Biomarker, Functional Status, and Quality of Life Trajectories Before Modes of Death in Heart Failure

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BACKGROUND

- Sudden death (SD) is a leading cause of mortality in patients with heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF), yet it remains uncertain whether these events are abrupt or preceded by measurable clinical decline.
- Identifying whether SD is preceded by distinct clinical and biological deterioration, compared with other modes of death, may help refine risk prediction and prevention strategies.

AIMS

In a *post hoc* analysis of the FINEARTS-HF trial, we examined temporal changes in New York Heart Association (NYHA) class, Kansas City Cardiomyopathy Questionnaire–Total Symptom Score (KCCQ-TSS), and N-terminal pro–B-type natriuretic peptide (NT-proBNP) prior to adjudicated SD, comparing patterns with other modes of death and survivors, to identify potential early signals of near-term SD risk.

METHODS

- FINEARTS-HF: Multicenter, event-driven, randomized trial evaluating finerenone vs. placebo in heart failure (HF) patients with LVEF ≥40%.

- Key inclusion criteria: Age ≥40 years, NYHA class ≥II, elevated natriuretic peptides (NT-proBNP ≥300 pg/mL or BNP ≥100 pg/mL in sinus rhythm; higher thresholds in atrial fibrillation), evidence of structural heart disease and recent diuretic use.

- Parameters were assessed at randomization and regular intervals
- NYHA class: 1, 3, 6, 9, 12 months, then every 2 months until 42 months.
- KCCQ-TSS: 6, 9, 12, 16, 24, 32, 40 months.
- NT-proBNP: 3, 12 months.

- Analysis: Longitudinal trajectories of parameters of interest using repeated measures regression with cubic splines.
- Changes analyzed before adjudicated SD and compared with those prior to end of follow-up among survivors, and prior to HF–related death, and non-sudden CV death.

RESULTS

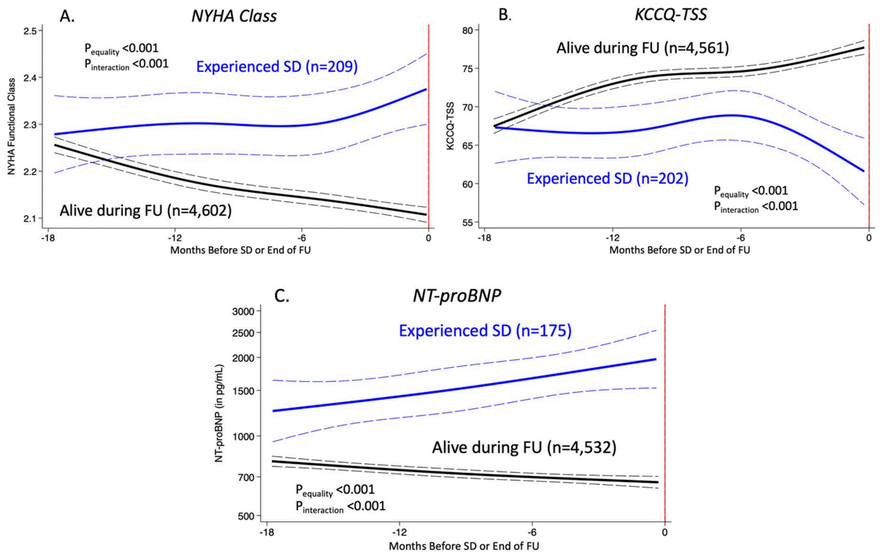
- Over a median 2.7-year follow-up, 215 SDs occurred.

- In the 6 months before death, SD was preceded by a slight worsening in physician-assigned NYHA class (from ~2.3 to 2.4), but worse self-reported health status (a ~8-point decline in KCCQ-TSS) and a gradual rise in NT-proBNP levels (from ~1,800 to 2,000 pg/mL) (**Figure 1**).

- Among patients who survived, NYHA class improved (from ~2.3 to 2.1), KCCQ-TSS increased (from ~68 to 77) and NT-proBNP levels declined (from ~800 to 650 pg/mL) over the 18 months before the end of follow-up (**Figure 1**).

- Comparable patterns of deterioration to those preceding SD, often more pronounced, were observed before other modes of death (**Figures 2 & 3**)

Figure 1. Trajectories of (A) NYHA Functional Class, (B) KCCQ-TSS, and (C) NT-proBNP Levels in the Period Preceding SD Versus in Patients Who Remained Alive Throughout Follow-Up (FU)



In this contemporary HFmrEF/HFpEF cohort, SD was preceded by modest worsening of symptoms, declining quality of life, and rising natriuretic peptide levels, suggesting many of these events may not have been entirely "sudden".

However, similar deterioration preceding other modes of death suggests limited specificity for SD.

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Figure 2. Trajectories of (A) NYHA Functional Class, (B) KCCQ-TSS, (C) NTproBNP, in the Period Preceding SD vs. HF-Related Death

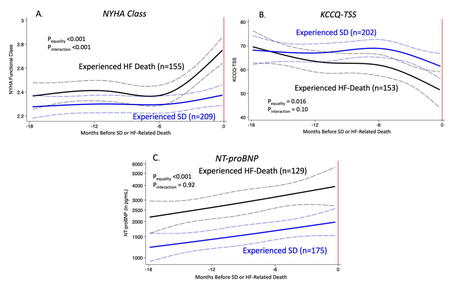
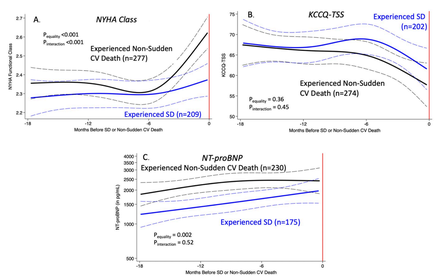


Figure 3. Trajectories of (A) NYHA Functional Class, (B) KCCQ-TSS, (C) NTproBNP, in the Period Preceding SD vs. Non-Sudden Cardiovascular Death



DISCUSSION

- SD was preceded by modest symptom worsening, declining KCCQ, and rising NT-proBNP, whereas survivors generally improved.

- Similar—often greater—deterioration preceded other modes of death, highlighting the limited specificity of these markers for SD; rather, they signal heightened near-term overall mortality risk.

- SD in HFpEF may reflect transient triggers superimposed on subacute multi-organ and hemodynamic decline, suggesting shared pathways with other modes of death rather than a purely abrupt arrhythmic event.

LIMITATIONS

- *Post-hoc* analysis of a randomized clinical trial and results are hypothesis-generating.

- Trajectories were derived from integrated timepoints across follow-up, reflecting group trends rather than individual variations. The analysis leveraged random visit intervals but may not fully capture within-patient fluctuations.

- The structured assessment schedule may have missed rapid or transient changes in NYHA class, KCCQ-TSS, and NT-proBNP that occurred immediately before events.

- FINEARTS-HF criteria may not fully represent all HFmrEF/HFpEF patients.

DISCLOSURE INFORMATION

The FINEARTS-HF trial was funded by Bayer. Dr. Lu has received research grant support or served on advisory boards for Bayer, AstraZeneca, Boehringer Ingelheim, Cytokinetics and Abbott.

The disclosures for all authors can be found at https://accscientificsession.acc.org/Plan-Your%20Program/Presenter-Disclosures

FINEARTS-HF
FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure

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