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RESEARCH ARTICLE

Anaemia in patients with heart failure and mildly reduced or preserved ejection fraction: A prespecified analysis of the FINEARTS-HF trial

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Aims Anaemia is common in heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) and associated with poor clinical outcomes. While renin–angiotensin system blockers reduce haemoglobin, little is known about the effect of mineralocorticoid receptor antagonists on haemoglobin and in patients with anaemia. We evaluated the effects of finerenone according to anaemia status in patients with HFmrEF/HFpEF enrolled in FINEARTS-HF. Additionally, we examined the effect of finerenone on haemoglobin, new-onset anaemia, and resolution of anaemia during follow-up.

Methods and results Anaemia was defined as haemoglobin <12 g/dl in women and <13 g/dl in men. The primary outcome was the composite of total (first and recurrent) heart failure events and cardiovascular death. Of 5665 patients analysed, 1584 (28.0%) had anaemia at baseline. Patients with anaemia were at higher risk of the primary endpoint compared to those without anaemia: event rate 24.3 (95% confidence interval [CI] 21.9–26.9) versus 13.1 (95% CI 12.0–14.3) per 100 person-years; rate ratio [RR] 1.67 (95% CI 1.45–1.92). Persistence of anaemia was associated with worse outcomes compared to resolution of anaemia, and patients with new-onset anaemia had worse outcomes than those who did not develop anaemia. The effect of finerenone on the primary endpoint was consistent in patients with and without anaemia (RR 0.89; 95% CI 0.73–1.10 vs. RR 0.76; 95% CI 0.64–0.91; interaction $p = 0.27$) and across the range of haemoglobin at baseline. Finerenone treatment did not increase the resolution of anaemia or prevent new-onset anaemia.

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Conclusions Finerenone reduces the risk of clinical outcomes regardless of anaemia status.
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Keywords Anaemia • Heart failure with mildly reduced ejection fraction • Heart failure with preserved ejection fraction • Finerenone • Heart failure hospitalization • Prognosis • Treatment effect

Introduction

Anaemia is common in patients with heart failure (HF) and is intricately associated with the pathophysiology of HF through multiple mechanisms. One such mechanism involves the reduction of oxygen delivery to both the myocardium and peripheral tissues, which is believed to exacerbate adverse cardiac remodelling, worsen the symptoms of HF, reduce exercise tolerance, and increase the risk of hospitalization and death.[1,2] These observations have led to a desire to understand the mechanisms of anaemia in HF and the effects of HF therapies on haemoglobin concentrations. Related to this is the need to examine the effects of HF therapies on patients with anaemia and an interest in anaemia itself as a therapeutic target in HF.[3–7]

To date, contrasting effects of evidence-based HF therapies on anaemia have been reported. As in chronic kidney disease, renin–angiotensin system (RAS) inhibitors reduce haemoglobin in HF by suppressing erythropoietin production, and, for angiotensin-converting enzyme (ACE) inhibitors, by increasing N-acetyl-seryl-aspartyl lysyl-proline, which inhibits haematopoiesis.[8–10] Adding a neprilysin inhibitor to an angiotensin receptor blocker reverses this effect and there was less decline in haemoglobin over time in patients with HF treated with sacubitril/valsartan compared with a RAS inhibitor alone, with greater anaemia correction, possibly as a result of neprilysin inhibition increasing substance P and reducing concentrations of its amino-terminal cleavage product SP (1–4) which, respectively, stimulate and inhibit haematopoiesis.[11,12] Sodium–glucose cotransporter 2 inhibitors (SGLT2i) lead to an increase in haemoglobin in patients with HF, partly in response to increased secretion of erythropoietin and reduction in hepcidin.[13,14] However, there are few reports on the effects of mineralocorticoid receptor antagonists (MRAs) on haemoglobin concentrations in HF, with small decreases reported.[15,16] On the other hand, experimentally, MRAs have been reported to reduce hepcidin secretion which could lead to iron mobilization and utilization and, potentially, erythropoiesis.[17,18] Therefore, we conducted a prespecified analysis of the FINEARTS-HF trial (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure) to evaluate the effects of the non-steroidal MRA finerenone in patients with and without anaemia.[19]

Methods

FINEARTS-HF trial design and objectives

The design and results of FINEARTS-HF are published.[19] Key inclusion criteria were age ≥40 years, symptomatic HF in New York Heart Association (NYHA) functional class II–IV, and left ventricular ejection fraction (LVEF) ≥40%. Patients were also required to have elevated concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP). Key exclusion criteria were estimated glomerular filtration rate (eGFR) <25 ml/min/1.73 m^2 and serum potassium >5.0 mmol/L. Patients with a haemoglobin concentration <10 g/dl were also excluded as were patients in whom anaemia was considered an alternative cause of their dyspnoea. Eligible participants were randomized in a 1:1 ratio to finerenone 20–40 mg once daily or matching placebo. Ethics Committees for the 653 participating institutions in 37 countries approved the protocol and all patients gave written informed consent.

Measurement of haemoglobin and definition of anaemia

Haemoglobin was measured at baseline, as well as 1, 3, 6, 9 and 12 months after randomization, and at four monthly intervals thereafter. All measurements were performed in a central laboratory. Anaemia was defined at baseline as a haemoglobin <12 g/dl in women and <13 g/dl in men. New-onset anaemia after randomization was defined as two consecutive haemoglobin concentrations below these thresholds at any time during follow-up. Correction of anaemia after randomization was defined as two consecutive haemoglobin above these thresholds at any time during follow-up.

Trial outcomes

The primary outcome was the composite of total (first and recurrent) HF events (including unplanned HF hospitalizations or urgent HF events) and cardiovascular death. The secondary outcomes included total HF events; change from baseline to 6, 9 and 12 months in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS); improvement in NYHA functional class from baseline to 12 months; time to first occurrence of composite renal endpoint; and all-cause death. Due to the small number of renal events, this endpoint was not examined in this analysis. In the sensitivity analysis, patients were stratified according to the severity of anaemia into the following categories: borderline anaemia (haemoglobin ≥13 g/dl and <14 g/dl in men; ≥12 g/dl and <13 g/dl in women), mild anaemia (haemoglobin ≥11 g/dl and <13 g/dl in men; ≥11 g/dl and <12 g/dl in women), and moderate to severe anaemia (haemoglobin <11 g/dl in both women and men). We then assessed the associations between anaemia severity and clinical outcomes. We also examined cardiovascular death, cardiovascular death or a first HF event, and a first HF event. Additionally, we compared clinical outcomes between patients whose anaemia corrected during the trial and those whose anaemia persisted, while also evaluating the effect of finerenone in these groups. Furthermore, we analysed outcomes in patients who developed new-onset anaemia during the trial versus those who remained non-anaemic throughout the

study, as well as the impact of finerenone on these groups. The prespecified safety outcomes included the incidence of hyperkalaemia (defined as serum potassium >5.5 mmol/L or >6.0 mmol/L), hypokalaemia (defined as serum potassium <3.5 mmol/L), elevation of serum creatinine (defined as serum creatinine ≥2.5 mg/dl or ≥3.0 mg/dl), and hypotension (defined as systolic blood pressure <100 mmHg).

Statistical analysis

Differences in baseline characteristics were assessed using the chi-square test for binary or categorical variables, and the Wilcoxon test and two-sample *t*-test for non-normal and normal continuous variables, respectively. Poisson regression models with robust standard errors were used to analyse the incidence rate by anaemia status, incorporating total follow-up time as an offset. To assess the effect of finerenone versus placebo by anaemia status, time-to-event data were evaluated with Kaplan–Meier curves and Cox proportional hazards models, with treatment assignment as a fixed effect and region and baseline LVEF (<60% or ≥60%) as stratification factors, reporting hazard ratios (HRs) and 95% confidence intervals (CIs). Total (first and recurrent) events were evaluated using Nelson–Aalen curves and rate ratios (RRs) with 95% CIs from semiparametric proportional rates models,[20] adjusting for variables mentioned above. Additional models adjusted for baseline variables: age, sex heart rate, body mass index, eGFR, NYHA functional class III/IV, LVEF, myocardial infarction, NT-proBNP (log), diabetes, history of atrial fibrillation, and history of HF hospitalization. The effect of finerenone across haemoglobin as a continuous variable was modelled using fractional polynominals. The proportion of patients with NYHA functional class improvement from baseline to 12 months was analysed using logistic regression models, adjusted for treatment and stratification factors, with odds ratios (ORs) and 95% CIs reported. Additional ORs adjusted for baseline variables were also reported. Changes in haematocrit and haemoglobin from baseline to 24 months, and KCCQ-TSS from baseline to 12 months, between treatment groups were analysed using mixed-effects models for repeated measurements, adjusted for baseline values, follow-up visits, treatment assignment, visit–treatment interaction, and stratification factors. Missing data were excluded, and least-squares mean differences between treatment groups were reported per visit. Separate covariance patterns were estimated for each treatment group using unstructured covariance to adjust for within-subject variance. The assumption of normality, homogeneity of variance of residuals, and linearity of continuous predictors were fulfilled. The cumulative incidence of new-onset or corrected anaemia was estimated using the Aalen–Johansen estimator, accounting for competing risk of death, and differences between treatment arms were assessed with Gray's test. The effect of finerenone on new-onset or corrected anaemia was evaluated using Cox proportional hazards models, stratified by region and baseline LVEF (<60% or ≥60%), adjusted for baseline haemoglobin, with HRs and 95% CIs reported. A Fine–Gray competing risk analysis, considering all-cause death as a competing risk, reported subdistribution HRs with 95% CIs. All models set the origin and start time at randomization, with follow-up until new-onset anaemia or correction of anaemia, death, or last contact. New-onset anaemia or correction of anaemia dates were confirmed by consecutive haemoglobin thresholds. Associations between new-onset or corrected anaemia and clinical outcomes were evaluated using Cox models for time-to-event data and semiparametric proportional-rates models for total (first and recurrent) events,[20] where an indicator of a new anaemia or resolution anaemia diagnosis was entered into the model as a time-updated covariate (with follow-up time starting at randomization). The period of risk before a new onset of anaemia or correction of anaemia was attributed to the group with no anaemia or anaemia, respectively, for the calculation of incidence rates. HRs and RRs, adjusted for treatment assignment, region, baseline LVEF, and baseline characteristics for the variables above, were reported. Safety endpoint incidences were estimated using logistic regression models adjusted for stratification factors for the variables above, with interaction by anaemia status at baseline tested via a likelihood ratio test. All statistical analyses were conducted with STATA version 18 (StataCorp LLC; College Station, TX, USA), and a *p*-value <0.05 was considered nominally significant.

Results

Overall, 5665 (94.4%) FINEARTS-HF participants had an available baseline haemoglobin concentration, of whom 1584 were anaemic (28.0%) with a similar proportion among those randomized to finerenone or placebo (775/2836 [27.3%] vs. 809/2829 [28.6%]; $p = 0.29$). The distribution of baseline haemoglobin by sex is shown in online supplementary *Figure Appendix S1*.

Patient characteristics according to anaemia status

The baseline characteristics of patients with and without anaemia are shown in *Table 1*. Compared to those without anaemia, anaemic patients were older, more likely to be male, have a lower eGFR, and higher urine albumin-to-creatinine ratio and NT-proBNP concentrations. Anaemic patients had overall worse NYHA functional class and KCCQ scores. History of diabetes and HF hospitalization were more common among patients with anaemia, compared to those without anaemia. Patients with anaemia were less likely to receive an ACE inhibitor/angiotensin receptor blocker (ARB), beta-blocker, or angiotensin receptor–neprilysin inhibitor, but were more often prescribed loop diuretics. At baseline and during follow-up, some patients received treatment for iron deficiency and/or anaemia: intravenous iron in 125/2836 (4.4%) and 119/2829 (4.2%), oral iron in 302/2836 (10.7%) and 318/2829 (11.2%), and blood transfusions in 77/2836 (2.7%) and 80/2829 (2.8%) of patients randomized to finerenone and placebo, respectively.

Clinical outcomes according to anaemia status at baseline

The incidence of the primary composite outcome, total (first and recurrent) HF events, and mortality endpoints are shown in online supplementary *Table Appendix S1*, *Figures S2* and *S3*. In the unadjusted analysis, the risk of each of these outcomes was higher in patients with anaemia compared to those without. After adjustment for recognized prognostic variables, the elevation of risk persisted although was somewhat attenuated. Furthermore, when anaemia was further examined by severity category, there was a progressive worsening of prognosis with increasing severity of anaemia (online supplementary *Figure S2*). When haemoglobin was examined as a continuous variable, there was a negative relationship between haemoglobin concentration

Table 1 Baseline characteristics of patients with and without anaemia in FINEARTS-HF

	Anaemia ($n = 1584$)	No anaemia ($n = 4081$)	*p*-value
Age (years)	76 [69–81]	72 [65–78]	<0.001
Male sex, *n* (%)	910 (57.5)	2186 (53.6)	0.008
Region, *n* (%)			<0.001
Asia	293 (18.5)	674 (16.5)	
Eastern Europe	536 (33.8)	1984 (48.6)	
Latin America	167 (10.5)	393 (9.6)	
North America	200 (12.6)	242 (5.9)	
Western Europe, Oceania, Other	388 (24.5)	788 (19.3)	
Race, *n* (%)			<0.001
Asian	296 (18.7)	680 (16.7)	
Black	34 (2.2)	45 (1.1)	
White	1205 (76.1)	3242 (79.4)	
Other	49 (3.1)	114 (2.8)	
Heart failure characteristics			
NYHA functional class, *n* (%)			<0.001
II	1030 (65.0)	2899 (71.1)	
III	543 (34.3)	1157 (28.4)	
IV	11 (0.7)	24 (0.6)	
LVEF (%)	54 [48–58]	52 [45–58]	<0.001
Improved LVEF ≥40%, *n* (%)	83 (5.2)	176 (4.3)	0.13
LVEF ≥60%, *n* (%)	336 (21.3)	745 (18.3)	0.01
KCCQ total symptom score	67 [48–84]	72 [52–88]	<0.001
KCCQ overall summary score	61 [43–79]	66 [48–82]	<0.001
KCCQ clinical summary score	64 [45–81]	69 [51–85]	<0.001
Physiological and laboratory measurements			
Systolic blood pressure (mmHg)	130 [118–141]	130 [120–140]	0.57
Diastolic blood pressure (mmHg)	73 [65–80]	77 [70–83]	<0.001
Heart rate (bpm)	69 [62–77]	71 [63–80]	<0.001
Body mass index (kg/m^2)	29 [25–33]	29 [26–34]	<0.001
Body mass index groups (kg/m^2), *n* (%)			<0.001
<18.5 (underweight)	24 (1.5)	37 (0.9)	
18.5–<25 (normal weight)	398 (25.2)	787 (19.3)	
25–<30 (overweight)	520 (32.9)	1348 (33.1)	
30–<35 (class I obesity)	359 (22.7)	1099 (27.0)	
≥35 (class II–III obesity)	279 (17.7)	803 (19.7)	
Waist circumference (cm)	102 [91–115]	103 [94–115]	0.03
Waist/hip ratio	0.96 [0.91–1.03]	0.96 [0.90–1.03]	0.26
eGFR (ml/min/1.73 m^2)	53 [40–69]	64 [49–80]	<0.001
eGFR <60 (ml/min/1.73 m^2), *n* (%)	982 (62.0)	1744 (42.7)	<0.001
eGFR <45 (ml/min/1.73 m^2), *n* (%)	542 (34.2)	718 (17.6)	<0.001
eGFR <30 (ml/min/1.73 m^2), *n* (%)	114 (7.2)	94 (2.3)	<0.001
NT-proBNP (pg/ml)	1371 [630–2622]	935 [404–1734]	<0.001
In patients with atrial fibrillation	2267 [1422–3460]	1590 [1075–2472]	<0.001
In patients without atrial fibrillation	907 [462–1849]	512 [276–1058]	<0.001
Haemoglobin (g/dl)	11.5 ± 0.9	14.1 ± 1.2	–
Borderline anaemia, *n* (%)[a]	–	1335 (32.7)	–
Mild anaemia, *n* (%)[a]	1181 (74.6)	–	–
Moderate to severe anaemia, *n* (%)[a]	403 (25.4)	–	–
Haematocrit (%)	36 [34–38]	42 [40–45]	–
Potassium (mmol/L)	4.4 [4.0–4.6]	4.4 [4.1–4.7]	0.11
HbA1c (%)	6.2 [5.7–6.9]	6.1 [5.7–6.7]	<0.001
UACR (mg/g)	30 [10–133]	15 [6–52]	<0.001
UACR category (mg/g), *n* (%)			0.002
<30	763 (49.8)	2567 (64.6)	
30 to <300	532 (34.8)	1097 (27.6)	
≥300	236 (15.4)	310 (7.8)	
Medical history, *n* (%)			
Hypertension	1413 (89.2)	3615 (88.6)	0.51
Diabetes mellitus	794 (50.1)	1519 (37.2)	<0.001

Table 1 (Continued)

	Anaemia ($n = 1584$)	No anaemia ($n = 4081$)	p-value
Myocardial infarction	367 (23.2)	1079 (26.4)	0.01
AF (history)	885 (55.9)	2218 (54.4)	0.30
Any prior hospitalization for HF	1017 (64.2)	2394 (58.7)	<0.001
Chronic obstructive pulmonary disease	231 (14.6)	492 (12.1)	0.01
Smoking status			<0.001
Current	95 (6.0)	389 (9.5)	
Former	530 (33.5)	1168 (28.6)	
Never	959 (60.5)	2524 (61.9)	
Stroke	238 (15.0)	556 (13.6)	0.17
Treatment, *n* (%)			
Beta-blocker	1315 (83.0)	3505 (85.9)	0.007
ACEi or ARB	1073 (67.7)	2930 (71.8)	0.003
ARNI	112 (7.1)	380 (9.3)	0.007
SGLT2i	215 (13.6)	552 (13.5)	0.96
Loop diuretics	1438 (90.8)	3508 (86.0)	<0.001
Digoxin	98 (6.2)	351 (8.6)	0.003
Anticoagulant	775 (48.9)	1948 (47.7)	0.42
Antiplatelet	228 (14.4)	547 (13.4)	0.33
Iron (only oral)	161 (10.2)	106 (2.6)	<0.001

Values are mean ± standard deviation, *n* (%), or median [interquartile range].
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio.
[a]Patients were stratified according to the severity of anaemia into the following categories: borderline anaemia (haemoglobin ≥13 and <14 g/dl in men; ≥12 and <13 g/dl in women), mild anaemia (haemoglobin ≥11 g/dl and <13 g/dl in men; ≥11 and <12 g/dl in women), and moderate to severe anaemia (haemoglobin <11 g/dl in both women and men).

and incidence rates of all the clinical outcomes of interest, that is higher haemoglobin concentrations were associated with lower event rates (online supplementary *Figure S3*). Regardless of treatment assignment, among patients with anaemia at baseline, KCCQ increased ≥5 points at 12 months in 54% of patients and 53% of patients achieved a KCCQ score >75 at that timepoint. In the absence of anaemia at baseline, KCCQ increased ≥5 points at 12 months in 56% of patients and 59% of patients achieved a KCCQ score >75 at that timepoint (online supplementary *Table Appendix S1*).

Incidence of new anaemia and resolution of existing anaemia

Changes in haemoglobin and haematocrit

At 24 months, the mean haemoglobin concentration was 0.12 (95% CI 0.05–0.18) g/dl lower in the finerenone group compared to the placebo group. At 24 months, the mean placebo-adjusted haematocrit was 0.39% (95% CI 0.17–0.60) lower in the finerenone group (*Figure 1* and online supplementary *Figure S4*).

New-onset anaemia

Among patients who were not anaemic at baseline, 18.8% in the finerenone group and 17.3% in the placebo group experienced new-onset anaemia (HR 1.12, 95% CI 0.97–1.30; $p = 0.12$). A Fine–Gray competing risk analysis supported this finding (sub-distribution HR 1.16, 95% CI 0.99–1.36; $p = 0.06$) (online supplementary *Figure S5A*). Patients who developed anaemia were older and had higher LVEF, systolic blood pressure, and baseline NT-proBNP concentrations, but lower body mass index, eGFR, and baseline haemoglobin concentrations, compared to those who did not develop anaemia. Additionally, patients developing anaemia had a higher prevalence of diabetes, were current or former smokers, were more frequently treated with ARBs, and less frequently with SGLT2 inhibitors. However, the use of ACE inhibitors was similar between the groups (online supplementary *Table S2*).

Resolution of existing anaemia

Of patients who were anaemic at baseline, 30.3% in the finerenone group and 34.1% in the placebo group showed resolution of their anaemia during follow-up (HR 0.85, 95% CI 0.71–1.01; $p = 0.07$). A Fine–Gray competing risk analysis, accounting for the competing risk of death, yielded a similar result (subdistribution HR 0.88, 95% CI 0.73–1.06; $p = 0.19$) (online supplementary *Figure S5B*). Patients showing resolution of anaemia were younger and had lower baseline NT-proBNP levels and higher body mass index, eGFR, and baseline haemoglobin concentrations compared to those with persistent anaemia. The two groups had similar rates of diabetes, but the use of ACE inhibitors and SGLT2 inhibitors was more common among those showing resolution of anaemia (online supplementary *Table S3*).

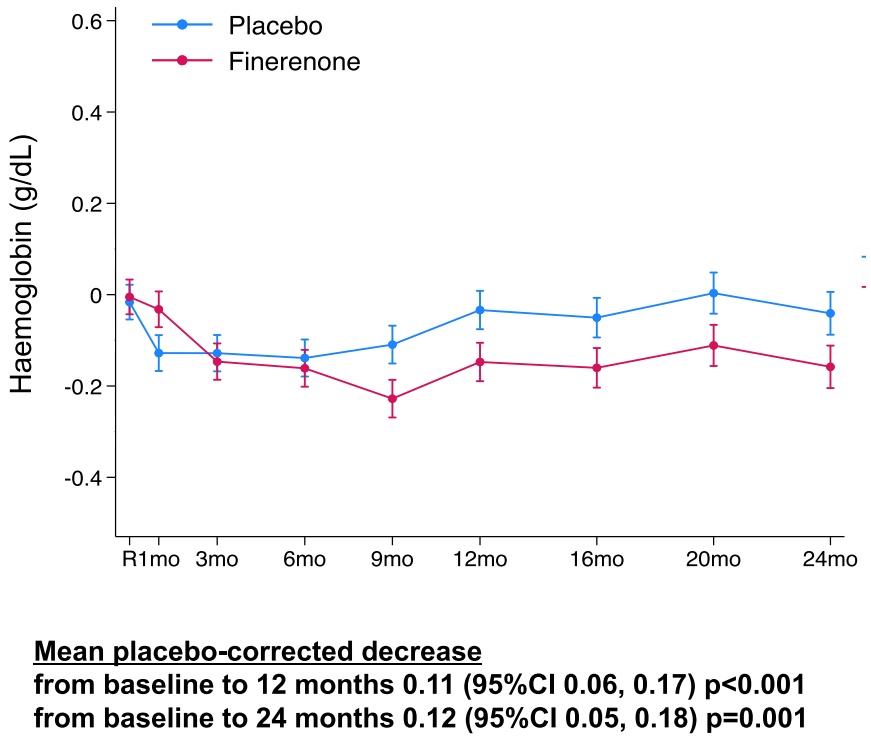

Figure 1 Change in haemoglobin concentration during follow-up according to treatment in FINEARTS-HF. Dots represent geometric means, and error bars represent 95% confidence intervals (CI).

Outcomes related to the development and resolution of anaemia

When new-onset anaemia was treated as a time-updated covariate, patients who were not anaemic at baseline but developed anaemia during follow-up ($n = 738$, 18%) had a higher rate of the primary endpoint compared to those who remained non-anaemic ($n = 3343$, 82%). The event rate was 22.6 per 100 person-years (95% CI 19.1–26.8) in those with new-onset anaemia versus 12.4 per 100 person-years (95% CI 11.2–13.6) for those remaining non-anaemic, giving an adjusted RR of 1.62 (95% CI 1.32–1.99) (online supplementary *Table S4* and *Figure S6*). A similar pattern was observed for the components of the primary endpoint and all-cause death (online supplementary *Table S4* and *Figure S6*).

Conversely, when the resolution of anaemia was treated as a time-updated covariate, patients who were anaemic at baseline but subsequently showed resolution of their anaemia ($n = 511$, 32%) had a lower rate of the primary endpoint compared to those with persistent anaemia ($n = 1073$, 68%). The event rate was 13.5 per 100 person-years (95% CI 10.5–17.4) for those showing resolution of their anaemia versus 31.8 per 100 person-years (95% CI 28.4–35.5) for participants with persistent anaemia, yielding an adjusted RR of 0.59 (95% CI 0.44–0.79) (online supplementary *Table S5* and *Figure S7*). This pattern was also observed for the components of the primary endpoint and all-cause death (online supplementary *Table S5* and *Figure S7*).

Consequently, patients showing resolution of their anaemia had outcomes similar to those who were not anaemic during follow-up, while those who developed anaemia experienced a similar prognosis to those with persistent anaemia during follow-up (online supplementary *Tables S6* and *S7*).

Effects of finerenone on outcomes according to anaemia status

The effects of finerenone in patients with and without anaemia are shown in *Table 2* and *Figures 2* and *3*. The effect of finerenone on the primary endpoint was consistent in both anaemic patients (HR 0.89, 95% CI 0.73–1.10) and non-anaemic patients (HR 0.76, 95% CI 0.64–0.91), with no indication that anaemia status modified the effect of finerenone (p for interaction = 0.27). This effect was also maintained across the spectrum of baseline haemoglobin concentrations when assessed as a continuous variable (*Figure 4*) and in patients developing new-onset anaemia and experiencing resolution of their anaemia (online supplementary *Tables S8* and *S9*).

Overall, the effects of finerenone on each component of the primary endpoint, cardiovascular death or a first HF event, a first HF event, and all-cause death were consistent across subgroups, including anaemic and non-anaemic patients, those with and without new-onset anaemia, and those with persistent or resolved anaemia (*Table 2*, *Figures 3* and *4*, online supplementary *Tables S8* and *S9*, and *Figures S8–S10*). Furthermore, when

Table 2 Effect of randomized treatment on outcomes in FINEARTS-HF according to anaemia status at baseline

	Anaemia ($n = 1584$)		No anaemia (n = 4081)		Interaction *p*-value
	Placebo ($n = 809$)	Finerenone ($n = 775$)	Placebo ($n = 2020$)	Finerenone ($n = 2061$)	
Primary composite outcome (total HF events and cardiovascular death)					
No. of events	470	414	750	580	
Event rate (95% CI)	25.4 (22.0–29.4)	23.1 (19.9–26.9)	14.9 (13.3–16.7)	11.3 (9.9–12.9)	
RR (95% CI)[a]	0.89 (0.73–1.10)		0.76 (0.64–0.91)		0.27
Total HF events					
No. of events	382	340	590	432	
Event rate (95% CI)	20.6 (17.5–24.3)	19.0 (16.1–22.4)	11.7 (10.3–13.3)	8.4 (7.2–9.8)	
RR (95% CI)[a]	0.90 (0.72–1.14)		0.72 (0.59–0.88)		0.17
Cardiovascular death or first HF event					
No. of events	243	226	438	351	
Event rate (95% CI)	15.3 (13.5–17.3)	14.6 (12.8–16.6)	9.5 (8.7–10.5)	7.3 (6.6–8.1)	
HR (95% CI)[a]	0.93 (0.78–1.12)		0.77 (0.67–0.88)		0.09
First HF event					
No. of events	200	180	343	260	
Event rate (95% CI)	12.6 (11.0–14.4)	11.6 (10.0–13.5)	7.5 (6.7–8.3)	5.4 (4.8–6.1)	
HR (95% CI)[a]	0.91 (0.74–1.11)		0.73 (0.62–0.85)		0.10
Cardiovascular death					
No. of events	89	74	160	149	
Event rate (95% CI)	4.8 (3.9–5.9)	4.2 (3.3–5.2)	3.2 (2.7–3.7)	2.9 (2.5–3.4)	
HR (95% CI)[a]	0.84 (0.61–1.14)		0.92 (0.74–1.15)		0.67
All-cause death					
No. of events	204	169	289	287	
Event rate (95% CI)	11.0 (9.6–12.6)	9.4 (8.1–11.0)	5.7 (5.1–6.4)	5.6 (5.0–6.3)	
HR (95% CI)[a]	0.85 (0.69–1.04)		0.97 (0.82–1.14)		0.31
Improvement in NYHA functional class from baseline to 12 months					
No.	139	137	380	384	
Odds ratio (95% CI)[a]	1.04 (0.80–1.34)		0.99 (0.84–1.16)		0.81
Change in KCCQ total symptom score from baseline to 12 months					
Mean change	7.6 (6.1–9.2)	8.3 (6.7–9.8)	5.9 (5.0–6.8)	8.1 (7.3–9.0)	
Placebo-corrected difference	0.6 (−1.4–2.7)		2.2 (1.1–3.3)		0.65

Event rate is the number of events per 100 person-years.
CI, confidence interval; HF, heart failure; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; RR, rate ratio.
[a]Models were stratified by region and baseline left ventricular ejection fraction (<60% or ≥60%), and adjusted for treatment assignment.

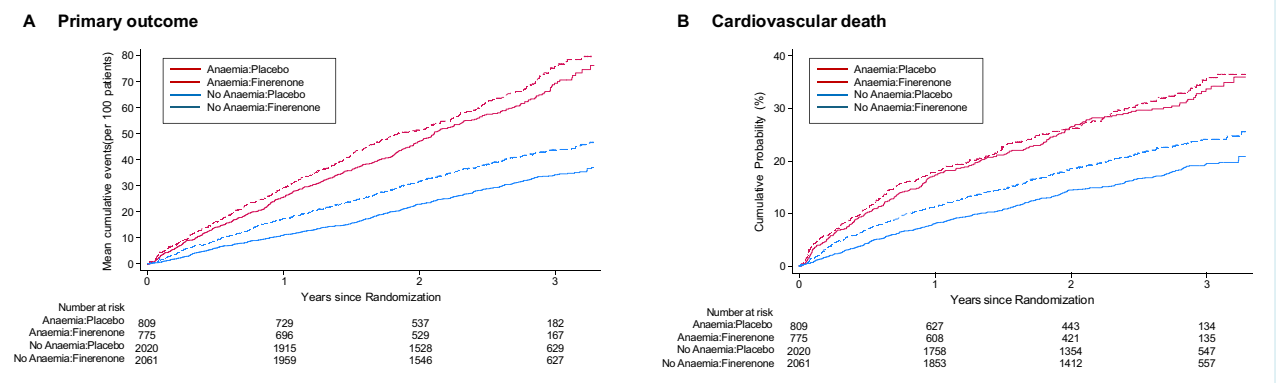

Figure 2 Cumulative hazard estimate for key trial outcomes according to anaemia status at baseline and treatment assignment. Effect of finerenone, compared with placebo, on the primary composite endpoint (*A*) and cardiovascular death (*B*) according to anaemia status at baseline. The Lin–Wei–Yang–Ying (recurrent events) is stratified by region and baseline left ventricular ejection fraction (<60% or ≥60%) and adjusted for treatment assignment.

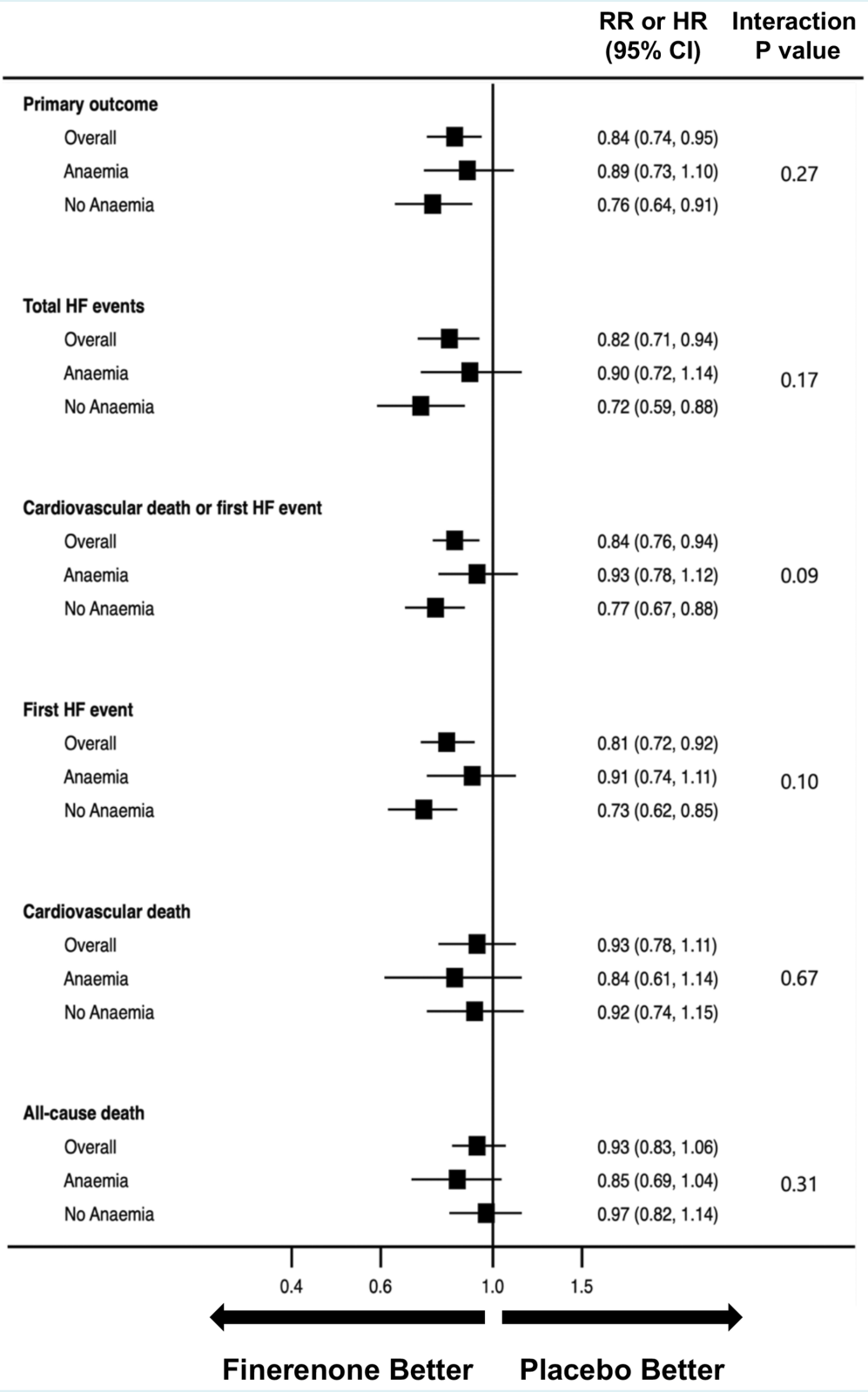

Figure 3 Effect of finerenone, compared with placebo, on clinical outcomes (primary composite outcome, total heart failure [HF] events, cardiovascular death or first HF event, first HF event, cardiovascular death, and all-cause death), overall in the trial and according to anaemia status at baseline. The effects of finerenone on all outcomes are consistent regardless of anaemia status at baseline. CI, confidence interval; HR, hazard ratio; RR, rate ratio.

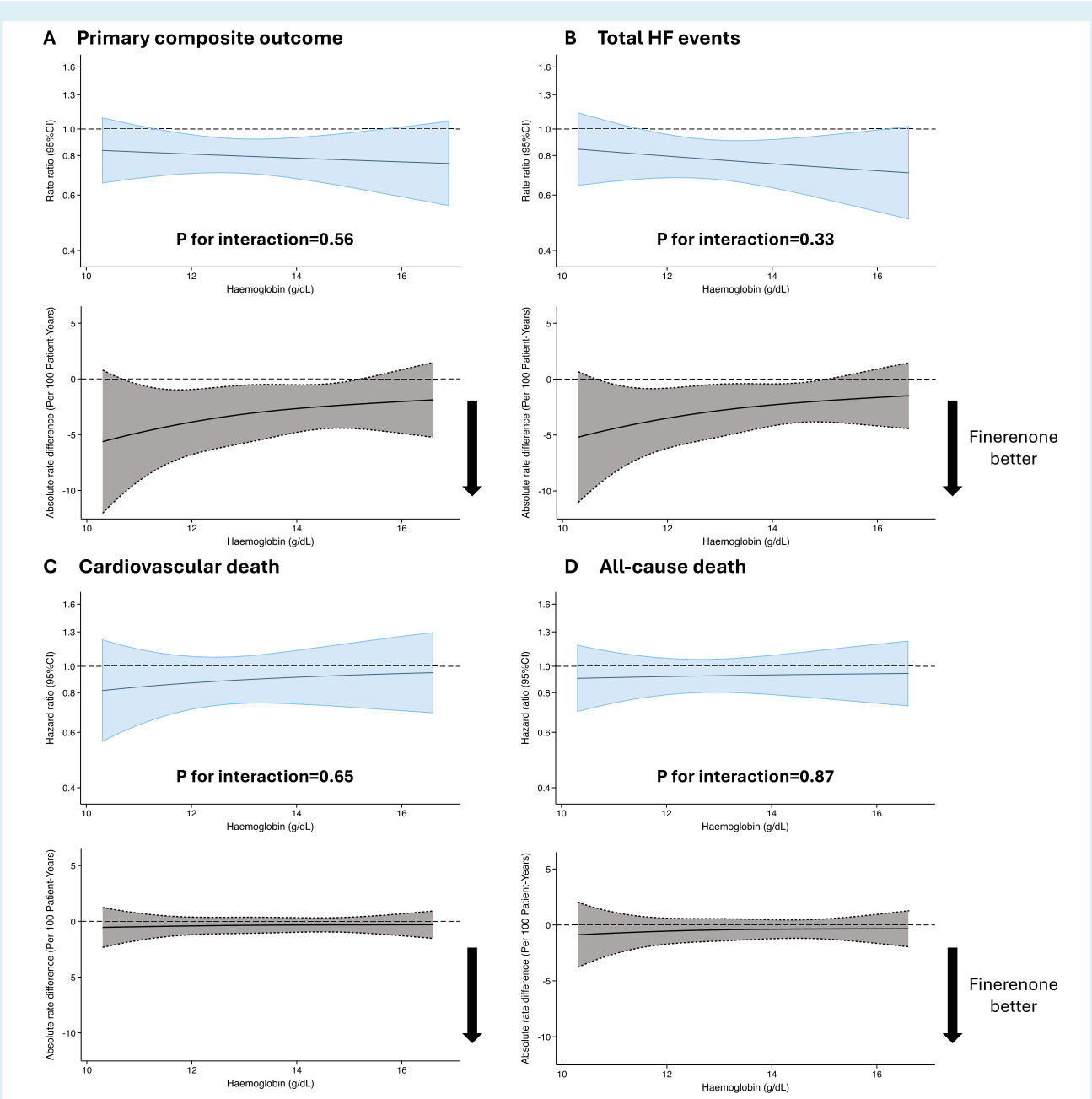

Figure 4 Effect of finerenone compared to placebo according to haemoglobin in FINEARTS-HF. The upper panels show the effect of finerenone, compared with placebo, on clinical outcomes according to haemoglobin concentration at baseline, shown as a continuous variable. The shaded area represents the 95% confidence interval (CI). Primary composite outcome (*A*), total heart failure (HF) events (*B*), cardiovascular death (C), and all-cause death (*D*). The lower panels show the absolute benefits of finerenone across the range of haemoglobin for the following outcomes: primary composite outcome (*A*), total HF events (*B*), cardiovascular death (*C*), and all-cause death (*D*). The *x*-axis shows the haemoglobin spectrum, and the *y*-axis shows the rate difference for the effect of finerenone compared to placebo. The black line represents the continuous rate difference, and the grey-shaded areas represent the 95% CI. A rate difference less than zero indicates a benefit of finerenone over placebo.

anaemia was analysed according to severity categories, the effect of finerenone on all outcomes remained consistent across these categories (online supplementary *Figures S11 and S12*). Given the higher event rates among anaemic patients, finerenone demonstrated a greater absolute risk reduction in patients with low haemoglobin concentrations at baseline compared to those with higher baseline haemoglobin concentrations (*Figure 4*).

The mean increase (improvement) in KCCQ-TSS from baseline to 12 months was greater with finerenone, compared to placebo, irrespective of anaemia status at baseline (p for interaction = 0.65) (*Table 2*).

Tolerability and safety according to anaemia status

Hypotension and elevated creatinine levels were more frequent in patients with anaemia at baseline, compared to those without anaemia. Overall, the incidences of hypotension, elevated creatinine levels, and hyperkalaemia were significantly higher with finerenone compared to placebo, while the incidence of hypokalaemia was lower with finerenone than with placebo. These differences were consistent, regardless of anaemia status at baseline (online supplementary *Table S10*).

Discussion

In this prespecified analysis of FINEARTS-HF, anaemia was present in 28% of patients at baseline and was associated with adverse clinical outcomes. Patients showing resolution of anaemia during follow-up exhibited outcomes similar to those who remained non-anaemic and significantly better than those with persistent anaemia. In contrast, patients who developed new-onset anaemia experienced worse outcomes than those who remained non-anaemic, with a prognosis similar to those with persistent anaemia. The reduction in risk of clinical outcomes with finerenone, compared to placebo, was consistent regardless of baseline haemoglobin and anaemia status. Additionally, compared to placebo, finerenone reduced the risk of adverse outcomes in patients with either new-onset or persistent anaemia.

The proportion (28%) of patients with anaemia at baseline was similar to previous studies in comparable populations that is, 28.5% in TOPCAT, 23.2% in PARAGON-HF, and 27.4% in DELIVER.[11,21,22] As in these other studies, anaemic patients were older and exhibited known predictors of poor prognosis, including higher rates of diabetes, lower eGFR, and elevated NT-proBNP levels. Therefore, the worse outcomes observed in anaemic patients were unsurprising and consistent with previous findings. However, it is also important to note that despite extensive correction for other prognostic variables, anaemia remained associated with poor outcomes, suggesting that low haemoglobin *per se* may contribute to prognosis, possibly by exacerbating impaired tissue oxygen delivery, which is one of the key pathophysiological mechanisms in HF. However, it remains possible that low haemoglobin is just a marker of some unmeasured pathophysiological processes such as congestion or inflammation. The overall prescription rate of SGLT2 inhibitors was low, reflecting enrolment in FINEARTS-HF before recommendation and approval of these drugs in HF with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF), and there was no difference in SGLT2 inhibitor prescription rates between patients with and without anaemia.

Notably, almost 20% of patients developed new anaemia during the trial. Patients with new-onset anaemia had a 1.5- to two-fold higher risk of primary outcome, worsening HF events, and mortality compared to those who did not develop anaemia, with a risk similar to patients with persistent anaemia. These findings emphasize that the development of anaemia is not just a laboratory finding, defined by haemoglobin crossing an arbitrary threshold, but a clinically important event. These findings also suggest that preventing new-onset anaemia might be beneficial in HF and potentially a therapeutic goal.[23–26]

An even larger proportion of patients (approximately 34% in the placebo group) demonstrated resolution of their anaemia over time. In FINEARTS-HF these patients had around half the risk of the primary outcome, worsening HF events, and mortality compared to those with persistent anaemia, similar to the risk of patients remaining non-anaemic throughout the trial. These data also suggest that therapeutic correction of anaemia might improve clinical outcomes, although existing trials with darbepoetin and intravenous iron have given conflicting results concerning this question.[3,23,24,27,28] In addition, an increase in haemoglobin may simply be a marker of decongestion and associated with better outcomes because of this.[29]

To the best of our knowledge, there is only one other report of the effect on an MRA on haemoglobin concentration in HF. Aldo-DHF randomized patients to 25 mg of spironolactone (n = 213) or matching placebo (n = 209).[15] In that trial, the placebo-corrected change in haemoglobin from baseline to 12 months was −0.2 (95% CI −0.4 to −0.1) g/dl (p = 0.003). In another trial[16] in patients with (or at high risk of) coronary disease, up to 9 months of treatment with spironolactone 50 mg (n = 251), compared to control (n = 255), led to a small decrease in haemoglobin of borderline statistical significance (−0.1 [−0.3 to 0.0] g/dl; p = 0.089). In FINEARTS-HF, the placebo-corrected change in haemoglobin from baseline to 12 months was −0.1 g/dl (95% CI −0.2 to −0.06; $p < 0.001$). The haemoglobin reduction in the finerenone group was consistent with previous trials, with a similarly small magnitude. This contrasts with other treatments such as renin–angiotensin system inhibitors, SGLT2 inhibitors and sacubitril/valsartan, as mentioned in the Introduction.[8–14] In the present analysis, finerenone lowered haemoglobin and haematocrit concentrations, compared to placebo, although the difference between treatments was small and the incidence of new-onset anaemia was not increased (or decreased) compared to placebo. It is interesting to contrast these findings to those with ACE inhibitors and ARBs, which reduce haemoglobin to a greater extent and increase the risk of incident anaemia, in both HF and chronic kidney disease.[8–10] Moreover, an increase, rather than decrease, in haemoglobin might have been anticipated with finerenone given the experimental evidence that MRAs reduce hepcidin secretion which should lead to iron mobilization and utilization.[17,18]

Importantly, finerenone provided clinical benefits in patients with anaemia as well as those without anaemia (and the absolute risk reduction for the primary endpoint was more pronounced in patients with lower haemoglobin concentrations because they were at higher risk).

Limitations

All studies have certain limitations. In the FINEARTS-HF trial, measurements of erythropoietin, ferritin, transferrin saturation, and reticulocyte count were not performed. Additionally, hepcidin, which is reportedly reduced by MRAs, was not measured.

Conclusions

In FINEARTS-HF, finerenone improved clinical outcomes and symptoms, regardless of baseline haemoglobin and anaemia status in patients with HFmrEF/HFpEF.

Supplementary Information

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

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