DETAILED METHODS

Data Sources

The data for this study came from the clinical research database of a large dialysis provider and the US Renal Data System (USRDS). The dialysis provider owns and manages over 1,500 outpatient dialysis facilities located in urban, rural, and suburban areas throughout the U.S. Their clinical database captures detailed clinical, laboratory, and treatment data on patients receiving care at all of their dialysis units. All data are collected using standardized electronic health record systems. For this study, we used the clinical data to obtain detailed information on iron formulation and dosing, epoetin alfa (EPO) use and dosing, clinical laboratory values (e.g., hemoglobin, transferrin saturation (TSAT), serum ferritin), current vascular access, and recent intravenous antibiotic use. The USRDS is a national data system funded by the NIDDK that collects, analyzes, and distributes information about the treatment of ESRD. The USRDS includes data from the Medical Evidence Report Form, the Medicare Enrollment database, the ESRD Death Notification Form, and the standard analytic files, which contain final action claims data.

We examined 5 years of data (2004 – 2008) from the clinical database to identify the cohort. These data were merged with data from the USRDS to obtain information on hospitalizations and also additional demographic and clinical characteristics (e.g., comorbidities).

Study Design

We utilized a retrospective cohort design with a 6-month baseline period (to identify potential confounders and effect modifiers), a one-month iron exposure period, and a three-month follow-up period. The index date of the exposure period was anchored on the day of a laboratory assessment of TSAT because this information is used to guide subsequent iron administration. Eligible subjects could contribute multiple exposure/follow-up periods.

We conducted three sensitivity analyses with shorter iron exposure and/or follow-up periods: 1) a two week exposure and six week follow-up period, 2) a one week exposure and six week follow-up period, and 3) a one month exposure and six week follow-up period.

Cohort Identification

Figure S1 depicts the creation of our sample. We first identified center-based, outpatient hemodialysis patients (defined as individuals with a vintage of 9 months or more who were receiving hemodialysis in a dialysis facility) covered by Medicare Parts A and B who had at least one TSAT measurement between January 30, 2004 and November 30, 2008 (the November 30th date was chosen to allow for the 1-month exposure period and at least one day of follow-up). This constituted our population of interest. We then excluded patients with polycystic kidney disease since many of these patients do not require exogenous erythropoiesis stimulating agents and therefore may have different

iron requirements. TSAT records were excluded if: 1) iron dextran or both ferric gluconate and iron sucrose were delivered in the exposure period (making it difficult to compare formulation effects); 2) the duration of Part A claims at baseline was insufficient (i.e., <120 days), suggesting incomplete data; 3) the exposure period overlapped with the follow-up period for a prior eligible TSAT for the same patient; or 4) there were fewer than 9 dialysis sessions in the last month of baseline or the exposure period (suggesting the individual was not receiving regular center hemodialysis). For the 2-week and 1-week exposure periods, TSAT records were excluded if there were fewer than 4 or fewer than 2 dialysis sessions, respectively. We also excluded TSAT records with missing covariate information.

Study Variables

Outcomes: We examined two outcomes related to infection, hospitalization for infection and death attributed to infection. These were determined by examining the Medicare inpatient and outpatient claims and death notification data and are defined in Table S1. We also created a composite outcome of infection-related hospitalization or death.

Because our definition of hospitalization for infection was specific to sepsis, vascular access infection, or pneumonia, we conducted sensitivity analyses with broader, more sensitive infection definitions: hospitalization for infection of any major organ system, use of intravenous antibiotics, and a composite of hospitalization and antibiotic use. (See Table S1)

Exposures: The primary exposures of interest were high dose versus low dose iron administration and bolus versus maintenance dosing. We defined high dose as >200 mg of IV iron in the one month exposure period. Low dose was defined as 1-200 mg of IV iron. We also created a no iron category for individuals who received no iron during the 1-month exposure period. For the 2-week and 1-week exposure periods, high doses were greater than 125 mg and 75 mg, respectively.

A month was classified as a "bolus month" if it contained administrations of at least 100mg iron during consecutive dialysis sessions. We also classified a month as a bolus month if it contained two or more administrations of iron >100 mg that had the potential to exceed 600 mg within 30 days based on spacing between the doses in the sequence. For example, two consecutive iron doses of 200 mg each, within 10 days, would qualify as a bolus dose according to our definition. Months that had no bolus dosing patterns were classified as “maintenance months.” We also included a no iron category.

To minimize the effects of total dose in our comparison of bolus versus maintenance dosing practices, we conducted a subgroup analysis among individuals who received 400-500 mg of iron per month and classified the months as bolus or maintenance as defined above.

Confounders: We included a wide range of covariates in our analyses. Covariates are defined in Table S2 and included demographic characteristics (e.g., age, sex, race, Medicaid eligibility, census region, year), clinical characteristics (e.g., cause of ESRD, vintage, BMI, type of vascular access,

number of hospital days), laboratory and anemia management variables (baseline hemoglobin, ferritin, TSAT, iron dose, EPO dose, albumin; receipt of a blood transfusion, EPO dose during exposure period), and several comorbidity measures based on the Elixhauser classification[1] _ENREF_25_ENREF_25 and content expertise of the investigative team. Because of the potential relation between iron use and infections, we created four "history of infection" variables: history of pneumonia, sepsis, or vascular access infection during the baseline period and history of any infection in the last month. Due to the extensive list of comorbidities, we selected ones to include in a parsimonious model and then examined how the inclusion of additional covariates and the use of propensity score methods affected our estimates.

Subgroup Analyses: We conducted our primary analyses (one month exposure and 3 month follow-up) on several demographic and clinical subgroups defined in Table S3 of the Appendix. Individuals were categorized based on race; catheter use; low TSAT and high ferritin at baseline; history of infection in last month of baseline; hypo-responsiveness to erythropoiesis stimulating agents at baseline; TSAT levels at baseline; and vintage. We created these subgroups based on stakeholder input and content-knowledge of the research team.

Statistical Analysis

To assess the relation between iron dosing practices and adverse outcomes, we used Cox proportional hazards regression analyses to estimate hazard ratios and semiparametric additive risks models to estimate risk differences.[2] To account for the within patient correlation of the repeated measures, we used a robust sandwich covariance estimator _ENREF_40 of the standard errors for the Cox models and multiplied the standard errors from the additive risk models by an estimated design effect.[3] Individuals were censored by death (for the hospitalization outcomes), loss to follow-up, receipt of a kidney transplant, or administratively by the end of available data. We first estimated an unadjusted hazard ratio (e.g. high versus low dose) for each outcome and then a multivariable-adjusted hazard ratio that included age, sex, race, BMI, EPO dose during baseline and the exposure period, baseline hemoglobin, baseline ferritin, index TSAT, current use of a catheter for vascular access, years on dialysis, serum albumin, number of hospital days, history in the last six months of diabetes, stroke, myocardial infarction, pneumonia, vascular access infection, sepsis, chronic obstructive pulmonary disease, cancer, gastrointestinal bleeding, and any infection in last month.

Sensitivity Analyses

In addition to expanding our definition of infection and varying the length of the exposure and follow-up periods, we assessed the sensitivity of our results to statistical modeling assumptions and the selection of variables for the statistical model. We examined how different levels of adjustment affected

the point estimate and how the addition of other potentially relevant covariates to our primary model affected results. The additional variables that we considered were reported cause of ESRD, year, region, Medicaid eligibility, and a number of additional comorbidities defined in Table S2.

We then conducted three types of propensity score analyses. Propensity scores for iron dose were estimated using multivariable linear regression to predict the log of iron dose among patients receiving iron. Propensity scores for bolus versus maintenance were estimated using logistic regression to predict receipt of bolus dosing among patients receiving iron, with selected interaction terms to improve covariate balance. The propensity score models included all covariates from our primary outcome model. For each propensity score analysis, the proportional hazards model included all covariates from our primary outcome model and was stratified across deciles of the propensity score.

For the first analysis, we included in the propensity score model only the covariates from our primary outcome model. For the second analysis, we added to the propensity score model two additional covariates: total iron from the first 5 months of baseline and total EPO from the first 5 months of baseline. These variables provided additional information on history of iron and EPO use as our original model included data on iron and EPO use only in the last month of baseline. Finally, we conducted a high dimensional propensity score analysis in which we added to the propensity score model data on all prevalent comorbidities identified in the Medicare claims for each subject.[4] Comorbidities were identified based on 3-digit ICD-9-CM diagnostic codes and were included if their prevalence was >1 percent.

Tables S11 and S12 present the results for the primary model and the additional sensitivity analyses. M0 (Model 0), the first row of each table, presents the unadjusted results. M1-M3 (Models 1-3) present results with the addition of selected covariates in blocks. M4 (Model 4) presents our *a priori* specified full model. Beyond our *a priori* specified full model, additional covariates (Model 5) had no meaningful effect on the estimated hazard ratios. The point estimates from the propensity score analyses (Models 6, 7, and 8) were also compatible with our main finding (Model 4).

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Table S1 – Adverse Study Outcomes

Outcome	Definition	Data Source
Primary Infection Outcomes		
Infection-related death	Primary cause of death: 33,34,45-48, 51,52,61-63,70	CMS death notification file
Hospitalized for infection	Any ICD-9-CM diagnostic codes of 996.62 (vascular access), 481.xx (pneumonia), 038.xx (sepsis)	CMS Part A claims
Infection Outcomes for Sensitivity Analyses		
Hospitalized for infection (all major organ systems)	Any hospital admission with one of the following ICD-9-CM diagnostic codes as the principal diagnostic code: 001–139, 254.1, 320–326, 331.81, 372–372.39, 373.0–373.2, 382–382.4, 383.0, 386.33, 386.35, 388.60, 390–393, 421–421.1, 422.0, 422.91–422.93, 460–466, 472–474.0, 475–476.1, 478.21–478.24, 478.29, 480–490, 491.1, 494, 510–511, 513.0, 518.6, 519.01, 522.5, 522.7, 527.3, 528.3, 540–542, 566–567.9, 569.5, 572–572.1, 573.1–573.3, 575–575.12, 590–590.9, 595–595.4, 597–597.89, 598, 599.0, 601–601.9, 604–604.9, 607.1, 607.2, 608.0, 608.4, 611.0, 614–616.1, 616.3–616.4, 616.8, 670, 680–686.9, 706.0, 711–711.9, 730–730.3, 730.8–730.9, 790.7–790.8, 996.60–996.69, 997.62, 998.5, and 999.3.	CMS Part A claims
Use of IV antibiotics	Any indication of the use of the following drugs: Amikin® (amikacin sulfate); ampicillin; Ancef®, Kefzol® (cefazolin); aztreonam; Cefizox® (ceftizoxime); Cefotan® (cefotetan); Fortaz®, Tazicef® (ceftazidime); Claforan® (cefotaxime); clindamycin; Cubicin® (daptomycin); ethambutol; gentamicin; Keflin® (cephalothin); Levaquin® (levofloxacin); Mefoxin® (cefoxitin); Merrem® (meropenem); nafcillin; Nebcin® (tobramycin); oxacillin; Penicillin G; Zosyn® (piperacillin and tazobactam); Primaxin® (imipenem and cilastatin); Rocephin® (ceftriaxone); streptomycin; Timentin® (ticarcillin and clavulanate potassium); Unasyn® (ampicillin and sulbactam); Vancocin® (vancomycin); Vibramycin® (doxycycline); Zinacef® (cefuroxime); Zyvox® (linezolid)	Clinical Database
Composite of hospitalized for infection and IV antibiotic use	All codes used above	CMS Part A claims, Clinical Database

Table S2 – Definition of Covariates

COVARIATE	DEFINITION	SOURCE
Demographic		
Age	Categorized as: 16-45; 46-60; 61-75; >75 yrs.	USRDS
Sex	Male or female	USRDS
Race	White, Black, Other	USRDS
Medicaid Eligibility	Indicator for dual eligibility during any part of the baseline	USRDS
Year of treatment	2004, 2005, 2006, 2007, 2008	Clinical Database
Census Region	Based on location of last dialysis center in baseline period: Northeast, South, Midwest, West	USRDS
Clinical		
Vintage	Categorized as 0; 1-3; 4 or more yrs.	USRDS
ESRD Reason	Diabetes, Glomerulonephritis, hypertension, other	USRDS
BMI	Categorized as underweight, normal, overweight, obese	Clinical Database & USRDS
Anemia Management		
Access	Most recent vascular access (catheter vs fistula/graft) prior to TSAT index date	Clinical Database
EPO dose (baseline)	Total EPO dose, (quintiles)	Clinical Database
EPO dose (exposure)	Total EPO dose, (tertiles plus a no-use category)	Clinical Database
Index TSAT	Last TSAT at baseline (quintiles)	Clinical Database
Iron dose	Total dose at last month of baseline, categorized as none, low (1-200 mg), or high (>200mg)	Clinical Database
Hemoglobin	Most proximal Hb lab prior to index TSAT date (<10,10-11,>11-12,>12-13,>13)	Clinical Database
Ferritin	Most proximal serum ferritin prior to index TSAT date (quintiles)	Clinical Database
Albumin	At baseline (<3.3, 3.3-3.9, >3.9)	Clinical Database
Comorbidities		
Hospital days in last month of baseline	Categorized as 0, 1-3, <=4	USRDS, Medicare Part A Claims
Infection in last month	Any hospital admission in the last month with one of the following ICD-9-CM diagnostic codes as the principal diagnostic code: 001–139, 254.1, 320–326, 331.81, 372–372.39, 373.0–373.2, 382–382.4, 383.0, 386.33, 386.35, 388.60, 390–393, 421–421.1, 422.0, 422.91–422.93, 460–466, 472–474.0, 475–476.1, 478.21–478.24, 478.29, 480–490, 491.1, 494, 510–511, 513.0, 518.6, 519.01, 522.5, 522.7, 527.3, 528.3, 540–542, 566–567.9, 569.5, 572–572.1, 573.1–573.3, 575–575.12, 590–590.9, 595–595.4, 597–597.89, 598, 599.0, 601–601.9, 604–604.9, 607.1, 607.2, 608.0, 608.4, 611.0, 614–616.1, 616.3–616.4, 616.8, 670, 680–686.9, 706.0, 711–711.9, 730–730.3, 730.8–730.9, 790.7–790.8, 996.60–996.69, 997.62, 998.5, and 999.3.	USRDS, Medicare Part A Claims
	Any claims with the following HCPCS codes for antibiotic use in last month of baseline: J3370, J0690, J0713, J0692, J0696, J1580, J3260, J0278, J1840, J1956.	USRDS, Medicare Part A & B Claims
	Any indication of the use of the following drugs: Amikin® (amikacin sulfate); ampicillin; Ancef®, Kefzol® (cefazolin); aztreonam; Cefizox® (ceftizoxime); Cefotan® (cefotetan); Fortaz®, Tazicef® (ceftazidime); Claforan® (cefotaxime);	Clinical Database

	clindamycin; Cubicin® (daptomycin); ethambutol; gentamicin; Keflin® (cephalothin); Levaquin® (levofloxacin); Mefoxin® (cefoxitin); Merrem® (meropenem); nafcillin; Nebcin® (tobramycin); oxacillin; Penicillin G; Zosyn® (piperacillin and tazobactam); Primaxin® (imipenem and cilastatin); Rocephin® (ceftriaxone); streptomycin; Timentin® (ticarcillin and clavulanate potassium); Unasyn® (ampicillin and sulbactam); Vancocin® (vancomycin); Vibramycin® (doxycycline); Zinacef® (cefuroxime); Zyvox® (linezolid)	
Pneumonia	Any ICD-9-CM diagnostic code of 481.xx – 486.xx in baseline period	USRDS, Medicare Part A & B Claims
Vascular Access Infection	Any ICD-9-CM diagnostic code of 996.62 in baseline period	
Sepsis	Any ICD diagnostic code 038.xx, 995.90, 995.91, 995.92 in baseline period	
Diabetes	Any ICD-9-CM diagnostic code of 250.xx in baseline period	
Ischemic Stroke	Any ICD-9-CM diagnostic code of 434.01, 434.11, 434.91, 435, 436, 437, 438, V12.54 in baseline period	
MI	Any ICD-9-CM diagnostic code of 410.xx in baseline period	
COPD	Any ICD-9-CM diagnostic code of 490.xx-496.xx, 505.xx, 506.4 in baseline period	
Cancer	Any ICD-9-CM diagnostic code of 140-172, 173.3, 173.9, 174.0-175.9, 179-195, 196-199, 232.9, 233.0, 233.1, 338.3, 789.51, 795.82, 799.4, V67.2, 200, 201, 202.0-202.3, 202.50-203.01,203.8, 238.6, 273.3 in baseline period	
GI bleeding	Any ICD-9-CM diagnostic code of 578.xx in baseline period	
Additional Comorbidities for Sensitivity Analyses		
Pulmonary circulation disease	Any ICD-9-CM diagnostic code of 415.xx-417.xx in baseline period	USRDS, Medicare Part A & B Claims
Peptic Ulcer Disease	Any ICD-9-CM diagnostic code of 530.2, 531.xx-534.xx, V12.71 in baseline period	
Liver disease	Any ICD-9-CM diagnostic code of 070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21, 571.0, 571.2, 571.3, 571.4, 571.5, 571.6, 571.8, 571.9, 572.3, 572.8, V42.7 in baseline period	
Other neurological problem	Any ICD-9-CM diagnostic code 331.9, 332.0, 333.4, 333.5, 334-335, 340, 341, 345.0, 345.1, 345.4, 345.5, 345.8, 345.9, 348.1, 348.3, 780.3, 784.3 in baseline period	
Substance abuse	Any ICD-9-CM diagnostic code 303.xx-305.xx in baseline period	
Ischemic Heart disease, other heart disease, peripheral vascular disease, history of CABG, Stent, PTCA	Any ICD-9-CM diagnostic code of 411.xx-414.xx, 420.xx-429.xx, 785.o, V45.0, v53.3, 402.11, 402.91, 404.11, 404.12, 404.91, 404.93, 093.2, 746.3-746.6, v42.2, v43.3, v43.4441.xx-443.xx, 447.1, 557.1, 557.9, 444.xx-445.xx; Procedure codes (both ICD-9-CM and CPT) of 00.66, 92982, 92985, 36.06, 36.07, 92980, 33510-33514, 33516-33519 in baseline period	
Hypertension	Any ICD-9-CM diagnostic code of 401.xx-405.xx, except 402.11, 402.91, 404.11, 404.13, 404.91, 404.93 in baseline period	
Rheumatic heart disease	Any ICD-9-CM diagnostic code of 393.xx -398.xx in baseline period	
Psychiatric problems	Any ICD-9-CM diagnostic code 295.xx-298.xx in baseline period	
Autoimmune disorders	Any ICD-9-CM diagnostic code of 564.1, 696.0, 696.1, 695.4, 710.0, 701.0, 710, 714, 720, 725 in baseline period	

Blood loss anemia	Any ICD-9-CM diagnostic code of 280.0 in baseline period	
Transfusion	Indicator for receipt of one or more transfusions during the baseline period, based on HCPCS codes P9010, P9011, P9016, P9021, P9022, P9038, P9039, P9040, 36430 and ICD-9 codes 99.03, 99.04	

Table S3 – Subgroup Definitions

Subgroup	Definition	Data Source
Race: Black Non-Black	Categorized as Black race or White/Other race	USRDS
Vintage: < 1year 1-<4 yrs. ≥4 yrs.	Years on dialysis, categorized into 3 groups	USRDS
Catheter	Most recent vascular access prior to index TSAT was catheter	Clinical Database
Recent Infection	Any hospital admission in the last month with one of the following ICD-9-CM diagnostic codes as the principal diagnostic code: 001–139, 254.1, 320–326, 331.81, 372–372.39, 373.0–373.2, 382–382.4, 383.0, 386.33, 386.35, 388.60, 390–393, 421–421.1, 422.0, 422.91–422.93, 460–466, 472–474.0, 475–476.1, 478.21–478.24, 478.29, 480–490, 491.1, 494, 510–511, 513.0, 518.6, 519.01, 522.5, 522.7, 527.3, 528.3, 540–542, 566–567.9, 569.5, 572–572.1, 573.1–573.3, 575–575.12, 590–590.9, 595–595.4, 597–597.89, 598, 599.0, 601–601.9, 604–604.9, 607.1, 607.2, 608.0, 608.4, 611.0, 614–616.1, 616.3–616.4, 616.8, 670, 680–686.9, 706.0, 711–711.9, 730–730.3, 730.8–730.9, 790.7–790.8, 996.60–996.69, 997.62, 998.5, and 999.3. Any claims with the following HCPCS codes for antibiotic use in last month of baseline: J3370, J0690, J0713, J0692, J0696, J1580, J3260, J0278, J1840, J1956. Any indication of IV antibiotic use in the last month of baseline.	USRDS, Medicare Part A Claims USRDS, Medicare Part A & B Claims Clinical Database
Hemoglobin (g/dL): <10 10-12 >12	Most proximal hemoglobin lab, categorized into 3 groups	Clinical Database
Hypo-responsive to ESA	Baseline hemoglobin 11 g/dL or less, and EPO dose at baseline in the top quartile	Clinical Database
TSAT (%): <20 20 – <50 50 or more	Index TSAT (last TSAT of baseline period), categorized into 3 groups	Clinical Database
Ferritin (mcg/L): <200 200-500 501-1200 >1200	Ferritin measure most proximal to index TSAT, categorized into 4 groups	Clinical Database
TSAT(%) * Ferritin (mcg/L): <25 * <500	6 combinations based on index TSAT and Ferritin measured most proximal to index TSAT	Clinical Database

<25 * 500-800 <25 * >800 ≥25% * <500 ≥25% * 500-800 ≥25% * >800		
Albumin (g/dL): <3 3-<3.5 3.5-<3.8 3.8-<4 ≥4	Albumin level most proximal to index TSAT, categorized into 5 groups	

Table S4: Sensitivity Analyses of High Dose versus Low Dose Comparisons to Study Design*

Exposure/ Follow-Up Period	Parameter Estimate (95% CI)	Hospitalized for Infection	Infection-Related Death	Infection-related Hosp./Death
1 month/3 months[1]	Unadj. HR	1.37 (1.33,1.40)	1.43 (1.32,1.55)	1.37 (1.34,1.40)
	Adj. HR	1.05 (1.02,1.07)	1.08 (0.99,1.19)	1.05 (1.02,1.08)
	Adj. RD**	12.1 (5.7, 18.8)	1.2 (-0.74, 2.8)	13.0 (6.2, 19.5)
1 month/6 weeks[1]	Unadj. HR	1.41 (1.36,1.45)	1.46 (1.28,1.66)	1.41 (1.37,1.46)
	Adj. HR	1.05 (1.01,1.09)	1.09 (0.95,1.26)	1.06 (1.02,1.09)
	Adj. RD**	13.6 (3.3, 23.0)	1.0 (-1.3, 3.7)	15.1 (5.9, 25.1)
2 weeks/6 weeks[2]	Unadj. HR	1.46 (1.41,1.51)	1.50 (1.31,1.72)	1.46 (1.41,1.51)
	Adj. HR	1.05 (1.01,1.09)	1.06 (0.91,1.23)	1.05 (1.01,1.08)
	Adj. RD**	15.2 (3.0, 26.8)	0.19 (-2.4, 2.5)	14.7 (1.2, 26.8)
1 week/6 weeks[3]	Unadj. HR	1.48 (1.43,1.54)	1.61 (1.39,1.86)	1.48 (1.43,1.54)
	Adj. HR	1.09 (1.05,1.14)	1.15 (0.98,1.35)	1.09 (1.05,1.14)
	Adj. RD**	27.3 (15.6, 37.7)	1.5 (-0.90, 3.7)	27.7 (16.0, 38.6)

*adjusted analyses controlled for the following variables at baseline: age; race; sex; vintage; number of hospital days in last month; history of infection in last month; BMI; most recent vascular access, hemoglobin; ferritin; index TSAT; iron dose; albumin level; EPO dose; history in last 6 months of pneumonia, sepsis, vascular access infection, diabetes, stroke, MI, COPD, cancer, GI bleeding; and EPO dose during exposure.

**Risk difference is the hazard difference per 1000 person years.

[1] N=776,203; [2] N=815,249; [3] N=828,270

Table S5: Sensitivity Analysis of Bolus versus Maintenance Dosing Comparisons to Study Design*

Exposure/ Follow-Up Period	Parameter Estimate (95% CI)	Hospitalized for Infection	Infection-Related Death	Infection-related Hosp./Death
1 month/3 months[1]	Unadj. HR	1.51 (1.47,1.56)	1.63 (1.48,1.78)	1.52 (1.48,1.56)
	Adj. HR	1.08 (1.05,1.11)	1.11 (1.00,1.23)	1.08 (1.05,1.11)
	Adj. RD**	24.8 (15.8, 33.1)	2.0 (-0.36, 4.1)	26.1 (17.6, 35.0)
1 month/6 weeks[1]	Unadj. HR	1.59 (1.53,1.64)	1.71 (1.48,1.97)	1.59 (1.53,1.65)
	Adj. HR	1.09 (1.05,1.14)	1.13 (0.97,1.32)	1.09 (1.05,1.14)
	Adj. RD**	31.5 (21.0, 43.4)	1.7 (-1.3, 5.6)	33.2 (23.3, 45.5)
2 weeks/6 weeks[2]	Unadj. HR	1.60 (1.54,1.66)	1.73 (1.50,2.01)	1.60 (1.54,1.66)
	Adj. HR	1.06 (1.02,1.11)	1.12 (0.95,1.31)	1.06 (1.02,1.11)
	Adj. RD**	24.8 (8.7, 37.6)	1.2 (-2.3, 4.4)	24.7 (9.3, 38.6)
1 week/6 weeks[3]	Unadj. HR	1.62 (1.56,1.69)	1.88 (1.60,2.21)	1.62 (1.56,1.69)
	Adj. HR	1.06 (1.01,1.10)	1.20 (1.01,1.43)	1.06 (1.01,1.10)
	Adj. RD**	23.1 (7.9, 36.7)	2.9 (-1.2, 7.1)	23.0 (7.6, 37.9)

*adjusted analyses controlled for the following variables at baseline: age; race; sex; vintage; number of hospital days in last month; history of infection in last month; BMI; most recent vascular access, hemoglobin; ferritin; index TSAT; iron dose; albumin level; EPO dose; history in last 6 months of pneumonia, sepsis, vascular access infection, diabetes, stroke, MI, COPD, cancer, GI bleeding; and EPO dose during exposure.
**Risk difference is the hazard difference per 1000 person years.
[1] N=776,203; [2] N=815,249; [3] N=828,270

Table S6 – Hazard Ratios for Bolus versus Maintenance Dosing Comparison Limited to Doses of 400-500 mg of Iron (N=66,167)

Parameter Estimate (95% CI)	Hospitalized for Infection	Infection-Related Death	Infection-related Hospitalization or Death
Unadjusted Hazard Ratio	1.32 (1.24,1.40)	1.38 (1.10,1.72)	1.33 (1.25,1.42)
Adjusted Hazard Ratio	1.10 (1.03,1.17)	1.13 (0.89,1.44)	1.11 (1.04,1.19)

*adjusted analyses controlled for the following variables at baseline: age; race; sex; vintage; number of hospital days in last month; history of infection in last month; BMI; most recent vascular access, hemoglobin; ferritin; index TSAT; iron dose; albumin level; EPO dose; history in last 6 months of pneumonia, sepsis, vascular access infection, diabetes, stroke, MI, COPD, cancer, GI bleeding; and EPO dose during exposure.

Table S7 – Full Model Results for Primary Cohort (1 month exposure, 3 month follow-up): High Dose versus Low Dose (N=776,203)

Parameter	Hospitalized for Infection	Infection-Related Death	Infection-Related Hospitalization/Death
High iron exposure (>200mg) (ref. none)	1.04 (1.01,1.08)	1.03 (0.93,1.14)	1.04 (1.01,1.07)
Low iron exposure (1-200mg) (ref. none)	1.00 (0.97,1.03)	0.95 (0.86,1.04)	0.99 (0.97,1.02)
High vs low iron contrast	1.05 (1.02,1.07)	1.08 (0.99,1.19)	1.05 (1.02,1.08)
EPO exposure tertile (ref. 0) 3	1.06 (0.99,1.14)	0.86 (0.69,1.07)	1.06 (0.99,1.13)
EPO exposure tertile (ref. 0) 2	0.95 (0.89,1.01)	0.71 (0.58,0.88)	0.95 (0.89,1.01)
EPO exposure tertile (ref. 0) 1	0.91 (0.86,0.97)	0.73 (0.59,0.89)	0.91 (0.85,0.96)
Age (ref. 76-103) 16-45	0.97 (0.93,1.00)	0.26 (0.22,0.30)	0.93 (0.90,0.97)
Age (ref. 76-103) 46-60	0.92 (0.89,0.95)	0.46 (0.41,0.51)	0.89 (0.87,0.92)
Age (ref. 76-103) 61-75	0.91 (0.88,0.93)	0.68 (0.63,0.73)	0.89 (0.87,0.92)
Black (ref. White)	1.04 (1.02,1.07)	0.83 (0.78,0.90)	1.03 (1.01,1.05)
Other race (ref. White)	0.96 (0.92,1.01)	0.75 (0.64,0.88)	0.95 (0.91,1.00)
Female	1.00 (0.98,1.02)	0.91 (0.85,0.98)	0.99 (0.97,1.01)
Baseline Hb (ref. High, >13) Low (<10)	1.08 (1.03,1.13)	1.06 (0.91,1.23)	1.07 (1.03,1.12)
Baseline Hb (ref. High, >13) Med low (10-11)	1.04 (1.00,1.07)	0.94 (0.82,1.07)	1.03 (0.99,1.07)
Baseline Hb (ref. High, >13) Med (>11-12)	0.98 (0.95,1.01)	0.93 (0.83,1.03)	0.98 (0.95,1.01)
Baseline Hb (ref. High, >13) Med high (>12-13)	0.97 (0.94,1.00)	0.94 (0.85,1.04)	0.97 (0.94,1.00)
Index TSAT quintile (ref. 5) 1	1.05 (1.02,1.09)	1.13 (1.01,1.27)	1.05 (1.02,1.09)
Index TSAT quintile (ref. 5) 2	1.00 (0.96,1.03)	1.05 (0.94,1.18)	1.00 (0.97,1.03)
Index TSAT quintile (ref. 5) 3	0.99 (0.96,1.02)	0.98 (0.88,1.10)	0.99 (0.96,1.02)

Parameter	Hospitalized for Infection	Infection-Related Death	Infection-Related Hospitalization/Death
Index TSAT quintile (ref. 5) 4	1.00 (0.97,1.03)	0.96 (0.85,1.08)	1.00 (0.96,1.03)
Baseline ferritin missing (ref. 4) 0	1.07 (0.98,1.18)	0.66 (0.45,0.96)	1.05 (0.96,1.15)
Baseline ferritin quartile (ref. 4) 1	1.04 (1.01,1.07)	0.88 (0.79,0.97)	1.03 (1.00,1.06)
Baseline ferritin quartile (ref. 4) 2	0.97 (0.94,1.00)	0.91 (0.82,1.00)	0.97 (0.94,1.00)
Baseline ferritin quartile (ref. 4) 3	0.98 (0.95,1.01)	0.93 (0.85,1.03)	0.98 (0.95,1.01)
Infection, last 6 mos.: pneumonia	1.14 (1.11,1.18)	1.13 (1.03,1.23)	1.14 (1.11,1.17)
Infection, last 6 mos.: vascular access	1.46 (1.42,1.50)	1.22 (1.11,1.34)	1.45 (1.41,1.49)
Infection, last 6 mos.: sepsis	1.54 (1.49,1.58)	1.38 (1.26,1.51)	1.53 (1.48,1.57)
Infection in last month	1.42 (1.38,1.45)	1.36 (1.25,1.49)	1.41 (1.38,1.45)
Catheter (ref. graft/fistula)	2.12 (2.07,2.16)	1.51 (1.40,1.63)	2.10 (2.05,2.14)
Years on dialysis (ref. 4+) 0 yrs	0.81 (0.78,0.85)	0.62 (0.54,0.71)	0.81 (0.78,0.84)
Years on dialysis (ref. 4+) 1-3 yrs	0.87 (0.86,0.89)	0.72 (0.67,0.77)	0.87 (0.85,0.89)
Albumin (ref. High, >3.9) Low (<3.3)	2.06 (1.99,2.13)	5.71 (5.09,6.41)	2.13 (2.06,2.21)
Albumin (ref. High, >3.9) Med (3.3 - 3.9)	1.35 (1.32,1.38)	2.02 (1.84,2.22)	1.36 (1.33,1.40)
Baseline EPO quintile (ref. 5) 1	0.73 (0.70,0.77)	0.65 (0.56,0.76)	0.73 (0.70,0.76)
Baseline EPO quintile (ref. 5) 2	0.75 (0.72,0.78)	0.67 (0.58,0.76)	0.75 (0.72,0.78)
Baseline EPO quintile (ref. 5) 3	0.83 (0.80,0.85)	0.73 (0.65,0.81)	0.82 (0.80,0.85)
Baseline EPO quintile (ref. 5) 4	0.89 (0.87,0.92)	0.81 (0.74,0.89)	0.89 (0.86,0.91)
Baseline iron 0 (ref. 1-200 mg)	1.02 (1.00,1.05)	1.06 (0.97,1.16)	1.02 (1.00,1.05)
Baseline iron >200 mg. (ref. 1-200 mg)	1.08 (1.05,1.10)	1.00 (0.91,1.09)	1.07 (1.05,1.10)

Parameter	Hospitalized for Infection	Infection-Related Death	Infection-Related Hospitalization/Death
BMI (ref. Obese) Underweight	1.30 (1.24,1.36)	1.66 (1.45,1.90)	1.31 (1.25,1.37)
BMI (ref. Obese) Normal	1.14 (1.11,1.17)	1.24 (1.13,1.36)	1.15 (1.12,1.18)
BMI (ref. Obese) Overweight	1.04 (1.01,1.07)	0.95 (0.86,1.05)	1.04 (1.01,1.07)
Diabetes	1.30 (1.27,1.33)	1.22 (1.13,1.31)	1.30 (1.27,1.33)
Stroke	1.29 (1.26,1.33)	1.23 (1.13,1.34)	1.29 (1.26,1.33)
MI	1.02 (0.98,1.07)	1.04 (0.91,1.19)	1.02 (0.98,1.06)
COPD	1.19 (1.17,1.22)	1.25 (1.16,1.35)	1.20 (1.17,1.23)
Cancer	1.04 (1.00,1.07)	1.13 (1.02,1.24)	1.04 (1.01,1.08)
GI problem	1.09 (1.05,1.13)	1.10 (0.98,1.24)	1.09 (1.05,1.13)
Hospital days, none (ref. 5+)	0.83 (0.80,0.86)	0.89 (0.80,0.99)	0.83 (0.80,0.86)
Hospital days, 1-4 (ref. 5+)	0.95 (0.91,0.99)	0.85 (0.74,0.98)	0.95 (0.91,0.99)

Table S8 – Full Model Results for Primary Cohort (1 month exposure, 3 month follow-up): Bolus versus Maintenance Dosing (N=776,203)

Parameter	Hospitalized for Infection	Infection-Related Death	Infection-Related Hospitalization/Death
Bolus dosing (ref. none)	1.07 (1.04,1.11)	1.06 (0.94,1.18)	1.07 (1.04,1.11)
Maintenance dosing (ref. none)	1.00 (0.97,1.02)	0.95 (0.87,1.04)	0.99 (0.97,1.02)
Bolus vs maintenance contrast	1.08 (1.05,1.11)	1.11 (1.00,1.23)	1.08 (1.05,1.11)
EPO exposure tertile (ref. 0) 3	1.06 (0.99,1.14)	0.86 (0.69,1.08)	1.06 (0.99,1.13)
EPO exposure tertile (ref. 0) 2	0.95 (0.89,1.01)	0.71 (0.58,0.88)	0.95 (0.89,1.01)
EPO exposure tertile (ref. 0) 1	0.91 (0.86,0.97)	0.73 (0.59,0.89)	0.91 (0.85,0.96)
Age (ref. 76-103) 16-45	0.97 (0.93,1.00)	0.26 (0.22,0.30)	0.93 (0.90,0.97)
Age (ref. 76-103) 46-60	0.92 (0.89,0.95)	0.46 (0.41,0.51)	0.89 (0.87,0.92)
Age (ref. 76-103) 61-75	0.91 (0.88,0.93)	0.68 (0.63,0.73)	0.89 (0.87,0.92)
Black (ref. White)	1.04 (1.02,1.06)	0.83 (0.78,0.90)	1.03 (1.01,1.05)
Other race (ref. White)	0.96 (0.92,1.01)	0.75 (0.64,0.88)	0.95 (0.91,1.00)
Female	1.00 (0.98,1.02)	0.91 (0.85,0.98)	0.99 (0.97,1.01)
Baseline Hb (ref. High, >13) Low (<10)	1.07 (1.02,1.12)	1.06 (0.91,1.23)	1.07 (1.02,1.12)
Baseline Hb (ref. High, >13) Med low (10-11)	1.03 (1.00,1.07)	0.93 (0.82,1.06)	1.03 (0.99,1.07)
Baseline Hb (ref. High, >13) Med (>11-12)	0.98 (0.95,1.01)	0.93 (0.83,1.03)	0.97 (0.94,1.00)
Baseline Hb (ref. High, >13) Med high (>12-13)	0.97 (0.94,1.00)	0.94 (0.85,1.04)	0.97 (0.94,1.00)
Index TSAT quintile (ref. 5) 1	1.04 (1.01,1.08)	1.12 (1.00,1.26)	1.05 (1.01,1.08)
Index TSAT quintile (ref. 5) 2	1.00 (0.97,1.03)	1.06 (0.94,1.19)	1.00 (0.97,1.03)
Index TSAT quintile (ref. 5) 3	0.99 (0.96,1.03)	0.99 (0.88,1.11)	0.99 (0.96,1.02)

Parameter	Hospitalized for Infection	Infection-Related Death	Infection-Related Hospitalization/Death
Index TSAT quintile (ref. 5) 4	1.00 (0.97,1.04)	0.96 (0.85,1.09)	1.00 (0.97,1.03)
Baseline ferritin missing (ref. 4) 0	1.08 (0.98,1.18)	0.66 (0.45,0.97)	1.05 (0.96,1.15)
Baseline ferritin quartile (ref. 4) 1	1.04 (1.01,1.07)	0.88 (0.79,0.97)	1.03 (1.00,1.06)
Baseline ferritin quartile (ref. 4) 2	0.98 (0.95,1.00)	0.91 (0.83,1.01)	0.97 (0.95,1.00)
Baseline ferritin quartile (ref. 4) 3	0.98 (0.96,1.01)	0.94 (0.85,1.03)	0.98 (0.96,1.01)
Infection, last 6 mos.: pneumonia	1.14 (1.11,1.18)	1.13 (1.03,1.23)	1.14 (1.11,1.17)
Infection, last 6 mos.: vascular access	1.46 (1.42,1.50)	1.22 (1.11,1.34)	1.45 (1.41,1.49)
Infection, last 6 mos.: sepsis	1.54 (1.49,1.58)	1.38 (1.26,1.51)	1.53 (1.48,1.57)
Infection in last month	1.41 (1.38,1.45)	1.36 (1.25,1.49)	1.41 (1.38,1.45)
Catheter (ref. graft/fistula)	2.12 (2.07,2.16)	1.51 (1.40,1.62)	2.09 (2.05,2.14)
Years on dialysis (ref. 4+) 0 yrs	0.81 (0.78,0.84)	0.62 (0.54,0.71)	0.81 (0.78,0.84)
Years on dialysis (ref. 4+) 1-3 yrs	0.87 (0.86,0.89)	0.72 (0.67,0.77)	0.87 (0.85,0.89)
Albumin (ref. High, >3.9) Low (<3.3)	2.06 (1.99,2.13)	5.71 (5.09,6.41)	2.13 (2.06,2.21)
Albumin (ref. High, >3.9) Med (3.3 - 3.9)	1.35 (1.32,1.38)	2.02 (1.84,2.22)	1.36 (1.33,1.40)
Baseline EPO quintile (ref. 5) 1	0.74 (0.70,0.77)	0.65 (0.56,0.76)	0.73 (0.70,0.77)
Baseline EPO quintile (ref. 5) 2	0.75 (0.72,0.78)	0.67 (0.58,0.77)	0.75 (0.72,0.78)
Baseline EPO quintile (ref. 5) 3	0.83 (0.80,0.86)	0.73 (0.65,0.82)	0.83 (0.80,0.85)
Baseline EPO quintile (ref. 5) 4	0.89 (0.87,0.92)	0.81 (0.74,0.89)	0.89 (0.86,0.91)
Baseline iron 0 (ref. 1-200 mg)	1.02 (0.99,1.05)	1.06 (0.97,1.16)	1.02 (0.99,1.05)
Baseline iron >200 mg. (ref. 1-200 mg)	1.08 (1.05,1.11)	1.01 (0.92,1.10)	1.08 (1.05,1.10)

Parameter	Hospitalized for Infection	Infection-Related Death	Infection-Related Hospitalization/Death
BMI (ref. Obese) Underweight	1.30 (1.24,1.36)	1.66 (1.45,1.90)	1.31 (1.25,1.37)
BMI (ref. Obese) Normal	1.14 (1.11,1.17)	1.24 (1.13,1.36)	1.15 (1.12,1.18)
BMI (ref. Obese) Overweight	1.04 (1.01,1.07)	0.95 (0.86,1.05)	1.04 (1.01,1.07)
Diabetes	1.30 (1.27,1.33)	1.22 (1.13,1.31)	1.30 (1.27,1.33)
Stroke	1.29 (1.26,1.33)	1.23 (1.13,1.34)	1.29 (1.26,1.33)
MI	1.02 (0.98,1.07)	1.04 (0.91,1.19)	1.02 (0.98,1.06)
COPD	1.19 (1.17,1.22)	1.25 (1.16,1.35)	1.20 (1.17,1.23)
Cancer	1.04 (1.00,1.07)	1.13 (1.02,1.24)	1.04 (1.01,1.08)
GI problem	1.09 (1.05,1.13)	1.10 (0.98,1.24)	1.08 (1.05,1.12)
Hospital days, none (ref. 5+)	0.83 (0.80,0.86)	0.89 (0.80,1.00)	0.83 (0.80,0.86)
Hospital days, 1-4 (ref. 5+)	0.95 (0.91,0.99)	0.85 (0.74,0.98)	0.95 (0.91,0.99)

Table S9 – Adjusted* Hazard Ratios and Risk Differences for Adverse Outcomes by Subgroups, High versus Low Dosing**

Group		Hospitalized for Infection		Infection-Related Death		Hospitalized for Infection/ Infection-Related Death	
		Hazard Ratio	Risk Diff.	Hazard Ratio	Risk Diff.	Hazard Ratio	Risk Diff.
Race:	**Black**	1.05 (1.01, 1.09)	14 (3, 25)	1.10 (0.95, 1.27)	1 (-2, 3)	1.06 (1.02, 1.10)	15 (5, 27)
	Non-black	1.04 (1.01, 1.08)	10 (0.4, 20)	1.08 (0.96, 1.21)	1 (-1, 4)	1.04 (1.01, 1.08)	11 (0.9, 20)
Vintage (y):	**<1**	1.02 (0.93, 1.12)	6 (-21, 36)	1.18 (0.84, 1.66)	3 (-4, 9)	1.02 (0.93, 1.12)	5 (-22, 33)
	1 - <4	1.03 (0.99, 1.07)	6 (-4, 13)	1.05 (0.92, 1.20)	0.3 (-2, 3)	1.03 (0.99, 1.07)	6 (-4, 13)
	≥ 4	1.07 (1.03, 1.12)	21 (11, 32)	1.10 (0.96, 1.25)	2 (-0.9, 5)	1.08 (1.04, 1.12)	22 (12, 33)
Dialysis Catheter		1.10 (1.06, 1.14)	49 (27, 70)	1.15 (1.00, 1.33)	4 (-0.9, 9)	1.10 (1.06, 1.14)	51 (27, 70)
Recent infection		1.02 (0.97, 1.07)	11 (-17, 40)	1.00 (0.84, 1.20)	-0.4 (-8, 6)	1.02 (0.97, 1.07)	10 (-17, 41)
EPO Hypo-responsive		0.98 (0.91, 1.06)	-8 (-54, 24)	0.98 (0.78, 1.24)	-1 (-12, 7)	0.98 (0.91, 1.06)	-12 (-53, 22)
TSAT (%):	**<20**	1.06 (1.01, 1.12)	15 (-2, 31)	1.03 (0.87, 1.21)	0.5 (-4, 5)	1.06 (1.00, 1.11)	15 (-2, 31)
	20-<50	1.05 (1.02, 1.08)	13 (5, 21)	1.08 (0.96, 1.21)	1 (-0.7, 3)	1.05 (1.02, 1.09)	14 (6, 22)
	≥ 50	1.01 (0.87, 1.18)	-1 (-36, 28)	1.56 (0.97, 2.50)	8 (-4, 20)	1.04 (0.90, 1.21)	7 (-30, 39)
Ferritin (mcg/L):	**<200**	0.97 (0.90, 1.04)	-8.0 (-31.4, 14.4)	1.44 (1.08, 1.92)	7.2 (2.4, 12.4)	0.98 (0.91, 1.05)	-4.3 (-27.7, 17.5)
	200-500	1.07 (1.02, 1.11)	17.3 (5.1, 26.4)	0.97 (0.83, 1.12)	-0.70 (-3.1, 1.9)	1.07 (1.02, 1.11)	17.4 (6.2, 26.7)
	501-1200	1.06 (1.02, 1.10)	13.0 (4.9, 24.2)	1.12 (0.98, 1.28)	1.8 (-1.4, 4.6)	1.06 (1.02, 1.11)	14.0 (5.8, 25.5)
	>1200	0.99 (0.86, 1.14)	0.76 (-43.6, 44.7)	1.15 (0.76, 1.74)	4.6 (-9.2, 17.9)	0.99 (0.87, 1.14)	1.2 (-42.7, 44.9)
TSAT*Ferritin:	**<25 * <500**	1.06 (1.01, 1.11)	15.7 (1.3, 28.8)	1.11 (0.94, 1.31)	2.4 (-1.5, 6.4)	1.06 (1.01, 1.11)	16.3 (0.98, 29.8)
	<25 * <500-800	1.08 (1.02, 1.15)	17.0 (1.1, 33.3)	1.12 (0.91, 1.38)	2.1 (-2.2, 6.6)	1.08 (1.02, 1.15)	17.8 (2.2, 34.2)
	<25 * >800	1.00 (0.90, 1.12)	1.7 (-37.1, 34.7)	1.20 (0.87, 1.67)	6.0 (-5.1, 16.0)	1.02 (0.91, 1.13)	6.4 (-33.9, 41.1)

Group		Hospitalized for Infection		Infection-Related Death		Hospitalized for Infection/ Infection-Related Death	
		Hazard Ratio	Risk Diff.	Hazard Ratio	Risk Diff.	Hazard Ratio	Risk Diff.
	≥25 * <500	1.05 (0.99, 1.11)	11.4 (-1.6, 23.9)	0.98 (0.80, 1.21)	-0.29 (-3.5, 2.7)	1.05 (1.00, 1.11)	12.2 (-0.92, 25.3)
	≥25 * 500-800	1.08 (1.01, 1.15)	14.5 (0.66, 29.3)	1.13 (0.89, 1.42)	1.4 (-3.0, 5.7)	1.08 (1.01, 1.15)	15.3 (1.3, 30.8)
	≥25 * >800	1.04 (0.94, 1.16)	11.5 (-11.9, 38.1)	1.14 (0.80, 1.62)	2.5 (-3.9, 10.6)	1.04 (0.94, 1.16)	12.5 (-12.1, 39.3)
Albumin (g/dL):	**<3**	1.06 (0.96, 1.16)	49.8 (-46.5, 130.1)	1.10 (0.88, 1.38)	13.7 (-13.7, 46.3)	1.06 (0.97, 1.17)	56.4 (-32.0, 147.5)
	3 - <3.5	1.03 (0.97, 1.09)	12.4 (-17.5, 43.2)	1.04 (0.87, 1.23)	1.4 (-7.1, 9.4)	1.03 (0.97, 1.08)	11.5 (-17.4, 40.4)
	3.5 - <3.8	1.04 (0.98, 1.09)	11.8 (-7.4, 27.9)	1.07 (0.88, 1.29)	1.2 (-2.5, 6.0)	1.04 (0.99, 1.09)	12.8 (-7.3, 28.9)
	3.8 - <4	1.03 (0.97, 1.10)	6.9 (-5.8, 19.2)	1.10 (0.88, 1.38)	1.3 (-2.5, 4.5)	1.04 (0.98, 1.10)	8.1 (-4.8, 20.7)
	≥4	1.08 (1.03, 1.13)	14.0 (5.9, 21.3)	1.17 (0.94, 1.46)	1.1 (-1.0, 3.0)	1.09 (1.03, 1.14)	15.2 (7.2, 22.5)
Hgb (g/dL)	**<10**	1.03 (0.94, 1.13)	13.7 (-26.5, 54.9)	1.02 (0.75, 1.38)	0.05 (-10.9, 12.6)	1.03 (0.94, 1.13)	12.3 (-31.1, 54.6)
	10-12	1.06 (1.01, 1.10)	15.7 (3.6, 24.7)	1.06 (0.92, 1.22)	0.83 (-2.0, 3.8)	1.05 (1.01, 1.10)	15.8 (3.3, 25.3)
	>12	1.04 (1.01, 1.08)	10.1 (0.57, 18.1)	1.13 (0.99, 1.29)	1.9 (-0.26, 4.2)	1.05 (1.01, 1.09)	11.9 (2.9, 20.5)

*adjusted analyses controlled for the following variables at baseline: age; race; sex; vintage; number of hospital days in last month; history of infection in last month; BMI; most recent vascular access, hemoglobin; ferritin; index TSAT; iron dose; albumin level; EPO dose; history in last 6 months of pneumonia, sepsis, vascular access infection, diabetes, stroke, MI, COPD, cancer, GI bleeding; and EPO dose during exposure.

**Risk difference is the estimated difference in number of events per 1,000 person years.

Table S10 – Adjusted* Hazard Ratios and Risk Differences for Adverse Outcomes by Subgroups, Bolus versus Maintenance Dosing**

		Hospitalized for Infection		Infection-Related Death		Hospitalized for Infection/ Infection-Related Death	
Group		Hazard Ratio	Risk Diff.	Hazard Ratio	Risk Diff.	Hazard Ratio	Risk Diff.
Race:	**Black**	1.09 (1.04, 1.13)	28 (14, 41)	1.21 (1.03, 1.41)	3 (-0.4, 6)	1.09 (1.05, 1.14)	30 (15, 43)
	Non-black	1.06 (1.02, 1.11)	21 (9, 34)	1.06 (0.93, 1.21)	1 (-2, 5)	1.07 (1.03, 1.11)	22 (10, 35)
Vintage (y):	**<1**	1.10 (1.00, 1.22)	31 (-5, 60)	1.12 (0.79, 1.59)	3 (-7, 10)	1.10 (1.00, 1.21)	30 (-10, 59)
	1 - <4	1.05 (1.01, 1.10)	17 (6, 31)	1.09 (0.94, 1.27)	1 (-2, 4)	1.06 (1.02, 1.10)	19 (8, 33)
	≥ 4	1.10 (1.05, 1.15)	33 (16, 46)	1.11 (0.96, 1.29)	3 (-1, 6)	1.10 (1.05, 1.15)	33 (17, 48)
Dialysis Catheter		1.12 (1.08, 1.17)	73 (48, 99)	1.09 (0.93, 1.27)	2 (-3, 9)	1.12 (1.08, 1.17)	75 (49, 103)
Recent infection		1.09 (1.03, 1.14)	57 (19, 99)	1.03 (0.86, 1.24)	0.4 (-8, 9)	1.09 (1.03, 1.15)	60 (24, 102)
EPO Hypo-responsive		0.97 (0.90, 1.04)	-21 (-58, 21)	1.01 (0.80, 1.28)	-0.3 (-12, 10)	0.96 (0.89, 1.04)	-24 (-61, 18)
TSAT (%):	**<20**	1.09 (1.04, 1.14)	27 (14, 40)	1.02 (0.87, 1.19)	0.2 (-5, 5)	1.09 (1.04, 1.14)	27 (15, 41)
	20-<50	1.08 (1.04, 1.13)	26 (16, 38)	1.17 (1.02, 1.34)	3 (0.0, 6)	1.09 (1.04, 1.13)	27 (17, 40)
	≥ 50	1.10 (0.93, 1.30)	27 (-19, 68)	1.16 (0.65, 2.08)	3 (-12, 16)	1.12 (0.95, 1.33)	33 (-13, 78)
Ferritin (mcg/L):	**<200**	1.06 (0.99, 1.14)	22.3 (-2.6, 45.0)	1.39 (1.05, 1.84)	7.7 (1.1, 13.6)	1.07 (1.00, 1.16)	26.2 (1.2, 49.5)
	200-500	1.10 (1.05, 1.15)	31.3 (16.5, 48.5)	1.10 (0.93, 1.31)	2.1 (-1.5, 5.9)	1.10 (1.05, 1.15)	32.4 (16.5, 49.1)
	501-1200	1.07 (1.02, 1.12)	20.6 (9.1, 34.0)	1.06 (0.91, 1.24)	0.82 (-3.5, 4.9)	1.07 (1.02, 1.12)	21.2 (9.2, 34.4)
	>1200	1.02 (0.88, 1.17)	9.8 (-43.7, 61.4)	0.91 (0.59, 1.40)	-3.1 (-17.5, 15.5)	1.02 (0.89, 1.17)	11.6 (-39.0, 64.5)
TSAT*Ferritin:	**<25 * <500**	1.11 (1.06, 1.16)	32.4 (19.1, 47.5)	1.17 (0.99, 1.38)	3.8 (-1.5, 8.3)	1.11 (1.06, 1.16)	33.9 (19.2, 49.9)
	<25 * <500-800	1.08 (1.01, 1.15)	19.9 (2.5, 39.1)	1.03 (0.82, 1.29)	0.43 (-4.9, 6.2)	1.08 (1.01, 1.15)	20.7 (2.5, 39.4)

Group		Hospitalized for Infection		Infection-Related Death		Hospitalized for Infection/ Infection-Related Death	
		Hazard Ratio	Risk Diff.	Hazard Ratio	Risk Diff.	Hazard Ratio	Risk Diff.
	<25 * >800	1.01 (0.91, 1.13)	2.9 (-33.9, 42.4)	1.11 (0.80, 1.54)	3.2 (-8.9, 15.1)	1.02 (0.92, 1.14)	7.3 (-26.9, 48.3)
	≥25 * <500	1.10 (1.02, 1.18)	27.4 (5.0, 49.5)	1.25 (0.96, 1.62)	3.6 (-1.4, 9.1)	1.10 (1.03, 1.18)	29.4 (6.2, 51.4)
	≥25 * 500-800	1.11 (1.01, 1.22)	30.0 (4.3, 56.2)	1.01 (0.72, 1.42)	-0.47 (-6.2, 7.3)	1.10 (1.00, 1.21)	27.9 (2.2, 55.5)
	≥25 * >800	1.10 (0.97, 1.23)	34.0 (1.4, 79.2)	1.08 (0.73, 1.62)	2.0 (-7.2, 13.4)	1.10 (0.98, 1.24)	36.7 (4.4, 83.8)
Albumin (g/dL):	**<3**	1.00 (0.91, 1.11)	-1.1 (-94.8, 88.8)	1.10 (0.87, 1.39)	13.9 (-20.3, 50.7)	1.00 (0.91, 1.10)	-2.1 (-91.0, 97.5)
	3 - <3.5	1.06 (1.00, 1.13)	31.5 (-2.9, 62.0)	1.14 (0.94, 1.37)	6.4 (-2.7, 15.4)	1.07 (1.00, 1.13)	34.5 (1.5, 66.3)
	3.5 - <3.8	1.11 (1.05, 1.17)	38.3 (17.5, 56.7)	1.02 (0.82, 1.26)	0.06 (-5.0, 4.9)	1.11 (1.05, 1.17)	38.1 (17.6, 56.1)
	3.8 - <4	1.06 (0.99, 1.14)	17.3 (1.0, 34.5)	1.04 (0.80, 1.34)	0.66 (-4.3, 5.0)	1.06 (1.00, 1.14)	18.5 (2.7, 35.3)
	≥4	1.10 (1.04, 1.16)	21.3 (9.8, 30.8)	1.28 (1.00, 1.64)	2.0 (-0.65, 4.3)	1.11 (1.05, 1.17)	23.3 (11.3, 33.2)
Hgb (g/dL)	**<10**	1.00 (0.91, 1.10)	4.9 (-36.5, 52.0)	1.03 (0.77, 1.39)	0.36 (-9.9, 15.3)	1.00 (0.91, 1.09)	2.9 (-41.4, 46.2)
	10-12	1.07 (1.02, 1.11)	23.1 (10.0, 35.4)	1.08 (0.93, 1.26)	1.6 (-2.5, 5.6)	1.07 (1.02, 1.11)	24.0 (10.2, 37.7)
	>12	1.11 (1.06, 1.15)	29.1 (17.3, 42.8)	1.18 (1.01, 1.37)	3.1 (-0.25, 6.3)	1.11 (1.07, 1.16)	31.3 (19.2, 44.6)

*adjusted analyses controlled for the following variables at baseline: age; race; sex; vintage; number of hospital days in last month; history of infection in last month; BMI; most recent vascular access, hemoglobin; ferritin; index TSAT; iron dose; albumin level; EPO dose; history in last 6 months of pneumonia, sepsis, vascular access infection, diabetes, stroke, MI, COPD, cancer, GI bleeding; and EPO dose during exposure.

**Risk difference is the estimated difference in number of events per 1,000 person years.

Table S11 – Results of High vs Low Dosing (1 month exposure, 3 month follow up), Covariate Blocks and Sensitivity Analyses Adding Covariates

High (200mg) vs Low	Hospitalized for Infection	Infection-Related Death	Hospitalized for Infection or Infection-Related Death
M0: Unadjusted	1.37 (1.33,1.40)	1.43 (1.32,1.55)	1.37 (1.34,1.40)
M1: EPO Dose during exposure	1.23 (1.20,1.26)	1.26 (1.15,1.37)	1.23 (1.20,1.26)
M2: Demographics	1.23 (1.20,1.26)	1.27 (1.16,1.38)	1.23 (1.20,1.26)
M3: Baseline ferritin, Hb, TSAT	1.14 (1.11,1.17)	1.16 (1.06,1.26)	1.14 (1.12,1.17)
M4: Baseline iron, EPO, comorbidities.	1.05 (1.02,1.07)	1.08 (0.99,1.19)	1.05 (1.02,1.08)
M5: ESRD reason, other comorbidities, year, region	1.04 (1.02,1.07)	1.08 (0.98,1.18)	1.05 (1.02,1.08)
M6: Propensity (PS) model	1.04 (1.01,1.07)	1.06 (0.96,1.17)	1.04 (1.02,1.07)
M7: PS model with expanded history of EPO & iron use added	1.04 (1.01,1.07)	1.05 (0.95,1.16)	1.04 (1.01,1.07)
M8: High-dimensional PS model	1.04 (1.01,1.07)	1.06 (0.96,1.17)	1.04 (1.01,1.07)

Table S12 – Results of Bolus vs Maintenance Dosing (1 month exposure, 3 month follow-up), Covariate Blocks & Sensitivity Analyses Adding Covariates

Bolus vs Maintenance	Hospitalized for Infections	Infection-related Death	Infection-related Hospitalization or Death
M0: Unadjusted	1.51 (1.47,1.56)	1.63 (1.48,1.78)	1.52 (1.48,1.56)
M1: EPO Dose during exposure	1.32 (1.28,1.36)	1.38 (1.26,1.52)	1.32 (1.29,1.36)
M2: Demographics	1.32 (1.28,1.36)	1.39 (1.26,1.52)	1.32 (1.29,1.36)
M3: Baseline ferritin, Hb, TSAT	1.19 (1.16,1.22)	1.21 (1.10,1.34)	1.19 (1.16,1.23)
M4: Baseline iron, EPO, comorbidities	1.08 (1.05,1.11)	1.11 (1.00,1.23)	1.08 (1.05,1.11)
M5: ESRD reason, other comorbidities, year, region	1.07 (1.04,1.10)	1.11 (1.00,1.22)	1.08 (1.05,1.11)
M6: PS model	1.09 (1.05,1.12)	1.11 (1.00,1.23)	1.09 (1.06,1.12)
M7: PS model with past EPO & iron use	1.09 (1.05,1.12)	1.10 (0.99,1.22)	1.09 (1.05,1.12)
M8: High dimensional PS model	1.08 (1.05,1.11)	1.11 (0.99,1.23)	1.08 (1.05,1.12)

Figure S1 – Cohort Identification