

# Practical approaches to treat anaemia with erythropoiesis-stimulating agents in patients with chronic kidney disease

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## Preface

Anaemia is a common complication in patients with chronic kidney disease (CKD). Increasing evidence highlights it as a major risk factor for cardiovascular morbidity and mortality and points its clinical relevance, and the necessity of its therapeutic correction. About 20 years ago, the introduction of erythropoiesis-stimulating agents (ESA) radically advanced the management of anaemia associated with CKD. For patients with CKD, the European Best Practice Guidelines recommend a target haemoglobin (Hb) of  $\geq 11$  g/dl, and the National Kidney Foundation Dialysis Outcome Quality Initiative (KDOQI) recommends target Hb levels of 11 – 12 g/dl, but not greater than 13 g/dl. Recent studies have indicated an increased risk of cardiovascular hazards with a Hb of above 13 g/dl. Although most patients can achieve the desired target Hb levels with adequate treatment, the difficulty in fact is to consistently maintain their Hb levels within the recommended target ranges over time, resulting in cycling. Moreover, data indicate that failing to uphold Hb levels within guidelines ranges over time may increase the risk of adverse outcomes, including mortality.

This Dialysis Update will discuss the challenges of controlling Hb with ESA in different groups of CKD patients (pre-dialysis, during dialysis and following failed renal transplantation). Thereby also practical aspects to consider for the ESA prescription will be elucidated. *KB*

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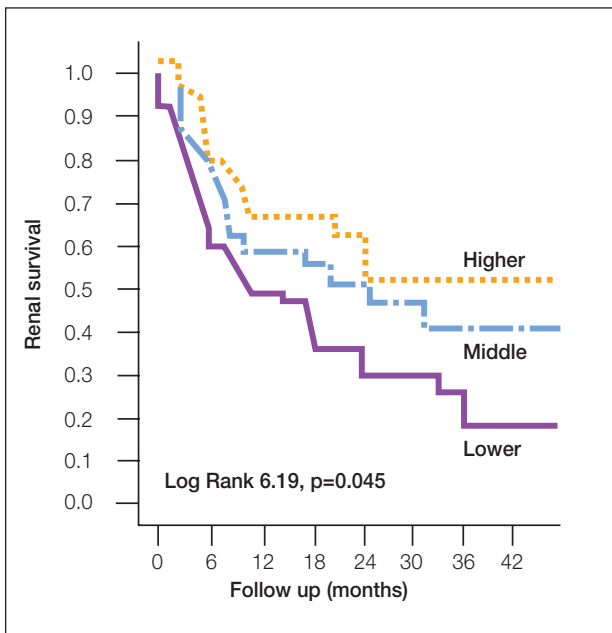
## 1. Stability of target hemoglobin levels during the first year of epoetin treatment in patients with chronic kidney disease

In patients who have chronic kidney disease (CKD) and are not yet on haemodialysis (HD), anaemia has a significant prevalence and acts as an independent risk factor for cardiovascular disease and end stage renal disease. In this observational study, **De Nicola L et al.** evaluated patients with CKD during the first year of ESA (erythropoiesis-stimulating agents) therapy to gain insights into the time spent within target haemoglobin (Hb)  $\geq 11$  g/dl by each individual patient. In addition, they analyzed the association between time within target and renal survival (defined as time from the end of the first year of ESA therapy to all-cause death or dialysis or renal transplantation) in view of the fact that in HD patients, the protective effects of anaemia correction depend not only on the achievement of Hb target but also on its steadiness over time.

In two Italian academic outpatient renal clinics, a retrospective analysis of 119 adult CKD patients with anaemia and starting ESA therapy for the first time between April 30, 2002, and April 30, 2005, was conducted. Data from basal visit, when the first dose of ESA was prescribed, and from 6 subsequent visits were collected. After the end of the first year of ESA therapy, the patients started a follow-up until February 2007, only to assess renal death.

At baseline, women were slightly younger than men ( $59 \pm 18$  versus  $64 \pm 14$  yr;  $p = 0.102$ ). Iron deficiency was found in 47% of the entire cohort. Most patients were treated with multiple antihypertensive therapy, including at least one inhibitor of the renin-angiotensin system. Blood pressure (BP) was  $<130/80$  mmHg in 21%, and no patient had BP  $>160/100$  mmHg. After the basal visit, complete data were collected in 798 visits for a median period of 12.0 months (mo). Overall,

the median number of visits per patient was seven. BP and number of antihypertensive drugs, serum albumin levels and body weight remained unchanged during the follow-up. Similarly, ferritin levels did not vary and ESA dosage remained on average unchanged throughout the first year of observation. Hb levels  $>13$  g/dl were detected in 86 [11%] of 798 visits; in these cases, ESA therapy was generally maintained, being temporarily stopped in only five of the 86 visits. Hb increased to target, at least in one visit, in all patients except four who constantly had Hb  $<11$  g/dl. The median time required to reach target was 1.5 mo (0.2 to 10.7). Only 29 patients had Hb at target from first control after starting ESA to the 12-mo visit. The median value of time within target of the whole cohort was 8.2 mo (0 to 12.8). The multiple regression analysis identified male gender, basal glomerular filtration rate and Hb levels, first dose of ESA, and initial iron supplementation to be directly associated with length of time within target. When patients were categorized in three tertiles of time within Hb target, 40 were at target only for 3.2 mo (0 to 6.2 [lower tertile]), 40 for 8.2 mo (6.5 to 10.3 [middle tertile]), and 39 for 11.3 mo (10.3 to 12.8 [higher tertile]). In the lower and middle tertiles, the extent of time within target was similarly determined by duration of time to target and length of the period with Hb  $<11$  g/dl after first-time achievement of target. While in the higher tertile approximately 70% of patients did not require dosage adjustment because of adequate response to the first ESA dose in terms of achievement and maintenance of target, the vast majority of patients in the middle and lower tertiles required therapy intensification; in these patients, however, therapy was increased in only 15% of visits in which intensification was indicated. Patients who during the first year of ESA spent less time at target had a lower renal survival in the subsequent period of observation (**Figure 1**). Risk for renal death was 58% lower in the higher versus the lower tertile of time in target ( $p = 0.012$ ).



**Fig. 1:** Time to renal death (defined as time from the end of the first year of ESA therapy to all-cause death or dialysis or renal transplantation) by tertiles of time within Hb target. Higher tertile 11.3 mo (10.3 to 12.8); middle tertile 8.2 mo (6.5 to 10.3); and lower tertile 3.2 mo (0 to 6.2).

*In conclusion, in CKD patients, time spent within the haemoglobin target during the first year of ESA therapy is frequently short. The extent of time within target is determined by the length of the period to reach target, but also by the subsequent haemoglobin fluctuations.*

CL

De Nicola L, Conte G, Chiodini P, Cianciaruso B, Pota A, Bellizzi V, Tirino G, Avino D, Catapano F, Minutolo R. Stability of target hemoglobin levels during the first year of epoetin treatment in patients with chronic kidney disease; Clin J Am Soc Nephrol 2, 938-46, 2007

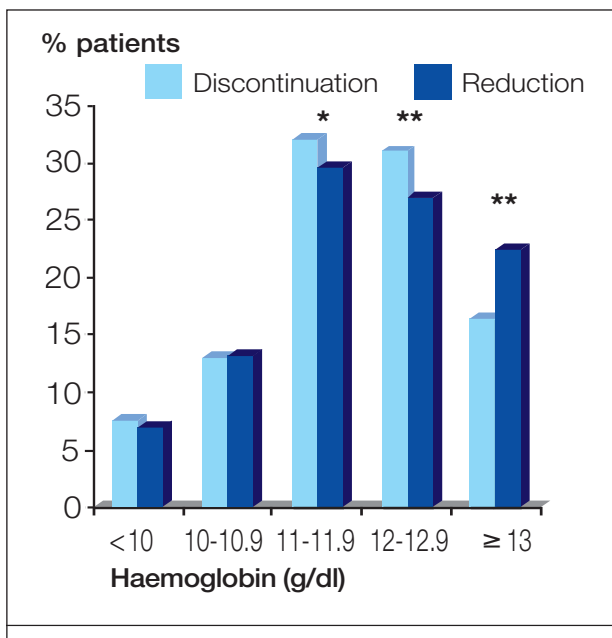
## 2. Reducing versus discontinuing erythropoietin at high haemoglobin levels

Current guidelines from the National Kidney Foundation Dialysis Outcome Quality Initiative (KDOQI) recommend a haemoglobin (Hb) value between 11 – 12 g/dl and no greater than 13 g/dl for haemodialysis (HD) patients. Since it is very difficult to keep this narrow range, often a cycling of Hb values can be observed with possible discontinuation and re-initiation of erythropoiesis-stimulating agents (ESAs). However, the literature indicates the hazards of Hb cycling, associated with a higher hospitalisation and mortality rate. To keep the Hb value as constant as possible, the question regarding the optimal modality of ESA dose arises. The KDOQI guidelines do not provide any information to this issue.

The Centers for Medicare and Medicaid Services (CMS) implemented a new erythropoietin (EPO) Monitoring Policy on April 3<sup>rd</sup>, 2006, allowing **continued EPO** dosing at Hb levels  $\geq 13$  g/dl, but mandating a **25% reduction** in total EPO dose for patients exceeding this level. This was in contrast to their former policy recommending a **discontinuation of EPO** when Hb  $\geq 13$  g/dl. The aim of the study by **Weiner DE et al.** was to examine data from dialysis units which used computerised protocols from October 1<sup>st</sup>, 2005 on to evaluate the effect of reducing rather than discontinuing EPO at higher Hb levels.

Data on 1688 prevalent HD patients from 18 dialysis units in the USA were used. All centres used the computerised discontinuation protocol and switched then to the reduction protocol. Individual data from a five months Hb period of the “old” protocol (discontinuation) were compared with those of a five months Hb period from the “new” protocol (reduction). Hb was generally measured once or twice monthly although in patients not receiving EPO, Hb level was assessed weekly or biweekly to facilitate timely reinitiation of EPO.

Mean Hb value during the discontinuation protocol was  $11.8 \pm 1.3$  g/dl and  $11.9 \pm 1.4$  g/dl for the patients on the reduction protocol ( $p < 0.0001$ ). There was no significant difference between protocols on the proportion of patients falling into the range of 10.9 g/dl. However, in comparison to the reduction protocol, significantly more patients on the discontinuation protocol reached the preferable Hb range of 11 – 12.9 g/dl and significantly less patients were found within the undesired Hb range of  $\geq 13$  g/dl (see **Figure 2**).



**Fig. 2:** Distribution of Hb measurements by discontinuation or reduction protocol; \* $p = 0.004$ , \*\* $p < 0.0001$

The median EPO dose per treatment was 3219 units on the discontinuation protocol and 3477 units on the reduction protocol ( $p < 0.0001$ ). Moreover, when differentiating according to Hb groups listed in figure 2, the EPO dose was significantly higher for those groups on the reduction protocol with Hb values  $\geq 12$  g/dl than on the discontinuation protocol. Finally, more than 50% of patients on the discontinuation or the reduction protocol showed high variable Hb values of  $< 11$  g/dl and  $\geq 12.5$  g/dl during the five months' periods, resp.

In view of the results of the reduction protocol, CMS terminated the reduction protocol and replaced it by a modification of the discontinuation protocol on December 1<sup>st</sup>, 2006.

*In conclusion, this study showed that EPO discontinuation rather than reduction for Hb values  $\geq 13$  g/dl resulted in a higher percentage of HD patients reaching the preferable Hb targets of 11 – 12.9 g/dl and less patients finding within the undesired Hb target of  $\geq 13$  g/dl. Moreover, more EPO was necessary for patients on the reduction protocol than on the discontinuation protocol.*

KB

Weiner DE, Miskulin DC, Seefeld K, Ladik V, Zager PG, Singh AK, Johnson HK, Meyer KB. Reducing versus discontinuing erythropoietin at high haemoglobin levels; J Am Soc Nephrol 18, 3184 – 3191, 2007

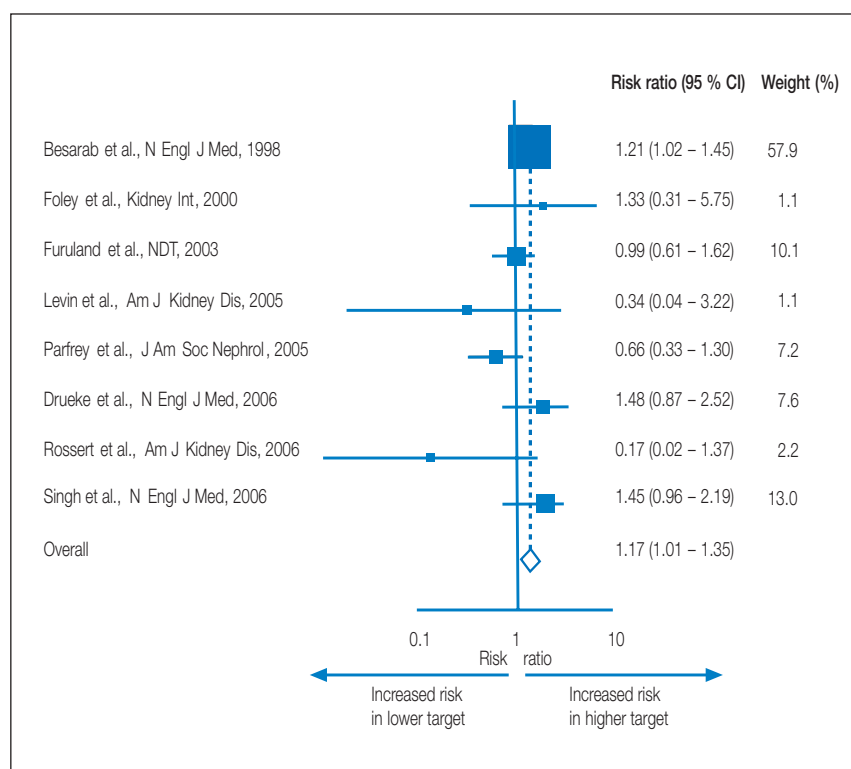
### 3. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis

Anaemia is one of the most frequent and resource-consuming complications in patients with chronic kidney disease (CKD). The most relevant pathogenic factor for renal anaemia is probably insufficient production of erythropoietin. A logical and commonly used measure to take care of this disorder represents the treatment with recombinant human erythropoietin. However, controversial discussions exist regarding the “optimal” haemoglobin (Hb) concentration and the starting point of treatment with recombinant human erythropoietin. **Phrommintikul A et al.** performed this meta-analysis to determine whether targeting different Hb concentrations when treating anaemic CKD patients with erythropoiesis-stimulating agents is associated with altered all-cause mortality and cardiovascular events. For this meta-analysis, prospective, randomised, controlled clinical trials were identified via MEDLINE and EMBASE (1966 – 2006 or 1974 – 2006, respectively). Those studies were included, which assessed the effects of targeting different Hb concentrations with erythropoiesis-stimulating agents, as epoetin alfa, epoetin beta and darbepoetin. Studies had to consist of more than 100 patients and have a duration of treatment and follow-up of at least 12 weeks. Those with Hb concentrations lower than < 8 g/dl were excluded from the primary analysis.

From 255 potentially eligible articles, nine trials with 5143 patients met the specified criteria. Most of the studies included patients in the

age range of 50 to 65 years with moderately to severely reduced glomerular filtration rate or kidney failure and a follow-up of 12 to 48 months.

The results of the meta-analysis showed a significantly higher risk of all-cause mortality in the higher Hb target group (RR: 1.17, CI: 1.01 – 1.35,  $p = 0.031$ ) than in the lower Hb target group (see Figure 3). Data of myocardial infarction were available from seven studies. No difference was seen in the effect of recombinant human erythropoietin on myocardial infarction between the groups (RR: 0.98, CI: 0.73 – 1.31,  $p = 0.88$ ). The risk of poorly controlled blood pressure was significantly higher in the higher Hb target group than it was in the lower Hb target group (RR: 1.27, CI: 1.08 – 1.50,  $p = 0.004$ ) with the fixed effects model, however this was not significant in the random effects model (RR: 1.31, CI: 0.97 – 1.78,  $p = 0.075$ ). Finally there was a significantly higher risk of arteriovenous access thrombosis in the higher Hb target group than in the lower Hb target group (RR: 1.34, CI: 1.16 – 1.54,



**Fig. 3:** Risk of all-cause mortality in the higher Hb target group compared with the lower Hb target group

$p = 0.0001$ ). The findings of the authors seemed neither to be affected by the stage of advanced CKD nor by dialysis.

The authors discuss the possible reasons for a higher mortality rate in the group with higher Hb concentrations. On the one hand there could be an increased propensity to cardiovascular thrombosis or raised blood pressure, which might contribute to increases in lethal cardiovascular events. On the other hand erythropoietin could increase blood viscosity as a result of increased erythrocyte mass, or it could increase thrombotic risk via increased inflammation and anti-fibrinolytic activity, independently from Hb concentration.

*In conclusion, the most important finding of this meta-analysis was the significant increase in the risk of all-cause mortality occurring by achieving target Hb concentrations of 12 – 16 g/dl. According to the authors, an upper limit for target Hb concentrations should be considered in the next revision of guidelines. KB*

Phrommintikul A, Haas SJ, Elisik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis; *Lancet* 369, 381 – 388, 2007

## 4. Epoetin use and Kidney Disease Outcomes Quality Initiative hemoglobin targets in patients returning to dialysis with failed renal transplants

Despite advances in the field of renal transplantation, a substantial proportion of patients experience progressive graft loss and have to return to dialysis therapy. Anaemia treatment guidelines for dialysis patients, such as the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, do not differentiate according to previous transplantation history. **Solid CA et al.** attempted to assess the prevalence of anaemia in patients returning to dialysis therapy with failing renal transplants and investigated the time required to reach K/DOQI-recommended haemoglobin (Hb) levels.

Patients returning to dialysis with failed renal transplants were compared to incident dialysis patients with respect to intravenous iron use, epoetin use, Hb levels, and epoetin dose. The study population included patients aged 18 years and older who began dialysis (210 635 incident dialysis patients) or returned to dialysis (9922 patients) between Jan 1, 1996, and Dec 31, 2001, and survived without transplantation for the following 6 months. Patients with failed transplants had an interval of at least 1 year between transplantation and return to dialysis.

Within 6 months after returning to dialysis, 64% of patients with failed transplants received intravenous iron therapy and 82% received epoetin. The corresponding percentages were marginally higher for incident dialysis patients with no prior transplants, of whom 67% received intravenous iron therapy and 85% received epoetin (for both  $p < 0.001$ ). When adjustment was made for year of dialysis initiation, sex, race, comorbid conditions, and infectious hospitalisations, patients with failed transplants were 1.47 times more likely than incident dialysis patients to receive intravenous iron therapy ( $p < 0.0001$ ) and 1.57

times more likely to receive epoetin ( $p < 0.0001$ ). Compared with incident dialysis patients with no prior transplants, patients with failed transplants were more anaemic and had higher epoetin doses in each month of follow-up (**Figure 4**). Patients with failed transplants were 1.5 times more likely than incident dialysis patients to have Hb levels  $<11$  g/dl ( $p < 0.0001$ ) and 1.73 times more likely to have epoetin-to-haemoglobin ratios  $> 1030$  U/week per g/dl ( $p < 0.0001$ ) in month 6 of dialysis.

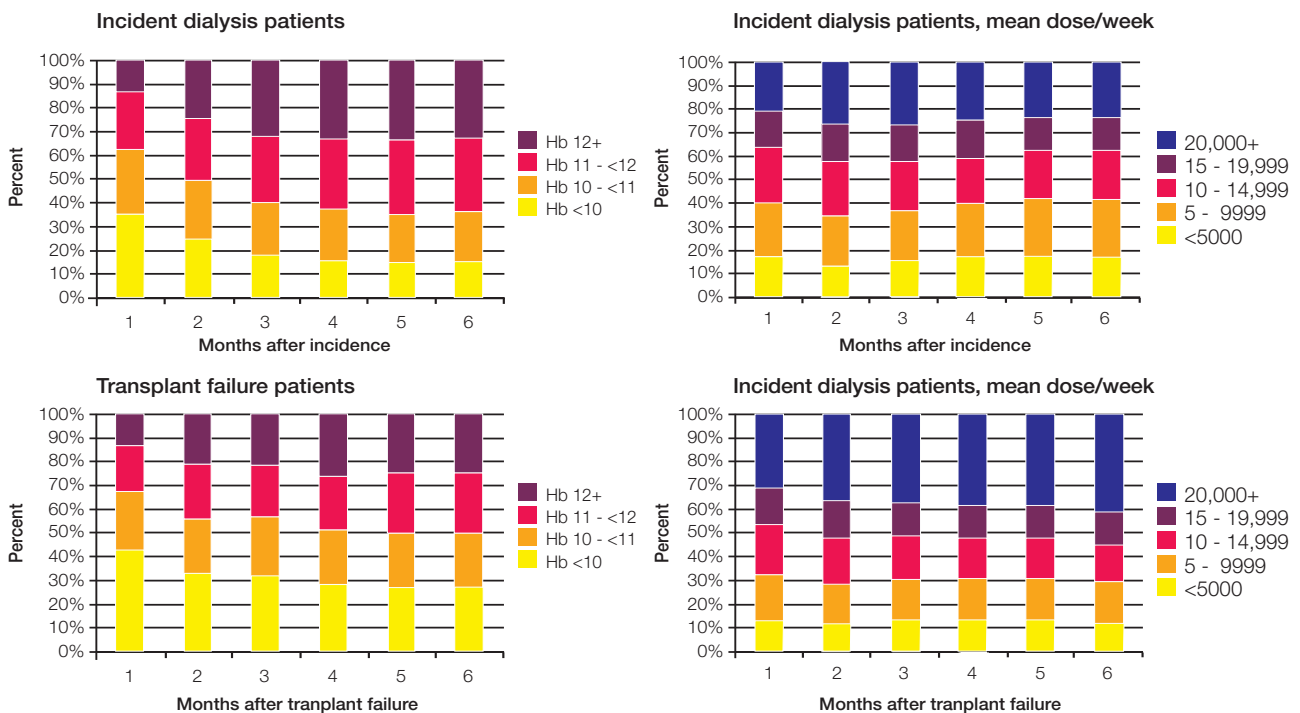
The authors discuss that anaemia is relatively common in patients with functioning renal transplants. Impaired glomerular filtration would be the dominant association; other associations include the use of angiotensin-converting enzyme inhibitors and known myelo-suppressant agents such as azathioprine and mycophenolate, kidneys from older donors, and recent infections. According to them it would be tempting to suggest that some of these factors may have been involved in the apparent epoetin resistance that was observed in their study patients returning to

dialysis with failed transplants. Also, conceivably, ongoing chronic allograft nephropathy and recurrence of a primary renal disease of an inflammatory nature may account for some of the findings. Despite several limitations of their study (e.g. a retrospective analysis was performed) the study would suggest that current management of anaemia in patients with recently failed renal transplants may be suboptimal.

*In conclusion, Solid CA et al. found that patients returning to dialysis after failed renal transplantation were much more likely to start therapy with intravenous iron and epoetin; nevertheless, they were much less likely to attain K/DOQI haemoglobin targets, and the observation of substantially higher epoetin-to-haemoglobin ratios suggests that lower haemoglobin targets may have resulted, in part, from epoetin resistance.*

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Solid CA, Foley RN, Gill JS, Gilbertson DT, Collins AJ. Epoetin use and Kidney Disease Outcomes Quality Initiative hemoglobin targets in patients returning to dialysis with failed renal transplants; *Kidney Int* 71, 425-30, 2007



**Fig. 4:** Haemoglobin levels and epoetin doses for incident dialysis patients and patients returned to dialysis because of failed renal transplant



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