FAIR-HF2 Trial

Intravenous iron in patients with systolic heart failure and iron deficiency to improve morbidity & mortality

Stefan D. Anker, MD PhD on behalf of the FAIR-HF2 Steering Committee, Trial Committees, Investigators & Coordinators

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EudraCT: 2016-000068-40
NCT 03036462

ACC Congress – Chicago, 30th March, 2025

Patient Recruitment

FAIR-HF 2
DZHK TRIAL 05

	FCM (n=558)	Placebo (n=547)
Age (years)	70.1 ± 11.4	69.7 ± 12.0
Men (N, %)	359 (64.3%)	378 (69.1%)
Diabetes (N, %)	248 (44.4%)	255 (46.6%)
History of atrial fibrillation or flutter (N, %)	282 (50.5%)	290 (53.0%)
Body Mass Index (kg/m^2)	28.1 ± 5.7	28.2 ± 5.5
Ischaemic cause of cardiomyopathy (N, %)	428 (76.7%)	430 (78.6%)
NYHA Class II (N, %)	369 (66.1%)	359 (65.6%)
NYHA Class III (N, %)	186 (33.3%)	184 (33.6%)
NT-proBNP (pg/mL)	4,345 ± 6,990	4,060 ± 6,018
Six Minute Walk Test Distance (m)	315 ± 120	313 ± 116
Estimated Glomerular Filtration Rate	60 ± 23	60 ± 23
Heart failure therapy		
ACEI (N, %)	240 (43.0%)	215 (39.3%)
ARB (N, %)	100 (17.9%)	90 (16.5%)
ARNI (Sacubitril/Valsartan) (N, %)	200 (35.8%)	219 (40.0%)
Beta blocker (N, %)	504 (90.3%)	512 (93.6%)
MRA (N, %)	386 (69.2%)	393 (71.9%)
SGLT2 inhibitor (N, %)	130 (23.3%)	131 (24.0%)
Diuretics (N, %)	461 (82.6%)	445 (81.4%)
Laboratory measurements, mean (SD)		
Haemoglobin [g/dL]	12.5 ± 1.1	12.4 ± 1.1
Ferritin [µg/L]	72 ± 52	74 ± 58
Transferrin saturation [%]	18.6 ± 9.3	17.9 ± 9.0

- Symptomatic CHF with LVEF ≤45% &Hgb 9.5–14.0 g/dL
- Iron deficiency: serum ferritin <100 µg/L or ferritin 100-299 ng/mL with TSAT <20%
- HF hospitalization in past 12mo OR stable ambulatory & BNP >100 pg/mL or NT-proBNP >300 pg/mL

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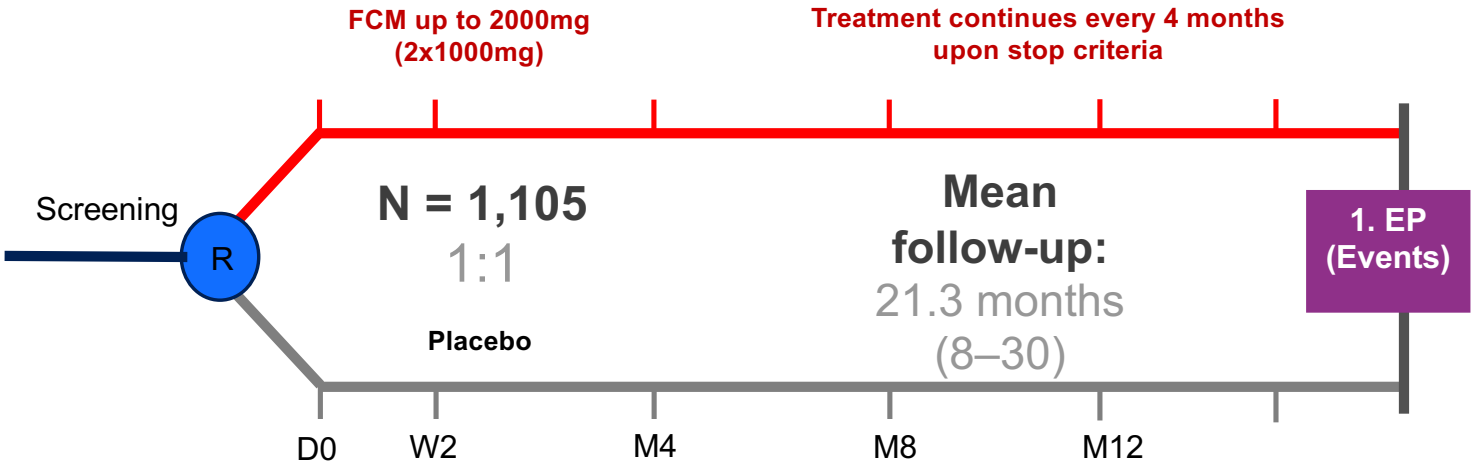
(FAIR-HF2 Baseline Data.)

FAIR-HF2 – Design

Design: Multi-centre, randomised (1:1), double-blinded, placebo-controlled

Iron dosing: Correction dose (up to 2,000 mg FCM)
Maintenance dose (500 mg every 4 months)

FPFV: March 2017
LPFV: November 2023
LPLV: May 2024
DB lock: 23 Dec 2024



Primary endpoints (3)

- CV death & HF hospitalization (time-to-first event): Cox regression
- HHF (rate of recurrent events): LWYY
- CV death & HF hospitalization (time-to-first event) in subgroup of patients with TSAT <20): Cox regression

Alpha = 0.05 significance level controlled across all primary EPs using Hochberg procedure

Secondary endpoints (4)

- Change in NYHA functional class, EQ-5D, PGA, 6MWT (baseline to 12 months) – Hochberg

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FAIR-HF2 Design.
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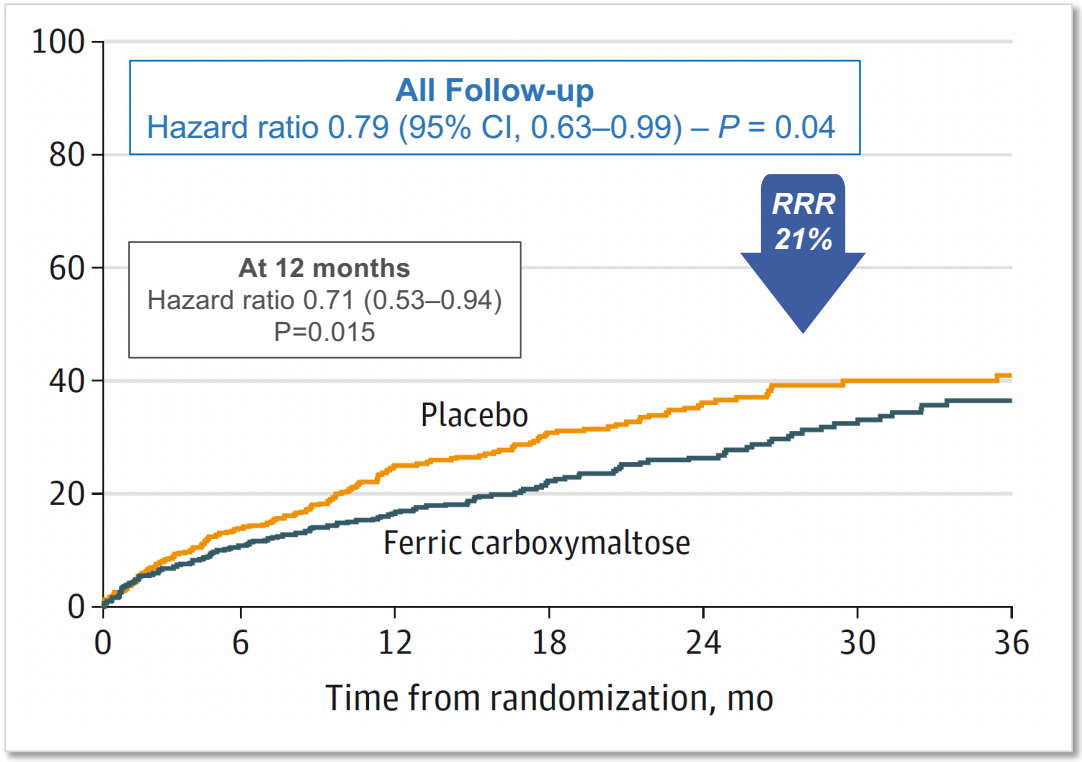
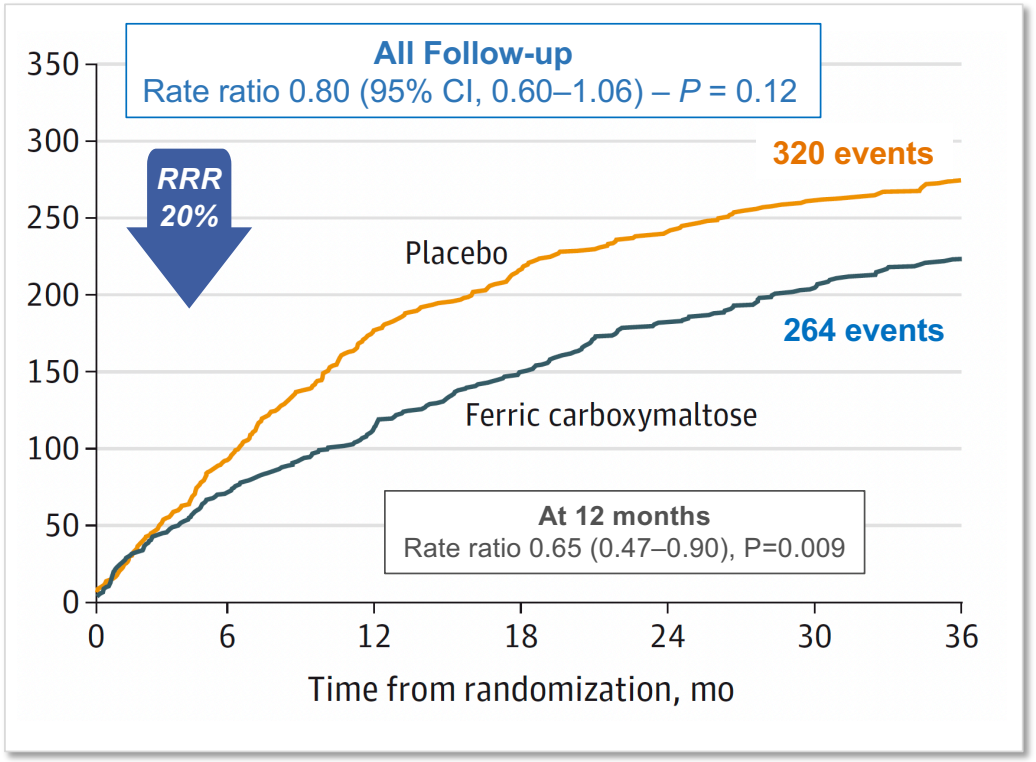
Primary Endpoint 1: CV death or HHF (time-to-first event)
Primary Endpoint 2: Recurrent HHF

CV death or HHF – time-to-first event (all patients)



Total (first & recurrent) HF hospitalisations



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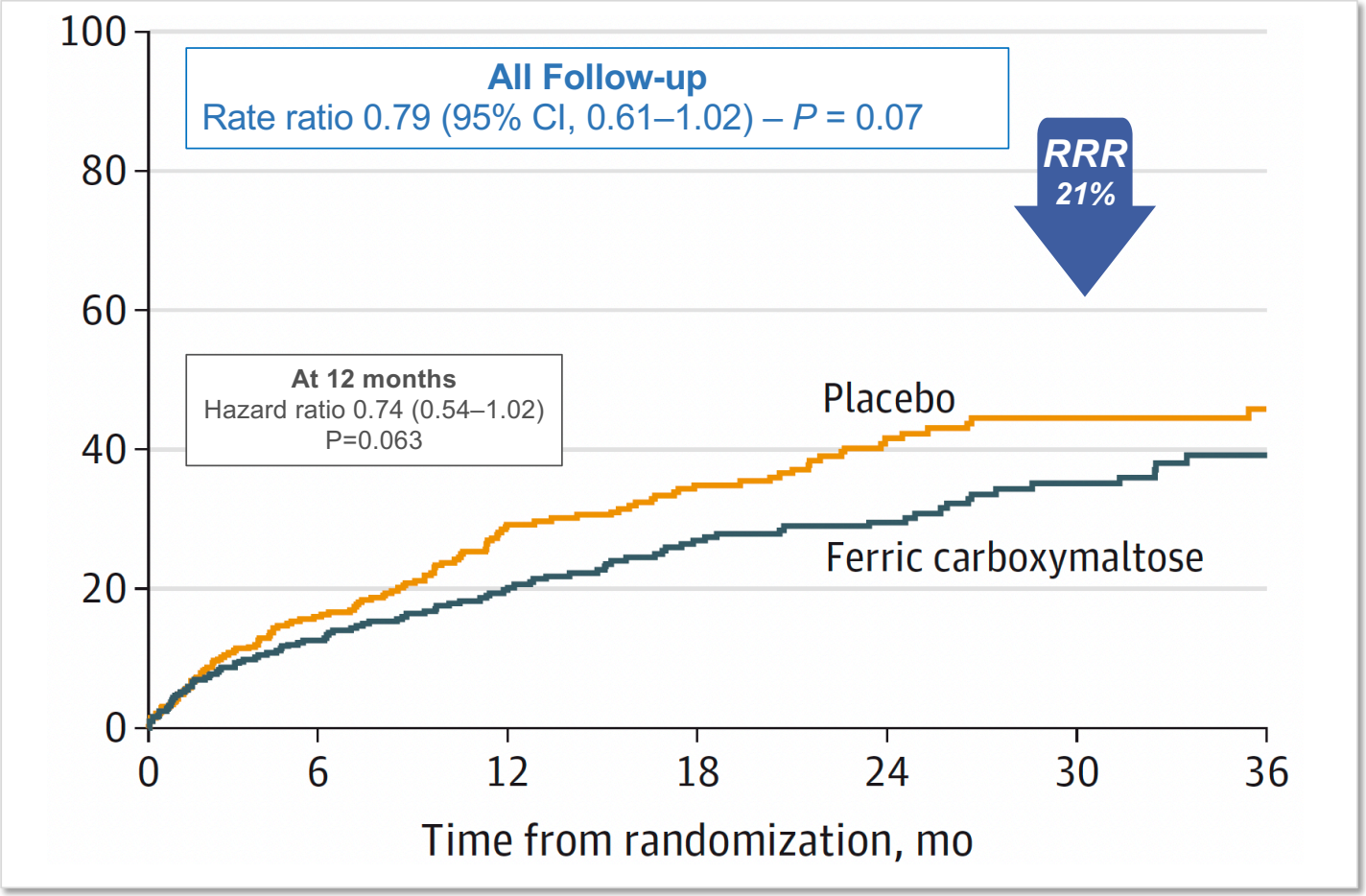
Primary Endpoint 3 – CV death or HHF (time-to-first event) in the subgroup of patients with TSAT <20% at baseline



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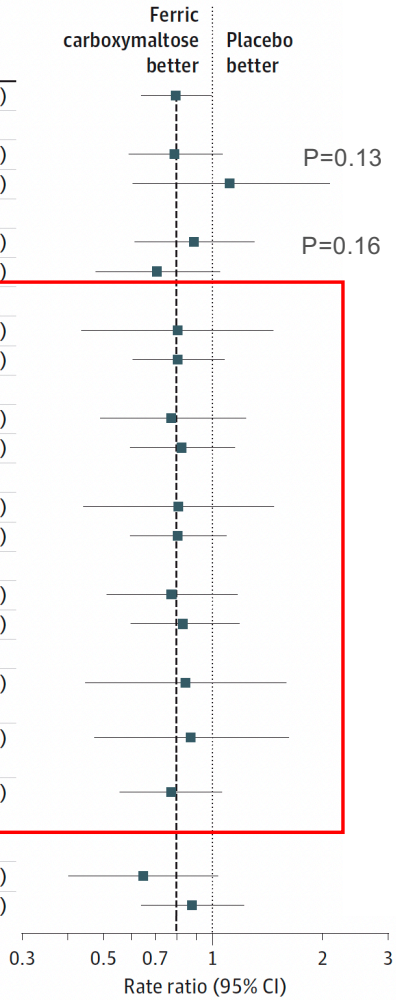
Key Subgroups (1) for Primary Endpoint 1 (HHF & CVD)

Source	No. of patients: Ferric carboxymaltose	No. of patients: Placebo	Cardiovascular death or HF hospitalization, % (No./total): Ferric carboxymaltose	Cardiovascular death or HF hospitalization, % (No./total): Placebo	Rate ratio (95% CI)
Overall	558	547	25.3 (141/558)	30.3 (166/547)	0.79 (0.63-0.99)
Sex					
Male	359	378	33.5 (211/630)	43.2 (281/650)	0.78 (0.57-1.06)
Female	199	169	14.3 (53/371)	12.6 (39/309)	1.14 (0.59-2.19)
Age, y					
≥70	324	304	28.8 (153/531)	31.0 (161/520)	0.89 (0.60-1.32)
<70	234	243	23.6 (111/470)	36.2 (159/439)	0.70 (0.46-1.05)
Transferrin saturation					
≥20%	190	167	22.3 (75/337)	26.5 (82/309)	0.80 (0.42-1.51)
<20%	368	380	28.5 (189/664)	36.6 (238/650)	0.80 (0.59-1.08)
Transferrin saturation					
≥Median	290	262	21.7 (112/517)	27.8 (136/490)	0.77 (0.48-1.24)
<Median	267	285	31.5 (151/479)	39.2 (184/469)	0.82 (0.58-1.16)
Ferritin level, ng/mL					
>100	87	100	32.9 (49/149)	41.2 (70/170)	0.80 (0.43-1.51)
≤100	471	447	25.2 (215/852)	31.7 (250/789)	0.80 (0.58-1.09)
Ferritin level					
≥Median	286	266	26.3 (129/490)	35.7 (163/457)	0.76 (0.50-1.17)
<Median	272	281	26.4 (135/511)	31.3 (157/501)	0.83 (0.58-1.19)
Combination of transferrin and ferritin					
Transferrin saturation <20% and ferritin ≤100 ng/mL	283	282	27.0 (141/522)	36.4 (176/483)	0.84 (0.43-1.63)
Transferrin saturation <20% and ferritin >100 but ≤300 ng/mL	84	96	31.2 (43/138)	37.3 (60/161)	0.87 (0.45-1.67)
Transferrin saturation ≥20% and ferritin ≤100 ng/mL	187	165	22.4 (73/326)	24.2 (74/306)	0.76 (0.54-1.07)
Body mass index[a]					
≥30	177	173	20.9 (72/345)	31.0 (90/290)	0.63 (0.38-1.04)
<30	379	369	29.4 (192/654)	34.6 (229/662)	0.88 (0.62-1.23)



for all hematinics
P ≥ 0.44

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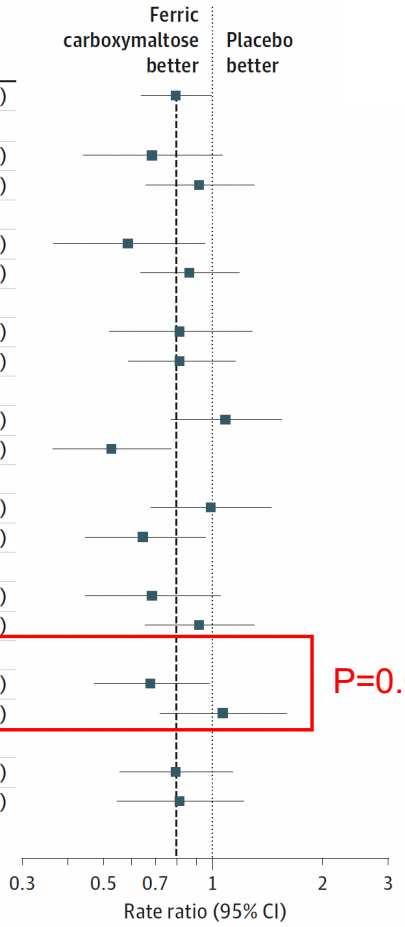
Key Subgroups (2) for Primary Endpoint 1 (HHF & CVD)

Source	No. of patients		Cardiovascular death or HF hospitalization, % (No./total)		Rate ratio (95% CI)
	Ferric carboxymaltose	Placebo	Ferric carboxymaltose	Placebo	
Overall	558	547	25.3 (141/558)	30.3 (166/547)	0.79 (0.63-0.99)
Level of LVEF					
≥Median	318	287	15.5 (87/561)	22.5 (104/463)	0.68 (0.42-1.07)
<Median	239	258	39.9 (174/436)	42.9 (211/492)	0.93 (0.64-1.33)
Ischemic etiology					
No	130	117	18.6 (44/237)	33.6 (79/235)	0.57 (0.35-0.94)
Yes	428	430	28.8 (220/764)	33.3 (241/724)	0.86 (0.62-1.20)
Estimated glomerular filtration rate					
≥Median	281	266	16.7 (85/510)	20.5 (92/449)	0.81 (0.51-1.30)
<Median	273	274	36.6 (177/484)	45.0 (224/498)	0.82 (0.58-1.16)
New York Heart Association classification[b]					
III or IV	187	187	55.1 (178/323)	51.1 (159/311)	1.11 (0.77-1.59)
I or II	370	359	12.7 (86/677)	24.9 (161/647)	0.51 (0.35-0.76)
Hospitalization for heart failure during previous 12 mo					
Yes	193	209	39.0 (146/374)	40.1 (147/367)	1.00 (0.68-1.48)
No	364	336	18.5 (115/623)	28.6 (168/588)	0.64 (0.43-0.95)
Diabetes					
Yes	248	255	24.3 (104/428)	37.8 (158/418)	0.67 (0.43-1.05)
No	310	292	27.9 (160/573)	30.0 (162/540)	0.92 (0.65-1.32)
Hemoglobin level, g/dL					
>12	384	357	21.6 (154/712)	33.5 (215/641)	0.67 (0.46-0.97)
≤12	174	190	37.9 (110/290)	33.1 (105/317)	1.08 (0.71-1.65)
Status at randomization					
Inpatient	292	295	26.8 (114/426)	32.0 (133/415)	0.79 (0.54-1.15)
Outpatient	266	252	26.1 (150/575)	34.4 (187/543)	0.81 (0.54-1.24)



P=0.02

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Secondary & Safety Endpoints

Secondary end points					
New York Heart Association classification, change from baseline to 12 mo[a]				OR, 0.69 (0.37 to 1.29)	P=0.08
EQ-5D score, change from baseline to 12 mo, mean (SD)[b]	0.02 (0.18)	−0.02 (0.19)	0.04 (0.26)	MD, 0.03 (0.01 to 0.06)	P=0.0088
Distance on 6-min walk test, change from baseline to 12 mo, mean (SD), m	27.2 (91.1)	19.7 (84.7)	7.5 (124)	MD, 10.7 (−1.44 to 22.9)	P=0.08
Patient-reported global assessment of well-being during follow-up until 12 mo				OR, 0.25 (0.17 to 0.37)	P<0.0001
Safety end points within 36 mo, No. of patients (rate/100 patient-years)					
All-cause mortality	104 (9.0)	111 (10.0)	−7 (−1)	HR, 0.94 (0.72 to 1.24)	P=0.68
Cardiovascular mortality	54 (5.8)	65 (7.5)	−11 (−1.7)	HR, 0.80 (0.55 to 1.14)	P=0.21

Abbreviations: HR, hazard ratio; MD, mean difference; OR, odds ratio; RR, rate ratio.

[a] Assesses severity of physical limitation in patients with heart failure.

[b] Ranges from −0.594 to 1; a score of 1 indicates perfect health; 0, death; and negative values, health status considered worse than death.

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Summary of Key Outcomes

Primary Endpoints

Heart failure hospitalizations or CV death (time-to-first)

21% ↓ in risk
P = 0.038*

**not statistically significant*

Rate of recurrent heart failure hospitalizations

20% ↓ in risk
P = 0.119

TSAT<20%: HF hospitalizations or CV death (time-to-first)

21% ↓ in risk
P = 0.070

Secondary Endpoints

EQ5D summary score (at 12 months)

improvement
P = 0.009

Self-reported PGA (at 12 months)

improvement
P < 0.0001

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Anker SD, Friede T, Butler J, et al

Intravenous Ferric Carboxymaltose in Heart Failure With Iron Deficiency

The FAIR-HF2 DZHK05 Randomized Clinical Trial

Published online March 30, 2025

American College of Cardiology annual meeting

Available at jama.com

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FAIR-HF2 Conclusions

Results of FAIR-HF2 in terms of the impact on M&M events are highly ***consistent with those of AFFIRM-AHF & IRONMAN***, but do not reach statistical significance within the trial.

FAIR-HF2 suggests that both the classical ID definition (using ferritin & %TSAT) or a simplified one (using only TSAT<20%) are useful.

FAIR-HF2 confirms the benefits of iv-iron therapy on quality of life and patient self-reported health status.

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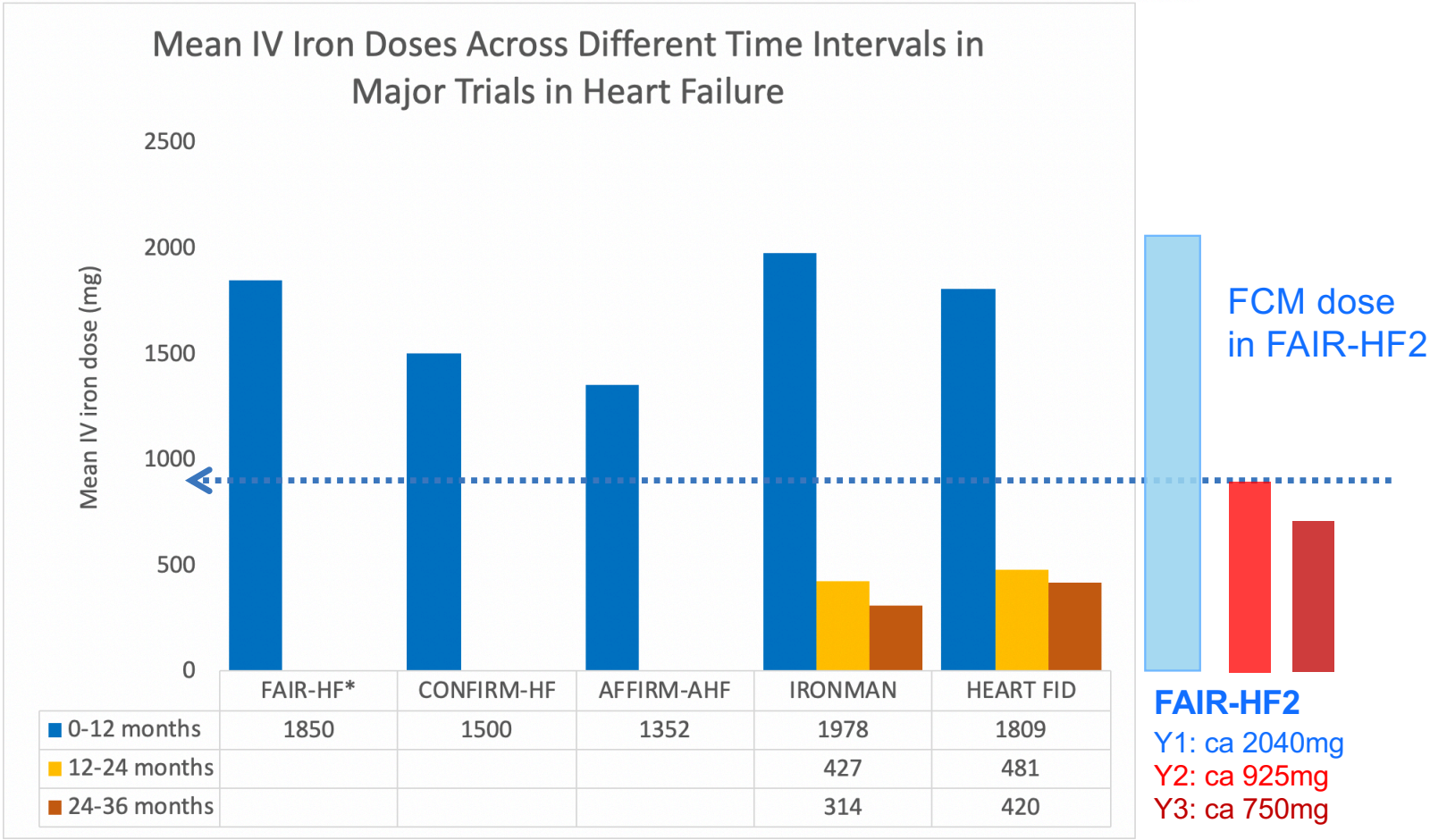
FAIR-HF2 Conclusions



	FAIR-HF*	CONFIRM-HF	AFFIRM-AHF	IRONMAN	HEART FID
0-12 months	1850	1500	1352	1978	1809
12-24 months				427	481
24-36 months				314	420

*FAIR-HF: IV iron was dosed over 6 months so 0-12 months actually denotes cumulative dose over 0-6 months

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Bayesian Meta-Analysis

2009 to 2025: 6 randomized controlled trials (>200 pats & 24+ weeks duration) with 7,175 patients
FAIR-HF, CONFIRM-HF, AFFIRM-AHF, IRONMAN, HEART-FID, FAIR-HF2

Primary Endpoint:

- Combined endpoint of recurrent events of HF hospitalizations or CV death
  a) up to 12 months follow-up and b) during the complete follow-up time available

Key Secondary Endpoints:

- Recurrent events of HF hospitalizations during the complete follow-up time available.
- CV mortality during the complete follow-up time available.
- All-cause mortality during the complete follow-up time available.

Tertiary endpoints:

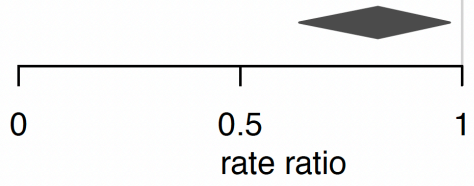
- *Infection events and hospitalizations for infections up to 12 months and during the complete follow-up time available (with a focus on safety and as much as it is available)*
- *Other relevant time intervals such as up to 24 months of follow-up time*

PROSPERO Registration – 07 January 2025

The Final Meta-Analysis – Recurrent events HHF & CVD (all FU)

Recurrent Events of HF hospitalizations or CV death
Bayesian Random Effects Meta-Analysis

study	effect (RR)	95% CI
FAIR–HF	0.460	[0.177, 1.195]
CONFIRM–HF	0.514	[0.277, 0.952]
AFFIRM–AHF	0.757	[0.600, 0.955]
IRONMAN	0.820	[0.660, 1.019]
HEART–FID	0.955	[0.819, 1.114]
FAIR–HF2	0.797	[0.616, 1.031]
overall mean effect	**0.810**	**[0.633, 0.973]**



Heterogeneity (tau): 0.12 [0.00, 0.39]

Recurrent HF Hospitalisations and CV death
(all follow-up)
–19%

Sensitivity Analysis: 0.812 (0.675–0.978)
(Hartung & Knapp) p=0.035 (tau 0.103)

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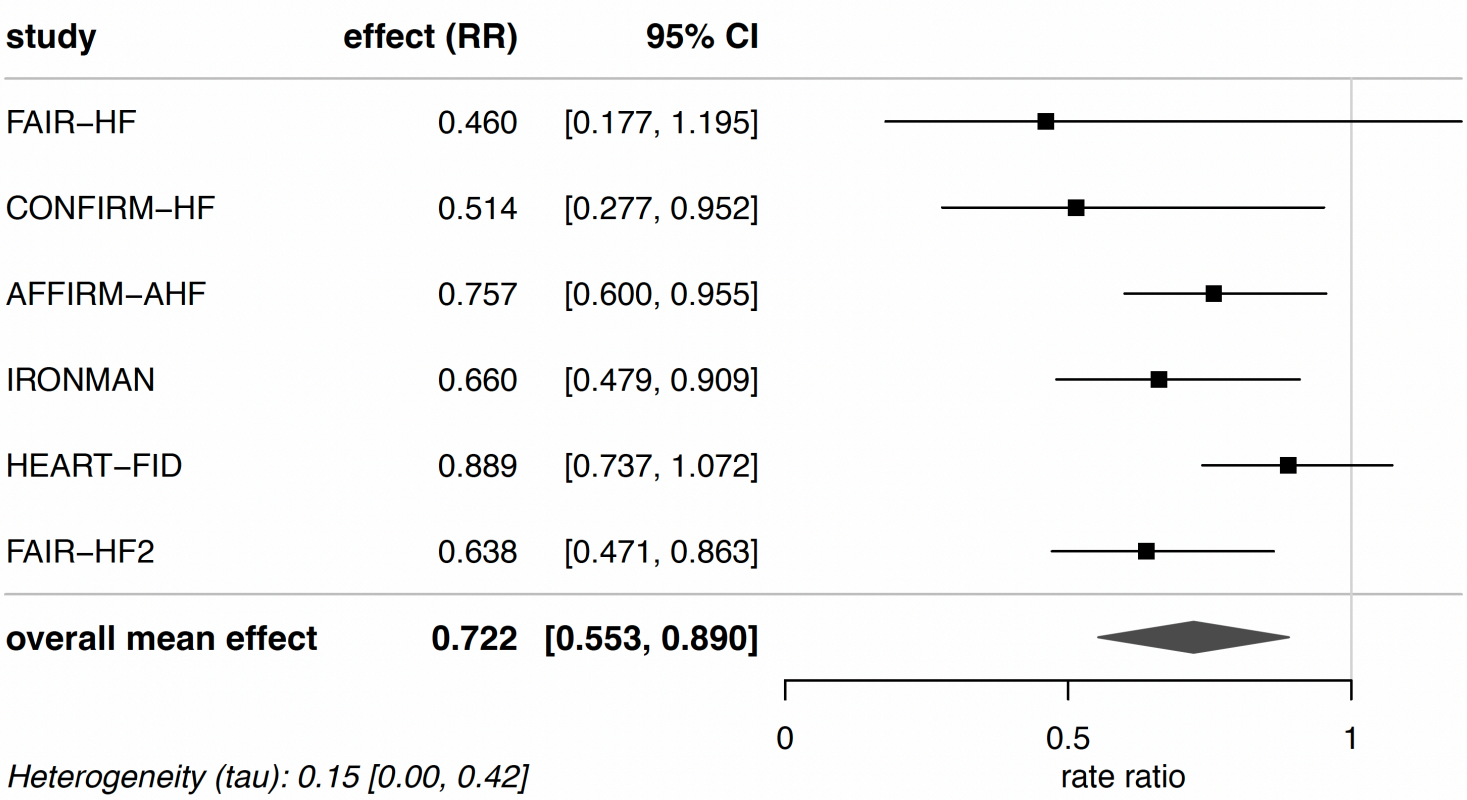
The Final Meta-Analysis – Recurrent events HHF & CVD (12mo FU)

Recurrent Events of HF hospitalizations or CV death
Bayesian Random Effects Meta-Analysis



Recurrent HF Hospitalisations and CV death
(12 months)
–28%

Sensitivity Analysis: 0.731 (0.600–0.891)
(Hartung & Knapp) p=0.010 (tau 0.096)

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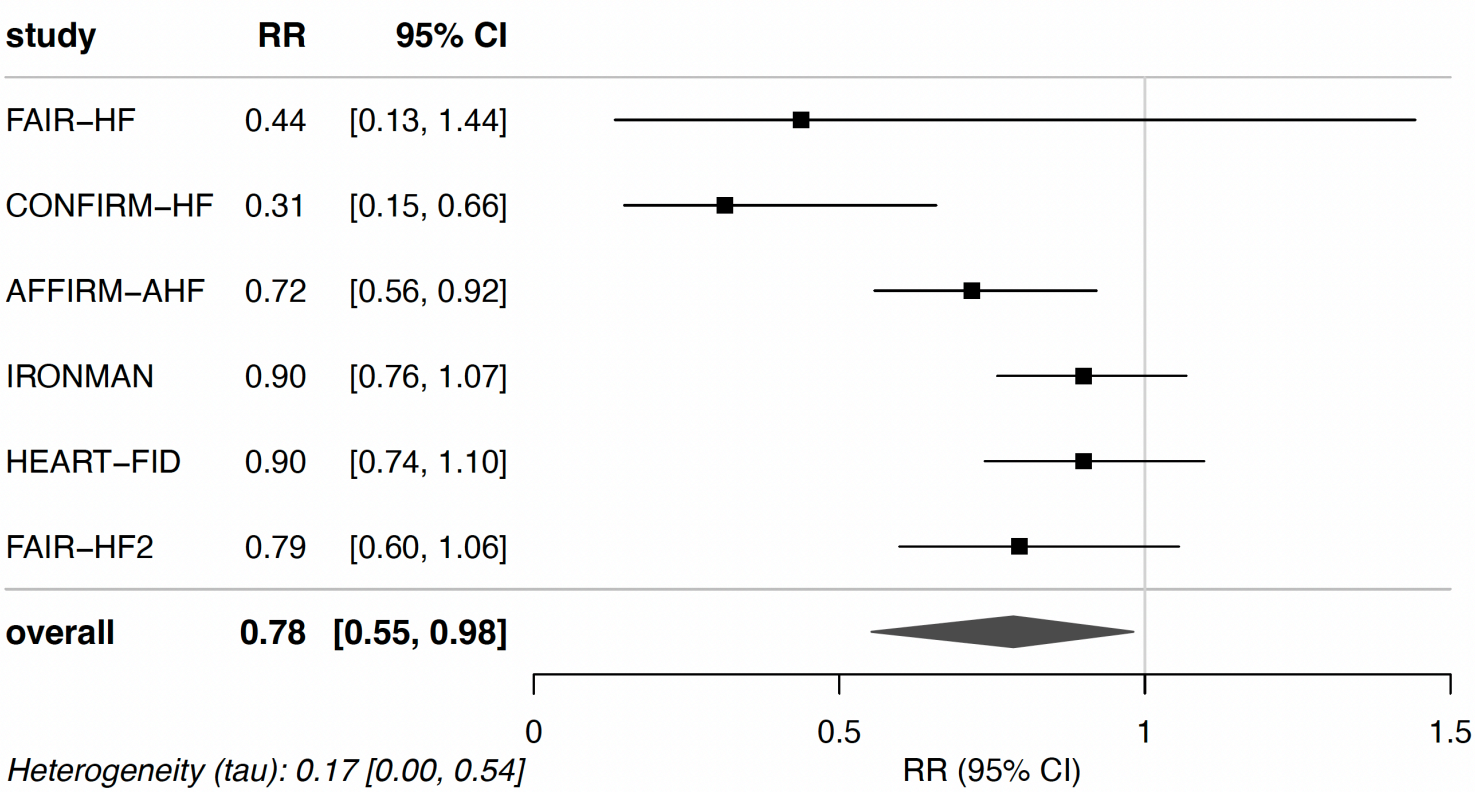
The Final Meta-Analysis – Recurrent HHF (all FU)

Recurrent Events of HF hospitalizations (LWYY)
Bayesian Random Effects Meta-Analysis



Recurrent HF hospitalisations
(all follow-up)

–22%

at 12 months: –31%

Sensitivity Analysis: 0.74 (0.52–1.06)
(Hartung & Knapp) p=0.081 (tau 0.27)

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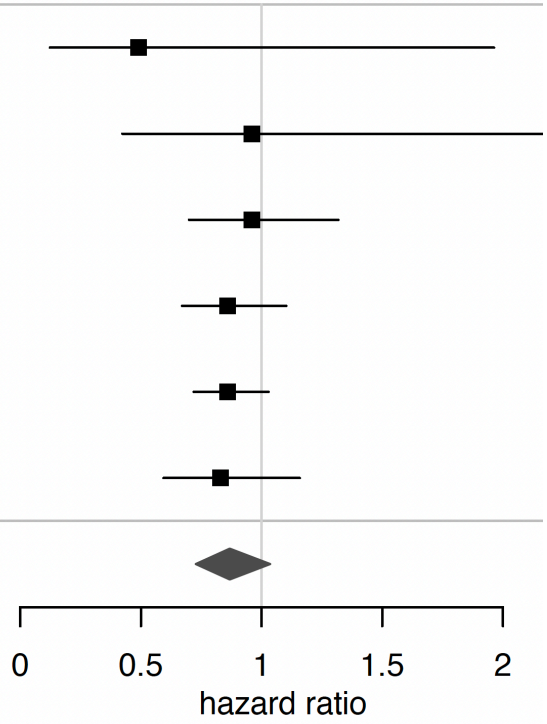
The Final Meta-Analysis – CV Mortality (all FU)

CV Mortality – Bayesian Random Effects Meta-Analysis

study	effect (HR)	95% CI
FAIR–HF	0.491	[0.123, 1.963]
CONFIRM–HF	0.960	[0.423, 2.177]
AFFIRM–AHF	0.960	[0.699, 1.318]
IRONMAN	0.860	[0.671, 1.102]
HEART–FID	0.860	[0.719, 1.029]
FAIR–HF2	0.829	[0.594, 1.158]
overall mean effect	**0.868**	**[0.727, 1.036]**



Heterogeneity (tau): 0.071 [0.000, 0.284]

CV Death
(all follow-up)
–13%

at 12 months: –18%

Sensitivity Analysis: 0.868 (0.741–1.017)
(Hartung & Knapp) p=0.070 (tau 0.000)

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Meta-analysis iv-iron vs control – Subgroups

8 subgroups for the endpoint **"Recurrent events HHF & CVD"**

(analysed analogous to Table 2 in Anker et al. (EJHF 2023) and all based on IRONMAN publications)

Subgroup definition	Effects in subgroups	Interaction
	RR (95% CI)	RRR (95% CI)
Sex: female vs. male	0.98 [0.75, 1.26]	0.76 [0.56, 0.95]	1.40 [1.05, 1.86]
Age (years): <69.4 vs. ≥69.4	0.73 [0.49, 0.98]	0.87 [0.70, 1.06]	0.84 [0.59, 1.16]
HF aetiology: ischaemic vs. non-ischaemic	0.74 [0.56, 0.92]	0.90 [0.65, 1.18]	0.84 [0.59, 1.22]
TSAT (%): <20 vs. ≥20	0.77 [0.60, 0.94]	0.96 [0.72, 1.26]	0.85 [0.61, 1.16]
eGFR (mL/min/1.73m²): ≤60 vs. >60	0.81 [0.65, 0.98]	0.84 [0.60, 1.12]	0.96 [0.70, 1.32]
Haemoglobin (g/dL): <11.8 vs. ≥11.8	0.78 [0.58, 1.01]	0.84 [0.62, 1.08]	0.94 [0.62, 1.43]
Ferritin (µg/L): <35 vs. ≥35	0.85 [0.65, 1.16]	0.77 [0.53, 1.01]	1.14 [0.74, 1.95]
NYHA class: I-II vs. III-IV *	0.73 [0.50, 1.02]	0.86 [0.66, 1.09]	0.87 [0.57, 1.29]

* In FAIR-HF there was only 1 event in 82 patients with NYHA class II.
Hence, this subgroup analysis of FAIR-HF was omitted from the meta-analysis.

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Clinical Implications – The Big Picture

FAIR-HF2, on its own, did not demonstrate significant benefits in terms of reducing M&M events in HF patients with ID. However, the results were highly consistent with those of AFFIRM-AHF & IRONMAN.

FAIR-HF2 confirms the benefits of iv-iron therapy in patients with HFrEF and ID on quality of life and patient self-reported health status.

A meta-analysis using Bayesian statistical approaches, provides evidence of a benefit of intravenous iron to reduce rates of CV death & HF hospitalizations.

The subgroup results for women – where no event reductions for CV death & HF hospitalizations were found – need further exploration.

We need to still understand how to best provide intravenous iron in the long-term.