Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement

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ABSTRACT

Recently, the Kidney Disease: Improving Global Outcomes (KDIGO) group has produced comprehensive clinical practice guidelines for the management of anaemia in CKD patients. These guidelines addressed all of the important points related to anaemia management in CKD patients, including therapy with erythropoiesis stimulating agents (ESA), iron therapy, ESA resistance and blood transfusion use. Because most guidelines were 'soft' rather than 'strong', and because global guidelines need to be adapted and implemented into the regional context where they are used, on behalf of the European Renal Best Practice Advisory Board some of its members, and other external experts in this field, who were not participants in the KDIGO guidelines group, were invited to participate in this anaemia working group to examine and comment on the KDIGO documents in this position paper. In this article, the group concentrated only on those guidelines which we considered worth amending or adapting. All guidelines not specifically mentioned are fully endorsed.

INTRODUCTION

The European Renal Best Practice (ERBP) group was created in 2008 with the aim of issuing suggestions for clinical practice in areas in which evidence is either lacking or weak, or position statements about guidelines produced by other bodies, such as the Kidney Disease: Improving Global Outcomes (KDIGO) [1]. KDIGO is a non-profit organization governed by an international board that aims to improve the care and outcomes of kidney disease patients worldwide by...
promoting coordination, collaboration and integration of initiatives to develop and implement clinical practices guidelines. As a result of a large, international effort, KDIGO has already produced a number of evidence-based guidelines on different topics in the field of nephrology.

In 2009 the ERBP Anaemia Working Group published its first position paper [2], which focused on the 2007 update on the haemoglobin (Hb) targets by the National Kidney Foundation: Dialysis Outcome Quality Initiative [3] and on emerging issues that were not covered by the complete set of KDOQI recommendations in 2006 [4].

In 2009, the Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) study was published [5]. This large, randomized, placebo-controlled trial raised a number of safety issues about erythropoiesis-stimulating agent (ESA) use in the chronic kidney disease (CKD) population with type 2 diabetes when administered with the aim of normalizing Hb values. Promptly, the Anaemia Working Group of ERBP published a second position paper [6] giving guidance on the interpretation of these new findings together with their possible implication on Hb targets and treatment strategy when using ESAs in CKD patients.

The TREAT study, which is the largest study performed so far in the field of renal anaemia, is an important part of the available evidence about anaemia management in CKD patients. Indeed, the KDIGO guidelines on anaemia management were only started after its publication.

These guidelines have recently been published [7]. Under the auspices of the ERBP, some of its members and other experts in the field, who were not participants in the KDIGO guidelines group, were invited to participate in this ERBP Anaemia Working Group to examine and comment the KDIGO guidelines in the present position paper. Importantly for the nephrological community, even if the KDIGO-produced recommendations were graded according to the available evidence, many of these are clearly derived from low-grade evidence. As a result, many recommendations are largely opinion based and quite vague. Consequently, they may not fulfill one of the main aims of guidelines, i.e. aiding clinical decision-making on the part of doctors who cannot integrate all of the published data concerning new technology and knowledge in their everyday clinical practice. This is because though the TREAT study was a very important advance in knowledge, there are still many areas of clinical uncertainty. Consequently, a number of recommendations have to be given not solely on the findings by themselves but also on their interpretation.

The ERBP group felt there was a need to adapt some of the recommendations of the KDIGO guidelines to the European population. Consequently, we concentrated only on those guidelines which we considered worth amending or adapting. All guidelines not specifically mentioned are fully endorsed. We also decided to focus only on the adult population with CKD.

This position paper is not intended to represent a set of new guidelines, as it is not the result of a systematic review of the evidence, but is intended to be of most use to the practicing kidney specialist, and those allied to the clinical team, when dealing with anaemia management in the CKD population in everyday clinical practice. This is particularly apposite and valuable considering the marked trend towards treatment individualization, which has become an important strategy leaving the practising physician with too many treatment options and complex risk/benefit balances to make informed and sensible clinical decisions.

**CHAPTER 1: DIAGNOSIS OF ANAEMIA IN CKD**

**KDIGO 1.3.1**

Diagnose anaemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dL (or 130 g/L) in males and <12.0 g/dL (or 120 g/L) in females. (Not Graded)

Precision around the diagnosis of anaemia is relevant for two reasons. First, it is intended to alert physicians that if a patient’s Hb level falls below a certain value then physicians and those concerned with the diagnosis and treatment of renal anaemia should consider whether an anaemia workup should be started to identify possible causation. The earlier this is done, the greater is the possibility to correct any underlying disease and avoid further decline in Hb values. Conversely, if this workup is done too early, patients may undergo unnecessary testing. This can be a complex judgement. Second, the definition of anaemia influences the prevalence of this disease/complication across epidemiological studies. Indeed, the prevalence of anaemia between phase III and IV of the National Health and Nutrition Examination Survey (NHANES) slightly differs partially because a different definition is used [8, 9]. According to the chosen definition the prevalence of anaemia across populations may also influence the role of this condition as a poor outcome predictor in several diseases including CKD.

The definition of anaemia in CKD patients has been changing across guidelines over the last few years. In 2004 the Revised European Best Practice Guidelines on Anaemia indicated as a definition for anaemia in CKD the following: ‘In patients living below 1500 m, Hb values were considered below normal if they were <11.5 g/dL in women and <13.5 g/dL in men (<12 g/dL in those aged >70 years)’ [10]. This definition had the advantage of differentiating the definition of anaemia between older or younger males but did not differentiate between post-menopausal and younger women. It had perhaps the disadvantage of missing anaemia diagnosis in male patients >70 years, given a relatively low threshold in this category.

In 2006 the KDOQI guidelines on anaemia suggested that the diagnosis of anaemia should be made, and further evaluation should be undertaken, when Hb concentrations were <13.5 g/dL in adult males and <12.0 g/dL in adult females [4]. This definition was obtained from the mean Hb of the lowest fifth percentile of the sex-specific general adult population and assumes a lack of adjustment downward for age in males and an adjustment upward for iron deficiency in females [4]. This definition is simple and easy to remember, increasing the likelihood that physicians may apply it in everyday clinical practice.
The new KDIGO suggestion [7] is based on the World Health Organisation (WHO) definition of anaemia [11]. It is true that this definition has been applied across populations, but it also true that it has been derived from very few data using older methodologies by a WHO expert committee [12]. Its primary aim was to screen for malnutrition and it is therefore perhaps inappropriately applied to the general population of developed countries, and especially so for a population of patients affected by a chronic disease. Given that the majority of the European population is of Caucasian ethnicity, it should also be taken into account that Caucasian men have an Hb set point that is 1–2 g/dL higher than African Americans [13]. Similar differences have been described between Caucasian, African American and Asian women. According to the Scripp-Kaiser database, the lower limit of normality of Hb values should be of 13.7 g/dL for Caucasian men aged between 20 and 60 years and 13.2 g/dL for older men. For women of all ages the set point should be 12.2 g/dL [14]. Similarly, higher Hb values were found in the Caucasian population of NHANES III.

In the opinion of the ERBP Working Group, the WHO definition of anaemia is useful for epidemiological purposes but it may be too blunt a tool and thus has the potential to miss a number of anaemia diagnoses in everyday clinical practice.

Independently from these reference Hb values, a diagnosis of anaemia should be considered in the presence of a falling level of Hb in patients on whom baseline Hb levels are normal.

We suggest using for the European population with CKD the following:

The diagnosis of anaemia should be made and further evaluation should be undertaken when Hb concentrations are <13.5 g/dL in adult males (13.2 g/dL in men >70 years) and <12.0 g/dL in adult females of all ages.

**CHAPTER 2: USE OF IRON TO TREAT ANAEMIA IN CKD**

**KDIGO 2.1.2**

For adult CKD patients with anaemia not on iron or ESA therapy, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):

- an increase in Hb concentration without starting ESA treatment is desired
- and TSAT is ≤30% and ferritin is ≤500 ng/mL (≤500 μg/L)

It is well known that iron therapy is an important step in the treatment of anaemia in CKD patients, as both absolute and functional iron deficiencies are common. In the TREAT study [5], the patients in the control group maintained a relatively high mean Hb level during the follow-up despite the fact that they received minimal darbepoetin alfa doses [median 0, interquartile range (IQR) 0–5 μg/month] as a rescue therapy. This was partially influenced by the fact that many of these patients were not fully iron-replete [median transferrin saturation (TSAT) 23%, IQR 18–29%] and thus received a course of oral or IV iron. These results have certainly contributed to re-evaluate the role of iron therapy not only in patients who are iron deficient but also in those with apparently adequate iron stores (as defined by serum biomarkers) [15, 16].

Thus, we agree with this recommendation about the possibility first to perform a trial of IV iron (or oral iron therapy in the ND-CKD population when tolerated) in anaemic CKD patients if an increase in Hb levels is desired. This would also be helpful in reducing the need for blood transfusions [17]. In ND-CKD patients with mild to moderate anaemia, oral iron should be used as first-line therapy for a minimum of 3 months in the absence of known gastrointestinal intolerance to preserve the veins of the arm for possible future dialysis access (AV fistula). Conversely, IV iron is the first choice in this population in the presence of severe anaemia or when oral iron is ineffective.

We also agree with the statement that ‘For any individual patient the optimal balance of Hb level, ESA dose, and iron dose at which clinical benefit is maximized and potential risk is minimized is not known’ [7, 18]. Indeed, peripheral–iron blood indices of iron storage transport and handling have limited utility in identifying depletion of bone marrow iron stores.

However, in our opinion, the proposed limits of serum ferritin and TSAT, which the new KDIGO guidelines suggest should help drive the decision on whether or not administer iron therapy in patients not receiving ESA, are too wide and are not adoptable for a number of reasons.

First, no clear distinction is made between absolute and functional iron deficiency when giving the strength of the recommendation whether to start iron therapy. For patients with absolute iron deficiency (serum ferritin <100 ng/mL and TSAT <20%), the indication for iron therapy should be stronger since the likelihood of obtaining an increase in Hb level following iron therapy is much higher. Conversely, it is true that even in patients with adequate bone marrow iron stores, sometimes, it is possible to obtain an increase in Hb levels following iron therapy. However, this quantitative effect is lower in patients who are not iron deficient. Stancu et al. [15] showed that, following the administration of 1000 mg of IV iron to 100 patients with ND-CKD, an erythropoietic response was obtained in 63% of those who had iron-deplete bone marrow but only in 30% in those who were iron-replete. The chances of a positive response increased by 7% for each 1% decrease in TSAT [15]. In this European, mostly Caucasian population, the median serum ferritin and TSAT values were much lower (176 ng/mL and 23%, respectively) than the upper threshold up to which iron therapy could be prescribed according to KDIGO recommendations (i.e. serum ferritin ≤500 ng/mL and TSAT ≤30%). Of note, ferritin values in the Stancu’s paper were much <500 ng/mL despite the fact that two-thirds of the patients were chronically inflamed (C-reactive protein level >10 mg/L).

Spinowitz et al. [19] studied another cohort of 304 ND-CKD patients who were given two 510-mg doses of
ferumoxytol IV or 200 mg of elemental oral iron daily for 21 days in a 3:1 ratio. Among patients who were not receiving ESAs (n = 188), Hb increased by 0.62 ± 1.02 g/dL with ferumoxytol and by 0.13 ± 0.93 g/dL with oral iron. In this population, mean baseline serum ferritin and TSAT were ∼145 ng/mL and 10%, respectively.

We agree with the KDIGO group that the available evidence on this topic is inadequate and scanty. However, we believe that before deciding whether or not to give a course of iron therapy, the physician should know that this evidence has been obtained only in the ND-CKD population and that in the available studies, mean/median ferritin levels were well below the now proposed upper limit of 500 ng/mL. These considerations clearly suggest the need to differentiate in this recommendation between non-dialysis and dialysis patients, and not lump these together in an overarching recommendation. Given the paucity of evidence, we have no information about safety when prescribing long-term iron therapy at higher ferritin levels than those previously recommended in the ND-CKD population.

The safety of administering IV iron therapy to ESA-naïve haemodialysis patients with high serum ferritin levels has not been established. For instance, increased circulating ferritin levels have been found associated with an impaired immune response of monocytes, possibly increasing infection risk [20]. We feel that it is likely that the magnitude of the obtained increase in Hb level after IV iron therapy would be rather small in haemodialysis patients; so, the start of ESA treatment would be probably more effective (also considering that evidence-based concerns related to ESA use in the dialysis population seem less concerning than in the ND-CKD population). Therefore, a course of IV iron therapy despite ferritin values >300 ng/mL should be considered in those haemodialysis patients in whom ESA therapy may be contraindicated or considered risky (see KDIGO section about ESA initiation). Conversely, in ESA-naïve anaemic patients who have adequate iron stores, the concomitant start of ESA and iron therapy may be appropriate to prevent iron deficiency due to increased erythropoiesis stimulation.

Moreover, it is clear that an operative interval is lacking. After reading this recommendation, the physician remains confused because the upper limit for prescribing iron therapy coincides with the proposed limit not to be exceeded in treatment. This implies the risk of reaching very high serum ferritin levels when IV iron therapy is started at the upper edge of the interval (especially with single high doses given for long periods).

Finally, whether or not to treat CKD patients with Hb values >12 g/dL and absolute iron deficiency remains an open issue. At present, it seems wise to suggest that we do treat these patients (in the absence of clear risks of targeting towards higher Hb values) but as we do so being careful to avoid intentionally exceeding an Hb value of 13 g/dL. If these patients are receiving ESA treatment, this additional iron therapy should be at least temporarily halted (see following sections about ESA initiation and ESA maintenance therapy).

We suggest using for the European population with CKD the following:

For adult CKD patients with anaemia not on iron or ESA therapy we suggest a trial with iron therapy (either IV or, when tolerated, orally as a first step in ND-CKD patients, especially in CKD II to III, or in PD patients) if:

- there is an absolute iron deficiency (TSAT <20% and serum ferritin <100 ng/mL)
- OR
- an increase in Hb concentration without starting ESA treatment is desired
- and TSAT is <25% and ferritin is <200 ng/mL in ND-CKD patients and <25% and ferritin is <300 ng/mL in dialysis patients. Following iron treatment, the limit of TSAT of 30% and serum ferritin of 500 ng/mL should not be intentionally exceeded in both ND-CKD and dialysis patients

**KDIGO 2.1.3**

For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C) an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤30% and ferritin is ≤500 ng/mL (≤500 μg/L).

In CKD patients receiving ESA therapy, iron stores may be nearly normal, but they may be insufficient for the increased erythropoiesis which typically follows bone marrow ESA stimulation. In this context, iron therapy reduces significantly ESA doses requirements. This is of particular importance given concern related to ESA use especially at high doses (even if this association is limited by the bias that patients receiving higher ESA doses are usually those with more comorbidities). The fact that iron deficiency (absolute or relative) is a major cause of ESA hyporesponsiveness in CKD patients [21, 22] suggests that there is still room to augment iron therapy in many CKD patients. Unfortunately, TSAT and ferritin have limitations and low power to diagnose functional iron deficiency and predict response to IV iron. Other markers such as hypochromic red cells or reticulocyte Hb may add some information when available [23]. According to recent findings of 120 dialysis facilities of the Dialysis Outcomes and Practice Patterns Study (DOPPS) Practice Monitor in the USA [24], following the change in the ESA label by the Food and Drug Administration (FDA) in June 2010, from August 2010 to August 2011, the percentage of dialysis patients receiving IV iron went from 57 to 71%. This went together with a significant decline in ESA dosing and a slight decrease in median Hb levels.

However, a larger use of iron therapy caused a substantial increase in ferritin levels. Indeed, in these patients the median ferritin level increased from 556 to 650 ng/mL with 34% of the patients exceeding the value of 800 ng/mL. Conversely, the percentage of patients with TSAT ≥50%
remained around 10%. Interestingly, every 100 mg of IV iron raised TSAT by 0.43% in those subjects having TSAT values <30% but only by 0.10% in those having higher TSAT levels; Hb values remained unchanged [25]. This may suggest that targeting to TSAT levels ≥30% with IV iron therapy does not improve erythropoiesis and exposes patients to the risk of iron overload.

In Europe, dialysis patients have lower median ferritin levels than those in the USA. According to the data of the UK Renal Registry, in 2009 in haemodialysis patients, the median ferritin value was of 417 ng/mL (IQR 270–598) [26]. This value was similar in 2010 [444 ng/mL (IQR 299–635)] [27]. However, no major changes in guideline recommendations about anaemia management took place in Europe in this period (thus, it is too early to observe ferritin changes in the European population).

The safety of persistently very high ferritin levels is still unknown. In 453 men with non-dialysis CKD, a trend towards higher mortality was observed in patients with a serum ferritin level >250 ng/mL [28]. However, the study was not adequately powered to properly analyse survival data. In dialysis patients, high serum ferritin has been associated with increased mortality as well. In a cohort of 58,058 prevalent haemodialysis patients in the USA, both all-cause and cardiovascular mortality had increasing rates across increasing ferritin levels, whereas the opposite (inverse) association was observed for TSAT increments. Serum ferritin levels between 200 and 1200 ng/mL and iron saturation ratio between 30 and 50% were associated with the lowest all-cause and cardiovascular death risks [29]. However, association studies are biased by the fact that serum ferritin is also a marker of inflammation [30]. Indeed, in unadjusted, time-varying model, serum ferritin >800 ng/mL during each quarter was associated with increased death rate.

The Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) trial [31], found that IV iron was effective in increasing Hb levels and reducing ESA doses in patients with high ferritin (500–1200 ng/mL) and low transferrin saturation levels (TSAT ≤25%). However, the sample size was quite small and the overall follow-up (6 weeks + 6 weeks in the DRIVE II extension period [32]) was adequate for testing acute iron toxicity but too short to provide information about safety and iron overload in the long term.

High-dose baseline iron therapy has been found to be associated with poor outcome in haemodialysis patients [33]. However, this likely reflects an indication bias, because no statistically significant association was detected between mortality and any level of iron dosing [32].

According to an autopsy study of 36 haemodialysis patients published 30 years ago when erythropoietin was still not available [34], serum ferritin did not always correlate with bone-marrow iron stores but correlated well with the degree of hepato-splenic siderosis, probably because hepato-splenic stores failed to be mobilized to the bone marrow. This should be taken into account when administering IV iron, which by passes the intestinal mechanism for the regulation of iron absorption, especially in inflamed patients in whom inhibitory factors, such as hepcidin, decrease iron release from reticulo-endothelial and hepato-cyte stores [35]. The regulatory role of hepcidin may thus change the relationship between ferritin levels, iron stores and Hb levels [36]. This is why a number of patients with high serum ferritin may have functional iron deficiency and have an increase in Hb levels following iron therapy. Compared with those days, this mechanism is likely to be amplified at any level of serum ferritin level. Indeed, the CKD population has substantially changed compared with the first haemodialysis patients, who were much younger and with fewer comorbidities compared with nowadays. After the introduction of ESA in clinical practice, following a much lower use of blood transfusion, clinically significant iron overload has become a rare event [37]. However, it has been hypothesized that iron administration may exacerbate oxidative stress and increase the risk of infection, cardiovascular events and death well before causing signs of iron overload [38–40]. At present, evidence coming from clinical trials testing IV iron molecules has not shown a significant increase in deaths, cardiovascular events or infections following IV iron use. However, these studies were not adequately sized to test mortality or hard end points. Long-term safety studies examining these practices are urgently required and long overdue.

Some years ago, a study was published which featured direct, non-invasive measurements of non-haeme hepatic iron content by magnetic resonance in 40 dialysis patients treated with IV iron. This study showed that two-third of the patients had signs of mild to severe iron overload despite the fact that only one-third of the patients had serum ferritin exceeding 500 ng/mL. [41]. According to the receiver operating characteristic analysis, the best specificity/sensitivity ratio to identify iron overload was obtained for ferritin >340 ng/mL [39]. Recently, significant iron overload in the liver and spleen (assessed through T2 magnetic resonance) has been described in 19 of 21 haemodialysis patients with serum ferritin >1000 ng/mL and severe comorbidities who were treated with IV iron [42]. Similarly, Rostoker et al. [43] prospectively studied a cohort of 119 fit haemodialysis patients who were receiving iron and ESA therapy and measured their liver iron content by means of T1 and T2 magnetic resonance. Mild to severe hepatic iron overload was observed in 84% of the patients, 36% of whom had severe iron overload approaching that found in haemochromatosis. Liver iron content is significantly related to the cumulative iron dose received [42, 44] and can rapidly decrease following iron therapy discontinuation [42].

Despite the fact that excess iron in the liver is potentially harmful, the clinical consequences of high iron content estimated by magnetic resonance is not known.

As is the case for ESA-naïve patients, the indication to iron therapy should be stronger for absolute iron deficiency that increases ESA dose requirements inappropriately and perhaps also the risk of cardiovascular events [45].

It is true that we have no clear evidence indicating an upper limit for ferritin level that can be considered either safe or dangerous. However, the fact that the current KDIGO guideline on this topic indicates the possibility of...
administering a trial of iron therapy even in patients who already have high serum ferritin levels (~500 ng/mL) will certainly cause a significant rise in ferritin levels in the CKD population, especially in the haemodialysis setting, shifting to the right the frequency distribution curve. This will occur regardless of the presence or absence of signs of chronic inflammation. In our opinion, also considering that increasing TSAT above 30% does not substantially modify Hb levels, in the absence of clear evidence, prudence should prevail to limit over treatment, at least in European countries with no particular restriction to ESA treatment.

Following these considerations, we agree with the KDIGO recommendation 2.1.3 that in adult CKD patients treated with ESA a trial of iron therapy may be useful if an increase in Hb concentration or a decrease in ESA dose is desired. However, caution is needed in patients with already high ferritin levels, because the safety of treating these patients is still unknown. Conversely, we agree with the KDIGO group that this is an important topic that needs to be investigated by future research.

We suggest using for the European population the following:

- For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (in ND-CKD patients oral iron therapy should be started as a first step if tolerated) if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is <30% and ferritin is <300 ng/mL.

- In haemodialysis patients, a course of IV iron therapy can be considered in those having higher serum ferritin levels in the presence of hyporesponsiveness to ESA or a risk/benefit ratio going against ESA use.

- Caution is suggested in exceeding a ferritin value of 500 ng/mL during combined iron and ESA treatment in dialysis patients, especially in those patients with adequate TSAT percentage (>30%).

CHAPTER 3: USE OF ESAS AND OTHER AGENTS TO TREAT ANAEMIA IN CKD

ESA initiation

3.2: In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anaemia-related symptoms against the risks of harm in individual patients (e.g. stroke, vascular access loss, hypertension). (1B)

3.3: We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(1B), a history of stroke (1B), or a history of malignancy (2C).

Following the secondary analyses of the TREAT study, we agree with the greater part of these two recommendations. In particular, even if in the TREAT study data about malignancies were obtained from a secondary analysis with a relatively few number of events [5], these findings are consistent with concerns raised about the use of ESA on increased tumour growth and death in the setting of oncology in some types of cancer (especially when used off-label) [46]. However, this is still a grey area since a clear relationship between the expression of the EPO receptor in neoplastic cells and cancer proliferation following ESA administration has not been clearly established [47].

Conversely, the risk of stroke following ESA treatment aimed at complete anaemia correction in CKD patients deserves further commentary. First, it is unclear whether CKD patients without diabetes have an increased risk of stroke following ESA treatment. In 2005 in a trial about complete anaemia correction with epoetin alfa in haemodialysis patients with asymptomatic heart disease Parfrey et al. [48] found a trend of towards an increase in cerebrovascular events in those randomized to the higher Hb group (n = 12, 4% and n = 4, 1%, respectively; P = 0.045). However, the number of events was rather small, and this imbalance was possibly due to statistical fluctuation. Moreover, differing from the TREAT study [5], all these patients received ESA treatment. The increased risk was thus possibly related to different Hb targets (in the two treatment groups, achieved Hb levels were 13.1 and 10.8 g/dL, respectively). Second, according to a recent, secondary analysis of the TREAT study [49], as reported by the KDIGO guidelines, ‘the relative increase in risk of stroke related to darbepoetin alfa use was not statistically different in patients with and without a past history of stroke.’ This relationship may be possibly not significant because of an insufficient statistical power in a secondary analysis’. Indeed, the authors found a near double increase in the relative risk of stroke in those with a previous history than in the control group. However, the risk of stroke was independent of Hb level or darbepoetin treatment [45]. The fact that in the experimental group of the TREAT study, the darbepoetin dose was similar in patients with or without a stroke and Hb levels were lower in those developing a stroke (even if this was not statistically significant) and that no other factor had been significantly related to the risk of this event [45] suggest that ESA therapy and achieved Hb levels are not a major cause but that likely there are other unknown factors explaining the higher occurrence of stroke in patients receiving darbepoetin alfa in the TREAT trial. Indeed, while measured blood pressure values were similar in the two groups of the trial, it is possible that masked increases in blood pressure values during the day may have contributed to the increased risk of stroke. This was also in light of the fact that it is well known that ESA use aiming at higher Hb values usually worsens blood pressure control and/or increases the need of antihypertensive drugs.

In the overall TREAT population, at multivariate analysis a lower body mass index was an independent predictor of stroke [P = 0.044; 95% confidence interval (95% CI) 1.00–1.05]. This may reinforce the hypothesis that a chronic inflammatory state may increase cardiovascular risk in the CKD population receiving ESA (often at high doses because of hyporesponsiveness). This concept is further reinforced by the fact that lower Hb values were another independent risk of stroke at multivariate analysis.
Following these considerations, we believe that the degree of evidence of the history of stroke given by the KDIGO recommendation (1B) is overrated considering the available evidence.

We suggest using for the European population with CKD the following:

Risk factors for stroke (including a past history of stroke) and the presence of active malignancy or a past history of malignancy should be taken into account when weighing the risk/benefit ratio of prescribing ESA therapy. However, these are not absolute contraindications to ESA treatment and the nephrologist should discuss them together with the single patient, balancing with him/her the risk benefit ratio.

**CKD-ND PATIENTS**

3.4.1: For adult CKD ND patients with Hb concentration ≥10.0 g/dL (≥100 g/L), we suggest that ESA therapy not be initiated. (2D)

3.4.2: For adult CKD ND patients with Hb concentration <10.0 g/dL (<100 g/L), we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anaemia. (2C)

The ERBP group on anaemia already produced a position statement following the publication of the TREAT study [5]. As already underlined, this paper provided high-quality scientific evidence about ESA use in the CKD population with diabetes. However, the interpretation of the TREAT findings is complex, and there are a number of grey areas that still need more satisfactory answers. In particular, the decision of the KDIGO group in not giving a lower Hb threshold at which ESA treatment should be started in general is questionable for a number of reasons. First, the fact that in the control group the mean achieved Hb levels were well above the reference value of 9 g/dL (median Hb of 10.6 g/dL; IQR 9.9–11.3 g/dL) implies that the TREAT study cannot be considered good evidence to support the conclusion that CKD patients not on dialysis can be maintained long term at very low Hb levels safely without starting ESA therapy. Indeed, according to a meta-analysis, cohorts of CKD patients with severe anaemia (Hb <10 g/dL) had a left ventricular mass index (LVMI) >125 g/m² in a much larger percentage than those with moderate anaemia (mean baseline Hb ≥10 g/dL <12 g/dL) (89 and 43%, respectively) [50]. Following partial anaemia correction, only those having severe anaemia at baseline experienced a significant reduction in LVMI. In addition to this, even if we were to consider the TREAT study as the starting point for giving the recommendation, the study protocol foresaw rescue therapy with darbepoetin alfa when Hb values fell below 9 g/dL. Despite this rescue option, achieved Hb values progressively increased during the follow-up (from a median value of 10.4 g/dL at baseline to 11.2 g/dL at the end of the study). This positive trend is against the common observation that CKD patients show a decrease in Hb values during the course of their disease (although the trial effect in improving patient care is well known). The fact that 46% of the control group received at least a dose of darbepoetin alfa but the median dose was of 0 μg suggests that many of these patients were not affected by severe chronic anaemia but that they occasionally reached an Hb value <9 g/dL because of intercurrent events (i.e. infections, bleeding, surgical procedures, inflammation etc.). After only a few doses of darbepoetin alfa and following iron therapy and/or resolution or improvement of the medical condition, they did not need chronic therapy with ESA to maintain their Hb values in a satisfactory target range. Thus, this cannot be considered good evidence that CKD patients should be maintained at low Hb levels without starting ESA therapy in the long term.

Recently, a secondary analysis of the control group of the TREAT study showed that those patients who received five or more doses of darbepoetin alfa were more likely to receive IV iron therapy and blood transfusions and to progress to renal replacement treatment (but were not at higher risk of death) than those not receiving rescue darbepoetin alfa doses [51]. The strongest predictors of requiring darbepoetin alfa (≥5 doses) were lower baseline Hb level, lower estimated GFR and higher proteinuria level. This may be a further confirmation that the more advanced the CKD stage, the more likely is it that the patient needs intervention for anaemia. If an ESA is not prescribed, the likelihood of blood transfusion increases.

In the experimental group of the TREAT study, the mean dose of darbepoetin alfa (~175 μg/month) was higher than that found in general in Europe in the same patient population [5, 52]; it is also well known that in haemodialysis patients, ESA requirements are much lower in Europe than in the USA. This may suggest that KDIGO recommendations driven by the TREAT data may not necessarily be applicable to the European CKD population. The fact that the drug was administered once a month in the majority of the patients and some of them were not fully iron-replete may have contributed to these high-dose requirements. In this regard, a pre-specified subgroup analysis of the TREAT study comparing the different participating regions showed that in Western Europe and Australia there was a trend towards a reduced hazard ratio (HR) of reaching the primary composite end-point favouring the experimental group (36 events of 172 patients in the darbepoetin group, 57 events of 198 patients in the control group; HR 0.66, 95% CI 0.43–1.01). Conversely, in Eastern Europe the HR between the two groups was neutral (1.04, 95% CI 0.79–1.37) [5]. Nevertheless, the risk of statistical fluctuations in this kind of secondary analysis is very high.

Recently, Akizawa et al. [53] performed a small, controlled, randomized, clinical trial of 321 ND-CKD patients and tested the effect of correcting anaemia with ESA to intermediate Hb levels (11–13 g/dL) compared with Hb levels <11 g/dL. During the 48 week follow-up, they found a similar rate of cardiovascular events in the two groups (n = 42 in the higher-Hb group compared with n = 51 in the lower-Hb one).
However, correcting anaemia towards intermediate Hb levels led to significant improvement in all quality of life and vitality scores compared with a lower Hb target. While LVMi remained stable in the lower Hb group, it significantly decreased in the higher Hb group (P < 0.001). Three-year cumulative renal survival rate was better in the higher than in the lower Hb group (39.9 versus 32.4%, respectively; log-rank test P = 0.111, HR 0.71, 95% CI 0.52–0.98) [54].

Finally, it should also be considered that patients with symptomatic ischaemic heart disease might benefit from higher Hb levels, as demonstrated by a lower rate of revascularization procedures of coronary arteries in the group randomized to higher Hb values and darbepoetin therapy in the TREAT study [5].

Following these considerations, we agree with the KDIGO group that the decision of whether and when to start ESA therapy in CKD-ND patients should be individualized. However, we believe that Hb values should not let be allowed to routinely fall below 10 g/dL, at least if there is no obvious temporary reason for Hb fall and/or if the causing factor causes resistance to ESA. Repletion of iron stores should be ensured before and during ESA therapy.

We suggest using for the European population the following:

- **The decision of whether and when to start ESA therapy in CKD-ND patients should be individualized** taking into account the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anaemia.
- Hb values should not routinely be allowed to fall below 10 g/dL in ND-CKD patients
- ESA therapy should not be started if there is a temporary and obvious cause of anaemia potentially reversible (inflammation, infections, bleeding, iron deficiency, surgical procedures etc).
- In low-risk patients (i.e. in younger patients with very few comorbidities) or in those in whom a clear benefit on quality of life can be foreseen, the start of ESA therapy could be considered at higher Hb values (no >12 g/dL).
- In high risk patients, including those with asymptomatic ischaemic heart disease, treatment initiation with ESA should be started at Hb values between 9 and 10 g/dL in order to maintain a Hb value ~10 g/dL during maintenance therapy.
- In the patients with ischaemic heart disease with worsening ischaemic symptoms associated with anaemia, ESA treatment initiation could be considered at higher Hb levels (>10 g/dL).

### ESA maintenance therapy

3.5.1: **In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dL (115 g/L) in adult patients with CKD. (2C)**

3.5.2: **Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dL (115 g/L) and will be prepared to accept the risks. (Not Graded)**

3.6: **In all adult patients, we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dL (130 g/L). (1A)**

There is a high degree of evidence showing that Hb normalization using ESA therapy has no benefit or can even be harmful in CKD patients compared with partial anaemia correction or placebo. Recommendation 3.6 is thus accepted in full.

Conversely, as demonstrated by the low grade of evidence of recommendation 3.5.1 and 3.5.2, the upper limit of Hb levels that should not be exceeded intentionally with ESA therapy in CKD patients is still a grey area. In 2007 following the publication of the Cardiovascular Reduction Early Anaemia Treatment Epoetin beta (CREATE) [56] and Correction of Haemoglobin and Outcomes in Renal Insufficiency
(CHOIR) [57] studies, KDOQI guidelines set a lower Hb limit (11.0 g/dL) and suggested an upper limit around 12 g/dL without intentionally exceeding 13 g/dL. This was accepted in full by the first position paper of the ERBP on the topic [2]. In the same period, a panel of experts of the KDIGO group concluded that levels of 9.5–11.5 g/dL were considered associated with better outcomes than those of >13 g/dL, but that there was no evidence either way for intermediate levels (11.5–13 g/dL) [58].

The TREAT trial further increased the degree of evidence that complete anaemia correction has no benefit (the study showed a neutral effect on the risk of death or of reaching a cardiovascular composite end point compared with the placebo arm) [5]. The increased risk of stroke and death for malignancies in those with a previous history of cancer, which was found in the experimental harm of the TREAT trial, has already been discussed in the section about ESA initiation.

Unfortunately, the trial design does not help us to fill in the gap in knowledge about intermediate Hb values given that many patients of the control group remained at intermediate Hb levels (from a median value of 10.4 g/dL at baseline to 11.2 g/dL at the end of the study, with a median value of 10.6 g/dL during the trial follow-up). These achieved values are very close to the upper limit of Hb level suggested by the current KDIGO guidelines [7]. As already discussed, the fact that in the control group of the TREAT study, Hb levels had a positive trend during follow-up despite minimal or no ESA therapy may indicate that these findings are not necessarily applicable to the overall CKD populations.

Another point deserving a comment is the possibility of a different risk of increased death or cardiovascular events following ESA therapy according to the CKD stage. In 2007 the KDOQI group performed a meta-analysis of available trials in the dialysis and non-dialysis populations and found a trend towards increased cardiovascular risk only in patients not on dialysis assigned to higher Hb targets [3]. The reason for this discrepancy is not clearly understandable, considering that dialysis patients have in general a higher burden of comorbidities, are exposed to high Hb values following the dialysis session and are more likely to receive higher ESA doses and intravenous iron, possibly exposing patients to enhanced oxidative stress. The impact of marked haemoconcentration at the end of the dialysis session, especially in patients with high interdialytic body increases, has not been taken into account by KDIGO recommendations when suggesting a lower Hb target for ND-CKD patients.

Following the publication of the TREAT trial [5], Palmer et al. [59] performed a meta-analysis of 27 randomized trials of ESAs in CKD patients with anaemia and found no statistically significant difference in the risk for all-cause mortality, serious cardiovascular events, or fatal and nonfatal myocardial infarction between a higher and lower Hb target. Unfortunately, the separate analysis of the 10 studies including only ND-CKD patients was done only on the risk of reaching ESRD. Moreover, the study by Parfrey et al. [44] was excluded by the sub-analysis about the risk of stroke.

Recently, Coyne [60] reanalysed the data of the Normal Haematocrit Trial [55] using the clinical trial report filed by the FDA in 1996. Summarizing, he found that randomization to the higher target increased significantly the risk for the primary end point (in the 1998 publication the P value was not given), the risk of death (risk ratio 1.27, 95% CI 1.04–1.54), non-access thrombotic events (P = 0.041), and hospitalization rate (P = 0.04). While according to the 1998 publication achieved Hb values were related with improvement in ‘physical function’, no improvement was found at the intention-to-treat analysis (randomization to the higher Hb target). The authors of the Normal Haematocrit Trial [61] strongly disagreed with this data.

Altogether, these findings are in line with the KDIGO recommendation (Grade 1A) that ‘ESAs should not be used to intentionally increase the Hb concentration above 13 g/dL’.

Conversely, no data suggest clear harm at the Hb range values suggested by previous guidelines (11–12 g/dL). This is especially true for CKD stage 5D patients in whom no further clinical trials have been published since 2007.

In this light, we feel that caution should be used in the specific patient populations with some particular risk factors especially among diabetic patients (symptomatic limb arteriopathy, stroke or asymptomatic ischaemic heart disease, cancer) or in those who are hyporesponsive to ESA treatment and considering that in the control groups of trials testing partial versus complete anaemia correction Hb values ranged between 9 and 12 g/dL, in the opinion of the group it is reasonable to use ESA therapy to generally maintain CKD patients with Hb values ranging between 10 and 12 g/dL.

This suggestion is consistent with the previous one given by the Anaemia Group of ERBP following the publication of the TREAT trial [5], advising to aim to Hb values between 11 and 12 g/dL in general in CKD patients treated with ESA but aim at a lower Hb target in high-risk patients [6].

In the opinion of the group, this Hb range is deliberately and helpfully reasonably wide which we feel is better to be used in everyday clinical practice avoiding excessive Hb variability and leaving room for physicians to set their patients to the lower or higher edge of the range according to patient characteristics or ‘informed’ preferences. In this regard, it is important to consider that from an epidemiological perspective if we shift the Gaussian curve too much to the left of Hb distribution in CKD patients treated with ESA, we inevitably increase the number of transfusions. This aspect has to be taken into account also in light of the fact that there is a worldwide shortage looming in the supply and availability of blood and blood products.

This trend is already on-going, as testified by recent epidemiological data in the USA following the publication of the FDA warning about ESA therapy in 2010 and changes in reimbursement policies of ESAs. According to the US Renal Data System, in each of the first 9 months of 2011, the share of dialysis patients covered by Medicare who received blood transfusions increased by 9–22% over the corresponding months in 2010 [62]. This was paralleled by an 18% decrease in ESA dose from 2010 to 2011. Similar findings were shown by an analysis of the DOPPS study in the same time period [24].
We suggest using for the European population the following:

- Hb values >13 g/dL should not be intentionally aimed for during ESA therapy.
- It is reasonable to use ESA therapy to generally maintain CKD patients with Hb values ranging between 10 and 12 g/dL, individualizing the value in this target range according to the possible comorbidities of the patients.
- Caution should be used in patients with specific risk factors especially among diabetics (symptomatic limb arteriopathy, stroke or non-symptomatic ischaemic heart disease, cancer) or in those who are hyporesponsive to ESA treatment). In these patients, if ESA therapy is used, it seems wise to aim towards the lower Hb levels of the suggested target range (10–12 g/dL).

### CHAPTER 4: RED CELL TRANSFUSION TO TREAT ANAEMIA IN CKD

4.1.1: When managing chronic anaemia, we recommend avoiding, when possible, red cell transfusions to minimize the general risks related to their use. (1B)

- In patients eligible for organ transplantation, we specifically recommend avoiding, when possible, red cell transfusions to minimize the risk of allosensitization. (1C)

4.1.2: In patients eligible for organ transplantation, we specifically recommend avoiding, when possible, red cell transfusions to minimize the risk of allosensitization. (1C)

4.2.1: When managing chronic anaemia, we suggest that the benefits of red cell transfusions may outweigh the risks in patients in whom (2C):

- ESA therapy is ineffective (e.g. haemoglobinopathies, bone marrow failure, ESA resistance)
- The risks of ESA therapy may outweigh its benefits (e.g. previous or current malignancy, previous stroke)

In the opinion of the group, these recommendations together with their rationale are wise and acceptable. According to our comment in the section about ESA initiation, the risk of stroke in those with a previous history is not significantly increased by darbepoetin alfa use and complete anaemia correction [45]. Consequently, it is questionable that the benefits of red cell transfusions may outweigh the risks in patients with a previous stroke.

4.2.2: We suggest that the decision to transfuse a CKD patient with non-acute anaemia should not be based on any arbitrary Hb threshold, but should be determined by the occurrence of symptoms caused by anaemia. (2C)

This recommendation is based on previous guidelines [63, 64] emphasizing that blood transfusion should be driven mainly by patient symptoms and not on a given Hb level threshold. In the opinion of the group, this point is critical and deserves a number of comments.

First, it is true that the exact Hb threshold at which a haemodynamically stable medical patient with anaemia could benefit of a blood transfusion in terms of outcome is still a grey area. This is particularly true for CKD patients in whom evidence regarding this aspect is lacking (except the frustrating experience with blood transfusions when ESA therapy was still not available). It is also clear that the more restrictive the transfusion strategy, the lower the risk of infectious and non-infectious complications related to blood transfusions and the lower the blood use. The fact that at very low Hb levels platelet function may be compromised should also be taken into account. In the future, the supply of blood products will become more difficult as blood donors become rarer due to the demographic aging of the general population with fewer potential donors and more patients with medical conditions in need of a blood transfusion.

Anaemia-related symptoms may be vague and their occurrence is not tightly associated with anaemia severity. Considering that, as already pointed out by the KDIGO group, at Hb levels below 10 g/dL transfusion needs markedly increase, based mainly on symptoms, the decision of whether or not to transfuse a given patient implies the risk of submitting CKD patients to unnecessary blood transfusion and conflating this therapeutic strategy as an equal alternative to ESA therapy, especially in cases in whom the risk of ESA therapy may be vague. As already pointed out in the section about ESA maintenance therapy, the number of haemodialysis patients receiving blood transfusions is already increasing in the USA [62]. Compared with CKD-5D, the ND-CKD population is even more likely to experience a marked increase in blood transfusion in the near future following the publication of KDIGO guidelines. Indeed, for this patient population, a lower Hb value at which one can recommend in general the start of ESA therapy cannot be foreseen. Many of these patients may be future candidates for kidney transplantation; so, the possible risk of allosensitization following blood transfusion should be considered when taking the decision to start ESA therapy or setting the optimal Hb value during treatment.

In addition to these considerations, after the closure of the process of development of KDIGO guidelines [7], the American Association of Blood Bank published a new set of clinical practice guidelines on red blood cell transfusion [65]. These guidelines clearly remark that a liberal transfusion strategy would be acceptable over a restrictive one only if reliable evidence demonstrates its superiority. According to the panel, a liberal transfusion strategy is unlikely to result in clinically important reduction in mortality or on other secondary end-points but exposes patients to a much higher number of blood transfusions [56]. In hospitalized, haemodynamically, stable patients transfusion decision should be influenced both by symptoms and Hb values. In particular, they suggest considering transfusion at Hb values ≤7 g/dL or at Hb values ≤8 g/dL in postoperative surgical patients [56]. In hospitalized patients with pre-existing cardiovascular disease, transfusion should be considered at Hb values ≤8 g/dL or in the presence of symptoms (chest pain, orthostatic hypotension, tachycardia unresponsive to fluid resuscitation or congestive heart failure) [56].

Altogether, in the opinion of the group, at present there is no evidence that in CKD patients a liberal transfusion
strategy mainly driven by symptoms improves patient outcome or that it is not harmful. Moreover, the group feels that it is important to remark that blood transfusions should be used wisely in the CKD population. In the individual haemodynamically stable patient, a blood transfusion should be considered in the presence of stringent indications (i.e. very low Hb levels, clear symptoms related to anaemia, ESA resistance and considerable risk in using ESA therapy).

Another aspect to be commented on is the role of blood transfusion therapy in the management of CKD patients with chronic anaemia in whom physicians have decided that risks of ESA therapy outweigh the benefits. According to the experience driven from hereditary or acquired transfusion-dependent anaemia, transfusions provide effective treatment and prevention of many complications, but iron overload is an inevitably serious complication of chronic blood transfusions and can lead to significant morbidity and mortality if left untreated. Moreover, despite the efficiency of red cell transfusions in increasing Hb levels acutely, patients requiring chronic transfusion experience long periods of suboptimal Hb levels. According to the experience gathered from patients with myelodysplastic syndrome, those who are transfusion dependent have a significantly higher percentage of hypertrophic cardiac remodelling than those who are not [66].

In the opinion of the group, these aspects should also be considered when balancing the risk/benefit of blood transfusion compared with ESA therapy in the single patient.

The investigation of the burden of iron overload following an increase in the number of transfusions in the CKD population (especially in those periodically receiving blood transfusions) should be an objective of future research.

We suggest using for the European population with CKD the following:

- A restrictive blood transfusion strategy is recommended in the CKD population.
- In the individual haemodynamically stable patient, a blood transfusion should be considered in the presence of stringent indications (i.e. very low Hb levels (Hb values <7 g/dL or at Hb values <8 g/dL in postoperative surgical patients and in patients with pre-existing cardiovascular disease), clear symptoms related to anaemia, ESA resistance, considerable risk using ESA therapy).

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