Individualizing anaemia therapy

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Abstract
Individualized strategies for managing renal anaemia with erythropoiesis-stimulating agents (ESAs) need to be advanced. Recent outcomes from clinical studies prompted a narrowing of the guideline-recommended haemoglobin target (11–12 g/dL) due to increased mortality and morbidity when targeting higher haemoglobin concentrations. Maintaining a narrow target is a clinical challenge, as haemoglobin concentration tends to fluctuate. The goal of individualized treatment is to achieve the haemoglobin target at the lowest ESA dose while avoiding significant fluctuations in haemoglobin concentrations and persistently low or high concentrations. This may require changes to the ESA dose and dosing frequency over the course of treatment.

Keywords: anaemia; erythropoiesis-stimulating agents; haemoglobin

Introduction
Anaemia in patients with chronic kidney disease (CKD) is a complex condition that is associated with morbidity and mortality and a decline in quality of life (QOL) [1–4]. Erythropoiesis-stimulating agents (ESAs) have been shown to effectively improve and maintain haemoglobin (Hb) levels and reduce the need for red-cell transfusions [5,6] and have become a standard of care for managing renal anaemia [7–11]. Since the introduction of the first ESA in 1989, advances in treatment have focused on the needs of patients and healthcare providers, including the development of longer-acting ESAs and various dosing strategies. Guidelines for renal anaemia were introduced to provide a framework for treating patients appropriately, recommending the range in which Hb concentrations should be maintained with some discussion of individualized treatment [7–13].

As our knowledge of managing renal anaemia with ESAs has grown, new clinical challenges have emerged. Early observational studies in dialysis and non-dialysis CKD populations described associations between low Hb levels and increased risk of mortality and morbidity [2,14,15]. Furthermore, observational and some prospective studies reported that higher or normalized Hb levels in CKD patients were not associated with increased risk of adverse outcomes [2,16–18] and might improve mortality and morbidity outcomes, particularly cardiovascular outcomes, and QOL [14,18–23]. These and other findings led to a series of randomized controlled trials in dialysis patients and then in non-dialysis patients to assess the efficacy and safety of targeting high Hb levels with ESAs. While it was hypothesized that high Hb would provide morbidity and mortality benefits, results from these trials consistently showed that intervention with ESAs to a high Hb target provided no clinical benefit compared with the control treatment [24–27] and, in some situations, increased morbidity and mortality risk [27–30].

The publication of data from the trials investigating high Hb targets in non-dialysis patients in 2006 [27,28,31] led to important changes to renal anaemia guidelines [10,12,13]. The 2004 European Best Practice Guidelines (EBPGs) for renal anaemia recommended a Hb target of >11 g/dL for most patients, with an exact target defined by the individual patient’s gender, age, ethnicity, activity, comorbid conditions and disease state [7]. The upper Hb limit was generally to be maintained below 14 g/dL, particularly for haemodialysis patients, and below 12 g/dL for CKD patients with severe cardiovascular disease or diabetes. In 2009 and 2010, the European Renal Best Practice Working Group (formerly EBPG) recommended that all CKD patients should be treated to a target Hb between 11 and 12 g/dL, with the exception of patients with type-2 diabetes mellitus (T2DM) and a history of stroke (recommended target of 10–12 g/dL) [12,13]. The Working Group recognized that Hb levels for individual patients would probably fall outside this narrow target over the course of treatment but recommended that levels above 13 g/dL should not intentionally be exceeded, and levels above 12 g/dL should not be targeted in patients with T2DM. Similar changes had been made to the Kidney Disease Outcomes Quality Initiative Guidelines in 2007 [10].

Treatment goals for patients with renal anaemia will continue to be refined as our knowledge broadens. However, the discordance between observational and clinical trial data and the significant changes to guidelines are challenging for clinicians [32–35] and patients [36], particularly in view of the recommendation to treat all CKD patients to a narrow Hb target. The CKD population is diverse. Patients differ by
disease severity, age, medical history, healthcare behaviours and other factors [2,37,38]. There is significant interpatient variability in the response to ESAs [39,40], as the complex interactions among physiological, environmental and medical factors that affect erythropoiesis vary among patients [40–43]. The individual patient’s Hb levels may fluctuate (i.e. intrapatient variability).

In view of these new challenges, there is a need to reassess individualized treatment for renal anaemia. The subsequent sections will review clinical data regarding high Hb targets, ESA dose and Hb variability, followed by a discussion of individualized anaemia therapy.

### Haemoglobin targets

Table 1 summarizes data from four randomized controlled trials that assigned CKD patients to intervention with an ESA to achieve a high versus low Hb target—the Normal Hematocrit Cardiac Trial (NHCT) [30], the Correction of

| Study | Patient population | Treatment arms (Hb/HCT target) | Outcomes<sup>a</sup> (High vs low target) |
|-------|--------------------|---------------------------------|------------------------------------------|
| Normal haematocrit study (Besarab et al. [30]) | USA HD CHF or IHD, n = 1233 | Epoetin alfa (HCT 42%) Epoetin alfa (HCT 30%) | Composite (death or first non-fatal MI)<sup>e</sup> 1.3 (0.9–1.9) Non-fatal MI 3 vs 2% (P = 0.48) Transfusions 21 vs 31% (P < 0.001) Hospitalization for all causes 72 vs 69% (P = 0.29) CHF hospitalization 13 vs 15% (P = 0.41) Angina pectoris hospitalization 13 vs 12% (P = 0.93) CABG 3 vs 3% (P = 0.88) PTCA 3 vs 2% (P = 0.86) Thrombosis of vascular access 39 vs 29% (P = 0.001) |
| CHOIR (Singh et al. [28]) | USA Non-dialysis CKD (stage 3/4), n = 1432 | Epoetin alfa (Hb 13.5 g/dL) Epoetin alfa (Hb 11.3 g/dL) | Composite (death, MI, CHF hospitalization or stroke)<sup>b</sup> 1.34 (1.03–1.74) Death 1.48 (0.97–2.27) MI 0.91 (0.48–1.73) Stroke 1.01 (0.45–2.25) CHF hospitalization 1.41 (0.97–2.05) RRT 1.19 (0.94–1.49) Hospitalization 1.18 (1.02–1.37) Cardiovascular hospitalization 1.23 (1.01–1.48) Transfusions 0.78 (0.53–1.14) |
| CREATE (Drueke et al. [27]) | Multinational Non-dialysis CKD (stage 3/4), No advanced CVD, n = 603 | Epoetin beta (Hb 13–15 g/dL) Epoetin beta if Hb <10.5 g/dL (Hb 10.5–11.5 g/dL) | Composite (sudden death, MI, acute HF, stroke/TIA, angina pectoris or cardiac arrhythmia hospitalization or PVD complication)<sup>b</sup> 0.66 (0.38–1.15) Cardiovascular death 0.74 (0.33–1.70) Cardiovascular intervention 7 vs 6% Hospitalization 61 vs 59% Dialysis 127 vs 111 pts (P = 0.03) Transfusions 26 vs 33 pts |
| TREAT (Pfeffer et al. [29]) | Multinational Non-dialysis CKD (stage 3/4) with T2DM, No cardiovascular events within 12 weeks, n = 4038 | Darbepoetin alfa (Hb 13 g/dL) Placebo (rescue darbepoetin alfa for Hb <9 g/dL) | Composite (death, non-fatal MI, CHF, stroke or hospitalization for myocardial ischaemia)<sup>b</sup> 1.05 (0.94–1.17) Composite (death or ESRD)<sup>b</sup> 1.06 (0.95–1.19) Death 1.05 (0.92–1.21) MI 0.96 (0.75–1.22) Stroke 1.92 (1.38–2.68) HF 0.89 (0.74–1.08) Myocardial ischaemia 0.84 (0.55–1.27) ESRD 1.02 (0.87–1.18) Cardio revascularization 0.71 (0.54–0.94) Transfusions 0.56 (0.49–0.65) |

<sup>a</sup>Hazard or risk ratio (95% confidence interval) unless otherwise noted (<1 favours high target, >1 favours low target).

<sup>b</sup>Primary study endpoint.

<sup>c</sup>Study halted early because of trend in risk.

CABG, coronary artery bypass grafting; CHF, congestive heart failure; CVD, cardiovascular disease; ESRD, end-stage renal disease; Hb, haemoglobin; HCT, haematocrit; HD, haemodialysis; HF, heart failure; IHD, ischaemic heart disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease; RRT, renal replacement therapy; T2DM, type-2 diabetes mellitus; TIA, transient ischaemic attack.
Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial [28], the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial [27] and the more recent Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) [29].

The NHCT study randomized haemodialysis patients with congestive heart failure (CHF) or ischaemic heart disease who had been receiving epoetin alfa to continue treatment to achieve a haematocrit (HCT) target of 42% (normalized HCT) versus 30% [30]. By 6 months, the mean HCT had increased to the target range in the normal HCT group, corresponding to a 3-fold increase in the epoetin alfa dose. The study was halted early because of a trend towards increased risk of the composite endpoint of death or first non-fatal myocardial infarction (MI) associated with the normal HCT target [hazard ratio (HR) = 1.3; 95% confidence interval (95% CI) 0.9–1.9]. There was no difference between treatment arms with regard to secondary endpoints with the exception of transfusion rate, which was significantly lower in the normal HCT compared with the low HCT group (21 vs 31%; P < 0.001). Thrombosis of the vascular access occurred more frequently which was significantly lower in the normal HCT arm (39 vs 29%; P = 0.001).

In the CREATE study, non-dialysis patients without advanced cardiovascular disease were randomized to achieve a Hb target of 13–15 g/dL with epoetin beta versus a target of 10.5–11.5 g/dL with epoetin beta if Hb levels fell below 10.5 g/dL. There was no significant difference in the risk of mortality or cardiovascular morbidity associated with the high Hb target compared with the low Hb target, but there was a significant increase in the number of patients progressing to dialysis in the high Hb target group (127 vs 111 pts; P = 0.03) [27]. The median weekly epoetin beta dose was 500 and 2000 IU in the high and low Hb target groups, respectively.

The CHOIR study randomized non-dialysis patients to achieve a target Hb of 13.5 vs 11.3 g/dL with epoetin alfa therapy. The high Hb target of 13.5 g/dL compared with the low target of 11.3 g/dL was associated with greater risk of the composite outcome of death, MI, CHF hospitalization or stroke (HR = 1.34; 95% CI 1.03–1.74) [28]. The high Hb target was also associated with increased risk of hospitalization (HR = 1.18; 95% CI 1.02–1.37) and cardiovascular hospitalization (HR = 1.23; 95% CI 1.01–1.48). The mean weekly epoetin alfa dose was 11 215 and 6276 IU, respectively.

More recently, the TREAT study randomized non-dialysis patients with T2DM and Hb ≤11 g/dL to a Hb target of 13 g/dL with darbepoetin alfa versus placebo with rescue darbepoetin alfa if Hb fell below 9 g/dL [29]. Patients who had had a cardiovascular event within 12 weeks of enrollment were not eligible. In the placebo arm, 46% of patients required at least one dose of darbepoetin alfa. The median monthly dose was 6 μg (interquartile range 0–5 μg) in the placebo arm and 176 μg (interquartile range 104–305 μg) in the intervention arm. There was no significant difference between groups for the co-primary composite endpoints of death, non-fatal MI, CHF, stroke or hospitalization for myocardial ischaemia or of renal disease or death. There was an almost 2-fold increase in the risk of stroke in the intervention arm versus the placebo arm (HR = 1.92; 95% CI 1.38–2.68). Transfusions were administered to 14.8 vs 24.5% of patients (P < 0.001) in the intervention and placebo arms, respectively.

Despite differences in patient populations, ESA treatment and Hb targets, there was no clinical benefit to targeting high versus low Hb levels across these studies, and the high Hb target was associated with increased risk for some adverse outcomes in each. The TREAT results have prompted some to reconsider the use of ESAs as standard treatment in diabetes patients with low but adequate Hb levels [31]. In addition, the use of large ESA doses to achieve the high Hb target in these studies has prompted further investigation of ESA dose as a marker of risk.

**ESA dose**

Observational studies have reported associations between ESA dose and risk of morbidity and mortality [44–49]. A 2004 study of the United States Renal Data System reported a non-linear relationship between epoetin dose and mortality independent of HCT in a large cohort of haemodialysis patients [46]. More recently, a large observational study of incident haemodialysis patients indicated that increased mortality risk was not independently linked to high ESA doses but appeared to be the combination of high ESA dosing and high HCT [45]. In this study of US dialysis centres, patients were grouped into HCT ranges, and mortality risk was assessed by HCT group and then by ESA dose quintile for each HCT group. Monthly mortality rates were highest in patients with HCT <30% and lowest in patients with HCT ≥36% (mortality, 2.1 and 0.7%, respectively). In the HCT <30% group, more intensive use of ESAs and iron was associated with a decreased risk of mortality. Conversely, in the groups with HCT 33–35.9 and ≥36%, higher ESA dosing was associated with increased risk of mortality, and in the HCT ≥36% group, more intensive use of iron was also associated with an increased risk of mortality.

In the NHCT study, an analysis by average HCT showed that the mortality rate was consistently higher in the normal than the low HCT group across categorical ranges of HCT, but the rate decreased at higher HCT ranges in each treatment arm [30]. In fact, patients in the normal HCT group with average HCT levels within the target range (39.0–41.9%) had the lowest mortality rate. Thus, higher HCT level alone did not appear to confer risk. Despite the high dosing requirements in the normal HCT group, post hoc analyses did not demonstrate an association between mortality risk and higher ESA dosing. However, more patients in the normal HCT group received intravenous iron and in greater quantities, and intravenous iron treatment was associated with mortality risk. In addition, the investigators noted that dialysis adequacy during the study decreased in the normal HCT group but increased in the low HCT group.

The large dose requirements in the CHOIR study for the high Hb target prompted the investigators to conduct a secondary analysis to assess the potential relationship of ESA dose with outcomes during the trial. Their analysis found that patients in the high Hb target group who were not achieving the Hb target and were receiving a high ESA dose had the lowest mortality rate.
dose (≥20 000 IU; ESA resistant or hyporesponsive) experienced a greater rate of composite events than those achieving the Hb target or receiving a lower ESA dose [47]. Similar trends were reported in the lower Hb target group. In an adjusted Cox proportional hazards model of the 4-month landmark dataset, high-dose ESA (HR = 1.57; 95% CI 1.04–2.36) and previous coronary artery bypass grafting (CABG) (HR = 2.44; 95% CI 1.70–3.49) were independently associated with increased risk of the primary composite endpoint, while Hb target, not achieving Hb target, self-reported hypertension and use of IV iron were not associated with risk; for the 9-month landmark dataset, only previous CABG remained statistically significant.

The data from observational studies and the CHOIR analysis underscore the complexity of evaluating the potential relationship between ESA dose, Hb level and risk. A similar analysis is warranted for the TREAT study. Despite the relatively high median darbepoetin alfa dose (176 μg) in the intervention arm, the median Hb was only 12.5 g/dL (interquartile range 12.0–12.8) [29]. Thus, a significant proportion of patients in the intervention arm did not reach the target Hb despite high dosing. In the placebo arm, the median Hb was 10.6 g/dL (interquartile range 9.9–11.3).

While a secondary analysis of the TREAT data should provide some additional insights, there are important caveats to these analyses as confounding factors limit interpretation and conclusions. Patients who require a high ESA dose to maintain a Hb target may represent a cohort of patients with poorer prognosis than those who can achieve target Hb at a low ESA dose [49,50]. A large chart review study in which findings were adjusted for time-dependent confounding by indication suggested that, on average, epoetin dosages >30 000 IU/week do not confer additional harm or benefit in elderly haemodialysis patients [51].

More detailed dosing algorithms for ESA therapy would be helpful to clinicians, particularly for patients who do not achieve target Hb levels in whom large doses would be ineffective and expensive and might increase risk. Data from well-designed, controlled trials are needed to more clearly define whether risk is due to ESA dose alone or to underlying conditions that require high dosing to obtain a sufficient response. The phase III Clinical Evaluation of the Dose of Erythropoietins Trial (NCT00827021) should provide some critical data. This fixed-dose study, initiated in 2009, randomized haemodialysis patients with Hb < 10 g/dL to low (4000 IU/week) or high (18 000 IU/week) ESA dosing. Patients will be followed for 48 months for the composite endpoint of all-cause mortality, non-fatal MI and stroke, hospitalizations due to acute coronary syndrome, transitory ischaemic attacks, unplanned coronary revascularization procedures and peripheral revascularization procedures.

**Haemoglobin variability**

Haemoglobin variability, a common phenomenon in CKD populations, has recently emerged as another potential marker of mortality and morbidity risk. Observational studies in CKD patients have demonstrated associations between variability in Hb levels and adverse outcomes [3,52–56]; however, there is also growing evidence that persistently low Hb concentrations may be a more important predictor of adverse outcome in both dialysis [16,53,57] and non-dialysis populations [3].

The Chronic Disease Research Group recently conducted two large, retrospective, observational studies of US haemodialysis patients (>150 000 patients for each study) to examine the relationship between Hb patterns and adverse outcomes for 6-month periods in 2003 and 2004 [53,57]. The first study defined comparison groups by the monthly measured Hb concentration (low [<11 g/dL], intermediate [11 to <12.5 g/dL], high [≥12.5 g/dL]) and Hb fluctuation (consistent, low amplitude, high amplitude) over the 6-month period and assessed the relationship of these Hb patterns with hospitalization and morbidity [53]. The second study assessed mortality in a similar manner but defined groups based on the monthly Hb concentration (low, intermediate, high) and the lowest and highest monthly Hb concentration over the 6-month period (e.g. low–low, low–high) [57]. Although both studies found associations between Hb variability and adverse outcomes, patients with consistently low Hb levels were at a notably higher risk of hospitalization, morbidity and mortality than all other groups.

In a similar study of European haemodialysis patients (n = 5037), Eckardt et al. [79] observed that in a multivariate model, consistently low Hb and low-amplitude fluctuation with low Hb were independent predictors of mortality after adjusting for a number of factors, including medical history, dialysis parameters, markers of inflammation and ESA use. The risk observed in other Hb groups (e.g. high-amplitude Hb fluctuation, consistently high Hb) in the crude model was not maintained in the adjusted model. As with the ESA dosing data, the Hb variability data are limited by confounding indication.

**Individualizing therapy**

As our knowledge of renal anaemia continues to evolve, clinicians will need to incorporate changes to treatment guidelines into practice while also addressing the individual needs of their patients [58]. They will need to keep abreast of the latest findings, such as those reported in the TREAT study. Based on our current knowledge of Hb targets, ESA dose and Hb variability, a basic framework can be constructed to help individualize treatment. As recommended in the latest guidelines, Hb levels generally should be maintained within a target of 11–12 g/dL. Targeting Hb levels >12 g/dL with ESA treatment should be approached with caution and, as noted earlier, is not recommended by guidelines across the spectrum of CKD [10,12]. It will also be prudent to minimize the ESA dose, as well as Hb variability, until more definitive data assessing these markers of risk become available.

A practical management strategy is to first conduct a global assessment of the patient to determine the Hb threshold at which ESA therapy should be initiated. Haemoglobin levels consistently <11 g/dL is a general threshold for initiating therapy, but a lower Hb threshold
may be advisable for higher-risk dialysis and non-dialysis patients such as those with diabetes or cardiovascular disease unless symptomatic anaemia is present [34]. ESA therapy should be avoided in patients with cerebrovascular risk. A patient’s iron status should be evaluated and supplementation initiated prior to initiation of ESA therapy for patients with iron deficiency. The benefits and risks of ESA treatment should be discussed openly with the patient, as well as treatment goals, which are likely to differ according to the lifestyle of the patient (e.g. active vs sedentary) [58].

All currently available ESAs have the same mode of action and have been shown to effectively improve and maintain Hb concentration in patients with renal anaemia (reviewed in [59–61]). However, the pharmacological properties of the various ESAs differ, which affects dosing frequency options and dosing efficiency (dose required to achieve Hb target). Thus, selecting the type of ESA that best matches the needs of the patient is a relevant consideration for individualized treatment. A patient who is not on dialysis may prefer the convenience of subcutaneous self-administration and a less frequent dosing schedule, while this may not be an advantage to a patient who receives routine dialysis.

ESA treatment should be initiated in iron-replete patients at a low dose and then titrated incrementally to avoid rapid increases in Hb and to achieve the Hb target at the lowest possible dose [13, 58]. If increasing the ESA dose does not lead to the expected rise in Hb, further increases should be contemplated only after careful risk evaluation of the individual patient. Hopefully, updates to the treatment guidelines will address the issue of maximum allowable ESA dose. The 2004 EBPG defined resistance to ESAs as the failure to achieve the Hb target while receiving more than ~20 000 IU/week of epoetin alfa/beta or ~100 μg/week of darbepoetin alfa or the need for consistently high ESA doses to maintain target Hb [7].

Until more data become available to better understand the benefit-to-risk profile of treating various CKD patient populations to different targets, the Hb target will need to remain narrow for all CKD patients. For patients with CKD and significant comorbidities (e.g. cardiovascular disease or diabetes), a cautious approach is warranted with a Hb target of 10–11 g/dL with levels not exceeding 12 g/dL [13, 34]. On the other hand, a Hb target of 11–12 g/dL is practical for CKD patients without significant comorbidities with the realization that Hb levels may rise above this limit on occasion because of Hb variability [12]. Levels should not exceed 13 g/dL. During maintenance treatment, adequate iron supplementation is an important element of ESA therapy. Variation in Hb levels is expected, but large fluctuations and persistently low or high Hb levels outside the target should be avoided. If a definite trend of increasing or decreasing Hb levels has been determined, ESA dose changes should be implemented after other factors that may impact Hb levels (e.g. infection) have been addressed. Dose changes should be incremental to reduce the risk of Hb levels cycling across and outside the target [62].

In view of these parameters, several treatment- and patient-related factors should be considered for the individual patient to minimize the ESA dose and to help maintain stable Hb levels within target [63–67]. Switching the ESA type, route of administration or the dosing frequency may help to improve ESA dose efficiency and Hb stability in some patients [6, 65, 68]. Table 2 summarizes some of the patient-related factors and intercurrent events that are associated with Hb variability and resistance to ESAs. Several such factors, including iron status, inflammation and infection [40, 41, 43, 69, 70], are modifiable, and strategies can be implemented to mitigate their impact [63–67]. Infection and inflammation frequently occur in CKD patients and should be treated promptly. Acute infections should be treated with antibiotics, and the presence of occult infections should be evaluated in patients who become hyporesponsive to ESA therapy [63]. For dialysis patients, high-quality dialysis water and biocompatible membranes, daily dialysis and on-line haemofiltration may reduce inflammation episodes [71–74]. Protein-energy malnutrition may exacerbate inflammation [70, 75]; thus, it is important to follow nutritional markers to facilitate early interventions. Prior to inpatient procedures, an incremental increase in ESA dose may be warranted and should also be considered immediately after a hospitalization to maintain stable Hb levels [65]. Initiation of certain medications, such as angiotensin-converting enzyme inhibitors [76], may affect erythropoiesis.
poiesis. In such cases, alternative medications can be considered, the medication dose can be reduced or the ESA dose can be increased if appropriate [77].

Conclusions

It is becoming more apparent that a general approach to managing renal anemia—a protociled, ‘one size fits all’ approach—does not maximize the benefit of ESA treatment. Managing anemia in CKD patients is complex. It is affected by the underlying disease, comorbid conditions, the environment and several other factors that differ among patients. Thus, anemia management in these patients needs an individualized approach. Selection of the Hb target based on the patient’s disease state, comorbidities and other characteristics has been an essential part of a treatment strategy [7]. However, the risks associated with high Hb targets in recent studies [27,28] prompted updates to the guidelines to recommend a narrower Hb target: 11–12 g/dL and not exceeding 13 g/dL for most patients and 10–12 g/dL for patients with T2DM avoiding levels above 12 g/dL, particularly for those at risk of stroke [10,12,13]. Ultimately, properly designed and powered prospective studies will be needed to better understand the complex relationship between Hb concentration, ESA dose and underlying disease status. Until then, a reasonable strategy is to first discuss the benefits and risks of ESAs with patients and involve them in the decision-making process [36,58]. For those electing ESA treatment, each patient should be treated to the Hb target with the lowest effective ESA dose while avoiding large fluctuations in Hb levels or prolonged excursions outside the target [78]. This strategy may necessitate changes to the ESA dose, dosing frequency and iron supplementation over the course of a patient’s treatment and proactive management of conditions that can affect ESA responsiveness. While all ESAs effectively increase Hb levels, differences with respect to route of administration, pharmacokinetics and dosing frequency and efficiency should be considered to maximize the benefits of ESA treatment for the individual patient.

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References

1. Finkelstein FO, Story K, Firanek C et al. Health-related quality of life and hemoglobin levels in chronic kidney disease patients. Clin J Am Soc Nephrol 2009; 4: 33–38
2. Pisoni RL, Bragg-Gresham JL, Young EW et al. Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2004; 44: 94–111
3. Boudvильe NC, Djurdjev O, Macdougall IC et al. Hemoglobin variability in nondialysis chronic kidney disease: examining the association with mortality. Clin J Am Soc Nephrol 2009; 4: 1176–1182
4. Leaf DE, Goldfarb DS. Interpretation and review of health-related quality of life data in CKD patients receiving treatment for anemia. Kidney Int 2009; 75: 15–24
5. Cody J, Daly C, Campbell M et al. Recombinant human erythropoietin for chronic renal failure anemia in pre-dialysis patients. Cochrane Database Syst Rev 2005 CD003266
6. Cody J, Daly C, Campbell M et al. Frequency of administration of recombinant human erythropoietin for anaemia of end-stage renal disease in dialysis patients. Cochrane Database Syst Rev 2005 CD003895
7. Locatelli F, Aljama P, Barany P et al. Revised European Best Practice Guidelines for the management of anemia in patients with chronic renal failure. Nephrol Dial Transplant 2004; 19: i1–i47
8. Renal Association and the Royal College of Physicians of London. Treatment of Adults and Children with Renal Failure - Standards and Audit Measures 2002 3rd edn. http://www.renal.org/Standards/standards.html (16 March 2009, date last accessed)
9. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis 2006; 47: S11–S145
10. KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. Am J Kidney Dis 2007; 50: 471–530
11. Pollock C, McMahon L. The CARI guidelines. Biochemical and haematological targets guidelines. Haemoglobin. Nephrol (Curtin) 2005; 10: S108–S115
12. Locatelli F, Covic A, Eckardt KU et al. Anaemia management in patients with chronic kidney disease: a position statement by the Anemia Working Group of European Renal Best Practice (ERBP). Nephrol Dial Transplant 2009; 24: 348–354
13. Locatelli F, Aljama P, Canaud B et al. Target haemoglobin to aim for with erythropoiesis-stimulating agents: a position statement by ERBP following publication of the Trial to Reduce Cardiovascular Events with Aranesp(R) Therapy (TREAT) Study. Nephrol Dial Transplant 2010; 25: 2846–2850
14. Xue JL, St Peter WL, Ebben JP et al. Anemia treatment in the pre-ESRD period and associated mortality in elderly patients. Am J Kidney Dis 2002; 40: 1153–1161
15. Silberberg J, Racine N, Barre P et al. Regression of left ventricular hypertrophy in dialysis patients following correction of anemia with recombinant human erythropoietin. Can J Cardiol 1990; 6: 1–4
16. Ofsthun N, Labrecque J, Lascon E et al. The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients. Kidney Int 2003; 63; 1908–1914
17. Rossert J, Levin A, Roger SD et al. Effect of early correction of anemia on the progression of CKD. Am J Kidney Dis 2006; 47: 738–750
18. Furlan H, Linde T, Ahlmen J et al. A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. Nephrol Dial Transplant 2003; 18: 353–361
19. McMahon LP, Mason K, Skinner SL et al. Effects of haemoglobin normalization on quality of life and cardiovascular parameters in end-stage renal failure. Nephrol Dial Transplant 2000; 15: 1425–1430
20. Eschbach JW, Aquilising T, Haley NR et al. The long-term effects of recombinant human erythropoietin on the cardiovascular system. Clin Nephrol 1992; 38 Suppl 1: S98–S103
21. Jones M, Ibels L, Schenkel B et al. Impact of epoetin alfa on clinical end points in patients with chronic renal failure: a meta-analysis. Kidney Int 2004; 65: 757–767
22. Ma JZ, Ebben J, Xia H et al. Hematocrit level and associated mortality in hemodialysis patients. J Am Soc Nephrol 1999; 10: 610–619
23. Portoles J, Torralbo A, Martin P et al. Cardiovascular effects of recombinant human erythropoietin in predialysis patients. Am J Kidney Dis 1997; 29: 541–548
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24. Foley RN, Parfrey PS, Morgan J et al. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int 2000; 58: 1325–1335*

25. Parfrey PS, Foley RN, Witretech BH et al. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol 2005; 16: 2018–2028*

26. Strippoli GF, Navancehan SD, Craig JC. Haemoglobin and haematocrit targets for the anaemia of chronic kidney disease. *Cochrane Database Syst Rev 2006: CD003967*

27. Druke TB, Locatelli F, Clyne N et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med 2006; 355: 2071–2084*

28. Singh AK, Szczech L, Tang KL et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med 2006; 355: 2085–2098*

29. Pfeffer MA, Burdman EA, Chen CY et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med 2009; 361: 2019–2032*

30. Besarab A, Bolton WK, Browne JK et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med 1998; 339: 584–590*

31. Pfeffer MA, Eckardt KU, Toto R. Darbepoetin alfa and chronic kidney disease [author response]. *N Engl J Med 2010; 362: 653–655*

32. Macdougall IC, Eckardt KU, Locatelli F. Latest US KDOQI Anaemia Management on hemoglobin outcomes in ESRD. *Clin J Am Soc Nephrol 2007; 2: 309–312*

33. de Francisco AL, Ajalma P, Arias M et al. Anaemia correction in diabetic patients with chronic kidney disease without substitutive treatment: teachings from TREAT study. *Nefrologia 2010; 30: 15–20*

34. Roger SD, Levin A. Epoetin trials: randomised controlled trials don’t always mimic observational data. *Nephrol Dial Transplant 2007; 22: 2738–2742*

35. Levin A. Understanding recent haemoglobin trials in CKD: methods and lesson learned from CREATE and CHOIR. *Nephrol Dial Transplant 2007; 22: 309–312*

36. Goodkin DA, Bragg-Gresham JL, Koenig KG et al. Association of comorbidity conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol 2003; 14: 3270–3277*

37. Perez-Garcia R, Martin-Malo A, Fort J et al. Baseline characteristics of an incident haemodialysis population in Spain: results from AN-SWER—a multicentre, prospective, observational cohort study. *Nephrol Dial Transplant 2009; 24: 578–588*

38. Lacson E Jr, Ofshun N, Lazarus JM. Effect of variability in anemia management on hemoglobin outcomes in ESRD. *Am J Kidney Dis 2003; 41: 111–124*

39. Rossert J, Gassmann-Mayer C, Frei D et al. Prevalence and predictors of epoetin hyporesponsiveness in chronic kidney disease patients. *Nephrol Dial Transplant 2007; 22: 794–800*

40. Kalantar-Zadeh K, Lee GH, Miller JE et al. Predictors of hyporesponsiveness to erythropoiesis-stimulating agents in hemodialysis patients. *Am J Kidney Dis 2009; 53: 823–834*

41. Brookhart MA, Schneeweiss S, Avorn J et al. The effect of altitude on dosing and response to erythropoietin in ESRD. *J Am Soc Nephrol 2008; 19: 1389–1395*

42. Locatelli F, Andruitty S, Memoli B et al. Nutritional-inflammation status and resistance to erythropoietin therapy in haemodialysis patients. *Nephrol Dial Transplant 2006; 21: 991–998*

43. Kainz A, Mayer B, Kramar R et al. Association of ESA hypo-responsiveness and haemoglobin variability with mortality in haemodialysis patients. *Nephrol Dial Transplant 2010; 25: 3701–3706*

44. Brookhart MA, Schneeweiss S, Avorn J et al. Comparative mortality risk of anaemia management practices in incident hemodialysis patients. *JAMA 2010; 303: 857–864*

45. Zhang Y, Thamer M, Stefanik K et al. Epoetin requirements predict mortality in hemodialysis patients. *Am J Kidney Dis 2004; 44: 866–876*

46. Szczech LA, Barnhart HX, Inrig JK et al. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney Int 2008; 74: 791–798*

47. Regidor DL, Kopple JD, Kovesdy CP et al. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol 2006; 17: 1181–1191*

48. Bradford BY, Wang O, Critchlow CW et al. Exploring relative mortality and epoetin alfa dose among hemodialysis patients. *Am J Kidney Dis 2008; 51: 62–70*

49. Cotter DJ, Thamer M, Zhang Y. Relative mortality and epoetin alpha dose in hemodialysis patients. *Am J Kidney Dis 2008; 51: 865 author reply 865–866*

50. Zhang Y, Thamer M, Cotter D et al. Estimated effect of epoetin dosage on survival among elderly hemodialysis patients in the United States. *Clin J Am Soc Nephrol 2009; 4: 638–644*

51. Brunelli SM, Joffe MM, Irani RK et al. History-adjusted marginal structural analysis of the association between hemoglobin variability and mortality among chronic hemodialysis patients. *Clin J Am Soc Nephrol 2008; 3: 777–782*

52. Ebben JP, Gilbertson DT, Foley RN et al. Hemoglobin level variability: associations with comorbidity, intermittent events, and hospitalizations. *Clin J Am Soc Nephrol 2006; 1: 1205–1210*

53. Yang W, Irani RK, Brunelli SM et al. Hemoglobin variability and mortality in ESRD. *J Am Soc Nephrol 2007; 18: 3164–3170*

54. Minutolo R, Chiodini P, Cianciaruso B et al. Epoetin therapy and hemoglobin level variability in nondialysis patients with chronic kidney disease. *Clin J Am Soc Nephrol 2009; 4: 552–559*

55. De Nicola L, Conte G, Chiodini P et al. Stability of target hemoglobin levels during the first year of epoetin treatment in patients with chronic kidney disease. *Clin J Am Soc Nephrol 2007; 2: 938–946*

56. Gilbertson DT, Ebben JP, Foley RN et al. Hemoglobin level variability: associations with mortality. *Clin J Am Soc Nephrol 2008; 3: 133–138*

57. Agarwal R. Individualizing decision-making—resurrecting the doctor-patient relationship in the anemia debate. *Clin J Am Soc Nephrol 2010; 5: 1340–1346*

58. Elliot S, Pham E, Macdougall IC. Erythropoietins: a common mechanism of action. *Exp Hematol 2008; 36: 1573–1584*

59. Deicher R, Holr WH. Differentiating factors between erythropoiesis-stimulating agents: a guide to selection for anemia of chronic kidney disease. *Drugs 2004; 64: 499–509*

60. Macdougall IC, Robson R, Opattrna S et al. Pharmacokinetics and pharmacodynamics of intravenous and subcutaneous continuous erythropoietin receptor activator (C.E.R.A.) in patients with chronic kidney disease. *Clin J Am Soc Nephrol 2006; 1: 1211–1215*

61. Fishbane S, Berns JS. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. *Kidney Int 2005; 68: 1337–1343*

62. de Francisco AL, Stenvinkel P, Vaulont S. Inflammation and its impact on anaemia in chronic kidney disease: from haemoglobin variability to hyporesponsiveness. *NDT Plus 2009; 2: 118–126*

63. De Nicola L, Minutolo R, Conte G. Anaemia management in nondialysis chronic kidney disease: flexibility of target to target stability? *Nephron Clin Pract 2010; 114: c236–c241*

64. Kalantar-Zadeh K, Aronoff GR. Hemoglobin variability in anemia of chronic kidney disease. *J Am Soc Nephrol 2009; 20: 479–487*

65. Singh AK, Milford E, Fishbane S et al. Managing anemia in dialysis patients: hemoglobin cycling and overshoot. *Kidney Int 2008; 74: 679–683*

66. Yee J, Zasuwa G, Frnak S et al. Hemoglobin variability and hyporesponsiveness: much ado about something or nothing?. *Adv Chronic Kidney Dis 2009; 16: 83–93*

67. Bonafont X, Bock A, Carter D et al. A meta-analysis of the relative doses of erythropoiesis-stimulating agents in patients undergoing dialysis. *NDT Plus 2009; 2: 347–353*

68. Yaqub MS, Leiser J, Molitoris BA. Erythropoietin requirements increase following hospitalization in end-stage renal disease patients. *Am J Nephrol 2001; 21: 390–396*
70. Kalantar-Zadeh K, McAllister CJ, Lehn RS et al. Effect of malnutrition-inflammation complex syndrome on EPO hyporesponsiveness in maintenance hemodialysis patients. *Am J Kidney Dis* 2003; 42: 761–773

71. Schindler R, Boenisch O, Fischer C et al. Effect of the hemodialysis membrane on the inflammatory reaction in vivo. *Clin Nephrol* 2000; 53: 452–459

72. Sitter T, Bergner A, Schiffl H. Dialysate related cytokine induction and response to recombinant human erythropoietin in haemodialysis patients. *Nephrol Dial Transplant* 2000; 15: 1207–1211

73. Ayus JC, Mizani MR, Achinger SG et al. Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. *J Am Soc Nephrol* 2005; 16: 2778–2788

74. Ramirez R, Carracedo J, Merino A et al. Microinflammation induces endothelial damage in hemodialysis patients: the role of convective transport. *Kidney Int* 2007; 72: 108–113

75. Fouque D, Kalantar-Zadeh K, Kopple J et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int* 2008; 73: 391–398

76. Hayashi K, Hasegawa K, Kobayashi S. Effects of angiotensin-converting enzyme inhibitors on the treatment of anemia with erythropoietin. *Kidney Int* 2001; 60: 1910–1916

77. Macdougall IC. The role of ACE inhibitors and angiotensin II receptor blockers in the response to epoetin. *Nephrol Dial Transplant* 1999; 14: 1836–1841

78. Singh AK. The controversy surrounding hemoglobin and erythropoiesis-stimulating agents: what should we do now? *Am J Kidney Dis* 2008; 52: S5–S13

79. Eckardt KU, Kim J, Kronenberg F et al. Hemoglobin variability does not predict mortality in European hemodialysis patients. *J Am Soc Nephrol* 2010 [Epub ahead of print]

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