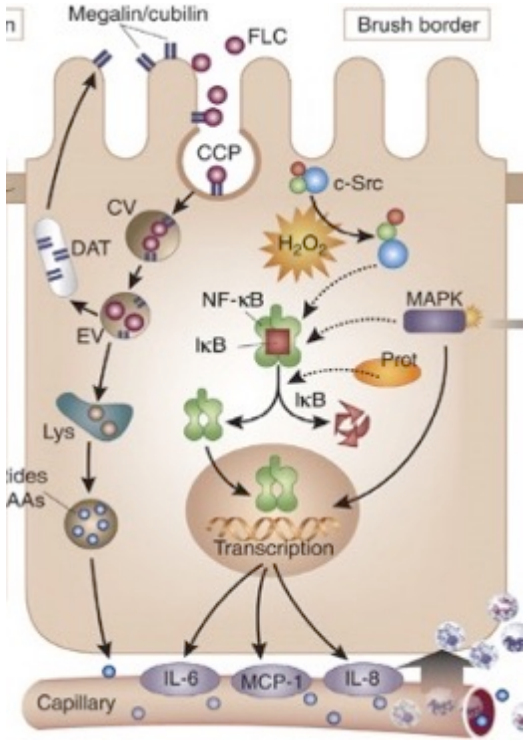
Organ Crosstalk

The case of Heart, Lungs and Kidney

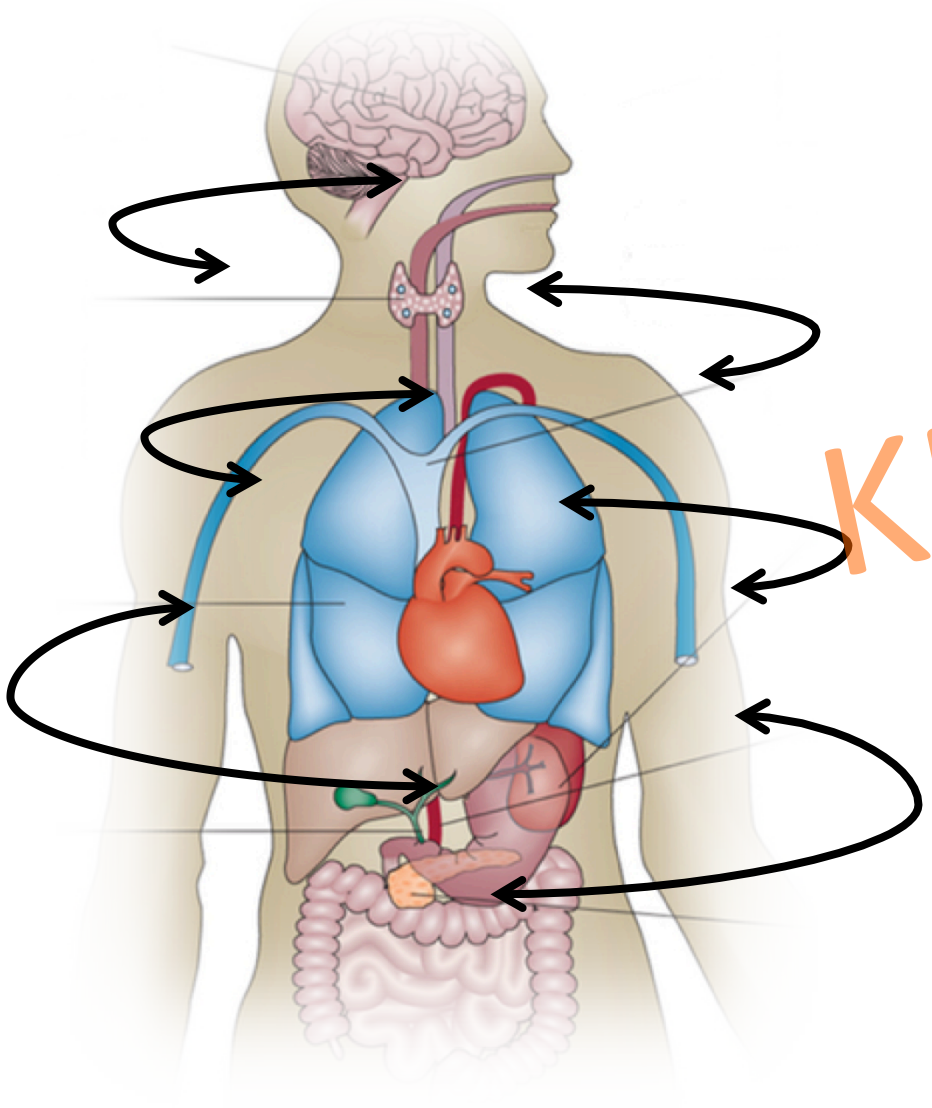




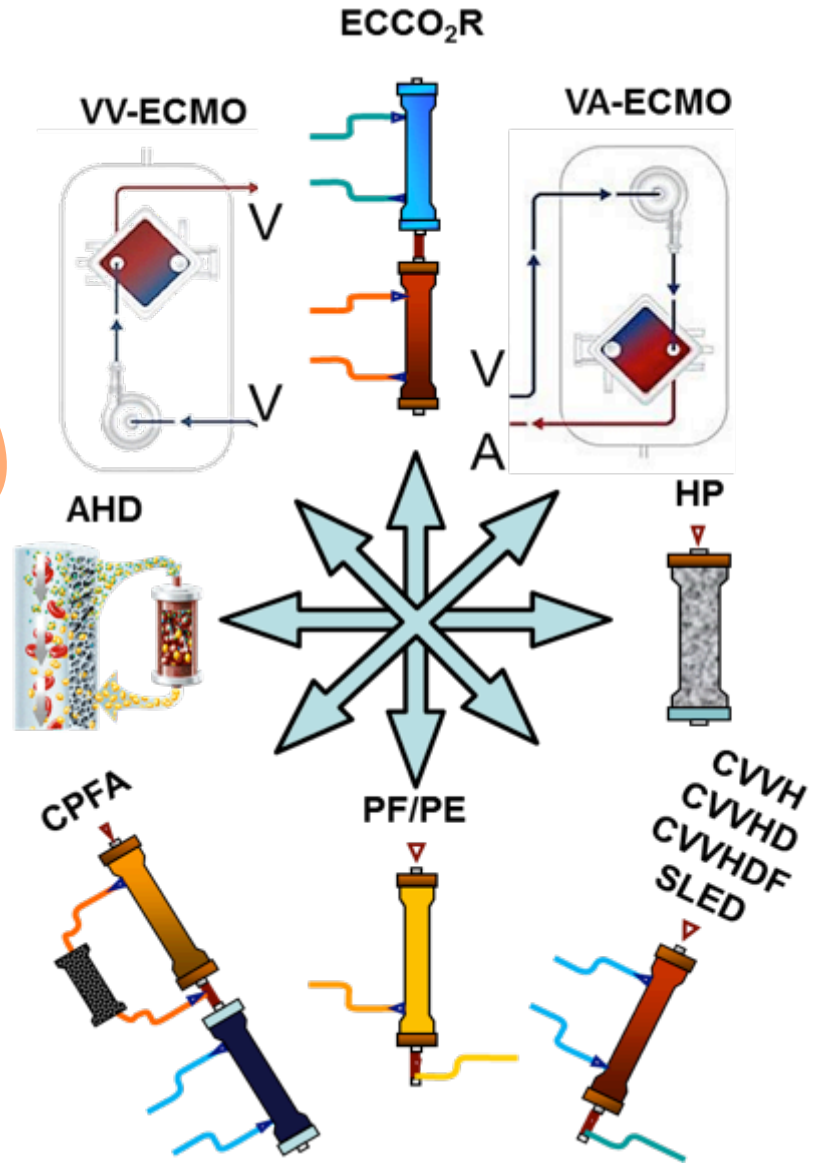


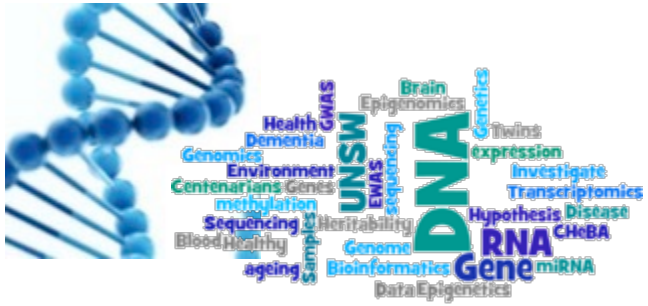


From Native to Artificial Organ Crosstalk



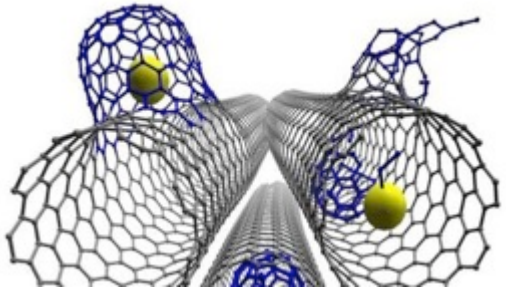
KDIGO





Genetics

Robotics



Nanosciences

G.R.E.E.N.

E- Health, ICT

Echo compatibility

We need to provide the evidence and the foundations for the next generation KDIGO AKI guidelines, and specifically in the following areas:

- Nomenclature & Diagnostic Criteria
- AKI Risk Stratification & Assessment
- Fluid Management & Hemodynamic Support
- Nephrotoxic Agents & Drugs affecting the Kidney
- Renal Replacement Therapy