

Implementation of guidelines: The practicalities of giving IV iron

Carla Plymen
Cardiology Consultant & Heart Failure Specialist

Quick recap...

- Iron deficiency is very common and can occur with a normal haemoglobin
- Iron deficiency is linked to adverse outcome in HFrEF
- Iron repletion is associated with improvements in symptoms, functional status and decrease in HF hospitalisation

Definition of iron deficiency in Heart Failure

Functional iron deficiency	Inadequate iron supply to meet demand despite normal or abundant iron stores Normal or high ferritin (100-300ng/ml) TSAT <20% High hepcidin
Absolute iron deficiency	Depleted body iron stores Low serum ferritin (<100ng/ml) TSAT <20% Low hepcidin

ESC guidance

Recommendations for diagnostic tests in patients with heart failure

Recommendations	Class ^a	Level ^b
<p>The following diagnostic tests are recommended/should be considered for initial assessment of a patient with newly diagnosed HF in order to evaluate the patient's suitability for particular therapies, to detect reversible/treatable causes of HF and co-morbidities interfering with HF:</p> <ul style="list-style-type: none"> - haemoglobin and WBC - sodium, potassium, urea, creatinine (with estimated GFR) - liver function tests (bilirubin,AST,ALT,GGTP) - glucose, HbA1c - lipid profile - TSH - ferritin, TSAT = TIBC - natriuretic peptides 	I	C
	IIa	C

SIGN guidance



SIGN 147 • Management of chronic heart failure

A national clinical guideline

March 2016



- R** Patients with heart failure with reduced ejection fraction, NYHA class III with an LVEF $\leq 45\%$, or NYHA class II, LVEF $\leq 40\%$, who have a haemoglobin level of 9.5 to 13.5 and iron deficiency (defined as ferritin < 100 microgm/l or < 300 microgm/l if TSAT $< 20\%$) should be considered for therapy with intravenous iron.

Who to check for iron deficiency?



The NEW ENGLAND JOURNAL of MEDICINE

HOME

ARTICLES & MULTIMEDIA ▾

ISSUES ▾

SPECIALTIES & TOPICS ▾

FOR AUTHORS ▾

CME >

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^{*}
N Engl J Med 2009; 361:2436-2448 | [December 17, 2009](#) | DOI: 10.1056/NEJMoa0908355

Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure (EFFECT-HF)



Dirk J. van Veldhuisen, Piotr Ponikowski, Marco Metra,
Michael Böhm, Peter van der Meer, Artem Doletsky,
Adriaan A. Voors, Iain MacDougall, Bernard Roubert,
Stefan D. Anker, Alain Cohen Solal
for the EFFECT-HF Investigators.



[Eur Heart J](#). 2015 Mar 14; 36(11): 657–668.

PMCID: PMC4359359

Published online 2014 Aug 31. doi: [10.1093/eurheartj/ehu385](https://doi.org/10.1093/eurheartj/ehu385)

Editor's choice

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

Who to check for iron deficiency?

Chronic heart failure

LVEF \leq 45%

NYHA class II-IV

(Raised NTpro-BNP/BNP)

Where to find the patients to check

All HF patient should be getting 6 monthly review as per NICE guidelines

Can be checked at consultant review, HF specialist nurse or GP review

What form of iron to use?



IRONOUT vs FAIR, CONFIRM, EFFECT

IV iron is the preferred form of delivery in HF



What kind of iron do we use in HFrEF?



The NEW ENGLAND JOURNAL of MEDICINE

HOME

ARTICLES & MULTIMEDIA ▾

ISSUES ▾

SPECIALTIES & TOPICS ▾

FOR AUTHORS ▾

CME >

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*

N Engl J Med 2009; 361:2436-2448 | [December 17, 2009](#) | DOI: 10.1056/NEJMoa0908355

Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure (EFFECT-HF)



Dirk J. van Veldhuisen, Piotr Ponikowski, Marco Metra,
Michael Böhm, Peter van der Meer, Artem Doletsky,
Adriaan A. Voors, Iain MacDougall, Bernard Roubert,
Stefan D. Anker, Alain Cohen Solal
for the EFFECT-HF Investigators.



[Eur Heart J](#). 2015 Mar 14; 36(11): 657–668.

PMCID: PMC4359359

Published online 2014 Aug 31. doi: [10.1093/eurheartj/ehu385](https://doi.org/10.1093/eurheartj/ehu385)

Editor's choice

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

What kind of iron do we use in HFrEF?

i.v. ferric carboxymaltose (FCM) has demonstrated benefit in clinical trials in patients with HFrEF and iron deficiency

ESC guidance

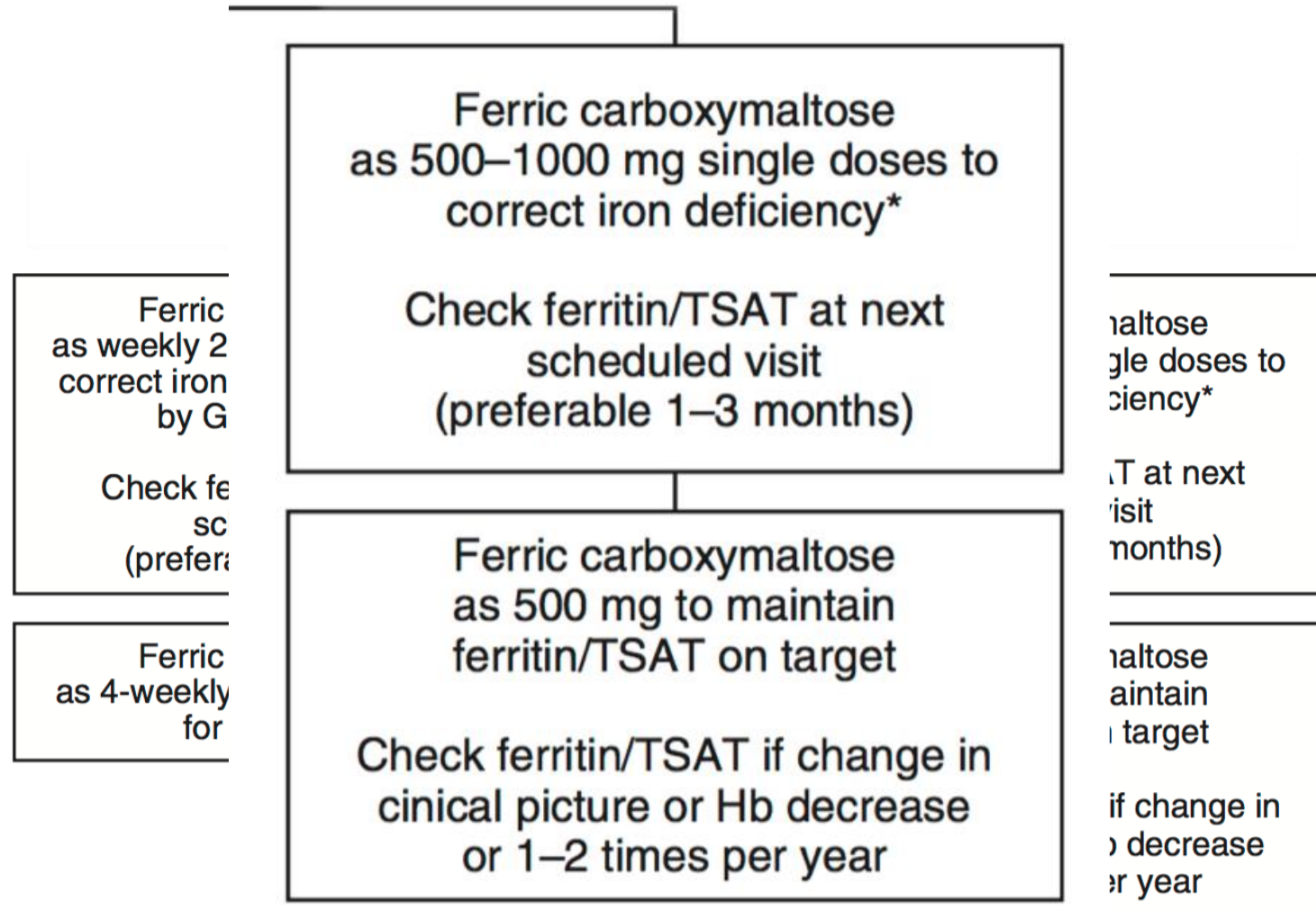
Recommendations	Class ^a	Level ^b	Ref ^c
Iron deficiency			
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A	469, 470



"I CAN'T BELIEVE THIS! YOU'RE LOW IN IRON."

So what happens next?

Suggested algorithm to treat iron deficiency



ESC Guidance: Administration Protocol

- Ferric carboxymaltose (FCM) is administered by IV injection or infusion
 - IV infusion is preferred
- For IV infusion, the solution must be **diluted with 0.9% NaCl**
- Maximum single dose is 20mg iron/kg of body weight to a **maximum of 1000mg**

Implementing ESC Guidance: Administration Protocol

- Maximum recommended cumulative dose of FCM is 1,000 mg of iron (20 mL FCM) per week
 - Patients requiring higher cumulative doses than permitted by single infusion will come back for their second dose *at least one week after*.
- Patients should be monitored for 30 mins following infusion before being allowed home



Implementing ESC Guidance: Dosing Regime

Hb (g/l)	Body weight 35kg to < 70kg	Body weight >70kg
<100	1500mg	2000mg
>100	1000mg	1500mg

Patients requiring >1000mg of FCM will need to come back for their second dose at least one week after the first

Reassessment of iron deficiency

- Reassessment of iron status should be undertaken at least one month after iron replacement in order to allow adequate time for erythropoiesis and iron utilisation
- In the event the patient requires further iron repletion, the iron need should be recalculated using the table in the same way as previous

Implementing ESC Guidance: Dilution plane and administration rates

Volume of FCM required	Equivalent iron dose	Maximum amount of 0.9% NaCl solution	Administration rate
2-4ml	100-200mg	50ml	No min. rate
>4-10ml	>200 to 500mg	100ml	6 minutes
>10-20ml	>500-1000mg	250ml	15 minutes

Patients should be monitored for 30 mins following infusion before being allowed home

Implementing ESC Guidance: Risks & Reactions

- FCM should be administered by trained staff who can manage anaphylactic reactions. These are rare (test doses of IV iron are not necessary) however resuscitation equipment should be present on site when administering this drug.
- Risk of anaphylactoid reaction $<1/1000$
- IV iron administration should be *rescheduled* in those who have concurrent systemic illness.



Risks & Reactions

Common side effects:

- Hypophosphataemia
- Headache or dizziness
- Injection / Infusion site reactions
- Flushing, Hypertension
- Nausea



Administration of iron is the easy part!

- IV agent
- Trained staff
- Resuscitation training and equipment
- Requires a hospital visit of about 1 hr

However....

- Need to be able to facilitate that service ...

Administration of iron is the easy part!

- Consider using a service already providing IV iron facilities:
 - Renal
 - Haematology
 - Gastroenterology
- Using an established ambulatory service
- Set up a dedicated day case cardiology/heart failure service
 - Could link it to CQUIN?

Burden & Cost effectiveness

- ~50% of HFrEF patients are thought to be iron deficient
 - 68% of 81449 patients have HFrEF
 - 27,693 patients/year needing iron infusion
 -and these are just the discharges!
- Trained staff and equipment may incur additional costs to services.

Cost effectiveness – Financial burden of HF

- IV FCM has been shown to be cost effective vs placebo (↑QoL and ↓ hospitalisation) over 24 weeks.
- UK-based analysis showed that IV FCM had a costing of £12,482 per QALY gained (threshold of £20,000-£30,000/QALY gained typically used by NICE)
- Improved symptoms and better quality of life contributed to this result..
- Specialist HF services decrease cost to 40% of total HF budget (driven by reduction in hospitalisation)
 - Iron repletion will play a significant role in this

But what about NICE: Diagnosis

1.2.12 Perform an ECG and consider the following tests to evaluate possible aggravating factors and/or alternative diagnoses:

- chest X-ray
- blood tests:
 - renal function profile
 - thyroid function profile
 - liver function profile
 - lipid profile
 - glycosylated haemoglobin (HbA_{1c})
 - full blood count
- urinalysis
- peak flow or spirometry. [2010, amended 2018]

But what about NICE?

Clinical review

1.7.1 All people with chronic heart failure need monitoring. This monitoring should include:

- a clinical assessment of functional capacity, fluid status, cardiac rhythm (minimum of examining the pulse), cognitive status and nutritional status
- a review of medication, including need for changes and possible side effects
- an assessment of renal function^[2]. [2010, amended 2018]

But what about NICE?

- ‘No Recommendation’ was given with regards to iron repletion
- This is the final version – following on from stakeholder comments
- I will continue to follow the ESC guidance for diagnostic workup and clinical review for many reasons:
 - Ferritin is essential to rule out iron overload cardiomyopathy. This is a really easy test to do.
 - We have established today that iron repletion is an important part of HF management
 - ECG should be routine at least yearly as QRSd can change
 - I would suggest that LFT’s, TFT’s and FBC should also be undertaken yearly.

Horizon scanning - in the pipeline...

AFFIRM-AHF

- Randomised, double-blind placebo controlled trial comparing IV ferric carboxymaltose in iron deficient patients admitted for acute heart failure
- Phase 4 study
- CV hospitalisations and mortality

IRONMAN

- Randomised, open-label multicentre trial comparing the effectiveness of IV isomaltoside (Monofer) vs standard care in patients with chronic heart failure and iron deficiency
- Phase 4 study
- Mortality or hospitalisation for worsening heart failure

Summary

- Ferritin & TSAT's should be checked at least 6 monthly in HFrEF & NYHA II-IV
- If iron deficient, ESC guidelines recommend IV ferric carboxymaltose should be given as per dosing regime in one or two divided doses
- Requires trained staff and on site resuscitation equipment
- A cost-analysis study has shown IV iron in HFrEF to be cost effective; driven by reduced hospitalisation and improved quality of life

Remember to check
ferritin +/- TSAT levels
in all patients with
reduced LVEF every 6
months.

