Title: Heart failure hospitalization in adults receiving maintenance hemodialysis and effect of intravenous iron therapy: A report from PIVOTAL.

Short title: Intravenous iron, hemodialysis and heart failure

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ABSTRACT

BACKGROUND: Heart failure is a common and deadly complication in patients receiving hemodialysis and it is difficult to diagnose and treat.

OBJECTIVE: To examine the effect of intravenous iron on heart failure events in hemodialysis patients.

METHODS: We analysed heart failure events in the PIVOTAL trial, which compared intravenous iron administered proactively in a high-dose regimen, with a low-dose regimen, administered reactively. Heart failure hospitalization was an adjudicated outcome, a component of the primary composite outcome and a prespecified secondary endpoint in the trial.

RESULTS: Overall, 2141 participants were followed for a median of 2.1 years. A first fatal or non-fatal heart failure event occurred in 51 of 1093 patients (4.7%) in the high-dose iron group and in 70 of 1048 patients (6.7%) in the low-dose group (hazard ratio 0.66, 95% confidence interval 0.46 to 0.94; P=0.023). There was a total of 63 heart failure events (including first and recurrent events) in the high-dose iron group and 98 in the low-dose group, giving a rate ratio of 0.59 (0.40-0.87); p=0.0084. Most patients presented with pulmonary oedema and they were mainly treated by mechanical removal of fluid. History of heart failure and diabetes were independent predictors of a heart failure event.

CONCLUSION: Compared with a lower-dose regimen, high-dose intravenous iron decreased the occurrence of first and recurrent heart failure events in patients undergoing hemodialysis, with large relative and absolute risk reductions.

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Key Words: Iron, anemia, dialysis, kidney disease, heart failure

INTRODUCTION

Heart failure is a common and deadly complication of chronic kidney disease (CKD) and it is difficult to diagnose and treat.[12] Most treatments tested in CKD to prevent cardiovascular events have failed, with the exception of angiotensin receptor blockers and sodium-glucose co-transporter 2 inhibitors, which reduce the risk of heart failure hospitalization in patients with CKD with and without diabetes, and statins which appear to prevent atherothrombotic events in patients with CKD Stages 1-3A.[3456789] However, no treatment has been shown to reduce major adverse cardiovascular events in patients requiring hemodialysis. Notably, erythropoiesis stimulating agents (ESAs), used to correct anemia which is common in each condition, failed to reduce heart failure hospitalization, or any other cardiovascular event, in large randomized controlled trials in patients with CKD or in a trial in patients with heart failure.[1011121314] Conversely, in patients with heart failure, intravenous (but not oral) iron therapy has been shown to improve symptoms, quality of life, and exercise capacity in a number of randomized controlled trials.[15161718] The modestly-sized AFFIRM-AHF trial (n=1132) has recently reported that intravenous iron in heart failure with reduced ejection fraction causes a borderline reduction in the combined endpoint of CV death and total HF hospitalizations with a significant reduction in total HF hospitalizations[19]. Three other trials are in progress to look at these outcomes (IRONMAN – NCT 02642562, FAIR-HF2 - NCT03036462; HEART-FID NCT0303793). In the Proactive IV Iron Therapy in Hemodialysis Patients trial (PIVOTAL), we compared intravenous iron administered proactively in a high-dose regimen, with a low-dose regimen, administered reactively. Heart failure hospitalization was an adjudicated outcome, a component of the primary composite outcome and a prespecified secondary endpoint in the trial.[2021] Here we describe in detail the occurrence and consequences of heart failure hospitalization in hemodialysis patients and the effect of the two intravenous iron therapy regimens used.

METHODS

The design, baseline characteristics and results of PIVOTAL are published[2021]. Briefly, 2141 adults with end-stage kidney disease in whom maintenance hemodialysis had been initiated no more than 12 months previously, who had a ferritin concentration <400 μg per litre and a transferrin saturation (TSAT) <30%, and who were receiving an ESA were enrolled.[2021] Any existing iron therapy was stopped, and participants were randomized in a 1:1 ratio, to receive a regimen of high-dose intravenous iron administered proactively or a regimen of low-dose intravenous iron administered reactively. Ferritin concentration and TSAT were measured monthly and the results used to determine the monthly dose of iron sucrose. In the high-dose group, 400 mg of iron sucrose was prescribed, with safety cut-off limits (ferritin >700 μg per litre or TSAT >40%) above which further iron was withheld until the next test one month later. Patients in the low-dose group 0 mg to 400 mg of iron sucrose monthly, as needed, to maintain ferritin ≥200 μg per litre and TSAT ≥20%, in line with current guidelines. The protocol required the use of an ESA in a dose sufficient to maintain hemoglobin 100 to 120 g per litre, but otherwise patients were treated according to usual practice.[2021]

Baseline information related to heart failure:

Investigators were asked about the presence of heart failure on the electronic case-report form at baseline, but no further information was collected e.g. about New York Heart Association functional class, brain natriuretic peptides or left ventricular ejection fraction (LVEF). Use of cardiovascular medications, including diuretics, renin-angiotensin system blockers, beta-blockers, digitalis glycosides and mineralocorticoid receptor antagonists was documented.

Clinical outcomes:

The primary outcome of the trial was the composite of myocardial infarction, stroke, hospitalization for heart failure or death from any cause, analysed as time-to-first event.

Hospital admission for heart failure was a pre-specified, adjudicated secondary outcome.[2021] For this paper the composite outcomes of a) time-to-first hospital admission for heart failure or heart failure death heart failure (i.e. first fatal or non-fatal heart failure event) and b) time-to-first hospital admission for heart failure or cardiovascular death were also analysed, the latter representing the most commonly used primary endpoint in heart failure trials. In addition to the first fatal or non-fatal heart failure event occurring during the trial, we also analysed recurrent events, to account for the cumulative burden of events over time. We examined mortality during the length of follow up in the trial in those who did or did not have a first fatal or non-fatal heart failure event. We also investigated mortality within 30 days of hospital discharge after a hospitalization for heart failure.

Adjudication of outcomes:

All potential endpoints and all deaths were adjudicated by an independent Committee, blinded to treatment allocation. For confirmation of hospitalization for heart failure, the following were required: 1) the admission had to be as an emergency/unplanned to a hospital (emergency room, observation or inpatient unit) that led to at least one overnight stay (i.e. a date change) and each of 2) clinical manifestations of new or worsening heart failure, 3) investigative evidence of structural or functional heart disease (if available) and 4) the need for new/increased therapy specifically for the treatment of heart failure. The committee also had to be satisfied that heart failure was the primary disease process accounting for the clinical presentation.

Recognising the difficulty of diagnosing heart failure in patients receiving maintenance dialysis, the endpoint adjudication committee consisted of a nephrologist as well as cardiologists and the committee charter further required that new/increased therapy specifically for the treatment of heart failure included at least one of: i) initiation of intravenous diuretic, inotrope, vasodilator or other recognised intravenous heart failure treatment or up titration of such intravenous therapy if already receiving it, ii) mechanical or

surgical intervention (e.g. mechanical or non-invasive ventilation, mechanical circulatory support), or iii) alteration to the dialysis schedule to facilitate extra mechanical fluid removal (extra dialysis sessions or longer dialysis). The committee recorded when criterion iii) was met.

Statistical analysis:

Baseline characteristics were summarised as means and standard deviations, medians and interquartile ranges, or percentages according to heart failure hospitalization status. The characteristics were compared with the use of chi-square test and two-sample t-tests (or Mann-Whitney tests where appropriate) for categorical and continuous variables respectively.

The time-to-first-event analyses of the outcomes were performed in the intention-to-treat population using Cox proportional hazards regression. Treatment effects and 95% confidence intervals were reported from these models which also adjusted for the stratification variables at randomisation (vascular access, diagnosis of diabetes and duration of hemodialysis treatment). Recurrent events were analysed using the proportional-means model of Lin, Wei, Yang and Ying and described in the form of mean frequency functions (method of Ghosh and Lin). Cumulative incidence plots, accounting for the competing risk of any deaths not included in the endpoint, were used to estimate event rates.

To identify potential predictors of a heart failure event, the following baseline characteristics were included in a multivariable model: randomised treatment; age; sex; history of heart failure, myocardial infarction, and diabetes; systolic blood pressure; heart rate and atrial fibrillation.

Lengths of stay for the first heart failure hospitalization event were compared between the treatments using Mann-Whitney tests.

The cumulative dose of IV iron, ESA therapy dose and hemoglobin dose were displayed in figures by mean values and 95% confidence intervals at each visit.

Analyses were performed using SAS software, version 9.4 (SAS Institute) or R version 3.6.0.

RESULTS

Overall, 2141 eligible men and women were randomised, of whom 86 (4.0%) had an investigator-reported diagnosis of heart failure at baseline. In total, 121 (5.7%) patients experienced a first fatal or non-fatal heart failure event during the median follow-up of 2.1 years (maximum 4.4 years). The first event during follow-up was a heart failure hospitalization in 110 patients and heart failure death in 28 (Table 2).

Baseline characteristics and treatment of patients with and without a first heart failure event

Individuals with a heart failure event were numerically older (65 years compared with 63 years in those without a heart failure event, p=0.075) and more often male (74.4% versus 64.8%, respectively, p=0.031) (Table 1). The mean duration of dialysis was similar in patients with a heart failure event, as were mean baseline levels of hemoglobin, ferritin and TSAT.

Among the participants experiencing a heart failure event during follow-up, more had a history of heart failure at baseline (9.1% compared with 3.7% in those without a heart failure event, p=0.014), as well as a history of atherothrombotic disease e.g. peripheral artery disease (16.5% versus 8.3%, respectively, p=0.006), although not of hypertension. However, the largest difference between those experiencing a heart failure event and those who did not have a history of diabetes (60.3% versus 43.3%, respectively, p<0.001).

Patients with a heart failure event were, numerically, less often treated with renin-angiotensin system blockers (although the differences were not statistically significant). Use of beta-blockers and diuretic was similar in the two groups (Table 1). Use of glucose-lowering therapy, including insulin, was greater among patients experiencing a heart failure event than among those not.

Predictors of a first heart failure event

In a multivariable analysis, the only independent predictors of a first fatal or non-fatal heart failure event were history of diabetes and history of heart failure at baseline, as well as randomized treatment.

Dose of iron, ESA therapy and hemoglobin change

In the trial overall, patients in the high-dose, proactive iron treatment group received a higher cumulative dose of iron and were treated with a lower cumulative dose of non-randomized ESA therapy, compared with the low-dose, reactive iron treatment. Patients in the high-dose group also had a more rapid increase in hemoglobin level than patients in the low-dose iron group. Identical changes n each of these measures, according to treatment assignment, were seen in patients with and without a subsequent heart failure event (Supplementary Appendix Figures 1-3).

Clinical outcomes according to treatment assignment – first events

Overall, first fatal or non-fatal heart failure event during follow-up occurred in 51 of 1093 patients (4.7%; 2.31 events per 100 person-years) in the high-dose iron group and in 70 of 1048 patients (6.7%; 3.40 events per 100 person-years) in the low-dose group (hazard ratio 0.66, 95% confidence interval 0.46 to 0.94; P=0.023) (Table 2 and Figure 1B).

High-dose iron also reduced the risk of heart failure hospitalization alone and the composite outcome of hospital admission for heart failure or cardiovascular death (Table 2 and Figure 1A and 1C).

Overall, there were 246 deaths (22.5%) due to any cause in the high-dose iron group and 269 deaths (25.7%) in the low-dose group (p=0.054). Of these, 91 (8.3% of all patients/37.0% of all deaths) and 96 (9.2%/35.7%) were attributed to cardiovascular causes in the high-dose and low-dose iron groups, respectively (p=NS). The numbers adjudicated as due to heart failure

were 12 (1.1% of all patients/13.2% of cardiovascular deaths) and 16 (1.5%/16.7%), respectively (Table 2).

Clinical outcomes according to treatment assignment - recurrent events

There was a total of 63 heart failure events (including first and recurrent events) in the high-dose iron group (2.85 events per 100 person-years) and 98 in the low-dose group (4.75 events per 100 person-years), giving a rate ratio of 0.59, 95% confidence interval 0.40 to 0.87; p=0.0084) (Table 3 and Figure 2A). When cardiovascular death was added to the model as a composite endpoint, the reduction in heart failure hospitalizations and cardiovascular death with high-dose iron was somewhat less marked (rate ratio 0.73, 95% confidence interval 0.56 to 0.93; p=0.013; Supplementary Table 1 and Figure 2B).

Heart failure hospitalizations: clinical findings, investigation, treatment and length of stay

While new or worsening exertional dyspnoea and dyspnoea at rest was reported for approximately 80% of admissions, orthopnoea (40%) and paroxysmal nocturnal dyspnoea (19%) were less common. On clinical examination, pulmonary oedema was detected in 44% of cases, although radiological pulmonary oedema/congestion was reported in 76%. By contrast, peripheral oedema was described in only 29% of cases. An echocardiogram was carried out in 40% of cases and natriuretic peptide testing in only 10%. Among those undergoing echocardiography, left ventricular systolic dysfunction was identified in 70% of cases.

By far the most common treatment was mechanical removal of fluid (88%), with intravenous diuretic used in only 15% of cases and other intravenous drugs (vasodilators, vasopressors and inotropes) or invasive/non-invasive ventilation in <3% of cases.

The median (IQR) length of stay (LOS) for heart failure admissions was 5 (2-11) days, compared with a median length of stay for stroke 14 (5-33) and MI 7 (4-14) ; LOS among

patients in the high-dose group was 5.0 (3-11) days, compared with 5.5 (2-15) in the low-dose iron group (p value =0.86).

Survival according to heart failure admission

In patients who did not experience a heart failure hospitalization (n=2031), the risk of death during the up to 4 years of follow-up in the trial was 22.3% compared with 56% in those who were hospitalised with heart failure (n=110). With a focus on the 30 days after non-fatal heart failure hospitalization, the risk of death was 19% (21 of 110 patients).

DISCUSSION

We found that, compared with lower-dose iron therapy, high-dose iron treatment reduced the risk of fatal and non-fatal heart failure events by 34%, driven by a 44% reduction in heart failure hospitalization. This benefit was observed for recurrent, as well as first, events, with a proportionally larger reduction in repeat admissions. As a result, the number of patients needed to treat (NNT), for a median of 2.1 years, to prevent one heart failure event, was only 28.

We believe that this benefit is clinically important both because of its magnitude and because, after myocardial infarction, heart failure is the next most frequent major cardiovascular complication of end-stage kidney disease.[12] Indeed, in PIVOTAL, heart failure events were twice as common as stroke. The beneficial effect on heart failure hospitalization was notable because of the increased risk in this outcome with other experimental therapies for chronic kidney disease, including endothelin receptor antagonists and bardoxolone.[22232 4] Conversely, the size of relative risk reduction in heart failure with high-dose iron therapy was nearly as large as that seen, recently, with the sodium-glucose co-transporter-2 inhibitors canagliflozin dapagliflozin and sotagliflozin, in patients with CKD with and without diabetes.[789] The benefit observed is also plausible and consistent with data from one modest sized trial (AFFIRM-AHF), and three other small trials in patients with heart failure where intravenous iron has been shown to improve quality-of-life and increase exercise capacity.[19151617] In a meta-analysis of these trials using ferric carboxymaltose, a 31% relative reduction in heart failure hospitalizations was reported (RR 0.69, 95% CI 0.61 to 0.78, p = 0.043)[25]. Three trials are in progress which will clarify the effect of intravenous iron on clinical outcomes (IRONMAN – NCT 02642562, FAIR-HF2 - NCT03036462; HEART-FID NCT0303793). Although the trials in heart failure enrolled patients with a different underlying disease and were placebo-controlled, thefindings of this meta-analysis are consistent with the benefit observed in PIVOTAL.

Why might intravenous iron reduce the risk of heart failure hospitalization in patients on hemodialysis (and with chronic heart failure)? One possibility is that increase in hemoglobin and correction of anemia is important. However, this is unlikely for a variety of reasons. Firstly, in several trials in patients with chronic kidney disease, anemia correction with an erythropoiesis stimulating agent did not reduce the risk of heart failure (and this was also the case in a large trial in patients with heart failure).[10][11][12][13][14] Although in PIVOTAL, hemoglobin levels increased more rapidly in the high-dose iron group, compared with the low-dose group, hemoglobin concentrations were similar in the two treatment groups by about 6 months after randomization. However, as discussed above, high-dose iron therapy had a benefit on recurrent heart failure events, many of which occurred after hemoglobin equalisation. In keeping with this, iron deficiency is predictive of worse outcomes in patients with heart failure, independently of anemia and, in the heart failure trials discussed above, iron treatment had a similar benefit in those with and without anemia at baseline.[15][16][17][26]

As well as its effect on hematopoiesis and hemoglobin-mediated oxygen transport, iron plays an important role in cellular oxygen storage (myoglobin) and cell metabolism, especially in tissue with a high energy demand such as cardiomyocytes (and skeletal muscle myocytes).[27][26][28][29][30][31][32][33][34] In these cells, mitochondria are the most important sites of energy production. In animal experiments, induction of iron deficiency leads to myocardial hypertrophy and development of systolic dysfunction, in which the sympathetic nervous system appears to play a contributory role.[31][32] Cardiomyocytes from the explanted hearts of patients undergoing cardiac transplantation for advanced heart failure show iron depletion and dysfunction of iron-dependent mitochondrial enzymes.[30][33][34] The cause of this is uncertain, but reduced transferrin receptor-1 expression has been demonstrated and may be induced by norepinephrine, aldosterone and cytokines, all of which are elevated in heart failure and in chronic kidney disease.[30] Therefore, it is plausible that the non-hematopoietic role of iron in oxidative metabolism and cellular energetics accounts for the benefits of high-dose iron therapy in PIVOTAL. If so, iron replenishment may also benefit skeletal muscle

function, an effect thought to contribute to the improvement in symptoms and functional capacity with iron therapy in chronic heart failure.[27262628293031323334] However, iron-containing proteins are also involved in vasomotor regulation (e.g. iron is a co-factor for soluble guanylate cyclase) and other cellular processes as fundamental as growth, innate immunity, growth and inflammation.[27262829303132334]

Several other findings in the present study are noteworthy. Other than history of heart failure at baseline, diabetes was the most important predictor of heart failure, in keeping with the high incidence of heart failure identified in recent trials of novel glucose-lowering therapies in patients with type 2 diabetes.[735] Of interest, having a dialysis fistula at baseline was not predictive of heart failure hospitalization, despite concerns to the contrary.[36] Presentation with heart failure was primarily with pulmonary rather than peripheral oedema, in contrast to that reported in patients with chronic heart failure without end-stage kidney disease.[37] In keeping with other reports of management of cardiovascular disease in patients with dialysis, investigation was suboptimal, with an echocardiogram carried out in only 40% of cases and natriuretic peptide testing in only 10%.[38] However, among those having echocardiography, left ventricular systolic dysfunction was identified in 70% of cases, which is perhaps surprising given the hypertension-left ventricular hypertrophy phenotype often described in these patients and which might be expected to lead to heart failure with preserved rather than reduced ejection fraction.[1239] By far the most common initial treatment was mechanical removal of fluid (88%) with very few patients receiving any other acute intervention. Unfortunately, we did not collect longer-term therapy following hospital admission with heart failure, although the high prevalence of systolic dysfunction indicates that several potentially life-saving therapies are available for at least some of these patients.[40]

The length of stay for heart failure hospitalizations in PIVOTAL were 5 days. This is shorter than hospitalizations for heart failure in patients who are not on hemodialysis in the United

Kingdom but similar to those in the USA and some European countries. Removal of fluid by hemodialysis may be more rapid and allow more rapid resolution of congestion than intravenous diuretics.

Mortality in patients who experienced a hospitalization for heart failure in PIVOTAL was very high (56% in those with a HF hospitalization during the course of the trial). The 19% 30-day mortality after hospitalization for HF also emphasises that patients receiving hemodialysis are at especially high risk of death. Efforts to understand the causes of death in patients with heart failure and hemodialysis are necessary.

This study has limitations as well as strengths. Although heart failure was a pre-defined and adjudicated endpoint, PIVOTAL was not powered to test the effect of intravenous iron on this outcome alone. As mentioned above, the heart failure phenotype was not identified in all patients and long-term oral heart failure therapy was not recorded.

In summary, when added to standard care in patients receiving maintenance dialysis, high-dose intravenous iron decreased the occurrence of first and recurrent heart failure events in patients undergoing hemodialysis, with large relative and absolute risk reductions.

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Table 1 - Baseline characteristics and treatment: All patients, patients experiencing at least one heart failure event and patients without a heart failure event.

	All patients (n=2141)	**Patients with a fatal or non-fatal heart failure event (n=121)**	**Patients without a heart failure event (n=2020)**	**p-value**
Age, yr.	63	65	63	0.075
Male sex, (%)	65.3	74.4	64.8	0.031
Race (%)				
White/European	79.3	77.7	79.4	0.274
Black/African descent	8.9	5.8	9.1	
Asian	8.6	12.4	8.4	
Other	3.2	4.1	3.1	
BMI, kg/m^2	28.7	28.8	28.7	0.951
Weight, kg	82.1	83.4	82.0	0.465
Systolic BP, mm Hg	145	147	145	0.257
Median duration of dialysis, months	4.8	4.9	4.8	0.469
Vascular access, %				0.283
Dialysis catheter	41.0	48.8	40.5	
Arteriovenous fistula or graft	59.0	51.2	59.5	
History, %				
Heart failure	4.0	9.1	3.7	0.014
Hypertension	72.7	71.1	72.8	0.473
Diabetes	44.4	60.3	43.3	<0.001
Atrial fibrillation	7.7	11.6	7.4	0.238

Myocardial infarction	8.6	13.2	8.3	0.172
Peripheral artery disease	8.7	16.5	8.3	0.006
Stroke	8.2	8.3	8.2	0.992
Smoking status, %				
Never	11.6	13.2	11.5	0.283
Previous	25.5	30.6	25.2	
Current	62.9	56.2	63.3	
Laboratory measurements				
Hemoglobin, g/l	106	104	106	0.196
Ferritin, µg/l	216	230	215	0.314
Transferrin saturation, %	20.0	21.0	20.0	0.514
C-reactive protein, mg/l	6.0	8.0	6.0	0.026
Cardiovascular medications, %				
Diuretic	43.3	43.8	43.3	0.908
β-Blocker	44.3	42.2	44.4	0.627
Calcium-channel blocker	48.2	47.1	48.3	0.804
ACE inhibitor	17.1	12.4	17.4	0.154
ARB	11.5	10.7	11.6	0.779
Mineralocorticoid antagonist	1.54	0.83	1.58	0.511
Digitalis glycoside	1.73	3.31	1.63	0.170
Diabetes medications, %				
Any glucose-lowering therapy	33.9	44.6	33.3	0.010
Oral glucose-lowering drug	11.0	12.4	10.9	0.607
Insulin	25.8	33.9	25.4	0.037

ACE = angiotensin converting enzyme ARB = angiotensin receptor blocker MRA = mineralocorticoid receptor antagonist

Table 2: Heart failure outcomes according to randomized iron treatment group (high-dose or low-dose)

	High-dose iron (n=1093) n (%)	Incidence rate (per 100 py)	Low-dose iron (n=1048) n (%)	Incidence rate (per 100 py)	HR* (95% CI)	P value
HF hospitalization and composite outcome						
HF hospitalization	42 (3.8)	1.90	68 (6.5)	3.30	0.56 (0.38,0.82)	0.003
HF death or HF hospitalization	51 (4.7)	2.31	70 (6.7)	3.40	0.66 (0.46,0.94)	0.023
CV death or HF hospitalization	126 (11.6)	5.70	140 (13.4)	6.79	0.81 (0.64,1.03)	0.092
Deaths						
HF death	12 (1.1)	0.54	16 (1.5)	0.78	0.69 (0.33,1.47)	0.337
CV death	91 (8.3)	4.12	96 (9.2)	4.66	0.87 (0.66,1.16)	0.352
All-cause death	246 (22.5)	11.13	269 (25.7)	13.05	0.84 (0.71,1.00)	0.054

*HR = hazard ratio (95% CI) adjusted for stratification variables; vascular access, diabetic status and time on dialysis; p-value from Wald test

HF = heart failure CV = cardiovascular

Table 3: First and recurrent heart failure events (heart failure hospitalization or heart failure death)

	High-dose iron (n=1093)	**Low-dose iron (n=1048)**
Events per patient	n (%)	n (%)
0	1042 (95.3)	978 (93.3)
1	42 (3.8)	49 (4.7)
2	6 (0.6)	15 (1.4)
3	3 (0.3)	5 (0.5)
4	0 (0)	1 (0.1)
	n (per 100 p-y)	**n (per 100 p-y)**
Total number of first events	51 (2.31)	70 (3.40)
Total number of events (first and recurrent)	63 (2.85)	98 (4.75)*

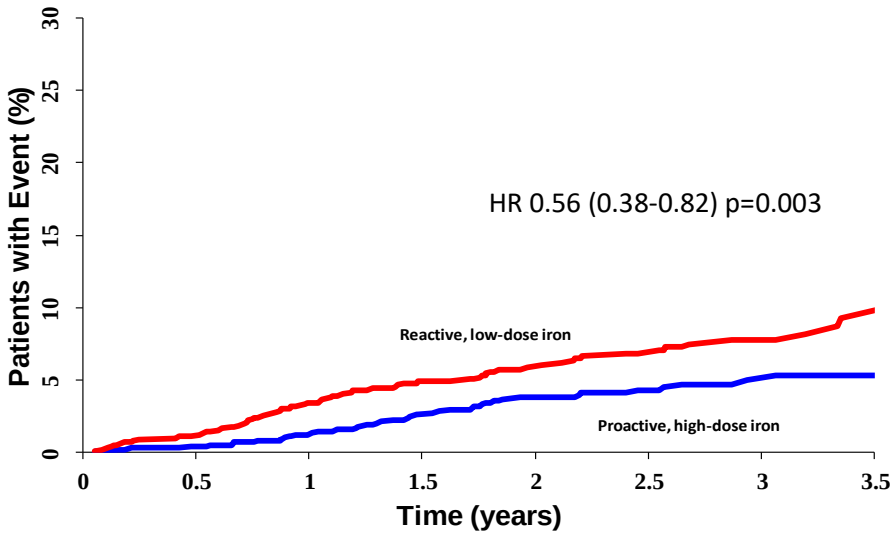
*Rate ratio 0.59 (95% CI 0.40,0.87), p=0.0084

per 100 p-y = per 100 person-years of follow-up

Figures

Figure 1: Heart failure events in PIVOTAL: A] Time to first heart failure hospitalization. B] Time to first heart failure hospitalization or death due to heart failure (non-fatal or fatal heart failure event). C] Time to heart failure hospitalization or death due to cardiovascular causes.

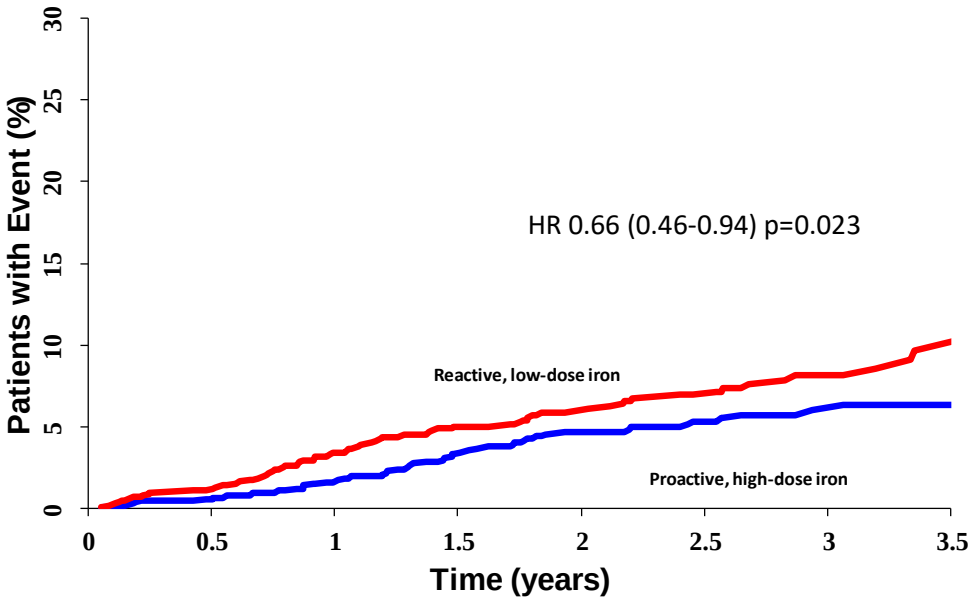
A)



Numbers at risk:

Proactive, high-dose iron	1093	834	586	215
Reactive, low-dose iron	1048	768	532	205

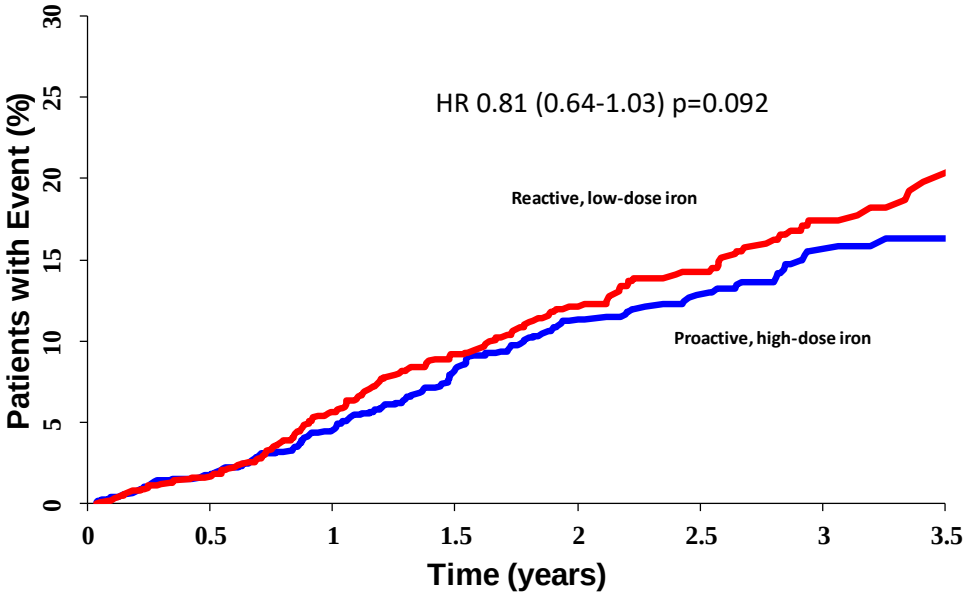
B)



Numbers at risk:

Proactive, high-dose iron	1093	834	586	215
Reactive, low-dose iron	1048	768	532	205

C)

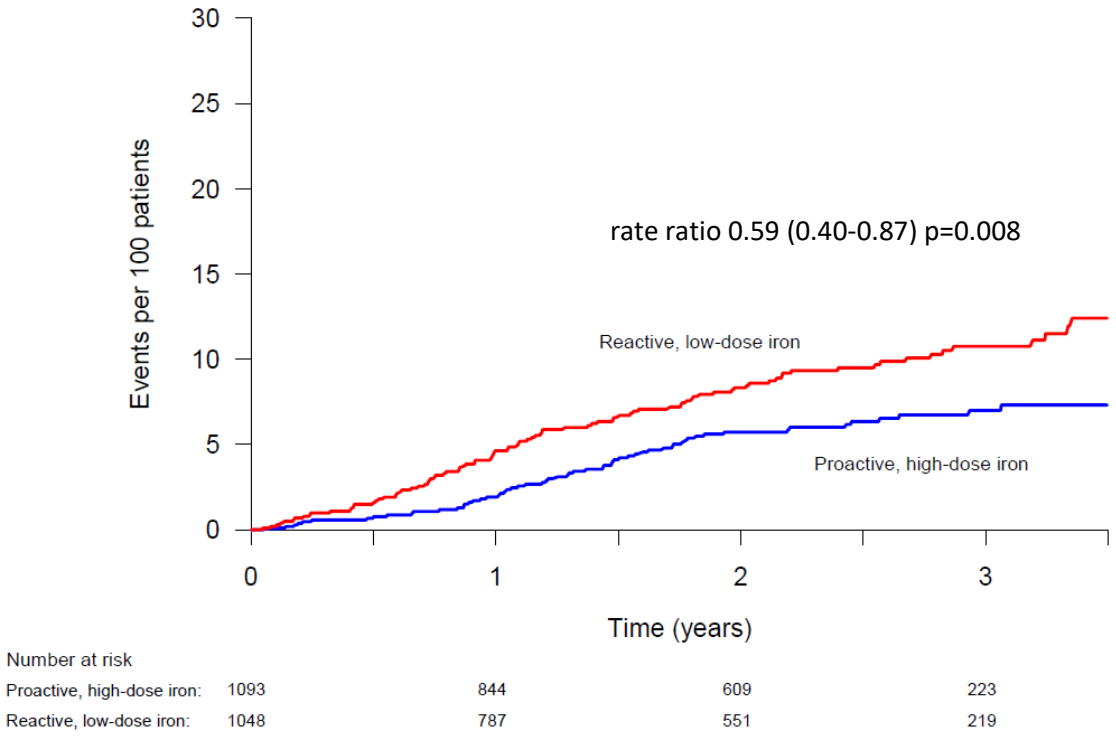


Numbers at risk:

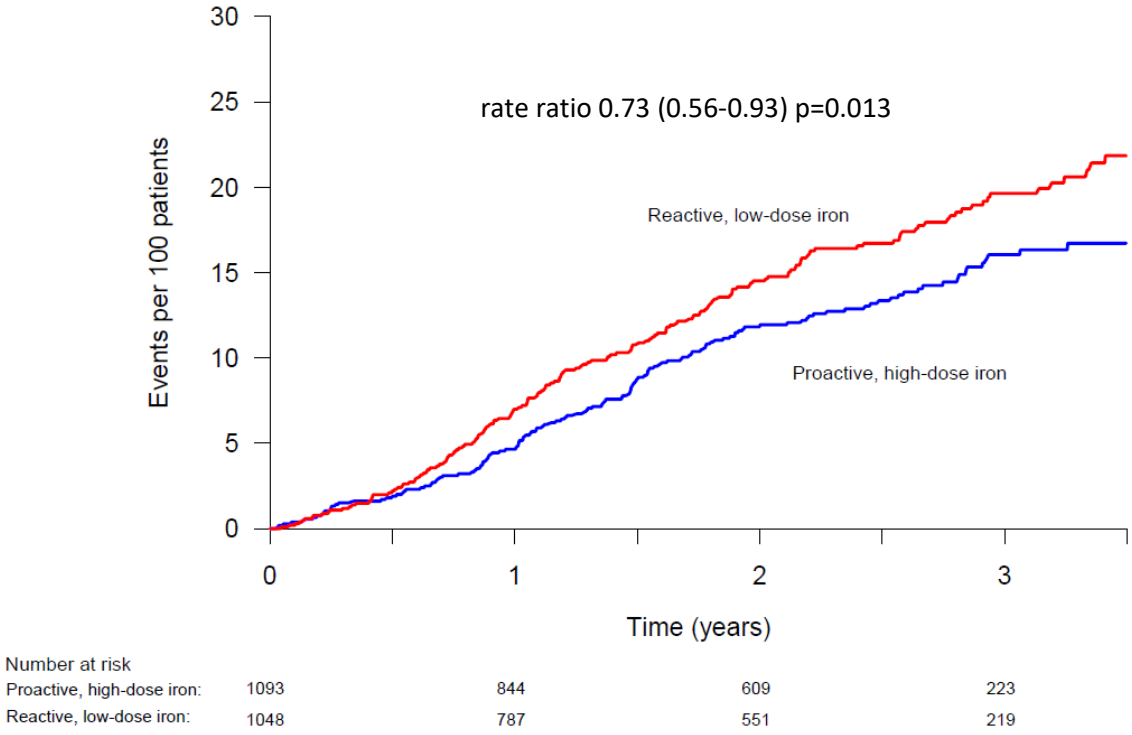
Proactive, high-dose iron	1093	834	586	215
Reactive, low-dose iron	1048	768	532	205

Figure 2: Cumulative incidence of recurrent events A) recurrent HF hospitalization/HF death B) recurrent HF hospitalization/CV death

A)



B)



Number at risk				
Proactive, high-dose iron:	1093	844	609	223
Reactive, low-dose iron:	1048	787	551	219

Appendix Figure 1 - Mean IV iron dose in those who had a HF hospitalization/ HF death versus those without a HF hospitalization/ HF death

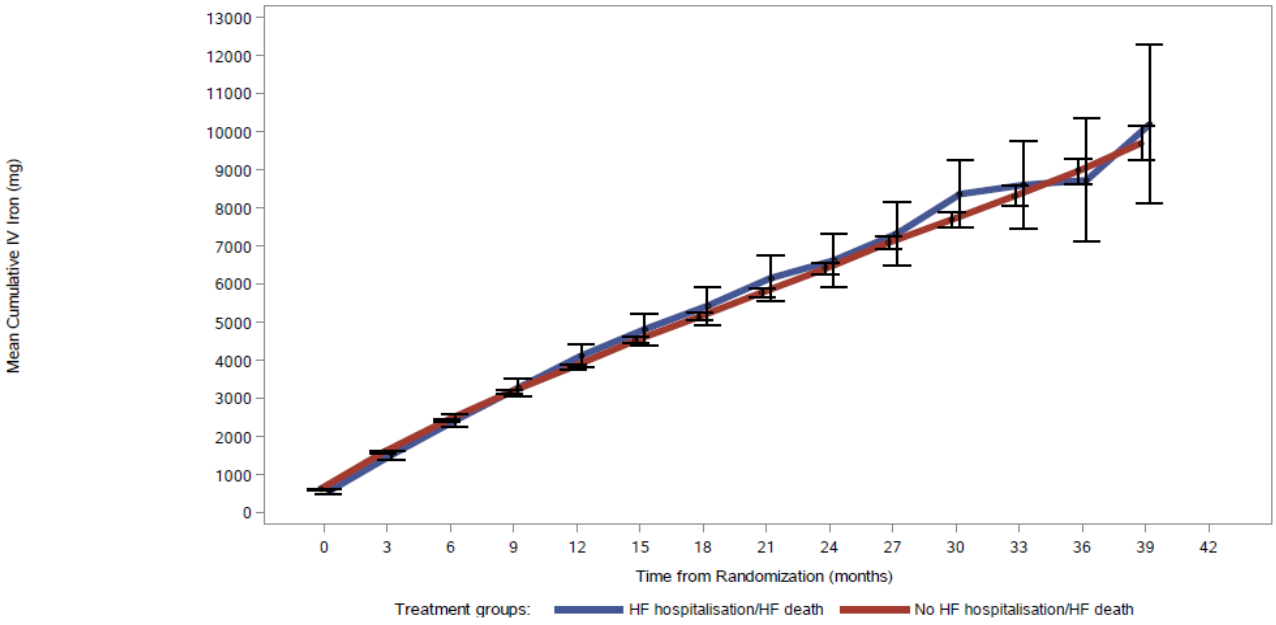
Appendix Figure 2 - Mean cumulative ESA dose in those who had a HF hospitalization/ HF death versus those without a HF hospitalization/ HF death

Appendix Figure 3 - Mean hemoglobin in those who had a HF hospitalization/ HF death versus those without a HF hospitalization/ HF death

Appendix Table 1 - Adjudicated causes of death

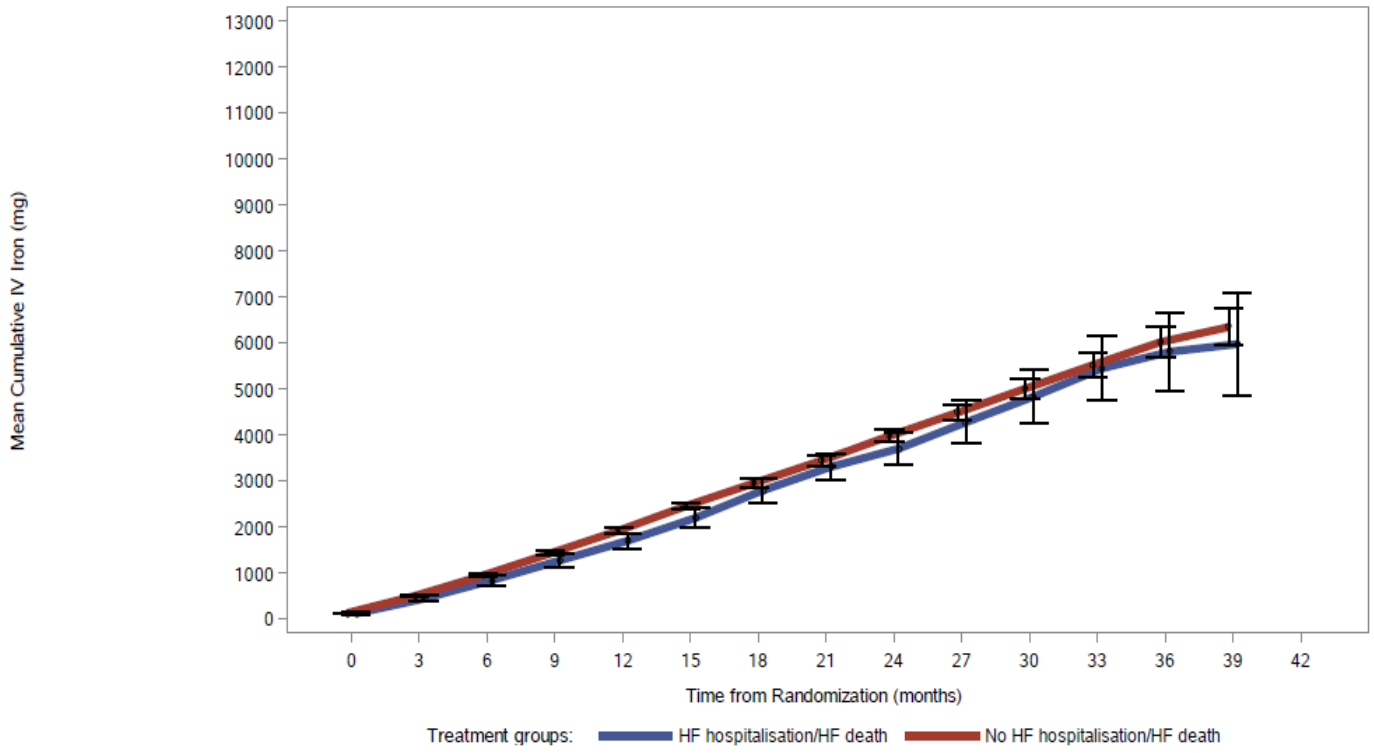
Appendix Figure 1

A) Mean IV iron dose in those who had a HF hospitalization/ HF death versus those without a HF hospitalization/ HF death (PROACTIVE ARM)



Number of patients														
HF hospitalisation/HF death	51	48	47	45	39	36	33	31	31	24	17	11	8	6
No HF hospitalisation/HF death	1042	965	906	849	39	740	691	639	563	463	367	282	203	131

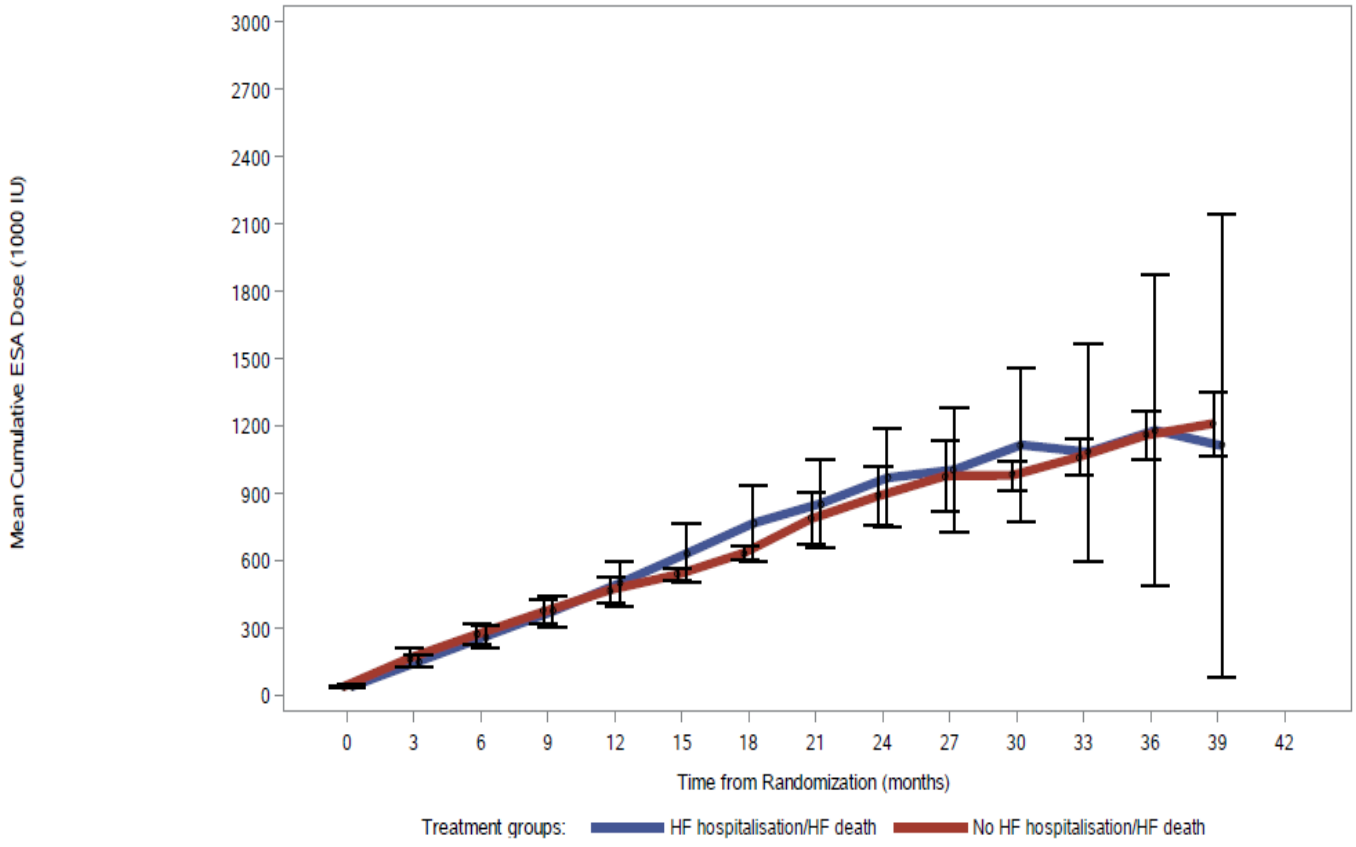
B) Mean IV iron dose in those who had a HF hospitalization/ HF death versus those without a HF hospitalization/ HF death (REACTIVE ARM)



Number of patients														
HF hospitalisation/HF death	70	69	66	60	57	53	50	47	42	33	27	23	20	15
No HF hospitalisation/HF death	978	910	843	782	57	658	606	561	489	407	342	259	193	121

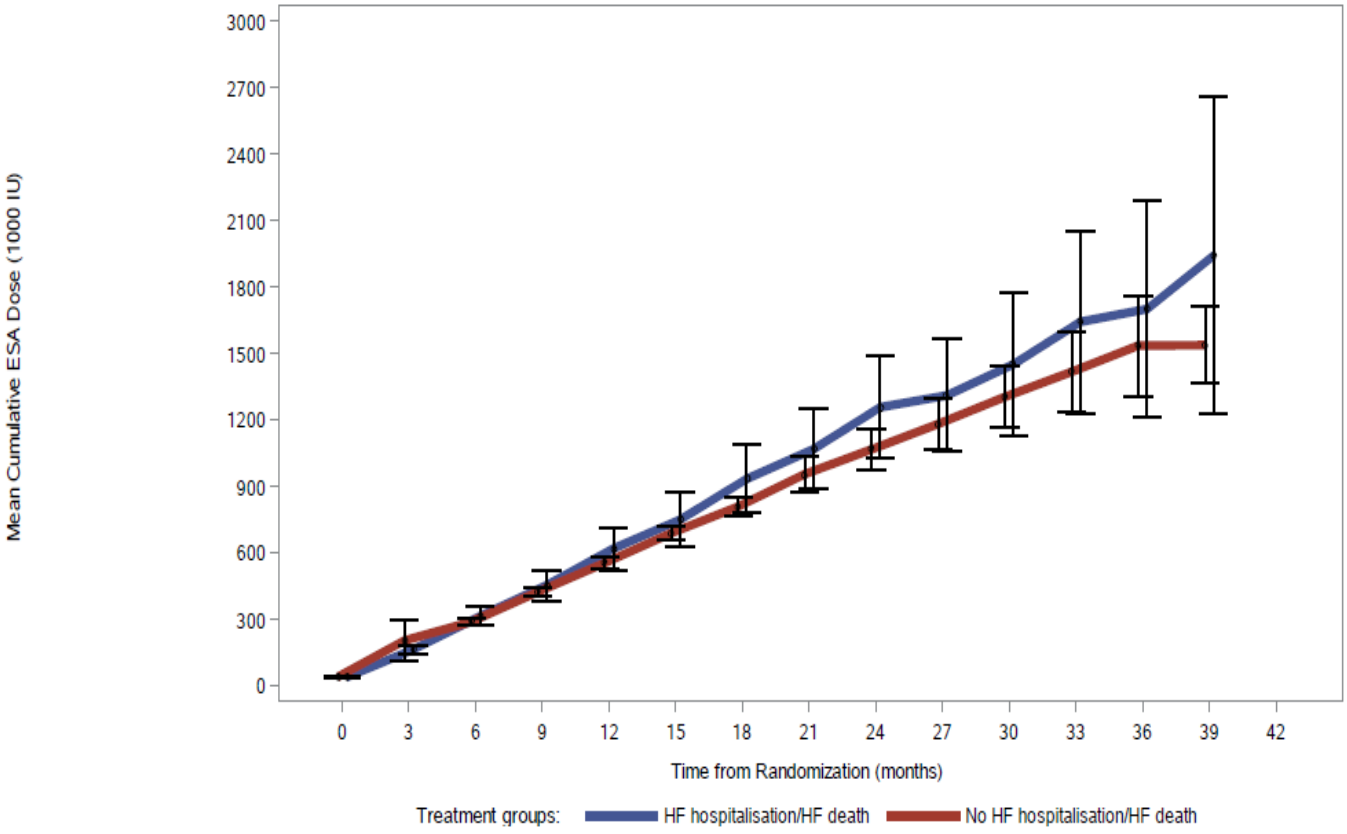
Appendix Figure 2

A) Mean cumulative ESA dose in those who had a HF hospitalization/ HF death versus those without a HF hospitalization/ HF death (PROACTIVE ARM)



Number of patients														
HF hospitalisation/HF death	51	48	47	45	39	36	33	31	31	24	17	11	8	6
No HF hospitalisation/HF death	1042	965	906	849	39	740	691	639	563	463	367	282	203	131

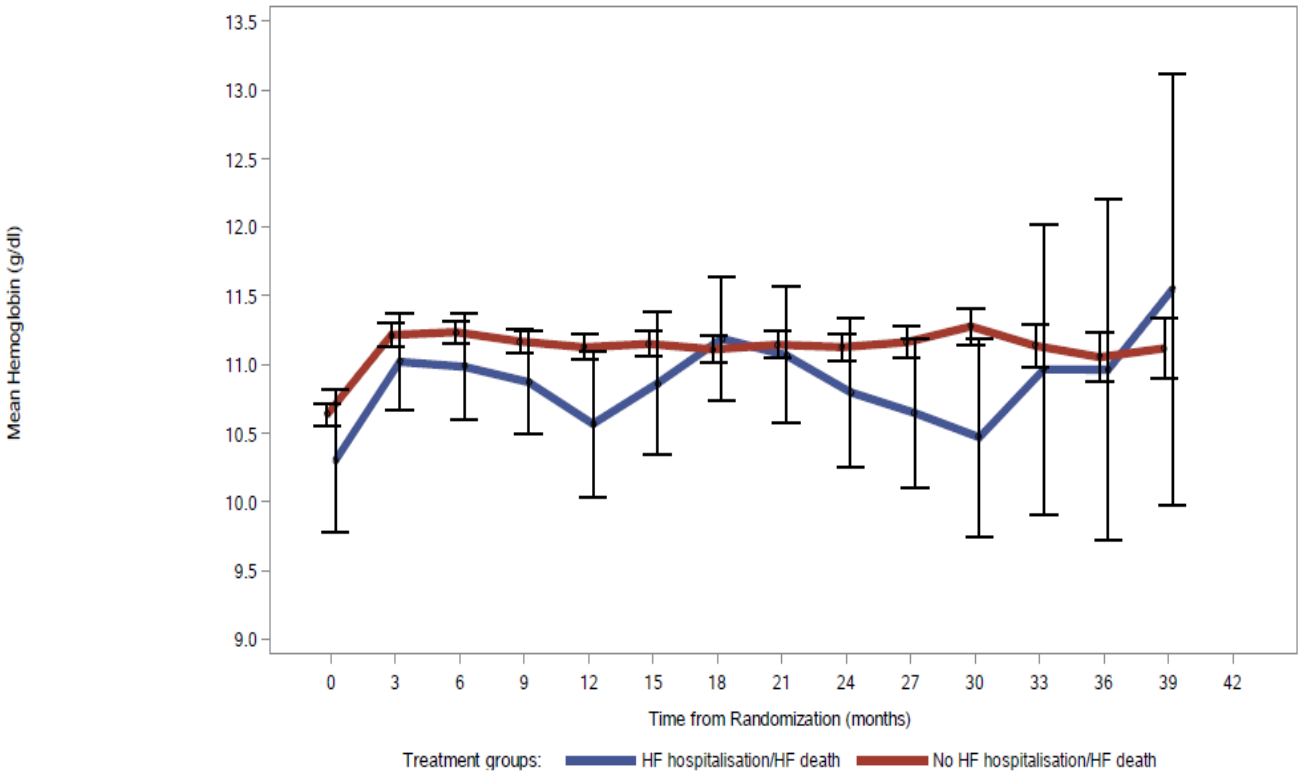
B) Mean cumulative ESA dose in those who had a HF hospitalization/ HF death versus those without a HF hospitalization/ HF death (REACTIVE ARM)



Number of patients														
HF hospitalisation/HF death	70	69	66	60	57	53	50	47	42	33	27	23	20	15
No HF hospitalisation/HF death	978	910	842	782	57	658	606	561	489	407	342	259	193	121

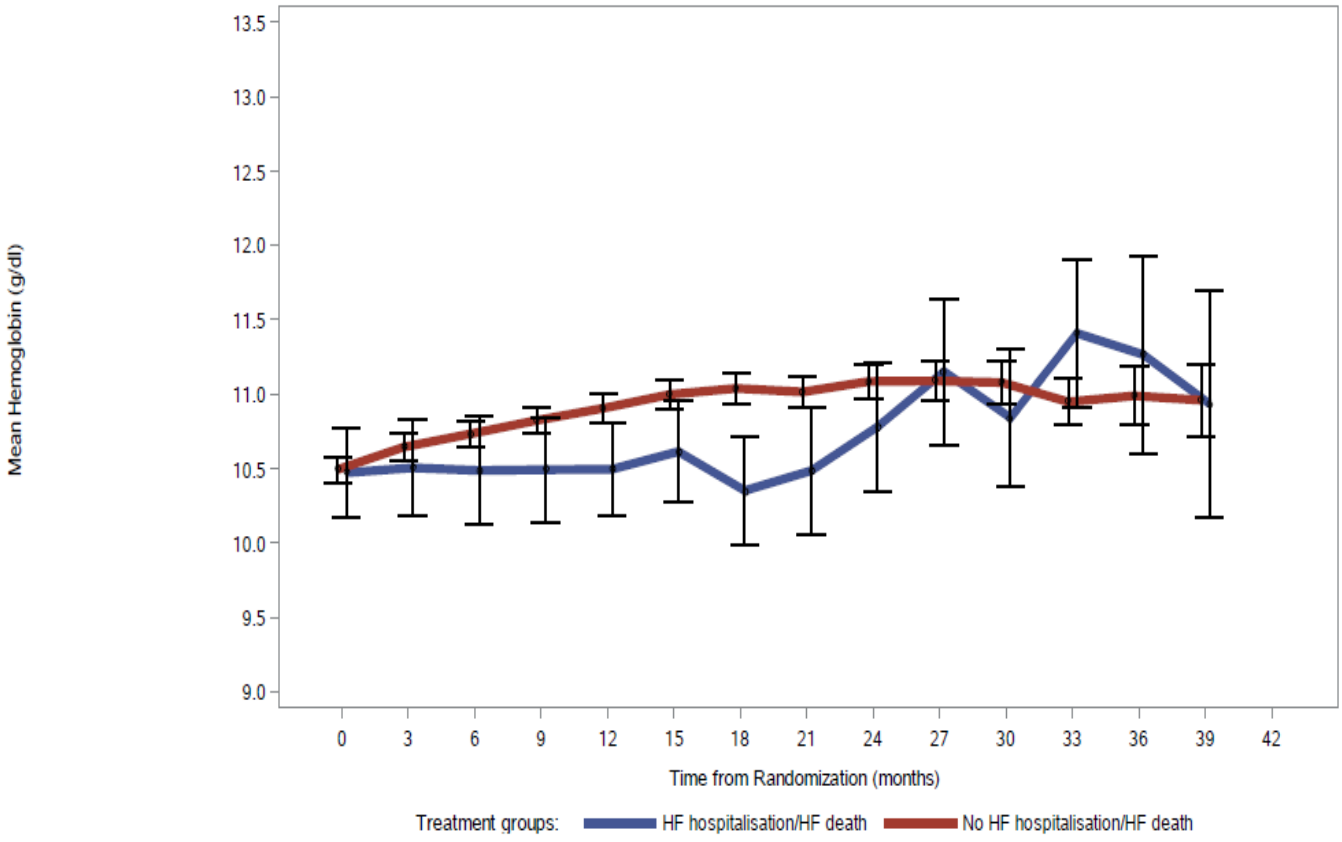
Appendix Figure 3

A) Mean hemoglobin in those who had a HF hospitalization/ HF death versus those without a HF hospitalization/ HF death (PROACTIVE ARM)



Number of patients														
HF hospitalisation/HF death	51	48	47	45	39	36	33	31	31	24	17	11	8	6
No HF hospitalisation/HF death	1042	965	906	849	39	740	691	639	563	463	367	282	203	131

B) Mean hemoglobin in those who had a HF hospitalization/ HF death versus those without a HF hospitalization/ HF death (REACTIVE ARM)



Number of patients														
HF hospitalisation/HF death	70	69	66	60	57	53	50	47	42	33	27	23	20	15
No HF hospitalisation/HF death	978	910	843	782	57	658	606	561	489	407	342	259	193	121

Supplementary table 1 First and recurrent events (heart failure hospitalization or cardiovascular death)

	High-dose iron (n=1093)	**Low-dose iron (n=1048)**
Events per patient	**n (%)**	**n (%)**
0	967 (88.5)	908 (86.6)
1	114 (10.4)	110 (10.5)
2	9 (0.8)	23 (2.2)
3	0 (0.3)	6 (0.6)
4	0 (0)	1 (0.1)
	n (per 100 p-y)	**n (per 100 p-y)**
Total number of first events	126 (5.70)	140 (6.79)
Total number of events (first and recurrent)	141 (6.38)	178 (8.64)*

*Rate ratio 0.73 (95% CI 0.56, 0.93), p=0.013

per 100 p-y = per 100 person-years of follow-up

Supplementary table 2 - Adjudicated causes of death

Adjudicated causes of death (data are numbers and percentages of subjects with cause of death in each category)		
Primary cause	**No heart failure hospitalization (N=2031)**	**Heart failure hospitalization (N=110)**
All deaths	453 (22.3)	62 (56.4)
Cardiovascular death	156 (7.7)	31 (28.2)
Myocardial Infarction	25 (1.2)	0
Stroke	25 (1.2)	0
Extra-axial haemorrhage	5 (0.2)	0
Sudden cardiac death	66 (3.0)	10 (9.1)
Heart failure	11 (0.5)	17 (15.5)
Cardiovascular procedure/operation	3 (0.1)	0
Other cardiovascular cause	20 (1.0)	4 (3.6)
Unknown cardiovascular cause	1 (<0.1)	0 (0)
Non-cardiovascular death	203 (10.0)	19 (17.3)
Infection	82 (4.0)	5 (4.5)
Pulmonary cause (excluding infection)	4 (0.2)	2 (1.8)
Renal cause (excluding infection)	11 (0.5)	1 (0.9)
Gastrointestinal cause (excluding infection)	10 (0.5)	4 (3.6)
Malignancy	33 (1.6)	3 (2.7)
Withdrawal of dialysis	58 (2.9)	3 (2.7)
Non-cardiovascular surgery	0	0
Other non-cardiovascular cause	5 (0.2)	1 (0.9)
Unknown cause	94 (4.6)	12 (10.9)