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Clinical and economic impact of ferric carboxymaltose treatment for iron deficiency in patients stabilized following acute heart failure: a multinational study

Phil McEwan[a], Piotr Ponikowski[b], Tinevimbo Shiri[a], Giuseppe M. C. Rosano[c], Andrew J. S. Coats[d], Fabio Dorigotti[e], Antonio Ramirez de Arellano[e] and Ewa A. Jankowska[f]

aHealth Economics and Outcomes Research Ltd, Cardiff, UK; bInstitute of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; cCardiovascular and Cell Sciences Research Institute, St George's University, London, UK; dHeart Research Institute, Sydney, Australia; eCSL Vifor, Glattbrugg, Switzerland; fInstitute of Heart Diseases, University Hospital, Wrocław, Poland

ABSTRACT

Objective: To estimate clinical events and evaluate the financial implications of introducing ferric carboxymaltose (FCM) to treat iron deficiency (ID) at discharge in patients hospitalized for acute heart failure (AHF) with left ventricular ejection fraction (LVEF) <50% in the UK, Switzerland and Italy.

Methods: A decision analytic cost-offset model was developed to evaluate the costs associated with introducing FCM for all eligible patients in three countries compared to a world without FCM, over a five-year time horizon. Data from AFFIRM-AHF clinical trial were used to model clinical outcomes, using an established cohort state-transition Markov model. Country-specific prevalence estimates were derived using data from real-world studies to extrapolate number of events and consequent cost totals to the population at risk on a national scale.

Results: The cost-offset modeling demonstrated that FCM is projected to be a cost-saving intervention in all three country settings over a five-year time horizon. Savings were driven primarily by reduced hospitalizations and avoided cardiovascular deaths, with net cost savings of −£14,008,238, −CHF25,456,455 and −€105,295,146 incurred to the UK, Switzerland and Italy, respectively.

Limitations: Although AFFIRM-AHF was a multinational trial, efficacy data per country was not sufficiently large to enable country-specific analysis, therefore overall clinical parameters have been assumed to apply to all countries.

Conclusions: This study provides further evidence of the potential cost savings achievable by treating ID with FCM at discharge in patients hospitalized for AHF with LVEF <50%. The value of FCM treatment within the healthcare systems of the UK, Switzerland and Italy was demonstrated even within a limited time frame of one year, with consistent cost savings indicated over a longer term.

Introduction

Heart failure (HF) is a life-threatening chronic disease, currently affecting approximately 1–2% of the adult population in developed countries[1]. Patients with HF have impaired cardiac function, are at increased risk of cardiovascular (CV) events and CV-related mortality[2], and the symptom burden associated with HF, notably edema, fatigue and dyspnea, is substantial and debilitating[3–7]. HF is most common in elderly patients, affecting ≥10% of patients aged over 70 years. Consequently, with an aging population, HF prevalence is set to rise[1,2,8].

An estimated 40–50% of patients with HF with left ventricular ejection fraction (LVEF) <50% have concomitant iron deficiency (ID)[9–13]. In patients with HF, ID has a significant impact on morbidity and mortality and is associated with reduced quality of life (QoL)[14], New York Heart Association (NYHA) class severity and increased risk of hospitalizations[15], independent of anemia. ID is now recognized as a comorbidity of HF and routine screening for ID in this population is recommended in the 2021 European Society of Cardiology (ESC) guidelines for acute and chronic HF, in order to improve disease management[16].

Over the last decade the economic burden of HF has risen sharply in Europe, with the highest proportion of healthcare costs driven by hospitalizations. In the United Kingdom (UK), Italy and Switzerland, HF hospitalizations account for approximately 5% of all emergency medical hospital admissions and readmission rates are high, ranging from 24% at 3

months to 44% at 12 months post-hospital discharge[17,18]. Overall, HF treatment costs account for approximately 1–2% of total healthcare budget and is projected to rise[19].

Oral iron therapy is inexpensive and a frequently-used therapy for ID, however most HF patients with ID fail to respond[20–22] and it often has suboptimal results[21]. In addition, oral iron therapy can be poorly tolerated, with significant gastrointestinal perturbation reported in the majority of hospitalized patients[23]. Hence, the ESC guidelines recommend not using oral iron to treat ID in patients with HF[16].

Intravenous (IV) iron therapy is now gaining traction for the treatment of iron deficiency in HF[24,25]. Despite reports on various AE risks, associated with different formulations of IV iron, findings from these studies yield contradictory results for the relative frequencies of certain AEs[26–32]. Furthermore, a Cochrane review of iron deficiency anemia treatments concluded no significant differences in the rates of AEs arising from different IV iron therapies[33].

Ferric carboxymaltose (FCM) is a high dose IV therapy for ID with a robust, established benefit-risk profile based on numerous clinical trial programs, including in patients with HF[16,34–40]. In AFFIRM-AHF, a multi-center randomized controlled trial, FCM treatment reduced risk of subsequent hospitalizations with no apparent effect on the risk of CV death in patients admitted for acute HF (AHF) with LVEF <50% and concomitant ID, compared to placebo[38]. Patients receiving FCM reported significant improvements in their health status from week 4 to week 24[36]. Accordingly, the ESC guidelines recommend that treatment with FCM should be considered in symptomatic HF patients recently hospitalized for HF and with LVEF <50%[16]. Based on data from AFFIRM-AHF, cost-effectiveness analysis demonstrated that FCM dominates standard care (quality-adjusted life year [QALY] gains combined with cost savings) in the UK and Switzerland, and is highly cost effective in Italy, with an incremental cost-effectiveness ratio of €1,269 per QALY[41].

Given the population-level burden of hospitalizations in HF patients, treatment of ID with FCM has the potential to have a significant beneficial impact on healthcare budgets as well as improving patient outcomes. Currently, no published literature exists for the UK, Swiss or Italian public healthcare settings regarding the budget impact of FCM from the payer's perspective. Hence, the objectives of this study were to estimate the clinical events (hospitalizations, adverse events [AEs] and mortality) and assess the financial implications of introducing FCM to treat ID in eligible patients with LVEF <50% who had stabilized after hospitalization for an acute HF episode, in three European countries; the UK, Switzerland and Italy.

Methods

A decision analytic cost-offset model was developed to assess the potential cost savings of implementing IV FCM for the treatment of concomitant ID in patients at discharge after AHF with LVEF <50% in three European countries; the UK, Switzerland and Italy. The model evaluated the costs associated with treating all eligible patients with FCM,

compared to those associated with a world without IV iron therapy (referred to hereafter as "standard care"), over a time horizon of five years. Clinical outcomes were modeled using data from AFFIRM-AHF, using a previously published cohort state-transition Markov model[41]. The estimated cumulative number of clinical events and cumulative monthly costs were then used as inputs in the cost-offset model. Real-world epidemiology data were used to derive country-specific prevalence estimates in order to extrapolate the number of events and consequent overall cost to the population at risk on a national scale. Clinical data underlying the model remained consistent across country adaptations, assuming patients in AFFIRM-AHF were representative of the country-specific patient populations in the UK, Italy and Switzerland. Cost parameters and epidemiological inputs were varied to more accurately model economic outcomes within the specific country settings.

Costs were considered primarily from a healthcare's perspective and summarized as i) the incremental healthcare costs of implementing FCM versus standard care, with standard care represented by the placebo arm of AFFIRM-AHF, and ii) costs saved due to avoided events associated with FCM treatment. All costs were discounted at 3.5% for the UK and 3% for Switzerland and Italy.

Epidemiology and eligible population

The target population was aligned with the inclusion and exclusion criteria of the AFFIRM-AHF (NCT02937454) trial[38]. As in the AFFIRM-AHF trial, the study population was defined as patients hospitalized for AHF, with LVEF <50% within a 12-month period prior to randomization, and established ID; the latter defined as serum ferritin <100 ng/mL, or between 100 and 299 ng/mL with transferrin saturation <20%.

To derive the eligible population in each country, a targeted literature review was carried out to identify estimates of the population hospitalized for AHF, the prevalence of ID within AHF patients and the population with comorbid ID and LVEF <50% in UK, Italy and Switzerland (Table 1). No Italy-specific data for the prevalence of ID within hospitalized AHF patients could be identified, therefore the prevalence of ID within AHF observed from France and Spain were used as a proxy[42].

Clinical outcomes

The modeled outcomes integrated into the cost-offset analysis were hospitalization for HF (HHF), hospitalization for non-HF causes (HnHF), CV death, all-cause mortality (ACM), and serious AEs that occurred in at least 1% of patients in each treatment arm in AFFIRM-AHF: atrial fibrillation (AF), acute kidney injury (AKI), pneumonia and sepsis[41]. The incidence of HHF and HnHF events were modeled using generalized estimating equations in order to capture recurrent events (Table S1).

Patient mortality outcomes were estimated using parametric survival models fitted to the AFFIRM-AHF patient-level data. The survival model fitting and selection process were

Table 1. Eligible population based on country-specific epidemiology

Event	UK		Switzerland		Italy	
	Fraction	Population	Fraction	Population	Fraction	Population
Hospitalizations for AHF	1.000	78,805[46]	1.000	21,936[48]	1.000	167,047[50]
With ID	0.337[46]	26,557	0.540[49]	11,845	0.775[42]	129,461
With LVEF <50%	0.660[73]	52,011	0.450[49]	9,871	0.533[51]	89,036
Eligible population	0.222	17,528	0.243	5,330	0.413	69,003

Abbreviations. AHF, acute heart failure; ID, iron deficiency; LVEF, left ventricular ejection fraction.

consistent with published guidelines[43–45] and explored standard parametric survival functions: Weibull, log-logistic, log-normal, Gompertz, generalized gamma and gamma. Goodness-of-fit was assessed using the Akaike Information Criteria. A Weibull distribution was selected on the basis of clinical plausibility of long-term survival estimates in addition to providing the best fit to the trial data. Modeled mortality outcomes were adjusted for age, sex and other clinical characteristics.

Input values to the cost-offset model are presented in Table S2–S4. Incidence of AEs was derived from the AFFIRM-AHF trial data (Table S2). The base case analyses assume a market share of 100% over the five-year horizon period.

Cost parameters

All costs were based on 2020 prices. Direct medical costs accrued in the cost-offset model consisted of drug acquisition and administration, hospitalization, treatment-emergent AEs, and CV-related mortality.

Drug acquisition costs presented in Table S3 were aligned with AFFIRM-AHF treatment protocol. Participants received IV FCM or placebo prior to their initial discharge for AHF, and again at further study visits if the patient continued to present with ID. Acquisition costs for FCM were supplied by CSL Vifor and were calculated according to the mean dose recorded in the AFFIRM-AHF trial data. Acquisition and administration costs for placebo were assumed to have no charge.

Hospitalization and AE costs were applied as discrete events. Costs of the incident AHF hospitalization were not included. Mortality costs were applied only for CV mortality; all other cause mortality was assumed to incur no cost to the healthcare system. CV mortality costs compromised end of life care costs for people with worsened CV conditions. All event costs and sources are summarized in Table S3.

Scenario and sensitivity analyses

The base case for the UK and Switzerland used country-specific studies to inform the proportion of patients with ID, which provided conservative estimates compared to alternative published sources from other country settings. A scenario where the proportion of patients with ID in the UK and Switzerland was increased to reflect that reported in prospective studies from other countries was undertaken. For the Italian case, ID prevalence within the population was assumed to be 77.5%, a midpoint of the range 72–83% observed in Spain and France[42]. Subsequent scenario

analysis was conducted applying an average of the UK and Swiss ID figures in order to present a more optimistic scenario of FCM impact in Italy.

A deterministic sensitivity analysis (DSA) was performed to assess the impact of changes in parameters on model results. The parameters varied in the DSA included the target population in each country, exclusion of life tables from analyses, the use of unadjusted survival equations, the cost of FCM, hospitalization costs, CV death and AE costs. Standard errors were used to vary parameters included in the DSA.

Results

Derivation of the population eligible for treatment in the UK, Switzerland and Italy

The base case population size eligible for treatment with FCM in this indication derived for the UK, Switzerland and Italy was 17,528, 5,330 and 69,003, respectively (Table 1). The UK eligible population stemmed from a retrospective cohort study of 78,805 incident cases of AHF in England requiring hospitalization, of which 33.7% patients had concomitant ID[46]. The proportion of those patients with LVEF <50% was derived from a survey of patients based in England and Wales, which reported 66% of AHF patients had LVEF <50%[47].

In Switzerland, an analysis of hospital records identified 65,807 incident cases of AHF requiring hospitalization between 2012 and 2015, which averages to 21,936 per year[48]. In another Swiss study, 45% of admitted AHF patients presented with LVEF <50%. The study found no statistical difference in ID prevalence across HF phenotypes, so the proportion of 54% of LVEF <40% patients presenting with comorbid ID was assumed to apply to the full LVEF <50% population[49].

In Italy, 167,047 incident cases of AHF requiring hospitalization were reported in 2018[50]. In patients admitted for AHF, the proportion of persons presenting with LVEF <50% was 53.3%[51], while a recent review estimated the prevalence range of ID in acute decompensated HF to be 72%–83%; in the absence of Italy-specific data, the average of these bounds were taken as a proxy[42].

Predicted impact of FCM on hospitalizations

Without FCM intervention, the predicted number of HF-related hospital bed days were 20,942, 6,370 and 82,363 within the UK, Swiss and Italian patient populations, respectively (Table 2). Treatment with FCM was associated with a reduction of 4,100, 1,248 and 16,097 HF-hospitalizations in the UK (with a target at risk population of 17,528),

Table 2. Modeled outcomes, associated costs and net budget impact over five years.

Outcome	Component	UK			Switzerland			Italy		
		FCM	Standard care	Difference	FCM	Standard care	Difference	FCM	Standard care	Difference
Events										
Hospitalizations	HHF	16,842	20,942	−4,100	5,122	6,370	−1,248	66,266	82,363	−16,097
	HnHF	9,193	9,502	−309	2,796	2,890	−94	36,171	37,373	−1,202
Mortality	CV death	7,683	8,986	−1,303	2,337	2,734	−397	30,229	35,339	−5,110
	ACM	11,176	12,231	−1,056	3,398	3,719	−321	44,014	48,199	−4,185
Adverse events	AF	1,141	392	748	347	119	228	4,488	1,542	2,945
	Pneumonia	1,141	1,585	−444	347	482	−135	4,488	6,232	−1,745
	AKI	827	491	337	252	149	102	3,256	1,929	1,326
	Sepsis	723	886	−163	220	270	−50	2,846	3,485	−639
	Total	3,832	3,354	479	1,166	1,020	145	15,077	13,189	1,888
Costs			£			CHF			€	
Treatment	First month	3,130,150	0	3,130,150	1,493,733	0.00	1,493,733	13,788,179	0	13,788,179
	Second month	1,128,241	0	1,128,241	529,254	0.00	529,254	4,894,945	0	4,894,945
	Total	4,258,391	0	4,258,391	2,022,987	0.00	2,022,987	18,683,125	0	18,683,125
Hospitalizations	HHF	47,697,610	59,307,524	−11,609,915	69,895,949	86,924,356	−17,028,407	462,793,668	575,212,593	−112,418,925
	HnHF	12,199,831	12,609,622	−409,791	27,135,222	28,051,264	−916,042	107,242,432	110,806,488	−3,564,056
Mortality	CV death	24,018,334	28,091,105	−4,072,771	59,589,780	69,707,258	−10,117,478	77,647,719	90,774,003	−13,126,285
Adverse events	AF	769,611	263,618	504,993	673,458	231,599	441,859	10,881,455	3,739,829	7,141,627
	Pneumonia	7,767,922	10,792,313	−3,024,391	2,124,527	2,952,233	−827,705	13,305,660	18,478,329	−5,172,669
	AKI	2,615,937	1,550,978	1,064,959	4,211,335	2,497,335	1,714,001	12,410,706	7,355,148	5,055,558
	Sepsis	3,200,111	3,919,824	−719,713	3,312,258	4,057,928	−745,670	8,438,700	10,332,221	−1,893,521
Overall	Including FCM costs	102,527,747	116,535,984	−14,008,238	168,965,516	194,421,973	−25,456,456	711,403,465	816,698,612	−105,295,147
	Excluding FCM costs	98,269,356	116,535,984	−18,266,627	166,942,530	194,421,973	−27,479,443	692,720,340	816,698,612	−123,978,272

Abbreviations. ACM, all-cause mortality; AF, atrial fibrillation; AKI, acute kidney injury; CV, cardiovascular; FCM, ferric carboxymaltose; HHF, hospitalization for heart failure; HnHF, hospitalization not for heart failure.
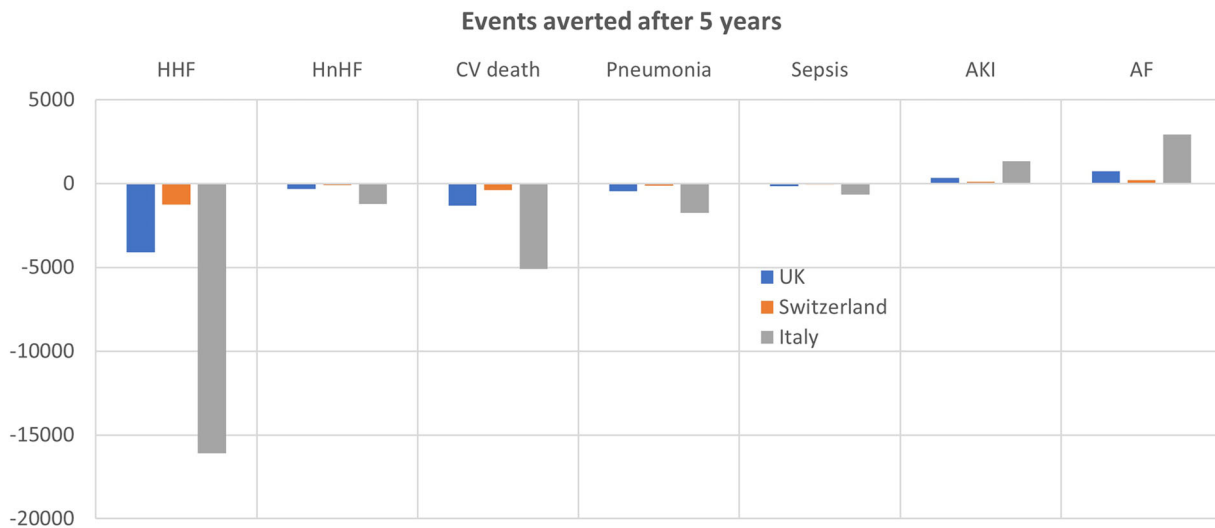
Figure 1. Events averted in five years after introducing FCM in the UK, Switzerland and Italy. The number of hospitalizations, CV deaths and AEs averted over five years in the UK, Switzerland and Italy after introducing FCM. Abbreviations. AE, adverse events; AF, atrial fibrillation; AKI, acute kidney injury; CV, cardiovascular; HHF, heart failure hospitalizations; HnHF, hospitalizations due to non-heart failure.

Switzerland (population of 5,330) and Italy (population of 69,003), respectively, over five years, versus standard care (Table 2 and Figure 1), leading to total HF-hospitalization cost savings of £11,609,915, CHF17,028,407, and €112,418,925, respectively. This corresponded to a saving of £662, CHF3,195 and €1,629 in hospital costs per patient with FCM treatment over five years in the UK, Switzerland and Italy, respectively (Figure 2).

In addition, FCM treatment was predicted to result in reductions in non-HF related hospitalizations: 309 in the UK, 94 in Switzerland and 1,202 in Italy across the five-year time horizon (Table 2). The reduction in non-HF hospitalization was associated with cost savings of £23, CHF172 and €52 per patient in the UK, Switzerland and Italy, respectively.

Predicted impact of FCM on CV deaths and adverse events

The model predicted 8,986, 2,734 and 35,339 CV-related deaths in the world without FCM treatment, compared to 7,683, 2,337 and 30,229 CV-related deaths in the world with FCM treatment, for the UK, Switzerland and Italy, respectively (Table 2). This was associated with cost savings of £4,072,771, CHF 10,117,478 and €13,126,285 in the UK, Switzerland and Italy, respectively.

In the UK, the net AE-related costs associated with the use of FCM in the UK resulted in cost savings of £2,174,152 over a five-year time horizon compared to standard care (Table 2 and Figures S1–S6). In contrast, the net cost of AE

Total savings over the risk population associated with cases observed after 5 years

Total savings per patient after 5 years

Figure 2. Budget impact of introducing FCM in the UK, Switzerland and Italy. Budget impact over five years for the UK, Switzerland and Italy. Abbreviations. AF, atrial fibrillation; AKI, acute kidney injury; CV, cardiovascular; HHF, heart failure hospitalizations; HnHF, hospitalizations due to non-heart failure.

management in Switzerland and Italy increased with FCM compared to standard care, by CHF582,485 and €5,130,994, respectively (Table 2 and Figures S1–S6).

Budget impact of FCM

The total combined cost associated with hospitalizations, AEs and CV mortality was lower when the predicted eligible population was treated with FCM compared to standard care (Figure 2), therefore FCM is projected to be cost saving. The differences in these outcomes between FCM and standard care was modeled to result in total cost-savings of £18,266,627, CHF27,479,443 and €123,978,272 were estimated for the UK, Switzerland and Italy, respectively. When FCM acquisition costs were accounted for, the net budget impact was −£14,008,238, −CHF25,456,456 and −€105,295,147 for the UK, Switzerland and Italy, respectively. This corresponds to net cost savings of £799, CHF4,776 and €1,526 per patient over five years for the UK, Switzerland and Italy, respectively.

Scenario and sensitivity analysis

The base case in the UK and Switzerland used country-specific estimates of the proportion of eligible patients with ID, which are potentially conservative, since several prospective studies from other European countries have reported higher estimates[42]. In order to explore the budget impact in the UK and

Switzerland if a higher proportion of patients are eligible, a scenario was constructed where at least 70% of the patients admitted for AHF with LVEF <50% had ID, based on a range 72-83% reported in France and Spain[42]. If all eligible patients in this scenario were treated with FCM, cost savings of £46 million and CHF77 million were estimated for the UK and Switzerland, respectively, after considering drug acquisition costs.

For Italy, to explore the eventuality of a smaller eligible population, an ID prevalence aligned with the other country base cases was applied. Averaging the proportion of patients with diagnosed ID within the UK and Switzerland returned a lower estimate of 43.9%, in contrast to the 77.5% applied in the Italian base case. This scenario returned five-year potential cost savings of over €59 million when accounting for FCM administration within the population.

The results of the DSA indicated that the analyses were robust to parameter changes (Figure 3(A–C) and Table S5). The three most influential parameters were increased target populations in the countries, which led to increased net budget impact, hospitalization for heart failure costs and use of unadjusted survival curves.

Discussion

This study is the first to capture the impact of FCM treatment for the treatment of concomitant ID in patients hospitalized for AHF with LVEF <50% on the healthcare budgets

(a)

(b)

(c)
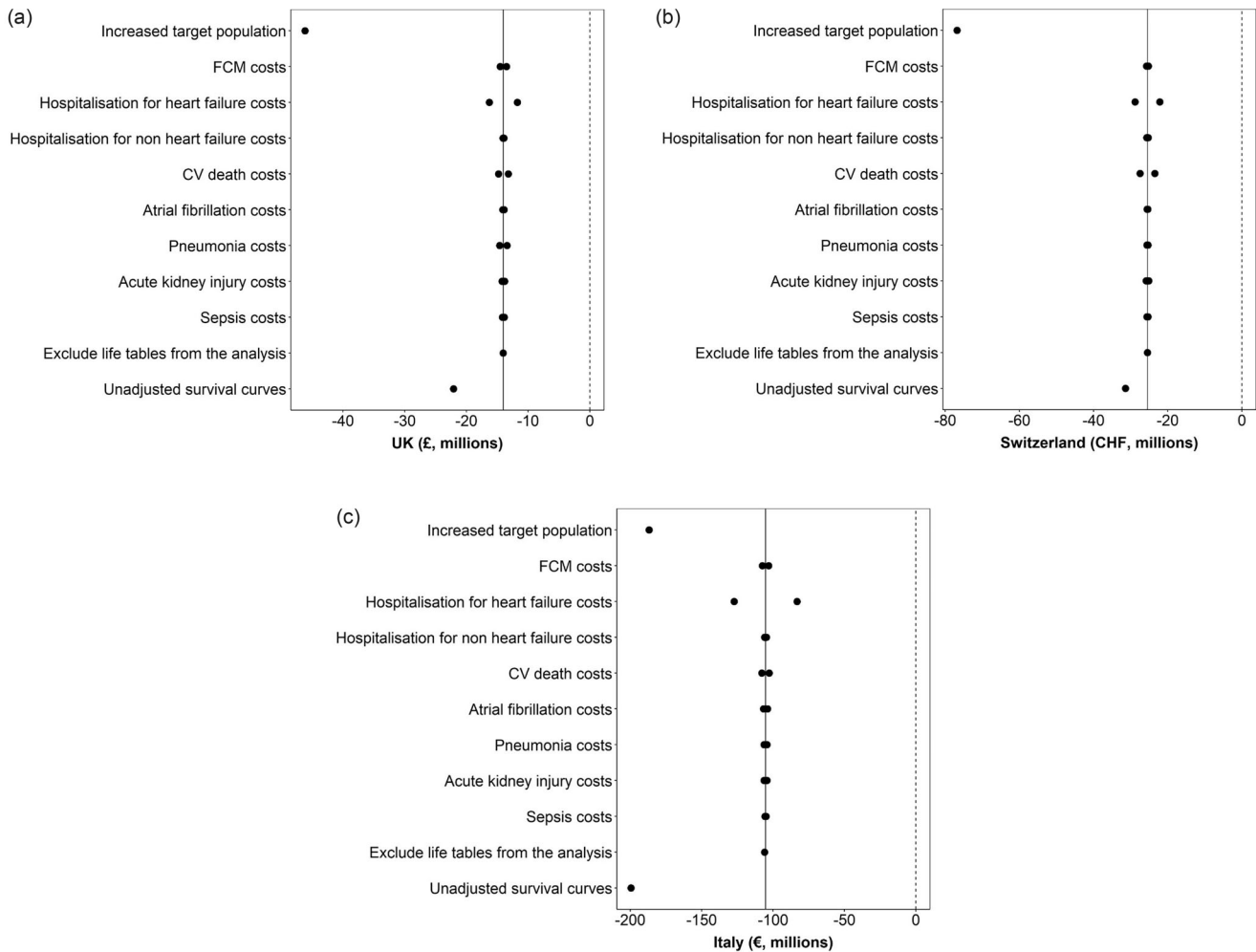
Figure 3. Tornado plot summarizing the effect of varying the most influential parameters in the UK (A), Switzerland (B) and Italy (C).

of the UK, Italy and Switzerland. Additionally, this analysis was novel in the contextualization of preventable hospital bed days under an economic lens. The cost-offset modeling demonstrates that FCM is a cost-saving intervention in all three country settings over a five-year time horizon. Although FCM acquisition costs may appear high (£4,258,391, CHF2,022,987 and €18,683,125 for the UK, Switzerland and Italy, respectively), when offset against the savings associated with adverse clinical outcomes avoided, the overall impact on total healthcare expenditure is small, and is fully offset within one year. Total cost savings of £14,008,238, CHF25,456,456 and €105,295,147 were incurred to the respective healthcare systems after accounting for FCM acquisition costs. These savings were driven primarily by reduced hospitalization events for worsening HF associated with FCM use, which accounted for economic savings of £662, €1,629 and CHF3,195 per patient within the UK, Italian and Swiss healthcare budgets.

The model also predicted cost savings in each country setting attributable to fewer CV mortality events associated with FCM use. The AFFIRM-AHF trial demonstrated no statistically significant effect of FCM on CV mortality, however, there was a small numerical difference in CV mortality between the trial arms[38]. In the cost-effectiveness model, patient-level data from AFFIRM-AHF were used to extrapolate CV mortality using

parametric multivariable survival analysis[41]. When this extrapolation was performed, in order to predict outcomes over a longer time than the trial period, and applied on a population level, this numerical difference in CV mortality events resulted in the cost savings presented in the current analysis.

When considered at the population level, modeled AEs were also predicted to impact costs. Although the overall incidence in AFFIRM-AHF of each of the modeled AEs was low, as illustrated in Figures S1–S3, small numerical differences between the arms applied on the scale of the eligible population in each country, combined with country-specific AE management costs, translated to a small cost increase associated with FCM in Switzerland and Italy, while in the UK model, the net AE costs resulted in a cost saving. However, despite higher total AE costs in Switzerland and Italy, there is little uncertainty around the overall cost-offsetting capacity of FCM; FCM treatment remained a cost saving option in these countries as the AE costs were outweighed by the savings accrued from other avoided events, including HHF, HnHF and CV-related mortality.

A discrepancy in the prevalence of ID reported in the eligible patient population was identified, particularly when comparing retrospective cohort studies versus prospective cohort studies, which is presumed to reflect underdiagnosis in real-world populations. The base case in the UK and

Switzerland used prevalence figures from country-specific studies to estimate the eligible population, as a conservative assumption reflecting likely current prescribing patterns. However, the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic HF[16] recommend that all patients with HF are regularly screened for ID, and that IV iron supplementation with FCM should be considered in symptomatic HF patients recently hospitalized for HF and with LVEF <50%. Implementation of these guidelines may lead to increased diagnosis and treatment rates and therefore the potential for greater budget impact, therefore data from a prospective study reflecting the potential eligible population were used in a scenario analysis. As expected, the cost savings associated with this larger population were greater, highlighting that guideline-recommended treatment should provide economic benefit to healthcare systems as well as clinical benefit to patients.

In Europe, HF prevalence is rising due to increasing life expectancy and advances in treatment, particularly for patients with reduced LVEF. In addition, increased use of revascularization procedures and improved acute treatment has resulted in increased post-myocardial infarction survival rates, leading to a larger pool of patients at risk of developing HF[52–59]. The number of hospital admissions for HF is projected to double over the next 25 years[60]. Given the high prevalence of ID in this population[12,61], particularly if patients are screened and treated for ID with FCM in accordance with the ESC 2021 HF guidelines, the impact of FCM therapy worldwide on hospital bed availability, which has potential implications for cost savings as well as freeing up capacity that could be directed elsewhere, would be significant. Increasing hospital capacity within highly saturated healthcare systems, particularly during the Covid-19 pandemic, would have a great impact on both emergency and elective procedures, with significant health economic and resourcing advantages[62]. Furthermore, HHF is associated with worsening functional status for the patient, leading to vicious cycle of reduced QoL and recurrent hospitalizations. FCM treatment would reduce time spent in hospital and potentially break this cycle, positively impacting on the patient's QoL and re-hospitalizations.

Health economic studies have consistently demonstrated the benefits of FCM treatment in HF patients with ID in the US[41] and across Europe, including Austria[63,64], Denmark[65], Finland[65], Italy[41,66], Norway[65], Spain[67,68], Sweden[65], UK[41] and Switzerland[41]. This budget impact analysis was based on data for patients with a recent AHF episode, representing a very high-risk subgroup; however, the findings are relevant to all patients with HF and align with those from prior budget impact studies in patients with chronic HF and ID. Cost savings are driven mainly by reduced hospitalizations in Austria[63], France[69], Italy[66], Spain[68] and Romania[70], respectively. In Austria three years after introducing FCM, savings reached €684,443[63]. A French budget analysis showed that FCM treatment in HF patients with ID led to savings of €0.9M over five years[69]. While a Romanian budget impact analysis demonstrated overall healthcare savings, with an annual saving of €8,800 per 1000 patients treated with FCM[70]. In a Spanish healthcare system, FCM reduced annual costs by €534.8 per patient[68]. Furthermore, with the adoption of increased screening for ID in HF patients, FCM treatment was associated with cost saving of up to €69.9 million in an Italian setting[66,71]. In a German budget impact analysis, despite beneficial impact with FCM treatment in HF patients with ID, including improved symptoms, lowered NYHA class and reduced rates of hospitalization, significant savings from reduced hospitalizations were not fully offset by additional treatment costs, resulting in a small incremental cost[72]. These data support our findings and demonstrate cost savings or small incremental cost with FCM treatment in a broad spectrum of patients with HF and ID.

There were some limitations to the analysis presented. While AFFIRM-AHF was a multinational trial across Europe, South America and Singapore, efficacy data per country was not sufficiently large to enable reliable country-specific analysis. Consequently, the results from each country adaptation of the cost-offset model, where clinical parameters were unchanged, may not fully represent the treatment guidelines and diversity of clinical outcomes for each local setting. Tailoring of model inputs within the country adaptations was made wherever possible; although these inputs were subject to the availability and quality of the data that could be sourced from relevant literature. The application of country-specific prevalence data was successful in the UK and Swiss models, but the use of a European proxy for ID prevalence in the Italian base case was required. Further, the population at risk of AHF in Italy was reported as patients hospitalized for an episode of either HF or stroke, with no disaggregated figure reported. The combined impact of these input assumptions results in an undetermined effect on the population at risk and associated cost savings generated of FCM in the Italian setting; nevertheless, the consistency of the DSA results with the base case give confidence to the robustness of the central model.

A further limitation is that incidence of hospitalization events did not take into account the potential impact of length of stay (LOS), which varies between countries. Given the improved prognosis of the FCM treatment cohort, cost savings could be greater than currently presented if the analysis had accounted for uncertainty around LOS. Additionally, the analysis does not account for any potential disparity in background healthcare utilization between patients at different stages of the HF disease pathway or between treatment groups i.e. any differences in patient experience of HF with and without FCM, which may have cost implications that were consequently not captured; related to this, the model did not include costs of standard pharmacotherapy in HF patients with LVEF <50% in either cohort. Furthermore, despite clinical and physiological differences between newly-diagnosed acute heart failure (de novo HF) and acute decompensation of pre-existing chronic HF, it was not possible to distinguish between them in our eligible population since there is a paucity of available country specific epidemiology data in HF population with ID. A final limitation is that trial follow-up was limited to one year, requiring the extrapolation of outcomes data over a five-year time horizon.

Nevertheless, model results indicated FCM to be cost saving within the first year, demonstrating its value over a short time horizon.

The results of this study are intended to be informative specifically for the UK, Switzerland and Italy, as the specification of the country adaptations limits the transferability of results to alternative settings. Further studies from other country perspectives would contribute more accurate results to the discourse on the cost-saving capacity of FCM treatment for patients with ID at discharge after acute HF.

Conclusion

ID has a substantial impact on both clinical and economic outcomes in HF, contributing to increased hospitalizations, rehospitalization, QoL and worsening of symptoms. Treatment with FCM has potential to save on costs and improve outcomes in HF patients with ID. This study provides further evidence of the potential cost savings associated with using FCM to treat ID at patients discharge after acute HF with LVEF <50%. In this multinational study, savings were driven primarily by reduced hospitalizations and avoided CV deaths, with total net cost savings of £14,008,238, CHF25,456,455 and €105,295,146 incurred in the UK, Switzerland and Italy, respectively. Overall, the value of FCM treatment within these healthcare systems is demonstrated even within a limited time frame of one year, with consistent cost savings indicated in the longer term. This evaluation of the budgetary impacts of FCM therapy provides healthcare decision makers with a range of potential cost benefits that may be realized through the utilization of FCM treatment, in alignment with the ESC 2021 HF guideline recommendations, which focus on the provision of improved diagnosis and treatment rates for ID.

Transparency

Declaration of funding

Declaration of financial/other relationships

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Author contributions

PM and ARdA conceptualized and designed the study. TS was responsible for data analysis. All authors contributed to interpretation of the results, preparation and review of the manuscript and approval of the final manuscript for publication.

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