

# How to select appropriate hemoglobin target levels on health-related quality of life and outcomes for patients with chronic kidney disease?

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## ABSTRACT

According to the European guidelines and the American Kidney Disease Improving Global Outcomes (KDIGO) guidelines, in dialysis patients with chronic kidney disease (CKD), treatment target hemoglobin (Hb) values should be 11-12 g/dL without exceeding 13 g/dL. Doses of erythropoiesis-stimulating agent therapy should be considered to achieve the target hemoglobin level. Caution is recommended in diabetic CKD patients who do not require dialysis. In patients with ischemic heart disease or a previous history of stroke, possible benefits should be assessed against an increased risk of stroke recurrence, when selecting the Hb level.

## Toward a sustainable and wise medicine: toward frugality in internal medicine

Patients with chronic kidney disease (CKD) on dialysis treatment often present normocytic normochromic anemia secondary to a blunted response to erythropoietin (EPO) and to a reduced renal production of EPO. The introduction of recombinant human EPO in the treatment of anemia of CKD has decreased the need for blood transfusions and improved the quality of life of CKD patients.<sup>1,2</sup> After the introduction of  $\alpha$  and  $\beta$  erythropoietin, subsequent molecular modifications generated two erythropoiesis-stimulating agents (ESAs) with longer *in vivo* half-lives: darbepoietin  $\alpha$ , which contains 2 extra N-linked carbohydrate chains, and the continuous erythropoietin receptor activator, which has an added polyethylene glycol chain, offering

potentially less frequent administration, once every two weeks and once every four weeks.<sup>3,4</sup> The question that has naturally emerged after the early trials of ESAs was whether further increases in hemoglobin (Hb) levels would improve tissue oxygenation, thereby reducing the high rates of adverse events in patients with CKD. These patients have a high cardiovascular risk and preliminary reports showed that an effective anemia management with EPO could improve cardiovascular outcomes, with reduced left ventricular hypertrophy and left ventricular mass index.<sup>5,6</sup> These preliminary data from observational studies were not correctly interpreted: firstly, the mortality rates did not statistically differ in the range of hematocrit between 36% and 39% and no J curve was really found; secondly, in these studies the patients with the highest hemoglobin level required the lowest ESA doses, probably because patients with a lower level of hemoglobin had higher rates of ESA resistance (due to comorbid illnesses). Now it is still to be ascertained whether the exposure to the ESA itself might account for the increased risk reported, because observational data, although conflicting, seem to show that high doses of ESA are harmful, despite they cannot prove any causal relationship, given their very nature.<sup>7</sup>

Hence the debate on the Hb level in CKD patients on EPO treatment has attracted the attention of many researchers for years (it is still a hot topic) and consequently a remarkable number of reports on this issue have been published. On the basis of the assumption that a complete correction of anemia could reduce cardiovascular events in the population of CKD patients, 2 randomized controlled studies were performed: the CREATE (cardiovascular risk reduction by early anemia treatment with epoetin  $\beta$ ) study and the CHOIR (correction of hemoglobin and outcomes in renal insufficiency) study. During the 3-year CREATE study, complete correction of anemia did not affect the like-

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likelihood of a cardiovascular event, and the left ventricular mass index remained stable in both groups. The authors concluded that, in patients with CKD, early and complete correction of anemia did not reduce the risk of cardiovascular events.<sup>8</sup> Data from the CHOIR study, in which patients received  $\alpha$  erythropoietin until complete correction of anemia, showed an increase in a composite endpoint of mortality and cardiovascular events in the group receiving a dose aimed to achieve higher hemoglobin levels.<sup>9</sup> Subsequently the TREAT (trial to reduce cardiovascular events with Aranesp<sup>®</sup> therapy) study showed that in diabetic CKD patients not receiving dialysis the risk of stroke increased by a factor of 2, when the targeted hemoglobin level was about 13 g/dL.<sup>10</sup> These data suggests that partial correction of anemia is preferable to complete correction and that more caution is needed when treating anemia with EPO in CKD patients. Consequently international nephrology societies published position statements with new recommendations in the existing guidelines (Table 1). Following the findings of these studies, the Anemia Working Group of the European Renal Best Practice (ERBP) issued by the European Dialysis and Transplant Association (EDTA) stated that Hb values of 11-12 g/dL should be generally maintained in the CKD population without exceeding 13 g/dL and that doses of ESA therapy should also be considered to achieve the target hemoglobin level. More caution is suggested when treating anemia with EPO therapy in patients with type 2 diabetes not receiving dialysis (and probably in diabetics at all CKD stages). In patients with ischemic heart disease or with a previous history of stroke, possible benefits should be measured against an increased risk of stroke recurrence, when selecting the Hb level to aim for. In these

patients a lower Hb target (10-12 g/dL) is preferable, considering the risk-to-benefit ratio of the treatment and the desired Hb target in the individual patient. It is also important to involve the patients in the decision-making and seek their personal views after discussing about benefits and risks of treatment. The patient's opinion should be carefully taken into consideration in order to achieve a tailored therapy.<sup>11</sup> The American Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest that EPO should not be used to maintain Hb concentration above 11.5 g/dL (115 g/L) in adult patients with CKD and that individualization of therapy is necessary, as some patients may have an improvement in the quality of life at Hb concentration above 11.5 g/dL (115 g/dL) and may be prepared to accept the risks. Furthermore in all adult patients, EPO should not be used to intentionally increase the Hb concentration above 13 g/dL (130 g/dL).<sup>12</sup> In the opinion of KDIGO experts, these recommendations derive from the results of the recent trials which point to more harm than benefits at higher Hb concentrations. Furthermore the upper limit of the Hb concentration in the control group of these prominent trials did not exceed 11.5 g/dL and no data exists on the benefits of Hb targets between 11.5 and 13 g/dL. This explains the differences between KDIGO and ERBP guidelines: in the clinical practice the upper limit of Hb concentration (12 g/dL or 11.5 g/dL) should be considered on the basis of the clinical setting of the patients (*i.e.* comorbidity with diabetes, ischemic heart disease, chronic obstructive pulmonary disease, history of stroke). The correct iron supplementation with intravenous iron administration is an important factor for a successful treatment of renal anemia, in order to use the lowest dose of ESAs for

**Table 1. Proposals for a sustainable and wise medicine.**

Question, problem, application	Essential elements of discussion	Statement
1. What is the optimal Hb target during treatment with EPO in patients with CRF on hemodialysis?	The introduction of therapy with recombinant EPO in patients with CRF on hemodialysis, reduced the need for blood transfusions and improved the quality of life of these patients. Data from CREATE and CHOIR studies has demonstrated that normalization of hematocrit has no benefits, but the result is an increase of risk and cardiovascular events	Therefore, the guidelines establish that the optimal Hb target in these patients must be between 11 and 12 g/dL of Hb
2. What is the optimal Hb target during treatment with EPO in patients with CRF not on hemodialysis treatment?	In diabetic patients with CFR but not receiving hemodialysis the normalization of hematocrit induced an increase in the risk of events like stroke, as evidenced by the TREAT study	Therefore, the guidelines established that the Hb target in CRF patients not receiving hemodialysis treated with EPO must be between 11 to 12 g/dL, but in diabetic patients a lower target (10-12 g/dL) is preferable. The treatment must be customized and adapted to each individual patient, evaluating the risk-to-benefit ratio, and sharing with the patient treatment decisions

Hb, hemoglobin; EPO, erythropoietin; CRF, chronic renal failure; CREATE, cardiovascular risk reduction by early anemia treatment with epoetin  $\beta$  study; CHOIR, correction of hemoglobin and outcomes in renal insufficiency study; TREAT, trial to reduce cardiovascular events with Aranesp<sup>®</sup> therapy.

reaching and maintaining the desired Hb target. The ESA treatment should not be started in patients who are iron-deficient. Iron replacement should be used first in any CKD patient who has proven to be iron-deficient. Subsequently when the iron levels are restored, the ESA therapy can be initiated. In CKD patients, the ESA treatment should be considered, when Hb levels are consistently (*i.e.* measured twice at least 2 weeks apart) below 11 g/dL (possibly <10 g/dL in patients with type 2 diabetes and with a history of strokes), and all other causes of anemia have been excluded. The threshold for treatment should be decided according to patient characteristics and symptoms, and the desired Hb target. The ESA treatment should be started at a low dose, to avoid overshooting to high Hb levels. Dose adjustments should be made smoothly in the following months in order to avoid an excessively rapid increase in Hb levels (Hb increases of >2 g/dL per month should be avoided if possible). The use of high ESA doses in patients who are hyporesponsive to treatment should be carefully evaluated. Increased cardiovascular risk should be measured against the possible benefits of anemia correction. It seems wise to avoid a progressive increase in the ESA dose in the patients who do not respond to treatment as expected or in whom it is obvious that worsening of anemia is linked to non-renal factors. Patients with chronic hypoxemic pulmonary disease may benefit from a higher Hb target. The risk-to-benefit ratio of red cell transfusions should be carefully considered, especially for patients eligible for transplantation. The impact of selecting a high hemoglobin target level on health-related quality of life for CKD patients was reviewed in a meta-analysis suggesting that targeting hemoglobin levels in excess of 12.0 gr/dL leads to small and clinically insignificant improvements in the quality of life. However with regard to the ESA therapy for anemia in renal patients, some important questions still remain open: for example there is no data about the level of cardiovascular risk in the hemoglobin targets between 11.5 and 13 g/dL. Therefore it is still unclear at what hemoglobin level the risk of adverse events increases and consequently the recommendation to individualize therapy and ESA doses according to patient's status is obviously ambiguous and difficult to apply in the clinical practice. Recently a new molecule was approved in the United States for the treatment of anemia caused by CKD in adult dialysis patients: peginesatide, a peptide-based ESA with no sequence homology with erythropoietin and a longer half-life. However therapy with peginesatide in patients not receiving dialysis (Pearl 1 and Pearl 2 studies) showed an increase in composite safety end-point events, including sudden death, underscoring the need

for additional data to clarify the risk-to-benefit profile of these molecule.<sup>13</sup> In addition to significant safety concerns, this suggests that hemoglobin levels that are not above 12 g/dL are preferable and that upper targets do not give further benefits in terms of cardiovascular risk reduction, clinical outcome and quality of life. Also the introduction of new molecules does not seem to give more advantages especially in the population of CKD patients not receiving dialysis.

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