

REVIEW / PRACA POGLĄDOWA

Dorota Śmigiel-Staszak, Rafał Donderski, Jacek Manitius

**ANEMIA IN CHRONIC KIDNEY DISEASE (CKD).  
DO WE KNOW HOW TO TREAT IT PROPERLY?**

**NIEDOKRWISTOŚĆ W PRZEWLEKŁEJ CHOROBY NEREK (PCHN).  
CZY WIEMY JAK PRAWIDŁOWO NALEŻY JĄ LECZYĆ?**

Department of Nephrology, Hypertension and Internal Medicine L. Rydygier Collegium Medicum in Bydgoszcz,  
Nicolaus Copernicus University in Toruń, Poland  
Head: prof. dr hab. med. Jacek Manitius

**S u m m a r y**

Renal anemia is one of the major complications observed in patients with chronic kidney disease (CKD). It is caused mainly by a relative erythropoietin deficiency due to progressive damage of renal parenchyma. The primary goal of anemia treatment using available today ESAs is not only to improve the quality of life of patients but, above all to reduce cardiovascular mortality. The target hemoglobin concentration

during application of ESA in CKD patients treated conservatively and renal replacement therapy patients was and still is being discussed among nephrologists. Based on the clinical trials performed so far, it seems that in patients with renal anemia we should individualise treatment with ESA, seeking partial rather than complete correction of anemia.

**S t r e s z c z e n i e**

Niedokrwistość nerkopochodna jest jednym z istotnych powikłań obserwowanych u pacjentów z przewlekłą chorobą nerek (PCHN). Jest ona spowodowana głównie względnym niedoborem erytropoetyny wskutek postępującego uszkodzenia miąższu nerek. Podstawowym celem leczenia niedokrwistości przy pomocy dostępnych współcześnie czynników stymulujących erytropoezę (ESA) jest nie tylko poprawa jakości życia chorych, ale przede wszystkim zmniejszenie śmiertelności sercowo-naczyniowej. Docelowe

stężenie hemoglobiny w czasie stosowania ESA u pacjentów z PChN leczonych zachowawczo, jak i dializowanych, było i nadal jest przedmiotem dyskusji w środowisku nefrologicznym. W oparciu o przeprowadzone do tej pory badania kliniczne wydaje się, iż w przypadku chorych z niedokrwistością nerkopochodną należy prowadzić indywidualizację leczenia z zastosowaniem ESA, dążąc raczej do częściowej niż całkowitej korekcji niedokrwistości.

**Key words:** renal anemia, chronic kidney disease, iron, hemoglobin, erythropoietin

**Słowa kluczowe:** niedokrwistość nerkopochodna, przewlekła choroba nerek, żelazo, hemoglobina, erytropoetyna

**INTRODUCTION**

Anemia is one of the symptoms of chronic kidney disease (CKD) and an important cause of morbidity and cardiovascular mortality. ARIC Study

(Atherosclerosis Risk In Communities) showed that the slight increase in serum creatinine levels (> 1.2 mg/dl in women, > 1.5 mg/dl in men) together with anemia occurrence was associated with almost 3-fold risk of coronary artery disease (CAD). A similar relationship

was not observed in patients with elevated creatinine level without accompanying anemia [1]. DOPPS study, which was published in 2004, showed that 1.0g/dl rise (from the baseline) in hemoglobin reduces mortality by 5% [2].

In accordance with the criteria proposed by the WHO we recognize anemia when Hb is less than 13 g/dl in men and postmenopausal women, and less than 12 g/dl in women before menopause. According to the DOQI (Dialysis Outcome Quality Initiative), we deal with anemia when the Hb is about 1 g / dl lower than those defined by WHO [3].

#### THE PATHOGENESIS OF RENAL ANEMIA

One of the important cause of anemia in CKD is reduced red blood cell production by the bone marrow, caused by deficiency of erythropoietin due to the progressive renal damage. The main site of erythropoietin production in adults are tubular epithelial cells and interstitial fibroblasts at the border of the cortex and outer core of the kidney. Erythropoietin synthesis is regulated in a feedback mechanism, depending on the oxygen partial pressure of blood flowing through the kidney.

Red blood cell survival time in patients in advanced stages of chronic kidney disease is reduced to 1/3 survival time of erythrocytes in healthy individuals. Shorten survival time of erythrocytes is a consequence of accumulation of uremic toxins and erythrocytes damage, as a result of mechanical and osmotic or oxidative stress as well as.

Increased production of reactive oxygen species and impaired efficiency of antioxidant mechanisms in CKD lead to oxidative stress. This leads to increased plasma levels of lipid peroxidation products, protein, carbohydrates, and deoxyribonucleic acid [4]. It is believed that the impairment of the natural antioxidant system in erythrocytes is one of the most important factors increasing lipid peroxidation in erythrocyte membranes. This results in blood cell hemolysis, and therefore, intensification of anemia in patients with CKD [5]. CKD patients present significantly elevated plasma homocysteine level which is responsible for increased LDL oxidation in vascular wall. This results from the cytotoxic effects of homocysteine on the extracellular superoxide dismutase, whose activity decreases in direct proportion to the increase in concentration of homocysteine. In this way the vessel wall is deprived of the physiological antioxidant

protection and becomes more susceptible to the harmful effects of reactive oxygen species [6]. Probably, intensification of lipid peroxidation in cellular membranes is one of the factors jointly responsible for the reduction of erythrocyte survival and development of renal anemia.

On the other hand, it should be remembered that patients with CKD are exposed to repeated, frequent loss of blood due to gastrointestinal tract bleeding, frequent blood sampling for laboratory test and hemodialysis procedures itself (blood lose in extracorporeal circuit). It is estimated that during one hemodialysis session blood lose is approximately 20 ml as a result of puncture of arteriovenous fistula and loss of blood in the dialyzer. It gives blood lose of approximately 3 000 ml per year.

Moreover, drugs administration particularly commonly used ACE-I and AT1-blockers may aggravate renal anemia. It is related with deficiency of angiotensin II, which directly stimulates the synthesis of erythropoietin, reduce hypoxia, and is a strong stimulus for EPO production and may inhibit the proliferation of erythroblasts [7]. Thiazide diuretics administration may also (together with ARBs or ACE-I treatment) diminish endogenous production of erythropoietin by reducing oxygen supply as a result of active Na-Cl cotransporter inhibition in distal tubules [8].

Iron deficiency is the most common deficiency in CKD. Absolute iron deficiency in stage 4 - 5 CKD occurs when the transferrin saturation falls below 20% and ferritin levels is below 100 mg/ml [9]. In clinical practice, it is important to distinguish between functional iron deficiency, which corresponds to the treatment, and iron deficiency called 'inflammation block'. The latter is accompanied by chronic diseases caused by inflammation, and there is no improvement due to iron supplementation in this case.

The main objective of anemia treatment in patients with CKD is to improve quality of life and reduce mortality. It has been shown that the decrease in Hb of 1 g/dl was associated with increased mortality in 14-18% of the population of patients on dialysis, and the concentration of Hb below 8 g/dl resulted in two fold higher risk of death than the level of Hb 10-11 g/dl [10]. In many studies, both retrospective and prospective recommended range of concentrations of Hb was evaluated. Most of the researchers confirmed that the concentration of Hb > 11 g/dl affects better outcomes and and better improvement in quality of life

in both predialysis and renal replacement therapy patients. Hb concentration > 13 g/dl, paradoxically increases the morbidity and mortality. The target hemoglobin concentration should depend on clinical status, age, gender, physical activity, the coexistence of other factors of cardiovascular disease and dialysis modality.

#### CONTROVERSY IN RENAL ANEMIA TREATMENT

The CREATE STUDY and the CHOIR STUDY, the results of which were published in 2006, were the first trials to answer the question about hemoglobin concentration in chronic renal failure patients. Which therapeutic option is better – partial or complete correction of hemoglobin level?

In the CREATE Study (Cardiovascular Risk Reduction by Early Anemia Treatment) 603 patients with chronic kidney disease (CKD) stage 3 and 4 (eGFR range 15 to 35 ml/min per 1.73 m<sup>2</sup> of body-surface area) and mild-to-moderate anemia (hemoglobin level, 11.0 to 12.5 g per deciliter) were randomly assigned to a group with a target hemoglobin value in the normal range (13.0 to 15.0 g per deciliter, group 1) and to a group with subnormal range (10.5 to 11.5 g per deciliter, group 2). Subcutaneous erythropoietin (epoetin beta) was initiated at randomization (group 1) or only after the hemoglobin level fell below 10.5 g per deciliter (group 2). During the 3 years observation, in spite of better quality of life in arm with higher hemoglobin concentration, there were no differences in left ventricular mass index between these two groups noted. Complete correction of anemia did not affect the likelihood of a first cardiovascular event (58 events in group 1 vs. 47 events in group 2). The mean estimated GFR was 24.9 ml per minute in group 1, and 24.2 ml per minute in group 2 at baseline, and decreased by 3.6 and 3.1 ml per minute per year, respectively (P=0.40). Dialysis was required in more patients in group 1 than in group 2 (127 vs. 111, P=0.03). There were no differences in total mortality, cardiovascular mortality, hospitalizations rate between group 1 and group 2 [11]. The authors of the trial concluded that in patients with chronic renal failure, early complete correction of anemia does not reduce the risk of cardiovascular events.

The CHOIR study (Correction of Hemoglobin and Outcomes in Renal Insufficiency) compromised 1432

patients with CKD and Hb level below 11.0g per deciliter. Patients were randomly assigned to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 13.5 g per deciliter and other group to receive a dose targeted to achieve a level of 11.3 g per deciliter. Early termination of study was performed after 16 months because patients assigned to high hemoglobin group (target level 13,5g/dl) showed higher rate of cardiovascular events (CV death and hospitalization related to decompensated heart failure.) [12, 13].

The results of these 2 studies proved that complete renal anemia correction is not beneficial for CKD patients and there is no reduction in cardiovascular mortality and the incidence of new cardiovascular events in this population. It is worth noticing that higher morbidity and mortality rate in higher hemoglobin concentration arm was mainly related to toxicity of high dose of erythropoietin and intravenous iron administration but not by hemoglobin concentration >13.0g/dl itself. It appears that high dose of erythropoietin may activate RAAS, increase endothelin-1 (ET-1) production and diminish tromboxane and prostacycline release in vascular wall. This may lead to higher blood pressure and higher cardiovascular events rate [14]. Moreover, high erythropoietin dose in renal anemia treatment may contribute to tissue remodeling, intensification of chronic inflammation via activation of kB nuclei factor and increase production of many cytokines, growth factors and procoagulation mediators. This may lead to profibrogenic action of erythropoietin and other erythropoietin stimulation agents (ESA). [15].

High doses of ESA and fast correction of anemia may cause detrimental effects and may contribute to acceleration of CKD in patients on conservative treatment with Hb level above 13.0g/dl achieved in a very short time. On the other hand, in hemodialysis patients posthemodialysis hemoconcentration in individuals with Hb level>13.0g/dl may also cause higher cardiovascular events rate. Therefore, anemia treatment in this population should be very cautious.

Another worth mentioning study is the TREAT trial (Trial to Reduce Cardiovascular Events with Aranesp Therapy) the results of which were published in 2009 [16]. The TREAT was a randomized, double-blind, placebo-controlled trial conducted at 623 sites in 24 countries. The TREAT trial tested the hypothesis that the use of ESA would improve outcomes in patients with diabetes and CKD. 4038 patients with diabetes

and CKD on conservative treatment were enrolled to the study. 2012 patients were randomized to darbopoetin alfa treatment to achieve Hb- 13.0g/dl and 2026 to placebo arm. In placebo arm usage of darbopoetin alfa as a 'rescue therapy' was possible in patients with Hb level <9.0g/dl. The primary endpoints in this trial were: time to composite outcome of death from any cause or a CV event (MI, stroke, CHF, hospitalization for myocardial ischemia) and time to ESRD or death. Mean Hb concentration in darbopoetin-alfa arm was 12.5g/dl and in placebo arm it was 10.6g/dl. In this trial there were no statistically significant differences in death of any cause, occurrence of CV events (non fatal myocardial infarction (MI), unstable angina, heart failure, or stroke) and ESRD with dialysis requirements. In darbopoetin-alfa arm there was twofold increase in stroke risk and higher risk of death because of cancer in these patients in whom darbopoetin-alfa was started and there was cancer occurrence at the beginning of treatment with ESA. There was a reduction in the need for packed red blood cell transfusion with darbopoetin alfa, but a higher risk of venous and arterial thromboembolic events, as well as stroke, and a trend toward hypertension with the use of darbopoetin alfa. In placebo group, higher need for iron administration was observed. The authors of TREAT Trial concluded that there is no need for the routine use of ESAs in patients with diabetes and CKD on conservative treatment, and in each of patients commencement of ESA treatment requires awareness of benefits and risks of such decision.

The range of Hb value during anemia treatment is still matter of debate. In the end of 2010 Food and Drug Administration suggested Hb range between 10-12g/dl, NFK-DOQI recommendations from 2007 suggested range between 11-12g/dl. It seems sensible not to exceed the value of 12.0g/dl during the correction or maintain phase of treatment. In spite of a great controversy in anemia treatment with usage of ESAs, such therapy is still valuable for CKD patients but should be individualized and safe in each case [17].

Iron deficiency plays an important role in pathogenesis of renal anemia, (it is the most common cause of hyporesponsiveness to ESAs) and iron status needs monitoring during ESAs administration. Iron plays crucial role not only in erythropoiesis. Free iron activation may cause induction of inflammation, oxidative stress, and kidney damage especially when correction is made by intravenous iron administration.

Iron absorption, transport and storage is regulated by specific protein such as transferrin and ferritin. Annual iron loss in hemodialysis patients is approximately 2.0g. Iron deficiency can be easily corrected by intravenous iron administration, which is more effective than oral iron supplementation because of inadequate iron absorption. Correction of iron deficiency may cause rise in hemoglobin level in most patients. There is strong suggestion that high dose of intravenous iron supplementation may accelerate cardiovascular damage and increased risk of bacterial infection. Several recent clinical studies have shown the opposite effects as long as intravenous iron was adequately dosed [18]. According to KDOQI guidelines, ferritin level in hemodialysis patients should be greater than 200mg/dl, but level greater than 500mg/dl is an indication to iron supplementation withdrawal [3]. In the DRIVE study intravenous administration of ferric gluconate was highly efficacious in anemic hemodialysis patients with high serum ferritin level (>800mg/dl) and low transferrin saturation. 12 weeks of ferric gluconate supplementation in patients with ferritin level between 500-1200mg/dl showed significant hemoglobin increase and diminish of ESAs dosage. But limitation of this study was: short time of observation and lack of information about the iron overdosing risk. [19]. In conclusion, we should always be aware of ESAs overdosing/toxicity, iron overdosing and toxicity during anemia treatment. Such awareness facilitates the application of the best management strategy in both ESAs and iron dose titration in correction and maintenance therapy [20]. Commencement of ESAs treatment without iron status correction is appropriate.

In American population based study, Ht range between 33-36% was related with lowest all caused, cardiovascular mortality and hospitalization rate due to infection in compare to Ht range between 30-33% [21]. In Normal Hematocrit Study – prospective study comparing outcomes in 1233 hemodialysis patients with congestive heart failure or ischemic heart disease receiving treatment with epoetin alfa who were randomly assigned to the normal-hematocrit group, and to the low-hematocrit group - attainment hematocrit level of 42% was related with 7% higher incidence of death in compare to low –hematocrit group. In high hematocrite group incidence of vascular-access thrombosis was significantly higher than in the low-hematocrit group. There was no statistically significant differences in non fatal myocardial infarction, stroke or

hospitalization rate between two groups [22]. The authors of the study concluded that detrimental outcomes were associated with a normal hematocrit level and the target hematocrit value of 42% cannot be recommended in patients with cardiac disease who are undergoing hemodialysis. The results of this study were in accordance with further outcomes of the CHOIR study and the CREATE study.

Safety Hb value during ESAs treatment in CKD patients on conservative treatment and these on renal replacement therapy is still matter of debate. According to NFK-DOQI guidelines from 2007 it was ascertain that Hb level should be greater than 11.0g/dl but less than 13.0g/dl because harm related with higher Hb level may be greater than benefits of such therapy in spite of quality of life improvement and avoidance of blood transfusion [13]. According to EBPG recommendations in individuals with diabetes or cardiovascular complications Hb level should be less than 12.0g/dl. Hb values above 14,0g/dl are not recommended. In each patient ESAs therapy should be individualized and concomitant diseases should be taken into consideration. In European guidelines, Hb value greater than 14.0g/dl is detrimental and such values may cause life threatening complications. As it was mentioned before the optimal Hb range is between 10g/dl to 12.0g/dl. Deleterious effects of ESAs treatment may be rather related with EPO overdosing/toxicity than high Hb level itself. [23].

## CONCLUSIONS

1. High cardiovascular events rate in renal anemia patients may be rather related with oxidative stress and inflammation than anemia itself.
2. Complications of ESAs therapy and iron supplementation during renal anemia treatment may be related with ESAs/iron overload and toxicity.
3. Safety Hb range during ESAs treatment is estimated between 10g/dl to 12g/dl. Hb>12.0g/dl may be dangerous for CKD patients and higher cardiovascular events may be observed.

## REFERENCES

1. Jurkovitz CT, Abramson JL, Vaccarino LV et al.: "Association of high serum creatinine and anemia increases the risk of coronary events: results from the prospective community-based atherosclerosis risk in communities (ARIC) study." *J Am Soc Nephrol* 2003; 14:2919-2925
2. Pisoni RL, Bragg-Gresham JL, Young EW et al.: "Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS)". *Am J Kidney Dis* 2004;44:94-111
3. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia In Chronic Kidney Disease. *Am J Kidney Dis* 2006; 47:S11-145
4. Samouilidou EC, Grapsa EJ, Kakavas I et al.: "Oxidative stress markers and C-reactive protein in end-stage renal failure patients on dialysis". *Int. Urol. Nephrol.*, 2007; 39: 1323-1324
5. Dirican M, Sarandol E, Serdar Z et al.: "Oxidative status and prevalent cardiovascular disease in patients with chronic renal failure treated by hemodialysis". *Clin Nephrol.* 2007;68:144-150
6. Kuusniemi AM, Lapatto R, Holmberg C et al.: "Kidneys with heavy proteinuria show fibrosis, inflammation, and oxidative stress, but no tubular phenotypic change". *Kidney Int.*, 2005, 68, 121-132
7. Marathias KP, Agroyannis B, Mavromoustakos T et al.: "Hematocrit-lowering effect following inactivation of renin-angiotensin system with angiotensin converting enzyme inhibitors and angiotensin receptor blockers". *Curr Top Med. Chem* 2004;4:483-486
8. Slagman C.J. Martje, Sinkeler Steef J. et al.: Erythropoetin is reduced by combination of diuretic therapy and RAAS blockade in proteinuric renal patients with preserved renal function. *Nephrol Dial Transplant* 2010; 25: 3256-3260
9. Macdougall IC. : Iron supplementation in the non-dialysis chronic kidney disease (ND-CKD) patient: oral or intravenous? *Curr. Med. Res. Opin.* 2010 Feb;26(2):473-82
10. Levin A: "Anemia and left ventricular hypertrophy In chronic kidney disease populations: A review of the current state of knowledge". *Kidney Int. Suppl.* 2002; 80:35-38
11. Drueke TB, Locatelli F, Clyne N et al.: "Normalization of hemoglobin level in patients with chronic Sidney disease and anemia". *N. Engl. J. Med.* 2006; 355:2071-2084
12. Singh A., Szczech L, Tang KL et al.: "Correction of anemia with epoetin alfa in chronic kidney disease". *N. Engl. J. Med.* 2006;355:2085-2098
13. KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease, 2007 update of hemoglobin target. *Am J. Kidney Dis* 2007; 50:471-530
14. Takahashi K, Totsune K, Imai Y et al.: "Plasma concentrations of immunoreactive-endothelin in patients with chronic renal failure treated with recombinant human erythropoietin" *Clin Sci* 1993;84:47-50
15. Bittorf T, Büchse T, Sasse T et al.: "Activation of the transcription factor NF-kappa B by the erythropoietin receptor: structural requirements and biological significance". *Cell Signal* 2001;13:673-681

16. Pfeffer MA, Pfeffer MA, Burdmann EA et al.: "A trial of darbopoetin alfa in type 2 diabetes and chronic kidney disease". *N Eng J Med* 2009; 361: 2019-2032.
17. Więcek A: "To TREAT or not to TREAT-that is the question" *Nat Rev Nephrol.* 2010;6:254-255
18. Agarwal R, Vasavada N, Sachs NG et al.: "Oxidative stress and renal injury with intravenous iron in patients with chronic kidney disease" *Kidney Int.* 2004; 65:2279-2289
19. Kapoian T, O'Mara NB, Singh AK et al.: "Ferric gluconate reduces epoetin requirements in hemodialysis patients with elevated ferritin." *J Am. Soc. Nephrol.* 2008; 19: 372-379
20. Silverberg DS.: The role of erythropoiesis stimulating agents and intravenous (IV) iron in the cardio renal anemia syndrome *Heart Fail Rev.* 2011 Nov;16(6):609-14.
21. Xia H, Ebben J, Ma JZ et al. : "Hematocrit levels and hospitalization risks in hemodialysis patients." *J Am Soc Nephrol.* 1999;10:1309-1316
22. Besarab A, Bolton WK, Browne JK et al.: "The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med.* 1998;339:584-590
23. Vaziri D, Xin J. Zhou: "Potential mechanisms of adverse outcomes in trials of anemia correction with erythropoietin in chronic kidney disease". *Nephrol Dial Transplant* 2009; 24:1082-1088

Address for correspondence:

dr med. Dorota Śmigiel-Staszak  
Department of Nephrology, Hypertension  
and Internal Medicine  
University Hospital No. 1 in Bydgoszcz  
ul. Skłodowskiej-Curie 9, 85-094 Bydgoszcz  
tel./fax 52 5854030  
e-mail: nerka@nerka.cpro.pl

Received: 8.05.2011

Accepted for publication: 4.12.2012