Hemoglobin variability in epoetin-treated hemodialysis patients

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Background. Understanding the clinical variability of hemoglobin measurements in epoetin-treated hemodialysis patients is important, particularly when this therapy is aimed at maintaining patient hemoglobin levels within a narrow range, such as the 11 to 12 g/dL range recommended in National Kidney Foundation Kidney Dialysis Outcomes Quality Initiative (NKF-K/DOQI) guidelines. This study examines hemoglobin variability under conditions of standard clinical practice in epoetin-treated hemodialysis patients.

Methods. We studied 987 hemodialysis patients participating in an observational retrospective study that evaluated anemia management practices from October 1, 1996 to December 31, 1997 at 11 United States dialysis centers that were randomly selected from a pool of nearly all United States dialysis facilities. Each participating facility maintained its own anemia management protocols without specific anemia management recommendations or interventions made as part of this study. Hemoglobin variability was determined by calculating the 1-month and 2- to 6-month rolling average hemoglobin for each patient. The range of mean hemoglobin values that included the middle 50% (25th to 75th percentile), 80% (10th to 90th percentile), and 90% (5th to 95th percentile) of values were determined. The hemoglobin ranges that included 1 standard deviation (SD) (67%) of the study values and 2 SD (95%) of the study values for each time period were calculated.

Results. The mean hemoglobin was between 10.9 and 11.2 g/dL throughout the study. The hemoglobin range encompassing 50%, 80%, and 90% of values from a single month was 1.7, 3.3, and 4.4 g/dL, respectively. A progressive narrowing in the range of hemoglobin values encompassed by each percentile grouping (i.e., hemoglobin variability) was observed as longer rolling intervals were averaged. The hemoglobin range within the 25th to 75th percentile was 1.7 g/dL using single-month hemoglobin values and 1.1 g/dL using a 6-month rolling average. The range of hemoglobin values that encompassed 90% of patients was 4.4 g/dL using single-month values, 3.7 g/dL using 3-month rolling averages, and 3.2 g/dL using 6-month rolling averages. Fewer than 50% of patients had hemoglobin values within the 1.0 g/dL NKF-K/DOQI recommended range, even when a 6-month rolling average was applied. When hemoglobin values were measured for 1 month, 1 SD was 1.4 g/dL; for the 3-month rolling average, 1 SD was 1.1 g/dL; and for the 4-, 5-, and 6-month rolling averages, 1 SD was 1.0 g/dL. Greater hemoglobin variability correlated with higher mean corpuscular hemoglobin ($P = 0.003$) and serum ferritin ($P = 0.047$), and inversely correlated with age ($P = 0.006$) and serum albumin ($P = 0.0001)$.

Conclusion. Substantial variability occurs in hemoglobin values in epoetin-treated hemodialysis patients. The NKF-K/DOQI recommended hemoglobin range appears to be too narrow in clinical practice. Expanding the target range and use of rolling average hemoglobin intervals of 3 to 6 months as a clinical and quality assurance measure avoids clinical variability inherent with the use of isolated hemoglobin values or single-month hemoglobin averages.

Anemia is a common complication in patients with end-stage renal disease (ESRD) treated with chronic maintenance hemodialysis. In hemodialysis patients, the treatment of anemia with epoetin [recombinant human erythropoietin (rHuEPO)] improves physiologic and quality-of-life measures, and higher hematocrit and hemoglobin levels are associated with lower mortality and hospitalization and serve as an important indicator of quality of care [1–6]. In 1997, the National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-DOQI) [7] recommended guidelines for hematocrit and hemoglobin targets of 33% to 36% and 11 to 12 g/dL, respectively, in patients with chronic kidney disease, including those on dialysis. Since then, payors, networks, and corporate dialysis providers have challenged nephrologists caring for dialysis patients to maintain the hemoglobin or hematocrit of their patients within these or other similar ranges, which have been supported more recently in other clinical practice guidelines, including the updated NKF Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines [8–10].

Key words: anemia, recombinant human erythropoietin, epoetin, hemodialysis, variability, target.

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In dialysis facilities, hemoglobin or hematocrit are typically measured frequently, anywhere from weekly to monthly, leading to adjustments in the dose of epoetin, often on the basis of standing anemia management protocols, to maintain these values within some desired range. Hemoglobin has been recommended as the preferred measure for anemia management [8]. There has been some concern that the recommended hemoglobin range of 11 to 12 g/dL may be too narrow for routine clinical practice. Understanding the normal clinical variability of hemoglobin measurements is therefore critical to optimal clinical management aimed at maintaining patient hemoglobin levels within this (or any) range. In addition to laboratory variation, which is reported to be less with hemoglobin than hematocrit [8, 11], week-to-week and month-to-month variability in hemoglobin levels may be related to epoetin dose adjustments, route of epoetin administration [12], variation in hydration status [13], inflammatory processes [14], administration of intravenous iron and correction of iron deficiency, blood loss such as that due to access surgery, dialysis adequacy [15], and even seasonal influences [16].

Unfortunately, little is known about the clinical variability of hemoglobin measurements in hemodialysis patients. The study reported here examines hemoglobin variability under conditions of standard clinical practice in hemodialysis patients.

METHODS

The Anemia Management Practices (AMP) study was an observational retrospective study with a historical prospective design (i.e., a simulation of a prospective trial, but with all events occurring at a prior time), designed primarily to assess the impact of the 1997 Health Care Financing Administration (HCFA) Hematocrit Management Audit (HMA) program. The study monitored anemia management practices at 11 United States dialysis centers from October 1, 1996 to December 31, 1997. To ensure that participating dialysis centers reflected a variety of geographic areas and included not-for-profit, for-profit, privately owned, corporate-chain owned, university-affiliated, free-standing, and hospital-affiliated facilities, and to ensure that a case mix of patients was included that would capture differences in anemia management between various dialysis centers, hemoglobin data from dialysis facilities that participated in the Amgen Optional Hematocrit Incentive Program, which is virtually all dialysis units in the United States, were screened. From this group of dialysis facilities, 135 dialysis units were identified as having at least 40 hemodialysis patients receiving treatment and meeting one of the following criteria: (1) >75% of the patients had hematocrit ≥33% or (2) <50% of the patients had hematocrit ≥33%, based on hematocrit data during the month of May 1997, which was the midpoint of the study period. Forty-eight of the units met the criteria of having >75% of their patients with hematocrit ≥33% (group A) and 87 of these units had <50% of their patients with hematocrit ≥33% (group B).

Facilities were pooled by four main geographic regions in the United States. Nested randomization by region was performed to ensure that two facilities were selected from each region, after which the nesting was automatically removed. The sample size necessary to detect a 4% decrease in the percent of patients with a hematocrit of ≥33% following implementation of the HMA guidelines with a 95% power at an alpha of 0.01 was 960 patients. Therefore, random selection of additional facilities without regard to geographic area was continued until the total number of patients in the selected facilities exceeded 1100. The final selection included 11 dialysis clinics that participated in this study; six facilities were in group A, and five facilities were in group B (see Acknowledgments for a list of participating investigators and centers, and the location and type of each dialysis facility). By virtue of the study design, the mean hematocrit was higher in group A compared to group B. However, the mean and median hemoglobin values did not differ between these two groups either at baseline or when analyzed over the entire duration of the study (data not shown). Since hemoglobin is preferred to hematocrit as the measure of anemia in dialysis patients [8], the two groups were therefore combined for the analysis of hemoglobin variability in the present study.

The patient population included between 50 and 150 hemodialysis patients from each center who met the following inclusion criteria. All patients were over 18 years old, had been on hemodialysis for >3 months prior to the start of data collection (October 1, 1996), and were alive on December 31, 1997. Excluded from the study were patients who had received red blood cell transfusions within 10 weeks of start of the data collection period and patients with hemoglobinopathies, hemochromatosis, malignancy, known human immunodeficiency virus (HIV) infection, or active inflammatory disease or gastrointestinal bleeding. In larger facilities in which more than 150 patients would have been eligible for inclusion, a subgroup of no more than 150 qualified patients was randomly selected to participate from a list of all eligible patients within the facility.

Each physician and facility maintained its own anemia management protocols and policies, and any changes in anemia management that may have occurred during the period of interest for this study were at the discretion of treating nephrologists and facility medical directors. There were no specific anemia management interventions made as part of this study, no recommendations for changes in anemia management were suggested by the study sponsor, and, given the retrospective design of
this study, study data that might have affected anemia management at individual facilities were not available to participants. Laboratory tests were performed at the usual clinical laboratory for each facility; different hemoglobin assays may have been used by the various facilities but did not change during the course of the study at any facility.

Data parameters

Hemoglobin measurements were taken 1, 2, or 4 times monthly, according to the clinical practices at each participating facility. Hemoglobin variability was determined by calculating the rolling average hemoglobin for each patient across different time intervals during the 15 months of the study (averages for intervals of 2, 3, 4, 5, and 6 months). Using the patients’ mean hemoglobin values for each interval, the range of mean hemoglobin values that included the middle 50% (25th to 75th percentile), 80% (10th to 90th percentile), and 90% (5th to 95th percentile) of values were determined. In addition, the hemoglobin ranges that included 1 standard deviation (SD) (67% of the interval’s values) and 2 SD (95% of the interval’s values) for each time period were calculated.

To assess what parameters contributed to variability, the SD of hemoglobin was used as a dependent variable and demographic, clinical, and laboratory parameters were evaluated as independent variables. Demographic variables included age, gender, and race. Clinical variables included the presence or absence of diabetes mellitus, cause of ESRD, time on dialysis, epoetin treatment, and comorbid conditions present at study entry. Laboratory measurements included hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, ferritin, transferrin saturation (TSAT), Kt/V, albumin, and intact parathyroid hormone (iPTH).

Data collection and statistical methods

Clinical and laboratory data were collected for 987 patients. Data available electronically were obtained in the format generated by each dialysis center’s computer system, and integrated into a standard SAS platform. The remaining data were captured using data entry screens constructed using Microsoft Access with Visual Basic customization, and analyses were done using SAS software. Stepwise regression with backward elimination was performed using the 15-month trend for the independent variables listed above, and frequencies were used for the categorical data. The final model was obtained after 14 iterative steps and was significant at $P = 0.0001$. Testing for statistical significance was performed using single-group or two-group $t$ tests for continuous variables and McNemar’s chi-square test for categorical variables. Log transformations were applied to normalize the distribution of skewed data (epoetin dose, serum ferritin, and iPTH).

RESULTS

Demographic characteristics of the study population are summarized in Table 1. Mean values for key laboratory parameters during each 3-month period throughout the duration of the study (beginning the first calendar quarter of 1996 through the fourth quarter of 1997) along with mean administered epoetin doses are presented in Table 2. In each quarter, between 94% and 96% of patients received epoetin and between 65% and 79% of patients received intravenous iron. Of factors that might have affected hemoglobin levels, only serum ferritin levels, which increased, changed consistently over the duration of the study. Mean epoetin doses varied and were significantly different from baseline in only two of the subsequent four study periods. There was not a consistent change or trend for TSAT, serum albumin, or Kt/V. While iPTH levels tended to fall, this did not reach statistical significance. The mean hemoglobin ranged between 10.9 and 11.2 g/dL throughout the study. The 25th to 75th, 10th to 90th, and 5th to 95th percentile hemoglobin ranges for the 1-month and 2- through 6-month rolling averages are provided in Table 3.

The hemoglobin range encompassing 50%, 80%, and 90% of values from a single month was 1.7, 3.3, and 4.4 g/dL, respectively. As expected, a progressive narrowing in the range of hemoglobin values encompassed by each percentile grouping (i.e., hemoglobin variability) was observed as longer rolling intervals were averaged. For instance, the hemoglobin range within the 25th to 75th percentile grouping continued to narrow with increasing rolling average intervals, from 1.7 g/dL using single-month hemoglobin values, down to 1.1 g/dL using a 6-month rolling average. The range of hemoglobin values that encompassed 90% of patients was 4.4 g/dL using single-
month values, 3.7 g/dL using 3-month rolling averages, and 3.2 g/dL using 6-month rolling averages. The hemoglobin ranges that encompassed 50%, 80%, and 90% of patients over periods of 1 to 6 months with rolling averages are also shown in Figure 1. Fewer than 50% of patients had hemoglobin ranges within the recommended NKF-DOQI guidelines of 1.0 g/dL, in place at the time of this study, even when a 6-month rolling average was applied.

By analysis of aggregate SD data, it was determined that when hemoglobin values were measured for 1 month, 1 SD was 1.4 g/dL so that approximately 67% of values were included in a 2.8 g/dL range and 95% of values were included in a 5.6 g/dL range. For the 3-month rolling average, 1 SD was 1.1 g/dL with a 2.2 g/dL and 4.4 g/dL range that included 67% and 95% of values, respectively. For the 4-, 5-, and 6-month rolling averages, 1 SD was 1.0 g/dL with a 2.0 g/dL and 4.0 g/dL range that included 67% and 95% of values, respectively (Table 4).

Greater hemoglobin variability was significantly correlated with higher mean corpuscular hemoglobin ($P = 0.003$) and serum ferritin ($P = 0.047$), and inversely correlated with age ($P = 0.006$) and serum albumin ($P = 0.0001$). A decline in albumin of 1 g/dL correlated with an increase in SD of 0.3 g/dL. A 100 ng/mL increase in

### Table 2.
Quarterly means for various anemia management-related laboratory values and epoetin doses administered for entire study population ($N = 987$) throughout 15-month study period, beginning the fourth calendar quarter of 1996 (Q4-96) and ending the fourth quarter of 1997 (Q4-97)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Q4-96</th>
<th>Q1-97</th>
<th>Q2-97</th>
<th>Q3-97</th>
<th>Q4-97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit %</td>
<td>33.8 (3.4)</td>
<td>34.3 (3.8)</td>
<td>34.4 (3.4)</td>
<td>33.9 (3.3)</td>
<td>33.6 (3.4)</td>
</tr>
<tr>
<td>Hemoglobin g/dL</td>
<td>11.1 (1.2)</td>
<td>11.2 (1.2)</td>
<td>11.2 (1.2)</td>
<td>11.0 (1.1)</td>
<td>10.9 (1.1)</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin pg/dL</td>
<td>29.9 (2.9)</td>
<td>29.8 (2.8)</td>
<td>30.1 (4.2)</td>
<td>30.2 (5.8)</td>
<td>30.0 (2.8)</td>
</tr>
<tr>
<td>Mean corpuscular volume fl</td>
<td>90.7 (7.1)</td>
<td>91.5 (7.4)</td>
<td>92.1 (7.5)</td>
<td>92.4 (7.4)</td>
<td>91.9 (7.1)</td>
</tr>
<tr>
<td>Ferritin ng/mL</td>
<td>385 (421)</td>
<td>495 (504)</td>
<td>539 (509)</td>
<td>609 (513)</td>
<td>611 (501)</td>
</tr>
<tr>
<td>Transferrin saturation %</td>
<td>29.8 (14.6)</td>
<td>29.4 (12.7)</td>
<td>32.4 (14.3)</td>
<td>31.8 (14.1)</td>
<td>30.7 (13.1)</td>
</tr>
<tr>
<td>Albumin g/dL</td>
<td>3.8 (0.4)</td>
<td>3.9 (0.4)</td>
<td>3.9 (0.3)</td>
<td>3.9 (0.4)</td>
<td>3.9 (0.4)</td>
</tr>
<tr>
<td>Intact parathyroid hormone g/dL</td>
<td>313 (376)</td>
<td>354 (437)</td>
<td>306 (354)</td>
<td>237 (277)</td>
<td>275 (426)</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.45 (0.31)</td>
<td>1.51 (0.68)</td>
<td>1.47 (0.29)</td>
<td>1.49 (0.27)</td>
<td>1.51 (0.28)</td>
</tr>
<tr>
<td>Epoetin dose U/week</td>
<td>13090 (8134)</td>
<td>12335 (8210)</td>
<td>11884 (8506)</td>
<td>12478 (9109)</td>
<td>11996 (8827)</td>
</tr>
</tbody>
</table>

Data shown as ± SE in parenthesis.

### Table 3.
Hemoglobin range, expressed as both width of the range and actual hemoglobin range, encompassing specified percentages of patient's hemoglobin values for 1-month values and rolling averages of 2 to 6 months

<table>
<thead>
<tr>
<th>Rolling average interval</th>
<th>25th–75th percentile (50% of patients) g/dL</th>
<th>10th–90th percentile (80% of patients) g/dL</th>
<th>5th–95th percentile (90% of patients) g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>One month</td>
<td>1.7 (10.3–12.0)</td>
<td>3.3 (9.4–12.7)</td>
<td>4.4 (8.8–13.2)</td>
</tr>
<tr>
<td>Two-month rolling average</td>
<td>1.4 (10.4–11.8)</td>
<td>3.0 (9.5–12.5)</td>
<td>3.9 (9.0–12.9)</td>
</tr>
<tr>
<td>Three-month rolling average</td>
<td>1.3 (10.5–11.8)</td>
<td>2.7 (9.7–12.4)</td>
<td>3.7 (9.1–12.8)</td>
</tr>
<tr>
<td>Four-month rolling average</td>
<td>1.3 (10.5–11.8)</td>
<td>2.5 (9.8–12.3)</td>
<td>3.4 (9.3–12.7)</td>
</tr>
<tr>
<td>Five-month rolling average</td>
<td>1.2 (10.5–11.7)</td>
<td>2.3 (9.9–12.2)</td>
<td>3.2 (9.4–12.6)</td>
</tr>
<tr>
<td>Six-month rolling average</td>
<td>1.1 (10.6–11.7)</td>
<td>2.3 (9.9–12.2)</td>
<td>3.2 (9.4–12.6)</td>
</tr>
</tbody>
</table>

Fig. 1. Width of hemoglobin (Hgb) range encompassing specified percentages and percentile groups of patient’s hemoglobin values for 1-month values and rolling averages of 2 to 6 months.

### Table 4.
Width of hemoglobin range encompassing 1 SD and specified percentages of patient’s hemoglobin values for 1-month values and rolling averages of 2 to 6 months

<table>
<thead>
<tr>
<th>Range</th>
<th>1 SD g/dL</th>
<th>Range width for 67% of patients g/dL</th>
<th>Range width for 95% of patients g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>One month</td>
<td>1.4</td>
<td>2.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Two-month rolling average</td>
<td>1.2</td>
<td>2.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Three-month rolling average</td>
<td>1.1</td>
<td>2.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Four- to six-month rolling average</td>
<td>1.0</td>
<td>2.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>
in the first quarter of 2000, only 38.4% of patients had dialysis chain (Fresenius Medical Care North America). Other demographic and clinical variables, including epoetin dose, and other laboratory parameters, including Kt/V and iPTH, levels, were not significantly correlated with increased hemoglobin variability.

**DISCUSSION**

Anemia management has become a major focus of the care of hemodialysis patients as a result of the availability of epoetin therapy and evidence linking clinical outcomes to hemoglobin and Hct levels [1–6]. Specific target hematocrit or hemoglobin ranges have been recommended by the NKF-DOQI guidelines [7], the subsequent NKF-K/DOQI guidelines [8] and guidelines from the European and Canadian renal communities [9, 10]. The hemoglobin target of 11 to 12 g/dL, as recommended by the NKF-K/DOQI guidelines [8], has become well accepted in the United States. Hemoglobin, now preferred to hematocrit as the measure of anemia [8], is typically measured on a weekly or monthly basis, with changes in epoetin dosing made accordingly, often driven by standing anemia management protocols.

In clinical practice it is often difficult to maintain hemoglobin levels within such a narrow range due to substantial inter- and intrapatient variability. Our findings show that large variability occurs in hemoglobin values among hemodialysis patients. The wide variability in hemoglobin among hemodialysis patients is likely a consequence of frequent adjustments of epoetin doses, withholding doses when certain hemoglobin targets are exceeded, variability in route of administration [12] and response to epoetin [17, 18], iron deficiency, the hematopoietic response to iron therapy, surgery-related blood loss, inflammatory or infectious disease processes [14, 19–21], hyperparathyroidism [21–23], dialysis adequacy [15, 24, 25], and laboratory variation and error. Interdialytic weight gains also affect measured hemoglobin values [13]. Seasonal fluctuations in hemoglobin and other clinical and laboratory parameters have also been reported [16].

Lacson, Ofsthun, and Lazarus [26] recently published a detailed analysis of hemoglobin variability among hemodialysis and peritoneal dialysis patients from a single dialysis chain (Fresenius Medical Care North America). In the first quarter of 2000, only 38.4% of patients had mean 3-month rolling average hemoglobin values within the range of 11 to 12 g/dL, with an average intrapatient hemoglobin SD of ±1.3 mg/dL. These authors evaluated intrapatient variability based on 3-month rolling average hemoglobin levels over the course of a year, demonstrating that there was a broad distribution of SD for this average. The median and 75th percentile intrapatient SD were ±0.7 g/dL and ±1.0 g/dL, respectively, with a range of 0.1 to 2.5 g/dL. Thus, a patient with the median SD would have a ±1.4 g/dL fluctuation in 3-month rolling average hemoglobin over the course of a year. Based on these SDs, the authors concluded that a patient from their cohort with hemoglobin measured twice monthly and a 3-month rolling average hemoglobin of 11.5 g/dL would have 42% of samples outside the range of 11 to 12 g/dL based on the median SD and 58% of samples outside this range based on the 75th percentile SD.

Hemoglobin or hematocrit variability in hemodialysis patients has also been the subject of two other preliminary reports recently. Freund and Nielsen evaluated hematocrit values from 680 hemodialysis patients with 10 or more results measured at a commercial laboratory [abstract; Freund LE et al, J Am Soc Nephrol 11:1401A, 2000]. Individual patient hematocrit value SDs were normally distributed, ranging from 0.5 to 7.5, reflecting the highly variable nature of hematocrit in this population. The authors noted that a patient with an overall hematocrit average of 33% and average SD of 2.94 would be expected to have a hematocrit above 36% in about 10% of the monthly samples. More recently, Brier et al analyzed data from the Renal Network Data System for patients from dialysis facilities in Illinois, Indiana, Kentucky, and Ohio, for the last 3 months of 1999 [abstract; Brier ME et al, J Am Soc Nephrol 13:628A, 2002]. Using 3-month averages, only 66% of patients were maintained within the 11 to 12 g/dL target range. These authors calculated that a hemoglobin range of 11.0 to 12.24 g/dL would encompass 75% of patients, a range of 11.0 to 12.96 g/dL would encompass 90% of patients, and a range of 11.0 to 13.96 g/dL would encompass 95% of patients, and suggested that the anemia goal should be modified to account for clinical variability.

Data from our 15-month study indicates that 1-month hemoglobin values exhibit the greatest degree of variability; a 3.3 g/dL range included only 80% of patients and a 4.4 g/dL range would be needed to include 90% of patients. Increasing the length of the hemoglobin monitoring period reduces this variability and narrows the hemoglobin range that encompasses the various percentile fractions of the entire hemodialysis patient population. Use of the 3-month rolling average, as is currently the practice for claims review by Centers for Medicare and Medicaid Services (CMS), is associated with less variability than 1-month values. Nonetheless, even for 3-month rolling averages, a 2.7 g/dL range would include

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>0.289</td>
<td>17.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean corpuscular hormone</td>
<td>0.025</td>
<td>9.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Age</td>
<td>0.004</td>
<td>7.7</td>
<td>0.006</td>
</tr>
<tr>
<td>Ferritin</td>
<td>0.0001</td>
<td>4.0</td>
<td>0.047</td>
</tr>
</tbody>
</table>
80% of hemoglobin values. However, extending the monitoring period to 5 or 6 months reduces the range that encompasses 80% of the values to 2.3 g/dL.

Parameters identified as being correlated with increased hemoglobin variability included lower serum albumin, higher serum ferritin and mean corpuscular hemoglobin, and age (younger patients had higher variability, compared with older patients). The correlations with serum albumin and ferritin may reflect the effects of infection and inflammation on albumin and ferritin levels and erythropoiesis. The reason for an association between advanced age and narrower hemoglobin variability is unclear.

There are some limitations to our study that should be considered. First, our data were collected in 1996 and 1997, just prior to and during implementation of the new repealed HCFA HMA program, so changes in anemia management practices or targets during this period and since then may have affected hemoglobin variability. Anemia management practices may also have changed during the period of our study in response to the NKF-DOQI guidelines (subsequently renamed the NKF-K/DOQI guidelines), which were published in 1997 [7], but were previously presented at national meetings in 1996. In fact, however, the percentage of patients with hematocrit or hemoglobin values within the NKF-K/DOQI range reported in our study and several subsequent reports from other sources are quite similar [26–29]. In the most recently published United States Renal Data System (USRDS) annual report, approximately two thirds of patients (i.e., those which would encompass 1 SD around the mean) had 1-month hematocrit values of 30% to 37.5%, corresponding to a hemoglobin range of approximately 2.5 g/dL, which is remarkably similar to the value of 2.8 g/dL we observed. Another concern is that if the upper limits of the hemoglobin target range applied in practice has increased since our study was initiated, as is suggested by a trend toward greater numbers of patients with hemoglobin levels ≥12 g/dL since 1997 [29], this may impact on overall hemoglobin variability. A report from Richardson, Bartlett, and Will [30] would suggest that anemia management practices aimed at higher hemoglobin targets is likely to be associated with increased hemoglobin variability. Comparing a protocol with a ceiling value of 13 g/dL and another with a ceiling value of 12 g/dL (above which epoetin doses were decreased), the SD (1-month averages) was higher for the group whose ceiling for epoetin therapy was 13 g/dL (2.07) versus the group whose ceiling was 12 g/dL (1.37) [30].

In contrast, Lacson, Ofsthun, and Lazarus [26] found that despite an increase in mean hemoglobin levels between 1995 and 2000, overall hemoglobin variability as measured by the population SD around the mean, remained steady at 1.3 to 1.5 g/dL. Also, in a summary of annual data from the ESRD Clinical Performance Measures Project, Wish [31] showed that, although the mean hemoglobin and percent of patients with hemoglobin ≥11 g/dL increased between 1997 and 2001, the hemoglobin SD varied only between 1.22 and 1.29 without a consistent trend during this period.

Our study included a small sample of the entire United States dialysis population, and it is possible that in a much larger sample less hemoglobin variability would be encountered. Nonetheless, our findings are consistent with those in reports described above and elsewhere [27–29]. The percentage of patients in our study who were African American was about twice that in the United States dialysis population at the time our study was done [32]. Ours was not a random sample of the entire United States hemodialysis population and the demographic characteristics of our study likely reflect features of the study design (i.e., excluding units with fewer than 40 patients) and location of participating centers (i.e., urban and larger metropolitan areas). Race, however, was not correlated with hemoglobin variability in our analysis. Finally, given the nature of our study, detailed information about the specific anemia management practices at each dialysis facility, such as epoetin and iron dosing protocols, and assessment of the contribution to hemoglobin assay variability on our overall findings are not available. In the study of Lacson, Ofsthun, and Lazarus [26], though, hemoglobin interassay variability amounted to a SD effect of only 0.11 to 0.16 g/dL at a hemoglobin level of 12 g/dL and the effect of hemoglobin testing variability on overall hemoglobin variability was suggested to be less than 0.3 g/dL for a 3-month rolling average.

A major strength of our study is that our analysis of complete data from nearly 1000 patients is derived from dialysis facilities across the country of various sizes and types, rather than from a single for-profit dialysis chain, region, or network, thus perhaps providing a more widespread view of hemoglobin variability across different dialysis settings and in response to various anemia management practices. Although we do not have the ability to analyze hemoglobin variability related to use of different hemoglobin assays among centers in our study, the fact that our data are derived from a variety of clinical laboratories using various hemoglobin assays should enhance the generalizability of our findings to the broad population of hemodialysis patients. Another strength of our study is that our analysis was confined to hemodialysis patients only, evaluated hemoglobin and other anemia-related parameters over an extended 15-month period, and analyzed hemoglobin variability using single-month data as well as rolling averages over periods of 2 to 6 months.

While single-month hemoglobin values are of obvious importance in the month-to-month monitoring and management of individual patients, extending the rolling average hemoglobin interval from 3 to 6 months appears to provide a more clinically applicable measure of mainte-
nance anemia management outcomes and avoids clinical variability inherent with the use of single-month values. The NKF-K/DOQI recommended hemoglobin range appears to be too narrow in clinical practice and for quality assurance and reimbursement purposes. Even if rolling average periods of 6 months are considered, a 1.1 g/dL range (similar to the NKF-K/DOQI range) included fewer than 50% of patients. In our study, a 2- to 3-month rolling average range of 2.4 g/dL, virtually identical to that observed in the study of Lacson, Ofsthun, and Lazarus [26], encompassed over 67% of patients. Use of extended rolling averages would likely create less urgency in maintaining patients within a specific hemoglobin range each month; lessen the impulse to frequently adjust epoetin doses; and create a broader, more stable, assessment of anemia status. As a quality assurance monitor, use of 3- to 6-month rolling averages is also likely to provide assessments that are more meaningful than use of single-month values. It is not known what if any economic impact, either beneficial or detrimental, on payors or dialysis providers would result from a broadening of the target hemoglobin range.

There is increasing evidence that there are clinical benefits to maintaining higher hemoglobin values, even approaching the normal range [5, 6, 33–36], but there is also concern about the potential risks of such therapy [37]. As an alternative to the currently defined narrow NKF-K/DOQI target range of 11.0 to 12.0 g/dL (hematocrit target of 33% to 36%), a more practical approach that would likely optimize patient care and clinical outcomes might be to adopt a goal of maintaining all single-month hemoglobin values ≥11 g/dL (hematocrit ≥33%) similar to the European Best Practices Guideline recommendation [38] but with use of a 3- or 4-month rolling average range that encompasses at least 80% of patient hemoglobin values for quality assurance and anemia protocol management purposes. Based on our data, this would necessitate a hemoglobin range of at least 2.5 g/dL. This, or any other recommended approach, will require appropriate testing for clinical outcomes and cost-benefit assessment.

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