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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.

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Determinants of Quality of Life of Patients with Heart Failure and Iron Deficiency Treated with Ferric Carboxymaltose: FAIR-HF sub-analysis

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Conflict of interest
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research support from Vifor Pharma. P.P and G.F. report receiving fees from Vifor Pharma as members of the FAIR-HF Executive Committee; PP reports receiving lecture and consulting fees from Vifor Pharma and Amgen. T.D.S. and A.M.P. report no conflict of interest.

**Keywords**

quality of life; heart failure; anaemia; iron deficiency; ferric carboxymaltose; multivariate analysis
Abstract

Background
Heart failure (HF) is a burden to patients and health care systems. The objective of HF treatment is 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 randomized, 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 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.
**Introduction**

Heart failure (HF) is a leading cause of morbidity and mortality and poses a significant burden to health systems.\(^1\) It contributes 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-minute 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), randomized, 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 Pounds 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 aim is 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

Methods

This is a retrospective within-trial analysis of the FAIR-HF intention-to-treat (ITT) population including 459 patients with NYHA functional class II and III, an 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.\(^{18}\)

**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-minute 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 and ischaemic heart disease and treatment regimen (for a complete list of
candidate predictors please refer to Table 1).

**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).

**Selection of candidate predictors for multivariante 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 multivariante analysis if a trend was seen in univariate analysis
($p \leq 0.25$).

**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.

Results

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.\textsuperscript{10}). Patients were enrolled from June 2007, through December 2008, in 75 sites in 11 countries.\textsuperscript{10}

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Table 1 about here

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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 (Figure 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 (Figure 1).

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Figure 1 about here
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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/m²). 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-minute 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.

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Table 2 about here
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In the multivariate model including baseline HRQoL, which focuses on the influence of effects occurring after baseline, the effects of 6-minute 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 were 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.

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-minute 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.

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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.

**Discussion**

**Principal findings**

One important finding of the FAIR-HF trial was that i.v. iron substitution can improve HRQoL in iron deficient CHF patients. 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-minute 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 inter-country 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-minute walk test) on HRQoL observed in our results is in line with findings in the literature.\textsuperscript{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.\textsuperscript{25} The observation of a significant impact of history of stroke on HRQoL is also consistent with the literature.\textsuperscript{26, 27} History of ischaemic heart disease and hypertension had an effect on HRQoL in some sensitivity analyses. Such associations were also previously reported\textsuperscript{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.\textsuperscript{16, 30-32} In contrast to findings in the literature,\textsuperscript{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.

Limitations
Our population consisted of CHF patients with iron deficiency; iron deficiency has been estimated to have a prevalence of <30% in anemic CHF patients\textsuperscript{33} and of nearly 50% in unselected populations of stable CHF patients\textsuperscript{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.\textsuperscript{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.

**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 practice. 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.
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# Tables

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-minute walk test distance – meters §§ | 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) |
|                  | FAIR-HF (N=85) | Placebo (N=48) |
|------------------|----------------|---------------|
| **Valvular Heart Disease**  | 85 (28.0) | 48 (31.0) |
| **Atrial Fibrillation**     | 94 (30.9) | 44 (28.4) |

**Procedures**

| Procedure                                      | FAIR-HF (N=85) | Placebo (N=48) |
|------------------------------------------------|----------------|---------------|
| Coronary Angiography §                         | 85 (28.0) | 39 (25.2) |
| Coronary Revascularization (CABG, PTCA)        | 64 (21.0) | 31 (20.0) |

**HRQoL at baseline**

|             | EQ-5D utility | EQ-5D VAS scores | KCCQ     |
|-------------|---------------|------------------|----------|
| FAIR-HF     | 57.7±18.8     | 54.3±17.1        | 52.8±19.5|
| Placebo     | 57.7±17.9     | 54.1±15.2        | 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. * 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)

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, gram; 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
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-minute walk test      | 0.03        | 0.01 ; 0.05  | 0.02  | -           | -          | -     |
| EQ5D 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

* Per increase by 1

† for a one unit increase in eGFR (mL/min)
eGFR, estimated glomerular filtration rate; i.v., intravenous
| Predictor          | Coef. | 95% CI   | p   | Coef. | 95% CI   | p   |
|--------------------|-------|----------|-----|-------|----------|-----|
|                    |       | **model without baseline HRQoL** |     |       | **model with baseline HRQoL** |     |
|                    |       | **(n=425)** |     |       | **(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-minute 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

* Per increase by 1

† for a one unit increase in eGFR (mL/min)
eGFR, estimated glomerular filtration rate; i.v., intravenous; TSAT, transferrin saturation
**Figure legend**

Figure 1. Boxplot showing median, range, interquartile range and outliers of the mean EQ-5D utility and KCCQ summary score at baseline and week 24.
Figure

Figure 1. Boxplot showing median, range, interquartile range and outliers of the mean EQ-5D utility and KCCQ values at baseline and week 24.