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Hofmarcher, Thomas; Borg, Sixten

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Cost-effectiveness analysis of ferric carboxymaltose in iron-deficient patients with chronic heart failure in Sweden

Thomas Hofmarcher[1,2]; Sixten Borg[3,4]

[1]Department of Economics, Lund University, Lund, Sweden; [2]IHE - The Swedish Institute for Health Economics, Lund, Sweden; [3]Department of Clinical Sciences in Malmö, Lund University, Lund, Sweden; [4]Evidera, London, UK

Corresponding author:

Thomas Hofmarcher

P.O. Box 7082

SE-22007 Lund, Sweden

Tel: +46 46-222 00 00

E-mail: thomas.hofmarcher@nek.lu.se

Abstract

Objective. Iron deficiency is a common but treatable comorbidity in chronic heart failure (CHF) that is associated with impaired health-related quality of life (HRQoL). This study evaluates the cost-effectiveness of the intravenous iron preparation ferric carboxymaltose (FCM) for the treatment of iron deficiency in CHF from a Swedish healthcare perspective.

Methods. A cost-effectiveness analysis with a time horizon of 24 weeks is performed to compare FCM treatment with placebo. Data on health outcomes and medical resource use are mainly taken from the FAIR-HF trial and combined with Swedish cost data. An incremental cost-effectiveness ratio (ICER) is calculated as well as the change in per-patient costs for primary care and hospital care.

Results. In the FCM group compared with placebo quality-adjusted life years (QALYs) are higher (difference 0.037 QALYs), but also per-patient costs are higher [(difference SEK 2,789 (€303)]. Primary care and hospital care equally share the additional costs, but within hospitals there is a major shift of costs from inpatient care to outpatient care. The ICER is SEK 75,389 (€8,194) per QALY. The robustness of the result is supported by sensitivity analyses.

Conclusions. Treatment of iron deficiency in CHF with FCM compared with placebo is estimated to be cost-effective. The ICER in the base case scenario is twice as high as previously thought, but noticeably below SEK 500,000 (€54,300) per QALY, an informal average reference value used by the Swedish Dental and Pharmaceutical Benefits Agency. Increased HRQoL and fewer hospitalizations are the key drivers of this result.

Keywords: Chronic heart failure, Iron deficiency, Cost-effectiveness analysis, Healthcare costs, Ferric carboxymaltose

Introduction

Chronic heart failure (CHF) is a common medical condition affecting 2.2% of the population in Sweden (1). Uncommon in persons aged younger than 50 years, CHF becomes more prevalent with increasing age and affects 6–10% of the population aged 65 years and older (2). CHF impairs patients' quality of life, physical health and functioning, as well as cognitive health (3-5). Besides hypertension, ischemic heart disease and atrial fibrillation, a frequent comorbidity in CHF is anemia (6). Until recently the importance of iron deficiency as a stand-alone comorbidity in CHF, independent of anemia status, has been underestimated (7). Iron deficiency seems to (i) be more common than anemia in CHF and affect up to 50% of patients, (ii) relate to disease severity of CHF, and (iii) be a strong and independent predictor of mortality with a greater predictive power than anemia (8, 9). Mounting evidence and understanding of the role of iron deficiency in CHF has led to the acknowledgment of iron deficiency as a comorbidity in CHF by the European Society of Cardiology (ESC) in 2012 (10).

Iron deficiency is amenable to medical treatment. Iron repletion with the intravenous (IV) iron preparation ferric carboxymaltose (FCM)[*] has shown promising results in the treatment of iron-deficient CHF patients in the FAIR-HF study (11). The FAIR-HF was a multinational, placebo-controlled, double-blind, randomized phase III trial with 459 CHF patients with New York Heart Association (NYHA) functional class II or III, a left ventricular ejection fraction of 40% or less (for patients in NYHA class II) or 45% or less (for NYHA class III), iron deficiency (defined as ferritin level <100 μg/L or 100–299 μg/L, if the transferrin saturation was <20%), and a hemoglobin level of 9.5–13.5 g/dL. Patients were randomly assigned to receive either ferric carboxymaltose (hereinafter referred to as the FCM group) or saline

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[*] FCM is marketed as Ferinject in Sweden by Vifor Pharma Nordiska AB, Stockholm, Sweden.

(hereinafter referred to as the placebo group) in a 2:1 ratio (12). In the FCM group significant improvements were recorded in NYHA functional class, self-reported Patient Global Assessment, distance on the 6-Minute Walk Test, and health-related quality of life (HRQoL) compared with placebo after 24 weeks follow-up. The results were similar in patients with and without anemia (defined as hemoglobin level ≤12 g/dL at baseline). The rates of death as well as serious and non-serious adverse events were similar in the two study groups (11).

The Swedish healthcare system is decentralized with the provision of healthcare being mainly in the hands of 21 county councils and regions. Primary healthcare centers (PHCC) are the initial contact point with the healthcare system in non-acute cases (13). Patients with symptoms of CHF are typically referred to hospital-based or PHCC-based heart failure (HF) clinics for diagnosing and treatment initiation. Regular follow-up visits occur at HF clinics and partly also at ordinary PHCCs (14, 15). Reimbursement of new drugs through inclusion in the national drug benefit scheme is decided by the Dental and Pharmaceutical Benefits Agency (TLV). The reimbursement decision is principally based on the cost-effectiveness of a new drug compared to the current standard treatment (13). The TLV approved FCM for the treatment of iron deficiency in 2008 (16). However, neither FCM nor any other iron preparations are used to treat iron deficiency in CHF in clinical practice in Sweden today, as iron deficiency (as opposed to anemia) is not commonly tested for in CHF patients leaving the condition undetected and untreated.

The cost-effectiveness of FCM in iron-deficient CHF compared with placebo has previously been assessed in the context of the National Health Service in the UK (17). Differences in healthcare systems and the exclusion of relevant treatment-related medical resources limit the

external validity of these results. The aim of this study is to address these shortcomings and to examine the cost-effectiveness of FCM treatment compared with placebo in iron-deficient CHF patients from a Swedish healthcare perspective.

Methods

The cost-effectiveness analysis is built around the setup of the FAIR-HF trial but includes several adjustments to reflect current clinical practice in Sweden. The appropriate comparator for FCM treatment of iron deficiency in CHF is no treatment (represented by the placebo group), as under current clinical practice iron deficiency in CHF remains most often undetected and thus untreated. The time horizon in the analysis is 24 weeks corresponding to the follow-up period in the FAIR-HF trial. Even though it seems that the effects observed in this trial persist at least throughout the whole first year after treatment initiation (18), we have no data at hand which would justify an extrapolation of the time horizon.

The analysis estimates the health outcomes and the associated costs in each study group. Health outcomes are measured as HRQoL and expressed in quality-adjusted life years (QALYs). Costs are obtained by combining resource use and unit cost data. Given the short time horizon, health outcomes and costs are not discounted. The result of the analysis is an incremental cost-effectiveness ratio (ICER), expressed in cost per QALY, which interrelates the difference in costs of treatment with FCM and placebo with the difference in HRQoL.

Health outcomes

The intention-to-treat population in the FAIR-HF trial was composed of 453 patients from ten European countries and six patients from Argentina (11). No patients were recruited in Sweden, but the clinical study results should be reasonably valid for the Swedish population

given the predominantly European study population. Table 1 compares baseline patient characteristics from the FAIR-HF trial with patients managed in outpatient hospital care from the Swedish Heart Failure Registry (S-HFR) (19).

In the FAIR-HF trial HRQoL was inter alia measured with the EuroQoL five dimensions (EQ-5D) questionnaire and the EuroQoL Visual Analogue Scale (EQ VAS) at baseline and at weeks 4, 12 and 24. Both measures can be used to calculate utility values, i.e., an index between 0 and 1, where 0 represents death and 1 best possible health. The calculation of utilities requires the use of validated value sets. The UK time trade-off value set for EQ-5D is commonly used in Swedish cost-effectiveness analyses (20). As the previous cost-effectiveness analysis for the UK applied this value set, we use its published QALY values. In this study, QALYs were obtained for each individual by multiplying the utilities by the appropriate time interval (17). Any changes in utility were assumed to occur in the middle of the intervals defined by the four assessment time points. Observations with missing values were imputed with the value of the last observation. We use the resulting QALY values in the base case scenario, but we run also a sensitivity analysis with QALY values based on full records on utility only.

Resource use

Our analysis takes the Swedish healthcare perspective and includes four resource categories which are directly affected by the treatment; diagnostic tests, FCM, administration of FCM, CHF-related hospitalization. Costs that fall outside the remit of the healthcare payer could not be included. Table 2 details all resource parameters used in the analysis.

In clinical practice FCM must only be administered, if the diagnosis of iron deficiency is based on laboratory tests (we include hemoglobin level, ferritin level and transferrin saturation). In the FCM group the resources for diagnosing all patients intended for treatment (and not only those with a positive diagnosis) are included, assuming a prevalence of iron deficiency of 50% in CHF (9). The base case scenario does not include a separate healthcare visit for diagnostics, as this is probably physician-initiated in conjunction with a regular healthcare visit. However, we include a follow-up visit for diagnostic testing. In the placebo group no such resources are consumed, as these tests are not yet routinely performed in CHF patients in Sweden.

Dosing of FCM (and with that the number of administrations) is based on the approved simplified dosage regimen rather than the old regimen used in the FAIR-HF trial. Correct dosing is determined by the body weight and hemoglobin level resulting in four possible dosing combinations (we assume no patients with hemoglobin level ≥ 14 g/dL) (21). In the base case scenario we assume a hypothetical patient population that is spread equally across all combinations. If administered as an IV infusion, the maximum single dose of FCM is 1,000 mg of iron per day and should not exceed 20 mg/kg body weight. As a result, 75% of the patients will require two healthcare visits to administer the cumulative iron dose and 25% only one visit (we assume no patients with <50 kg body weight). The cumulative iron dose is supposed to suffice for 24 weeks.

As described before, the management of CHF patients is shared between healthcare providers in Sweden. Outpatient hospital care and primary care manage each around half of all CHF patients (14, 15). Younger and more severe cases (as defined by NYHA class) are predominantly managed in outpatient hospital care (14, 15, 22). In line with the patient

recruitment in the FAIR-HF trial, it is expected that FCM will be mainly used in these patients. In the base case scenario we assume that 80% of the patients are treated in outpatient hospital care and 20% in primary care.

In the FAIR-HF trial there was a borderline significant trend towards a lower rate of hospitalization for any cardiovascular cause in the FCM group compared with the placebo group (hazard ratio 0.53; 95% confidence interval (CI) 0.25–1.09; p=0.08) (11). In the FCM group 16 such hospitalizations were recorded among the 305 patients during the 24 weeks period, and 18 hospitalizations among the 154 patients in the placebo group. The latter value corresponds to 0.12 hospitalizations per patient or, if extrapolated to a full year, to 0.25 hospitalizations per patient per year. In contrast, the Swedish National Board of Health and Welfare registered 33,921 hospitalizations with a primary diagnosis of CHF (ICD-10 code I50) in 2013 (23). Given a prevalence of CHF of 2.2% (1) in the total Swedish population (9.6 million people), this would correspond to 0.16 hospitalizations per patient in 2013. The higher hospitalization rate in the placebo group in the FAIR-HF trial can be explained by (i) the higher proportion of severe CHF cases in the study population compared with the general CHF population (see Table 1); (ii) the Swedish prevalence estimate which includes patients with both CHF as primary and secondary diagnosis; (iii) the Swedish value referring solely to CHF and not any cardiovascular cause.

As hospital length of stay (LOS) in CHF patients varies greatly between countries (24), we do not apply the LOS recorded in the FAIR-HF trial to the number of hospitalizations per patient. Instead we use the average LOS of CHF patients in Sweden from the S-HFR (19).

Unit costs

Swedish cost data on inpatient and outpatient care services at hospitals and in primary care were sourced from the Board of the Southern Health Care Region, which utilizes a Diagnosis Related Groups system (25). Unit prices for FCM used in primary care were taken from the Swedish Medicines Information Engine (26). Unit prices for FCM used in outpatient hospital care were provided by Vifor Pharma Nordiska, Stockholm, Sweden. All costs are reported in Swedish kronor (SEK) and euros (€) in 2014 prices; see Table 2. An exchange rate of SEK 9.2 for €1 was applied.

Sensitivity analysis

Deterministic and probabilistic sensitivity analyses were conducted to examine the robustness of the resource parameters and the underlying assumptions in the base case. In the deterministic sensitivity analyses we simulated various scenarios to test the impact of a separate healthcare visit for diagnostic tests, the treatment setting (outpatient hospital care vs. primary care) in which FCM is administered, dosing and cost of FCM, different definitions of the number of hospitalizations per patient, hospital LOS, computation of and the difference in QALY. In the probabilistic sensitivity analysis (second-order Monte Carlo simulation) we assumed a normal distribution of all parameters included; see Table 2. 1,000 sets of randomly drawn input parameters were used. The analysis was performed in Microsoft® Excel 2013 (Microsoft Corporation, Redmond, WA, USA).

Results

In the base case scenario, total costs per patient in the FCM group amounted to SEK 8,602 (€935) and to SEK 5,812 (€632) in the placebo group over the 24 weeks study period, corresponding to a cost difference of SEK 2,789 (€303). Broken down by cost categories

there were costs of SEK 497 (€54) for diagnostic tests, SEK 3,390 (€369) for FCM, SEK 2,106 (€229) for FCM's administration, and SEK 2,609 (€284) for hospitalization in the FCM group. In the placebo group total costs coincide with SEK 5,812 (€632) for hospitalization. During the study period average QALYs amounted to 0.336 in the FCM group compared with 0.298 in the placebo group, corresponding to a QALY difference of 0.037 (bootstrap-based 95% CI 0.017–0.060) (17). As a result, the ICER equals to SEK 75,389 (€8,194) per QALY; see Table 3.

Our result is distinctly below the informal average reference value of SEK 500,000 (€54,300) per QALY used by the TLV to determine cost-effectiveness. This indicates a favorable cost-effectiveness profile of FCM treatment. The study of FCM treatment in the UK yielded an ICER of €4,414 (SEK 40,600) per QALY (17). Our estimate is almost twice as high, stemming partly from methodological differences, and partly from different relative prices for healthcare services.

Since we distinguish in which treatment setting FCM is administered, we can analyze how the additional per-patient costs are shared between healthcare providers. Diagnostic tests and FCM treatment would increase the costs in primary care by SEK 1,413 (€154) and in outpatient hospital care by SEK 4,580 (€498). On the other hand, SEK 3,204 (€348) would be saved in inpatient care. Thus, primary care and hospital care would almost equally share the additional costs, but within hospitals we estimate a major shift of costs from inpatient care to outpatient care.

Sensitivity analysis

In the deterministic sensitivity analysis the results ranged from an ICER of SEK 32,469 (€3,529) per QALY to SEK 164,081 (€17,835) per QALY; see Table 3. The parameters with the greatest impact on the result were the QALY difference and its computation, the number of hospitalizations per patient, and the hospital LOS. The parameters with a modest impact were diagnostic tests, the healthcare setting in which FCM is administered, the dosing of FCM, and the unit cost of FCM.

The probabilistic sensitivity analysis led to an average difference in total costs of SEK 2,777 (€302) [95% CI: SEK 1,243–4,310 (€135–468)] and an average QALY difference of 0.037 (95% CI: 0.021–0.054). The average ICER was SEK 78,804 (€8,566) per QALY [95% CI: SEK 18,026–139,582 (€1,959–15,172) per QALY]. Of the 1,000 simulations 998 were below SEK 200,000 (€21,700) per QALY. A cost-effectiveness scatterplot and a cost-effectiveness acceptability curve are shown in Figure 1 and Figure 2, respectively. In short, the sensitivity analyses confirm the results to be robust.

Discussion

The economic burden of CHF is high and has been estimated to equal about 2% of the total healthcare budget in Sweden (14). CHF patients are frequently hospitalized and CHF is the most common cause of hospitalization in patients aged over 65 years (19). Hospitalization is by far the greatest cost component of total healthcare expenditure for CHF, accounting for 47–69% of total expenditures, whereas medications stand for some 18% and the remainder for nursing homes, primary and ambulatory care visits (14, 27). Apart from the economic burden, CHF is a major cause of reduced HRQoL (4).

Only recently it has been discovered and acknowledged that iron deficiency (independent of anemia status) is a common and treatable comorbidity in CHF (10). The two viable treatment options are oral iron therapy and IV iron therapy. In therapeutic areas other than CHF oral iron therapy is usually the first-line treatment for iron deficiency because of convenience and low cost. However, there is currently no clinical evidence on the effectiveness of oral iron in iron-deficient CHF (28). Poor absorption, adverse gastrointestinal effects leading to non-compliance and premature treatment discontinuation, and a longer time span to restore depleted iron stores have been put forward as factors that possibly undermine the effectiveness of oral iron in this patient group (28-30). Historically, safety concerns of IV iron have prevented its widespread use (31). Nowadays, safe IV iron preparations for the treatment of iron deficiency in CHF are available, which are not associated with an increased rate of adverse events, but rather reduce the risk of hospitalization, and increase HRQoL as well as physical functionality (32).

To date, the positive effects of IV iron in the treatment of iron deficiency in CHF have only been convincingly demonstrated for two preparations, iron sucrose and FCM. The only crux with iron sucrose is the dosage regimen according to which only 200 mg iron can be comfortably administered per day. Full iron replenishment necessitates thus multiple clinic visits which drive up the cost for administration. By contrast, FCM can be given at doses up to 1,000 mg iron per day, thereby limiting the number of clinic visits. Direct head-to-head comparisons of FCM to oral iron therapy or to other IV iron preparations in iron-deficient CHF patients are lacking. Despite the availability of different iron preparations, this patient group remains currently by and large untreated in Sweden. Therefore we conducted an evaluation of the cost-effectiveness of FCM against no treatment in this study.

Limitations

Several limitations in our analysis originated from the design of the FAIR-HF trial. The most important ones were the short 24 weeks follow-up period, the usage of the old dosage regimen for the administration of FCM, and the underpowered study design to detect significant differences in hospitalizations. The CONFIRM-HF study addressed many of these issues. The CONFIRM-HF was a multi-center, double-blind, placebo-controlled phase III trial with 304 iron-deficient CHF patients, who were treated with FCM according to the current dosage regimen over a 1-year period (18). It is important to note that the CONFIRM-HF study used the same definition of iron deficiency as the FAIR-HF study and our findings should be interpreted against the backdrop of this definition of the eligible patient population.

Bearing strong resemblance to the FAIR-HF study, the CONFIRM-HF study recorded significant improvements in distance on the 6-Minute Walk Test, change in NYHA functional class, self-reported Patient Global Assessment, and HRQoL as well as similar number of deaths and adverse events rates in the FCM group compared to placebo (18). These measures are partly captured by the number of QALYs, which we identified as a key driver of our result. This strengthens the evidence on the positive impact of FCM treatment on health outcomes and suggests a stable effect throughout the first year of treatment.

Since hospitalization constitutes the most important cost component in CHF patients, it is not surprising that the sensitivity analysis identified it as the other key driver of our result. In the FAIR-HF trial there was a clear trend towards a lower number of hospitalizations in patients receiving FCM compared with placebo, yet the difference was only borderline significant (11), probably because the trial was not powered to detect such differences (12). The CONFIRM-HF study observed an even stronger decrease in hospitalizations in the FCM group compared with placebo during the first year of treatment (18). In our deterministic

sensitivity analysis three scenarios utilize this newer data on hospitalization. They indicate more favorable outcomes than the base case result.

In the estimation of costs for FCM and its administration, we applied the current dosage regimen to a hypothetical patient population, which was supposed to better reflect the eligible population in clinical practice. In the base case scenario the average amount of iron administered was 1,500 mg, and the average number of administrations was 1.75. The outcomes of the CONFIRM-HF study supported our approach, as throughout the first year of treatment the average amount of iron administered was 1,500 mg, and over 75% of the patients required a maximum of two administrations of FCM to correct and maintain the iron parameters (18).

We used conservative assumptions in the estimation of costs for diagnostic tests. In the placebo group we assumed no diagnostic tests, even though the hemoglobin level is routinely assessed in CHF patients in Sweden. In case of abnormal findings further laboratory tests may be performed, which possibly examine the ferritin level and transferrin saturation. We did not include the cost for a separate healthcare visit to perform the initial diagnostic tests, as this will probably be initiated by a physician in conjunction with one of the several outpatient care visits that a CHF patient typically makes each year due to the treatment of numerous comorbidities (14, 22). For the same reason, the costs for a follow-up visit to check the iron parameters, which we included, might be overestimated.

The inability to take on a societal perspective in our analysis and include resources outside the remit of the healthcare payer, such as productivity loss and informal care, should not invalidate our results. For the United States it has been estimated that indirect costs constitute

10% of the total costs for CHF (33). This small share of indirect costs can partly be explained by the advanced age of CHF patients. Many of them are already retired which means that no productivity loss arises. Nevertheless, it can be speculated that informal care requirements might be reduced, if patient health and physical activity improves as observed in the clinical trials. Other healthcare resources such as outpatient care visits not related to the administration of FCM or use of cardiac and non-cardiac medications might also be affected by FCM treatment, but could not be included in the analysis due to a lack of data.

In view of the findings in both the FAIR-HF and the CONFIRM-HF trial, we consider the assumptions in our analysis to be based on solid evidence. This contributes to the generalizability of the results to other country settings where iron deficiency remains to be an overlooked and untreated comorbidity in CHF. Owing to the favorable cost-effectiveness profile of FCM corroborated in this study, the detection and treatment of iron deficiency in CHF patients should become a priority for clinical practice in Sweden. However, further evidence on the effects of FCM on HRQoL and use of healthcare resources after the first year of treatment is needed. To facilitate and support health economic decision-making, future studies should also directly compare FCM with other IV iron preparations and oral iron therapy in the treatment of iron deficiency in CHF patients based on hard endpoints.

Conclusion

The treatment of iron deficiency in CHF with FCM compared with placebo is estimated to be cost-effective. The ICER amounts to SEK 75,389 (€8,194) per QALY, which is almost twice as high as a previous study indicated. Nonetheless, the ICER is noticeably below SEK 500,000 (€54,300) per QALY, an informal average reference value used by the TLV to determine cost-effectiveness. Improved HRQoL and a reduction in hospitalizations are

identified as the key drivers of this result. The introduction of FCM treatment would also have consequences for how the economic burden is split between healthcare providers. The estimated cost increase of SEK 2,789 (€303) per patient would be equally shared between primary care and hospital care, but within hospitals there is a major shift of costs from inpatient care to outpatient care.

Transparency

Declaration of funding

Declaration of financial/other relationships

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Table 1: Characteristics of Swedish patients and FAIR-HF study population at baseline

Characteristic	Swedish Heart Failure Registry (19)	FAIR-HF trial (11)	
Patient population	Primary or secondary diagnosis of CHF (ICD-10 code I50)	Iron-deficient CHF patients	
Healthcare setting	Outpatient hospital care	Ambulatory care	
		FCM group	Placebo group
Number of patients	52,731	304	155
Age, years	~75	68 (10)	67 (11)
Females, %	39%	52%	55%
BMI, kg/m²	26.7	28 (5)	28 (5)
NYHA class	I 11% II 44% III 38% IV 6%	II 17% III 83%	II 19% III 81%
Hemoglobin, g/dL	13.1	11.9 (13)	11.9 (14)
Serum ferritin, μg/L	N/A	53 (55)	60 (67)
Transferrin saturation, %	N/A	18 (13)	17 (8)
Concomitant disease			
Atrial fibrillation	51%	31%	28%
Hypertension	50%	80%	83%
Ischemic heart disease	47%	81%	79%

Previous myocardial infarction	~36%	55%	58%
Diabetes mellitus	~25%	31%	24%
Previous stroke	~12%	8%	6%
Concomitant treatment			
Beta blockers	90%*	86%	83%
RAS blockers	87%*	92%	91%
Diuretics	79%*	92%	90%

Data refer to mean value (standard deviation) or share of patients affected.

BMI = body mass index; CHF = chronic heart failure; N/A = not available; NYHA = New York Heart Association; RAS = renin-angiotensin system.

*Refers only to CHF patients with reduced left ventricular ejection fraction.

Table 2: Parameters for the cost-effectiveness analysis and the sensitivity analysis

Parameter	Value	Variation in the deterministic sensitivity analysis	Distribution parameters in the probabilistic sensitivity analysis*
Health outcomes			
QALY difference between study groups (17)	0.037	0.017–0.060	Normal (0.037; 0.01)
Resource use			
Patients (Hb <10 g/dL, weight <70 kg) receiving 1x1000 mg + 1x500 mg FCM	25%	0%	Normal (0.25; 0.1)
Patients (Hb <10 g/dL, weight ≥70 kg) receiving 2x1000 mg FCM	25%	100%	Normal (0.25; 0.1)
Patients (Hb ≥10 g/dL, weight <70 kg) receiving 1x1000 mg FCM	25%	0%	Normal (0.25; 0.1)
Patients (Hb ≥10 g/dL, weight ≥70 kg) receiving 1x1000 mg + 1x500 mg FCM	25%	0%	Normal (0.25; 0.1)
Patients treated in primary care	20%	0–100%	Normal (0.2; 0.1)
Patients treated in outpatient hospital care	80%	0–100%	Normal (0.8; 0.1)
Hospitalizations per patient† (11)	FCM: 0.052	No difference	Normal (0.064; 0.01)

	Placebo: 0.117		for difference
Average hospital LOS of CHF patients, days (19)	7.0	4.6–10.7	Normal (7.0; 1.5)

Unit costs (in 2014 SEK (€))

Costs for diagnostic tests‡

Laboratory tests$ (25)	58 (6)	-	-
Healthcare visit solely for diagnostic tests (25)	323 (35)	Inclusion	-
Drug costs for FCM			
In primary care: 500 mg (1x10 ml vial)¶ (26)	1,854 (202)	±20%	-
In primary care: 1,000 mg (1x20 ml vial)¶ (26)	3,700 (402)	±20%	-
In outpatient hospital care: per 100 mg	190 (21)	±20%	Normal (190; 19)
Administration costs for FCM			
In primary care: per visit (25)	580 (63)	-	-
In outpatient hospital care (HF clinic): per visit (25)	1,359 (148)	-	-
Inpatient care costs			
Hospitalization in HF clinic: first day** (25)	9,755 (1,060)	-	-
Hospitalization in HF clinic: any additional day†† (25)	6,662 (724)	-	-

CHF = chronic heart failure; Hb = hemoglobin level; HF = heart failure; LOS = length of stay; QALY = quality-adjusted life year; SEK = Swedish kronor; € = euros.

* For all included parameters a normal distribution (mean; standard deviation) is assumed. To ensure non-negative values, the normal distribution of each parameter has been truncated to the 95% confidence interval. The sum of the patient shares in the four dosing groups is always scaled to 100%.

† Based on the parameter "hospitalization for any cardiovascular cause".

‡ Same price in primary care and outpatient hospital care.

$ Includes tests for hemoglobin in blood (SEK 10), serum ferritin (SEK 27), serum transferrin (SEK 12), fP iron (SEK 9), P-transferrin saturation (SEK 0).

¶ Pharmacy purchase price.

** Includes cost for admission to the clinic (SEK 3,093) + nursing (SEK 6,472) + physician visit (SEK 190).

†† Includes cost for nursing (SEK 6,472) + physician visit (SEK 190).

Table 3: Results of the cost-effectiveness analysis and the deterministic sensitivity analysis (in 2014 prices)

	Parameter	Parameter value	Cost difference, SEK (€)*	QALY difference*	ICER, SEK (€) per QALY
Base case scenario			2,789 (303)	0.037	75,389 (8,194)
Scenarios in the deterministic sensitivity analysis					
Resource use	Include a separate healthcare visit for initial diagnostic tests	SEK 646	3,435 (373)	0.037	92,848 (10,092)
	Share of patients receiving FCM in outpatient hospital care	100%	2,522 (274)	0.037	68,152 (7,408)
	Share of patients receiving FCM in outpatient hospital care	50%	3,191 (347)	0.037	86,243 (9,374)
	Share of patients receiving FCM in primary care	100%	3,860 (420)	0.037	104,335 (11,341)
	Share of patients receiving 2x1000 mg FCM	100%	4,220 (459)	0.037	114,048 (12,397)
	Hospitalizations per patient	Same in both study groups	5,993 (651)	0.037	161,973 (17,606)
	Hospitalizations for worsening heart failure per patient (11)	FCM: 0.023; Placebo: 0.058	4,228 (460)	0.037	114,274 (12,421)
	Hospitalizations for any cause per patient (11)	FCM: 0.092; Placebo: 0.143	3,454 (375)	0.037	93,358 (10,148)
	Hospitalizations for worsening heart failure per patient (18)	FCM: 0.031; Placebo: 0.098	2,659 (289)	0.037	71,873 (7,812)
	Hospitalizations for any cardiovascular reason per patient (18)	FCM: 0.080; Placebo: 0.156	2,220 (241)	0.037	59,987 (6,520)
	Hospitalizations for any cause per patient (18)	FCM: 0.142; Placebo: 0.211	2,544 (276)	0.037	68,751 (7,473)
	Hospital LOS for CHF in Sweden (19)	Minimum: 4.6 days	3,819 (415)	0.037	103,228 (11,220)
	Hospital LOS for CHF in Sweden (19)	Maximum: 10.7 days	1,201 (131)	0.037	32,469 (3,529)
Resource costs	Price of FCM	+20%	3,467 (377)	0.037	93,715 (10,186)
	Price of FCM	−20%	2,111 (229)	0.037	57,062 (6,202)

Health outcome	QALY difference (11)	Lower bound 95% CI	2,789 (303)	0.017	164,081 (17,835)
	QALY difference (11)	Upper bound 95% CI	2,789 (303)	0.060	46,490 (5,053)
	Computation of QALYs (11)	EQ VAS-derived QALYs	2,789 (303)	0.023	121,278 (13,182)
	Computation of QALYs (11)	Only complete records on utility	2,789 (303)	0.039	71,523 (7,774)

CHF = chronic heart failure; CI = confidence interval; EQ VAS = EuroQoL Visual Analogue Scale; ICER = incremental cost-effectiveness ratio; LOS = length of stay; QALY = quality-adjusted life year; SEK = Swedish kronor; € = euros.

*A positive cost (QALY) difference indicates that FCM is more expensive (effective) than placebo.
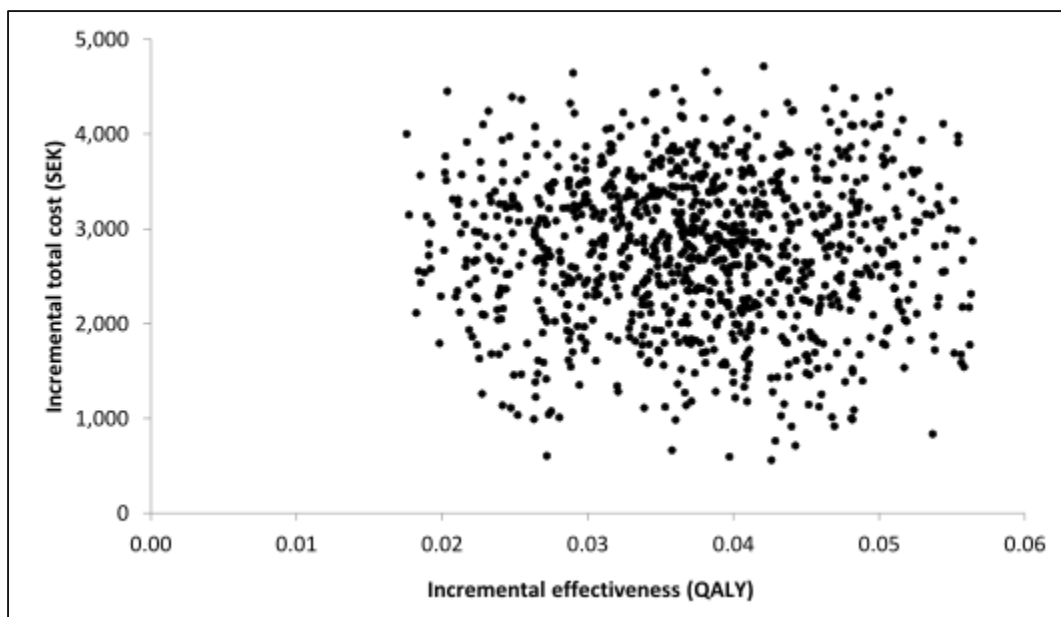
Figure 1: The cost-effectiveness scatterplot depicts 1000 simulations (each represented as a dot) of the difference in total cost and QALY between the two study groups. For each simulation, parameters were simultaneously and randomly sampled for each group. All simulations fell into the upper right quadrant of the cost-effectiveness plane, where treatment with FCM is more costly and more effective than placebo.
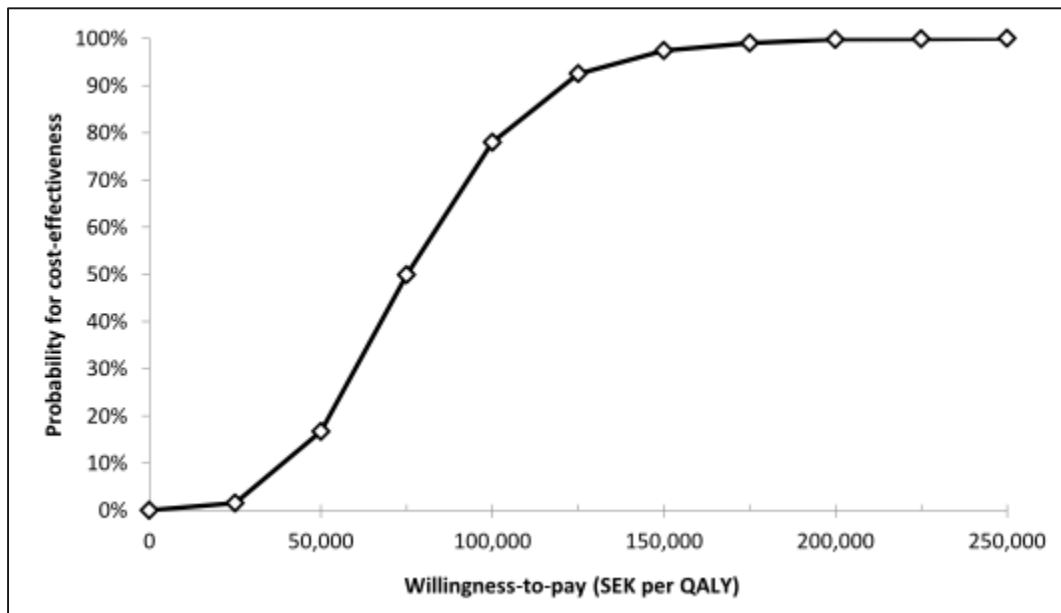

Figure 2: The cost-effectiveness acceptability curve indicates the probability that FCM is cost-effective compared with placebo for different willingness-to-pay values. The willingness-to-pay value can be interpreted as the maximum value one would be willing to pay for gaining one QALY.