The benefits of iron supplementation outweigh the risks

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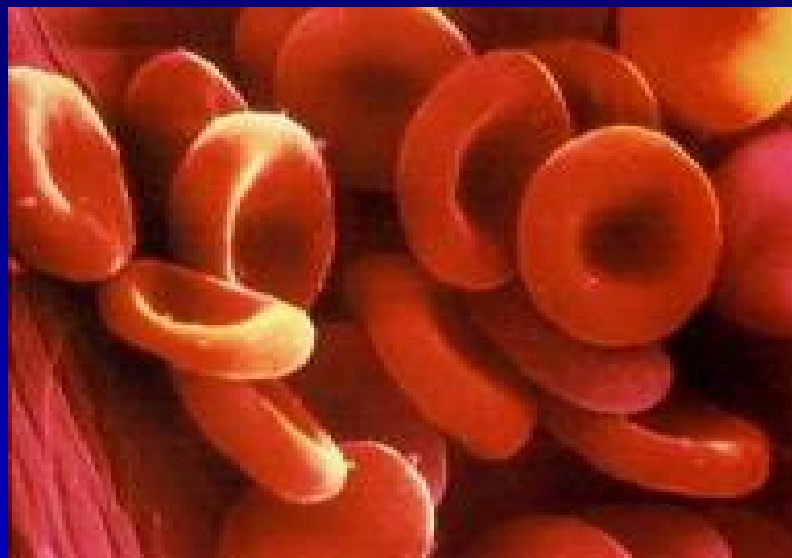

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Appointment Professor of Haematology
Research Department of Haematology
Cancer Institute
Faculty of Medical Sciences

Academic Background

1980	MRCP	Member of the Royal College of Physicians	Royal College of Physicians
1977	MB.ChB	Bachelor of Medicine, Bachelor of Surgery	University of Cambridge
1974	BA Hons	Bachelor of Arts (Honours)	University of Cambridge

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Cohen, A. R., Glimm, E., & Porter, J. B. (2008). **Effect of transfusional iron intake on response to chelation therapy in {beta}-thalassemia major**. *Blood, 111 (2)*, 583-587. doi:10.1182/blood-2007-08-109306

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3 Research Activities — **Status**

Anaemia in Surgery	Active
Mechanisms and regulation of cellular iron, glucose and phosphate transport	Active
high risk matero-fetal health	Active

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There are no Achievements to display

‘The benefits of iron supplementation outweigh the risk’

Premise of my argument

- Iron supplementation is definitely of benefit
- There is no robust clinical evidence of harm

Another premise

- To scientifically assess the benefits and/or risks of a therapeutic intervention, one can draw on evidence from:-
  - laboratory research
  - animal data
  - observational / epidemiological data
  - randomised controlled trials

IV iron – randomised controlled trials

Heart failure
FAIR-HF
CONFIRM-HF
CKD
FIND-CKD
Qunibi et al
PAH
Smith et al
Viethen et al
IBD
FERGIcor
FERGImain
Obs / Gynae
Seid et al
Van Wyck et al

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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†

ABSTRACT

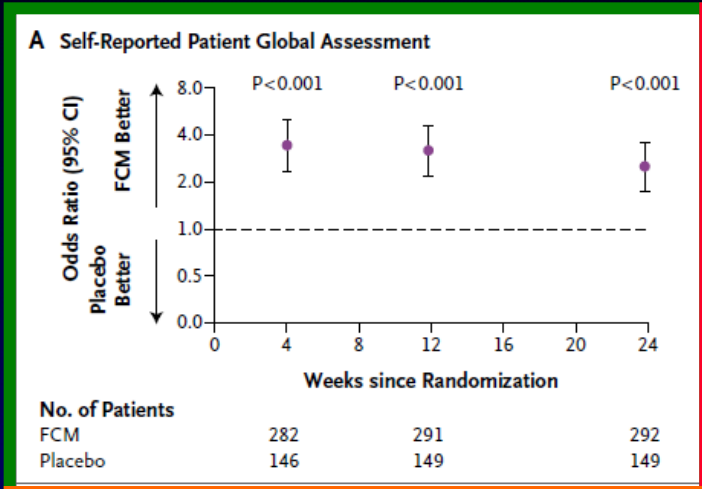
BACKGROUND

Iron deficiency may impair aerobic performance. This study aimed to determine whether treatment with intravenous iron (ferric carboxymaltose) would improve symptoms in patients who had heart failure, reduced left ventricular ejection fraction, and iron deficiency, either with or without anemia.

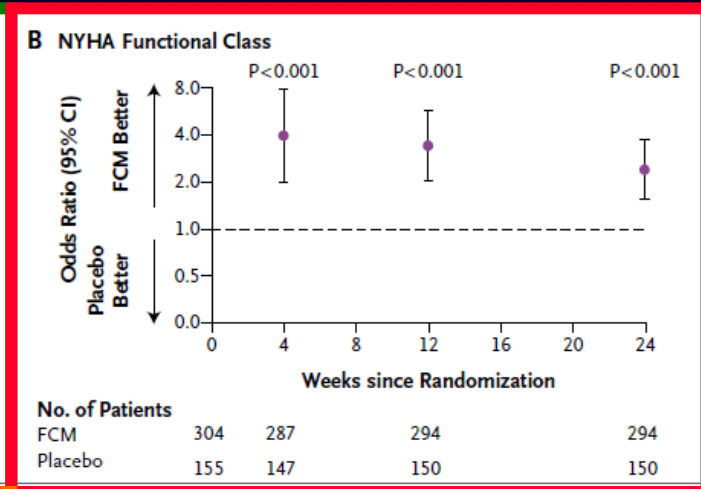
METHODS

We enrolled 459 patients with chronic heart failure of New York Heart Association (NYHA) functional class II or III, a left ventricular ejection fraction of 40% or less (for patients with NYHA class II) or 45% or less (for NYHA class III), iron deficiency (ferritin level <100 μg per liter or between 100 and 299 μg per liter, if the transferrin saturation was <20%), and a hemoglobin level of 95 to 135 g per liter. Patients were randomly assigned, in a 2:1 ratio, to receive 200 mg of intravenous iron (ferric carboxymaltose) or saline (placebo). The primary end points were the self-reported Patient Global Assessment and NYHA functional class, both at week 24. Secondary end points included the

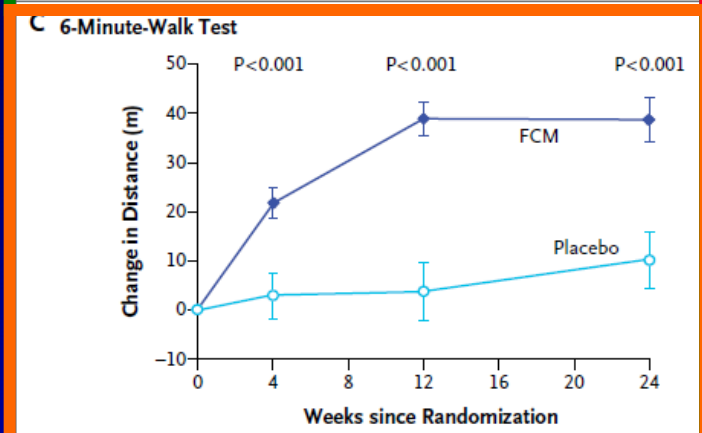
FAIR-HF: Improved QoL and functional status



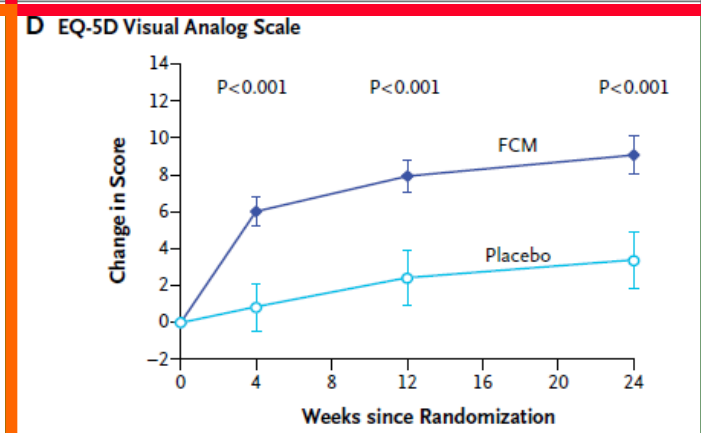
No. of Patients				
FCM	282	291		292
Placebo	146	149		149



No. of Patients				
FCM	304	287	294	294
Placebo	155	147	150	150



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	295	274	283	285
Mean score	54±1	60±1	62±1	63±1
Placebo				
No. of patients	152	140	145	146
Mean score	54±1	54±2	56±2	57±2
Mean Study-Treatment Effect		6±1	6±2	7±2

FAIR-HF: Safety

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
Any hospitalization or death	33	30 (21.2)	26	19 (27.7)	0.38
Hospitalization for any cardiovascular cause or death	21	20 (13.9)	22	16 (22.9)	0.14
First hospitalization for worsening heart failure or death	12	11 (7.5)	13	10 (13.9)	0.15

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doi:10.1093/eurheartj/ehu385

FASTTRACK ESC HOT LINE
Heart failure/cardiomyopathy

Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†

Piotr Ponikowski[1,2]*, Dirk J. van Veldhuisen[3], Josep Comin-Colet[4], Georg Ertl[5,6], Michel Komajda[7], Viacheslav Mareev[8], Theresa McDonagh[9], Alexander Parkhomenko[10], Luigi Tavazzi[11], Victoria Levesque[12], Claudio Mori[12], Bernard Roubert[12], Gerasimos Filippatos[13], Frank Ruschitzka[14], and Stefan D. Anker[15], for the CONFIRM-HF Investigators

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Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†

Aim

The aim of this study was to evaluate the benefits and safety of long-term i.v. iron therapy in iron-deficient patients with heart failure (HF).

Methods and results

CONFIRM-HF was a multi-centre, double-blind, placebo-controlled trial that enrolled 304 ambulatory symptomatic HF patients with left ventricular ejection fraction ≤45%, elevated natriuretic peptides, and iron deficiency (ferritin <100 ng/mL or 100–300 ng/mL if transferrin saturation <20%). Patients were randomized 1 : 1 to treatment with i.v. iron, as ferric carboxymaltose (FCM, $n = 152$) or placebo (saline, $n = 152$) for 52 weeks. The primary end-point was the change in 6-min-walk-test (6MWT) distance from baseline to Week 24. Secondary end-points included changes in New York Heart Association (NYHA) class, Patient Global Assessment (PGA), 6MWT distance, health-related quality of life (QoL), Fatigue Score at Weeks 6, 12, 24, 36, and 52 and the effect of FCM on the rate of hospitalization for worsening HF. Treatment with FCM significantly prolonged 6MWT distance at Week 24 (difference FCM vs. placebo: 33 ± 11 m, $P = 0.002$). The treatment effect of FCM was consistent in all subgroups and was sustained to Week 52 (difference FCM vs. placebo: 36 ± 11 m, $P < 0.001$). Throughout the study, an improvement in NYHA class, PGA, QoL, and Fatigue Score in patients treated with FCM was detected with statistical significance observed from Week 24 onwards. Treatment with FCM was associated with a significant reduction in the risk of hospitalizations for worsening HF [hazard ratio (95% confidence interval): 0.39 (0.19–0.82), $P = 0.009$]. The number of deaths (FCM: 12, placebo: 14 deaths) and the incidence of adverse events were comparable between both groups.

Conclusion

Treatment of symptomatic, iron-deficient HF patients with FCM over a 1-year period resulted in sustainable improvement in functional capacity, symptoms, and QoL and may be associated with risk reduction of hospitalization for worsening HF (ClinicalTrials.gov number NCT01453608).

NDT Advance Access published June 2, 2014

Nephrol Dial Transplant (2014) 0: 1–10
doi: 10.1093/ndt/gfu201

Original Article

FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia

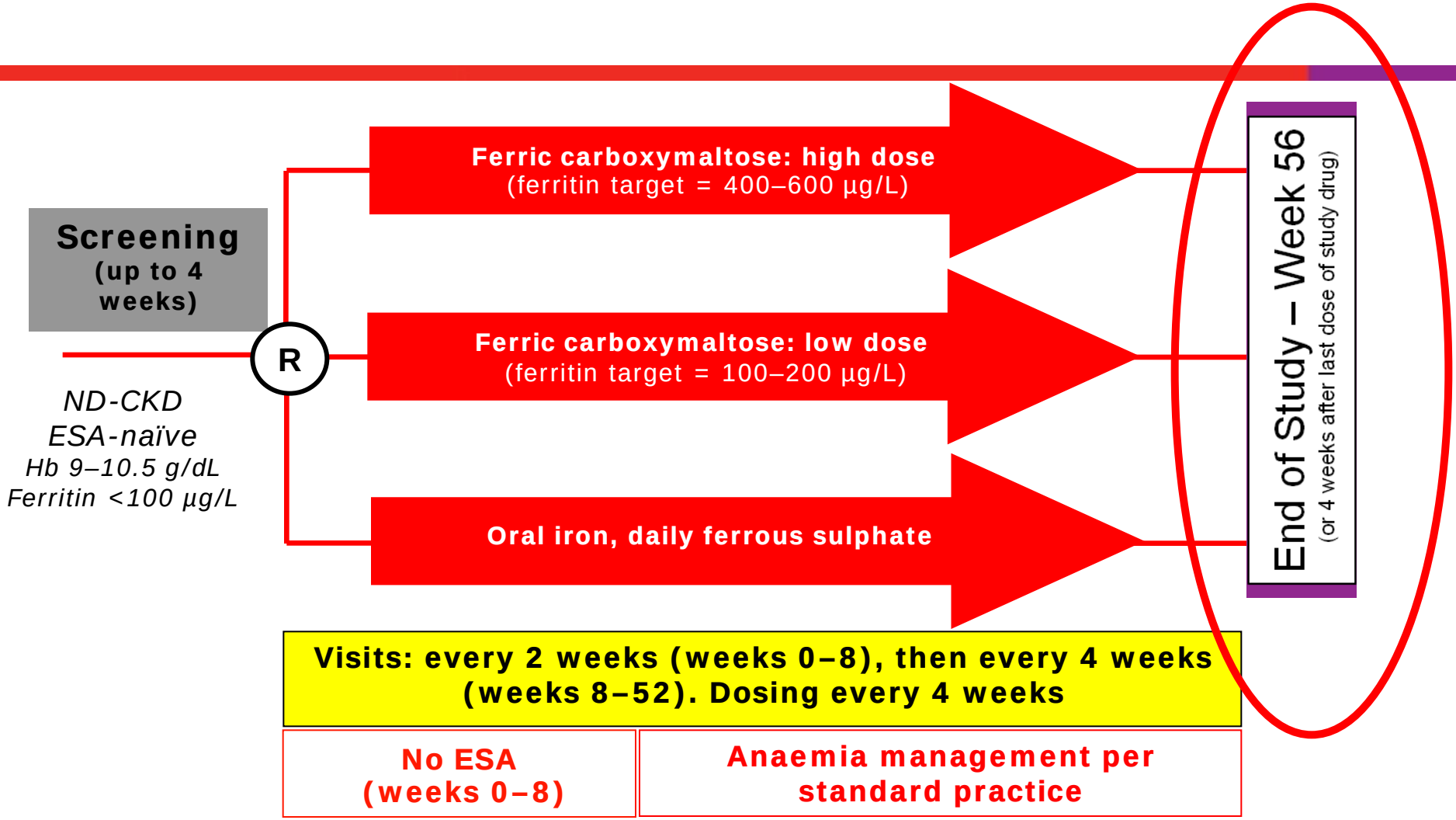
Iain C. Macdougall[1], Andreas H. Bock[2], Fernando Carrera[3], Kai-Uwe Eckardt[4], Carlo Gaillard[5], David Van Wyck[6], Bernard Roubert[7], Jacqueline G. Nolen[7] and Simon D. Roger[8] on behalf of the FIND-CKD Study Investigators[†]

[1]Department of Renal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK, [2]Department of Nephrology, Kantonsspital Aarau, Aarau, Switzerland, [3]Eurodial, DaVita, Leiria, Portugal, [4]Department of Nephrology and Hypertension, University of Erlangen-Nürnberg, Erlangen, Germany, [5]Department of Nephrology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands, [6]DaVita Healthcare Partners Inc., Denver, CO, USA, [7]Vifor Pharma, Glattbrugg, Switzerland and [8]Renal Research, Gosford, NSW, Australia

Correspondence and offprint requests to: Iain C. Macdougall; E-mail: iain.macdougall@nhs.net

[†]Members of the Ferinject® assessment in patients with Iron deficiency anaemia and Non-Dialysis-dependent

The FIND-CKD trial



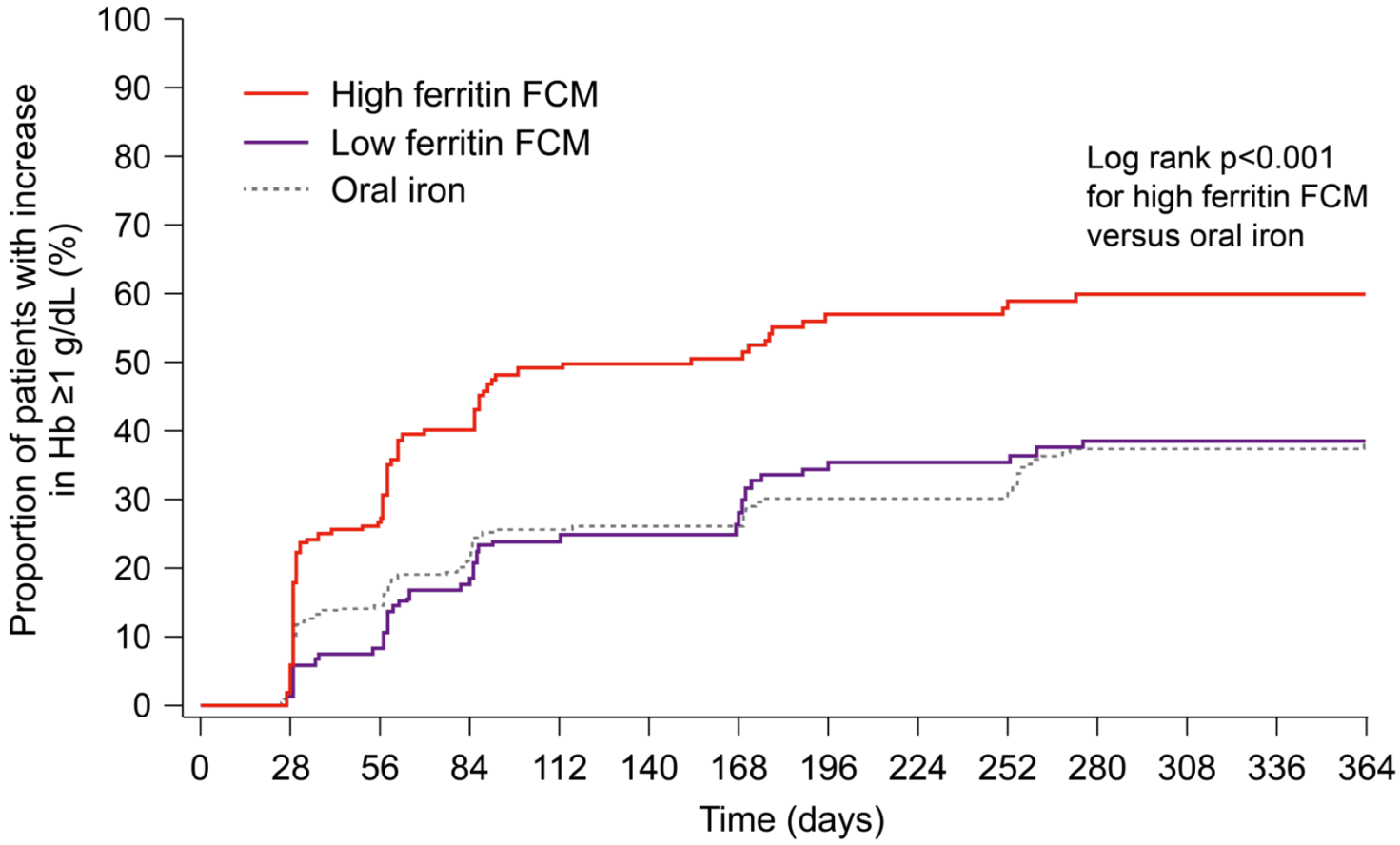
Primary objective: To evaluate the long-term efficacy of ferric carboxymaltose (using targeted ferritin levels to determine dosing) or oral iron to delay and/or reduce ESA use in ND-CKD patients with iron deficiency anaemia

Secondary objectives: To evaluate the ESA requirements, to evaluate the long-term safety and tolerability of iron therapy and evaluate the health resource and economic burden of the treatment of anaemia of ND-CKD

Primary Endpoint: Time to initiation of other Anaemia Management or Hb trigger

	High ferritin FCM (n=153)	Low ferritin FCM (n=152)	Oral iron (n=308)
Number of events (%)	36 (23.5)	49 (32.2)	98 (31.8)
Hazard ratio (95% CI)	Reference	0.70 (0.46, 1.08)	**0.65 (0.44, 0.95)**
Log rank p value	Reference	0.10	**0.026**

Increase in Hb ≥1 g/dL



Adverse Events, n (%) (1)

	High ferritin FCM (n=154)	Low ferritin FCM (n=150)	Oral iron (n=312)
Any adverse event, n (%)	126 (81.8)	130 (86.7)	255 (81.7)
Gastrointestinal disorders	32 (20.8)	38 (25.3)	128 (41.0)
Diarrhea	15 (9.7)	11 (7.3)	45 (14.4)
Constipation	2 (1.3)	5 (3.3)	37 (11.9)
Nausea	9 (5.8)	7 (4.7)	15 (4.8)
Dyspepsia	2 (1.3)	3 (2.0)	17 (5.4)
Infections	**51 (33.1)**	**51 (34.0)**	**95 (30.4)**
Urinary tract infection	18 (11.7)	10 (6.7)	17 (5.4)
Nasopharyngitis	13 (8.4)	10 (6.7)	16 (5.1)
Influenza	4 (2.6)	8 (5.3)	7 (2.2)
General disorders and administrative site conditions	36 (23.4)	35 (23.3)	67 (21.5)
Peripheral oedema	21 (13.6)	21 (14.0)	29 (9.3)

JAMA. 2009 Oct 7;302(13):1444-50. doi: 10.1001/jama.2009.1404.

Effects of iron supplementation and depletion on hypoxic pulmonary hypertension: two randomized controlled trials.

Smith TG[1], Talbot NP, Privat C, Rivera-Ch M, Nickol AH, Ratcliffe PJ, Dorrington KL, León-Velarde F, Robbins PA.

Author information

Abstract

CONTEXT: Hypoxia is a major cause of pulmonary hypertension in respiratory disease and at high altitude. Recent work has established that the effect of hypoxia on pulmonary arterial pressure may depend on iron status, possibly acting through the transcription factor hypoxia-inducible factor, but the pathophysiological and clinical importance of this interaction is unknown.

OBJECTIVE: To determine whether increasing or decreasing iron availability modifies altitude-induced hypoxic pulmonary hypertension.

DESIGN, SETTING, AND PARTICIPANTS: Two randomized, double-blind, placebo-controlled protocols conducted in October-November 2008. In the first protocol, 22 healthy sea-level resident men (aged 19-60 years) were studied over 1 week of hypoxia at Cerro de Pasco, Peru (altitude 4340 m). In the second protocol, 11 high-altitude resident men (aged 30-59 years) diagnosed with chronic mountain sickness were studied over 1 month of hypoxia at Cerro de Pasco, Peru.

INTERVENTION: In the first protocol, participants received intravenous infusions of Fe(III)-hydroxide sucrose (200 mg) or placebo on the third day of hypoxia. In the second protocol, patients underwent staged isovolemic venesection of 2 L of blood. Two weeks later, patients received intravenous infusions of Fe(III)-hydroxide sucrose (400 mg) or placebo, which were subsequently crossed over.

MAIN OUTCOME MEASURE: Effect of varying iron availability on pulmonary artery systolic pressure (PASP) assessed by Doppler echocardiography.

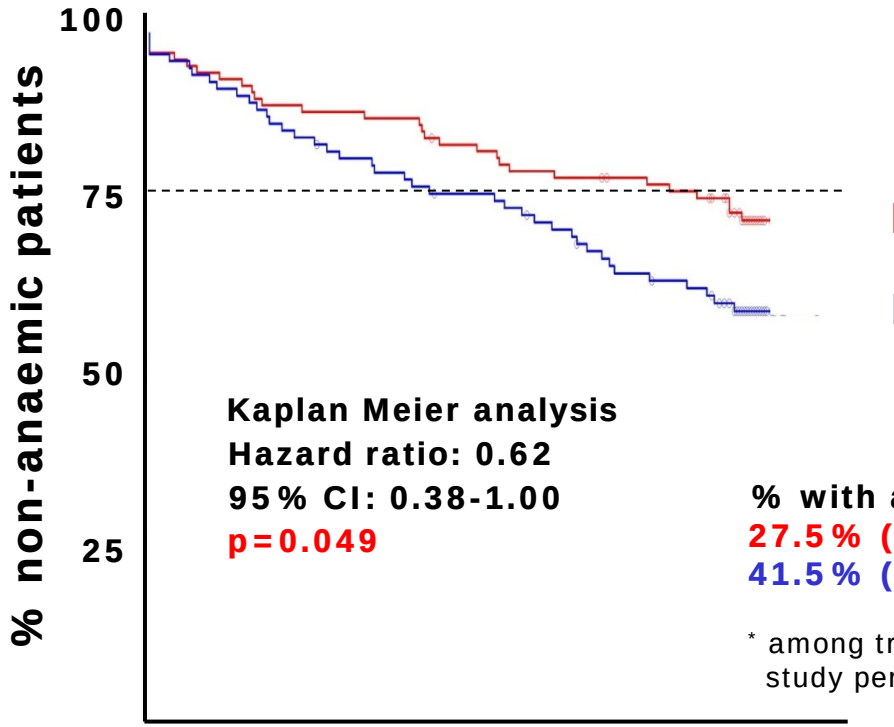
RESULTS: In the sea-level resident protocol, approximately 40% of the pulmonary hypertensive response to hypoxia was reversed by infusion of iron, which reduced PASP by 6 mm Hg (95% confidence interval [CI], 4-8 mm Hg), from 37 mm Hg (95% CI, 34-40 mm Hg) to 31 mm Hg (95% CI, 29-33 mm Hg; P = .01). In the chronic mountain sickness protocol, progressive iron deficiency induced by venesection was associated with an approximately 25% increase in PASP of 9 mm Hg (95% CI, 4-14 mm Hg), from 37 mm Hg (95% CI, 30-44 mm Hg) to 46 mm Hg (95% CI, 40-52 mm Hg; P = .003). During the subsequent crossover period, no acute effect of iron replacement on PASP was detected.

CONCLUSION: Hypoxic pulmonary hypertension may be attenuated by iron supplementation and exacerbated by iron depletion.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00952302.

Primary endpoint: Longer time to recurrence of anaemia with FCM

- Time to recurrence of anaemia in 25% of patients: **7.6 months (FCM)** vs. **4.7 months (placebo)**



FCM	105	94	87	81	21
Placebo	99	84	74	63	19

Evstatiev R et al. Clin Gastroenterol Hepatol 2012

FERGImain: Safety results

n (%)	FCM (N=105)	Placebo (N=99)	No Treatment (N=41)	p-value*
Any TEAE	62 (59.0)	50 (50.5)	16 (39.0)	0.09
Any SAE	7 (6.7)	8 (8.1)	3 (7.3)	0.95
Related TEAE	8 (7.6)	1 (1.0)	1 (2.4)	0.04†
Related SAE	0	0	0	
Related TEAE leading to discontinuation	2 (1.9)	0	0	0.65
Death	0	0	0	

* over all groups (FCM, Placebo, No Treatment), † FCM vs. Placebo

- Most common TEAE was worsening of UC (6.7% [FCM], 12.1% [placebo])
- GI symptoms were less frequent with FCM (20.0% vs. 28.3%; p=0.17)

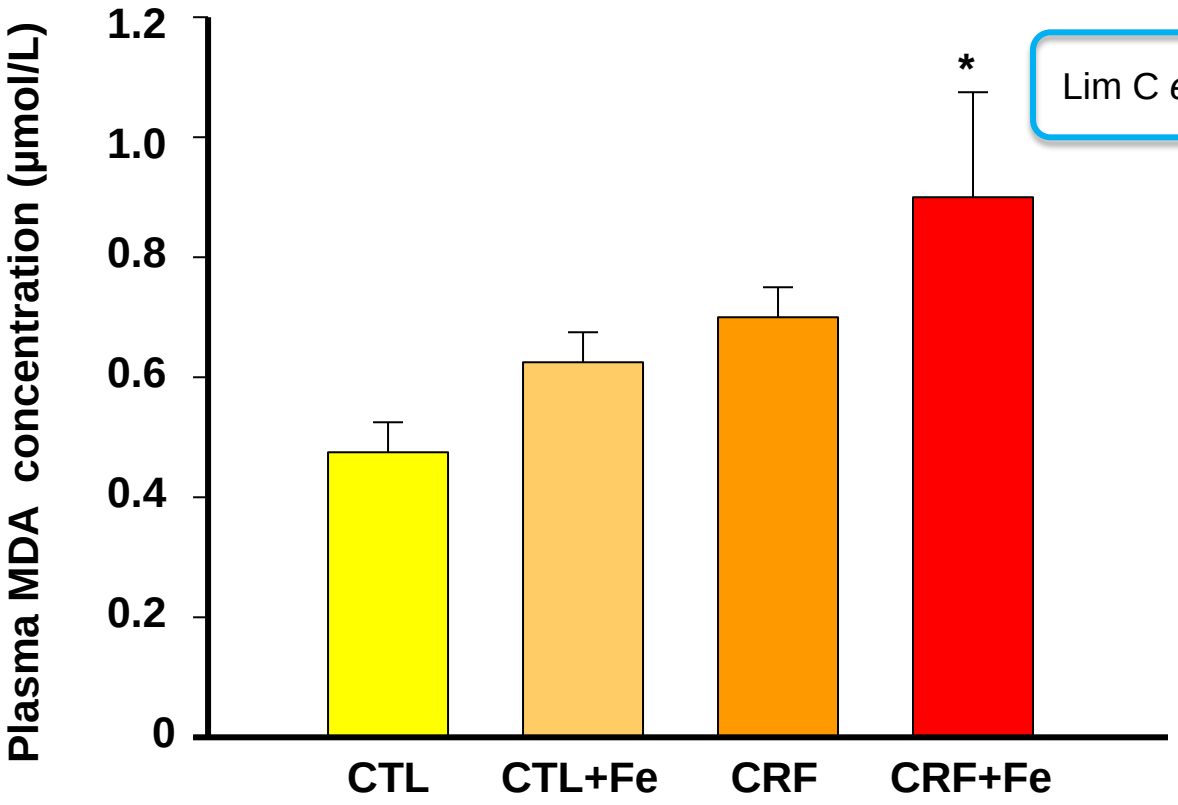
TEAE treatment-emergent adverse event;
UC ulcerative colitis; GI, gastrointestinal.

Evstatiev R et al. Clin Gastroenterol Hepatol 2012.

IV iron

Safety / harm / risks

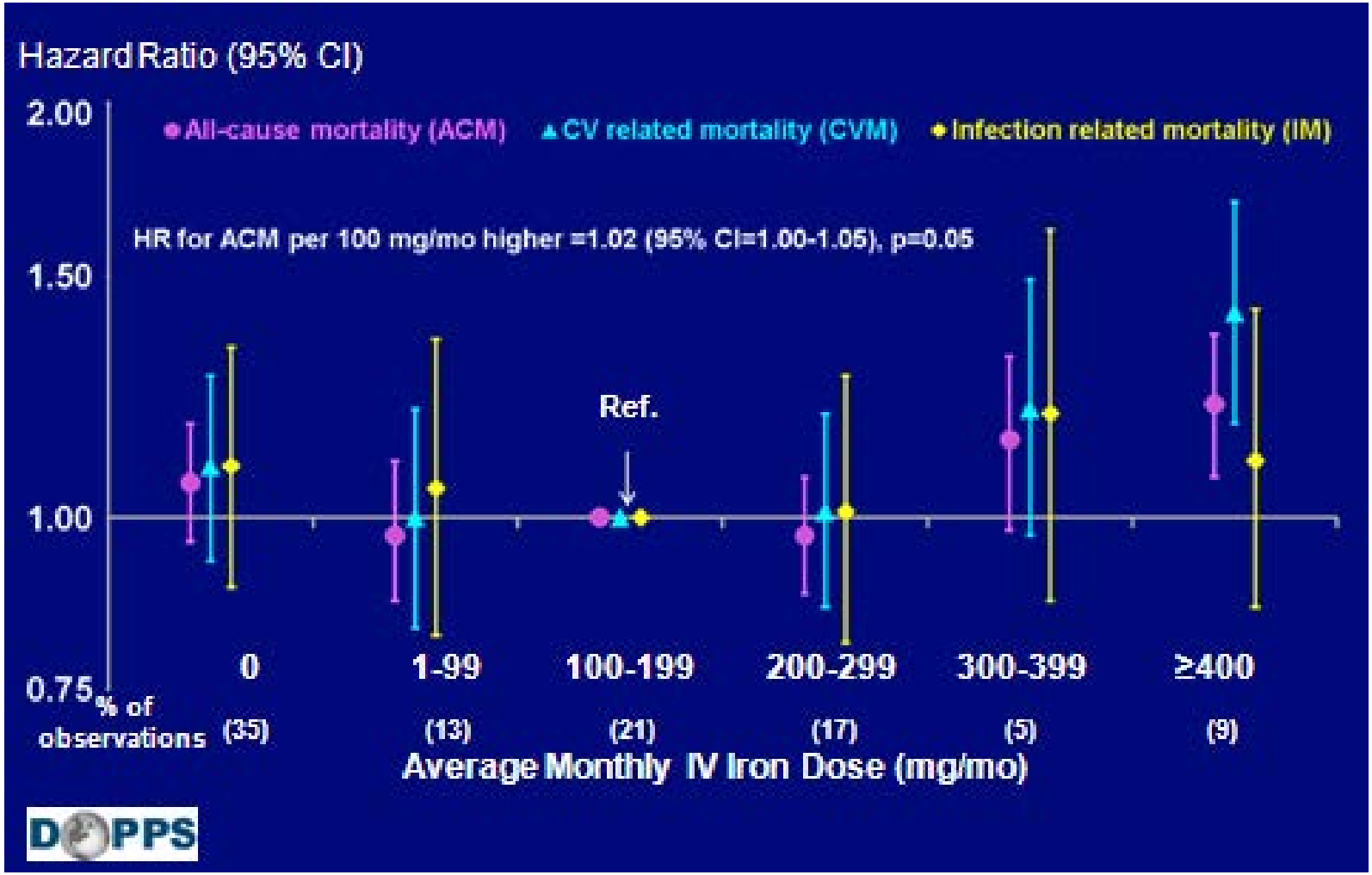
Iron and oxidative stress



Lim C *et al. Kidney Int* 2004;65:1802–9.

Plasma malondialdehyde (MDA) levels in control rats (CTL), Fe-injected control rats (CTL+Fe), chronic renal failure rats (CRF), and Fe-injected CRF rats (CRF+ Fe). (*N = 6 in each group) ⁎P < 0.05 vs. CTL group.*

Associations between IV iron dose and mortality



PIVOTAL

Proactive IV irOn Therapy in haemodiALysis patients

Proactive IV iron arm – IV iron sucrose 400 mg/month

(withhold if ferritin >700 µg/L)

Incident new HD patients (0–12 mths)

On ESA

R

Reactive – minimalistic IV iron arm (give IV iron if ferritin <200 µg/L)

Primary endpoint

Time to all-cause mortality or composite of MI, stroke, HF hosp

Up to 4 weeks screening

Total study period approximately 4 years *(event-driven)* – projected treatment duration per patient ≥ 2 years

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

Network of Sites

King's College Hospital NHS
NHS Foundation Trust

49 Participating sites

England

Queen Elizabeth Hospital, Birmingham; Heartlands Hospital, Birmingham; Royal Free, London, King's College Hospital, London; Guy's & St Thomas', London; St Helier, Surrey; St George's, London; Royal Liverpool Hospital, University Hospital Aintree; Sheffield Teaching Hospital; Lister Hospital, Stevenage; Salford Royal Hospital, Manchester; Manchester Royal Hospital; Queen Alexandra Hospital, Portsmouth; Kent & Canterbury Hospital, Leicester General Hospital, Hull Royal Infirmary; Freeman Hospital, Newcastle; Churchill Hospital, Oxford; University Hospital of North Staffordshire, Stoke-on-Trent; Southmead Hospital, Bristol; Royal Cornwall Hospital; Nottingham City Hospital; Norfolk & Norwich Hospital; New Cross Hospital, Wolverhampton; Royal London Hospital; Wirral University Teaching Hospital; Royal Shrewsbury Hospital, Royal Devon & Exeter Hospital, Royal Preston Hospital, St James' Hospital, Leeds; Hammersmith Hospital, London; Gloucestershire Royal Hospital, Bradford Teaching Hospital, Coventry University Hospital, Worthing Hospital, Southend Hospital, Ipswich Hospital, Brighton Hospital

Wales

Morriston Hospital, Swansea; University Hospital, Cardiff

Scotland

Western Infirmary, Glasgow; Victoria Hospital, Kirkcaldy; Ninewells Hospital, Dundee; Dumfries (PI tbc), Edinburgh (PI tbc)

N. Ireland

Belfast City Hospital, Antrim Area Hospital, Daisy Hill Hospital, Newry

THE RENAL ASSOCIATION
founded 1950
Kidney Research Consortium : Renal Anaemia CSG

Kidney Research UK
Funding research to save lives

www.kidneyresearchuk.org

Conclusions

- Iron supplementation is of benefit
- There is no robust clinical evidence of harm