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SECTION II. Targets for anaemia treatment

Guideline II.1: What are the appropriate haemoglobin targets for anaemia treatment?

Recommendation

I. In general, patients with chronic kidney disease (CKD) should maintain a target haemoglobin (Hb) concentration of >11 g/dl [haematocrit (Hct) >33%]—or reach this target within 4 months of starting treatment—regardless of age, gender or ethnicity.

- **Patients starting treatment with extremely low Hb concentrations should reach this target as soon as possible, with a monthly increase in Hb as specified in Recommendation V of Guideline III.1.**
- **For patients on haemodialysis (HD), Hb concentration should be determined from a sample taken prior to the dialysis session.**
  (***Evidence level B***)

Note: Please see Recommendations II and III of this guideline for target Hb values for various patient subgroups.

Rationale and commentary

There is abundant evidence that treatment with erythropoiesis-stimulating agents (ESAs) leads to improved quality of life in patients with renal anaemia [1–4]. There is also some evidence that treatment with ESAs confers protection against cardiovascular disease (CVD) [5,6]. A correlation between survival and Hb concentration has been established in large retrospective studies [7–9] and in a prospective cohort study [10], but no prospective data have yet shown an improvement in survival in any single group of patients treated with ESAs. In a large, ongoing observational study of HD patients in five European countries, higher Hb levels were seen to be associated with a decreased relative risk for mortality and hospitalization [11]. However, although there is abundant evidence that the Hb concentration should be raised above 10 g/dl, the optimum Hb level to aim for above this concentration remains unclear.

An extensive, but sometimes conflicting, collection of data on the optimum Hb level for CKD patients exists. Strippoli *et al*. [12] conducted a Cochrane structured analysis of 15 randomized controlled trials, which examined the effect of 'low' (Hb ≤10 g/dl or Hct ≤30%) and 'high' (Hb >10 g/dl or Hct >30%) targets in pre-dialysis [3,13–19], peritoneal dialysis (PD) [20] and HD patients [5,21–23], as well as in all three groups of patients together [24].

The studies by Besarab *et al*. [23] and Brandt *et al*. [24] focused on differences between 'partial' Hb correction (~11 g/dl) and 'full' normalization of Hb concentration (≥13 g/dl). The largest trial in the Cochrane analysis, the study of Besarab *et al*. [23], consisted only of HD patients with severe heart failure and/or angina, half of whom had diabetes. This study was terminated prematurely because it appeared unlikely that patients would receive any extra benefit from a high/normal Hb concentration. At the point of termination, mortality in the group with 'high' Hb concentrations was greater than in the group with 'standard' Hb concentrations, but this between-group difference was not significant. Furthermore, when treated as a continuous variable within and across both patient groups, a high Hb level correlated with lower mortality.

The other 14 trials in the analysis of Strippoli *et al*. [12] involved a mixed group of patients, with varying degrees of cardiovascular involvement. Strippoli *et al*. [12] concluded that patients reaching Hb targets of <10 g/dl with both cardiovascular impairment and CKD were less likely to die than those with an Hb of 14 g/dl. The clinical benefits of higher Hb targets (e.g. reduced incidence of seizures) did not outweigh the risks (hypertension, thrombosis and mortality).

In the Scandinavian study of Furuland *et al*. [25], which was not included in the original analysis of Strippoli *et al*. [12], 416 pre-dialysis, PD and HD patients without severe heart failure and/or angina were randomized to 'usual' and 'normal' Hb concentrations; one-fifth of these patients also had diabetes. In the normalized group, the Hb concentration was raised to 13.5–16.0 g/dl, while the Hb concentration in the control group was maintained at 9.0–12.0 g/dl. Results from a follow-up period of 12–19 months showed that there was no between-group difference in total or cardiovascular mortality in patients without major CVD, but this trial was not powered to detect minor differences in mortality.

The conclusions of the structured analysis of Strippoli *et al*. [12] are problematic because they are largely derived from the results of the large trial of Besarab *et al*. [23], which was confined to HD patients

with severe CVD and a high proportion (80%) of vascular access grafts. In addition, the other trials in the analysis of Strippoli *et al*. [12] included a mix of patients with and without CVD. The study by Furuland *et al*. [25] suggests that the conclusions reached in the large study of Besarab *et al*. may not be applicable to patients without severe CVD. Ethnicity may also be an important factor as almost half the patients in the study of Besarab *et al*. [23] were Afro-American (who tend to have a higher cardiovascular risk than Caucasians), whereas the Scandinavian study [25] comprised only Caucasian patients. In addition, a previous Cochrane analysis [26] confining itself to 12 studies on pre-dialysis patients (but including some trials that were excluded from the study of Strippoli *et al*. [12]) concluded that there was insufficient data to draw firm conclusions about the benefits of raising Hb to levels approaching normal values.

In terms of cardiovascular risk, CKD patients with chronic anaemia may develop a fibrotic left ventricular (LV) hypertrophy [27], increasing the risk of cardiovascular events and death [28,29]. Increasing Hb from <10 to >10 g/dl in CKD patients has been linked to improved cardiac performance with regression of cardiac enlargement in a large number of studies [30–41]. Raising or maintaining higher Hb concentrations may also reverse the deleterious effects of previous low levels [4,6].

In the current literature, there are two randomized controlled trials on the effects of Hb normalization on cardiovascular performance and cardiac morphology [5,6]. McMahon *et al*. [6] showed that normalization of Hb also reduced the elevated cardiac output compared with those patients with Hb levels of 10–11 g/dl [6,42]. The study by Foley *et al*. [5] found similar cardiac output results but showed no improvement in LV mass or dilatation in patients with 'normalized' Hb. In an uncontrolled sequential study of patients with severe heart failure and CKD not on dialysis, the measured ejection fractions improved modestly in patients both with and without diabetes following a rise in mean Hb from almost 10.5 to 13 g/dl [43].

Strippoli *et al*. [12] excluded quality of life (QOL) assessments from their analysis because the data on QOL vary widely, and because, in most studies, only certain parameters of assessment show improvement following normalization of Hb. However, because improved QOL, rather than improved survival, currently is the principal benefit of raising Hb, it is useful to summarize the available data.

Benefits in QOL were apparent in earlier randomized controlled trials [1–3], and higher Hb concentrations have since been shown to confer a number of favourable outcomes [4]. While quality of life benefits are not evident when Hb is only raised to <10 g/dl [1,44], improvements have been almost universally reported when Hb is raised above 10 g/dl [23,45–58].

Raising Hb concentrations to >11 g/dl (Hct 33%), or full 'normalization', has been shown to lead to further improvements in quality of life in CKD patients [59–61]. Furuland *et al*. [25] showed that some indicators of QOL (e.g. physical symptoms, fatigue, depression and frustration) but not all (e.g. exercise tolerance) improved in patients with normalized Hb compared with patients with Hb concentrations of ~11.5 g/dl [25]. Foley *et al*. [5] also concluded that Hb normalization reduced fatigue and depression, but did not improve physical symptoms or reduce frustration. Other studies have found that patients (including the elderly) with 'normalized Hb' were physically and psychosocially healthier than those with only partially corrected anaemia [6,62]. However, Painter *et al*. [63] found that raising Hct did not improve oxygen uptake and exercise function to the expected levels. In summary, QOL, excluding exercise-related parameters, appears to improve following normalization of Hb to levels above 10–11 g/dl, up to a mean of 14 g/dl.

Results from a large retrospective survey of dialysis patients have shown that higher Hb concentrations are also associated with lower hospital admission rates [64]. In an uncontrolled but prospective study, Moreno *et al*. [62] showed that Hb normalization in non-diabetic HD patients without CVD significantly reduced their rate of hospital admission, compared with patients with Hb concentrations of ~11 g/dl. In addition, normalization of Hb in patients with mild to moderate renal failure and severe heart failure (both with and without diabetes) was shown to dramatically reduce the number of admissions [43]. A recent, large observational study of HD patients, encompassing five European countries, has also found a correlation between higher Hb levels and lower hospital admission rates [10,11].

However, in fully controlled prospective studies, rates of admission were not significantly different between normalized and non-normalized patients. In the Scandinavian study [25], rates of admission for patients with normalized Hb and those kept at ~11.5 g/dl were 4.8 and 3.8%, respectively. Similarly, there was no difference in hospital admissions and length of stay between HD patients randomized to targets of 10 and 13.5 g/dl Hb in the trial of Foley *et al*. [5]. The Besarab *et al*. [23] study of patients on HD with severe CVD again showed no difference in admission rates, with 69% of patients in the low Hct group and 72% of patients in the normalized Hb group having at least one admission during the period of study.

Adverse events

Much of the early reluctance to raise Hb concentrations above 10 g/dl derived from fears of increased hypertension and access thrombosis from altered blood rheology. In fact, there is some evidence that rheology is unaffected by rising Hb levels [65]. Although a tendency towards increased hypertension (as judged by increased need for antihypertensive therapy) was reported in the large studies discussed above, in practice, blood pressure levels remain constant when

Hb levels are raised. This is supported by the results of some smaller, controlled studies of continuous ambulatory 24 h blood pressure monitoring, where no significant increases were seen in either blood pressure level or amount of therapy [66,67] when Hb was raised to normal concentrations.

Access thrombosis was not a problem in the Scandinavian study [25] or in the study of Moreno *et al*. [62], although it was a major problem in the large trial of Besarab *et al*. [23]. The presence of heart failure in these patients probably increased the incidence of this adverse event in the Besarab trial [23]. Other possible adverse events associated with a rise in Hb concentration, apart from a possible increase in cardiovascular events and mortality, are discussed in more detail in the guideline on ESA therapy (see Guideline III.1).

Impact of Hb level on rate of progression of renal failure

In patients with CKD, raising the Hb concentration does not appear to increase the rate of progression of renal failure, as based on evidence from controlled trials. Strippoli *et al*. [12] did not examine this issue in their analysis, but evidence from a number of randomized controlled trials [3,13–15,18,19,24,68] has shown that there are no differences in plasma creatinine concentrations between those left severely anaemic (Hb <10 g/dl) and those with Hb levels of 10–11 g/dl. Furthermore, in the Scandinavian trial [25], glomerular filtration rate (GFR) (assessed by iohexol or ^{51}Cr EDTA) in 46 patients not on dialysis fell from 16 ± 9 to 13 ± 10 ml/min/1.73 m^2 in the group whose Hb concentration was normalized ($n = 24$) and from 17 ± 10 to 16 ± 10 ml/min/1.73 m^2 in the control group, who were left at an Hb of 11 g/dl ($n = 22$). These rates of progression were not significantly different, suggesting that normalization is also safe in this respect. In the study of Silverberg *et al*. [43] focusing on patients with heart failure, the rate of decline in renal function actually decreased from –1.12 to + 0.21 ml/min/month in non-diabetic patients and from –1.2 to +0.1 ml/min/month during normalization of Hb to 13.0 g/dl over a 1-year period. Similar data from a retrospective study have also been reported by Jungers *et al*. [69]. Fears that raising the Hb concentration might adversely affect subsequent transplantation outcomes have also proved to be unfounded [70].

In summary, for individuals without severe CVD, although some benefits of normalization of Hb concentrations are evident compared with maintenance at a level of 11–11.5 g/dl, there is insufficient evidence to warrant a general recommendation of Hb normalization for this patient group. On the other hand, there is no evidence that Hb normalization leads to harm in these patients and, for individual cases, Hb normalization may be desirable. However, there is a considerable opportunity cost to raising Hb, particularly above 12 g/dl [71], and, given that the evidence for improved outcomes of further raising the Hb is weak, a decision will have to be made about whether resources within a renal service should be spent on raising Hb or on other aspects of the service—such as the ability to accept more patients for dialysis treatment.

Recommendation

II. Exact target Hb concentrations >11 g/dl should be defined for individual patients, taking gender, age, ethnicity, activity and co-morbid conditions into account. In HD patients, pre-dialysis Hb concentrations above 14 g/dl are not desirable due to the risks associated with the effects arising from post-dialysis haemoconcentration. (***Evidence level C***)

Rationale and commentary

In Recommendation I of this guideline, the same target Hb concentration is recommended for all populations of patients with CKD. The only exceptions to this general recommendation are those patients described in Recommendation III of this guideline. However, as detailed in Appendix A on Hb methodology, Hb concentrations in individuals without CKD vary with age, sex, gender, altitude of residence and smoking habits. In addition, the physical activity level of a patient will determine the degree to which anaemia will impact his or her life. Therefore, within the constraints of Recommendation I, it may be necessary to tailor the target Hb concentration for individual patients from 11 g/dl, to as high as 14 g/dl. However, the latter figure should not be exceeded in those on HD, because haemoconcentration during HD will raise this figure to potentially dangerous concentrations [72].

Recommendation

III. The optimal target Hb concentration may vary in patients with significant co-morbidity:

- **Hb concentrations >12 g/dl are not recommended for patients with severe cardiovascular disease [defined as class III and above of the New York Heart Association Classification of Congestive Heart Failure (Table 2, Appendix C)] unless continuing severe symptoms (e.g. angina) dictate otherwise.** (***Evidence level A***)
- **Until data become available, it seems prudent to recommend a cautious approach to raising Hb concentrations to levels >12 g/dl in patients with diabetes, especially with concurrent peripheral vascular disease.** (***Evidence level C***)
- **Patients with chronic hypoxaemic pulmonary disease may benefit from a higher Hb target.** (***Evidence level C***)

- **In patients with CKD and sickle cell disease receiving ESAs, the aim should be to titrate the dose of ESAs to prevent the level of haemoglobin S (HbS) becoming much greater than 30%. Even with high-dose ESA therapy, patients are unlikely to achieve an Hb greater than ~7–8 g/dl due to ongoing red cell destruction from haemolysis.**
  (***Evidence level C***)

Rationale and commentary

Severe cardiovascular disease

The large controlled study of Besarab *et al*. [23] showed that, in patients with severe cardiovascular disease (New York Heart Association class III and above), total mortality was higher in patients randomized to a normal Hb as compared with those patients left at 11 g/dl. In fact, total mortality difference approached significance ($P \sim 0.05$) when these patients' Hb concentrations were raised to within normal limits, although there was no difference in the number of deaths from cardiovascular causes (125/618 in the low Hct group *vs* 112/615 in those normalized). In addition, there was a much higher incidence of access thrombosis in the normalized Hb group. Therefore, it is recommended that patients with severe CVD and vascular access grafts be kept at a lower Hb concentration of ~11–12 g/dl, unless angina or other symptoms dictate otherwise.

Diabetes

No controlled data on raising Hb concentrations in diabetic patients currently exist. However, diabetic patients have different blood rheology and viscosity, even when non-uraemic, principally because of high plasma fibrinogen concentrations, combined with non-enzymatic glycosylation of the red cell membrane and plasma proteins. Combined with the rheological changes found with uraemia [73] [probably induced by carbamylation and the formation of other advanced glycosylation end (AGE)-related products], red cell deformability is markedly abnormal in patients who are both uraemic and diabetic, and both blood and plasma viscosity are increased [74]. Most uraemic, diabetic patients also suffer from (often severe) peripheral vascular disease, which further complicates rheology. Given that diabetic patients now comprise 20–40% of patients being treated in end-stage renal disease (ESRD) programmes worldwide, it is even more unfortunate that, although some studies are in progress, no controlled data currently exist.

Between 10 and 50% of patients in the studies included in the meta-analysis of Strippoli *et al*. [12], including 44% of patients in the study of Besarab *et al*. [23], were diabetic. In the Scandinavian trial of Furuland *et al*. [25], 17% of patients were diabetic. However, diabetic patients were not analysed as a separate group in either of these investigations. The only study of normalization of Hb (to 13.1 g/dl) in diabetic patients to date is an uncontrolled sequential trial using within-patient analysis in 84 type II diabetic patients with severe heart failure and mild to moderate renal failure [43]. After a mean of 12 months, heart failure was much improved in these patients. However, only eight deaths occurred, precluding any analysis of mortality. It is possible that, as found in the Besarab *et al*. study [23], the level of excess mortality found in patients with severe CVD (including the 44% of patients in the study with diabetes) whose Hb was normalized may also occur in diabetic patients without evident CVD; however, there are no data on this important point. One retrospective study reported more severe peripheral vascular disease, and an increased requirement for amputation in 84 diabetics allocated to ESA therapy, when compared with those not receiving the drug, even though Hb concentrations were similar in both groups [75]. Therefore, at the present time, it seems prudent to recommend that Hb concentrations should be raised slowly in diabetic patients to levels no higher than 12 g/dl.

Sickle cell disease

Patients with CKD and homozygous sickle cell disease represent a difficult group to treat, and setting a specific target Hb is less relevant in this patient cohort. This is due to the fact that, even with high-dose ESA therapy, patients are unlikely to achieve an Hb greater than ~7–8 g/dl due to ongoing red cell destruction from haemolysis. Because of their genetic defect, patients with sickle cell disease can only manufacture HbS, along with possibly a small amount of haemoglobin F (HbF). Red cells containing HbS are very prone to haemolysis, and thus most patients remain transfusion dependent. The main aim in this patient population is, therefore, not to correct their anaemia, but to reduce their frequency of blood transfusions, which result in iron overload and usually terminal cardiac failure.

Reducing haemolysis may be achieved by co-administration with hydroxyurea, which boosts the levels of HbF [76], and this may assist in the management of this patient population. The HbS and HbF levels, and reticulocyte count, should be measured in patients with CKD and sickle cell disease receiving ESAs, and the aim should be to titrate the dose of ESAs to prevent the level of HbS becoming much greater than 30%, thereby reducing the risk of exacerbating a sickling crisis.

Chronic hypoxaemic pulmonary disease

There are no data on the correct management of patients with chronic hypoxaemic pulmonary disease once they become uraemic or require treatment for ESRD. As congestive heart failure can occur in these patients, even in the absence of uraemia, a cautious approach should be taken to raising Hb concentrations.

Recommendation

IV. The target Hb concentrations recommended in this guideline should not be used as targets for patients being treated with blood transfusions.
(***Evidence level C***)

The recommended target Hb concentrations provided are intended for patients being treated with ESAs and iron, and are not appropriate for those patients being treated with blood transfusions.

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Guideline II.2: What are the appropriate iron targets for anaemia treatment?

Recommendation

I. Patients with chronic kidney disease (CKD) should be in iron balance, or have sufficient iron, to maintain (or reach) a haemoglobin (Hb) concentration of >11 g/dl [haematocrit (Hct) ≥33%].
(***Evidence level B***)

Rationale and commentary

In healthy individuals, iron is found in Hb (1800–2800 mg), hepatocytes and macrophages (800–1200 mg), erythroid marrow (150 mg) and in plasma (4 mg). Iron is almost completely recycled, with only ~1 mg/day being both lost and ingested in most healthy people. However, menstruating women need an extra 1.8–2.5 mg iron/24 h and are often iron deficient, even in developed countries [1,2]. Vegans/vegetarians may be marginally iron deficient due to minimal ingestion of haem iron and impaired iron absorption from dietary phytates; however, iron deficiency is generally rare if there is no blood loss.

There is a synergistic relationship between erythropoiesis-stimulating treatments and iron therapy. Erythropoiesis-stimulating agents (ESAs) increase the need for iron as they stimulate the synthesis of 2 million new red cells/second [3]. If there is not enough iron, reticulocytes leave the marrow with suboptimal quantities of Hb [4]. In the first 3 months of ESA therapy, a haemodialysis (HD) patient needs ~1000 mg (up to 30 mg/24 h) supplemental iron, of which 400 mg replaces dialyser and sampling losses. Adequate iron availability increases erythropoiesis and reduces ESA requirements [5]. Increasing iron stores may benefit uraemic patients more during early treatment when ESAs are used to correct Hb levels, rather than to maintain Hb levels.

There are surprisingly few data on iron absorption in uraemic patients. The ability to absorb iron from the gastrointestinal tract may be impaired in uraemic patients [6–9]. However, one small, single-armed trial has reported that uraemic patients retain sufficient intestinal iron absorption to cover daily gastrointestinal and sampling iron losses [10], although it was not sufficient to cover the degree of blood loss associated with HD.

Certain uraemic patients, especially those on HD, have additional sources of blood loss, e.g. gastrointestinal, which further reduces Hb concentration. About 3 mg/24 h of iron [~120–3000 mg iron/year (250–7000 ml blood)] may be lost during dialysis compared with 1 mg/24 h in healthy individuals [11,12]. However, only 2–5 ml blood per dialysis session is lost using modern dialysers. This amounts to 150–300 mg of iron (300–750 ml of blood) per year. Blood may also be lost during routine blood sampling [in both HD and peritoneal dialysis (PD) patients]. In non-uraemic patients, common causes of anaemia and blood loss need to be considered if ferritin or Hb concentrations are unusually low, or if patients do not respond to iron or ESAs.

Recommendation

II. To reach and maintain target Hb concentration, sufficient iron should be administered to attain the following targets in all patients:

- **serum ferritin >100 μg/l**
- **hypochromic red cells <10% [or transferrin saturation (TSAT) >20%, or reticulocyte Hb content (CHr) >29 pg/cell].**
  (***Evidence level B***)

In practice, to achieve these recommended minimum criteria, it will be necessary to aim for targets in the treatment population as a whole of:

- **serum ferritin 200–500 μg/l**
- **hypochromic red cells <2.5% (or TSAT 30–40%, or CHr ~35 pg/cell).**
  (***Evidence level C***)

Rationale and commentary

The targets given here are only appropriate for patients undergoing treatment with an ESA. As already mentioned in the Rationale and commentary for Recommendation I of this guideline, ESA administration increases the demand for iron and, therefore, these patients will have iron requirements which are different from those of patients who are anaemic, but are not receiving this form of treatment.

The different methods used to assess iron availability and iron stores are described in detail in Appendix B on iron methodology. In clinical practice, no single test adequately monitors iron stores or availability. Throughout these guidelines, the preferred assessment for iron stores is serum ferritin concentration and, for iron availability, the percentage of circulating hypochromic red cells. If the latter is unavailable, either TSAT, measured several times, or the CHr, could be used. CHr could replace the percentage of hypochromic red cells or TSAT, or be measured in addition to them.

Neither the concentration of free transferrin receptor nor that of zinc protoprophyrin (ZPP) is recommended (see Appendix B).

Targets: TSAT and serum ferritin values

As most studies focus on young or middle-aged Caucasians, some of the same factors that may influence target Hb (gender, ethnicity, age and concurrent undiagnosed diseases) apply to target levels of stored or available iron. However, unlike Hb, there are few comparative data for iron stores or availability in uraemic patients, or targets, administration and optimum dose in other groups of patients.

Serum ferritin concentrations are generally much lower in menstruating women than in men or non-menstruating women [1,2,13], and thus it is difficult to determine the 'normal' serum ferritin level for women in general. However, serum ferritin concentrations in European post-menopausal women are equal to those in men [13]. Ethnicity may also affect normal concentrations; ferritin levels are higher in some black populations [14,15]. The recommended minimum serum ferritin concentration for patients in renal failure without inflammation is $>100\,\mu g/l$. This lower limit is only just below the mean concentration in healthy individuals. A serum ferritin target for the treatment population of 200–250 µg/l ensures that 85–90% of patients attain a serum ferritin of 100 µg/l.

Population data suggest that, when Hb values are plotted against TSAT, the resulting curves flattened out at a mean Hb of 15 g/dl in men and 13.5 g/dl in women, when TSAT levels reach ~30% (Figure 1) [16]. The NHANES III data also indicate a similar relationship between TSAT and Hb [17]. In addition, the results of one study suggest that patients maintained at a TSAT of >30% require less ESA than those patients maintained at 20–30%, resulting in possible savings in the cost of treatment [5]. Therefore, a target TSAT of >30% is suggested.

Mean CHr (±SD) in the general population is 32 ± 3.25 pg. Levels of 26–29 pg indicate iron deficiency, which is diagnosed by the absence of stainable iron stores [18]. The recommended CHr is >29 pg/cell

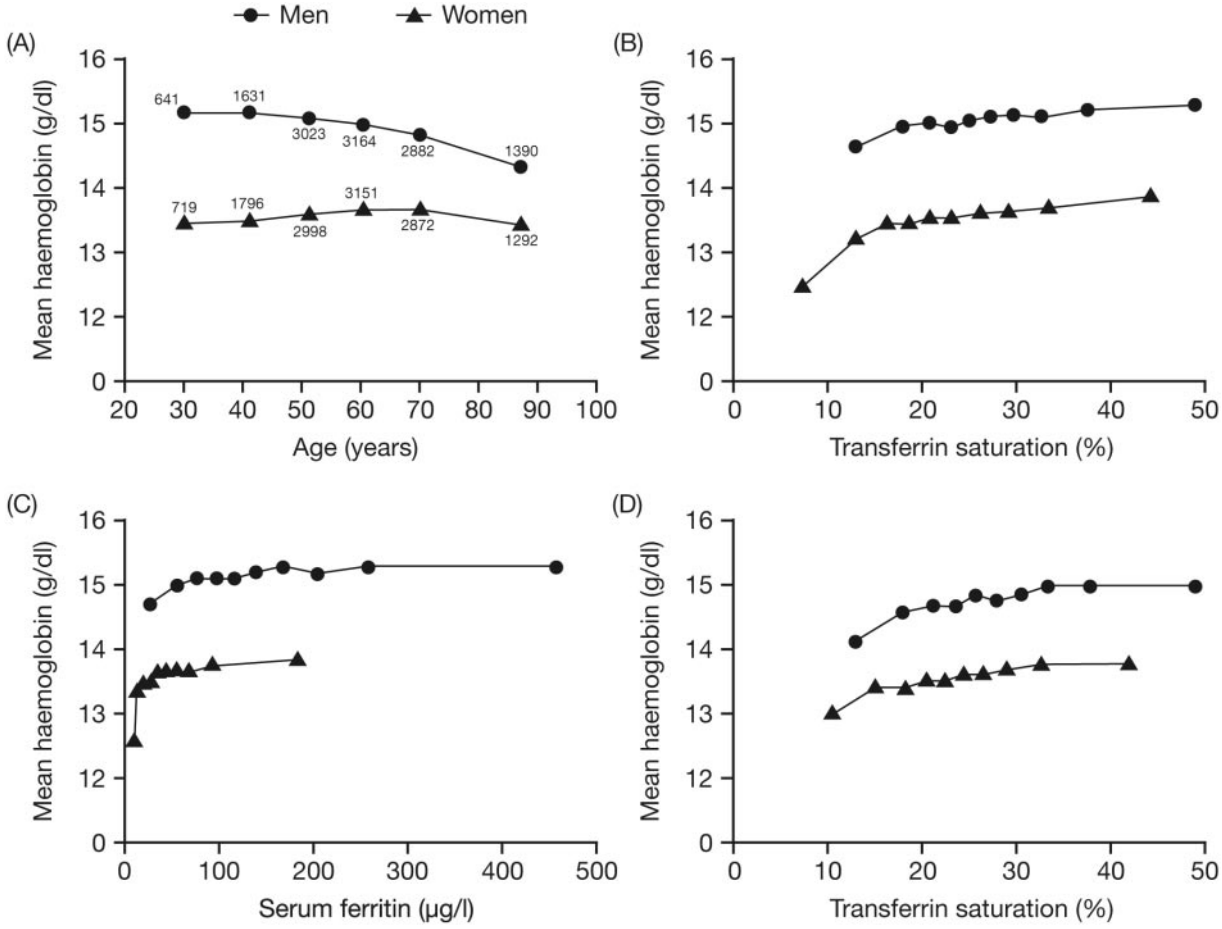

Fig. 1. Population data showing the haemoglobin mean concentration of healthy white individuals as a function of percentage transferrin saturation in: (**B**) 26–55 year olds; (**D**) >55 year olds, divided into tenths and plotted at the mean for each tenth. Mean concentration of haemoglobin plotted *vs* age, stratified as 26–35, 36–45, 46–55, 56–65, 66–75 and 76–99 years, is shown in (**A**), plotted at the interval midpoint; the number of participants is shown. Mean concentration of haemoglobin plotted as a function of serum ferritin concentration in 26–55 year olds is shown in (**C**) [16]. Reproduced with permission from the BMJ Publishing Group.

[5,19], so a higher target should be set to ensure that most patients reach this level.

Iron toxicity

The suggested upper limit of serum ferritin for all patient groups is 800 μg/l, with the target level of 200–500 μg/l. In the pre-ESA era, dialysis patients often had iron overload (frequently with ferritin levels >1000 μg/l) due to polytransfusion [20]. Indeed, plasma ferritin concentrations of >1000–2000 μg/l were not uncommon, and became a source of concern due to their association with tissue deposition and cell damage [21–24], although a significant complication in these studies was the presence of hepatitis C virus, which is highly prevalent in polytransfused patients. Estimating a safe upper limit of ferritin is hampered by the lack of data comparing histological iron stores and ferritin concentrations in patients receiving only intravenous (i.v.) iron without blood transfusions, but a reasonable compromise between efficacy and safety suggests an upper ferritin limit of 800 μg/l. It should be noted that ferritin is an acute-phase reactant and that concentrations usually increase by 2- to 4-fold in inflammatory states. In addition, most excess parenterally administered iron is deposited in the reticuloendothelial system and is thus unavailable to cause parenchymal damage.

It is important to consider the potentiating effect of a relationship between excess iron and the incidence and severity of infections. This relationship is due, at least in part, to inhibition of phagocytosis, but it is complex and unclear. Iron itself may not be the culprit, since anaemia [25], transfusions [26] and secondary splenic dysfunction all increase infection risk. However, some uncontrolled studies suggest that removing iron with desferrioxamine, or treatment with ESAs, does improve phagocytic function, although ferritin concentrations remained >1000 μg/l in several studies [27,28]. Higher mean corpuscular Hb concentrations were also found in patients without bacteraemic episodes [29]. Although the data are not conclusive, it is still recommended that, as a precaution, i.v. iron is stopped in patients with ongoing bacteraemia.

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Appendix C: Tables, conversions and abbreviations

This appendix contains the following supplemental information:

- Tables
- Formulae for calculating the glomerular filtration rate (GFR)
- Conversion factors for haemoglobin (Hb)
- Abbreviations used throughout the guidelines

Tables

Table 1. Definition of the five stages of chronic kidney disease (CKD)

Stage	Description	GFR (ml/min/1.73 m^2)	Action
	At increased risk	≥90 (with CKD risk factors)	Screening, CKD risk reduction
1	Kidney damage with normal or increased GFR	≥90	Diagnosis and treatment, treatment of co-morbid conditions, slowing progression, CVD risk reduction
2	Kidney damage with mild decrease in GFR	60–89	Estimating progression
3	Moderate decrease in GFR	30–59	Evaluating and treating complications
4	Severe decrease in GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uraemia present)

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Table 2. New York Heart Association classification of congestive heart failure patients

Class	Description
I	Patients with documented heart disease of any type who are completely symptom free
II	Slight limitation of physical activity; symptoms (shortness of breath, chest pain) occur only with more than ordinary physical activity
III	Marked limitation of physical activity; symptoms occur even with ordinary physical activity (e.g. eating meals)
IV	Severe limitation of physical activity; symptoms occur even at rest (e.g. in a sitting or lying position)

Reproduced with permission from [2]

Formulae for calculating the GFR

The following formulae can be used to calculate the GFR.

Cockcroft–Gault formula

If using μmol/l as a measure of serum creatinine, use the following formula:

$$\text{GFR} = \frac{(140 - \text{age}) \times \text{weight in kg}\,(\times 0.85 \text{ if female})}{0.810 \times \text{serum creatinine (μmol/l)}}.$$

If using mg/dl for serum creatinine, use the following formula:

$$\text{GFR} = \frac{(140 - \text{age}) \times \text{weight in kg}\,(\times 0.85 \text{ if female})}{72 \times \text{serum creatinine (mg/dl)}}.$$

To convert μmol/l to mg/dl, multiply by 0.0113.
To convert mg/dl to μmol/l, multiply by 88.4.

MDRD formula

The MDRD formula below is derived from the Modification of Diet in Renal Disease Trial [3].

$$\begin{aligned}\text{GFR} = {} & 170 \times \text{serum creatinine concentration}^{-0.999}_{(\text{mg/dl})} \\ & \times \text{age}^{-0.176} \\ & \times 0.762 \text{ (if female)} \\ & \times 1.18 \text{ (if race is black)} \\ & \times \text{blood urea nitrogen concentration}^{-0.17} \\ & \times \text{serum albumin concentration}^{+0.318}\end{aligned}$$

A GFR calculator using the MDRD formula can also be found on the National Kidney Foundation K/DOQI website: www.kdoqi.org. GFR can be calculated by inputting the required laboratory and demographic data.

Conversion factors for Hb

Throughout these guidelines, Hb concentrations are expressed in g/dl. To convert g/dl to g/l, multiply by 10. Other units, such as mmol/l, are used in some countries in Europe, including Denmark and The Netherlands. To convert g/dl to mmol/l, multiply by 0.62.

Abbreviations used throughout the guidelines

AGE = advanced glycosylation end
CHr = reticulocyte Hb content
CKD = chronic kidney disease
CRP = C-reactive protein
CVD = cardiovascular disease
DST = donor-specific transfusion
ESA = erythropoiesis-stimulating agent
ESRD = end-stage renal disease
FID = functional iron deficiency
GFR = glomerular filtration rate
Hb = haemoglobin
Hct = haematocrit
HD = haemodialysis
HLA = histocompatibility leukocyte antigens
HRC = hypochromic red blood cells
iPTH = intact parathyroid hormone
KDQ = Kidney Disease Questionnaire
MCH = mean corpuscular haemoglobin
MCV = mean corpuscular volume
PD = peritoneal dialysis
PRCA = pure red cell aplasia
PTFE = polytetrafluoroethylene
QOL = quality of life
TBIC = total iron-binding capacity
sTfR = soluble transferrin receptor
TSAT = transferrin saturation
VO_2max = maximal rate of oxygen consumption
ZPP = zinc protoporphyrin

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