Brigham and Women's Hospital
Founding Member, Mass General Brigham

Pathophysiology of Acute Kidney Injury

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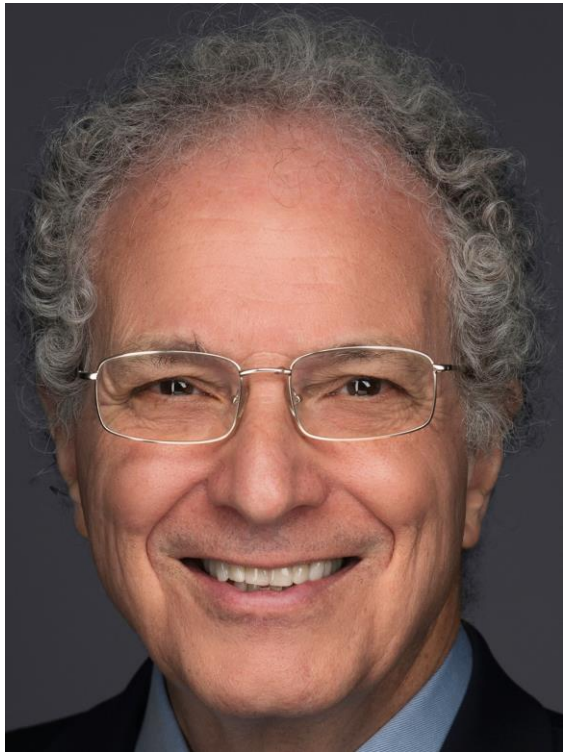
CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Joseph V Bonventre, MD, PhD



Harvard Medical School
Medicine Residency @ Massachusetts General Hosp.
Nephrology Fellowship @MGH
Professor of Medicine@ HMS
Chief Emeritus, Nephrology Division, MassGenlBrigham
Founding Chief, Division of Engineering in Med. BWH
Research focus:

- Kidney Injury, Repair and Regeneration

DISCLOSURES

Advisory Board/Consultant: Praxis, Sarepta
Mitsubishi Tanabe, Nimbus, Otsuka, Dynamicure,
Verge Genomics, Kiora, Mediar, Crinetics, PepGen

Equity: Innoviva, Pacific Biosciences, MediBeacon
Autonomous Medical Devices Inc

Patents: Co-Inventor on KIM-1 patents assigned to
Partners Healthcare

OBJECTIVES

To better understand

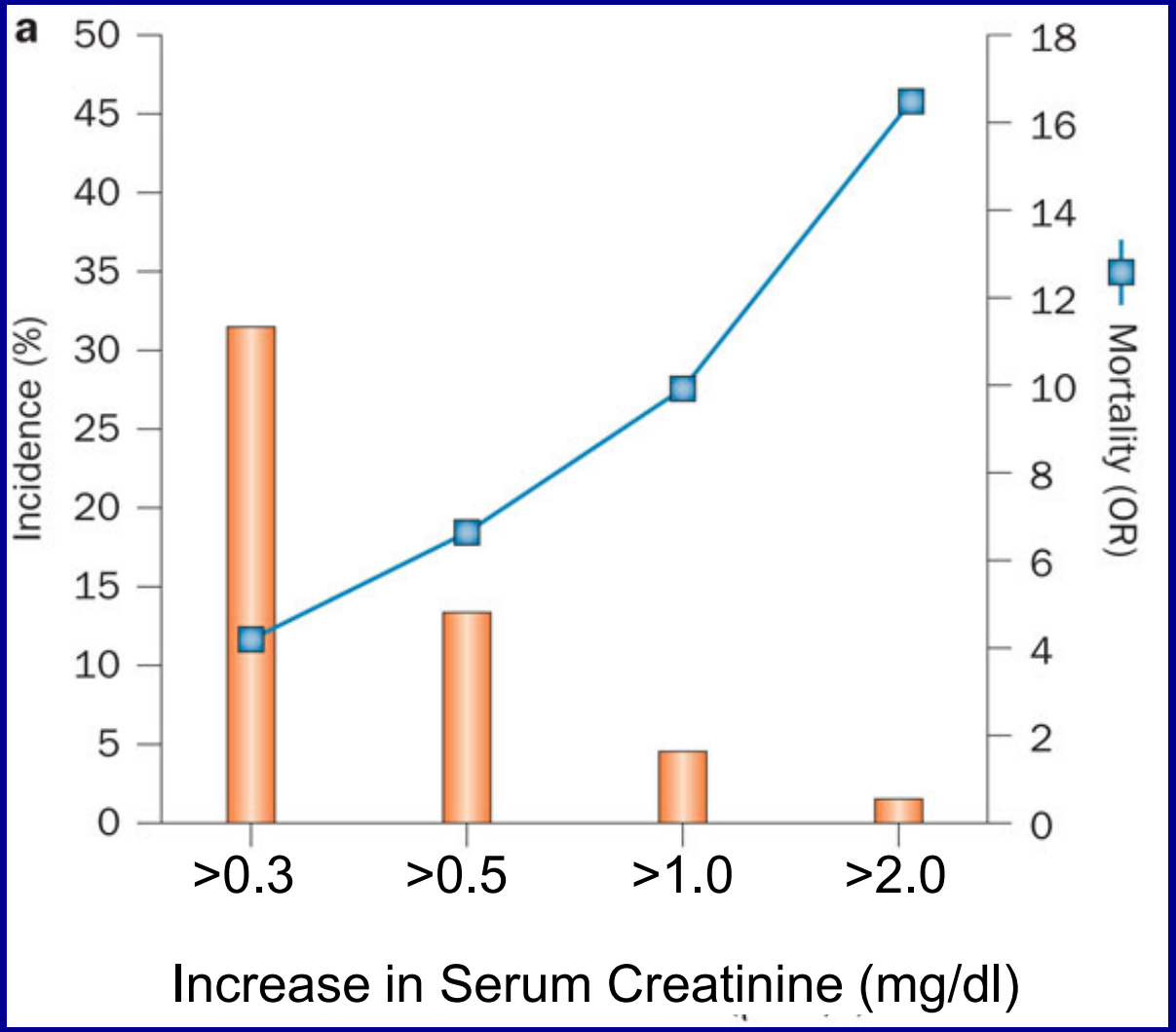
- The pathophysiology of ischemic and toxic acute kidney injury.

- The implications of this pathophysiology for progression to chronic kidney disease and approach to therapy.

Pathophysiology of Acute Kidney Injury

- Definitions
- Pathophysiology of Injury
  - Tubules
  - Blood Vessels
  - Inflammation
- Maladaptive Repair leading to Chronic Kidney Disease
- Therapeutic Approaches Motivated by Pathobiology

Hospital survival, stratified by KDIGO stages of acute kidney injury



Chertow
Burdick
Honour
Bonventre
Bates
JASN 16:
3365-70, 2005

Rewa, O. & Bagshaw, S. M. (2014) *Nat. Rev. Nephrol.* 2013

KDIGO Definition of AKI

Acute kidney injury is defined when one of the following criteria is met:

- Serum creatinine rises by ≥ 26μmol/L (0.3 mg/dl) within 48 hours or
- Serum creatinine rises ≥ 1.5 fold from the reference value, which is known or presumed to have occurred within 7 days or
- Urine output is < 0.5 ml/kg/hr for >6 consecutive hours

KDIGO = **K**idney **D**isease to **I**mprove **G**lobal **O**utcomes

KDIGO staging system for acute kidney injury

Stage	Increase in serum creatinine	Urine output
1	➢0.3mg/dL increase in 48 hr; 1.5-1.9 > ref SCr	< 0.5 mL/kg/hr for > 6 h
2	≥ 2.0 to 2.9 X ref SCr	< 0.5 mL/kg/hr for > 12 h
3	≥ 3.0 X ref SCr or commenced on renal replacement therapy irrespective of stage > 0.5 mg/dL	< 0.3 mL/kg/hr for > 24 h or anuria for > 12 h

What Has Held Up Progress

Definition of AKI relies on Δ sCreat

- Serum creatinine rises by ≥ 26μmol/L (0.3 mg/dl) within 48 hrs or
- Serum creatinine rises ≥ 1.5 fold from the reference value, which is known or presumed to have occurred within one week, or
- Urine output is < 0.5ml/kg/hr for > 6 consecutive hours

BUT

Acute kidney injury ≠ Acute tubular/interstitial injury

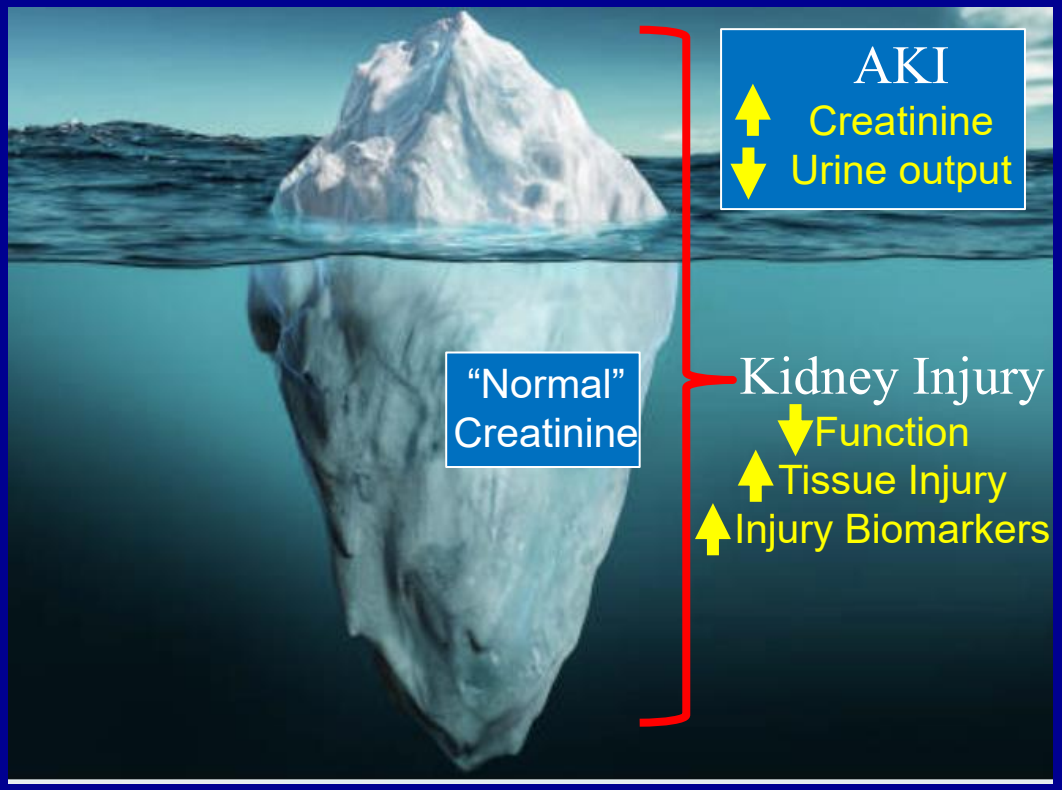
We want biomarkers that measure tubular-interstitial injury

Barasch, Zager and Bonventre. Lancet 389: 779-781, 2017

Creatinine is a poor marker of AKI

- Production and release into circulation is highly variable with age, gender, meat intake, muscle mass, disease
- 10-40% is due to tubular excretion
- Drugs can inhibit tubular secretion (eg cimetidine and trimethoprim)
- Assay is subject to interference (e.g.acetoacetate, hyperbilirubinemia)
- Time delay in reflecting injury to the kidney
- Nonlinear relationship to fall in GFR impairs sensitivity
- Creatinine can increase in functional states without damage

Incidence of Kidney Dysfunction/Injury >> AKI



AKI Criteria

+

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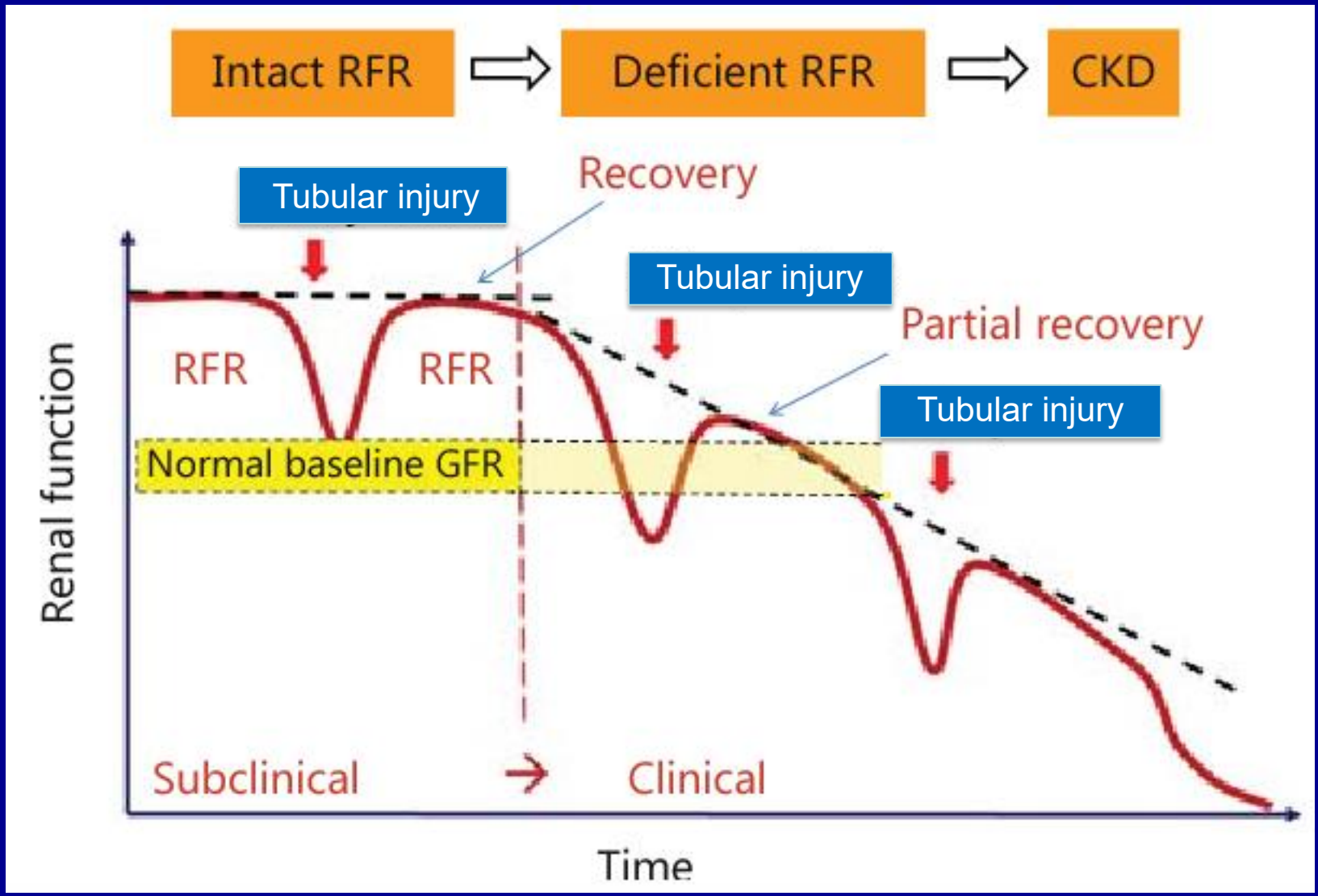
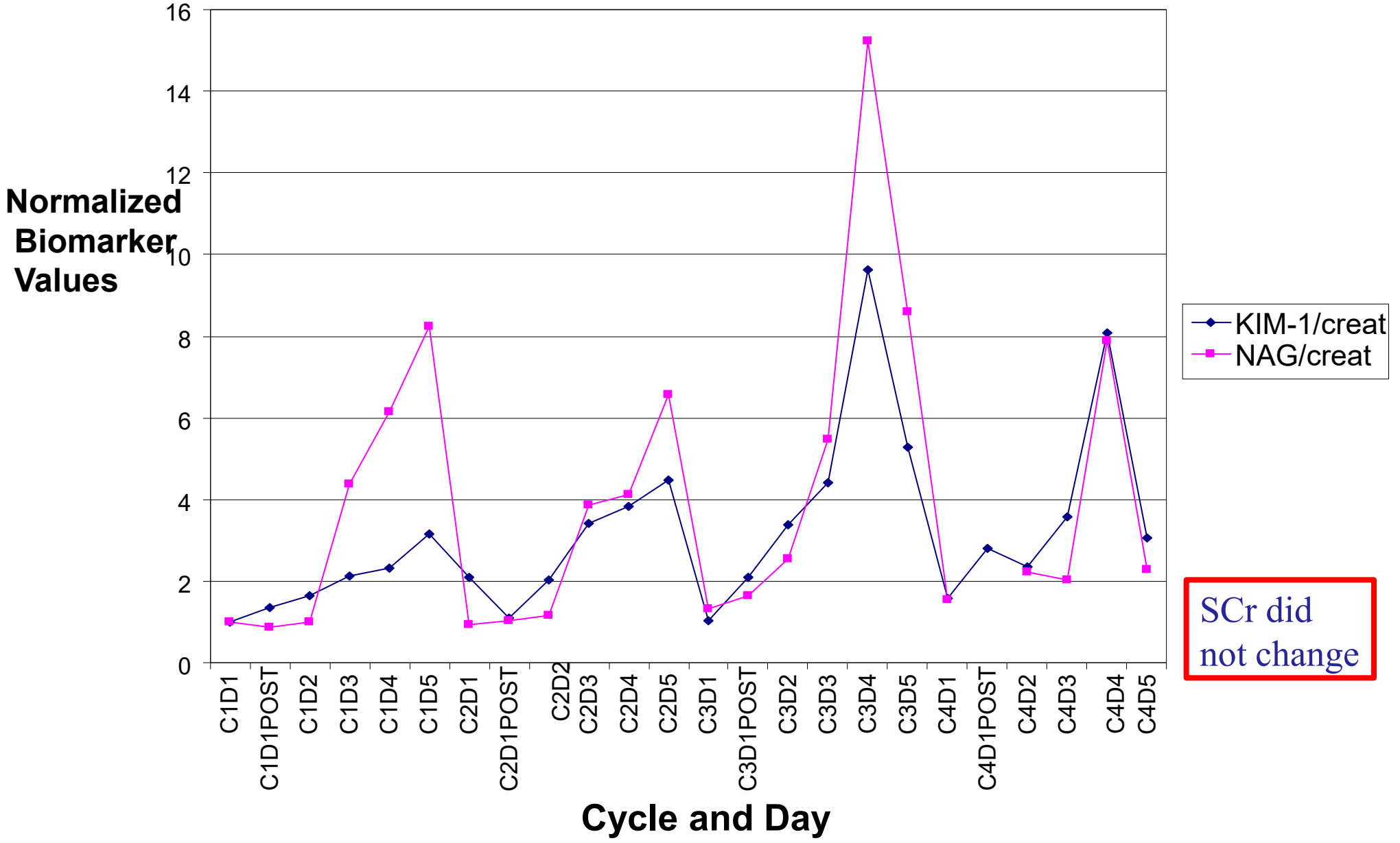
Renal Functional Reserve



Modified from
Sharma,Mucino and Ronco
Nephron Clin Prac
127:94-100, 2014

Mean Urinary KIM-1 and NAG Levels During Cisplatin Treatments In Patients with Testicular Cancer



FDA Qualified Safety Biomarker Panel

Acronym	Name (Unique ID (Uniprot))	Description
CLU	Urinary Clusterin (P10909)	A heterodimeric highly conserved secreted glycoprotein expressed in the proximal and distal tubules, glomerulus and collecting duct.
CysC	Cystatin-C (P01034)	A small serum protein produced by all nucleated cells and found in most tissues and body fluids. CysC is freely filtered by the glomerulus and completely reabsorbed and catabolized in healthy renal tubular epithelium.
KIM-1	Kidney Injury Molecule -1 (Q96D42)	A type I transmembrane glycoprotein containing an ectodomain consisting of an immunoglobulin-like domain and a mucin domain that is strongly induced by ischemic and toxic insults to the kidney.
NAG	N-acetyl-beta-D-glucosaminidase (O60502)	A large lysosomal enzyme with two isoforms and is mainly expressed in proximal tubules.
NGAL	Neutrophil gelatinase-associated lipocalin (P80188)	Expressed in various tissues at low levels with upregulated transcription in tubuloepithelial cells following ischemic and nephrotoxic kidney injuries.
OPN	Osteopontin (P10451)	A highly acidic glycoprotein expressed by many tissues that acts as a macrophage adhesion and chemotactic molecule.

Center for Drug Evaluation and Research, FDA 2018

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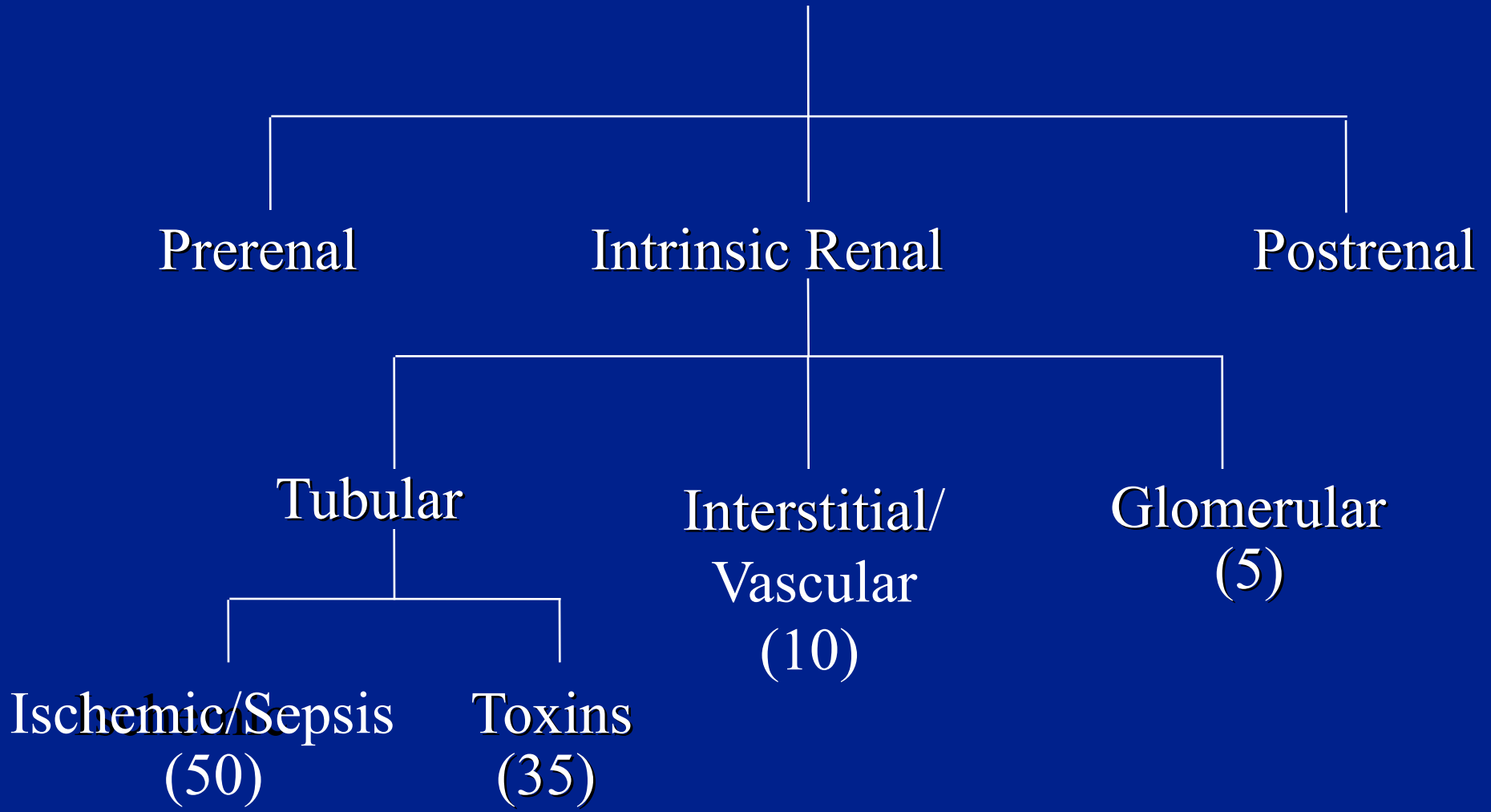
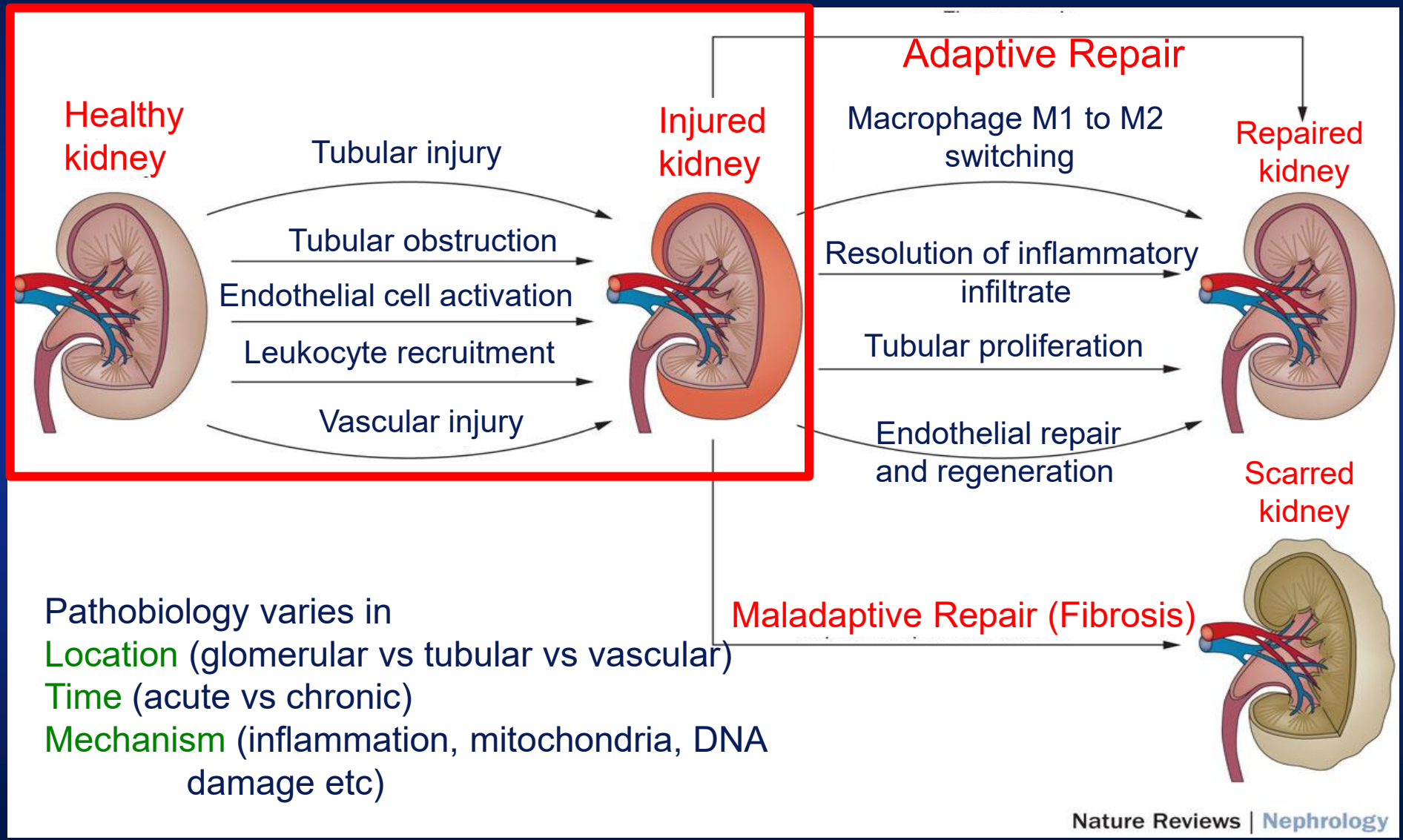
Acute Kidney Injury



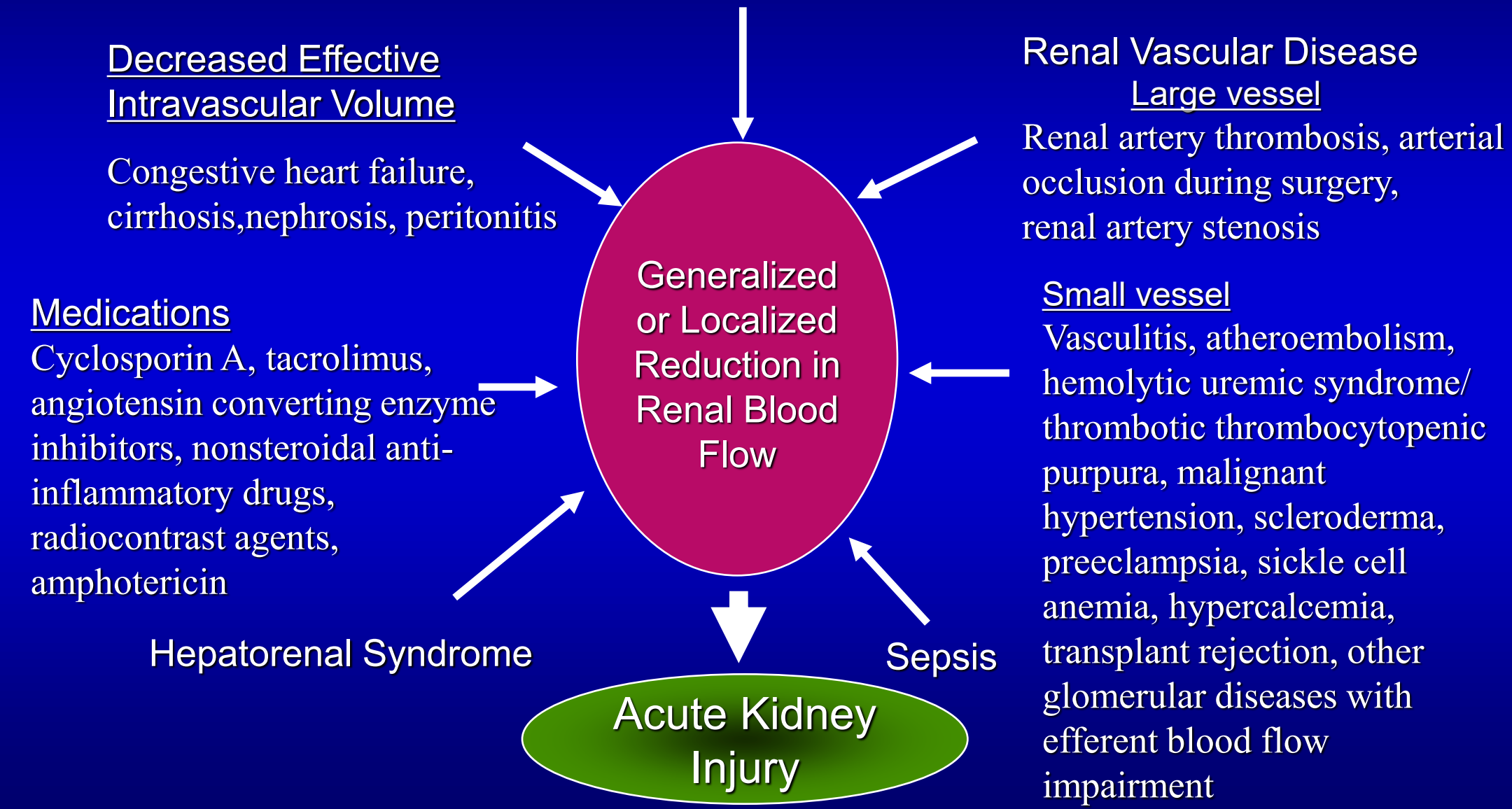
Some mechanisms involved in initial tissue injury and subsequent repair of the kidney after acute kidney injury



Ferenbach & Bonventre, *Nat. Rev. Nephrol.* (2015)

Intravascular Volume Depletion and Hypotension

Gastrointestinal, renal, dermal losses, and hemorrhage



Kidney Pathology in Patients Dying of Sepsis

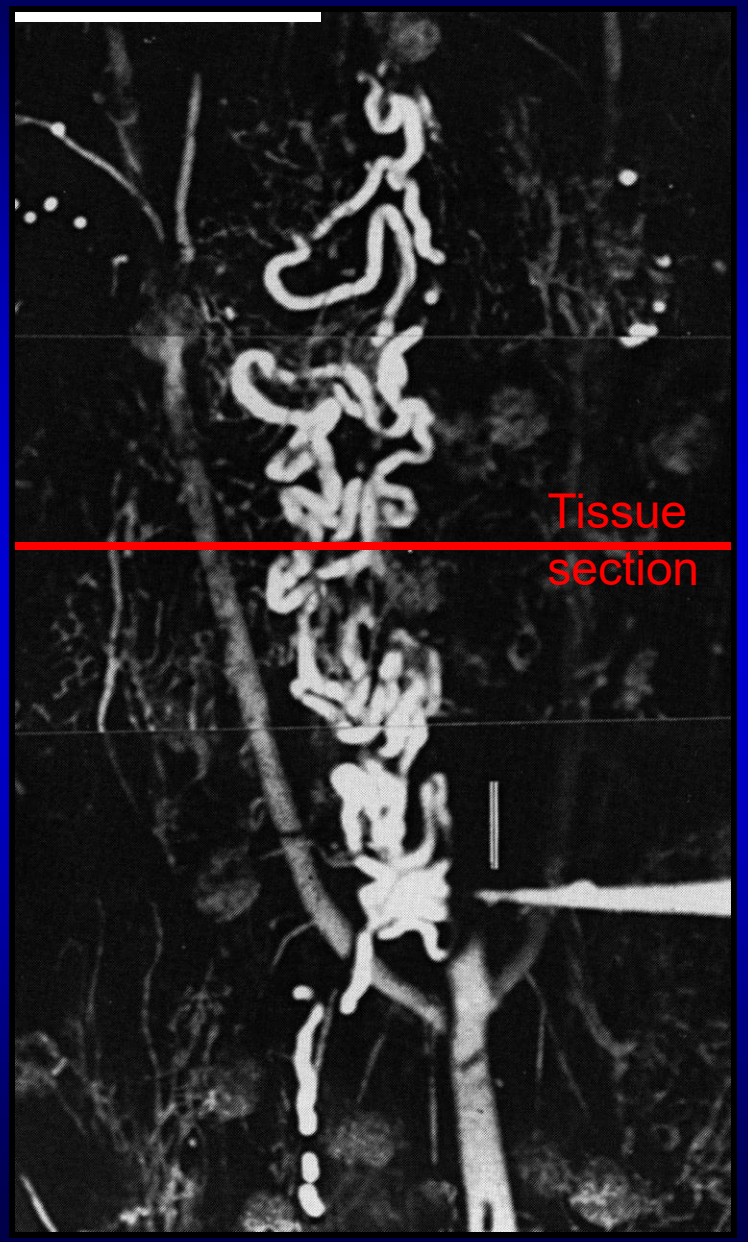
Statement from Literature That Underestimates the Importance of Tubular Injury In Sepsis induced AKI

"Renal tubular injury is common in sepsis but presents focally:
Most renal tubular cells appear normal.
The degree of cell injury and death does not account for severity of sepsis-induced organ dysfunction."

- Proximal tubule vacuolization: 77% of septic patients
- KIM-1 expression: 32.3% corticomedullary junction
  19.6% cortical labyrinth tubules

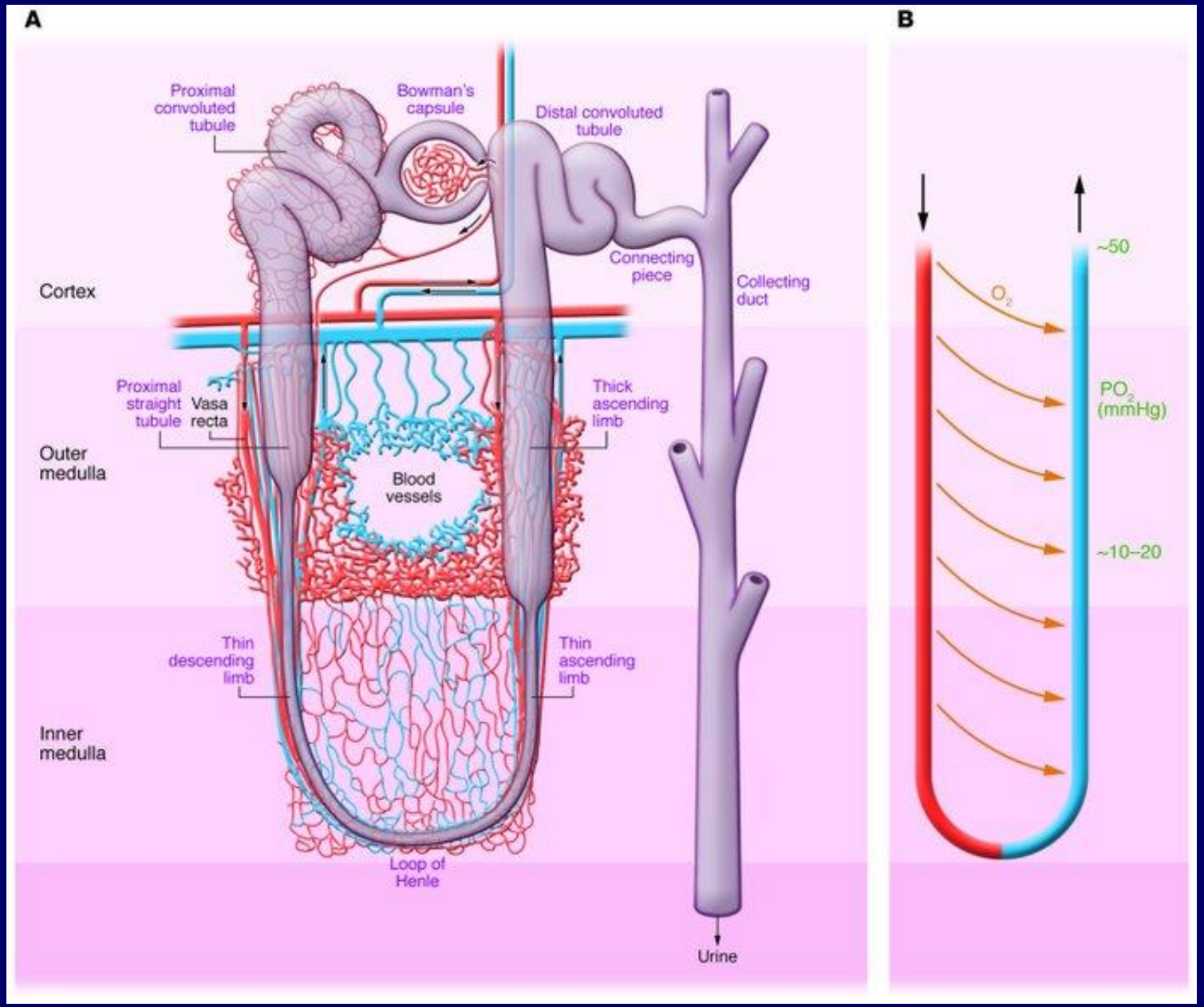
Takasu….Hotchkiss Am J Resp Crit Care Med. 187:509-517, 2013

Complexity of Proximal Tubule



Beeuwkes and Bonventre, Am. J. Physiol., 1975

Nephron, corticomedullary oxygen gradient, and microvascular anatomy.

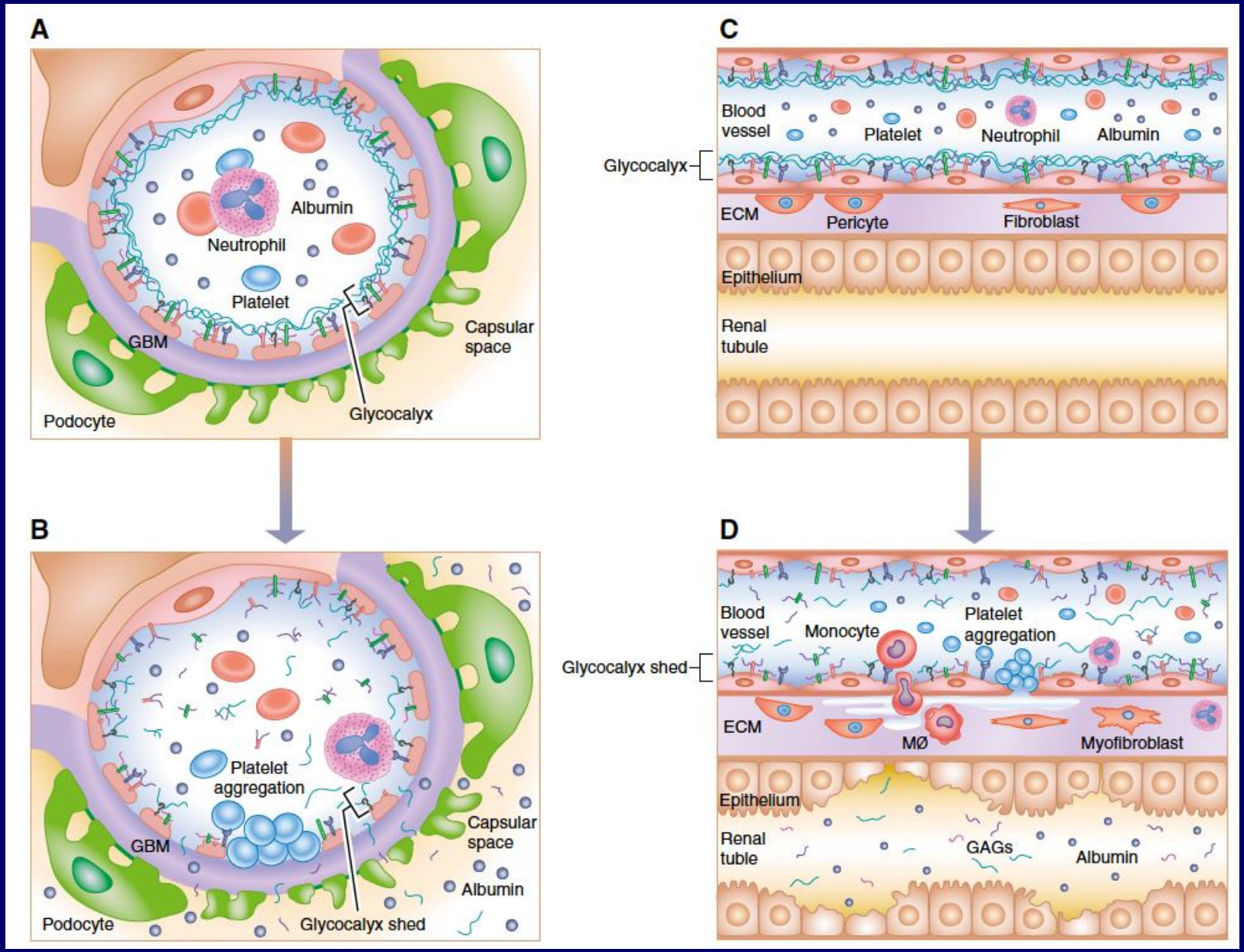


Bonventre and Yang J. Clin. Invest. 121: 4210-4221, 2011

Endothelial and Epithelial Injury and Glycocalyx Disruption in AKI

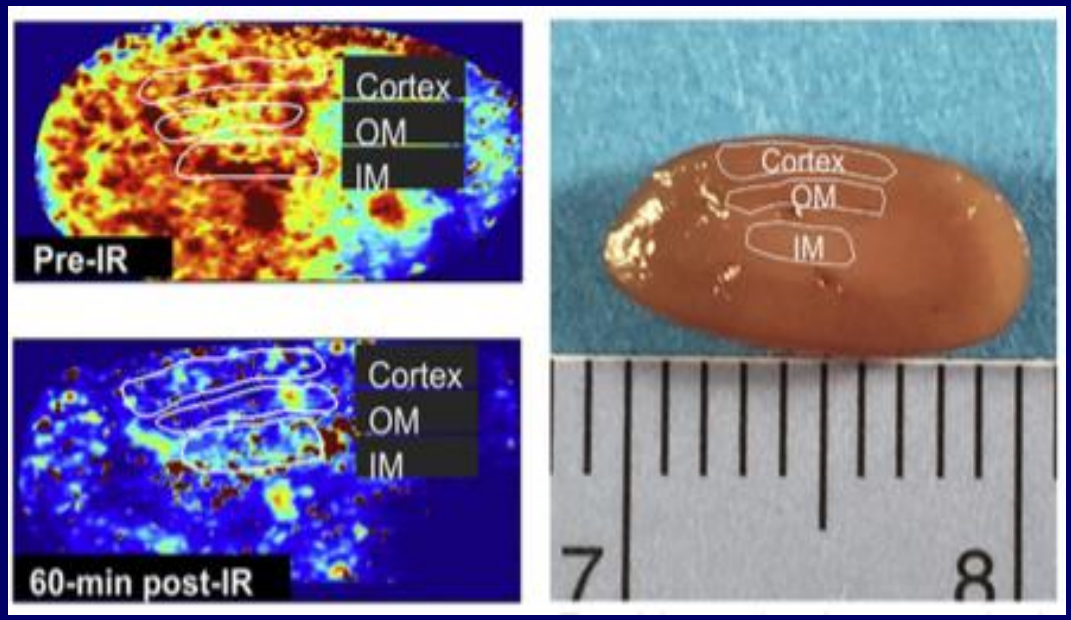
Normal

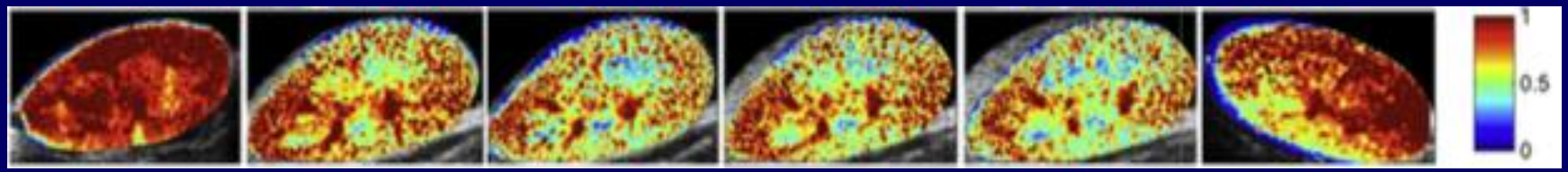
Post AKI



Li and Bonventre Am J Resp Crit Care Med 194:390-3, 2016

Perfusion Maps of the Mouse Kidney using Contrast-Enhanced Ultrasound



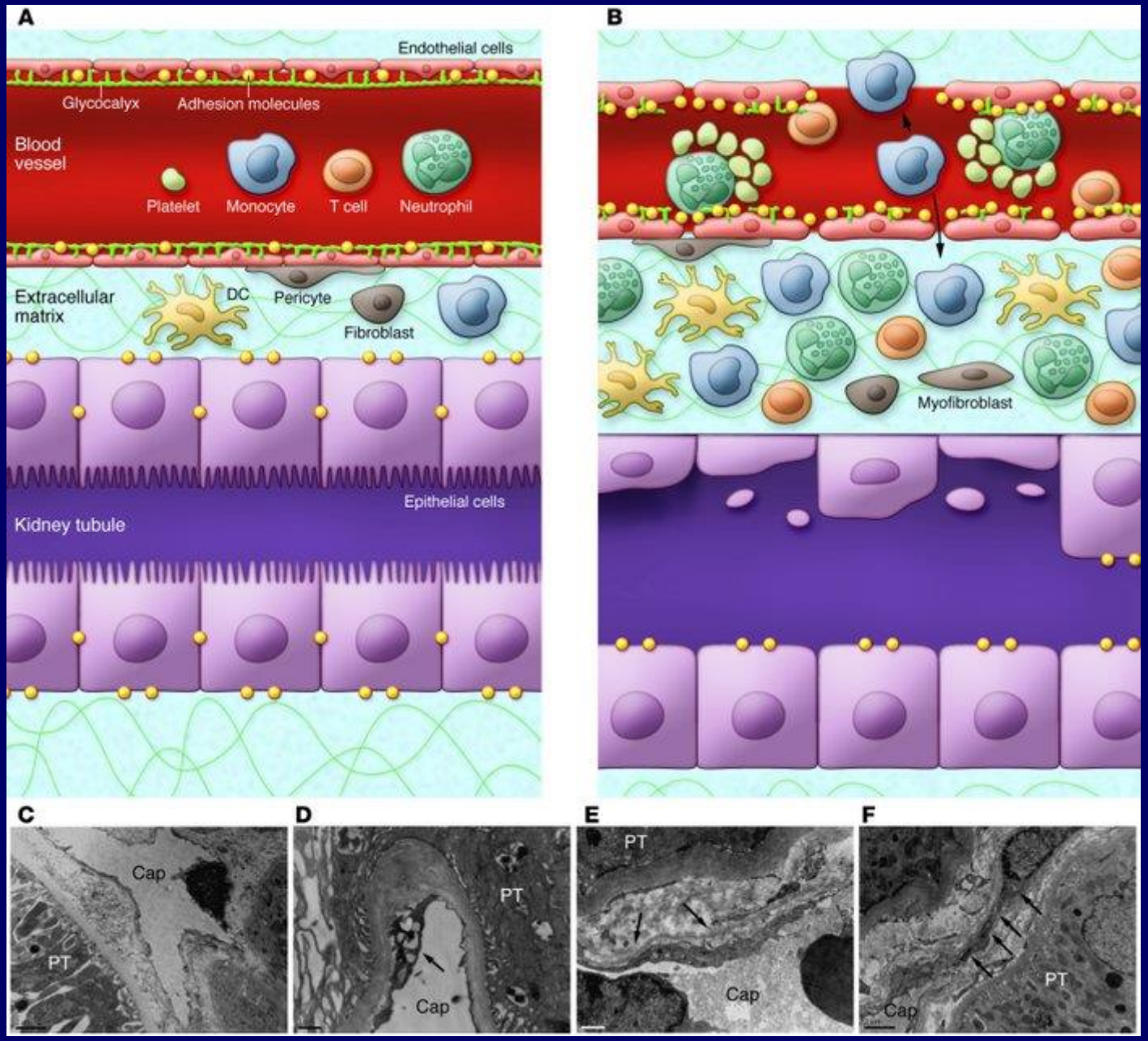


15 min 30 min 45 min 60 min 24 hr

Pre-I/R Post-I/R

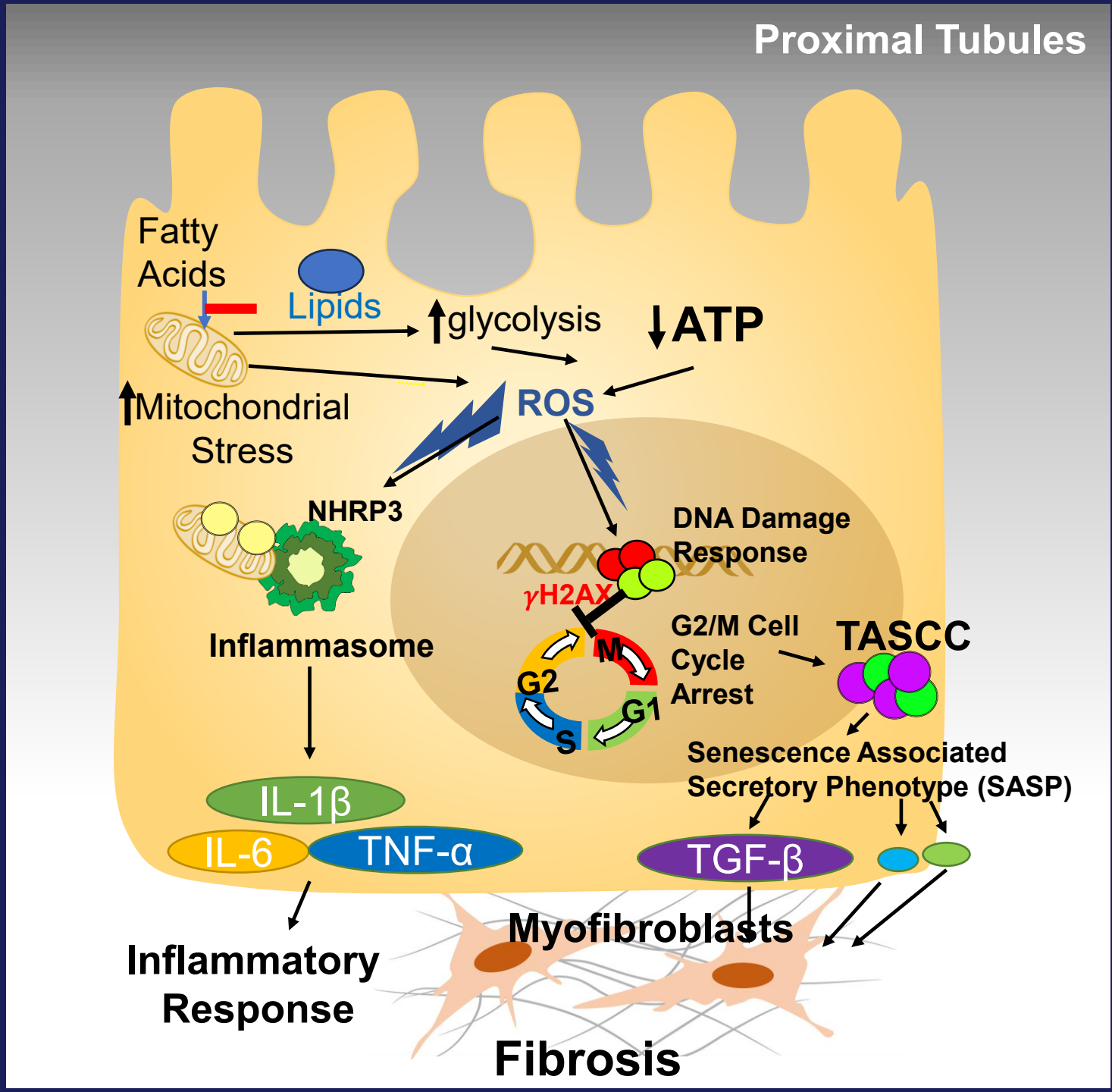
Fischer…Bonventre. Kidney International, 2016

Endothelial and Epithelial Injury, Inflammation and AKI



Bonventre and Yang J. Clin. Invest. 121: 4210-4221, 2011

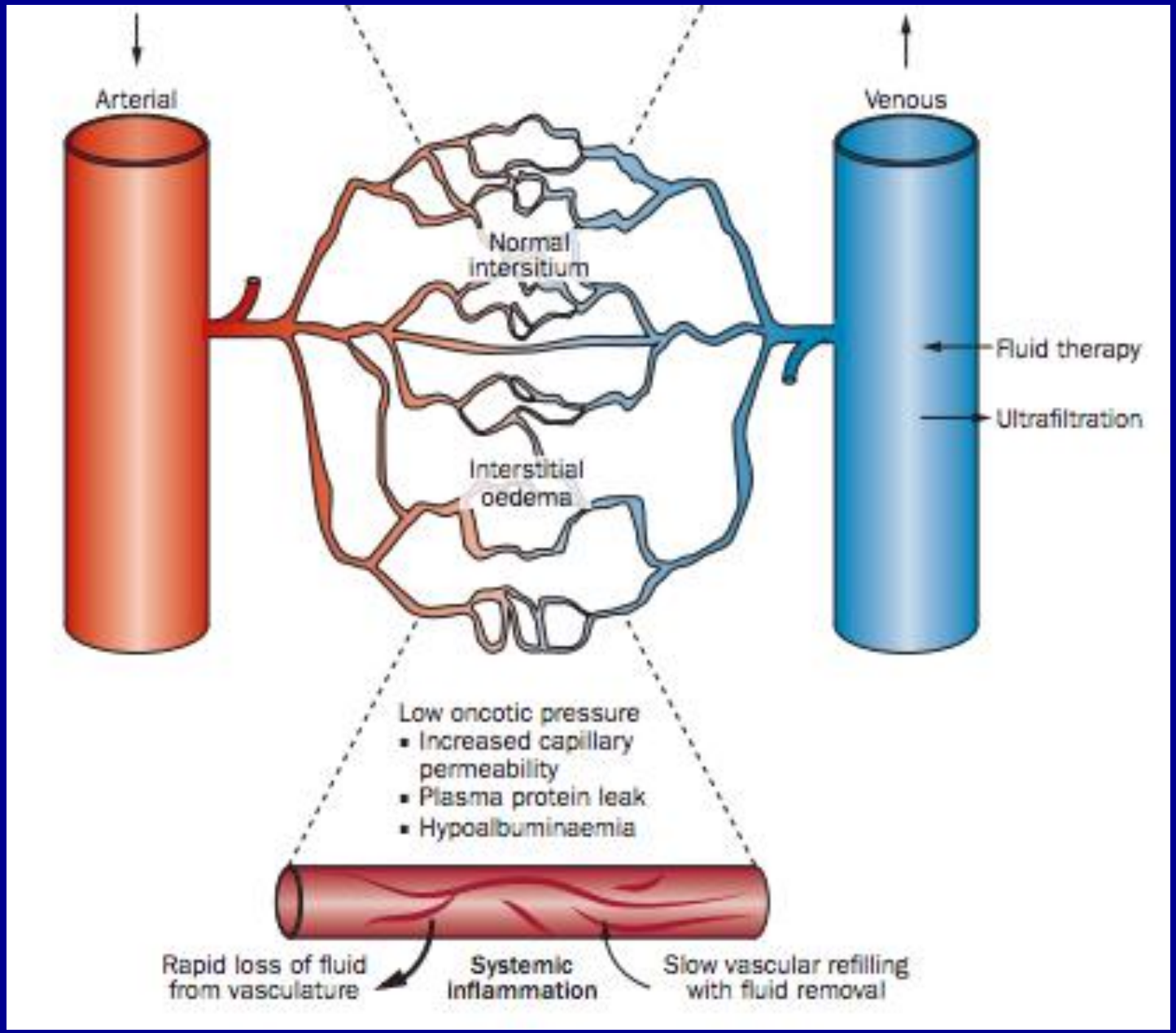
Simpified Pathobiology of AKI



Normally a cell can undergo >1 million DNA changes per day.

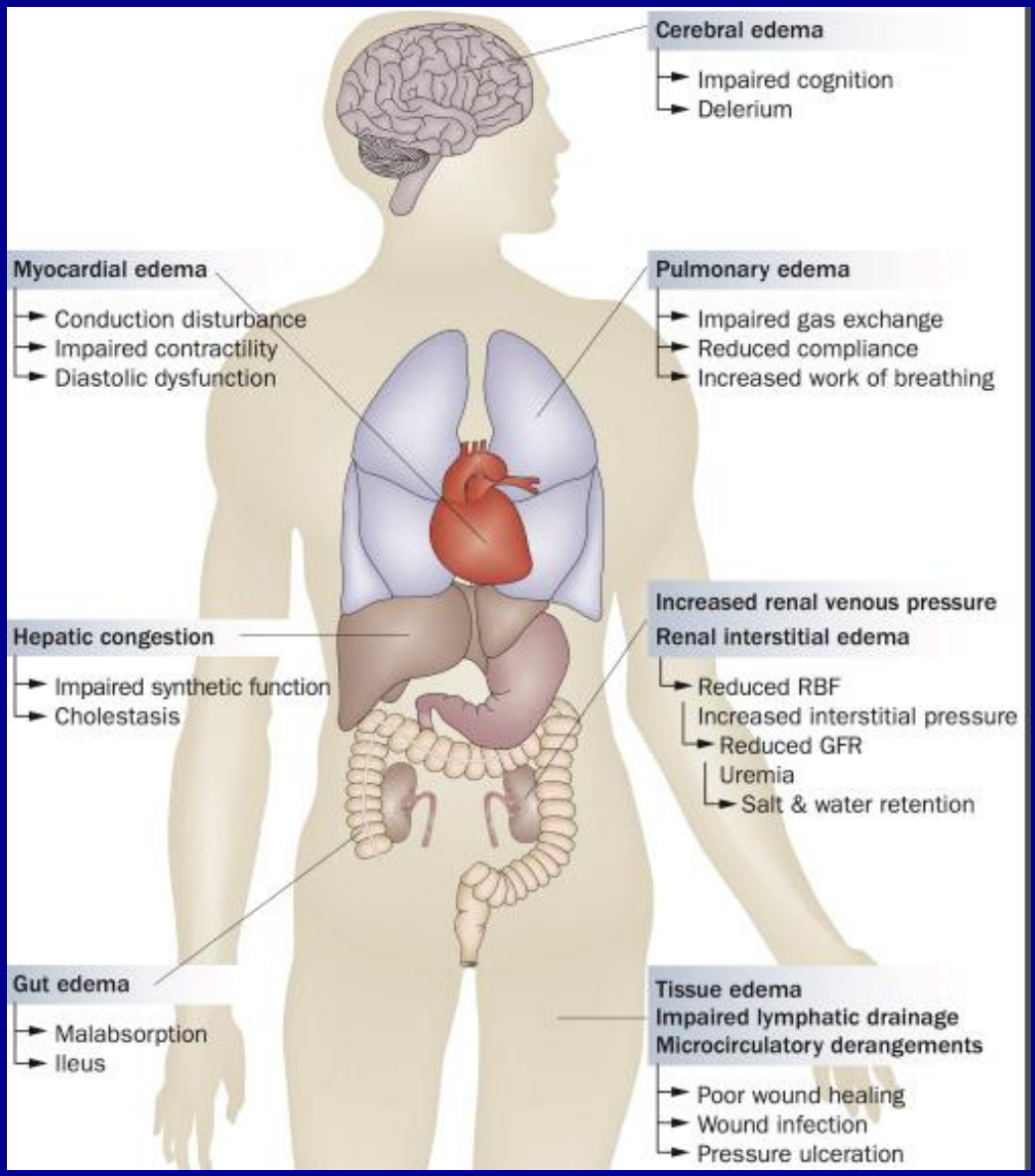
(Lodish et al, Mol Bio Cell)

Fluid may be very bad for AKI



Prowle et al
Nat Rev Neph
10:37-47, 2015

Effects of Fluid Overload on Organ Systems



O'Connor and Prowle
Crit Care Clin
31:803-21-47, 2015

Fluid Management in Septic Patients at Risk of AKI

According to the Surviving Sepsis Campaign guidelines, which type of fluid is recommended for initial resuscitation Of patients with sepsis-induced hypoperfusion and AKI

A. Buffered solutions (Ringer's lactate, Hartmann's solution, Plasma Lyte)

B. 5% Albumin

C. 0.9% saline.

D. Starch, gelatin and dextrans

Fluid Therapy for Patients at Risk of Acute Kidney Injury

General Principle: In AKI oliguria is not an indication for fluid administration. Intravascular hypovolemia should be the only indication. Optimal fluid composition has not been defined.

Crystalloids: Buffered solutions (Ringer's lactate, Hartmann's solution, Plasma Lyte) are recommended for patients at risk of AKI who are not hypochloremic.

0.9% saline is recommended for only hypovolemic, hypochloremic patients (with close monitoring of chloride)

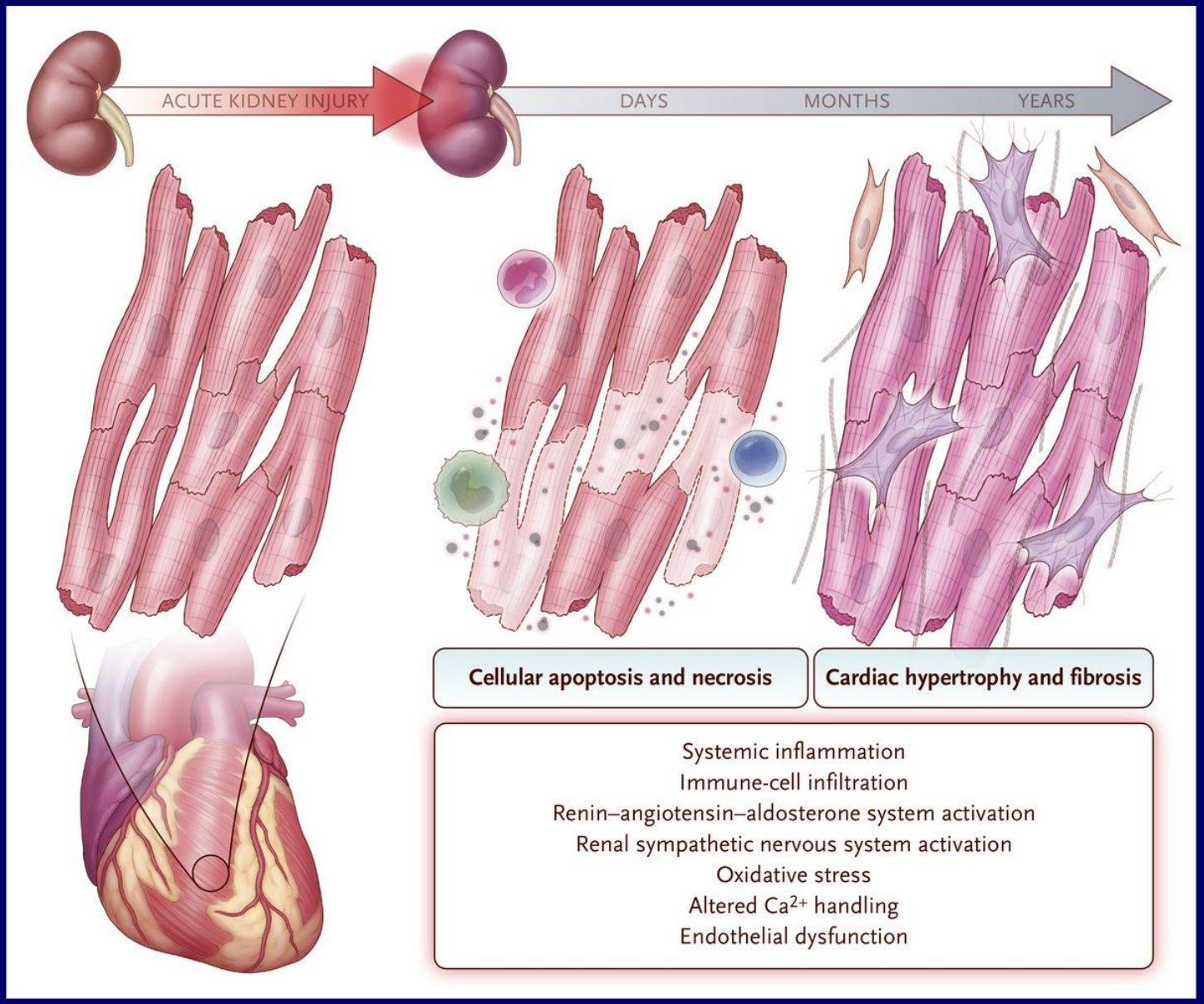
Colloids: Gelatin based fluids should be avoided

Albumin does not provide a survival benefit compared with crystalloid.

Albumin decreases fluid requirements for resuscitation but does not reduce the need for RRT.

Starch should be avoided.

Pathophysiological Features of Cardiac Damage after Acute Kidney Injury



M Legrand, P Rossignol. N Engl J Med 2020;382:2238-2247.

The NEW ENGLAND JOURNAL of MEDICINE

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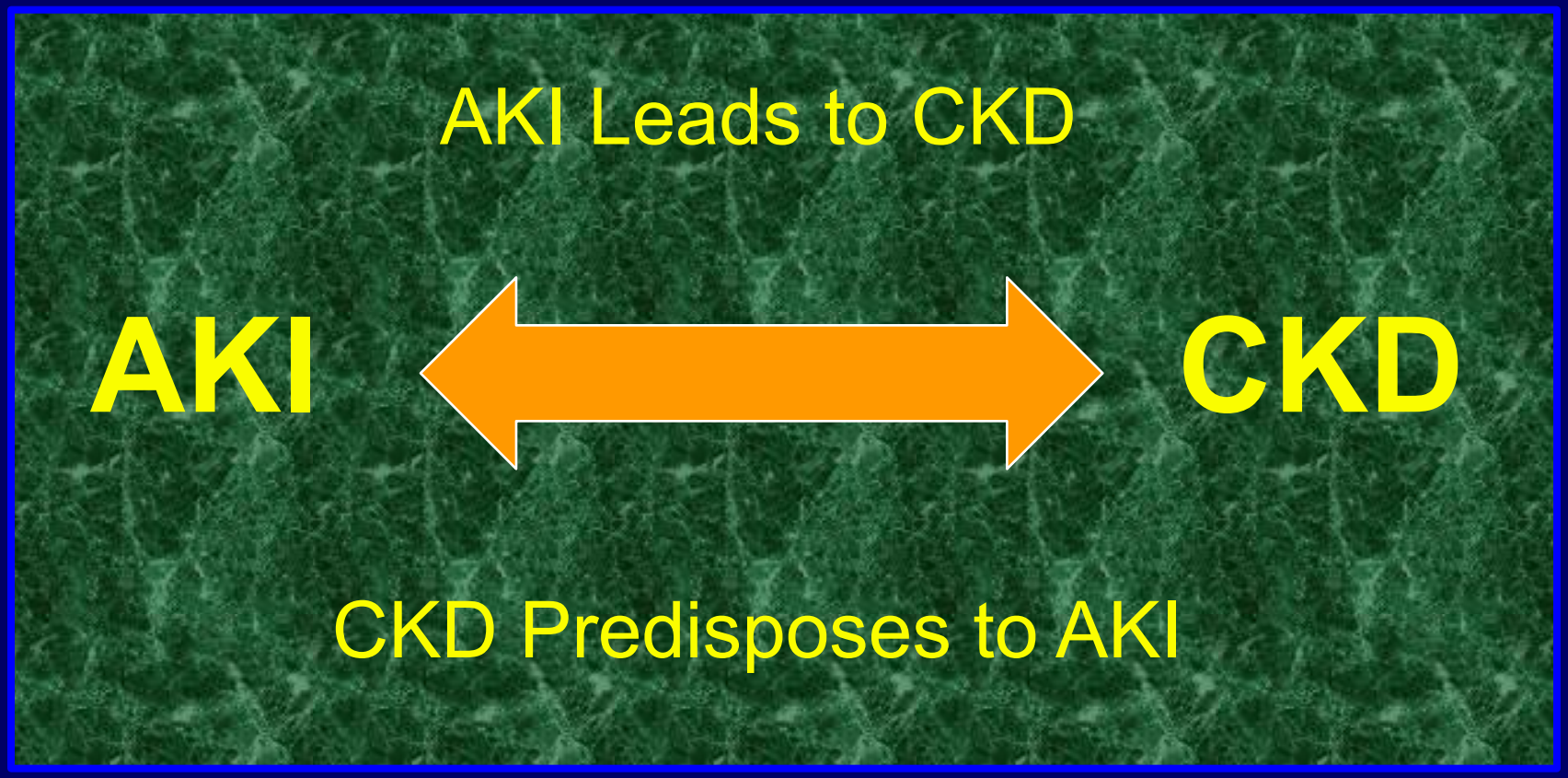
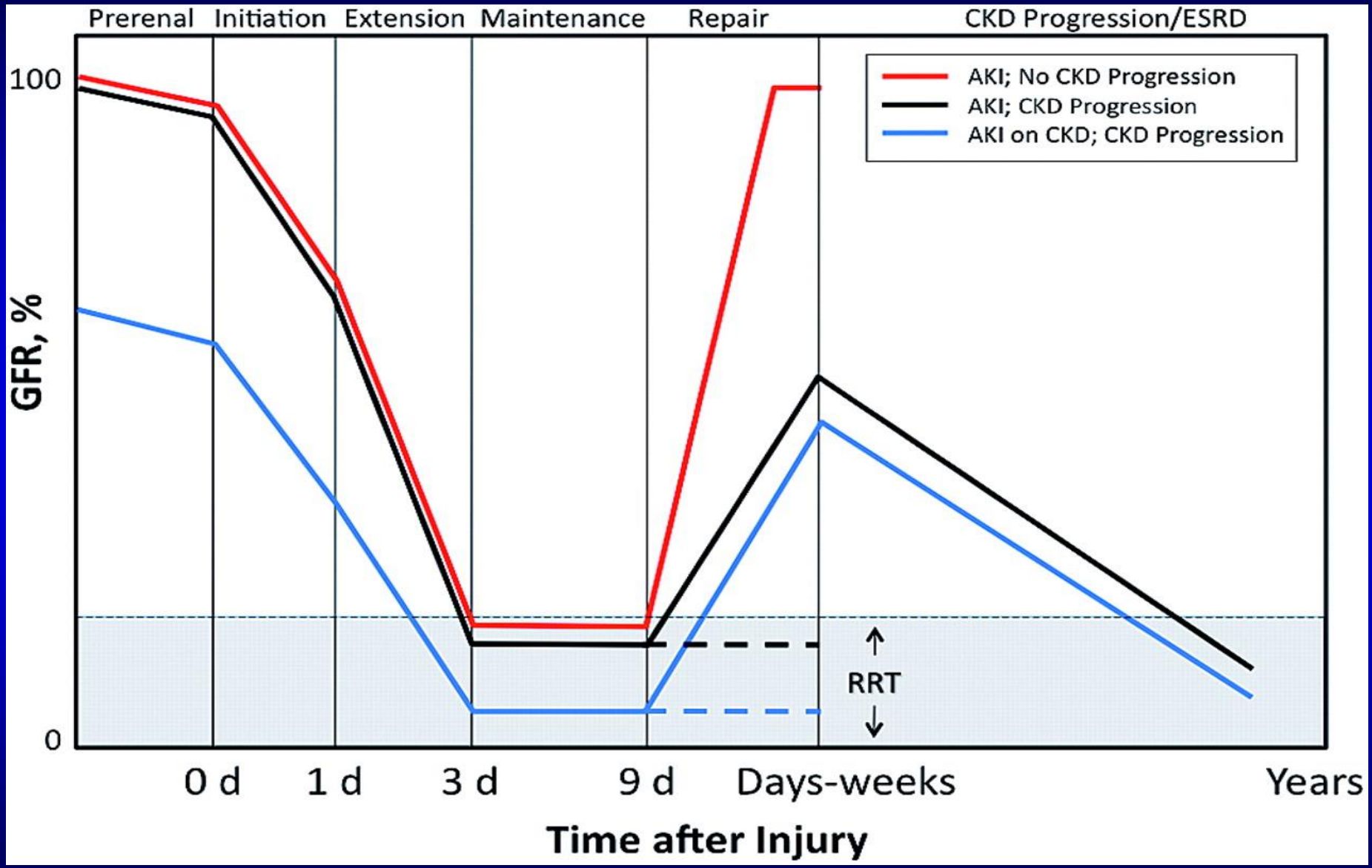

AKI Leads to CKD
AKI
CKD
CKD Predisposes to AKI

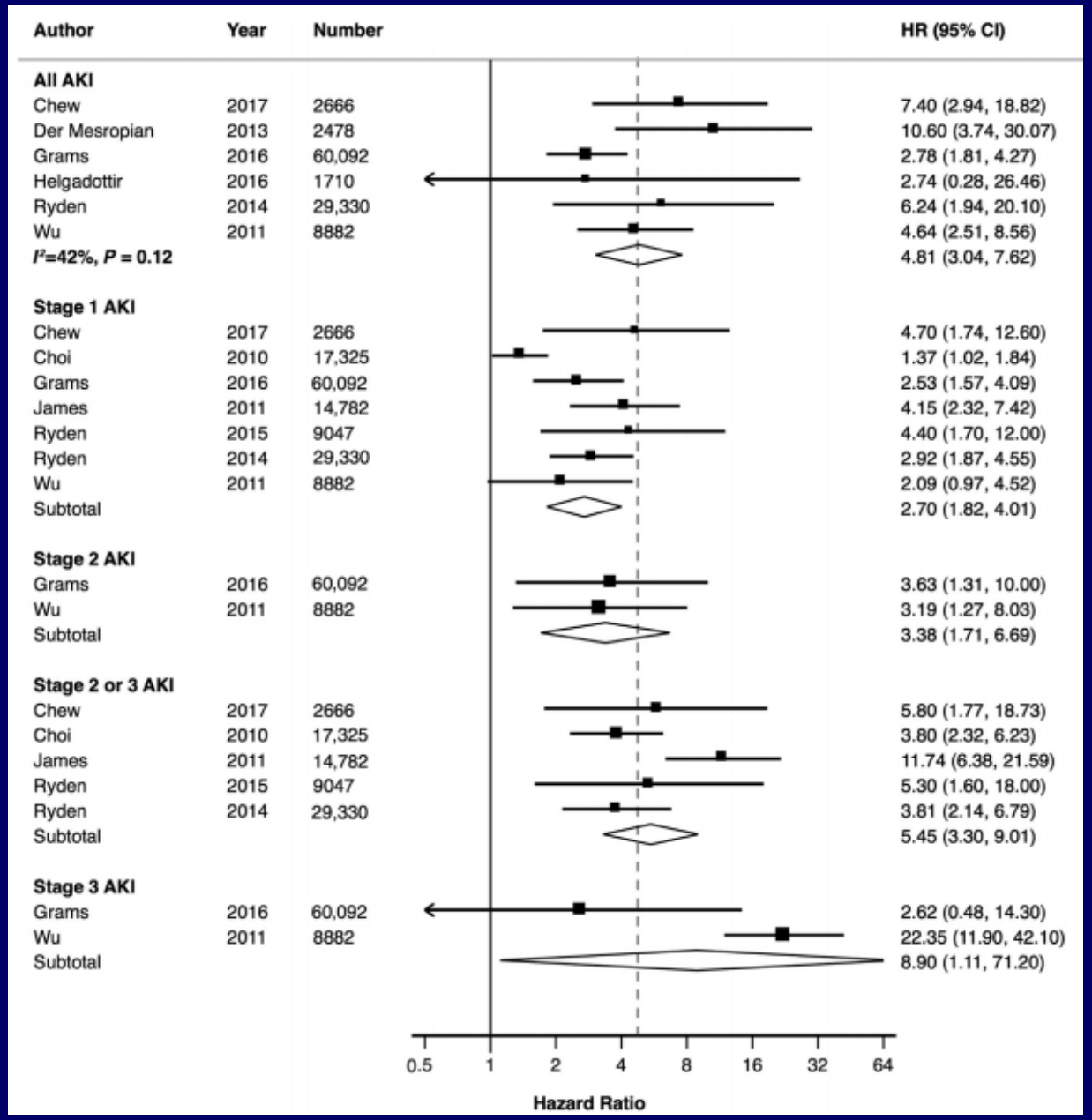
Natural history of acute kidney injury (AKI).



Okusa M D et al. CJASN 2009;4:520-522

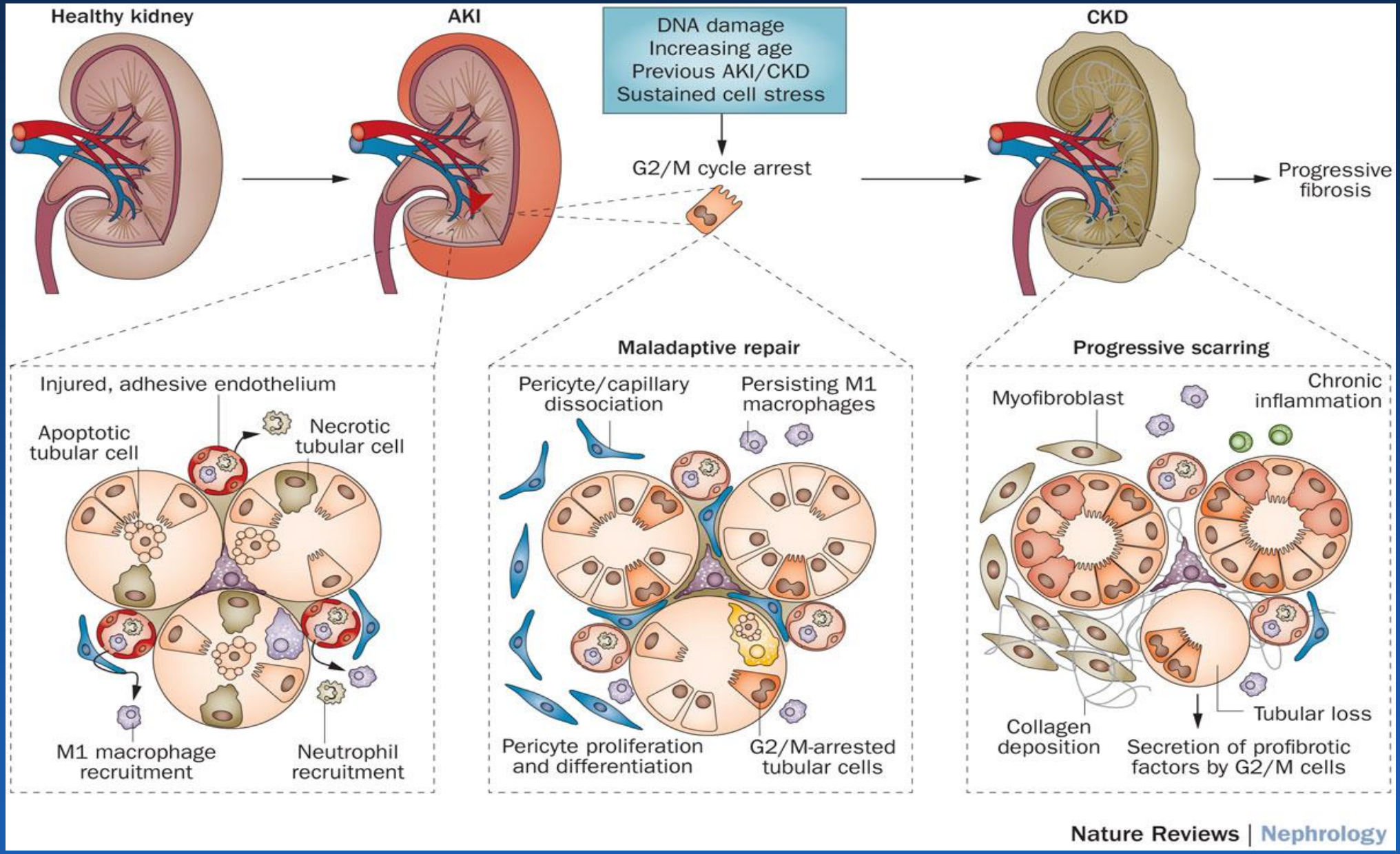
CJASN

Meta-analysis of the risk of Chronic Kidney Disease after AKI



See et al. Kid Int 95:160-170, 2019

Maladaptive repair of AKI leads to CKD



Ferenbach & Bonventre, *Nat. Rev. Nephrol.* (2015)

Multimodal single-cell and Spatial Atlas: Integrated Transcriptomics, Epigenomic and Imaging Data from Three Major Consortia (HuBMAP, KPMP and Human Cell Atlas)

- Putative adaptive or maladaptive repair signatures within the epithelial segments …may reflect a failure to complete differentiation and tubulogenesis.
- Epithelial repair states have elevated cytokine production, increased interactions with the distinct fibrotic and inflammatory cell types, and expression signatures linked to senescence and progression to end-stage kidney disease.
- Failure of these cells to complete tubulogenesis…might ultimately contribute to a progressive decline in kidney function.
- The high-cytokine-producing nature of these cells may further contribute to kidney disease through promotion of fibrosis.

Lake et al. Nature, July,2023

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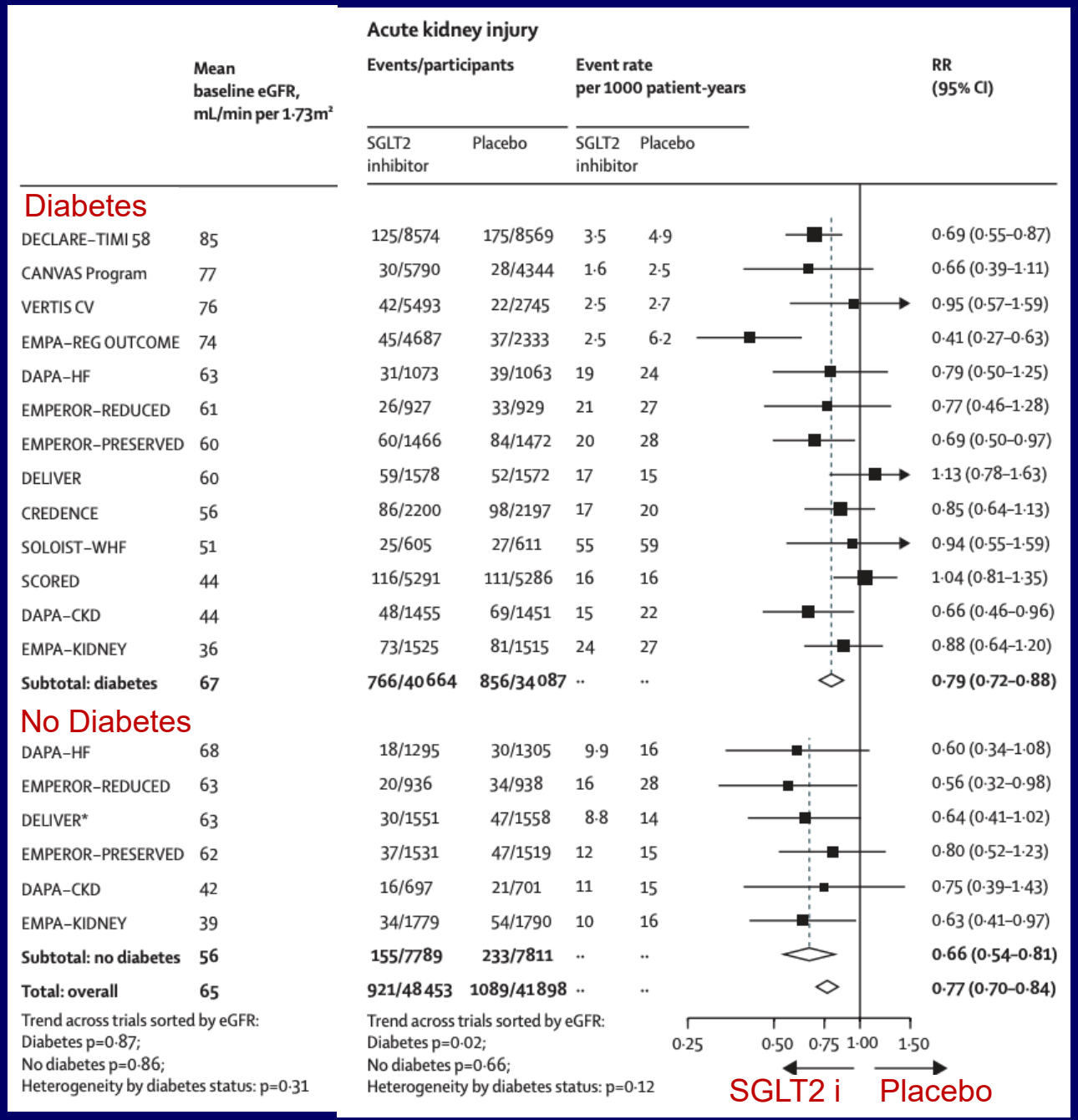
Effects of SGLT2 Inhibitors on Acute Kidney Injury

Which Statement(s) is (are) correct?

- ❑ SGLTi's predispose to volume depletion and AKI
- ❑ SGLTi's have been shown to reduce the incidence of AKI

Meta-analysis SGLT2i Effects on Acute Kidney Injury (13 Trials)



The Neuffield Department of Population Health Renal Studies Group and The SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists Consortium. Lancet 400: 1788-1801, 2022

SGLT2 Inhibitor Effects on Hemodynamics and Oxygenation

↓Proximal tubule Na+ and Glucose Reabsorption

↑Delivery of Volume and NaCl to Macula Densa

↑Vasoconstriction of the Glomerular Afferent Arteriole

↓Glomerular Filtration Rate and Hyperfiltration

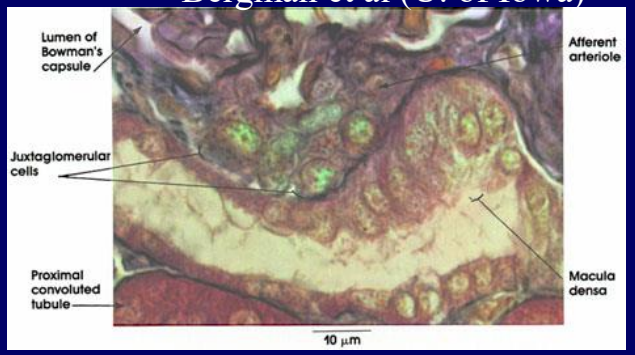
↓O_2 Utilization

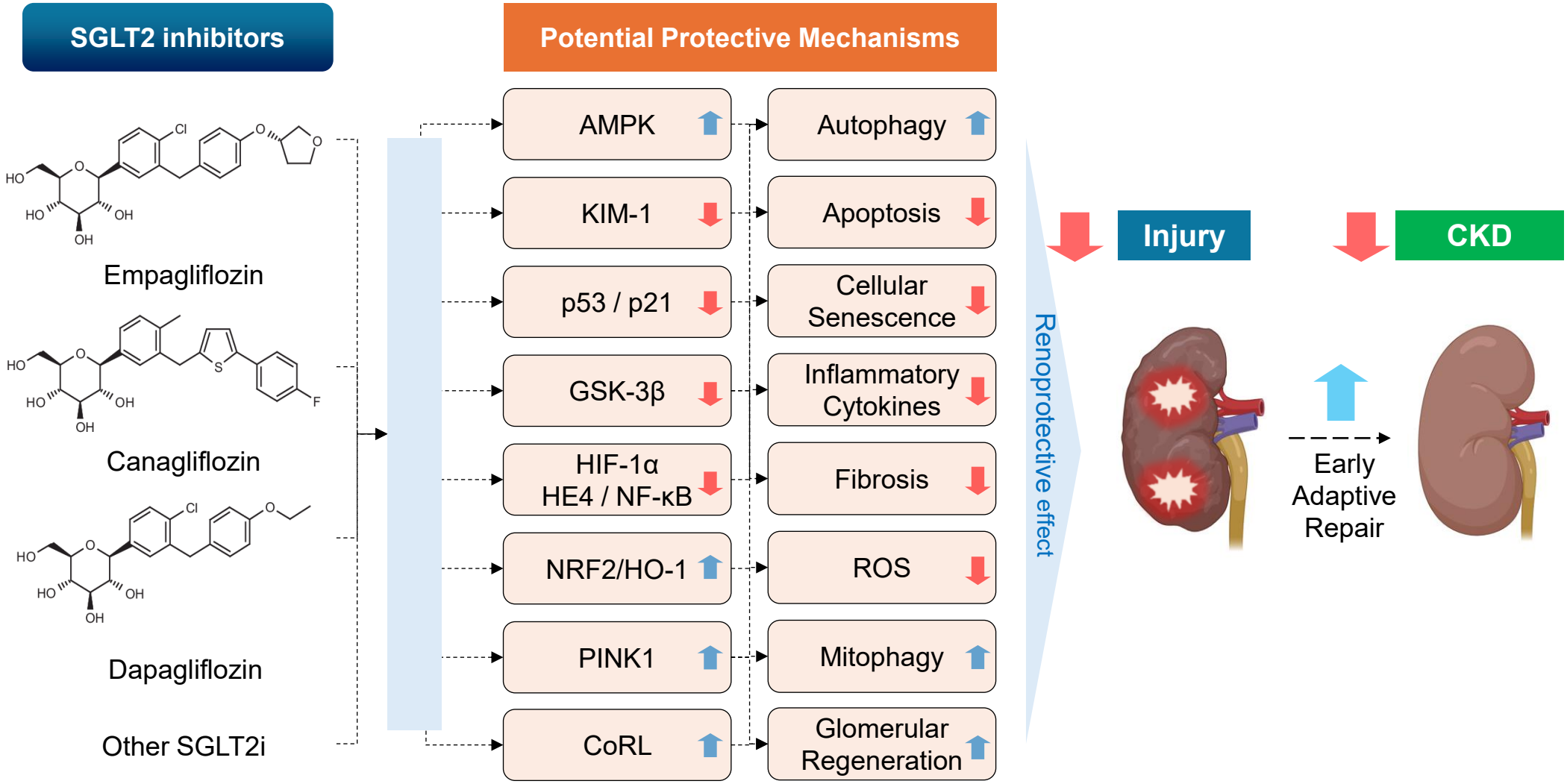
↑O_2 Tissue Delivery

↑Tissue ATP

↓Podocyte Injury and Proximal Cell Stress, Senescence and Tissue Inflammation, Fibrosis

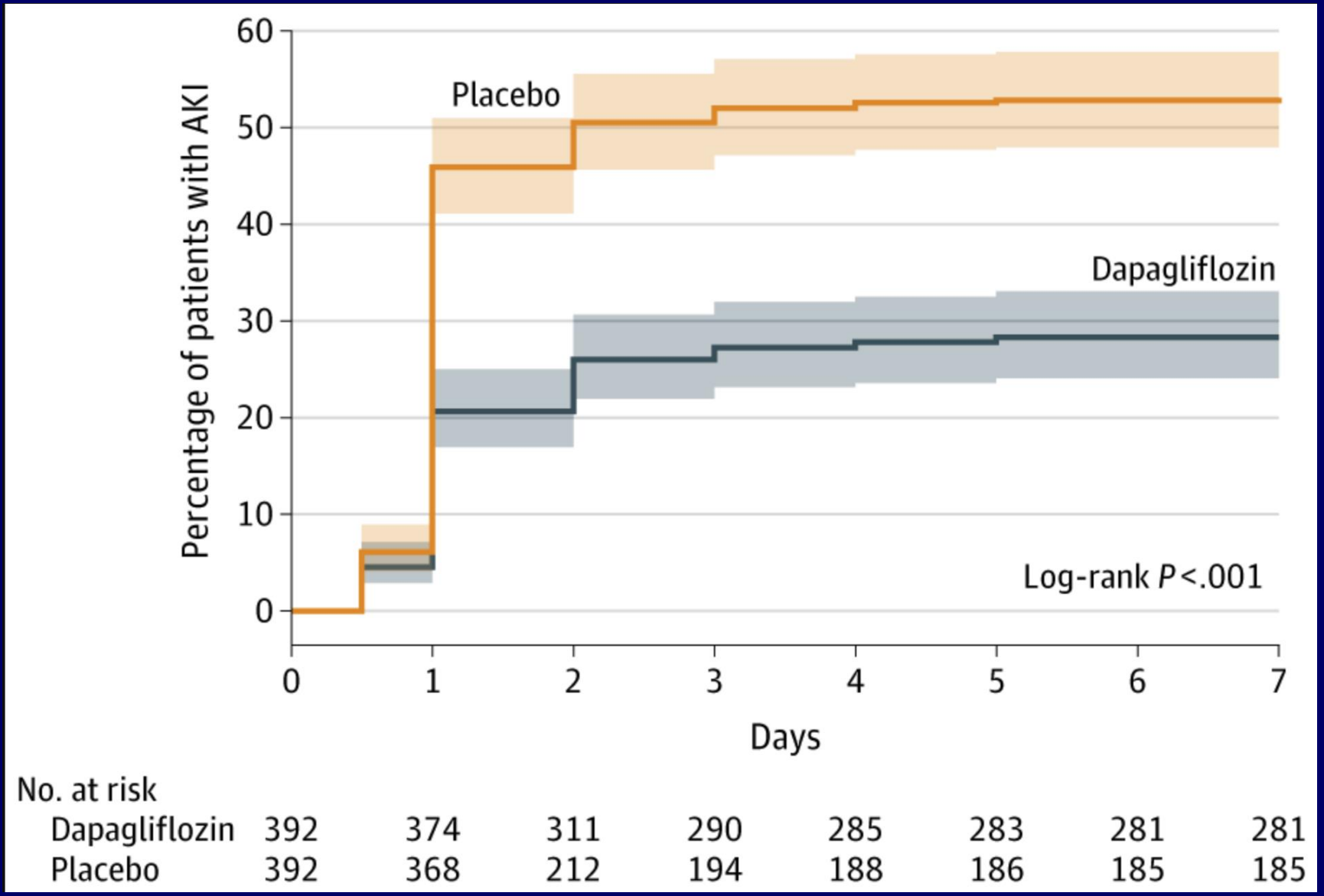
Bergman et al (U. of Iowa)




SGLT2 inhibitors
Empagliflozin
Canagliflozin
Dapagliflozin
Other SGLT2i
Potential Protective Mechanisms
AMPK
KIM-1
p53 / p21
GSK-3β
HIF-1α
HE4 / NF-κB
NRF2/HO-1
PINK1
CoRL
Autophagy
Apoptosis
Cellular Senescence
Inflammatory Cytokines
Fibrosis
ROS
Mitophagy
Glomerular Regeneration
Renoprotective effect
Injury
CKD
Early Adaptive Repair

MERCURI-2 Trial

Time to Acute Kidney Injury



No. at risk

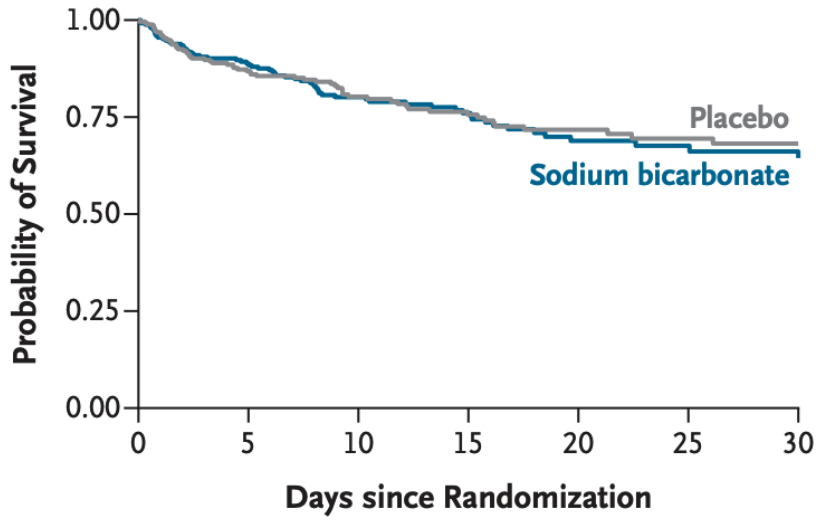
Dapagliflozin	392	374	311	290	285	283	281	281
Placebo	392	368	212	194	188	186	185	185

Dapagliflozin 10 mg/day

Oosterom-Eijmael et al. JAMA July 30, 2026

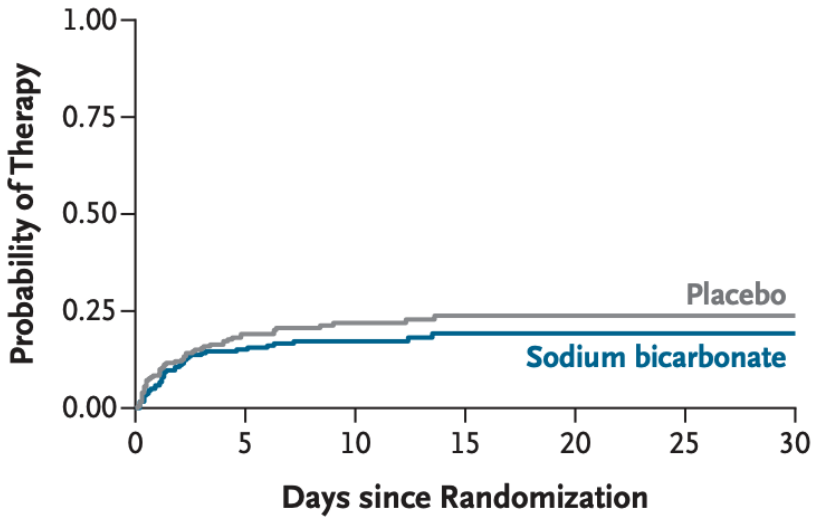
Na Bicarbonate in Metabolic Acidotic Patients on Pressors in the ICU

In-Hospital Survival by Day 30



No. at Risk							
Sodium bicarbonate	244	205	141	97	66	46	39
Placebo	254	208	140	103	76	55	48

Renal Replacement Therapy by Day 30



No. at Risk							
Sodium bicarbonate	244	175	109	67	45	32	27
Placebo	254	174	106	73	56	36	32

Neto et al. NEJM June 12, 2026

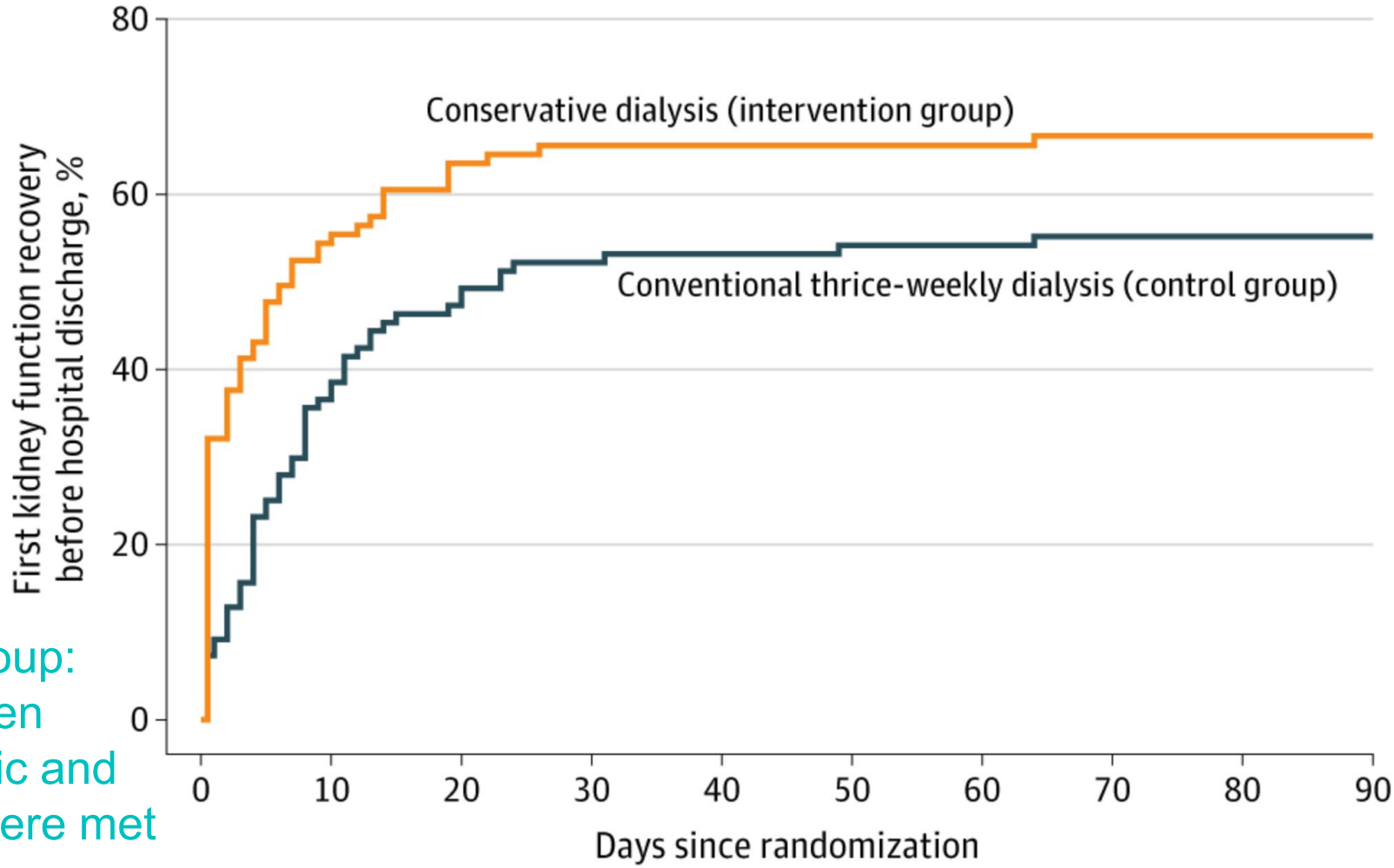
Conventional (3X/wk) vs Conservative Dialysis for AKI

LIBERATE-D

Baseline eGFR: 65ml/min/1.73m^2

Subjects started Dialysis a median of 9 days before randomization

Conservative group: Dialysis only when specific metabolic and clinical criteria were met



No. of patients without kidney function recovery										
Conservative dialysis	109	45	36	33	31	31	31	30	30	30
Conventional thrice-weekly dialysis	109	65	54	49	47	46	46	45	45	45

Liu et al. JAMA 335, 2026

Some Currently Studied Therapeutics for AKI and Pathobiology Targeted

Anti-inflammatory

- Alkaline Phosphatase
- α-MSH analogs (ABT-719)
- Complement Inhibitors
- DPP-4 Inhibitors
- CD28 antagonists
- Sphingosijne-1-P analogs
- Anti-IL6 antibodies
- Heme arginate
- Mesenchymal Stem Cells
- Extracellular Vesicles
- Remove monocytes/neutrophils

Anti-oxidants

- Iron chelators
- NGAL
- Heme arginate
- Bardoxalone
- Propofol
- Curcumin
- α-lipoic acid
- NOX inhibitors

Vasoactive

- Angiotensin II
- Levosimendan

Senolytic

- Navitoclax

Facilitate Regeneration

- Hepatocyte Growth Factor
- BMP receptor agonists

Improve Mitochondria

- Nicotinamide Adenine Dinucleotide
- Cardiolipin

? Cell Cycle/ ? Cell Death

- P53 siRNA

Take Home Messages

To Develop New Therapies for Human AKI
We need:

- More efficient ways to select high risk patients
  -GFR, Renal Reserve, with other clinical features
- Qualification of blood and urine biomarkers using better ways to determine kidney injury than by using creatinine
- New non-invasive tools to interrogate metabolism, cellular repair response and pathobiology, particularly endothelial pathology
- Animal models which incorporate underlying co-morbidities that characterize our patients.
- Human tissue obtained at well characterized stages of early AKI
- Human tissue models to mimic AKI and AKI▸CKD
- Cell type specific characterization of the human tissue
- Better understanding of effects of genetics predisposition to AKI and propensity to maladaptive repair humans

References

Barasch J, Zager R, Bonventre JV. Acute kidney injury: a problem of definition. Lancet 389: 779-781, 2017

Yu SM, Bonventre JV. Acute kidney injury and maladaptive tubular repair leading to renal fibrosis. Curr Opin Nephrol Hypertens. 29:310-318, 2020

Lake BB et al. An atlas of healthy and injured cell states and niches in the human kidney. Nature 619: 585-594, 2023

Ostermann M et al. Acute Kidney Injury. Lancet 405: 241-256, 2025

Thank You