the glomerulus in disease states. There is evidence, for example, that glomerular expression of a key regulator of angiopoietin-2 function, vascular endothelial growth factor A (VEGF-A), is upregulated in some glomerular diseases (notably diabetic nephropathy) and downregulated in others.[14]

This is a critical issue because angiopoietin-2 has different effects on vascular remodeling and endothelial integrity depending on the coincident levels of VEGF-A.[10] On this basis, we might expect increased levels of angiopoietin-2 and VEGF-A in diabetic glomeruli to have different effects from those of angiopoietin-2 overexpression in other glomerular diseases. These issues can be addressed only by evaluating the impact of decreasing angiopoietin-2 expression in appropriate experimental models. However, these studies cannot be performed using germline *angiopoietin-2* null mice, because these mice die within the first 2 weeks of life with severe defects in the lymphatic system.[15] Studies in *angiopoietin-2* heterozygous null mice might be informative if gene dosage has an impact on angiopoietin-2 expression and function. Otherwise, we will have to wait for definitive studies in which the effect of temporally controlled, cell-specific deletion of *angiopoietin-2* is evaluated experimentally. It may be some time before we obtain a definitive answer to these questions, as the necessary floxed *Ang-2* mutants have yet to be generated.

DISCLOSURES

None.

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See the related article, "Podocyte-Specific Expression of Angiopoietin-2 Causes Proteinuria and Apoptosis of Glomerular Endothelia," on pages 2320–2329.

Hemoglobin Variability in Dialysis Patients

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Hemoglobin variability is the extent to which multiple measured hemoglobin values differ from each other. 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, both variability within patients (an index of individual stability) and between patients (an index of the extent to which values differ between patients) may be relevant. As West *et al.* observe in the current issue of *JASN*,[1] the adjustment of epoetins in the management of anemia in renal disease, whether done by clinical judgment, the use of simple clinical decision rules, or a more complex computer program essentially follows the principles of a negative-feed-

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back loop; that is, a derangement leads to a dose adjustment in the direction predicted to bring the patient's hemoglobin back toward the desired value or into the desired range. This mechanism means that instability and, in some cases, a degree of periodicity is an inherent and inevitable feature of the system.

Different methods have been used to quantify the degree of variability. West *et al.* use the absolute value of the rate of hemoglobin change (calculated from curve-fitting computer algorithms), which they call the trajectory, measured in g/dl per mo.[1] Based on individual curve fitting, it is applicable only to the assessment of within-patient variability, although, as they have done, these values can then be aggregated and compared between groups using standard statistical techniques. Other measures of variability that can be assessed within a patient or across a group of patients are the SD or the coefficient of variation (the ratio of the SD to the mean). Finally, the proportion of time outside certain thresholds can be assessed on the basis of either actual hemoglobin measurement or rolling averages of hemoglobin measurements.

Targets may be defined for a number of purposes. First, a target might be defined from basic and clinical science data to encompass the values thought to be associated with the optimal combination of quality and length of life. Second, clinical decision rules or algorithms often set target ranges pragmatically as a range of values within which no dose adjustment is necessary. And third, target ranges may be used by individuals, groups,[2] or by society[3] to assess the efficacy of treatment in meeting specified goals. We suggest that these three purposes are quite distinct, and the optimal target and range for each may differ.

Reasons for variability include abrupt changes caused by distinct comorbid events such as bleeding or transfusion. In addition, chronic comorbidity (particularly inflammation), iron stores, dialysis adequacy, water quality, residual renal function, hyper- or hypoparathyroidism, B12 or folate deficiencies, seasonal effects, the use of angiotensin-converting enzyme inhibitors and possibly angiotensin receptor–blocking drugs, and inherent, currently unmeasurable patient-specific factors all may lead to variability between patients. Changes in these factors would lead to increased variability within an individual patient over time. The current work by West *et al.* suggests a new metric: The sum of these factors may reflect the sensitivity of the patient. Changes in volume status and unavoidable sampling and laboratory measurement errors lead to further variability. Finally, the frequency of measurement, frequency of dose adjustment, frequency of dosing, and pharmacokinetics of the epoetin used are important further factors that, even in a perfectly stable situation, affect the amplitude and periodicity of the hemoglobin trajectory.

West *et al.* have used a novel methodology to assess within-patient variability. Individual patients' hemoglobin values are plotted and curves fitted that pass through or near data points. This permits the calculation of the slope, or rate of hemoglobin change, a value that changes instantaneously. The average of this value assesses an individual patient's variability. Plotting rate of hemoglobin change against the absolute value for an individual patient allows graphical interpretation in that tighter ellipses are indicative of better control. This offers a new methodology for assessment of variability in future studies.

Variability has previously been shown to be increased in patients who are younger, have lower albumin and higher serum ferritin (likely because these last are inflammatory markers), and have higher mean corpuscular hemoglobin.[4] Important unanswered questions in this area relate to modifiable variables: The optimal frequency of measurement, frequency of dose adjustment and magnitude of dose increments in unselected patients receiving specific epoetins, and optimal iron protocols. Iron-loading strategies may cause more abrupt increases in hemoglobin than iron-maintenance protocols.[5] It is probable that longer-acting agents lead to greater stability at a given dose frequency—under the experimental conditions used in the current paper, stability was greater with a longer-acting epoietin compared with a shorter-acting agent.[1,6]

The width of the target range may also affect variability, but empiric data here are confusing. Two previous randomized controlled trials conducted by Will's group in the same population of patients compared a target range of 10.5 to 14 g/dl with a range of 11.5 to 14 g/dl, and a target range of 11 to 12 g/dl with a range of 11 to 13 g/dl.[7,8] In the first study, no statistically significant reduction in group SD resulted from the narrower target range; however, in the second study a statistically significant reduction occurred in the group managed with the narrower target.[7,8] This second study was also of interest as an example of a difference between thresholds for intervention and the thresholds used as a measure of success. The authors argued that to maintain hemoglobin above 10 g/dl in a large proportion of patients, the dose must be changed proactively as the hemoglobin crosses a threshold that is higher than this.[7]

Why is it important to maximize hemoglobin stability? In the management of anemia with epoetins, physicians steer individual patients between the Scylla of increased mortality caused by higher hemoglobin targets[9,10] and the Charybdis of symptoms and lower quality of life from severe anemia[11]—increased variability reflects an increased probability of patients veering toward one of these hazards. Increased variability will also increase the proportion of patients outside given targets at a particular time or over a period of time, leading to poor performance in meeting audit targets; in some countries, exceeding hemoglobin ceilings is undesirable *per se* because of funding implications.[3] Studies of the relationship between variability and clinical outcomes are however, to our knowledge, lacking.

Research in this area is of more than technical interest. Given the high costs of epoetins, more information on cost-effective methods to maximize hemoglobin stability and clinical benefits is needed. We further suggest that future trials on any issue in anemia management consistently report the between- and within-patient SD and the statistical significance of any differences, especially in studies evaluating extended erythropoietin dosing strategies. Algorithms that take into account the current hemoglobin trajectory or trend,[6] as well as

the most recent value or rolling average of values, as used by West *et al.* in this issue, appear particularly worthy of further investigation. Neural networks also have shown some promise in this area and require further testing in clinical practice.[12]

DISCLOSURES

C.M. Clase served on the advisory board for Hoffman-La Roche (1998). K.S. Brimble received study funding from Janssen-Ortho (2001) and served on the advisory board for Janssen-Ortho (2002).

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See the related article, "Functional Data Analysis Applied to a Randomized Controlled Clinical Trial in Hemodialysis Patients Describes the Variability of Patient Responses in the Control of Renal Anemia," on pages 2371–2376.

Errata

CORRECTION

Erratum for de Lind van Wijngaarden et al.: Chances of Renal Recovery for Dialysis-Dependent ANCA-Associated Glomerulonephritis. *J Am Soc Nephrol* 18: 2189–2197, 2007. The coauthors regret that Charles D. Pusey was previously omitted as coauthor of this paper by unfortunate accident. He should be a coauthor of this paper.

CORRECTION

Erratum for Brimble and Clase: Hemoglobin Variability in Dialysis Patients. *J Am Soc Nephrol* 18: 2218–2220, 2007. We stated that instability was greater with the shorter than with the longer-acting epoetin in the work of West et al.[1] This was not the case: the mean value for patients receiving weekly erythropoietin β was 0.58 g/dl per mo (standard deviation [SD] 0.29 g/dl per mo) and for darbepoetin was 0.68 g/dl per mo (SD 0.26 g/dl per mo).[1] A two-sample *t* test indicated statistical significance at the 5% level ($P = 0.03$). We gave two references, the second of which was incorrect.

We wrote: "It is probable that longer-acting agents lead to greater stability at a given dose frequency—under the experimental conditions used in the current paper, stability was greater with a longer acting epoietin compared with a shorter-acting agent.[1,6]" This should be revised to read:

"While one might expect stability, at a given dose frequency, to be greater with a longer-acting agent, data from West et al show that the converse is true.[1] This interesting observation warrants further study."

We apologize for the error.

REFERENCE

1. West RM, Harris K, Gilthorpe MS, Tolman C, Will EJ: Functional data analysis applied to a randomized controlled clinical trial in hemodialysis patients describes the variability of patient responses in the control of renal anemia. J Am Soc Nephrol 18: 2371–2376, 2007