AHA 2020: New Insights on Iron Deficiency and Heart Failure

Iron Deficiency

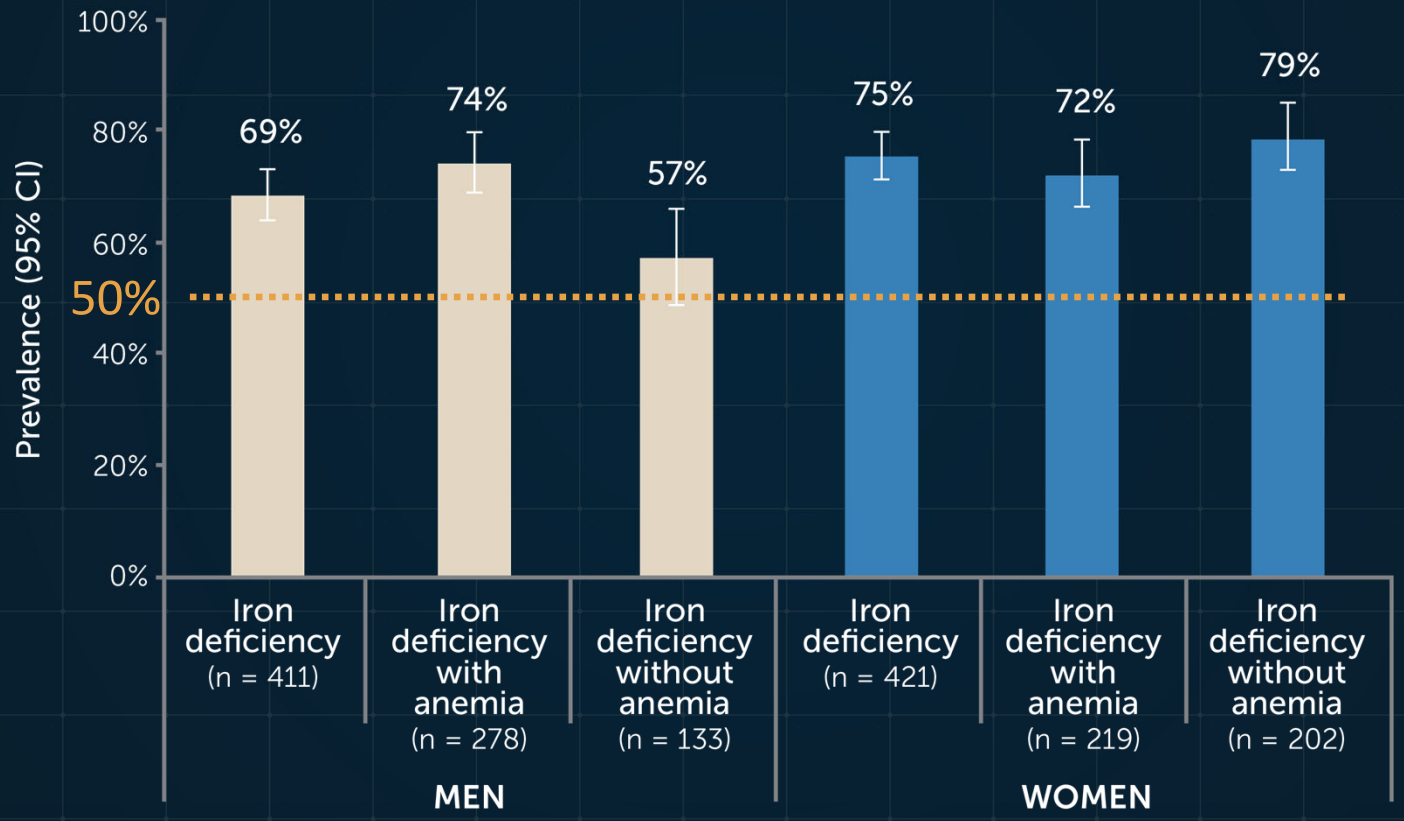
- Iron deficiency is related to:
  - Worse dyspnea class
  - Worse exercise capacity
  - Worse quality of life
  - Higher mortality rates
  - Higher cardiac transplantation rates

Treatment with Intravenous Iron

- Improves quality of life and cardiac function
- Increases exercise tolerance, maximal O_2 consumption
- Reduces hospitalization in HFrEF

HFrEF, heart failure with reduced ejection fraction; O_2, oxygen

Iron Deficiency: Prevalent in Acute Heart Failure



Cohen-Solal A, et al. *Eur J Heart Fail.* 2014;16(9):984-991.

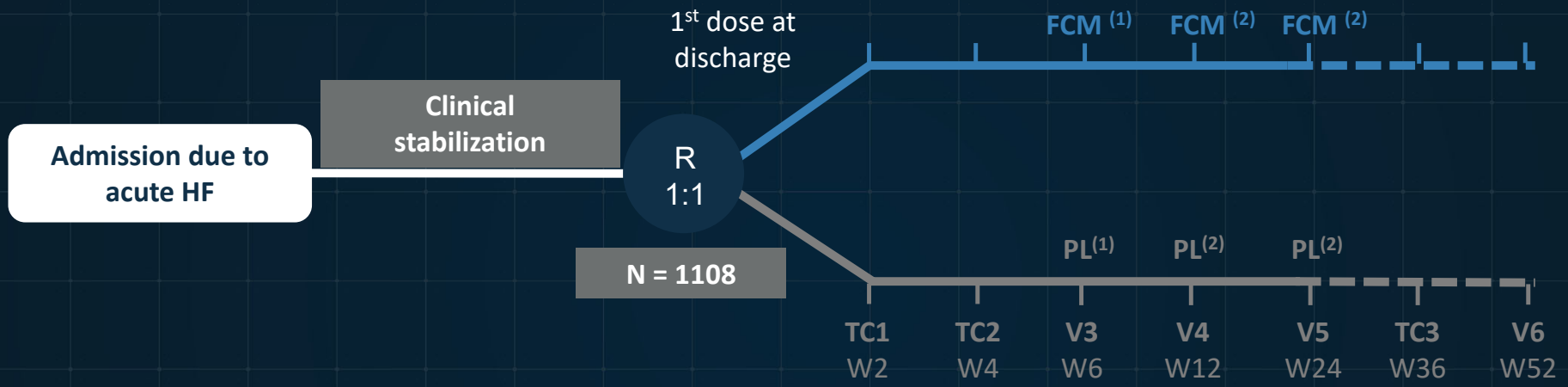
AFFIRM-AHF Study Design

- Inclusion criteria
  - Patients hospitalized with acute HF
  - Iron deficiency: serum ferritin <100 ng/mL or 100-299 ng/mL if TSAT <20%
  - LVEF <50% within 12 months
- Exclusion criteria
  - Dyspnea due to noncardiac causes
  - ACS, TIA, or stroke within 30 days
  - CABG, PTCA, cardiac device implant/resynchronization, or major surgery leading to significant blood loss within 30 days
  - Other medical-related conditions
  - Active infection
- Primary endpoint
  - Composite total HF hospitalizations and cardiovascular death up to 52 weeks after randomization

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; HF, heart failure; LVEF, left ventricular ejection fraction; PTCA, percutaneous transluminal coronary angioplasty; TSAT, transferrin saturation, TIA, transient ischemic attack.

Ponikowski P, et al. *Eur J Heart Fail*. 2019;21(12):1651-1658.

AFFIRM-AHF Study Design



[1] Administered dose of study treatment based on iron need as assessed at the baseline visit.

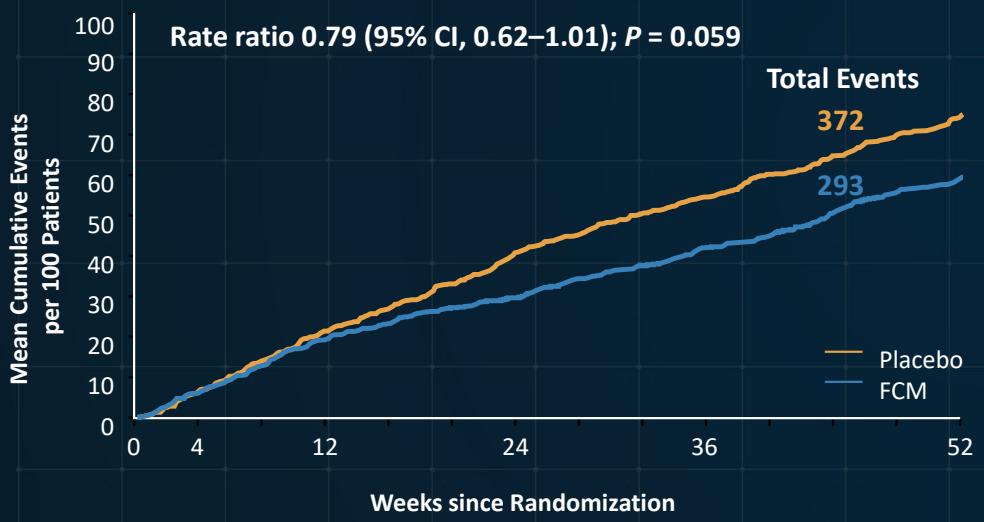
[2] Study treatment administered only if iron deficiency persisted.

FCM, ferric carboxymaltose; HF, heart failure; PL, placebo; R, randomization; TC, telephone contact; V, visit; W, week.

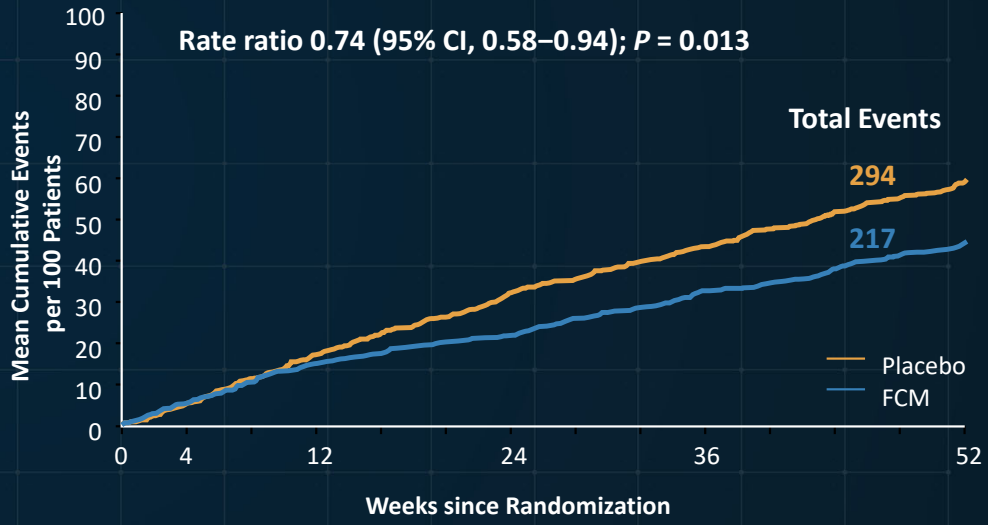
Ponikowski P, et al. *Eur J Heart Fail*. 2019;21(12):1651-1658.

AFFIRM-AHF: FCM in Acute HF

Primary Endpoint:
Total HF Hospitalizations and CV Death



Component Primary Endpoint:
Total HF Hospitalizations



mITT population. CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure.

Ponikowski P, et al. *Lancet*. Published online November 12, 2020. doi:10.1016/S0140-6736(20)32339-4

Pre-COVID-19 Sensitivity Analysis

- The COVID-19 sensitivity analyses were performed on the modified intention-to-treat (mITT) population
  - mITT population: all randomized patients in whom study treatment was started and for whom at least one post-randomization value was available
- Patient follow-up was censored in each country when the first COVID-19 patient was reported

AFFIRM-AHF: Recurrent Event Outcomes with COVID-19 Sensitivity Analysis

	Hazard Ratio (95% CI)	*P* value
Modified intention-to-treat analysis		
Total heart failure hospitalizations[1] or cardiovascular death	0.79 (0.62-1.01)	0.059
Total cardiovascular hospitalizations[1] or cardiovascular death	0.80 (0.64-1.00)	0.050
Total heart failure hospitalizations[1]	0.74 (0.58-0.94)	0.013
COVID-19 sensitivity analysis[2]		
Total heart failure hospitalizations[1] or cardiovascular death	0.75 (0.59-0.96)	0.024
Total cardiovascular hospitalizations[1] or cardiovascular death	0.77 (0.62-0.97)	0.024
Total heart failure hospitalizations[1]	0.70 (0.55-0.90)	0.005

[1]Included first and recurrent events; [2]Patients were censored in each country on the date when the first patient with COVID-19 was reported in the respective country. Ponikowski P, et al. *Lancet*. Published online November 12, 2020. doi:10.1016/S0140-6736(20)32339-4

“…intravenous iron in patients with iron deficiency stabilized after an episode of acute heart failure reduces the risk of subsequent heart failure hospitalizations”

Ongoing Trials in HF and ID

Study Name	IRONMAN	FAIR-HF2	HEART-FID	FAIR-HFpEF
# of Patients	1,300	1,200	3,014	200
Diagnosis	HFrEF EF <45%	HFrEF EF ≤45%	HFrEF EF ≤40%	HFpEF **EF ≥45%**
Blinding	**Open label**	Double blind	Double blind	Double blind
Study Arm	**Iron (III) isomaltoside**	FCM	FCM	FCM
Duration	120 weeks	Event driven + at least 12 mos f/u	Event driven + 12 mos last patient	52 weeks
Primary Endpoint	CV death or HF hospitalization	HF hospitalization + CV death	All-cause mortality + total HF hospitalization through 12 mos and Δ 6MWT after 6 mos	Δ 6MWT from baseline to Week 24
Anticipated Completion	February 2021	December 2021	June 2022	July 2021

6MWT, 6-minute walk test; CV, cardiovascular; EF, ejection fraction; FCM, ferric carboxymaltose; f/u, follow-up; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ID, iron deficiency.

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

Take-Home Messages

- Patients hospitalized with acute HF should be assessed for iron deficiency
- Treat iron deficiency to decrease HF hospitalization
- Iron deficiency is common in acute HF
- Easily detected before hospital discharge
- Treat with ferric carboxymaltose
- 1-2 infusions of ferric carboxymaltose improves outcomes in most patients

HF, heart failure.

Take-Home Messages (con't.)

- Screening for iron deficiency in patients hospitalized with acute HF is important for reducing adverse events
- Treatment of iron deficiency
  - Improves outcomes
  - Reduces the risk of recurrent hospitalization