IRONMAN:

a randomized trial of intravenous ferric derisomaltose in heart failure with reduced ejection fraction

Paul R Kalra

On behalf of the IRONMAN investigators

Paul Kalra, Chief Investigator, Portsmouth Hospitals University NHS Trust and University of Glasgow, UK

Ian Ford, Study Director, University of Glasgow, UK

Background

- Iron deficiency is common in patients with heart failure and associated with impaired quality of life, reduced exercise capacity and higher risk of hospitalization for heart failure and death

- IV ferric carboxymaltose improves quality of life and exercise capacity to 24 weeks, and reduces re-hospitalizations for heart failure up to 12 months (AFFIRM-AHF)

- The longer-term (>12 months) efficacy and safety of IV iron in patients with heart failure is uncertain

Methods

- Investigator-initiated, event driven, linked to electronic health records
- IV ferric derisomaltose (FDI) vs usual care
- PROBE – prospective, randomized, open-label, blinded endpoint
    - all hospitalizations and deaths were adjudicated
- Funded by the British Heart Foundation
- Pharmacosmos donated FDI & provided additional funds

ClinicalTrials.gov Identifier: NCT02642562
Kalra PR et al. Heart 2022 Aug 10;heartjnl-2022-321304.

Main eligibility criteria

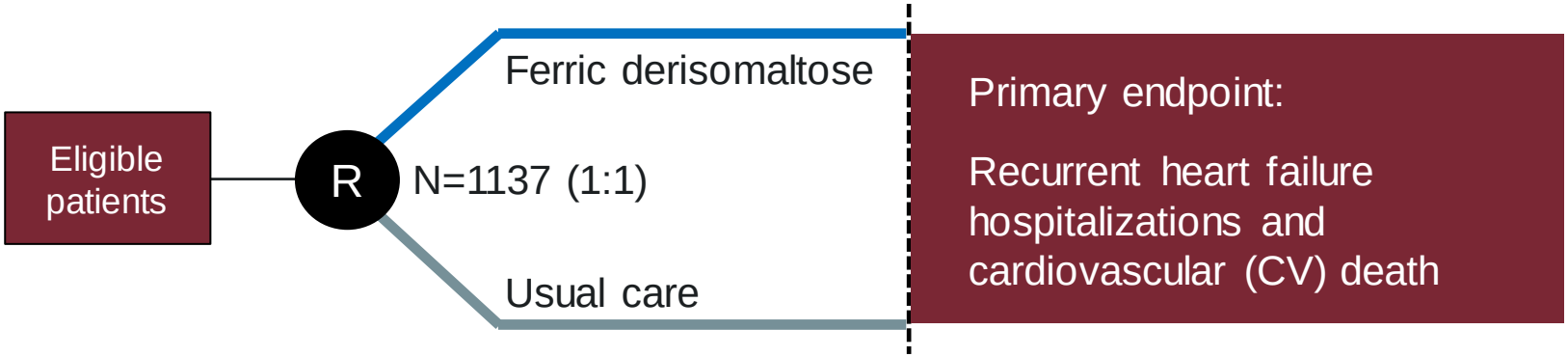
Inclusion criteria
Age ≥18 years
LVEF <=45% within the last 2 years
NYHA class II – IV
TSAT <20% or ferritin <100 ug/L
Increased risk of CV events, with either • Current or recent (<6 months) HF hosp. or • elevated natriuretic peptide
Able and willing to provide informed consent

Exclusion criteria
Hb <9.0 g/dL
Hb >13 g/dL in women or >14g/dL in men
Ferritin >400ug/L
eGFR <15ml/min/1.73m^2
MI, stroke or cardiac procedure in prior 3 mnth
Planned cardiac surgery or revascularization
Cardiac transplant or LVAD (planned or received)
Active infection
Disease (other than HF) with life-expectancy <2 yrs
Contra-indication to IV iron

Kalra PR et al. Heart 2022 Aug 10;heartjnl-2022-321304.

IRONMAN

Review at week 4, month 4, and 4 monthly thereafter
Re-dose if either ferritin <100 µg/L or TSAT <25% (provided ferritin was ≤400 µg/L)



Hb	BW<50 kg	BW 50 to <70 kg	BW≥70 kg
≥10 g/dL	20 mg/kg	1000 mg	20 mg/kg up to a maximum of 1500 mg
<10 g/dL	20 mg/kg	20 mg/kg	20 mg/kg up to a maximum of 2000 mg

Kalra PR et al. Heart 2022 Aug 10;heartjnl-2022-321304.

Outcomes

Key secondary

- Recurrent heart failure hospitalizations
- CV death
- First event: CV death, or hospitalization for heart failure, MI or stroke
- All cause mortality
- Overall MLHFQ at 4 months and 20 months

Primary safety

- Deaths and hospitalizations due to infection

Kalra PR et al. Heart 2022 Aug 10;heartjnl-2022-321304.

Power calculation

The power calculation was modified during the trial because event rates and recruitment (impacted by COVID-19) were lower than anticipated, and a meta-analysis suggested a larger treatment effect than originally anticipated

The final power calculation assumed a hazard ratio of 0·75, requiring 379 patients to reach a first primary endpoint in order to provide 80% power at the 5% significance level

Kalra PR et al. Heart 2022 Aug 10;heartjnl-2022-321304.

Prespecified COVID-19 sensitivity analysis

- During the pandemic in 2020 and 2021, recruitment slowed or ceased; many patients were not permitted or did not want to attend visits in person

- Consistent with FDA and EMA guidance to reduce the impact of the pandemic on the trial results

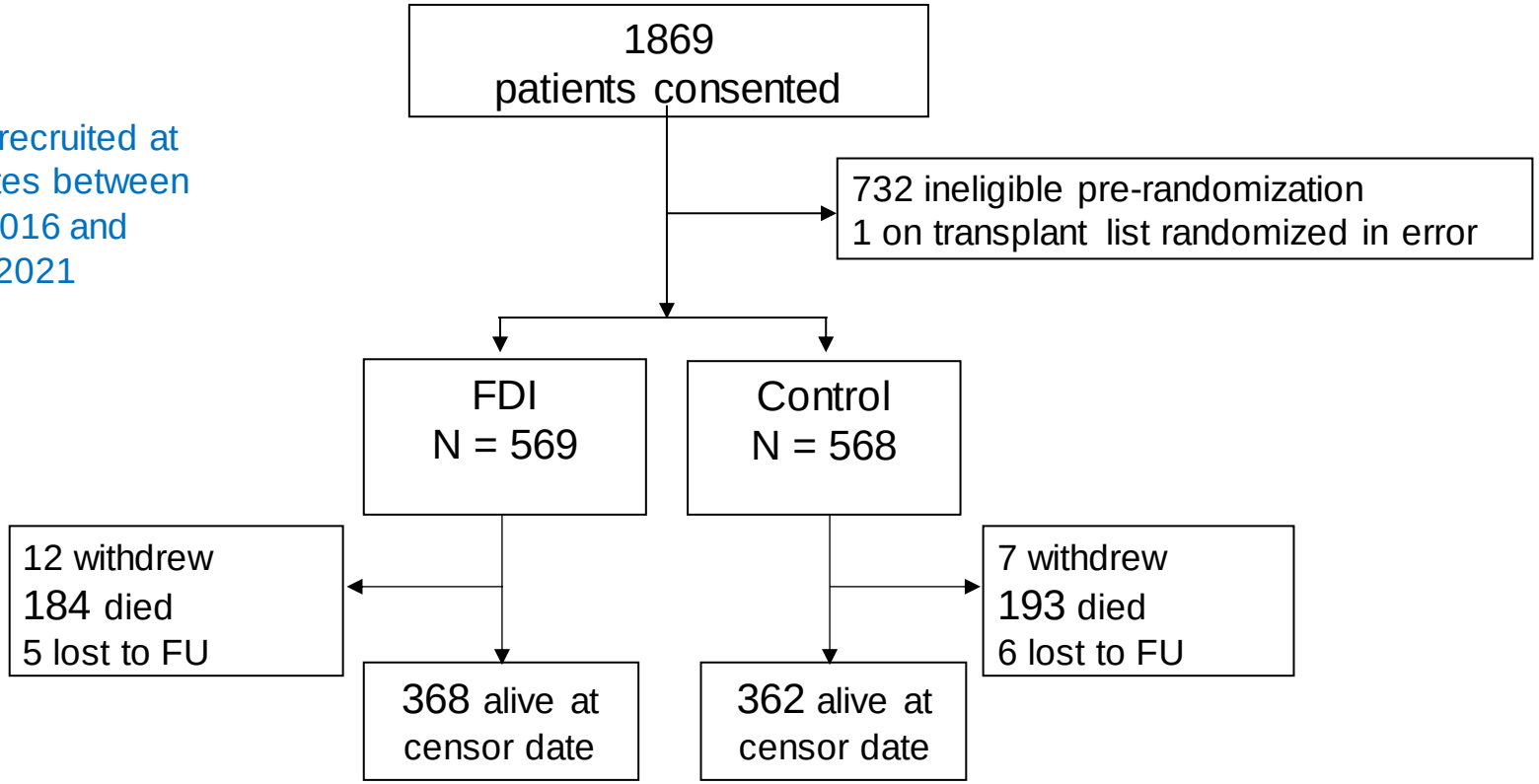
- All patients randomized until March 31st 2020 (first UK lockdown) with censoring date 6 months later (assuming that iron repletion would be maintained for at least 6 months after the last dose)

- Post hoc sensitivity analysis requested by referee to permit comparison with AFFIRM-AHF trial with censoring at one year in addition to the above

CONSORT Diagram

median (IQR) duration of follow-up 2·7 (1·8 to 3·6) years

Patients recruited at 70 UK sites between August 2016 and October 2021



Baseline characteristics

Characteristic	FDI (N=569)	Usual care (N=568)
Age (median, IQR) - yrs	73 (67 - 80)	74 (67 - 79)
Male gender – no. (%)	427 (75%)	410 (72%)
Recruitment context – no. (%)		
- Inpatient	80 (14%)	84 (15%)
- Recent hospitalization	106 (19%)	102 (18%)
- Elevated natriuretic peptide	383 (67%)	382 (67%)
NYHA class – no. (%) - II	328 (58%)	320 (56%)
- III	230 (40%)	238 (42%)
- IV	11 (2%)	10 (2%)
Ischaemic aetiology – no. (%)	331 (58%)	316 (56%)
Atrial fibrillation – no. (%)	284 (50%)	250 (44%)
Hypertension – no. (%)	297 (52%)	315 (56%)
Diabetes mellitus – no. (%)	252 (44%)	269 (47%)

Baseline characteristics

Characteristic	FDI (N=569)	Usual care (N=568)
LVEF (median, IQR) - %	32 (25 - 37)	35 (26 - 38)
Haemoglobin (median, IQR) – g/dL	12.1 (11.2 - 12.8)	12.1 (11.2 - 12.9)
TSAT (median, IQR) - %	15 (11 - 20)	15 (10 - 19)
Ferritin (median, IQR) - µg/L	49 (30 - 86)	50 (30 - 85)
eGFR (median, IQR) - ml/min/1.73m^2	52 (38 - 68)	50 (38 - 69)

Baseline treatment

Characteristic	FDI (N=569)	Usual care (N=568)
ACE inhibitor, ARB or sacubitril valsartan – no. (%)	486 (85%)	498 (88%)
Beta-blocker – no. (%)	500 (88%)	509 (90%)
Mineralocorticoid receptor antagonist – no. (%)	325 (57%)	307 (54%)
Loop diuretic – no. (%)	458 (81%)	468 (82%)
SGLT-2 inhibitor – no.	15 (2%)	14 (2%)
Device therapy – no. (%)		
- ICD	91 (16%)	72 (13%)
- cardiac resynchronisation therapy	125 (22%)	118 (21%)

Follow-up and dosing with IV FDI

- Fewer patients attended follow-up visits in person as the trial progressed,

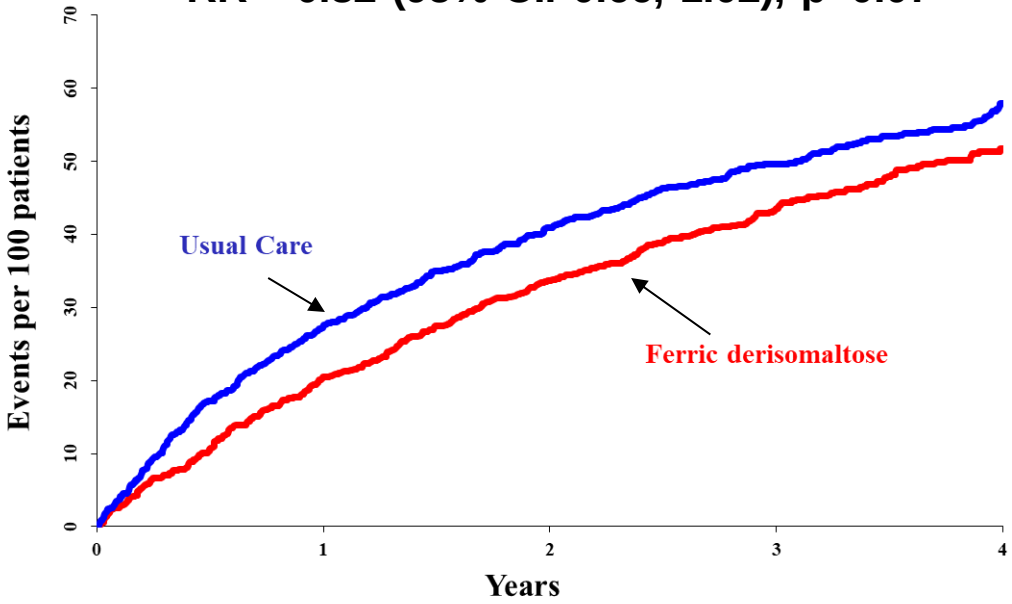
- 559 (98%) of those assigned to IV FDI received at least one dose
    - 217 received only one infusion;
    - 226 received two infusions;
    - 116 received three or more infusions

- Of those assigned to usual care, 95 (17%) received one or more doses of IV iron (despite this not being permitted in the protocol)

Primary outcome:

Recurrent HF hospitalizations and CV death

RR = 0.82 (95% CI: 0.66, 1.02), p=0.07



Number at risk					
Ferric derisomaltose	569	485	405	237	86
Usual Care	568	483	406	227	87

Outcomes

Primary outcome	FDI (n=569)	Usual care (n=568)	Est. treatment effect (RR or HR, 95% CI)	P value
Recurrent HF hosp. and CV death*	336 (22.4*)	411 (27.5*)	RR 0.82 (0.66 – 1.02)	0.070
Key secondary outcomes				
HF hospitalizations*	250 (16.7*)	313 (20.9*)	RR 0.80 (0.62 – 1.03)	0.085
CV death, n (%)	119 (21%)	138 (24%)	HR 0.86 (0.67 – 1.10)	0.23
First event: CV death, or hosp. for HF, MI or CVA	209 (37%)	246 (43%)	HR 0.83 (0.69 – 1.00)	0.045
All cause mortality	184 (32%)	193 (34%)	HR 0.95 (0.78 – 1.17)	0.64
MLHFQ 4 months	36.9	40.2	-3.33 (-6.67 to 0.00) ‡	0.050
MLHFQ 20 months	40.1	42.7	-2.57 (-6.72 to 1.59) ‡	0.23

* no. of events (rate per 100 patient-year) ‡ estimated mean difference

COVID sensitivity analysis

Primary outcome	Prespecified analysis FDI (n=527) Usual care (UC, n=536)	Post hoc analysis at 1 year FDI (n=527) Usual care (n=536)
Recurrent HF hosp. and CV death*	RR 0.76 (0.58 – 1.00) P = 0.047 *FDI 210 (22.3) *UC 280 (29.3)	RR 0.66 (0.48 – 0.91) P = 0.011 *FDI 97 (22.6) *UC 149 (34.2)
Key secondary outcomes		
Recurrent HF hospitalizations*	RR 0.76 (0.56 – 1.03) P = 0.077 *FDI 163 (17.3) *UC 218 (22.8)	RR 0.66 (0.46 – 0.94) P = 0.020 *FDI 75 (17.5) *UC 115 (26.4)
CV death, n (%)	HR 0.79 (0.57 – 1.09) P = 0.15 FDI 67 (12.7) UC 86 (16.0)	HR 0.67 (0.42 – 1.07) P = 0.091 FDI 29 (5.5) UC 44 (8.2)

* no. of events (rate per 100 patient-year)

COVID sensitivity analysis

Key secondary outcome	Prespecified analysis FDI (n=527) Usual care (n=536)	Post hoc analysis at 1 year FDI (n=527) Usual care (n=536)
All cause mortality, n (%)	HR 0.91 (0.70 – 1.19) P = 0.48 FDI 103 (19.5) UC 115 (21.5)	HR 0.72 (0.48 – 1.08) P = 0.12 FDI 39 (7.4) UC 55 (10.3)
First event: CV death, or hosp. for HF, MI or CVA, n (%)	HR 0.78 (0.62 – 0.98) P = 0.03 FDI 137 (26.0) UC 175 (32.6)	HR 0.78 (0.59 – 1.05) P = 0.097 FDI 82 (15.6) UC 105 (19.6)
All cause hospitalization, n (%)	HR 0.89 (0.75 – 1.05) P = 0.18 FDI 260 (49.3) UC 288 (53.7)	HR 0.86 (0.70 – 1.08) P = 0.17 FDI 166 (31.5) UC 191 (35.6)

Safety

Prespecified safety outcomes	FDI (n=559)	Usual Care (n=568)	Estimated treatment effect (RR or HR, 95% CI)	P value
Hosp. due to infection*	175 (11.7)	213 (14.2)	RR 0.82 (0.62 - 1.08)	0.16
Death due to infection (%)	34 (6%)	28 (5%)	HR 1.22 (0.74 - 2.02)	0.43
Serious adverse events (MedDRA) N (%)			**Difference (95% CI)**	
All	410 (73%)	435 (77%)	-3.2 (-8.3 to 1.8)	0.21
Cardiac	200 (36%)	243 (43%)	-7.0 (-12.7 to -1.3)	0.016

* no. of events (rate per 100 patient-year)

Conclusions

- In a broad range of patients with heart failure, a reduced LVEF and iron deficiency, administration of IV FDI was associated with a lower risk of recurrent heart failure hospitalizations and CV death, which approached statistical significance

- In the prespecified COVID-19 sensitivity analysis, the primary endpoint was nominally statistically significant

- There were fewer serious adverse cardiac events and no increase in serious adverse events related to infection with IV FDI

Implications for practice

The IRONMAN trial provides

- Additional evidence that correcting iron deficiency by administering high-dose IV iron improves well-being and prognosis for a broad range of patients with heart failure
- Reassurance about the long-term safety of IV ferric derisomaltose in patients with heart failure