Determinants of quality of life of patients with heart failure and iron deficiency treated with ferric carboxymaltose: FAIR-HF sub-analysis ☆,☆☆,★

Florian S. Gutzwiller [a,*], Alena M. Pfeil [a], Josep Comin-Colet [b], Piotr Ponikowski [c,d], Gerasimos Filippatos [e], Claudio Mori [f], Peter G. Braunhofer [f], Thomas D. Szucs [a], Matthias Schwenkglenks [a,g,1], Stefan D. Anker [h,i,1]

[a] Institute of Pharmaceutical Medicine/ECPM, Universität Basel, Basel, Switzerland
[b] Universitat Autonoma de Barcelona, Barcelona, Spain
[c] Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland
[d] Centre for Heart Diseases, Military Hospital, Wroclaw, Poland
[e] Athens University Hospital Attikon, Athens, Greece
[f] Vifor Pharma AG, Glattbrugg, Switzerland
[g] Institute of Social and Preventive Medicine, Universität Zürich, Switzerland
[h] Applied Cachexia Research, Department of Cardiology, Charité Universitätsmedizin Berlin, Germany
[i] Centre for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy

ARTICLE INFO

ABSTRACT

Background: Heart failure (HF) is a burden to patients and health care systems. The objectives of HF treatment are to improve health related quality of life (HRQoL) and reduce mortality and morbidity. We aimed to evaluate determinants of health-related quality of life (HRQoL) in patients with iron deficiency and HF treated with intravenous (i.v.) iron substitution or placebo.
Methods: A randomised, double-blind, placebo-controlled trial (n = 459) in iron-deficient chronic heart failure (CHF) patients with or without anaemia studied clinical and HRQoL benefits of i.v. iron substitution using ferric carboxymaltose (FCM) over a 24-week trial period. Multivariate analysis was carried out with various clinical variables as independent variables and HRQoL measures as dependent variables.
Results: Mean change from baseline of European Quality of Life — 5 Dimensions (EQ-5D) (value set-based) utilities (on a 0 to 100 scale) at week 24 was 8.91 (i.v. iron) and 0.68 (placebo; p < 0.01). In a multivariate analysis excluding baseline HRQoL, a higher exercise tolerance and i.v. iron substitution positively influenced HRQoL, whereas impaired renal function and a history of stroke had a negative effect. The level of HRQoL was also influenced by country of residence. When baseline HRQoL was factored in, the multivariate model remained stable.
Conclusion: In this study, i.v. iron substitution, exercise tolerance, stroke, country of residence and renal function influenced measures of HRQoL in patients with heart failure and iron deficiency.

© 2013 The Authors. Published by Elsevier Ireland Ltd. Open access under CC BY license.

1. Introduction

to about 2% of all inpatient bed days and approximately 5% of all emergency medical admissions to hospitals in the United Kingdom (UK) [2] and is the primary diagnosis on admission to German hospitals [3]. The primary objective of HF treatment is to improve health-related quality of life (HRQoL) and reduce mortality and morbidity [2,4]. Previous multivariate analyses have reported New York Heart Association (NYHA) class, the 6-min walk test and depression as predictors of HRQoL in HF patients [5–7].

In the cycle of oxygen uptake, transport and storage, iron plays an important role [8,9]. It has been shown that intravenous (i.v.) repletion of iron can diminish symptoms and improve HRQoL in chronic heart failure (CHF) patients [10–12]. Treatment with ferric carboxymaltose (FCM), an i.v. iron preparation, resulted in improved

HRQoL in FAIR-HF, an international (Table 1), randomised, double-blind, placebo-controlled trial (n = 459) that enrolled iron-deficient CHF patients with or without anaemia. Study patients were treated with i.v. iron substitution or placebo over the 24 week trial period [10]. A recent analysis showed that in the FAIR-HF trial, mean utilities measured by the European Quality of Life − 5 Dimensions (EQ-5D) questionnaire [13] were higher in the i.v. iron substitution arm, resulting in an incremental cost-effectiveness ratio of 3977 pound sterling (£), which was below the threshold of £20,000–£30,000

typically used by the UK National Institute for Health and Clinical Excellence [14]. Health-state utilities are preference-based measures of HRQoL with a foundation in economic theory. They are frequently used in health economic analyses to calculate quality-adjusted life years (QALYs) [15]. The EQ-5D is a commonly used measure for this purpose [14].

This multivariate analysis further explores the EQ-5D-based utility effect observed in the i.v. iron substitution group of the FAIR-HF trial, by evaluating a wider range of determinants of HRQoL. The aims are

Table 1
Baseline demographic and clinical characteristics of the FAIR-HF intention-to-treat population, according to study group.

	Variable	Ferric carboxymaltose (n = 304)	Placebo (n = 155)
Demographics	Age − years[§§]	67.8 ± 10.3	67.4 ± 11.1
	Female sex[§§]	159 (52.3)	85 (54.8)
	Country[§§]		
	Argentina	5 (1.6)	1 (0.6)
	Czech Republic	13 (4.3)	4 (2.6)
	Germany	8 (2.6)	3 (2.0)
	Spain	14 (4.6)	8 (5.2)
	Greece	6 (2.0)	5 (3.2)
	Italy	7 (2.3)	4 (2.6)
	Norway	0 (−)	2 (1.3)
	Poland	43 (14.1)	17 (11.0)
	Romania	10 (3.3)	6 (3.9)
	Russia	133 (43.7)	67 (43.2)
	Ukraine	65 (21.4)	38 (24.5)
	Employment status[§§]		
	Unemployed, employed or regularly retired	254 (83.6)	133 (86.0)
	Early retirement due to CHF	50 (16.4)	22 (14.2)
Clinical characteristics	Anaemic[*]	181 (59.5)	82 (53.0)
	NYHA class[§§]		
	II	53 (17.4)	29 (18.7)
	III	251 (82.6)	126 (81.3)
	LVEF − %	31.9 ± 5.5	33.0 ± 6.1
	Heart rate − beats per minute[§]	70.9 ± 11.4	71.9 ± 11.7
	eGFR − mL/min[§§]	63.7 ± 21.2	64.8 ± 25.3
	BMI − kg/m²[§§]	27.9 ± 4.7	28.1 ± 5.1
	Aetiology of CHF: ischaemic[§§]	245 (80.6)	123 (79.4)
	6-min walk test distance − metres[§§]	274 ± 105	269 ± 109
	Concomitant medication		
	Angiotensin receptor blocker[§]	33 (10.9)	22 (14.2)
	Angiotensin-converting-enzyme inhibitor	227 (74.7)	104 (67.1)
	Laboratory measurements		
	Haemoglobin − g/L[†§§]	119 ± 12.6	119.5 ± 13.8
	Serum ferritin − μg/L	52.5 ± 54.5	60.1 ± 66.5
	Transferrin saturation − %	17.7 ± 12.6	16.7 ± 8.4
Risk factors/medical History of…	Smoking		
	Non-smoker	225 (74.0)	114 (73.6)
	Former smoker	56 (18.4)	27 (17.4)
	Current smoker	23 (7.6)	14 (9.0)
	Hypertension (treated with drug)[§§]	243 (79.9)	128 (82.6)
	Dyslipaemia (treated with drug)[§§]	144 (47.4)	70 (45.2)
	Diabetes	93 (30.6)	37 (23.9)
	Myocardial infarction (MI)	168 (55.3)	90 (58.1)
	Angina pectoris[§] (AP)	171 (56.3)	89 (57.4)
	MI and AP[§]	95 (31.2)	57 (36.8)
	Stroke[§§]	24 (7.9)	9 (5.9)
	Transient ischemic attack	9 (3.0)	6 (3.9)
	Valvular heart disease	85 (28.0)	48 (31.0)
	Atrial fibrillation	94 (30.9)	44 (28.4)
	Procedures		
	Coronary angiography[§]	85 (28.0)	39 (25.2)
	Coronary revascularization (CABG, PTCA)	64 (21.0)	31 (20.0)
HRQoL at baseline[**]	EQ-5D utility	57.7 ± 18.8	57.7 ± 17.9
	EQ-5D VAS scores	54.3 ± 17.1	54.1 ± 15.2
	KCCQ	52.8 ± 19.5	52.4 ± 17.3

Data presented are mean value ± SD or number (%) of patients. Values were calculated from the study data by the authors. In FAIR-HF a 2:1 randomisation was used [10].
AP, angina pectoris; BMI, body mass index; CABG, coronary artery bypass graft; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; EQ-5D, European Quality of Life − 5 Dimensions; g, gramme; IDA, iron deficiency anaemia; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PTCA, percutaneous transluminal coronary angioplasty; μg, micrograms.
  [*] Defined as Hb < 120 g/L for females and Hb < 130 g/L for males.
  [†] Due to missing values, the n for haemoglobin are 298 (i.v. iron) and 153 (placebo).
  [§] Determinants chosen as candidate predictors in univariate analysis (p ≤ 0.25).
  [§§] Determinants chosen as possible determinants for the multivariate analysis (p ≤ 0.05).
  [**] Due to missing values, the n for EQ-5D utility are 298 (i.v. iron) and 154 (placebo); for EQ-5D VAS scores 295 (i.v. iron) and 152 (placebo); for KCCQ 286 (i.v. iron) and 145 (placebo).

to gain a better understanding of determinants of utility and HRQoL in CHF patients and to validate predictors of HRQoL previously identified from the FAIR-HF dataset in univariate analyses [16].

2. Methods

This is a retrospective within-trial analysis of the FAIR-HF intention-to-treat (ITT) population including 459 patients with NYHA functional classes II and III, impaired left ventricular ejection fraction, and iron deficiency. Patients were randomly assigned to receive either i.v. iron substitution with FCM or placebo. During a correction phase, patients received weekly injections until iron repletion was achieved. A subsequent maintenance phase with 4-weekly injections followed. Further details were previously described [10,17]. Table 1 shows baseline demographic and clinical characteristics of the study population.

All analyses were performed at the patient level following an a-priori specified analysis plan. Available data for independent variables were the data from FAIR-HF baseline assessments. Data for dependent variables were from the FAIR-HF assessments at week 24 (end of trial). HRQoL measures from FAIR-HF used for this analysis include EQ-5D-based utilities and the Kansas City Cardiomyopathy Questionnaire (KCCQ) [18] measurements at baseline and week 24. The main endpoint was EQ-5D-based utility measured at week 24. The secondary endpoint consisted of HRQoL represented by KCCQ summary score at week 24. In the case of missing values of single questionnaire items, the last recorded observation was imputed using the 'last observation carried forward' (LOCF) method. Patients with missing baseline information for a given endpoint, and patients with only baseline information, were excluded from the respective analyses.

The EQ-5D is an instrument designed for self-completion by respondents. It comprises two parts: First, respondents report their health status according to a five-dimensional classification including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is represented by a three level ordered category item, which leads to a total of 243 possible health ratings. In the current analysis, these ratings were valued using the standard European time trade-off value set to achieve utility estimates [19]. Second, the respondents record their self-perceived health status using a graduated visual analogue scale (VAS), with grades from 0 meaning "death" to 100 meaning "perfect health". The EQ-5D is a generic, i.e. non-disease-specific HRQoL instrument which has been validated and shown to be sensitive, internally consistent, and reliable in the general population and different patient groups [20–22]. The KCCQ is a self-administered, disease-specific 23-item questionnaire for measuring HRQoL in patients with CHF. It quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and HRQoL [18].

3. Approach to covariate selection

Available baseline variables from the FAIR-HF trial data were selected as candidate predictors (independent variables) if a potential influence on HRQoL could be assumed, i.e. if an association (e.g. clinical or biological) with the response variables (dependent variables, HRQoL outcomes) was expected on biological or clinical grounds. Factors selected as candidate predictors of HRQoL were demographic factors such as country of residence, age and gender; clinical factors, such as NYHA class at baseline, exercise tolerance (6-min walk test), estimated glomerular filtration rate (eGFR) and depression (approximated by the EQ-5D anxiety/depression item), and medical history items, such as history of stroke, hypertension, angina pectoris, ischaemic heart disease and treatment regimen (for a complete list of candidate predictors please refer to Table 1).

4. Statistical analysis

Endpoints and covariates were described (Table 1); continuous and discrete numerical variables based on the mean with standard deviation (SD), median and range. Non-plausible, outlying values were excluded from analysis. For binary and categorical variables, frequencies and percentages were used. All analyses were performed using Stata/MP 11 or Stata/SE 12 (StataCorp LP, College Station, TX, USA).

4.1. Selection of candidate predictors for multivariate analysis (univariate analysis)

Univariate analyses were performed depending on the underlying distribution of the involved variables. Based on graphical inspection, it was assumed that variables with small deviations from the normal

distribution would not distort any results, thus they were treated as normally distributed. Associations of candidate predictors and the continuous endpoints were determined. For continuous predictors, Pearson (for linear association, assumption of normality) or Spearman rank (for monotone association, non-normality) correlations were performed to measure the strength of the association. Scatter plots were used to describe associations graphically (data on file). Given approximate normality of the endpoint variables, unpaired t-tests or ANOVA were performed to assess associations with binary or categorical predictors, respectively. All statistical tests were carried out two-sided at a 5% significance level, and 95% confidence intervals (CIs) were obtained, if applicable. Candidate predictors were further assessed in multivariate analysis if a trend was seen in univariate analysis ($p \leq 0.25$).

5. Multivariate analysis

Normality of endpoint variables was assessed graphically using histograms. In the absence of relevant skewness, multivariate linear regression was used to assess the joint explanatory value of the candidate predictors. The analysis was carried out with and without HRQoL (EQ-5D utility or KCCQ score) at baseline. The rationale behind this approach is that an analysis without baseline HRQoL is more suitable for showing the influence of pre-existing factors (that might otherwise be absorbed into the effect of baseline HRQoL), whereas an analysis with baseline HRQoL better shows effects occurring after baseline and during the trial period.

The selection process of potential predictors for the multivariate analysis was performed using both stepwise backward selection and stepwise forward selection procedures, results were compared for consistency. Decision criterion for variable selection into the final model was $p \leq 0.05$. Interactions and collinearities between explanatory variables were assessed. To avoid over-modelling, significant interaction terms were to be included in final models only if they influenced the main effects substantially. Model fit was assessed using normal quantile plots of residuals and plots of residuals against explanatory variables and fitted values. The predictive ability of the final models and the explanatory value of the individual covariates were monitored using the adjusted R-squared statistic that shows the fraction of variance of the dependent variable that is explained by the model.

For comparison, alternative multivariate regression models were also estimated using (a) EQ-5D VAS scores (instead of EQ-5D questionnaire-based utilities) at baseline as a predictor variable and (b) the log of the main endpoint variable (due to a slightly skewed distribution of the endpoint variable) and (c) the KCCQ score at week 24 as the endpoint (with and without baseline HRQoL). In the model with KCCQ as endpoint and baseline HRQoL, the EQ-5D anxiety/depression item (baseline value) was tested as an additional possible predictor. Because Russian and Ukrainian patients accounted for a large part of the patient population, the regression additionally was performed using a variable distinguishing Russian and Ukrainian patients from all others, instead of the variable representing individual countries that was otherwise used.

6. Results

6.1. Characteristics of the study patients

Relevant clinical characteristics of the FAIR-HF ITT population of n = 459 patients are presented in Table 1 (for a consort diagram see Anker et al. [10]). Patients were enrolled from June 2007, through December 2008, in 75 sites in 11 countries [10].
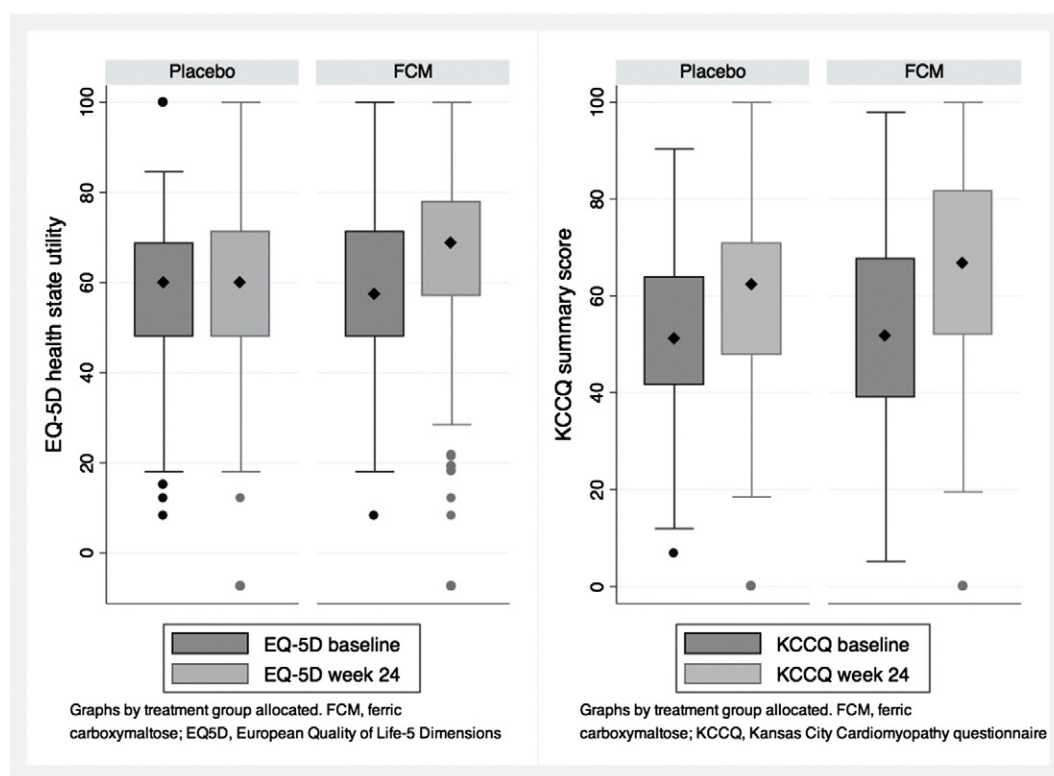
Fig. 1. Boxplot showing median, range, interquartile range and outliers of the mean EQ-5D utility and KCCQ values at baseline and week 24.

6.2. Description of endpoints

In the analyses involving EQ-5D utilities, 7 observations with missing values at baseline were excluded from analysis. In the analyses additionally including EQ-5D VAS scores, 12 observations with missing values were excluded. In the case of the KCCQ summary score, exclusions amounted to 11 observations with missing values at baseline and 17 with values only for baseline. Both endpoints, EQ-5D utility and KCCQ summary score, indicated better HRQoL at week 24 than at baseline; the improvement was significantly higher in the i.v. iron substitution arm (Fig. 1). Change from baseline for EQ-5D utility was 8.9 (i.v. iron; SD ± 22.43; 15%) and 0.7 (placebo; SD ± 21.15; 1%), respectively. For KCCQ summary scores change from baseline was 12.8 (i.v. iron; SD ± 21.22; 24%) and 6.2 (placebo; SD ± 18.46; 12%), respectively (Fig. 1).

6.3. Predictors of EQ-5D utility

A total of 20 candidate predictors showed a possible relationship with the main endpoint variable ($p < 0.25$) in univariate analysis and were subsequently included in the multivariate analysis as possible determinants. The BMI variable only had $p < 0.25$ due to two outlying values (with BMI values of 48 and 49 kg/m^2). BMI was thus not included in the multivariate analysis.

Multivariate analysis without baseline HRQoL, which reflects influences of pre-existing factors well, showed i.v. iron substitution, lower NYHA class and a better result in the 6-min walk test to be associated with higher HRQoL; history of stroke and reduced renal function were associated with lower HRQoL (Table 2). There was also an effect of country of residence on HRQoL. Apart from country, i.v. iron substitution showed the strongest impact on the adjusted R-squared; which for the overall model was 0.17.

In the multivariate model including baseline HRQoL, which focuses on the influence of effects occurring after baseline, the effects of 6-min walk test and NYHA class became non-significant. Other

effects remained stable. (Table 2). This model had an adjusted R-squared of 0.32.

When instead of single countries, Russian and Ukrainian patients were compared to the patients from all other countries, the effects of the other predictor variables remained stable (with and without baseline HRQoL). When the log of EQ-5D questionnaire-based utility or EQ-5D VAS scores was used as alternative endpoints, the effects of all predictor variables remained stable. This was also true when analysed without LOCF performed at EQ-5D item level.

6.4. Predictors of KCCQ-based HRQoL

The effects observed in the models of EQ-5D questionnaire-based utility remained stable when KCCQ summary scores from week 24 were used as the endpoint (Table 3).

When baseline KCCQ values were included, history of hypertension was observed as an additional determinant ($p = 0.03$, coefficient 4.83) and the 6-min walk test and NYHA class became non-significant. When, in addition to the baseline KCCQ values, the EQ-5D anxiety/depression item (baseline value) was included as a potential predictor, it was not significant.

Significant interactions for the model with KCCQ baseline were found between i.v. iron substitution and KCCQ baseline. This interaction did not substantially improve the explanatory value of the model and was therefore not included in the final version.

Analysis of residuals did not indicate any issues with model specifications. Collinearities between explanatory variables were not found to be problematic in their respective context.

7. Discussion

7.1. Principal findings

One important finding of the FAIR-HF trial was that i.v. iron substitution can improve HRQoL in iron deficient CHF patients [10,16].

Table 2
Main effects model of EQ-5D at time point 24 weeks with and without baseline HRQoL (EQ-5D).

Predictor	Coefficient	95% CI	p	Coefficient	95% CI	p
	Model without baseline HRQoL (n = 459)			Model with baseline HRQoL (n = 452)		
i.v. iron	7.98	3.80; 12.15	<0.01	8.12	4.38; 11.86	<0.01
NYHA class	6.34	0.51; 12.18	0.03	–	–	–
eGFR[†]	0.15	0.05; 0.24	<0.01	0.20	0.11; 0.23	<0.01
Stroke	−9.03	−16.71; −1.35	0.02	−8.62	−15.52; −1.71	0.02
6-min walk test	0.03	0.01; 0.05	0.02	–	–	–
EQ-5D utility baseline[*]	–	–	–	0.57	0.47; 0.66	<0.01
Poland	Reference			Reference		
Argentina	−0.09	−19.49; 19.32	0.99	4.01	−13.40; 21.42	0.65
Czech Republic	−9.76	−21.36; 1.84	0.09	−6.87	−17.20; 3.45	0.19
Germany	−20.83	−34.80; −6.87	<0.01	−19.77	−32.13; −7.40	<0.01
Spain	−7.00	−17.98; 3.98	0.21	−14.13	−24.05; −4.21	<0.01
Greece	−27.23	−42.25; −13.20	<0.01	−20.97	−33.25; −8.69	<0.01
Italy	−27.93	−41.90; −13.97	<0.01	−24.33	−36.63; −12.03	<0.01
Norway	−0.40	−30.89; 30.09	0.98	3.02	−24.01; 30.04	0.83
Romania	−0.53	−12.37; 11.30	0.93	−0.91	−11.48; 9.65	0.86
Russia	−18.95	−25.19; −12.71	<0.01	−16.97	−22.49; −11.45	<0.01
Ukraine	−19.11	−26.33; −11.88	<0.01	−15.75	−22.01; −9.49	<0.01
Constant	54.63			27.26		

All countries combined: p < 0.01.
eGFR, estimated glomerular filtration rate; i.v., intravenous.

[*] Per increase by 1.
[†] For a one unit increase in eGFR (mL/min).

In this additional within-trial study, we put this result into perspective by providing a broader analysis of correlates of HRQoL in this patient group. We found that i.v. iron substitution using FCM, lower NYHA class and a better result in the 6-min walk test positively influenced HRQoL of HF patients, whereas impaired renal function and a history of stroke negatively affected HRQoL of HF patients. A further finding was that patients with a higher HRQoL at baseline were more likely to maintain or even improve their HRQoL over time. HRQoL levels differed between countries, which may be attributable to cultural differences, potential differences among the investigated collectives. The fact that the models did not change in relevant aspects when either EQ-5D utility or EQ-5D VAS scores were used, indicates that the observed intercountry differences were most probably not due to issues related to either questionnaire comprehensibility or use of the European EQ-5D value set. However, given small patient numbers in some countries, the observed differences may partially be centre-effects in some countries.

The distinct influence of NYHA class and exercise tolerance (6-min walk test) on HRQoL observed in our results is in line with findings in the literature [10,5,6,23,24]. It has also been reported that kidney function is an important factor for a patient's HRQoL, a result which we could reproduce in our model [25]. The observation of a significant impact of history of stroke on HRQoL is also consistent with the literature [26,27]. History of ischaemic heart disease and hypertension had an effect on HRQoL in some sensitivity analyses. Such associations were also previously reported [28,29] and might have been stronger if the analysis had not been done in a population entirely affected by CHF. We could not confirm influences of gender, BMI or haemoglobin level, in contrast to previous reports based on univariate analysis [16,30–32]. In contrast to findings in the literature

Table 3
Effects model of KCCQ at time point 24 weeks with and without baseline HRQoL.

Predictor	Coef.	95% CI	p	Coef.	95% CI	p
	Model without baseline HRQoL (n = 425)			Model with baseline HRQoL (n = 448)		
i.v. iron	6.67	2.80; 10.54	<0.01	6.60	3.17; 10.03	<0.01
NYHA class	11.15	5.74; 16.56	<0.01	–	–	–
eGFR[†]	0.16	0.07; 0.25	<0.01	0.20	0.12; 0.27	<0.01
Stroke	−7.42	−14.46; −0.37	0.04	−7.29	−13.56; −1.03	0.02
6-min walk test	0.03	0.01; 0.05	0.01	–	–	–
Hypertension	–	–	–	4.83	0.49; 9.17	0.03
KCCQ baseline[*]	–	–	–	0.56	0.48; 0.65	<0.01
Poland	Reference			Reference		
Argentina	4.43	−15.00; 23.86	0.65	−0.41	−17.78; 16.95	0.96
Czech Republic	−6.00	−16.47; 4.48	0.26	−11.69	−21.05; −2.34	0.01
Germany	−17.22	−29.84; 4.60	<0.01	−20.97	−32.11; −9.84	<0.01
Spain	−10.42	−22.53; 1.69	0.09	−20.36	−31.26; −9.45	<0.01
Greece	−23.43	−37.10; −9.75	<0.01	−18.21	−29.63; −6.79	<0.01
Italy	−18.74	−31.36; −6.12	<0.01	−16.93	−28.00; −5.87	<0.01
Norway	−5.04	−32.59; 22.51	0.72	−9.16	−33.40; 15.08	0.46
Romania	5.44	−5.51; 16.39	0.33	0.65	−9.06; 10.37	0.90
Russia	−17.55	−23.23; −11.88	<0.01	−18.76	−23.92; −13.60	<0.01
Ukraine	−15.93	−22.48; −9.38	<0.01	−17.42	−23.13; −11.70	<0.01
Constant	53.35			27.63		

All countries combined: p < 0.01.
eGFR, estimated glomerular filtration rate; i.v., intravenous; TSAT, transferrin saturation.

[*] Per increase by 1.
[†] For a one unit increase in eGFR (mL/min).

[7], depression, in our analysis represented by the EQ-5D anxiety/depression item, was not found to be a significant predictor of HRQoL expressed as KCCQ scores. This may have been due to simultaneous inclusion of baseline KCCQ as a predictor variable, as the EQ-5D anxiety/depression item would have been significant without baseline KCCQ. It should also be noted that this isolated use of an item of the EQ-5D, in the absence of a more suitable indicator of depression, is not a validated approach.

Regarding the mechanisms through which the determinants we found may influence HRQoL, the primary pathway is most likely via direct improvement of physiological parameters, such as provision of oxygen to the body. It is possible that improvement of these parameters additionally influences the patients' social activities and allows them to be more mobile and autonomous. With this in mind, monitoring of clinical signs and symptoms, and improving them where needed, should aim at restoring the social activities and contacts of patients, in order to improve their overall HRQoL.

7.2. Limitations

Our population consisted of CHF patients with iron deficiency; iron deficiency has been estimated to have a prevalence of <30% in anaemic CHF patients [33] and of nearly 50% in unselected populations of stable CHF patients [9]. In populations different from the one analysed, with different proportions of iron-deficient patients, predictors of HRQoL and effect sizes might be different from our observed results. A further limitation of our study is that information on some possible determinants that might be important for a more complete understanding of the HRQoL of CHF patients was not available from the FAIR-HF data set. These determinants could include patients' social status and social support received as well as psychological well-being. The organisation of care and, specifically, participation in disease management programmes may also play a role. Dyspnoea, orthopnea, fatigue and peak oxygen uptake are further potential factors of relevance that were not available to us [5,6].

The effect of i.v. iron substitution was observed during a limited treatment duration and we do not have any information on how sustainable this effect may be. Further research on the role of this treatment option should focus on investigating sustained effects of i.v. iron after substitution and under maintenance therapy.

8. Conclusions

In this study, i.v. iron substitution using FCM, NYHA class, stroke, country of residence, exercise tolerance and renal function influenced measures of HRQoL in CHF patients with iron deficiency. Determinants of HRQoL with easily measurable clinical correlates, such as kidney function and iron status, should be followed closely; stroke prevention, improvement of exercise tolerance and improvement in NYHA functional class should have high priority in clinical practise. Information on important determinants of HRQoL in CHF patients can help clinicians to identify those at risk of reduced HRQoL and to target interventions appropriately.

References

[1] Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation 2012;125(1): e2-220.
[2] National Clinical Guideline Centre. Chronic heart failure. National clinical guideline for diagnosis and management in primary and secondary care. National Institute for Clinical Excellence (NICE). London: NICE; 2010.
[3] Neumann T, Biermann J, Erbel R, et al. Heart failure: the commonest reason for hospital admission in Germany: medical and economic perspectives. Dtsch Arztebl Int 2009;106(16):269–75.
[4] Heart Failure Association (HFA) of the European Society of Cardiology. Constitution and rules for management. Available online http://www.escardio.org/communities/HFA/Documents/HFA-Constitution-May-2011.pdf; 2011 . [Accessed Nov 2012].
[5] Juenger J, Schellberg D, Kraemer S, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. Heart 2002;87(3):235–41.
[6] Rector TS, Anand IS, Cohn JN. Relationships between clinical assessments and patients' perceptions of the effects of heart failure on their quality of life. J Card Fail 2006;12(2):87–92.
[7] Peters-Klimm F, Kunz CU, Laux G, Szecsenyi J, Mueller-Tasch T. Patient- and provider-related determinants of generic and specific health-related quality of life of patients with chronic systolic heart failure in primary care: a cross-sectional study. Health Qual Life Outcomes 2010;8:1–11.
[8] van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC. Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. Nat Rev Cardiol 2011;8(9):485–93.
[9] Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J 2010;31(15):1872–80.
[10] Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009;361(25):2436–48.
[11] Okonko DO, Grzeslo A, Witkowski T, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. J Am Coll Cardiol 2008;51(2):103–12.
[12] Usmanov RI, Zueva EB, Silverberg DS, Shaked M. Intravenous iron without erythropoietin for the treatment of iron deficiency anemia in patients with moderate to severe congestive heart failure and chronic kidney insufficiency. J Nephrol 2008;21(2):236–42.
[13] The EuroQol Group. EuroQol — a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199–208.
[14] 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 2012;14(7): 782–90.
[15] Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 3rd ed.Oxford: Oxford University Press; 2005 .
[16] Comin Colet J, Lainscak M, Dickstein K, et al. The effect of intravenous ferric carboxymaltose on health-related quality of life in patients with chronic heart failure and iron deficiency: a subanalysis of the FAIR-HF study. Eur Heart J 2013;34:30–8.
[17] Anker SD, Comin Colet J, Filippatos G, et al. Rationale and design of Ferinject Assessment in patients with IRon deficiency and chronic Heart Failure (FAIR-HF) study: a randomized, placebo-controlled study of intravenous iron supplementation in patients with and without anaemia. Eur J Heart Fail 2009;11(11):1084–91.
[18] Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35(5):1245–55.
[19] Szende A, Oppe M, Devlin NJ. EQ-5D value sets: inventory, comparative review and user guide. Springer; 2006 .
[20] Hurst NP, Jobanputra P, Hunter M, Lambert M, Lochhead A, Brown H. Validity of Euroqol – a generic health status instrument – in patients with rheumatoid arthritis. Economic and Health Outcomes Research Group. Br J Rheumatol 1994;33(7):655–62.
[21] Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33(5):337–43.
[22] Dorman PJ, Waddell F, Slattery J, Dennis M, Sandercock P. Is the EuroQol a valid measure of health-related quality of life after stroke? Stroke 1997;28(10):1876–82.
[23] Lee DT, Yu DS, Woo J, Thompson DR. Health-related quality of life in patients with congestive heart failure. Eur J Heart Fail 2005;7(3):419–22.
[24] Santos JJ, Plewka JE, Brofman PR. Quality of life and clinical indicators in heart failure: a multivariate analysis. Arq Bras Cardiol 2009;93(2):159–66.
[25] Wyld M, Morton RL, Hayen A, Howard K, Webster AC. A systematic review and meta-analysis of utility-based quality of life in chronic kidney disease treatments. PLoS Med 2012;9(9):e1001307.
[26] Clarke P, Black SE. Quality of life following stroke: negotiating disability, identity, and resources. J Appl Gerontol 2005;24(4):319–36.
[27] Owolabi MO. Impact of stroke on health-related quality of life in diverse cultures: the Berlin–Ibadan multicenter international study. Health Qual Life Outcomes 2011;9:81.
[28] Xie J, Wu EQ, Zheng ZJ, Sullivan PW, Zhan L, Labarthe DR. Patient-reported health status in coronary heart disease in the United States: age, sex, racial, and ethnic differences. Circulation 2008;118(5):491–7.
[29] Nunes MI. Quality of life in the elderly hypertensive. J Cardiovasc Risk 2001;8(5): 265–9.
[30] Anandacoomarasamy A, Caterson ID, Leibman S, et al. Influence of BMI on health-related quality of life: comparison between an obese adult cohort and age-matched population norms. Obesity (Silver Spring) 2009;17(11):2114–8.
[31] Nejat EJ, Polotsky AJ, Pal L. Predictors of chronic disease at midlife and beyond—the health risks of obesity. Maturitas 2010;65(2):106–11.
[32] Stewart KJ, Turner KL, Bacher AC, et al. Are fitness, activity, and fatness associated with health-related quality of life and mood in older persons? J Cardiopulm Rehabil 2003;23(2):115–21.
[33] Tang YD, Katz SD. Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. Circulation 2006;113(20):2454–61.