APPENDIX

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SUPPLEMENTAL METHODS

Study Population

We excluded patients who recovered kidney function within 90 days of starting dialysis, started on a modality other than in-center HD, or when there was a difference of >60 days between the dialysis start date recorded in DCI and the USRDS.

Intravenous Iron Exposure

If a patient received a dialysis treatment and no iron was recorded, we considered the dose to be 0 mg. If the patient missed greater than 30 days of treatments at DCI (N=1,071 observations; 0.3%), we used information from the USRDS (where iron dose is recorded monthly), as IV iron received at facilities other than DCI could have been recorded here. To combine iron data from the USRDS to the DCI data, we converted monthly IV iron dose data from USRDS to daily doses and matched to the analytic iron exposure windows. We assumed patients who were hospitalized for less than 30 days did not receive iron. We censored patients who were absent from DCI for > 90 consecutive days as the IV iron dose during their absence was unknown.

Iron Dose Categorization: Patients receiving "No Iron" comprised over one-third of the 1-month cohort. Among the remaining group, we attempted to achieve a reasonably well-distributed categorization of iron which we felt also reflected lower, moderate, and higher iron doses observed in clinical practice. For the one month model, the categories were: no iron (0 mg), low dose IV iron (>0mg to 150 mg), moderate dose IV iron (>150mg to 350 mg), and high dose IV iron (>350 mg). The 3-month and 6-month dose level categories were multiples of the corresponding 1-month level (e.g., iron dose for level 2 of the 3-month iron dose was 3 times the dose of level 2 of the 1-month iron dose).

Definition of Confounders:

Baseline Demographics and Comorbidity

We ascertained patient demographics, date of dialysis initiation, and cause of ESRD from the USRDS Center for Medicare Services Form 2728 and DCI.

Time Dependent Confounders:

EPO

More than 99% of the ESA administered during the study period was EPO; patient observations during which other ESAs were used were excluded. Change in weekly EPO dose was calculated as the difference of the average weekly dose between 0 to -30 days and -30 to -60 days prior to the exposure window.

TSat and Ferritin

Missing Data When a value for percent saturation of transferrin was unavailable in DCI, we defined TSat as serum iron/ TIBC *100 or if this was unavailable, as iron/transferrin*70.9. In the case when TSAT and Ferritin were missing in the 90-days prior to the iron exposure window, we carried forward values from the previous 135 to 91 days. When TSAT and Ferritin were still missing (i.e., not available during the previous 135 to 91 days before exposure), we imputed values (imputation described below). TSAT and Ferritin were missing individually 2% and 0.96% for 1-month models, 2% and 0.90% for 3-month models, and 2% and 0.64% for 6 month models. The combined TSAT-Ferritin variable was missing 2.53%, 2.49%, and 2.26% in the 1-month, 3-month, and 6-month models, respectively.

Rationale Behind Categories of TSat and Ferritin: The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) Clinical Practice Guidelines during the time period over which these data were collected, recommended administering IV iron to target a serum Ferritin > 200 ng/mL and TSat >20% and to avoid routinely administering IV iron at serum Ferritin > 500 ng/mL [30].

In clinical practice, IV iron is increasingly being used in patients at serum ferritin >200 and even 500 ng/mL and when TSAT is > 20%, reflecting variation from guidelines. We created a 5-level category to attempt to capture the variation in clinical practice around iron prescribing. The categories were as follows: Ferritin <500 and TSat<20% (probably iron deficient); Ferritin <500 and TSat 21-30% (probably iron deficient); Ferritin 501-800 and TSat <20% (possibly iron replete); and Ferritin >800 regardless of TSat (possibly iron overloaded). We also implemented an “Other” category, reflecting patients who were probably iron replete (i.e., Ferritin <500 and TSat >30 or Ferritin 501-800 and TSat >20).

Other Variables

We used the Hemoglobin (Hb), serum albumin and serum creatinine values closest to, but not more than 45 days prior to the start of the iron exposure window. We created a time-varying condition, 'Hemoglobinopathy', which included a group of conditions (Appendix A) that cause anemia independently of iron or EPO deficiency. Post-dialysis weight and pre-dialysis sitting systolic blood pressure (SBP) were averaged over the 2 weeks prior to the iron exposure window. Change in these variables was defined as the difference in their respective averages between 0 to -30 days and -60 to -90 days prior to the exposure.

Conditions Included in Hemoglobinopathy Variable (Conditions causing anemia independent of EPO and iron deficiency): Defined at baseline from the Cause of ESRD on CMS Form 2728 (hereditary hemolytic anemia: 282,69; sickle cell/sickle cell trait, 282.60; multiple myeloma, 203.00) and every 30 days using ICD9 codes from inpatient and outpatient claims for hemolytic anemia (282.9), sickle cell anemia (282.60), and myelodysplasia (238.7), thalassemia (282.4, 282.41, 282.42, 282.49), and multiple myeloma (203.00, 203.10, 203.90).

ICD9 and HCPCS Codes defining Infectious Events

Infection was ascertained using data from the Dialysis Clinic, Inc. clinical database and data from the United States Renal Data System (USRDS) in the following manner:

(1) IV Antibiotic Use:

An infectious event was defined as use of an IV antibiotic for $\geq$ 2 days. Multiple infectious events occurring within 1 – 6 days of each other were considered one infectious event.

Using prescription medication data from the DCI clinical database, we identified IV antibiotic prescriptions using Generic Product Index (GPI) codes (GPI category codes 01 [Anti-infective Agents] and 08 [Genitourinary Products]) with intravenous (IV) mode of delivery to identify prescriptions for IV antibiotics.

Using inpatient and outpatient claims data from the USRDS, we identified Health Care Common Procedure Coding System (HCPCS) Level II J-Codes for intravenous antibiotics (J0120, J0133, J0200, J0278, J0285, J0287, J0288-J0290, J0295, J0348, J0390 ,J0456, J0530, J0540, J0550, J0559, J0560, J0570, J0580, J0637, J0690, J0692, J0694, J0696-J0698, J0710, J0713, J0715, J0720, J0740, J0744, J0850, J0878, J1335, J1364, J1450, J1455, J1565, J1570, J1580, J1590, J1835, J1840, J1850, J1890, J1956, J2010, J2020, J2185, J2248, J2280, J2460, J2510, J2540,

J2543, J2545, J2700, J3000, J3243, J3260, J3320, J3370, J3465, J3485, J7310, J7676, J7682, J7685).

(2) Infectious Hospitalization:

Infectious hospitalizations were identified International Classification of Diseases, version 9 (ICD-9) for hospitalizations (**Table 1**) using inpatient and outpatient claims data from the USRDS as well as episodes of hospitalization in the DCI clinical database.

Table 1. International Classification of Diseases (ICD) 9 Codes used for assignment of Infectious Hospitalizations

Definition or Term	ICD-9 CM Primary Diagnosis Codes
Sepsis	038, 790.7
Access related infection	996.62, 567, 996.68, 999.31
Endocarditis	036.42, 421
Respiratory Tract Infection	011, 012, 033, 034, 460-466, 473, 480-488, 490, 513, 491.1, 494, 510-511, 513.0, 518.6, 519.01,
Skin/bone/joint infections	015, 035, 036.82, 730, 680-686.9, 711, 996.66, 996.67, 706.0
Gastrointestinal lumen infections	001, 002, 003,004, 005, 006, 007, 008, 009, 567, 014, 569.5
Central nervous system infections	036.0, 036.1, 036.2, 047, 049, 320, 324, 013, 036.81, 045-049, 062, 063, 064, 320-326
Fungal infections	112, 117
Genitourinary infections	016, 590-590.9, 595-595.4, 597-597.89, 598.0, 599.0, 601-601.9, 604-604.9, 607.1, 607.2, 608.0, 608.4, 614-616.1, 616.3-616.4, 616.8, 670, 996.64, 996.65,
Other	010, 017, 018, 020-027, 030, 031, 032, 036.3, 036.4,036.40, 036.41, 036.43, 036.89, 036.9, 037, 039, 040, 041, 042, 050-059, 060, 061, 065, 066, 070-079, 080-088, 090-099,100-139, 254.1, 331.81, 372-372.39, 373.0-373.2, 388.60, 382-382.4, 383.0, 386.33, 386.35, 390-393, 422.0, 422.91-422.93, 472-474.0, 475-476.1, 478.21-478.24, 478.29, 522.5, 522.7, 527.3, 528.3, 540-542, 566, 572-572.1, 573.1-573.3, 575-575.12, 611.0, 790.8, 996.60, 996.61, 996.63, 996.69, 997.62, 998.5, 999.3

STATISTICAL ANALYSES

We compared differences in baseline characteristics of patients across categories of iron exposures in unadjusted analyses using chi-square tests and ANOVA.

Marginal Structural Models

MSM analyses account for time-varying confounding and are designed to produce unbiased estimates of the causal mortality rate ratio across treatments (that is, per treatment pairing, a ratio comparing a population's mortality rate when all its members receive a given treatment to the rate when all its members receive another given treatment). The analysis envisions a study in which individuals are successively randomized to treatment categories in each month, and it estimates, say, the next-monthly relative mortality risk between treatment groups under these circumstances. Accounting for the 90-day time window to define time-varying predictors for the 1,-3 and 6- month exposure windows, patients had to survive for a minimum of 120, 180, and 270 days to contribute to the 1-, 3- and 6- month models of iron exposure, respectively **(Figure 1, Appendix).**

Weights were constructed as per Hernan et al[31], with the denominator defined as the cumulatively multiplied predicted probabilities of being on one's observed profile as a function of past treatment and time-varying covariates over intervals up to that defining each current risk set, and the numerator defined analogously as cumulatively multiplied predicted probabilities of being on one's observed profile as function of past treatment. Time-varying confounders used to develop weights comprised 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).

Weights were stabilized by including time-invariant demographic factors (age, sex, race, ethnicity, cause of ESRD, BMI, baseline comorbidity, year start dialysis, and baseline iron doses) in models used to produce both numerator and denominator predictions. Analogous "censoring" weights were also developed, using a procedure identical to that just described except that logistic regression was used to develop predictions of the probability of censoring in an interval. The product of the treatment and censoring weights for each patient in each interval represented the final weights for the MSM. Supplementary Appendix B Table 4 displays the distribution of weights for all models. In outcome models time was modeled as a linear, quartic, cubic and quartic function of monthResulting fits closely paralleled those of models employing time-varying intercepts.

Discrete-time survival models. In addition to MSM analyses we also fitted traditional (unweighted) discrete-time survival models of treatment associations with mortality. Provision of these aimed to supply a comparator for findings preceding the advent of MSM in the ESRD literature, develop inferences on descriptive associations between treatment as it arises in practice and mortality outcomes, and facilitate model checking. To evaluate observational confounding in these models, covariates were added sequentially beginning with time-invariant demographic characteristics and then augmenting cumulatively to include time-varying (i) measures of case-mix and inflammation (hemoglobinpathies, serum albumin, serum creatinine, pre-dialysis systolic BP, post-dialysis weight, change in post dialysis weight), (ii) infectious risk (time varying vascular access type, non-infectious hospitalization within past 21 days, infection within past 21 days), and (iii) iron stores and anemia management parameters (TSAT/Ferritin, Hemoglobin, Weekly Epogen Dose, Changes in Epogen Dose). Global Wald statistics were constructed to test the null hypothesis of no mortality differences across iron dose categories.

Model checks. For MSMs we performed model checks on the treatment model, the censoring model, and the discrete time proportional hazard model for outcomes. We also performed model checks

on the traditional (unweighted) discrete-time survival models. Plots of Pearson residuals versus predicted values, Pearson residuals versus covariate values, and record-wise added variable plots were produced. Spline terms were incorporated to accommodate nonlinear associations for albumin (at 3 g/dL), pre-dialysis systolic blood pressure (at 120 mmHg and 160 mmHg), and change in weight (at -3 kg, 0 kg, and 3 kg). We evaluated the assumption of proportional hazards by adding interactions between time and treatment to primary models. These interactions were found to be not significant, consistent with no strong violation of our proportional hazards modeling assumption.

Methodology for Imputation of Missing Values

We multiply imputed records missing data on albumin (N=5,406, 2.0%), serum creatinine (N=6,744, 2.6%), post dialysis weight (N=2,644, 1.0%), pre-dialysis sitting blood pressure (N=2,506, 0.9%), Ferritin (N=2,539, 1.0%), TSAT (N=5,499, 2.1%), hemoglobin (N=2,870, 1.1%), primary cause of ESRD (N=8, 0.003%), vascular access (N=306, 0.1%), EPO (N=16,164, 6.1%), and iron (N=6,004, 1.8%). The variables included in our data and used for imputation of the missing covariates included non-missing covariates including age, gender, ethnicity, baseline comorbidity index, baseline BMI, baseline 90-day cumulative iron, hemoglobinopathies, infection, non-infectious hospitalization, race, and year of dialysis initiation.

We used the sequential regression multivariate imputation (SRMI) approach to impute missing values using IVEware (http://www.isr.umich.edu/src/smp/ive/). In imputing the missing values, we performed 10 iterations creating 5 imputed data sets.

Each conditional regression was based on one of the following models:

1. A normal linear regression model on a suitable scale if the covariate was continuous (e.g., albumin, creatinine, post-dialysis weight, pre-dialysis sitting systolic blood pressure, ferritin, TSAT, and hemoglobin, baseline comorbidity index);
2. A logistic regression model if covariate was binary (e.g., gender, ethnicity, infection, non-infectious hospitalization);
3. A polytomous or generalized logit regression model if covariate is categorical (e.g., race, primary cause of ESRD; vascular access, year initiated dialysis);
5. A two stage model where zero on zero status is imputed using logistic regression, and conditional on nonzero status, a normal linear regression model is used to impute nonzero values, if variable is mixed (e.g., EPO, iron).

We evaluated the success of the imputation by randomly selecting 100 cases with complete observations and set them to missing. We then imputed the whole data set and compared the observed values to the within-person means of imputed values. A correlation of 0.788 was observed, and an associated scatter plot revealed a tight relationship. We transformed the non-normal data to achieve normality before imputation and then after the imputation we transformed them back again.

Reference: Raghunathan TE, Lepkowski JM, Van Howeyk J, Soleberger P. A Multivariate Technique for Multiply Imputing Missing Values Using a Sequence of Regression Models. Survey Method, 2001, 27(1):85-95

SUPPLEMENTARY TABLES

Table 1: Characteristics of Cohorts Used in Analyses of 1-, 3 and 6- month IV Iron Dose

	Cohort for 1-month IV Iron Analysis	Cohort for 3-month IV Iron Analysis	Cohort for 6-month IV Iron Analysis
n	14,078	12,646	10,899
Demographics			
Age in years (median)	64.0	63.0	63.0
Sex (%)			
Female	44.9	45.1	45.1
Race (%)			
White	60.2	59.2	58.2
Black	35.6	36.4	37.3
Other	4.3	4.4	4.5
Ethnicity (%)			
Hispanic	5.6	5.7	5.7
Non-Hispanic	94.5	94.3	94.3
Cause of ESRD (%)			
Diabetes	47.7	48.2	48.8
Hypertension	27.7	27.7	27.8
Glomerulonephritis	9.1	9.1	8.9
Other	15.5	15.0	14.6
Baseline Comorbidities			
Index ^	4.0 (1.0, 6.0)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)
CHF (%)	40.5	39.8	39.4
Diabetes (%)	61.4	61.6	62.1
Hemoglobinopathy[&] **(%)**	3.6	3.4	3.2
Ferritin (ng/ml) and TSat (%) Combination			
Ferritin ≤500 and TSat ≤20%	46.7	46.8	46.9
Ferritin ≤500 and TSat 21-30%	20.8	21.2	21.7
Ferritin 501-800 and TSat ≤20%	5.7	5.6	5.4
Ferritin >800 regardless of TSat	8.6	8.2	7.9
Other	18.2	18.2	18.1
Ferritin < 500 and TSat > 30	8.7	8.8	8.8
Ferritin > 501-800 and TSat > 20	9.5	9.4	9.3
Hb g/dL (%)			
≤10	7.8	7.5	7.3
10.1-11	11.3	11.2	10.9
11.1-12	24.1	24.1	24.3
>12	56.7	57.2	57.6
Mean Weekly Epogen Dose units /week (%)			
≤5000	18.3	18.4	18.2
5001-12000	18.7	18.9	28.9

12001-25000	30.2	30.4	32.1
>25000	32.8	32.4	20.8
Vascular Access (%)			
Arteriovenous Fistula	17.7	18.4	18.7
Arteriovenous Graft	9.4	9.7	10.2
Central Venous Catheter	72.9	71.9	71.1
Serum Albumin (g/dL) ^	3.6 (3.3, 3.9)	3.6 (3.3, 3.9)	3.6 (3.4, 3.9)
Serum creatinine (g/dL) ^	6.1 (4.6,8.1)	6.2 (4.6,8.1)	6.2 (4.7,8.2)
Body Mass Index (kg/m^2)^	27.2 (23.1,32.6)	27.2 (23.2,C32.7)	27.3 (23.4,32.8)
Infection within past 21 days (%)	19.1	18.1	17.4
Non-infectious hospitalization within past 21 days (%)	6.5	6.1	5.8
Iron (mg) over the past 3 months ^	1000 (300, 1600)	1000 (300, 1600)	1000 (250, 1550)

Table 2: Patient Characteristics According to 3-Month Intravenous Iron Dose

		IV Iron Dose (mg)				
	Total Cohort	**None**	**>0 to 450**	**>450 to 1050**	**>1050**	**p-value[#]**
n	12,646	2082	1634	3859	4916	
Demographics						
Age in years (median)	63.0	63.0	64.0	64.0	63.0	0.007
Sex (%)						0.08
Female	45.1	44.0	43.8	46.7	44.7	
Race (%)						
White	59.2	58.1	59.4	58.4	60.3	0.10
Black	36.4	37.7	35.3	36.9	35.8	
Other	4.4	4.3	5.3	4.7	3.9	
Ethnicity (%)						
Hispanic	5.7	5.5	6.6	6.3	5.0	0.02
Non-Hispanic	94.3	94.5	93.5	93.7	95.0	
Cause of ESRD (%)						
Diabetes	48.2	44.6	45.7	48.7	50.1	
Hypertension	27.7	27.3	27.6	28.8	27.0	< 0.0001
Glomerulonephritis	9.1	9.9	10.4	8.6	8.8	
Other	15.0	18.3	16.3	13.8	14.2	
Baseline Comorbidities						
Index [^]	3.0 (1.0, 6.0)	4.0 (1.0, 6.0)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)	4.0 (1.0, 6.0)	0.0004
CHF (%)	39.8	41.2	36.2	38.6	41.3	0.0006
Diabetes (%)	61.6	56.6	58.9	62.0	64.3	<0.0001
Hemoglobinopathy[&] (%)	3.4	5.4	2.8	2.9	3.0	< 0.0001
Ferritin (ng/ml) and TSat (%) Combination						
Ferritin ≤500 and TSat ≤20%	46.8	33.2	26.1	41.9	62.9	
Ferritin ≤500 and TSat 21-30%	21.2	22.7	21.6	24.2	18.2	
Ferritin 501-800 and TSat ≤20%	5.6	3.5	6.5	5.7	6.1	
Ferritin >800 regardless of TSat	8.2	17.8	16.0	6.8	2.9	< 0.0001
Other	18.2	22.8	29.9	21.4	9.9	
Ferritin < 500 and TSat > 30	8.8	12.4	14.6	10.2	4.3	
Ferritin > 501-800 and TSat > 20	9.4	10.5	15.3	11.2	5.6	
Hb g/dL (%)						< 0.0001
≤10	7.5	10.7	5.9	6.2	7.7	
10.1-11	11.2	12.8	10.4	9.6	12.0	
11.1-12	24.1	24.3	22.5	23.5	25.0	
>12	57.2	52.2	61.2	60.7	55.4	

Mean Weekly Epogen Dose units /week (%)						< 0.0001
≤5000	18.4	25.5	27.5	19.8	11.5	
5001-12000	18.9	20.0	24.9	21.6	14.4	
12001-25000	30.4	28.2	26.9	30.3	32.5	
>25000	32.4	26.3	20.7	28.3	41.7	
Vascular Access (%)						
Arteriovenous Fistula	18.4	15.9	18.9	18.5	19.1	0.007
Arteriovenous Graft	9.7	11.4	9.2	9.9	9.1	
Central Venous Catheter	71.9	72.7	71.9	71.6	71.8	
Serum Albumin (g/dL) ^	3.6 (3.3, 3.9)	3.6 (3.3, 3.9)	3.6 (3.3, 3.9)	3.6 (3.4, 3.9)	3.6 (3.3, 3.9)	0.10
Serum creatinine (g/dL) ^	6.2 (4.6, 8.1)	6.2 (4.6, 8.2)	6.3 (4.4, 8.2)	6.2 (4.6, 8.1)	6.1 (4.6, 8.1)	0.54
Body Mass Index (kg/m^2)^	27.2 (23.2, 32.7)	26.6 (22.7, 31.7)	26.4 (22.7, 31.3)	26.9 (23.2, 32.3)	28.1 (23.8, 33.7)	< 0.0001
Infection within past 21 days (%)	18.1	18.4	17.9	18.5	17.8	0.8344
Non-infectious hospitalization within past 21 days (%)	6.1	6.8	6.2	5.8	6.0	0.5183
Iron (mg) over the prior 3 months ^	1000 (300, 1600)	0 (0, 0)	1000 (125, 1200)	1100 (550, 1500)	1400 (1000, 1900)	<0.0001

^ Median and IQR

& Includes sickle cell, myelodysplasia, multiple myeloma, and other causes of anemia not due to erythropoietin or iron deficiency

Comparison across subgroups of 3-month cumulative IV iron dose

Table 3: Patient Characteristics According to 6-Month Intravenous Iron Dose

		IV Iron Dose (mg)				
	Total Cohort	**None**	**>0 to 900**	**>900 to 2100**	**>2100**	**p-value[#]**
n	10,899	796	1,700	5,180	3,032	
Demographics						
Age in years (median)	63.0	62.5	65.0	64.0	62.0	< 0.0001
Sex (%)						
Female	45.1	42.1	45.2	45.9	44.5	0.17
Race (%)						
White	58.2	56.7	58.2	57.4	59.9	< 0.0001
Black	37.3	39.9	36.4	37.2	37.3	
Other	4.5	3.4	5.4	5.4	2.7	
Ethnicity (%)						
Hispanic	5.7	4.7	6.8	6.4	4.2	< 0.0001
Non-Hispanic	94.3	95.4	93.2	93.6	95.8	
Cause of ESRD (%)						
Diabetes	48.8	44.1	47.0	48.3	51.8	
Hypertension	27.8	26.6	29.3	28.6	25.9	< 0.0001
Glomerulonephritis	8.9	9.7	9.4	8.4	9.2	
Other	14.6	19.6	14.3	14.8	13.1	
Baseline Comorbidities						
Index [^]	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)	4.0 (1.0, 7.0)	< 0.0001
CHF (%)	39.4	38.2	38.9	37.6	43.0	<0.0001
Diabetes (%)	62.1	55.0	59.8	61.9	65.6	<0.0001
Hemoglobinopathy[&] (%)	3.2	6.2	3.3	2.9	2.9	< 0.0001
Ferritin (ng/ml) and TSat (%) Combination						
Ferritin ≤500 and TSat ≤20%	46.9	33.1	31.6	43.7	64.1	
Ferritin ≤500 and TSat 21-30%	21.7	22.3	21.3	23.8	18.2	
Ferritin 501-800 and TSat ≤20%	5.4	3.3	5.6	6.2	4.6	
Ferritin >800 regardless of TSat	7.9	19.5	15.5	6.8	2.8	
Other	18.1	21.7	25.9	19.5	10.3	< 0.0001
Ferritin < 500 and TSat > 30	8.8	12.4	13.1	9.3	4.7	
Ferritin > 501-800 and TSat > 20	9.3	9.3	12.8	10.3	5.6	

Hb g/dL (%)						
≤10	7.3	11.6	5.5	5.9	9.6	
10.1-11	10.9	12.1	9.3	9.5	13.8	< 0.0001
11.1-12	24.3	24.1	22.8	23.4	26.5	
>12	57.6	52.2	62.4	61.2	50.1	
Mean Weekly Epogen Dose units /week (%)						
≤5000	18.2	30.1	24.6	16.9	9.9	
5000-12000	28.9	29.8	33.2	30.1	19.8	< 0.0001
12000-25000	32.1	24.5	29.1	33.9	33.7	
>25000	20.8	15.6	13.1	19.0	36.7	
Vascular Access (%)						
Arteriovenous Fistula	18.7	18.2	17.9	19.5	18.1	
Arteriovenous Graft	10.2	11.3	11.3	10.5	8.8	0.01
Central Venous Catheter	71.1	70.5	70.8	70.0	73.1	
Serum Albumin (g/dL) ^	3.6 (3.4, 3.9)	3.6 (3.4, 3.9)	3.7 (3.4, 3.9)	3.7 (3.4, 3.9)	3.6 (3.3, 3.9)	0.0006
Serum creatinine (g/dL) ^	6.2 (4.7, 8.2)	6.4 (4.7, 8.2)	6.2 (4.7, 8.2)	6.2 (4.7, 8.2)	6.2 (4.7, 8.3)	0.98
Body Mass Index (kg/m^2)^	27.3 (23.4, 32.8)	26.4 (22.5, 32.1)	26.7 (22.7, 31.4)	27.0 (23.1, 32.4)	28.6 (24.2, 34.5)	< 0.0001
Infection within past 21 days (%)	17.4	14.9	17.1	16.9	19.1	0.01
Non-infectious hospitalization within past 21 days (%)	5.8	7.4	5.2	5.5	6.3	0.06
Baseline iron ^	1000 (250, 1550)	0 (0, 0)	500 (0, 1200)	1050 (500, 1500)	1400 (950, 1900)	<.0001

^ Median and IQR

& Includes sickle cell, myelodysplasia, multiple myeloma, and other causes of anemia not due to erythropoietin or iron deficiency

Comparison across subgroups of 6-month cumulative IV iron dose

Table 4. Sensitivity Analysis (CVD with and without Lag): Marginal Structural Model Analysis of IV Iron dose with Time to Cardiovascular Death: Original Iron Categories

			With 30-Day Lag				Without 30-Day Lag			
		Doses (mg)	**n (patient-months)**	**%**	**CVD Mortality With 30-Day Lag**	**P-value[&]**	**n (patient-months)**	**%**	**CVD Mortality Without 30-Day Lag**	**P-value[&]**
Original Iron Categories					Hazard Ratio (95% CI)					
	One Month Iron Exposure	**None**	85,526	34.16	1.11 (0.84, 1.48)	0.66	90,178	34.32	0.97 (0.76, 1.24)	0.06
		>0 to 150	50,123	20.02	Reference		53,302	20.16	Reference	
		>150 to 350	60,279	24.08	1.08 (0.80, 1.44)		63,327	23.96	0.73 (0.55, 0.96)	
		>350	54,435	21.74	0.95 (0.70, 1.29)		56,993	21.56	0.76 (0.56, 1.03)	
	Three Month Iron Exposure	**None**	43,165	19.30	1.06 (0.72, 1.54)	0.49	45,247	19.17	1.21 (0.87, 1.67)	0.66
		>0 to 450	58,773	26.29	Reference		60,407	25.59	Reference	
		450 to 1050	77,537	34.68	0.87 (0.67, 1.14)		81,396	34.48	0.99 (0.74, 1.35)	
		>1050	44,122	19.73	1.02 (0.74, 1.41)		49,038	20.77	1.03 (0.73, 1.46)	
	Six Month Iron Exposure	**None**	17,531	9.18	1.46 (0.98, 2.16)	0.28	18,555	9.19	1.67 (1.14, 2.46)	0.08
		>0 to 900	59,257	31.03	Reference		62,845	31.14	Reference	
		>900 to 2100	90,045	47.16	1.15 (0.85, 1.56)		95,058	47.10	1.25 (0.91, 1.71)	
		>2100	24,110	12.63	1.17 (0.76, 1.79)		25,375	12.57	1.18 (0.74, 1.87)	

The weighting on cumulative iron doses received was based on iron history, age, sex, race, ethnicity, baseline comorbidity at 90 days, baseline BMI, cause of ESRD, year start dialysis, baseline iron doses, hemoglobinopathies, TSAT/Ferritin categories, hemoglobin categories, weekly EPO doses categories, change in EPO, interaction of TSAT/Ferritin categories and hemoglobin categories, albumin, creatinine, pre-dialysis systolic blood pressure, body weight, change in weight, vascular access type, non-infectious hospitalization and infection. Baseline comorbidity and demographics were included in the outcome models.

[&] Global tests of iron exposure

Table 5: Discrete-time Proportional Hazards Analysis of IV Iron dose with Time to All-Cause, Cardiovascular and Infectious Death

	Doses (mg)	n (patient-months)	%	All-Cause Mortality	P-value	Cardiovascular Mortality	P-value	Infectious Mortality ^	P-value
				Hazard Ratio (95% CI)		Hazard Ratio (95% CI)		**Hazard Ratio (95% CI)**	
One Month Iron Exposure	**None**	90,178	34.32	1.02 (0.93, 1.12)	0.65	1.03 (0.91, 1.17)	0.63	0.94 (0.73, 1.20)	0.59
	>0 to 150	53,302	20.16	Reference		Reference		Reference	
	>150 to 350	63,327	23.96	0.86 (0.78, 0.95)	0.003	0.96 (0.83, 1.11)	0.60	0.69 (0.50, 0.94)	0.02
	>350	56,993	21.56	0.77 (0.69, 0.85)	<0.01	0.82 (0.70, 0.96)	0.01	0.81 (0.59, 1.11)	0.18
Three Month Iron Exposure	**None**	45,247	19.17	1.09 (0.98, 1.21)	0.11	1.05 (0.91, 1.20)	0.55	1.16 (0.86, 1.58)	0.32
	>0 to 450	60,407	25.59	Reference		Reference		Reference	
	450 to 1050	81,396	34.48	0.91 (0.82, 1.00)	0.05	0.93 (0.80, 1.07)	0.30	0.88 (0.66, 1.17)	0.38
	>1050	49,038	20.77	0.88 (0.80, 0.97)	0.01	0.94 (0.81, 1.09)	0.50	0.89 (0.65, 1.22)	0.47
Six Month Iron Exposure	**None**	18,555	9.19	1.29 (1.13, 1.47)	<0.01	1.19 (0.98, 1.45)	0.08	1.09 (0.71, 1.67)	0.68
	>0 to 900	62,845	31.14	Reference		Reference		Reference	
	>900 to 2100	95,058	47.10	1.04 (0.95, 1.14)	0.38	1.10 (0.97, 1.25)	0.14	1.01 (0.77, 1.32)	0.95
	>2100	25,375	12.57	1.03 (0.89, 1.18)	0.71	1.27 (1.04, 1.54)	0.02	1.03 (0.67, 1.59)	0.88

Models adjusted for age, sex, race, ethnicity, baseline comorbidity at 90 days, baseline BMI, cause of ESRD, year start dialysis, baseline iron doses, hemoglobinopathies, albumin, creatinine, pre-dialysis systolic blood pressure, body weight, change in weight, vascular access type, non-infectious hospitalization, infection, TSAT/Ferritin categories, hemoglobin categories, weekly EPO doses categories, change in EPO and interaction of TSAT/Ferritin categories and hemoglobin categories.

^ Models were adjusted for all covariates included in all-cause and CVD morality models except recent infection

[&] Global tests of iron exposure

Table 6. Distribution of the Weights

	Percentile Distribution					
	10th	**25th**	**50th**	**75th**	**90th**	**99th**
All Cause Mortality						
One Month	0.04	0.16	0.54	1.03	2.06	25.75
CVD Mortality						
One Month	0.04	0.17	0.54	1.02	2.06	24.5
Infectious Mortality						
One Month	0.04	0.16	0.53	1.02	2.04	26.42

Table 7: Effects of Weight Truncations: All Cause Mortality and 1-Month Iron Exposure

	Weights truncated at 10 (original)				Weights truncated at 3				Weights truncated at 5			
All cause, 1-month	**HR**	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**
None vs. 0 to 150 mg	0.98	0.79	1.22	0.86	0.99	0.84	1.16	0.87	0.98	0.82	1.18	0.85
150 to 350 mg vs. 0 to 150 mg	0.78	0.64	0.95	0.01	0.81	0.70	0.93	0.00	0.79	0.67	0.93	0.01
>350 mg vs. 0 to 150 mg	0.79	0.62	0.99	0.04	0.76	0.65	0.89	0.00	0.77	0.64	0.91	0.00

Weights truncated at 20				Weights truncated at 100			
HR	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**
0.99	0.74	1.31	0.94	1.19	0.72	1.99	0.49
0.78	0.60	1.01	0.06	0.78	0.49	1.25	0.30
0.82	0.60	1.12	0.21	1.02	0.58	1.78	0.96

Table 8: Effects of Weight Truncations: CV Mortality and 1- Month Iron Exposure

	Weights truncated at 10 (original)				Weights truncated at 3				Weights truncated at 5			
CV-cause, 1-month	**HR**	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**
None vs. 0 to 150 mg	1.11	0.84	1.48	0.47	1.01	0.82	1.23	0.96	1.04	0.82	1.30	0.75
150 to 350 mg vs. 0 to 150 mg	1.08	0.80	1.44	0.62	1.04	0.84	1.29	0.73	1.05	0.82	1.33	0.72
>350 mg vs. 0 to 150 mg	0.95	0.70	1.29	0.74	0.98	0.80	1.20	0.83	0.96	0.76	1.21	0.71

Weights truncated at 20				Weights truncated at 100			
HR	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**
1.18	0.82	1.70	0.36	1.37	0.74	2.52	0.31
1.15	0.80	1.65	0.46	1.37	0.72	2.62	0.34

0.95	0.65	1.40	0.80	1.03	0.51	2.09	0.93

Table 9: Effects of Weight Truncations: Infectious Mortality and 1- Month Iron Exposure

	Weights truncated at 10 (original)				Weights truncated at 3				Weights truncated at 5			
Infectious cause, 1-month	**HR**	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**
None vs. 0 to 150 mg	0.92	0.54	1.57	0.77	0.80	0.53	1.20	0.29	0.80	0.50	1.29	0.36
150 to 350 mg vs. 0 to 150 mg	0.77	0.47	1.27	0.30	0.68	0.46	1.01	0.06	0.69	0.45	1.07	0.09
>350 mg vs. 0 to 150 mg	1.26	0.75	2.13	0.37	0.90	0.59	1.37	0.63	1.00	0.63	1.58	0.99

Weights truncated at 20				Weights truncated at 100			
HR	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**
1.08	0.57	2.03	0.82	1.86	0.69	4.97	0.22
0.84	0.47	1.52	0.57	0.98	0.43	2.27	0.97
1.54	0.86	2.76	0.15	1.80	0.87	3.72	0.12

Table 10: Effects of Weight Truncations: All-Cause Mortality and 3- Month Iron Exposure

	Weights truncated at 10 (original)				Weights truncated at 3				Weights truncated at 5			
All cause, 3-month	**HR**	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**
None vs. >0 to 450 mg	1.19	0.90	1.57	0.22	1.11	0.92	1.35	0.28	1.15	0.92	1.43	0.23
>450 to 1050 mg to >0 to 450 mg	0.99	0.81	1.20	0.89	0.96	0.82	1.11	0.58	0.96	0.81	1.14	0.67
>1050 to >0 to 450 mg	1.09	0.84	1.42	0.52	1.04	0.87	1.25	0.64	1.04	0.84	1.29	0.70

Weights truncated at 20				Weights truncated at 100			
HR	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**
1.25	0.88	1.78	0.22	1.68	0.93	3.02	0.08
1.02	0.81	1.28	0.90	1.17	0.80	1.70	0.41
1.18	0.86	1.63	0.31	1.27	0.78	2.05	0.33

Table 11: Effects of Weight Truncations: CV Mortality and 3- Month Iron Exposure

	Weights truncated at 10 (original)				Weights truncated at 3				Weights truncated at 5			
CV-cause, 3-month	**HR**	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**
None vs. >0 to 450 mg	**1.06**	**0.72**	**1.54**	**0.77**	**1.03**	**0.79**	**1.34**	**0.84**	**1.01**	**0.74**	**1.37**	**0.95**
>450 to 1050 mg to >0 to 450 mg	**0.87**	**0.67**	**1.14**	**0.32**	**0.94**	**0.78**	**1.13**	**0.49**	**0.88**	**0.71**	**1.09**	**0.24**
>1050 to >0 to 450 mg	**1.02**	**0.74**	**1.41**	**0.91**	**1.18**	**0.93**	**1.49**	**0.16**	**1.08**	**0.83**	**1.41**	**0.55**

Weights truncated at 20				Weights truncated at 100			
HR	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**
1.14	0.72	1.79	0.58	1.34	0.66	2.70	0.42
0.87	0.63	1.20	0.39	0.75	0.46	1.24	0.27
1.01	0.67	1.52	0.97	1.06	0.50	2.23	0.89

Table 12: Effects of Weight Truncations: Infectious Mortality and 3-Month Iron Exposure

	Weights truncated at 10 (original)				Weights truncated at 3				Weights truncated at 5			
Infectious cause, 3-month	**HR**	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**
None vs. >0 to 450 mg	**0.86**	**0.38**	**1.96**	**0.73**	**0.93**	**0.53**	**1.65**	**0.81**	**0.86**	**0.44**	**1.68**	**0.65**
>450 to 1050 mg to >0 to 450 mg	**0.99**	**0.56**	**1.74**	**0.96**	**0.89**	**0.58**	**1.39**	**0.62**	**0.90**	**0.55**	**1.46**	**0.67**
>1050 to >0 to 450 mg	**1.69**	**0.87**	**3.28**	**0.12**	**1.29**	**0.77**	**2.16**	**0.33**	**1.35**	**0.76**	**2.39**	**0.31**

Weights truncated at 20				Weights truncated at 100			
HR	**lowercl**	**uppercl**	**Pvalue**	**HR**	**lowercl**	**uppercl**	**Pvalue**
1.02	**0.37**	**2.80**	**0.98**	**2.30**	**0.56**	**9.42**	**0.25**
1.09	**0.58**	**2.07**	**0.79**	**1.11**	**0.52**	**2.34**	**0.79**
2.22	**1.09**	**4.56**	**0.03**	**3.01**	**1.30**	**7.01**	**0.01**

Table 13: Effects of Weight Truncations: All-Cause Mortality and 6-Month Iron Exposure

	Weights truncated at 10 (original)				Weights truncated at 3				Weights truncated at 5			
All cause, 6-month	HR	lowercl	uppercl	Pvalue	HR	lowercl	uppercl	Pvalue	HR	lowercl	uppercl	Pvalue
None vs. >0 to 900 mg	1.24	0.92	1.69	0.16	1.23	0.98	1.55	0.07	1.25	0.97	1.61	0.09
900 to 2100 mg vs. >0 to 900 mg	0.98	0.80	1.21	0.87	1.01	0.87	1.18	0.85	1.00	0.85	1.18	0.98
>2100 mg vs. >0 to 900 mg	1.12	0.81	1.57	0.49	1.18	0.93	1.50	0.17	1.14	0.87	1.50	0.35

Weights truncated at 20				Weights truncated at 100			
HR	lowercl	uppercl	Pvalue	HR	lowercl	uppercl	Pvalue
1.21	0.85	1.71	0.29	1.41	0.85	2.33	0.18
0.96	0.75	1.23	0.73	0.91	0.56	1.48	0.69
1.16	0.78	1.73	0.46	1.07	0.56	2.04	0.84

Table 14: Effects of Weight Truncations: Cardiovascular Mortality and 6-Month Iron Exposure

	Weights truncated at 10 (original)				Weights truncated at 3				Weights truncated at 5			
CV-cause, 6-month	HR	lowercl	uppercl	Pvalue	HR	lowercl	uppercl	Pvalue	HR	lowercl	uppercl	Pvalue
None vs. >0 to 900 mg	1.46	0.98	2.16	0.06	1.30	0.94	1.79	0.11	1.35	0.95	1.93	0.10
900 to 2100 mg vs. >0 to 900 mg	1.15	0.85	1.56	0.36	1.11	0.91	1.36	0.29	1.12	0.88	1.42	0.37
>2100 mg vs. >0 to 900 mg	1.17	0.76	1.79	0.48	1.32	0.98	1.78	0.07	1.23	0.87	1.74	0.24

Weights truncated at 20				Weights truncated at 100			
HR	lowercl	uppercl	Pvalue	HR	lowercl	uppercl	Pvalue
1.42	0.91	2.21	0.12	1.51	0.76	3.02	0.24
1.13	0.76	1.69	0.54	1.04	0.58	1.84	0.90
1.05	0.61	1.81	0.86	0.97	0.38	2.43	0.94

Table 15: Effects of Weight Truncations: Infectious Mortality and 6-Month Iron Exposure

	Weights truncated at 10 (original)				Weights truncated at 3				Weights truncated at 5			
Infectious cause, 6-month	HR	lowercl	uppercl	Pvalue	HR	lowercl	uppercl	Pvalue	HR	lowercl	uppercl	Pvalue
None vs. >0 to 900 mg	0.75	0.29	1.95	0.56	0.91	0.46	1.82	0.80	0.83	0.37	1.86	0.66
900 to 2100 mg vs. >0 to 900 mg	0.98	0.53	1.81	0.96	1.03	0.62	1.70	0.91	1.00	0.58	1.73	1.00
>2100 mg vs. >0 to 900 mg	1.59	0.73	3.46	0.24	1.29	0.69	2.43	0.43	1.35	0.68	2.68	0.39

Weights truncated at 20				Weights truncated at 100			
HR	lowercl	uppercl	Pvalue	HR	lowercl	uppercl	Pvalue
0.79	0.26	2.41	0.68	1.11	0.20	6.26	0.89
0.97	0.48	1.99	0.94	0.66	0.19	2.30	0.51
1.77	0.75	4.18	0.20	1.45	0.45	4.74	0.53