Iron Supplementation and Mortality in Incident Dialysis Patients

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INTRODUCTION

Imbalances of iron homeostasis are a frequent finding in dialysis patients. Intravenous iron supplementation and ESA have been used in clinical practice to increase hemoglobin levels in dialysis patients, decrease the need for red blood cell transfusions and possibly improve patients' general quality of life by reducing anemia-related symptoms. Specifically, iron supplementation is necessary to correct true iron deficiency, prevent its development in ESA-treated patients, increase responsiveness to ESA, and reduce ESA dosages. Studies investigating the effect of iron supplementation on mortality of dialysis patients are rare and have produced conflicting results. No prospective randomized controlled trials of iron supplementation evaluating solid clinical end-points are available so far.

Therefore, this study aimed to investigate the association between iron supplementation and all-cause mortality, cardiovascular and sepsis-related mortality in a well-characterized inception cohort of incident dialysis patients who were followed for up to more than seven years.

PATIENTS AND METHODS

- Single Center prospective, observational cohort study of incident hemodialysis and peritoneal dialysis patients (INVOR-study).
- All incident dialysis patients starting chronic dialysis treatment between May 1st, 2000 and April 30th, 2006 were enrolled. A total of 235 patients were included in the study and followed for a maximum of 7.6 years until December 31th, 2007 or until death.
- Clinical, laboratory and medication data were collected prospectively, starting at initiation of dialysis.
- All available measurements of ferritin, CRP, albumin and hemoglobin were used in a multivariable-adjusted time-dependent Cox regression model.
- The outcomes of interest were all-cause mortality as well as cardiovascular or sepsis-related mortality.

RESULTS

Tab. 1. Clinical characteristics of patients at baseline and during follow-up stratified for iron supplementation

	All patients (n=235)	Iron supplementation (n=204)	No iron supplementation (n=31)
Sex			
Male, n (%)	146 (62.1%)	126 (61.8%)	20 (64.5%)
Female, n (%)	89 (37.9%)	78 (38.2%)	11 (35.5%)
Age (years)	61.7 ± 14.0	61.7 ± 13.7	62.0 ± 16.0
Body Mass Index (kg/m²)	26.1 ± 4.5	26.2 ± 4.6	25.2 ± 3.8
Start of dialysis with			
Hemodialysis, n (%)	197 (83.8%)	181 (88.7%)	16 (51.6%) [d]
Peritoneal dialysis, n (%)	38 (16.2%)	23 (11.3%)	15 (48.4%) [d]
Year of start of dialysis			
2000-2003	122 (51.9%)	106 (52.0%)	16 (51.6%)
2004-2006	113 (48.1%)	98 (48.0%)	15 (48.4%)
Diabetes mellitus, n (%)	82 (34.9%)	77 (37.7%)	5 (16.1%) [a]
Systolic blood pressure (mmHg)	154.0 ± 22.7	153.9 ± 22.6	154.6 ± 23.5
Diastolic blood pressure (mmHg)	83.0 ± 12.3	82.7 ± 12.6	82.9 ± 11.9
	[78.0; 84.0; 90.0]	[77.0; 83.0; 90.0]	[78.0; 85.0; 91.0]
Medication at baseline			
ESA, n (%)	183 (77.9%)	164 (80.4%)	19 (61.3%) [a]
Iron supplements, n (%)	53 (22.6%)	53 (26.0%)	0 (0.0%) [c]
ESA and iron supplements, n (%)	51 (21.7%)	51 (25.0%)	0 (0.0%) [c]
Laboratory parameters at baseline			
Ferritin (ng/mL)	174 ± 207	155 ± 192	320 ± 251 [d]
	[44; 111; 234]	[42; 93; 195]	[188; 251; 416]
Iron (µg/dl)	51.4 ± 31.5	50.0 ± 30.8	62.4 ± 34.8 [a]
	[30.0; 44.0; 61.0]	[30.0; 41.0; 61.0]	[42.8; 53.5; 79.0]
Transferrin (mg/dL)	202.5 ± 44.5	204.4 ± 44.0	188.3 ± 46.5
Transferrin saturation (%)	18.6 ± 11.3	17.8 ± 10.7	24.1 ± 13.8 [b]
	[10.9; 16.0; 22.8]	[10.0; 15.0; 22.0]	[14.6; 21.7; 28.0]
Hemoglobin (g/dL)	11.17 ± 1.72	11.17 ± 1.67	11.12 ± 1.99
C-reactive protein (mg/dL)	3.24 ± 5.34	3.21 ± 5.50	3.45 ± 4.20
	[0.30; 0.98; 3.00]	[0.30; 0.89; 2.79]	[0.57; 1.52; 4.81]
Creatinine (mg/dL)	7.28 ± 2.64	7.23 ± 2.65	7.67 ± 2.54
	[5.50; 6.80; 8.60]	[5.50; 6.70; 8.35]	[5.60; 8.20; 8.70]
Albumin (g/dL)	3.71 ± 0.65	3.72 ± 0.65	3.65 ± 0.69
Calcium (mg/dL)	8.5 ± 1.1	8.3 ± 1.1	8.7 ± 1.0
Phosphorus (mg/dL)	6.1 ± 1.9	6.0 ± 1.9	5.6 ± 1.9
iPTH (pg/mL)	350.5 ± 264.9	360.5 ± 273.6	279.9 ± 180.2
	[156.5; 287.2; 468.7]	[159.4; 292.7; 468.7]	[147.9; 222.9; 397.0]
Bicarbonate (mEq/L)	21.00 ± 3.59	20.93 ± 3.44	21.75 ± 4.98
Erythrocytes (T/L)	3.73 ± 0.62	3.75 ± 0.62	3.61 ± 0.65
Leukocytes (G/L)	8.18 ± 3.29	8.27 ± 3.26	7.64 ± 3.43
	[6.10; 7.40; 9.90]	[6.20; 7.50; 9.95]	[5.43; 7.05; 8.83]
Total cholesterol (mg/dL)	189.8 ± 51.0	189.7 ± 50.7	190.3 ± 54.7
Comorbidities at baseline			
CAD *, n (%)	40 (17.0%)	36 (17.6%)	4 (12.9%)
CVD **, n (%)	70 (29.8%)	63 (30.9%)	7 (22.6%)
PAD ***, n (%)	40 (17.0%)	35 (17.2%)	5 (16.1%)
Follow-up			
ESA, n (%)	234 (99.6%)	204 (100.0%)	29 (93.5%)
Follow-up time (months) ‡	38.2 ± 23.2	40.4 ± 22.6	24.0 ± 22.4 [d]
Transplantation, n (%)	58 (24.7%)	49 (24.0%)	9 (29.0%)
All-cause mortality, n (%)	82 (34.9%)	66 (32.4%)	16 (51.6%) [a]
CV mortality #, n (%)	38 (16.2%)	32 (15.7%)	6 (19.4%)
Sepsis mortality, n (%)	21 (8.9%)	16 (7.8%)	5 (16.1%)
CV and/or sepsis mortality, n (%)	59 (25.1%)	48 (23.5%)	11 (35.5%)

Mean ± SD [25th, 50th and 75th percentile for cases of non-normal distribution] or number (%).
[a] p<0.05; [b] p<0.01; [c] p<0.005; [d] p<0.001, comparison between patients who ever received iron supplementation and patients who never received iron supplementation during the observation period.

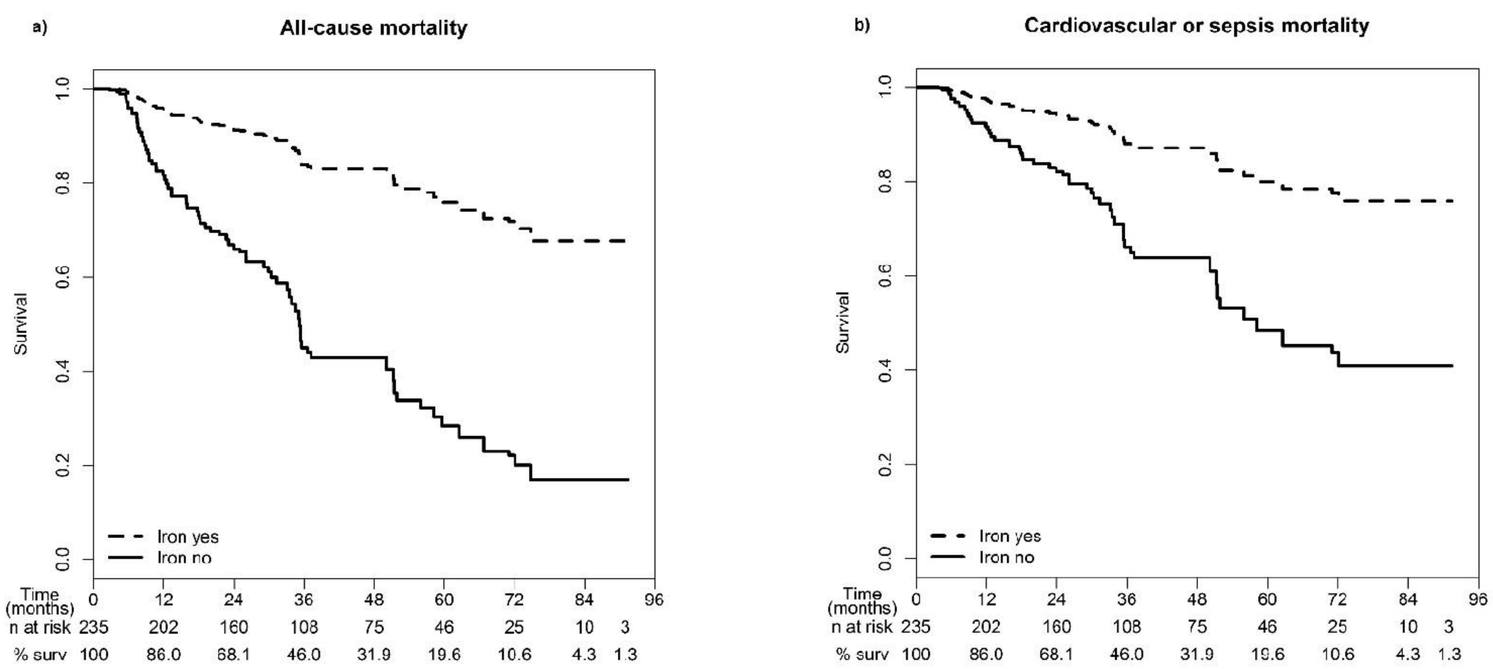

Fig. 1. Survival curves for **a)** all-cause mortality and **b)** cardiovascular or sepsis-related mortality adjusted for age, sex, time-dependent type of renal replacement therapy, diabetes, time-dependent C-reactive protein, albumin and hemoglobin and patients stratified for iron supplementation. The number of patients at risk for each year of observation is given with the last observation time at 91 months. "% surv" indicates the percentage of survivors for each 12-month interval.

Tab. 2. Association between iron supplementation and all-cause mortality and cardiovascular or sepsis-related mortality using time-dependent Cox proportional hazards models.

	All-cause mortality			CV or sepsis mortality**		
	HR	(95% CI)	P-value	HR	(95% CI)	P-value
Age (years)	1.05	(1.03-1.08)	<0.001	1.04	(1.02-1.07)	<0.001
Sex						
Female	Ref.			Ref.		
Male	1.14	(0.68-1.90)	0.6	1.38	(0.73-2.60)	0.3
Type of renal replacement therapy						
Hemodialysis	Ref.			Ref.		
Peritoneal dialysis	0.28	(0.07-1.03)	0.06	0.55	(0.14-2.12)	0.4
Transplantation	0.47	(0.14-1.54)	0.2	0.38	(0.08-1.72)	0.2
Diabetes mellitus						
No	Ref.			Ref.		
Yes	1.31	(0.81-2.12)	0.3	1.54	(0.87-2.73)	0.1
Iron supplementation						
No	Ref.			Ref.		
Yes	0.22	(0.08-0.58)	0.002	0.31	(0.09-1.04)	0.06
C-reactive protein (mg/dL)	1.13	(1.10-1.17)	<0.001	1.11	(1.07-1.15)	<0.001
Albumin (g/dL)	0.33	(0.21-0.50)	<0.001	0.31	(0.18-0.53)	<0.001
Hemoglobin (g/dL)	0.95	(0.81-1.12)	0.5	0.90	(0.75-1.08)	0.3

* Adjusted for age, sex, diabetes mellitus and the time-dependent variables type of renal replacement therapy, C-reactive protein, albumin and hemoglobin.
** **Cardiovascular or sepsis mortality**: myocardial infarction (MI), heart failure, sudden death, ischemic stroke, hemorrhagic stroke, sepsis.

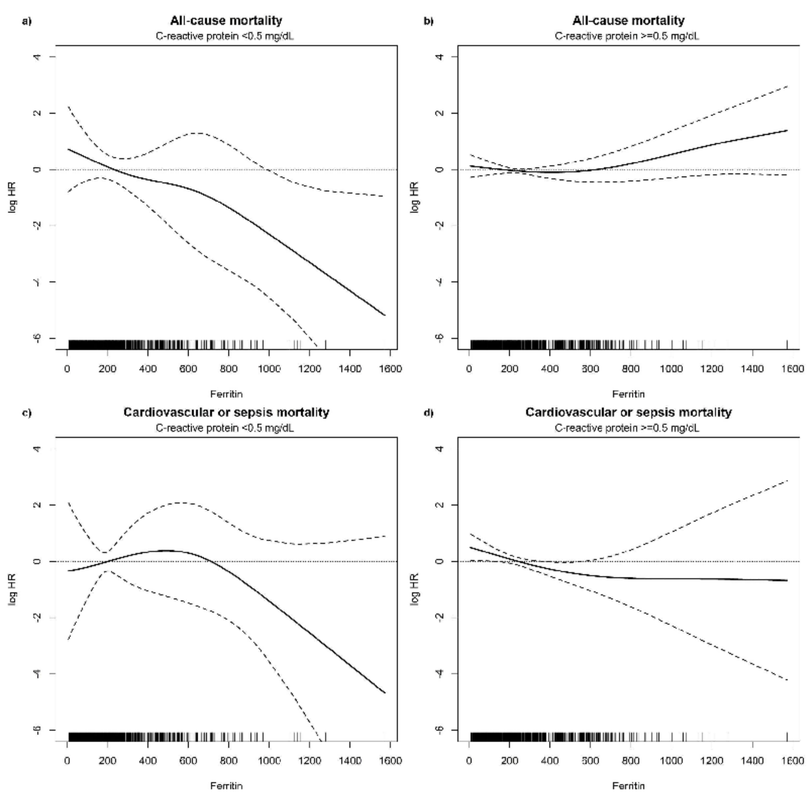

Fig. 2. Cox regression results: P-splines to explore the functional form of the effect of ferritin values on the log hazard ratio for the risk of all-cause mortality (a,b) and cardiovascular or sepsis-related mortality (c, d) in patients with C-reactive protein <0.5 mg/dL (a,c) and ≥0.5 mg/dL (b, d) during follow-up, adjusted for age, sex, diabetes mellitus and time-dependent albumin and hemoglobin. Dashed lines are the point wise 95% CI. The rugplot at the bottom of the figures displays the number of measurements. Time-dependent Cox proportional hazards model using all CRP- and ferritin-values collected during follow-up.

CONCLUSIONS

Iron supplementation is associated with a decreased all-cause mortality risk in incident dialysis patients. Our findings provide cautious support for the safety and benefit of judicious iron supplementation to achieve serum ferritin levels of up to approximately 600-800 ng/mL. Additional studies are needed to determine the influence of various iron dosing regimens and ferritin threshold targets on clinical outcomes such as cardiovascular disease, severe infection and overall mortality.

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485--MP
M) Dialysis. M5) Anaemia in CKD 5D.
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DOI: 10.3252/pso.eu.51era.2014
Poster presented at: 51 ERA-EDTA CONGRESS AMSTERDAM 2014
PosterSessionOnline.com