Hemoglobin Level Variability: Associations with Comorbidity, Intercurrent Events, and Hospitalizations

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National payment policies target a hemoglobin range of 11 to 12.5 g/dl for patients with ESRD. However, clinical complications and provider practices may contribute to wide fluctuations over time. This study evaluated the frequency with which patients maintain stable hemoglobin levels below, within, and above the Centers for Medicare & Medicaid Services target range and assessed patterns of hemoglobin level change that resulted in large fluctuations across the target range during a 6-mo period. All hemodialysis patients who survived the first 6 mo of 2003, had Medicare as primary payer, and had Medicare outpatient erythropoietin claims in each of the first 6 mo of 2003 (n = 152,846) were studied. Six patient groups were defined on the basis of patterns of hemoglobin level fluctuation: Consistently low (<11 g/dl), consistently target range (11 to 12.5 g/dl), consistently high (≥12.5 g/dl), low-amplitude fluctuation with low hemoglobin levels, low-amplitude fluctuation with high hemoglobin levels, and high-amplitude fluctuation. Only 10.3% of patients maintained stable hemoglobin levels during the 6 mo and only 6.5% in the target range. The consistently low group had the highest percentage of hospitalizations and the highest number of comorbid conditions. High-amplitude fluctuation was the most common pattern (39.5%), with hemoglobin levels falling below and rising above the target range during the 6-mo period. Hemoglobin levels in almost 90% of patients are in some degree of flux at any point in time, and the fluctuation is highly associated with clinical complications and provider practices.

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Anemia treatment has changed considerably since the introduction of epoetin alfa in June 1989. Initial clinical trials targeted hematocrit levels of 35%, but concerns over hypertension and seizures arose when levels increased by >4% per week (1). On the basis of these observations, the Food and Drug Administration approved epoetin alfa for clinical use, stipulating a target hematocrit range of 30 to 36% and including labeling instructions requiring dosage reduction when levels exceeded the upper end of the range. Initial Centers for Medicare & Medicaid Services (CMS) payment policy for epoetin treatment allowed a fixed $40 per administration, leading to some improvements in hematocrit levels but resulting in disparities across demographic groups. Later payment policies allowed $11, then $10, and now $9.76 per 1000 units of epoetin, with patients whose hematocrit levels exceed 37.5% audited for medical justification. These changes were associated with increasing hemoglobin levels, which reduced the disparities noted under the fixed payment policy. In 1997, CMS sought to reduce the number of patients with hematocrit levels above 36% by withholding epoetin treatment payments if the level exceeded 37.5% (Hematocrit Measurement Audit). Hematocrits across all levels subsequently declined, and CMS rescinded the policy (2).

Also in 1997, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) developed clinical practice guidelines for anemia, setting a target hematocrit level range of 33 to 36% (hemoglobin level 11 to 12 g/dl) for patients with ESRD (3). CMS continued to require medical justification for epoetin treatment when hematocrit levels exceeded 37.5%, with providers potentially audited for repayment. Providers thus may interrupt epoetin dosage to keep hemoglobin levels within the target range, which may lead to further fluctuations over time. Unfortunately, few data existed at the time the policy was implemented regarding fluctuation in hemoglobin levels or its cause or frequency of occurrence.

Subsequent observational studies have shown considerable fluctuation over time, with only 5% of patients staying in the target range during a 6-mo period (4). Additional research reported on the clinical conditions that are associated with persistent hemoglobin levels below the target range (5). The frequency with which patient hemoglobin levels fluctuate across the target range and the magnitude of change over time were reported recently by Fishbane and Berns (6), who described a phenomenon of hemoglobin levels cycling up and down, passing through the target range of 11 to 12.5 g/dl, yet the implications of this observation are unknown on a national level.

To characterize the extent of the fluctuations in hemoglobin levels and the related clinical circumstances, we studied the frequency with which patients maintain stable hemoglobin lev-

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els below, within, and above the target range of 11 to 12.5 g/dl. We also assessed patterns of hemoglobin level change that result in large fluctuations across the target range during a 6-mo period. This report summarizes the findings and provides a national view of the complexity of managing anemia correction to a specific target range.

Materials and Methods

The study population included all hemodialysis patients who survived the first 6 mo of 2003, had Medicare as primary payer, and had Medicare outpatient erythropoietin (EPO) claims in each of the first 6 mo of 2003 (n = 152,846). Hemoglobin levels were obtained from the EPO claims, the only source of these data, and classified as low (<11.0 g/dl), within target (11.0 to <12.5 g/dl), or high (≥12.5 g/dl) for each of the 6 mo. This classification system of three hemoglobin groups in each of 6 mo leads to 729 (3^6) possible patterns of hemoglobin level fluctuation during the 6-mo period.

To assess the frequency and the size of the fluctuations in hemoglobin levels over time, we defined six groups of patients on the basis of their overall pattern of fluctuation: Consistently low (all 6 mo with low hemoglobin levels), consistently within the target range (all 6 mo with target-range hemoglobin levels), consistently high (all 6 mo with high hemoglobin levels), low-amplitude fluctuation with low hemoglobin levels (LAL; all 6 mo with low or target-range hemoglobin levels), low-amplitude fluctuation with high hemoglobin levels (LAH; all 6 mo with target-range or high hemoglobin levels), and high-amplitude fluctuation (HA; low, target-range, and high hemoglobin levels within the 6-mo period).

International Classification of Diseases, Ninth Revision, Clinical Modification codes and *Current Procedural Terminology* codes were used to determine comorbid conditions from Medicare Part A institutional and Part B physician/supplier claims. A comorbid condition was regarded as present when Medicare Part A or Part B claims during the 6-mo study period so indicated. The following comorbid conditions were included: Atherosclerotic heart disease, congestive heart failure, dysrhythmia, other cardiac disease (including valvular disease), cerebrovascular accident/transient ischemic attack, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, gastrointestinal bleeding, and hepatic disease.

Hospital admissions and number of hospital days for the study period were obtained from the Medicare Inpatient Standard Analytical File. Hospitalization cause was determined from the principal *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code.

For a more complete description of the relationship between fluctuation pattern and hospitalizations and comorbidity, three logistic regression models were created, each adjusted for age, gender, and race, and each with fluctuation pattern as the primary independent variable of interest. The dependent variables for the three models were (*1*) hospitalization during the 6-mo study period, yes *versus* no; (*2*) at least one comorbid condition, yes *versus* no; and (*3*) infectious hospitalization, yes *versus* no.

Results

Distribution of monthly hemoglobin levels for the overall study population is presented in Figure 1, a cross-sectional, population-based view showing the percentage of patients who were in the low, target-range, and high hemoglobin level groups and remained stable across the 6-mo period. In contrast, Figure 2 presents patient-based views, showing the monthly means and SD of hemoglobin levels for patients who were classified as low, target-range, or high in each month of the study period. Panel 1 shows the data for patients who were classified in month 1; panel 2 shows the data for patients who were classified in month 2. The remaining panels show the data for patients who were classified in months 3 through 6. Within 1 mo, the mean hemoglobin level for each group begins to regress toward the population mean. After 6 mo, the mean hemoglobin level for each group is indistinguishable from the

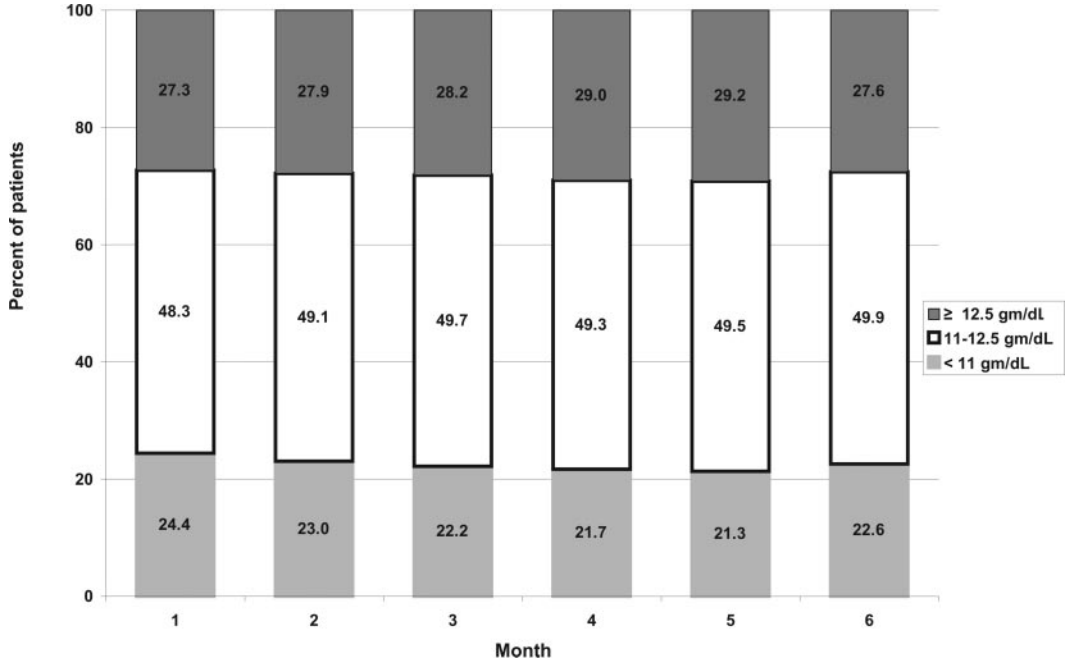

Figure 1. Distribution of monthly hemoglobin levels for the overall study population.

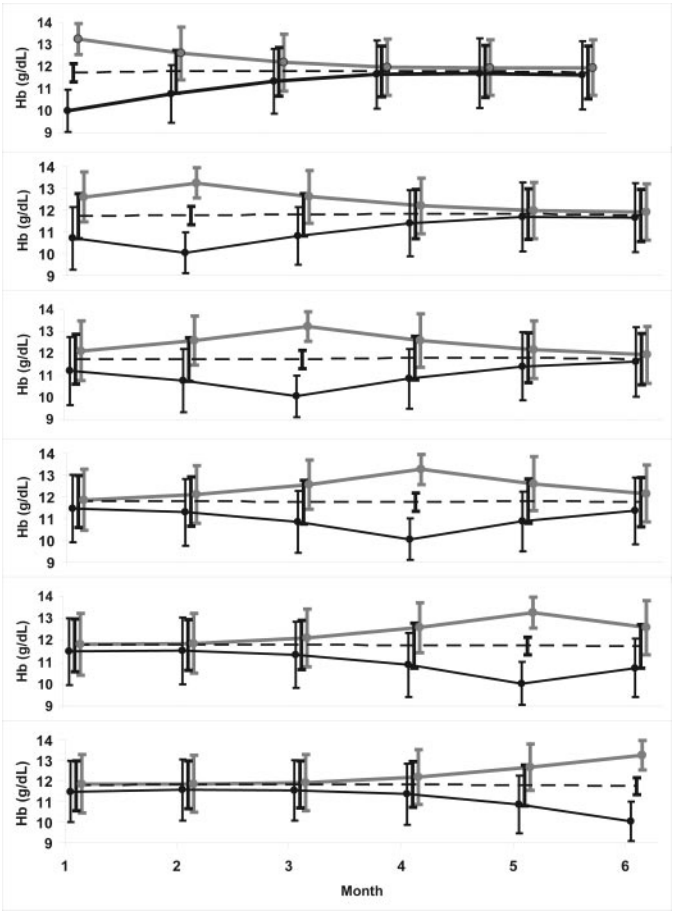

Figure 2. Monthly means and SD of hemoglobin levels for patients who were classified as low, target-range, or high. (Panel 1) Mean hemoglobin levels in each month of the study period for patients who were classified as low, target-range, or high in month 1. (Panel 2) Mean hemoglobin levels in each month of the study period for patients who were classified as low, mid-range, or high in month 2. The remaining panels show mean hemoglobin levels in each month of the study period for patients who were classified in months 3 through 6. Within 1 mo, the mean hemoglobin level for each group begins to regress toward the population mean. After 6 mo, the mean hemoglobin for each group is indistinguishable from the population mean. Hb, hemoglobin. Black line, low hemoglobin level, <11 g/dl; dashed line, target-range hemoglobin level, 11 to <12.5 g/dl; gray line, high hemoglobin level, ≥12.5 g/dl.

population mean. These observations are consistent with providers' attempting to move hemoglobin levels toward the recommended target range over time.

By tracking patients forward during the 6 mo or backward from the sixth through the first months, Figure 2 shows patient redistribution on the basis of fluctuating hemoglobin levels from month to month, with a high SD. Therefore, although population percentages in each group remain fairly constant over time, different patients make up the groups at any given time.

We observed 727 of the 729 possible patterns of hemoglobin level fluctuation in our study population. Table 1 shows the patient characteristics for the low, target-range, high, LAL, LAH, and HA hemoglobin level groups. Patients who were classified in the low (<11 g/dl; 1.8% of patients), target-range (11 to 12.5 g/dl; 6.5%), and high (≥12.5 g/dl; 2.0%) groups remained stable within their original hemoglobin level ranges during the 6-mo study period. These groups account for only 10.3% of the study population. Nearly 90% of patients showed some pattern of hemoglobin level fluctuation over time, as shown in Figure 3, a Pareto chart displaying percentages of patients in each group, ordered by decreasing percentage.

Patients who were classified in the LAL (21.3%) and LAH (28.9%) groups showed fluctuations in their hemoglobin levels near the lower and upper levels of the target range, such that their hemoglobin levels crossed one of the boundaries at 11 or 12.5 g/dl during the 6-mo period. Patients who were classified in the HA group showed large fluctuations in their hemoglobin levels, such that they crossed both the upper and the lower boundaries of the target range. This was the most common pattern (39.5%) of hemoglobin level fluctuation over time, with levels falling below or rising above the target range of 11 to <12.5 g/dl during the 6-mo period. The consistently low hemoglobin level group was younger and had the highest percentage of black patients. The HA group had the lowest percentage of men. Other characteristics were similar across groups.

Table 2 shows hospitalization and comorbidity results. Patients with persistently low hemoglobin levels during the study period represent 1.8% of the study population and had the highest percentage of hospital admissions, the highest percentage of admissions for infection, the longest hospital stays, and the highest number of comorbid conditions compared with other groups. The consistently target-range hemoglobin level group had the lowest percentage of admissions, the lowest percentage of admissions for infection, the shortest hospital stays, and the fewest comorbid conditions. The patterns were the same for numbers of hospital admissions (data not shown). We analyzed each of the 10 comorbid conditions separately, with consistent results across the groups (data not shown).

Figures 4 through 6 show results from logistic regression models relating fluctuation pattern to occurrence of hospitalizations (Figure 4), number of comorbidities (Figure 5), and occurrence of infectious hospitalizations (Figure 6). The patterns across the three figures are similar, showing that patients with six or more hospital days, with two or more comorbid conditions, or with an infectious hospitalization are considerably more likely to be in the consistently low group than in the target-range group. These patients also are more likely to be in the LAL or the HA group than in the target-range group. Owing to our large sample size, almost all findings are statistically significant.

Discussion

We determined that fluctuations in hemoglobin levels are very common, with almost 90% of patients having hemoglobin levels in some degree of flux at any point in time. Our detailed assessment of the possible patterns of hemoglobin level fluctuation during the 6-mo study period showed 729 possible pat-

Table 1. Patient characteristics by hemoglobin level fluctuation classification[a]

Characteristic	Hemoglobin					
	Low	Target	High	LAL	LAH	HA
% of total	1.8	6.5	2.0	21.3	28.9	39.5
Age						
mean	56.6	63.3	62.2	61.8	63.1	62.3
SD	16.2	14.6	14.9	15.2	14.9	15.4
Gender (%)						
male	53.1	53.7	57.1	50.8	52.7	48.9
female	46.9	46.3	42.9	49.2	47.3	51.1
Race (%)						
white	48.7	56.1	52.0	54.4	53.8	53.0
black	46.9	37.5	41.8	39.8	39.8	41.0
other race	4.3	6.4	6.3	5.9	6.5	6.0
Cause[b] (%)						
diabetes	32.7	42.3	41.5	42.1	42.7	42.8
hypertension	27.9	29.6	28.8	28.8	30.3	29.7
glomerulonephritis	13.9	12.2	12.9	12.6	11.5	11.4
other	25.5	15.9	16.8	16.5	15.5	16.1

[a]HA, high amplitude; LAH, low amplitude, high hemoglobin; LAL, low amplitude, low hemoglobin.
[b]Primary cause of renal failure; data from the ESRD Medical Evidence Report, Centers for Medicare & Medicaid form 2728.

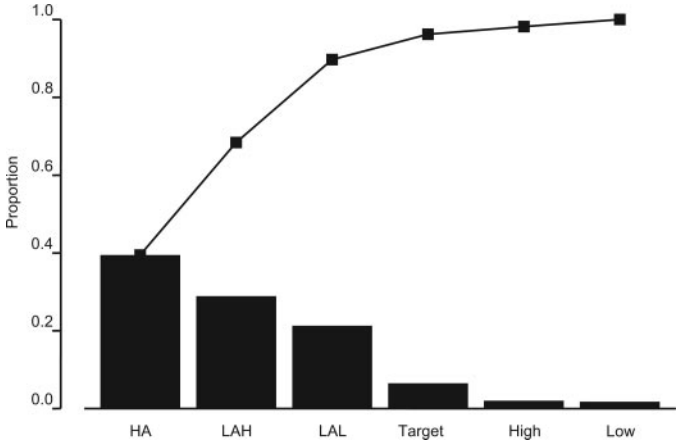

Figure 3. Pareto chart showing the percentage of patients in each hemoglobin level fluctuation group, sorted by decreasing proportion within each category. The line shows the cumulative proportion of patients. HA, high-amplitude fluctuation; LAH, low-amplitude fluctuation with high hemoglobin; LAL, low-amplitude fluctuation with low hemoglobin.

terns, and 727 are represented in the national data. The patterns of fluctuating hemoglobin levels over time were significantly associated with comorbidity and severity of disease as measured by hospitalizations, hospitalizations for infection, length of hospital stays, and number of comorbid conditions. Not unexpectedly, patients with persistently low hemoglobin levels had the highest degree of comorbidity and hospitalization, a finding that is consistent with earlier studies that reported the characteristics of individuals with persistently low hemoglobin levels (7). Surprisingly, however, the HA group, which had large fluctuations in hemoglobin levels, had degrees of comorbidity and hospitalization similar to those with hemoglobin levels near the lower boundary of the target range.

Clinical monitoring of hemoglobin levels traditionally has centered on a cross-sectional view of monthly hemoglobin data that are submitted to payers. On the basis of this approach, overall distribution of hemoglobin levels across the population under treatment seems to change very little (Figure 1). From this perspective, providers seem to be making little progress toward bringing patient hemoglobin levels into the K/DOQI target range. However, as Figure 2 shows, when the patients who were classified in the first month are followed over time, hemoglobin levels for the group regress toward the population mean, moving within the K/DOQI target range with large SD. When the patients who were classified at the end of the 6-mo study period are tracked backward to month 1, their hemoglobin levels also approached the population mean within the target range at the beginning of the study period. From this perspective, hemoglobin levels of patients with ESRD seem rarely to remain stable.

The patterns described in our study on a large-population level are similar to those described by Fishbane and Berns (6) as evidence of the cycling of patient hemoglobin levels over time. Fluctuation of hemoglobin levels seems to be a common clinical event and seems to be associated with comorbidity and infectious complications. Fishbane and Berns (6) suggested that adjusting epoetin doses when patient hemoglobin levels exceed the audit level of 12.5 g/dl may be a major source of the fluctuation of patients' hemoglobin levels once they reach that point. Our study did not use provider-level data; the impact of this and other provider practices should be assessed in detail on the basis of provider ownership status and its change over time.

Table 2. Hospitalization and comorbidity by hemoglobin level fluctuation classification[a]

Hemoglobin	Hospital Admission (%)	Admission for Infection (%)	Average LOS (d)	Average Comorbidity (*n*)
Low	69.2	29.5	12.7	2.4
Target	25.3	6.2	1.9	1.1
High	29.8	7.4	2.2	1.2
LAL	51.1	17.6	6.5	1.8
LAH	33.5	9.3	2.8	1.3
HA	54.0	17.7	6.4	1.8

[a]LOS, length of hospital stay.

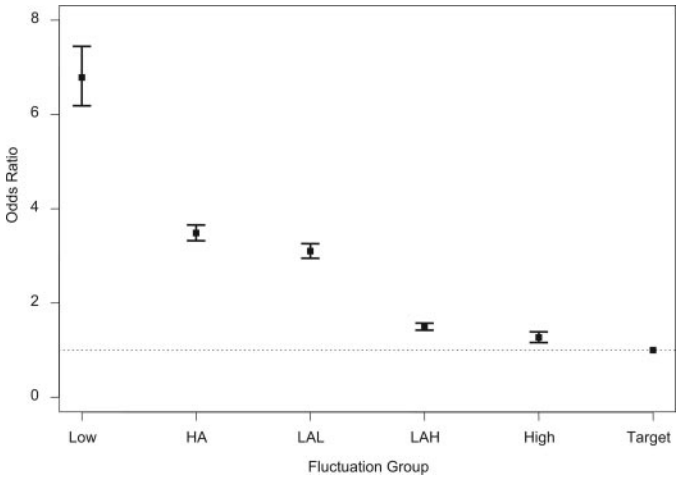

Figure 4. Logistic regression model showing relationship between hemoglobin level fluctuation group and hospitalization, yes *versus* no. All odds ratios (OR) are statistically significant.

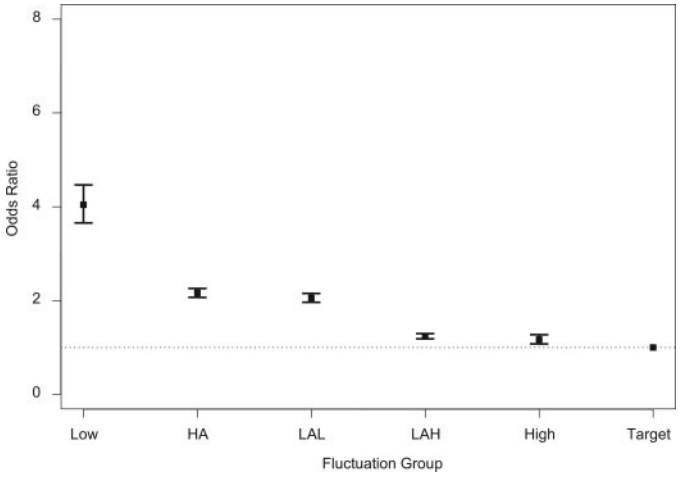

Figure 5. Logistic regression model showing relationship between hemoglobin level fluctuation group and number of comorbidities, 1 or more *versus* 0. All OR are statistically significant.

Although Fishbane and Berns (6) suggested provider practices as the main reason for the cycling of hemoglobin levels, their study also showed significant degrees of comorbidity and

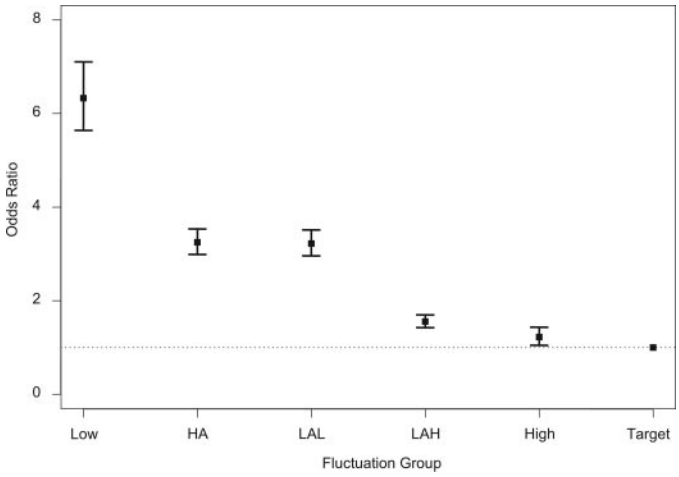

Figure 6. Logistic regression model showing relationship between hemoglobin level fluctuation group and infectious hospitalizations, yes *versus* no. All OR are statistically significant.

hospitalization, even though they assessed patients with fewer than 10 d of hospitalization during their study period. In contrast to their analyses, we found that comorbidity and hospitalization for infection play important roles as random events that may be outside the control of providers. Catheter infections, pneumonias, and gastrointestinal bleeding episodes all contribute to fluctuating hemoglobin levels and help to create the marked instability of hemoglobin levels over time. Preventing these clinical infectious events may be difficult, but attempts to do so could help to reduce both morbidity and the fluctuation of hemoglobin levels, yielding more cost-effective anemia treatment. The Fistula First program that was initiated by CMS promotes the reduction of dialysis catheter use and the attendant infectious complications and costly hospitalizations. Vaccinations for influenza and pneumococcal pneumonia potentially could reduce these complications. Unfortunately, there are few data to indicate that these measures will change the frequency of hemoglobin level fluctuations.

Our study has important limitations that should be considered. The data that are available for this large national assessment were from reported claims for epoetin treatment, which require the submission of the last hemoglobin level before the last epoetin dose of the billing period. Many providers assess hemoglobin levels weekly or every 2 wk, possibly affecting the

changes in epoetin dosages and subsequent hemoglobin levels and making the exact relationship of hemoglobin level to EPO dosage change difficult to determine. Clinical protocols by providers that address guidelines for adjustments to epoetin dosages may vary but are not reported on the CMS claims, making assessment of the effect of provider differences from this data set difficult. Similarity in results from our study, based on a large sample size, and from the Fishbane and Berns (6) study, based on all hemoglobin level data from a single provider, point toward the likelihood that the patterns noted would persist and may represent both provider dosing practices and morbidity factors.

Because EPO claims are the only source of hemoglobin level data, the impact of excluding patients with no claims during 1 or more months of the study period cannot be assessed fully. Although EPO doses may be held when patient hemoglobin levels are elevated, this tends to be a random event of a transient nature. Because some providers seem to dose even when levels are elevated, held doses may have a minor effect on the observations. Nearly 90% of the EPO-treated patients experienced major variability, suggesting the contribution of other patterns.

The impact of fluctuating patterns of hemoglobin levels on patient outcomes is unclear and should be assessed. The significant associations between the fluctuation patterns and the degree of morbidity and infectious complications suggest that the hemoglobin level data are highly confounded by provider practices and medical complications. The marked fluctuations in hemoglobin levels over time create substantial classification bias that changes over even a few months. The time-dependent nature of the hemoglobin level fluctuations and the frequent morbidity events make anemia-related outcome studies more complex than previously appreciated, such that simple Cox regression outcomes with fixed covariates may have substantial biases that are based on misclassification. More advanced time-dependent marginal structural models and structural nested models may be needed to address these complex biochemical and comorbidity relationships. Future analyses also should be carried out to define degrees of variability; differentiate more complex variability patterns and their effects on outcomes; identify clinician dosing adjustment practices; and focus on the major causes of variability, such as medical and surgical hospitalizations, infections, and gastrointestinal bleeding.

As of April 2006, CMS policy mandates a 25% reduction in EPO dosage for patients whose hemoglobin levels exceed 13 g/dl in any given month and reduces payment by 25% regardless of whether the dosage is reduced. The new payment policy likely will reduce EPO dosages for patients whose hemoglobin levels exceed 13 g/dl. However, whether the policy will reduce, increase, or have no effect on variability is unclear, and this should be evaluated as the data become available.

Overall, our study demonstrates that during a 6-mo period, hemoglobin levels in almost 90% of patients seem to be in flux across the K/DOQI target boundaries such that cross-sectional assessment of anemia management cannot give an accurate picture of anemia treatment. Forty percent of patients seem to have large fluctuations in hemoglobin levels, which may represent some type of cycling, intercurrent morbidity events, or overcorrection of low hemoglobin levels. The instability of patient hemoglobin levels may have significant implications in outcome studies that attempt to assess hemoglobin levels as they relate to morbidity, mortality, and cost. The exact relationship between provider practices in changing epoetin dosages and comorbidity events and patterns of fluctuation needs further investigation. At a minimum, anemia treatment seems to be very complex, and hemoglobin levels at any single point in time should be viewed cautiously because they are likely to change. Furthermore, hemoglobin levels that are averaged over time also may be inaccurate because the averages do not account for changing levels in almost 90% and large changes in 40% of the hemodialysis population. Investigators need to address these complex issues before any clarity can be brought to the relationship between anemia treatment and associated morbidity and mortality.

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References

1. Eschbach JW, Abdulhadi MH, Browne JK, Delano BG, Downing MR, Egrie JC, Evans RW, Friedman EA, Graber SE, Haley NR, *et al.*: Recombinant human erythropoietin in anemic patients with end-stage renal disease. Results of a phase III multicenter clinical trial. *Ann Intern Med* 111: 992–1000, 1989
2. Berns JS, Fishbane S, Elzein H, Lynn RI, Deoreo PB, Tharpe DL, Meisels IS: The effect of a change in epoetin alfa reimbursement policy on anemia outcomes in hemodialysis patients. *Hemodial Int* 9: 255–263, 2005
3. National Kidney Foundation: DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. *Am J Kidney Dis* 30[Suppl 3]: S194–S240, 1997
4. Lacson E Jr, Ofsthun N, Lazarus JM: Effect of variability in anemia management on hemoglobin outcomes in ESRD. *Am J Kidney Dis* 41: 111–124, 2003
5. Li S, Foley RN, Gilbertson DT, Liu J, Collins AJ: Clinical factors associated with achieving K/DOQI hemoglobin targets in hemodialysis patients. *Int Urol Nephrol* 35: 399–405, 2003
6. Fishbane S, Berns JS: Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. *Kidney Int* 68: 1337–1343, 2005
7. Kausz AT, Solid C, Pereira BJ, Collins AJ, St Peter W: Intractable anemia among hemodialysis patients: A sign of suboptimal management or a marker of disease? *Am J Kidney Dis* 45: 136–147, 2005