DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

National Institute of Diabetes and
Digestive and Kidney Diseases
Bethesda, Maryland 20892

June 22,2007

The Honorable F. Pete Stark
Chairman, Subcommittee on Health
Committee on Ways and Means
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

Thank you for your letter of June 18 regarding trends in dosing of erythropoiesis stimulating agents in the treatment of anemia associated with dialysis in patients with end-stage kidney disease. Your questions concern data presented in the 2006 Annual Data Report of the U.S. Renal Data System (USRDS). I have directed members of my staff with detailed knowledge of the USRDS to prepare the enclosed responses to your questions. The responses indicate that use of erythropoiesis stimulating agents has increased over the past 15 years and that patients undergoing dialysis display variation in their hemoglobin levels.

I welcome the opportunity to share information about NIDDK's research efforts with the Committee, and I hope that you find this information helpful.

Sincerely,

Griffin P. Rodgers, M.D., M.A.C.P.
Director

Summary of NIDDK Responses to Questions on the United States Renal Data System

1. How are patients distributed by mean monthly hemoglobin (USRDS Chart 5.27)? What percentage of patients exceed the recommended maximum hemoglobin (Hb) of 12 grams per deciliter (g/dl)? What percentage of patients are below Hb of 10 g/dl. How have those trends changed over time?

In general, the percentage of patients with hemoglobin levels lower than 10 g/dl has declined, while the fraction of patients with hemoglobin levels above 12 g/dl has increased over time. By 2005, over half of patients had hemoglobin levels of 12.0 g/dl or greater. About 6 percent were below 10 g/dl.

2. How has mean EPO dose per week changed over time (USRDS Chart 5.30)?

Between 1991 and 2005, the average weekly dose of EPO more than doubled.

3. Page 198 of the 2006 USRDS Annual Report states, "We assessed provider practice patterns on dosing changes and found that DaVita tends to adjust the least and DCI the most when hemoglobin levels exceed 12–13 g/dl." How was this assessment conducted? What information was reviewed? Did NIH review anemia management guidelines? In what manner does DaVita make adjustments as compared to DCI? How do the other chains, such as Fresenius, compare?

This assessment examined patient months in which hemoglobin levels exceeded 12 g/dl, and determined the frequency with which such patients subsequently had their EPO dose reduced by at least 12.5 percent. Dialysis providers made appropriate dose reductions in about half of cases; frequency ranged from 55.2 percent for Gambro to 44.3 percent for Davita.

4. How does patient hemoglobin vary across dialysis centers (USRDS chart 10.21)? Which chains have the most patients exceeding Hb of 12 g/dl? Which chains have the largest proportion of patients within the target range of 10 to 12 g/dl?

The percentage of patients whose hemoglobin exceeds 12 g/dl varies widely across dialysis providers, ranging from 65 percent (Davita) to 20 percent (DCI) The chains with the largest proportion of patients within the target range of 10–12 g/dl are DCI (65 percent) and National Nephrology Associates (54 percent).

5. What are the trends for Medicare spending on erythropoiesis stimulating agents (ESAs) in recent year (USRDS Chart 11.26)? How does growth in spending on ESAs compare to spending on other parts of ESRD care? How do ESA costs per member month vary by dialysis chain?

The cost of services associated with dialysis increased by 72 percent between 1991 and 2004. The two primary components of this cost are the dialysis itself and erythropoiesis stimulating agents (ESA). Over this time period, dialysis costs increased 17 percent and ESA costs increased 235 percent. ESA costs by chain range from $654 per patient month for Gambro to $516 for hospital-based dialysis.

NIDDK Responses to Questions on the United States Renal Data System

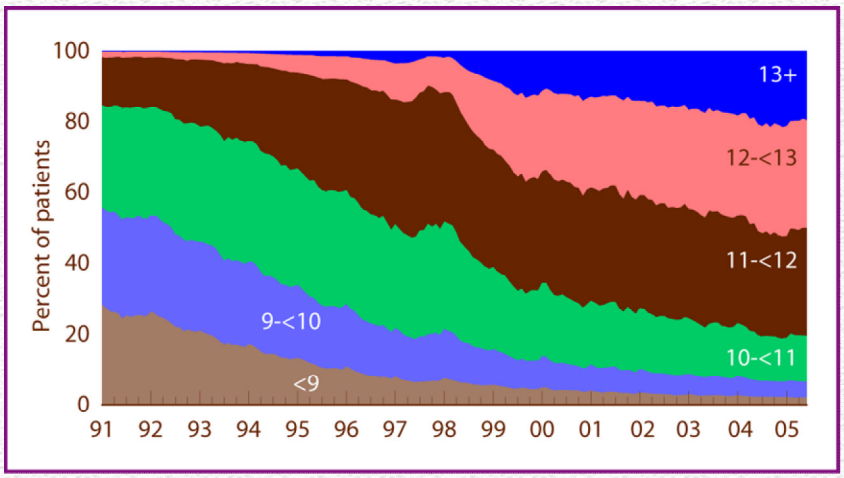
1. How are patients distributed by mean monthly hemoglobin (USRDS Chart 5.27)? What percentage of patients exceed the recommended maximum hemoglobin (Hb) of 12 grams per deciliter (g/dl)? What percentage of patients are below Hb of 10 g/dl. How have those trends changed over time?

Figure 5.27, shown on the next page, is from the 2006 Annual Data Report of the United States Renal Data System (USRDS). It shows the 15 year trend in average hemoglobin levels of kidney failure patients on hemodialysis whose treatment is reimbursed through Medicare. Normal hemoglobin values in adults range from 13.5 to 16.5 grams per deciliter (g/dl) of blood for men and 12 to 15.5 g/dl for women. Based on end-of-year figures for each year from 1991 to 2005, the following trends are displayed. In 1991, 52.4 percent of patients had a hemoglobin level of less than 10 g/dl, 16.4 percent of patients had achieved the target hemoglobin level of 11.0 g/dl, and 1.9 percent had a level of 12.0 or greater. By 2005, the percentage of patients with a hemoglobin level below 10.0 dropped to 6.4 percent, 30.5 percent of patients achieved the target hemoglobin level of 11.0, and the percent of patients with a level of 12.0 or greater increased to 50.1 percent.

The USRDS is a national data system that collects, analyzes, and distributes information about end-stage renal disease (ESRD) in the United States. The USRDS is funded directly by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in conjunction with the Centers for Medicare and Medicaid Services (CMS).

Patient distribution, by mean monthly hemoglobin (g/dl)

Figure 5.27



period prevalent dialysis patients with EPO claims; monthly hemoglobin includes all claims with a hematocrit value between 10 & 50; weekly EPO dose includes all claims for patients with an average number of administrations per month of ≤20. EPO doses prior to 2005 are adjusted for inpatient days.

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Figure 5.27

2. How has mean EPO dose per week changed over time (USRDS Chart 5.30)?

Figure 5.30, shown on the next page (top), from the 2006 Annual Data Report of the USRDS, shows the EPO dosing and hemoglobin experience of new patients during the 6 months following the initiation of dialysis. These analyses are based on billing data, therefore, only patients for whom Medicare was the primary payer are included.

The left panel shows EPO dosing during the first 6 months following initiation of hemodialysis by year. For patients who started dialysis in 2000, the average weekly EPO dose in the first month was 12,298 units. This increased to 19,392 units in the second month and gradually decreased to 17,055 by the sixth month. The same pattern is seen in 2002 and 2004, although the EPO dose levels are higher in these years. The first, second, and sixth month weekly doses were 14,377, 22,738, and 18,495 units in 2002, and 16,783, 21,086, and 20,801 units in 2004. The maximum weekly dose occurred in the third month of 2004 and was 25,635 units.

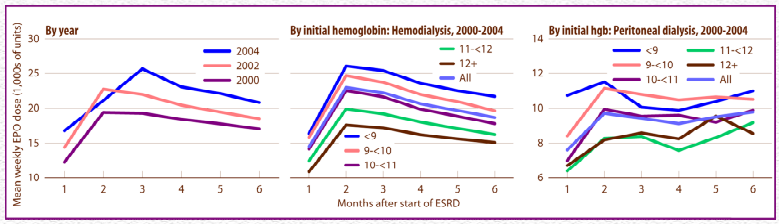
The center panel shows EPO dosing as it relates to the patients' hemoglobin levels at the initiation of hemodialysis. Patients with the lowest initial hemoglobin levels had the highest levels of EPO dosing. For example, patients with less than 9 g/dl had first, second, and sixth month average EPO doses of 16,383, 26,006, and 21,672 units. EPO dose levels with patients with initial hemoglobin levels of greater than 12 g/dl were 10,858, 17,603, and 15,092 over the same time period.

The right panel shows EPO dosing as it relates to the patients' hemoglobin levels at the initiation of peritoneal dialysis. EPO dosing levels were approximately one-half the amount as for hemodialysis patients. As with hemodialysis patients, higher doses were given to those patients with the lowest starting hemoglobin levels.

Figure 5.28, shown on the next page (bottom), illustrates the overall trend in average weekly dose of EPO from 1991 to 2005. In 1991, the average weekly dose was 8,184 units. By 2005, the weekly dose doubled to 18,673 units.

Anemia treatment in incident dialysis patients, by modality & initial hemoglobin level: mean EPO dose per week

Figure 5.30



incident dialysis patients with a first EPO claim within the first 30 days of the ESRD start date & at least one EPO claim in each of the first six months. Graphs by modality: 2000–2004 combined. Hemoglobin group determined by the patient's hematocrit on the Medical Evidence form. EPO doses adjusted for inpatient days.

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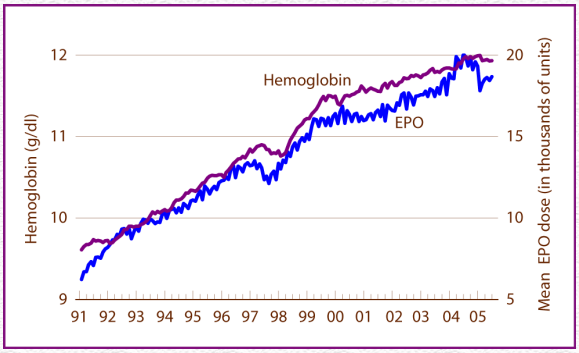
Figure 5.30

Mean monthly hemoglobin & mean EPO dose per week

Figure 5.28



period prevalent dialysis patients with EPO claims; monthly hemoglobin includes all claims with a hematocrit value between 10 & 50; weekly EPO dose includes all claims for patients with an average number of administrations per month of ≤20. EPO doses prior to 2005 are adjusted for inpatient days.

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Figure 5.28

3. Page 198 of the 2006 USRDS Annual Report states, "We assessed provider practice patterns on dosing changes and found that DaVita tends to adjust the least and DCI the most when hemoglobin levels exceed 12–13 g/dl." How was this assessment conducted? What information was reviewed? Did NIH review anemia management guidelines? In what manner does DaVita make adjustments as compared to DCI? How do the other chains, such as Fresenius, compare?

It is expected that a reduction in EPO dose should occur following a month in which the hemoglobin level exceeds the K/DOQI (Kidney Disease Outcomes Quality Initiative) upper limit of the target range—12 g/dl. The manufacturer recommends reducing the dose of EPO by 25 percent when hemoglobin is rising and approaching this limit. Dose and hemoglobin data used here—derived from the Medicare billing data—contain only monthly detail, and because dose adjustments can occur at any time during a given month, a monthly dose reduction of 12.5 percent was used to define an appropriate response. For each month in which an EPO claim reported hemoglobin exceeded 12 g/dl, the following month's EPO claim was examined for a dose reduction of at least 12.5 percent. If the reduction was found, this was judged to be an appropriate response.

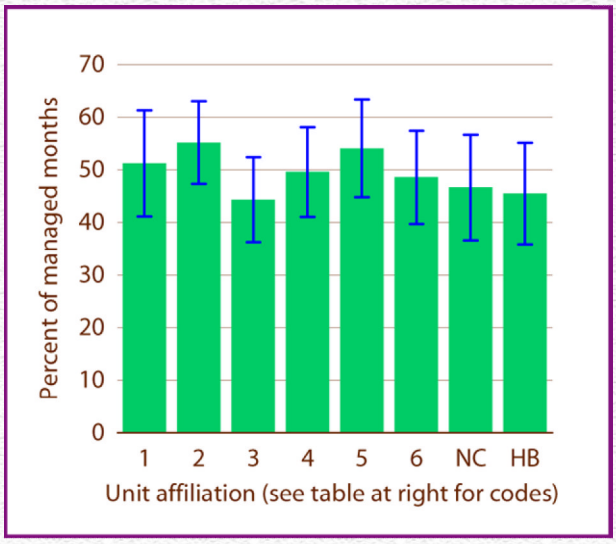
Based on the definition above, about 50 percent of all potential response months resulted in an appropriated dose reduction. As shown in Figure 10.16, from the 2006 USRDS Annual Data Report, the results by chain affiliation were as follows:

- Gambro – 55.2 percent
- DCI – 54.1 percent
- Fresenius – 51.1 percent
- Renal Care Group – 49.5 percent
- National Nephrology Associates – 48.6 percent
- Non chain units – 46.6 percent
- Hospital based units – 45.5 percent
- DaVita – 44.3 percent

Because this analysis was based only on observational billing data, it is not possible to determine the manner, or process, by which adjustments are made. The enclosed peer reviewed version of this analysis was published in the January issue of the *American Journal of Kidney Diseases*. The citation for this analysis is as follows: Collins AJ, Ebben JP, and Gilbertson DT. EPO Adjustments in Patients with elevated Hemoglobin Levels: Provider Practice Patterns Compared with Recommended Practice Guidelines. *Am. J. Kidney Dis*. 49:135–142, 2007.

Average managed months with 12.5% EPO dose reduction

Figure 10.16



Chain 1 · Fresenius
Chain 2 · Gambro
Chain 3 · DaVita
Chain 4 · Renal Care Group
Chain 5 · Dialysis Clinics, Inc.
Chain 6 · Nat'l Nephrology Assoc.
NC · Non-chain units
HB · Hospital-based units
U · Unknown

EPO-treated dialysis patients prevalent on January 1, 2004; includes all EPO claims for the population in calendar year 2004.

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Figure 10.16

4. How does patient hemoglobin vary across dialysis centers (USRDS chart 10.21)? Which chains have the most patients exceeding Hb of 12 g/dl? Which chains have the largest proportion of patients within the target range of 10 to 12 g/dl?

Figure 10.21 from the USRDS 2006 Annual Data Report shows the distribution of patients at various hemoglobin levels by chain. In descending order of frequency, chains have the following percent of patient months greater than 12 g/dl:

- DaVita – 65.1 percent
- Gambro – 50.9 percent
- Renal Care Group – 47.3 percent
- Fresenius – 46.0 percent
- Hospital based – 43.1 percent
- Non chain – 42.4 percent
- National Nephrology Associates – 33.4 percent
- DCI – 20.3 percent.

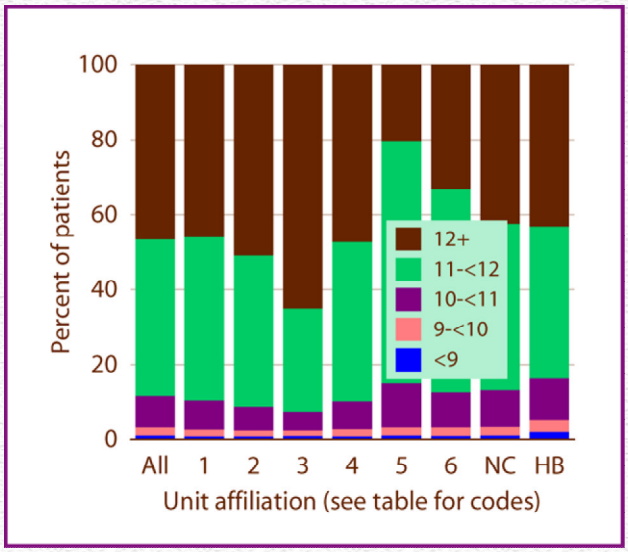
In descending order of frequency, chains have the following percent of patient months in the target range of 10 to 12 g/dl:

- DCI – 64.8 percent
- National Nephrology Associates – 54.1 percent
- Non chain – 44.4 percent
- Fresenius – 43.6 percent
- Renal Care Group – 42.5 percent
- Hospital based – 40.6 percent
- Gambro – 40.3 percent
- DaVita – 27.5 percent.

These data represent aggregated monthly data. Most patients will be measured more than once, and some as many as 12 times. A patient could fall into one category for a few months, and one or more hemoglobin levels in other months. Therefore, these averages could be more accurately termed "patient months" of therapy. The data are self-weighting; that is, a patient with 12 months of hemoglobin data will contribute 12 data points to the final assessment, whereas a patient with only 3 months of data will contribute only 3 data points.

Patient distribution by hemoglobin & chain affiliation, 2004

Figure 10.21



Chain 1 · Fresenius
Chain 2 · Gambro
Chain 3 · DaVita
Chain 4 · Renal Care Group
Chain 5 · Dialysis Clinics, Inc.
Chain 6 · Nat'l Nephrology Assoc.
NC · Non-chain units
HB · Hospital-based units
U · Unknown

Includes only EPO-treated patients; mean hemoglobin represents the average hemoglobin value for the year across all patients.

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Figure 10.21

5. What are the trends for Medicare spending on erythropoiesis stimulating agents (ESAs) in recent year (USRDS Chart 11.26)? How does growth in spending on ESAs compare to spending on other parts of ESRD care? How do ESA costs per member month vary by dialysis chain?

Services provided as part of a dialysis session include dialysis, ESAs, intravenous iron, intravenous vitamin D, other injectibles, and laboratory procedures otherwise covered by the composite rate. In 1991 these services averaged $1,244 per patient month. By 2004, this had increased by 72 percent to $2,134. The two major cost components of the dialysis session are dialysis and ESA. Dialysis increased by 17 percent, from $970 to $1,135, whereas ESAs increased by 235 percent, from $173 to $580. ESAs accounted for 14 percent of dialysis-related costs in 1991 and 27 percent in 2004.

Medicare expenditures for ESAs per patient month by chain affiliation are as follows (in descending order), and are also illustrated in Figure 11.26 (next page, top panel).

- Gambro – $654
- Renal Care Group – $606
- DaVita – $588
- Fresenius – $576
- DCI and independents – $550
- National Nephrology Associates – $543
- Hospital based – $516

More detail is provided in figure 11.28 (next page, bottom panel).

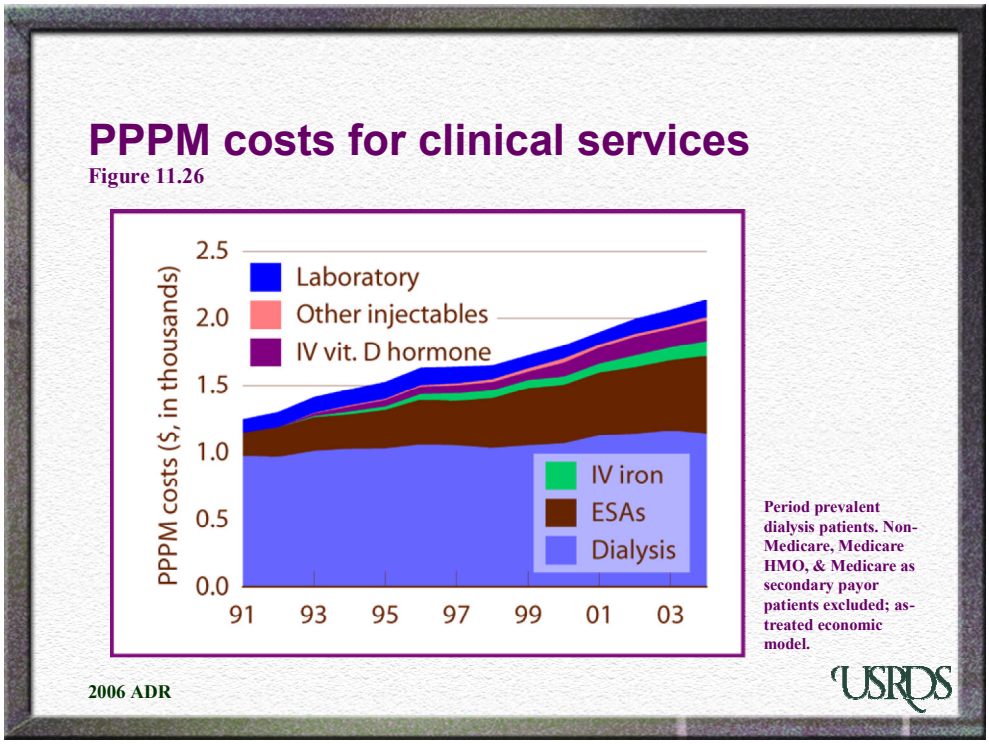

Figure 11.26

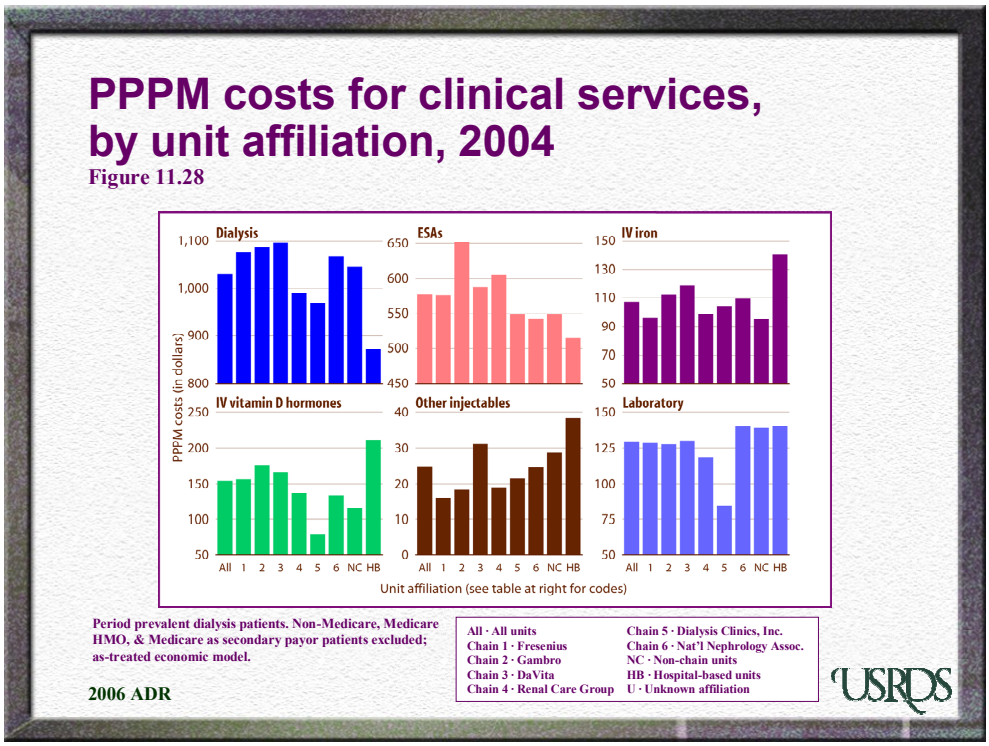

Figure 11.28

EPO Adjustments in Patients With Elevated Hemoglobin Levels: Provider Practice Patterns Compared With Recommended Practice Guidelines

Allan J. Collins, MD, FACP, James P. Ebben, BS, and David T. Gilbertson, PhD

Background: This study investigates provider practices regarding recombinant human erythropoietin (rHuEPO) dose when patient hemoglobin levels exceeded National Kidney Foundation–Dialysis Outcomes Quality Initiative target levels and reached 13 g/dL or greater (≥130 g/L).

Methods: The study population (N = 167,796) was hemodialysis patients prevalent on January 1, 2003, who were on renal replacement therapy at least 90 days with Medicare as primary payer and rHuEPO claims in 2 or more consecutive months. Patient characteristics were obtained from the Centers for Medicare & Medicaid Services (CMS) Medical Evidence Report, and comorbid conditions were determined from Medicare claims. Providers and rHuEPO claims were linked by using CMS-assigned provider numbers and the CMS Annual End-Stage Renal Disease Facility Survey. Between-provider differences in patient characteristics were examined by using chi-square test, and provider effect on appropriate response, by using logistic regression.

Results: DaVita's percentage of monthly claims for patients with hemoglobin levels of 13 g/dL or greater (≥130 g/L; 16.7%) and mean monthly rHuEPO dose (54,299 units) were highest. Dialysis Clinic Inc's percentage of such claims (2.0%) and mean monthly dose (38,687 units) were lowest. Dialysis Clinic Inc, Fresenius, and Renal Care Group had the highest percentage of recommended dose adjustments (mean, 70% of units); hospital-based units had the lowest (59%). By adjusted odds ratio, adjustments were 20% more likely for Dialysis Clinic Inc, Fresenius, and Renal Care Group compared with DaVita, National Nephrology Associates, hospital-based units, and independents (17% to 28% less likely).

Conclusion: rHuEPO dose reduction practices are dependent on specific dialysis providers and whether units are hospital based or independent.

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INDEX WORDS: Hematocrit; hemodialysis (HD); hemoglobin; recombinant human erythropoietin.

The introduction of recombinant human erythropoietin (rHuEPO) into clinical practice for the treatment of anemia related to end-stage renal disease (ESRD) led to substantial improvements in hemoglobin levels.[1,2] The dramatic increase in mean hemoglobin levels from the early 1990s to 2003 is paralleled by similar increases in rHuEPO doses and iron management.[3]

Target hemoglobin levels became an important aspect of care in autumn 1997, with the introduction of clinical practice guidelines by the National Kidney Foundation under its Dialysis Outcomes Quality Initiative. These guidelines, which were developed from the US Food and Drug Administration (FDA) labeling indication for epoetin, intervention trials, and expert opinion, suggested a target hemoglobin level of 11.0 to 12.0 g/dL (110 to 120 g/L) with rHuEPO treatment.[4] Providers' ability to maintain hemoglobin levels within the target range has been a matter of concern, given natural variability and other clinical factors that interfere with rHuEPO effectiveness.[5,6] Centers for Medicare & Medicaid Services (CMS) payment policies requiring medical justification for rHuEPO treatment when hematocrit levels exceeded 37.5%, with possible auditing for repayment, also may have contributed to variability. Cross-sectional data gathered

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monthly indicate that approximately 30% of patients have hemoglobin levels less than 11 g/dL (<110 g/L), 36% have levels between 11 and 12 g/dL (110 to 120 g/L), and the remaining third have hemoglobin levels greater than 12 g/dL (>120 g/L). Although this overall distribution appears to be consistent month to month, few patients remain within a particular group, such that by year end, only 5% are still in their original groups.[5,6]

The increasing percentage of patients with hemoglobin levels exceeding the current National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (KDOQI) target level of 12 g/dL (120 g/L) has been accompanied by a decreased percentage of patients with hemoglobin levels less than 11 g/dL (<110 g/L).[7] These developments appear to be the result of many factors, including concurrent illnesses, fluid overload leading to hemodilution, and rHuEPO hyporesponsiveness. However, as reported by the US Renal Data System (see *Annual Data Report* chapters on providers and economic costs),[3] there is considerable variation among dialysis providers in the distribution of patient hemoglobin levels. The increasing percentage of patients with hematocrits greater than 39% has caused concern because findings in at least 1 clinical trial suggested that high hematocrits (close to 42%) may constitute a risk for vascular access thrombosis and potentially increased mortality.[8] The recommended hemoglobin level range was defined on the basis of clinical trials suggesting safety at lower levels, but providers may not always decrease doses accordingly. Lack of attention to these targets, particularly at the upper end of the range, may lead to overuse of rHuEPO, driving hemoglobin to higher levels and overshooting the target range.

Recently, a new policy for rHuEPO use was implemented by the CMS.[9] It requires reduction in payment for rHuEPO doses for patients with hematocrits of 39% or greater. It is unclear how frequently providers adjust doses and whether there are differences across large groups. In this study, we investigate provider practice patterns related to rHuEPO dose and its adjustment when patient hemoglobin levels were at least 13 g/dL (130 g/L), a level consistent with CMS monitoring policy for use by fiscal intermediaries.

METHODS

The study population (N = 167,796) consisted of hemodialysis patients prevalent on January 1, 2003, who had been receiving renal replacement therapy for at least 90 days as of January 1, 2003; had Medicare as primary payer; and had rHuEPO claims in at least 2 consecutive months. Patient characteristics (age, sex, race, primary cause of renal failure, and dialysis vintage) were obtained from the CMS Medical Evidence Report (CMS-2728). Comorbid conditions were determined from Medicare Part A institutional and Part B physician/supplier claims, using *International Classification of Diseases, Ninth Revision, Clinical Modification,* codes according to a previously described method.[10] Conditions characterized included atherosclerotic heart disease, congestive heart failure, cardiac arrhythmia, other cardiac disease, cerebrovascular accident/transient ischemic attack, peripheral vascular disease, chronic obstructive pulmonary disease, cancer (including melanoma, but not skin cancer), liver disease, and gastrointestinal bleeding.

All rHuEPO claims for the study population for 2003 were analyzed to characterize anemia management, with specific attention to claims with a reported hemoglobin level of at least 13 g/dL (130 g/L). For each such claim, the rHuEPO dose was compared with the dose reported on the rHuEPO claim for the next month. To reduce the potential for incomplete dosing information, only claims for months in which the patient was not hospitalized were considered. KDOQI guidelines and the FDA-approved manufacturer's recommendations for anemia management call for a dose reduction of 25% for patients with a hemoglobin level of at least 12 g/dL (120 g/L). Recognizing the difficulty maintaining levels at the upper end of the recommended range (12 g/dL [120 g/L]) without exceeding it and based on the new CMS payment policy, we used a cutoff point for dose reduction 1 g/dL greater than the recommended level. Because claims data generally yield rHuEPO dosing information for 1 claim per month, we could detect dosage changes only from one month to the next, but the dose could have changed at any time during the month. To accommodate this imprecision, we classified a month-to-month dose reduction of one half the guideline (ie, 12.5% reduction) as an appropriate response to a hemoglobin level of at least 13 g/dL (130 g/L).

Using the CMS-assigned provider number included on the rHuEPO claim and the CMS Annual ESRD Facility Survey, rHuEPO claims were linked to individual dialysis providers, which were analyzed by chain (DaVita, Dialysis Clinic Inc, Fresenius, Gambro, National Nephrology Associates, and Renal Care Group). Providers not part of a chain were classified as hospital based or independent, defined from the CMS facility survey. If CMS identified a unit as hospital based, we classified it as hospital based. If CMS identified a unit as freestanding and it was not a part of 1 of the major chains named, we classified it as independent. Provider numbers that could not be linked to ESRD Facility Survey data were classified as "unknown affiliation." Providers with fewer than 10 qualifying rHuEPO claims were excluded from analysis.

For each provider, a measure of anemia management was calculated as the number of appropriate responses (rHuEPO

dose reduction ≥ 12.5% in the month after a reported hemoglobin level of at least 13 g/dL [130 g/L]) divided by the number of claims with a reported hemoglobin level of at least 13 g/dL (130 g/L), for which an rHuEPO claim was present for the following month and the patient had no hospital days in either month. Results for individual providers were aggregated into the provider classifications described. Chi-square tests were used to examine differences in patient demographics and comorbid conditions between providers. A logistic regression model was used to examine the effect of provider on appropriate response (1 or 0), adjusted for patient age, sex, race, primary cause of renal failure, and 10 comorbid conditions.

RESULTS

As listed in Table 1, patient characteristics generally were consistent across provider groups, with some variation in racial mix. Statistical differences were not clinically significant because recommendations are irrespective of demographic variables. As listed in Table 2, comorbidity was very similar among provider groups; statistical differences among comorbid conditions were not clinically significant, with the possible exception of liver disease, for which values varied widely among providers. For each provider, mean rHuEPO dose in response to a reported hemoglobin level of at least 13 g/dL (130 g/L) was as follows: DaVita, 54,299 U/mo; independent, 49,634 U/mo; hospital based, 49,598 U/mo; Fresenius, 49,407 U/mo; Renal Care Group, 48,772 U/mo; Gambro, 42,629 U/mo; National Nephrology Associates, 41,992 U/mo; and Dialysis Clinic Inc, 38,687 U/mo. Each provider was significantly different from every other provider with the following exceptions: Fresenius versus Renal Care Group, Fresenius versus hospital based, Gambro versus National Nephrology Associates, and hospital based versus independent.

Table 3 lists the total number of qualifying rHuEPO claims and the percentage of claims with a reported hemoglobin level of at least 13 g/dL (130 g/L). DaVita units had the highest percentage (16.7%) of claims with high hemoglobin levels, and Dialysis Clinic Inc units had the lowest percentage (2.0%).

Figure 1 shows means and SDs of the anemia management measure (percentage of managed months) for the provider groups. There was considerable variation among provider groups; Dialysis Clinic Inc, Fresenius, and Renal Care Group had an average anemia management measure of more than 70% and hospital-based units had a measure of 59%. Error bars, representing SDs of the percentages of managed months, show the range of variation.

Figure 2 shows the distribution of the anemia management measure for individual units within each provider group. The width of the frequency distribution curves shows the variation. The peak of the curve represents the approximate mean, and the width represents the SD. For example, the curve for Renal Care Group peaks sharply at 70% to 80%, indicating close adherence to the guidelines, whereas the curve for Dialysis Clinic Inc has a very broad peak, stretching from 60% to 70% to more than 90%, indicating a more varied adherence.

Figure 3 shows results of logistic regression analysis of the anemia management measure. In response to high hemoglobin levels, rHuEPO dose reductions were 20% more likely to occur in Dialysis Clinic Inc, Fresenius, and Renal Care Group units than Gambro units. Dose reductions were significantly less likely to occur in DaVita (19%), National Nephrology Associates (20%), hospital-based units (28%), and independent units (17%) than Gambro units. The distribution of units adjusting doses based on recommended practice was broad, ranging from a low of 10% to 20% to a high of 90%. The odds of a provider reducing the rHuEPO dose by the KDOQI-recommended 25% was significantly lower for DaVita, National Nephrology Associates, hospital-based units, and independent units compared with Gambro units.

Mean monthly hemoglobin levels were stable during the course of the year, remaining within ±0.1 g/dL for each provider group (data not shown). SDs also were stable within provider groups, but there were differences in means and SDs between provider groups. The highest was DaVita at 12 ± 1.5, and lowest was Dialysis Clinic Inc at 11.4 ± 1.2.

Sensitivity analysis results show that the effect of specifying a dosage percentage reduction less than the recommended 25% is to shift distributions to the right, with little or no effect on the shape of the distribution. Similarly, specifying a larger percentage of change shifts the distribution to the left with little or no effect on the shape.

Table 1. Patient Characteristics

Characteristic	All	DaVita	DCI	Fresenius	Gambro	NNA	RCG	Hospital	Independent	Unknown
No. of patients	167,796*	25,025	7,638	47,585	25,382	3,160	13,372	20,496	35,794	1,425
Age, y										
Median	64.0	63.0	63.0	64.0	64.0	64.0	64.0	66.0	65.0	65.0
Mean	61.9	61.4	60.9	61.6	61.9	61.9	61.5	62.8	62.3	62.2
SD	15.3	15.2	15.5	15.0	15.2	14.9	15.5	15.9	15.3	16.2
Distribution (%)										
0-19	0.3	0.3	0.4	0.2	0.2	0.1	0.3	0.8	0.2	1.7
20-44	14.3	14.7	15.6	14.4	14.3	13.9	15.1	13.5	14.1	13.5
45-64	36.4	37.2	37.7	37.4	36.6	37.7	36.3	33.0	35.2	34.0
65-74	25.9	26.3	25.2	26.3	25.7	25.4	25.7	26.0	25.8	25.8
≥75	23.1	21.6	21.1	21.6	23.2	22.9	22.7	26.7	24.7	25.0
Sex (%)										
Male	52.3	52.7	51.5	52.1	52.3	51.2	51.9	53.4	52.6	52.0
Female	47.7	47.3	48.5	47.9	47.7	48.8	48.1	46.6	47.4	48.0
Race (%)										
White	53.0	51.0	48.4	52.3	47.2	49.0	55.5	60.7	57.3	62.0
Black	40.8	40.3	47.6	43.2	48.0	47.7	39.4	29.9	35.9	29.3
Native American	1.6	3.1	2.1	0.8	0.9	0.7	3.1	2.5	1.1	1.1
Asian	3.7	4.9	1.5	2.6	3.3	1.9	1.5	6.0	4.5	6.4
Other/unknown	0.9	0.7	0.4	1.1	0.7	0.7	0.4	0.9	1.1	1.3
Primary cause of renal failure (%)										
Diabetes	42.2	42.6	40.4	42.3	41.6	41.8	42.7	40.8	41.9	41.2
Hypertension	29.6	30.1	28.9	30.7	31.5	31.2	29.9	25.4	28.5	24.4
Glomerulonephritis	12.0	11.5	12.6	11.6	11.5	12.2	11.9	14.2	12.6	13.8
Other	12.8	12.2	14.4	12.1	12.3	12.0	12.5	15.4	13.5	15.0
Unknown	3.5	3.5	3.7	3.3	3.1	2.9	3.0	4.2	3.5	5.6
Vintage (y)	4.3 ± 4.2	4.2 ± 4.2	4.6 ± 4.6	4.3 ± 4.3	4.2 ± 4.1	4.2 ± 4.1	4.2 ± 4.3	4.3 ± 4.4	4.1 ± 4.2	4.1 ± 4.1

Note: Values expressed as mean ± SD or percent unless noted otherwise. All *P* less than 0.0001 for age, sex, race, and primary cause of renal failure, by chi-square test.
Abbreviations: DCI, Dialysis Clinic Inc; NNA, National Nephrology Associates; RCG, Renal Care Group.
*The sum of patients for each provider type does not equal the total number because patients who switched providers were counted in each.

Table 2. Cumulative Comorbid Conditions

Condition	All	DaVita	DCI	Fresenius	Gambro	NNA	RCG	Hospital	Independent	Unknown
Atherosclerotic heart disease (%)	55.2	54.1	50.2	54.8	54.6	62.1	53.0	57.2	56.9	53.1
Congestive heart failure (%)	60.4	59.9	56.8	61.4	59.9	60.4	58.3	59.8	60.4	59.5
Cardiac arrhythmias (%)	42.2	42.1	41.3	41.3	42.7	40.5	39.4	43.5	42.9	42.3
Other cardiac disease (%)	53.7	53.4	51.6	54.4	53.4	56.6	52.9	52.9	53.8	51.1
Cerebrovascular accident/transient ischemic attack (%)	28.4	28.3	26.7	28.3	28.7	28.8	27.6	27.9	28.4	27.0
Peripheral vascular disease (%)	52.5	52.5	50.1	52.1	51.8	50.6	52.5	54.2	52.4	51.8
Chronic obstructive pulmonary disease (%)	27.3	26.5	26.7	27.2	27.3	27.3	26.8	27.6	27.4	30.1
Cancer (%)	12.9	12.7	12.7	12.8	12.5	12.3	11.8	14.4	13.8	13.0
Liver disease (%)	23.7	32.1	10.5	26.0	15.7	23.8	16.4	22.1	26.8	19.8
Gastrointestinal bleeding (%)	25.7	25.1	26.2	25.6	25.8	26.1	24.5	25.4	26.1	24.0

Note: Within each comorbid condition, all P less than 0.0001 by chi-square test.
Abbreviations: DCI, Dialysis Clinic Inc; NNA, National Nephrology Associates; RCG, Renal Care Group.

DISCUSSION

The continued growth in rHuEPO dosing and the increase in hemoglobin levels have raised concerns among payers and policymakers that providers may not be achieving optimal anemia management. Monitoring of care under the ESRD Clinical Performance Measures Project[11] and the unit-level reports distributed under Medicare's Dialysis Facility Compare show that providers have varying percentages of patients who meet or exceed target hemoglobin levels. The US Renal Data System's *2004 Annual Data Report* shows that in some provider groups, at least half the patients have an average hemoglobin level of at least 12 g/dL (120 g/L) during the entire year.[3] Our study shows that some provider groups have a high percentage of patients with hemoglobin levels not only greater than 12 g/dL (>120 g/L), but greater than 13 g/dL (>130 g/L). In other groups, less than 8% of patients have a hemoglobin level of at least 13 g/dL (130 g/L). This wide variation in achieved hemoglobin levels suggests that some providers have targets different from those recommended in the KDOQI guidelines, which are consistent with FDA recommendations. Even within a single group of providers, there is a wide range of adjustment patterns, suggesting inconsistent adherence to the recommended dose modification.

A more detailed assessment indicates that provider practice patterns associated with rHuEPO dose reduction are highly dependent on the specific large dialysis organization and whether dialysis units are hospital based or independent. Although there are small differences in demographic characteristics of patients served by the individual dialysis chains, hospitals, and independent dialysis providers, DaVita, National Nephrology Associates, and hospital-based units appear to adjust doses 20% less than the reference chains and as much as 40% less than other large dialysis organizations. These findings are based on a minimal dose reduction of 12.5% across 2 months with a reported hemoglobin level of at least 13 g/dL (130 g/L). These minimal changes yielded, on average, a 70% rate of management (versus that recommended), but the variation is considerable. Results do not change across 3 months of claims.

We also found inverse relationships among the providers. For example, DaVita has the lowest number of managed months and the highest percentage of hemoglobin levels greater than 11 g/dL (>110 g/L), whereas Dialysis Clinic Inc has the highest number of managed months and lowest percentage of hemoglobin levels greater than 11 g/dL. Despite an inverse relationship between hemoglobin level greater than 13 g/dL (>130 g/L) and percentage of hemoglobin levels less than 11 g/dL (<110 g/L), the percentage of patients within the recommended hemoglobin level range of 11 to 12 g/dL (110 to 120 g/L) is highly dependent on the provider.[7] Dialysis Clinic Inc had the highest percentage of patients with levels within the recommended range and the lowest percentage with levels greater than 12 g/dL (>120 g/L). DaVita had almost 3 times as many patients with levels greater than 12 g/dL

Table 3. rHuEPO Claims

	All	DaVita	RCG	Fresenius	Hospital	Independent	Unknown	Gambro	NNA	DCI
Total claims	1,713,706	235,046	128,053	459,481	194,044	338,761	11,453	242,379	30,470	74,019
Claims with hemoglobin ≥ 13 g/dL										
No.	179,637	39,352	16,256	47,715	20,030	33,375	1,076	18,709	1,672	1,452
%	10.5	16.7	12.7	10.4	10.3	9.9	9.4	7.7	5.5	2.0

Note: To convert hemoglobin in g/dL to g/L, multiply by 10.
Abbreviations: DCI, Dialysis Clinic Inc; NNA, National Nephrology Associates; RCG, Renal Care Group.

Figure 1. Anemia management measure (percentage of managed months) for the provider groups studied. Error bars are SDs. Abbreviations: DCI, Dialysis Clinic Inc; NNA, National Nephrology Associates; RCG, Renal Care Group.

(>120 g/L), but the lowest percentage with levels less than 11 g/dL (<110 g/L). Provider practices appear to vary with regard to exceeding the guideline, raising the concern that practices focusing on a single component of the guideline recommendations (eg, hemoglobin level < 11 g/dL [<110 g/L]) may distort the more comprehensive FDA-approved package insert and KDOQI recommendations, which focus on keeping hemoglobin levels within 11 to 12 g/dL (110 to 120 g/L).

Reasons for the broad differences observed are not immediately apparent. One possibility is between-provider variation in the percentage of patients with medical indications for hemoglobin level to exceed recommended levels. A detailed analysis of diagnosis codes included on dialysis claims may help clarify this issue, but the justifications reported to fiscal intermediaries may not be passed on through the CMS system and may be unavailable for analysis. Also, parent corporations or owners may subject providers to performance measures linked to manager or staff compensation. Economic incentives to achieve certain targets may reduce the likelihood that rHuEPO doses would be changed, particularly if the percentage of patients for whom hemoglobin levels decreased to less than the KDOQI target is monitored, as opposed to the percentage of patients who were managed appropriately and those achieving a hemoglobin level of at least 11 g/dL (110 g/L). Provider efforts to reduce the percentage of patients with hemoglobin levels less than 11 g/dL (<110 g/L) may affect revenue streams. Finally, providers may be reluctant to reduce doses as recommended for fear that patients'

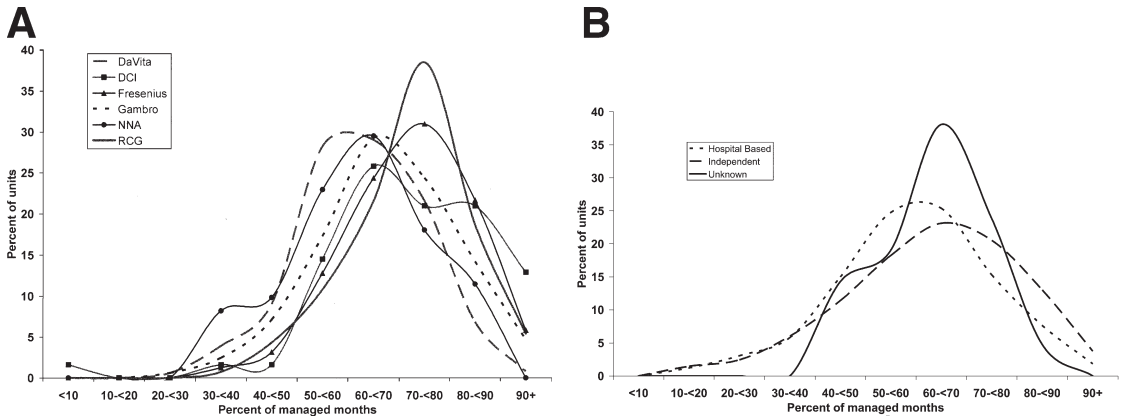

Figure 2. Distribution of anemia management by unit within provider group: (A) chain providers, (B) nonchain providers. Abbreviations: DCI, Dialysis Clinic Inc; NNA, National Nephrology Associates; RCG, Renal Care Group.

levels may decrease further into and past the KDOQI targets, leading to cycling of patient hemoglobin levels as described by Fishbane and Berns.[12]

Clearly, provider practices are associated significantly with the likelihood of performing adjustments irrespective of age, sex, race, and comorbidity in the covered population. A more complete assessment of provider dosing practices is needed to determine whether these practices are associated with any positive, neutral, or adverse outcomes in patients. This complex assessment should address the greatest concerns, such as vascular access thrombosis and cardiovascular events, issues of concern in the normal-hematocrit trial by Besarab et al.[8] Because achieved hemoglobin levels may be highly confounded by disease burden, such advanced methods as a marginal structural model may be required.[13] Patient safety with hemoglobin levels exceeding the recommended range should be assessed further. Such analyses are beyond the scope of the current investigation, which focuses on describing patterns of practice and their potential variation.

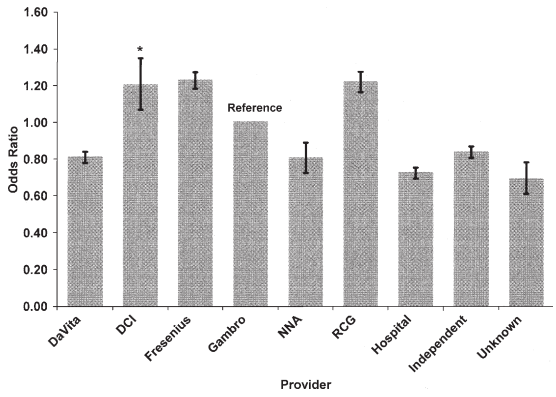

Figure 3. ORs for anemia management. $P < 0.0001$, except as noted. *$P = 0.0022$. Abbreviations: DCI, Dialysis Clinic Inc; NNA, National Nephrology Associates; RCG, Renal Care Group.

The limitations of our study deserve careful consideration. Only monthly hemoglobin levels are reported on rHuEPO claims. Providers may have access to multiple hematocrit values during the month that indicate a change in rHuEPO dose and allow for determination of the necessity of dose reductions for patients with a hemoglobin level that exceeds KDOQI targets. Because of hematocrit data limitations, determining the exact date during the month in which rHuEPO dose was decreased is difficult, and our ability to assess whether the total percentage of reduction was the suggested 25% is limited. To address this problem, we used a 12.5% reduction, reasoning that, on average, rHuEPO doses may change randomly throughout the month and the full amount of the change would not be reflected comparing it with the following month. Other unmeasured factors may influence a provider's likelihood of decreasing the rHuEPO dose, particularly in patients with high hemoglobin levels or with hospitalizations. Information regarding medical justifications offered for maintaining dosages in patients with higher hemoglobin levels is incomplete. To some ex-

tent, predictors of rHuEPO dose reduction show a greater likelihood in patients with cerebrovascular accidents and transient ischemic attacks. A more detailed analysis of indications for medical treatment exceeding the recommended levels is required to more accurately assess provider practices in rHuEPO dose reduction in patients with higher hemoglobin levels.

In summary, we assess the management of rHuEPO dose for patients with hemoglobin levels exceeding the KDOQI guidelines and find it to be highly related to the individual dialysis provider. In general, approximately 70% of providers' dialysis units adjust rHuEPO doses consistent with KDOQI guidelines and the FDA labeling instructions when hemoglobin levels exceed the recommended targets (13 g/dL [130 g/L]). The distribution is broad, suggesting that substantial improvement in the management of patients with elevated hemoglobin levels, with a decrease in rHuEPO dose, should be considered. Hemoglobin levels and rHuEPO dosing practices may change substantially with the recent changes in epoetin payment policies by CMS. Continued monitoring of these practices is warranted to determine whether providers are following recommended practices, thereby ensuring both safety and efficacy of anemia treatment for the dialysis population.

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