Study of patients with iron deficiency and HF in Ireland: prevalence and treatment budget impact

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This study aims to present the screening, prevalence and treatment of heart failure (HF) patients with iron deficiency in an Irish hospital and use an economic model to estimate the budget impact of treating eligible patients with intravenous ferric carboxymaltose (IV FCM).

Retrospective data were collected on 151 HF patients over a one-year period from all newly referred HF patients to a secondary care hospital. This included 36 patients with preserved ejection fraction (HFpEF) and 115 with reduced ejection fraction (HPrEF). An existing budget impact model was adapted to incorporate Irish unit cost and resource use data to estimate the annual budget impact of treating patients with IV FCM.

The total number of HFrEF patients who met criteria for iron replacement was 44 (38% of total HFrEF patients); of this, only nine (20%) were treated. The budget impact model estimates that treating all eligible patients with IV FCM in this single centre would save 40 bed-days and over €7,600/year.

To improve the quality of life and reduce hospitalisation, further identification and treatment of iron deficient patients should be implemented. Expanding the use of IV iron nationally would be cost and bed saving.

Introduction

Heart failure (HF) is a clinical syndrome characterised by breathlessness, leg swelling and fatigue, which is caused by a primary cardiac abnormality. HF can be categorised into HF with a reduced ejection fraction (HFrEF; ejection fraction <50%) or HF with a preserved ejection fraction (HFpEF; ejection fraction >50%).[1]

It was estimated in 2012, in Ireland, that 90,000 people had HF, with another 160,000 people at risk of developing the disease.[2] There are also an estimated 10,000 new cases of HF every year.[2] Both prevalence and incidence have likely increased since 2012 due to the ageing population and increases in comorbidities, such as hypertension and diabetes. Among those aged over 65 years, one in six presenting with breathlessness to primary care will have unrecognised HF.[3] In 2012, it was estimated that the total direct cost of treating HF in Ireland amounted to 1% of total healthcare spend or €158 million.[2] The main driver of costs was hospitalisations. The most recent data show that HF resulted in 6,568 inpatient admissions to Irish public hospitals in 2018, representing 1% of all admissions.[4] However, in those over 65 years of age, HF hospitalisations accounted for 3% of all hospital admissions.[4] HF is associated with longer hospital stays (10.1 days for HF *vs.* 5.7 days for all patients[4]), high hospital readmission rates (≥50% patients readmitted to hospital within six months of discharge[5]) and increased mortality outcomes following hospitalisation.[6]

Iron deficiency (ID) in patients with HFrEF is associated with an increase in mortality.[7] Treating ID intravenously has been studied in several randomised-controlled trials in HFrEF and has been shown to have multiple benefits.[8-10] Intravenous (IV) iron repletion significantly improves quality of life[8] and exercise tolerance, measured by both six-minute walk test[8] and peak VO_2,[9] both in patients with and without anaemia. The 2015 CONFIRM-HF (Compare the Use of Ferric Carboxymaltose With Placebo in Patients With Chronic Heart Failure and Iron Deficiency) study, a multi-centre, double-blinded and placebo-controlled trial, showed a sustained improvement in New York Heart Association (NYHA) classification, an early and sustained improvement in fatigue score and a significant reduction in recurrent hospitalisations.[10]

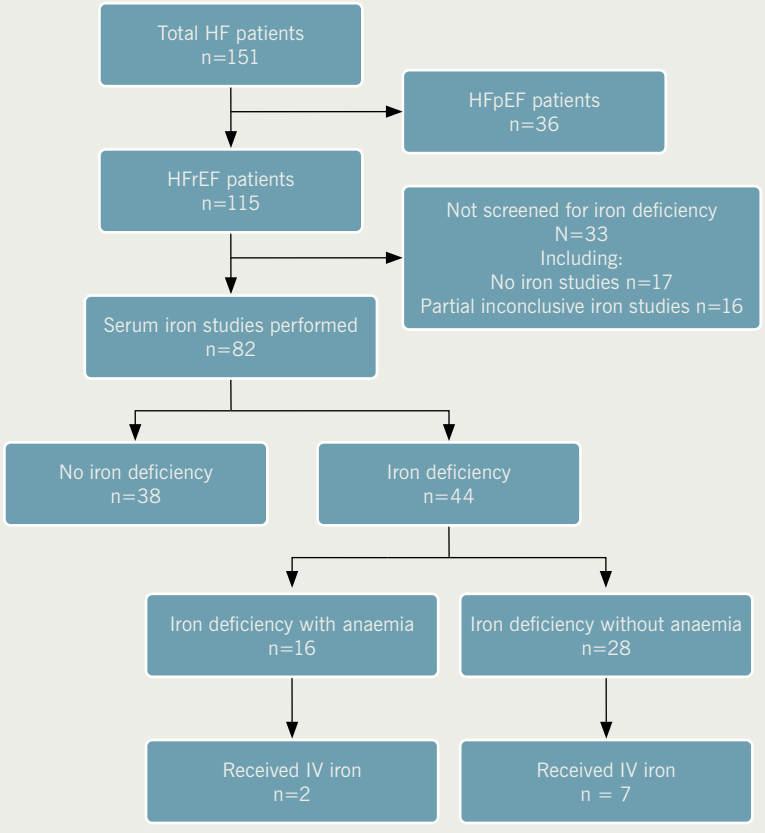
IRONMAN (Intravenous Iron Treatment in Patients

Table 1. Resource use and unit costs for budget impact model

	Resource use (per year)	Unit costs
Outpatient	3.5 visits*	€178 per visit*
GP	8.8 visits*	€48 per visit*
Hospitalisation		€6,788 per visit*
IV iron (Ferinject®)		€243.68 for 1 g, €128.25 for 500 mg**
Administration visits		€32 per visit***
Other medication		€301 per year*

* The Heartbeat Trust, 2012; ** Vifor Pharma; *** HSE salary scales, 2018[19]

Figure 1. Patient flow



Key: HF = heart failure, HFrEF = heart failure with reduced ejection fraction <50%; HFpEF= heart failure with a preserved ejection fraction >50%; IV = intravenous

With Heart Failure and Iron Deficiency) is a large, multi-centre, randomised-controlled trial currently recruiting in the UK, which aims to recruit 1,300 patients with a follow-up of 2.5 years and a primary outcome of cardiovascular mortality or HF hospitalisation as per the Clinical Trials register.[11] If IRONMAN indeed shows a reduction in cardiovascular mortality, this could have huge implications to the practice of IV iron repletion, and evidence of cost savings or minimal budgetary impact will support its widespread use.

IV iron only minimally increases haemoglobin concentration in those without anaemia and, therefore, this is unlikely to be the mechanism for improved outcomes in non-anaemic ID.[12] Instead, the mechanism of action is likely related to improved musculoskeletal function. Intracellular iron is a component of the mitochondrial enzymes that are essential for cellular muscle energy production and IV iron repletion in HFrEF has been shown to significantly improve muscle energetics.[12]

The prevalence of ID in HF patients depends on the criteria used; ranging from 21% to 42% of all HF patients.[8] The currently agreed diagnostic values for ID in HFrEF are defined as serum ferritin <100 μg/L, or ferritin of between 100 and 300 μg/L with transferrin saturation (TSAT) of <20%.[8] It is recommended, with a class IIa recommendation, that IV iron be considered as a treatment for ID patients with HFrEF.[1] There is no evidence for the use of IV iron in patients with HFpEF.

The budget impact of treating ID in HF with IV ferric carboxymaltose (FCM) has been studied in several other countries and has been shown to be cost saving or impose a minimal budget impact.[13-16] As costs and resource use are health-system specific, this study estimates the budgetary impact of treating eligible patients with IV iron in a centre in Ireland. This study is the first of its kind presenting the characteristics, screening, prevalence and treatment of HF patients with ID, and adapting an existing model to estimate the annual budget impact of treating these patients with IV FCM in the context of the Irish healthcare system.

Method

Connolly Hospital ethical research committee approved this study. Patient baseline characteristics, prescribed antiplatelet agents and anticoagulants were collected retrospectively from the medical records of all newly referred and confirmed HF patients from both hospital and primary care, one year after initial assessment, from September 2017 to 2018 in Connolly Hospital, Dublin.

An existing budget impact model built for Germany was adapted to reflect the characteristics of patients who are eligible for IV iron in the Irish healthcare setting.[14] The

objective of the model was to compare the annual direct costs of treating two cohorts of HF patients: one treated with IV FCM and the other cohort with no iron. Direct costs included medication, GP and outpatient visits, administration and hospital admission costs.

The budget impact model originally used for Germany has been described in detail elsewhere.[14] Briefly, individual patient data from four double-blind, randomised-controlled trials were pooled,[17] and multivariate statistical methods were used to predict changes in NYHA class, resource use and hospitalisations for the two cohorts of patients over a one-year period. The characteristics common to both the German and Irish analyses are the clinical data and the economic model. Patient characteristics, resource use, unit costs, the dose of FCM (Ferinject®) and the size of the cohort differed between the two analyses. Resource use and unit cost data used in the Irish model are contained in **table 1**.

Statistical analyses were performed using SPSS version 23.0 for Windows (IBM Corporation, Chicago, IL) to compare ID and non-ID patient characteristics. A p value of <0.05 was considered statistically significant.

The dose of FCM and the number of administrations used in the model were calculated individually for each of the eligible patients based on the dosing schedule in the Summary of Product Characteristics and their individual weight and haemoglobin levels.[18] The cost of administering IV FCM was based on the cost of 60 minutes of a Staff Nurse's time using 2018 HSE salary scales,[19] as per the Health Information and Quality Authority guidelines.[20] Unit costs were updated to 2018 prices, where applicable, using the consumer price index for health.[21]

Table 2. Patient characteristics

Patient characteristics	ID n=44	NID n=38	p value
Female, n (%)	23 (52%)	9 (24%)	0.01*
Mean age, years (SD)	73 (13.0)	69 (13)	0.50
NYHA II, n (%)	38 (87%)	25 (66%)	0.03*
Mean haemoglobin, g/dL (SD)	12.89 (1.47)	13.22 (1.73)	0.37
Mean NT pro-BNP, pg/mL (SD)	3,201 (4,920)	1,563 (2,271)	0.05
Mean weight, kg (SD)	78.5 (16.7)	86 (15.6)	0.37
Mean dose of Ferinject®, mg	1,100	N/A	N/A
Comorbidities, n (%)			
Chronic kidney disease	5 (11%)	3 (8%)	0.60
Diabetes	13 (30%)	8 (21%)	0.38
COPD	14 (32%)	8 (21%)	0.27
Ischaemic heart disease	6 (14%)	7 (18%)	0.55
Hypertension	22 (50%)	18 (47%)	0.81
Cancer	7 (9%)	5 (13%)	0.65
Hyperlipidaemia	5 (11%)	6 (16%)	0.58
Stroke	4 (9%)	4 (11%)	0.38
Atrial fibrillation	24 (55%)	17 (45%)	0.38
Ventricular arrhythmia	2 (5%)	0 (0%)	0.18
Single antiplatelet agent	14 (32%)	11 (29%)	0.78
Dual antiplatelet agents	0 (0%)	3 (8%)	0.06
Antiplatelet + anticoagulant	1 (2%)	3 (8%)	0.24
Anticoagulant	21 (48%)	12 (32%)	0.14
Triple therapy	0 (0%)	0 (0%)	N/A

* p value <0.05 comparing ID and non-ID patient characteristics

Key: COPD = chronic obstructive pulmonary disease; ID = iron deficient; N/A = not applicable; NID = non-iron deficient; NT pro-BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation; triple therapy = dual antiplatelet therapy plus anticoagulant

Results

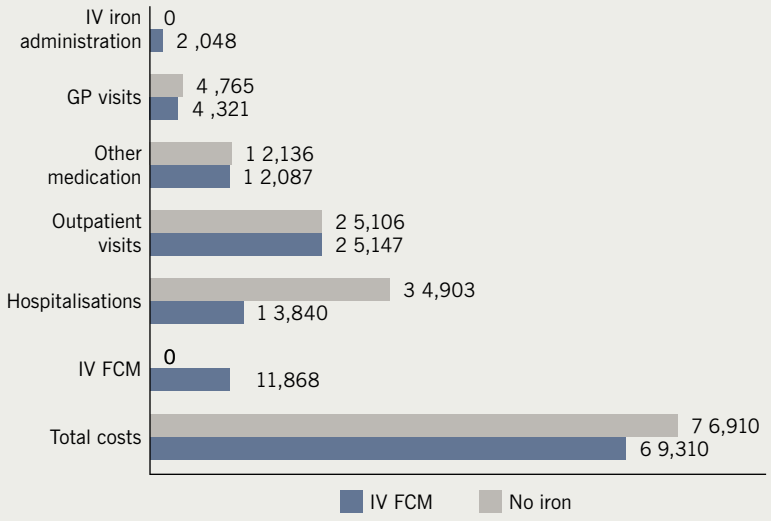
Figure 1 contains the patient flow. A total of 151 patients with HF were included in this study. After the exclusion of patients with HFpEF (n=36), there were 115 patients (76%) with HFrEF. HFrEF was classified as an EF <50% by echocardiography or alternate imaging modality.

Iron studies were not performed in 17 patients (15%). Partial iron studies were performed in 16 patients (14%). We classified patients with partial iron studies as those who had either ferritin or TSAT individually performed but not both; thereby, rendering the result inconclusive of ID unless the individual results of ferritin was >300 μg/L or the TSAT >20%, in which case the patients were classified as non-ID. This equates to 33 (17 and 16) patients not having complete iron studies performed, representing 29% of HFrEF patients. Normal iron levels were identified in 38 (33%) HFrEF patients. The total number of HFrEF patients who met criteria for IV iron was 44 (38%).

Of the 44 (38%) patients with ID, 10 (9%) were not able/eligible to receive IV iron. Reasons included death (three, 3%), declined treatment (three, 3%), did not attend follow-up (two, 2%) and subsequent normalisation of iron studies without treatment (two, 2%). In total, only nine of the 44 patients (20%) received IV iron.

Not all patients with ID are anaemic; 64% of

Figure 2. Breakdown of estimated budget impact



Key: FCM = ferric carboxymaltose; GP = general practitioner; IV = intravenous

our cohort of ID patients were non-anaemic. Non-anaemic females made up the highest proportion of ID patients (41%). The patient baseline characteristics of patients with ID and non-ID are contained in **table 2**.

The patient characteristics that are highlighted in **table 2** are used in the budget impact model. **Figure 2** shows the budgetary impact of treating our cohort of 44 patients with IV iron. The most expensive component of treatment is hospitalisations. The model estimates that six of the 44 patients who received no iron would be hospitalised, compared with two patients if IV iron was received. This results in an overall cost saving of €7,600 and an estimated 40 hospital bed-days saved.

Discussion

In this study, we present the prevalence, management and budget impact of treating ID in patients with HF in an Irish hospital for the first time. Partial and full screening of ID was done in 85% of HFrEF patients; 15% of patients were not screened. This could have been because of lack of awareness of guidelines or lack of standard protocol for screening newly referred patients. In the study hospital, the biochemical requests for "iron studies" do not include TSAT as standard protocol, and, therefore, due to human error not adding the additional TSAT blood test request resulted in only partial iron study panels. For future studies and audit, these two identified areas can be improved by departmental and national education together with a change in standardising the request procedure to include both TSAT and ferritin in the study hospital.

Almost a third (29%) of the HFrEF patients did not have complete iron studies performed. This means that the budget impact analysis is likely to underestimate the impact of treating with IV iron by excluding these patients in the analysis.

There are similarities from this study to the largest HF registry.[22] This includes the mean age (71 *vs.* 69 years), the proportion of diabetes (26% *vs.* 34%) and hypertension (49% *vs.* 62%). Comparing the ID patient cohort to the non-ID cohort, two significant differences are gender and NYHA class. In the ID population, there is a higher proportion of women (52% *vs.* 24%, p=0.01), and more patients are NYHA class II (87% *vs.* 66%, p=0.03). The number of NYHA class I patients is a lot less in our cohort of patients compared with other registries, and this is likely because the patients who are included in our study are newly referred patients to secondary care, who are more likely to be symptomatic. Non-anaemic women showed the highest prevalence of ID. The probable reason for this is that women are more likely to be iron deficient compared with men.[23] This highlights the importance of screening for ID in non-anaemic patients. This may be another reason why patients are not adequately screened when their baseline full blood count is normal.

Atrial fibrillation was present in 55% of patients who had ID. Comparing the ID and non-ID cohorts, there was a similar proportion of patients on single antiplatelet agents (32% *vs.* 29%). Although not statistically significant, there was a trend towards more ID patients being on anticoagulation (48% *vs.* 32%) compared with non-ID patients. Anticoagulation increases bleeding risk,[24] and, therefore, has the potential to aggravate subclinical bleeding, which could deplete iron stores. This could be a potential mechanism in patients on anticoagulation but without significant anaemia.

Alternative IV iron repletion products have progressed over the last 20 years.[25] Different IV iron treatments including blood products, iron isomaltoside or older products such as iron dextran infer different costs. Older products required a test dose, which required more time for administration, and also costs associated with potential adverse reactions such as allergy or anaphylaxis. Newer agents such as FCM (used in this study) or iron isomaltoside do not require test doses, and higher doses can be administered in a single dose, thereby minimising the administration costs with a favourable safety profile. As the allergy risk is rare for IV FCM, the costs of allergic reaction were not included in this study.

IV iron is frequently used in other chronic medical conditions. These include: chronic kidney disease with or without haemodialysis, ID anaemia associated with chronic diseases, anaemia associated with pregnancy and chronic occult blood loss.[26] Chronic kidney disease and HF often co-exist and repleting iron stores in these patients have been associated with a reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.[27] High-dose IV iron in haemodialysis patients is associated with a lower risk of

major adverse cardiovascular events and mortality.[28] The economic evaluation of IV FCM in kidney disease has been shown to have a favourable budget impact, due to an overall improvement in anaemia and a reduction in the dose and use of erythropoiesis stimulating agents.[29]

This study demonstrates IV FCM in ID HF patients is cost saving in an Irish healthcare setting. This is consistent with similar studies conducted in France, Germany and Italy.[13-15] These studies showed that cost savings are specific to the dose of FCM used, as well as country-specific costs related to hospitalisation, average length of stay, administration costs and HF patient-risk profile (which includes NYHA classification and female gender).[14] In our analysis, the actual dose of FCM used in Irish clinical practice for each patient was applied, resulting in more accurate estimates. Limitations of this analysis include the generalisability of the pooled clinical data from nine other countries to HF patients in Ireland, small patient numbers, and the exclusion of the effect of IV iron on quality of life. Previous economic evaluations that include both cost and quality of life found IV iron to be cost-effective compared with no iron.[30]

In conclusion, this single-centre study shows that 38% of HFrEF patients were iron deficient, with only 20% of patients treated. This represents a large number of patients who are not being adequately identified and treated with IV iron. Treating ID in HFrEF with IV FCM is cost-saving in the Irish healthcare system. Effectively managing these patients could improve patients' quality of life, reduce hospitalisations and reduce costs to the healthcare system

Key messages

- Many heart failure with reduced ejection fraction (HFrEF) patients with iron deficiency have a normal haemoglobin level
- Women, compared with men, with HFrEF have a higher prevalence of iron deficiency
- All patients with HFrEF should be screened for iron deficiency with haemoglobin, serum ferritin and transferrin saturation (TSAT) measurements
- Intravenous iron repletion in patients with HFrEF is cost saving in the Irish healthcare system

Conflicts of interest

None declared.

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Study approval

Connolly Hospital ethical research committee approved this study.

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