# FAIR-HF2 Trial

## Intravenous Iron in Patients With Systolic Heart Failure and Iron Deficiency to Improve Morbidity & Mortality

FAIR-HF 2
DZHK TRIAL 05

EudraCT: 2016-000068-40
NCT 03036462

Global Heart Failure Academy

ACC Congress Chicago, IL
March 30, 2025

# Patient Recruitment

| | 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

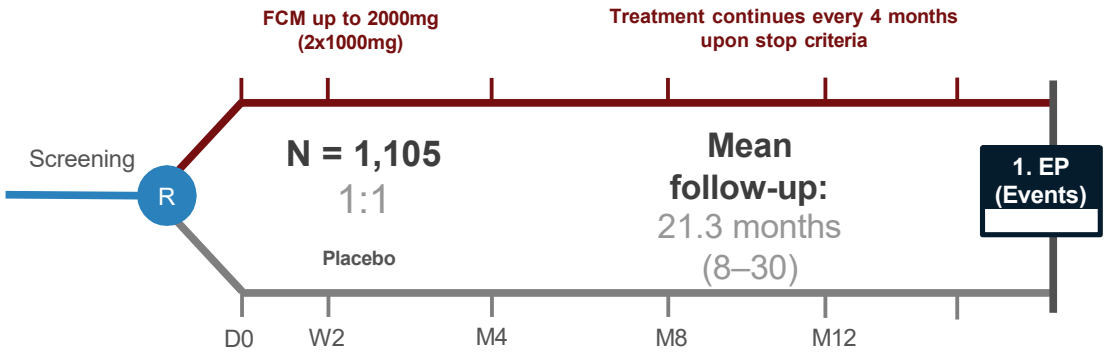

Anker SD, et al. *Eur J Heart Fail*. Published online January 28, 2025. doi:10.1002/ejhf.3574

# FAIR-HF2 – Design

**Design:** Multi-center, randomized (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: Dec 23 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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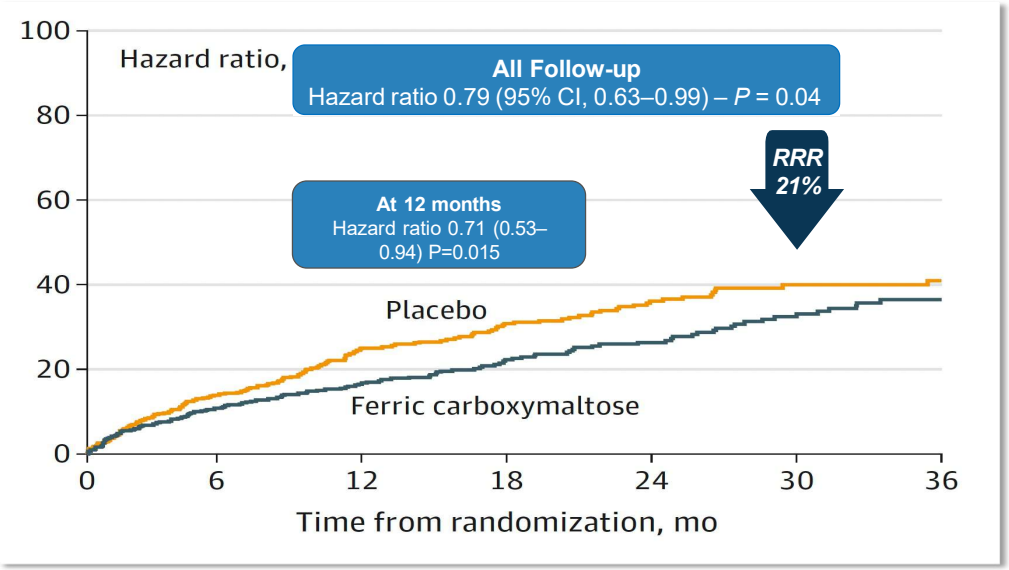
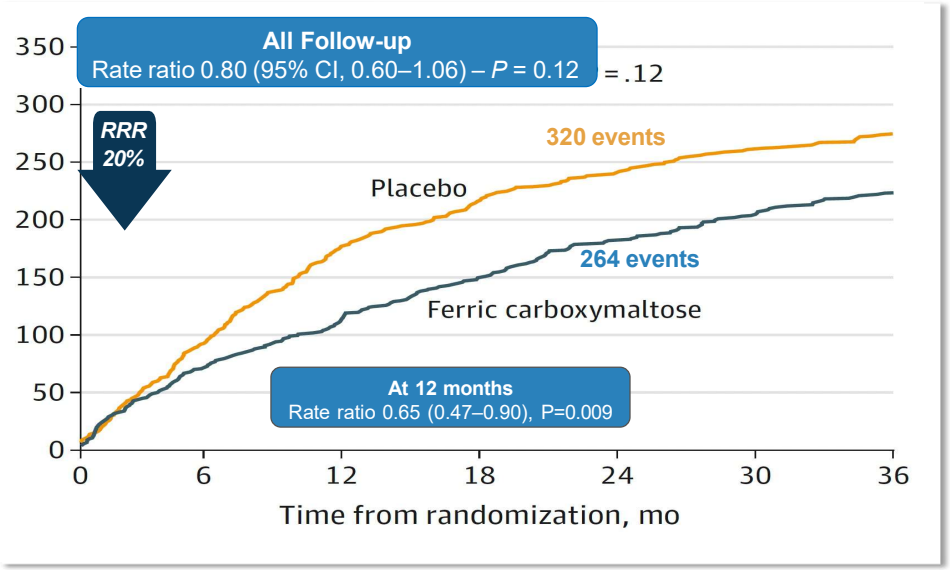
# Primary Endpoint 1: CV death or HHF (time-to-first event)
# Primary Endpoint 2: Recurrent HHF

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

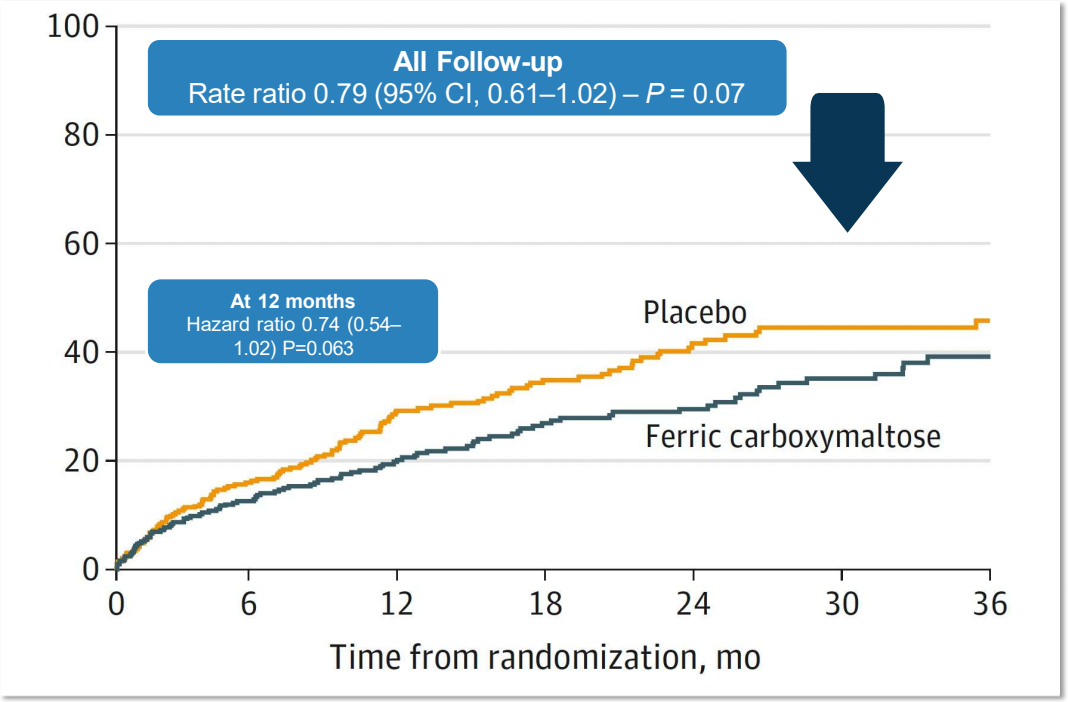



*Total (first & recurrent) HF hospitalizations*




Anker SD, et al. *JAMA*. Published online March 30, 2025. doi: 10.1001/jama.2025.3833

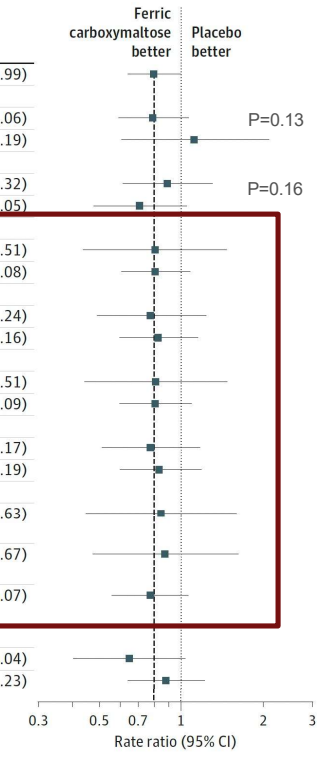
# Primary Endpoint 3 – CV Death or HHF (Time-to-First Event) in the Subgroup of Patients With TSAT <20% at Baseline




Anker SD, et al. *JAMA*. Published online March 30, 2025. doi:10.1001/jama.2025.3833

# 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
$P \geq 0.44$

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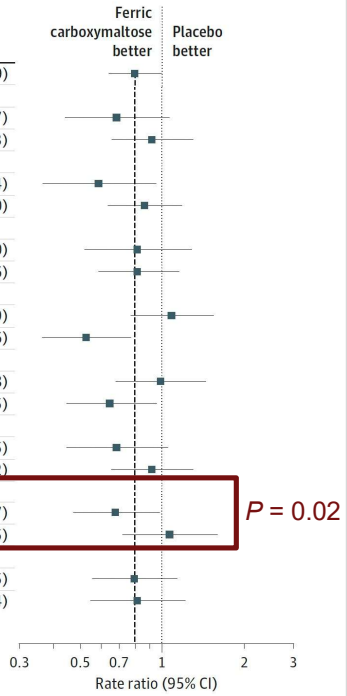
# Key Subgroups (2) for Primary Endpoint 1 (HHF & CVD)

| 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) |
| 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** **$P = 0.038$*** |
|  | *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** **$P < 0.0001$** |

*not statistically significant

# 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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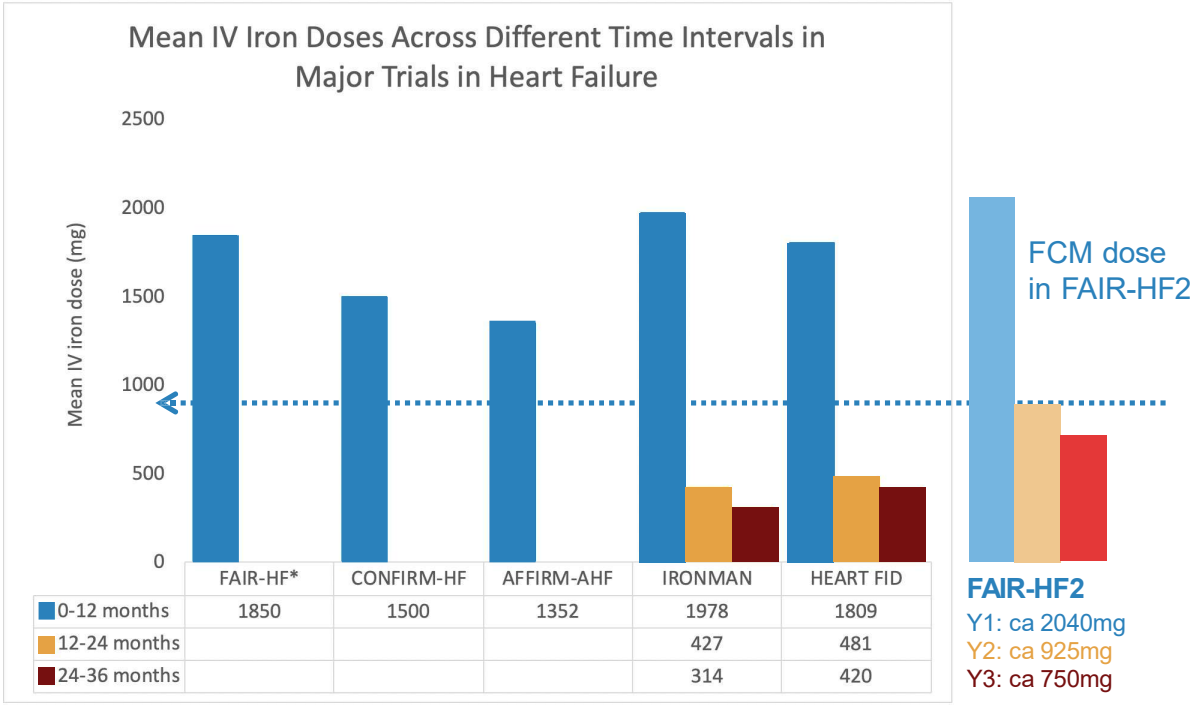
# FAIR-HF2 Conclusions




| | 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:***

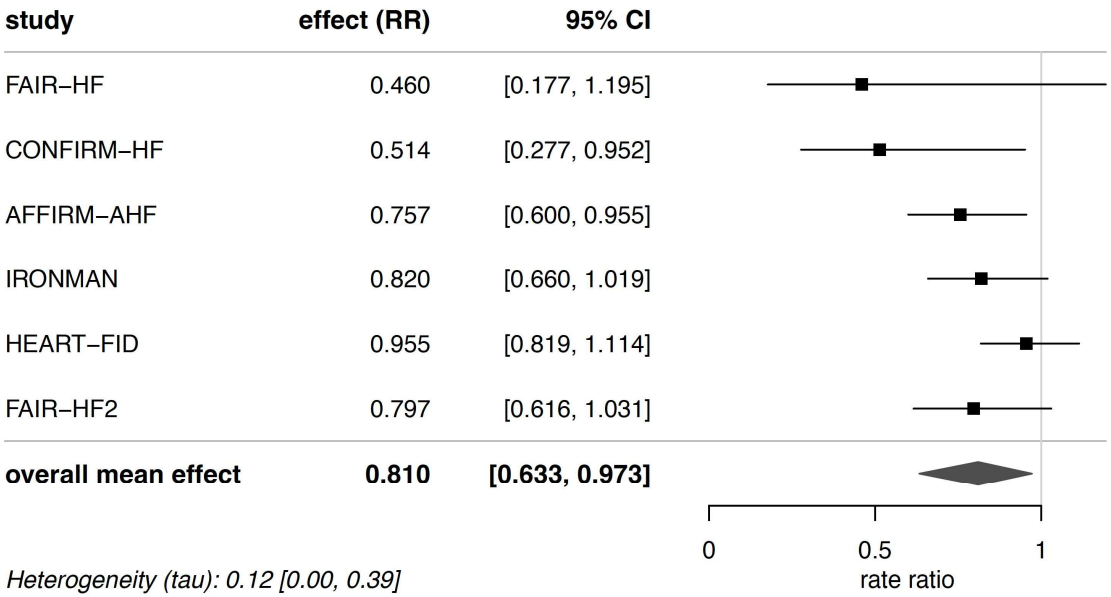
- *Infection events and hospitalizations for infections up to 12 months and during the complete follow-up time available (with a focus on safety and as much as it is available)*
- *Other relevant time intervals such as up to 24 months of follow-up time*

PROSPERO Registration – January 7, 2025

Anker SD, et al. *Nat Med*. Published online March 30, 2025. doi:10.1038/s41591-025-03671-1

# The Final Meta-Analysis – Recurrent Events HHF & CVD (All FU)

Recurrent Events of HF Hospitalizations or CV Death Bayesian Random Effects Meta-Analysis




Sensitivity Analysis: (Hartung & Knapp)

0.812 (0.675–0.978)
*P* = 0.035 (tau 0.103)

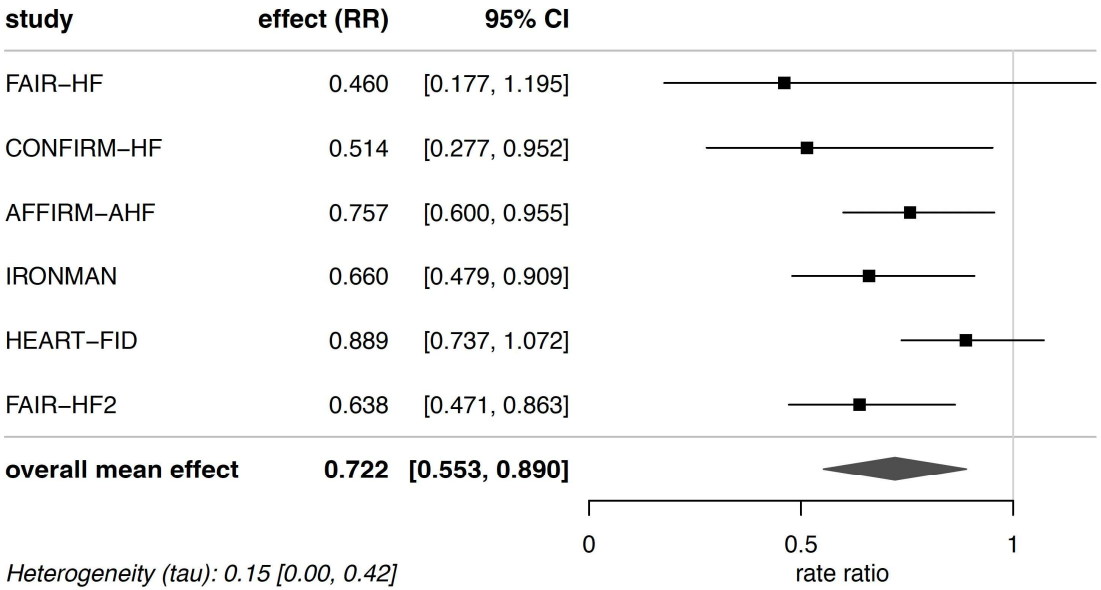
Recurrent HF Hospitalizations and CV death *(all follow-up)*

–19%

Anker SD, et al. *Nat Med*. Published online March 30, 2025. doi:10.1038/s41591-025-03671-1

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

Recurrent Events of HF Hospitalizations or CV Death Bayesian Random Effects Meta-Analysis




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

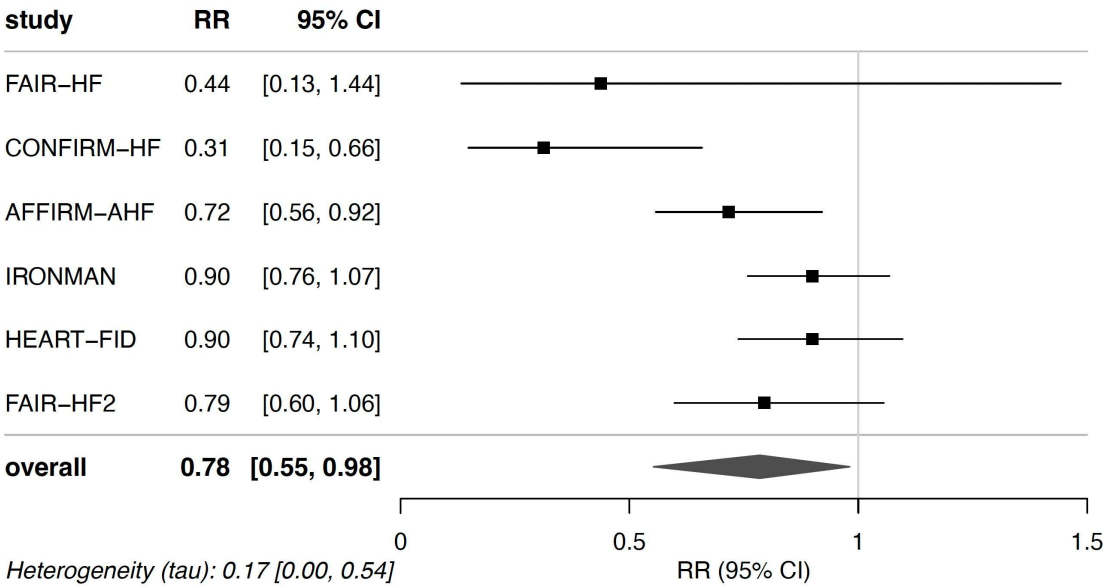
Recurrent HF Hospitalizations and CV death *(12 months)*

–28%

Anker SD, et al. *Nat Med*. Published online March 30, 2025. doi:10.1038/s41591-025-03671-1

# The Final Meta-Analysis – Recurrent HHF (All FU)

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




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

Recurrent HF Hospitalizations *(all follow-up)*

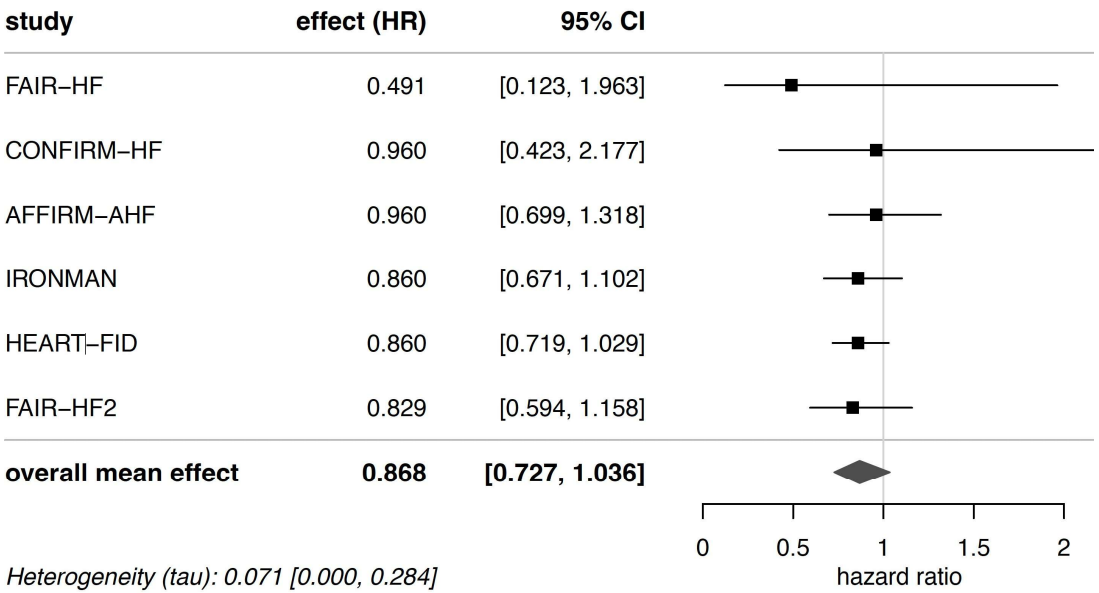
–22%

*at 12 months: –31%*

Anker SD, et al. *Nat Med* (2025). https://doi.org/10.1038/s41591-025-03671-1

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

CV Mortality – Bayesian Random Effects Meta-Analysis




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

CV Death
*(all follow-up)*
–13%

*at 12 months: –18%*

Anker SD, et al. *Nat Med* (2025). https://doi.org/10.1038/s41591-025-03671-1

# 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) | 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.

Anker SD, et al. *Nat Med* (2025). https://doi.org/10.1038/s41591-025-03671-1

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