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Hemoglobin Variability and Hyporesponsiveness: Much Ado About Something or Nothing?

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Hemoglobin Variability and Hyporesponsiveness: Much Ado About Something or Nothing?

Jerry Yee, Gerard Zasuwa, Stanley Frinak, and Anatole Besarab

Hemoglobin (Hb) variability is considered a discrete clinical entity that when present may presage poor clinical outcomes. However, Hb variability is an intrinsic property of biological systems and is present in all patients, those with and without the anemia of chronic kidney disease. Taken together, variability actually represents the integration of multiple influences at multiple levels in the life of a red cell, namely the summation of positive and negative influences on erythropoiesis. Thus, Hb variability may be interpreted as a mathematic function of time and is the result of a host of influences including definition of the normal Hb range, native erythron responsiveness/hyporesponsiveness, temporal changes in endogenous and exogenous erythropoiesis-stimulating agent (ESA) levels, the algorithms used to dose ESAs and their duration of action, the presence of biologically available iron, red cell turnover, and recyclable and non-recyclable blood loss and gain. When viewed within this construct of matrixed determinants, the source of hemoglobin variability is more readily identified. When variability is present but the etiology is not easily discerned, erythropoietic hyporesponsivess must be considered and evaluated. Finally, integration of all of these concepts is possible within the context of an anemia management protocol.

Index Words: Anemia; Chronic kidney disease; Variability; Sensitivity; Hyporesponsiveness; Erythropoiesis-stimulating agent; Iron deficiency

Variability is defined as the degree by which repetitive measures of a tested parameter vary.[1,2] The case is no different for hemoglobin (Hb). The range of any given Hb level is bounded by ascertainment of the parameter within the general population and the coefficient of variation inherent to the measuring device, the latter yielding the coefficient of difference of the variable.[2] Variability can be construed within the context of a single patient (intraindividual) or in a given population (interindividual). Generally, the clinician focuses on intrapatient variability, although interpatient variability is also significant and may render insights into processes of care rather than individual therapeutic processes.

For the anemia of chronic kidney disease (CKD), variability may be defined by the standard deviation or the coefficient of variation of the Hb for a single patient or population.[3] Variability has also been evaluated by the resident proportion of time outside stated limits of Hb, and the term "rolling hemoglobin"[4] has often been used to characterize this form of variability. An alternative description has been that of assessing the change in consecutive Hb measurements categorized as (1) all changes $\leq$0.5 g/dL, (2) Hb decrease $>$0.5 g/dL, (3) Hb increase $>$0.5 g/dL, and (4) both Hb decrease and increase $>$0.5 g/dL.[5] More recently, variability, particularly that referred to as "cycling" has been characterized by the Hb amplitude, defined as the difference between the highest and lowest Hb levels during a period of observation.[6] Lastly, variability has been considered as "trajectory," the first derivative or slope/trajectory of Hb and time.[7,8] In these models, the Hb intercept defines the absolute

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Hb level, the Hb slope represents the change of Hb levels over time, and the residual standard deviation (SD) represents the Hb variability.[9,10]

Importantly, Hb variability is a normal biological event, and a normal subject's Hb may vary by nearly 1 g/dL over the course of a year.[11,12] This is shown in Figure 1. The variation of Hb around a mean of 15.1 g/dL has an SD of 0.6 g/dL. Lastly, the aforementioned Hb variations are greater than those expected from the accuracy of the measurement of Hb for which the coefficient of variation is <1.5% in dialysis patients[3] and even less in normal subjects.[13]

In CKD patients, one would expect even greater variability than in healthy people because of blood losses from frequent measurement, sampling errors and alterations of extracellular fluid volume, and seasonal variation,[14] and this is particularly true of patients with minimal or no residual kidney function.[15] Similar, systematic determinations of "normal" variability of Hb in CKD have not been determined, stratified by CKD stage, or validated by multiple observers. The only available data suggest that variability is less than that in end-stage renal disease (ESRD) patients but greater than in healthy people.[16] Moreover, the CKD patient is often subjected to greater frequencies of Hb monitoring and also to alterations of dosing of iron and/or erythropoiesis-stimulating agents (ESAs). Therefore, the "abnormal" Hb variability discussed in the literature is a convention that cannot be directly compared against the "normal" variability of normal subjects. Nonetheless, it is the amplitudes of difference between CKD patients and normal individuals that the literature espouses as "variability."

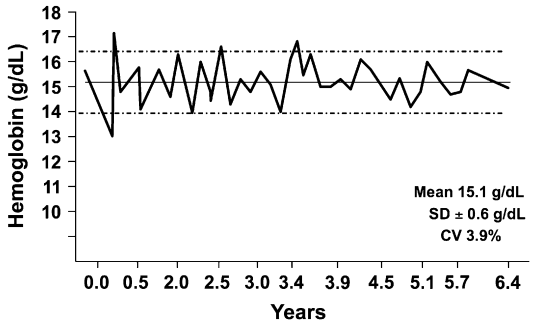

Figure 1. Time-varying hemoglobin (Hb) levels in a normal individual.

Despite the artificiality of the term, variability remains significant, and determining its cause in a CKD patient is a therapeutic mandate, for it may be sentinel for adverse events. This is usually true when the Hb trajectory or amplitude of variability is downward, but this is not always the case. Conversely, upward amplitudes in Hb are generally positively received but may be associated with unfavorable outcomes as well. This review delineates Hb variability as a dynamic entity that is a function of multiple influences. Variability will be described within the context of a broad range of intrapatient and interpatient determinants that affect Hb, including intrinsic and extrinsic forces. In addition, a mechanistic approach to elucidating causation for erythropoietic hyporesponses will be offered.

Hemoglobin: Values and Variability

Normal

The intra-assay coefficient of variation (CV) of corpuscular Hb is about 5.5% to 8%,[17-19] with an SD of 1.8 to 2.7 g/dL. Given these relatively small CVs for corpuscular Hb, the variability of Hb among individuals and groups of patients generally should not be attributed to laboratory measurement in the absence of flawed systematic quantitation error(s) or specimen acquisition. Indeed, the CV for Hb is generally low, approximately 0.68 to 0.82, with SDs of 0.019 to 0.10.[20]

In large population studies such as National Health and Nutrition Examination Survey III and the Scripps-Kaiser Database, blacks and whites have mean Hb levels ranging from 13 to 15 g/dL with an SD of 0.8 to 1.2 g/dL. White males experience a mild decile-dependent drop in Hb with age.[21] In addition, Hb declines "normally" with aging by a modest degree.[22] Notably, analysis of the Scripps-Kaiser data eliminated individuals with iron deficiency (thresholds for exclusion: transferrin saturation <16% or serum ferritin <10 g/L).

Abnormal

Hemoglobin variability is greater in CKD patients and in older patients. Notably some of the more elderly patients may not have been recognized as having CKD because serum creatinines were not transformed to estimated glomerular filtration rates.[23] The CV for Hb has a larger negative SD in whites with a serum creatinine level >1.4 mg/dL (124 μmol/L), C-reactive protein levels >1 mg/L, or erythrocyte sedimentation rate levels >20 mm/hr.[14] Namely, these individuals were more anemic with CKD and/or inflammation. Correspondingly, in the analysis of an aging Netherlands cohort, much greater degrees of anemia were positively associated with increased mortality.[22] However, CRP levels were not reported in this analysis.

The mortality association between worsening anemia and mortality has also been identified in several populations. In patients hospitalized with acute myocardial infarction, the frequency of death was inversely related to the entry hematocrit (Hct), and an increasing death rate followed the 30-day decline in Hb.[24] At Hct levels of 30% to 33%, the tangential slopes of the curvilinear relationship between death and Hct decreased. Consequently, in a follow-up letter to this report, the authors recommended that individual Hct levels should be maintained at >33% (Hb ~11 g/dL) in patients experiencing acute myocardial infarction.[25] A similar relationship was found between anemia and heart failure in a meta-analysis.[26] Anemia, and, hence, population-based variability, is also greater in elderly blacks in comparison to whites and correlates with mortality, impaired cognitive function, and functional status.[27] In this prospective, cohort study of 1,774 elderly male and female community-dwelling participants of the Duke Established Populations for Epidemiologic Studies of the Elderly, a component of the National Institute on Aging study, anemia was present in 24% of individuals using World Health Organization criteria. This prevalence was significantly higher than those of the 11.0% in males and 10.4% in females that were reported in the noninstitutionalized US population of the third National Health and Nutrition Examination Survey (1988-1994).[28]

Taken collectively, lower Hb values are related to CKD, aging, and cardiovascular disease events. Lower Hb values are significantly associated with greater morbidity and mortality, particularly at Hb levels <10 g/dL in cardiovascular disease patients. Hb declines with age from whichever cause, and CKD is evident in some of these individuals. In conclusion, because intraindividual Hb variability is a function of time-varying Hb, which is unlikely to vary substantially at any single point in time, the magnitude of the decrease in Hb is the best predictor of adverse outcomes.

Hb Variability in CKD and Outcomes

The definition of Hb variability in CKD is itself variable. In most cases, Hb variability is evaluated during a period of 3 to 6 months, using nearly all Hb measurements available during the specified interval. Because the frequency of Hb monitoring varies from weekly to monthly, generally, a sufficient number of values are available to determine Hb variability in a particular patient.

The following definitions have been used in the literature. Yang et al[9] and Brunelli et a[10] developed the following novel, linear regression-based metrics of Hb variability: intercept defining an absolute Hb level, slope equating to the change of time-varying Hb, and residual SD representing variability. This group concluded that greater variability positively correlated with mortality as an independent risk factor.

Lacson et al[3] defined Hb level variability in terms of 3-month rolling average Hb levels, noting that this variability depended on interpatient variability. The SD of these averages representing intrapatient variability was 1.2 g/dL, 0.3 g/dL greater than the general US population. Twenty-eight percent of patients with a rolling average Hb <11 g/dL increased their levels to >12 g/dL during 1 year of observation. The investigators concluded that Hb level variability was the result of multiple factors, including laboratory assays, biological influences, and individual therapeutic responses to the treatment of anemia. Standardized treatment algorithms were

recommended as a measure to improve quality while reducing variability.

Regidor et al[5] characterized the change in consecutive Hb measurements in 4 ways during their retrospective analysis of nearly 40,000 maintenance hemodialysis patients: (1) all changes ≤0.5 g/dL, (2) an Hb decrease >0.5 g/dL, (3) an Hb increase >0.5g/dL, and (4) both an Hb decrease and increase >0.5 g/dL. After adjustment for time-varying confounders, this group concluded that ESA dosing was beneficial from a survival standpoint. Lastly, the authors correlated decreased survival with a falling Hb that precipitated higher levels of ESA dosing.

Hb variability has been defined in terms of amplitude, the difference between the highest and lowest Hb levels during the baseline period. Fishbane and Berns[6] identified the principal components of recurrent cycling in ESRD patients. These were ESA therapy that was used to attain the target Hb and a narrow target Hb range, which ironically induced frequent ESA dosing changes and "cycling."

Ebben et al[29] classified ESRD patients into 6 groups in their 6-month study of Hb level fluctuations in ESRD patients receiving Medicare with claims for epoetin alfa. Three groups were classified based on Hb level: low (<11.0 g/dL), within target (11.0-12.5 g/dL), and high (≥12.5 g/dL). Subsequently, 6 groups were defined as consistently low for 6 months, consistently within target range, consistently high, low-amplitude fluctuation with low Hb, low-amplitude fluctuation with high Hb, and high-amplitude fluctuation (HA; low, target range, and high Hb). Just 10.3% of patients could maintain a stable Hb for the study duration. The consistently low experienced hospitalizations most frequently and had the most comorbid illnesses. HA was the most common pattern at 39.5%. In a later, similarly conducted study, the same group determined that Hb <11 g/dL for >3 months, rather than variability, was associated with mortality.[30]

Determinants of Hb Variability and a Suboptimal Response to ESA Therapy

Hb variability results from multiple sources. When it is associated with declines of Hb, it is frequently coupled with suboptimal responses to ESA therapy (ie, monthly Hb increases of <0.5 g/dL). Etiologically, hyporesponses may be related to patient-related factors, intercurrent events, and practice pattern-related issues (Table 1). These hyporesponses may also be subdivided into 3 other categories: blood loss, nonpathological, and pathological. Blood loss produces a negative trajectory of Hb over time. Nonpathological causes of variability typically increase Hb when evaluated in a time-varying fashion, whereas pathological influences generally induce Hb declines.

Blood loss occurs in multiple formats including occult or overt gastrointestinal blood loss from whichever cause, the annual 1 to 2 g of procedural blood losses in hemodialysis lines and filter,[31] surgical interventions, or hospitalizations with their associated multiple phlebotomy procedures. In a retrospective review of 65 hemodialysis patients, Hb levels were on average 0.7 g/dL lower 2 months after discharge, despite an escalation of the ESA dose of 45%.[32] No effects of comorbid factors, including surgery or discharge diagnosis, on Hb changes or epoetin alfa requirements were detected. Patients transfused in hospital had lower Hb levels and higher ESA doses before and after hospitalization. Remarkably, despite that hospitalization-associated blood loss can be cut by nearly 75% simply by the utilization of pediatric-sized tubes, this practice has never been adopted on a widespread basis.[33]

Nonpathological causes of Hb variability can be operationally defined as clinical circumstances that are unassociated with blood loss or a specific disease entity or state. The inadequate treatment of the anemia of CKD by iron supplementation is chief among these. Absolute or functional iron deficiency in nondialysis (ND)-CKD and ESRD patients renders ESA therapy suboptimal.[34,35] The correction of iron deficiency characteristically reduces or maintains the preiron exposure ESA dose and increases Hb.[36-38] When iron therapy does not correct anemia, an insufficient ESA dose, blood loss, or a pathological cause of Hb variability should be suspected.

Another reason for nonpathological Hb variability is per protocol treatment of anemia.

Table 1. Etiology of Suboptimal Response to ESA Therapy

Patient-Related Factors	Intercurrent Events	Practice Pattern-Related Issues
ESA sensitivity	Iron deficiency (absolute, functional)	Inadequate protocol design
Erythrocyte lifespan	Infection(s): obvious, occult (AVG)	Facility- and provider-level protocol adherence
Parathyroid hormone level	Hospitalization (phlebotomy)	Patient-level adherence (protocol, medications)
Inflammatory illness	Blood loss (bleeding, hemolysis)	Laboratory monitoring frequency
Diabetes	Pure red cell aplasia	Narrow Hb target range
Malignancy	Medications	Dialysis adequacy, poor
Hematologic disease (hemolysis)	Seasonal variation	Payment restrictions (ESRD MUE: darbepoetin alfa 1,200 mcg/mo; epoetin alfa 400,000 units/mo)
Malnutrition Vitamin deficiency (B12, folate)	Inter-dialytic weight gain	

Abbreviations: AVG, arteriovenous graft; ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; MUE, medically unbelievable edit.

Essentially, in these circumstances, variability is a function of process of care. Patients have varying degrees of intrinsic, biological sensitivity to ESAs.[39,40] Namely, small ESA dose increments will produce a given positive change of Hb in some, but the same incremental Hb change may require much larger ESA doses in others (ie, ESA pseudoresistance). Furthermore, others may show intermediate levels of sensitivity to ESA. Given the differential ESA sensitivities of ESRD patients, coupled with an inability to determine sensitivity a priori and the narrow constraint of maintaining an idealized target Hb of 11 to 12 g/dL, the Hb can be highly variable at any given time point in a particular individual. However, when greater duration is permitted to achieve the target, variability decreases. Nonetheless, fewer than 50% of patients had hemoglobin values within the 1.0 g/dL National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K-DOQI) recommended range in the retrospective, observational study (N = 987) of Berns et al,[4] despite the use of a 6-month rolling Hb. At 1 month, 1 SD of Hb was 1.4 g/dL; at 3 months, 1 SD was 1.1 g/dL; and at months 4 to 6, 1 SD was 1.0 g/dL. In total, a 4.4-g/dL Hb spread was required to encompass 90% of Hb values, with the Hb range encompassing 50% and 80% of levels from a single month at 1.7 and 3.3 g/dL, respectively. The 6-year Hb trend analysis of 65,009 patients by Lacson et al[3] corroborate those mentioned earlier. Their analysis of the Fresenius Medical Care North America database concluded that a 3-month rolling Hb would exceed 12.5 g/dL in 13% to 31% of facility-managed patients given an expectation that 90% of Hb levels were ≥10 g/dL.[7] During 3 successive quarters of analysis, approximately 38% of patients were at the target Hb of 11 to 12 g/dL, although many individuals moved above and below the target. The "average individual patient" was predicted to experience an Hb fluctuation of 1.4 g/dL. Lastly, the authors concluded that increasing the upper bound of the target Hb range would lessen Hb variability.

The correction of a deficiency of a critical vitamin deficiency that imposes a state of ineffective erythropoiesis should also be considered among the causes of nonpathological causes of Hb variability. The adequate repletion of vitamins B12 and/or folate in deficiency states may generate a brisk upward slope of the Hb versus time curve, and their assessment is recommended early on during the investigation of anemia in CKD patients.[41,42] Another prominent cause of Hb variability of nonpathological origin is suboptimal outpatient adherence to oral hematinic therapy or, possibly, ESA dosing because CKD/ESRD patients are susceptible to

medication-related problems and challenged by the number of medications that they must take,[43,44] the estimates of which can be considered among the "unknown knowns." ESRD patients experience nonpathological Hb variations in both directions. These include the following: seasonal variations in Hb with peak Hb values that were 0.6 g/dL higher in July[8]; heterogeneous times of Hb assay, which may occur after large or small interdialytic extracellular fluid volume changes; pregnancy[45]; pain or anxiety during the venipuncture; geographic altitude of the hemodialysis unit with hypoxia-driven erythropoiesis at greater elevations; cigarette smoking; and patient position.[15]

Pathological Hb variability deflects Hb downward (ie, negative variability), excludes nutritional deficiencies, aging, and bleeding, and specifies that an alteration or change of Hb stems from an abnormal condition that inhibits optimal erythropoiesis. Such conditions are often of an inflammatory nature. The etiologies are myriad and induce hyporesponsiveness to ESA therapy. Excluding the intrinsic inflammation of ND-CKD and ESRD, which includes increased concentrations of C-reactive protein, pernicious cytokines, hepcidin, and enhanced oxidative stress-related markers, all of these states impair erythropoiesis at various stages.[46-49] Diabetic kidney disease, itself an inflammatory state,[50] is associated with worse anemia than those without diabetes.[51,52] LiVecchi et al[52] examined 3 groups of patients: type 2 diabetics without CKD (n = 75), type 2 diabetics with CKD (n = 106), and nondiabetic CKD (n = 100). Anemia was most frequent in diabetic kidney disease (70.5%) but also present in diabetes alone (16%). In CKD stages 4 and 5, anemia prevalence was greater in diabetics than in nondiabetics. Hence, it might be anticipated that diabetic kidney disease is associated with greater Hb variability than in nondiabetic CKD individuals and attributable to those factors that drive the anemia. Proteinuria has been posited as one of these factors because erythropoietin losses are one consequence of albuminuria[53] after observations in the proteinuric rat, but this supposition has not been rigorously tested, experimentally or clinically.

Pathological variability resulting from acquired infections is common. Hospitalizations occur 4 to 5 times more frequently in CKD patients than in those without the diagnosis.[54] Conceivably, the prolonged recovery of Hb after infection-related hospitalization is, in part, attributable to and exacerbated by the inflammatory milieu incited by the infectious agent. Notwithstanding the obvious infections incurred by hospitalized CKD patients, occult infections from a variety of sources should be ruled out (eg, abdominal abscesses, infective endocarditis, and osteomyelitis). Included among these are nonfunctional arteriovenous grafts. These must be suspected as a source bacterial infection in iron-replete patients manifesting sluggish responses after ESA exposure.[55] The discovery of this particular cause of ESA hyporesponsiveness has tremendous implications for hemodialysis units with a large proportion of nonfunctional grafts, from both patient care and ESA utilization standpoints. Lastly, inflammation from concomitant nonrenal diseases may provoke ESA resistance including HIV/acquired immunodeficiency syndrome, rheumatoid arthritis, lupus, and inflammatory bowel disorders, among others.

Other pathological processes that impair the net response to anemia therapy and negatively increase Hb variability can be categorized into 3 groups: bone marrow disorders (fibrotic, infiltrative, inflammatory, and myelosuppressive), hemolysis, and acquired red cell production disorders (lead and aluminum). Inflammatory marrow fibrosis from secondary hyperparathyroidism of CKD has been described by multiple observers. Nearly 2 decades ago, in a single-center experience of 7 patients who required a mean epoetin alfa dose of 174 U/kg to maintain an Hct of 35%, marrow fibrosis was correlated to the extent of hyperparathyroidism.[56] More recently, the original observation that hyperparathyroidism is associated with worse anemia was confirmed.[57] Myelophthisic disease from a myelodysplastic disorder or infiltration by malignancy may similarly impose ESA hyporesponsiveness. A search for a plasma cell dyscrasia must always be made when the cause of CKD has not been established and anemia is disproportionate to the

stage of CKD. Hemolytic anemia investigations should be prompted by failure to establish one of the usual suspects that induce resistance to ESA and includes a thorough review for medications that provoke hemolysis and for those that depress red cell production (eg, zidovudine and chemotherapeutic agents). Abrupt, severe (>0.5 g/dL/wk) declines in Hb after exposure to an ESA for >4 weeks, with normal platelet and white cell counts, may signal acquired pure red cell aplasia,[58] a neutralizing antibody disorder primarily linked to the antigenicity of a now-discontinued epoetin formulation and leachates from the rubber stoppers of the vials containing it. Lead exposure remains a scourge of society,[59,60] and chronic aluminum ingestion[61,62] as phosphate-binder therapy is rare today; however, the presence of either must be ruled out when hyporesponsiveness to ESA therapy is unresolved.

Reduction of Hemoglobin Variability in Non–Dialysis-Dependent Chronic Kidney Disease

Considering many of the reasons for variability, our group endeavored to offset variability by developing an automated, algorithmic approach to anemia management in our ND-CKD population. Using 2 parallel treatment algorithms that deliver oral or intravenous iron and monthly subcutaneous darbepoetin alfa, we have attempted to treat and maintain nearly 600 patients to the KDOQI target. This computerized program, the Computerized Anemia-Management Program (CAMP©, version 3.0; Henry Ford Health System, Detroit, MI), performs trend analysis of Hb, transferrin saturation, and ferritin before calculating and prescribing iron and ESA therapies (Fig 2). Internal calculation of the slope of Hb versus time, in 3-month intervals, prevents Hb from rising too rapidly and from "overshooting."

By establishing monthly dosing limits, futile attempts to treat hyporesponsive patients are avoided and simple evaluation of albumin levels may facilitate recognition of these individuals.[63] CAMP also stores within its database procedural information from the patient encounter including patient vital signs, dose of iron and ESA administered, prescribing health care provider, and site of administration. Any or all of the stored parameters are queryable for application in continuous quality improvement efforts. For example, one could identify, analyze, and print a report of those patients whose Hb levels were <10 g/dL, despite receipt of >300 μg of monthly darbepoetin (Fig 3).

By using this approach, nearly 80% of patients who adhered to the program for 5 months fell into the Hb range of 10.5 and 12.5 g/dL. More importantly, the 20% of patients who fall outside of the target range are identified. The most ESA-resistant and most ESA-sensitive patients are generally found within this group, and CAMP automatically generates "warnings" on these patients that are e-mailed to respective health care providers. Thus, although our results show that the target Hb cannot be perfectly struck as a "bull's eye," one may be close and achieve clinically satisfactory results. The latter is in accordance with the recently updated KDOQI clinical practice guideline statement 2.1.1[41] that permits individualized therapy for the asymptomatic patient who is "doing well" at an Hb that is <11 g/dL. In this instance, further treatment is not absolutely required, and CAMP automatically determines the treatment strategy for such individuals and informs the health care provider of its decision who may choose to override the decision based on the clinical context. The integration of "softer" boundaries essentially melds into our algorithm the prior information of Lacson et al[3] and Berns et al[4] that describes the implausibility that all patients can be treated to a narrow 1 g/dL Hb range and prevents clinically unnecessary Hb cycling.

Conclusions

Hb variability is an inherent phenomenon of man in both health and disease. It must be anticipated during the treatment of anemia in CKD. Hb variability is neither inherently bad or good, but an integrated response of the patient, which reflects a composite of iron availability to the erythron, ESA dose, and erythropoietic responsiveness/sensitivity and the multiple external forces that may

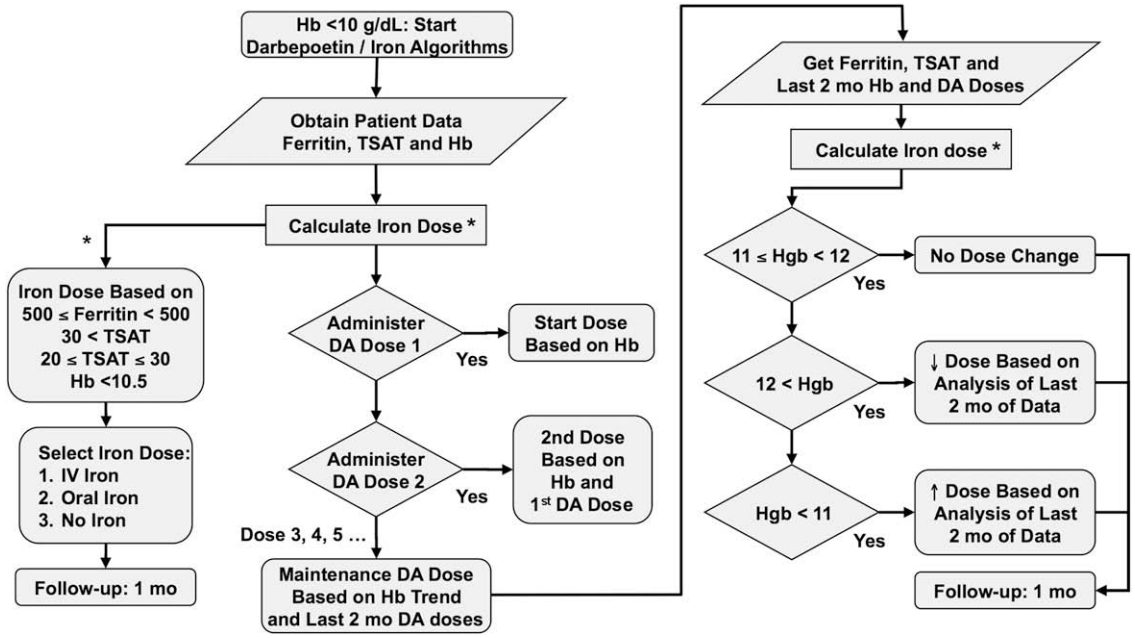

Figure 2. Computerized Anemia Management Program (CAMP©) algorithms for iron and darbepoetin therapy in chronic kidney disease. Hb, hemoglobin; TSAT, transferrin saturation; DA, darbepoetin alpha.

inhibit it. Relaxation of Hb target ranges prevents protocol-driven swings in variability and conforms to current clinical guidelines and recommendations. The imprecision of the term "variability" has been "much ado about nothing." However, persistently negative variability and ultrahigh ESA dosing to attain a Hb target and preclude downward

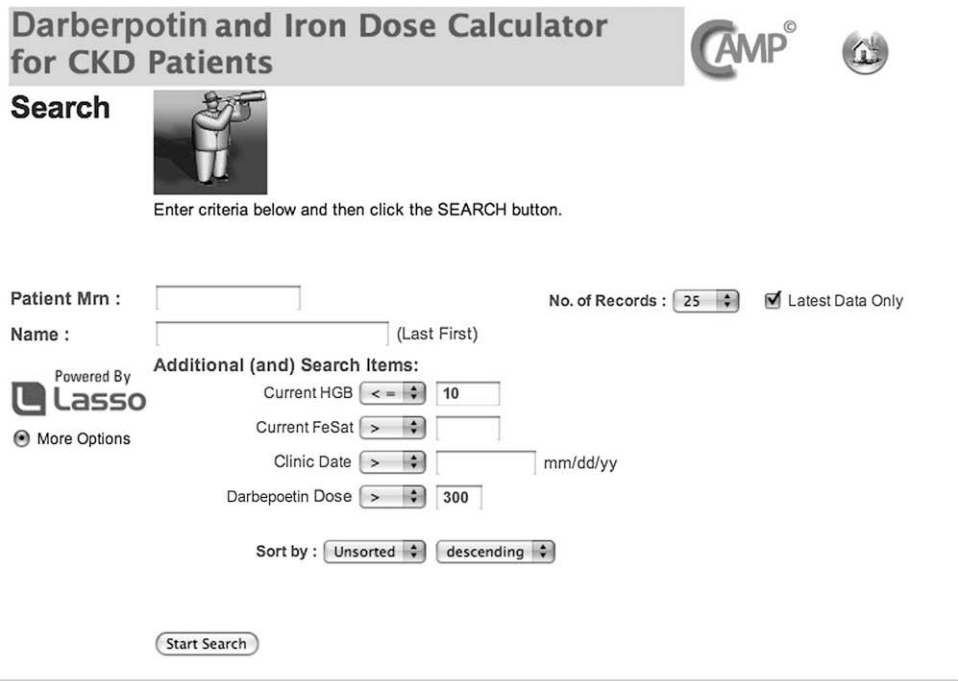

Figure 3. Sample query of chronic kidney disease (CKD) patients receiving 300 μg or more of darbepoetin with a hemoglobin concentration of 10 g/dL or less and from Computerized Anemia Management Program (CAMP©).

cycling are "much ado about something"[64] and contrasts the situation in which greater ESA responsiveness is associated with a survival benefit.[65] We posit that anemia management protocolization and operationalization can create Hb stability and quality performance at the individual and facility levels, and protocols should target those patients who require it the most.

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