El Ferro:
sòlid pilar del tractament
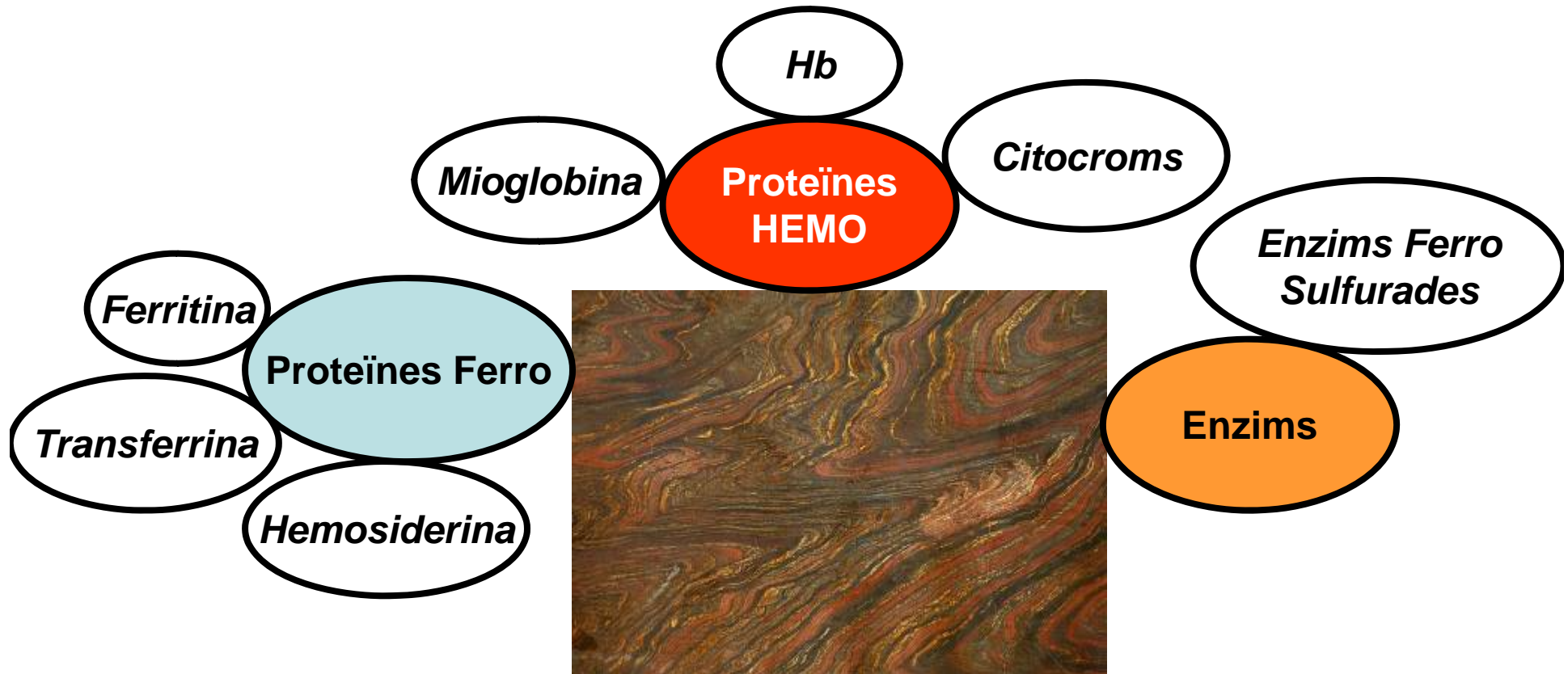
Dr. Josep Comín Colet
Programa d' IC integrat AIS Litoral-Mar (Barcelona)

La Importància del Ferro

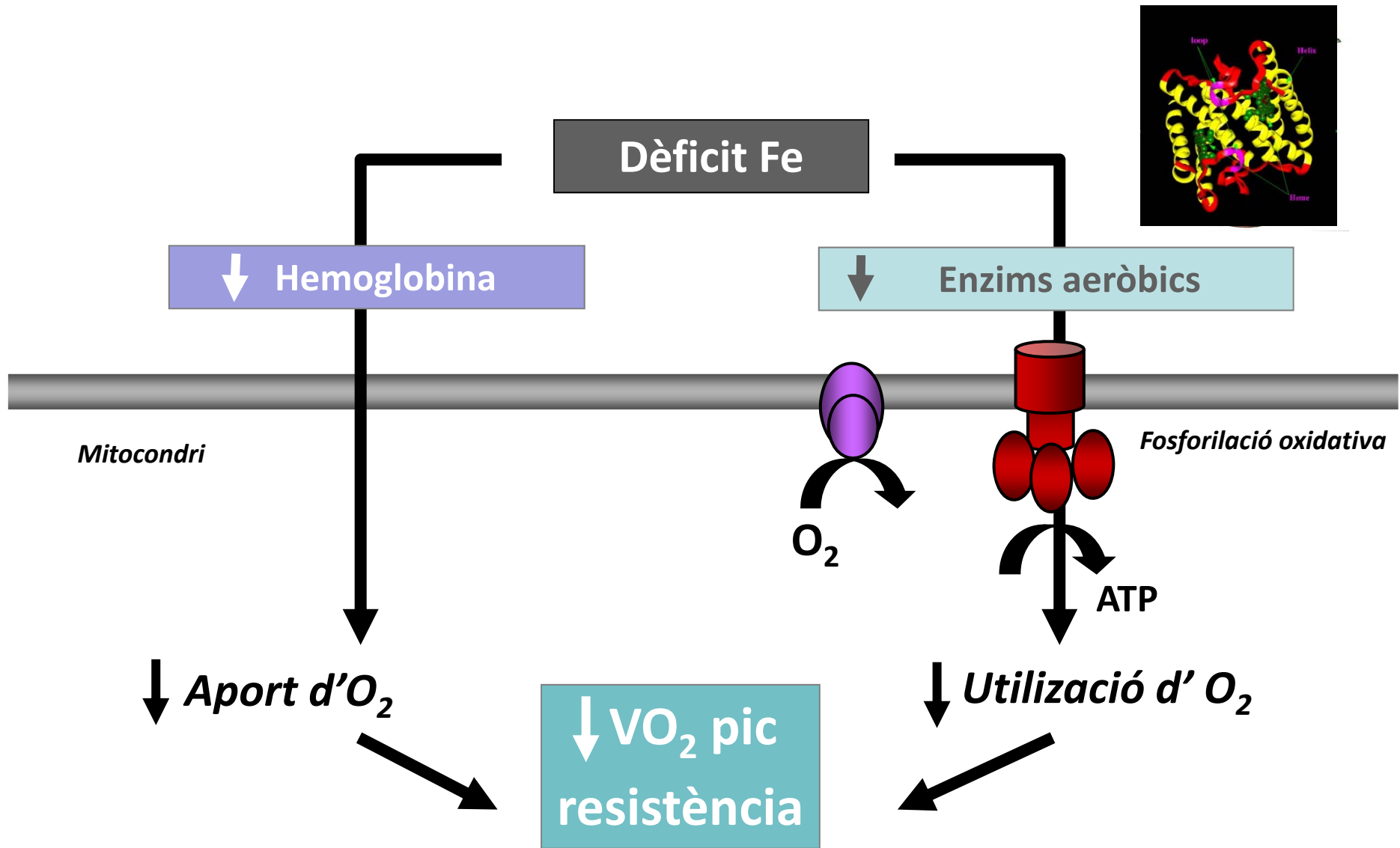# Proteïnes Portadores de Ferro

Ferro – Essencial pel Desenvolupament i la Supervivència

- Capacitat de **donar i acceptar electrons**
- Enzims catalítics i **proteïnes crucials** per a la síntesi d' AND, transport d' oxígen, **respiració cel·lular**, **fosforilació oxidativa** i d' altres víes bioquímiques
- **Sistemes de transport** i transportadors de membrana **especialitzats**
- No mecanismes d' **eliminació** fisiològics
- **Homeostasi** del Ferro regulada per la seva **absorció** i **reciclat**

Ferro: Element Vital

Dèficit Fe

↓ **Hemoglobina**

↓ **Enzims aeròbics**

Mitocondri

O_2

Fosforilació oxidativa

ATP

↓ *Aport d'O_2*

↓ **VO$_2$ pic resistència**

↓ *Utilizació d' O_2*

Haas and Brownlie. *J Nutr* 2001;131:676S–88S; Dallman PR. *J Intern Med* 1989;226:367–72.
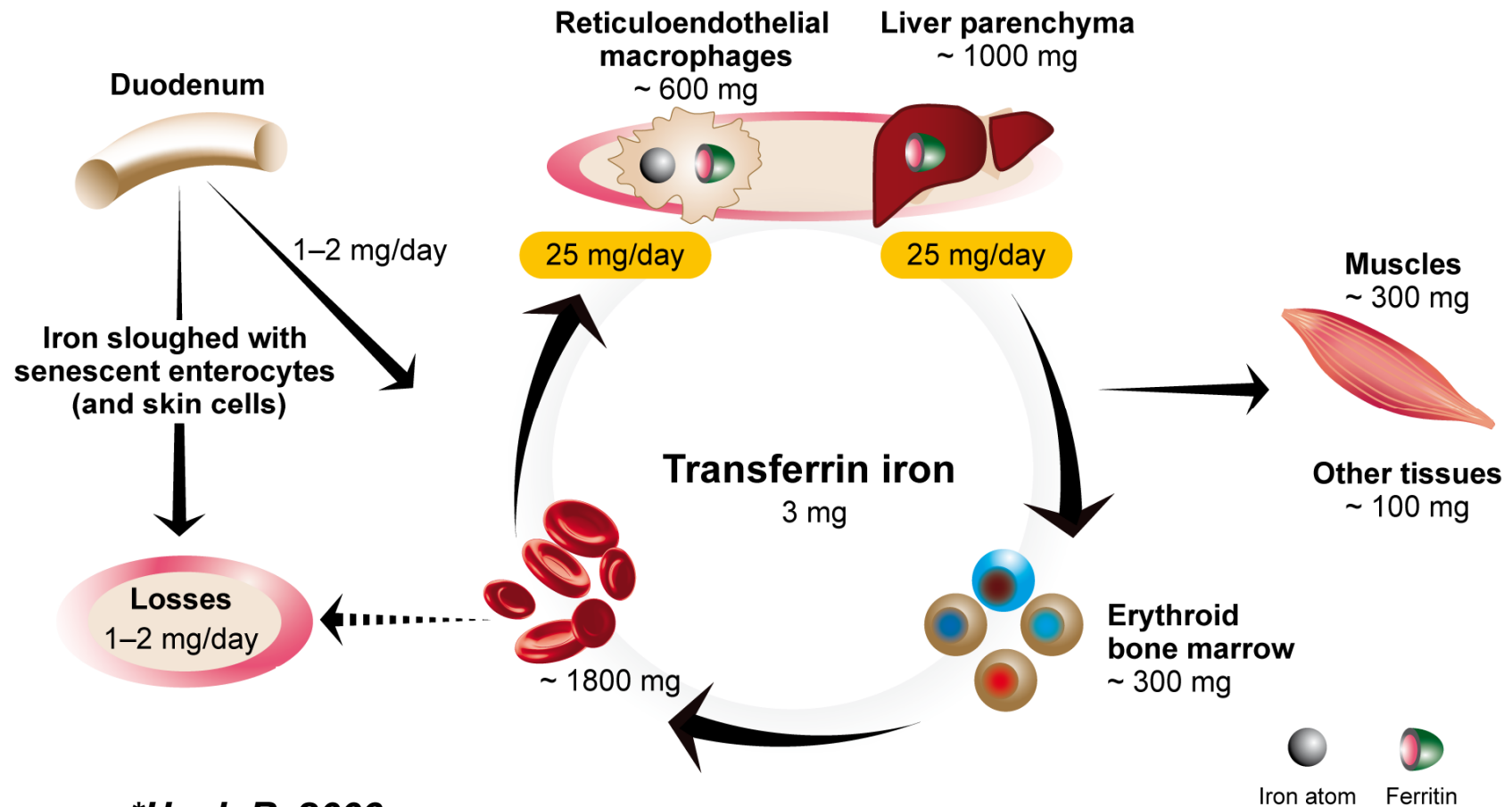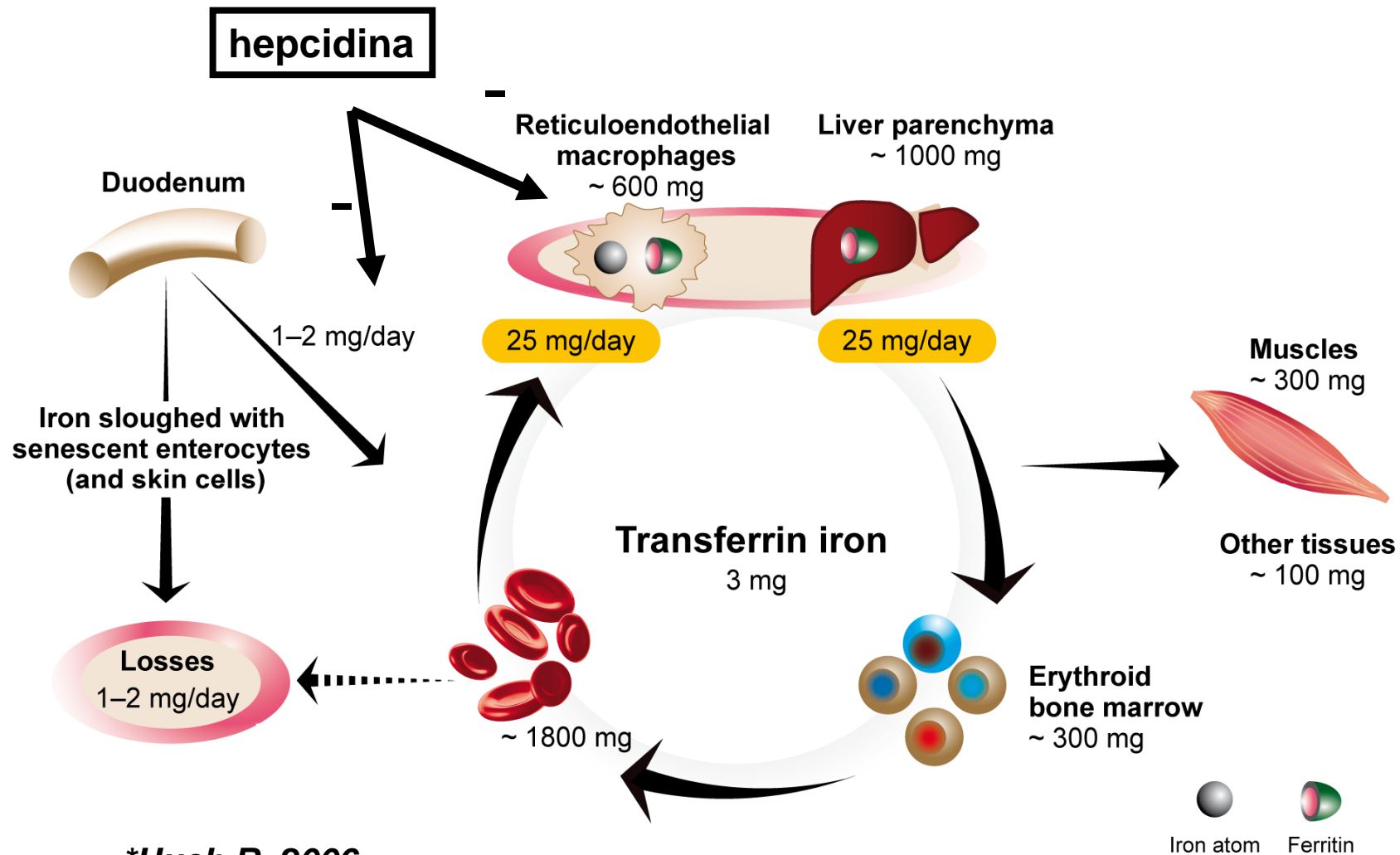
Fisiologia i Patofisiologia del Fe

Distribució i Recanvi del Fe*: 2.5-4 g

*Huch R, 2006

hepcidina

Duodenum

1–2 mg/day

Iron sloughed with
senescent enterocytes
(and skin cells)

Losses
1–2 mg/day

Huch R, 2006

Reticuloendothelial
macrophages
~ 600 mg

Liver parenchyma
~ 1000 mg

25 mg/day

25 mg/day

Transferrin iron
3 mg

Muscles
~ 300 mg

Other tissues
~ 100 mg

Erythroid
bone marrow
~ 300 mg

~ 1800 mg

Iron atom   Ferritin
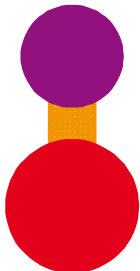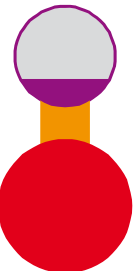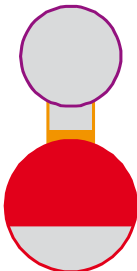
Evaluació del Metabolisme del Fe

Estat del Fe sense inflamació

		Estadio 1	Estadio 2
	Normal	Déficit de Hierro	Anemia por déficit de hierro
Hierro de Depósito			
Hierro de Transporte			
Hierro Eritroide			
Ferritina (µg/l)	100±60	< 25	< 10
Saturación de Transferrina (%)	35±15	< 30	< 10
Hemoglobina (g/dl)	Normal (12-13)	Normal (12-13)	Baja (< 12-13)

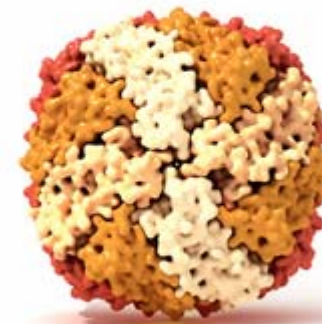*Crichton RR, 2006
WHO Definition

La Ferritina: millor predictor de dèficit de ferro
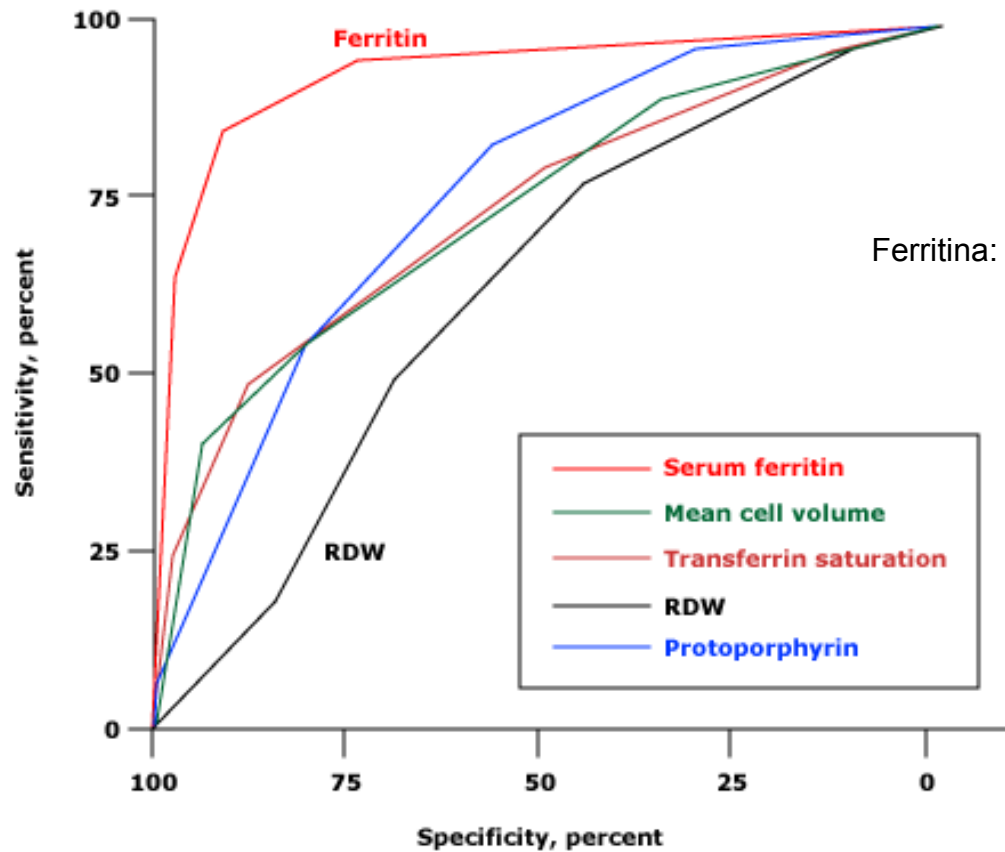
Ferritina

Subunitat simple de ferritina

Ferritina: proteïna formada per 24 sub-unitats

Secció Transversal

ANEMIA i IC : Rol Clau de la Inflamació

Adaptat de Malyszko et al. 2007
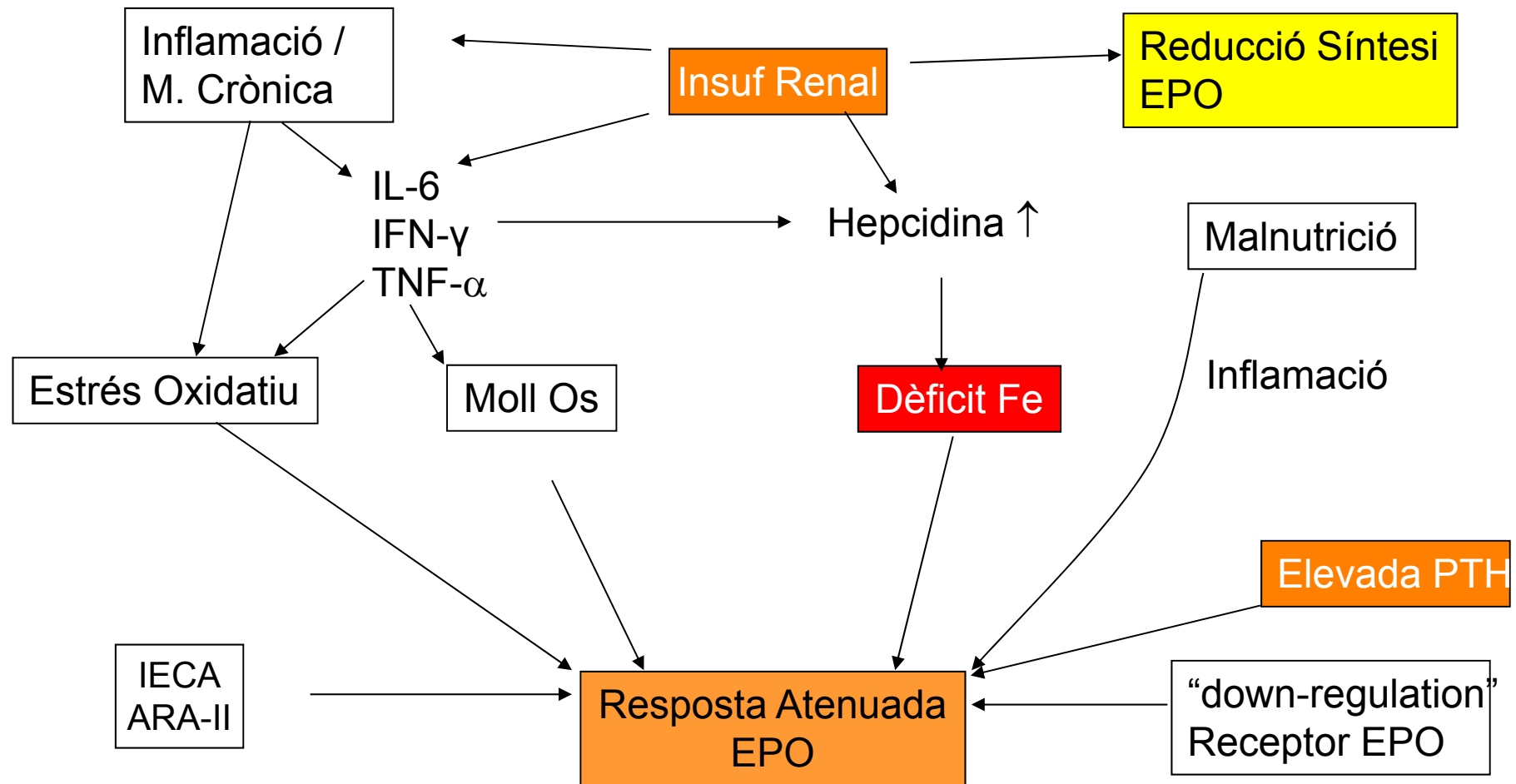
Heart Failure

Etiology of Anemia in Patients With Advanced Heart Failure

John N. Nanas, MD, PhD, FESC,* Charis Matsouka, MD,† Drosos Karageorgopoulos, MD,*
Anastasia Leonti, MD,‡ Elias Tsolakis, MD,* Stavros G. Dr
George D. Maroulidis, MD,* George P. Alexopoulos, MD,*
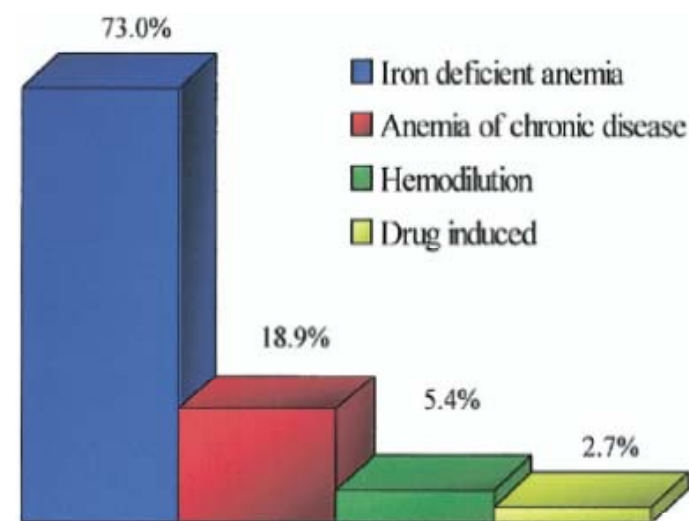Maria I. Anastasiou-Nana, MD, FESC*

Athens, Greece

Figure 1. Distribution of various etiologies of anemia among 37 patients with advanced congestive heart failure.

Nanas JN et al. J Am Coll Cardiol 2006;48 (12):2486

Table 3. Baseline Hematological and Biochemical Measurements in Iron-Deficient Versus Non–Iron-Deficient Patients

	Iron Deficient (n = 27)	Non–Iron Deficient (n = 10)	p Value
Hemoglobin, g/dl	10.2 ± 0.9	10.0 ± 0.9	0.61
Hematocrit, %	32.4 ± 2.8	31.1 ± 2.9	0.28
Mean corpuscular volume, fl	80.7 ± 8.8	87.7 ± 5.2	0.024
Mean corpuscular hemoglobin, pg	25.5 ± 3.4	28.5 ± 2.3	0.014
Iron, γ/dl	51.3 ± 23.3	54.6 ± 25.7	0.73
Ferritin, ng/ml	75.3 ± 59.1	211.9 ± 99.9	0.00001
Erythropoietin, μU/ml	74.8 ± 58.2	52.3 ± 42.3	0.27
Fibrinogen, g/l	349.8 ± 68.3	485.1 ± 124.1	0.0002
C-reactive protein, mg/dl	2.9 ± 3.5	4.7 ± 4.6	0.22
Erythrocyte sedimentation rate, mm/h	39.6 ± 21.9	65.9 ± 26.7	0.005
Serum sodium, mEq/l	135.1 ± 3.2	138.6 ± 4.9	0.0162
Daily dose of furosemide, mg	428.7 ± 288.1	510.5 ± 306.3	0.46
Brain natriuretic peptide, pg/ml	1,283.7 ± 1,260.0	1,670.0 ± 1,950.7	0.53
Serum creatinine, mg/dl	1.7 ± 0.6	1.7 ± 0.6	0.75
Creatinine clearance, ml/min	53.1 ± 25.1	47.9 ± 16.4	0.54
Thyroid-stimulating hormone, μIU/ml	3.9 ± 4.9	5.6 ± 8.0	0.46

Values are expressed as mean ± SD.

Nanas JN et al. J Am Coll Cardiol 2006;48 (12):2486
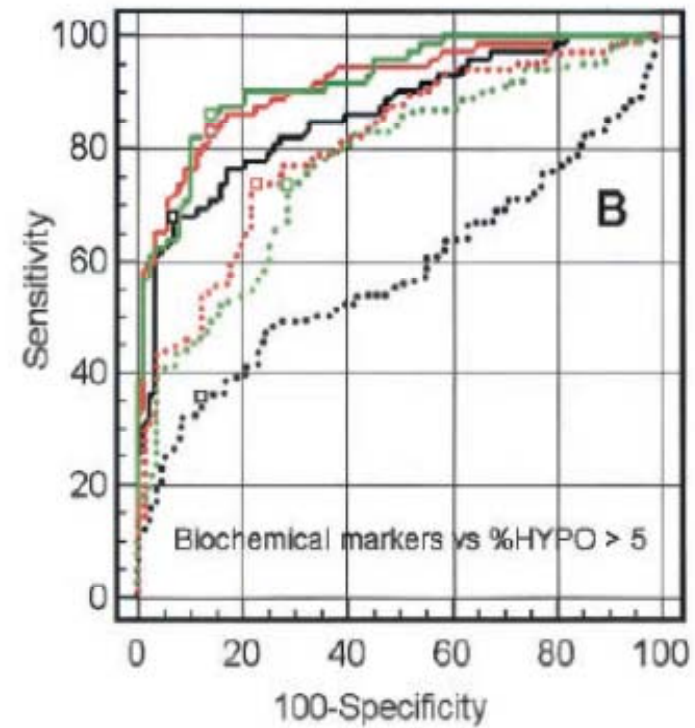
Avaluació del Metabolisme del Ferro a la ICC

Tot un repte!

Avaluació de l' Eritropoiesi Deficient en Ferro

Exàmen Moll de l' Os

% HIPO

CHr

sTfR
sTfR/log Ferritina

Ferritina
SAT Transf
Transferrina

Ferritina   sTfR   Index de Ferritina
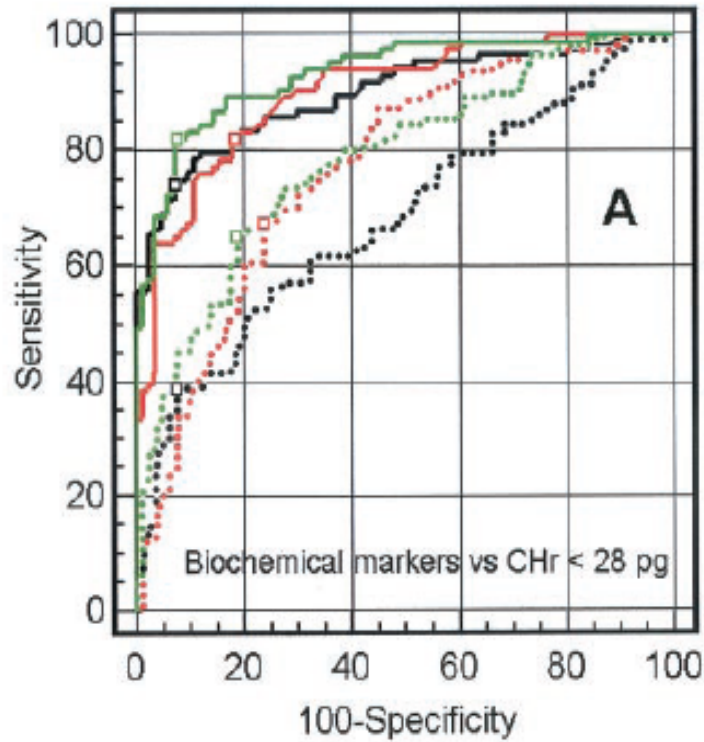
Thomas C. et al. Clinical Chemistry 2002;48(7):1066-1076

Criteris Diagnòstics Simples, Disponibles i Econòmics

Aprenem del Nefròlegs

Absolute & functional iron deficiency

Absolute iron deficiency	• Depleted body iron stores
	  – Low serum ferritin (<100ng/ml) or
	  – TSAT <20%

Functional iron deficiency	• Inadequate iron supply to meet demand despite normal or abundant iron stores
	  – Normal or high ferritin levels
	  – TSAT <20%

Wish JB. Clin J Am Soc Nephrol 2006;1:S4-8

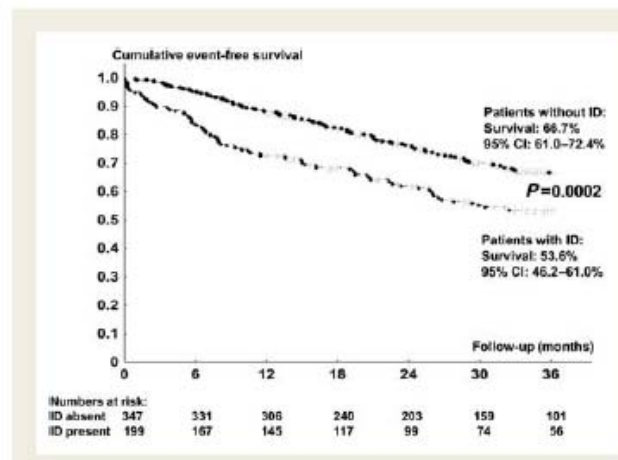# És freqüent el dèficit de Ferro a la ICC?

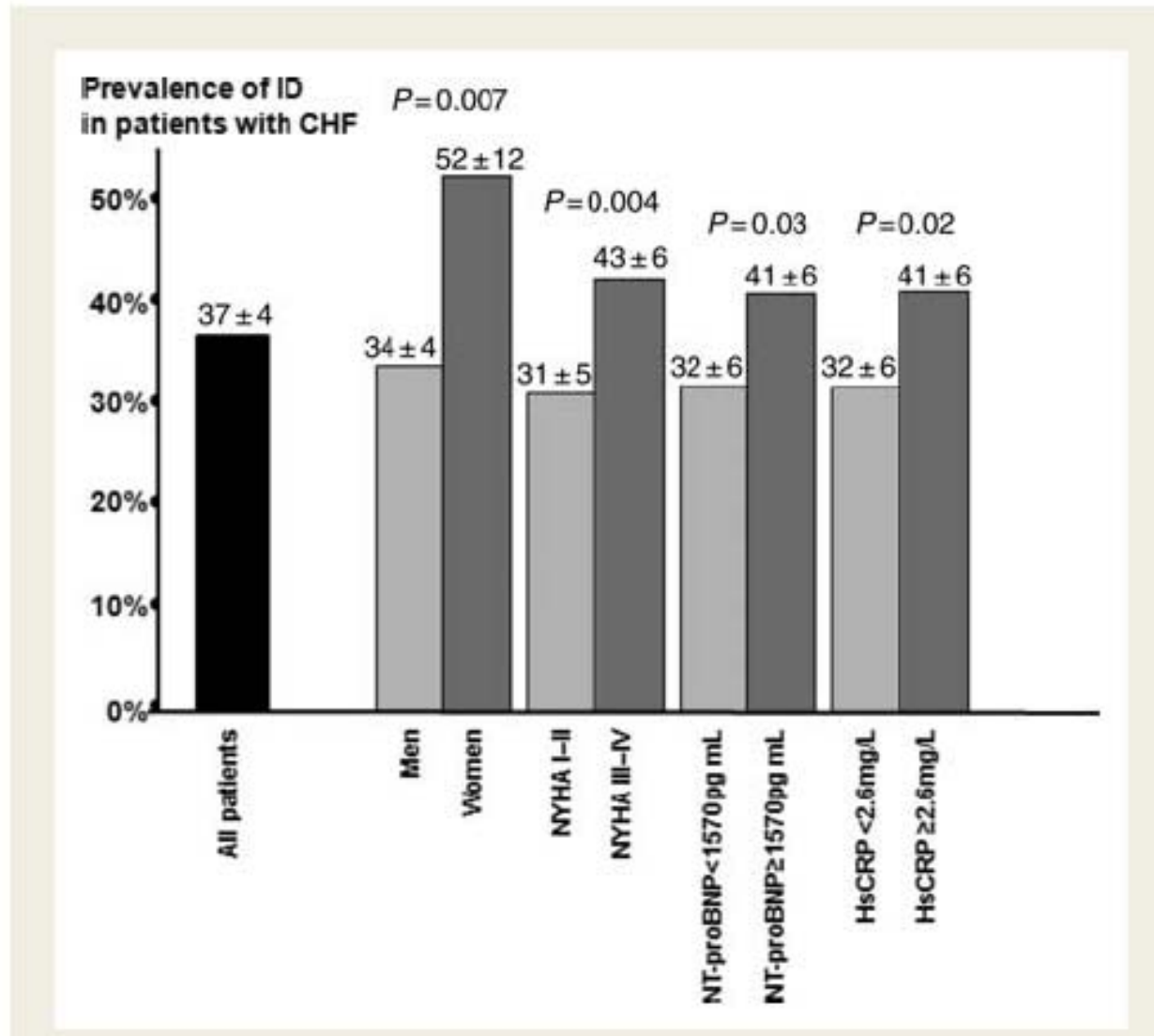# Iron deficiency: an ominous sign in patients with systolic chronic heart failure

Ewa A. Jankowska[1,2]*, Piotr Rozentryt[3], Agnieszka Witkowska[2], Jolanta Nowak[3],
Oliver Hartmann[4], Beata Ponikowska[5], Ludmila Borodulin-Nadzieja[5],
Waldemar Banasiak[2], Lech Polonski[3], Ger   lurray[7],
Stefan D. Anker[4,8], and Piotr Ponikowski[1,

Prevalència

Tractament amb Ferro

Evidències

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

Darlington O. Okonko, BSc, MRCP,* Agnieszka Grzeslo, MD,† Tomasz Witkowski, MD,†
Amit K. J. Mandal, MRCP,‡ Robert M. Slater, MBBS,‡ Michael Roughton, MSc,*
Gabor Foldes, MD, PHD,* Thomas Thum, MD,*§ Jacek Majda, MD,†
Waldemar Banasiak, MD, PHD,† Constantinos G. Missouris, MD,‡
Philip A. Poole-Wilson, MD, FMEDSCI,* Stefan D. Anker, MD, PHD,*‖ Piotr Ponikowski, MD, PHD†

London and Slough, United Kingdom; Wroclaw, Poland; and Würzburg and Berlin, Germany

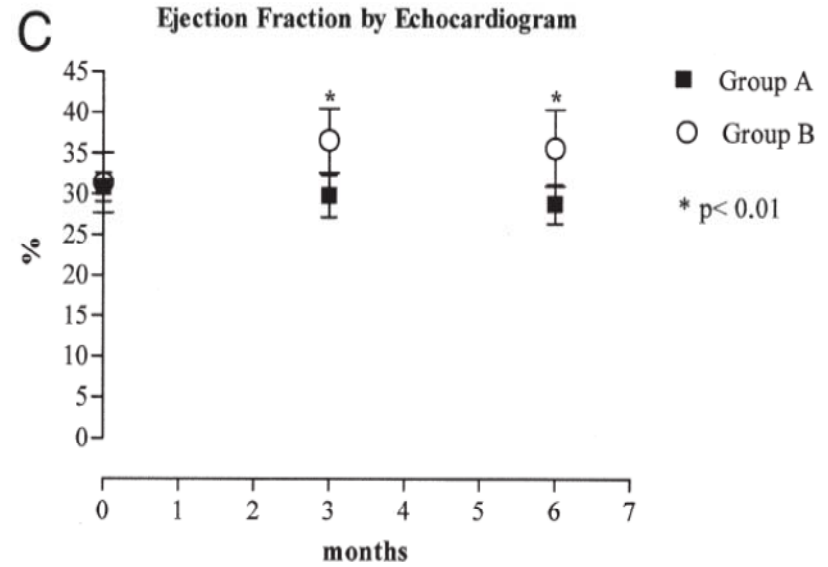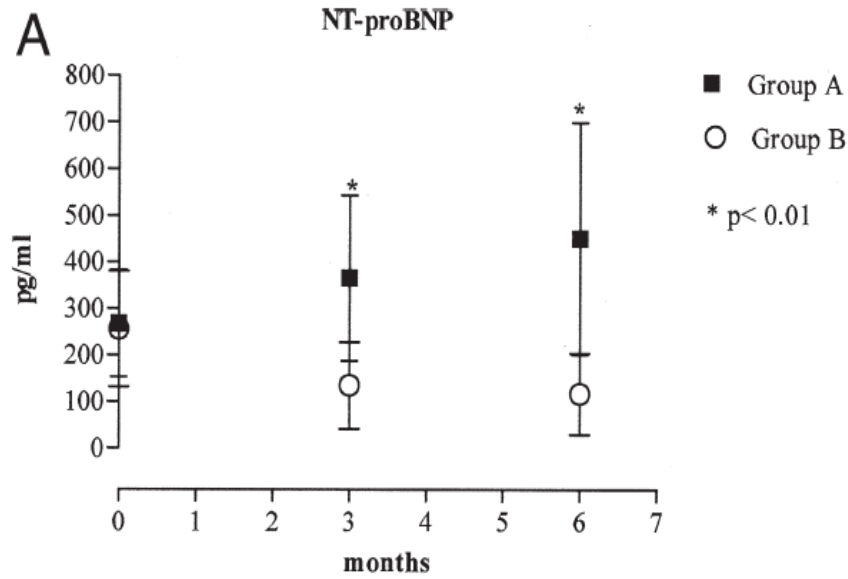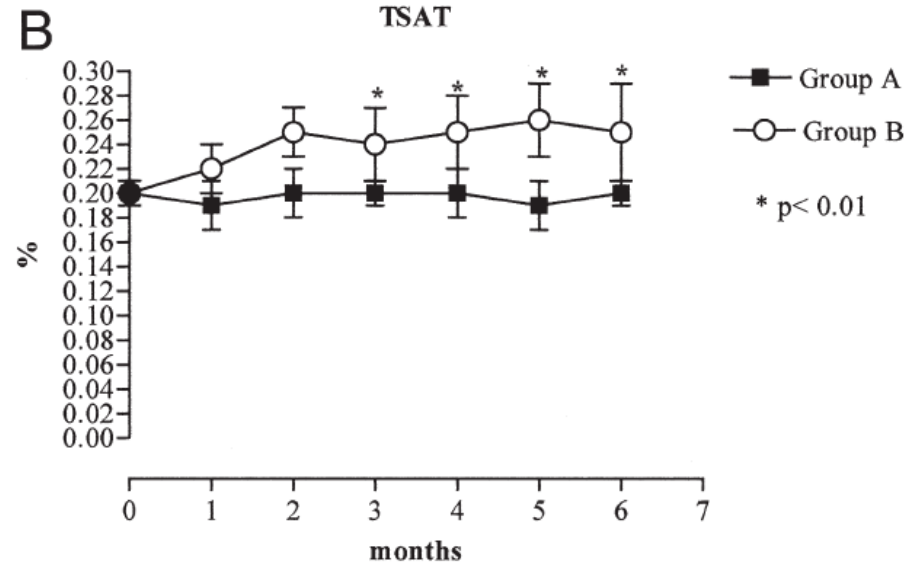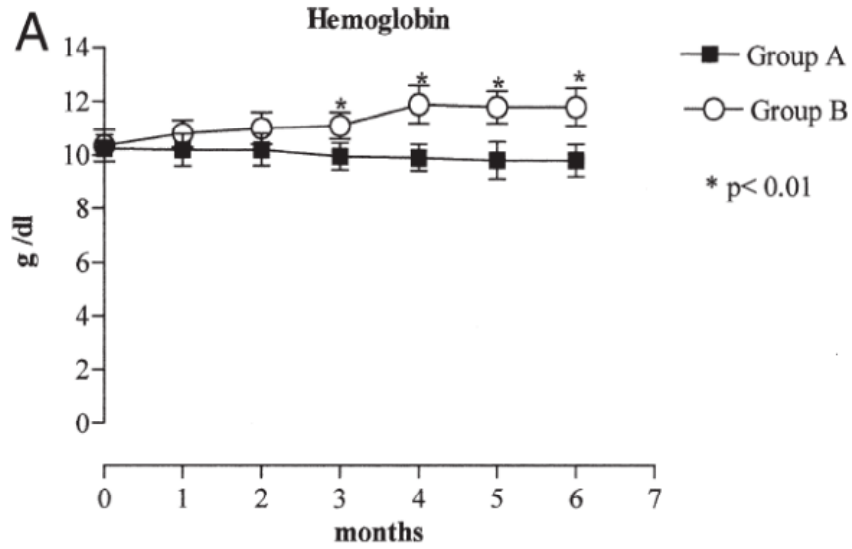## Table 3 End Points for Anemic and Nonanemic Subgroups

	Baseline		Week 18		Change		Effect	p Value
	Control	IV Iron	Control	IV Iron	Control	IV Iron		
Anemic patients								
Absolute peak Vo₂ (ml/min)	1,224 ± 314	880 ± 259	1,178 ± 260	1,038 ± 224	46 ± 116	158 ± 182‡	204 (31 to 378)	0.02
Peak Vo₂/kg (ml/kg/min)	14.7 ± 3.6	12.9 ± 2.8	13.6 ± 2.9	15.7 ± 4.5	−1.1 ± 0.9*	2.8 ± 3.2†	3.9 (1.1 to 6.8)	0.009
Exercise duration (s)	506 ± 71	441 ± 188	526 ± 169	504 ± 214	20 ± 114	63 ± 97	43 (−66 to 153)	0.41
Transferrin saturation (%)	18 ± 4	18 ± 6	20 ± 4	32 ± 11	2 ± 7	14 ± 9‡	12 (3 to 22)	0.01
Ferritin (ng/ml)	91 ± 58	44 ± 33	132 ± 88	343 ± 199	41 ± 79	299 ± 187‡	258 (87 to 429)	0.006
Hemoglobin (g/dl)	11.4 ± 0.7	11.7 ± 1.0	12.0 ± 1.0	12.5 ± 1.0	0.6 ± 1.1	0.8 ± 1.5	0.2 (−1.3 to 1.7)	0.78
NYHA functional class	2.5 ± 0.5	2.4 ± 0.5	2.7 ± 0.8	2.1 ± 0.5	0.2 ± 0.4	−0.3 ± 0.5*	−0.5 (−1.0 to 0)	0.048
Heart rate (beats/min)	66 ± 8	77 ± 8	75 ± 10	73 ± 10	9 ± 5†	−4 ± 12	−13 (−24 to −2)	0.02
Nonanemic patients								
Absolute peak Vo₂ (ml/min)	1,174 ± 382	1,226 ± 288	1,183 ± 409	1,218 ± 262	9 ± 132	−8 ± 54	−17 (−110 to 76)	0.71
Peak Vo₂/kg (ml/kg/min)	13.6 ± 2.4	14.9 ± 2.2	13.3 ± 2.1	15.0 ± 2.1	−0.3 ± 1.9	0.1 ± 0.8	0.4 (−0.9 to 1.7)	0.53
Exercise duration (s)	492 ± 270	510 ± 180	438 ± 228	534 ± 162	−55 ± 98	27 ± 66	83 (−3 to 169)	0.06
Transferrin saturation (%)	26 ± 11	23 ± 10	27 ± 12	33 ± 10	1 ± 8	10 ± 8†	9 (0 to 19)	0.046
Ferritin (ng/ml)	86 ± 72	81 ± 32	148 ± 166	430 ± 217	62 ± 100	349 ± 197‡	287 (87 to 487)	0.008
Hemoglobin (g/dl)	13.1 ± 0.3	13.6 ± 0.6	13.3 ± 1	13.8 ± 0.9	0.2 ± 0.8	0.2 ± 0.7	0 (−0.9 to 0.8)	0.96
NYHA functional class	2.4 ± 0.5	2.6 ± 0.5	2.6 ± 0.9	2.2 ± 0.6	0.2 ± 0.4	−0.4 ± 0.7*	−0.6 (−1.3 to 0.1)	0.08
Heart rate (beats/min)	69 ± 4	70 ± 11	75 ± 11	76 ± 12	6 ± 9	6 ± 8	0 (−9 to 10)	0.97

Heart Failure

Intravenous Iron Reduces NT-Pro-Brain Natriuretic Peptide in Anemic Patients With Chronic Heart Failure and Renal Insufficiency

Jorge Eduardo Toblli, MD, PhD, Alejandra Lombraña, MD, Patricio Duarte, MD,
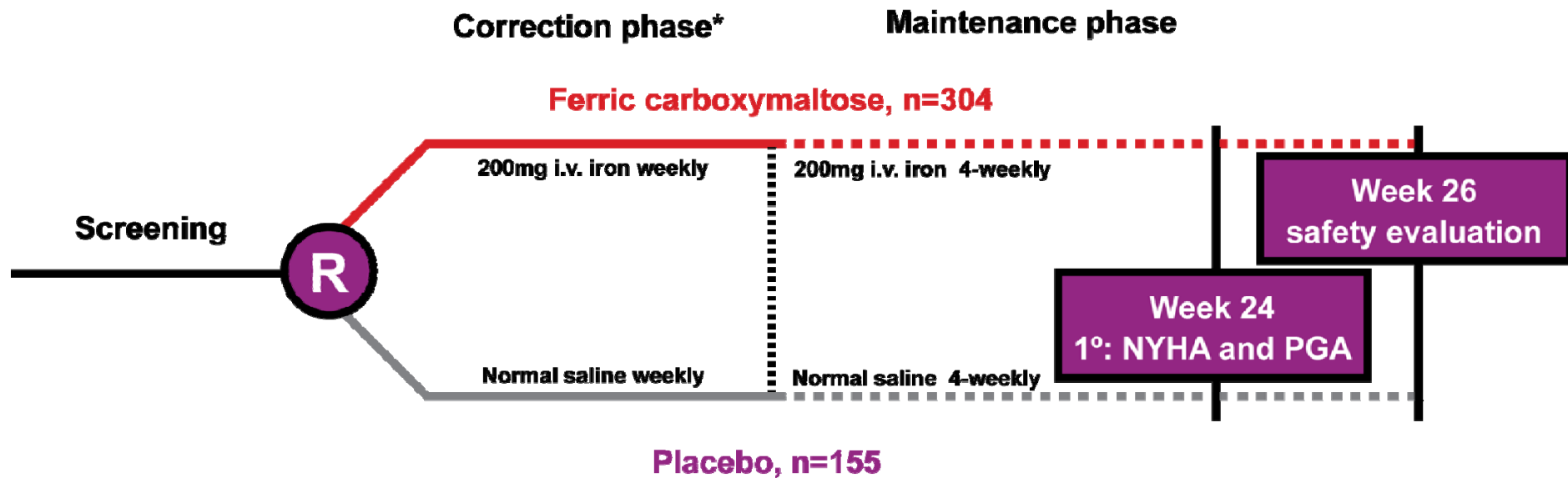Federico Di Gennaro, MD

Buenos Aires, Argentina

A Hemoglobin

B TSAT

A NT-proBNP

C Ejection Fraction by Echocardiogram

Rationale and design of Ferinject® Assessment in patients with IRon deficiency and chronic Heart Failure (FAIR-HF) study: a randomized, placebo-controlled study of intravenous iron supplementation in patients with and without anaemia

Stefan D. Anker[1,2]*, Josep Comin Colet[3,4], Gerasimos Filippatos[5], Ronnie Willenheimer[6,7], Kenneth Dickstein[8,9], Helmut Drexler[10†], Thomas F. Lüscher[11], Claudio Mori[12], Barbara von Eisenhart Rothe[12], Stuart Pocock[13], Philip A. Poole-Wilson[14†], and Piotr Ponikowski[15] on behalf of the FAIR-HF committees and investigators[‡]

Study design

Correction phase* | Maintenance phase

Ferric carboxymaltose, n=304

Screening

R

200mg i.v. iron weekly | 200mg i.v. iron 4-weekly

Normal saline weekly | Normal saline 4-weekly

Week 26 safety evaluation

Week 24 1°: NYHA and PGA

Placebo, n=155

- 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%

*total dose required for repletion calculated using the Ganzoni formula

Anker SD and Comin-Colet J et al. Eur J Heart Failure 2009;11:1084-1091

Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

Stefan D. Anker, M.D., Ph.D., Josep Comin Colet, M.D.,
Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D.,
Kenneth Dickstein, M.D., Ph.D., Helmut Drexler, M.D.,*
Thomas F. Lüscher, M.D., Boris Bart, M.D., Waldemar Banasiak, M.D., Ph.D.,
Joanna Niegowska, M.D., Bridget-Anne Kirwan, Ph.D., Claudio Mori, M.D.,
Barbara von Eisenhart Rothe, M.D., Stuart J. Pocock, Ph.D.,
Philip A. Poole-Wilson, M.D.,* and Piotr Ponikowski, M.D., Ph.D.,
for the FAIR-HF Trial Investigators†

Demographics (2/2)

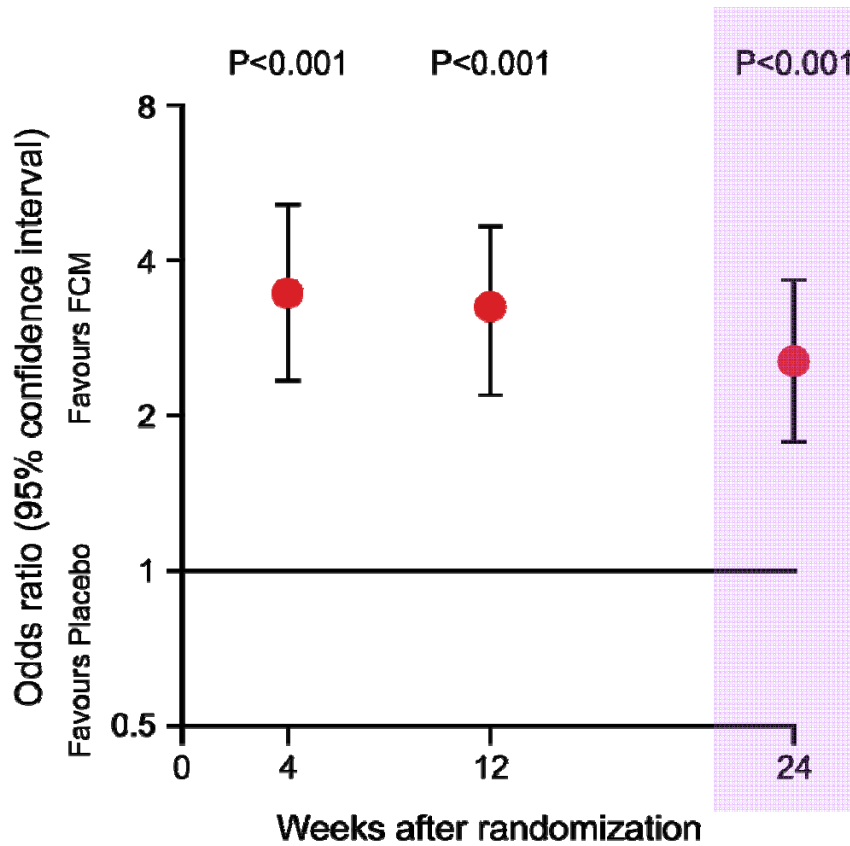|	FCM (N=304)	Placebo (N=155)
NYHA class II, n (%)	53 (17.4)	29 (18.7)
NYHA class III, n (%)	251 (82.6)	126 (81.3)
6-min walk test distance (m)*	274 ± 105	269 ± 109
Hb (g/L)*	119 ± 13	119 ± 14
MCV (mm³)*	92 ± 8.1	92 ± 6.7
Serum ferritin (mg/L)*	53 ± 55	60 ± 67
TSAT (%)*	17.7 ±12.6	16.7 ± 8.4
CRP (mg/L)*	7.5 ± 5.3	9.1 ± 5.5
Creatinine (mg/dL)*	1.2 ± 0.6	1.2 ± 0.6
Estimated GFR (mL/min/1.73m²)*	64 ± 21	65 ± 25

*mean ± SD

Anker SD , Comin-Colet J et al. NEJM 2009;361:2436

PGA & NYHA functional class

Self-reported Patient Global Assessment Score — New York Heart Association Functional Score

Anker SD , Comin-Colet J et al. NEJM 2009;361:2436
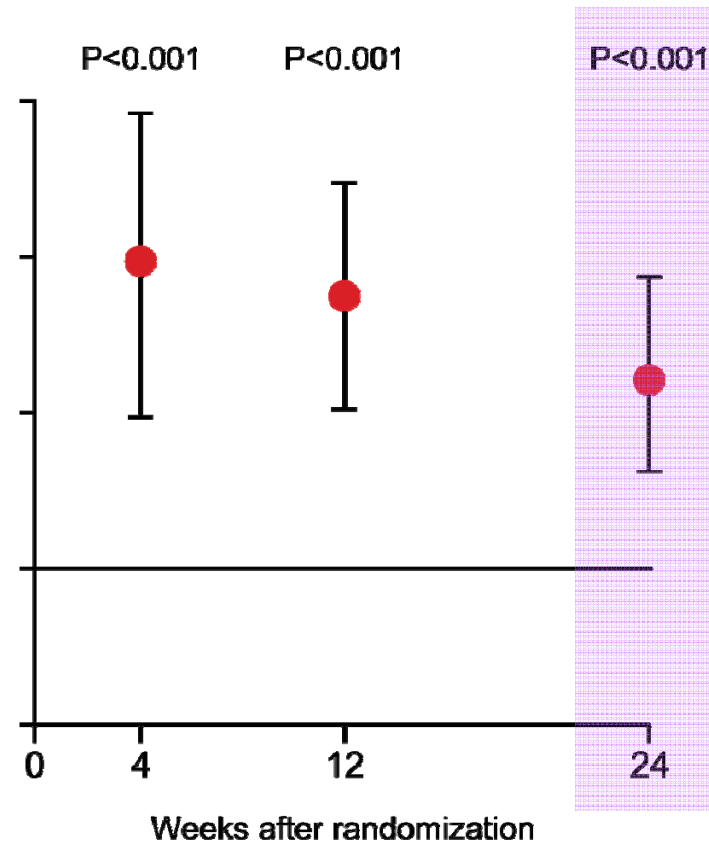
6-Minute Walk Test at Week 4, 12 & 24
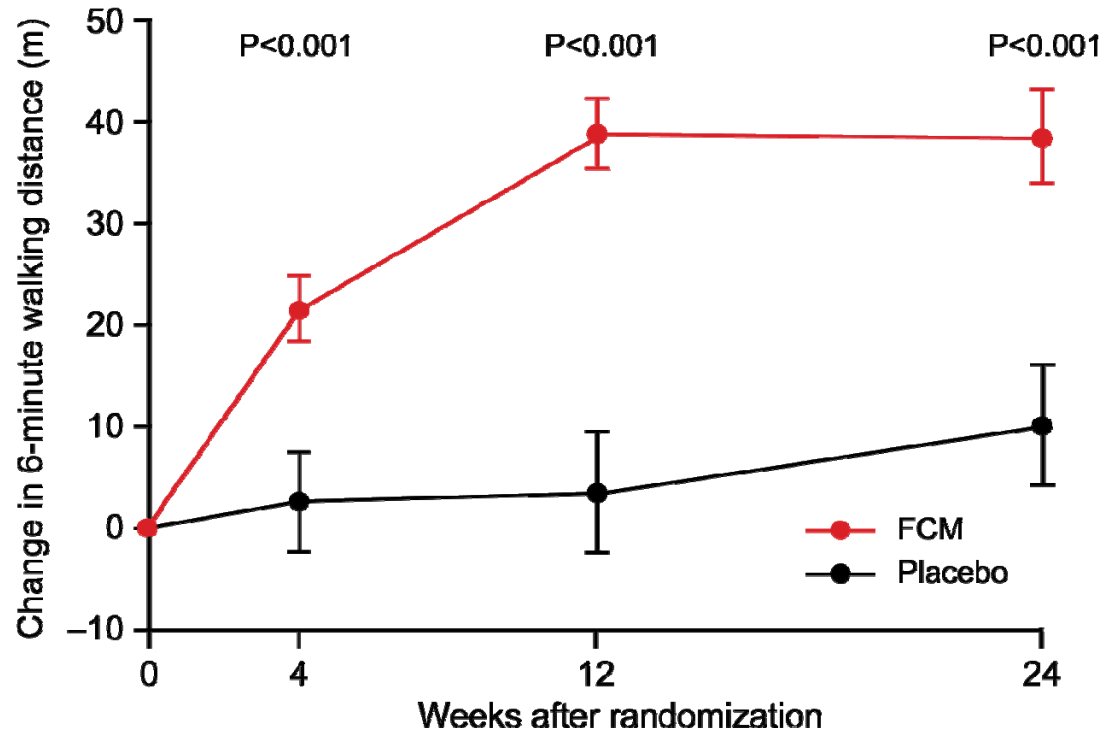
FCM				
No. of patients	303	284	280	268
Distance (mean±SE)	274±6	294±7	312±6	313±7
Placebo				
No. of patients	155	144	141	134
Distance (mean±SE)	269±9	269±10	272±10	277±10
Treatment effect (mean±SE)	-	21±6	37±7	35±8

Anker SD , Comin-Colet J et al. NEJM 2009;361:2436

Influence of intravenous ferric carboxymaltose on health-related quality of life measures in patients with chronic heart failure and iron deficiency: an analysis from the FAIR-HF study

FAIR-HF

Josep Comin Colet, MD; Mitja Lainscak, MD; Kenneth Dickstein, MD, PhD; Gerasimos Filippatos, MD; Patrick Johnson, PhD; Thomas Lüscher, MD; Claudio Mori, MD; Ronny Willenheimer, MD; Piotr Ponikowski, MD, PhD; Stefan D Anker, MD PhD; for the FAIR-HF Trial Investigators
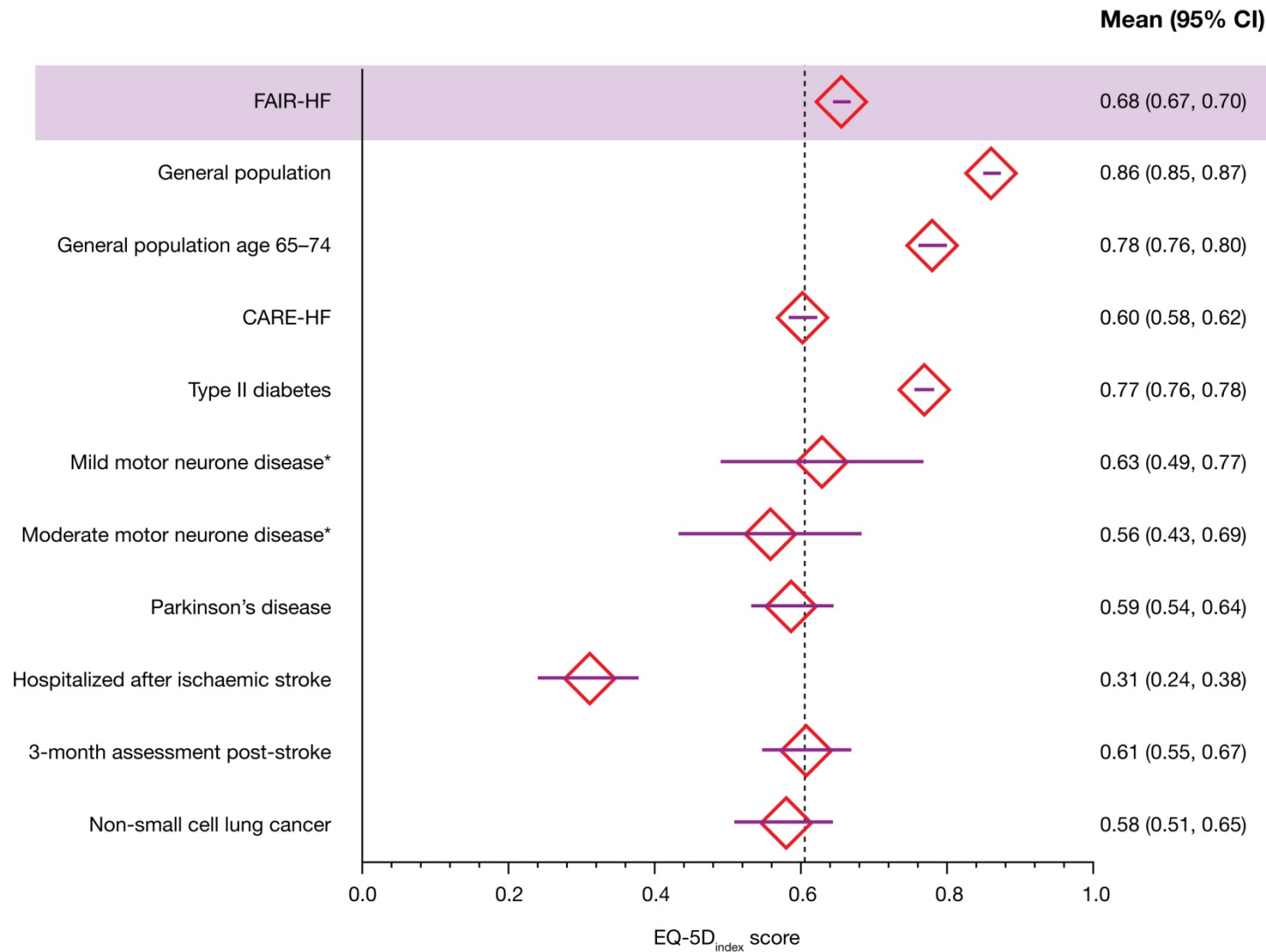
Presented in:

Heart Failure Meeting 2010, ESC Meeting 2010, AHA Scientific Meeting (Nov 2010)
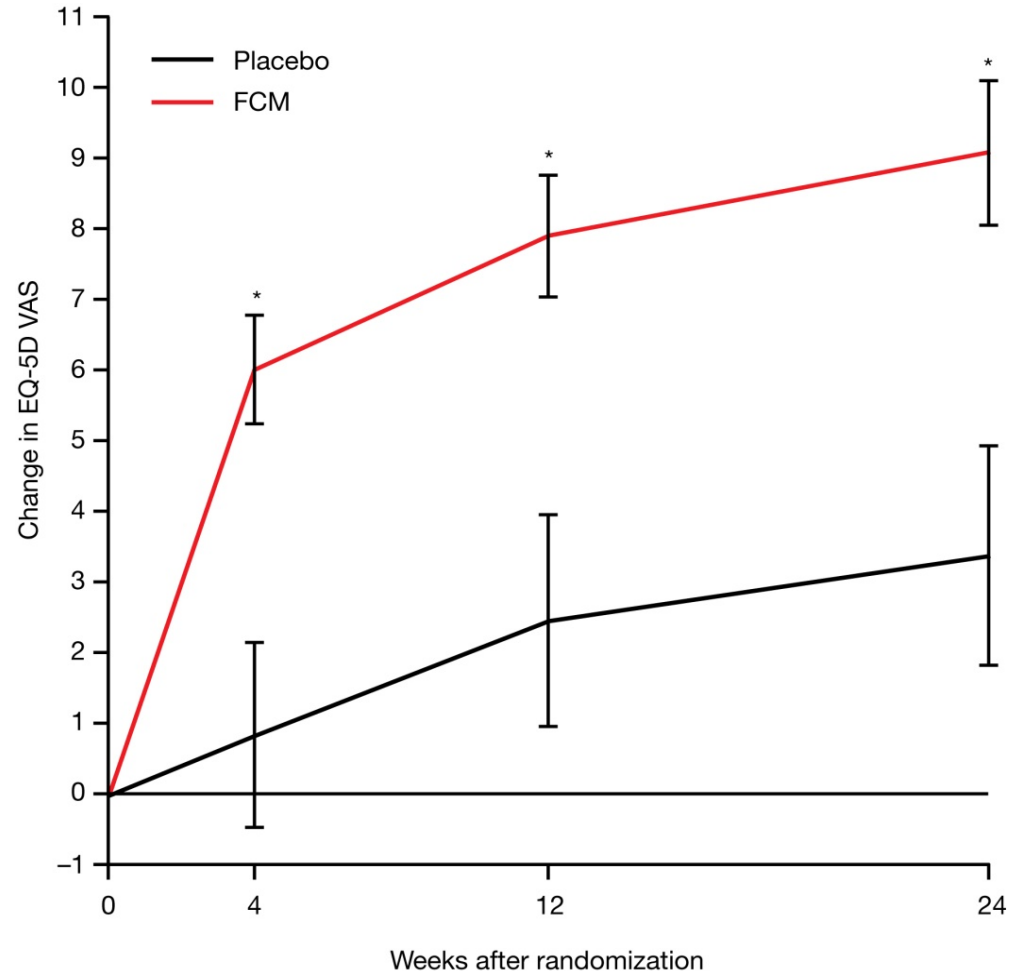
Paper Submited

Baseline QoL: Impaired in FAIR-HF patients

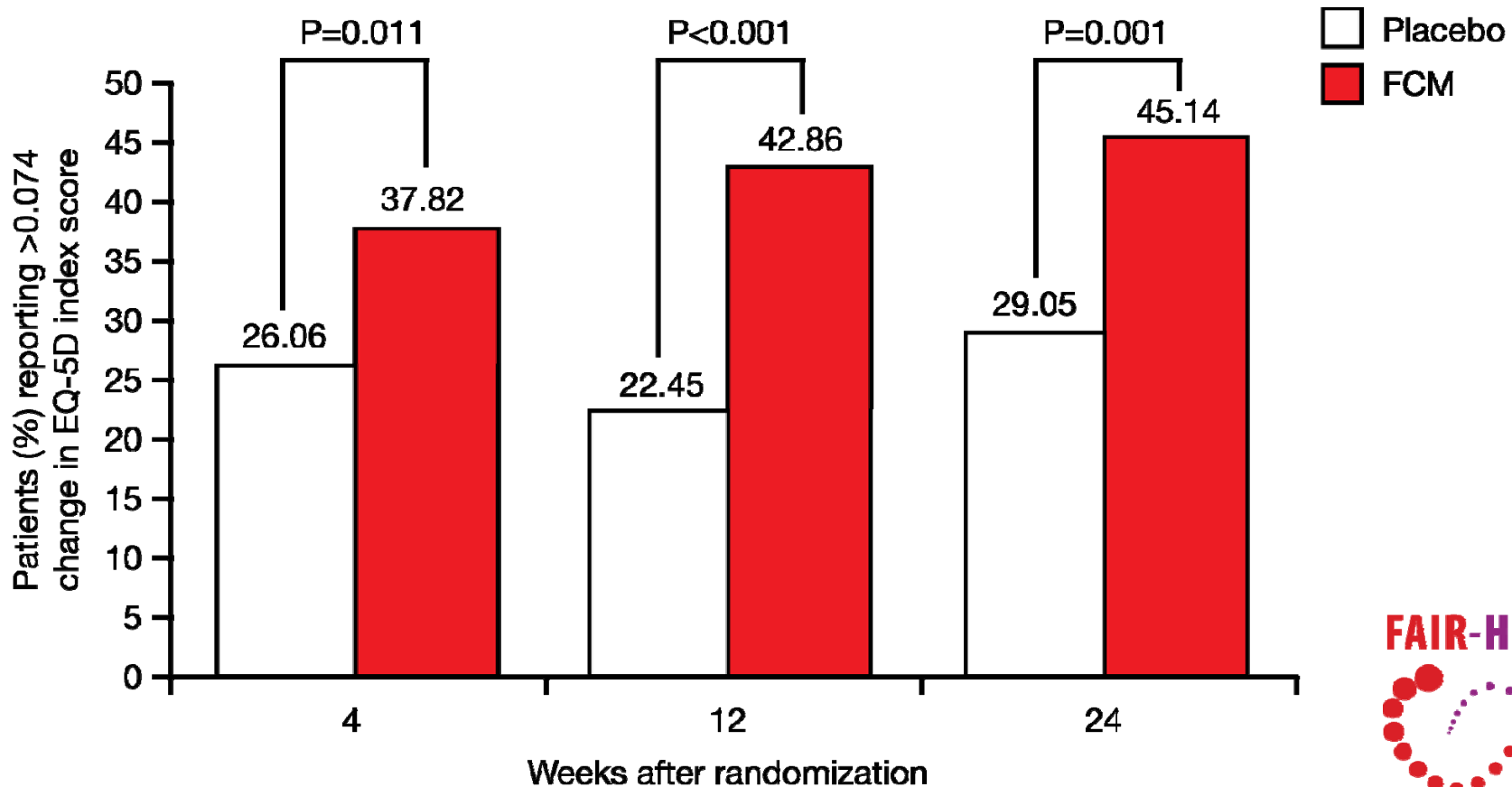Adapted from: Calvert MJ *et al. Eur J Heart Fail* 2005;7:243-51.

Treatment effects: EQ-5D VAS

n (FCM)   295   274   283   285

n (placebo)   152   140   145   146

Mean ± SE
*P<0.001 vs placebo

FAIR-HF

Treatment effects: EQ-5D index 'minimally important difference'

Fisher's exact test

Treatment effects: KCCQ

Mean ± SE; *P<0.001 vs placebo
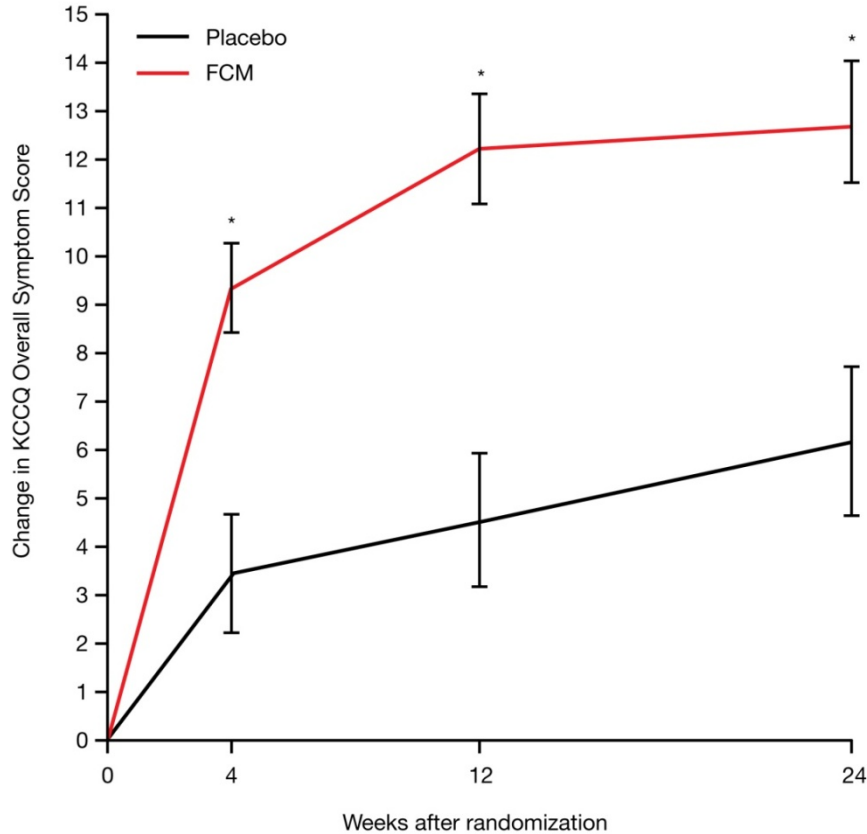
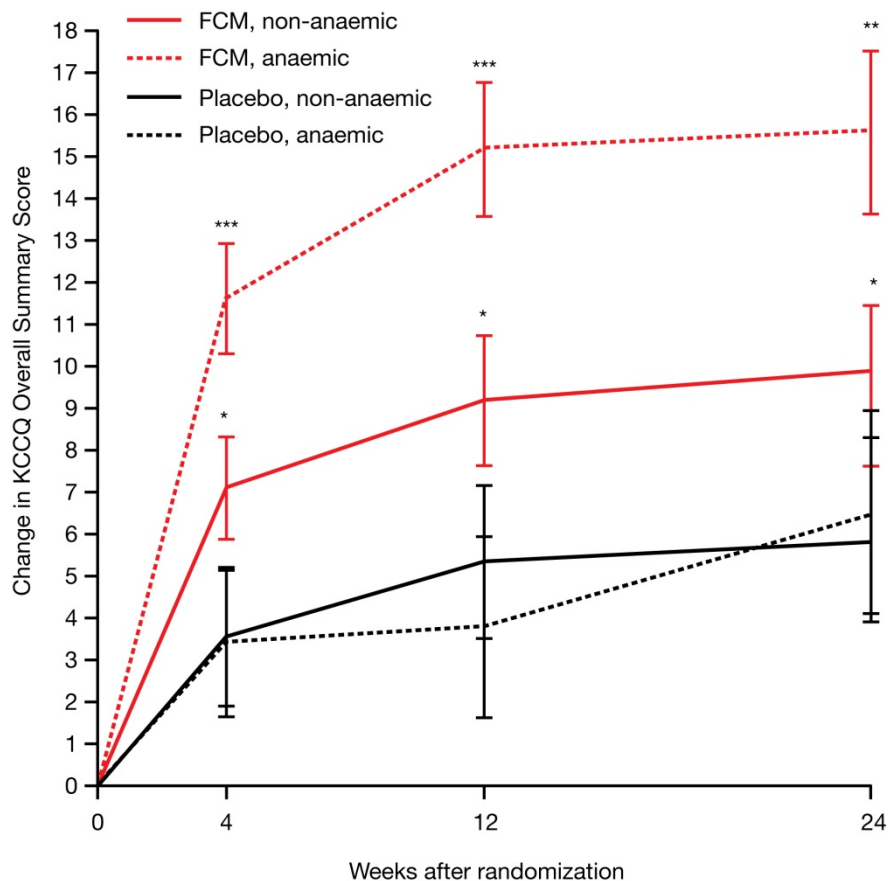|	0	4	12	24
n (FCM)	297	277	286	286
n (PBO)	151	140	144	145

P values for FCM effect vs placebo in each domain
(Repeated measures ANCOVA)

KCCQ score/domain	Week		
	4	12	24
Clinical summary score	<0.001	<0.001	<0.001
Physical limitation	<0.001	<0.001	0.003
QoL	0.004	<0.001	<0.001
Self efficacy	0.323	0.016	0.091
Social limitation	0.002	0.049	0.082
Symptom burden	<0.001	<0.001	<0.001
Symptom frequency	<0.001	<0.001	<0.001
Symptom stability	<0.001	<0.001	<0.001
Total symptom score	<0.001	<0.001	<0.001

Effect of FCM on QoL independent of baseline anaemia status: KCCQ OSS

Conclusions

- El ferro és essencial per a molts processos biològics

- El metabolisme del ferro és anormal en la majoria de malalties cròniques incloent la IC i pot tenir una repercussió negativa en la seva evolució

- Els paràmetres bioquímics pel diagnòstic de dèficit de ferro s' han de combinar per a obtenir un major rendiment

- Les evidències inicials suggereixen dades positives en milloria de símptomes, capacitat funcional i QoL amb un bon perfil de seguretat

jcomin@hospitaldelmar.cat
www.hospitaldelmar.cat/insuficiencia-cardiaca