Αναιμία και Καρδιακή Ανεπάρκεια

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Καρδιολόγος

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Α’ Καρδιολογική Κλινική Νοσοκομείο ΑΧΕΠΑ

PREVALENCE and DEFINITIONS

HF &

- **Iron Deficiency (50%)**
- **Anemia (37%)**

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

Anemia WHO

- ❑ Hb level <13 g/dl in men
- ❑ Hb level <12 g/dl in women.

Iron Deficiency:

- ❖ ferritin 15-100 ng/ml or
- ❖ ferritin 100-299 ng/ml with a transferrin saturation <20%

EHJ 2016
JACC 2018

Prevalence of Anemia in Heart Failure

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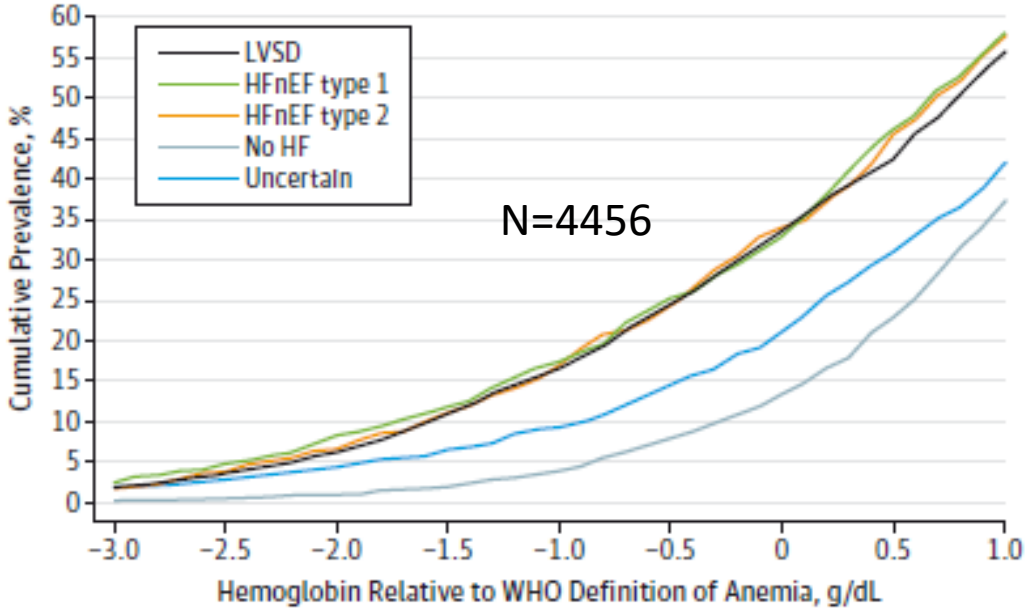
Figure 1. Prevalence of Anemia by Severity and Cardiac Phenotype

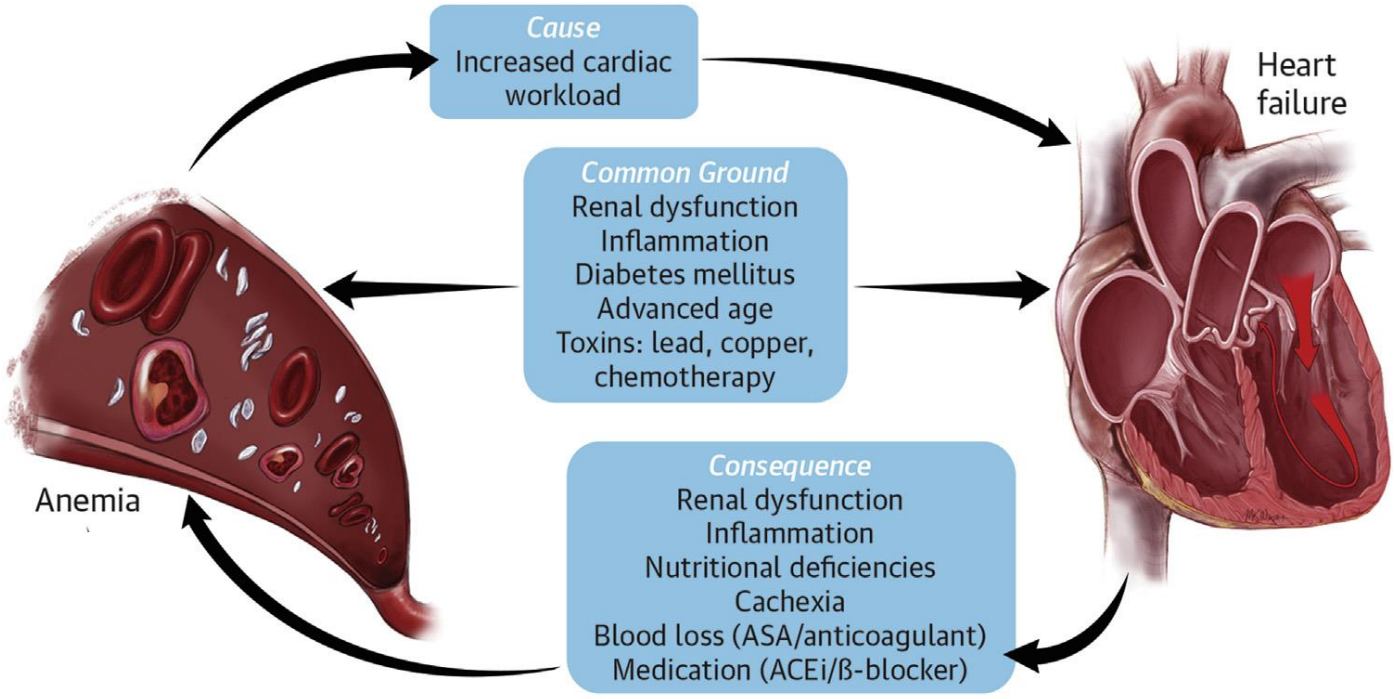


Overall, 1237 patients (27.8%) had anemia,

- Mild in 643 (14.4%),
- Moderate in 354 (7.9%),
- Marked in 240 (5.4%)

JAMA 2016

Anemia in Heart Failure: Common Ground, Cause, or Consequence?



The etiology of anemia in patients with HF is multifactorial:

- **iron deficiency**: patients with HF often (50%) have hematinic deficiencies, especially iron deficiency
- **CKD**: low production of erythropoietin occurs in the kidney → Inadequate levels of erythropoietin
- **chronic inflammation** in HF is an important cause of (functional) iron deficiency and of erythropoietin resistance
- intrinsic **bone marrow defects** further increases the susceptibility to anemia.
- activated renin-angiotensin-aldosterone system results in salt and fluid retention leading to **pseudo-anemia.**
- **Medication** induced: ACEis and Carvedilol

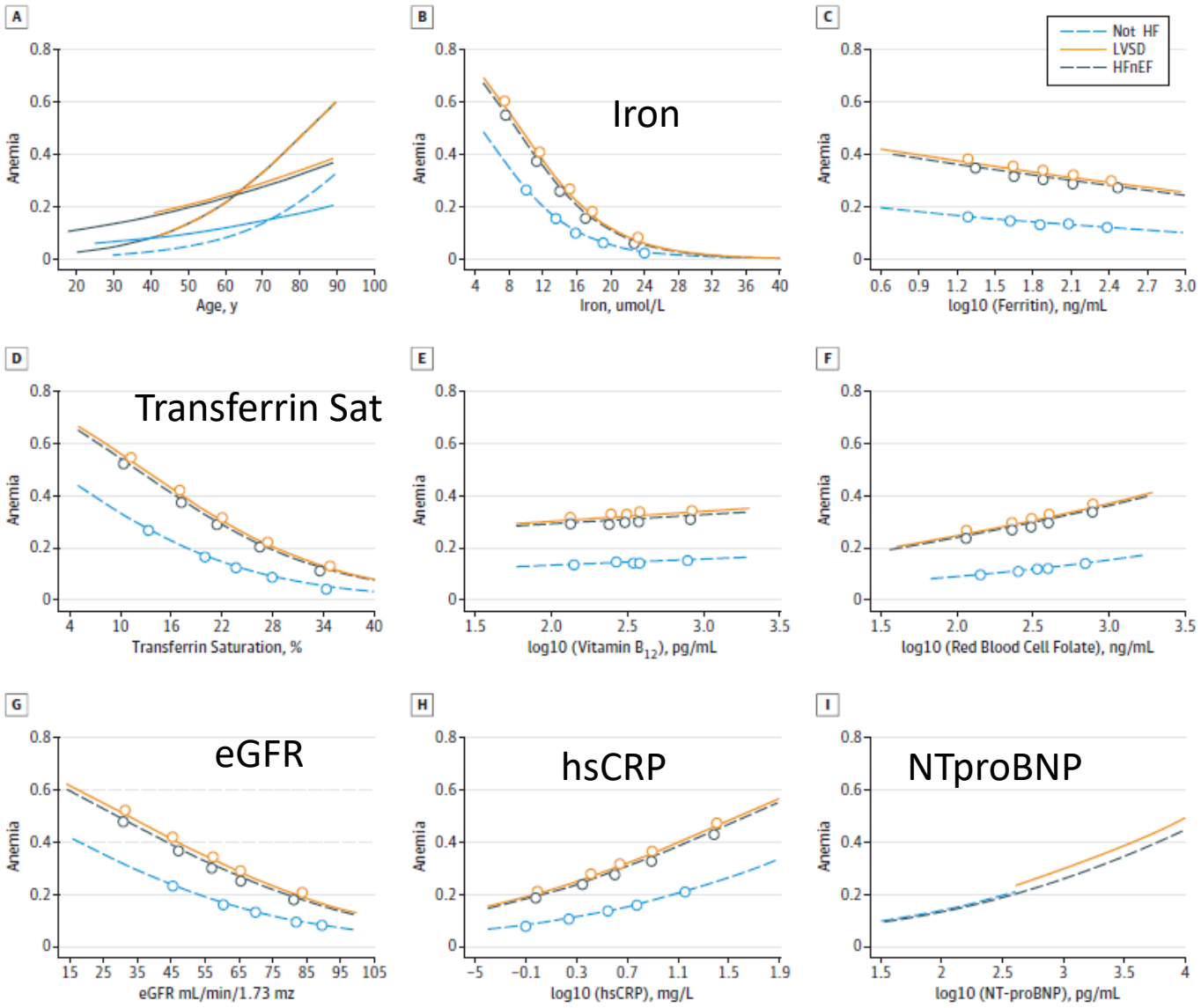
Table 1 Aetiology of iron deficiency in heart failure[4–6]

Cause	Mechanism	Comment
Reduced iron intake	Low protein diet Anorexia	Low protein diets may be recommended for concomitant renal disease
Impaired intestinal absorption	Mucosal oedema	Can alter intestinal epithelial permeability
	Decreased gastric emptying Modified intestinal motility	Contributing factors include overactivation of the sympathetic nervous system, concomitant drugs, co-morbid diabetic gastroparesis
	Reduced intestinal villus blood flow and/or mesenteric and portal blood flow	Restricts passive diffusion from intestinal tissue to blood
	Disrupted iron uptake process	Impaired expression of iron transporters observed in the duodenum
Gastrointestinal tract damage	Gastritis Ulcers	Iron loss through gastrointestinal bleeding
Uraemia	Loss of iron in protein	Proteinuria associated with concomitant chronic renal failure
Medication	Antiplatelet drugs, e.g. aspirin Anticoagulants	Can contribute to gastrointestinal blood loss
	Erythropoiesis-stimulating agents	Provoke iron deficiency through enhanced demand for erythropoiesis
Venepuncture	Frequent venepuncture for blood tests	
Chronic inflammation	Impaired release of iron from storage cells (functional iron deficiency)	Inflammatory cytokines stimulate increased hepcidin production and release, which inhibits transport of iron out of macrophages and hepatocytes by blocking export via ferroportin

Table. Clinical Characteristics and Hematologic Profile by Cardiac Phenotype[a]

Variable	No. of Patients (% Missing)	Overall (n = 4456)	LVSD (n = 1791)	HFnEF Type 1 (n = 707)	HFnEF Type 2 (n = 465)	Not HF (n = 841)	No LVSD but Missing NT-proBNP (n = 652)	*P* Value[b]
eGFR (4-variable), mL/min/1.73 m^2	4049 (91)	61.8 (47.8-76.4)	58 (45-72)	59 (46-71)	58 (44-73)	72 (59-84)	66 (50-81)	<.001
Hemoglobin, g/dL	4456 (0)	13.5 (12.3-14.6)	13.5 (12.2-14.5)	13.0 (11.9-14.2)	13.2 (12.1-14.4)	13.8 (12.9-14.8)	13.7 (12.5-14.7)	<.001
Anemia (WHO definition)	4456 (0)	1237 (28%)	597 (33%)	232 (33%)	158 (34%)	113 (13%)	137 (21%)	<.001
MCHC, pg/cell	4363 (2.1)	29.8 (28.5-31.0)	29.8 (28.3-31.1)	29.6 (28.0-31.0)	29.9 (28.5-31.0)	29.9 (28.8-31.0)	30.0 (28.7-31.1)	.01
MCV, μm^3	4432 (0.5)	91.5 (87.9-95.1)	91.6 (87.8-95.6)	91.7 (87.8-95.6)	91.7 (88.0-95.3)	91.0 (87.9-94.1)	91.8 (88.1-94.9)	.11
Iron, µg/dL	3545 (20.4)	84 (61-101)	78 (56-101)	73 (56-101)	78 (84-101)	89 (67-106)	84 (89-106)	<.001
Transferrin saturation, %	2751 (38.3)	23.0 (17.0-29.0)	22.0 (16.0-30.0)	19.0 (14.0-27.0)	23.0 (17.8-30.0)	24.0 (18.0-29.0)	23.0 (18.0-30.0)	<.001
Ferritin, ng/mL	3373 (24.3)	83 (45-150)	92 (50-169)	68 (39-130)	96 (50-167)	76 (41-139)	79 (42-135)	<.001

Figure 3. Association of Variables to the Probability of Anemia by Cardiac Phenotype Using Logistic Regression Models



The impact of iron deficiency and anaemia on exercise capacity in patients with chronic HF.

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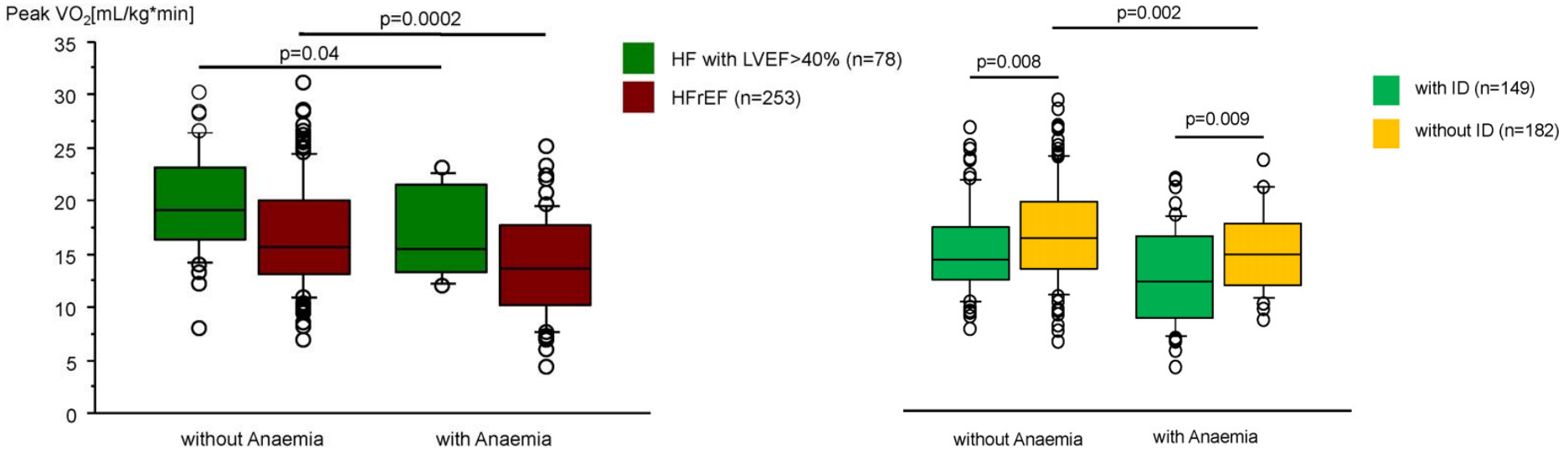

Anemia Consequences (DEATH) in HF

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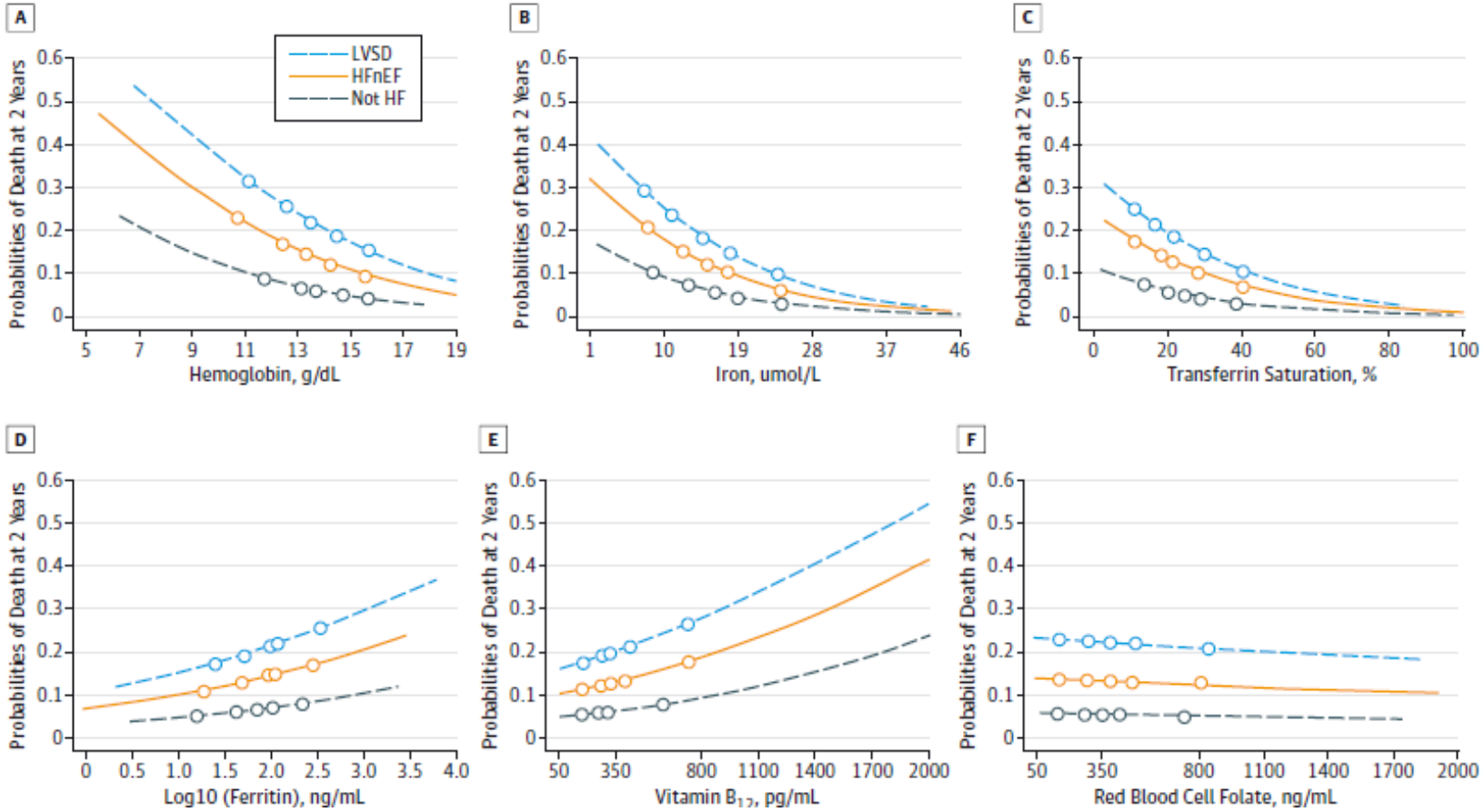
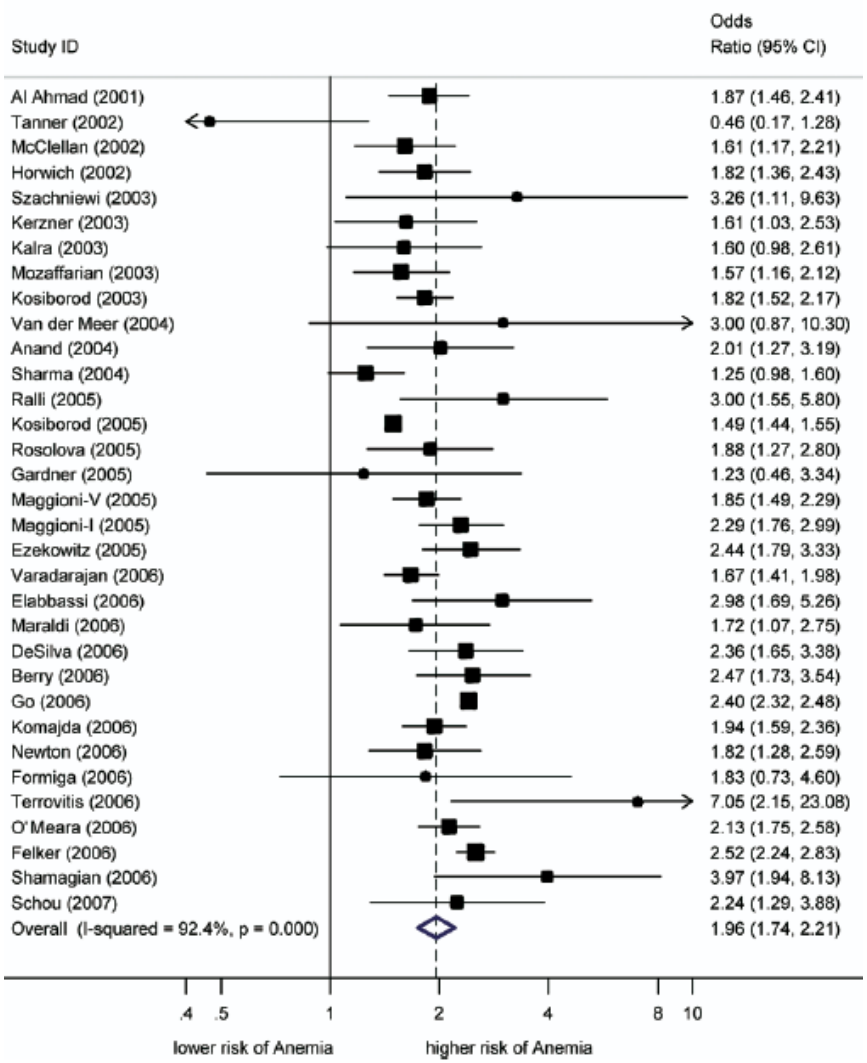
Figure 4. Association Between Hematinic Variables and All-Cause or Cardiovascular Mortality at 2 Years by Cardiac Phenotype



JAMA 2016

Anemia and Mortality in Heart Failure Patients

A Systematic Review and Meta-Analysis



Meta-analysis of

153,180 CHF patients

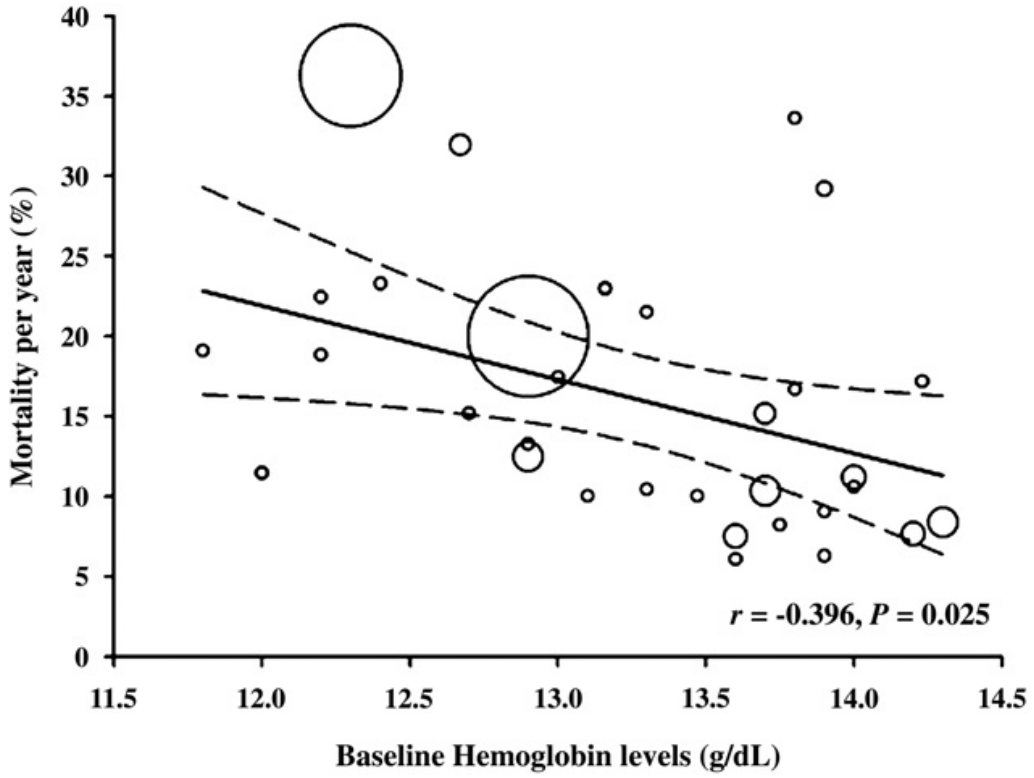
37.2% were anemic

Risk of All-Cause Mortality of

Anemic Vs Non-anemic

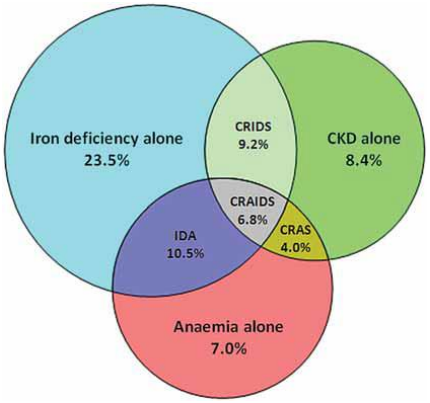
CHF Patients

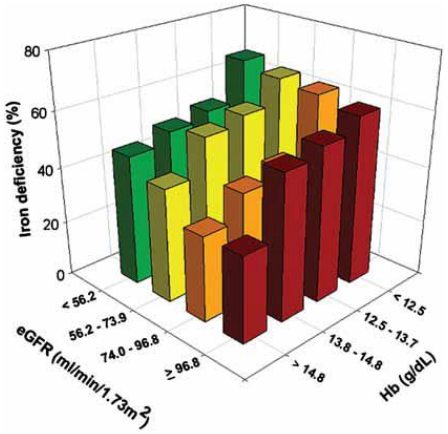
Relationship Between Baseline Hemoglobin and Annual Mortality



HF patients:
Systolic or Diastolic HF

cardiorenal–anaemia syndrome





Iron deficiency (ID), anaemia, and chronic kidney disease (CKD) are common co-morbidities in chronic heart failure

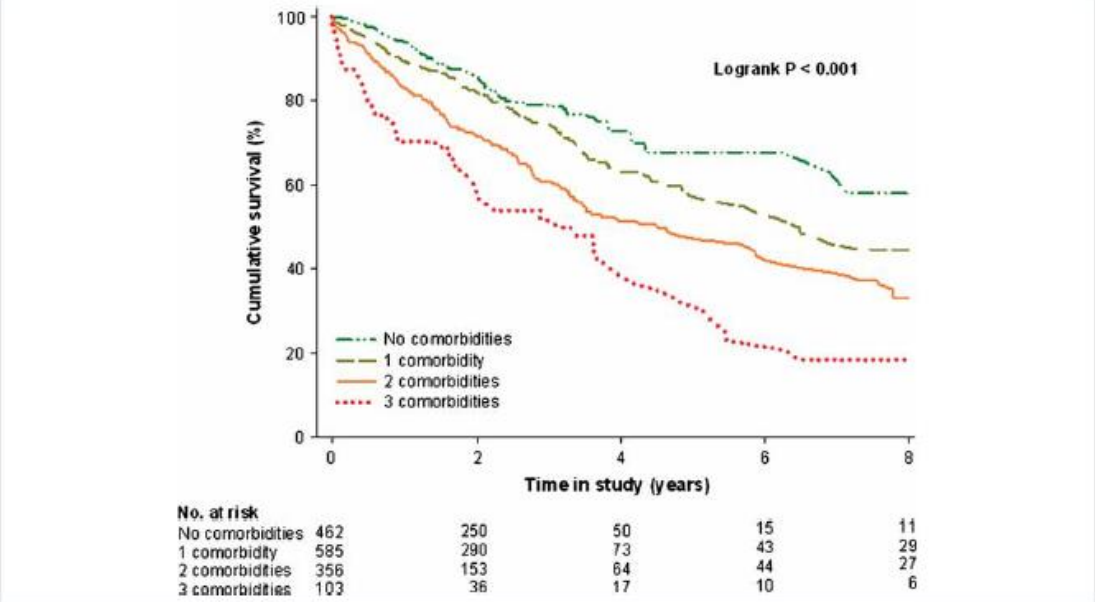


Figure 4 Survival analysis. Kaplan–Meier curves depicting event-free survival rates with an increasing number of co-morbidities in patients with chronic heart failure.

N= 1506 patients
with HF
systolic or diastolic

EJHF 2014

European Journal of Heart Failure (2011) **13**, 656–663
doi:10.1093/eurjhf/hfr044

Anaemia among patients with heart failure and preserved or reduced ejection fraction: results from the SENIORS study

N=2069 HF patients
HFrEF=1343
LVEF >35% = 726

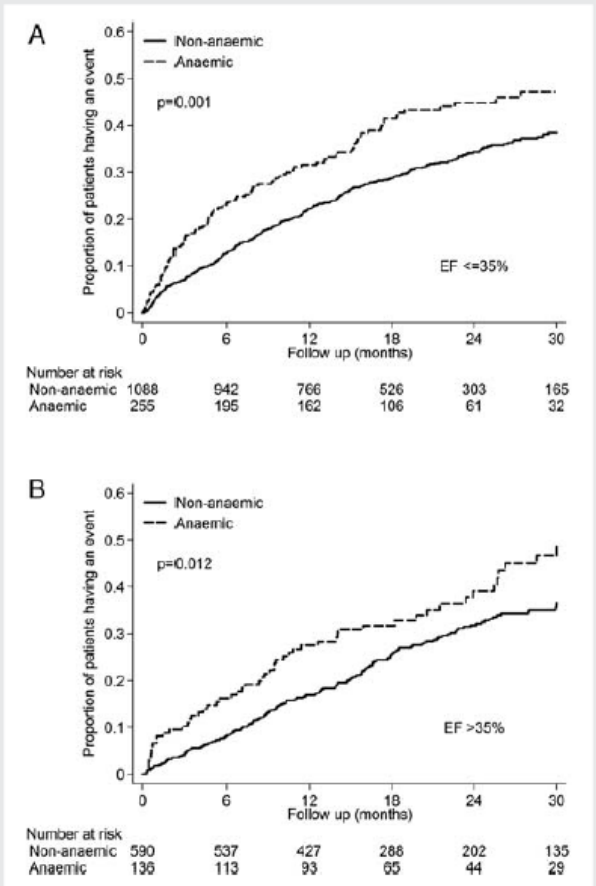
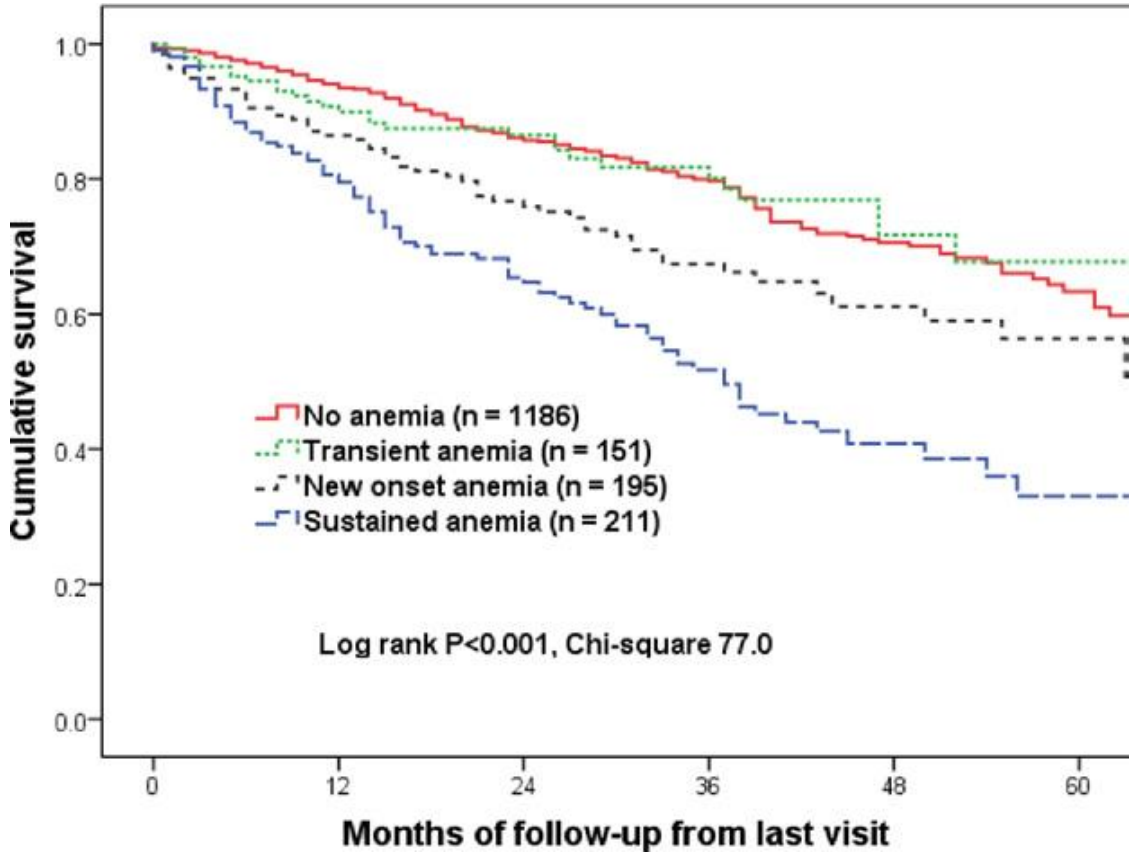


Figure 2 Cumulative proportion of patients who experienced the combined primary endpoint of all-cause mortality or hospitalization for cardiovascular reasons, according to ejection fraction. (*A*) Patients with reduced left ventricular ejection fraction ≤35%, (*B*) those with normal or mildly reduced ejection fraction >35%.

EJHF 2011

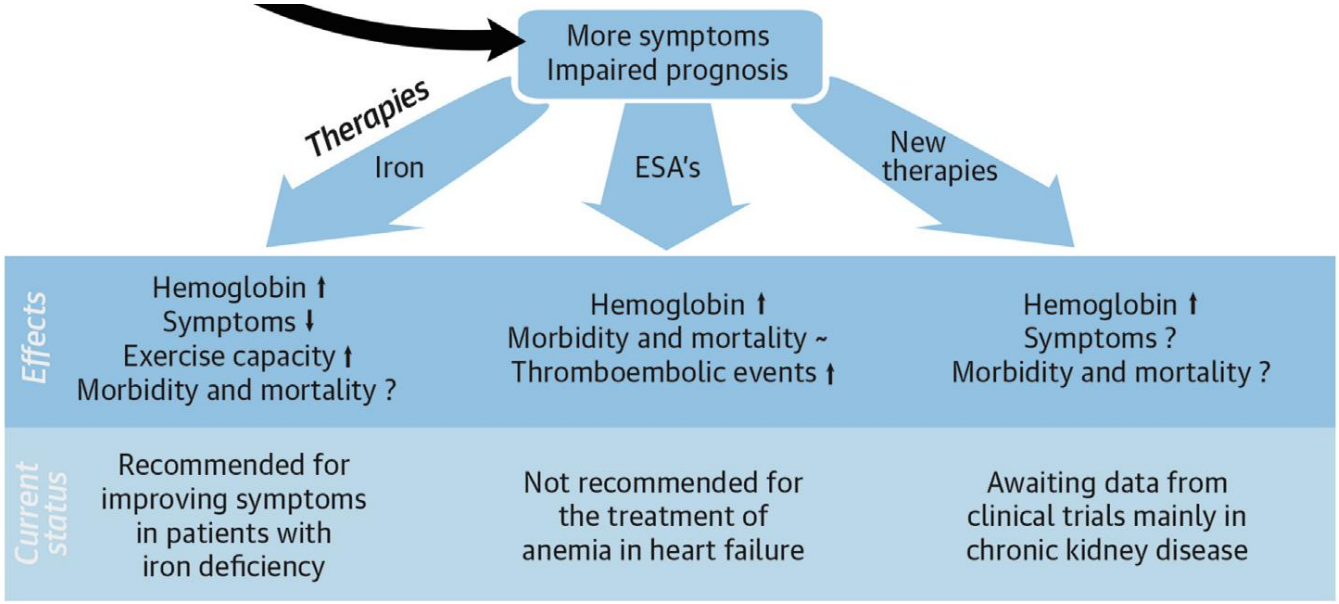
Norwegian Heart Failure Registry

1,743 HF Outpatients



Transient anemia in 40%.

Anemia Treatment in HF



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CLINICAL RESEARCH — Clinical Trial

Effect of Intravenous Iron Sucrose on Exercise Tolerance in Anemic and Nonanemic Patients With Symptomatic Chronic Heart Failure and Iron Deficiency

FERRIC-HF: A Randomized, Controlled, Observer-Blinded Trial

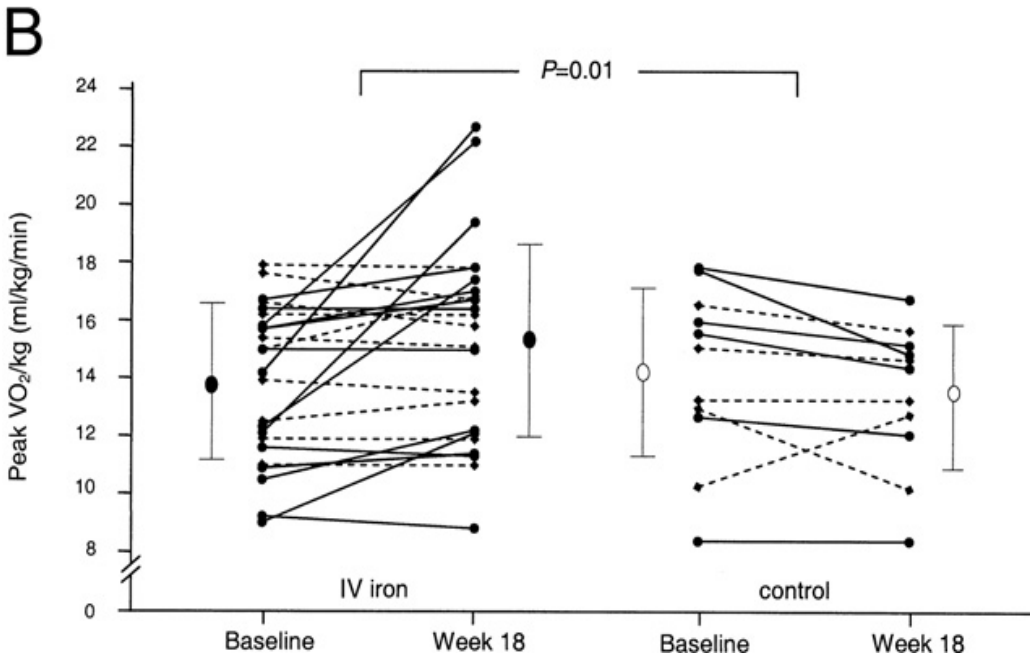
Patients

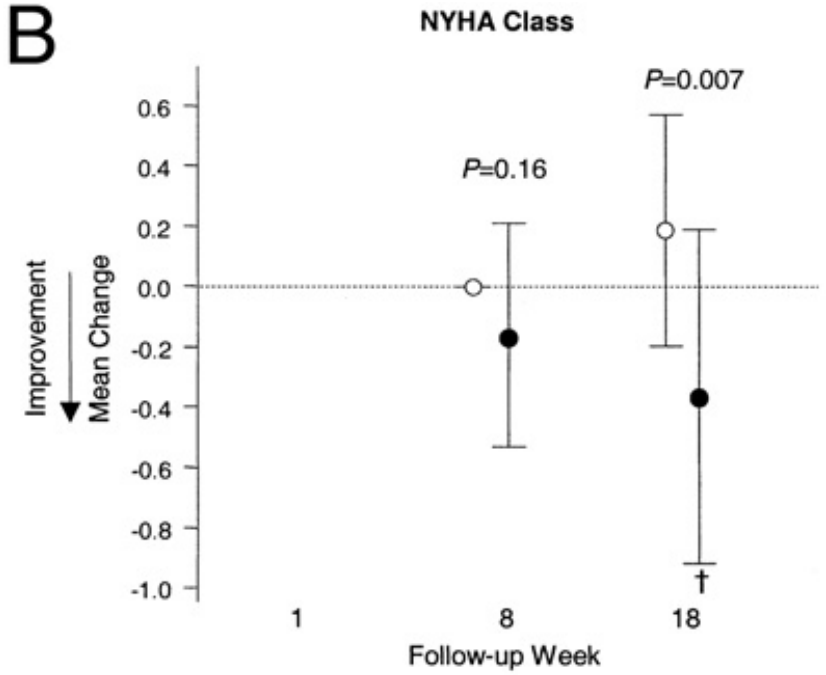
- NYHA class II or III
- Hb <12.5 g/dl (anemic group) or 12.5 - 14.5 g/dl (nonanemic group);
- Ferritin <100 g/l or 100 g/l - 300 g/l with a transferrin saturation <20%;
- LVEF <45%

Treatment:

- Iron sucrose (Venofer) IV infusion in 5-ml ampules (20 mg iron/ml).
- The treatment group received iron weekly (therapeutic phase) unless ferritin was 500 ng/ml
- then at weeks 4, 8, 12 and 16 (maintenance phase).
- Total dose was estimated : body weight (kg) x2.4 x(15- Hb [g/dl]) +500 mg (for stores) .
- Each dose was administered as 200-mg aliquots in 50 ml normal saline infused over 30 min.
- A test infusion (10 ml over 10 min) was performed before the first treatment.
- Patients were observed for drug reactions for up to 1 h after all visits.

FERRIC-HF: A Randomized, Controlled, Observer-Blinded Trial



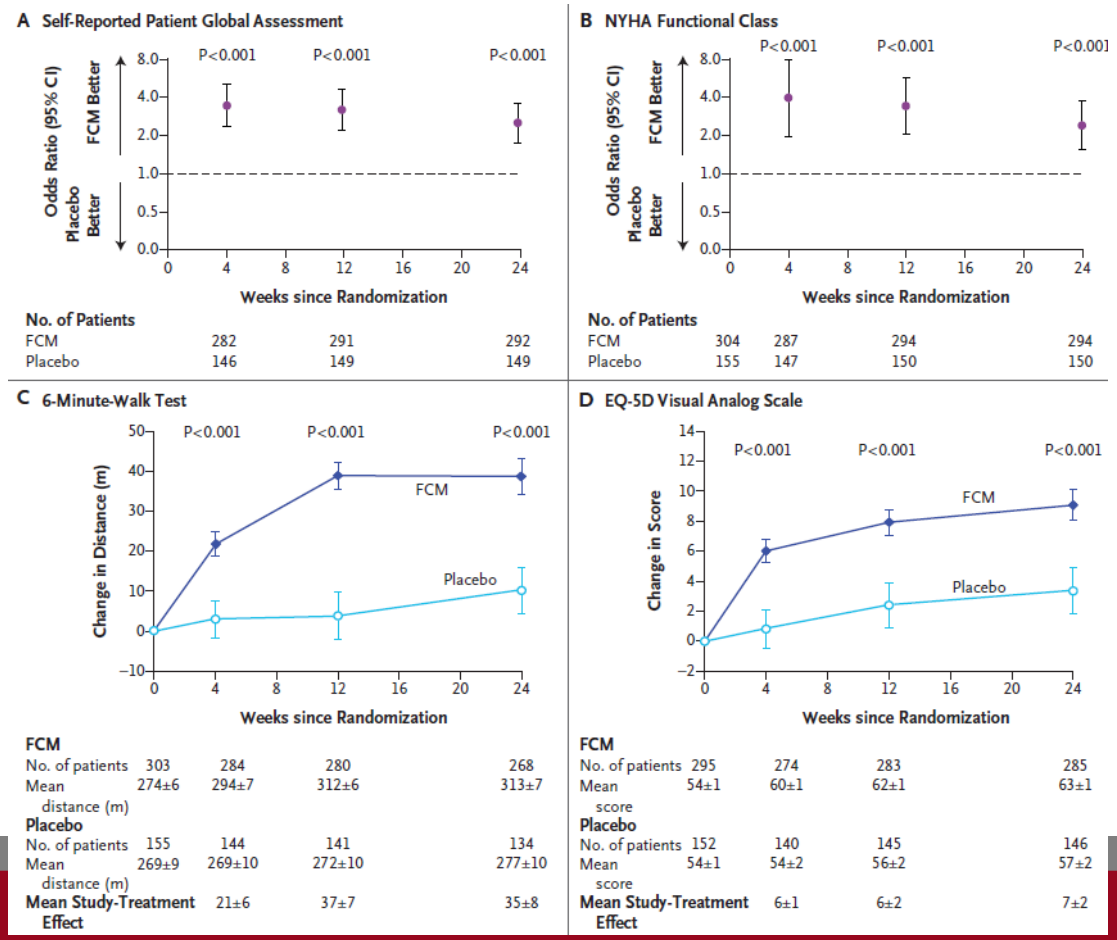


JACC 2008

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

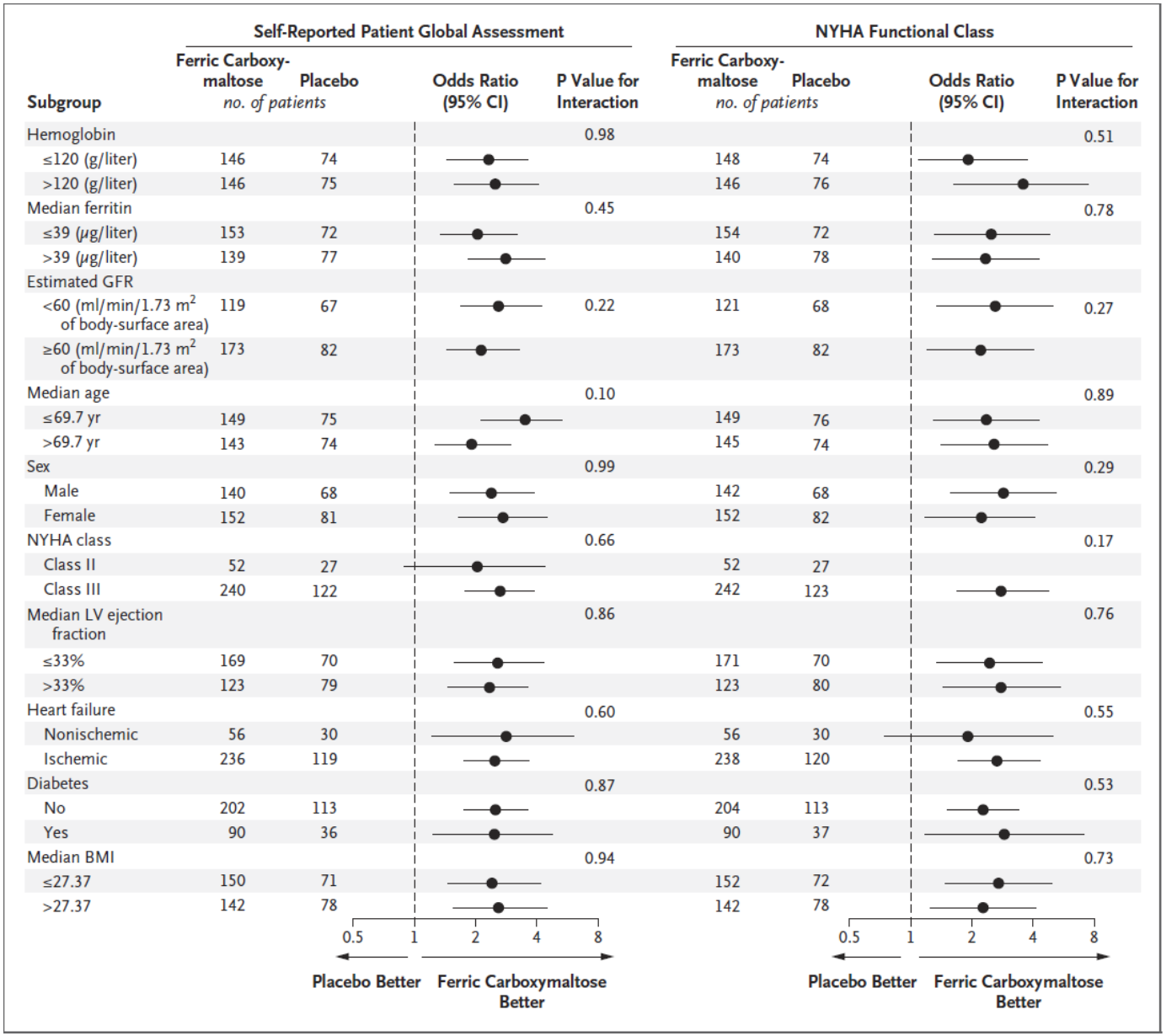


FAIR HF

Randomised 2:1

304 vs 155 placebo

NEJM 2009



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NEJM 2009

24 weeks later

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

24 weeks later

Table 2. Safety End Points and Serious and Nonserious Adverse Events, According to Study Treatment Received.*

End Point or Event	Ferric Carboxymaltose (N=305)		Placebo (N=154)		P Value
	No. of End Points or Serious Adverse/ Any Adverse Events	No. of Patients with End Point or Event (incidence/ 100 patient-yr at risk)	No. of End Points or Serious Adverse/ Any Adverse Events	No. of Patients with End Point or Event (incidence/ 100 patient-yr at risk)	
Safety end point					
Death	5	5 (3.4)	4	4 (5.5)	0.47
Death due to cardiovascular causes	4	4 (2.7)	4	4 (5.5)	0.31
Death due to worsening heart failure	0	0	3	3 (4.1)	
First hospitalization	28	25 (17.7)	22	17 (24.8)	0.30
Hospitalization for any cardiovascular cause	16	15 (10.4)	18	14 (20.0)	0.08
Hospitalization for worsening heart failure	7	6 (4.1)	9	7 (9.7)	0.11

European Journal of Heart Failure (2013) **15**, 1267–1276
doi:10.1093/eurjhf/hft099

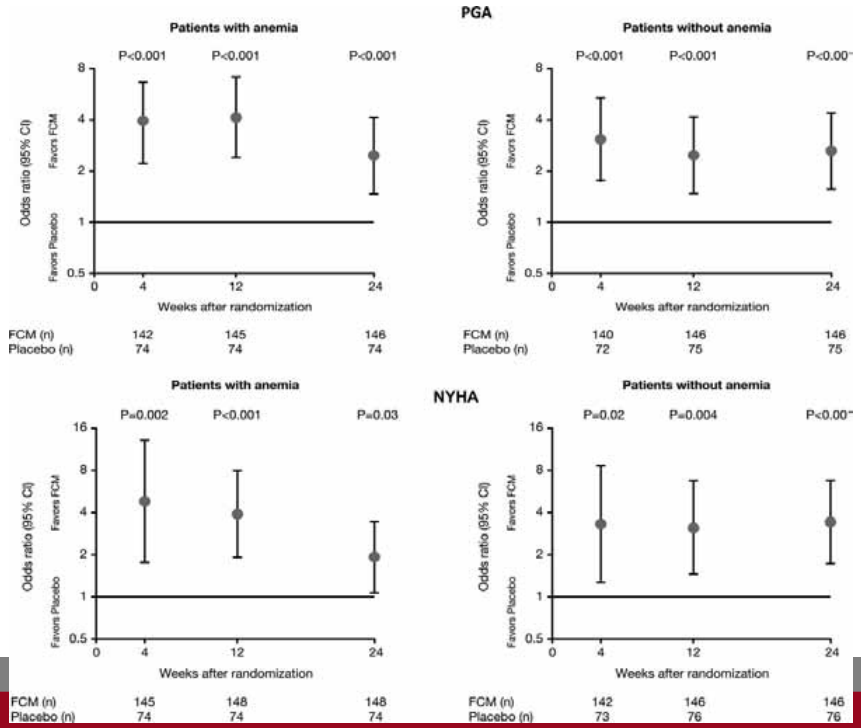
Intravenous ferric carboxymaltose in iron-deficient chronic heart failure patients with and without anaemia: a subanalysis of the FAIR-HF trial

Fair HF

Meta-analysis

Anemia vs no-anemia

459 patients with CHF, NYHA class II or III,
impaired LVEF (≤ 40% for NYHA II or ≤ 45% for NYHA III),
iron deficiency [serum ferritin ,100 mg/L or 100–299 mg/L if transferrin saturation <20%],



EJHF 2013

Fair HF Trial

FCM was administered as an i.v. push injection
dose 200 mg iron weekly until achievement of iron repletion (correction phase)
then every 4 weeks thereafter (maintenance phase).

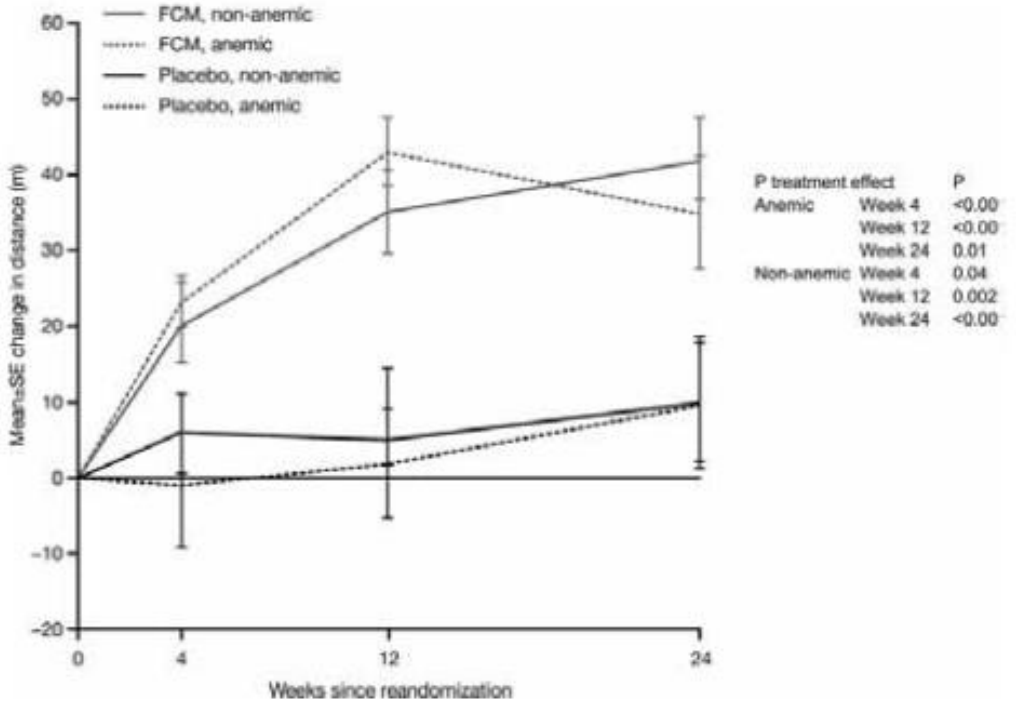


Figure 3 Mean changes from baseline in 6 min walk test (6MWT) distance according to the presence or absence of anaemia at baseline and treatment arm [ferric carboxymaltose (FCM) or placebo].

CONFIRM HF Trial

HF and ID patients N=351 1:1. 2-years FU

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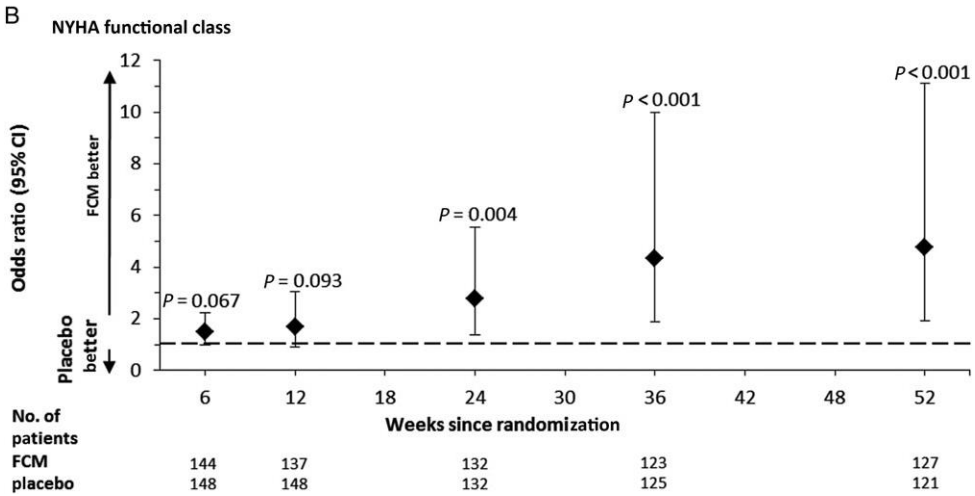
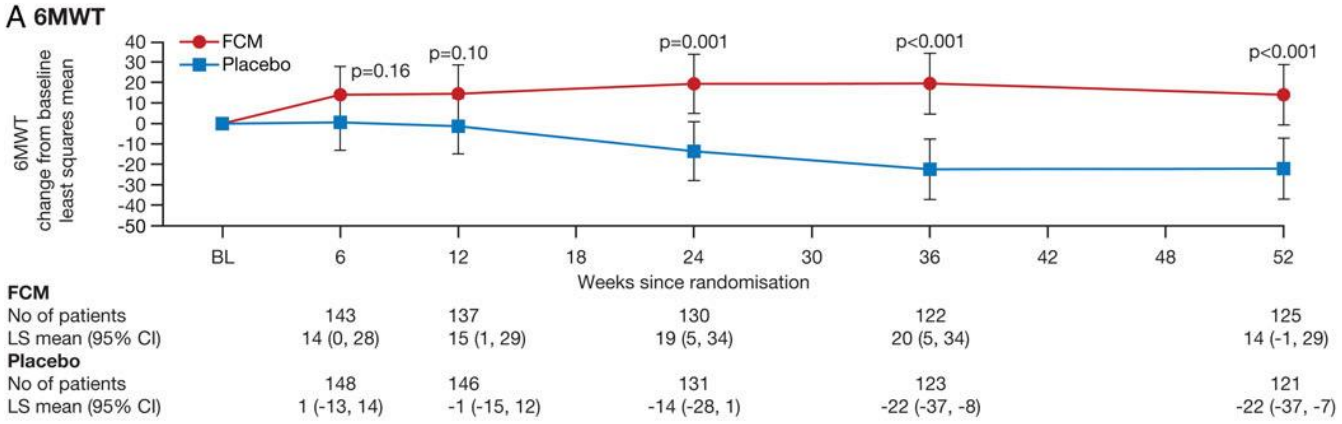
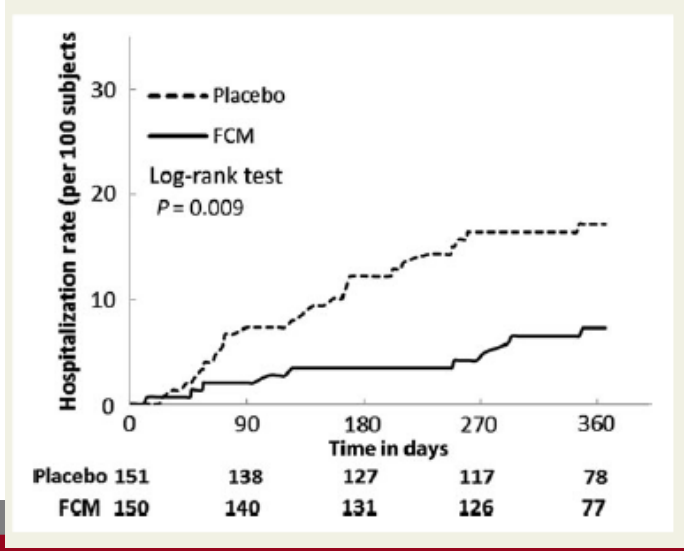




EHJ 2015

Table 2 Hospitalizations and deaths (full-analysis set)

End-point or event	FCM (n = 150)		Placebo (n = 151)			
	Total number of events	Incidence/100 patient-years at risk	Total number of events	Incidence/100 patient- years at risk	Time to first event hazard ratio 95% CI	*P*-value
Death	12	12 (8.9)	14	14 (9.9)	0.89 (0.41– 1.93)	0.77
Death for any cardiovascular reason	11	11 (8.1)	12	12 (8.5)	0.96 (0.42– 2.16)	0.91
Death due to worsening HF	4	4 (3.0)	3	3 (2.1)	1.39 (0.31–6.21)	0.67
Death due to other cardiovascular reason	7	7 (5.2)	9	9 (6.4)	0.81 (0.30–2.17)	0.68
Hospitalizations	46	32 (26.3)	69	44 (37.0)	0.71 (0.45–1.12)	0.14
Hospitalizations for any cardiovascular reason	26	21 (16.6)	51	33 (26.3)	0.63 (0.37–1.09)	0.097
Hospitalizations due to worsening HF	10	10 (7.6)	32	25 (19.4)	0.39 (0.19–0.82)	0.009
Hospitalizations due to other cardiovascular reason	16	13 (10.0)	19	15 (11.0)	0.91 (0.43–1.92)	0.81



iv Iron

Table 5 Overview of randomized trials of intravenous iron in patients with heart failure

Study	Design and duration	Population	I.v. iron regimen/ comparator(s)	n	Outcomes at end of study					
					Symptom severity/ quality of life	NYHA class	Exercise capacity	Hb	Ferritin	TSAT
Ponikowski et al., 2014 (CONFIRM-HF)[16]	Double-blind, randomized, 52 weeks	NYHA class II–III, LVEF ≤45%, ferritin <100 ng/mL or 100–300 ng/mL with TSAT <20%, Hb <15 g/dL	Ferric carboxymaltose 500–2000 mg iron in therapy phase (baseline and week 6); 500 mg iron as maintenance (weeks 12, 24, 36) if iron deficiency still present	152	Improved vs. placebo ($P = 0.001$)[a, b] Reduced hospitalization for worsening heart failure ($P = 0.009$)	Improved vs. placebo ($P < 0.001$)	Improved vs. placebo ($P = 0.002$)[c]	Increased vs. placebo ($P < 0.001$)	Increased vs. placebo ($P < 0.001$)	Increased vs. placebo ($P < 0.001$)
			Placebo	152						
Anker et al., 2009 (FAIR-HF)[15]	Double-blind, randomized, 24 weeks	NYHA class II (LVEF ≤40%) or III (LVEF ≤45%), ferritin <100 ng/mL or 100–299 ng/mL with TSAT <20%, Hb 9.5–13.5 g/dL	Ferric carboxymaltose 200 mg iron/week until iron repletion[d]	304	Improved vs. placebo ($P < 0.001$)[a, e]	OR for improvement by one class vs. placebo: 2.40; 95% CI 1.55 ($P < 0.001$)	Greater improvement from baseline vs. placebo ($P < 0.001$)[c]	No difference ($P = 0.21$)	Increased vs. placebo ($P < 0.001$)	Increased vs. placebo ($P < 0.001$)
			Placebo	155						
Okonko et al., 2008[32]	Observer-blinded, randomized, 18 weeks	Ferritin <100 ng/mL or 100–300 ng/mL with TSAT <20%, Hb <14.5 g/dL	Iron sucrose 200 mg iron/week[f]	24	Improved vs. controls ($P < 0.002$)[a]	Improved vs. controls ($P = 0.03$)	Trend to improvement vs. controls ($P = 0.08$)	No difference ($P > 0.2$)	Increased vs. controls ($P < 0.001$)	Increased vs. controls ($P < 0.001$)
			No treatment	11						
Toblli et al., 2007[79]	Double-blind, randomized, 26 weeks	LVEF ≤35%, Hb <12.5 g/dL, ferritin <100 ng/mL, TSAT <20%, b <12.5 g/dL (men), <11.5 g/dL (women)	Iron sucrose 200 mg iron/week for 5 weeks	20	Improved vs. controls ($P < 0.01$)[g]	Improved vs. controls ($P < 0.01$)	Improved vs. placebo ($P < 0.01$)[c]	Increased vs. placebo ($P < 0.01$)	Increased vs. placebo ($P < 0.01$)	Increased vs. placebo ($P < 0.01$)
			Placebo	20						

IRONOUT HF Trial

Ά Καρδιολογική Κλινική ΑΧΕΠΑ

Effect of **oral iron** repletion on exercise in HFrEF with ID.

N=225 1:1 (iron polysaccharide 150mg x2/day vs. placebo). 16 weeks F/U.

	Oral Iron Week 16 values*	Placebo Week 16 values*	Oral Iron Δ Week 16	Placebo Δ Week 16	Difference (95% CI)	*P* value
Primary end point						
Change in peak VO_2 at 16 weeks, median (IQR), ml/min	1218 (892 to 1500)	1187 (902 to 1425)	23 (−84 to 142)	−2 (−110 to 104)	21 (−34 to 76)	0.46
Change in peak VO_2 at 16 weeks, ml/kg/min	13.5 (11.7 to 16.3)	13.0 (10.2 to 15.9	0.20 (−1.1 to 1.6)	0.01 (−1.1 to 0.9)	0.30 (−0.27 to 0.87)	0.30
Secondary end points						
Change in 6-minute walk distance at 8 weeks, meters	380 (322 to 467)	376 (286 to 448)	15 (−17 to 55)	21 (−24 to 56)	−1 (−24 to 23)	0.95
Change in 6-minute walk distance at 16 weeks, meters	366 (315 to 456)	397 (299 to 472)	19 (−19 to 51)	32 (−12 to 66)	−13 (−32 to 6)	0.19
Change in mean response time (O_2 uptake kinetics), s	52 (46 to 61)	47 (40 to 58)	2.5 (−7 to 9)	1 (−10 to 6)	3 (−2 to 8)	0.19
Change in ventilatory efficiency (V_E/V_{CO2} slope)	34.8 (29.9 to 41.1)	33.5 (29.4 to 38.9)	−0.3 (−3.0 to 2.1)	−0.3 (−4.6 to 2.8)	0.8 (−0.3 to 2.6)	0.35
Change in NT-proBNP, pg/ml	889 (376 to 2373)	1085 (447 to 2582)	4 (−342 to 288)	−37 (−412 to 363)	159 (−280 to 599)	0.48
Change in KCCQ clinical summary score at 8 weeks	81.3 (70.8 to 91.7)	75.0 (58.9 to 87.5)	5.2 (−2.1 to 12.5)	1.0 (−7.3 to 8.3)	3.4 (−0.4 to 7.2)	0.08
Change in KCCQ clinical summary score at 16 weeks	80.7 (67.7 to 91.6)	77.1 65.1 to 89.6)	3.1 (−4.2 to 13.5)	3.0 (−4.2 to 10.4)	1.0 (−2.4 to 4.4)	0.57
Exploratory Endpoints						
Change in ventilatory threshold at 16 weeks (ml/min)	685 (546 to 884)	714 (558 to 873)	22 (−49 to 127)	−2 (−86 to 75)	36 (−3 to 76)	0.07
Change in creatinine at 16 weeks, mg/dL	1.31 (1.01 to 1.56)	1.21 (0.90 to 1.49)	0.03 (−0.10 to 0.13)	0.00 (−0.10 to 0.11)	−0.02 (−0.09 to 0.05)	0.65
Change in cystatin C at 16 weeks, mg/L	1.06 (0.86 to 1.38)	1.02 (0.78 to 1.31)	0.02 (−0.04 to 0.09)	0.01 (−0.08 to 0.07)	0.03 (−0.01 to 0.08)	0.12
Safety end points, No. (%)					**Odds Ratio (95% CI)**	
Adverse events	39 (35%)	45 (39%)			0.83 (0.48 to 1.43)	0.50
Serious adverse events	11 (10%)	10 (9%)			1.14 (0.47 to 2.81)	0.77
Permanent study drug discontinuation	15 (14%)	17 (15%)			0.90 (0.45 to 1.79)	0.76
Death or cardiovascular re-hospitalization	14 (13%)	12 (11%)			1.19 (0.55 to 2.59)	0.64

JAMA 2017

Why iv is more effective than oral

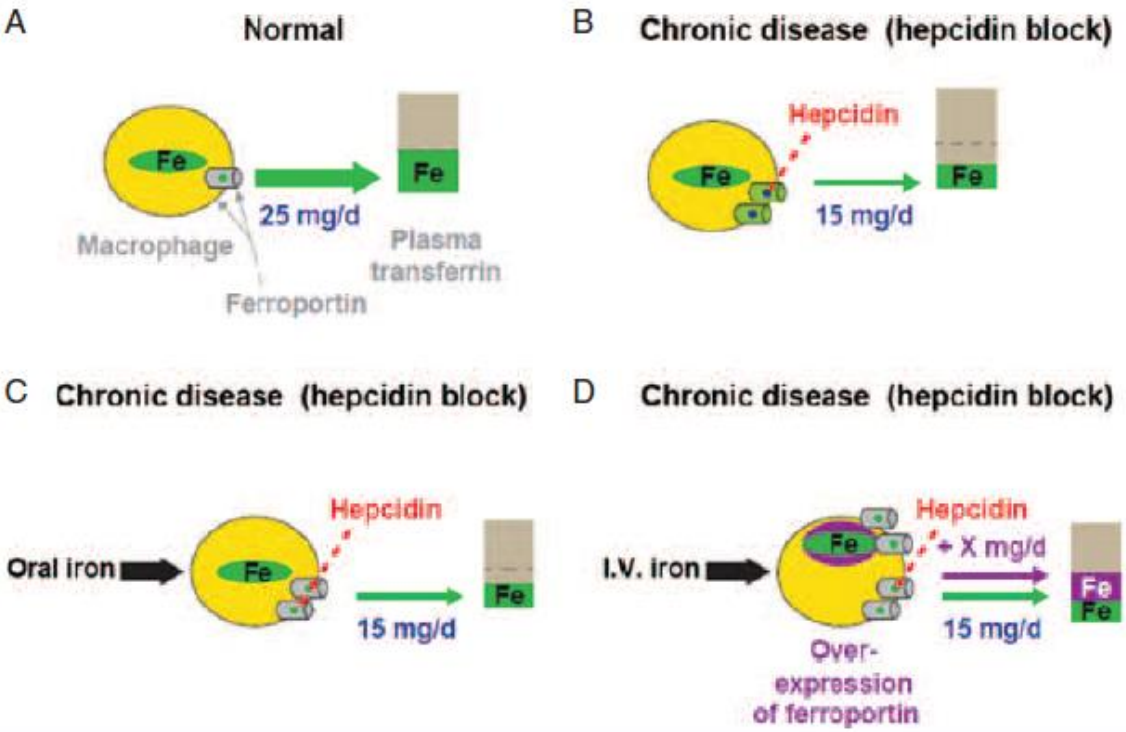
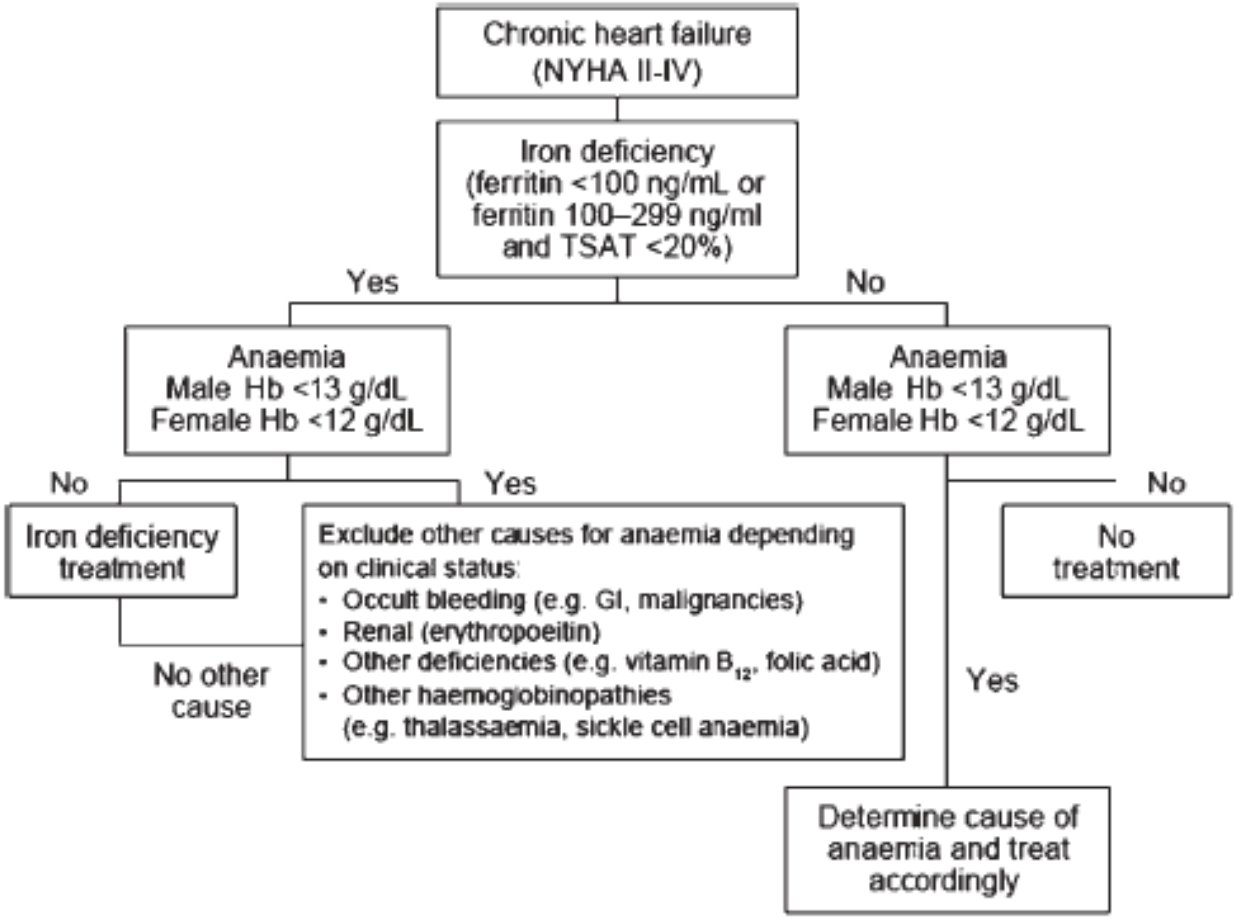
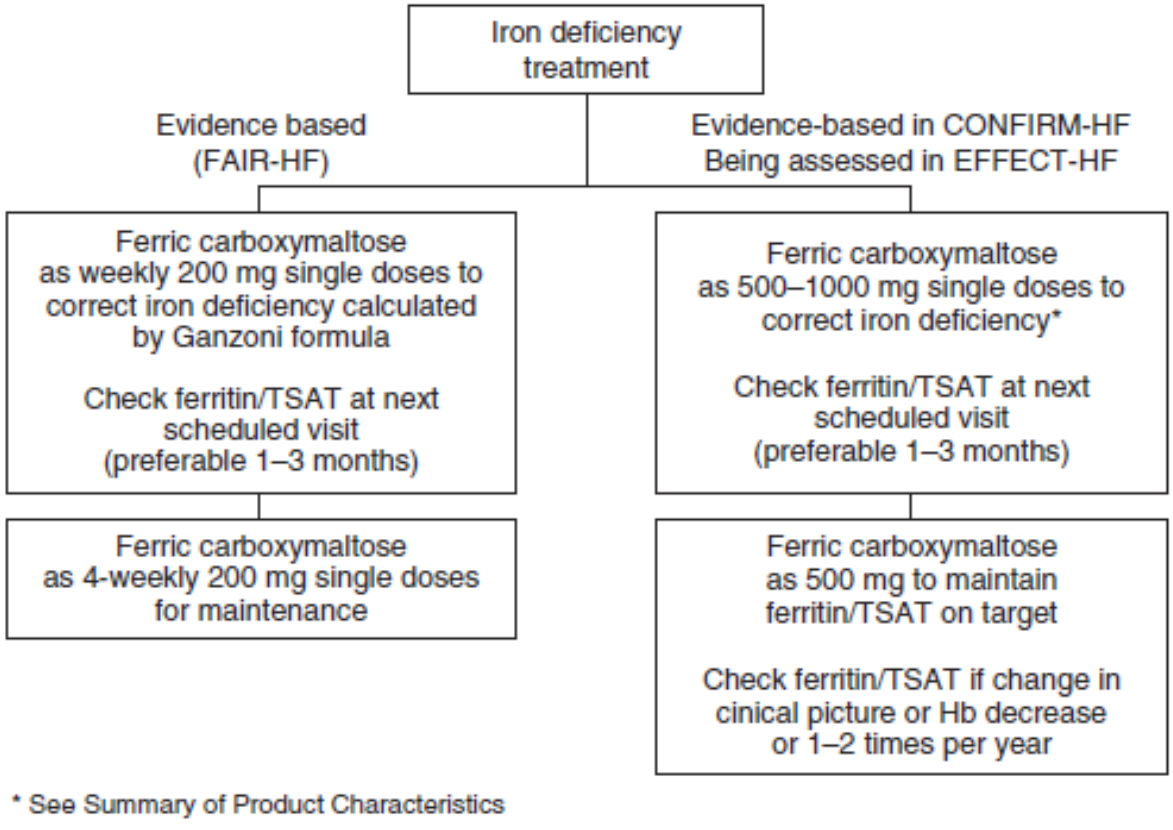


Figure 2 Effect of oral or i.v. iron therapy on 'hepcidin block' of iron release from macrophages. (*A*) Under normal circumstances, ~25 mg of stored iron per day is transported out of macrophages to plasma transferrin by the iron transporter protein ferroportin. (*B*) In chronic disease, elevated levels of hepcidin cause degradation of ferroportin, restricting ferroportin-mediated transport to ~15 mg iron/day, (*C*) The rate of iron absorption from iron therapy is inadequate to influence this 'hepcidin block'. (*D*) I.v. iron therapy results in high intracellular iron levels which overcome the 'hepcidin block' by stimulating overexpression of ferroportin (modified from Aapro *et al.*[46]).

Algorithm for diagnosis and treatment of Iron Deficiency and Anemia



Suggested algorithm for diagnosis of iron deficiency in patients with heart failure.[54–59] TSAT, transferrin saturation.



15mg iron/kg

Figure 3 Suggested algorithm for treatment of iron deficiency in patients with heart failure.[15–17,59,60,88] TSAT, transferrin saturation.

Oral Iron + Erythropoiesis-stimulating agent

Table 4 Overview of randomized trials of oral iron with erythropoiesis-stimulating agent therapy or with placebo in patients with heart failure

Study	Design and duration	Population	Oral iron	ESA/placebo treatment groups	*n*	Outcomes for oral iron alone (placebo group) at end of study					
						Symptom severity/ quality of life	NYHA class	Exercise capacity	Hb	Ferritin	TSAT
Ghali *et al.*, 2008[73]	Randomized, double-blind, 52 weeks	HF ≥3 months, LVEF ≤40%, Hb 9–12.5 g/dL, TSAT ≥15%	Daily until ferritin >800 ng/mL (type/dose not specified)	Darbepoetin alpha 0.75 μg/kg every 2 weeks	162	71% reported improvement on PGA	Minor improvement [mean (SE) 0.13 (0.04)]	No change vs. baseline	No change vs. baseline	NA	NA
				Placebo	157						
Kourea *et al.*, 2008[75]	Randomized, single-blind, 12 weeks	NYHA class II–III, LVEF <40%, Hb <12.5 g/dL, SCr <2.5 mg/dL	Ferrous sulfate 250 mg b.i.d.	Darbepoetin alpha 1.5 μg/kg every 20 days	21	No change vs. baseline	NA	Significant deterioration vs. baseline ($P = 0.044$)	No change vs. baseline	NA	NA
				Placebo	20						
Van Veldhuisen *et al.*, 2007[74]	Randomized, double-blind, 26 weeks	HF ≥3 months, LVEF ≤40%, Hb 9–12.5 g/dL, TSAT ≥15%	200 mg iron/day (type not specified)	Darbepoetin alpha 0.75 μg/kg every 2 weeks	56	Minor improvement [mean (SE) 4.9 (2.1)] on KCCQ[a]	Minor improvement [mean (SE) 0.23 (0.08)][a]	No relevant change vs. baseline[a]	No relevant change vs. baseline[a]	No change vs. baseline[a]	No relevant change vs. baseline[a]
				Darbepoetin alpha 50 μg every 2 weeks	54						
				Placebo	55						
Palazzuoli A *et al.*, 2006[72]	Randomized, double-blind, 12 weeks	NYHA class III-IV, LVEF <35%, Hb <11 g/dL, mild renal dysfunction	Ferrous gluconate 300 mg/day	Epoetin beta 6000 IU twice weekly	20	NA	No change vs. baseline	No change vs. baseline	No change vs. baseline	NA	NA
				Placebo	20						

EJHF 2015

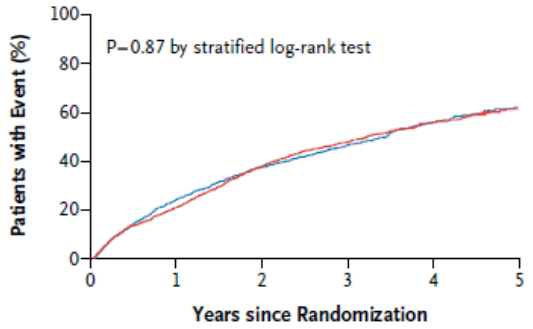
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Anemia with Darbepoetin Alfa in Systolic Heart Failure

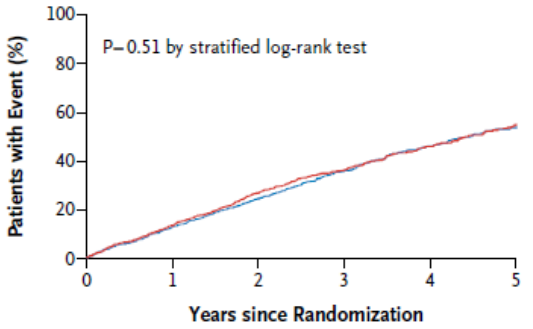
RED-HF Trial

A Primary Composite Outcome



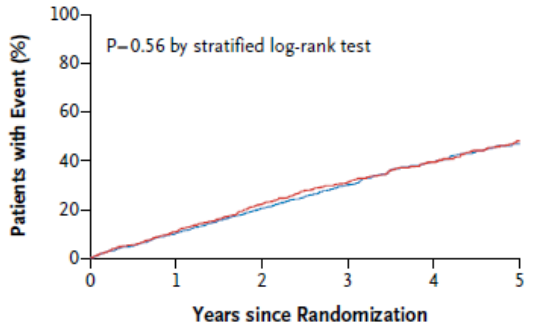
No. at Risk											
Placebo	1142	956	818	695	591	497	395	290	211	154	92
Darbepoetin alfa	1136	975	855	712	581	473	385	281	212	161	101

B Death from Any Cause



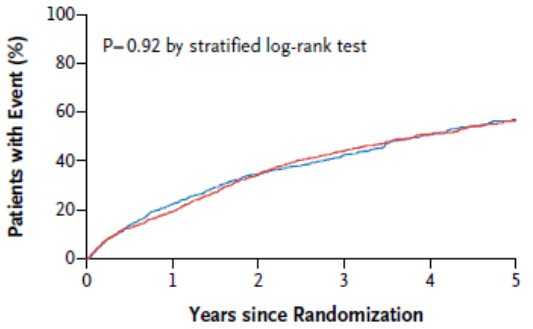
No. at Risk											
Placebo	1142	1055	942	824	715	599	481	352	264	192	118
Darbepoetin alfa	1136	1053	940	816	687	573	474	351	272	201	124

C Death from Cardiovascular Causes



No. at Risk											
Placebo	1142	1055	942	824	715	599	481	352	264	192	118
Darbepoetin alfa	1136	1053	940	816	687	573	474	351	272	201	124

D Death from Cardiovascular Causes or First Hospitalization for Worsening Heart Failure



No. at Risk											
Placebo	1142	956	818	695	591	497	395	290	211	154	92
Darbepoetin alfa	1136	975	855	712	581	473	385	281	212	161	101

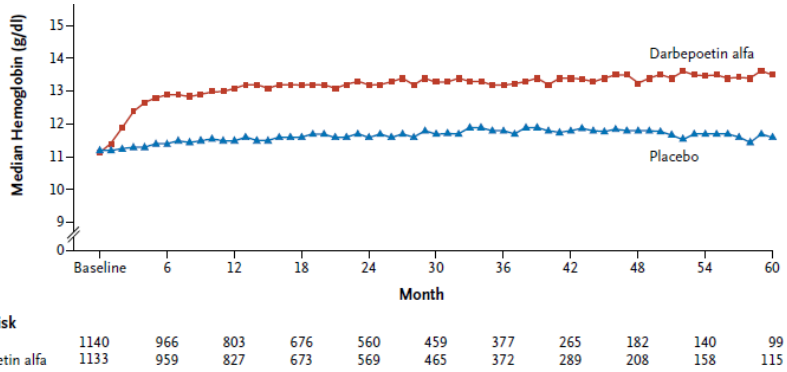


Figure 1. Monthly Hemoglobin Levels through 60 Months According to Study Group.

Table 3. Adverse Events of Interest.*

Adverse Event	Darbepoetin Alfa (N=1133)	Placebo (N=1140)	Risk Difference (95% CI)†	P Value‡
	no. of patients (%)		*percentage points*	
Any event of interest	660 (58.3)	662 (58.1)	0.2 (–3.9 to 4.2)	0.93
Cardiac failure	438 (38.7)	459 (40.3)	–1.6 (–5.6 to 2.4)	0.43
Ischemic heart disease	155 (13.7)	164 (14.4)	–0.7 (–3.6 to 2.2)	0.63
Cerebrovascular disorder				
Any	61 (5.4)	45 (3.9)	1.4 (–0.3 to 3.2)	0.10
Hemorrhagic	39 (3.4)	30 (2.6)	0.8 (–0.6 to 2.2)	0.26
Ischemic	51 (4.5)	32 (2.8)	1.7 (0.2 to 3.2)	0.03
Embolic and thrombotic events				
Any	153 (13.5)	114 (10.0)	3.5 (0.9 to 6.1)	0.009
Arterial§	87 (7.7)	73 (6.4)	1.3 (–0.8 to 3.4)	0.24
Venous¶	29 (2.6)	20 (1.8)	0.8 (–0.4 to 2.0)	0.19
Vessel type unspecified and mixed arterial and venous‖	51 (4.5)	27 (2.4)	2.1 (0.6 to 3.6)	0.005

RED-HF, post hoc analysis

Ά Καρδιολογική Κλινική ΑΧΕΠΑ

Nonresponders: patients in the lowest quartile of hemoglobin change after 4 weeks

Median initial hemoglobin change in nonresponders (n=252) was −0.25 g/dL
and +1.00 g/dL in the remainder of patients (n=756).

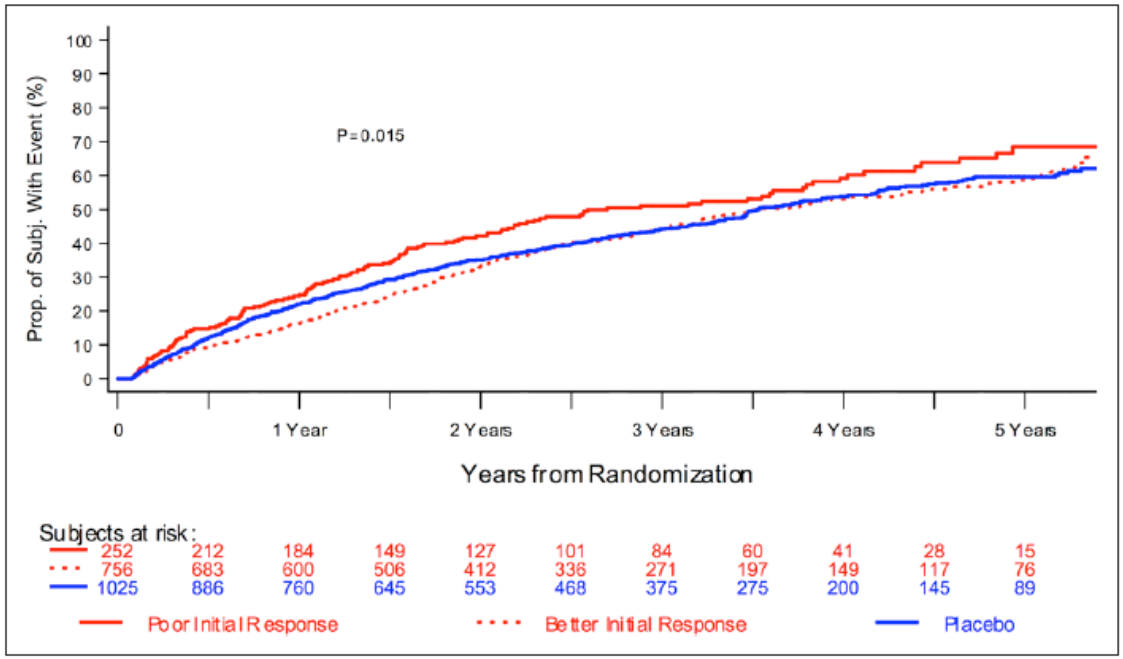
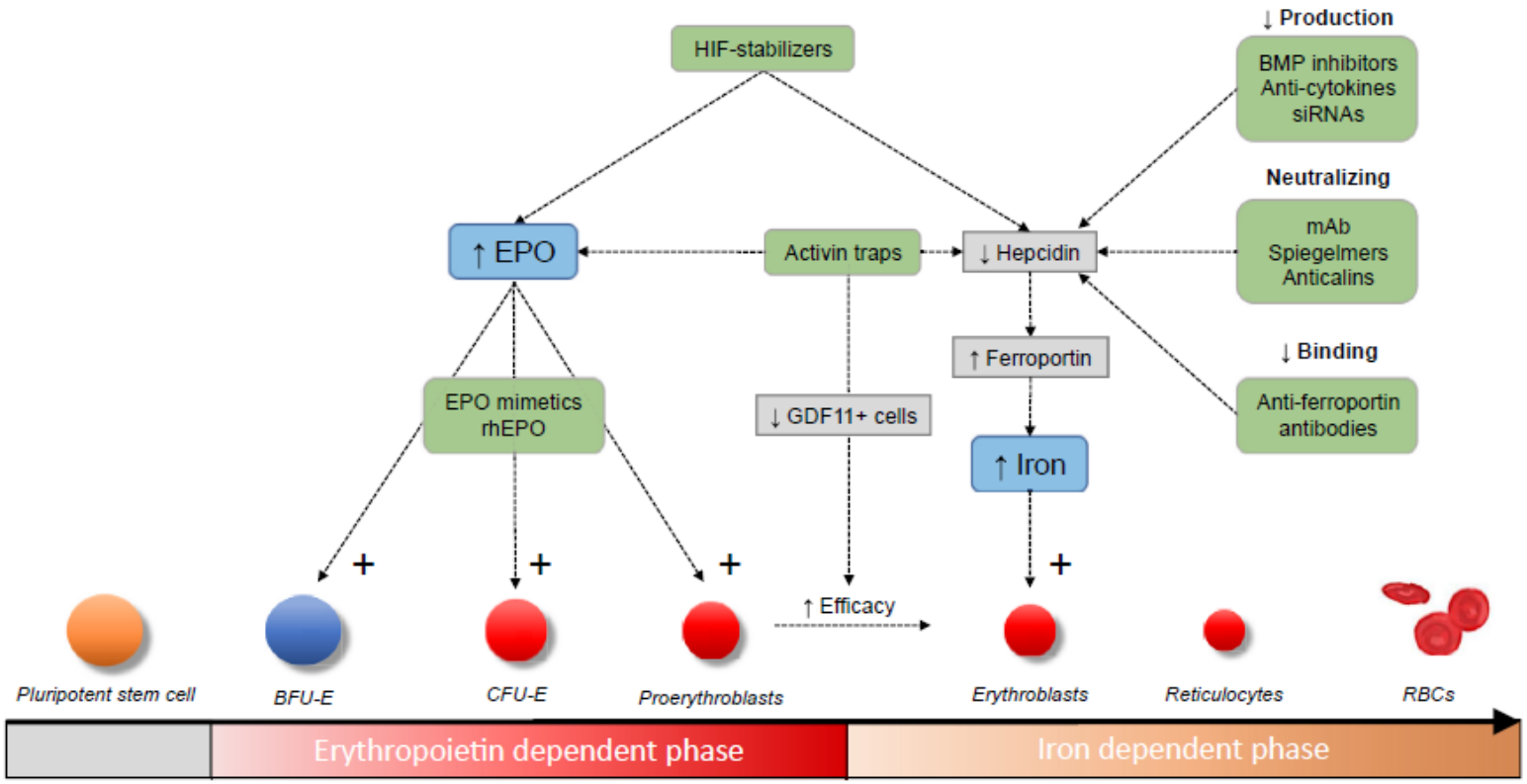


Figure. Rates of the primary composite end point for those with a poor compared with a better initial hematopoietic response.

Kaplan–Meier plot on the primary composite end point of all-cause death or first hospitalization for worsening heart failure of patients with a poor initial response compared with those with a better initial response and placebo. The *P* value for difference between poor compared with a better initial hematopoietic response is noted.

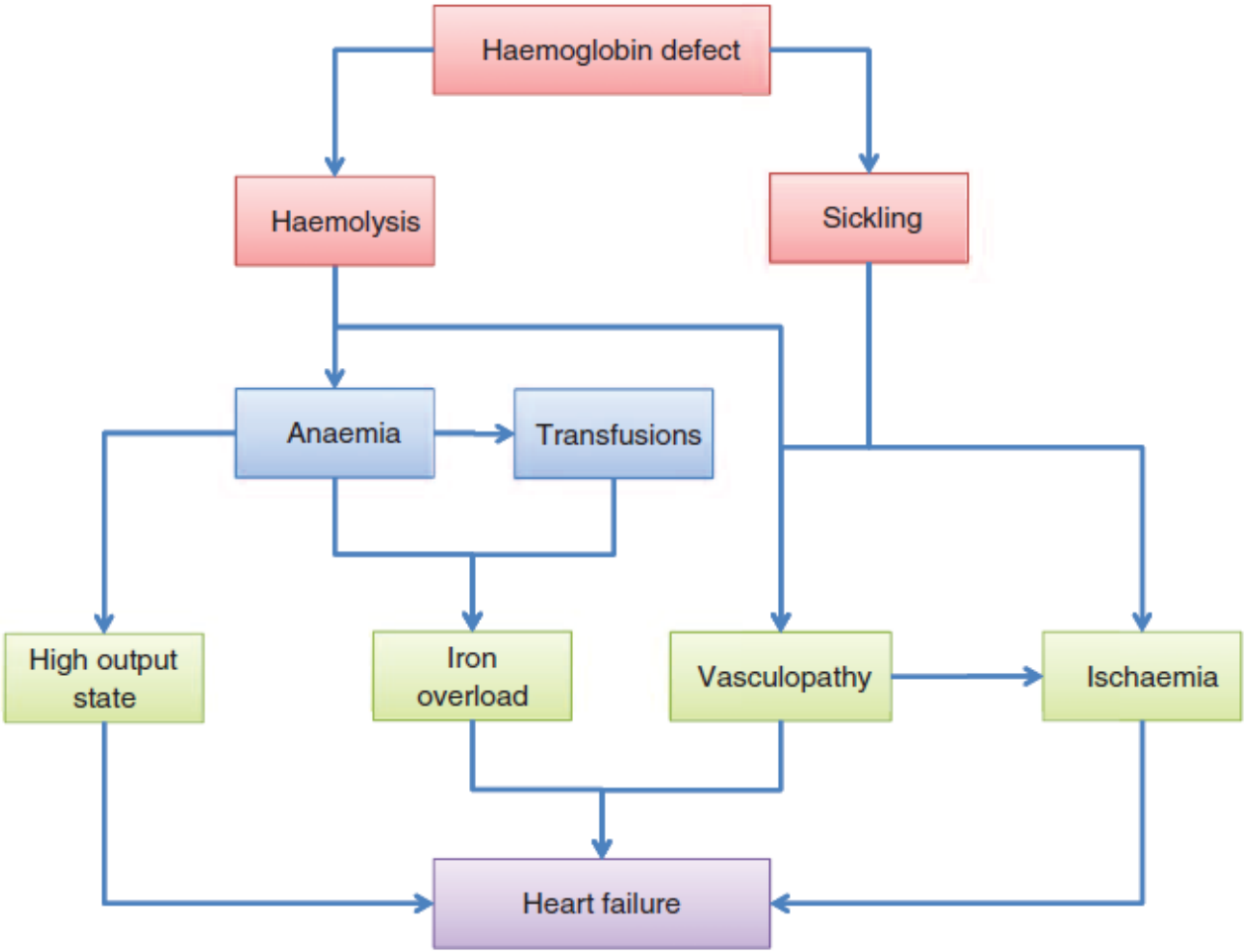
FIGURE 1 New Therapies for Anemia and Their Targets in Erythropoiesis



The process of production of new red blood cells (RBCs): erythropoiesis. The first stages are dependent on erythropoietin (EPO). During the erythroblasts stage, iron availability is essential as it is incorporated in hemoglobin. Most new therapies target either EPO or iron. Hypoxia-inducible factor (HIF) stabilizers affect both pathways. Although not fully understood, the data suggest that activin receptor ligand traps also addresses both pathways and increases efficacy of erythropoiesis by reducing the number of growth differentiation factor (GDF)-11-positive cells. Hepcidin can be antagonized by decreasing hepcidin production, neutralizing hepcidin, or preventing hepcidin-ferroportin interaction. As a result of hepcidin inhibition, ferroportin expression is increased, and iron absorption and iron availability for erythropoiesis increase. BFU-E = erythroid burst-forming units; BMP = bone morphogenic protein; CFU-E = erythroid colony-forming units; mAb = monoclonal antibodies; rhEPO = recombinant human erythropoietin; siRNA = small interfering ribonucleic acid.

Thalassemia causes Heart Failure

Ά Καρδιολογική Κλινική ΑΧΕΠΑ



An overview of the pathophysiology of heart failure in haemoglobinopathies.

Farmakis et al. EJHF 2017

Clinical phenotypes of Heart Failure

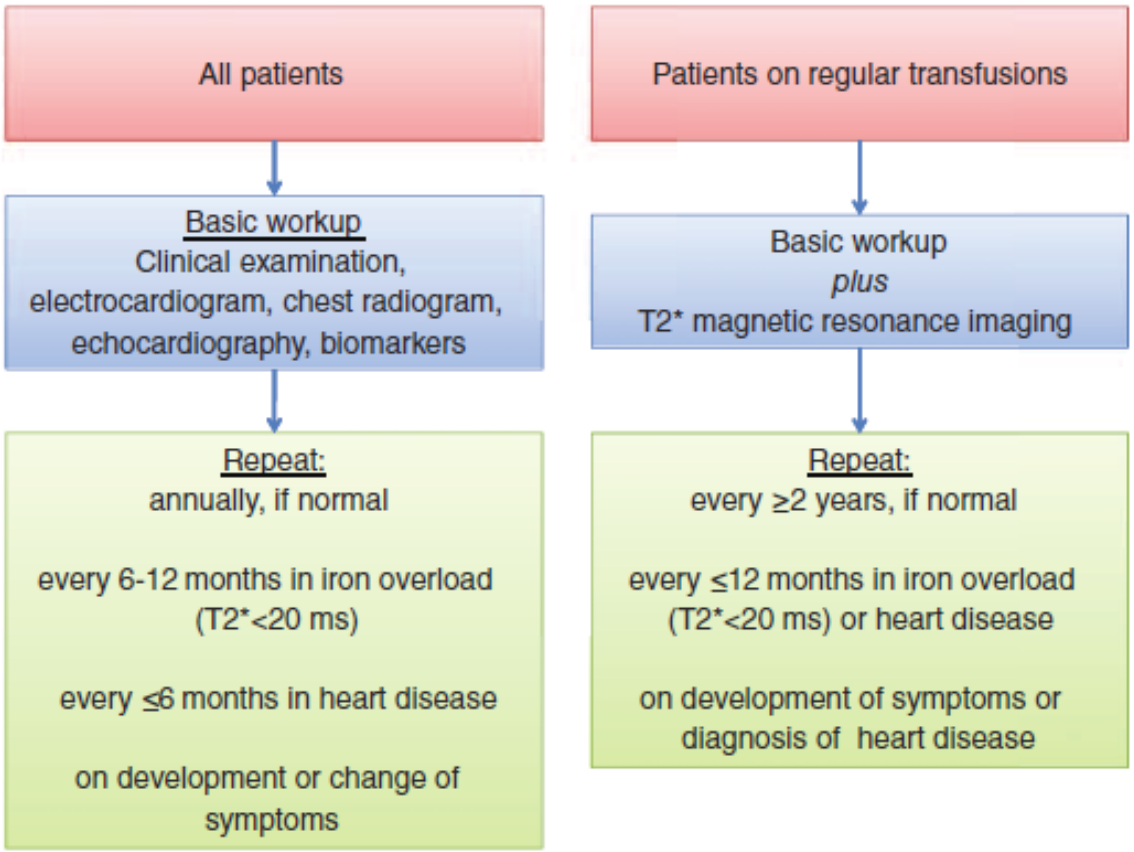
Table 1 Phenotypes of heart disease and heart failure observed in patients with haemoglobinopathies

Cardiac phenotype	Haemoglobinopathy
Dilated cardiomyopathy: LV dilatation and reduced LVEF	TM
Restrictive cardiomyopathy: LV restrictive filling with preserved LVEF	TM
High output state: LV and RV dilatation, eccentric hypertrophy, and increased LVEF	TI, poorly treated TM, SCA, SThal
Isolated RV cardiomyopathy	TM
Pulmonary hypertension with preserved LVEF	TI, SCA, SThal
Acute myocarditis	TM
Acute pericarditis	Poorly treated TM, TI
Chronic constrictive pericarditis	Poorly treated TM, TI
Myocardial infarction or ischaemia without haemodynamically significant coronary artery lesions	SThal
Valvular disorders: calcification, mitral valve prolapse, mitral regurgitation, aortic stenosis	TI, poorly treated TM, SCA, SThal

RV, right ventricular; SCA, homozygous sickle cell anaemia; SThal, sickle thalassaemia; TI, thalassaemia intermedia; TM, thalassaemia major.

Farmakis et al. EJHF 2017

Diagnostic Algorithm



Basic algorithm for the cardiac evaluation of patients with haemoglobinopathies.

Farmakis et al. EJHF 2017

European Journal of Heart Failure (2017) 19, 340–347
doi:10.1002/ejhf.701

RESEARCH ARTICLE

Ά Καρδιολογική Κλινική ΑΧΕΠΑ

Ferritin levels and risk of heart failure—the Atherosclerosis Risk in Communities Study

Low or High Ferritin

Survival free of HF

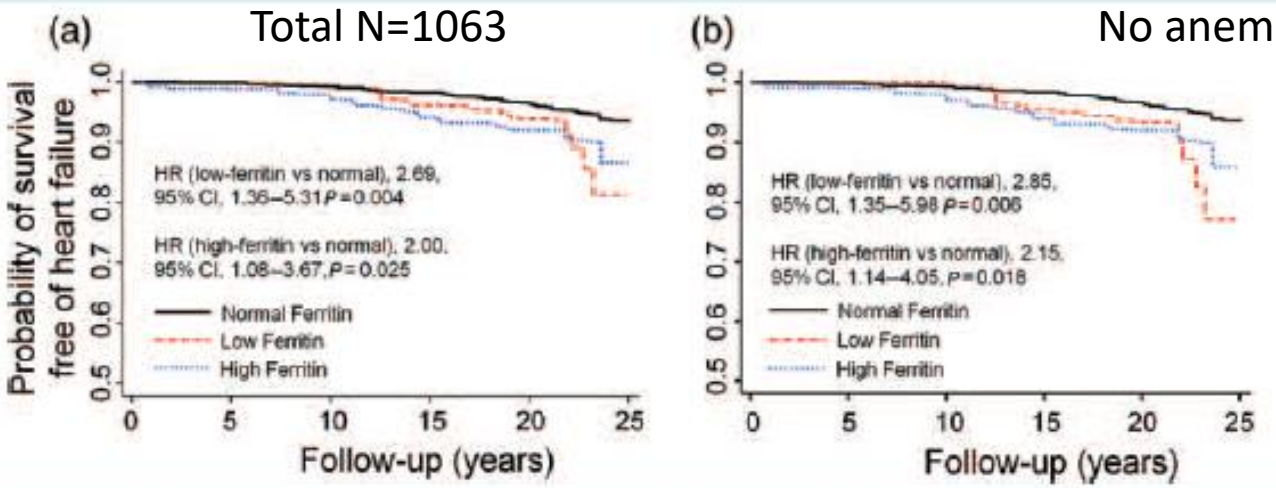
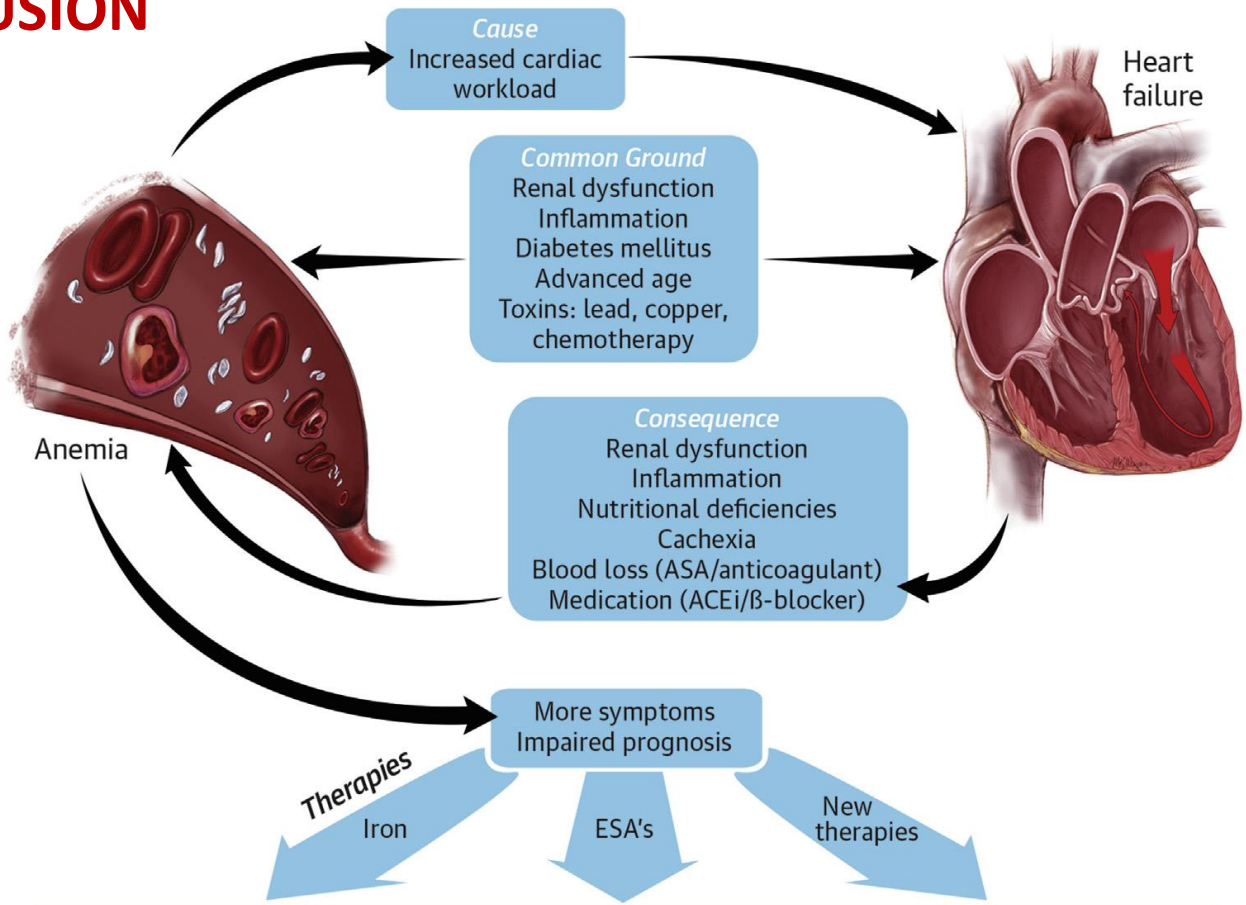


Figure 1 Ferritin serum levels and incident heart failure (ARIC Study, 1987–2011). Kaplan–Meier curves for patients with low (red large dashed line), normal (black line), and high ferritin (blue short dashed line) serum levels for the outcome of heart failure (hospitalization and death). Adjusted for age, sex, and race, standardized to a population that is 62% male, 55% white, and aged 50 years. (a) Whole sample; (b) only participants without anaemia were included. Low ferritin, <30 ng/mL; normal ferritin 30–200 ng/mL in women and 30–300 ng/mL in men; high ferritin, >200 ng/mL in women and >300 ng/mL in men. Hazard ratio (HR) was from a Cox regression adjusted for age, sex, and race. CI, confidence interval.

CONCLUSION



	Iron	ESA's	New therapies
Effects	Hemoglobin ↑ Symptoms ↓ Exercise capacity ↑ Morbidity and mortality ?	Hemoglobin ↑ Morbidity and mortality ~ Thromboembolic events ↑	Hemoglobin ↑ Symptoms ? Morbidity and mortality ?
Current status	Recommended for improving symptoms in patients with iron deficiency	Not recommended for the treatment of anemia in heart failure	Awaiting data from clinical trials mainly in chronic kidney disease

European Heart Journal (2016) 37, 2129–2200
doi:10.1093/eurheartj/ehw128

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Recommendations for the treatment of other co-morbidities in patients with heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
Iron deficiency			
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (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.	IIa	A	469, 470

1. FAIR HF
2. CONFIRM HF

- A diagnostic workup to seek a cause for any finding of anaemia is indicated (e.g. occult blood loss, iron deficiency, B12/folate deficiency, blood dyscrasias), although in many patients no specific cause is found.

- The safety of i.v. iron is unknown in patients with HF and haemoglobin >15 g/dL.

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Ά Καρδιολογική Κλινική ΑΧΕΠΑ

STATE-OF-THE-ART REVIEW

Anemia in Heart Failure

Still Relevant?

Niels Grote Beverborg, MD, Dirk J. van Veldhuisen, MD, PhD, Peter van der Meer, MD, PhD

However, it is unclear whether anemia leads to advanced HF and worse outcome or if anemia is merely a sign of more advanced disease.

ΕΥΧΑΡΙΣΤΩ