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Original Articles

Effect of intravenous iron use on hospitalizations in patients undergoing hemodialysis: a comparative effectiveness analysis from the DEcIDE-ESRD study

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ABSTRACT

Background. Intravenous iron use in hemodialysis patients has greatly increased over the last decade, despite limited studies on the safety of iron.

Methods. We studied the association of receipt of intravenous iron with hospitalizations in an incident cohort of hemodialysis patients. We examined 9544 patients from Dialysis Clinic, Inc. (DCI). We ascertained intravenous iron use from DCI electronic medical record and USRDS data files, and hospitalizations through Medicare claims. We examined the association between iron exposure accumulated over 1-, 3- or 6-month time windows and incident hospitalizations in the follow-up period using marginal structural models accounting for time-dependent confounders. We performed sensitivity analyses including recurrent events models for multiple hospitalizations and models for combined outcome of hospitalization and death.

Results. There were 22 347 hospitalizations during a median follow-up of 23 months. Higher cumulative dose of intravenous iron was not associated with all-cause, cardiovascular or infectious hospitalizations [HR 0.97 (95% CI: 0.77–1.22) for all-cause hospitalizations comparing >2100 mg versus 0–900 mg of iron over 6 months]. Findings were similar in models examining the risk of hospitalizations in 1- and 3-month windows [HR 0.88 (95% CI: 0.79–0.99) and HR 0.88 (95% CI: 0.74–1.03), respectively] or the risk of combined outcome of hospitalization and death in the 6-month window [HR 0.98 (95% CI: 0.78–1.23)].

Conclusions. Higher cumulative dose of intravenous iron may not be associated with increased risk of hospitalizations in hemodialysis patients. While clinical trials are needed, employing higher iron doses to reduce erythropoiesis-stimulating agents does not appear to increase morbidity in routine clinical care.

Keywords: anemia, hemodialysis, hospitalizations, intravenous iron

INTRODUCTION

Intravenous iron and erythropoiesis-stimulating agents (ESAs) are the principal therapies for anemia management in patients

on hemodialysis [1, 2]. While ESA use peaked in the dialysis population in 2007–2008, the use of intravenous iron in anemia management has continued to steadily rise [3, 4]. In particular, the introduction of bundled payments for injectable medications administered at dialysis treatments and the publication of clinical trials showing harms with higher doses of ESAs, has led to a sharp increase in the use of intravenous iron for anemia management at the expense of decreasing ESA therapy [5–9].

Recent studies have shown that the majority of patients on dialysis may suffer from hepatic iron overload as diagnosed by imaging, and in more than one-third of patients, the iron overload can be severe [10, 11]. The risk may be particularly elevated in patients with high ferritin that are treated with intravenous iron, an increasingly common scenario in US dialysis units [3, 4, 10, 12]. Furthermore, *in vivo* and *in vitro* studies suggest an association between higher free iron availability and an increased risk of infection, as well as oxidative stress and cardiovascular disease [13–16]. To date, however, it is unclear whether patients' receipt of higher doses of intravenous iron during the course of routine dialysis care are associated with patients' risk of serious morbidity requiring medical intervention.

While a recent cohort study of prevalent dialysis patients showed an increased risk of infectious morbidity with higher iron doses, the risk of cardiovascular events in the same cohort was not affected by the receipt of iron [17]. This study involved a prevalent dialysis population, and as such, did not account for prior exposure to iron or survivor bias. Given the high risk of infectious, cardiovascular and all-cause morbidity in the dialysis population, additional studies on all potential adverse outcomes resulting from cumulative exposure to intravenous iron therapy in incident patients are urgently needed.

To inform clinical practice and health policy, we studied the association between lower versus higher doses of intravenous iron with incident and recurrent hospitalizations in a cohort of incident dialysis patients.

MATERIALS AND METHODS

Study population

We studied the association between intravenous iron dose and patients' risk of hospitalization in a retrospective cohort study of patients who initiated hemodialysis at Dialysis Clinic, Inc. (DCI) facilities. Patients initiated hemodialysis between 2003 and 2008 and were receiving Medicare Part A and Part B at 90 days following initiation ($n = 21\,233$). To ensure that only incident patients were included, we excluded patients with more than 60 days between the date of start of dialysis recorded in the United States Renal Data System (USRDS) and the date of start of dialysis recorded in the DCI database ($n = 1211$). We also excluded patients who did not have data for a dialysis treatment at DCI or those who started on peritoneal or home hemodialysis (Figure 1). DCI data were linked to the United States Renal Data System as previously described [18]. The study was approved by the research ethics board at Johns Hopkins Medical Institute.

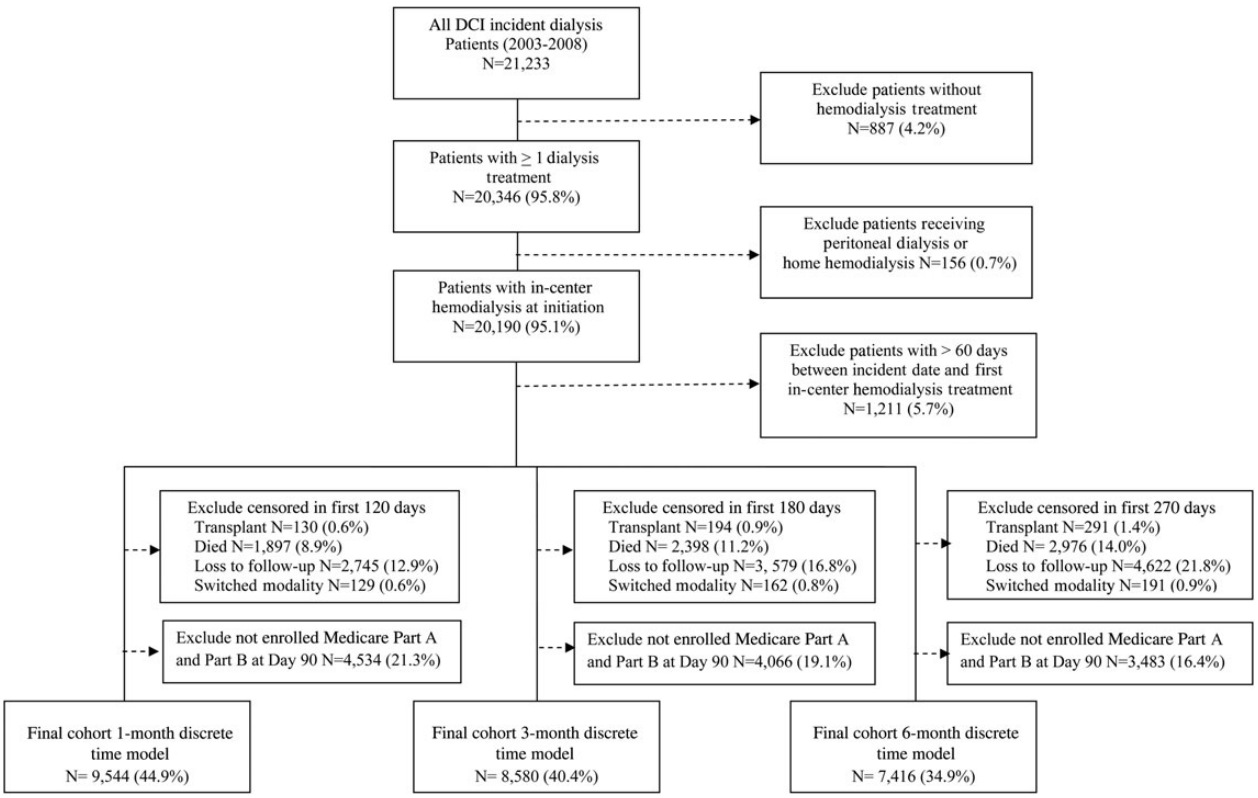

FIGURE 1: Flow diagram of study population.

Cohort construction. We constructed three separate analytic cohorts to quantify associations between intravenous iron exposure accumulated over 1-, 3-, or 6-months with hospitalizations. We followed patients from their first hemodialysis session at the start of the baseline period through 31 December 2008. We allowed for a 90-day time period prior to 1-, 3-, and 6-month intravenous iron exposure windows to define time-varying covariates. Patients therefore had to survive for a minimum of 120, 180 and 270 days to contribute to the 1-, 3- and 6-month analysis cohorts, respectively. Each analysis ascertained the risk of hospitalization from exposure to intravenous iron over the 1-, 3- or 6-month time period immediately preceding it in a time-varying fashion. Patients were censored if they underwent kidney transplantation, switched to a PD or home hemodialysis modality, transferred to a non-DCI facility, were withdrawn from dialysis or were lost to follow-up (Figures 1 and 2).

Key exposures, potential confounders and outcomes

We determined baseline covariates [demographics, comorbid conditions and body mass index (BMI)] at the start of dialysis. For time-varying covariates, the accrual period was 1–3 months before the iron exposure windows, as described below. Variables obtained more frequently such as hemoglobin preceding iron exposure were ascertained in the month immediately before iron exposure, whereas, iron storage parameters, typically obtained monthly to quarterly, were ascertained in the 3 months preceding the iron exposure window. We chose covariates that were clinically plausible confounders of iron receipt and its potential relation with morbidity or were statistically associated with iron exposure or the morbidity outcome.

Primary exposure: intravenous iron. The primary exposure in our analysis was the cumulative dose of intravenous iron prescribed over 1-, 3- or 6-month rolling windows (Figure 2). We obtained information on patients' intravenous iron prescriptions from the DCI electronic medical record for all dialysis treatments received at DCI facilities. If treatments were missed for greater than 30 consecutive days, we examined data from the USRDS Medicare claims to ascertain intravenous iron dose. We calculated the total dose of intravenous iron over 1-, 3- and 6-month time windows, and categorized doses into four groups.

Outcomes: all-cause, infectious and cardiovascular hospitalizations. The primary outcome of our analysis was all-cause hospitalization, which we ascertained through linkage with Medicare claims, occurring during the 30 days after the end of the 1-, 3- or 6-month window in which intravenous iron exposure was ascertained. Our secondary outcomes included hospitalization attributable to infectious and cardiovascular causes, which are the leading causes of morbidity and mortality in patients on dialysis [18]. We treated death as a censoring event in the primary analysis, and as part of a composite outcome event (i.e. occurrence of hospitalization or death) in our secondary analysis.

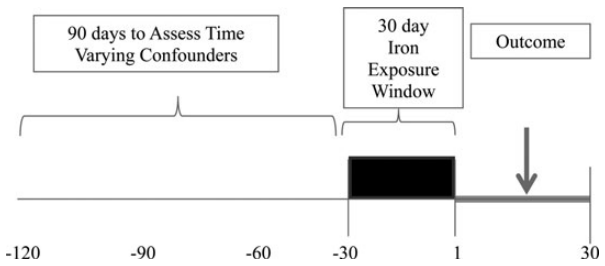

FIGURE 2: Timing of predictor, exposure and outcome windows (example from 1-Month Intravenous Iron Exposure Cohort).

Potential confounders. We ascertained the presence of comorbid disease using the International Classification of Disease codes (ICD-9) from inpatient and outpatient claims accrued during the patient's first 30 days after starting dialysis. We derived information on patients' age, gender, race, ethnicity, primary cause of end stage renal disease (ESRD) and BMI at baseline primarily through clinical data (DCI), or using administrative information (from USRDS Center for Medicare and Medicaid Services-2728 form) in the case of missing values.

Laboratory values. We used longitudinal data from the DCI database on each patient's entire laboratory variables obtained during the course of their routine clinical care. To assess markers of patients' iron storage, we used each patient's closest serum iron, total iron binding capacity and serum ferritin values not more than 90 days prior to the intravenous iron exposure window. We considered each patient's most recent hemoglobin, serum albumin and creatinine in the 30 days prior to the start of the intravenous iron exposure window to be potential confounders. If these values were missing, we used the most recent value up to 60 days prior to the intravenous iron exposure window.

Dialysis treatment variables. We defined each patient's weight and pre-dialysis systolic blood pressure as the mean of their post-dialysis weight and pre-dialysis systolic blood pressure (SBP), respectively, over the 2 weeks prior to the start of the intravenous iron exposure window. We calculated change in weight and SBP as the respective mean value in the 0–30 days preceding intravenous iron exposure minus the average value in the 60–90 days preceding intravenous iron exposure. We defined vascular access type from DCI treatment records as the vascular access [arteriovenous fistula (AVF) or graft (AVG) or catheter] in use on the first day of the month preceding the intravenous iron exposure window.

ESA dose. We assessed the prescribed dose of ESA as the value recorded from the DCI electronic medical record. We summed each patient's total ESA use over each 7.5 day period and converted this value to an average weekly dose during each 30-day period. We used weekly dose for consistency with clinical practice, and the existing literature, and to avoid misclassification as patients may receive their dose divided over one to three treatments. We then divided the weekly ESA doses into four categories.

Recent infection. We also ascertained patients' presence of recent infection (within 21 days of the exposure window) as a

potential confounder. We defined infection as use of an intravenous antibiotic on at least two separate treatment days, or occurrence of an infection related hospitalization as recorded in the DCI medical record, USRDS or Medicare claims.

Statistical analysis

We compared the characteristics of patients included in the cohorts assessing 1-, 3- and 6-month intravenous iron exposure using ANOVA and χ^2 tests as appropriate. In all outcome models, intravenous iron, categorized into four groups, was our primary exposure variable. We assessed patients' risk of first hospitalization occurring in the study period due to all causes (primary outcome), or due to infectious causes or cardiovascular causes (secondary outcomes) among those receiving higher versus the lowest intravenous iron doses and among those receiving no iron compared with the lowest intravenous iron doses.

Time to first event marginal structural models. In order to account for the effect of specified variables on treatment decisions and the risk of hospitalizations, as well as the effect of past prescribing decisions on current prescribing patterns, we used marginal structural modeling (MSM) as our primary methodology for analyzing associations between iron receipt and morbidity [19]. We modeled time as a linear, quartic, cubic and quartic function of month; resulting fits closely paralleled those of models employing time-dependent intercepts. We calculated cumulative iron doses during the 1-, 3- or 6-month rolling windows before each month at risk (risk period) during the follow-up time for each patient and we defined covariates over a 3-month window prior to the iron exposure, as described earlier.

We fitted both unweighted (standard discrete-time proportional hazard models) and weighted (MSM) models. In unweighted models, we adjusted for baseline and time-varying covariates in sequential models. For MSM analyses, a first step was to develop the treatment weights. We calculated weights from the inverse of the probability that each subject belonged to the dosing category in which his or her own observed iron dose at each follow-up month fell [19]. We then fit discrete-time proportional hazards models (binomial regressions for event using complementary log-log link) incorporating these weights. Weights were truncated at 5 in primary analyses.

We developed nested sets of models (unweighted analyses) or treatment weights (MSM analyses) in which we sequentially considered covariates a priori to be associated with treatment. These included parameters reflective of anemia management (TSAT/ferritin, EPO dose, Hb, an interaction of TSAT/ferritin* Hb, baseline demographics [age, sex, race, ethnicity], baseline comorbidity, BMI, cause of ESRD, hemoglobinopathies, baseline iron dose and the year of dialysis initiation) parameters reflective of increased inflammation (albumin, creatinine, systolic blood pressure, post-dialysis body weight and change in post-dialysis body weight), and parameters reflective of increased risk of infection and lower Hb (recent infection and recent non-infectious hospitalization, vascular access) and treatment history (iron prior to exposure period).

Recurrent events models. To examine the effect of intravenous iron on the risk of recurrent hospitalizations, we constructed discrete time proportional hazards models for multiple hospitalizations mimicking the approach described by Andersen and Gill [20], by analyzing time to first hospitalization, time between first and second hospitalization, time between second and third hospitalization and so forth, within a single model incorporating repeated hospitalizations on individuals. By this approach, the risk set for the $\hat{j}$th hospitalization initially comprises individuals surviving a $(\hat{j}-1)$st hospitalization and evolves in the usual way thereafter until the person becomes at risk for the $(j+1)$st hospitalization. This secondary analysis assumed that risk factors for single and multiple hospitalizations are consistent; however, the baseline hazard function was allowed to vary with the hospitalization (first, second, etc.).

Verification of model assumptions. We performed model checks on the treatment model, the censoring model and the discrete time proportional hazards model for outcomes. All analyses used generalized estimating equations [21] to account for outcome clustering by dialysis facilities and robust standard errors to assure conservative inferences given the weighting. All statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). Statistical significance was defined as $P < 0.05$ using two-tailed tests. Multiple sensitivity analyses were performed to ensure that our findings were robust. A detailed description of our statistical analysis is provided in Supplementary data, Appendix SA.

RESULTS

Patient demographics and factors associated with increased iron

Between 2003 and 2008, 21 233 patients initiated hemodialysis at a DCI facility. Of these, 9544 had Medicare A and B as their primary source of health insurance and survived the first 120 days after hemodialysis initiation. These patients were then included in our analysis using the 1-month exposure cohort. We also constructed 3- and 6-month exposure cohorts, where the first days at risk were Days 181 and 271, respectively, and iron doses were allowed to accumulate over a longer time period.

In the 6-month exposure cohorts, 7416 patients were included (Figure 1). The average iron dose per patient in this cohort was 313.1 mg per month in the first 6 months of dialysis of the 6-month cohort and then decreased to 201.7 mg per month over the remaining follow-up time. At the end of follow-up in this cohort, 2284 patients had died, and 301 had received a kidney transplant.

Supplementary data, Table S1a and b and Table 1 describe the demographic and laboratory characteristics associated with increased intravenous iron dose among the 1-, 3- and 6-month intravenous iron exposure cohorts. Patients receiving the highest doses of intravenous iron tended to be younger, male and white. Diabetes was more common in patients receiving higher iron doses (>900 mg and >2100 mg/6 months),

Table 1. Patient characteristics by 6-month intravenous iron dose

	Total cohort	Intravenous iron dose (mg)				P-value[a]
		None	>0–900	>900–2100	>2100	
N	7416	539	1157	3587	2022	
Demographics						
Age in years (median)	65.53	65.00	67.00	66.00	64.00	<0.01
Sex (%)						0.02
Female	45.71	2.94	7.30	23.05	12.42	
Race (%)						<0.01
White	58.00	4.20	9.25	28.04	16.51	
Black	37.71	2.96	5.75	18.60	10.40	
Other	4.28	0.22	0.84	2.46	0.77	
Ethnicity (%)						0.05
Hispanic	5.27	0.30	0.93	2.83	1.20	
Non-Hispanic	94.73	7.08	14.91	46.27	26.48	
Cause of ESRD (%)						<0.01
Diabetes	48.23	3.24	7.57	23.27	14.14	
Hypertension	29.62	1.98	4.93	15.06	7.65	
Glomerulonephritis	7.98	0.63	1.33	3.70	2.33	
Other	14.17	1.52	2.01	7.08	3.56	
Baseline comorbidities						
Index[b]	4.00	4.00	4.00	4.00	4.00	<0.01
CHF (%)	43.09	3.27	6.75	20.22	12.85	<0.01
Diabetes (%)	62.40	4.19	9.47	30.57	18.17	<0.01
Hemoglobinopathy[c] (%)	4.13	0.55	0.63	1.79	1.16	<0.01
Ferritin (ng/mL) and TSAT (%) Combination						<0.01
Ferritin ≤500 and TSAT ≤20%						
Ferritin ≤500 and TSAT 21–30%	47.05	2.35	5.08	21.70	17.92	
Ferritin 501–800 and TSAT ≤20%	21.26	1.50	3.30	11.41	5.05	
Ferritin >800 regardless of TSAT	5.61	0.24	0.83	3.24	1.30	
Other	8.35	1.38	2.52	3.52	0.91	
Ferritin <500 and TSAT >30	8.80	0.86	2.20	4.52	1.23	
Ferritin >501–800 and TSAT >20	8.94	0.66	1.84	4.89	1.55	
Hb g/dL (%)						<0.01
<10	7.29	0.86	1.01	2.83	2.60	
10-Nov	10.51	0.91	1.34	4.45	3.81	
11-Dec	24.23	1.71	3.62	11.37	7.53	
>12	57.96	3.85	9.81	30.49	13.80	<0.01
Mean weekly epogen dose units /week (%)						
≤5000	18.12	1.86	4.53	9.37	2.37	
5000–12 000	19.31	1.46	3.54	10.63	3.68	
12 000–25 000	30.90	2.22	4.43	15.43	8.81	
>25000	31.67	1.65	3.35	13.81	12.86	
Vascular access (%)						
Arteriovenous fistula	17.69	1.24	2.52	9.12	4.82	<0.01
Arteriovenous graft	10.88	1.05	2.00	5.13	2.71	
Central venous catheter	71.42	4.87	11.25	35.04	20.25	
Serum albumin (g/dL) [b]	3.60	3.65	3.60	3.60	3.60	<0.01
Serum creatinine (mg/dL) [b]	6.10	6.40	6.15	6.10	6.10	0.6
Body mass index (kg/m^2)[b]	27.10	26.37	26.44	26.80	28.25	<0.01
Infection within past 21 days (%)	18.03	1.20	2.74	8.61	5.48	0.1
Non-infectious hospitalization within past 21 days (%)	8.01	0.74	1.16	3.67	2.44	0.08

Conversion factors for units: serum creatinine in mg/dL to μmol/L, x88.4.
[a]Comparison across subgroups of 6-month cumulative intravenous iron dose.
[b]Reported as median.
[c]Includes sickle cell, hereditary spherocytosis, myelodysplasia, multiple myeloma.

and hypertension was less common as the primary cause of ESRD in this population. Despite being younger, patients receiving more intravenous iron had a greater burden of comorbid conditions, but fewer had hemoglobinopathies. As would be expected, in the 1-month cohort, patients receiving the highest dose of iron were more than twice as likely to be iron deficient at the beginning of the study period (TSAT <20 and ferritin <500, -22 versus 9% in the lowest category). In addition, they were also more likely to have higher hemoglobins (>10 g/dL), but required significantly higher doses of ESA (15% required >25 000 units weekly versus 8% requiring <5000 units, respectively). Findings were similar in 3- and 6-month cohorts (Supplementary data, Table S1a and b, and Table 1).

Hospitalization events

Patients had 22 347 hospitalizations during the study period, with an average of 2.2 hospitalizations and median hospital stay of 5 days (IQR: 3–9; Table 2) per patient. Among all hospitalizations, 31% were attributed to cardiovascular causes while 23% were attributed to infectious causes.

Association of intravenous iron and hospitalization

Marginal structural models: time to first hospitalization. In our primary analysis using marginal structural models to control for time-dependent confounders (including recent hospitalizations and ESA dose), we observed no consistent association of intravenous iron dose level with patients' risks of first hospitalization among the 1-, 3- or 6-month cohorts when hospitalizations were considered alone or in the composite outcome combining hospitalizations or death (Table 3, and Supplementary data, Tables S4, S6a–c, and S7a–c). Intravenous iron dose level was also not associated with cardiovascular or infectious hospitalizations considered alone or in the composite outcome with death in the 1- or 3-month models. We observed a marginally statistically significant increased hazard for the composite outcome of infectious hospitalization or death among the 6-month cohort [HR 1.37 (95% CI 1.02–1.84) for >2100 mg of iron versus 900 mg over 6 months], but this was accompanied by a null finding for the outcome of all-cause hospitalization or death as well as cardiovascular hospitalization or death in the same models [HR 0.98 (95% CI 0.78–1.23) and 1.05 (0.81–1.36)]. Furthermore, we observed no association between intravenous iron dose and the risk of infectious events in models for the 1- and 3-month cohorts. [HR 0.91 (95% CI 0.77–1.09) and 1.08 (0.86–1.36), respectively].

Table 2. Hospitalizations events in study population

Category	1-month iron exposure	3-month iron exposure	6-month iron exposure
Total number of hospitalizations (*N*)	22 347	21 956	20 904
Hospitalizations per patient median (IQR)	1 (0–3)	2 (0–3)	2 (1–4)
Days per hospitalization Median (IQR)	5 (3–9)	5 (3–9)	5 (3–9)
Hospitalization categories			
Cardiovascular (%)	30.7	30.6	30.5
Infectious (%)	22.8	22.7	22.5
Other (%)	46.5	46.6	46.9

Multiple hospitalizations discrete time models

We did not observe a consistent association of intravenous iron with all-cause or cause-specific hospitalizations in the repeated events analysis (Table 4). This was unchanged when all hospitalizations were considered, or when the number of hospitalizations was censored to a maximum of 5 per patient. Among the 1-, 3- and 6-month cohorts, the association between intravenous iron and morbidity was strongest in the unadjusted analyses, but became increasingly attenuated after sequential adjustment (Supplementary data, Tables S8a–c). Among the 6-month cohort only, patients' receipt of the highest intravenous iron dose (>2100 mg/6 months) was associated with an increased risk for all-cause hospitalizations [HR 1.13 (95% CI: 1.04–1.24)] when compared with patients receiving <900 mg of iron over 6 months. However, this finding was not replicated in the 1- or 3-month cohorts, or in models examining the risk of cause-specific hospitalizations.

Sensitivity analyses

We conducted several sensitivity analyses to test the validity of our study findings. We tested multiple combinations of iron-dose categories, and categories for iron storage parameters (TSAT/ferritin) and found no differences in treatment effects. In addition, we performed sensitivity analyses on our marginal structural models. In these analyses, we truncated weights at thresholds of 3, 5, 10, 20 and 100. We did not

Table 3. Relationship of intravenous iron dose with time to first all-cause, cardiovascular and infectious hospitalization after accounting for time-dependent confounding - marginal structural modeling

	Doses (mg)	*n* (patient-months)	%	*N* (death)	*N* (hospitalization)	Any hospitalization[a] Hazard ratio (95% CI)	P-value	Cardiovascular hospitalization[a] Hazard ratio (95% CI)	P-value	Infectious hospitalization[b] Hazard ratio (95% CI)	P-value
1-month iron exposure	None	29 232	33.4	256	2187	0.93 (0.82, 1.06)	0.3	0.91 (0.71–1.16)	0.5	0.92 (0.76, 1.11)	0.4
	>0 to 150	17 122	19.5	126	1200	1 (ref)		1 (ref)		1 (ref)	
	>150 to 350	21 525	24.6	165	1648	0.95 (0.84, 1.08)	0.5	0.88 (0.73–1.06)	0.2	0.94 (0.77, 1.15)	0.6
	>350	19 759	22.6	168	1825	0.88 (0.79, 0.99)	0.03	1.03 (0.85, 1.26)	0.8	0.91 (0.77, 1.09)	0.3
3-month iron exposure	None	15 563	19.1	129	1047	0.84 (0.71, 1.00)	0.05	0.80 (0.57–1.12)	0.2	1.03 (0.81, 1.33)	0.8
	>0 to 450	21 038	25.9	129	1381	1 (ref)		1 (ref)		1 (ref)	
	450 to 1050	28 360	34.9	196	2151	0.92 (0.80, 1.07)	0.3	0.92 (0.76–1.11)	0.4	1.01 (0.81, 1.25)	0.9
	>1050	16 419	20.1	162	1513	0.88 (0.74, 1.03)	0.1	0.91 (0.73–1.14)	0.4	1.08 (0.86, 1.36)	0.5
6-month iron exposure	None	6605	9.1	48	399	0.87 (0.66, 1.15)	0.3	1.07 (0.75–1.52)	0.7	1.15 (0.79, 1.68)	0.5
	>0 to 900	22 489	31.1	117	1383	1 (ref)		1 (ref)		1 (ref)	
	>900 to 2100	34 227	47.3	238	2589	0.97 (0.83, 1.13)	0.7	1.19 (0.99–1.43)	0.07	0.94 (0.75, 1.19)	0.6
	>2100	9008	12.5	86	845	0.97 (0.77, 1.22)	0.8	0.97 (0.74–1.28)	0.8	1.26 (0.94, 1.69)	0.1

[a]The weighting on cumulative iron dose received is based on iron history, age, race, sex, ethnicity, baseline comorbidity, baseline BMI, primary cause of ESRD, year start dialysis, TSAT/ferritin, hemoglobin, weekly epogen dose, changes in EPO dose and interaction between TSAT/Ferritin and Hb, hemoglobinopathies, infection within past 21 days, compliance, albumin, creatinine, pre-dialysis SBP, post -dialysis weight, change in post-weight, vascular access type, baseline hospital days.
[b]Model is adjusted for all the covariates in all-cause and CVD hospitalizations models except recent infection.

Table 4. Relationship of intravenous iron dose with multiple all-cause, cardiovascular and infectious hospitalization after accounting for time-dependent confounding - marginal structural modeling-weighted Anderson–Gill models

	Doses (mg)	*n* (patient-months)	%	*N* (death)	*N* (hospitalization)	Any hospitalization[a] Hazard ratio (95% CI)	P-value	Cardiovascular hospitalization[a] Hazard ratio (95% CI)	P-value	Infectious hospitalization[b] Hazard ratio (95% CI)	P-value
1-month iron exposure	None	57 586	33.9	904	6223	1.00 (0.94, 1.06)	0.9	0.95 (0.83, 1.07)	0.4	1.08 (0.94, 1.23)	0.3
	>0 to 150	34 961	20.6	462	3598	1 (ref)		1 (ref)		1 (ref)	
	>150 to 350	40 711	23.9	539	4389	0.98 (0.92, 1.04)	0.5	0.97 (0.85, 1.11)	0.7	0.96 (0.82, 1.11)	0.6
	>350	36 498	21.5	495	4604	0.99 (0.73, 1.06)	0.7	0.95 (0.83, 1.09)	0.5	1.07 (0.92, 1.24)	0.4
3-month iron exposure	None	29 235	19.1	437	2962	0.98 (0.91, 1.05)	0.6	0.88 (0.76, 1.03)	0.1	1.11 (0.94, 1.32)	0.2
	>0 to 450	41 154	26.9	510	4105	1 (ref)		1 (ref)		1 (ref)	
	450 to 1050	52 940	34.6	670	5753	0.98 (0.91, 1.04)	0.5	0.97 (0.85, 1.10)	0.6	1.01 (0.87, 1.17)	0.9
	>1050	29 866	19.5	480	3906	1.03 (0.96, 1.11)	0.4	0.97 (0.84, 1.12)	0.7	1.13 (0.96, 1.34)	0.1
6-month iron exposure	None	11 879	9.0	185	1176	1.08 (0.95, 1.21)	0.2	1.09 (0.87, 1.36)	0.5	1.19 (0.93, 1.52)	0.2
	>0 to 900	41 635	31.6	495	3919	1 (ref)		1 (ref)		1 (ref)	
	>900 to 2100	61 925	47.0	822	6905	1.05 (0.99, 1.12)	0.1	1.12 (0.98, 1.29)	0.1	1.01 (0.86, 1.18)	0.9
	>2100	16 209	12.3	258	2199	1.13 (1.04, 1.24)	0.01	1.08 (0.90, 1.31)	0.4	1.09 (0.88, 1.35)	0.4

For all-cause models, we censored at the 5th hospitalization and for CVD and infectious models we censored at the 3rd hospitalization. All models include number of hospitalization as intercept, number of hospitalization and time interaction. All Anderson–Gill models adjusted for cluster effect of patients nested in clinics.

[a]The weighting on cumulative iron dose received is based on iron history, age, race, sex, ethnicity, baseline comorbidity, baseline BMI, primary cause of ESRD, year start dialysis, TSAT/Ferritin, hemoglobin, weekly epogen dose, changes in EPO dose and interaction between TSAT/Ferritin and Hb, hemoglobinopathies, infection within past 21 days, compliance, albumin, creatinine, pre-dialysis SBP, post-dialysis weight, change in post-weight, vascular access type, baseline hospital days.

[b]Model is adjusted for all the covariates in all-cause and CVD hospitalizations models except recent infection.

observe significant differences in treatment effects when weights were truncated at varying thresholds. We also performed a sensitivity analysis of the MSM models without censoring weights and found no difference in the findings. Finally, in an attempt to address potential survivor bias, we conducted sensitivity analyses with all the confounders defined within the intravenous iron exposure windows instead of before the exposure periods, and we used a shorter iron-treatment history (30 days) when creating the treatment weights. Again, we found that the results were similar to our primary analyses.

DISCUSSION

In this national study of patients receiving hemodialysis, we did not observe a consistent association between patients' intravenous iron dosing with their risks of all-cause, cardiovascular or infectious hospitalizations over a variety of time intervals. Findings were robust after accounting for multiple potential confounders of the potential association between intravenous iron dose and morbidity, including the presence of recent infection and the occurrence of recent hospitalizations. Given increasing concern over ESA use in patients on dialysis, our findings may provide clinicians and policy makers with the knowledge that currently employed strategies to manage anemia with intravenous iron are not associated with patients' risks of morbidity.

Our findings contrast with a similar recent study of prevalent dialysis patients receiving dialysis from 2004 to 2008, and a recent meta-analysis of randomized trials which compared intravenous iron to no iron/oral iron in all populations (dialysis/non-dialysis) [17, 22]. The dialysis investigators studied patterns of intravenous iron administration and intravenous iron dosing, and found that patients who received 400 mg of intravenous iron over 1 month were at an increased risk of infectious hospitalizations, when compared with those who received 125 mg over the same period. Similarly, the meta-analysis also found an increased risk of infection with intravenous iron when compared with no iron/oral iron. There are some important differences between our study and this prior observational study. First, the prior study investigated only infectious hospitalizations as the outcome of interest, and did not report data on all-cause hospitalizations. We did not observe an increase in the risk of all-cause, cardiovascular or infectious hospitalizations in our 1- and 3-month cohorts, but even in the 6-month cohort, where findings were nominally statistically significant, the hazard ratio for all-cause hospitalization was not statistically significant. Second, our study enrolled patients who survived at least 120 days after hemodialysis initiation. As such, our findings may be at less risk of being subject to survivor bias compared with previous investigation, which included prevalent patients who had to survive at least 9 months. Finally, we employed marginal structural models to account for time-dependent confounders, and we employed a recurrent events model to examine risks beyond the incident hospitalization. Although previous studies have used MSMs to determine the effect of iron on morbidity, our findings reflect recent practice patterns in an era where intravenous iron is increasingly used at higher doses to manage anemia in dialysis patients, while ESA use is being curtailed [23–25]. For example, to our knowledge, none of the prior studies that employed MSMs evaluated the association of intravenous iron doses higher than 20004 mg over 6 months with outcomes, and studies did not include populations with relatively replete iron stores. In addition, although the previous meta-analysis found an association of intravenous iron and infection, no change in serious adverse mortality was found, and no dose–response relationship was detected. These findings also suggest that the elevated infection risk associated with intravenous iron may be inconclusive, and subject to multiple potential confounders.

In our study, we used several complimentary statistical approaches and examined multiple time windows for the exposure of intravenous iron to demonstrate the robustness of our findings. The marginal structural modeling approach mimics a design in which individuals are re-randomized to iron treatments monthly and models are fitted on this basis. Our primary analysis mimics a study design in which individuals are re-randomized after every 30-day period, and seeks to determine the relation between cumulative iron prescribed by the end of a given exposure interval and hospitalization/death within the next 30 days. However, it then may be used to evaluate longer-term effects by defining covariates aggregating iron doses over a longer-term history. As such, our findings suggest that even the administration of >2100 mg of iron over a 6-month period does not increase patients' risk of all-cause or cardiovascular hospitalizations. We also employed a recurrent events model to facilitate comparisons with the existing literature. Our null finding for any association of intravenous iron with cardiovascular hospitalization is consistent with recent studies in a large prevalent dialysis population, and further supports our conclusions. We did observe a trend towards lower risks of all-cause cardiovascular hospitalizations with the receipt of iron in our 1- and 3-month cohorts. However, this finding should also be interpreted with caution, as it is subject to bias from multiple testing and lacks a dose response relationship.

Limitations of our study should be noted. First, we studied incident patients who received dialysis at a single, medium sized, national not-for-profit dialysis provider from 2003 to 2008. Anemia management strategies, including the use of intravenous iron, might differ for DCI compared with other dialysis providers. Anemia management may also have changed since the time period of our study. For instance, our outcome definition required linkages with Medicare claims data, and lag times for these linkages made a study of the association of intravenous iron with outcomes after implementation of CMS bundled payment regulations for dialysis services impossible at the time of this investigation [26]. Nevertheless, while our study period preceded CMS policies, intravenous iron use had begun to increase in the United States as early as 2004 [3]. Updated analyses may be needed to better assess the association of intravenous iron dosing with outcomes since these recent policy changes. Also, despite the use of robust methods for causal inference and adjustment for time-dependent confounding, our study was observational in design, and may be susceptible to residual confounding by indication. Randomized controlled trials with adjudicated events and long follow-up are needed to provide the most robust evidence of intravenous iron safety. Finally, our primary analysis used history of iron exposure and defined covariates in the 90–180-day period prior to the window of interest. As such, patients needed to have survived 120, 180 and 270 days to be included in our 1-, 3- and 6-month cohorts. Although we found similar results in sensitivity analyses that allowed time at risk to begin at 90 days, our findings remain at risk for potential survivor bias (i.e. that patients surviving long enough to receive intravenous iron for longer periods may be different from those not surviving as long).

In conclusion, we found no consistent association between intravenous iron dose and patients' risks for all-cause, cardiovascular or infectious hospitalizations, even among patients receiving iron doses exceeding 2100 mg over a period of 6 months. These findings suggest higher doses of intravenous iron prescribed in the course of routine anemia management of hemodialysis patients may not be associated with considerable harm. However, to further support findings from this observational study, rigorously performed randomized controlled trials are needed to provide definitive evidence of iron safety.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

AUTHORS' CONTRIBUTIONS

N.T., D.M., K.B.R. and L.E.B. participated in the study design, statistical analysis, manuscript preparation and final approval of the work. W.M., D.C., B.J., P.E., J.S., S.S., T.S. and K.M. participated in study design and edited the manuscript for content. J.Z., A.M. and K.B.R. performed statistical analysis. N.T. takes primary responsibility for the manuscript.

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CONFLICT OF INTEREST STATEMENT

N.T. has attended medical advisory board meetings held by Takeda Inc. Takeda licenses ferumoxytol (an intravenous iron formulation) for use in patients with CKD. AHRQ Disclosure: identifiable information, on which this report, presentation or other form of disclosure is based, is confidential and protected by federal law, Section 903(c) of the Public Health Service Act, 42 USC 299a-1(c). Any identifiable information that is knowingly disclosed is disclosed solely for the purpose for which it has been supplied. No identifiable information about any individual supplying the information or described in it will be knowingly disclosed except with the prior consent of that individual. The authors declare that they have no competing interests. USRDS Disclosure: the data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

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