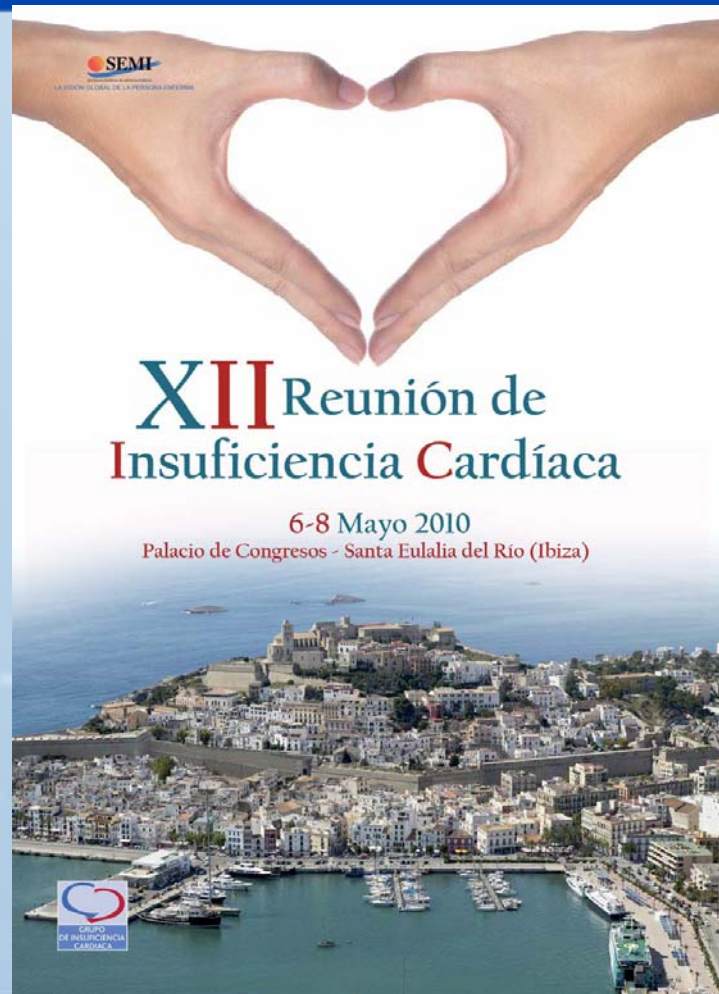
Badalona Serveis Assistencials

Insuficiencia Cardiaca y anemia

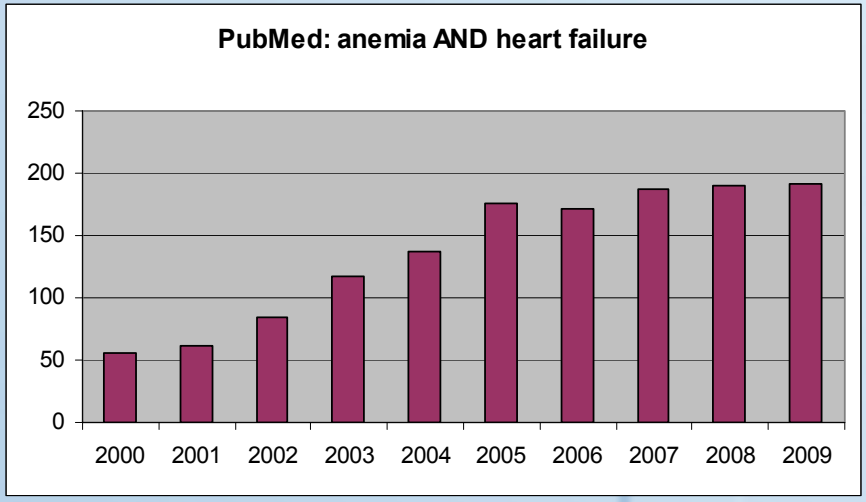
J. Grau Amorós

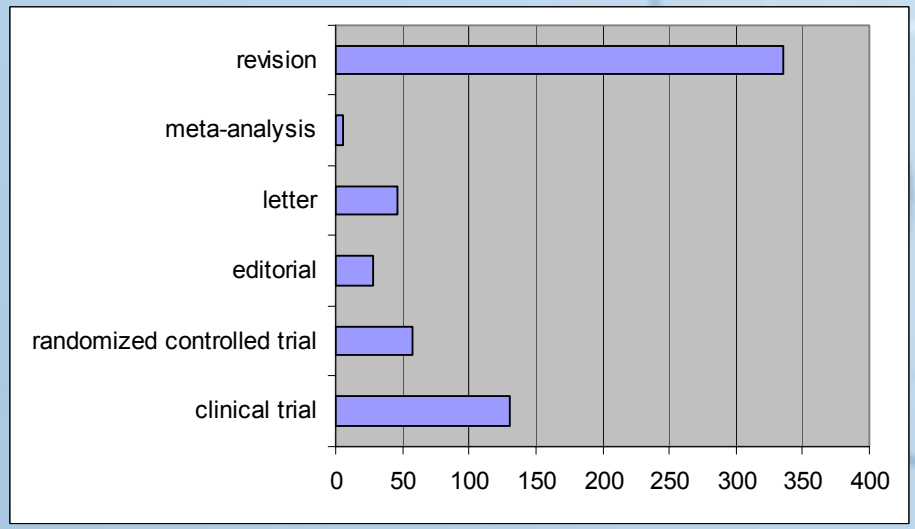
Hospital Municipal de Badalona



Insuficiencia Cardiaca y anemia

- Prevalencia
- Etiología
- Pronóstico
  - Niveles EPO
  - Valor RDW
- Tratamiento
  - Transfusión
  - Fe
    - FAIR-HF
  - EPO
    - STAMINA-HeFT
- Propuesta actuación



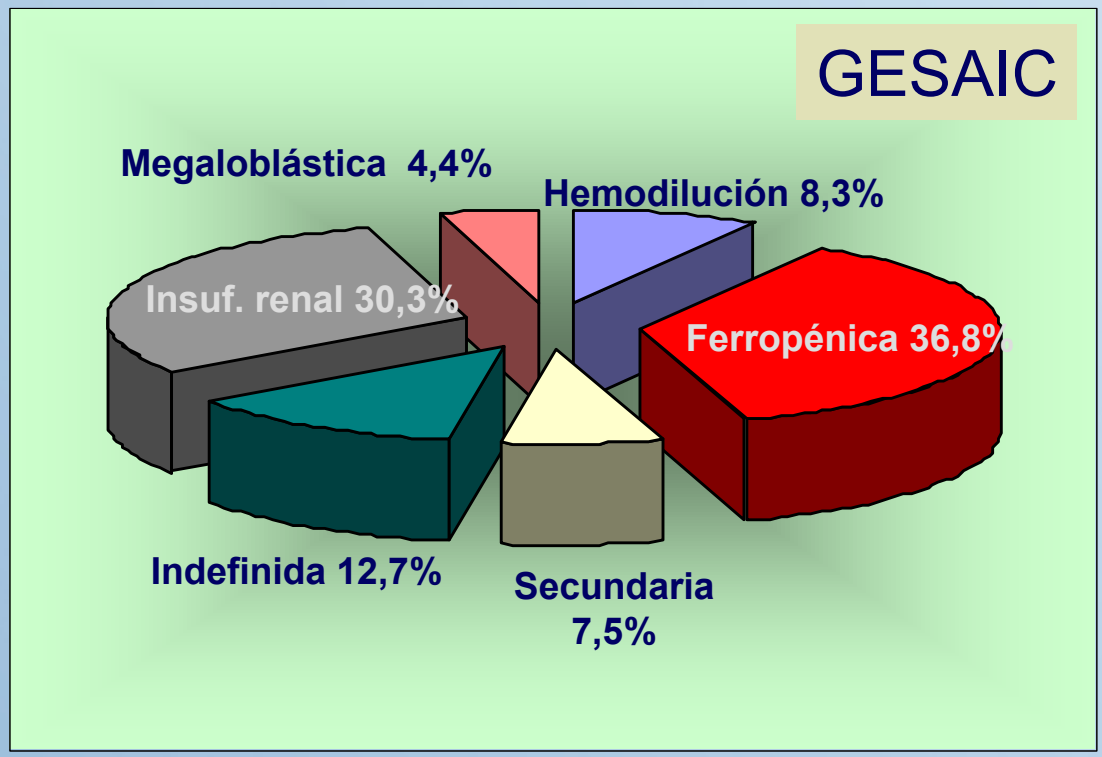


Insuficiencia Cardiaca y anemia: prevalencia

GESAIC	Criterios de anemia			
	OMS	Hb < 12g	Htº < 40%	Htº < 37%
Anemia al ingreso	58,3	50,13	67,1	48,6
Anemia al alta	52,7	45,2	62,2	46,3
Hombres	53,9	36,4	55,0	41,7
Mujeres	51,9	51,9	66,8	49,2
FEVI < 45 %	41,8	32,8	50,0	33,6
FEVI > 45 %	61,0	53,6	70,1	54,6
Debut IC	36,2	32,5	46,8	34,9
Clase III-IV NYHA	59,1	74,1	68,9	54,1

Grau Amorós J. Rev Clin Esp 2008;208(5):211-5

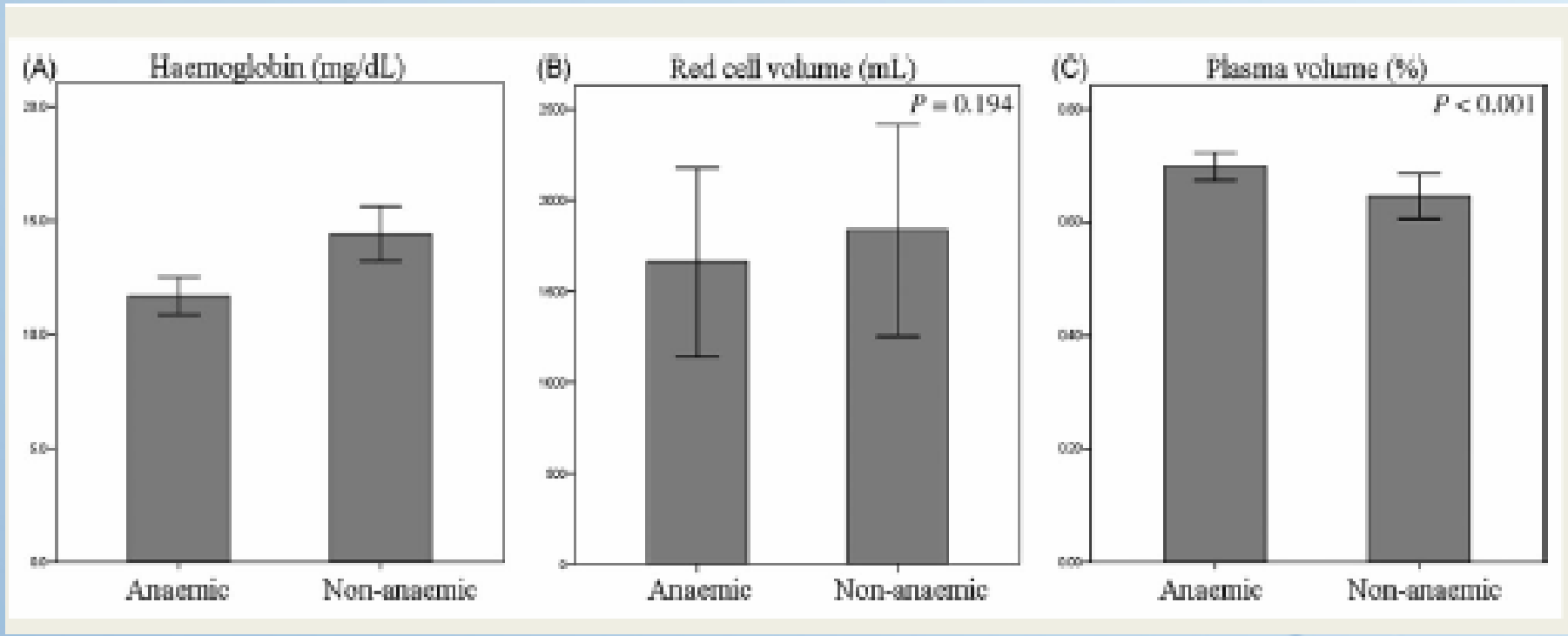
Insuficiencia Cardiaca y anemia: etiología



- Excluir hemodilución
- Descartar ferropenia
- Anemia enf. crónica

Grau Amorós J. Med Clin(Barc) 2009; 132:447-53

Insuficiencia Cardiaca y anemia: hemodilución



N=99
LVEF < 45%

"... Haemodilution appears to be the most potent factor for the development of low haemoglobin levels in patients with a broad spectrum of severity of heart failure..."

Adlbrecht C et al. Eur Heart J 2008, 29:2343-50

Insuficiencia Cardiaca y anemia: hemodilución

Columbia University Medical Center Heart Failure Center

Subjects aged>21 years with HF for >3 months' duration with stable symptoms

Hb < 13 g/dl men and 12.0 g/dl women

Creat < 3.5 mg/dl

	HFLEF n=22	HFPEF n=24	*p*
Blood volume (ml)	5,809 ± 925	4,487 ± 1,170	<0.05
Red cell volume (ml)	1,760 ± 338	1,317 ± 340	<0.05
Plasma volume (ml)	4,049 ± 650	3,170 ± 867	< 0.05
Hypovolemia	0%	38%	
Normovolemia	36%	42%	
Hypervolemia	64%	20%	
Dilutional anemia	41%	12%	

Abramov D. Am J Cardiol 2008; 102:1069-72

Fisiopatología anemia crónica

↑ Citoquinas

IL 6

Interferon γ

IL 10

↑ hepcidina

ferritina

↑ transportador Fe

↑ receptor transferrina

↓EPO

↓ absorción Fe

↑captación Fe

↓ferroportina 1

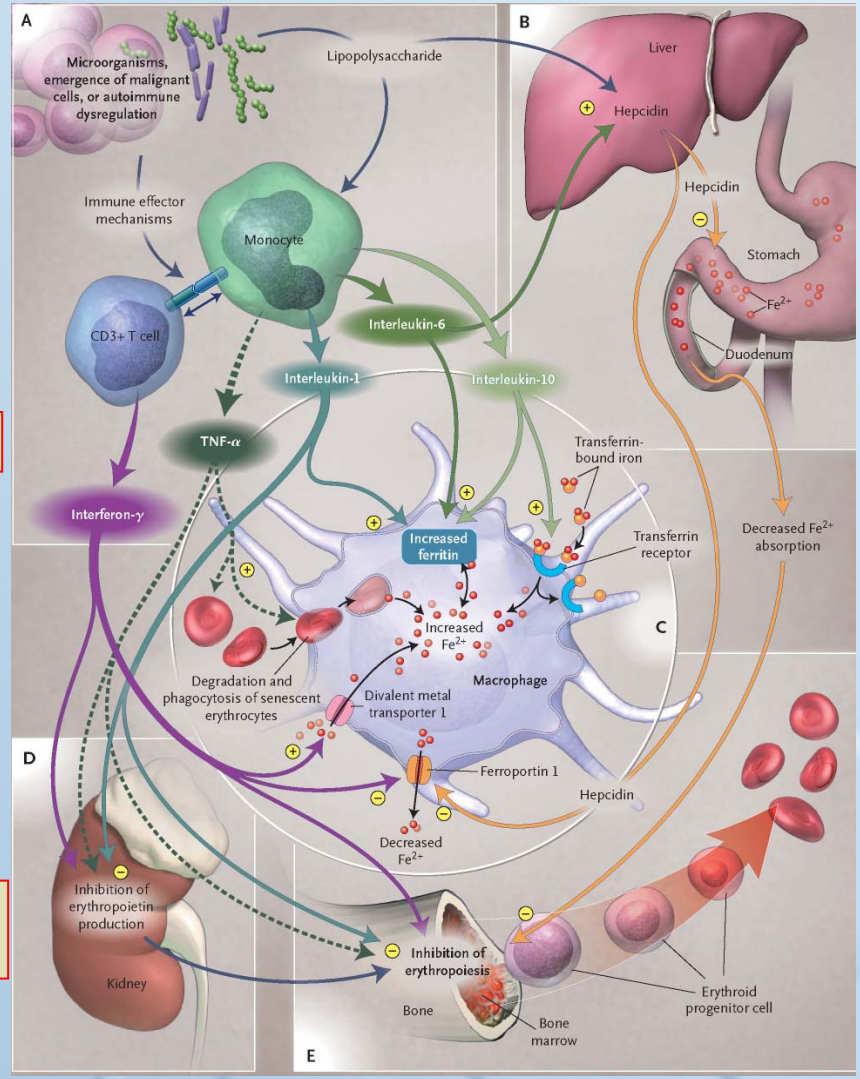
Bloqueo Fe

↑TNF α

↑fagocitosis hematies

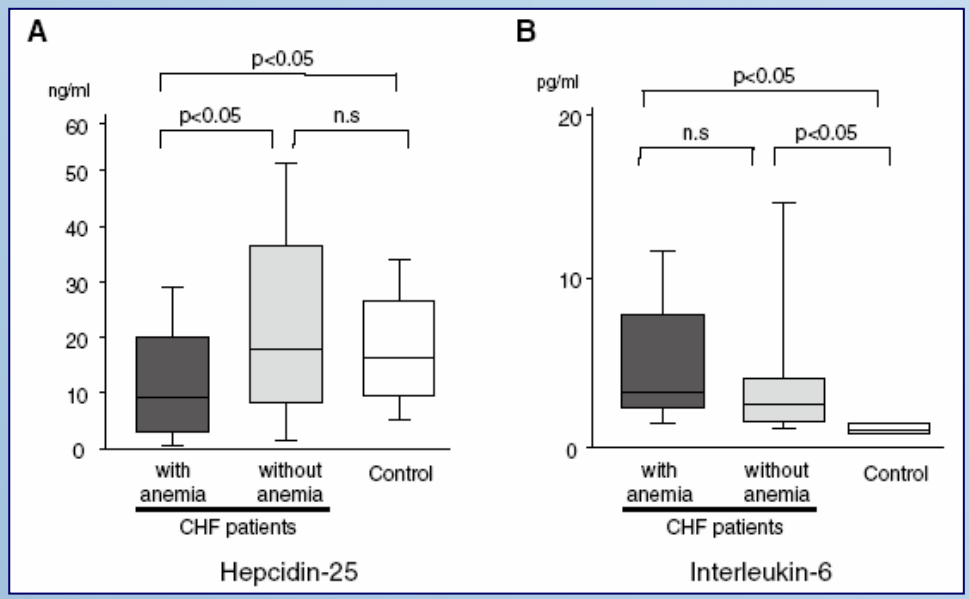
↓stem cell

IL1

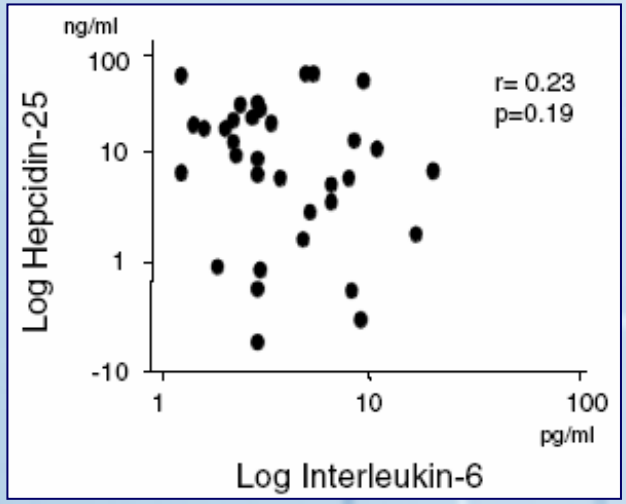


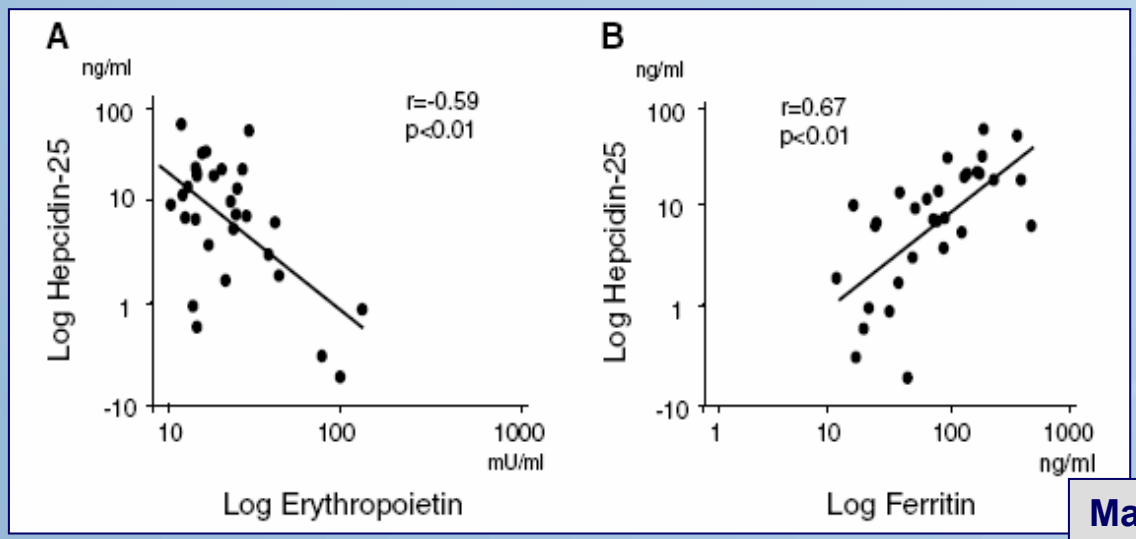
Weiss G. N Engl J Med 2005;352:1011-23.

Insuficiencia Cardiaca y anemia: etiología



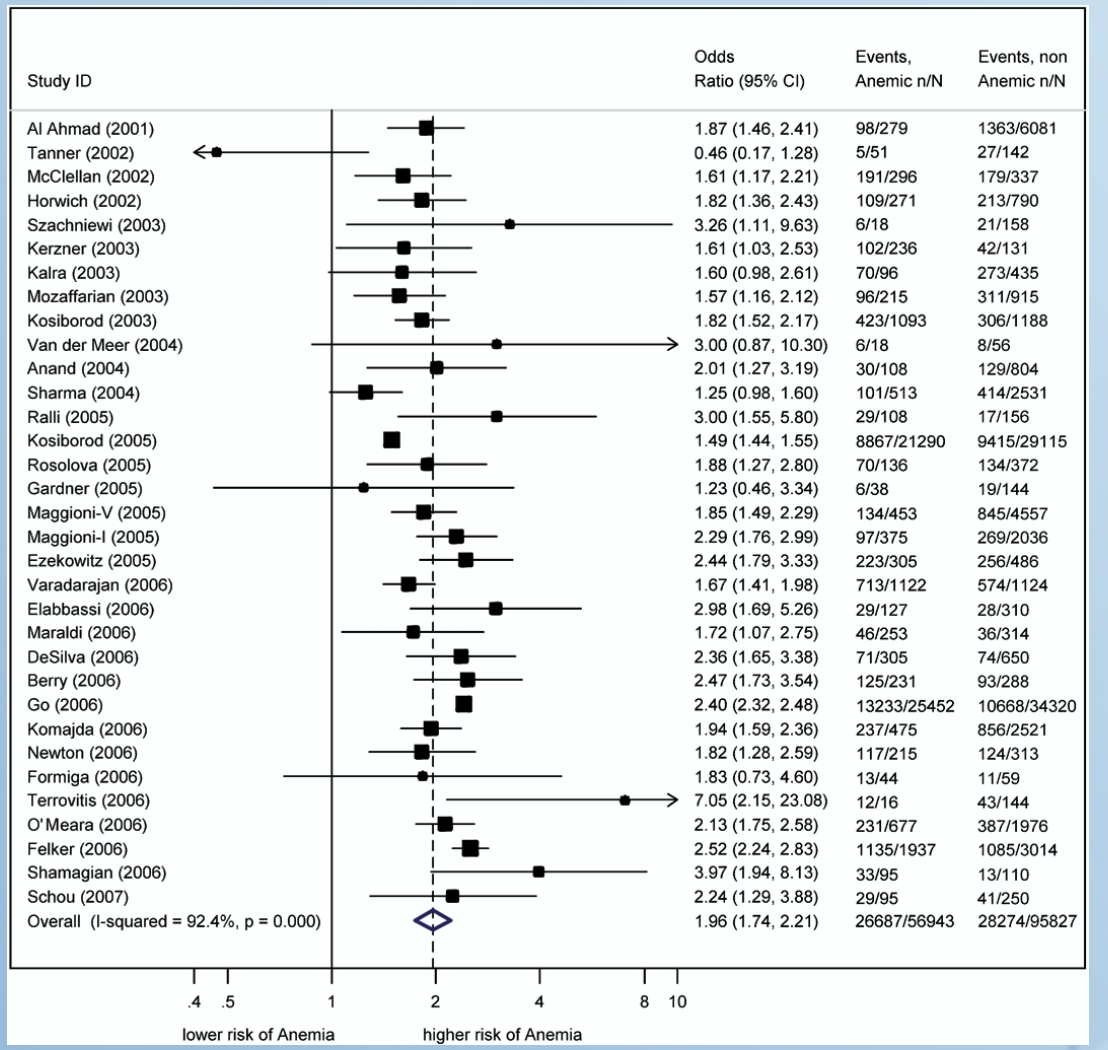
"...We showed that serum hepcidin-25 concentrations are regulated by EPO and iron storage but not by IL-6 in CHF patients with anemia..."

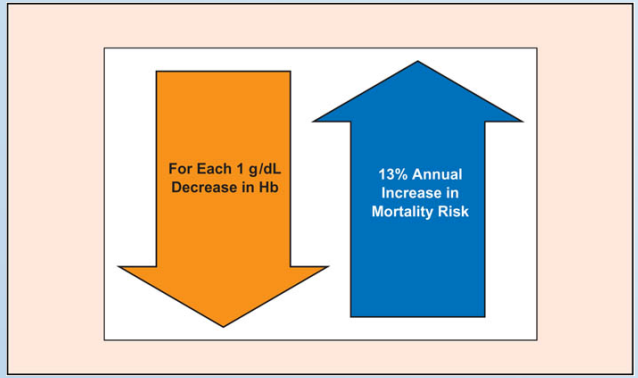




Matsumoto M et al. Circ J 2010; 74: 301-6.

Pronóstico anemia en la IC

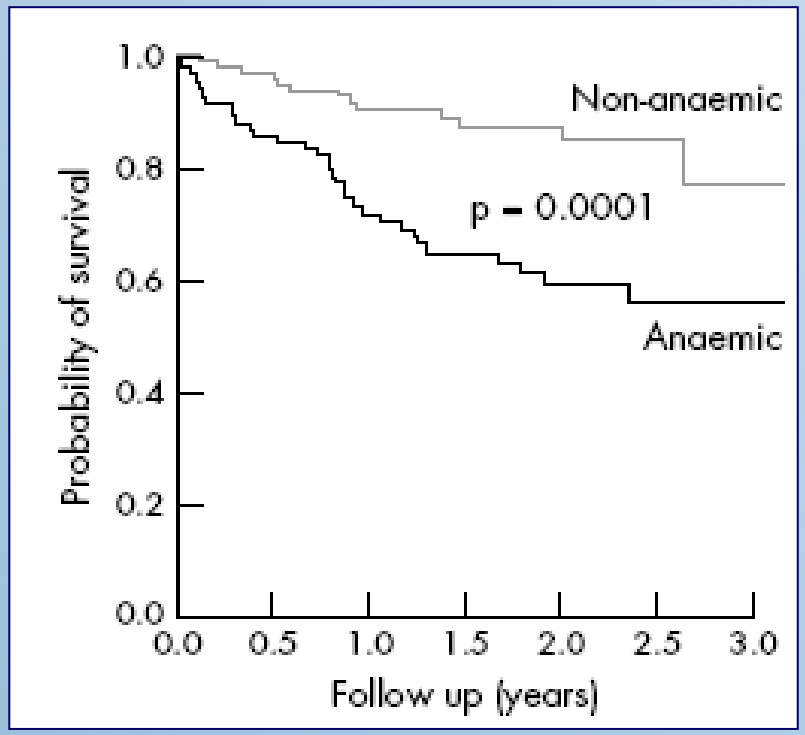




"...The mortality risk associated with the presence of anemia was not significantly different between patients with systolic CHF (OR: 1.96, 95% CI: 1.70 to 2.25, p 0.001) and diastolic CHF (OR: 2.09, 95% CI: 1.53 to 2.86, p 0.001)..."

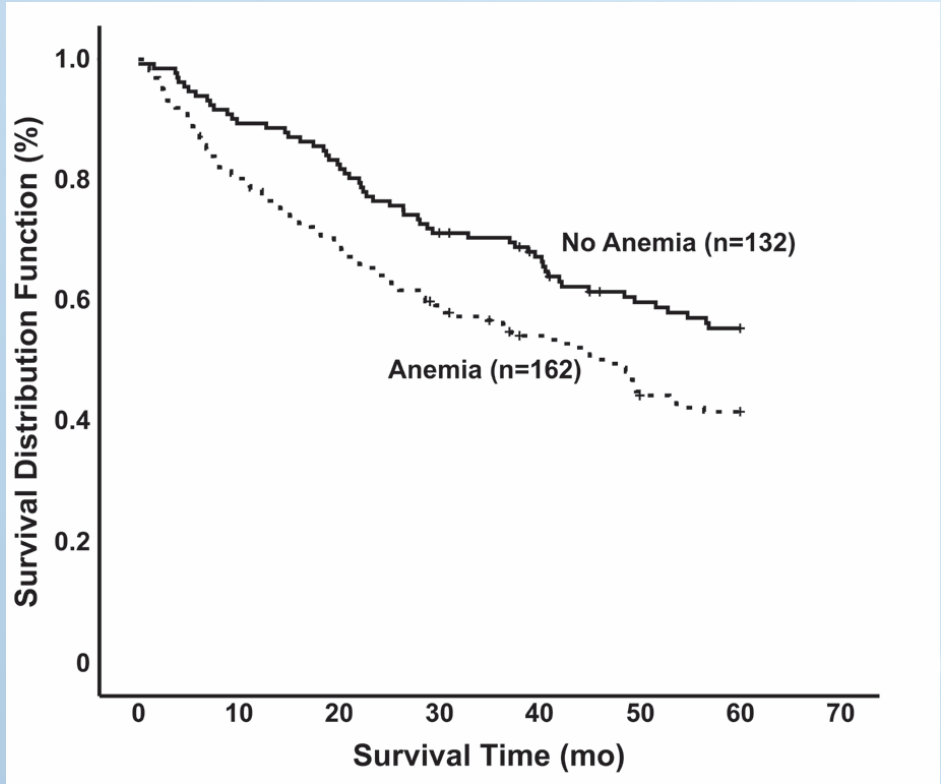
Groenveld HF et al. J Am Coll Cardiol 2008;52:818-27

Pronóstico anemia en la IC con FEVIP



Kaplan-Meier survival curves for patients with congestive heart failure (CHF) with preserved left ventricular systolic function (left ventricular ejection fraction (LVEF) >50%), with and without anaemia.

L Grigorian et al. Heart 2006;92;780-784



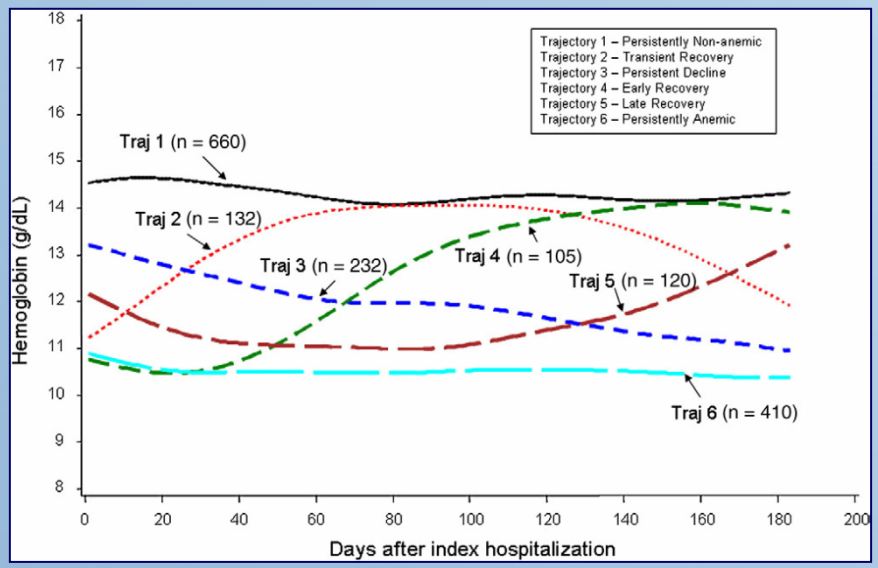
Kaplan-Meier survival curve throughout the follow-up period compares the 162 anemic patients with the 132 nonanemic patients (P=0.01).

Tehrani F et al. Tex Heart Inst J 2009;36:220-5

Pronóstico anemia persistente en la IC

Hb (g/dL)	Mortality, HR (95% CI)	Mortality or HF hospitalization, HR (95% CI)
<10	4.37 (3.51-5.43)	3.74 (3.09-4.53)
10 to <12	1.83 (1.51-2.22)	1.79 (1.53-2.10)
12 to <13	1.00 (reference)	1.00 (reference)
13 to <15	0.83 (0.67-1.03)	0.81 (0.68-0.97)
15 to <17	0.83 (0.64-1.09)	0.80 (0.64-1.00)
≥17	0.59 (0.31-1.12)	0.72 (0.47-1.12)

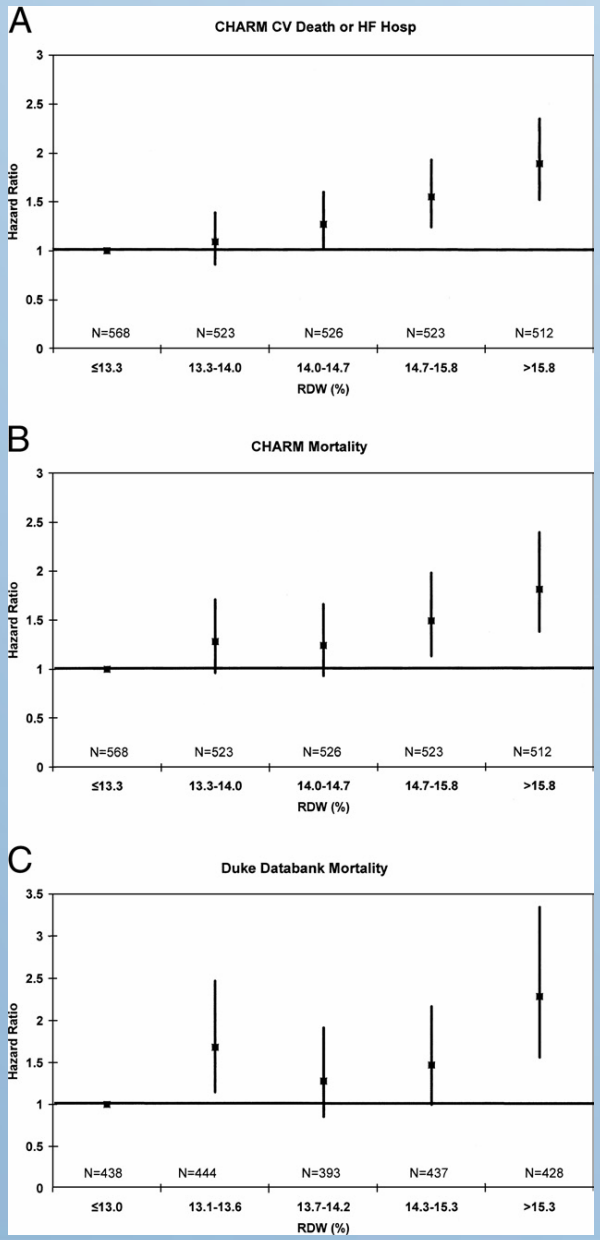
"…An additional 21% of patients who were not anemic at baseline developed anemia at some point in their subsequent clinical course. We found that longitudinal characterization of anemia has even greater prognostic significance than baseline measures…"



Trajectory group	n (%)	Mortality, HR (95% CI)	Mortality or HF hospitalization, HR (95% CI)
1—Persistently nonanemic	660 (40%)	1.00 (reference)	1.00 (reference)
2—Transient recovery	132 (8%)	1.01 (0.69-1.48)	0.95 (0.71-1.29)
3—Persistent decline	232 (14%)	1.54 (1.16-2.05)	1.60 (1.29-1.99)
4—Early recovery	105 (6%)	0.85 (0.56-1.29)	0.98 (0.70-1.36)
5—Late recovery	120 (7%)	0.89 (0.57-1.41)	1.26 (0.93-1.71)
6—Persistently anemic	410 (25%)	1.65 (1.27-2.14)	1.61 (1.32-1.96)

Peterson PN. Am Heart J 2010;159:81-9

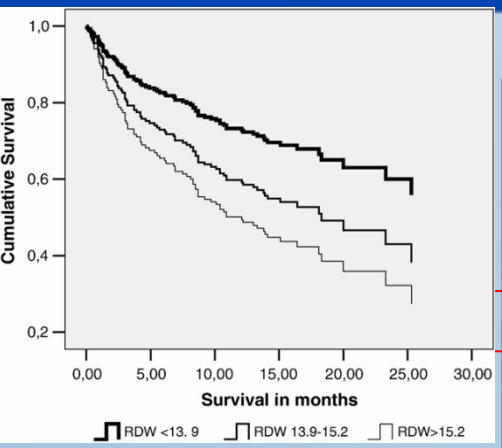
Pronóstico en la IC: RDW



"... higher red cell distribution width (RDW) showed the greatest association with morbidity and mortality (HR 1.17 per 1-SD increase, p 0.001)..."

Felker GM et al. J Am Coll Cardiol 2007; 50:40-7

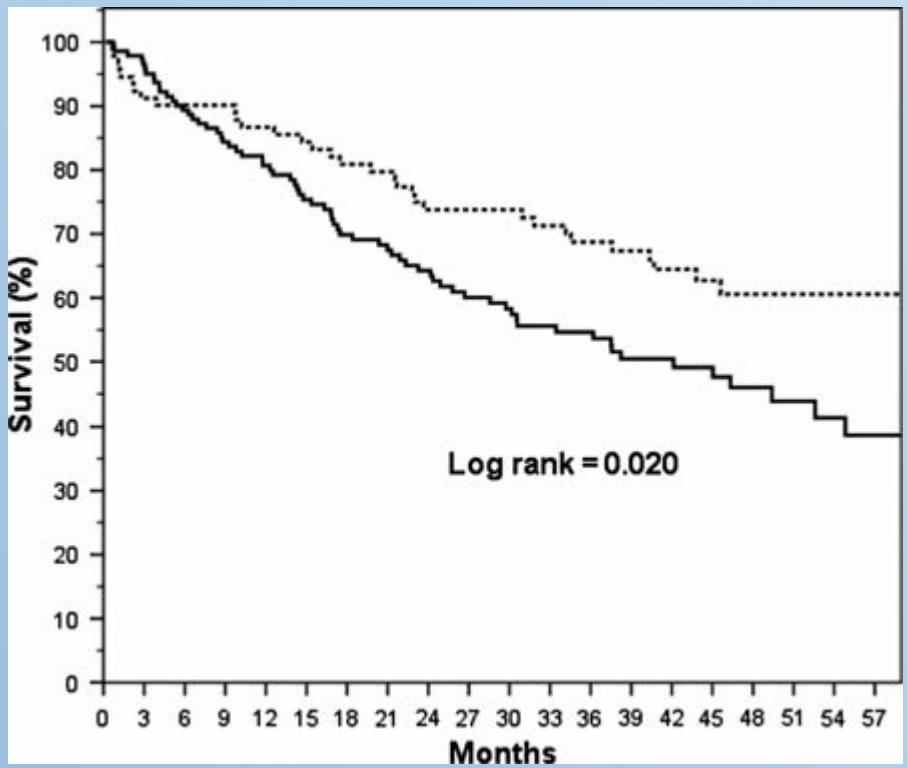
Pronóstico en la IC: RDW

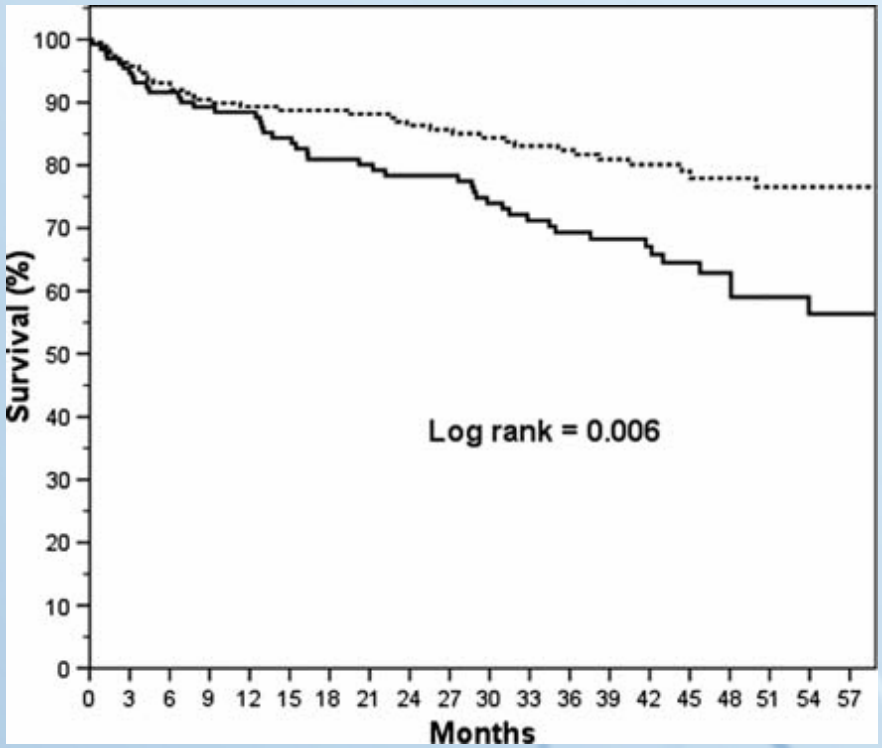


	RDW ≤13.9%		RDW 13.9%-15.2%		RDW ≥15.2%		
	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	P*
Markers of ineffective erythropoiesis							
Iron (μmol/L)	15.4	10.9-19.4	13	9-16.9	10	6.64-13.7	<.0001
Ferritin (μg/L)	140.7	94.6-259.4	135.8	66.5-220.7	98.8	57.6-157.9	.01
Transferrin (g/L)	2.7	2.4-3.0	2.7	2.4-3.1	2.8	2.4-3.2	.53
Transferrin sat. (%)	23	18-28	18.5	13.5-24	16	10-20	<.0001
Soluble transferrin receptor (nmol/L)	2.3	2.7-4.3	4.8	5.9-7.8	5.9	4.7-7.2	<.0001
EPO (U/mL)	8.9	4.9-15.2	12.6	7.4-18.9	14.1	7.9-25.7	.002
Markers of inflammation							
IL-6 (pg/mL)	6.62	3.88-12.35	10.89	6.89-14.18	14.59	8.52-25.32	.0001
TNF-α (pg/mL)	2.03	1.07-3.62	2.37	1.68-3.47	2.78	1.73-4.75	.077
TNF-RI (ng/mL)	4.61	3.42-6.69	6.64	3.81-10.37	6.93	4.22-10.68	.0007
TNF-RII (ng/mL)	3.40	2.34-4.57	4.42	3.40-5.78	5.07	3.75-6.68	<.0001
Prealbumin (g/L)	0.26	0.21-0.30	0.21	0.17-0.27	0.18	0.14-0.24	<.0001
CRP (mg/L)	4.2	1.7-10.7	8.36	3.6-15.3	6.7	3.9-15.9	.01
Markers of damaged renal function							
GFR (mL/1.73 m^2 per min)	75	59-95	65.5	45-81	55	38-77.5	<.0001
Creatinine (μmol/L)	91	75-105	97.5	78-142	111.5	84.5-165.5	.0045
Markers of nutritional deficiency							
Albumin (g/L)	43	40.5-45	41	39-44	39	36-42	<.0001
Total protein (g/L)	72	67-76	73	69-78	70	62.76	.052
Total cholesterol (mmol/L)	4.21	3.81-5.31	4.48	3.89-5.11	3.62	2.95-4.14	<.0001

Förhécz Z. Am Heart J 2009;158:659-66

Pronóstico en la IC: RDW



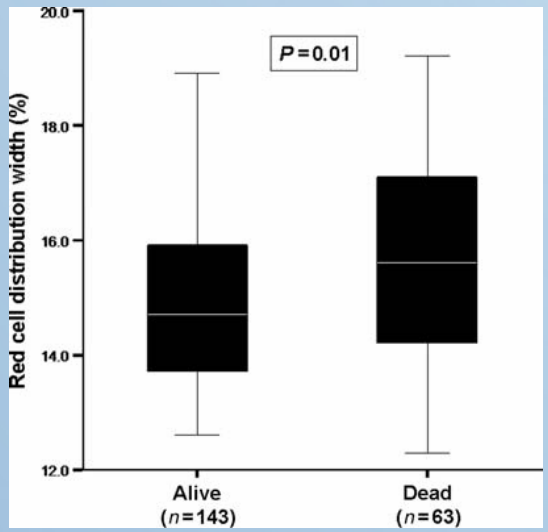


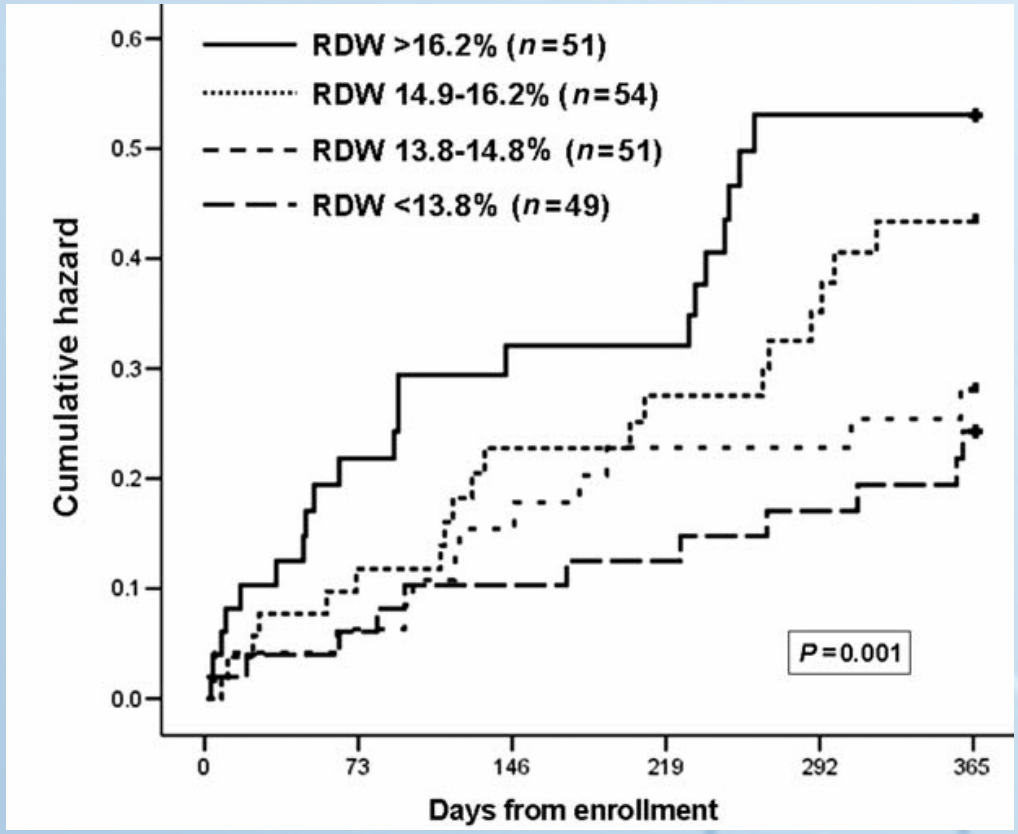
Anaemic patients (n ¼ 263): Kaplan–Meier survival curves according to red blood cell distribution width values above (continuous line) or below (dotted line) the median (14.4%).

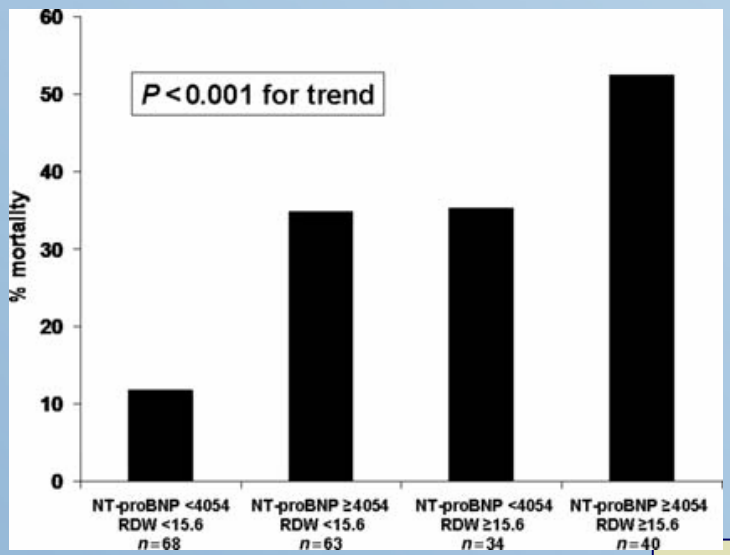
Non-anaemic patients (n ¼ 365): Kaplan–Meier survival curves according to red blood cell distribution width values above (continuous line) or below (dotted line) the median (14.4%).

Pascual Figal DA et al. Eur J Heart Fail 2009; 11:840-6

Pronóstico en la IC: RDW



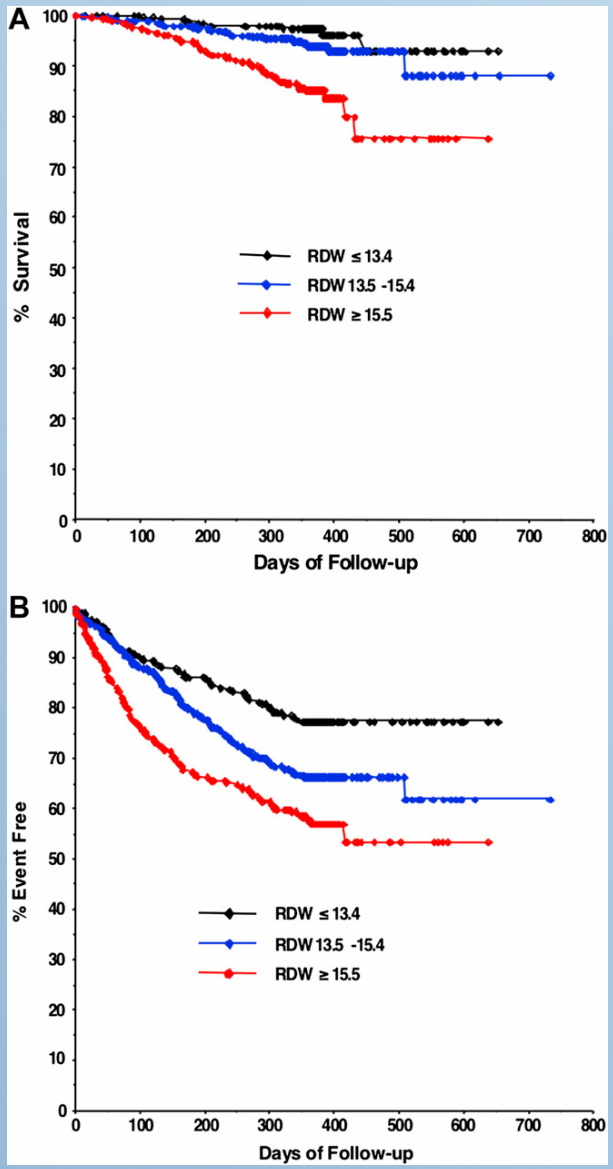




1 year after presentation with acute heart failure

van Kimmenade R.R.J et al. Eur J Heart Fail 2010; 12:129-36

Pronóstico en la IC: RDW



STAMINA-HFP + UNITE-HF

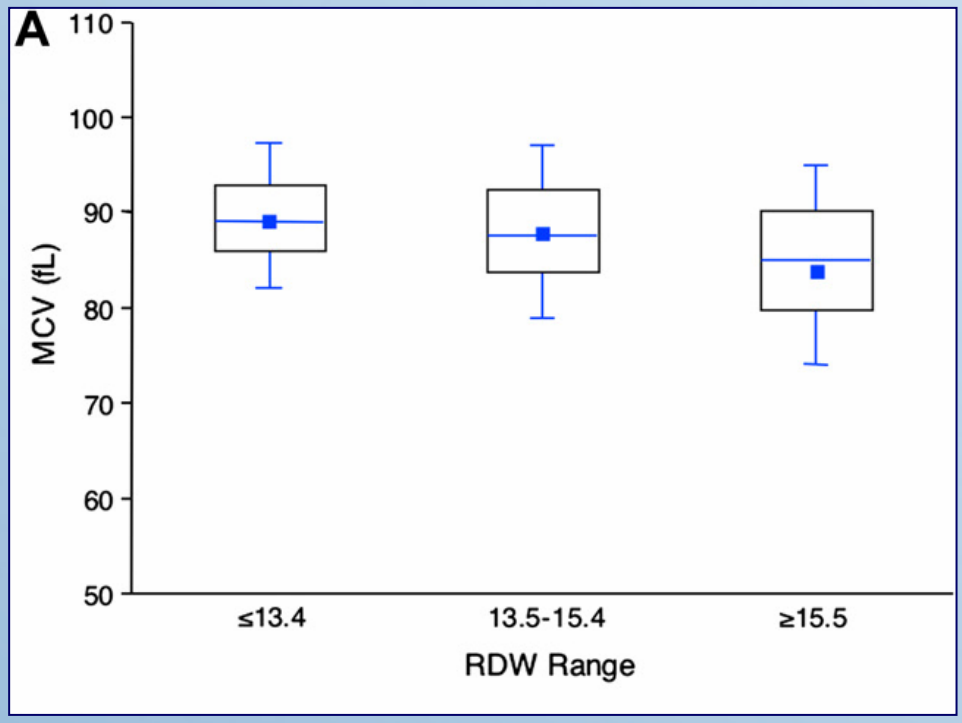
↑ 1% in RDW :

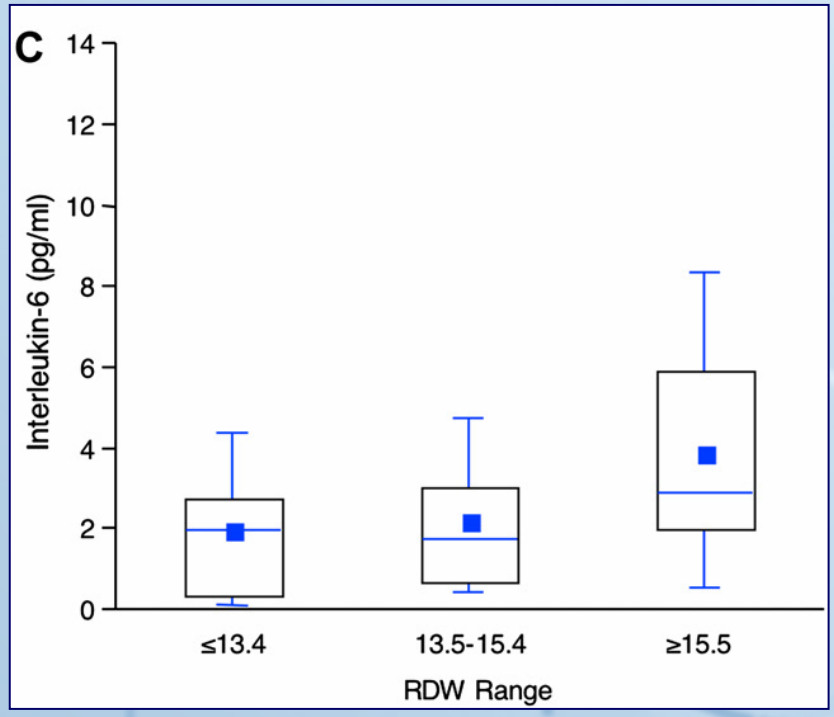
- HR mortality 1.06 (1.01-1.12)
- HR hospitalization or mortality 1.06 (1.02-1.10)

↑ RDW correlated with decreasing hemoglobin, increasing interleukin-6 and impaired iron mobilization

Allen LA et al. J Cardiac Fail 2010; 16:230-8

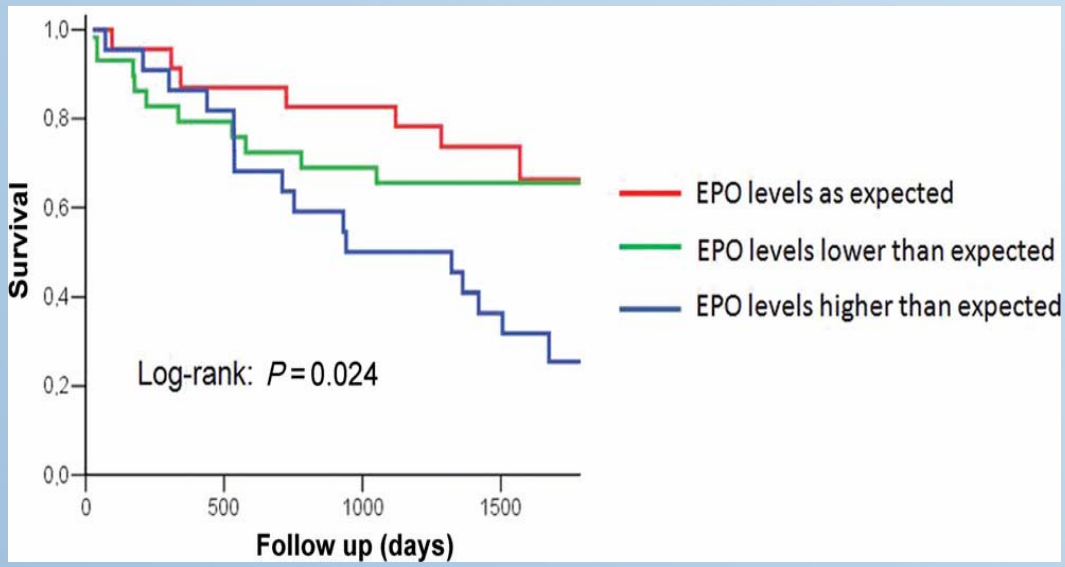
Pronóstico en la IC: RDW





Allen LA et al. J Cardiac Fail 2010; 16:230-8

Pronóstico niveles EPO en IC



Log (EPO) P = 4.46 – (0.74 * Hb)

Ratio O/P < 0.916 = lower production

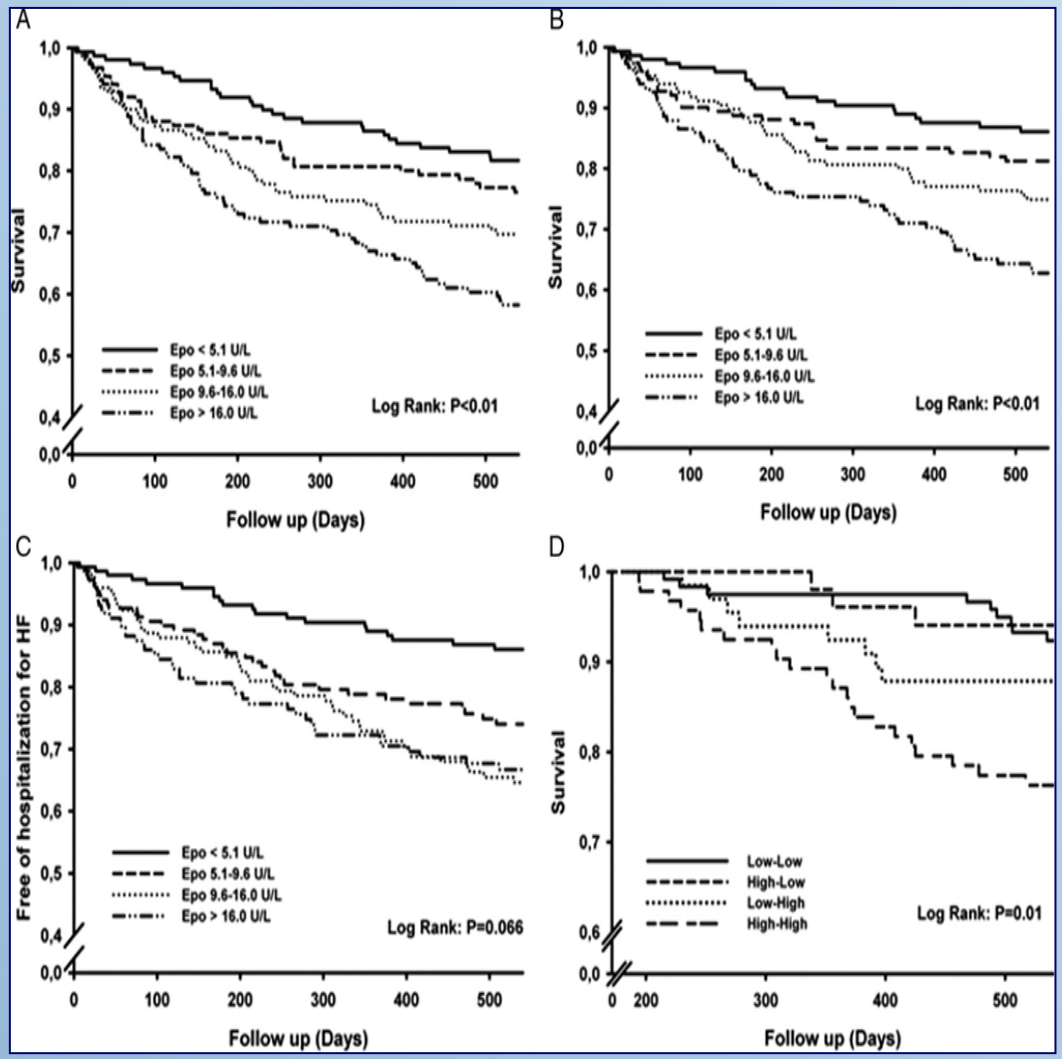
Ratio O/P > 1.087 = higher production

N= 74
Age 73 ± 8
68% male
92% class III
Mortality 47%
Median follow-up 4.9 years

Variable	Multivariable		
	HR	CI	P
O/P ratio (%)	1.020	1.004–1.036	0.012
Sex (male)	2.541	1.089–5.805	0.031
cGFR (mL/min/1.73 m^2)	0.958	0.931–0.985	0.003
Age (10 years)	1.335	0.817–2.182	0.249
ntproBNP (10 pmol/L)	1.001	0.996–1.005	0.814
Haemoglobin (g/dL)	0.748	0.367–1.521	0.422

van der Meer P et al. Eur Heart J 2008; 29: 1510-5

Pronóstico niveles EPO en IC



EPO baseline (at 6 months in 330)
N = 605
Age 71 ± 11
62% male
92% class III
Mortality 47%
Median follow-up 4.9 years

Conclusions: "… In anemic HF patients, the majority had a low observed/predicted ratio. However, a higher observed/predicted ratio may be related to an independent increased mortality risk.

Log (EPO) P = 4.46 – (0.274* Hb)

Ratio O/P < 0.916 = lower production

Ratio O/P > 1.087 = higher production

Belonje AM. *Circulation*. 2010; 121:245-51

Anemia en la IC: Transfusión

Mortality	BT		P	OR/HR* (95% CI)	P
	No. (n = 2169)	Yes (n = 166)		BT vs no BT	
During hospitalization	113 (5.2%)	18 (10.8%)	.002	0.48 (0.21-1.11)	.08
30 d	183 (8.5%)	18 (11.0%)	.27	0.29 (0.13-0.64)	.02
1 y	616 (28.5%)	65 (39.6%)	.003	0.74 (0.50-1.09)	.12
4 y	1284 (59.5%)	114 (69.5%)	.01	0.86 (0.64-1.14)	.29

*Odds ratio (OR) by logistic regression analysis for in-hospital and 30-day mortality and hazard ratios (HR) by Cox proportional hazard model for 1- and 4-year mortality with adjustment for age, sex, hypertension, diabetes mellitus, current smoking, concurrent ACS, heart rate, systolic blood pressure, left ventricular ejection fraction, estimated glomerular filtration rate, and propensity score.

Table III. Mortality based on BT status

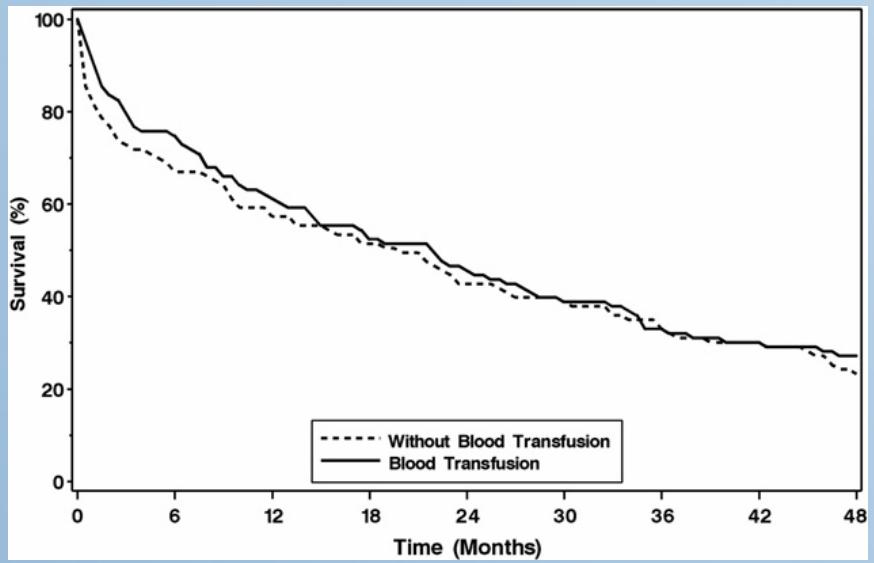


Figure 1. Kaplan-Meier survival curves of 103 matched pairs of patients who did or did not receive BT.

Garty M et al. Am Heart J 2009;158:653-8

Anemia en la IC: Ensayos con Fe

Autor/año	método	N Fe iv	N control	edad	FEVI	Hb	Obs. días	resultados
Bolger 2006	A	16	-	68±11,5	26	11,2	92	↑ Hb a 12,6 g/dl Mejoría NYHA - 14 en el MLFHQ + 44 m Test 6 mn
Toblli 2007	DC	20	20	60-94	31	10,3	180	↑ Hb (11,8 vs 9,8 g/dl) ↓ 333,4 pg/ml Nt-ProBNP ↓ PCR (2,3 vs 6,5 mg/dl) ↑ FEVI (35,7 vs 28,8 %) Mejoría NYHA (2 vs 3,3) ↓ 18 en el MLFHQ + 56 m Test 6 mn
Okonko DO 2008	CS	24	11	64 ± 13				↑ Hb (13 vs 12,6 g/dl) Mejoría NYHA (2,1 vs 2,6) ↑ O2 tisular
Usmanov RI 2008	A	32	0			< 11		↑ Hb en 3 g/dL Mejoría NYHA si clase III ↑ FEVI si clase III
Anker DA 2009	CS	304	155	68 ± 10		11,9	182	↑ Hb (13 vs 12,5 g/dl) + 7 en el KCCQ + 35 m Test 6 mn Mejoría NYHA

Anemia en la IC: Ensayos con Fe

Criterio inclusión: ferritina

Anemia en la IC: Ensayos con Fe

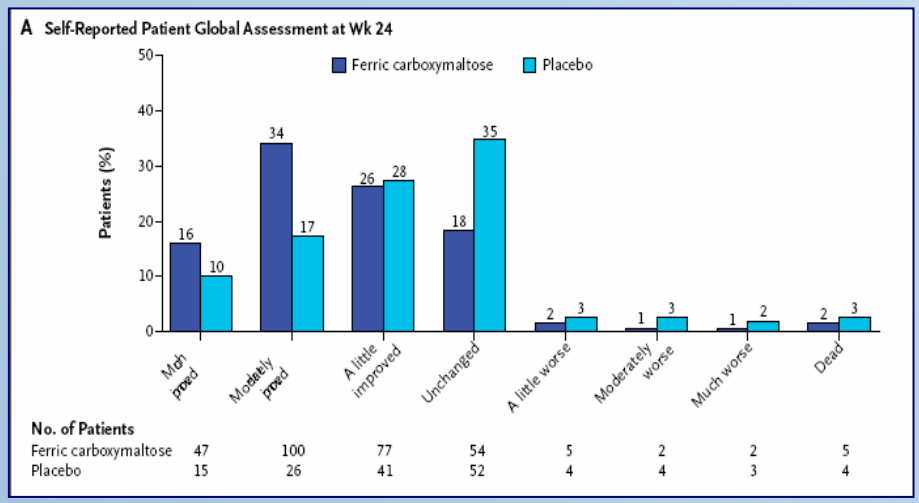
Study Design (2/2)

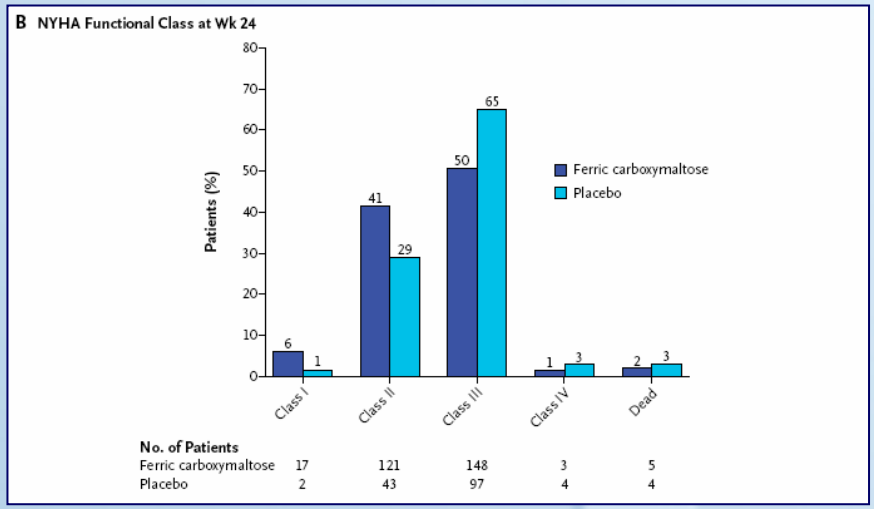
FAIR-HF

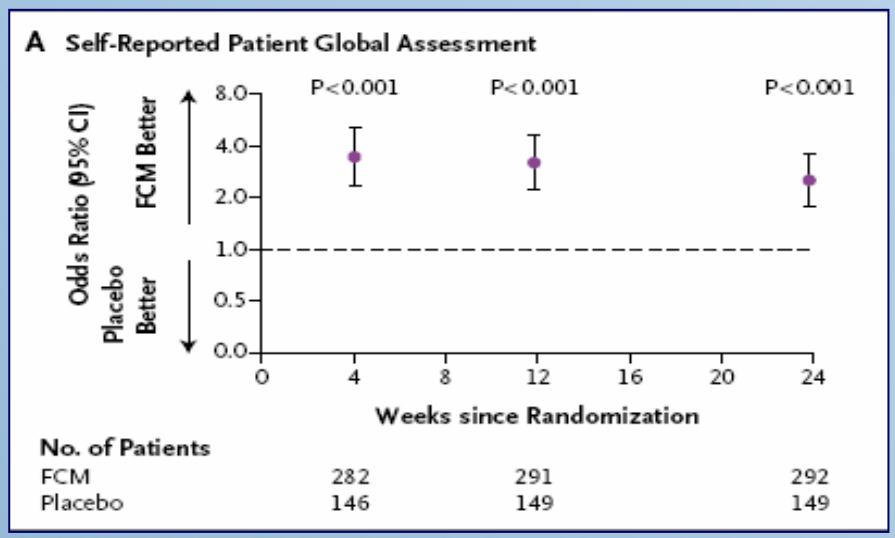
- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤40% (NYHA II) or ≤45% (NYHA III)
  - Hb 95–135g/L
  - Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%
- **Main exclusion criteria:**
  - Uncontrolled hypertension, inflammation (CrP >20 mg/L)
  - Significant liver or renal dysfunction
- **Treatment adjustment algorithm:**
  - Interruption: Hb >160 g/L or ferritin >800 µg/L or ferritin >500 µg/L, if TSAT >50%
  - Restart: Hb <160 g/L and serum ferritin <400 µg/L and TSAT <45%
- **Blinding:**
  - Clinical staff: unblinded and blinded personnel
  - Patients: usage of curtains and black syringes for injections

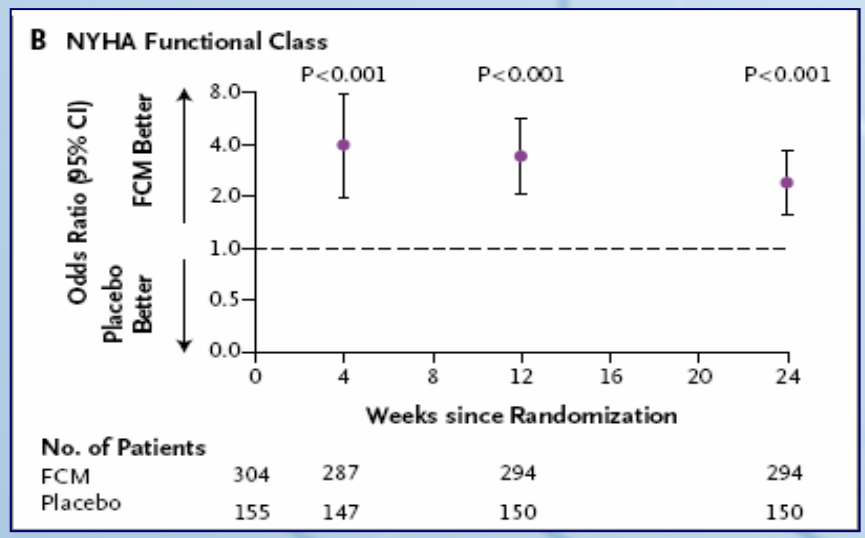
Anker *et al, Eur J Heart Failure* 2009;11:1084-1091

Anemia en la IC: Ensayos con Fe



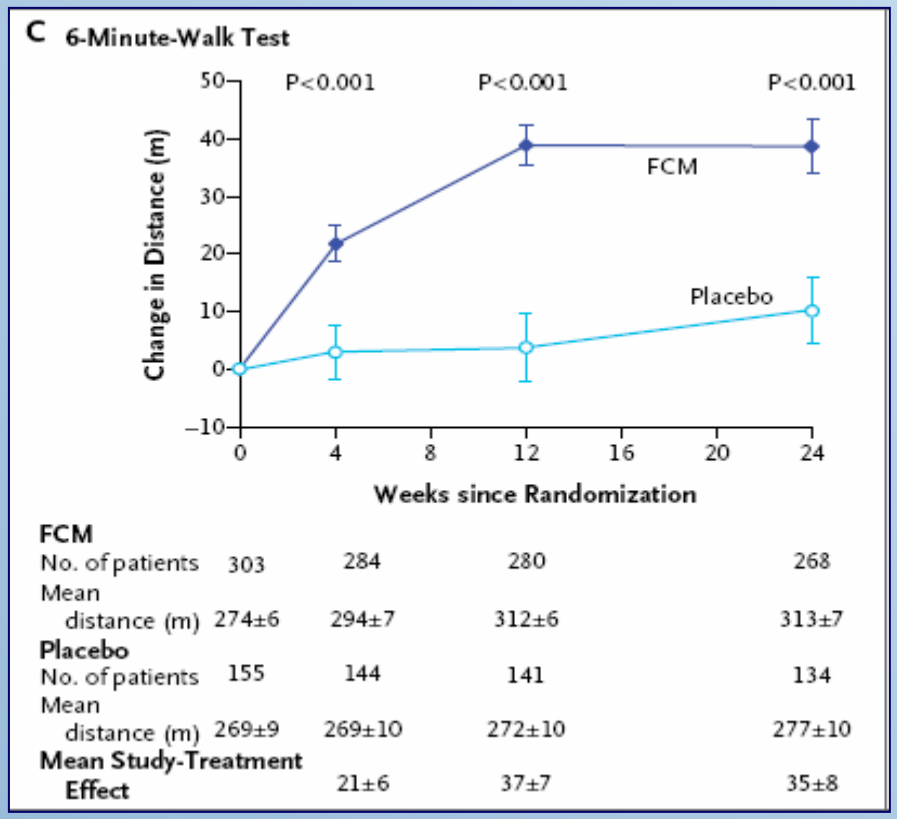




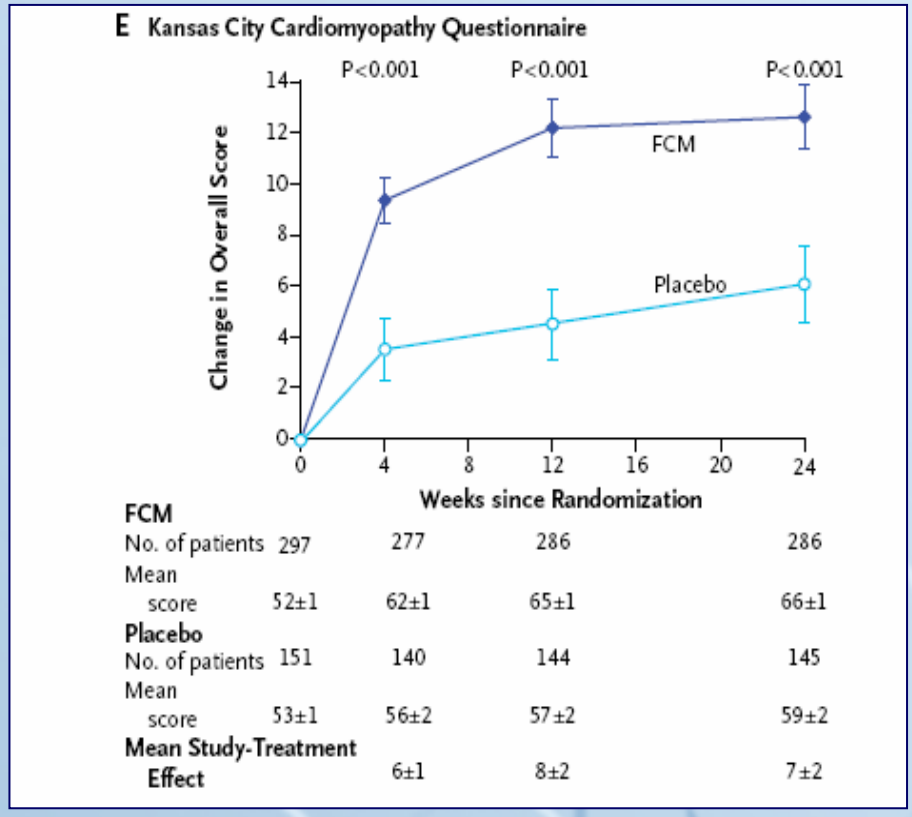


Anker SD. Ferric car-boxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009;361. DOI: 10.1056/NEJMoa0908355.

Anemia en la IC: Ensayos con Fe



FCM				
No. of patients	303	284	280	268
Mean distance (m)	274±6	294±7	312±6	313±7
Placebo				
No. of patients	155	144	141	134
Mean distance (m)	269±9	269±10	272±10	277±10
Mean Study-Treatment Effect		21±6	37±7	35±8



FCM				
No. of patients	297	277	286	286
Mean score	52±1	62±1	65±1	66±1
Placebo				
No. of patients	151	140	144	145
Mean score	53±1	56±2	57±2	59±2
Mean Study-Treatment Effect		6±1	8±2	7±2

Anker SD. Ferric car-boxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009;361. DOI: 10.1056/NEJMoa0908355.

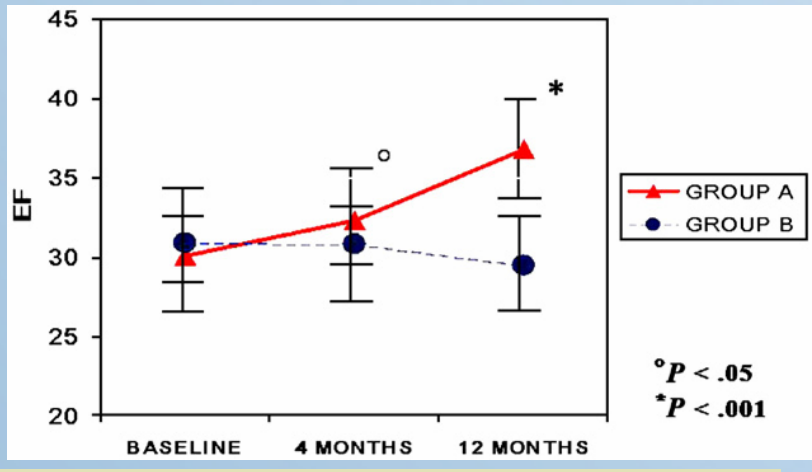
Ensayos con EPO en IC

autor	año	diseño	N tratº	N control	Tratº	Tº (dias)	Objetivo + relevante
Silverberg DS	2000	abierto	26		EPO α + Fe IV	216	↓NYHA 2,6 vs 3,6
Silverberg DS	2001	R - A	16	16	EPO α + Fe IV	246	↓dias hospital 2,9 vs 15,6
Silverberg DS	2003	abierto	179		EPO α + Fe IV	354	↓ NYHA 3,9 vs 2,5
Mancini DM	2003	R - DC	15	8	EPO α + Fe or	90	↑ VO2 12,7 vs 9,5
Silverberg DS	2003	abierto	40		EPO α + Fe IV	522	↑ FEVI 41 vs 31
Silverberg DS	2005	abierto	78		EPO ß + Fe IV	621	↓ NYHA 3,7 vs 2,5
van Veldhuisen DJ	2007	R - DC	110	55	darbepoetina + Fe or	87	↑ KCCQ 8 vs 4,9
Ponikowski P	2007	R - DC	19	22	darbepoetina + Fe or	189	↑VO2 0,5 ml/kg
Palazzuoli A	2008	R - DC	26	25	EPO ß + Fe or	365	↑ FEVI 37 vs 30%
Parissis JT	2008	R - CS	21	11	darbepoetina + Fe or		
Ghali JK	2008	R - DC	162	157	darbepoetina + Fe or	371	↓ mortalidad
Comín J	2009	abierto	27	38	EPO ß + Fe IV	450	↓ ingresos 26% vs 76%
Total			719	332			

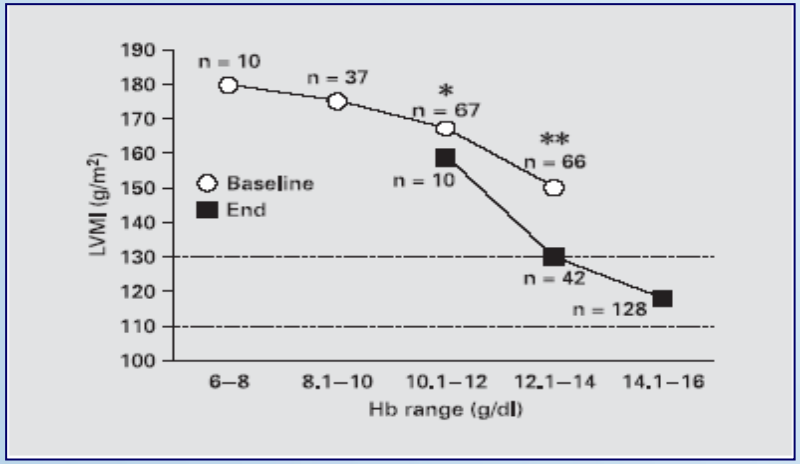
Ensayos con EPO

autor	año	N tratº	N control	Tratº	Tº dias	Objetivo + relevante
Silverberg DS	2001	16	16	EPO α+Fe IV	246	↓dias hospital 2,9 vs 15,6
Mancini DM	2003	15	8	EPO α+Fe or	90	↑ VO2 12,7 vs 9,5
van Veldhuisen DJ	2007	110	55	darbepoetina+Fe or	87	↑ KCCQ 8 vs 4,9
Ponikowski P	2007	19	22	darbepoetina+Fe or	189	↑VO2 0,5 ml/kg
Palazzuoli A	2008	26	25	EPO ß+Fe or	365	↑ FEVI 37 vs 30%
Parissis JT	2008	21	11	darbepoetina+Fe or	90	↑ FEVI 31 vs 25% ↑ Test 6 mn 129 m
Ghali JK	2008	162	157	darbepoetina+Fe or	371	↓ mortalidad
Total		369	294	*media*	*205*	

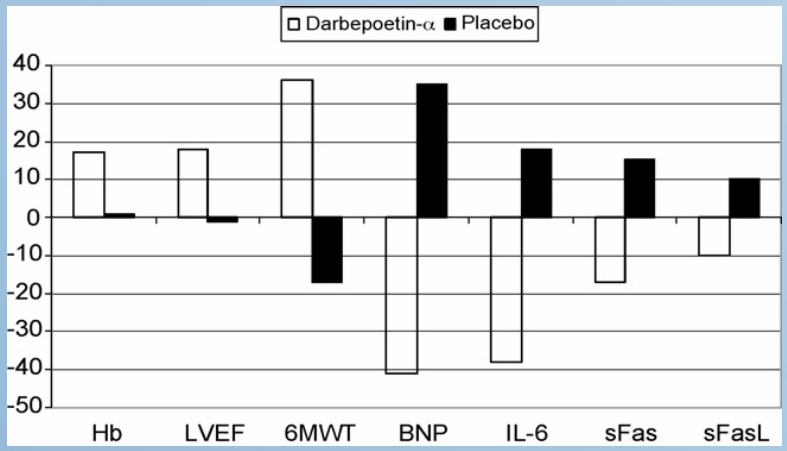
Ensayos con EPO



Palazzuoli A. Am Heart J 2006; 152:1096.e9-.e15



Hampl H. Am J Nephrol 2005;25:211–220

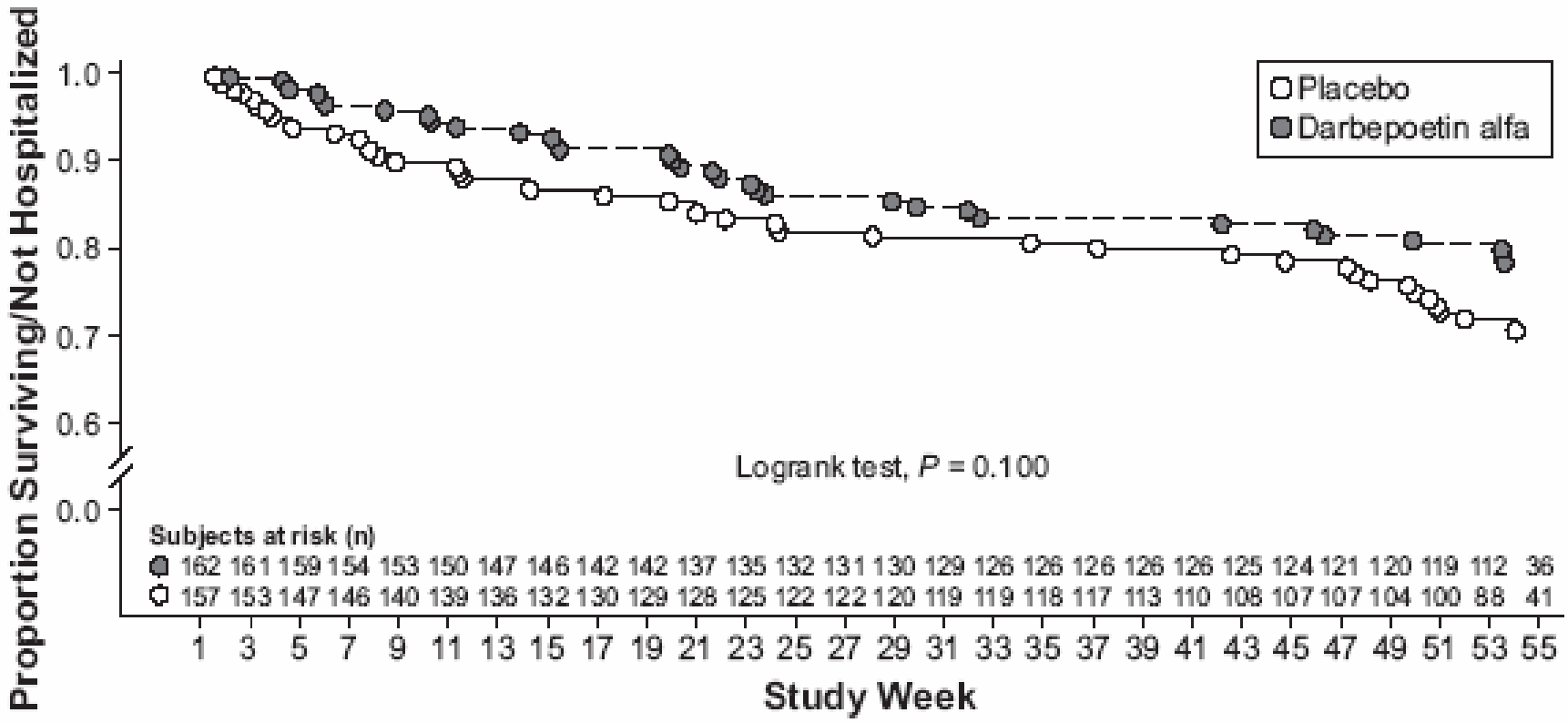


Kourea K. Atherosclerosis. 2008 Jul;199:215-21

	Darbepoetin α (n = 21)		Placebo (n = 11)		Interaction	
	Baseline	Final	Baseline	Final	F	P
LV end-diastolic diameter (mm)	67.6 ± 9	65.8 ± 8	63.9 ± 6	65.9 ± 7	4.860	.035
LV end-systolic diameter (mm)	57.8 ± 10	55.1 ± 9.5	55.1 ± 7	56.9 ± 6	12.126	.002
LVEF (%)	26 ± 6	31 ± 6	28 ± 6	25 ± 5	22.001	<.001
LV end-diastolic volume (mL)	241 ± 74	227 ± 65	210 ± 46	226 ± 54	4.549	.041
LV end-systolic volume (mL)	172 ± 73	154 ± 64	151 ± 44	162 ± 39	9.298	.005
LV ESWS (g/cm²)	172 ± 83	132 ± 41	135 ± 33	135 ± 26	4.934	.034
PWs (cm)	1.16 ± 0.34	1.34 ± 0.34	1.26 ± 0.19	1.29 ± 0.20		NS
MAPSE (cm)	0.96 ± 0.24	1.09 ± 0.36	1.05 ± 0.43	0.90 ± 0.41	6.710	.015
E (m/s)	1.00 ± 0.36	0.96 ± 0.39	0.90 ± 0.4	0.95 ± 0.33		NS
A (m/s)	0.50 ± 0.27	0.51 ± 0.19	0.74 ± 0.48	0.65 ± 0.41		NS
E/A	2.34 ± 1.18	2.14 ± 1.37	1.77 ± 1.26	2.07 ± 1.35		NS
E, deceleration time (ms)	159 ± 59	193 ± 76	177 ± 81	163 ± 55		NS
IVRT (ms)	96 ± 20	102 ± 23	106 ± 36	95 ± 25	4.909	.035
e (m/s)	0.08 ± 0.02	0.08 ± 0.03	0.07 ± 0.03	0.06 ± 0.03		NS
E/e	13.2 ± 7	13.7 ± 8.1	13.6 ± 8	19.7 ± 12.3	7.833	.009
RV systolic pressure (mm Hg)	51 ± 15	44 ± 12	48 ± 14	49 ± 13	7.715	.009
RVEF (%)	45 ± 9	51 ± 9	51 ± 13	46 ± 10	9.264	.005
TAPSE (cm)	1.4 ± 0.3	1.6 ± 0.3	1.6 ± 0.4	1.40 ± 0.3	9.264	.005
Flow propagation velocity (cm/s)	29 ± 5	32 ± 5	29 ± 6	31 ± 6		NS

Parissis JT Am Heart J 2008;155:751.e1-751.e7

Ensayos con EPO



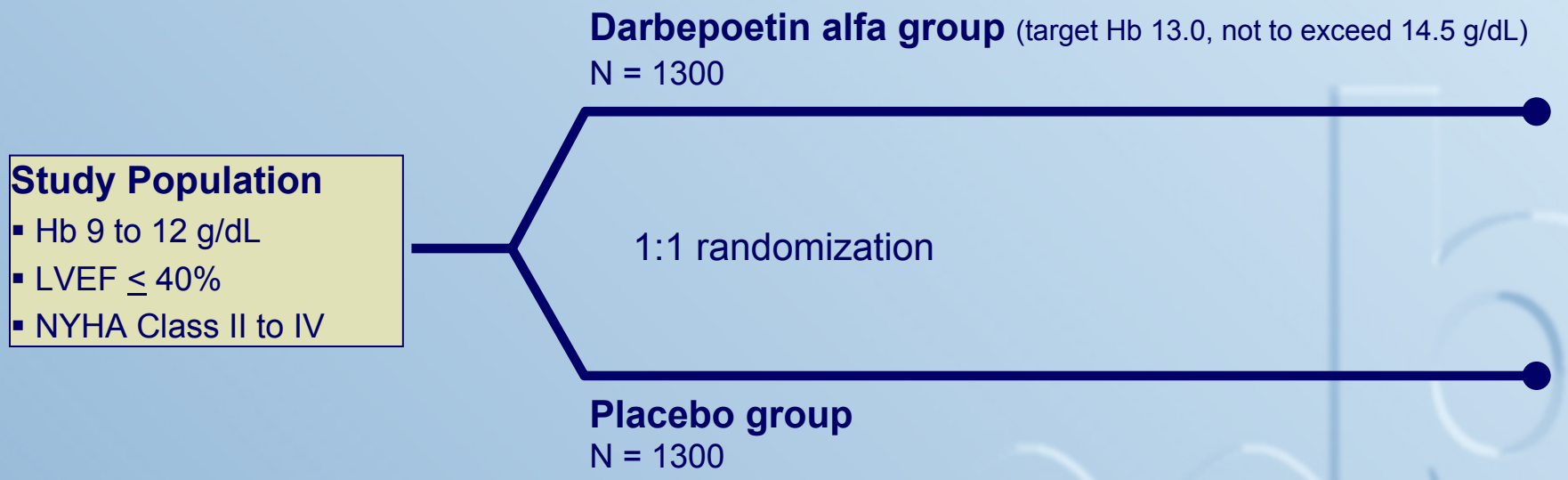
Hazard ratio (95% CI) darbepoetin alfa (N = 162) vs placebo (N = 157)	
All-cause mortality or first HF-related hospitalization	0.68 (0.43, 1.08)
All-cause mortality	0.56 (0.27, 1.19)
HF-related hospitalization	0.74 (0.44, 1.26)

STAMINA-HeFT. 2008;117: 526-35

RED-HF™ Trial: Hypothesis And Study Design

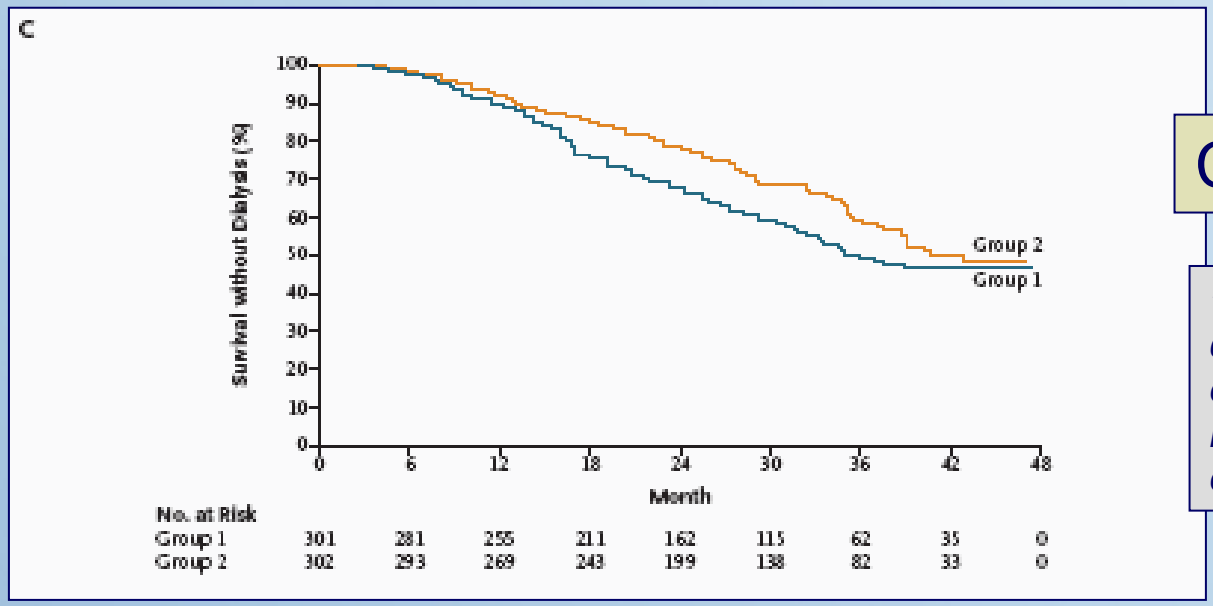
Hypothesis:

Treatment of anemia with darbepoetin alfa in subjects with symptomatic left ventricular systolic dysfunction and anemia decreases the risk of all-cause mortality or hospital admission for worsening HF



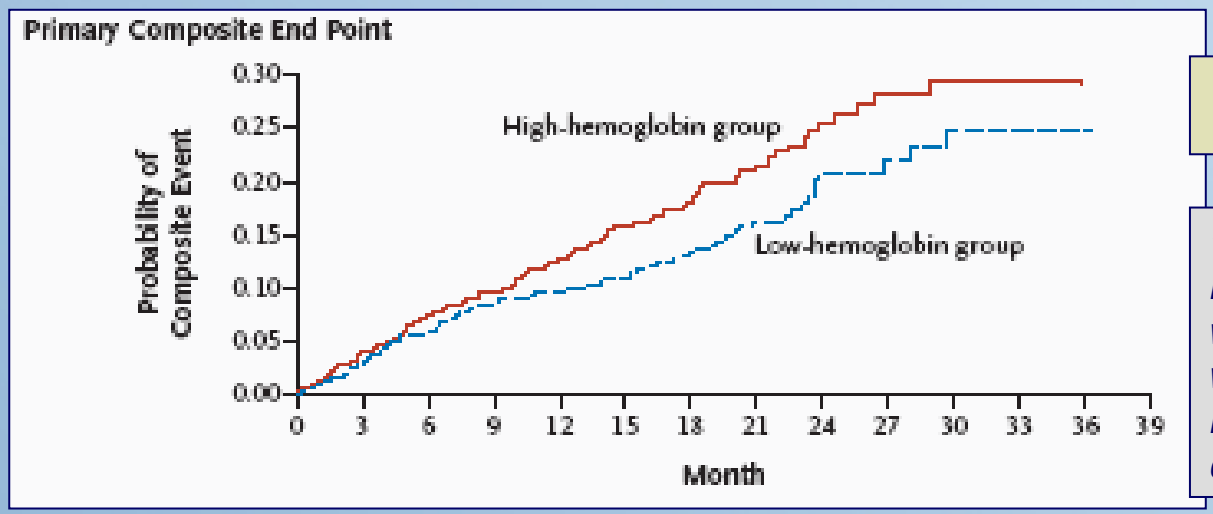
The primary endpoint is the time to death from any cause or first hospital admission for worsening HF, whichever occurs first. The study will complete when approximately 1150 subjects experience a primary endpoint.

Ensayos con EPO en IRC



CREATE

"In patients with chronic kidney disease, early complete correction of anemia does not reduce the risk of cardiovascular events."



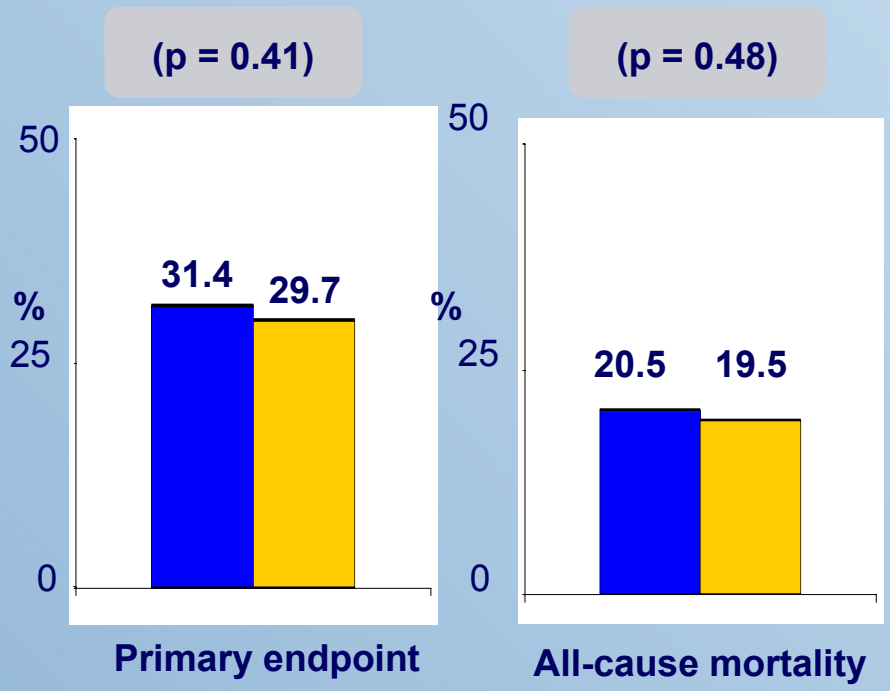
CHOIR

"The use of a target hemoglobin level of 13.5 g /dl (as compared with 11.3 g/dl) was associated with increased risk and no incremental improvement in the quality of life."

Ensayos con EPO en IRC

Trial design: Patients with chronic kidney disease, diabetes, and anemia were randomized to receive either darbepoetin alfa or placebo. Patients were followed up for a mean period of 29.1 months.

TREAT



Results

- Primary outcome (death, MI, CHF, unstable angina, stroke): 31.4% vs. 29.7%
- Mortality: 20.5% vs. 19.5%; MI: 6.2% vs. 6.4%, p = 0.73; stroke: 5% vs. 2.6%, p < 0.001; ESRD: 16.8% vs. 16.3%, p = 0.83
- Diastolic BP, venous, arterial thromboembolic events ↑ in darbepoetin alfa arm (p < 0.05)

Conclusions

- Use of darbepoetin alfa in anemic patients at high risk for CV and renal events is not associated with superior outcomes
- Potentially associated with a higher risk of stroke, thromboembolic episodes, and hypertension; argues against its routine use

Pfeffer MA, et al. N Engl J Med 2009;Oct 30:Epub

Insuficiencia Cardiaca y anemia. Apuntes

- La anemia es muy frecuente en la IC
- Señala peor pronóstico
- Siempre tratamos la anemia si no hay IC
- Al corregirla hay mejoría en algunos parámetros
- La EPO no está exenta de riesgos
- No hay guía de tratamiento actual

ALGORITMO TRATAMIENTO ANEMIA -IC