Mode of Death in Patients with Heart Failure with Mildly Reduced or Preserved Ejection Fraction: The FINEARTS-HF Trial

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Background

- Mechanisms of cardiovascular (CV) death in patients with heart failure and mildly reduced or preserved ejection fraction (HFmrEF/HFpEF, LVEF > 40%) remain unclear, particularly for the relatively understudied subset of patients with ongoing heart failure symptoms despite improvement in EF to greater than 40% (HFimpEF)
- Although treatment with finerenone was shown to reduce the composite of total worsening HF events (defined as first or recurrent unplanned hospitalizations or urgent visits for HF) and death from CV causes in the randomized FINEARTS-HF (FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure) trial , the impact on cause-specific mortality has not previously been reported.

Study Aims

- In this prespecified analysis of the FINEARTS-HF trial, we evaluated:
  1. Mode of death according to ejection fraction and in those with HFimpEF
  2. Treatment effects of finerenone vs. placebo on cause-specific mortality

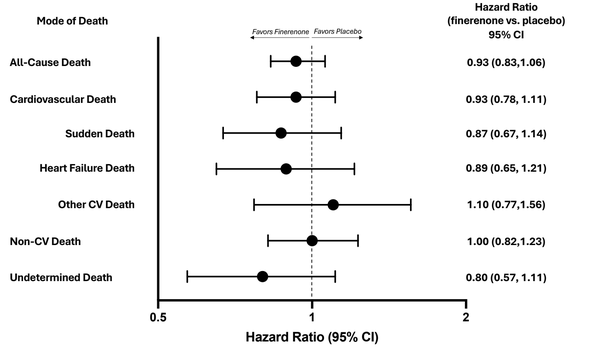
Methods

- Mode of death was centrally adjudicated according to standardized criteria by a clinical endpoints committee (CEC) blinded to randomized treatment assignment.
- The CEC classified all deaths as CV, non-CV, or undetermined, and further subclassified CV deaths as sudden deaths or non-sudden deaths due to acute myocardial infarction (MI), heart failure, stroke, or other CV causes.
- Adjudicated mode of death was examined in subgroups defined by categories of baseline LVEF (<50%, >=50-<60%, and >=60%) and separately among patients with HFimpEF.
- The effect of randomized treatment on cause-specific death was evaluated in Cox regression models, stratified by geographic region and baseline LVEF (<60% or ≥60%).

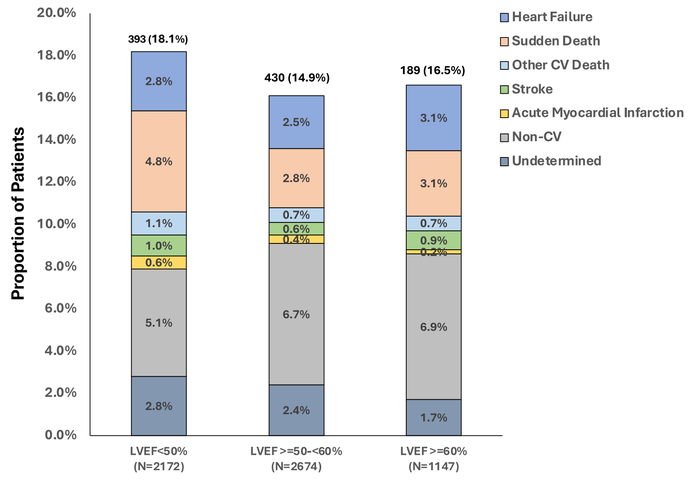
Baseline Characteristics by Mode of Death among patients who died (N=1013), FINEARTS-HF

	CV Death n=502	Non-CV Death n=368	Undetermined n=143	p-value (all groups)
Age (years)	73.43 ± 9.82	76.23 ± 8.67	75.76 ± 9.41	<0.001
Men	299 (59.6%)	219 (59.5%)	76 (53.1%)	0.36
Race				
Asian	78 (15.5%)	45 (12.2%)	33 (23.1%)	0.14
Black	4 (0.8%)	5 (1.4%)	2 (1.4%)	
White	410 (81.7%)	311 (84.5%)	106 (74.1%)	
Other	10 (2%)	7 (1.9%)	2 (1.4%)	
Region				
Asia	78 (15.5%)	45 (12.2%)	32 (22.4%)	
Eastern Europe	222 (44.2%)	137 (37.2%)	64 (44.8%)	
Latin America	61 (12.2%)	40 (10.9%)	12 (8.4%)	<0.001
North America	34 (6.8%)	42 (11.4%)	19 (13.3%)	
Western Europe, Oceania and Others	107 (21.3%)	104 (28.3%)	16 (11.2%)	
Any prior HF hospitalization	346 (68.9%)	239 (64.9%)	104 (72.7%)	0.2
Recency of HF event				
≤ 7 days from randomization	127 (25.3%)	91 (24.7%)	32 (22.4%)	0.54
> 7 days ≤ 3 months	164 (32.7%)	104 (28.3%)	44 (30.8%)	
> 3 months or no index HF event	211 (42.0%)	173 (47.0%)	67 (46.9%)	
Systolic Blood Pressure (mmHg)	127.73 ± 15.68	129.28 ± 15.57	127.12 ± 17.41	0.25
Body Mass Index (kg/m2)	29.84 ± 6.49	29.39 ± 6.40	29.41 ± 7.53	0.56
Creatinine (mg/dL)	1.23 ± 0.39	1.27 ± 0.41	1.24 ± 0.37	0.4
eGFR (mL/min/1.73m2)	56.59 ± 19.16	54.13 ± 19.02	53.77 ± 19.06	0.1
UACR (mg/g)	38 [11,145]	27 [9,131]	40 [14, 180]	0.8
Potassium (mmol/L)	4.34 ± 0.52	4.34 ± 0.50	4.40 ± 0.51	0.37
LVEF (%)	51.57 ± 8.00	53.46 ± 8.08	51.49 ± 7.38	<0.001
NT-proBNP (pg/mL)	1773 [950, 3329]	1533 [746, 2974]	1865[873,3574]	0.03
NYHA class				
NYHA class II	291 (58.0%)	217 (59.0%)	86 (60.1%)	0.62
NYHA class III	202 (40.2%)	145 (39.4%)	57 (39.9%)	
NYHA class IV	9 (1.8%)	6 (1.6%)	0 (0.0%)	
History of Hypertension	447 (89.0%)	331 (89.9%)	128 (89.5%)	0.91
Diabetes Mellitus	255 (50.8%)	199 (54.1%)	68 (47.6%)	0.37
Atrial fibrillation on baseline electrocardiogram	225 (44.8%)	152 (41.3%)	62 (43.4%)	0.59
History of Stroke	68 (13.5%)	48 (13.0%)	22 (15.4%)	0.78
History of myocardial infarction	159 (31.7%)	104 (28.3%)	33 (23.1%)	0.12
Prior LVEF<40% (HFimpEF)	24 (4.8%)	13 (3.5%)	4 (2.8%)	0.47
Beta blocker use	414 (82.5%)	312 (84.8%)	110 (76.9%)	0.11
ACEI/ARB/ARNI use	380 (75.7%)	275 (74.7%)	98 (68.5%)	0.22
SGLT-2 inhibitor use	77 (15.3%)	44 (12.0%)	16 (11.2%)	0.24
Loop diuretic	464 (92.4%)	331 (89.9%)	138 (96.5%)	0.044

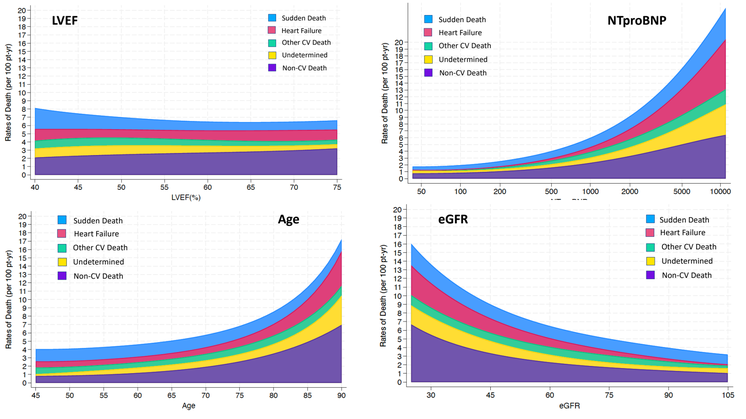
Effect of finerenone compared with placebo on cause-specific mortality, FINEARTS-HF



Adjudicated Mode of Death According to LVEF, FINEARTS-HF



Variation in incidence of adjudicated mode of death by continuous LVEF, NT-proBNP, Age, and eGFR



Results

- Of 1013 (16.9%) patients who died during median follow up of 32 months, mode of death was ascribed to CV causes in 502 (49.6%), non-CV causes in 368 (36.3%), and undetermined cause in 143 (14.1%). Of CV deaths, 215 (42.8%) were due to sudden death, 163 (32.4%) to HF, 48 (9.6%) to stroke, 25 (5.0%) to myocardial infarction, and 51 (10.2%) to other CV causes .
- The proportion of all-cause, CV, and sudden death was higher in those with EF<50%. The proportion of deaths related to HF was similar across EF categories, and that due to MI, stroke and other CV causes was low regardless of EF .
- Rates of non-CV death did not vary significantly by LVEF, but did increase steeply in relationship to older age and lower eGFR. Rates of both CV and non-CV mortality appeared to increase in relationship to higher NT-proBNP, particularly death to worsening HF.
- The incidence of death from any cause and the distribution of cause-specific mortality were similar in the 273 (4.5%) patients with HFimpEF and the residual population with no prior history of LVEF<40% (data not shown)
- Randomization to finerenone did not significantly reduce death or cause-specific death compared with placebo in any EF category .

Conclusions

- In this prespecified analysis of patients with HF and LVEF≥40% enrolled in the FINEARTS-HF trial, roughly one-half of deaths during median follow up of 32 months were related to CV causes
- Three-fourths of CV deaths were attributed to sudden death or HF progression,
- Higher rates of CV death in those with LVEF<50% were driven by higher rates of sudden cardiac death in this group.
- The proportionate contribution of non-CV death did not appear to vary by LVEF, but was higher in those with older age and lower eGFR.
- Overall mortality rates and the distribution of mode of death were similar in the 4.5% of enrolled patients who had prior history of LVEF<40% (HFimpEF) and those with LVEF consistently ≥40%
- Assignment to finerenone did not appear to reduce overall mortality or cause-specific mortality in any LVEF subgroup

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