Efficacy and safety of finerenone and empagliflozin in patients with initial decline in estimated glomerular filtration rate: A CONFIDENCE trial prespecified analysis

#WCN26-AB-5829

Hiddo J. L. Heerspink,[1] Amy K. Mottl,[2] Julio Rosenstock,[3] Masaomi Nangaku,[4] Janet B. McGill,[5] Jennifer B. Green,[6] Peter Rossing,[7] Muthiah Vaduganathan,[8] Johannes F. E. Mann,[9] Jose Luis Gorriz,[10] Na Li,[11] Meike Brinker,[12] Charlie Scott,[13] Mario Berger,[14] Rajiv Agarwal[15]

[1]Department of Clinical Pharmacy and Pharmacology, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands; [2]University of North Carolina Kidney Center, University of North Carolina School of Medicine, Chapel Hill, NC, USA; [3]University of Texas Southwestern Medical Center, Dallas, TX, USA; [4]Division of Nephrology and Endocrinology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan; [5]Division of Endocrinology, Metabolism & Lipid Research, Washington University in St. Louis, St. Louis, MO, USA; [6]Division of Endocrinology, Department of Medicine and Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA; [7]Department of Clinical Medicine, Steno Diabetes Center Copenhagen and University of Copenhagen, Copenhagen, Denmark; [8]Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [9]Department of Nephrology & Hypertension, KfH Kidney Centre, Munich, Germany and Friedrich Alexander University, Erlangen, Germany; [10]Servicio de Nefrología, Hospital Universitario Clínic de Valencia, Instituto de Investigación Sanitaria (INCLIVA), Universitat de València, Valencia, Spain; [11]Global Medical and Evidence, Bayer Healthcare, Beijing, China; [12]Cardiology and Nephrology Clinical Development, Bayer AG, Wuppertal, Germany; [13]Clinical Statistics and Analytics, Bayer Healthcare Inc, Whippany, NJ, USA; [14]Research and Development, Translational Sciences, Bayer AG, Wuppertal, Germany; [15]Division of Nephrology, Richard L. Roudebush VA Medical Center and Indiana University School of Medicine, Indianapolis, IN, USA

Introduction

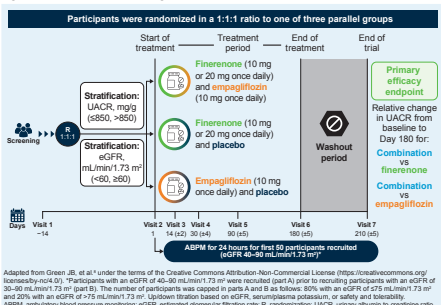
- In patients with type 2 diabetes (T2D) and chronic kidney disease (CKD), the sodium–glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin and the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone slow kidney function decline over time and reduce the incidence of kidney failure.[1,2]
- The kidney-protective mechanisms of SGLT2is and finerenone can be accompanied by a dip in estimated glomerular filtration rate (eGFR) on treatment initiation,[3–5] which is largely reversible after treatment discontinuation.[6,7]
- The CONFIDENCE trial (NCT05254002) was undertaken to assess efficacy and safety of simultaneous initiation of finerenone and empagliflozin in participants with T2D and CKD.[8]
  - Primary results demonstrated that this combination was well tolerated and more effective at lowering the urinary albumin-to-creatinine ratio (UACR) after 180 days than either therapy alone.[9]
  - However, simultaneous initiation also led to a larger acute reduction in eGFR compared with either therapy alone.[9]
- This prespecified analysis of the CONFIDENCE trial aimed to test the hypothesis that the acute eGFR dip upon simultaneous initiation of finerenone and empagliflozin was not associated with safety signals and reflects a pharmacodynamic effect.

Methods

Study design

- CONFIDENCE was a phase 2, randomized, double-blind, active-controlled trial.[8,9]
- Details of the study design are presented in **Figure 1**.

Figure 1. CONFIDENCE trial design



Adapted from Green JB, et al.[8] 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 was 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.

Study participants and data collection

- The main inclusion criteria were:
  - Age ≥18 years, T2D as defined by the American Diabetes Association[10] (glycated hemoglobin <11%), eGFR 30–90 mL/min per 1.73 m², albuminuria (UACR 100 to <5000 mg/g), and treatment with the maximally tolerated dose of a renin–angiotensin system inhibitor for >1 month.

Study objectives

- The focus of this analysis was acute eGFR change.
  - Acute change was defined as percentage or absolute change in eGFR at Day 14, the first time point after treatment initiation at which follow-up eGFR measurements were available.
- Further outcomes included:
  - Treatment-emergent adverse events (TEAEs), serious TEAEs, and change from baseline in systolic blood pressure (SBP) and UACR at Day 14.
  - Changes from baseline in urinary kidney damage biomarkers at Day 30 were also investigated (first morning void urine samples), specifically, clusterin, cystatin-C, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and osteopontin.

Analysis

- Changes in eGFR from visit to visit were modeled using a mixed model for repeated measures.
- Logistic regression models were employed to assess association of baseline variables with achieving an eGFR decrease of ≥10% at Day 14.
- As a sensitivity analysis, results were generated defining the acute phase from baseline to Day 30.
- To evaluate associations between changes in UACR and SBP with changes in eGFR, descriptive statistics and linear regression models were employed.
- TEAEs, defined as adverse events occurring within 3 days of the last intake of study medication, were summarized descriptively within each subgroup, including three adverse events of special interest: hyperkalemia, hypotension, and acute kidney injury (AKI).
- Biomarkers were measured at baseline and Day 30 using Olink ExploreHT proteomics. Changes from baseline to Day 30 were also modeled using linear models.

Results

Participants

- Of the 800 randomized participants included in the full analysis set in the CONFIDENCE trial, a total of 761 (95%) participants had eGFR data available at baseline and Day 14.
- Baseline characteristics by Day 14 acute change in eGFR are presented in **Table 1**.

Table 1. Baseline characteristics by category of acute change in eGFR (Day 14 vs baseline)

	Participants with acute eGFR reduction (≥10%) (n=345)	Participants with modest eGFR reduction (0–<10%) (n=244)	Participants with acute eGFR increase (n=172)
Age, years, mean±SD	67.0±10.1	66.1±10.3	66.3±10.3
Female sex, n (%)	82 (23.8)	63 (25.8)	46 (26.7)
Race, n (%)			
White	173 (50.1)	95 (38.9)	66 (38.4)
Asian	142 (41.2)	124 (50.8)	88 (51.2)
Black or African American	25 (7.2)	22 (9.0)	16 (9.3)
Other	4 (1.2)	0	1 (0.6)
Missing	1 (0.3)	3 (1.2)	1 (0.6)
Ethnicity, n (%)			
Hispanic or Latino	38 (11.0)	31 (12.7)	13 (7.6)
Geographic region, n (%)			
Asia	138 (40.0)	121 (49.6)	86 (50.0)
Europe	106 (30.7)	58 (23.8)	36 (20.9)
North America	101 (29.3)	65 (26.6)	50 (29.1)
HbA1c, % (mmol/mol), mean±SD	7.2±1.2	7.4±1.3	7.2±1.2
Body weight, kg, mean±SD	84.9±22.3	80.0±17.9	78.3±19.4
BMI, kg/m², mean±SD	30.0±6.4	29.2±5.5	28.0±5.7
eGFR, mL/min/1.73 m², mean±SD	56.5±17.4	55.5±16.9	47.5±14.9
UACR, mg/g, median (range)	601 (27–9238)	592 (47–5790)	535 (0–5375)
UACR category, mg/g, n (%)			
≤850	218 (63.2)	162 (66.4)	114 (66.3)
>850	118 (34.2)	80 (32.8)	55 (32.0)
SBP, mmHg, mean±SD	136.4±13.0	134.5±13.6	133.3±13.7
Serum potassium, mmol/L, mean±SD	4.5±0.4	4.5±0.4	4.5±0.5
Medical history, n (%)			
Hypertension	298 (86.4)	224 (91.8)	148 (86.0)
ASCVD	108 (31.3)	59 (24.2)	46 (26.7)
Diabetic retinopathy	51 (14.8)	48 (19.7)	26 (15.1)
Atrial fibrillation	30 (8.7)	10 (4.1)	9 (5.2)
Heart failure	17 (4.9)	6 (2.5)	5 (2.9)
Concomitant medications, n (%)			
ACEis/ARBs	339 (98.3)	240 (98.4)	169 (98.3)
Statins	272 (78.8)	177 (72.5)	119 (69.2)
Metformin	220 (63.8)	149 (61.1)	98 (57.0)
Antiplatelet agents	145 (42.0)	93 (38.1)	64 (37.2)
Diuretics	140 (40.6)	81 (33.2)	54 (31.4)
Insulin	140 (40.6)	88 (36.1)	73 (42.4)
Beta blockers	122 (35.4)	82 (33.6)	60 (34.9)
DPP4 inhibitors	102 (29.6)	82 (33.6)	62 (36.0)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; DPP4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; SD, standard deviation; UACR, urinary albumin-to-creatinine ratio.

Results continued

Acute reduction in eGFR and reversibility after discontinuation

- Least-squares mean reductions from baseline in eGFR (mL/min/1.73 m² [95% confidence interval; CI]) on Day 14 were −6.1 (−7.1, −5.1), −1.3 (−2.3, −0.3), and −4.0 (−5.1, −3.0) in the combination, finerenone, and empagliflozin groups, respectively.
  - An acute reduction in eGFR ≥10% occurred more frequently in the combination group (148/253 [58.5%]) compared with the finerenone (75/250 [30.0%]) or empagliflozin (122/258 [47.3%]) groups.
  - Few participants experienced an acute reduction in eGFR >30% at Day 14.
  - Differences between treatment groups were similar when eGFR reductions from baseline were assessed at Day 30, compared with Day 14.
- At Day 14, there were greater eGFR reductions with combination therapy compared with finerenone (−4.8 mL/min/1.73 m² [95% CI −6.2, −3.4) and empagliflozin (−2.0 mL/min/1.73 m² [95% CI −3.4, −0.6]) (**Figure 2**).
  - At 4 weeks after study drug discontinuation, eGFR increased more with combination therapy compared with finerenone (least-squares mean difference 2.2 mL/min/1.73 m² [95% CI 0.6, 3.8]) or empagliflozin (0.9 mL/min/1.73 m² [95% CI −0.7, 2.5]).

Clinical correlates of acute reduction in eGFR ≥10%

- Univariate analysis showed that the likelihood of a reduction in eGFR ≥10% was significantly increased among individuals with higher baseline eGFR and those receiving combination treatment vs finerenone or empagliflozin alone.
- In multivariate analysis, odds of an acute eGFR reduction ≥10% increased by 245% in combination vs finerenone therapy groups (odds ratio [OR] 3.45 [95% CI 2.38, 5.0) and by 61% in combination vs empagliflozin therapy groups (OR 1.61 [95% CI 1.14, 2.33]).

Safety and study drug discontinuation

- The number of participants with TEAEs and safety outcomes are presented in **Table 2**.
  - Overall (n=761), TEAEs occurred in 404 (53.1%) participants, serious TEAEs in 51 (6.7%), and AKI was reported in six participants (0.8%).

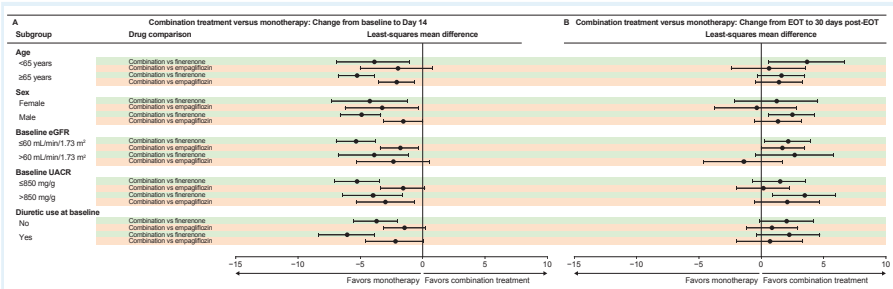
Changes in urinary kidney damage markers at Day 30

- There were no increases in cystatin-C and KIM-1. Clusterin was modestly increased in all treatment groups. Osteopontin was increased with combination treatment and empagliflozin; NGAL was increased with combination treatment (**Figure 3**).
  - Importantly, changes from baseline were consistent across categories of acute eGFR change within each treatment group, with no clear evidence of increases in the subgroup of participants with an acute reduction in eGFR ≥10%.

Correlations between acute change in eGFR and changes in SBP and albuminuria

- Progressively larger reductions in UACR and SBP were observed among participants with greater acute eGFR reductions.
  - A similar pattern was observed when acute eGFR reduction was categorized by quartile (**Figure 4**).
  - A similar trend with all groups was shown in relation to SBP.
- Results were confirmed when acute change in eGFR was modeled on a continuous scale.
  - In univariate models, a 1 mmHg decrease in SBP was associated with a 0.12 mL/min/1.73 m² reduction in eGFR independent of treatment.
  - Reductions in UACR were also significantly associated with reductions in eGFR, such that a 30% reduction in UACR was associated with an average eGFR decrease of 1.97 mL/min/1.73 m².

Figure 2. Forest plot of changes in eGFR, (A) effects of combination treatment vs finerenone or empagliflozin on acute change in eGFR (Day 14 vs baseline), (B) effects of combination treatment vs finerenone or empagliflozin on the change in eGFR from the end of treatment to 30 days after end of treatment (Day 180 vs Day 210)



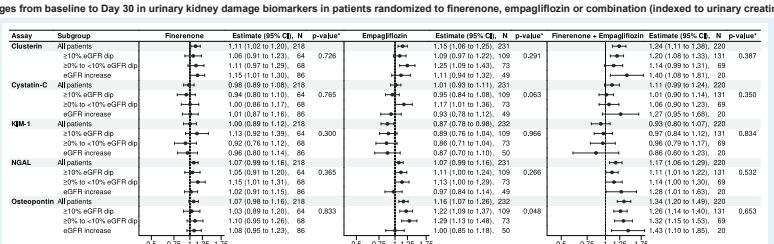
Circles represent point estimates and horizontal lines represent 95% CIs. Changes in eGFR from visit to visit were modeled using a mixed model for repeated measures. Acute change defined as change in eGFR from baseline to Day 14; rebound defined as change in eGFR from EoT visit to 30 days post-EoT. Magnitude of both acute change and rebound analyzed within a set of predefined subgroups.
CI, confidence interval; eGFR, estimated glomerular filtration rate; EoT, end of treatment; UACR, urinary albumin-to-creatinine ratio.

Table 2. Numbers of participants with TEAEs and safety outcomes by category of acute change in eGFR (Day 14 vs baseline)

	Participants with acute eGFR reduction (≥10%) (n=345)				Participants with modest eGFR reduction (0–<10%) (n=244)				Participants with acute eGFR increase (n=172)				All participants (N=761)
	Combo (n=148)	Fin (n=75)	Empa (n=122)	Total (N=345)	Combo (n=81)	Fin (n=78)	Empa (n=85)	Total (N=244)	Combo (n=24)	Fin (n=97)	Empa (n=51)	Total (N=172)	
Any TEAE, n (%)	89 (60.1)	40 (53.3)	66 (54.1)	195 (56.5)	41 (50.6)	42 (53.8)	39 (45.9)	122 (50.0)	9 (37.5)	50 (51.5)	28 (54.9)	87 (50.6)	404 (53.1)
TEAE leading to treatment discontinuation, n (%)	7 (4.7)	2 (2.7)	6 (4.9)	15 (4.3)	2 (2.5)	5 (6.4)	2 (2.4)	9 (3.7)	1 (4.2)	2 (2.1)	1 (2.0)	4 (2.3)	28 (3.7)
Any serious TEAE, n (%)	14 (9.5)	3 (4.0)	10 (8.2)	27 (7.8)	3 (3.7)	4 (5.1)	5 (5.9)	12 (4.9)	1 (4.2)	9 (9.3)	2 (3.9)	12 (7.0)	51 (6.7)
Serious TEAE leading to treatment discontinuation, n (%)	2 (1.4)	1 (1.3)	2 (1.6)	5 (1.4)	0	1 (1.3)	0	1 (0.4)	0	1 (1.0)	0	1 (0.6)	7 (0.9)
TEAE with death as the outcome, n (%)	1 (0.7)	0	1 (0.8)	2 (0.6)	0	0	1 (1.2)	1 (0.4)	0	0	0	0	3 (0.4)
Hyperkalemia, n (%)*	20 (13.5)	9 (12.0)	7 (5.7)	36 (10.4)	2 (2.5)	6 (7.7)	2 (2.4)	10 (4.1)	2 (8.3)	12 (12.4)	1 (2.0)	15 (8.7)	61 (8.0)
AKI, n (%)	3 (2.0)	2 (2.7)	0	5 (1.4)	0	0	0	0	0	1 (1.0)	0	1 (0.6)	6 (0.8)
eGFR decline >30% from baseline, n (%)	49 (33.1)	21 (28.0)	24 (19.7)	94 (27.2)	7 (8.6)	14 (17.9)	3 (3.5)	24 (9.8)	2 (8.3)	9 (9.3)	2 (3.9)	13 (7.6)	131 (17.2)
Hypotension, n (%)	3 (2.0)	0	0	3 (0.9)	0	0	0	0	0	0	0	0	3 (0.4)

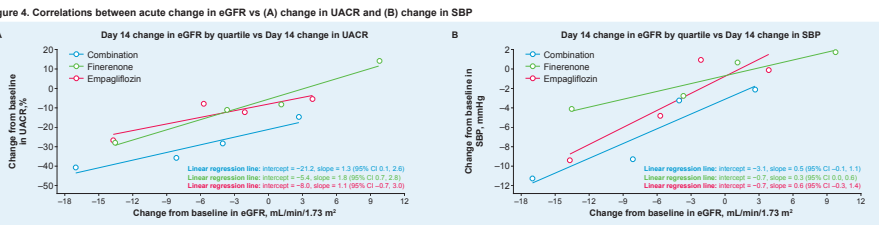
*Preferred terms 'hyperkalemia' and 'blood potassium increased' were considered.
AKI, acute kidney injury; Combo, combination treatment; eGFR, estimated glomerular filtration rate; Empa, empagliflozin treatment; Fin, finerenone treatment; TEAE, treatment-emergent adverse event.

Figure 3. Changes from baseline to Day 30 in urinary kidney damage biomarkers in patients randomized to finerenone, empagliflozin or combination (indexed to urinary creatinine)



*Nominal P-values are shown for the interaction with treatment and eGFR changes categories. Changes from baseline to Day 30 in the urinary kidney damage markers also modeled using linear models. Model included treatment, predefined acute eGFR reduction categories, with treatment by acute eGFR reduction subgroup interaction as factors, and age and sex as covariates. Differences between acute eGFR reduction categories within each treatment arm were estimated from the model and globally tested using subgroup-specific contrasts.
CI, confidence interval; eGFR, estimated glomerular filtration rate; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin.

Figure 4. Correlations between acute change in eGFR vs (A) change in UACR and (B) change in SBP



Linear regression models were employed to evaluate association between changes in UACR and SBP with changes in eGFR. Each variable (SBP and UACR) was analyzed individually by incorporating change from baseline to Day 14, along with respective baseline measurements, as predictors in a model with acute change in eGFR as the dependent variable.
CI, confidence interval; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

Conclusions

- Among patients with T2D and CKD, acute reductions in eGFR were more common with combination therapy compared with either finerenone or empagliflozin alone.
- However, acute eGFR reduction was not associated with an unfavorable urinary kidney damage marker profile.
- Acute eGFR reduction correlated with acute reductions in SBP and UACR.
- These results support simultaneous initiation of finerenone and empagliflozin, and may help guide optimal use of combination therapy in clinical practice.

References

1. Agarwal R, et al. *Eur Heart J*. 2021;43(6):474–484.
2. Herrington WG, et al. *N Engl J Med*. 2023;388(2):117–127.
3. Heerspink HJL, et al. *Clin J Am Soc Nephrol*. 2021;16(8):1278–1280.
4. Navaneethan S, et al. *Kidney Int*. 2025;108(1):136–144.
5. Herrington WG, et al. *Lancet Diabetes Endocrinol*. 2025;13(12):1003–1014.
6. Kraus BJ, et al. *Kidney Int*. 2021;99(3):750–762.
7. Bakris GL, et al. *JAMA*. 2015;314(9):884–894.
8. Green JB, et al. *Nephrol Dial Transplant*. 2023;38(4):894–903.
9. Agarwal R, et al. *N Engl J Med*. 2025;393(6):533–543.
10. American Diabetes Association. *Diabetes Care*. 2021;44(Suppl 1):S15–S33.

Acknowledgments

Medical writing support was provided by Eleanor Roberts, PhD, and editorial support, including formatting and proofreading, was provided by Melissa Ward, BA, both of the Prime Group of Companies (Knutsford, UK), supported by Bayer according to Good Publication Practice guidelines.

Disclosures

This study is sponsored by Bayer AG. The authors developed the poster with the assistance of a medical writer funded by the sponsor. The sponsor was involved in the study design and the writing of the poster. **H.J.L.H.** has received consulting fees from Alexion, AstraZeneca, Bayer, Boehringer Ingelheim, BioCity, Dimerix, Eli Lilly, Janssen, Novartis, Novo Nordisk, Roche, and Travere Therapeutics, all paid to his employer; research support from AstraZeneca, Boehringer Ingelheim, Bayer, Janssen, and Novo Nordisk, all paid to his employer; honoraria from AstraZeneca and Novo Nordisk; and travel expenses from AstraZeneca and Eli Lilly.

Presenter details: Name: Hiddo J. L. Heerspink; Email: h.j.lambers.heerspink@umcg.nl