Iron Deficiency Anemia in Heart Failure: Comparing Oral with Intravenous Iron

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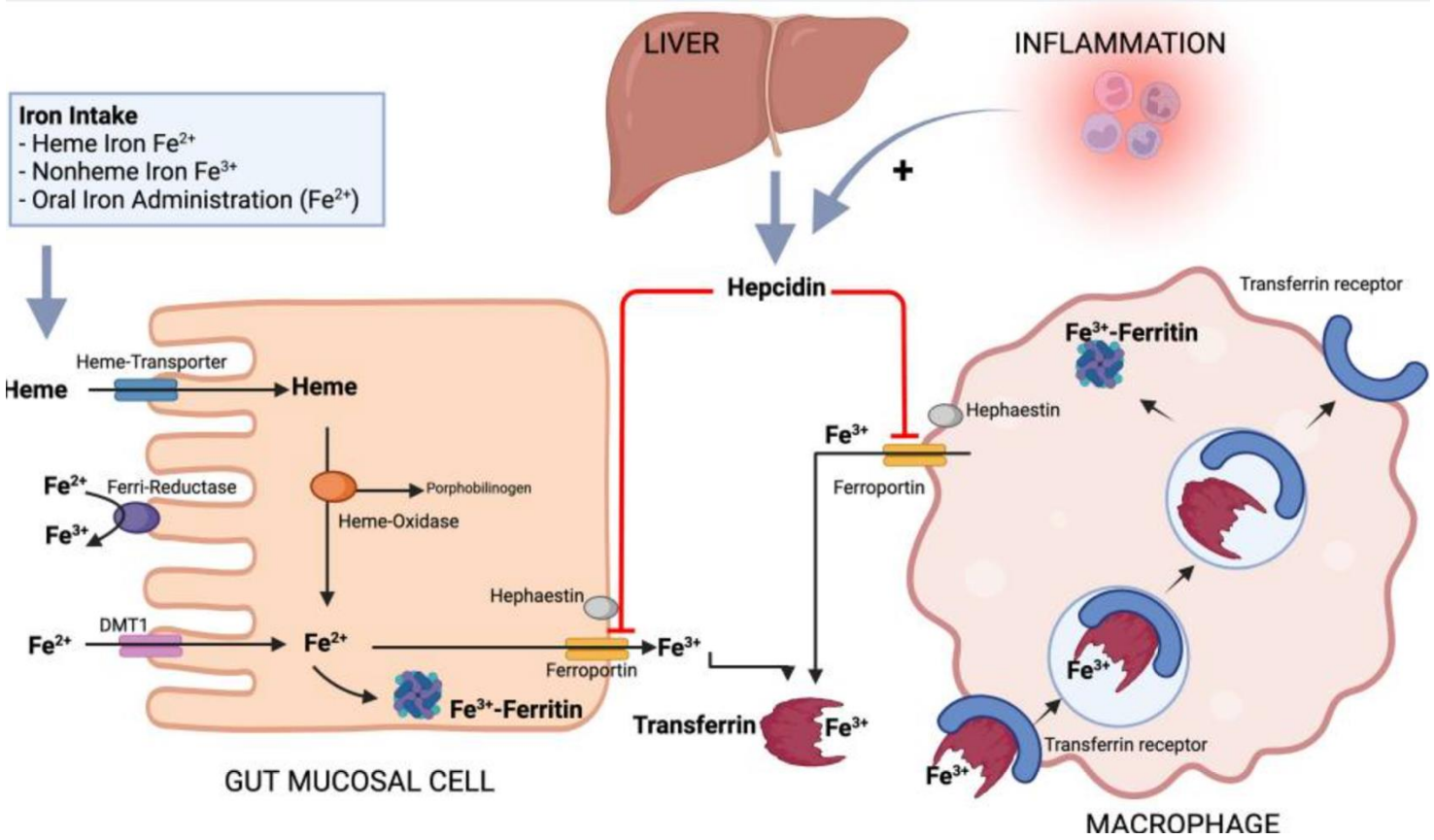
Background

- Iron deficiency anemia (IDA) affects ~50% of heart failure patients
- IDA exacerbates heart failure by impairing oxygen delivery
- Standard of care: intravenous Iron
- **Oral iron** = lower cost, ease of administration, broad accessibility both inpatient and outpatient

Iron Absorption



- Absorbed in duodenum
- Stored in gut (ferritin) or
- Exported to blood (via ferroportin)
- **Absorption and iron sequestration blocked by hepcidin**
- **Inflammation ↑ hepcidin**

Saverese, 2023

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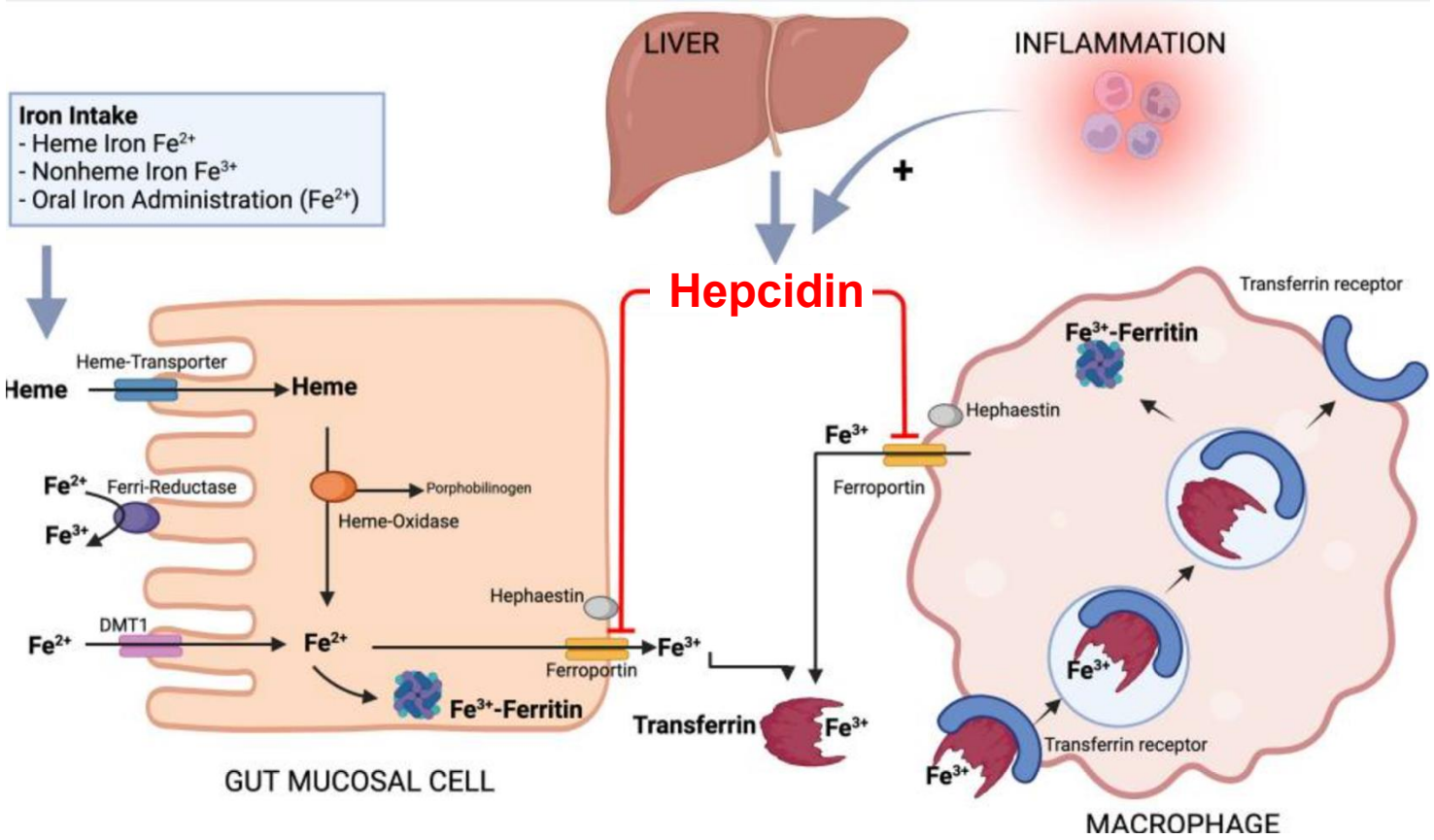

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IV Iron in Heart Failure (with reduced ejection fraction)

- **2009 FAIR-HF, 2015 CONFIRM-HF**: improved 6-minute walk test
- **2020 AFFIRM-HF**: reduction in recurrent hospitalizations
- **2022 IRONMAN**: reduction in serious adverse events (not statistically significant)
- **2023 HEART-FID**: reduced hospitalizations and improved walk test
- **2025 FAIR-HF2**: no effect on HF hospitalizations nor CV death, but improved walk test
- **2025 Meta-analysis**: reduced HF hospitalizations and CV mortality

2022 AHA Guidelines for Heart Failure Management

Management of Anemia or Iron Deficiency		
2a	B-R	1. In patients with HFrEF and iron deficiency with or without anemia, intravenous iron replacement is reasonable to improve functional status and QOL.[1–4]

The IRONOUT HF [trial] showed no improvement with oral iron... Therefore, oral iron is not adequate to treat iron deficiency anemia in patients with HF. Although these trials were underpowered, 2 meta-analyses have suggested intravenous iron is associated with a reduction in cardiovascular deaths and hospitalizations.

IRONOUT-HF Trial: details

- 203 patients with heart failure and reduced ejection fraction
- 150mg iron bid for 16 weeks vs placebo
- Endpoints: change in peak O2 uptake, 6-minute walk distance, quality of life, iron biomarkers
- No significant difference between iron group and placebo
- Elevated hepcidin levels at baseline associated with lower transferrin saturation and ferritin levels after 16 weeks
- Limitations: no comparison of PO vs IV, small sample size, no consideration of HF patients with normal EF

Our study design

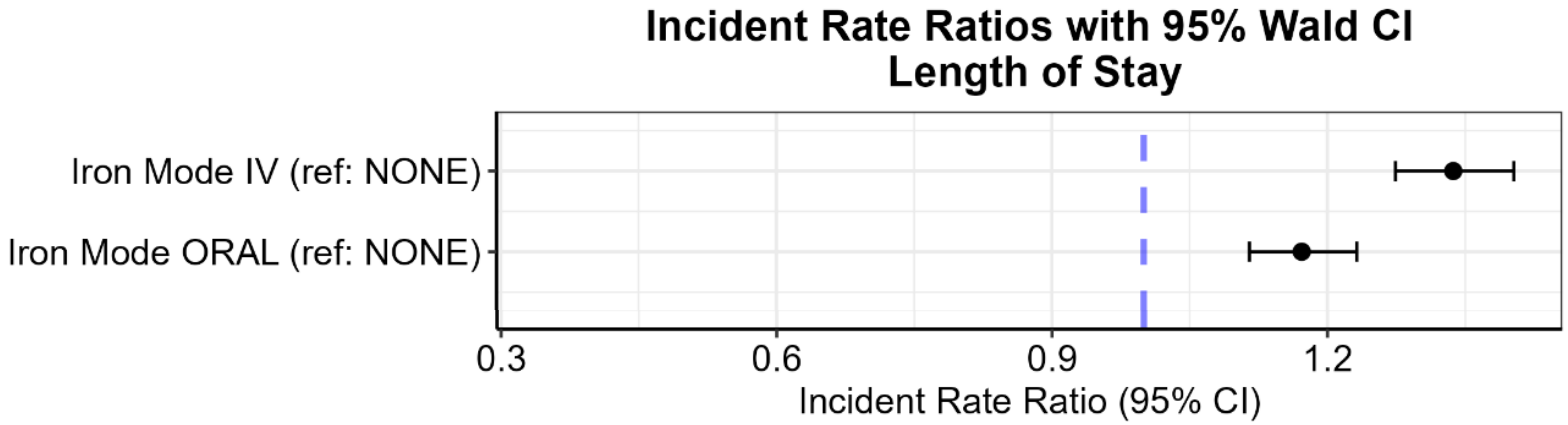
- **Primary objective**: compare clinical outcomes in acute HF exacerbation with IDA treated with IV vs. Oral vs. no iron
- **Outcomes**: LOS, in-hospital mortality, 30-day mortality, 30-day readmission, ICU admission and discharge disposition
- Retrospective observational cohort study
- HCA multi-division database (2016 – 2023), ICD-10 codes chart review
- Inclusion criteria: adults with diagnosis of HF (**HFpEF and HFrEF**) and IDA
- Exclusion criteria: > 90 y/o, court transfers, left AMA, missing BMI, < 100 mg of total iron received, comorbid conditions, inpatient dialysis or transfusions

Demographics

Patient Characteristic	Overall N = 5,030	IRON MODE		
		IV N = 1,290	ORAL N = 1,844	NONE N = 1,896
AGE				
Mean (SD)	69.71 (13.63)	69.60 (13.38)	70.03 (13.97)	69.49 (13.48)
Median (Q1, Q3)	72.0 (62.0, 80.0)	72.0 (62.0, 80.0)	73.0 (63.0, 80.0)	71.5 (62.0, 80.0)
SEX, n (%)				
F	2,756 (54.8%)	716 (55.5%)	1,041 (56.5%)	999 (52.7%)
M	2,274 (45.2%)	574 (44.5%)	803 (43.5%)	897 (47.3%)
RACE_BIN, n (%)				
NONWHITE	1,626 (32.3%)	399 (30.9%)	592 (32.1%)	635 (33.5%)
WHITE	3,404 (67.7%)	891 (69.1%)	1,252 (67.9%)	1,261 (66.5%)
RACE_ETH, n (%)				
AFAM	1,124 (22.3%)	283 (21.9%)	405 (22.0%)	436 (23.0%)
HISP	349 (6.9%)	73 (5.7%)	130 (7.0%)	146 (7.7%)
OTHER	224 (4.5%)	49 (3.8%)	92 (5.0%)	83 (4.4%)
WHITE	3,333 (66.3%)	885 (68.6%)	1,217 (66.0%)	1,231 (64.9%)
PAYER, n (%)				
COMMERCIAL	441 (8.8%)	107 (8.3%)	160 (8.7%)	174 (9.2%)
MEDICAID	267 (5.3%)	69 (5.3%)	94 (5.1%)	104 (5.5%)
MEDICARE	2,020 (40.2%)	499 (38.7%)	772 (41.9%)	749 (39.5%)
NONE/OTHER	2,302 (45.8%)	615 (47.7%)	818 (44.4%)	869 (45.8%)
BMI				
Mean (SD)	33.16 (10.72)	34.16 (11.14)	32.84 (10.59)	32.78 (10.51)
Median (Q1, Q3)	31.0 (26.0, 38.0)	32.0 (26.0, 40.0)	30.0 (26.0, 37.0)	31.0 (26.0, 38.0)
BMI_CAT, n (%)				
NORMAL_WEIGHT	956 (19.0%)	205 (15.9%)	374 (20.3%)	377 (19.9%)
OVERWEIGHT	1,224 (24.3%)	301 (23.3%)	463 (25.1%)	460 (24.3%)
OBESE	2,850 (56.7%)	784 (60.8%)	1,007 (54.6%)	1,059 (55.9%)
ELIX				
Mean (SD)	6.61 (1.88)	6.79 (1.91)	6.54 (1.83)	6.55 (1.90)
Median (Q1, Q3)	6.0 (5.0, 8.0)	7.0 (6.0, 8.0)	6.0 (5.0, 8.0)	6.0 (5.0, 8.0)
HF_CAT, n (%)				
HF_R_EF	1,582 (33.6%)	405 (33.1%)	386 (33.2%)	791 (33.9%)
HF_COMB_EF	689 (14.6%)	179 (14.6%)	182 (15.6%)	328 (14.1%)
HF_P_EF	2,246 (47.6%)	617 (50.5%)	557 (47.9%)	1,072 (46.0%)
HF_NULL_EF	198 (4.2%)	21 (1.7%)	38 (3.3%)	139 (6.0%)

- IV iron: 1,290
- PO iron: 1,844
- No iron: 1,896
- HF category
  - HFrEF 33%
  - HFmrEF 14%
  - HFpEF 47%

Results: Length of Stay (LOS)

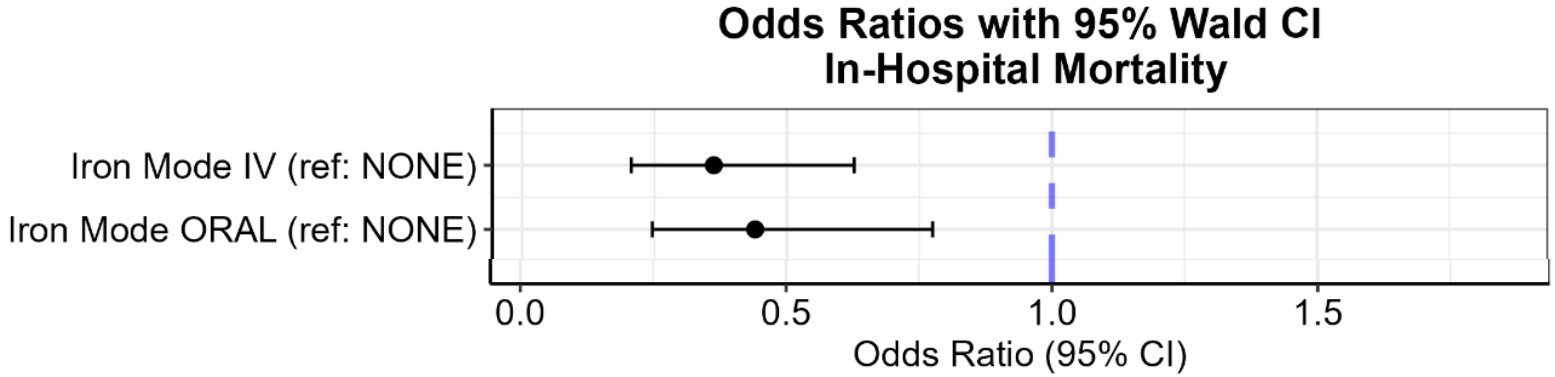


IRR	95% CI
1.337	[1.274, 1.403]
1.172	[1.115, 1.232]

- 7.2 days (IV) vs 6 days (oral) $p<0.0001$

- Compared to no iron:
  - 33.7% increase for IV iron, $p < 0.0001$
  - 17.2% increase for oral iron, $p < 0.0001$

Results: In-Hospital Mortality



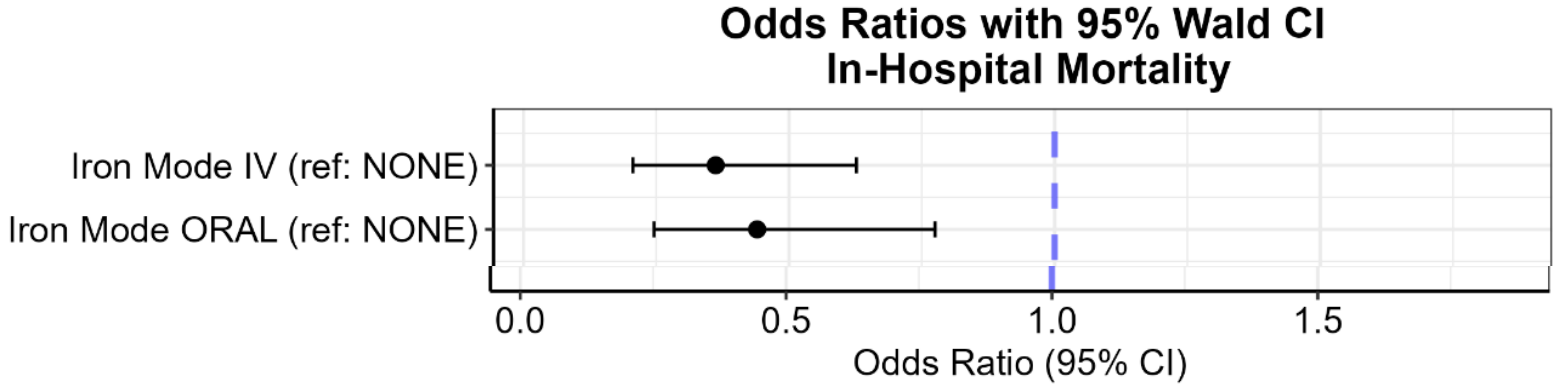
OR	95% CI
0.362	[0.206, 0.627]
0.440	[0.246, 0.775]

- 4.1% (IV) vs. 4% (oral) p=0.65
- Compared to no iron:

  63.8% reduction for IV iron, $p < 0.0001$

  56% reduction for oral iron, $p = 0.005$

Results: In-Hospital Mortality



OR	95% CI
0.362	[0.206, 0.627]
0.440	[0.246, 0.775]

- 4.1% (IV) vs. 4% (oral)
  p=0.65
- Compared to no iron: (Similar findings for 30-day mortality)

  63.8% reduction for IV iron,
  $p < 0.0001$

  56% reduction for oral iron,
  $p = 0.005$

Summary and discussion of our study

- Large, diverse cohort (n = 5,030) of real-world inpatient data
- Included patients across all HF subtypes, unlike prior trials limited to HFrEF
- IV iron associated with higher LOS
- No significant differences in readmission
- Oral and IV iron → **similar reductions in in-hospital & 30-day mortality**
- Our results suggest potential broader clinical utility for oral iron

Limitations and future directions

- Retrospective design, obese study population, short follow-up
- Limited to hospitalized patients
- Iron studies not available
- Specific iron formulation/elemental iron amounts could not be determined
- ICD-10 approach
- Underscores need for large-scale prospective studies with:
  - Iron indices (hepcidin, etc) and biomarkers
  - Patients with and without reduced EF
  - Dosing strategies

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- My co-authors

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Questions