

REVIEW

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UK kidney association clinical practice guideline: update of anaemia of chronic kidney disease

Sunil Bhandari^{1*}, Sebastian Spencer¹, Ben Oliveira², Ashraf Mikhail³, Owain Brooks³, Gareth Bryant⁴, Michelle Willicombe⁵, Richard Baines⁶, Louise Alldridge⁷ and Sally Haslam-England⁸

Abstract

Anaemia is common in chronic kidney disease (CKD) encompassing non-dialysis dependent CKD (NDD-CKD) and dialysis dependent CKD (DD-CKD); people on peritoneal dialysis (PD) and haemodialysis (HD); and kidney transplant recipients (KTR). Iron deficiency and erythropoietin deficiency are the most common causes of anaemia in people with CKD, especially those requiring kidney replacement therapy (KRT). The Renal National Service Framework and National Institute for Health and Clinical Excellence in the UK, and Kidney Disease Improving Global Outcomes (KDIGO), all advocate treatment of anaemia in people with CKD. Blood transfusions are infrequently required, and newer therapies such as Hypoxia-Inducible Factor (HIF-PHI) stabilisers are now in current use. This guideline provides evidence based graded practice guidance on the use of iron; comments on iron deficiency without anaemia in people with CKD; provide further information on anaemia management in people with a transplant and provide guidance in the use of the new HIF-PHI drugs. It also provides audit and research recommendations.

Keywords Anaemia, Erythropoietin, Hypoxia inducible factor prolyl hydroxylase, Iron, Kidney, Transplant

Background

Anaemia is a common complication of CKD. It is associated with left ventricular dysfunction and heart failure, in addition to a reduction in exercise capacity and quality of life.

The recent 25th UK Renal Registry report (2021 data) shows that 53.8% of people receiving KRT had a

Hb < 100 g/L. The median haemoglobin (Hb) for kidney transplant recipients, people on peritoneal dialysis (PD) and haemodialysis was 107, 106 and 94 g/L respectively [1].

Indeed, over 20% of people with DD-CKD have a Hb < 90 g/L. In the UK, including Scotland, 20.3% of people receiving in-centre HD had a Hb < 100 g/L and 20.9% had a Hb > 120 g/L; 13.3% had a ferritin < 200 µg/L. The 25th UK Renal Registry report (2021 data) also shows that 22.1% of people receiving PD in the UK had a Hb < 100 g/L and 24.2% had a Hb > 120 g/L. 18.8% had a ferritin < 100 µg/L.

Iron therapies, Erythropoiesis Stimulating Agents (ESAs) and more recently Hypoxia Inducible Factor inhibitors (HIF-PHI) have allowed improved anaemia management in people with CKD (including those on kidney replacement therapy).

*Correspondence:

Sunil Bhandari

Sunil.bhandari@nhs.net

¹Hull University Teaching Hospitals NHS Trust, Hull, UK

²Barts Health NHS Trust, London, UK

³Swansea Bay University Health Board, Swansea, UK

⁴Cardiff and Vale University Health Board, Cardiff, UK

⁵Imperial College Health Care Trust, London, UK

⁶University Hospitals of Leicester NHS Trust, Leicester, UK

⁷New Cross Hospital, Wolverhampton, UK

⁸Nottingham University Hospitals NHS Trust, Nottingham, UK



Hepcidin modulators and ferroportin activator data remains preliminary and none of these agents have received a UK marketing authorisation at the time of publication of this guideline.

Guideline structure

This manuscript provides an overview of the Recommendations made within the guideline with associated rationale. More information can be found in the full guideline document which is provided as a Supplementary appendix. The guideline Working Group provided recommendations on the use of therapies to manage anaemia of chronic kidney disease, how they can be used, research recommendations (what areas of ongoing clinical uncertainty exist) and audit recommendations (how effective implementation can be demonstrated). The group have reviewed the additional evidence from July 2016 using systematic literature searches to identify all published clinical evidence relevant to the review questions, via database (MEDLINE, PUBMED, Embase, and The Cochrane Library) searches using relevant medical subject headings, free-text terms and study-type filters where appropriate.

This guideline update from the previous published 2017 guidance [2] covers the management of anaemia in adults, children and young people with anaemia associated with CKD.

The evidence for these recommendations has been assessed using the modified GRADE system [3, 4]. The modified GRADE system defines both the strength of the recommendations of the guideline authors and the level of evidence upon which each of the recommendations is based (Table 1). This grading system classifies expert

recommendations as “strong” (Grade 1) or “weak” (Grade 2) based upon the balance between the benefits and risks, burden and cost. The quality or level of evidence is designated as high (Grade A), moderate (Grade B), low (Grade C) or very low (D) depending on factors such as study design, directness of evidence and consistency of results. Grades of recommendation and quality of evidence may range from 1 A to 2D.

A summary of all the clinical practice guidelines on anaemia of chronic kidney disease is in Table 2.

Rationale for clinical practice guidelines for anaemia of CKD

Guideline 1.1 - Evaluation of chronic anaemia - Screening for anaemia

We suggest that haemoglobin (Hb) levels should be routinely measured to screen for anaemia:

- At least annually in people with CKD G3
- At least twice a year in people with CKD G4-5 not on kidney replacement therapy (2B)

Rationale

Please see 2017 clinical practice guidelines for rationale, no significant change since then [2].

Guideline 1.2 - Evaluation of anaemia - Haemoglobin level

We recommend that all people with chronic anaemia associated with chronic kidney disease should be investigated for the cause and possible treatment, irrespective of the grade of kidney disease or requirement for kidney replacement therapy if:

- Their haemoglobin (Hb) levels are less than 110 g/L (less than 105 g/L if younger than 2 years), or they develop symptoms attributable to anaemia. This is to ensure the correct diagnosis and management of anaemia. (1 A)

Rationale

Please see 2017 clinical practice guidelines for rationale, no significant change since then [2].

Guideline 1.3 - Evaluation of anaemia - Kidney function

We suggest that CKD should be considered as a possible cause of anaemia when the glomerular filtration rate (GFR) is <60 ml/min/1.73m². It is more likely to be the cause if the GFR is <30 ml/min/1.73m² (<45 ml/min/1.73m² in people with diabetes) and no other cause, e.g., blood loss, folic acid or vitamin B12 deficiency, is identified. (2B)

Table 1 UK kidney association’s grading system for recommendations’ strength and evidence quality level of evidence quality

Grade 1	Recommendation is a strong recommendation to do (or not do) something, where the benefits clearly outweigh the risks (or vice versa) for most, if not all patients (i.e. recommendations)
Grade 2	Recommendation is a weaker recommendation, where the risks and benefits are more closely balanced or are more uncertain (i.e. suggestions)
Grade A	Evidence means high-quality evidence that comes from consistent results from well-performed randomised controlled trials, or overwhelming evidence of some other sort
Grade B	Evidence means moderate-quality evidence from randomised trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strength
Grade C	Evidence means low-quality evidence from observational studies, or from controlled trials with several very serious limitations
Grade D	Evidence is based only on case studies or expert opinion

Table 2 Summary of recommendations for use

Guideline	TITLE	COMMENT	Grade
1.1	Evaluation of Chronic Anaemia - Screening for Anaemia	We suggest that haemoglobin (Hb) levels should be routinely measured to screen for anaemia: • At least annually in people with CKD G3 • At least twice a year in people with CKD G4-5 not on kidney replacement therapy	2B
1.2	Evaluation of Anaemia - Haemoglobin Level	We recommend that all people with anaemia associated with chronic kidney disease should be investigated for the cause and possible treatment, irrespective of the grade of kidney disease or requirement for kidney replacement therapy if: • Their haemoglobin (Hb) levels are less than 110 g/L (less than 105 g/L if younger than 2 years), or they develop symptoms attributable to anaemia. This is to ensure the correct diagnosis and management of anaemia.	1 A
1.3	Evaluation of Anaemia - Kidney Function	We suggest that CKD should be considered as a possible cause of anaemia when the glomerular filtration rate (GFR) is < 60 ml/min/1.73m ² . It is more likely to be the cause if the GFR is < 30 ml/min/1.73m ² (< 45 ml/min/1.73m ² in people with diabetes) and no other cause, e.g., blood loss, folic acid or vitamin B12 deficiency, is identified.	2B
1.4	Evaluation of Anaemia - Erythropoietin Measurement	We recommend that measurement of erythropoietin levels should <i>NOT</i> routinely be considered for the diagnosis or management of anaemia for people with CKD.	1 A
1.5	Evaluation of Anaemia – Baseline Investigations	We recommend that initial clinical and laboratory evaluation of anaemia should be performed prior to initiation of treatment for anaemia in people with CKD	1 A
1.5.1		We recommend that laboratory evaluation should include the following tests • Full blood count (FBC) in addition to the Hb concentration • Red blood cell indices: • Mean corpuscular haemoglobin [MCH] • Mean corpuscular volume [MCV] • Mean corpuscular haemoglobin concentration [MCHC] • White blood cell count and differential count • Platelet count • Absolute reticulocyte count to assess bone marrow responsiveness (if indicated) Tests to Determine Iron Status: • Percentage of hypochromic red blood cells (% HRC), but only if processing of blood sample is possible within 6 h or • Reticulocyte Hb count (CHr) or equivalent tests e.g., reticulocyte Hb equivalent (RET-He) or • Combination of transferrin saturation (TSAT) and serum ferritin if the above tests are not available or the person has thalassemia or thalassemia trait • Serum ferritin to assess iron stores Plasma/serum C-reactive protein (CRP) to assess possible Inflammation	1B
1.5.2		Based on initial assessment, we recommend the following tests to diagnose the cause of anaemia in selected cases: • Serum B12 and serum folate concentrations • Tests for haemolysis (plasma/serum levels of haptoglobin, lactate dehydrogenase, bilirubin, Coombs' test) • Plasma/serum and/or urine protein electrophoresis • Hb electrophoresis • Free light chains and bone marrow examination	1B
2.1	Treatment of Anaemia with Iron therapy – Iron Repletion	We recommend that people should be iron replete to achieve and aim to maintain target Hb range, whether receiving ESA or HIF-PHI or not Iron repletion is usually defined as: • %HRC < 6% / CHr or RET-He > 31 pg / ferritin and TSAT (> 100 µg/L and > 20%) in people with non-dialysis dependent CKD (NDD-CKD) or on PD and > 200 µg/L in people on HD. (2B) • A target ferritin level greater than 100 µg/L for children with CKD on dialysis as well as children with CKD not on ESA or HIF-PHI therapy. (not graded) • In ensuring iron repletion, iron should be considered when ferritin is < 500 mcg/L and/or the TSAT < 30%.	1B
2.2	Treatment of Anaemia with Iron Therapy - Initiation of ESA/ HIF-PHI and Iron Status	We recommend that people on ESA or HIF-PHI therapy should remain iron replete before and during therapy either with oral iron or intravenous iron.	1B

Table 2 (continued)

Guideline	TITLE	COMMENT	Grade
2.2.1		We recommend that ESA or HIF-PHI therapy should not be initiated in the presence of absolute iron deficiency (ferritin < 100 mcg/L in NDD-CKD and < 200 mcg/L in DD-CKD) or functional Iron deficiency (TSAT < 20% with normal or elevated ferritin levels) until this is corrected and anaemia persists. Iron supplements should be given prior to or when initiating ESA or HIF-PHI therapy.	1B
2.2.2		We suggest that to define functional iron deficiency (FID) ("iron restricted erythropoiesis"), a TSAT < 20% and a normal or elevated ferritin in people with NDD-CKD or maintained on PD and in those receiving HD be used. Normal or high serum ferritin values do not exclude iron deficiency, as it could be due to other causes such as infection or inflammation	2B
2.3		Treatment of Anaemia with Iron Therapy - Route of Administration: We suggest that for people with CKD not requiring HD, or people currently receiving PD who are being considered for ESA therapy, intravenous iron should be considered to reduce ESA dose requirements	2B
2.3.1		We suggest for people with NDD-CKD or maintained on PD (i.e. not requiring HD), the choice between oral vs. parenteral iron depends on a shared decision and should include the impact of the severity of iron deficiency, the previous response and side effects, the availability of venous access and the need to initiate ESA or HIF-PHI therapy.	2 A
2.3.2		We recommend that most people receiving haemodialysis will require IV iron.	1 A
2.3.3		We suggest when offering IV iron therapy to people not receiving in-centre HD, consider high dose, low frequency (HiD/LF) IV iron as the treatment of choice for adults and young people when trying to achieve iron repletion, considering all the following • Availability of venous access • Preferences of the person with anaemia of CKD or, where appropriate, their family or carers • Nursing and administration costs • Cost of local drug supply • Provision of resuscitation facilities	2B
2.3.4		We suggest the frequency of administration of HiD/LF IV iron for people with CKD not requiring HD and for people receiving PD needs to be tailored for each person as there are no clear data.	Not graded
2.4	Treatment of Anaemia with Iron Therapy - Upper Limit for Iron Therapy	For people not on HD, we recommend that serum ferritin should not exceed 600 mcg/L in those treated with iron. To achieve this, iron management should be reviewed when ferritin is > 500 mcg/L, recognising that a level of > 800 mcg/L may reflect iron toxicity.	1B
2.4.1		For people receiving HD, we recommend that proactive high-dose IV iron, initially 600 mg in divided doses in the first month and then 400 mg every month (or equivalent), should be given unless ferritin > 700 mcg/L or TSAT > 40%.	1 A
2.4.2		We suggest a tailored approach by clinicians to assess the risk and benefit of starting a proactive IV iron protocol in people who have been established on HD for > 12 months.	2B
2.5	Treatment of Iron Deficiency without Anaemia:	We recommend for people with CKD with iron deficiency without anaemia and concomitant heart failure, administration of IV iron to improve well-being, physical function and to reduce heart failure admissions.	1 A
2.5.1		We suggest for people with CKD with iron deficiency but without anaemia and no concomitant heart failure, a trial of oral or IV iron for improvement in clinical symptoms such as restless legs	2B
2.6	Administration of IV Iron - Safety	We recommend that resuscitative medication and personnel trained to evaluate and resuscitate be present in the event of anaphylaxis at each administration of intravenous iron.	1 A
2.6.1		We recommend avoiding parenteral iron therapy in people with active infection.	1 C
2.6.2		We suggest avoiding iron therapy in people with the following conditions. • Hepatitis C virus infection (Positive PCR test) • Hepatitis B • Haemochromatosis both Primary and secondary	Not graded
2.6.3		We suggest caution in prescribing parenteral iron in people with • Chronic liver disease • Heterozygous for any of the haemochromatosis genes (C282Y (c.845G > A), H63D (c.187 C > G) and S65C (c.193 A > T)).	Not graded
2.6.4		We suggest choice of parenteral iron be tailored, considering the benefits and risks associated with available iron preparations.	2 C
2.7	Monitoring of Treatment - Iron Therapy	We recommend regular monitoring of iron status (every 1–3 months) in people receiving intravenous iron to avoid toxicity (defined as a serum ferritin of > 800 mcg/L or TSAT > 40%).	1B
2.7.1		We recommend that a serum ferritin consistently > 800 mcg/L with no evidence of inflammation (normal CRP) is suggestive of iron overload or potential toxicity.	1B

Table 2 (continued)

Guideline	TITLE	COMMENT	Grade
3.1	Investigations Before Initiating ESA Therapy	We recommend that all correctable causes of anaemia should be ruled out before considering treatment with ESAs.	1B
3.2	Treatment of Anaemia with Iron Therapy - Initiation of ESA and Iron Status	We recommend that ESA therapy should NOT be initiated in the presence of absolute iron deficiency, (ferritin < 100 mcg/L in people with non-dialysis dependent CKD (NDD-CKD) and < 200 mcg/L in people who are dialysis dependent) until this is corrected and it is determined that anaemia persists, in conjunction with a shared decision of the advantages and risks of ESA therapy. In people with functional iron deficiency, iron supplements should be given prior to or when initiating ESA therapy	1B
3.3	Treatment of Anaemia - Erythropoiesis Stimulating Agents	We recommend that treatment with ESAs should be offered to people with anaemia of CKD, in conjunction to a shared decision of the advantages and risks, who are likely to benefit in terms of quality of life and physical function and to avoid blood transfusion; especially in people considered suitable for transplantation.	1B
3.4	Treatment of Anaemia with ESA therapy - Target Haemoglobin Range	We recommend that people with non-dialysis dependent CKD (NDD-CKD) or those receiving dialysis, who are on ESA therapy, should achieve Hb between: • 100 and 120 g/L in adults, young people and children aged 2 years and older. • 95 and 115 g/L in children younger than 2 years of age (reflecting the lower normal range in that age).	1B 2B
3.5	Treatment of Anaemia without ESA Therapy - Target Haemoglobin Range	We suggest that this Hb target range applies exclusively to people with CKD receiving ESAs and is not intended to apply to the treatment of iron deficiency in people receiving iron therapy without the use of ESAs.	2B
3.6	Treatment of Anaemia - Choice of ESA	We recommend that the choice of ESA is based on local availability and cost of ESAs	1B
3.7	Treatment of Anaemia - Initial ESA Dose	We suggest that the initial ESA dose (whether short acting - epoetin alpha or beta, or long acting - darbepoetin alfa and methoxy polyethylene glycol-epoetin beta) should be determined by the individual's Hb level, the desired target Hb range, the observed rate of increase in Hb level and clinical circumstances.	2B
3.8	Treatment of Anaemia with ESA Therapy - Route of Administration	We suggest that the route of ESA administration should be determined by the CKD grade, individual recipient preference, treatment setting, efficacy, safety, and class of ESA used. Subcutaneous (SC) use is preferable in people who are not receiving HD to avoid puncture of peripheral veins. In some circumstances – such as individuals requiring high doses of IV ESA – use of subcutaneous ESA can be considered for patients on haemodialysis due to evidence suggesting greater efficacy with this route.	2B
3.9 -	Treatment of Anaemia with ESA Therapy - Frequency of Administration	We suggest that the frequency of administration should be determined by the CKD grade, person preference, treatment setting and class of ESA. Less frequent administration using long-acting ESAs may be the treatment of choice in people with CKD not on haemodialysis.	2B
3.10	Treatment of Anaemia with ESA Therapy - ESA Dose Adjustments	We recommend that adjustments to ESA doses should be considered when Hb is < 105 or > 115 g/L in adults, young people and children aged 2 years and older	1 A
3.10.1		We suggest these thresholds for intervention should achieve a population distribution centered on a mean of 110 g/L with a range of 100–120 g/L.	2B
3.10.2		We suggest in children younger than 2 years to keep the Hb level within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment (for example, act when Hb levels are within 5 g/L of the range's limits).	Not graded
3.10.3		We suggest that ESA doses should ideally be decreased rather than withheld when a downward adjustment of Hb level is desirable	2B
3.11	Treatment of Anaemia with ESA Therapy - Specific Situations	We suggest that ESA administration in ESA-dependent people should continue during acute illness, surgical procedure, or any other cause of hospitalisation, unless there is a clear contra-indication (for example, acute stroke or vascular access thrombosis).	2B
3.12	Caution in Prescribing ESA in Certain People with CKD	We suggest exerting caution while prescribing ESA therapy in people with CKD with a history of stroke, or malignancy, particularly in those with active malignancy when cure is the anticipated outcome.	2 C

Table 2 (continued)

Guideline	TITLE	COMMENT	Grade
3.13	Monitoring of ESA Treatment - Haemoglobin during ESA Therapy	We suggest that Hb concentration should be monitored every 2–4 weeks in the correction phase or after a dose adjustment and every 1–3 months for stable individuals in the maintenance phase of ESA treatment. More frequent monitoring will depend on clinical circumstances	2B
3.14	Monitoring of ESA Treatment - Resistance to ESA Therapy	We recommend that inadequate response ('resistance') to ESA therapy is defined as failure to reach the target Hb range despite SC epoetin dose > 300 IU/kg/week (450 IU/kg/week IV epoetin), or darbepoetin dose > 1.5 mcg/kg/week, or equivalent dose of methoxy ethylene glycol epoetin beta following investigation and treatment of other causes	1 A
3.14.1		We suggest that clinicians consider accepting lower aspirational haemoglobin target ranges in those on high, escalating ESA doses with inadequate response, or consider alternative therapy such as a trial use of HIF-PHI.	2 C
3.15	Monitoring of ESA Treatment - Evaluation for ESA Induced Pure Red Cell Aplasia	We recommend that a diagnosis of ESA induced pure red cell aplasia (PRCA) should be considered whenever a person receiving long term ESA therapy (> 8 weeks) develops all the following A sudden decrease in Hb concentration at the rate of 5 to 10 g/L per week or requirement of transfusions at the rate of approximately 1 to 2 per week • Normal platelet and white cell count. • Absolute reticulocytes count less than 10,000/μl • High serum ferritin level	1 A
3.15.1		We recommend that all ESA therapy should be stopped in people who develop ESA-induced PRCA.	1 A
3.15.2.		We recommend that individuals who remain transfusion dependent after withdrawing ESA therapy should be treated with immunosuppressant medications guided by the level of anti EPO antibodies	1B
3.15.3		We do not recommend routine screening for anti-erythropoietin antibodies among people with CKD regularly treated with ESAs.	1B
3.16	Monitoring of ESA treatment - Hypertension during ESA therapy	We recommend that blood pressure should be monitored in all people receiving ESAs and, if present, hypertension be treated by volume removal and/or antihypertensive drugs	1 A
4.1	Treatment of Anaemia - HIF-PHI Agents	We recommend that treatment with HIF-PHI agents should be offered after iron repletion, to people with symptomatic anaemia (Hb < 105 g/L) of CKD (stages 3–5 (eGFR < 60 ml/min/1.73m ²)) who are not receiving dialysis at the start of therapy and who are likely to benefit in terms of quality of life and physical function and to avoid blood transfusion; especially in people considered suitable for transplantation.	1B
4.1.1	Treatment of Anaemia - DD-CKD and HIF-PHI Agents	We suggest that that treatment with HIF-PHI agents should be considered after iron repletion, to people with DD-CKD and symptomatic anaemia (Hb < 105 g/L) who are likely to benefit in terms of quality of life and physical function and to avoid blood transfusion; especially in people considered suitable for transplantation	2B
4.1.2	Treatment of Anaemia - People intolerant to ESA	We suggest that that treatment with HIF-PHI agents should be considered, after iron repletion, to people who are intolerant to ESA therapy.	2 C
4.1.3	Choosing between ESA and HIF-PHI therapy for people with non-dialysis dependent CKD and DD-CKD	We suggest, when deciding between ESA and HIF-PHI therapy for people with non-dialysis dependent CKD or DD-CKD, considerations include the preference of the person with anaemia of CKD, or, where appropriate, their family or carers; the cost of local drug supply, nursing and administration costs and previous treatment with ESA or HIF-PHI.	2B
4.2	Treatment of Anaemia	We suggest that HIF-PHI administration in HIF-PHI-dependent people should continue during acute illness, surgical procedures or any other cause of hospitalisation, unless there is a clear contra-indication such as accelerated hypertension or thrombosis.	2 C
4.3	Treatment of Anaemia with HIF- PHI therapy - Target Haemoglobin	We suggest that people over the age of 18 years with NDD-CKD on HIF-PHI therapy should achieve a Hb between: • 100 and 120 g/L in adults and young people, like ESA therapy • In children and those younger than 2 years of age no data is currently available	Not graded 2B Not graded

Table 2 (continued)

Guideline	TITLE	COMMENT	Grade
4.3.1		We suggest that people over the age of 18 years with DD-CKD on HIF-PHI therapy should achieve a Hb between: • 100 and 120 g/L in adults and young people like ESA therapy but this may depend on the choice of HIF-PHI where a Hb of 100–110 g/L is recommended. • In children and those younger than 2 years of age no data is currently available	2B
4.4	Treatment of Anaemia - Initial HIF-PHI dose	We recommend that the initial HIF-PHI dose should be based on the person's weight, Hb level and the observed rate of increase in Hb level, and clinical circumstances. The appropriate dose should follow label recommendations until further data is available.	1B
4.4.1		We suggest that the starting HIF PHI dose should be lower for those who are ESA-naïve versus those who are not.	2B
4.5	Treatment of Anaemia with HIF-PHI therapy - Frequency of Administration	We suggest that the frequency of administration should be determined by the response to therapy to maintain the desired Hb target range of 100–120 g/L.	2B
4.6	Treatment of Anaemia with HIF-PHI Therapy - Dose Adjustments	We suggest that adjustments to HIF-PHI doses should be considered when Hb is < 105 or > 115 g/L in adults to balance the benefit and safety to people given the current evidence base	2B
4.7	Prescribing HIF-PHI in Sub-Groups of People with CKD	We recommend that HIF-PHI should be avoided or used cautiously in people with active malignancy.	1B
4.7.1		We recommend that HIF-PHI should be avoided or used cautiously in people with autosomal dominant polycystic kidney disease until further data are available.	1D
4.7.2		We recommend that HIF-PHI should be avoided or used cautiously in people with a history of seizures.	1B
4.7.3		We recommend caution in using HIF-PHI in people with uncontrolled hypertension.	1B
4.7.4		We recommend caution in using HIF-PHI therapy in people with diabetic retinopathy.	1D
4.7.5		We recommend caution in people with a history of thrombotic events following the SmPC for contra-indications	1 A
4.7.6		We suggest that HIF-PHI may be considered in people with hyporesponsiveness to ESA therapy or underlying inflammation, but further high-quality randomised trials are needed to confirm its effectiveness	2 C
4.8	Safety of HIF-PHI	We suggest the cautious use of HIF-PHI in people with CKD and either known CVD or thrombotic events and consideration of lower dose regimes to reduce rapid rises in Hb.	2 C
4.9	Monitoring Response to HIF-PHI	We recommend that Hb levels should be monitored every two weeks until the desired Hb target range of 100 to 120 g/L is achieved and stabilised, and every 4 weeks thereafter, or as clinically indicated	1B
5.1	Blood Transfusion in People with Anaemia of CKD	We recommend that in people with anaemia of CKD, especially those in whom kidney transplantation is an option, red blood cell transfusion should be avoided, if possible, to minimise the risk of allosensitisation	1 A
5.1.1		We recommend that if red blood cell transfusion becomes essential (usually in the setting of acute blood loss, acute haemolysis or severe sepsis), transfusion should be based on policies set by local transfusion guidelines rather than Hb target range for ESA therapy in anaemia of CKD.	1B
5.1.2		We suggest using single unit transfusion, where possible, for stable non-bleeding people with CKD who clinically require transfusion	2B
5.1.3		We suggest that kidney transplant recipients, those on the transplant waiting list or people on immuno-suppressive therapy should receive only hepatitis E negative blood components (all UK blood components are tested), but neither CMV negative nor irradiated blood is required.	2B
6.1	Peri-Transplant Anaemia:	We suggest that anaemia management should be optimal pre-transplant in all people with CKD on the transplant wait-list, to minimise the risk of a post-transplant transfusion.	2B
6.1.1		We suggest that for people with CKD undergoing kidney transplantation, ESA therapy may be continued, after a shared decision with the patient taking account of risks and benefits, until endogenous EPO production is sufficient to maintain Hb concentrations. For HIF-PHI therapy we make no recommendation until further data are available.	2 C
6.2	Blood Transfusion	We suggest for stable non-bleeding individuals who clinically require a red cell transfusion, use single unit transfusion, where possible.	2B

Table 2 (continued)

Guideline	TITLE	COMMENT	Grade
6.3	Post-Transplant Anaemia:	We suggest that consideration is given to identify (and correct) reversible transplant-specific causes of anaemia	2B
6.3.1		We recommend that the treatment guidelines for anaemia in kidney transplant recipients should be like those for people with CKD not on dialysis (NDD-CKD).	1B
6.3.2		We suggest for stable non-bleeding individuals who clinically require a red cell transfusion, use single unit transfusion, where possible	2B
6.3.3		We suggest the use of HIF-PHI therapy in transplant recipients should be as in people with NDD-CKD.	2B
7.1	Malignancy	We suggest treating symptomatic anaemia in people with CKD and cancer when Hb < 100 g/L	2B
7.2	Haematological Disease	We suggest ESA therapy be considered in people with myelodysplastic syndrome (MDS), myeloma and others with CKD and haematological disease. We make no recommendations on HIF-PHI therapy.	Not graded
7.3	Pregnancy	We recommend that pregnant and post-partum women with CKD are given parenteral iron, if indicated, from the second trimester onwards, if the benefit is judged to outweigh the potential risk for the mother and fetus and according to SmPC guidance.	1 C
7.3.1		We recommend that ESA therapy during pregnancy be continued unless there is a major contra-indication (e.g., hypertension or thrombosis risk).	2 C

Rationale

Please see 2017 clinical practice guidelines for rationale, no significant change since then [2].

Guideline 1.4 - Evaluation of anaemia - Erythropoietin measurement

We recommend that measurement of erythropoietin levels should NOT routinely be considered for the diagnosis or management of anaemia for people with CKD. (1 A)

Rationale

Please see 2017 clinical practice guidelines for rationale, no significant change since then [2].

Guideline 1.5 - Evaluation of anaemia – Baseline investigations

We recommend that initial clinical and laboratory evaluation of anaemia should be performed prior to initiation of treatment for anaemia in people with CKD. (1 A)

Guideline 1.5.1

We recommend that laboratory evaluation should include the following tests (1B):

- Full blood count (FBC) including—in addition to the Hb concentration:
- Red blood cell indices:
- Mean corpuscular haemoglobin [MCH]
- Mean corpuscular volume [MCV]
- Mean corpuscular haemoglobin concentration [MCHC])
- White blood cell count and differential count
- Platelet count
- Absolute reticulocyte count to assess bone marrow responsiveness (if indicated)

- Percentage of hypochromic red blood cells (% HRC), but only if processing of blood sample is possible within 6 h or
- Reticulocyte Hb count (CHr) or equivalent tests e.g., reticulocyte Hb equivalent (RET-He) or
- Combination of transferrin saturation (TSAT) and serum ferritin if the above tests are not available or the person has thalassemia or thalassemia trait
- Serum ferritin to assess iron stores
- Plasma/serum C-reactive protein (CRP) to assess possible inflammation

Guidelines 1.5.2

Based on the initial assessment we recommend in selected cases; the following tests may be useful to diagnose the cause of anaemia (1B):

- Serum B12 and serum folate concentrations
- Tests for haemolysis (plasma/serum levels of haptoglobin, lactate dehydrogenase, bilirubin, Coombs' test)
- Plasma/serum and/or urine protein electrophoresis
- Hb electrophoresis
- Free light chains and bone marrow examination

Rationale

Please see 2017 clinical practice guidelines for rationale, no significant change since then [2].

Guideline 2.1 - Treatment of anaemia with iron therapy – Iron repletion

We recommend that people should be iron replete to achieve and maintain target Hb range, whether receiving ESA or HIF PHI or not. (1B)

Iron repletion is usually defined as:

Tests to Determine Iron Status:

- %HRC < 6% / CHr or RET-He > 31 pg / ferritin and TSAT (> 100 µg/L and > 20%) in people with non-dialysis dependent CKD (NDD-CKD) or on PD, and > 200 µg/L in people receiving HD. (2B)
- Aim for a target ferritin level greater than 100 µg/L for children with CKD receiving dialysis as well as children with CKD not on ESA or HIF-PHI therapy. (not graded)
- To ensure iron repletion, iron therapy should be considered when ferritin is < 500 mcg/L and/or the TSAT < 30%.

Rationale

The definition of “adequate” iron status [5] is:

- Serum ferritin
 - 200–700 µg/L in people receiving HD
 - 100–600 µg/L in people with NDD-CKD and
- HRC < 6%, or CHr / RET-He > 31 pg
- TSAT 20–40%

The aim of iron treatment targets is to:

1. Minimise the ESA or HIF PHI doses required to maintain target Hb levels in those on ESA or HIF PHI therapy
2. Maximise the Hb level and minimise the need to initiate ESA or HIF PHI therapy to achieve target-range Hb levels in those not on ESA or HIF PHI therapy and;
3. Minimise potential iron toxicity

During ESA or HIF-PHI induction therapy, iron requirements will depend on the rate of erythropoiesis, the Hb deficit and ongoing iron losses. Once the target Hb has been reached and Hb stabilised, iron requirements will be dependent on ongoing iron losses. When adequate iron status is achieved, those on ESA or HIF-PHI therapy should be given maintenance iron treatment as required.

Several studies have demonstrated an inverse relationship between iron stores and the erythropoiesis-stimulating agent (ESA) dose required to achieve and maintain a target haemoglobin (Hb) level [6–11]. Evidence supporting the recommendation to maintain transferrin saturation (TSAT) above 20% comes from a randomised controlled trial (RCT) where participants targeting a TSAT of 30–50% required 40% less ESA compared to those targeting a TSAT of 20–30% [12]. In another study evaluating TSAT and serum ferritin in 47 haemodialysis patients with baseline serum ferritin < 600 mcg/L, participants received intravenous iron dextran (1000 mg over ten haemodialysis sessions). Iron

deficiency was defined as either a $\geq 5\%$ increase in haematocrit or a $\geq 10\%$ reduction in erythropoietin dose within two months. Receiver operator curve (ROC) analysis found that none of the iron indices demonstrated both sensitivity and specificity > 80%. The study concluded that TSAT and serum ferritin should be interpreted alongside the patient's erythropoietin responsiveness. For erythropoietin-responsive participants, TSAT < 18% or serum ferritin < 100 mcg/L indicates inadequate iron, while in erythropoietin-resistant individuals, thresholds of TSAT < 27% or serum ferritin < 300 mcg/L are recommended to guide iron management [13].

Reticulocyte haemoglobin content (CHr) has emerged as a reliable marker for iron status, particularly in haemodialysis (HD) patients with chronic kidney disease (CKD). In a randomised controlled trial of 157 HD participants, CHr proved significantly more stable than serum ferritin and transferrin saturation, allowing for effective iron management that maintained comparable haematocrit levels and epoetin dosing while reducing intravenous iron exposure [14]. Low CHr (< 26 pg) has been shown to indicate functional iron deficiency, with one study demonstrating that a baseline CHr < 26 pg predicted iron deficiency with 100% sensitivity and 80% specificity, outperforming other markers such as ferritin, transferrin saturation, and percentage of hypochromic red blood cells [15]. Tessitore et al. highlighted that although percentage hypochromia > 6% was the most accurate marker of responsiveness to intravenous iron, CHr had a diagnostic efficiency of 78% at a cut-off of ≤ 29 pg [16]. Similarly, a study in Sri Lanka suggested that increasing the CHr cut-off for iron repletion from 29 pg to 31 pg improved both sensitivity and specificity, further supporting its utility as a diagnostic tool [17]. These findings underscore the potential of CHr to optimise iron management in CKD and HD populations.

NICE guidelines for the evaluation of iron therapy in people with CKD suggests that for people on haemodialysis, %HRC > 6% dominated all other iron evaluation strategies (leading to more QALYs and lower cost) [5]. For people not on HD, TSAT < 20% alone or serum ferritin < 100 mcg/L alone were the least cost-effective strategy. %HRC was the most cost-effective [5].

To determine iron status and predict response to iron therapy, NICE guidelines on anaemia management in people with CKD suggest to:

- Use percentage of hypochromic red blood cells (% HRC; > 6%), but only if processing of blood sample is possible within 6 h. Since a fresh blood sample is needed, this test may be difficult to use routinely in clinical practice.
- If using percentage of hypochromic red blood cells is not possible, use reticulocyte Hb content (CHr < 31

pg or equivalent tests – for example, reticulocyte Hb equivalent.

- If these tests are not available or the person has thalassaemia or thalassaemia trait, use a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 µg/L).

We believe that CHr (<31 pg) is more sensitive in determining iron depletion than %HRC [14–18] because CHr reflects haemoglobin content of young reticulocytes, therefore reflecting iron availability in the preceding few days; while %HRC reflects haemoglobin contents of the whole erythrocyte pool, and since senescent erythrocytes tend to get smaller in volume, the test may be affected by the overall rate of erythropoiesis.

- If neither test is available, we recommend testing both serum ferritin and transferrin saturation rather than relying on either test separately unless the serum ferritin is <100 mcg/L and suggests absolute iron deficiency [5, 13].
- For children, a target ferritin >100 mcg/L for dialysis and NDD-CKD, not on ESA therapy is appropriate [19]. There is no evidence that a higher ferritin target of 200 mcg/L is beneficial or safe in paediatric HD.

Guideline 2.2 - Treatment of anaemia with iron therapy - Initiation of ESA/HIF-PHI and iron status

We recommend that people on ESA or HIF-PHI therapy should remain iron replete before and during therapy either with oral iron or intravenous iron. (1B)

Guideline 2.2.1

We recommend that ESA or HIF-PHI therapy should not be initiated in the presence of absolute iron deficiency (ferritin <100 mcg/L in NDD-CKD and <200 mcg/L in DD-CKD) or functional Iron deficiency (TSAT <20% will normal or elevated ferritin levels) until this is corrected and anaemia persists. Iron supplements should be given prior to or when initiating ESA or HIF-PHI therapy. (1B)

Guideline 2.2.2

We suggest that to define functional iron deficiency (FID) (“iron restricted erythropoiesis”), a TSAT <20% in people with NDD-CKD or maintained on PD, and in those receiving HD be used. Normal or high serum ferritin values do not exclude iron deficiency, as it could be due to other causes such as infection or inflammation. (2B)

Rationale

Iron is required for production of new red cells. Iron must be supplied to the erythropoietic tissue at an adequate rate, particularly if stimulated by ESA or HIF-PHI therapy.

- For people with CKD on dialysis (DD-CKD), percentage of HRC >6%, or CHr/RET-He <31 pg are ideal test to assess iron status.
- If these tests are not available or the person has thalassaemia or thalassaemia trait, a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 mcg/L) could be a suitable alternative [5].

A consistent finding in the series of trials using HIF-PHI (Roxadustat) was the effect on iron metabolism. In the non-dialysis trials against placebo (ANDES, ALPS and OLYMPUS), there was a 50% reduction in the requirement for IV iron use, such that the monthly dose of iron required was significantly reduced [20–22]. This suggests that HIF-PHI therapy may simultaneously correct anaemia and iron depletion. In the DOLOMITES trial, the use of either IV or oral iron was also reduced in the Roxadustat vs. darbepoetin alfa groups [23].

In some trials that assessed the impact of HIF-PHI on iron use, iron protocols differed between treatment and comparator groups within a trial, while other trials tested similar iron protocols [24–26]. Other potential trial design limitations included differences in Hb targets and the actual achieved Hb between treatment arms, differences in the proportion of participants with baseline iron deficiency and baseline imbalances in iron and hepcidin status and potentially relevant co-morbidities. Therefore, further data from randomised controlled trials is needed to confirm these secondary findings on iron utilisation before definitive guidance can be given.

Iron parameters should be monitored during treatment with HIF-PHI therapy and iron deficiency should be avoided because it is associated with thromboembolic events, impaired red blood cell production [27], lower health related quality of life (HRQoL), higher rates of cardiovascular events and higher mortality [28].

Guideline 2.3 - Treatment of anaemia with iron therapy - Route of administration

We suggest that for people with CKD not requiring HD, or people currently receiving PD who are being considered for ESA therapy, intravenous iron should be considered to reduce ESA dose requirements. (2B)

Guideline 2.3.1

We suggest for people with NDD-CKD or maintained on PD (i.e. not requiring HD), the choice between oral vs. parenteral iron depends on a shared decision and should include the impact of the severity of iron deficiency, the previous response and side effects, the availability of venous access and the need to initiate ESA or HIF-PHI therapy. (2 A)

Guideline 2.3.2

We recommend that most people on haemodialysis require IV iron. (1 A)

Guideline 2.3.3

We suggest when offering IV iron therapy to people not receiving in-centre HD, to consider high dose, low frequency (HiD/LF) IV iron as the treatment of choice for adults and young people when trying to achieve iron repletion, considering all the following (2B):

- Availability of venous access
- Preferences of the person with anaemia of CKD or, where appropriate, their family or carers
- Nursing and administration costs
- Cost of local drug supply
- Provision of resuscitation facilities

Guideline 2.3.4

We suggest the frequency of administration of HiD/LF IV iron for people with CKD not requiring HD and for people receiving PD needs to be tailored for each person as there is no clear data. (not graded)

Rationale

The evidence supporting intravenous (IV) iron over oral iron in individuals with chronic kidney disease (CKD) who are pre-dialysis or on peritoneal dialysis (PD) is limited. Oral iron, when tolerated, is generally sufficient for most patients, particularly when used alongside erythropoiesis-stimulating agent (ESA) therapy. However, in cases where patients are resistant to ESA therapy with oral iron or intolerant to oral supplementation, a therapeutic trial of IV iron may be warranted.

One randomised study of 188 pre-dialysis participants compared IV iron (1000 mg iron sucrose in divided doses over 14 days) with oral iron (ferrous sulphate 325 mg three times daily) and found greater improvements in haemoglobin (Hb) in the IV iron group, with more participants achieving an Hb increase of >10 g/L. However, there was no difference in the proportion of participants requiring ESA initiation during the study [29]. Two additional studies in pre-dialysis populations not receiving ESAs also demonstrated improved Hb outcomes following IV iron therapy, including one study that assessed IV iron after oral iron therapy (30–31).

Oral iron remains an inexpensive and simple treatment option but switching to IV iron is reasonable in patients with CKD who do not respond to or cannot tolerate oral iron. Two randomised controlled trials (RCTs) comparing oral and IV iron supplementation in participants with advanced non-dialysis-dependent CKD (NDD-CKD) receiving concomitant ESA therapy found no significant differences in Hb or ESA dose requirements between

groups. The first study of 45 participants (Hb <110 g/L) compared ferrous sulphate 200 mg three times daily with monthly IV iron sucrose 300 mg over 5.2 months and reported similar Hb outcomes, although iron stores were greater in the IV group. Confounding factors included a higher prevalence of diabetes and ACEi/ARB use in the oral iron group [32]. Similarly, a second study of 96 participants compared 5 weeks of IV iron sucrose (200 mg weekly) with 29 days of oral ferrous sulphate 325 mg three times daily. Again, Hb and ESA dose requirements were comparable, but ferritin levels increased more in the IV group, which also had fewer gastrointestinal side effects, such as constipation (34.5% vs. 12.5%) and nausea (10.4% vs. 4.2%) [33].

Iron dosing strategies vary between high-dose, low-frequency (HiD/LF) regimens—defined as a maximum of two infusions with at least 500 mg iron per infusion—and low-dose, high-frequency (LD/HF) regimens, which involve more than two infusions, typically with 100–200 mg iron per dose. It is important to note that as of publication, IV iron products in the UK do not have marketing authorisation for all paediatric and adolescent age groups for this indication. Clinicians should refer to the SmPC for specific iron preparations.

Compelling data from a recent RCT demonstrates that third-generation iron products, such as ferric carboxymaltose and iron isomaltoside, are less prone to causing iron deposition in the liver and spleen compared to traditional iron therapies like iron sucrose. In a study involving 54 dialysis patients, liver iron concentration (LIC) was assessed using MRI across different iron treatments. Patients receiving 1.2–2.4 g of IV iron sucrose experienced a significant increase in LIC ($p < 0.001$), whereas no significant changes were observed in those treated with ferric carboxymaltose or iron isomaltoside ($p > 0.05$). The absolute differences in LIC after therapy were markedly higher in the iron sucrose groups, reaching 25 $\mu\text{mol/g}$ in the 1.2 g group and 35 $\mu\text{mol/g}$ in the 2.4 g group, compared to just 5 $\mu\text{mol/g}$ in the ferric carboxymaltose and iron isomaltoside groups ($p < 0.0001$). Furthermore, the increase in abnormal LIC was mainly seen in patients treated with iron sucrose, with a significant rise in group A (1.2 g) and group B (2.4 g) ($p = 0.001$ and $p = 0.0001$, respectively), whereas no significant changes occurred in the groups treated with ferric carboxymaltose and iron isomaltoside. This evidence suggests that third-generation iron formulations are associated with less iron deposition in the liver, highlighting their potential benefits in long-term management of iron deficiency in dialysis patients [34].

A retrospective study evaluated the effectiveness, safety, and cost-effectiveness of IV ferric carboxymaltose (FCM) in people on HD with iron deficiency anaemia (IDA) who were unresponsive or intolerant to IV ferric gluconate

(FG) while receiving ESAs. Seventy-seven patients (mean age 68 ± 15 years) were switched from FG to FCM, and key iron status parameters, ESA usage, and economic outcomes were assessed over six months. The erythropoietin resistance index (ERI) decreased from 24.2 ± 14.6 pre-switch to 20.4 ± 14.6 after six months of FCM, indicating improved ESA responsiveness. Haemoglobin (Hb) levels of ≥ 10.5 g/dL were observed in 75.3% of patients post-switch, compared to 61% pre-switch ($p=0.042$), with a 1 g/dL Hb increase seen in 26% of patients. Additionally, there was a 37.7% increase in patients achieving transferrin saturation (TSAT) $> 20\%$. FCM treatment led to a sustained increase in Hb, TSAT, and ferritin levels while reducing ESA requirements. A mixed-model analysis confirmed these findings. Safety outcomes were favourable, with no hypersensitivity reactions and only one reported adverse event. Moreover, FCM treatment resulted in a cost saving of €11.11 per patient per month. These findings highlight the superiority of FCM over FG in improving iron status, reducing ESA dependence, and offering a cost-effective alternative for managing IDA in haemodialysis patients [35].

There is increasing evidence that using IV iron in CKD-PD is safe, improves Hb levels and reduces ESA dose requirements [36]:

- A cross-over study of oral and IV iron demonstrated higher Hb and lower ESA doses with IV iron after 4 months oral [37].
- A retrospective study evaluating ferric carboxymaltose (FCM) in a population of 91 people with CKD-PD over 12 months found no SAEs including hypersensitivity. More than 60% of participants achieved ferritin 200–800 mcg/L and TSAT $> 20\%$ and a reduced ESA dose was necessary to maintain Hb levels [38].
- A study demonstrated that abnormal iron status is associated with an increased risk of mortality in people treated with PD. Functional Iron Deficiency (FID) had the greatest all-cause and cardiovascular mortality [39].

The safety of intravenous (IV) iron compared to oral iron in individuals with non-dialysis-dependent chronic kidney disease (NDD-CKD) and iron deficiency anaemia remains a topic of ongoing investigation. One study in participants with stage 3 and 4 NDD-CKD compared oral ferrous sulphate (325 mg three times daily for 8 weeks) to IV iron sucrose (200 mg every 2 weeks, total 1 g) and was terminated early due to a higher risk of serious adverse events in the IV iron group. The IV iron group experienced more serious cardiovascular events (adjusted incidence rate ratio [IRR]: 2.51, 95% CI: 1.56–4.04) and infections requiring hospitalisation (adjusted IRR: 2.12,

95% CI: 1.24–3.64), raising concerns about its safety in this population [40]. This trial had several potential limitations including the results becoming significant after adjustment for baseline variables, the study was single centre, there was a single investigator adjudication of all serious adverse events and only 99 patients completed the trial.

However, these findings were not replicated in a larger trial involving 626 participants with NDD-CKD and anaemia not receiving ESAs. Participants were randomised to either IV ferric carboxymaltose (FCM) targeting high (400–600 mcg/L) or low (100–200 mcg/L) ferritin levels, or oral iron. Higher ferritin targets with IV FCM delayed the need for additional anaemia management and reduced ESA dosage. The IV iron group achieved greater increases in haemoglobin (Hb) compared to oral iron, with a higher proportion of participants achieving an Hb increase of ≥ 10 g/L. Importantly, adverse event rates were similar across all groups, alleviating concerns about safety in this study [41].

Similarly, a trial comparing IV iron isomaltoside with oral iron in 351 participants with stage G5 NDD-CKD found no significant safety differences. IV iron resulted in greater improvements in Hb, serum ferritin, and TSAT compared to oral iron, and fewer participants in the IV group withdrew due to adverse events (4.3% vs. 0.9%, $p=0.2$) [42]. The FERWON trial, involving 1,538 participants with NDD-CKD and iron deficiency anaemia, compared 1 g iron isomaltoside to iron sucrose (200 mg given up to five times). No significant differences were observed in hypersensitivity reactions, while the iron isomaltoside group had a lower incidence of composite cardiovascular adverse events (4.1% vs. 6.9%, $p=0.25$) [43].

While oral iron remains the first-line treatment for people with NDD-CKD due to its convenience and cost-effectiveness, IV iron is recommended for those who are intolerant of oral iron or fail to achieve adequate iron repletion despite its use. Limitations such as short follow-up durations and insufficient data on long-term adverse effects, including oxidative stress, warrant caution. NICE guidelines emphasise the importance of individualising therapy.

In haemodialysis (HD) patients, additional iron losses from gastrointestinal bleeding, frequent blood tests, and dialysis circuits necessitate maintenance IV iron, which significantly reduces ESA requirements and costs. Maintaining steady-state iron stores in HD populations requires approximately 50–60 mg/week of IV iron. The optimal repletion strategy, however, remains an area of active study (5, 8, 10–11, 44–48).

Guideline 2.4 - Treatment of anaemia with iron therapy - Upper limit for iron therapy

For people not on HD, we recommend that serum ferritin should not exceed 600 mcg/L in those treated with iron. To achieve this, iron management should be reviewed when ferritin is >500 mcg/L, recognising that a level of >800 mcg/L may reflect iron toxicity. (1B)

Guideline 2.4.1

For people receiving HD, we recommend that proactive high-dose IV iron, initially 600 mg in divided doses in the first month and then 400 mg every month (or equivalent) should be given unless ferritin >700 mcg/L or TSAT >40%. (1 A)

Guideline 2.4.2

We suggest a tailored approach by clinicians to assess the risk and benefit of starting a proactive IV iron protocol in people who have been established on HD for >12 months. (2B)

Rationale

Iron overload is defined as increased total body iron content with the possible risk of organ dysfunction [49]. There is no clinically available method that accurately determines total body iron content. An elevated serum ferritin does not always correlate with elevations in liver iron content (50–51). Elevated serum ferritin together with elevated serum transferrin saturation remain the most clinically accurate parameter of iron overload in people with CKD.

Discontinuation of adequate maintenance IV iron when an individual's ferritin is >500 mcg/L produces a population mean that straddles the 600 mcg/L ceiling [10].

Deciding on the need for further iron therapy should include concomitant assessment of changes in iron status, Hb and ESA or HIF-PHI dose over time. For example:

- A decreasing ferritin as well as decreasing Hb levels signifies blood loss. Iron therapy is indicated, and further investigation may be required.
- A decreasing ferritin after initiation of ESA therapy with a concomitant rise in Hb indicates a response to ESA with a shift of iron from stores to bone marrow. Further iron therapy is guided by serum ferritin.
- An increasing ferritin after a reduction in ESA dose to reduce Hb to target range indicates a reduction in Hb synthesis. Iron therapy may be postponed.
- A rising ferritin and reducing TSAT suggests an inflammatory condition e.g. sepsis, vascular access, surgery or recent hospitalisation. Further iron therapy depends on serum ferritin and clinical scenario.

- Ongoing high IV iron doses to maintain ferritin indicated blood loss which may require further investigation.

The finding of a TSAT <20% coupled with a ferritin >500 mcg/L poses a particularly difficult problem for clinicians. This situation may be caused by iron test variability [13], inflammation, or reticulo-endothelial iron blockade. Evidence on the risks and benefits of IV iron therapy in this population is not well established.

The PIVOTAL trial compared a high-dose, proactive IV iron sucrose regimen to a low-dose, reactive IV iron sucrose regimen in 2141 adult people in their first year of HD receiving an ESA [52]. The high-dose group received 600 mg of IV iron initially in the first month and then 400 mg IV iron sucrose proactively every month unless serum ferritin was >700 µg/L or transferrin saturation (TSAT) ≥40%. The low-dose group received 0 to 400 mg monthly, with a serum ferritin of <200 µg/L or a TSAT of <20% being a trigger for iron administration. A total of 320 (29.3%) in the high-dose group had a primary end-point event (composite of nonfatal myocardial infarction, nonfatal stroke, hospitalisation for heart failure, or death), compared with 338 (32.3%) in the low-dose group (HR, 0.85; 95% CI, 0.73 to 1.00; $p < 0.001$ for noninferiority; $p = 0.04$ for superiority). There was no significant difference in infection rates or hospitalisation for any cause between the two groups. The authors concluded that a high-dose IV iron regimen administered proactively was superior to a low-dose regimen administered reactively: resulting in a lower risk of death or major adverse cardiovascular events and requiring lower doses of ESA and a lower incidence of blood transfusions [52].

It should be noted that the PIVOTAL trial investigated incident HD participants only. We recommend an individualised approach by clinicians to assess the risk and benefit of starting a proactive IV iron protocol in people who have been established on HD for >12 months.

Guideline 2.5 - Treatment of iron deficiency without anaemia

We recommend for people with chronic kidney disease with iron deficiency without anaemia and concomitant heart failure administration of IV iron to improve well-being, physical function, and to reduce heart failure admissions. (1 A)

Guideline 2.5.1

We suggest for people with CKD with iron deficiency but without anaemia and no concomitant heart failure, a trial of oral or IV iron for improvement in clinical symptoms such as restless legs. (2B)

Rationale

The benefits of treating iron deficiency in people with chronic kidney disease (CKD) and haemoglobin (Hb) > 120 g/L remain unclear. Trials in related populations provide mixed insights. The FAIR-HF trial showed that intravenous (IV) ferric carboxymaltose improved patient-reported outcomes and New York Heart Association (NYHA) functional class in heart failure patients with iron deficiency, but its relevance to CKD populations is uncertain [53]. Similarly, CONFIRM-HF demonstrated improved 6-minute walk test (6MWT) distances with ferric carboxymaltose, including in subgroups with reduced eGFR, but CKD-specific outcomes were not the focus [54].

The IRONMAN trial in heart failure reported a non-significant trend toward reduced hospitalisations and cardiovascular death with IV ferric derisomaltose (RR 0.82, $p=0.070$) [55]. Trials such as Iron and Heart and Iron and Muscle, which specifically included CKD participants, found no significant improvements in 6MWT distance with IV iron (56–57). A systematic review of iron-deficient but non-anaemic adults associated iron supplementation with subjective fatigue improvements but not objective physical performance gains, though CKD-specific data was not assessed [58].

In haemodialysis (HD) populations, two randomised trials explored IV iron for restless leg syndrome (RLS), finding transient symptom improvement (59–60). A systematic review confirmed iron's benefit for RLS but noted increased, non-severe adverse events (RR 2.04) [61]. Guedes et al. linked low iron stores to poorer quality of life, increased mortality, and cardiovascular risk in non-dialysis CKD patients, with or without anaemia [27]. Profound iron deficiency, defined as ferritin < 30 mcg/L and TSAT < 16%, has been suggested as a treatment threshold, but supporting data remain limited.

Oral iron supplementation may suffice for those with milder iron deficiency and preserved Hb, but in severe cases or when oral is ineffective, IV iron could be considered, especially for symptom relief or functional improvement. However, further research is needed to define thresholds and benefits in CKD-specific populations.

Guideline 2.6 - Administration of IV iron - Safety recommendations

We recommend that resuscitative medication and personnel trained to evaluate and resuscitate be present in the event of anaphylaxis at each administration of intravenous iron. (1 A)

Guideline 2.6.1

We recommend avoiding parenteral iron therapy in people with active infection. (1 C)

Guideline 2.6.2

We suggest avoiding iron therapy in people with the following conditions (not graded):

- Hepatitis B virus infection
- Hepatitis C virus infection (Positive PCR test)
- Haemochromatosis (primary or secondary)

Guideline 2.6.3

We suggest caution in prescribing parenteral iron in people with (not graded):

- Chronic liver disease.
- Heterozygous for any of the haemochromatosis genes (C282Y (c.845G > A), H63D (c.187 C > G) and S65C (c.193 A > T)).

Guideline 2.6.4

We suggest choice of parenteral iron be tailored, considering the benefits and risks associated with available iron preparations. (2 C)

Rationale

The impact of intravenous (IV) iron on infection risk in haemodialysis (HD) and non-dialysis-dependent chronic kidney disease (NDD-CKD) populations has been extensively studied, though findings remain mixed. Parenteral iron can modulate immune responses, reducing circulating TNF α levels but potentially impairing monocyte and macrophage antimicrobial functions depending on the iron preparation used, with iron sucrose showing more pronounced effects [62–66].

Studies examining the relationship between serum ferritin and infection risk in HD populations suggest higher ferritin levels (> 500–1,000 $\mu\text{g/L}$) are associated with increased bacterial infections and mortality, with excess infections ranging from 16 to 50 per 100 patient-years in high ferritin groups [67]. Observational data indicate that higher IV iron doses or frequent administration may increase infection-related hospitalisation or mortality, particularly in patients with catheters or recent infections [68–70]. For example, bolus dosing (median 700 mg monthly) was associated with a higher risk of infection-related hospitalisation compared to maintenance dosing (200 mg monthly), but lower, consistent dosing did not show the same risks [70]. Other studies found no association between IV iron use and infection, particularly with doses ≤ 400 mg/month [71–75].

Randomised controlled trials (RCTs) offer further insights. The PIVOTAL trial, which compared proactive high-dose (400 mg/month) and reactive low-dose (0–400 mg/month) IV iron regimens in 2,141 HD patients, found no significant differences in infection rates, hospitalisations, or deaths from infection between

dosing strategies. Infection risk was higher in patients with central venous catheters regardless of iron regimen [76]. A meta-analysis by Hougen et al. supported these findings, showing no increased infection risk with high-dose IV iron (>400 mg/month) compared to low-dose regimens [77]. Conversely, Shah et al.'s meta-analysis of 154 RCTs across disease states found a modestly increased infection risk with IV iron compared to oral or no iron (RR 1.17), though variability in how infections were defined and reported limits the interpretation [78].

Overall, the balance of evidence suggests that while excessive iron doses or bolus regimens may elevate infection risk, maintenance dosing within recommended limits (e.g., ≤ 400 mg/month) appears safe. Careful individualisation of therapy and monitoring are crucial, particularly in patients with high infection susceptibility, such as those with central venous catheters or elevated baseline ferritin levels. All intravenous (IV) iron formulations are associated with acute adverse events (AEs), with immune mechanisms, such as IgE-mediated responses or complement activation-related pseudo-allergy, implicated in some cases [79]. Anaphylactoid reactions are more common with high molecular weight iron dextran, with life-threatening reactions occurring in 0.6–0.7% of cases [80–82]. Labile or free iron reactions, known as Fishbane reactions, occur more frequently with non-dextran iron forms and are infusion rate related. These reactions, characterised by symptoms such as facial flushing, back pain, chest tightness, and dyspnoea, often resolve upon stopping the infusion and can be managed by resuming therapy at a lower infusion rate [79].

A study of 2,534 haemodialysis (HD) patients receiving sodium ferric gluconate (SFGC) or placebo found low rates of anaphylaxis with non-dextran irons, with reactions generally manageable [83–84]. A retrospective cohort study comparing five IV iron preparations reported the highest anaphylaxis rate with iron dextran (9.8 per 10,000 first doses), followed by ferumoxytol (4.0), ferric gluconate (1.5), iron sucrose (1.2), and ferric carboxymaltose (0.8) [85].

The IRONMAN trial, involving 1,127 heart failure patients with reduced ejection fraction (HFrEF) and iron deficiency, reported no significant differences in serious adverse events between the IV ferric derisomaltose and usual care groups. Only one participant experienced an infusion-related reaction, which resolved after observation [86].

The MHRA has issued updated guidance on IV iron use due to the potential for serious and rarely fatal hypersensitivity reactions, particularly in pregnant women. Such reactions can occur even with prior tolerance and are more common in individuals with allergies, immune or inflammatory conditions, or atopic history. Key recommendations include:

- Strict adherence to product-specific administration guidelines.
- Monitoring for hypersensitivity during and for at least 30 min post-administration.
- Ensuring staff trained in anaphylaxis management and resuscitation facilities are available.
- Caution in high-risk individuals, with IV iron only administered when benefits outweigh risks [87].

Rationale

Oral iron treatments for iron deficiency anaemia often cause gastrointestinal side effects, leading to poor adherence, while intravenous (IV) iron can generate reactive oxygen species (ROS) due to high levels of non-bound iron. To address these issues, novel iron preparations have been developed to enhance tolerability and efficacy. These include nanosized compounds like ferric citrate, ferric maltol, and sucrosomial iron, which offer high bioavailability and reduced side effects, making them viable options for chronic kidney disease (CKD)-related anaemia.

Alternative iron preparations

Ferric Citrate: Primarily used in dialysis for phosphate binding, ferric citrate also improves iron parameters and haemoglobin (Hb). Meta-analyses and trials confirm its ability to increase Hb and reduce erythropoietin-stimulating agent (ESA) and IV iron requirements in both dialysis and non-dialysis CKD populations across various trials, such as the ASTRIO trial and studies comparing ferric citrate with other phosphate binders like lanthanum carbonate. These studies highlight ferric citrate's dual role in managing both phosphate levels and iron deficiency, with reductions in ESA dosing observed in haemodialysis (HD) populations [88–90].

Ferric Maltol: This oral iron preparation minimizes free iron exposure in the gut, reducing oxidative stress and gastrointestinal side effects. The AEGIS-CKD trial demonstrated significant Hb increases with ferric maltol compared to placebo at 16 weeks, with stable Hb levels observed up to 52 weeks for patients continuing treatment. Adverse events, mainly gastrointestinal, were mild and led to few withdrawals [91].

Ferric Pyrophosphate Citrate (FPC): Delivered via dialysate, FPC maintains Hb levels while reducing ferritin and CHr decline compared to placebo. Phase 3 CRUISE trials in HD patients confirmed its safety and efficacy, with adverse event rates comparable to standard dialysate [92].

Sucrosomial Iron: This formulation encapsulates ferric pyrophosphate in a phospholipid membrane, enhancing absorption and reducing gastrointestinal side effects. In a study of CKD patients with iron deficiency anaemia, sucrosomial iron was comparable to IV iron gluconate

in improving Hb over three months, with fewer adverse events and better tolerability [93].

Hypophosphataemia and intravenous iron

Hypophosphataemia is a known side effect of some IV iron therapies, particularly ferric carboxymaltose (FCM). Symptoms range from fatigue and muscle weakness to severe complications like osteomalacia and fractures. Monitoring serum phosphate is essential, especially in patients receiving multiple doses, those with risk factors, or kidney transplant recipients.

Studies such as PHOSPHERE-IDA and PHOSPHERE-IBD demonstrated significantly higher rates of hypophosphataemia with FCM compared to ferric derisomaltose (FDI), with associated changes in bone metabolism markers like FGF23, calcium, and PTH [94–96]. Schafer et al. further confirmed FCM's higher hypophosphataemia risk compared to other IV iron preparations in a meta-analysis of 42 trials [97].

In kidney transplant recipients, FCM has been linked to persistent hypophosphataemia, requiring careful monitoring due to potential effects on cardiovascular health, graft function, and bone metabolism. One study reported hypophosphataemia in 56.5% of transplant patients receiving FCM, with normalization taking up to 41 days [98–99].

Considerations for practice

While novel oral and IV iron therapies offer promising alternatives for managing anaemia in CKD, treatment selection must balance efficacy, tolerability, and risks. Physicians should consider patient-specific factors such as adherence potential, risk of hypophosphataemia, and long-term safety when incorporating these therapies into anaemia management strategies. Further research is needed to optimize use, particularly in vulnerable populations like HD and transplant patients.

Guideline 2.7 - Monitoring of treatment - Iron therapy

We recommend regular monitoring of iron status (every 1–3 months) in people receiving intravenous iron to avoid toxicity (defined as a serum ferritin > 800 mcg/L or TSAT > 40%) (1B).

Guideline 2.7.1

We recommend that a serum ferritin consistently > 800 mcg/L with no evidence of inflammation (normal CRP) is suggestive of iron overload or potential iron toxicity. (1B)

Rationale

Intravenous iron therapy has potential risks as well as benefits. Ongoing iron losses on HD necessitate regular monitoring to avoid worsening iron deficiency (100–101).

The safety of persistently very high ferritin levels remains unknown. In a cohort of 58,058 prevalent people receiving haemodialysis in the USA, both all-cause and cardiovascular mortality were increased with increasing ferritin levels, whereas the opposite (inverse) association was observed for TSAT increments. Serum ferritin levels between 200 and 1200 µg/L, and iron saturation ratio between 30 and 50% were associated with the lowest all-cause and cardiovascular death risks. However, association studies are biased by the fact that serum ferritin is also a marker of inflammation. In unadjusted, time-varying model, serum ferritin > 800 µg/L during each quarter was associated with increased death rate [77].

There is growing body of evidence regarding iron overload, particularly in patients with ESKD undergoing HD, and the role of quantitative liver MRI in assessing hepatic and cardiac iron deposition. Studies have highlighted the high prevalence of hepatic iron overload in this population, with a pooled prevalence of mild to moderate hepatic iron overload at 52%, and severe hepatic iron overload at 23%, as demonstrated in a systematic review with meta-analysis of seven studies (339 patients) [102].

Significant iron overload in the liver and spleen (assessed through *T* 2 magnetic resonance) has been described in 19 of 21 people receiving HD with serum ferritin > 1000 µg/L and severe comorbidities who were treated with IV iron [103]. Similarly, Rostoker et al. [104] prospectively studied a cohort of 119 fit people receiving HD who were receiving iron and ESA therapy and measured their liver iron content by means of *T* 1 and *T* 2 magnetic resonance. Mild to severe hepatic iron overload was observed in 84% of the people, 36% of whom had severe iron overload approaching that found in haemochromatosis.

Additionally, evidence from the CONTRAST study suggests that while elevated hepcidin-25 levels are associated with an increased risk of cardiovascular events, they do not independently predict all-cause mortality in HD patients. Notably, hepcidin-25 levels were found to be significantly linked to fatal and non-fatal CV events, even after adjusting for confounders like CRP. This reinforces the importance of hepcidin as a potential marker for CV risk in the HD population [105].

Furthermore, the relationship between iron overload and liver fat content, as seen in MRI studies of dialysis patients, is critical. A study of 68 dialysis patients revealed that those with moderate to severe hepatic iron overload exhibited higher proton density fat fraction (PDFF) levels, suggesting an interplay between iron accumulation and liver fat deposition. This dynamic relationship was further explored in a subgroup of patients receiving IV iron, where both PDFF and liver iron concentration (LIC) increased with therapy, while reductions

in iron therapy led to decreases in both PDFF and LIC [106].

Lastly, research on 55 HD patients with hyperferritinaemia due to IV iron supplementation further emphasized the impact of iron overload on liver health. Severe liver siderosis was associated with advanced liver fibrosis and elevated markers of liver dysfunction. Serum iron and TSAT levels were found to be useful in identifying patients at risk for advanced liver fibrosis, underlining the importance of closely monitoring iron levels and liver function in HD patients [107].

While iron overload remains a significant concern in ESKD, particularly with respect to hepatic health, uncertainties remain about the full scope of its impact and the precise role of hepcidin in predicting outcomes. Further research is needed to refine diagnostic strategies, improve monitoring of iron therapy, and clarify the relationship between iron overload and patient outcomes, especially concerning cardiovascular risk and liver fibrosis.

Clinical settings in which more frequent iron testing may be necessary include the following:

1. Initiation of ESA therapy
2. Achieving less-than-target Hb level during ongoing ESA therapy
3. Recent bleeding
4. After surgery
5. After hospitalisation
6. Monitoring response after a course of IV iron
7. Evaluation for ESA hypo-responsiveness

Treatment of anaemia with erythropoiesis stimulating agents (Guidelines 3.1–3.17)

Guideline 3.1- Investigations before initiating ESA therapy

We recommend that all correctable causes of anaemia should be ruled out before considering treatment with ESAs. (1B)

Rationale

Investigations for iron deficiency, folate and B12 deficiency, hyperparathyroidism, inflammatory states as well as gastro-intestinal blood losses should be investigated and addressed before initiating ESA therapy. Correcting any deficiencies before starting ESA treatment will allow for optimal ESA responses, minimising the dose required to maintain target haemoglobin levels [108, 109].

Guideline 3.2 - Treatment of anaemia with iron therapy - Initiation of ESA and iron status

We recommend that ESA therapy should **NOT** be initiated in the presence of absolute iron deficiency, (ferritin < 100 mcg/L in people with non-dialysis dependent CKD (NDD-CKD) and < 200 mcg/L in people who are dialysis dependent) until this is corrected and it is

determined that anaemia persists in conjunction to a shared decision of the advantages and risks of ESA therapy. In people with functional iron deficiency, iron supplements should be given prior to or when initiating ESA therapy. (1B)

Rationale

Iron is required for production of new red cells. Iron deficiency in CKD can be defined as a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 µg/L) [106]. The PIVOTAL trial has shown that in people receiving haemodialysis on a high-dose proactive iron regimen (400 mg a month after an initial dose of 600 mg in the first month) require smaller ESA doses to maintain desirable Hb level between 100 and 120 g/L, when compared to those patients on low dose iron regimen (0-400 mg monthly when required to maintain ferritin > 200 µg/L and a transferrin saturation > 20%). The people in the high dose arm experienced less cardiovascular events, which may be contributed to lower ESA doses use due to pro-active iron therapy [54].

Guideline 3.3 - Treatment of anaemia - Erythropoiesis stimulating agents

We recommend that treatment with Erythropoiesis Stimulating Agents (ESAs) should be offered to people with anaemia of CKD, who are likely to benefit in terms of quality of life and physical function and to avoid blood transfusion; especially in people considered suitable for transplantation. (1B)

Rationale

Please see 2017 clinical practice guidelines for rationale, no significant change since then [2].

Guideline 3.4 - Treatment of anaemia with ESA therapy - Target haemoglobin range

We recommend that people with non-dialysis dependent CKD (NDD-CKD) or those receiving dialysis, who are on ESA therapy, should achieve Hb between:

- 100 and 120 g/L in adults, young people and children aged 2 years and older. (1B)
- 95 and 115 g/L in children younger than 2 years of age (reflecting the lower normal range in that age). (2B)

Guideline 3.5 - Treatment of anaemia without ESA therapy - Target haemoglobin range

We suggest that this Hb target range applies exclusively to people with CKD receiving ESAs and is not intended to apply to the treatment of iron deficiency in people receiving iron therapy without the use of ESAs. (2B)

Rationale for guidelines 3.4 and 3.5

Covered in the 2017 guidelines with similar recommendations [2] New studies since this publication summarized below.

Post Hoc analysis of the PIVOTAL Trial of 2141 people receiving dialysis, examining the baseline data, and potential relationship to the primary outcome (all-cause mortality, myocardial infarction, stroke, and heart failure hospitalisation), and associations with key baseline characteristics and QoL was measured. CRP and transferrin saturation (TSAT) were associated with QoL. Hemoglobin was not an independent predictor of QoL. TSAT was an independent predictor of the Pain Catastrophising Scale. TSAT ≤ 20% was associated with worse physical component scores of QoL [110].

Several systematic reviews have looked at ESA or ESA and iron use, comparing various Hb target ranges and their effect on quality of life. One review by Spinowitz et al. looked at people receiving dialysis being treated with ESAs and without ESAs and its impact on their health-related quality of life (HRQoL). This showed that there may be some increase in HRQoL in those people treated with ESAs (with or without iron) vs. those without treatment. However, there was no evidence for higher Hb targets leading to improved reporting of HRQoL [111].

Guedes et al. found that, similarly, higher Hb targets (> 115 g/L) may be associated with a small decrease in fatigue levels when compared to those people with CKD aiming for the recommended target of 100–115 g/L. However, there was no significant effect seen on physical function or HRQoL [112].

NICE guidelines on managing anaemia in people with CKD suggest maintaining the “aspirational” Hb range between 100 and 120 g/L for adults [108]. The rationale behind choosing a wide target Hb range (100–120 g/L) for this guideline is that when the target Hb level is narrow (i.e. 10 g/L), variability in achieved Hb levels around the target is high, the fraction of prevalent patients with achieved Hb levels within the target range is low and ESA dose titration is required frequently during maintenance therapy.

It is also suggested to consider accepting Hb levels below the lower limit of the target range, if the target range cannot be achieved despite high, escalating doses of ESAs. High ESA doses are defined as: over 175 IU/kg per week for people receiving haemodialysis, over 125 IU/kg per week for peritoneal dialysis patients and over 100IU/kg per week for pre-dialysis patients [108].

The health economics of anaemia therapy using ESAs has been subject to a NICE systematic review which

concludes that treating to a target Hb 100–120 g/L is cost effective in HD patients [1]. Table 3 summarises the mean Hb data for prevalent UK dialysis patients from the 24th (2020) UK Renal Registry Reports [113].

Guideline 3.6 - Treatment of anaemia - Choice of ESA

We recommend that the choice of ESA is based on local availability and cost of ESAs. (1B)

Rationale

Many studies have been published comparing different ESA products against each other when used at different dosing intervals, by different routes of administration and in different patient groups [9, 10]. All the available products are efficacious when administered according to the manufacturers’ recommendations. The choice of ESA will be dependent upon the clinician and patient agreeing a management plan and local supply arrangements [108–118].

Guideline 3.7 - Treatment of anaemia - Initial ESA dose

We suggest that the initial ESA dose should be determined by the individual’s Hb level, the desired target Hb range, the observed rate of increase in Hb level and clinical circumstances. (2B)

Rationale

Please see 2017 clinical practice guidelines for rationale, no significant change since then [2]. In addition the choice of ESA therapy consists of either short or long-acting ESA therapy.

Short-acting ESA therapy: examples include epoetin alfa and epoetin beta, require more frequent dosing (e.g., twice or three times a week).

Long-acting ESA therapy: Examples include darbepoetin alfa and methoxy polyethylene glycol-epoetin beta (PEG-epoetin). require less frequent dosing (e.g., once a week or once every two to four weeks).

Short-acting ESA therapy: examples include epoetin alfa and epoetin beta, require more frequent dosing (e.g., twice or three times a week).

Long-acting ESA therapy: Examples include darbepoetin alfa and methoxy polyethylene glycol-epoetin beta (PEG-epoetin). require less frequent dosing (e.g., once a week or once every two to four weeks).

Guideline 3.8 - Treatment of anaemia with ESA therapy - Route of administration

We suggest that the route of ESA administration should be determined by the CKD grade, patient preference, treatment setting, efficacy, safety, and class of ESA used. Subcutaneous (SC) use is preferable in people who are not receiving HD to avoid puncture of peripheral veins.

Table 3 Hb data for UK prevalent people receiving HD [107]

Median Hb (g/L)	% Hb < 100 g/L	% Hb > 120 g/L
111	19.6	22.9

In some circumstances - such as individuals requiring high doses of IV ESA - use of subcutaneous ESA can be considered for patients on haemodialysis due to evidence suggesting greater efficacy with this route. (2B)

Rationale

Please see 2017 clinical practice guidelines for rationale, no significant change since then [2].

Guideline 3.9 - Treatment of anaemia with ESA therapy - Frequency of administration

We suggest that the frequency of administration should be determined by the CKD grade, preferences of treated population, treatment setting and class of ESA. Less frequent administration using long-acting ESAs may be the treatment of choice in people with CKD not on haemodialysis. (2B)

Rationale

Please see 2017 clinical practice guidelines for rationale, no significant change since then [2].

Guideline 3.10 - Treatment of anaemia with ESA therapy - ESA dose adjustments

We recommend that adjustments to ESA doses should be considered when Hb is < 105 or > 115 g/L in adults, young people and children aged 2 years and older. (1 A)

Guideline 3.10.1

We suggest these thresholds for intervention should achieve a population distribution centered on a mean of 110 g/L with a range of 100–120 g/L. (2B)

Guideline 3.10.2

We suggest in children younger than 2 years to keep the Hb level within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment (for example, take action when Hb levels are within 5 g/L of the range's limits). (not graded)

Guideline 3.10.3

We suggest that ESA doses should ideally be decreased rather than withheld when a downward adjustment of Hb level is desirable. (2B)

Guideline 3.11 - Treatment of anaemia with ESA therapy - Specific situations

We suggest that ESA administration in ESA-dependent people should continue during acute illness, surgical procedures or any other cause of hospitalisation, unless there is a clear contra-indication (for example, acute stroke or vascular access thrombosis). (2B)

Rationale for guidelines 3.10 and 3.11

Please see 2017 clinical practice guidelines for rationale, no significant change since then [2].

Guideline 3.12 - Caution in prescribing ESA in certain people with CKD

We suggest exerting caution while prescribing ESA therapy in people with CKD with a history of stroke, or malignancy, particularly in those with active malignancy when cure is the anticipated outcome. (2 C)

Rationale

Please see 2017 clinical practice guidelines for rationale, no significant change since then [2].

Guideline 3.13 - Monitoring of ESA treatment - Haemoglobin during ESA therapy

We suggest that Hb concentration should be monitored every 2–4 weeks in the correction phase or after a dose adjustment and every 1–3 months for stable individuals in the maintenance phase of ESA treatment. More frequent monitoring will depend on clinical circumstances. (2B)

Rationale

It is important to closely monitor Hb response to treatment to monitor for possible adverse events and plan ESA dose modification. More frequent Hb monitoring may be needed, an individual's response can vary greatly dependent on other clinical variables. During ESA initiation therapy, after drug dose adjustments or changes in an individual's clinical condition, more frequent monitoring is advised in order that under-treatment and over-treatment may be avoided [107, 119, 120].

Guideline 3.14 - Monitoring of ESA treatment - Resistance to ESA therapy

We recommend that inadequate response ('resistance') to ESA therapy is defined as failure to reach the target Hb range despite SC epoetin dose > 300 IU/kg/week (450 IU/kg/week IV epoetin), or darbepoetin dose > 1.5 mcg/kg/week, or equivalent dose of methoxy ethylene glycol epoetin beta following investigation and treatment of other causes. (1 A)

Guideline 3.14.1

We suggest clinicians consider accepting lower aspirational haemoglobin target range in those on high, escalating ESA doses with inadequate response or consider alternative therapy such as a trial use of HIF-PHI for non-dialysis dependent CKD (NDD-CKD). (2 C)

Rationale

Extensive publications are available on the topic of resistance to ESA therapy including the Revised European Best Practice Guidelines [121] which defines ESA resistance as above. Failure to respond at an earlier stage in therapy should however raise suspicion of ESA resistance.

It is suggested to consider accepting lower Hb target levels in individuals who require high escalating doses of ESA, where the aspirational range cannot be achieved. High doses are defined as:

- > 175 IU/kg per week for people on HD
- > 125 IU/kg per week for people on PD
- > 100 IU/kg per week for people who have CKD and aren't dialysis dependent (NDD-CKD)

Individuals on these doses, should start to receive investigations into potential other reversible causes of low haemoglobin levels [108].

Suggested approaches to investigate ESA hypo-responsiveness:

- Check adherence If poor, attempt to improve (if self-injection)
- Check reticulocyte count If > 100,000/microL (> 3%), look for blood loss or hemolysis: endoscopy, colonoscopy, hemolysis screen
- Check serum vitamin B12 and folate, if low, replenish
- Check iron status, if low, replenish iron
- Check serum PTH, if elevated, manage hyperparathyroidism
- Check Serum CRP, if elevated, check for and treat infection or inflammation
- Check efficiency of dialysis. If underdialysed, improve dialysis efficiency
- Check if on ACEi/ARB use If yes, consider reducing dose or discontinuing drug
- Perform bone marrow biopsy and manage any condition diagnosed e.g., dyscrasia, infiltration, fibrosis [122].

There are two putative mechanisms by which ACE inhibitors can potentially suppress erythropoiesis. First, ACE inhibitors reduce circulating insulin-like growth factor 1 and thereby restrict erythropoiesis [123]. Second, ACE inhibitors increase plasma levels of the natural stem cell regulator N-acetyl-seryl-aspartyl-lysylproline (AcSDKP), which prevents the recruitment of pluripotent hematopoietic stem cells [124, 125]. There have been a number of observational cohort studies, some demonstrating a neutral effect and others demonstrating a deleterious effect of ACEi and ARB on ESA responsiveness. Therefore, we would suggest it seems reasonable to suggest a

trial of cessation of ACEi/ARB in patients if there is no other identifiable cause for their ESA hyporesponsiveness [126].

Guideline 3.15 - Monitoring of ESA treatment - Evaluation for ESA induced pure red cell aplasia

We recommend that a diagnosis of ESA induced pure red cell aplasia (PRCA) should be considered whenever a person receiving long term ESA therapy (> 8 weeks) develops all the following (1 A):

- A sudden decrease in Hb concentration at the rate of 5 to 10 g/L per week **or** requirement of transfusions at the rate of approximately 1 to 2 per week
- Normal platelet and white cell counts
- Absolute reticulocyte count less than 10,000/ μ L
- High serum ferritin

Guideline 3.15.1

We recommend that all ESA therapy should be stopped in people who develop ESA induced PRCA. (1 A)

Guideline 3.15.2

We recommend that individuals who remain transfusion dependent after withdrawing ESA therapy should be treated with immunosuppressant medications guided by the level of anti EPO antibodies. (1B)

Guideline 3.15.3

We do not recommend routine screening for anti-erythropoietin antibodies among people with CKD regularly treated with erythropoiesis stimulating agents. (1B)

Rationale

ESA induced PRCA is a very rare condition, with the overall incidence of reported cases between 1989 and June 2004 was 1.6 per 10,000 patient-years of subcutaneous exposure [127], and 0.02 per 10,000 patient-years of intravenous exposure [128]. Nevertheless, most reported cases of anti-erythropoietin antibody-associated PRCA have occurred in people with CKD who have received the drug subcutaneously [129–131].

Pure red cell aplasia (PRCA) due to anti-erythropoietin (EPO) antibodies should be suspected in an individual who has previously responded to EPO if the haemoglobin (Hb) level declines by > 20 g/L per month or the reticulocyte count is < 20,000 /uL [130].

PRCA is specifically characterized by the following clinical features [131]:

- A drop in Hb level of > 7 to 10 g/L per week without transfusions or transfusion requirement of at least one unit per week to maintain adequate Hb, despite continued use of ESA at high doses.

- Markedly reduced reticulocyte count ($<10,000$ /uL).
- Normal platelet and white blood cell count.
- Elevated serum transferrin saturation and serum ferritin.
- Rarely, allergic urticarial skin reactions at sites of earlier subcutaneous EPO injections have been described [132].

The diagnosis of PRCA is established by:

- Bone marrow examination: which confirms severe hypoplasia of erythroid precursors ($<5\%$).
- The presence of anti-erythropoietin antibodies:
 - There are several available tests to detect antibodies to erythropoietin, with varying sensitivities and specificities [133].
 - People with suspected ESA induced PRCA who test positive using binding antibodies should have the diagnosis confirmed with the definitive testing for neutralising antibodies [134].

ESA induced PRCA is an immune mediated process. While spontaneous remissions after cessation of EPO therapy have been reported, one study reported that the highest recovery rates were among those treated with immunosuppressive therapy, particularly a combination of cyclophosphamide and prednisone [135]. Other options such as rituximab, danazol or even plasma exchange may be considered.

Verhelst et al. [136] compared various immunosuppressive agents in 37 people with antibody mediated PRCA compared to 10 with no treatment and found benefit with cyclophosphamide, plasma exchange and ciclosporin and also transplantation.

Given these data, it is advisable that retreatment with ESA may be considered in people with a history of PRCA only if anti-EPO antibody level is no longer detectable. If epoetin therapy is to be reconsidered for these people, only the intravenous rather than the subcutaneous route should be considered for drug administration.

Guideline 3.16 - Monitoring of ESA treatment - Hypertension during ESA therapy

We recommend that blood pressure should be monitored in all people receiving ESAs and, if present, hypertension be treated by volume removal and/or hypotensive drugs. (1A)

Rationale

Hypertension is the most common complication in CKD and can be aggravated by ESA treatment [125]. Earlier studies demonstrated higher incidence rates of hypertension though ESA doses used were higher and Hb

responses faster in these trials. It is now more common to start at low doses and increase gradually according to response. The commonest cause of hypertension in CKD is not ESA therapy.

Exacerbation of hypertension in patient on ESA therapy may be associated with polycythaemia or rapidly rising haemoglobin levels. These complications should be looked for in patients with hypertension but in the absence of these complicating factors and in the absence of severe hypertension, ESA therapy can usually continue. Hypertension should be adequately controlled prior to initiating ESA therapy. ESA therapy should be discontinued in malignant hypertension.

Treatment of anaemia with HIF-PHI agents (Guidelines 4.1–4.9)

Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHI therapy) also known as HIF stabilisers have emerged as a groundbreaking class of compounds that play a pivotal role in regulating various cellular processes.

Under hypoxic conditions, such as those encountered at high altitudes or in cases of anaemia, HIFs activate the transcription of EPO genes within the kidneys and liver, promoting erythropoiesis to enhance oxygen delivery to tissues [137, 138]. Additionally, HIFs mediate the expression of genes involved in iron transport, uptake, and absorption. These genes contribute to the efficient utilisation of iron, a vital element for multiple physiological processes including oxygen transport, extraction, energy production, and DNA synthesis [137–139].

In the presence of oxygen, prolyl hydroxylase enzymes hydroxylate the oxygen-regulated HIF- α subunit, thereby targeting it for proteasomal degradation [140]. HIF-PHI therapy inhibit this proteasomal degradation, thereby stimulating erythropoiesis primarily by upregulating endogenous EPO production, promoting red blood cell production and ameliorating anaemia. Clinical studies have consistently demonstrated the efficacy and safety of HIF-PHI therapy in addressing the anaemia associated with CKD [20–23].

Guideline 4.1 - Treatment of anaemia - HIF-PHI agents

We recommend that treatment with HIF-PHI agents should be offered after iron repletion, to people with symptomatic anaemia ($Hb < 105$ g/L) of CKD (stages 3–5 ($eGFR < 60$ ml/min/1.73m²)) who are not receiving dialysis at the start of therapy and who are likely to benefit in terms of quality of life and physical function and to avoid blood transfusion; especially in people considered suitable for transplantation. (1B)

Guideline 4.1.1 – Treatment of anaemia - DD-CKD and HIF-PHI agents

We suggest that that treatment with HIF-PHI agents should be considered after iron repletion, to people with DD-CKD and symptomatic anaemia (Hb < 105 g/L) who are likely to benefit in terms of quality of life and physical function and to avoid blood transfusion; especially in people considered suitable for transplantation. (2B)

Guideline 4.1.2 – Treatment of anaemia - Patients intolerant to ESA

We suggest that that treatment with HIF-PHI agents should be considered as an option, after iron repletion, to people who are intolerant to ESA therapy. (2 C)

Guideline 4.1.3 – Choosing between ESA and HIF-PHI therapy for people with non-dialysis dependent CKD and DD-CKD

We suggest, when deciding between ESA and HIF-PHI therapy for people with non-dialysis dependent CKD or DD-CKD, considering the preference of the person with anaemia of CKD, or, where appropriate, their family or carers, the cost of local drug supply, nursing and administration costs and previous treatment with ESA or HIF-PHI. (2B)

Guideline 4.2 - Treatment of anaemia

We suggest that HIF-PHI administration in HIF-PHI-dependent people should continue during acute illness, surgical procedures or any other cause of hospitalisation, unless there is a clear contra-indication such as accelerated hypertension or thrombosis. (2 C)

Rationale

Phase III trials have confirmed the efficacy and safety of this class of drug. Roxadustat is available and approved in the UK and has been recommended in the UK by NICE for people who have stage 3 to 5 CKD with no iron deficiency and are not on dialysis at the start of HIF-PHI treatment but can be continued when the person progresses to dialysis therapy. Vadadustat has also been recommended in the UK by NICE for people on dialysis therapy. NICE has recommended that HIF-PHIs can be used as an alternative to ESAs for people, especially if they find self-injecting difficult or painful or rely on others to give them their injections [141]. The drug can also be used in people receiving dialysis according to the SmPC but this has not been reviewed by NICE for this purpose.

Health related quality of life in the trials to date have given variable results. Some trials have suggested improvement in Health-related quality of life in comparison to ESA therapy, but these are confounded by changes in haemoglobin concentrations [24, 142]. Others suggest

no significant change in health-related quality of life measures or functional health scores [20–23, 140].

“Potential” clinical and practical benefits of HIF-PHI therapy include:

- Reduced exposure to high peak serum EPO concentrations
- Increased endogenous EPO/erythropoietin production
- Enhanced enteric iron absorption, mobilisation and iron utilisation based on secondary outcome data
- Possible reduction in intravenous iron frequency and requirements
- Oral route of administration

Large, randomised trials have demonstrated that Roxadustat [21, 23, 24, 143–150], Vadadustat [151–154], and Daprodustat [155–161] are superior to placebo and/or non-inferior to ESAs in correcting and/or maintaining Hb at target levels in NDD-CKD and incident and prevalent people with DD-CKD. These findings have also been seen with Molidustat, Enarodustat, and Desidustat [162–171]. The Hb response when using HIF-PHI therapy is dose-dependent and there are variations depending on the molecule used and trial protocol. Some molecules depending on the starting doses used, increased the Hb more rapidly than others. Rates of blood transfusion are similar among patients receiving HIF-PHI therapy versus ESA therapy and lower than among those receiving placebo in randomised trials.

Several meta-analyses have confirmed the clinical findings from these RCTs [172–178]. A recent meta-analysis of the phase 3 RCTS comparing HIF-PHI therapy to active comparator has confirmed the efficacy of this class of drug in both people on dialysis (both peritoneal and haemodialysis) and not on dialysis [179]. The authors found a statistically higher change in Hb levels from baseline between HIF-PHI therapy at the dose selected compared to ESA of 1.0 g/L (95% CI 0.2–1.7) favouring HIF-PHI use but perhaps not clinically significant. There was no difference in those reaching the pre-specified Hb target (OR 1.04; 95% CI 0.88–1.22) [179].

Guideline 4.3 - Treatment of anaemia with HIF- PHI therapy - Target haemoglobin

We suggest that people over the age of 18 years with NDD-CKD on HIF-PHI therapy should achieve a Hb between:

- 100 and 120 g/L in adults and young people similar to ESA therapy (2B)
- In children and those younger than 2 years of age no data is currently available (not graded)

Guideline 4.3.1

We suggest that people over the age of 18 years with DD-CKD on HIF-PHI therapy should achieve a Hb between:

- 100 and 120 g/L in adults and young people similar to ESA therapy but this may depend on the choice of HIF-PHI where a Hb of 100–110 g/L is recommended. (2B)
- In children and those younger than 2 years of age no data is currently available

Rationale

The current HIF-PHI trials compared with active comparator used standard Hb targets based on ESA therapy. These varied depending on the country with lower targets in the USA compared to Europe and the UK. No HIF-PHI trials to date involving people in the UK or Europe have compared Hb normalisation or near-normalisation with the currently recommended lower Hb targets for people with CKD.

The randomised open-label phase 3 ESA-controlled DOLOMITES trial in NDD-CKD, included 28 countries and the UK reported that the safety of the HIF-PHI was comparable to the ESA's in the majority of safety variables in people with NDD-CKD [23]. They also reported no evidence of increased cardiovascular safety or mortality risk when compared with ESA's [23]. The study included NDD-CKD people with symptomatic anaemia and stage 3, 4 or 5 CKD with Hb levels < 105 g/L at the start of treatment. NICE committee recommends treatment at a Hb level of less than 100 g/L (1141).

The NICE Committee reported that HIF-PHI therapy was non inferior to ESA therapy in all measures of quality of Life and that the DOLOMITES trial demonstrated that people with NDD-CKD required less IV iron than those treated with an ESA [141].

In the case of non-responsiveness, treatment with HIF-PHI should **not** be continued beyond 24 weeks after the start of treatment and other causes of anaemia be investigated [180].

Meta analysis of RCTS comparing HIF-PHI with ESA therapy have also demonstrated that there was no significant difference in adjudicated MACE events (10 trials) (1.00, 95% CI 0.94–1.07). For MACE + again no difference was seen between HIF-PHI and ESA therapy (1.01, 95% CI 0.95–1.06) even after sensitivity analysis [179]. There was also no difference in the mortality rate, but one must be cautioned as the duration of follow up was relatively short.

Vadadustat, recently approved by the EMA and NICE has a recommended Hb range of 100–110 g/L. The two RCTs, INNOVATE 1 ($n = 369$) and 2 ($n = 3554$) in CKD patients undergoing dialysis, on pooled analysis showed

non inferiority to darbepoetin alpha during 52 weeks follow up [151, 152].

Guideline 4.4 - Treatment of anaemia - Initial HIF-PHI dose

We recommend that the initial HIF-PHI dose should be based on the person's weight and Hb level and the observed rate of increase in Hb level and clinical circumstances. The appropriate dose should follow label recommendations until further data is available. (1B)

Guideline 4.4.1

We suggest that the starting HIF PHI dose should be lower for those who are ESA-naïve versus those who are not. (2B)

Guideline 4.5 - Treatment of anaemia with HIF-PHI therapy - Frequency of administration

We suggest that the frequency of administration should be determined by the response to therapy to maintain the desired Hb target range of 100–120 g/L. (2B)

Guideline 4.6 - Treatment of anaemia with HIF-PHI therapy - Dose adjustments

We suggest that adjustments to HIF-PHI doses should be considered when Hb is < 105 or > 115 g/L in adults to balance the benefit and safety to people given the current evidence base. (2B)

Rationale

Starting doses are based on weight, and dose changes are based on response to treatment and changes in Hb levels. The correction phase lasts up to approximately 3 months from starting treatment or until a stable Hb level of 100–120 g/L is achieved and stabilised. The maintenance phase starts immediately after the correction phase.

Adjustments to HIF-PHI doses should be considered when Hb is < 105 or > 115 g/L in adults to balance the benefit and safety to people given the current evidence base. These thresholds for intervention should achieve a population distribution centred on a mean of 110 g/L with a range of 100–120 g/L, similar to ESA based therapy.

The intermittent dosing strategy with HIF-PHI for the treatment of anaemia in people with chronic kidney disease was developed to maintain its effectiveness. This is the case for Roxadustat with a half-life of 15 h administered three times per week, enabling HIF transcriptional activity to return to baseline between doses, which results in the intermittent induction of hypoxia-inducible target genes involved in erythropoiesis. However, for Vadadustat which has a half-life of approximately 4.5–9.2 h it is given daily.

The appropriate dose should follow label recommendations. We would suggest that starting HIF.

PHI dose should be lower for those who are ESA-naïve versus those who are not. Based on the current Hb and the achieved change in Hb (typically over a 4-week period), the dosing in phase 3 trials was maintained or changed in stepwise fashion. Treatment was temporarily discontinued when Hb exceeded 120–130 g/L in most studies [21, 23, 24, 143–178]. It should be noted that Roxadustat is more than 90% protein bound so caution should be used when the drug is used in patients with nephrotic syndrome due to the potentially higher levels of free drug which may lead to adverse events and more rapid rise in haemoglobin.

Guideline 4.7 - Prescribing HIF-PHI in sub-groups of people with CKD

We recommend that HIF-PHI should be avoided or used cautiously in people with active malignancy. (1B)

Guideline 4.7.1

We recommend that HIF-PHI should be avoided or used cautiously in people with autosomal dominant polycystic kidney disease until further data is available. (1D)

Guideline 4.7.2

We recommend that HIF-PHI should be avoided or used cautiously in people with a history of seizures. (1B)

Guideline 4.7.3

We recommend caution in using HIF-PHI in people with uncontrolled hypertension. (1B)

Guideline 4.7.4

We recommend caution in using HIF-PHI therapy in people with diabetic retinopathy. (1D)

Guideline 4.7.5

We recommend caution in people with a history of thrombotic events following the SmPC for contra-indications. (1 A)

Guideline 4.7.6

We suggest consideration of use of HIF-PHI in people with hyporesponsiveness to ESA therapy or underlying inflammation, but further high-quality randomised trials are needed to confirm its effectiveness. (2 C)

Guideline 4.8 - Safety of HIF-PHI

We suggest that cautious use of HIF-PHI in people with CKD and either known CVD or thrombotic events and consideration of lower dose regimes to reduce rapid rises in Hb. (2 C)

Rationale

Malignancy

Hypoxia inducible factor-1 alpha (HIF-1 α) is a key transcription factor in tumour progression [180]. HIF-1 α inhibitors are currently used in cancer treatment [181]. Genetic HIF activation is a central mechanism of tumorigenesis in people with the von Hippel-Lindau (VHL) disease and clear cell renal carcinomas [182]. These data suggest that HIF-PHI may potentially increase the risk of initiation/ progression of malignancy in people with CKD. Data from the most recent metanalysis of over 24,000 people indicate the risk estimate for malignancy was 7% lower in the HIF-PHI arm compared to ESA (non-significant RR 0.93; 95% CI 0.76 to 1.13) [179]. However, once again follow-up was relatively short- and longer-term data is needed to assess for the development of new cancers and impact on previous cancers. Those with established cancer or a history of cancer were excluded from all trials.

In the ASCEND-ND trial, cancer-related death or tumour progression or recurrence was numerically more common in those randomised to daprodustat (72 of 1937, 3.7%) versus darbepoetin alfa (49 of 1933, 2.5%), with a relative risk of 1.47 (95% CI: 1.03–2.10) [156]. *Post hoc* analyses that accounted for differential dosing frequency attenuated this observed risk [156]. Molidustat in clinical trials also reported neoplasms in 9.8% of trial participants in the Molidustat group compared with 5.3% in the darbepoetin group [171].

There has been no consistent signal across the published HIF-PHI trials of an excess risk of malignancy-related adverse events, but since patients with a history of recent or active malignancy were excluded from trials, it is difficult to conclude with confidence of the absence of a clinically relevant risk of the use of these drugs compared with ESAs. It is therefore advisable that the use of this product should be avoided or used cautiously in people with known active malignancy.

Polycystic kidney disease

People with CKD who have underlying Polycystic Kidney Disease were excluded from trials using HIF PHI's because of the potential risk of malignant transformation of cysts. HIF activation occurs in polycystic kidneys in humans and rodents and activation of the HIF-pathway has been shown to enhance cyst expansion in preclinical models. However, whether the use of HIF-PHI therapy to treat anaemia may enhance cyst growth remains to be further clarified [183].

Hypertension

Pre-clinical studies in healthy rats and rats with CKD demonstrated that HIF-PHI therapy generate significant

dose-dependent blood-pressure lowering effects [184–185]. However, so far, no significant blood pressure safety concerns have been reported in any HIF-PHI phase 3 programs.

Retinopathy

Diabetic retinopathy may be exacerbated potentially by the effect of HIF-PHI therapy on neo-vascularisation [186]. There were few participants with significant retinopathy recruited to the current published phase 3 clinical trials. Data from a pooled Japanese analysis of trials in NDD-CKD and DD-CKD using daprodustat did not report any increased risk for retinal events or deterioration in disease [187]. One relatively large study, the SYMPHONY-ND study which compared Enarodustat to ESA therapy did show an increase in the levels of VEGF levels and an increase in reported retinal adverse events (3.7 vs. 0.9%) [164]. Other NDD-CKD trials have not shown increased risk of eye disease with HIF-PHI therapy (145, 1149, 154, 156).

In dialysis patients the SYMPHONY-HD trial which examined Enarodustat versus darbepoetin did find an increased risk of retinal adverse events (6.9 vs. 3.5%) [165]. Again, in the ASCEND-ID trial of daprodustat compared to ESA therapy there was a reported increased incidence of eye disease (3.4 vs. 0.79/100 patient-years) [147].

Thromboembolic events

Administration of HIF-PHI therapy has been associated with a higher risk of thrombotic events, including dialysis vascular access thrombosis compared with ESAs or placebo [185, 188]. The underlying mechanisms are complex and may be related to the rapid rate of rise in Hb for roxadustat [189]. In addition, the impact of HIF-PHI on iron metabolism (upregulation of transferrin, or interference of the coagulation system (increased expression of plasminogen activator inhibitor) may contribute to thrombotic risk [190, 191]. Roxadustat showed an excess risk of thrombosis in both NDD-CKD (versus ESA) and DD-CKD (versus placebo) trials [192]. A pooled analysis of roxadustat trials demonstrated that higher risks were associated with the rate of Hb rise [193]. Lower doses of roxadustat, may lead to a slower rate of Hb rise, and thus ameliorate thrombosis risk while maintaining efficacy.

Data from the meta-analysis from 17 of the trials reported on DVT and PE events and found no difference. Again, there was no difference in AVF thrombosis incidence from 14 of those trials [178].

Patients hyporesponsive to ESAs

By lowering hepcidin levels, HIF-PHI therapy may theoretically be more effective in treating people who are hyporesponsive to ESAs because of chronic inflammation

or functional iron deficiency. Preliminary data from the randomised trials suggest that whereas higher doses of ESAs are needed for people with high C-reactive protein (CRP) levels, this may not be true for HIF-PHI therapy [23, 144]. However, CRP concentrations that were considered high in trial participants were only slightly elevated, and sicker and more inflamed patients may have been less likely to have been enrolled in trials of HIF-PHI therapy. Therefore, more evidence from randomised controlled trials is needed before recommendations for routine use in the population can be made.

Although the use of HIF-PHI therapy in combination with ESAs might theoretically be advantageous for people who are ESA hyporesponsive, there are no data available to support this strategy in clinical practice at present.

Non-responsive treatment with roxadustat should not be continued beyond 24 weeks after initiation. Conversion of people receiving dialysis otherwise stable on ESA treatment is only to be considered when there is a valid clinical reason and after a shared decision with the patient on the risks and benefits. For stable ESA treated people with anaemia associated with CKD and not on dialysis, this risk could not be estimated as these patients have not been studied. A decision to treat these patients with roxadustat should be based on a shared decision with the patient of the benefits and risks for that particular individual patient.

Children

There are insufficient data supporting the use of HIF-PHI therapy in paediatric patients with anaemia of CKD because people under the age of 18 years were excluded from all Phase 3 trials.

Cardiovascular disease

For MACE outcomes, all trials with a HIF-PHI met the non-inferiority margin set by the regulator except Vada-dustat in people with NDD-CKD. However, there is bias in these trials due to the withdrawal of large number of people in both arms (over 20%). A recent meta-analysis has shown no difference as described previously [179]. A Cochrane meta-analysis of 51 trials with almost 31,000 participants with NDD-CKD or DD-CKD found no difference in CV death (RR 1.05; 95% CI 0.88 to 1.26); non-fatal MI (RR 0.91; 95% CI 0.76 to 1.00 or non-fatal stroke (RR 1.06; 95% CI 0.71 to 1.56) [172]. The secondary outcome studied in the DOLOMITES trial was the impact of roxadustat compared to the active comparator (darbepoetin alfa) on CV safety, based on the number of major adverse cardiac events [23]. The hazard ratio (HR) For MACE was 0.89; 95% CI 0.60 to 1.33; and for MACE+ (a composite of MACE plus unstable angina or congestive heart failure requiring hospitalisation) was 0.93; 95% CI

0.65 to 1.32, indicating no increased risk with roxadustat compared to darbepoetin alfa. In addition, there was no extension of the risk beyond the non-inferiority margin set by the regulator. It must be noted that in the dialysis patients, there was a potential increase in risk in the pooled analysis of those patients who switched therapy from ESA to Roxadustat [188, 189].

Three studies of roxadustat compared to ESA involving people receiving dialysis ($N=3880$) were meta-analysed [194]. The analyses of the effect of roxadustat for MACE were discordant based on the analytical approach: in the primary, on-treatment + 7-day analyses, the risk of MACE was similar in the roxadustat and ESA groups: HR 1.02; 95% CI: 0.88–1.20. In the sensitivity, on-treatment analysis, the HR for the risk of MACE in patients treated with roxadustat versus ESA was 1.14; 95% CI: 1.00–1.30 (not statistical significance for non-inferiority). A fourth trial conducted in Europe and not included in the pooled meta-analysis, permitted the use of two different ESAs (epoetin alfa or darbepoetin alfa) as comparators, demonstrated a higher risk of death in roxadustat vs. ESA-treated patients (8.9 per 100 patient years (PY) vs. 6.3 per 100 PY; HR 1.54, 95% CI 1.04–2.28) [25].

The differences observed in the stable DD population maybe somewhat challenging to accurately interpret due to the different treatment strategies for the Roxadustat and the comparator arm. While in the comparator arm in the stable dialysis dependent CKD (SDD) studies the treatment was not changed (patients continued ESA therapy) in the Roxadustat arm were switched from ESA therapy with inherent risks related to this change which created an imbalance between the two arms. Several contributing factors may impact this risk, including treatment non-responsiveness, and converting stable ESA treated people receiving dialysis.

Pooled results from two randomized trials involving NDD-CKD persons in which Vadadustat was compared with darbepoetin alfa were analysed [188]. One trial involved ESA naïve patients ($n=1751$) and the other involved patients who were receiving active ESA therapy ($n=1725$). Pooled analysis showed that while Vadadustat met its margin with respect to hematologic efficacy in each trial, it did not meet its pre-specified non inferiority margin (HR 1.3) with respect to MACE, defined as death from any cause, non-fatal myocardial infarction, or non-fatal stroke, with a higher risk of MACE in the Vadadustat arm [157]. The excess risk was accounted for by non-fatal MI and death from non-cardiovascular causes. Subgroup analyses found a regional difference in the study results, with the increased MACE risk observed in non-U.S. study sites (HR 1.30; 95% CI 1.05–1.62) but no difference in risk in the U.S. study sites (HR 1.06; 95% CI 0.87–1.29).

Two randomised trials involving DD-CKD patients compared Vadadustat with darbepoetin alfa. One trial involved prevalent ($n=3554$) and the other incident ($n=369$) participants [195]. Pooled analysis of results from both trials showed similar MACE rates in the two arms and met non-inferiority (HR 0.96; 95% CI: 0.83–1.11) [195].

A phase 3 trial assessed the safety and efficacy of daprodustat against an active comparator (darbepoetin alfa) for the treatment in people with NDD-CKD. Daprodustat was non-inferior to the active comparator as it met the pre-specified non-inferiority margins of a HR of 1.25 in primary analyses (HR: 1.03; 95% CI: 0.89–1.19) [193]. However, in the sensitivity on-treatment MACE analysis, which censored patients at 28 days after the last dose, participants randomised to daprodustat had a higher incidence of MACE than those randomised to ESA (14.1% vs. 10.5%, HR 1.40; 95% CI: 1.17–1.68). The trial authors suggested that differences in the dosing frequency of daprodustat versus ESAs in this trial and differences in definitions of treatment periods may have led to potential bias that disadvantaged daprodustat [193].

Daprodustat, compared to the active comparators, met the pre-specified non-inferiority margin of 1.25 in primary analyses of the DD-CKD populations (DD: 0.93; 95% CI: 0.81–1.07). Similar conclusions were obtained from sensitivity analysis [152].

Overall, meta-analyses have reassured the short-term safety of these drugs in comparison to ESA therapy. Natale et al. [172] found not difference in MACE and MACE+; similar to those from Takkavatakarn et al. [174]. A meta-analysis limited to only non-dialysis and active comparator (9 studies with 9470 people) there was no difference in CV outcomes [179].

More long-term data will be needed to reassure on the impact of HIF-PHI therapy and their potential off-target effects including the systemic response to their action via inhibition of alpha ketoglutarate which may have effects of cardiovascular and heart failure complications [196]. Several studies are ongoing including comparing roxadustat combined with sacubitril/valsartan versus recombinant human erythropoietin combined with ACEI or ARB in Chinese patients with cardiorenal syndrome and anaemia (NCT05053893) and examining the safety and efficacy of roxadustat in the treatment of HF in patients with CKD and anaemia (NCT05691257).

Guideline 4.9 - Monitoring response to HIF-PHI

We recommend that Hb levels should be monitored every two weeks until the desired Hb target range of 100 to 120 g/L is achieved and stabilised, and every 4 weeks thereafter, or as clinically indicated. (1B)

Rationale

The recommendations are based on current SmPC guidance and the protocols from RCTs.

Treatment of anaemia of CKD with blood transfusions (Guidelines 5.1–5.1.3)

Guideline 5.1 Blood transfusion in people with anaemia of CKD

We recommend that in people with anaemia of CKD, especially those in whom kidney transplantation is an option, red blood cell transfusion should be avoided, if possible, to minimise the risk of allosensitisation. (1 A)

Guideline 5.1.1

We recommend if red blood cell transfusion becomes essential (usually in the setting of acute blood loss, acute haemolysis or severe sepsis) transfusion should be based on policies set by local transfusion guidelines rather than Hb target range for ESA therapy in chronic anaemia of CKD. (1B)

Guideline 5.1.2

We suggest using single unit transfusion, where possible for stable non-bleeding people with CKD who clinically require transfusion. (2 C)

Guideline 5.1.3

We suggest that kidney transplant recipients, those on the transplant waiting list or people on immunosuppressive therapy should receive only hepatitis E negative blood components (all UK blood components are tested), but neither CMV negative nor irradiated blood is required. (2B)

Rationale for guideline 5.1

Please see 2017 clinical practice guidelines for rationale, no significant change since then [2].

Table 4 Causes of post-transplant anaemia

Risk factor	Cause	Timing
Blood loss	Surgery	Early
	Blood tests	Early
	Malignancy	Late
Impaired EPO Production	Allograft dysfunction	Any
Drugs	Immunosuppression (induction and maintenance)	Early > Late
	Anti-microbials (prophylaxis and treatment)	
	ACE inhibitors and angiotensin receptor blockers	Early > Late
Infection/Inflammation	Any severe infection	Early > Late
	Viral – CMV, EBV, Parvovirus	Early > Late
Iron and other nutritional deficiencies		Any
Haemolysis	Infection, drugs, rejection	Early > Late

Management of peri-transplant and post-transplant anaemia (Guidelines 6.1–6.3.3)

Guideline 6.1 - Peri-transplant anaemia

We suggest that anaemia management should be optimal pre-transplant in all people with CKD on the transplant wait-list, to minimise the risk of a post-transplant transfusion. (2B)

Guideline 6.1.1

We suggest for people with CKD undergoing kidney transplantation, that recombinant EPO maybe continued, after a shared decision of the risks and benefits with the patient, until endogenous EPO production is sufficient to maintain Hb concentrations. For HIF-PHI therapy we make no recommendation until further data is available. (2 C)

Guideline 6.2 - Blood transfusion

We suggest for stable non-bleeding individuals who clinically require a red cell transfusion, using single unit transfusion, where possible. (2B)

Rationale (Guideline 6.1–6.2)

Anaemia post-transplant is extremely common; the aetiology of which is multi-factorial and influenced by the timing post-transplant (Table 4) [197–199].

Apart from the usual causes of anaemia due to CKD, kidney transplant recipients have various unique factors predisposing to anaemia.

Factors causing post-transplant anaemia (PTA):

1. GFR: anaemia in people with a kidney transplant reflects the degree of GFR similar to other people with CKD [199].
2. Immunosuppressive medications: Mycophenolate and azathioprine are myelosuppressive agents. Calcineurin inhibitors may cause anaemia by microangiopathic haemolysis [200–204]. OKT3 may also cause haemolytic uraemic syndrome (HUS) [205, 206]. Tacrolimus has also been associated with anaemia [207–209]. It may interfere with post erythropoietin receptor binding intracellular signalling and may occasionally cause HUS [209, 210]. Mammalian target of rapamycin (mTOR) inhibitors may cause anaemia through alterations in iron homeostasis and absorption, and via effects on erythroid cell proliferation [211].
3. Angiotensin converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) use: ACE inhibition has been linked with anaemia [209, 212]. Its pathogenesis is multifactorial and may include inhibition of endogenous EPO production, production of an erythropoiesis-inhibiting protein

[213] and inhibition of angiotensin II mediated stimulation of erythrocyte precursors [214].

4. Antibiotic use: various common antibiotics may cause anaemia including trimethoprim-sulfamethoxazole.
5. Infections: viral infections such as cytomegalovirus and parvovirus B19 and antiviral agents such as ganciclovir may cause anaemia in people with a kidney transplant [215, 216].
6. Malignancy: malignancies including post-transplant lymphoproliferative disorder may result in anaemia.
7. Haemolytic anaemia: haemolytic anaemia may result from HUS or minor blood group incompatibility in people with a kidney transplant [217–219].
8. Rejection episodes: Acute rejection may cause reduced endogenous EPO production [220]. Severe vascular rejection may cause microangiopathy.
9. Chronic inflammation: Failing kidney transplant causes a chronic inflammatory state resulting in EPO hypo-responsiveness.

Early post-transplant anaemia (PTA) can be seen in the first 6 months following transplantation due to iron deficiency and the slow production of EPO from the new transplant graft [221].

The prevalence of red cell transfusions early post-transplant is high, averaging 40% in reported series [222]. Risk factors for peri-transplant transfusion include female gender, non-white ethnicity, time on dialysis pre-transplant and receiving a deceased donor transplant. The requirement of a peri-transplant transfusion has been shown to be associated with poor allograft outcomes, through mechanisms which are yet to be elucidated [222]. Patient blood management, that is optimal management of anaemia and preserving a patient's own blood, are therefore important in the early post-transplant period [223–225]. Optimal anaemia management of the person with CKD prior to transplantation, as has been set out in this guideline, is important to minimise complications of anaemia.

Although blood loss occurring via the transplant surgery itself will contribute to early post-transplant anaemia, transfusion usually occurs in the first two weeks post-transplant [222]. Endogenous EPO is sustained from 28 days post-transplant in the setting of primary graft function [226]. Studies have shown that in the early post-transplant period ESA (erythropoiesis stimulating agent) is safe and effective, although the dose required may be higher than in the pre-transplant period [227, 228]. Given the increasing use of marginal donor kidneys, associated with delayed graft function and suboptimal function, there may be a longer requirement for EPO.

When a red cell transfusion is required clinically post-transplant in the stable patient, single unit transfusions

should be utilised where possible [209]. Although red cell transfusions are recognised to be associated with HLA sensitisation in the pre-transplant setting, less data are available on the risk of de novo alloimmune responses post-transplant whilst receiving immunosuppression [229, 242]. There are data that the development of de novo transfusion specific antibodies post-transplant can occur post-transplant; plus, additional evidence of a potential link between the receipt of a red cell transfusion and de novo donor specific antibodies [229]. Limiting exposure to multiple red cell donors is therefore advisable, if possible.

Late transplant anaemia occurs more than 6 months after transplantation and can be seen in up to 36% of patients [230]. This is influenced by the function of the transplant graft, but also a combination of the factors listed above as well as iron deficiency.

After the early post-transplant period, the frequency of transfusions is markedly reduced. Anaemia management is more in line with that of CKD, however, there remain specific risk factors for anaemia which will be present and need consideration in terms of reversibility and management.

The JACK-II study looked at the association between PTA and graft function in 1307 kidney transplant recipients. This study found that 46.3% of the cohort had PTA at 7 years post transplantation, with low Hb levels associated to an increase in transplant graft failure (hazard ratio = 1.83, 95% CI: 1.66–2.02, $P < 0.001$) [231].

This association was previously reported in the TransQoL-HU Study, looking at a cohort of 938 kidney transplant recipients with a 4-year follow-up period. This study showed that mortality and graft failure were significantly higher in people who were anaemic vs. those who were not anaemic. Mortality rates were reported at 18% vs. 10% ($p < 0.001$) and graft failure rates were 17% vs. 6% ($p < 0.001$) [232].

Gafer-Gvili et al. assessed 266 people and found that 51.3% experienced early PTA and 36.6% experienced late PTA. The study found that there was higher mortality after 4 years in those who experienced early PTA, which progressed to late PTA vs. those who did not have anaemia and lower Hb was associated with increased mortality (hazard ratio [HR] 0.716, 95% confidence intervals [CI] 0.541–0.948, for every increment of 1 g/dL) and increase graft failure (HR 0.775, 95% CI: 0.619–0.969, for every increment of 1 g/dL) [233].

Scechter et al. [230] also found similar results in their cohort of 1139 kidney transplant recipients. 36.2% of the cohort had PTA and 11.7% had severe anaemia (Hb < 11 g/dL). Early PTA was associated with graft loss or mortality (hazard ratio (HR) 3.64, 95% CI: 2.34–5.66, $p < 0.001$) but a weaker association as seen with late PTA (HR 1.44, 95% CI: 0.97–2.13, 0.07). Severe anaemia was

associated with an increase in all-cause mortality. It was also found that PTA secondary to AKI, acute rejection, infection is associated with a higher risk of death or graft loss (HR 9.32, 95% CI: 5.3–26.41, $p < 0.001$ and HR 3.99, 95% CI: 2.01–7.95, $p < 0.001$, respectively) [230].

Safety of ESA in transplant patients

A few early retrospective studies suggested increased incidence of delayed graft function in people on ESA prior to transplantation [234, 235]. However, Registry data has since shown reduced incidence of delayed graft function despite increasing use of ESA. It has also been shown that ESA use prior to kidney transplantation does not reduce production of or response to endogenous EPO [236, 237]. Studies in the early post-transplant period did not show significant adverse events including delayed graft function or hypertension [228, 238]. Studies in the late transplant period have shown increased incidence of hypertension [239, 240]. ESAs, most probably, do not accelerate rate of graft function decline and one study suggested that correction of anaemia slowed the decline in allograft function [241].

In another prospective study that assessed the effect of correction of anaemia on progression of allograft dysfunction in people with a kidney transplant; 128 people from 17 centres in France treated with ESA were randomised to full correction of anaemia (haemoglobin values 130–150 g/L, $n = 63$) versus partial correction of anaemia (Hb value 105–115 g/L, $n = 62$). This study found that in the group of patients with a haemoglobin level close to normal (~ 130 g/L), the rate of decline of kidney function was lower compared with the group of control participants, and the number graft failures was lower in this treatment group compared with the control group, suggesting that correcting anaemia in people with a kidney transplant reduces the rate of decline of kidney function and reduces the number of grafts lost [242].

A similar study from Japan compared the effect of maintaining higher Hb levels (125–135 g/L, $n = 64$) using ESAs, with maintaining Hb at 105–115 g/L ($n = 63$). This study found that those people in the lower Hb target group (mean levels 115 ± 12 g/L) had significantly higher rate of eGFR decline at 12, 18, 24 and 36 ($p = 0.02$) months, compared to those in the higher Hb target group. Similar levels of adverse events were seen in both groups [243].

A further single centre study showed no change in the rate of decline in allograft function over 2 years with epoetin beta therapy (target Hb 115–135 g/L). However, the study did show a significant increase in the vitality and mental health domains of the medical outcomes short form health survey [244].

Efficacy of ESA in people with a kidney transplant

Studies in the early post-transplant period have shown that ESA is effective in these people, although the dose required may be higher than in pre-transplant period [228, 238]. Similarly, studies in late post-transplant period have shown efficacy of ESA in these people [239, 240, 245, 246].

In the Neo-PDGF study, high dose epoetin beta (30,000 IU) was administered during the first 2 weeks around kidney transplantation. Doses were given just before surgery, 12–24 h after transplantation, at 7 days and at 14 days post transplantation. When compared to the group not receiving any ESA, there was found to be significantly increased haemoglobin levels at 1 month after transplantation (mean Hb 111 g/L vs. 105 g/L $p = 0.038$). However, there was no significant difference in the incidence of delayed graft function (32% vs. 38.5%), the incidence of slow graft function (26 vs. 25%) or eGFR (42.7 vs. 44.3 ml/min/1.73m²) of epoetin beta versus control [247].

Guideline 6.3 - Post-transplant anaemia

We suggest that consideration is given to identifying (and correcting) reversible transplant specific causes of anaemia. (2B)

Guideline 6.3.1

We recommend that the treatment guidelines for anaemia in kidney transplant recipients should be similar to those for people with CKD not receiving dialysis (NDD-CKD). (1B)

Guideline 6.3.2

We suggest for stable non-bleeding individuals who clinically require a red cell transfusion, using single unit transfusion, where possible. (2B)

Guideline 6.3.3

We suggest the use of HIF-PHI therapy in transplant recipients should be as in people with NDD-CKD. (2B)

Rationale

Data on the use of HIF-PHI therapy in kidney transplant recipients are limited to small case series and non-randomised real-world evidence. In the randomised controlled trials transplant patients were excluded in the majority and hence data is limited to draw any conclusions. However, in reports thus far, the use of HIF-PHI therapy appears to be effective in raising Hb levels to the current recommended target range in the short term with limited documented adverse effects [248, 249]. The numbers of people treated are too small to currently make any specific recommendations of use of HIF-PHI in people with a kidney transplant [248, 249]. In the recent published studies from Asia, there were approximately 73

patients in the 4 studies from Asia [250–253]. A growing experience exists in Europe and the UK (personal communication). A specific consideration in the transplant population, would be the additive theoretical risk of malignancy in the long term.

Special populations

The guidelines detail suggested recommendations in people with CKD and cancer who are symptomatic with a Hb < 100 g/L despite iron replacement and indicate ESAs may be offered to patients, on active treatment for cancer (chemotherapy), whose cancer treatment is not curative or if a person had a previous cancer which is deemed cured. ESA therapy may also be considered in haematological disease such as myelodysplastic syndrome (MDS).

In those who are pregnant parenteral iron, if indicated, can be used from the second trimester. The rationale for this is that iron deficiency in pregnancy can contribute to maternal mortality, increased maternal morbidity, impaired infant development and potential negative effects on pregnancy outcomes (low birth weight, placental abruption, peripartum blood loss) [254, 255]. Parenteral iron is considered safe in pregnancy and breastfeeding [256–259].

ESA therapy during pregnancy may be continued unless there is a major contra-indication such as hypertension or thrombosis risks. The Rationale is based on the fact that Hb values < 85 g/L are associated with a 62% increase in the risk of low birth weight (< 2,500 g) and a 72% increase in the risk of preterm delivery before 37 weeks, across ethnic groups [260]. Reviews have commented that ESA therapy are considered safe in pregnancy, as they are large molecules which is unlikely to cross the placenta [261, 262].

A number of research and audit recommendations have been detailed in Tables 5 and 6.

Lay summary

Anaemia is a commonly diagnosed complication among people suffering with chronic kidney disease. If left untreated, it may affect quality of life. There are several causes for anaemia in this population. As the kidney function deteriorates, together with medications and dietary restrictions, people with chronic kidney disease may develop iron deficiency, resulting in reduction of iron supply to the bone marrow (which is the body organ responsible for the production of different blood elements). People with chronic kidney disease may not be able to use their own body's iron stores well and hence, many people, particularly those receiving haemodialysis, may need additional iron treatment, usually provided by injection.

With further weakening of kidney function, people with chronic kidney disease may need additional

Table 5 Clinical research recommendations

RCT to evaluate the impact of IV versus oral iron in people on peritoneal dialysis
RCT of IV iron on hard clinical outcomes in people with non-dialysis dependent CKD but without anaemia.
RCT of oral iron dosing in people with non-dialysis dependent CKD
Determination of optimal iron dosing and regimes for HIF-PHI based therapy.
Use of HIF-PHI in certain sub-groups such as DM, ADPKD, diabetic retinopathy, ESA hyporesponsiveness and allergy to IV iron.
Impact of HIF-PHI on quality of life and functional capacity in people with CKD.
The safety and haemoglobin correction benefits of HIF-PH inhibitors in people with adult polycystic kidney disease
The safety and efficacy of HIF-PH inhibitors in people with a functioning kidney transplant.
Whether HIF-PHI therapy is safe and beneficial in people with advanced heart failure.
Whether HIF-PHI therapy is safe and beneficial in people with systemic chronic inflammatory diseases affecting the kidneys.
The safety and efficacy of HIF-PHI- therapy in young people and children under 18 years of age.
The factors that influence people with kidney disease and health professionals to choose between HIF-PHI and ESA therapies
Combination therapy of HIF-PHI with ESA to lower doses and improve outcomes.
Comparison of different HIF-PHI agents head-to-head
Whether SGLT2-inhibitor therapy can safely prevent and correct anaemia in people with non-dialysis dependent CKD.
Safety of HIF-PHI use in people with an underlying malignancy (active or recent).
Whether HIF-PHI use reduces the frequency of IV iron infusions in people with CKD.

treatment with a substance called erythropoietin which drives the bone marrow to produce its own blood. This substance, which is naturally produced by the kidneys, becomes relatively deficient in people with chronic kidney disease. These people will eventually need treatment with erythropoietin or similar products that are given by injection.

Over the last few years, several iron and erythropoietin products (synthetic products and those stimulating the body's own erythropoietin) have been licensed for treating anaemia in people with chronic kidney disease. In addition, several publications discussed the benefits of each treatment and possible risks associated with long term treatment. The current guidelines provide advice to health care professionals on how to screen people with chronic kidney disease for anaemia, which people to investigate for other causes of anaemia, when and how to treat people with different medications, how to ensure safe prescribing and monitoring of treatment and how to diagnose and manage complications associated with anaemia and the drugs used for its treatment.

Table 6 Audit recommendations

Proportion of people starting an ESA without prior measurement of serum ferritin and TSAT (or % HRC or Chr or Ret-He).
Proportion of people with non-dialysis dependent CKD with an eGFR < 30 ml/min/1.73m ² (CKD-EPI) with an annual haemoglobin level.
Proportion of people with non-dialysis dependent CKD stage 4–5 with Hb 100–120 g/L.
Proportion of people with dialysis dependent CKD on Peritoneal Dialysis receiving iron therapy; type: oral vs. parenteral.
Proportion of people with non-dialysis dependent CKD and people receiving PD who are iron replete
Proportion of people on HD who are iron replete.
Proportion of people with non-dialysis dependent CKD with serum ferritin > 600 mcg/L
Proportion of people on HD with a serum ferritin > 700 mcg/L or TSAT > 40%
Proportion of people with non-dialysis dependent CKD and heart failure and non-dialysis dependent CKD without anaemia who have iron parameters (ferritin and TSATs) checked in the last 4 months.
Proportion of people with non-dialysis dependent CKD and heart failure with iron deficiency but preserved haemoglobin treated with iron
Proportion of people on kidney replacement therapy (haemodialysis or peritoneal dialysis for more than 3 months) with Hb < 100 g/L who are not prescribed an ESA.
Proportion of people with non-dialysis dependent CKD with serum ferritin levels < 100 µg/L, %HRC > 6% or a Chr/Ret-He < 31 pg at start of treatment with ESA or HIF-PHI.
Proportion of people with dialysis dependent CKD with serum ferritin levels < 200 micrograms/L, %HRC > 6% or a Chr/Ret-He < 31 pg at start of treatment with ESA or HIF-PHI.
The proportion of people with CKD treated with an ESA or HIF-PHI with Hb > 120 g/L.
Mean (median) ESA dose in people with CKD maintained on ESA therapy.
Mean (median) HIF-PHI dose in people with CKD maintained on HIF-PHI therapy.
Prevalence of resistance or hyporesponsiveness to ESA among people receiving kidney replacement therapy.
The proportion of people with anaemia associated with CKD treated with HIF-PHI requiring IV iron infusions.
Proportion of people receiving HD who received a blood transfusion within the previous year.
Proportion of people with advanced non-dialysis dependent CKD (eGFR < 30 ml/min/1.73m ²) who received a blood transfusion in the previous year.

Abbreviations

ACEi	Angiotensin converting enzyme inhibitor
AKI	Acute kidney injury
AEs	Adverse events
ARB	Angiotensin receptor blocker
CKD	Chronic kidney disease
Chr	Reticulocyte Hb count
CI	Confidence interval
CRP	C reactive Protein
CMV	Cytomegalovirus
CVD	Cardiovascular disease
DD-CKD	Dialysis dependent CKD
DVT	Deep venous thrombosis
DNA	Deoxyribonucleic acid
EBV	Epstein Barr virus
EMA	European Medicines Agency
EPO	Erythropoietin

ESA	Erythropoiesis Stimulating Agent
FBC	Full blood count
FCM	Ferric carboxymaltose
FID	Functional iron deficiency
FDI	Ferric derisomaltose
FPC	Ferric Pyrophosphate Citrate
FGF23	Fibroblast growth factor 23
GFR	Glomerular filtration rate
Hb	Haemoglobin
HD	Haemodialysis
HR	Hazard Ratio
HFrEF	Heart failure patients with reduced ejection fraction
HiD/LF	High dose, low frequency
HRQoL	Health related quality of life
HIF-1α	Hypoxia inducible factor-1 alpha
HIF-PHI	Hypoxia-Inducible Factor
HUS	Haemolytic uraemic syndrome
IRR	Incident rate ratio
IV	Intravenous
IU	International Unit
KDIGO	Kidney Disease Improving Global Outcomes
KTR	Kidney transplant recipient
LD/HF	Low-dose, high-frequency
MACE	Major adverse cardiac events
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MCHC	Mean corpuscular haemoglobin concentration
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MDS	Myelodysplastic syndrome
NYHA	New York Heart Association
NICE	National Institute for Health and Care Excellence
NDD-CKD	Non-dialysis dependent CKD
PD	Peritoneal dialysis
OR	Observed risk
%HRC	Percentage hypochromic red cells
PTH	Parathyroid hormone
PRCA	Pure red cell aplasia
PKD	Polycystic kidney disease
PE	Pulmonary embolism
PCR	Polymerase chain reaction
PY	Patient year
PTA	Post-transplant anaemia
QALYs	Quality adjusted life years
ROC	Reactive oxygen species
RR	Relative risk
RET-He	Reticulocyte Hb equivalent
RCT	Randomised controlled trial
ROC	Receiver operator curve
6MWT	Six-minute Walk test
SmPC	Summary of product characteristics
SC	Subcutaneous
SGLT2-inhibitor	Sodium-glucose-co-transporter-2 inhibitor
SDD	Stable dialysis dependent CKD
SFGC	Sodium ferric gluconate
TSAT	Transferrin Saturation
TNFα	Tumour necrosis factor alpha
UK	United Kingdom
USA	United states of America
VEGF	Vascular endothelial growth factor

Supplementary Information

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Supplementary Material 1

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