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## Anaemia management in patients with chronic kidney disease: a position statement by the Anaemia Working Group of European Renal Best Practice (ERBP)

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### Introduction

Over the last few years, much has been done to develop guidelines on the basis of the strongest possible evidence because this allows an accurate description of the quality and/or degree of uncertainty of the recommendations and provides physicians with a valuable tool for judicious decisions. However, creating and updating evidence-based guidelines is extremely costly, and so the nephrological community has been trying to build up a single set of international guidelines under the aegis of Kidney Disease Improving Global Outcomes (KDIGO) [1]. As part of this unifying effort, the working group responsible for the 2006 update of the National Kidney Foundation–Kidney Disease Outcome Quality Initiative (NKF-KDOQI) guidelines on anaemia management in patients with chronic kidney disease (CKD) [2], and the 2007 update on haemoglobin (Hb) targets [3], included members from Europe, Middle East, Mexico and Canada. However, this international effort may not be correctly perceived by European nephrologists, who sometimes feel that differences in practice patterns make it difficult to apply guidelines developed outside Europe; on the other hand, the latest update of the European Best Practice Guidelines (EBPG) [4] may appear outdated in some respects.

A specially appointed ERA-EDTA Work Group met in Paris to discuss European guideline planning in early January 2008, and agreed that the Association should con-

tinue producing and updating guidelines in collaboration with KDIGO [5]. It also agreed that ERA-EDTA should issue suggestions for clinical practice in areas in which evidence is lacking or weak, which will be presented as 'position statements' rather than clinical guidelines [5]. It was also decided to issue position statements about guidelines (recommendations issued by other bodies, of which the current publication is the first result). Finally, the group opted to change the name EBPG to European Renal Best Practice (ERBP) as a means of acknowledging that, especially in nephrology, it is difficult to generate real 'guidelines' because of the lack of sufficient evidence.

In this context, and while awaiting the publication of the KDIGO anaemia guidelines possibly in 2011, an *ad hoc* work group was commissioned by the ERBP Advisory Board to give its opinion on the 'hot topic' of Hb targets, including recently raised issues that were not covered by KDOQI in 2006 [2]. These points are summarized in the present position paper, which is not intended to represent a set of new guidelines as it is not the result of a systematic review of the evidence.

### NKF-KDOQI update, 2006

In May 2006, the NKF published a revised set of guidelines on managing anaemia in CKD [2]. The Guideline Committee attempted to integrate new evidence using the 2004 EBPG revision [4] and the 2000 KDOQI guidelines as a starting point [6]. The update also involved a systematic review of the evidence based on an extensive search of the literature and the grading of the strength of the evidence, and separated evidence-based guidelines, which could be used to measure clinical performance when appropriate, and clinical practice recommendations primarily based on expert judgement. The result was a solid document summarizing the evidence available up until September 2005.

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## Haemoglobin target: NKF-KDOQI update, September 2007

In 1997, the DOQI guidelines on anaemia treatment recommended a target range for haematocrit/Hb of between 33% (Hb 11 g/dl) and 36% (Hb 12 g/dl) [7]. While waiting for the results of clinical trials concerning complete anaemia correction other than Besarab's study [8], almost similar recommendations were made in the 2000 update of the KDOQI guidelines [6] and by EBPG [4] although no upper limit was defined for the early stages of CKD, while normalization of Hb levels was generally not recommended for patients with diabetes or cardiovascular disease. The 2006 update of the NKF-DOQI guidelines recommended that the target Hb range should generally be  $\geq 11.0$  g/dl (lower limit) and stated that there was insufficient evidence to recommend routinely maintaining Hb levels of  $\geq 13.0$  g/dl in ESA-treated patients (upper limit) [2]. At this time, the available findings of randomized clinical trials and meta-analysis [9] did not suggest any major effect of complete anaemia correction on hard, intermediate or surrogate endpoints except the quality of life. Two large-scale randomized trials studying the effect of complete anaemia correction on mortality in patients not on dialysis were published in November 2006 [10,11]. In the CREATE study [10], 603 patients with stage 3 and 4 CKD and mild-moderate anaemia were randomly assigned to a target Hb range of 13–15 g/dl (normal range) or 10.5–11.5 g/dl (subnormal range). During the 3 years of the study, the number of cardiovascular events was not significantly different between the two groups (58 versus 47) and there was no difference in the frequency of death from any cause or cardiovascular causes, nor in the incidence of hospitalization. However, patients randomized to complete anaemia correction had a shorter time in need of dialysis. The CHOIR study [11] was an open-label trial in which 1432 CKD patients were randomly assigned to achieve an Hb level of 14.3 g/dl or 11.3 g/dl. The median duration of the follow-up was 16 months, but the trial was stopped early for safety and futility because it had become unlikely that the group randomized to the higher Hb target would obtain any benefit and was associated with an increased risk of reaching the primary composite end-point (death, myocardial infarction or hospitalization because of congestive heart failure or stroke). Despite the differences in their populations and the results of secondary analyses, these two large-scale, prospective randomized trials showed that attempts to correct anaemia completely do not reduce mortality or cardiovascular disease in CKD patients in comparison with partial anaemia correction [10,11]. A meta-analysis by Phrommintikul *et al.* [12] (which also included these two trials) led to the conclusion that the patients in the higher Hb target group were at significantly greater risk of all-cause mortality and arterio-venous access thrombosis.

In March 2007, the US Food and Drug Administration (FDA) changed the labelling for erythropoiesis stimulating agents (ESAs) and added a boxed warning stating that Hb targets of  $>12$  g/dl should be avoided because of the increased risk of death and serious cardiac events, and also noted that ESAs should increase Hb only to the lowest level necessary to avoid transfusion.

These recommendations created considerable confusion and concern, and the new evidence was considered significant enough to justify updating the statements by the NKF-KDOQI guideline working group concerning Hb targets. An Evidence Review Team analysed all data from randomized controlled trials of anaemia management in CKD, including CREATE [10], CHOIR [11] and four additional studies not included in the previous update. Combining mortality outcomes from eight studies involving 3038 subjects with non-dialyzed CKD revealed no difference between the higher and lower Hb target [3], but combining adverse cardiovascular events from six studies involving 2850 subjects showed an increased risk among the patients assigned to the higher Hb targets (a RR of 1.24, 95% CI 1.02–1.51) [3], although it is worth noting that the CHOIR and CREATE studies contributed most of the weight to the analysis. Among dialysis patients, combining mortality (four studies, 2391 subjects) or cardiovascular outcomes (three studies, 1975 subjects) showed no statistically significant difference between the higher and lower Hb level; here the study by Besarab *et al.* [8] contributed most of the weight to the analysis.

The meta-analysis by NKF-KDOQI differed from that by Phrommintikul *et al.* [12] as it included studies with a longer minimum follow-up (without any restriction on study size), kept the data concerning dialyzed and non-dialyzed patients separate and had a broader definition of cardiovascular outcomes as it combined all cardiovascular events (Phrommintikul *et al.* only considered myocardial infarction).

On the basis of these results, the NKF-KDOQI working group reformulated its recommendations by stating that the Hb target in patients receiving ESAs should generally be 11–12 g/dl and not  $>13$  g/dl because 'the possibility of causing harm weighs more heavily than the potential of improving the quality of life and decreasing transfusions' [3].

## Kidney Disease Improving Global Outcomes (KDIGO)

KDIGO, which was established in 2003, is a non-profit foundation governed by an international board that has the aim of 'improving the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration and integration of initiatives to develop and implement clinical practices guidelines'. In October 2007, it called a meeting to coordinate a response to the issue of anaemia management after the publication of the NKF-KDOQI update concerning Hb targets [13]. On the basis of the available evidence, it was concluded that an Hb level of  $>13$  g/dl may be associated with harm in subjects treated with ESA; that levels of 9.5–11.5 g/dl are 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) in comparison with higher or lower levels.

Limitations of the current knowledge of CKD-related anaemia were also identified, as well as topics for future research.

It was generally agreed that there were insufficient new data to justify an immediate revision of the anaemia

guidelines. On the basis of the anticipated results of key on-going studies, particularly the Trial to Reduce Cardiovascular Events with Aranesp(R) (darbepoetin alfa) Therapy (TREAT) [14], which is a 4000-patient, multicentre, double-blind RCT, designed to determine the impact of anaemia therapy with darbepoetin alpha on mortality and non-fatal cardiovascular events in patients with CKD and type 2 diabetes mellitus, it was planned to start a review of the new evidence no earlier than 2009 with the expectation of completing it in 2011. Given the clear need to avoid duplication, these guidelines will be the result of a coordinated effort undertaken by KDIGO.

## The position of ERBP

### Haemoglobin target

In 2004, EBPG suggested an Hb target of  $\geq 11$  g/dl; values of  $> 14$  g/dl were considered undesirable in general, and the limit for patients with cardiovascular disease was set at 12 g/dl. Caution of not exceeding the value of Hb concentrations  $\geq 12$  g/dl was recommended to be given also for patients with diabetes, especially if they had concurrent peripheral vascular disease. Since September 2007, when the KDOQI Hb target update was published, no further data from new clinical trials have been published. In response to a request from the editors of the *New England Journal of Medicine*, the authors of the Normal Hematocrit Study [8] provided supplementary data about events occurring after the dataset had been analysed by the Independent Data and Safety Monitoring Committee [15]; the inclusion of these additional events in the survival analysis did not substantially modify the risks of death or myocardial infarction.

- In the opinion of the ERBP Work Group, it appears reasonable to maintain the lower limit of the target, although the actual evidence for choosing this value is also very limited. On the basis of new evidence, Hb values of 11–12 g/dl should be generally sought in the CKD population without intentionally exceeding 13 g/dl.

Although harm is possible when aiming at higher Hb targets, it is likely that this applies most to selected populations such as patients with diabetes and/or clinically significant cardiovascular disease. However, current evidence shows no benefit for higher targets in any subgroup and increased expenditure on higher ESA doses.

A secondary analysis of the CHOIR trial showed that patients in the high target group who reached an Hb level of 11 g/dl but could not reach 13 g/dl showed a higher rate of adverse outcomes, and the patients who needed a high ESA dose had a 6% greater risk of reaching a study end-point regardless of the target [16].

- The ERBP Work Group believes that there is a need for better understanding as to whether any harm may be associated with attempts to reach higher Hb values in patients with comorbidities or those who are hyporesponsive to ESAs.

It is more difficult to keep patients within a narrow target window mainly because of haemoglobin variability [17], and so physicians need to accept that patients may be below or above the target for a given period of time. The

possibility that there may be a causal relationship between Hb variability and patient outcome has been suggested by association studies [18,19].

- The ERBP Work Group agrees with the recent position of KDIGO [13] that the available quality of life data vary in quality and are often inconclusive. As more reliable methods of assessing patient-related outcomes and functional status are now available, there is room for new studies testing the effect of anaemia correction on more robust measures of the quality of life.

### Anaemia evaluation

In 2004, EBPG defined anaemia in CKD patients on the basis of their gender and age. 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), and it was recommended that an anaemia work-up be started when Hb levels fall below these limits.

In 2006, KDOQI modified this definition by giving a single criterion for diagnosing anaemia in adult males (Hb  $< 13.5$  g/dl, regardless of age) because the decrease in Hb among males aged  $> 60$  years is often attributable to concurrent diseases.

- The ERBP Work Group agrees with this new definition.

### Targets for iron therapy

Traditionally, the most widely used iron tests are serum ferritin and transferrin saturation (TSAT) levels. In 2004, EBPG recommended lower limits of ferritin and TSAT of, respectively, 100 ng/ml and 20%, with target ranges of, respectively 200–500 ng/ml and 30–50%. In 2006, and in light of patient safety, KDOQI defined the lower ferritin limit on the basis of CKD status (100 ng/ml in non-HD-CKD and 200 ng/ml in HD-CKD); if serum ferritin levels are  $> 500$  ng/ml, iron administration should be discouraged.

No key study has been published since the publication of the 2006 KDOQI guidelines, but it is interesting to note the results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) trial [20], which evaluated the efficacy of intravenous ferric gluconate in 134 patients with high ferritin (500–1200 ng/ml) and low transferrin saturation levels (TSAT  $\leq 25\%$ ) who were anaemic despite a high rHuEPO dose ( $\geq 225$  IU/kg/week or  $\geq 22\ 500$  IU/week). After 6 weeks, the patients receiving ferric gluconate (125 mg i.v. at eight consecutive haemodialysis sessions) showed a significant increase in Hb in comparison with controls. However, the study has a number of limitations because, given the short follow-up, it provides no information about safety and iron overload.

- The ERBP Work Group agrees with the recommendations of the KDOQI guidelines.

### New ESAs

The 2004 revision of EBPG and the 2006 KDOQI guidelines [2] made recommendations concerning the use of the three ESAs available at that time: epoetin alpha, epoetin beta and darbepoetin alpha. Since then, two other ESAs

have been introduced: epoetin delta and continuous erythropoiesis receptor activator (CERA).

*Epoetin delta.* Epoetin delta has the same amino acid sequence as endogenous epoetin, and epoetin alpha and beta, but is synthesized in human cells [21], a process that may theoretically circumvent problems arising from species-dependent differences in protein folding or post-translational modifications. However, such theoretical problems have so far not become obvious and the pharmacodynamics and pharmacokinetics of epoetin delta are also similar to those of other recombinant human erythropoietins [22]; clinical trials indicate that it corrects renal anaemia in rHuEPO-naïve patients [23] and can be used in the maintenance therapy of those already receiving epoetin alpha [24–27].

- In the opinion of the group, epoetin delta should be administered similarly to epoetin alpha.

*Continuous erythropoiesis receptor activator (CERA).* CERA is a modified recombinant human erythropoietin (rHuEPO) that incorporates a large polyethylene glycol polymer [28], which increases its molecular weight (~60 kD) and alters pharmacodynamics and pharmacokinetics. In particular, CERA has a considerably longer half-life than the other licensed ESAs (~130 h) [29,30]. It also has a lower total binding affinity for the erythropoietin receptor than epoetin beta, mainly due to a much slower association rate [31]. These receptor-binding properties may contribute to its distinct pharmacological characteristics. Phase II and III studies have shown that it corrects anaemia in EPO-naïve patients, and has a recommended starting dose of 0.60 µg/kg once every 2 weeks [32–35]. Other phase II and III clinical trials have tested its non-inferiority for maintenance therapy with a currently available ESA [36–41], and found that it can be given once every 4 weeks i.v. or s.c. during the maintenance phase.

- Based on the evidence available, the frequency of CERA administration should be once every 2 weeks for correction and once every 4 weeks for maintenance.
- The ERBP Work Group considers the safety and tolerability of CERA to be similar to that of other ESAs.

### Biosimilars

In December 2004, the patent of epoetin alpha expired in Europe, and that of epoetin beta expired in many European countries in 2005, thus opening the way to biosimilars. HX575, a biosimilar of epoetin alpha, received marketing authorization throughout the European Union in August 2007; it is marketed by three companies under three different brand names. In December 2007, epoetin zeta, which is another biosimilar of epoetin alpha, received EMEA marketing authorization as well.

While biosimilars may remove some of the current economical pressures on health care systems, the safety record of these compounds is much smaller as compared to the original ESAs and they need to be submitted to the same stringent pharmacovigilance measures as the other ESAs. To ensure this it appears mandatory that biosimilars are not used in exchange of other rHUEPOs without physician's

approval. It is also noteworthy that ESA biosimilars are currently only approved for intravenous administration in CKD patients.

- The ERBP Work Group recommends stringent pharmacovigilance for biosimilars of epoetin alpha that can be administered only intravenously.

### Pure red cell aplasia

Antibody-mediated pure red cell aplasia (PRCA) is a rare but serious adverse event related to ESA therapy. There has been an upsurge in the number of PRCA cases since 1998, mainly associated with the subcutaneous use of Eprex<sup>®</sup>, the epoetin alpha produced outside the United States [42]. This coincided with a change in the Eprex<sup>®</sup> formulation (the replacement of human serum albumin by polysorbate 80 was requested by EMEA because of the fear of bovine spongiform encephalopathy), and it has been postulated that polysorbate 80 may elicit the formation of possibly immunogenic epoetin-containing micelles [43]. Alternatively, it has been suggested that leachates released by the uncoated rubber stoppers of the pre-filled syringes may interact with polysorbate 80 and act as an adjuvant of the immune reaction. The breaking of cold chain is potentially an important factor.

The subcutaneous use of Eprex<sup>®</sup> in CKD patients had been contraindicated in Europe by regulatory authorities since December 2002, and was strongly discouraged in Canada and Australia.

The number of reported cases of PRCA has decreased sharply since 2003 and with no more cases reported in 2007. This may be due to a change in the route of administration, the reinforcement of the product cold chain or the elimination of uncoated rubber syringe stoppers. The regulatory authorities consider the latter as the most significant factor and have recently readmitted the subcutaneous use of Eprex<sup>®</sup> when the vascular access is not available in conjunction with an extensive pharmacovigilance plan.

- The ERBP Work Group considers it essential that suspected PRCA cases are carefully worked up and confirmed cases are carefully monitored.

As there were few data concerning the outcome of ESA treatment in patients who have recovered from PRCA, the 2004 EBPG could not make any recommendation about whether to resume its administration in such patients. In 2005, a follow-up report concerning 170 CKD patients who developed epoetin-associated PRCA was made available by the Research on Adverse Drug Events and Reports (RADAR) Project [44]. Of the 34 patients who received epoetin after the onset of PRCA, 56% recovered epoetin responsiveness; the highest rate of epoetin responsiveness was observed among those who had no detectable anti-erythropoietin antibodies at the time of epoetin administration (89%).

- Given these data, the ERBP Work Group considers that retreatment with ESA can be considered in patients with a history of PRCA, if anti-EPO antibodies are no longer detectable.

It has very recently been reported that hematide, a non-peptidic erythropoietin receptor agonist that is currently

under clinical development, corrects the anaemia induced by the presence of anti-erythropoietin antibodies [45] as previously shown in a rat PRCA model [46].

### Safety concerns in CKD patients with cancer

The ubiquitous expression of erythropoietin receptor (EPOr) in non-erythroid cells has been associated with the discovery that EPO has various biological functions in non-haematopoietic tissues, and a number of experimental findings link EPO-EPOr signalling to angiogenesis. This pleiotropic effect is a possible physiological response to ischaemia and may elicit the growth of solid tumours. However, no direct relationship between the presence of EPOr on tumour cells and tumour proliferation in response to exogenous EPO has yet been established. The use of ESAs may also increase the risk of venous thromboembolism in cancer patients.

ESA therapy is approved in patients with non-myeloid malignancies who have developed chemotherapy-associated anaemia in order to decrease transfusion requirements. However, safety concerns have been raised in cancer patients since 2004 [47], particularly in relation to off-label indications such as anaemia not secondary to chemotherapy or an Hb target of > 12 g/dl.

In May 2007, the Oncologic Drugs Advisory Committee of the Food and Drug Administration (FDA) reassessed the ESA-related risks of venous thromboembolism, poorer cancer outcomes and cardiovascular disease in cancer patients receiving chemotherapy [48], and subsequently ordered that

boxed warnings for safety information be added to the labels of the available ESAs recommending the use of the lowest ESA dose to increase Hb to a level high enough to avoid red blood cell transfusions. According to FDA indications, an Hb target of > 12 g/dl should be avoided.

- In the opinion of the ERBP Work Group, ESA therapy should be cautiously used in patients with CKD and malignancies as no information is available concerning the risk of mortality and tumour growth in this subset of patients.

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### Appendix: summary of recommendations

	EBPG 2004	KDOQI 2006/2007	ERBP: anaemia group position, 2008
Definition of anaemia	Hb <11.5 in women Hb <13.5 in men ≤70 years Hb <12 in men >70 years	Hb <12 in females Hb <13.5 in males	Hb <12 in females Hb <13.5 in males
Haemoglobin target	Hb >11 g/dl; Hb >14 g/dl not desirable (>12 g/dl in CVD)	<sup>a</sup> Generally Hb 11–12 g/dl, target Hb should not be >13 g/dl	Generally Hb 11–12 g/dl target Hb should not be >13 g/dl
Targets for iron therapy	TSAT (%) Lower limit: 20 Target: 30–50 Ferritin (ng/ml)  Lower limit: 100 Target 200–500	TSAT (%) Lower limit: ≥20 Ferritin Lower limit: 100 in non-HD, 200 in HD Do not routinely exceed 500	TSAT (%) Lower limit: ≥20 Ferritin Lower limit: 100 in non-HD, 200 in HD Do not routinely exceed 500
Pure red cell aplasia sc Eprex <sup>®</sup>	Contraindicated	Not sold in the USA	Readmitted for s.c. use, i.v. use already possible
Retreatment of PRCA pts with ESA	Insufficient information to give recommendations	–	Careful rechallenge possible, especially in the absence of anti-EPO antibodies
New erythropoiesis stimulating agents Epoetin delta CERA	–	–	Use as other rHuEPOs Starting dose: 0.6 µg/kg Frequency: once every 2 weeks for correction; once every 4 weeks for maintenance Administration route: i.v. or s.c.
Biosimilars			Use as originator compounds, strict post marketing surveillance, only IV administration
HX575 and Epoetin zeta	–	–	Use as epoetin alpha; strict post-marketing surveillance
CKD patients with cancer	–	–	Use caution; do not aim for Hb >12 g/dl

<sup>a</sup>Recommendation from the 2007 KDOQI revision about Hb target [3].

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## Are the synergistic effects of high-volume haemofiltration and enhanced adsorption the missing key in sepsis modulation?\*

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### Introduction

Despite major recent therapeutic improvements, septic shock remains a leading cause of mortality in intensive care patients [1]. For more than a decade, it has been

advocated [2,3] that the reduction of blood cytokine levels could, at least theoretically, lead to reduced mortality. However, in view of the complexity of the pharmacodynamics and pharmacokinetics of cytokines, this concept seems too oversimplified to apply. In this issue of the journal, Rimmelé and co-authors attempt to demonstrate that high-volume haemofiltration (HVHF) with enhanced adsorption (EA) can modulate and ameliorate sepsis-induced haemodynamical instability [4]. It is suggested in this paper that membranes with EA are key and that increased extraction from the central circulation is sufficient to obtain a beneficial clinical effect. It seems at least theoretically reasonable that effective removal of mediators from the tissue, where they are harmful, and transporting them to the central circulation must be effective. Therefore, HVHF and EA must work synergistically in this model. In order to consolidate this hypothesis, it seems fruitful to discuss the three

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