ACC Middle East Conference 2018

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Saudi Heart Association

Comorbidities in Heart Failure: Iron Deficiency

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ACC Middle East
Conference 2018

Iron Deficiency in Heart Failure

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Le Meridian Jeddah
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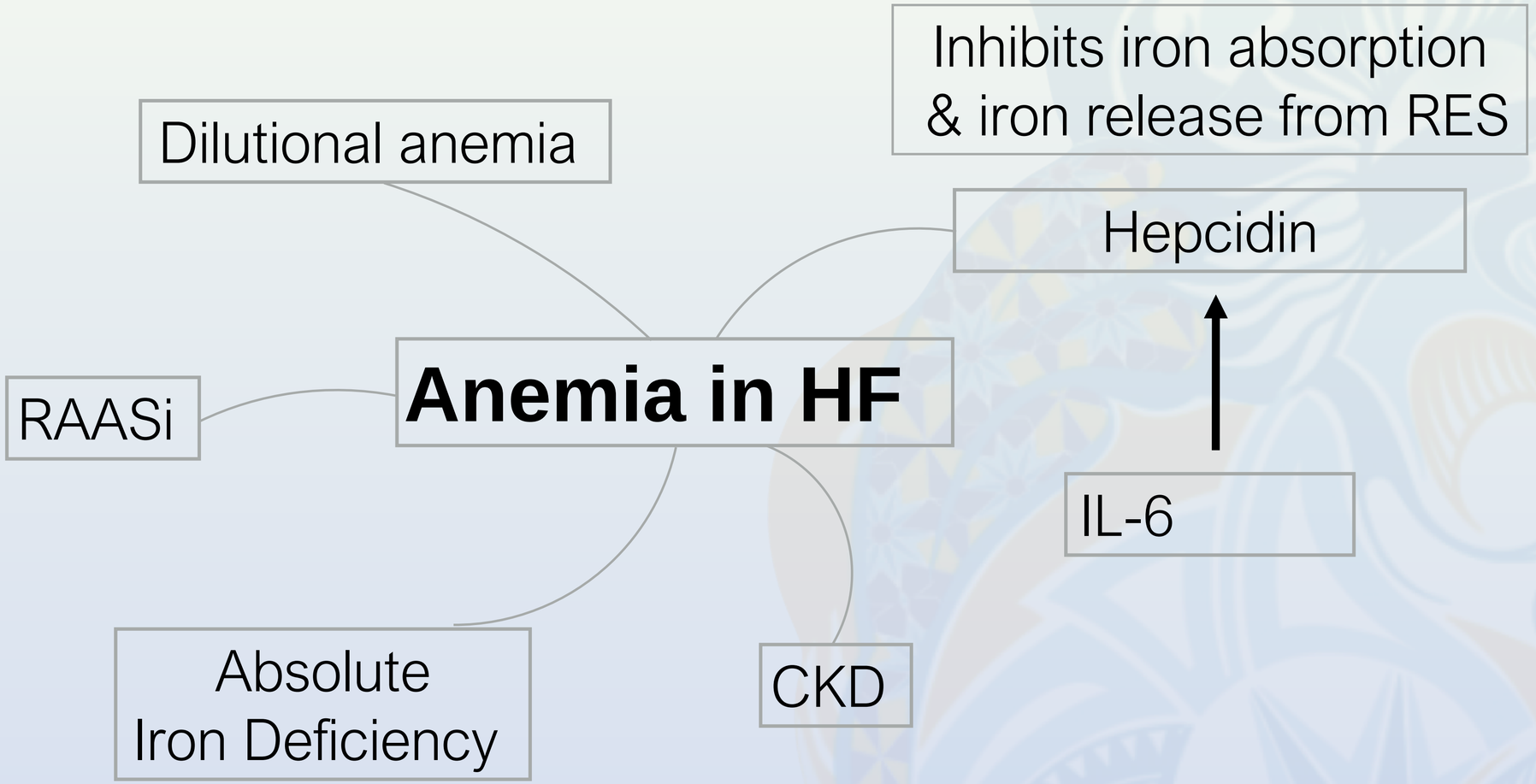
Outline

- Associations between HF, anemia, and iron deficiency
- Evidence for treating iron deficiency
- Guideline recommendations
- Ongoing clinical trials

Anemia in HF

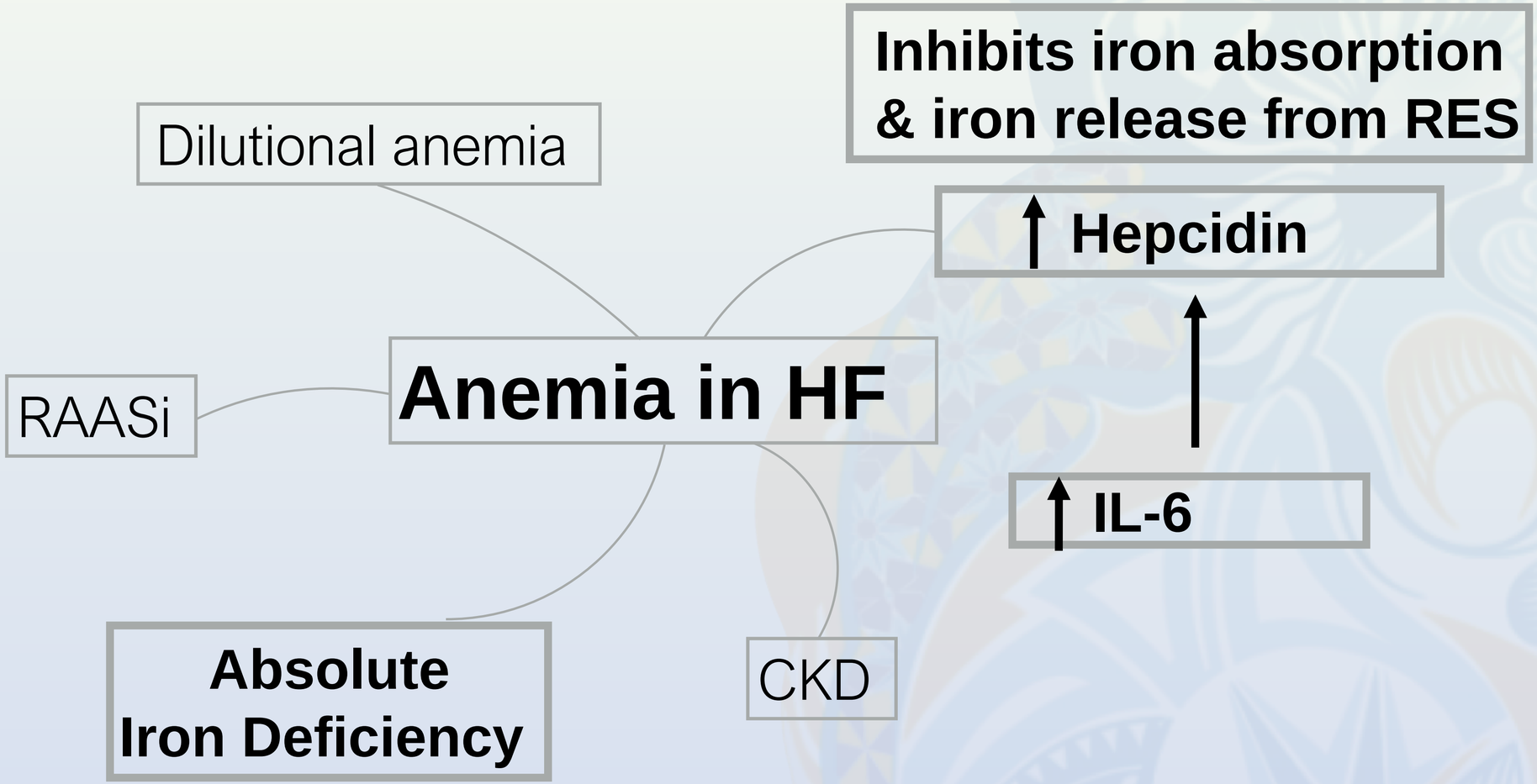
- **Anemia is common in HF (15-55% prevalence)**
- **Independent prognostic marker (up to two folds hazard)**
- **Correcting anemia with erythropoesis stimulating agents is not beneficial (RED-HF Trial)**

Mechanisms of Anemia in Heart Failure



D'Angelo, et al. Blood Res 2013;48:10-5

Mechanisms of Anemia in Heart Failure



D'Angelo, et al. Blood Res 2013;48:10-5

Study	Main HF population criteria	Include HFrEF	Include HFpEF	Applied ID definition	Anaemia definition (HGB, g/dL)	Prevalence of ID (%)		
						All patients	Anaemic patients	Non-anaemic patients
Nanas et al. 2006 [54]	Acute HF hospitalization	+	–	ID in bone marrow smear	<12.0 men <11.5 women	–	73	–
Cohen-Solal et al. 2014 [55]	Acute HF hospitalization	Not stated	Not stated	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	<13.0 men <12.0 women	69 in men 75 in women	–	57 in men 79 in women
Jankowska et al. 2014 [26]	Acute HF hospitalization	Not stated	Not stated	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	–	65	–	–
de Silva et al. 2006 [56]	Chronic HF	+ (≤45%)	–	Serum iron <34 µmol/L and/or serum ferritin <30 µg/L	<13.0 men <12.0 women	24	43	15
Jankowska et al. 2010 [24]	Chronic HF	+ (≤45%)	–	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	<13.0 men <12.0 women	37	57	32
Parikh et al. 2011 [45]	Self-reported congestive HF (survey)	Not stated	Not stated	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	<13.0 men <12.0 women	61	73	56
Okonko et al. 2011 [14]	Chronic HF	+ (≤45%)	–	Ferritin <100 µg/L or ferritin 100–300 µg/L and TSAT <20%	<13.0 men <12.0 women	65	78	65
Klip et al. 2013 [23]	Chronic HF	+	+	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	<13.0 men <12.0 women	50	61	46
Comín-Collet et al. 2013 [46]	Chronic HF	+	+	Ferritin <100 µg/L or ferritin <800 µg/L and TSAT <20%	–	63	–	–
Kasner et al. 2013 [47]	Chronic HF	Not stated	Not stated	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	–	58	–	–
Rangel et al. 2014 [48]	Chronic HF	+ (≤45%)	–	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	<13.0 men <12.0 women	36	43	34
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Vega et al. 2015 [57]	Chronic HF (retrospective study)	Not stated	Not stated	Ferritin <100 µg/L or ferritin 100–300 µg/L and TSAT <20%	–	51	–	–

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Prevalence
24 - 75% (~50%)

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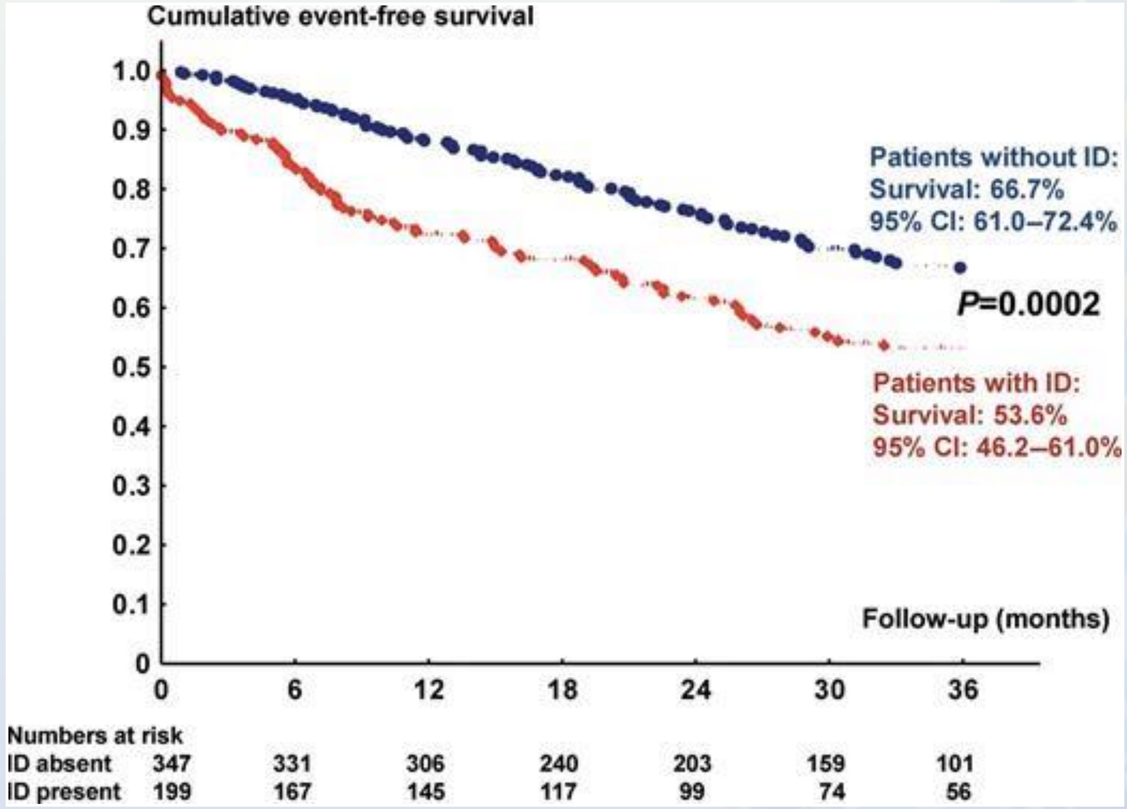
Anemic
43- 78% (~60%)

Non-anemic
15- 65% (~40%)

Impact of Iron Deficiency on HF Survival



Jankowska E, et al. Eur Heart J. 2013 Mar;34(11):816-29

Rationale for Considering Iron deficiency a Treatment Target in HF

- **Iron is essential in hemoglobin synthesis, mitochondrial biogenesis and respiratory chain, oxidative phosphorylation, and citric acid cycle**

Hoes M, et al. Eur J of Heart Fail. (2018) 20, 910–919

Rationale for Considering Iron deficiency a Treatment Target in HF

- **Iron is essential in hemoglobin synthesis, mitochondrial biogenesis and respiratory chain, oxidative phosphorylation, and citric acid cycle**

- **In animal models, iron deficiency can precipitate neurohormonal activation, LVH, LV dilatation, severe LV dysfunction, mitochondrial swelling**

Naito Y, et al. Am J Physiol Heart Circ Physiol 2009;296:H585–93

Rationale for Considering Iron deficiency a Treatment Target in HF

- **Iron is essential in hemoglobin synthesis, mitochondrial biogenesis and respiratory chain, oxidative phosphorylation, and citric acid cycle**

- **In animal models, iron deficiency can precipitate neurohormonal activation, LVH, LV dilatation, severe LV dysfunction, mitochondrial swelling**

- **Reduced expression of tranferrin receptor (Tfr) on cardiomyocites, low myocardial iron level (by 16-29%), impaired mitochondrial function, no correlation with anemia**

Maeda M, et al. J Am Coll Cardiol 2011;58:474–80)

Lab Characteristics of Iron Deficiency in HF

	Transferrin Sat	Ferritin	Hepcidin
Iron Deficiency	Low	Low	Low

D'Angelo, et al. Blood Res 2013;48:10-5

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Lab Characteristics of Iron Deficiency in HF

	Transferrin Sat	Ferritin	Hepcidin
Iron Deficiency	Low	Low	Low
Anemia of Chronic Disease	Low	Normal/high	High
Iron deficiency in Chronic Disease	Low Tsat < 20%	< 100 or 100-299 + Tsat < 20%	High

D'Angelo, et al. Blood Res 2013;48:10-5

IV Iron Replacement

	Elemental Iron Per Dose	Dose Calculation	Properties	Number of Clinical Trials/Pts
Iron Dextran	20 mg / kg over 4-6 hrs	max 100 mg daily Ganzoni Formula	Test dose required	1
Iron Sucrose	100 -200 mg	Ganzoni Forumla 200 mg weekly	No test dose	7 (n=136)
Ferric Carboxymaltose	50 mg/ml up to1000 mg	Weekly Ganzoni Formula or HB and weight based	No test dose Observe for 30 mins Hypersensitivity<1% Avoid extravasation	2 (n=763)

Total Iron Deficit (Ganzoni's formula) = Weight x (Target Hb in g/dL - Actual Hb in g/dL) x 2.4 + Iron Stores

Drozd M, et al. Am J Cardiovasc Drugs (2017) 17:183–201

Clinical Trials of Iron Therapy in HF

	FAIR-HF (NEJM 2009)	CONFIRM-HF (EHJ 2015)
N	459 (2:1)	304 (1:1)
Patients	NYHA II/III (**80%**), LVEF < 45, HB 9.5 - 13.5 (**11.9**), Ferritin <100 ng/ml or 100-299 **(52)** + Tsat <20% (**avg 17)**	NYHA II/III **(50%)**, LVEF < 45, BNP> 100 pg/ml (PBNP >400), Ferritin <100 ng/ml or 100-299 + Tsat <20%, HB <15 g/dl
Intervention	IV Ferric Carboxymaltose (correction + maintenance)	IV Ferric Carboxymaltose (correction + maintenance)
Outcome	Primary: Week 24 NYHA class, PGA Secondary: KCCQ, 6 MWT	Primary: 6MWT distance at 24 wks Sec: NYHA, PGA, KCCQ

Anker SD, et al. N Engl J Med 2009;361:2436-48

Ponikowski P, et al. Eur Heart J. 2015 Mar 14;36(11):657-68

Clinical Trials of Iron Therapy in HF

	FAIR-HF (NEJM 2009)		CONFIRM-HF (EHJ 2015)

Haemoglobin (g/dL)	Weight (kg)	Dose of ferric carboxymaltose depending on visit		
		Week 0 (mg)	Week 6	Week 12, 24, 36 (mg)
<10	<70	1000	500 mg	500[a]
<10	≥70	1000	1000 mg	500[a]
10–14	<70	1000	No dose	500[a]
10–14	≥70	1000	500 mg	500[a]
≥14, <15	All	500	No dose	500[a]

Outcome	Secondary: KCCQ, 6 MWT	Sec: NYHA, PGA, KCCQ

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FAIR-HF

Table 3. Levels of Iron-Metabolism Markers and Hemoglobin at Week 24 According to Study Treatment.*

Variable	Ferric Carboxymaltose (N=305)	Placebo (N=154)	P Value
All patients			
Ferritin (μg/liter)	312±13	74±8	<0.001
Transferrin saturation (%)†	29±1	19±1	<0.001
Hemoglobin (g/liter)	130±1	125±1	<0.001
Mean corpuscular volume (μm^3)	97±0	94±1	<0.001
Patients with anemia (hemoglobin ≤120 g/liter)			
Ferritin (μg/liter)	275±18	68±11	<0.001
Transferrin saturation (%)†	29±1	17±1	<0.001
Hemoglobin (g/liter)	127±1	118±2	<0.001
Mean corpuscular volume (μm^3)	98±1	93±1	<0.001
Patients without anemia (hemoglobin >120 g/liter)			
Ferritin (μg/liter)	349±19	80±11	<0.001
Transferrin saturation (%)†	30±1	22±1	<0.001
Hemoglobin (g/liter)	133±1	132±1	0.21
Mean corpuscular volume (μm^3)	96±1	95±1	0.91

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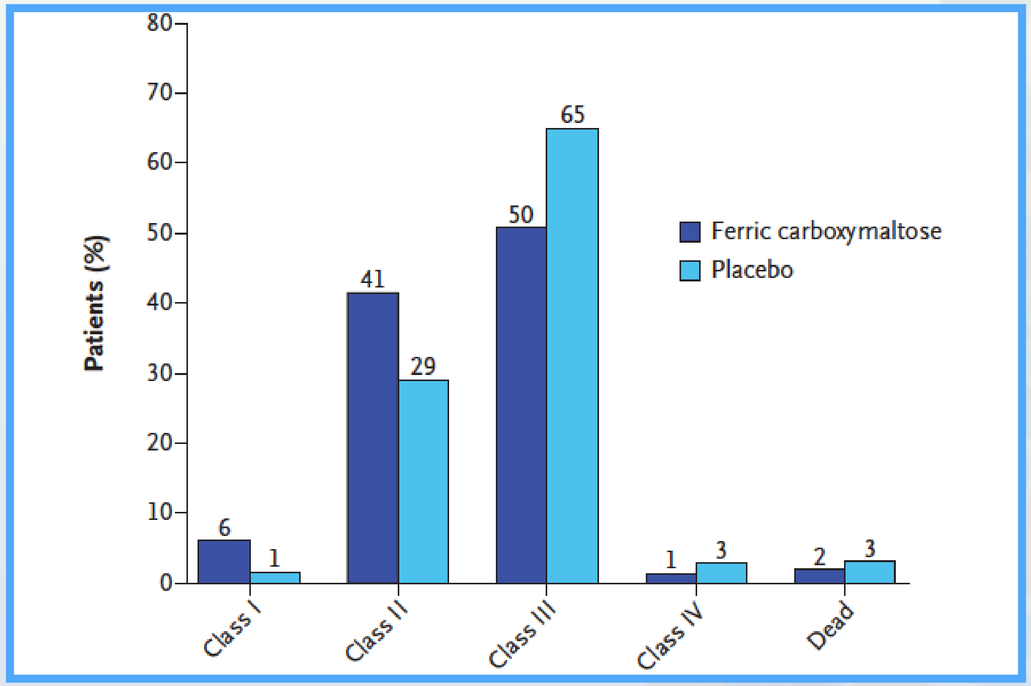
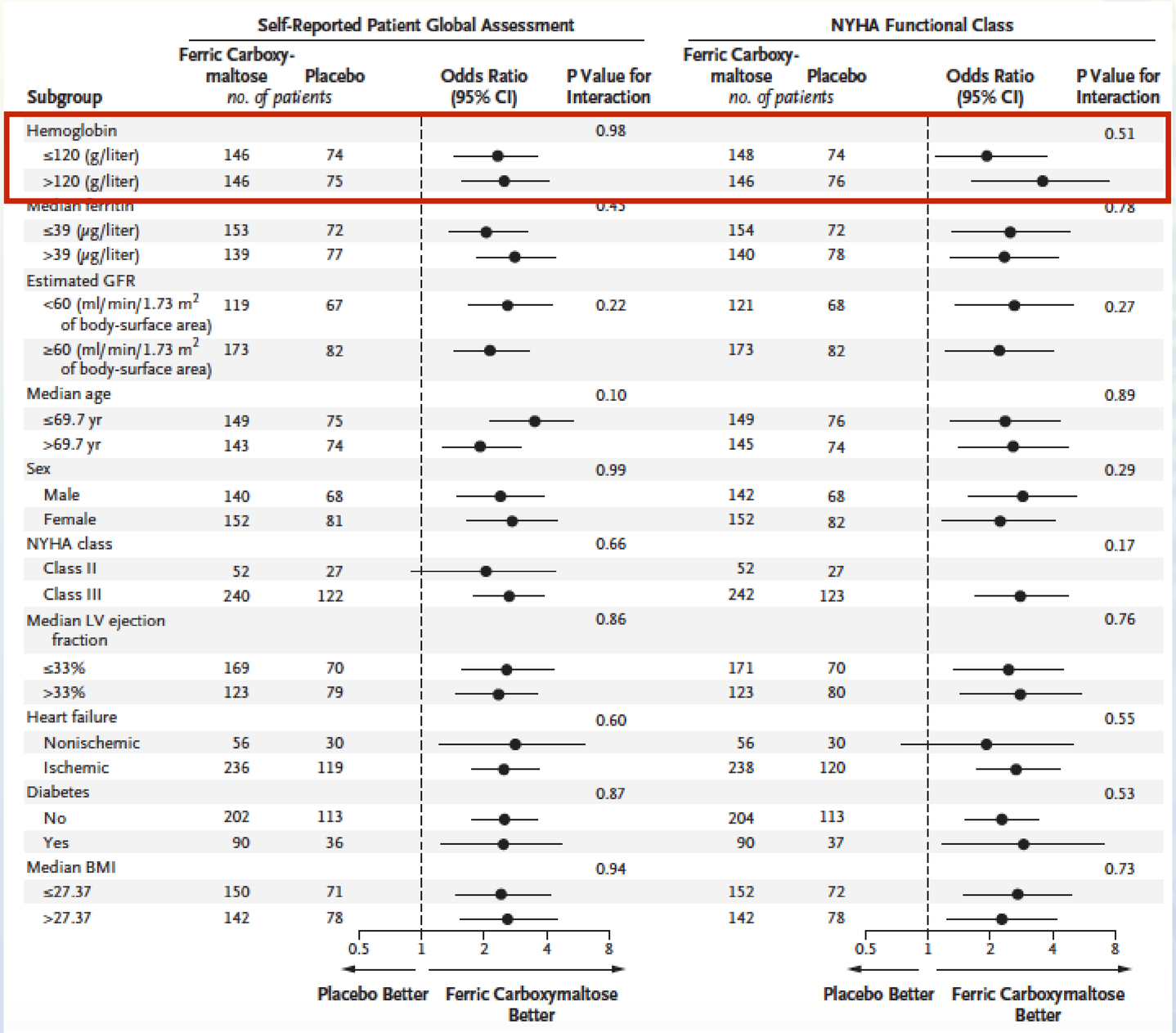
FAIR-HF



47% NYHA I or II vs. 30% in the placebo group
(OR of improvement by one class, 2.40; 95% CI, 1.55 to 3.71; P<0.001
Hospitalizations HR 0.53 95% CI, 0.25 to 1.09; P = 0.08

Anker SD, et al. N Engl J Med 2009;361:2436-48



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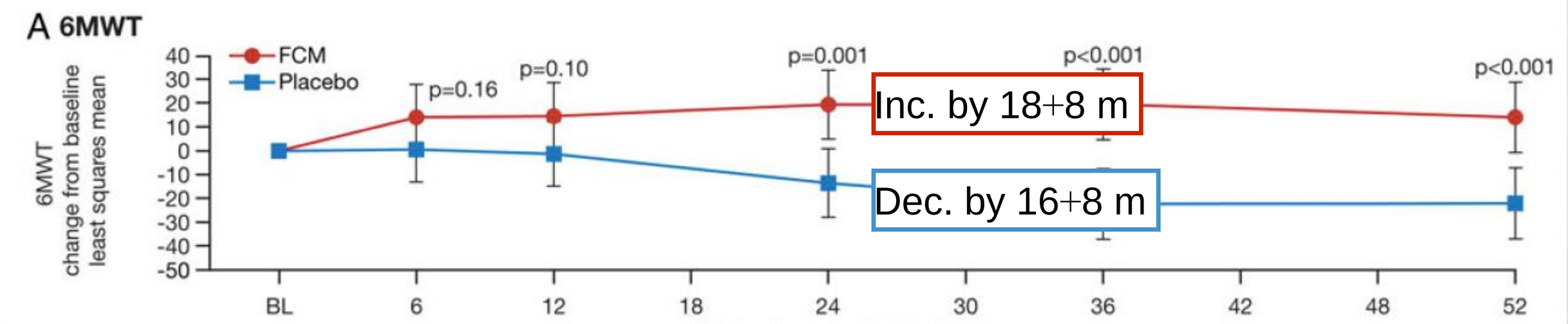
CONFIRM-HF



HR for hospitalizations 0.39 (0.19–0.82), p=0.009

Ponikowski P, et al. Eur Heart J. 2015 Mar 14;36(11):657-68

Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Chronic Heart Failure and Iron Deficiency

van Veldhuisen D, et al. Circulation. 2017;136:1374–1383

Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Chronic Heart Failure and Iron Deficiency

- **N = 174 (open label)**

  NYHA II (71%)
  NYHA III (29%)
  NT-pBNP > 400
  LVEF < 45% (33%)

- **Ferritin < 100 ng/ml**
  Ferritin 100-300 + Tsat < 20%

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- **Ferritin < 100 ng/ml**
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- **Primary analysis:**

  Decrease in pVO2 in control arm (–1.19±0.389 mL/min/kg)
  No change in pVO2 in iron treatment arm , p = 0.02

- **Per protocol: No difference in pVO2**

van Veldhuisen D, et al. Circulation. 2017;136:1374–1383

Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Chronic Heart Failure and Iron Deficiency

Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis

Anker S, et al. Eur J Heart Fail. 2017 Apr 24

Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis

- Four RCTs
- N = 844
- HFrEF
- Rx = IV FCM

Outcomes	Total events, *n* (incidence per 100 patient-years of follow-up)		RR (95% CI)	*P*-value
	FCM pool (*n* = 504)	Placebo pool (*n* = 335)		
CV hospitalisations and CV mortality	69 (23.0)	92 (40.9)	0.59 (0.40–0.88)	0.009
HF hospitalisations and CV mortality	39 (13.0)	60 (26.7)	0.53 (0.33–0.86)	0.011
CV hospitalisations and all-cause mortality	71 (23.7)	94 (41.8)	0.60 (0.41–0.88)	0.009

Anker S, et al. Eur J Heart Fail. 2017 Apr 24

Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Chronic Heart Failure and Iron Deficiency

Effects of ferric carboxymaltose on hospitalisations and mortality rates in ir
in

JAMA | Original Investigation

Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency
The IRONOUT HF Randomized Clinical Trial

Lewis G, et al. JAMA. 2017;317(19):1958-1966

JAMA | Original Investigation

Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency

The IRONOUT HF Randomized Clinical Trial

- **N = 225**
- **HFrEF**
  - **NYHA II (67%)**
  - **NYHA III (33)**
  - **LVEF < 40% (25%)**

Lewis G, et al. JAMA. 2017;317(19):1958-1966

JAMA | Original Investigation

Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency

The IRONOUT HF Randomized Clinical Trial

- N = 225
- HFrEF
  - NYHA II (67%)
  - NYHA III (33)
  - LVEF < 40% (25%)
- Oral iron polysaccharide 150 mg twice daily vs. placebo for 16 wks
- No statistically significant difference in pVO_2
- + 3.3% increase in Tsat (p = 0.003), +11ng/ml in ferritin (p=0.06) (vs 70%, 550% inc in FAIR-HF)

Lewis G, et al. JAMA. 2017;317(19):1958-1966

Guideline Recommendations for Managing Iron Deficiency in Heart Failure

COR, LOE	ESC 2016 HF Guideilnes
Class IIa, LOE A	Intravenous FCM **should be considered** in symptomatic patients (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life

Guideline Recommendations for Managing Iron Deficiency in Heart Failure

COR, LOE	Canadian Cardiovascular Guidelines 2017 Update
Strong Recommendation; Moderate-Quality Evidence	We **recommend** that I.V. iron therapy be considered for patients with HFrEF and ID, in view of improving exercise tolerance, quality of life, and reducing HF hospitalizations

Guideline Recommendations for Managing Iron Deficiency in Heart Failure

COR, LOE	ACC 2017 Update of ACC 2013 HF Guidelines
Class IIb, LOE B	In patients with NYHA class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation is <20%), intravenous iron replacement **might be** reasonable to improve functional status and QoL

Ongoing Clinical Trials

- **FAIR-HF2**
  N = 1200
  Primary end-point: Composite of HF hospitalization and CV mortality at 1 year
  Start & end dates: Feb 2017 - October 2020

- **IRONMAN**
  N = 1300
  NYHA II-IV, LVEF < 45%
  Primary endpoint: CV mortality or HF hospitalization
  Start & end dates: August 2016 - February 2021

- **HEART-FID**
  N = 3014
  Stable NYHA II-IV patients on OMT, LVEF < 35%
  Primary end-point: Time to all-cause death, HF hospitalization at 1 yr, change in 6 MWT at 6 months
  Start & end dates: March 15, 2017 - June 2022

- **Affirm-AHF**
  Hospitalized patients with AHF after initial stabilization, EF < 50%
  Primary end-point: Composite of HF hosp and CV mortality at 1 year
  Start & end dates: April 2017 - December 2019

- **FAIR-HFpEF**
  N = 200
  Primary endpoint: 6 MWD
  Start & end dates: August 2017 - July 2019

Source: www.ClinicalTrials. gov

Clinical Pathway

Chronic HFrEF
NYHA II-IV

Ferritin < 100 or
Ferritin100-299
+ Tsat < 20%

HB < 13 in men
HB < 12 in women

Evaluate for other
causes of anemia

HB 13 - 15 in men
HB 12 - 15 in women

HB > 15

Do not treat

IV FCM

Haemoglobin		Patient body weight		
g/dL	mmol/L	<35 kg	35 kg to <70 kg	≥70 kg
<10	<6.2	500 mg	1500 mg	2000 mg
10 to <14	6.2 to <8.7	500 mg	1000 mg	1500 mg
≥14 to 15	≥8.7 to 9.3	500 mg	500 mg	500 mg

Ferritin + Tsat
after 3 months
then x1 or x2 / year

Modified from McDonagh T, et al. Eur J Heart Fail. 2018 Oct 12. doi: 10.1002/ejhf.1305

Conclusions

- **Anemia is common in HF patients, and is a marker of poor prognosis**
- **Iron deficiency in HF is common regardless of anemia, and is a predictor of poor survival**
- **IV FCM, not oral iron, is associated with improved symptoms, quality of life, and possibly reduction in HF hospitalizations in HFrEF patients**
- **A consensus for a strong recommendation for IV iron therapy will have to await ongoing clinical trials**