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SHORT REPORT

Effects of finerenone on natriuretic peptide levels in heart failure with mildly reduced or preserved ejection fraction: The FINEARTS-HF trial

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Aims N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations serve as markers of prognosis and therapeutic response in patients with heart failure (HF). The effect of the non-steroidal mineralocorticoid receptor antagonist finerenone on NT-proBNP in patients with HF with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) is currently unknown.

Methods and results The FINEARTS-HF trial randomized patients with HFmrEF/HFpEF and NT-proBNP ≥300 pg/ml (≥900 pg/ml if atrial fibrillation) or B-type natriuretic peptide ≥100 pg/ml (≥300 pg/ml if atrial fibrillation) to finerenone versus placebo. Core laboratory NT-proBNP was measured at baseline, 3, and 12 months after randomization. We evaluated the association between log-transformed NT-proBNP and the primary outcome (cardiovascular death and total HF events), whether baseline NT-proBNP modified the effect of finerenone on this outcome, and the effect of finerenone on NT-proBNP concentration. Baseline NT-proBNP was available in 5843 of 6001 patients analysed (median 1041 [interquartile range 449–1946] pg/ml) and was strongly associated with risk of the primary outcome (adjusted rate ratio 1.44 per doubling in biomarker concentration, 95% confidence interval [CI] 1.37–1.51], $p < 0.001$). Baseline NT-proBNP did not modify the benefit of finerenone on the primary outcome ($p_{interaction} = 0.92$). Finerenone reduced NT-proBNP by 12.1% (95% CI 8.5–15.4%) at 3 months and 12.5% (95% CI 8.1–16.7%) at 12 months, compared to placebo.

Conclusions In patients with HFmrEF/HFpEF, finerenone reduced NT-proBNP within months of initiation, and improved clinical outcomes regardless of baseline NT-proBNP concentration.
Clinical Trial Registration: ClinicalTrials.gov NCT04435626, EudraCT 2020-000306-29.

Keywords Finerenone • Heart failure • Mineralocorticoid receptor antagonists • Natriuretic peptides

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Introduction

N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations in plasma are widely used for diagnosis and risk stratification in patients with heart failure (HF).[1] Changes in NT-proBNP in response to therapy have correlated closely with treatment effects on HF hospitalizations in previous clinical trials.[2] The non-steroidal mineralocorticoid receptor antagonist finerenone reduced NT-proBNP concentrations by 18% at 4 months in patients with type 2 diabetes and chronic kidney disease.[3] Among patients with HF with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) in the FINEARTS-HF (FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure) trial, finerenone reduced the primary outcome of total HF events and cardiovascular death by 16%, but its effect on NT-proBNP in this population is not known.

We investigated the treatment effect of finerenone across baseline concentrations of NT-proBNP and on NT-proBNP concentrations over time in patients with HFmrEF/HFpEF in the FINEARTS-HF trial.

Methods

The FINEARTS-HF trial compared finerenone and placebo in 6001 patients with symptomatic HFmrEF/HFpEF (≥40%), structural heart disease, and recent diuretic use. Elevated natriuretic peptides at baseline were required for inclusion: for patients in sinus rhythm, NT-proBNP ≥300 pg/ml (B-type natriuretic peptide ≥100 pg/ml), measured within 30 days (in those without recent worsening HF event) or within 90 days (in those with recent worsening HF event). These thresholds were tripled for patients in atrial fibrillation at screening. Finerenone or matching placebo were planned to be titrated to either 20 or 40 mg (based on baseline estimated glomerular filtration rate [eGFR]) at 1 month post-randomization. The design and results of the trial have been previously published.[4]

NT-proBNP was measured at baseline, 3 and 12 months after randomization using standard central lab chemiluminescence-based analysers. We first evaluated the association between log-transformed baseline NT-proBNP and the primary endpoint (total HF events and cardiovascular death) using semiparametric proportional rates models. The components of the primary endpoint, total HF events alone and cardiovascular death, were evaluated using a semiparametric proportional rates model and a Cox proportional hazards model, respectively. Models were adjusted for 12 clinically relevant covariates: age, sex, region, systolic blood pressure, body mass index (BMI), eGFR, ejection fraction, history of myocardial infarction, stroke, or hospitalization for HF, and baseline diabetes mellitus or atrial fibrillation. We then tested whether finerenone's effect on the primary endpoint was modified by baseline NT-proBNP concentrations by interaction testing. Additionally, we evaluated the placebo-corrected effect of finerenone on NT-proBNP concentrations at 3 and 12 months using linear regression, adjusted for the baseline value. Statistical analyses were performed using Stata, version 16 (StataCorp, LLC; College Station, TX, USA); p-values of <0.05 were considered statistically significant.

Results

Among 5843 patients (97%) with available data, median baseline NT-proBNP was 1041 (interquartile range [IQR] 449–1946 pg/ml). NT-proBNP was higher in participants with older age, lower BMI, lower eGFR, and (by design) atrial fibrillation (*Table 1*). Median NT-proBNP was 1714 (IQR 1152–2807) pg/ml for participants with atrial fibrillation on baseline electrocardiogram and 588 (IQR 313–1255) pg/ml for participants without atrial fibrillation. NT-proBNP was strongly and independently associated with risk of the primary outcome (adjusted rate ratio 1.44 per doubling, 95% confidence interval [CI] 1.37–1.51, $p < 0.001$) and with each component alone: total HF events (adjusted rate ratio 1.41 [95% CI 1.34–1.49], $p < 0.001$) and cardiovascular death (adjusted hazard ratio 1.52 [95% CI 1.43–1.63], $p < 0.001$). Baseline NT-proBNP was furthermore associated with risk of all-cause death (adjusted hazard ratio 1.44 [95% CI 1.38–1.51], $p < 0.001$). Adding NT-proBNP concentration at 3 months to a regression model including baseline NT-proBNP and clinical covariates improved prediction of subsequent first HF or cardiovascular death events (c-statistic 0.73 vs. 0.71, $p < 0.001$).

Baseline NT-proBNP did not significantly modify the beneficial effects of finerenone on relative risk of the primary outcome ($p_{interaction} = 0.92$); finerenone reduced the risk of primary outcome events across the spectrum of baseline NT-proBNP concentrations (*Figure 1*). No significant treatment interaction was observed for key secondary outcomes including total HF events ($p_{interaction} = 0.91$), cardiovascular death ($p_{interaction} = 0.98$), and all-cause death ($p_{interaction} = 0.47$) (online supplementary *Figure S1*). For the primary outcome, NT-proBNP did not significantly modify the effect of finerenone in patients with atrial fibrillation ($p_{interaction} = 0.49$) or without atrial fibrillation ($p_{interaction} = 0.62$) (online supplementary *Figure S2*).

Finerenone reduced NT-proBNP by 12.1% (95% CI 8.5–15.4%) at 3 months in 5218 patients with available data and 12.5% (95% CI 8.1–16.7%) at 12 months in 4655 patients with available data, compared to placebo (*Figure 2*). The effect of finerenone on NT-proBNP concentrations at 3 months was not significantly modified by age, sex, race, atrial fibrillation, BMI, eGFR, or left ventricular ejection fraction.

Discussion

In this prespecified analysis of the FINEARTS-HF trial, finerenone reduced total HF events and cardiovascular death in patients with HFmrEF/HFpEF with any degree of natriuretic peptide elevation. This absence of treatment interaction differs from the TOPCAT trial with the steroidal mineralocorticoid receptor antagonist spironolactone in HFmrEF/HFpEF, which found less benefit in patients with higher natriuretic peptide concentrations.[5] Aligned with these clinical benefits, we found early and sustained reductions in NT-proBNP with finerenone. Among patients with HFmrEF/HFpEF, the 12% reduction in NT-proBNP with finerenone is greater than with empagliflozin (4%) and lower than sacubitril/valsartan (19%), acknowledging differences in trial inclusion

Table 1 Baseline characteristics by N-terminal pro-B-type natriuretic peptide tertile in patients with and without atrial fibrillation

	NT-proBNP tertile			
Patients without atrial fibrillation	**Tertile 1 (*n* = 1202)**	**Tertile 2 (*n* = 1202)**	**Tertile 3 (*n* = 1202)**	***p*-value**
NT-proBNP, pg/ml	233 [137–313]	588 [479–764]	1760 [1255–2940]	<0.001
Age, years	69 [62–74]	72 [65–77]	74 [66–80]	<0.001
Women, *n* (%)	556 (46.3)	533 (44.3)	526 (43.8)	0.22
Race, *n* (%)				
Asian	133 (11.1)	207 (17.2)	244 (20.3)	<0.001
Black	24 (2.0)	22 (1.8)	21 (1.7)	
Other	48 (4.0)	27 (2.2)	34 (2.8)	
White	997 (82.9)	946 (78.7)	903 (75.1)	
Previous hospitalization for HF, *n* (%)	635 (52.8)	636 (52.9)	806 (67.1)	<0.001
Diabetes mellitus, *n* (%)	530 (44.1)	491 (40.8)	558 (46.4)	0.25
Systolic blood pressure, mmHg	131 [123–139]	131 [120–142]	131 [120–141]	0.59
Body mass index, kg/m^2	31 [27–35]	29 [26–34]	28 [24–32]	<0.001
eGFR, ml/min/1.73 m^2	71 [56–86]	63 [49–79]	56 [41–72]	<0.001
Left ventricular ejection fraction, %	55 [48–59]	53 [46–58]	50 [45–56]	<0.001
Patients with atrial fibrillation	**Tertile 1 (*n* = 747)**	**Tertile 2 (*n* = 745)**	**Tertile 3 (*n* = 745)**	***p*-value**
NT-proBNP, pg/ml	979 [733–1152]	1718 [1516–1963]	3415 [2807–4740]	<0.001
Age, years	73 [66–78]	76 [70–81]	77 [71–82]	<0.001
Women, *n* (%)	328 (43.9)	357 (47.9)	355 (47.7)	0.15
Race, *n* (%)				
Asian	130 (17.4)	152 (20.4)	124 (16.6)	0.31
Black	5 (0.7)	5 (0.7)	6 (0.8)	
Other	32 (4.3)	17 (2.3)	18 (2.4)	
White	580 (77.6)	571 (76.6)	597 (80.1)	
Previous hospitalization for HF, *n* (%)	457 (61.2)	433 (58.1)	549 (73.7)	<0.001
Diabetes mellitus, *n* (%)	255 (34.1)	271 (36.4)	270 (36.2)	0.40
Systolic blood pressure, mmHg	129 [11–139]	129 [117–139]	126 [116–136]	0.02
Body mass index, kg/m^2	31 [27–35]	29 [25–33]	28 [24–32]	<0.001
eGFR, ml/min/1.73 m^2	65 [52–79]	57 [46–70]	50 [38–63]	<0.001
Left ventricular ejection fraction, %	53 [47–57]	55 [48–58]	50 [45–57]	0.002

Categorical variables are presented as *n* (%) and continuous variables as median [25th–75th percentile].
eGFR, estimated glomerular filtration rate; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Atrial fibrillation was determined on the baseline electrocardiogram. NT-proBNP tertiles were defined separately in patients with and without atrial fibrillation.

criteria. The treatment effect on NT-proBNP in FINEARTS-HF was somewhat lower than in patients with chronic kidney disease and type 2 diabetes in the FIDELITY trials (18% [95% CI 10–24%]),[3] though CIs overlap. Spironolactone compared to placebo reduced NT-proBNP by 20% (95% CI 0–40%) in the TOPCAT trial, 14% (95% CI 1–25%), and approximately 20–25% in HOMAGE,[6–8] though these studies enrolled different patient populations from FINEARTS-HF and had smaller sample size. In the TOPCAT trial, collection of follow-up natriuretic peptide data was not protocolized for all participants; data were available only in a limited biomarker substudy. Concordant effects on NT-proBNP and primary outcome events in FINEARTS-HF support NT-proBNP as a reliable surrogate outcome in HF clinical trials, consistent with a prior analysis of many HF randomized trials reporting treatment effects on both NT-proBNP and clinical outcomes.[2]

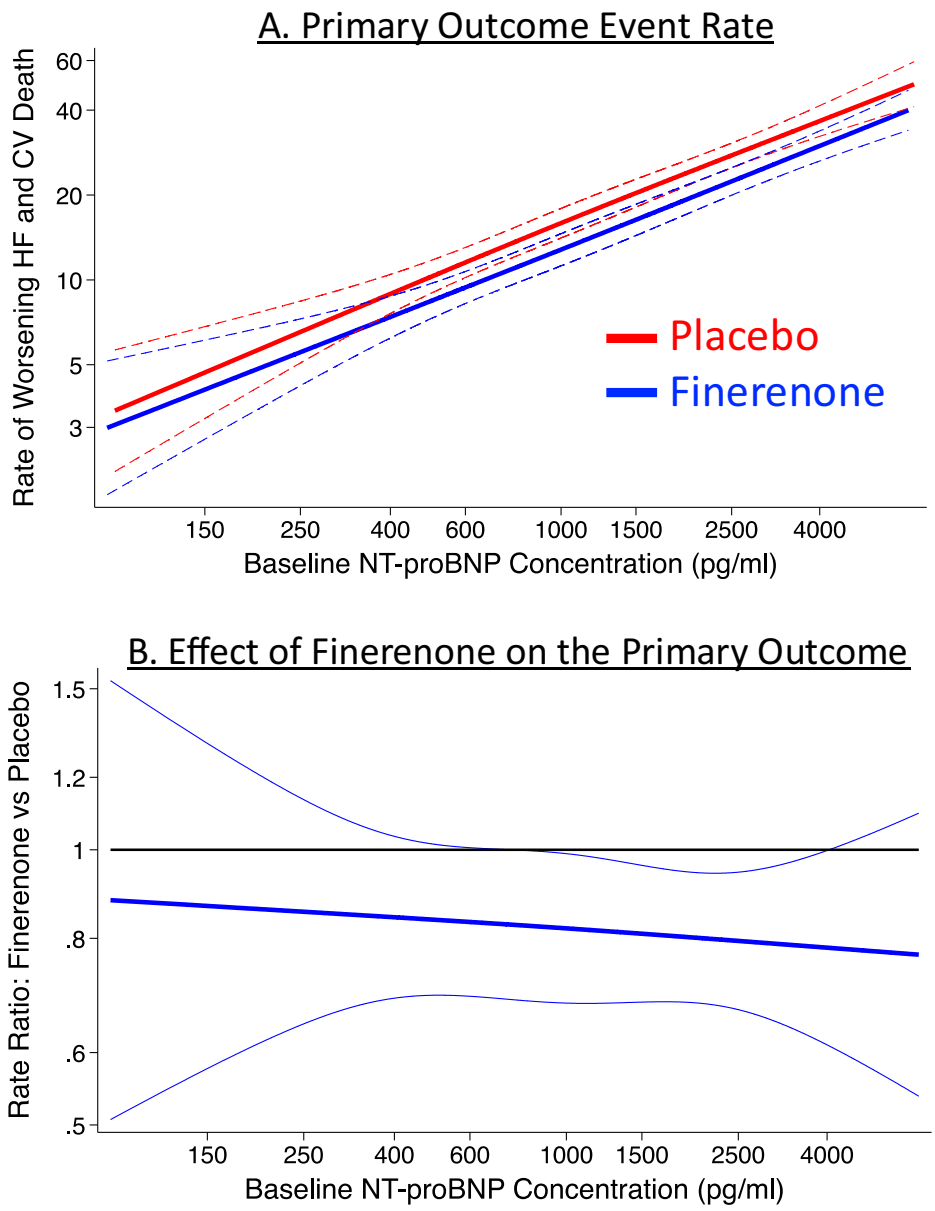

Figure 1 Clinical benefit of finerenone across the spectrum of N-terminal pro-B-type natriuretic peptide (NT-proBNP). (*A*) The restricted cubic spline displays the predicted rate of the primary outcome, total heart failure (HF) events and cardiovascular (CV) death, by baseline NT-proBNP concentration in each treatment group. Dashed lines indicate 95% confidence intervals. (*B*) The restricted cubic spline displays the ratio for the primary outcome, total HF events and CV death, according to baseline NT-proBNP. Baseline NT-proBNP does not significantly modify the relative reduction in the primary outcome with finerenone.

These results should be interpreted in the context of several limitations. The FINEARTS-HF trial required elevated natriuretic peptides for inclusion; thus findings may not generalize to patients with normal natriuretic peptide concentrations. NT-proBNP concentrations were higher in patients with atrial fibrillation, both because atrial fibrillation induces natriuretic peptide release and because the minimum NT-proBNP required for inclusion was higher in atrial fibrillation. Associations between NT-proBNP and clinical outcomes may be confounded by atrial fibrillation. Missing data were likely not random, but rather driven by death, worsening clinical status, or study drug discontinuation. Study design strengths include large sample size, randomized treatment exposure, and protocol-driven measurements of NT-proBNP at a central laboratory.

In conclusion, in patients with HFmrEF/HFpEF, finerenone led to a fast (within 3 months of initiation) and sustained reduction of NT-proBNP, and reduced the risk of worsening HF and cardiovascular death regardless of baseline NT-proBNP concentration.

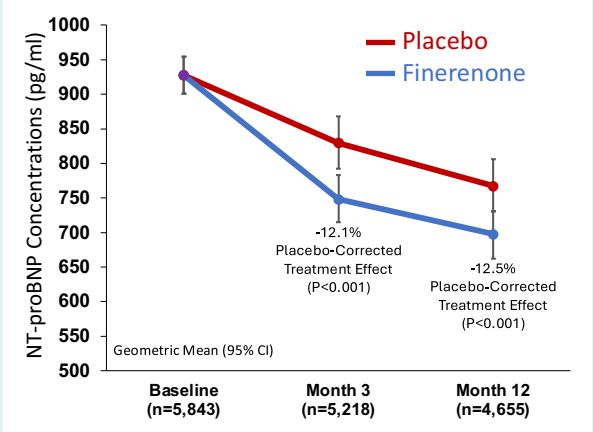

Figure 2 Treatment effect of finerenone on N-terminal pro-B-type natriuretic peptide (NT-proBNP). Geometric mean (95% confidence interval [CI]) NT-proBNP concentrations are shown at baseline and 3 and 12 months after randomization. Patients with missing NT-proBNP data at baseline were excluded at all three timepoints.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: J.W.C. reports personal consulting fees from us2.ai, Occlutech, and Edgewise Therapeutics. B.L.C. has received personal consulting fees from Alnylam, Bristol Myers Squibb, Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia, Rocket, and has served on a data safety monitoring board for Novo Nordisk. M.V. has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, BMS, Boehringer Ingelheim, Chiesi, Cytokinetics, Fresenius Medical Care, Idorsia Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Milestone Pharmaceuticals, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health, and participates in clinical trial committees for studies sponsored by Amgen, AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. 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