Administration of Parenteral Iron and Mortality among Hemodialysis Patients

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Abstract. The objective of this study was to evaluate whether the apparent relationship demonstrated in prior studies between iron dosing and mortality in hemodialysis (HD) patients was confounded by incomplete representation of iron dosing and morbidity over time. A cohort study was conducted among 32,566 patients who received at least 1 yr of HD at the Fresenius Medical Corporation dialysis centers during 1996 to 1997. The outcome measure was all-cause mortality through mid-1998. A total of 19 demographic, comorbidity, and laboratory characteristics were available. By proportional hazards analysis, no adverse effect on 2-year survival was found for baseline iron dose over 6 mo of $\leq$ 1000 mg, but statistically significant elevated mortality was demonstrated for iron doses $>$1000 mg to 1800 mg (adjusted hazards ratio [HR] = 1.09; 95% confidence interval [CI], 1.01 to 1.17) and $>$1800 mg (adjusted HR = 1.18; 95% CI, 1.09 to 1.27). However, fitting multivariable models that appropriately account for time-varying measures of iron administration as well as other fixed and time-varying measures of morbidity, the authors found no statistically significant association between any level of iron administration and mortality. This study suggests that previously observed associations between iron administration and higher mortality may have been confounded, and it provides cautious support for the safety of the judicious administration of cumulative iron doses $>$1000 mg over 6 mo if needed to maintain target hemoglobin levels among patients treated with maintenance HD.

Effective treatment of the anemia of chronic kidney disease (CKD) with recombinant human erythropoietin (epoetin) improves survival, decreases morbidity, improves quality of life, and decreases overall cost (1–3). Despite the widespread use of epoetin, the percentage of patients who do not maintain the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines' target hemoglobin levels remains high at over 50% in 1998.

The most common cause of poor hemoglobin response to epoetin, in either the initial or maintenance phase of epoetin use, is iron stores that are inadequate to support epoetin-stimulated erythropoiesis (1). The 2000 NKF-KDOQI guidelines recommend parenteral iron repletion for many hemodialysis (HD) patients whose hemoglobin levels are below target levels, and maintenance parenteral iron dosing is now recommended for the majority of HD patients. United States Renal Data System (USRDS) data reveal a steady increase in use of parenteral iron in incident and prevalent HD patients from 1994 to 1998 (4,5).

It has been suggested that high cumulative doses of iron may contribute to the increased morbidity and mortality among the end-stage renal disease (ESRD) population, perhaps due to elevated risk of infection (6,7) or increased oxidative stress leading to atheromatous change (8–10). However, epidemiologic studies examining the associations of parenteral iron dose to morbidity and mortality have yielded conflicting results (11–15). We recently published analysis of data from the USRDS Dialysis Morbidity and Mortality Studies (DMMS) (16) that corroborated other authors' findings (14) that high cumulative parenteral iron dose was associated with higher rates of hospitalization and diminished survival. However, these studies could not rule out the possibility that high iron dose is not an independent cause of mortality, but rather a marker for prior morbidities that mediate the statistical relationship between iron administration and subsequent poor clinical outcomes. In particular, causes of anemia poorly responsive to epoetin, frequently prompting iron administration, may themselves be associated with higher rates of mortality. Because of this, we hypothesized that more comprehensive representation of iron dosing and potentially confounding vari-

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ables not possible in prior studies might diminish the apparent relationship between iron administration and mortality. The purpose of the study we now report was to examine this hypothesis in a large sample of US HD patients for which we had the opportunity to account for detailed iron dose information over time and to control extensively for both baseline and time-varying comorbidity.

Materials and Methods

Overview

Our initial modeling approach (baseline model), done primarily for comparison with our earlier analysis (16), considered the association of total iron dose received during a 6-mo baseline period to mortality over subsequent follow-up. Our primary analytic approach ("time-dependent models") incorporated detailed iron dosing and comorbidity information over time by examining the probability of survival as a function of cumulative iron dose over rolling 6-mo intervals for the duration of follow-up. We developed both "unlagged" and "lagged" time-dependent models to address the possibility that the association of 6-mo iron dosing with mortality changes with increasing time following iron administration.

Study Population

Information on demographics, comorbidity, survival, hospitalization, and iron dosing was obtained from the Fresenius Medical Corporation (FMC) electronic roster of HD patients. Two enrollment periods were designated: (*1*) from January 1, 1996 to June 30, 1996; (*2*) from July 1, 1996 to December 31, 1996. All subjects eligible for this study remained in the FMC electronic roster for the duration of at least one enrollment period. Because our analysis of baseline 6-mo iron dose mandated survival for 6 mo beyond the end of the enrollment period to enable characterization of potentially confounding variables *prior* to the baseline iron exposure period, we chose to restrict all analyses to patients who survived beyond December 31, 1996 and June 30, 1997 for the first and second enrollment periods, respectively.

A total of 31,095 patients (26,138 and 4957 from the first and second enrollment periods, respectively) were eligible for the time-varying analyses. Of these, 27,280 and 28,081 had complete covariate characterization for inclusion in the baseline and unlagged time-dependent multivariable analyses, respectively; 23,241 and 19,436 had complete covariate characterization for inclusion in the 6- and 12-mo lagged time-dependent analyses, respectively.

Study Data

Mortality and Censoring Events. Death data from the FMC electronic roster were obtained for follow-up from the end of the enrollment periods until September 30, 1998. Censoring events included transfer of care away from FMC at any time during the follow-up period.

Exposure to Parenteral Iron. For each month beginning 6 mo after the end of the enrollment period and continuing until death or censoring, parenteral iron exposure over the most recent 6 mo was categorized, with no iron received as the reference category.

Iron exposure was defined as the total iron dose administered: (*1*) for the baseline analysis, over the 6-mo time period immediately following the end of the enrollment period; (*2*) for the unlagged time-dependent analysis, over rolling intervals representing the cumulative iron dose over the 6 most recent months; and (*3*) for the lagged time-dependent analyses, over rolling intervals representing the cumulative iron dose 6 to 12 and 12 to 18 mo previously. Figure 1 demonstrates four examples of rolling exposure windows and the 1-mo period of risk for death associated with each window for the unlagged time-dependent analysis.

Potential Confounding Variables. Potential confounders available included demographic, comorbidity, clinical, and laboratory data from the FMC data set. Demographic variables included gender, race,

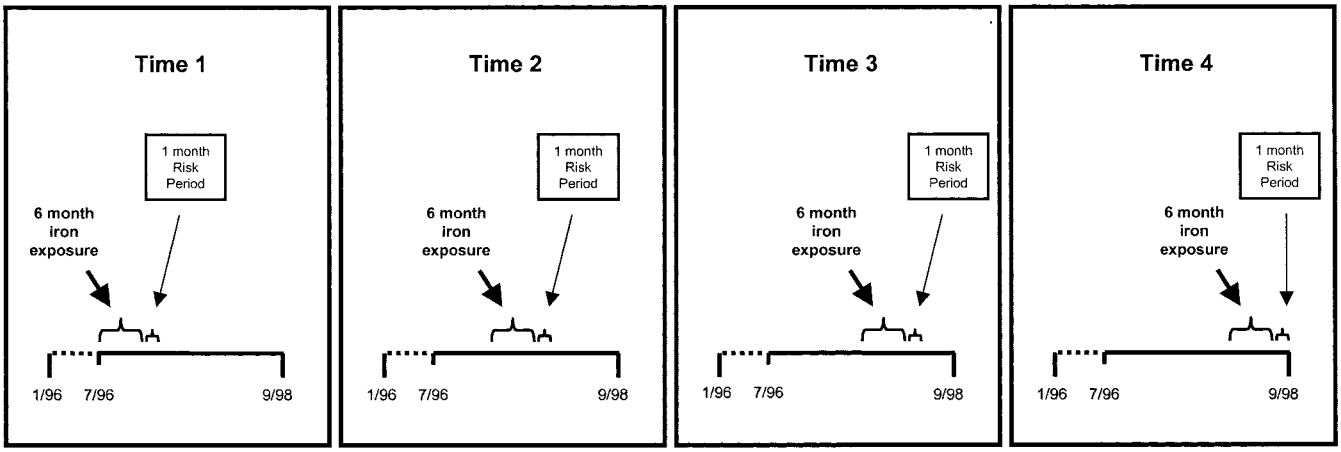

Figure 1. Rolling iron exposure windows and the risk period for death associated with each window for the unlagged time-dependent model. The dashed line designates the enrollment period from January 1, 1996 to June 30, 1996. For each month of follow-up beginning 6 mo after the end of this enrollment period and lasting until September 30, 1998, the association of mortality to the cumulative iron dose over the 6 most recent months was examined. This figure simplifies our approach by showing only four examples of iron dosing exposure intervals (of 21 total intervals) and the associated period of risk of death for each of these four intervals. Levels of other time-varying variables (not shown here) were considered both (*1*) over the 1 mo immediately before each rolling iron exposure window and (*2*) during each rolling iron exposure window. A second enrollment period from July 1, 1996 to December 31, 1996 (not shown in this figure) was also designated. The association of cumulative 6-mo iron dose to mortality until September 30, 1998 was examined using the same approach as for subjects entering in the first enrollment period.

and age at study entry. Comorbidity data included duration of ESRD at study entry, diabetic status, and clinical information obtained during the enrollment period, including hospitalization (yes/no) and parenteral antibiotic use (none, one dose, more than one dose). Variables available through the entire study period were epoetin dose and laboratory data, including serum albumin, aspartate aminotransferase (AST/SGOT), bicarbonate, calcium, ferritin, hemoglobin, parathyroid hormone (PTH), phosphate, transferrin saturation (TSAT), and urea reduction ratio (URR). Mean laboratory values and epoetin dose were determined for (1) the enrollment period for the baseline analysis and (2) rolling 1-month intervals throughout follow-up for time-dependent analyses.

Statistical Analyses

We considered the association of mortality to the total iron dose received during the baseline 6-mo interval immediately after the enrollment period and over rolling 6-mo intervals for the duration of follow-up. All analyses used SAS version 8.2 and Stata version 8.

A descriptive analysis examined the frequency distributions of enrollment period characteristics, including comorbidity and laboratory values, and of cumulative iron dose during the baseline period and during rolling follow-up intervals. The distribution of baseline iron dosing was examined by patient characteristics. We also characterized the unadjusted relationship between iron dosing and survival using Cox proportional hazards models (17).

Our initial modeling approach considered the association of cumulative baseline 6-mo iron dose with mortality over the subsequent 21 mo. We used the Cox proportional hazards model (17), including terms for covariates during the enrollment period immediately before the baseline iron-dosing interval.

Analyses of mortality as a function of iron dose administered over a designated baseline period may be biased because this approach provides no direct representation of the effects of iron received subsequent to the baseline period. Failure to incorporate iron dosing received throughout follow-up is equivalent to assuming that iron dosing remains constant over time. In reality, physicians commonly change levels of iron administered to patients in the clinical setting in response to changes in indicators of need for the drug (*e.g.*, hemoglobin levels). For this reason, we incorporated time-varying measures of iron administration into our primary analytic models, developing weighted Poisson regression approximations to the Cox proportional hazards model that examined the rate of dying in a particular month as a function of iron received during the previous 6 mo (unlagged time-dependent model, illustrated in Figure 1), or during the intervals 6 to 12 or 12 to 18 mo previously (lagged time-dependent models) (18).

Like administered iron, some predictors of both subsequent iron dose and mortality, such as hemoglobin, vary with time. To reduce the likelihood of detecting confounded associations between iron dosing and mortality, we incorporated time-varying levels of hemoglobin and other potentially confounding variables into our time-dependent analyses of the relationship of iron dosing to mortality. We used two distinct approaches to account for the influence of potentially confounding time-varying variables *before* and *during* the rolling 6-mo windows for which the relationship of administered iron to mortality was examined.

To adjust for time-varying variables measured *before* each 6-mo iron dosing window, we used traditional regression methods (19,20) by adding to our model levels of time-dependent covariates that were the most recent monthly values obtained before the start of each iron administration window. However, the use of these traditional regression methods for controlling confounding by time-varying variables *during* the iron exposure window could yield biased results because these variables may potentially both predict subsequent iron use and mortality and serve on the causal pathway between iron administration and death. One approach to deal with this type of confounding by time-varying covariates without inappropriately adjusting for any role they may have as intermediate variables is to estimate a modified form of a marginal structural model using weighted Cox proportional hazards regression (21–26). Using this method, we developed individual-level weights for our mortality model with parameters including rolling 6-mo iron dose, baseline covariates, and levels of time-varying covariates at the start of each 6-mo window. Weights were calculated from the inverse of the probability of having the iron treatment history a patient actually had during each patient-month of follow-up. These probabilities were derived from polychotomous logistic regression models of the probability of a particular level of iron dosing in each month as a function of previous iron dose, hemoglobin, ferritin, and other fixed (age, race, gender, diagnosis of diabetes) and time-dependent (epoetin dosing, URR, albumin, AST, bicarbonate, calcium, ferritin, hemoglobin, and TSAT) variables. To overcome the limitations of standard software, we used a weighted Poisson regression approximation to a weighted Cox proportional hazards model. The adjusted hazard ratios from these models are numerically comparable to hazard ratios from proportional hazards regression and more closely approximate the results of standard analyses of a randomized trial than do other regression approaches that incorporate time-dependent variables (24,25). The models we fit assumed that the effect of iron did not vary with time since ESRD; we tested this assumption by including a term for the interaction of iron dose and time since ESRD.

Results

Descriptive Analyses

Data were available for a total of 19 comorbidity variables, laboratory values, and other patient characteristics among all patients who were potentially eligible for analysis. Table 1 summarizes these characteristics during the baseline study period for the 27,280 patients eligible for our baseline analyses who had complete covariate information.

During the 6-mo baseline period, 27% of subjects received no intravenous iron, 12% received >0 to 700 mg, 13% received >700 to 1000 mg, 23% received >1000 to 1800 mg, and 25% received >1800 mg. The mean and median doses of administered iron were 1001 mg and 1000 mg, respectively. The distribution of iron dosing during follow-up expressed as mg per 6 mo was as follows: 6% received no intravenous iron, 21% received >0 to 700 mg, 17% received >700 to 1000 mg, 40% received >1000 to 1800 mg, and 15% received >1800 mg. The mean and median doses of iron administered per 6 mo of follow-up were 1123 mg and 1088 mg, respectively.

Table 1 also provides the distribution of iron dosing by baseline characteristics selected for the subsequent models. Receiving epoetin at baseline and low levels of hemoglobin were associated with substantially higher probabilities of receiving iron ($P \leq 0.0001$ for each). Iron dosing was also associated with race, diabetic status, baseline hospitalization period and antibiotic use, (shorter) duration of ESRD, URR, albumin, AST/SGOT, calcium, ferritin, phosphate, and TSAT

Table 1. Distributions of selected patient characteristics

	Distribution across Full Cohort		Stratum-Specific Distribution by Baseline Iron Dose (%)			
	n	(%)	None	> 0 to 1000 mg	> 1000 mg	*P*-value
Baseline period iron dosing[a]						
total iron dose received (mg)						
none	7241	(26.5)	-	-	-	-
> 0 to 700	3327	(12.2)	-	-	-	
> 700 to 1000	3569	(13.1)	-	-	-	
> 1000 to 1800	6391	(23.4)	-	-	-	
> 1800	6752	(24.8)	-	-	-	
Demographic and comorbidity variables						
gender						
male	13744	(50.4)	27.6	24.6	47.8	0.0026
female	13536	(49.6)	25.5	26.0	48.6	
age (yr)[b]						
18 to <40	3097	(11.4)	28.0	25.5	46.5	0.0021
40 to <60	9193	(33.7)	27.6	24.3	48.2	
≥ 60	14990	(55.0)	25.6	25.9	48.5	
race						
Asian/Pacific Islander	433	(1.6)	46.2	22.9	31.0	< 0.0001
Black	12543	(46.0)	24.9	25.2	49.9	
Native American	218	(0.8)	22.9	37.6	39.5	
White	12928	(47.4)	26.8	25.0	48.2	
other	1158	(4.2)	35.0	26.9	38.1	
diabetes[b]						
no	15077	(55.3)	28.7	25.3	45.9	< 0.0001
yes	12203	(44.7)	23.8	25.2	51.0	
duration of ESRD (yr)[b]						
0.5 to < 2	11390	(41.8)	22.7	23.7	53.5	< 0.0001
2 to < 4	7386	(27.1)	27.2	25.8	47.1	
≥4	8504	(31.2)	31.1	26.9	41.9	
Enrollment period variables[c]						
hospitalizations						
0	15008	(55.0)	30.5	25.2	44.3	< 0.0001
≥ 1	12272	(45.0)	21.7	25.4	53.0	
IV antibiotic doses administered						
0	19504	(71.5)	27.8	25.1	47.0	< 0.0001
1	2056	(7.5)	24.5	26.8	48.8	
≥ 2	5720	(21.0)	22.9	25.3	51.8	
epoetin (units/mo)						
none	1838	(6.7)	64.5	13.1	22.4	< 0.0001
> 0 to 20,000	3209	(11.8)	29.5	30.5	40.0	
20,000 to 40,000	6925	(25.4)	25.8	28.5	45.7	
> 40,000	15308	(56.1)	21.7	24.2	54.1	
albumin (g/dl)						
< 3.5	2727	(10.0)	24.3	23.4	52.4	< 0.0001
3.5–4	13525	(49.6)	25.2	25.0	49.7	
> 4	11028	(40.4)	28.7	26.1	45.2	
AST/SGOT (U/L)						
< 50	26651	(97.7)	26.3	25.3	48.3	< 0.0001
≥ 50	629	(2.3)	35.3	23.1	41.7	
bicarbonate (mEq/L)						
< 18	4634	(17.0)	25.7	24.0	50.3	0.0004
18 to < 21	11121	(40.8)	26.2	25.3	48.5	
≥ 21	11525	(42.3)	27.2	25.8	47.0	

Continued

Table 1. Continued

	Distribution across Full Cohort		Stratum-Specific Distribution by Baseline Iron Dose (%)			
	n	(%)	None	> 0 to 1000 mg	> 1000 mg	*P*-value
calcium (mg/dl)						
< 8	2131	(7.8)	25.6	23.9	50.5	< 0.0001
8 to < 9	11510	(42.2)	25.4	25.1	49.6	
9 to < 10	10950	(40.1)	27.0	26.3	46.8	
10 to < 11	2576	(9.4)	30.6	23.3	46.1	
≥ 11	113	(0.4)	31.0	20.4	48.7	
ferritin (ng/ml)						
< 100	5636	(20.7)	35.4	23.4	41.2	< 0.0001
100 to < 800	18991	(69.6)	22.8	25.7	51.6	
≥ 800	2653	(9.7)	34.8	26.4	38.8	
hemoglobin (g/dl)						
< 8	574	(2.1)	32.2	16.2	51.6	< 0.0001
8 to < 10	10128	(37.1)	23.2	23.3	53.4	
10 to < 12	15549	(57.0)	27.6	26.8	45.6	
≥ 12	1029	(3.8)	40.3	26.3	33.3	
phosphate (mg/dl)						
< 5	7022	(25.7)	28.4	26.0	45.6	< 0.0001
5 to < 7	13877	(50.9)	26.9	25.4	47.8	
≥ 7	6381	(23.4)	23.8	24.3	51.9	
PTH (pg/ml)						
< 200	14773	(57.4)	26.6	25.1	48.3	0.014
200 to < 500	6286	(24.4)	25.9	24.8	49.3	
500 to < 1000	2637	(10.3)	26.5	25.3	48.2	
≥ 1000	2039	(7.9)	30.2	25.2	44.6	
TSAT (%)						
< 20	6197	(22.7)	26.6	23.0	50.5	< 0.0001
20 to < 35	16522	(60.6)	24.8	25.1	50.1	
35 to < 50	3799	(13.9)	30.5	29.4	40.1	
≥ 50	762	(2.8)	44.8	26.3	29.0	
URR (%)						
< 62	4213	(15.4)	24.3	23.2	52.5	< 0.0001
≥ 62	23067	(84.6)	27.0	25.7	47.4	

The two 6-mo enrollment periods were January 1, 1996 to June 30, 1996 and July 1, 1996 to December 31, 1996.
[a] The baseline iron exposure period was designated as the 6 mo immediately following the enrollment period.
[b] Demographic and comorbidity variables were collected at the end of the enrollment period.
[c] Mean values during the enrollment period.

(all $P \leq 0.0001$); age ($P = 0.0021$); bicarbonate level ($P = 0.0004$); PTH ($P = 0.014$); and gender ($P = 0.0026$).

Among 31,095 subjects available for the unlagged time-dependent model, there were 6480 deaths during the study period, the total person-time of follow-up was 39725 yr, and the death rate was 0.16 per year.

Multivariable Analysis

Baseline Model. In the adjusted proportional hazards analysis relating baseline iron dose to survival, doses of iron over 1000 mg in the 6-mo baseline period were associated with increased risk of mortality (Table 2). Subjects in the highest dose category (>1800 mg) had a 18% higher adjusted mortality rate than did subjects not receiving iron, and subjects in the >1000 to 1800 mg category had a 9% higher adjusted mortality than did subjects not receiving iron. Also associated with mortality in this model (not shown) were age, race/ethnicity, gender, duration of ESRD, and diabetic status; enrollment period laboratory values including URR, albumin, AST/SGOT, bicarbonate, calcium, ferritin, phosphate, TSAT, and hemoglobin; and enrollment period hospitalizations, parenteral antibiotic use, and epoetin use.

Time-Dependent Models. Fitting a weighted Poisson regression model to approximate Cox proportional hazards regression, we estimated the adjusted probability of dying in a particular month as a function of cumulative iron dose received during the previous (*1*) 0 to 6 mo, (*2*) 6 to 12 mo, and (*3*) 12 to 18 mo. Table 2 summarizes the adjusted associations of iron

Table 2. Summary of modeling results for the adjusted hazard ratios for mortality by iron dosing

	Baseline Model	Time-Dependent Models		
		Iron 0 to 6 mo Earlier (Unlagged)	Iron 6 to 12 mo Earlier (Lagged)	Iron 12 to 18 mo Earlier (Lagged)
Total iron dose over 6 mo (mg)				
None	Reference	Reference	Reference	Reference
> 0 to 700	1.01 (0.93–1.11)	1.04 (0.91–1.19)	1.01 (0.84–1.22)	0.83 (0.67–1.04)
> 700 to 1000	1.03 (0.94–1.12)	1.00 (0.87–1.14)	0.96 (0.82–1.13)	0.99 (0.80–1.23)
> 1000 to 1800	1.09 (1.01–1.17)	0.96 (0.84–1.09)	1.06 (0.90–1.23)	0.96 (0.79–1.18)
> 1800	1.18 (1.09–1.27)	1.04 (0.90–1.21)	1.05 (0.89–1.24)	1.16 (0.94–1.44)
P value	< 0.0001	0.78	0.80	0.10

dose with mortality, expressed as hazard ratios, for all three models. By each of these three modeling approaches (one unlagged and two lagged time-dependent models), no statistically significant association was detected between mortality and any level of iron dosing. For the association of mortality with iron dose in the interval 12 to 18 mo earlier, the highest category of iron dose was associated with the greatest rate of mortality (hazard ratio [HR] = 1.16; 95% confidence interval [CI], 0.94 to 1.44) and the lowest dose with a somewhat lower rate of mortality (HR = 0.83; 95% CI, 0.67 to 1.04) compared with no iron use, although these findings were not statistically significant as indicated by the width of the confidence intervals. The hazard ratios for mortality for all covariates in the unlagged time-dependent model are provided in Table 3. These values were similar for the two lagged time-dependent models (data not shown). We did not find that the effect of iron dose varied with time since ESRD ($P > 0.1$ for each of the three models with different time lags).

Discussion

Consistent with findings from our previous work using 1994 USRDS data, (16) selected analyses from this study that did not incorporate time-varying data showed that doses of >1000 mg of iron over 6 mo were associated with an increased rate of mortality. The consistency of these findings remained despite the study of entirely different cohorts and the marked increase in iron administration between 1994 and 1996. In recognition of the possibility that these relationships were confounded by incomplete assessment of iron administration and morbidities that are indications for iron dosing, we incorporated time-varying data into the analyses. They permitted consideration of iron exposures beyond the baseline period as well as potentially confounding morbidity that developed over time. The principal finding of this study is the absence of a statistically significant association between cumulative iron dose and mortality using analytical techniques that account for changing iron dosing and morbidity over time.

Few studies before our work have examined the association of iron use with overall mortality in HD patients. In a study of prevalent HD patients using USRDS data, Collins *et al.* (14,27) found that 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 hospitalization. Nurko *et al.* (13) published, in abstract form, a study that described no association between parenteral iron use and 2-yr mortality among 2662 nationally representative HD patients in 1993, although they did observe a significant relationship between iron use and 2-yr mortality from infection. Our prior analysis using USRDS DMMS data found an 11% increase in the rate of death with doses of >1000 mg of iron over 6 mo after extensive adjustment for baseline comorbidity (16). Nonetheless, as we demonstrate in the current study, even extensive characterization of baseline iron exposure and adjustment for baseline confounding variables may be inadequate for the evaluation of iron toxicity unless the complex interplay between changing morbidity and iron dosing over time is addressed analytically. Our analyses presented here that do incorporate time-varying iron dosing and morbidity suggest that the analysis of baseline iron exposure also reported here as well as the previously observed associations between iron administration and higher mortality were confounded relationships.

A number of contrasts between this study and our prior work using USRDS DMMS data are noteworthy. The patient samples for these two studies were drawn from different populations and were separated in time by 2 yr. Notably, iron dosing patterns changed markedly in the US over this relatively brief interval. In this study's 1996 FMC cohort, 48% received >1000 mg of iron over a 6-mo baseline period compared with just 17% over 6 mo in our 1994 USRDS study. Despite these differences between the two patient samples, both studies remarkably found very similar relationships between iron dosing during baseline and mortality in multivariable models that did not incorporate time-varying data [HR = 1.09 (95% CI, 1.01 to 1.17) for 1000 to 1800 mg iron *versus* none (FMC) and HR = 1.12 (95% CI, 1.01 to 1.25) for the >1000 mg *versus* none (USRDS)]. These similar findings emphasize the generalizability of the FMC data set to a national sample of US HD patients.

Our finding of an association between mortality and higher serum ferritin levels 6 mo before death in our time-dependent regression (Table 3, [HR = 1.29 (95% CI, 1.13 to 1.47) for ferritin level ≥ 800 *versus* 100 to 799 ng/ml] deserves additional mention. Given the known influence of inflammation on

Table 3. Results of weighted multivariable model for the probability of mortality as a function of iron administered during the prior 6 mo

Variable	Category	Adjusted[a]	
		Hazard Ratio (95% CI)	*P* value
Iron (mg)[b]	None	Ref.	0.78
	> 0 to 700	1.04 (0.91–1.19)	
	> 700 to 1000	1.00 (0.87–1.14)	
	> 1000 to 1800	0.96 (0.84–1.09)	
	> 1800	1.04 (0.90–1.21)	
Gender	Male	Ref	0.07
	Female	0.90 (0.81–1.01)	
Race	White	Ref	< 0.0001
	Black	0.74 (0.66–0.83)	
	Native American	1.01 (0.70–1.46)	
	Asian/Pacific Islander	0.91 (0.69–1.21)	
	Other	0.86 (0.70–1.05)	
Age (yr)[c]	18 to < 30	Ref	< 0.000100
	30 to < 40	2.53 (1.33–4.81)	
	40 to < 50	2.47 (1.37–4.43)	
	50 to < 60	3.26 (1.82–5.83)	
	60 to < 70	5.04 (2.83–9.00)	
	70 to < 80	6.45 (3.62–11.48)	
	≥ 80	7.89 (4.38–14.22)	
Duration of ESRD (yr)[f]	0.5 to < 2	Ref.	< 0.0001
	2 to < 3	1.03 (0.74–1.43)	
	3 to < 4	1.21 (0.88–1.69)	
	4 to < 6	1.30 (0.93–1.80)	
	6 to < 8	1.41 (1.01–1.99)	
	≥ 8	1.65 (1.17–2.31)	
Diabetic status[c]	Non-diabetic	Ref.	< 0.0001
	Adult-onset	1.29 (1.03–1.61)	
	Juvenile-onset	0.82 (0.74–0.91)	
Hospitalizations[d]	0	Ref.	< 0.0001
	≥ 1	1.56 (1.41–1.73)	
IV antibiotic doses administered[d]	0	Ref.	0.01
	1	1.16 (0.97–1.39)	
	≥ 2	1.20 (1.06–1.37)	
URR (%)[e]	< 53.4	1.26 (0.97–1.64)	0.22
	53.4 to < 58.7	1.13 (0.90–1.41)	
	58.7 to < 62.4	1.14 (0.90–1.44)	
	62.4 to < 67	1.13 (0.98–1.31)	
	≥ 67	Ref.	
Epoetin dose (units/mo)[e]	0	Ref.	0.22
	> 0 to 20,000	0.94 (0.69–1.28)	
	> 20,000 to 40,000	1.03 (0.76–1.38)	
	> 40,000	1.10 (0.83–1.47)	
Albumin (g/dl)[e]	≤ 3	4.96 (3.55–6.92)	< 0.0001
	3.0 to < 3.5	2.97 (2.25–3.92)	
	3.5 to < 4	2.02 (1.57–2.61)	
	4 to < 4.5	1.32 (1.03–1.68)	
	≥ 4.5	Ref.	
AST/SGOT (U/L)[e]	< 50	Ref.	< 0.0001
	≥ 50	1.63 (1.29–2.07)	

Continued

Table 3. Continued

Variable	Category	Adjusted[a]	
		Hazard Ratio (95% CI)	*P* value
Bicarbonate (mEq/L)[e]	6 to < 18	1.28 (1.08–1.52)	0.01
	18 to < 21	1.03 (0.89–1.18)	
	21 to < 24	1.07 (0.93–1.24)	
	24 to < 35	Ref.	
Calcium (mg/dl)[e]	5 to < 8	0.95 (0.77–1.17)	0.87
	8 to < 9	1.02 (0.90–1.15)	
	9 to < 10	Ref.	
	10 to < 11	1.02 (0.89–1.17)	
	11 to < 15	0.90 (0.70–1.17)	
Ferritin (ng/ml)[e]	< 100	0.96 (0.82–1.12)	0.0005
	100 to < 800	Ref.	
	≥ 800	1.29 (1.13–1.47)	
Hemoglobin (g/dl)[e]	< 7	1.68 (1.09–2.58)	0.09
	7 to < 8	1.25 (0.95–1.64)	
	8 to < 9	1.20 (0.99–1.46)	
	9 to < 10	1.23 (1.05–1.44)	
	10 to < 11	1.12 (0.97–1.30)	
	11 to < 12	Ref.	
	12 to < 16	1.05 (0.85–1.30)	
Phosphate (mg/dl)[e]	< 5	Ref.	0.62
	5 to < 7	1.04 (0.92–1.17)	
	≥ 7	1.08 (0.93–1.25)	
TSAT (%)[e]	< 20	1.26 (1.13–1.41)	< 0.0001
	≥ 20	Ref.	

[a] Adjusted for other variables in the table.
[b] Cumulative iron dose during rolling 6 mo windows.
[c] At end of enrollment period.
[d] During enrollment period.
[e] During the month prior to each rolling 6-mo iron dosing window.
[f] At the beginning of the 6-mo iron dosing window; in the final model, a separate coefficient was included for each duration (in mo) of time since ESRD.

ferritin levels and the fact that the ferritin-mortality relationship was adjusted for *subsequent* iron administration, the ferritin findings should not be interpreted as indicating a link between iron stores and mortality. Rather, this association between higher ferritin and the rate of death may reflect a causal relationship between mortality and factors other than iron administration (*e.g.* inflammation) that elevate ferritin and for which we had no direct measure.

Our decision to perform unlagged and lagged analyses enabled us to consider the possibility that the association of administered iron dose with subsequent survival, if any, may differ according to the follow-up time interval examined. In part, we chose this approach because potential mechanisms by which it has been speculated that parenteral iron administration might lead to adverse outcomes include elevated risk of serious infection and increased oxidative stress leading to atheromatous change (6–10). No clear epidemiologic links have been established between iron administration and an elevated population risk of either infection (11,12,28–30) or atherosclerosis in ESRD or other populations (31–36). However, the effect, if any, of iron dosing on mortality due to life-threatening infection most plausibly should be highest shortly after a dose and fall over time, whereas toxicity mediated through oxidative stress and atheromatous change may become clinically manifest only after a lag following iron administration.

Our finding of no statistically significant adjusted association between mortality and iron dosing by any of our time-dependent modeling approaches does not support any association of iron dosing with mortality. However, the finding of a statistically nonsignificant elevated HR for mortality (HR = 1.16; 95% CI, 0.94-1.44 *versus* no iron dosing) for cumulative iron dose >1800 mg administered during the interval 12 to 18 mo previously makes us unable to exclude the possibility of a true, but lagged, association between this level of dosing and mortality, given the limitations of statistical power to examine this relationship. Investigation of whether iron dose may be associated specifically with infectious or cardiovascular morbidity and mortality was precluded in this study because we did not have data available that provided detailed information about morbidity that developed during follow-up or about cause of death.

Our study has several other notable limitations. First, we cannot rule out residual confounding from unmeasured or incompletely specified clinical characteristics. However, the source of our data, the FMC electronic roster of HD patients, has enabled substantially more comprehensive representation of iron dosing and potentially confounding variables than prior published studies of iron dosing and mortality using USRDS Medicare claims data (14,16). Second, subsequent to our study period of 1996 to 1998, the use of parenteral iron in HD units has continued to rise. This changing pattern of iron utilization 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. Third, the use of maintenance doses of parenteral iron to maintain hemoglobin within the NKF-KDOQI target range, rather than bolus iron given when more overtly iron-deficient, has become much more widespread than when these data were collected. Although we know of no mechanistic explanation for why this change in regimen would alter the clinical sequelae caused by administered iron, we cannot entirely rule out this possibility. Fourth, this study examined survival among subjects who had received at least 1 yr of HD. As such, it may not be generalizable to patients new to dialysis, who often have more comorbidities than patients well enough to have survived the initial dialysis period.

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. Zager *et al.* (9) recently found that iron sucrose was associated with greater *in vitro* cell death than iron dextran or iron gluconate, although all of these parenteral iron preparations induced lipid peroxidation (indicative of oxidative activity). Whether these different iron preparations are associated in humans with different levels of oxidative stress or with clinically manifest disease such as atherosclerosis is unknown. Additional studies will be needed to confirm our results for preparations other than iron dextran.

In summary, this study demonstrated no association between mortality and iron dosing patterns over time as practiced between 1996 and 1998 in the United States. A number of studies have recently demonstrated morbidity, mortality, and quality-of-life advantages to maintaining a hemoglobin level $\geq$11 g/dl in HD patients (37–43), and it is now widely appreciated that most patients require parenteral iron to achieve and maintain hemoglobin levels at or above this level (1,2). To our knowledge, no multicenter clinical trials are underway that have been designed *a priori* to compare the relative safety of different cumulative iron doses in HD patients. In the absence of such data, this study's findings provide cautious support for the safety of the judicious administration of cumulative doses of iron $>$1000 mg over 6 mo if needed to maintain target hemoglobin levels. Additional studies of the relationship between iron administration and patient outcomes are also needed to account for changing patterns of comorbidity and changing patterns of parenteral iron use, as well as to evaluate preparations of iron other than iron dextran.

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