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Permalink

Journal

ISSN

Authors

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Publication Date

DOI

Copyright Information

Peer reviewed

Hemoglobin Variability in Anemia of Chronic Kidney Disease

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ABSTRACT

Hemoglobin levels in individuals with chronic kidney disease fluctuate frequently above or below the recommended target levels within short periods of time even though the calculated mean hemoglobin remains within the target range of 11 to 12 g/dl. Both pharmacologic features and dosing of erythropoiesis-stimulating agents may lead to cyclic pattern of hemoglobin levels within the recommended range. Several longitudinal studies highlight the complexity of maintaining stable hemoglobin levels over time. As a consequence, patients may risk increased hospitalization and mortality, because both low and high hemoglobin levels are associated with increased cardiovascular events and death. The duration of time that hemoglobin remains higher or lower than the target thresholds may be important to adverse outcomes. It is not clear whether adverse effects of hemoglobin variability are because of the therapy with erythropoiesis-stimulating agents and/or iron or despite such a therapy. Several factors affect hemoglobin variability, including those that are drug related, such as pharmacokinetic parameters, patient-related differences in demographic characteristics, and factors affecting clinical status, as well as clinical practice guidelines, treatment protocols, and reimbursement policies. Strategies that consider each of these factors and reduce hemoglobin variability may be associated with improved clinical outcomes.

Anemia develops as a frequent complication of chronic kidney disease (CKD) with an incidence and severity that are proportional to the degree of renal dysfunction.[1] Correction of anemia and maintenance of stable hemoglobin levels using erythropoiesis-stimulating agents (ESA) is an important aspect of disease management.[1,2] In clinical studies, moderate increase in hemoglobin concentration is associated with relief from symptoms of anemia, improved quality of life, and decreased blood transfusion rate.[3,4] The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend target hemoglobin levels in the range 11 to 12 g/dl, whereas hemoglobin >13

g/dl should be avoided.[5] Several recent randomized clinical trials showed targeting hemoglobin levels >13 g/dl to "normalize" hemoglobin in CKD may be associated with poor clinical outcomes,[6–10] and recent expert review by the Food and Drug Administration has left the target range between 10 and 12 g/dl unchanged.[11]

Although average hemoglobin levels have steadily increased since the introduction of ESA, until recently, approximately 15 to 20% of maintenance dialysis patients had average hemoglobin levels <11 g/dl.[12] The standard deviation (SD) of hemoglobin in maintenance dialysis populations in the United States is 1.1 to 1.3 g/dl,[12,13] which may explain the rela-

tively high frequency of hemoglobin level outside the recommended range of 11 to 12 g/dl. Whereas hemoglobin levels are generally higher for patients who receive ESA treatment, evidence from various clinical trials as well as the US Renal Data System (USRDS) suggests many patients who receive ESA experience fluctuations in hemoglobin over time, with a great degree of variability above and below the target range.[14–17] Recent analyses of USRDS data also suggest that considerably higher amounts of ESA are prescribed in for-profit dialysis care providers, leading to higher hemoglobin levels than other dialysis centers.[14,18,19] This may be related to the high profit margin from the ESA trades and utilization or simply a natural trend in patient care.[20]

DEFINITION AND CLINICAL EVIDENCE OF HEMOGLOBIN VARIABILITY

Hemoglobin variability is the fluctuation of hemoglobin above or below the target

range over time. Hence, hemoglobin variability is the extent to which multiple measured hemoglobin values differ from each other within a given time span, whereas the calculated mean of all hemoglobin levels may still remain within the target range.[21] ESA therapy may produce short, intermittent, nonbiologic bursts of plasma erythropoietin availability. The result can be a rising and falling of hemoglobin in a cyclic pattern that varies from patient to patient. This is in contrast to untreated, healthy individuals, in whom during homeostasis hemoglobin levels are maintained within a narrow range by close regulation of oxygen sensing, erythropoietin-producing, and erythropoietic systems.[1]

A 2-yr study by Ofsthun et al.[22] showed that of 41,919 dialysis patients, >50% spent >1.2 to 6.0 mo at hemoglobin levels <11 g/dl. A longitudinal analysis that was conducted by Lacson et al.[23] and involved >65,000 dialysis patients showed only approximately 38% had hemoglobin levels within the range of 11 to 12 g/dl. Despite a mean hemoglobin level of 11.5 g/dl, the average individual patient had a ±1.4-g/dl fluctuation in hemoglobin during the course of 1 yr on the basis of 3-mo rolling average values.[23] A 15-mo retrospective study of standard clinical practice conditions demonstrated substantial hemoglobin variability in 987 epoetin-treated hemodialysis patients.[24] The range of mean hemoglobin values (10.9 to 11.2 g/dl) that included the middle 50, 80, and 90% of values from a single month were within 1.7, 3.3, and 4.4 g/dl, respectively. One-month hemoglobin values exhibited the greatest degree of variability, with longer rolling intervals being associated with narrower hemoglobin ranges; however, even when a 6-mo rolling average was applied, <50% of hemodialysis patients had hemoglobin values within the KDOQI-recommended 11- to 12-g/dl range. Hemoglobin levels >12 g/dl were predicted to occur approximately 21% of the time.[24]

The foregoing findings were confirmed by the recent USRDS analysis, in which patients were categorized into one of three baseline hemoglobin cohorts of <11.0 g/dl (23%), 11.0 to 12.5 g/dl (47%), and ≥12.5 g/dl (30%).[12] As shown in Figure 1, there was significant movement between and within hemoglobin groups during a 3-mo time period. For example, 14% of patients who started with a hemoglobin level ≥12.5 g/dl fell below 11 g/dl at 3 mo, whereas 25% of patients who started with a hemoglobin level <11 g/dl had a hemoglobin ≥12.5 g/dl at 3 mo. In fact, only 55% of patients who were in the range of 11.0 to <12.5 g/dl stayed within that target range at 3 mo.[12]

In another USRDS analysis by Ebben et al.,[17] hemoglobin fluctuations during a 6-mo period were categorized into a few common patterns: Hemoglobin levels that were consistently <11.0 g/dl (low-hemoglobin group), between 11.0 and 12.5 g/dl (target hemoglobin group), or ≥12.5 g/dl (high-hemoglobin group) for all 6 mo; hemoglobin levels that crossed one boundary, in effect, varied between low and target groups or between high and target groups during the 6 mo; and hemoglobin levels that varied across all three hemoglobin boundaries.[17] As illustrated in Figure 2, only 10% of patients maintained hemoglobin levels within a single hemoglobin category during the entire 6-mo period. Overall, 29% of patients experienced hemoglobin fluctuations between the high and target hemoglobin groups, and 21% experienced fluctuations between the low and target hemoglobin groups. In almost 90% of patients, hemoglobin levels were in some degree of flux at any point in time. Fluctuation across all three hemoglobin categories during the 6-mo period was observed in nearly 40% of patients.[17]

Fishbane et al.[16] analyzed the movement of hemoglobin levels over time in 281 individual hemodialysis patients who were treated with epoetin. Hemoglobin cycling, repeated up-and-down undulations of hemoglobin levels, was found in >90% of patients. The patterns were somewhat predictable and were interrupted by periods of illnesses and hospitalizations. Hemoglobin excursions (defined as half of one hemoglobin cycle) occurred at a mean rate of 3.1 ± 1.1 per patient/yr, at a mean amplitude of 2.51 ± 0.89 g/dl, and for a mean duration of 10.3 ± 5.1 wk.[16]
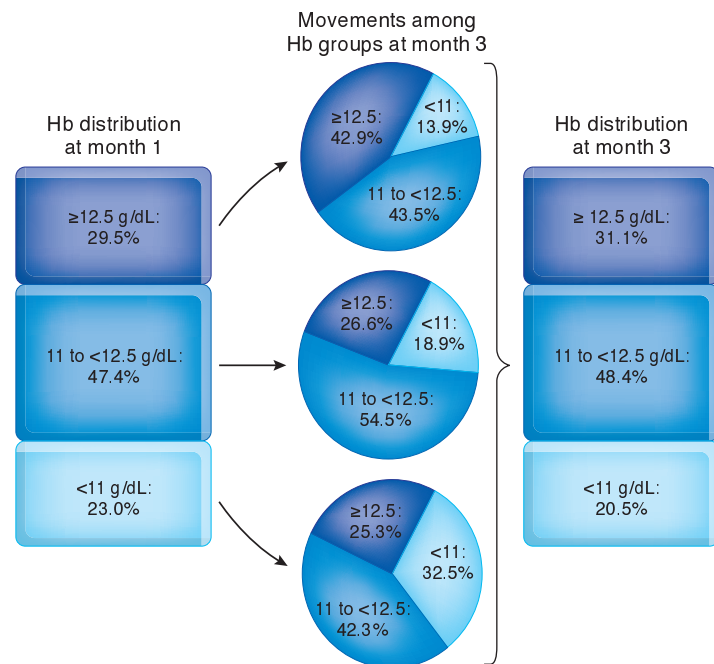

Figure 1. Fluctuations in hemoglobin levels over 3 mo. Although hemoglobin (Hb) distribution among the three groups remained consistent, only 33% of patients starting in the low-Hb group, 55% of patients starting in the mid-Hb group, and 43% of patients starting in the high-Hb group were still in those groups after 3 mo. Adapted from United States Renal Data System.[12]
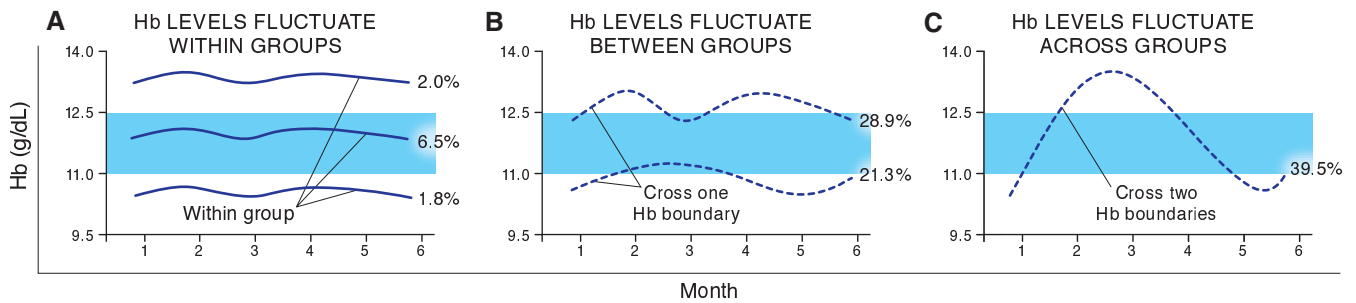
Figure 2. Patterns of fluctuations in Hb levels during a 6-mo period (*n* = 152,846). Hb values were divided into three groups. Only 6.5% of the patients remained within the range of 11.0 to 12.5 g/dl for 6 mo. (A) During 6 mo, 51.2% strayed outside their initial Hb groups into the next closest group (B), and 39.5 varied across two groups (C). Adapted from Ebben *et al.*[17]

The foregoing studies reveal the complexity of maintaining stable hemoglobin levels over time and indicate that traditional point-in-time analyses of hemoglobin levels may not accurately reflect anemia management in the clinical setting. Understanding the nature of hemoglobin variability is of particular importance when assessing the incidence of morbidity and mortality in this patient population, particularly because fluctuations in hemoglobin levels are themselves associated with adverse outcomes.[25]

MEASURING HEMOGLOBIN VARIABILITY

Variability may be assessed within the same patient or between patients in a group. In the context of clinical practice, it is generally the variability within a patient that is important, whereas for quality assurance purposes, variability both within patients (an index of individual stability) and between patients (an index of the extent to which values differ between patients) are relevant.[21] Different methods have been used to quantify the degree of hemoglobin variability (Box 1), including the conventional SD; the coefficient of variation, that is, the ratio of the SD to the mean; the proportion of time outside certain thresholds (Figure 2), on the basis of either actual hemoglobin measurement or rolling averages of hemoglobin measurements[17]; the magnitude of the residual SD or the average of the absolute SD changes[25]; and the absolute value of the rate of hemoglobin

Box 1. Measures of hemoglobin variability

Nontemporal methods
  SD of hemoglobin values
  coefficient of hemoglobin variation: Ratio of the SD to the mean hemoglobin
  slope of linear regression of hemoglobin values
  residual SD: Linear regression of hemoglobin SD values
  decomposition of the hemoglobin variability slopes into intra- and interpatient variabilities using repeated measure models
Temporal methods
  proportion of time outside certain thresholds
    based on actual hemoglobin measurement
    based on rolling averages of hemoglobin measurements
  absolute value of the rate of hemoglobin change or trajectory: Calculated from curve-fitting computer algorithms (measured in g/dl per month)
  changed in the slope of linear regression of hemoglobin values over time periods

change or trajectory (calculated from curve-fitting computer algorithms) measured in g/dl per month.[26] As depicted in Figure 3, however, the linear regression slope may not discriminate be-

tween the *inter*-patient variance, which implies the population level variability, and the *intra*-patient variability; that is, the variability at the individual level, which is the relevant metric to study hemoglobin variability. More sophisticated repeated measure models may be required to decompose the variability slope into its different individual patient- and population-based components. Because the frequency and the direction of the changes over time are usually relevant in studying variability, methods that more accurately integrate the element of time, such as calculating the slope of the change over smaller periods of time using regression models, seem more desirable.[27]

CONSEQUENCES OF HEMOGLOBIN VARIABILITY

To the best of our knowledge, the relationship between hemoglobin variability and outcomes in an earlier (predialysis) CKD population has not been well studied. In maintenance dialysis patients, however, hemoglobin variability seems to be associated with increased risk for death according to at least two studies.[25,28] In a recent USRDS analysis of 151,000 hemodialysis patients, Gilbertson *et al.*[28] found the 1-yr mortality risk was lowest in the few patients (6.5%) who consistently maintained hemoglobin within 11.0 to 12.5 g/dl. In these patients, both the number of times the hemoglobin level dropped to <11 g/dl and the time spent at <11 g/dl were predictive of mortality risk.[28] In another recent
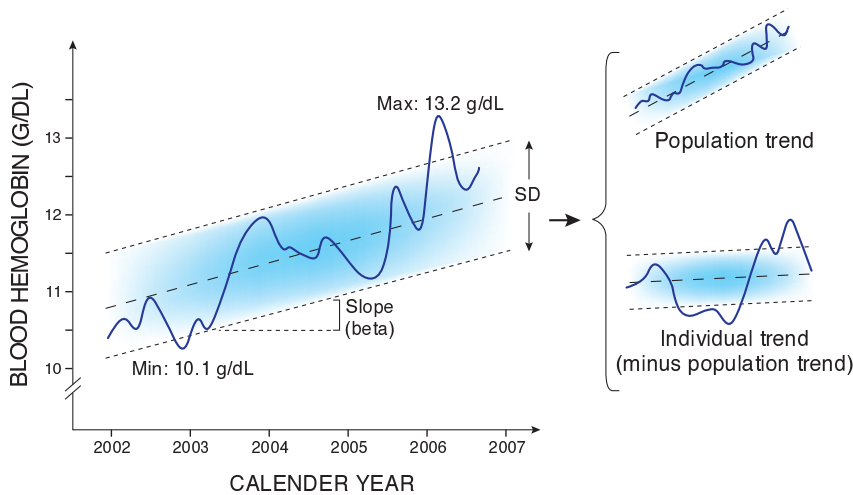
Figure 3. Schematic representation of the hemoglobin variability over time representing both population and individual slopes.
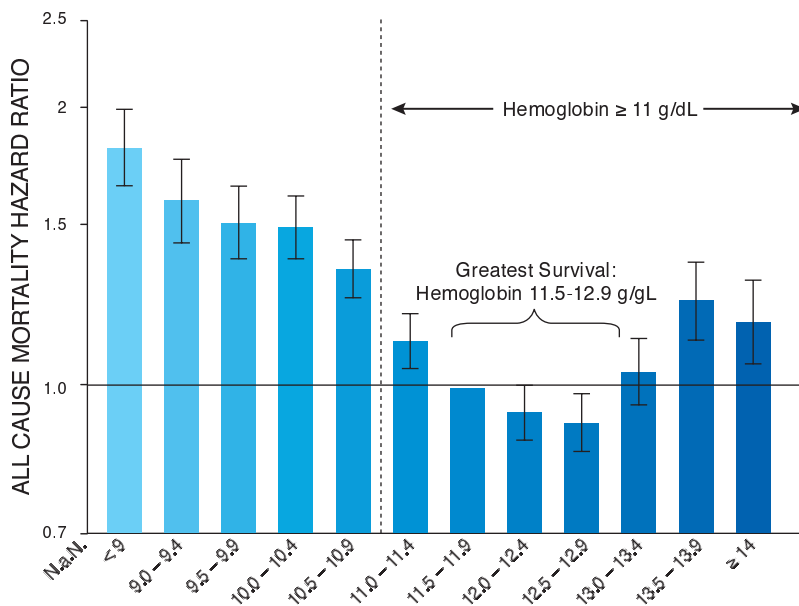

Figure 4. Hazard ratio for all-cause mortality on the basis of time-dependent hemoglobin levels that change quarterly (*i.e.*, every 13 wk) over 8 calendar quarters (July 2001 through June 2003). The greatest overall survival occurred for patients with hemoglobin values between 11.5 and 12.9 g/dl. Adapted from Regidor *et al.*[13]

retrospective cohort study of 34,963 hemodialysis patients, each 1-g/dl increase in the residual SD was independently associated with a 33% increased death rate.[25] Of note in this study, patient characteristics accounted for only a small portion of the variation in this hemoglobin variability metric.[25]

Because hemoglobin variability seems to be associated with mortality, it is expected that both low and high hemoglobin levels would be associated with increased death risk. Consistent with the foregoing notion, in several recent observational studies, a U-shaped or inverse J-curve relationship was observed between hemoglobin levels and clinical outcomes, whereby a specific range of hemoglobin was associated with greatest survival, rather than an incremental or

linear association between hemoglobin and survival.[13,29,30] A recent retrospective study of 58,058 maintenance hemodialysis patients also demonstrated an inverse J-curve relationship between hemoglobin levels and adverse outcomes (Figure 4),[13] in that hemoglobin levels between 11.5 and 13.0 g/dl were associated with the lowest death risk. A decrease in hemoglobin over time is also associated with a higher risk for death, whereas an increase in hemoglobin over time is associated with a lower death risk, an effect probably due to the overrepresentation by those whose baseline hemoglobin level to start is lower than usual. Improved survival outcomes are observed in dialysis patients using ESA at any dosages, whereas among those who received an ESA, a higher dosage requirement is a surrogate of higher death risk.[13]

The inconsistency of studies regarding upper hemoglobin threshold is also of clinical interest. Many observational studies indicated a strictly incremental improvement in survival with higher hemoglobin levels without any changing trend of increased death risk in both nondialysis[31] and dialysis[32] patients with CKD. This is, however, in sharp contradistinction to several recent studies showing increased death risk beyond certain *achieved*[13] or *targeted*[6,8,9] hemoglobin threshold levels, usually approximately or >13 g/dl in the CKD population (Figure 4). The discrepancy between randomized clinical trials and some but not all epidemiologic studies may be related to the observational nature and/or methods used to analyze mortality risk factors in the latter studies.[31,32] In particular, physician use of ESA in observational studies is not randomly assigned. Furthermore, although descriptive data can be used to determine correlations, they cannot definitively determine causality; however, there are also several advantages of observational studies, because such data can be more representative of real-world use and outcome of treatments. In contrast, randomized, controlled trials have restrictive inclusion/exclusion criteria and more ideal patterns of patient encounter than occur in usual care.

In addition to associations of blood hemoglobin with mortality and hospitalizations in the CKD population, anemia is associated with fatigue, weakness, shortness of breath, and a decreased health-related quality of life.[33,34] Furthermore, hemoglobin overshoot may be associated with various safety concerns, including the development of elevated BP with risk for hypertensive encephalopathy,[35] iron deficiency,[36] high platelet count,[37–39] thrombotic events,[40] and accelerated left ventricular dysfunction and hypertrophy.[7]

FACTORS AFFECTING HEMOGLOBIN VARIABILITY

Minor fluctuations above and below the target range may be normal in any setting; however, wide and/or prolonged fluctuations in hemoglobin are usually associated with several internal and external factors that can influence ESA response and hemoglobin stability. These factors can be grouped into several categories, as listed in Box 2.

Drug-Related Factors

Drug-related factors such as differences in pharmacokinetic and bioavailability parameters among ESA and different routes of administration (intravenous *versus* subcutaneous[41,42]) may affect hemoglobin stability in patients with CKD. Longer dosing intervals may lead to less variability in hemoglobin levels over time by producing fewer peaks and troughs and thereby requiring fewer dosage adjustments.[43–45] Both epoetin and darbepoetin have been studied over extended intervals beyond the currently approved regimens,[27,45,46] and similar data on newer ESA including continuous erythropoietin receptor activator are emerging.[43,44] Conversely, it is also possible more frequent dosing with agents with shorter half-lives is associated with better control of hemoglobin variability. Whether extended *versus* shorter dosing intervals with any of these ESA agents are associated with less variability in hemoglobin levels remains to be confirmed in clinical trials. In addition, medications that modulate hemoglobin synthesis such as iron preparations[47,48] or cardiovascular medications such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers[49,50] that are commonly used in this patient population, as well as medications for cancer chemotherapy, may lead to hemoglobin variability, especially at the initiation, discontinuation, and dosage titration.

Patient-Related Factors

Hemoglobin levels vary by age, gender, and race. In general, lower hemoglobin levels have been observed with increasing age, in women compared with men, and in black patients compared with white patients.[51–53] Although no major differences in ESA response are observed by age, gender, or race in clinical trials, these factors should be considered during ESA dosage selection and adjustment, because treat-

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Box 2. Potential contributors to hemoglobin variability in patients with CKD[a]

Drug-related factors
    ESA pharmacokinetics
    ESA dosing/frequency and administration route (intravenous, subcutaneous)
    Type of iron supplements (PO vs. IV) and dose and frequency of administration
    medications that can interfere with erythropoiesis, such as ACEI, ARB, cancer chemotherapeutic agents, HIV medications, and others
Factors related to patient demographics and clinical status
    age, gender, race, and other demographics or socioeconomic status
    laboratory and normal subjects variation
    fluid status, timing of blood draw, and other hemodilution-related factors
    patient compliance
    preexisting comorbid conditions (*e.g.*, diabetes, cardiovascular disease)
    hospitalization
    type of kidney disease and CKD stage
    CKD-related comorbid condition (*e.g.*, hyperparathyroidism)
    Concurrent hematologic disorders (*e.g.*, sickle cell anemia)
Iron deficiency
    iron loss as a result of comorbid conditions (*e.g.*, gastrointestinal bleeding)
    ongoing iron loss related to hemodialysis treatment and frequent blood testing
    iron deficiency as a result of ESA treatment–related increase in hematopoiesis
    functional iron deficiency as a result of proinflammatory cytokines
Infections
    overt infections such as dialysis catheter–related infections, pneumonia, and urinary tract infections
    latent infections such as mild peritonitis, hepatitis C, and chronic gum infection
Inflammation
    systemic inflammatory diseases (*e.g.*, lupus erythematosus)
    chronic inflammation (*e.g.*, malnutrition-inflammation complex syndrome)
Malignancies
    erythropoietin-producing neoplasms (*e.g.*, renal cell carcinoma)
    cancer-related cachexia/anorexia syndrome with cytokine release
    cancer chemotherapy medications
Practice pattern– and reimbursement-related factors
    practice guidelines (*e.g.*, KDOQI and KDIGO recommendations)
    reimbursement policies (*e.g.*, CMS regulations, payment bundling)

[a]ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CMS, Centers for Medicare and Medicaid Services; KDIGO, Kidney Disease Initiative Global Outcome.

ment may need to be individualized to maintain hemoglobin levels within target ranges. Laboratory variation of hemoglobin measurement amounts to 0.5 g/dl within a given blood sample.[54] Normal individuals may exhibit varying hemoglobin by ≥1 g/dl within a short period of time.[54] In dialysis patients, blood samples drawn at the beginning of the week may have lower hemoglobin values as a result of hemodilution as compared with midweek draws.[55]

Additional reasons for hemoglobin variability include acute or chronic comorbidities[17]; alteration in iron stores[56]; infection or inflammation[57,58]; blood loss or transfusion[59]; dialysis treatment features such as dialysis adequacy[60] or water quality[61]; stage of CKD and residual renal function[31]; level of parathyroid hormone[62]; vitamin and mineral status such as vitamin D, B_{12}, or folate deficiencies[63]; and seasonal effects.[61] Hemoglobin variability is more prominent in patients who are younger, have lower albumin or higher serum ferritin levels, or have changes in appetite[64] possibly related to alterations in nutritional or inflammatory status[57] and higher mean corpuscular hemoglobin.[24] Iron supplementation strategies, for example, intravenous iron maintenance *versus* repletion, may cause different patterns of variations in hemoglobin level.

Factors Related to Medical Care and Reimbursement Policies

Hemoglobin variability is also affected by anemia management practice patterns, which in turn are influenced by clinical practice guidelines, treatment protocols, and, in particular, reimbursement policies.[65] Management of CKD, including dialysis treatment, contributes substantially to the economic burden on the US health care system.[66] The presence of anemia has been identified as a major driver of health care costs in patients with CKD, and, as a result, anemia management is often a target of various cost-containment policies[65]; however, formulary restrictions, payment policies, and other cost-containment issues that require clinicians to maintain hemoglobin levels within a certain range increase the likelihood of hemoglobin variability. It is possible the recent debates and hearings on ESA use in patient populations with CKD and cancer by Congress and the Food and Drug Administration[67] and the recent inclusion of black box warnings for the currently approved ESA[68–70] have some impact on anemia management and hemoglobin variability.

MANAGEMENT OF HEMOGLOBIN VARIABILITY

Because fluctuations in actual or achieved hemoglobin levels above and below the target range are common in clinical practice, there are ongoing efforts to minimize the variability. Box 3 shows proposed strategies that can be used to prevent or manage hemoglobin variability in patients with CKD. Selecting and administrating an ESA and adjusting its dosing, whether initiated by a physician on the basis of clinical judgment or whether used through clinical decision algorithms by nonphysician health care providers, should follow the principles of a "negative-feedback loop."[21] Setting a narrow hemoglobin target of 11 to 12 g/dl may increase the

Box 3. Strategies for reduction of hemoglobin variability

More frequent hemoglobin monitoring (*e.g.*, weekly to biweekly rather than monthly)

Shortening of the time lapse between the blood draw and result review by the nephrologist or other anemia management providers

Fine-tuned (rather than drastic) changes in ESA dosage (*e.g.*, 25% change in the ESA and/or iron dosage rather than doubling the dosage or withholding the ESA[a])

Preemptive adjustment of the ESA dosage for temporal trends that are still within the target range (*e.g.*, dosage reduction [or increase] by 25% with upward [or downward] trends[a])

Switch to different types of ESA (*e.g.*, longer acting ESA for noncompliant patients with frequent missing of dialysis treatments)

Preemptive increase in ESA dosage during infectious or inflammatory conditions or bleeding (*e.g.*, dialysis access surgeries, heavy menstruations) or immediately after a hospitalization

Prompt and effective treatment of infection and inflammation in ESA-hyporesponsive patients

Optimal management of hyperparathyroidism including appropriate use of vitamin D analogs, calcimimetics, and phosphorus binders

Maintenance iron supplementation during ESA treatment (*e.g.*, weekly to monthly low-dosage intravenous iron[b])

Avoidance of iron-ESA dosage discrepancy (*e.g.*, high ESA dosage with little or no iron and vice versa)

Adequate attention to and appropriate interpretation of iron markers

Timely workup of persistent ESA hyporesponsiveness or erythrocytosis for prompt detection and management gastrointestinal or other types bleeding or malignancies associated with internal ESA production

Implementing strategies to improve patient compliance with dialysis treatment attendance

Development and ongoing improvement of facility-specific algorithms for anemia management tailored to the need of the regional population

Considering novel computerized intelligent methods to model the hemoglobin variability across patients and clinics

[a]Transient withholding ESA/iron (*e.g.*, for ≥1 wk) for hemoglobin values >13 g/dl range[71] or doubling the dosage for hemoglobin values below 9 to 10 g/dl may also be considered.
[b]More concrete examples include once a week administration of 25 to 50 mg of iron sucrose or dextran, 31.0 to 62.5 mg of iron gluconate, or similar dosages for ferumoxytol and other intravenous iron agents.

chances of observing actual hemoglobin levels that deviate out of range. It could also be argued that a wider target range would lead to the greater variability by allowing more flexible ESA dosing. Values above or below a certain target range or a trajectory toward such deviations usually leads to an ESA dosage adjustment in the desired direction. The degree of hemoglobin fluctuations as well as occurrence can also be minimized by controlling for many patient-related factors that are manageable and by streamlining anemia practice patterns. In general, the challenge is to anticipate the changes on the basis of recent trends and to adjust the dosage and frequency of ESA, iron, and other medications accordingly, rather than waiting for hemoglobin values to be outside the target zones. Even though many protocols recommend fine-tuned rather than drastic changes in ESA dosage (Box 3), a recent study suggested that discontinuation, rather than reduction, of ESA treatment was more appropriate when hemoglobin level reaches 13 g/dl in hemodialysis patients.[71] Changing the ESA dosage or frequency while maintaining the same dosage and frequency of intravenous iron may or may not be appropriate and needs to be examined in clinical studies.

CONCLUSIONS

Minimizing hemoglobin variability can have important short- and long-term clinical consequences. In the short run, fewer fluctuations above 12 g/dl may minimize the occurrence of serious cardiovascular events associated with high hemoglobin levels, whereas fewer fluctuations below 11.0 g/dl provide improved symptomatic relief and maximize survival. Increased hemoglobin stability also means better performance in meeting audit targets, because in some jurisdictions, exceeding upper hemoglobin thresholds may have reimbursement implications.[21,72] The traditional desire to maximize the fraction of patients with CKD and with a blood hemoglobin level >11 g/dl along with recent efforts to minimize the proportion of patients with

hemoglobin level >12 g/dl contributes to some of the challenges in the management of hemoglobin variability. Hemoglobin target ranges could be recommended on the basis of clinical or scientific data to indicate the ranges shown to be associated with the optimal combination of quality and length of life.[21] Targets that require least frequent ESA dosage adjustment and yet meet the criteria set forth by regulatory or consensus bodies should be pragmatically selected. Because the foregoing purposes may be distinct, the optimal hemoglobin target range for each may differ.[21] Future studies need to examine extended *versus* more frequent ESA dosing strategies, algorithms based on hemoglobin trends,[73] or neural network based on reinforcement learning[74-76] or iron supplementation strategies.

ACKNOWLEDGMENTS

DISCLOSURES

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