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STUDY DESIGN

Rationale and design of the AFFIRM-AHF trial: a randomised, double-blind, placebo-controlled trial comparing the effect of intravenous ferric carboxymaltose on hospitalisations and mortality in iron-deficient patients admitted for acute heart failure

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Aims

Iron deficiency (ID) is a common co-morbidity in heart failure (HF), associated with impaired functional capacity, poor quality of life and increased morbidity and mortality. Treatment with intravenous (i.v.) ferric carboxymaltose (FCM) has shown improvements in functional capacity, symptoms and quality of life in stable HF patients with reduced ejection fraction. The effect of i.v. iron supplementation on morbidity and mortality in patients hospitalised for acute HF (AHF) and who have ID has yet to be established. The objective of the present article is to present the rationale and design of the AFFIRM-AHF trial (ClinicalTrials.gov NCT02937454) which will investigate the effect of i.v. FCM (vs. placebo) on recurrent HF hospitalisations and cardiovascular (CV) mortality in iron-deficient patients hospitalised for AHF.

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Methods AFFIRM-AHF is a multicentre, randomised (1:1), double-blind, placebo-controlled trial which recruited 1100 patients hospitalised for AHF and who had iron deficiency ID defined as serum ferritin <100 ng/mL or 100–299 ng/mL if transferrin saturation <20%. Eligible patients were randomised (1:1) to either i.v. FCM or placebo and received the first dose of study treatment just prior to discharge for the index hospitalisation. Patients will be followed for 52 weeks. The primary outcome is the composite of recurrent HF hospitalisations and CV mortality. The main secondary outcomes include the composite of recurrent CV hospitalisations and CV mortality, recurrent HF hospitalisations and safety-related outcomes.

Conclusion The AFFIRM-AHF trial will evaluate, compared to placebo, the effect of i.v. FCM on morbidity and mortality in iron-deficient patients hospitalised for AHF.

Keywords Acute heart failure • Iron deficiency • Ferric carboxymaltose • Recurrent heart failure hospitalizations • Cardiovascular mortality

Introduction

Hospitalisation for acute heart failure (AHF) is frequent and is associated with post-discharge heart failure (HF) readmission rates of between 30% and 40% in the following 6 months.[1–3] Additionally, mortality in these patients remains unacceptably high – the recent European Society of Cardiology (ESC) Heart Failure Long-Term Registry reports 1-year mortality in AHF patients reaching almost 24%.[4–6] Currently, there is no evidence-based therapy which has improved clinical outcomes, mortality and morbidity in this population.[7]

Acute HF represents a broad spectrum of disease states, with heterogeneous clinical presentations, but may be characterized by either a progressive or rapid onset of worsening of signs and symptoms, leading to urgent hospitalisation. Co-existing cardiovascular (CV) and non-CV co-morbidities are common in patients hospitalised for AHF and these co-morbidities impact on the management and the natural course in this acute phase of the disease. The 2016 ESC HF guidelines endorse that co-morbidities should be considered when defining the overall treatment management strategies for HF patients, with HF syndrome.[8]

Iron deficiency (ID) is recognized as a prevalent co-morbidity in HF, and is known to be present in approximately 50% of patients with stable HF irrespective of the presence of anaemia. In addition, ID has been shown to be an independent predictor of morbidity and mortality in such patients.[9–12]

Iron is necessary for a multitude of processes within the human body, such as oxygen transport and storage, cardiac and skeletal muscle metabolism, energy production in the mitochondria (via the Krebs cycle and respiratory chain reaction), synthesis and degradation of proteins, lipids and ribonucleic acid.[13–15] In order to meet the high energy demands of the heart, cardiomyocytes contain many mitochondria, with iron being an essential component of energy production.[10,16–20] The effect of ID on the function of the heart itself, such as a decrease in energy production in the mitochondria and adverse effects on cardiomyocyte contractility and relaxation, has been evidenced by recent pre-clinical studies. An *in vitro* model showed that by restoring intracellular iron levels these adverse effects could be reverted.[21] In particular during mechanical effort, the reduced iron availability enhances anaerobic glycolysis and extracellular lactate production, whilst decreasing mitochondrial aerobic pathway in cardiomyocytes.[22] Further, it was demonstrated in an ID mouse model that impaired mitochondrial metabolism due to ID results in reduced physical performance and decreased left ventricular function. After treatment with intravenous ferric carboxymaltose (FCM), these abnormalities reversed.[23] The beneficial effects of FCM were confirmed in an ID mouse model[24] and an ID rat model,[25] respectively.

Iron is essential for the transport and storage of oxygen, for the oxidative metabolism in the skeletal and heart muscle and for the synthesis and breakdown of lipids, carbohydrates, DNA and RNA.[14,26] ID leads to mitochondrial dysfunction, and the negative impact of ID is seen predominantly in tissues with a high-energy demand, such as skeletal and heart muscles.[18,21,22,27–30] Iron is thus indispensable for the correct functioning of both haematopoietic and non-haematopoietic tissues.[14,31]

Pathophysiological consequences of ID in HF are multifactorial but are still not well characterized (*Figure 1*). In the presence of impaired erythropoiesis and concomitant anaemia, deleterious effects are associated with low haemoglobin and resemble that seen in anaemic HF patients.[32] On the other hand, the presence of ID alone results in decreasing oxygen storage in myoglobin, abnormal oxidative metabolism and cellular energy handling, impaired reactive oxygen species defense,[18,33] all of which contribute to an exacerbation of mitochondrial dysfunction – one of the key underlying pathologies of the HF syndrome.[17] Recent studies report that ID in HF contributes to abnormal muscle function with specific form of skeletal myopathy.[27,34–36]

It has been suggested that ID could be present in up to 80% of patients hospitalised for AHF.[37,38] ID was found to be a predictor of poor outcome, regardless of previous history of HF, natriuretic peptide levels and ejection fraction (%), suggesting that depleted iron stores may have a strong unfavourable impact on the natural history of this clinical syndrome beyond the CV status.[39,40] The mechanisms underlying the unfavourable outcomes related to a depleted iron status in AHF have yet to be investigated in a clinical setting. An episode of worsening HF is a clinical entity, where the maintenance of energetic homoeostasis is of fundamental importance, not only at the level

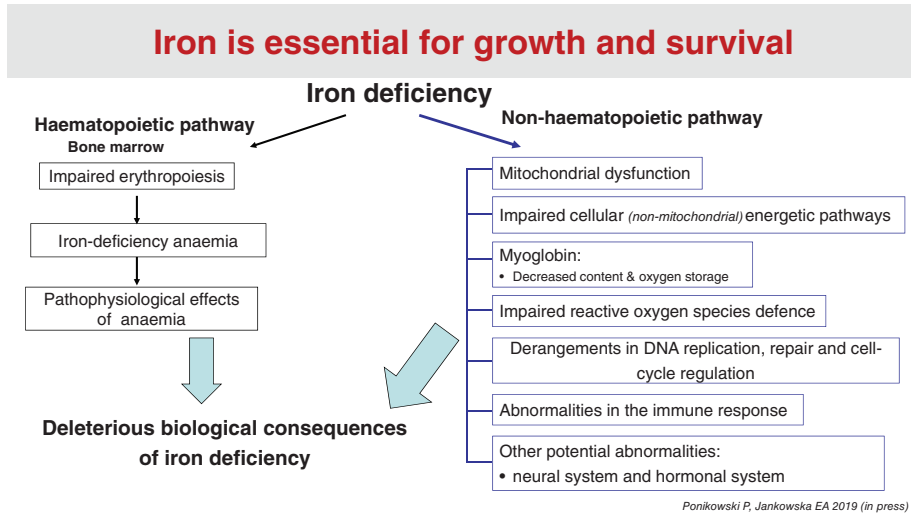


Figure 1 Role of iron in cell metabolism.

of the failing myocardium, but also in the other organs critical to struggle with decompensation (kidneys, liver, and skeletal muscles). There may be an association between bioenergetic inefficiency due to decreased iron content and abnormal handling of the latter. In addition, together with the combination of worsening neuroendocrine and pro-inflammatory activation, and oxidative stress, all factors would unfavourably impact on the duration of hospitalisation and on the early post-discharge phase where the risk of readmission and death is the highest. Therefore, correcting ID in patients recently hospitalised for AHF may be an attractive and easily implemented treatment option for such patients.

Randomized clinical trials (RCTs) have shown that treatment with intravenous (i.v.) FCM improves functional capacity, exercise tolerance, symptoms and quality of life in stable HF with reduced ejection fraction (HFrEF) patients with ID.[41–43] A recent individual patient data meta-analysis also suggested that treatment of ID with i.v. FCM in ambulatory systolic HF patients may decrease recurrent CV hospitalisations and thus i.v. FCM may potentially represent a beneficial addition to the standard medical management of HF.[44] However, the impact of treatment with i.v. FCM on morbidity and mortality in HF patients admitted for an episode of AHF and who present in addition with ID is unknown. The AFFIRM-AHF trial is the first adequately powered trial to investigate this, relative to placebo, the effect of i.v. FCM on mortality and morbidity in iron-deficient patients hospitalised for AHF.

Study design

The AFFIRM-AHF trial is a multicentre, randomised (1:1), placebo-controlled, double-blind superiority study, which was designed by members of the steering committee in collaboration with the sponsor (NCT02937454).

Between April 2017 and 31 July 2019, 1100 patients were randomised to receive either i.v. FCM or placebo in sites located in Western and Eastern Europe, Middle East, South America, and Asia (Singapore). Each patient will be followed for 52 weeks.

The trial, which is conducted in strict compliance with Good Clinical Practice from the International Council for Harmonisation (ICH GCP) and with the Declaration of Helsinki, was approved by the appropriate Regulatory Authorities and Ethics Committees. All patients who agreed to participate were asked to provide written informed consent before any trial-related procedure is performed.

Patient population

Male or female patients aged ≥18 years and who are hospitalised (i.e. index hospitalisation) with the primary reason of AHF, were considered for participation. Eligible patients must have presented with typical signs, symptoms of AHF, must have elevated natriuretic peptides and must be treated with minimally furosemide 40 mg i.v. (or equivalent i.v. diuretic) (*Table 1*). Left ventricular ejection fraction, not older than 12 months at the time of randomisation, must be <50%. Patients must have ID, defined as serum ferritin <100 ng/mL or 100 ng/mL ≤ serum ferritin ≤299 ng/mL if transferrin saturation <20%. The key inclusion/exclusion criteria are shown in *Table 1* and the complete inclusion and exclusion criteria are shown in online supplementary *Table S1*.

Study procedures and visit schedule

The study procedures and visit schedule are shown in *Figure 2*. The first dose of study treatment was administered before discharge for the index hospitalisation. Following discharge, patients were contacted either by telephone or in-person at the outpatient clinic at the defined time-points shown in *Figure 2*.

At each contact, the patient's well-being in addition to the occurrence of adverse events and/or hospitalisations is evaluated. Patients are requested to complete the self-administered Kansas

Table 1 Main inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Relating to the index hospitalisation • Primary reason for index hospitalisation: acute HF • Presented with typical signs, symptoms of acute HF • BNP ≥400 pg/mL or NT-proBNP ≥1600 pg/mL; AF present, BNP ≥600 pg/mL or NT-proBNP ≥2400 pg/mL obtained maximally 72 h after admission • Treated with minimally 40 mg i.v. furosemide or equivalent **Iron status** • Iron deficient: serum ferritin <100 ng/mL or if TSAT <20%, 100 ng/mL ≤ serum ferritin ≤299 ng/mL **Ejection fraction measurement** • Left ventricular ejection fraction not older than 12 months, <50%	**Cardiovascular-related** • Dyspnoea of non-CV origin • Clinical evidence of ACS, TIA or stroke within the last 30 days • CABG, PTCA, cardiac device implant/resynchronisation therapy or major surgery leading to significant blood loss within last 30 days **Other medical conditions** • Hb <8 g/dL (<10 g/dL for sites in The Netherlands, Spain and Singapore) or Hb >15 g/dL • Known anaemia not attributed to ID or history of iron overload • Known severe allergies • ESA, i.v. iron or blood transfusion administered in last 3 months • Oral iron (>100 mg/day) in previous 4 weeks

ACS, acute coronary syndrome; AF, atrial fibrillation; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CV, cardiovascular; ESA, erythropoietin-stimulating agent; Hb, haemoglobin; HF, heart failure; ID, iron deficiency; i.v., intravenous; NT-proBNP, N-terminal pro-brain natriuretic peptide; PTCA, percutaneous transluminal coronary angiography; TIA, transient ischaemic attack; TSAT, transferrin saturation.

City Cardiomyopathy Questionnaire. During the outpatient clinic visits, blood samples are drawn and analysed locally to determine serum ferritin, transferrin saturation, haemoglobin, and phosphorus. A biomarker blood sample is be drawn in a subset of consenting patients. During the outpatient visits, vital signs will be measured and HF signs/symptoms evaluated, including New York Heart Association functional class. Throughout the follow-up period, patients continue to receive their standard therapy for HF and medical emergencies treated according to local routine.

Randomisation and study treatment dosing regimen

Patients were randomised to either FCM or placebo using a secure web-based randomisation system and subject randomisation was determined by a minimisation algorithm. The study treatment dosing phases was based on a repletion and a maintenance phase. The first and second study treatment doses were determined using the patient's screening visit body weight measurement and haemoglobin value (*Table 2*). During the outpatient clinic visits at weeks 12 and 24, study treatment was administered if ID persisted, based on the laboratory test results performed at the respective visits.

Study treatment is prepared by unblinded site personnel using black syringes and, once prepared, is administered thereafter using a curtain (or similar) to maintain patient blinding. Each patient remains under observation for at least 30 minutes after each study treatment administration. The unblinded site personnel are not operationally involved in performing any study assessments (efficacy or safety) for the patient concerned.

Study outcomes

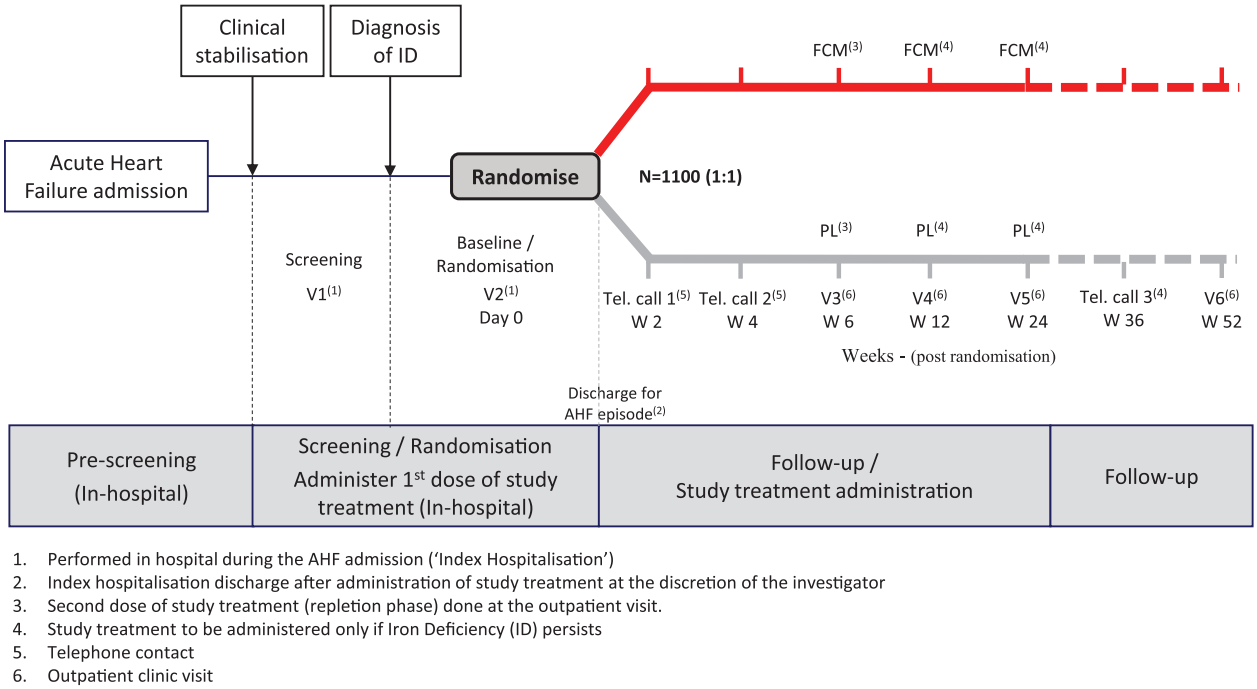
The primary outcome is the composite of recurrent HF hospitalisations and CV death up to 52 weeks after randomisation, comparing i.v. FCM with placebo (*Table 3*). The secondary outcomes are shown in online supplementary *Table S2*.

Sample size considerations and statistical analysis

Sample size calculations were done using data from the EVEREST trial and ESC HF registry.[45,46] Compared to the placebo group, it was assumed that there would be a 30% reduction in HF hospitalisations for patients allocated to FCM and that CV mortality rates would be similar between the FCM and placebo groups. The rate ratio between FCM and placebo for the composite of recurrent HF hospitalisations and CV mortality was estimated to be approximately 25%.

Based on these assumptions, it was determined that in total 1000 patients (500 per treatment group) would be required to demonstrate a statistically significant rate ratio of 0.75 (i.e. 25% reduction of recurrent events between the FCM and placebo groups) with a power of 80% and a two-sided alpha of 0.05. Assuming a 9% loss to follow-up, a sample size of 1100 patients (550 per treatment group) was planned. The sample size calculation was done using NCSS PASS-14,[47] using the sample size formula proposed by Zhu and Lakkis[48] comparing two negative binomial rates.

All analyses will be detailed in a Statistical Analysis Plan which will be finalised prior to database lock and unblinding. Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category for the parameter concerned will be presented (with a category for missing data if appropriate). For continuous variables, the mean, median, standard deviation, first and third quartiles, and minimum and maximum values will be presented. The level of significance to be used for tests will be 0.05. The analyses



1. Performed in hospital during the AHF admission ('Index Hospitalisation')
2. Index hospitalisation discharge after administration of study treatment at the discretion of the investigator
3. Second dose of study treatment (repletion phase) done at the outpatient visit.
4. Study treatment to be administered only if Iron Deficiency (ID) persists
5. Telephone contact
6. Outpatient clinic visit

Figure 2 Study procedures and visit schedule. AHF, acute heart failure; ID, iron deficiency; FCM, ferric carboxymaltose; PL, placebo; V, visit; W, week.

Table 2 Study treatment dosing regimen

	Study treatment dosing regimen (ml)				
	Weight <70 kg		Weight ≥70 kg		Any weight
Visit # /week #	8(1)≤Hb <10 g/dL	10≤Hb≤14 g/dL	8(1)≤Hb <10 g/dL	10≤Hb≤14 g/dL	14<Hb≤15 g/dL
Visit 2 (Week 0)	2x10 mL(3)		2x10 mL		1x10 mL
Visit 3 (2) (Week 6)	10 mL	No dose	2x10 mL	1x10 mL	No dose
Visit 4 (week 12); Visit 5 (Weeks 12	1x10 mL (only if ID persists)				

Hb, haemoglobin; ID, iron deficiency.
(1) 10 g/dL for patients from The NL, Spain and Singapore.
(2) Dosing at Week 6 (Visit 3) – second repletion dose; Study treatment will only be administered in subjects for whom Hb ≤15 g/dL.
(3) 10ml of study treatment contained either 500 mg iron or 10 ml of normal saline. ID defined as serum ferritin <100 ng/mL, or 100 ng/mL ≤ serum ferritin ≤299 ng/mL if transferrin saturation (TSAT) <20%.

will be performed on the full-analysis set in accordance with the intention-to-treat principle. The adjudicated data will be used in the analysis for hospitalisations and cause of death. For the recurrent event analysis, descriptive statistics (total number of events, number of subjects with at least one event, number of events per subject, follow-up duration, rate per 100 subject-years) will be provided, and a negative binomial model will be used to estimate the rate ratio between treatment groups. A sensitivity analysis will be performed on the per-protocol analysis dataset.

Study committees

Four committees – Steering Committee, Executive Committee, Data Safety Monitoring Committee (DSMC) and Adjudication Committee (AC) – have been established for the AFFIRM-AHF trial. The membership of these committees is shown in online supplementary *Table S3*.

The Steering Committee oversees the scientific integrity of the trial while the Executive Committee, a subset of the Steering Committee, is responsible to oversee the operational conduct

Table 3 Primary and secondary outcomes

Primary outcome
• Composite of recurrent HF hospitalisations and CV death up to 52 weeks after randomisation
Secondary outcomes
• The composite of recurrent CV hospitalisations and CV death up to 52 weeks after randomisation
• HF hospitalisations up to 52 weeks after randomisation (analysed as recurrent event)
• CV mortality analysed as time to first event at 52 weeks after randomisation
• The composite of HF hospitalisations or CV death analysed as time to first event at 52 weeks after randomisation
• Days lost due to HF hospitalisations or CV death at 52 weeks after randomisation

CV, cardiovascular; HF, heart failure.

of the trial. The DSMC is composed of a group of independent experts responsible to oversee patient safety. The DSMC will meet and review patient data at the pre-specified time points defined in the DSMC charter.

The AC independently adjudicate all hospitalisations and deaths using the detailed criteria in the adjudication charter. The criteria will follow that detailed by Hicks *et al.*[49]

Quality assurance and quality control

The investigator will be responsible to ensure that all trial-related site source data, study-related documents and reports will be available, and the provision of direct access for monitoring, auditing and/or inspections.

Accurate and reliable data collection will be assured by source data verification and cross-checking of the electronic case record forms vs. the source data. A comprehensive validation check programme will verify the data and queries will be generated for resolution by the investigator. Audits will be performed in accordance with the AFFIRM-AHF Quality Management Plan.

Discussion

The advances in the understanding of the pathophysiology of HF in addition to the recent introduction of novel HF therapies has significantly reduced mortality in this clinical syndrome.[50] As HF patients are now living longer, they are exposed to numerous conditions that may lead to clinical deterioration with subsequent need for urgent hospital admissions with a diagnosis of AHF. Given that AHF represents a broad spectrum of disease states, with heterogeneous clinical presentation, the identification of existing co-morbidities and in particular ID may well help clinicians to determine and direct treatment strategies more correctly by targeting specific underlying conditions and precipitating factors.[5]

Iron deficiency (ID) is one of the co-morbidities that are commonly present in HF and AHF and is a predictor of poor outcomes, thus suggesting that depleted iron stores may have an unfavourable impact on the natural course of this clinical syndrome.[39,40] Interestingly, the pattern of deranged iron status seen in AHF, characterized by depleted iron stores accompanied by unmet cellular iron requirements for maintenance of energetic homeostasis at the periphery, identifies patients at the highest risk of death after an episode of AHF.[39] Preservation of optimal energetics in the myocardium and the end-organs may be of key importance to effectively overcome all deleterious consequences of cardiac decompensation.

Currently, there is no evidence-based therapy that has improved clinical outcomes, mortality and morbidity in AHF.[1–3,7] This thus points in the direction that the identification and targeting of co-morbidities is an important component of the treatment strategy in AHF. Current HF guidelines for the treatment of HF recommend identification of co-morbidities and to take them into consideration when planning an overall treatment strategy for the HF patient in both the ambulatory and acute settings.[8]

Recent studies have demonstrated that in stable HFrEF patients with ID, the supplementation with i.v. iron in iron-deficient HFrEF patients has a positive impact on physical performance and quality of life.[41–43,51] There are, however, no RCTs that have investigated if the supplementation with i.v. FCM in iron-deficient patients recently admitted for an AHF episode has a favourable impact on mortality and morbidity.

In designing the AFFIRM-AHF trial, the presence (or not) of ID during the index hospitalisation will be evaluated with a blood test taken after stabilisation during the index hospitalisation for AHF, and thus, does not create any additional burden for the treating physician. According to the current HF guidelines,[8] identification of co-morbidities should be part of the treatment strategy for HF patients, so this will also help to increase the awareness of the need to check iron status in patients hospitalised for AHF. Regarding the latter, the post-discharge period is considered as the most 'vulnerable' phase in the natural history of a HF patient, with a high risk of hospital readmission or death.[52] The supplementation of i.v. iron in iron-deficient patients during this post-discharge period may be efficacious to improve the outcome in this phase.

The impact of the supplementation of i.v. FCM on morbidity and mortality in iron-deficient patients hospitalised for AHF has yet to be established. The AFFIRM-AHF is the first adequately powered RCT that addresses the question whether i.v. FCM, compared to placebo, in stabilised iron-deficient patients following AHF is superior regarding the favourable effect on mortality and morbidity. In designing this trial we aimed to be pragmatic and mirror clinical practice, as an administration of i.v. FCM is easily done in clinical practice and there are no restrictions with respect to treatments for HF either during the in-hospital or post-discharge phases. In addition, this trial will enable the collection of safety

data concerning the use of i.v. FCM when administered in patients stabilised after an AHF episode.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. AFFIRM-AHF – complete inclusion and exclusion criteria.

Table S2. Other study outcomes.

Table S3. Committees membership.

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