BRIGHAM AND WOMEN'S HOSPITAL

FINEHEART

HARVARD MEDICAL SCHOOL

Scientific Sessions

Major Adverse Cardiovascular Events Across The Spectrum Of Cardio-kidney-metabolic Syndrome: A FINE-HEART Pooled Analysis

Sara Siqueira, MD on behalf of:

Maria Pabon, MD; Tracy T. Makuvire, MD MPH; Brian L. Claggett, PhD; Gerasimos Filippatos, MD; Safia Chatur, MD; Akshay S. Desai, MD MPH; Pardeep S. Jhund, MD PhD; Alasdair Henderson, PhD; Meike Brinker, MD; James Lay-Flurrie, MSc; Katja Rohwedder, MD; Carolyn S.P. Lam, MD PhD; Michele Senni, MD; Sanjiv J. Shah, MD; Adriaan A. Voors, MD; Faiez Zannad, MD; Peter Rossing, MD; Luis M. Ruilope, MD PhD; Stefan D. Anker, MD; Bertram Pitt, MD; Rajiv Agarwal, MD; John J.V. McMurray, MD; Scott D. Solomon, MD; Muthiah Vaduganathan, MD MPH

American Heart Association.

#AHA25

DISCLOSURES

- The FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF trials were sponsored by Bayer AG.
- Presenter declares no conflicts of interest related to this presentation.

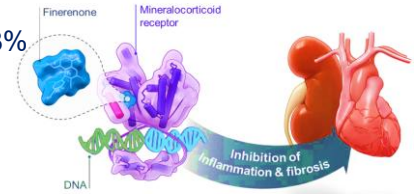
BACKGROUND

The increasing overlap between HF, T2D and CKD is well recognized as CKM syndrome, a distinct multisystem condition driving premature morbidity and mortality.

- **MR overactivation → inflammation, fibrosis, oxidative stress, endothelial injury → atherosclerosis**, **cardiac** and kidney **dysfunction**, despite contemporary therapy.
- Clinically, this leads to **progressive risk escalation** of **MACE-4** (CV death, nonfatal MI, nonfatal stroke or HHF) and **all-cause mortality**.

Finerenone is a novel, selective, nonsteroidal MRA that blocks MR overactivation.

- Pooled **FIDELIO-DKD / FIGARO-DKD** (**FIDELITY**): ↓**CV composite** by **14%**; ↓ kidney progression by 23% in **CKD + T2D.**
- **FINEARTS-HF**: ↓ **total HF events + CV death** by **16%** in **HFmrEF/HFpEF**, regardless of CKD/T2D.



The FINE-HEART program, the pooled data from FINEARTS-HF, FIDELIO-DKD and FIGARO-DKD (FIDELITY), enhanced precision to evaluate finerenone's broad CV effects in patients with a broad and substantial burden of CKM multimorbidity.

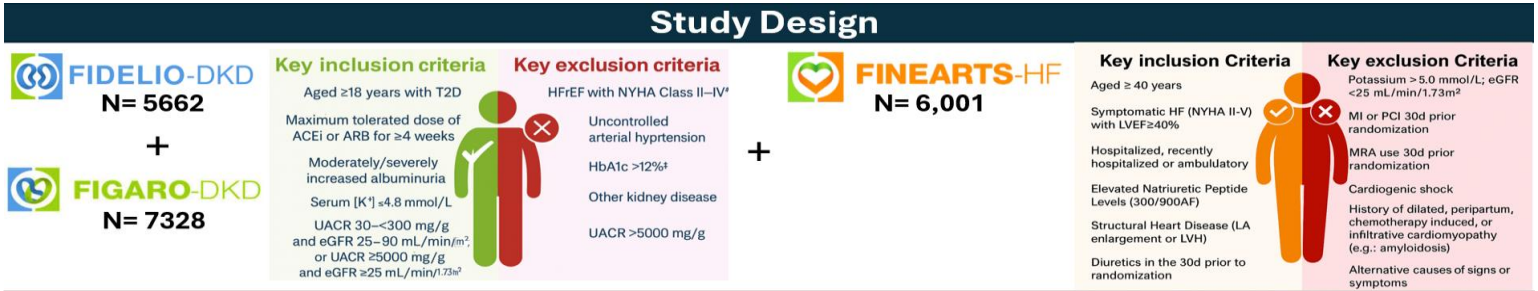
CKD, Chronic Kidney Disease; CKM, Cardio-Kidney-Metabolic; CV, Cardiovascular; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; FIGARO-DKD, Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease; FINEARTS-HF, Finerenone in Heart Failure With Preserved Ejection Fraction (HFpEF) and Mildly Reduced Ejection Fraction (HFmrEF); HFmrEF, Heart Failure With Mildly Reduced Ejection Fraction; HFpEF, Heart Failure With Preserved Ejection Fraction; HHF, Hospitalization for Heart Failure; MACE, Major Adverse Cardiovascular Events; MRA, Mineralocorticoid Receptor Antagonist; MR, Mineralocorticoid Receptor; T2D, Type 2 Diabetes.

Agarwal R et al. European Heart Journal 2022; Solomon SD, et al. NEJM 2024; Vaduganathan, M. et al. Nat Med 2024.

AIMS AND METHODS

This FINE-HEART prespecified analysis explored the treatment effect of finerenone on MACE-4 and quantified the risk of mortality following a nonfatal CV event across a broad CKM spectrum

Study Design



FINE-HEART program included 18,991 participants with HF and CKD with T2D, a broad spectrum of CKM multimorbidity, randomized 1:1 to finerenone or placebo

Inclusion criteria:
Full set **(N= 18,991)**

FINEHEART

Outcomes (prespecified):
Time to first MACE-4, the composite of:
- CV death (excluding undetermined causes) or
- Nonfatal CV events (MI or stroke or HHF)

Individual components of MACE-4
All-cause death

Effect of finerenone vs placebo on outcomes:
- **Cox proportional hazards models, stratified by trial and geographic region**
- Sensitivity analysis:
  - reclassified undetermined deaths as CV deaths
  - competing risks regression: all-cause mortality treated as a competing event.

Association between a first nonfatal CV event and risk of mortality:
- **Time-updated Cox models, adjusted for potential covariates, stratified by trial and region**

N, indicates the number of randomized participants without critical Good Clinical Practice violations.
ACEi, Angiotensin-converting enzyme inhibitor; AF, Atrial fibrillation; ARB, Angiotensin II receptor blocker; CKD, Chronic kidney disease; CKM, Cardio–kidney–metabolic; CV, Cardiovascular; DKD, Diabetic kidney disease; eGFR, Estimated glomerular filtration rate; HHF, Hospitalization for heart failure; LA, Left atrial; LVH, Left ventricular hypertrophy; LVEF, Left ventricular ejection fraction; MACE-4, Major adverse cardiovascular events (CV death, nonfatal MI, nonfatal stroke, or HHF); MI, Myocardial infarction; MRA, Mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; T2D, Type 2 diabetes; UACR, Urinary albumin-to-creatinine ratio.

RESULTS

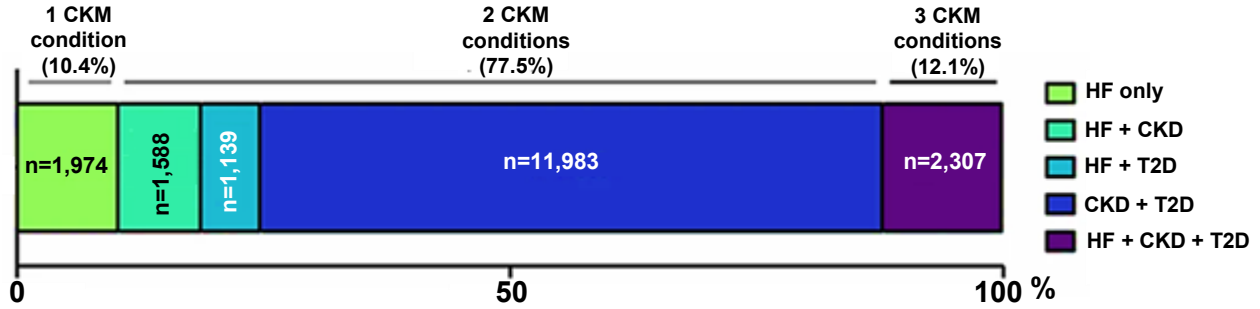
FINEHEART

American Heart Association.

Key baseline status

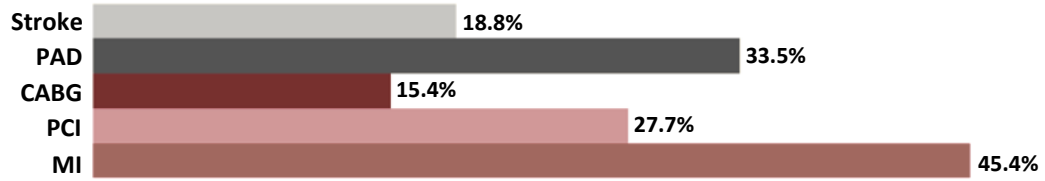
18,991 participants

- Mean age: 67 ± 10 years
- 35% women



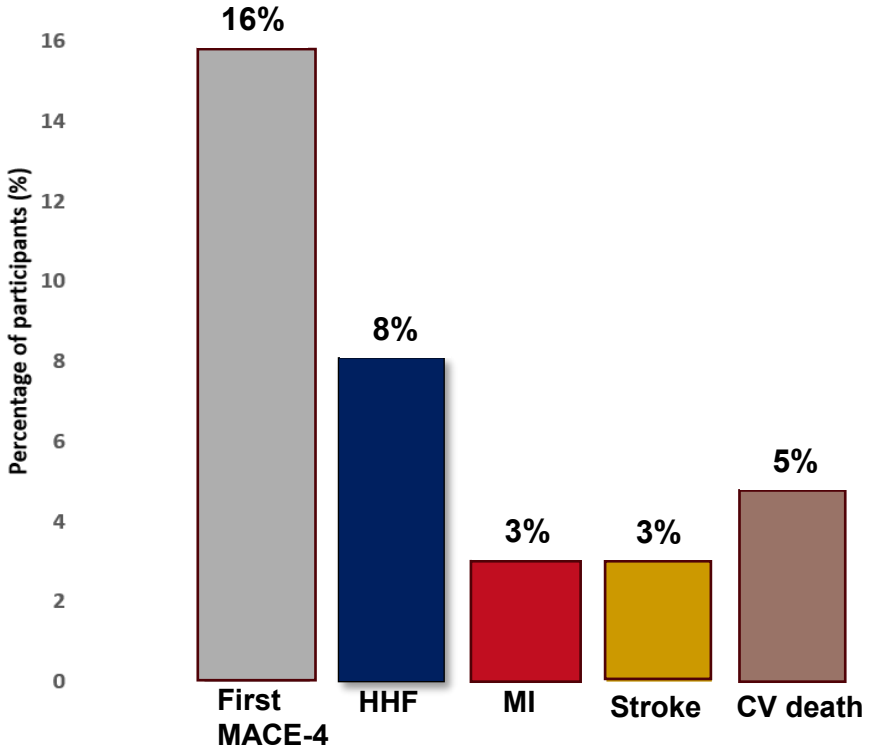
Kidney risk	Low	Moderate	High	Very High
	11.1%	16.0%	34.6%	38.3%

7,845 patients with ASCVD (41,3%)

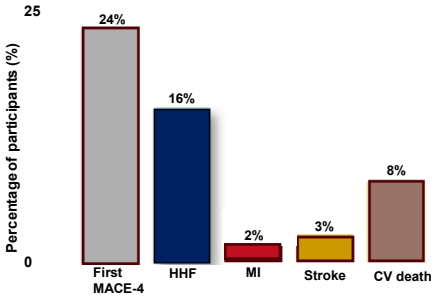


ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass grafting; CKM, cardiovascular-kidney-metabolic; CKD, chronic kidney disease; HF, heart failure; KDIGO, Kidney Disease: Improving Global Outcomes; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary Intervention; T2D, type 2 diabetes mellitus

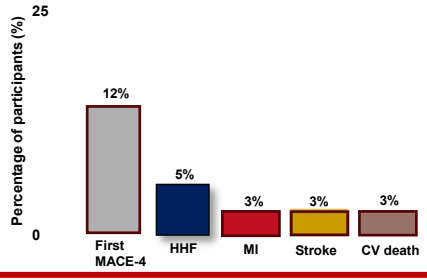
Among 18,991 patients, 2,982 (16%) experienced a first MACE-4 during a median follow-up of 2.9 years



FINEARTS-HF trial
Sample size: 6,001 patients
First MACE-4 events: 1,458 patients (24%)
Median follow-up: 2.6 years



Pooled FIDELIO-DKD and FIGARO-DKD trials
Sample size: 12,990 patients
First MACE-4 events: 1,524 patients (12%)
Median follow-up: 3.0 years

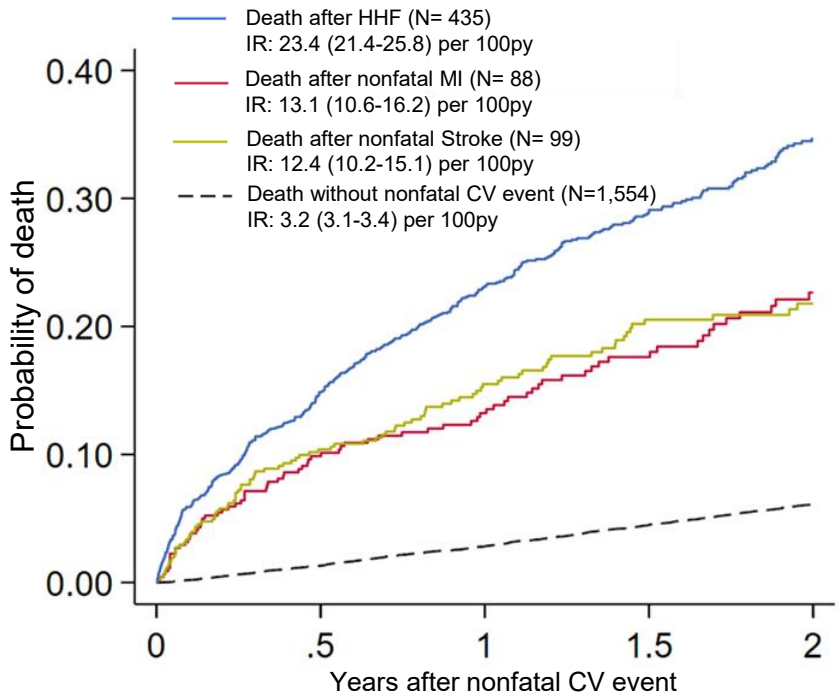


MACE-4 points, major adverse cardiovascular events (a composite of nonfatal myocardial infarction [MI], nonfatal stroke, hospitalization for heart failure [HHF] or cardiovascular [CV] death)
Percentages for individual components of MACE-4 reflect the total number of participants who experienced each event type at any time during follow-up.

Risk of mortality after nonfatal CV event

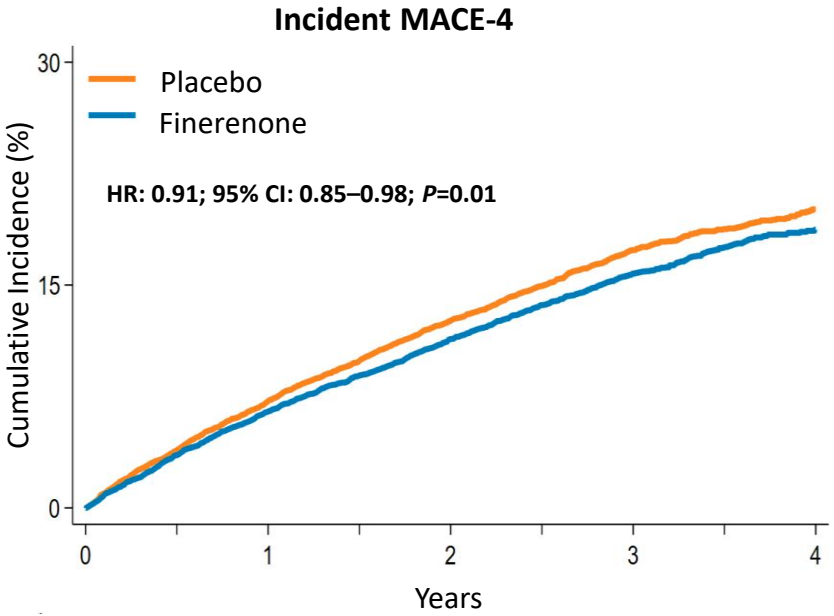
Outcomes	Before nonfatal CV Event Events/Rate per 100py	After nonfatal CV Event Events/Rate per 100py HR* (95% CI);*P*-value	*P*-int (trial)
CV death	569/1.1 (Ref)	323/9.7 6.45 (5.54-7.51); *P*<0.001	0.50
All-cause death	1,556/3.1 (Ref)	622/18.7 4.29 (3.87-4.74); *P*<0.001	0.08

Death after nonfatal CV event, by type of event



CV, cardiovascular; HHF, hospitalization for heart failure; MI, myocardial infarction; py, patient-years.
*Models stratified by trial and region. Adjusted for baseline variables: age, sex, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, body mass index, history of type 2 diabetes mellitus, history of atherosclerotic cardiovascular disease, systolic blood pressure, treatment assignment, smoking status, use of aspirin, use of a statin.
$P_{int\ (interaction)}$ values are reported for interaction between the effect of after vs. before nonfatal CV event and trial (FINEARTS-HF vs Diabetic Kidney Disease Outcomes trials (pooled FIDELIO-DKD/FIGARO-DKD)

Effect of Finerenone on onset of MACE-4 and its components

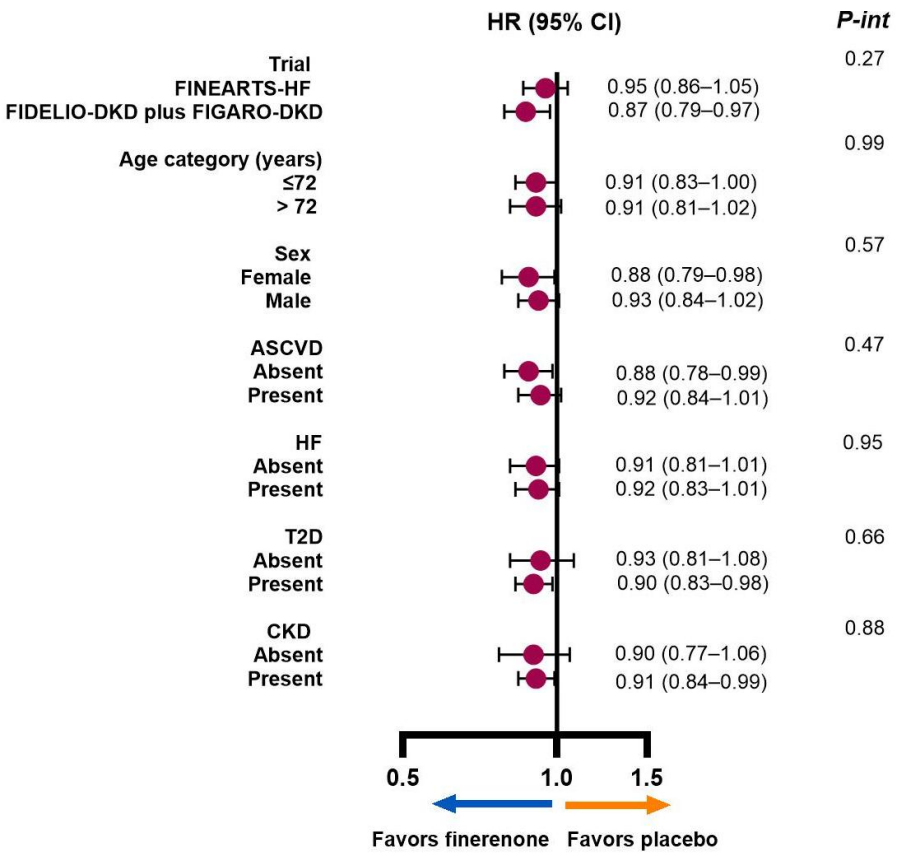


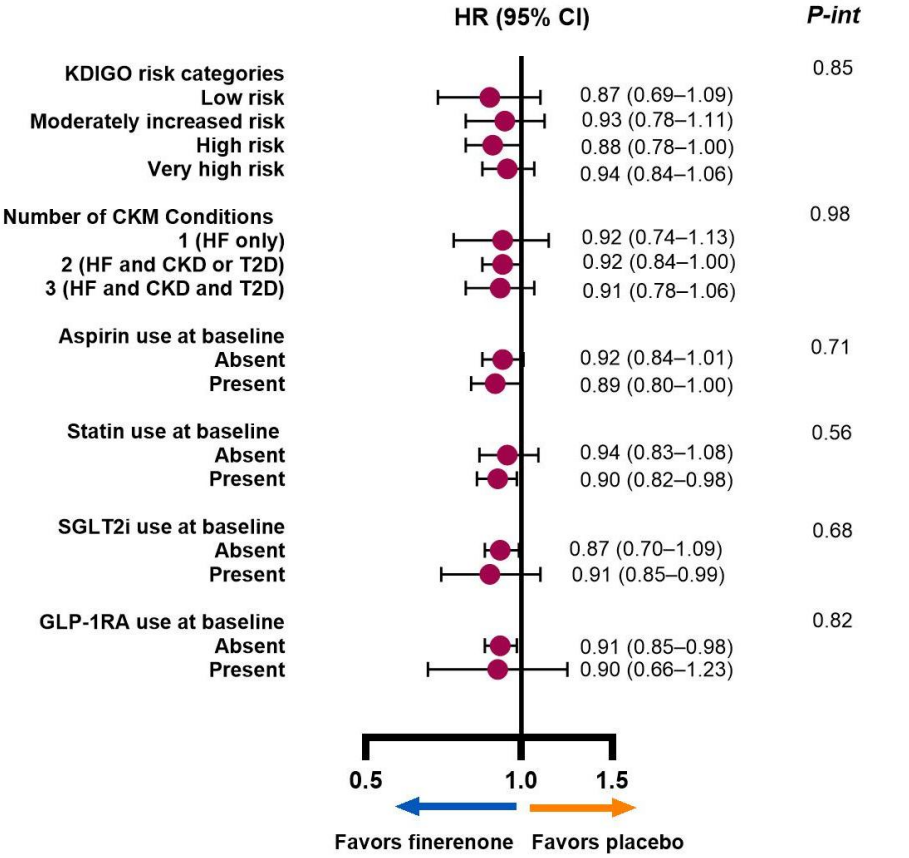
Outcomes	Placebo (N = 9,490) Events/Rate per 100py	Finerenone (N = 9,501) Events/Rate per 100py	HR* (95% CI); *P*-value	*P*-int (trial)
MACE-4	1,554/ 6.2	1,428/ 5.6	0.91 (0.85–0.98); *P*=0.01	0.27
CV death	471/1.7	421/1.6	0.89 (0.78–1.01); *P*=0.08	0.49
Nonfatal MI	244/0.9	256/1.0	1.05 (0.88–1.25); *P*=0.61	0.016†
Nonfatal Stroke	276/1.0	294 /1.1	1.06 (0.90 –1.25); *P*=0.49	0.24
HHF	839/3.2	705/2.7	0.83 (0.75-0.92); *P*<0.001	0.33

*Models stratified by trial and region.
$P_{int\ (interaction)}$ values are reported for interaction between treatment effect and trial (FINEARTS–HF vs Diabetic Kidney Disease Outcomes trials (pooled FIDELIO–DKD/FIGARO–DKD)
† Nonfatal MI events were infrequent (FINEARTS–HF: finerenone 83 vs. placebo 56; pooled FIDELIO–DKD/FIGARO–DKD: 173 vs. 188), and the observed interaction was likely driven by the limited number of events in FINEARTS–HF.

MACE–4 points, major adverse cardiovascular events (a composite of nonfatal myocardial infarction[MI], nonfatal stroke, hospitalization for heart failure [HHF] or cardiovascular [CV] death); py, patient-years.

Effects of Finerenone on onset MACE-4 across Major Clinical Subgroups





CONCLUSION

In a broad CKM population, MACE-4 were frequent, strongly prognostic and modestly reduced with finerenone.

Finerenone effect was largely driven by reducing HHF, the most frequent component of the composite CV risk.

Mortality risk increased markedly after nonfatal CV events, especially after HHF, highlighting the need for prevention.

These findings support the role of finerenone as a disease-modifying therapy providing broad CV protection in high-risk patients across the CKM spectrum, with its greatest impact on reducing HF-related morbidity.