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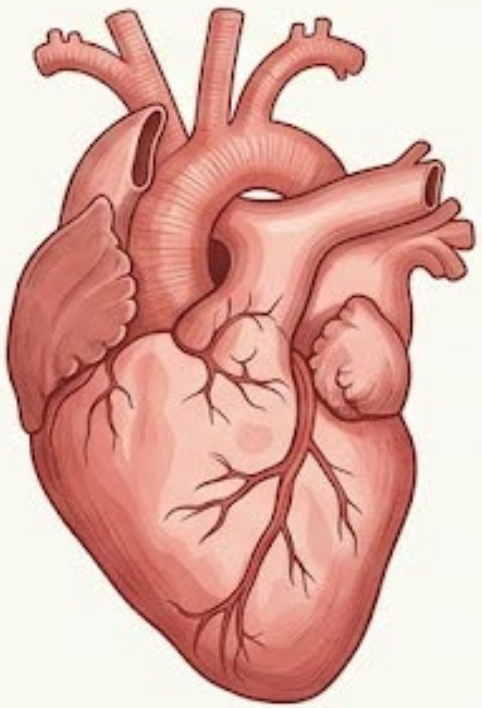
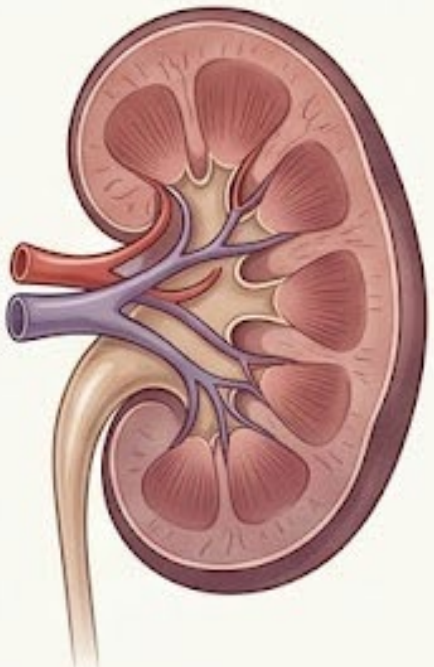




IRANIAN SOCIETY OF NEPHROLOGY · WEBINAR 2026

AKI in Heart Failure & Permissive AKI

An Introductory Discussion of Acute Kidney Injury in Cardiorenal Syndrome — from basics to the 2026 evidence

Dr. Mohammadtaghi Najafi

Associate Professor of Nephrology · NRCC · Tehran University of Medical Sciences

ROADMAP

Lecture Outline — 45 Minutes

01		**Foundations: Heart & Kidney as One Unit** What is cardiorenal syndrome? The 5 types · bidirectional crosstalk	6′
02		**AKI in Heart Failure — The Basics** What AKI is · epidemiology · the 3 mechanisms (congestion first)	8′
03		**Not All AKI Is Equal** Induced vs spontaneous creatinine rise · the AKI→AKD→CKD timeline	6′
04		**Permissive AKI — The Core Concept** Definition · why eGFR dips · McCallum / Parikh-Coca / Brenner thresholds	12′
05		**What's New: CONFIDENCE 2025 & KDIGO 2026** Finerenone + SGLT2i · AKI safety · new consensus & biomarkers	8′
06		**Bedside Algorithm + 2 Cases + Take-Home** A practical decision tree · applied cases · 5 key messages	5′

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

SECTION 01

Foundations: One Cardiorenal Unit

Why heart and kidney must be managed as a single system

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

What Is Cardiorenal Syndrome (CRS)?

Dysfunction of one organ drives dysfunction of the other — the link is bidirectional.

Why they are linked

Honert, why are linked

Why it matters

Cardiorenal it factios

Key mindset:

ask WHY, not just HOW MUCH

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

What Is Cardiorenal Syndrome (CRS)?

Definition: A disorder of the heart and kidneys in which acute or chronic dysfunction of one organ induces acute or chronic dysfunction of the other. The link is ***bidirectional*** — injury and therapy in one organ inevitably stress the other.

WHY THEY ARE LINKED

- Shared circulation & volume status
- Common neurohormonal axis (RAAS, SNS)
- Shared risk factors: HTN, diabetes, age
- Systemic inflammation affects both

WHY IT MATTERS

- Coexistence sharply raises mortality
- Every HF drug alters kidney function
- Creatinine rises frighten clinicians
- Good therapy is often stopped too early

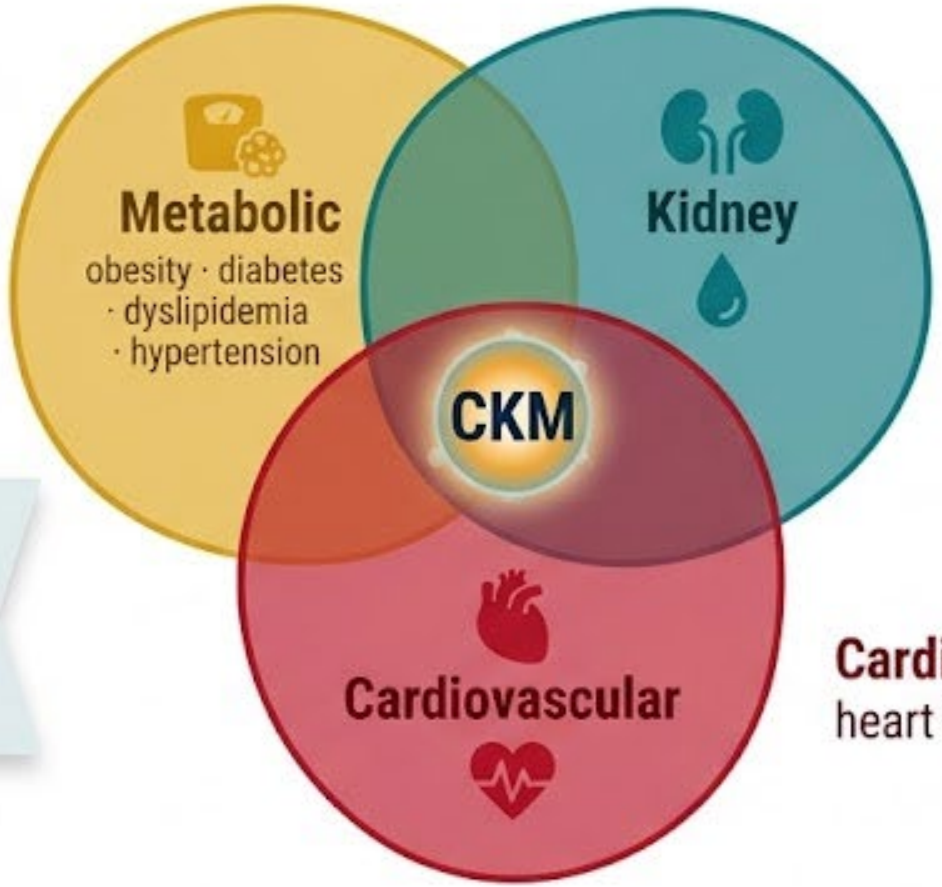
THE KEY MINDSET

- Treat the unit, not one organ
- A creatinine rise is data — not a verdict
- Ask WHY it rose, not only HOW MUCH
- Context decides good vs bad

Ronco C et al. JACC 2008 · KDIGO Controversies Conference (Kidney Int / JACC:HF 2026) · AJKD Core Curriculum 2025

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Cardiovascular–Kidney–Metabolic (CKM) Syndrome



Kidney — chronic kidney disease · albuminuria

Cardiovascular — heart failure · CAD · stroke

AHA 2023: a systemic disorder linking obesity / type 2 diabetes, chronic kidney disease, and cardiovascular disease — **cardiorenal** syndrome is one part of it.

Stage 0 — No risk factors

Stage 1 — Excess / dysfunctional dysfunctional adiposity

Stage 2 — Metabolic risk factors or CKD

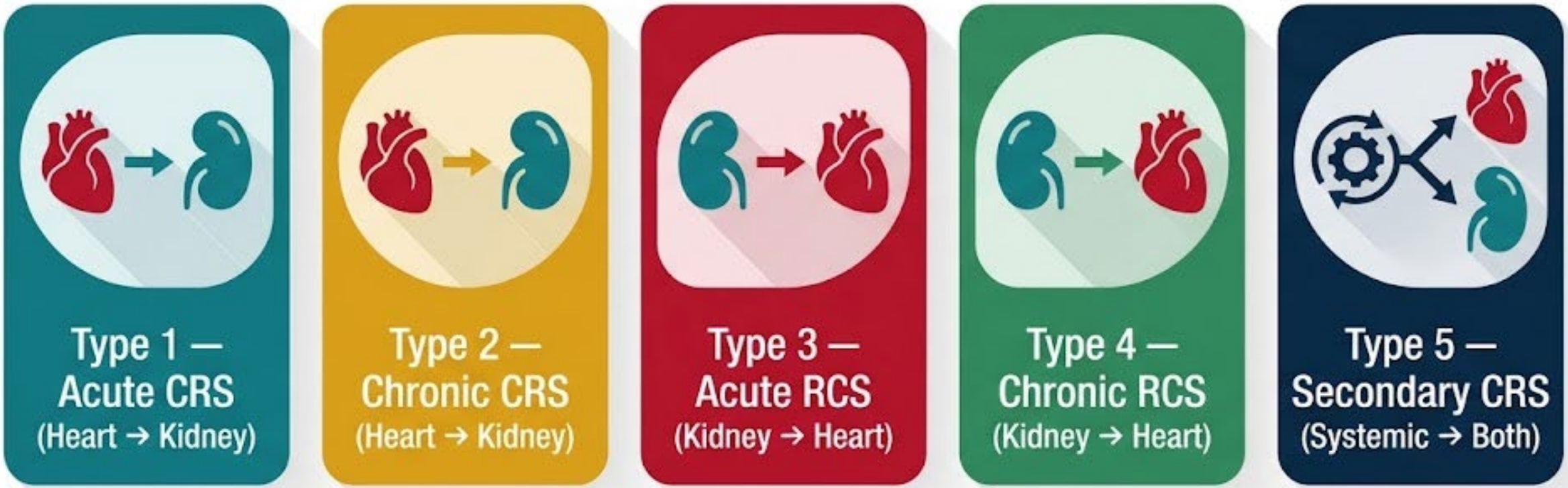
Stage 3 — Subclinical CVD

Stage 4 — Clinical CVD (± kidney failure)

The same therapies acting across all CKM domains — SGLT2i, finerenone, RAASi, GLP-1 RA — drive the permissive eGFR dip.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

The Five Types of Cardiorenal Syndrome



Every treatment in one organ transiently stresses the other.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Why Does the Failing Heart Injure the Kidney?

Neurohormonal
RAAS, SNS, ADH

Hemodynamic
low cardiac output & venous congestion

Inflammatory
IL-6, TNF, oxidative stress

KDIGO 2026: venous congestion often matters more than low cardiac output — decongest first.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Why Does the Failing Heart Injure the Kidney?

HEMODYNAMIC

- ↓ Cardiac output → ↓ renal perfusion
- Venous congestion (↑CVP) → ↑ renal interstitial pressure
- ↓ Net glomerular filtration gradient
- Afferent vasoconstriction; renal “tamponade” (↑IAP)

NEUROHORMONAL

- RAAS overactivation (↑ Ang II, aldosterone)
- Sympathetic (SNS) overactivation
- ↑ ADH → water retention
- Endothelin-1, TGF-β → vasoconstriction & fibrosis

INFLAMMATORY

- ↑ IL-6, TNF-α, IL-1β (systemic inflammation)
- Reactive oxygen species / oxidative stress
- Leukocyte infiltration → tubular damage
- Uremic toxin accumulation (kidney → heart)

KDIGO 2026 message: Venous congestion (↑CVP) is often a STRONGER determinant of AKI in heart failure than low cardiac output. Decongest first.

Mullens W et al. JACC 2009 · Boorsma EM et al. (renal tamponade) · Biegus J et al. ESC Heart Failure 2025 · AJKD Core Curriculum 2025

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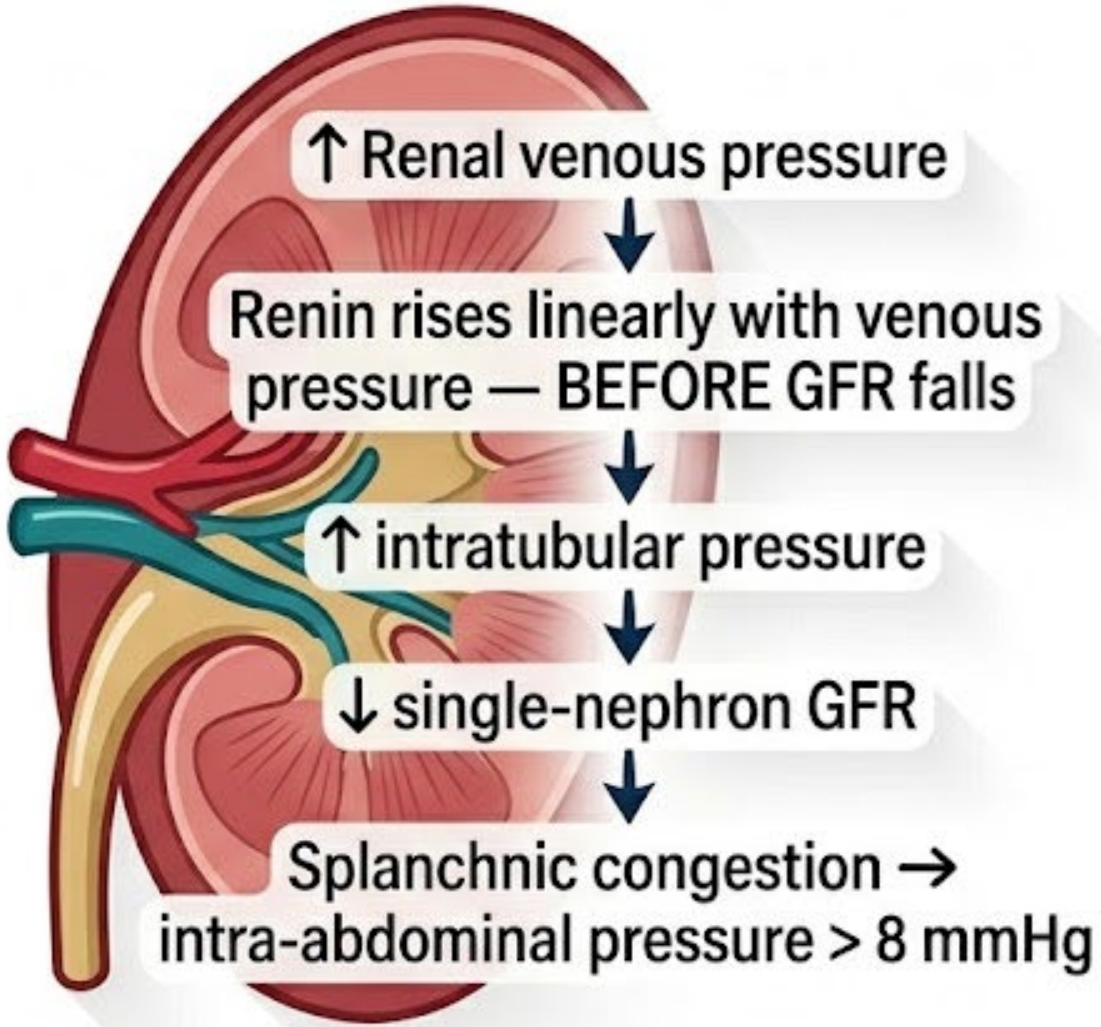
Venous Congestion, Renin, and Why Decongestion Helps



↑ Renal venous pressure

↓

Renin rises linearly with venous pressure — BEFORE GFR falls

↓

↑ intratubular pressure

↓

↓ single-nephron GFR

↓

Splanchnic congestion → intra-abdominal pressure > 8 mmHg

RAAS & SNS are upstream and central — a persistent sodium-avid state

Congestion, not low output, drives poor outcomes — decongest first; the kidney follows

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Venous Congestion, Renin, and Why Decongestion Helps

THE CONGESTION CASCADE

- ↑ Renal venous pressure (RVP)
- Renin rises linearly with RVP — BEFORE any fall in RBF or GFR
- ↑ pressure transmitted to tubules → ↑ intratubular pressure
- ↓ hydrostatic gradient across Bowman's capsule → ↓ single-nephron GFR
- Splanchnic congestion → ↑ intra-abdominal pressure (>8 mmHg) → worse kidney function

RAAS & SNS are upstream and central

Maladaptive RAAS and sympathetic activity drive a persistent **sodium-avid state** that sustains the vicious cycle of congestion — so optimizing neurohormonal blockade is itself disease-modifying, not just symptomatic.

Why decongestion matters

Congestion — not low cardiac output — is the dominant driver of poor outcomes.

A creatinine rise that occurs WHILE decongesting does not confer added risk; **decongest first — the kidney follows.**

Practical corollary: address both — efficient decongestion (watch for diuretic resistance) AND early neurohormonal optimization.

Disorders of Volume: Core Curriculum 2025 & Kidney Dysfunction in HF: Core Curriculum 2025, Am J Kidney Dis 2025;85(6):767–786 · Coca SG, Nephron 2022

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

SECTION 02

AKI in Heart Failure: The Basics

What AKI is, how common it is, and the three ways it happens

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

What Is Acute Kidney Injury? (KDIGO Definition)

AKI = ANY ONE OF (KDIGO 2012):

- ↑ Serum creatinine ≥ 0.3 mg/dL within 48 hours, or
- ↑ Serum creatinine ≥ 1.5× baseline within 7 days, or
- Urine output < 0.5 mL/kg/h for ≥ 6 hours

THE CRITICAL CATCH

These criteria rely on serum creatinine — a **functional marker of filtration, not of structural damage.** Creatinine can rise from a benign hemodynamic shift OR from true tubular injury. The number cannot tell them apart.

STAGE 1	1.5–1.9× baseline or ↑≥0.3 mg/dL
STAGE 2	2.0–2.9× baseline
STAGE 3	≥3.0× · sCr ≥4.0 or dialysis

KDIGO Clinical Practice Guideline for Acute Kidney Injury 2012 · Kwong YD, Liu KD, Hsu RK. Kidney Int Rep 2022

SECTION 02 · EPIDEMIOLOGY

The Burden of AKI in Heart Failure

30–40%

of ADHF hospitalizations develop AKI during treatment

~50%

of worsening renal function is KDIGO Stage 1 only (sCr ↑≥0.3)

30–60%

of HF patients have concurrent CKD at baseline

2–3×

higher mortality when AKI occurs WITH persistent congestion

↑15 yrs

ESKD delay: SGLT2i + RAASi vs RAASi alone (kidney trials)

52% ↓

UACR with finerenone + SGLT2i combination (CONFIDENCE 2025)

AJKD Core Curriculum 2025 · KDIGO 2026 (Kidney Int / JACC:HF) · Agarwal R et al. NEJM 2025 (CONFIDENCE)

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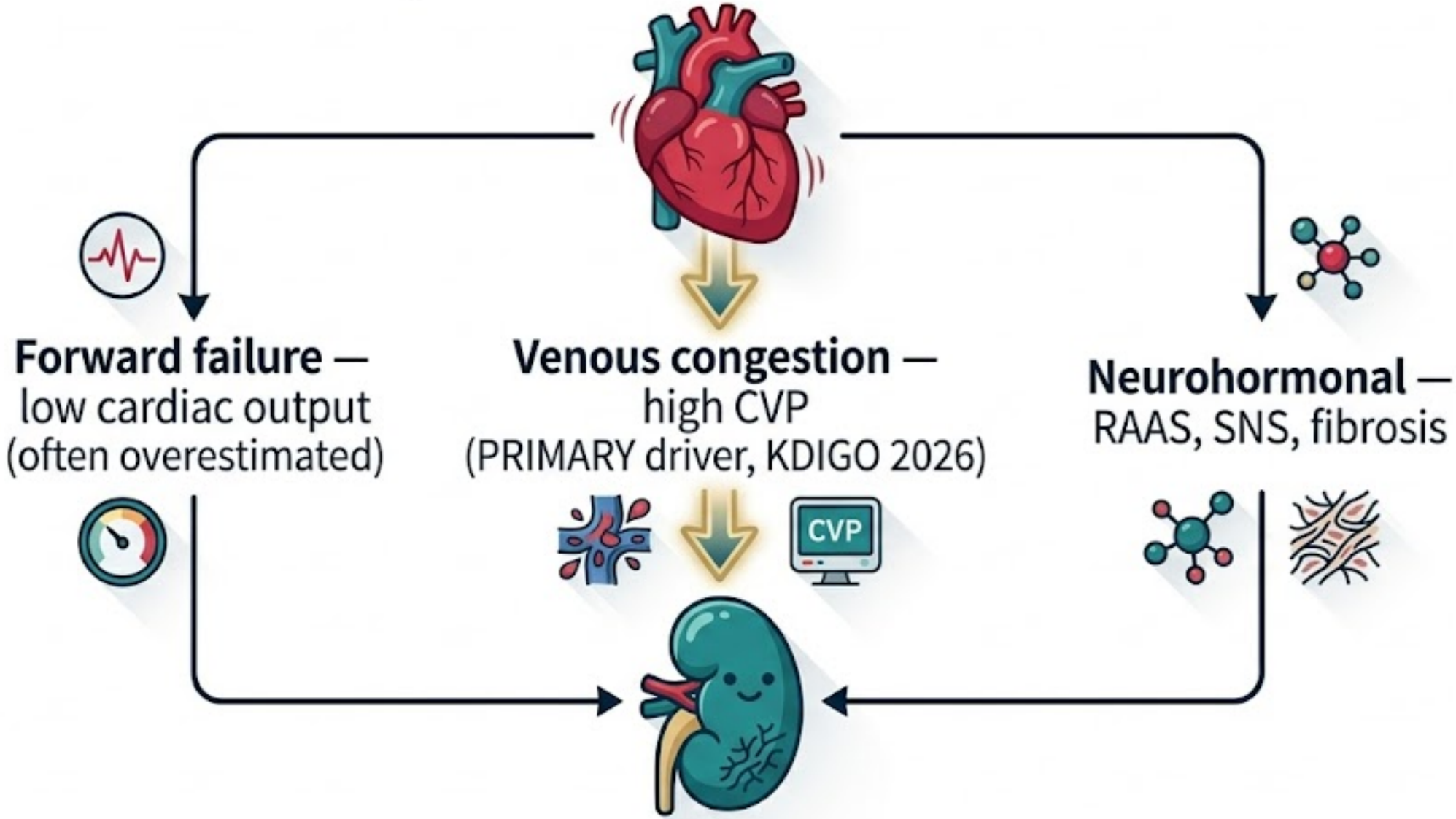
Three Pathways of AKI in Acute Heart Failure



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Three Pathways of AKI in Acute Heart Failure

ACUTE HEART FAILURE

FORWARD FAILURE

Often OVERESTIMATED

- ↓ CO → ↓ renal perfusion
- Pre-renal azotemia (FeNa <1%)
- RAAS activation, afferent constriction
- Responds well to decongestion

VENOUS CONGESTION

KDIGO 2026: PRIMARY DRIVER

- ↑ CVP → renal venous hypertension
- ↓ filtration gradient
- ↑ intratubular / interstitial pressure
- Persists if not decongested

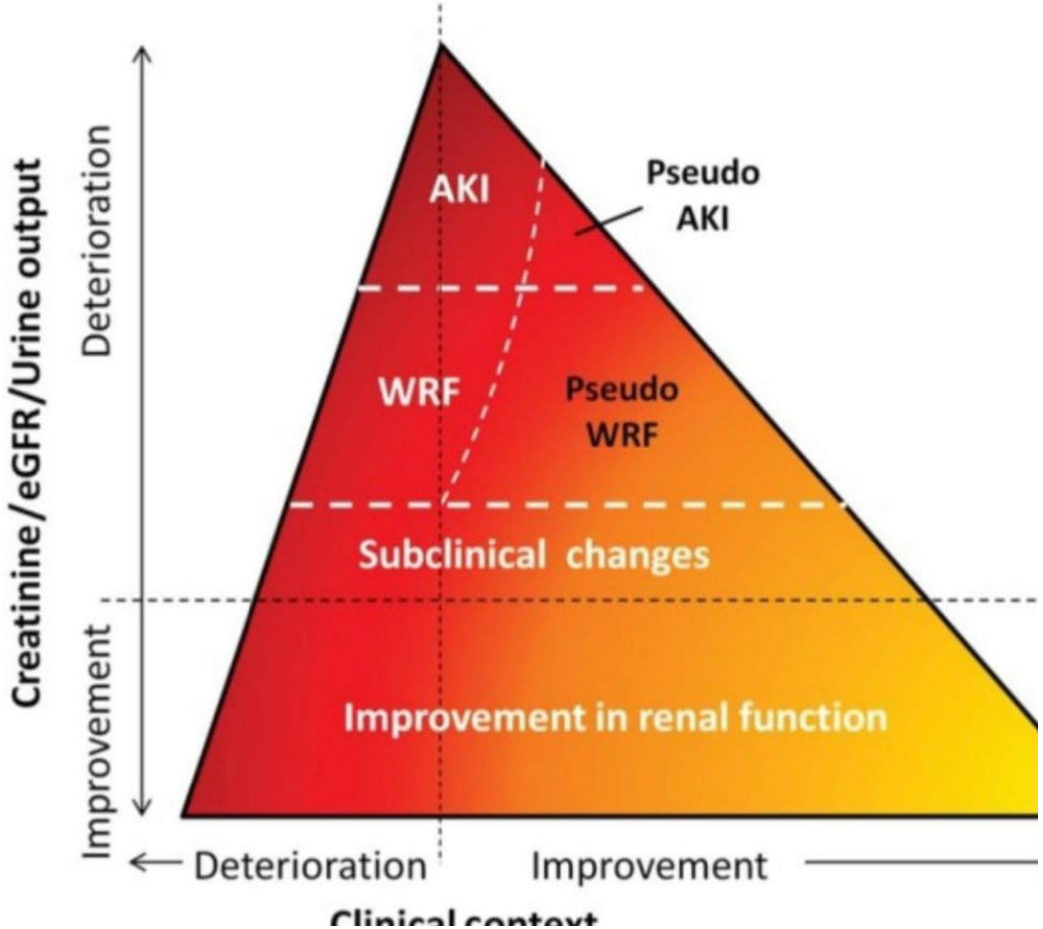
NEUROHORMONAL

Long-term maladaptive

- ↑ RAAS · ↑ SNS · ↑ ADH
- Aldosterone → fibrosis
- Inflammatory cytokines, ROS
- Cardiorenal remodeling

AJKD Core Curriculum 2025 · Biegus J et al. ESC Heart Failure 2025 (venous congestion > low CO) · Mullens W et al. JACC 2009

When Does a Creatinine Rise Actually Matter?



The single most important idea

Only when BOTH the creatinine rises AND the patient is clinically deteriorating do outcomes worsen.

A creatinine rise while the patient is decongesting and feeling better is **expected and benign** — this is the “permissive” / Pseudo-WRF zone.

Reacting to the number alone leads to stopping life-saving therapy.

Brenner & Rector, The Kidney, 11th ed. 2020, Ch. 40 — Cardiorenal Syndrome (original figure)

SECTION 03

Not All AKI Is Equal

The same creatinine rise can mean opposite things — context is everything

Induced vs Spontaneous Creatinine Rise

Induced AKI — GOOD

Diuresis / decongestion
RAAS inhibitor
SGLT2 inhibitor
Intensive BP control
Biomarkers negative

VS

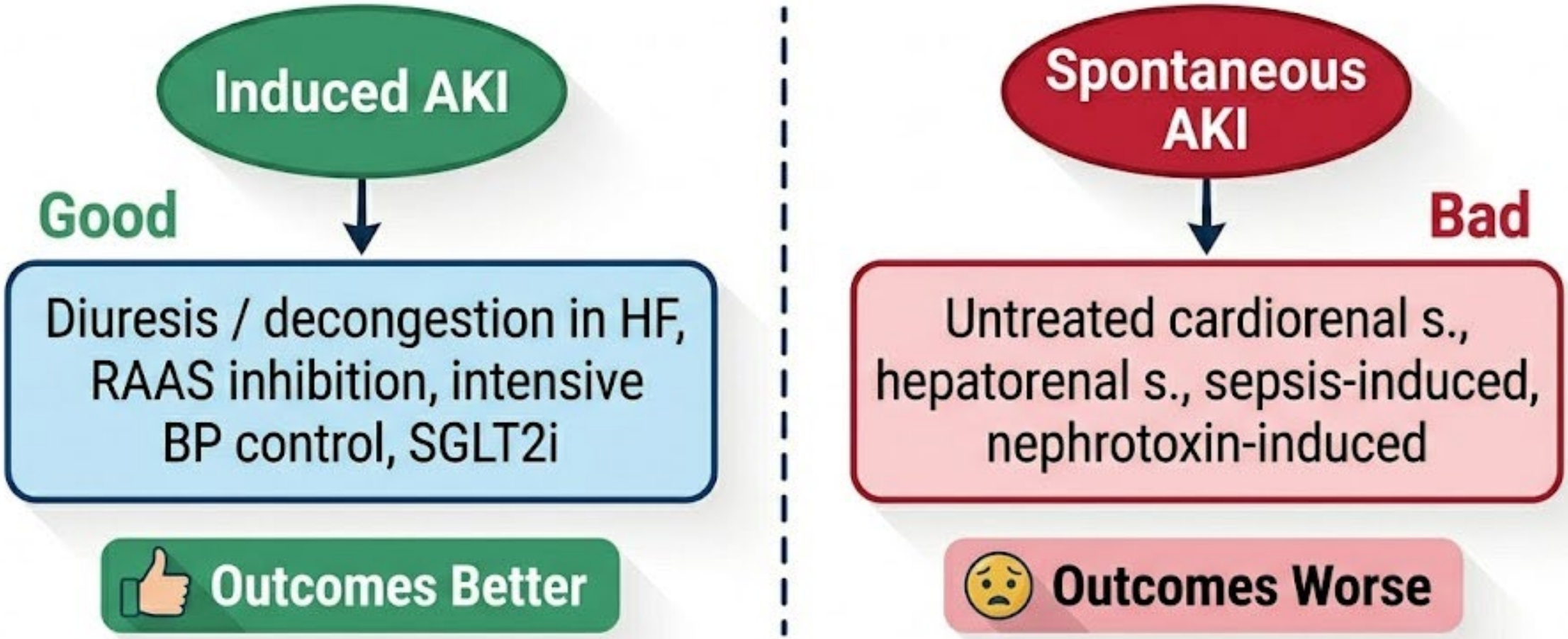
Spontaneous AKI — BAD

Untreated cardiorenal syndrome
Hepatorenal syndrome
Sepsis
Nephrotoxins
Biomarkers positive

Ask **WHY** — not just **HOW MUCH**.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Acute sCr Elevations: Implications Are Context-Dependent



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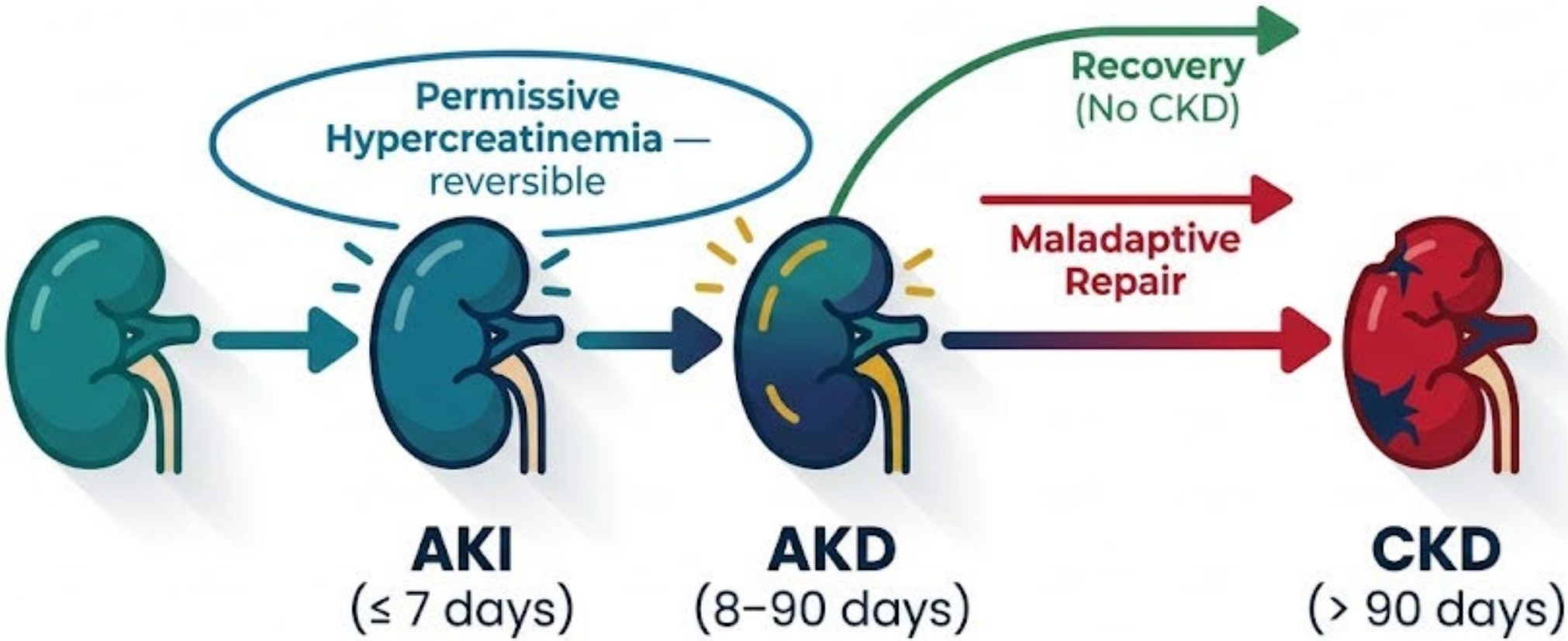
AKI → AKD → CKD: The Modern Framework



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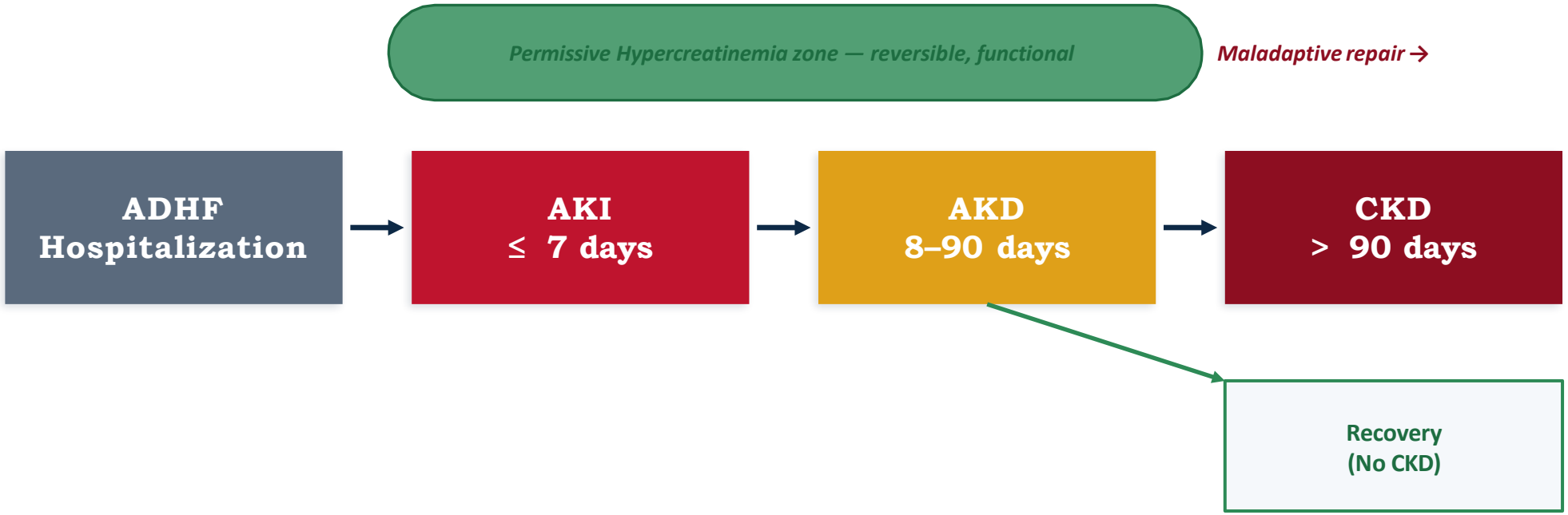
AKI → AKD → CKD: The Modern Framework



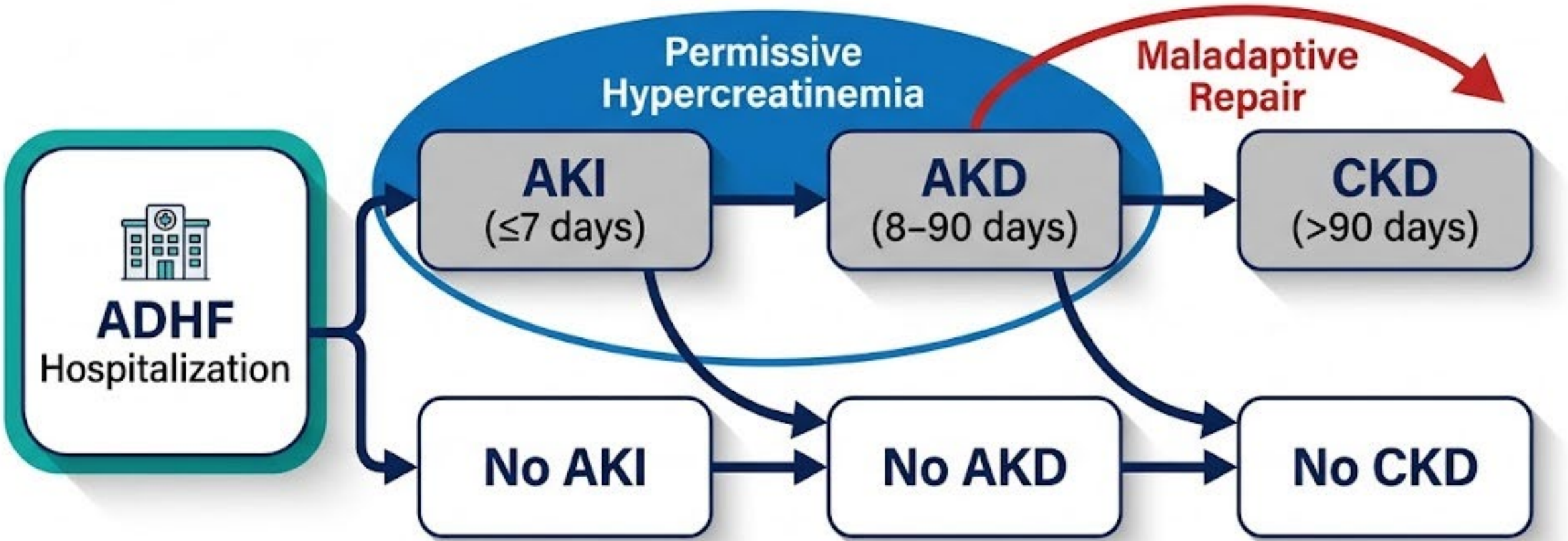
AKD is the new entity
Persistent kidney dysfunction 8–90 days after ADHF. Bridges AKI and CKD.

Biomarkers separate the paths
Cystatin C, NGAL & KIM-1 distinguish functional (permissive) from structural (true ATN).

Timeline + context define it
Not every sCr rise during ADHF is AKI. The trajectory and clinical picture matter.

Kwong YD, Liu KD, Hsu RK. Kidney Int Rep 2022 · KDIGO 2020 AKD definition · KDIGO 2026 (Kidney Int / JACC:HF)

Framework for AKD Diagnosis After ADHF



The AKI→AKD window is reversible — it only progresses if it tips into maladaptive repair.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Why Permissive Azotemia May Help the Kidney Recover (Chawla)

Acute Kidney Injury

↓

Inflammation, ROS, cell-cycle arrest, M1 macrophage infiltration, fibrotic response

Presence of Uremic Milieu

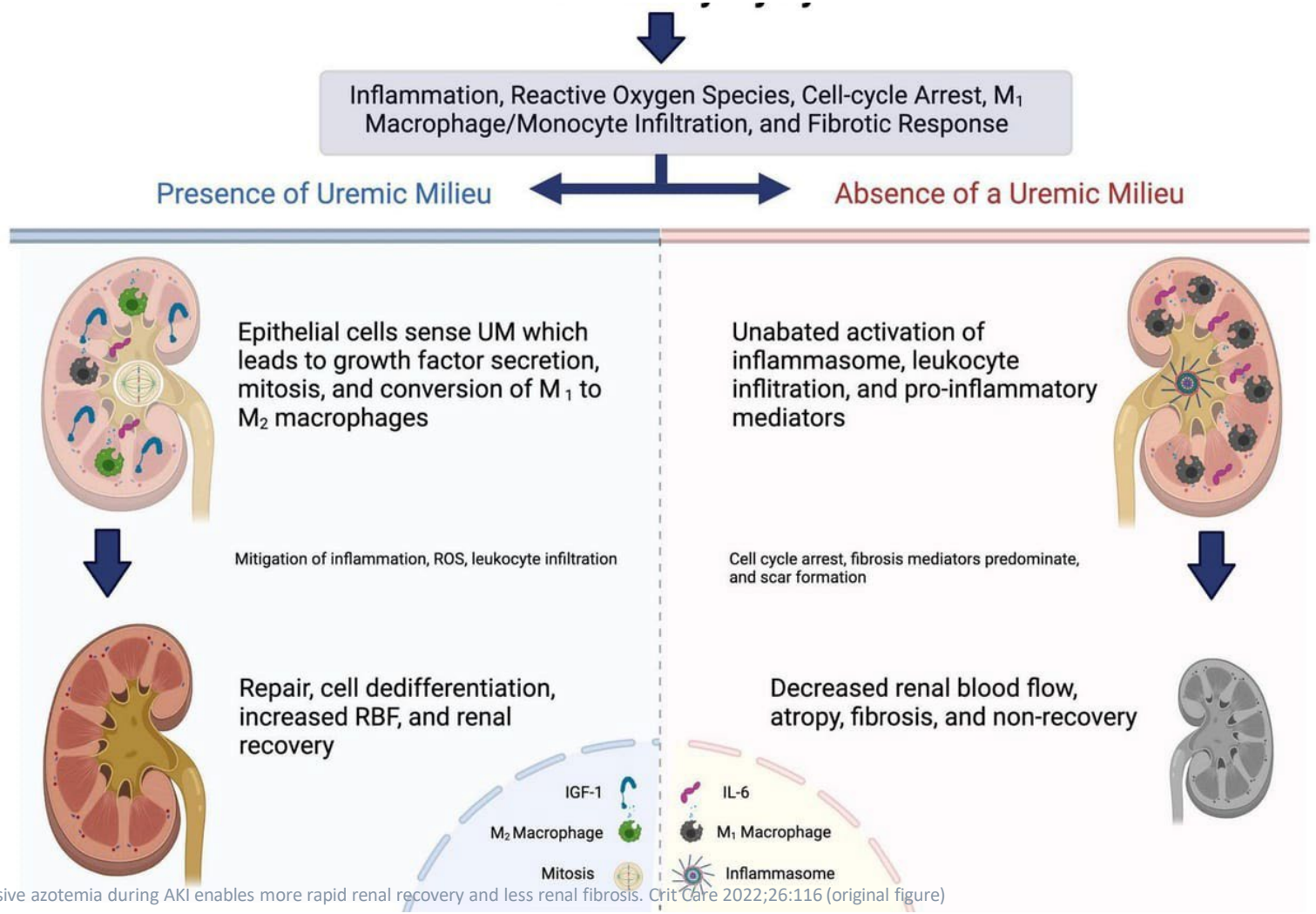
→ Growth-factor signaling, M1→M2 macrophage shift, mitosis → repair & recovery

Absence of Uremic Milieu

→ Unabated inflammasome activation → fibrosis, scarring, non-recovery

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Why Permissive Azotemia May Help the Kidney Recover



The hypothesis

A transient uremic milieu (controlled azotemia) may dampen inflammation after AKI.

Presence of uremic milieu

Growth-factor signaling, M1→M2 macrophage shift, mitosis → repair & recovery.

Absence of uremic milieu

Unabated inflammasome activation → fibrosis, scarring, non-recovery.

Chawla LS. Permissive azotemia during AKI enables more rapid renal recovery and less renal fibrosis. Crit Care 2022;26:116 (original figure)

SECTION 04

Permissive AKI: The Core Concept

Why the eGFR dip is the drug working, not the kidney failing

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Permissive AKI — Definition & Three Triggers

A treatment-induced creatinine rise in a therapy proven to improve long-term outcomes — tolerated, not treated.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

“Permissive AKI — ”Definition & Three Triggers

“Permissive AKI” / “permissive hypercreatinemia”: an acute, treatment-induced rise in serum creatinine (or decline in eGFR) that occurs in the context of a therapy proven to improve long-term cardiac and kidney outcomes — and is therefore tolerated rather than treated.

RAAS INHIBITORS
ACEi / ARB / ARNI / MRA

Efferent arteriolar vasodilation

↓

↓ intraglomerular pressure

↓

↑ sCr — expected & protective

SGLT2 INHIBITORS
Dapa / Empa / Cana

Tubuloglomerular feedback

↓

Afferent constriction

↓

Initial eGFR dip — expected

DECONGESTION
Loop diuretics / UF

Volume removal

↓

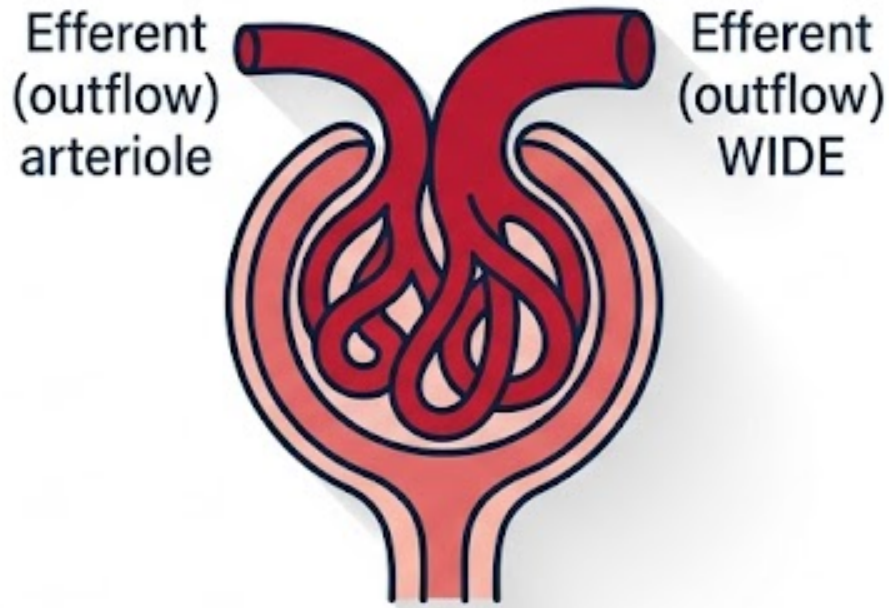
Hemoconcentration

↓

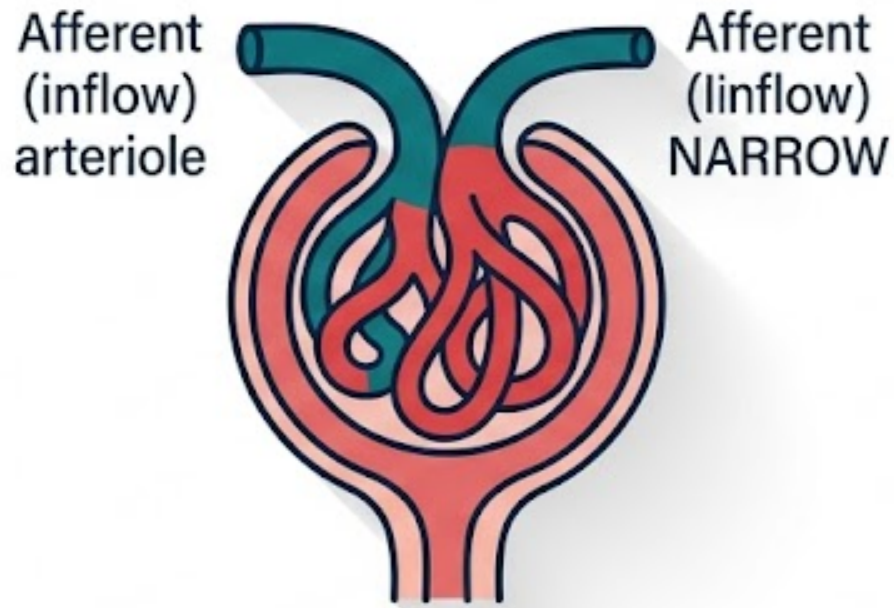
↑ sCr — pseudo-WRF

Parikh CR & Coca SG. Kidney Int 2019 · Chawla LS. Critical Care 2022 · Macedo E & Wettersten N. CJASN context · JACC HF-ARC 2024

Why the eGFR Dips: It’s Hemodynamics, Not Damage



RAAS inhibitors — efferent arteriole
DILATES → expected creatinine rise



SGLT2 inhibitors — afferent arteriole
CONSTRICTS → initial eGFR dip

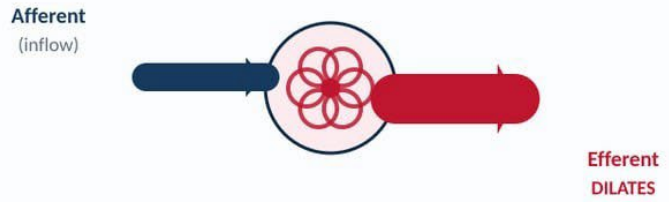
Both lower intraglomerular pressure — the dip IS the mechanism of benefit.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Why the eGFR Dips: It's Hemodynamics, Not Damage

RAAS INHIBITORS

ACEi · ARB · ARNI · MRA



Efferent (outflow) arteriole dilates

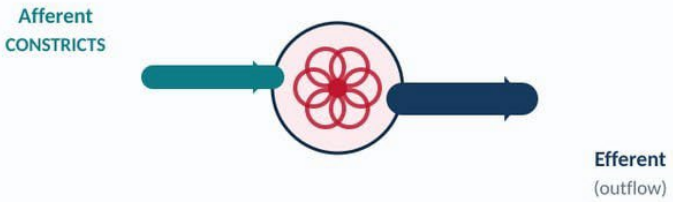
↓ intraglomerular pressure

↑ Serum creatinine

expected & protective — not damage

SGLT2 INHIBITORS

Dapagliflozin · Empagliflozin



Afferent (inflow) arteriole constricts

tubuloglomerular feedback restored

Initial eGFR dip

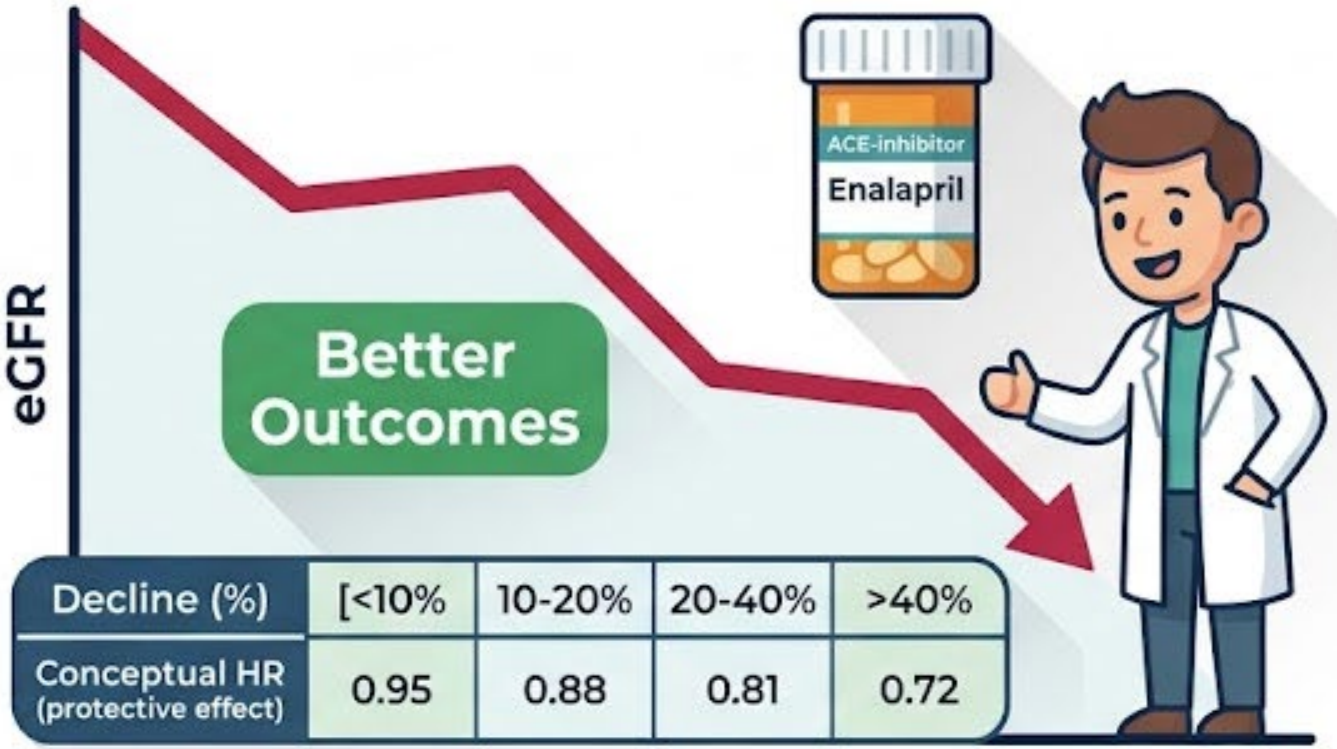
expected — then long-term protection

Both converge: ↓ intraglomerular pressure → small acute eGFR dip → long-term protection. ***The dip IS the mechanism of benefit — the tortoise beats the hare.***

Meraz-Munoz A et al. Kidney Int Rep 2021 ("tortoise & the hare") · Heerspink HJL et al. — SGLT2i mechanism · Bakris GL — RAASi efferent dilation

McCallum 2019 (SOLVD): eGFR Decline on Enalapril → Better Outcomes

- 6,245 HFrEF patients · enalapril vs placebo
- Even a 40% eGFR decline was linked to IMPROVED outcomes
- All hazard ratios below 1.0



Decline (%)	[<10%	10-20%	20-40%	>40%
Conceptual HR (protective effect)	0.95	0.88	0.81	0.72

Do not stop enalapril for a rising creatinine in HFrEF.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

SECTION 04 · EVIDENCE 1

McCallum 2019: eGFR Decline on Enalapril → Better Outcomes

SOLVD trial re-analysis · 6,245 HFrEF patients · enalapril vs placebo · **even a 40% eGFR decline was associated with IMPROVED outcomes.**

Reference group	% eGFR decline	All-cause mortality HR (95% CI)	HF hospitalization HR (95% CI)
Point a — "Magnified"	40% decline	**0.77 (0.62–0.96)**	**0.55 (0.43–0.70)**
Point b — "Intermediate"	15% decline	**0.86 (0.77–0.97)**	**0.67 (0.51–0.88)**
Point c — "Conservative"	10% decline	**0.87 (0.77–0.99)**	**0.78 (0.61–0.98)**

Read the HRs

Every hazard ratio is **below 1.0** — more drug-driven eGFR decline tracked with MORE benefit, not harm.

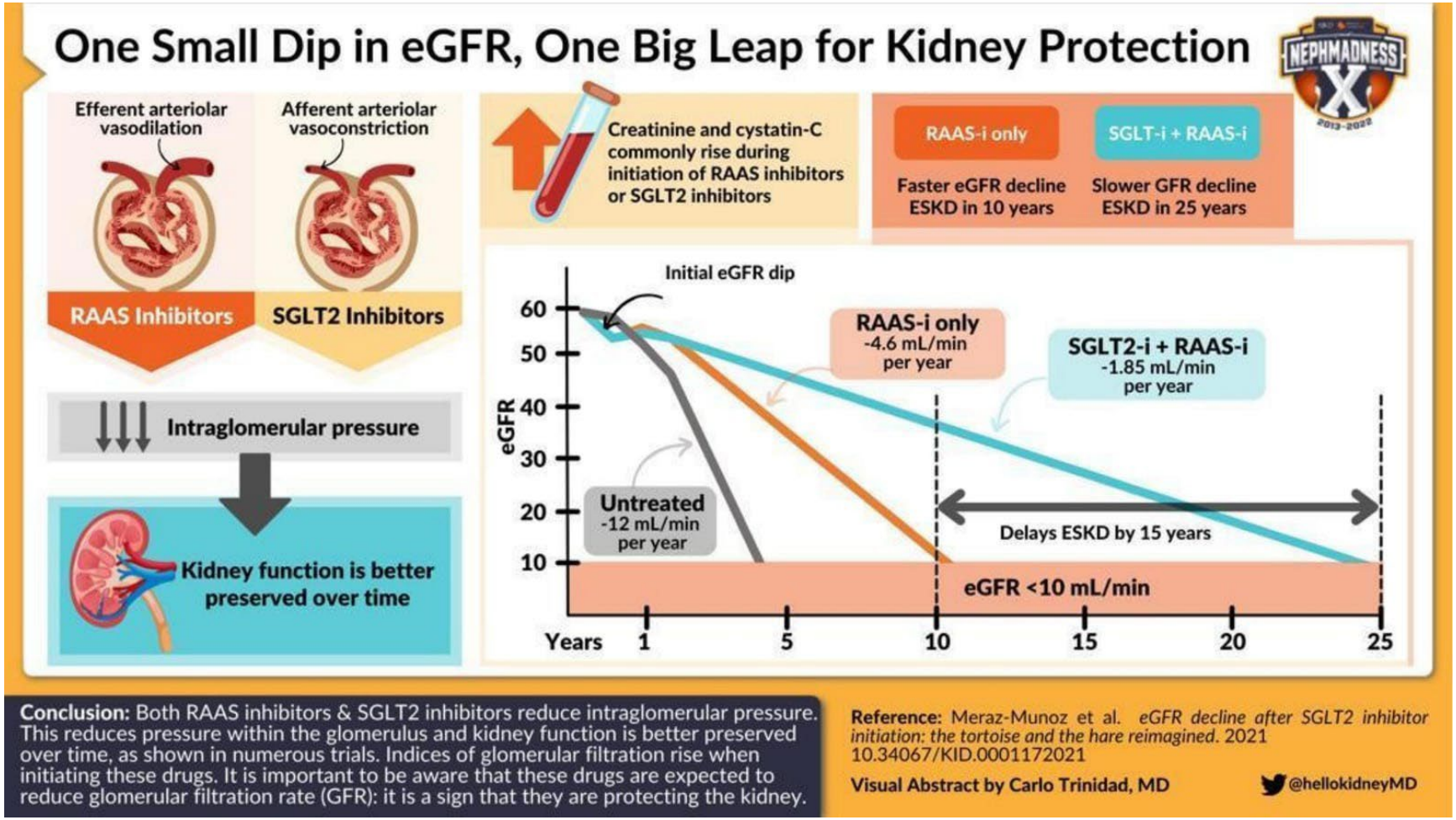
Do not stop enalapril for a rising creatinine in HFrEF.

Bottom line: In HFrEF, compelling reasons beyond a moderate acute eGFR decline ought to be present before ACE-inhibitor therapy is withdrawn.

McCallum W, Tighiouart H, Ku E, Salem D, Sarnak MJ. Kidney Int 2019;96(5):1185–1194 (SOLVD re-analysis)

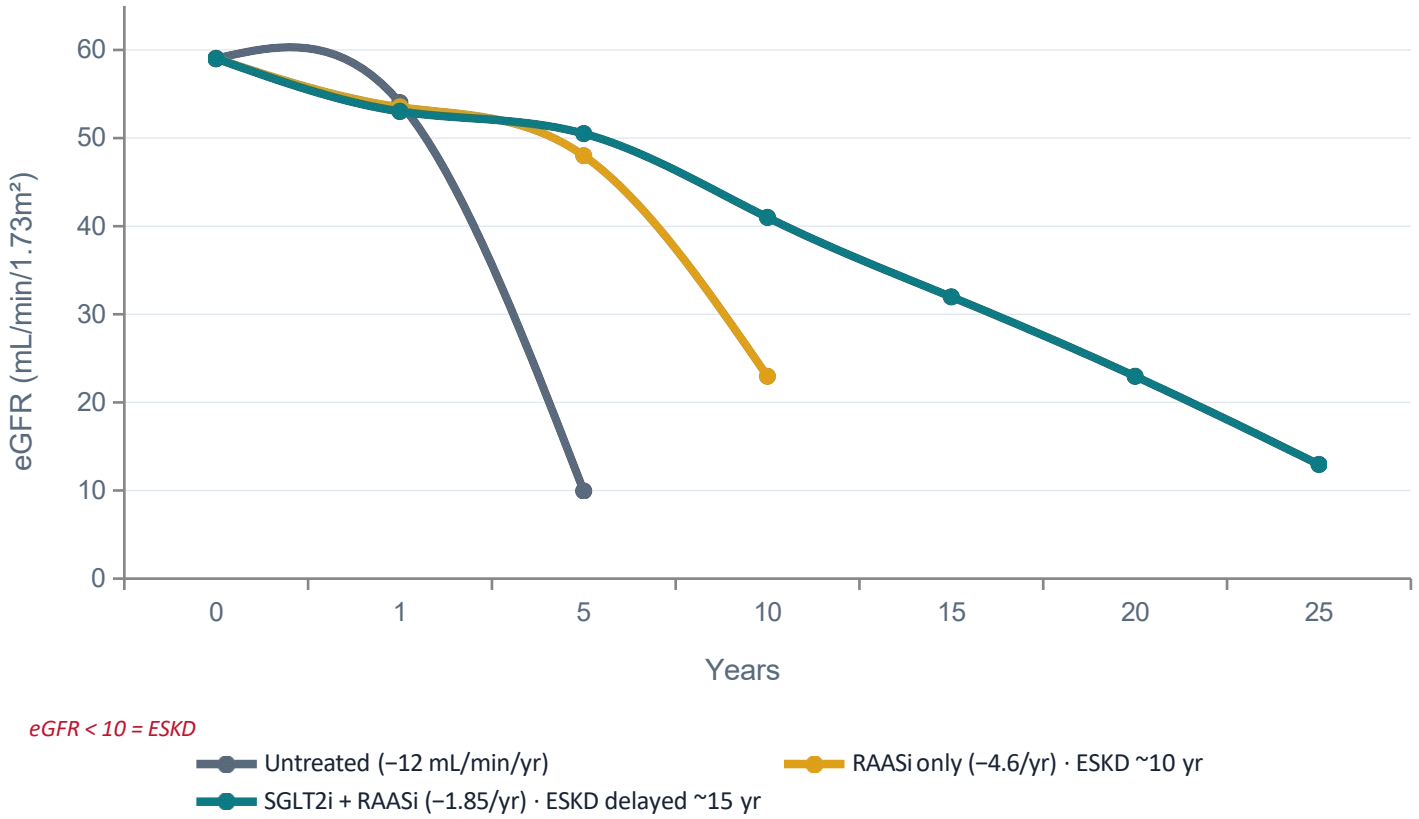
Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Both RAASi & SGLT2i Lower Intraglomerular Pressure



Meraz-Munoz A et al. eGFR decline after SGLT2i initiation: the tortoise & the hare reimagined. Kidney Int Rep 2021 · Visual abstract: Carlo Trinidad MD (@hellokidneyMD)

One Small Dip → One Big Leap for Kidney Protection



The initial dip is expected

It is NOT damage — do not stop the medication.

Slower decline wins

Treated kidneys decline far slower; ESKD is delayed by ~15 years.

The tortoise beats the hare

A worse-looking early number buys far better long-term outcomes.

Schematic adapted from Meraz-Munoz A et al. Kidney Int Rep 2021 · CREDENCE / DAPA-CKD / EMPA-KIDNEY (illustrative trajectories)

RAAS + SGLT2: A Marriage of Complementary Mechanisms

Efferent Dilation (RAASi)

↓ Afterload
↓ Filtration fraction
↓ Albuminuria

Afferent Constriction (SGLT2i)

↓ Preload
↓ Volume overload
↓ Intraglomerular pressure

Dual Protection

The combination hits all three key cardiorenal targets simultaneously:

1. Heart:
↓ stress,
preload, afterload

2. Glomerulus:
↓ intraglomerular
pressure & proteinuria

3. Tubule:
↓ energy demand
& metabolic stress

The eGFR dip is a small price for global cardiorenal protection.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

The Tortoise & the Hare: Slower Decline Wins

A worse-looking early number buys a much longer kidney lifespan.

START
(diagnosis)

Tortoise = TREATED (RAASi + SGLT2i)
- **–1.85** mL/min/yr
- ESKD delayed **~15 yr**

Hare = UNTREATED
- –12 mL/min/yr
- ESKD fast

ESKD
(dialysis)

A worse-looking early number buys a much longer kidney lifespan.

Dr. Mohammadtaghi Najafi – Associate Professor of Nephrology, TUMS

Numeric Thresholds for RAAS-Inhibitor Management

CONTINUE

Rise ≤ 50%
- creatinine ≤ 3.0 mg/dL
- eGFR ≥ 25

REDUCE DOSE

Rise 50–100%
- creatinine 3.0–3.5
- potassium > 5.5

HOLD

Rise > 100%
- creatinine > 3.5
- eGFR < 20
- symptomatic hypotension

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Numeric Thresholds for RAAS-Inhibitor Management

CONTINUE
Permissive zone

- sCr rise ≤ 50% above baseline
- sCr absolute ≤ 3.0 mg/dL (266 µmol/L)
- eGFR ≥ 25 mL/min/1.73m²
- No electrolyte disturbance
- Clinical status stable / improving

Continue · monitor sCr + K^+

REDUCE DOSE
Caution zone

- sCr rise 50–100% above baseline
- sCr 3.0–3.5 mg/dL
- eGFR 20–25 mL/min/1.73m²
- Serum K^+ > 5.5 mEq/L
- Look for precipitants

Reduce dose · treat precipitant

HOLD
Stop temporarily

- sCr rise > 100% above baseline
- sCr > 3.5 mg/dL (310 µmol/L)
- eGFR < 20 mL/min/1.73m²
- Symptomatic hypotension
- Suspect bilateral renal-artery stenosis

Hold · rechallenge when resolved

Brenner & Rector, The Kidney 2020, Ch. 40 — Cardiorenal Syndrome · Parikh CR & Coca SG. Kidney Int 2019 · UpToDate (HFrEF) 2025

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

SECTION 05

What's New: 2025–2026

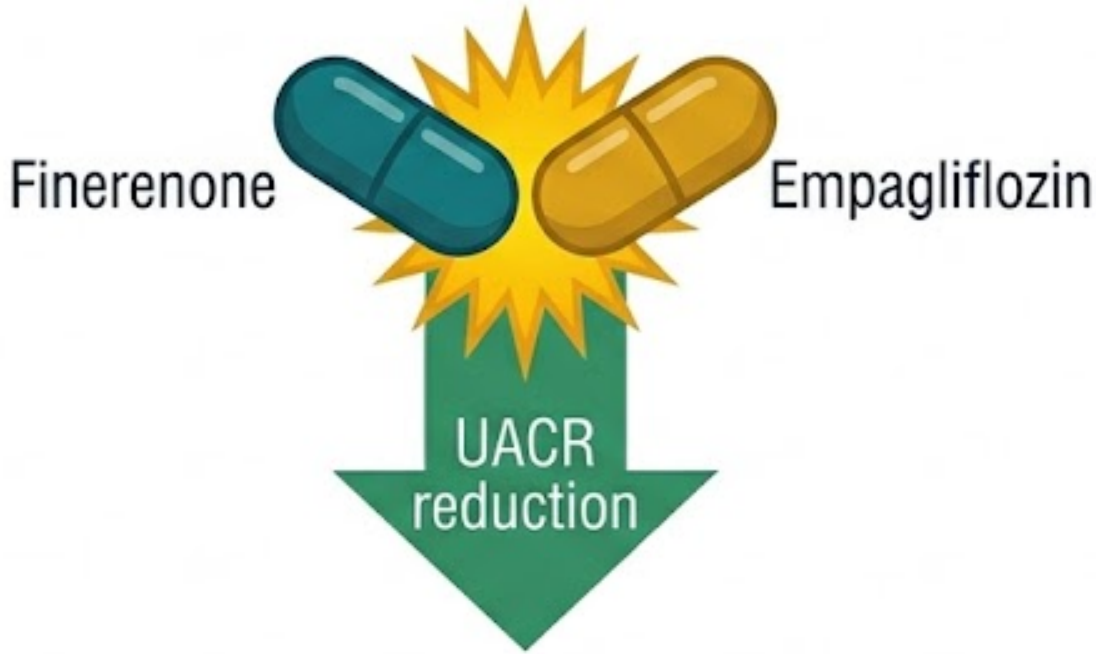
CONFIDENCE, the KDIGO heart-failure consensus, and biomarkers

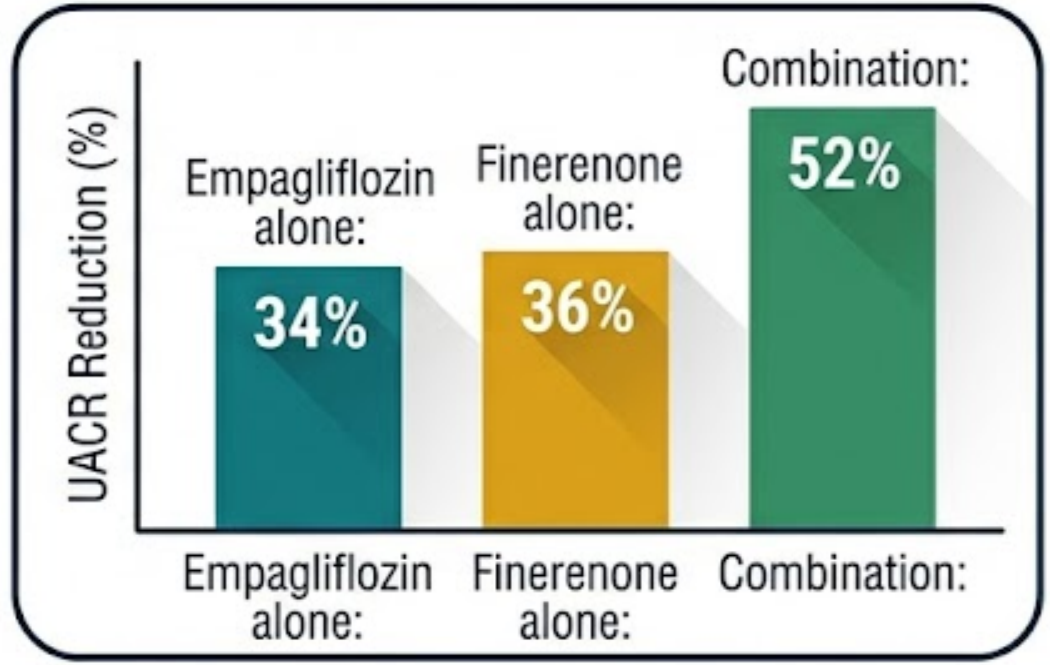
CONFIDENCE, the KDIGO heart-failure consensus, and biomarkers

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

CONFIDENCE: Finerenone + Empagliflozin (NEJM 2025)

Phase 2 RCT · 818 randomized (790 evaluable) · CKD + type 2 diabetes



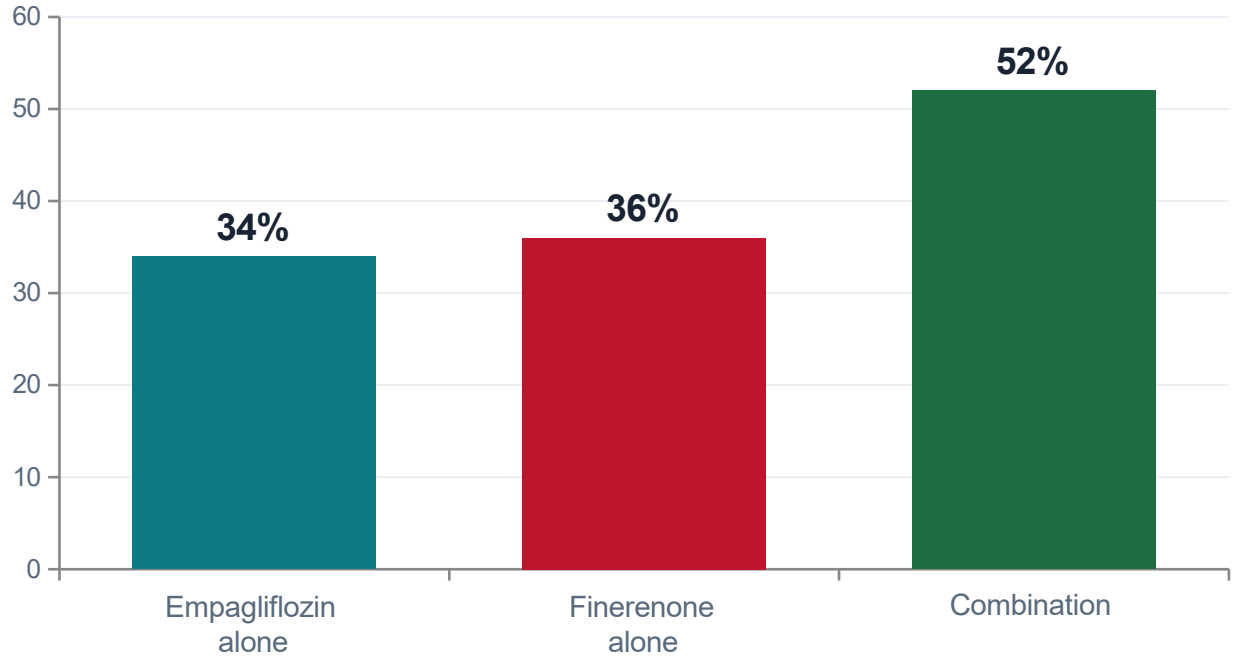


Additive benefit — start them together.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

CONFIDENCE: Finerenone + Empagliflozin (NEJM 2025)

Agarwal R et al. N Engl J Med 2025 · ERA 2025 (Vienna) · **Phase 2 RCT · 818 randomized (790 evaluable) · CKD + type 2 diabetes · simultaneous initiation**



52% UACR reduction

with the combination — vs 34–36% for either drug alone.

Additive, not redundant

+29% vs finerenone alone; +32% vs empagliflozin alone (both p<0.001). Complementary pathways.

Start them together

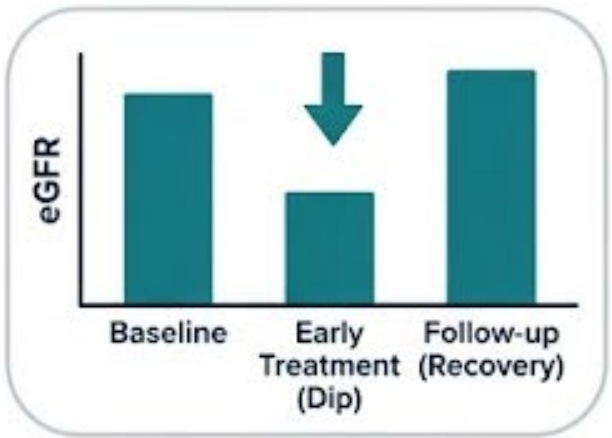
Simultaneous initiation is now evidence-based — no need to wait and add stepwise.

Agarwal R, Green JB, Heerspink HJL, et al. Finerenone with empagliflozin in CKD and type 2 diabetes. N Engl J Med 2025;393(6):533–543

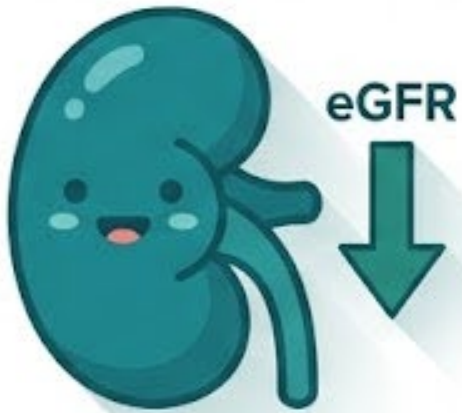
CONFIDENCE: The eGFR Dip Is Permissive, Not AKI

✓ **safe / hemodynamic**

All three arms show an early eGFR dip — all hemodynamic



true AKI damage



a early eGFR dip

AKI rate stayed **under 2% even** with the combination

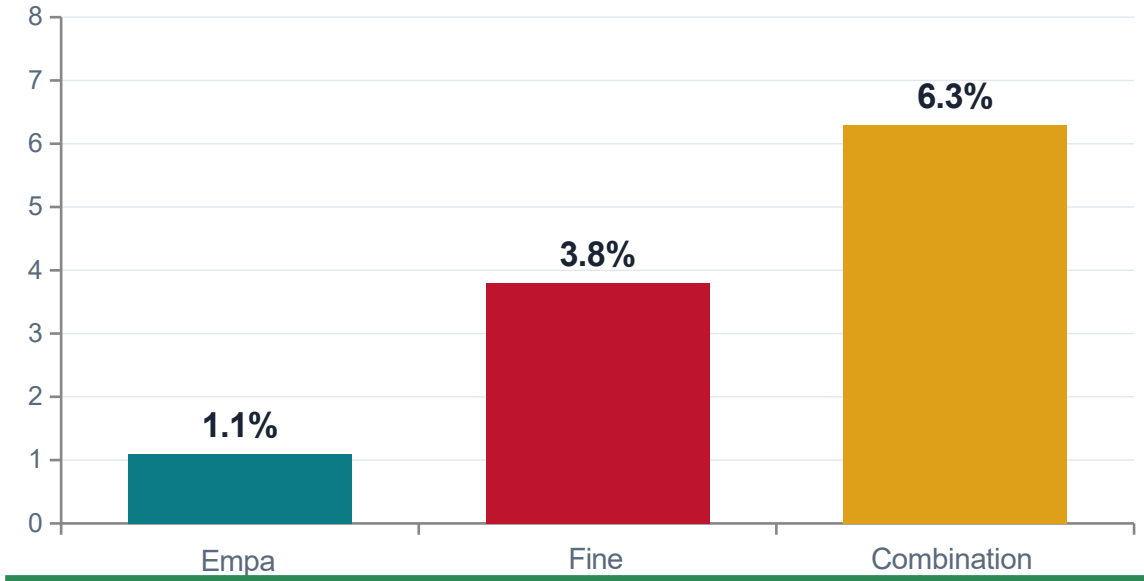
No unexpected safety signals

The dip should not deter use of this renoprotective therapy.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

CONFIDENCE: The eGFR Dip Is Permissive, Not AKI

Early eGFR decline ≥30% (day 30) — hemodynamic / permissive



ACTUAL AKI EVENTS (N = 790 evaluable)

- Empagliflozin alone: 0.0% (0 patients)
- Finerenone alone: ~1.1%
- Combination: <2%

No unexpected safety signals across arms.

Conclusion: All three arms show an early eGFR dip — all are hemodynamic. AKI rate stays under 2% even with the combination. The dip should not deter use of this renoprotective therapy.

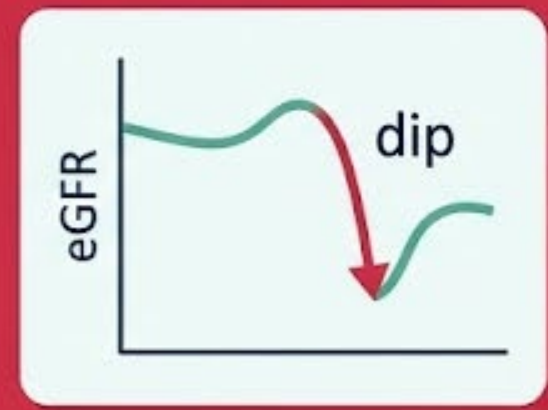
Agarwal R et al. NEJM 2025 · ERA 2025 LBA (Vienna) · Vaduganathan M et al. NDT 2025 (kidney-risk spectrum analysis)

The Clinical Dilemma: Benefit vs the “Dip”

The Benefit

Simultaneous finerenone + empagliflozin improves UACR reduction in CKD + type 2 diabetes.

The Barrier



But the combination precipitates an acute eGFR decline — the “dip”.

Is the dip a sign of injury — or of pharmacodynamics? (Agarwal, JASN 2026)

The Clinical Dilemma: Benefit vs the “Dip”

THE BENEFIT

Simultaneous initiation of finerenone + empagliflozin improves UACR reduction in people with CKD and type 2 diabetes.

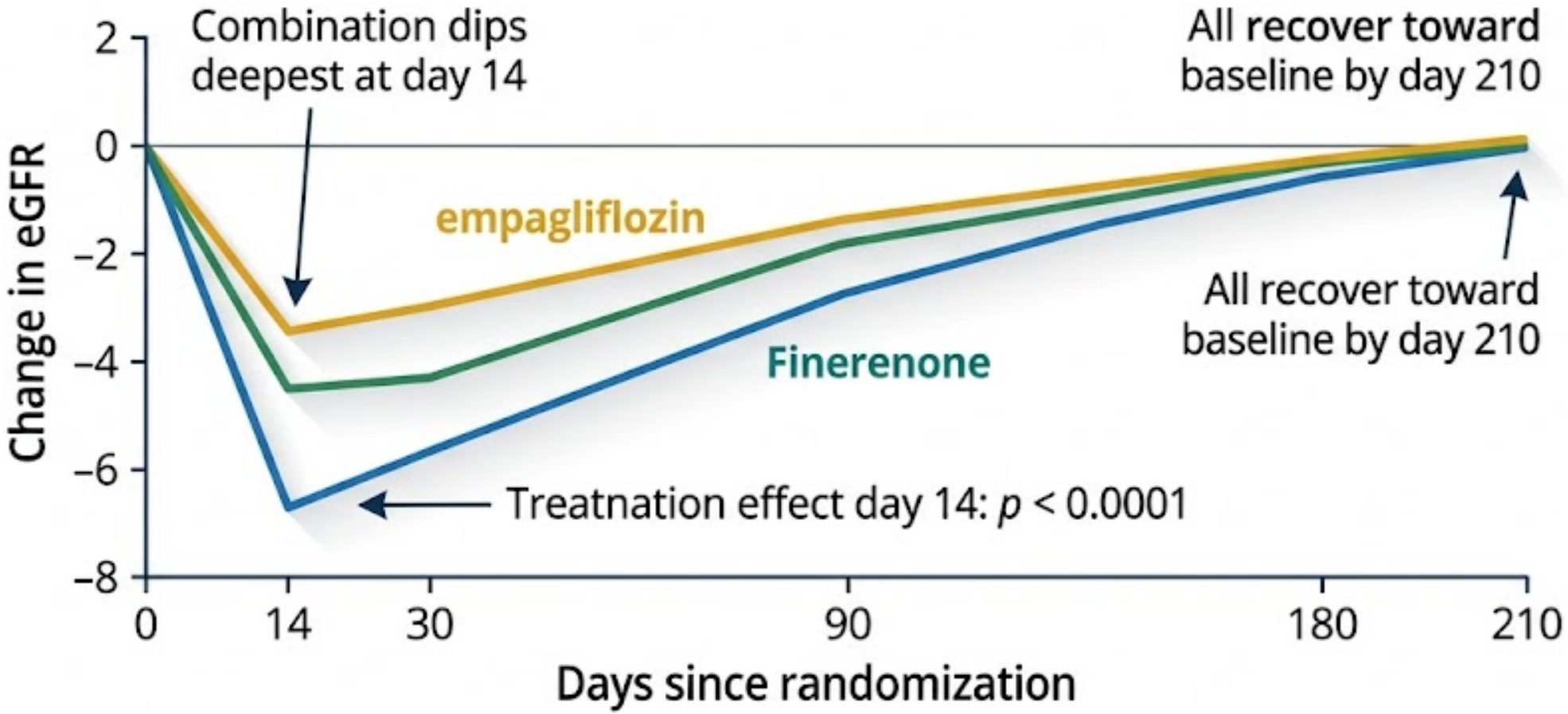
THE BARRIER

But combination therapy precipitates an acute eGFR decline — the “dip” — that often frightens clinicians into stopping therapy.

The question Agarwal answered (JASN 2026):
Is the dip a sign of injury — or of pharmacodynamics? Using the CONFIDENCE trial, he characterized the acute eGFR decline (>30% to day 14), its drivers, its reversibility, and whether it mediates the albuminuria benefit.

Agarwal R et al. Acute eGFR changes and mediation of albuminuria reduction. J Am Soc Nephrol 2026 · WCN'26 (ISN, Yokohama, March 2026)

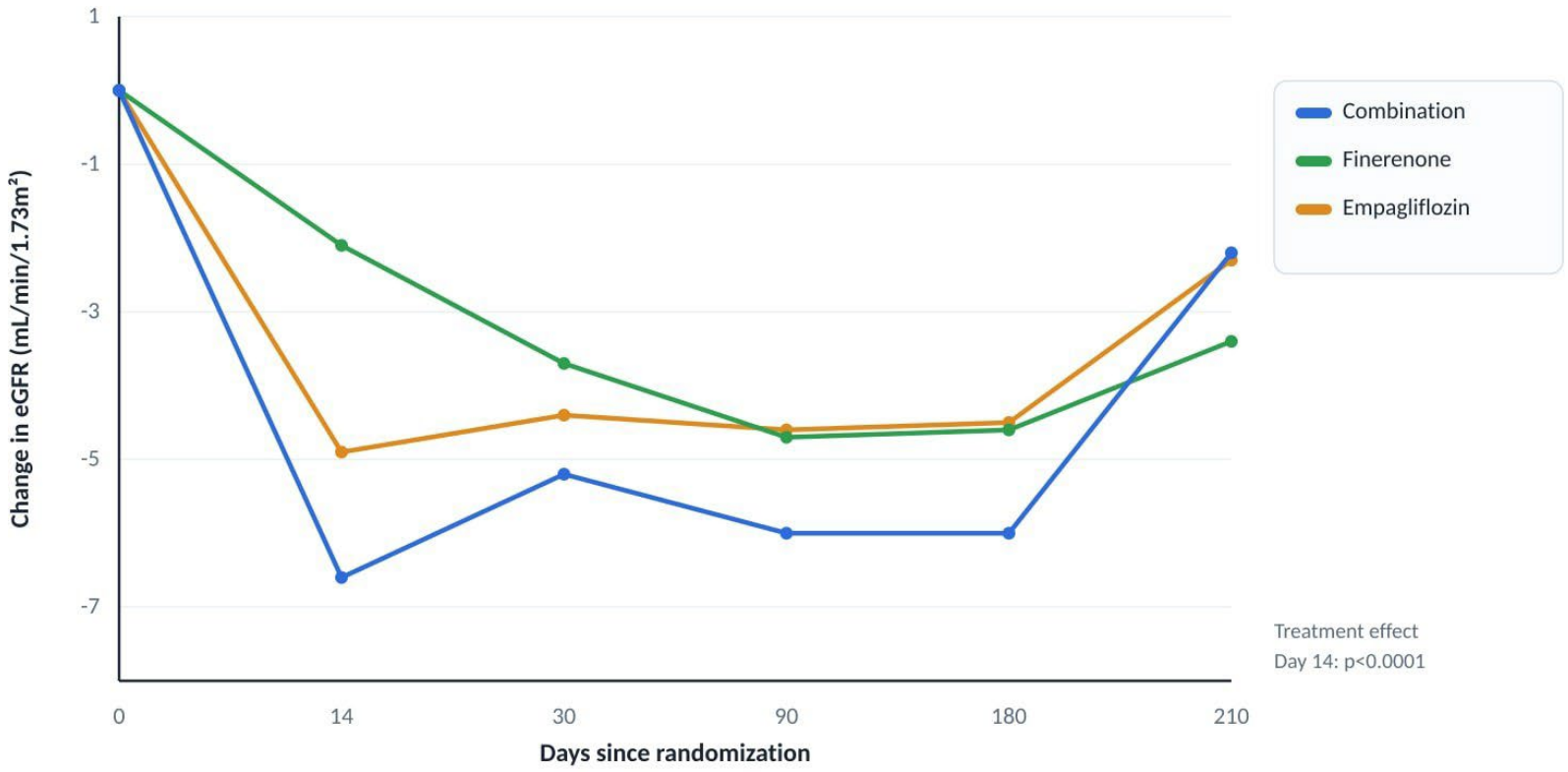
eGFR Trajectories Differ by Treatment — and Reverse



Reversibility is the hallmark of a hemodynamic, not structural, change.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

eGFR Trajectories Differ by Treatment — and Reverse



The dip is real and largest with combination

~6–7 mL/min drop at day 14 with combination (treatment effect p<0.0001).

It is reversible

All arms recover toward baseline by day 210 (after washout) — a hallmark of a hemodynamic, not structural, change.

Different drugs, different shapes

Finerenone and empagliflozin curves differ, but all return — the dip tracks pharmacodynamics.

Agarwal R et al. J Am Soc Nephrol 2026 (CONFIDENCE eGFR analysis) · WCN'26, ISN Yokohama — trajectory schematic redrawn for teaching

Know the Drivers: Higher eGFR & Diuretics — Not BP

Higher baseline eGFR — OR 1.24 per 10 mL/min higher (95% CI 1.11–1.39; p=0.0001)

Diuretics & combination therapy — the dip is most pronounced

NOT blood pressure — SBP does not associate (day-14 p=0.053)

The best kidney function dips the most — most room to unload.
The dip is glomerular unloading, not damage.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Know the Drivers: Higher eGFR & Diuretics — Not BP

HIGHER BASELINE eGFR

Probability of an acute eGFR decline rises with higher baseline eGFR.

OR 1.24 per 10 mL/min higher (95% CI 1.11–1.39; p=0.0001)

DIURETIC USE & COMBINATION

The dip is most pronounced with combination therapy and in patients on diuretics.

Greatest with combination + background diuretics

NOT BLOOD PRESSURE

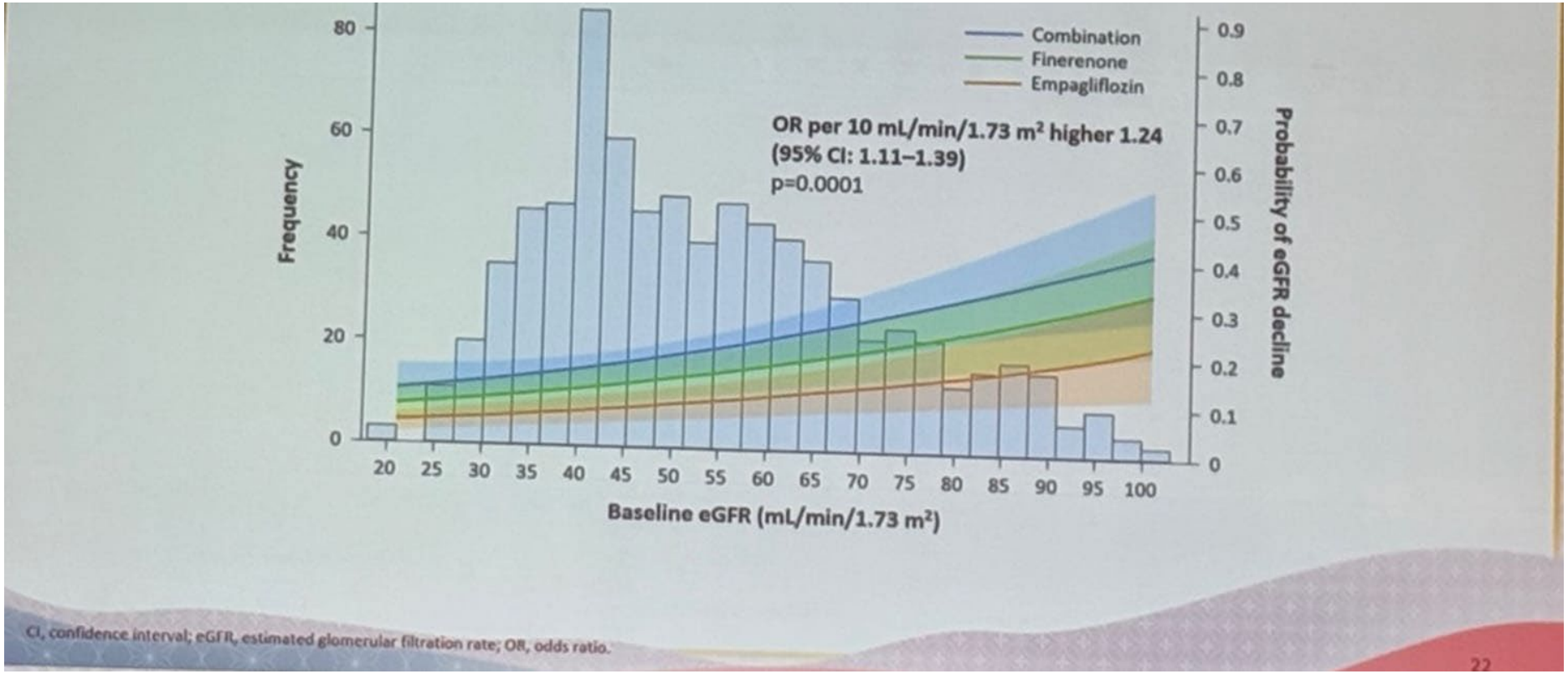
Baseline systolic BP does NOT associate with the acute eGFR decline or its trajectory.

SBP effect day 14: p=0.053
SBP × visit interaction: p=0.38

Counterintuitive but key: the patients with the BEST kidney function dip the most — because they have the most hemodynamic "room" to unload. The dip is glomerular unloading, not damage.

SECTION 05 · CONFIDENCE — THE DATA

Probability of eGFR Decline Rises with Higher Baseline eGFR



The curves

For all three arms, the probability of an acute eGFR decline climbs as baseline eGFR increases.

The number

OR 1.24 per 10 mL/min higher baseline eGFR (95% CI 1.11–1.39; p=0.0001).

The meaning

More filtration reserve = more room to unload. Highest-eGFR patients dip most — and tolerate it best.

Agarwal R et al. J Am Soc Nephrol 2026 — figure presented at WCN'26 (ISN, Yokohama, March 2026)

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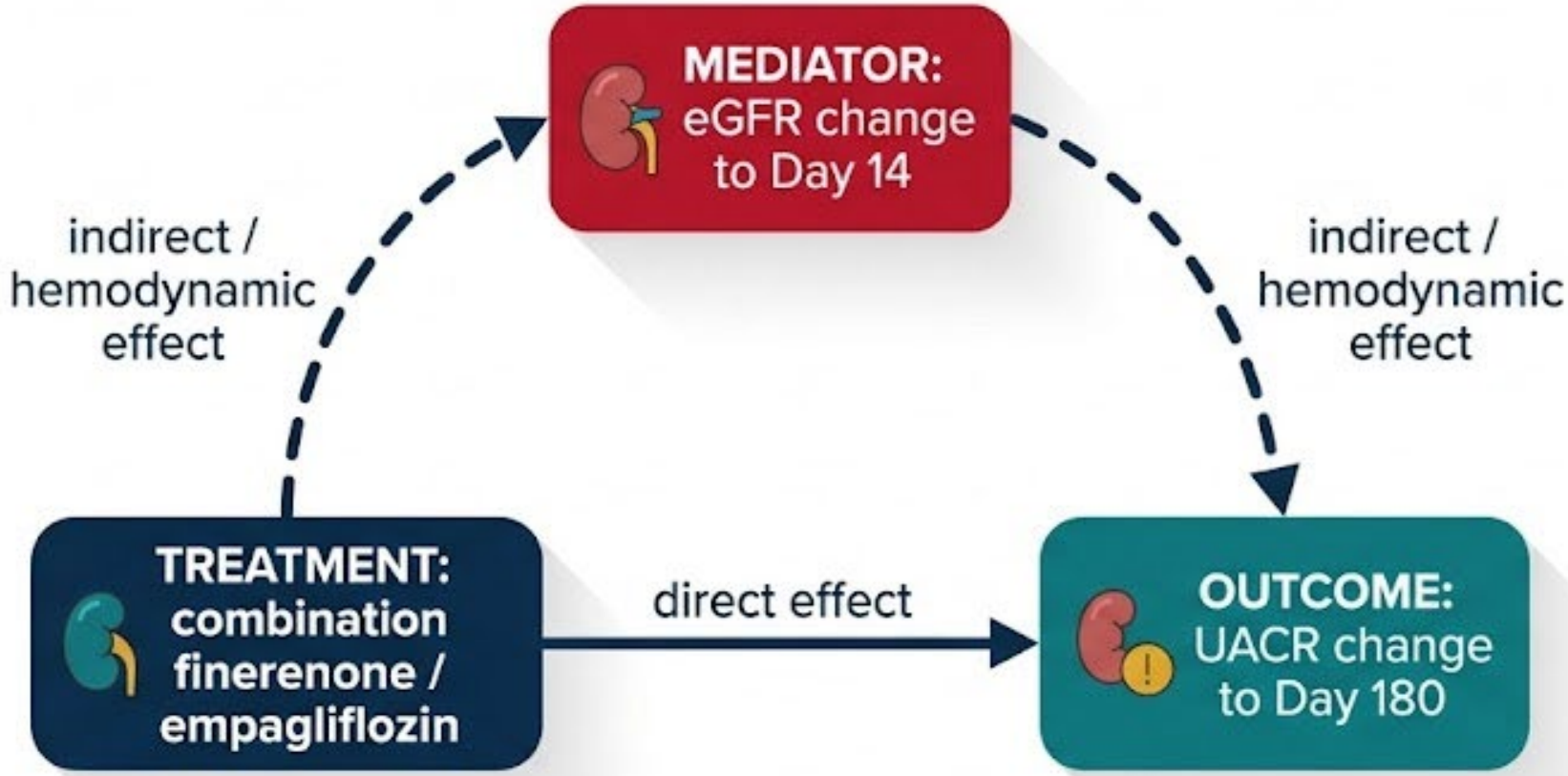
Is the Albuminuria Benefit Driven by the Dip?

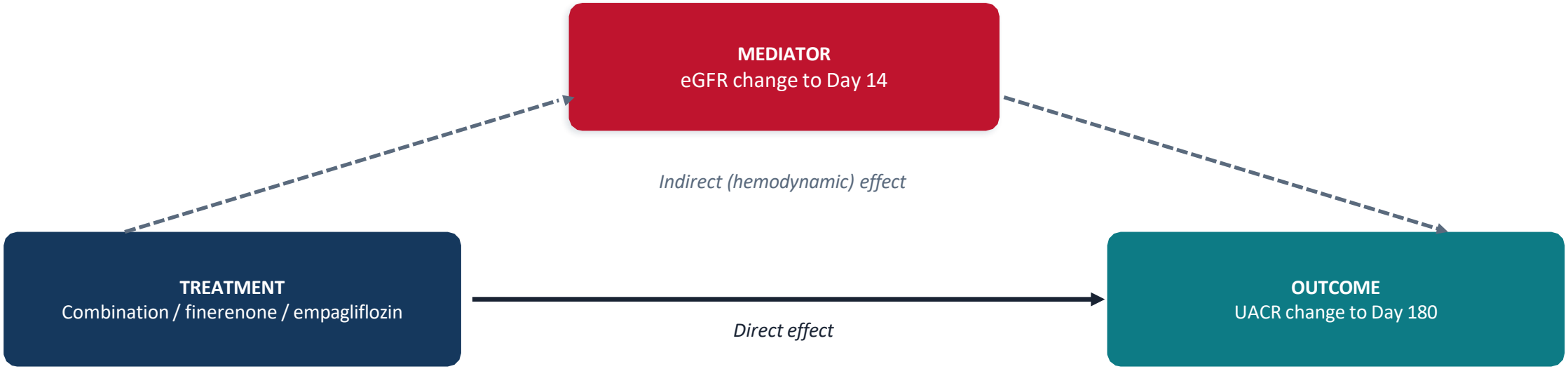


Empagliflozin: ~28% of UACR lowering is mediated by eGFR change — partly hemodynamic

Finerenone (added): only ~5% — its benefit is essentially NONhemodynamic

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Is the Albuminuria Benefit Driven by the Dip?



Empagliflozin

~28% of its UACR lowering is mediated by the eGFR change — partly hemodynamic.

Finerenone (added)

Only ~5% mediated by eGFR change — its additive UACR benefit is essentially NONhemodynamic.

Agarwal R et al. J Am Soc Nephrol 2026 (CONFIDENCE mediation analysis) · method: Lee H et al. JAMA 2021;326:1045 · WCN'26

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Pharmacodynamics, Not Failure

1

Expect the drop — the acute eGFR decline is glomerular unloading

2

Know the drivers — high baseline eGFR and diuretics, not blood pressure

3

Monitor, don't stop — watch potassium (≥30% dip ≈ 2× hyperkalemia risk), continue therapy

Maintain confidence in the combination to preserve long-term kidney function.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

SECTION 05 · AGARWAL'S BOTTOM LINE

Pharmacodynamics, Not Failure

1

EXPECT THE DROP

The acute eGFR decline is a sign of glomerular unloading — anticipate it.

2

KNOW THE DRIVERS

Driven by high baseline eGFR and diuretics — not by blood pressure.

3

MONITOR, DON'T STOP

Monitor potassium (≥30% dip ≈ 2× hyperkalemia risk), but continue therapy as appropriate.

"Maintain confidence in the combination to preserve long-term kidney function." The dip reflects how the drugs work — not that the kidney is failing.

Agarwal R. "Pharmacodynamics, not failure." WCN'26 (ISN, Yokohama, March 2026) · based on Agarwal R et al. J Am Soc Nephrol 2026

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Key Takeaways

1.

Context is Everything

- Induced vs Spontaneous Rise
- ASK **WHY**, not just **HOW MUCH**.

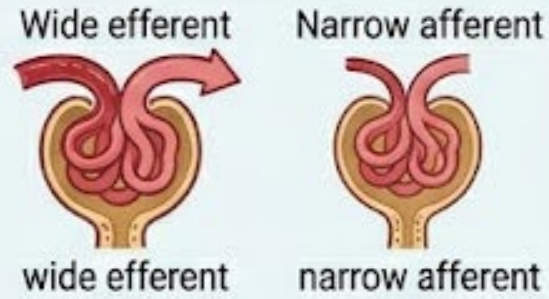
induced green & induced/spontaneous

2.

Tolerated RISE, Not DAMAGE

- GFR dips are accepted for therapeutic benefit.
- tolerated for drug effectiveness

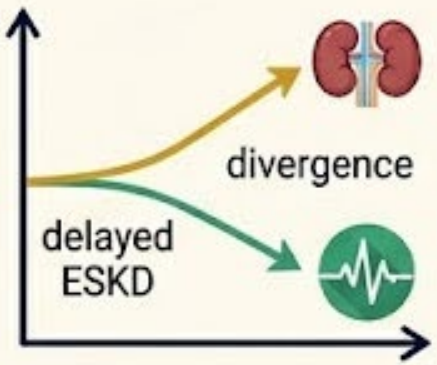
3.



Hemodynamics vs True AKI

- Hemodynamic dips are reversible & often signal beneficial reduction in intraglomerular pressure.

4.



Focus on Long-Term Protection

- Small early GFR dip buys years & decades of lifespan before ESKD.

5.

Structured Management

- Use thresholds (creatinine, GFR, potassium).
- Don't hold tment unnecessarily.
- Maintain treatment for benefit.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

SECTION 05 · KDIGO 2026 CONSENSUS

KDIGO Heart Failure & Kidney Disease — Key Messages

Conference March 2024 · executive report 2026 in Kidney International & JACC: Heart Failure

1. **Small declines, keep going** — Small kidney-function declines after starting guideline-directed HF therapy generally do NOT require stopping it — they are usually hemodynamic and not linked to poor outcomes.

2. **Decongest first** — Persistent congestion — not the creatinine — is the true risk marker. Prioritize decongestion over preserving the number.

3. **Look beyond creatinine** — Assess cystatin C alongside sCr (less confounded by muscle mass); NGAL & KIM-1 help separate functional from structural injury.

4. **The four pillars apply** — SGLT2i, RAASi, finerenone and GLP-1 RA all benefit both HF and CKD; the initial eGFR dip is expected and not a contraindication.

5. **Advanced CKD: individualize** — Evidence in eGFR <30 remains limited — individualize, but do not reflexively stop SGLT2i / RAASi in this group.

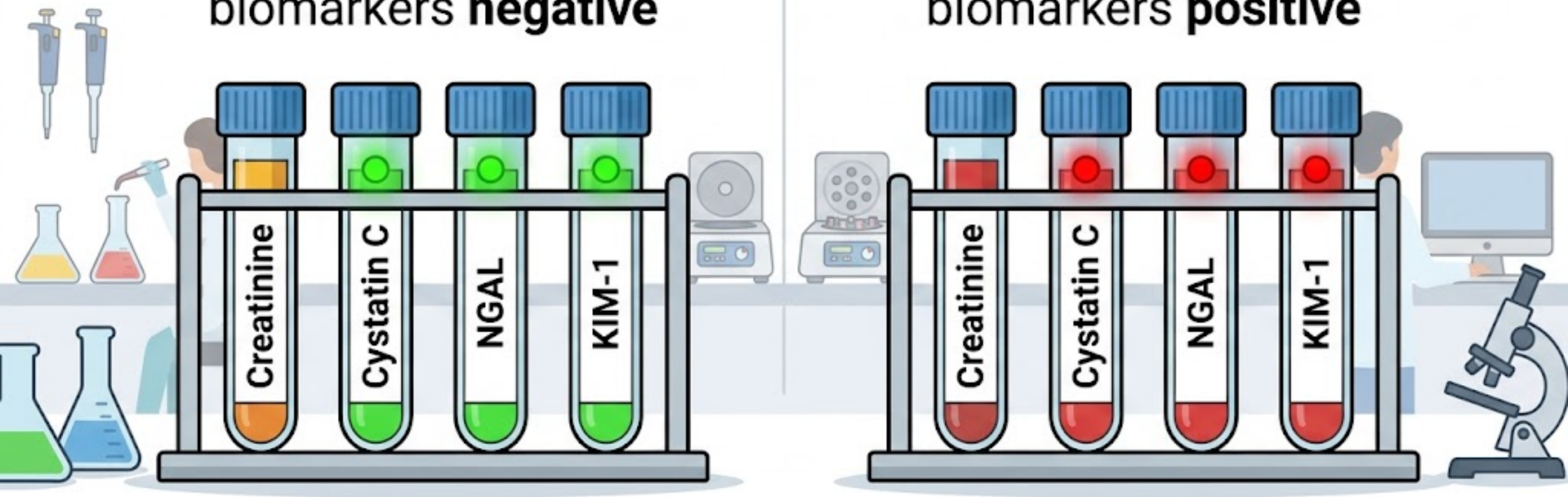
Lam CSP, Bozkurt B, Cherney DZI, et al. Kidney disease and heart failure: conclusions from a KDIGO Controversies Conference. Kidney Int / JACC Heart Fail 2026

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Beyond Creatinine: Permissive vs True AKI

Permissive (functional): biomarkers **negative**

True AKI (structural): biomarkers **positive**



Tip: All negative → continue therapy. Any positive → investigate.

SECTION 05 · BIOMARKERS

Beyond Creatinine: Telling Permissive from True AKI

Biomarker	What it reflects	Permissive (functional)	True AKI (structural)
Serum creatinine	Filtration (delayed, muscle-dependent)	**↑ (hemodynamic)**	**↑ (with damage)**
Cystatin C	Filtration, muscle-independent	**Mirrors sCr, less noise**	**↑**
NGAL	Tubular stress / injury	**Negative / low**	**Positive / high**
KIM-1	Proximal tubular injury	**Negative**	**Positive**
Urine output / FeNa	Perfusion vs intrinsic injury	**Preserved · FeNa low**	**Falling · FeNa variable**

Practical tip: When sCr rises unexpectedly, check cystatin C + NGAL + KIM-1. All negative → permissive, continue therapy. Any positive → investigate for structural injury.

AJKD Core Curriculum 2025 · KDIGO 2026 (Kidney Int / JACC:HF) · EMPA-KIDNEY & DAPA-CKD biomarker sub-studies

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

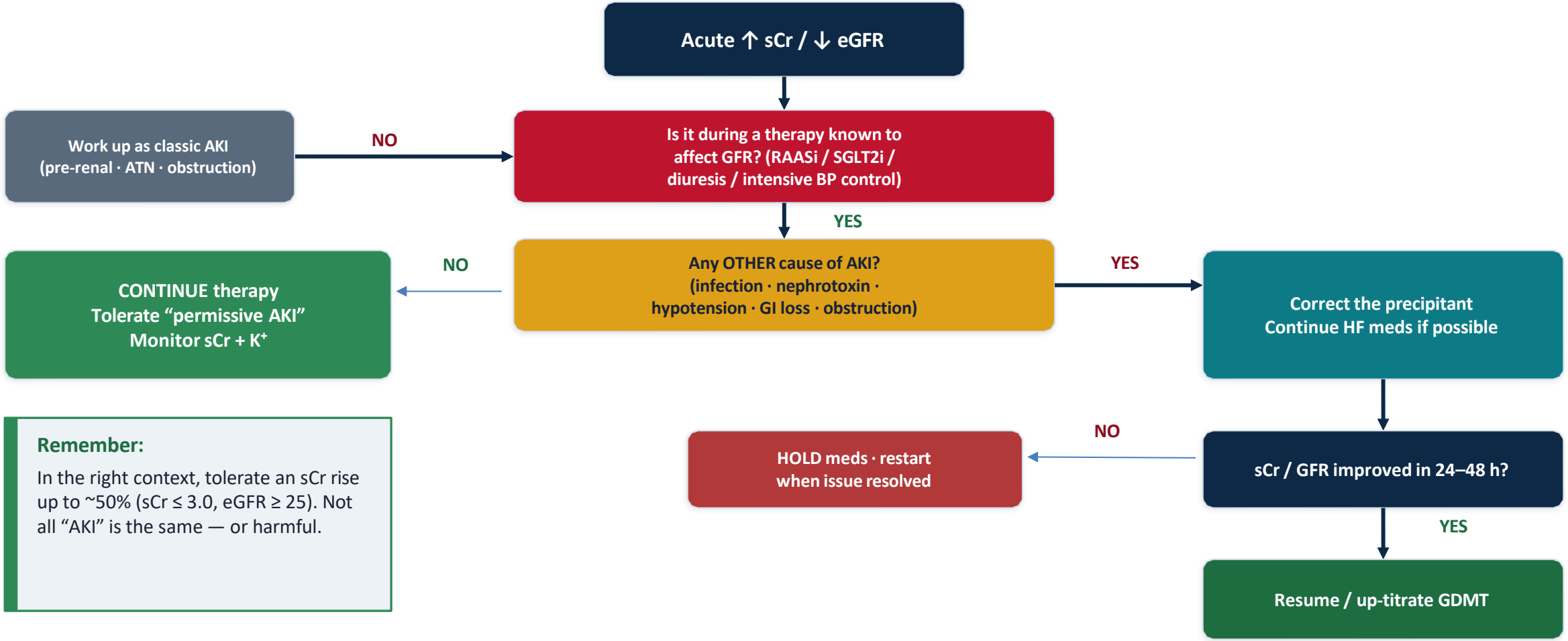
SECTION 06

At the Bedside

A decision algorithm, applied cases, and the take-home messages

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Acute ↑sCr During HF Therapy — What to Do



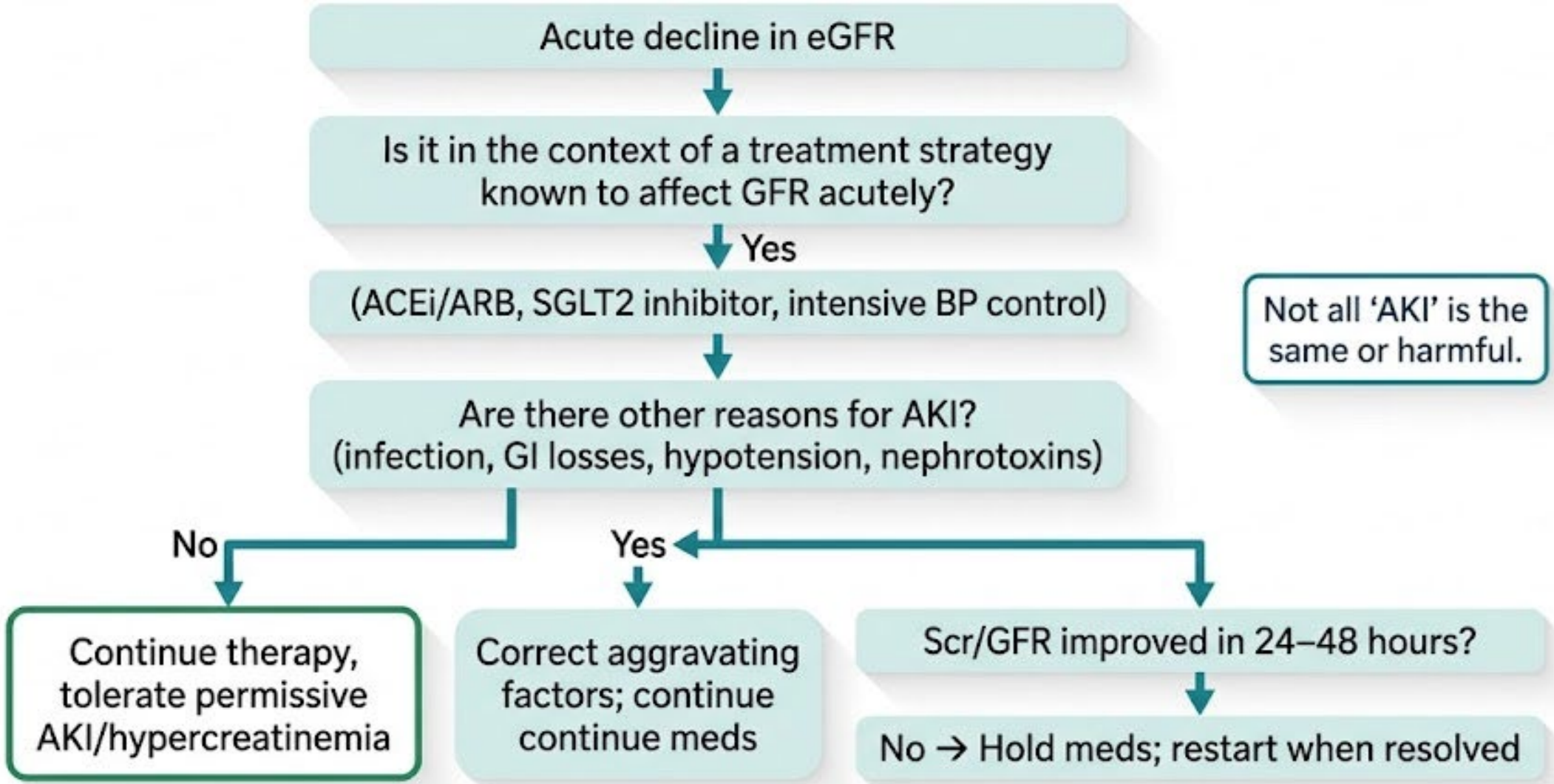
Remember:

In the right context, tolerate an sCr rise up to ~50% (sCr ≤ 3.0, eGFR ≥ 25). Not all "AKI" is the same — or harmful.

Adapted from Parikh CR & Coca SG. Kidney Int 2019 (clinical algorithm) · Brenner The Kidney 2020 · AJKD Core Curriculum 2025

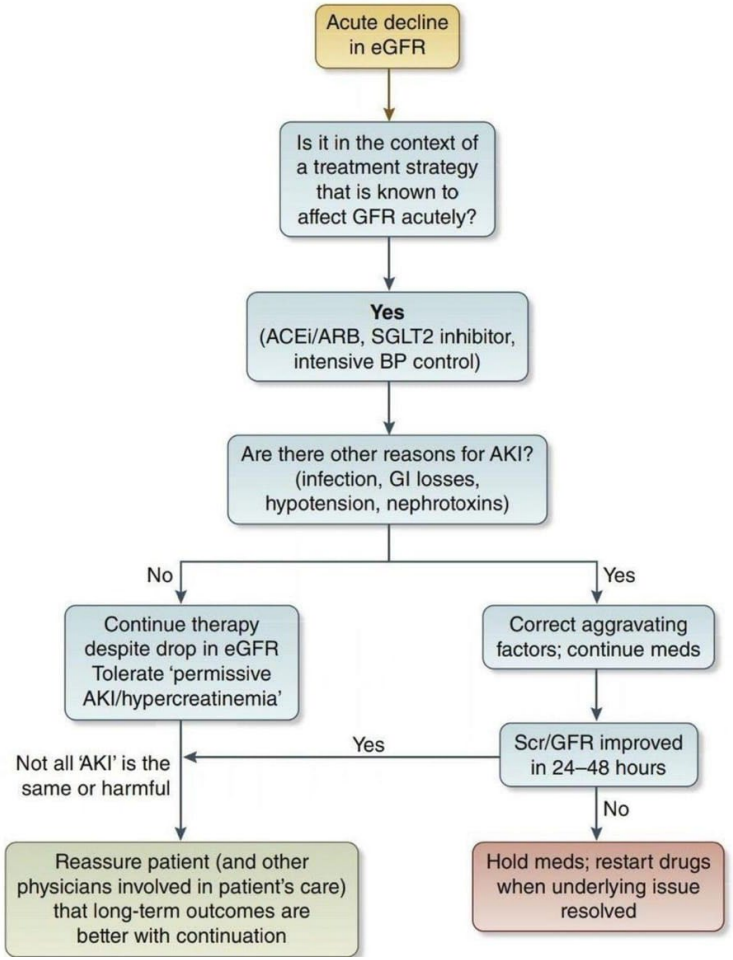
Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Parikh & Coca: Managing an Acute eGFR Decline



Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Parikh & Coca: Managing an Acute eGFR Decline



Ask the context first

Is the decline from a strategy known to affect GFR acutely (ACEi/ARB, SGLT2i, intensive BP)?

Rule out other causes

Infection, GI losses, hypotension, nephrotoxins — correct them, but keep the meds where possible.

Tolerate permissive AKI

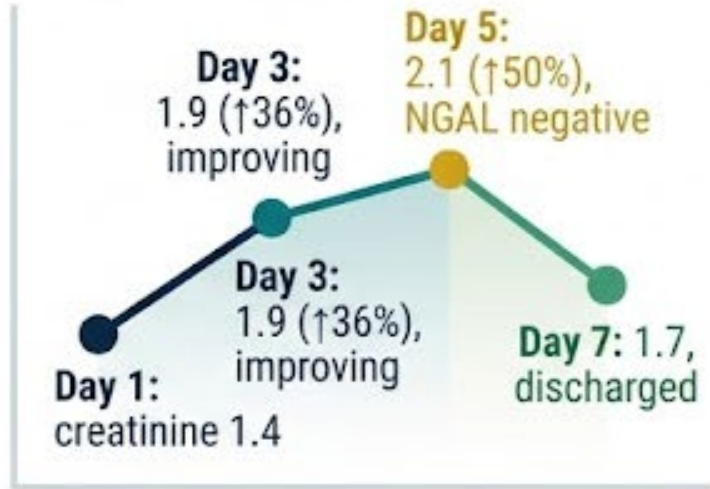
If no other cause: continue therapy, reassure patient and team — long-term outcomes are better.

When to hold

Only if Scr/GFR fails to improve in 24–48h after correcting aggravating factors.

Parikh CR & Coca SG. "Permissive AKI" with treatment of heart failure. Kidney Int 2019;96:1066–1068 (original algorithm)

Case 1 — 62 M, HFrEF, Aggressive Decongestion



Permissive AKI — continue therapy, decongest first.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

SECTION 06 · CASE 1

Case 1 — 62 M, HFrEF, Aggressive Decongestion

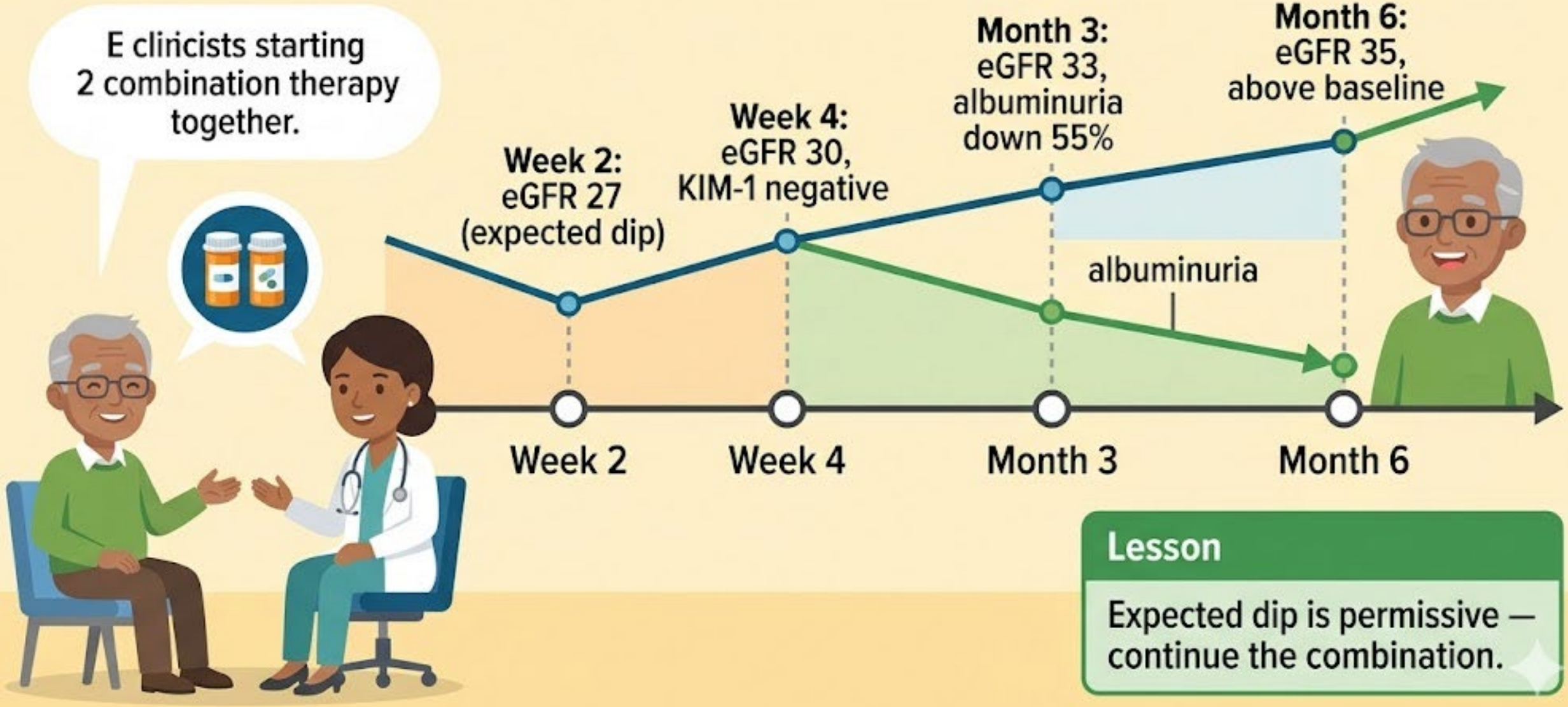
62 M · HFrEF (EF 30%) · admitted with ADHF, +8 kg, raised JVP, bibasal crepitations · on enalapril 10 mg BD + carvedilol. Baseline sCr 1.4 mg/dL.

Day 1	**sCr 1.4**	IV furosemide 80 mg BD started · enalapril CONTINUED
Day 3	**sCr 1.9**	sCr ↑36% · good urine output · weight −3.5 kg · JVP falling · patient better
Day 5	**sCr 2.1**	sCr ↑50% · NGAL negative · no hypotension · decongesting well
Day 7	**sCr 1.7**	sCr improving · weight −6 kg · JVP normalized · discharged on GDMT

Diagnosis: PERMISSIVE AKI. sCr rose 50% (Brenner's acceptable limit) during decongestion, NGAL negative, patient improving. Continue therapy — decongest first, the kidney follows.

Parikh & Coca, Kidney Int 2019 · Brenner The Kidney 2020 (sCr ≤50% rise = permissive) · illustrative teaching case

Case 2 — 68M, CKD3b + HFrEF + Diabetes, Combination Therapy



Lesson

Expected dip is permissive — continue the combination.

SECTION 06 · CASE 2

Case 2 — 68 M, CKD3b + HFrEF + T2D, Starting Combination

68 M · CKD G3b · HFrEF (EF 32%) · T2D · on sacubitril/valsartan + carvedilol + furosemide. Starting finerenone + an SGLT2i (CONFIDENCE context). Baseline sCr 1.9, eGFR 32.

Week 2	**eGFR 27**	eGFR dip −5 · TGF (SGLT2i) + hemodynamic (finerenone) · expected — continue both
Week 4	**eGFR 30**	sCr stabilizing · KIM-1 negative · UACR already falling · no symptomatic hypotension
Month 3	**eGFR 33**	eGFR recovering · UACR ↓~55% · BP controlled · NT-proBNP improving
Month 6	**eGFR 35**	eGFR above baseline · UACR still falling · HF hospitalization avoided

CONFIDENCE lesson: the expected eGFR dip with simultaneous finerenone + SGLT2i is permissive (hemodynamic). KIM-1 negative, UACR falling — continue the combination.

Agarwal R et al. NEJM 2025 (CONFIDENCE) · Vaduganathan M et al. NDT 2025 · KDIGO 2026 · illustrative teaching case

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

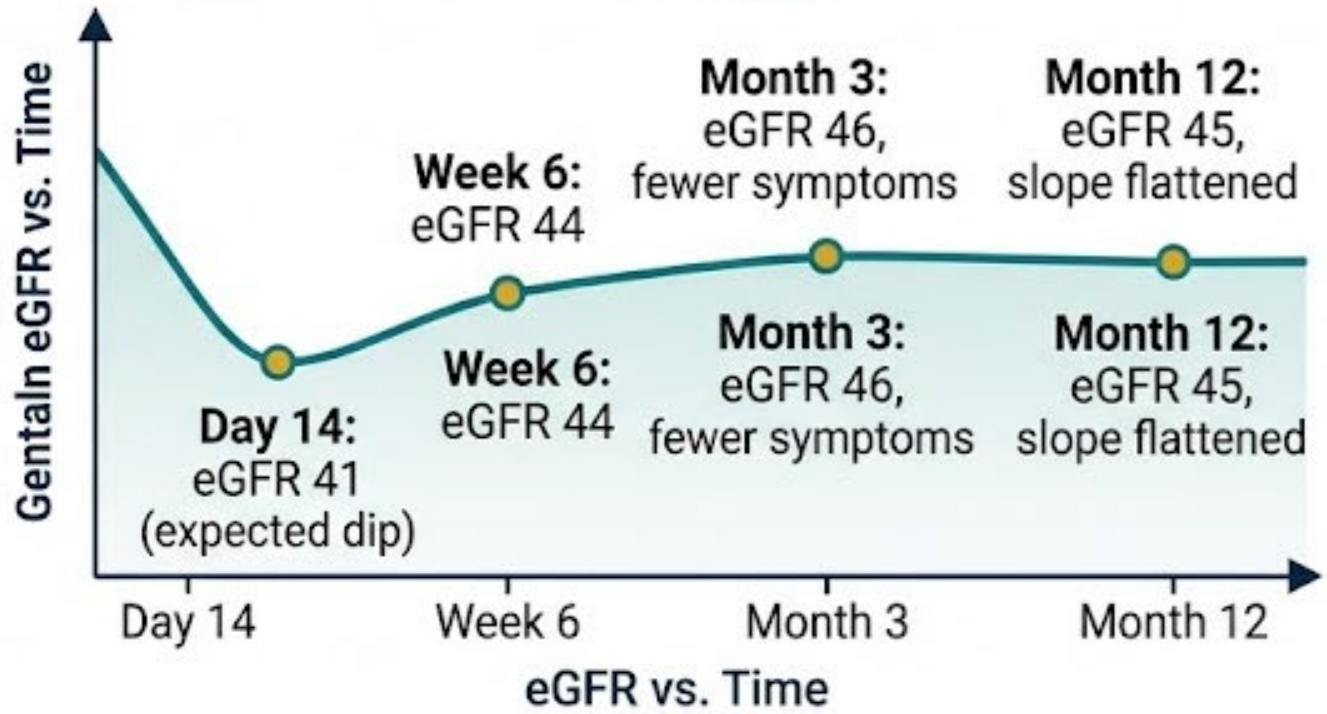
Case 3 — 74 F, HFpEF + CKD, Starting an SGLT2 Inhibitor

HFpEF

Kidney

Supportive

Permissive



The SGLT2i dip is the same expected hemodynamic effect in HFpEF — do not stop.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

SECTION 06 · CASE 3

Case 3 — 74 F, HFpEF + CKD, Starting an SGLT2 Inhibitor

74 F · HFpEF (EF 58%) · CKD G3a · T2D · HTN · on ARB + loop diuretic. SGLT2 inhibitor (empagliflozin) just started for HF + kidney protection. Baseline eGFR 48.

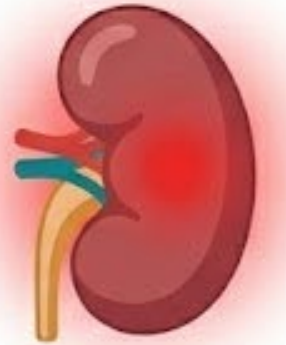
Day 14	**eGFR 41**	Expected initial dip (−7) from tubuloglomerular feedback · asymptomatic · euvolemic
Week 6	**eGFR 44**	eGFR partially recovered · no volume depletion · continue
Month 3	**eGFR 46**	Stabilized near baseline · fewer HF symptoms · weight stable
Month 12	**eGFR 45**	Stable; slope flattened vs prior trajectory · therapy maintained

Lesson (HFpEF too): the SGLT2i “dip” is the same expected hemodynamic effect in HFpEF as in HFrEF. Anticipate −3 to −5 (up to ~30%), do not stop — the long-term slope benefits.

EMPEROR-Preserved / DELIVER · KDIGO 2026 (Kidney Int / JACC:HF) · AJKD Core Curriculum 2025 · illustrative teaching case

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Case 4 — 70 M, When It Is NOT Permissive AKI



Day 1: creatinine 2.6 (↑100%), oliguria, hypotensive, NGAL CEEARWQUE, hypotensive, NGAL POSITIVE, worsening

Assessment: sepsis + volume + depletion + + hypotension

Action: hold ACEi/MRA, resuscitate, treat infection

Recovery: creatinine 1.4, then rechallenge rechallenge GDMT

SPONTANEOUS / TRUE AKI — hold, correct, then rechallenge. Knowing the difference is the skill.

Dr. Mohammadtaghi Najafi — Associate Professor of Nephrology, TUMS

Case 4 — 70 M, When It Is NOT Permissive AKI

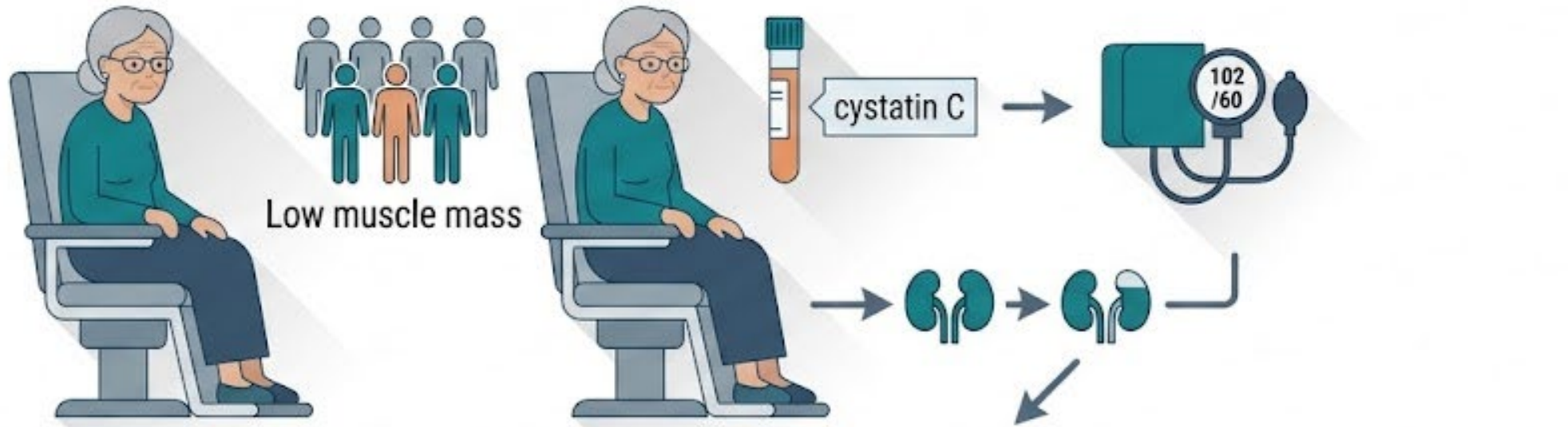
70 M · HFrEF · on ACEi + MRA + loop diuretic. Admitted with fever, diarrhea, hypotension (BP 88/54). Baseline sCr 1.3 → now rising. The key is recognizing this is different.

Day 1	**sCr 2.6**	sCr ↑100% · oliguria · hypotensive · NGAL POSITIVE · clinically WORSENING
Assessment	—	Sepsis + volume depletion + hypotension — a clear alternative cause of AKI
Action	—	Hold ACEi/MRA temporarily · resuscitate · treat infection · review nephrotoxins
Recovery	**sCr 1.4**	After sepsis resolves & BP restored → rechallenge GDMT and titrate back up

Diagnosis: SPONTANEOUS / TRUE AKI. rise WITH clinical deterioration, positive biomarkers, and an obvious precipitant. This is NOT permissive — hold, correct, then rechallenge. Knowing the difference is the skill.

Parikh & Coca, Kidney Int 2019 (algorithm) · Coca SG, Nephron 2022 · Brenner The Kidney 2020 · illustrative teaching case

Case 5 — 81 F, Frail, Diuretic-Related Rise & Hypotension



Day 3: creatinine 1.6 → 2.2 during diuresis, JVP flat, BP 102/60

Caveat: low muscle mass underestimates GFR — check cystatin C

Action: ease diuretic to lowest effective dose, avoid hypoperfusion, continue ACEi

Day 7: creatinine 1.8, settling

Permissive during decongestion — but in the frail use cystatin C, target true euvolemia, avoid hypotension.

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Case 5 — 81 F, Frail, Diuretic-Related Rise & Hypotension

81 F · HFrEF · frail, low muscle mass · on ACEi + high-dose furosemide. Aggressive diuresis for ADHF. sCr rising; the question is over-diuresis vs permissive decongestion.

Day 3	**sCr 1.6→2.2**	sCr ↑ during diuresis · JVP now flat · BP 102/60 · still mild orthostatic symptoms
Caveat	—	Low muscle mass → sCr underestimates true GFR; check cystatin C · watch for over-diuresis
Action	—	Reached euvolemia → ease diuretic to lowest effective dose · avoid hypoperfusion · continue ACEi
Day 7	**sCr 1.8**	sCr settling · orthostasis resolved · discharged on tailored GDMT

Lesson (nuance in the elderly): permissive sCr rise during decongestion is fine — but in frail, low-muscle patients use cystatin C, target true euvolemia (not beyond), and avoid hypotension/hypoperfusion, which IS harmful.

Brenner The Kidney 2020 · AJKD Core Curriculum 2025 (cystatin C; over-diuresis) · UpToDate HFrEF 2025 · illustrative teaching case

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Five Things to Remember

1. Cardiorenal syndrome is bidirectional — decongest first

2. Not every creatinine rise is AKI — context defines it

Creatinine

3. The eGFR dip is the drug working — tolerate it

4. CONFIDENCE 2025: combination is safe and additive

study

5. KDIGO 2026: continue therapy despite the dip

TAKE-HOME MESSAGES · 2026

Five Things to Remember

01 **CRS is bidirectional** — Venous congestion (↑CVP) often drives AKI more than low cardiac output. On the Brenner triangle, only sCr↑ WITH clinical deterioration = poor outcome. Decongest first.

02 **Not every sCr rise is AKI** — Context, mechanism and biomarkers define it: induced/functional/permissive vs spontaneous/structural.

03 **The eGFR dip IS the drug working** — Tolerate it — Brenner limits: ≤50% rise, sCr ≤3.0, eGFR ≥25. RAASi (efferent), SGLT2i (TGF), diuresis (hemoconcentration) — all expected.

04 **CONFIDENCE 2025–26** — Simultaneous finerenone + SGLT2i: UACR ↓52% vs 34–36%; AKI <2%. The eGFR dip is hemodynamic, reversible, driven by high eGFR & diuretics — finerenone's benefit is nonhemodynamic. “Pharmacodynamics, not failure.”

05 **KDIGO 2026** — Decongest first · use cystatin C + NGAL/KIM-1 · continue GDMT despite the dip. Permissive hypercreatinemia is now endorsed.

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Key References

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Questions & Discussion

‘Not all AKI is the same — or harmful.’

Parikh & Coca, *Kidney International* 2019

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