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Critiques of Clinical Guidelines in Nephrology: Anaemia

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Key Words

Anaemia · Chronic kidney disease · Clinical practice guidelines · Erythropoietin · Erythropoiesis-stimulating agents

Abstract

Chronic kidney disease (CKD) is characterised by reduced erythropoietin production and anaemia. The introduction in the late 1980s of recombinant human erythropoietin transformed the quality of life and the blood transfusion requirements of patients with advanced CKD, and several erythropoietin analogues or derivatives with the collective name of erythropoiesis-stimulating agents (ESAs) are now available. However, despite the treatment of hundreds of thousands of patients with ESAs there have still been relatively few randomised controlled trials comparing outcomes at pre-specified haemoglobin (Hb) concentrations. Several unanswered questions remain regarding the optimal use of ESAs, including the ideal target Hb level for an individual and a CKD population. The conclusion from the available interventional studies is that there is no evidence for a beneficial effect of complete correction of Hb and there is weak evidence of harm with an increase in cardiovascular events and mortality. This has prompted some renal advisory bodies to modify their guidance on ESA prescribing. This critique reviews current clinical guidelines and recommendations, their scientific basis, and identifies areas of controversy including the role of newer agents, the long-term safety of ESAs, the influence of the pharmaceutical industry, and the associated healthcare costs.

Introduction

The association between anaemia and chronic kidney disease (CKD) is well established. Erythropoietin, the principal regulator of erythropoiesis, is synthesized primarily in the kidney and is present in picomolar concentrations in serum [1]. The production of erythropoietin is regulated by a renal oxygen-sensing homeostatic feedback mechanism. Erythropoietin binds to and activates its receptor on red cell progenitor cells promoting their differentiation into mature erythrocytes [2]. CKD is characterised by reduced erythropoietin production and normochromic normocytic anaemia [3].

The development and introduction of recombinant human erythropoietin (rHuEPO, EPO, epoetin) in the late 1980s had a major impact on the quality of life (QoL) and blood transfusion requirements of patients with end-stage renal disease (ESRD) [4]. There are now several erythropoetin analogues or derivatives, with the collective name of erythropoiesis-stimulating agents (ESAs) [5].

From initially modest therapeutic targets for haemoglobin (Hb) concentrations there has been a trend to increased Hb levels in patients with CKD. In the USA, the mean Hb concentration in haemodialysis (HD) patients rose from 9.7 g/dl in 1991 to 12.0 g/dl in 2005 [6]. However, results from several large randomized controlled trials (RCTs) have raised doubts about the benefits of fully correcting erythropoietin deficiency with evidence of at best non-benefit, and at worst increased mortality, associated with the achievement of normal Hb concentrations [7].

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Table 1. Summary of current renal anaemia guidelines

	RA (2007)	EBPG (2004)	KDOQI (2006)	KDOQI (2007)
Evaluation				
Hb, g/dl				
Male	<13.0	<13.5; <12.0[a]	<13.5	
Female	<13.0; <12.0[b]	<11.5	<12.0	
GFR, ml/min/1.73 m^2 BSA	<60	all CKD	all CKD	
Initiation Hb, g/dl	<11.0	<11.0	unspecified	<10.0
Target Hb, g/dl	10.5–12.5	>11.0	≥11.0	11.0–12.0
Maximum Hb, g/dl	unspecified	14.0 (HD); 12.0 (CCF); 12.0 (DM)	13.0 caution	13.0
ESA				
Agent	unspecified	unspecified	unspecified	
Route	SC short-acting	SC in non-HD; SC/IV in HD	SC in non-HD; IV in HD	
Adjust	<11.0; >12.0	unspecified	unspecified	
Iron				
Route	IV for HD	IV for HD	IV for HD	
Ferritin, μg/l				
Target	200–500	200–500 population; >100 individual	>100 non-HD; >200 HD	
Upper	800 (r/v >500)	800	500	
HRC, %	<6	<2.5 population; <10 individual	unspecified	
TSAT, %	>20	30–40 population; >20 individual	≥20	

r/v = Review; HRC = hypochromic red cells; TSAT = transferrin saturation.
[a] If >70 years old. [b] Pre-menopausal.

Several unanswered questions remain regarding the optimal use of ESAs, including the ideal target Hb level for an individual and a CKD population, the role of newer ESAs, the long-term safety of ESAs, their associated healthcare costs, and the role of the pharmaceutical industry in determining clinical practice guidelines. This critique reviews current clinical guidelines and recommendations, their scientific basis, and identifies areas of controversy.

Brief Summary of Existing Guidelines

Best practice guidelines are developed to aid the physician in providing the optimal care for patients by analyzing and summarizing the available scientific literature on a particular topic. They may also serve to highlight the deficiency of good evidence to support current practice. The Kidney Disease Outcomes Quality Initiative (KDOQI) now delineates clinical practice guidelines distinct from clinical practice recommendations to improve clarity in this area in their publications.

Guidelines devoted to the management of anaemia in CKD are often sizeable documents. The common and most salient points from the latest United Kingdom Renal Association (RA) [8], European Best Practice Guidelines (EBPG) [9] and United States KDOQI [10, 11] guidelines are summarized in table 1. The EBPG were last updated in 2004, KDOQI published guidelines in 2006 and revised these again in 2007, and the RA also completed a review of their recommendations in 2007.

These advisory bodies differ with respect to the lowest Hb concentration in a patient with CKD that should trigger further evaluation. Although all guidelines are gender specific, only those from the RA differentiate between pre- and post-menopausal females. The EBPG distinguish between men younger and older than 70 years. There is consensus between the RA and EBPG concerning the Hb level at which to initiate ESA therapy (Hb consistently <11 g/dl), with the new KDOQI guidance now specifying a lower Hb level of <10 g/dl before commencing ESA therapy.

It is notable that an upper limit has been added to the target Hb concentration in 2007 by both the RA and

KDOQI. The latter now have a narrow target Hb range of 1 g/dl (11.0–12.0 g/dl) in contrast to the 2 g/dl range of the RA guidelines (10.5–12.5 g/dl). The EBPG are consistent with the available literature in 2004 in that a maximum Hb concentration is recommended in specific sub-groups only: those with diabetes mellitus (12.0 g/dl), heart failure of stage III or IV New York Heart Association classification (12.0 g/dl), and those on HD (14.0 g/dl).

There is some consensus regarding ESA prescribing. The choice of ESA is left to local discretion, reflecting the comparative efficacy between agents. The RA guidelines are not prescriptive concerning the route of administration but state that subcutaneous (SC) administration of epoetins is more economical. KDOQI recommendations are based on the perceived convenience of administration: SC for those not receiving HD and intravenous (IV) in HD patients. The EBPG suggest the SC route in non-HD CKD but acknowledge the potential conflict of interest between cost effectiveness and comfort/convenience in HD patients, leaving the final choice to the individual clinician.

Critique of Existing Guidelines

Evolution of Guidelines

Clinical practice guidelines rest on the evidence base derived from the scientific literature. Although in recent years there have been numerous publications of variable quality concerning target Hb concentration, ESA use, and outcomes, there are only a limited number of RCTs in this area. Arguably, overreliance on available observational data has contributed to some of the problems with renal anaemia guideline development.

The RA first produced recommendations in 1997, suggesting that 85% of dialysis patients should have an Hb of at least 10 g/dl within 3 months of dialysis start. This target was retained in the 2002 guideline review but allowed 6 months to achieve this Hb level. The target Hb was refined to a range of 10.5–12.5 g/dl in 2007 [8].

The EBPG for renal anaemia were first published in 1999 with the recommendation that 85% of dialysis patients should have an Hb exceeding 11.0 g/dl within 4 months of initiation of dialysis [12]. It was noted that achievement of this standard would most likely result in population mean and median Hb levels in the range of 12.0–12.5 g/dl. The revision of the EBPG in 2004 retained the same target Hb concentration [9].

The KDOQI guidelines were originally published in 1997 under the auspices of the National Kidney Foundation Dialysis Quality Outcome Initiative (NKF-DOQI). At this time, and also in the 2001 revision, the target Hb was 11.0–12.0 g/dl (haematocrit, Hct, 33–36%). Surprisingly, the 2006 guidelines were released just prior to publication of two large RCTs considering the outcomes associated with higher Hb concentrations. At this time the upper limit for Hb concentration was raised to 13.0 g/dl [10]. Six months later a review was prompted, with a concurrent warning from the Food and Drug Administration, concerning the upper acceptable limit of Hb [13]. The target Hb concentration suggested by KDOQI was then revised to the previous 11.0–12.0 g/dl [11].

Observational Studies

The intuitive link between anaemia, left ventricular (LV) dysfunction, and death in patients with CKD was highlighted in a prospective study of over 400 dialysis patients, published in 1996, which concluded that anaemia was an independent risk factor for cardiac disease and mortality in this population [14]. An earlier report, in a small series of 9 patients, indicated that partial correction of severe anaemia (mean Hb 5.9 g/dl to mean Hb 10.2 g/dl) was associated with reversal of LV hypertrophy [15]. Subsequently several large observational studies have described the relationship between Hb concentration, cardiovascular disease and mortality. The important studies in dialysis and non-dialysis CKD populations are now reviewed.

Association between Hb Concentration and Mortality in Dialysis Patients

From 1998 to 2006, six large observational studies were published relating Hb/Hct concentration and mortality in HD patients, with study populations ranging from approximately 5,000 to 95,000 [16–21]. The crude collective conclusion from these observational studies was that higher Hb/Hct values are associated with reduced mortality. In light of the controversy concerning the safety of higher Hb levels it is useful to review the Hb/Hct levels observed in these studies, the number of patients in the highest Hb categories, and their outcomes. This information is summarised in table 2.

The Lombardy Register considered Hct >32% as the highest cohort with fewer than 1,500 patients in this group [16]. Only 1% (685) of patients in the study by Ma et al. [17] had an Hct >36% and they had a similar outcome to patients with the reference Hct range of 30 to <33%. In the study by Collins et al. [18], 7.3% (4,862) of patients exceeded this Hct level and there was a significant reduction in hospitalisation but not in mortality in

Table 2. Observational studies (association between Hb concentration and mortality) in haemodialysis patients

First author	Year	Higher Hct/Hb groups	Patient number	Reference range	Evaluation of mortality risk		95% CI	p value
Locatelli [16]	1998	>32.0	1,498	crude mortality rate only				
Ma [17]	1999	>36.0	685	30.0–<33.0	adjusted RR	1.06	0.89–1.27	0.49
Collins [18]	2001	36.0–<39.0	4,307	33.0–<36.0	adjusted RR	0.99	0.92–1.07	>0.05
		≥39.0	555			1.05	0.86–1.28	>0.05
Ofsthun [19]	2003	12.0–<13.0	5,515	11.0–<12.0	adjusted RR	0.84	unknown	0.007
		≥13.0	1,090			0.82		>0.05
Pisoni [20]	2004	≥12.0	1,403	11.0–<12.0	adjusted RR	0.92	unknown	0.19
Regidor [21]	2006	12.0–<12.5	unknown	11.5–<12.0	adjusted HR	0.94	0.88–1.01	0.07
		12.5–<13.0				0.92	0.85–0.98	0.02
		13.0–<13.5				1.04	0.96–1.13	0.4
		13.5–<14.0				1.24	1.12–1.37	<0.001
		≥14.0				1.17	1.06–1.30	0.002

Hct = Haematocrit %; Hb = haemoglobin, g/dl; RR = relative risk; HR = hazard ratio; CI = confidence interval.

this group compared to those with an Hct from 33 to <36%. In the study by Ofsthun et al. [19], after adjustment for covariates, there was a significant reduction in relative risk of mortality in patients with an Hb from 12.0 to <13.0 g/dl (n = 5,515), but this trend was not significant in patients with an Hb >13.0 g/dl (n = 1,090). Pisoni et al. [20] considered the same reference range of 11.0 to <12.0 g/dl but found the difference in mortality was non-significant for patients with an Hb ≥12.0 g/dl (n = 1,403). Finally, Regidor et al. [21] noted a survival advantage in patients with an Hb up to 13.0 g/dl (reference range 11.5–12.0 g/dl, n = unknown) with a significant increase in mortality when the Hb exceeded 13.5 g/dl.

Thus only two observational studies reported a statistically significant improvement in mortality with an Hb between 12.0 and 13.0 g/dl. This apparent survival advantage was not sustained at even higher Hb levels, and two studies found no significant difference. Ma et al. [17] argue that very large sample sizes are required to detect the true impact of Hb/Hct on survival, independent of the complex interactions with co-morbidity and disease severity. Their sensitivity analysis suggested up to 16,000 observations in the 33–36% group would be needed. Clearly, none of the observational studies had close to this number of patients in the higher Hb cohorts.

Association between Hb Concentration and Cardiovascular Disease in Dialysis Patients

Three of the six observational studies in table 2 reported on cardiovascular mortality in addition to all-cause mortality. There was no association between Hct and cardiovascular death in the Lombardy Dialysis Register [16]. In the report by Ma et al. [17] the relative risk of cardiovascular death was highest in those with an Hct <27% compared to a reference group with Hct 30 to <33% (RR 1.40, 95% CI 1.30–1.52), but there was no advantage from an Hct >36% in reducing cardiovascular-related death. Similarly there was no benefit in terms of cardiovascular mortality with an Hct >36% in Collins' study, but an Hct <33% was significantly associated with an increased risk of cardiovascular death compared to the reference group with Hct 33 to <36% [18].

Association between Hb Concentration, Mortality and Cardiovascular Disease in Non-Dialysis Patients

Two large observational studies have considered the association between anaemia, cardiac disease, and death in patients with non-dialysis CKD, and a third reported on cardiovascular events but not all-cause mortality. The first study considered a population of 3,015 with diabetes mellitus (DM) with a median follow-up of 8.6 years [22] of whom 8% had anaemia (Hct <39% men, <36% women) and 13% CKD (eGFR 15–60 ml/min/1.73 m^2). Anaemia was reported as an independent risk fac-

Table 3. RCTs (association between Hb concentration and mortality) in haemodialysis patients; summary of meta-analysis performed by Strippoli et al. [24]

Trials	Patients	Achieved Hb, g/dl		Mortality	
				RR	95% CI
No EPO vs. EPO					
12	638	no EPO	7.5–10.4	1.83[a]	0.48–7.06
		with EPO	9.5–13.3		
Low vs. high Hb					
7	2,058	low Hb	9.0–12.0	0.84[b]	0.71–1.00
		high Hb	11.9–15.0		

[a] Pooled survival analysis of 3 trials (n = 255).
[b] Pooled survival analysis of 4 trials (n = 1,949).

tor for cardiovascular disease and all-cause mortality in patients with CKD [22].

The second study identified 275 patients with anaemia (Hct <39% men, <36% women) in a community population of 2,423 persons with CKD stages 3–5 (mean eGFR 51 ml/min/1.73 m^2) [22]. Lower Hb concentrations were associated with a significant increased risk of the composite end-point of myocardial infarction (MI), stroke, and death. The combination of anaemia and LV hypertrophy was particularly disadvantageous.

The third study analysed insurance claims for hospitalisation with ischaemic heart disease, stroke, congestive heart failure (CHF) and new start of dialysis in 88,657 individuals with CKD (creatinine >1.4 mg/dl men, >1.2 mg/dl women) and considered the associated risk with Hb concentration, using Hb 12.0–12.9 g/dl as the reference cohort [23]. There was a significant association between lower Hb concentrations and cardiovascular disease as estimated by this outcome measure.

All three studies are consistent in reporting an association between moderate or severe anaemia and cardiovascular disease in patients with CKD. Nevertheless, it is important to remember that these observational studies are subject to a number of limitations including confounding by factors such as chronic inflammation that can contribute to both anaemia and cardiovascular disease. Although causality cannot be inferred, these observations are still useful for generating hypotheses that can be tested in appropriate randomized clinical trials.

Randomised Controlled Trials

The RCT evidence examining the relationship between Hb concentration and cardiovascular disease and mortality in dialysis and non-dialysis CKD patients is now summarised.

Association between Hb Concentration, Mortality and Cardiovascular Disease in Dialysis Patients

A comprehensive meta-analysis of the available RCTs assessing Hb/Hct and mortality in dialysis patients was published in 2004 [24], summarised in table 3. There were 12 trials (total patients = 638) that compared the use and non-use of ESAs, three of which were suitable for pooled survival analysis. There was no significant difference in mortality, RR 1.83, although the 95% confidence interval is notably wide (0.48–7.06). These patients had no overt cardiovascular disease.

Seven trials (total patients = 2,058) considered high and low Hb concentrations, with four included in survival analysis. The relative mortality was reduced with a lower Hb concentration (Hb <12 g/dl vs. >13.0 g/dl), RR 0.84, and this just reached statistical significance (p = 0.05). The absolute risk of death was 3% lower, in theory avoiding one death for every 30 patients maintained with an Hb <12 g/dl compared to Hb >13 g/dl. The Normal Hematocrit Study [25] was the primary determinant of this meta-analysis result, contributing 86% of the weight. The other trials were inadequately powered to demonstrate benefit or harm. There have been no substantive RCTs in this field published since this meta-analysis.

The 1,233 subjects enrolled in the Normal Hematocrit Study [26] were prevalent HD patients with established cardiovascular disease, with a mean age of approximately 65 years. The high and low Hct targets were 42% and 30%. The primary end-point was length of time to death or non-fatal MI. The trial was halted early when it was considered highly unlikely that there would be a beneficial effect in the higher haematocrit group, and the evidence indicating a detrimental effect in this group was approaching statistical significance. The risk ratio for death or non-fatal MI in the normal haematocrit group was 1.3 (95% CI 0.9–1.9). Interestingly, this mortality risk was inversely related to Hct within both the low and high Hct groups, and analysis of Hct as a continuous rather than a categorical variable suggested a risk reduction of 0.7 (95% CI 0.6–0.8) per 10% increase in Hct. The higher Hct group received significantly more IV iron supplement and had poorer solute clearance (as assessed by Kt/V) in the first year compared to the low Hct group. The relevance of these factors to the primary outcome mea-

Table 4. Summary of CREATE and CHOIR studies

	CREATE [29]	CHOIR [30]
Geography	Europe	USA
Patients	603	1,432
eGFR, ml/min/1.73 m^2	15–35	15–50
Target Hb, g/dl		
Low	10.5–11.5	11.3
High	13.0–15.0	13.5[a]
Achieved Hb difference between groups, g/dl	1.5–1.9	1.3
Mean follow-up, months	35	16
Primary outcome (composite)	8 CV events	death, MI, stroke CHF hospitalisation
Outcome		
HR	0.78	1.34
95% CI	0.53–1.14	1.03–1.74
p value	0.20	0.03

HR = Hazard ratio; CI = confidence interval; CV = cardiovascular.

[a] Mean achieved Hb 12.6 g/dl.

sure is unknown. The conclusion at best is that normalisation of Hct concentrations in HD patients with overt cardiovascular disease has no evidence of benefit and may be harmful.

There were no significant differences between the lower and higher Hct groups in the Normal Hematocrit Study in terms of the frequency of cardiovascular events [25]. Similarly negative findings were reported by Furuland et al. [26] whose RCT included 344 patients on dialysis and 72 pre-dialysis patients.

Association between Hb Concentration and Echocardiograph Abnormalities in Dialysis Patients

Foley et al. randomised 146 HD patients with asymptomatic LV hypertrophy or dilation to a target Hb of 10 g/dl or 13.5 g/dl [27]. After a study period of 48 weeks, there was no correlation between Hb concentration and regression of cardiac structural abnormalities. Similarly, negative findings were reported by Parfrey et al. [28] who considered changes in LV structure in 596 HD patients without symptomatic heart disease or LV dilation. The achieved mean Hb values in the two groups were 10.9 and 13.3 g/dl, respectively, with a follow-up period of 72 weeks.

Thus, just one small open label study with only 9 patients suggested that improvement in LV structure in HD patients can be expected with partial correction of severe anaemia [15], but there is no evidence from RCTs that achieving Hb concentrations greater than 10 g/dl provides any additional benefit except improvement in perceived QoL.

Association between Hb Concentration, Mortality and Cardiovascular Disease in Non-Dialysis Patients

Prior to 2006, there was very limited data available concerning the optimal Hb concentration for survival in non-dialysis CKD patients, so advice in clinical guidelines was more opinion based. Publication of the Cardiovascular Risk reduction by Early Anaemia Treatment with Epoetin Beta (CREATE) trial [29] and the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial [30] provided valuable information on mortality and cardiovascular disease in this group of patients (trials are compared in summary form in table 4).

CREATE enrolled 603 European patients with CKD (eGFR 15–35 ml/min/1.73 m^2) who were randomised to achieve a target Hb of 10.5–11.5 g/dl or 13.5–15.0 g/dl with the use of SC epoetin beta. The achieved difference in Hb concentrations between the two groups was 1.9, 1.7, and 1.5 g/dl at 1, 2, and 3 years, respectively. The primary end-point was a composite of eight different cardiovascular events including sudden death; the secondary endpoints included death from any cause, LV mass index, time to renal replacement therapy, and QoL assessment. Over 3 years of follow-up, there was no difference in cardiovascular event rate, all-cause mortality, cardiovascular death, or LV mass index. Significantly more patients randomised to a higher Hb commenced renal replacement therapy, although the higher Hb group had better QoL scores. The early complete correction of anaemia therefore did not reduce the risk of cardiovascular events, HR 0.78 (95% CI 0.53–1.14, p = 0.20).

The CHOIR trial involved 1,432 US patients with CKD (eGFR 15–50 ml/min/1.73 m^2) who received epoetin alpha, randomised to a target Hb of 11.3 or 13.5 g/dl. The achieved mean Hb in the higher Hb group was 12.6 g/dl. The primary outcome measure was a composite of death, MI, hospitalisation with CHF, and stroke. The median duration of follow-up was 16 months with early termination after the second interim analysis as there was considered to be a very low likelihood of detecting a true benefit in the high Hb group by the end of the study. Patients within the higher Hb target group had a significantly higher risk of the primary end-point, HR 1.34 (95% CI 1.03–1.74, p = 0.03), were more likely to have a serious adverse event, had a non-significant trend towards a higher rate of renal replacement therapy, and had

no improvement in QoL compared to those in the lower Hb cohort. When the secondary end-points were considered, it was apparent that there was no difference between the incidence of MI or stroke between the two groups. Hospitalisation with CHF accounted for 75% of the composite primary end-point, with a trend also to increased mortality in the higher Hb cohort.

Interestingly there are substantial differences between the CREATE and CHOIR trials with a cardiovascular event rate approximately three times greater in the CHOIR study, despite a higher baseline eGFR. Much higher doses of epoetin were required in the CHOIR than the CREATE trial to achieve approximately equivalent Hb concentrations.

Clearly the relationship between anaemia, cardiovascular disease, CKD, and mortality is complex. Although anaemia is an established risk factor for cardiovascular disease, based on these RCT results, the complete correction of anaemia does not improve outcomes in this high-risk population. Could it be that the causal factors for anaemia are more relevant to outcomes than the Hb level per se? Is it the rise in Hb concentration concomitant with an increase in blood pressure, viscosity, and platelet adhesiveness that confers a higher relative risk than the usual properties of the uraemic milieu [31]? Is the treatment itself (with potentially larger doses of supplemental iron, or intermittent high doses of ESAs) detrimental?

A much larger RCT continues in this area. The Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT) has recruited approximately 4,000 anaemic patients with DM and CKD (eGFR 20–60 ml/min/1.73 m^2) [32] and thus should be adequately powered to detect clinically significant end-points (a criticism of the CREATE study). There is also wider separation between the target Hb concentrations with the higher group targeted to an Hb >13 g/dl, and the lower group receiving placebo unless darbepoetin alpha (Aranesp) is necessary to maintain Hb >9 g/dl. The composite primary end-point is the time to mortality and four pre-specified non-fatal cardiovascular events.

Association between Hb Concentration and Echocardiograph Abnormalities in Non-Dialysis Patients

Several small RCTs have reported on the influence of Hb concentration on LV mass index and progression of renal disease in non-dialysis CKD populations. The largest was the Anaemia CORrection in Diabetes (ACORD) study reported in 2007 by Ritz et al. [33]. This trial recruited 172 patients with diabetic nephropathy and stages 1–3 CKD, who were randomised to two different target Hb groups. The achieved Hb concentrations at the end of the study were 13.5 g/dl in one cohort and 12.2 g/dl in the other. There was no significant difference in LV mass index or progression of kidney disease. Similar findings were reported by Roger et al. [34] who studied 155 patients with CKD over 2 years, and Levin et al. [35] who also found that early and higher correction of Hb did not prevent or delay a rising LV mass index in patients with CKD. The mean achieved Hb in the lower Hb cohorts in these studies, Hb 10.8 g/dl [34] and Hb 11.6 g/dl [35], exceeded the original targets. In contrast, the treatment of severe anaemia (Hb <10 g/dl) in an open-labelled study by Ayus et al. [36] (40 patients, eGFR 10–40 ml/min/1.73 m^2) resulted in regression of LV hypertrophy independently of changes in blood pressure. The mean change in Hb concentration was from 9.1 to 11.3 g/dl.

These results are similar to the studies of serial cardiac structural change in the dialysis population, where regression of LV hypertrophy was only reported with an improvement in Hb to >10 g/dl and not with further increases [15, 27, 28]. This suggests that detectable reversal of LV structural abnormality is possible in the setting of severe anaemia with more pronounced structural changes, and that there is nothing to be gained from complete normalization of Hb concentrations.

Influence of Hb Concentration on CKD Progression

The studies by Ritz et al. [33] and Roger et al. [34] also assessed CKD progression and found no correlation between renal survival and Hb concentration. This is in contrast to the results of some earlier smaller studies [37, 38]. A more recent Cochrane Database Systematic Review concluded that an Hb <12 g/dl compared to Hb >13 g/dl did not influence the time to development of ESRD (RR 1.05, 95% CI 0.50–2.22) [39].

Summary of Scientific Evidence

The principal papers available to inform clinical practice in relation to optimal Hb concentration in patients with CKD have been discussed. There are observational and randomised controlled trials considering mortality, cardiovascular disease, and structural cardiac abnormalities in both dialysis and non-dialysis patients with CKD.

Mortality in Dialysis Patients

Two observational studies reported that an Hb of 12–13 g/dl (but not exceeding 13 g/dl) was better than 11–12 g/dl [19, 21], and three observational studies of comparative size found no significant difference in survival at

these Hb levels [17, 18, 20]. The one RCT of substantive size (n = 1,233) concluded that an Hct of 42% compared with 30% was of no benefit and potentially harmful in HD patients with overt cardiovascular disease [25].

Mortality in Non-Dialysis CKD Patients

Two observational studies concluded that there was an association between moderate anaemia (Hct <39% men, <36% women) and mortality [22, 40]. Two published RCTs (CREATE n = 603, and CHOIR n = 1,432) did not confirm causality with no difference in mortality in the CREATE study [29], and a trend to increased mortality with a higher Hb (mean Hb 12.6 g/dl vs. 11.3 g/dl) in the CHOIR study [30].

Cardiovascular Disease in Dialysis Patients

Two out of three observational studies demonstrated a reduction in cardiovascular death with an Hct up to but not exceeding 36% compared to reference groups with Hct range from 30 to <36% [17, 18]. There is no RCT evidence to support a beneficial effect of higher Hb concentration on cardiovascular event rate [25, 26].

Cardiovascular Disease in Non-Dialysis CKD Patients

One large observational study (n >88,000) reported an association between lower Hb concentration (compared to a reference range of 12.0–12.9 g/dl) and cardiovascular disease [23]. Two smaller observational studies also reported moderate anaemia as an independent risk factor for cardiovascular events [22, 40]. The interventional trials did not support these findings. In CREATE, there was no risk reduction with higher Hb levels [29], and in the CHOIR trial, there was an increase in hospitalisation for CHF in this group [30]. Publication of TREAT is awaited.

Structural Cardiac Changes in Dialysis Patients

Correction of severe anaemia to an Hb >10 g/dl in a small study was associated with regression of LV hypertrophy [15]. Two RCTs reported no correlation between cardiac structural abnormalities and Hb concentration when the lower range of Hb was approximately 10–11 g/dl and the upper range >13 g/dl [27, 28].

Structural Cardiac Changes in Non-Dialysis CKD Patients

Two interventional trials (n = 152 and n = 155) reported no difference in LV mass index between lower Hb (approximately 10.8 and 11.6 g/dl) and higher Hb (approximately 12.1 and 12.8 g/dl) concentrations [34, 35].

Continued Areas of Uncertainty

Despite the treatment of hundreds of thousands of patients with ESAs, there have still been relatively few RCTs comparing patient outcomes at pre-specified Hb concentrations. The optimal Hb concentration for both dialysis-dependent and non-dialysis patients has not been irrefutably established. Other issues, such as the choice of ESA, route and frequency of administration, are less critical since the evidence suggests equivalent efficacy between agents and local costing may determine the choice [41].

Hb Targets

The absence of upper limits to Hb targets, only added to the RA and KDOQI guidelines in 2007, may have inadvertently compromised the Hippocratic principle of 'first do no harm'. In the UK, the percentage of HD patients achieving an Hb >10 g/dl increased from 65% in 1997 to 85% in 2006 [42], but the mean Hb concentration has remained constant in recent years (11.8 g/dl in 2002 and 11.7 g/dl in 2006). This may reflect adherence to the more modest RA Hb target, >85% of dialysis patients with an Hb >10 g/dl. Since the last update was in 2004, the EBPG target remains one sided, and the writers acknowledged at the time that achievement of the target of 85% of patients with an Hb >11 g/dl is likely to result in a population mean Hb of 12.0–12.5 g/dl [9]. Inevitably in clinical practice a proportion of patients will exceed upper target Hb limits potentially placing them at higher risk, particularly if they have co-existing cardiovascular disease.

The conclusion from the available interventional studies is that there is no evidence for a beneficial effect of complete correction of Hb and there is weak evidence of harm with an increase in cardiovascular events and mortality. A target Hb exceeding 12 g/dl is not recommended.

Unexpected Effects of ESAs

Furthermore, it is important to note that ESAs may have unexpected actions beyond their influence on erythropoiesis. For instance, several oncology studies employing ESAs have raised concerns regarding the potential effect of ESAs on the rate of tumour growth, neovascularisation, and thrombotic risk [43–46]. These concerns prompted the US Food and Drug Administration to issue an alert in 2007 regarding the use of ESAs for cancer-associated anaemia [13].

Undoubtedly the intermittent dosing of large quantities of ESAs does not mimic normal physiological regula-

tion and homeostasis [47]. The effects of the pharmacological dosing of epoetin in non-erythroid tissues, that also express erythropoetin receptors, are still being elucidated [48, 49].

Economic Implications

There are substantial economic implications associated with the use of ESAs in CKD. In 2005, the cost of ESAs use in the USA, in the ESRD population only, approached USD 2 billion [50]. In 2003, Tonelli et al. [51] estimated the economic implications of normalizing Hb levels in HD patients. Using the cost per Quality Adjusted Life Year (QALY) as the unit of measurement and a reference Hb range of 9.5–10.5 g/dl, they estimated cost based on the expected necessary quantity of IV epoetin to reach an Hb of 11.0–12.0, 12.0–12.5 and 14.0 g/dl. To achieve the current recommended target, the estimated cost per QALY was just over USD 55,000. However, to reach the next Hb target (12.0–12.5 g/dl) required an estimated additional cost in excess of USD 600,000. Normalisation of Hb (14.0 g/dl) was estimated to require more than USD 800,000 above this again, i.e. to raise Hb from 12.0–12.5 to 14.0 g/dl. The expected savings in hospitalisations would make no significant indent in this expenditure. Thus in terms of health economics, the cost-benefit ratio to achieve an Hb concentration above 12 g/dl in the HD population is unfavourable and prohibitive for healthcare systems.

The Influence of Pharmaceutical Industry

Concerns have been voiced regarding the ability of the pharmaceutical industry to influence clinicians' management of renal anaemia. In the USA, reimbursement of injectable medications including ESAs is an important revenue source for privately owned dialysis units [52], and despite less favourable pharmacokinetics [47] and economics the IV route of administration is predominantly used in these facilities [53].

The role of industry in the development of clinical practice guidelines has also come under scrutiny, particularly given the timing of the publication of the KDOQI guidelines in 2006. Concern was expressed regarding the possibility of vested interests resulting in higher Hb target levels than were justifiable and the issues of the 'funding of guideline development, disclosure of industrial affiliations, and conflicts of interest' remain 'hot topics' [54]. The EBPG in 2004 was sponsored by an educational grant from Amgen, Roche, Ortho Biotech and Vifor International [9], all companies with more than a passing interest in the guidelines that are produced. No such funding is associated with the production of the UK RA guidelines. Do such financial associations really alter the integrity of those on the working group of guideline development? Is it feasible to have expert clinicians who have no links with the pharmaceutical industry? Assessment of large quantities of scientific evidence and the production of comprehensive guidelines is a time-consuming and worthy task, but the final clinical recommendations must be in the best interests of patients and devoid of commercial bias.

Intra-Individual Variation in Hb Concentration

The intra-individual variation in Hb concentrations, also known as Hb cycling, ensures that maintaining individual patients within an Hb target range is challenging in practice.

Lacson et al. [55] reported an observational study assessing the variation in Hb concentration in over 48,000 HD patients, using a 3-monthly rolling Hb average. 8% of patients had an Hb persistently below 11 g/dl; 18% had an Hb persistently above 12 g/dl; 29% moved either from below to above the target range (11.0–12.0 g/dl) or vice versa. The authors estimated that if 90% of patients had a 3-month rolling average Hb over 10 g/dl, there would be 13–31% of patients with an Hb concentration exceeding 12.5 g/dl.

Fishbane and Berns [56] studied individual fluctuations in Hb concentration in more detail in 281 HD patients for 1 year. The mean Hb was 11.8 g/dl (95% CI 11.2–12.1), and the mean number of changes in ESA dose per year was 6.3 ± 3.3. Hb cycling (levels going up and down or vice versa) was almost universal with over 90% of patients' Hb levels varying by at least 1.5 g/dl for a minimum period of 8 weeks. A change in Hb concentration either up or down of >1.5 g/dl (which was termed an Hb excursion) was also common occurring on average three times per year in addition to Hb cycling. Independent predictors were change in ESA prescribing, change in IV iron prescribing and hospitalisations. It was also noted that there was considerable variation in individuals' sensitivity to epoetin.

It is unclear exactly what the biological implications of such non-physiological oscillations in Hb concentration are, although two recent studies have reported a significant association between highly variable Hb levels and mortality in HD patients [57, 58]. It is postulated that the fluctuation in oxygen delivery to vital organs must have a negative impact [56].

The narrow target Hb concentration of 1 g/dl advocated by the KDOQI guidelines is likely to precipitate fre-

quent dose changes in ESA prescribing, particularly if excursions outside of this range are associated with financial penalties. The broader target range of 10.5–12.5 g/dl suggested by the UK RA seems a more pragmatic and clinically useful guideline. The absence of an upper target by the EBPG is outdated in light of the evidence available since 2004 and an updated version is awaited. A wider target range, less frequent assessment of Hb concentration, and weekly iron prescribing aiming for 'smoother' iron storage kinetics are practical suggestions aimed at reducing the frequency of dose changes in ESAs and Hb cycling [56].

Conclusion

A robust evidence base is needed to develop clinical practice guidelines. The randomised controlled trials of ESA treatment of CKD-related anaemia have delivered some surprising results that contrast with the data derived from observational studies. The expected 'benefits' of achieving higher target Hb concentrations have not been realised in the RCTs. The financial costs associated with the treatment of anaemia in CKD patients continues to increase mainly in parallel with the growth of the ESRD population. The target ranges for Hb levels published by KDOQI and the UK RA (with their respective upper limits for Hb concentration) provide guidance to nephrologists treating CKD populations. The continuing challenge is to individualise treatment of renal anaemia to improve both the quality and quantity of life for persons with CKD.

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