Understanding the Recent Increase in Ferritin Levels in United States Dialysis Patients: Potential Impact of Changes in Intravenous Iron and Erythropoiesis-Stimulating Agent Dosing

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Abstract

Background and objectives Anemia management changed substantially among dialysis patients in the United States around the time of implementation of the new Centers for Medicare & Medicaid Services bundled payment system and erythropoiesis-stimulating agent (ESA) label change in 2011. Among these, average ferritin levels increased dramatically and have remained high since; this study sought to gain understanding of this sustained rise in ferritin levels.

Design, setting, participants, & measurements Trends in mean ferritin, hemoglobin, IV iron dose, and ESA dose from 2009 to 2013 were examined in 9735 patients from 91 United States Dialysis Outcomes and Practice Patterns Study facilities. Linear mixed models were used to assess the extent to which intravenous (IV) iron and ESA dose accounted for patients' changes in ferritin over time.

Results Mean ESA dose and hemoglobin levels declined throughout the study. Mean IV iron dose increased from 210 mg/mo in 2009–2010 to a peak of 280 mg/mo in 2011, then declined back to 200 mg/mo and remained stable from 2012 to 2013. Mean ferritin increased from 601 ng/ml in the third quarter of 2009 to 887 ng/ml in the first quarter of 2012; models suggest that higher IV iron dosing was a primary determinant during 2011, but lower ESA doses contributed to the sustained high ferritin levels thereafter. In a subset of 17 facilities that decreased IV iron dose in 2011, mean ferritin rose by 120 ng/ml to 764 ng/ml, which appeared to be primarily due to ESA reduction. Together, changes in IV iron and ESA doses accounted for 46% of the increase in ferritin over the study period.

Conclusions In contrast to expectations, the rise in average IV iron dose did not persist beyond 2011. The sustained rise in ferritin levels in United States dialysis patients after policy changes in 2011, to average levels well in excess of 800 ng/ml, appeared to be partly due to reductions in ESA dosing and not solely IV iron dosing practices. The effect of these changes in ferritin on health outcomes requires further investigation.

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Introduction

The new bundled payment system for dialysis patients implemented by the Centers for Medicare and Medicaid Services (CMS) in January 2011 included erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron (1). The implementation of the payment system provided dialysis facilities a financial incentive to rely more on IV iron and less on ESA to treat anemia because IV iron is less expensive than ESA therapy and often results in reduced ESA dose requirements. In June 2011, the Food and Drug Administration modified the ESA label, replacing the target hemoglobin range of 10–12 g/dl with a recommendation to individualize ESA use to avoid the need for red blood transfusions, curtail ESA use when hemoglobin levels approach or exceed 11 g/dl, and halt further dose increases if patients did not respond to three prior dose increases (2). These events led to significant changes in anemia management (3).

Serum ferritin levels in United States hemodialysis (HD) patients began to increase noticeably in late 2010 (4,5), likely reflecting practice changes made in anticipation of the new bundled payment system. The increase became dramatic in 2011 and continued through early 2012, resulting in high levels of ferritin, which were sustained into 2013 (4). Concern has been raised that these high ferritin levels reflect excessive iron stores, which have been associated with increased morbidity and mortality in some studies (6). Nevertheless, the longer-term consequences of consistently high serum ferritin levels and any variation in the cause of high ferritin remain uncertain. The

recommended upper target for serum ferritin has historically varied widely. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommended keeping serum ferritin at <800 ng/ml in 2001; the guidelines were updated to a target of <500 ng/ml in 2006 (7,8). More recently, the Kidney Disease Improving Global Outcomes (KDIGO) Anemia Work Group released a more nuanced ferritin guideline in 2012, recommending consideration of IV iron when a rise in Hgb is desired and ferritin is <500 ng/ml, and evaluating on a case-by-case basis when ferritin exceeds 500 ng/ml (9). The KDOQI response to the KDIGO guideline suggested consideration of IV iron when a rise in hemoglobin is desired and ferritin is <800 ng/ml, noting an absence of compelling data that long-term IV iron administration in moderate doses is associated with adverse outcomes (10). However, recent data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) Practice Monitor indicate that the mean serum ferritin level among HD patients in the United States was 764 ng/ml in August 2014, with 41% of patients exceeding 800 ng/ml (4).

ESA therapy was introduced to the market in 1989, leading to higher hemoglobin levels in dialysis patients (11). A small study published the same year reported a rapid fall in serum ferritin soon after initiation of ESA therapy due to increases in red blood cell production and iron utilization (12). We postulated that the recent reductions in ESA dosing across dialysis facilities nationwide, which have also led to decreases in erythropoiesis, hemoglobin levels, and iron utilization may lead to sustained increases in serum ferritin levels, independent of IV iron dosing.

In this study, we took advantage of this natural experiment to analyze the effect of policy-related changes in anemia management on serum ferritin levels. Because IV iron dosing directly raises ferritin levels, we hypothesized that an increase in iron dose was the primary driver of the observed high ferritin. We analyzed changes in patient characteristics over time and variations in anemia management practices across facilities operated by two large dialysis organizations in the United States to determine the relative contributions of higher IV iron doses and lower ESA doses on the observed increase in serum ferritin.

Materials and Methods

Data Source

The DOPPS is an international prospective cohort study of in-center HD patients age ≥18 years. A combination of incident and prevalent HD patients was randomly selected from national samples of dialysis facilities in each country, with replacement of patients who died or left the facility every 4 months throughout the study (13,14). In this analysis, participants from 91 facilities in two large dialysis organizations in the United States were studied because we had detailed laboratory and medication data at each dialysis session for participating patients. Data from July 1, 2009 (third quarter [Q3] of 2009), to September 30, 2013 (Q3 2013) were used.

Variables of Interest

To report crude quarterly trends, laboratory data (hemoglobin, ferritin) were summarized as the mean of all values within each patient quarter. ESA administration was almost exclusively (>98%) IV epoetin; few patients received darbepoetin or subcutaneous epoetin (15). For IV iron and ESA dosing, doses administered each month were calculated for each patient and expressed as mg/mo for IV iron and units/wk for ESA. Patient-months were included in the quarterly summary if the patient was receiving dialysis in a single facility for 10–14 treatments over a span of at least 23 days during the month. All patient-months (1–3 per patient) in each quarter were averaged to calculate quarterly doses of IV iron and ESA; doses of 0 were included in the calculations. Non–anemia-related patient characteristics were abstracted from the DOPPS Practice Monitor (15).

To analyze within-patient changes in ferritin, we used the interval between two ferritin measurements as the unit of analysis. We restricted to ferritin-measurement intervals from 14 to 120 days (97% of intervals) and required that each patient receive dialysis in the facility an average of 2.5 to 3.5 times per week during the interval. Interval length (14–120 days) was categorized into four groups: 2–3 weeks, 4–5 weeks, 6–12 weeks, and 13–17 weeks. IV iron dose and ESA dose were summed across all dialysis sessions during the interval and divided by the interval length; doses were expressed as IV iron dose in mg/mo and IV iron and ESA dose were expressed as units/wk to be consistent with common convention. A bolus dose of IV iron was defined as ≥500 mg during any 2-week period during an interval. Ferritin values >5000 ng/ml (0.1% of records) were excluded to minimize influence of outliers.

Facilities were categorized into three groups based on the change in mean IV iron dose from 2010 to 2011. Mean IV iron dose was calculated by averaging all patient-months within each year for each facility. From 2010 to 2011, mean IV iron dose increased by >50 mg/mo in 16 facilities (group A), increased by <50 mg/mo in 24 facilities (group B), and decreased in 17 facilities (group C). Of the 91 DOPPS facilities in this study, these 57 facilities had at least 100 patient-months of medication data in each full year before (2010), during (2011), and after (2012) the policy changes; most of the remaining 34 facilities were recruited to the DOPPS after implementation of the new bundled payment system (January 2011), and thus we could not assess this change in practice.

Statistical Analyses

Crude quarterly trends are reported for ferritin, hemoglobin, IV iron dose, and ESA dose. To estimate the degree to which IV iron dose and ESA dose accounted for the trend in ferritin levels, we modeled within-patient changes in ferritin over time and assessed whether covariate adjustment for concurrent changes in IV iron dose and/or ESA dose attenuated the time effect. Linear mixed models were used to model ferritin as the outcome. Multiple observations per patient were considered, and models accounted for within-patient clustering using a random intercept. The time effect was modeled as a linear spline with knots at October 1, 2010 and January 1, 2012 to approximate points where the slope of the mean crude ferritin changed. The covariates in the base model included time, the length of the interval since the previous ferritin measurement, and the patient's previous ferritin. We then incrementally

added adjustments for factors that may affect within-patient ferritin changes, and thus may explain a portion of the increase in ferritin over the study period: the Baron-Kenny approach for effect decomposition analysis (16,17). We first adjusted for IV iron dose (per month) given during the interval between ferritin measurements; a product term for IV iron dose and interval length was also included to model the observed effect modification by interval length. Next, we adjusted for ESA dose (per week) administered during the interval, categorized into five groups as detailed in Table 1. Predicted values for change in ferritin over time relative to the reference point (October 1, 2009) were plotted based on the estimated slope during each time period; we present results unadjusted for dose, adjusted for IV iron dose, and adjusted for both IV iron dose and ESA dose. We chose to focus the effect decomposition analysis on treatment variables, IV iron dose and ESA dose rather than hemoglobin because only the treatments are directly associated with the covariate of interest (time effect) we attempt to mediate. Adjustment for hemoglobin was considered but abandoned because doing so would be tantamount to adjusting for another response variable.

In a sensitivity analysis, we tested whether the increase in ferritin could be attributed to the method by which IV iron was administered (bolus versus maintenance dosing) by adjusting for a bolus dosing indicator in addition to adjusting for IV iron dose. We also performed sensitivity

Table 1. Trends in anemia variables, by year

Variable	2009	2010	2011	2012	2013
No. of ferritin measurements	3730	20,692	16,449	14,090	10,842
Unique patients (*n*)	1821	4009	4165	4400	3427
Interval since previous ferritin measurement					
2–3 wk	4	4	3	4	4
4–5 wk	76	64	36	30	35
6–11 wk	6	11	13	14	12
12–14 wk	14	21	47	50	46
15–17 wk	0	1	1	2	4
Ferritin					
50–199 ng/ml	11	11	7	5	6
200–499 ng/ml	34	30	22	15	16
500–799 ng/ml	31	30	27	24	26
800–1199 ng/ml	18	20	27	37	35
1200–1499 ng/ml	5	5	10	13	11
1500–5000 ng/ml	2	4	7	8	6
IV iron dose					
No dose	24	30	29	32	32
1–124 mg/mo	19	18	12	14	15
125–249 mg/mo	26	21	28	30	31
250–399 mg/mo	11	11	9	8	8
≥400 mg/mo	19	20	22	17	15
Received bolus dose of IV iron	10	14	22	21	19
TSAT					
< 20%	17	18	15	13	14
20–29%	40	39	35	34	33
30–49%	36	36	39	43	43
≥50%	7	8	11	10	10
Hemoglobin					
<10 g/dl	6	7	8	12	14
10–11 g/dl	18	19	24	40	45
11–12 g/dl	42	44	50	37	30
≥12 g/dl	34	30	18	11	11
ESA dose					
No dose	2	4	8	10	13
1–4999 U/wk	19	20	24	31	34
5000–9999 U/wk	19	20	22	24	23
10,000–24,999 U/wk	34	32	30	25	22
≥25,000 U/wk	26	24	17	10	9

Unless otherwise noted, values are percentages with denominator as the number of ferritin measurements. There were 65,803 ferritin intervals (the time between two consecutive ferritin measurements) from 7434 unique patients. Intravenous iron dose and ESA dose were summed across all treatments during the interval and divided by the interval length. A bolus dose of intravenous iron was defined as receiving ≥500 mg of intravenous iron during any 2-week period during an interval. Hemoglobin was calculated as the mean of all hemoglobin measurements during the interval. Transferrin saturation at time of ferritin measurement was recorded. IV, intravenous; TSAT, transferrin saturation; ESA, erythropoiesis-stimulating agent.

analyses adjusting for ESA/hemoglobin ratio or ESA resistance index rather than either of the individual components, allowing us to account for ESA resistance without explicitly including hemoglobin in the model.

The crude quarterly trends and within-patient ferritin models were also analyzed within each of the three facility groups on the basis of changes in average IV iron dosing practice from 2010 to 2011. This analysis allowed us to evaluate (*1*) whether ferritin increased by a larger magnitude in group A (mean IV iron dose increased >50 mg/mo) and, if so, whether adjustment for higher IV iron doses accounted for a large proportion of this ferritin increase, and (*2*) whether ferritin increased at all in group C (mean IV iron dose decreased) and, if so, to what extent adjustment for lower ESA doses accounted for this ferritin increase. Because ESA doses were uniformly decreased across all United States facilities in this study, facilities were not further grouped by patterns in ESA dosing due to a lack of variability. All analyses used SAS software, version 9.3 (SAS institute, Cary, NC).

Results

Descriptive Analyses

Descriptive trend analyses by calendar quarter included a total of 9735 patients from 91 United States HD facilities from July 1, 2009 to September 30, 2013: 9229 patients with at least one hemoglobin measurement, 8991 patients with at least one ferritin measurement, and 8640 patients with at least one month of medication data. The number of patients per quarter ranged from 2709 to 4177. The median number of hemoglobin measurements per quarter was 9 (interquartile range: 6, 13). Ferritin was measured less frequently; the most common number of measurements was 1 (66%), 2 (15%), or 3 (18%) per quarter. Figure 1 (T1-T2) shows trends in quarterly mean ferritin, IV iron dose, hemoglobin, and ESA dose for all patients. ESA dose and hemoglobin levels had similar patterns of decline during the study period; changes were most pronounced beginning in late 2010 through 2012, and especially following the ESA label change in June 2011. In contrast to ESA and hemoglobin, trends in IV iron dose and ferritin level did not mirror one another during the study period. Mean ferritin level rose modestly from 2009 to 2010 and then more sharply in late 2010 through 2011. After peaking in the first quarter (Q1) of 2012, mean ferritin declined slightly through Q3 2013 but remained much higher than in 2009–2010. Meanwhile, mean IV iron dose remained stable at about 210 mg/mo through Q3 2010, then increased starting in the fourth quarter (Q4) of 2010, peaked at 280 mg/mo in the second quarter of 2011, and declined back to 2009–10 levels by Q1 2012, remaining stable through the end of the study in Q3 2013.

Figure 1 (A1-A2, B1-B2, C1-C2) subdivides the same data into three groups by the magnitude of change in IV iron dose during 2011 at the facility level: group A (>50 mg/mo increase in IV iron dosing in 2011), group B (<50 mg/mo increase in IV iron dosing in 2011), and group C (decrease in IV iron dosing in 2011). In group A and group B, the increase in IV iron dose aligns closely with the increase in ferritin levels during 2011, though ferritin remained high after the IV iron dose decreased in 2012—similar to the overall trend in the left panel of Figure 1 (T1). In group C, however, ferritin levels moderately increased through Q4 2011 despite the decrease in IV iron dose. ESA dose and hemoglobin levels decreased throughout the period in all three groups; in group C, the sharpest decreases in both ESA dose and hemoglobin levels followed the ESA label change in June 2011 and appeared to align with the increase in ferritin that began during the latter half of 2011.

Table 1 shows the distribution of patient characteristics by year, with the interval between two ferritin measurements serving as the unit of analysis; after application of the inclusion criteria described in the Materials and Methods section, 65,803 intervals from 7434 unique patients were included. The most common interval lengths between ferritin measurements were 13 weeks (31% of intervals), 4 weeks (30%), and 5 weeks (15%). Facilities began measuring ferritin less often in 2011; the proportion of intervals equivalent to approximately 3 months (12–14 weeks) increased from 21% to 47% between 2010 and 2011. Trends in ferritin, IV iron dose, hemoglobin, and ESA dose are consistent with Figure 1 (T1-T2). Transferrin saturation (TSAT) levels increased during the study period, especially from 2010 to 2012. Table 1 also shows the trend in the prevalence of bolus iron dosing, which became more commonplace in 2011.

Trends in other patient characteristics abstracted from the DOPPS Practice Monitor national sample data are shown in Table 2. Minimal changes in case-mix variables, such as age, sex, and diabetes were observed during the study period. Median vintage increased nominally from 2.7 to 2.9 years, although the proportion of incident patients remained similar. Median serum albumin was stable from 2010 to 2011 and increased only slightly during the study period, from 3.84 to 3.90 g/dl from August 2010 to August 2013. Catheter use declined slightly from 18% to 16% during the study period. The proportion of patients receiving a transfusion in a given month increased from 2.5% to 3.3% according to CMS claims data.

Statistical Modeling of Within-Patient Changes in Ferritin

Figure 1 (T3) shows models of within-patient changes in ferritin over time ("time effect") and the effect of covariate adjustment for IV iron dose and ESA dose on attenuation of the time effect among all study facilities. Predicted values for changes in ferritin are plotted on the basis of the estimated slope during each time period. Time was modeled as a piecewise linear spline with knots at October 1, 2010 and January 1, 2012. The base model (model 1) accounts for the length of the interval between ferritin measurements and the patient's previous ferritin. The shape of the ferritin trend in model 1 is similar to the crude trend observed in Figure 1 (T1).

To estimate the degree to which changes in IV iron dosing were responsible for these trends in ferritin, model 2 additionally adjusts for IV iron dose per month administered during the interval and the interaction between IV iron dose and the length of the interval. From study start through the end of 2011, adjustment for increases in IV iron dose accounted for about 35% of the increase in ferritin (comparing the predicted ferritin values for models 1 and 2). From Q1 2012 through the end of follow-up, ferritin

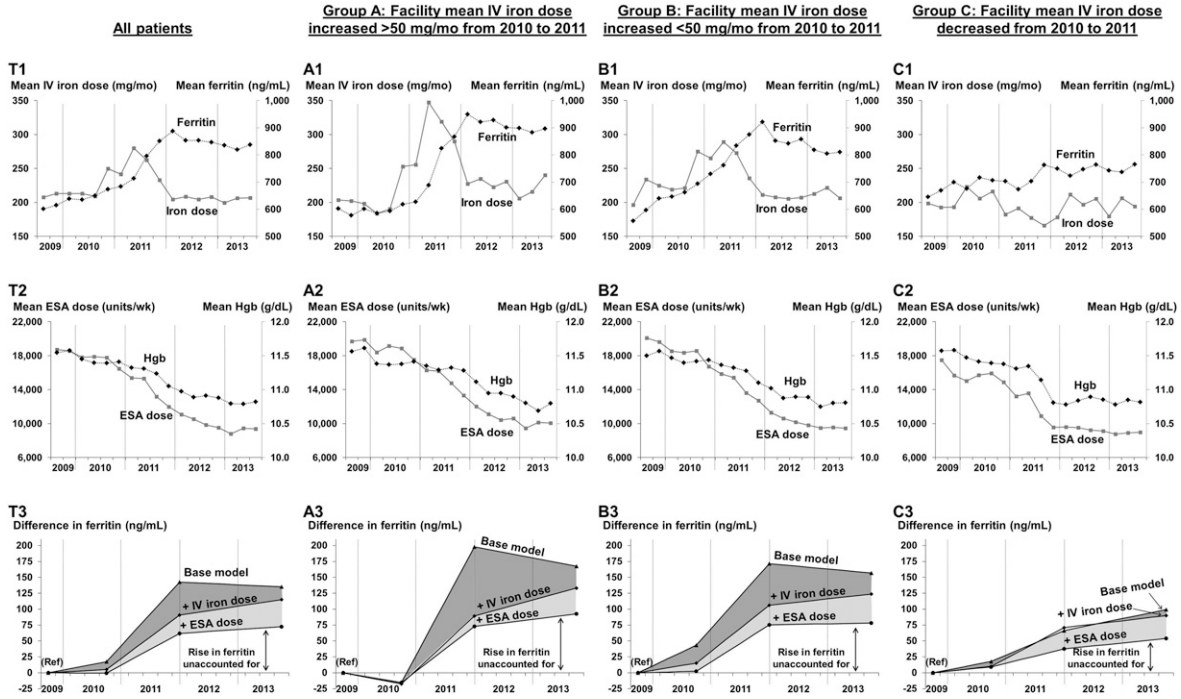

Figure 1. | **Trends in ferritin, IV iron dose, hemoglobin, and ESA dose**. Row 1 shows crude trends in ferritin and intravenous (IV) iron dose. Row 2 shows crude trends in hemoglobin and erythropoiesis-stimulating agent (ESA) dose. Hemoglobin and ferritin are summarized as the within-patient mean of all measurements in the quarter. Intravenous iron and ESA doses of 0 were included in the calculations. Row 3 shows statistical modeling of trends in within-patient changes in ferritin. Predicted values for change in ferritin over time relative to the reference point are plotted according to the estimated slope during each time period. Results are displayed for the base model (adjusted for time + interval length + previous ferritin), and progressive adjustment for IV iron dose and then ESA dose. All results are shown overall (T) and among 3 groups of facilities (A, B, C) based on the change in mean facility IV iron dose from 2010 to 2011. Group A: 16 facilities where mean IV iron dose increased by >50 mg/mo; group B: 24 facilities where mean IV iron dose increased by <50 mg/mo; group C: 17 facilities where mean IV iron dose decreased. New CMS bundle was implemented in January 2011 and ESA label was modified in June 2011.

levels were relatively stable but adjusting for IV iron dose led to higher predicted ferritin values; in other words, if IV iron dose levels had remained high after 2011, we would have expected ferritin levels to have continued to increase. Model 3 added an adjustment for ESA dose per week administered during the interval; the increase in ferritin

Table 2. Trends in patient characteristics in United States dialysis patients

Patient Characteristic	August 2010	August 2011	August 2012	August 2013
Age (yr)	63 (52, 73)	63 (52, 73)	63 (52, 73)	63 (53, 73)
Vintage (yr)	2.7 (1.1, 5.1)	2.8 (1.2, 5.5)	2.9 (1.3, 5.7)	2.9 (1.3, 5.7)
Vintage <90 d (%)	5.2	4.1	4.8	4.9
Men (%)	56	55	56	56
Black race (%)	32	33	37	34
Body mass index (kg/m^2)	27.0 (22.9, 32.2)	27.3 (23.3, 32.1)	27.5 (23.4, 32.3)	27.2 (23.5, 32.4)
Diabetes (%)	64	63	61	62
Systolic BP (mmHg)	148 (131, 163)	147 (131, 163)	148 (132, 165)	146 (130, 163)
Treatment time (min)	212 (195, 240)	212 (195, 240)	215 (196, 240)	215 (199, 241)
Single pool Kt/V	1.56 (1.41, 1.72)	1.58 (1.43, 1.75)	1.62 (1.47, 1.78)	1.60 (1.44, 1.77)
Serum phosphorus (mg/dl)	4.9 (4.1, 6.0)	4.9 (4.1, 5.9)	4.8 (3.9, 5.8)	4.8 (4.0, 5.8)
Serum parathyroid hormone (pg/ml)	247 (163, 379)	307 (192, 488)	311 (196, 501)	322 (198, 496)
Serum albumin (g/dl)	3.84 (3.57, 4.06)	3.85 (3.59, 4.07)	3.89 (3.61, 4.10)	3.90 (3.69, 4.17)
Transfusions (%)[a]	2.5	3.1	3.3	–
Catheter use (%)	18	19	16	16

Values are expressed as median (interquartile range) or proportion of patients.
[a]Values for each month reflect proportion of Medicare ESRD beneficiaries transfused; the maximum number of procedures per inpatient claim in this CMS dataset increased from 6 to 25 starting in January 2011 (15,26).

was further attenuated throughout the study period, especially from mid-2011 to the end of follow-up, because higher ESA doses were associated with subsequent within-patient decreases in serum ferritin. At the end of the study period, adjustment for changes in IV iron dose and ESA dose accounted for about 50% of the rise in ferritin level.

Sensitivity analyses adjusting for ESA/hemoglobin ratio or ESA resistance index rather than absolute ESA doses yielded similar results. Results adjusting for a bolus IV iron dosing indicator in addition to adjusting for IV iron dose (not shown) were very similar to model 2, indicating that the amount of IV iron administered was a much stronger predictor of long-term changes in ferritin than was the use of bolus versus maintenance dosing.

Within-patient changes in ferritin were also modeled separately for each of the three facility groups, with results shown in Figure 1 (A3, B3, C3). In group A, a large proportion of the sharp increase in ferritin in 2011 was attenuated by adjustment for the increase in IV iron dose; adjustment for changes in ESA dose had minimal impact. The proportion of the increase in ferritin attenuated by adjustment for changes in IV iron dose declined through 2012–2013 as IV iron doses decreased to pre-2011 levels while ferritin levels remained high. Additional adjustment for ESA dose, which continued to decline, helped to partially account for the sustained high ferritin levels. In contrast, the total rise in ferritin was much lower in group C. Because IV iron doses did not increase but rather decreased in these facilities, adjustment for IV iron dose in the model had minimal effect, as evidenced by the lines in the base model and model 2 that are almost superimposed. Adjustment for the decreasing ESA dose throughout the study period, especially during 2011, attenuated a large proportion of the ferritin rise in these facilities. Results from group B were similar to the overall results. In each of the three groups, as in the total sample, changes in IV iron dose and ESA dose combined to explain only about 50% of the increase in ferritin over the study period.

Discussion

This detailed data set of United States DOPPS patients receiving HD allowed us to examine national trends in key anemia indicators and treatments before and after the new CMS bundled payment system was implemented in January 2011. Mean serum ferritin rose sharply, up to a peak of nearly 900 ng/ml after the bundle, with these high levels of ferritin sustained into 2013. The consistently high ferritin levels might be presumed to result directly from sustained large IV iron doses following the bundle. However, the increase in IV iron dosing was surprisingly transient, as mean IV iron dosing actually declined to pre-2011 levels in 2012–2013. Our results suggest that while increased IV iron dosing was an important factor in the initial rise in ferritin, lower ESA dosing after the label change in June 2011 partially contributed to the persistently high ferritin levels thereafter.

The rise in serum ferritin levels in the United States has been well documented (4,18). High serum ferritin is a predictor of short-term morbidity and mortality (6) and is associated with other noniron markers of nutrition and inflammation (19), although the consequences of consistently high serum ferritin remain unclear. The Proactive IV irOn Therapy in haemodiaALysis patients (PIVOTAL) trial underway in the United Kingdom will investigate the effect of a proactive high-dose compared with a reactive low-dose IV iron regimen on clinical outcomes (20). Ferritin levels in the proactive high-dose arm will only target a serum ferritin up to 700 ng/ml, which is lower than the mean serum ferritin level in the United States. The relation between serum ferritin levels and outcomes in the United States will require further investigation.

IV iron dosing practices varied across DOPPS facilities throughout the study period: from 2010 to 2011, some facilities greatly increased IV iron dosing while other facilities did not increase IV iron dosing or even decreased IV iron dosing. The increase in ferritin levels after the bundle was expectedly largest among facilities where mean IV iron dosing increased by >50 mg/mo in 2011. However, ferritin levels were also higher after the ESA label change (June 2011) in facilities that did not increase or even decreased IV iron dosing, indicating that factors other than IV iron dosing must have played a role.

Our findings that ESA dose reductions partially contributed to the rising ferritin over time are driven by (*1*) declining ESA doses over the study period and (*2*) the inverse association between ESA dose and subsequent within-patient changes in serum ferritin. This observed association is in the same direction as found in early analyses around the time of ESA therapy introduction (12). Van Wyck *et al.* showed that in 1989, when ESA first came on the market, patients naive to ESA therapy showed a rapid fall in serum ferritin after ESA administration (12). Our findings and those of Van Wyck *et al.* are consistent with basic iron physiology, namely that iron is exchanged dynamically between red blood cells and iron storage sites as hemoglobin levels fluctuate. This process is mediated in part by hepcidin and, in situations where erythropoietin levels are elevated, the newly identified hormone erythroferrone (21,22). In addition, at a lower hemoglobin level, there is less iron lost per milliliter of blood loss. In sum, if there is a lower requirement of iron for erythropoiesis and a smaller amount of iron lost due to bleeding, giving the same dose of iron would be expected to lead to a higher serum ferritin level, as we have observed.

We can postulate that if IV iron doses had been decreased even further in late 2011—to levels below those seen in 2009–2010—then mean ferritin levels may have begun to decline. In clinical practice, a greater decrease in IV iron dose did not take place at this time, likely because of the concurrent increases in the target ferritin and TSAT levels that predictably occurred in response to the policy and regulatory changes (1,2). In addition to hemoglobin levels, IV iron dosing in the United States is guided principally by the upper ferritin target limit and lower TSAT limit. Both rose from 2010 to 2011. In 2010, 50% of study sites had a ferritin upper target of 800 ng/ml and 35% had a target ≥1000 ng/ml, while in 2011, 27% had a target of 800 ng/ml and 65% had a target ≥1000 ng/ml (DOPPS Medical Director Survey data, unpublished). Over the same time period, the proportion of study sites with a lower TSAT limit of 20% decreased from 75% to 55% while the proportion with a lower limit of 25%–30% increased from

21% to 41% (DOPPS Medical Director Survey data, unpublished). We observed a corresponding change in mean TSAT values in our data set; these increased from approximately 30% throughout 2009–2010 to 32% in Q3 2011, an increase sustained through the end of the study period (Supplemental Figure 1).

Our analytic models were able to account for approximately half of the rise in ferritin from 2009 to 2013 in the effect decomposition analysis; however, complete mediation (100%) is rare because of the prevalence of multiple potential mediators (16,23). Besides average IV iron and ESA dose between ferritin measurements, other factors related to IV iron therapy and monitoring of treatment may affect patients' serum ferritin levels. For example, bolus dosing of IV iron became more common in 2011 (22% of intervals compared with 14% in 2010); however, a sensitivity analysis showed that bolus dosing did not account for any of the remaining change in ferritin. Although we presume that patients administered a bolus dose exhibited a high initial peak in serum ferritin, these patients did not exhibit a larger increase in ferritin than patients administered maintenance dosing of IV iron as measured at the end of the interval. In addition, the increase in ferritin also could not be attributed to bias resulting from the proximity of IV iron dosing to ferritin measurement; the proportion of patients administered IV iron during the dialysis treatment before ferritin measurement varied minimally over the study period: 17% in 2010, 19% in 2011, and 17% in 2012.

Patients who have been receiving dialysis for a longer time have lower IV iron doses (24) and higher serum ferritin levels (25). However, because incident patients are continuously joining the study, mean vintage is stable in the DOPPS (15); thus, a vintage effect would probably not account for the temporal trend in higher ferritin levels observed during the study period. The vintage effect, or natural rise in ferritin during time on dialysis, could be caused by inflammation or cumulative iron exposure. If due to a cumulative iron exposure, this may help explain why the high ferritin levels initiated by high IV iron doses, seen in some facilities, did not decline following the subsequent decrease in IV iron dosing. Thus, while we need to consider the possible contribution of cumulative iron exposure for patients who received these large doses of IV iron in 2011, this would not explain the sustained rise in ferritin observed in 2011 among the facilities that lowered their IV iron doses.

Other factors that may be associated with ferritin levels include patient characteristics, catheter use, and markers of inflammation. Case-mix (*e.g.*, age, vintage, diabetes) remained stable during the study period. Catheter use decreased minimally and thus is unlikely to have played a role in the increasing ferritin levels. Levels of serum albumin and neutrophil-lymphocyte ratio (data not shown), surrogate markers of inflammation measured in our data, were relatively stable throughout the study period. C-reactive protein is not regularly measured in the United States and, therefore, was not available in our data set.

To our knowledge, this is the first thorough investigation of factors associated with the recent rise in ferritin levels in the United States. We were able to incorporate granular dialysis treatment-level medication and laboratory data from two large dialysis organizations that contributed substantially to the variation observed in facility anemia management practices during the period of this study. Another key strength of the study was the continuous collection of data before, during, and after the implementation of the bundled payment system in January 2011 and ESA label change in June 2011.

Our study has several limitations. First, we acknowledge that this study cannot estimate the relative causal contributions of changes in IV iron or ESA dose on serum ferritin because of the observational design and our reliance on aggregated data; however, one advantage of this study design is that the data reflect variations in everyday dialysis practice. Second, the irregular measurement of serum ferritin in patients (typically 1 month or 3 months apart) is inherent to the observational nature of our data. The effect of IV iron dose on ferritin level differs according to the interval length between ferritin measurements; for instance, a patient not administered any IV iron over 3 months will likely experience a larger decrease in ferritin than a patient not administered any IV iron over 1 month. We accounted for this by dividing dose by interval length, adjusting for interval length, and including an interaction term (dose $\times$ interval length) when adding IV iron dose to the models. Third, it is possible that different iron formulations may result in changes in the amount of iron that may be mobilized in response to ESA; however, type of iron formulation changed minimally over the study period (15). Fourth, the data set used did not have data on blood transfusions, which can influence the key indicators and treatments for anemia used in our analysis. This may have affected about 3% of patients in a 1-month interval, with a range of 2.5%–3.3% during the study period (26). Because of the small absolute number of transfusions and the small change in percentage of transfusions (delta 0.8% over 1 month, or a maximum of 2.4% over 3 months as transfusions cluster within patients), we would not expect transfusions to have caused such a large shift in the distribution of ferritin levels. Fifth, we were not able to account for iron use outside the dialysis center, either prior to dialysis initiation or while in the hospital. Finally, because we included patients from only two large dialysis organizations, our results may not be generalizable to the entire HD population in the United States.

Our study demonstrates a rise and sustained elevated level of mean ferritin in the United States not observed in the pre-bundle ESA era. However, increased mean IV iron doses were observed only in Q4 2010 through Q4 2011 before returning to prior levels, while ferritin levels remained high through the end of the study (Q3 2013). The subset of dialysis facilities that had no increase or a decrease in IV iron dosing is informative because reduced ESA dose (and consequently reduced hemoglobin levels) appeared to be an important determinant of the rise in ferritin in these facilities. Overall, these results indicate that the sustained high ferritin levels after 2011 do not reflect IV iron doses that were higher than previously administered, but rather the decreased need for iron due to reduced erythropoiesis and lower hemoglobin levels. Approximately half of the rise in ferritin during the study period remains unaccounted for in our models and merits additional study. The potential effect on health outcomes of

these increased ferritin levels in HD patients in the United States also require further investigation.

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Disclosures

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Supplementary Figure 1

Crude trends in mean TSAT and IV iron dose shown. TSAT summarized as the within-patient mean of all measurements in the quarter. IV iron doses of 0 were included in the calculations. Results are shown overall and among 3 groups of facilities (A, B, C) based on the change in mean facility IV iron dose from 2010 to 2011. Group A: 16 facilities where mean IV iron dose increased by >50 mg/month. Group B: 24 facilities where mean IV iron dose increased by <50 mg/month. Group C: 17 facilities where mean IV iron dose decreased.