FINEHEART

Finerenone in Heart Failure and Chronic Kidney Disease with Type 2 Diabetes: the FINE-HEART Pooled Analysis of Cardiovascular, Kidney, and Mortality Outcomes

Muthiah Vaduganathan on behalf of

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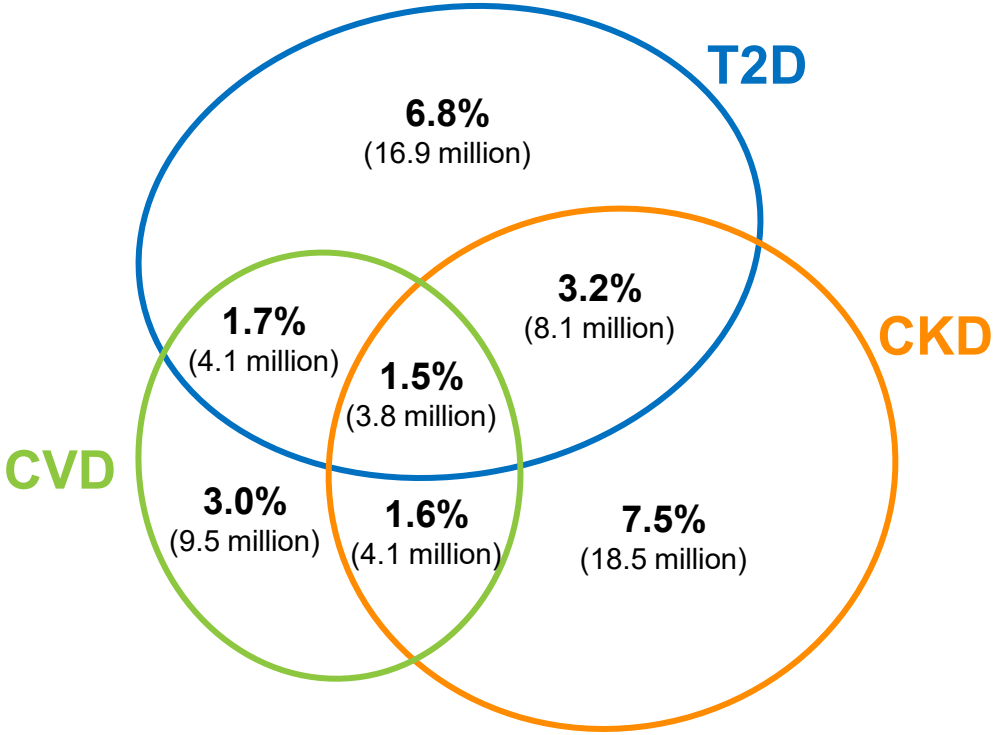
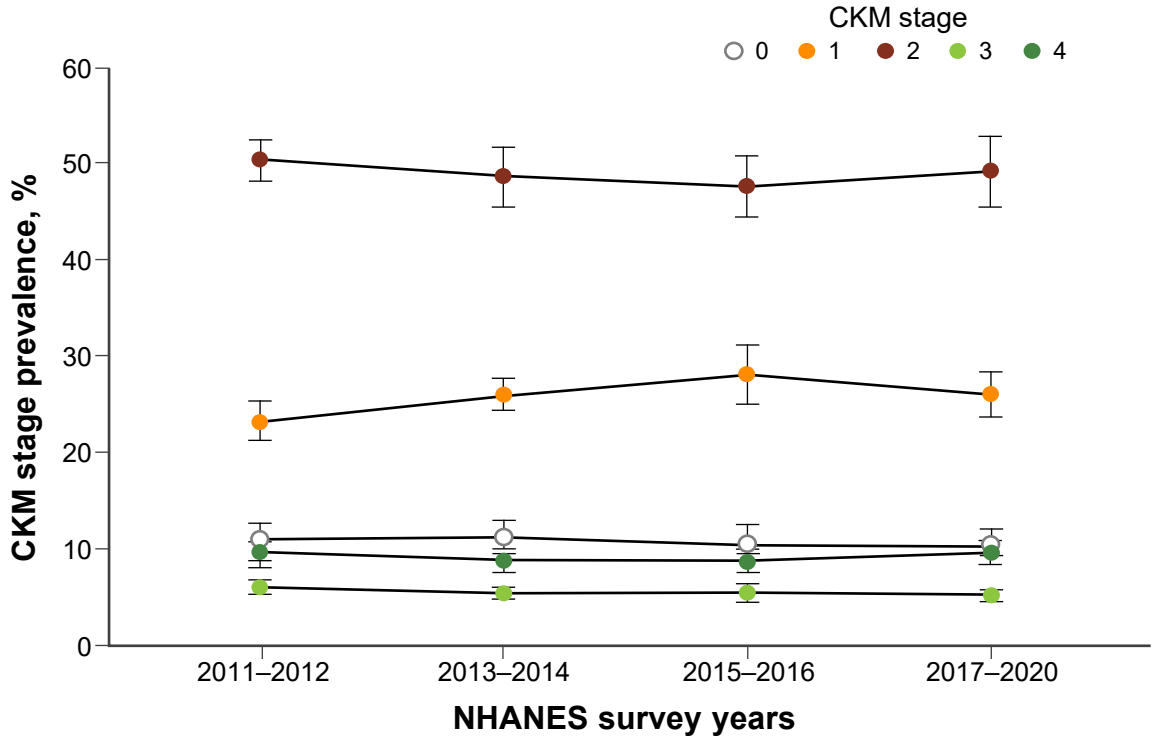
PROSPERO CRD42024570467

Strong Epidemiological Overlap of Cardiovascular, Metabolic, and Kidney Disorders

US NHANES survey cycles 1999–2020



US NHANES survey cycles 2011–2020

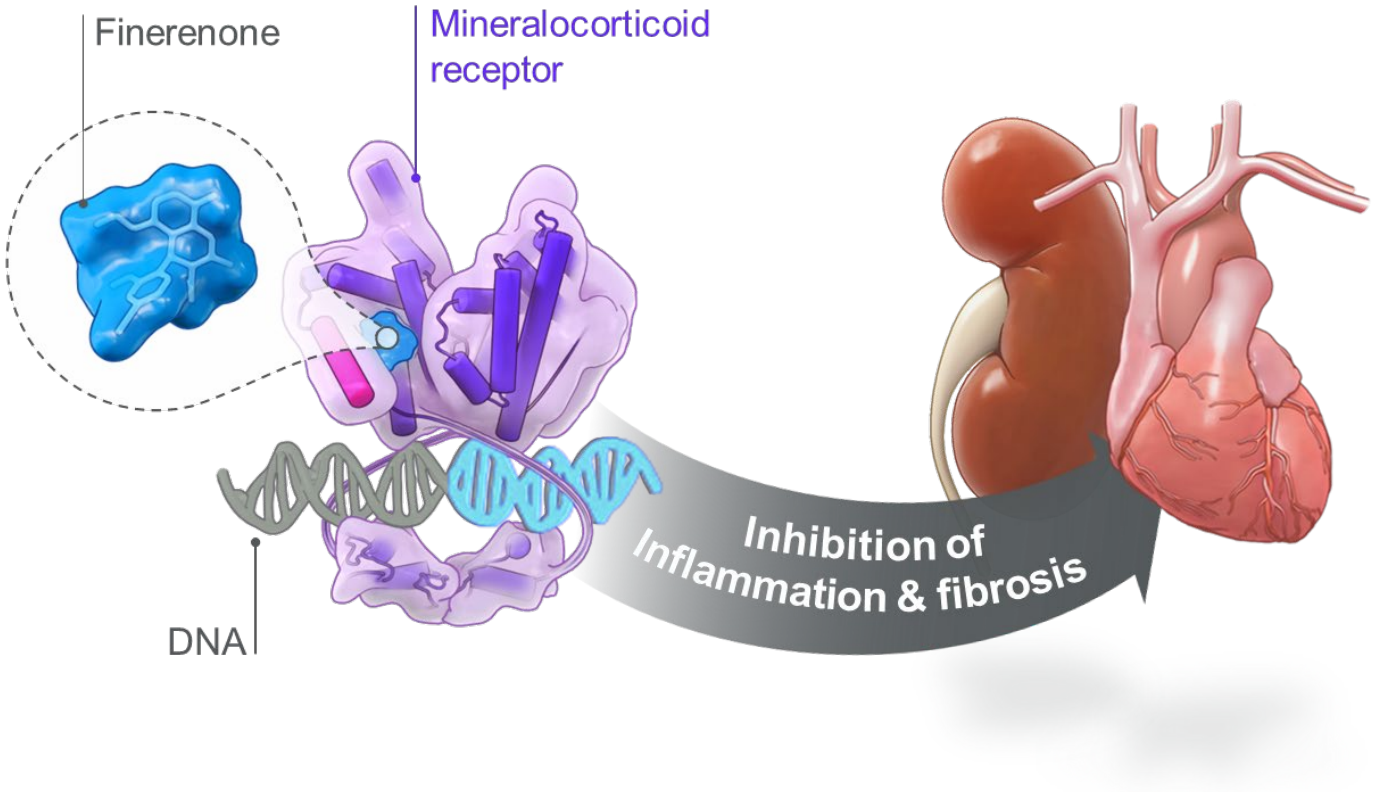


US NHANES Survey Cycles 1999-2020
Ostrominski J…Vaduganathan M. JAMA Cardiology 2023

US NHANES Survey Cycles 2011-2020
Aggarwal R…Vaduganathan M. JAMA 2024

Could the Non-Steroidal MRA, Finerenone, Modify Risk across the Cardio-Kidney-Metabolic Spectrum?

- **Finerenone is a non-steroidal MRA that has been studied in RCTs of patients with T2D and CKD and separately in patients with HF (with and without T2D).**
- **However, none of these trials were individually powered to evaluate treatment effects on mortality outcomes or effects in key subgroups.**



Design of FINE-HEART Umbrella Program

FINEHEART

Prospectively Registered:
PROSPERO CRD42024570467

(n=18,991 Participants)

FINEARTS-HF

FIDELIO-DKD

FIGARO-DKD

Pooling data in the FINE-HEART program increased precision to robustly assess the efficacy and safety of the non-steroidal MRA finerenone on important cardio-kidney outcomes and is enriched for participants with a high burden of CKM multimorbidity.

Study Designs of the Individual Trials

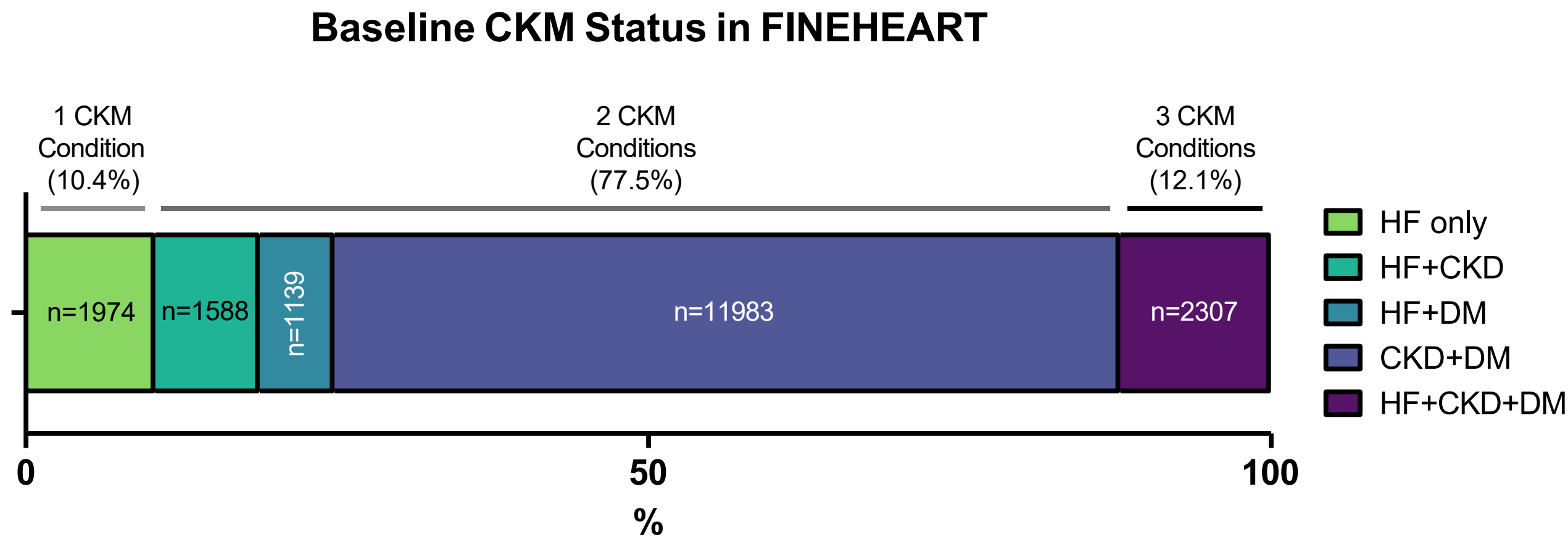
	FINEARTS-HF	FIDELIO-DKD and FIGARO-DKD
Validly Randomized	6,001	12,990
Countries	37	48
Patient population	HFmrEF or HFpEF	CKD and T2D
Inclusion criteria	• Adults (≥40 years) • Symptomatic HF • LVEF ≥40% • Elevation natriuretic peptides • Structural heart disease • Recent diuretic use	• Adults (≥18 years old) • T2D • UACR ≥ 30 mg/g • Maximally tolerated RASi
Exclusion criteria	Potassium ≤5.0 mmol/L	Potassium ≤4.8 mmol/L
Dosage and titration	eGFR ≤60: 10 up to 20 mg eGFR >60: 20 up to 40 mg (potentially down to 10 mg)	eGFR <60: 10 up to 20 mg eGFR ≥60: 20 mg (potentially down to 10 mg)
Study duration	2.6 years	2.6 years (FIDELIO-DKD) 3.4 years (FIGARO-DKD)

Baseline Characteristics of FINE-HEART Integrated Population

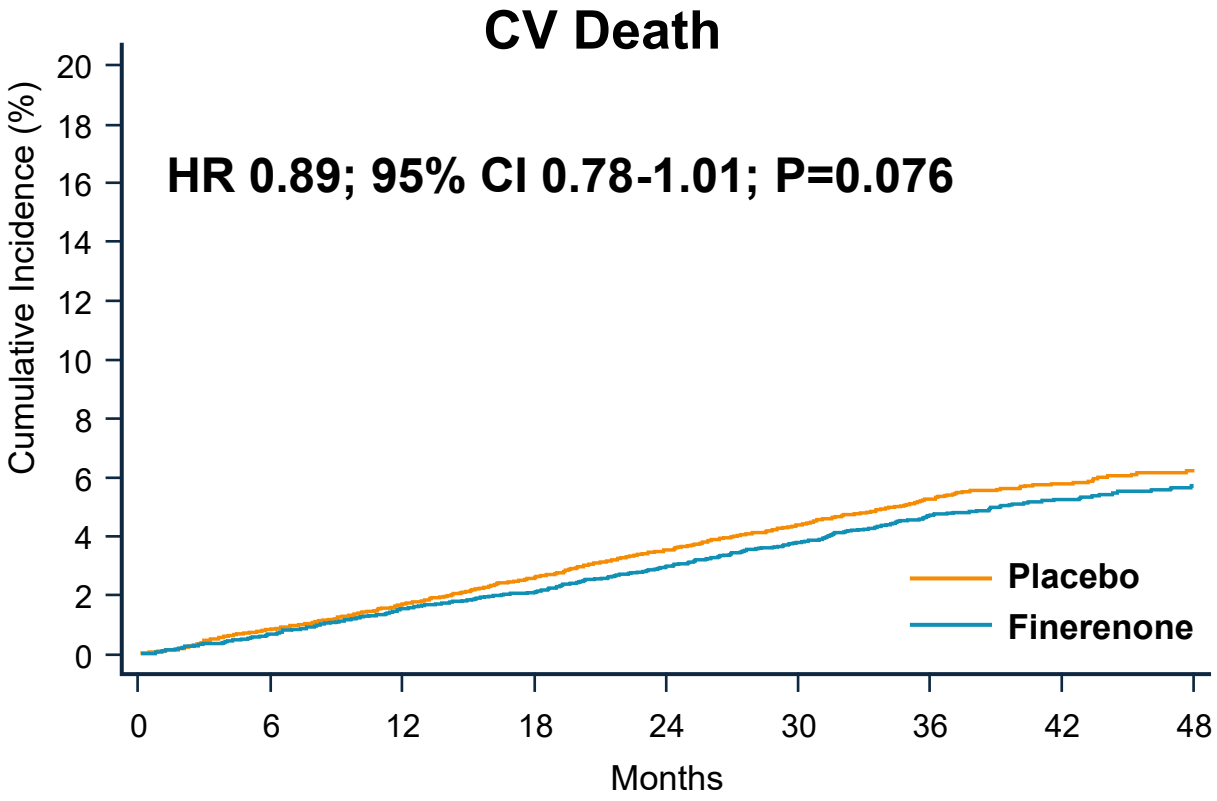
	Finerenone (n=9,501)	Placebo (n=9,490)
Age	67±10	67±10
Women	36%	35%
White Race	72%	72%
BMI (kg/m^2)	31±6	31±6
Systolic BP (mmHg)	135±15	134±15
Potassium (mmol/L)	4.4±0.5	4.4±0.5
eGFR (mL/min/1.73m^2)	59±21	59±21
<25	1%	1%
25 to <45	29%	29%
45 to <60	27%	26%
≥60	44%	44%
UACR (mg/g)	283 [46-836]	293 [47-855]
A1: <30	20%	20%
A2: 30 to <300	31%	31%
A3: ≥300	49%	50%

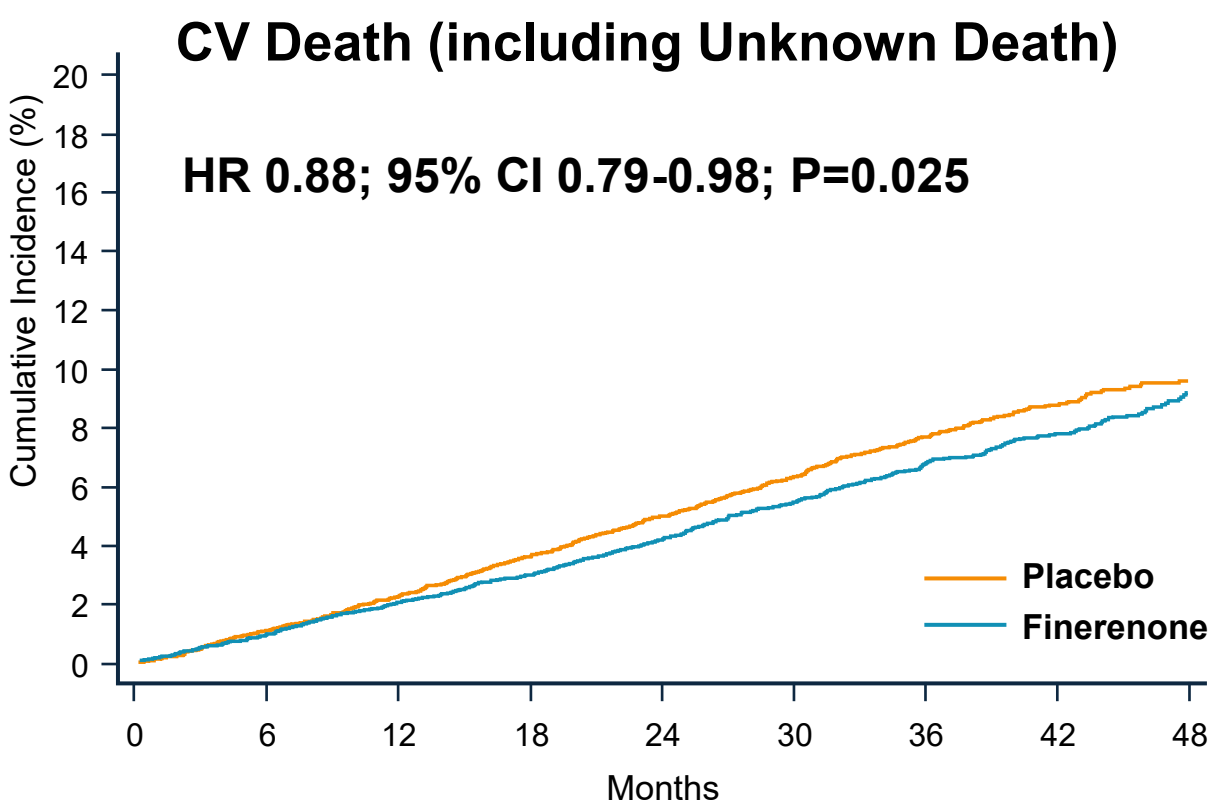
	Finerenone (n=9,501)	Placebo (n=9,490)
HbA1c (%)	7.3±1.4	7.3±1.4
HF	37%	37%
Diabetes	81%	81%
CKD	84%	84%
AF	15%	15%
Diuretics	66%	67%
ACEi/ARB/ARNI	93%	93%
Statins	70%	71%
SGLT2i	9%	9%
GLP-1RA	6%	6%

High Burden of Cardio-Kidney-Metabolic Disease Overlap



Primary Endpoint: CV Death

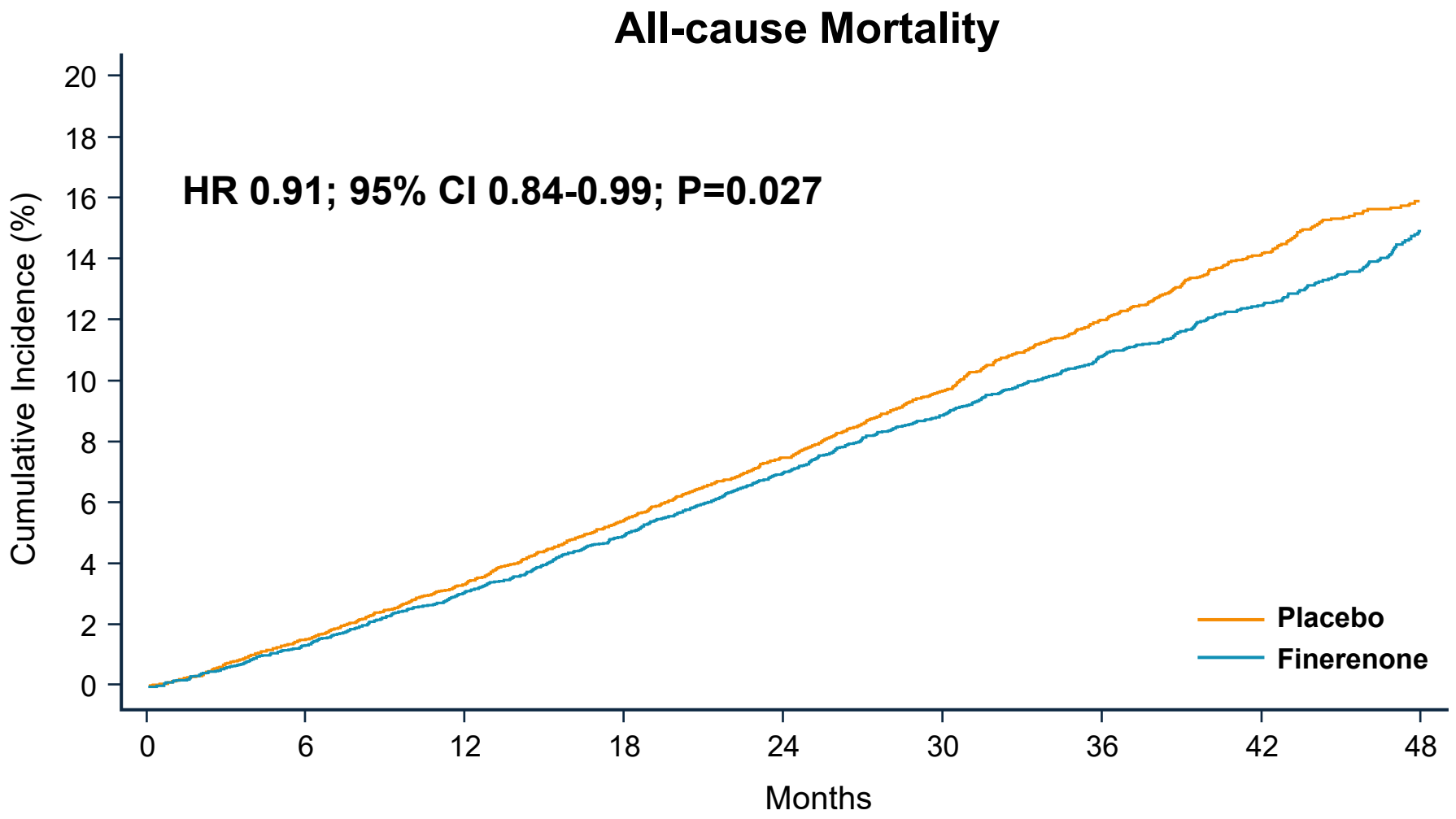




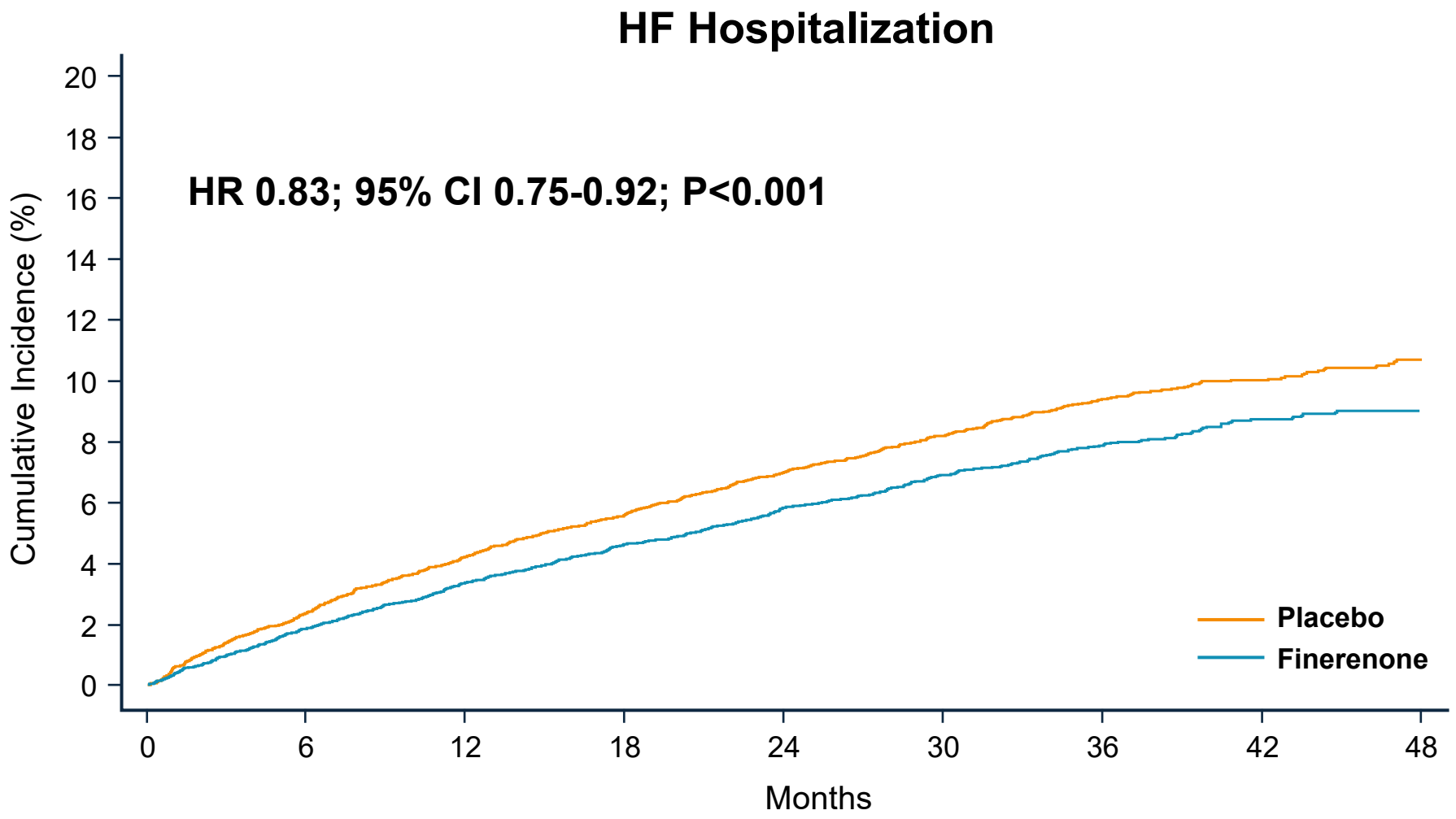
Primary Analysis:
CV Death Excluding Unknown Deaths
Finerenone 421 (4.4%) vs. Placebo 471 (5.0%)

Prespecified Sensitivity Analysis:
CV Deaths Including Unknown Deaths
Finerenone 627 (6.6%) vs. Placebo 703 (7.4%)

Secondary Endpoint: All-Cause Mortality

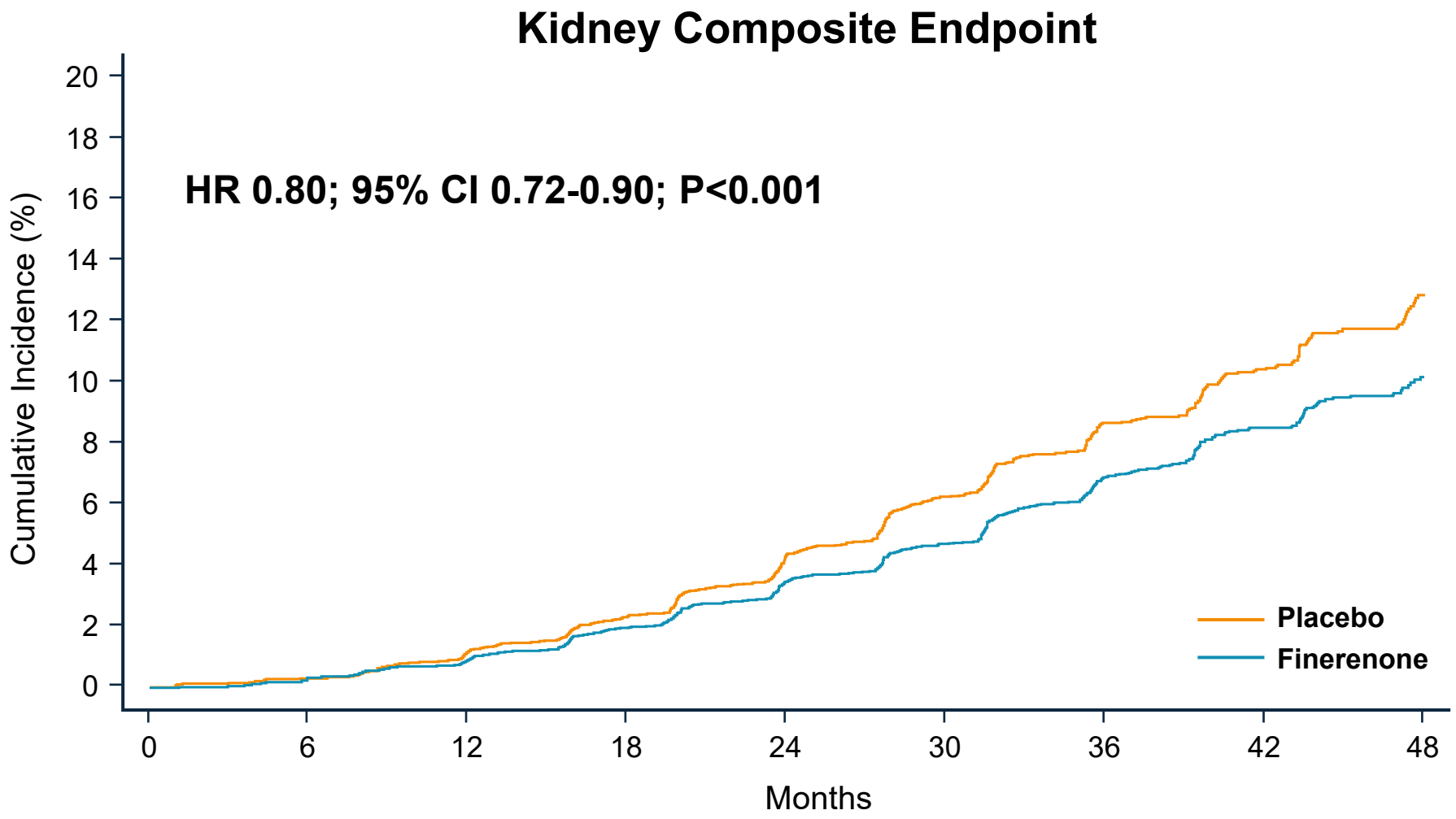


Secondary Endpoint: HF Hospitalization



Secondary Endpoint: Kidney Composite Endpoint

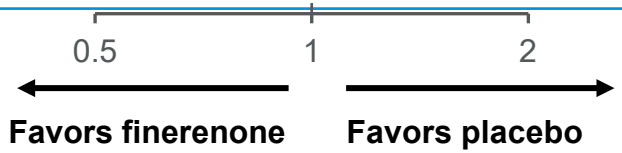
sustained eGFR decline of ≥50%, kidney failure*, or death due to kidney failure



*sustained eGFR < 15 ml/min/1.73m^2, chronic dialysis, or kidney transplantion

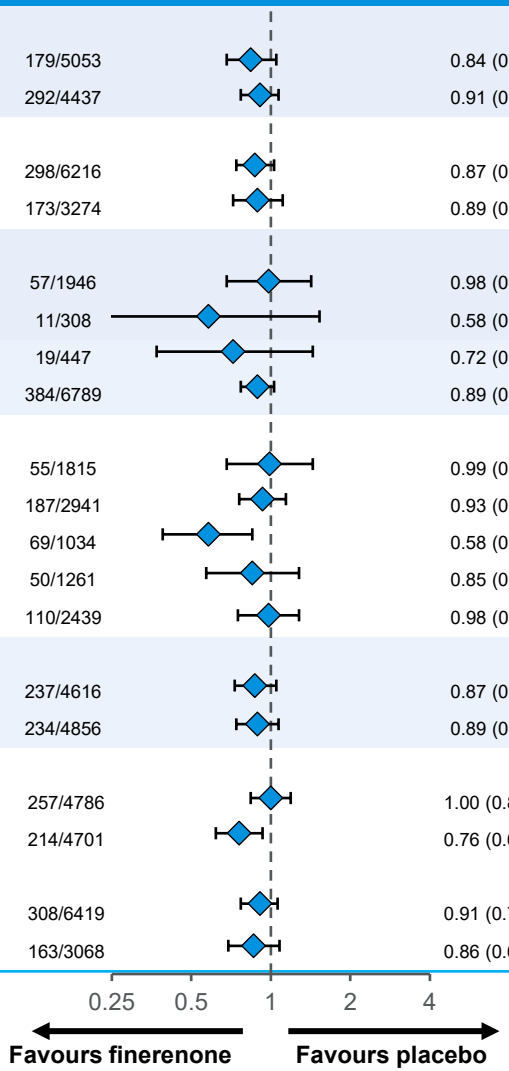
Summary of Prespecified Efficacy Endpoints

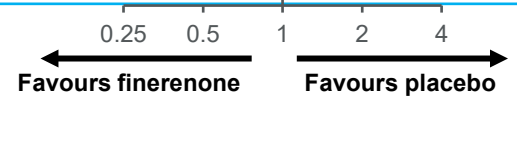
Outcome	HR (95% CI)	P-value
Primary Endpoint		
CV death (excluding undetermined death)	0.89 (0.78–1.01)	0.076
Prespecified sensitivity analysis: CV death (including undetermined death)	0.88 (0.79–0.98)	0.025
Secondary Endpoints		
Kidney Composite Endpoint	0.80 (0.72–0.90)	<0.001
HF Hospitalization	0.83 (0.75–0.92)	<0.001
CV Death or HF Hospitalization	0.85 (0.78–0.93)	<0.001
New-onset Atrial Fibrillation	0.83 (0.71–0.97)	0.018
Major Adverse Cardiovascular Events	0.91 (0.85–0.98)	0.010
All-cause Death	0.91 (0.84–0.99)	0.027
All-cause Hospitalization	0.95 (0.91–0.99)	0.025
All-cause Death or All-cause Hospitalization	0.94 (0.91–0.98)	0.007



Broad Consistency Across 17 Prespecified Subgroups for the Primary Endpoint (CV Death)

Category	Finerenone (n=9501) n/N	Placebo (n=9490) n/N	HR (95% CI)
Age			
≤ Median	149/5071	179/5053	0.84 (0.68–1.05)
>Median	272/4430	292/4437	0.91 (0.77–1.07)
Sex			
Male	265/6111	298/6216	0.87 (0.74–1.03)
Female	156/3390	173/3274	0.89 (0.72–1.11)
Race			
Asian	56/1910	57/1946	0.98 (0.68–1.42)
Black	7/300	11/308	0.58 (0.22–1.53)
Other	15/476	19/447	0.72 (0.37–1.44)
White	343/6815	384/6789	0.89 (0.77–1.03)
Region			
Asia	56/1808	55/1815	0.99 (0.68–1.44)
Eastern Europe	176/3001	187/2941	0.93 (0.76–1.14)
Latin America	40/1041	69/1034	0.58 (0.39–0.85)
North America	43/1259	50/1261	0.85 (0.57–1.28)
Western Europe, Oceania, Others	107/2392	110/2439	0.98 (0.75–1.28)
Baseline BMI (kg/m^2)			
<30 mg/m^2	210/4591	237/4616	0.87 (0.73–1.05)
≥30kg/m^2	210/4880	234/4856	0.89 (0.74–1.07)
Baseline Systolic Blood Pressure (mmHg)			
≤ Median	254/4790	257/4786	1.00 (0.84–1.19)
>Median	1664/4707	214/4701	0.76 (0.62–0.93)
Baseline Serum Potassium			
≤4.5 mmol/L	284/6746	308/6419	0.91 (0.77–1.06)
>4.5 mmol/L	137/3024	163/3068	0.86 (0.69–1.08)
KDIGO Risk Categories			
Low risk	48/1052	50/1034	0.94 (0.63–1.39)
Moderately increased risk	84/1545	88/1455	0.89 (0.66–1.20)
High risk	1203/3184	161/3318	0.78 (0.61–0.98)
Very high risk	157/3616	161/3577	0.96 (0.77–1.20)
History of HF			
Present	273/3488	299/3520	0.92 (0.78–1.08)
Absent	148/6013	172/5970	0.85 (0.68–1.06)
History of Diabetes Mellitus			
Present	294/7715	343/7714	0.85 (0.73–1.00)
Absent	127/1786	128/1776	0.98 (0.77–1.25)
History of CKD			
Present	330/7949	363/7929	0.90 (0.77–1.04)
Absent	91/1552	108/1561	0.84 (0.64–1.11)
Cardio-Kidney-Metabolic Conditions			
1 Condition	58/996	61/978	0.93 (0.65–1.33)
2 Conditions	250/7359	286/7351	0.87 (0.74–1.03)
3 Conditions	113/1146	124/1161	0.91 (0.71–1.18)
GLP-1RA at Baseline			
No	403/8925	453/8956	0.88 (0.77–1.01)
Yes	18/576	18/534	1.05 (0.54–2.07)
SGLT2i at Baseline			
No	375/8672	422/8629	0.88 (0.76–1.01)
Yes	46/829	49/861	0.96 (0.64–1.44)





Safety Outcomes

	Finerenone	Placebo
	n=9,482	n=9,467
Any serious adverse event	35%	37%
Any ae leading to treatment discontinuation	5%	5%
Any potassium >5.5 mmol/L	17%	8%
Any potassium >6.0 mmol/L	3%	1%
Any potassium <3.5 mmol/L	5%	10%
Hyperkalemia	13%	6%
Hyperkalemia leading to discontinuation	1.3%	0.5%
Hyperkalemia leading to hospitalization	0.8%	0.2%
Hyperkalemia leading to death	0%	0%
Acute kidney injury	4%	3%
Acute kidney injury leading to discontinuation	0.2%	0.1%
Acute kidney injury leading to hospitalization	2%	1%
Systolic blood pressure<100mmHg	11%	7%
Gynecomastia or breast hyperplasia	0.2%	0.2%

Treatment-emergent adverse events are defined as any adverse event occurring in any patient who has received at least one dose of study drug and within 3 days of permanent discontinuation. This safety table includes 1 patient who was randomized to placebo but who actually received finerenone.

Conclusions

- The FINE-HEART participant-level pooled analysis represents the largest analysis of the effects of the non-steroidal MRA finerenone across the CKM spectrum.
- While this pooled analysis failed to demonstrate significant reductions in cardiovascular death, finerenone was associated with significantly lower deaths of any cause, cardiovascular events, and kidney outcomes.
- Treatment effects were consistent across all tested clinical subgroups including those with multiple intersecting CKM conditions and on background SGLT2i or GLP-1RA.
- No new or unexpected safety signals were uncovered in this pooled analysis.

The totality of the evidence supports the disease-modifying potential of finerenone in broad, high-risk patient populations encompassing cardiovascular, kidney, and metabolic diseases.

Full Details Available Online in *Nature Medicine*

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In Memory of the Late Dr. George Bakris (1952-2024)

A pioneer in cardio-kidney-metabolic research,
physician, leader, colleague, and dear friend