Joint effects of UACR and eGFR on efficacy and safety with simultaneous initiation of finerenone and an SGLT2 inhibitor in the CONFIDENCE trial

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Introduction

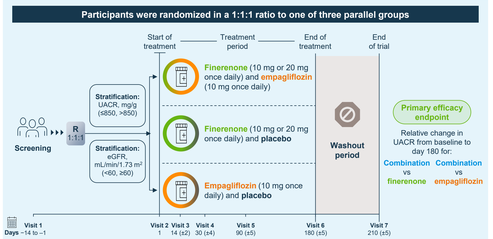
- Recent advances in the treatment of chronic kidney disease in people with type 2 diabetes include the nonsteroidal mineralocorticoid antagonist finerenone and sodium–glucose cotransporter 2 (SGLT2) inhibitors.[1–5]
  - These drug classes reduce the risk of meaningful decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease, renal death, hospitalization for heart failure, and cardiovascular death.
- The CONFIDENCE trial (NCT05254002) demonstrated that simultaneous initiation of finerenone and empagliflozin was superior to either monotherapy in reducing the magnitude of albuminuria at 180 days.[6]
  - Combination therapy was well tolerated, and rates of clinically significant hyperkalemia and hypotension were low.[6]
- Albuminuria and eGFR are independent and additive modifiers for progression of chronic kidney disease and mortality, and they may provide insight into potential treatment response.[7,8]
- Across pivotal trials of finerenone and SGLT2 inhibitors, relative risk reductions for major adverse kidney events have generally been consistent across albuminuria and eGFR categories.[3,9,10]
- In this post hoc analysis, we evaluated whether baseline urinary albumin-to-creatinine ratio (UACR) and/or baseline eGFR impacted the magnitude of albuminuria reduction in the CONFIDENCE trial, and whether the efficacy or safety of finerenone, empagliflozin, or their combination was modified by baseline UACR and/or eGFR.

Methods

Trial design

- CONFIDENCE was a randomized, three-arm, double-dummy, double-blind clinical trial.[6]
- Details of the trial design are presented in **Figure 1**.

Figure 1. CONFIDENCE trial design



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

Study participants

- **Inclusion criteria:** Age ≥18 years, eGFR 30–90 mL/min/1.73 m², type 2 diabetes, glycated hemoglobin (HbA1c) <11%, UACR 100 to <5000 mg/g, and treatment with maximally tolerated angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.
- **Exclusion criteria:** Blood pressure >160/100 mmHg or systolic blood pressure <90 mmHg, type 1 diabetes, serum potassium >4.8 mmol/L, chronic heart failure with reduced ejection fraction, or a cardiovascular event in the prior 90 days.

Procedures

- UACR, serum creatinine, and serum potassium were measured at every visit (baseline, and 14, 30, 90, 180, and 210 days) and were assessed at a central laboratory from first morning urine void samples.
- eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2009 creatinine-based equation with a modification for Japanese participants.[12,13]

Endpoints and statistical analysis

- For the purposes of this analysis, the population was split into four subgroups:
  1) UACR <300 mg/g and eGFR <60 mL/min/1.73 m².
  2) UACR <300 mg/g and eGFR ≥60 mL/min/1.73 m².
  3) UACR ≥300 mg/g and eGFR <60 mL/min/1.73 m².
  4) UACR ≥300 mg/g and eGFR ≥60 mL/min/1.73 m².

Logistic regression analysis

- UACR reductions from baseline at day 180 of >30%, >40%, and >50% with combination treatment compared with each of the two monotherapies were secondary endpoints in the CONFIDENCE trial.
- Logistic regression models were employed to assess the odds of achieving these reductions across treatment groups.

Linear regression analysis

- A linear mixed-effects model for repeated measures was used to evaluate the effects of baseline UACR and eGFR on relative change in UACR from baseline to day 180 (primary endpoint).

Safety

- Treatment-emergent adverse events (TEAEs) were defined as adverse events that started or worsened after the first dose, and within 3 days of the last intake, of study medication.
- Safety outcomes included hyperkalemia (serum potassium >5.5 or >6.0 mmol/L), acute drop in eGFR >30% at day 30, and symptomatic hypotension.

Results

Study population characteristics

- A total of 796 participants (264 finerenone, 265 empagliflozin, and 267 combination) who were appropriately randomized into the CONFIDENCE trial, had received at least one dose of the study drug, and had baseline values of eGFR and UACR were included in this post hoc analysis.
- Baseline characteristics of the CONFIDENCE trial participants, stratified by baseline eGFR/UACR category, are shown in **Table 1**.
  - Body mass index, systolic blood pressure, HbA1c, and prevalence of atherosclerotic cardiovascular disease were similar across groups.

Table 1. Baseline characteristics of participants stratified by baseline UACR and eGFR subgroups

	eGFR ≥60 mL/min/1.73 m²		eGFR <60 mL/min/1.73 m²		
	UACR		UACR		
Clinical characteristic	**<300 mg/g**	**≥300 mg/g**	**<300 mg/g**	**≥300 mg/g**	**Total**
Sample size, n (%)	89 (11)	186 (23)	121 (15)	400 (50)	796 (100)
Treatment group, n (%)					
Combination	33 (37)	60 (32)	40 (33)	134 (34)	267 (34)
Finerenone	24 (27)	72 (39)	46 (38)	122 (30)	264 (33)
Empagliflozin	32 (36)	54 (29)	35 (29)	144 (36)	265 (33)
Age, mean (SD)	66 (10)	64 (11)	68 (10)	67 (10)	66 (10)
Male sex, n (%)	70 (79)	137 (74)	81 (67)	311 (78)	599 (75)
Geographic region, n (%)					
North America	39 (44)	40 (22)	44 (36)	101 (25)	224 (28)
Europe	28 (31)	57 (31)	20 (17)	108 (27)	213 (27)
Asia	22 (25)	89 (48)	57 (47)	191 (48)	359 (45)
Body mass index, kg/m², mean (SD)	30.4 (6.7)	29.7 (6.3)	28.5 (5.6)	29.1 (5.9)	29.3 (6.1)
Serum potassium value, mmol/L, mean (SD)	4.4 (0.4)	4.4 (0.4)	4.6 (0.4)	4.5 (0.4)	4.5 (0.4)
Systolic blood pressure, mmHg, mean (SD)	134 (13)	138 (13)	132 (12)	135 (14)	135 (13)
History of atherosclerotic cardiovascular disease, n (%)	22 (25)	44 (24)	32 (26)	125 (32)	223 (29)
eGFR values, mL/min/1.73 m², mean (SD)	73 (11)	74 (11)	43 (9)	44 (9)	54 (17)
KDIGO CKD stage, n (%)					
G1 or G2	89 (100)	186 (100)	-	-	275 (35)
G3A	-	-	47 (39)	187 (47)	234 (29)
G3B	-	-	67 (55)	194 (48)	261 (33)
G4	-	-	7 (6)	19 (5)	26 (3)
UACR, mg/g, median (25th, 75th percentiles)	194 (124–256)	725 (442–1338)	177 (124–239)	787 (522–1469)	575 (291–1092)
Severity of albuminuria, n (%)					
<300 mg/g	89 (100)	-	121 (100)	-	210 (26)
300 to <1000 mg/g	-	121 (65)	-	243 (61)	364 (46)
>1000 mg/g	-	65 (35)	-	157 (39)	222 (28)
HbA1c, %, mean (SD)	7.0 (1.1)	7.5 (1.3)	7.2 (1.2)	7.3 (1.2)	7.3 (1.2)
Concomitant medications, n (%)					
ACE inhibitors or ARBs	88 (99)	184 (99)	117 (97)	394 (98)	783 (98)
Statins	78 (88)	142 (76)	91 (75)	284 (71)	595 (75)
Diuretics	31 (35)	56 (30)	41 (34)	160 (40)	288 (36)
Insulin	36 (40)	83 (45)	44 (36)	153 (38)	316 (40)
GLP-1 RAs	20 (22)	50 (27)	29 (24)	81 (20)	180 (23)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; SD, standard deviation; UACR, urinary albumin-to-creatinine ratio.

Efficacy

Logistic regression analysis

- In the adjusted logistic regression model, combination therapy was associated with increased odds of achieving a >30% reduction in UACR from baseline to day 180 compared with monotherapy with finerenone (**Table 2**; odds ratio [OR] 2.14 [95% confidence interval {CI} 1.45–3.17]) or empagliflozin (OR 2.21 [95% CI 1.50–3.27]).
  - Results were similar for >40% and >50% reductions in UACR.
- UACR/eGFR categories were not significantly associated with either >30%, >40%, or >50% UACR reduction.
- The odds of achieving a >30%, >40%, and >50% reduction in UACR were significantly increased with female sex and a history of atherosclerotic cardiovascular disease.
- The odds of achieving a >30% reduction in UACR were significantly increased with older age per 10 years.
- Body mass index and HbA1c were not associated with the odds of achieving a >30%, >40%, or >50% reduction in UACR.

Table 2. Odds of >30%, >40%, and >50% UACR reduction from baseline to day 180 by baseline UACR and eGFR subgroups

	>30% reduction in UACR		>40% reduction in UACR		>50% reduction in UACR	
	n/N	OR (95% CI)	n/N	OR (95% CI)	n/N	OR (95% CI)
Treatment group						
Combination versus empagliflozin	163/233 vs 122/235	2.21 (1.50–3.27)	151/233 vs 103/235	2.40 (1.64–3.51)	128/233 vs 76/235	2.63 (1.79–3.87)
Combination versus finerenone	163/233 vs 119/231	2.14 (1.45–3.17)	151/233 vs 102/231	2.28 (1.56–3.35)	128/233 vs 82/231	2.18 (1.48–3.20)
UACR eGFR combinations						
eGFR ≥60 mL/min/1.73 m² & UACR <300 mg/g	43/78	Reference	40/78	-	32/78	-
eGFR ≥60 mL/min/1.73 m² & UACR ≥300 mg/g	96/166	1.11 (0.62–1.98)	88/166	1.09 (0.62–1.94)	71/166	1.12 (0.62–2.01)
eGFR <60 mL/min/1.73 m² & UACR <300 mg/g	54/105	0.78 (0.42–1.45)	47/105	0.73 (0.39–1.36)	37/105	0.77 (0.41–1.47)
eGFR <60 mL/min/1.73 m² & UACR ≥300 mg/g	211/350	1.15 (0.68–1.95)	181/350	0.99 (0.59–1.66)	146/350	1.02 (0.60–1.74)
Age, per 10 years	-	1.23 (1.05–1.45)	-	1.15 (0.98–1.36)	-	1.12 (0.95–1.33)
Female sex	114/169	1.95 (1.32–2.86)	102/169	1.80 (1.24–2.61)	83/169	1.77 (1.22–2.57)
Geographic region						
North America	107/185	Reference	97/185	-	75/185	
Europe	115/190	1.07 (0.69–1.65)	103/190	1.05 (0.68–1.62)	92/190	1.34 (0.86–2.07)
Asia	182/324	1.08 (0.70–1.68)	156/324	0.98 (0.64–1.51)	119/324	0.99 (0.63–1.54)
Body mass index, kg/m², per unit change	-	0.99 (0.96–1.02)	-	1.00 (0.97–1.03)	-	1.00 (0.97–1.03)
History of atherosclerotic cardiovascular disease	128/192	1.63 (1.13–2.35)	112/192	1.50 (1.05–2.14)	100/192	1.86 (1.30–2.67)
HbA1c, %, per unit change	-	1.06 (0.93–1.21)	-	1.05 (0.92–1.19)	-	1.00 (0.88–1.14)

ORs were derived from multivariate adjusted logistic regression models. Covariates were all the factors indicated in the table above: treatment, UACR/eGFR category at baseline, age, sex, region, body mass index, history of atherosclerotic cardiovascular disease, and HbA1c.
CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; OR, odds ratio; UACR, urinary albumin-to-creatinine ratio.

Linear regression analysis

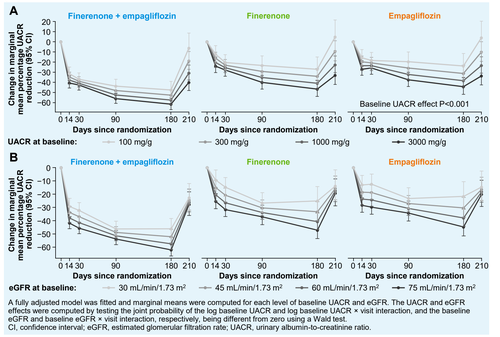
- Higher baseline UACR and eGFR (**Table 3**, **Figure 2**) were associated with a greater reduction in UACR from baseline to day 180 across all treatment groups (both P<0.001).
- Age and female sex were associated with a greater reduction in UACR at day 180 compared with baseline, independent of treatment (both P<0.01).

Table 3. Percent change in UACR from baseline at various time points by baseline eGFR and baseline log UACR, all three treatment groups combined

	Change in UACR from baseline per log baseline UACR, % (95% CI)	Change in UACR from baseline per 10 mL/min/1.73 m² baseline eGFR, % (95% CI)
Day 14	−4 (−8 to −0.5)	−4 (−6 to −2)
Day 30	−3 (−6 to 1)	−5 (−7 to −3)
Day 90	−7 (−11 to −2)	−3 (−6 to −0.7)
Day 180	−9 (−14 to −3)[a]	−7 (−11 to −4)[b]
Day 210	−12 (−18 to −7)	−1 (−5 to 2)

Marginal means and their 95% CIs were estimated after fitting the linear mixed Model 5 for estimating the effect of eGFR change and UACR change on percent UACR reduction. Covariates were treatment, visits, treatment × visit, log baseline UACR, UACR × visit, baseline eGFR, baseline eGFR × visit, treatment × visit, age, age × visit, sex, sex × visit, region, region × visit, baseline HbA1c, baseline HbA1c × visit, baseline history of atherosclerotic cardiovascular disease, baseline history of atherosclerotic cardiovascular disease × visit, baseline body mass index, and baseline body mass index × visit. Percent changes were calculated by exponentiating the ratio, subtracting 1, and multiplying the result by 100. Data are marginal means computed from mixed Model 5 (which used the covariates listed above).
CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; UACR, urinary albumin-to-creatinine ratio.
[a]Baseline UACR effect: P<0.001. [b]Baseline eGFR effect: P<0.001.

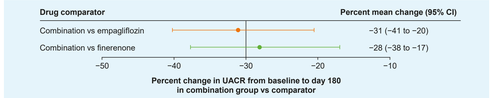
Figure 2. Percent change in UACR from baseline to various time points in the CONFIDENCE trial for participants with increasing levels of (A) baseline UACR and (B) baseline eGFR



A fully adjusted model was fitted and marginal means were computed for each level of baseline UACR and eGFR. The UACR and eGFR effects were computed by testing the joint probability of the log baseline UACR and log baseline UACR × visit interaction, and the baseline eGFR and baseline eGFR × visit interaction, respectively, being different from zero using a Wald test.
CI, confidence interval; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

- **Figure 3** shows the greater treatment effect on UACR reduction from baseline to day 180 of combination therapy compared with finerenone or empagliflozin alone.

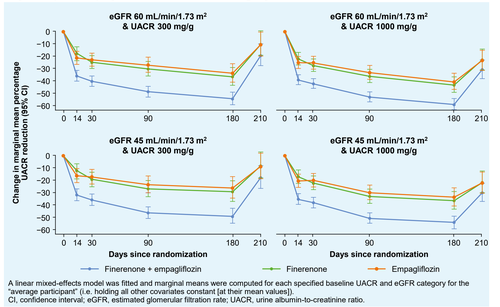
Figure 3. Forest plot of percent change from baseline UACR to 180 days in the combination versus monotherapy treatment arms



A linear mixed-effects model was fitted and marginal means were computed for each specified baseline UACR and eGFR category for the "average participant" (i.e. holding all other covariates constant [at their mean values]). Full forest plot of all mixed models for percent mean difference from baseline UACR to Day 180 in the combination versus monotherapy treatment arms is published; scan QR code.
CI, confidence interval; UACR, urinary albumin-to-creatinine ratio.

- The benefit of combination therapy on UACR reduction was consistent across different levels of baseline UACR and eGFR (**Figure 4**).

Figure 4. Expected change in mean percentage UACR reduction from baseline to day 180 (95% CI) by eGFR and UACR category in the CONFIDENCE trial



A linear mixed-effects model was fitted and marginal means were computed for each specified baseline UACR and eGFR category for the "average participant" (i.e. holding all other covariates constant [at their mean values]).
CI, confidence interval; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

Safety

- TEAEs, serious TEAEs, and deaths were evenly distributed across the eGFR and UACR strata.
- Symptomatic hypotension was uncommon, occurring in only two individuals (both in the combination therapy group and eGFR <60 mL/min/1.73 m² stratum; **Table 4**).
- Acute eGFR drop >30% at 30 days was more common in the combination therapy and finerenone treatment groups and among those with eGFR >60 mL/min/1.73 m² (**Table 4**).
- Investigator-reported hyperkalemia and hyperkalemia by central measurements tended to be higher in lower eGFR strata (**Table 4**).

Table 4. Hypotension, acute eGFR decline, serum potassium, and hyperkalemia events by baseline UACR and eGFR subgroups

	eGFR ≥60 mL/min/1.73 m²		eGFR <60 mL/min/1.73 m²		
	UACR		UACR		
Adverse events and treatment groups	**<300 mg/g**	**≥300 mg/g**	**<300 mg/g**	**≥300 mg/g**	**Total**
Symptomatic hypotension, n/N (%)					
Combination	0	0	1/40 (3)	1/134 (0.7)	2/267 (0.7)
Finerenone	0	0	0	0	0
Empagliflozin	0	0	0	0	0
Total	0	0	1/121 (0.8)	1/400 (0.3)	2/796 (0.3)
>30% Decline in eGFR from baseline to day 30, n/N (%)					
Combination	4/33 (12)	6/60 (10)	2/40 (5)	5/134 (4)	17/267 (6)
Finerenone	1/24 (4)	5/72 (7)	0	4/122 (3)	10/264 (4)
Empagliflozin	0	1/54 (2)	0	2/144 (1)	3/265 (1)
Total	5/89 (6)	12/186 (6)	2/121 (2)	11/400 (3)	30/796 (4)
Hyperkalemia reported by investigator, n/N (%)					
Combination	2/33 (6)	5/60 (8)	3/40 (8)	15/134 (11)	25/267 (9)
Finerenone	2/24 (8)	6/72 (8)	4/46 (9)	18/122 (15)	30/264 (11)
Empagliflozin	0	1/54 (2)	2/35 (6)	7/144 (5)	10/265 (4)
Total	4/89 (4)	12/186 (6)	9/121 (7)	40/400 (10)	65/796 (8)
Serum potassium level >5.5 mmol/L, n/N (%)					
Combination	4/33 (12)	5/59 (8)	3/40 (8)	28/132 (21)	40/264 (15)
Finerenone	3/24 (13)	8/71 (11)	10/45 (22)	27/115 (23)	48/255 (19)
Empagliflozin	1/31 (3)	6/52 (12)	3/35 (9)	15/140 (11)	25/258 (10)
Total	8/88 (9)	19/182 (10)	16/120 (13)	70/387 (18)	113/777 (15)
Serum potassium level >6.0 mmol/L, n/N (%)					
Combination	1/33 (3)	2/60 (3)	1/40 (3)	8/134 (6)	12/267 (4)
Finerenone	0	3/72 (4)	2/46 (4)	7/122 (6)	12/264 (5)
Empagliflozin	0	1/54 (2)	0	6/144 (4)	7/265 (3)
Total	1/89 (1)	6/186 (3)	3/121 (2)	21/400 (5)	31/796 (4)

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

Conclusions

- Simultaneous initiation of finerenone and an SGLT2 inhibitor conferred greater reductions in albuminuria at day 180 compared with monotherapy.
  - This benefit was consistent across baseline eGFR and UACR.
- A higher baseline eGFR or UACR, older age, female sex, and atherosclerotic cardiovascular disease history were all associated with a greater reduction in albuminuria across all treatment groups.
- A >30%, >40%, and >50% reduction in albuminuria was more often reached with combination therapy compared with either monotherapy.
- Compared with monotherapy, the effects of combination therapy on safety endpoints were consistent across baseline UACR and eGFR groups.

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