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ORIGINAL ARTICLE

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

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Take Home Message

- Finerenone is a nonsteroidal, selective mineralocorticoid receptor antagonist.
- Among patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, Finerenone therapy **improved cardiovascular outcomes** as compared with placebo.

The Comparison of Spironolactone and Eplerenone

Table 2
Pharmacodynamic and pharmacokinetic characteristics of mineralocorticoid receptor antagonists [6,30,37,47].

	Spironolactone
Class	Steroidal
Mineralocorticoid receptor IC_{50}	24 nM
Androgenic receptor IC_{50}	77 nM
Glucocorticoid receptor IC_{50}	2410 nM
Progesterone receptor EC_{50}	740 nM
Tissue (cardiac/renal distribution)	6-fold higher in kidney

IC_{50}: concentration required to inhibit 50% activation of the receptor.

Ruilope, L. M., & Tamargo, J. (2017). Renin–angiotensin system blockade: Finerenone. *Nephrologie & therapeutique*, *13*, S47-S53.

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	Spironolactone	Eplerenone
Class	Steroidal	Steroidal
Mineralocorticoid receptor IC_{50}	24 nM	990 nM
Androgenic receptor IC_{50}	77 nM	$\geq$21,240 nM
Glucocorticoid receptor IC_{50}	2410 nM	$\geq$21,980 nM
Progesterone receptor EC_{50}	740 nM	$\geq$31,210 nM
Tissue (cardiac/renal distribution)	6-fold higher in kidney	3-fold higher in kidney

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Spironolactone presents progestogenic and antiandrogenic activities.
- Produces sexual adverse effects, such as painful gynecomastia, painful enlargement of the breasts, loss of libido, impotence, and menstrual irregularities.

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Spironolactone presents progestogenic and antiandrogenic activities.
- Produces sexual adverse effects, such as painful gynecomastia, painful enlargement of the breasts, loss of libido, impotence, and menstrual irregularities.

Eplerenone presents 20–40-fold lower affinity for the mineralocorticoid receptor.
- Less efficient in patients with hypertension or with primary hyperaldosteronism

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What is Finerenone?

Table 2
Pharmacodynamic and pharmacokinetic characteristics of mineralocorticoid receptor antagonists [6,30,37,47].

	Spironolactone	Eplerenone	Finerenone
Class	Steroidal	Steroidal	Dihydropyridine
Mineralocorticoid receptor IC_{50}	24 nM	990 nM	17.8 nM
Androgenic receptor IC_{50}	77 nM	≥21,240 nM	≥10,000 nM
Glucocorticoid receptor IC_{50}	2410 nM	≥21,980 nM	≥10,000 nM
Progesterone receptor EC_{50}	740 nM	≥31,210 nM	≥10,000 nM
Tissue (cardiac/renal distribution)	6-fold higher in kidney	3-fold higher in kidney	Blanced between both tissues

Finerenone has
- high **affinity** for the mineralocorticoid receptor as **Spironolactone**.
- high **selectivity** for the mineralocorticoid receptor as **Eplerenone**. (non-steroidal).

Besides, Finerenone is a full antagonist in different cell types, while Spironolactone and Eplerenone have partial agonistic activity in some receptors, leading to early-onset HTN in men and gestational HTN in women.

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Research Question

Previous result

- Finerenone improved kidney outcomes in patients with predominantly stage 3 or 4 CKD with severely elevated albuminuria and type 2 diabetes.

Research question

- To understand if treatment with Finerenone would lead to lower risks of cardiovascular events and death from cardiovascular causes among patients with CKD with albuminuria and type 2 diabetes.

Methods – Trial Design

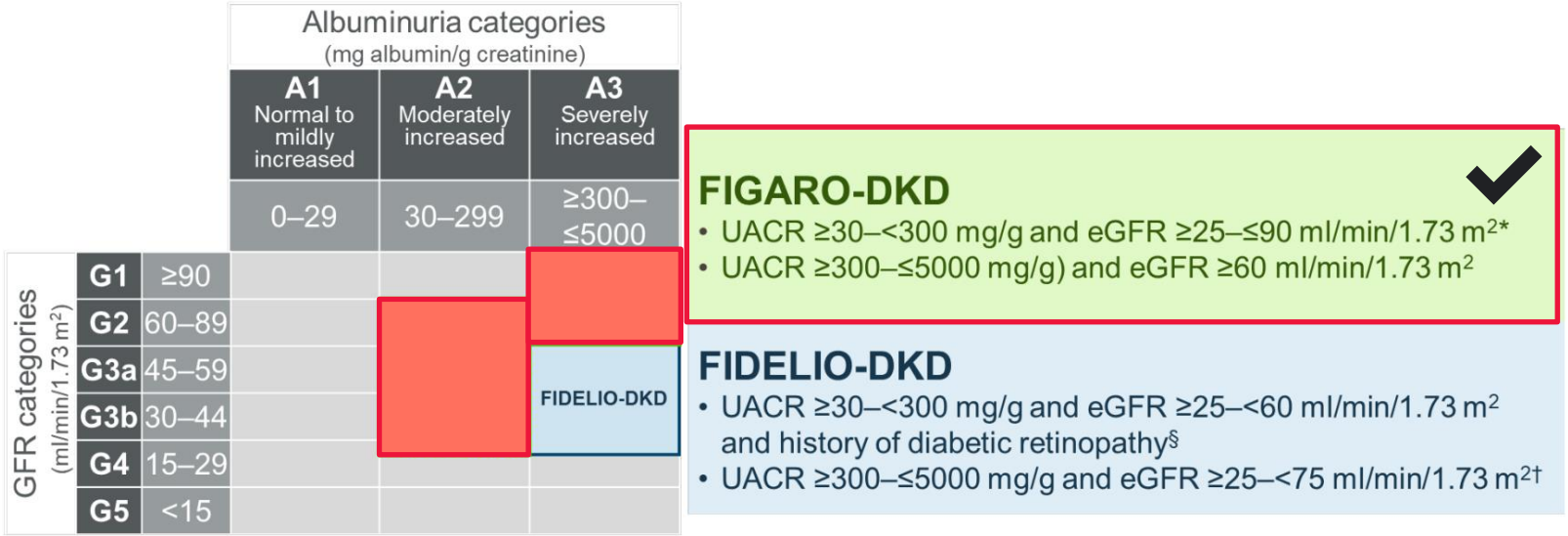
Research type

- Phase 3. Double-blind, randomized, placebo-controlled, multicenter clinical trial.

Methods – Trial Design

Patients

- Adults with T2DM and CKD with two inclusion criteria.



Methods – Trial Design

Patients

- Adults with T2DM and CKD with two inclusion criteria.
- Adults were treated with a renin– angiotensin system (RAS) inhibitor (**ACEi or ARB**) **at the maximum dose** on the manufacturer's label that did not cause unacceptable side effects

Methods – Trial Design

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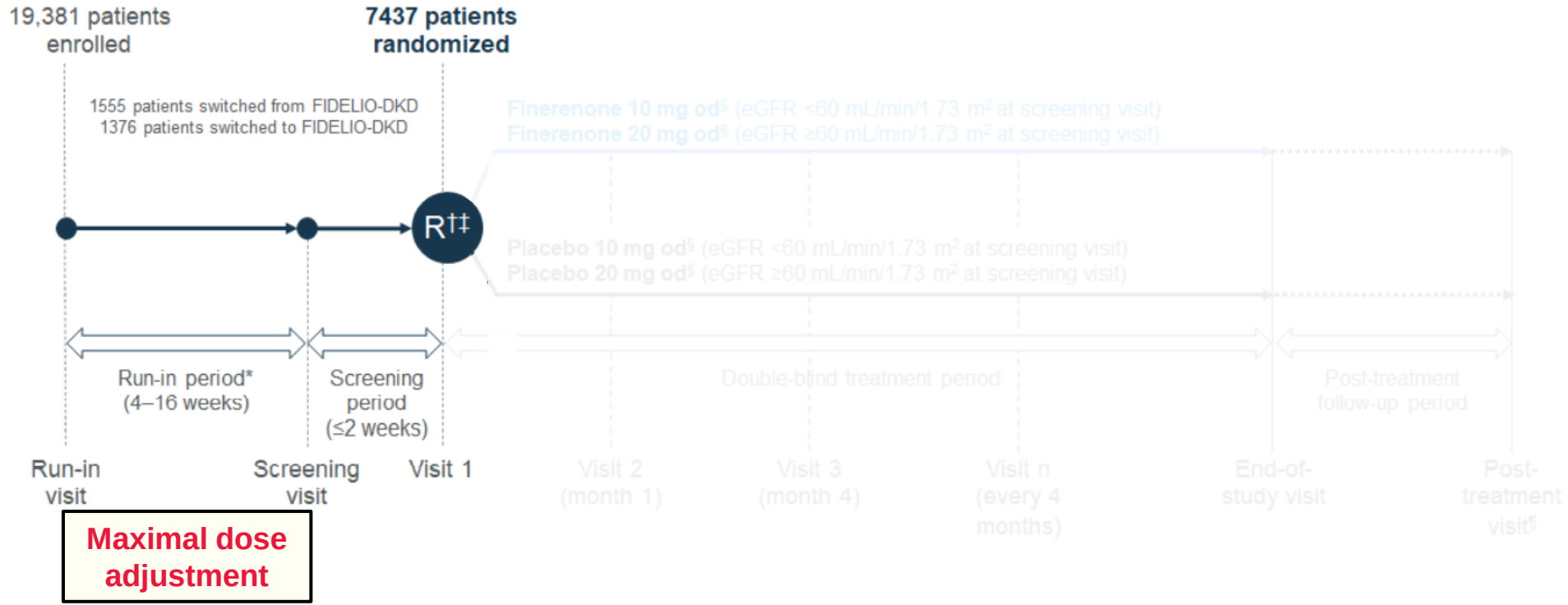
- Adults were treated with a renin– angiotensin system (RAS) inhibitor (**ACEi or ARB**) **at the maximum dose** on the manufacturer's label that did not cause unacceptable side effects
- Exclusion of patients who had symptomatic heart failure with a reduced ejection fraction.

Methods – Trial Procedure

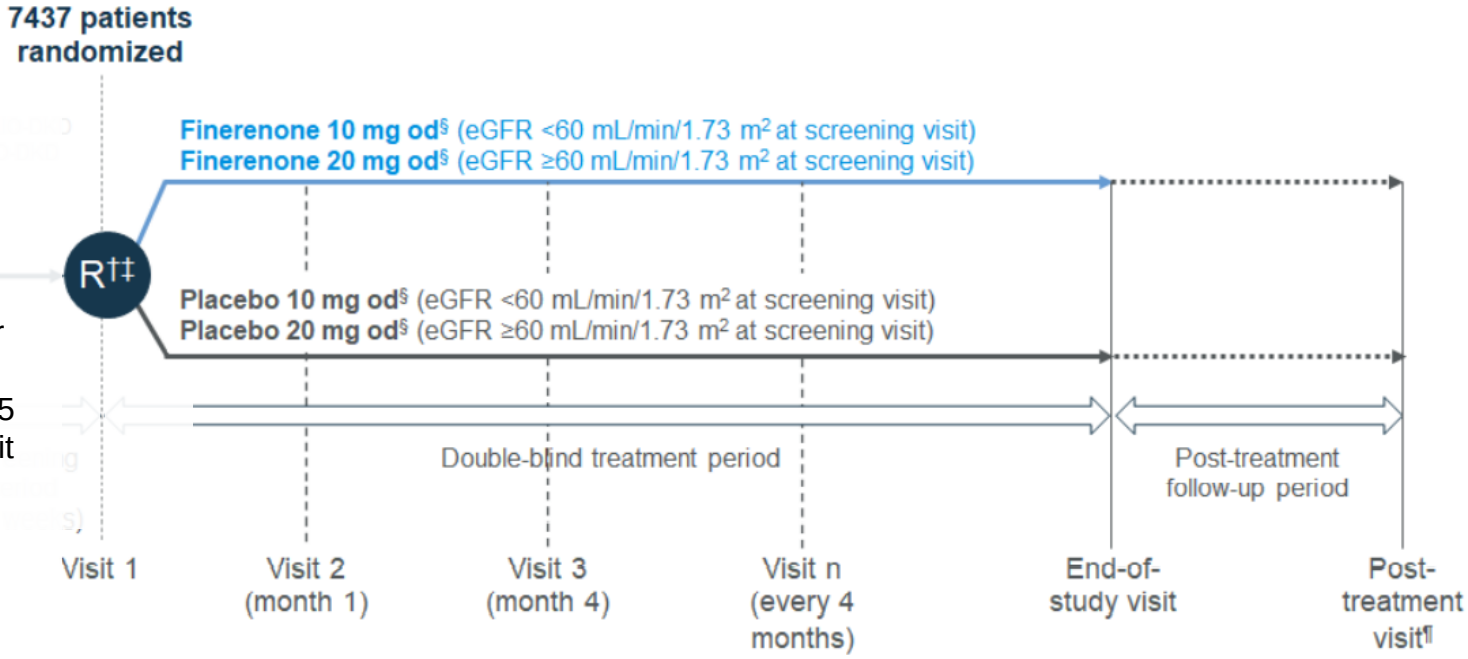


Maximal dose adjustment

Methods – Trial Procedure

Increase dosage (encouraged): From 10 to 20 mg once daily after 1 month, if serum potassium level was < 4.8 mEq.

Withdrawal: Finerenone or placebo was withheld if serum potassium level > 5.5 mEq and restarted when if it fell to 5.0 mEq or less.



Methods – Outcomes

Primary outcomes:

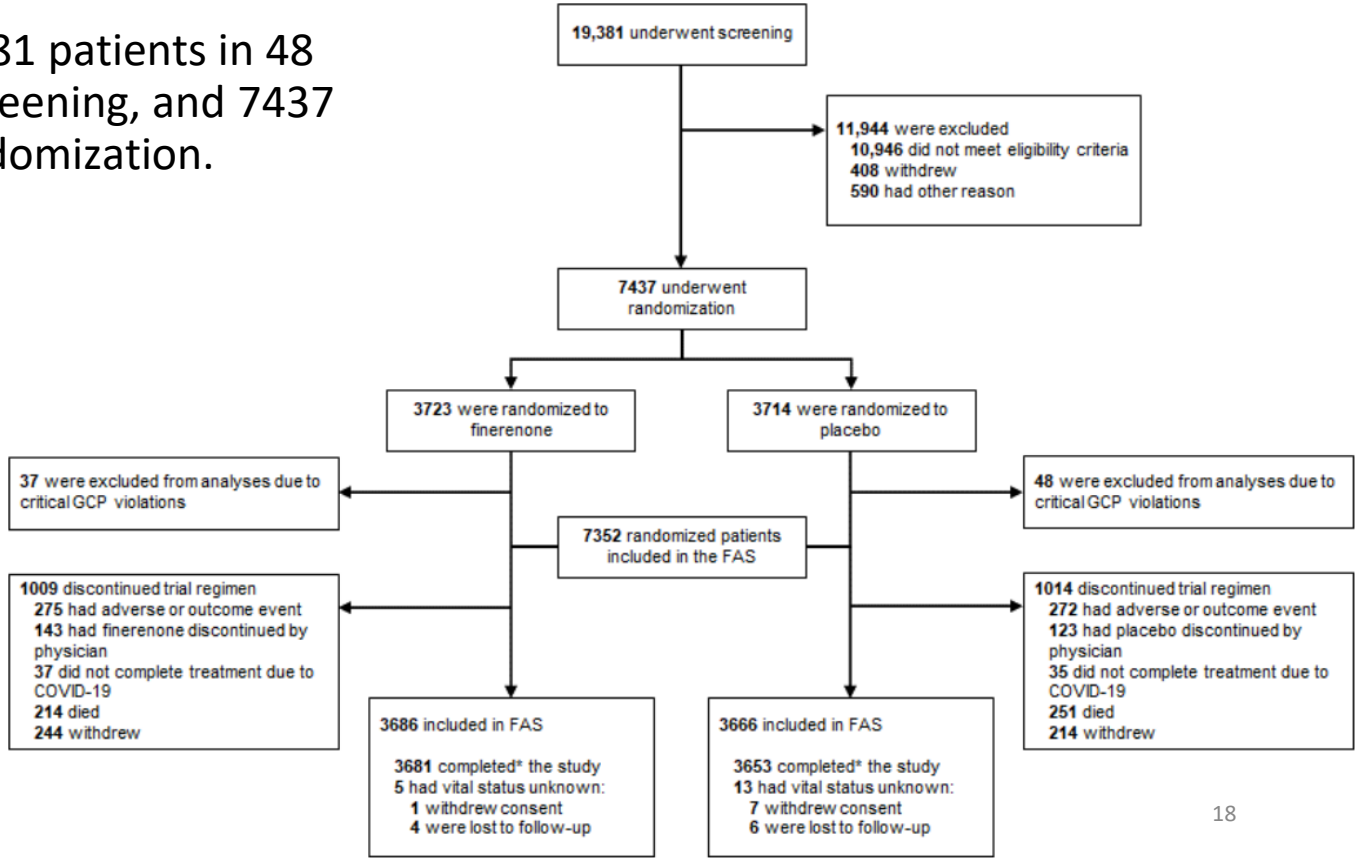
- Death from cardiovascular causes
- Nonfatal myocardial infarction
- Nonfatal stroke
- Hospitalization for heart failure

Secondary outcomes:

- Kidney failure (eGFR<15).
- A sustained decrease of at least 40% in the eGFR from baseline over a period of at least 4 weeks
- Death from renal causes.

Results – Demographic and Clinical Characteristics

From 2015 to 2018, 19381 patients in 48 countries underwent screening, and 7437 patients underwent randomization.



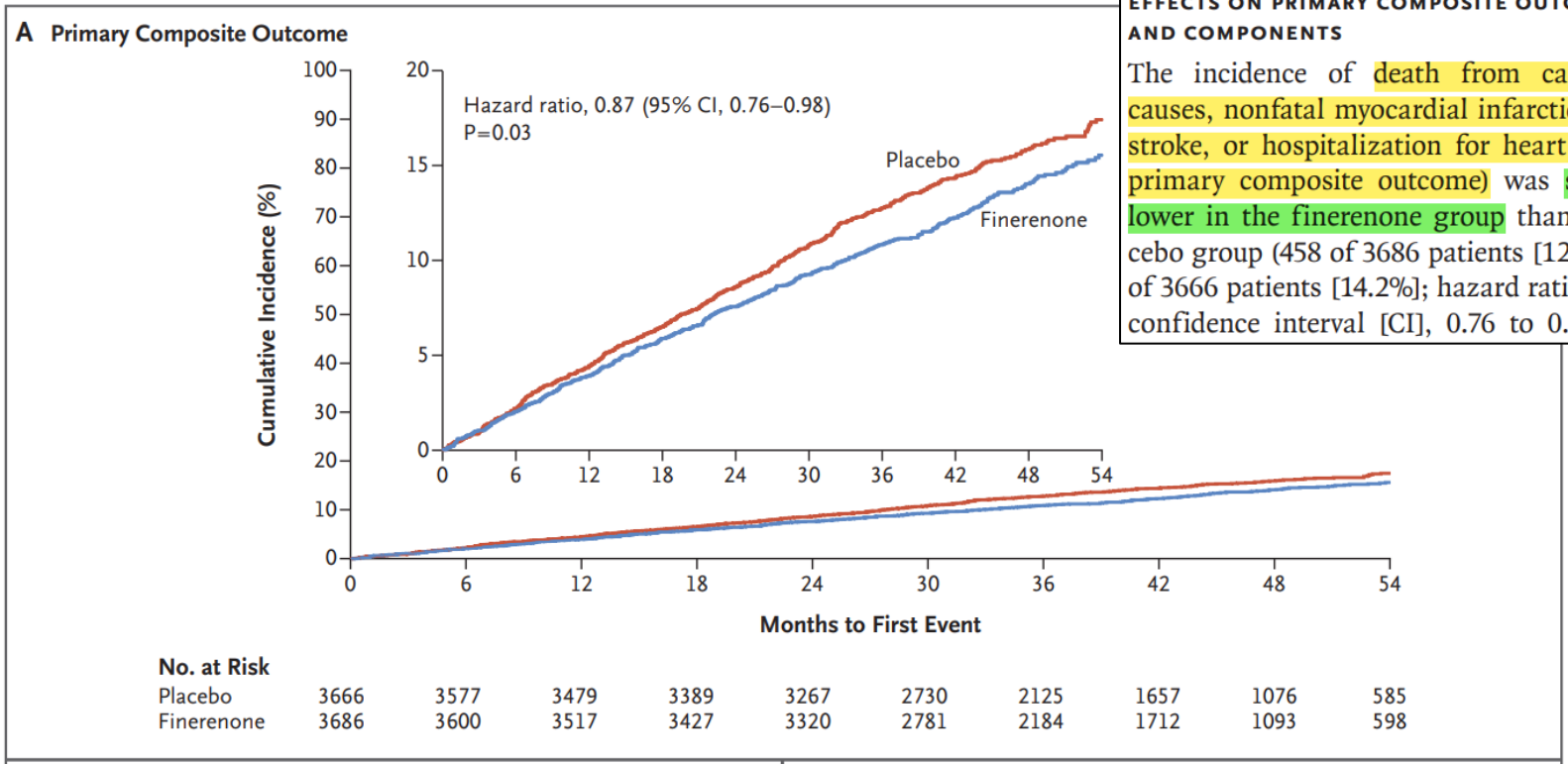
Results – Demographic and Clinical Characteristics

Table 1. Key Demographic and Clinical Characteristics of the Patients and Medications at Baseline.*

Characteristic	Finerenone (N = 3686)	Placebo (N = 3666)	Total (N = 7352)
Age — yr	64.1±9.7	64.1±10.0	64.1±9.8
Male sex — no. (%)	2528 (68.6)	2577 (70.3)	5105 (69.4)
Race or ethnic group — no. (%)†			
White	2672 (72.5)	2605 (71.1)	5277 (71.8)
Black	113 (3.1)	145 (4.0)	258 (3.5)
Asian	715 (19.4)	739 (20.2)	1454 (19.8)
Other	177 (4.8)	170 (4.6)	347 (4.7)
Missing data	9 (0.2)	7 (0.2)	16 (0.2)
Glycated hemoglobin — %	7.7±1.4	7.7±1.4	7.7±1.4
Systolic blood pressure — mm Hg	135.8±14.0	135.7±14.1	135.8±14.0
History of cardiovascular disease — no. (%)	1676 (45.5)	1654 (45.1)	3330 (45.3)

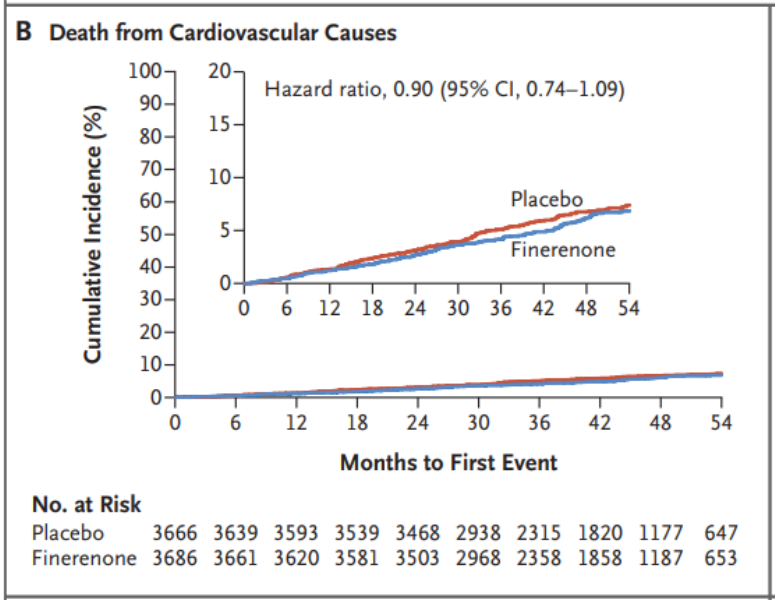
Estimated glomerular filtration rate			
Mean — ml/min/1.73 m^2	67.6±21.7	68.0±21.7	67.8±21.7
Distribution — no. (%)			
≥60 ml/min/1.73 m^2	2285 (62.0)	2254 (61.5)	4539 (61.7)
45 to <60 ml/min/1.73 m^2	745 (20.2)	789 (21.5)	1534 (20.9)
25 to <45 ml/min/1.73 m^2	641 (17.4)	610 (16.6)	1251 (17.0)
<25 ml/min/1.73 m^2	15 (0.4)	12 (0.3)	27 (0.4)
Missing data	0	1 (<0.1)	1 (<0.1)
Urinary albumin-to-creatinine ratio‡			
Median (interquartile range)	302 (105–749)	315 (111–731)	308 (108–740)
Distribution — no. (%)			
<30	109 (3.0)	98 (2.7)	207 (2.8)
30 to <300	1726 (46.8)	1688 (46.0)	3414 (46.4)
≥300	1851 (50.2)	1878 (51.2)	3729 (50.7)
Missing data	0	2 (0.1)	2 (<0.1)
Serum potassium — mmol/liter	4.33±0.43	4.33±0.43	4.33±0.43

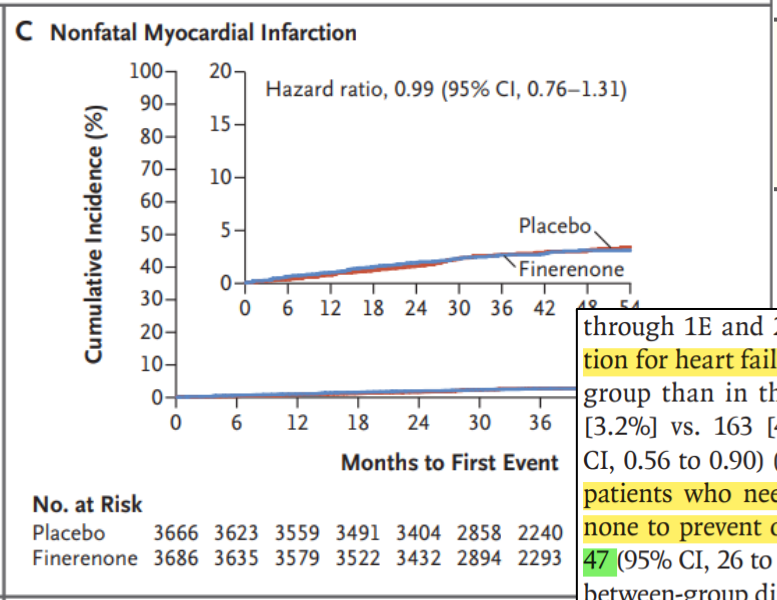
Results – Primary Outcome

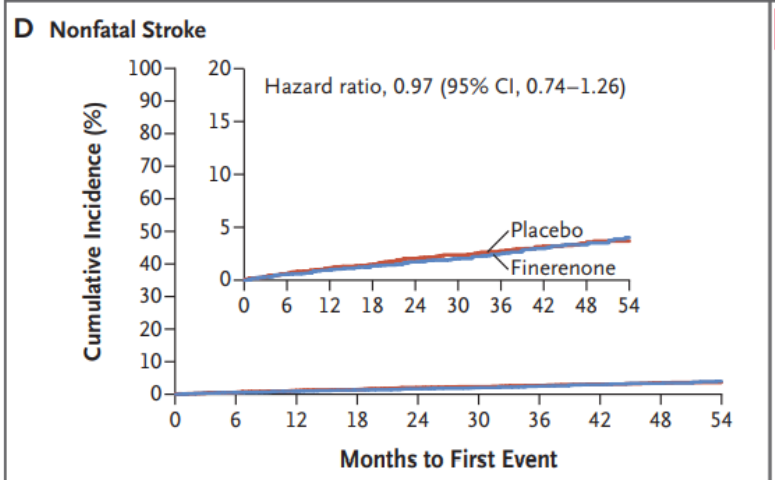


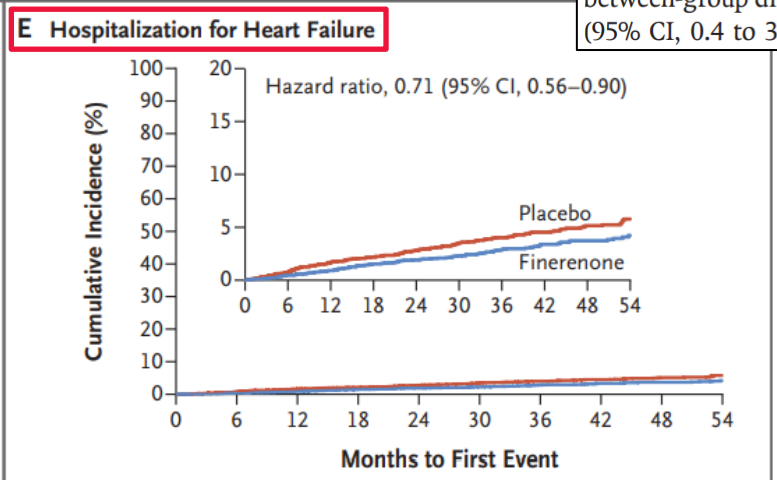
EFFECTS ON PRIMARY COMPOSITE OUTCOME AND COMPONENTS

The incidence of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (the primary composite outcome) was significantly lower in the finerenone group than in the placebo group (458 of 3686 patients [12.4%] vs. 519 of 3666 patients [14.2%]; hazard ratio, 0.87; 95% confidence interval [CI], 0.76 to 0.98; P=0.03)



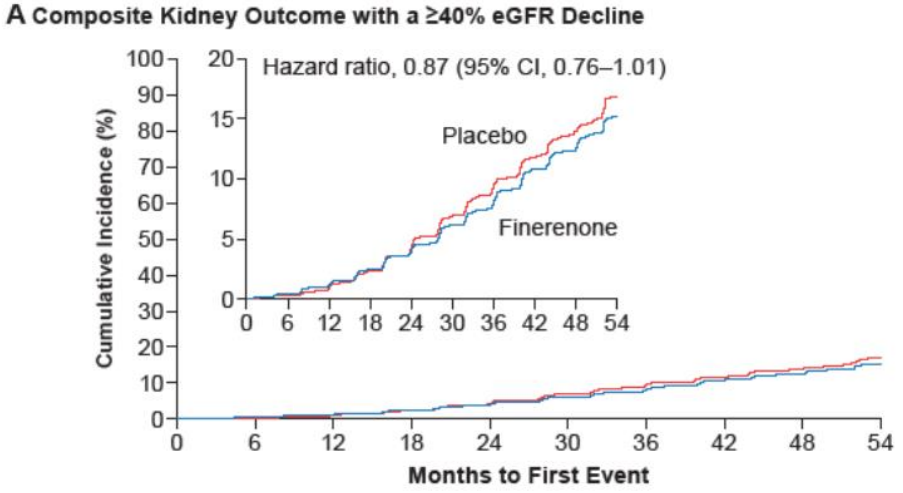


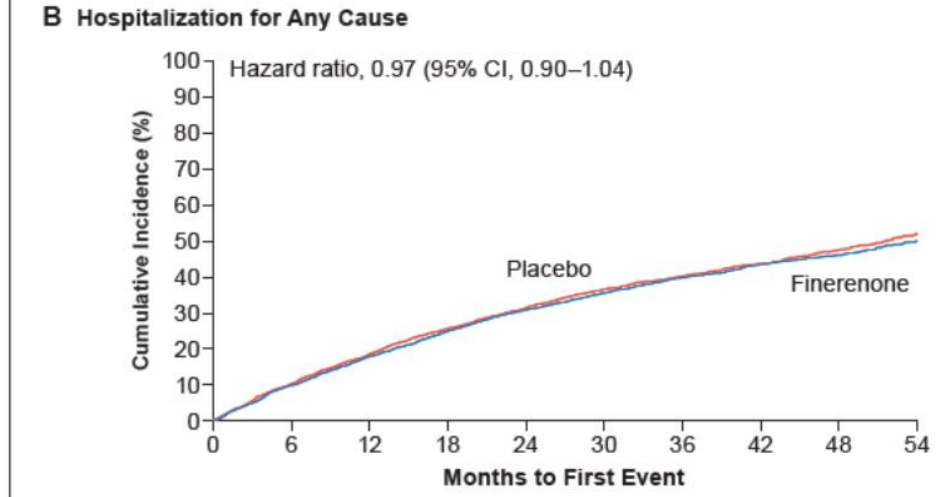




through 1E and 2. The incidence of hospitalization for heart failure was lower in the finerenone group than in the placebo group (117 patients [3.2%] vs. 163 [4.4%]; hazard ratio, 0.71; 95% CI, 0.56 to 0.90) (Figs. 1E and 2). The number of patients who needed to be treated with finerenone to prevent one primary outcome event was 47 (95% CI, 26 to 226), on the basis of an absolute between-group difference of 2.1 percentage points (95% CI, 0.4 to 3.8) after 3.5 years.

Results – Secondary Outcome



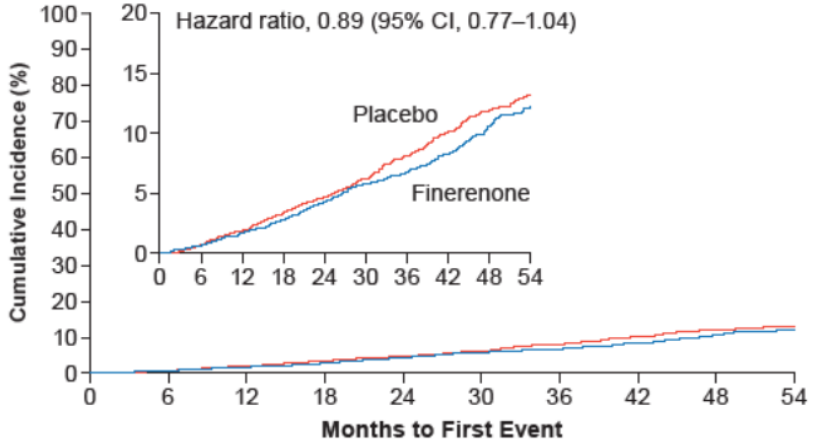


Results – Secondary Outcome

SECONDARY AND EXPLORATORY OUTCOMES

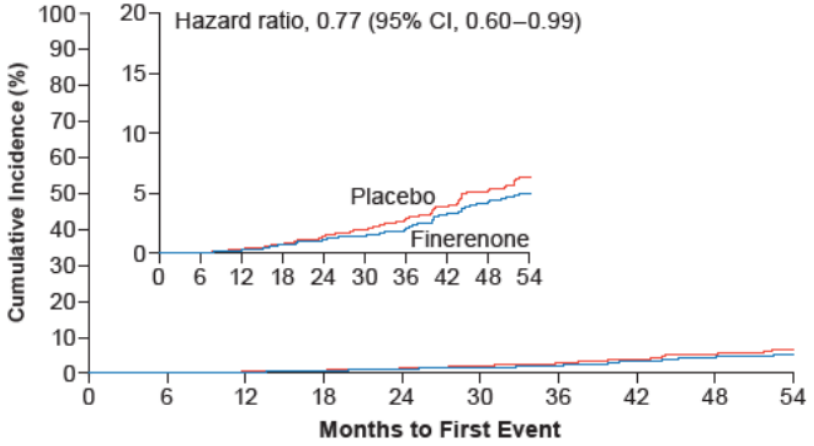
There was no significant between-group difference in the incidence of the first secondary composite outcome of kidney failure, a sustained decrease from baseline of at least 40% in the

C Death from Any Cause



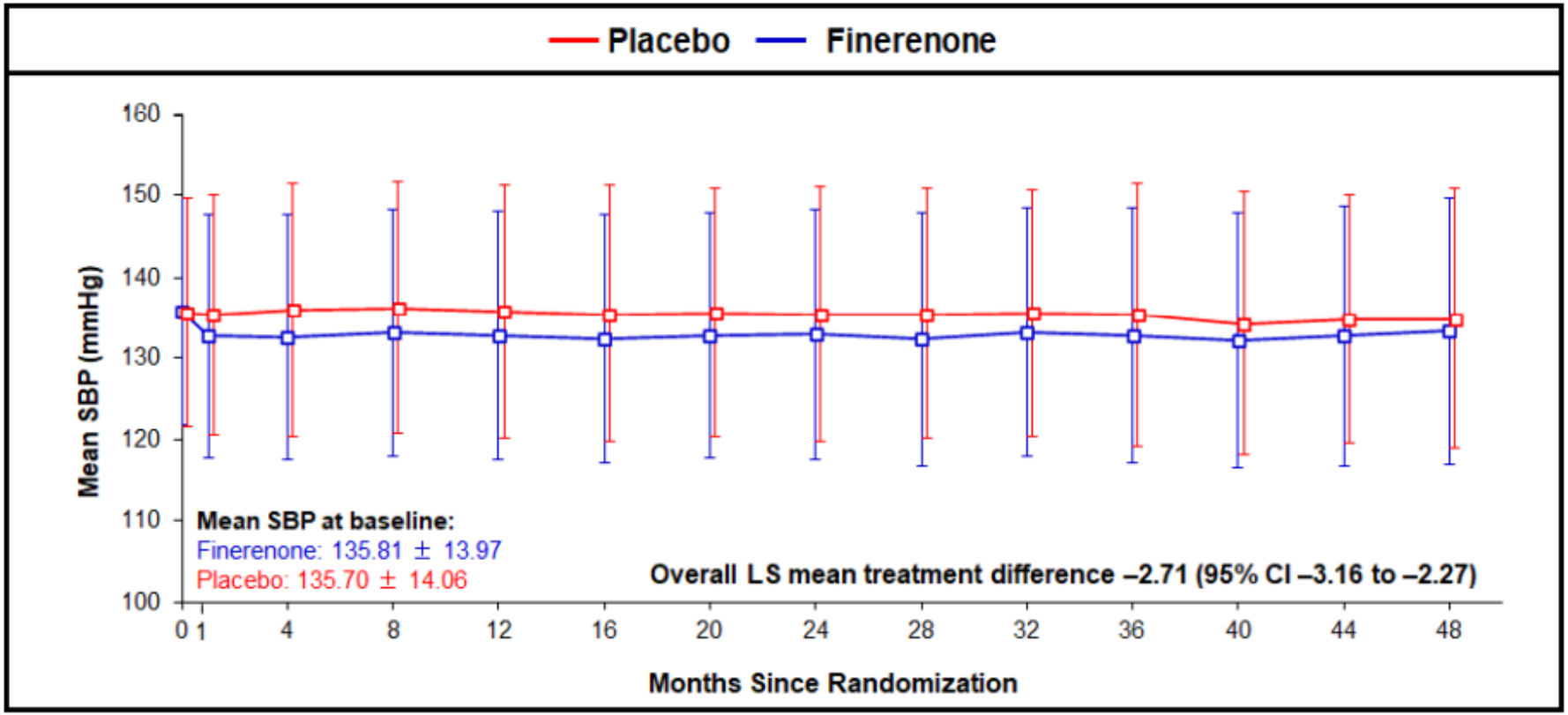
No. at Risk										
Placebo	3666	3639	3593	3539	3469	2938	2315	1820	1177	647
Finerenone	3686	3661	3620	3581	3505	2968	2358	1858	1187	653

D Composite Kidney Outcome with a ≥57% eGFR Decline



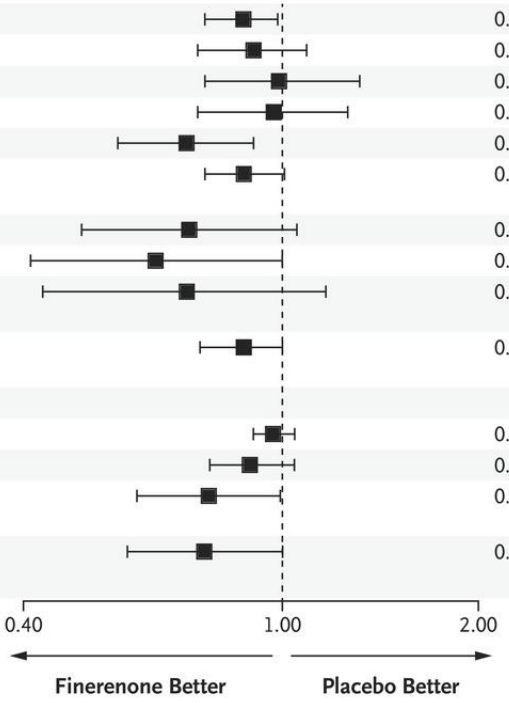
No. at Risk										
Placebo	3666	3552	3452	3325	3178	2615	2039	1538	970	520
Finerenone	3686	3559	3474	3356	3218	2651	2047	1582	973	522

Results – Other Outcomes



Results – Efficacy Outcomes

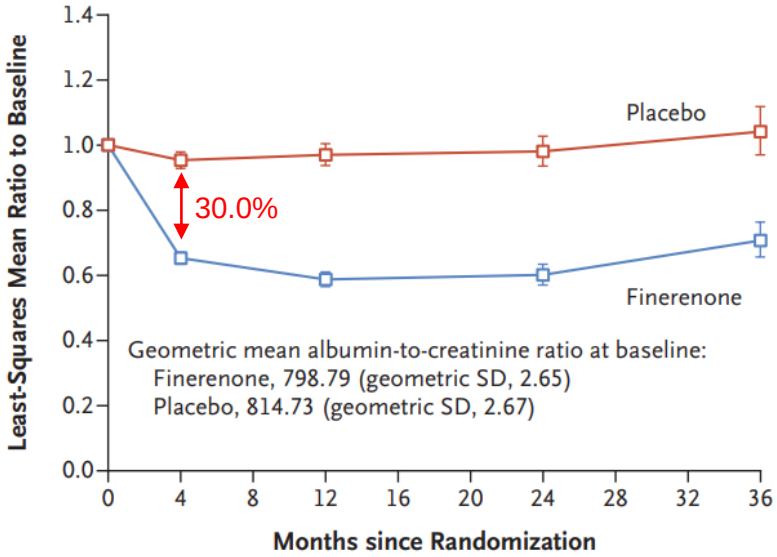
Outcome	Finerenone (N=3686)	Placebo (N=3666)	Finerenone (N=3686)	Placebo (N=3666)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	458 (12.4)	519 (14.2)	3.87	4.45	0.87 (0.76–0.98)	0.03
Death from cardiovascular causes	194 (5.3)	214 (5.8)	1.56	1.74	0.90 (0.74–1.09)	—
Nonfatal myocardial infarction	103 (2.8)	102 (2.8)	0.85	0.85	0.99 (0.76–1.31)	—
Nonfatal stroke	108 (2.9)	111 (3.0)	0.89	0.92	0.97 (0.74–1.26)	—
Hospitalization for heart failure	117 (3.2)	163 (4.4)	0.96	1.36	0.71 (0.56–0.90)	—
Kidney composite outcome with ≥40% decrease in eGFR	350 (9.5)	395 (10.8)	3.15	3.58	0.87 (0.76–1.01)	—
Kidney failure	46 (1.2)	62 (1.7)	0.40	0.54	0.72 (0.49–1.05)	—
End-stage kidney disease	32 (0.9)	49 (1.3)	0.26	0.40	0.64 (0.41–0.995)	—
Sustained decrease in eGFR of <15 ml/min/1.73 m^2	28 (0.8)	38 (1.0)	0.24	0.33	0.71 (0.43–1.16)	—
Sustained ≥40% decrease in eGFR from baseline	338 (9.2)	385 (10.5)	3.04	3.49	0.87 (0.75–1.00)	—
Death from renal causes	0	2 (0.1)	—	—	—	—
Hospitalization for any cause	1573 (42.7)	1605 (43.8)	16.9	17.5	0.97 (0.90–1.04)	—
Death from any cause	333 (9.0)	370 (10.1)	2.68	3.01	0.89 (0.77–1.04)	—
Kidney composite outcome with ≥57% decrease in eGFR	108 (2.9)	139 (3.8)	0.95	1.23	0.77 (0.60–0.99)	—
Sustained ≥57% decrease in eGFR from baseline	90 (2.4)	116 (3.2)	0.79	1.02	0.76 (0.58–1.00)	—



Results – Effects on Albuminuria and Serum Potassium

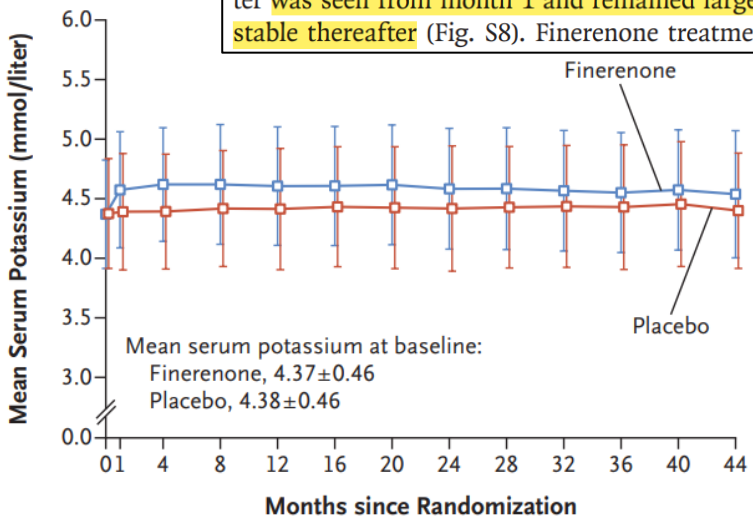
Finerenone treatment was associated with a greater increase in the serum potassium level from baseline than that observed with placebo. A between-group difference of 0.16 mmol per liter was seen from month 1 and remained largely stable thereafter (Fig. S8). Finerenone treatment

A Urinary Albumin-to-Creatinine Ratio



Mean Change from Baseline (percent)					
Finerenone	Ref.	−34.7	−41.3	−39.9	−29.3
Placebo	Ref.	−4.7	−3.0	−2.0	4.1

B Mean Serum Potassium



Mean Change from Baseline (mmol/liter)						
Finerenone	Ref.	0.25	0.24	0.21	0.21	0.20
Placebo	Ref.	0.02	0.04	0.05	0.07	0.07

Results – Safety Outcomes.

Adverse events and serious adverse events of pneumonia were less common with finerenone than with placebo (in 3.9% vs. 5.6% of the patients and in 2.0% vs. 3.1%, respectively), as were adverse events related to Covid-19 (in 2.3% vs.

Table 2. Safety Outcomes.*

Event	Finerenone (N=3683)	Placebo (N=3658)
Investigator-reported adverse events — no. (%)		
Any adverse event	3134 (85.1)	3129 (85.5)
Adverse event related to finerenone or placebo	560 (15.2)	413 (11.3)
Adverse event leading to discontinuation of trial regimen	207 (5.6)	183 (5.0)
Any serious adverse event	1158 (31.4)	1215 (33.2)
Serious adverse event related to finerenone or placebo	35 (1.0)	27 (0.7)
Serious adverse event leading to discontinuation of trial regimen	70 (1.9)	76 (2.1)
Adverse event with outcome of death	79 (2.1)	100 (2.7)
Hyperkalemia†	396 (10.8)	193 (5.3)
Hyperkalemia related to finerenone or placebo	240 (6.5)	114 (3.1)
Serious hyperkalemia	25 (0.7)	4 (0.1)
Hospitalization due to hyperkalemia	21 (0.6)	2 (0.1)
Permanent discontinuation of trial regimen due to hyperkalemia	46 (1.2)	13 (0.4)
Hypokalemia	42 (1.1)	88 (2.4)
Renal-related adverse events		
Acute kidney injury‡	91 (2.5)	98 (2.7)
Hospitalization due to acute kidney injury‡	32 (0.9)	39 (1.1)
Discontinuation of trial regimen due to acute kidney injury‡	9 (0.2)	3 (0.1)
Hospitalization due to acute renal failure§	45 (1.2)	49 (1.3)
Discontinuation of trial regimen due to acute renal failure§	26 (0.7)	12 (0.3)
Covid-19–related adverse event¶		
Any adverse event	84 (2.3)	116 (3.2)

Discussion - Early Stage and Late Stage Benefits

In this trial, the early reduction in albuminuria, early separation of the Kaplan–Meier curves for the key secondary outcome, and modest blood-pressure reduction suggest that some benefits of Finerenone may partly be mediated by **natriuretic mechanisms**.

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In this trial, the early reduction in albuminuria, early separation of the Kaplan–Meier curves for the key secondary outcome, and modest blood-pressure reduction suggest that some benefits of Finerenone may partly be mediated by **natriuretic mechanisms**.

Preclinical data showed that the kidney and cardiovascular benefits of Finerenone were associated with potent anti-inflammatory and anti-fibrotic effects through inhibition of overactivation of the mineralocorticoid receptor.

The delayed separation of the Kaplan–Meier curves for the primary outcome and persistent benefit over the trial duration provide evidence to support the hypothesis that Finerenone may **slow CKD progression by influencing tissue remodeling**.

Discussion - Limitations

- Patients with non-albuminuric CKD are not included.
- Only 4.7% of the participating patients identified themselves as Black.

Take Home Message

- Finerenone is a nonsteroidal, selective mineralocorticoid receptor antagonist.
- Among patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, Finerenone therapy **improved cardiovascular outcomes** as compared with placebo.