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Safety of Intravenous Iron in Hemodialysis: Longer-term Comparisons of Iron Sucrose Versus Sodium Ferric Gluconate Complex

Wolfgang C. Winkelmayer, M.D., Sc.D., Benjamin A. Goldstein, Ph.D., Aya A. Mitani, M.P.H., Victoria Y. Ding, M.Sc., Medha Airy, M.D., Sreedhar Mandayam, M.D., M.P.H., Tara I. Chang, M.D., M.Sc., M. Alan Brookhart, Ph.D., and Steven Fishbane, M.D.

Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, TX (WCW, MA, SM); Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, NC (BAG); Department of Biostatistics, Boston University School of Public Health, Boston, MA (AAM); Division of Nephrology, Department of Medicine (TIC), and Center for Biomedical Informatics Research (VYD), Stanford University School of Medicine, Palo Alto, CA; Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC (MAB); and Division of Kidney Diseases and Hypertension, Hofstra Northwell School of Medicine, Great Neck, NY (SF)

Abstract

Background—Controversy exists about any differences in longer-term safety across different intravenous iron formulations routinely used in hemodialysis (HD) patients. We exploited a natural experiment to compare outcomes of patients initiating HD in facilities that predominantly (in 90% of their patients) used iron sucrose (IS) *versus* sodium ferric gluconate complex (FG).

Study Design—Retrospective cohort study of incident HD patients.

Setting & Participants—Using the US Renal Data System, we hard-matched on geographic region and center characteristics HD facilities predominantly using FG with similar ones using IS. Subsequently incident HD patients were assigned their facility iron formulation exposure.

Intervention—Facility-level use of IS *versus* FG.

Correspondence to: Wolfgang C. Winkelmayer, MD, MPH, ScD, Section of Nephrology, Baylor College of Medicine, One Baylor Plaza, Suite ABBR R705, Houston, Texas 77030, winkelma@bcm.edu | Phone: +1 (713) 798-2625 | Fax: +1 (713) 798-5010.

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Outcomes—Patients were followed up for mortality from any, cardiovascular, or infectious cause. Medicare-insured patients were followed for infectious and cardiovascular (stroke, myocardial infarction) hospitalizations and for composite outcomes with the corresponding cause-specific deaths.

Measurements—Hazard ratios.

Results—We matched 2,015 IS facilities with 2,015 FG facilities, in which 51,603 patients (IS: 24,911; FG: 26,692) subsequently initiated HD. All recorded patient characteristics were balanced between groups. Over 49,989 person-years, 10,381 deaths (3908 cardiovascular; 1209 infectious) occurred. Adjusted all-cause (HR, 0.98; 95% CI, 0.93–1.03), cardiovascular (HR, 0.96; 95% CI, 0.89–1.03), and infectious mortality (HR, 0.98; 95% CI, 0.86–1.13) did not differ between IS and FG facilities. Among Medicare beneficiaries, no differences between FG and IS facilities were observed in fatal or non-fatal cardiovascular events (HR, 1.01; 95% CI, 0.93–1.09). The composite infectious end point occurred less frequently in IS *versus* FG facilities (HR, 0.92; 95% CI, 0.88–0.96).

Limitations—Unobserved selection bias from non-random treatment assignment.

Conclusions—Patients initiating HD in facilities almost exclusively using IS *versus* FG had similar longer-term outcomes. However, there was a small decrease in infectious hospitalizations and deaths in patients dialyzing in facilities predominantly using IS. This difference may be due to residual confounding, random chance, or a causal effect.

Keywords

intravenous iron; iron sucrose; sodium ferric gluconate complex; mortality; cardiovascular; safety; infectious hospitalization; myocardial infarction; stroke; hemodialysis; end-stage renal disease (ESRD); dialysis facility formulary; natural experiment

Patients with end-stage renal disease (ESRD) receiving maintenance hemodialysis (HD) have been estimated to lose 1–2 g of iron per year (in some patients as much as 4–5 g annually)(1) from a combination of subclinical or overt bleeding events, which are common in this population,(2) as well as through blood retained in and discarded with the extracorporeal circuit after each HD treatment. Since this iron loss exceeds what these patients can usually replace through intestinal absorption,(3) most HD patients depend on intravenous iron supplementation to remain iron replete and to optimize their response to treatment with erythropoiesis-stimulating agents. However, intravenous administration of iron is un-physiological and circumvents biological systems in place to control iron balance and to minimize the appearance of non-transferrin bound iron in the circulation. In addition to the extremely rare event of acute and sometimes life-threatening anaphylaxis, concerns have lingered for decades about potential longer-term consequences, such as infectious and cardiovascular events that may be mediated via immunological, inflammatory, and oxidative stress pathways.(1) Little attention has been given to any putative differences in longer-term safety among available iron formulations, which are structurally heterogeneous iron-carbohydrate nanoparticle complexes with considerably different pharmacologic stability and pharmacokinetic properties.(4) Almost no randomized or observational evidence exists

on the comparative outcomes among intravenous iron formulations in ESRD, and the few studies that exist had small sample sizes and/or very limited follow up.(5–7)

We conducted the present study to fill this evidence gap and compared the longer-term safety between the two intravenous iron formulations predominantly used for patients with ESRD receiving HD in the United States: iron sucrose (IS) and sodium ferric gluconate complex (FG). We employed an innovative design that exploited the natural experiment that arose when dialysis facilities treated all or almost all of their patients with a single iron formulation.

Methods

Overview

Most dialysis centers restrict the choice among injectable medications of a class, e.g. among erythropoiesis-stimulating agents, intravenous iron preparations, or vitamin D analogues, and often have formularies in place that require that all or almost all patients receive the preferred agent. These center-level decisions can be considered natural experiments if centers predominantly using one drug versus another do not differ systematically in other aspects of their care and, on average, the characteristics of their patients. If these assumptions hold true, the center can serve as an instrument and patient exposure defined on the predominant practice pattern of each center. We have recently used this design in two comparative safety studies of erythropoiesis-stimulating agents and of ferumoxytol, and the following resembles the methods described therein.(8, 9) This approach is particularly attractive for the intermittent nature of iron treatment, where iron storage parameters and (temporary and sometimes relative) contraindications will lead to potentially strong, and partly unobserved, time-dependent confounding that may be difficult to accommodate using traditional or novel (marginal-structural models) methods for time-dependent exposures.

Study Population: Patient Selection, Exposure Assignment, and Follow-up

From the US Renal Data System (USRDS), the national ESRD registry, we recorded from billing codes to Medicare all intravenous iron administrations for 1/1/1999–12/31/2011. For each HD center and calendar month, we then defined the proportion of intravenous administrations for IS *versus* FG *versus* other (iron dextran, ferumoxytol). For each center, we termed a calendar month an IS center-month if 90% of administered intravenous iron administrations in that center and month were IS; similarly, if 90% of administrations were for FG, we considered it a FG center-month. All other center-months were categorized as “mixed/other.” Since we were interested in studying “mature” use of each iron formulation of interest, centers were required to have predominantly used the same formulation for at least 12 months, prior to being eligible to contribute patients to the study cohort. Centers were then described by their geographic region (Northwest, Midwest, South, West), chain affiliation (yes *versus* no), and whether they were free-standing or hospital-based, and pairs of one IS and FG center each were hard-matched on these characteristics and calendar year.

Following the matching month, we enrolled all patients regardless of their insurance status who had incident ESRD and initiated HD in an IS facility and its matched FG facility. If a

facility switched back from predominant use of IS or FG, respectively, both matched facilities were no longer eligible to contribute new patients to the study and all existing patients in the matched set were censored for further follow-up. Since iron therapy is usually intermittent, depending on iron status measurements, dosing approach (bolus versus maintenance), and potential temporary contraindications (e.g., infections), included patients may have received continuous, intermittent, or no iron treatment at all during follow up. However, if treated, they usually received the intravenous iron formulation identified as predominantly used by their facility at the time.

The closed cohort that was selected this way was then followed up for all-cause and cause-specific (cardiovascular, infectious, other) mortality, since mortality is recorded in the USRDS regardless of insurance status and payor type. Patients were censored at end of database (12/31/2011), upon switching to peritoneal dialysis, when receiving a kidney transplant, switching to another HD facility, or when their facility or its match switched to predominant use of another intravenous iron formulation as described in detail in previous paragraph.

We used Medicare billing claims for the study of non-fatal outcomes; to do so, we identified the subsample of patients who survived 90 days from initiation of dialysis and whose primary payor at day 91 was Medicare (Parts A+B). By federal mandate, most patients with ESRD qualify for Medicare coverage at the beginning of the fourth month after incident ESRD, regardless of their age. Patients were followed up from day 91 after initiation of HD until censoring for the aforelisted reasons, as well as at loss of Medicare Parts A+B coverage, or if they died. In this subcohort, we also plotted for each month of follow up the percentages of patients receiving IS versus FG, to demonstrate the validity of using facility preference as the proxy for actual exposure over time. We further plotted mean hemoglobin concentrations and monthly doses of erythropoiesis-stimulating agents to investigate whether differences between the study groups existed in other anemia management aspects.

Patient Characteristics

From the USRDS patient file, we ascertained patients' age, sex, race (white, black, Asian, other), ethnicity (Hispanic versus non-Hispanic), and whether patients were covered by Medicaid (a proxy for low socioeconomic status). From the Medical Evidence Report, we recorded whether each of several comorbidities (diabetes, hypertension, arteriosclerotic heart disease, heart failure, peripheral artery disease, cerebrovascular disease, chronic obstructive lung disease, cancer, inability to ambulate or transfer, tobacco use, drug use, alcohol use) was reported. We also recorded body mass index and serum hemoglobin and serum albumin concentrations, and calculated from reported creatinine concentrations at initiation of dialysis the estimated glomerular filtration rate (eGFR).

Outcomes

Mortality from any cause, cardiovascular mortality, and mortality from an infectious cause were ascertained from the death file in the USRDS, which collates pertinent information from several federal sources. Non-fatal outcomes of interest were ascertained from International Classification of Diseases, 9th Revision (ICD-9), diagnosis codes from

inpatient Medicare claims using validated algorithms and included stroke (ICD-9: 430, 431, 432.x, 433.x1, 434.x1, 436, 437.1),(10) myocardial infarction (MI; ICD-9: 410.x1),(11) as well as a composite of stroke, MI, and cardiovascular mortality. In addition, we investigated infectious outcomes: hospitalized infection using a comprehensive set of diagnosis codes, (12) death reportedly due to an infectious cause, and their composite.

Statistical Analysis

We first tabulated the characteristics of the matched IS and FG facilities. We then tabulated the characteristics of all enrolled incident HD patients by whether they dialyzed in an IS *versus* a FG facility. Groups were compared using standardized differences, with <5% indicating excellent and 5%–<10% indicating good balance.(13) We examined cumulative incidence plots for all outcomes for any differences in event rates or censoring events. We used Cox proportional hazards regression stratified on matching set to estimate unadjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). We examined Schoenfeld residual plots to identify any violations of the proportionality assumption. We plotted the cumulative incidences of all outcome and censoring events to identify any potential informative censoring between the groups. We also fit demographics-adjusted models and models that included all reported comorbidities and biometric/laboratory characteristics. Missing data were addressed with multiple imputation by chained equation using the “mice” (multiple imputation by chained equations) package in R, version 3.1 (R Foundation for Statistical Computing).(14)

We conducted statistical analyses using SAS software, version 9.3 (SAS Institute Inc; www.sas.com) and R, version 3.1 (www.r-projects.org). The Institutional Review Boards of Baylor College of Medicine and Stanford University School of Medicine approved this work (approval numbers 17904 and H-36408, respectively); the need for informed consent was waived.

Results

We identified 2,015 individual dialysis centers that had predominantly used FG for 12 months and matched these with the same number of IS centers. In addition to the three center characteristics upon which matching was conducted, IS and FG centers were also quite similar in their distribution of profit status and size (Table 1). Subsequently, 51,603 patients initiated HD treatment in these centers: 24,911 (48.3%) in IS centers and 26,692 (51.7%) in FG centers. Patients had a median age of 65 years, 45% were women, and approximately two-thirds were white and one third black; 10% were Hispanic. Table 2 shows the distribution of all measured characteristics of these patients. Of note, not a single standardized difference exceeded 5%, indicating excellent balance of all observed characteristics.

The study patients contributed 49,989 person-years of follow-up during which 10,381 deaths occurred, 3908 from cardiovascular and 1209 from infectious causes. The corresponding incidence rates were 208, 78, and 24 events per 1000 person-years, respectively. Table 3 shows unadjusted and adjusted estimates of association, all of which had tight CIs owing to the large sample size and large numbers of outcomes observed. Unadjusted all-cause and

cardiovascular mortality was slightly lower in IS patients, but adjustment for demographics, and then for other observed characteristics rendered these associations null (HR, 0.98; 95% CI, 0.93–1.03). Similarly, there were no adjusted associations between iron formulation and either cardiovascular or infectious cause-specific mortality.

Of the 51,603 patients, 24,865 (48.2%) were alive and had Medicare (A+B) as their payor by day 90 after onset of ESRD (Table 4). The incidence rate of the composite cardiovascular end point was 150 events per 1000 person-years, without any difference between the two iron formulations (adjusted HR, 1.01; 95% CI, 0.93–1.09). Among the 24,865 patients in this subcohort, almost half (12,131 [48.8%]) had a hospitalized infection episode at an incidence rate of 940 per 1000 person-years. Patients receiving their maintenance dialysis at a center predominantly using IS had an 8% lower adjusted rate of hospitalized infections compared to patients receiving dialysis at a FG center (HR, 0.92; 95% CI, 0.88–0.96). When adding infectious-cause deaths, only 54 additional events were observed and the estimates of association were identical (Table 3).

All findings remained robust in complete case analysis. We found no indications that the proportionality assumption of Cox models was violated for any of the outcomes or for the presence of informative censoring between the two groups. Mean hemoglobin concentrations (Figure 1) and dosage of erythropoiesis-stimulating agents (Figure 2) appeared similar during follow-up between both groups. Adherence of individual dosing practices with the derived facility-preference exposure was high and exceeded 99% in both exposure groups and for all months of follow up (Figure 3).

Discussion

We exploited the natural experiment of facility-level iron supplementation practice defined by their predominant iron formulation used and conducted a large, registry-based comparative-effectiveness (safety) study of the two most widely used intravenous iron formulations in the United States (IS and FG) in unselected patients with ESRD undergoing routine HD care in typical dialysis care settings. Indeed, this natural experiment yielded comparison groups that were exceedingly similar on a large number of observed characteristics. We found no differences between the two iron formulations in all-cause mortality and cardiovascular outcomes. However, we did find an 8% reduction in the relative hazards of infectious hospitalizations in patients receiving dialysis at centers that predominantly used IS *versus* FG. While this reduction was small on the relative scale, the event of interest was quite common, with almost one such event occurring per year of follow-up. If one were to translate the 8% reduction in the relative rate into an absolute rate reduction (using the average incidence rate of 940 events per 1000 person years), assuming causality and representativeness, approximately 75 infection events per 1000 person years could be avoided if all patients in FG centers received IS instead. On the population-level, depending on the prevalence of FG use, a change to IS could translate into sizeable reductions in FG-related infections leading to excess morbidity, mortality, and cost to Medicare.

The concern for non-uniform treatment effects among intravenous iron preparations is grounded in plausible biological differences among these drugs. Since non-transferrin bound iron in tissues or circulation is highly toxic, all iron preparations wrap their iron cores in carbohydrate envelopes of different structure and complexity. As a result, the kinetics, dynamics, and overall pharmacology differ. It has been shown that even after a modest dose of intravenous iron, iron release into plasma occurs in quantities greater than the iron binding capacity of transferrin.⁽¹⁵⁾ While no studies have tested whether the extent of this leakage differs among intravenous iron agents, this could quite plausibly be the case.

Only few studies have examined the potential differences in clinical outcomes among intravenous iron preparations. Registrational trials usually compared one intravenous iron agent with placebo or an oral iron supplement and had focused on anemia treatment (hemoglobin concentration) end points. The few observational studies that exist mostly compared untreated and treated patients, with comparisons among different formulations embedded in the treated group, and/or were only able to investigate short-term outcomes owing to the intermittent nature of intravenous iron treatment and the high likelihood of time-dependent confounding by (contra)indication.⁽⁶⁾

We approached our hypothesis using a novel design that fits the specific scenario and intermittent nature of intravenous iron treatment in HD patients particularly well. We identified dialysis centers that predominantly used only one of these two formulations for almost all (90% of all intravenous iron administrations) of their patients requiring iron supplementation, and used it as a proxy (instrument) for treatment actually received by incident HD patients in these centers. This design assigns facility-level exposure to all patients regardless of whether and when they actually received such treatment, which avoids (time-dependent) treatment by indication bias and allows for the study of longer-term outcomes of intermittent treatments, which most standard methods for comparative effectiveness research (i.e. per-protocol analyses) cannot do. With our analytical approach, the effect estimate is assumed to be unbiased in its direction, but biased towards the null in magnitude, depending on the degree of individual-level “non-adherence” to facility-level exposure, which we also assume to be non-differential. This situation and assumption is not different to any (cluster) randomized trial with less than perfect adherence. Indeed, we found very high correspondence of individual iron formulation use with the derived facility-level preference to administer IS vs. FG.

The question of the safety of intravenous iron treatment is hotly debated, especially in light of recently evolving treatment patterns in the United States, where changing financial incentives have led to increasing use of intravenous iron even in patients with rather high serum ferritin concentrations.⁽¹⁶⁾ In April 2014, the KDIGO (Kidney Disease: Improving Global Outcomes) foundation hosted a “controversies conference” whose sole focus was on intravenous iron use in patients with chronic kidney disease and its safety.⁽¹⁾ Several areas of potential iron toxicity were explored; deficiencies of the current literature prevented any firm statement on safety but led to strong recommendations for further research on iron safety.⁽¹⁾ Given the heterogeneity of available intravenous iron products, and the potential for differential effects on safety outcomes, the paucity of data on the relative safety of these

drugs represents an important knowledge gap. We believe that our study and innovative methodology allowed for a critical contribution towards filling this evidence gap.

There are certain limitations of our study. Because the comparison of IS and FG was not randomized, residual confounding cannot be excluded. It is possible that such confounding would arise as a result of membership in a specific dialysis organization, which may mandate care practices other than those pertaining to anemia treatment. However, accounting for the identity of the dialysis organization analytically is not feasible since dialysis organizations also restrict their formularies to a single iron formulation. Hence, individual dialysis organization strata would lack heterogeneity of exposure and measures of association would be inestimable. Another limitation is that we only compared two iron drugs, IS and FG. While these are the predominant intravenous iron agents used in the United States, and accounted for 98.7% of recorded iron doses in our study, several other drugs are available and used to a greater extent globally.(17) A recent study evaluating ferumoxytol compared with FG/IS was hampered by low use of this formulation in US ESRD patients and the resulting wide confidence limits.(9) We cannot determine whether there were any differences in the doses of the two iron compounds administered, since the dose for each administration was not recorded in Medicare billings during the majority of years of our study. It is indeed likely that individually administered iron doses differed between IS and FG facilities, since FG is formulated in 62.5 or 125 mg dosing whereas IS is formulated as 100 or 200 mg. We did not have information on the presence or use of central venous HD catheters. Previous research has demonstrated that differences in outcomes across groups defined by iron treatment strategies were modified and accentuated by this form of dialysis access. Studies demonstrating that the risk of intravenous iron strategies may be modified by presence of central venous HD catheters used electronic health records data, whereas we used claims data in which dialysis access is not reported. Finally, we did not study anaphylaxis events, a rare but important complication of intravenous iron treatment, for which a different study design would have been required.(18)

In conclusion, we have found that the two most commonly utilized intravenous iron drugs in the US ESRD population, IS and FG, appear to have generally similar longer-term safety profiles. One difference, and potentially a clinically relevant one, was an increased risk for infectious hospitalizations among patients treated at dialysis facilities where FG was the predominant drug used. Whether this drug safety signal is due to residual confounding, differences in dosing, or random chance, or is reflective of a causal effect, needs to be settled through a sufficiently-powered and well-executed randomized trial.

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Dr Winkelmayer reports having served as a scientific advisor to Akebia, AMAG, Amgen, AstraZeneca, Bayer, and Relaysa and on data safety monitoring boards for Medtronic and Zoll. Dr Brookhart has received investigator-

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Figure 1. Mean Monthly Hemoglobin Concentration During Follow-up

Assessed among Patients with Medicare (Parts A+B) Coverage from Day 91 after ESRD incidence. Shown are means and 95% confidence bands. Sodium ferric gluconate complex in blue; iron sucrose in red.

Figure 2. Mean Monthly Erythropoietin Dose During Follow-up

Assessed among Patients with Medicare (Parts A+B) Coverage from Day 91 after ESRD incidence. Shown are means and 95% confidence bands. Sodium ferric gluconate complex in blue; iron sucrose in red.

Figure 3. Monthly Proportions of Iron Formulation Used in Concordance with Facility-Derived Exposure During Follow-up

Assessed among Patients with Medicare (Parts A+B) Coverage from Day 91 after ESRD incidence. Monthly percent of all iron administrations being IS in IS facilities and FG in FG facilities, respectively. Sodium ferric gluconate complex in blue; iron sucrose in red.

Table 1

Characteristics of Sodium Ferric Gluconate Complex and Matched Iron Sucrose Facilities

Variable	Ferric Gluconate		Iron Sucrose	
No. of facilities	2015 (100.0)		2015 (100.0)	
Facility Type *				
Non-chain	831 (41.2)		831 (41.2)	
Chain	1184	(58.8)	1184	(58.8)
Facility Type *				
Free-standing	1753	(87.0)	1753	(87.0)
Hospital	262	(13.0)	262	(13.0)
Profit status				
Missing	<10	(<0.5)	20	(1.0)
Not for profit	405	(20.1)	405	(20.1)
For profit	1601	(79.5)	1590	(78.9)
Facility size				
0–49 patients	849	(42.1)	877	(43.5)
50 patients	1166	(57.9)	1138	(56.5)
Region *				
Northwest	340	(16.9)	340	(16.9)
Midwest	406	(20.1)	406	(20.1)
South	997	(49.5)	997	(49.5)
West	272	(13.5)	272	(13.5)

Note: Values are given as count (percentage).

* Hard matched on these facility characteristics

Characteristics of Patients Initiating Dialysis in Sodium Ferric Gluconate Complex and Matched Iron Sucrose Facilities

Table 2

Variable	All Patients (N=51,603 [100%])	Ferric Gluconate (n=26,692 [100%])	Iron Sucrose (n=24,911 [100%])	Std Diff
Age, y	65 (53–75)	65 (53–76)	64 (53–75)	–3.8
Female sex	23068	11993	11075	1.0
Race (0.1% missing)				
White	32598	16659	15939	1.2
Black	15989	8520	7469	–3.9
Asian	2030	1033	997	0.9
Other	932	449	483	1.6
Hispanic ethnicity (2.2% missing)	5396	2687	2709	2.6
Medicaid eligibility	12981	6746	6235	–0.6
Comorbidities				
Diabetes	27481	14003	13478	3.2
Hypertension	43031	22241	20790	0.2
Arteriosclerotic heart disease	13016	6869	6147	–2.5
Heart Failure	18121	9530	8591	–2.6
PVD	7848	4173	3675	–2.5
Cerebrovascular Disease	5163	2757	2406	–2.3
COPD	4985	2649	2336	–1.9
Cancer	3853	2036	1817	–1.3
Unable to ambulate or transfer	3464	1760	1704	1.0
Tobacco Use	3321	1632	1689	2.7
Drug Use	775	421	354	–1.3
Alcohol Use	768	393	375	0.3
Reported measurements				
BMI category (1.7% missing)	27.2	27.1	27.4	3.2

Variable	All Patients (N=51,603 [100%])	Ferric Gluconate (n=26,692 [100%])	Iron Sucrose (n=24,911 [100%])	Std Diff
<18.5 kg/m ²	2016 (3.9)	1043 (3.9)	973 (3.9)	<0.0
18.5–24.9 kg/m ²	16333 (31.7)	8653 (32.4)	7680 (30.8)	–3.6
25.0–29.9 kg/m ²	14351 (27.8)	7431 (27.8)	6920 (27.8)	–0.1
30.0 kg/m ²	18013 (34.9)	9110 (34.1)	8903 (35.7)	3.5
Hemoglobin, g/dL (7.1)	9.8 (8.8–10.9)	9.8 (8.8–10.9)	9.9 (8.9–11.0)	3.4
Serum Albumin, g/dL (19.6)	3.2 (2.7–3.6)	3.2 (2.7–3.6)	3.2 (2.7–3.6)	–0.8
eGFR at time of dialysis initiation, mL/min/1.73 m ² (2.2)	9.7 (7.0–13.1)	9.7 (7.0–13.0)	9.7 (7.1–13.2)	2.1

Note: Values for categorical variables are given as count (percentage); for continuous variables, as median [interquartile range]. All incident hemodialysis patients in these centers were captured for analysis of all-cause and cause-specific mortality end points regardless of their health insurance status.

Abbreviations: BMI, body mass index; eGFR – estimated glomerular filtration rate; ESRD – end-stage renal disease; Std Diff – standardized difference; COPD, Chronic Obstructive Lung Disease; PVD, Peripheral Vascular Disease

Table 3

Comparative outcomes by facility choice of intravenous iron formulation, iron sucrose versus sodium ferric gluconate complex

Outcome	Sample Size	F/U Time (y)	No. of Events	IR (per 1000 person-y)	Unadjusted HR (95% CI)	Model 1 HR* (95% CI)	Model 2 HR** (95% CI)
Mortality	51603	49989	10381	207.7	0.93 (0.89–0.98)	0.98 (0.94–1.03)	0.98 (0.93–1.03)
Cardiovascular Mortality	51603	49989	3908	78.2	0.90 (0.83–0.97)	0.96 (0.89–1.04)	0.96 (0.89–1.03)
Infectious Mortality	51603	49989	1209	24.2	0.97 (0.84–1.11)	0.99 (0.87–1.14)	0.98 (0.86–1.13)
Cardiovascular Composite [^]	24865	22373	3346	149.6	0.96 (0.89–1.05)	1.00 (0.92–1.09)	1.01 (0.93–1.09)
Infectious Hospitalization	24865	12902	12131	940.3	0.93 (0.89–0.97)	0.93 (0.89–0.97)	0.92 (0.88–0.96)
Infectious Composite ^{^^}	24865	12902	12185	944.5	0.93 (0.89–0.97)	0.93 (0.89–0.97)	0.92 (0.88–0.96)

Note: HRs are for iron sucrose compared with sodium ferric gluconate complex (referent). Time-to-event analyses started on day of reported incidence of ESRD for mortality outcomes and on day 91 after ESRD for non-fatal and composite outcomes. CI, confidence interval; ESRD, end-stage renal disease; F/U, follow-up; HR, hazard ratio; IR, incidence rate;

* Adjusted for year of ESRD incidence, age, sex, race, ethnicity (multiply imputed)

** Additionally adjusted for body mass index, comorbidities, laboratory measurements (multiply imputed)

[^] Stroke, Myocardial Infarction, Cardiovascular Mortality

^{^^} Infectious Hospitalization, Infectious Mortality

Characteristics of Patients with Medicare Parts A+B Coverage Initiating Dialysis in Sodium Ferric Gluconate Complex and Matched Iron Sucrose Facilities

Table 4

Variable	All Patients (n=24,865 [100%])	Ferric Gluconate (n=12,771 [100%])	Iron Sucrose (n=12,094 [100%])	Std Diff
Age, y	68 (56–77)	68 (56–77)	68 (56–77)	–3.6
Female sex	11273	5737	5536	–1.7
Race (0.1% missing)				
White	16100	8189	7911	0.5
Black	7508	3964	3544	–3.4
Asian	777	376	401	2.8
Other	466	232	234	1.1
Hispanic ethnicity (2.1% missing)	2185	1079	1106	2.5
Medicaid eligibility	7006	3564	3442	1.2
Comorbidities				
Diabetes	13522	6864	6658	2.5
Hypertension	20904	10739	10165	–0.4
Arteriosclerotic Heart Disease	7020	3729	3291	–4.5
Heart Failure	9428	4895	4533	–1.8
PVD	4146	2180	1966	–2.2
Cerebrovascular Disease	2745	1477	1268	–3.5
COPD	2678	1405	1273	–1.6
Cancer	1987	1036	951	–1.0
Unable to ambulate or transfer	1789	882	907	2.3
Tobacco Use	1679	808	871	3.5
Drug Use	345	183	162	–0.8
Alcohol Use	360	181	179	0.5
Reported measurements				
BMI category (1.6% missing)	27.2	27.0	27.3	3.8
<18.5 kg/m ²	963	535	428	–0.7

Variable	All Patients (n=24,865 [100%])		Ferric Gluconate (n=12,771 [100%])		Iron Sucrose (n=12,094 [100%])		Std Diff
18.5–24.9 kg/m ²	8525	(32.5)	4605	(32.9)	3920	(32.0)	−4.3
25.0–29.9 kg/m ²	7440	(28.4)	3947	(28.2)	3493	(28.6)	<0.1
30.0 kg/m ²	8873	(33.8)	4675	(33.4)	4198	(34.3)	4.4
Hemoglobin, g/dL (6.8)	9.9	(8.9–11.0)	9.8	(8.9–10.9)	9.9	(8.9–11.0)	3.8
Serum Albumin, g/dL (18.7)	3.2	(2.7–3.6)	3.2	(2.7–3.6)	3.2	(2.7–3.6)	−1.3
eGFR at time of dialysis initiation, mL/min/1.73 m ² (2.0)	9.9	(7.2–13.3)	9.9	(7.2–13.3)	10.0	(7.3–13.4)	1.4

Note: Values for categorical variables are given as count (percentage); for continuous variables, as median [interquartile range].

Abbreviations: BMI, body mass index; eGFR – estimated glomerular filtration rate; ESRD – end-stage renal disease; IQR – interquartile range; Std Diff – standardized difference; COPD, Chronic Obstructive Lung Disease; PVD, Peripheral Vascular Disease