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MECHANISMS OF CARDIOVASCULAR BENEFIT WITH FINERENONE—A CAUSAL MEDIATION ANALYSIS OF THE JOINT EFFECTS OF SYSTOLIC BLOOD PRESSURE AND ALBUMINURIA REDUCTION

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BACKGROUND

Cardiovascular disease is a leading cause of morbidity and mortality in people with type 2 diabetes (T2D) and chronic kidney disease (CKD). Over 3 years of median follow up in people with T2D and CKD, cardiovascular events occurred in 14.4% of the patients whereas kidney outcome events were observed in 7.1%. Thus, in T2D even among those with CKD, cardiovascular outcomes are twice as common as kidney failure outcomes. [1]

In people with T2D and CKD, finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, reduces kidney failure and cardiovascular outcomes [1]. Although cardiovascular protection of finerenone in people with T2D and CKD is well established, the mechanism(s) that mediate this protection remains unknown. In a previous analysis from the same cohort, whereas the change in albuminuria from baseline to 4 months mediated 84% of the kidney failure outcome, it accounted for 37% of the cardiovascular outcome [2]. Whether other mechanisms mediated the cardiovascular protection afforded by finerenone remains unknown. Thus, the objective of this post hoc study was to explore pathways by which finerenone mediates cardiovascular clinical benefits.

METHODS

Using pooled data from two phase 3 clinical trials of finerenone (NCT02540993 and NCT02545049) [3-5], among 12143 patients with T2D and CKD randomly assigned to finerenone or placebo (1:1), we evaluated the following mediation variables: change from baseline to month 4 in body weight and systolic blood pressure, electrolyte mineralocorticoid effect (serum potassium), and urine albumin to creatinine ratio. Direct acyclic graph of the mediation model is shown in **Figure 1**. For mediation analysis we used parametric accelerated failure time regression outcome models with Weibull distribution. We used R, SAS, and Stata for statistical analyses.

Figure 1. Directed acyclic graph of the mediation model

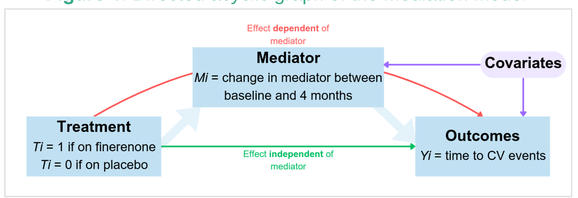


Figure 3. Cumulative cardiovascular outcomes

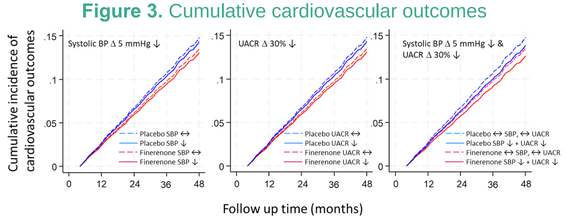


Table 1. Baseline characteristics of the study sample

	Finerenone	Placebo	Total
Sample size, n (%)	6077 (50.0%)	6066 (50.0%)	12143 (100.0%)
Clinical trial name			
FIDELIO-DKD, n (%)	2638 (43.4%)	2647 (43.6%)	5285 (43.5%)
FIGARO-DKD, n (%)	3439 (56.6%)	3419 (56.4%)	6858 (56.5%)
Combined, n (%)	6077 (50.0%)	6066 (50.0%)	12143 (100.0%)
Age, years (SD)	64.7 (9.3)	64.7 (9.7)	64.7 (9.5)
Sex, men, n (%)	4182 (68.8%)	4292 (70.8%)	8474 (69.8%)
Region, n (%)			
Europe	2735 (45.0%)	2727 (45.0%)	5462 (45.0%)
Latin America	672 (11.1%)	664 (10.9%)	1336 (11.0%)
North America	933 (15.4%)	935 (15.4%)	1868 (15.4%)
Asia	1521 (25.0%)	1518 (25.0%)	3039 (25.0%)
New Zealand, Australia, South Africa	216 (3.6%)	222 (3.7%)	438 (3.6%)
Race, n (%)			
White	4114 (67.7%)	4106 (67.7%)	8220 (67.7%)
Black	223 (3.7%)	235 (3.9%)	458 (3.8%)
Asian	1371 (22.6%)	1391 (22.9%)	2762 (22.7%)
Not reported, mulitple races, or other	369 (6.1%)	334 (5.5%)	703 (5.8%)
History of atherosclerotic cardiovascular disease	2729 (44.9%)	2725 (44.9%)	5454 (44.9%)
eGFR, mL/min/1.73m^2 (SD)	57.7 (21.6)	57.8 (21.8)	57.7 (21.7)
eGFR ≥ 60, n (%)	2377 (39.1%)	2373 (39.1%)	4750 (39.1%)
eGFR ≥ 45 to < 60, n (%)	1668 (27.4%)	1669 (27.5%)	3337 (27.5%)
eGFR ≥ 25 to <45, n (%)	2032 (33.4%)	2024 (33.4%)	4056 (33.4%)
Hemoglobin A_{1c}, % (SD)	7.7 (1.4)	7.7 (1.4)	7.7 (1.4)
Median UACR, mg/g (Q1 - Q3)	516 (198 - 1131)	515 (202 - 1148)	516 (199 - 1137)
Systolic blood pressure, mmHg (SD)	136.8 (14.1)	136.7 (14.1)	136.7 (14.1)
Body weight, kg, (SD)	87.9 (20.2)	88.1 (20.0)	88.0 (20.1)
Serum potassium, mEq/L, (SD)	4.35 (0.44)	4.35 (0.44)	4.35 (0.44)
Glucagon-like peptide-1 receptor agonist, n (%)	468 (7.7%)	409 (6.7%)	877 (7.2%)
Sodium-glucose cotransporter-2 inhibitor, n (%)	413 (6.8%)	405 (6.7%)	818 (6.7%)
History of heart failure, n (%)	440 (7.2%)	470 (7.7%)	910 (7.5%)
Renin-angiotensin system inhibitor, n (%)	6067 (99.8%)	6054 (99.8%)	12121 (99.8%)

Table 3. Mediation analysis of cardiovascular composite outcome (n = 12143)

Mediator and effect	Relative mean survival (95% CI)	
	without A * M interaction	with A * M interaction
Urine albumin to creatinine ratio (UACR)		
Independent of reduction in log UACR (NDE)	1.07 (1.00-1.16)	1.08 (1.00-1.17)
Mediated by reduction in log UACR (NIE)	1.04 (1.02-1.06)	1.04 (1.02-1.07)
Total effect (TE)	1.12 (1.04-1.20)	1.12 (1.04-1.21)
Proportion mediated	**0.36 (0.07-0.64)**	**0.39 (0.07-0.71)**
Systolic blood pressure (mmHg)		
Independent of reduction in systolic BP (NDE)	1.09 (1.01-1.17)	1.09 (1.01-1.18)
Mediated by reduction in systolic BP (NIE)	1.02 (1.01-1.03)	1.02 (1.01-1.04)
Total effect (TE)	1.11 (1.03-1.20)	1.11 (1.03-1.20)
Proportion mediated	**0.22 (0.05-0.39)**	**0.21 (0.03-0.40)**
Weight (kg)		
Independent of reduction in weight (NDE)	1.11 (1.03-1.20)	1.12 (1.04-1.20)
Mediated by reduction in weight (NIE)	1.00 (1.00-1.01)	1.00 (1.00-1.01)
Total effect (TE)	1.12 (1.04-1.20)	1.12 (1.04-1.21)
Proportion mediated	0.03 (-0.01-0.06)	0.04 (-0.01-0.09)
Potassium (mEq/L)		
Independent of change in serum potassium (NDE)	1.13 (1.04-1.22)	1.12 (1.04-1.21)
Mediated bychange in serum potassiun (NIE)	0.99 (0.97-1.01)	0.98 (0.96-1.01)
Total effect (TE)	1.12 (1.04-1.20)	1.12 (1.04-1.21)
Proportion mediated	-0.09 (-0.26-0.09)	-0.15 (-0.38-0.07)
Joint model UACR + systolic BP		
(NDE)	1.06 (0.99-1.14)	1.06 (1.00-1.16)
Mediated by reduction in log UACR or systolic BP (NIE)	1.05 (1.03-1.07)	1.05 (1.03-1.09)
Total effect (TE)	1.11 (1.03-1.21)	1.11 (1.05-1.19)
Proportion mediated	**0.47 (0.26-1.00)**	**0.50 (0.21-1.00)**

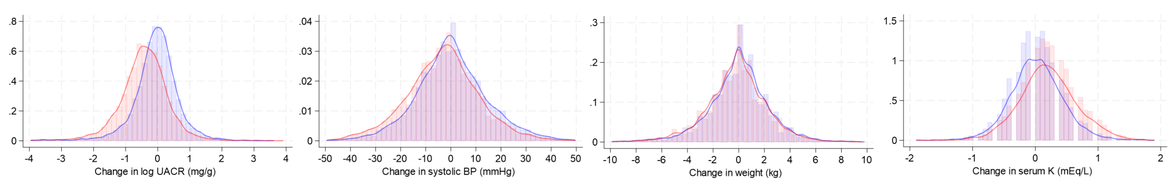
NDE = natural direct effect, NIE = natural indirect effect. Proportion mediated is the percent of total effect of finerenone on cardiovascular outcome that is due to the mediator. The proportions mediated by change in body weight and serum potassium were not significant.

Table 2. Description of baseline, changes, and difference in changes in mediator variables

	Baseline		Change at 4 months		Difference in change
Variable	**Placebo**	**Finerenone**	**Placebo**	**Finerenone**	**Finerenone - Placebo**
UACR (mg/g) median (IQR)	515 (202 - 1148)	516 (198 - 1131)	-6.1% (-8.0% to -4.1%)	-36.3% (-37.6% to -35.0%)	-32.2% (-34.2% to -30.3%)
Systolic blood pressure (mmHg) mean (95% CI)	136.8 (136.5 to 137.2)	136.7 (136.3 to 137.0)	0.4 (0.1 to 0.8)	-3.2 (-3.5 to -2.9)	-3.6 (-4.1 to -3.1)
Body weight (kg) mean (95% CI)	88.1 (87.6 to 88.6)	87.9 (87.4 to 88.4)	0.01 (-0.06 to 0.07)	-0.22 (-0.29 to -0.15)	-0.23 (-0.32 to -0.13)
serum potassium (mEq/L) mean (95% CI)	4.35 (4.33 to 4.36)	4.35 (4.34 to 4.36)	0.02 (0.01 to 0.03)	0.21 (0.20 to 0.22)	0.19 (0.17 to 0.20)

All analyses for the changes at 4 months are adjusted for the following variables: age, sex, race, use of ace inhibitor or angiotensin receptor blocker, history of cardiovascular disease, baseline eGFR stratum, baseline weight, potassium, UACR, and systolic BP, use of SGLT2 inhibitor or GLP1RA at baseline, and HgbA1c.

Figure 2. Change from baseline to 4 months in hemodynamic and kidney markers



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RESULTS

Baseline characteristics of the study sample are shown in **Table 1**. The original FIDELITY sample included 13026 participants, but considering violations of Good Clinical Practices at one site, a few participants were removed. Nearly all participants, all of whom had type 2 diabetes and CKD, were treated with an ACE inhibitor or an angiotensin receptor blocker. The mean age was 65 years, 70 percent were men, baseline systolic BP was 137 mmHg and HbA1C 7.7%. The median UACR was 516 mg/g creatinine, mean eGFR 58 mL/mn/1.73m2, weight was 88 kg, and serum K 4.4 mEq/L.

Table 2 shows the change from baseline to month 4 in body weight and systolic blood pressure, electrolyte mineralocorticoid effect (serum potassium), and urine albumin to creatinine ratio. **Figure 2** shows the distribution of the change in each of the 4 biomarkers for placebo and finerenone. Compared to placebo, finerenone at month 4, reduced UACR by 32.2% (95% CI 30.3% to 34.2%), systolic blood pressure by 3.6 mmHg (95% CI 3.1 to 4.1), body weight by 0.23kg (95% CI, 0.13 to 0.32) and increased serum potassium by 0.19 mEq/L (95% CI 0.17 to 0.20).

Figure 3 depicts the modeled cumulative cardiovascular outcomes for each of placebo and finerenone groups for 5 mmHg reduction in systolic BP, 30% reduction in UACR, and for joint reductions. Visually, the separation in cumulative survival curves for BP reduction is modest, for UACR reduction larger, and when jointly considered the largest. **Table 3** shows the mediation by each of the biomarkers on the primary prespecified cardiovascular outcome. Individually, the reduction in UACR mediated 39% (95% CI 7% to 71%) of the outcome, systolic BP 21% (95% CI 3% to 40%) of the outcome, and there was no effect of changes in body weight or serum potassium that mediated the cardiovascular outcome. Jointly considered the changes from baseline to 4 months in UACR and systolic BP mediated 50% (95% CI 23% to 100%) of the cardiovascular outcome.

LIMITATIONS

The results of this analysis are limited to finerenone and cannot be extrapolated to other drugs such as SGLT2 inhibitors. Although both SGLT2 inhibitors and finerenone have similar magnitude of reduction in UACR and systolic BP, what mediates the cardiovascular risk with the two drugs is different. For example, in the EMPA-REG OUTCOME trial examining cardiovascular outcomes in people with T2D and atherosclerotic cardiovascular disease, all the benefit was explained by the increase in hemoglobin.

CONCLUSIONS

Except for the change in UACR, the changes in each of the other 3 markers, systolic BP, serum K, and body weight, although statistically significant were relatively modest. Although finerenone altered each of the 4 biomarkers, only 2 mediated the CV outcomes, early systolic BP reduction and UACR reduction, each of which individually accounted for a modest proportion of cardiovascular outcomes with finerenone, both jointly mediated half of the cardiovascular benefit.

In summary, the improvement in albuminuria and systolic BP at 4 months after start of finerenone mediates half the treatment effect on cardiovascular outcomes an effect that may be due to improvement in endothelial function.