Research Article

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Ferric carboxymaltose for patients with heart failure and iron deficiency in Italy: cost–effectiveness and budget impact

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Aim: To evaluate the cost–effectiveness of intravenous ferric carboxymaltose (FCM) versus placebo for the management of iron deficiency in patients with chronic heart failure in the Italian healthcare system and to estimate its impact on the national healthcare budget. **Materials & methods:** A Markov model was developed to project costs and health outcomes over 1 year, based on data from literature. Healthcare resources consumption was derived from an e-survey administered to clinicians. Costs were obtained from official tariffs. **Results:** Treatment with FCM represents a dominant strategy compared with placebo, leading to national budget annual savings of 20–97 million Euros, according to different increasing utilization rates. **Conclusion:** FCM is a cost-saving option for the treatment of chronic heart failure patients with iron deficiency in Italy.

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Keywords: budget impact analysis • chronic heart failure • cost–effectiveness analysis • cost–utility analysis • ferric carboxymaltose

Heart failure (HF) is recognized as an alteration of the heart structure that leads to insufficient cardiac function. As a consequence, organs and tissues receive insufficient oxygen to meet their metabolic needs. The reaction of the organism to insufficient function of the heart leads to an accumulation of sodium and water in the lungs and tissues. Symptoms include shortness of breath, reduced exercise tolerance, fatigue, edema. The condition may deteriorate until it leads to acute pulmonary edema and death.

Approximately 600,000 people currently suffer from HF in Italy and it is estimated that its frequency doubles for every decade of age (after the age of 65 it reaches about 10%) [1]. HF in patients aged over 65 years is the most common cause of hospitalization and it accounts for about 5% of all urgent hospital access [2]. For these reasons, HF is considered a major public health problem.

Despite optimal conventional therapy, many patients with chronic heart failure (CHF) are subject to high rates of hospitalization and mortality [2–4]. About 50% of patients with CHF suffer from iron deficiency (ID), more pronounced symptoms, a higher risk of hospitalization and a lower quality of life [5–10].

Few randomized controlled trials (RCTs) comparing ferric carboxymaltose (FCM) with placebo have shown a clinical benefit after correcting ID in patients with CHF [8,11–13]. Following these observations, the European Society of Cardiology Heart Failure 2016 guidelines specifically recommended considering FCM for the treatment of ID in patients with HF [14]. This treatment may improve patients' clinical conditions, helping to reduce future hospitalizations, duration of hospital stay and increase their quality of life.

The aim of the present study was to develop knowledge on the clinical and economic implications that can support stakeholders at the national level in the overall assessment of choices regarding the management of patients with HF and ID. In particular, the main aim of the study was to perform a cost–effectiveness analysis (CEA) comparing FCM to placebo in CHF patients, from the Italian Healthcare System perspective. The secondary objective of this analysis was to assess the impact on the budget of the Italian Healthcare System of the appropriate

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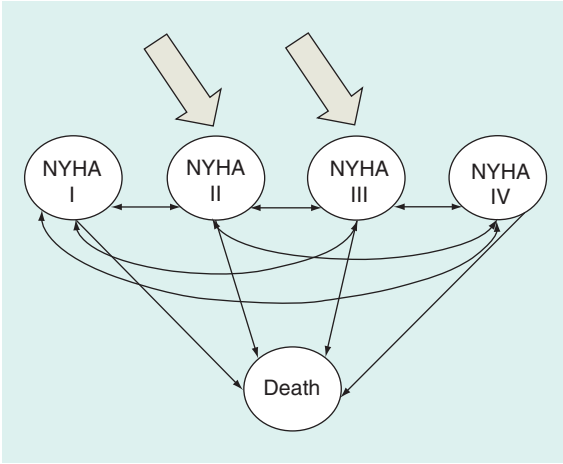

Figure 1. Schematic representation of the general model structure. Patients start the process in NYHA classes II (33%) and III (67%).
NYHA: New York Heart Association.

Table 1. Patient distribution over time according to different NYHA classes.

	Placebo (%)					FCM (%)				
NYHA class	I	II	III	IV	Death	I	II	III	IV	Death
Baseline	0	33	67	0	0	0	33	67	0	0
Week 4	0.1	30.1	65.6	4	0.2	0.9	51.6	46	1.4	0.1
Week 12	0.4	35.9	57.2	4.2	2.2	5.1	55.9	36.4	1.3	1.3
Week 24	0.5	43.3	45.8	6.3	4.1	5.4	63.1	27.3	1.9	2.3
Week 36	0.7	41.1	45.1	6.6	6.5	5.8	63.2	25.2	2	3.8
Week 52	0.9	39.2	44.2	6.9	8.9	6.1	63.1	23.5	2.1	5.2

FCM: Ferric carboxymaltose; NYHA: New York Heart Association.

diffusion of a screening strategy for patients with HF, in order to identify cases of ID with subsequent treatment with FCM.

Materials & methods

A CEA model was developed with TreeAge Pro Software (TreeAge Software, Inc., MA, USA) based on data related to a budget impact model published by Theidel and colleagues [15]. This model was developed to project lifetime health (life years and quality-adjusted life years [QALYs]) and economic outcomes associated with FCM and placebo in the population considered. The model was implemented from pooled patient level data from the main RCTs comparing FCM with placebo [8,11–13]. The health states in the implemented model include New York Heart Association (NYHA) classes from I to IV. As described previously [15], data derived from clinical trials were used to develop a model for the prediction of hospitalization rates for CHF and NYHA class distribution over the time horizon of 52 weeks. A 1-week Markov cycle length was chosen for baseline analysis. The model structure is presented in Figure 1.

Patients begin the process in NYHA classes II (33%) and III (67%) and subsequently move among the different NYHA classes in order to reproduce the distribution over time, as reported in Table 1. The model focuses on hospitalizations, exams and visits for CHF or related to CHF which are likely to be influenced by the NYHA classes. On the contrary, the rates of other types of events not related to the disease under consideration are assumed equal for the two cohorts and are excluded from the model. This assumption is also supported by the study by Anker and colleagues [16], which reported not statistically different rates of hospitalizations for all causes between the two populations ($p = 0.056$).

The aim of this study was to assess the cost–effectiveness of FCM compared with placebo, taking into account improvement in NYHA class and the decrease in related consumption of healthcare resources. A secondary objective was to estimate the expected changes in the expenditure for the Italian Healthcare Service in the hypothesis of an increased diffusion of FCM utilization in patients with CHF and ID.

The analyses were conducted in accordance with the Consolidated Health Economic Evaluation Reporting Standards Statement [17] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

Principles of Good Practice for Budget Impact Analysis [18]. The Consolidated Health Economic Evaluation Reporting Standards checklist is reported in the Supplementary Material.

Healthcare resource consumption & costs

This analysis was performed from the Italian Healthcare System perspective. In the model, only direct healthcare resource consumption (direct costs) was included.

The collection of data on the consumption of healthcare resources for the different NYHA classes was undertaken by administering an *ad hoc* developed e-survey to clinicians in five Italian hospitals. A Delphi approach was applied since experts were asked to answer the questionnaire independently [19]. The questionnaire was made available to complete from 3 October 2018 to 20 December 2018. The choice of the hospitals focused on Lombardy region, since this is the region with the highest number of outpatient services with expertise in the management of CHF patients in the clinical practice [20]. Clinicians were asked to refer to the typical cohort of patients with CHF and to report data on healthcare resource utilization according to the four NYHA classes based on their clinical experience.

The questionnaire was organized into different sections for the collection of the following data categories: hospitalizations for reasons related to CHF (e.g., kidney failure, atrial fibrillation, etc.), rehabilitative admissions, outpatient rehabilitation services, specialist medical visits, general practitioner visits, laboratory exams/imaging and pharmacological therapy. Clinicians were required to indicate for each outpatient service (e.g., specialist visit, general practitioner visit, laboratory exam, etc.), the percentage of patients involved and the mean number per year; the same was applied for hospital admissions. Regarding medication, the questionnaire investigated different treatments for CHF according to guidelines [14]: angiotensin-converting enzyme inhibitors, sartans, β-blockers, spironolactone, digoxin, sacubitril–valsartan, ivabradine and diuretics. For each treatment, clinicians were asked to report the percentage of treated patients, distinguishing the patients at target dose, with dose taken above 50% and below 100% and with a dose taken below 50% of the target dose.

At last, for each cost category, a weighted mean was calculated on the basis of the number of responders.

With regard to hospitalizations for CHF, the weekly rate for FCM (0.0010) and for placebo (0.0026) were obtained from [15], which calculated them starting from pooled data based on the four trials [8,11–13]. These values are in line with those obtainable from the data reported by Anker and colleagues in another pooled analysis [16] performed on the same trials, which highlighted the statistically significant difference between FCM and placebo ($p = 0.003$).

The monetary quantification (2018, Eur) of the consumption of healthcare resources for the management of patients in the different NYHA classes was performed through diagnosis-related group reimbursement rates for hospitalizations, regional tariff values for outpatient services and drug prices. Concerning drugs, we performed a search on the Italian Pharmaceutical Database [21] that reports cost data for the National Healthcare Service.

Literature review & quality of life estimates

A systematic literature review was performed in May 2018 in order to retrieve the utility coefficients for patients with CHF for the different NYHA classes. The search strategy is reported in the Supplementary Material.

Cost–effectiveness analyses

Both incremental cost–effectiveness ratio (ICER) and incremental cost–utility ratio of FCM versus placebo were calculated by dividing the incremental cost by the incremental health improvement. Health outcomes and costs were not discounted, considering the short time horizon used in the analysis. Costs, utilities and rates were entered into the model along with a distribution: β for utilities, log-normal for rates and γ for costs.

Univariate analyses were performed according to the model parameters. In order to take into account parameters variability, second-order Monte Carlo simulations (10,000 iterations) were performed. The resulting scatterplot was plotted in the cost–effectiveness plane.

Budget impact analysis

Starting from the CEA model, a budget impact analysis (BIA) model was developed to estimate the expected changes in the expenditure for the Italian Healthcare Service in the hypothesis of an increased diffusion of FCM utilization in patients with CHF and ID.

In order to perform the BIA, a research of epidemiological data was performed focusing on CHF patients with ID. Considering that the prevalence of CHF in Italy is 1.25% [22], that 78.8% of CHF patients belong to NYHA

classes II and III [23] and that 42.5% of these patients present ID [24], the total number of prevalent CHF patients with ID in Italy was estimated to be 253,201. The current patients' distribution between the two strategies, FCM and placebo, was estimated by clinicians as 5 and 95%, respectively.

A BIA was performed considering different scenarios of increased utilization rates of FCM for patients with CHF and ID (25, 50 and 100%) over placebo.

Results

Healthcare resource consumption & costs

Five clinicians were involved in the study and all completed the e-survey. The estimated healthcare resource utilization is reported in Supplementary Table 1, while unit costs are summarized in Table 2. With regard to pharmacological treatment, we considered recommended daily doses according to 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF [14].

Weekly costs related to the healthcare resource consumption for the different NYHA classes are reported in Table 3. The weekly cost for hospital admission for CHF was calculated by multiplying the weekly rate for FCM and placebo (not distinguished by NYHA class as reported by the reference trial [15]) by the Hospital admission cost for CHF. The cost difference of about €5 is due to the lower weekly rate of hospitalization for FCM. For the other cost components reported in Table 3, weekly costs have been calculated by multiplying the weekly healthcare resource consumption by the corresponding unit costs. In general, higher CHF severity corresponded to higher costs.

Literature review & quality of life estimates

The literature search (see Supplementary Material) yielded a total of six studies reporting utility coefficient values for at least one NYHA class. A summary of retrieved studies and related utility values is reported in Table 4.

A meta-analysis (Stata software, metaan command) was performed in order to obtain utility coefficients for all NYHA classes (Table 5). Meta-analysis was only possible to perform for studies reporting confidence intervals or standard deviation estimates associated to the reported utility weights [27,29].

Cost–utility results

In the baseline scenario, the model estimated a mean cost per patient undergoing FCM of €3296 and a cost of €3699 for untreated patient. With regard to health outcomes, over the time horizon of 1 year, the model estimated an average life expectancy of 0.974 (0.703 QALYs) and 0.956 (0.642 QALYs) years for patients administered FCM and for those not treated with FCM, respectively. Treatment with FCM was associated with lower cost and higher life expectancy and QALYs, therefore emerging as a dominant strategy compared with patients with CHF and ID not receiving treatment.

Several one-way sensitivity analyses were performed on the main model parameters. Variations of ±50% in weekly costs for visits/exams, other hospital admissions and other outpatient services for the different NYHA classes were considered. Variations in the weekly cost of hospitalizations for CHF were estimated by varying the weekly hospitalization rates from 0.001 to 0.01, as reported in Table 6. The analyses revealed that the weekly rate of hospitalization for CHF (for FCM strategy) is the parameter which mainly influences variations in ICER. On the other hand, the variations on weekly costs for the different NYHA classes and rate of hospitalization for CHF for placebo strategy always reported the dominance of FCM (data not shown).

A probabilistic sensitivity analysis has been performed according to variations in parameters summarized in Supplementary Table 2. The scatterplot of incremental costs versus incremental QALYs obtained from the Monte Carlo simulations is reported in Figure 2 applying a cost–effectiveness threshold of €20,000/QALY; the totality of points lies below this line, highlighting that FCM leads to better QALYs at lower costs.

BIA results

Considering a total of 253,201 prevalent CHF patients with ID in Italy, the current national annual budget impact was estimated to be €931,488,616. The adoption of enlarged screening for ID patients in this setting, leading to FCM utilization rates of 25, 50 and 100%, may result in a decrease in the total national budget of €20,408,003, €45,918,007 and €96,938,015, respectively (Table 7).

Table 2. Costs used in the model.

Cost item	Value	Code	Ref.
Hospitalizations:			
– Hospital admission for CHF	€3052	DRG 127	National DRG reimbursement
– Hospital admission for atrial fibrillation	€2375	DRG 138	National DRG reimbursement
– Hospital admission for atherosclerosis	€990	DRG 133	National DRG reimbursement
– Hospital admission for renal failure	€3734	DRG 316	National DRG reimbursement
– Rehabilitation hospital admission	€2870	DRG 463	National DRG reimbursement
Outpatient services:			
– Outpatient rehabilitation services (1 cycle)	€19.11	93.36	National Healthcare Service price list
– Cardiological visit	€16.01	89.01.3	National Healthcare Service price list
– Other specialist visits (e.g., nephrologist)	€17.90	89.01.B	National Healthcare Service price list
– GP visit	€15.19		[25] uplifted to 2018
– GP home visit	€29.12		[25] uplifted to 2018
– Iron infusion	€9.71	99.23	National Healthcare Service price list
Lab exams/imaging:			
Liver function evaluation: – ALT – ALP – AST – Bilirubin – Albumin – Proteins – γ-glutamyl transferase – LDH – Prothrombin time	 €1.00 €1.04 €1.04 €1.13 €1.42 €1.13 €1.13 €1.13 €2.85	 90.04.5 90.23.5 90.09.2 90.10.4 90.05.1 90.38.5 90.25.5 90.29.2 90.75.4	National Healthcare Service price list
Kidney function evaluation: – Azotemia – Creatinine – Sodium – Potassium	 €1.13 €1.13 €1.02 €1.02	 90.44.1 90.16.3 90.40.4 90.37.4	National Healthcare Service price list
Blood cell count	€3.17	90.62.2	National Healthcare Service price list
Natriuretic peptide	€24.68	90.21.2	National Healthcare Service price list
Potassium	€1.02	90.37.4	National Healthcare Service price list
Lipid evaluation: – Total cholesterol – Cholesterol HDL – Cholesterol LDL – Triglycerides	 €1.04 €1.43 €0.67 €1.17	 90.14.3 90.14.1 90.13.C 90.43.2	National Healthcare Service price list
Urine examination	€2.17	90.44.3	National Healthcare Service price list
Uric acid	€1.13	90.43.5	National Healthcare Service price list
Thyroid-stimulating hormone	€5.46	90.42.1	National Healthcare Service price list
Magnesium	€1.55	90.32.5	National Healthcare Service price list
Electrocardiogram	€11.62	89.52	National Healthcare Service price list
Echocardiogram	€51.65	88.72.1	National Healthcare Service price list
Stress test	€55.78	89.41	National Healthcare Service price list
Stress test (including assessment of oxygen consumption)	€83.67	89.44.1	National Healthcare Service price list
Dynamic electrocardiogram (Holter)	€61.97	89.50	National Healthcare Service price list
Magnetic resonance imaging heart	€120.08	88.92.3	National Healthcare Service price list
Coronarography	€1142	DRG 125 (Day-Hospital)	National DRG reimbursement
Drugs:			
FCM (100 mg, 2 ml)	€7.752		Public price according to 'Determinazione Dirigenziale N. 0666–17, 12/12/2017' (available from http://www.ao.lodi.it)
ACE-inhibitors (Ramipril 10 mg die)	€0.31/day		[21]
Sartans (Valsartan 320 mg die)	€0.51/day		[21]

ACE: Angiotensin-converting enzyme; CHF: Chronic heart failure; DRG: Diagnosis-related group; FCM: Ferric carboxymaltose; GP: General practitioner; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

Table 2. Costs used in the model (cont.).

Cost item	Value	Code	Ref.
β-blockers (Nebivolol 10 mg die)	€0.44/day		[21]
Spironolactone (50 mg die)	€0.35/day		[21]

ACE: Angiotensin-converting enzyme; CHF: Chronic heart failure; DRG: Diagnosis-related group; FCM: Ferric carboxymaltose; GP: General practitioner; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

Table 2. Costs used in the model (cont.).

Cost item	Value	Code	Ref.
Digossin (0.1875 mg die)	€0.20/day		[21]
Sacubitril-valsartan (1 cp 97 mg/103 mg bid)	€6.85/day		[21]
Ivabradine (15 mg die)	€0.71/day		[21]
Furosemide (25 mg)	€0.05/day		[21]

ACE: Angiotensin-converting enzyme; CHF: Chronic heart failure; DRG: Diagnosis-related group; FCM: Ferric carboxymaltose; GP: General practitioner; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

Table 3. Cost components for the different NYHA classes.

Cost component	Weekly cost NYHA I	Weekly cost NYHA II	Weekly cost NYHA III	Weekly cost NYHA IV
Hospital admission for CHF – FCM – Placebo			€3.14 €8.00	
Other hospital admissions	€8.58	€24.86	€31.56	€61.16
Visits/exams and other outpatient services	€6.10	€9.64	€14.13	€16.50
Drugs	€7.00	€18.74	€28.37	€14.64

CHF: Chronic heart failure; FCM: Ferric carboxymaltose; NYHA: New York Heart Association.

Table 4. Summary of studies and utility values.

Study	Population	Number of patients	NYHA I	NYHA II	NYHA III	NYHA IV
[26]	Patients at least 18 years of age, with evidence of heart failure for at least 6 weeks, and in NYHA class III or IV	813	–	–	0.61	0.44
[27]	Patients belonging to NYHA classes from I to IV	64	0.934 (SD: 0.089)	0.782 (SD: 0.244)	0.553 (SD: 0.361)	0.371 (SD: 0.407)
[28]	Patients with moderate to severe heart failure and left ventricular systolic dysfunction	5313	0.82	0.74	0.64	0.46
[29]	Patients with CHF after acute myocardial infarction	1395	0.855 (95% CI: 0.845–0.865)	0.771 (95% CI: 0.761–0.781)	0.673 (95% CI: 0.665–0.69)	0.532 (95% CI: 0.48–0.584)
[30]	Patients with advanced heart failure	99	0.97	0.8	0.65	0.3
[31]	Subjects with documented systolic HF or diastolic HF	1069	0.75	0.66	0.61	0.61

CHF: Chronic heart failure; HF: Heart failure; NYHA: New York Heart Association; SD: Standard deviation.

Table 5. Meta-analysis of utility coefficients for the different NYHA classes.

NYHA class	Utility coefficient (95% CI)
I	0.89 (0.82–0.97)
II	0.77 (0.76–0.78)
III	0.62 (0.50–0.74)
IV	0.46 (0.30–0.61)

NYHA: New York Heart Association.

Table 6. One-way sensitivity analyses performed on the main model parameters.

Parameter variation	ICUR (FCM vs placebo)	Δ cost (FCM vs placebo)	Δ QALYs (FCM vs placebo)
Baseline scenario	FCM dominant	-€403	0.061
Time horizon (weeks):			
– 24	FCM dominant	-€104	0.023
– 28	FCM dominant	-€147	0.027
– 32	FCM dominant	-€191	0.033
– 36	FCM dominant	-€234	0.038
– 40	FCM dominant	-€276	0.043
– 44	FCM dominant	-€319	0.049
– 48	FCM dominant	-€362	0.054
– 52	FCM dominant	-€403	0.061
Total FCM dose (mg):			
– 1679	FCM dominant	-€403	0.061
– 1761	FCM dominant	-€397	0.061
– 1843	FCM dominant	-€390	0.061
– 1925	FCM dominant	-€384	0.061
– 2007	FCM dominant	-€377	0.061
– 2090	FCM dominant	-€371	0.061
– 2172	FCM dominant	-€365	0.061
– 2254	FCM dominant	-€358	0.061
– 2336	FCM dominant	-€352	0.061
– 2418	FCM dominant	-€346	0.061
– 2500	FCM dominant	-€339	0.061
Weekly rate of hospitalization for CHF (FCM):			
– 0.001	FCM dominant	-€403	0.061
– 0.002	FCM dominant	-€248	0.061
– 0.003	FCM dominant	-€94	0.061
– 0.004	€993	€61	0.061
– 0.005	€3543	€215	0.061
– 0.006	€6092	€370	0.061
– 0.007	€8642	€524	0.061
– 0.008	€11,191	€679	0.061
– 0.009	€13,741	€833	0.061
– 0.01	€16,290	€988	0.061

CHF: Chronic heart failure; FCM: Ferric carboxymaltose; ICUR: Incremental cost–utility ratio; QALY: Quality-adjusted life year.

Discussion

HF is defined as a global pandemic, affecting 26 million people worldwide [32]. ID is a common comorbidity for patients with CHF, affecting approximately 50% of them [5]. ID is also associated with increased disease severity and is a strong and independent predictor of outcome [5].

Recently, several studies have shown that ID correction through the supplementation of intravenous iron in this kind of patients could improve functional status and quality of life [8,11–13]. The present study aimed to perform a CEA and BIA in order to support decision makers in assessing the value of intravenous iron therapy for ID in CHF patients in Italian clinical practice.

The CEA model development relied on clinical data from RCTs and on healthcare resource consumption mainly derived from clinical practice. Considering a time horizon of one year, intravenous therapy with FCM resulted in a cost-saving strategy compared with placebo for the treatment of CHF patients with ID in Italy. Probabilistic sensitivity analyses showed the robustness of the CEA model: all simulations reported the cost-saving of FCM over placebo.

The CEA model showed that for Italy, FCM has a better cost–effectiveness profile than placebo compared with few other published studies undertaken in Europe. In particular, a study conducted in the UK [9] developed a

Table 7. Budget impact analysis.

	Current scenario			Alternative scenario 25%			Alternative scenario 50%			Alternative scenario 100%		
	Percentage of patients	Number of patients	Total cost	Percentage of patients	Number of patients	Total cost	Percentage of patients	Number of patients	Total cost	Percentage of patients	Number of patients	Total cost
Ferinject	5%	12,660	€41,727,530	25%	63,300	€208,637,650	50%	126,601	€417,275,301	100%	253,201	€834,550,601
No treatment	95%	240,541	€889,761,086	75%	189,901	€702,442,963	50%	126,601	€468,295,309	0%	0	€0
Total budget impact			**€931,488,616**			**€911,080,613**			**€885,570,609**			**€834,550,601**
Savings in comparison to current scenario						**-€20,408,003**			**-€45,918,007**			**-€96,938,015**

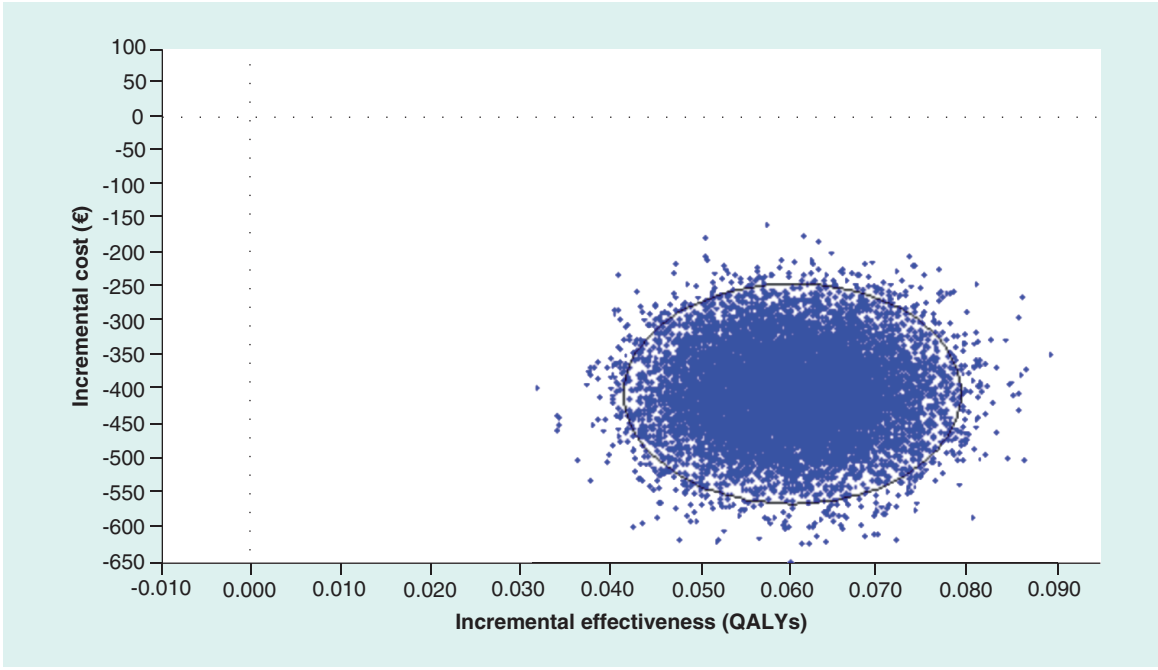

Figure 2. Scatterplot of incremental costs versus incremental quality-adjusted life years obtained from Monte Carlo simulations for the comparison ferric carboxymaltose versus placebo.
QALY: Quality-adjusted life year.

CEA model based on the FAIR-HF trial from the National Health Service perspective with a time horizon of 24 weeks. The ICER of FCM compared with placebo was found to be €4414 per QALY gained, highlighting the cost–effectiveness of FCM. Another study conducted in Spain [33] and based on the same UK model showed that FCM treatment in patients with CHF and ID is cost effective with a cost per QALY gained of €6123.78, compared with no ID treatment. Similar results were observed by a study conducted in Sweden applying the same model [34]. They reported an ICER of €8194 per QALY for FCM compared with placebo. These CEA models provide insight into the cost–effectiveness of FCM compared with placebo but these studies are also limited by the short time horizon used for the analyses of only 24 weeks. Furthermore, these studies consider clinical data only from the FAIR-HF RCT, which involved 459 patients.

The results of the present study are confirmed by a recent cost–utility analysis conducted in four Nordic countries (Denmark, Finland, Norway and Sweden) by Hofmarcher and colleagues [35] with a time horizon of one year based on clinical data from CONFIRM-HF study. The authors reported for FCM higher QALYs (increase of 0.050 QALYs per patient) and lower costs (reductions from €36 to €484 per patient).

For the development of the CEA model for Italy, we relied on the study by [15] in the German setting which reported the results of a BIA model based on clinical outcomes from 833 patients participating in four different clinical trials. This approach allowed us to improve data robustness and to use the longer time horizon (52 weeks). Moreover, the lower cost applied in Italy for FCM compared with other European countries further highlights FCM dominance compared with no treatment.

Our model was implemented in order to perform a CEA but was also extended to perform a BIA in the Italian context. The BIA showed that it is possible to save from 20 to about 97 million Euros per year according to increased utilization rates of FCM of 25, 50 and 100% over no treatment in CHF patients with ID. As a consequence of the dominance of FCM over placebo, the results also show a saving profile of the use of FCM in Italian clinical practice. Of course, in countries where the cost of FCM is much higher than in Italy (e.g., USA), the cost benefit may be lost.

The present study has a number of limitations. First of all, the model results are greatly influenced by patients' distribution among the different NYHA classes derived from RCT data for FCM and placebo, therefore the generalizability to a broader real-world setting should be performed with caution.

Another limitation refers to the costs for hospitalizations for CHF; although the reference trial [15] reported accurate hospitalization rates for the two alternatives considered, the study did not report hospitalization rates distinguished by NYHA class, and a more precise analysis could not be performed.

Third, we relied on clinical experts' opinions through a Delphi approach in order to inform healthcare resource utilization for the model. Key opinion leaders were based in the Lombardy Region and may not necessarily represent the entire clinical community for other regions. A positive aspect worth noting is the fact that the consumption of healthcare resources was presented in natural units, as suggested by EUnetHTA guidelines [36], this will facilitate cost adjustment for other regions or countries.

As with other intravenous irons, treatment with FCM can be associated with decreased levels of phosphorus in the blood, also known as hypophosphataemia, which could affect even 40% of patients or more [37]. Hypophosphataemia is a well-documented adverse drug reaction stated in the EU Ferinject Summary of Product Characteristics. Incidental cases of hypophosphataemia requiring medical attention were reported mainly in patients with existing risk factors and after prolonged exposure to high-dose intravenous iron. However, most instances are transient and are not associated with clinical signs or symptoms, therefore the management of these events has been excluded from the present analysis.

Despite these limitations, this study provides an estimate of the potential savings from increased utilization rates of intravenous FCM for the treatment of patients with ID in Italy. Data emerging from observational studies or registries in the future will provide further evidence to strengthen models in order to obtain more accurate results.

Future perspective

In HF, ID is linked to disease severity and is recognized as a marker of poor prognosis, independent of other prognostic factors. Based on the evidence derived from trials investigating the use of FCM, the European Society of Cardiology guidelines for the management of HF patients made a specific recommendation that this iron formulation should be considered in symptomatic patients to alleviate HF symptoms and improve exercise capacity and quality of life. Ongoing and future studies will be able to confirm whether other third generation iron formulations have a similar impact on patients' health.

Summary points

- Chronic heart failure (CHF) is recognized as an alteration of the heart structure that leads to insufficient cardiac function. About 50% of patients with CHF suffer from iron deficiency (ID), more pronounced symptoms, a higher risk of hospitalization and a lower quality of life.
- Few randomized controlled trials comparing ferric carboxymaltose (FCM) with placebo have shown a clinical benefit after correcting ID in patients with CHF.
- In this study we performed a cost–effectiveness analysis comparing FCM to placebo in CHF patients with ID from the Italian Healthcare System perspective. Moreover, a budget impact analysis was undertaken considering different scenarios of increased utilization rates of FCM for patients with CHF and ID (25, 50 and 100%) over placebo.
- A Markov model was developed to project costs and health outcomes associated to the considered strategies. Clinical data and data on patients' quality of life were derived from published literature, while data on the consumption of healthcare resources was undertaken by administering an e-survey to clinicians.
- Considering a time horizon of one year, the analyses showed that FCM can be considered a dominant strategy in comparison to placebo for the treatment of CHF patients with ID.
- Increasing utilization rates of FCM in the considered population may lead to national budget savings of 20–97 million Euros per year.
- The present study supports the use of FCM in patients with CHF and ID. Data emerging from observational studies or registries in the future will be able to provide further evidence to confirm these conclusions.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2019-0074

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Ministero della Salute (2019). http://www.salute.gov.it/portale/salute/p1_5.jsp?lingua=italiano&id=43&area=Malattie_cardiovascolari
2. Cowie MR, Anker SD, Cleland JGF *et al.* Improving care for patients with acute heart failure: before, during and after hospitalization. *ESC Heart Fail.* 1(2), 110–145 (2014).
3. Go AS, Mozaffarian D, Roger VL *et al.* Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. *Circulation* 127(1), e6–e245 (2013).
4. Maggioni AP, Dahlström U, Filippatos G *et al.* EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur. J. Heart Fail.* 15(7), 808–817 (2013).
5. Klip IT, Comin-Colet J, Voors AA *et al.* Iron deficiency in chronic heart failure: an international pooled analysis. *Am. Heart J.* 165(4), 575.e3–582.e3 (2013).
6. Jankowska EA, von Haehling S, Anker SD *et al.* Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *Eur. Heart J.* 34(11), 816–829 (2013).
7. Okonko DO, Mandal AK, Missouris CG *et al.* Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. *J. Am. Coll. Cardiol.* 58(12), 1241–1251 (2011).
8. Ponikowski P, van Veldhuisen DJ, Comin-Colet J *et al.* Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur. Heart J.* 36, 657–668 (2015).

•• **Clinical study comparing ferric carboxymaltose (FCM) to placebo.**

9. Gutzwiller FS, Schwenkglenks M, Blank PR *et al.* Health economic assessment of ferric carboxymaltose in patients with iron deficiency and chronic heart failure based on the FAIR-HF trial: an analysis for the UK. *Eur. J. Heart Fail.* 14(7), 782–790 (2012).

• **European cost–effectiveness analysis.**

10. Comín-Colet J, Enjuanes C, González G *et al.* Iron deficiency is a key determinant of health-related quality of life in patients with chronic heart failure regardless of anaemia status. *Eur. J. Heart Fail.* 15(10), 1164–1172 (2013).
11. Anker SD, Comin Colet J, Filippatos G *et al.* Ferric carboxymaltose in patients with heart failure and iron deficiency. *N. Engl. J. Med.* 361, 2436–2448 (2009).

•• **Clinical study comparing FCM to placebo.**

12. Arutyunov G. The safety of intravenous (IV) ferric carboxymaltose versus IV iron sucrose on patients with chronic heart failure (CHF) and chronic kidney disease (CKD) with iron deficiency (ID). *Eur. J. Heart Fail.* 8, ii71 (2009).

•• **Clinical study comparing FCM to placebo.**

13. Effect of ferric carboxymaltose on exercise capacity and cardiac function in patients with iron deficiency and chronic heart failure (EFFICACY-HF) (data on file). US National Institutes of Health (2009). https://clinicaltrials.gov/ct2/show/NCT00821717

•• **Clinical study comparing FCM to placebo.**

14. Ponikowski P, Voors AA, Anker SD *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* 37(27), 2129–2200 (2016).
15. Theidel U, Väätäinen S, Martikainen J, Soini E, Hardt T, Doehner W. Budget impact of intravenous iron therapy with ferric carboxymaltose in patients with chronic heart failure and iron deficiency in Germany. *ESC Heart Fail.* 4(3), 274–281 (2017).

•• **Reference study for the developed model.**

16. Anker SD, Kirwan BA, van Veldhuisen DJ *et al.* Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur. J. Heart Fail.* 20(1), 125–133 (2018).
17. Husereau D, Drummond M, Petrou S *et al.* Consolidated health economic evaluation reporting standards (CHEERS) – explanation and elaboration: a report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. *Value Health* 16, 231–250 (2013).
18. Sullivan SD, Mauskopf JA, Augustovski F *et al.* Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health* 17(1), 5–14 (2014).
19. Esmé G, Trevelyan J, Robinson C. Delphi methodology in health research: how to do it? *Eur. J. Integr. Med.* 7(4), 423–428 (2015).
20. La rete cardiologica per la cura del malato con scompenso cardiaco: organizzazione dell'assistenza ambulatoriale (2016). http://www.anmco.it/uploads/u_cms/media/2016/6/69730b48ccd65dce09bf23dae9ef32fb.pdf
21. Federfarma (2019). http://www.federfarma.it
22. Piccinni C, Antonazzo IC, Simonetti M *et al.* The burden of chronic heart failure in primary care in Italy. *High Blood Press. Cardiovasc. Prev.* 24(2), 171–178 (2017).
23. D'ambrosio G. La gestione dei pazienti con scompenso cardiaco in Medicina Generale: i risultati preliminari di un audit condotto per via telematica. Esperienze e ricerche in Medicina Generale. Società Italiana di Medicina Generale. Rivista della Società Italiana di Medicina Generale. N.4, AgostoAugust 2010 (2010). https://www.simg.it/documenti/rivista/2010/04_2010/3.pdf
24. von Haehling S, Gremmler U, Krumm M *et al.* Prevalence and clinical impact of iron deficiency and anaemia among outpatients with chronic heart failure: The PrEP Registry. *Clin. Res. Cardiol.* 106(6), 436–443 (2017).
25. Garattini L, Castelnuovo E, Lanzeni D, Viscarra C. Durata e costo delle visite in medicina generale: il progetto DYSCO. (Duration and cost of GP visits). *Farmeconomia e percorsi terapeutici* 4(2), 109–114 (2003).
26. Calvert MJ, Freemantle N, Yao G *et al.* Cost–effectiveness of cardiac resynchronization therapy: results from the CARE-HF trial. *Eur. Heart J.* 26(24), 2681–2688 (2005).
27. Kirsch J, McGuire A. Establishing health state valuations for disease specific states: an example from heart disease. *Health Econ.* 9(2), 149–158 (2000).
28. Griffiths A, Paracha N, Davies A *et al.* The cost–effectiveness of ivabradine in the treatment of chronic heart failure from the UK National Health Service perspective. *Heart* 100(13), 1031–1036 (2014).
29. Göhler A, Geisler BP, Manne JM *et al.* Utility estimates for decision-analytic modeling in chronic heart failure – health states based on New York Heart Association classes and number of rehospitalizations. *Value Health* 12(1), 185–187 (2009).
30. Lewis EF, Johnson PA, Johnson W *et al.* Preferences for quality of life or survival expressed by patients with heart failure. *J. Heart Lung Transplant.* 20(9), 1016–1024 (2001).
31. Smith B, Hughes-Cromwick PF, Forkner E, Galbreath AD. Cost–effectiveness of telephonic disease management in heart failure. *Am. J. Manag. Care* 14(2), 106–115 (2008).
32. Ponikowski P, Anker SD, AlHabib KF *et al.* Heart failure: preventing disease and death worldwide. *ESC Heart Fail.* 1, 4–25 (2014).
33. Comín-Colet J, Rubio-Rodríguez D, Rubio-Terrés C *et al.* A cost–effectiveness analysis of ferric carboxymaltose in patients with iron deficiency and chronic heart failure in Spain. *Rev. Esp. Cardiol. (Engl. Ed.)* 68(10), 846–851 (2015).

• **European cost–effectiveness analysis.**

34. Hofmarcher T, Borg S. Cost–effectiveness analysis of ferric carboxymaltose in iron-deficient patients with chronic heart failure in Sweden. *J. Med. Econ.* 18(7), 492–501 (2015).

• **European cost–effectiveness analysis.**

35. Hofmarcher T, Cabrales Alin D, Linde C. Cost–effectiveness of implementing ESC guidelines for treatment of iron deficiency in heart failure in the Nordic countries. *Scand. Cardiovasc. J.* 52(6), 348–355 (2018).

• **European cost–effectiveness analysis.**

36. European Network for Health Technology Assessment (EUnetHTA) (2019). www.eunethta.eu
37. Wolf M, Chertow GM, Macdougall IC *et al.* Randomized trial of intravenous iron-induced hypophosphatemia. *JCI Insight* 3(23), pii: 124486 (2018).