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Original Article

ORIGINAL ARTICLE

Additive effects of dapagliflozin and finerenone on albuminuria in non-diabetic CKD: an open-label randomized clinical trial

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ABSTRACT

Background. Dapagliflozin and finerenone reduce albuminuria and slow CKD progression, but additive effects remain unstudied. We compared their individual and combined efficacy and safety in patients with non-diabetic CKD.
Methods. In an open-label, randomized clinical trial, we included patients aged 18–80 on maximal tolerated ACE inhibitor or angiotensin receptor blocker with eGFR 25–45 mL/min/1,73 m^2 and albuminuria 150–2000 mg/g. Participants received either finerenone 20 mg/day or dapagliflozin 10 mg/day for four weeks, followed by combination therapy for four weeks. Data were collected at baseline, 4 and 8 weeks.
Results. Twenty patients (10 per group) with a mean mGFR of 34 mL/min/1,73 m^2 and a mean urine albumin creatinine ratio (UACR) of 469 mg/g were included. Finerenone alone or in addition to dapagliflozin resulted in −24% (95% CI, −36% to −11%) and −34% (95% CI, −47% to −18%) change in UACR, respectively. Dapagliflozin alone or in addition to finerenone resulted in −8% (95% CI, −22 to 9%) and −10% (95% CI, −28% to 12%) change in UACR, respectively. Overall, UACR change after 8 weeks was −36% (95% CI, −46% to −24%). After 8 weeks, systolic blood pressure and mGFR were reduced by 10 mmHg (95% CI, 6–13 mmHg) and 7 mL/min/1,73 m^2 (95% CI, 5–8 mL/min/1,73 m^2). Adverse effects were minimal.
Conclusions. The combination of finerenone and dapagliflozin was safe and significantly reduced albuminuria. The effect of combination therapy was at least equal to the calculated, combined effect of each of the drugs, suggesting an additive effect on albuminuria. Larger studies assessing long-term effects and safety are warranted.

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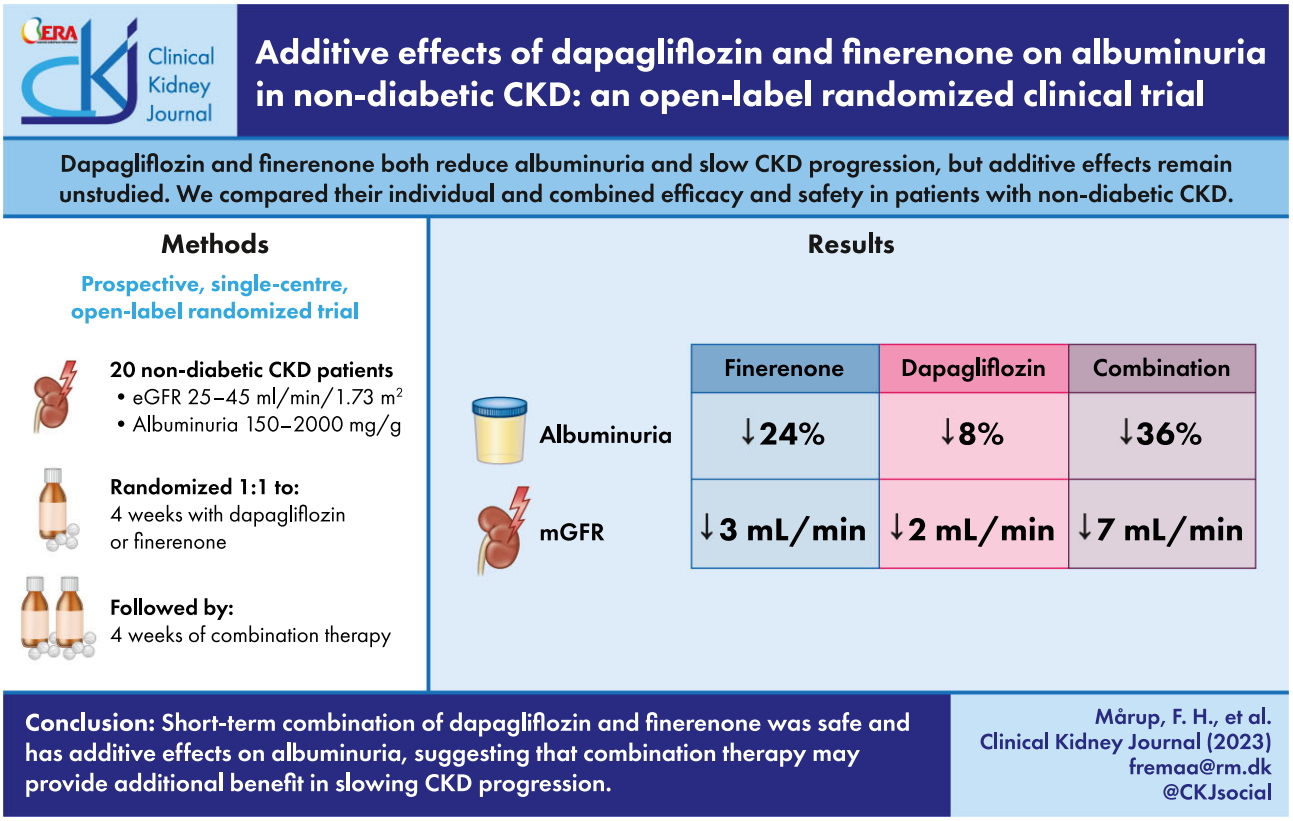
GRAPHICAL ABSTRACT



Keywords: albuminuria, chronic kidney disease, mineralocorticoid receptor antagonists, sodium-glucose transporter 2 inhibitors

KEY LEARNING POINTS

What was known:

- SGLT2-inhibitors and non-steroidal mineralocorticoid receptor antagonists (nsMRA) both reduce albuminuria and disease progression rate in patients with CKD. However, the additive effects have not been studied in non-diabetic CKD.

This study adds:

- Four weeks of combination therapy with an SGLT2-inhibitor (dapagliflozin) and a nsMRA (finerenone) resulted in additive reductions in albuminuria.
- The combination of dapagliflozin and finerenone results in an acute reduction in measured GFR, which is comparable to the added effect of each drug.
- No safety concerns were observed with short term combination therapy.

Potential impact:

- The combination of an SGLT2-inhibitior and a nsMRA should be investigated for the prevention of progression in CKD. The combined, acute effect on GFR should be considered.

INTRODUCTION

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and mineralocorticoid receptor antagonists (MRA) are promising treatment options to halt the decline in glomerular filtration rate (GFR) in chronic kidney disease (CKD) [1]. A renal protective effect of SGLT2i has been confirmed in both diabetic and non-diabetic CKD patients [2–4]. Dapagliflozin reduces albuminuria, a surrogate marker of CKD progression [5], by 15% and 30% in non-diabetic and diabetic CKD, respectively [6]. Similarly, MRAs reduce albuminuria [7], and the novel non-steroidal MRA finerenone reduces albuminuria by 30–36% [8, 9]. Moreover, finerenone significantly reduces the risk of the combined

cardiorenal and renal endpoints in patients with type 2 diabetes and CKD, while the effect in non-diabetic CKD is unknown [10, 11].

SGLT2is are recommended for the treatment of both diabetic and non-diabetic CKD, while non-steroidal MRAs are recommended in patients with type 2 diabetes and albuminuria > 30 mg/g [12]. However, the effect of SGLT2i and finerenone in combination has not been systematically examined, and only 6.7% of the patients in the FIDELITY-analysis, combining the FIDELIO-DKD and FIGARO-DKD finerenone trials, were on an SGLT2i at baseline [13]. Post hoc analyses of these trials showed similar reductions in urine albumin creatinine ratio (UACR) and no difference in the effects on cardiorenal outcomes when comparing patients that were on SGLT2i at baseline with those that were not [13, 14]. Reciprocally, a post-hoc analysis of the DAPA-CKD showed that the kidney protective effects of dapagliflozin were comparable regardless of baseline use of steroidal MRA [15]. Again, with low use of MRA at baseline (5.3%).

Importantly, none of these studies were randomized and therefore carry the potential for bias. Furthermore, patients on dual therapy were treated with SGLT2i or MRA, respectively, at baseline. Thus, the post hoc analyses were unable to assess the additive effects of combination therapy.

So far, only one randomized crossover trial has investigated this aspect. The ROTATE-3 trial compared the clinical effects of dapagliflozin, the steroidal MRA eplerenone, and their combination in CKD patients with albuminuria on maximal ACEi/ARB therapy [16]. The study showed an additive effect on UACR with combination therapy. With current guidelines recommending the use of a non-steroidal MRA, there is a need for prospective randomized trials assessing the effectiveness of combined therapy with a non-steroidal MRA and SGLT2i in addition to ACEi/ARB [13]. The current study was designed to assess the short-term effects of finerenone and dapagliflozin separately and in combination on albuminuria, GFR and safety in patients with albuminuric, non-diabetic CKD.

MATERIALS AND METHODS

Study design and patients

This study was a single-centre, prospective randomized open-label clinical trial conducted at the Department of Renal Medicine, Aarhus University Hospital, Denmark. The study was approved by 'The Central Denmark Region Committees on Health Research Ethics', approval number 2203976, and registered with the European Union Clinical Trials Register (EU 2022-000740-29) and performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave their written informed consent before any specific study procedures commenced.

Patients aged 18–80 years with eGFR 25–45 mL/min/1.73 m^2, UACR between 150–2000 mg/g, and who were on stable maximal tolerated dose of ACEi or ARB for a minimum of 4 weeks were eligible for inclusion. Key exclusion criteria were previous renal transplantation, diabetes, autosomal dominant polycystic kidney disease, systolic blood pressure >160 mmHg, diastolic blood pressure >100 mmHg, plasma potassium >4.5 mmol/L, plasma sodium <130 mmol/L, active malignancy, heart failure with ejection fraction <40%, active glomerulopathy or other conditions requiring ongoing or planned immunosuppressive treatment. Patients already on dapagliflozin were allowed to enter the study after a 4-week washout period. Patients on other SLGT2is were not eligible for inclusion. Dietary counselling, including restrictions on potassium intake, was not a part of the study and normally performed only at the discretion of the treating physician.

Procedures

After a screening visit to assess eligibility, included participants were randomized 1:1 to four weeks of finerenone 20 mg/day followed by another four weeks of finerenone in combination with dapagliflozin 10 mg/day (FINEDAPA group) or four weeks of dapagliflozin 10 mg/day followed by four weeks of dapagliflozin in combination with finerenone 20 mg/day (DAPAFINE group). There was no washout period between finerenone/dapagliflozin and their combination. A 4-week treatment period was considered sufficient to see the full effect of SGLT2i/MRA on albuminuria based on results from previous studies [6, 17–19]. Randomization was performed as permuted block randomization with random varying block sizes of 2, 4 and 6 used to allocate participants to start either finerenone or dapagliflozin. Study medication was dispensed at the beginning of each of the two 4-week treatment periods, and patients were instructed to take the tablets with their other medications in the morning. Concomitant medication was kept stable when possible.

Measurements

Samples were collected at the randomization visit, after four weeks of dapagliflozin or finerenone and subsequently after an additional four weeks of combination therapy. Patients collected two morning spot urine samples and one 24 h urine sample at home on the two days prior to these visits. To minimize variability, the average of the UACR measured from the two morning spot urines was used [20]. GFR was measured (mGFR) as plasma technetium-99m-DTPA clearance. Four samples were collected 3–4 h after injection in 20 min intervals from participants with eGFR greater than 40 mL/min/1.73 m^2, and five samples were collected 3–5 hours after injection in 30 min intervals from participants with eGFR equal to or below 40 mL/min/1.73 m^2. Blood pressure was measured with a calibrated sphygmomanometer (Microlife WatchBP Office, Microlife AG, Widnau, Switzerland) in a seated position after at least five minutes of rest. Six automated readings were taken at one-minute intervals, and the average of the last five readings was recorded. A physical examination including patient weight was performed and recorded at randomization and at 8 weeks. Height was measured at screening. Pill count was performed at four and eight weeks and used for adherence assessment.

Endpoints

The primary endpoint was the change in UACR from randomization to eight weeks among all participants measured as the average of two consecutive morning spot urine samples taken one day apart. Secondary endpoints were the change in UACR, albuminuria measured on a 24 h urine sample, blood pressure, eGFR, and mGFR during each 4-week treatment period. Safety endpoints were investigator-reported adverse events.

Calculations and statistics

To achieve a statistically significant detection of a 30% reduction in UACR, a power calculation indicated that a total of 18 participants was required. This calculation was based on an α level of 0.05, a power of 80%, and an assumed standard deviation of 15% for the differences in UACR. The effect size was based on

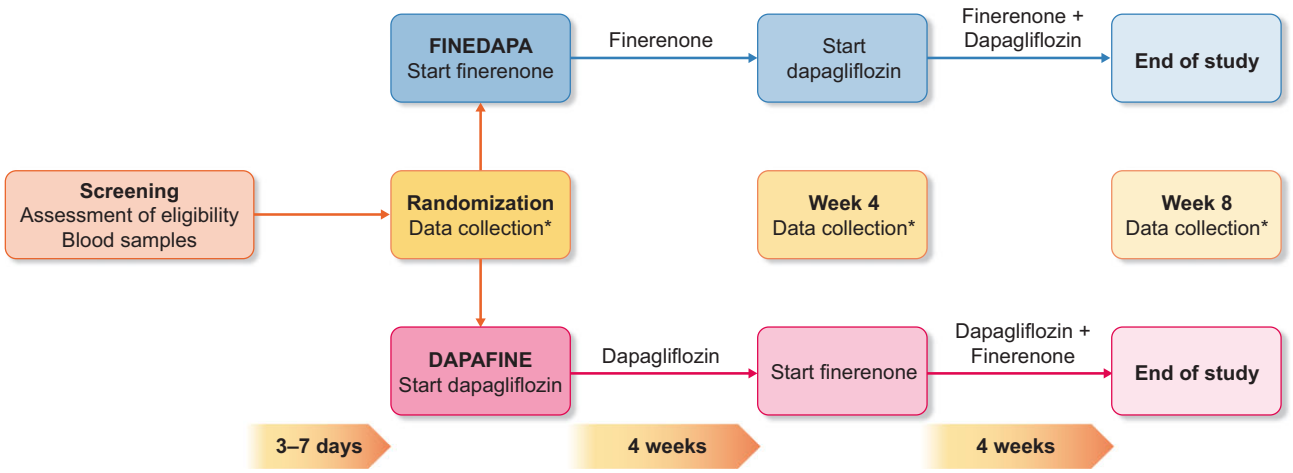


Figure 1: Flowchart of the study. *Data collection: Measured glomerular filtration rate (measured using technetium-99m-DTPA), two urine albumin creatinine ratio measurements, 24 h urine albumin excretion, blood samples and blood pressure. Blood samples from the screening visit were used as baseline samples.

previous studies showing a 15% reduction in albuminuria following dapagliflozin treatment in patients without diabetes and a 35% reduction following finerenone treatment in patients with diabetes [6, 11]. To account for potential dropouts, a total of 20 participants were planned to be included in the study. Data from all endpoints were analysed as intention-to-treat.

The changes in UACR, 24 h urine albumin, eGFR, mGFR, plasma potassium, and blood pressure were analysed using multivariate repeated measurements ANOVA with time and group (and the interaction between them) as factors. Albuminuria was log-transformed before being used in the model. The estimated, additive effect on UACR of dapagliflozin and finerenone based on the effects of each drug during the first 4 weeks of treatment was calculated by multiplying the ratios of UACR (UACR at 4 weeks divided by UACR at baseline) in the DAPAFINE and FINEDAPA groups, respectively, which is most appropriate given the non-normal distribution of the UACR variable. This allowed for estimation of the combined effects. The ratios between the estimated additive effect and the observed combined effect from baseline to 8 weeks in both groups was compared using the multivariate repeated measurements ANOVA model. The correlations between changes in UACR with finerenone and dapagliflozin were analysed using a linear regression model.

Statistical analyses were performed using the STATA version 17.0 software package (StataCorp LP, College Station, TX, USA). A two-sided *P*-value <0.05 was considered statistically significant. Figures were made using GraphPad Prism version 9.5.1 for Windows (GraphPad Software, Boston, Massachusetts USA).

RESULTS

Patients and baseline characteristics

Twenty-four patients were screened between June 2022 and December 2022. Twenty were included in the study (Fig. 1). All participants completed the entire study with no loss to follow-up. Baseline characteristics of the two groups were similar with regard to age, eGFR, albuminuria, potassium, blood pressure and antihypertensive treatment (Table 1). Only mean BMI was notably greater in the FINEDAPA group (mean 30.6 kg/m^2) compared with the DAPAFINE group (mean 24.9 kg/m^2).

The median duration of all treatment periods was 28 days [interquartile range (IQR) 28–28 days], and the median adherence as assessed by pill count was 100% (IQR 100%–100%). There was no difference between adherence to the two drugs or the duration of the individual 4-week treatment periods.

Effects on albuminuria

The primary endpoint of change in mean UACR from baseline to 8 weeks in both groups combined (Table 2) revealed a significant change of −36% (95% CI −46% to −24%, $P < 0.001$).

Effect of finerenone

The change in UACR with finerenone from baseline to week 4 in the FINEDAPA group was −24% (95% CI, −36% to −11%, $P = 0.004$) (Table 2, Fig. 2a), while the change from week 4 to week 8 when finerenone was added to dapagliflozin in the DAPAFINE group was −34% (95% CI, −47% to −18%, $P = 0.002$). These changes were not significantly different ($P = 0.35$). The pooled effect of four weeks of finerenone treatment on UACR in the two groups was −29% (95% CI, −39% to −18%, $n = 20$).

Effect of dapagliflozin

A change in UACR of −8% (95% CI, −22% to 9%, $P = 0.34$) was observed with dapagliflozin from baseline to week 4 in the DAPAFINE group (Table 2, Fig. 2a), which was not significantly different ($P = 0.85$) from the −10% (95% CI, −28% to 12%, $P = 0.35$) change in UACR when dapagliflozin was added to finerenone from week 4 to week 8 in the FINEDAPA group. Thus, in this small cohort dapagliflozin had only non-significant effects of UACR, which appeared to be independent of prior treatment with finerenone. The pooled effect of four weeks of dapagliflozin treatment on UACR in the two groups was −9% (95% CI, −21% to 5%, $n = 20$).

Interactions between the effects of finerenone and dapagliflozin

The estimated, additive effect on UACR of finerenone and dapagliflozin based on multiplying the independent effects of each drug alone (baseline to week 4 in the FINEDAPA group and DAPAFINE groups, respectively) was a change of −30% (95% CI, −45% to −12%), corresponding to a ratio of 0.70. This is consistent with the observed combined mean effect of −36%, corresponding to

Table 1: Baseline characteristics.

	FINEDAPA	DAPAFINE
Age, years	61 (17)	59 (15)
mGFR, mL/min/1,73 m^2	37 (6)	30 (9)
eGFR, mL/min/1,73 m^2	36 (5)	32 (3)
UACR, mg/g [median (IQR)]	449 (102)	491 (479)
P-Potassium, mmol/L	4.2 (0.3)	4.1 (0.3)
Systolic blood pressure, mmHg	127 (11)	130 (12)
Diastolic blood pressure, mmHg	81 (8)	79 (4)
Males (*n*)	8	7
White race (*n*)	10	10
BMI, kg/m^2	30.6 (4.7)	24.9 (5.1)
ACEi (*n*)	6	4
Ramipril (*n*)	4	4
Ramipril, mg/day	6.9 (1.9)	7.5 (1.4)
Enalapril (*n*)	2	0
Enalapril, mg/day	7.5 (2.5)	
ARB (Losartan) (*n*)	4	6
Losartan, mg/day	78 (22)	88 (9)
Loop (furosemide) (*n*)	6	4
Thiazide (*n*)	2	2
Ca-antagonist (*n*)	6	6
Betablocker (*n*)	4	3
Other (*n*)	1	0
No. of antihypertensives (*n*, SD)	2.9 (1.3)	2.5 (0.9)
Previous kidney biopsy (*n*)	4	4
Cause of CKD[a] (*n*)		
Unknown	6	6
FSGS	2	1
Hypertension	2	2
IgA nephropathy	0	1
Co-morbidities		
Hypertension	9	10
Heart failure	0	3
Stroke	0	1
Atrial fibrillation/flutter	2	1
PAD	0	1
COPD	2	1
Gout	4	2

Baseline characteristics of the patients starting the study on finerenone (FINEDAPA group) and dapagliflozin (DAPAFINE group). Data given as mean (SD) unless otherwise indicated. ACEi: angiotensin converting enzyme inhibitor; COPD: chronic obstructive pulmonary disease; FSGS: focal segmental glomerulosclerosis; IQR: interquartile range; mGFR: measured GFR (measured as plasma technetium-99m-DTPA clearance); PAD: peripheral artery disease; P-potassium: plasma potassium; SD: standard deviation; UACR: urine albumin creatinine ratio. [a]The cause of CKD was derived from patient records. Diagnoses of IgA nephropathy ($n = 1$) and FSGS ($n = 3$) were based on a previous renal biopsy. An additional four participants had a previous biopsy showing unspecific pathology. Their cause was categorized as "unknown".

a ratio of 0.64. There was no significant difference between the calculated, additive effects and the observed effects of combination therapy on the UACR ratios ($P = 0.47$). The reductions in albuminuria observed in individual patients with either finerenone or dapagliflozin were only weakly correlated in both the FINEDAPA (R^2 and *P*-value: 0.35 and 0.07, respectively) and DAPAFINE group (R^2 and *P*-value: <0.01 and 0.97, respectively) (Fig. 3). Thus, the effect of the initial administered drug on UACR did not predict the effect on UACR of the subsequent drug.

Effects on mGFR, eGFR, blood pressure, 24 h urinary albumin excretion, and weight

A significant reduction in mGFR from baseline to 8 weeks was observed in both groups (Fig. 2b, Table 2). The change in mGFR from baseline to 8 weeks in both groups combined was −7 mL/min/1,73 m^2 (95% CI, −8 to −5, $P < 0.001$). Although numerically greater reductions in mGFR were observed with the second drug compared to the first in both groups, the changes in mGFR when adding either finerenone or dapagliflozin to the other were not significantly different from the changes when introduced at baseline ($P = 0.43$ and 0.22, respectively). The mGFR and eGFR reductions from baseline to 8 weeks correlated positively, although not significantly (Fig. S1, see online supplementary material). The eGFR reductions were slightly smaller compared to the corresponding changes in mGFR. The combination therapy resulted in a significant change both in systolic BP (−10 mmHg, 95% CI, −13 to −6, $P < 0.001$) and diastolic BP (−6 mmHg, 95% CI, −9 to −4, $P < 0.001$) when compared to baseline. The largest reductions in BP followed the introduction of dapagliflozin (Table 2). The mean relative reductions in 24 h urinary albumin excretion with treatment were similar to morning spot UACR (Table 2). Baseline weight (84.3 kg) was reduced to 83.4 kg at 8 weeks. The change was –0.9 kg (95% CI, −1.6 to −0.3 kg, $P = 0.006$).

Safety

After the addition of finerenone, P-potassium levels decreased by 0.1 mmol/L in the FINEDAPA group and increased 0.4 mmol/L in the DAPAFINE group. Furthermore, one patient in the FINEDAPA group and two patients from the DAPAFINE group developed a P-potassium >5.0 mmol/L (5.1, 5.2, and 5.2 mmol/L, respectively). The events were self-limiting. There were no reports of urinary tract infections. Adverse events were mild (Table S1, see online supplementary material) and neither drug required discontinuation in any participant during the study period.

DISCUSSION

Combining dapagliflozin and finerenone leads to a large and significant reduction in albuminuria in patients with non-diabetic CKD. The reduction with the combined treatment is at least equal to the calculated, combined effects of the reductions observed with each drug separately. Furthermore, the effect of either drug is similar regardless of pre-treatment with the other, and large reductions in albuminuria with one drug did not exclude further reductions when adding the other.

The effects of finerenone and dapagliflozin on albuminuria and blood pressure in our study are similar to what has previously been reported in both diabetic and non-diabetic CKD [6, 8, 9]. The fact that the effect of dapagliflozin on UACR alone did not reach statistical significance is likely due to the relative low number of patients included. Furthermore, our results align with the findings of the ROTATE-3 study [16]. The greater reduction in albuminuria observed in that study (53%) could be attributed to the high prevalence of patients with type 2 diabetes in their cohort, as previous research has shown that patients with type 2 diabetes have greater reductions in albuminuria with SGLT2i compared to patients without diabetes [6, 21]. Our study confirms that these results are also applicable to a cohort of purely non-diabetic patients with more advanced CKD, and with the use of a non-steroidal MRA [12].

Furthermore, combination therapy was safe and did not cause severe hyperkalaemia or acute kidney injury (AKI) despite mild increases in P-potassium with finerenone and decreases in mGFR with both treatments. We did not observe an increase in P-potassium with finerenone alone but did see an increase when finerenone was added to dapagliflozin (DAPAFINE group). This

Table 2: Treatment effects.

	Base-line	4 weeks	8 weeks	Baseline to 4 weeks	4 weeks to 8 weeks	Baseline to 8 weeks
FINEDAPA ($n = 10$)				***Finerenone***	***Dapagliflozin***	***Combination***
UACR, mg/g	449	339	304	−24% (−36% to −11%)	−10% (−28% to 12%)	−32% (−47% to −14%)
24 h albumin[a], mg/day	853	564	497	−34% (−47% to −18%)	−12% (−33% to 17%)	−42% (−54% to −23%)
mGFR, mL/min/1,73 m^2	37	34	30	−3 (−6 to −1)	−4 (−7 to −2)	−7 (−10 to −5)
eGFR, mL/min/1,73 m^2	36	33	32	−3 (−6 to 0)	−1 (−4 to 1)	−4 (−6 to −2)
P-potassium, mmol/L	4.2	4.1	4.2	−0.1 (−0.2 to 0.1)	0.1 (−0.1 to 0.3)	0.1 (−0.2 to 0.3)
Systolic BP, mmHg	127	126	117	−1 (−6 to 3)	−9 (−15 to −2)	−10 (−15 to −4)
Diastolic BP, mmHg	81	78	73	−3 (−7 to 1)	−5 (−10 to 1)	−8 (−11 to −4)
DAPAFINE ($n = 10$)				***Dapagliflozin***	***Finerenone***	***Combination***
UACR, mg/g	491	453	299	−8% (−22% to 9%)	−34% (−47% to −18%)	−39% (−52% to −22%)
24 h albumin, mg/day	683	655	412	−4% (−22% to 18%)	−37% (−52% to −17%)	−40% (−52% to −24%)
mGFR, mL/min/1,73 m^2	30	28	24	−2 (−4 to 1)	−4 (−7 to −2)	−6 (−9 to −4)
eGFR, mL/min/1,73 m^2	32	31	27	−1 (−4 to 2)	−4 (−8 to −2)	−6 (−8 to −4)
P-potassium, mmol/L	4.1	4.0	4.4	−0.1 (−0.2 to 0.1)	0.4 (0.2–0.6)	0.3 (0.1–0.5)
Systolic BP, mmHg	130	125	121	−5 (−9 to 0)	−5 (−11 to 2)	−9 (−15 to −4)
Diastolic BP, mmHg	79	75	74	−4 (−8 to 0)	−1 (−6 to 5)	−5 (−8 to −1)
Both groups combined ($n = 20$)				***Dapagliflozin/finerenone 10/10***[b]	***Dapagliflozin/finerenone 10/10***[c]	***Combination***
UACR, mg/g	469	392	301	−17% (−26% to −6%)	−23% (−34% to −10%)	−36% (−46% to −24%)
24 h albumin[a], mg/day	764	617	453	−20% (−32% to −7%)	−26% (−39% to −10%)	−41% (−50% to −30%)
mGFR, mL/min/1,73 m^2	34	31	27	−3 (−4 to −1)	−4 (−6 to −3)	−7 (−8 to −5)
eGFR, mL/min/1,73 m^2	34	32	29	−2 (−4 to 0)	−3 (−5 to −1)	−5 (−6 to −3)
P−potassium, mmol/L	4.1	4.1	4.3	−0.1 (−0.2 to 0.1)	0.2 (0.1 to 0.4)	0.2 (0.0 to 0.3)
Systolic BP, mmHg	128	125	119	−3 (−6 to 0)	−7 (−11 to −2)	−10 (−13 to −6)
Diastolic BP, mmHg	80	77	74	−3 (−6 to −1)	−3 (−7 to 1)	−6 (−9 to −4)

Treatment effects of finerenone, dapagliflozin and their combination in the FINEDAPA and DAPAFINE groups. Columns two to four are the mean values at the specified timepoints, except for albuminuria which is reported as the median. Columns five to seven are the mean relative changes between the timepoints with 95% confidence intervals, except albuminuria which is reported as ratios with 95% confidence intervals. BP: blood pressure; mGFR: measured glomerular filtration rate (measured using technetium-99m-DTPA); P-potassium: plasma potassium; UACR: urine albumin creatinine ratio.

[a]One missing value.

[b]The mean effect of finerenone and dapagliflozin.

[c]The mean effect of finerenone in addition to dapagliflozin and dapagliflozin in addition to finerenone.

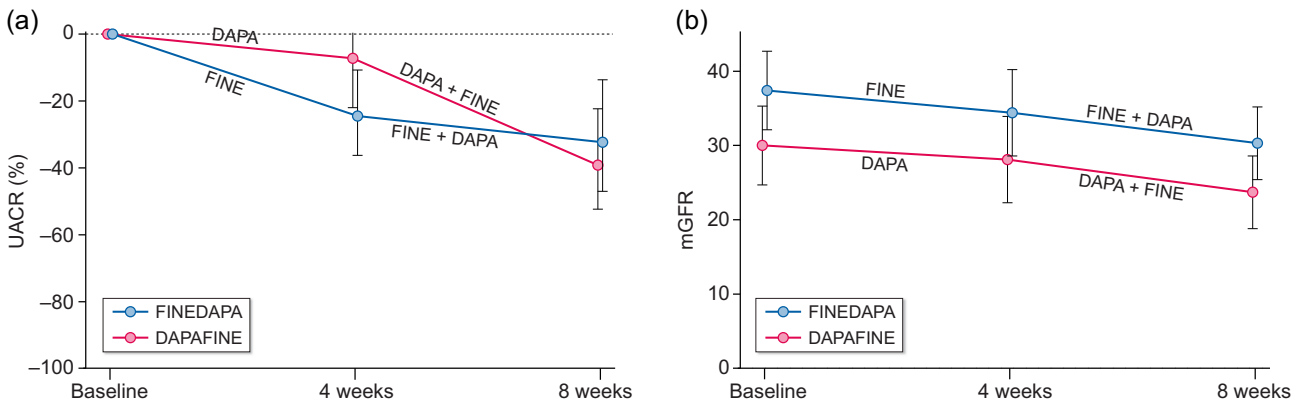


Figure 2: The effect of dapagliflozin (DAPA), finerenone (FINE) and their combination (DAPA + FINE or FINE + DAPA) on the relative change in UACR (**a**) and on mGFR (**b**) from baseline to 8 weeks. UACR error bars (**a**) are 95% confidence intervals of the relative change from baseline. Note that the upper confidence interval (+ 9%) at 4 weeks in the DAPAFINE group is cropped. mGFR error bars (**b**) are 95% confidence intervals of the mean. The graphs of the two groups are slightly shifted on the x-axis to avoid overlapping bars. UACR: urine albumin creatinine ratio; mGFR: measured glomerular filtration rate (measured as plasma technetium-99m-DTPA clearance).

contrasts with previous suggestions that SGLT2i may alleviate hyperkalaemia from MRA [22]. While this could be a result of additive effects on GFR resulting in significantly reduced filtration in a group of patients with advanced CKD, it may just as likely be explained by random effects in a small cohort not related to treatment.

Although a numerically greater reduction in mGFR was observed when dapagliflozin was added to finerenone compared

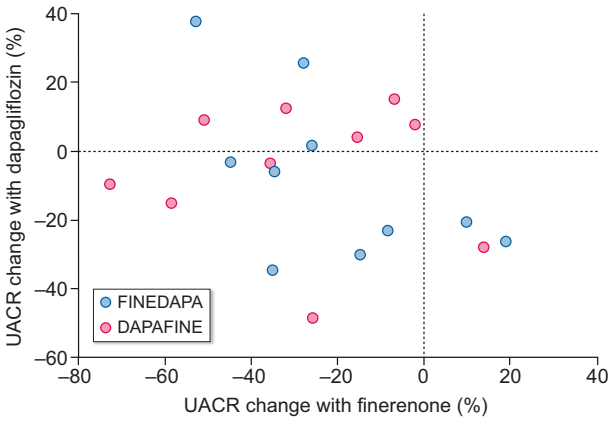


Figure 3: The correlation between the change in urine albumin creatinine ratio (UACR) with finerenone and dapagliflozin in each of the 20 patients. Note that dapagliflozin was added to finerenone in the FINEDAPA group and finerenone was added to dapagliflozin in the DAPAFINE group. The change in UACR is expressed as the percentage change in UACR from beginning to end of each of the two 4-week treatment periods from baseline to 4 weeks and 4 weeks to 8 weeks.

to dapagliflozin alone, as well as when finerenone was added to dapagliflozin compared to finerenone alone, these differences were not significant in this small study. The ROTATE-3 study also did not show indications of an excess reduction in kidney function with combination therapy when measured using eGFR, and a post-hoc analysis of the FIDELIO-DKD study did not show a significant difference in the acute eGFR effect of finerenone depending on concurrent treatment with SGLT2i [23].

Notably, both SGLT2i and MRAs induce a true reduction in GFR as documented by mGFR here. The two classes of drugs exert their effect on complimentary physiological pathways. MRA have been shown to have anti-inflammatory and anti-fibrotic effects [24], while SGLT2i reduce glomerular hyperfiltration and may reduce metabolic demand, thereby improving renal oxygenation [25]. However, both MRA and SGLT2i cause an acute decline in GFR and may both reduce glomerular hyperfiltration. This suggests shared mechanisms of action, which could potentially lead to a less-than-additive effect on albuminuria or an increased risk of adverse events such as excess reduction in kidney function or acute kidney injury. SGLT2i are believed to increase tubuloglomerular feedback from an increased sodium delivery to the macula densa, leading to an initial reduction in GFR [26]. The mechanism behind the acute decline in GFR following MRA is less clear but may involve reduced hyperfiltration by alleviating a relative hyperaldosteronism-mediated constriction of the efferent arteriole [27–29]. The initial decline in GFR with SGLT2i is linked to renal protection, has not been associated with worse outcomes, and is reversible after cessation [30]. Reversibility has also been observed with MRAs [16, 31], but it remains to be established if the added acute reductions in GFR with combination therapies are associated with similar long-term benefits and increased risk of AKI.

Similarly, the significant reduction in blood pressure from combination therapy is advantageous in patients with hypertension but may limit its utility in patents with lower blood pressure. Albuminuria is a surrogate marker of disease progression, and the benefits of non-steroidal MRA on kidney endpoints in patients with non-diabetic CKD will have to be established in larger studies. Such studies include the ongoing FIND-CKD study [32]. In addition, CONFIDENCE will compare the effect of single SLGT2i or non-steroidal MRA to combination therapy with a longer follow-up, although only in patients with type 2 diabetes [33].

Our study has some important strengths compared to existing data. First, the randomized design eliminates bias and allows for a comparison of the effect of either drug against the combination. Second, we used a non-steroidal MRA currently being the only MRA with established effects on hard renal outcomes. Third, despite the relatively small size, randomized patients were very well matched (Table 1). Fourth, prior to inclusion, patients were treated in accordance with established guidelines: all patients were administered high doses of ACEi/ARB, and blood pressure was well controlled. Fifth, this is the first study that compares SLGT2i and MRA in a purely non-diabetic population, and our findings suggest that benefits of combination therapy already documented in the diabetic population are applicable to the non-diabetic population as well.

Our study does have some limitations. First, the relatively small sample size increases risk of type II errors. Thus, while both drugs appear equally effective when given as add-ons to each other or as independent treatment, and although the effect of combination therapy is at least as effective, if not more so, than the calculated, combined effect from independent treatments, we cannot rule out minor differences in this apparent additive effect. Second, follow-up was relatively short. We recorded no serious adverse events or any event requiring intervention or cessation of either drug, but this will have to be confirmed in larger studies with longer follow-ups. Third, we did not include a placebo treatment. Without a placebo group, there may be an effect of time on endpoints. However, the short follow-up would diminish such effects, and our results are in line with placebo-controlled studies [6, 11]. Fourth, for practical reasons, we did not include a wash-out period between single and combination therapy. It is possible that there was some carry-over effect of the first drug into the period of combination therapy. Indeed, one study has suggested that the full effect of finerenone might take longer than four weeks [9]. However, we saw no indication of such carry-over effect from our data, as larger effects of finerenone as the first drug did not result in larger reductions from dapagliflozin as the second.

In conclusion, the combination of dapagliflozin and finerenone leads to a large and significant reduction in albuminuria in patients with non-diabetic CKD within 8 weeks and without any major safety concerns. The effects of either drug were independent of previous treatment with the other, and the effect of the combination was at least equal to the calculated, combined effects of the independent drugs. These findings suggest that the positive effects of SGLT2i and MRA are additive and independent of prior treatment with the opposite drug, supporting the use of ACEi/ARB, SGLT2i and non-steroidal MRA in combination to slow the progression of albuminuric CKD. Larger studies will have to confirm the effect of finerenone on hard kidney endpoints in non-diabetic CKD as well as the long-term safety of combination therapy.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

F.H.M. and H.B. conceived and designed the study. F.H.M. and M.B.T. collected the data. F.H.M. performed data analysis and wrote the manuscript. H.B. supervised and revised the manuscript. All authors provided critical feedback and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

F.H.M. has received consulting fees, speaker honoraria and/or support for attending meetings from AstraZeneca and CSL Vifor. H.B. has received a research grant from Glaxo Smith Kline and Vifor Pharma (paid to institution) and has received consulting fees and/or speaker honoraria from Vifor Pharma, AstraZeneca, Boehringer Ingelheim, GSK, Galapagos, Alexion, MSD, and Novo Nordisk, as well as support for attending meetings from Novartis and AstraZeneca. M.B.T. has no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

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