Kidney International, Vol. 63 (2003), pp. 1908–1914

The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients

NORMA OFSTHUN, JOHN LABRECQUE, EDUARDO LACSON, MARCIA KEEN, and J. MICHAEL LAZARUS

Fresenius Medical Care—North America, Lexington, Massachusetts; and Amgen, Inc., Thousand Oaks, California

The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients.

Background. The introduction of recombinant human erythropoietin for the treatment of anemia of chronic renal failure provided the opportunity to correct anemia in this patient population. The optimal target hemoglobin for patients with end-stage renal disease (ESRD) remains controversial. A large database of hemodialysis patients was analyzed to determine whether increasing hemoglobin level above the current Kidney Dialysis Outcomes Quality Initiative (K/DOQI) recommendations was associated with increased risk of mortality and hospitalization.

Methods. A longitudinal study of hemodialysis patients in Fresenius Medical Care–North America facilities was performed. Selection was restricted to patients in the census for 6 consecutive months from July 1, 1998 through June 30, 2000. Patient mean hemoglobin and other covariates measured during the initial 6 months were related to survival, number of hospitalizations, and length of stay over the subsequent 6 months of follow-up.

Results. Patients with hemoglobin <9 g/dL had an adjusted relative risk of death of 2.11 compared to those patients with 11 ≤ hemoglobin < 12 g/dL ($P < 0.0001$). The adjusted relative risk of death was 0.84 for 12 ≤ hemoglobin < 13 g/dL ($P = 0.007$). These data suggest there is no increased risk of mortality associated with hemoglobin above the current recommended values. Both number of hospitalizations and length of stay decreased as hemoglobin increased. Patients with hemoglobin ≥13 g/dL had an adjusted length of stay of 9.6 days compared to 10.9 days for those with 11 ≤ hemoglobin < 12 g/dL ($P < 0.0001$).

Conclusion. These data indicate the relative risk of death and hospitalization are inversely associated with hemoglobin levels, with no apparent additional risk associated with hemoglobin levels > 12 g/dL.

The anemia of chronic renal failure is primarily due to a deficiency of endogenous erythropoietin. The introduction of recombinant human erythropoietin (rHuEPO) in 1989 to treat the anemia of chronic renal failure marked a major milestone in nephrology clinical practice [1]. Several studies have shown that treatment of anemia with rHuEPO leads to overall improvements in quality of life, increased exercise capacity, decreased sleep disturbances, and improved cognitive function in end-stage renal disease (ESRD) patients [2–8]. Anemia is considered to be one of the important risk factors in the development of left ventricular hypertrophy (LVH), a major contributor to cardiac mortality and morbidity in ESRD patients [9]. The use of rHuEPO to raise hemoglobin levels in ESRD patients leads to partial regression of LVH, and improvement in other cardiovascular conditions that accompany chronic renal failure [2, 9–11].

While these benefits of anemia treatment have been well established, the optimal target hemoglobin for ESRD patients has remained controversial. The publication of the National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-DOQI); now known as Kidney Disease Outcomes Quality Initiative or K/DOQI Clinical Practice Guidelines for Anemia of Chronic Renal Failure recommended a target hemoglobin of 11 g/dL to 12 g/dL (corresponding to a hematocrit of 33% to 36%), based on the available evidence [1, 12]. In hormone deficiency states, generally the treatment goal is to correct the deficiency, if possible; partial correction of the hormone deficiency is rarely a treatment goal. Thus, greater patient benefit may be obtained by normalization of hemoglobin levels (i.e., achieving values >12 g/dL for women and >13 g/dL for men) [13, 14].

A study of prevalent Medicare ESRD patients receiving rHuEPO showed a statistically significant ($P < 0.001$) higher risk of all-cause mortality when hematocrit was <33% (hemoglobin <11 g/dL) compared to the reference value of 33% to 36% [15]. The number of patients with hematocrit >36% was small ($N = 685$), thereby reducing the ability to detect if there was any survival benefit to patients with hematocrit >36% (hemoglobin >12 g/dL). Additional analyses of the same Medicare database showed a statistically significant ($P = 0.0001$) reduction in the risk of hospitalization when hematocrit

Key words: hemoglobin, mortality, hospitalization, anemia, erythropoietin, hemodialysis.

Received for publication September 12, 2002
and in revised form November 27, 2002
Accepted for publication January 3, 2003

was 33% to 36%, compared to hematocrit <33% [16]. In 2001, using an incident ESRD patient cohort, Collins et al [17] reported further reduction in the relative risk of mortality and hospitalization in those patients with hematocrit 36% to <39% compared to the reference value of 33% to <36%. However, the difference for mortality was not statistically significant between the reference group and the categories of 36% to <39% and ≥39%. In contrast, the relative risk of hospitalization in patients with hematocrit of 36% to <39% and ≥39% was significantly lower compared to the reference group. However, a randomized controlled clinical trial in a high-risk group of hemodialysis patients with significant cardiac disease suggested that targeting hemoglobin to normal levels did not confer benefit (intent-to-treat analysis) [18]. The recommendation from the trial was that hemodialysis patients with clinically evident heart disease should not have hematocrit raised to a normal value (42% or hemoglobin 14 g/dL). Therefore, further examination of hemoglobin concentrations in a large group of ESRD patients might be useful in evaluating the relative risk of adverse outcomes, such as mortality and hospitalizations with higher hemoglobin levels.

Fresenius Medical Care North America (FMCNA) is a dialysis provider that treated approximately 125,000 ESRD patients in more than 900 facilities in the United States during the period July 1998 to June 2000. FMCNA maintains an extensive database of demographic, treatment, and laboratory data on all patients. The purpose of this study was to analyze this database to evaluate the association of hemoglobin level with mortality, incidence of hospitalization, and length of hospital stay in ESRD patients.

METHODS

This was a retrospective, longitudinal study of ESRD patients in the FMCNA database. The selection for analysis was restricted to patients who were in the census for at least 6 consecutive months (baseline) during the period July 1, 1998 through June 30, 2000. Data were available for patient age, gender, race, presence of diabetes (yes, no), time on dialysis (vintage), height and weight from which body mass index (BMI) was calculated, and missed treatments (more than one electively missed treatment in a 6-month period). Selected laboratory variables also were analyzed, including hemoglobin, albumin, transferrin saturation, and urea reduction ratio (URR, %). Data were not available on prevalence or severity of comorbid conditions in the population or iron administered during the baseline or follow-up period.

The covariates used in the analyses were hemoglobin, age, race, gender, and diabetes status, BMI, albumin, missed treatments, and URR. Laboratory variables were based on averaging the baseline (i.e., first 6 months) data for each patient. The addition of hemoglobin^2 (a quadratic model in hemoglobin) as an independent variable was designed to highlight the potential for hemoglobin to have a nonlinear risk profile. Specifically, the quadratic may enhance the appearance of a U-shaped risk profile, in case hemoglobin has a negative effect at both extremely low and high values. Analyses were performed (*1*) using only hemoglobin and hemoglobin^2 as independent variables and (*2*) using hemoglobin and hemoglobin^2 plus the additional covariates age, race, gender, diabetes, BMI, albumin, missed treatments, and URR. To further explore any nonlinear relationship between survival and hemoglobin, the same models were examined using the six hemoglobin categories, or hemoglobin <9 g/dL, 9 ≤ hemoglobin < 10 g/dL, 10 ≤ hemoglobin < 11 g/dL, 11 ≤ hemoglobin < 12 g/dL, 12 ≤ hemoglobin < 13 g/dL, and hemoglobin ≥13 g/dL in place of the continuous variables hemoglobin and hemoglobin^2.

The primary outcomes measured in the study were mortality, time to death, number of hospitalizations, and total length of hospital stay. These outcomes were considered only for the 6 months following the baseline entry period. They were analyzed as functions of mean hemoglobin concentration during the baseline period. The patient's time to death was censored at the earlier of (*1*) date of permanent discharge from FMCNA or (*2*) the end of the 6-month follow-up period. The total hospital length of stay and the number of hospitalizations were considered only for a patient's follow-up period. Since some patients died or otherwise left the system during the follow-up period, the total hospital length of stay and number of hospitalizations were estimated per 6 months of follow-up by performing a weighted analysis in which the weight was proportional to the fraction of the follow-up for which the patient was observed.

The analyses for number of hospitalizations and total hospital length of stay were based on the same models used in the survival analyses: (*1*) using only hemoglobin and hemoglobin^2 (or the six hemoglobin categories) as independent variables and (*2*) using hemoglobin and hemoglobin^2 (or the six hemoglobin categories) plus the additional covariates age, race, gender, diabetes, BMI, albumin, missed treatments, and URR.

Analyses of survival were performed using PROC PHREG and PROC LIFETEST (SAS 8.2; SAS Institute, Cary, NC, USA). Poisson analyses of hospital length of stay and number of hospitalizations were performed using PROC GENMOD (SAS 8.2; SAS Institute, Cary, NC, USA).

RESULTS

Basic demographic descriptors of the population included in these analyses are shown in Table 1. As can be seen, there were 44,550 patients eligible for inclusion

Table 1. Demographics of patient population

Age *M ± SD*	59.73 ± 15.3
Gender, females *number*	21,276 (47.8%)
Race, African Americans *number*	16,966 (38.1%)
Diabetes *number*	21,326 (47.9%)
BMI *M ± SD*	25.83 ± 6.03
Total	44,550

in the data set. This sample represents approximately 36% of all ESRD patients treated in FMCNA facilities during the time period. The population had a mean age of 59.7 years, with 38.1% of patients designated as African Americans. Males were the majority (53.2%) and approximately half of the patients had been diagnosed with diabetes. BMI averaged 25.83 kg/m^2.

As shown in Table 2, patients had a mean vintage of 25.4 months. Mean hemoglobin was 11.2 on an average weekly dose of rHuEPO of 17,824 units. Albumin averaged 3.8 and mean URR was above the K/DOQI minimum value. Average transferrin saturation was 29.3%. The last column in Table 2 shows the mean observations per patient for each parameter.

Patients were stratified by mean hemoglobin concentration (Table 3). There was a higher proportion of African American and female patients in the lower hemoglobin strata, while diabetic patients were equally distributed across hemoglobin categories. Mean albumin was higher in the upper hemoglobin categories as was transferrin saturation. The URR was similar across all hemoglobin strata. Mean rHuEPO dose decreased as hemoglobin increased.

Using hemoglobin as a continuous variable for the first (unadjusted) analysis of mortality, only the coefficient for hemoglobin (linear model) was significant ($P < 0.0001$); for the quadratic term, $P = 0.7$. For the second (adjusted) analysis, both coefficients were significant: $P = 0.001$ and $P = 0.044$, respectively.

To further describe the relationship between patient survival and hemoglobin, the relative risk of death was plotted versus six hemoglobin categories in unadjusted and adjusted models (Fig. 1). These analyses revealed that patients with hemoglobin <9 g/dL had an adjusted relative risk of death of 2.11 compared to the reference value for 11 ≤ hemoglobin < 12 ($P < 0.0001$). The relative risk of death continued to decrease as hemoglobin levels increased, with adjusted relative risk of death of 0.84 for the group with 12 ≤ hemoglobin < 13 g/dL ($P = 0.007$), and 0.82 (P = NS) for the group with hemoglobin ≥13 g/dL compared to the reference group of 11 ≤ hemoglobin < 12 g/dL. The results support the adequacy of the assumption of linear fit of relative risk of death as a function of hemoglobin level unadjusted for the additional covariates (Fig. 1). In the adjusted model (Fig. 1), the decrease in relative risk appeared to flatten for the highest two hemoglobin categories, thus supporting a quadratic model in hemoglobin when adjusting for the other covariates.

Table 2. Clinical and biochemical parameters for patient population

Parameter	Mean	Standard error	Mean/median observations per patient
Time on dialysis *months*	25.4	0.17	NA
rHuEPO dose *U/week*[a]	17,824	48	22/25 weeks
Median dose *U/week = 16,300*			
Hemoglobin *g/dL*[a]	11.2	0.005	17/15
Albumin *g/dL*[a]	3.8	0.002	6/6
Urea reducation ratio %[a]	68.95	0.03	6/6
Transferrin saturation %[a]	29.3	0.05	5/6

[a] Data obtained for first 6 months of study

To examine the impact of hemoglobin on time to death, Kaplan-Meier plots were constructed for each of the hemoglobin categories (Fig. 2). These data showed a progressive improvement in the proportion of patients surviving as a function of the hemoglobin category. Patients with hemoglobin <9 g/dL had the lowest proportion of patients surviving, and those patients with hemoglobin ≥13 g/dL had the highest proportion of patients surviving across time. The results from this analysis demonstrate a positive relationship between survival at the end of follow-up and higher hemoglobin level. The estimated survival at the end of the 6-month follow-up period is shown in Table 4.

For the number of hospitalization analyses, the coefficients for both hemoglobin and hemoglobin^2 were significant in each analysis ($P \leq 0.0002$). To further explore the relationship between number of hospitalizations and hemoglobin, the same models were examined using the six hemoglobin categories in place of the continuous variables hemoglobin and hemoglobin^2. The expected average number of hospitalizations for the 6-month study period decreased monotonically from 3.62 for the group with hemoglobin <9 g/dL to 1.44 for the group with hemoglobin ≥13 g/dL, although this reduction was not as pronounced after adjustment for covariates: 2.45 to 1.65 (Fig. 3).

For the hospital length of stay analyses, the coefficients for both hemoglobin and hemoglobin^2 were significant in each analysis: $P < 0.0001$ for the linear term in both analyses, and $P = 0.04$ and $P = 0.03$, respectively, for the quadratic terms. To further explore the relationship between length of stay and hemoglobin, the same models were examined using the six hemoglobin categories in place of the continuous variables hemoglobin and hemoglobin^2. The expected average length of stay for the 6-month study period decreased monotonically from 22.0 average number of days per patient for the group with hemoglobin <9 g/dL to 9.1 days for the group with hemoglobin ≥13 g/dL in the unadjusted analysis (Fig. 4). After

Table 3. Characteristics of patient population stratified by hemoglobin levels

Hemoglobin *g/dL*	<9	9 to <10	10 to <11	11 to <12	12 to <13	≥13
Number	1607	4268	11790	18758	6670	1457
Mean age *years*	54.8	51.8	56.9	59.7	61.0	58.0
African American %	59.3	47.2	40.9	35.2	31.8	28.2
Female %	55.3	55.3	52.2	47.0	39.0	30.6
Vintage *years*	1.9	1.63	1.66	1.71	1.47	1.99
Diabetic %	37.4	46.8	49.0	48.6	48.2	43.2
Mean albumin	3.50	3.58	3.72	3.82	3.83	3.87
Mean % transferrin saturation	28.61	25.88	27.60	30.21	31.53	31.98
Mean urea reduction ratio	66.15	67.15	68.64	69.71	69.28	68.52
Mean rHuEPO *U/week*	26,700	24,700	20,400	15,700	13,600	12,800
Mean rHuEPO *U/kg/week*	392	368	299	229	197	181
Mean hemoglobin	8.36	9.59	10.57	11.47	12.36	13.64

rHuEPO is human recombinant erythropoetin.

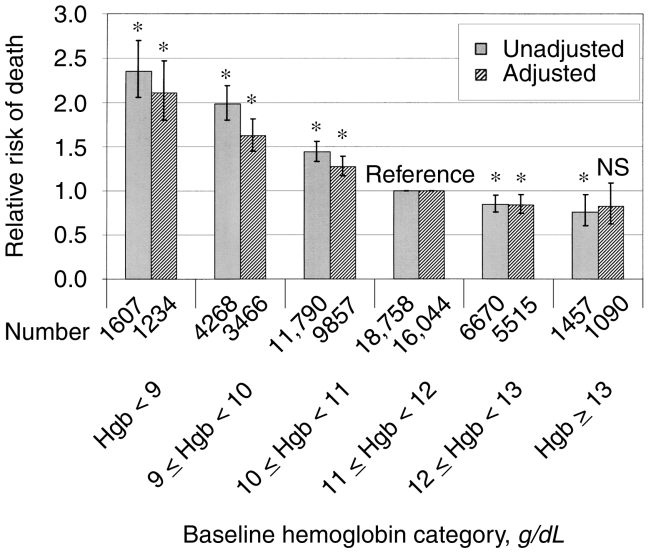

Fig. 1. Patient survival versus hemoglobin (Hgb) level, unadjusted and adjusted for covariates. Relative risk of death in the 6-month follow-up period for each group based on hemoglobin levels during the study baseline. Values were adjusted for age, race, gender, diabetes, body mass index (BMI), albumin, missed treatments, and urea reduction ratio (URR). The reference value for the analysis was 11 ≤ hemoglobin < 12. *Statistically significant difference from reference; 95% CI intervals shown.

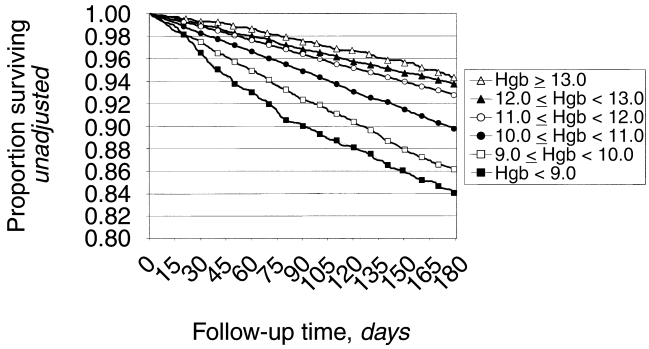

Fig. 2. Kaplan-Meier analysis of patient survival (unadjusted for covariates). The overall test of significance for differences among the six curves is $P < .0001$. All pair-wise comparisons among the curves (unadjusted for multiplicity) have P values <0.025 except for the curves representing categories 12 ≤ hemoglobin (Hgb) < 13 g/dL, and ≥13 g/dL ($P = 0.37$).

adjustment for covariates, the decrease was from 16.2 days to 9.6 days (Fig. 4).

DISCUSSION

The anemia of chronic renal failure develops in the early stages of kidney failure, yet management of anemia is suboptimal for a large proportion of patients [19]. Early management of anemia can lead to a reduction in the severity of comorbid conditions and may slow the progression of renal failure [20]. Several studies in ESRD patients have demonstrated that correcting anemia with rHuEPO has significant benefits, including improvement in quality-of-life indicators [2, 4], cardiac status [11, 21], exercise capacity [22, 23], and cognitive function [6–8]. Many of these studies examined patients with hemoglobin levels in the range of 10 to 11 g/dL (corresponding approximately to hematocrit levels between 30% to 33%), and only recently has attention focused on potential benefits of normalizing hemoglobin (hemoglobin >12 g/dL). A hematocrit normalization study in 1200 hemodialysis patients with significant preexisting cardiac disease (congestive heart failure and/or ischemic cardiac disease) was stopped after an interim analysis indicated that there were more deaths in the group randomized to achieve a target hematocrit of 42% compared to the group with a target hematocrit of 30% [18]. However, mortality rates decreased with increasing hematocrit values in both normal hematocrit and low hematocrit groups. The results were further potentially confounded by other variables such as dialysis adequacy (Kt/V), which declined in the high hematocrit group, and more frequent iron dextran infusions required to achieve the higher hematocrit target. It is not possible to explain the difference in observed results between the randomized

Table 4. Kaplan-Meier survival rates at the end of the second 6 months versus hemoglobin category

Hemoglobin category	Lower limit 95% CI	Survival rate	Upper limit 95% CI	Number
Hemoglobin <9 g/dL	0.819	0.838	0.856	1607
9 ≤ hemoglobin < 10 g/dL	0.849	0.860	0.871	4268
10 ≤ hemoglobin < 11 g/dL	0.890	0.896	0.901	11790
11 ≤ hemoglobin < 12 g/dL	0.923	0.926	0.930	18758
12 ≤ hemoglobin < 13 g/dL	0.931	0.937	0.943	6670
Hemoglobin ≥13 g/dL	0.931	0.943	0.955	1457

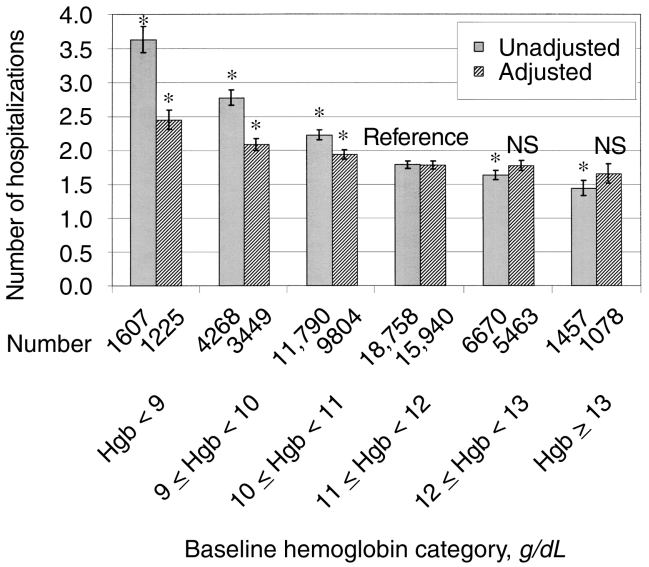

Fig. 3. Number of hospitalizations versus hemoglobin (Hgb) level, unadjusted and adjusted for covariates. The number of hospitalizations per 6 months follow-up for each group based on hemoglobin levels during the study baseline. Values were adjusted for age, race, gender, diabetes, body mass index (BMI), albumin, missed treatments, and urea reduction ratio (URR). The reference value for the analysis was 11 ≤ hemoglobin < 12. The number of hospitalizations was calculated by weighted analysis with the weights proportional to the length of time a subject was observed during the 6 months follow-up period. *Statistically significant difference from reference; 95% CI intervals shown.

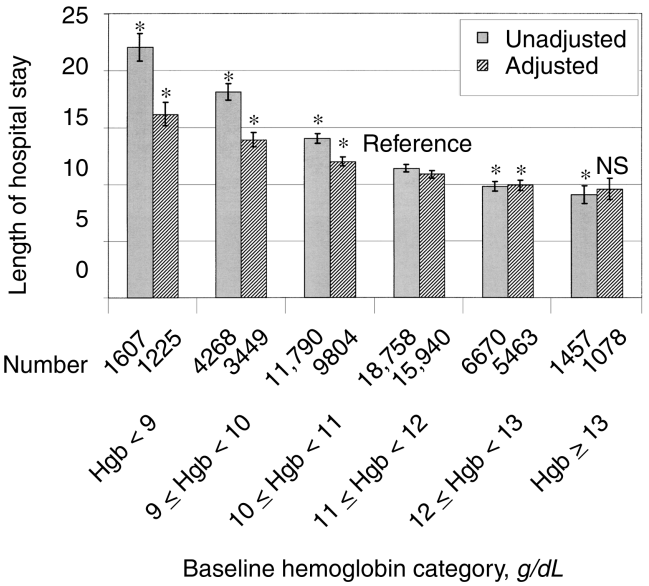

Fig. 4. Total hospital length of stay versus hemoglobin (Hgb) level, unadjusted and adjusted for covariates. Total hospital length of stay per 6 months follow-up for each group based on hemoglobin levels during the study baseline. Values were adjusted for age, race, gender, diabetes, body mass index (BMI), albumin, missed treatments and urea reduction ratio (URR). The reference value for the analysis was 11 ≤ hemoglobin < 12. The length of hospital stay was calculated by weighted analysis with the weights proportional to the length of time a subject was observed during the 6 months follow-up period. *Statistically significant difference from reference; 95% CI shown.

trial and the associations in the retrospective analyses. The randomized trial selected only patients with existing heart disease, including 19% of patients with congestive heart failure, New York Heart Association Class 3. In general, the trial patients were older (65 years of age) with more coexisting diseases compared to the general dialysis population. The FMCNA database analyzed for this report included only those patients that survived for at least 6 consecutive months, and data were not available on comorbid conditions. Based on the results of the randomized trial, electively raising hematocrit to normal levels in patients with existing cardiac disease is not recommended.

Recent studies indicate that raising hemoglobin levels into the lower end of the normal range does not appear to pose additional risk to ESRD patients in the apparent absence of severe ischemic cardiac disease or heart failure. The study of prevalent Medicare ESRD patients examined mortality over a 12-month period based on hematocrit levels over the preceding 6 months. The analyses were adjusted for a number of comorbid conditions. Patients with hematocrit <30% (hemoglobin <10.0 g/dL) had the greatest risk of all-cause and cause-specific death, and there was a further reduction in risk for patients with hematocrit between 33% and 36% (hemoglobin of 11 to 12 g/dL) [15]. Additional analyses showed that patients with hematocrit <30% had the highest risk of future hospitalization, while those with hematocrit between 33% and 36% had the lowest risk [16]. These results were extended by subsequent analyses of incident Medicare ESRD patients showing that for patients with hematocrit 36% to <39%, mortality rates were not dif-

ferent, but hospitalization rates were 16% to 22% lower, compared to patients with hematocrit of 33% to <36% [17]. In addition, Medicare Part A and B expenditures were 8.3% to 8.5% less over the 1-year follow-up when hematocrit was 36% to <39%, compared to 33% to <36%, which could represent significant savings to the Medicare program. Expenditure estimates for the different hemoglobin categories were not available for inclusion in this analysis.

The results reported here support the conclusions drawn from the Medicare ESRD patient studies. Patients with hemoglobin <9 g/dL had the lowest 6-month survival rate of all groups, and survival rates increased with increasing hemoglobin levels. Unadjusted relative risk of death decreased as hemoglobin levels increased, although the difference was smaller for the groups with 12 ≤ hemoglobin <13 g/dL and hemoglobin ≥13 g/dL after adjustment for covariates. The small patient sample for the hemoglobin ≥13 g/dL limited the probability of demonstrating further reduction in relative risk of death. Patients in the hemoglobin categories ≥12.0 g/dL may be the group of patients with fewer comorbidities and thus able to achieve higher hemoglobin levels. However, these data suggest that there is no increased risk of mortality associated with hemoglobin higher than the values recommended by the K/DOQI guidelines and, perhaps, some decreased risk. Furthermore, these data show that higher hemoglobin correlates with reduced hospital length of stay, suggesting that an improvement in anemia status may be beneficial to hospitalized patients. There was no increase in either number of hospitalizations or hospital length of stay over the 6-month follow-up period for groups with hemoglobin >12 g/dL, indicating that anemia correction to hemoglobin levels >12 g/dL did not appear to pose additional risks for ESRD patients. Longer follow-up beyond 6 months might demonstrate longer-term benefit by reducing LVH and/or cardiac dilatation.

Although cardiovascular comorbidities were not collected for these analyses, there is evidence from a small, multicenter Canadian study of hemodialysis patients that normalization of hemoglobin levels can prevent progressive LV dilation [11]. The study also concluded that normalization of hemoglobin may lead to improved quality of life. Another small study demonstrated that raising hemoglobin levels to 14 g/dL (compared to a baseline of hemoglobin 10 g/dL) resulted in an improvement in several cardiac parameters and quality of life indicators [2].

Normalizing hemoglobin will require more iron supplementation during the titration phase. More frequent iron administration has been suggested as a potential factor in increased cardiovascular complications and infection in dialysis patients [18]. Additional studies are needed to establish beneficial effects of normalizing hemoglobin levels on biochemical and clinical parameters in hemodialysis patients.

While raising hemoglobin levels to the range recommended by the K/DOQI guidelines should be the goal for every patient, additional benefits may be obtained by targeting higher hemoglobin levels (>12 g/dL for females and >13 g/dL for males) in some patients. Because of variability in patient physiologic parameters, optimal anemia management will require an individualized approach to patients [14]. Mortality risk, time to death, number of hospitalizations, and length of hospital stay, at least for the short term, do not appear to be worse when hemoglobin exceeds 12 g/dL compared to the reference group of 11 to 12 g/dL in this large cohort of hemodialysis patients.

There are several limitations of this study. It is a retrospective descriptive study based on observations and does not infer causality between hemoglobin and selected outcomes. The follow-up period was only 6 months, and ESRD patients had to survive for at least 6 months during the observation period to be included in the sample, which may have introduced selection bias, as well as limiting generalizability.

It should also be noted that comorbid conditions were not available to use in the adjusted analyses. It has been observed that hemodialysis patients with more severe coexisting conditions may also be those patients in the lower hemoglobin categories, and the analyses reported here could not adjust for those conditions. Observational studies are subject to confounding by unmeasured factors, such as the comorbid conditions cited above. Therefore, observational studies should be confirmed or disconfirmed by well-designed experimental studies.

In the absence of direct adverse outcomes related to hemoglobin >12 g/dL, specific benefits leading to improvement in biochemical parameters, ease of patient management, and quality of life may be further explored. These data support the need for prospective studies with longer follow-up to demonstrate the potential benefits of higher hemoglobin levels in ESRD patients as appropriate in those without apparent severe cardiovascular disease or heart failure.

Reprint requests to J. Michael Lazarus, M.D., Fresenius Medical Care—North America, 95 Hayden Avenue, Lexington, MA 02420.
E-mail: michael.lazarus.md@fmc-na.com

REFERENCES

1. NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure: National Kidney Foundation—Dialysis Outcomes Quality Initiative. *Am J Kidney Dis* 30:S192–S240, 1997
2. McMahon LP, Mason K, Skinner SL, *et al*: Effects of haemoglobin normalization on quality of life and cardiovascular parameters in end-stage renal failure. *Nephrol Dial Transplant* 15:1425–1430, 2000
3. Moreno F, Sanz-Guajardo D, Lopez-Gomez JM, *et al*: Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. Spanish Cooperative Renal

Patients Quality of Life Study Group of the Spanish Society of Nephrology. *J Am Soc Nephrol* 11:335–342, 2000
4. Beusterien KM, Nissenson AR, Port FK, *et al*: The effects of recombinant human erythropoietin on functional health and well-being in chronic dialysis patients. *J Am Soc Nephrol* 7:763–773, 1996
5. Moreno F, Aracil FJ, Perez R, Valderrabano F: Controlled study on the improvement of quality of life in elderly hemodialysis patients after correcting end-stage renal disease-related anemia with erythropoietin. *Am J Kidney Dis* 27:548–556, 1996
6. Nissenson AR: Epoetin and cognitive function. *Am J Kidney Dis* 20:21–24, 1992
7. Pickett JL, Theberge DC, Brown WS, *et al*: Normalizing hematocrit in dialysis patients improves brain function. *Am J Kidney Dis* 33:1122–1130, 1999
8. Marsh JT, Brown WS, Wolcott D, *et al*: Treatment improves brain and cognitive function of anemic dialysis patients. *Kidney Int* 39:155–163, 1991
9. Berweck S, Hennig L, Sternberg C, *et al*: Cardiac mortality prevention in uremic patients. Therapeutic strategies with particular attention to complete correction of renal anemia. *Clin Nephrol* 53:S80–85, 2000
10. Silverberg DS, Wexler D, Blum M, *et al*: The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 35:1737–1744, 2000
11. Foley RN, Parfrey PS, Morgan J, *et al*: Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 58:1325–1335, 2000
12. National Kidney Foundation: NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: Update 2000. *Am J Kidney Dis* 37:S182–S238, 2001
13. Eckardt KU: Target hemoglobin in patients with renal failure. *Nephron* 89:135–143, 2001
14. Ritz E, Schwenger V: The optimal target hemoglobin. *Semin Nephrol* 20:382–386, 2000
15. Ma JZ, Ebben J, Xia H, Collins AJ: Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 10:610–619, 1999
16. Xia H, Ebben J, Ma JZ, Collins AJ: Hematocrit levels and hospitalization risks in hemodialysis patients. *J Am Soc Nephrol* 10:1309–1316, 1999
17. Collins AJ, Li S, St. Peter W, *et al*: Death, hospitalization and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39. *J Am Soc Nephrol* 12:2465–2473, 2001
18. Besarab A, Bolton WK, Browne JK, *et al*: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 339:584–590, 1998
19. Kazmi WH, Kausz AT, Khan S, *et al*: Anemia: An early complication of chronic renal insufficiency. *Am J Kidney Dis* 38:803–812, 2001
20. Kausz AT, Khan SS, Abichandani R, *et al*: Management of patients with chronic renal insufficiency in the Northeastern United States. *J Am Soc Nephrol* 12:1501–1507, 2001
21. Levin A, Thompson CR, Ethier J, *et al*: Left ventricular mass index increase in early renal disease: Impact of decline in hemoglobin. *Am J Kidney Dis* 34:125–134, 1999
22. Clyne N, Jogestrand T: Effect of erythropoietin treatment on physical exercise capacity and on renal function in predialytic uremic patients. *Nephron* 60:390–396, 1992
23. McMahon LP, Johns JA, McKenzie A, *et al*: Haemodynamic changes and physical performance at comparative levels of haemoglobin after long-term treatment with recombinant erythropoietin. *Nephrol Dial Transplant* 7:1199–1206, 1992