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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	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

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.

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 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

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

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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 to **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

- Finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, reduced albuminuria in short-term trials involving patients with chronic kidney disease (CKD) and type 2 diabetes.
- Although previous trials have examined cardiovascular outcomes in patients with type 2 diabetes and varying degrees of CKD, there remains scant evidence from dedicated clinical trials to support the use of therapies to improve cardiorenal outcomes in patients with less-advanced CKD.
- In other words, the long-term effects of Finerenone on kidney and cardiovascular outcomes are unknown.

Methods – Trial Design

Research type

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

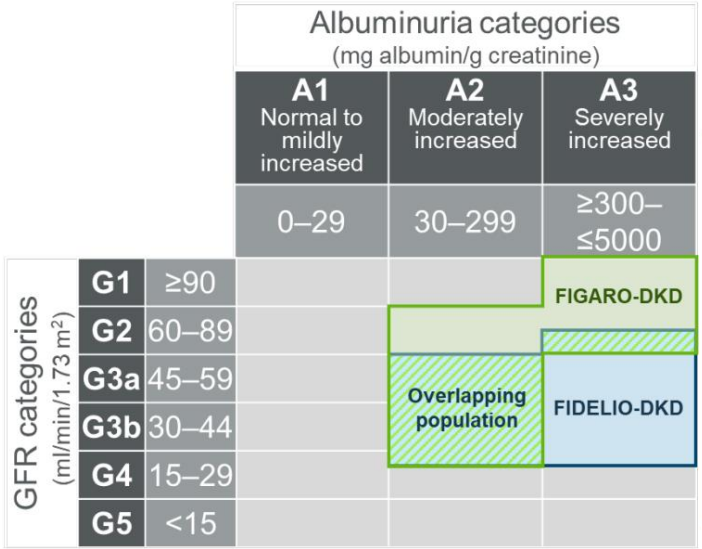
Patients

- Inclusion of adults with T2DM and CKD.
- Exclusion of patients who had symptomatic heart failure with a reduced ejection fraction.
- In the run-in period, patients were treated with ACEi or ARB at maximum dose without unacceptable side effects.

Methods – Trial Design

Patients

- Adults with T2DM and CKD with two inclusion criteria.



FIGARO-DKD

- UACR ≥30–<300 mg/g and eGFR ≥25–≤90 ml/min/1.73 m²*
- UACR ≥300–≤5000 mg/g) and eGFR ≥60 ml/min/1.73 m²

FIDELIO-DKD

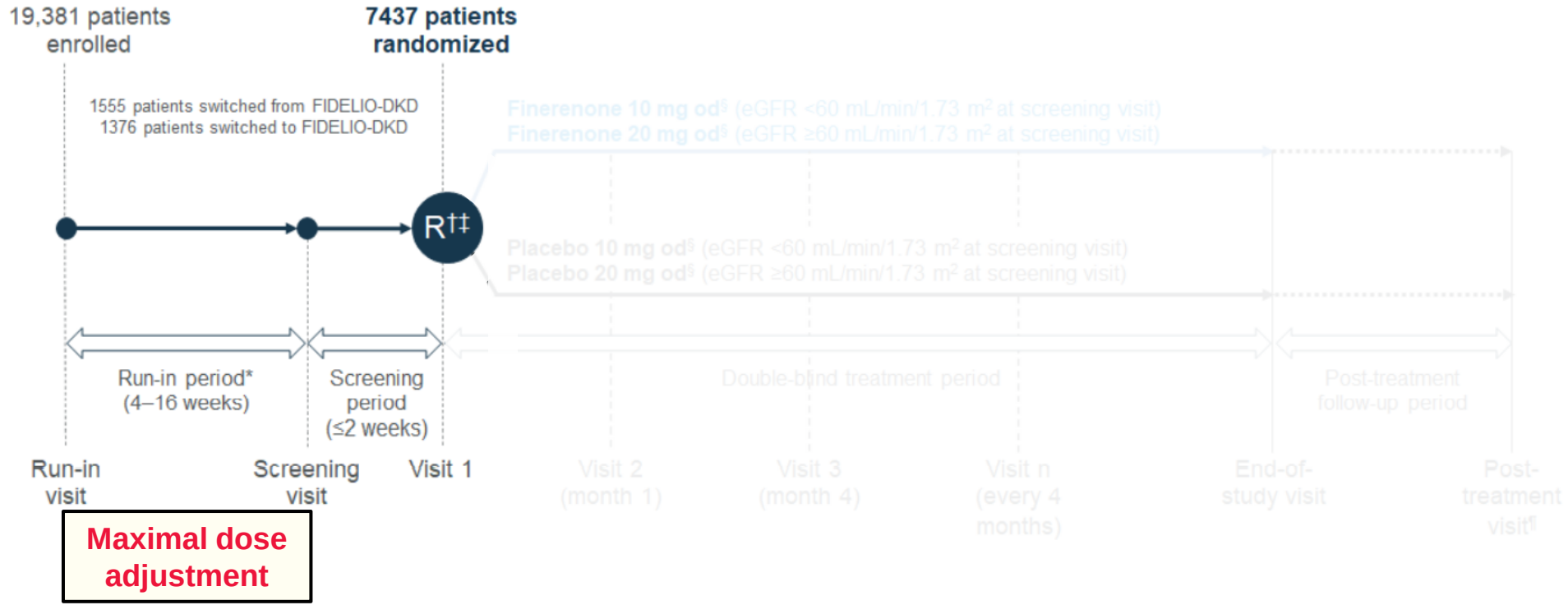
- UACR ≥30–<300 mg/g and eGFR ≥25–<60 ml/min/1.73 m² and history of diabetic retinopathy§
- UACR ≥300–≤5000 mg/g and eGFR ≥25–<75 ml/min/1.73 m²†

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 Procedure

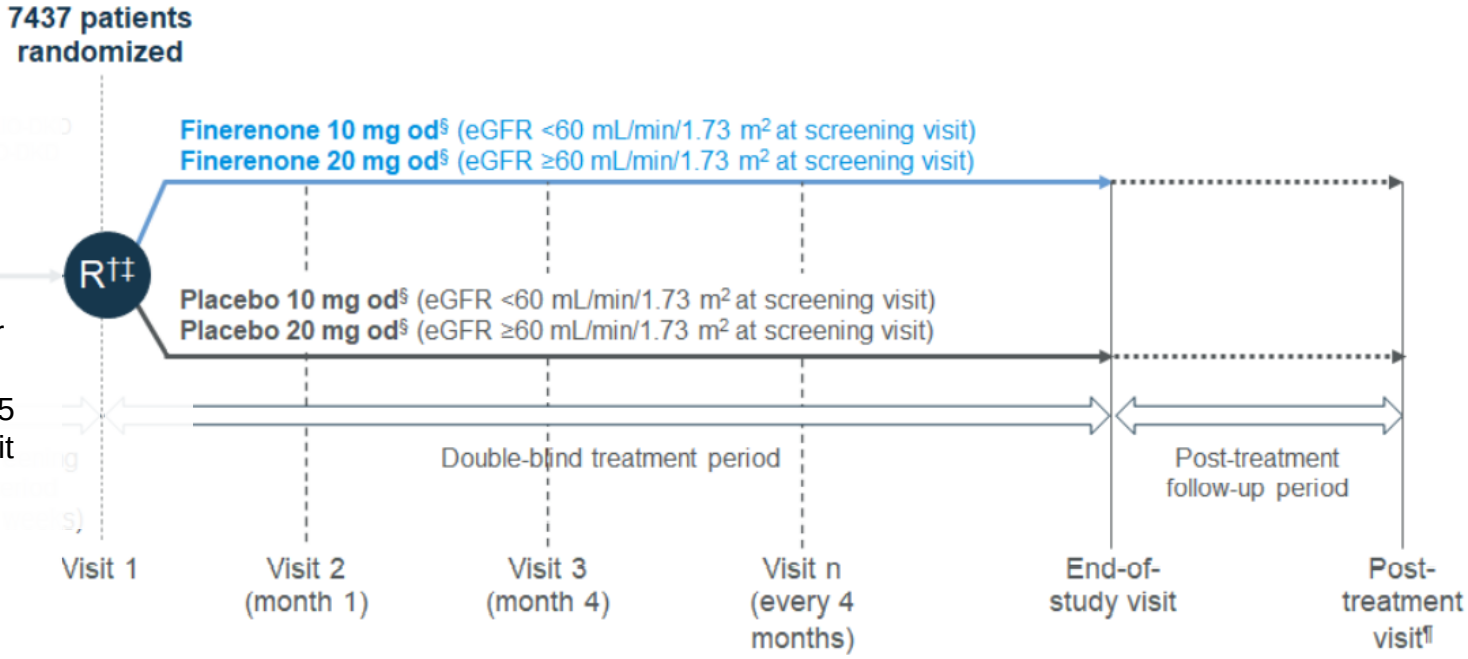


Maximal dose adjustment

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 outcome:

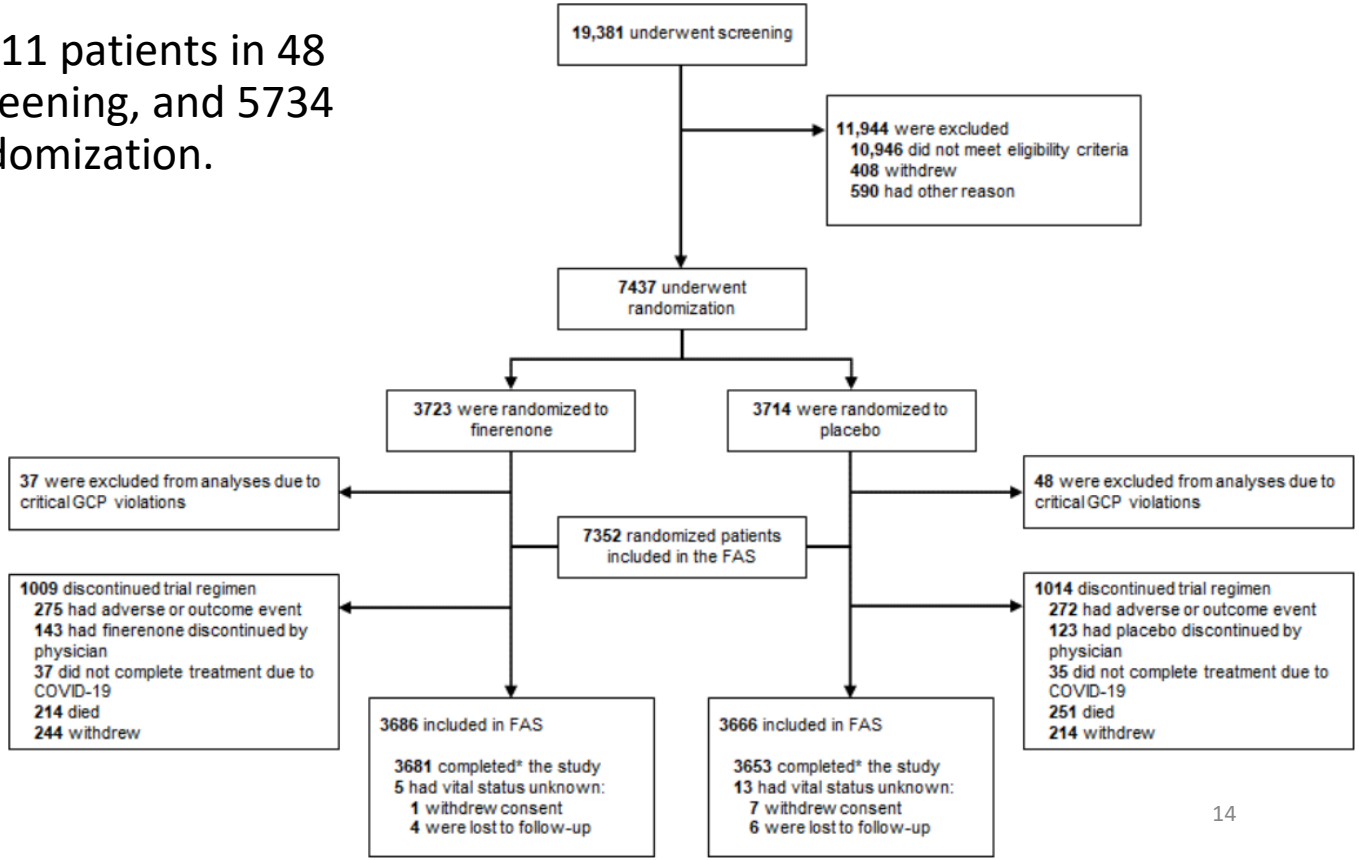
- Death from cardiovascular causes
- Nonfatal myocardial infarction
- Nonfatal stroke
- Hospitalization for heart failure.

Secondary outcome:

- 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, 13,911 patients in 48 countries underwent screening, and 5734 patients underwent randomization.



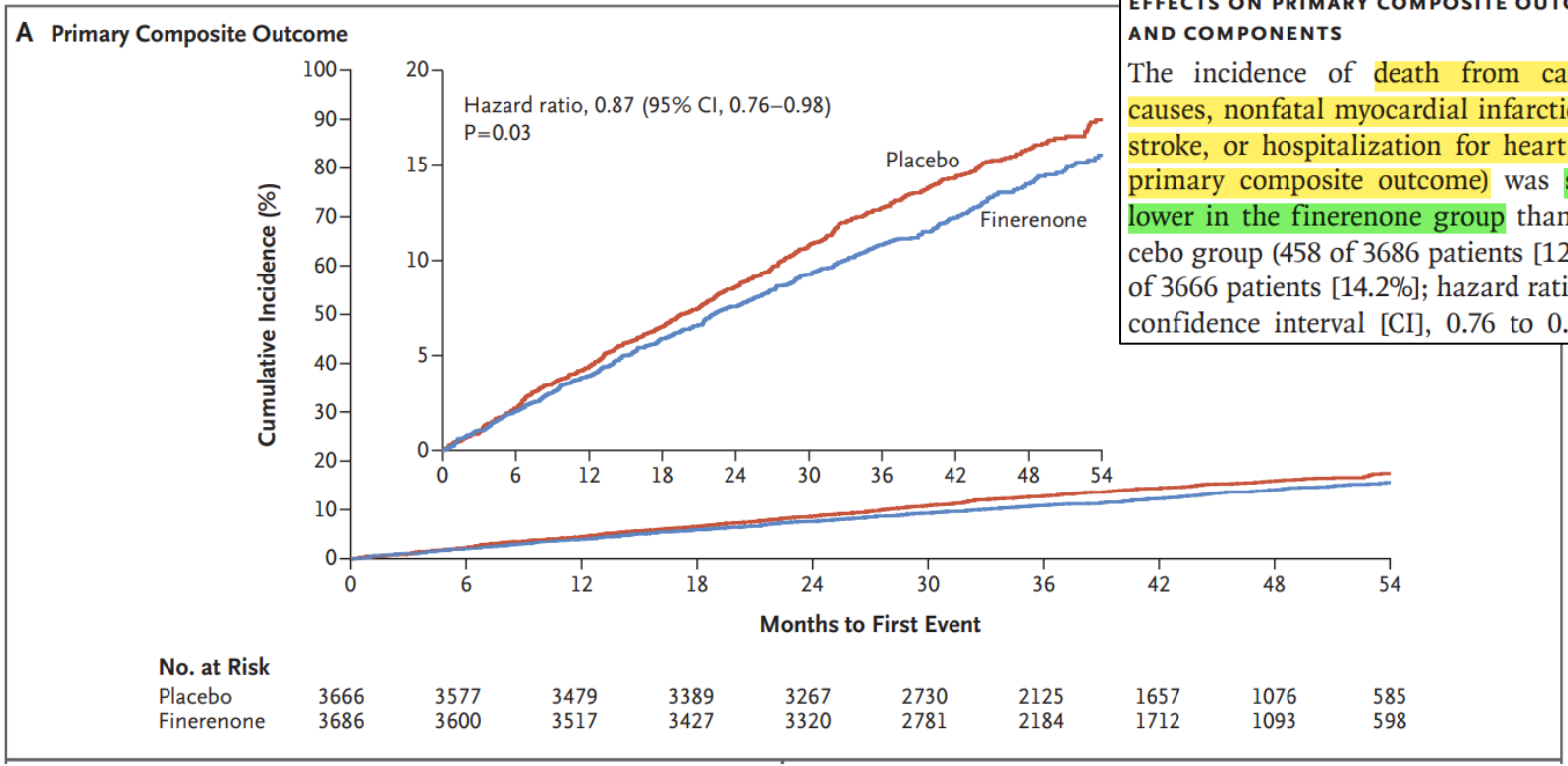
Results – Demographic and Clinical Characteristics

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

Characteristic	Finerenone (N = 2833)	Placebo (N = 2841)	Total (N = 5674)
Age — yr	65.4±8.9	65.7±9.2	65.6±9.1
Male sex — no. (%)	1953 (68.9)	2030 (71.5)	3983 (70.2)
Race — no. (%)†			
White	1777 (62.7)	1815 (63.9)	3592 (63.3)
Black	140 (4.9)	124 (4.4)	264 (4.7)
Asian	717 (25.3)	723 (25.4)	1440 (25.4)
Other	199 (7.0)	179 (6.3)	378 (6.7)
Duration of diabetes — yr	16.6±8.8	16.6±8.8	16.6±8.8
Glycated hemoglobin — %	7.7±1.3	7.7±1.4	7.7±1.3
Systolic blood pressure — mm Hg	138.1±14.3	138.0±14.4	138.0±14.4

Estimated glomerular filtration rate			
Mean	44.4±12.5	44.3±12.6	44.3±12.6
Distribution — no. (%)			
≥60 ml/min/1.73 m^2	318 (11.2)	338 (11.9)	656 (11.6)
45 to <60 ml/min/1.73 m^2	972 (34.3)	928 (32.7)	1900 (33.5)
25 to <45 ml/min/1.73 m^2	1476 (52.1)	1505 (53.0)	2981 (52.5)
<25 ml/min/1.73 m^2	66 (2.3)	69 (2.4)	135 (2.4)
Missing data	1 (<0.1)	1 (<0.1)	2 (<0.1)
Urinary albumin-to-creatinine ratio‡			
Median (IQR)	833 (441–1628)	867 (453–1645)	852 (446–1634)
Distribution — no. (%)			
<30	11 (0.4)	12 (0.4)	23 (0.4)
30 to <300	350 (12.4)	335 (11.8)	685 (12.1)
≥300	2470 (87.2)	2493 (87.8)	4963 (87.5)
Missing data	2 (<0.1)	1 (<0.1)	3 (<0.1)
Serum potassium — mmol/liter	4.37±0.46	4.38±0.46	4.37±0.46

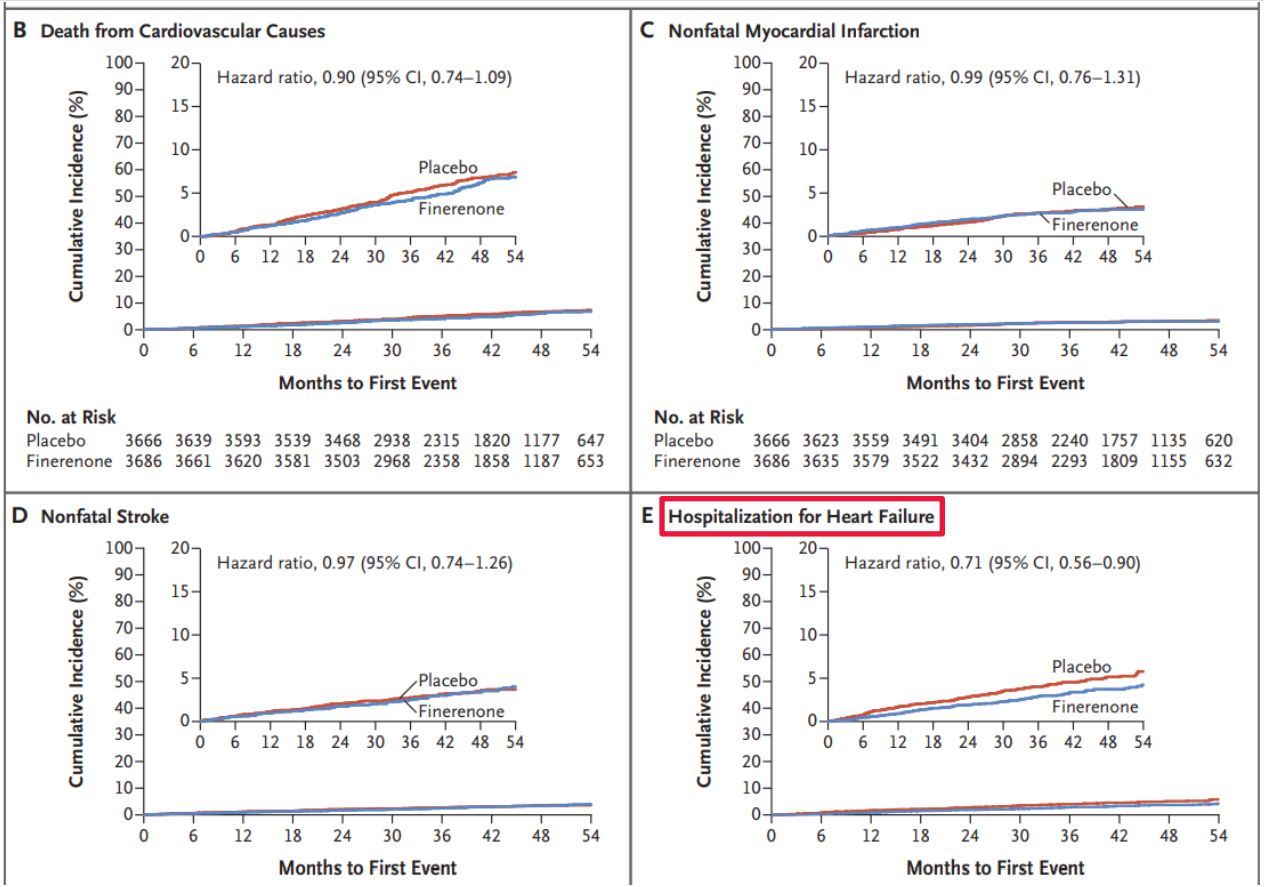
Results – Primary Outcome



EFFECTS ON PRIMARY COMPOSITE OUTCOME AND COMPONENTS

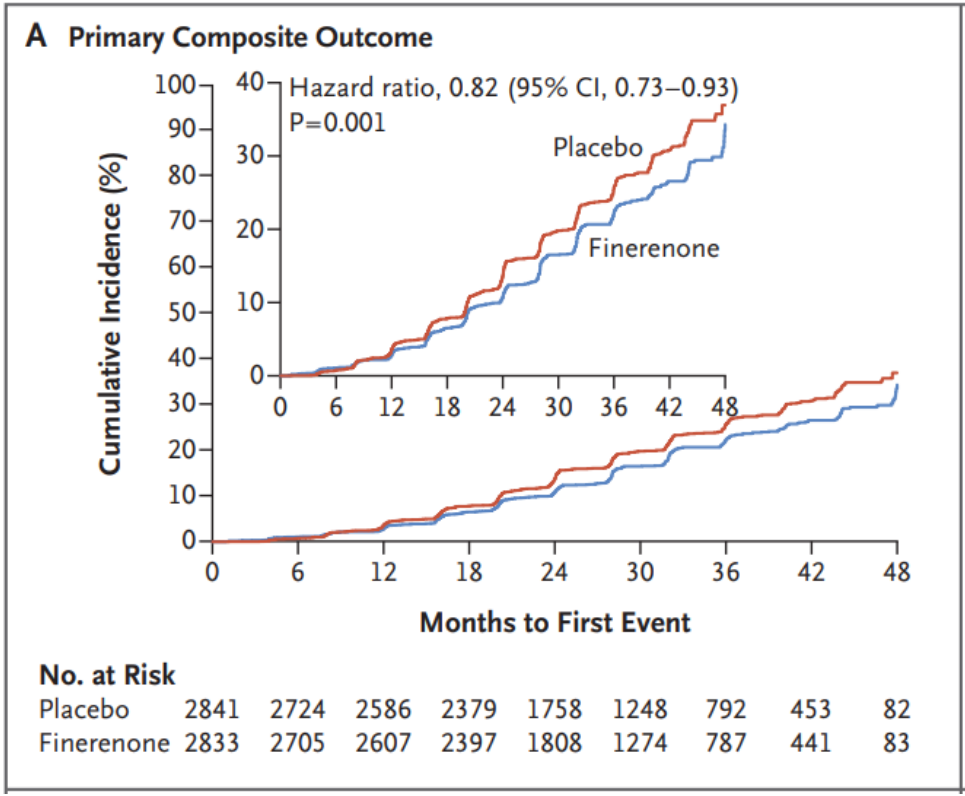
The incidence of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (the primary composite outcome) was significantly lower in the finerenone group than in the placebo group (458 of 3686 patients [12.4%] vs. 519 of 3666 patients [14.2%];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

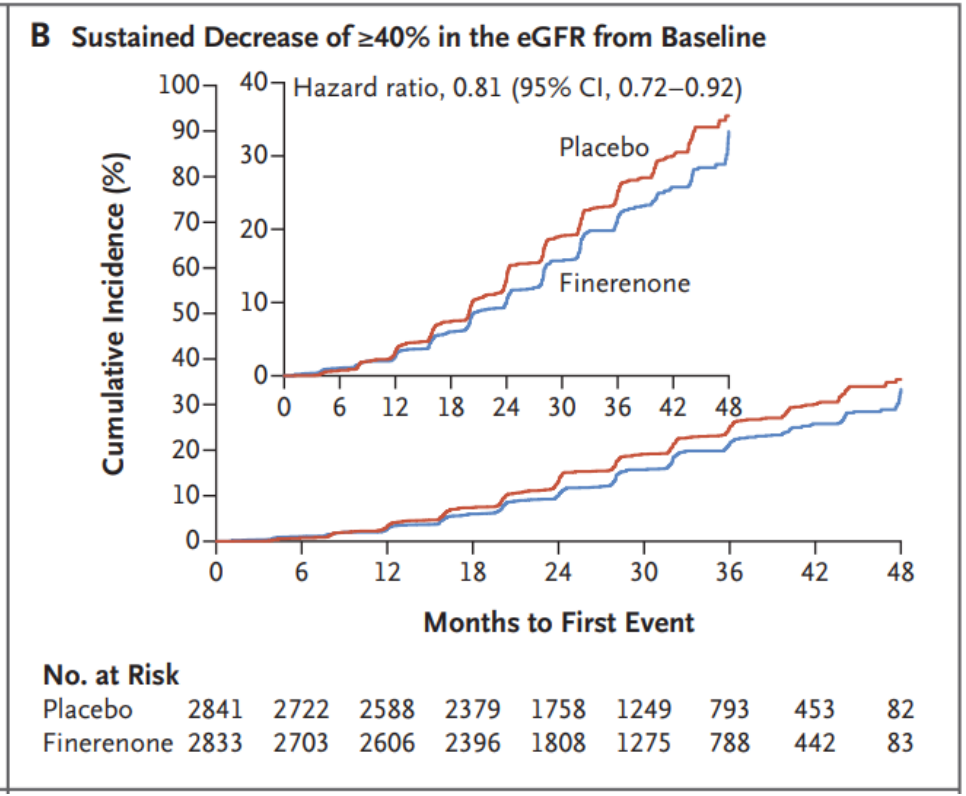
Results – Primary Outcome



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



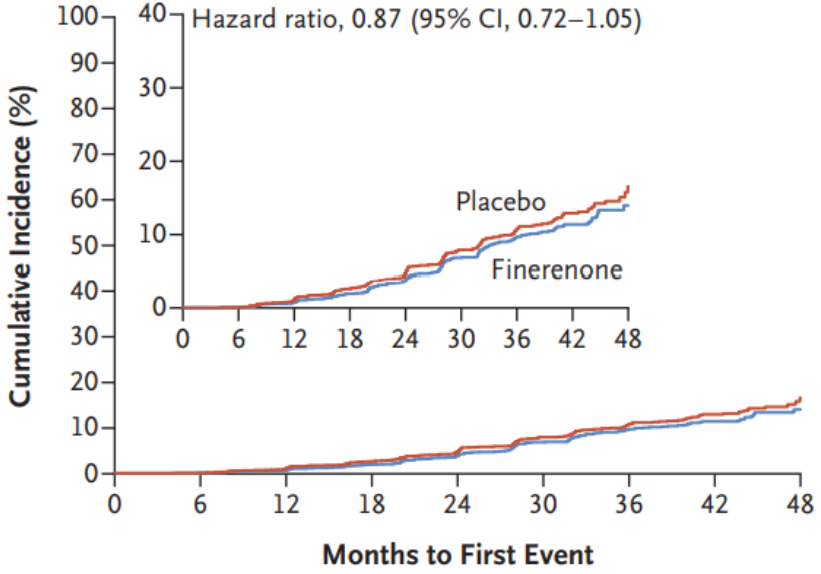


Results –Secondary Outcome

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

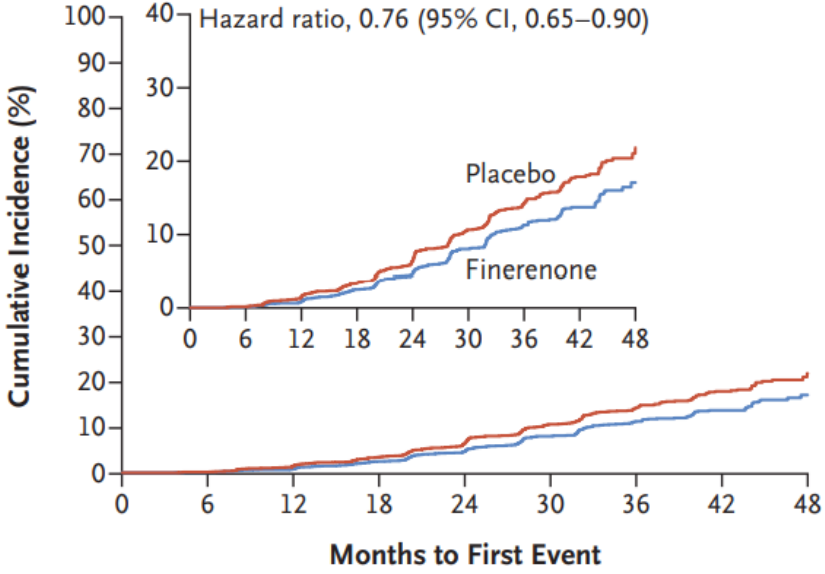
C Kidney Failure



No. at Risk

Placebo	2841	2741	2645	2508	1911	1390	892	513	103
Finerenone	2833	2733	2658	2506	1932	1393	897	510	104

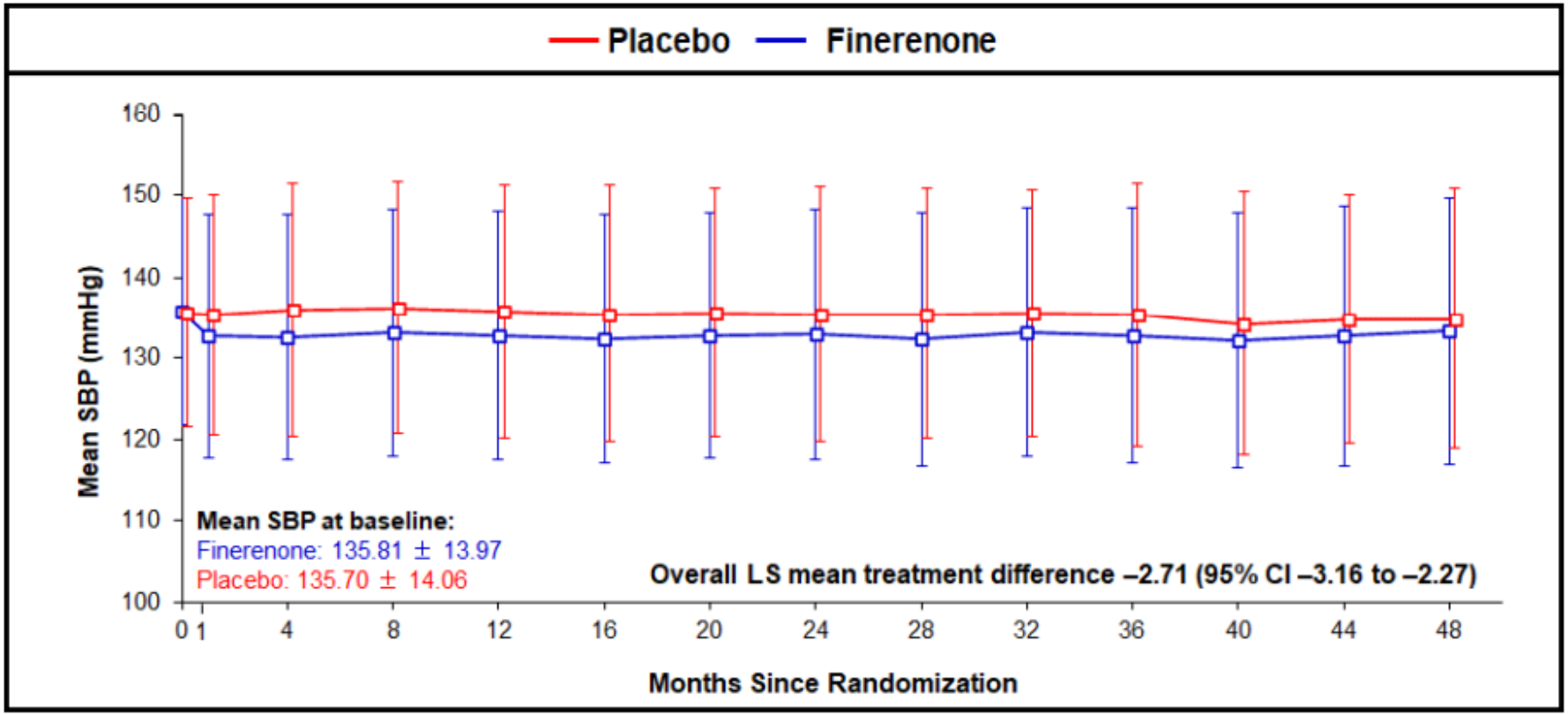
D Secondary Composite Outcome



No. at Risk

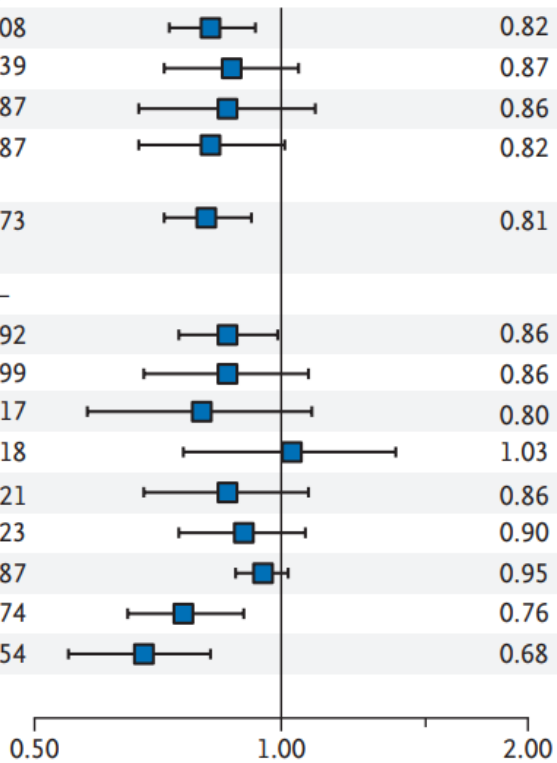
Placebo	2841	2740	2636	2490	1887	1364	873	499	98
Finerenone	2833	2732	2655	2492	1915	1377	883	501	101

Results – Other Outcomes



Results – Efficacy Outcomes

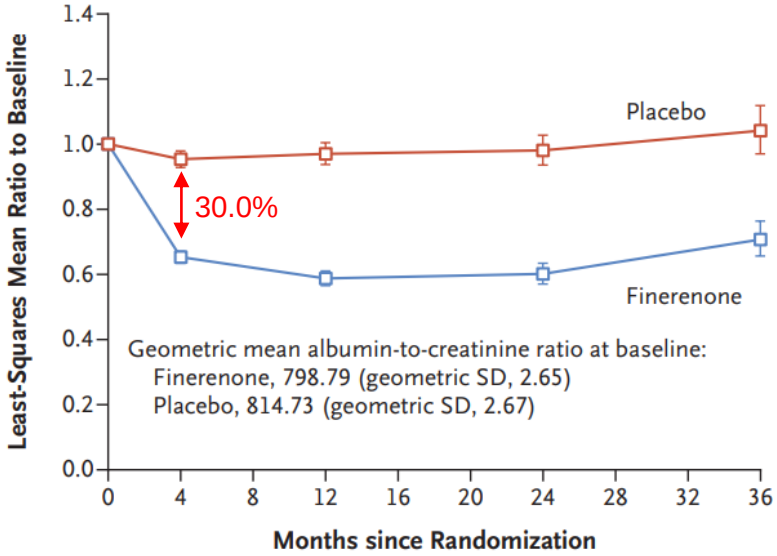
Outcome	Finerenone (N=2833)	Placebo (N=2841)	Finerenone (N=2833)	Placebo (N=2841)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	504 (17.8)	600 (21.1)	7.59	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	235 (8.3)	2.99	3.39	0.87 (0.72–1.05)	—
End-stage kidney disease	119 (4.2)	139 (4.9)	1.60	1.87	0.86 (0.67–1.10)	—
Sustained decrease in eGFR to <15 ml/min/1.73 m^2	167 (5.9)	199 (7.0)	2.40	2.87	0.82 (0.67–1.01)	—
Sustained decrease of ≥40% in eGFR from baseline	479 (16.9)	577 (20.3)	7.21	8.73	0.81 (0.72–0.92)	—
Death from renal causes	2 (<0.1)	2 (<0.1)	—	—	—	—
Key secondary composite outcome	367 (13.0)	420 (14.8)	5.11	5.92	0.86 (0.75–0.99)	0.03
Death from cardiovascular causes	128 (4.5)	150 (5.3)	1.69	1.99	0.86 (0.68–1.08)	—
Nonfatal myocardial infarction	70 (2.5)	87 (3.1)	0.94	1.17	0.80 (0.58–1.09)	—
Nonfatal stroke	90 (3.2)	87 (3.1)	1.21	1.18	1.03 (0.76–1.38)	—
Hospitalization for heart failure	139 (4.9)	162 (5.7)	1.89	2.21	0.86 (0.68–1.08)	—
Death from any cause	219 (7.7)	244 (8.6)	2.90	3.23	0.90 (0.75–1.07)	—
Hospitalization for any cause	1263 (44.6)	1321 (46.5)	22.56	23.87	0.95 (0.88–1.02)	—
Secondary composite kidney outcome	252 (8.9)	326 (11.5)	3.64	4.74	0.76 (0.65–0.90)	—
Sustained decrease of ≥57% in eGFR from baseline	167 (5.9)	245 (8.6)	2.41	3.54	0.68 (0.55–0.82)	—



Results – Effects on Albuminuria and Serum Potassium

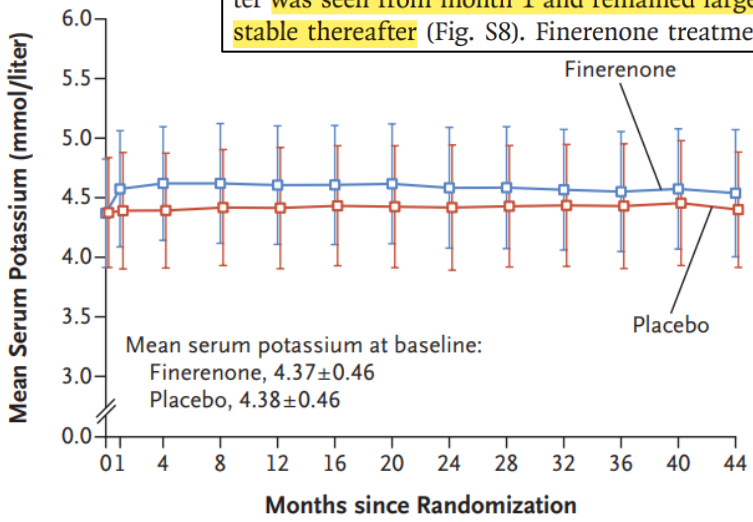
Finerenone treatment was associated with a greater increase in the serum potassium level from baseline than that observed with placebo. A between-group difference of 0.16 mmol per liter was seen from month 1 and remained largely stable thereafter (Fig. S8). Finerenone treatment

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=2827)	Placebo (N=2831)
	no. of patients (%)	
Any adverse event	2468 (87.3)	2478 (87.5)
Adverse event related to trial regimen	646 (22.9)	449 (15.9)
Adverse event leading to discontinuation of trial regimen	207 (7.3)	168 (5.9)
Any serious adverse event†	902 (31.9)	971 (34.3)
Serious adverse event related to trial regimen†	48 (1.7)	34 (1.2)
Serious adverse event leading to discontinuation of trial regimen†	75 (2.7)	78 (2.8)
Investigator-reported hyperkalemia‡	516 (18.3)	255 (9.0)
Hyperkalemia related to trial regimen	333 (11.8)	135 (4.8)
Serious hyperkalemia†	44 (1.6)	12 (0.4)
Hospitalization due to hyperkalemia	40 (1.4)	8 (0.3)
Permanent discontinuation of trial regimen due to hyperkalemia	64 (2.3)	25 (0.9)
Investigator-reported hypokalemia	28 (1.0)	61 (2.2)
Investigator-reported renal-related adverse events		
Acute kidney injury§	129 (4.6)	136 (4.8)
Hospitalization due to acute kidney injury§	53 (1.9)	47 (1.7)
Discontinuation of trial regimen due to acute kidney injury§	5 (0.2)	7 (0.2)
Hospitalization due to acute renal failure¶	70 (2.5)	71 (2.5)
Discontinuation of trial regimen due to acute renal failure¶	31 (1.1)	36 (1.3)
Adverse events affecting ≥5% of patients in either group§		
Hyperkalemia	446 (15.8)	221 (7.8)
Nasopharyngitis	241 (8.5)	250 (8.8)
Hypertension	212 (7.5)	273 (9.6)
Anemia	209 (7.4)	191 (6.7)
Peripheral edema	186 (6.6)	304 (10.7)

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**.

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 and CKD not due to type 2 diabetes.
- 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.