
Management of Anemia on Hemodialysis

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<http://dx.doi.org/10.5772/52399>

1. Introduction

The definition of anemia is controversial. The WHO defines anemia as hemoglobin (Hb) <13 g/dL for men and <12 g/dL for women [1]. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative, which is the criteria used for Medicare reimbursement, defines anemia in adult men and postmenopausal women as Hb <12 g/dL, or <11 g/dL in a premenopausal woman [2]. Anemia represents a significant problem to deal with in patients with chronic kidney disease (CKD) on hemodialysis (HD). Renal anemia is typically an isolated normochromic, normocytic anemia with no leukopenia or thrombocytopenia [3]. This is a frequent complication and contributes considerably to reduced quality of life (QoL) [4-6] of patients with CKD. It has also been associated with a number of adverse clinical outcomes, increased morbidity and mortality [5, 7-13]. In general, there is a progressive increase in the incidence and severity of anemia with declining renal function. The reported prevalence of anemia by CKD stage varies significantly and depends, to a large extent, on the definition of anemia and whether study participants selected from the general population, are at a high risk for CKD. Data from the National Health and Nutrition Examination Survey (NHANES) showed that the distribution of Hb levels starts to fall at an estimated glomerular filtration rate (eGFR) of less than 75 ml/min per 1.73 m² in men and 45 ml/min per 1.73 m² in women [14]. Among patients under regular care and known to have CKD, the prevalence of anemia was found to be much greater, with mean Hb levels of 12.8 ± 1.5 g/dl (CKD stages 1 and 2), 12.4 ± 1.6 g/dl (CKD stage 3), 12.0 ± 1.6 g/dl (CKD stage 4), and 10.9 ± 1.6 g/dl (CKD stage 5) [15]. Although renal anemia is independent of the etiology of kidney disease, there are two important exceptions. Renal anemia in diabetic patients develops more frequently, at earlier stages of CKD, and more severely at a given level of renal impairment [16-18]. In patients with polycystic kidney disease, Hb is higher than in other patients with similar degrees of renal failure, and polycythemia may occasionally develop [19]. Many patients not yet on dialysis still receive no specific treatment for their anemia. In contrast, in

patients on dialysis,, average Hb values have steadily increased during the past 15 years, following the advent of erythropoietin (EPO) and the development of clinical practice guidelines for anemia management [16, 17]. Anemia contributes to significant healthcare costs associated with CKD [20]. The average Hb value, however, varies considerably between countries, reflecting variability in practice patterns [21]. Before the availability of recombinant human erythropoietin (rhuEPO, or epoetin), patients on dialysis frequently required blood transfusions, exposing them to the risks of iron overload, transmission of viral hepatitis, and sensitization, which reduced the chances of successful transplantation. Anemia in CKD patients except from the lack of EPO [22, 23], is a multifactor process. Shorter lifespan of red blood cells, iron and vitamin deficiency due to dietary restrictions, and rarely bleeding that accompanies uremia seem to be other important factors [24, 25]. Adequate dialysis can contribute to anemia correction through many mechanisms, including the removal of molecules that may inhibit erythropoiesis using high-flux dialyzers [26-30]. It also seems that residual renal function is important in dialysis patients and its decline also contributes significantly to anemia, inflammation, and malnutrition in patients on dialysis [31, 32]. It is also affected by the underlying disease, co morbid conditions, malignancy, infection, heart failure, as mentioned above, the environment and several other factors (therapeutic treatment with angiotensin-converting enzyme(ACE) inhibitors, [33-37] increased PTH, [38-43] osteodystrophy [44, 45]) that differ among patients. Thus, anemia management in these patients needs an individualized approach. Each patient should be treated according to an Hb target with the lowest effective Erythropoiesis Stimulating Agents (ESA) dose, while avoiding large fluctuations in Hb levels or prolonged periods outside the target. This strategy may necessitate changes to the ESA dose, dosing frequency and iron supplementation over the course of a patient's treatment, and proactive management of conditions that can affect ESA responsiveness. While all ESAs effectively increase Hb levels, differences with respect to route of administration, pharmacokinetics, and dosing frequency and efficiency should be considered to maximize the benefits of ESA treatment for the individual patient [46]. Substitution of the subcutaneous route of administration for the intravenous route for epoetin-alfa can reduce drug acquisition and costs, the two largest components of healthcare costs in CKD patients [20]. Hence, treating anemia in CKD patients on HD seems to be very complex and has to be managed step by step correcting all the factors that affect this process.

2. Diagnostic approach of anemia in hemodialysis patients

The diagnosis of anemia and the assessment of its severity are best made by measuring the Hb concentration rather than the hematocrit. Hb is a stable analyte measured directly in a standardized fashion, whereas the hematocrit is relatively unstable, indirectly derived by automatic analyzers, and lacking of standardization. Within-run and between-run coefficients of variation in automated analyzer measurements of Hb are one half and one third those for hematocrit, respectively [16]. There is considerable variability in the Hb threshold used to define anemia in CKD patients. According to the definition in the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, anemia should be diag-

nosed at Hb concentrations of less than 13.5 g/dl in adult men and less than 12.0 g/dl in adult women [16]. These values represent the mean Hb concentration of the lowest 5th percentile of the sex-specific general adult population. In children, age-dependent differences in the normal values have to be taken into account. Normal Hb values are increased in high-altitude residents [16]. The end of the short interdialytic period is the most appropriate timing for anemia assessment [47]. Although renal anemia is typically normochromic and normocytic, [48, 49] deficiency of vitamin B12 or folic acid may lead to macrocytosis, whereas iron deficiency or inherited disorders of Hb formation (such as thalassemia) may produce microcytosis. Macrocytosis with leucopenia or thrombocytopenia suggests a generalized disorder of hematopoiesis caused by toxins, nutritional deficit, or myelodysplasia. Hypochromia probably reflects iron-deficient erythropoiesis. An absolute reticulocyte count, which normally ranges between 40,000 and 50,000 cells/ μ l of blood, is a useful marker of erythropoietic activity. Iron status tests should be performed to assess the level of iron in tissue stores or the adequacy of iron supply for erythropoiesis. Although serum ferritin is so far the only available marker of storage iron, several tests reflect the adequacy of iron for erythropoiesis, including transferrin saturation, MCV, and MCHC; the percentage of hypochromic red blood cells (PHRC); and the content of Hb in reticulocytes (CHr) [50]. Storage time of the blood sample may elevate PHRC, MCV and MCHC are below the normal range only after long-standing iron deficiency. It is important to identify anemia in CKD patients because it may signify nutritional deficits, systemic illness, or other conditions that warrant attention, and even at modest degrees, anemia reflects an independent risk factor for hospitalization, cardiovascular disease, and mortality [16, 51]. Drug therapy such as ACE inhibitors may reduce Hb levels by: firstly, direct effects of angiotensin II on erythroid progenitor cells, [52] secondly, accumulation of N-acetyl-seryl-lysyl-proline (Ac-SDKP), an endogenous inhibitor of erythropoiesis, [53] and thirdly, reduction of endogenous EPO production, potentially due to the hemodynamic effects of angiotensin II inhibition [54]. Myelosuppressive effects of immunosuppressants may further contribute to anemia [55]. The measurement of serum EPO concentrations is usually not helpful in the diagnosis of renal anemia because there is relative rather than absolute deficiency, with a wide range of EPO concentrations for a given Hb concentration that extends far beyond the normal range of EPO levels on healthy, non-anemic individuals. Abnormalities of other laboratory parameters should be investigated, such as a low MCV or MCHC (may indicate an underlying hemoglobinopathy), a high MCV (may indicate vitamin B12 or folic acid deficiency), or an abnormal leukocyte or platelet count (may suggest a primary bone marrow problem, such as myeloma or myelodysplastic syndrome).

3. Clinical manifestations

Due to the fact that anemia reduces tissue oxygenation, it is associated with widespread organ dysfunction and hence an extremely varied clinical picture. In mild anemia there may be no symptoms or simply increased fatigue and a slight pallor. As anemia becomes more marked the symptoms and signs gradually appear. Pallor is best discerned in the mucous

membranes; the nailbeds and palmar creases, although often said to be useful sites for detecting anemia, are relatively insensitive for this purpose. Cardiorespiratory symptoms and signs include dyspnea, tachycardia, palpitations, angina or claudication, night cramps, increased arterial pulsation, capillary pulsation, a variety of cardiac bruits, reversible cardiac enlargement. Neuromuscular involvement is reflected by headache, vertigo, light-headedness, faintness, tinnitus, roaring in the ears, cramps, increased cold sensitivity. Acute anemia may occasionally give rise to papilledema. Gastrointestinal symptoms include loss of appetite, nausea, constipation, and diarrhea. Genitourinary involvement causes menstrual irregularities, urinary frequency, and loss of libido. There may also be a low-grade fever. In the elderly, to whom associated degenerative arterial disease is common, anemia may be manifested with the onset of cardiac failure. Alternatively, previously undiagnosed coronary narrowing may be unmasked by the onset of angina [56].

In the early clinical trials of EPO performed in the late 1980s, the mean baseline Hb concentration was about 6 to 7 g/dl, and this progressively increased to about 11 or 12g/dl after treatment. Patients subjectively felt much better, with reduced fatigue, increased energy levels, and enhanced physical capacity, and there were also objective improvements in cardiorespiratory function [57]. Thus, it is now clear that many of the symptoms previously attributed to the “uremic syndrome” are indeed due to the anemia associated with CKD. Although the avoidance of blood transfusions and improvement in quality of life are obvious early changes, there are also possible effects on the cardiovascular system. The physiologic consequences of long-standing anemia are an increase in cardiac output and a reduction in peripheral vascular resistance. Anemia is a risk factor for the development of left ventricular hypertrophy in CKD patients and exacerbate left ventricular dilation. Sustained correction of anemia in CKD patients results in a reversal of most of these cardiovascular abnormalities, with the notable exception of left ventricular dilation. Once the left ventricle is stretched beyond the limits of its elasticity, correction of anemia cannot reverse this [58]. It may, however, prevent the development of LV dilation, and this leads to improved quality of life [59]. Anemia correction may improve QoL, [60, 61] cognitive function, sleep patterns, nutrition, sexual function, menstrual regularity, immune responsiveness, and platelet function [62-66].

4. Therapeutic approach

As mentioned above, renal anemia is a multifactor process and its treatment has to focus on a step by step correction of all factors which are involved in this process [67]. First of all, iron deficiency has to be treated before adding more expensive therapies such as EPO therapy.

4.1. Iron deficiency

Iron is an essential ingredient for heme synthesis, and adequate amounts of this mineral are required for the manufacture of new red cells. Thus, under enhanced erythropoietic stimulation, greater amounts of iron are used, and many CKD patients have inadequate amounts of available iron to satisfy the increased demands of the bone marrow [68]. Patients with CKD,

on HD treatments, may lose up to 3gr of iron each year because of frequent blood losses, so they are at particularly high risk of iron store depletion with subsequent iron deficiency anemia [17]. Even before the introduction of ESA therapy, many CKD patients were in negative iron balance as a result of poor dietary intake, poor appetite, and increased iron losses due to occult and overt blood losses. Losses on HD patients are up to 5 or 6 mg a day, compared with 1 mg on healthy individuals, and this may exceed the absorption capacity of the gastrointestinal tract, particularly when there is any underlying inflammation. Iron deficiency can be defined as absolute or functional [17, 68, 69]. Absolute iron deficiency develops as the body's iron stores become depleted to such a low level that not enough iron is available for the production of Hb [70, 71]. This is usually indicated by a decline in serum ferritin levels to $<15 \mu\text{g/l}$ in patients with normal kidney function, [70, 71] or $<12 \text{ ng/mL}$ [72] according to other studies and TSAT levels below 16% [73]. Absolute iron deficiency in CKD patients has been defined as serum ferritin levels $<100 \text{ ng/mL}$ and TSAT levels $<20\%$. The functional iron deficiency describes the state when iron cannot be mobilized from stores (despite an adequate dietary supply) to meet the demand for erythropoiesis [70]. Serum ferritin levels can appear normal ($200\text{--}500 \mu\text{g/l}$) or increased in chronic inflammatory disorders, [70] while levels of transferrin saturation (TSAT), which is serum iron divided by total iron-binding capacity, [68] will be low (typically $<20\%$), indicating limited transport of iron to the erythron for erythropoiesis [70, 74, 75] and increased hypochromic red cells ($>10\%$). The distinction between absolute and functional iron deficiency is crucial to understanding what constitutes adequate TSAT and serum ferritin levels on Epoetin-treated patients. The iron deficit limits the effectiveness of EPO therapy, and, to optimize the treatment, patients must receive an oral or intravenous (IV) iron supplement [76-78]. Thus, higher doses of ESAs may worsen iron depletion and lead to an increased platelet count (thrombocytosis), ESA hyporesponsiveness, and hemoglobin variability. Hence, ESA therapy requires concurrent iron supplementation [17, 79]. On the other hand, serum ferritin $<200 \text{ ng/mL}$ suggests iron deficiency in CKD patients, ferritin levels between 200 and $1,200 \text{ ng/mL}$ may be related to inflammation, latent infections, malignancies, or liver disease. In part, this is due to the fact that, in addition to reflecting body iron stores, serum ferritin is also an acute phase reactant. As such, it can increase in the setting of either acute or chronic inflammation. Available data demonstrate that the lower the TSAT and the serum ferritin, the higher the likelihood that a patient is iron deficient, and the higher the TSAT and the serum ferritin, the lower the likelihood that a patient is iron deficient [77, 80]. A serum ferritin concentration of $100\text{--}500 \text{ ng/mL}$ is the target during oral and intravenous (i.v.) iron therapy for pre-dialysis and peritoneal dialysis patients, but use of the i.v. route of administration and a target serum ferritin concentration of $200\text{--}500 \text{ ng/mL}$ is recommended for HD patients by NKF [81]. Due to the fact that parenteral iron administration has potential risks that are immediate (eg, toxic effects and anaphylactic reactions) and long-term (e.g., decreased polymorphonuclear leukocyte function, increased risk of infections, organ damage), it is essential to select patients who need iron supplementation. Although oral iron administration is the primary treatment for iron deficiency, it has also disadvantages, such as poor iron absorption and adverse gastrointestinal reactions, which often lead to poor compliance. Oral iron is ineffective in many CKD patients, and parenteral iron administration is required, particularly on those receiving hemo-

dialysis [68]. Nevertheless, even with these limitations of oral iron absorption, the cheap costs of using this route, along with convenience for the patient, often persuade physicians to try oral iron supplementation first on non-dialysis patients; if, however, there is insufficient response after 2 to 3 months, intravenous iron should be administered. However, the use of IV iron reduces the risk of adverse gastrointestinal reactions and overcomes the problem of poor compliance with oral therapy [82, 83]. Another advantage of the i.v. route is that the iron will not be eliminated by first-pass effects or by high efficiency dialysis membranes and the iron can be quickly released into the reticuloendothelial system and used for erythropoiesis, thus increasing its bioavailability. Intravenous iron administration may not only decrease hemoglobin variability and ESA hyporesponsiveness, it may also reduce the greater mortality associated with the much higher ESA doses that have been used in some patients when targeting higher hemoglobin levels [84]. Other, longer term concerns about intravenous administration of iron include the potential for increased susceptibility to infections and oxidative stress. Much of the scientific evidence for this has been generated in *in vitro* experiments, the clinical significance of which is unclear. There is emerging evidence that intravenous iron may improve the anemia of CKD in up to 30% of patients not receiving ESA therapy and have a low ferritin level [85]. Abnormalities of iron metabolism and anemia in chronic renal failure seem to correlate with levels of serum Heparin [86]. Heparin is a recently discovered protein of expeditious action produced in the liver and that may play an important role in iron homeostasis [87-89]. Heparin limits the absorption of iron from the intestine and iron release from macrophages and hepatocytes [90]. Iron absorption capacity in patients with CKD is considerably lower than in non-uremic individuals, particularly in the presence of systemic inflammatory activity, and this is probably mediated by Heparin up-regulation [91, 92]. The data in CKD and particularly in ESRD is limited both in hemodialysis and in peritoneal dialysis [93]. Because of its excretion in the urine [94, 95] and regulation by the presence or absence of inflammation, it is likely that its metabolism is affected by renal function and consistently influences the absorption of iron from the intestine and the stores of iron [96-99]. Originally due to the inability to measure serum levels of Heparin, its role in chronic kidney disease had not been adequately studied and most studies involved heparin's levels in urine. It has been attempted to measure proheparin a precursor peptide of Heparin in CKD patients [100, 101]. According to our recently unpublished data Heparin levels were increased in hemodialysis patients in relation to normal individuals. The U.S. [16] and European [17] guidelines on renal anemia management suggest that the ferritin level be maintained in the range of 200 to 500 $\mu\text{g/l}$, with an upper limit of 800 $\mu\text{g/l}$. Levels of ferritin above this threshold usually do not confer any clinical advantage and may exacerbate iron toxicity. The optimal transferrin saturation is above 20% to 30% to ensure a readily available supply of iron to the bone marrow. Several studies support the maintenance of the percentage of hypochromic red cells at levels of less than 6%. Other measures of iron status, such as serum transferrin receptor levels [102] and erythrocyte zinc protoporphyrin levels, are mainly research tools and have not been established in routine clinical practice. Intramuscular administration of iron is not recommended in CKD, given the enhanced bleeding tendency, the pain of the injection, and the potential for brownish discoloration of the skin. Thus, intravenous administration of iron has become the

standard of care for many CKD patients, particularly those receiving hemodialysis [17, 68, 69, 103]. An important advantage of i.v. iron over oral iron is that it may bypass hepcidin actions by directly loading transferrin and making iron available to macrophages. Despite a reduction in the short-term risks, there is still concern about the potential for long-term toxicity of i.v. iron use (e. g. atherosclerosis development, infection and increased mortality) [104, 105]. The association of atherosclerosis with iron overload remains unclear. Alternatively, the relative risk for mortality or hospitalization from infection in patients undergoing HD and receiving i.v. iron was shown not to be higher than that observed in the overall HD population. Indeed, doses of i.v. iron up to 400 mg/month were associated with improved patient survival. There are several intravenous iron preparations available worldwide, including iron dextran, iron sucrose, and iron gluconate and Ferric carboxymaltose (table 1).

AVAILABLE IRON PREPARATIONS	IV MAXIMUM DOSE	ADMINISTRATION	TEST DOSE
Dextran Iron*	1000mg	0.0442 (Desired Hb - Observed Hb) x LBW + (0.26 x Lean body weight in kg) (For males: LBW = 50 kg + 2.3 kg for each inch of patient's height over 5 feet; for females: LBW = 45.5 kg + 2.3 kg for each inch of patient's height over 5 feet.)	A test dose of 25 mg diluted in 50 ml normal saline and infused over 5 minutes should be given. Infusion should then be stopped for 1 hour. If there is no reaction after 1 hour continue.
Gluconate Iron*	125mg	The recommended dosage of Sodium Ferric Gluconate for the repletion treatment of iron deficiency in hemodialysis patients is 10 mL of Ferrlecit (125 mg of elemental iron). Ferrlecit may be diluted in 100 mL of 0.9% sodium chloride administered by intravenous infusion over 1 hour per dialysis session	No test
Iron Sucrose*	500mg	Administer Venofer 100 mg undiluted as a slow injection over 2 to 5 minutes, or as an infusion of 100 mg diluted in a maximum of 100 mL of 0.9% NaCl over a period of at least 15 minutes, per consecutive session. Venofer should be administered early during the dialysis session.	No test dose

AVAILABLE IRON PREPARATIONS	IV MAXIMUM DOSE	ADMINISTRATION	TEST DOSE
Ferric Carboxymaltose**	A cumulative dose of 500 mg should not be exceeded for patients with body weight < 35 kg. A single dose of Ferinject should not exceed 1000 mg of iron (20 ml) per day. Do not administer 1000 mg of iron (20 ml) more than once a week.	1000 mg of iron during a minimum administration time of ≤ 15 minutes.	No test dose

Table 1. Available i.v. iron preparations. *: www.globalrph.com - **: www.medicines.org.uk

All of these preparations contain elemental iron surrounded by a carbohydrate shell, which allows them to be injected intravenously. The liability of iron release from these preparations varies, with iron dextran being the most stable, followed by iron sucrose and then iron gluconate. Iron is released from these compounds to plasma transferrin and other iron-binding proteins and is eventually taken up by the reticulo-endothelial system. In hemodialysis patients, it is easy and practical to give low doses of intravenous iron (e.g., 10 to 20 mg every dialysis session) or, alternatively, 100 mg weekly. The more stable the iron preparation, the larger the dose administration rate that can be used. For example, 1 gr of iron dextran may be given by intravenous infusion, whereas the maximum recommended dose of iron sucrose at any one time is 500 mg. For iron gluconate, doses in excess of 125 to 250 mg are best avoided. A 100 mg dose of iron sucrose is administered at 10 consecutive HD sessions. If after the end of the first 10-dose cycle patients remain iron deficient they complete another 10-dose cycle. If TSAT is 20-50% and SF 100-800 ng/mL, the patients start the maintenance regimen. If TSAT > 50% or SF > 800 ng/mL then no further iron supplementation was deemed necessary. Iron replete patients received the iron maintenance regimen, consisting of 10 one weekly doses of up to 100 mg iron sucrose over 5 minutes. Iron repletion is defined as TSAT

20-50% and SF 100-800 ng/mL [106, 107]. Iron sucrose appears to offer the most favorable safety profile when compared to iron dextran and sodium ferric gluconate in treating hemodialysis patients. Oxidative stress and hypersensitivity reactions are common problems encountered when administering intravenous iron [108]. Therapy with dextran-free iron formulations is an essential part of anemia treatment protocols, and was not found to be associated with either short- or long-term serious side-effects [109]. Results suggest that 200 mg/FeIV/month is effective and that, of the markers tested, TSAT would be the most suitable one to the practicing nephrologist so as to optimize intravenous iron in the long run [110]. Sodium ferric gluconate is well tolerated when given by intravenous push without a test dose [111]. SFGC has a significantly lower incidence of drug intolerance and life-threatening events as compared to previous studies using iron dextran. The routine use of iron dextran in hemodialysis patients should be discontinued [112]. Nevertheless, older i.v. iron formulations have their limitations, including the potential for immunogenic reactions induced by dextran molecules (iron dextran) [113], dose limitations, a slow rate of administration (to prevent acute, labile iron-induced toxicity and vasoactive reactions) [70, 113] and the compulsory requirement for a test dose (iron dextrans in USA [114] and Europe. All-event reporting rates were 29.2, 10.5 and 4.2 reports per million 100 mg iron dose equivalents, while all-fatal-event reporting rates were 1.4, 0.6 and 0.0 reports per million 100 mg dose equivalents for iron dextran, sodium ferric gluconate and iron sucrose, respectively [115]. Recently, two new iron preparations have become available for intravenous use (ferumoxytol in the United States and ferric carboxymaltose in Europe) [116]. Both of these compounds allow higher doses of intravenous iron to be administered rapidly as a bolus injection, without the need for a test dose. Ferric carboxymaltose [FCM; FerinjectR; Vifor (International) Inc., St Gallen, Switzerland] is a next-generation parenteral, dextran-free iron formulation designed to overcome the limitations of existing i.v. iron preparations. The FCM is a macromolecular ferric hydroxide carbohydrate complex, composed of a poly-nuclear iron(III) hydroxide complexed to carboxymaltose [117]. As FCM is a strong and robust iron complex, and it can be administered in high doses, it does not release large amounts of reactive ('free') iron into the circulation and does not trigger dextran-associated immunogenic reactions [111, 117-119]. All intravenous iron preparations carry a risk for immediate reactions, which may be characterized by hypotension, dizziness, and nausea. These reactions are usually short-lived and caused by too large a dose given during too short a time. Iron dextran also carries the risk for acute anaphylactic reactions due to preformed dextran antibodies, and although this risk may be less with the lower molecular weight iron dextrans, the potential for anaphylaxis still remains. In such patients, a response to intravenous iron alone may occur within 2 to 3 weeks of iron administration. In those already receiving ESAs, there is considerable evidence that concomitant intravenous iron may enhance the response to the ESAs and result in lower dose requirements [17, 21, 68]. Ferric carboxymaltose also replenishes depleted iron stores and improves health-related quality-of-life (HR-QoL) on patients with iron-deficiency anemia. FCM is at least as effective as iron sucrose and as ferrus sulfate with regards to end point relative to serum ferritin, transferrin saturation and HR-QoL. Commonly reported drug-related adverse events include headache, dizziness, nausea, abdominal pain, constipation, diarrhea, rash and injection-site reactions. The incidence of drug-

related adverse events on patients receiving intravenous FCM was generally similar to that in patients receiving oral ferrous sulfate. In general, rash and local injection-site reactions were more common with ferric carboxymaltose, whereas gastrointestinal adverse events were more frequent with ferrous sulfate [120]. Based on the No-Observed-Adverse-Effect-Levels (NOAELs) found in repeated-dose toxicity studies and on the cumulative doses administered, FCM has good safety margins. Lastly, no evidence of irritation was found in local tolerance studies with FCM [70]. Ferric carboxymaltose may represent a cost-saving option compared with the most likely alternative existing therapies used for the management of anemia [121, 122].

4.2. Correction of vitamin B and Acid Folic

Vitamin abnormalities in patients with CKD are frequent and appear early even with mild renal failure; fat-soluble vitamin supplements (A and E) should be avoided and their dietary intake limited [123]. Deficiency and/or altered metabolism of vitamins in ESRD is caused by uremic toxins, dietary restrictions, catabolic illness, losses during dialysis and drug interaction. In patients with polyneuropathy high doses of thiamine pyrophosphate (Coccarboxylase), given i.v., can be helpful in this respect. There are conflicting reports concerning plasma level of vitamin B2 (riboflavin) in ESRD patients. Some authors recommend its supplementation. The majority of patients with ESRD exhibit biochemical and clinical signs of vitamin B6 deficiency. A univocal opinion exists that supplementation of this vitamin effects the cellular immune system and the amino acid metabolism as well. An adequate dose of vitamin B6 is still a matter of dispute. Evidence of vitamin B12 deficiency has been reported rarely, thus, only few authors recommend the supplementation of it, mainly in CAPD patients. According to most authors the losses of folic acid and ascorbic acid during dialysis require oral supplementation. Despite the divergences in opinions concerning the deficiency of water-soluble vitamins in ESRD patients, the supplementation of these vitamins is practiced in many nephrological centers. The amount and the route of vitamins, administered to ESRD patients, should be individualized [124-126]. In ESRD patients under maintenance hemodialysis, oral L-carnitine supplementation may reduce triglyceride and cholesterol and increase HDL and hemoglobin and subsequently reduce needed erythropoietin dose without effect on QoL [127]. Adjuvant therapy includes: iron, vitamin C and D, L-carnitine, folic acid, cytokines and growth factors. Vitamin C (500 mg, after every hemodialysis) is very helpful in cases of functional iron deficiency. L-carnitine stabilizes the membrane of erythrocytes and prolongs their lives. Folic acid (10 mg/day) enhances response to EPO [128]. According to other authors supplementations of pyridoxine in the dose of 20 mg/day and of folic acid 5 mg/week in hemodialyzed patients during erythropoietin treatment are necessary [129].

4.3. Erythropoiesis Stimulating Agents

Erythropoiesis is a complex physiologic process through which homeostasis of oxygen levels in the body is maintained. It is primarily regulated by EPO, a 30-kD, 165-amino acid

hematopoietic growth factor that is produced primarily by renal tubular and interstitial cells. Under normal conditions, endogenous EPO levels change according to O₂ tension. EPO gene expression is induced by hypoxia-inducible transcription factors (HIF) [130]. In the presence of EPO, bone marrow erythroid precursor cells proliferate and differentiate into red blood cells. In its absence, these cells undergo apoptosis [131]. Endogenous EPO and rHuEPO share the same amino acid sequence, with slight but functionally important differences in the sugar profile. In clinical practice, rHuEPO is typically administered as a bolus injection, and the dosage is titrated to give the desired effect [131]. There is no significant difference between once weekly versus thrice weekly subcutaneous administration of rHu EPO. Once weekly administration of rHu EPO would require an additional 12U/kg/week for patients on hemodialysis [132].

Recombinant human erythropoietin has been used for more than 20 years for the treatment of renal anemia, revolutionizing its treatment in patients with CKD when it was approved for use in the United States in 1989, [133, 134] with epoetin-alfa and -beta representing the common traditional preparations. By the modification of the molecule's carbohydrate moiety or structure a longer duration of erythropoietin receptor stimulation was achieved. The administration of darbepoetin or C.E.R.A. once or twice a month is also sufficient to achieve serum hemoglobin target levels, [135] making the treatment safer and more comfortable both for the patients and the personnel. These synthetic erythropoietin receptor stimulating molecules, along with recombinant human erythropoietin, are together called "Erythropoiesis Stimulating Agents". The recombinant human erythropoietins and allied proteins (epoetin-alfa, attempted copies and biosimilar variants of epoetin-alfa, epoetin beta, epoetin delta, epoetin zeta, epoetin theta, epoetin omega, darbepoetin-alfa, and methoxy-polyethylene glycol-epoetin beta) are among the most successful and earliest examples of biotechnologically manufactured products to be used in clinical medicine (Table 2) [136].

AVAILABLE ESAs	DOSE REGIMEN
Prototype	
epoetin-alfa*	<p>Correction phase: 50 IU/kg, 3 times per week.</p> <p>When a dose adjustment is necessary, this should be done in steps of at least four weeks. At each step, the increase or reduction in dose should be of 25 IU/kg, 3 times per week.</p> <p>Maintenance phase: Dosage adjustment in order to maintain haemoglobin values at the desired level: Hb between 10 and 12 g/dl (6.2 - 7.5 mmol/l).</p> <p>The recommended total weekly dose is between 75 and 300 IU/kg.</p>
epoetin beta*	<p>1. Correction phase</p> <p>- Subcutaneous administration:</p> <p>- The initial dosage is 3 x 20 IU/kg body weight per week. The dosage may be increased every 4 weeks by 3 x 20 IU/kg and week if the increase of Hb is not adequate (< 0.25 g/dl per week).</p>

AVAILABLE ESAs	DOSE REGIMEN
	<p>- The weekly dose can also be divided into daily doses.</p> <p>- Intravenous administration:</p> <p>The initial dosage is 3 x 40 IU/kg per week. The dosage may be raised after 4 weeks to 80 IU/kg three times per week - and by further increments of 20 IU/kg if needed, three times per week, at monthly intervals.</p> <p>For both routes of administration, the maximum dose should not exceed 720 IU/kg per week.</p> <p>2. Maintenance phase</p> <p>To maintain an Hb of between 10 and 12 g/dl, the dosage is initially reduced to half of the previously administered amount. Subsequently, the dose is adjusted at intervals of one or two weeks individually for the patient (maintenance dose).</p>
darbepoetin-alfa*	<p>Correction phase:</p> <p>The initial dose by subcutaneous or intravenous administration is 0.45 µg/kg body weight, as a single injection once weekly.</p> <p>If the rise in haemoglobin is greater than 2 g/dl (1.25 mmol/l) in four weeks reduce the dose by approximately 25%. Dosing should be titrated as necessary to maintain the haemoglobin target.</p> <p>If a dose adjustment is required to maintain haemoglobin at the desired level, it is recommended that the dose is adjusted by approximately 25%</p>
Methoxy-polyethylene glycol-epoetin beta*	<p>a starting dose of 0.6 microgram/kg bodyweight may be administered once every two weeks as a single intravenous or subcutaneous injection in patients on dialysis or not on dialysis. The dose may be increased by approximately 25% of the previous dose if the rate of rise in haemoglobin is less than 1.0 g/dl (0.621 mmol/l) over a month. Further increases of approximately 25% may be made at monthly intervals until the individual target haemoglobin level is obtained.</p>
Biosimilar	
epoetin zeta*	<p>1. Correction phase:</p> <p>50 IU/kg 3 times per week. When a dose adjustment is necessary, this should be done in steps of at least four weeks. At each step, the increase or reduction in dose should be of 25 IU/kg 3 times per week.</p> <p>2. Maintenance phase:</p> <p>Dose adjustment in order to maintain haemoglobin (Hb) values at the desired level: Hb between 10 and 12 g/dl (6.2-7.5 mmol/l). The recommended total weekly dose is between 75 and 300 IU/kg.</p>
epoetin delta**	<p>For Epoetin delta it is recommended to adjust the dose individually to maintain the target haemoglobin in the range 10 to 12 g/dl. A starting dose is recommended of 50 IU/kg three times a week if given intravenously or twice a week if given subcutaneously</p>

AVAILABLE ESAs	DOSE REGIMEN
epoetin omega***	<p>Starting with 20 to 50 IU / kg three times a week, with a gradual increase in dose or frequency of issuance before the impact. Beyond hemoglobin levels to 12 g / m and Hematocrit-35 %. Dose reduction or no treatment. If there Effect dose increase to 40 to 55 IU / kg three times a week for two weeks, if necessary, until 60-75 IU / kg The course continues until the level Hematocrit (35 vol. %) And hemoglobin (12 g / m); Total weekly dose should not exceed 225 IU / kg supporting-60 IU / kg per week for 2-3 reception</p>
epoetin theta**	<p>Correction phase</p> <p>Subcutaneous administration: The initial posology is 20 IU/kg body weight 3 times per week. The dose may be increased after 4 weeks to 40 IU/kg, 3 times per week, if the increase in haemoglobin is not adequate (< 1 g/dl [0.62 mmol/l] within 4 weeks). Further increases of 25% of the previous dose may be made at monthly intervals until the individual target haemoglobin level is obtained.</p> <p>Intravenous administration: The initial posology is 40 IU/kg body weight 3 times per week. The dose may be increased after 4 weeks to 80 IU/kg, 3 times per week, and by further increases of 25% of the previous dose at monthly intervals, if needed.</p> <p>For both routes of administration, the maximum dose should not exceed 700 IU/kg body weight per week.</p> <p>Maintenance phase</p> <p>The dose should be adjusted as necessary to maintain the individual target haemoglobin level between 10 g/dl (6.21 mmol/l) to 12 g/dl (7.45 mmol/l), whereby a haemoglobin level of 12 g/dl (7.45 mmol/l) should not be exceeded. If a dose adjustment is required to maintain the desired haemoglobin level, it is recommended that the dose be adjusted by approximately 25%. Subcutaneous administration: The weekly dose can be given as one injection per week or three times per week.</p> <p>Intravenous administration: Patients who are stable on a three times weekly dosing regimen may be switched to twice-weekly administration. If the frequency of administration is changed, haemoglobin level should be monitored closely and dose adjustments may be necessary.</p> <p>The maximum dose should not exceed 700 IU/kg body weight per week</p>

Table 2. Available ESAs worldwide. *: [ww.medicines.org.uk](http://www.medicines.org.uk), **: www.ema.europa.eu, ***: www.pharmabook.net

In hemodialysed patients the intravenous route is preferred, but the subcutaneous administration can substantially reduce dose requirements [137-139]. However, there are studies according to which conversion from SC to IV epoetin administration did not result in changes in Hb levels or epoetin dosage requirements in iron-replete hemodialysis pa-

tients, [140] but it seems that SC route of administration was associated with modestly higher hemoglobin variability [138].

There are ongoing clinical trials with erythropoiesis stimulating molecules that can be administered by inhalation or per os [137]. It is also known from other studies that some comorbidities like antecedents of malignant neoplasm are associated with EPO responsiveness [141]. In a pre-dialysis population, female gender, cardiovascular disease, malnutrition and inflammation are associated with ESA hyporesponsiveness [142]. EPO resistance in a pediatric dialysis cohort was predicted by nutritional deficits, inflammation, poor dialysis, and hyperparathyroidism, while iron and folic acid deficits were the major determinants in adults. Although confounded by the pattern of EPO prescription, neither age nor gender was predictive of EPO resistance in the two study groups [143]. Additionally delivered dialysis ($Kt/V(\text{urea})$) does not seem to be a significant predictor of erythropoietin responsiveness [144]. It also seems that there is difference in EPO hyporesponsiveness prevalence among different countries and different modalities [145]. The proportion of age has a limited influence on the level of anemia in pre-dialysis patients and is similar in both genders [146]. There are, although, studies according to which there is higher proportion of anemia in female patients [147]. In a multicenter study with 8154 dialysis patients, females, blacks, patients between 18 and 44 years old on hemodialysis less than six months exhibited significantly lower mean hemoglobin values despite being prescribed, on average, significantly higher epoetin alfa doses than males, whites and older patients, on hemodialysis more than six months. A significant regional variation in the prescribing patterns for s.c. epoetin alfa and i.v. iron has been described in this study [148]. Comparisons between patients from western and from eastern/central Europe show that patients from eastern/central Europe are less likely to receive epoetin treatment before starting dialysis, and have lower Hb concentrations at the start of epoetin treatment as well as at the start of dialysis [149]. In another multicenter study by Nissenson et al. there were wide variations in hemoglobin response rate among patients on hemodialysis, hemofiltration and hemodiafiltration [150].

Other factors such as cytokines like IL6 are induced by malignant tumors and may impair erythropoiesis. Also, TNF- α is known to inhibit this pathway [151]. Low ESA responsiveness was associated with higher mortality in both HD and PD patients [152]. In patients with persistently low Hb levels, mortality risk is strongly associated with the patient's ability to achieve a hematopoietic response rather than the magnitude of EPO dose titrations [153]. ESA dosing may be directly associated with risk of death, but the nature of the association likely varies according to hemoglobin concentration. Small doses with hemoglobin ≤ 12 g/dl and large doses with hemoglobin ≥ 10 g/dl may both be associated with poor outcomes [154].

Serum albumin concentration is an important predictor of both baseline Hb and EPO sensitivity in chronic hemodialysis patients. Factors that improve serum albumin may also improve Hb in hemodialysis patients [155]. Hyperleptinemia reflects better nutritional status and rHuEPO response in long-term HD patients. Increasing energy intake improves erythropoiesis, which may be mediated in part by an increase in serum leptin levels [156, 157]. Statin therapy may improve responsiveness to erythropoietin-stimulating agents in patients with end-stage renal disease, increasing erythropoiesis by targeting hepcidin and iron regu-

latory pathways, independent of erythropoietin [158, 159]. The initial and sustained erythropoietic responses are independent from each other and are associated with different factors. Treatment focusing on these factors may improve the response [160]. A pleiotropic effect of EPO has been shown in the kidney, the central nervous system, and the cardiovascular system, [161] such as significant slowing of progression and substantial retardation of maintenance dialysis [162, 163].

Although ESA use in patients with chronic kidney disease or/and on dialysis were studied extensively, the optimal target hemoglobin concentration as well as the required ESA dose and dosing interval to achieve this concentrations remain elusive (NHS, CREATE, CHOIR and TREAT) [164-167]. Hb can be increased with erythropoiesis-stimulating proteins (ESPs); however, 5-10% of patients respond poorly. The patient incidence of hyporesponse seems to be around 14%, and a mean 9% of patients is hyporesponsive at any given time. The most common potential causes of hyporesponse is iron deficiency (being reported in 39% of hyporesponse events), medication (immunosuppressive agents, ACE inhibitors), secondary hyperparathyroidism [168] and inflammation/malnutrition [169]. The safety profile of epoetin-alfa and darbepoetin-alfa are similar, but the longer half-life of darbepoetin-alfa permits administration on a once a week or once-monthly basis in patients with CKD and anemia. Extended dosing of CERA also appears safe and effective on dialysis patients with CKD [81].

Epoetin alfa: is a recombinant form of erythropoietin, a glycoprotein hormone which stimulates red blood cell production by stimulating the activity of erythroid progenitor cells. Intravenous and subcutaneous therapy with epoetin alfa raises hematocrit and hemoglobin levels, and reduces transfusion requirements, in anemic patients with end-stage renal failure undergoing hemodialysis. The drug is also effective in the correction of anemia on patients with chronic renal failure not yet requiring dialysis and does not appear to affect renal hemodynamics adversely or to precipitate the onset of end-stage renal failure. Epoetin alfa does not appear to exert any direct cerebrovascular adverse effects [170]. Administration of epoetin alfa at once weekly and fortnightly intervals are potential alternatives to three times per week dosing for the treatment of anemia [171-173].

Epoetin beta: is a recombinant form of erythropoietin. The drug binds to and activates receptors on erythroid progenitor cells which then develop into mature erythrocytes. Epoetin beta increases reticulocyte counts, hemoglobin levels and hematocrit in a dose-proportional manner. Increases of 15 to 54% in hemoglobin levels and 17 to 60% in hematocrit were reported after subcutaneous or intravenous epoetin beta therapy in studies of 8 weeks' to 12 months' duration. Comparative data indicate that dosage reductions of approximately 30% compared with intravenous therapy are possible when subcutaneous administration of epoetin beta is used. Hematocrit increased more rapidly in 5 multicenter studies on patients who received epoetin beta subcutaneously than on those who received the same dosage intravenously. It also causes significant improvements on quality of life, exercise capacity and overall well-being. Results of clinical studies indicate that subcutaneous administration is desirable where possible in the majority of patients [174].

Darbepoetin-alfa: It is a hyperglycosylated analog of recombinant human erythropoietin with the same mechanism of action as erythropoietin, but with a three-fold longer terminal

half-life after intravenous administration than recombinant human erythropoietin and the native hormone both in animal models and in humans. It is administered less frequently (once weekly or every other week) [175, 176]. The recommended starting dose in chronic renal failure patients is 0.45mcg/kg once weekly for both intravenous and subcutaneous administration, with subsequent titration based on the hemoglobin concentration. The adverse event profile of darbepoetin-alfa is similar to that of recombinant human erythropoietin in both settings, [177, 178] and effectively maintains hemoglobin in the target range in dialysis patients with renal anemia [179]. It also has been shown to be effective when administered once/week and once every 2, 3, or 4 weeks [180]. There are no reports of antibody formation associated with darbepoetin-alfa on chronic renal failure patients, and three cases of antibody formation, with neutralizing activity in one of the cases, reported on cancer patients [181-184].

Cera: Methoxy polyethylene glycol-epoetin beta (MPG-EPO; Mircera®, Roche, Basel, witzerland) is an agent that has a different interaction with the erythropoietin receptor than previous agents and has a long elimination half-life (approximately 130 hours) [185]. MPG-EPO is the only ESA generated by chemical modification of glycosylated erythropoietin, by the integration of one specific, long, linear chain of polyethylene glycol. The resultant molecule has a molecular weight of approximately 60 kDa, which is twice that of epoetin. The methoxy polyethylene glycol polymer chain is integrated through amide bonds between the N-terminal amino group or the ϵ -amino group (predominantly lysine-52 or lysine-45) with a single butanoic acid linker [186]. In ESA-naïve patients, the recommended starting dose is 0.6 μ g/kg administered once every 2 weeks as a subcutaneous or intravenous injection, in order to reach a hemoglobin level of 11 g/dL. The dose may be increased by approximately 25% if hemoglobin levels increase by 1.0 g/dL over a month. Further increases of approximately 25% may be made once per month until the individual target hemoglobin level is reached. If a hemoglobin level of 11 g/dL is reached for an individual patient, MPG-EPO may be continued once per month using a dose equal to twice the previous dose once every 2 weeks. Patients currently being treated with ESA can be directly converted to MPG-EPO administered once per month as a single intravenous or subcutaneous injection. The starting dose of this agent is based on the calculated weekly equivalent dose of DA or epoetin at the time of conversion [187]. The first injection of MPG-EPO should start at the next scheduled dose of the previously administered DA or epoetin dose. On patients receiving treatment with ESA and those naïve to ESA, the MPG-EPO dose should be reduced by approximately 25% if the hemoglobin level increases by more than 2 g/dL in 1 month or if the hemoglobin level approaches 12 g/dL. If hemoglobin levels continue to increase, MPG-EPO administration should be interrupted until these levels begin to decrease (a decrease of approximately 0.35 g/dL per week is expected). Therapy should then be resumed at a dose approximately 25% less than the previously administered dose. Dose adjustments should not be made more frequently than once per month [17, 188]. Once-monthly CERA therapy maintains stable Hb values with low intra-individual variability and few dose adaptations in hemodialysis patients when administered entirely according to local practice, and the regimen is well-tolerated [189]. C.E.R.A. can be administered to patients at any time during hemodialysis or hemofiltration without appreciable loss in the extracorporeal circuit [190].

Peginesatide (formerly known as *Hematide*TM): is a synthetic, peptide-based erythropoiesis-stimulating agent linked to polyethylene glycol. Based on extensive preclinical and clinical data substantiating the efficacy and safety of this agent, it was approved in the U.S. in March 2012 for the treatment of anemia due to chronic kidney disease in adult patients on dialysis. Peginesatide (Omontys®) was launched in the U.S. in April 2012 [191, 192]. A drug capable of stimulating erythropoiesis is the first ESA that bears no structural similarity to rhuEPO. Peginesatide is a synthetic, dimeric peptide that is covalently linked to polyethylene glycol (PEG). Peginesatide binds to and activates the human EPO receptor, stimulating the proliferation and differentiation of human red cell precursors in vitro in a manner similar to ESAs [193]. Peginesatide administered once monthly was as effective as epoetin alfa given thrice weekly (dialysis patients) or darbepoetin given once weekly (nondialysis patients), in correcting anemia of chronic kidney disease as well as maintaining hemoglobin within the desired target range [194-196].

4.4. Biosimilar

Epoetin zeta: Epoetin zeta is therapeutically equivalent to epoetin alfa in the maintenance of target Hb levels on patients with renal anemia. No unexpected adverse effects were seen [197-201].

Epoetin theta: Has efficacy comparable with epoetin beta (s.c.) in pre-dialysis patients with renal anemia based on Hb changes from baseline to end of treatment (non-inferiority). The safety profile was also comparable. Patients could be switched from maintenance treatment with epoetin beta to epoetin theta without relevant dose changes [202].

Epoetin omega: Epoetin-omega is a sialoglycoprotein with smaller amounts of O-bound sugars, less acidic and with different hydrophylity than the other 2 epoetins. The initial weekly dose of epoetin-omega was 90 units per kg of body weight (b.w.) divided in 3 equal portions and administered subcutaneously after each dialysis session. After correction of the hemoglobin, the dose of rHuEPO was individualized to keep Hb within target limits of 100-120 g/l. The mean dose of epoetin-omega during the correction period never exceeded 100 U/kg b.w. per week and the average maintenance dose between 50-60 U/kg b.w. per week [203, 204].

HX575: Is a biosimilar version of epoetin- α that is approved for the treatment of anemia associated with chronic kidney disease (CKD) using the intravenous route of administration [205, 206]. In a study for S.C. use two patients developed neutralizing antibodies (NAb) to erythropoietin, which resulted in the study being terminated prematurely [207].

4.5. Adverse effects of EPO therapy

Adverse effects of EPO therapy are uncommon, apart from a moderate increase in blood pressure and an increased rate of vascular access thrombosis. In spite of the fact that, these effects are probably dependent to a large degree on the increase in Hb concentrations, there are some concerns that ESA therapy may enhance thrombogenicity and tumor growth on patients with malignant disease as well as exacerbate vascular events in CKD independently of Hb concentrations [208]. In treatment with epoetin alfa hypertension occurs in 30 to 35% of patients with

end-stage renal failure, but this can be managed successfully with correction of fluid status and antihypertensive medication where necessary, and is minimized by avoiding rapid increases in hematocrit. Although vascular access thrombosis has not been conclusively linked to therapy with the drug, increased heparinisation may be required when it is administered to patients on hemodialysis [170]. On patients who receive epoetin beta, hypertension may occur but may be minimized by avoiding rapid increases in hematocrit ($> 0.5\%/week$), and is managed in most cases with control of fluid status and antihypertensive medication. Although clotting of the vascular access has not been conclusively linked to epoetin beta, caution is recommended on patients undergoing hemodialysis. Increased heparinisation is recommended to prevent clotting in dialysis equipment [174]. Before 1998, EPO alfa in Europe was formulated with human serum albumin, but because of a change in European regulations, this was replaced with polysorbate 80. EPO beta is formulated with polysorbate 20, along with urea, calcium chloride, and five amino acids as excipients. The importance of the formulation of the EPO products was highlighted in 2002 with an upsurge in cases of antibody-mediated pure red cell aplasia in association with the subcutaneous use of EPO alfa after its change for indication. Patients affected by this complication develop neutralizing antibodies against both rhuEPO and the endogenous hormone, which result in severe anemia and transfusion dependence [209, 210]. The cause of this serious complication in which there is a break in B-cell tolerance remains obscure, although it seems likely that factors such as a breach of the cold storage chain were relevant, and the subcutaneous application route was a prerequisite; circumstantial evidence also suggested that rubber stoppers of prefilled syringes used in one of the albumin-free EPO alfa formulations may have released organic compounds that acted as immunologic adjuvants [211].

4.6. Which target is the best for the correction of anemia on hemodialysis patients?

There has been considerable debate in recent times about the optimal target range of Hb in CKD patients [133]. The improvement in quality of life with increasing Hb concentrations supports a level above 10 to 11 g/dl in all CKD patients, [16, 17] but some studies have indicated increased risks associated with attempts to completely correct anemia. No survival benefit is evident at a higher level of anemia correction, [13, 164, 165, 167] although quality of life and exercise capacity may be greater. Thus, there is a possible tradeoff between improved quality of life and increased cost and risk for harm, so that a target level of Hb above 13 g/dl should be avoided [16]. Clinical trials of erythropoiesis-stimulating agents indicate that targeting the complete correction of anemia in patients with chronic kidney disease results in a greater risk of morbidity and mortality despite improved hemoglobin and quality of life [59, 164, 212]. Although there are studies that state the opposite [213, 214]. Relationships between hemoglobin concentration and mortality differed between African Americans and whites. Additionally, the relationship of lower mortality with greater achieved hemoglobin concentration seen in white patients was observed for all-cause, but not cardiovascular mortality [215]. Erythropoiesis-stimulating agents should be used to target hemoglobin 11-12 g/dl on patients with chronic kidney disease. However, a risk-benefit evaluation is warranted in individual patients, and high ESA doses driven by hyporesponsiveness should be avoided [216]. Intravenous iron may be beneficial for patients with hemoglobin less than

11 g/dl and transferrin saturation less than 25% despite elevated ferritin (500-1200 ng/ml) [217, 218]. TREAT and other large randomized, controlled trials of ESA treatment on patients with CKD have not demonstrated a clinical benefit in terms of mortality, morbidity, or quality of life improvement of targeting Hb levels greater than 12-13 g/dl. Some of these studies have demonstrated increased risk of stroke, vascular access thrombosis, hypertension, and other events [219]. The European Renal Best Practice (ERBP), which are issued by ERA-EDTA, are suggestions for clinical practice in areas in which evidence is lacking or weak, together with position statements on published randomized controlled trials, or on existing guidelines and recommendations. In 2009, the Anemia Working Group of ERBP published its first position statement about the hemoglobin target to aim for with erythropoietin-stimulating agents (ESA) and on issues that were not covered by K-DOQI in 2006-07. Following the findings of the TREAT study, the Anemia Working Group of ERBP maintains its view that 'Hb values of 11-12 g/dL should be generally sought in the CKD population without intentionally exceeding 13 g/dL and that the doses of ESA therapy to achieve the target hemoglobin should also be considered. More caution is suggested when treating anemia with ESA therapy on patients with type 2 diabetes not undergoing dialysis (and probably in diabetics at all CKD stages). To those with ischemic heart disease or with a previous history of stroke, possible benefits should be weighed up against an increased risk of stroke recurrence, when deciding which Hb level to aim for. These recommendations are not intended to represent a new guideline as they are not the result of a systematic review of evidence [220]. The National Kidney Foundation (NKF) and the Food and Drug Administration (FDA) recommend different target levels for hemoglobin in patients with terminal kidney disease treated by hemodialysis [79, 221]. The NKF recognizes also the importance of individualizing the treatment of anemia. The optimal range of target hemoglobin levels in Kainz et al analysis of hemodialysis patients was 11 g/day. Furthermore, ESA hypo-responders showed an increased risk of mortality with higher hemoglobin levels, and ESA responders actually exhibited a decreased risk [222]. A corrected weekly ESA dose up to 16 000 units with achieved hemoglobin levels ~11 g/dL exhibited the lowest mortality risk. Hemoglobin variability as well as ESA hypo-response causing low hemoglobin levels was associated with a numerically increased risk of mortality compared with patients with stable hemoglobin levels between 10 and 12 g/dL. Furthermore, ESA response requiring more than 16 000 units per week was also associated with an increased risk of death in ESA responders [222]. The Japanese Society for Dialysis Therapy (JSDT) guideline committee presents the Japanese guidelines entitled "Guidelines for Renal Anemia in Chronic Kidney Disease." These guidelines replace the "2004 JSDT Guidelines for Renal Anemia in Chronic Hemodialysis Patients," and contain new, additional guidelines for peritoneal dialysis (PD), non-dialysis (ND), and pediatric CKD patients [223]. Values for diagnosing anemia are based on the most recent epidemiological data from the general Japanese population. To both men and women, Hb levels decrease along with an increase in age and the level for diagnosing anemia has been set at <13.5 g/dL on males and <11.5 g/dL on females. Renal anemia is identified as an "endocrine disease." It is believed that in this way defining renal anemia will be extremely beneficial for ND patients exhibiting renal anemia despite having a high GFR. We have also emphasized that renal anemia may not only be treated with ESA therapy but also with ap-

propriate iron supplementation and the improvement of anemia associated with chronic disease, which is associated with inflammation, and inadequate dialysis, another major cause of renal anemia. In Japanese HD patients, Hb levels following hemodialysis rise considerably above their previous levels because of ultrafiltration-induced hemoconcentration; and (ii) as noted in the 2004 guidelines, although 10 to 11 g/dL was optimal for long-term prognosis if the Hb level prior to the hemodialysis session in an HD patient had been established at the target level, it has been reported that, based on data accumulated on Japanese PD and ND patients, higher levels have a cardiac or renal function protective effect, on patients without serious cardiovascular disease, without any safety issues. Accordingly, the guidelines establish a target Hb level in PD and ND patients of 11 g/dL or more, and recommend 13 g/dL as the criterion for dose reduction/withdrawal. If the serum ferritin is <100 ng/mL and the transferrin saturation rate (TSAT) is <20%, then the criteria for iron supplementation will be met; if only one of these criteria is met, then iron supplementation should be considered unnecessary [223]. Italian Society of Nephrology in its guidelines for the treatment of anemia in chronic renal failure supports that before beginning epoetin treatment, it is essential to evaluate the level of anemia by the measuring Hb concentration, Red blood cell indices (MCV, MCH, MCHC), Reticulocyte count, Iron stores and availability and C-reactive protein (CRP). The minimum target Hb concentration to be attained is 11 g/dL. The upper limit is established individually on a clinical basis. Pending further data, it is advisable to maintain and not exceed 12 g/dL for patients with cardiovascular disease, diabetes, and graft access. In the presence of adequate reserves of iron the need for higher dosages of epoetin define a state of resistance [224].

Iron deficiency (60%) measured by ferritin levels and TSAT at start of dialysis was found in Predialysis Survey on Anemia Management (21 European countries, Israel and South Africa) despite the majority of patients under nephrologist's care for more than twelve months. Only 27% of patients had started epoetin treatment before dialysis therapy. Thirteen percent had started dialysis therapy first, 33% had started epoetin and dialysis therapy simultaneously, and 28% had not been administered epoetin at any time (total n = 4,095).

[225] Difference in hemoglobin levels was found in DOPPS study and mean Hgb levels were 12 g/dL in Sweden; 11.6 to 11.7 g/dL in the United States, Spain, Belgium, and Canada; 11.1 to 11.5 g/dL in Australia/New Zealand, Germany, Italy, the United Kingdom, and France; and 10.1 g/dL in Japan. Hgb levels were substantially lower for new patients with end-stage renal disease, and EPO use before ESRD ranged from 27% (United States) to 65% (Sweden) [21].

At present, there is a "grey zone" also between the intervention threshold of Hb < 9 g/dl and an Hb level > 13 g/dl, at which CKD is associated with a higher risk of cardiovascular events. It seems to be clearly evident that ESA activate platelets directly and indirectly, and that pathologically extended bleeding time is normalized when an Hb level of 10 g/dl is reached; from the hemostaseological perspective, a threshold level for treatment of renal anemia with ESA is thus defined. According to the present state of knowledge, an Hb target range of 10-11 g/dl seems reasonable for renal anemia; this is also compatible with current recommendations by ESA producers and the Food and Drug Administration (FDA) [226]. This target range avoids the upper and lower risk levels for Hb, and probably ensures a pos-

itive ESA effect on quality of life; it is much more cost-efficient than the target range of 11-12 g/dl recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI) in 2007 [227]. ESA treatment for renal anemia should be aimed at reducing transfusion risk, with a treatment target in most patients of 10-12 g/dl; therapy should be individualized, rapid increases in Hb level should probably be avoided, and lowest appropriate ESA doses should be used. Temptation to increase ESA doses to very high levels in an attempt to overcome ESA hypo responsiveness should be resisted [219]. It seems that greater hemoglobin variability is independently associated with higher mortality [228]. Variability caused by laboratory assays, biological factors, and therapeutic response determines patient Hb level variability. Improving factors that can be manipulated (e.g., standardizing EPO and iron algorithms) and adjustment of the target Hb level range, specifically, by increasing the upper bound, likely will decrease the observed variability and further enhance the quality of anemia management [229, 230].

5. Conclusion

It is obvious that renal anemia in hemodialysis patients remain a serious problem. This was greater before EPO era, when blood transfusion was the only therapeutic approach. Insufficiency of iron and EPO are the most important causes of this anemia. Nowadays with the availability of new I.V. iron supplementation and ESAs this problem became more manageable. The high cost of the EPO treatment makes the iron therapy essential in order to maximize EPO administration result with the lower dose. The ideal hemoglobin target has to be established despite the numerous trials worldwide, and the treatment has to be individualized.

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