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ESTIMATED GLOMERULAR FILTRATION RATE, SYSTOLIC BLOOD PRESSURE, AND URINARY ALBUMIN-TO-CREATININE RATIO – UNRAVELLING THE INTERPLAY IN COMBINATION: FINDINGS FROM THE RANDOMIZED CONFIDENCE TRIAL

WCN26-AB-8677

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Indianapolis, IN, USA

DISCLOSURES

- Nonfinancial support from Akebia Therapeutics, Alnylam, Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, Intercept, and Novartis
- Consulting fees from Akebia Therapeutics, Alnylam, Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, Intercept, and Novartis
- Royalties or licenses from UptoDate and Wolters Kluwer
- Member of the data safety monitoring committees for Chinook and Vertex
- Associate editor of the *American Journal of Nephrology* and *Nephrology Dialysis Transplantation*; author and editor for UpToDate
- Research grants from the National Institutes of Health and the US Veterans Administration

Presented on behalf of the steering committee and CONFIDENCE investigators

Funding: This work was supported by Bayer AG, who funded the CONFIDENCE trial

THE CLINICAL DILEMMA

The benefit

Simultaneous initiation of **finerenone** + **empagliflozin** improves UACR reduction in individuals with CKD and T2D[1]

CKD, chronic kidney disease; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

1. Agarwal R, et al. *N Engl J Med.* 2025;393(6):533–543.

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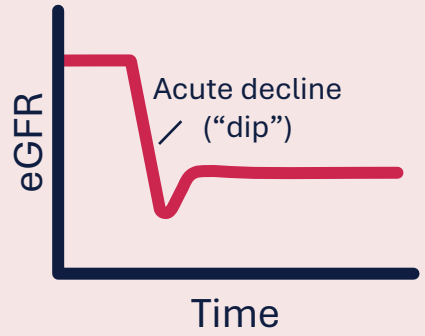

Combination therapy precipitates an acute **eGFR decline (the “dip”)**[1,2]

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

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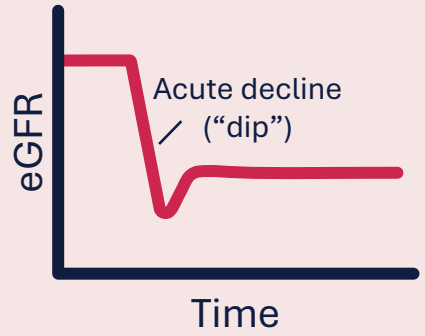

Combination therapy precipitates an acute **eGFR decline (the “dip”)**[1,2]

The question: Does this acute decline represent structural injury, or is it a functional marker of glomerular pressure relief?

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

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STUDY OBJECTIVES

01 Quantify

Measure the magnitude of acute eGFR change (baseline to Day 14) and chronic trajectory (Day 14–180)

eGFR, estimated glomerular filtration rate.

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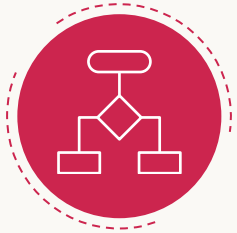


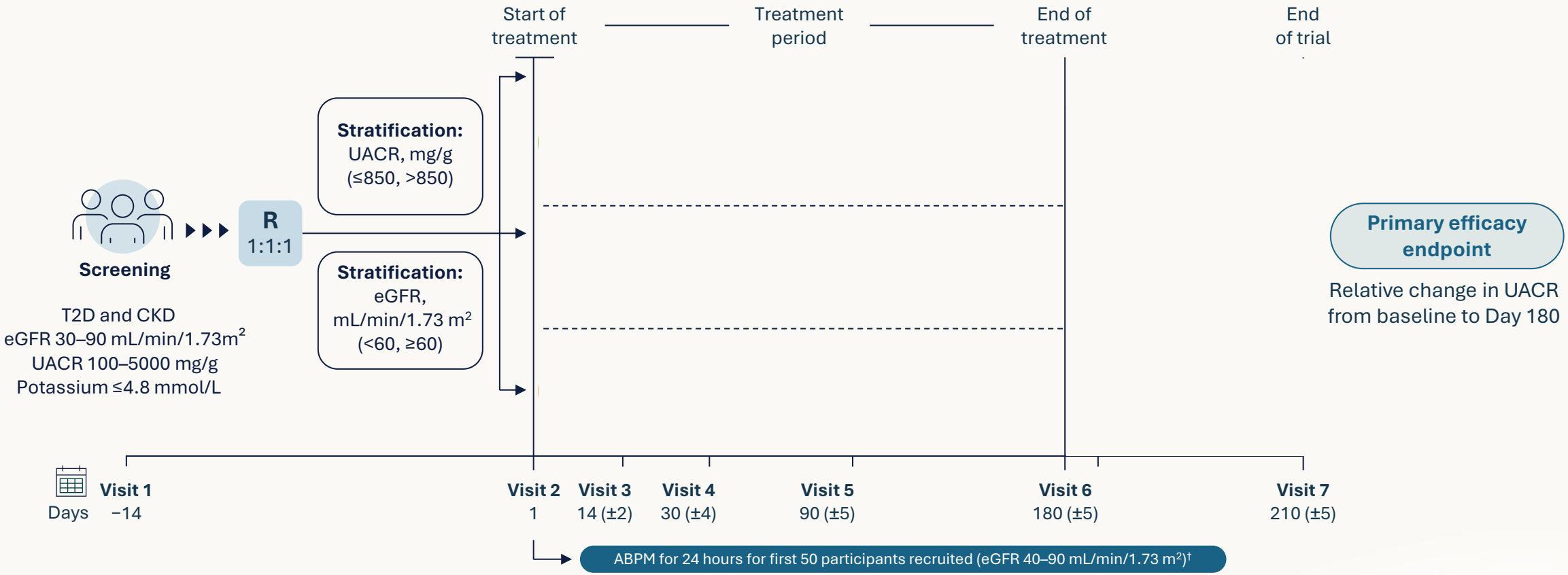
03 Causal pathway

Explore if the acute eGFR “dip” mediates the reduction in UACR using causal mediation analysis

eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

CONFIDENCE TRIAL DESIGN

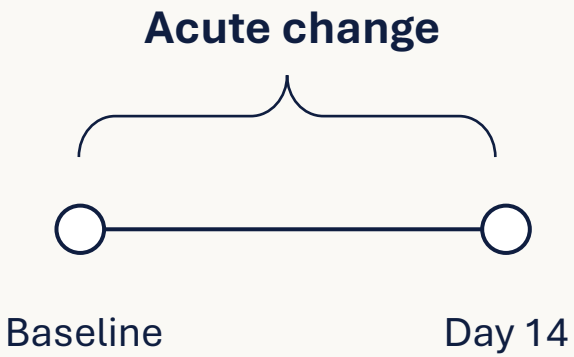
Participants were randomized in a 1:1:1 ratio to one of three parallel groups



This figure is adapted from Green JB, et al.[1] under the terms of the Creative Commons Attribution-Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/).
†Participants with an eGFR of 40–90 mL/min/1.73 m^2 were recruited (part A) prior to recruiting participants with an eGFR of 30–90 mL/min/1.73 m^2 (part B). The number of participants was capped in parts A and B as follows: 80% with an eGFR of ≤75 mL/min/1.73 m^2 and 20% with an eGFR of >75 mL/min/1.73 m^2. Up/down titration of finerenone was based on eGFR, serum/plasma potassium, and safety and tolerability. ABPM, ambulatory blood pressure monitoring; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; R, randomization; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.
1. Green JB et al. *Nephrol Dial Transplant.* 2023;38:894–903. 2. Agarwal R, et al. *N Engl J Med.* 2025;393(6):533–543.

STUDY DESIGN: DEFINING THE TRAJECTORY AND THE MECHANISM

Timeline and definitions



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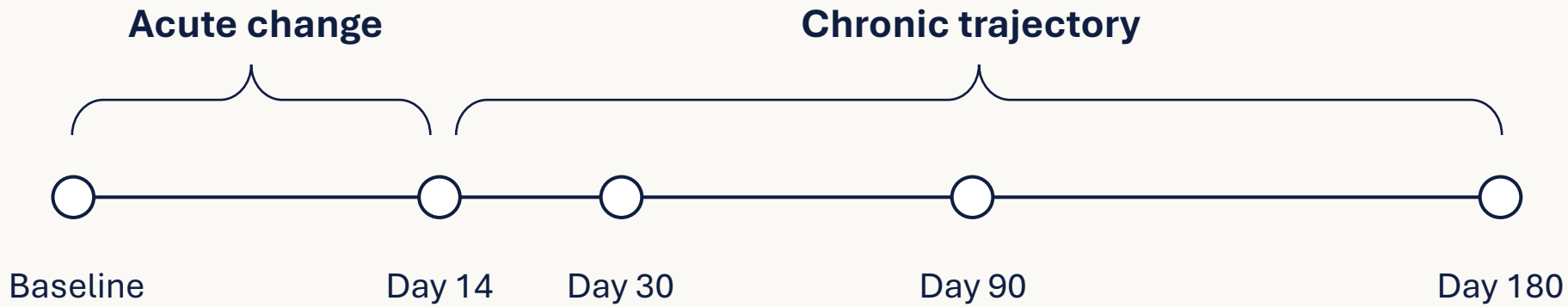

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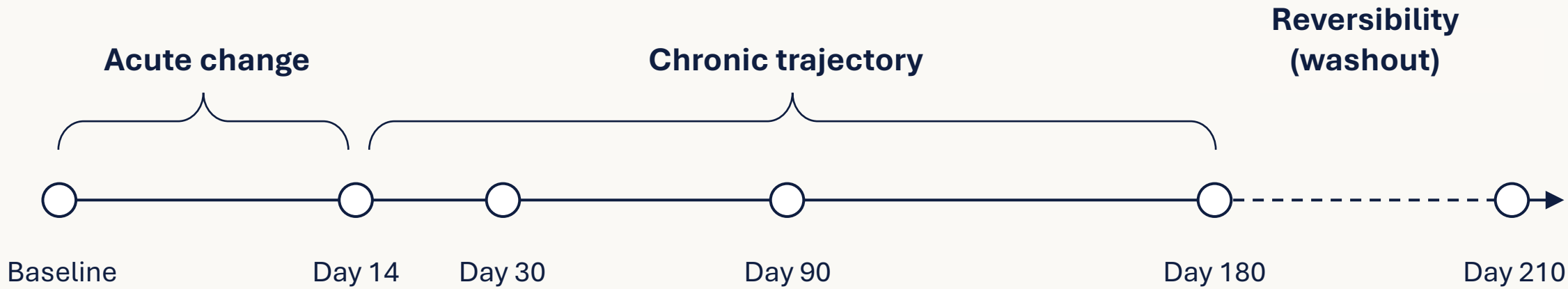

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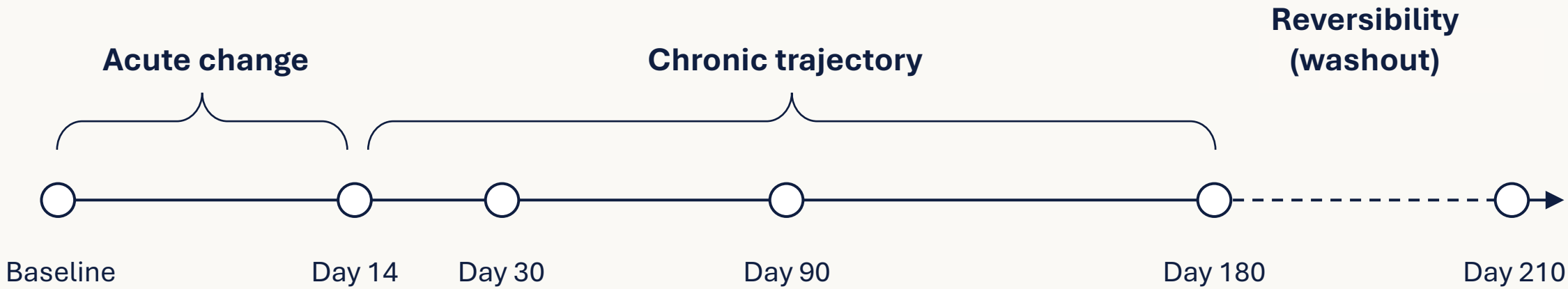
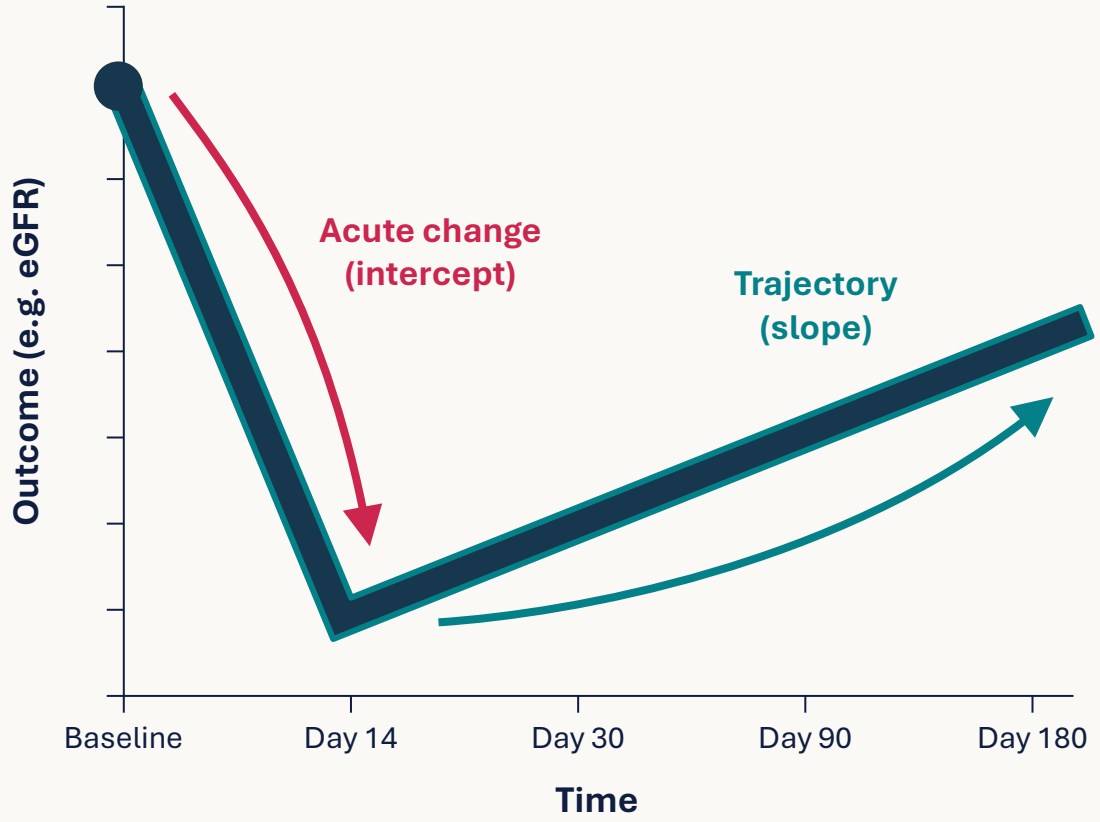


Acute hemodynamic effect

Reversibility assessment

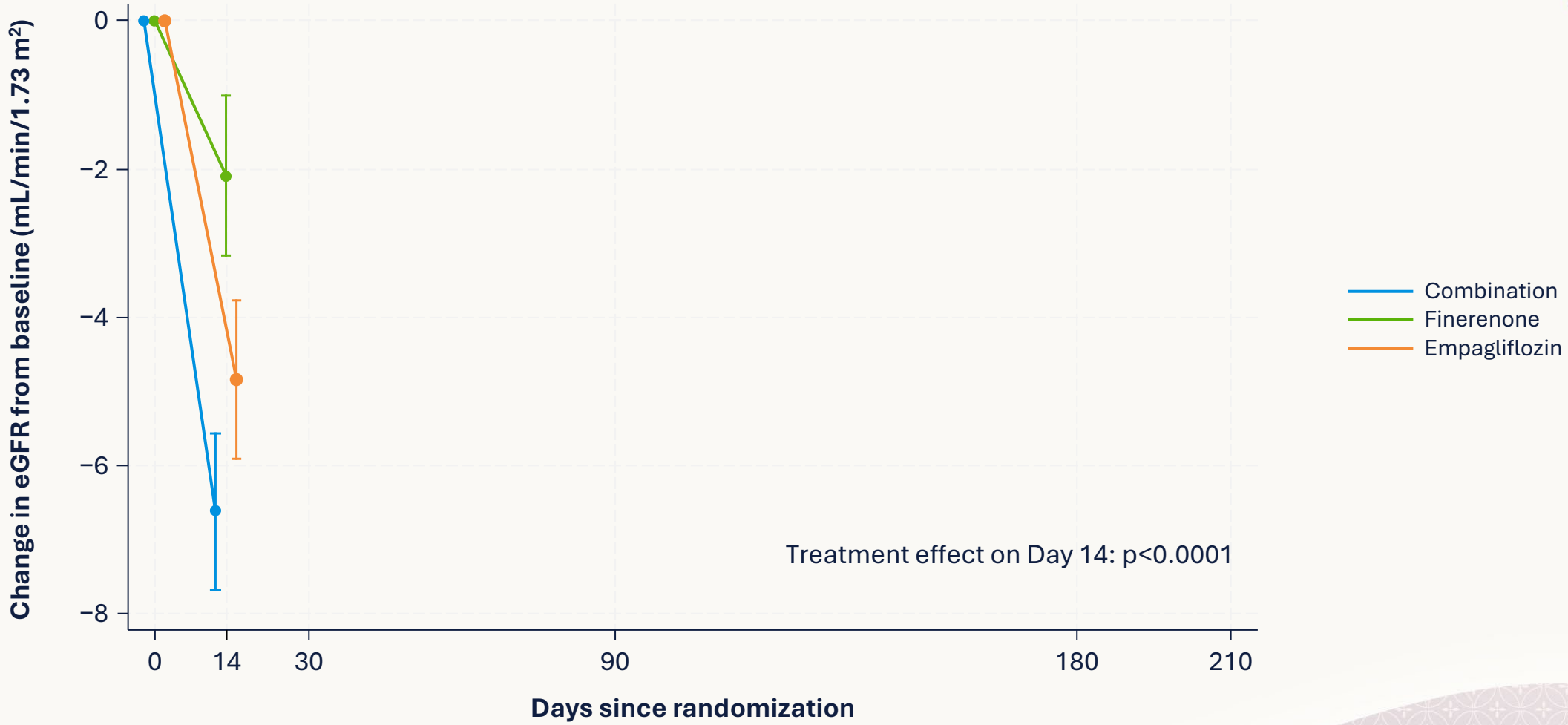
METHODOLOGY: LINEAR MIXED MODEL†



Purpose:	Estimate determinants of mean acute change and subsequent trajectory
Reference point:	Day 14 (first post-baseline measurement)
Fixed effects:	Treatment, visit, baseline eGFR, baseline UACR, baseline SBP, baseline diuretic use
Interactions:	e.g. baseline eGFR × visit (defining trajectory)

†A linear mixed model[1] was used to estimate determinants of the mean acute change in eGFR and the trajectory of change.
eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.
1. Holden JE, et al. *Am J Nephrol.* 2008;28(5):792–801.

PATTERNS OF eGFR TRAJECTORIES DIFFERED BY TREATMENT



eGFR, estimated glomerular filtration rate.

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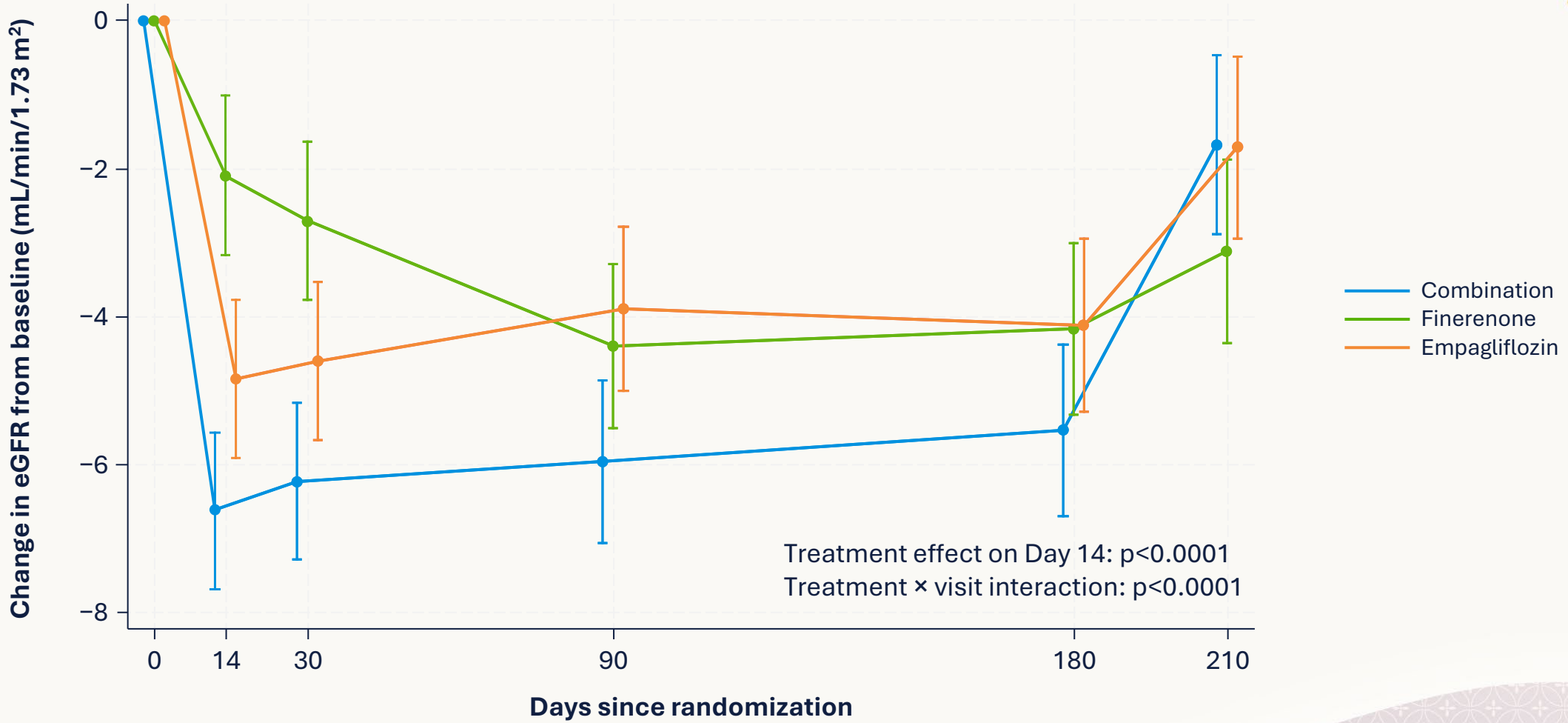
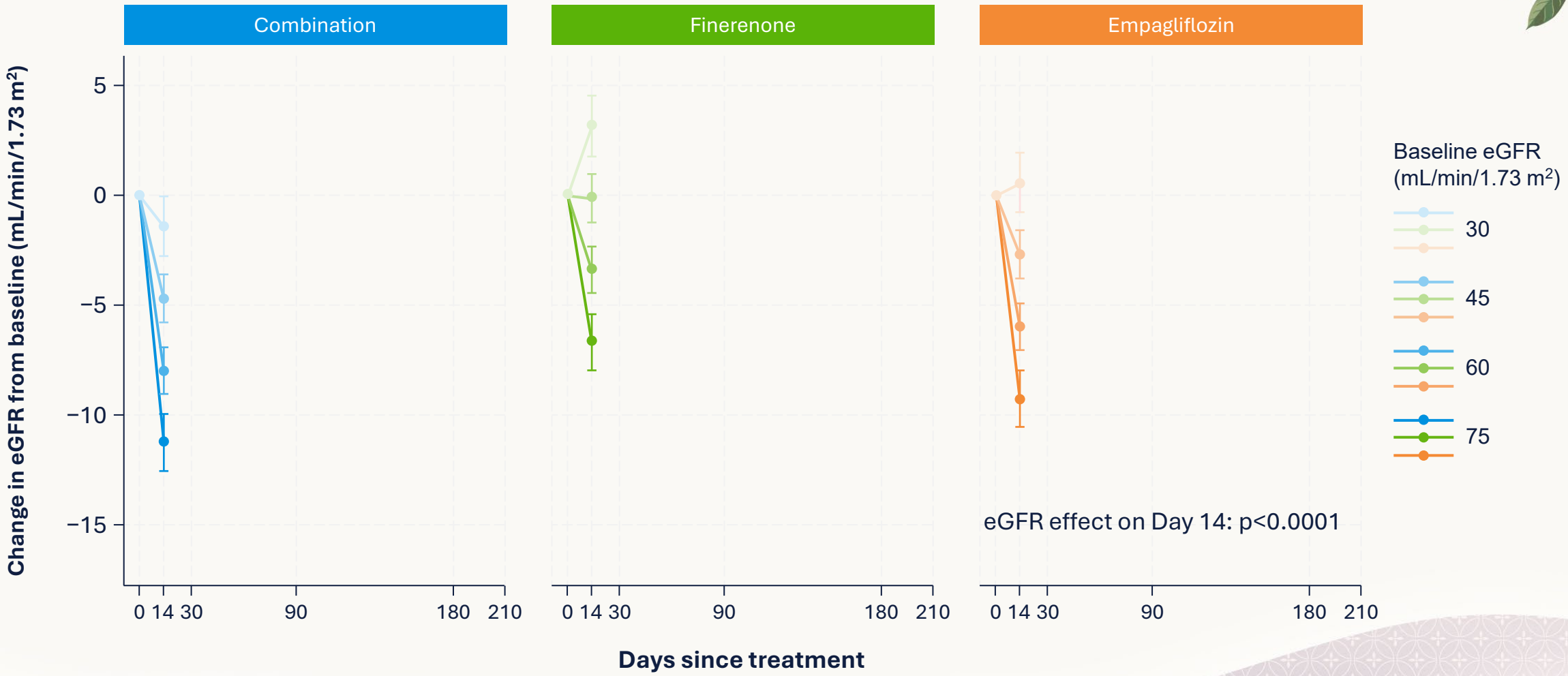


eGFR, estimated glomerular filtration rate.

BASELINE eGFR ASSOCIATES WITH ACUTE eGFR DECLINE AND ITS TRAJECTORY



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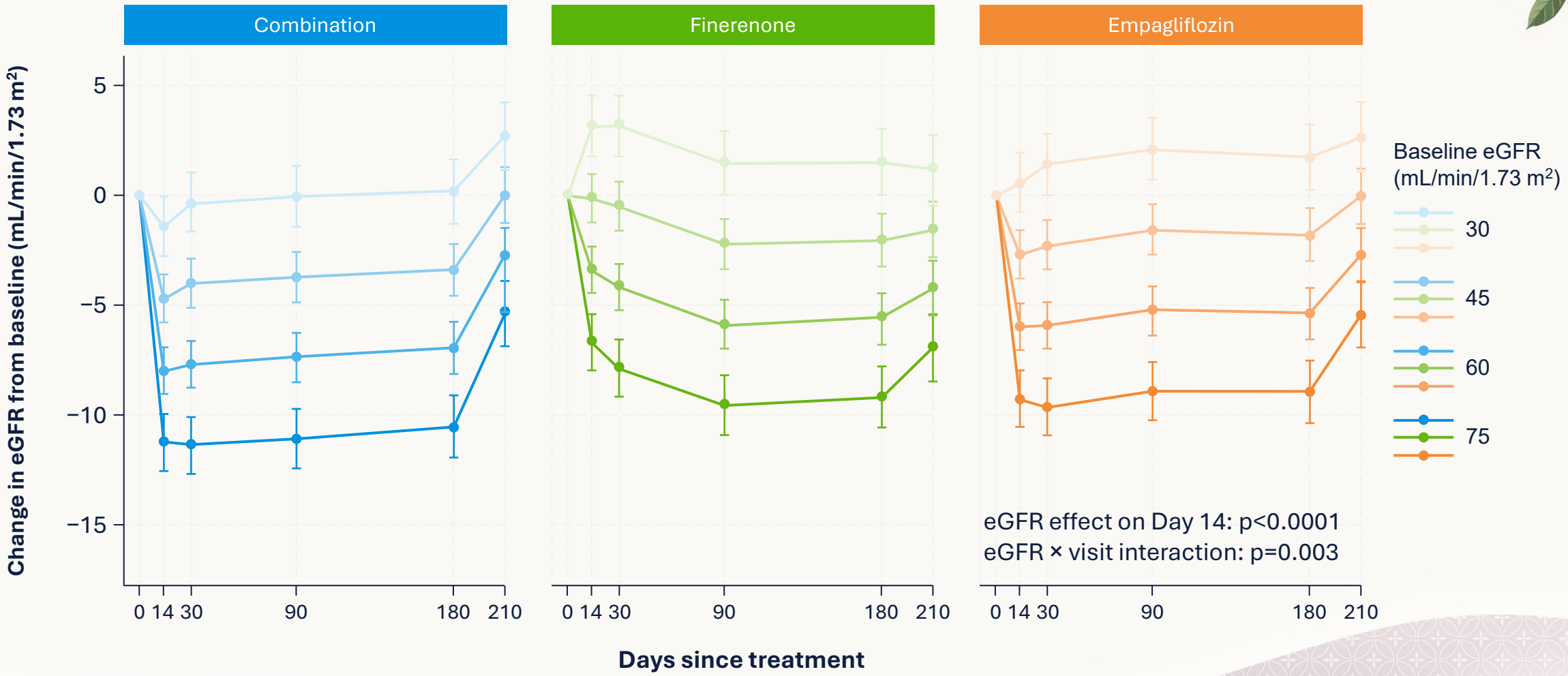

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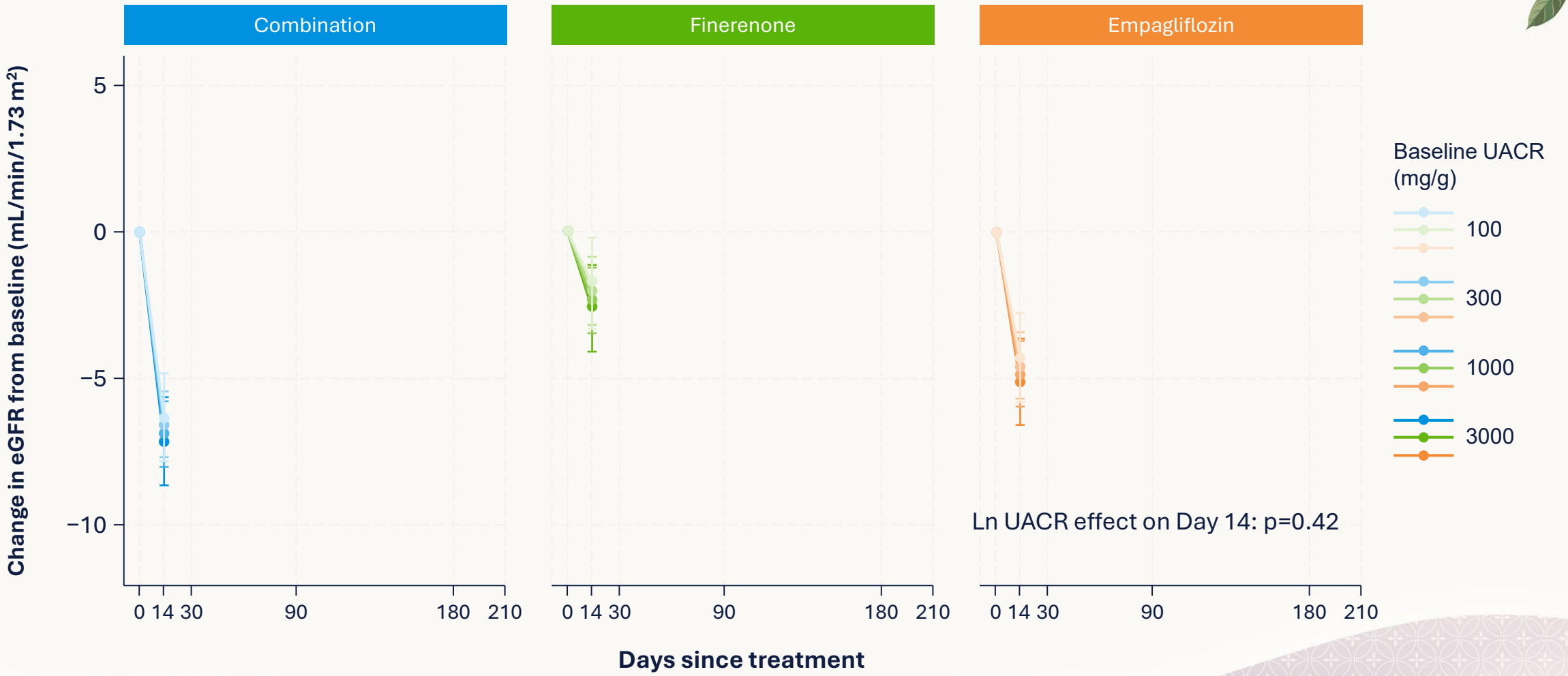
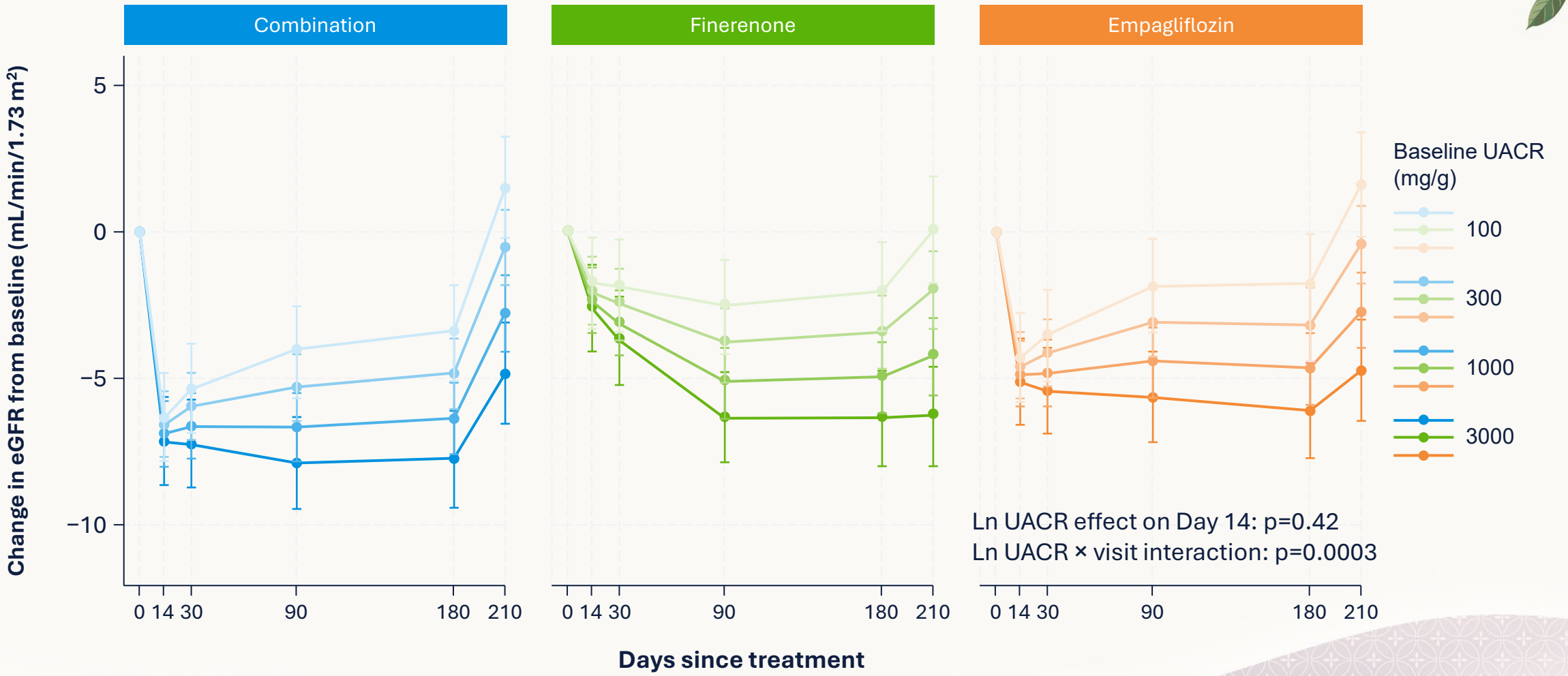
BASELINE UACR DOES NOT ASSOCIATE WITH ACUTE eGFR DECLINE; IT ASSOCIATES WITH ITS TRAJECTORY



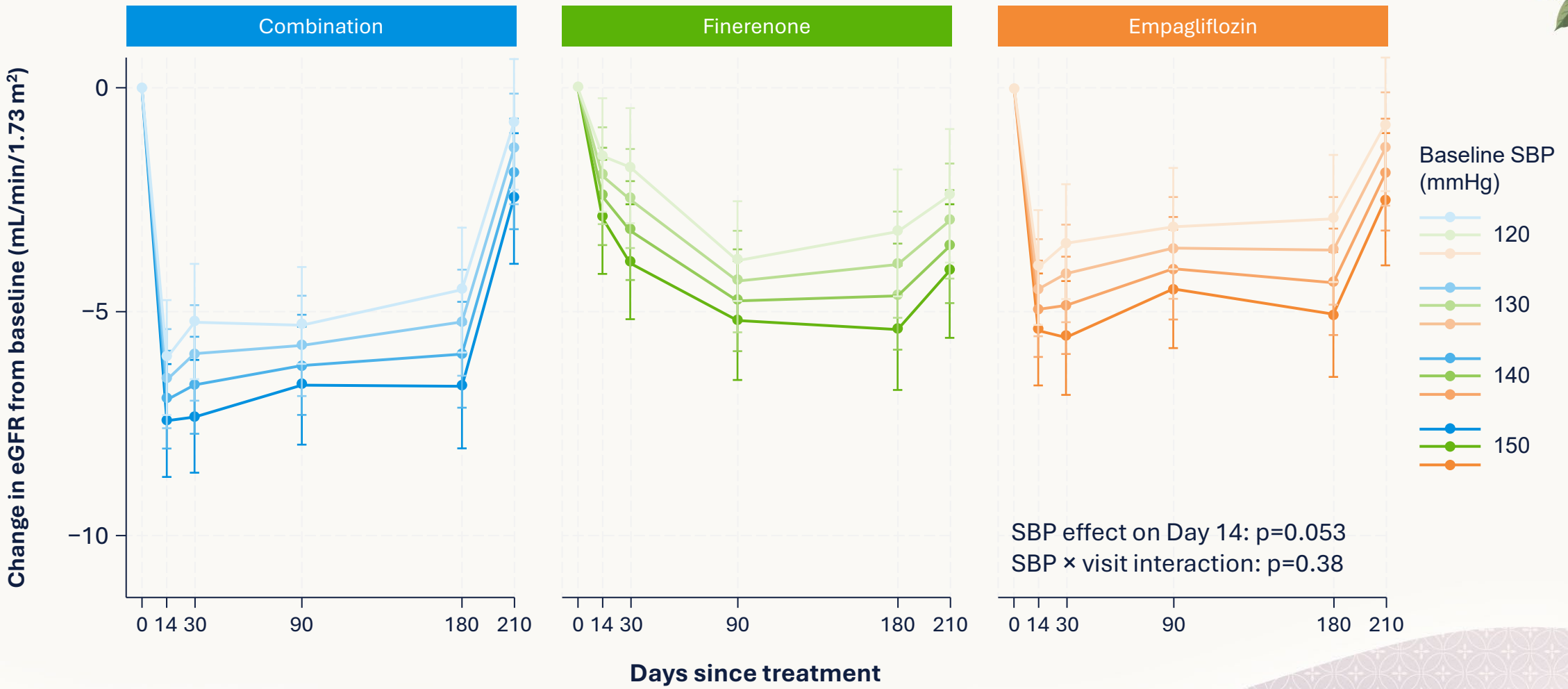
eGFR, estimated glomerular filtration rate; Ln, natural log; UACR, urinary albumin-to-creatinine ratio.

BASELINE UACR DOES NOT ASSOCIATE WITH ACUTE eGFR DECLINE; IT ASSOCIATES WITH ITS TRAJECTORY



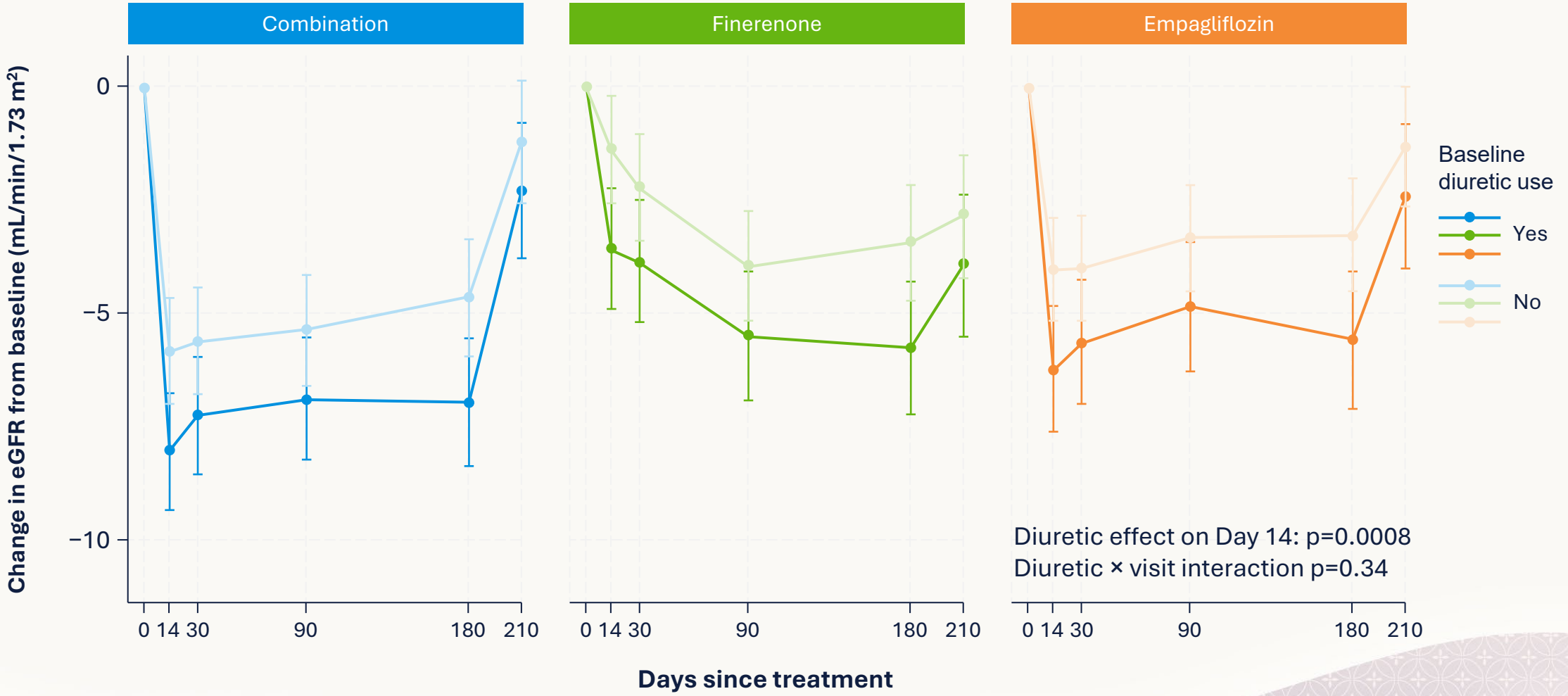
eGFR, estimated glomerular filtration rate; Ln, natural log; UACR, urinary albumin-to-creatinine ratio.

BASELINE SBP DOES NOT ASSOCIATE WITH ACUTE eGFR DECLINE OR ITS TRAJECTORY



eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

BASELINE DIURETIC USE ASSOCIATES WITH ACUTE eGFR DECLINE, BUT NOT THE TRAJECTORY



eGFR, estimated glomerular filtration rate.

DISSECTING THE eGFR: ACUTE DIP VERSUS 6-MONTH TRAJECTORY

Acute hemodynamic dip

- A manageable, **hemodynamic effect** related to volume and pressure[1,2]
- Driven by factors of hemodynamic reserve:
  - Higher baseline eGFR
  - Diuretic use
- **Key finding**: This acute dip was **completely abrogated** (absent) in participants with severe CKD (eGFR = 30 mL/min/1.73 m^2)

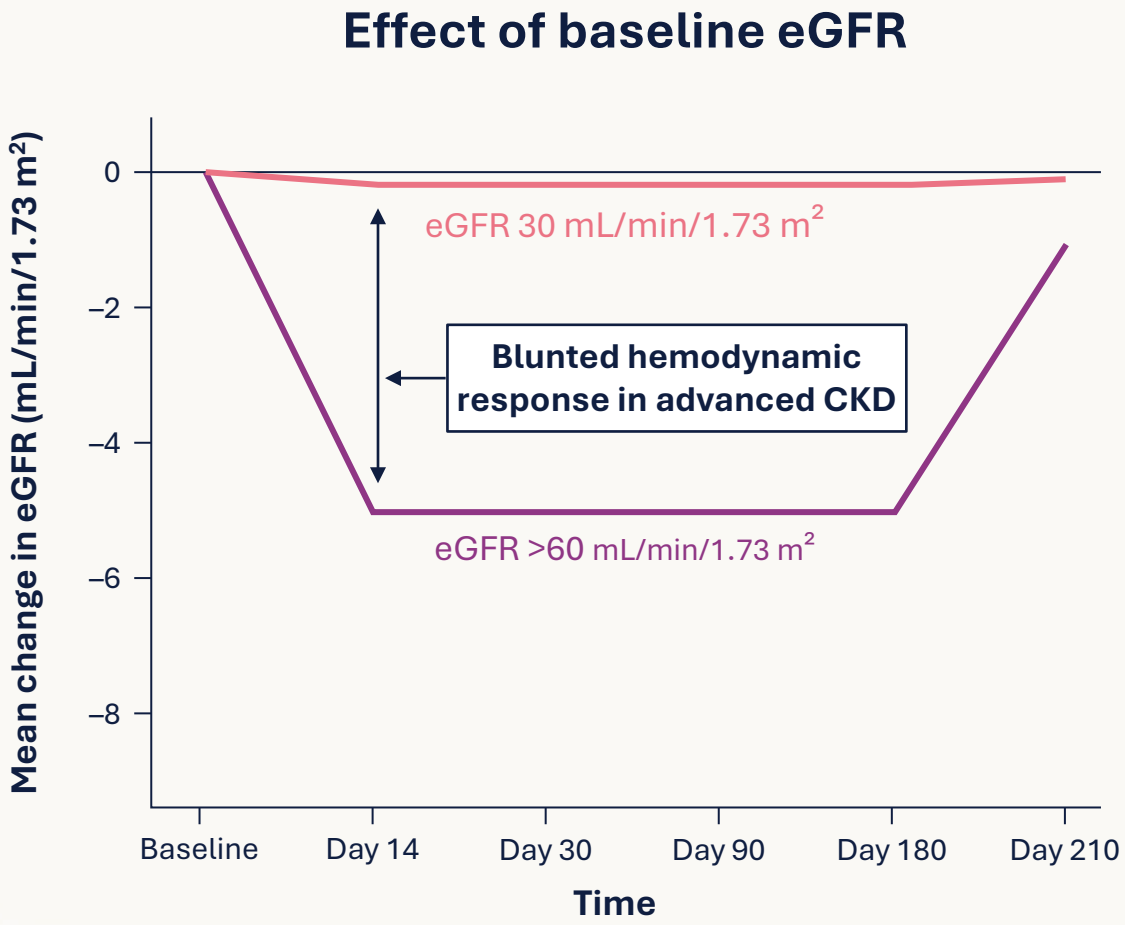
Trajectory

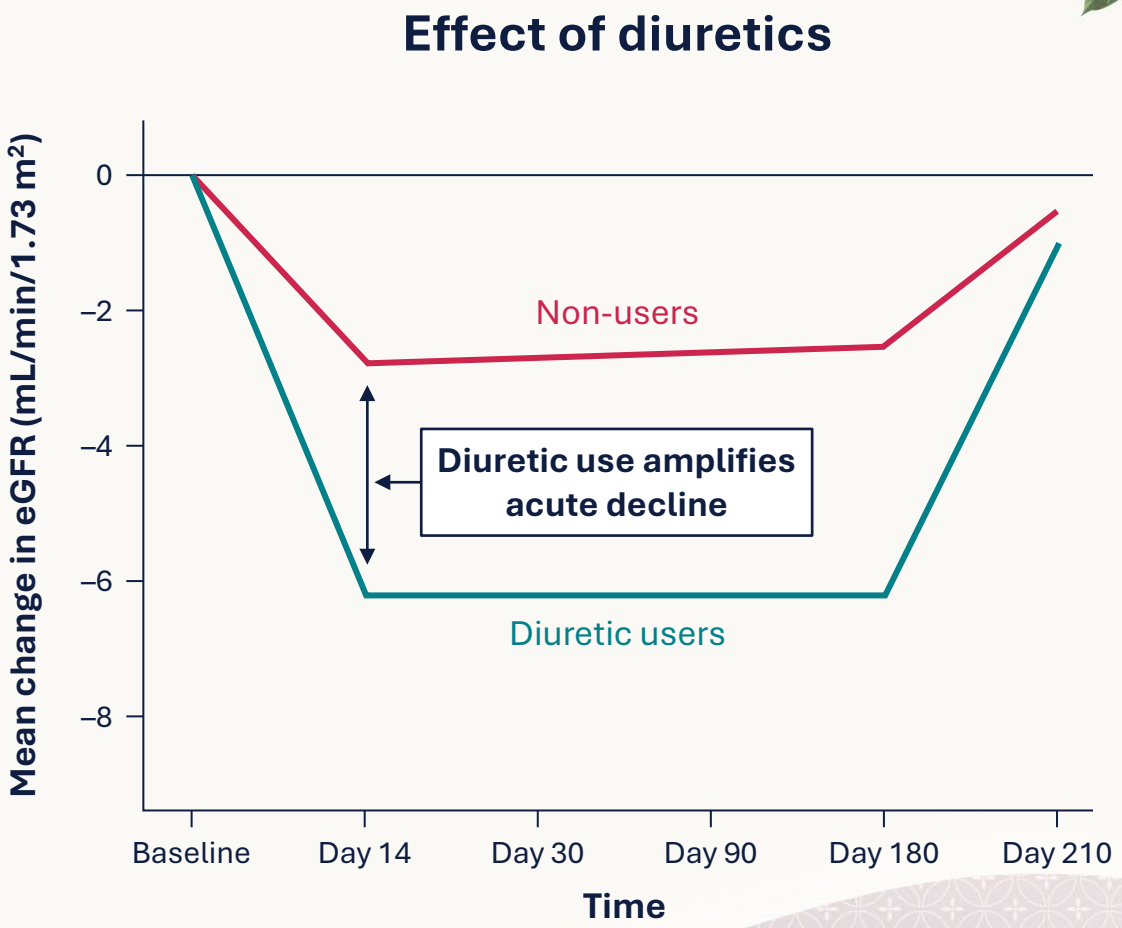
- Driven by disease factors
  - Higher baseline eGFR
  - Higher UACR
- **Key finding**: The 6-month eGFR is linked to the participant's underlying risk profile

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int.* 2024;105(4S):S117–S314. 2. Kolkhof P, et al. *Int J Mol Sci.* 2022;23(16):9243.

DISSECTING THE eGFR: ACUTE DIP





CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

DISSECTING THE eGFR: ACUTE DIP

- **Not driven** by SBP
- **Not driven** by UACR

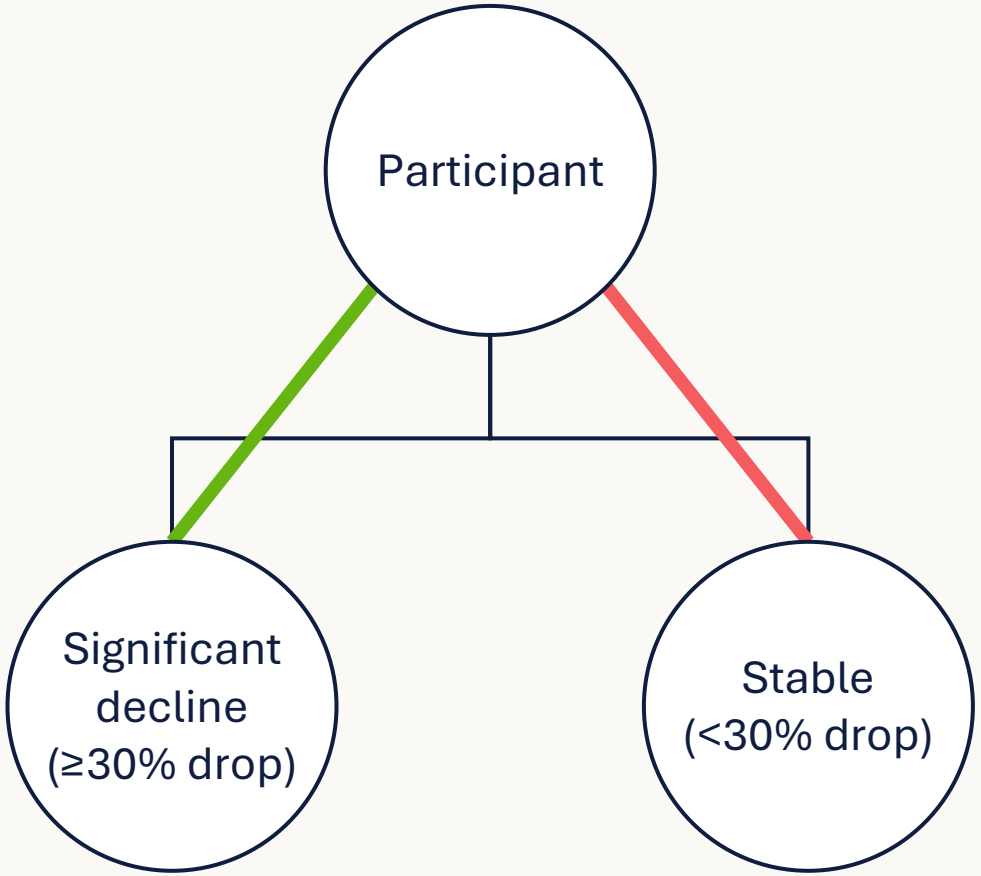
eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

DISSECTING THE eGFR 6-MONTH TRAJECTORY

- **Not driven** by SBP
- UACR: higher UACR, greater decline
- eGFR: higher eGFR, greater decline

eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

METHODOLOGY: LOGISTIC REGRESSION MODEL



Outcome definition:	≥30% eGFR decline from baseline at any visit during treatment (Day 14–180)
Covariates:	Treatment group, baseline log UACR, baseline eGFR, baseline diuretic use, baseline SBP
Goal:	Calculate OR

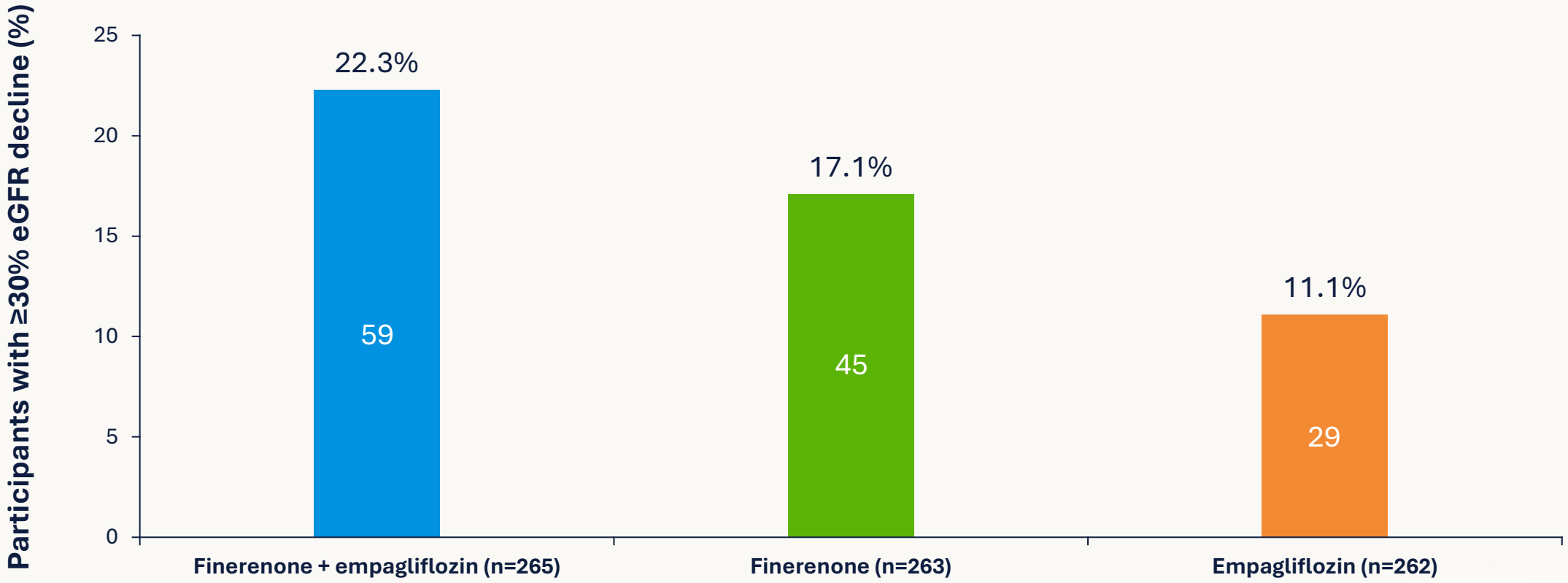
eGFR, estimated glomerular filtration rate; OR, odds ratio; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

BASELINE CHARACTERISTICS BY eGFR DROP SEVERITY

	No drop (<30%)	Drop (≥30%)
Incidence, n (%)	657 (83)	133 (17)
Baseline eGFR, mean	53 mL/min/1.73 m^2	59 mL/min/1.73 m^2 ↑
Diuretic use, n (%)	219 (33)	67 (50) ↑

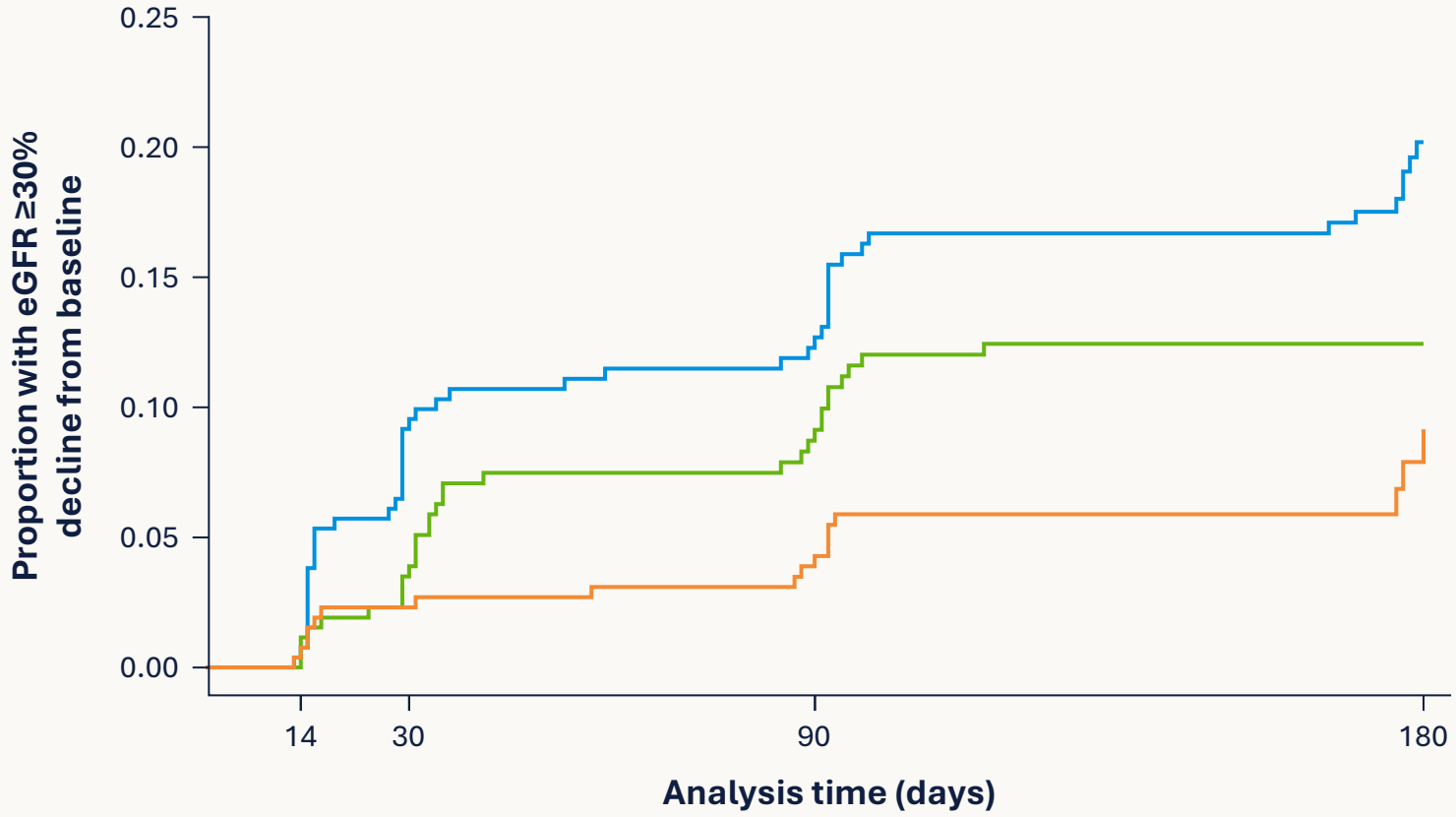
eGFR, estimated glomerular filtration rate.

CUMULATIVE INCIDENCE OF ≥30% eGFR DECLINE AT 180 DAYS



eGFR, estimated glomerular filtration rate.

DISTRIBUTION OF ≥30% eGFR DECLINES

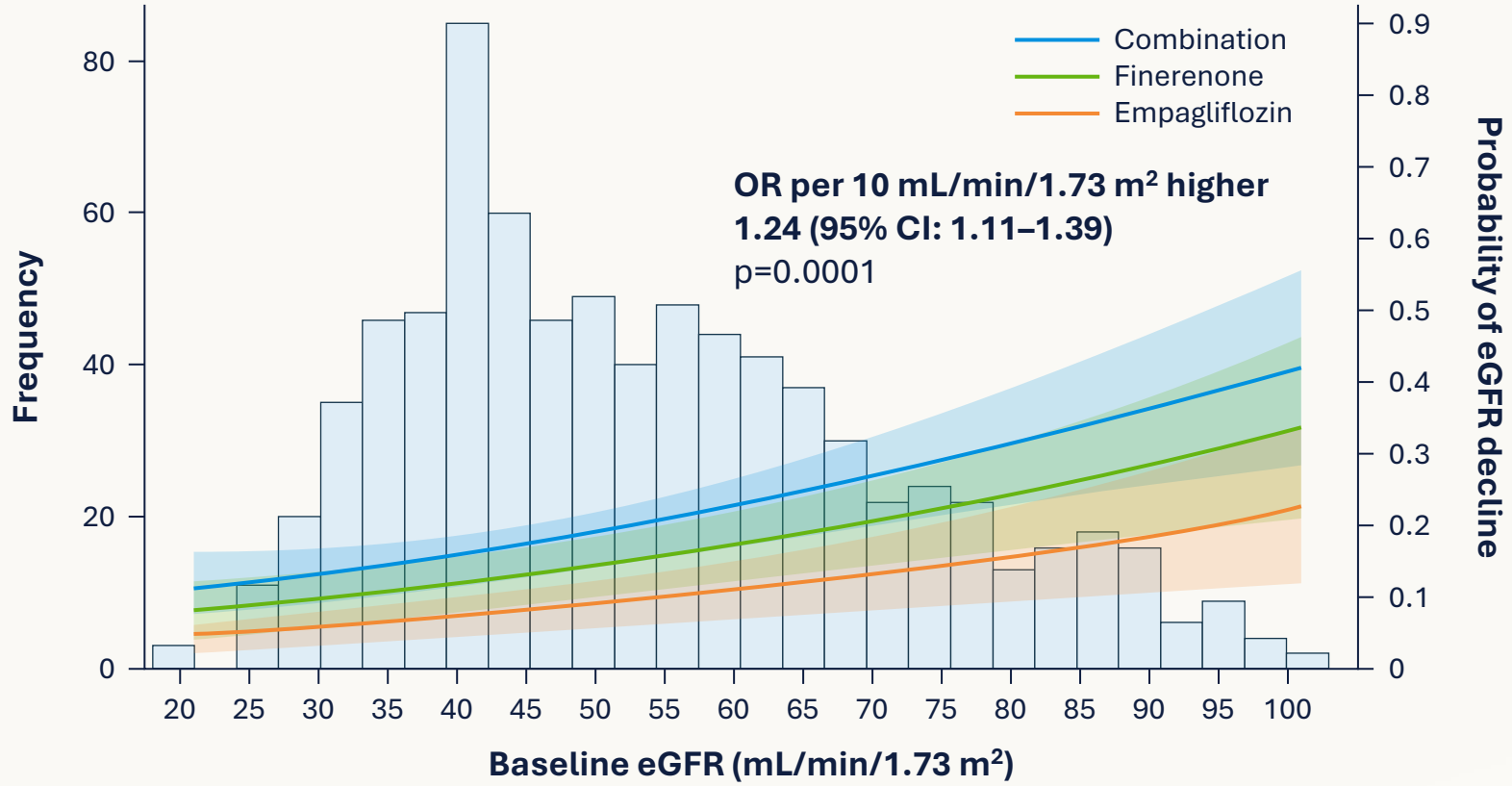


Number at risk:

Combination	261	237	219	128
Finerenone	260	243	221	142
Empagliflozin	259	251	241	146

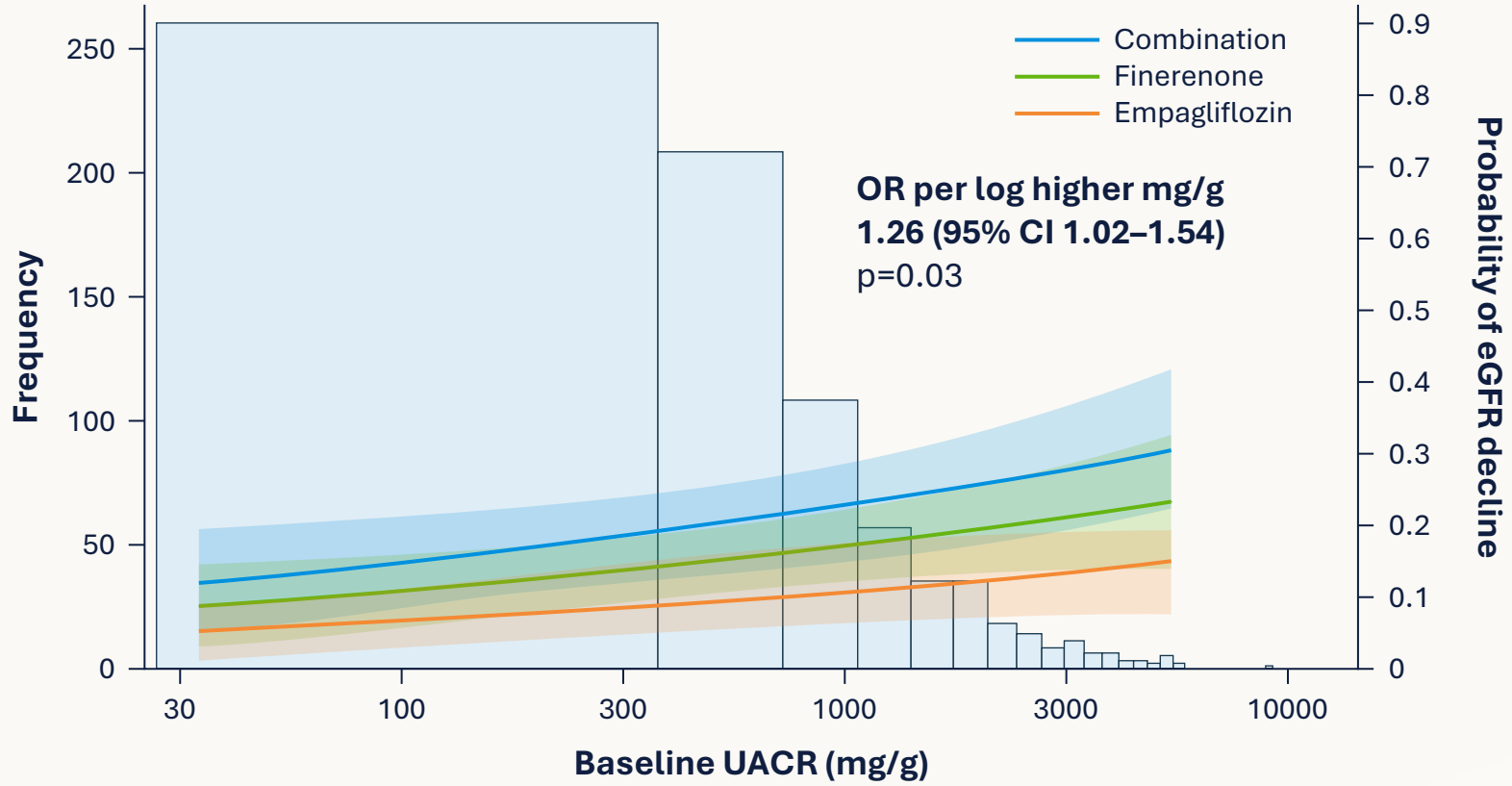
eGFR, estimated glomerular filtration rate.

PROBABILITY OF eGFR DECLINE INCREASES WITH HIGHER BASELINE eGFR



CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

PROBABILITY OF eGFR DECLINE INCREASES WITH HIGHER BASELINE UACR



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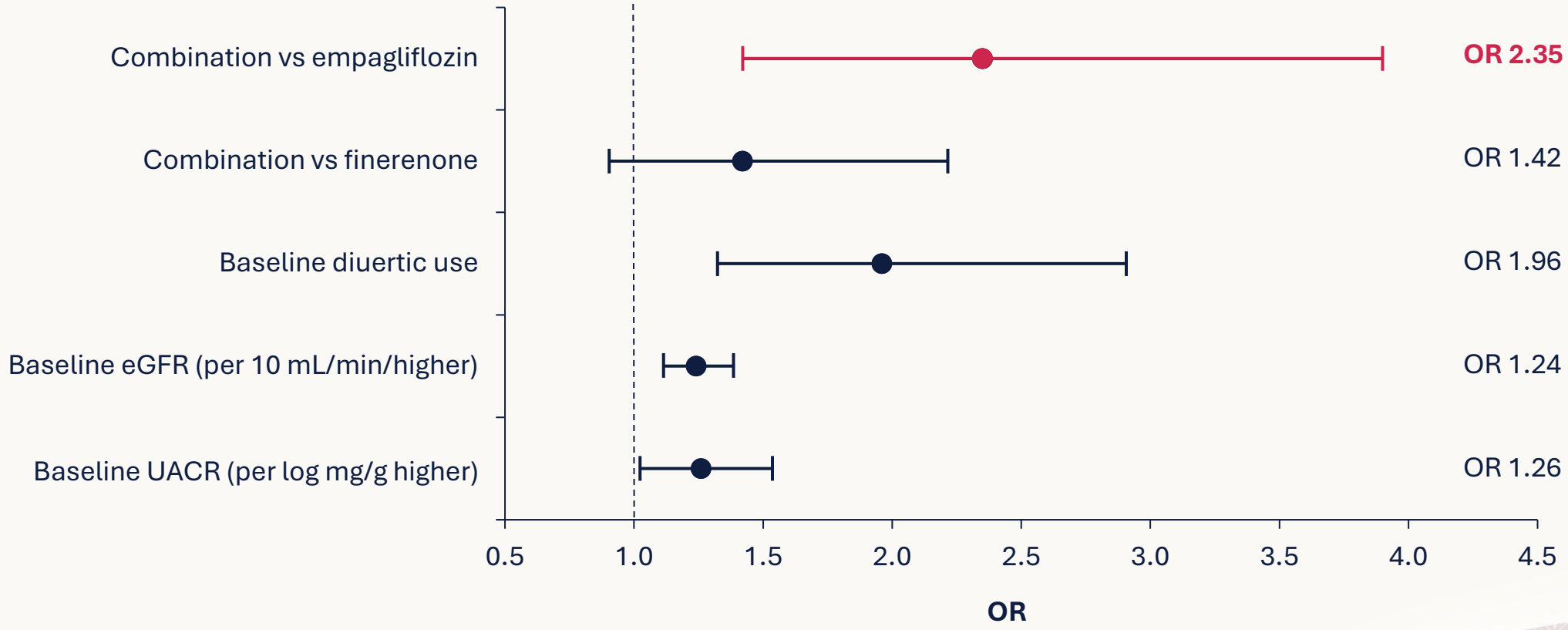
PREDICTORS OF ≥30% eGFR DECLINE

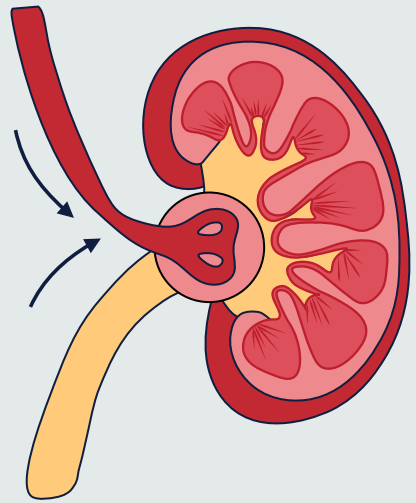


eGFR, estimated glomerular filtration rate; OR, odds ratio; UACR, urinary albumin-to-creatinine ratio.

FUNCTIONAL CHANGE, NOT STRUCTURAL INJURY

Hemodynamic unloading[1,2]

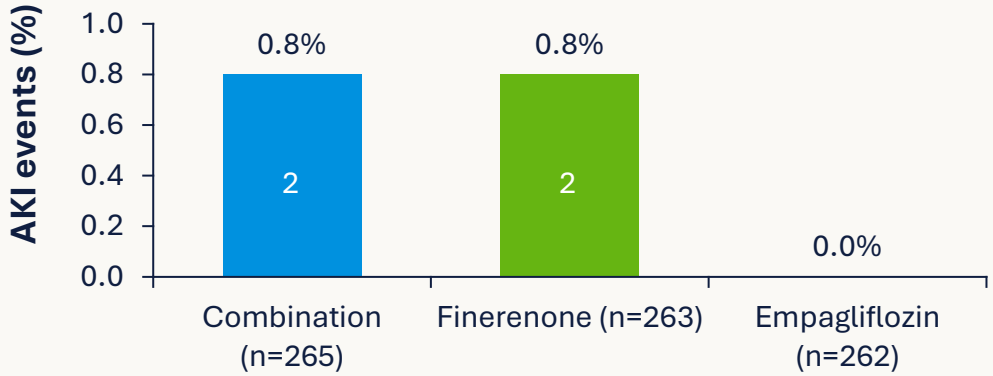
→ Intraglomerular pressure reduction



Reversibility

→ eGFR trends back toward baseline upon withdrawal, indicating no nephron loss

AKI rare



Balanced safety profile across all arms

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

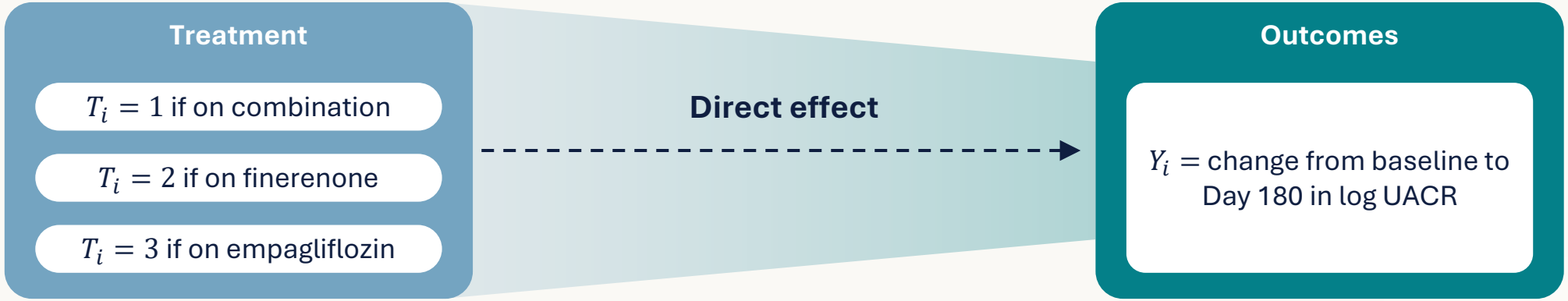
1. Vallon V. *Am J Hypertens*. 2024;37(11):841–852. 2. Kolkhof P, et al. *Int J Mol Sci*. 2022;23(16):9243.

HYPERKALEMIA WAS TWICE AS FREQUENT AMONG THOSE WHO HAD A DROP IN eGFR ≥30%

	No drop (<30%)	Drop (≥30%)
Hyperkalemia, n/N (%)	82/657 (12)	31/133 (23)

eGFR, estimated glomerular filtration rate.

eGFR DECLINE AS MEDIATOR OF UACR LOWERING



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Lee H, et al. *JAMA*. 2021;326(11):1045–1056.

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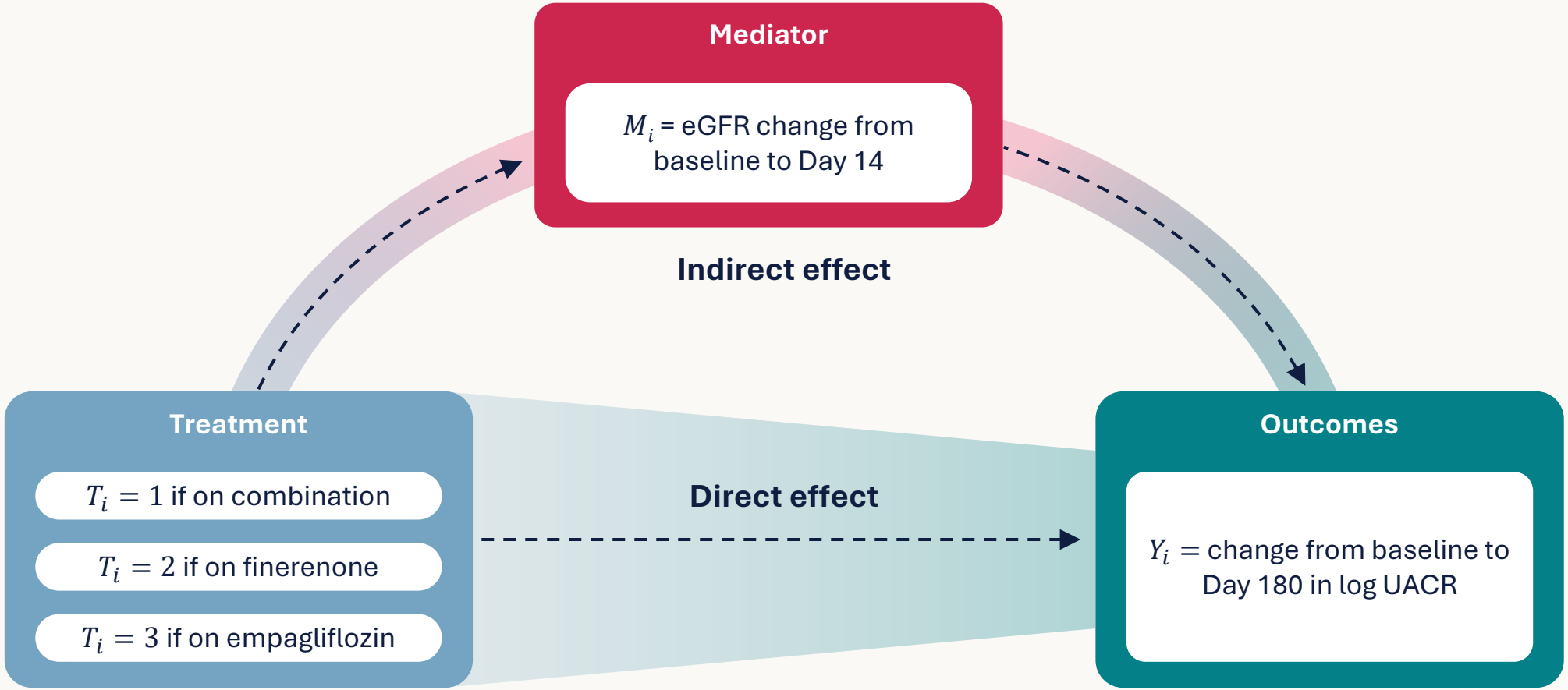

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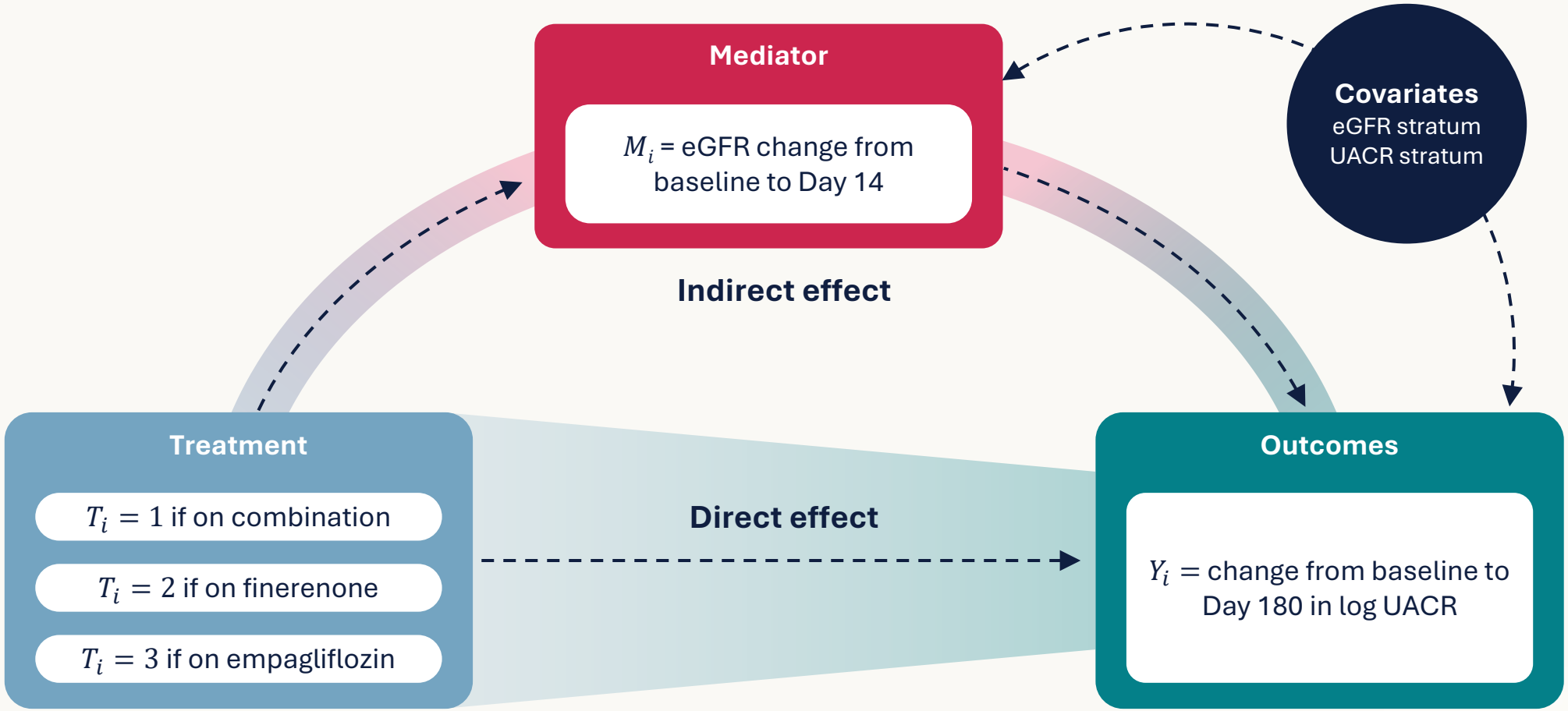

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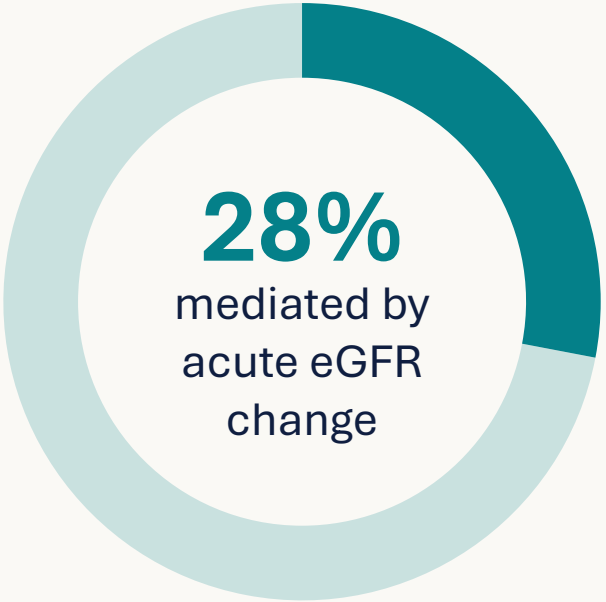
EMPAGLIFLOZIN EFFICACY IS MEDIATED BY HEMODYNAMICS

Adding empagliflozin to finerenone

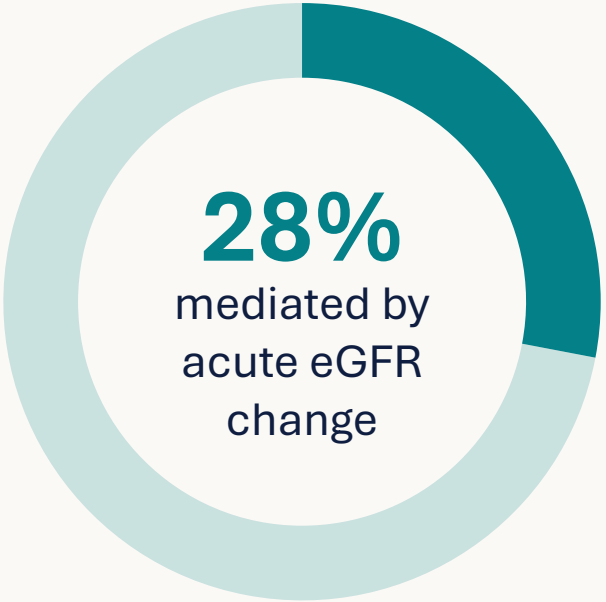


Empagliflozin benefit is driven by hemodynamic unloading

eGFR, estimated glomerular filtration rate.

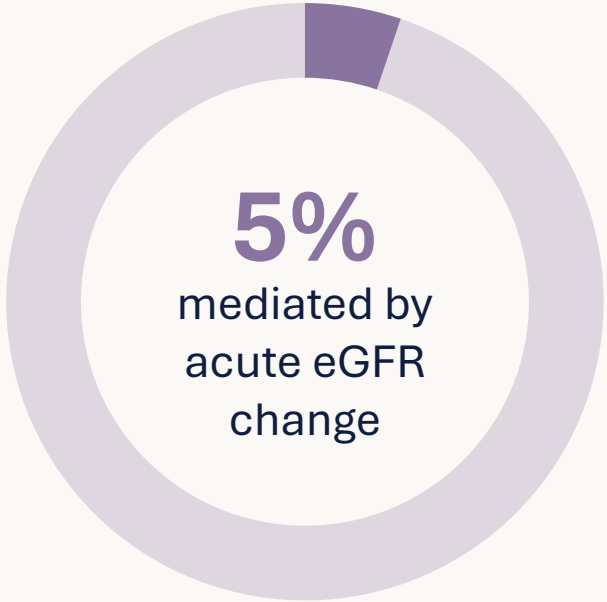
FINERENONE EFFICACY IS NOT MEDIATED BY HEMODYNAMICS

Adding empagliflozin to finerenone



Empagliflozin benefit is driven by hemodynamic unloading

Adding finerenone to empagliflozin



Finerenone benefit is largely independent of hemodynamic changes

eGFR, estimated glomerular filtration rate.

SUMMARY AND CLINICAL IMPLICATIONS

01

Expect the dip

- Acute decline in eGFR is a functional, hemodynamic signature of combination therapy
- It is most pronounced in participants with preserved eGFR and those on diuretics

02

It is reversible

- The decline in eGFR represents glomerular unloading, not structural injury
- AKI rates were low and eGFR returned to baseline after washout

03

Monitor potassium

- eGFR drops ≥30% are associated with a ~2-fold increased risk of hyperkalemia
- Monitor potassium closely in “dippers” but maintain therapy for long-term benefit

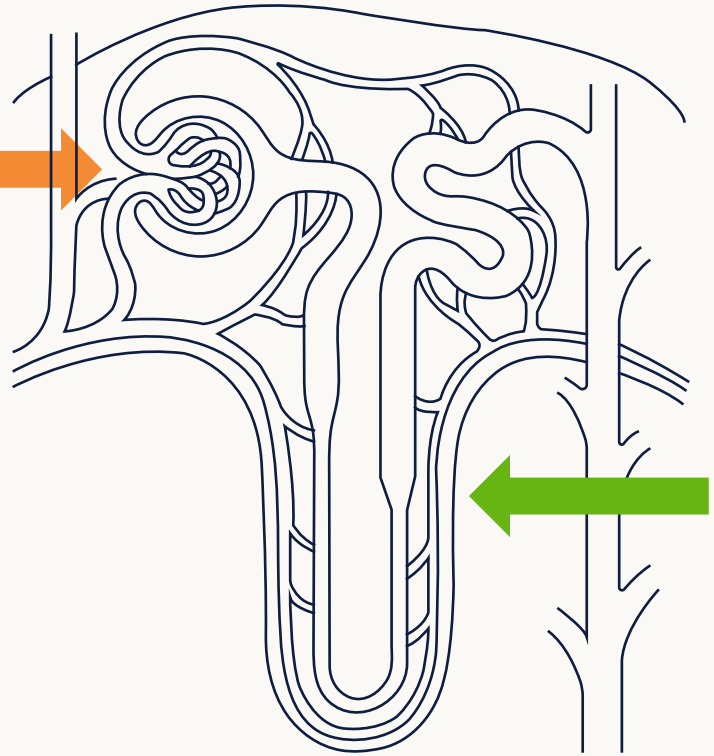
AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

A MECHANISTIC RATIONALE FOR COMBINATION THERAPY

Empagliflozin[1]

Tubuloglomerular feedback

- Afferent constriction
- Hemodynamic unloading



Finerenone[2]

MR blockade

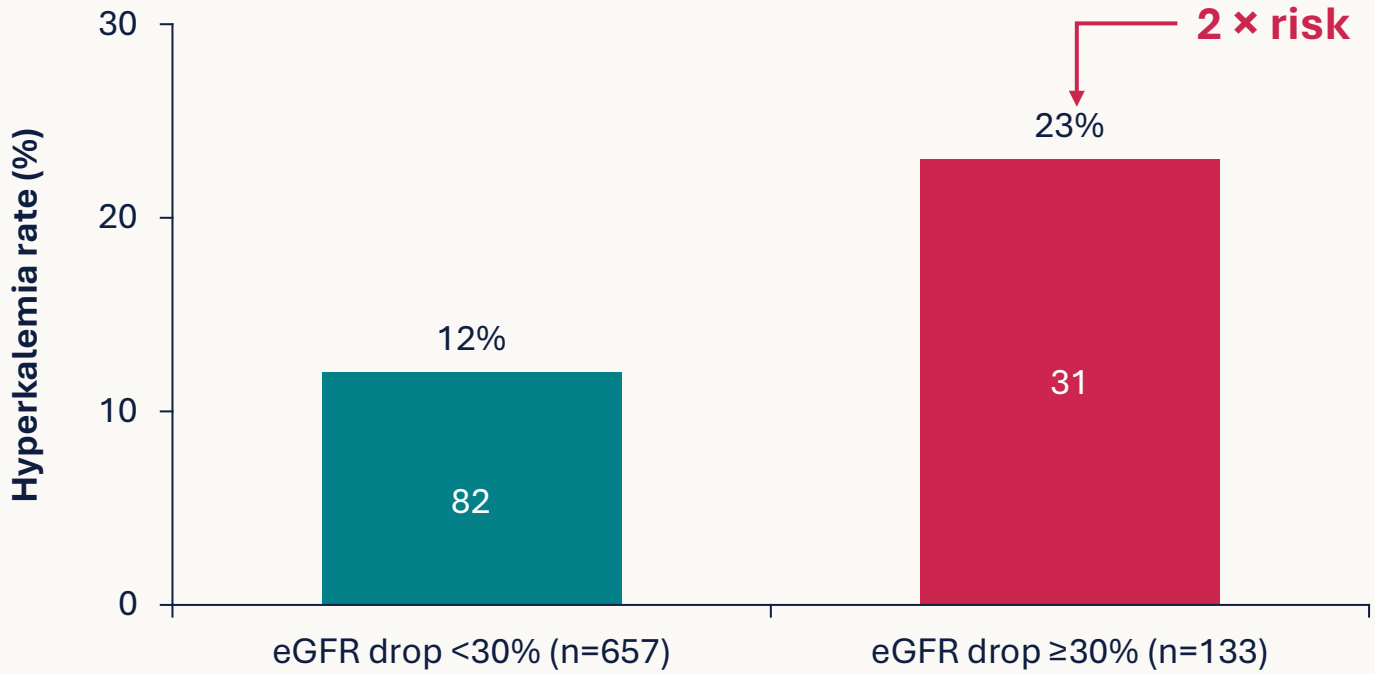
- Anti-inflammation and anti-fibrosis
- Tissue protection

Distinct, complementary angles of attack against CKD

CKD, chronic kidney disease; MR, mineralocorticoid receptor.

1. Vallon V. *Am J Hypertens*. 2024;37(11):841–852. 2. Kolkhof P, et al. *Int J Mol Sci*. 2022;23(16):9243.

THE “DIP” (≥30%) AS A RISK MARKER FOR HYPERKALEMIA

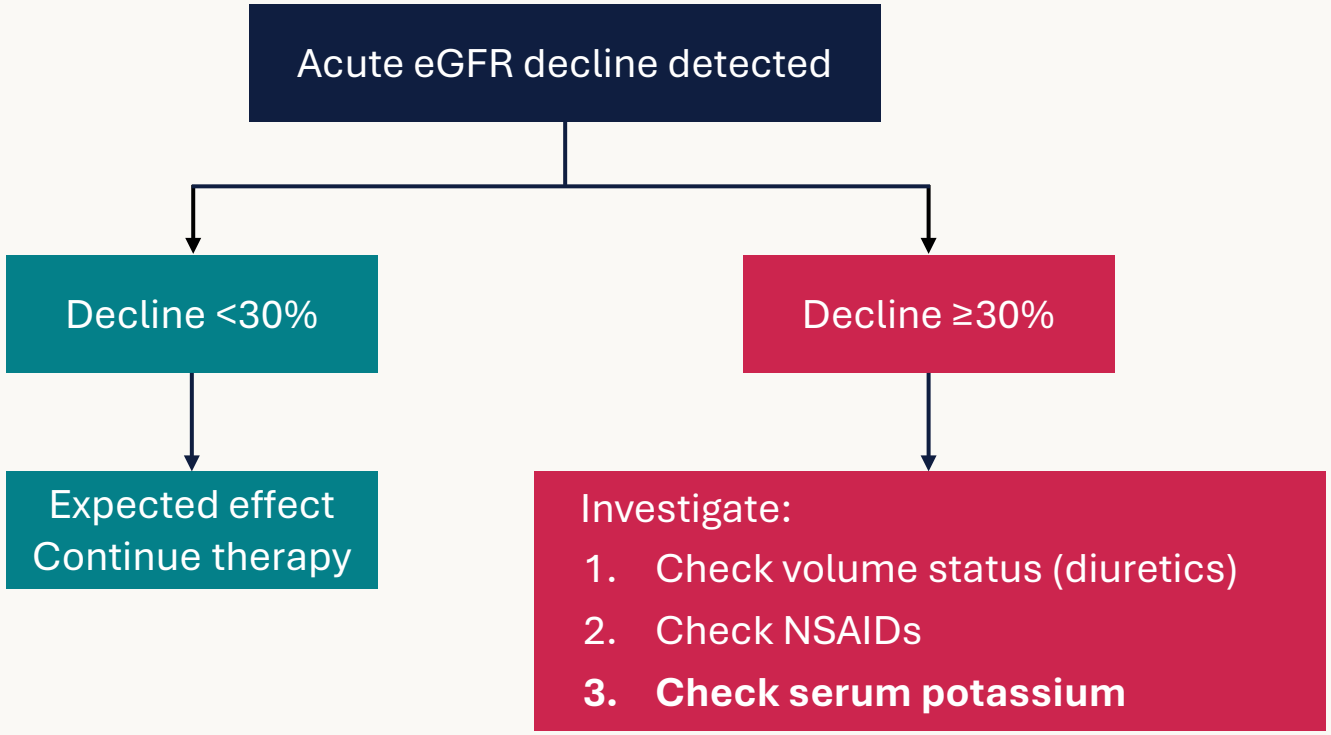


Severe hyperkalemia (potassium >6.0 mmol/L) is 4-fold more likely in participants with a significant eGFR drop than those without

Key message: An eGFR drop (≥30%) is not a signal to stop the drug, but a signal to monitor potassium

eGFR, estimated glomerular filtration rate.

NAVIGATING THE ACUTE DROP: A CLINICAL ALGORITHM[1]



Treat the drop as an expected pharmacodynamic consequence of glomerular hemodynamic unloading

eGFR, estimated glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs.

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int*. 2024;105(4S):S117–S314.

PHARMACODYNAMICS, NOT FAILURE

Expect the drop

Acute decline is a sign of glomerular unloading

Know the drivers

Driven by high baseline eGFR and diuretics

Monitor, don't stop

Monitor hyperkalemia, but continue therapy as appropriate

eGFR, estimated glomerular filtration rate.

PHARMACODYNAMICS, NOT FAILURE

Expect the drop

Acute decline is a sign of glomerular unloading

Know the drivers

Driven by high baseline eGFR and diuretics

Monitor, don't stop

Monitor hyperkalemia, but continue therapy as appropriate

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

eGFR, estimated glomerular filtration rate.

THANK YOU TO MY CO-AUTHORS, INVESTIGATORS, STAFF, AND TRIAL PARTICIPANTS

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