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

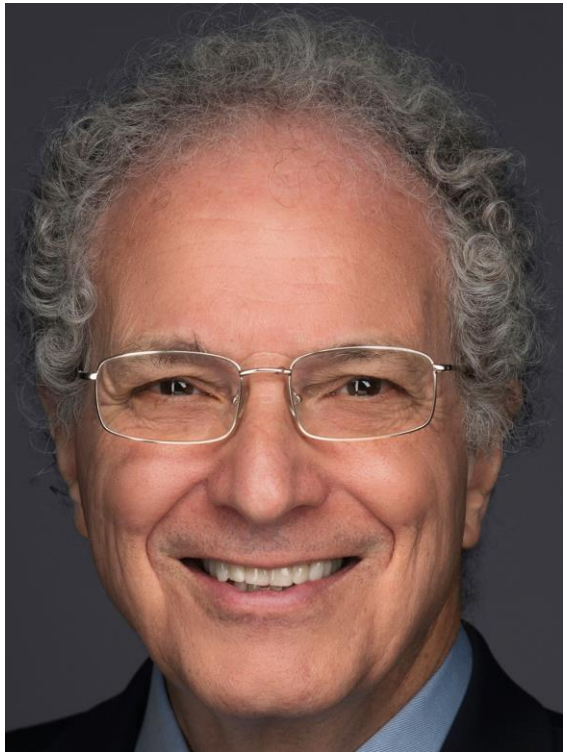
Pathophysiology of Acute Kidney Injury

Department of Medicine
Brigham and Women's Hospital
Distinguished Samuel A. Levine Professor of Medicine
Harvard Medical School
Past-President, American Society of Nephrology

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, Renal Division, BWH
Founding Chief, Division of Engineering in Med. BWH

- Research focus: Kidney Injury and Repair

DISCLOSURES

Advisory Board/Consultant: Praxis, Sarepta Mitsubishi Tanabe, Nimbus, Otsuke, Dynamicure, Verge Genomics

Equity: Innoviva, Pacific Biosciences

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

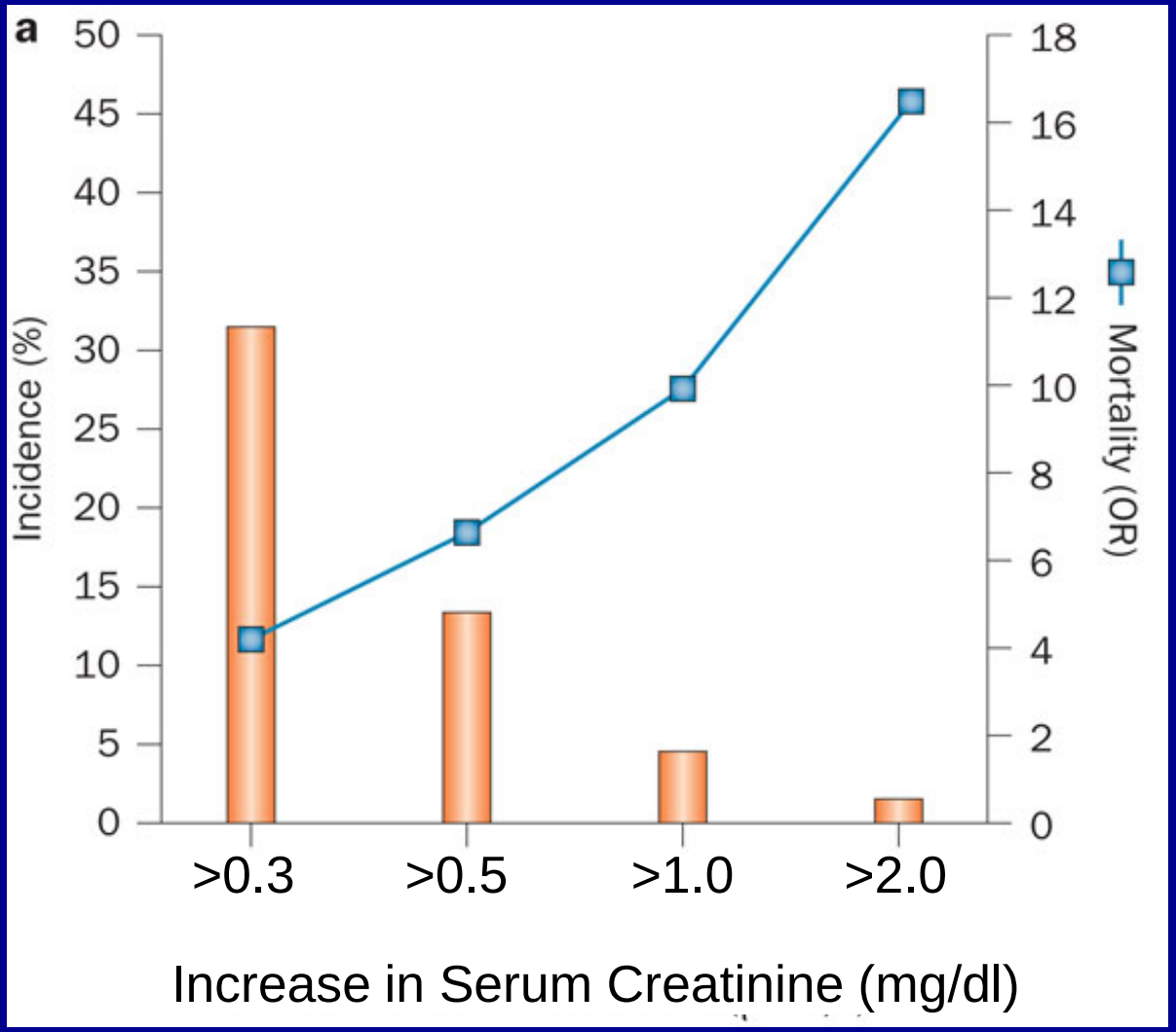
KDIGO Definition of AKI

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

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

Risk Factors for Acute Kidney Injury

AKI Risk Factors	
Older age	Shock
Diabetes	Sepsis
Hypertension	Nephrotoxins
Chronic kidney disease	(NSAIDs, ARB, ACEi, contrast)
Cardiovascular disease	Surgery
Chronic liver disease	Hyperuricemia
Chronic obstructive pulmonary disease	Hypoalbuminemia
HIV infection	Hyperglycemia
Obesity	Anemia

Gameiro et al. J Clin Med 9:1704, 2020

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

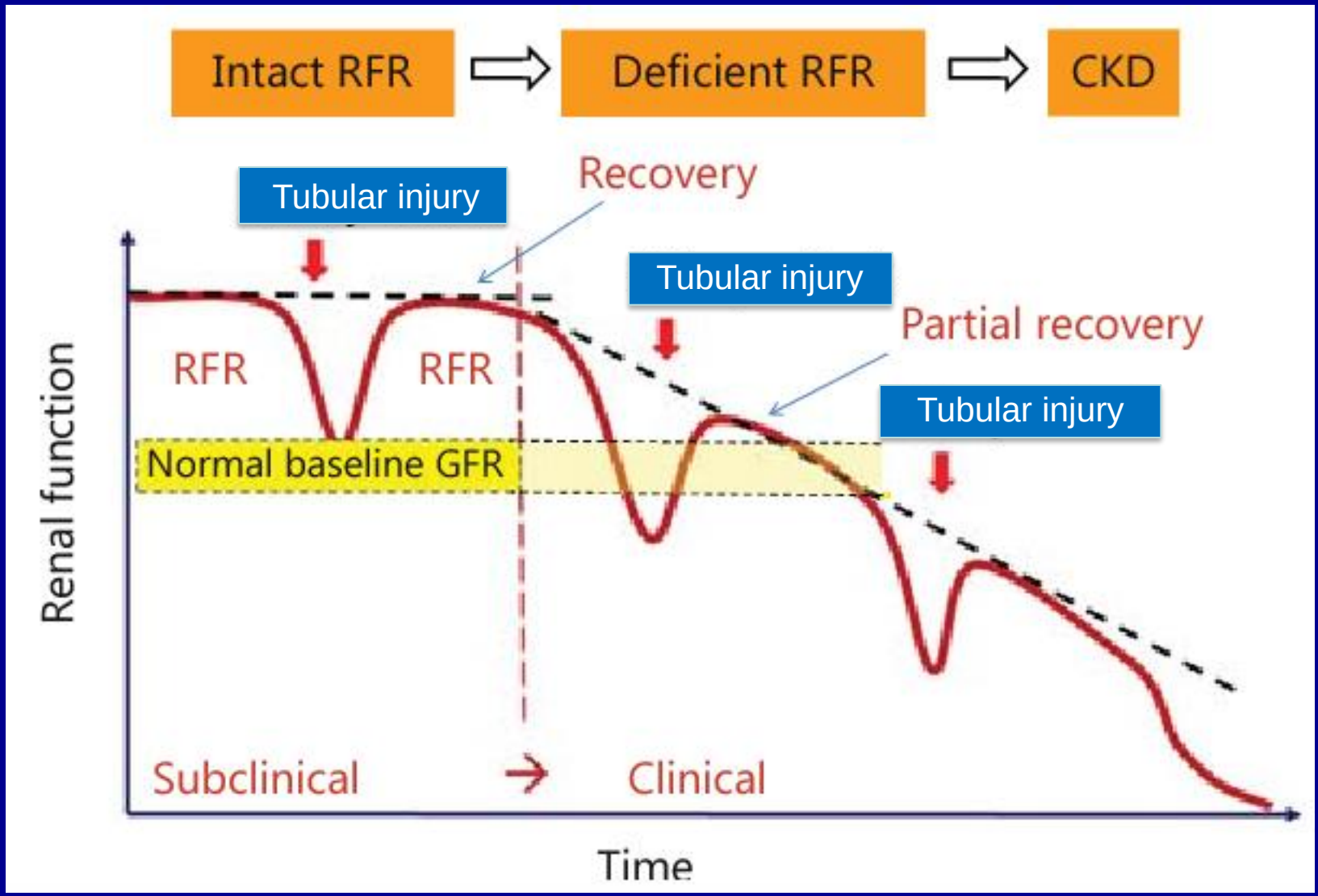
BUT

Acute kidney injury ≠ Acute tubular/interstitial injury

We want biomarkers that measure tubular-interstitial injury

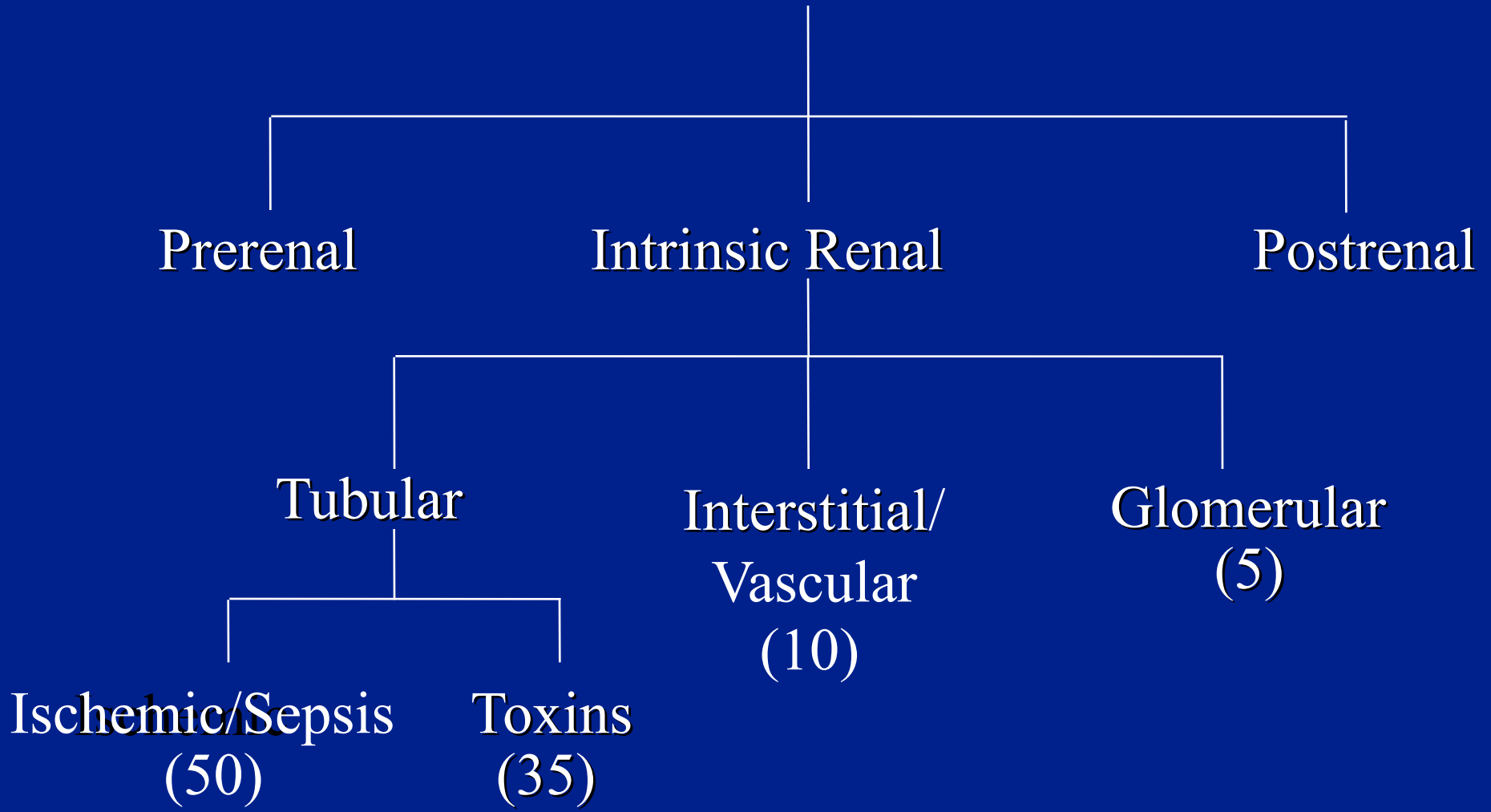
Barasch, Zager and Bonventre. Lancet 389: 779-781, 2017

Renal Functional Reserve

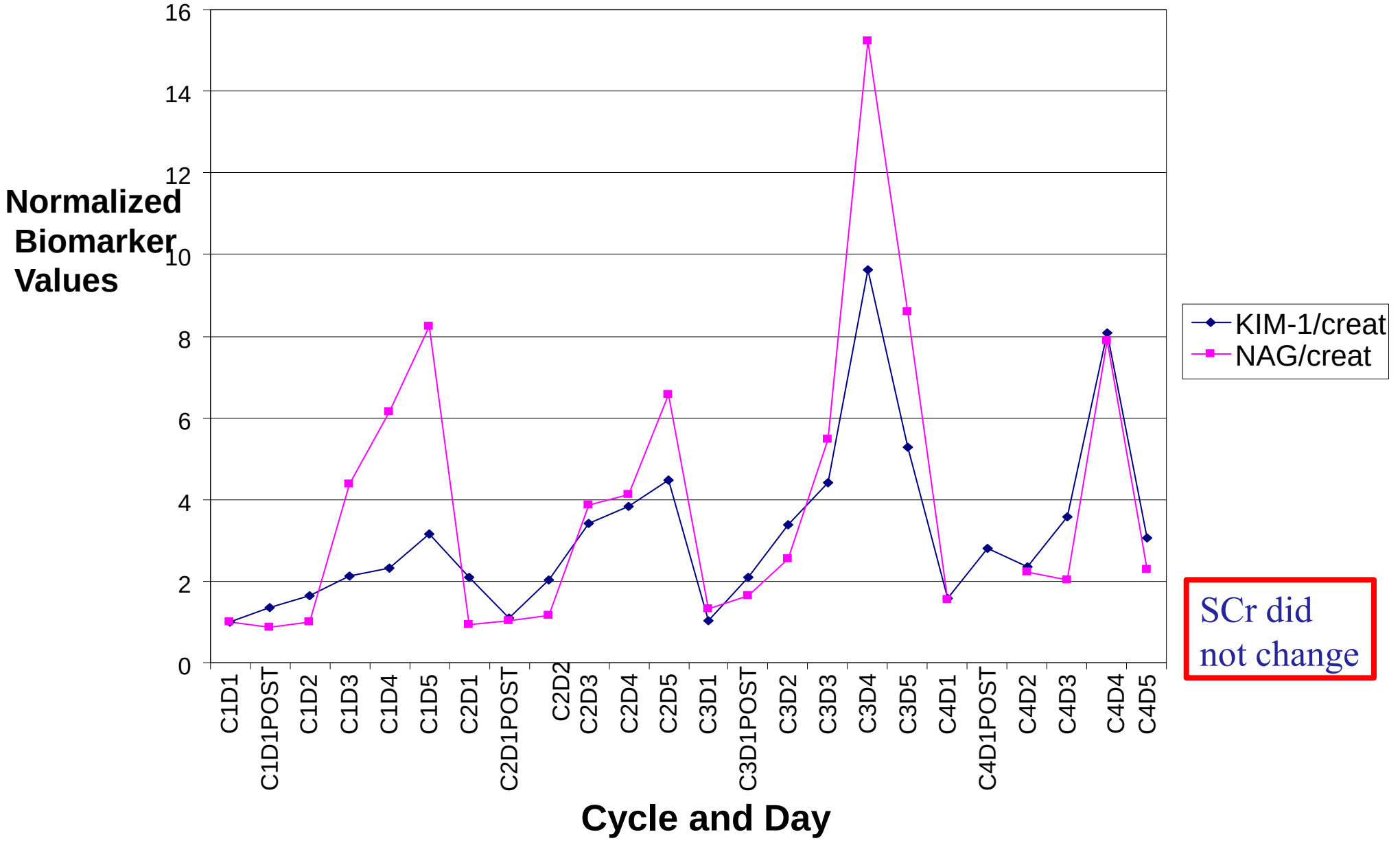


Modified from
Sharma,Mucino and Ronco
Nephron Clin Prac
127:94-100, 2014

Acute Kidney Injury



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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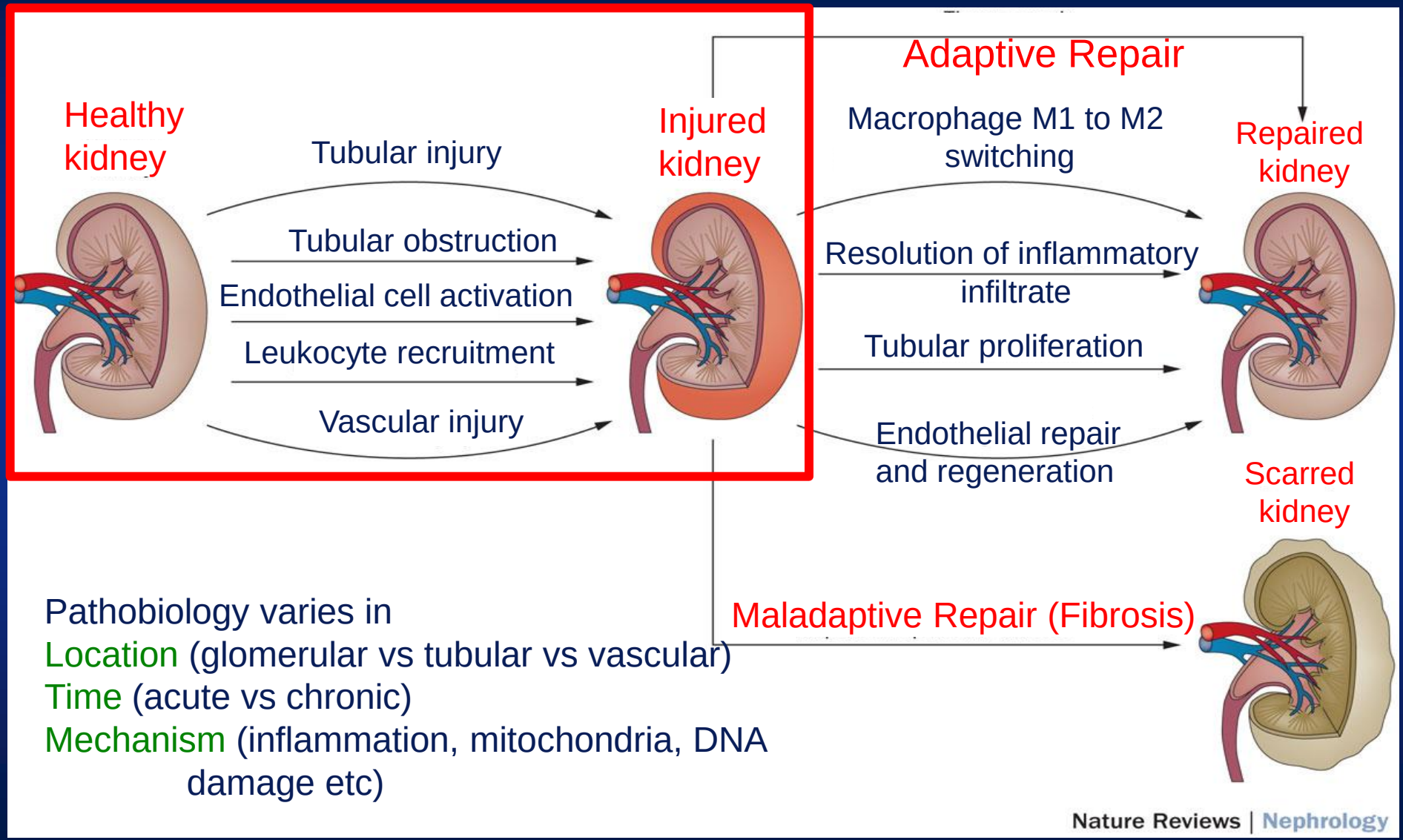
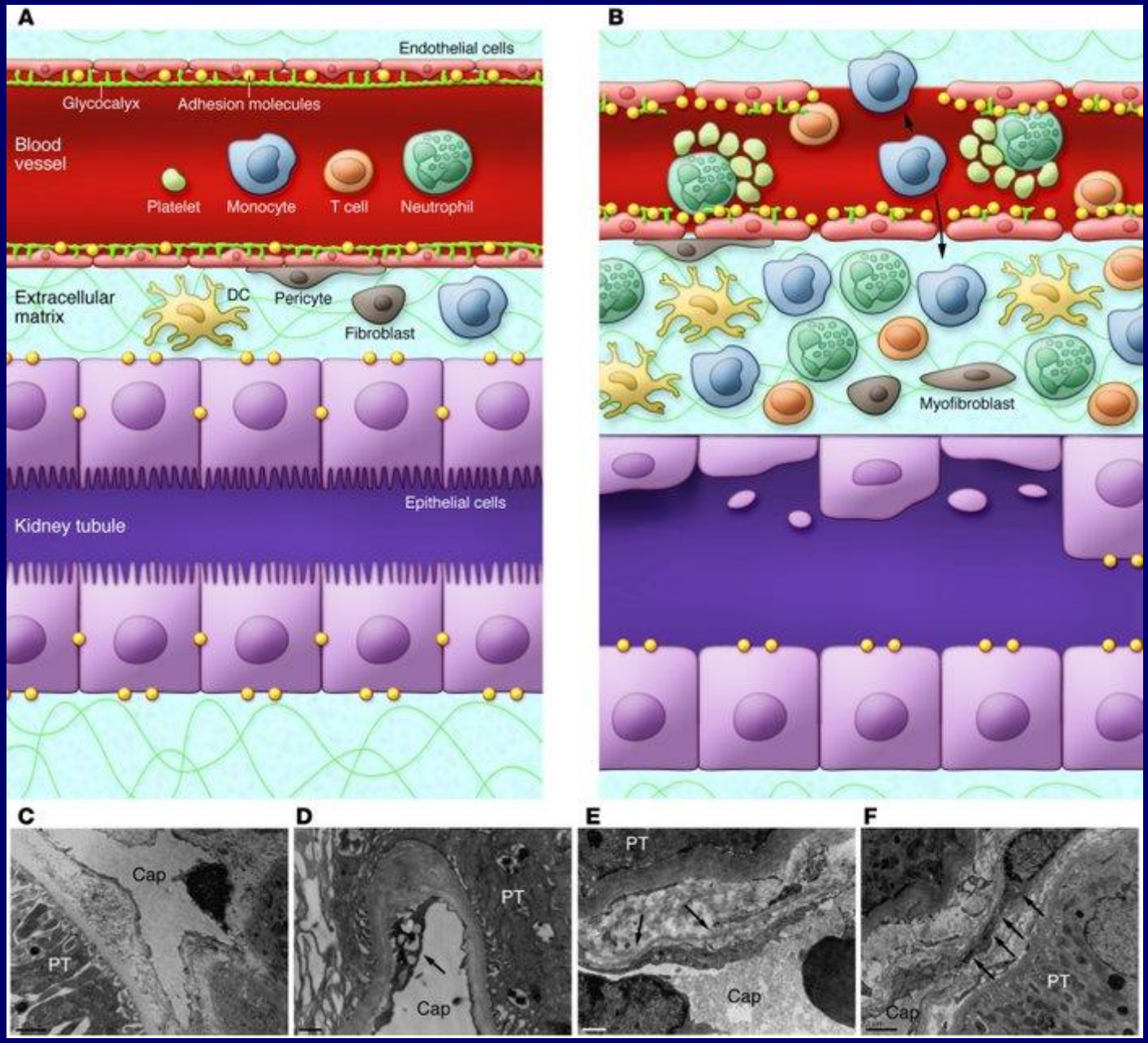
- Therapeutics Approaches

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



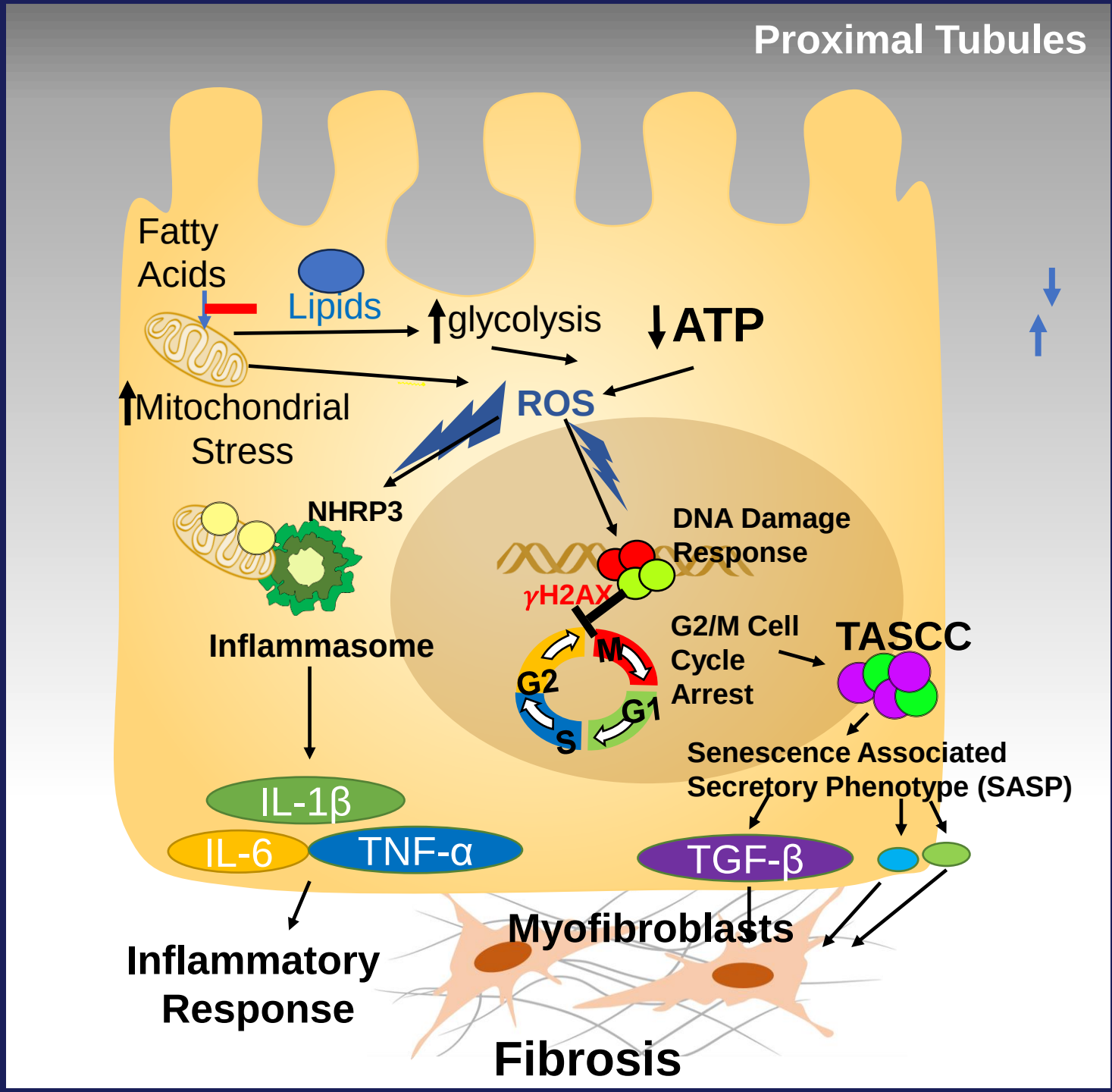
Ferenbach & Bonventre, *Nat. Rev. Nephrol.* (2015)

Endothelial and Epithelial Injury, Inflammation and AKI



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

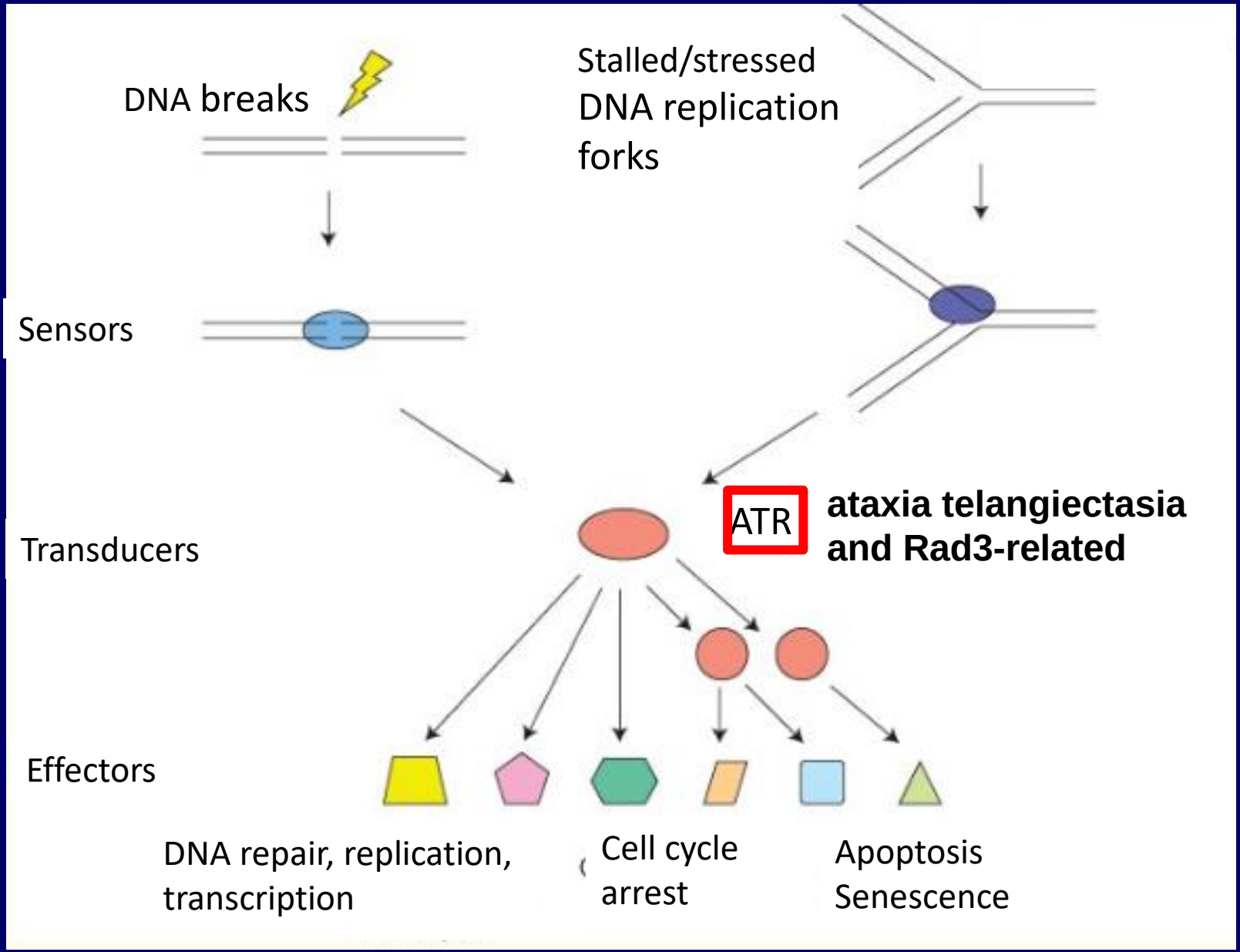
Simpified Pathobiology of AKI



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

(Lodish et al, Mol Bio Cell)

Downstream of DNA Repair Pathways



Modified from Marechai and Zou Cold Spring Harb Perspect Biol 2013

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

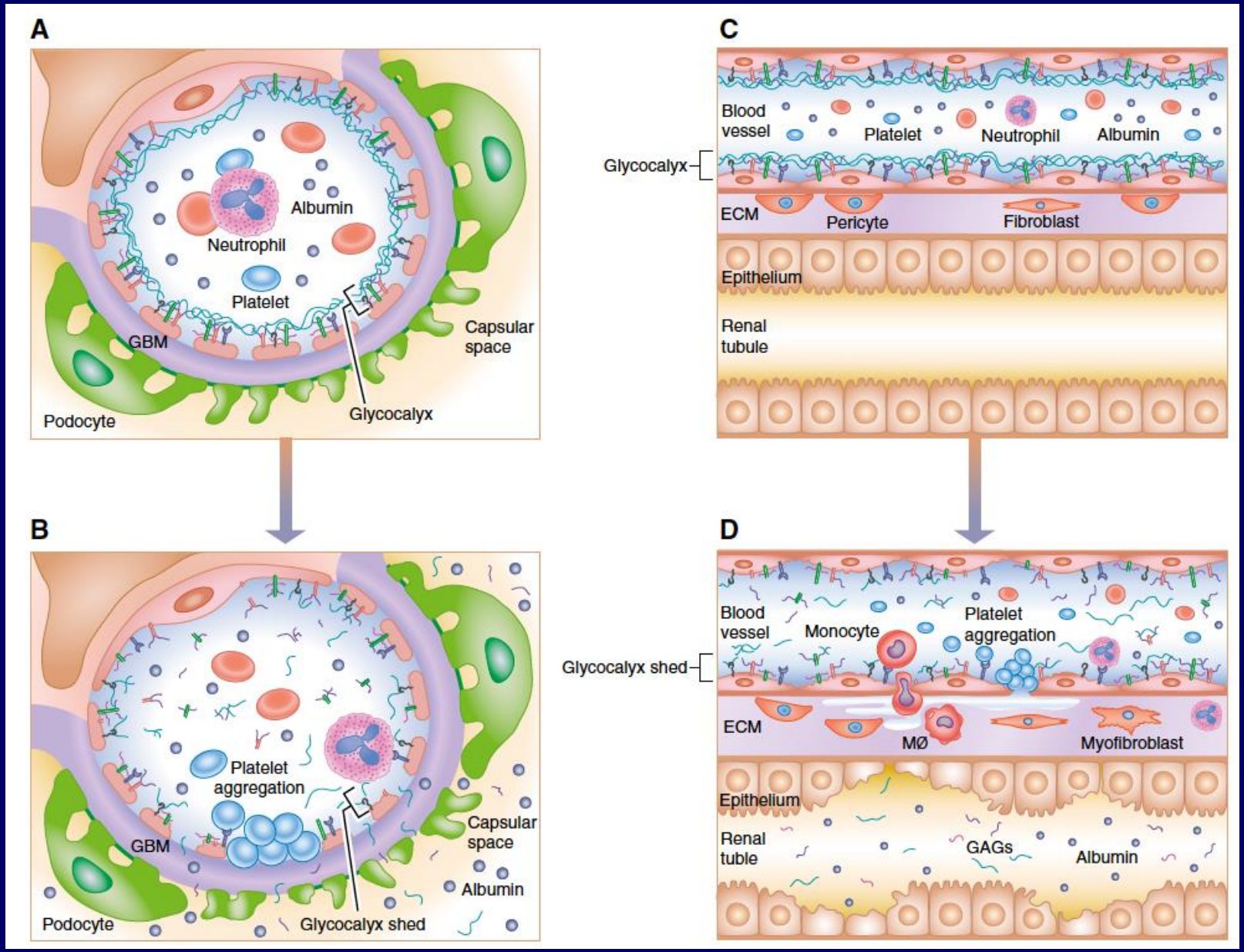
- Putative adaptive or maladaptive repair signatures within the epithelial segments …may reflect a failure to complete differentiation and tubulogenesis.
- Epithelial repair states have elevated cytokine production, increased interactions with the distinct fibrotic and inflammatory cell types, and expression 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

Endothelial and Epithelial Injury and Glycocalyx Disruption in AKI

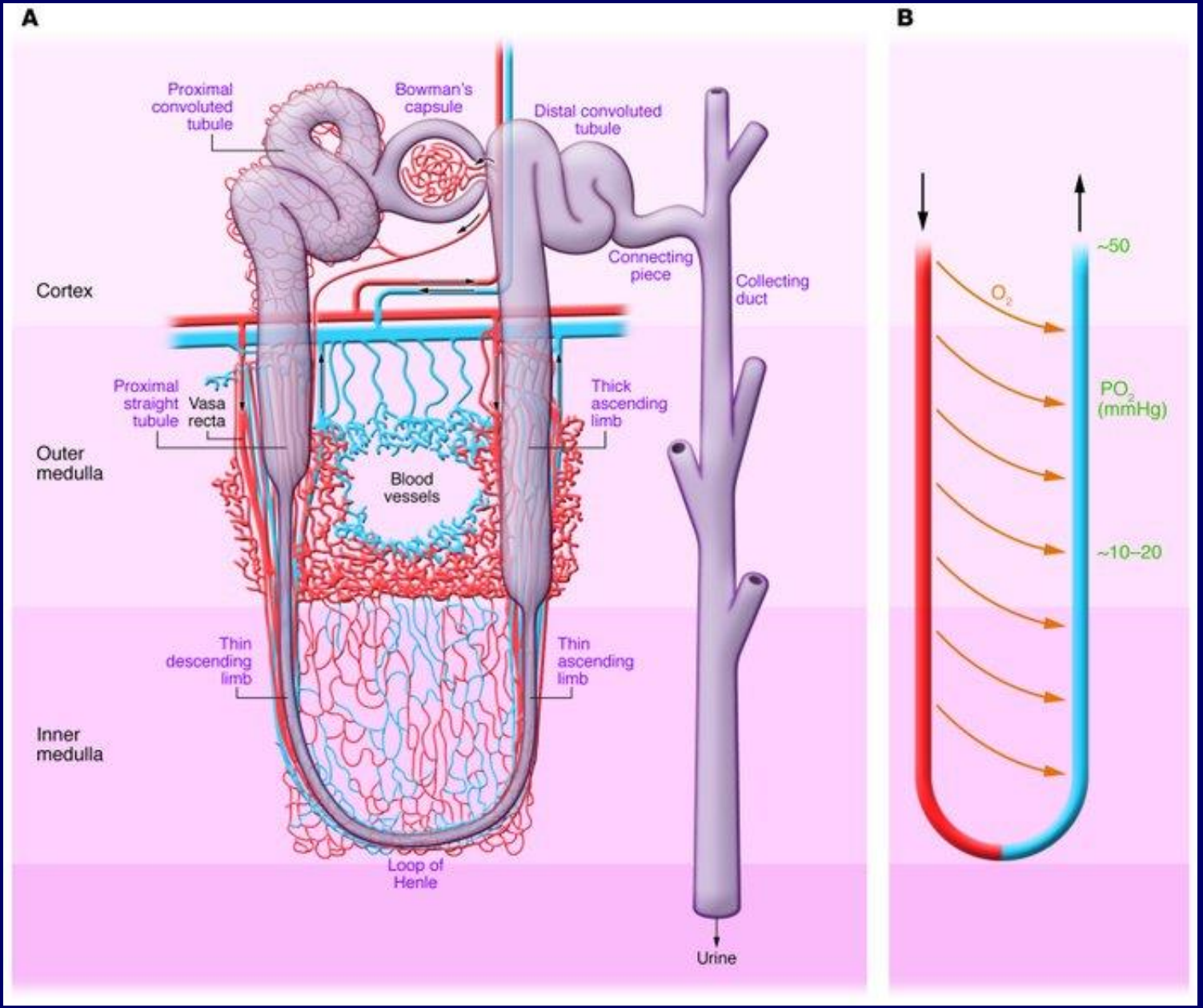
Normal

Post AKI



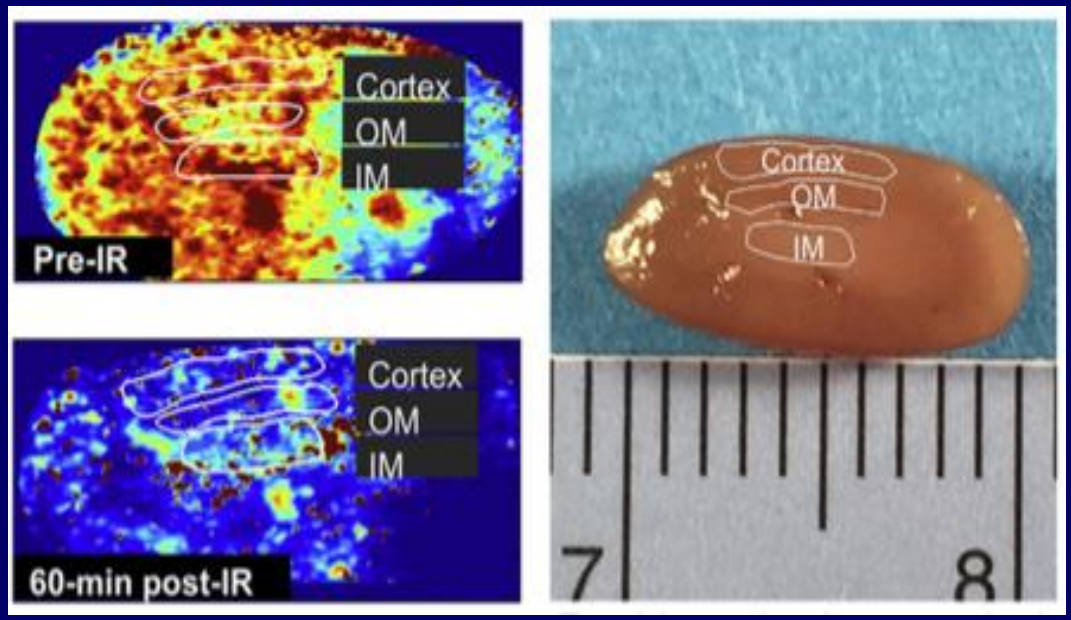
Li and Bonventre Am J Resp Crit Care Med 194:390-3, 2016

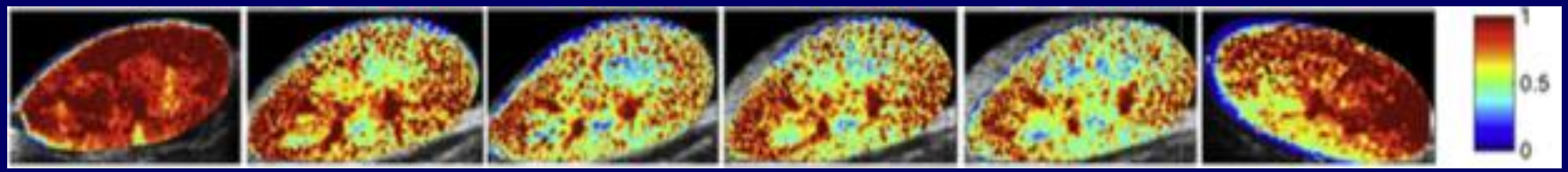
Nephron, corticomedullary oxygen gradient, and microvascular anatomy.



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

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

Kidney Pathology in Patients Dying of Sepsis

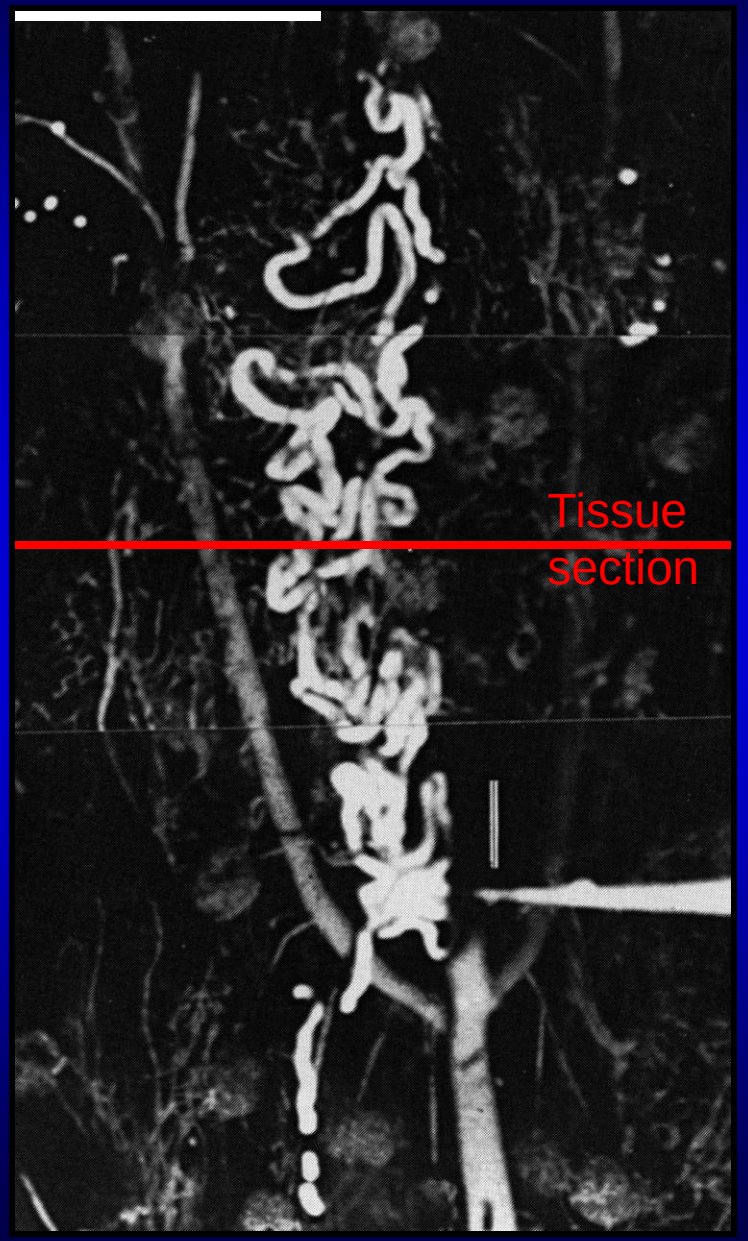
Statement from Literature That Underestimates the Importance of Tubular Injury In Sepsis induced AKI

"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

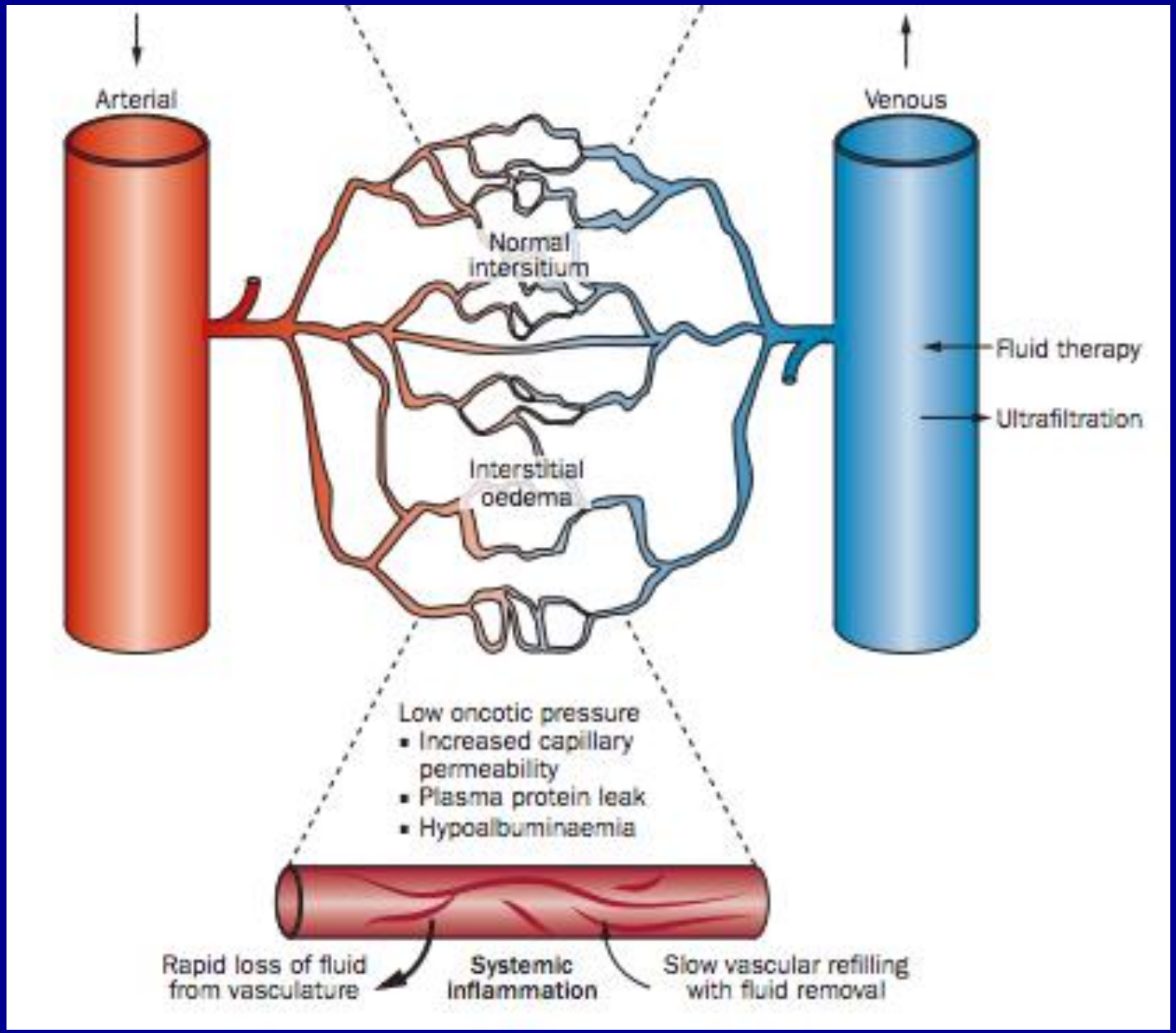
Takasu….Hotchkiss Am J Resp Crit Care Med.
187:509-517, 2013

Complexity of Proximal Tubule



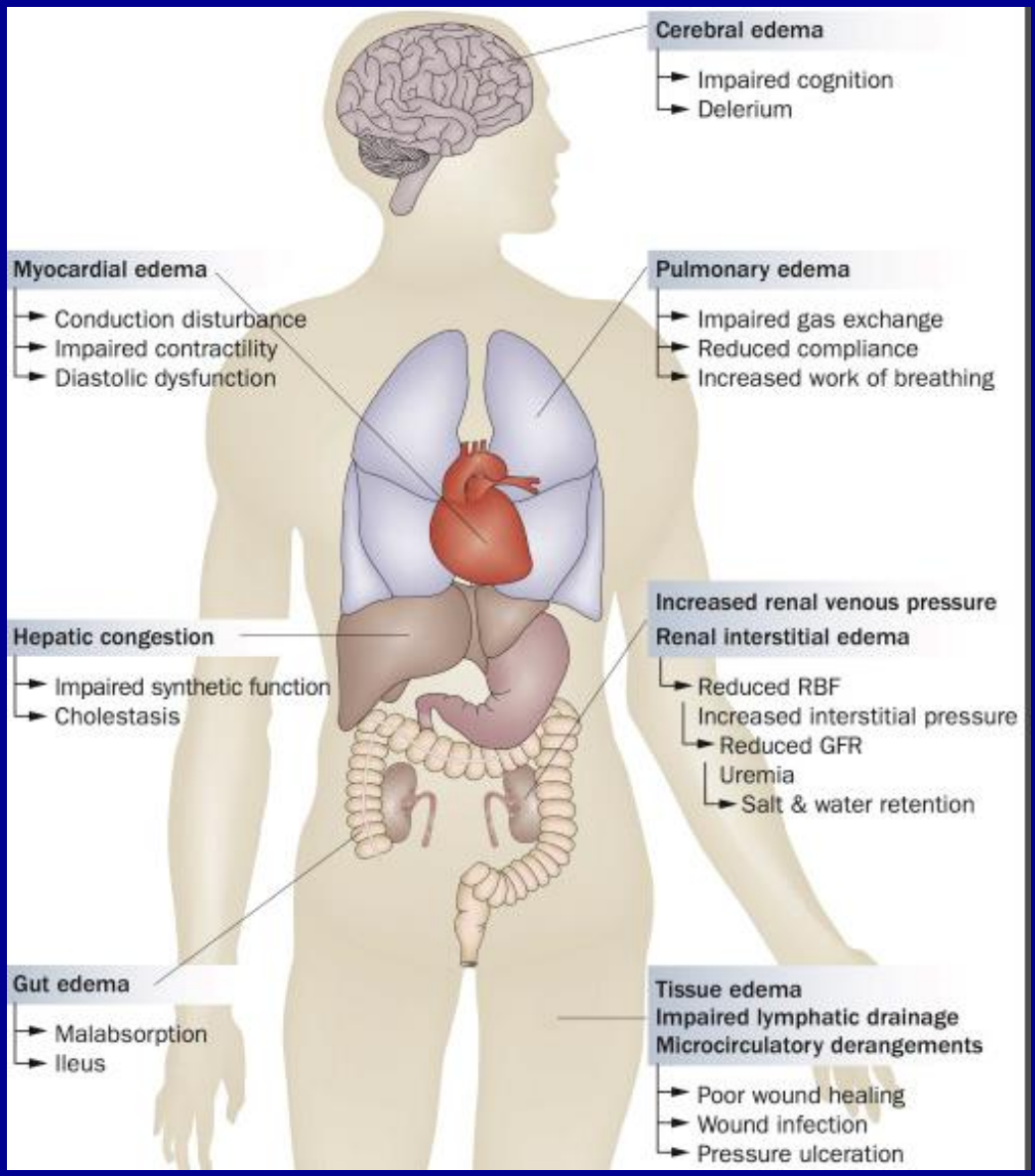
Beeuwkes and Bonventre,
Am. J. Physiol., 1975

Fluid may be very bad for AKI



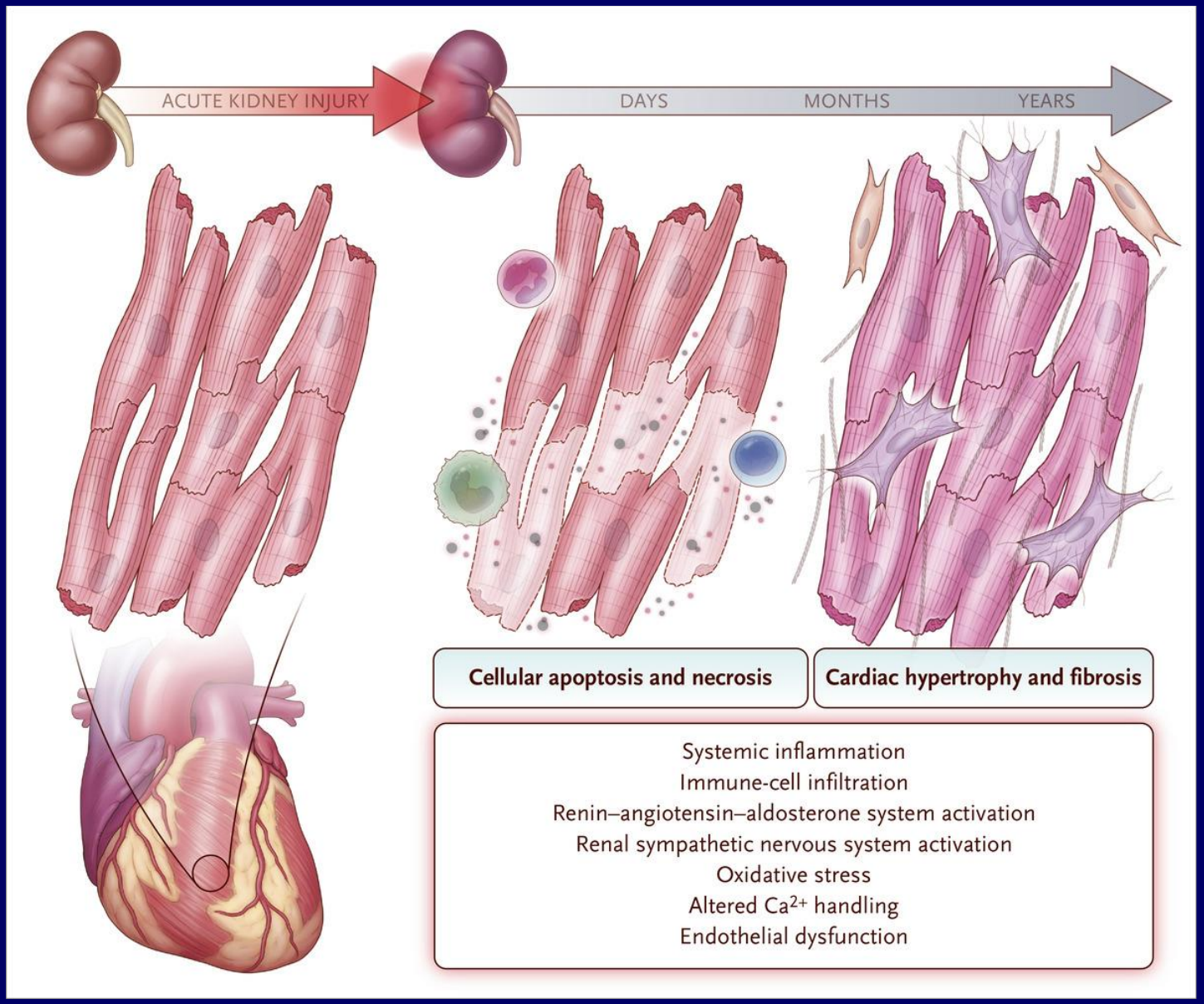
Prowle et al
Nat Rev Neph
10:37-47, 2015

Effects of Fluid Overload on Organ Systems



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

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

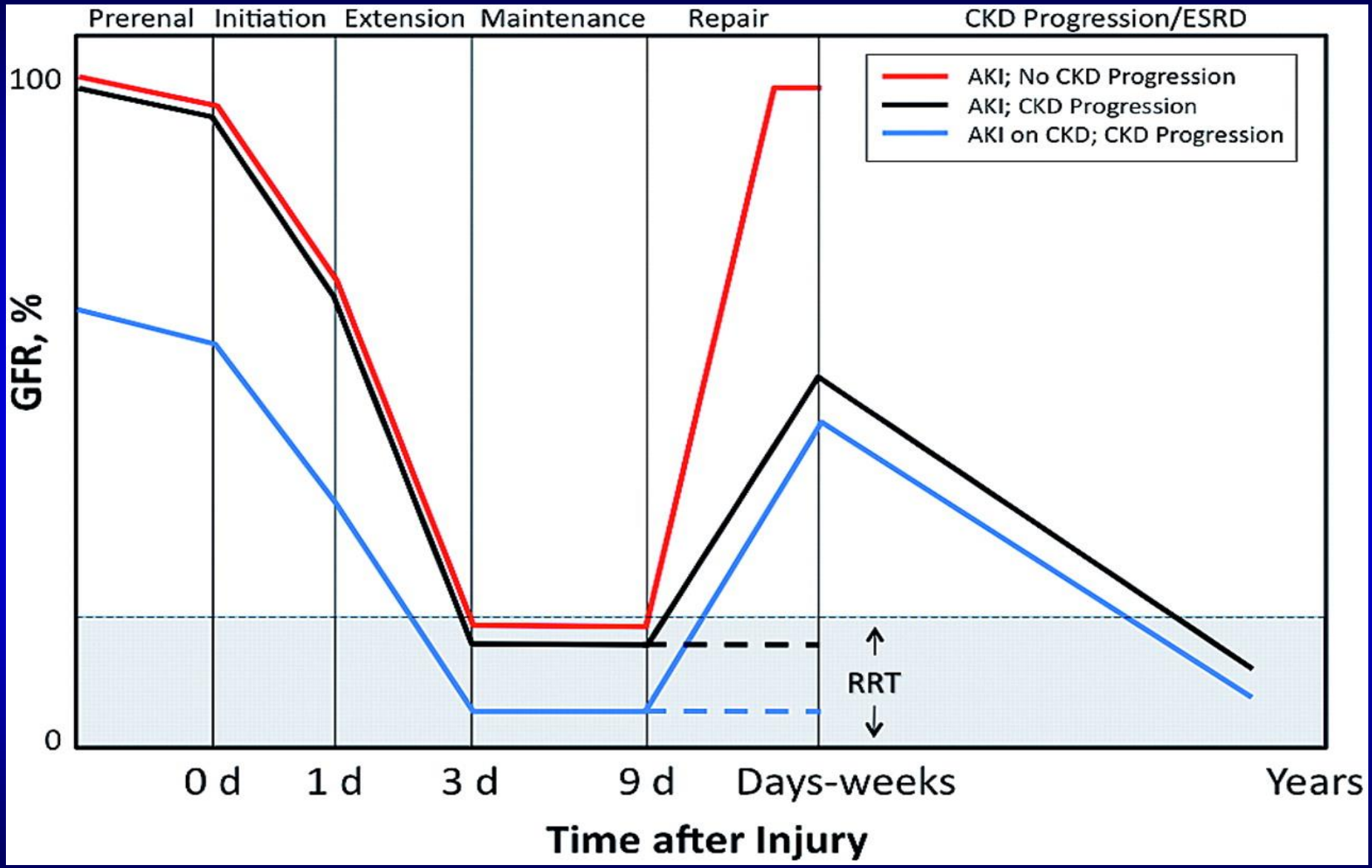
Pathophysiology of Acute Kidney Injury

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

AKI Leads to CKD

CKD Predisposes to AKI

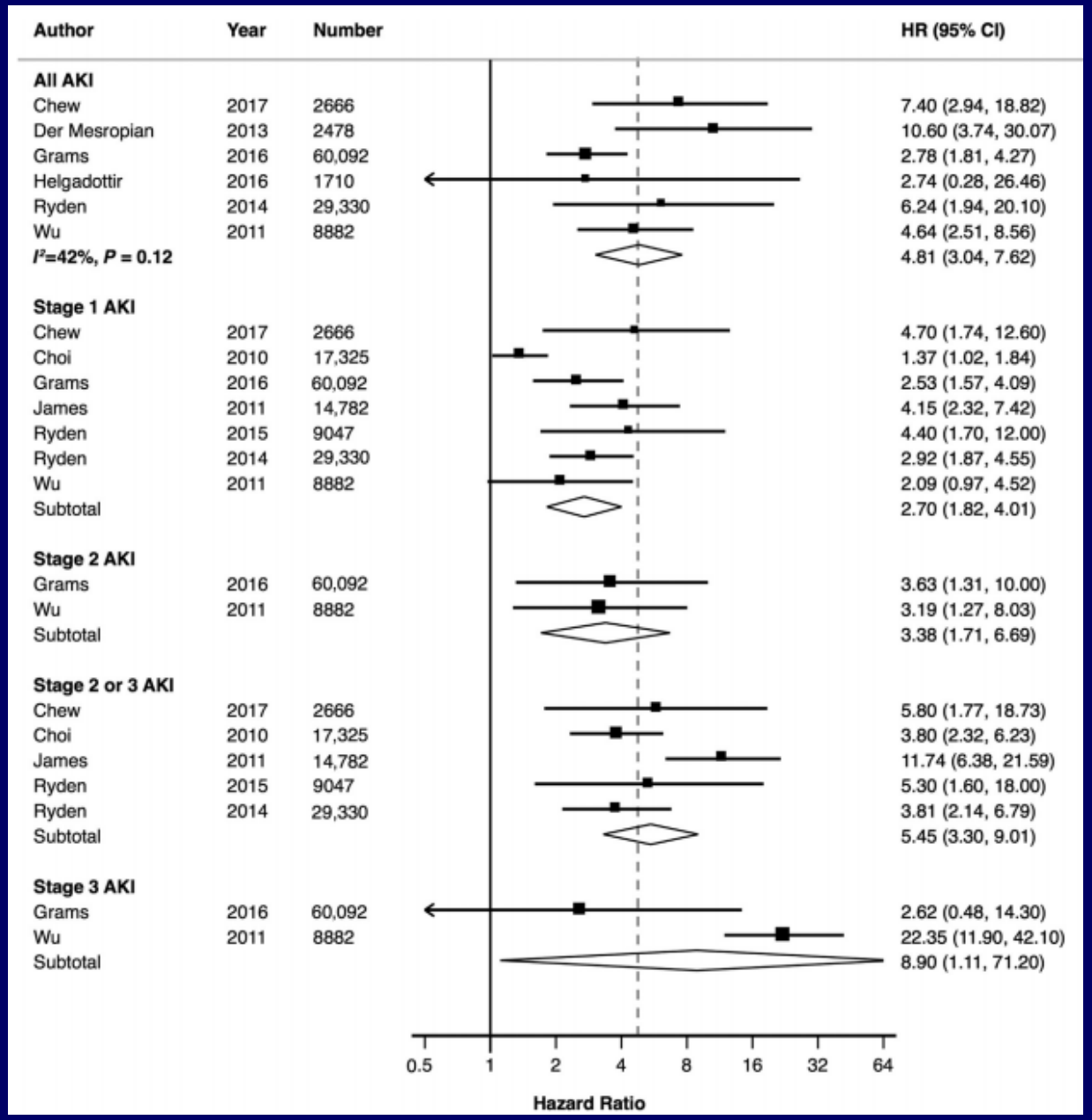
Natural history of acute kidney injury (AKI).



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

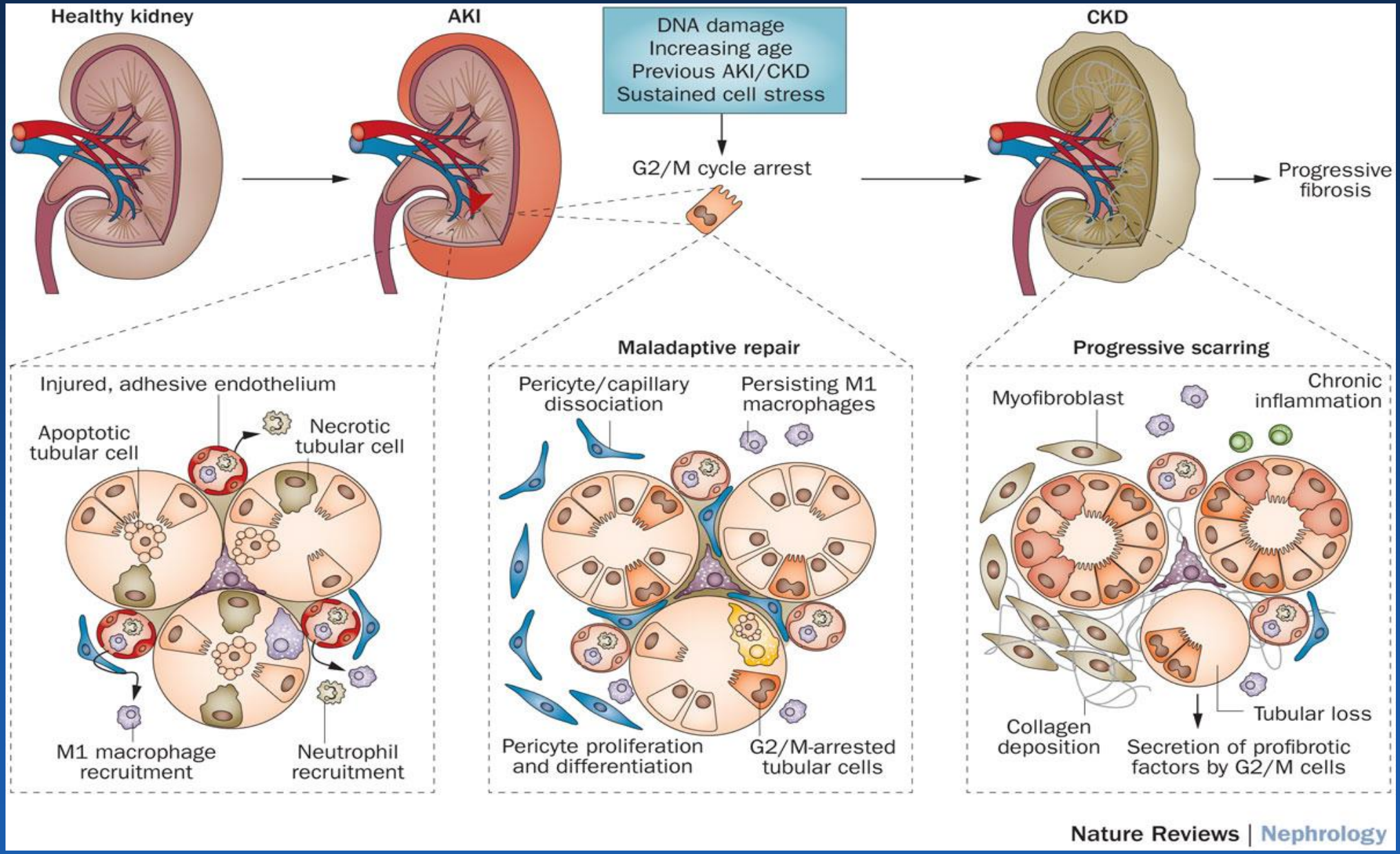
CJASN

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



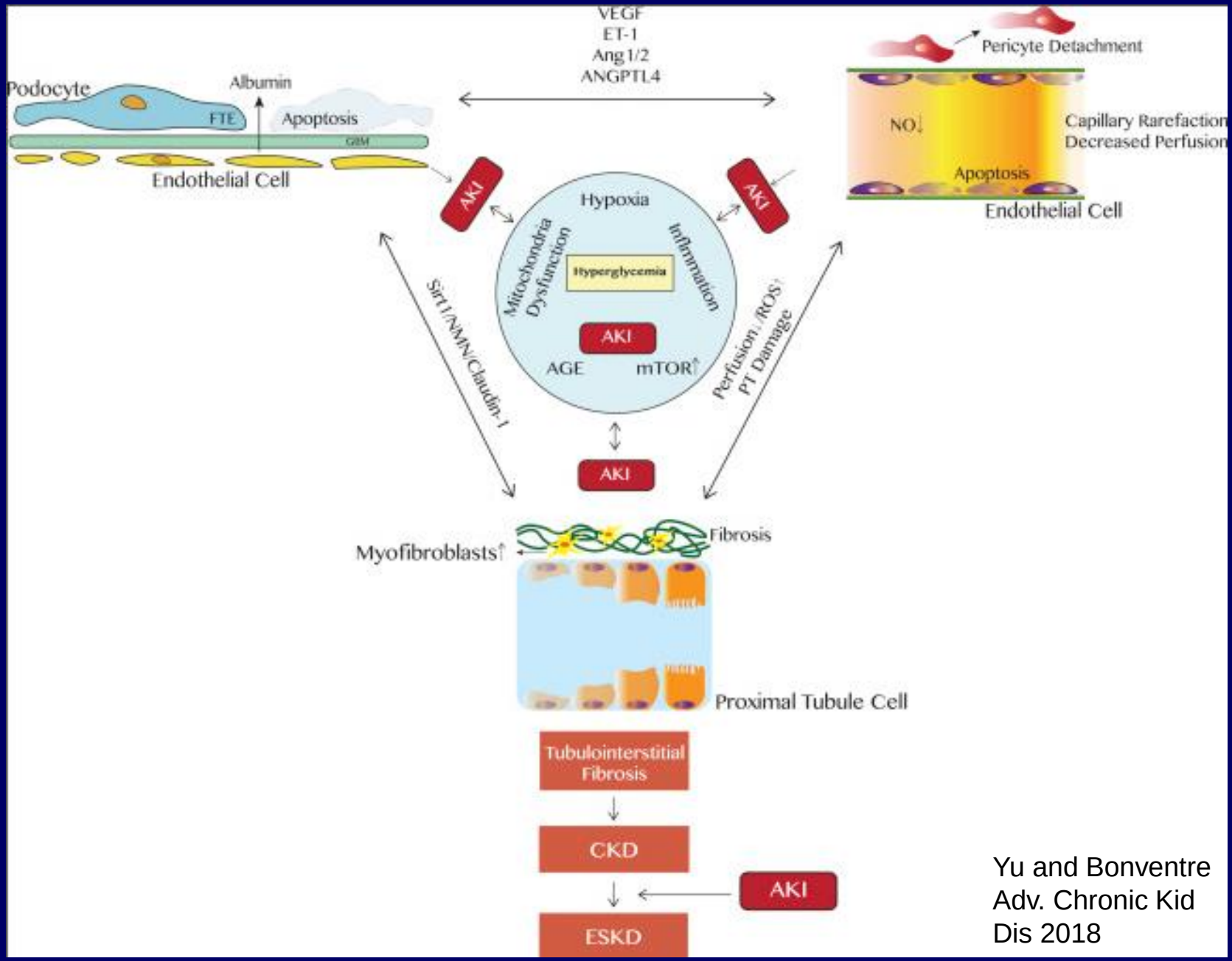
See et al. Kid Int 95:160-170, 2019

Maladaptive repair of AKI leads to CKD



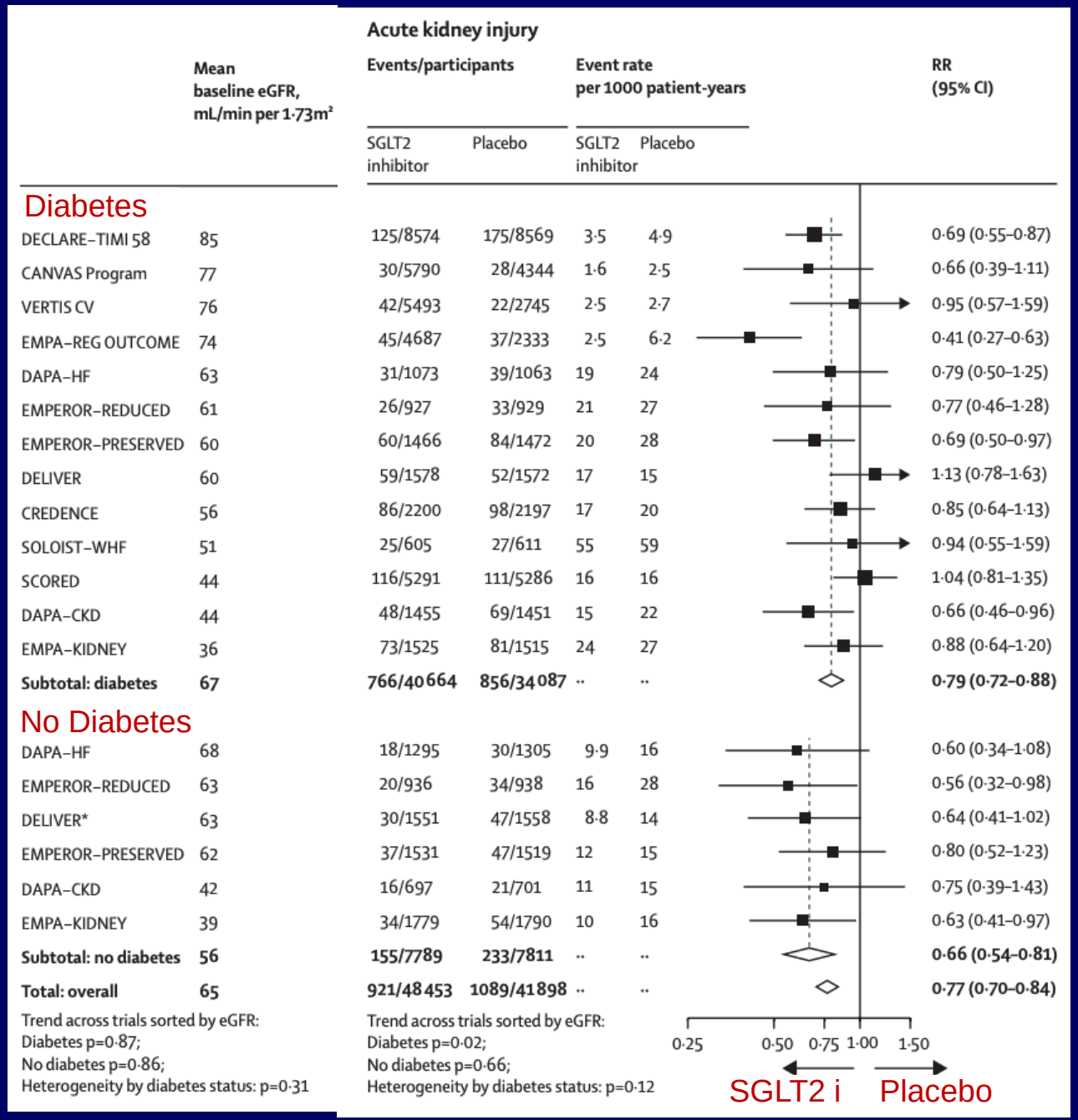
Ferenbach & Bonventre, *Nat. Rev. Nephrol.* (2015)

AKI and Progression of Diabetic Kidney Disease



Yu and Bonventre
Adv. Chronic Kid
Dis 2018

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

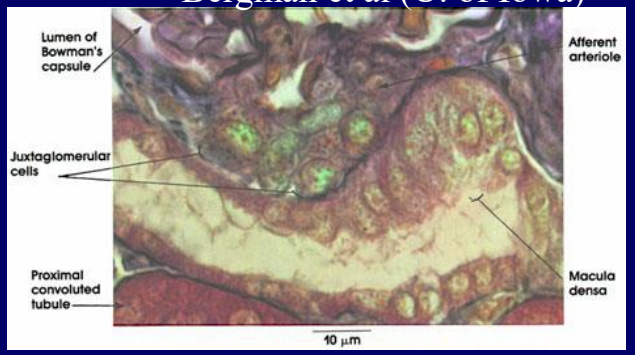
↓ O_2 Utilization

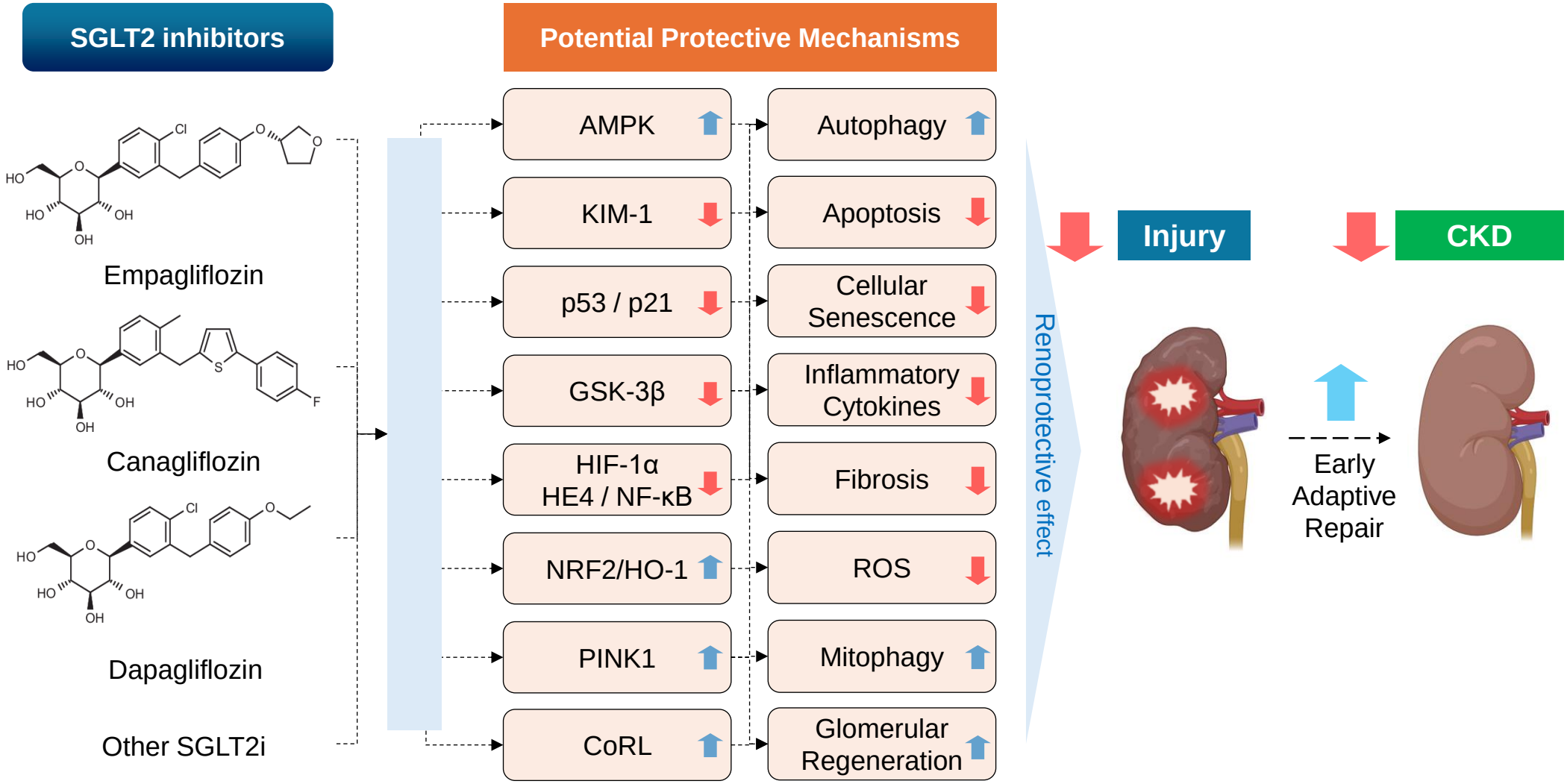
↑ O_2 Tissue Delivery

↑ Tissue ATP

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

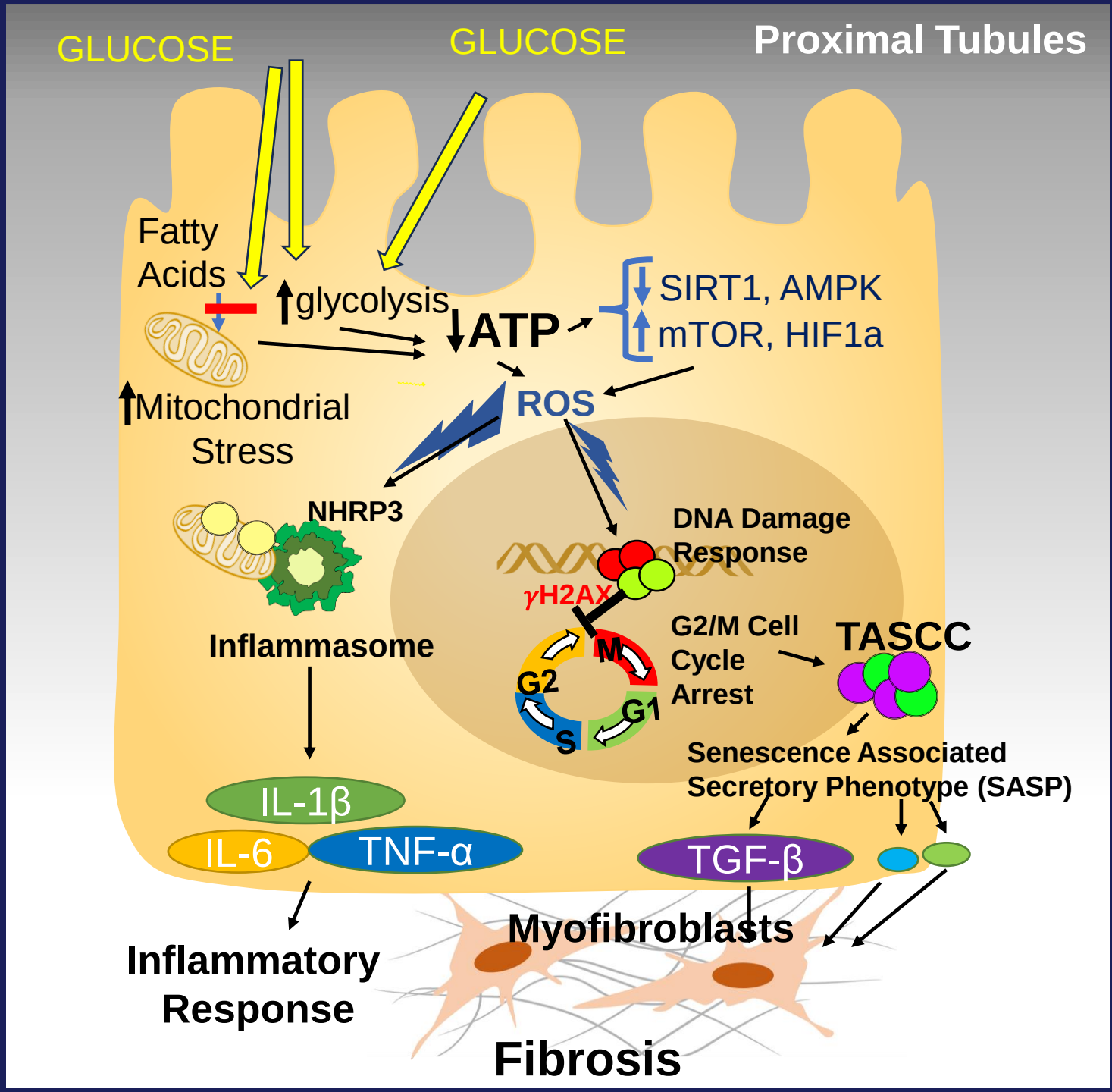
Bergman et al (U. of Iowa)




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

Effects of Glucose Uptake on Proximal Tubular Metabolism

SGLTi will Inhibit these maladaptive changes



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(Lodish et al, Mol Bio Cell)

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Kidney Replacement Therapy in Critically ill Patients

Which Statement is false

- In the absence of severe AKI complications medical management has been shown to be inferior to KRT
- Higher effluent flows (>20-25 ml/kg/hr) do not increase survival
- Greater frequency than 3x/week does not improve outcome
- No strong data that continuous therapy is better than intermittent

Gaudry et al. NEJM 386:964-975, 2022

Indications for Kidney Replacement Therapy in Critically ill Patients

Urgent indications in patients with AKI

Refractory, severe hyperkalemia†
Refractory, severe metabolic acidosis†
Refractory, severe pulmonary edema†
Uremic complications: pericarditis, bleeding, and encephalopathy‡

Urgent indications in patients without AKI

Severe intoxication due to lithium, toxic alcohol poisoning (especially from ethylene glycol or methanol), metformin, or salicylate

Nonurgent indications

Persistent, severe AKI with blood urea nitrogen level >112 mg/dl, oliguria or anuria for more than 72 hr, or both§

No indications

Severe AKI (KDIGO stage 3) in the absence of complications¶
Sepsis in the absence of complicated AKI

Gaudry et al. NEJM 386:964-975, 2022

Fluid Management in AKI

Which of the following is False

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

B. Albumin decreases fluid requirements for resuscitation, improves survival and reduces the need for RRT compared to crystalloid.

C. Starch, gelatin and dextrans should be avoided.

D. 0.9% saline can cause vasoconstriction

Fluid Therapy for 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: Hyperchloremia associated with 0.9% saline may cause renal vasoconstriction

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 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.

Some Currently Studied Therapeutics for AKI and Pathobiology Targeted

Anti-inflammatory

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

Anti-oxidants

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

Vasoactive

- Angiotensin II
- Levosimendan

Senolytic

- Navitoclax

Improve Mitochondria

- Nicotinamide Adenine Dinucleotide
- Cardiolipin

Facilitate Regeneration

- Hepatocyte Growth Factor
- BMP receptor agonists

? Cell Cycle/ ? Cell Death

- P53 siRNA

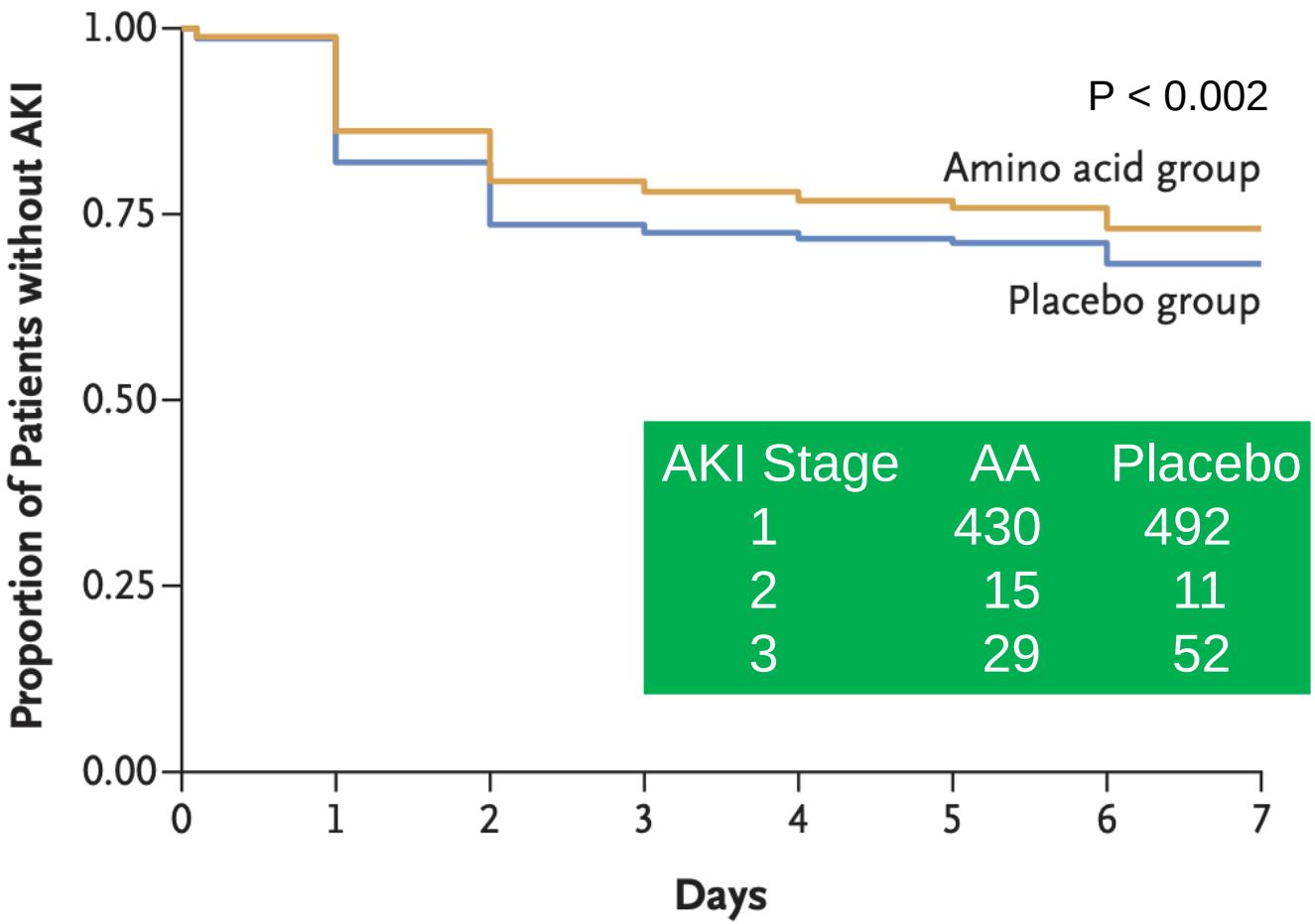
Cardiac Surgery Patients without AKI within 7 days of Randomization

Intervention
Balanced Amino Acids (2g/kg) for 72 hr or ICU discharge or CRRT or death.

Median infusion 30h

Endpoint
AKI by KDIGO

Death 2.8% in each group



AKI Stage	AA	Placebo
1	430	492
2	15	11
3	29	52

No. at Risk

Amino acid group	1759	1739	1516	1397	1372	1351	1334	1285
Placebo group	1752	1728	1436	1289	1270	1256	1246	1197

PROTECTION TRIAL

Landoni et al. NEJM June, 2024

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