The Role of Anemia Management in Improving Outcomes for African-Americans with Chronic Kidney Disease

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Key Words

Anemia management • Diabetes mellitus • Hypertension • Chronic kidney disease • Dialysis

Abstract

Chronic kidney disease (CKD) is a serious threat to African-American public health. In this population CKD progresses to end-stage renal disease (ESRD) at quadruple the rate in Caucasians. Factors fueling progression to ESRD include diabetes and hypertension, which show high prevalences and accelerated renal damage in African-Americans, as well as possible nutritional, socioeconomic, and genetic factors. Anemia, a common and deleterious complication of CKD, is more prevalent and severe in African-American than Caucasian patients at each stage of the disease. Proactive management of diabetes, hypertension, anemia, and other complications throughout the course of CKD can prevent or delay disease progression and alleviate the burden of ESRD for the African-American community. Currently, African-Americans with CKD are less likely than Caucasian patients to receive anemia treatment before and after the onset of dialysis. Although African-Americans often require higher doses of erythropoiesis-stimulating agents, this may result from late treatment initiation, lower hemoglobin levels, or the pres-

ence of comorbidities such as diabetes and inflammation, although racial differences in response cannot be excluded. This review explores racial-specific challenges and potential solutions in renal anemia management to improve outcomes in African-American patients.

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Introduction

Chronic kidney disease (CKD) is highly prevalent in adults in the United States, with African-Americans and other racial and ethnic minority groups at increased risk of the disease [1, 2]. Decline of renal function is fueled by diabetes and hypertension, risk factors widespread in the African-American population [3]. Compared with Caucasians, African-Americans show an incrementally larger prevalence across advancing stages of CKD progression [4–6], and a 3- to 4-fold greater incidence of end-stage renal disease (ESRD) [2, 4, 7]. Anemia, a common consequence of CKD, is more prevalent and severe in African-American than Caucasian CKD patients [2, 5], is intensified by diabetes [8], and is associated with cardiovascular risk [9] and accelerated loss of renal function [10, 11].

Table 1. Stages and prevalences of CKD by ethnic group

	eGFR, ml/min/1.73 m ²	Prevalence among non-Hispanic African-American NHANES 1999–2004 participants (%; 95% CI)	Prevalence among non-Hispanic Caucasian NHANES 1999–2004 Participants (%; 95% CI)
Stage 1	≥90 with evidence of kidney damage	9.4 (8.0–10.9)	4.2 (3.7–4.9)
Stage 2	60–89 with evidence of kidney damage	4.8 (3.9–5.7)	5.8 (5.0–6.6)
Stage 3	30–59	4.7 (4.0–5.6)	5.8 (5.3–6.4)
Stages 4 and 5 combined	<30 including dialysis	1.1 (0.7–1.6)*	0.3 (0.2–0.5)

eGFR = Estimated glomerular filtration rate; NHANES = National Health and Nutrition Examination Survey.

* NHANES 1999–2004 data [4] calculated combined prevalences for stages 4 and 5. Stages adapted from reference [117].

Disproportionate progression to ESRD among racial and ethnic minorities creates added public health burdens for local communities. The excess prevalence has been estimated to contribute more than 25% of the total cost in the US ESRD system, which now exceeds USD 32 billion a year [2, 7]. Earlier detection and intervention to treat both the causes of CKD (e.g. diabetes, hypertension) and its consequences (anemia, cardiovascular disease, bone disease) may prevent or delay the progression of CKD [3].

Healthy and iron-replete African-Americans typically have lower average hemoglobin (Hb) levels than Caucasians, reflecting, among other factors, the effects of an alpha-thalassemia deletion allele (gene frequency 0.169) [12]. Iron deficiency anemia is also frequent in African-Americans, with prevalences ranging up to 19% in premenopausal black women [13]. These baseline factors, combined with the erythropoietic deficits of CKD, result in lower mean Hb and greater risk of anemia in African-American than Caucasian patients throughout the course of CKD [2, 5]. Consequences of untreated anemia of CKD include fatigue, cognitive impairment, and reduced exercise tolerance [14] as well as increased cardiovascular morbidity [15–17], leading to increased hospitalization [18, 19], economic burden [19, 20], and mortality [21–23]. Patients with early CKD and untreated anemia have been shown to progress to ESRD more rapidly than treated anemic patients or non-anemic patients [10, 11].

Treatment for anemia of CKD began in the 1960s and 1970s with blood transfusions, but these were associated with iron overload [24], immune sensitization [25], and occasional viral transmission [26]. Androgen treatment of anemia has been associated with adverse hepatic and endocrine events [27]. The development of recombinant erythropoietins in the 1980s revolutionized anemia treatment in CKD [28], and such erythropoiesis-stimulating

agents (ESAs) remain the foundation of current anemia management [27]. Recent years have seen an evolution in ESA therapies toward agents with longer half-lives and extended administration intervals [29, 30].

Despite recent improvements in anemia management, African-Americans still have suboptimal rates of achieving recommended hemoglobin targets [2]. This article surveys current data on the epidemiology, course, and treatment of CKD and its complications in African-Americans; highlighting racial-specific challenges and potential solutions for improving anemia management in the patient with CKD or ESRD.

CKD Prevalence and Progression to ESRD in African-Americans

A recent analysis of NHANES 1999–2004 data [4] indicates that the overall prevalence of CKD is only slightly higher among African-Americans (19.9%) than Caucasians (16.1%). In this data set, stage 1 CKD (with near-normal estimated glomerular filtration rate [eGFR] but evidence of proteinuria or kidney damage) was more prevalent among African-Americans than Caucasians. By contrast, rates of stages 2 and 3 were higher among Caucasians (table 1). A similar prevalence pattern was reported for the Kidney Early Evaluation Program participants, with stages 1 and 2 CKD being more common in African-Americans than Caucasians [5]. In contrast to the modest differences in early-CKD prevalences and trends toward lower rates of stages 2 and 3 CKD among African-Americans, ESRD is roughly 4 times as prevalent among African-Americans as among Caucasians [2].

Research into the causes of racial disparities in CKD-related health outcomes is ongoing. Known risk factors

for progressive kidney disease include African-American race, level of blood pressure control, proteinuria, low socioeconomic status, and genetic influences [6, 35, 36, 37, 41, 42]. The incidence of hypertension among 20- to 44-year-old men is 20 times greater for African-Americans than their Caucasian counterparts [2]. Family history of ESRD predicts increased risk of ESRD [34, 35], and 2 genetic loci (the plasma kallikrein gene and the human homolog of the rodent renal failure 1 gene) have been correlated with ESRD in African-American kindreds [34]. Albuminuria or proteinuria, a common initial presentation of nephropathy, is associated with CKD progression in both diabetic and hypertensive patients [41–43]. The African-American Study of Kidney Disease and Hypertension (AASK) found that increasing rates of proteinuria at a given GFR level predicted worsening clinical outcomes [41]; additionally, GFR decline accelerated at low levels of renal function [53]. Furthermore, poverty and low educational attainment are strong socioeconomic predictors of proteinuria in African-Americans [44].

Because African-Americans have a high prevalence of CKD and a differential risk of progression to ESRD, vigorous screening and treatment for diabetes, hypertension, and early stages of CKD are especially important in the African-American population. Primary care physicians should take action to reduce behavioral risk factors (smoking, substance abuse, poor nutrition, sedentarism), monitor patients longitudinally for albuminuria/proteinuria and abnormal GFR, and refer them to nephrologists as appropriate. Management of conditions predisposing to CKD and ESRD can reduce the public health burden attributable to kidney failure.

Clinical Management of CKD and Anemia

Prevention and care of hypertension and diabetes in the general African-American population can help reduce the burden of CKD. Patients with established CKD, regardless of stage, require proactive treatment of clinical perturbations as they develop (e.g. hypertension, diabetes, anemia) to retard disease progression and attenuate the ESRD burden for the African-American community. Strategies for clinical management of hypertension, diabetes, and anemia to improve the renal prognosis in this population are discussed below.

Hypertension

Aggressive treatment of hypertension is essential to reduce the burden of nephropathy in this population. In

African-Americans with hypertension, a systolic blood pressure goal of 135–140 mm Hg is reasonable; however, African-Americans with CKD or diabetes require a lower blood pressure goal of $\leq 130/80$ mm Hg [55]. Available data including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [56] support the use of diuretics as first-line treatment to reduce blood pressure and risk of cardiovascular disease in African-Americans with hypertension; however, as in other patients, combination therapy may be more effective in achieving blood pressure reduction goals [57]. For patients with uncomplicated hypertension $\geq 155/100$ mm Hg, recent guidelines for therapy in African-American patients [40] suggest first-line combinations of a diuretic with a different drug class (beta-blocker, angiotensin-converting enzyme inhibitor, or angiotensin-receptor blocker).

Combination antihypertensive therapy for patients with diabetes or known CKD should include renoprotection with an agent acting on the renin-angiotensin system [3].

In a 36-month interim analysis of the AASK trial, the angiotensin-converting enzyme inhibitor ramipril slowed GFR decline and reduced proteinuria in patients with mild to moderate renal insufficiency (baseline proteinuria >300 mg/day) [58, 59].

Diabetes

African-Americans are more likely than Caucasians to have diabetes [61]; poorly controlled diabetes increases risk of renal failure and premature cardiovascular disease [62]. With long-standing diabetes (10–15 years), glomerular histologic changes lead to frank diabetic nephropathy [63]. Preventing or halting diabetic nephropathy requires a comprehensive intervention to restore and maintain normoglycemia, reduce blood pressure to $\leq 130/80$ mm Hg, control proteinuria, reduce glycated hemoglobin and dyslipidemia, and address behavioral risk factors [64]. Evidence supports blood pressure control as arguably, the most important intervention to retard progressive renal disease as well as other microvascular complications of diabetes [125, 126].

Anemia

Anemia resulting from renal endocrine dysfunction accompanies CKD regardless of the source of kidney damage, with hemoglobin (Hb) measurably decreasing as GFR falls below 60 ml/min/1.73 m². In the Prevalence of Anemia in Early Renal Insufficiency (PAERI) survey, the prevalence of anemia (Hb <12 g/dl) increased from 26.7%

Table 2. Prevalence of anemia among Kidney Early Evaluation Program participants with CKD [5] by stage and race

	Anemia, WHO definition ^a prevalence, %		Anemia, KDOQI definition ^b prevalence, %	
	African-Americans	Caucasians	African-Americans	Caucasians
Stage 1 (with albumin/creatinine ratio ≥ 30)	23.3	6.4	13.5	3.3
Stage 2 (with albumin/creatinine ratio ≥ 30)	20.9	10.1	12.7	6.5
Stage 3	26.4	12.7	21.3	9.5
Stages 4–5	70.5	51.2	59.1	42.1

KDOQI = Kidney Disease Outcomes and Quality Initiative; WHO = World Health Organization.

^a Hb <13.0 g/dl in men and postmenopausal women or <12.0 g/dl in premenopausal women [68].

^b Hb <11.0 g/dl in premenopausal women and prepubertal children and <12.0 g/dl in postmenopausal women and adult men [27].

Adapted from data in reference [5].

in stage 3 CKD to 76% in stage 5 [65]; anemia is near-universal in incident ESRD patients. Anemia develops earlier and more severely in patients with diabetic nephropathy than in CKD patients without diabetes [8, 66].

In the general population as well as in all stages of CKD, anemia has been shown to be more prevalent in African-Americans than Caucasians (table 2) [5], perhaps reflecting low Hb prior to CKD onset [12] and/or higher prevalence of iron deficiency [13]. African-American PAERI participants had prevalence odds ratios of 1.61 (95% CI 1.40–1.85; $p < 0.0001$) for Hb <12 g/dl and 2.03 (95% CI 1.63–2.52; $p < 0.0001$) for Hb <10 g/dl relative to Caucasian patients [65]. Current guidelines for diagnosing anemia [27] do not take into account gender or racial differences in baseline Hb.

When anemia decreases tissue oxygenation, the cardiovascular system compensates with tachycardia, vasodilation, and increased cardiac work, leading over time to left ventricular hypertrophy [67]. Roughly 39% of stage 3–4 CKD patients have left ventricular hypertrophy [68]; its prevalence rises to almost 75% at dialysis initiation [69], suggesting that cardiac remodeling begins early in the course of CKD [9]. Hypertension also contributes to left ventricular hypertrophy in African-Americans [70]. Among African-American Atherosclerosis Risk in Communities participants aged 50–75 years, lower Hb predicted larger left ventricular diameter even after adjusting for kidney function [9].

Treating anemia of CKD with ESAs augments diminished renal erythropoietin production and alleviates tissue hypoxia, which in turn may prevent or reverse left ventricular hypertrophy [21, 71]. Anemia treatment at CKD stages prior to dialysis is associated with improved quality of life [72] and physical activity [14]. With safe Hb

targets generally in the range of 11–12 g/dl [73], ESA treatment may attenuate cardiovascular [21, 71] and renal complications [74–76]. Untreated anemia is associated with accelerated progression to ESRD [10, 11]. Conversely, observational studies indicate that receipt of anemia treatment before reaching ESRD is strongly associated with delayed ESRD onset [11] and reduced mortality on dialysis [20, 22, 77]. Recent clinical trials [78, 79] have raised cautions [73, 80] regarding the optimal Hb target range and patient selection for erythropoietic treatment. The exact mechanism underlying the increased morbidity and mortality with higher than currently recommended hemoglobin levels remain unclear. According to the 2007 Kidney Disease Outcome Quality Initiative (KDOQI) guideline update [73], Hb targets ≥ 13.0 g/dl are associated with increased cardiovascular risk; however, among patients treated to appropriate Hb targets (11–12 g/dl), attainment of higher Hb levels within the target range is associated with decreased mortality and hospitalization.

ESAs currently approved in the US include epoetin alfa (half-life 4–11 h i.v., 19–25 h s.c. [81]; administered 1–3 times weekly [TIW–Q1W]) and darbepoetin alfa (AranespTM; half-life 18–25 h i.v., 49 h s.c. [81]; administered every 1–2 weeks [Q1W–Q2W]). For extended dosing options, the novel agent methoxy polyethylene glycol epoetin beta (CERA), a continuous erythropoietin receptor activator, has a prolonged half-life unaffected by administration route (134 h i.v.; 137 h s.c. [82]), permitting dosing intervals as infrequent as once monthly [83]. Phase II and III studies show that CERA effectively corrects and maintains Hb in ESRD patients requiring dialysis [83, 84] and CKD patients not requiring dialysis [85]. CERA was recently approved by the US Food and Drug Administra-

tion but it is not currently available for use in the US due to a recent patent legal ruling.

An important challenge in managing the anemia of CKD is to maintain adequate iron utilization and stores. ESAs are not maximally effective in the setting of iron deficiency. Decreased iron stores (absolute iron deficiency) or decreased availability of iron (functional iron deficiency) are the most common reasons for ESA resistance in patients with CKD/ESRD. It is recommended in CKD patients that iron saturation should be >20% and serum ferritin be >100–200 (in CKD and ESRD, respectively) before ESAs are started. It has been well-described that African-Americans have lower serum hemoglobins compared to Caucasians [130]; however, one report does not indicate that this difference is due to iron deficiency [128]. Others have reported that serum ferritins are higher in African-Americans citing genetic/familial segregations [129].

Additional anemia therapies are also on the horizon. Hematide is a synthetic, nonrecombinant peptide with a novel amino acid sequence unrelated to erythropoietin; it activates the erythropoietin receptor to induce proliferation and differentiation of erythroid progenitor cells into mature erythrocytes [86, 87]. Emerging small-molecule agents FG-2216 and FG-4592 [88] act upstream of erythropoietin and its receptor by stabilizing hypoxia-inducible factor (HIF-1 α), a nuclear transcription factor that activates erythropoietin gene production [89] and regulates iron absorption, metabolic response, and vasculogenesis. Thus, these agents are reported to increase erythropoiesis and improve iron balance in patients with anemia and systemic inflammation. HIF-1 α stabilizers are the first oral erythropoietic therapies developed for renal anemia, and are currently in phase 2 of clinical development [88].

Anemia Management in African-Americans through the Course of CKD

African-Americans at all stages of CKD benefit from early and ongoing anemia management. Although these patients often receive higher ESA doses [90–92], it is difficult to distinguish the effects of nutritional deficiency, lower pretreatment Hb levels, and delayed ESA initiation from possible racial-specific biological effects on ESA responsiveness [1, 93]. In the Procrit® Dosed Once Weekly in the Patients with Anemia due to Early Renal Insufficiency (POWER) study [94], a post-hoc analysis reported that African-American nonsmokers demonstrated a sta-

tistically significant decreased response to epoetin alfa compared with nonsmokers of other races (mean Hb at week 16: 11.61 vs. 11.86 g/dl, $p = 0.02$); however, whether this was a clinically significant difference in response is not known. In this same trial, African-American smokers responded comparably to other participants according to statistical analyses.

Anemia Treatment at Stages prior to ESRD

Only about a third of incident dialysis patients receive treatment for anemia before the transition to dialysis [68]. The rate of pre-ESRD anemia treatment varies geographically [95] and ethnically [96]. Among 56,593 incident dialysis patients in Georgia and the Carolinas, fewer African-Americans than Caucasians had received ESAs before dialysis onset (22.5 vs. 27.2%; OR 0.78, 95% CI 0.75–0.81) despite significantly lower mean Hb at presentation [96]. A recent report of 620,674 patients initiating dialysis between 1995 and 2003 showed that non-Hispanic Blacks had lower hematocrit levels and less likely to receive ESA therapy than non-Hispanic Whites [131]. The effects of anemia or ESA use on the progression of CKD have been studied predominantly in Caucasian patients [68], and more specific research is needed to explore the consequences of anemia and the outcomes of its treatment in African-Americans with CKD [1].

ESA treatment is typically initiated when Hb concentration falls to ≤ 11.0 g/dl [14]. Iron status should be assessed before ESA initiation and monitored during therapy [97]. Iron supplementation is required to maximize erythropoietic yield. A course of oral iron supplementation (e.g. ferrous sulfate) is reasonable in CKD patients with serum ferritin <100 ng/ml or transferrin saturation <20%; if this is ineffective or poorly tolerated, intravenous iron may be appropriate [14]. Novel iron agents are under investigation; of special note for CKD outpatients, heme iron polypeptide has been reported to enhance oral absorption through the gut heme iron receptor [98].

In outpatients with CKD, extended ESA administration intervals are desirable for convenience and enhanced adherence [27]. Although the approved intervals of existing agents are frequent (Q1W–TIW for epoetin alfa and Q1W–Q2W for darbepoetin alfa), investigations are underway to assess the potential of using current ESAs at extended dosing intervals (table 3). In the Procrit® for Maintenance Phase Treatment of Patients with Anemia due to Chronic Kidney Disease (PROMPT) study [99], the proportion of patients maintaining mean Hb ≥ 11 g/dl declined as the epoetin dosing interval increased. A retrospective chart review of extended epoetin intervals

Table 3. Studies of extended dosing intervals with current ESAs

Drug	Study and reference	Patients	Regimen	Key results
<i>Patients with CKD not on dialysis</i>				
Epoetin- α	PROMPT (randomized maintenance study) [99]	previously treated with epoetin ≥ 2 months (n = 519; modified ITT population n = 445; mean pre-study dose 11,478 U)	10,000 U/week Q1W (n = 130; 26.1% Afr. Am.) 20,000 U/week Q2W (n = 131; 22.1% Afr. Am.) 30,000 U/week Q3W (n = 132; 25.8% Afr. Am.) 40,000 U/week Q4W (n = 126; 24.9% Afr. Am.) 16 wk treatment	mean final Hb of Q2, Q4W groups statistically non-inferior to Q1W group; Hb ≥ 11.0 g/dl maintained in 93.5% of Q1W, 89.5% of Q2W, 77.2% of Q3W, and 76.0% of Q4W patients
Epoetin- α	retrospective chart review [100]	treated with epoetin Q2W to $>Q4W$ for ≥ 3 months in private US nephrology practices (n = 243; 11.6% Afr. Am.)	Q1W (n = 37), mean dose $11,080 \pm 3,730$ U Q2W (n = 124), $15,984 \pm 8,788$ U Q3W (n = 22), $21,000 \pm 10,415$ U Q4W (n = 30), $16,700 \pm 6,839$ U $>Q4W$ (n = 9), $17,333 \pm 8,832$ U	Hb ≥ 11.0 g/dl maintained in 73.0% of Q1W, 78.9% of Q2W, 95.5% of Q3W, 90.0% of Q4W, and 100.0% of $>Q4W$ patients
Darbepoetin- α	multicenter open-label study [101]	treated with stable dose of s.c. darbepoetin Q2W for ≥ 6 weeks before enrollment (n = 98, 35% Afr. Am.; modified ITT population n = 97)	converted from prior Q2W to once monthly for 29 weeks (mean baseline dose 88.7 ± 49.9 μ g; mean evaluation period dose 86.6 ± 78.8 μ g)	Hb 10–12 g/dl maintained in 77% overall (95% CI 71–87%) and 85% (95% CI 78–93%) of those completing evaluation period
Darbepoetin- α	simplify the treatment of anemia with Aranesp (STAAR) [102]	previously treated with Q1W epoetin (n = 524; 21.2% Afr. Am.)	s.c. Q2W darbepoetin (20 weeks' titration, 12 week evaluation; up to 20 weeks extension period; mean baseline dose 49.7 ± 21.9 μ g; mean evaluation period dose 48.9 ± 35.5 μ g)	baseline mean Hb 11.2 ± 1.27 g/dl; evaluation period least-squares mean Hb 11.4 ± 0.04 g/dl
<i>Patients with anemia of CKD on dialysis</i>				
Epoetin	meta-analysis [118]	11 studies totaling 719 patients	TIW, BIW, Q1W	no significant difference in maintaining target Hb between BIW and Q1W (one study, 20 patients: RR 1.00, 95% CI 0.42–2.40) no significant difference in maintaining target Hb between TIW and Q1W (three studies: weighted mean difference -0.31 , 95% CI -0.67 to 0.06)
Darbepoetin	multicenter, open-label, exploratory study [119]	previously stable on darbepoetin Q2W i.v. or s.c. with mean Hb 10–13 g/dl; n = 58, 8% Afr. Am.	extended to darbepoetin Q3W for 16-wk titration (n = 54); if Hb 10–13 g/dl during a 4-week evaluation period, switched to Q4W for further 16-week titration and 4-week evaluation	of 54 patients extended to Q3W, 38 qualified for switching to Q4W; 30 successfully maintained Hb 0–13 g/dl, with mean final Hb 11.16 ± 0.60 g/dl
Afr. Am. = African-American; BIW = twice weekly; CKD = chronic kidney disease; Q1W = once weekly; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; TIW = three times weekly; U = units.				

[100] revealed higher doses at increasing intervals. Of note, only 1 of 28 African-American patients achieved an extended interval (Q4W) in this study. Long-interval darbepoetin regimens have also been studied extensively in patients not requiring dialysis (table 3) [101, 102].

Anemia Treatment in the Dialysis Population

African-American patients experience more severe anemia on dialysis than Caucasian patients [90, 92, 96]. In a large incident dialysis cohort in 3 southern states [96], African-Americans had significantly lower mean

Hb than Caucasians (9.7 ± 4.1 vs. 10.2 ± 3.6 g/dl; $p < 0.0001$). The rate of anemia treatment during dialysis varies not only regionally [103] but also by neighborhood ethnicity within cities [104]. Lack of transportation is a frequent obstacle to dialysis adherence in this population [105]; anemia management regimens relying on frequent in-center ESA and iron administration can be destabilized by the resulting missed sessions [106, 107].

African-Americans on hemodialysis are more likely than Caucasian patients to receive a suboptimal dose of dialysis [90], especially in inner-city dialysis facilities

[104]. Adequate dialysis enhances anemia management and reduces ESA dose requirements [108]. Iron loss incurred in hemodialysis requires intravenous repletion, for which iron sucrose or iron gluconate are often used [68]. Emerging iron agents suitable for dialysis patients include infusible preparations designed to minimize free iron toxicity, as well as intradialysate ferric pyrophosphate [88].

Fewer African-American patients than Caucasian or Asian-American patients select peritoneal dialysis, a modality typically associated with lesser ESA doses and iron requirements [109, 110]. About 80–90% of peritoneal dialysis patients require ESA therapy to maintain Hb >11 g/dl [27, 111]. In a US retrospective study, 80% of hemodialysis patients and 25% of peritoneal dialysis patients were receiving EPO 3 months after dialysis, at average doses of 60,000 and 30,000 units, respectively [110]. African-Americans comprised 25% of the hemodialysis cohort and 13% of the peritoneal cohort [110]. Peritoneal dialysis patients were less likely to receive ESA treatment and received lower doses than hemodialysis patients in this study. Nevertheless, it is difficult to distinguish whether this represented reduced ESA requirements (peritoneal dialysis causes less blood loss than hemodialysis) or less-aggressive ESA treatment strategies for peritoneal dialysis versus hemodialysis patients. Given the naturally lower baseline Hb levels seen in African-Americans, it is not known if the concerns raised by aggressive Hb normalization would be intensified in this patient group.

Hemoglobin Targets and Safety Considerations

Publication in 2006 of 2 clinical trials of EPO therapy in CKD patients not on dialysis [78, 79] resulted in FDA-mandated ESA labeling changes [80, 112, 113] and rethinking of Hb targets [73]. The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) study [78] (n = 603 patients with Hb 11–12.5 g/dl) examined treatment with epoetin- β to increase Hb to either 13.0–15.0 g/dl or 10.5–11.5 g/dl; ethnicities were not reported. Complete correction of Hb levels to 13.0–15.0 g/dl did not increase time to first cardiovascular events in comparison with partial correction to Hb levels of 10.5–11.5 g/dl; frequency of or time to cardiovascular or all-cause death did not differ between groups. The CREATE results indicated that Hb targets exceeding 13 g/dl did not provide additional benefit in comparison to the lower Hb target group [73].

In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial [79], 715 patients

(28.6% African-American) received epoetin- α treatment to a Hb target of 13.5 g/dl; 717 patients (29.3% African-American) were treated to a target of 11.3 g/dl. The composite endpoint (death, myocardial infarction, hospitalization for congestive heart failure without dialysis onset, and stroke) occurred more frequently in the high-Hb group than the low-Hb group (125 vs. 97 events, respectively; hazard ratio, 1.34; 95% confidence interval, 1.03–1.74; p = 0.03), and the trial was stopped prematurely [79]. Of note, 38% of CHOIR patients withdrew from the study early, and the distribution of prevalent hypertension and coronary artery bypass histories suggests that the groups may have begun with unequal cardiovascular risk burdens. Additionally, hyporesponse to epoetin may have increased dose-dependent adverse events in CHOIR. Patients who never attained target Hb received mean doses of 11,098 units/week in the low-Hb group and 12,884 units/week in the high-Hb group, whereas those attaining target Hb averaged 6,057 units/week (low-Hb group) and 10,694 units/week (high-Hb group).

The CREATE and CHOIR results echo an earlier study in dialysis patients [114] showing increases in blood pressure and cardiovascular events in ESRD patients with congestive heart failure or ischemic heart disease randomized to achieve normalization of Hb. Of interest, even patients who did not achieve higher Hb levels in the group randomized to reach normal Hb levels had increased mortality, suggesting that excessive administration of ESAs and iron to hyporesponsive patients may contribute to excess mortality. The ongoing Trial to Reduce Cardiovascular Events with Aranesp (TREAT), comparing darbepoetin treatment (target Hb 13.0 g/dl) versus placebo in patients with diabetic nephropathy, was recently evaluated by its Data Safety and Monitoring Board in view of CHOIR and CREATE, and interim results supported its continuation [115]. Thus, the debate continues as to the potential adverse effects of achieving higher Hb levels in CKD versus the manner in which a higher Hb is achieved.

The ACCORD (The Anemia Correction in Diabetes) study was recently concluded and reported that there was no difference in left ventricular mass nor was there a difference in the rate of decrease in creatinine clearance in subjects randomized to a Hb target of 13.5 vs. 12.1 [127]. However, there was improved quality of life with the higher Hb target with no difference in adverse events between the two groups [127].

While the risk of elevated hemoglobin values continues to be debated, the adverse consequences of a low hemoglobin level was recently reinforced by Ishani et al.

[132] who reported on over 50,000 dialysis patients and found a 1.7-fold relative risk of hospitalization and 2.5-fold relative risk of mortality in those with more months with hemoglobin below the K/DOQI target of 11 g/dl.

Importantly, patients in ESA clinical trials receive high doses of ESAs and iron supplementation intended to achieve rapid separation of mean Hb between high and low target groups; this approach differs from real-world clinical practice. Even so, typically around 50% of trial participants achieve goal Hb, and some fail to respond despite receiving high ESA doses. Further research is needed to ascertain whether adverse events result from aggressively increasing ESA doses in hyporesponsive patients without correcting the source of hyporesponse (inflammation or other comorbidities). In clinical practice, a conservative approach to ESA therapy with Hb goal of 11–12 g/dl and early and stringent blood pressure control is presently recommended for all patients, irrespective of their racial origin [73].

Eliminating Ethnic Disparities in Anemia and Chronic Kidney Disease: Strategies and Goals

In summary, as discussed above, CKD is highly prevalent among African-Americans, progressing to ESRD at roughly quadruple the rate in Caucasians [2, 7]. Early diagnosis and treatment of CKD may be lifesaving; 20–50 times as many patients die in the predialysis stages of CKD (often from cardiovascular complications) than survive to ESRD requiring dialysis or transplantation [5]. As we have seen, diabetes and hypertension, contribute to disproportionate CKD progression among African-Americans, and for various reasons this patient population may respond differently to treatment regimens. Moreover, African-Americans have lower Hb levels at dialysis initiation and are less likely to receive ESA treatment prior to dialysis.

Once dialysis is initiated, African-Americans receive higher ESA doses [90–92]; however, it is difficult to distinguish the effects of nutritional deficiency, lower pretreatment Hb levels, and delayed ESA initiation from possible racial-specific biological effects on ESA responsiveness. Awareness of racial-specific challenges in anemia management in addition to CKD risk factors, progression, complications, and treatment responses will help physicians serve African-American kidney patients more effectively. Racial Hb variations superimposed on the effects of CKD warrant further review and possibly racial-specific guidelines for anemia diagnosis and treatment [12].

Crucial interventions to reduce CKD progression and cardiovascular disease include lifestyle modification and the treatment of hypertension, diabetes, dyslipidemia, as well as anemia [1]. Physicians need to advocate for improved healthcare access in minority communities and counsel patients on nutrition, exercise, and prevention of obesity and substance abuse [105]. Early identification of CKD and anemia in African-Americans is paramount in order to prevent progression of CKD and cardiovascular disease.

Clinical outcomes, comorbidities, disease progression, and health-related behavior and attitudes in minority populations require further study [90]. Ethnic minorities are currently underrepresented in clinical trials, contributing to lacunae in evidence-based recommendations [1]; ethnically diverse trials are necessary to understand possible differences in response to pharmacotherapy for CKD-related conditions such as anemia [94]. Increased understanding of the patterns and causes of racial disparities in CKD will allow for a more tailored management strategy for different racial and ethnic groups [105]. Proactive management of CKD and its complications, including anemia, throughout its course can alleviate the impact of ESRD on African-Americans at a public health level.

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