BSA Hospital Municipal

SESIÓN CONJUNTA SEC/SEMI

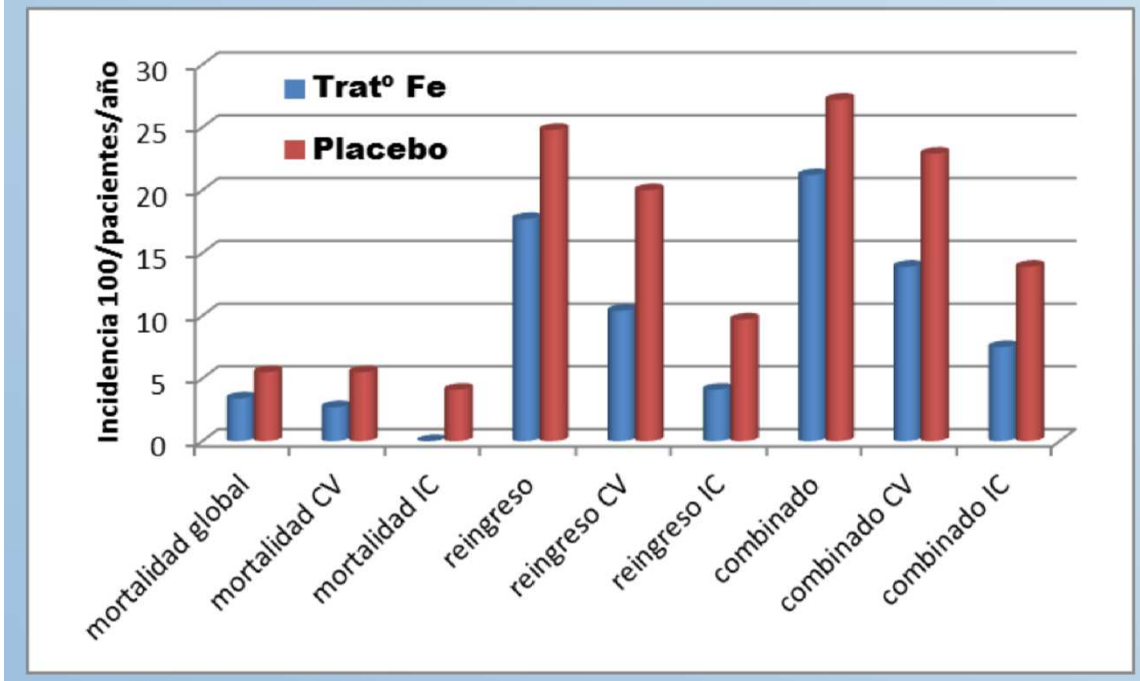
NUEVAS EVIDENCIAS EN EL TRATAMIENTO DE LA IC Y SUS COMORBILIDADES

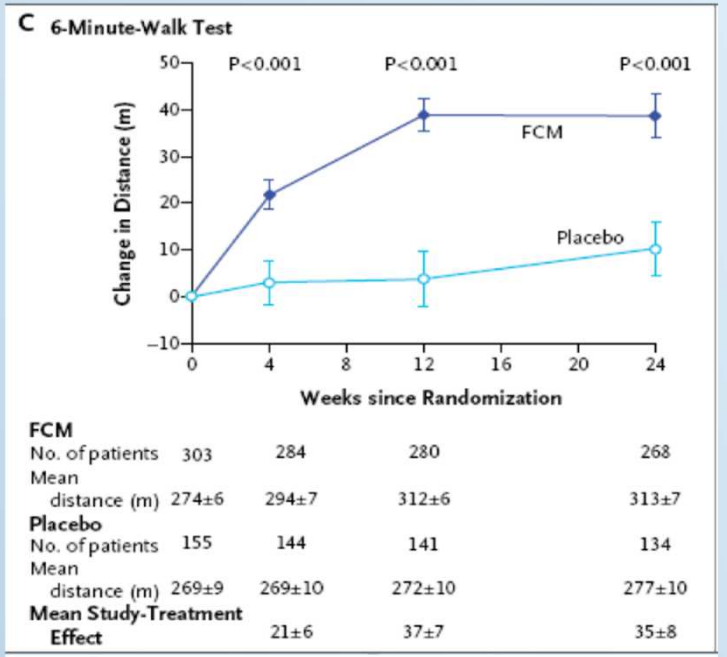
Anemia

Dr. Jordi Grau Amorós

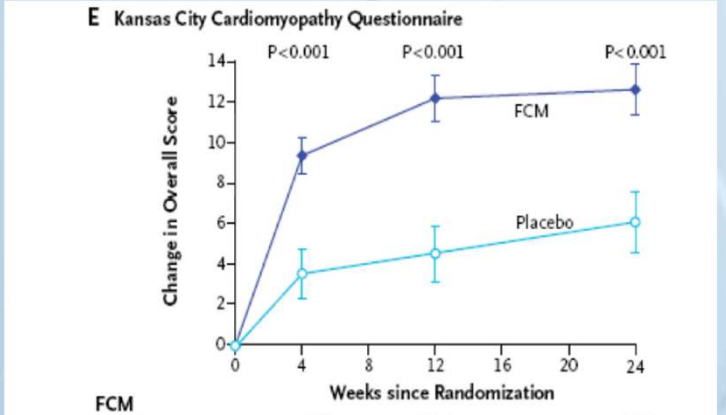
Badalona Serveis Assistencials

Estudio FAIR-HF





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

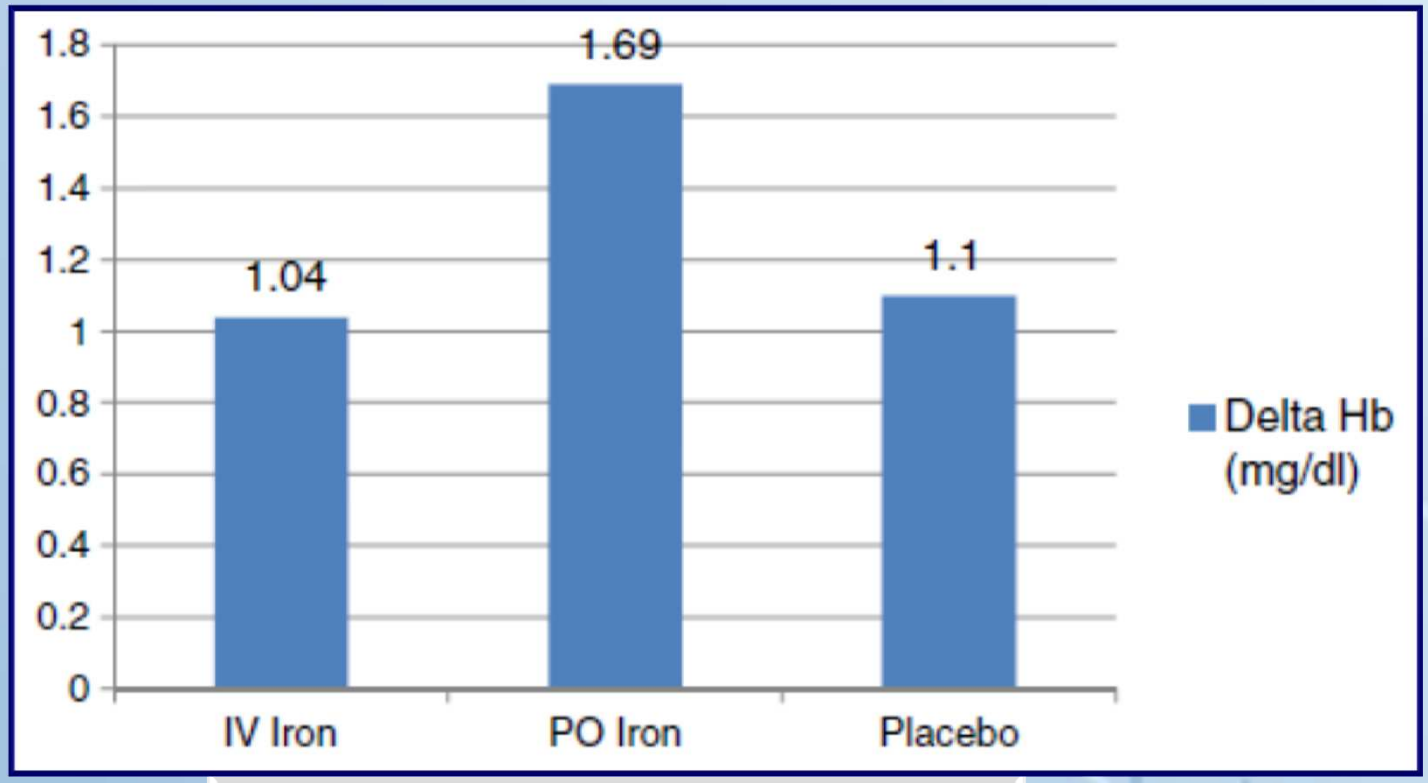


FCM				
No. of patients	297	277	286	286
Mean score	52±1	62±1	65±1	66±1
Placebo				
No. of patients	151	140	144	145
Mean score	53±1	56±2	57±2	59±2
Mean Study-Treatment Effect		6±1	8±2	7±2

Anker SD. N Engl J Med 2009;361:2436.

Tratamiento Fe EV vs OR

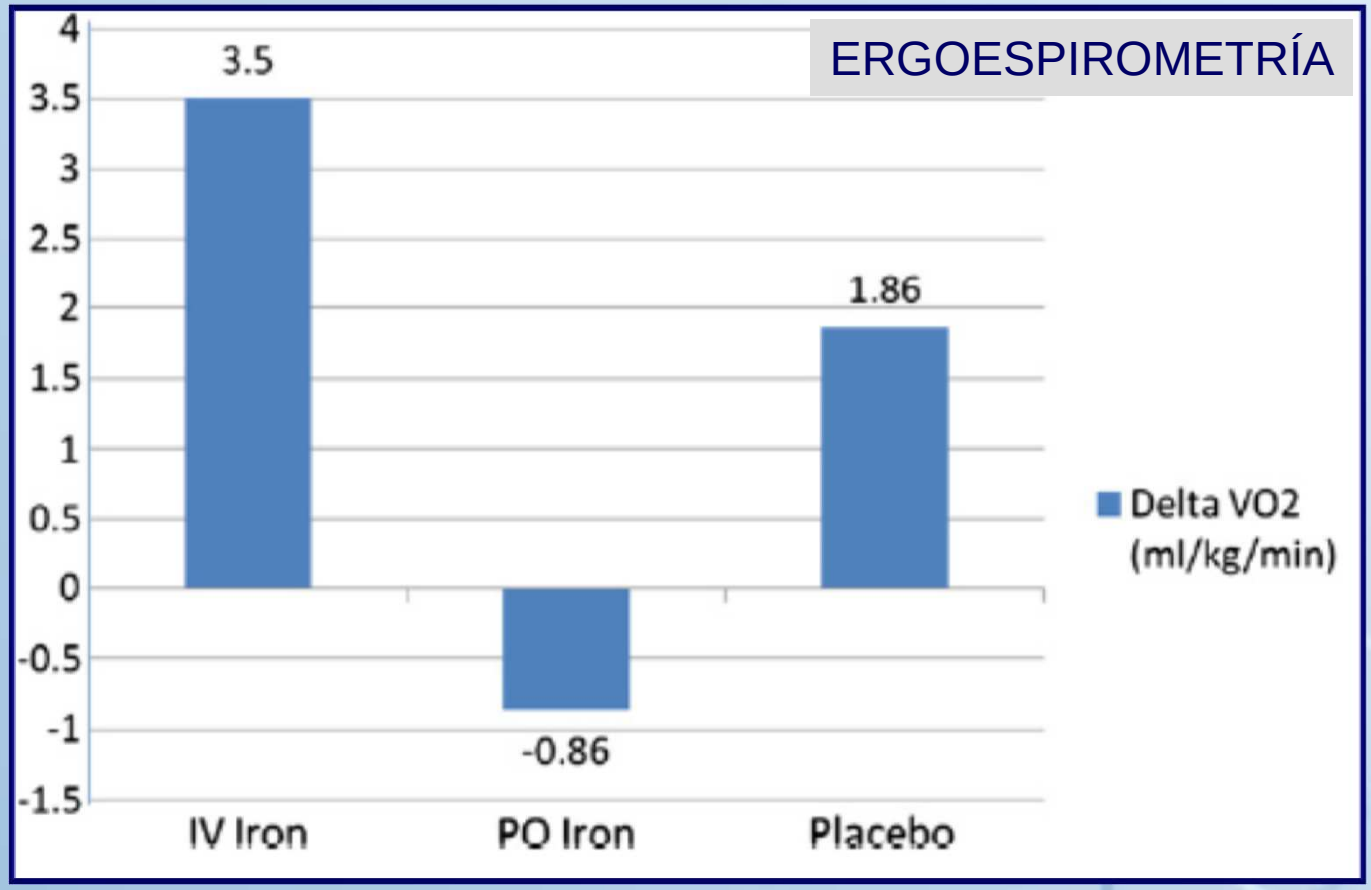
Fe oral corrige mejor la anemia



8 **7** **5**

L. Beck da Silva. Int J Cardiol 2013; 68:3439

Tratamiento Fe EV vs OR

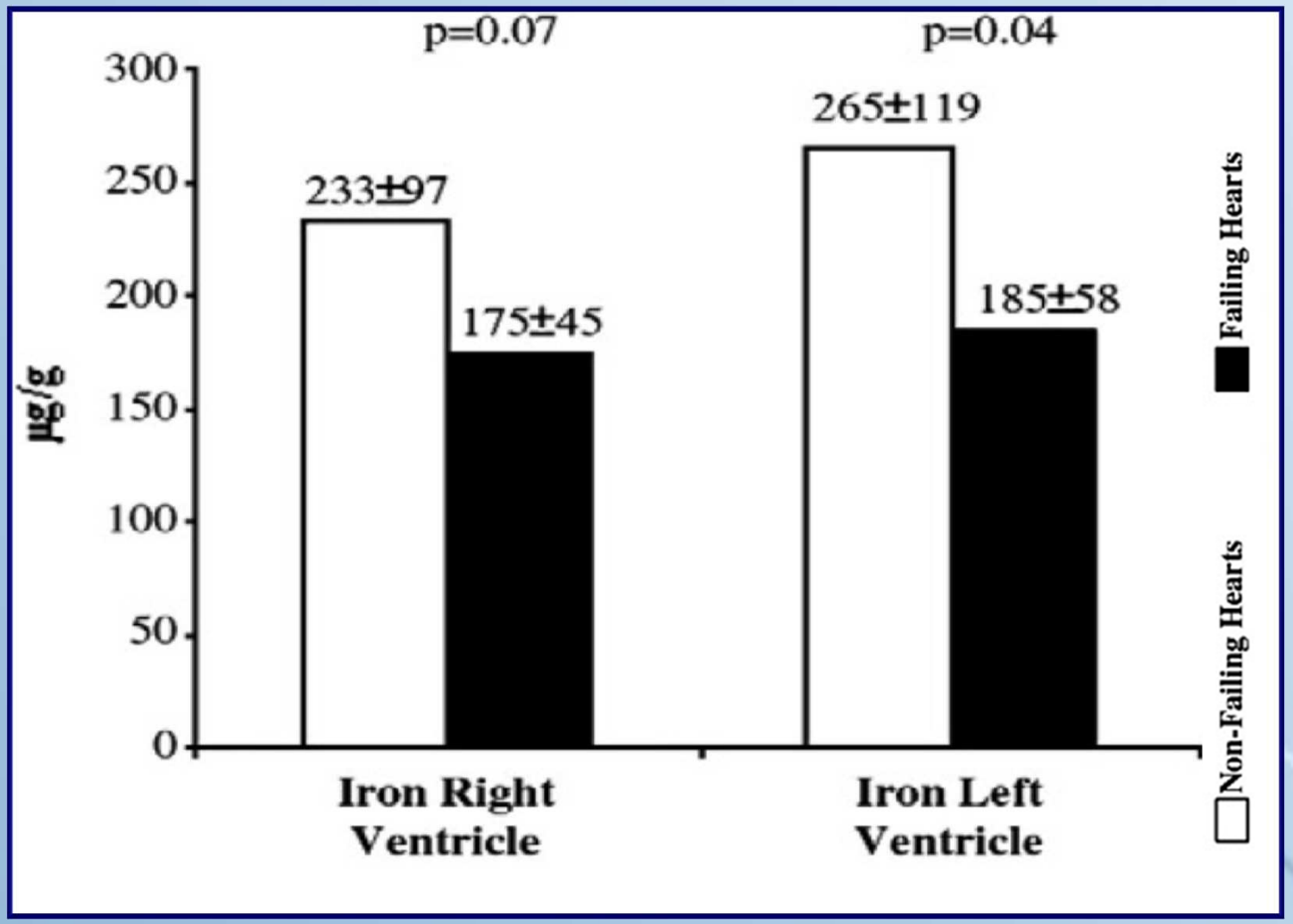


Fe parenteral es superior al Fe oral en mejorar la capacidad funcional

L. Beck da Silva. Int J Cardiol 2013; 68:3439

Fisiopatología Fe miocárdico

Fe en el miocardio de la IC está disminuido



P. Leszek. Int J Cardiol 2012;159:47

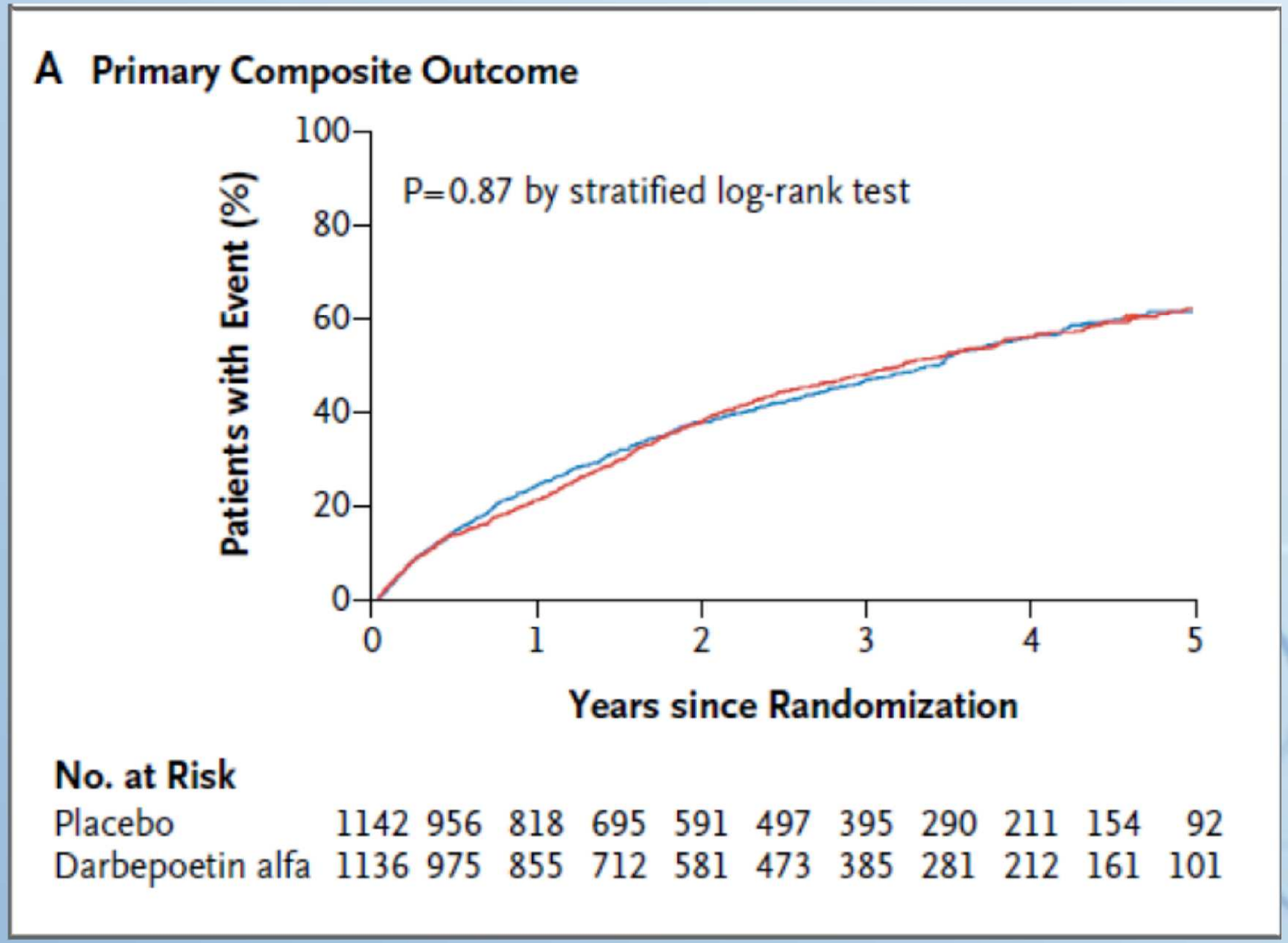
Fisiopatología Fe miocárdico

Relación entre Fe miocárdico y valores séricos de marcadores de la homeostasis del Fe tisular en la IC							
		Iron	Hb	Transferrin	Sat Tf	RsTf	FR
VD	Fe	r=0.11	r=0.24	r=−0.34	r=0.20	r=−0.44	r=0.26
		p=0.60	p=0.22	p=0.11	p=0.37	p=0.03	p=0.21
	Ferritina	r=0.04	r=0.14	r=−0.48	r=0.20	r=−0.38	r=0.42
		p=0.82	p=0.43	p=0.009	p=0.30	p=0.04	p=0.03
	RsTf	r=−0.29	r=0.12	r=0.61	r=−0.34	r=0.52	r=−0.47
		p=0.17	p=0.50	p=0.0005	p=0.08	p=0.004	p=0.01
VI	Fe	r=−0.07	r=−0.22	r=−0.17	r=−0.03	r=−0.38	r=0.13
		p=0.77	p=0.26	p=0.54	p=0.90	p=0.07	p=0.54
	Ferritina	r=−0.05	r=−0.08	r=−0.38	r=0.02	r=0.29	r=0.42
		p=0.79	p=0.68	p=0.04	p=0.91	p=0.16	p=0.03
	RsTf	r=−0.20	r=0.15	r=0.36	r=−0.26	r=0.64	r=−0.40
		p=0.31	p=0.39	p=0.06	p=0.17	p=0.0002	p=0.03

Marcadores clínicos no reflejan los niveles tisulares

P. Leszek. Int J Cardiol 2012;159:47

Estudio RED-HF



K. Swedberg. N Engl J Med 2013; 368:1210

Estudio RED-HF

Efectos adversos				
Episodio	Darbepoetina N = 1133 N (%)	Placebo N = 1140 N (%)	Riesgo Δ%(95% CI)	*p*
Global	660 (58.3)	662 (58.1	0.2 (−3.9 to 4.2)	0.93
IC	438 (38.7)	459 (40.3)	−1.6 (−5.6 to 2.4)	0.43
Coronario	164 (14.4)	155 (13.7)	−0.7 (−3.6 to 2.2)	0.63
Ictus	61 (5.4)	45 (3.9)	1.4 (−0.3 to 3.2)	0.10
Hemorrágico	39 (3.4)	30 (2.6)	0.8 (−0.6 to 2.2)	0.26
Isquémico	**51 (4.5)**	**32 (2.8)**	**1.7 (0.2 to 3.2)**	**0.03**
Tromboemb.	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
Venoso	29 (2.6)	20 (1.8)	0.8 (−0.4 to 2.0)	0.19
Mixto	51 (4.5)	27 (2.4)	2.1 (0.6 to 3.6)	0.005
HTA	81 (7.1)	69 (6.1)	1.1 (−0.9 to 3.1)	0.29
Cáncer	69 (6.1)	68 (6.0)	0.1 (−1.8 to 2.1)	0.90
Convulsiones	4 (0.4)	5 (0.4)	−0.1 (−0.6 to 0.4)	1.00
Hipersensibilidad	99 (8.7)	96 (8.4)	0.3 (−2.0 to 2.6)	0.79

K. Swedberg. N Engl J Med 2013; 368:1210

American College of Physicians guideline

	Mortal.	Evento CV	Calidad vida	Cap. ejercicio	Ingreso	Riesgo CV
Transf.						
EPO ± Fe	±	±	±	±	±	-
Fe iv	±	+	+	+	+	±

"ACP no recomienda el uso de agentes estimuladores de la eritropoyesis en pacientes con anemia leve o moderada en IC o enfermedad coronaria"

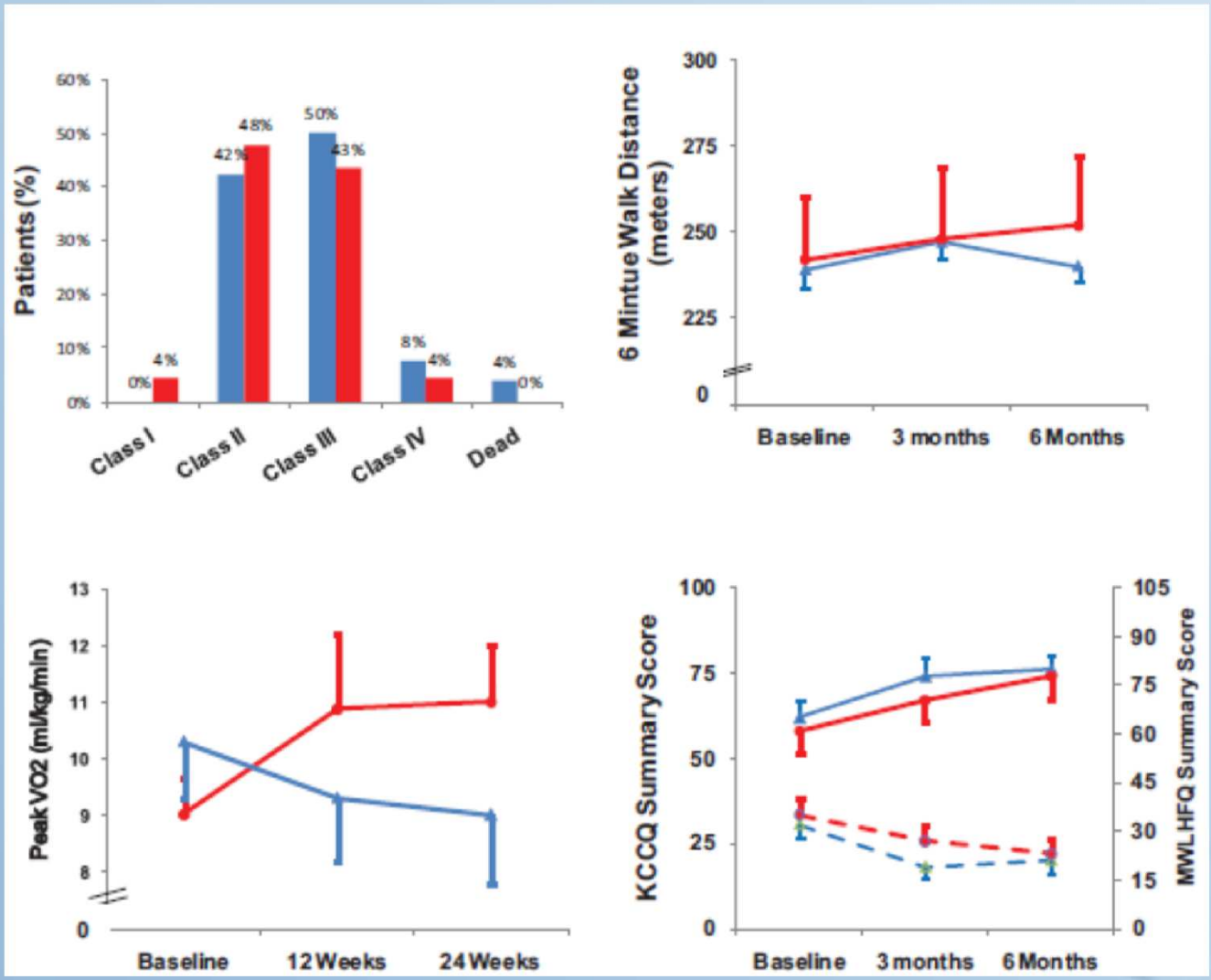
Ann Intern Med 2013; 159:770-9

Estudio RED-HC

Comentarios

- **Objetivo terapéutico: 13 g/dL de Hb**
- **Interrupción del estudio 58,2%**
  - **24% exitus**
  - **6,5% por efecto adverso**
- **Disminución necesidad de transfusión (10,9% vs 16,5%; *p*< 0,001)**
- **Disminución en reingresos por IC (572 vs 695, *p*=0.06)**
- **Mejoría en la calidad de vida KQQC:**
  - **Global: 6,68 vs 4,48; *p* = 0,005**
  - **Síntomas: 6,2 vs 3,91; *p* = 0,01**

EPO en IC con FEVIP



Hb 9-12 g/dl
N=56
Edad 77 ±11
Mujer 66%
HTA 100%
Diabetes 66%
IRC 59%

Placebo

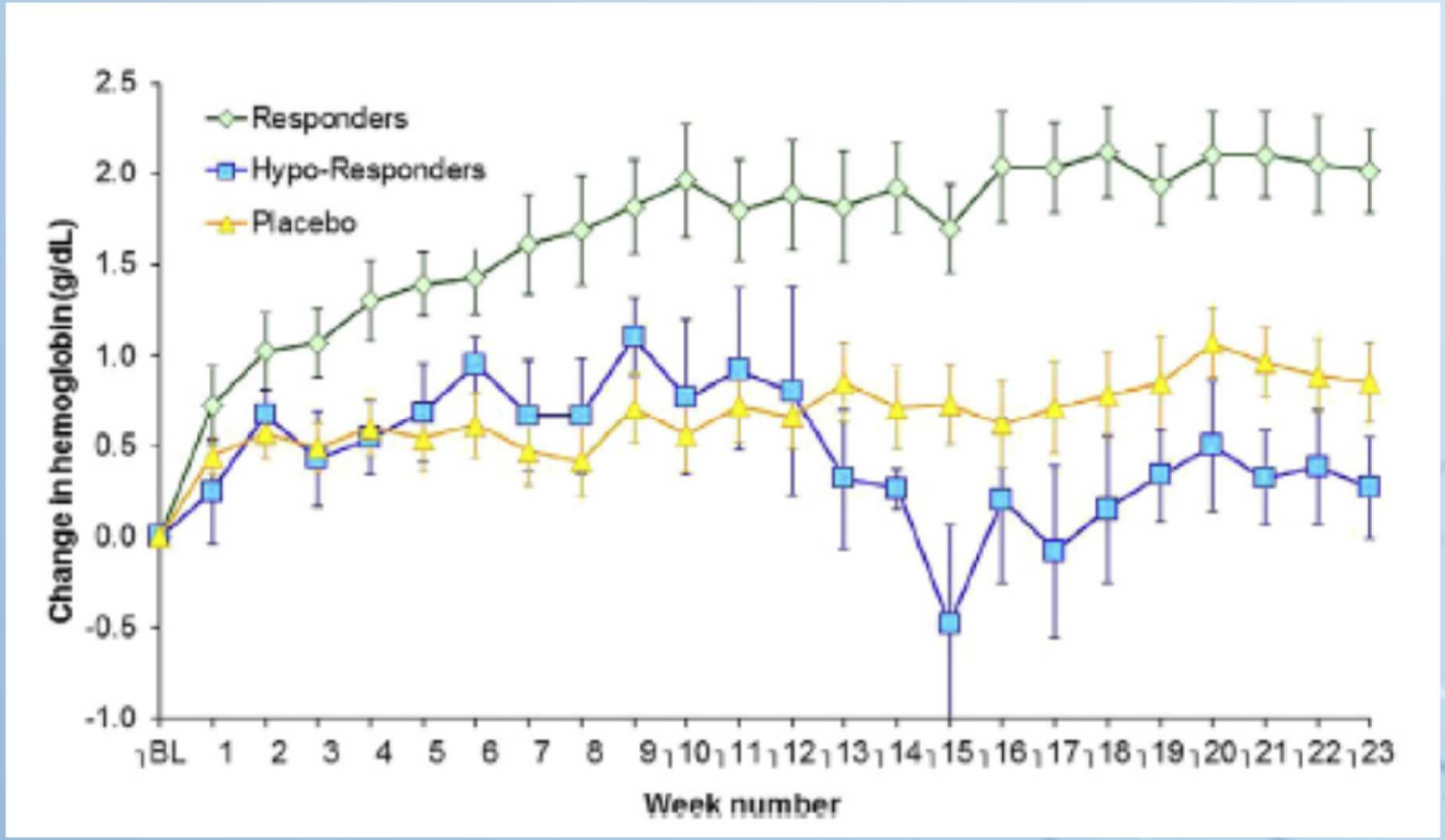
EPO

M.S. Maurer. Circ Heart Fail 2013;6:254

Resistencia EPO

Volumen plasmático con albúmina -^{131} I

EPO resistencia: Δ <1 g/dL en 4 semanas



M. Borovka. J Cardiac Fail 2013; 19:685.

Resistencia EPO

Los no respondedores tienen anemia dilucional

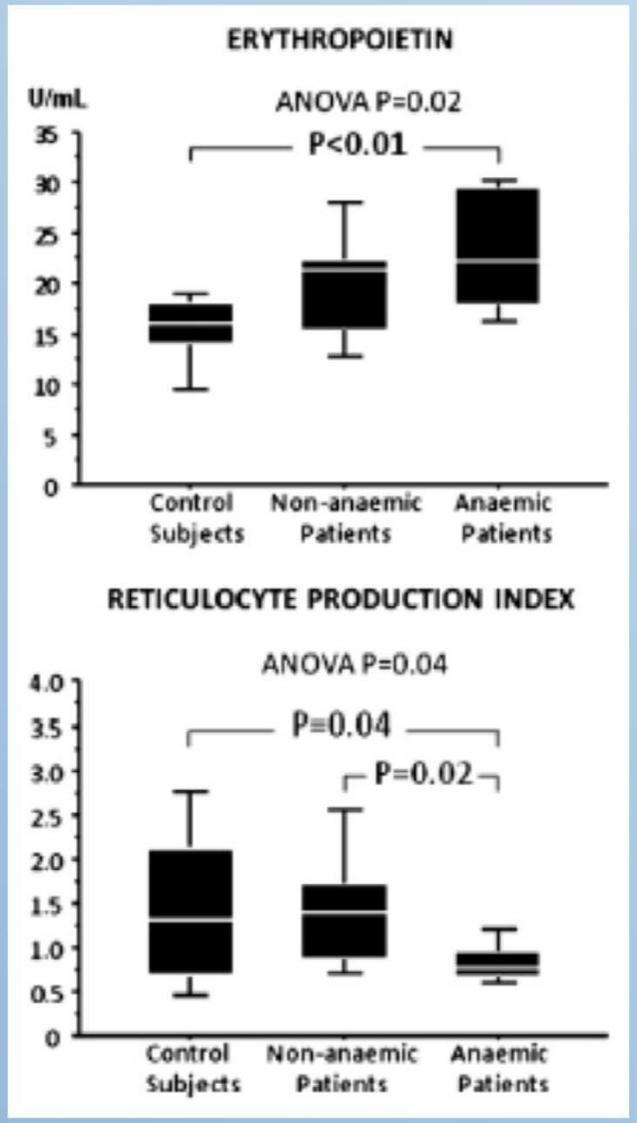
Table 2. Patient Blood Volume Characteristics at Baseline Evaluation

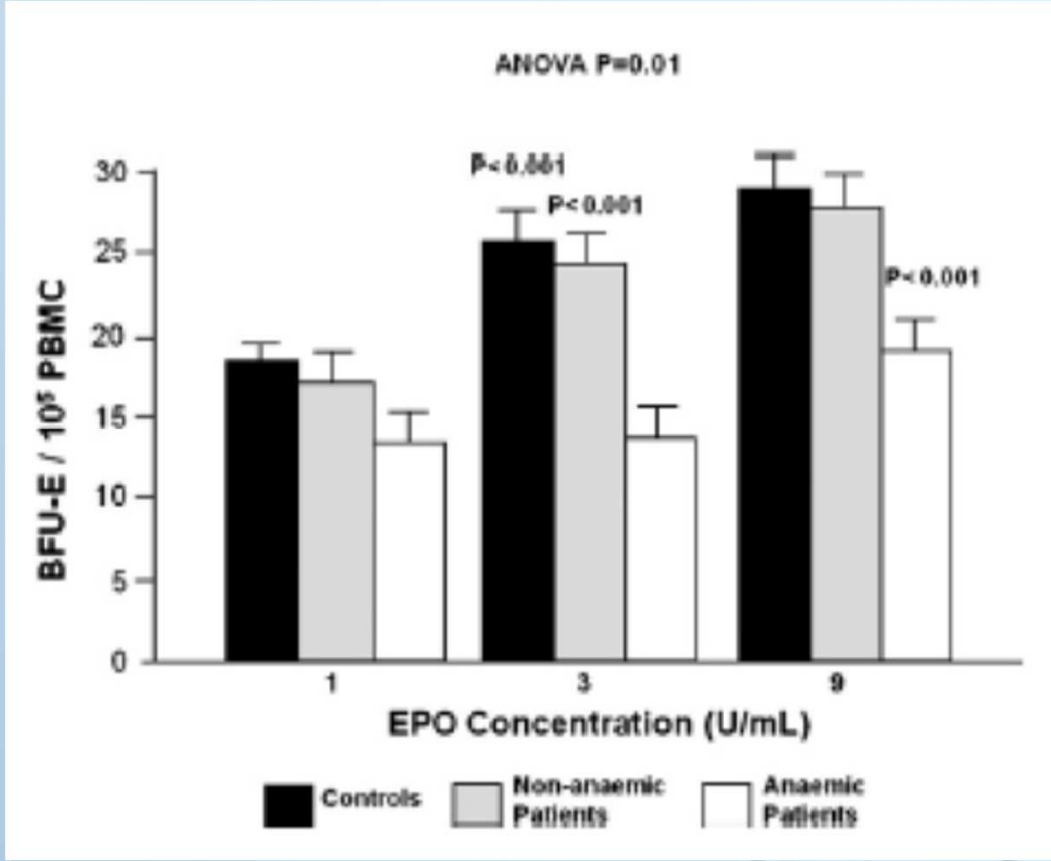
Parameter	Controls	Responders	Hyporesponders
No. of participants	24	14	6
Measured blood volume (cc)	4,586.3 ± 194.0	4,778.2 ± 326.2	6,131.8 ± 513.0*
Ideal blood volume (cc)	4,266.0 ± 132.1	4,549.4 ± 179.3	4,867.2 ± 216.5
Blood volume excess/deficit (cc)	320.3 ± 124.9	228.8 ± 205.6	1,264.7 ± 387.0*
Blood volume deviation (%)	7.5 ± 3.0	4.3 ± 3.9	25.5 ± 7.2*
Measured blood volume indexed (cc/kg)	62.7 ± 2.0	56.5 ± 1.9	69.6 ± 3.7*
Ideal blood volume indexed (cc/kg)	58.4 ± 1.0	54.4 ± 1.4	55.8 ± 2.7
Measured red cell volume (cc)	1,322.7 ± 58.8	1,318.1 ± 99.0	1,769.8 ± 175.1*
Ideal red cell volume (cc)	1,632.3 ± 62.7	1,720.6 ± 86.0	1,866.0 ± 106.2
Red cell volume excess/deficit (cc)	−309.6 ± 33.0	−402.5 ± 80.6	−96.2 ± 126.0
Red cell volume deviation (%)	−18.9 ± 1.9	−23.2 ± 3.9	−5.6 ± 6.9*
Measured red cell volume indexed (cc/kg)	18.1 ± 0.6	15.6 ± 0.6	19.9 ± 1.0*
Ideal red cell volume indexed (cc/kg)	22.3 ± 0.5	20.5 ± 0.7	21.4 ± 1.3
Measured plasma volume (cc)	3,263.7 ± 143.2	3,430.0 ± 244.1	4,362.0 ± 345.6*
Ideal plasma volume (cc)	2,633.8 ± 74.2	2,828.9 ± 99.9	3,001.2 ± 130.8
Plasma volume excess/deficit (cc)	629.9 ± 112.1	601.1 ± 165.5	1,360.8 ± 264.5*
Plasma volume deviation (%)	24.1 ± 4.4	19.9 ± 4.9	44.9 ± 7.5*
Measured plasma volume indexed (cc/kg)	44.7 ± 1.6	40.4 ± 1.4	49.7 ± 2.8
Ideal plasma volume indexed (cc/kg)	36.1 ± 0.6	33.9 ± 0.9	34.4 ± 1.6
Hematocrit	32.2 ± 0.6	31.9 ± 0.9	32.8 ± 0.8
Normalized hematocrit	34.3 ± 0.9	31.9 ± 1.5	40 ± 2.7*

Values are presented as mean ± standard error.
*$P < .05$ (Wilcoxon signed rank test score).

M. Borovka. J Cardiac Fail 2013; 19:685.

Fisiopatología EPO resistencia



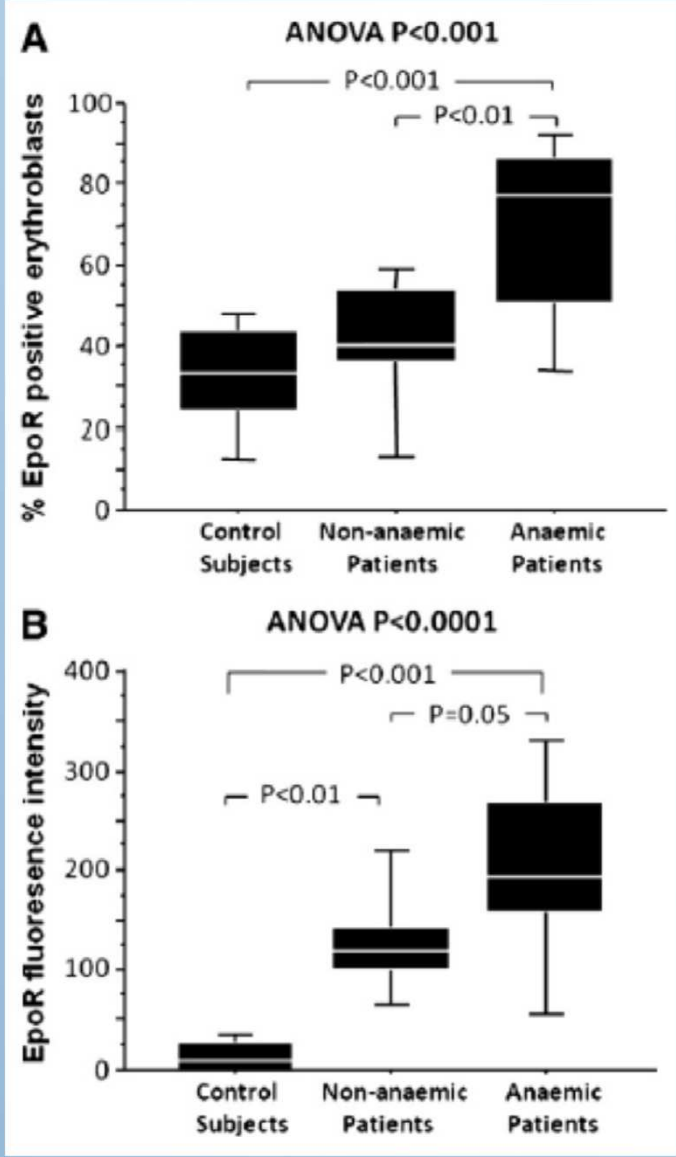


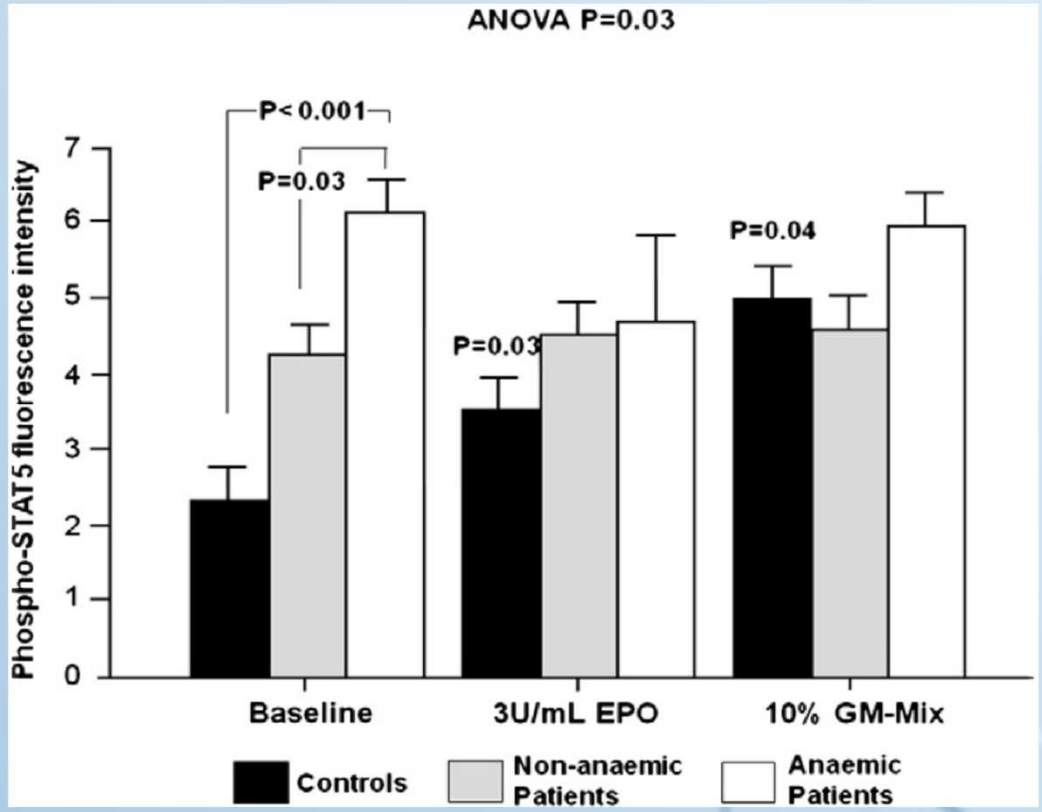
Pacientes con anemia:

- **Niveles más altos de EPO**
- **Menor nº de reticulocitos**
- **Mayor dosis de EPO**

D. O. Okonko. Int J Cardiol 2013; 164:359

Fisiopatología EPO resistencia





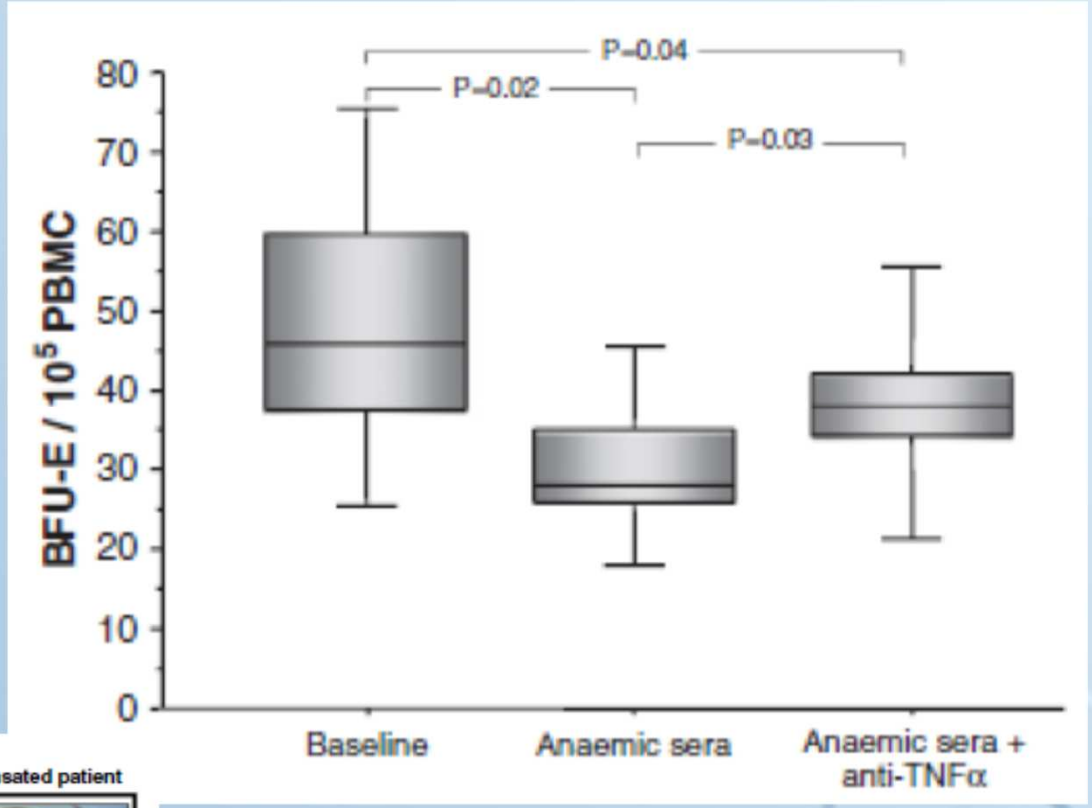
Pacientes con anemia muestran:

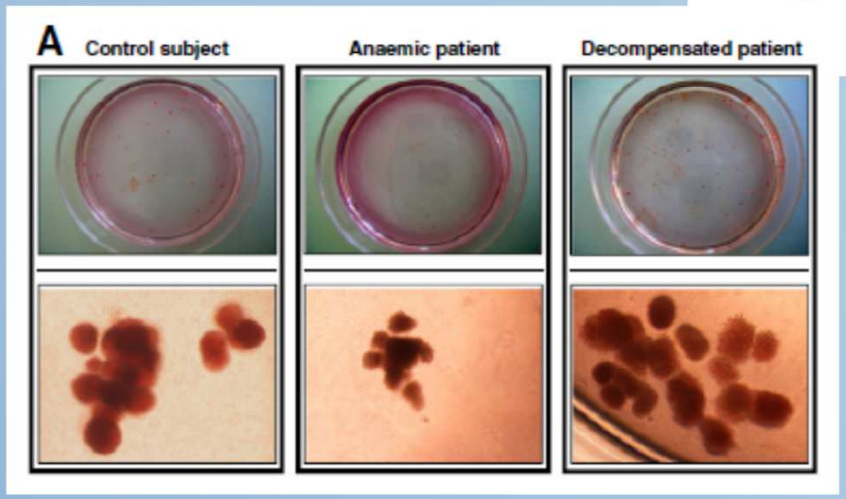
- ↑ receptor EPO en eritroblastos
- ↑ activador quinasa reguladora del receptor
- STAT5 no ↑ con EPO o GM-Mix

D. O. Okonko. Int J Cardiol 2013; 164:359

Fisiopatología: Supresión eritropoyesis

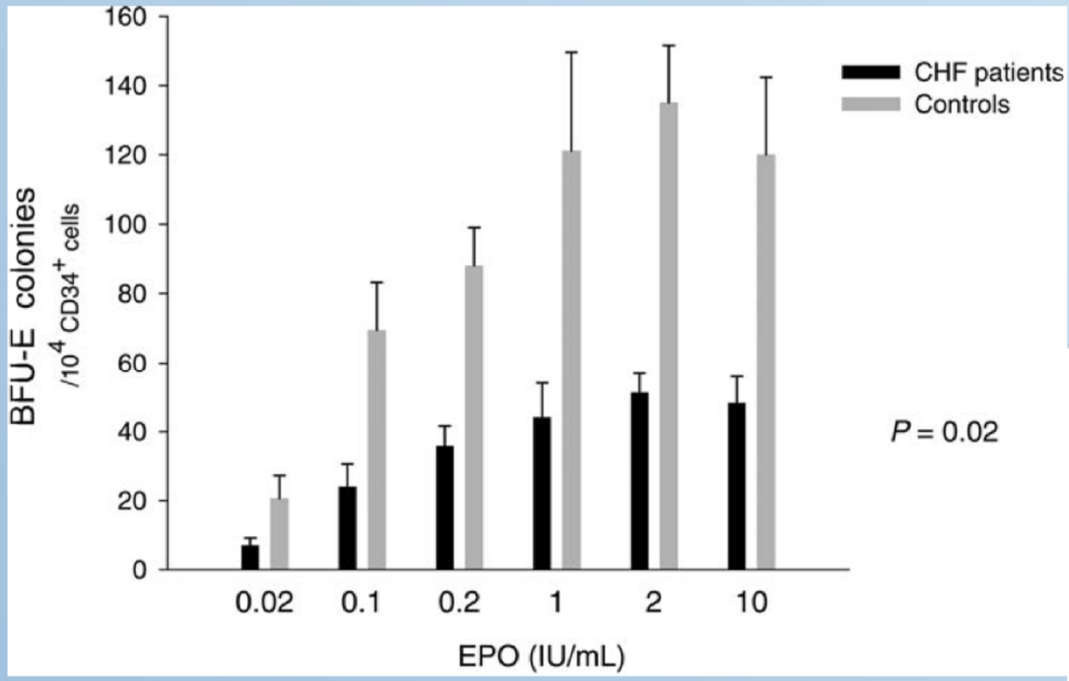
"... La anemia inexplicable en pacientes con insuficiencia cardiaca crónica resulta parcialmente de una eritropoyesis suprimida, en parte, por efecto directo de TNFα sobre las células eritroides..."



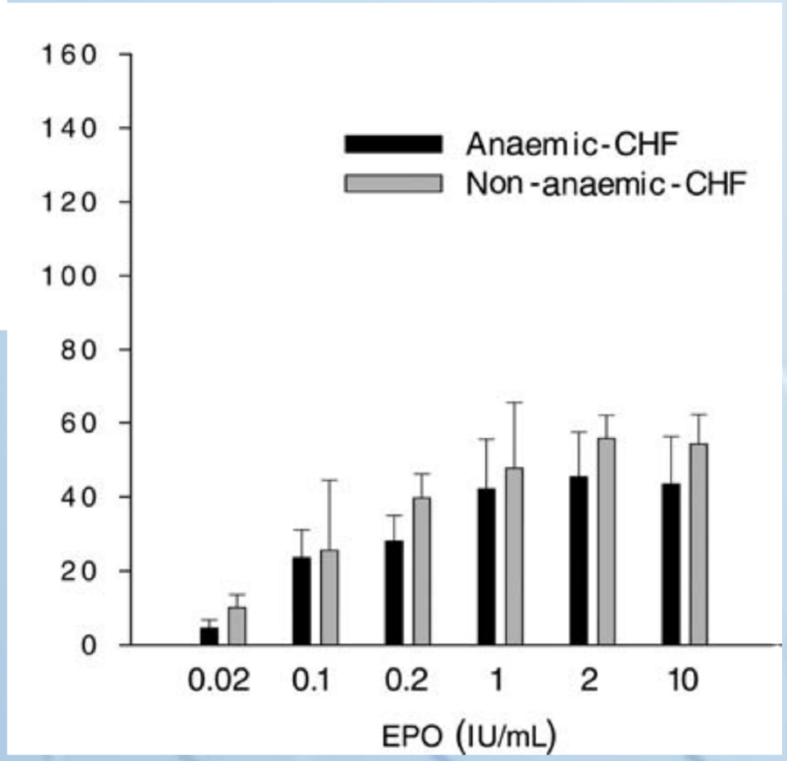


D.O. Okonko. Int J Cardiol 2013; 166:664.

Fisiopatología: Disfunción médula ósea



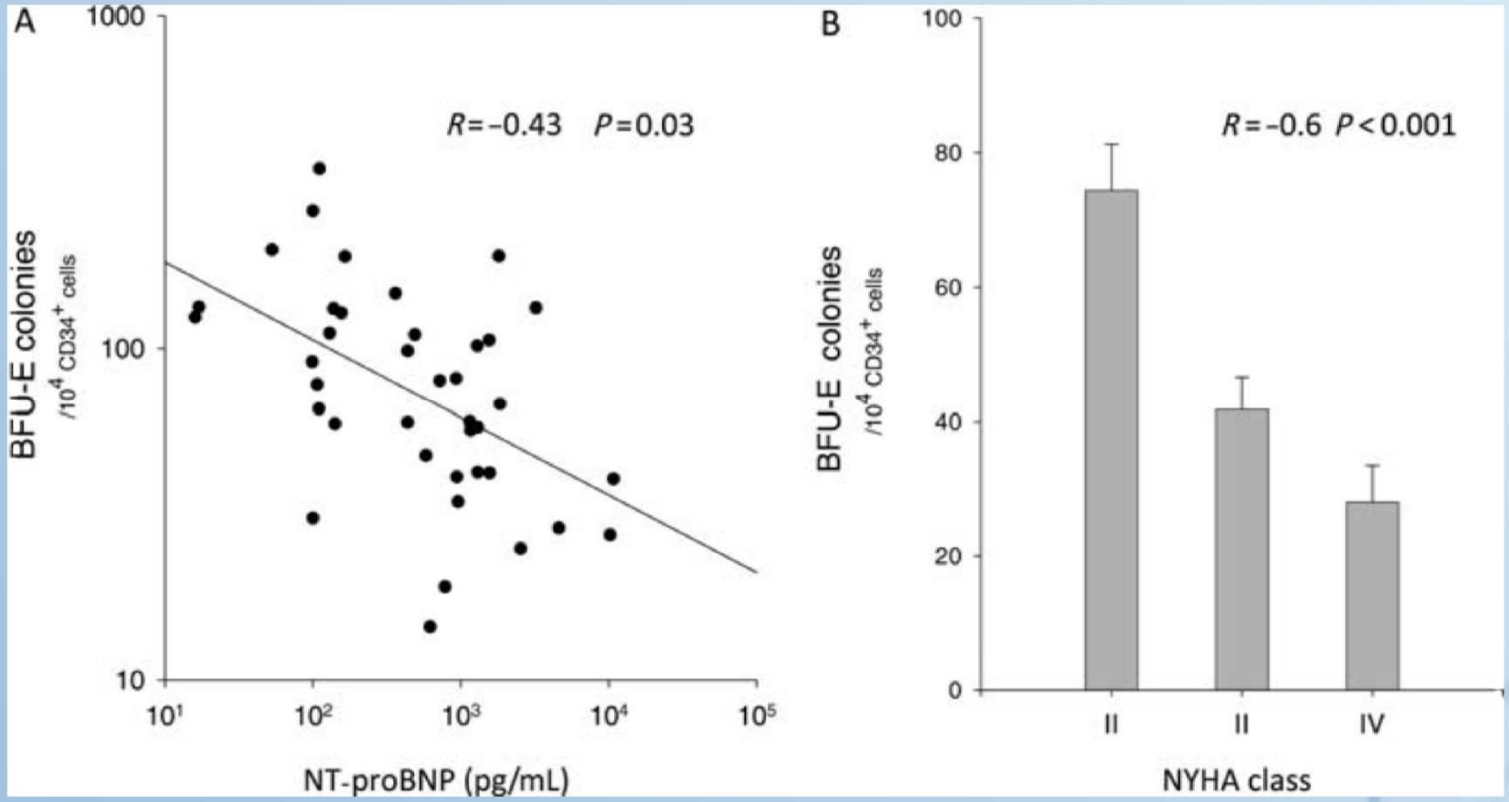
20 IC
Bypass coronario
FEVI < 40%



"..el nº de colonias eritroblásticas tras 14 días de cultivo era 3 veces inferior en IC que en controles...
··· y no difería entre pacientes anémicos o no anémicos..."

B. D. Westenbrink. Eur J Heart Fail 2010;12:676

Fisiopatología: Disfunción médula ósea

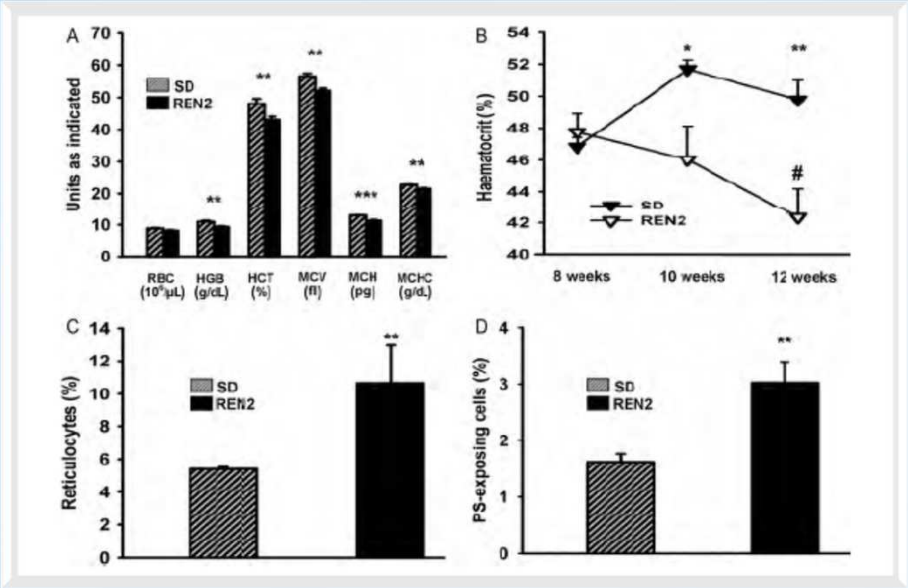


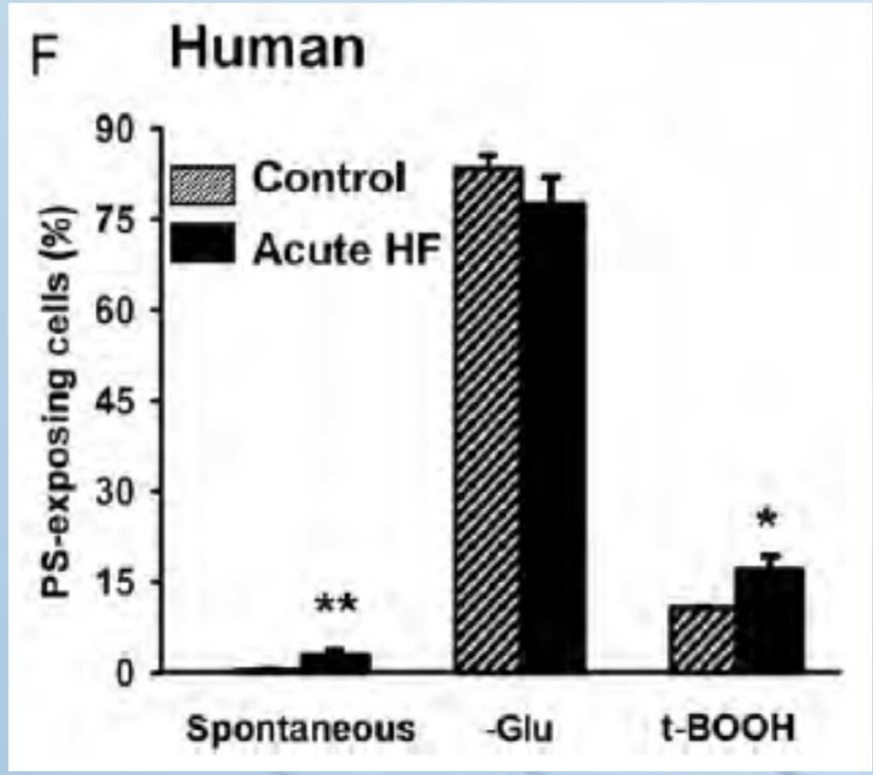
"…demostramos que los pacientes con insuficiencia cardiaca crónica tienen una disfunción de médula ósea severa y general, afectando simultaneamente múltiples líneas hematopoyéticas...

B. D. Westenbrink. Eur J Heart Fail 2010;12:676

Fisiopatología: eryptosis

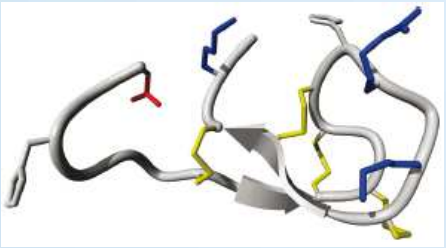
Novedoso mecanismo de anemización que puede disminuir con tratº con timol





H. Mahmud. Cardiovasc Res 2013; 98:37.

Fisiopatología hepcidina



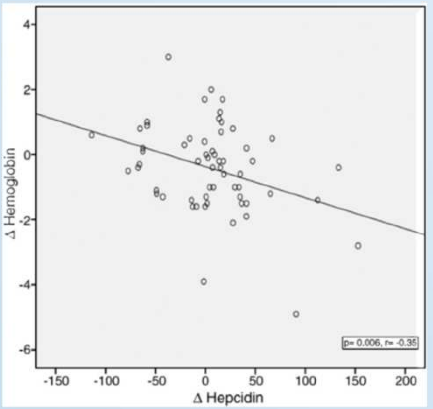
N = 59
Edad: 54±14 años
Varones 83%
Clase II NYHA
Sin anticoagulantes o antiagregantes
Sin anemia, transfusión previa o tratº con Fe
Insuficiencia renal estadio 2-3
FEVI 28±10%
Tratº óptimo:
Betabloqueo 100%
IECA o ARA II 100%
diuréticos asa 100%

Variable	Baseline	Δ 12 months
Hemoglobin (g/dL)	14.7 [13.9–15.5]	−0.4 [−1.3 to 0.5]
CRP (mg/dL)	0.2 [0.1–0.4]*	+0 [0–0.2]
sTNFRI (ng/mL)	1.6 [1.1–2.3]**	+0.4 [−0.2 to 0.9]##
IL6 (pg/mL)	3.2 [2.2–5.6]	+0.2 [−0.8 to 1.9]
Fe (mcg/dL)	91 [73–105]	+5 [−19 to 33]
Ferritin (ng/dL)	132 [74–212]	+25 [−48 to 114]
Transferrin (mg/dL)	259 [208–304]	+6 [−46 to 56]
Transferrin saturation (%)	26.6 [22–32]	−10 [−7.2 to 6]
sTfR (mg/dL)	0.3 [0.2–0.4]	+0 [−0 to 0]
Hepcidin (ng/mL)	14.7 [3.5–63]	+7 [−15 to 29.4]##
GDF15 (pg/mL)	3391 [1634–4715]	+255 [−1254 to 1377]
NT proBNP (pg/mL)	587 [127–1313]	−40 [−294 to 49]
Hs TnT (ng/mL)	0.01 [0–0.03]	+0 [−0 to 0]
GFR (mL/min/1.73 m^2)	64.3 [51–78]	+12 [1.3–22]

A. Martínez-Ruiz. Clin Biochem 2012; 45:1455.

Fisiopatología: hepcidina

"En IC sin anemia, el aumento del estado inflamatorio (receptor soluble tipo I del FNTα) y el posterior deterioro en el metabolismo del Fe (hepcidina) fueron los principales determinantes en el descenso de la Hb y la aparición de anemia en el período de seguimiento"

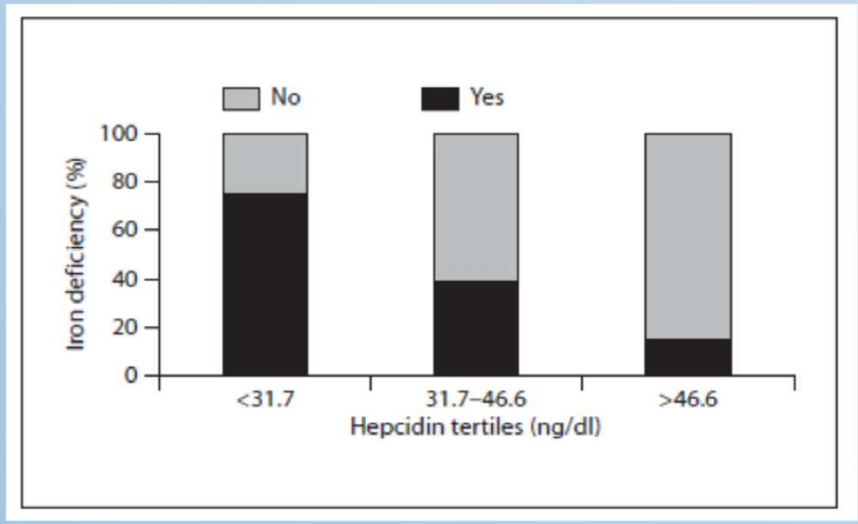


Biological parameters associated with the onset of anemia at 1 year.

Variable	No anemia	Anemia	*p*
	n = 51	*n* = 8	
Hemoglobin (g/dL)	14.6 ± 1.2	12.2 ± 0.6	**<0.001**
Δ Hepcidin (ng/mL)	−3.1 ± 43.6	59.2 ± 59.5	**0.001**
Δ Ferritin (ng/dL)	11.1 ± 229.6	128.6 ± 212.8	**0.034**
Δ sTNFRI (ng/dL)	0.2 [−0.3 to 0.7]	0.9 [0.6–2.1]	**0.008**
Δ GDF15 (pg/mL)	236.4 ± 245.6	1359.3 ± 3416.8	**0.034**

A. Martínez-Ruiz. Clin Biochem 2012; 45:1455.

Fisiopatología: hepcidina

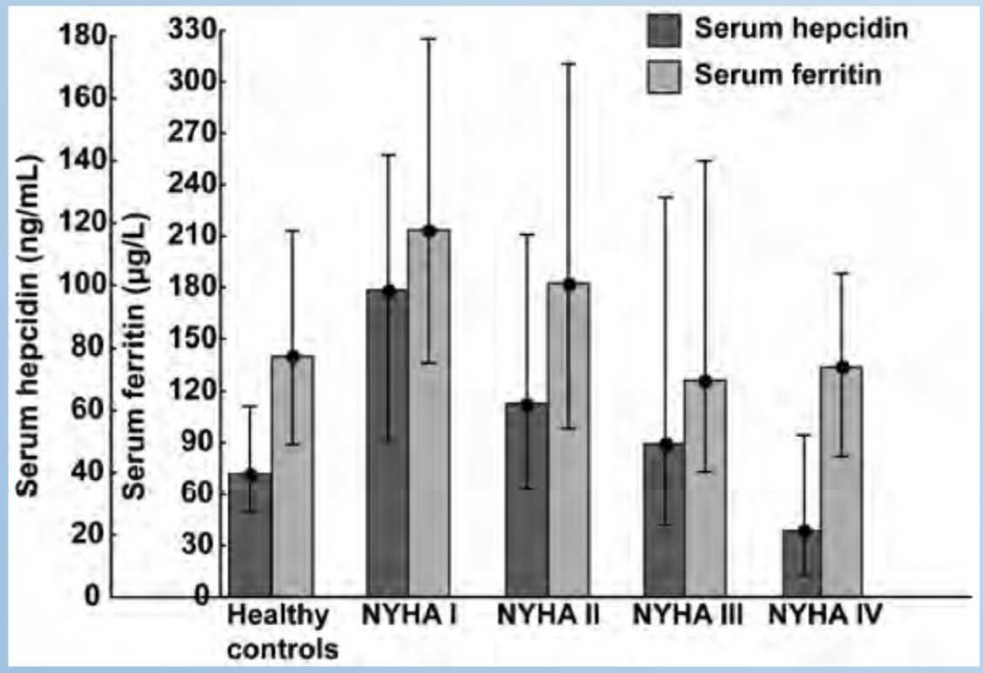


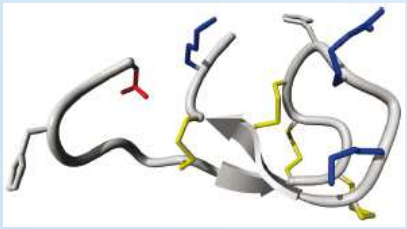
" en pacientes estables con IC sistólica y anemia, los niveles bajos de hepcidina están más estrechamente asociados a la deficiencia de Fe que al estado inflamatorio"

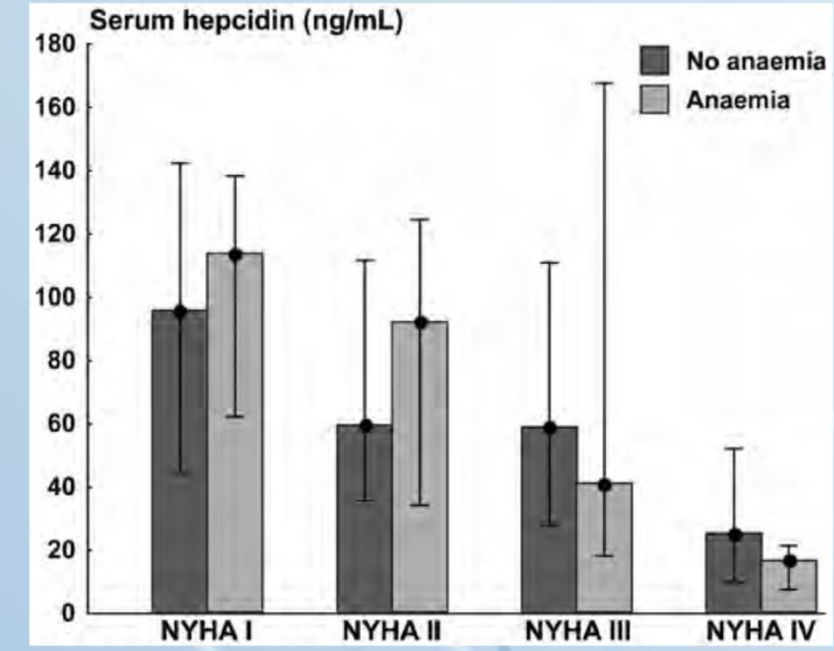
Variable	Anemia (n = 38)	No anemia (n = 22)	p
Hemoglobin, g/dl	11.4 ± 1	13.8 ± 1.1	<0.01
Hematocrit, %	35.5 ± 2.8	42 ± 3.3	<0.01
MCV, fl	91.7 ± 5.1	90.9 ± 5.7	0.60
RDW, %	14.6 ± 1.6	13.9 ± 1.4	0.12
Albumin, g/dl	4.1 ± 0.3	4.2 ± 0.3	0.46
Creatinine, mg/dl	1.4 (0.7–4.5)	1.15 (0.6–2.2)	0.04
eGFR, ml/min/1.73 m^2	53.1 ± 24.8	69.6 ± 22.8	0.01
Vitamin B_{12}, pg/ml	498 ± 232	378 ± 178	0.05
Folic acid, ng/ml	13 ± 4.4	12.6 ± 4.4	0.75
Ferritin, ng/ml	168 (31–776)	231 (21–1,473)	0.24
Iron, µg/dl	68.5 ± 28.4	88.2 ± 27.4	0.01
TSAT, %	21.5 ± 9.1	26.2 ± 9.2	0.06
TIBC, µg/dl	317 ± 62	345 ± 59	0.09
sTfR, nmol/l	35.8 (21.3–126.9)	31.1 (15.1–98.6)	0.08
Hepcidin, ng/ml	39 ± 13	31.6 ± 10.7	0.03
TNF-α, pg/ml	7.7 ± 3.6	5.5 ± 2.6	0.02
Erythropoietin, mIU/ml	19.2 (3.1–86.9)	21.1 (7.0–80.4)	0.85

C. S. Weber. Acta Haematol 2013;129:55

Fisiopatología: Hepcidina



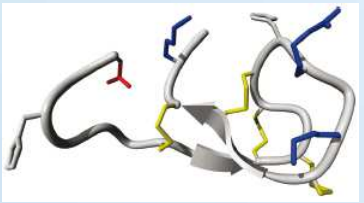




"Valores altos de hepcidina caracterizan estadios iniciales en IC, y no se acompañan de anemia o estado inflamatorio…"

E. A. Jankowska. Eur Heart J 2013; 34: 827

Fisiopatología: Hepcidina



Variables, units	Healthy subjects (*n* = 66)	NYHA I (*n* = 72)	NYHA II (*n* = 144)	NYHA III (*n* = 87)	NYHA IV (*n* = 18)	*P*-value for variance among HF patients
Haemoglobin, g/dL	14.4 ± 1.2	14.4 ± 1.2	14.2 ± 1.4	13.6 ± 1.6	13.5 ± 1.8	<0.001
MCV, fL	88.9 ± 3.6	88.5 ± 4.3	89.1 ± 4.3	88.1 ± 4.8	87.8 ± 5.1	0.43
RDW, %	12.9 (12.5–13.2)	13.1 (12.7–13.3)*	13.5 (12.8–14.3)	14.1 (13.3–15.2)	14.5 (13.7–18.0)	<0.001
Ferritin, µg/L	140 (89–213)	214 (137–325)**	182 (98–311)	126 (73–254)	134 (82–188)	<0.001
Iron, µg/dL	121 ± 38	122 ± 41	114 ± 46	98 ± 41	90 ± 58	<0.001
TIBC, µg/dL	279 ± 41	298 ± 40**	308 ± 61	319 ± 62	330 ± 58	0.05
Tsat, %	43 ± 11	41 ± 14	38 ± 14	32 ± 14	27 ± 17	<0.001
STfR, mg/L	1.13 (0.98–1.32)	1.17 (0.98–1.46)	1.23 (1.05–1.60)	1.51 (1.05–2.28)	1.71 (1.52–2.80)	<0.001
Hepcidin, ng/mL	39.6 (27.6–61.4)	98.4 (50.0–141.8)***	62.2 (34.8–116.3)	49.3 (23.4–128.2)	21.3 (7.2–52.2)	<0.001
hs-C-reactive protein, mg/L	0.9 (0.5–1.3)	1.54 (1.19–4.02)**	2.15 (1.30–5.63)	4.89 (1.41–9.05)	7.84 (1.24–15.0)	<0.001
IL-6, pg/mL	1.4 (1.2–2.0)	3.8 (2.9–5.2)***	4.8 (3.4–7.2)	5.7 (4.5–9.0)	14.8 (7.1–21.1)	<0.001

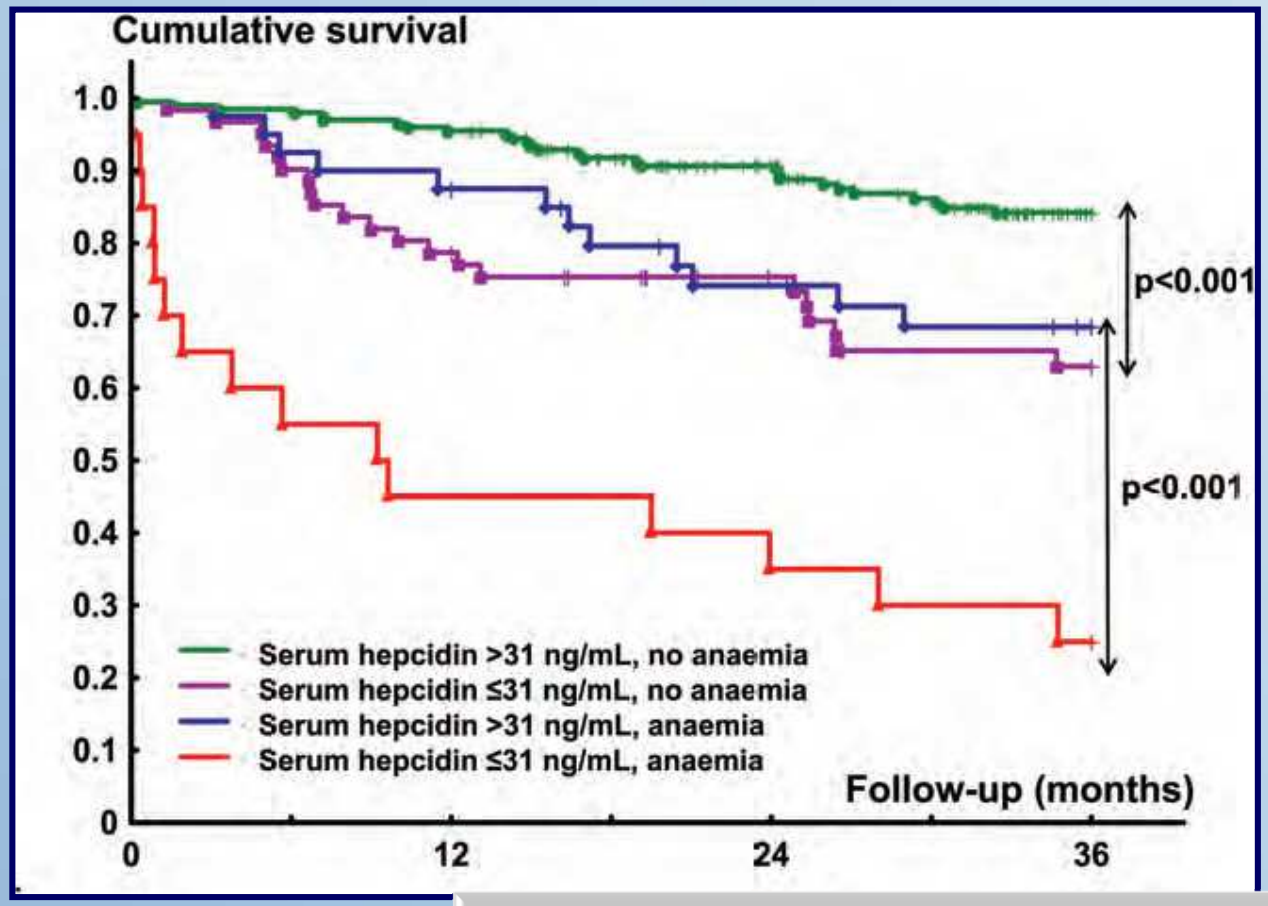
Según empeora la clase funcional:

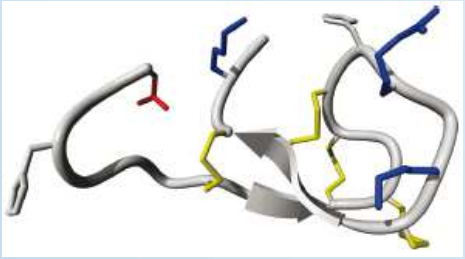
- aumenta el RDW, PCR y IL-6
- disminuye Hb, sat TF y hepcidina

E. A. Jankowska. Eur Heart J 2013; 34: 827

Fisiopatología: Hepcidina

Valores bajos de hepcidina se relacionan con mayor mortalidad."





El mecanismo de la anemia en la IC parece no ser el mismo que el de otras enfermedades crónicas

E. A. Jankowska. Eur Heart J 2013; 34: 827

FEVIP

IRC 60%

ANEMIA 30-

FEVID

¿30-40%?

BSA Hospital Municipal

- Investigar déficit Fe
- ¿Hay pacientes tributarios de EPO?
- Fisiopatología distinta y variada
  - clase funcional
  - comorbilidades
  - fármacos

Campo de investigación abierto