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Iron Administration and Clinical Outcomes in Hemodialysis Patients

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Abstract. To evaluate the impact of parenteral iron administration on the survival and rate of hospitalization of US hemodialysis patients, a nonconcurrent cohort study of 10,169 hemodialysis patients in the United States in 1994 was conducted. The main outcome measures were patient survival and rate of hospitalization. After adjusting for 23 demographic and comorbidity characteristics among 5833 patients included in multivariable analysis, bills for ≤10 vials of iron over 6 mo showed no adverse effect on survival (adjusted relative risk [RR] = 0.93; 95% confidence interval [CI], 0.84 to 1.02; $P = 0.14$) when compared with none, but bills for >10 vials showed a statistically significant elevated rate of death (adjusted RR = 1.11; 95% CI, 1.00 to 1.24; $P = 0.05$). Bills for ≤10 vials of iron over 6 mo also showed no significant association with hospitalization (adjusted RR = 0.92; 95% CI, 0.83 to 1.03; $P = 0.15$), but bills for >10 vials showed statistically significant elevated risk (adjusted RR = 1.12; 95% CI, 1.01 to 1.25; $P = 0.03$). Prescribing iron in quantities of ≤10 vials over 6 mo had no association with an elevated risk of death or rate of hospitalization. More intensive dosing was associated with diminished survival and higher rates of hospitalization, even after extensive adjustment for baseline comorbidity. Although these potential risks may be offset by the known elevations in morbidity and mortality associated with anemia, these findings indicate that caution is warranted when prescribing >10 vials (1000 mg) of iron dextran over a period of 6 mo.

Patients with end-stage renal disease (ESRD) almost invariably develop anemia due to decreased production of erythropoietin by the kidneys. Chronic blood loss to the dialysis circuit worsens anemia in hemodialysis patients. The introduction of recombinant erythropoietin more than a decade ago revolutionized the treatment of the anemia of ESRD, having led to a marked reduction in the need for transfusion and its attendant complications.

Despite the widespread use of erythropoietin, as of 1996 approximately 84% of patients in the United States still had hematocrit levels below the target level of 33% (1). Resistance to erythropoietin may occur for several reasons, including inflammation, infection, hyperparathyroidism, and most commonly, iron deficiency (2,3). Many patients develop iron deficiency during the initial phase of administration of erythropoietin due to depletion of iron stores as the result of the increase in red blood cell mass. After achievement of target hemoglobin levels, patients continue to require maintenance iron administration to replete the ongoing losses that result from residual blood discarded in the dialyzer and tubing after each dialysis session. Furthermore, ongoing administration of parenteral iron preserves levels of hemoglobin and reduces the requirement for administration of erythropoietin (4–9). Given the relative costs of iron and erythropoietin, it is clear that an appropriate use of iron can have substantial cost savings.

Recently, concern has arisen that administration of large doses of parenteral iron may be associated with morbidity and mortality, in particular from infection. These concerns arise, in part, from the known role of iron as a growth factor for bacteria (10,11), its suspected inhibition of neutrophil function (12–17), and clinical studies relating iron overload to infectious morbidity (18–23). More recently, large doses of administered iron have also been associated with elevated rates of hospitalization and mortality (24–28). Although these latter studies may indicate toxicity from high doses of parenteral iron, another explanation for the observed associations between iron administration and elevated morbidity is the nature of the patients treated. In particular, the clinical indication for iron administration, anemia poorly responsive to erythropoietin is itself likely to be associated with higher rates of morbidity and mortality. We hypothesized that administration of high doses of parenteral iron is an indicator of greater morbidity at baseline and subsequent susceptibility to morbid and fatal events, accounting, in part, for the observed association between iron administration of poor clinical outcomes. The purpose of this

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study was to examine this hypothesis by prospectively studying a large representative sample of US hemodialysis patients for whom extensive baseline information on comorbidity was available.

Materials and Methods

Sources of Data

Information on demographics, comorbidity, survival, hospitalization, and iron dosing was obtained from the United States Renal Disease System (USRDS). Data were used from patients enrolled in waves 1, 3, and 4 of the USRDS Dialysis Morbidity and Mortality Studies (DMMS), representing 16,736 hemodialysis patients alive at the end of 1993. The DMMS was a cross-sectional study of a quasi-random sample of US dialysis patients. Because the DMMS collected only limited information on iron dosing, these data were obtained separately from Medicare data files available in the USRDS Standard Analytical File and Physician/Supplier Claims and linked to the DMMS files.

Study Population

Among the 16,736 patients included in waves 1, 3 and 4 of the DMMS, 1753 patients could not be linked to the Medicare data files because of missing identification numbers. In addition to these, we excluded 414 patients because of duplicate identification numbers or missing or nonsensical data on timing of first dialysis.

Table 1. Demographics

Variable	*n*	%
Gender		
male	5159	50.7
female	5010	49.3
Race		
Native American	147	1.4
Asian	316	3.1
African American	4368	43.0
White	5331	52.5
Ethnicity		
Hispanic origin	1217	12.4
not of Hispanic origin	8591	87.6
Education		
less than 12 yr	3916	45.9
high school graduate	2973	34.8
some college	947	11.2
college graduate	704	8.2
Marital status		
single	1811	18.8
married	4632	48.0
widowed	1797	18.6
separated/divorced	1404	14.6
Age (yr)		
18 to 30	373	3.7
30 to 40	929	9.1
40 to 50	1374	13.5
50 to 60	1757	17.3
60 to 70	2543	25.0
70 to 80	2398	23.6
80 and older	783	7.7

Table 2. Distribution of iron prescriptions[a]

Amount	*n*	%
None	6403	63.0
1 to 7 vials	1058	10.4
8 to 10 vials	951	9.4
11 to 18 vials	995	9.8
19+ vials	762	7.5

[a] Baseline iron distribution (January 1, 1994 to June 30, 1994). All subjects eligible for inclusion in survival model.

Because we chose to characterize iron administration during a 6-mo baseline period spanning from January 1, 1994 to June 30, 1994 and observed its association with subsequent mortality, we excluded patients who did not survive until July 1, 1994. To assure the availability of Medicare data on iron and erythropoietin dosing during the baseline period, we also excluded patients based on two other conditions. First, we excluded 1674 patients who were not entitled to Medicare insurance until after December 31, 1993 because of the 3-mo waiting period for Medicare insurance after the onset of ESRD. Second, we excluded 1392 patients who had evidence of a primary payer other than Medicare at any time during the first 6 mo of 1994. Iron dosing that is paid for by payers other than Medicare is not represented in either the USRDS or the Medicare data files. After all exclusions, 10,169 DMMS patients were potentially available for analysis. As outlined in our presentation of results, some data elements were missing for about 4500 of these patients, and they were, therefore, excluded from multivariate analyses. Owing to concerns about potential resultant selection bias, we explored for differences in the relationship of iron and survival in the groups of subjects with and without missing data on comorbidity. We examined this potential interaction between iron's effect and missing data using proportional hazard models unadjusted for comorbidity.

Study Data

Exposure to Parenteral Iron. We defined exposure to parenteral iron as the number of 100-mg vials of iron billed for in the Medicare data between January 1, 1994 and June 30, 1994 for each patient. Iron exposure was categorized first as a dichotomous indicator of whether or not the patient ever had bills for iron and then in ordered categories of the number of iron vials billed, including no bills for iron as a reference category.

Potential Confounding Variables. Potential confounders included demographic and comorbidity data from the DMMS data set. Demographic variables included age, gender, and race. To characterize baseline comorbidity, we reduced the raw USRDS comorbidity data into a set of discrete, clinically coherent comorbidity variables. These variables were coronary artery disease, cerebrovascular disease, peripheral vascular disease, heart failure, pericarditis, diabetes, lung disease, neoplasms, AIDS, and HIV. Additional comorbidity variables included independent transfer, independent eating, smoking status, undernourished, prior transplant, living in a nursing home, duration of ESRD, body mass index, and type of angioaccess. Laboratory measures included serum creatinine, albumin, hemoglobin, cholesterol, hematocrit, bicarbonate, and phosphorous. We also controlled for profit status of dialysis providers, use of erythropoietin, and iron administration in the baseline period.

Table 3. Categorized iron dosing January 1, 1994 to June 30, 1994 by patient characteristics (%)[a]

Category	None	Low (0 to 1000 mg)	High (>1000 mg)	*P*
Race				
Native American	50.0	23.8	26.2	0.13
Asian	68.1	16.9	15.0	
Black	63.6	19.6	17.1	
White	61.4	20.5	18.1	
Peripheral vascular disease				
no	63.5	19.8	16.6	0.001
yes	58.8	20.7	20.5	
Smoker				
no	63.4	19.3	17.3	0.012
yes	59.1	22.3	18.6	
Able to transfer independently				
no	61.1	20.3	18.6	0.46
yes	62.4	20.0	17.6	
History of diabetes				
no	64.9	19.4	15.7	<0.001
yes	58.4	21.0	20.6	
Gender				
male	64.0	18.5	17.5	0.02
female	60.5	21.6	17.9	
Transplant before December 31, 1993				
no	62.2	20.0	17.8	0.68
yes	63.1	20.0	16.9	
Average change in BUN <62				
no	61.0	20.7	18.3	0.05
yes	64.0	19.2	16.8	
Hospitalized during baseline period				
no	63.8	19.2	17.0	0.017
yes	60.4	21.1	18.5	
Received EPO at baseline				
no	62.4	21.3	16.2	0.41
yes	62.0	17.5	20.5	
Albumin				
<3.5	60.3	21.0	18.7	0.16
3.5 to 4	62.0	19.5	18.5	
>4	63.8	20.6	15.6	
Creatinine				
<7.5	60.4	19.3	20.3	0.06
7.5 to 12.5	61.4	21.3	17.3	
>12.5	64.9	18.2	16.9	
Age (yr)				
18 to 40	61.6	19.3	19.1	0.76
40 to 60	61.9	19.9	18.2	
>60	62.5	20.3	17.2	
CAD				
no	63.0	19.8	17.2	0.26
yes	61.5	20.3	18.2	
Heart disease				
no	64.1	19.1	16.8	0.06
yes	61.1	20.7	18.2	

Statistical Analyses

Survival Analyses. We performed a descriptive analysis of baseline characteristics, including comorbidity and pertinent laboratory values, and of iron and erythropoietin dosing during follow-up. We also examined frequency distributions of study variables. We used the Kaplan Meier product limit estimator to characterize the unadjusted survival distribution of subgroups of patients defined by comorbid conditions and iron administration. We compared Kaplan Meier curves describing different subgroups of patients using the log rank test (29). We also characterized the unadjusted relationship between iron and survival using bivariate Cox proportional hazards models (30).

Table 3.—Continued

Category	None	Low (0 to 1000 mg)	High (>1000 mg)	*P*
Length of ESRD				
<2 yr	61.5	19.4	19.1	0.02
2 to 4 yr	60.9	20.6	18.5	
>4 yr	64.3	20.4	15.3	
Hemoglobin				
<8	62.4	18.6	19.0	<0.001
8 to 10	58.5	21.3	20.2	
10 to 12	63.6	20.2	16.2	
>12	71.7	15.1	13.2	
BMI < 24				
no	61.7	20.6	17.7	0.52
yes	62.8	19.5	17.7	
Phosphorous <5				
no	61.4	21.2	17.4	0.22
yes	64.1	17.4	18.4	
Bicarbonate				
<18	62.0	19.4	18.6	0.84
18 to 21	62.0	20.3	17.7	
>21	62.6	20.3	17.1	
Access				
synthetic graft	60.4	20.6	19.0	0.001
permanent catheter	61.8	21.2	17.0	
temporary catheter	63.1	18.4	18.4	
AV fistula	66.5	18.7	14.8	
Undernourished				
no	62.3	20.0	17.7	0.95
yes	62.0	20.3	17.6	

[a] BUN, blood-urea nitrogen; EPO, erythropoietin; CAD, coronary artery disease; ESRD, end-stage renal disease; BMI, body mass index.

We also used Cox proportional hazards regression analysis to examine the adjusted relationship between iron administration and survival. Adherence to the assumption of proportional hazards was confirmed graphically using Ln(−Ln) plots (30). Proportional hazards models are well suited to accommodate baseline representations of iron administration and other potential confounders. To develop multivariable models relating iron dosing to patient mortality adjusted for underlying comorbidity, we initially examined the adjusted relationship between comorbid conditions and study outcomes without iron parameters in the models. Variable selection was guided by unadjusted survival analyses relating comorbidity characteristics to survival. We used a stepwise algorithm to fit a multivariable model of baseline comorbidity measures that were independent predictors of patient survival. We used these sets of comorbidity measures to adjust analyses relating iron dosing to these outcomes by adding iron parameters to these models. We used robust estimators of variance to account for the clustered nature of the data (31,32).

Hospitalization Analyses. We initially described the rate of hospitalization among study subjects overall and among subgroups on the basis of levels of iron administration. We characterized the unadjusted relationship between iron administration and hospitalization by using bivariate Poisson regression (33). We also based the analysis of the adjusted relationship between iron administration and the rate of hospitalization on Poisson regression. These models assume that the rate of hospitalization remains constant for the entire period of observation. We fit multivariable models by using a strategy parallel to that used for the proportional hazards analysis. Some subjects could have multiple events; the period at risk for a hospitalization was the total time a subject was followed and not in the hospital. To account for nonindependence of events within clusters, we used generalized estimating equations (GEE) to fit the models and estimate the standard errors (34).

Results

Descriptive Analyses

Data were available for a total of 34 comorbidity variables, laboratory values, and other patient characteristics among all patients who were potentially eligible for analysis. Table 1 summarizes demographic characteristics of the 10,169 patients who were eligible for analysis. Of these patients, half (50.7%) were men, 52% were white, and 43% were African American.

Almost 40% of patients had ESRD for less than 2 yr, and 87.4% were taking erythropoietin as of December 31, 1993. As of December 1993, 3.8% had had a blood transfusion and 12.7% were undernourished. Diabetic patients accounted for 40.9% of subjects, 13.2% had lung disease, and 9.6% had had a neoplasm. For cardiovascular disease, coronary artery disease, peripheral vascular disease, and congestive heart failure, the prevalence of severe disease was 12.3%, 20.1%, 8.4%, and

Table 4. Survival model: iron and comorbidity estimates[a]

Variable	Unadjusted		Adjusted	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Iron				
none	1.0 (reference)		1.00 (reference)	
low	1.00 (0.91 to 1.11)	0.922	0.93 (0.84 to 1.02)	0.141
high	1.18 (1.07 to 1.30)	0.001	1.11 (1.00 to 1.24)	0.05
Race				
Native American			0.50 (0.34 to 0.75)	
Asian			0.80 (0.63 to 1.01)	
Black			0.77 (0.71 to 0.85)	
White			1.0 (reference)	0.000
Age (yr)				
18 to 30			1.0 (reference)	<0.001
30 to 40			1.50 (0.97 to 2.33)	
40 to 50			1.97 (1.30 to 3.00)	
50 to 60			2.28 (1.53 to 3.41)	
60 to 70			2.91 (1.95 to 4.34)	
70 to 80			3.93 (2.63 to 5.86)	
≥80			6.35 (4.21 to 9.57)	
Gender				
female			0.81 (0.74 to 0.88)	
male			1.0 (reference)	<0.001
Bicarbonate				
≤18			1.0 (reference)	0.0402
>18 and <21			0.92 (0.83 to 1.02)	–
>21 and <24			0.85 (0.77 to 0.95)	
≥24			0.92 (0.82 to 1.04)	
Albumin				
≤3			1.56 (0.85 to 2.87)	<0.001
>3 and <3.5			1.77 (1.02 to 3.10)	
>3.5 and <4			1.49 (0.86 to 2.58)	
>4 and <4.5			1.20 (0.70 to 2.08)	
≥4.5			1.0 (reference)	
Creatinine				
≤5			1.0 (reference)	<0.001
>5 and <7.5			1.08 (0.87 to 1.34)	
>7.5 and <10			1.03 (0.84 to 1.27)	
>10 and <12.5			0.98 (0.78 to 1.23)	
>12.5 and <15			0.81 (0.64 to 1.03)	
≥15			0.60 (0.45 to 0.79)	
Phosphorus				
≤5			1.0 (reference)	<0.001
>5 and <7			1.11 (1.01 to 1.22)	
≥7			1.15 (1.03 to 1.22)	
Hemoglobin				
≤7			1.17 (0.86 to 1.60)	
>7 and <8			1.35 (1.09 to 1.67)	
>8 and <9			1.18 (0.99 to 1.41)	
>9 and <10			1.02 (0.86 to 1.22)	
>10 and <11			1.01 (0.86 to 1.19)	
>11 and <12			0.84 (0.71 to 1.00)	
≥12			1.0 (reference)	<0.001

Table 4.—Continued

Variable	Unadjusted		Adjusted	
	RR (95% CI)	*P*	RR (95% CI)	*P*
BMI				
≤20			1.0 (reference)	<0.001
>20 and <24			0.91 (0.80 to 1.03)	
>24 and <28			0.84 (0.74 to 0.95)	
≥28			0.79 (0.69 to 0.90)	
Percent change BUN				
<62			1.09 (1.00 to 1.19)	
≥62			1.0 (reference)	0.041
Length of ESRD				
≤2 yr			1.0 (reference)	<0.001
>2 and <3			1.17 (1.05 to 1.31)	
>3 and <4			1.28 (1.12 to 1.46)	
>4 and <6			1.20 (1.05 to 1.36)	
>6 and <8			1.52 (1.30 to 1.78)	
≥8			1.01 (0.86 to 1.18)	
Undernourished, December 1993				
yes			1.33 (1.19 to 1.50)	
no			1.0 (reference)	<0.001
Able to transfer independently				
yes			0.76 (0.68 to 0.85)	
no			1.0 (reference)	<0.001
Smoker				
yes			1.35 (1.24 to 1.47)	
no			1.0 (reference)	<0.001
CAD				
severe			1.39 (1.25 to 1.54)	
mild/moderate			1.17 (1.06 to 1.29)	
none			1.0 (reference)	<0.001
PVD				
yes			1.25 (1.14 to 1.36)	
no			1.0 (reference)	<0.001
Heart disease				
severe			1.40 (1.27 to 1.54)	
mild/moderate			1.34 (1.21 to 1.50)	
none			1.0 (reference)	<0.001
Diabetes				
yes			1.27 (1.16 to 1.39)	
no			1.0 (reference)	<0.001
Transplant before December 1993				
yes			0.83 (0.68 to 1.01)	
no			1.0 (reference)	0.056
Access				
synthetic graft			1.0 (reference)	0.0102
permanent catheter			1.29 (1.06 to 1.56)	
temporary catheter			0.97 (0.77 to 1.22)	
AVF			0.91 (0.83 to 1.00)	
Hospitalized during baseline period				
yes			1.30 (1.18 to 1.42)	
no			1.0 (reference)	<0.001
Days spent in hospital during baseline period			1.01 (1.01 to 1.01)	<0.001
EPO used during baseline period				
yes			0.92 (0.84 to 1.00)	0.0405
no			1.0 (Reference)	

[a] RR, relative risk; CI, confidence interval; PVD, peripheral vascular disease; AVF, arteriovenous fistula.

Table 5. Hospitalization model: iron and comorbidity estimates

Variable	Unadjusted		Adjusted	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Iron				
none	1.0 (reference)		1.0 (reference)	
low (1 to 1000 mg)	1.01 (0.90 to 1.14)	0.833	0.92 (0.83 to 1.03)	0.149
high (>1000 mg)	1.25 (1.11 to 1.41)	0.0002	1.12 (1.01 to 1.25)	0.029
Race				
Asian			0.64 (0.49 to 0.84)	
African American			0.83 (0.75 to 0.91)	
Native American			0.48 (0.33 to 0.68)	
White			1.0 (reference)	0.0001
Age (yr)				
18 to 30			0.43 (0.27 to 0.68)	
30 to 40			0.48 (0.37 to 0.61)	
40 to 50			0.63 (0.52 to 0.77)	
50 to 60			0.63 (0.53 to 0.74)	
60 to 70			0.72 (0.63 to 0.83)	
70 to 80			0.81 (0.70 to 0.92)	
≥80+			1.0 (reference)	<0.0001
Gender				
female			0.91 (0.83 to 1.00)	
male			1.0 (reference)	0.0398
Bicarbonate				
≤18			1.24 (1.09 to 1.41)	
>18 and <21			1.08 (0.95 to 1.22)	
>21 and <24			1.04 (0.91 to 1.18)	
≥24			1.0 (reference)	0.0029
Albumin				
≤3			2.17 (1.12 to 4.22)	
>3 and <3.5			2.47 (1.36 to 4.47)	
>3.5 and <4			2.15 (1.19 to 3.87)	
>4 and <4.5			1.70 (0.95 to 3.05)	
≥4.5			1.0 (reference)	<0.0001
Creatinine				
≤5			1.42 (1.04 to 1.92)	
>5 and <7.5			1.66 (1.33 to 2.08)	
>7.5 and <10			1.59 (1.29 to 1.96)	
>10 and <12.5			1.56 (1.27 to 1.93)	
>12.5 and <15			1.57 (1.27 to 1.93)	
≥15			1.0 (reference)	0.0002
Hemoglobin				
≤7			1.09 (0.78 to 1.54)	
>7 and <8			1.32 (1.06 to 1.66)	
>8 and <9			1.21 (1.00 to 1.46)	
>9 and <10			1.12 (0.94 to 1.33)	
>10 and <11			1.10 (0.93 to 1.31)	
>11 and <12			0.96 (0.79 to 1.15)	
≥12			1.0 (reference)	0.0187
BMI				
≤20			1.14 (0.98 to 1.31)	
>20 and <24			1.71 (1.04 to 1.32)	
>24 and <28			1.10 (0.97 to 1.24)	
≥28			1.0 (reference)	0.0861

Table 5.—Continued

Variable	Unadjusted		Adjusted	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Percent change BUN				
<62			1.08 (0.98 to 1.18)	
≥62			1.0 (reference)	0.1131
Undernourished December 1993				
yes			1.15 (1.01 to 1.30)	
no			1.0 (reference)	0.0283
Able to transfer independently				
yes			0.84 (0.75 to 0.94)	
no			1.0 (reference)	0.0018
Smoker				
yes			1.28 (1.16 to 1.41)	
no			1.0 (reference)	<0.0001
CAD				
severe			1.26 (1.13 to 1.41)	
mild/moderate			1.11 (1.00 to 1.23)	
none			1.0 (reference)	0.0003
PVD				
yes			1.20 (1.10 to 1.31)	
no			1.0 (reference)	0.0001
Heart disease				
severe			1.32 (1.19 to 1.46)	
mild/moderate			1.14 (1.01 to 1.28)	
none			1.0 (reference)	<0.0001
Diabetes				
yes			1.23 (1.12 to 1.36)	
no			1.0 (reference)	<0.0001
Transplant before December 1993				
yes			0.75 (0.61 to 0.93)	
no			1.0 (reference)	
Access				
synthetic graft			1.21 (1.09 to 1.34)	
permanent catheter			1.54 (1.24 to 1.91)	
temporary catheter			1.27 (0.98 to 1.63)	
AVF			1.0 (reference)	0.0001
Hospitalized during baseline period				
yes			1.59 (1.45 to 1.76)	
no			1.0 (reference)	<0.0001
Days spent in hospital during baseline period			1.01 (1.01 to 1.01)	<0.0001

37.9%, respectively. The majority of patients could eat independently (97.0%) and transfer independently (85.5%); very few (5.3%) lived in a nursing home. Almost two thirds of subjects had synthetic angioaccess grafts (64.6%), with the remaining subjects using arteriovenous fistulae (28.7%), permanent catheter (4.2%), or a temporary catheter (2.5%).

Table 2 describes the iron dosing for the baseline study period, between January 1, 1994 and June 30, 1994. The majority of subjects (63.0%) had no bills for any iron, 19.8% had bills for a total of 10 or fewer 100-mg vials, and 17.3% had bills for more than 10 vials.

Table 3 provides the distribution of iron dosing by baseline characteristics. Iron dosing was statistically ($P \leq 0.05$) associated with a history of peripheral vascular disease, smoking, diabetes mellitus, gender, change in blood-urea nitrogen during treatment, hospitalization during the baseline period, duration of ESRD, hemoglobin, and type of angioaccess.

Survival Analyses

There were 4925 deaths during the study period. The total survival time was 20,887 yr. The overall death rate was 0.236 (95% confidence interval [CI], 0.23 to 0.24). Results of the

unadjusted and adjusted proportional hazards analyses are presented in Table 4. Owing to missing data, 5833 of 10,169 subjects were included in our final model. We evaluated the impact of missing data on our findings by examining the interaction between iron administration and missing data. In particular, we tested the interaction between an indicator of missing data and the unadjusted relationship between iron administration and survival. The absence of a statistically significant interaction ($P = 0.59$) indicates that the relationship between iron prescription and survival among subjects in our final model was representative of this relationship among subjects excluded from this model owing to missing data.

Compared with none, bills for 10 or fewer vials of iron over a 6-mo period were not associated with changes in survival (relative risk [RR] = 1.0; 95% CI, 0.91 to 1.11; $P = 0.92$). Bills for more than 10 vials over 6 mo were associated with an 18% elevated rate of death (RR = 1.18; 95% CI, 1.07 to 1.30; $P = 0.001$). After adjusting for the 23 demographic and comorbidity characteristics that were independent predictors of survival, the relationship between iron and survival was somewhat attenuated. Bills for 10 or fewer vials showed no adverse effect on survival (adjusted RR = 0.93; 95% CI, 0.84 to 1.02; $P = 0.14$), but bills for greater than 10 vials showed a reduced, but still statistically significant, 11% elevated rate of death (adjusted RR = 1.11; 95% CI, 1.00 to 1.24; $P = 0.05$).

Hospitalization Analysis

The overall rate of hospitalization was 1.35/patient-year at risk (95% CI, 1.34 to 1.37). The analogous rates for patients billed for none, 10 or fewer vials, and greater than 10 vials of iron were 1.31/patient-year (95% CI, 1.29 to 1.33), 1.36/patient-year (95% CI, 1.32 to 1.39), and 1.51/patient-year (95% CI, 1.47 to 1.56), respectively. displays the results of the unadjusted and adjusted Poisson regression analyses. Again, because of missing data, 5434 of 9426 subjects were included in our final model. Compared with none, bills for 10 or fewer vials of iron had no significant association with hospitalization rates (RR = 1.01; 95% CI, 0.90 to 1.14; $P = 0.83$), but bills for greater than 10 vials were associated with a 25% elevated rate of hospitalization (RR = 1.25; 95% CI,1.11 to 1.41; $P < 0.001$). After adjusting for demographic and comorbidity variables, the relationship between iron and morbidity was attenuated. Bills for 10 or fewer vials of iron continued to have no significant association with hospitalization (adjusted RR = 0.92; 95% CI, 0.83 to 1.03; $P = 0.15$), and bills for greater than 10 vials showed a reduced but still statistically significant 12% elevated risk (adjusted RR = 1.12; 95% CI, 1.01 to 1.25; $P = 0.03$).

Discussion

The results of this study demonstrated that compared with none, billing for 10 or fewer 100-mg vials of iron dextran over a 6-mo period was not associated with an increased risk of death or an elevated rate of hospitalization. In contrast, compared with none, billing for more than 10 100-mg vials over a 6-mo period was associated with an increased risk of death and hospitalization even after extensive adjustment for comorbidity. Compared with no iron, dosing of 10 or fewer vials may be associated with a lower rate of death. This latter finding, however, should be interpreted with caution given its associated broad confidence interval.

Several mechanisms have been postulated to explain a potential etiological link between parenteral iron administration and morbidity. First, it has been shown that the availability of iron increases the virulence of certain microorganisms (10,11,35). However, few data are available to indicate an increased risk of septicemia from iron with common gram-positive and gram-negative bacteria. Thus, it would appear unlikely that our findings are an indication of increased virulence of the pathogens typical in dialysis patients.

Second, conditions of iron overload among hemodialysis patients have been linked with impaired white cell function and an elevated risk of infection (12–17,22). For example, Patruta *et al.* (18) demonstrated impaired neutrophil function among patients treated with parenteral iron even in the absence of overt iron overload. Although an iron-induced defect in cellular immunity may potentially lead to a greater risk of bacteremia, the clinical significance of this finding is unknown. Furthermore, reduction of iron stores with desferrioxamine and erythropoietin can improve impaired phagocytosis associated with iron overload (15,16,22).

Third, it has been speculated that the transient presence of free iron as it transits from its bound form to the reticuloendothelial system may lead to increased oxidative stress, the production of reactive oxygen species, and subsequent atheromatous changes (36). Lim *et al.* (36) recently reported that hemodialysis patients demonstrated a greater decrease in the plasma levels of the antioxidant enzyme superoxide dismutase and a greater increase in lipid peroxides compared with normal controls after administration of 100 mg of intravenous ferric saccharate (37). Nonetheless, clinical studies relating iron metabolism with cardiovascular disease outside of the dialysis setting have not consistently demonstrated a relationship (38,39).

A number of clinical studies have been reported relating iron stores or administered iron with subsequent morbidity. Hoen *et al.* (23) prospectively followed adult patients in French dialysis units for 6 mo from late 1989 through early 1990, examining the correlates of bacterial infection. Although these investigators did not study parenteral iron, serum ferritin was included as a potential risk factor for infection. At the end of follow-up, 118 of 607 patients had at least one bacterial infection. Thirty of these infections were associated with at least one positive blood culture. Multiple logistic regression analysis identified three significant risk factors for bacterial infection: a history of bacterial infection, use of a catheter angioaccess device, and an elevated level of serum ferritin. In a subsequent report, however, Hoen *et al.* (40) examined the relationship between practice patterns and bacteremia. Forty-four of 865 patients developed bacteremia with four significant risk factors being identified in multivariable analysis: use of a catheter, two or more previous episodes of bacteremia, current immunosuppressive treatment, and lower hemoglobin. Neither serum fer-

ritin nor any iron administration in the prior 6 mo was a significant risk factor for bacteremia.

Our findings are consistent with several earlier studies of the relationship between administered iron and morbidity in dialysis patients (25–28). In an analysis of iron dosing patterns and mortality, Collins, *et al.* (24–27) studied prevalent hemodialysis patients using data from the USRDS and Medicare. Four cohorts of patients were each followed for 1 yr during which the prescription of more than 17 vials of iron over a period of 3 to 6 mo was associated with an increased risk of death from any cause and from infection after adjustment for prior comorbidity requiring hospitalization. These investigators also reported that prescriptions for more than 17 vials of iron over 5 to 6 mo were associated with a 13% increased risk of hospitalization for bacteremia (25). Owing to limitations of their data, these investigations were unable to adjust for multiple measures of morbidity such as serum albumin, body mass index, and functional status among others, all of which were available to us from the DMMS data.

Nurko *et al.* (28) published an abstract describing their study of the relationship between parenteral iron use and 2-yr mortality among the 2662 nationally representative hemodialysis patients alive in 1993. Although no association between iron use and 2-yr mortality was detected overall, they observed a significant relationship between iron use and 2-yr mortality from infection. Death from infection was not associated with ferritin levels or transferrin saturation.

Our study has several notable limitations. First, we did not have any data on changes in comorbidity or iron dosing over the period of follow-up. Since 1994, when we measured iron administration, its use has risen substantially. This changing pattern of iron use raises the possibility that the patients we studied who were administered parenteral iron differ with respect to characteristics such as the level of comorbidity compared with similarly treated patients today. The generalizability of our findings to current day practice depends on the extent to which we were successful in measuring and adjusting for comorbidity. Despite extensive clinical data on our study subjects, we did not have access to all potentially important information on comorbidity, including changes in patients' health status over time. Although often observed in causal relationships, the absence of a gradient effect in our findings may suggest a threshold over which iron dosing is associated with lower survival. Second, our sample size was constrained by the large number of subjects in the USRDS database missing data on one or more comorbidity variables. Nonetheless, we were able to detect an association between iron prescriptions for greater than 10 vials over 6 mo and reduced survival. Furthermore, the prescription of 10 or fewer vials was not associated with an elevated risk of death; this is unlikely to change even with a larger study, because the upper bound of the confidence interval was very close to 1.0. However, because of our limited sample size, we were not able to explore subanalyses of death from infection or cardiovascular disease. Third, it is conceivable that the exclusion of a large number of subjects from our multivariable analysis because of missing data may have led to selection bias. Despite this possibility, our finding that the unadjusted iron dosing/survival relationship did not differ across subgroups with and without missing data suggests that selection bias played little role in our study. Fourth, we obtained our measure of iron exposure from Medicare billing data and could not be certain that study subjects received the quantity of iron for which their dialysis providers submitted bills to Medicare. Fifth, although we had extensive data on comorbidity, as noted earlier, we cannot rule out residual confounding from unmeasured or incompletely specified clinical characteristics. Finally, although we studied patients during a time when iron dextran was the only parenteral preparation available in North America, other parenteral preparations are now marketed and increasing in usage. Although we know of no theoretical basis for not generalizing our findings to these other preparations, additional studies would be needed to confirm our study results for these iron preparations.

Prescribing iron in quantities of 10 or fewer vials over 6 mo, a dosing scheme well within the guidelines established by the National Kidney Foundation's Dialysis Outcomes Quality Initiative (41), had no association with an elevated risk of death or rate of hospitalization and may be associated with a small reduction. Although intensive dosing regimens were associated with diminished adjusted survival and higher adjusted rates of hospitalization, these potential risks need to be balanced against the known elevations in morbidity and mortality associated with anemia. Hemoglobin levels less than 10 g/dl have been associated with an elevated risk of death (41). Furthermore, it is now widely appreciated that most hemodialysis patients require parenteral iron to achieve a hemoglobin target of 11 g/dl (42).

Although we cannot eliminate the possibility that our findings regarding dosing of more than 10 vials (1000 mg) of iron dextran are a result of residual confounding from incomplete measurement of comorbidity, caution is warranted when prescribing this amount of parenteral iron over a period of 6 mo, especially if adequate iron stores and hemoglobin levels can be achieved with lower doses. Additional studies of the relationship between iron administration and patient outcomes should include measures of the changing pattern of comorbidity, iron dosing, and erythropoietin dosing over time and evaluation of preparations of iron in addition to iron dextran.

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