Prior IV Iron Studies (HFrEF + HFmEF)

Trial	Patients	Time	Primary endpoint
FAIR-HF	459	24	Self-reported patient global assessment and NYHA functional class
CONFIRM-HF	304	52	6-MWD
EFFECT-HF	172	24	Peak VO_2

Improvements in:

- Patient global assessment
- Functional status (6-MWD, peak VO_2, NYHA class)
- Biomarkers (BNP)
- Reduction in HF hospitalizations

6-MWD, 6-minute walk distance; BNP, brain natriuretic peptide; HF, heart failure; HFmEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; NYHA, New York Heart Association; VO_2, volume of oxygen.

Lewis GD, et al. *Circ Heart Fail*. 2016;9(5):e000345. Anker SD, et al. *N Engl J Med*. 2009;361(25):2436-2448. Ponikowski P, et al. *Eur Heart J*. 2015;36(11):657-668. van Veldhuisen DJ, et al. *Circulation.* 2017;136(15):1374-1383.

Select Large and/or Ongoing HFrEF Trials

Study Name	AFFIRM-AHF	IRONMAN	HEART-FID	FAIR-HF-2
# of Patients	1,132	1,300	3,014	1,200
Diagnosis	Acute HF EF < 50%	Chronic HF EF < 45%	Chronic HF EF ≤ 40%	Chronic HF EF ≤ 45%
Blinding	Double blind	Open label	Double blind	Double blind
Study Arm	**Ferric carboxymaltose**	**Ferric derisomaltose**	**Ferric carboxymaltose**	**Ferric carboxymaltose**
Duration	52 weeks	120 weeks	Event driven + 12 mos last patient	Event driven + at least 12 mos f/u
Primary Endpoint	HF hospitalizations + CV death	CV death or HF hospitalizations	All-cause mortality + total HF hospitalizations through 12 mos and 6-month 6MWD	HF hospitalizations + CV death
Anticipated Completion Date	**Completed**	**Completed**	**June 2023**	**May 2024**

von Haehling S, et al. *JACC Heart Fail.* 2019;7(1):36-46.

Impact of COVID on Clinical Trials With IV Iron

- Affected 3 major clinical trials testing IV iron
  - AFFIRM-AHF
  - IRONMAN
  - HEART-FID
- Patients avoided follow-up visits for full intended treatment
  - Diluted benefit in results
- Further sensitivity analysis was necessary to overcome impact

Impact of COVID on Clinical Trials With IV Iron

Recurrent Event Outcomes

	Ferric carboxymaltose (n = 558)		Placebo (n = 550)		Rate ratio (95% CI)	*P* value
	Number of events	Rate per 100 patient-years	Number of events	Rate per 100 patient-years		
Modified intention-to-treat analysis						
Total heart failure hospitalizations* and cardiovascular death	293	57.16	372	72.51	0.79 (0.62–1.01)	0.059
Total cardiovascular hospitalizations* and cardiovascular death	370	76.04	451	95.13	0.80 (0.64–1.00)	0.050
Total heart failure hospitalizations*	217	31.72	294	43.15	0.74 (0.58–0.94)	0.013
Days lost due to heart failure hospitalizations and cardiovascular death†	NA	369.00	NA	548.40	0.67 (0.47–0.97)	0.035
COVID-19 sensitivity analysis‡						
Total heart failure hospitalizations* and cardiovascular death	274	55.24	363	73.48	0.75 (0.59–0.96)	0.024
Total cardiovascular hospitalizations* and cardiovascular death	350	75.07	440	97.35	0.77 (0.62–0.97)	0.024
Total heart failure hospitalizations*	202	31.19	287	44.30	0.70 (0.55–0.90)	0.005

NA, not applicable. *Total hospitalizations included first and recurrent events. If a patient was hospitalized for heart failure and died within 24 h of admission or if a patient was hospitalized for a cardiovascular reason and died within 24 h of admission, this was counted as one event. †Number of days lost due to heart failure hospitalizations or cardiovascular death corresponds to the total number of days in hospital for heart failure from randomization to censoring (follow-up). Days lost due to cardiovascular death is added to the number of days lost due to heart failure hospitalization. The total number of days lost is divided by the total patient-years of follow-up in each treatment group multiplied by 100. ‡Patients were censored in each country on the date when its first COVID-19 patient was reported in the respective country.

Ponikowski P, et al. *Lancet*. 2020;396(10266):1895-1904.

IRONMAN Primary Endpoint Analysis

	Ferric derisomaltose group (n = 527)	Usual care group (n = 536)	Estimated treatment effect (95% CI)	*P* value
Cardiovascular death and hospital admission for heart failure, number of events (rate per 100 patient-years)	336 (22.4)	411 (27.5)	0.82 (0.66 to 1.02)*	0.070
COVID-19 analysis	210 (22.3)	280 (29.3)	0.76 (0.58 to 1.00)*	0.047

*Rate ratio

Kalra PR, et al. *Lancet*. 2022;400(10369):2199-2209.

PIVOTAL Trial: Rate of All Episodes of Infection

	High-dose iron regimen	Low-dose iron regimen
Rate of all episodes of infection (events per 100 patient-years)	63.3	69.4

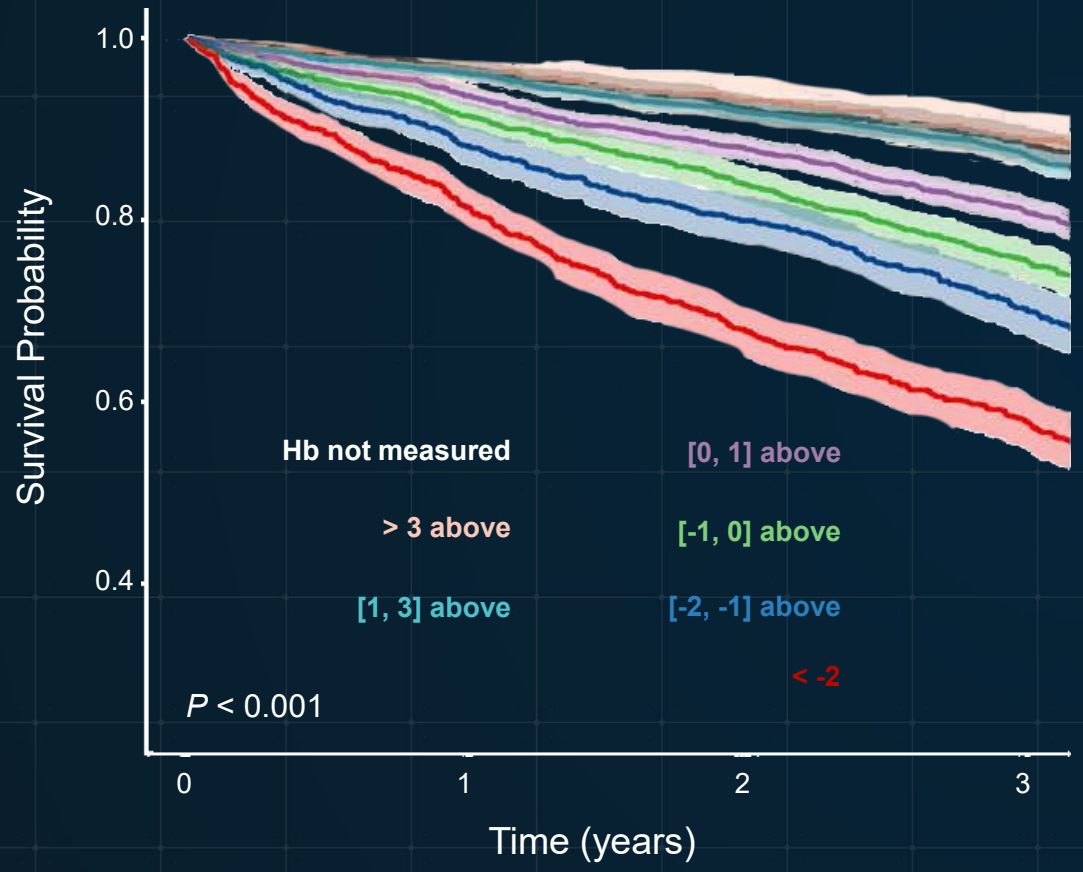
(rate ratio, 0.91; 95% CI, 0.79 to 1.05)

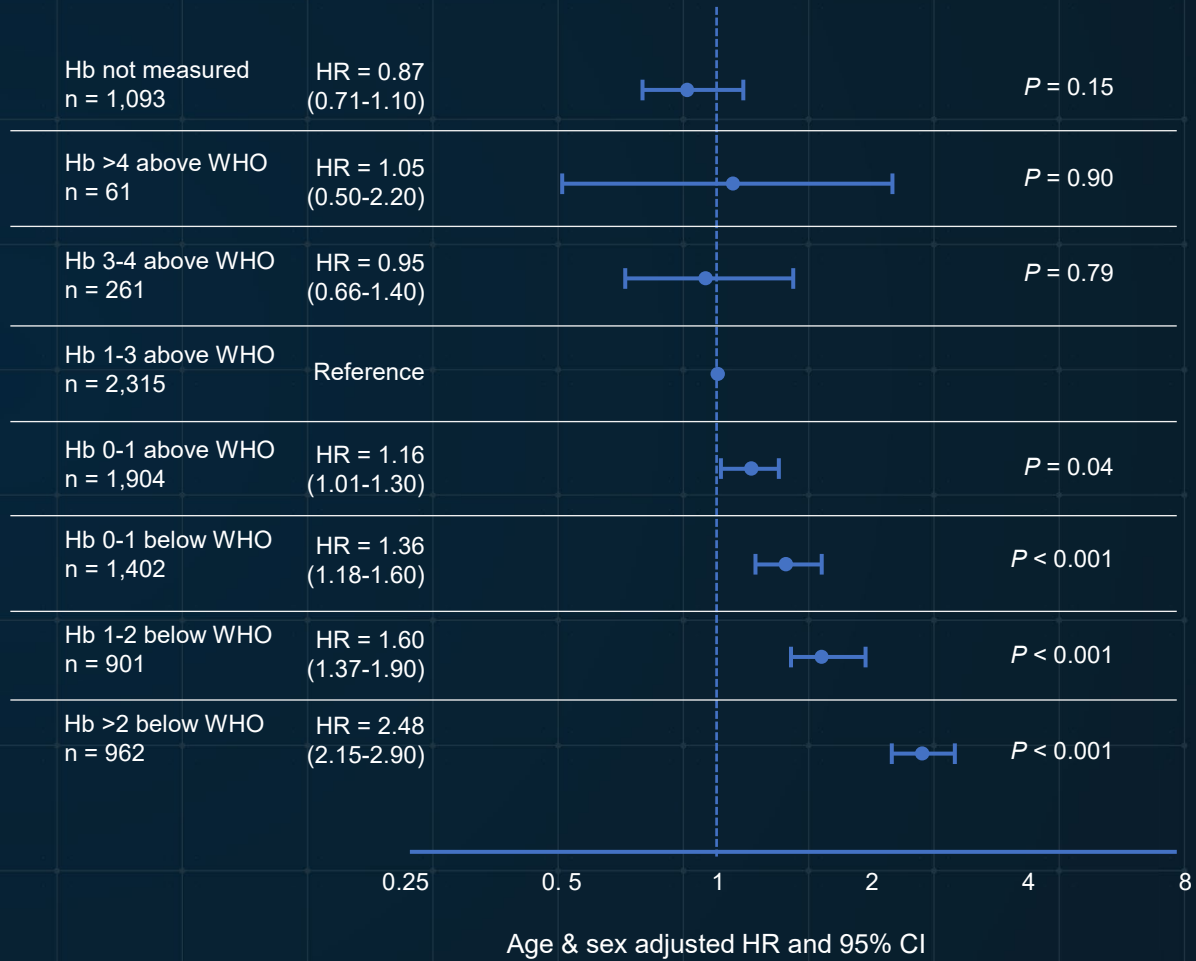
- Adults with end-stage kidney disease in whom maintenance hemodialysis had been initiated no more than 12 months before the initial screening visit, who had a ferritin concentration of less than 400 µg/L and a transferrin saturation of less than 30%, and who were receiving an erythropoiesis-stimulating agent were eligible to participate. Any iron therapy that had been prescribed previously was discontinued at the screening visit.
- Patients randomly assigned participants, in a 1:1 ratio, to receive a regimen of high-dose intravenous iron administered proactively or a regimen of low-dose intravenous iron administered reactively; patients were then evaluated monthly.

Macdougall IC, et al. *N Engl J Med*. 2019;380(5):447-458.

Anemia as a Marker for Mortality

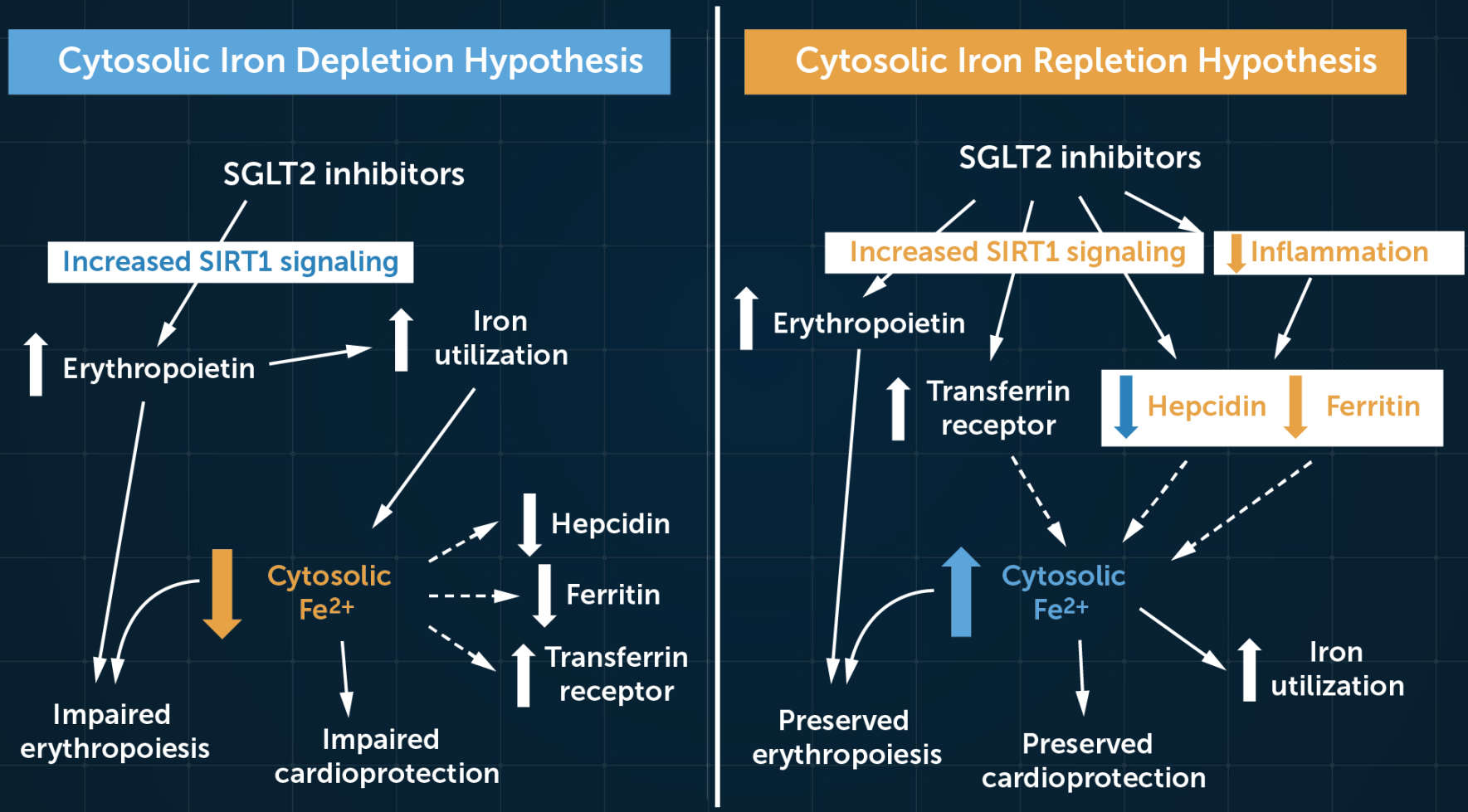
Associations Between Hemoglobin Concentration and All-Cause Mortality in Patients With Prevalent Heart Failure





Graham FJ, et al. *Heart*. 2023;109(17):1294-1301.

Two Conceptual Frameworks to Explain Worsening of Indices of Iron Deficiency During Treatment With SGLT2 Inhibitors



Packer M. *JACC Heart Fail*. 2023;11(1):106-114.

The Most Recent IV Iron Clinical Trials Included SGLT2 Inhibitors[1]

Canagliflozin was the first SGLT2 inhibitor approved on March 29, 2013[2]

Study Name	FAIR-HF-1	AFFIRM-AHF	IRONMAN	HEART-FID
# of Patients	459	1,132	1,300	3,014
Diagnosis	Chronic HF EF ≤ 45%	Acute HF EF < 50%	Chronic HF EF < 45%	Chronic HF EF ≤ 40%
SGLT2 Inhibitor	No	Yes	Yes	Yes
Study Arm	Ferric carboxymaltose	Ferric carboxymaltose	**Ferric derisomaltose**	Ferric carboxymaltose
Duration	24 weeks	52 weeks	120 weeks	Event driven + 12 mos last patient
Primary Endpoint	Self-reported patient global assessment and NYHA functional class	HF hospitalizations + CV death	CV death or HF hospitalizations	All-cause mortality + total HF hospitalizations through 12 mos and 6-month 6MWD
Completion Date	**2009**	**2020**	**2022**	**2023**

1. von Haehling S, et al. *JACC Heart Fail.* 2019;7(1):36-46. 2. Kaushal S, et al. *N Am J Med Sci.* 2014 Mar;6(3):107-113.

Key Takeaway: John Cleland, MD

"So anemia with a TSAT less than 20%, I think those are the patients who get the really big benefit from intravenous iron.”

Key Takeaway: Piotr Ponikowski, MD

"I think we need to be reassured that the real clinical benefit is there with IV iron in patients with iron deficiency. We just need to identify those who would benefit mostly…"

Key Takeaway: Stefan Anker, MD

"Let’s not forget quality of life symptoms and exercise capacity are also beneficially affected by intravenous iron.”