Heart Failure with Preserved or Mildly Reduced Ejection Fraction

Impacting Clinical Outcomes with Non-steroidal MRAs

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Declaration

- **I have no disclosure.**

Outline

- Introduction
- Burden and Mortality risk across spectrum of HF
- Stages of CKM Syndrome & Epidemiological overlap between HF & CKD
- Key pathophysiological mechanism
- Challenge in Management of Patients with HFpEF/HFmrEF
- Improving Clinical Outcomes in HFpEF/HFmrEF with Non-steroidal MRAs
- Conclusion

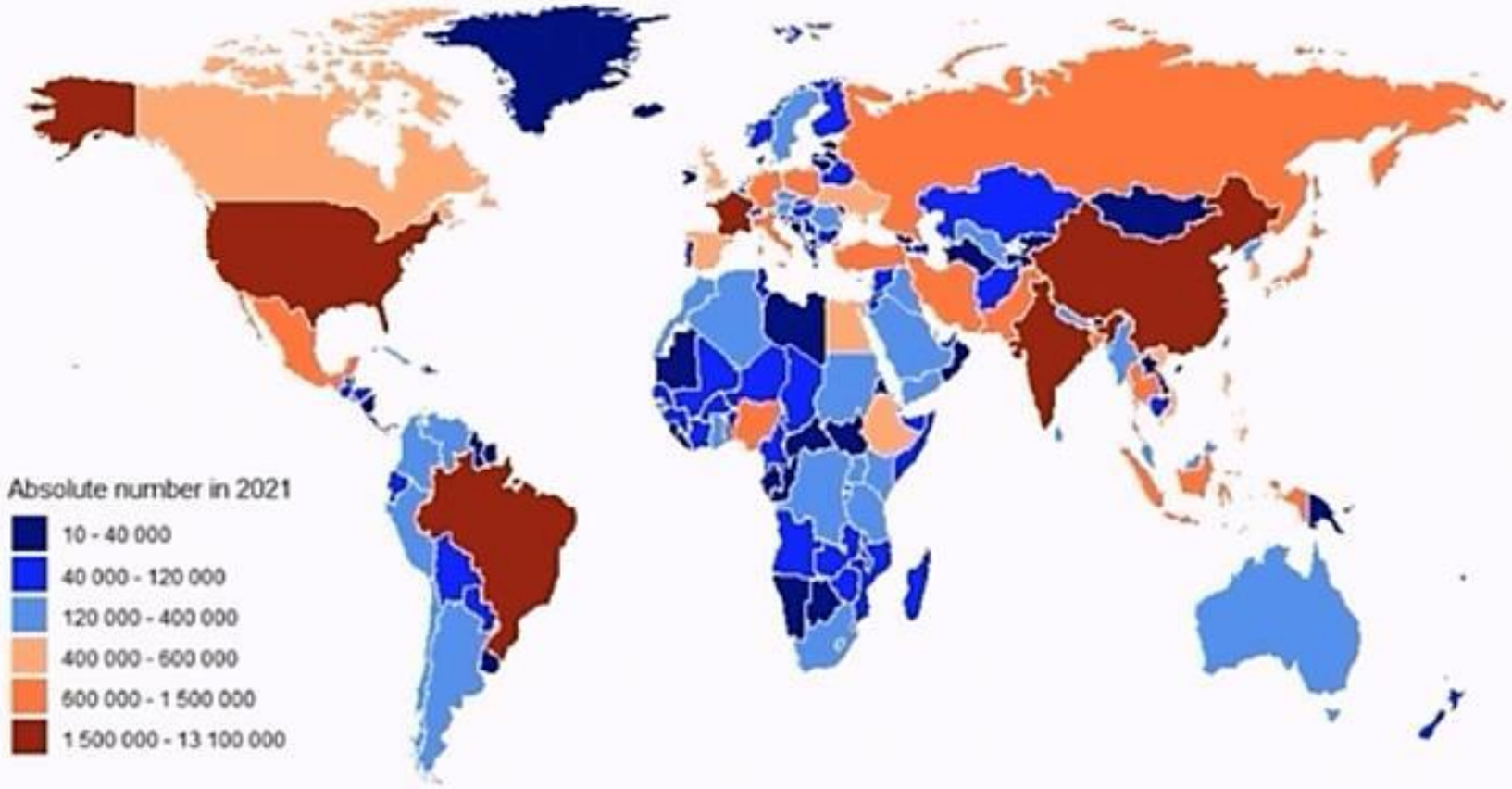
Introduction

- **Heart failure with mildly reduced or preserved ejection fraction (EF ≥40%) poses a treatment challenge with limited targeted therapies.**
- **SGLT2 inhibitors have shown benefits, but gaps remain in effective treatments for this population.**
- **Steroidal MRAs (e.g., spironolactone) have demonstrated efficacy in HF with reduced EF, but their role in preserved EF remains uncertain.**
- **Finerenone, a nonsteroidal MRA, has shown promise in chronic kidney disease and HF with diabetes, warranting investigation in a broader HF population.**

Global prevalence of HF

GBD data on 204 countries and territories, 2021

- 56.2 million (95%UI 46.4 - 67.8) people live with HF
- >½ have HFpEF



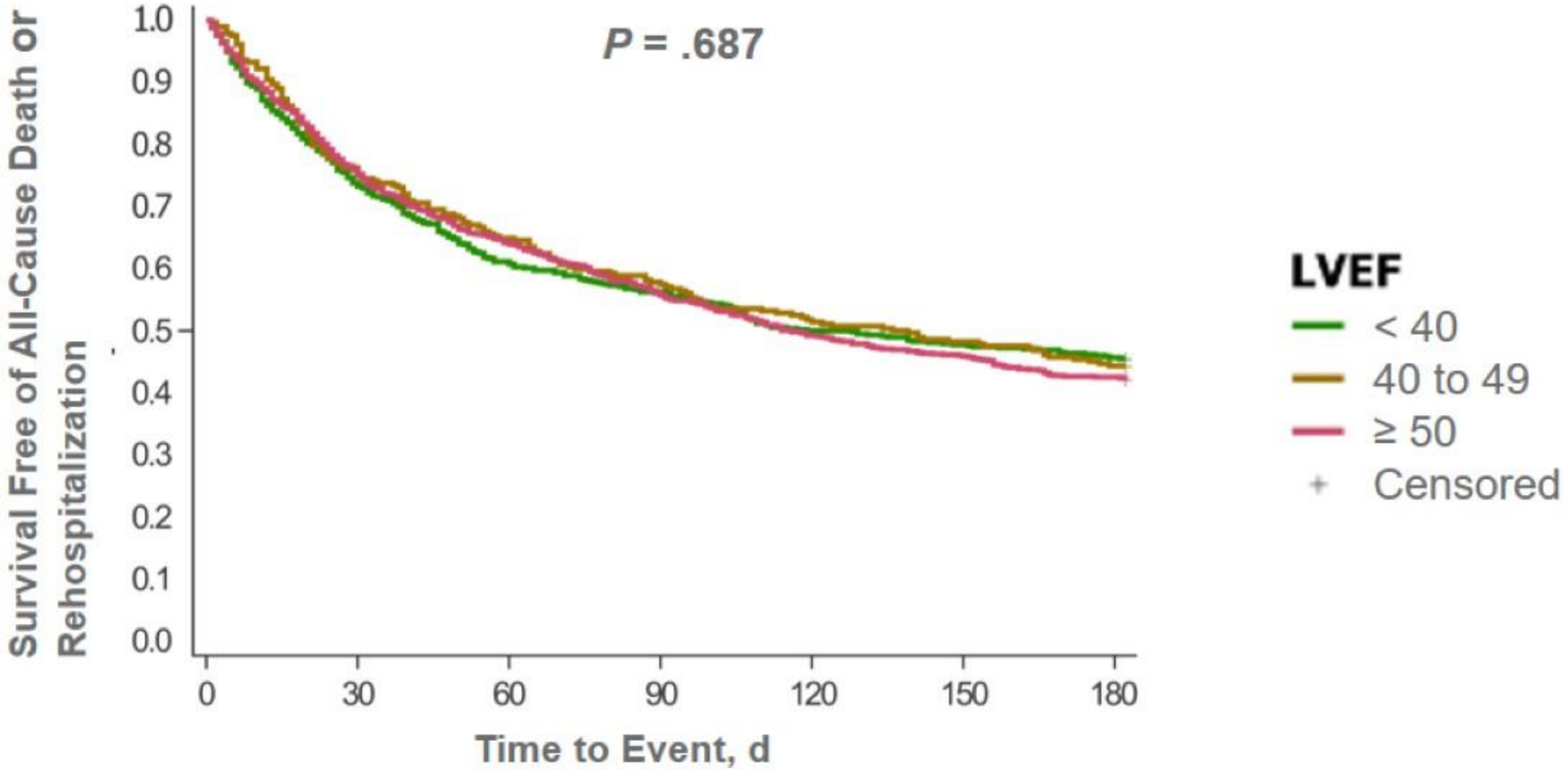
Wei S, Miranda JJ, Mamas MA, Zuhlke L, Kontapantelis E, Thabane L, **Van Spall HGC**. EHJ QCCO 2022
Beaudry G, … **Van Spall HGC**. EJHF 2025

@hvanspall

HF Portends High Risk Across LVEF Categories

PACT-HF: Substudy of the Patient-Centered Care Transitions in HF Trial (N = 1693)[1,2]

6-MO Risk of Death/Readmission = 56%

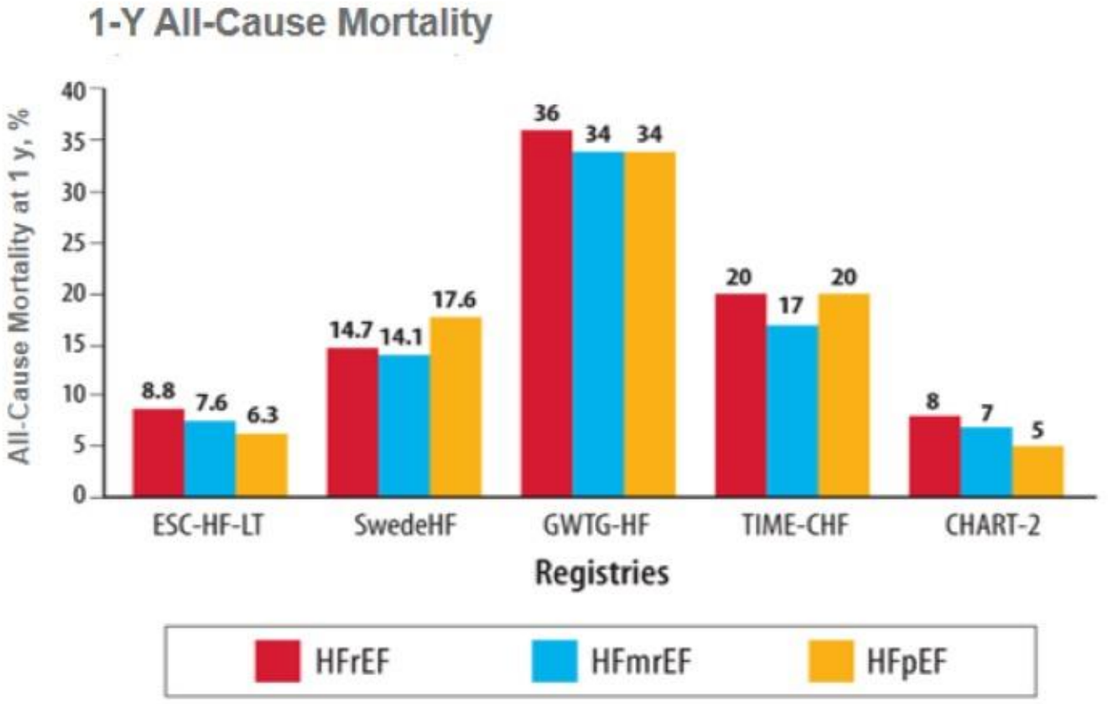


d, day.

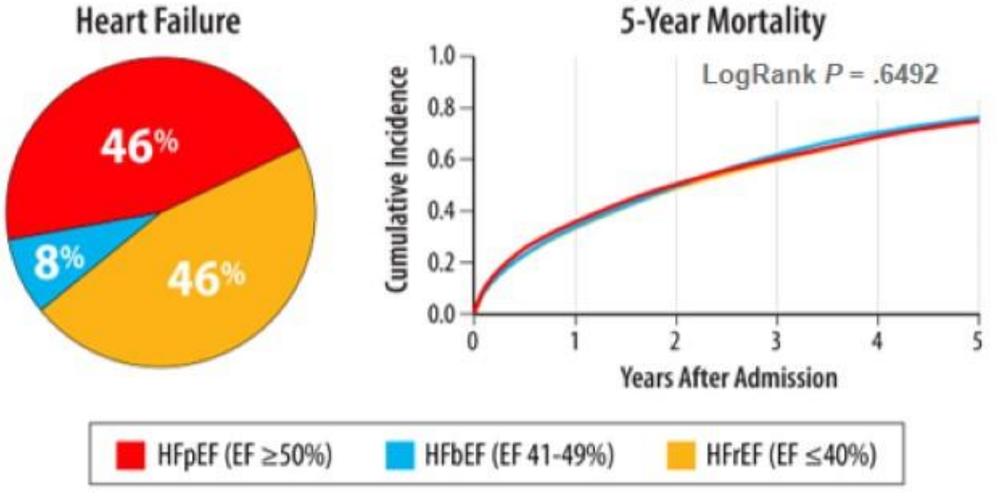
1. Gevaert AB, et al. ESC Heart Fail. 2021;8:2741-2754; 2. Van Spall HGC, et al. JAMA. 2019;321:753-761.

Mortality Rates in Patients With HFrEF, HFmrEF, and HFpEF Are Similar

1-Y All-Cause Mortality in Registries Across the EF Spectrum[1]



GWTG-HF: 5-Y Outcomes in Patients Hospitalized With HFpEF, HFbEF, and HFrEF (N = 39,982)[2],a



Outcomes: 5-Year Event Rates (%)

	Mortality	Readmission	CV Readmission	HF Readmission	Mortality/Readmission
HFrEF	75.3	82.2	63.9	48.5	96.4
HFbEF	75.7	85.7	63.3	45.2	97.2
HFpEF	75.7	84.0	58.9	40.5	97.3

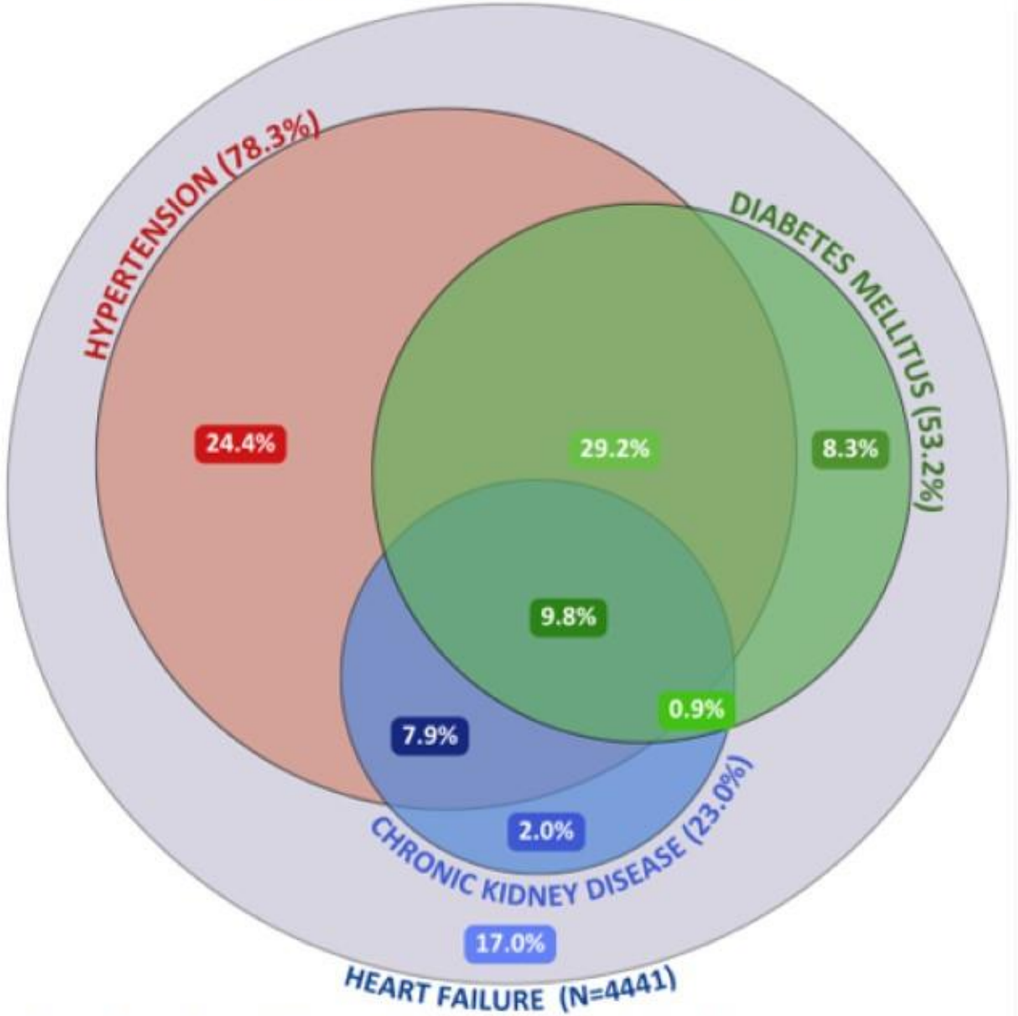
[a]In the new HF guidelines, HFbEF has been changed to HFmrEF.

ESC-HF-LT, European Society of Cardiology Heart Failure Long-Term Registry; GWTG-HF, Get With The Guidelines Heart Failure Registry; HFbEF, HF with borderline EF; NA, not available; RCT, randomized controlled trial; SwedeHF, Swedish Heart Failure Registry.

1. Adapted from Savarese G, et al. Nat Rev Cardiol. 2022;19:100-116; 2. Modified from Shah KS, et al. J Am Coll Cardiol. 2017;70:2476-2486.

CKD Is Common in HF and Increases the Risk of Death
PACT-HF RCT Exploratory Analysis

1/4 at Incident HFH



Unadjusted Survival by CKD Status

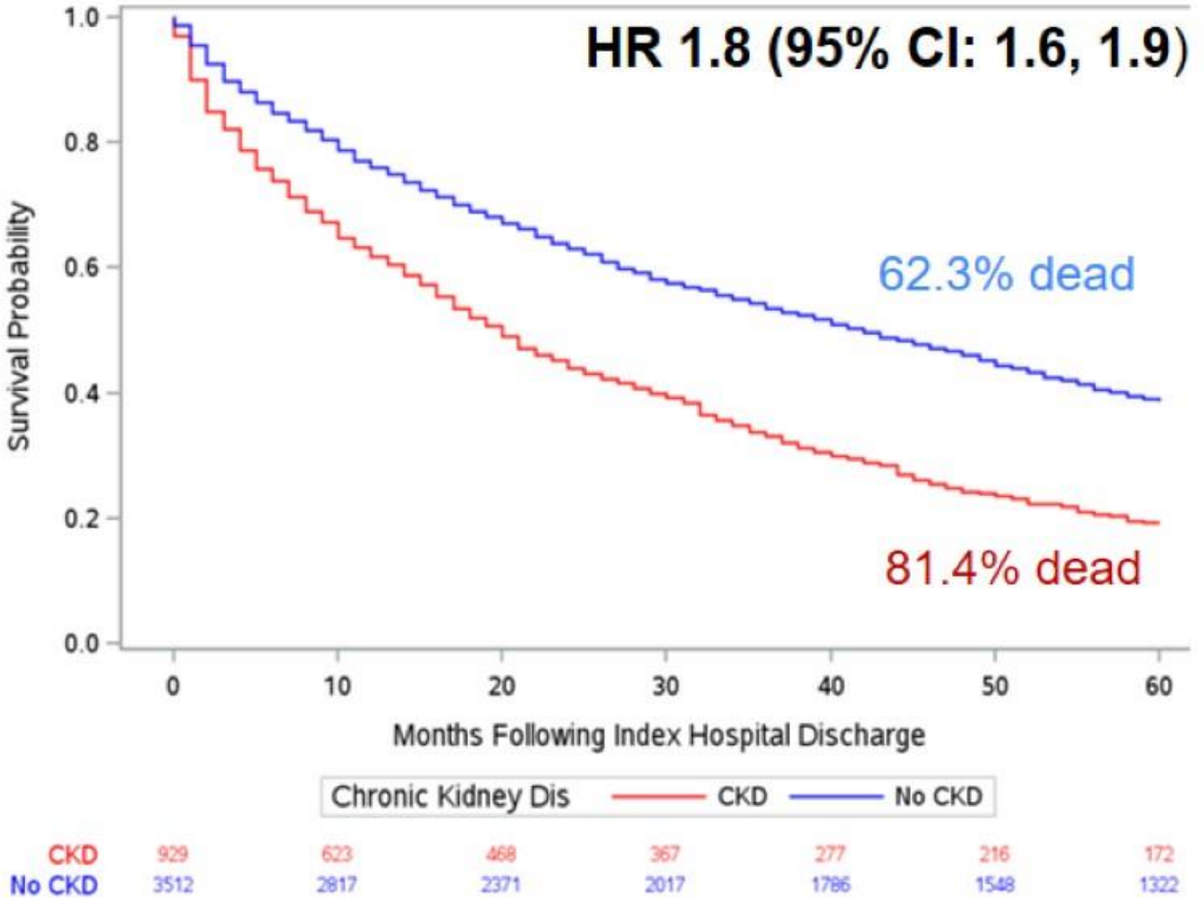


Image Courtesy of Harriette G.C. Van Spall, MD, MPH, FRCPC (Cardiologist).

Averbuch T, Van Spall HGC, et al. Under review. Van Spall HGC, et al. JAMA. 2019;321:753-761.

Stages of Cardiovascular-Kidney-Metabolic (CKM) Syndrome

From the Presidential Advisory from the American Heart Association

Stage 0:
No Risk Factors

A focus on primordial prevention and preserving cardiovascular health

Stage 1:
Excess/Dysfunctional Adipose Tissue

- Overweight/obesity
- Abdominal obesity
- Impaired glucose tolerance

Stage 2: Metabolic Risk Factors

- Hypertension
- Hypertriglyceridemia
- Metabolic syndrome
- Moderate- to high-risk CKD
- Type 2 diabetes

Nonmetabolic etiologies of hypertension

Nonmetabolic etiologies of CKD

Stage 3: Subclinical CVD in CKM Syndrome

- Subclinical HF
- Subclinical ASCVD

Stage 4: Clinical CKM Disease

- Stroke
- CHD
- HF
- PAD
- Afib

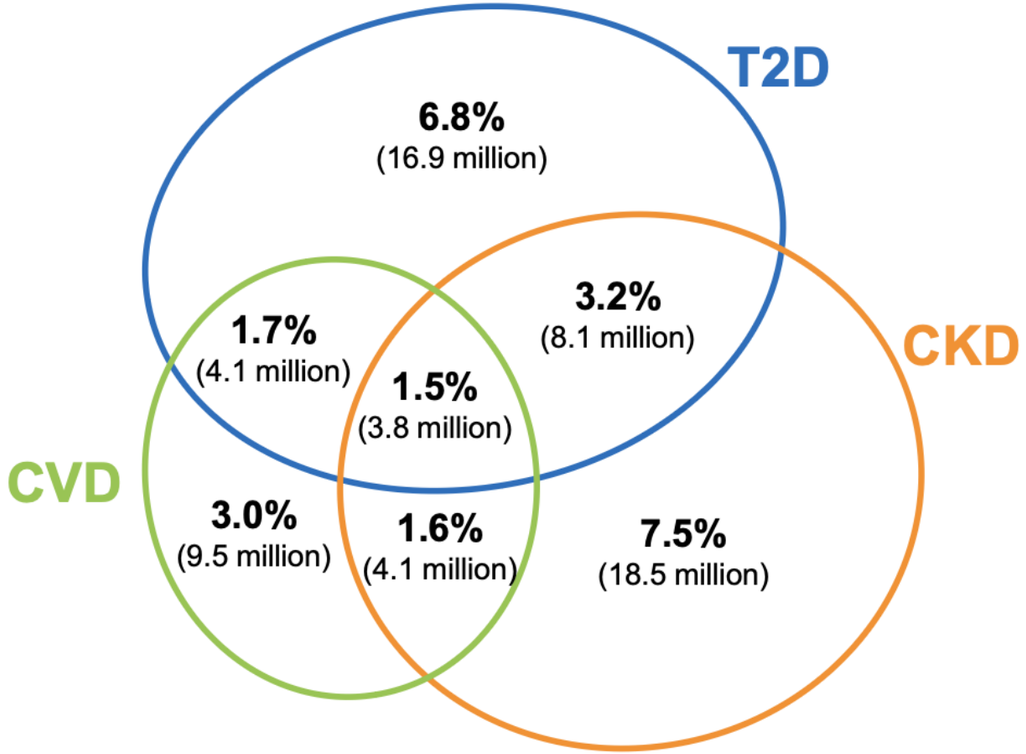
Risk equivalents of subclinical CKD in CKM Stage 3:
- Very high-risk CKD (G stage 4 and 5 CKD or by KDIGO heat map)

- Afib, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure; KDIGO, Kidney Disease Improving Global Outcomes; PAD, peripheral artery disease.

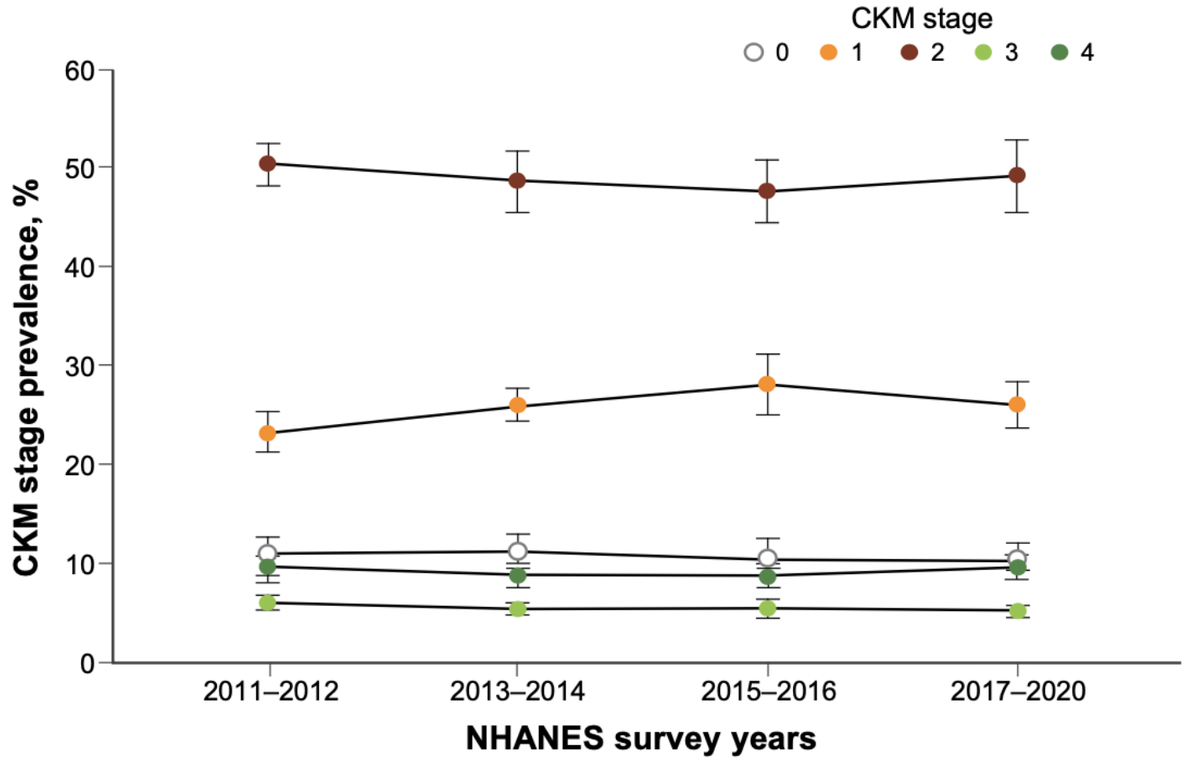
Ndumele CE, et al. Circulation. 2023;148:1606-1635.

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

The Overlap Between HF and CKD

Underlying Metabolic Disease and MR Overactivation are Key Pathophysiological Mechanisms in Both HF and CKD[1,2]

Glomerular injury
Fibrosis
Kidney failure

MR Overactivation[1,2]

Sodium and fluid retention
Inflammation, dysglycemia, adiposity
Hemodynamic factors
Cardiac/vascular hypertrophy

Fibrosis
Cardiac remodelling
Heart failure

Pathophysiological heart-kidney interplay

Figure adapted from Savarese G et al. 2024
MR, mineralocorticoid receptor.
1. Savarese G et al. Diabetologia. 2024;67:246–262; 2. Jia G, et al. Hypertension 2018;72;537–548.

The Challenge in Management of Patients with HFpEF/HFmrEF

Management of HF According to Existing Guidelines

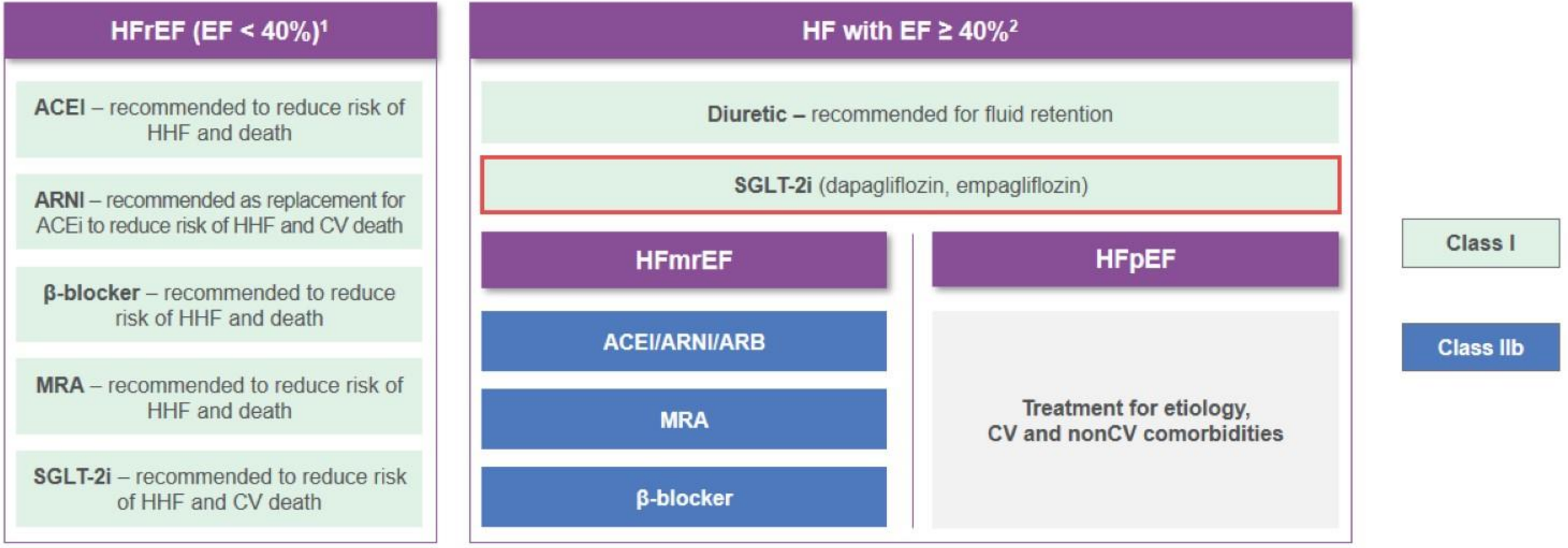
At risk of HF (Stage A)	PreHF (Stage B)	HF (Stage C)	HF (Stage C)	HF (Stage C)	Advanced HF (Stage D)
▪ Risk prevention and lifestyle modification	▪ If LVEF ≤ 40%: ACEI or ARB, β-blocker	HFrEF (LVEF ≤ 40%)	HFmrEF (LVEF 41% to 49%)	HFpEF (LVEF ≥ 50%)	Referral to a specialist, consideration of heart transplantation, MCS, palliative care
▪ SGLT2 inhibitors in patients with type 2 diabetes	▪ SGLT2 inhibitors in patients with type 2 diabetes	▪ Diuretics if congested	▪ Diuretics if congested	▪ Diuretics if congested	
▪ Treatment of risk factors (such as hypertension, ischaemic heart disease, obesity and diabetes	▪ ACEI or ARB; SGLT2 inhibitors or finerenone in patients with type 2 diabetes and CKD, albuminuria or abnormal uACR	▪ ACEI or ARB, ARNI ▪ SGLT2 inhibitor ▪ β -blocker ▪ MRA	▪ SGLT2 inhibitor	▪ SGLT2 inhibitor	
▪ HF screening		▪ Hydralazine or nitrates in black patients	▪ ACEI or ARB ▪ ARNI ▪ MRA ▪ β-blocker	▪ ARNI ▪ MRA ▪ ARB	
▪ Vaccination		▪ Ivabradine			
		▪ Vericiguat ▪ Digoxin			
Lifestyle modification					

Class I recommendation | **Class IIa recommendation** | **Class IIb recommendation**

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; ESC, European Society of Cardiology; HF, heart failure; HFmrEF, HF with mildly reduced ejection fraction; HFrEF, heart failure with reduced EF; MCS, mechanical circulatory support; SGLT2, sodium-glucose cotransporter 2.

Bozkurt B. Nat Rev Cardiol. 2024;21:545-555.

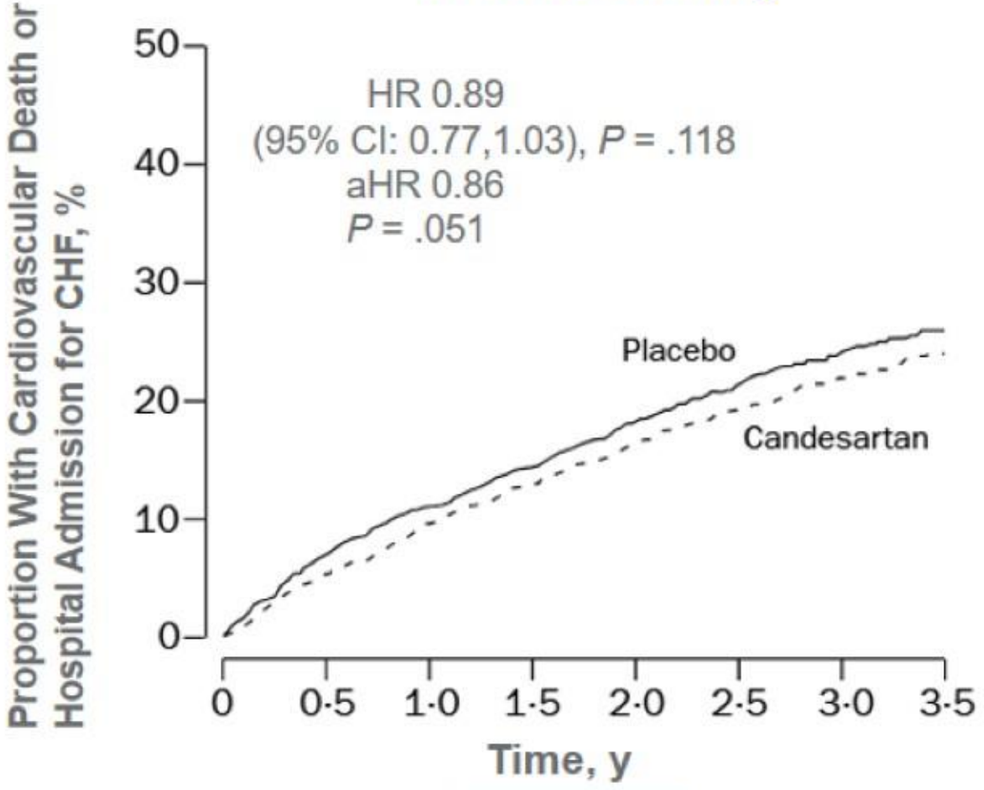
2023 ESC HF Guidelines



Please refer to guidelines for details.
SGLT2i, SGLT2 inhibitor.
1. McDonagh TA, et al. Eur Heart J. 2021;42:3599-3726. Correction in: Eur Heart J. 2021;42:4901; 2. McDonagh TA, et al. Eur Heart J. 2023;44:3627-3639. Correction in: Eur Heart J. 2024;45:53.

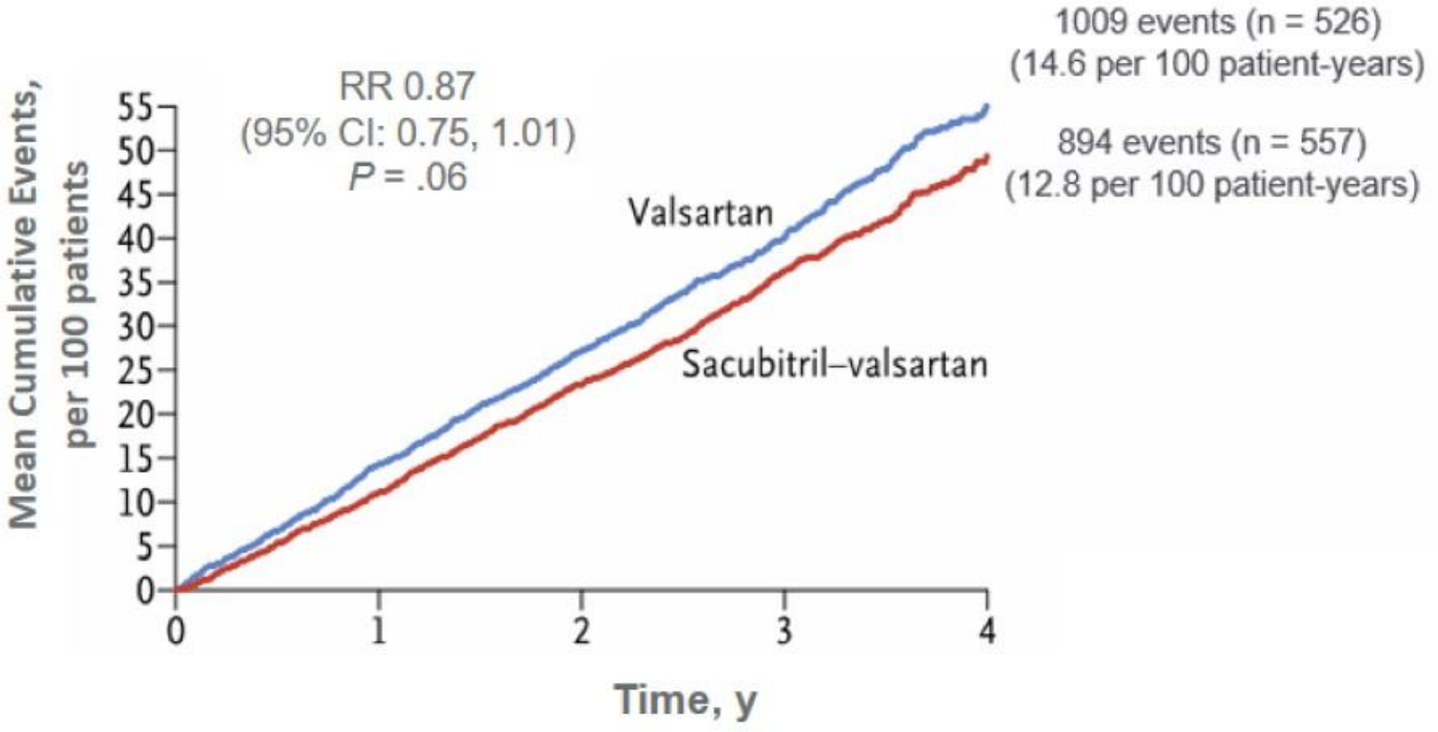
Outcomes in HFmrEF/HFpEF With Current Therapies

CHARM-Preserved[1]
Time to CV Death or Hospital Admission for HF Worsening



ARB

PARAGON-HF[2]
Primary Composite Outcome: CV Death/HHF



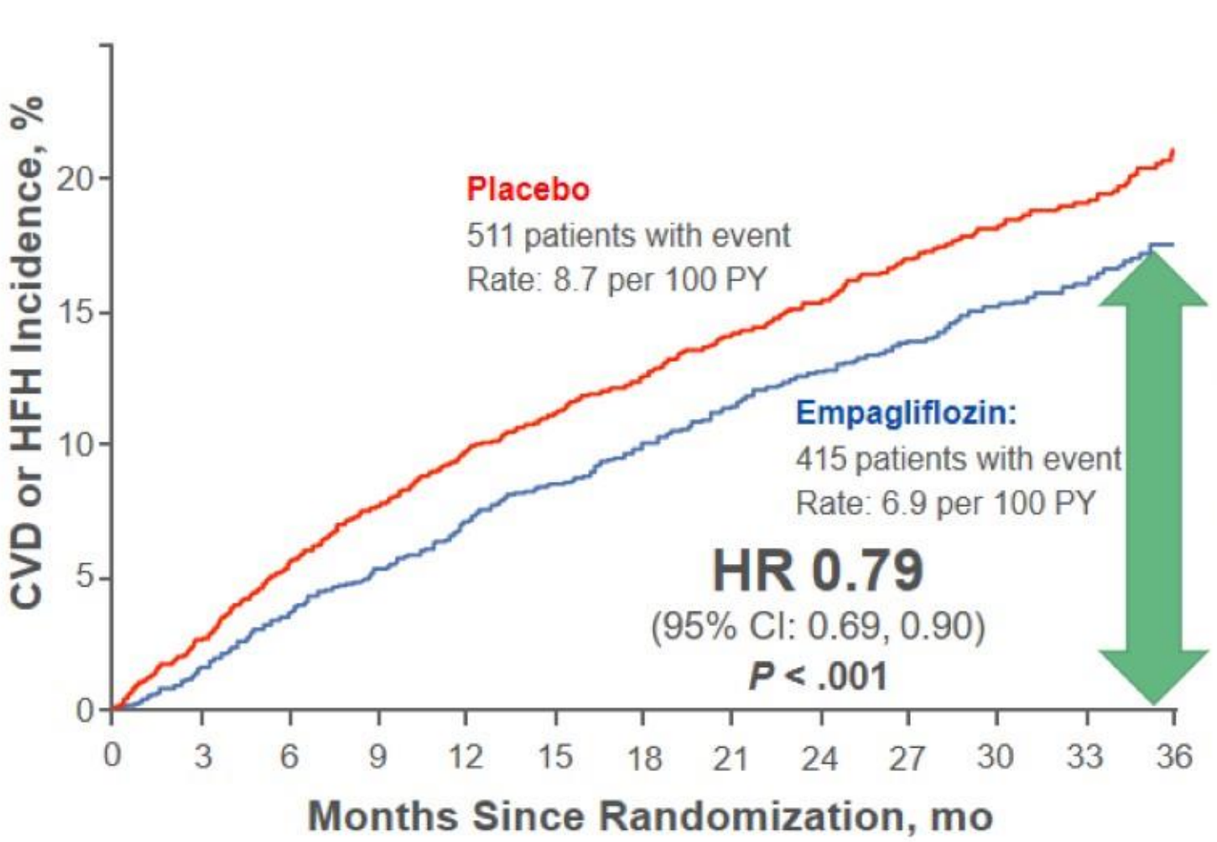
ARNI

aHR, adjusted HR; CHF, congestive heart failure; NNT, number needed to treat; PY, patient-year; RR, risk ratio.

1. Yusuf S, et al. Lancet. 2003;362:777-781; 2. Solomon SD, et al. N Engl J Med. 2019;381:1609-1620.

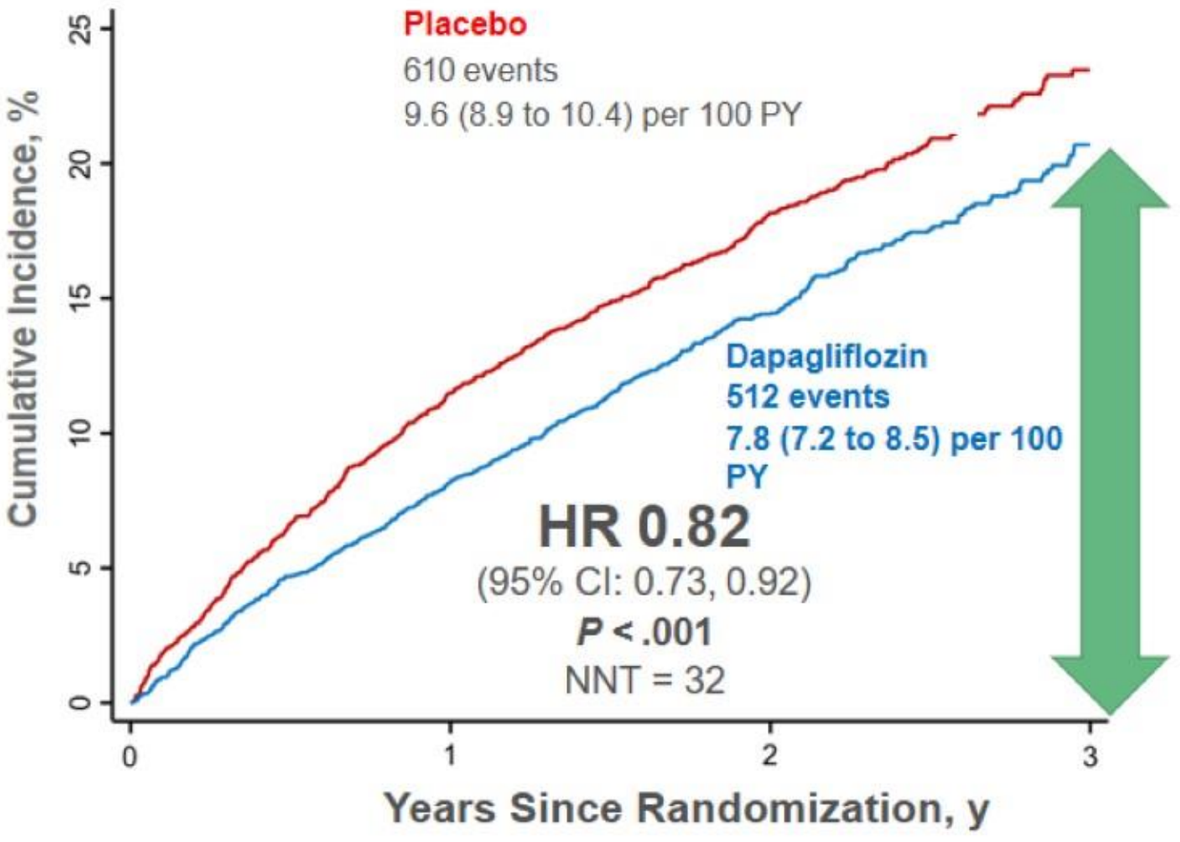
SGLT2i in HFmrEF and HFpEF, and Then What?

EMPEROR-Preserved[1]



5988 patients with class II-IV HF, EF > 40%
empagliflozin (10 mg once daily) or placebo

DELIVER-HF[2]



6263 patients with HF and EF > 40%
dapagliflozin (10 mg once daily) or placebo

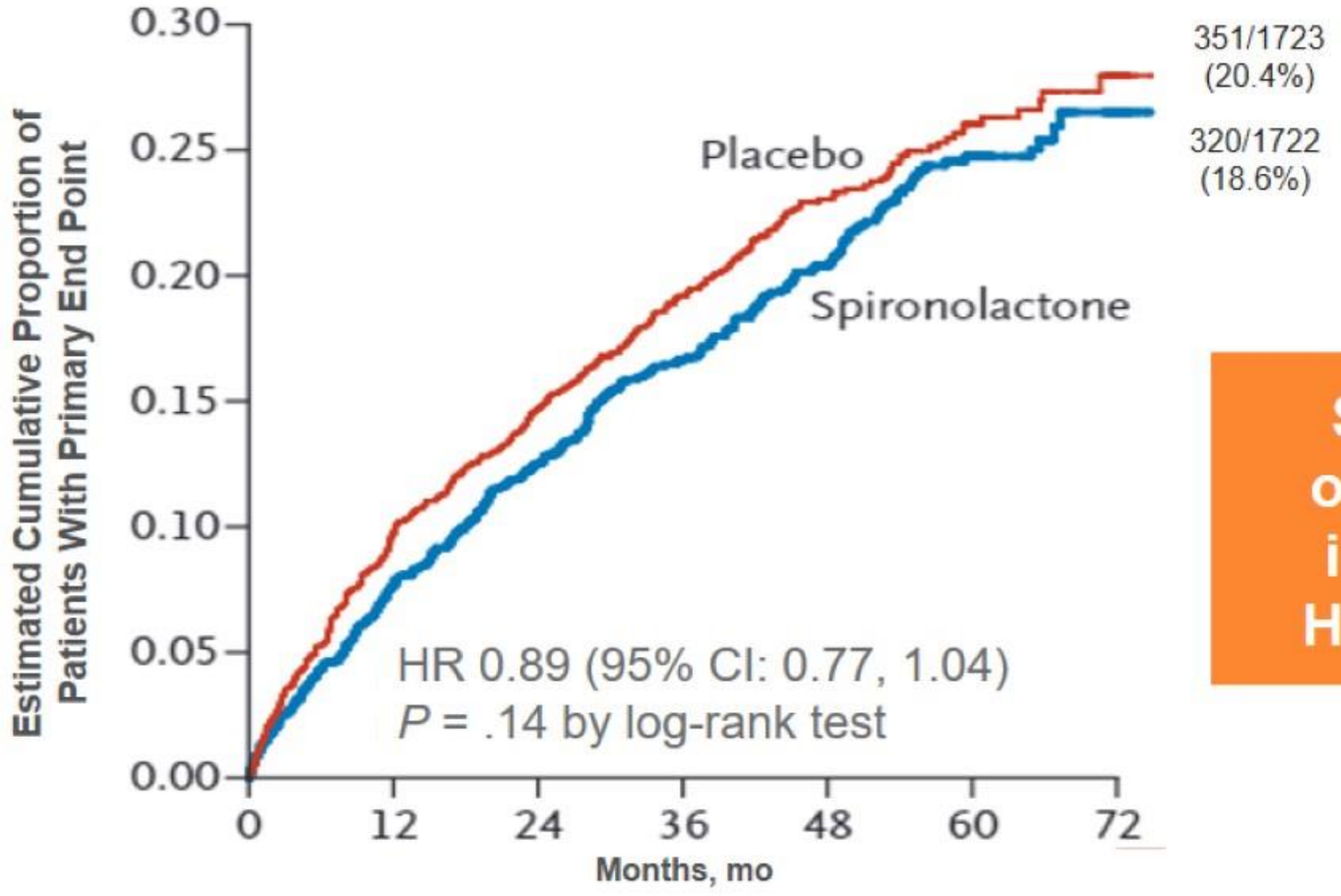
CVD, cardiovascular disease; mo, month.

1. Anker SD, et al. N Engl J Med. 2021;385:1451-1461; 2. Solomon SD, et al. N Engl J Med. 2022;387:1089-1098.

Steroidal MRAs vs Placebo in LVEF ≥ 45%
TOPCAT

International Trial in Patients with Symptomatic HF and LVEF ≥ 45% (N = 3445) Randomized to Spironolactone or Placebo

Time to First Confirmed Primary Outcome Event[1]
(Death from CV causes, aborted cardiac arrest, or hospitalization)



Strong evidence of steroidal MRAs in HFrEF, but not HFpEF/HFmrEF[1-3]

1. Pitt B, et al. N Engl J Med. 2014;370:1383-1392; 2. Pitt B, et al. N Engl J Med. 1999;341:709-717; 3. Zannad F, et al. N Engl J Med. 2011;364:11-21.

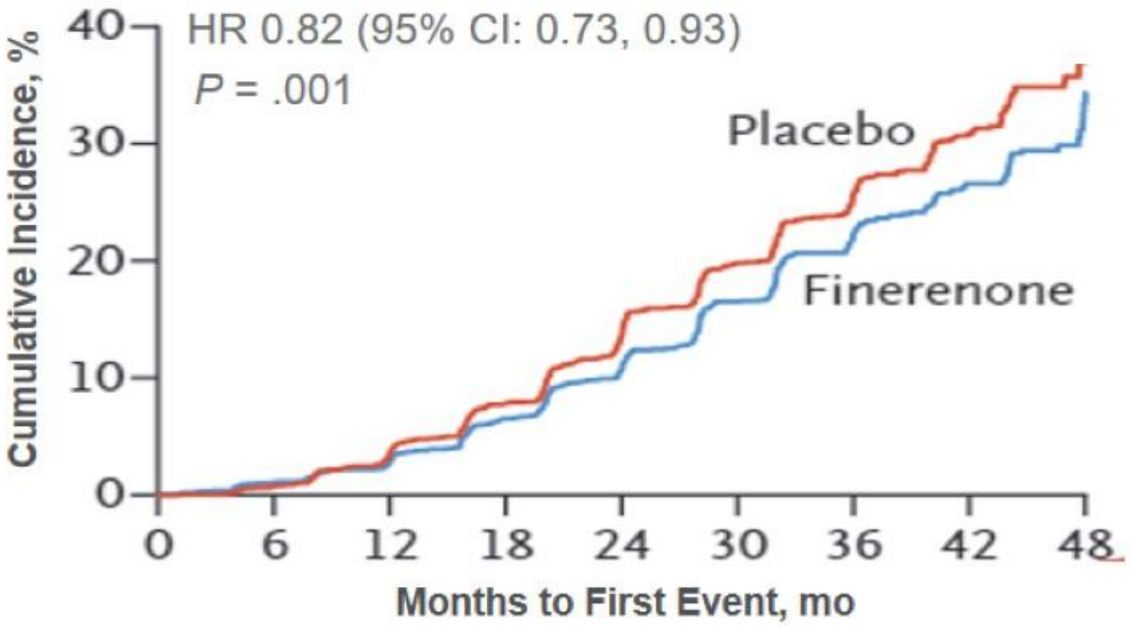
Unmet Needs in Patients with HFpEF/HFmrEF

Nonsteroidal MRA Finerenone in Patients With CKD and T2D

FIDELIO-DKD[1]

5734 Patients With Predominantly Stage 3 or 4 CKD and T2D With Background RAAS Blockade

Primary Endpoint: Kidney Failure,[a] Sustained ≥ 40% decrease in eGFR From Baseline, or Renal Death

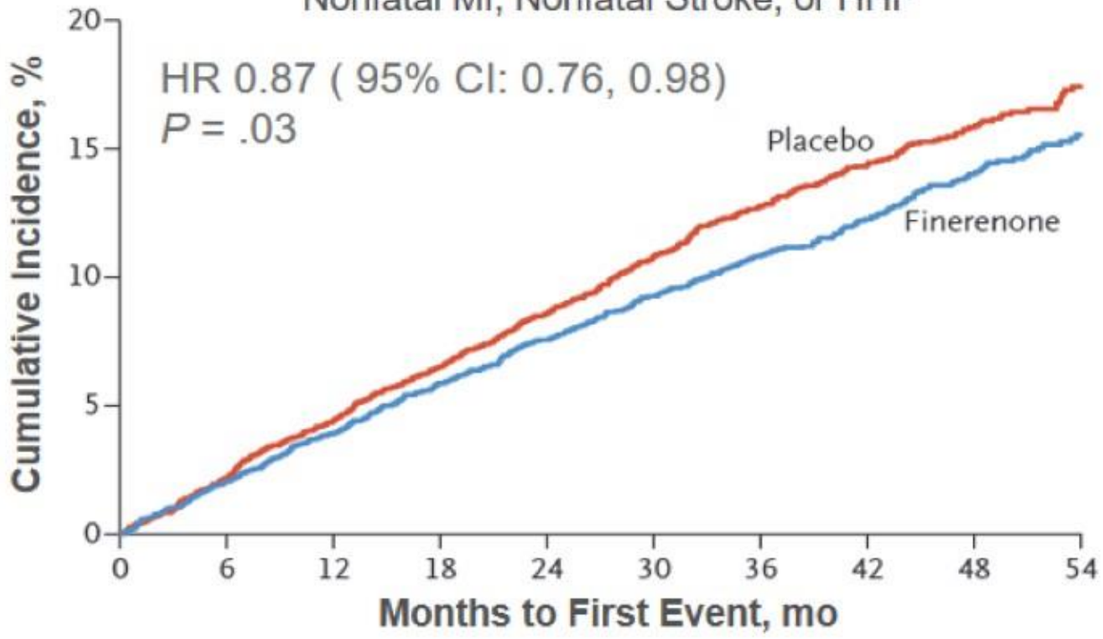


- Similar overall rates of AEs between groups
- Trial discontinuation due to hyperkalemia: finerenone (2.3%) vs placebo (0.9%)

FIGARO-DKD[2]

7437 Patients With Stage 1 to 4 CKD, Elevated Albuminuria, and T2D With Background RAAS Blockade

Primary Endpoint: Composite of CV Death, Nonfatal MI, Nonfatal Stroke, or HHF



- No substantial difference in overall rates of AEs between groups
- Trial discontinuation due to hyperkalemia: finerenone (1.2%) vs placebo (0.4%)

[a]End-stage kidney disease or an eGFR < 15 mL/min/1.73 m^2.

MI, myocardial infarction; RAAS, renin-angiotensin-aldosterone system.

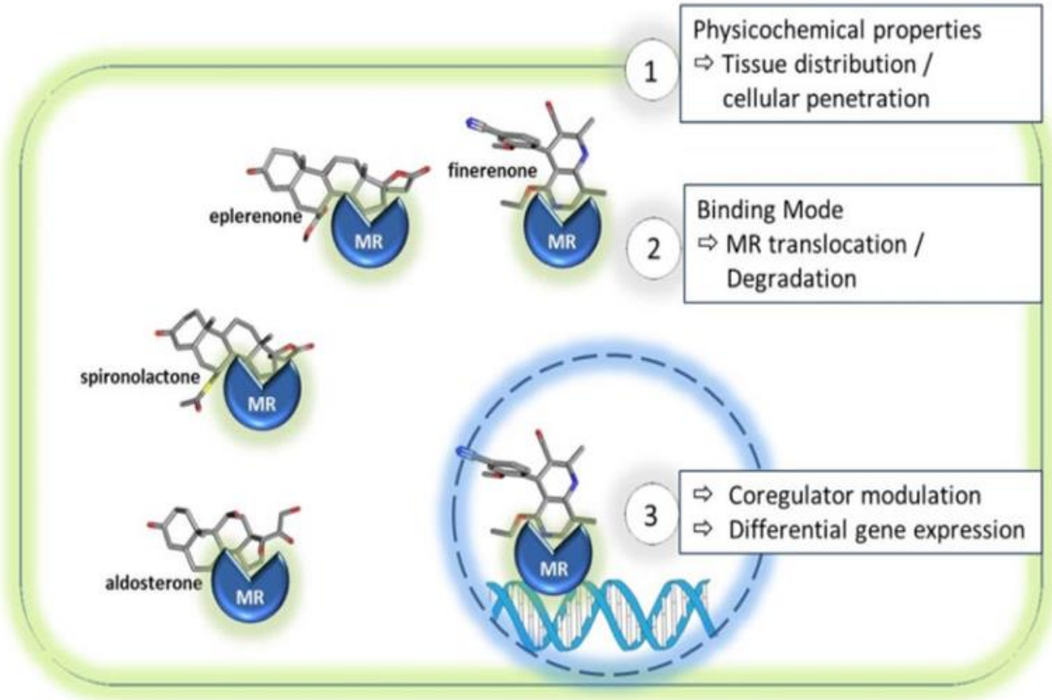
1. Bakris GL, et al. N Engl J Med. 2020;383:2219-2229; 2. Pitt B, et al. N Engl J Med. 2021;385:2252-2263.

Potency and Selectivity of MRAs

		Potency	Selectivity	Metabolites	Tissue Distribution[a] (Kidney/Heart)	Adverse Effects
Spironolactone[b]	Steroidal	High	Low	Multiple, active	Higher in kidney	▪ Sexual (eg, gynecomastia) ▪ Hyperkalemia ▪ BP reduction
Eplerenone[b]	Steroidal	Low	Medium	No active metabolites	Higher in kidney	▪ Rare sexual ▪ Hyperkalemia ▪ BP reduction
Finerenone[c]	Nonsteroidal	High	High	No active metabolites	Balanced in heart and kidney	▪ Rare sexual ▪ Hyperkalemia ▪ BP reduction

[a]Based on standard whole-body quantitative analysis in healthy rats. [b]FDA-/EMA-approved treatment of hypertension and HFrEF. [c]FDA/EMA approved for the treatment of CKD associated with T2D.
CKD, chronic kidney disease; EMA, European Medicines Agency; FDA, US Food and Drug Administration.
Kolkhof P, et al. Handb Exp Pharmacol. 2017;243:271-305; Agarwal R, et al. Eur Heart J. 2021;42:152-161; Dhillon S. Drugs. 2013;73:1451-1462.

Finerenone is a potent, highly selective nsMRA with equivalent Cardio:Renal tissue distribution & potential safety advantages over steroidal MRAs



Kolkhof P, Nowack C, Eitner F. *Curr Opin Nephrol Hypertens.* 2015;24:417-424.

- More selective for MR receptor than spironolactone or eplerenone
- High potent
- More balanced Heart/Kidney Distribution than steroidal MRAs

The Evidence

Improving Clinical Outcomes in HFpEF/HFmrEF with Non-steroidal MRAs

FINEARTS-HF Study Design

Randomized, Double-Blind, Placebo-Controlled Trial Testing the Hypothesis That Finerenone Would Reduce CV Death and Total Worsening HF Events in Patients With HFmrEF or HFpEF

Key Inclusion Criteria

- Symptomatic HF (NYHA class II-V) with LVEF ≥ 40%
- Hospitalized, recently hospitalized, or ambulatory
- Elevated natriuretic peptide levels
- Structural heart disease (LA enlargement or LVH)

Key Exclusion Criteria

- Diuretics in the 30 d prior to **randomization**
- Potassium > 5.0 mmol/L; eGFR < 25 mL/min/1.73 m^2
- MRA use 30 d prior to randomization
- History of peripartum, chemotherapy induced, or infiltrative cardiomyopathy (eg, amyloidosis)
- Alternative causes of signs or symptoms

R 1:1

Finerenone 10 mg , 20 mg or 20 mg, 40 mg (dosing based on eGFR: max dose 20 mg for ≤ 60 mL/min/1.73 m^2 and 40 mg for > 60 mL/min/1.73 m^2)

N = 6001 validly randomized

Uptitrate to maximally tolerated dose if [K^+] < 5.0 mmol/L and eGFR decrease < 30%

Matching placebo

Visits: mo 1, then every 3 mo for first 12 mo, visits every 4 mo thereafter, with telephone contact between

Study Endpoints

Primary Endpoint

- CV death and total HF events (hospitalizations/urgent visits)

Secondary Endpoints

- Total HF events
- KCCQ-TSS at 6 mo, 9 mo, and 12 mo
- NYHA class at 12 mo
- Renal composite endpoint
- All-cause mortality

LA, left atrial; LVH, left ventricular hypertrophy; max, maximum.

Solomon SD, et al; FINEARTS-HF Committees and Investigators. N Engl J Med. 2024;391:1475-1485; Solomon SD, et al. Presented at: ESC Congress 2024; September 1, 2024; London, United Kingdom.

FINEARTS-HF
Baseline Characteristics

	Finerenone n = 3003	Placebo n = 2998
Age, mean (SD), y	72 (10)	72 (10)
Female sex, %	45	46
Race, %		
Asian	17	17
BLACK	2	1
Other	3	3
WHITE	79	79
Region, %		
Asia	16	16
Eastern Europe	44	44
Latin America	11	11
North America	8	8
Western Europe, Oceania, and others	21	21
NYHA class, %		
II	69	69
III	30	30
IV	1	1
KCCQ-TSS, mean (SD)	68 (24)	67 (24)
LVEF, %	53 (8)	53 (8)
SBP, mean (SD), mm Hg	130 (15)	129 (15)

	Finerenone n = 3003	Placebo n = 2998
NT-proBNP, median, ng/L	1052 (467, 1937)	1028 (433, 1963)
eGFR, mean (SD), mL/min/1.73 m^2	62 (19)	62 (20)
eGFR < 60 mL/min/1.73 m^2, %	48	48
uACR, mg/g	18 (7, 67)	19 (7, 66)
Prior HFH, %	60	61
History of LVEF ≤ 40%, %	5	4
T2D, %	41	41
AF on electrocardiogram, %	38	38
History of HTN	88	90
History of MI, %	26	25
Loop diuretic, %	87	87
BB, %	85	85
ACEI, %	36	36
ARB, %	35	35
ARNI, %	9	9
Calcium channel blocker, %	32	34
SGLT2i, %	13	14

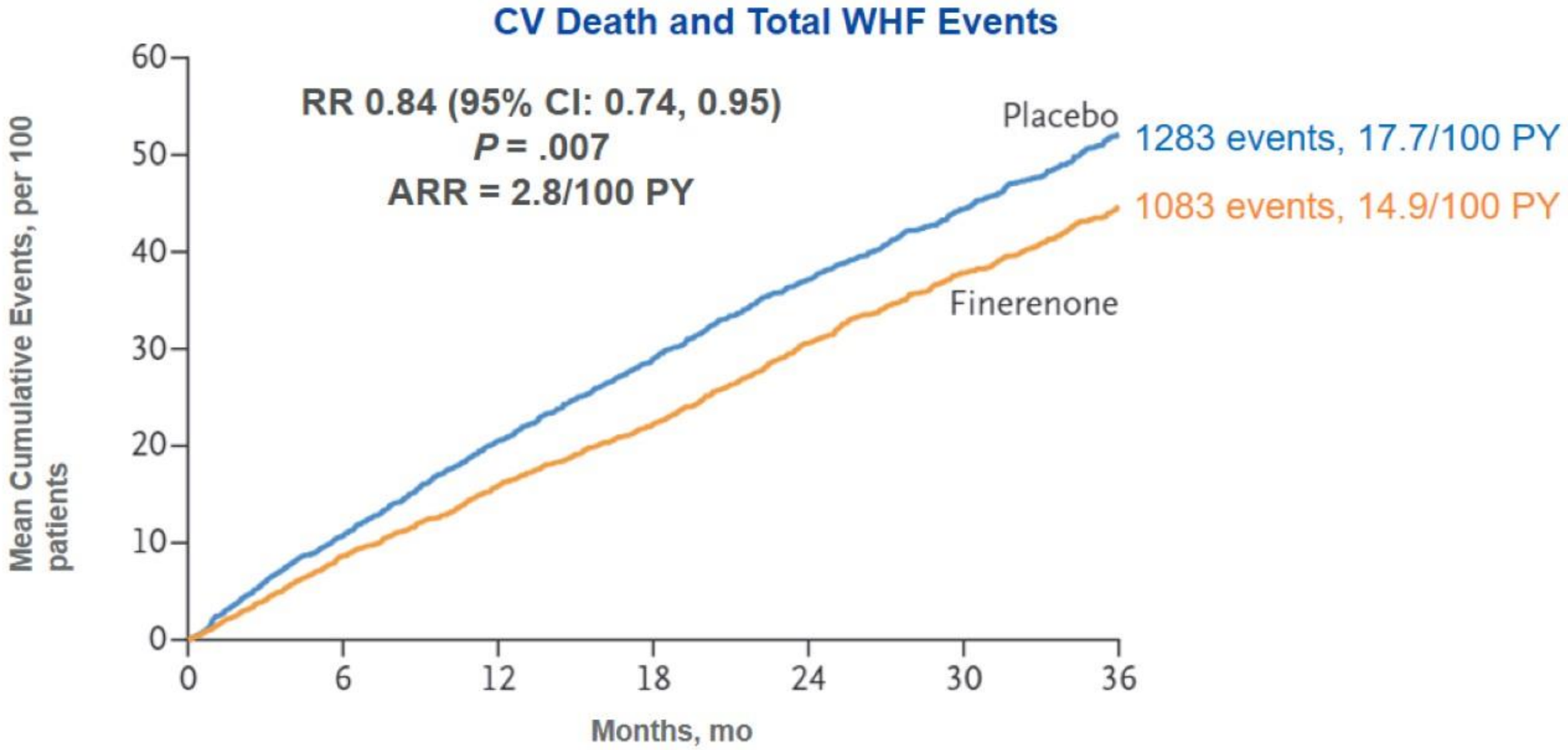
(n = 817 [13.6%])

AF, atrial fibrillation; ARNI, angiotensin receptor-neprilysin inhibitor; BB, β-blocker; HFH, heart failure hospitalization; SBP, systolic blood pressure.

Solomon SD, et al. Presented at: ESC Congress 2024; September 1, 2024; London, United Kingdom.

FINEARTS-HF
Primary Endpoint Results

Finerenone Reduced CV Death and Total WHF Events Over a Median Follow-Up of 32 MO

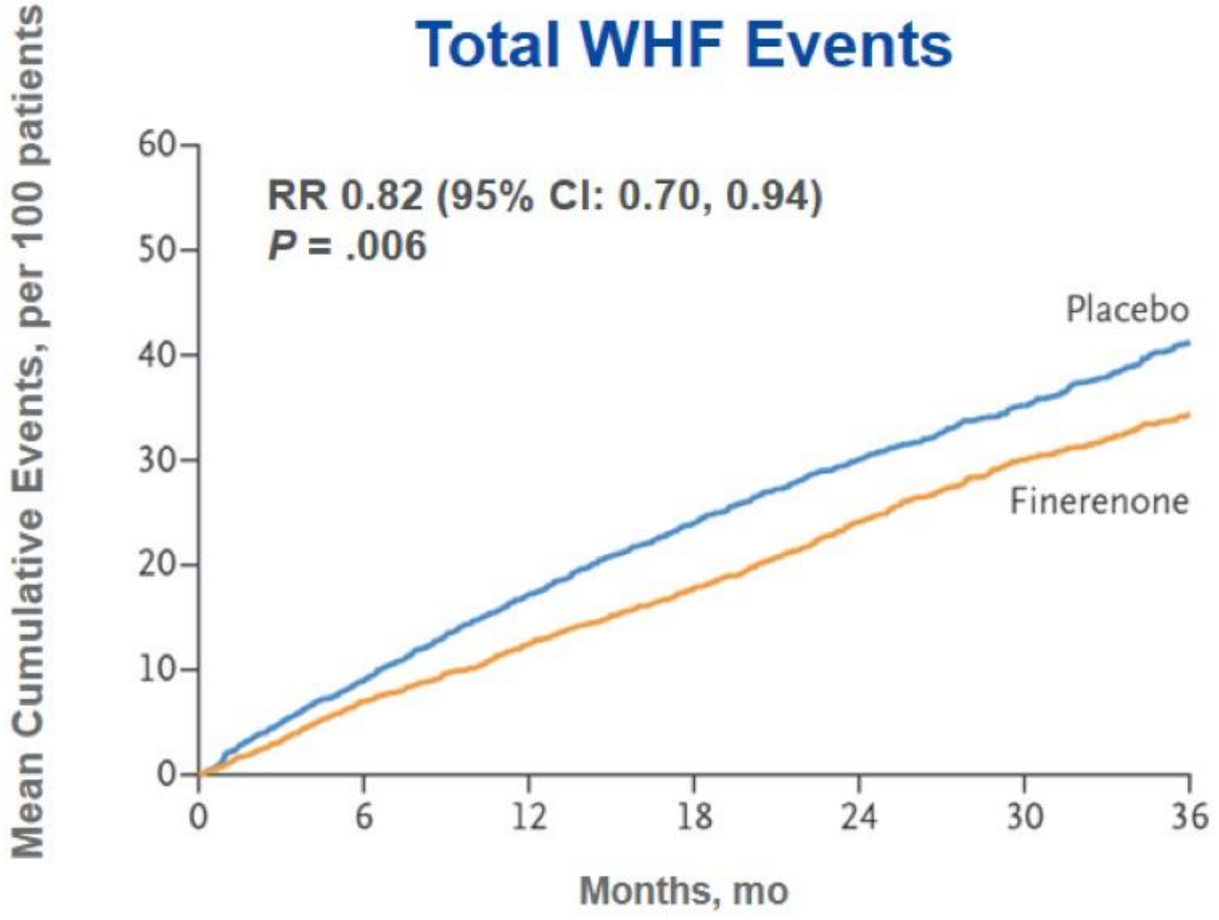


ARR, absolute risk reduction; WHF, worsening heart failure.

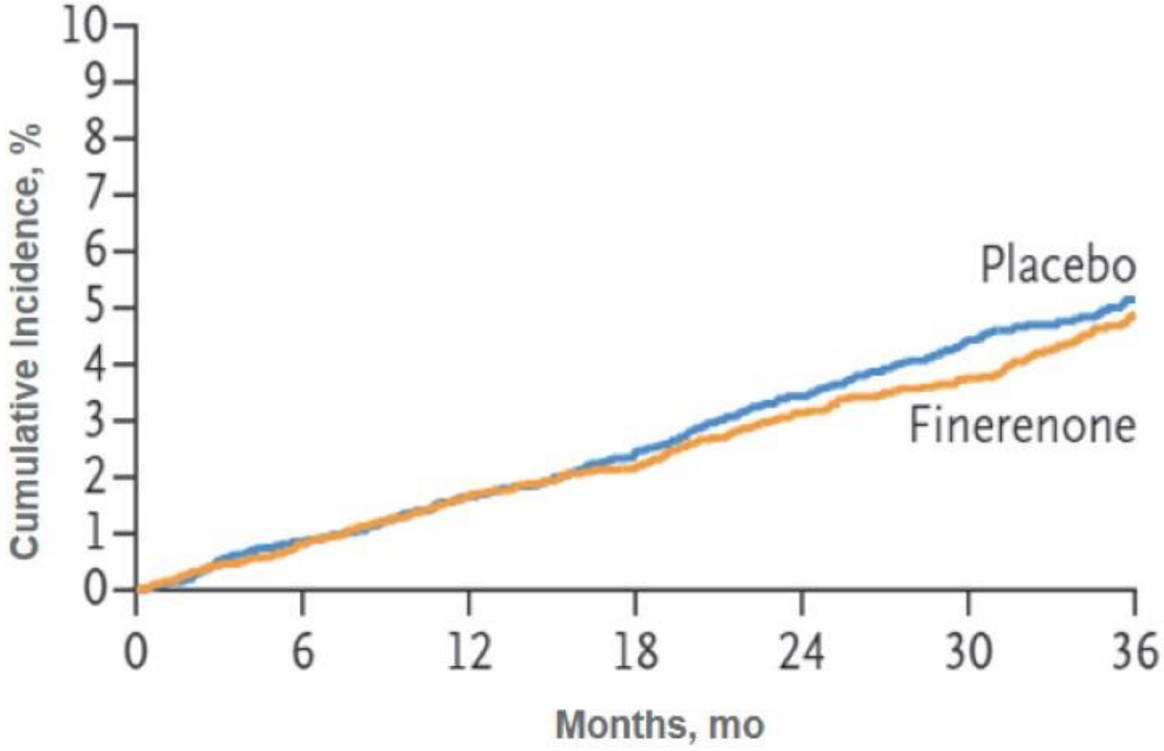
Solomon SD, et al; FINEARTS-HF Committees and Investigators. N Engl J Med. 2024;391:1475-1485; Solomon SD, et al. Presented at: ESC Congress 2024; September 1, 2024; London, United Kingdom.

FINEARTS-HF
Components of the Primary Endpoint

Total WHF Events



CV Death

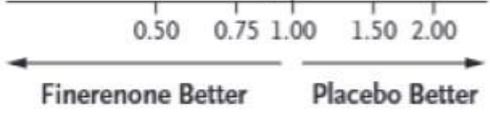


Solomon SD, et al; FINEARTS-HF Committees and Investigators. N Engl J Med. 2024;391:1475-1485; Solomon SD, et al. Presented at: ESC Congress 2024; September 1, 2024; London, United Kingdom.

FINEARTS-HF
Prespecified Subgroups for Primary Outcome

Consistent Treatment Effects Across all Prespecified Subgroups, Including EF and SGLT2i Use

Subgroup	Finerenone (no. of events)	Placebo (no. of events)	Rate Ratio (95% CI)
Age			
≤73 yr	468	623	0.76 (0.63–0.92)
>73 yr	615	660	0.92 (0.77–1.09)
Sex			
Male	632	691	0.88 (0.74–1.04)
Female	451	592	0.78 (0.65–0.95)
Race			
Asian	211	218	0.96 (0.72–1.29)
Black	29	22	0.98 (0.37–2.62)
Other	34	57	0.60 (0.26–1.42)
White	809	986	0.82 (0.71–0.95)
Geographic region			
Asia	211	218	0.95 (0.71–1.27)
Eastern Europe	322	389	0.83 (0.67–1.03)
Latin America	106	163	0.65 (0.43–0.98)
North America	122	118	0.98 (0.67–1.45)
Western Europe, Oceania, or other	322	395	0.82 (0.64–1.06)
NYHA functional class			
II	646	741	0.86 (0.73–1.02)
III or IV	437	542	0.79 (0.65–0.96)
Left ventricular ejection fraction			
<60%	877	1061	0.82 (0.71–0.94)
≥60%	206	222	0.94 (0.70–1.26)
NT-proBNP level at baseline			
≤1041 pg/ml	266	342	0.78 (0.62–0.99)
>1041 pg/ml	782	918	0.83 (0.71–0.96)
Time since heart failure event at randomization			
≤7 days	270	372	0.74 (0.57–0.95)
>7 days to 3 mo	404	492	0.79 (0.64–0.97)
>3 mo or no index event	409	419	0.99 (0.81–1.21)
ACEI, ARB, or ARNI use at baseline			
No	288	332	0.85 (0.66–1.11)
Yes	795	951	0.83 (0.72–0.96)
SGLT2 inhibitor use at baseline			
No	907	1049	0.85 (0.74–0.98)
Yes	176	234	0.83 (0.60–1.16)
Atrial fibrillation at baseline			
Yes	521	621	0.80 (0.66–0.97)
No	562	662	0.85 (0.72–1.01)
Diabetes mellitus at baseline			
Yes	524	638	0.83 (0.69–1.00)
No	559	645	0.85 (0.71–1.01)
Body-mass index			
<30	586	648	0.88 (0.74–1.05)
≥30	486	632	0.79 (0.66–0.95)
eGFR at baseline			
<60 ml/min/1.73 m^2	727	796	0.91 (0.78–1.07)
≥60 ml/min/1.73 m^2	356	487	0.72 (0.59–0.88)
Serum potassium level at baseline			
≤4.5 mmol/liter	714	875	0.81 (0.69–0.95)
>4.5 mmol/liter	369	408	0.91 (0.74–1.11)
Systolic blood pressure at baseline			
≤130 mm Hg	608	740	0.85 (0.72–1.01)
>130 mm Hg	475	543	0.84 (0.69–1.02)
Urinary albumin:creatinine ratio at baseline			
<30 mg/g	429	518	0.81 (0.67–0.97)
≥30 mg/g	601	705	0.88 (0.74–1.05)



Solomon SD, et al; FINEARTS-HF Committees and Investigators. N Engl J Med. 2024;391:1475-1485.

FINEARTS-HF
Safety Outcomes

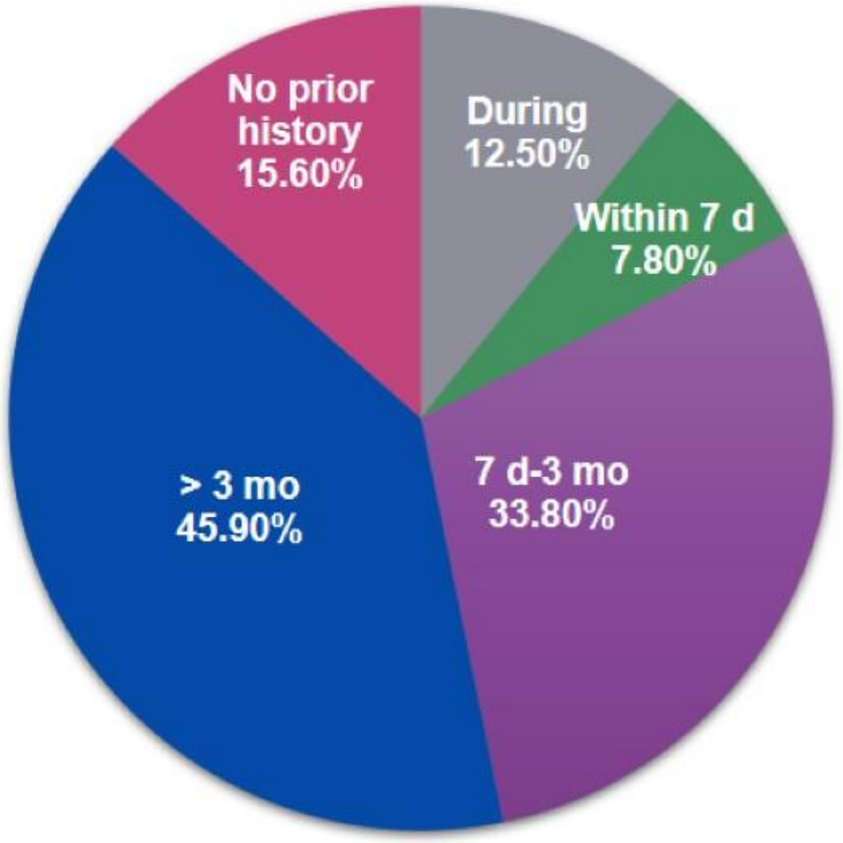
Treatment-Emergent Safety Outcome	Finerenone (n = 2993), %	Placebo (n = 2993), %
Any SAE	38.7	40.5
sCr ≥ 3.0 mg/dL	2.0	1.2
Serum potassium, mmol/L		
> 5.5	14.3	6.9
> 6.0	3.0	1.4
< 3.5	4.4	9.7
Investigator-reported hyperkalemia	9.7	4.2
Leading to hospitalization	0.5	0.2
Leading to death	0	0
SBP < 100 mm Hg	18.5	12.4

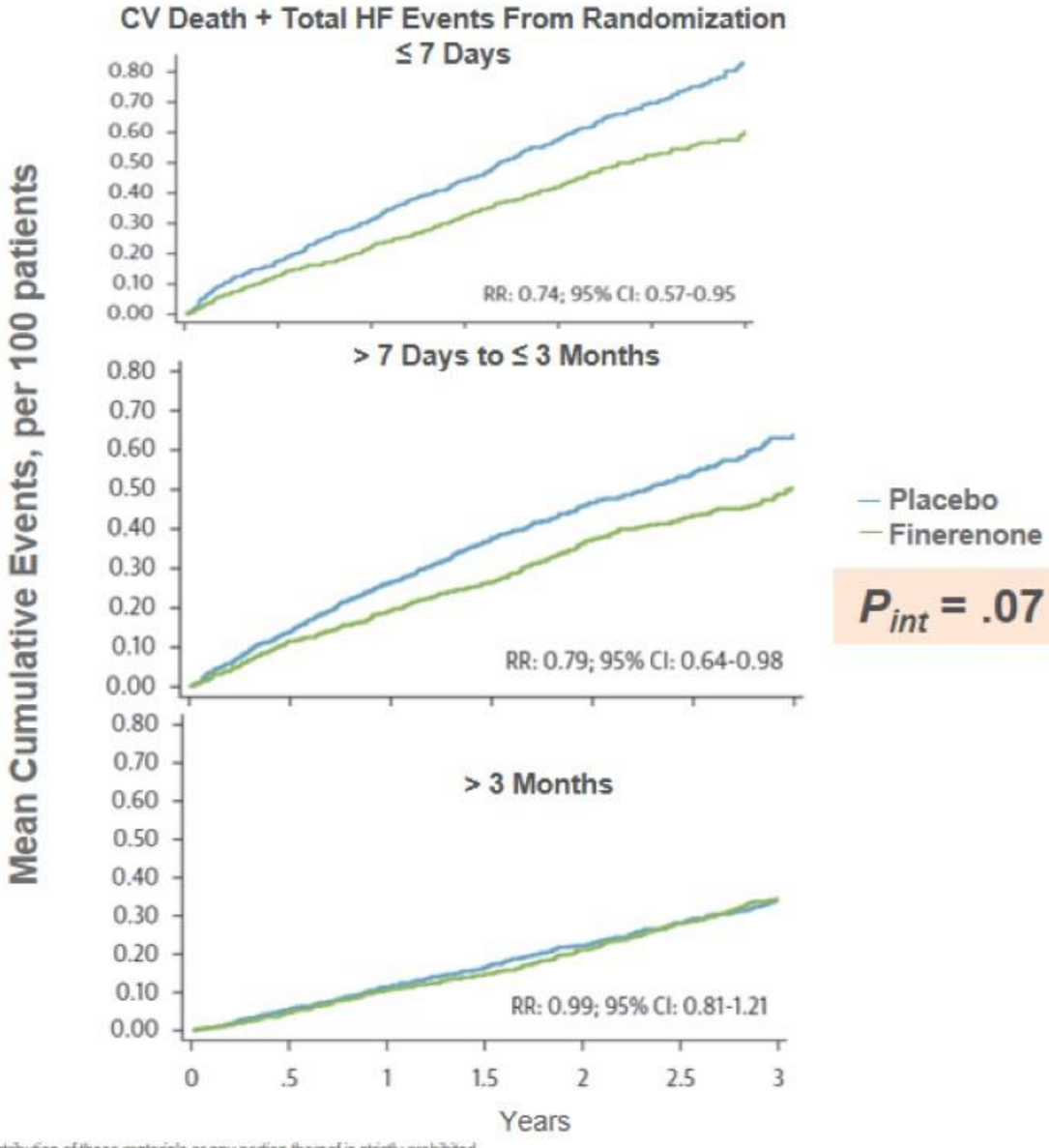
SAE, serious AE; sCr, serum creatinine.

Solomon SD, et al; FINEARTS-HF Committees and Investigators. N Engl J Med. 2024;391:1475-1485.

Finerenone in Patients With a Recent WHF Event
FINEARTS-HF Analysis

Patients Enrolled in FINEARTS-HF and Time From WHF Event (N = 6001)

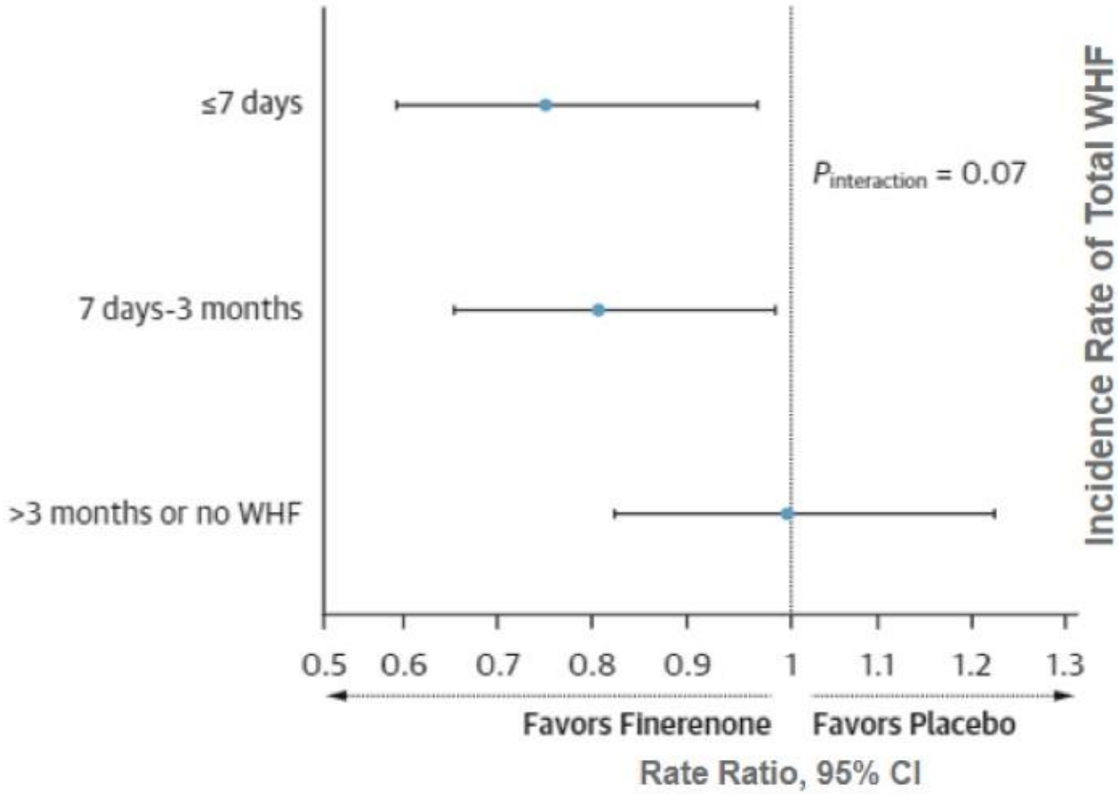


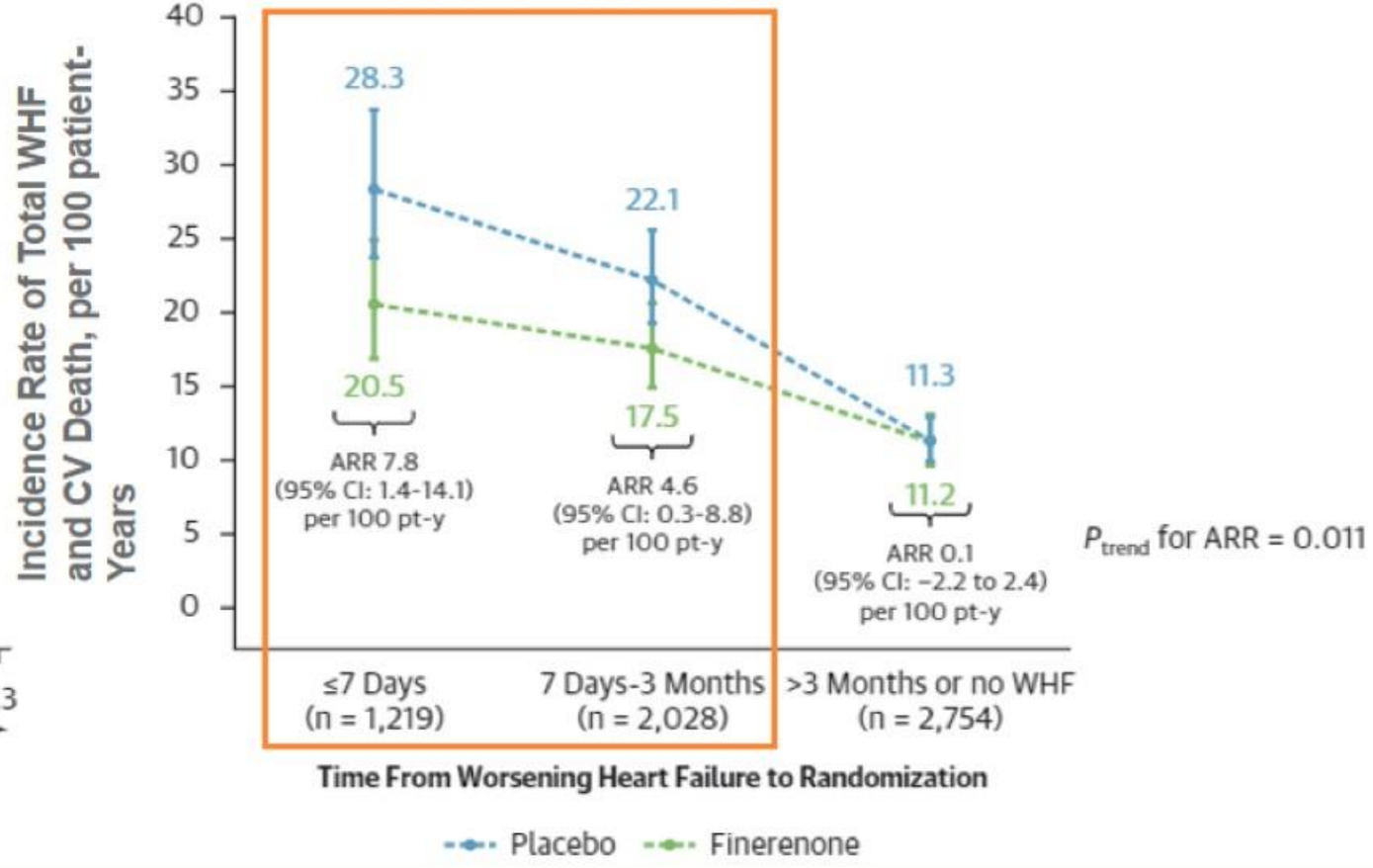


Desai AS, et al. J Am Coll Cardiol. 2024. doi:10.1016/j.jacc.2024.09.004 [Epub ahead of print].

Finerenone in Patients With a Recent WHF Event
FINEARTS-HF Analysis (cont)

Primary Composite Outcome of Total WHF Events and Death From CV Cause





Possible signal of absolute treatment benefit with finerenone in patients with HFpEF and recent WHF event warrants further investigation

Desai AS, et al. J Am Coll Cardiol. 2024. doi:10.1016/j.jacc.2024.09.004. [Epub ahead of print]

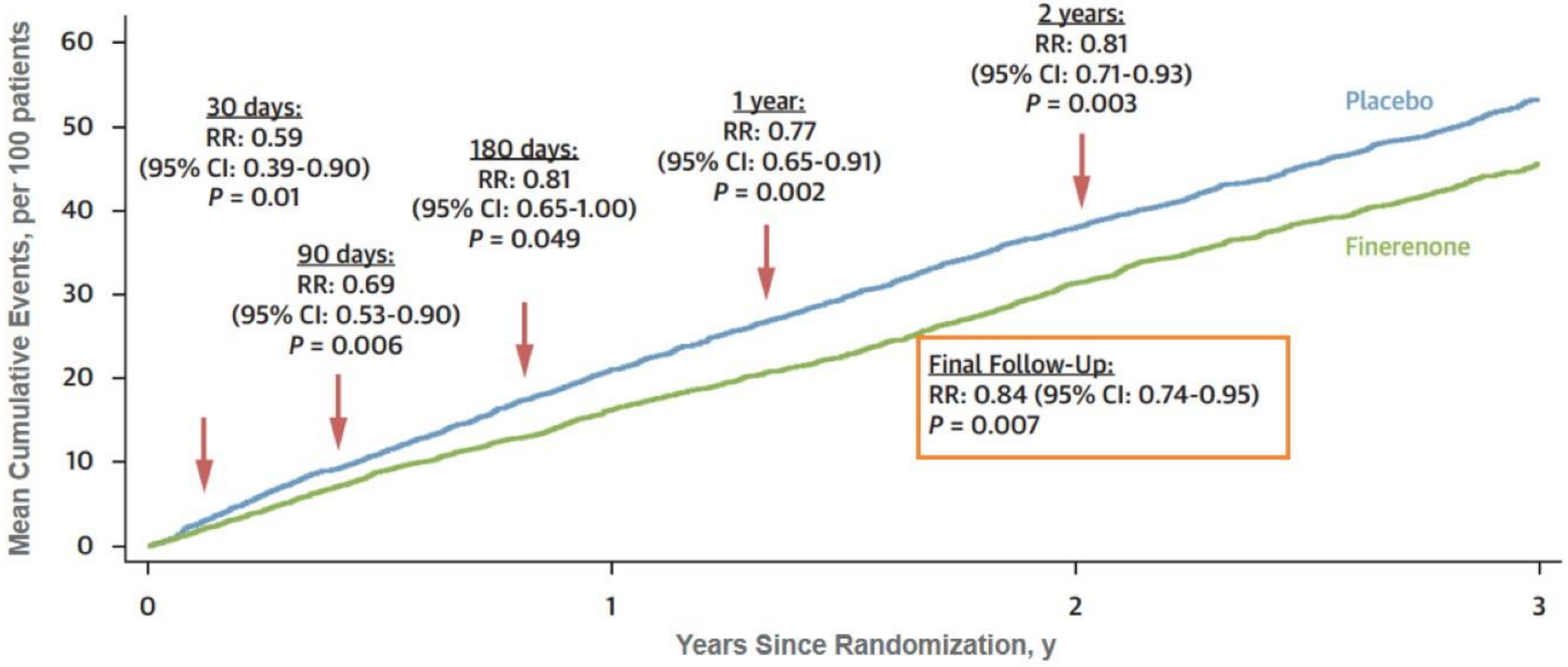
Treatment Effects of Finerenone by Concomitant SGLT2i Use: FINEARTS-HF Analysis

	No SGLT2i Use		SGLT2i Use		$P_{interaction}$
	Finerenone n = 2610	Placebo n = 2574	Finerenone n = 393	Placebo n = 424	
CV death and total WHF events					
Events, no.	907	1049	176	234	
Rate (per 100 PY)	14.0	16.5	21.8	26.5	
RR (95% CI)	0.85 (0.74, 0.98)		0.83 (0.60, 1.16)		.76
Total WHF events					
Events, no.	703	830	139	194	
Rate (per 100 PY)	10.9	13.0	17.2	22.0	
RR (95% CI)	0.83 (0.71, 0.97)		0.80 (0.55, 1.15)		.68
CV death					
Events, no. (%)	205 (7.9)	220 (8.5)	37 (9.4)	40 (9.4)	
Rate (per 100 PY)	3.2	3.5	4.6	4.5	
HR (95% CI)	0.92 (0.76, 1.11)		1.03 (0.65, 1.62)		.73
All-cause death					
Events, no. (%)	428 (16.4)	448 (17.4)	63 (16.0)	74 (17.5)	
Rate (per 100 PY)	6.6	7.0	7.7	8.4	
HR (95% CI)	0.94 (0.82, 1.07)		0.90 (0.64, 1.27)		.78

Vaduganathan M, et al. Circulation. 2024. doi:10.1161/CIRCULATIONAHA.124.072055. [Epub ahead of print]

Time to Significant Benefit of Finerenone in Patients With HFpEF
Prespecified Analysis of FINEARTS-HF

Treatment Effects on the Primary Endpoint at Multiple Time Points in Follow-Up in the FINEARTS-HF Trial



Treatment effects are summarized as RR (95% CI).

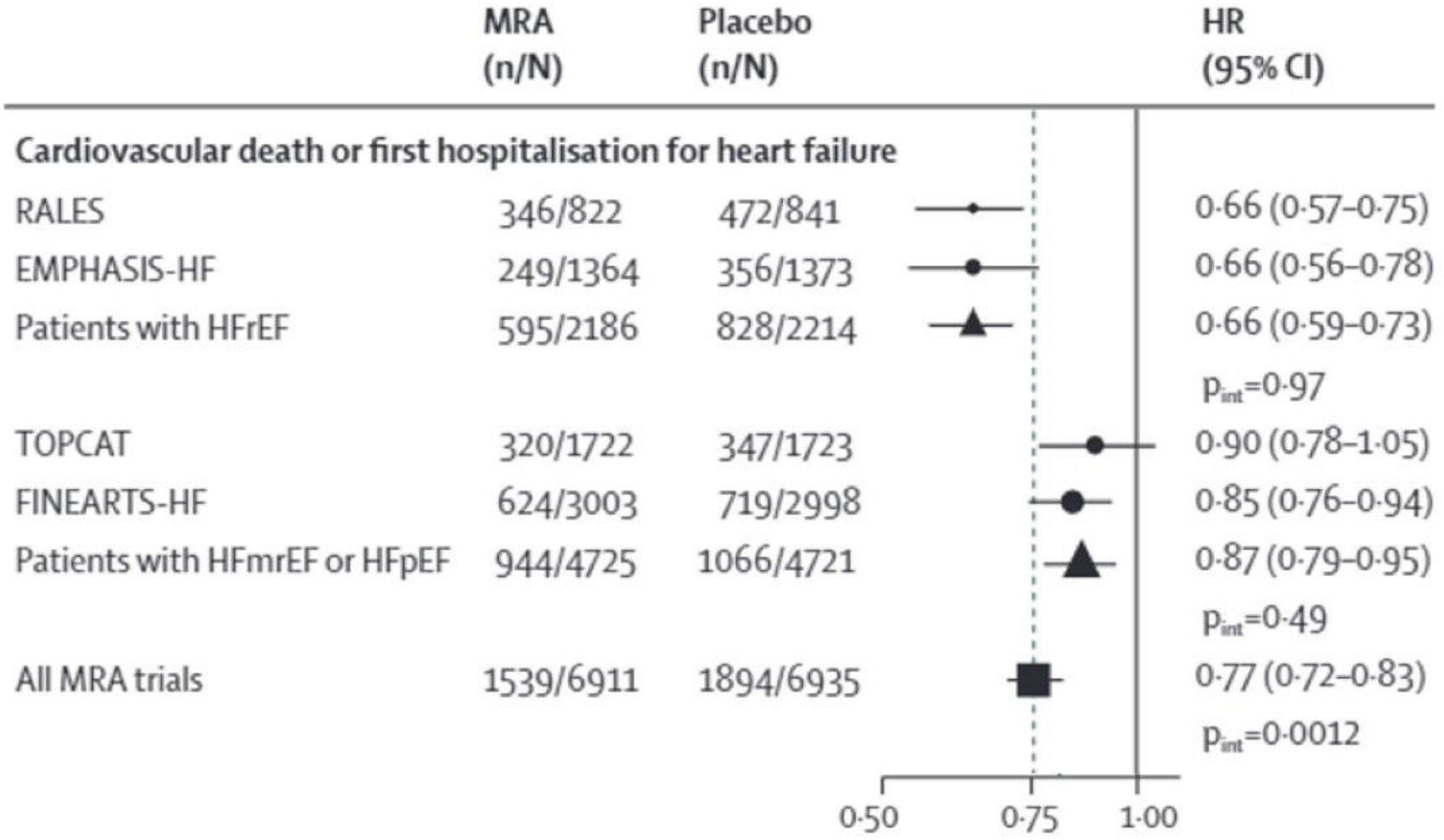
Vaduganathan M, et al. J Am Coll Cardiol. 2024. doi:10.1016/j.jacc.2024.09.018. [Epub ahead of print]

Conclusion of FINEARTS

- **Finerenone significantly reduces heart failure events in patients with HFmrEF/HFpEF, differentiating it from steroidal MRAs like spironolactone.**
- **Finerenone may be a valuable addition to HFmrEF/HFpEF treatment, especially for patients at high risk of hospitalization, but its impact on mortality remains uncertain**
- **The study highlights the need for further research on combination therapy, particularly with SGLT2 inhibitors**
- **Long-term studies are needed to assess finerenone's durability, safety, and potential benefits in a broader heart failure population.**

Meta-Analysis of MRAs Across the Full Spectrum of EF in HF

Meta-Analysis in ~ 14,000 Patients Confirms the Benefits of MRAs in HF



Jhund PS, et al. Lancet. 2024;404:1119-1131.

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

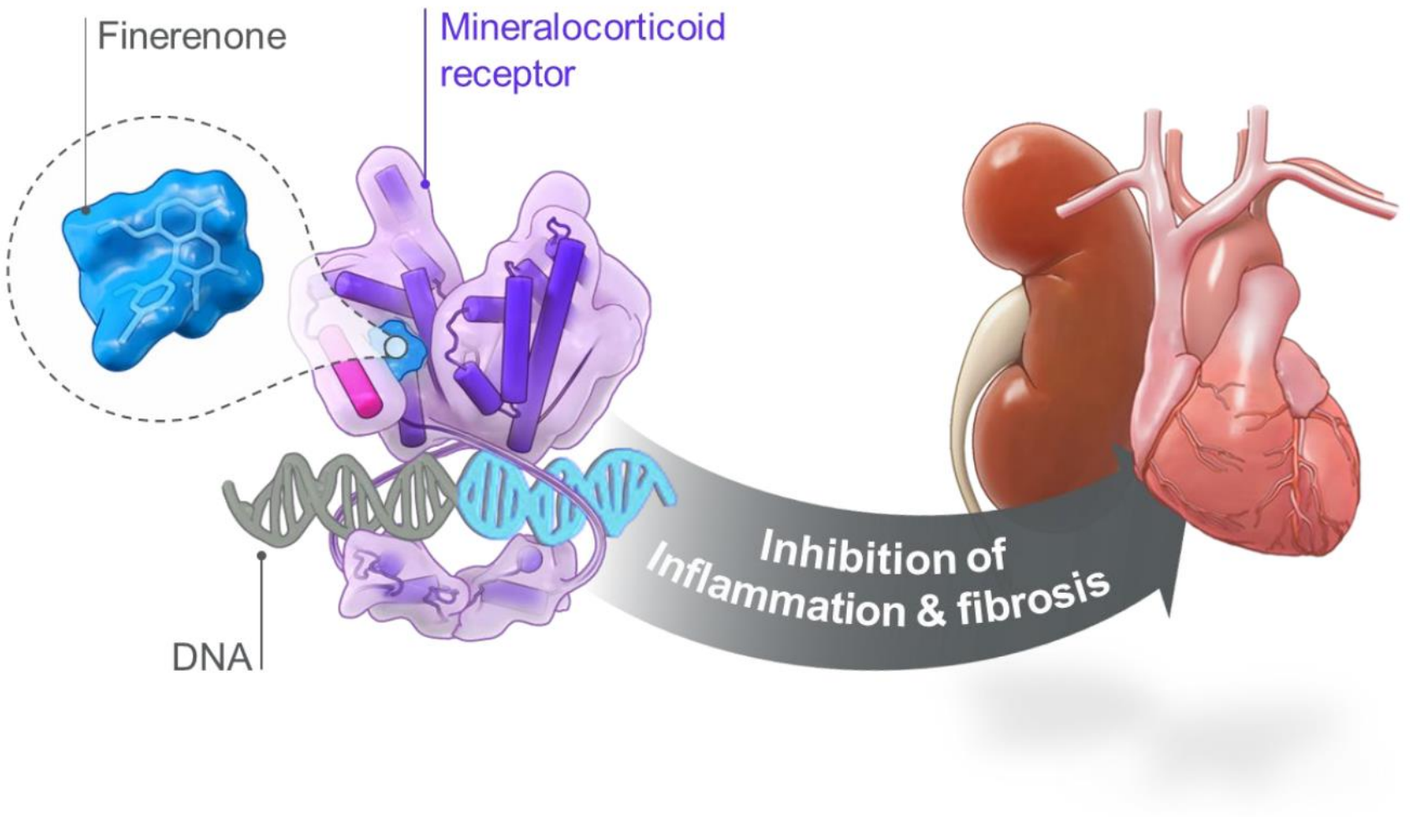
Gerasimos Filippatos; Brian Claggett; Akshay Desai; Pardeep Jhund; Alasdair Henderson; Meike Brinker; Peter Kolkhof; Patrick Schloemer; James Lay-Flurrie; Prabhakar Viswanathan; Carolyn Lam; Michele Senni; Sanjiv Shah; Adriaan A. Voors; Faiez Zannad; Peter Rossing; Luis Ruilope; Stefan Anker; Bertram Pitt; Rajiv Agarwal; John McMurray; Scott Solomon

PROSPERO CRD42024570467

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.**



FINE-HEART Clinical Program

FINE-HEART

(N = 18,991 Participants)

Prospectively Registered: PROSPERO CRD42024570467

Prespecified in Dedicated Statistical Analysis Plans

FINEARTS-HF

FIDELIO-DKD

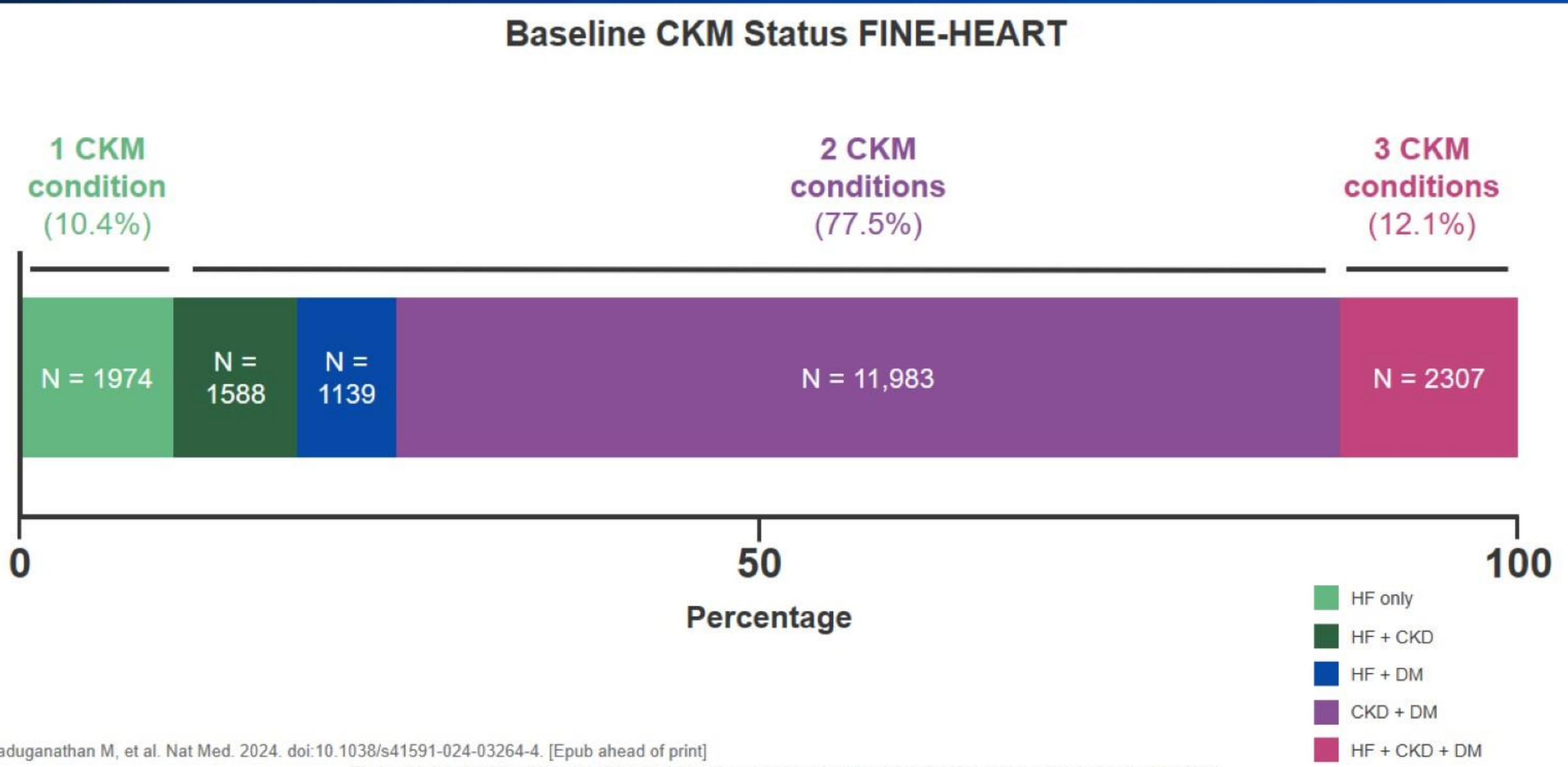
FIGARO-DKD

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

CKM, cardio-kidney-metabolic.

Vaduganathan M, et al. Nat Med. 2024. doi:10.1038/s41591-024-03264-4. [Epub ahead of print]

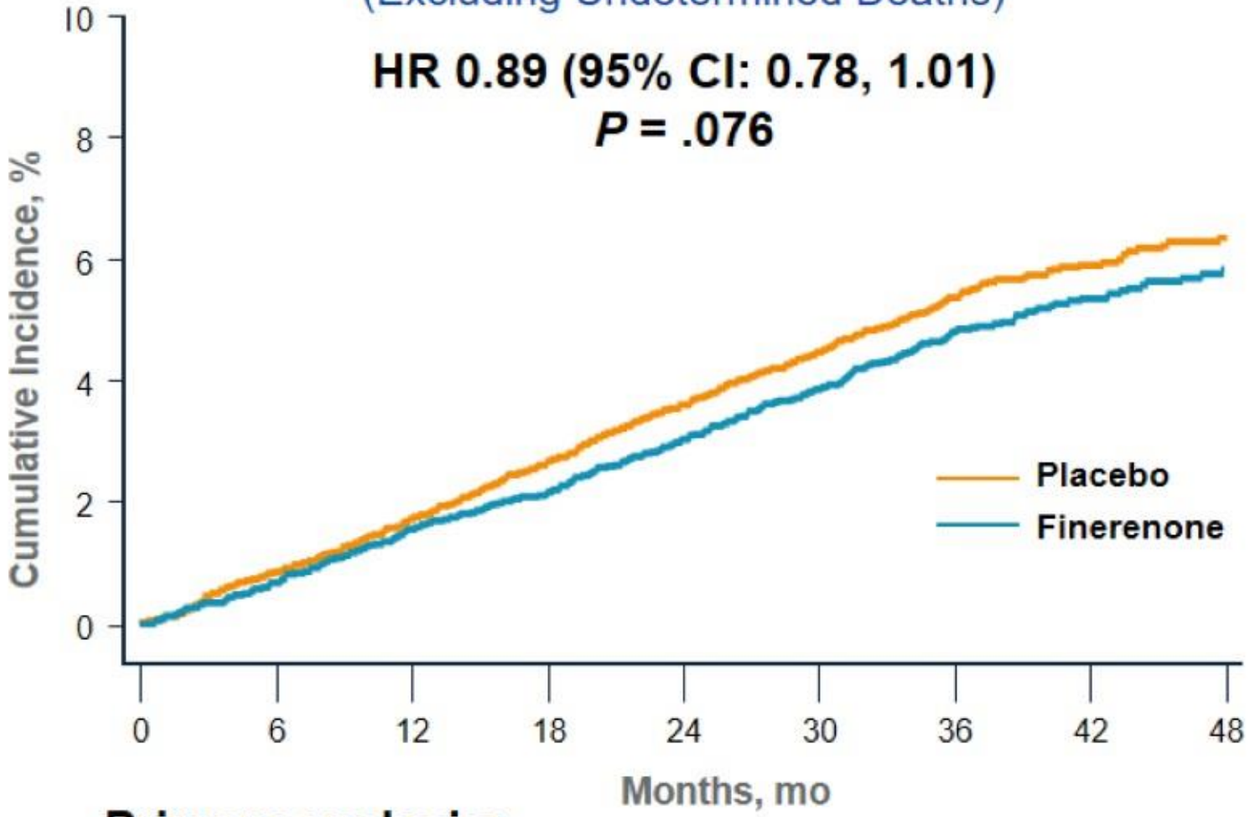
High Burden of Cardio-Kidney-Metabolic Overlap in FINE-HEART



Vaduganathan M, et al. Nat Med. 2024. doi:10.1038/s41591-024-03264-4. [Epub ahead of print]

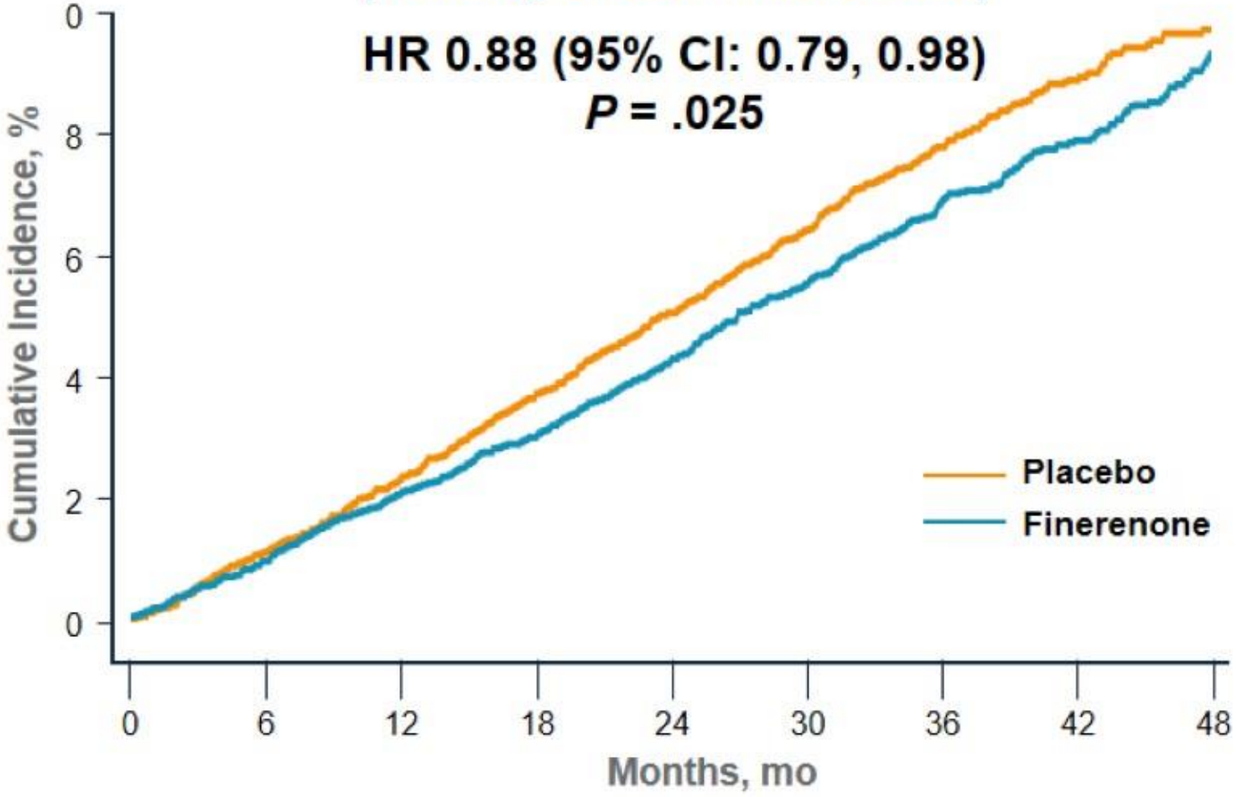
FINE-HEART
Primary Endpoint: CV Death

CV Death
(Excluding Undetermined Deaths)



Primary analysis:
finerenone 421 (4.4%) vs placebo 471 (5.0%)

CV Death
(Including Undetermined Deaths)

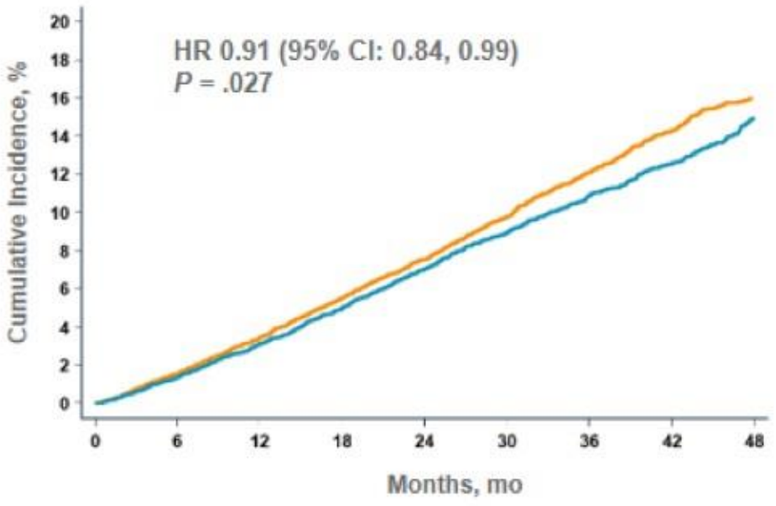


Prespecified sensitivity analysis:
finerenone 627 (6.6%) vs placebo 703 (7.4%)

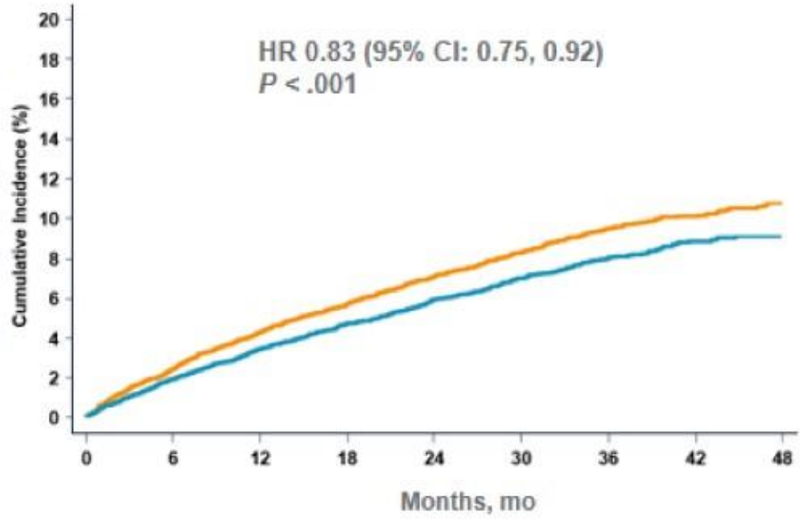
Vaduganathan M, et al. Nat Med. 2024. doi:10.1038/s41591-024-03264-4. [Epub ahead of print]; Vaduganathan M, et al. Presented at: ESC Congress 2024. Abstract.

FINE-HEART
Secondary Endpoints

All-Cause Mortality

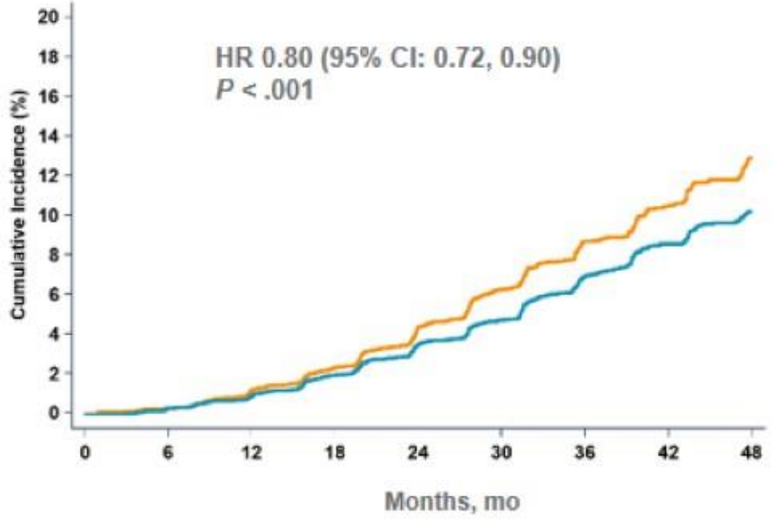


HF Hospitalization



Kidney Composite Endpoint

(Sustained eGFR Decline of ≥ 50%, Kidney Failure[a], or Death due to Kidney Failure)



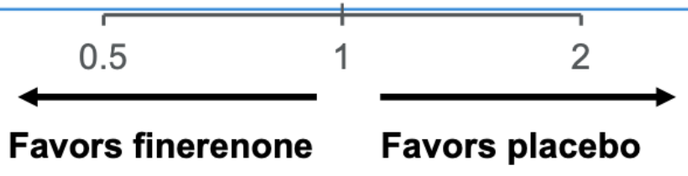
Placebo
Finerenone

a. Sustained eGFR < 15 mL/min/1.73m^2, chronic dialysis, or kidney transplantion.

Vaduganathan M, et al. Nat Med. 2024. doi:10.1038/s41591-024-03264-4 [Epub ahead of print]. Vaduganathan M, et al. Presented at: ESC Congress 2024; Nat Med.2024. Abstract.

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



Conclusions of FINE-HEART

- Largest analysis of the effects of nsMRA, Finerenone across the CKM spectrum
- While this pooled analysis failed to demonstrate significant reduction in CV death, Finerenone was associated with significantly lower death of any cause, CV events & kidney outcomes
- No new or unexpected safety signals were uncovered in this pooled analysis

Clinical Trials With MRAs

EF Category → **HFrEF** | **HFmrEF** | **HFpEF**

HFrEF

Completed

- **RALES:** reduction in death from any cause with spironolactone
- **EMPHASIS-HF:** reduction in CVD + HHF with eplerenone
- **ARTS-HF:** similar reduction in NT-proBNP and rates of hyperkalemia with finerenone vs eplerenone

Ongoing

- **FINALITY-HF:** finerenone in patients intolerant to or ineligible for steroidal MRA for CVD + HF events

HFmrEF / HFpEF

Completed

- **TOPCAT:** no difference in CVD + HHF + aborted cardiac arrest between spironolactone and PBO
- **FINEARTS-HF:** reduction in CVD + HF events with finerenone

Ongoing

- **SPIRIT-HF:** spironolactone vs PBO for CVD + HHF
- **SPIRRIT:** spironolactone + usual care vs usual care alone for CVD + HHF
- **REDEFINE-HF:** finerenone vs PBO in patients hospitalized for acute HF for CVD + HF events
- **Polydiuretic therapy for HFpEF (a pilot trial):** eplerenone + empagliflozin + bumetanide vs empagliflozin alone for cardiorenal health measures

Ongoing Clinical Trials Enrolling Patients With Any EF

- **CONFIRMATION-HF:** early initiation of finerenone + empagliflozin for patients with acute HF vs usual care for a composite death from any cause, HF events, and QoL
- **BalanceD-HF:** balcinrenone + dapagliflozin vs dapagliflozin only for a composite of CVD + HHF + HF events

Green, trials that met primary outcome; Red, trials that did not meet primary outcome.
PBO, piperonyl butoxide.

Chang J, et al. JACC Heart Fail. 2024. doi:10.1016/j.jchf.2024.08.007. [Epub ahead of print]

Summarizing the Role of MRAs in HF

- MRAs have now been definitely proven to improve outcomes in HFrEF (steroidal MRAs) & HFmrEF/HFpEF (non-steroidal MRAs)
- In the FINEARTS, elevated creatinine & hyperkalemia were seen more commonly with finerenone and less incidence of hypokalemia
- MRAs increase serum K+, but the benefit outweighs the risk in most patients with HF
- Should not neglect the MR axis in CKM disease

Conclusion

- **Patients with HFmrEF/HFpEF portend high risk of death & hospital readmission, not different than HFrEF**
- **Underlying metabolic disease and MR over-activation are key pathological mechanisms in both HF & CKD**
- **Among existing HF therapies, SGLT2 inhibitors have demonstrated strong benefit in HFmrEF/HFpEF**
- **In the treatment with nsMRA, Finerenone demonstrated a reduction of CV death and worsening HF events on top of background HF therapy, such as SGLT2 inhibitors, with benefits seen as early as, it may improve long-term event-free survival**
- **US FDA approval of use of Finerenone in patients with HFmrEF/HFpEF**

THANK YOU