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

Brief running title: Intravenous iron, hemodialysis and heart failure

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ABSTRACT

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

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

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% CI 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

ABBREVIATIONS

CKD – Chronic kidney disease

ESA - erythropoiesis stimulating agent

HF – heart failure

CV – cardiovascular

TSAT – transferrin saturation

LVEF – left ventricular ejection fraction

CI – confidence intervals

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 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]. The trial was approved by the relevant health authorities and institutional review boards, and all the patients provided written informed consent 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. Mean doses of iron administered in high and low dose groups have been previously published.[21] 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. Hospitalization for heart failure was a pre-specified, adjudicated secondary outcome.[2021] For this paper the composite outcomes of a) time-to-first hospital hospitalization for heart failure or heart failure death (i.e. first fatal or non-fatal heart failure event) and b) time-to-first hospital hospitalization 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 hospitalization 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:

Statistical analysis:

Baseline characteristics were summarised as medians and lower and upper quartiles ranges for continuous variables and counts and percentages for categorical variables, according to heart failure hospitalization status. The characteristics were compared with the use of the Mann-Whitney U test or Pearson's chi-square test as appropriate. 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). Cumulative incidence plots, accounting for the competing risk of any deaths not included in the endpoint, were used to estimate the accumulation of first events. Recurrent events were analysed using the proportional-means model of Lin, Wei, Yang and Ying[22] and described graphically in the form of mean frequency functions (method of Ghosh and Lin[23]).

To identify potential predictors of a fatal or non-fatal heart failure event, the following baseline characteristics were included in a multivariable Cox regression model: randomised treatment; age; sex; history of heart failure, myocardial infarction, and diabetes; systolic blood pressure; heart rate and atrial fibrillation. The model was refitted using forward stepwise regression (with P = 0.05 to enter).

Lengths of stay for the first heart failure hospitalization event were compared between the treatment arms using the Mann-Whitney U test.

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, there was a greater prevalence of heart failure history at baseline (9.1% versus 3.7% in participants without a heart failure event, p=0.014), as well as a history of atherothrombotic disease such as peripheral artery disease (16.5% versus 8.3%, respectively, p=0.006), although this was not the case with hypertension. The greatest difference between participants experiencing a heart failure event and participants who did not was a history of diabetes (60.3% versus 43.3%, 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 (Supplementary table 3).

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 in 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% CI 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 hospitalization 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% CI 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% CI 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 hospitalizations, orthopnoea (40%) and paroxysmal nocturnal dyspnoea (19%) were less common. Pulmonary oedema was detected in 44%, although radiological pulmonary oedema/congestion was reported in 76%. Peripheral oedema was described in only 29% of cases. An echocardiogram was carried out in 40% of cases and natriuretic peptide testing in 10%. Left ventricular systolic dysfunction was identified in 70% of cases.

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

The median (IQR) length of stay (LOS) for heart failure hospitalizations 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 hospitalizations. 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 renal 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.[242526] 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)[27]. Although the trials in heart failure enrolled patients with a different underlying disease and were placebo-controlled, the findings of this meta-analysis are consistent with the benefit observed in PIVOTAL. Three trials are in progress which will clarify the effect of intravenous iron on clinical outcomes in heart failure (IRONMAN – NCT 02642562, FAIR-HF2 - NCT03036462; HEART-FID NCT0303793).

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][28]

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.[7][29] 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 renal disease.[30] 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%.[31] 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.[1232] By far the most common initial treatment was mechanical removal of fluid (88%) with very few patients receiving any other acute intervention.

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. The low dose iron regimen is one of several that could have been selected as comparators for high dose iron. There is a possibility that if a different low dose regimen had been used, for example that recommended by the 2012 KDIGO guidelines[33], that a difference between high and low dose iron would not have been observed. The results observed in PIVOTAL may not be generalizable to patients who have been on dialysis for longer. Whether or not different iron preparations of iron would yield the same results can also not be certain.

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.

Clinical Perspectives

6% of patients on hemodialysis were admitted to hospital with heart failure over a 2-year period.

Hospitalizations for heart failure can be reduced by prescribing high dose rather than low dose intravenous iron.

Patients who are hospitalized for heart failure were at very high risk of death (56%) versus those who were not hospitalised (22%).

Translational outlook

Attempts to supplement iron (in those with iron deficiency) can reduce heart failure hospitalizations in patients on hemodialysis. Future research into iron repletion may result in reduced clinical events in different iron deficient populations.

Mortality rates are high in patient on hemodialysis. Research should attempt to reduce mortality.

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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.

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

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

	All patients (n=2141)	**With a fatal or non-fatal heart failure event (n=121)**	**Without a heart failure event (n=2020)**	**p-value**
Age, yr. (median [LQ, UQ])	64 (52, 75)	66 (56, 77)	64 (52, 75)	0.096
Male sex, (n, %)	1398 (65.3%)	90 (74.4%)	1308 (64.8%)	0.031
Race (n, %)				
White/European	1698 (79.3%)	94 (77.7%)	1604 (79.4%)	0.27
Black/African descent	190 (8.9%)	7 (5.8%)	183 (9.1%)	
Asian	185 (8.6%)	15 (12.4%)	170 (8.4%)	
Other	68 (3.2%)	5 (4.1%)	63 (3.1%)	
BMI, kg/m^2 (median [LQ, UQ])	27.5 (23.7, 32.7)	28.2 (24.5, 32.6)	27.5 (23.6, 32.7)	0.53
Weight, kg (median [LQ, UQ])	79.5 (67.1, 94.7)	80.2 (71.0, 95.0)	79.4 (67.0, 94.7)	0.34
Systolic BP, mm Hg (median [LQ, UQ])	144 (65, 84)	146 (130, 163)	144 (128, 160)	0.33
Median duration of dialysis, months (median [LQ, UQ])	4.8 (2.8, 8.2)	4.9 (3.1, 8.6)	4.8 (2.8, 8.2)	0.47
Vascular access, (n, %)				0.073
Dialysis catheter	877 (41.0%)	59 (48.8%)	818 (40.5%)	
Arteriovenous fistula or graft	1264 (59.0%)	62 (51.2%)	1202 (59.5%)	
History, (n, %)				
Heart failure	86 (4.0%)	11 (9.1%)	75 (3.7%)	0.014
Hypertension	1557 (72.7%)	86 (71.1%)	1471 (72.8%)	0.47
Diabetes	950 (44.4%)	73 (60.3%)	877 (43.4%)	<0.001
Atrial fibrillation	164 (7.7%)	14 (11.6%)	150 (7.4%)	0.24
Myocardial infarction	184 (8.6%)	16 (13.2%)	168 (8.3%)	0.17
Peripheral artery disease	187 (8.7%)	20 (16.5%)	167 (8.3%)	0.006
Stroke	176 (8.2%)	10 (8.3%)	166 (8.2%)	0.99
Smoking status, (n, %)				

Never	249 (11.6%)	16 (13.2%)	233 (11.5%)	0.28
Previous	545 (25.5%)	37 (30.6%)	508 (25.2%)	
Current	1347 (62.9%)	68 (56.2%)	1279 (63.3%)	
Laboratory data (median [LQ, UQ])				
Hemoglobin, g/l	106 (96, 115)	103 (95, 115)	106 (94, 115)	0.15
Ferritin, µg/l	216 (133, 304)	230 (142, 312)	215 (133, 302)	0.31
Transferrin saturation, %	20.0 (16.0, 24.0)	21.0 (16.0, 24.0)	20.0 (16.0, 24.0)	0.51
C-reactive protein, mg/l	6.0 (3.7, 14.0)	8.0 (4.0, 19.0)	6.0 (3.5, 14.0)	0.026
Cardiovascular medications, (n, %)				
Diuretic	927 (43.3%)	53 (43.8%)	874 (43.3%)	0.91
β-Blocker	948 (44.3%)	51 (42.1%)	897 (44.4%)	0.63
Calcium-channel blocker	1032 (48.2%)	57 (47.1%)	975 (48.3%)	0.80
ACE inhibitor	367 (17.1%)	15 (12.4%)	352 (17.4%)	0.15
ARB	247 (11.5%)	13 (10.7%)	234 (11.6%)	0.78
Mineralocorticoid antagonist	33 (1.54%)	1 (0.83%)	32 (1.58%)	0.51
Digitalis glycoside	37 (1.73%)	4 (3.31%)	33 (1.63%)	0.17
Diabetes medications, (n, %)				
Any glucose-lowering therapy	726 (33.9%)	54 (44.6%)	672 (33.3%)	0.010
Oral glucose-lowering drug	235 (11.0%)	15 (12.4%)	220 (10.9%)	0.61
Insulin	553 (25.8%)	41 (33.9%)	512 (25.3%)	0.037

ACE = angiotensin converting enzyme ARB = angiotensin receptor blocker MRA = mineralocorticoid receptor antagonist, LQ = lower quartile, UQ = upper quartile

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	0.003
HF death or HF hospitalization	51 (4.7)	2.31	70 (6.7)	3.40	(0.38,0.82)	0.023
CV death or HF hospitalization	126 (11.6)	5.70	140 (13.4)	6.79	0.66 (0.46,0.94)	0.092
					0.81 (0.64,1.03)	
Deaths						
HF death	12 (1.1)	0.54	16 (1.5)	0.78	0.69	0.337
CV death	91 (8.3)	4.12	96 (9.2)	4.66	(0.33,1.47)	0.352
All-cause death	246 (22.5)	11.13	269 (25.7)	13.05	0.87 (0.66,1.16)	0.054
					0.84 (0.71,1.00)	

*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