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MARCH 28-31, 2026 | YOKOHAMA, JAPAN

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EFFECT OF SIMULTANEOUS INITIATION OF FINERENONE AND EMPAGLIFLOZIN ON URINARY ALBUMIN-TO-CREATININE RATIO BY AGE AND SEX IN THE RANDOMIZED CONFIDENCE TRIAL

WCN26-AB-7771

Rajiv Agarwal, MD, MS

Consultant Nephrologist

Richard L Roudebush VA Medical Center and Indiana University School of Medicine

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

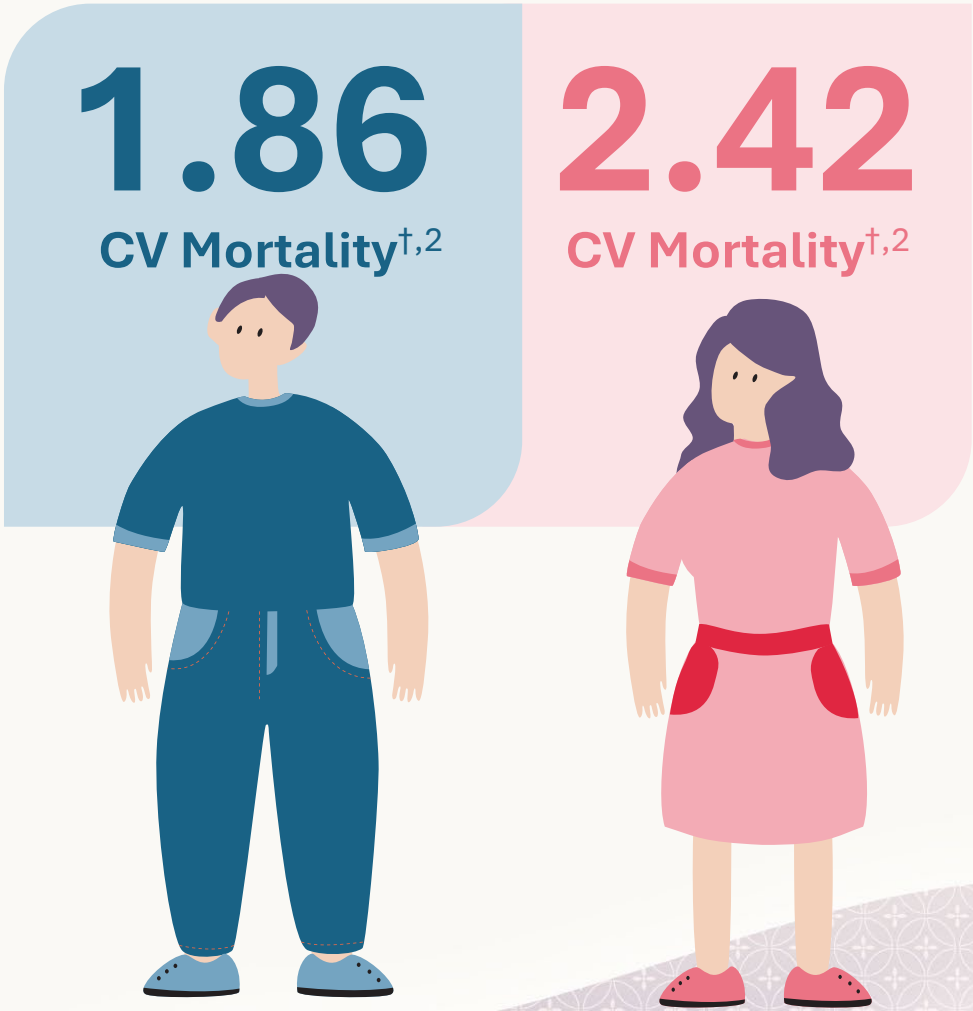
Funding: This work was supported by Bayer AG, who funded the CONFIDENCE trial

FEMALES AND CV RISK IN T2D

Paradoxical loss of CV protection in females with diabetes

Females with diabetes have a 2-fold excess CV risk compared with males with diabetes[1]

Females with diabetes have an earlier onset of fatal MI than males with diabetes[1]



†Relative risk compared with people without diabetes.
CV, cardiovascular; MI, myocardial infarction; T2D, type 2 diabetes.
1. Regensteiner JG, et al. *Circulation*. 2015;132(25):2424–2447. 2. Wang Y, et al. *BMC Med*. 2019;17(1):136.

THE AGE PARADOX

Earlier onset of T2D significantly increases relative risk for complications,[1] yet older patients face the most prescribing hesitancy[2,3]

In people with diabetes, CKD magnifies CV risk significantly[4,5]

CKD, chronic kidney disease; CV, cardiovascular; T2D, type 2 diabetes.

1. Morton JI, et al. *Diabetes Res Clin Pract*. 2022;190:110022. 2. Szoszkiewicz M, et al. *PLoS One*. 2025;20(12):e0337586. 3. Cherubini A, et al. *Drugs Aging*. 2012;29(6):463–475. 4. Afkarian M, et al. *J Am Soc Nephrol*. 2013;24(2):302–308. 5. Kidney Disease: Improving Global Outcomes Diabetes Work Group. *Kidney Int*. 2020;98(4S):S1–S115.

CRITICAL GAPS IN PRECISION NEPHROLOGY

SGLT2i trials lack sex-stratified albuminuria data

Longitudinal age-response relationship remains undefined

Treatment benefit disparity by age and sex is essentially unknown

Study	Baseline eGFR subgroups	Sex-specific UACR outcomes
EMPA-REG OUTCOME[1]	✓	○
CANVAS Program[2]	✓	○
DECLARE-TIMI 58[3]	✓	○
DAPA-CKD[4]	✓	○

eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

1. Zinman B, et al. *N Engl J Med*. 2015;373(22):2117–2128. 2. Neal B, et al. *N Engl J Med*. 2017;377(7):644–657. 3. Wiviott SD, et al. *N Engl J Med*. 2019;380(4):347–357.
4. Heerspink HJL, et al. *N Engl J Med*. 2020;383(15):1436–1446.

RESOLVING THE KNOWLEDGE GAP

Primary aim

Evaluate baseline clinical characteristics and longitudinal changes in UACR across specific age and sex cohorts

UACR, urinary albumin-to-creatinine ratio.

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Quantify the independent effects of age and sex on the anti-albuminuric efficacy of finerenone, empagliflozin, or their simultaneous combination

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Determine if safety profiles (specifically AKI and hyperkalemia) vary significantly by age or sex

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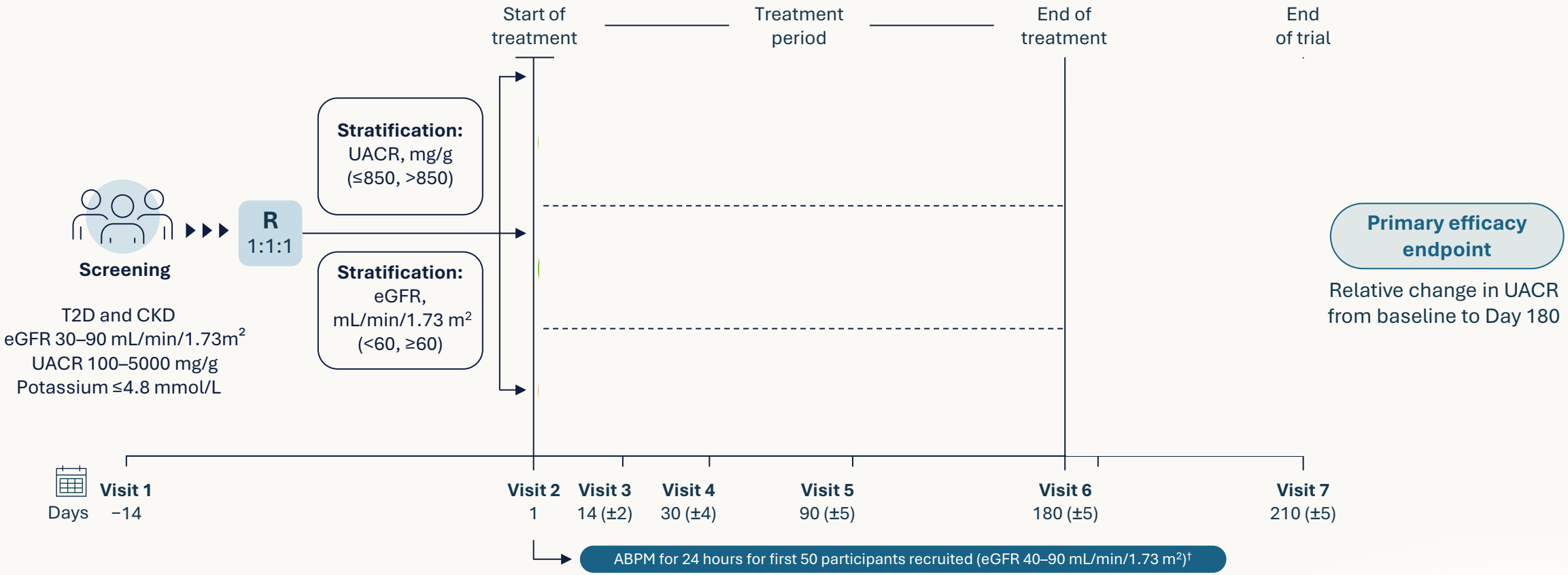
CONFIDENCE TRIAL DESIGN

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



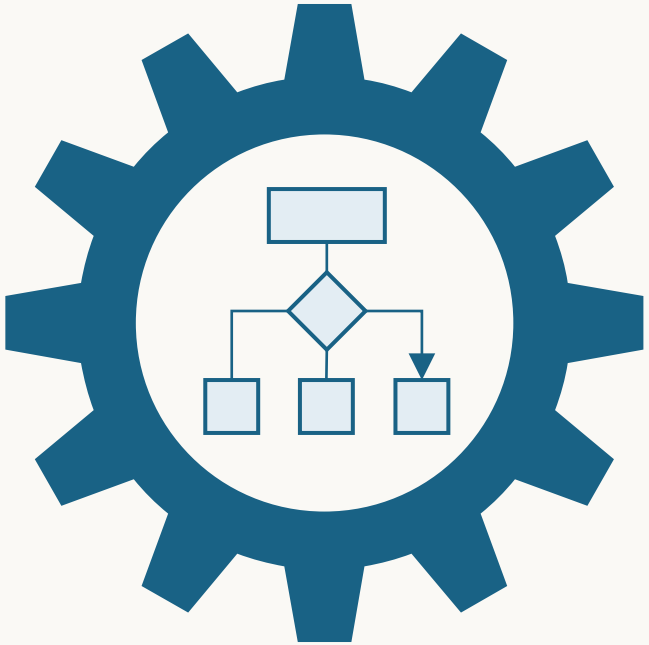
This figure is adapted from Green JB, et al.[1] under the terms of the Creative Commons Attribution-Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/).
†Participants with an eGFR of 40–90 mL/min/1.73 m^2 were recruited (part A) prior to recruiting participants with an eGFR of 30–90 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(4):894–903. 2. Agarwal R, et al. *N Engl J Med.* 2025;393(6):533–543.

STATISTICAL METHODOLOGY: LINEAR MIXED-EFFECTS MODELING†

Fixed effects

- Treatment
- Visit
- Treatment-by-visit interaction
- Region
- eGFR stratum
- UACR stratum
- Age
- Sex

Linear mixed-effects model



Maximal likelihood estimation:
Random effects: Subject and visit

Estimated mean change in UACR

†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; UACR, urinary albumin-to-creatinine ratio. 1. Holden JE, et al. *Am J Nephrol.* 2008;28(5):792–801.

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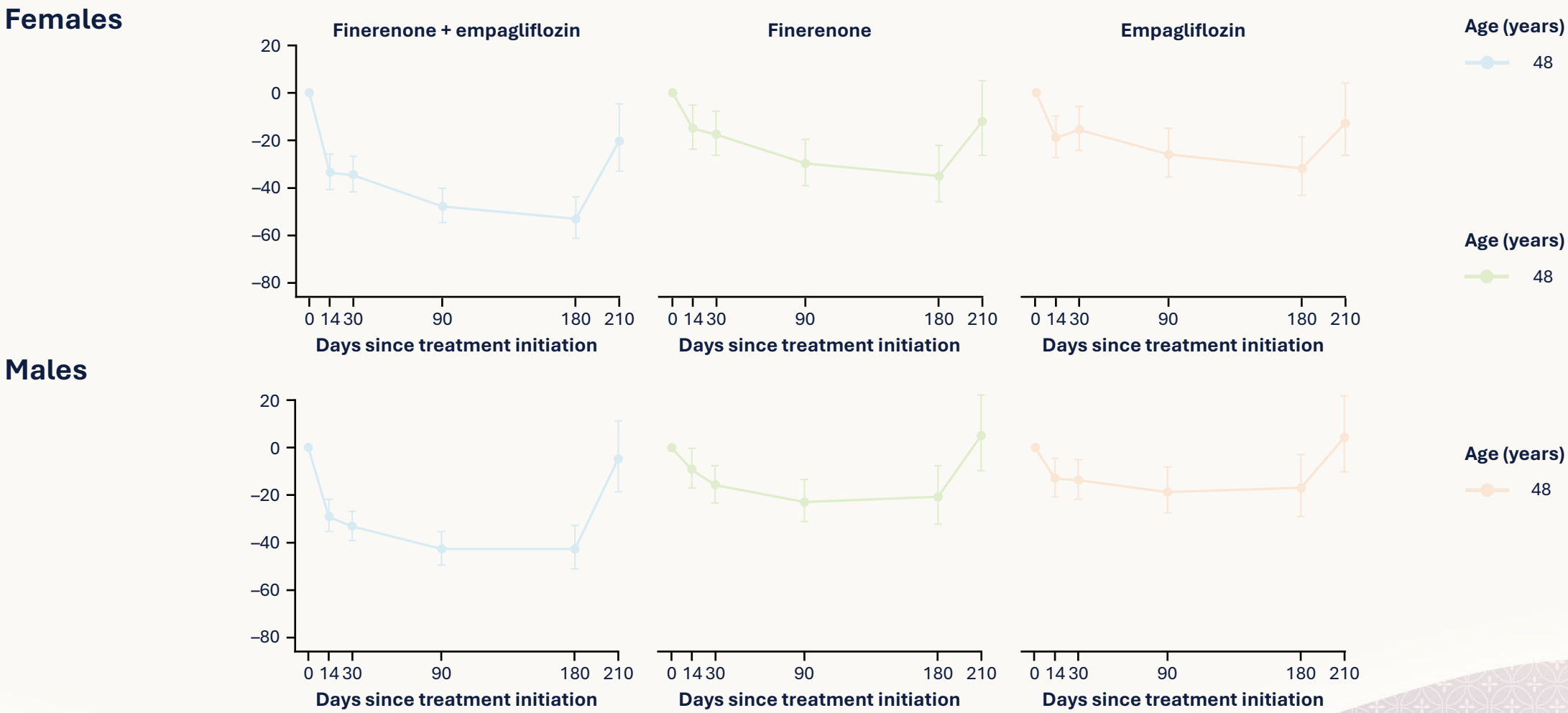
UACR REDUCTION SCALES WITH AGE AND SEX†



†p=0.001 for the effect of increasing age on UACR reduction.
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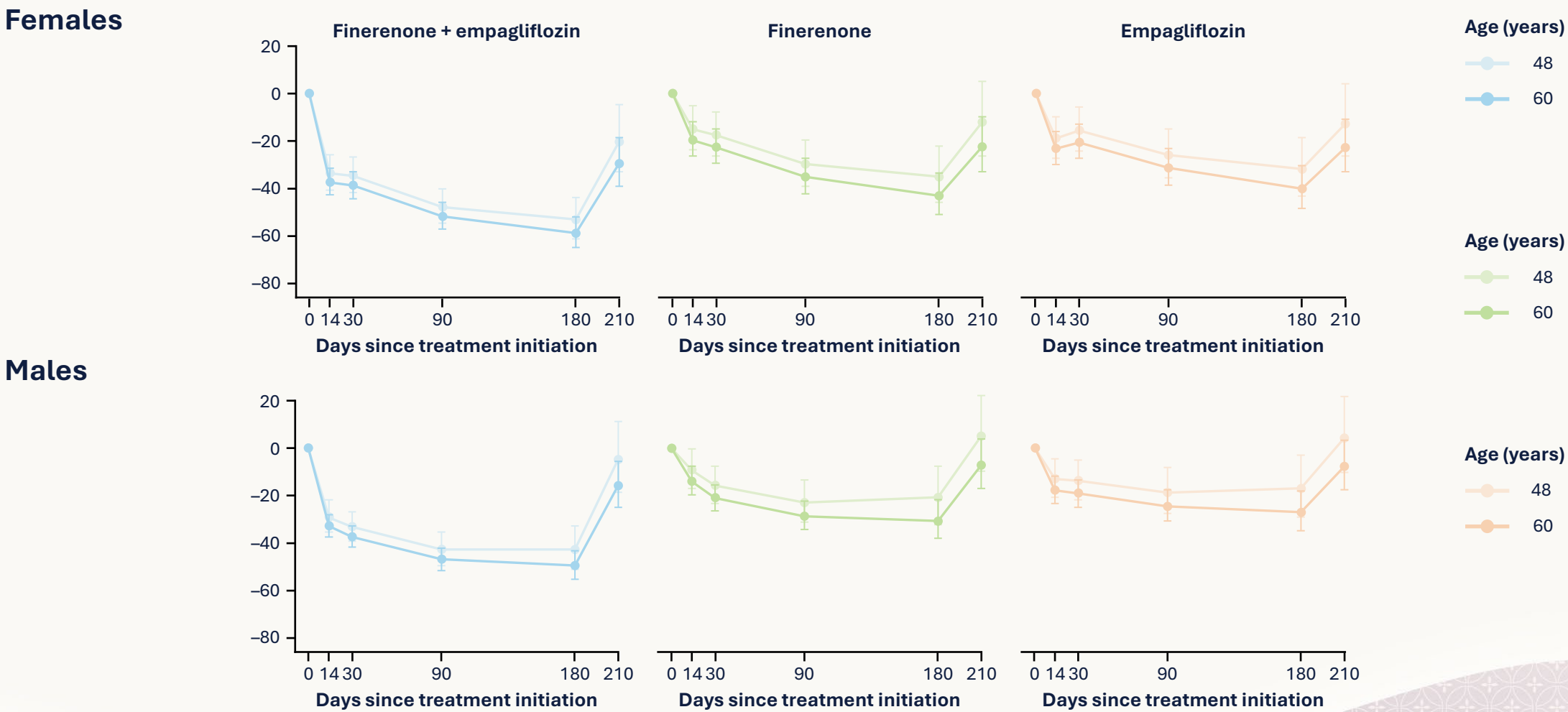

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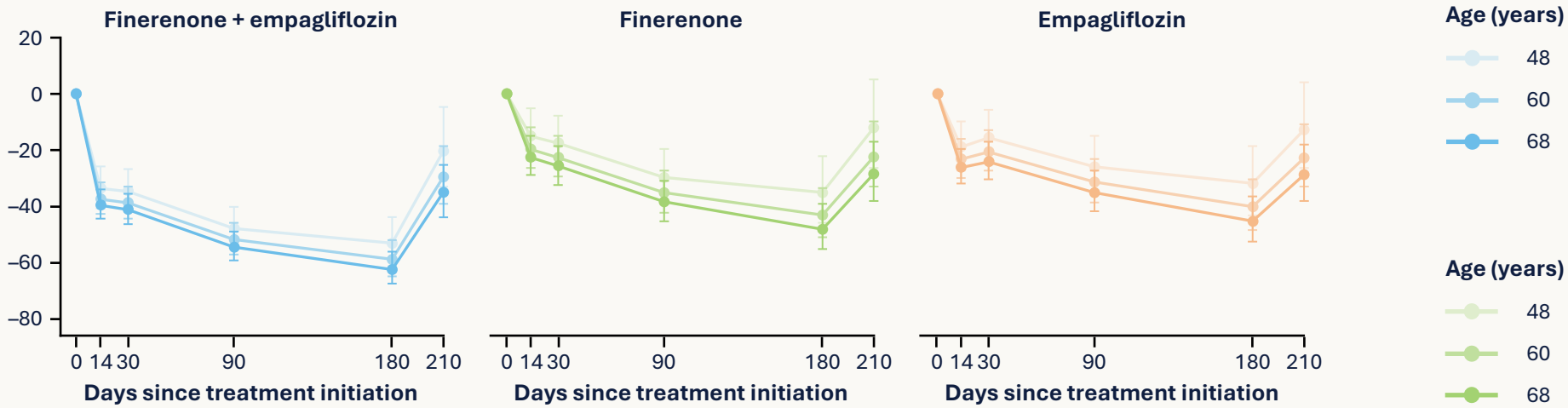
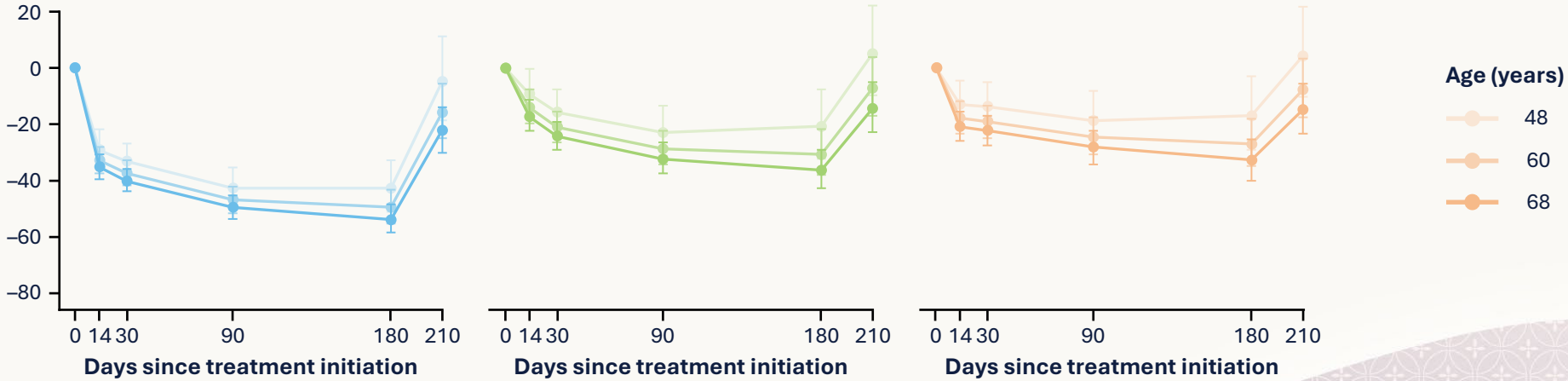
UACR REDUCTION SCALES WITH AGE AND SEX†

Females



Males



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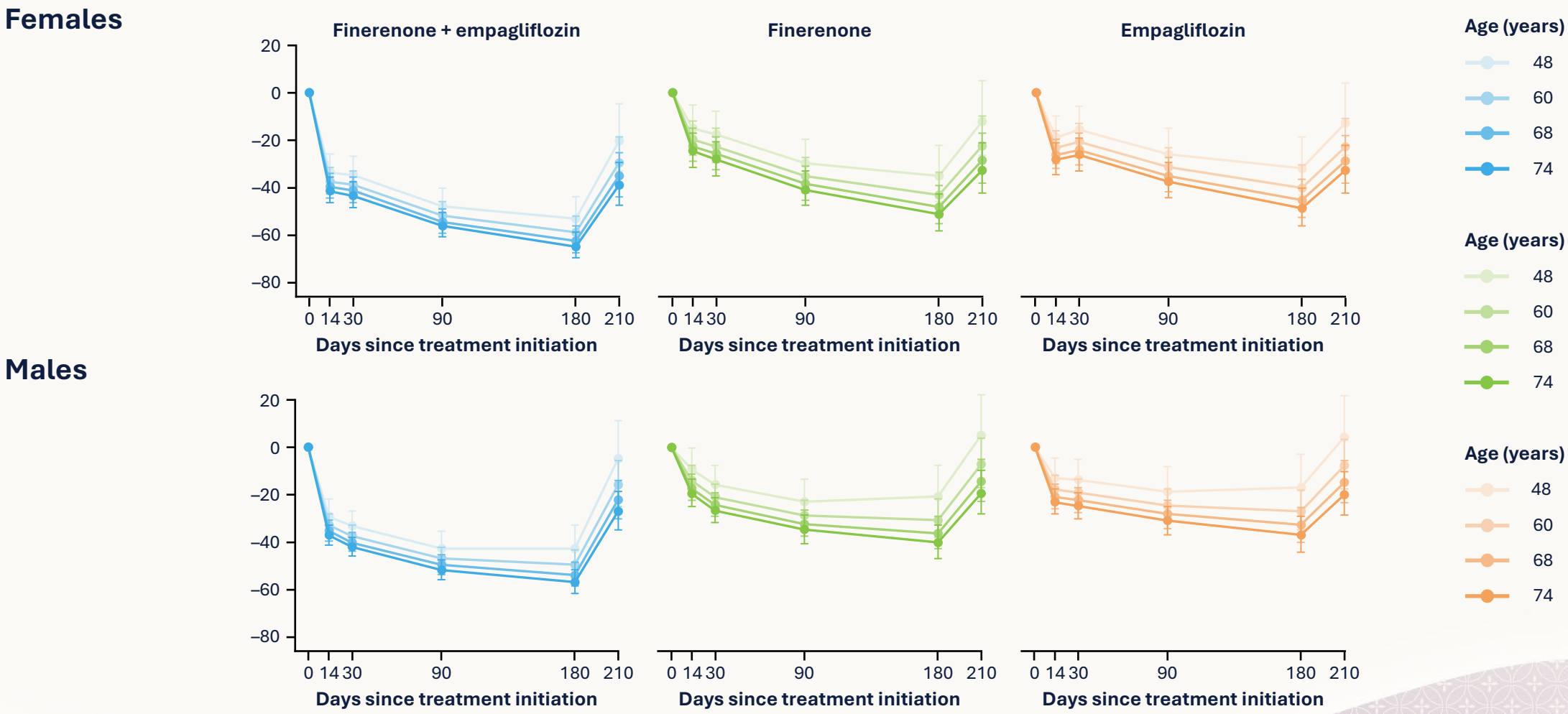

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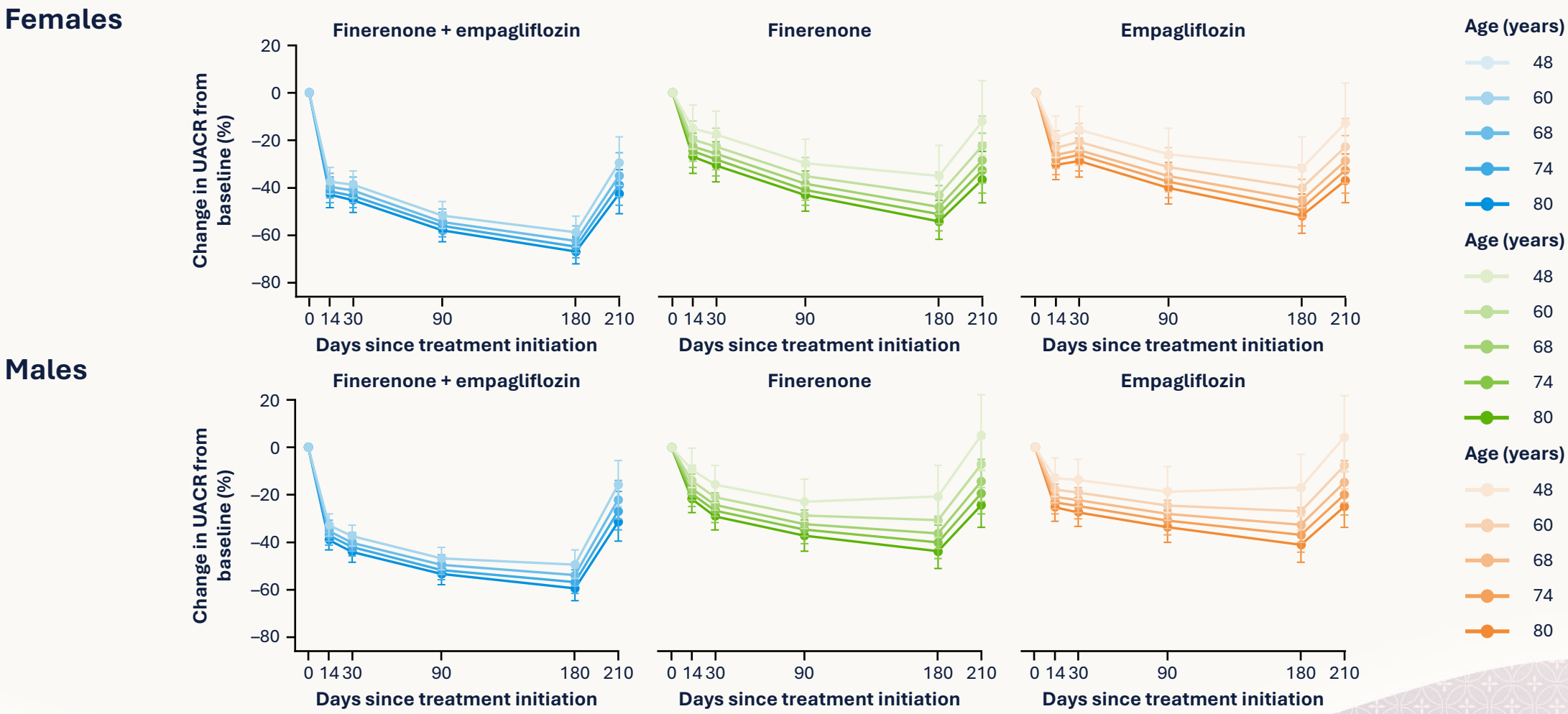

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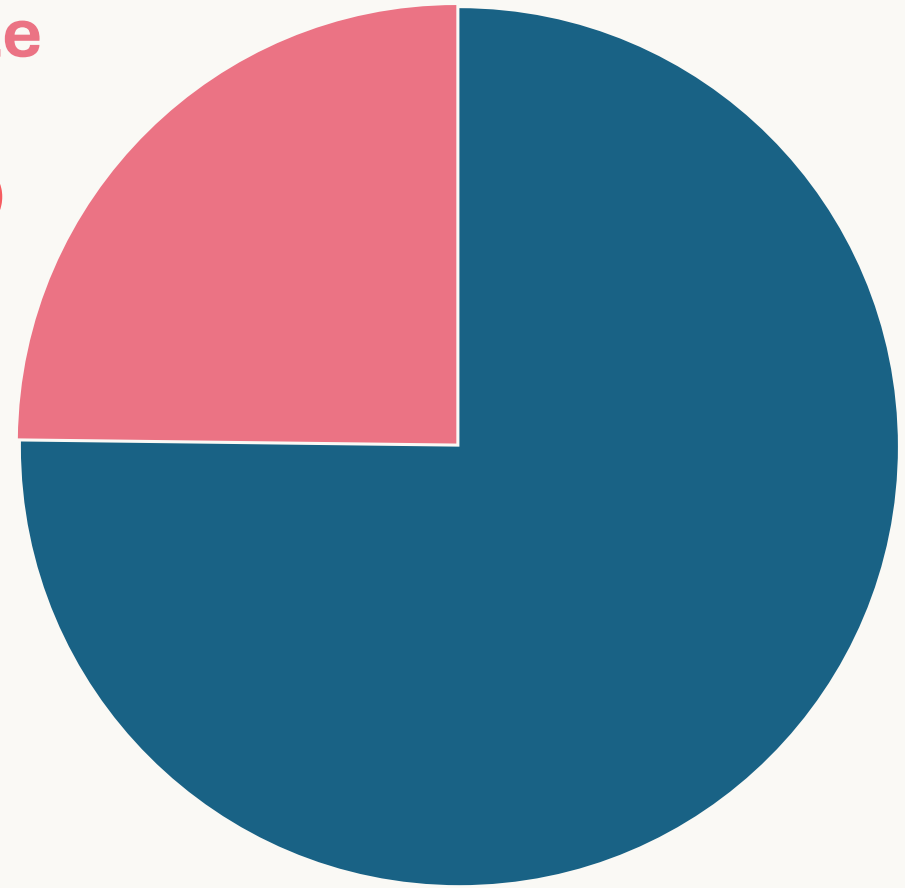
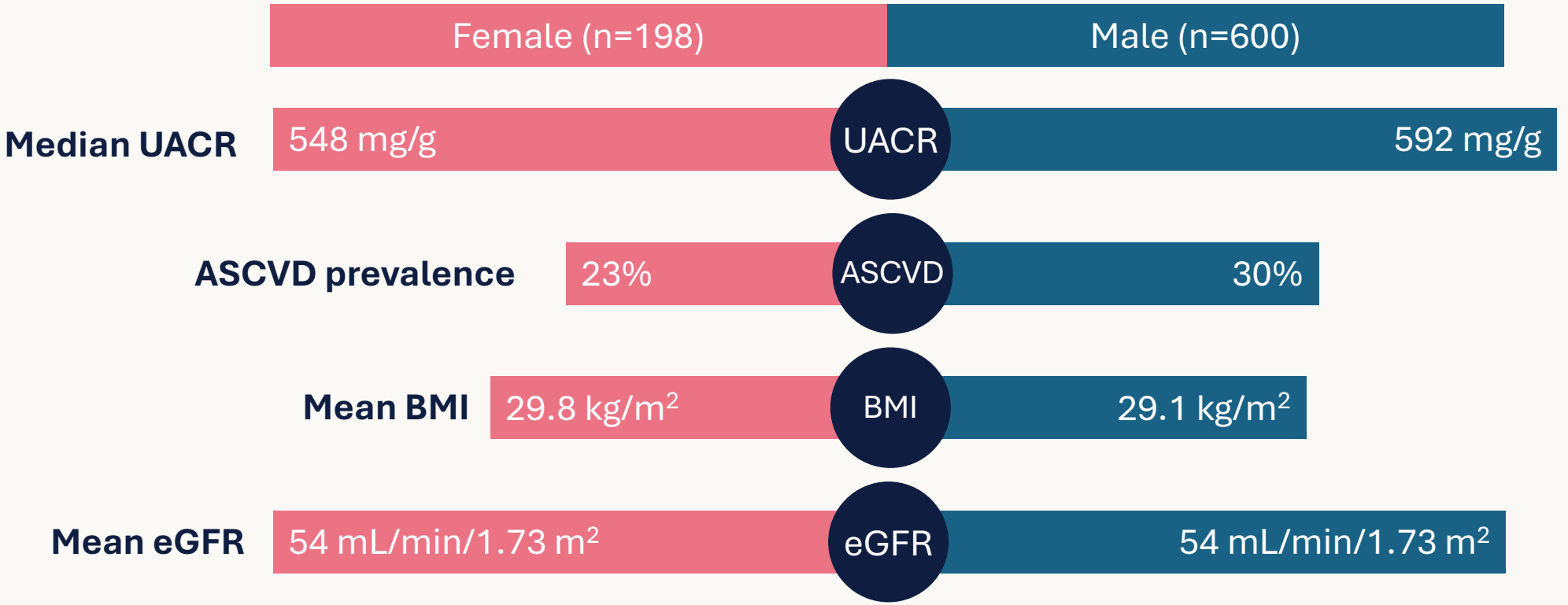
DISTRIBUTION BY BIOLOGICAL SEX

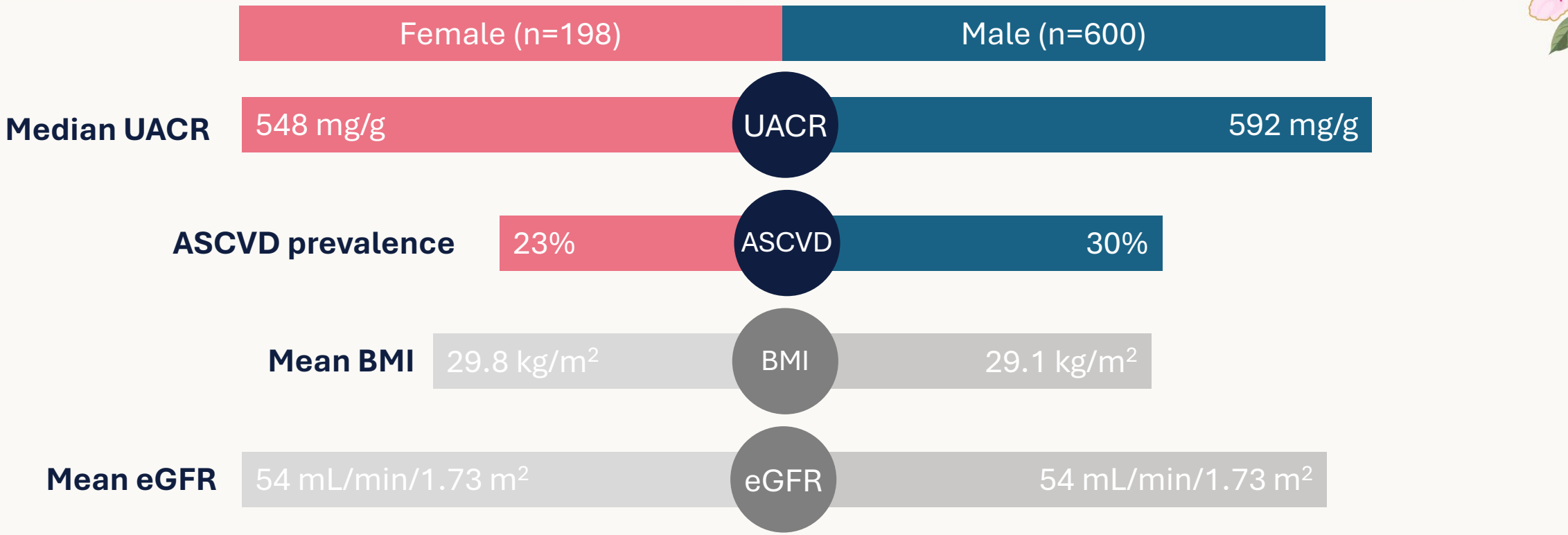


BASELINE CHARACTERISTICS BY BIOLOGICAL SEX



ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

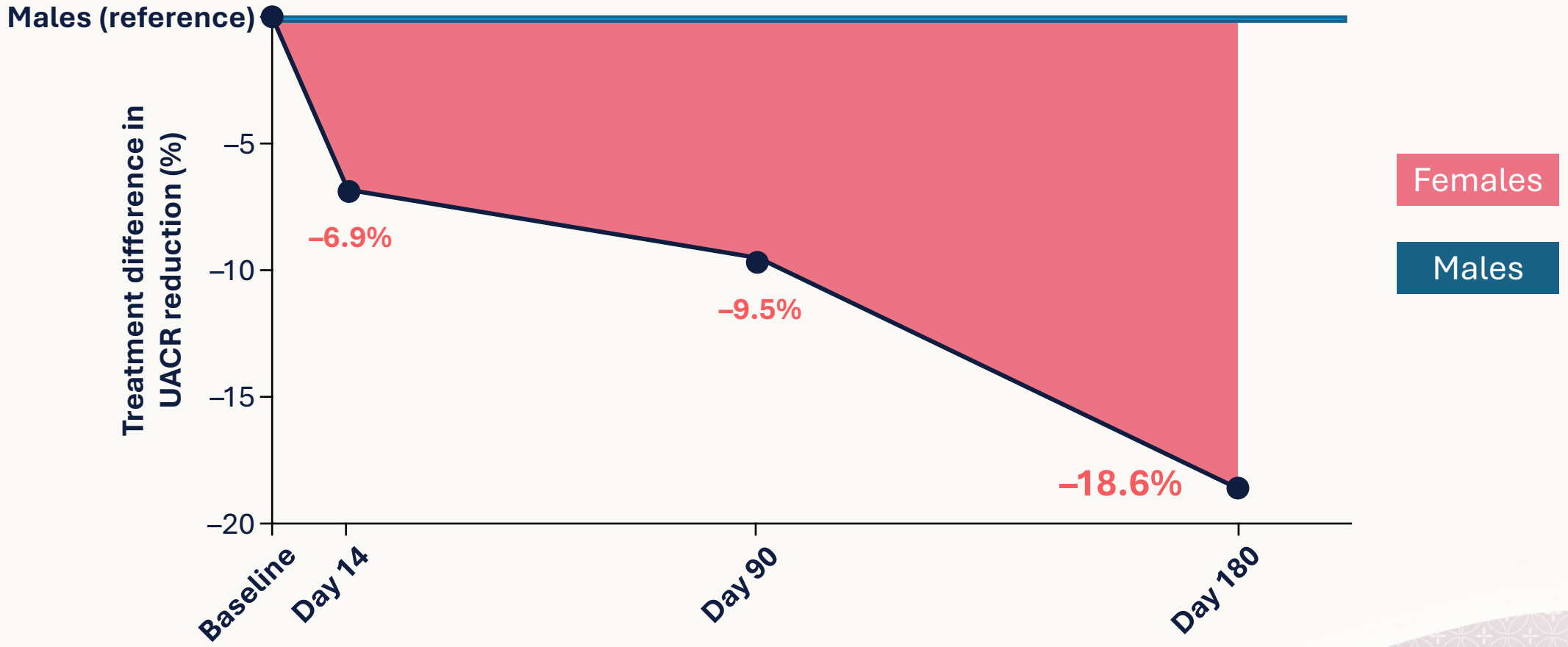
BASELINE CHARACTERISTICS BY BIOLOGICAL SEX



Females entered the trial with numerically lower baseline albuminuria and CV disease burden than males

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

SIGNIFICANT SEXUAL DIMORPHISM IN TREATMENT RESPONSE AMPLIFIES OVER TIME



UACR, urinary albumin-to-creatinine ratio.

SIGNIFICANT SEXUAL DIMORPHISM IN TREATMENT RESPONSE PERSISTS AFTER TREATMENT DISCONTINUATION

18.6%

Greater reduction in UACR for females than males at Day 180 (p=0.008)

Day 180

16.6%

Sustained greater reduction at Day 210, 30 days post-treatment

Day 210

UACR, urinary albumin-to-creatinine ratio.

SIGNIFICANT SEXUAL DIMORPHISM IN TREATMENT RESPONSE IS INDEPENDENT OF TREATMENT

Sex interaction

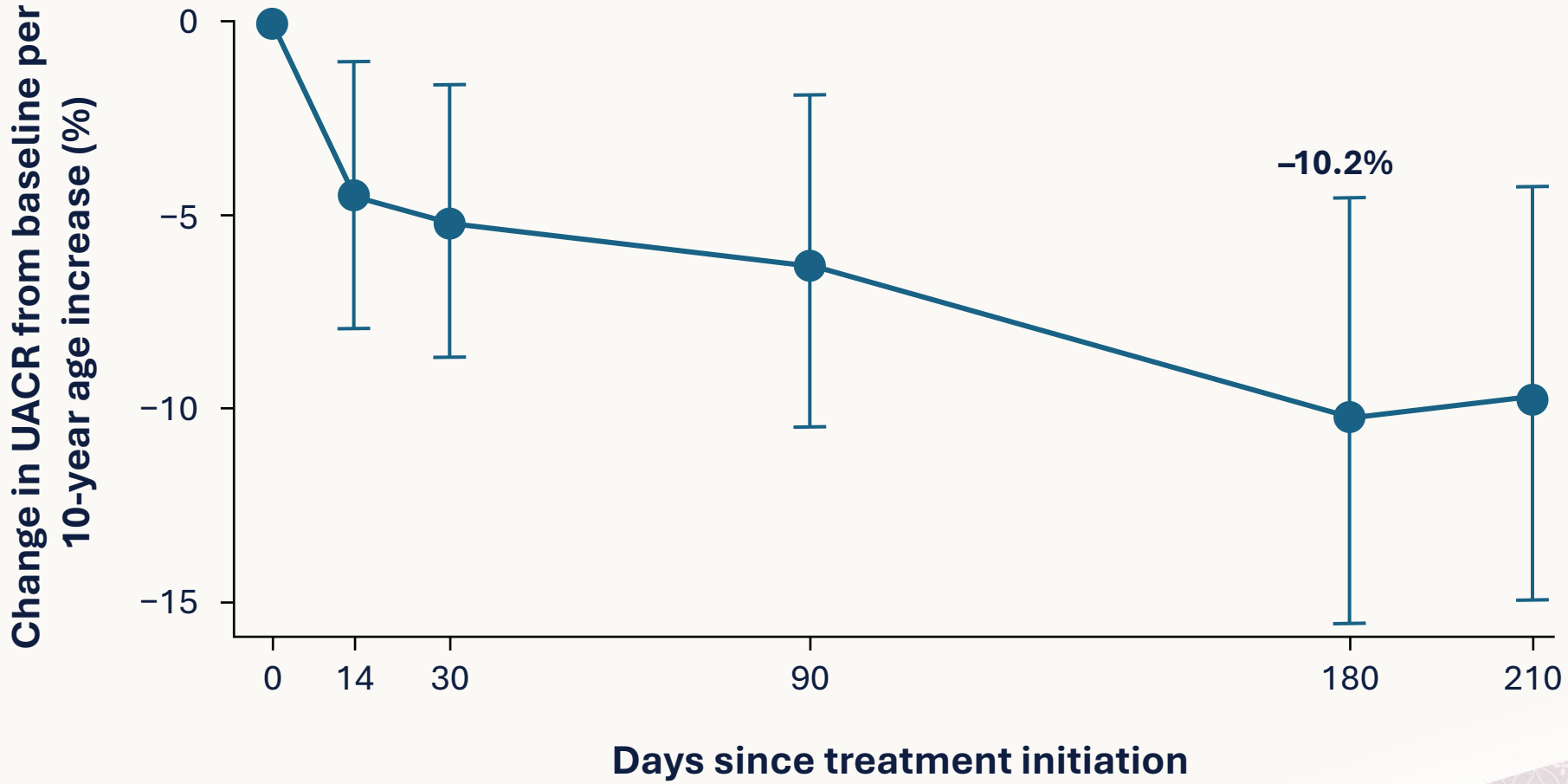
p=0.46

OLDER AGE → LOWER eGFR AND MORE ASCVD

	Q1 ≤60 years	Q2 61–68 years	Q3 69–74 years	Q4 >74 years
eGFR (mL/min/1.73 m^2), mean	57 **Decrease**	56	52	51
ASCVD, %	14	27	37	36 **Increase**
Statin use, %	66	74	83	78
Geography	Predominantly Asia (53%)		Predominantly North America/Europe (64%)	

ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; Q, quartile.

UACR REDUCTION SCALES LINEARLY WITH AGE



UACR, urinary albumin-to-creatinine ratio.

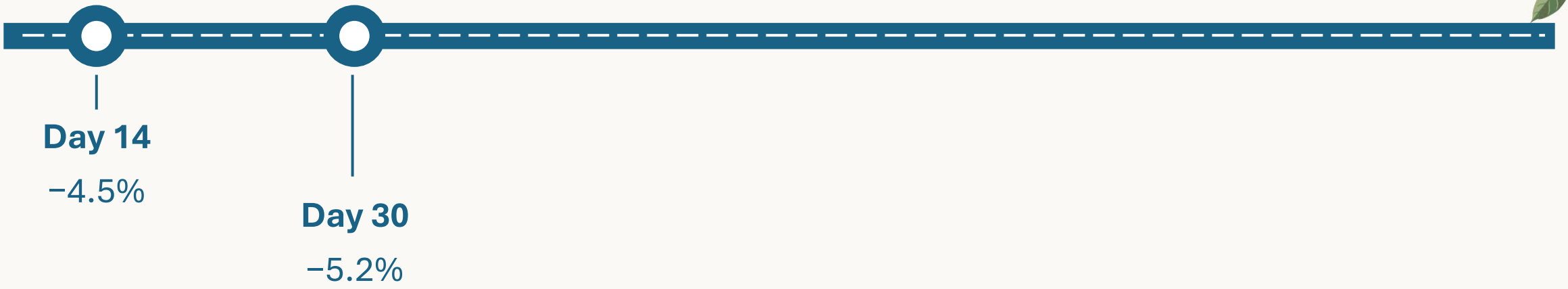
QUANTIFYING THE 10-YEAR INCREMENTAL BENEFIT†

Day 14

−4.5%

†UACR reductions per 10-year increase in age, calculated at each study timepoint.
UACR, urinary albumin-to-creatinine ratio.

QUANTIFYING THE 10-YEAR INCREMENTAL BENEFIT†



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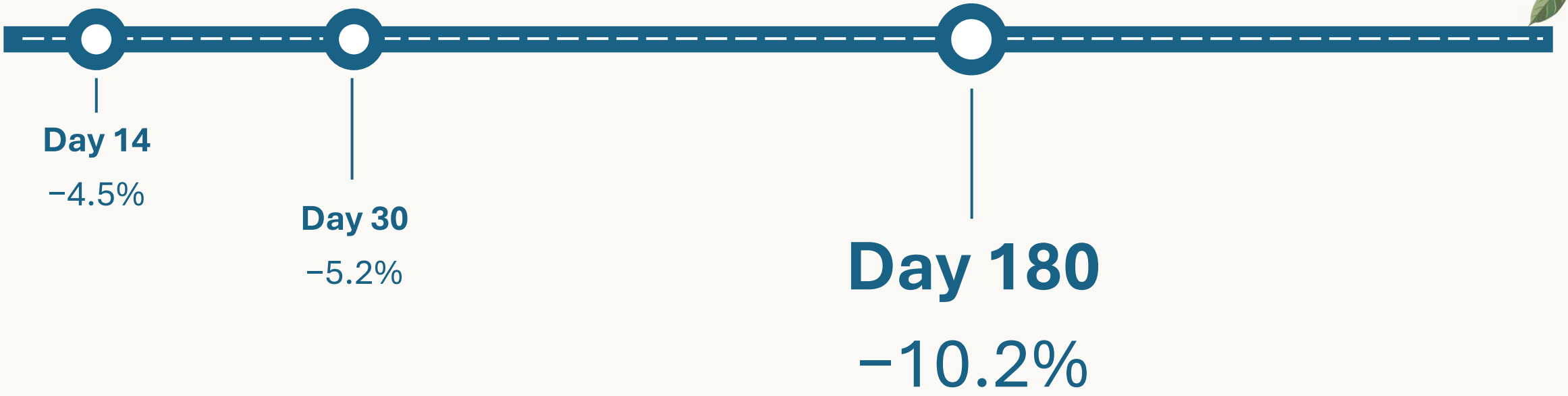

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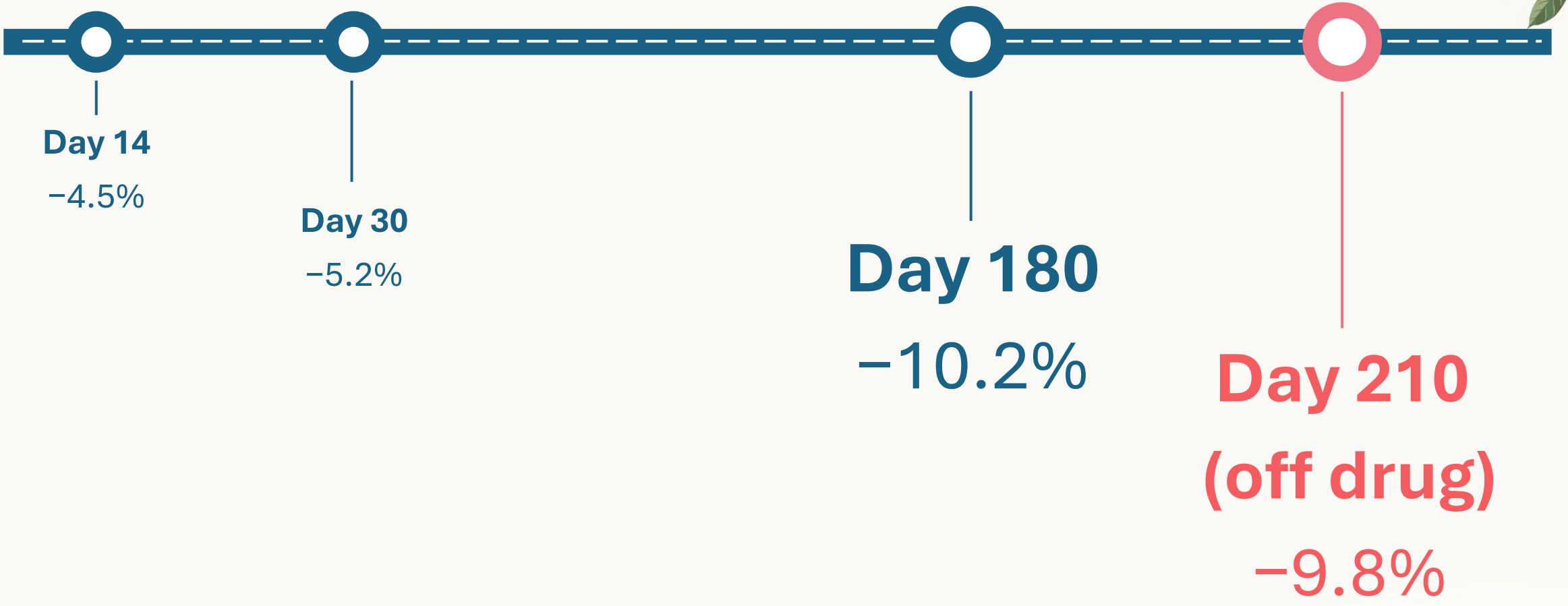

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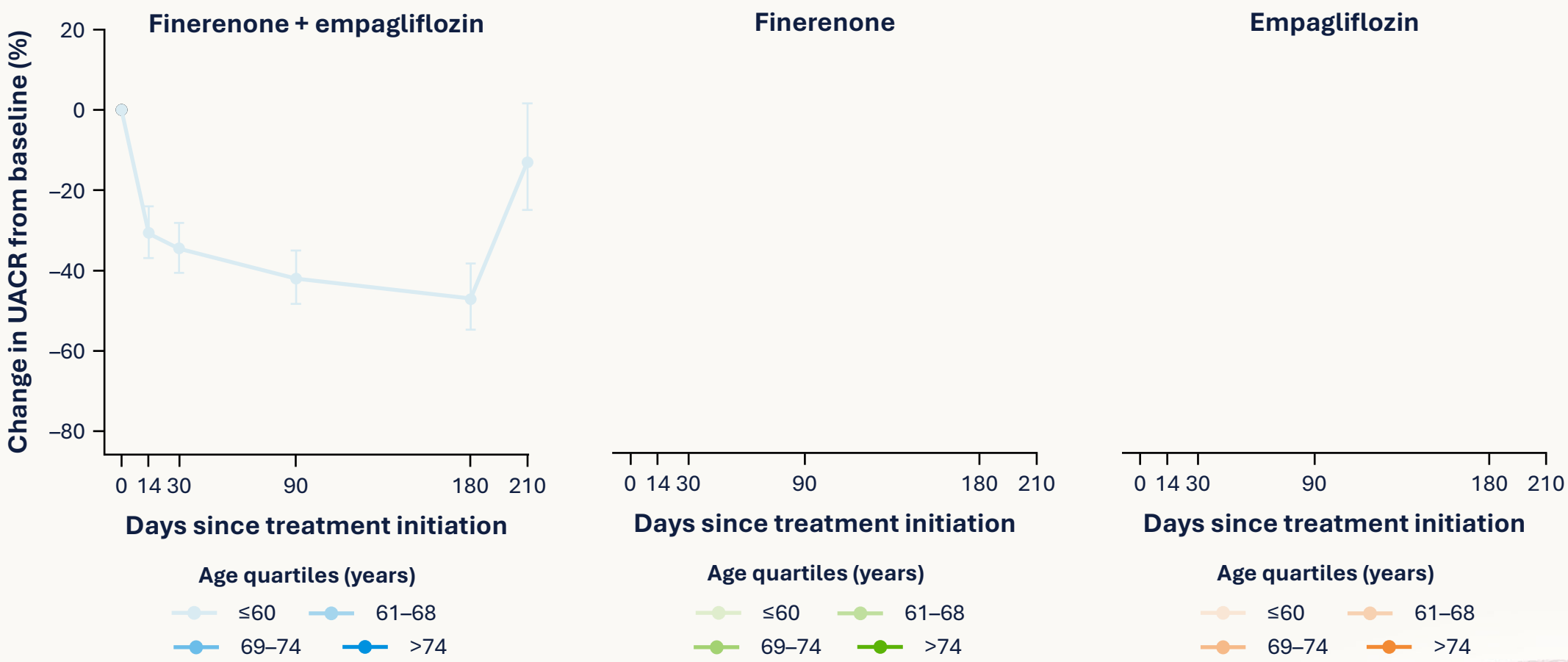
ROBUSTNESS OF AGE EFFECT ACROSS QUARTILES†



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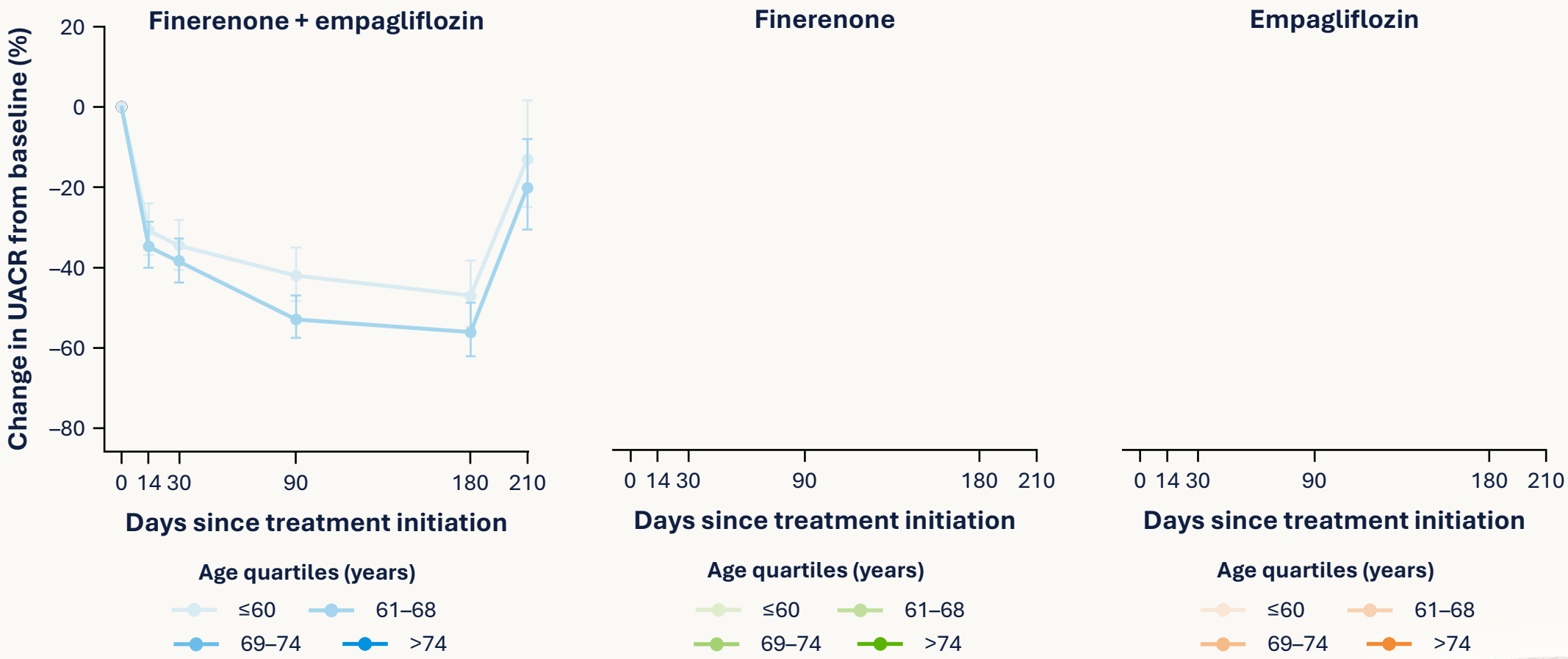

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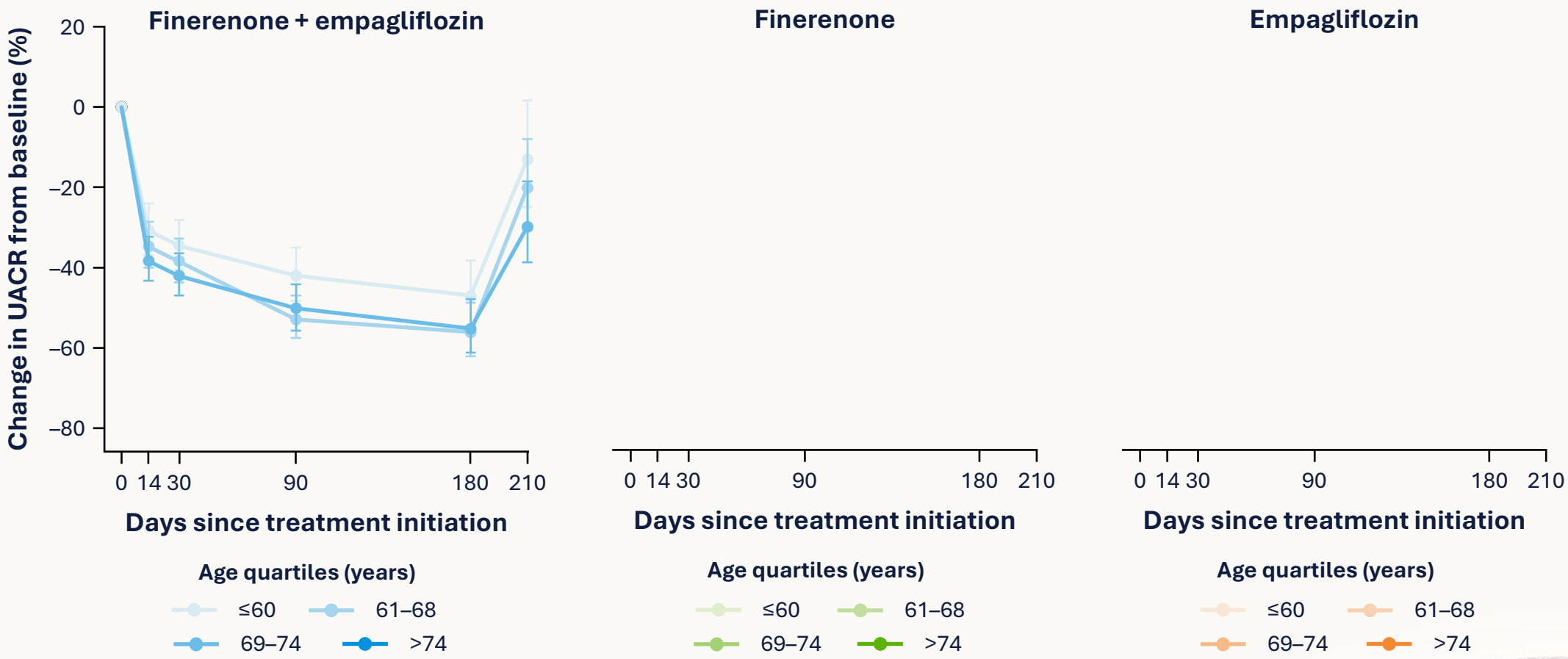

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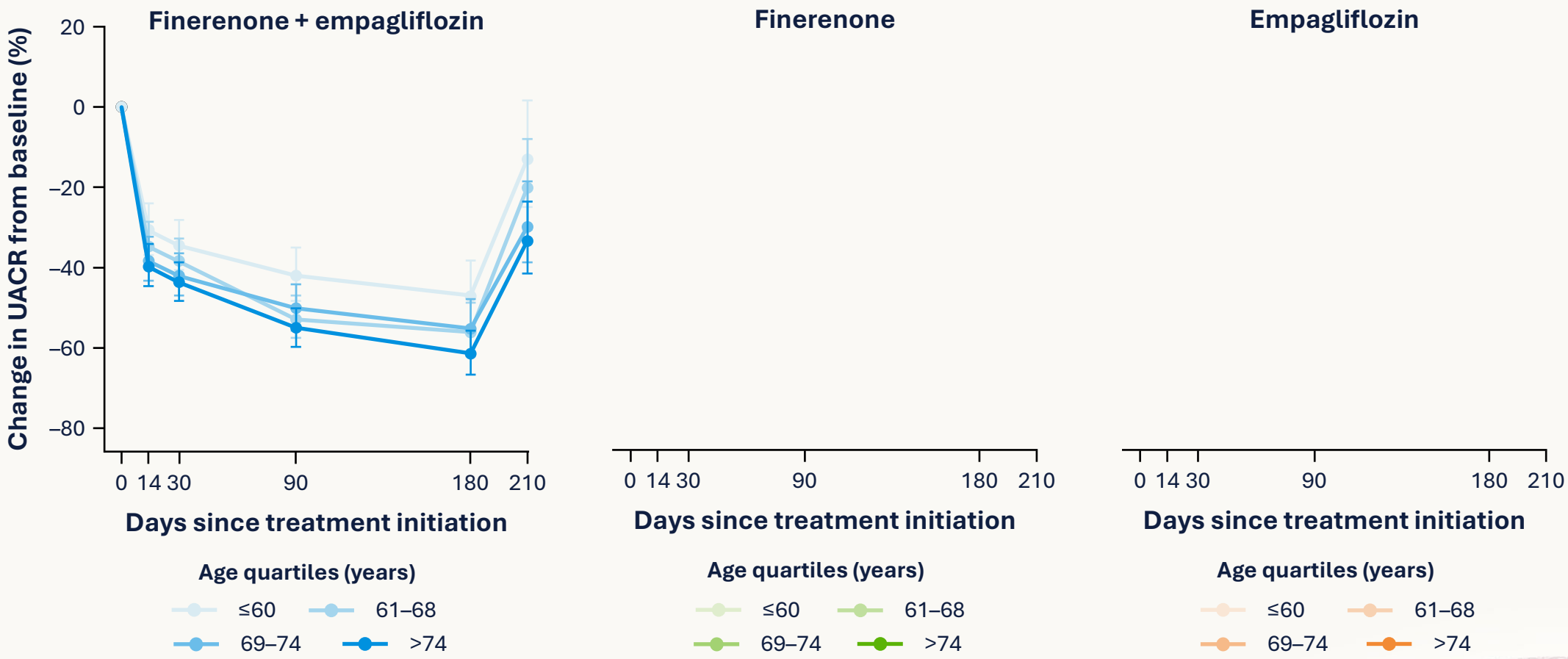

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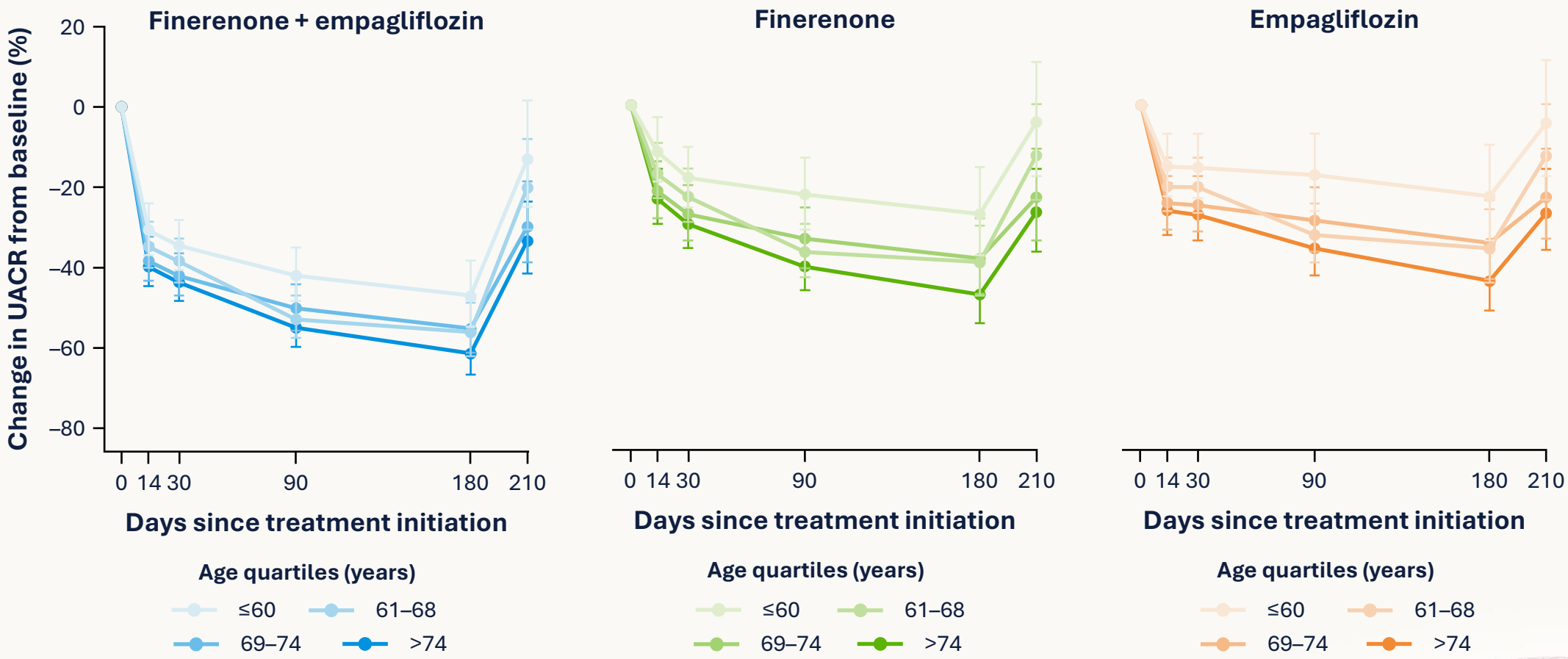

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AGE EFFECT IS INDEPENDENT OF TREATMENT ASSIGNMENT

Age interaction

p=0.28

ADVANCED AGE IS AN EFFICACY MULTIPLIER

Age effect

p=0.001

Key finding

Increasing age is associated with a progressively greater reduction in UACR from baseline at all observed time points

Linear effect

Findings hold true continuously and by predefined quartiles (p=0.009)

UACR, urinary albumin-to-creatinine ratio.

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SAFETY PROFILE MAINTAINED ACROSS DEMOGRAPHICS

Safety event, %	Age quartile 1 (youngest)	Age quartile 4 (oldest)
AKI	0.0	0.5
	No clinically relevant association	
Hyperkalemia	13.4	12.0
	Incidence consistent across age	
Symptomatic hypotension	0.0	0.0
	Rare events	

AKI, acute kidney injury.

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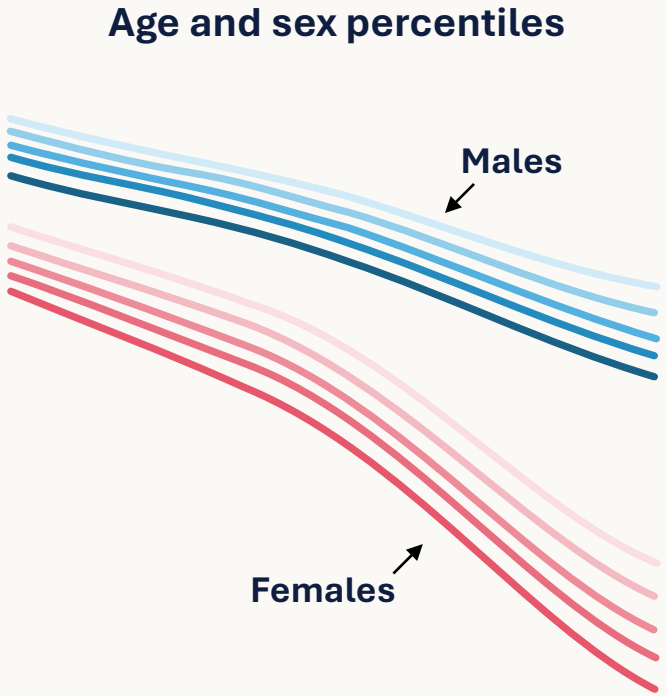
	Rare events	

Treatment remains tolerated even as age-related comorbidities increase

AKI, acute kidney injury.

VISUALIZING THE EFFICACY (UACR REDUCTION) TRAJECTORY



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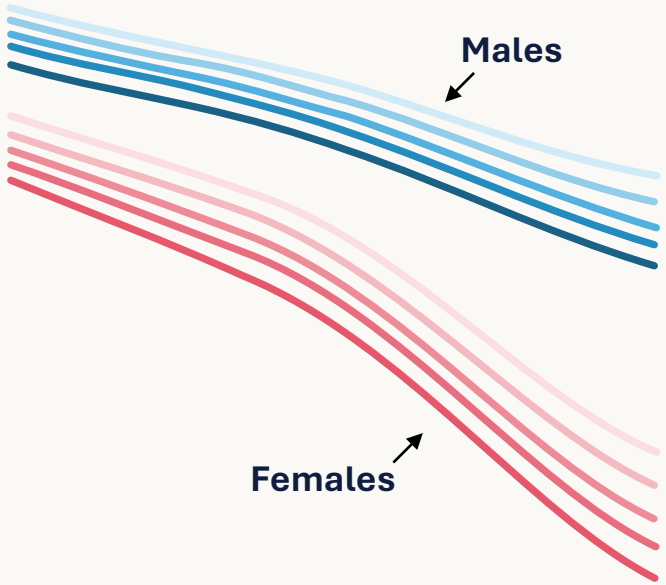
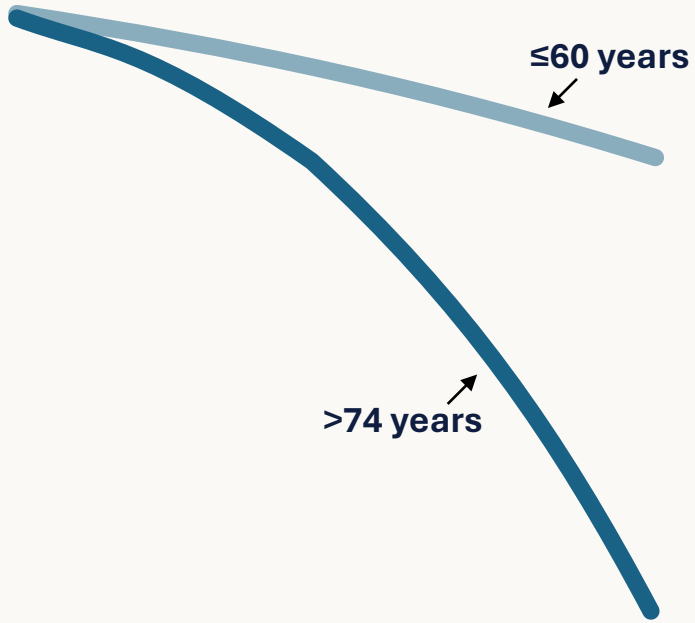
VISUALIZING THE EFFICACY (UACR REDUCTION) TRAJECTORY

Age and sex percentiles



Age quartiles (>74 vs ≤60 years)



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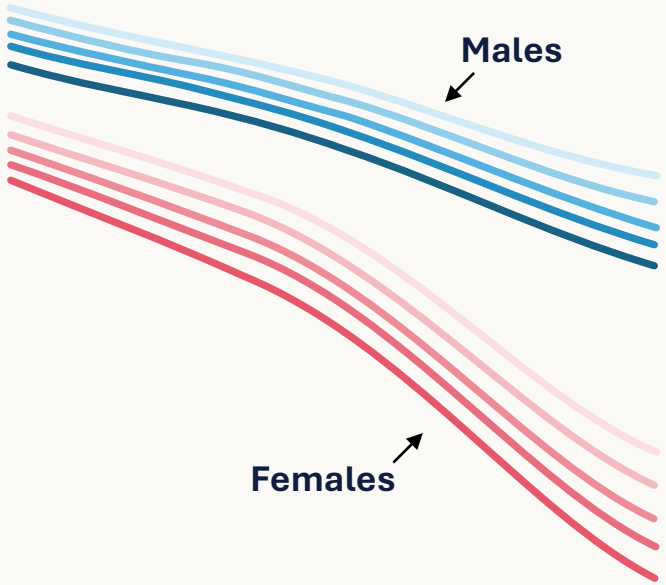

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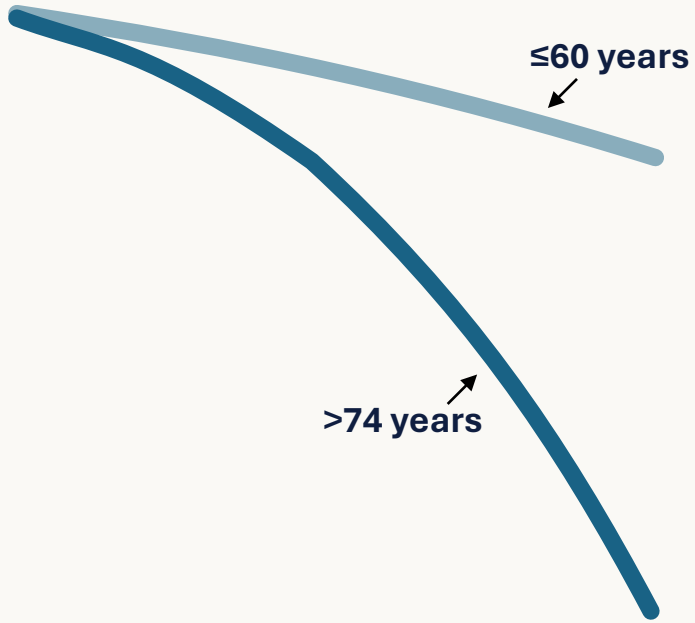
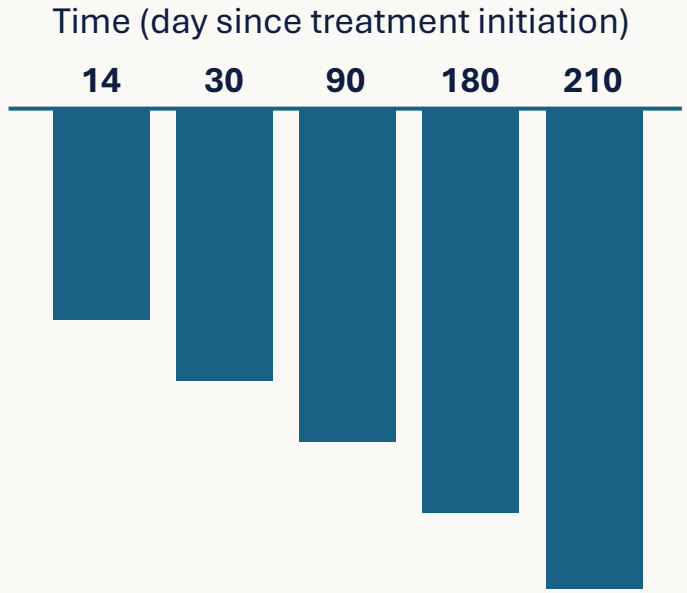


Increment per 10-year greater age (%)



UACR, urinary albumin-to-creatinine ratio.

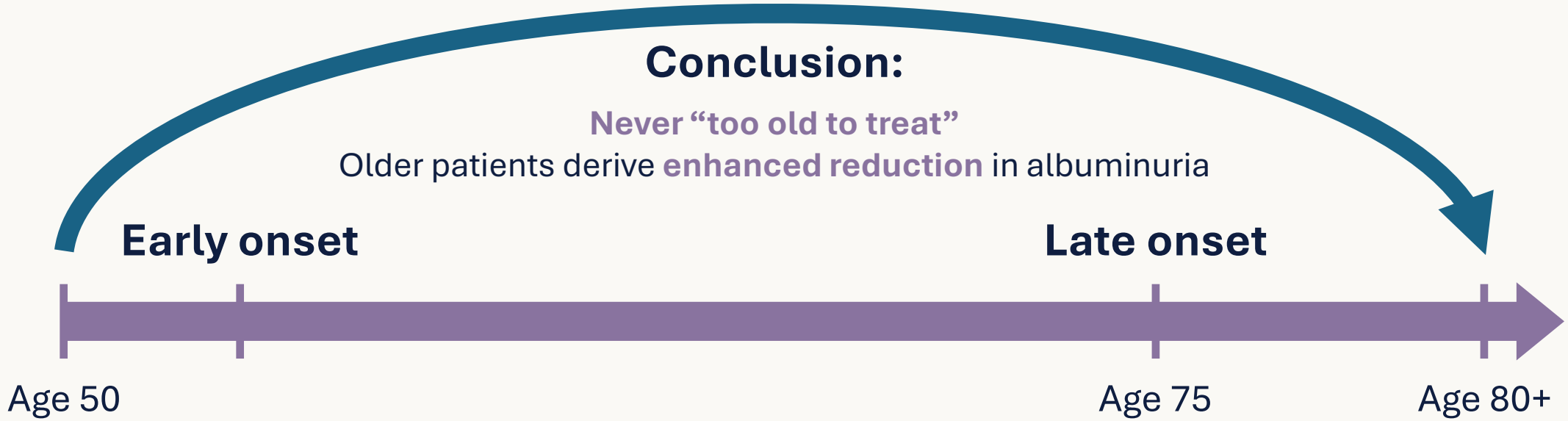
SUMMARY

The combination of empagliflozin and finerenone was beneficial in males and females, and across all ages

First evidence identifying clinically meaningful sex differences in UACR response with SGLT2is, finerenone, or their combination in T2D

SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

THE "LIFETIME" BENEFIT OF INTERVENTION



High CVD risk[1]

Treating now offers **"duration"** of protection

CONFIDENCE data:

"Magnitude" of response increases (**–10% extra/decade**)

CVD, cardiovascular disease; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

1. Cigolle CT, et al. *JAMA Netw Open*. 2022;5(9):e2232766.

CONFRONTING HISTORICAL CLINICAL PARADIGMS

- Revisiting female cardioprotection
  - A paradoxical ~20% greater UACR reduction in females vs males challenges assumptions of biological non-response in females
  - The greater increase in female CV/CKD risk with diabetes likely stems from historical underdiagnosis and undertreatment, not therapeutic resistance[1]

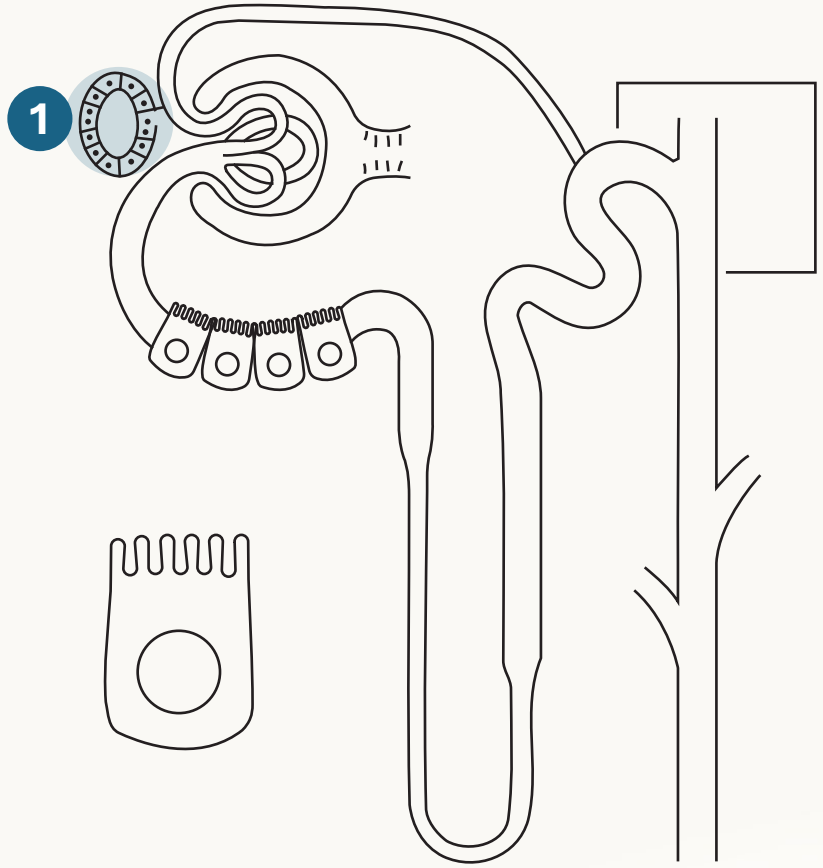
- The geriatric prescribing paradox
  - Older patients face the most prescribing hesitancy[2]
  - Our data counter that practice, proving peak structural UACR efficacy occurs in the oldest patients

CKD, chronic kidney disease; CV, cardiovascular; UACR, urinary albumin-to-creatinine ratio.

1. Regensteiner JG, et al. *Circulation*. 2015;132(25):2424–2447. 2. Szoszkiewicz M, et al. *PLoS One*. 2025;20(12):e0337586.

MECHANISTIC INTERPRETATION AND HYPOTHESIS GENERATION

1. Sex-specific tubuloglomerular feedback sensitivity differences to SGLT2 inhibition[1,2]



SGLT2, sodium-glucose cotransporter 2.

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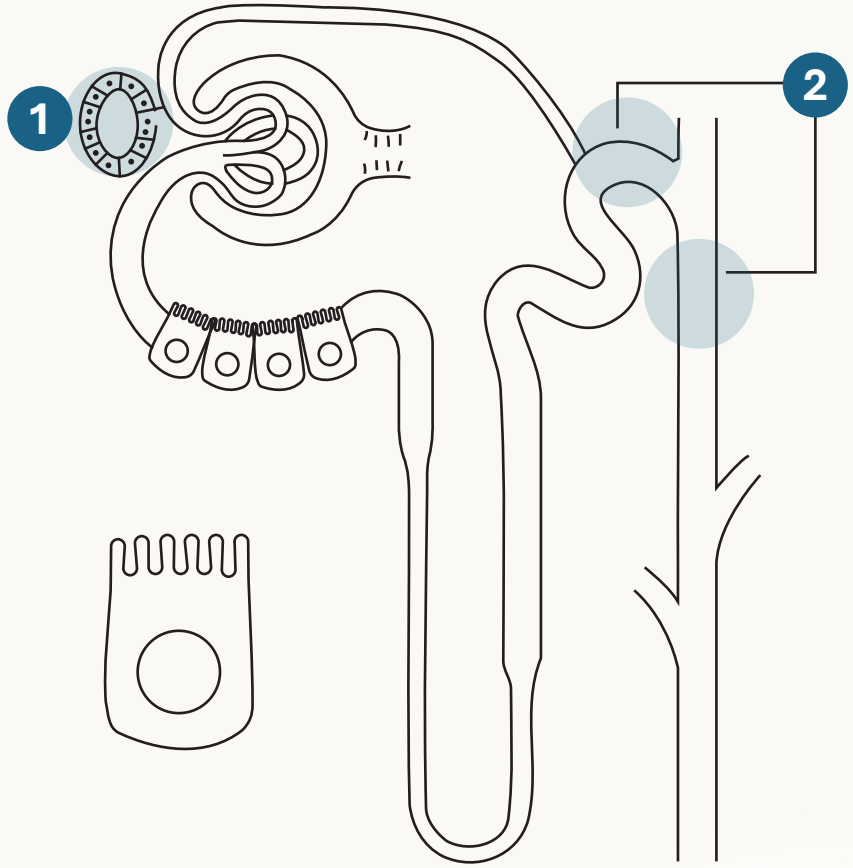

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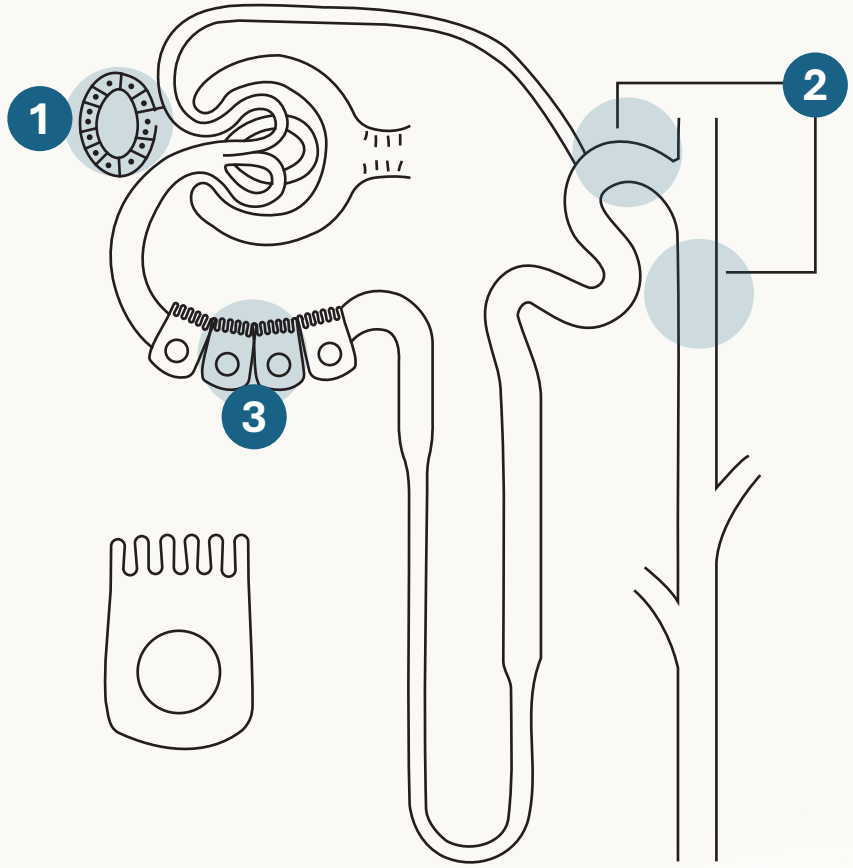

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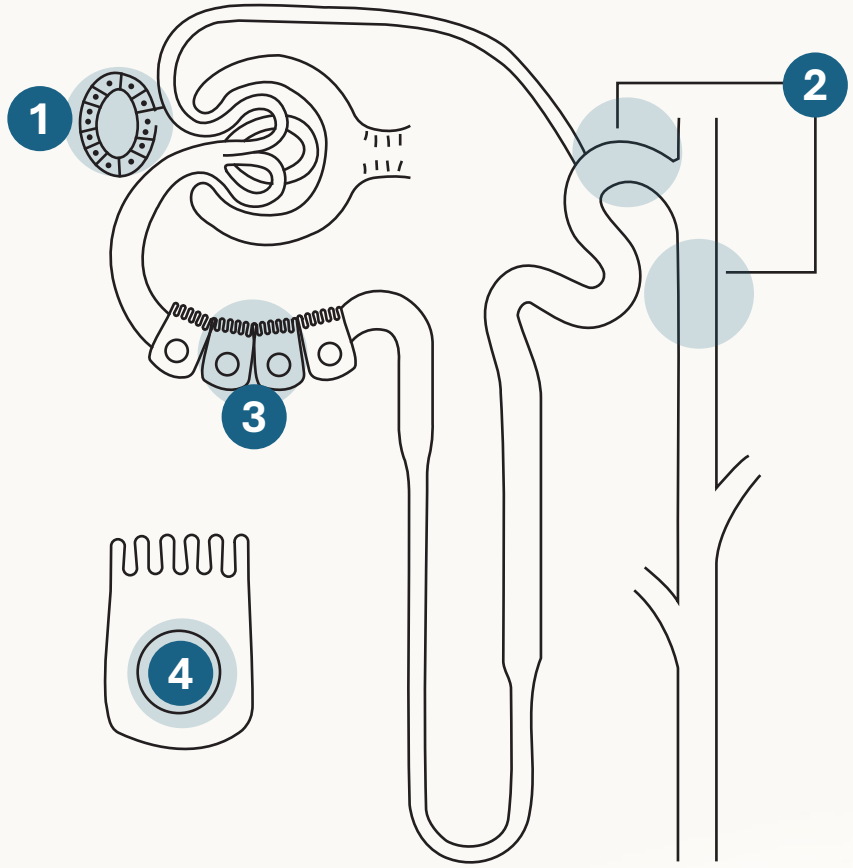

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Age effect – independent of treatment

Safety profile preserved with increasing age

UACR, urinary albumin-to-creatinine ratio.

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

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