FINERENONE REDUCES SUDDEN DEATH ACROSS THE SPECTRUM OF CARDIO-KIDNEY-METABOLISM: THE FINE-HEART POOLED ANALYSIS

Alberto Foà[1-2] on behalf of

Maria A. Pabon, Gerasimos Filippatos, Brian L. Claggett, Zi Michael Miao, Pardeep S. Jhund, Alasdair Henderson, Meike Brinker, Andrea Lage, Lucas Hofmeister, Yoriko De Sanctis, Carolyn S.P. Lam, Michele Senni, Sanjiv J. Shah, Adriaan A. Voors, Faiez Zannad, Peter Rossing, Luis M. Ruilope, Stefan D. Anker, Bertram Pitt, Rajiv Agarwal, John J.V. McMurray, Scott D. Solomon, Muthiah Vaduganathan, Akshay S. Desai

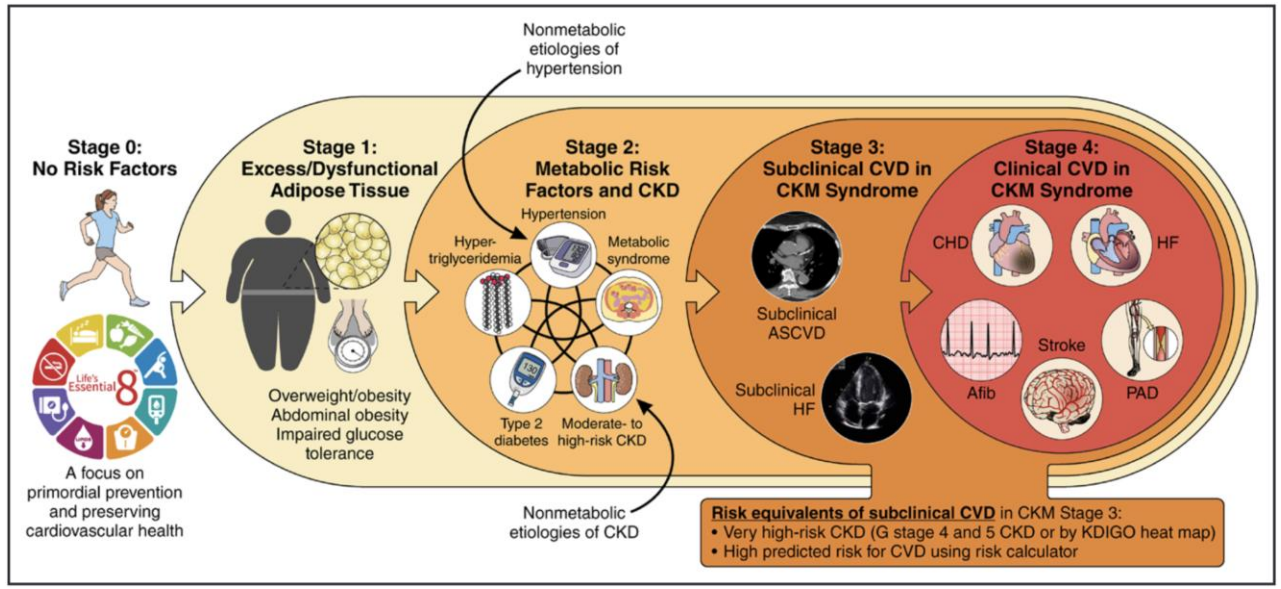
[1]Heart Failure and Transplant Unit - IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy
[2]Brigham and Women's Hospital, Cardiovascular Division, Harvard Medical School

PROSPERO: CRD42024570467

The trials included in this pooled analysis were funded by Bayer AG

#AHA25

CKM syndrome and mortality excess



The intersection of cardiac, kidney, and metabolic (CKM) dysfunction is associated with mortality excess

The individual components of CKM confer an increased risk of sudden death (SD) but little is known about SD in people with overlapping CKM conditions

The non-steroidal MRA finerenone has been shown to improve clinical outcomes in diabetic patients with CKD (FIDELIO-DKD and FIGARO-DKD trials), and in those with HFmrEF/HFpEF (FINEARTS-HF)

The anti-inflammatory and antifibrotic properties of finerenone are thought to reduce the arrhythmic substrate that lead to SD but clinical trials were underpowered to evaluate treatment effects on SD

Ndumele CE. Circulation. 2023 Nov 14;148(20):1606-1635.

FINE-HEART study design

FINEHEART

(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 non-steroidal MRA finerenone on important cardio-kidney outcomes and is enriched for participants with a high burden of CKM multimorbidity.

Objectives and Definitions

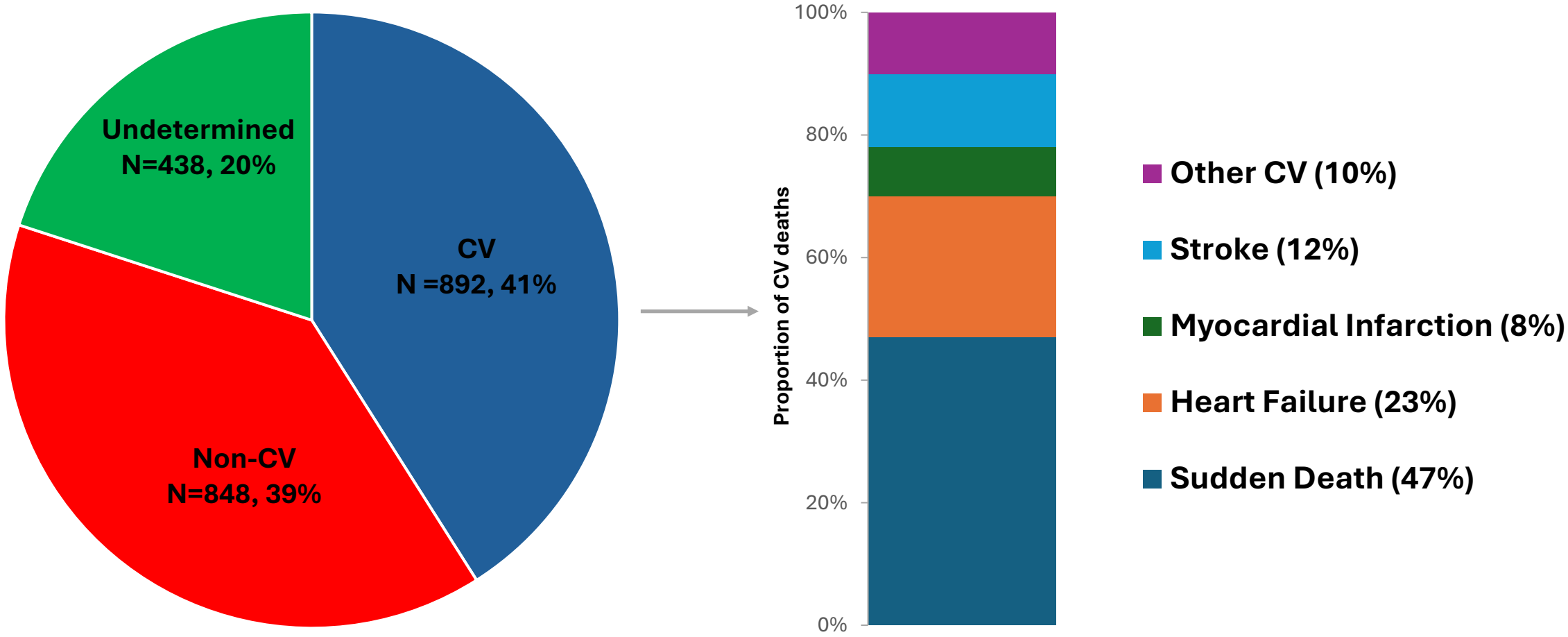
- In this prespecified analysis of FINE-HEART, we evaluated mode of death – including SD – and examined the effects of finerenone on SD across the CKM spectrum
- Causes of death were centrally adjudicated by a clinical endpoint committee in each trial
- SD was defined as death occurring unexpectedly in an otherwise stable subject with last contact within 24 hours
- Independent predictors of SD were assessed with multivariable Cox models
- Treatments effects were evaluated with Cox proportional hazard models

Individual Trials Study Designs

	FINEARTS-HF	FIDELIO-DKD and FIGARO-DKD
Validly randomized	6,001 participants	12,990 participants
Countries	37	48
Study population	HFmrEF/HFpEF	CKD and type 2 diabetes
Key inclusion criteria	• Age ≥ 40 years • Symptomatic chronic HF • LVEF ≥ 40% • Structural heart disease • Elevated natriuretic peptides	• Age ≥ 18 years • Type 2 diabetes • UACR ≥ 30 mg/g • Background therapy with ACEi/ARB
Dosage and titration	eGFR ≤ 60: 10 mg up to 20 mg eGFR > 60: 20 mg up to 40 mg	eGFR < 60: 10 mg up to 20 mg eGFR ≥ 20 mg
Median follow-up	2.6 years	FIDELIO-DKD: 2.6 years FIGARO-DKD: 3.4 years

Mode of Death in FINE-HEART

During a median follow-up of 2.9 years, 2,178 deaths occurred among the 18,991 participants of FINE-HEART, 12% in the placebo arm vs. 11% in the finerenone arm (p=0.030)



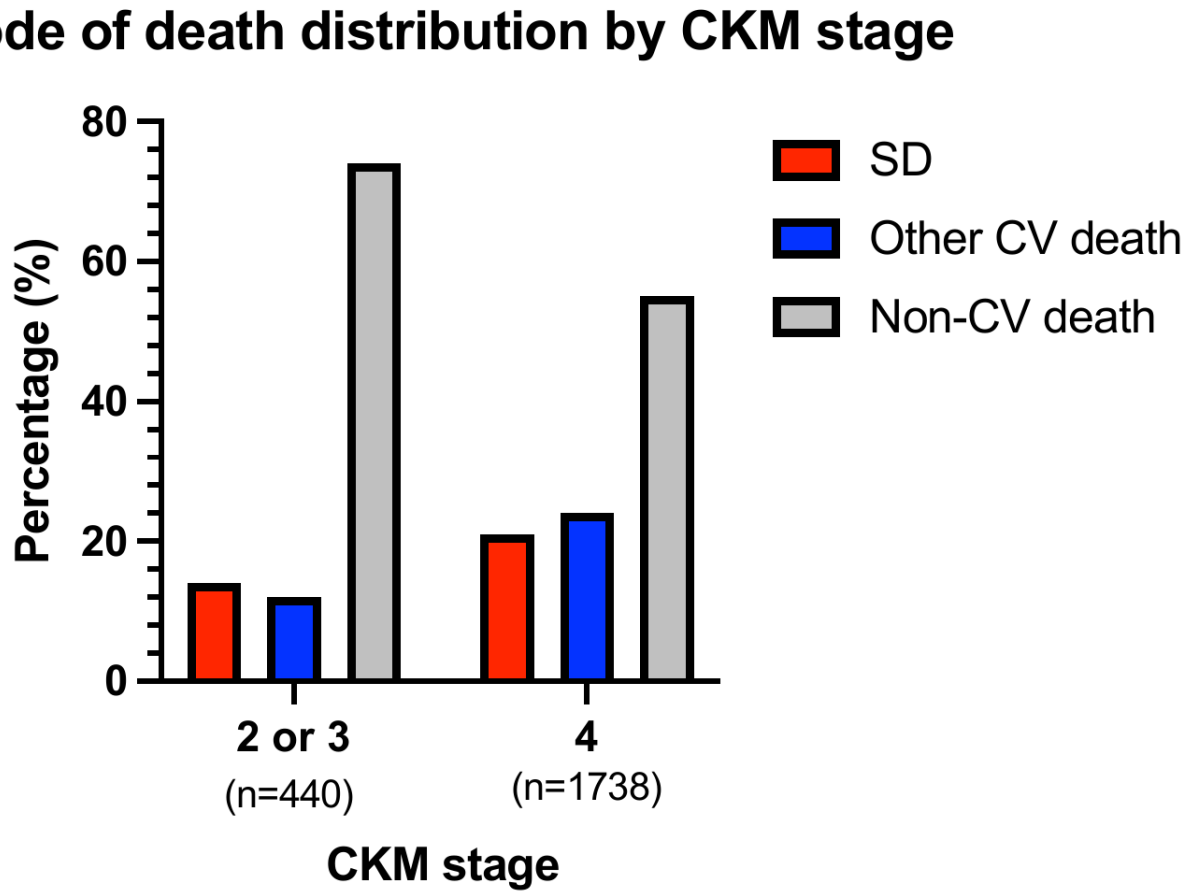
SD in FINE-HEART

SD occurred in 418 participants (2.2%) with an incidence rate of 0.8 per 100 patient-years

- FIDELIO-DKD: 77 (1.3%); 0.5 per 100 py
- FIGARO-DKD: 126 (1.7%); 0.5 per 100 py
- FINEARTS-HF: 215 (3.6%); 1.5 per 100 py

Compared to participants with stage 2 or 3 CKM, those with stage 4 CKM had nearly a three-fold higher risk of SD

HR 2.7 (95% CI 2.0, 3.7); p<0.001



Baseline characteristics according to SD

	No Sudden Death N=18,573	Sudden Death N=418	P value
Age	67 ± 10	69 ± 10	<0.001
Female sex	6521 (35%)	143 (34%)	0.70
Region			<0.001
Asia	3567 (19%)	56 (13%)	
Eastern Europe	5749 (31%)	193 (46%)	
Latin America	2026 (11%)	49 (12%)	
North America	2483 (13%)	37 (9%)	
Western Europe, Oceania and Others	4748 (26%)	83 (20%)	
Baseline SBP	135 ± 15	132 ± 15	<0.001
Baseline UACR	291 [47, 848]	134 [29, 743]	0.001
Atrial fibrillation on ECG	2711 (15%)	117 (28%)	<0.001
History of HF	6751 (36%)	257 (61%)	<0.001
History of DM	15125 (81%)	304 (73%)	<0.001
History of MI	3436 (18%)	125 (30%)	<0.001
Beta blockers use	11291 (61%)	303 (72%)	<0.001
Diuretic use	12291 (66%)	340 (81%)	<0.001
ACEi/ARB/ARNI use	17357 (93%)	369 (88%)	<0.001

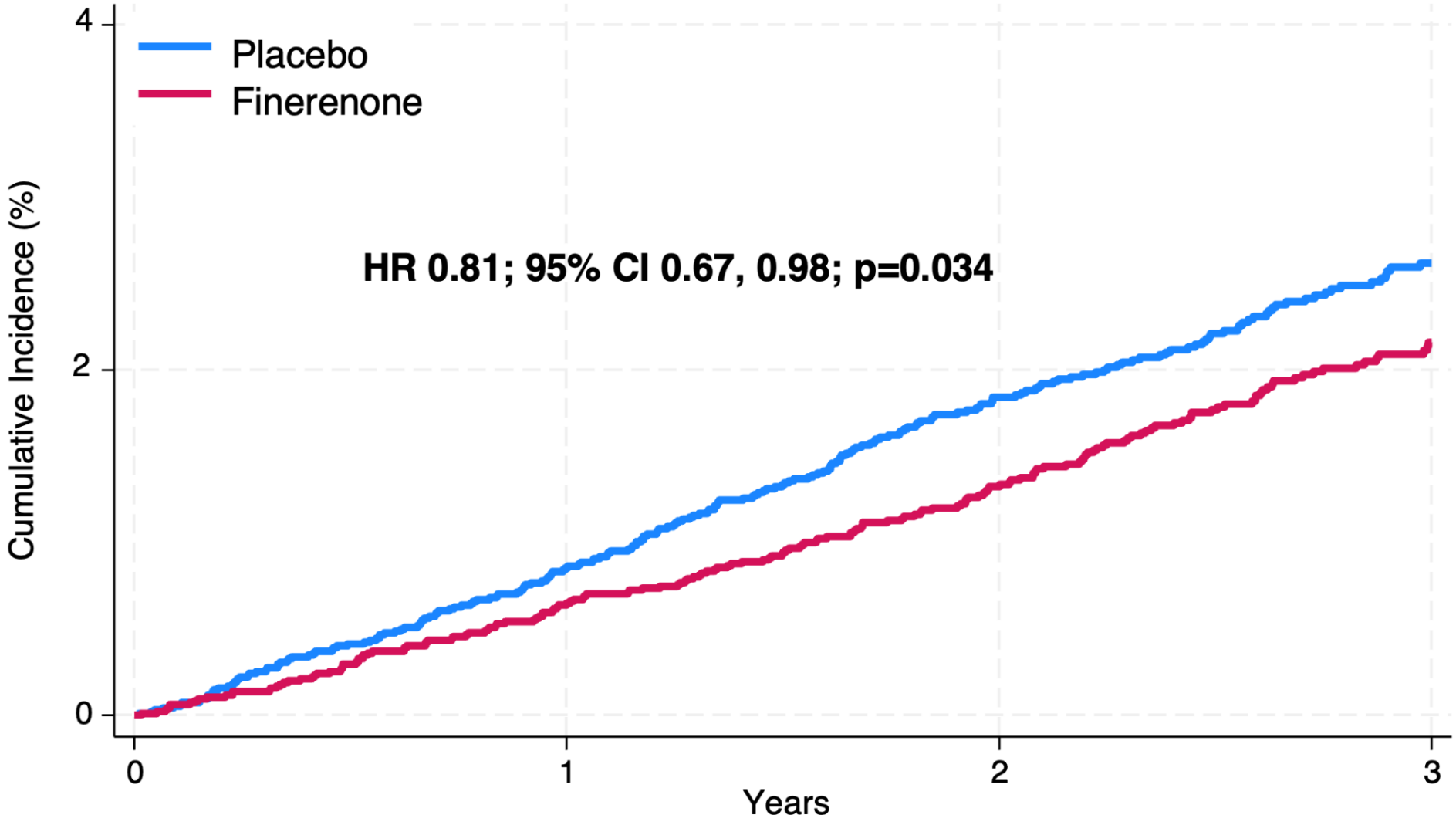
Independent predictors of SD

	HR (95% CI)	|z|	P value
History of heart failure	3.31 (2.50, 4.13)	9.1	<0.001
UACR (per doubling)	1.10 (1.06, 1.15)	4.6	<0.001
Atrial fibrillation	1.77 (1.36, 2.31)	4.2	<0.001
History of myocardial infarction	1.62 (1.29, 2.04)	4.2	<0.001
Region			
Asia	Reference		
Eastern Europe	1.75 (1.29, 2.38)	3.5	<0.001
Latin America	1.63 (1.10, 2.42)	2.4	0.015
North America	0.95 (0.62, 1.44)	0.3	0.80
Western Europe, Oceania, and Others	1.05 (0.74, 1.48)	0.3	0.79
HbA1c	1.13 (1.05, 1.21)	3.3	0.001
SBP (per 10 mmHg increase)	0.99 (0.98, 1.00)	2.8	0.005
Age (per 10-year increase)	1.18 (1.04, 1.33)	2.7	0.008
Aspirin use at baseline	1.33 (1.06, 1.66)	2.4	0.014
Randomization to finerenone	0.81 (0.67, 0.98)	2.1	0.035
eGFR (per 10 ml/min/1.73 m^2 increase)	0.95 (0.90, 1.00)	2.0	0.044
Statin use at baseline	0.80 (0.64, 0.99)	2.0	0.044

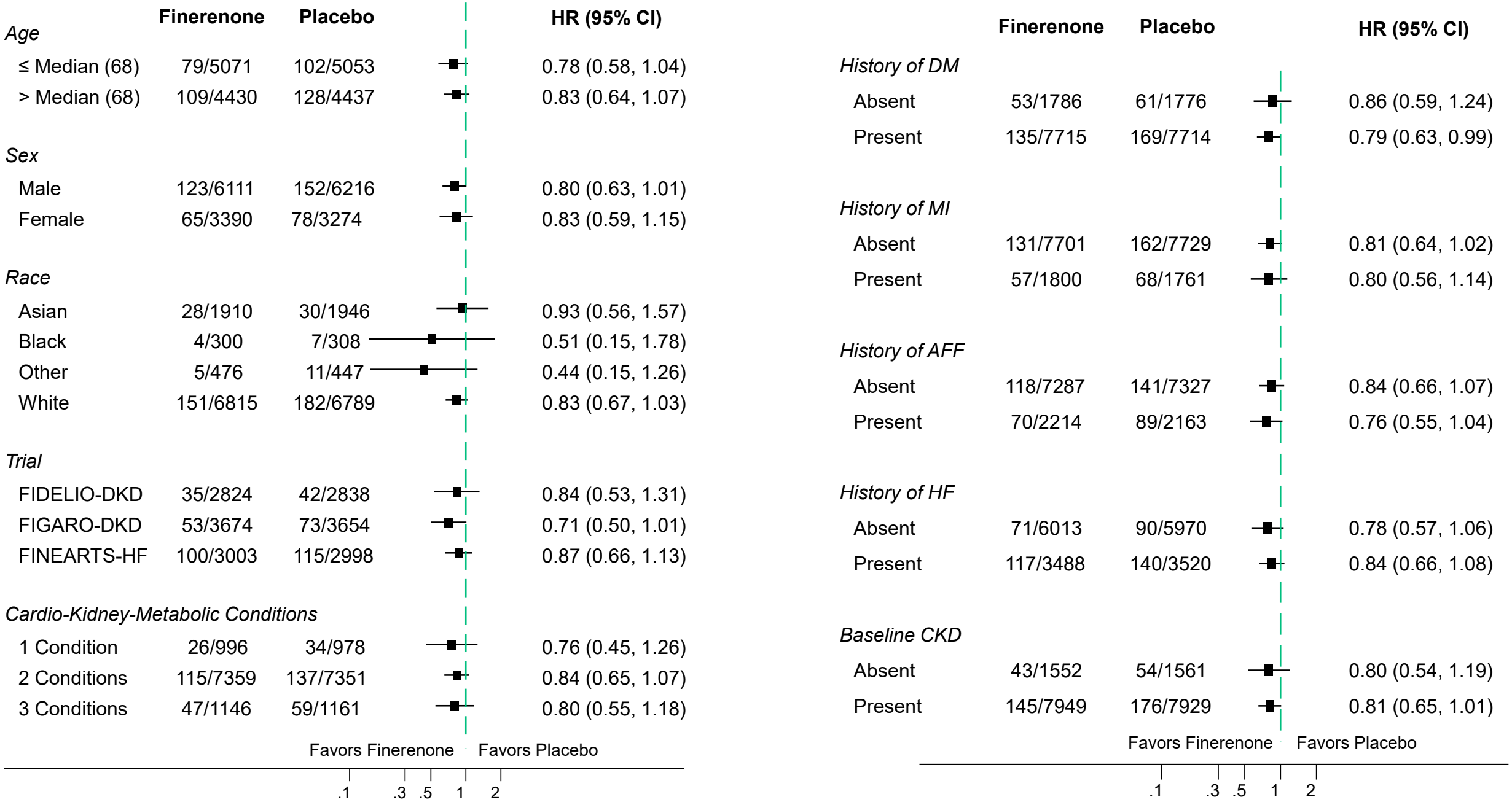
Randomization to finerenone led to a reduced risk of SD

Placebo
230 events
0.85 per 100 py

Finerenone
188 events
0.69 per 100 py



Consistent treatment effects across subgroups



Limitations

- Although causes of death were centrally adjudicated by experienced clinical endpoint committees, we cannot exclude potential misclassifications
- Since baseline LVEF was not collected in FIDELIO-DKD and FIGARO-DKD, associations between LVEF and SD were not investigated
- FINE-HEART represents a pooled population of three clinical trials with distinct study designs, introducing potential heterogeneity
- Given the stringent inclusion and exclusion criteria of clinical trials our results may not be generalizable to the real-world CKM population

Conclusions

- In this prespecified analysis of the FINE-HEART study population, SD was the leading cause of CV death, accounting for nearly 20% of overall mortality.
- Several baseline characteristics were independently associated with increased risk of SD, including history of HF, prior MI, atrial fibrillation, and kidney dysfunction.
- Finerenone therapy was associated with a 19% reduction in the risk of SD compared with placebo, with consistent benefits across major clinical subgroups.

These findings broaden the evidence supporting non-steroidal MRA use in patients with CKM syndrome, demonstrating benefits that extend beyond cardiovascular and renal protection to include potential mitigation of arrhythmic mortality.