62nd ERA CONGRESS
VIENNA & VIRTUAL
JUNE 4-7, 2025
Beyond Nephrology

in collaboration with

Österreichische Gesellschaft für Nephrologie

The CONFIDENCE trial

CONFIDENCE

Presented at the 62nd European Renal Association Congress June 5, 2025

Presenters



Peter Rossing, MD, PhD



Hiddo J. L. Heerspink, PhD



Rajiv Agarwal, MD, MS



Johannes F. E. Mann, MD

Presented on behalf of the steering committee and CONFIDENCE investigators

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Rationale of the trial

Peter Rossing, MD, PhD

Foundations of treatment for patients with CKD and T2D

Building the foundations[1]

- Cessation of tobacco smoking
- A healthy diet with a low glycemic index and restricted in sodium
- Maintenance of a healthy weight
- Optimizing physical behaviors
- Glycemic control, the level of which is individualized
- Lowering blood pressure to at least less than 130/80 mmHg
- Management of dyslipidemia that is centered on the administration of statins



Lifestyle interventions[1–4]

- Healthy diet
- Weight loss
- Physical activity
- Smoking cessation



Glycemic control[1–3,5]

- Individualized HbA1c target (6.5–8.0%)



Blood pressure control[1–3,6]

- Individualized blood pressure targets (<130/80–<140/90 mmHg)



Lipid control[1,2,7]

- Statins
- Ezetimibe
- Fibrates†
- PCSK9 inhibitor

†ESC guidelines suggest fibrates along with lifestyle modifications in people who are statin intolerant with low HDL cholesterol and high triglyceride levels.

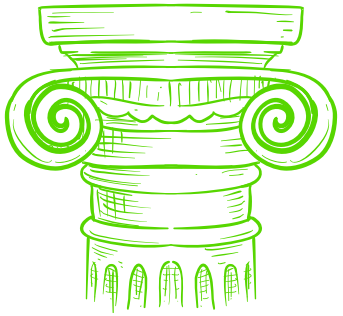
CKD, chronic kidney disease; ESC, European Society of Cardiology; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; T2D, type 2 diabetes.

1. Agarwal R et al. *Nephrol Dial Transplant* 2023;38:253–257; 2. Cosentino F et al. *Eur Heart J* 2020;41:255–323; 3. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int* 2020;98:S1–S115; 4. American Diabetes Association Professional Practice Committee. *Diabetes Care* 2022;45(Suppl 1):S60–S82; 5. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S125–S143; 6. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S175–S184; 7. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S144–S174.

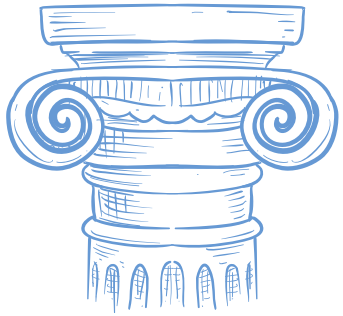
Standard of care in T2D and CKD: four pillars

T2D and CKD[1,2]

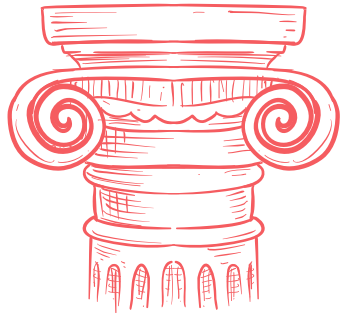
1. ACEi or ARB



2. SGLT2i



3. ns-MRA



4. GLP-1 RA



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; ns-MRA, non-steroidal mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

1. Agarwal R et al. *Nephrol Dial Transplant* 2023;38:253–257; 2. American Diabetic Association. *Diabetes Care* 2025:48:S239–S251.

Simultaneous start of combination therapies in hypertension

Quicker and greater blood pressure reduction

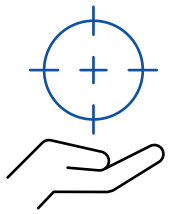
Addresses multiple pathophysiologic pathways





Potential for better tolerability

Lower doses of two drugs may reduce dose-dependent side effects



Increased target BP achievement

Improved adherence

Single-pill combinations enhance adherence and consistent BP control



Potential for improved CV outcomes





Guideline support

Major guidelines favor initial combination, especially for stage 2 hypertension or high CV risk

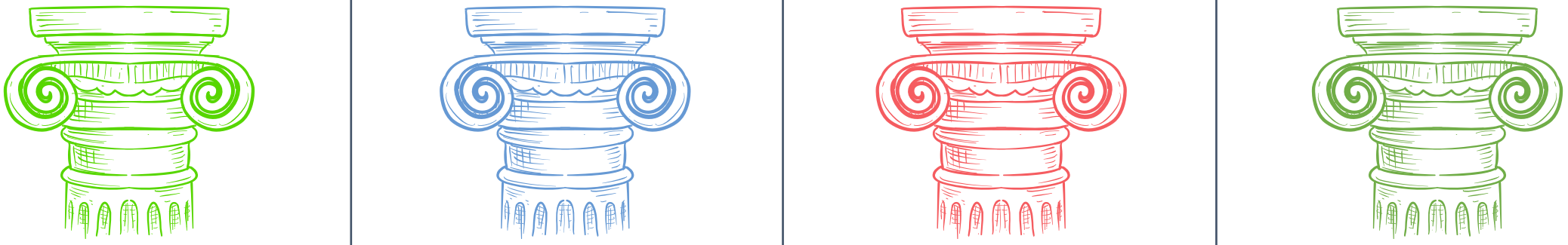
BP, blood pressure; CV, cardiovascular.

Mancia G et al. *Circ Res* 2019;124:1113–1123.

Standard of care in HFrEF: four pillars

HFrEF

1	2	3	4
ARNI/ACEi/ARB	**SGLT2i**	**MRA**	**ß-blocker**



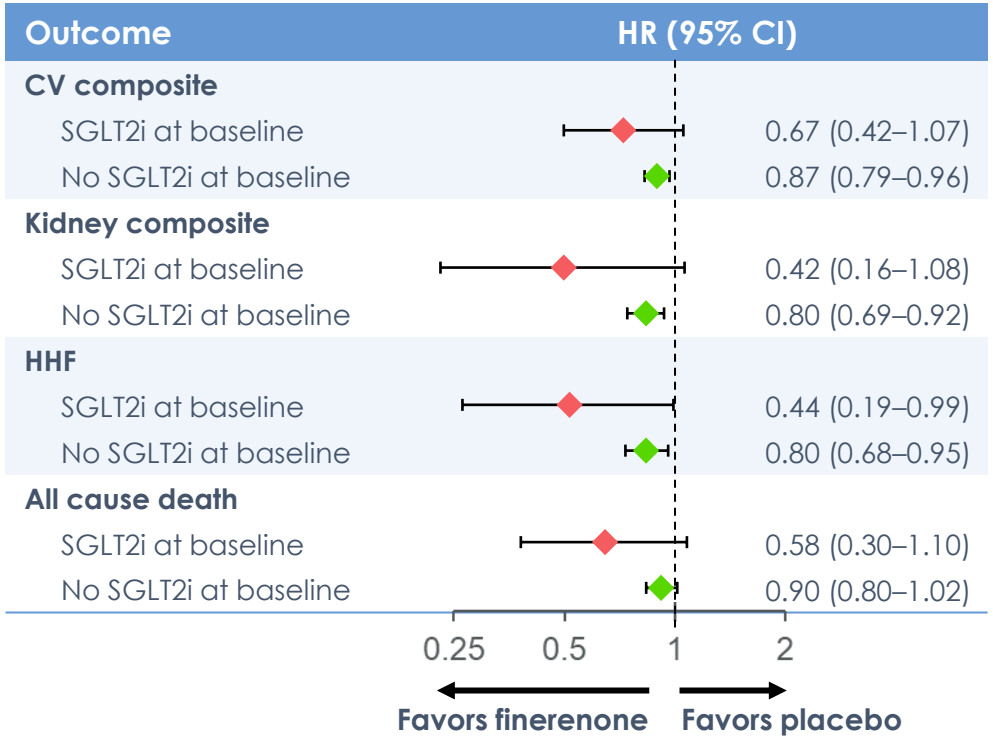
Implementation of the guidelines is evolving—**some of all, instead of all of some**[1,2]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

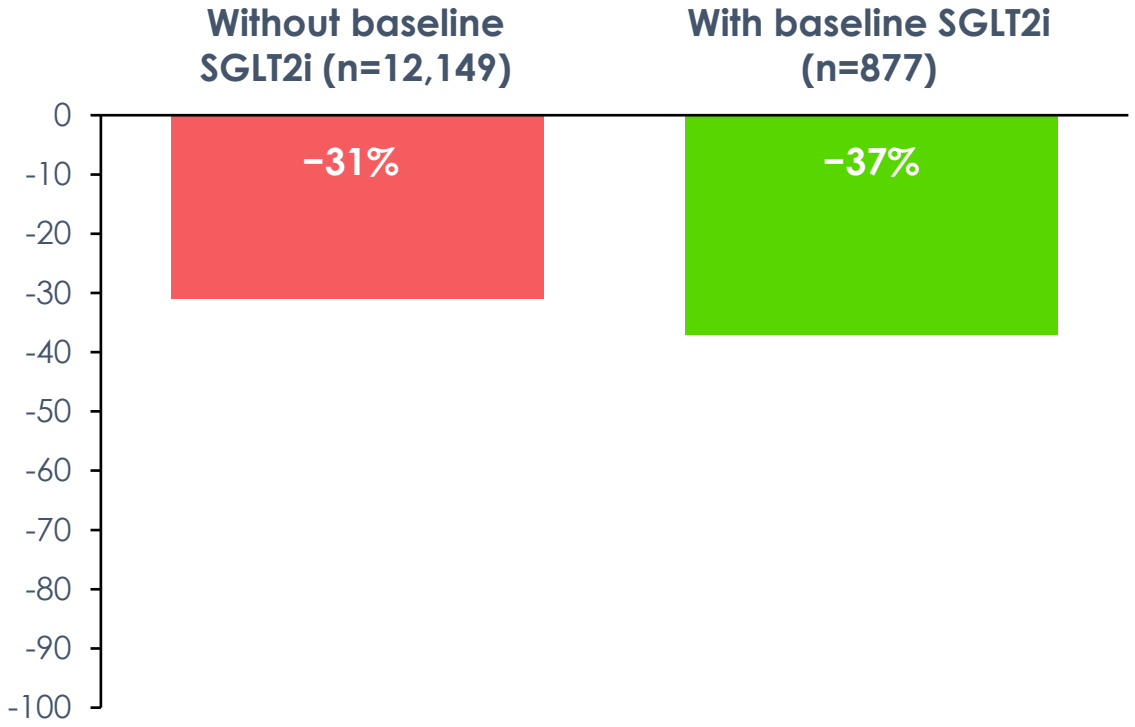
1. Brownell NK et al. https://www.acc.org/Latest-in-Cardiology/Articles/2022/03/04/17/40/Simultaneous-vs-Sequential-Initiation-of-HFrEF-Therapies; 2. Hu J-R et al. *Cardiol Clin* 2023;41:511–524.

FIDELITY subgroup analysis: UACR reduction with finerenone is similar with and without an SGLT2i at baseline

- Reduced risk of kidney and CV outcomes with finerenone versus placebo



- Reduction in UACR (%) with finerenone versus placebo at Month 4



CV composite outcome comprised CV death, nonfatal myocardial infarction, nonfatal stroke, or HHF
Kidney composite outcome comprised kidney failure, sustained ≥57% eGFR decline, or renal death

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio..
Rossing P et al. *Diabetes Care* 2022;45:2991–2998.

Additive effects of sMRA and SGLT2i on albuminuria

Methods



46 participants

- Diabetic and non-diabetic CKD
- Baseline urinary albumin excretion: 100–3500 mg/24 hours
- Baseline eGFR: >30–<90 mL/min/1.73 m^2
- Stable (>4 weeks) dose of ACEi or ARB

Randomized

Cross-over trial:
4 weeks of treatment with 4-week washout

Treatments

Eplerenone 50 mg vs dapagliflozin 10 mg vs combination

Results

	UACR reduction from baseline
Eplerenone 50 mg	**33.7%**
Dapagliflozin 10 mg	**19.6%**
Combination therapy	**53.0%**

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; sMRA, steroidal mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urinary albumin-creatinine ratio.

Provenzano M et al. *J Am Soc Nephrol* 2022;33:1569–1580.

Additive effects of finerenone and SGLT2i on albuminuria

Methods

20 participants

- Non-diabetic CKD
- Baseline UACR: 150–2000 mg/g
- Baseline eGFR: 25–45 mL/min/1.73 m^2
- On maximal tolerated ACEi or ARB

Randomized to:

4 weeks with finerenone or dapagliflozin

Followed by:

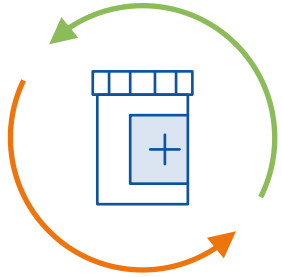
4 weeks of combination therapy

Results

	UACR reduction from baseline
Finerenone	**24%** at week 4
Dapagliflozin	**8%** at week 4
Combination therapy	**36%** at week 8

This figure is adapted from Marup, et al. 2023 under the terms of the Creative Commons Attribution-Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urinary albumin-creatinine ratio. Marup FH et al. *Clin Kidney J* 2023;17:1569–1580.

CONFIDENCE hypothesis



A **combination** of **finerenone** and an **SGLT2i** would decrease albuminuria more than either treatment alone

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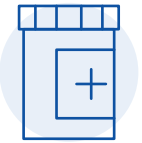
The trial also aimed to establish the safety of the combination



Blood pressure



Serum potassium levels



eGFR

eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

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Trial design and baseline characteristics

Hiddo J. L. Heerspink, PhD

CONFIDENCE trial design

Participants with CKD and T2D were enrolled



Screening

1 Key inclusion criteria

- eGFR 30–90 mL/min/1.73 m^{2†}
- UACR ≥100–<5000 mg/g
- T2D with HbA1c <11%
- Clinically maximum tolerated dose of ACEi/ARB for >1 month

2 Key exclusion criteria

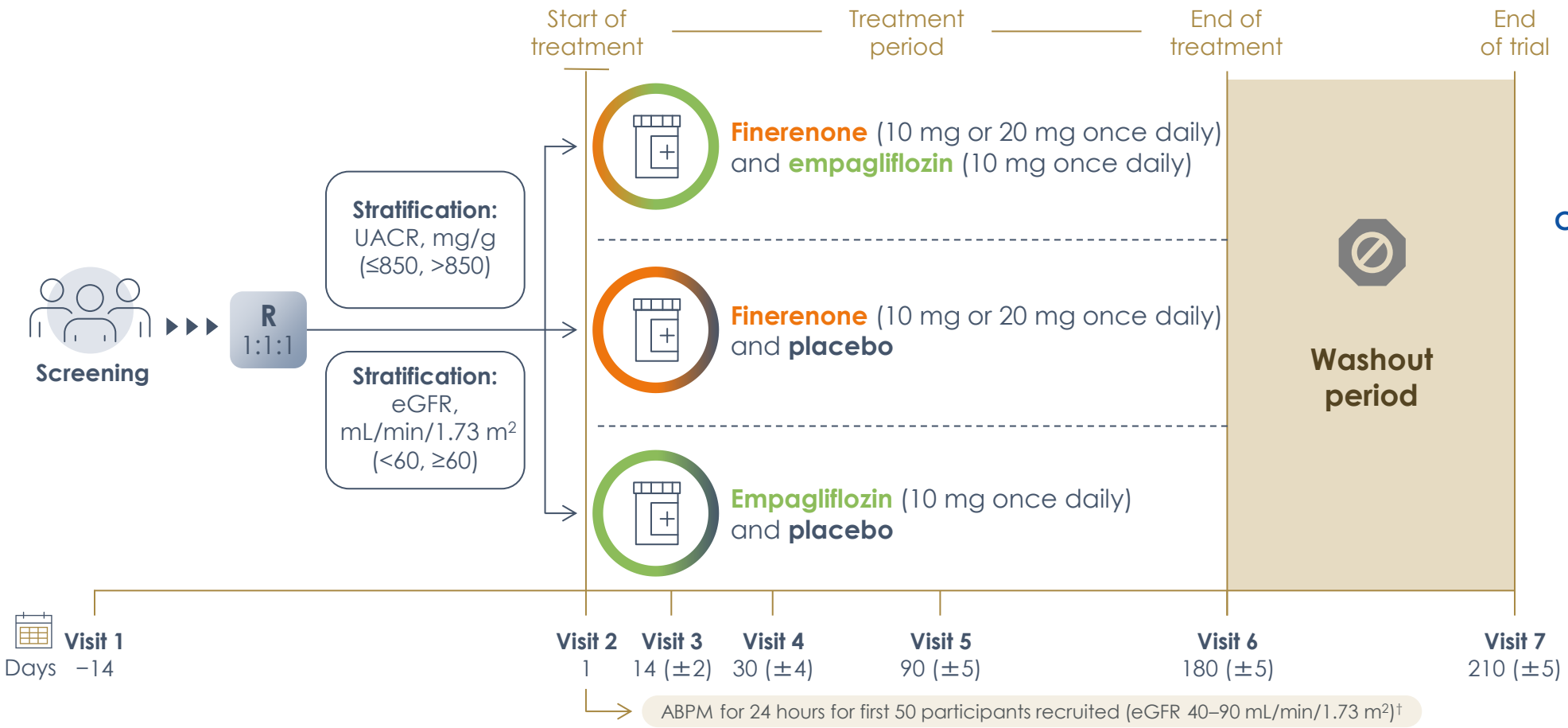
- T1D
- Serum K^+ >4.8 mmol/L
- HFrEF with NYHA class II–IV
- Treated with a mineralocorticoid receptor antagonist or SGLT2i within 8 weeks prior to screening visit

R

†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). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; K^+, potassium; NYHA, New York Heart Association; R, randomization; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio. **CONFIDENCE: NCT05254002; EudraCT 2021-003037-11.**

CONFIDENCE trial design

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



Primary efficacy endpoint

Relative change in UACR from baseline to Day 180 for:

Combination vs **finerenone**

Combination vs **empagliflozin**

Secondary efficacy endpoint

UACR reduction **>30%/>40%/>50%**

Relative change in UACR: **At EoT vs 30 days post EoT**

30 days post EoT vs baseline

This figure is adapted from Green JB, et al. 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 m² were recruited (Part A) prior to recruiting participants with an eGFR of 30–90 mL/min/1.73 m² (Part B). The number of participants will be capped in parts A and B as follows: 80% with an eGFR of ≤75 mL/min/1.73 m² and 20% with an eGFR of >75 mL/min/1.73 m². Up/down titration based on eGFR, serum/plasma potassium, or safety and tolerability. ABPM, ambulatory blood pressure monitoring; eGFR, estimated glomerular filtration rate; R, randomization; UACR, urinary albumin-to-creatinine ratio. Green JB et al. *Nephrol Dial Transplant* 2023;38:894–903. **CONFIDENCE: NCT05254002; EudraCT 2021-003037-11.**

CONFIDENCE trial design

Choice of efficacy endpoints[1,2]

Composite kidney endpoint

- Would require 41000 participants
- Limited feasibility
- Requires long follow-up (≥3 years)

UACR

UACR change in the short-term is associated with kidney protection in the long-term

- **30%** decline in UACR is associated with
- **27%** reduction in CKD progression

Sample size determination

N ≈ 807 was estimated to achieve **80%** power to reject the null hypothesis of equal means in UACR with SD of log-transformed UACR for both groups of 0.77, and significance level (alpha) = 0.025 (2-sided, 2-sample, equal variance t-test)



Group sample size (assuming a **15%** drop out rate)

sufficient to detect a **20%** further reduction in UACR in the combination arm versus finerenone or empagliflozin

Combination, n = 269;
finerenone, n = 269;
empagliflozin, n = 269

CKD, chronic kidney disease; SD, standard deviation; UACR, urinary albumin-to-creatinine ratio.

1. Green JB et al. *Nephrol Dial Transplant* 2023;38:894–903; 2. Heerspink HJL et al. *Lancet Diabetes Endocrinol* 2019;7:128–139. **CONFIDENCE: NCT05254002; EudraCT 2021-003037-11.**

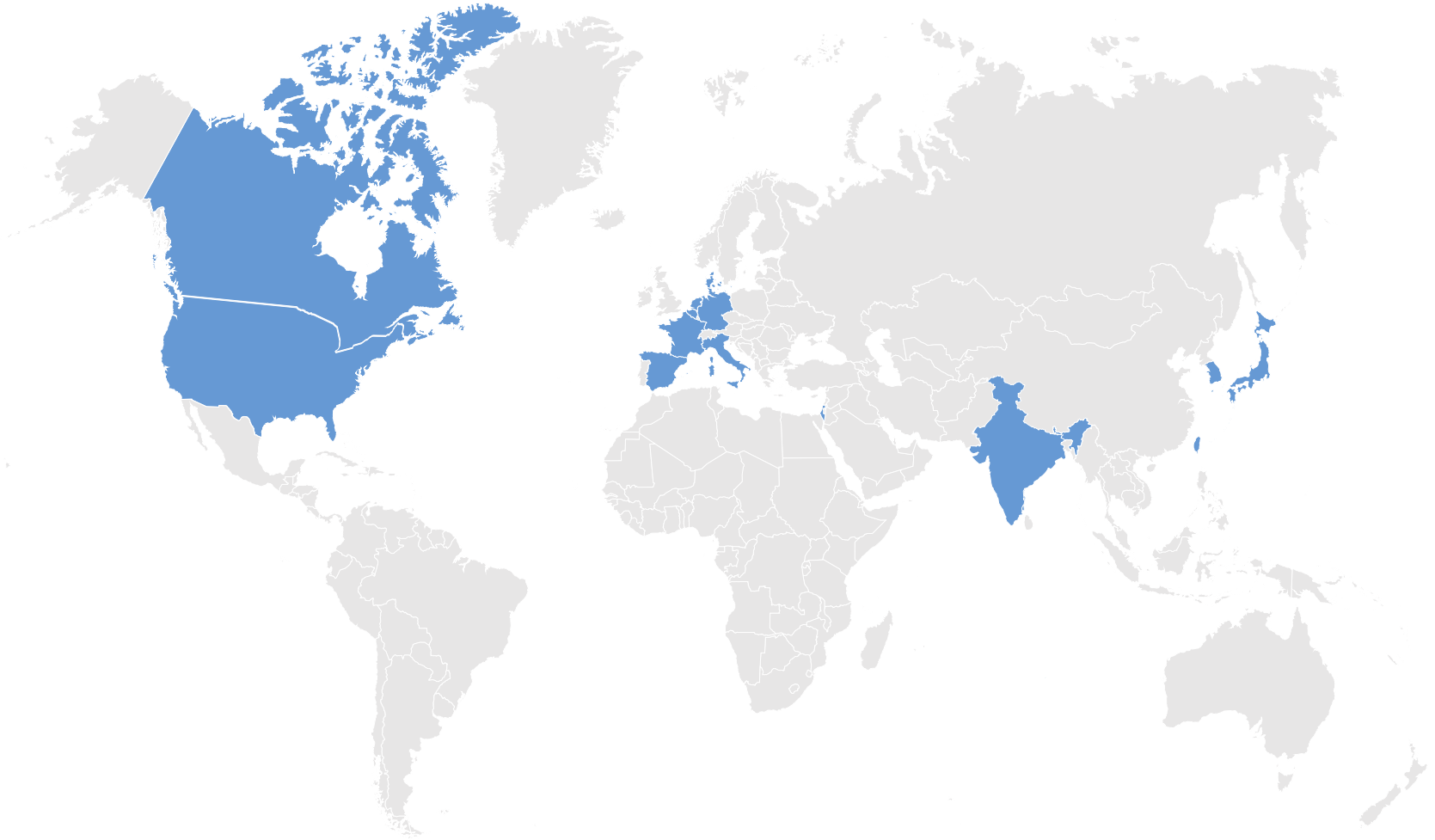
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CONFIDENCE: trial population

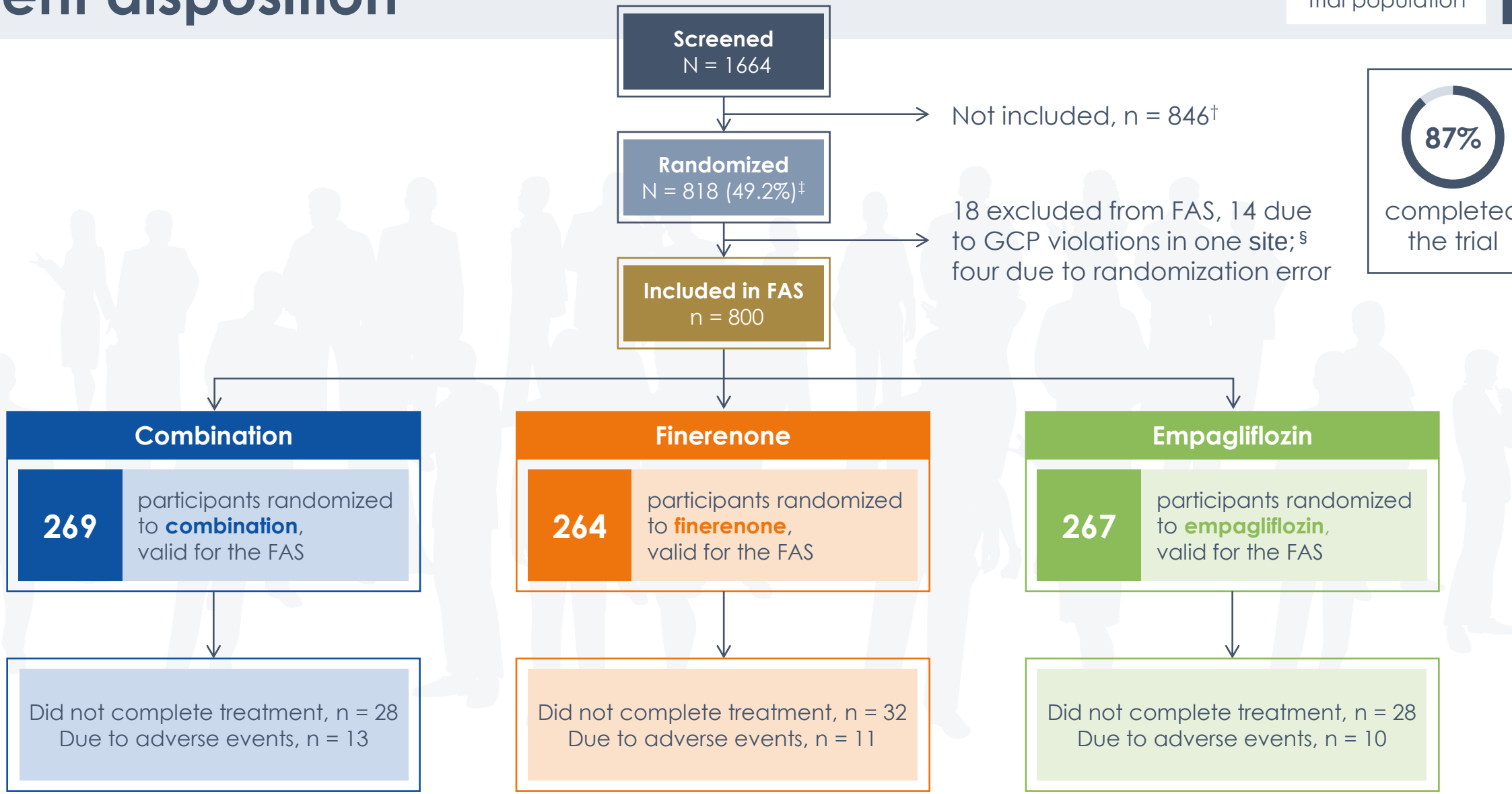
Trial sites



818 participants
were randomized across
143 sites in
14 countries/regions

- Belgium
- Canada
- Denmark
- France
- Germany
- India
- Israel
- Italy
- Japan
- The Netherlands
- Republic of Korea
- Spain
- Taiwan
- United States of America

Patient disposition



†Top screening failure reasons: not meeting inclusion criteria (CKD diagnosis) or meeting exclusion criteria (serum potassium ≥4.8 mmol/L). ‡Percentage of screened participants who were randomized.
§Exclusion required by Japanese authority.
CKD, chronic kidney disease; FAS, full analysis set; GCP, Good Clinical Practice.

Baseline demographics

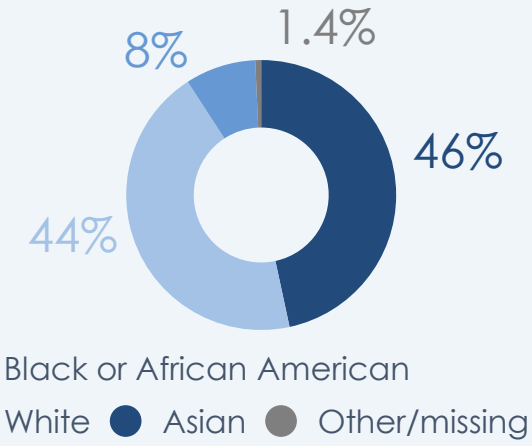
Patients: N = 800

Overall participant characteristics

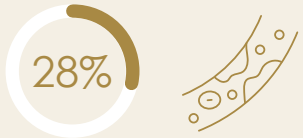
Mean age	Sex	Mean SBP	Mean BMI
67 years	75% 25%	135 mmHg	29 kg/m^2

Mean eGFR	Median UACR	Mean HbA1c %	Mean serum [K$^+$]
54 mL/min/1.73 m^2	579 mg/g	7.3%	4.5 mmol/L

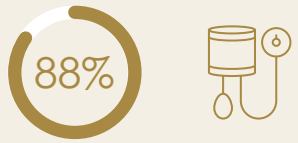
Race (%)



Medical history



ASCVD

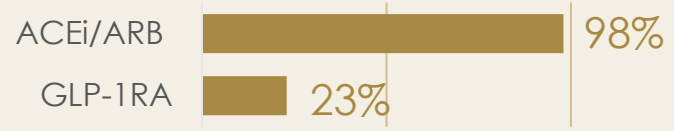


Hypertension



Diabetic retinopathy

Comedications



Data shown are means and proportion of participants.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; K$^+$, potassium; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

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Efficacy and safety

Rajiv Agarwal, MD, MS

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CONFIDENCE: UACR endpoints

Questions for the audience

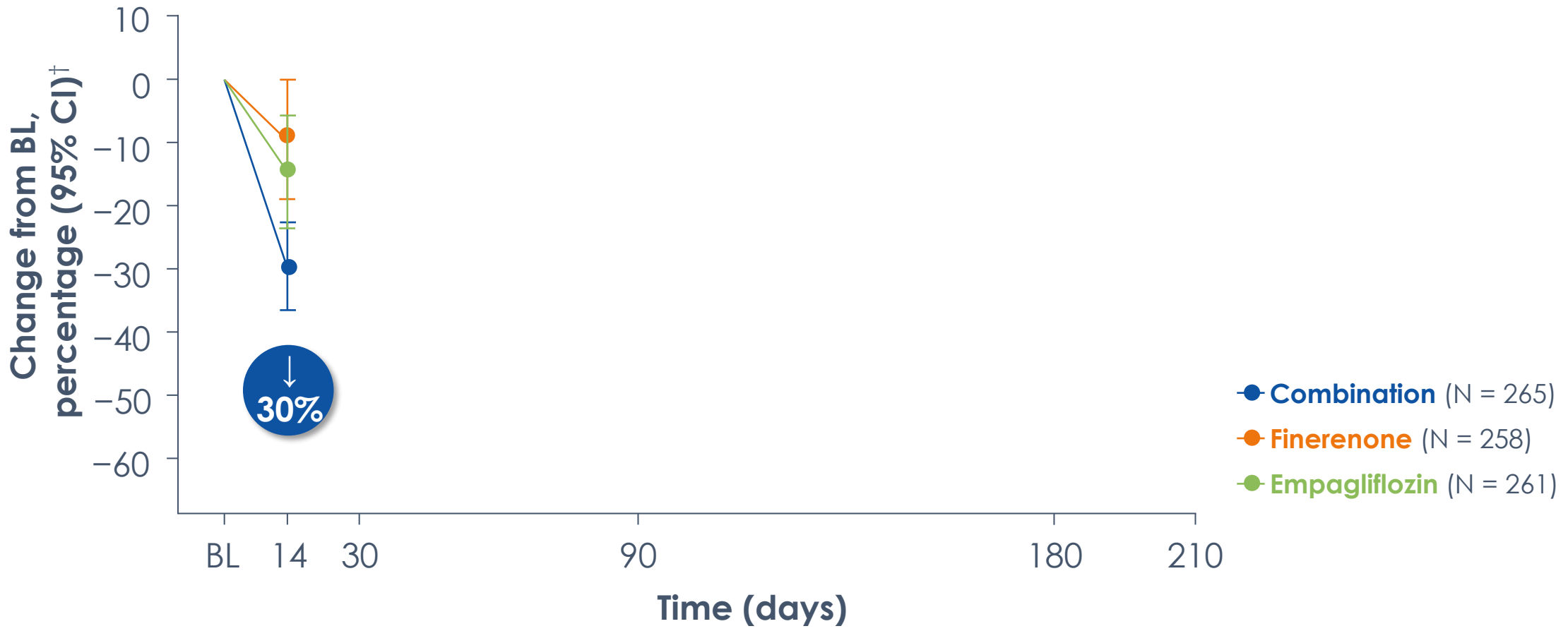


At 6 months, **what percentage reduction in UACR** would you expect to see in the combination group?

A. < 20 %
B. 20 – 30 %
C. 30 – 40 %
D. 40 – 50 %
E. 50 – 60 %
F. > 60 %

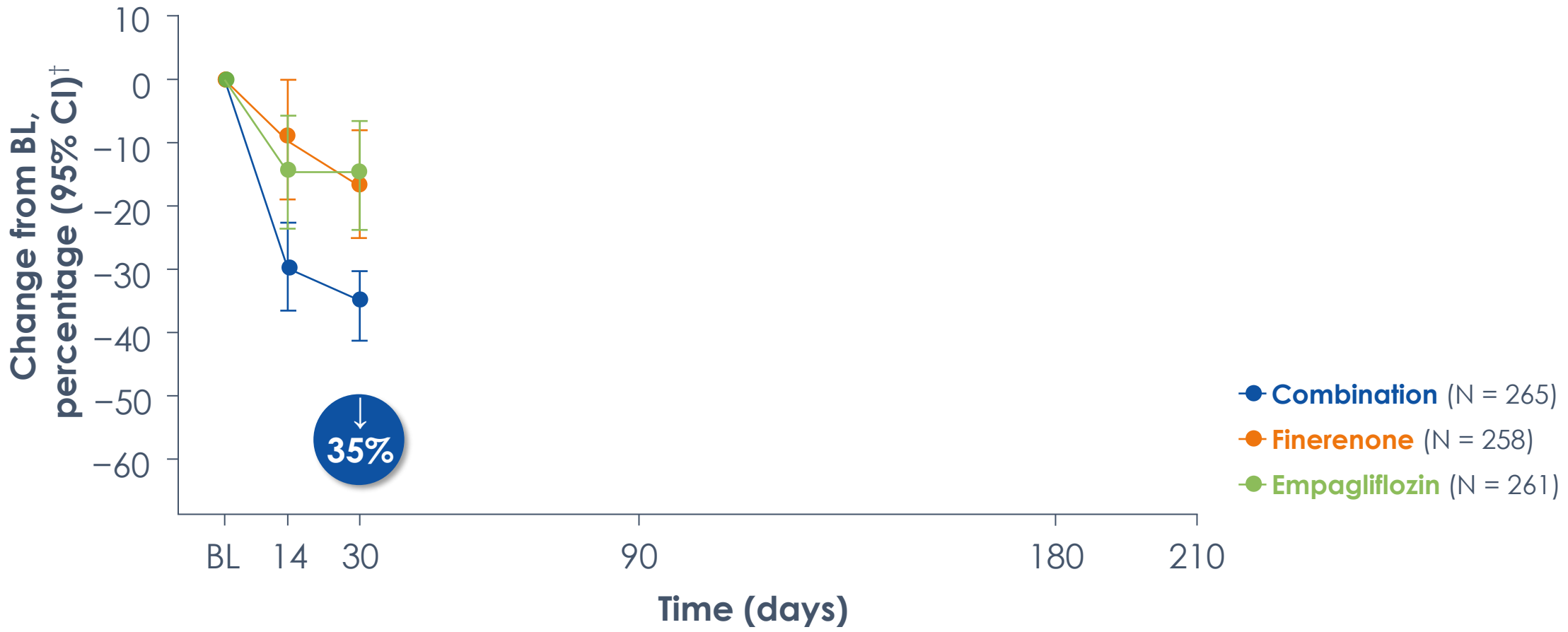
UACR, urinary albumin-to-creatinine ratio.

Simultaneous initiation of finerenone and SGLT2i led to early reduction of UACR



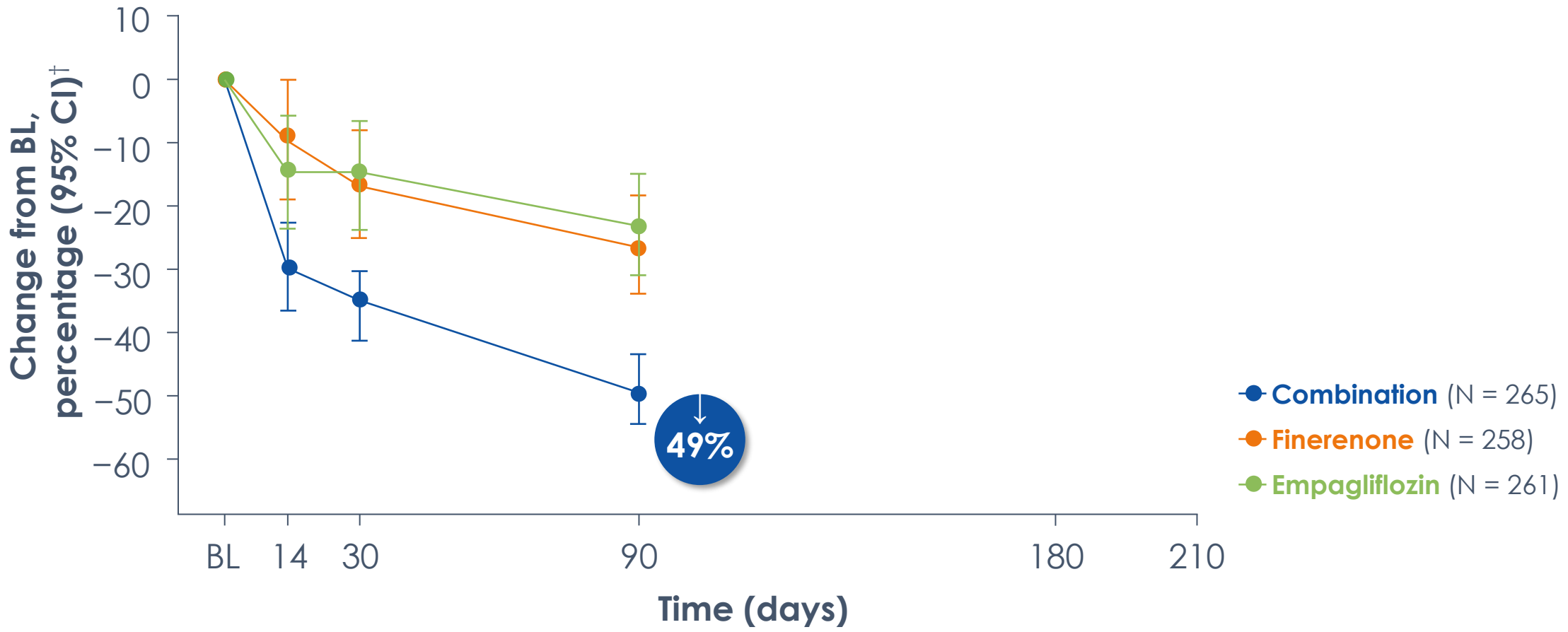
†Percentage change calculation = (least squares mean ratio to baseline − 1) × 100.
BL, baseline; CI, confidence interval; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

Simultaneous initiation of finerenone and SGLT2i led to early and additive reduction of UACR



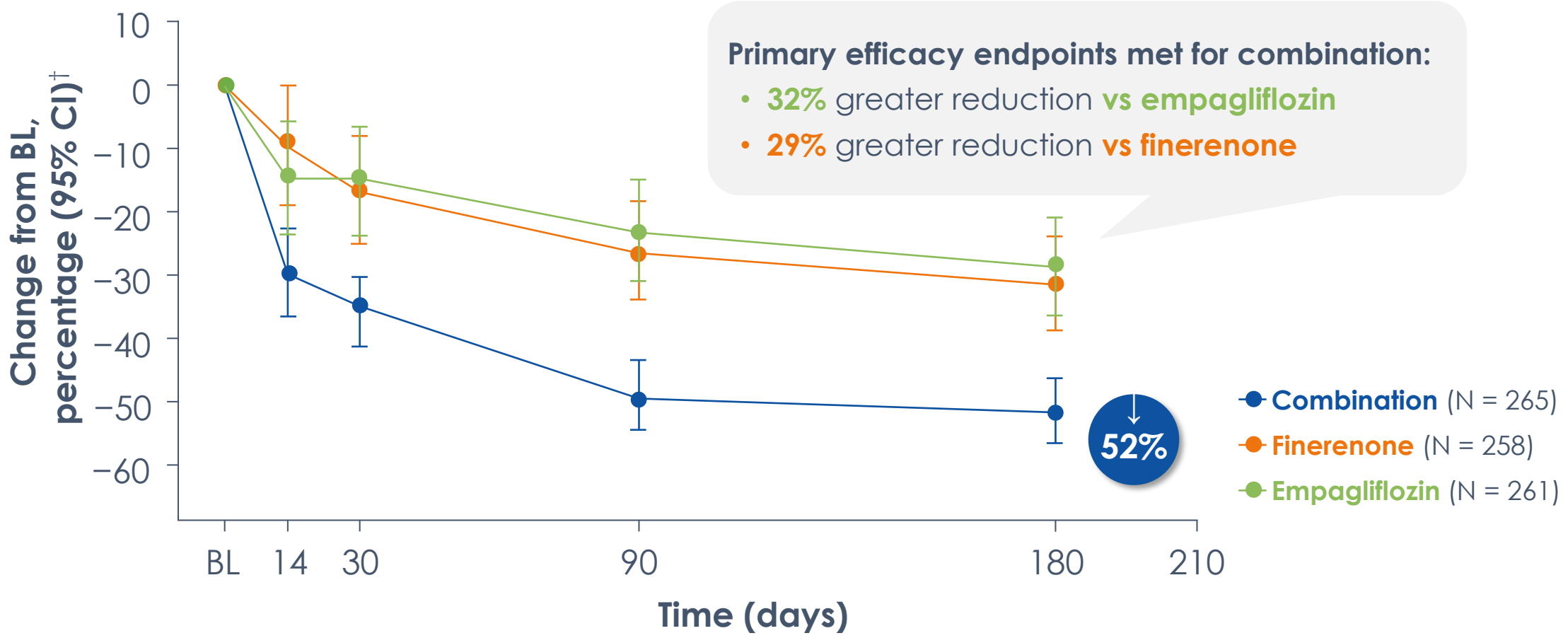
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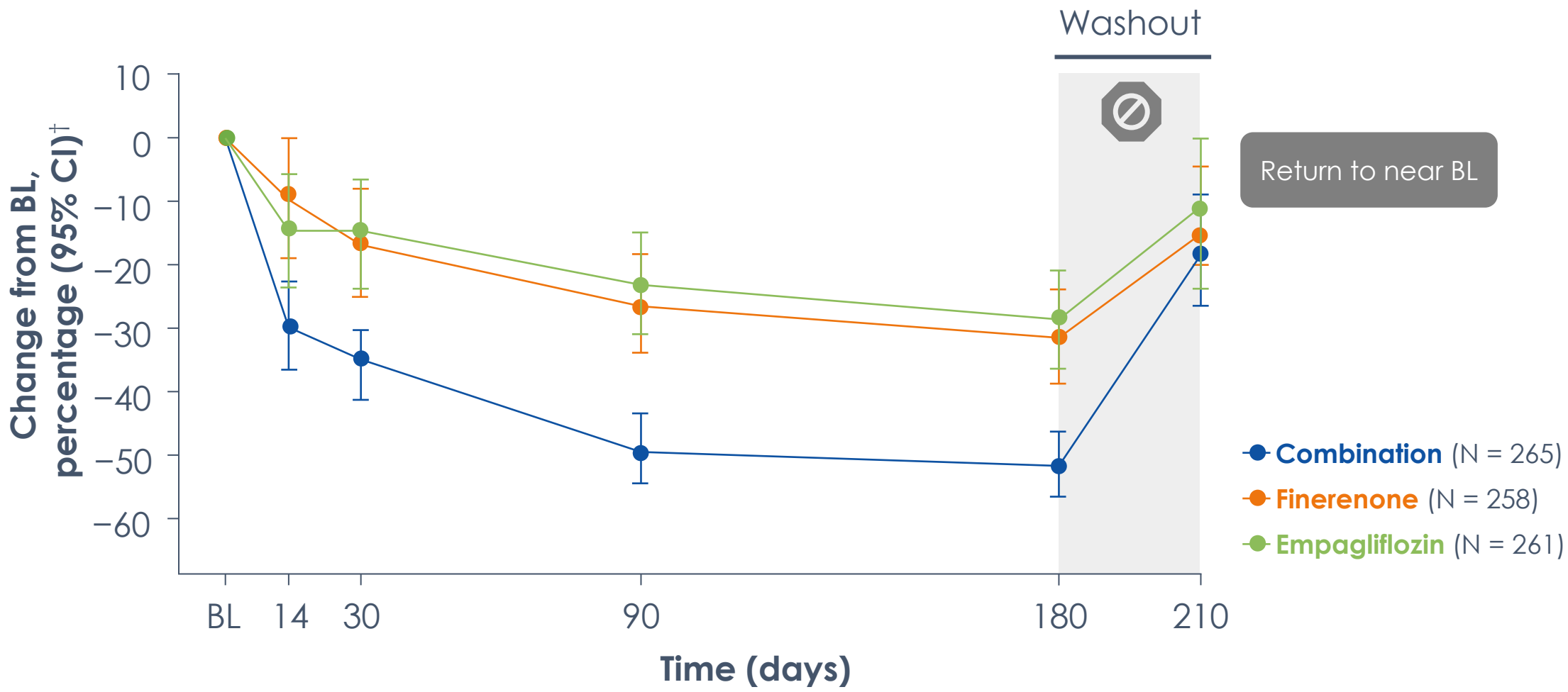
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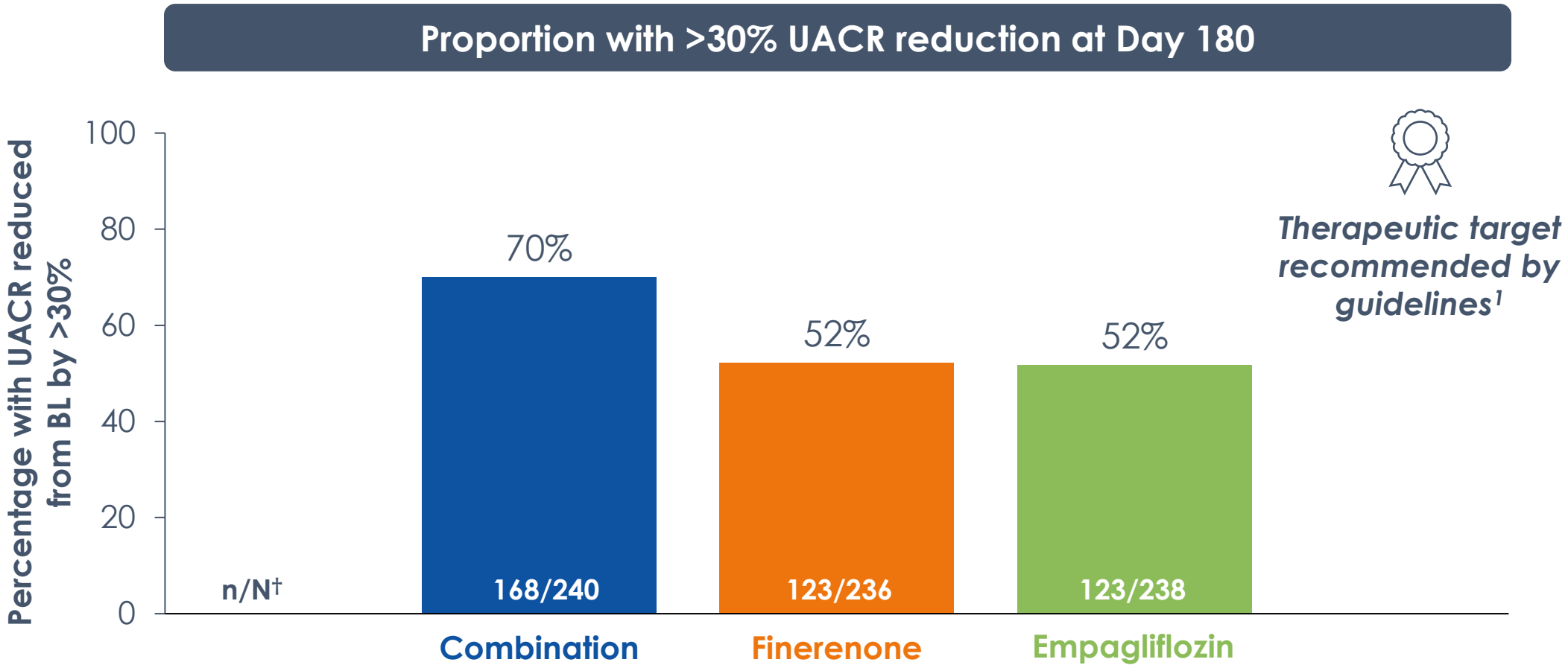
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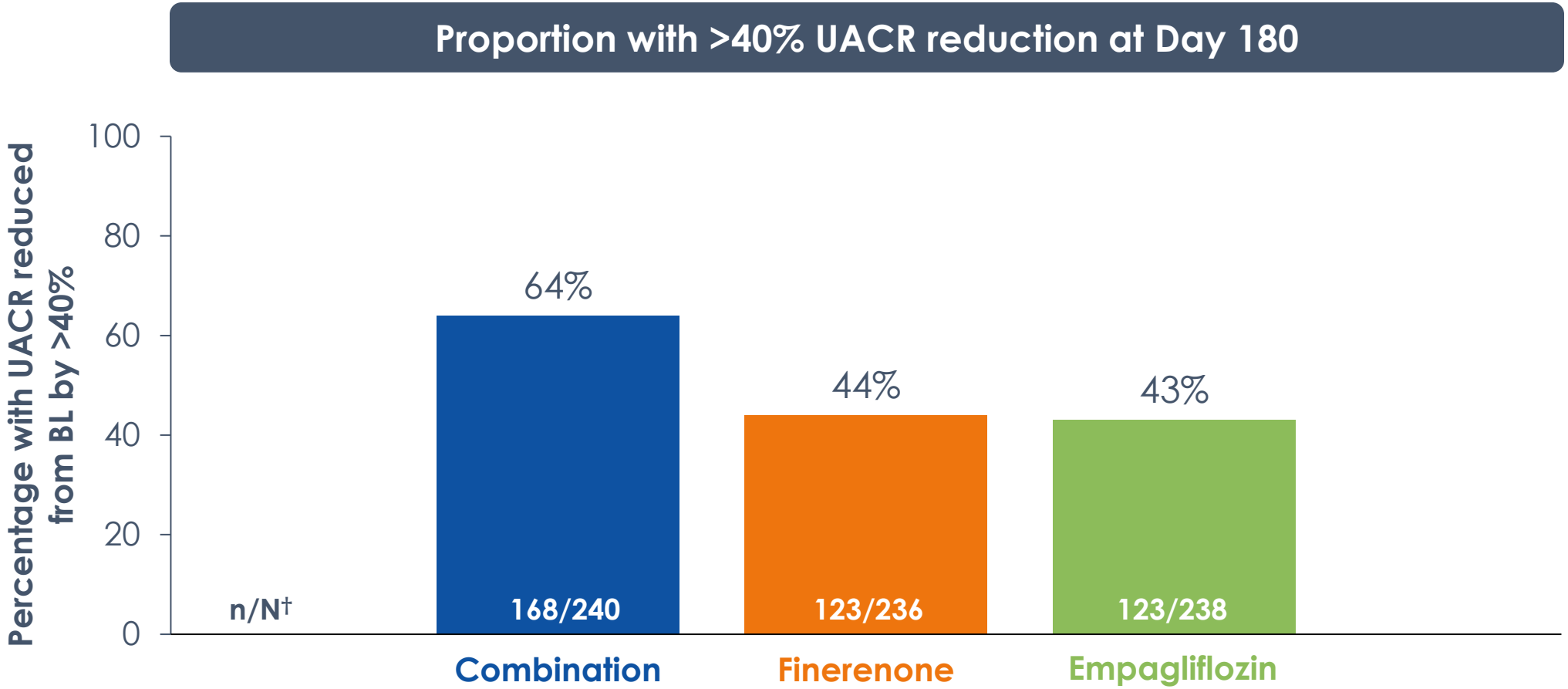
70% of patients achieved >30% reduction in UACR with simultaneous initiation of finerenone and SGLT2i



†The denominator represents all participants at risk for a treatment-emergent laboratory abnormality. Participants must have both a BL and post BL value and the BL value must be in the expected range for that criteria.
BL, baseline; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

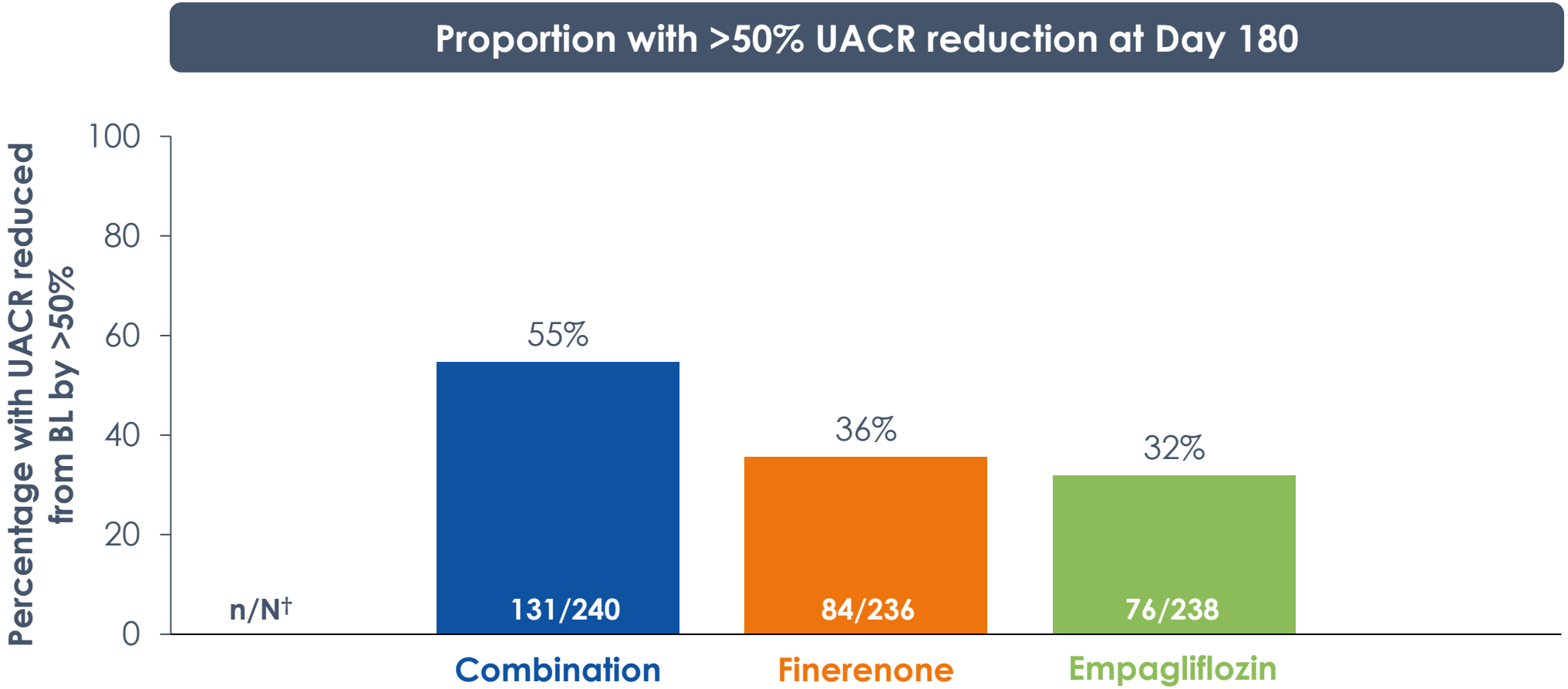
1. American Diabetes Association Professional Practice Committee. *Diabetes Care* 2025;48(Suppl 1):S239–S251.

64% of patients achieved >40% reduction in UACR with simultaneous initiation of finerenone and SGLT2i



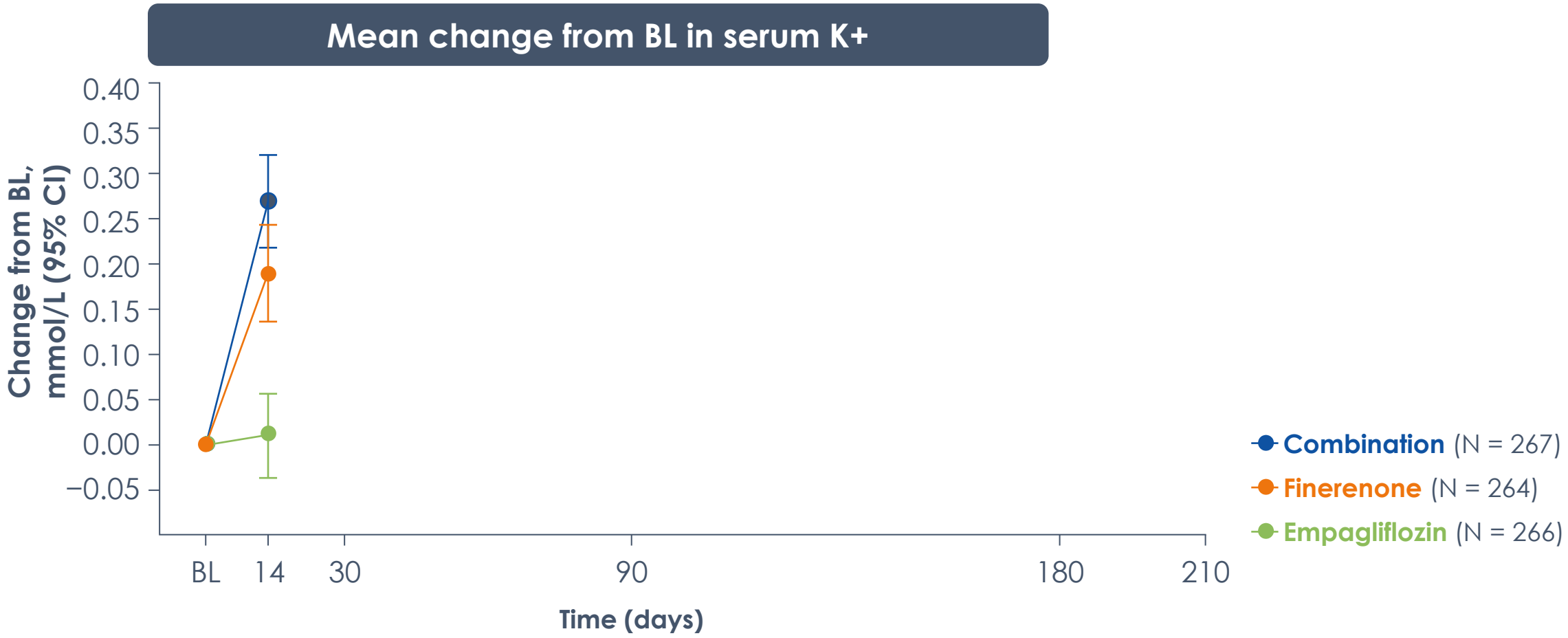
†The denominator represents all participants at risk for a treatment-emergent laboratory abnormality. Participants must have both a BL and post BL value and the BL value must be in the expected range for that criteria.
BL, baseline; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

55% of patients achieved >50% reduction in UACR with simultaneous initiation of finerenone and SGLT2i



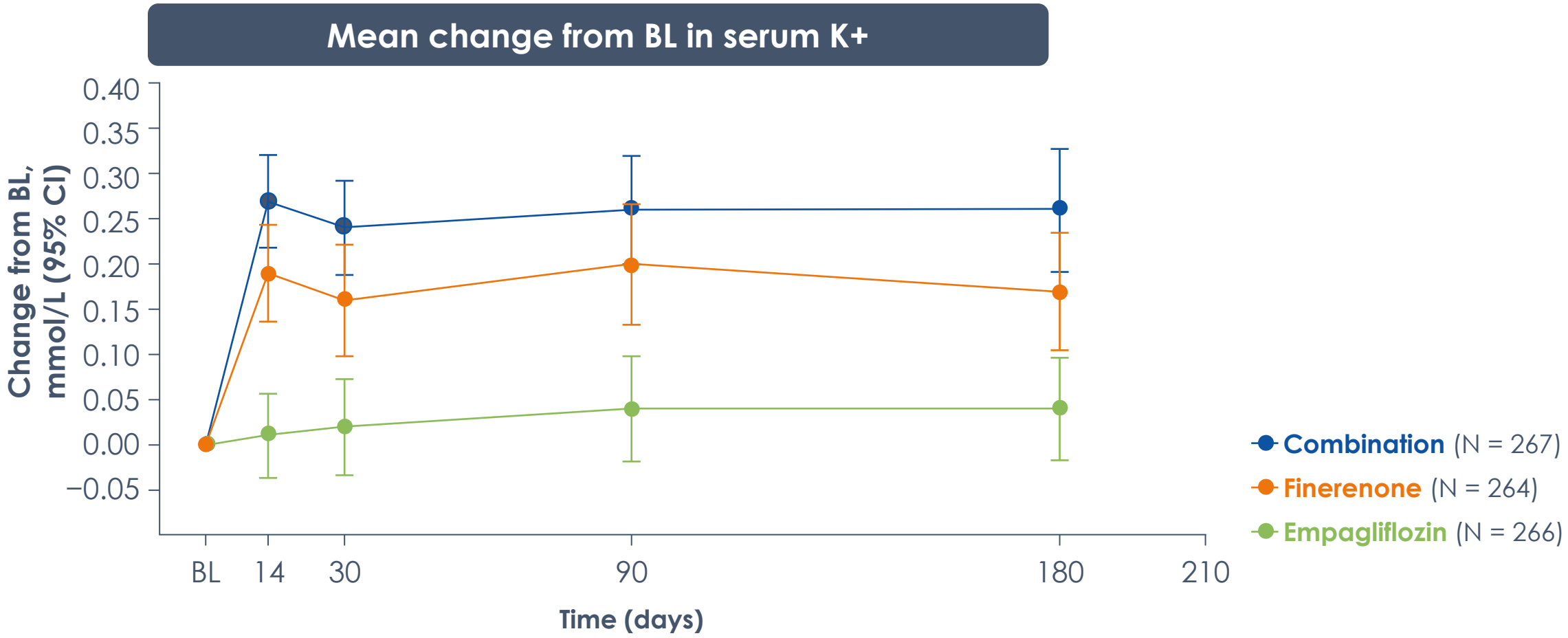
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BL, baseline; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

[K+] increased in combination and finerenone groups, returning to BL levels after drug withdrawal



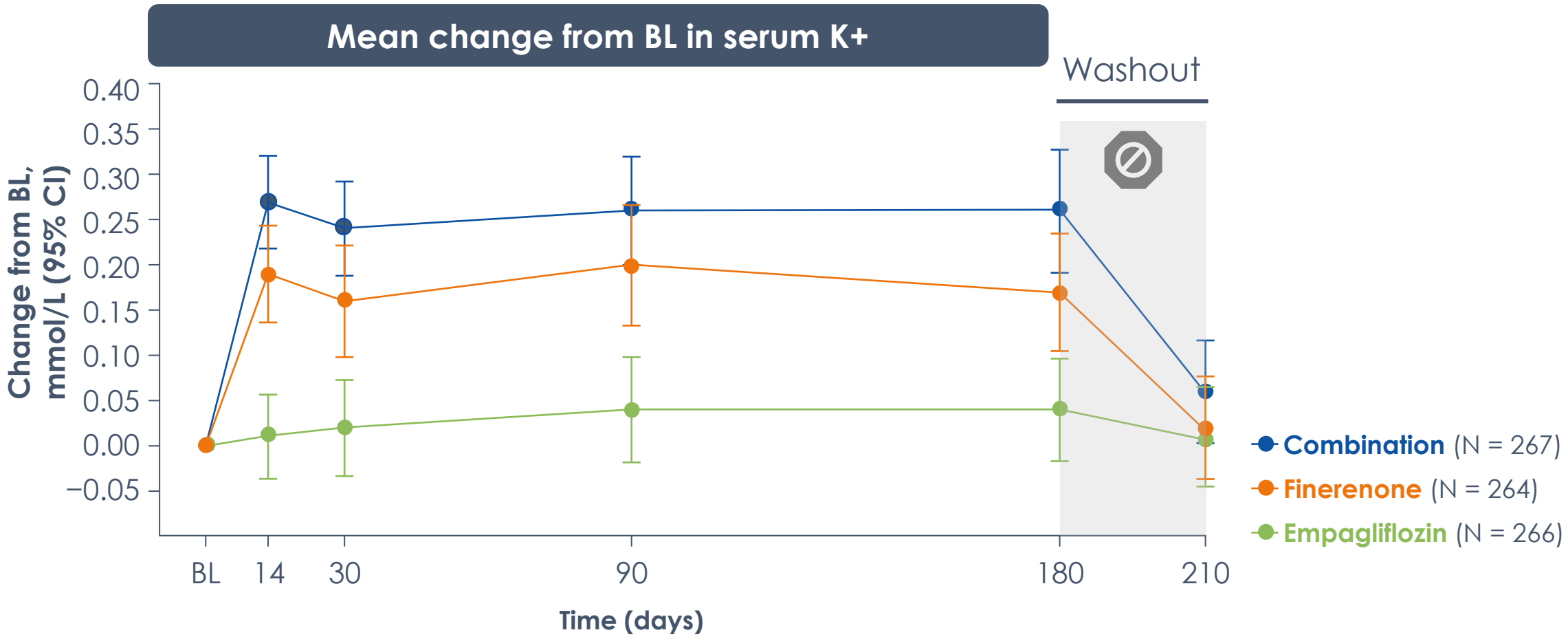
BL, baseline; CI, confidence interval; K+, potassium.

[K+] increased in combination and finerenone groups, returning to BL levels after drug withdrawal



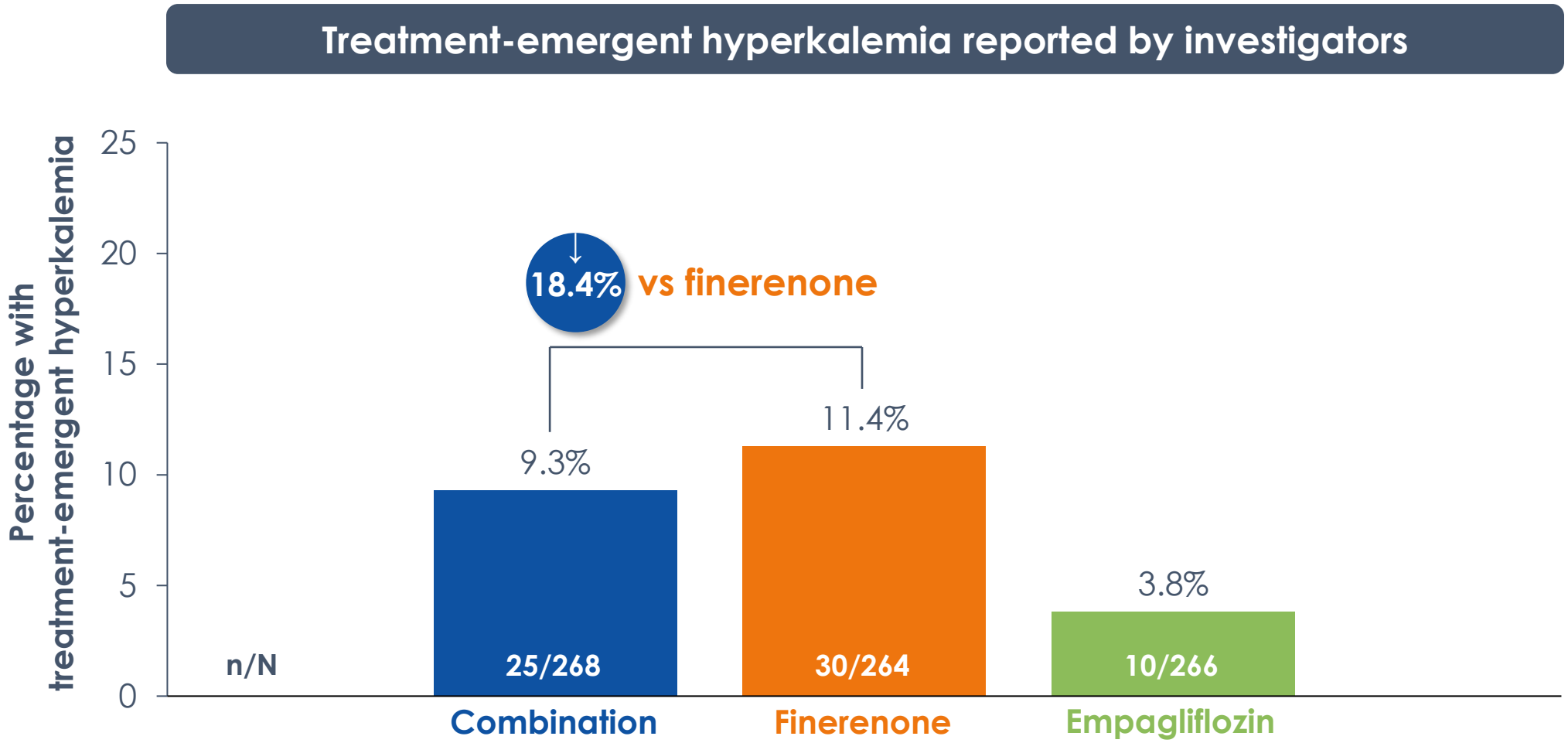
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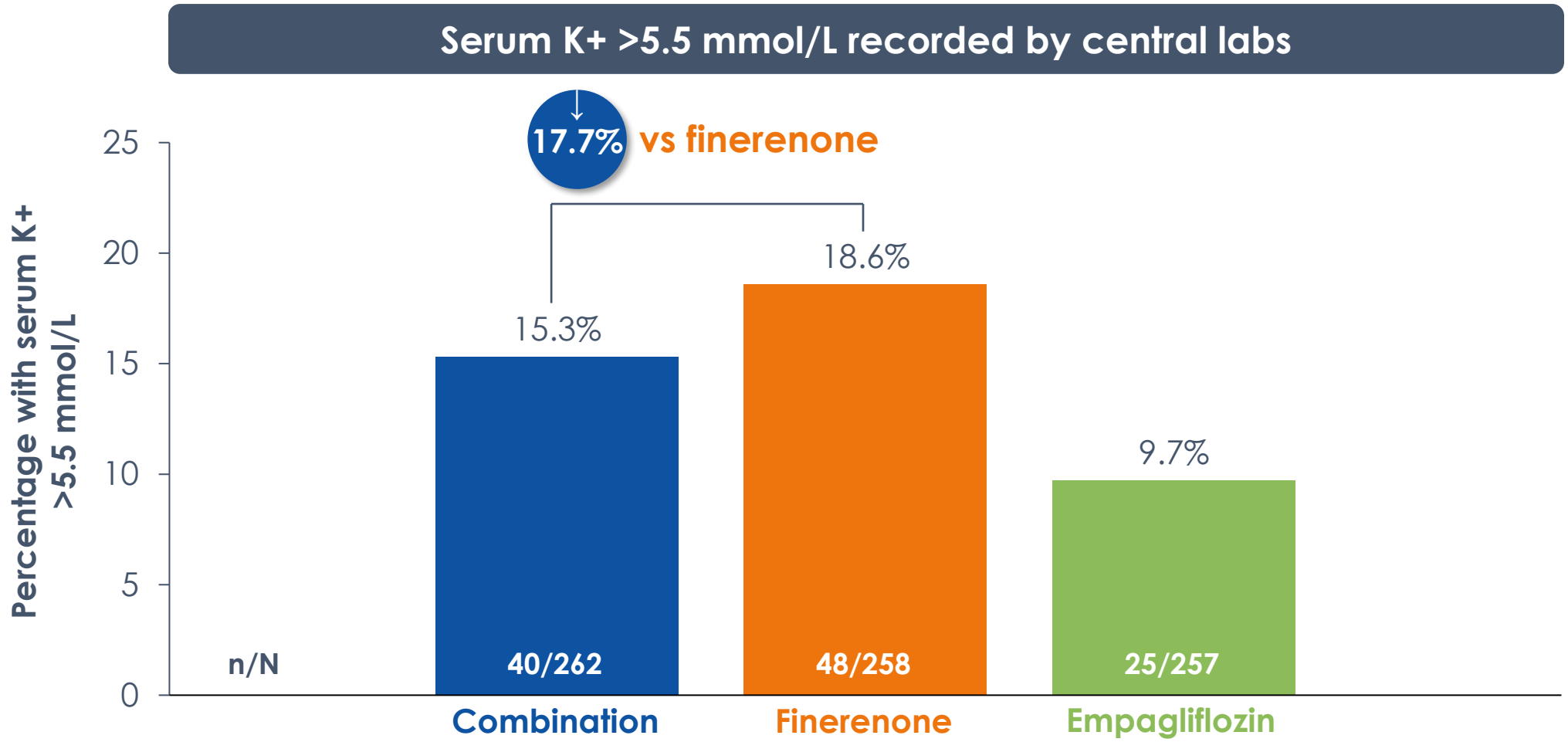


BL, baseline; CI, confidence interval; K+, potassium.

Numerically lower incidence of treatment-emergent hyperkalemia with combination therapy compared with finerenone



Numerically lower incidence of treatment-emergent hyperkalemia with combination therapy compared with finerenone



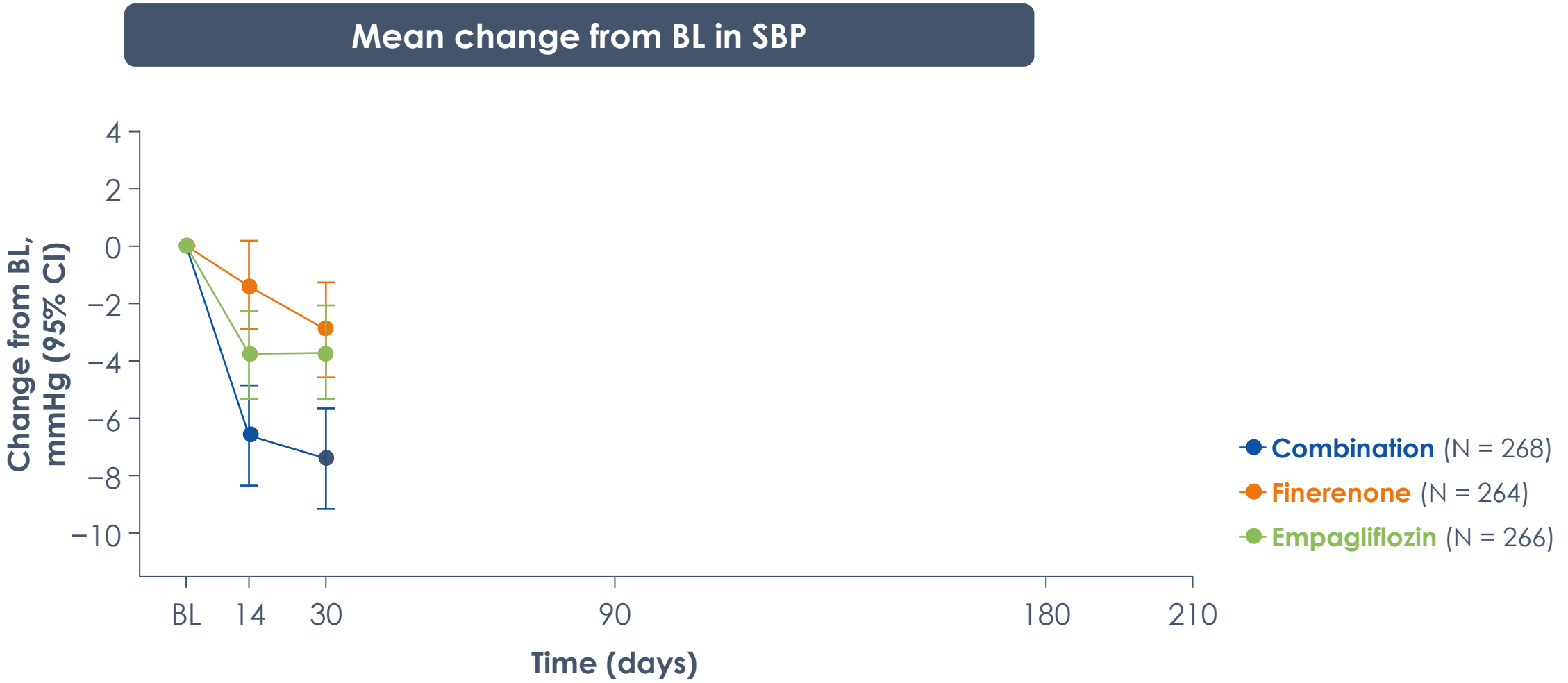
K+, potassium.

Treatment-emergent hyperkalemia events leading to permanent discontinuation of trial drug were uncommon

	Combination N = 268†	Finerenone N = 264†	Empagliflozin N = 266†
Treatment-emergent hyperkalemia,‡ n			
Leading to hospitalization	0	0	0
Leading to permanent discontinuation of trial drug	1	1	1
Serious adverse event	0	0	0
Leading to death	0	0	0

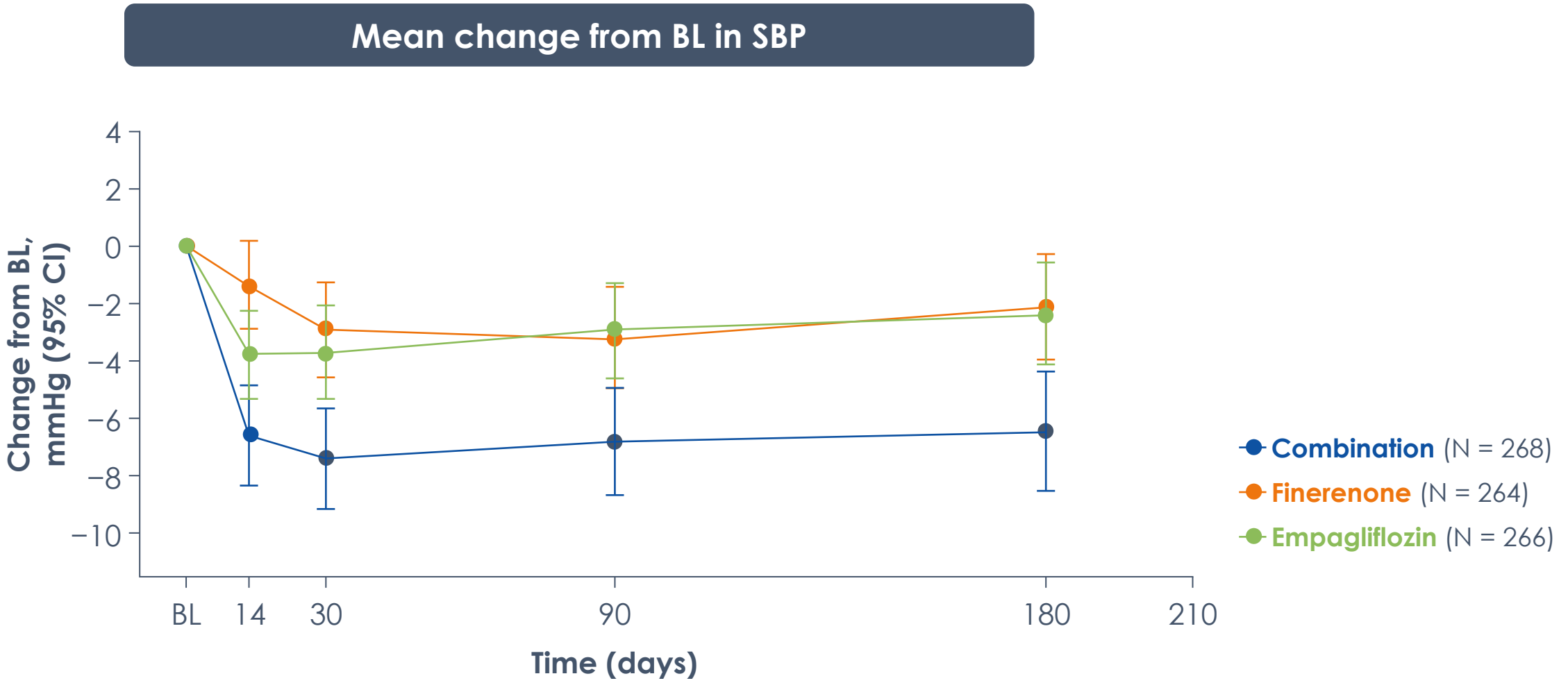
†SAS comprised all participants receiving at least one dose of trial medication. ‡Adverse events were defined as TEAEs if they occurred in patients who had received at least one dose of trial treatment and that started or worsened after the first dose of trial treatment and up to 3 days after any temporary or permanent interruption of trial treatment. The denominator represents all participants at risk for a treatment-emergent laboratory abnormality. Participants must have had both a BL and post-BL treatment-emergent value while the BL value must not have exceeded the displayed threshold. The numerator represents the number of participants at risk with at least one treatment-emergent laboratory assessment meeting the criterion. BL, baseline; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

Combination therapy had an additive impact on SBP



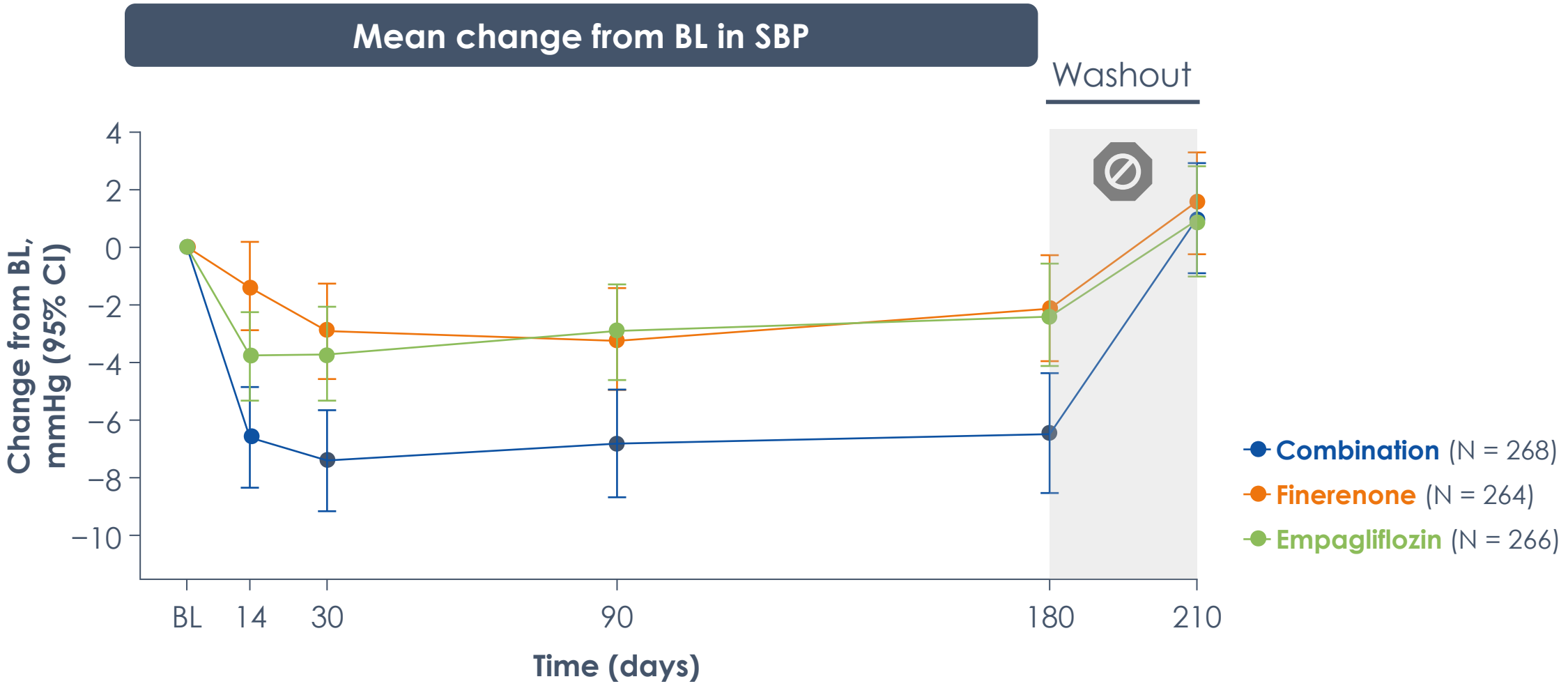
BL, baseline; CI, confidence interval; SBP, systolic blood pressure.

Combination therapy had an additive impact on SBP



BL, baseline; CI, confidence interval; SBP, systolic blood pressure.

Combination therapy had an additive impact on SBP



BL, baseline; CI, confidence interval; SBP, systolic blood pressure.

Incidence of symptomatic hypotension was low



Symptomatic hypotension incidence

1.1%
n = 3

Combination

0%
n = 0

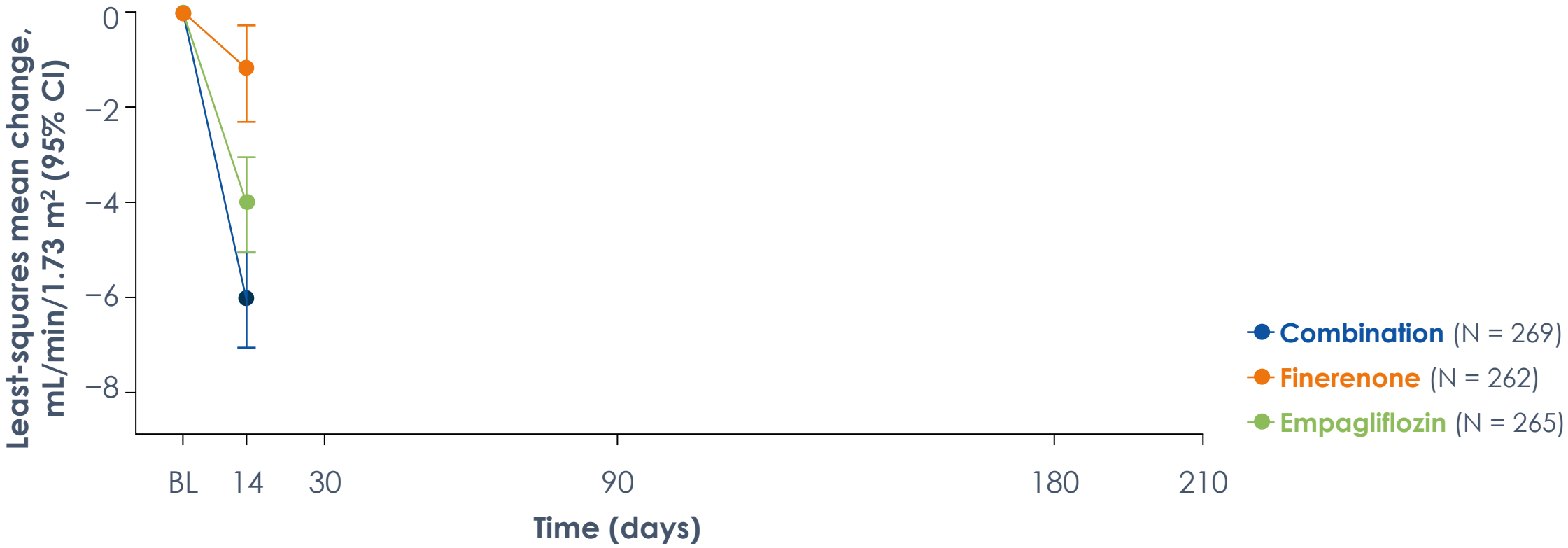
Finerenone

0%
n = 0

Empagliflozin

Initial eGFR decline following simultaneous initiation of combination therapy was predictable

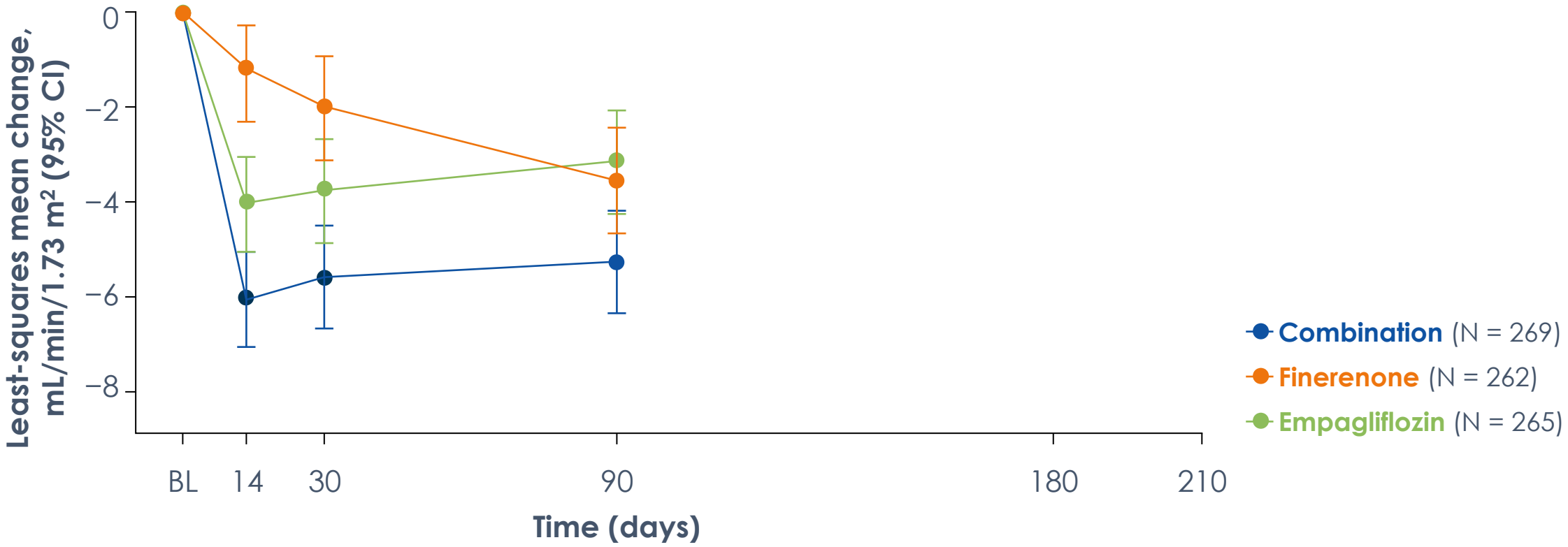
Findings suggest eGFR changes are hemodynamic



Least-squares mean difference (95% CI) for the mixed model repeated measures analysis of change from baseline in eGFR. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation with a modification to the equation for Japanese participants.
BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate.

Initial eGFR decline following simultaneous initiation of combination therapy was predictable

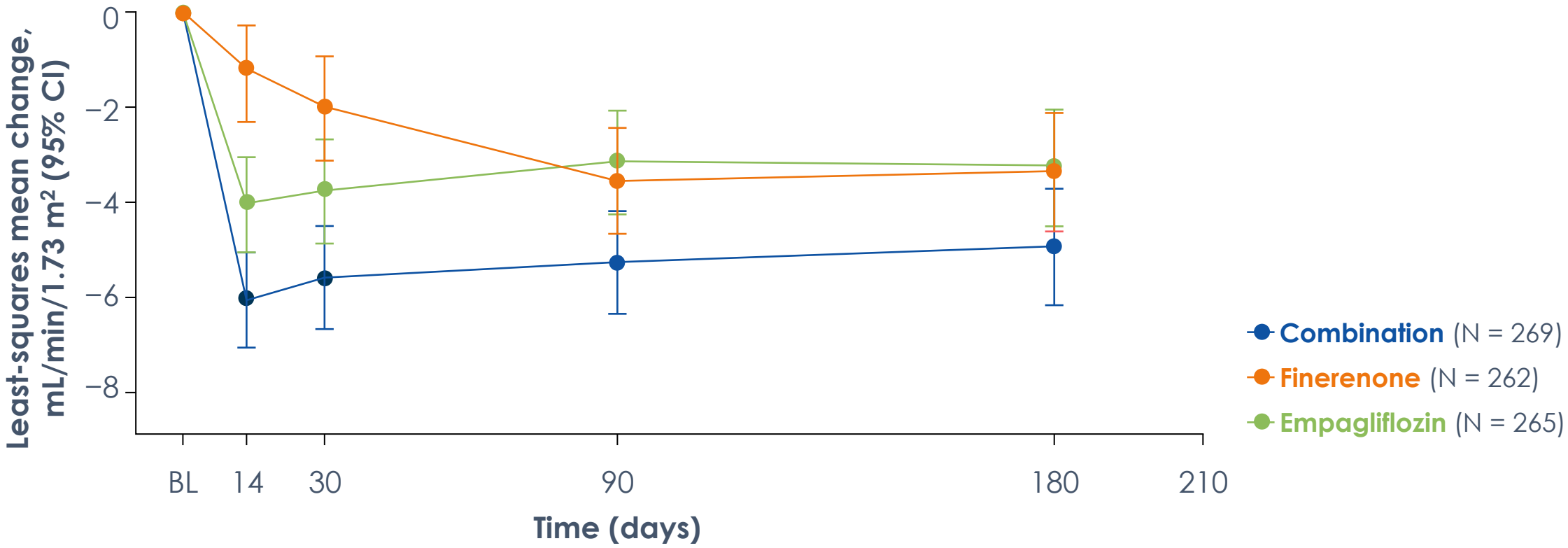
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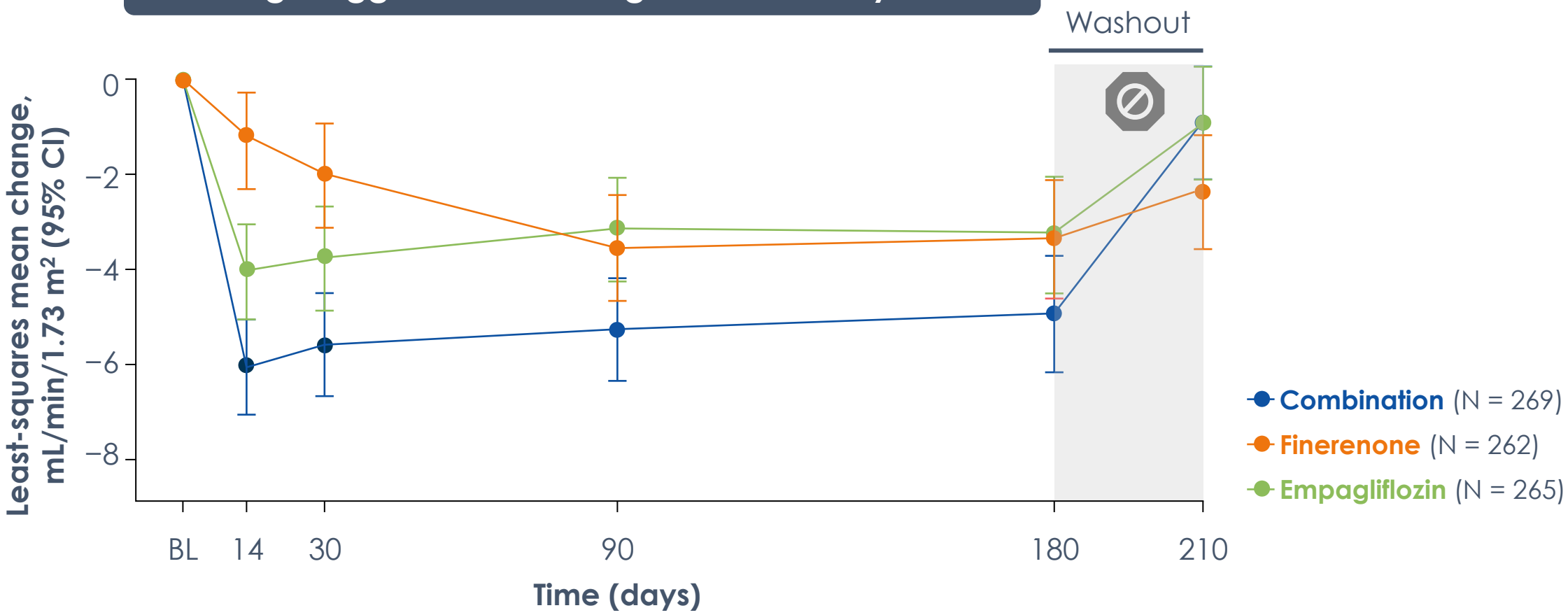
Findings suggest eGFR changes are hemodynamic



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BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate.

Initial eGFR decline following simultaneous initiation of combination therapy was predictable and largely reversible after drug withdrawal

Findings suggest eGFR changes are hemodynamic



Least-squares mean difference (95% CI) for the mixed model repeated measures analysis of change from baseline in eGFR. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation with a modification to the equation for Japanese participants.
BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate.

Low incidence of AKI after simultaneous initiation of combination therapy

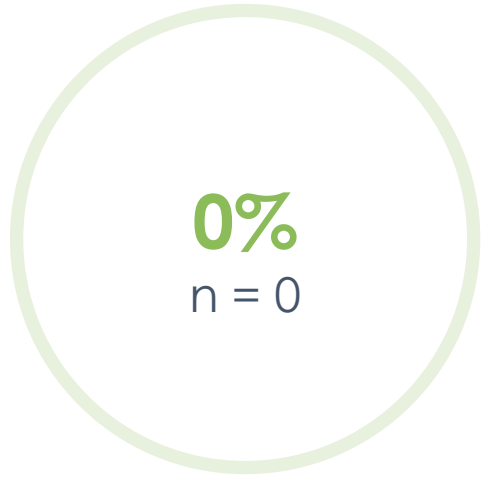
AKI incidence



Combination



Finerenone

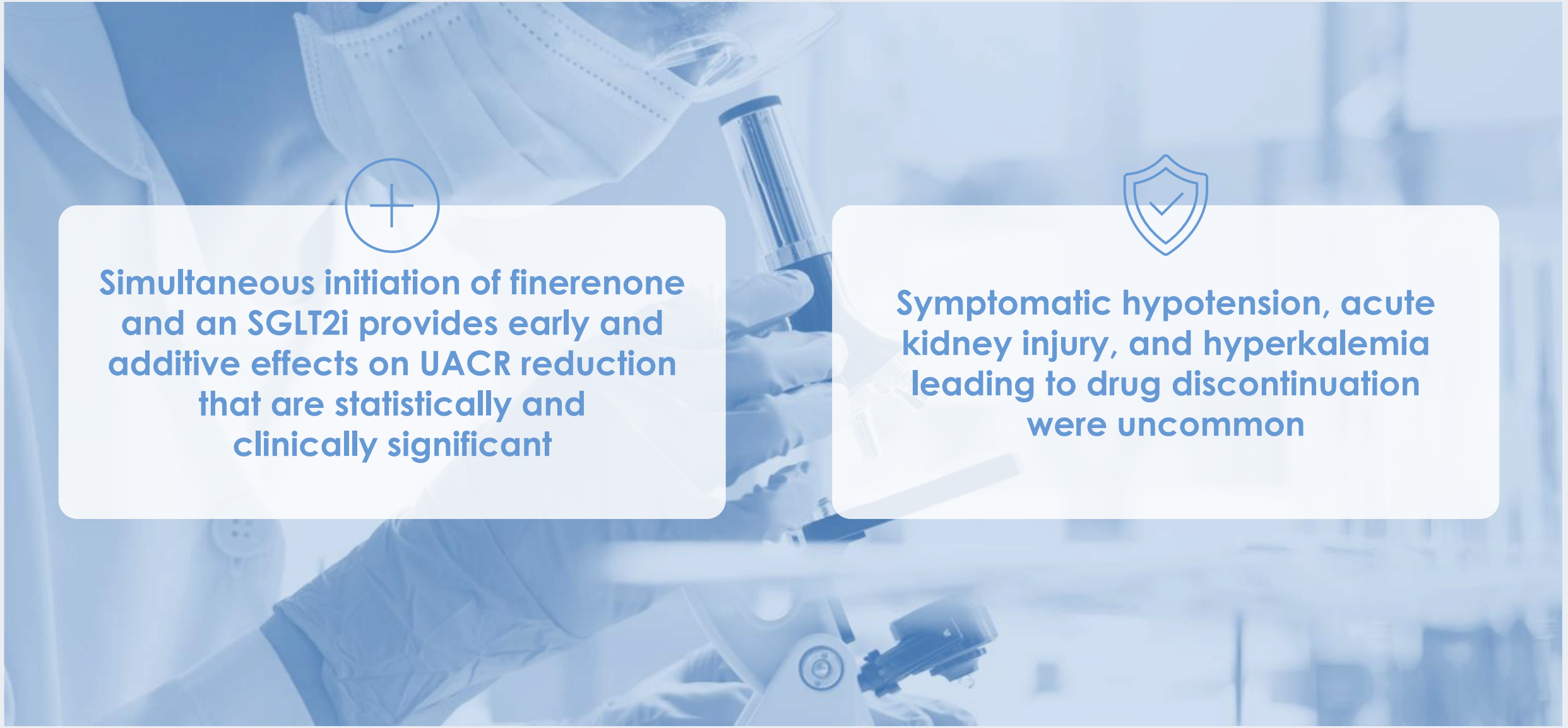


Empagliflozin

Incidence of adverse events leading to drug discontinuation was low

AKI, acute kidney injury.

Summary



Simultaneous initiation of finerenone and an SGLT2i provides early and additive effects on UACR reduction that are statistically and clinically significant

Symptomatic hypotension, acute kidney injury, and hyperkalemia leading to drug discontinuation were uncommon

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

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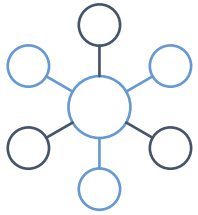
Interpretation

Johannes F. E. Mann, MD

Does albuminuria reduction mediate CKD outcomes in T2D?



Post hoc mediation analysis



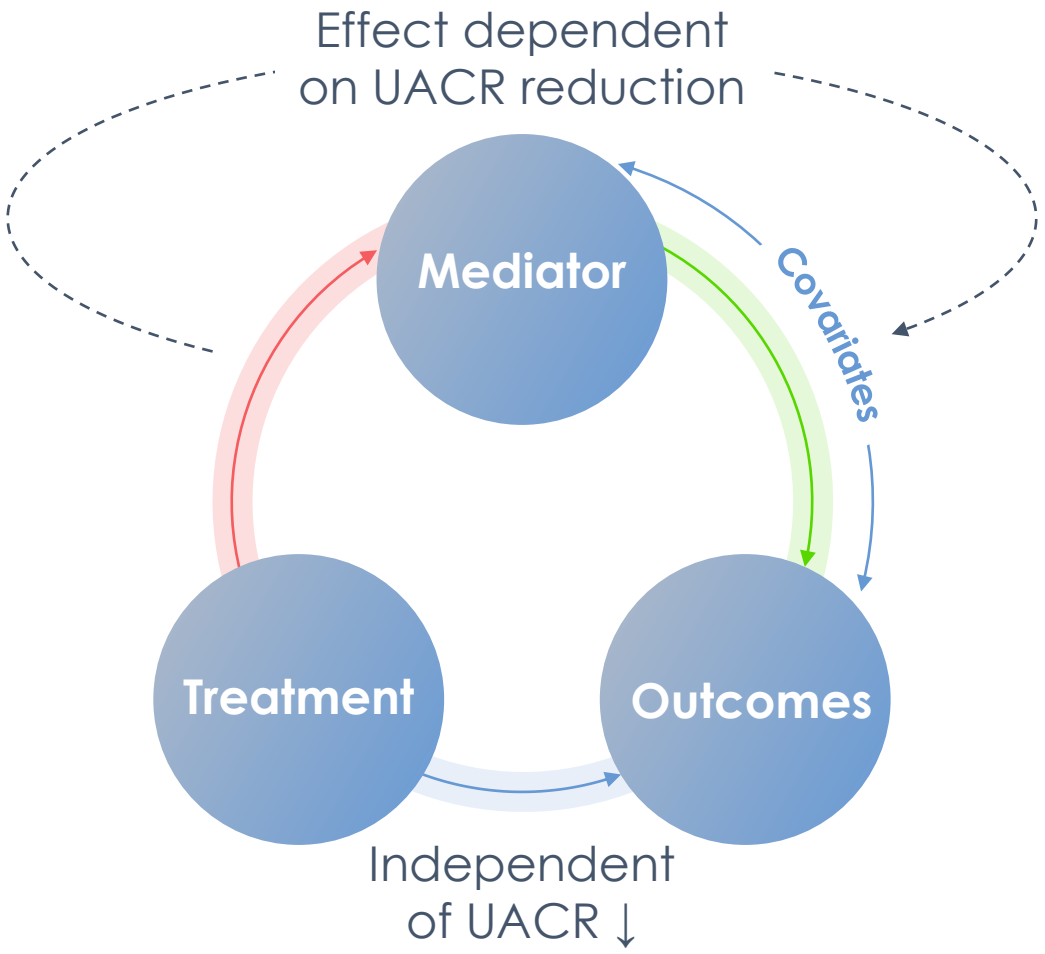
FIDELITY pooled data



12512 participants with CKD and T2D

CKD, chronic kidney disease; T2D, type 2 diabetes.
Agarwal R et al. *Ann Int Med* 2023;176:1606–1616.

Causal mediation analysis of UACR on kidney and CV outcomes



- **Mediator**

  M_i = change in UACR between baseline and 4 months

- **Outcomes**

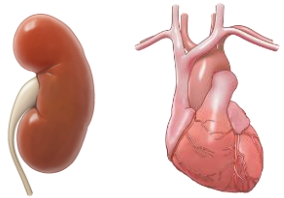
  Y_i = time to kidney and CV events

- **Treatment**

  T_i = 1 if on finerenone
  T_i = 0 if on placebo

CV, cardiovascular; UACR, urinary albumin-to-creatinine ratio.
Agarwal R et al. *Ann Int Med* 2023;176:1606–1616.

Percent of outcomes mediated by an early (baseline to 4 months) UACR reduction

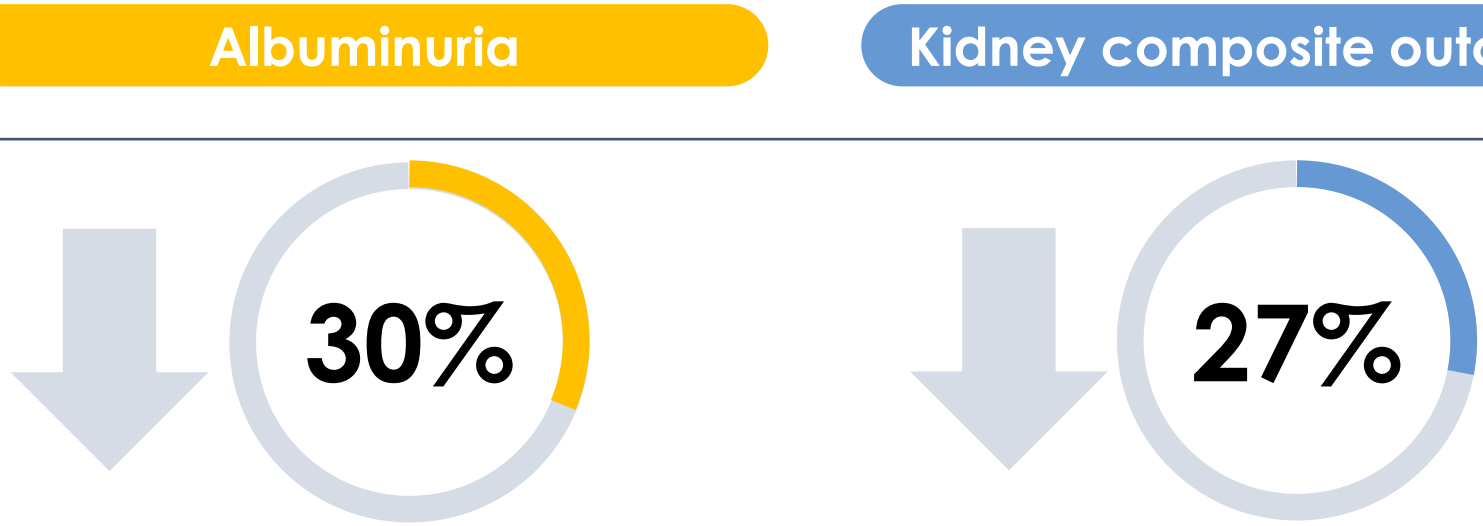


	Kidney	CV
UACR continuous	84%	37%

Early albuminuria reduction with finerenone in CKD and T2D mediates a large proportion of the treatment effect against CKD progression and a modest proportion of the effect against CV outcomes

CKD, chronic kidney disease; CV, cardiovascular; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.
Agarwal R et al. *Ann Int Med* 2023;176:1606–1616.

Early treatment effect on albuminuria associates with long-term kidney outcomes

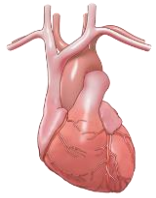


Association ≠ Causation

Median time to albuminuria = 6 months

Heerspink HJL et al. *Lancet Diab Endo* 2019, DOI 10.1016/S2213-8587(18)30314-0

Percent of CV outcomes mediated by an early (baseline to 4 months) UACR reduction and BP is additive

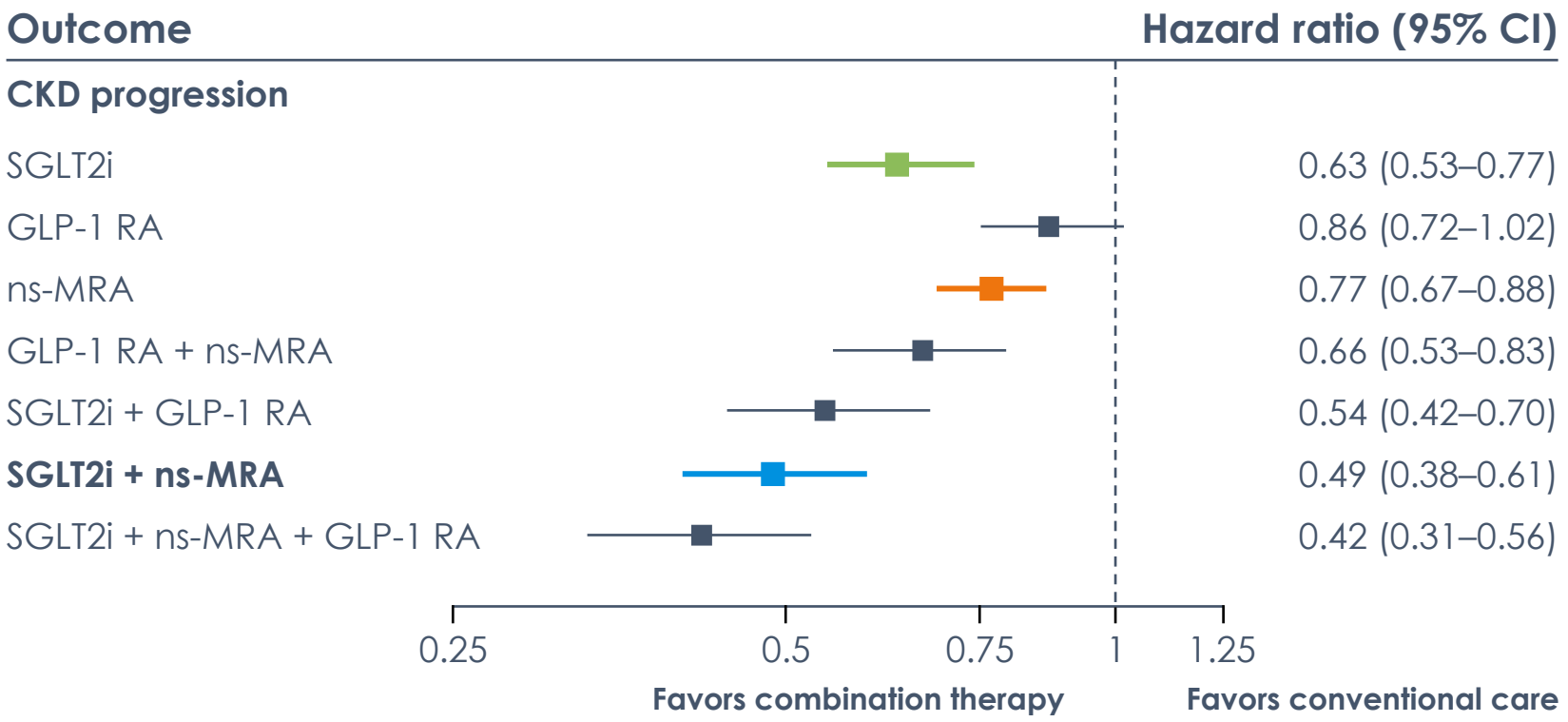


	UACR	SBP	UACR + SBP
Mediation	39%	21%	50%

Early albuminuria and BP reductions with finerenone in CKD and T2D jointly mediated half of the CV outcome

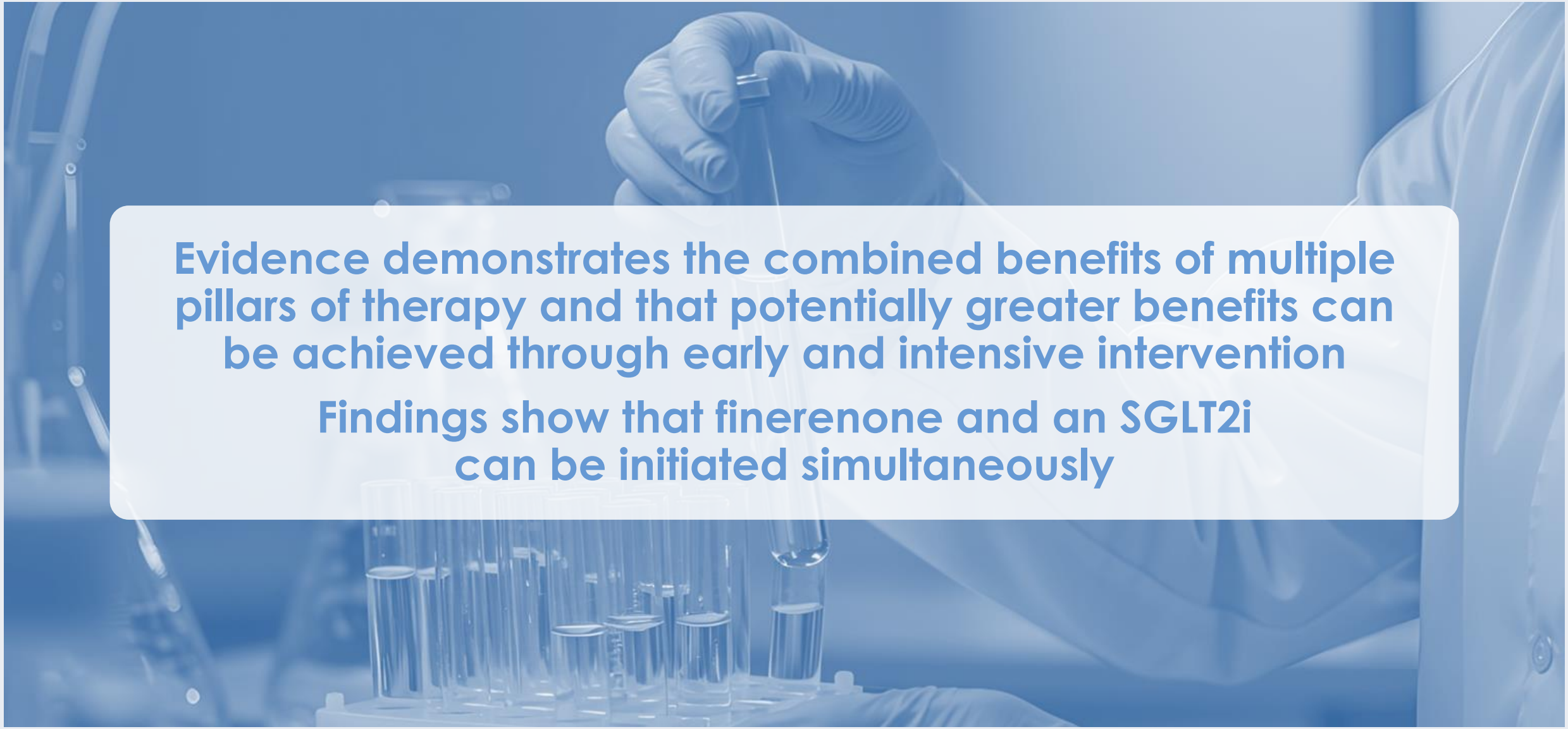
†Fewer participants were analyzed in this data set due to Good Clinical Practice violations at one site; therefore, the UACR mediation is not identical to the prior analysis.
BP, blood pressure; CV, cardiovascular; SBP, systolic blood pressure; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.
Agarwal R et al. *J Am Coll Cardiol* 2025; 85(SupplA):424.

CKD progression can potentially be slowed by combination therapy



CI, confidence interval; CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide receptor-1 agonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.
Neuen BL et al. *Circulation* 2024;149:450–462.

Summary



Evidence demonstrates the combined benefits of multiple pillars of therapy and that potentially greater benefits can be achieved through early and intensive intervention

Findings show that finerenone and an SGLT2i can be initiated simultaneously

For the published CONFIDENCE paper in the *New England Journal of Medicine*, scan this QR code

