Parenteral Iron Use: Possible Contribution to Exceeding Target Hemoglobin in Hemodialysis Patients

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Background and objectives: Use of parenteral iron for anemia management in dialysis patients has greatly increased. Exceeding hemoglobin target levels is not without risk, and whether parenteral iron administration contributes to exceeding targets has not been tested. The authors aimed to determine prevalence of parenteral iron administration and its contribution to exceeding hemoglobin target levels.

Design, setting, participants, & measurements: The authors performed a retrospective observational study of 149,292 hemodialysis patients using Centers for Medicaid & Medicare Services data. All patients were point prevalent on January 1, 2004; survived through June 30, 2004; had Medicare as primary payer; were treated with erythropoiesis stimulating agents (ESAs); and had valid hemoglobin values in April, May, and June, 2004.

Results: Of the cohort, 58% received parenteral iron; use was more likely among men, whites, younger patients, and patients with end-stage renal disease as a result of diabetes. Age > 75 yr, African American and other races, baseline hemoglobin > 12 g/dl, higher ESA dose, and iron use in months 1 to 4 of the study period were independently associated with the risk of exceeding hemoglobin levels of 12, 13, and 14 g/dl. Receiving iron in month 4 of the study period showed the highest probability of exceeding targets (odds ratios 1.49, 1.43, 1.50 for hemoglobin levels 12, 13, 14 g/dl, respectively).

Conclusions: Parenteral iron use is prevalent, and although adequate iron stores are central to ESA response, iron use may contribute to exceeding recommended hemoglobin levels. Only data from a prospective trial can confirm this association.

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Anemia, a near-universal feature of end-stage renal disease (ESRD), is caused mainly by deficiency in erythropoietin production from the failed kidneys (1). Use of erythropoiesis-stimulating agents (ESAs) by dialysis patients has alleviated the need for blood transfusions and has been linked to improved quality of life and well being (1–3). Recently, however, concerns have emerged regarding the safety of exceeding recommended hemoglobin levels (*i.e.*, to >13 g/dl) with ESAs, considering their propensity to increase cardiovascular events, particularly in hyporesponsive or resistant patients (4–6). These findings are not unique to the ESRD population but have been corroborated by data from the oncology literature (7–9). Although ESAs have been implicated in exceeding hemoglobin target levels, other factors must also be considered. Whether the recent increase in use of parenteral iron for anemia management contributes to exceeding hemoglobin level targets has not been tested. Moreover, medications administered during dialysis are reimbursed separately from the composite rate, possibly creating a financial incentive for providers to administer parenteral iron to dialysis patients.

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Exceeding recommended hemoglobin targets has emerged as an area of clinical concern. Given its very efficacy, it seems natural to hypothesize that parenteral iron administration could contribute to this phenomenon. We thus studied a large cohort of hemodialysis patients to determine the prevalence of parenteral iron use and to develop predictors of exceeding hemoglobin targets, with special emphasis on ESA dosing, demographic factors, and the role of implementing parenteral iron protocols. We tested the hypothesis that exceeding hemoglobin target levels might be at least partially related to parenteral iron administration, independently of the effect of ESAs and other factors.

Materials and Methods

Data Sources

ESRD patient demographic information was obtained from the Centers for Medicare and Medicaid Services (CMS) Medical Evidence Report (form CMS-2728). This form is completed by a nephrologist for each new ESRD patient within 45 d of renal replacement therapy initiation, and sent to CMS although the ESRD Networks. Hemoglobin values and ESA dosage information were obtained from Medicare Part A institutional outpatient and Part B physician/supplier claims, and hospitalization information from Part A institutional inpatient claims. Dialysis provider chain was determined by linking ESA claims to data from the provider survey, conducted by CMS and the ESRD Networks in December of each year.

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Patient Cohort

We studied 149,292 hemodialysis patients point prevalent on January 1, 2004, who survived through June 30, 2004, with Medicare as primary payer and both Part A and Part B coverage. Patients who initiated dialysis in the 90 d preceding January 1, 2004, received a kidney transplant, or were lost to follow-up during the 6-mo study period were excluded. All patients were treated with ESAs and had valid hemoglobin values recorded in each of the months of April, May, and June 2004. Hemoglobin values were calculated from hematocrit values provided by Medicare Part A institutional or Part B physician claims.

Patients entered the study on January 1, 2004, and were followed until June 30, 2004. Claims from January through April were used to characterize comorbid conditions by means of the standard method of one or more Part A inpatient or skilled nursing facility claims, or two or more Part B physician/supplier or Part A outpatient claims. ESA dosage and hemoglobin level in month 4 (April) were considered baseline values. Patients were defined as receiving maintenance iron if they received parenteral iron from January through March.

Age was determined as of the cohort entry date and was categorized as <20, 20 to <45, 45 to <65, 65 to <75, or ≥75 yr. Race was designated as white, African American, or other. Primary causes of ESRD were diabetes, hypertension, glomerulonephritis, and other. Comorbid conditions considered for this analysis were atherosclerotic heart disease, congestive heart failure, dysrhythmia, other cardiac, cerebrovascular accident/transient ischemic attack, peripheral vascular disease, cancer, diabetes, chronic obstructive pulmonary disease, gastrointestinal disease, and liver disease. Baseline hemoglobin values were categorized as <11, 11 to <11.5, 11.5 to <12, 12 to <13, and ≥13 g/dl.

Administered Medications

ESA dose was calculated in each calendar month as units per month and was categorized by the following quartiles: (*1*) <25,200 units/mo; (*2*) 25,200 to <44,800 units/mo; (*3*) 44,800 to <71,500 units/mo; (*4*) 71,500 to <119,600 units/mo; and (*5*) ≥119,600 units/mo. Three types of intravenous iron (low molecular weight iron dextran [Infed, Watson, Corona, CA], iron sucrose [Venofer, American Regent, Shirley, NY], or ferric gluconate [Ferrlecit, Watson, Corona, CA]) were administered. The total amount of doses of each type was obtained in each calendar month of the study period.

Statistical Analyses

Descriptive statistics are presented as mean ± SD. Categorized data are summarized using frequencies and percentages. To test bivariate associations between patient characteristics and receiving parenteral iron in month 4, *t* tests were used for continuous variables and χ^2 tests for categorical variables. A *P* value of <0.05 was considered significant. Logistic regression was used to assess the effect of iron administration in month 4 on exceeding hemoglobin levels of 12, 13, or 14 g/dl in months 5 or 6, adjusting for patient characteristics, comorbid conditions, and hemoglobin level and ESA dose in month 4. For exceeding each hemoglobin level (12, 13, or 14 g/dl), the following models were constructed (Figure 1).

Model 1 included age, sex, race, primary cause of ESRD, comorbid conditions, provider chain, hemoglobin level in month 4, ESA dosage in month 4, and iron use (none, intermittent, or maintenance) in months 1 through 3.

Model 2 included Model 1 plus ESA dosing change from month 3 to month 4 (decreased, stable, increased by at least 5%) and iron use (none, intermittent, or maintenance) in months 1 to 4.

Model 3 was constructed to address the effect of hospitalization on the relationship between iron use, ESA dosing pattern, and exceeding hemoglobin targets. Hospital stay was defined as any admission that took place in months 1 to 4. ESA dosing was categorized as stable, decreased, or increased, and iron administration as none, intermittent, or maintenance in months 1 to 4. Model 3 is thus Model 2 plus hospital stays in months 1 to 4, interaction of hospital stay and iron administration in months 1 to 4, hospital stay and ESA dosage change from month 3 to month 4.

Reference groups for all models were patients aged 45 to 64 yr, men, whites, patients with diabetes as primary cause of ESRD, patients with no comorbid conditions, average of all providers, and patients with baseline hemoglobin levels 11.5 to 12.0 g/dl.

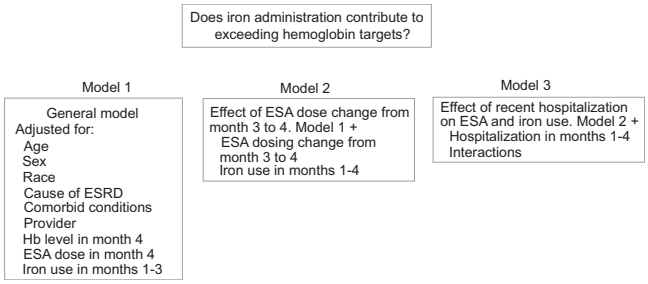

Figure 1. Multivariate analytical models studies. ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; Hb, hemoglobin.

Results

The original cohort included 209,982 hemodialysis patients point prevalent on January 1, 2004. In all, 30,524 patients were excluded from the cohort because of death, loss of Medicare coverage, or transplantation. After excluding patients without reported hemoglobin levels in April, May, or June of 2004, 149,293 remained in the cohort.

In month 4 of the study period, 86,768 patients (58%) received parenteral iron (Table 1). On average, patients who received iron tended to be younger, male, white, and more likely to have ESRD caused by diabetes. In addition, the comorbidity burden was heavier among patients who received iron; they were more likely to have atherosclerotic heart disease, congestive heart failure, arrhythmias, peripheral vascular disease, diabetes, chronic obstructive pulmonary disease, and gastrointestinal disease. Prevalence of cancer and cerebrovascular accident/transient ischemic attack was similar for patients who did and did not receive iron. Hemoglobin levels in month 4 of the study were 0.2 g/dl higher among patients who received intravenous iron.

Of patients treated with iron in month 4, 57% also received iron in each of months 1 to 3, whereas only 12% of those who did not receive iron in month 4 received maintenance therapy in months 1 to 3. Patients who received intravenous iron also received higher doses of ESAs in month 4. In each of months 4 to 6, 58% of patients received intravenous iron. Of these, 57% received the sucrose form, 40% the gluconate form, and 2% the dextran form.

In month 4, hemoglobin levels exceeded 13 g/dl in approximately 47% of patients. Of patients with hemoglobin levels below 11 g/dl in month 4, levels for 48.7% exceeded 12 g/dl if

Table 1. Characteristics of the study cohort ($N = 149,293$)

Characteristic	Parenteral Iron in Month 4		
Variable	Yes ($n = 86,768$)	No ($n = 62,525$)	P
Age (years)	61.9 ± 15.1	62.1 ± 15.2	0.02
Men (%)	51.8	51.3	0.04
Race (%)			
White	53.1	51.1	<0.0001
African American	41.2	41.6	0.14
Primary cause of ESRD (%)			
diabetes	44.2	40.9	<0.0001
glomerulonephritis	11.2	12.2	0.01
hypertension	29.5	30.2	<0.0001
Comorbid conditions (%)			
atherosclerotic heart disease	24.7	22.6	<0.0001
congestive heart failure	23.0	20.6	<0.0001
dysrhythmia	15.1	14.1	<0.0001
cardiac other	15.3	14.5	<0.0001
CVA/TIA	7.5	7.4	0.23
peripheral vascular disease	18.1	16.7	<0.0001
cancer	3.9	3.9	0.90
diabetes	51.7	47.6	<0.0001
chronic obstructive pulmonary disease	10.1	8.6	<0.0001
gastrointestinal disease	4.9	4.0	<0.0001
liver disease	6.5	6.9	0.0007
Hemoglobin level in month 4	12.0 ± 1.30	11.8 ± 1.29	<0.0001
Maintenance iron in months 1-3 (%)	57.2	12.0	<0.0001
ESAs in month 4 (units/month)	87,324 ± 85,985	72,657 ± 77,477	<0.001

CVA/TIA, cerebrovascular accident/transient ischemic attack; ESAs, erythropoiesis stimulating agents.

the patients did not receive intravenous iron. Results from the cumulative probability of exceeding hemoglobin levels of 12, 13, and 14 g/dl showed that iron administration was associated with a higher probability of exceeding these levels, independent of baseline hemoglobin level.

In fact, regardless of the hemoglobin level achieved, 43.9%, 45.1%, and 46.5% of patients received iron in each of months 4 to 6 after their hemoglobin levels exceeded 12, 13, and 14 g/dl in month 4, respectively (Table 2).

Logistic regression was performed to examine the likelihood of exceeding the hemoglobin target. Table 3 displays results from Model 2, for exceeding 13 g/dl; results were similar for factors associated with exceeding 12 and 14 g/dl. In Model 1, investigating the effect of iron administration on exceeding target hemoglobin, the following were found to be independent predictors: age > 75 yr, African American and other races, baseline hemoglobin > 12 g/dl, higher ESA dose, and iron administration in months 1 to 4. Likelihood of exceeding the targets was highest among patients at DaVita, Fresenius, Gambro, and RCG. Underlying heart disease was also an independent predictor of exceeding target hemoglobin levels. Women and cancer patients were less likely to exceed the targets.

Table 2. Percentage of patients with extra parenteral iron use in months 4 through 6

Number of Iron Doses in Months 4 through 6	Hemoglobin Level in Month 4		
	≥12 g/dl	≥13 g/dl	≥14 g/dl
0	26.4	24.5	22.6
1	13.7	13.8	13.6
2	16.0	16.6	17.3
3	43.9	45.1	46.5

Model 2 (results shown in Table 3), investigating ESA dosing patterns related to iron administration, confirmed that in addition to the independent predictors observed in Model 1, iron administration is an independent predictor of exceeding hemoglobin targets despite adjustment for variability in ESA doses. Adjustment for hospitalization in months 1 to 4 (Model 3, not shown) was predictive of exceeding targets, but there was no effect modification between ESA dose, iron administration, and hospital admissions. The effect of iron administration on exceeding targets also persisted in this model. Although any iron administration increased the probability of exceeding hemoglobin level targets, the relationship was strongest among patients receiving nonmaintenance iron. Of interest is the observation that receiving iron in month 4 clearly showed the highest probability of exceeding targets (odds ratios 1.49, 1.43, and 1.50 for hemoglobin levels 12, 13, and 14 g/dl, respectively; Figures

Table 3. Logistic regression model predicting the likelihood of hemoglobin levels exceeding 13 g/dl: Results from model 2

Predictor	Hemoglobin 13 g/dl		
	Chi-square	*P*	Odds Ratio (95% CI)
Hemoglobin in month 4			
<11	244.74	<0.0001	0.70 (0.67 to 0.73)
11 to <11.5	69.98	<0.0001	0.81 (0.77 to 0.85)
11.5 to <12			1
12 to <13	1221.13	<0.0001	1.99 (1.91 to 2.07)
≥13	7201.74	<0.0001	6.31 (6.05 to 6.59)
ESA dose in month 4			
<25200	588.94	<0.0001	0.60 (0.57 to 0.62)
25,200 to <44,800	187.81	<0.0001	0.76 (0.73 to 0.79)
44,800 to <71,500			1
71,500 to <119,600	237.10	<0.0001	1.33 (1.29 to 1.38)
≥119,600	559.95	<0.0001	1.56 (1.51 to 1.62)
Iron in months 1 through 4			
none			1
intermittent	130.19	<0.0001	1.69 (1.54 to 1.85)
maintenance	114.76	<0.0001	1.67 (1.52 to 1.83)
ESA dosage change, month 3 to 4			
decrease	2.70	0.10	0.93 (0.85 to 1.01)
stable			1
increase	291.73	<0.0001	2.14 (1.96 to 2.33)
Interaction of iron in month 4 and ESA dose change			
intermittent iron, decreasing dose	16.46	<0.0001	0.81 (0.73 to 0.90)
intermittent iron, increasing dose	24.21	<0.0001	0.77 (0.70 to 0.86)
maintenance iron, decreasing dose	11.90	0.00	0.83 (0.75 to 0.92)
maintenance iron, increasing dose	23.40	<0.0001	0.77 (0.69 to 0.85)
Age, yrs			
<20	4.24	0.04	1.30 (1.01 to 1.67)
20 to 44	0.00	0.96	1.00 (0.96 to 1.04)
45 to 64			1
65 to 74	0.25	0.62	1.01 (0.98 to 1.04)
≥75	2.56	0.1097	1.03 (0.99 to 1.06)
Sex			
female	0.76	0.38	0.99 (0.96 to 1.01)
male			1
Race			
White			1
African American	6.72	0.01	1.04 (1.01 to 1.06)
other	9.84	0.00	1.09 (1.03 to 1.14)
Primary cause of ESRD			
diabetes			1
glomerulonephritis	0.49	0.48	0.98 (0.94 to 1.03)
hypertension	1.13	0.29	1.02 (0.98 to 1.06)
other	0.44	0.51	1.01 (0.97 to 1.06)
Comorbidity conditions			
atherosclerotic heart disease	23.83	<0.0001	1.09 (1.05 to 1.12)
cancer	14.36	0.00	0.88 (0.83 to 0.94)
cardiac other	3.17	0.07	1.03 (1.00 to 1.07)
congestive heart failure	0.04	0.85	1.00 (0.97 to 1.04)
COPD	7.00	0.01	1.06 (1.02 to 1.11)
CVA/TIA	16.74	<0.0001	1.10 (1.05 to 1.16)
diabetes	0.61	0.43	0.99 (0.95 to 1.02)
dysrhythmia	6.76	0.01	0.95 (0.92 to 0.99)
gastrointestinal bleeding	1.57	0.21	1.04 (0.98 to 1.10)
liver disease	0.07	0.79	0.99 (0.95 to 1.04)
peripheral vascular disease	9.48	0.00	1.05 (1.02 to 1.09)
Provider			
DaVita	853.53	<0.0001	1.71 (1.65 to 1.77)
DCI	665.99	<0.0001	0.32 (0.29 to 0.35)
Fresenius	129.79	<0.0001	1.21 (1.17 to 1.25)
Gambro	155.63	<0.0001	1.27 (1.22 to 1.32)
hospital	2.15	0.14	1.05 (0.98 to 1.12)
independent	15.55	<0.0001	1.08 (1.04 to 1.11)
national	8.42	0.00	0.80 (0.69 to 0.93)
RCG	61.03	<0.0001	1.19 (1.14 to 1.24)
Intermittent vs. no iron, months 1 through 4			
dose decrease, month 3 to 4	147.56	<0.0001	1.37 (1.30 to 1.44)
dose stable, month 3 to 4	130.19	<0.0001	1.69 (1.54 to 1.85)
dose increase, month 3 to 4	54.93	<0.0001	1.40 (1.28 to 1.53)
Intermittent vs. maintenance iron, months 1 through 4			
dose decrease, month 3 to 4	1.37	0.24	1.06 (0.96 to 1.18)
dose stable, month 3 to 4	0.15	0.70	1.01 (0.94 to 1.09)
dose increase, month 3 to 4	3.12	0.08	1.10 (0.99 to 1.22)

Reference groups: ages 45 to 64 yr, male, white, diabetes as primary cause of end-stage renal disease, no comorbid conditions, average of all providers, baseline hemoglobin level 11.5 to <12, baseline ESA dosage 44,800 to <71,500, no iron in months 1 through 4, stable ESA dose from month 3 to month 4. COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; ESAs, erythropoiesis stimulating agents.

2 through 4), regardless of whether or not patients received maintenance iron in months 1 to 3.

Discussion

This analysis of a large cohort of dialysis patients indicates that parenteral iron use is prevalent, particularly in patients with a large comorbidity burden; that hemoglobin levels above the recommended target level of 13 g/dl are common; and that intravenous iron supplementation was associated with above-target hemoglobin levels in models that adjusted for demographic factors, ESA dosing patterns, different iron repletion strategies, and hospitalizations.

Adequate iron stores are central to ESA response, and most dialysis patients tolerate oral iron poorly (10–12). The limited bioavailability and the adverse effects associated with oral iron have resulted in more widespread use of the parenteral form of iron (10,13). In fact, parenteral iron administration has steadily increased over the past few years, and current estimates indicate that up to 70% of ESRD patients are receiving it (14–16). Provision of adequate iron stores is clearly important for successful erythropoiesis and is also important for key aspects of the immune system and physical well-being (17). Some circumstantial evidence indicates that iron may be associated with adverse cardiovascular events and increased susceptibility to infection, especially if administered in a setting of acute infection and in patients with temporary dialysis catheters (15,18–30). In dialysis patients, Besarab *et al.* (31) noted an adjusted mortality odds ratio of 2.4 for patients receiving iron dextran and assigned to the normal hematocrit group. Patients in the normal hematocrit group indeed received more intravenous iron before death or before being censored. On the other hand, more contemporary trials of ESA use in CKD and hemodialysis patients, such as CHOIR (4) and CREATE (5), used very little parenteral iron. Until more carefully collected prospective data are available, the contribution of iron to exceeding hemoglobin level targets should not be viewed as responsible for the increased risk of death and cardiovascular events. Similarly, excess cardiovascular death observed in cancer patients occurred with minimal to no parenteral iron use (7–9). The paradoxical increased death risk for patients with hemoglobin values > 13.0 g/dl in the recent reported trials might be explained by the sequence of higher ESA dose leading to iron deficiency leading to thrombocytosis (32). Of note, however, platelet counts exceeding 400K were rare. Thoughtful iron-repletion strategies not only sustain successful erythropoiesis but can lead to a significant decrease, up to 40%, of ESA use, with significant cost saving (33).

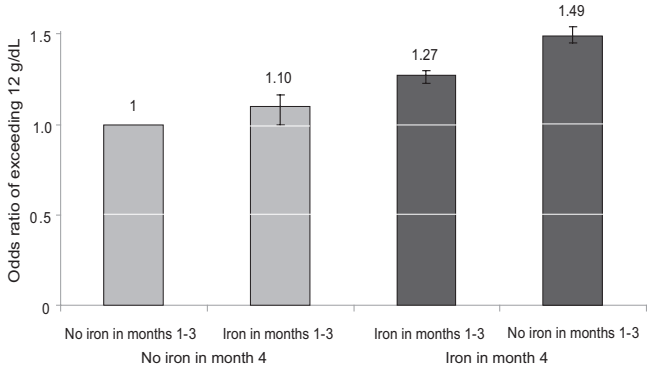

Figure 2. Risk of exceeding hemoglobin ≥12g/dl. The odds of exceeding the target were highest for patients who received parenteral iron in month 4 but were not receiving maintenance iron repletion.

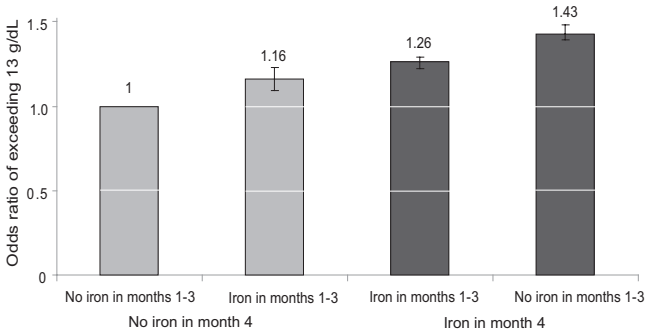

Figure 3. Risk of exceeding hemoglobin ≥13g/dl. The odds of exceeding the target were highest for patients who received parenteral iron in month 4 but were not receiving maintenance iron repletion.

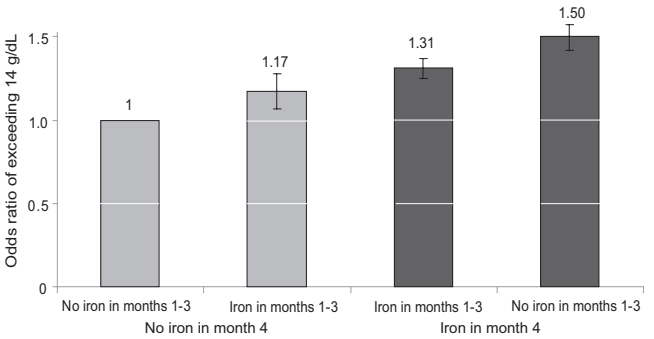

Figure 4. Risk of exceeding hemoglobin ≥14g/dl. The odds of exceeding the target were highest for patients who received parenteral iron in month 4 but were not receiving maintenance iron repletion.

Limitations of this study include the exclusion of a substantial number of patients for lack of hemoglobin values and the loss of more than 30,000 patients from the cohort as a result of death, loss of Medicare coverage, or transplantation. The remaining cohort, however, remains large and is quite representative of the U.S. ESRD population. The main shortcoming of this analysis, however, is the lack of correlation with iron studies to determine to what extent the practice of administering parenteral iron is dictated by proper assessment of iron stores. Moreover, we had no information on the percentage of patients taking oral iron. It is possible that escalating ESA doses lead to greater likelihood of iron deficiency and therefore parenteral iron use; despite proper adjustment in the multivariate models, this may be a major confounder in the observed relationship.

Parenteral iron use is common, and our data raise the possi-

bility that it may contribute to exceeding target hemoglobin levels. These results should not be interpreted to suggest that parenteral iron is a cause of harm; however, they highlight an area of research that deserves further study.

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Disclosures

None.

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