Associations between Changes in Hemoglobin and Administered Erythropoiesis-Stimulating Agent and Survival in Hemodialysis Patients

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Although treating anemia of chronic kidney disease by erythropoiesis-stimulating agents (ESA) may improve survival, most studies have examined associations between baseline hemoglobin values and survival and ignored variations in clinical and laboratory measures over time. It is not clear whether longitudinal changes in hemoglobin or administered ESA have meaningful associations with survival after adjustment for time-varying confounders. With the use of time-dependent Cox regression models, longitudinal associations were examined between survival and quarterly (13-wk averaged) hemoglobin values and administered ESA dose in a 2-yr (July 2001 to June 2003) cohort of 58,058 maintenance hemodialysis patients from a large dialysis organization (DaVita) in the United States. After time-dependent and multivariate adjustment for case mix, quarterly varying administered intravenous iron and ESA doses, iron markers, and nutritional status, hemoglobin levels between 12 and 13 g/dl were associated with the greatest survival. Among prevalent patients, the lower range of the recommended Kidney Disease Quality Outcomes Initiative hemoglobin target (11 to 11.5 g/dl) was associated with a higher death risk compared with the 11.5- to 12-g/dl range. A decrease or increase in hemoglobin over time was associated with higher or lower death risk, respectively, independent of baseline hemoglobin. Administration of any dose of ESA was associated with better survival, whereas among those who received ESA, requiring higher doses were surrogates of higher death risk. In this observational study, greater survival was associated with a baseline hemoglobin between 12 and 13 g/dl, treatment with ESA, and rising hemoglobin. Falling hemoglobin and requiring higher ESA doses were associated with decreased survival. Randomized clinical trials are required to examine these associations.

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Anemia is associated with poor survival in individuals who have advanced chronic kidney disease (CKD; stage 5), also known as ESRD, and receive maintenance dialysis treatment (1–5). Treatment of anemia using erythropoiesis-stimulating agents (ESA) has been reported frequently to improve survival in patients with CKD (6–11). However, most studies have examined the association between a baseline blood hemoglobin value and subsequent survival ignoring the *changes* in hemoglobin concentrations and other covariates over time. Blood hemoglobin may change drastically over time. This may be caused by the changes in the dose of ESA or intravenous iron or other biologic factors such as inflammation and nutritional status. Because the medical treatment of patients with CKD is based on the periodic measurement of blood tests, including hemoglobin over time, with frequent adjustment of therapy such as the dose of ESA, examining outcomes on the basis of longitudinal measurement of hemoglobin and ESA dose, rather than just at one point in time, may provide important additional insights.

A *fall* in blood hemoglobin concentration may worsen death risk, whereas a *rise* in hemoglobin may be associated with improved survival in patients with CKD. However, no study has examined the associations between *changes* in hemoglobin over time and survival. Moreover, the independent association between the ESA administration or changes in ESA dose over time and survival remains to be determined. If such associations indeed exist, then it would be important to determine whether they are related to the changes in hemoglobin or ESA dose *per se* or to the confounding effects of nutritional status or inflammation. For examination of the independent associations between the entire range of blood hemoglobin or administered ESA and survival in the contemporary dialysis population, large and relatively rich databases of recent origin (21st century) are required with *repeated measures over time* so that the confounding effect of other variables and their changes over time can be controlled for adequately. Such extensive time-varying multivariate adjustments are particularly important

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when assessing the impact of variations in the dose of ESA, because ESA hyporesponsiveness may be due to malnutrition-inflammation complex syndrome (MICS) and its severity fluctuation over time (12,13). Hence, we examined models that are based on time-varying values of repeated measures of not only blood hemoglobin and administered ESA but also a large number of additional laboratory and clinical measures and their changes over time. We hypothesized that the survival advantages of increased blood hemoglobin or administered ESA will persist in statistical models even after adjustment for time variations of surrogates of MICS in a large number of maintenance hemodialysis (MHD) patients, whose laboratory values were measured repeatedly in one single laboratory in the 21st century. In particular, we examined whether blood hemoglobin values within the currently recommended target of 11 to 12 g/dl by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) (7–10,14,15) are associated with the greatest survival.

Materials and Methods

Patients

We examined prospectively collected data of a 2-yr (July 1, 2001, through June 30, 2003) historical cohort of all MHD patients in the national database of DaVita, Inc., the second largest dialysis care provider in the United States. Database creation has been described elsewhere (16–19). This database included information on approximately 40,000 maintenance dialysis patients at any given time. All repeated measures for each patient within a given quarter (13-wk interval) were averaged to obtain one *quarterly* mean value and to mitigate the effect of short-term variations. Hence, up to eight repeated and quarterly varying values were available for each measure in each MHD patient over a 2-yr observation period. The study was approved by the Institutional Review Committees of Harbor-UCLA and DaVita, Inc.

History of tobacco smoking and preexisting cardiovascular and noncardiovascular comorbid conditions were obtained by linking the DaVita database to the Medical Evidence Form 2728 of the United States Renal Data System (20) and categorized into 10 comorbid conditions: (*1*) ischemic heart disease, (*2*) congestive heart failure, (*3*) status after cardiac arrest, (*4*) status after myocardial infarction, (*5*) pericarditis, (*6*) cardiac dysrhythmia, (*7*) cerebrovascular events, (*8*) peripheral vascular disease, (*9*) chronic obstructive pulmonary disease, and (*10*) cancer.

Laboratory Methods

All laboratory measurements were performed by DaVita Laboratories in Deland, FL, using standardized and automated methods. For each laboratory measure, the average of all available values that were obtained within any given calendar quarter were used in all analyses. Twelve categories of blood hemoglobin (<9 g/dl, ≥14 g/dl, and 10 increments of 0.5 g/dl in between) were created to cover the entire range of hemoglobin.

The following 11 time-varying (quarterly changing) laboratory variables with up to eight repeated measures per patient during the 2-yr cohort time also were included in the models as potential confounders: (*1*) Serum iron saturation ratio (ISAT), also known as transferrin saturation ratio; (*2*) serum ferritin; (*3*) serum albumin; (*4*) normalized protein nitrogen appearance (nPNA) or normalized protein catabolic rate (nPCR); (*5*) serum total iron binding capacity; (*6*) serum creatinine; (*7*) serum phosphorus; (*8*) serum calcium; (*9*) serum bicarbonate; (*10*) peripheral white blood cell count; and (*11*) lymphocyte percentage. The first two measures are known markers of iron stores, and the last nine measures are related to MICS and have been associated in other studies with important outcomes in dialysis patients as described elsewhere (16–19).

Administered In-Center Medications

The doses of the medications that were administered in-center (in dialysis facility)and were related to the management of anemia also were included in all case mix–adjusted models as additional time-varying covariates. The dose of ESA was calculated in each calendar quarter in units/wk. The ESA responsiveness (resistance) index was defined as the average weekly ESA dose divided by average blood hemoglobin as described elsewhere (12,21) to normalize the amount of prescribed ESA for the severity of anemia. To examine the association between the administered ESA and survival in MHD patients, we created five groups of ESA dose/status: (*1*) No ESA during the entire 13 wk of a given quarter; (*2*) ESA between 1 and 6000 units/wk; (*3*) ESA between 6000 and 12,000 units/wk; (*4*) ESA between 12,000 and 18,000 units/wk; and (*5*) ESA of 18,000 units/wk or greater. The total amount of administered doses of intravenous iron (gluconate, sucrose, and dextran) and intravenous vitamin D analog (paricalcitol and calcitriol) were obtained during each calendar quarter for each MHD patient.

Statistical Analyses

For every time-varying measure, up to eight independent quarterly values were obtained for each patient. For each analysis, three types of models were examined on the basis of the level of multivariate adjustment: (*1*) Unadjusted models included blood hemoglobin as the predicting variable, entry quarter as the covariate, and all-cause or cardiovascular mortality as the outcome variable; (2) case mix–adjusted models included additional covariates of age; gender; race and ethnicity; diabetes; vintage; catheter as dialysis access; primary insurance; marriage status; standardized mortality ratio of the dialysis clinic during entry quarter; continuous values of Kt/V, serum ferritin, and ISAT; administered doses of each of the three intravenous iron medications, vitamin D analogs, and ESA within each calendar quarter; and comorbid states and smoking status at baseline; and (3) case mix– and MICS-adjusted models included all of the above-mentioned covariates plus 12 indicators of nutritional status and inflammation, including the time-varying body mass index and the 11 above-mentioned time-varying laboratory values as surrogates of MICS (see Laboratory Methods). All laboratory markers, intravenous iron, vitamin D analog and ESA doses, Kt/V, and body mass index were included as time-varying covariates with up to eight independent quarterly values per variable per patient. When ESA dose was modeled as the predicting variable, time-varying hemoglobin was included as a case-mix covariate. Longitudinal (in between) missing repeated measures were imputed by the mean of the values of the given variable for each patient over eight calendar quarters. Baseline missing covariate data (usually <2% for each given variable) were imputed by the mean or the median of the existing values, whichever was most appropriate. All descriptive and multivariate statistics were carried out with the SAS, version 9.1 (SAS Institute, Inc., Cary, NC). Because of the large sample size, most *P* values tend to be small.

Results

A total of 69,819 MHD patients were in the database during the 2-yr study interval. After exclusion of patients who did not remain beyond 3 mo of MHD (5600 patients from the first seven quarters and 5870 patients from the last quarter), 58,349 MHD patients remained, 58,058 of whom had the required data for

Table 1. Baseline (first calendar quarter) data of 58,058 MHD patients (July 2001 to June 2003), including 37,049 patients from the first quarter (q1) and 21,009 patients from subsequent quarters (q2 to q8)[a]

Variable	Received ESA during the Baseline Quarter (n = 53,972)	Did not Receive ESA during the Baseline Quarter (n = 4,086)
Age (yr)	61 ± 15	58 ± 16
Gender (% women)	47	40
Diabetes (%)	45	40
Race/ethnicity (%)		
white	36	48
blacks	33	23
Hispanic	18	15
Vintage (time on dialysis; %)		
3–6 mo	42	31
6–24 mo[b]	22	20
2–5 yr	24	32
≥5 yr	13	17
Patients with a catheter (*versus* AV shunt)	22	23
Primary insurance		
Medicare (%)[c]	60	60
Known causes of death		
cardiovascular (% of all-cause)	52	42
infectious (% of all-cause)[b]	11	9
Standardized mortality ratio[c]	0.80 ± 0.22	0.80 ± 0.22
Cohort time (d)	467 (268)	518 (205)
Body mass index (kg/m^2)	26.1 ± 6.1	26.5 ± 5.4
Kt/V (single pool)	1.5 ± 0.3	1.5 ± 0.3
nPCR or nPNA (g/kg per d)	1.0 ± 0.2	1.0 ± 0.2
Serum albumin (g/dl)[c]	3.75 ± 0.41	3.74 ± 0.42
creatinine (mg/dl)	9.0 ± 3.3	9.5 ± 3.6
TIBC (mg/dl)	201 ± 42	210 ± 44
ferritin (ng/ml)	508 (305)	445 (284)
iron (ng/ml)	61 ± 26	64 ± 30
iron saturation ratio (%)[c]	30 ± 12	30 ± 13
bicarbonate (mEq/L)	21.8 ± 2.8	22.1 ± 3.0
phosphorus (mg/dl)[b]	5.7 ± 1.5	5.7 ± 1.6
calcium (mg/dl)[c]	9.2 ± 0.7	9.2 ± 0.8
intact PTH (pg/ml)[c]	223 (135)	229 (150)
Blood hemoglobin (g/dl)	12.0 ± 1.3	12.3 ± 1.5
WBC (×10^3/μl)	7.3 ± 2.3	7.5 ± 2.5
lymphocyte (% of total WBC count)	21 ± 8	20 ± 7
Proportion received intravenous iron	71	12

[a]Count data are in percentage, and continuous values are in mean ± SD if normally distributed or median (interquartile range) if skewed. $P < 0.001$ for the difference between the two groups, unless otherwise specified. AV, arteriovenous; ESA, erythropoiesis-stimulating agent; PTH, parathyroid hormone; TIBC, total iron binding capacity; WBC, white blood cell.
[b]$0.05 > P > 0.001$.
[c]$P > 0.05$.

the planned analyses. The latter group included 37,049 (64%) patients from the first quarter data set (q1) and the rest from the subsequent quarters (q2 through q8). Table 1 shows baseline demographic, clinical, and laboratory characteristics of the cohort according to ESA administration status. The inclusion of all new MHD patients who joined DaVita during the 2 yr of observation led to a larger-than-usual proportion of incident patients with a vintage <6 mo. Approximately 7% of the patients did not receive ESA during the first quarter. Similar proportions were observed in subsequent calendar quarters (data not shown). Patients who did not receive ESA were 3 yr younger and included more men and white individuals and fewer patients with diabetes.

Table 2 shows correlation coefficients of blood hemoglobin and administered ESA dose (both the total ESA dose per individual and ESA dose per kilogram of body weight) with relevant clinical and laboratory measures at baseline. A higher serum albumin concentration was associated with higher blood hemoglobin and lower administered ESA dose. Patients with a higher hemoglobin concentration required lower doses of ESA. Moreover, MHD patients with higher ISAT values required less ESA, but the latter association was relatively weak.

Table 3 and Figure 1 show the time-varying (calendar quarter) associations between the entire range of blood hemoglobin and 2-yr survival in the form of relative risk for all-cause and

Table 2. Bivariate (unadjusted) and multivariate correlation coefficients between ESA, hemoglobin, and some relevant variables at baseline in 58,058 MHD patients[a]

	Hemoglobin	ESA	ESA/Weight
Age	0.04[b]	−0.05	−0.04[b]
Gender	−0.06	0.02	**0.11**
Diabetes	0.02[c]	−0.01[c]	−0.07
Race (black)	−0.06	0.07	0.07
Kt/V	−0.03[c]	**−0.11**	−0.04
BMI	−0.00[c]	0.05	**−0.18**
Serum albumin	**0.25**	−0.16	**−0.28**
TIBC	**0.16**	−0.03[b]	**−0.15**
Ferritin	**−0.12**	−0.02[c]	0.02[c]
ISAT	0.09	**−0.15**	**−0.16**
Phosphorous	0.05	0.04[b]	0.00[c]
Calcium	**0.12**	−0.08	**−0.13**
Bicarbonate	−0.09	−0.01[c]	0.02[c]
Creatinine	0.01[c]	−0.01[c]	−0.09
Blood hemoglobin	NA	**−0.24**	**−0.33**
WBC	−0.02[c]	−0.01[c]	0.01[c]
Lymphocyte %	0.09	**−0.11**	**−0.14**
Intravenous iron (composite)	0.01[c]	0.06	0.07

[a]$P < 0.001$, unless otherwise specified. BMI, body mass index; ISAT, iron saturation ration; NA, not applicable.
[b]$0.05 > P > 0.01$.
[c]$P > 0.05$.

Table 3. Hazard ratio of death for hemoglobin categories based on time-dependent Cox regression models[a]

	Unadjusted		Case Mix–Adjusted		Case Mix– and MICS-Adjusted	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause death hemoglobin range (g/dl)						
<9.0	4.89 (4.48 to 5.34)	<0.001	3.08 (2.81 to 3.37)	<0.001	1.81 (1.65 to 1.99)	<0.001
9.0 to <9.5	3.58 (3.23 to 3.95)	<0.001	2.46 (2.22 to 2.73)	<0.001	1.58 (1.43 to 1.76)	<0.001
9.5 to <10	3.08 (2.82 to 3.36)	<0.001	2.19 (2.00 to 2.39)	<0.001	1.50 (1.37 to 1.64)	<0.001
10.0 to <10.5	2.64 (2.45 to 2.86)	<0.001	2.05 (1.89 to 2.21)	<0.001	1.48 (1.37 to 1.61)	<0.001
10.5 to <11	2.01 (1.88 to 2.16)	<0.001	1.67 (1.56 to 1.80)	<0.001	1.34 (1.25 to 1.44)	<0.001
11.0 to <11.5	1.35 (1.26 to 1.45)	<0.001	1.22 (1.14 to 1.31)	<0.001	1.12 (1.05 to 1.20)	0.001
11.5 to <12	1	NA	1	NA	1	NA
12.0 to <12.5	0.87 (0.81 to 0.93)	<0.001	0.91 (0.85 to 0.97)	0.004	0.94 (0.88 to 1.01)	0.07
12.5 to <13	0.86 (0.80 to 0.92)	<0.001	0.90 (0.83 to 0.96)	0.002	0.92 (0.85 to 0.98)	0.02
13.0 to <13.5	0.97 (0.89 to 1.05)	0.4	1.00 (0.92 to 1.08)	0.9	1.04 (0.96 to 1.13)	0.4
13.5 to <14	1.17 (1.06 to 1.29)	0.002	1.21 (1.10 to 1.33)	<0.001	1.24 (1.12 to 1.37)	<0.001
≥14.0	1.25 (1.13 to 1.38)	<0.001	1.15 (1.04 to 1.28)	0.006	1.17 (1.06 to 1.30)	0.002
CV death hemoglobin range (g/dl)						
<9.0	3.83 (3.30 to 4.44)	<0.001	2.49 (2.14 to 2.90)	<0.001	1.66 (1.41 to 1.94)	<0.001
9.0 to <9.5	3.39 (2.90 to 3.97)	<0.001	2.43 (2.07 to 2.85)	<0.001	1.71 (1.45 to 2.01)	<0.001
9.5 to <10	2.66 (2.31 to 3.06)	<0.001	1.91 (1.66 to 2.20)	<0.001	1.42 (1.23 to 1.63)	<0.001
10.0 to <10.5	2.51 (2.23 to 2.83)	<0.001	2.00 (1.77 to 2.25)	<0.001	1.54 (1.36 to 1.74)	<0.001
10.5 to <11	1.88 (1.69 to 2.09)	<0.001	1.60 (1.43 to 1.78)	<0.001	1.33 (1.19 to 1.49)	<0.001
11.0 to <11.5	1.43 (1.29 to 1.58)	<0.001	1.29 (1.17 to 1.43)	<0.001	1.21 (1.09 to 1.34)	<0.001
11.5 to <12	1	NA	1	NA	1	NA
12.0 to <12.5	0.90 (0.81 to 1.00)	0.04	0.94 (0.85 to 1.04)	0.25	0.96 (0.87 to 1.06)	0.4
12.5 to <13	0.93 (0.84 to 1.03)	0.17	0.96 (0.87 to 1.07)	0.5	0.96 (0.87 to 1.07)	0.5
13.0 to <13.5	1.04 (0.92 to 1.17)	0.5	1.06 (0.94 to 1.20)	0.3	1.08 (0.96 to 1.21)	0.22
13.5 to <14	1.18 (1.02 to 1.36)	0.03	1.22 (1.05 to 1.41)	0.009	1.21 (1.04 to 1.40)	0.01
≥14.0	1.23 (1.06 to 1.43)	0.006	1.15 (0.99 to 1.34)	0.07	1.14 (0.97 to 1.33)	0.11

[a]CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MICS, malnutrition-inflammation complex syndrome.

cardiovascular mortality. The hemoglobin range of 11.5 to 12 g/dl was selected as the reference group. The hemoglobin range between 12.0 and 13.0 g/dl was associated with lowest death risk, whereas the hemoglobin range of 11.0 to 11.5 g/dl, which is the lowest range of the recommended K/DOQI guidelines target (14), was associated with significantly higher death rate. Hemoglobin levels >13.5 g/dl also were associated with higher death risk but not significantly different from the death risk associated with hemoglobin in the range of 11 to 11.5 g/dl. Figure 2 shows the above-mentioned associations separately in incident (vintage <6 mo) and prevalent (vintage ≥6 mo) patients. In prevalent MHD patients, hemoglobin of 11 to 11.5 g/dl was associated with a higher death risk compared with the 11.5- to 12-g/dl range.

To examine whether a *change* in hemoglobin level over time is associated with survival independent of the baseline hemoglobin concentration or other clinical and laboratory values, we calculated the change in blood hemoglobin during the first 6 mo of the cohort in all 26,668 MHD patients of the first quarter who remained in the cohort for at least one more consecutive calendar quarter (Table 4). Patients whose blood hemoglobin did not increase or decreased beyond 0.8 g/dl were considered the stable (reference) group. This range was chosen so that approximately half (53%) of all patients can be categorized as having stable (unchanged) hemoglobin. Hemoglobin values above or below this range were subdivided further into three increments. Patients whose hemoglobin *dropped* over time, especially those with a drop of 2.0 g/dl or greater in 6 mo, had higher unadjusted death rates. However, no improved survival was evident in patients whose hemoglobin increased over time, which could be related to their lower baseline hemoglobin and serum albumin levels. To examine the independent effect of the change in hemoglobin after controlling for the baseline hemoglobin concentration and other covariates, we examined Cox regression models for categories of change in hemoglobin. Figure 3 illustrates the estimated hazard ratios of death for changes in hemoglobin during the first 6 mo of the cohort. In particular, the adjusted all-cause mortality risk in the subsequent 18 mo decreased linearly as patients' hemoglobin increased progressively in the first 6 mo. Therefore, a dose-response phenomenon was observed consistently for both rising and dropping hemoglobin during the 6-mo period.

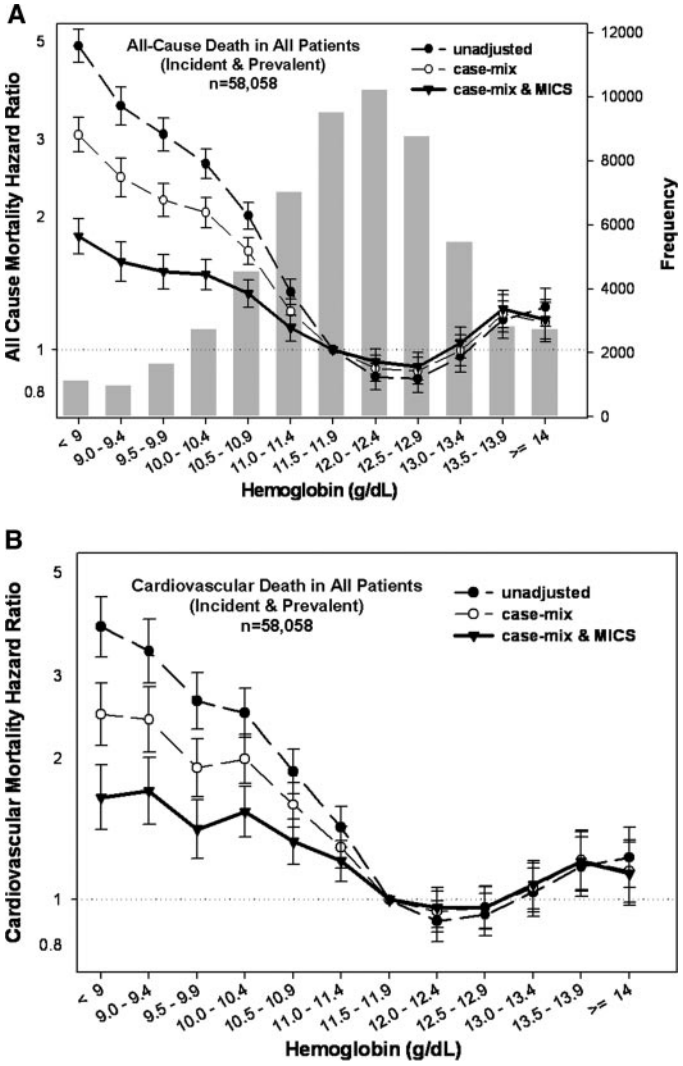

Figure 1. Association between the time-varying blood hemoglobin values and the relative risk for all-cause (top) and cardiovascular (CV; bottom) death in 58,058 maintenance hemodialysis (MHD) patients during a 2-yr interval (July 2001 to June 2003).

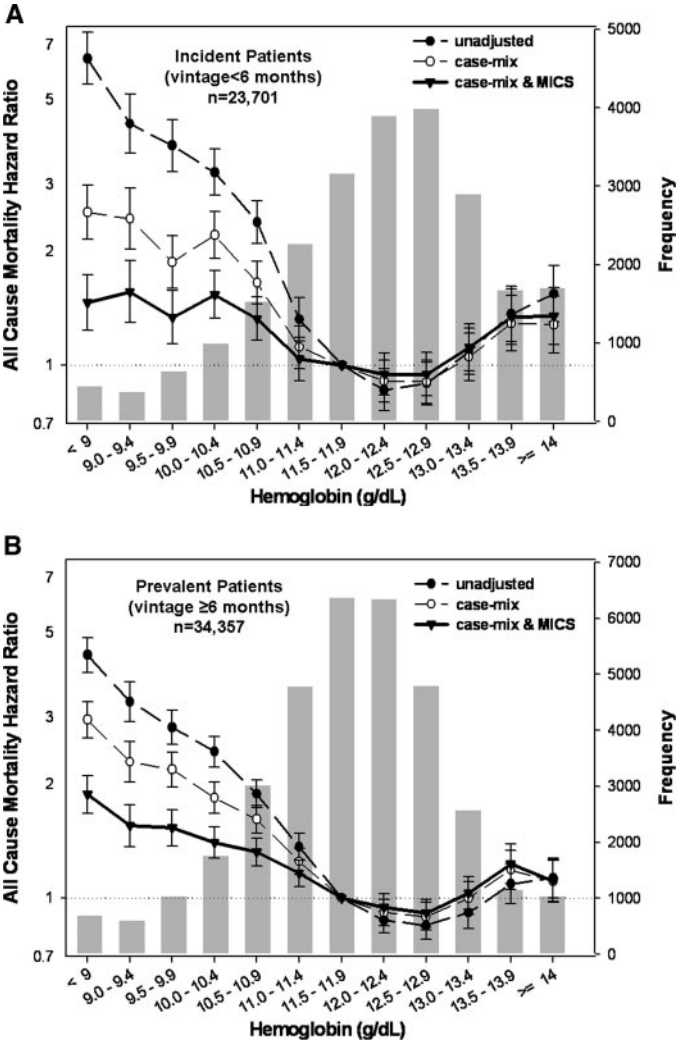

Figure 2. Comparing "incident" (vintage <6 mo, $n = 23{,}701$; top) and "prevalent" (vintage ≥6 mo, $n = 34{,}357$; bottom) MHD patients with regard to the association between the time-varying blood hemoglobin values and the relative risk for all-cause death during a 2-yr interval (July 2001 to June 2003).

Table 5 shows the entire range of the administered ESA dose in the studied MHD patients. Baseline hemoglobin and serum albumin concentrations are lower in those who received the highest ESA doses. When time-dependent Cox models were examined (Figure 4), survival was significantly improved among MHD patients who had received ESA. However, among patients who received ESA, those who required higher doses had progressively worse survival or higher cardiovascular mortality. To examine whether these associations were maintained for different ranges of hemoglobin, we repeated the same analyses for patients with baseline hemoglobin values <12 and >12 g/dl (Figure 5). In addition to modeling the ESA categories, we conducted survival analyses for the continuous values of ESA within the entire hemoglobin range. A death hazard ratio of 1.02 (95% confidence interval 1.01 to 1.03; $P < 0.001$) for each 10,000-units/wk increase in the required ESA dose was observed. Similar associations were also observed for the logarithmic and quadratic models of the continuous ESA dose (data not shown). All categorical and continuous analyses also were repeated using ESA dose divided by hemoglobin as a potential index of ESA hyporesponsiveness (12), and similar associations were observed (data not shown).

To examine the association between the administration of ESA (yes/no) and 2-yr survival observed in all demographic and laboratory subgroups of MHD patients and to explore potential interactions, we performed subgroup analyses using time-varying Cox models (Figure 6). The survival advantage associated with ESA administration seemed to be relatively universal and was independent of race, gender, age, serum albumin, protein intake, blood hemoglobin level, and iron store markers. The only exceptions were Asian MHD patients and those with an ISAT ≥50%, but the 95% confidence interval for these groups did not remain entirely on one side of the relative risk for death plot (Figure 5).

Table 4. Change in blood hemoglobin in first 6 mo and 2-yr mortality census (rate) among 26,668 MHD patients of the first quarter who had at least one additional averaged hemoglobin value during the subsequent quarter of the cohort[a]

Hemoglobin Change (g/dl in 6 mo)	Sample Size (%)	All-Cause Death (%)[b]	CV Death (%)[b]	Baseline Hemoglobin	Baseline Albumin
Dropped					
≤−2.0	1,691 (6)	557 (33)	239 (15)	13.2 ± 1.1	3.83 ± 0.36
−1.99 to −1.5	1,562 (5)	475 (30)	208 (14)	12.7 ± 1.0	3.84 ± 0.36
−1.49 to −0.8	4,033 (13)	1,087 (27)	461 (12)	12.5 ± 1.0	3.86 ± 0.34
Stable					
−0.79 to 0.79	16,130 (53)	4,225 (26)	1,877 (12)	12.0 ± 1.0	3.85 ± 0.33
Increased					
0.8 to 1.49	3,800 (12)	1,102 (29)	502 (14)	11.4 ± 0.9	3.79 ± 0.35
1.5 to 1.99	1,581 (5)	443 (28)	193 (13)	11.0 ± 1.0	3.74 ± 0.38
≥2.0	1,904 (6)	523 (27)	235 (13)	10.5 ± 1.1	3.68 ± 0.38

[a]Both ANOVA and trend *P* values for mortality rates are <0.001.
[b]The death rates in brackets pertain to the percentage of patients who died during a 2-yr interval in the given category. The denominator for all-cause mortality is the total sample of MHD patients with known hemoglobin change, whereas the denominator of CV death is slightly smaller as a result of missing documentation of causes of death. Death rates and baseline hemoglobin and albumin values are significantly different from each other across the categories (ANOVA $P < 0.001$).

Discussion

In a 2-yr cohort of 58,058 MHD patients across the United States with prospectively collected repeated measures of laboratory values and medication doses, all from the 21st century, we found that after extensive time-dependent and multivariate adjustment for case mix, intravenously injected iron and ESA doses and surrogates of iron stores, nutritional status, and inflammation, a hemoglobin level between 12 and 13 g/dl was consistently associated with the lowest all-cause and cardiovascular death risks during any given calendar quarter. Among prevalent MHD patients, the lower range of the recommended K/DOQI hemoglobin target (11 to 11.5 g/dl) was associated with a higher death risk compared with the 11.5- to 12-g/dl range. Moreover, a *rise* in hemoglobin over time was associated with a better survival independent of the baseline hemoglobin level, whereas a *fall* in hemoglobin conferred increased death risk; both of these associations displayed a dose-response phenomenon in that a higher magnitude of rise or fall in hemoglobin was associated with a greater or lower chance of survival, respectively. We also found that MHD patients who required higher doses of ESA to maintain given hemoglobin had a higher risk for death. However, compared with those who received ESA, patients who were not administered any ESA had a worse survival. The survival advantages of ESA were relatively consistent in a wide array of racial, gender, vintage, and laboratory subgroups and across different ranges of hemoglobin and iron markers.

Anemia is a frequent complication of CKD, and its prevalence increases with diminishing renal function (5,14,22). Amelioration of anemia by ESA results in improved quality of life in patients with CKD (9,23) and may confer protection against cardiovascular disease (24,25). Significant associations between baseline hemoglobin levels and survival in patients with CKD have been shown in previous studies (5,11,26,27). However, these studies examined the effect of one single baseline hemoglobin or hematocrit level or cluster at the start of the study and did not address the variation in hemoglobin over time. Moreover, most of these studies examined old cohorts of dialysis patients before the contemporary era of dialysis technique and dose and more universal use of intravenous iron and vitamin D analogs, which *per se* may be associated with improved survival (16,28). Strippoli *et al.* (4) reviewed 15 randomized, controlled trials, including the study by Besarab *et al.* (29), which targeted a hemoglobin concentration of 13 g/dl or higher. The clinical trial by Besarab *et al.* was terminated prematurely because of safety concerns. Therefore, a positive outcome for higher hemoglobin target, which was the *a priori* study end point, was not possible. The Strippoli review (4) concluded that the clinical benefits of increasing hemoglobin above 10 or 11 g/dl did not outweigh the risks, including hypertension, dialysis shunt thrombosis, and mortality. However, McMahon *et al.* (30,31) showed that achieving hemoglobin levels >11 g/dl reduced an elevated cardiac output, whereas the study by Foley *et al.* (8) found no improvement in left ventricular mass or dilation.

The K/DOQI guidelines (14) and the European Best Practice Guidelines (15) have recommended a hemoglobin target of 11 to 12 g/dl and >11 g/dl, respectively. In the United States, increasing hemoglobin concentrations above 12 g/dl (or hematocrit above 36%) is not yet recommended by K/DOQI guidelines, even though the clinical trial by Besarab *et al.* (29) concluded that administration of ESA to raise hematocrit to 42% might be associated with adverse outcomes but not lower than that. In our study, the death risk associated with a hemoglobin level of 11 to 11.5 g/dl (the lower range of the K/DOQI recommended target) was higher than the 11.5- to 12-g/dl range at least among prevalent MHD patients, a finding that may have clinical implications in treating anemia in these individuals if confirmed by other studies. We also found that hemoglobin

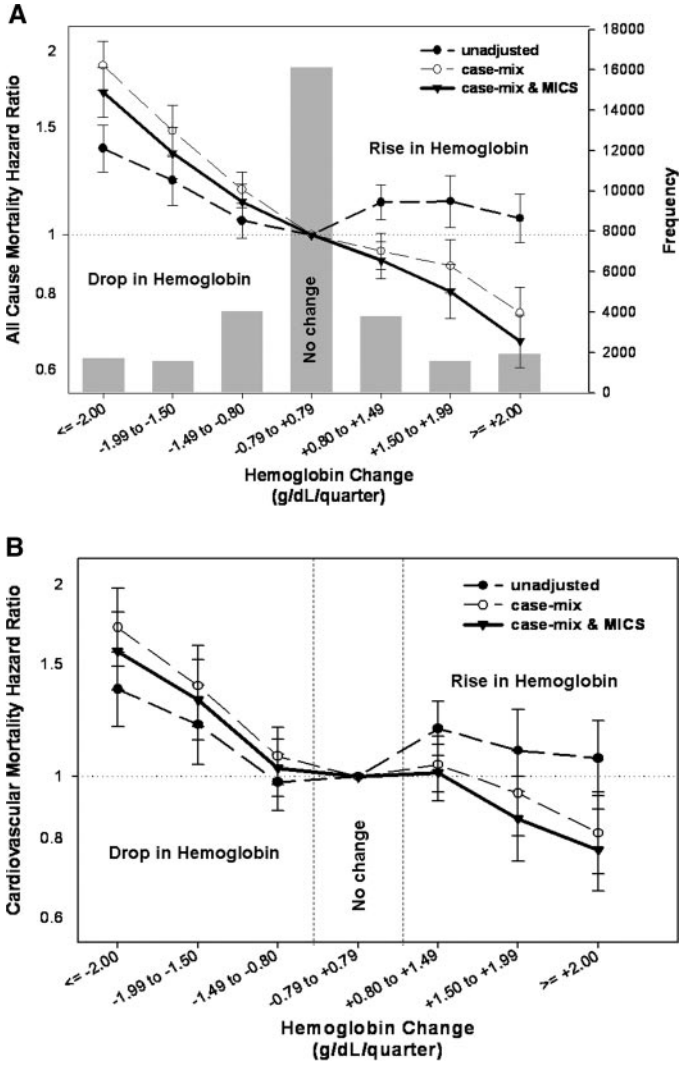

Figure 3. Association between the changes in blood hemoglobin during the first 6 mo of the cohort (July to December 2001) and the subsequent 18-mo (January 2002 to June 2003) risk for all-cause (top) and CV (bottom) death in 26,668 MHD patients. See also Table 3.

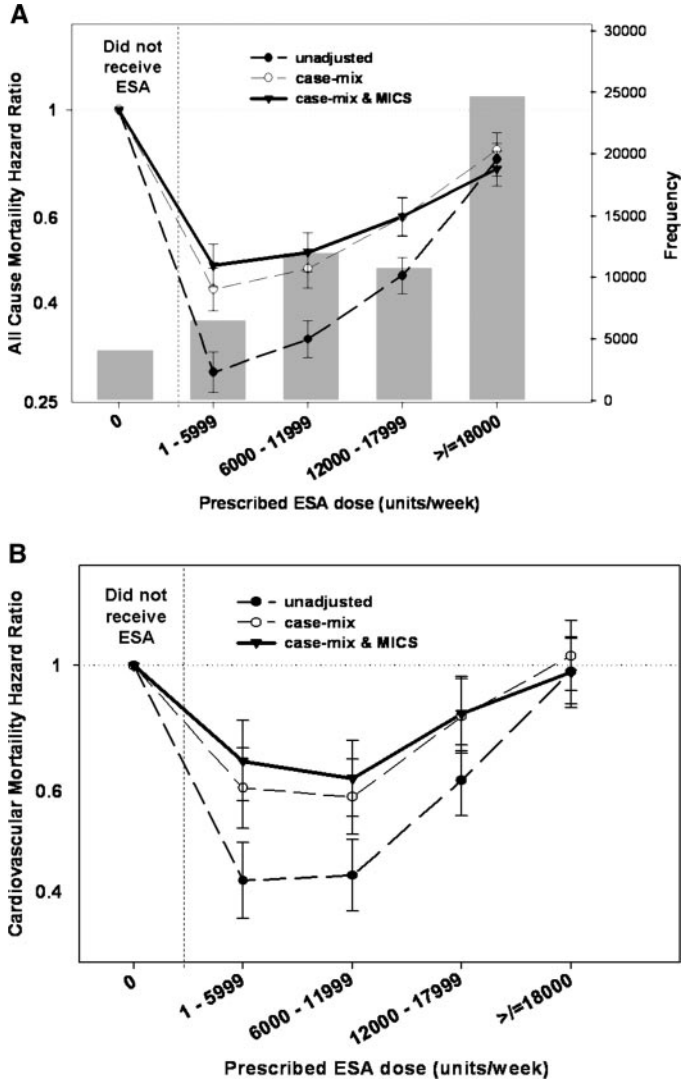

Figure 4. Association between the time-varying administered dose of erythropoiesis-Stimulating Agent (ESA) in each calendar quarter and the relative risk for all-cause (top) and CV (bottom) death in 58,058 MHD patients during a 2-yr interval (July 2001 to June 2003). See also Table 5.

levels between 12 and 13 g/dl were associated to greatest survival, whereas hemoglobin values >13.5 g/dl were associated with a trend toward increased death risk similar to that seen in the lower range of the K/DOQI hemoglobin level of 11.0 to 11.5 g/dl.

Since the introduction of ESA more than two decades ago, CKD-associated anemia has been managed successfully by this compound (11,22). Because treatment of anemia is associated with improved survival and quality of life, it is expected that patients whose hemoglobin rises over time have better survival, whereas those with a hemoglobin drop have a higher death risk. This study, for the first time to our knowledge, is consistent with this biologically plausible hypothesis (Figure 3). It is important, however, to appreciate that examining associations between a prescribed medication and outcome is amenable to bias by indication (32); such treatments usually are the result of sophisticated processes of active decision-making by well-trained and specialized physicians. Many nephrologists may practice according to the K/DOQI or other guidelines. However, we found that MHD patients who did not receive ESA did not have a substantially higher hemoglobin level (see Table 1), which poses questions about what drives the nephrologist's decision when prescribing ESA. Although use of such novel epidemiologic tools as marginal structural modeling may mitigate the degree of bias by indication (28), such models were not examined in our study. Therefore, the associations found should not be interpreted as causal relationships between the administered ESA and improved survival.

In many patients with CKD, anemia seems to be resistant to ESA treatment despite adequate iron supplementation and exclusion of other causes of refractory anemia, such as iron deficiency or hyperparathyroidism (22,33). Some recent studies

Table 5. Selected categories of administered ESA and 2-yr mortality census (rate) among 58,058 MHD patients

ESA (units/wk)	Sample Size (%)	All-Cause Death (%)[a]	CV Death (%)[a]	Baseline Hemoglobin	Baseline Albumin
No ESA (reference)	4,086 (7)	883 (22)	315 (8)	12.3 ± 1.5	3.74 ± 0.41
1 to 6,000	6,539 (11)	1,335 (20)	640 (10)	12.4 ± 0.9	3.89 ± 0.32
6,000 to 12,000	12,003 (21)	2,523 (21)	1,097 (9)	12.2 ± 1.0	3.84 ± 0.34
12,000 to 18,000	10,751 (19)	2,533 (24)	1,122 (11)	12.1 ± 1.1	3.79 ± 0.38
≥18,000	24,672 (43)	7,258 (29)	3,069 (13)	11.6 ± 1.4	3.64 ± 0.45

[a]The death rates in parentheses pertain to the percentage of patients who died during a 2-yr interval in the given category. Death rates and baseline hemoglobin and albumin values are significantly different from each other across the categories (ANOVA $P < 0.001$).

indicated that resistance to ESA is associated with a higher death risk factor (34,35). Consistent with the foregoing notions, our study also showed that a need for higher doses of ESA to maintain the target hemoglobin level, *i.e.*, the calculated ESA resistance index, was associated with incrementally higher death risks (Figures 4 and 5). A significant association has been demonstrated between ESA hyporesponsiveness and high levels of inflammatory markers in MHD patients (21,36–41). To that end, anti-inflammatory interventions may improve ESA resistance and outcome (39,42). Anemia frequently occurs in patients who have chronic inflammatory disorders even with normal kidney function (43). Inflammation seems to be much more common in dialysis patients than in the general population. Several mechanisms for cytokine-induced anemia have been proposed, including impaired iron metabolism and suppression of bone marrow erythropoiesis and ESA production (44,45). Therefore, studies that have shown the association between ESA dose and higher mortality in MHD patients have led to some confusion among physicians, because such studies might have inferred that ESA administration may lead to higher death rate, whereas there is an abundant basic science literature indicating the potential benefits of ESA, which can be interpreted to portend a potential survival advantage. Our study is the first to reconcile these conflicting results and hypotheses, because we have shown that the administration of ESA, irrespective of its dose, is associated with better survival in all subgroups of MHD patients, whereas among those who receive ESA, those who need incrementally higher doses to maintain hemoglobin at a given target level are at higher death risk.

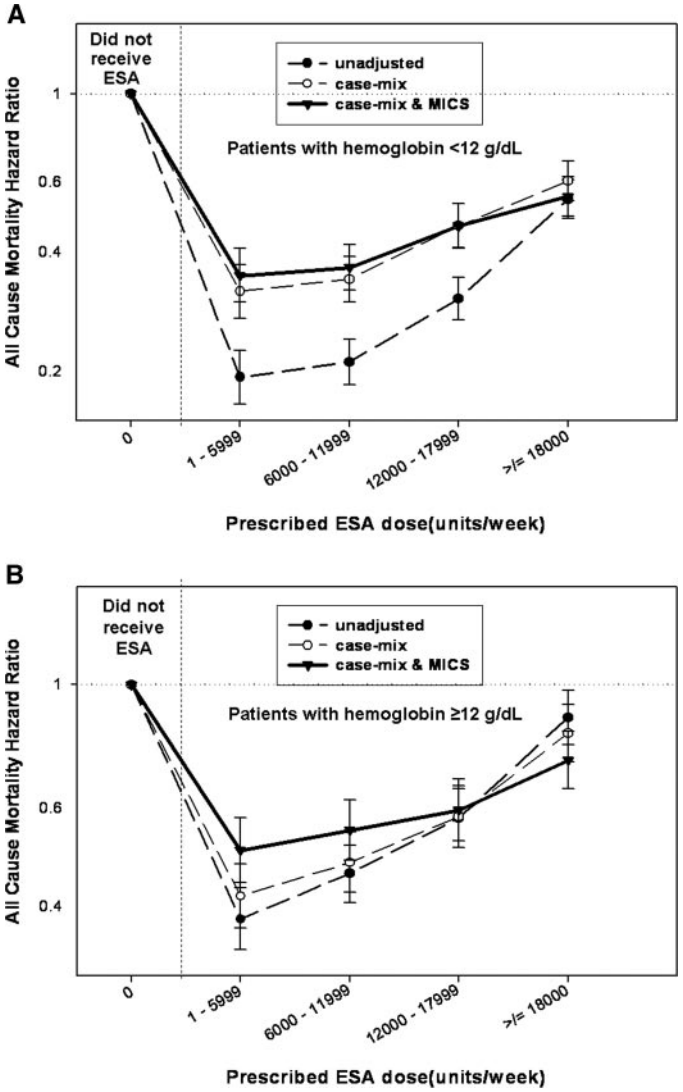

Figure 5. Association between the time-varying administered dose of ESA in each calendar quarter and the relative risk for all-cause mortality among patients with hemoglobin <12 g/dl (top) and those with hemoglobin ≥12 g/dl (bottom).

A limitation of our study is lack of explicit laboratory markers of inflammation such as C-reactive protein. However, we did use data on serum albumin, ferritin, and total iron binding capacity and white blood cells, which may have association with inflammation. Furthermore, we used 3-mo (13-wk) averaged measures rather than one single measure at baseline. We did not evaluate the predialysis era anemia management, which may have a bearing on anemia and outcome during the dialysis treatment era (46). However, our separate analyses of prevalent MHD patients indicted similar trends as in incident patients. In our study, the type of the dialysis access used as a covariate was based only on the presence or absence of the dialysis catheter at the start of each calendar quarter, and no information pertaining to the old or clotted arteriovenous graft was included, which could lead to ESA resistance (47,48). How-

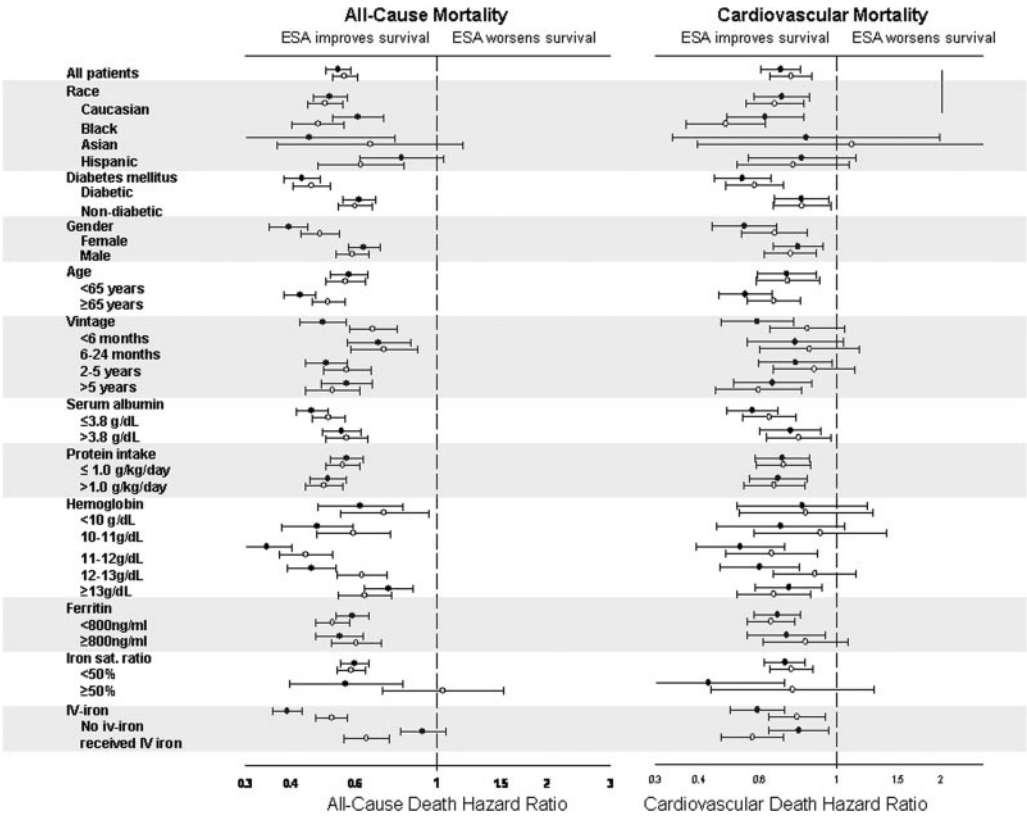

Figure 6. Examining the association between the administered ESA status and the relative risk for all-cause (left) and CV (right) death in different demographic, clinica, and laboratory subgroups of 58,058 MHD patients during a 2-yr interval (July 2001 to June 2003). ●, unadjusted death hazard ratios; ○, fully multivariate (case mix and malnutrition-inflammation complex syndrome) adjusted death hazard ratios.

ever, we controlled for the dialysis catheter status in case-mix models.

Another limitation of our study is the possible inclusion of patients with gastrointestinal bleeding, other sources of blood loss, or malignancies, which may lead to refractory anemia and poor outcome. Moreover, we did not have information on the routes of injection (intravenous *versus* subcutaneous), and MHD patients with intercurrent infections or systemic inflammatory diseases, in whom inflammation induced ESA hyporesponsiveness may be present, were not excluded. However, these cases are not frequent enough to cause major confounding, especially because the entire national database was examined and because the laboratory values were 13-wk averaged values. Finally, our study was limited to 2 yr of observation. However, MHD patients have an exceptionally high short-term mortality, which can be examined using short-period cohorts.

Strengths of our study include the following: (*1*) Study patient population was not limited to Medicare patients but all patients regardless of the type of insurance; (*2*) the full range of demographic, laboratory, and formulary information was available and studied in the form of repeated measures of longitudinal data using time-dependent models; and (*3*) a contemporary cohort of MHD patients in the 21st century was studied. Despite these advantages, it is important to appreciate that the observational nature of our study prompts caution in interpreting and generalizing our findings. Additional observational studies using other large databases or interventional studies, including randomized clinical trials, need to confirm our findings.

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