Clinical Practice Guideline:
Anaemia of Chronic Kidney Disease

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Method used to arrive at a recommendation

The recommendations for the first draft of this guideline resulted from a collective decision reached by informal discussion by the authors and, whenever necessary, with input from the Chair of the Clinical Practice Guidelines Committee. If no agreement had been reached on the appropriate grading of a recommendation, a vote would have been held and the majority opinion carried. However, this was not necessary for this guideline.

Conflicts of Interest Statement

All authors made declarations of interest in line with the policy in the UK Kidney Association Clinical Practice Guidelines Development Manual. Further details can be obtained on request from The UK Kidney Association.

Grading the evidence

The evidence for these recommendations has been assessed using the modified GRADE system. (5) 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. 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 1A to 2D.

Authors reviewed the evidence and came to a collective decision on the guidance, with input from the chair of the guidelines committee as needed.

Acknowledgements

This document has been externally reviewed by key stake holders according to the process described in the Clinical Practice Guidelines Development Policy Manual.

Contents

Executive Summary

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 (a consequence of impaired oxygen sensing by the failing kidneys) are perhaps the most common causes of anaemia in people with CKD, especially those requiring kidney replacement therapy (KRT/dialysis). 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. Anaemia is a major clinical problem in people suffering from CKD. This guideline adds to the previous 2017 and updated 2020 anaemia guidelines. Specifically, we aim to:

1. Provide guidance on the use of iron in people with NDD-CKD and DD-CKD with added information from several RCTs.
2. Comment on iron deficiency without anaemia in people with CKD.
3. Provide further information on anaemia management in people with a transplant.
4. Provide guidance in the use of the new HIF-PHI drugs in people with NDD-CKD and comment on use in DD-CKD.
5. Comment on the potential new therapies to be aware of for future.
6. Support safe implementation of therapies.
7. Update audit and research recommendations.

We offer evidence based graded practice guidance covering appropriate use of HIF-PHI in people with CKD, accompanied by recommendations for implementation, clinical research and audits.

I am enormously grateful to all the members of the guideline working group for volunteering so generously their time and expertise in revising and further developing this guideline. I would like to particularly thank my NIHR fellow Dr Sebastian Spencer for his efforts as a NIHR trainee.

Prof Sunil Bhandari
Chair of Guideline Working Group

Introduction

This 2024 clinical practice guideline provides updated recommendations on the management of Anaemia of Chronic Kidney Disease (ACKD) including people receiving kidney replacement therapy and serves to supersede all previously published UK guidelines. Recommendations have been graded using the modified GRADE system to indicate both the strength of each recommendation (strong or weak) and level of evidence for the recommendation (A-D) [1, 2]. The UK Kidney Association (UKKA) endorses the NICE Guideline for anaemia management in Chronic Kidney Disease (CKD) 2021 [3].

This 2024 guideline update covers the management of anaemia in adults, children and young people with anaemia associated with CKD. While there is no universally accepted classification for categorising the population with anaemia of CKD by age, this guideline adopts the classification set out in NICE Guideline [4] defined as follows:

- children: 0–13 years
- young people: 14–17 years
- adults: 18 years and over

This guideline has reviewed the additional evidence from July 2016 using systematic literature searches to identify all published clinical evidence relevant to the review questions. Databases were searched for all published papers between July 2016 and May 2023, using relevant medical subject headings, free-text terms and study-type filters where appropriate. All searches were conducted in MEDLINE, PUBMED, Embase, and The Cochrane Library. Data search used the following search terms:

- Anaemia and CKD and the US equivalent terms for “anemia”
- Anaemia and dialysis
- Anaemia and transplantation
- Anaemia and end stage kidney disease and equivalents
- Blood transfusion and dialysis
- Erythropoietin, EPO, ESA
- ESA Resistance
- Ferroportin
- Hepcidin
- Hypoxia inducible factor prolyl hydroxylase
- Hypoxia inducible factor inducers
- hypoxia inducible factor inhibitors, HIF-PHI
- Immunosuppression and anaemia
- Immunosuppression and EPO
- Immunosuppression and blood transfusion
- Iron anaphylaxis
- Iron deficiency
- Iron hypophosphataemia
- Iron therapy
- Iron sensitivity
- Iron toxicity
- SGLT2 inhibitors and anaemia
- SGLT2 inhibitors and Erythropoietin
- Pure red cell aplasia

- Renal anaemia
- Renal transplant and anaemia
- Renal transplant and blood transfusion
- Renal transplant and EPO

Previous guidelines covered the periods prior to the above dates. Articles not written in English were not assessed. Articles available in abstract forms, letters, case reports, editorials or review articles were also excluded. Articles were assessed for relevance to the guideline topic, eligibility for inclusion in the evidence base for that guideline and methodological quality.

Articles were considered of particular relevance if they were describing:

- Prospective randomised or quasi-randomised trials
- Controlled trials
- Meta-analysis of several trials
- Cochrane systematic reviews

Where evidence was available from the above sources, recommendations were based on these publications. Where there was a lack of evidence from high-quality studies, recommendations were based on current consensus from the guideline committee's experience and opinion of what constitutes good practice and that was made clear in the document:

We also reviewed all related guidelines including those listed below:

- European Renal Best Practice (ERBP) for Anaemia in CKD [5,6]
- Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines for Management of anaemia in CKD [7]
- Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Anaemia in Chronic Kidney Disease [8]
- The National Institute for Health and Care Excellence (NICE) guidelines (ng203) [3]

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 [9].

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).

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.

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Summary of Clinical Practice Guidelines on Anaemia of Chronic Kidney Disease

1. Assessment for Anaemia of CKD (Guidelines 1.1 – 1.5)

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)

Guideline 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. (1A)

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/1.73m^2. It is more likely to be the cause if the GFR is <30ml/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)

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. (1A)

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. (1A)

Guideline 1.5.1
We recommend that laboratory evaluation should include the following tests (1B):

- 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 hours **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 initial assessment, we recommend the following tests to diagnose the cause of anaemia in selected cases (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

2. Treatment of Anaemia of CKD with Iron (Guidelines 2.1 – 2.7)

Guideline 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. (1B)

Iron repletion is usually defined as:

- %HRC <6% / CHr or RET-He >31 pg / ferritin and TSAT (>100 microgram/L and >20%) in people with non-dialysis dependent CKD (NDD-CKD) or on PD and >200 microgram/L in people on HD. (2B)
- A target ferritin level greater than 100 microgram/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%.

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% 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)

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. (2A)

Guideline 2.3.2
We recommend that most people receiving haemodialysis will require IV iron. (1A)

Guideline 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 of 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 are no clear data. (not graded)

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%. (1A)

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)

Guideline 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. (1A)

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)

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. (1A)

Guideline 2.6.1
We recommend avoiding parenteral iron therapy in people with active infection. (1C)

Guideline 2.6.2 We suggest avoiding iron therapy in people with the following conditions (not graded):

- Hepatitis C virus infection (Positive PCR test)
- Haemochromatosis

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.187C>G) and S65C (c.193A>T).

Guideline 2.6.4
We suggest choice of parenteral iron be tailored, considering the benefits and risks associated with available iron preparations. (2C)

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 of > 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 toxicty. (1B)

3. 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)

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 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)

Guideline 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)

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)

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)

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)

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, 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. Subcutaneous administration of short-acting ESA preparations may be preferred in people receiving haemodialysis due to improved ESA efficacy at the EPO receptor, allowing for smaller doses to be used. However, convenience and choice may favour intravenous (IV) administration in people on HD. (2B)

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, 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)

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 (1A)

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 procedure or any other cause of hospitalisation, unless there is a clear contra-indication (for example, acute stroke or vascular access thrombosis). (2B)

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. (2C)

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)

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. (1A)

Guideline 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. (2C)

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 (1A):

- 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/µl
- High serum ferritin level

Guideline 3.15.1
We recommend that all ESA therapy should be stopped in people who develop ESA-induced PRCA. (1A)

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 ESAs. (1B)

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 antihypertensive drugs. (1A)

4. Treatment of Anaemia with HIF-PHI Agents (Guidelines 4.1-4.9)

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/1.73m^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)

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 - 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. (2C)

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, 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)

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. (2C)

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

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, 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)

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 are 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 retinopathy. (1D)

Guideline 4.7.5
We recommend caution in people with a history of thrombotic events following the SmPC for contra-indications. (1A)

Guideline 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. (2C)

Guideline 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. (2C)

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)

5. 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. (1A)

Guideline 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)

Guideline 5.1.2
We suggest using single unit transfusion, where possible, for stable non-bleeding people with CKD who clinically require transfusion. (2B)

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)

6. 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 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. (2C)

Guideline 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)

Guideline 6.3 - Post-Transplant Anaemia:
We suggest that consideration is given to identify (and correct) 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 on dialysis (NDD-CKD). (1B)

Guideline 6.3.2
We suggest for stable non-bleeding individuals who clinically require a red cell transfusion, use 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)

7. Special Populations (Guidelines 7.1-7.3)

Guideline 7.1 - Malignancy:
We suggest treating symptomatic anaemia in people with CKD and cancer when Hb <100 g/L. (2B)

Guideline 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)

Guideline 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. (1C)

Guideline 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). (2C)

Summary of Audit Measures on Anaemia of Chronic Kidney Disease

1. Proportion of people starting an ESA without prior measurement of serum ferritin and TSAT (or % HRC or CHr or Ret-He).
2. Proportion of people with non-dialysis dependent CKD with an eGFR < 30 ml/min/1.73m^2 (CKD-EPI) with an annual haemoglobin level.
3. Proportion of people with non-dialysis dependent CKD stage 4-5 with Hb 100-120 g/L.
4. Proportion of people with dialysis dependent CKD on Peritoneal Dialysis receiving iron therapy; type: oral vs. parenteral.
5. Proportion of people with non-dialysis dependent CKD and people receiving PD who are iron replete.
6. Proportion of people on HD who are iron replete.
7. Proportion of people with non-dialysis dependent CKD with serum ferritin >600 mcg/L.
8. Proportion of people on HD with a serum ferritin >700 mcg/L or TSAT >40 %.
9. 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.
10. Proportion of people with non-dialysis dependent CKD and heart failure with iron deficiency but preserved haemoglobin treated with iron.
11. 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.

12. Proportion of people with non-dialysis dependent CKD with serum ferritin levels < 100 microgram/L, %HRC >6% or a Chr/Ret-He <31 pg at start of treatment with ESA or HIF-PHI.
13. 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.
14. The proportion of people with CKD treated with an ESA or HIF-PHI with Hb > 120 g/L.
15. Mean (median) ESA dose in people with CKD maintained on ESA therapy.
16. Mean (median) HIF-PHI dose in people with CKD maintained on HIF-PHI therapy.
17. Prevalence of resistance or hyporesponsiveness to ESA among people receiving kidney replacement therapy.
18. The proportion of people with anaemia associated with CKD treated with HIF-PHI requiring IV iron infusions.
19. Proportion of people receiving HD who received a blood transfusion within the previous year.
20. 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.

Summary of Research Recomendations

We recommend the following further research including, wherever possible, randomised trials:

1. RCT to evaluate the impact of IV versus oral iron in people on peritoneal dialysis.
2. RCT of IV iron on hard clinical outcomes in people with non-dialysis dependent CKD but without anaemia.
3. RCT of oral iron dosing in people with non-dialysis dependent CKD.
4. Determination of optimal iron dosing and regimes for HIF-PHI based therapy.
5. Use of HIF-PHI in certain sub-groups such as DM, ADPKD, diabetic retinopathy, ESA hyporesponsiveness and allergy to IV iron.
6. Impact of HIF-PHI on quality of life and functional capacity in people with CKD.
7. The safety and haemoglobin correction benefits of HIF-PH inhibitors in people with adult polycystic kidney disease.
8. The safety and efficacy of HIF-PH inhibitors in people with a functioning kidney transplant.
9. Whether HIF-PHI therapy is safe and beneficial in people with advanced heart failure.
10. Whether HIF-PHI therapy is safe and beneficial in people with systemic chronic inflammatory diseases affecting the kidneys.
11. The safety and efficacy of HIF-PHI- therapy in young people and children under 18 years of age.
12. The factors that influence people with kidney disease and health professionals to choose between HIF-PHI and ESA therapies.
13. Combination therapy of HIF-PHI with ESA to lower doses and improve outcomes.
14. Comparison of different HIF-PHI agents head to head.
15. Whether SGLT2-inhibitor therapy can safely prevent and correct anaemia in people with non-dialysis dependent CKD.
16. The safety and efficacy of prospective therapies to treat anaemia in CKD; including Anticalin proteins directed against hepcidin, and anti–IL-6 ligand antibody, hepcidin monoclonal antibody, Bone Morphogenic Protein 6 (BMP6) monoclonal antibody and ferroportin antibody therapy.
17. Safety of HIF-PHI use in people with an underlying malignancy (active or recent).
18. Whether HIF-PHI use reduces the frequency of IV iron infusions in people with CKD.

Rationale for Clinical Practice Guidelines on Anaemia of Chronic Kidney Disease

1. Assessment for Anaemia of CKD (Guidelines 1.1 – 1.5)

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

There is insufficient literature to suggest the ideal frequency of Hb testing in people with CKD who are not on ESA therapy. Alternatively, data from clinical trials have shown that the rate of Hb decline in these people is gradual [1, 2]. In a Canadian study to assess the effect of ESA therapy on left ventricular mass in people with CKD [2] 172 people were assigned either to receive therapy with erythropoietin α subcutaneously to maintain or achieve Hb level targets of 120 to 140 g/L, or to the control/delayed treatment group with mean Hb levels of 90 ± 5 g/L. During 2 years' follow up a significant proportion of patients eventually required ESA therapy. However, among those who did not require ESA therapy, mean Hb values remained relatively stable throughout the study period. Hb level should be measured at least monthly in CKD G5 haemodialysis patients and every three months in CKD G5 peritoneal dialysis patients.

KDIGO 2012 guidelines suggest measurement of Hb at least annually in patients with NDD-CKD G3, at least twice per year in patients with NDD-CKD G4–5 and at least every 3 months in patients with CKD G5HD and CKD G5 PD. For those treated with an ESA, they recommend measuring Hb concentration when clinically indicated and at least every 3 months in patients with NDD-CKD G3–5 and CKD G5 PD and at least monthly in patients with CKD G5 HD [3].

References

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2. Levin A, Djurdjev O, Thompson C, et al. Canadian randomized trial of haemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. Am J Kidney Dis 2005; 46:799-811.
3. KDIGO Clinical Practice Guideline for Anaemia in Chronic Kidney Disease. Kidney Int Suppl 2012;2:279-33

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. (1A)

Rationale

The UK Kidney Association (UKKA) and Royal College of Physicians endorse the NICE Guidelines for Chronic Kidney Disease: Managing Anaemia [(1)]. The reader is referred to these guidelines as well as the European Renal Best Practice (ERBP) for Anaemia in CKD [(2,3)] and the KDOQI [(4)] Guidelines for management of anaemia in CKD. The KDIGO website (www.kdigo.org) [(5)] is a useful site of reference for comparison of evidence-based guidelines internationally.

Anaemia is defined as having a Hb value below the established cut off defined by the World Health Organisation [(4)]. Different defined groups have different cut offs. For adults:

- Men and postmenopausal women Hb <130 g/L
- Premenopausal women Hb <120 g/L
- Pregnant women Hb <110 g/L

In 2006, KDOQI modified this definition by giving a single criterion for diagnosing anaemia in adult males (Hb <135 g/L, regardless of age) because the decrease in Hb among males aged >60 years is often attributable to associated co-morbidities (4), while KDIGO suggest a diagnosis of anaemia in adults with CKD when the Hb concentration is <130 g/L in males and <120 g/L in females [(5)].

Anaemia is defined as a haemoglobin concentration less than the 5th percentile for age. Hb levels vary by age, and many laboratories use adult norms as references; therefore, the patient's Hb level must be compared with age-based norms to diagnose anaemia [(6)].

In addition to sex, age and pregnancy other factors influence Hb level including smoking, altitude, race and genetic disorders (thalassemia and sickle cell disease). In CKD, a person‘s anaemia should be defined using these same criteria. The degree of kidney impairment affects the likelihood of any person developing anaemia. Although current treatment with ESAs is not recommended unless Hb falls consistently below 110 g/L, other causes of anaemia should be excluded in persons with Hb below normal range. The current definition for anaemia applies to adult subjects older than 18 years, of all races and ethnic groups, and living at relatively low altitude (<1,000 m or 3,000 ft.) [(7)]. With increasing altitude, endogenous erythropoietin production is increased; as a result, Hb concentration can be expected to increase by about 6 g/L in women and 9 g/L in men for each 1,000 m of altitude above sea level [(8)].

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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/1.73m^2. It is more likely to be the cause if the GFR is <30ml/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)

Rationale

The prevalence of anaemia in people with NDD-CKD increases as the GFR progressively falls [(1)]. NHANES III data demonstrate a prevalence of anaemia of 1%, 9% and 33% in people with NDD-CKD with an eGFR of 60, 30 and 15 ml/min/1.73m^2 respectively [(2)]. UK data of > 112,000 unselected patients in the general population showed a population prevalence of NDD-CKD G3-G5 of 4.9% [(3)]. In these people the prevalence of sex specific anaemia (<120 g/L men: < 110 g/L women) was 12%.

Anaemia is more prevalent among people with diabetes. In addition, anaemia of CKD develops earlier in people with diabetes compared with people who do not have diabetes [(4-8)]. In a cross-sectional study involving over 800 people with diabetes, anaemia has been found to be two to three times more prevalent in patients with diabetes compared with the general population at all levels of GFR [(9)].

References

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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. (1A)

Rationale

In kidney anaemia, serum erythropoietin (EPO) levels are lower than appropriate for the degree of anaemia. In people with CKD and anaemia, erythropoietin titres are not lower but may be equal to or even higher than in normal non-anaemic individuals [1-3]. Measurement of erythropoietin level is very rarely helpful.

References

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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. (1A)

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)

Tests to Determine Iron Status:

- Percentage of hypochromic red blood cells (% HRC), but only if processing of blood sample is possible within 6 hours **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

Although relative erythropoietin deficiency is common among people with anaemia and CKD, other potential causes should be identified or excluded. A clinical and laboratory evaluation of the cause of anaemia should precede initiation of ESA therapy. The recommended laboratory evaluation aims at assessing:

- The degree and cause of anaemia,
- Bone marrow responsiveness, and
- Iron stores and iron availability for erythropoiesis.

Anaemia due to causes other than erythropoietin deficiency should be suspected when:

- The severity of the anaemia is disproportionate to the deficit in kidney function,
- There is evidence of iron deficiency,
- There is evidence of haemolysis, or
- There is evidence of bone marrow disorder as manifest by leucopoenia and/or thrombocytopenia.

a) Assessment of anaemia severity

In people with CKD not yet requiring dialysis and in those on peritoneal dialysis (PD), the timing of the blood sample draw is not critical because plasma volume in these people remains relatively constant. In people receiving haemodialysis (HD) one issue remains to be clarified. Haemoglobin concentrations are routinely measured in people receiving dialysis before dialysis. This potentially leads to lower haematocrit values as a result of dilution from fluid overload prior to ultrafiltration and an underestimate to actual haemoglobin value.

Interdialytic weight gain contributes to a decrease in Hb level, whereas intradialytic ultrafiltration

leads to an increase in Hb level. Thus, a pre-dialysis sample underestimates the euvolaemic Hb level, whereas a post dialysis sample over-estimates the euvolaemic Hb. Indeed, changes on haematocrit can vary from the start to the end of dialysis by up to 6% depending on the volume of ultrafiltration. In a study of 68 stable people receiving HD receiving erythropoietin subcutaneously, average mean pre-dialysis Hb was 10 g/L lower than average post dialysis Hb [(1)]. There was a strong linear inverse correlation between percentage of change in Hb and haematocrit (Hct) values and percentage of change in body weight. In another study of 49 stable HD patients, among all pre-HD and post-HD Hb values, levels measured at the end of short dialysis intervals were closest to the mean Hb value of the week, derived from calculation of the area under the curve for the readings of the week [(2)]. In unit-based haemodialysis persons receiving thrice weekly dialysis, Hb monitoring performed prior to a mid-week haemodialysis session would minimise Hb variability due to the longer inter-dialytic interval between the last treatment of one week and the first of the next.

References

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b) Assessment of Bone Marrow Responsiveness

In general, anaemia of CKD (anaemia of chronic disease) is normochromic and normocytic and is morphologically indistinguishable from the anaemia of chronic illness. Initial assessment of anaemia in people with CKD should aim at identifying other factors that may influence the response to treatment.

- In addition to Hb, other indices of the full blood count (FBC) report may provide important clinical information: Macrocytosis could be due to folate or vitamin B12 deficiency.
- In addition to anaemia of CKD, microcytosis could be due to iron deficiency or haemoglobinopathies.
- Macrocytosis with leucopenia or thrombocytopenia could be due to several factors such as alcohol intake, nutritional deficit (vitamin B12 or folate deficiency), or myelodysplasia.
- Serum folate is more prone to variation and can be affected by the person's diet immediately prior to blood being taken, alcohol, trauma and other factors therefore occasionally red cell folate may need to be measured where serum folate is equivocal.
- Haemolysis is suggested by the presence of macrocytosis, high lactate dehydrogenase and positive Coombs test.
- The normal absolute reticulocyte count ranges from 40,000 to 50,000 cells/µL. Although it has a significant inter-patient variability, this test may be useful as a semi-quantitative marker of erythropoietic activity.

c) Evaluating Iron Status in Anaemic People with CKD

The aim of evaluating iron status is to assess:

1. Iron level in tissue stores and
2. The adequacy of iron utilisation for erythropoiesis.

Serum ferritin level is the only available blood marker of storage iron. There are several tests to assess adequacy of iron for erythropoiesis: TSAT, MCV, MCH, percentage of hypochromic red blood cells (HRC) and reticulocyte Hb content (CHr) or RET-He. Serum iron has not routinely been studied in people with CKD.

Tests limitations

- HRC estimation is a useful test for assessment of iron availability but is limited by the effect of sample storage time and need for special analysers. Long sample storage time (> 6 hours) may spuriously increase HRC. Because a fresh sample is needed, this measure may not be practical in routine clinical practice, especially in satellite dialysis patients.

- If using percentage of hypochromic red blood cells from a fresh sample is not possible, reticulocyte Hb content (CHr) or RET-He could be a suitable alternative.

- If testing for CHr (or RET-He) is not feasible, it is preferable to test ferritin and TSAT together because the combination provides an important insight into erythropoiesis, iron storage and iron availability to bone marrow.

- Low serum ferritin is diagnostic of iron deficiency. High serum ferritin, in addition to expressing the adequacy of iron stores, could be due to inflammatory conditions. TSAT is influenced by nutritional status, timing and inflammation. TSAT is also limited by high day to day variations.

Historically in people with NDD-CKD, it was proposed that serum ferritin levels less than 25 ng/mL in males and less than 12 ng/mL in females were suggestive of depletion of iron stores as a cause of anaemia; but serum ferritin level is less reliable in the evaluation of iron stores in people with NDD-CKD and in those receiving HD, because ferritin level is affected by other factors in addition to iron storage status. In relatively healthy people receiving HD, before widespread use of IV iron therapy, the finding of a ferritin level less than 50 ng/mL was not uncommon [(1)] and was associated with absent bone marrow iron in approximately 80% of people [(2)]. However, in people receiving HD with several co-morbidities, absent iron stores may still be found at ferritin levels approaching or even exceeding 200 ng/mL [(3)].

Iron-deficiency is most likely to contribute to anaemia when TSAT results are less than 20%. However, the clinical utility of TSAT is impaired by the absence of a diagnostic threshold above which deficient iron utilisation can be excluded as a cause of anaemia [(4)].

There is little information in literature to guide the approach to people with CKD who show laboratory evidence of iron deficiency. Nevertheless, given the high prevalence of GI blood loss due to variety of causes in this population, deciding on a subsequent management plan, including endoscopy, depends on the clinical presentation. This supports the recommendation that people with CKD who present with anaemia and iron deficiency should undergo careful clinical assessment prior to the initiation of anaemia therapy [(5-7)].

Reduced iron availability for erythropoiesis can manifest as low mean corpuscular volume (MCV) and mean corpuscular Hb (MCH), but given the relatively long lifespan of circulating erythrocyte, this test

will not reflect the existing availability of iron at the time of testing. Testing the reticulocytes for their Hb content (CHr or RET-He) may allow more accurate estimation of iron availability, because reticulocytes are present in the circulation for 4-5 days, so give a discrete population to study. Reduced red cell Hb can be reflective of reduced haem availability or globin. Therefore, the red cell analyte values (%HRC, CHr, Ret-He) may be affected by the presence of haemoglobinopathies [4].

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2. Treatment of Anaemia of CKD with Iron (Guidelines 2.1 – 2.7)

Guideline 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. (1B)

Iron repletion is usually defined as:

- %HRC <6% / CHr or RET-He >31 pg / ferritin and TSAT (>100 microgram/L and >20%) in people with non-dialysis dependent CKD (NDD-CKD) or on PD and >200 microgram/L in people receiving HD. (2B)
- For children, aim for a target ferritin level greater than 100 microgram/L for children with CKD receiving 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%.

Rationale

The definition of “adequate” iron status [1] is:

- Serum ferritin
    - 200-700 microgram/L in people receiving HD
    - 100-600 microgram/L in people with NDD-CKD and

- HRC <6%, or CHr/RET-He >31 pg
- TSAT 20%-40%

It must be noted that the above ranges are not the optimum values to target with treatment as observed in some trials, if the treatment aims to minimise ESA dosage to maintain target Hb and maximising Hb levels and minimising the need to initiate ESA therapy. However, the aim of iron treatment targets is to optimise anaemia therapy while minimising potential toxicity. Therapy targets aim at:

1. Minimising the ESA or HIF PHI dose required to maintain target Hb levels in those on ESA or HIF PHI therapy and;
2. Maximising the Hb level and minimising the need to initiate ESA or HIF PHI therapy to achieve target-range Hb levels in those not on ESA or HIF PHI therapy.

Increasing the Hb in anaemic people with CKD places the greatest demand for iron in the erythropoietic tissues. 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, the 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 reported that the dose of ESA required to achieve and maintain a given Hb level is inversely related to iron stores [2-7]. Iron deficiency (absolute or functional) was the main cause of ESA resistance in the UK, but this has now been solved by parenteral iron replacement strategies [8]. The evidence behind the statement that TSAT generally should be maintained at greater than 20% stems from a single RCT comparing higher to lower TSAT targets; participants randomised to a target TSAT of 30% to 50% demonstrated a 40% reduction in ESA dose compared with those assigned to a target of 20% to 30% [9].

In a randomised controlled study involving 157 haemodialysis participants comparing iron management based on serum ferritin and transferrin saturation versus CHr, CHr was a markedly more stable analyte than serum ferritin or transferrin saturation. Iron management based on CHr resulted in similar haematocrit and epoetin dosing while significantly reducing IV iron exposure [10]. In another study involving 164 people with CKD on HD, low CHr (<26 pg) was suggestive of functional iron deficiency. When a subgroup of participants were randomly assigned to receive a single dose of IV iron dextran (1000 mg), a CHr <26 pg at baseline predicted iron deficiency with a sensitivity of 100% and specificity of 80%. The serum ferritin, transferrin saturation and percentage of hypochromic red blood cells were all less accurate. The time to correction of iron deficiency at the level of the reticulocyte was found to be within 48 hours as measured by correction of the mean CHr to >26 pg, and by the shift of the majority of the reticulocyte population to CHr >26 pg within this time span [11].

In a study comparing TSAT versus CHr as a guide of parenteral iron therapy in 197 Japanese people with CKD-PD, although CHr reflected the iron status more sensitively, TSAT was a better clinical marker for iron supplementation therapy [12]. A cross-sectional study of 72 DD-CKD (HD) was performed in which the mean haemoglobin was 9.6 ± 0.16 g/dL. Mean haemoglobin content of

reticulocytes (CHr) was normally distributed and correlated with MCV, MCH and red cell ferritin. A low CHr identified iron deficiency with normal serum ferritin or transferrin saturation [13].
Tessitore et al [14] compared the diagnostic efficiency of different iron markers in HD. Although percentage hypochromia >6% was the best marker to identify responsiveness to intravenous iron; CHr was 78% efficient at cut-off ≤ 29 pg.

TSAT and serum ferritin were evaluated in 47 people with HD with baseline serum ferritin levels <600 mcg/L. Participants were treated with IV dextran (1000 mg over ten haemodialysis treatments). Participants were classified as having iron deficiency if haematocrit value increased by 5% or if their erythropoietin dose decreased by 10% by 2 months. Receiver operator curves (ROC) demonstrated that none of the iron indices had a high level of utility (both sensitivity and specificity >80%). As such it was concluded that both tests should be interpreted in the context of the participant's underlying EPO responsiveness. In participants who are responsive to EPO, a TSAT <18% or serum ferritin level <100 mcg/L should be used to indicate inadequate iron. When EPO resistance is present, TSAT<27% or ferritin <300 mcg/L should be used to guide iron management [15].

A study of 209 participants with solid tumours or haematological malignancy using a threshold of CHr 32 pg ruled out iron deficiency with a negative predictive value of 98.5% [16]. An American study of 556 participants who were referred for anaemia management yielded a receiver operating characteristic analysis CHr cut-off of 30.7 pg to identify IDA with 68.2% sensitivity and 69.7% specificity [17]. A further study of 40 people with CKD-HD in the maintenance phase of erythropoietin therapy compared for each person: baseline after an iron-free period and a second sample after 4 weeks of IV iron. For a CHr cut-off of 30.8 pg the area under curve (AUC) was 0.84 (95% CI 0.64–0.93), sensitivity 78.7%, and specificity 87.2%. %HRC AUC was 0.78 (95% CI 0.64–0.91), at cutoff 2.4%, sensitivity 72.2%, and specificity 88.1% [18].

A cross-sectional study by Karunarathne et al of 100 people with CKD in Sri Lanka demonstrated for the already defined cut-off value of CHr 29 pg showed a sensitivity and specificity of 54% and 73% respectively, but from the ROC coordinates they suggest an increase to 31 pg will increase the sensitivity and specificity to 63% and 61% respectively [19].

NICE guidelines on the evaluation of iron therapy in people with CKD suggests that for people on haemodialysis, %HRC >6% dominated all other iron evaluation strategies (it led both to more QALYs and lower cost) [1]. For the other people, TSAT<20% alone or serum ferritin <100 mcg/L alone were the least cost-effective strategy, but %HRC was the most cost-effective [1].

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 hours. 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- revised in these guidelines but NICE remains currently at 29 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 microgram/L).

We believe that CHr (<31 pg) is more sensitive in determining iron depletion than %HRC [17-19]. This is because CHr reflects haemoglobin content of young reticulocytes, and therefore reflects iron availability in the preceding few days; while %HRC reflects haemoglobin contents of whole erythrocyte pool, and since senescent erythrocyte 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 [1,15].
- For children, a target ferritin >100 mcg/L for dialysis and NDD-CKD, not on ESA therapy is appropriate [20]. There is no evidence that a higher ferritin target of 200 mcg/L is beneficial or safe in paediatric HD.

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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 [(1)]

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 [(2-4)]. This led to reductions in serum ferritin but no change in TSAT or serum iron. However, the trials did not assess the quantity of oral iron use. 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. While iron administration was left to the investigator's discretion and/or were based on local clinical practice patterns in the darbepoetin alfa group, oral iron was requested by trial protocol in the Roxadustat group [(5)].

Another challenge in assessing the impact of HIF-PHI on iron use was that in some trials, iron protocols differed between treatment and comparator groups within a trial while other trials tested similar iron protocols [(6, 7, 8)]. 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 [(9)], lower health related quality of life (HRQoL), higher rates of cardiovascular events and higher mortality [(10)].

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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. (2A)

Guideline 2.3.2
We recommend that most people on haemodialysis will require IV iron. (1A)

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 of 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 base for IV iron over oral iron in people with CKD who are pre-dialysis or maintained on PD is limited. Oral iron, if tolerated, appears to be adequate in most people particularly in combination with ESA therapy. In people who appear resistant to ESA therapy on oral iron, or are intolerant of oral iron, a therapeutic trial of IV iron trial seems reasonable.

- One randomised study in 188 participants with IV iron (1000 mg iron sucrose in divided doses over 14 days) versus oral iron (ferrous sulphate 325 mg TDS) in pre-dialysis participants demonstrated a greater improvement in Hb outcome in those on IV iron (more participants achieved a Hb increased of >10 g/L) but no difference in the proportion of participants who had to commence ESA after the start of the study [1].
- Two studies in pre-dialysis populations not on ESA (one without oral iron and the other after oral iron therapy) demonstrated improvements in Hb outcome after IV iron [2, 3].

Oral iron is easy and cheap to prescribe. However, it seems reasonable to treat people with CKD who have not responded to, or have been intolerant of, oral iron with IV iron.

Two randomised controlled trials of oral versus IV iron supplementation in participants with advanced NDD-CKD receiving concomitant ESAs agree. In the first study of 45 participants with Hb <110 g/L given either ferrous sulphate 200 mg TDS versus 300 mg iron sucrose IV monthly, there was no difference in Hb or ESA dose between the oral and IV group receiving ESA over a mean 5.2 months follow-up [4]. Iron stores were greater in the IV than oral group. Five participants (55%) in the oral iron group had diabetes, compared to none on the IV iron group and this may have confounded the results on iron stores. In addition, more participants in the oral iron group were exposed to ACEi/ARBs.

Similar findings were reported in another study of 96 people with NDD-CKD comparing 5 weeks of IV iron sucrose (200 mg every 7 days for a total of 5 doses) versus 29 days of thrice daily oral iron (ferrous sulphate 325 mg TDS). There was no difference in Hb or ESA dose but greater increase in ferritin in the IV group [5]. In this study the frequency of gastrointestinal symptoms was greater in the oral iron group than the IV iron group (constipation 34.5% vs. 12.5%; nausea 10.4% vs. 4.2%).
High dose, low frequency (HiD/LF) is considered to be a maximum of 2 infusions. For adults this is considered to be a minimum of 500 mg of iron in each infusion. Low dose, high frequency (LD/HF) is considered to be more than 2 infusions. For adults, there would typically be 100–200 mg of iron in each infusion.

At the time of publication intravenous iron products available in the UK did not have a UK marketing authorisation for all ages of children and young people for this indication.
Refer to the Summary of Product Characteristics for the prescription of individual iron preparations.

There is increasing evidence that using IV iron in CKD-PD is safe, improves Hb levels and reduces ESA dose requirements [6]:

- A cross-over study of oral and IV iron demonstrated higher Hb and lower ESA doses with IV iron after 4 months oral [7].
- 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 [8].
- 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 [9].

The relative safety of parenteral iron compared with oral iron was assessed in a study involving participants with stage 3 and 4 NDD-CKD and iron deficiency anaemia. Study participants were randomly assigned to either oral ferrous sulphate (n=69 to 325 mg three times daily for 8 weeks) or IV iron sucrose (n=67 to 200 mg every 2 weeks, total 1 g). The trial was terminated early based of a higher risk of serious adverse events in the IV iron treatment group. There were 36 serious cardiovascular events among 19 participants assigned to the oral iron treatment group and 55 events among 17 participants of the intravenous iron group (adjusted incidence rate ratio 2.51 (1.56–4.04)). Infections resulting in hospitalisation had a significantly increased adjusted incidence rate ratio of 2.12 (1.24–3.64). The authors concluded that among people with NDD-CKD and anaemia, IV iron therapy could be associated with an increased risk of serious adverse events, including those from cardiovascular causes and infectious diseases [10].

Conversely, the above finding was not reproduced in another larger trial that involved 626 people with NDD-CKD with anaemia and iron deficiency not on ESAs [11]. In this trial, participants were randomised (1:1:2) to intravenous (IV) ferric carboxymaltose (FCM), targeting a higher (400–600 microgram/L) or lower (100–200 microgram/L) ferritin range or oral iron therapy. The primary end point was time to initiation of other anaemia management (ESA, other iron therapy or blood transfusion) or Hb trigger of two consecutive values <100 g/L during Weeks 8–52. Achieving a higher ferritin target range led to a delay in the need to initiate ESA therapy and also a reduction in ESA dosage. The increase in Hb was greater with high-ferritin FCM versus oral iron (P = 0.014) and a greater proportion of participants achieved an Hb increase ≥10 g/L with high-ferritin FCM versus oral iron (HR: 2.04; 95% CI: 1.52–2.72; P < 0.001). Rates of adverse events and serious adverse events were similar in all groups [11].

Similarly, no safety signal could be detected in another trial comparing intravenous iron isomaltoside versus oral iron in stage G5 NDD-CKD. In this trial 351 iron-deficient participants were randomised 2:1 to either iron isomaltoside 1000 or iron sulphate administered as 100 mg elemental oral iron twice daily (200 mg daily) for 8 weeks. Hb response, serum-ferritin and TSAT were significantly increased with IV iron compared with those treated with oral iron. Incidence of adverse drug reactions was not different between both groups. More participants treated with oral iron sulphate withdrew from the study due to adverse events (4.3 versus 0.9%, P = 0.2) [12].

At present oral iron should remain first line treatment among people with NDD-CKD and IV iron used if recipients are intolerant of oral iron or remain with absolute or FID despite oral iron therapy. The further interpretation of these results is limited by several factors including the relative short duration of follow-up and limited data on potential long term adverse effects such as the impact of oxidative stress. However, as indicated by NICE, therapy should be individualised, or perhaps tailored and a high dose low frequency intravenous regime should be employed.

People treated with HD have additional iron losses from GI bleeding, blood tests and losses in the dialysis circuit that result in iron supplementation requirements that outstrip the capacity of the gut to absorb iron effectively. Maintenance IV iron in HD greatly reduces ESA requirements and costs [1,4,13-18]. Maintaining iron stores at steady state in a HD population requires 50-60 mg/week of intravenous iron [14-16]. How this is repleted remains a subject under study. A recent open label, randomised, multicentre, non-inferiority trial conducted in 351 people on HD randomised 2 : 1 to either iron isomaltoside 1000 (Group A) or iron sucrose (Group B) [19]. Subjects in Group A were equally divided into A1 (500 mg single bolus injection) and A2 (500 mg split dose). Group B were also treated with 500 mg split dose. All treatments showed similar efficacy and safety [19].

The FERWON Trial of 1538 people with NDD-CKD and iron deficiency anaemia (Hb <110 g/L, SF <100 mcg/L or <300 mcg/L and TSAT<30% and stable dose of ESA, was a randomised, open label study. 1027 participants were randomised to 1g iron isomaltoside and 511 to iron sucrose (200 mg given in in total up to five time) [20]. The co-primary endpoints were serious or severe hypersensitivity reactions and change in Hb from baseline to week 8. There were additional key safety endpoints: the incidence of composite cardiovascular adverse events and frequency of hypophosphatemia (<0.65 mmol/L]). The results showed a faster and greater early response with iron isomaltoside for Hb, SF and TSAT compared to iron sucrose. There was no statistically significant difference in the frequency of serious or severe hypersensitivity reactions between the treatment groups. The incidence of composite cardiovascular AEs was statistically significantly lower in the isomaltoside group compared to the sucrose group (4.1% vs 6.9%; p=0.25).

A prospective case control study from rural India comparing oral (ferrous sulfate) vs IV iron (iron sucrose found that serum iron, ferritin and TSAT increased in the IV iron compared to the oral group [21]. There were significant increases in Hb in all stages of kidney disease with IV iron in contrast to not being achieved with oral iron [21].

A trial of 60 people with pre-dialysis CKD (NDD-CKD) oral ferric citrate (2 g three times daily) versus oral ferrous sulfate (325 mg TDS) showed greater increases in TSAT and ferritin but no difference in Hb or in incidence of adverse events at 12 weeks [22].

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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%. (1A)

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 [1]. 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 [2, 3]. Magnetic resonance imaging provides a reliable assessment of tissue iron content in people on HD regularly treated with parenteral iron [4]. However, the clinical relevance of increased liver iron remains unclear.
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 [5]. Ongoing iron therapy with ferritin >500 mcg/L results in a higher median ferritin outcome [6].

Interpretation of iron status results and deciding on the need for further iron therapy should include a concomitant assessment of changes in Hb level and ESA or HIF-PHI dose over time. Examples:

- A dropping ferritin as well as decreasing Hb levels signifies blood loss e.g., on HD or bowel related anaemia: iron therapy is indicated; further investigation may be required depending on the clinical scenario.

- A decreasing ferritin level after initiation of ESA therapy, with a concomitant rise in Hb level indicates a response to ESA with a shift of iron from stores to bone marrow: further iron therapy is guided by target ferritin level.
- An increasing ferritin level after reduction of ESA dose to bring Hb level down to target range indicates ferritin level is rising as Hb synthesis is dropping further iron therapy may be postponed.
- A rising ferritin level and a drop in TSAT suggest an inflammatory condition: a source of inflammation may be sought such as sepsis, vascular access, surgery, recent hospitalisation: further iron therapy depends on target ferritin level and clinical scenario.
- Ongoing high requirements for IV iron to maintain a given ferritin level also point to ongoing 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 [7], inflammation, or reticulo-endothelial iron blockade. Evidence on the risks and benefits of IV iron therapy in this population is not well established. The effect of iron therapy in this group was assessed in the DRIVE trial [8], which evaluated the efficacy of IV ferric gluconate in 134 participants with high ferritin (500–1200 mcg/L) and low TSAT levels (≤ 25%) who were anaemic despite a high rHuEPO dose (≥225 IU/kg/week or ≥22500 IU/week). After 6 weeks the participants receiving ferric gluconate (125 mg IV at eight consecutive HD sessions) showed a significant increase in Hb in comparison with controls. However, the study has a number of limitations because, given the small sample size and short follow-up, it provides no information about safety and iron overload.

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 [9]. 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. The primary end point was the composite of nonfatal myocardial infarction, nonfatal stroke, hospitalisation for heart failure, or death, assessed in a time-to-first-event analysis. Secondary end points included death, hospitalisation for any cause, infection rate and ESA dose. The median follow-up period was 2.1 years. The high-dose group received a median monthly iron dose of 264 mg, compared with 145 mg in the low-dose group. The median monthly dose of an ESA was 29,757 IU in the high-dose group and 38,805 IU in the low-dose group. Hence the trial found that patients in the proactive arm who achieved ferritin levels ~600 mcg/L required lower ESA doses overall than those patients who were in the reactive arm where ferritin levels were maintained ~ 200 mcg/L. A total of 320 (29.3%) in the high-dose group had a primary end-point event, 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 [9].

Therefore, intravenous iron administered at a low dose and high frequency may be more appropriate for adults who are receiving in-centre haemodialysis. It should be noted that the PIVOTAL trial

investigated incident HD participants only, those who were already established on HD for >12 months were excluded from recruitment. 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 but it seems likely to have similar benefits.

The FIND-CKD study assessed the 12-month efficacy and safety of IV ferric carboxymaltose (FCM) compared with oral iron in ND-CKD participants with anaemia and iron deficiency. Two different target ferritin levels were studied: higher (400–600 mcg/L) or lower (100–200 mcg/L). This RCT found that IV FCM targeting a higher ferritin is more effective than oral iron in delaying or reducing the ESA requirement and the occurrence of 2 consecutive Hb levels <10 g/dL [(10)].

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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. (1A)

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

Iron Deficiency and no Anaemia
It is not known whether treatment of people with CKD and Hb values >120 g/L in the presence of iron deficiency is beneficial. The Iron and Heart multicentre double-blinded randomised controlled clinical trial examined the effects of a single dose of intravenous iron vs. placebo on functional capacity using the 6-minute walk test, in non-anaemic iron deficient people (serum ferritin <100 µg/L and/or TSAT<20%) with NDD-CKD stage 3b-5. 54 individuals were randomised to receive ferric derisomaltose (n = 26) or placebo (n = 28) [1-3]. Secondary analysis showed no impact on markers of oxidative stress, inflammation, and endothelial function. There was a modest but statistically significant rise in E-selectin in the IV iron group at 1-month and 3-month follow-up (p = 0.030 and p = 0.002 respectively). These results suggest ferric derisomaltose administration in people with NDD-CKD iron deficient does not induce prolonged oxidative stress or inflammation. These preliminary secondary analyses suggest larger trials are required to quantify the benefit of IV iron administration in this group.

The FAIR-HF trial enrolled 459 participants with NYHA class II or III, iron deficiency (ferritin <100 µg/l or between 100 and 299 µ g/l if TSATs <20%), Hb 95 – 135 g/L [4]. Participants were randomised to receive 200 mg of IV iron (ferric carboxymaltose) or saline. The primary end points were NYHA functional class and self-reported Patient Global Assessment at 24 weeks. The distance walked in 6 minutes was a secondary end point. Participants receiving ferric carboxymaltose, 50% reported being much or moderately improved on the Patient Global Assessment as compared to 28% of participants receiving placebo (OR, 2.51; 95% CI: 1.75 to 3.61). In the ferric carboxymaltose group, 47% had a NYHA functional class I or II at week 24, as compared with 30% of participants assigned placebo (OR for improvement by one class, 2.40; 95% CI: 1.55 to 3.71). Significant improvements were seen in distance on 6-minute walk test. In a sub-group analysis, the benefits of ferric carboxymaltose were seen in people with eGFR both above and less than 60 ml/min/1.73m^2.
The CONFIRM-HF trial enrolled 304 symptomatic participants with heart failure with left ventricular ejection fraction < or = 45%, elevated natriuretic peptides, and iron deficiency (ferritin <100 ng/mL or 100-300 ng/mL if TSATS <20%) [5]. Participants were randomised to either IV iron (ferric carboxymaltose, given as 500 or 1000 mg) or placebo. The primary end point was 6-min-walk-test (6MWT) distance from baseline to week 24. Treatment with FCM significantly prolonged 6MWT at week 24 (difference FCM vs. placebo: 33 ± 11 m, p = 0.002). The finding was consistent across all sub-groups including those with eGFR < 60 mL/min/1.73m^2.

The IRONMAN trial was a randomised controlled trial in the UK of people with heart failure (LV ejection fraction < or equal to 45%) and TSATs < 20% or serum ferritin < 100 µg/L were eligible [6]. 1137 were enrolled and randomly assigned to receive ferric derisomaltose or usual care. The primary outcome was recurrent hospital admissions for heart failure and cardiovascular death. 336 primary endpoints (22.4 per 100 patient years) occurred in the ferric derisomaltose group and 4111 (27.5 per 100 patient years) in the placebo group (RR 0.82 (0.66 – 1.02) p = 0.070. In the COVID 19 analysis (censoring f/u on Sept 30th 2020) 210 primary endpoints (22·3 per 100 patient-years) occurred in the

ferric derisomaltose group compared with 280 (29·3 per 100 patient-years) in the usual care group (RR 0·76 [95% CI: 0·58 to 1·00]; p=0·047). In a subgroup analysis there was no difference between those with eGFR above or below 60 mL/min/1.73m^2. For < 60 mL/min/1.73m^2 group there were 248 events (26.86 per 100 patient-years) in the ferric derisomaltose group compared to 318 events (35.36 per 100 patient years) in the placebo group (RR 0.77 [0.60-0.98].

The Iron and Heart trial and the Iron and Muscle trial both randomised participants to intravenous iron (ferric derisomaltose and ferric carboxymaltose in the two studies respectively [2, 7]. Both recruited participants with CKD (eGFR < 60 mL/min/1.73m^2) and defined iron deficiency as a ferritin < 100µg/L and/or TSATs < 20%. Both used 6MWT distance one month as the primary outcome. Iron and Heart recruited 54 participants and the Iron and Muscle trial recruited 75. Adjusting for baseline 6MWT there was no statistically significant difference in 6MWT distance at 1 month in either study (p = 0.26 and 0.74 in the two studies respectively). A subgroup in the Iron and Muscle trial had mitochondrial function assessed by two methodologies: respirometry and by 31-phosphorus magnetic resonance spectroscopy. There was no difference in mitochondrial function between placebo and iron groups at 1 month (p = 0.84 and 0.84 for the two methodologies respectively).

In a systematic review of iron-deficient but not anaemic adults, iron supplementation was associated with and improvement in subjective measures of fatigue but not with objective improvements in physical capacity, as determined by aerobic tests. It should be noted that people with CKD were not specifically included or analysed in the studies examined [8].

Two randomised controlled trials explored the use of IV iron in the treatment of restless leg syndrome (RLS) in HD patients. They both identified a significant but transient improvement in symptoms. However, since IV iron is now an established treatment in haemodialysis they have limited impact [9, 10].

They were both included in a systematic review which found that treatment of RLS with iron was associated with an increased rate of adverse events RR 2.04 (95% CI: 1.46–2.85), however these were not severe and not associated with treatment discontinuation. Overall, iron supplementation was associated with improvement of RLS [11].

Guedes and colleagues [12, 13] have shown a direct association with biomarkers of iron stores with worse physical health-related quality of life in NDD-CKD patients with or without anaemia and also an association with increased risk of all-cause mortality and cardiovascular events in people with NDD-CKD, with or without anaemia. Some have suggested consideration of treatment or people with “profound iron deficiency defined as a serum ferritin of <30 mcg/L and TSAT <16% but data is lacking to confirm this.

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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. (1A)

Guideline 2.6.1
We recommend avoiding parenteral iron therapy in people with active infection. (1C)

Guideline 2.6.2
We suggest avoiding iron therapy in people with the following conditions (not graded):
- Hepatitis C virus infection (Positive PCR test)
- Haemochromatosis

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.187C>G) and S65C (c.193A>T).

Guideline 2.6.4
We suggest choice of parenteral iron be tailored, considering the benefits and risks associated with available iron preparations. (2C)

Rationale

All forms of IV iron may be associated with acute adverse events (AEs). Immune mechanisms (including IgE-mediated responses or complement activation-related pseudo-allergy) may have a role in some cases [1]. Anaphylactoid reactions appear to occur more frequently with high molecular weight iron dextran [2]. The rate of life-threatening reactions to iron dextran administration is 0.6% to 0.7% [3,4]. Labile or free iron reactions occur more frequently with non-dextran forms of iron [4]. These reactions, also known as Fishbane reactions, are infusion rate related and are characterised by facial flushing, back pain and chest tightness sometimes accompanied with dyspnoea. They can often be mistaken for anaphylaxis, however symptoms often disappear following cessation of the infusion. Patients should have their vital signs monitored following cessation of the infusion and if symptoms have disappeared, can continue the therapy at a lower infusion rate. This does not exclude the patient form receiving that form of IV iron in the future, however a slower rate of infusion would be required for subsequent treatment. [1]

In one study, a total of 2534 people receiving haemodialysis were directly observed after double-blind exposure to intravenous sodium ferric gluconate (SFGC) or placebo. One participant in each of the SFGC and placebo groups experienced anaphylactoid reactions. Additional cases with characteristics possibly consistent with anaphylaxis occurred in 0.4% of intravenous SFGC–treated participants and 0.1% of placebo-treated participants. The results suggest that there is a relatively low rate of anaphylaxis with non-dextran irons and that the reactions are generally easily managed [5, 6].

A retrospective cohort study compared anaphylaxis rates between five IV iron preparations: iron dextran, ferumoxytol, ferric gluconate, iron sucrose and ferric carboxymaltose. The adjusted IRs for anaphylaxis per 10 000 first administrations were 9.8 cases (95% CI: 6.2 to 15.3 cases) for iron dextran, 4.0 cases (CI: 2.5 to 6.6 cases) for ferumoxytol, 1.5 cases (CI: 0.3 to 6.6 cases) for ferric gluconate, 1.2 cases (CI: 0.6 to 2.5 cases) for iron sucrose, and 0.8 cases (CI: 0.3 to 2.6 cases) for ferric carboxymaltose [7].

In the IRONMAN trial, 1127 people with heart failure with HFrEF and iron deficiency were recruited to either receive IV ferric derisomaltose (n=559) or usual care (n=568) [8]. There were no differences between the two groups and the rate of serious adverse events. Only one person in the study had an infusion related reaction, reported to have experienced vomiting, back pain and dizziness after commencing infusion, but recovered fully after overnight observation [8].

The MHRA has issued an updated guidance on the use of parenteral iron. This was in response to concerns raised as a result of serious and rarely fatal hypersensitivity reaction, particularly in pregnant women. These reactions can occur even when a previous administration has been tolerated (including a negative test dose). The risk of hypersensitivity is increased in people with: known allergies (including drug allergies); immune or inflammatory conditions (e.g., systemic lupus erythematous, rheumatoid arthritis); or those with a history of severe asthma, eczema, or other atopic allergy. As a result, the MHRA updated guidelines recommend that [9]:

- IV iron should be administered in strict accordance with the posology and method of administration described in the product information for each individual product (note that advice varies between products).
- Caution is needed with every dose of intravenous iron that is given, even if previous administrations have been well tolerated.
- IV iron products should only be administered when staff trained to evaluate and manage anaphylactic or anaphylactoid reactions—as well as resuscitation facilities—are immediately available.
- Recipients should be closely monitored for signs of hypersensitivity during and for at least 30 minutes after every administration of an IV iron product.
- In people with increased risk of hypersensitivity, treatment with IV iron products should only be considered if the benefits are clearly judged to outweigh the potential risks.

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Rationale

Parenteral iron administration to people receiving haemodialysis has been shown to result in a reduction of circulating TNFα levels [(1)]. In addition, chronic iron loading has been associated with an impaired immune response of circulating monocytes to ex vivo stimulation with lipo-poly saccharide (LPS) [(2)]. Excess iron inhibits anti-microbial effector pathways of macrophages [(3, 4)]. This is exerted via blockade of LPS and interferon-gamma (IFNJ) inducible immune pathways, while production of macrophage de-activating cytokines such as interleukin10 (IL10) is increased [(5, 6)]. The effect of iron on immune function could be dependent on the iron preparation; one study has shown that iron sucrose had more prominent effects on monocyte differentiation than other clinically available compounds [(7)].

Ishida and Johansen critically reviewed available literature regarding the association between iron and infection in people receiving HD [(8)]. The authors identified studies that evaluated the association between the risk of infection, serum ferritin levels (13 studies) and iron usage (24 studies). Thirteen studies with sample sizes ranging from 61 to 2,662 have examined the link between serum ferritin and infection in haemodialysis patients. Among the 13 studies, nine studies reported an association, and four studies did not find an association between serum ferritin and infection. Among the studies that identified an association, high serum ferritin (typically defined as >500 or 1,000 microgram/L) was associated with higher incidence of bacterial infection or infection-related mortality. The incidence of bacterial infection ranged from 0.34 to 0.59 infections per patient-year (in studies evaluating the rate of infection) and 0.93% to 61.9% (in studies evaluating the proportion with infection) in the higher serum ferritin groups and 0.09 to 0.18 infections per patient-year and 0% to 37% in the lower serum ferritin groups. The authors concluded that these studies suggest an excess of 16 to 50 infections per 100 patient-years in the higher compared with the lower serum ferritin groups. In studies that expressed the association between serum ferritin and bacterial infection as ratios, higher serum ferritin was independently associated with a 1.5 to 3.1-fold higher incidence of bacterial infection or infection-related mortality. Among the 24 studies that evaluated the relationship between iron therapy and infection, twenty-two studies were observational with sample sizes ranging from 21 to 309,219 participants. Twelve of these studies found an association between any iron usage, higher dose or frequency of iron usage and infection or infection-related mortality.

One study compared mortality with different dosing patterns of IV iron [(9)]. Based on data from 117,050 people receiving HD, the study evaluated the effect of bolus versus maintenance IV iron dosing during repeated 1- month exposure periods on risks of mortality and infection-related hospitalisation during the subsequent 3 months. In multivariable additive risk models, compared to maintenance dosing (median monthly dose 200 mg), bolus dosing (median 700 mg) was associated with an increased risk of infection-related hospitalisation (risk difference, 25 additional events/1000 patient-years; 95% CI: 16 to 33), with the risk being largest among patients with a catheter or history

of recent infection. An association between bolus dosing and infection-related mortality was also observed. In contrast, maintenance and low-dose iron (125 mg) dosing were not associated with increased risks of infection-related hospitalisation or mortality outcomes when compared with no iron.

A multicentre study prospectively evaluated the association between serum ferritin levels and IV iron usage with adverse outcomes and mortality among 1086 Japanese people receiving chronic HD. By using Cox proportional hazard models and time-dependent variables, there was a significantly higher risk of infection with higher (above 100 microgram/L) compared to lower (below 100 ng/dl) serum ferritin levels, and with high (≥50 mg/week) and even low (<50 mg/week) doses of IV iron compared with no IV iron; they also reported significantly higher risk of death among people with high-amplitude ferritin fluctuations (serum ferritin level consistently above 100 microgram/L or upward trend from below to above 100 microgram/L) compared with those with low ferritin level [10].

In a study involving 626 people with pre-dialysis CKD. People were treated with intravenous ferric carboxymaltose (with a high and low ferritin target) or oral iron for 52 weeks. The percentage of deaths, myocardial infarctions, and infections was not significantly different between oral iron–treated and IVI-treated participants. However, the study was not powered to evaluate safety of parenteral iron [11].

Post-hoc analysis studied adverse events between the three arms. The incidence of one or more adverse events was 91.0, 100.0 and 105.0 per 100 patient-years in the high ferritin, low ferritin and oral iron groups, respectively. The incidence of adverse events with a suspected relation to study drug was 15.9, 17.8 and 36.7 per 100 patient-years in the three groups; for serious adverse events, the incidence was 28.2, 27.9 and 24.3 per 100 patient-years. The incidence of cardiac disorders and infections was similar between groups [12].

In a study evaluating the safety of parenteral iron therapy in 10,169 people receiving haemodialysis in the United States; after adjusting for 23 demographic and comorbidity characteristics among 5833 people included in the multivariable analysis; bills for ≤10 vials of iron over 6 months showed no adverse effect on survival when compared with none, but bills for >10 vials showed a statistically significant elevated rate of death [13]. Bills for ≤10 vials of iron over 6 months also showed no significant association with hospitalisation (adjusted = 0.92; 95% CI: 0.83 to 1.03; P = 0.15), but bills for >10 vials showed statistically significant elevated risk. More intensive dosing was associated with diminished survival and higher rates of hospitalisation, even after extensive adjustment for baseline comorbidity [13].

A subsequent analysis of 32,566 Fresenius Inc. people receiving haemodialysis by the same authors did not find an association between IVI iron dose and risk of death after adjusting for time-varying measures of iron treatment and fixed and time-varying measures of morbidity [14].

Kalantar-Zadeh et al. studied 58,058 DaVita Inc. people receiving dialysis [15]. For people who received 400 mg of IVI per month, the risk for death was found to be lower compared with people with no IV iron administered. By contrast, doses >400 mg per month were associated with an

increased risk of death [15].

Kshirsagar et al. studied 117,050 people receiving haemodialysis. No association was found between dose of IVI iron and short-term risk of myocardial infarction, stroke, or death [16].

A prospective observational study by Hoen et al. followed 988 people receiving HD from 19 French centres for 6 months. There were 51 episodes of bacteraemia, but no association with either IV iron dosing or serum ferritin concentration was detected [17]. A more recent study from the same group in 985 people receiving dialysis patients, demonstrated no significant increase in infection rates [18].

In the IRONMAN trial, 1127 people with heart failure and reduced ejection fraction (HFrEF) and iron deficiency were recruited to either receive IV ferric derisomaltose (n=559) or usual care (n=568). It was found that between the two groups, there were a similar rates of infections (25% vs 29%. HR -3.12; 95% CI: -8.30 to 2.06. p=0.24). Deaths due to infections were also similar in the two groups (6% vs 5%. HR 1.22, 95% CI: 0.74 to 2.02. p=0.43) as were hospitalisations due to infection (n= 175 vs 213. HR 0.82, 95% CI: 0.62 to 1.08. p=0.16) [19].

The PIVOTAL trial randomised 2141 people receiving HD who were within the first year of receiving haemodialysis to a high dose proactive iron regimen (400 mg monthly) or a low dose reactive regimen (0-400 mg monthly) based of TSAT and ferritin, showing a high dose iron regimen was superior in reducing rates of non-fatal MI, non-fatal stroke, hospitalisation due to heart failure or death [20]. Secondary analysis sought to address concerns around increasing infection rates in patients receiving IV iron. Secondary endpoints included infection, hospitalisation for infection and death from infection. It was found that there was no significant difference in secondary endpoints in the high dose vs low dose iron groups.

Results for “all infection episodes,” there were 508 first events (46.5%) in the proactive high-dose group versus 477 first events (45.5%) in the low-dose group (HR, 0.98; 95% CI: 0.87 to 1.11; P=0.80). Results for “hospitalisations for infections” were 323 first events (29.6%) in the proactive high-dose arm versus 307 first events (29.3%) in the reactive low-dose arm (HR, 0.99; 95% CI: 0.82 to 1.16; P=0.92). Results for “death from infections,” showed 46 events (4.21%) in the proactive high-dose arm versus 41 first events (3.91%) in the reactive low-dose arm (HR, 1.04; 95% CI: 0.69 to 1.59; P=0.84). Participants with central venous catheter were more likely to experience an infection, however no differences in all three infection endpoints (in relation to the treatment arms) were seen in those people dialysing via central venous access vs arteriovenous fistula [20, 21].

Meta-analysis from Hougen et al. also supported PIVOTAL findings by comparing infection rates from four RCT studies using high dose IV iron regimens (>400 mg a month) vs low dose IV iron or no iron regimens in people receiving haemodialysis [22]. This study concluded that there were no differences in infection rates in the high dose iron group (n=743; relative risk, 1.02; 95% confidence interval, 0.74 to 1.41). Eight observational studies using high dose IV iron regiments (>200 mg a month) showed no increase in infection risk (n=135,532; pooled hazard ratio, 1.13; 95% confidence interval, 0.99 to 1.28) [22].

Meta-analysis from Shah A et al. reviewed 154 RCTs looking at risk of infection with intravenous iron vs oral iron or no iron across various disease states. This study found that intravenous iron was associated with an increased risk of infection when compared with oral iron or no iron (RR, 1.17; 95% CI: 1.04-1.31; I2 = 37%; moderate certainty of evidence) most significantly in those with inflammatory bowel disease (IBD). Across the trials, there were significant variation in in how infection was defined or reported, leading to inconsistent reporting across the studies. There were no differences observed in mortality between the groups [23].

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Rationale

The most commonly used oral treatments for iron deficiency anaemia often cause gastrointestinal side effects, leading to discontinuation of treatment. Gastrointestinal side effects most often occur due to the conversion of bivalent iron into trivalent iron, along with the formation of reactive oxygen species (ROS). However, due to the nature of vascular access, intravenous iron administration is not well-accepted by many people who are not receiving haemodialysis and furthermore can lead to high non bound (labile) iron levels in the circulation, resulting in ROS generation.

To address these concerns, nanosized iron preparations have been developed. Reducing the particle size of iron compounds increases their surface area, improving solubility in gastric juice and enhancing absorption. Novel iron preparations like sucrosomial iron, ferric citrate, and ferric maltol offer high bioavailability and good tolerance, making them suitable options for anaemia in chronic kidney disease.

In summary, the available evidence suggests that the following alternative oral iron preparations may have several benefits in the treatment of anaemia in people with CKD, including increasing

haemoglobin levels, improving iron parameters, and reducing the need for intravenous iron and erythropoietin-stimulating agents. However, the specific effects can vary among studies, and further research is needed to clarify optimal use and long-term safety. Physicians should consider individual patient factors and preferences when deciding on the use of newer iron preparations as part of an anaemia management strategy in people with CKD.

Alternative Preparations:

Ferric Citrate

Ferric citrate is used in people with CKD undergoing dialysis primarily for phosphate binding but is also employed off-label as an iron supplement.

There have been two meta-analyses of ferric citrate and treatment of anaemia. One analysis of nine studies found that ferric citrate significantly increased haemoglobin levels compared to active control drugs (mean difference 0.43 g/dL) or placebo (mean difference 0.39 g/dL) [(1)]. A second meta-analysis of five studies showed that ferric citrate substantially increased haemoglobin levels compared to the comparator group (mean difference 0.65 g/dL) along with improvements in other laboratory parameters such as iron, ferritin, transferrin saturation, and bicarbonate levels [(2)].

In a sequential, randomised trial, subjects on ferric citrate achieved higher mean iron parameters (ferritin = 899±488 ng/ml; transferrin saturation = 39%±17%) compared to subjects on active control (ferritin = 628±367 ng/ml; transferrin saturation = 30%±12%). Haemoglobin levels were also statistically higher on ferric citrate [(3)].

A 12-week, double-blind, placebo-controlled trial of ferric citrate of 149 participants with eGFR <60 mL/min/1.73m^2, Hb, 90-120 g/L; TSAT ≤30%, ferritin ≤300 ng/mL). Ferric citrate treatment increased mean transferrin saturation (TSAT) from 22% ± 7% to 32% ± 14% and increased haemoglobin levels (from 105 ± 8 to 110 ± 10 g/L) compared to placebo [(4)].

The ASTRIO trial randomised 93 people who were undergoing HD and being treated with non-iron-based phosphate binders and ESA to receive 24 weeks of ferric citrate or to continue their non-iron-based phosphate binders. While Hb and Hct were not significantly changed, the ferric citrate group experienced a significant decrease ESA dose requirement compared to the control group [(5)].

In a prospective study of 60 participants on HD treated with lanthanum carbonate, participants were randomly assigned to 2 groups: lanthanum carbonate or switch to ferric citrate. The ferric citrate group had significantly increased serum iron, serum ferritin, transferrin saturation, and significantly decreased ESA doses compared to the control group [(6)].

A randomised double-blind clinical trial in adults with NDD-CKD and iron deficiency anaemia to compare the safety and efficacy of oral ferric citrate (n=117) versus placebo (n=115) was performed [(7)]. Ferric citrate-treated patients had a significantly higher proportion achieving a ≥10 g/L increase in haemoglobin, with a safety profile similar to the placebo group (7). A further analysis of this study found that ferric citrate showed a greater treatment effect on patients with lower baseline ferritin levels, resulting in a greater rate of haemoglobin rise [(8)].

A small RCT of 60 adults with moderate to severe NDD-CKD (eGFR 15-45 ml/min/1.73m^2) comparing ferric citrate and ferrous sulphate led to greater increases in transferrin saturation and ferritin

compared to ferrous sulphate, but there was no significant difference in haemoglobin levels and the incidence of adverse events did not differ between treatment arms [9].

In 441 subjects with end-stage kidney failure, ferric citrate (FC) increased ferritin and transferrin saturation levels, reduced intravenous iron use, and lowered ESA requirements [10]. Subjects were randomised to ferric citrate, sevelamer carbonate and/or calcium acetate and followed for 52 weeks. Subjects on FC had increased ferritin and TSAT levels by week 12 and needed less IV iron and less cumulative ESA over 52 weeks [10].

Ferric Maltol

Ferric maltol is a compound composed of ferric iron and maltol, a naturally occurring sugar derivative commonly found in various food products. This complex remains tightly bound in the intestinal tract until it reaches the point of absorption. At this stage, iron exhibits a stronger attraction to iron transport receptors on the surface of intestinal cells, leading to its separation from maltol. This unique mechanism ensures that there is no unbound or free iron in the gut, reducing the risk of generating harmful hydroxyl radicals and minimizing the potential for gastrointestinal side effects. Iron uptake from ferric maltol is subject to saturation and relies on the presence of iron transport receptors, ensuring controlled and efficient absorption.

AEGIS-CKD is a phase 3, double-blind, randomised, placebo-controlled trial, where participants were given oral ferric maltol at 30 mg or placebo twice daily for 16 weeks (2:1 randomisation), followed by ferric maltol at 30 mg twice daily for up to 36 weeks (all patients) [11]. 167 participants were randomised, with 111 receiving ferric maltol and 56 receiving a placebo. At week 16, haemoglobin significantly increased with ferric maltol compared to placebo. Ferritin, transferrin saturation, and serum iron levels also increased with ferric maltol but declined with placebo. Haemoglobin levels remained stable up to week 52 in patients continuing ferric maltol, and they increased in patients switching from placebo to ferric maltol. The most common adverse events were gastrointestinal, and adverse events led to treatment withdrawal in a small percentage of patients, with slightly more in the placebo group [11].

Ferric Pyrophosphate (FPC)

FPC is a complex iron salt which is administered along with dialysate. Two phase 3 trials, CRUISE 1 and 2, involving 599 iron-replete participants receiving chronic haemodialysis having been performed [12]. Participants received dialysate containing FPC-iron or a standard dialysate (placebo) for up to 48 weeks. Results showed that Hb concentration was maintained in the FPC group but decreased in the placebo group (0.4 g/dL decrease, $p < 0.001$). Placebo treatment also resulted in larger decreases in CHr and serum ferritin compared to FPC treatment. The proportions of patients with adverse events were similar in both treatment groups [12].

A Chinese study investigated the pharmacokinetics and safety of FPC in subjects with and without HD. In healthy subjects, the peak serum concentration was reached at the end of the infusion, with a Cmax of 33.46 µmol/L at a Tmax of 4.09 hours. In people receiving HD, there were differences in Cmax and Tmax between two doses of FPC. Adverse events were reported in both healthy subjects and people receiving HD, with a limited number of incidences [13].

Sucrosomial Iron

Sucrosomial iron comprises ferric pyrophosphate enclosed within a membrane made of phospholipids and sucrose esters of fatty acids.

In a randomised trial of 99 participants with CKD and iron deficiency anaemia (Hb ≤120 g/L, ferritin ≤100 ng/mL, TSAT ≤25%) were divided into two groups: one received oral liposomal iron (30 mg/day) and the other intravenous (IV) iron gluconate (total dose of 1000 mg, infused weekly) for 3 months. The IV iron group showed a faster increase in haemoglobin levels compared to the liposomal iron group during the first month of treatment, but both groups had similar haemoglobin levels by the end of the 3-month treatment period. After discontinuation of iron treatment, haemoglobin levels remained stable in the IV group but returned to baseline in the liposomal iron group. The incidence of adverse events was significantly lower in the oral liposomal iron group [(14)].

Hypophosphataemia

Hypophosphataemia is a known side effect of intravenous iron preparations as listed in the SmPCs of IV iron products. It is a common side effect with ferric carboxymaltose (FCM) [(15)]. As detailed in their SmPC, symptomatic hypophosphataemia leading to osteomalacia and fractures requiring clinical intervention including surgery has been reported in the post marketing setting. Patients should be asked to seek medical advice if they experience worsening fatigue with myalgias or bone pain. Serum phosphate should be monitored in patients who receive multiple administrations at higher doses or long-term treatment, and those with existing risk factors for hypophosphataemia. In case of persisting hypophosphataemia, treatment with ferric carboxymaltose should be re-evaluated.

Acute features can include muscle pain and weakness as well as fatigue, although often can be asymptomatic [(16)]. There is evidence that hypophosphataemia, secondary to IV iron therapy can lead to long term issues with bone metabolism, presenting as osteomalacia and fractures [(16)].

Wolf et al. made the first link between FCM causing a rise in Fibroblast growth factor 23 (FGF23), s hormone which regulates phosphate and vitamin D, causing a decrease in phosphate levels, calcitriol and calcium, with an increase in PTH levels. This study compared FCM to iron dextran treatment, measuring the difference in FGF23 and phosphate levels in people with iron deficiency, secondary to heavy uterine bleeding. Authors reported a significant rise in iFGF23 following treatment with FCM, but not iron dextran ($r = 0.59$; $p < 0.001$), with corresponding decrease in phosphate ($r = -0.50$; $p = 0.002$). Differences in vitamin D, calcium and PTH were not significant. Hypophosphataemia was reported to continue for up to 80 days [(17)].

Following on from this study, sub-analysis of the FIRM trial compared FGF23 and phosphate levels in a trial of FCM vs ferumoxytol in which hypophosphataemia was significantly decreased in the FCM group vs ferumoxytol group (<2.0 mg/dl, 50.8% vs. 0.9%; <1.3 mg/dl, 10.0% vs. 0.0%; $P < 0.001$), continuing for up to 5 weeks after FCM administration in 29.1% of participants. FCM only increased the FGF23 concentrations, which lead to a significant decrease in calcium (mean difference between iron treatment groups in change from baseline to week 2, 0.37 mg/dl; 95%CI 0.25–0.50; $P < 0.001$) and vitamin D (mean within-patient percentage change from baseline to week 2, –60.4 ± 25.9% vs. –2.5 ± 28.0%; $P < 0.001$), with a rise in PTH levels [(18)].

PHOSPHARE-IDA trials compared phosphate levels in people receiving ferric derisomaltose (FDI) or FCM, finding that incidence of hypophosphataemia was significantly higher in the FCM group vs the FDI group (74.4% versus 8.0%, respectively; $p < 0.001$), showing a significant rise in FGF23, a decrease in calcium and increase in PTH levels in the FCM group, as previously reported [(19)]. Sub-

analysis showed 57% of patients in the FCM group (vs 0% in FDI group) experienced persistent hypophosphataemia, with associated changes in bone metabolism biomarkers [20].

PHOSPHARE-IBD similarly showed higher rates of hypophosphataemia in the FCM group vs FDI group in the IBD population- 8.3% FDI vs 51.0% FCM (adjusted risk difference: -42.8% (95% CI: -57.1% to -24.6%) p<0.0001) [21].

Literature review by Schafer B et al. looked at 42 prospective clinical trials, which found that people, who have received FCM, are more likely to experience hypophosphataemia than those who have received FDI, with an incidence of 42% vs 4% across 42 clinical trials (95% CI: 36-58% vs. 95% CI: 2-5%). Significantly decreased levels in serum phosphate were also seen when comparing the two treatments, a decrease in 0.4mmol/L with FCM vs a decrease in 0.06mmol/L with FDI, with hypophosphataemia reportedly persisting after 3 months of treatment with FCM [7]. The only significant predictor of experiencing hypophosphataemia being the severity of anaemia at time of treatment, with no significant link seen between IV iron treatment in CKD [18,22]. However, FGF23 has been reported to increase after IV iron therapy in people with CKD, with a decrease in active vitamin D levels [23], despite higher baseline levels of FGF23 in patients with CKD, affecting bone metabolism long term [24].

Glaspy J et al. published a literature review that included 40 trials reviewing all of the IV iron products on the US market at the time. This included iron dextran, ferric gluconate, FCM, ferumoxytol and iron sucrose. This review found that people without CKD and who receive higher doses of iron are more likely to experience hypophosphataemia [25]. As with previous findings, FCM treatment was associated with the highest rate of reported hypophosphataemia [25].

Kidney transplant recipients can experience hypophosphataemia within the first 3 months post transplantation (secondary to phosphaturia), which is associated with high levels of FGF23 and PTH. This normalises in the recovery period and increasing again with declining graft function, leading to adverse effects on the cardiovascular system, graft function and bone metabolism [26]. 23 kidney transplant recipients received FCM, showing an average decrease in phosphate levels of 0.27 mmol/l (p = 0.003). 56.5% of participants experienced hypophosphataemia, with severe Hypophosphataemia (<0.5 mmol/L) seen in 34.8% of people. Hypophosphataemia persisted in 38.5% of patients with median normalisation of levels at 41 days [27]. This shows that kidney transplant recipients should receive FCM with caution and close monitoring [28].

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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. Toxicity associated with high ferritin outcomes was originally reported in the context of multiple transfusions in the pre-ESA era. The risk persists that intravenous iron may reproduce similar toxicity and thus regular monitoring during

therapy is required. Similarly with ongoing iron losses on HD regular monitoring to avoid worsening iron deficiency is required [1, 3]. The safety of persistently very high ferritin levels remains unknown. In a cohort of 58058 prevalent people receiving haemodialysis in the USA, both all-cause and cardiovascular mortality had increasing rates across increasing ferritin levels, whereas the opposite (inverse) association was observed for TSAT increments. Serum ferritin levels between 200 and 1200 microgram/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 microgram/L during each quarter was associated with increased death rate [4]. 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 microgram/L and severe comorbidities who were treated with IV iron [5]. Similarly, Rostoker *et al* [6]. 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 haemocromatosis [7].

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

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3. 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. By addressing any underlying causes and correcting any deficiencies, ESA use may be avoided. [(1)] Correcting any deficiencies, including iron deficiency, before starting ESA treatment will allow for optimal ESA responses, minimising the dose required to maintain target haemoglobin levels. [(2)]

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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 must be supplied to the erythropoietic tissue at an adequate rate, particularly if stimulated by ESA therapy. If iron stores are low ESAs can still be used if anaemia of CKD is a likely contributor, as long as iron is made directly available to the erythropoietic tissues coincident with the initiation of ESA therapy.

- For people with CKD, percentage of hypochromic red blood cells >6% or reticulocyte Hb content < 31 pg are good tests 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 microgram/L) are a suitable alternative [(1)].

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 100-120 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 median monthly dose of erythropoiesis-stimulating agent was 19.4% lower in people receiving the high-dose regimen (29,757 IU per month; interquartile range, 18,673 to 48,833) than in patients receiving the low-dose regimen (38,805 IU per month; interquartile range, 24,377 to 60,620) (median difference, −7539 IU per month; 95% CI, −9485 to −5582). 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 [(2)].

Several smaller prospective trials have also been carried out to confirm what was found in the PIVOTAL trial. One study compared the ESA requirements in Iranian people receiving haemodialysis receiving regular low dose iron (100 mg/month, n=30) and high dose iron (400 mg/month, n=30) regimens. It was found that the ESA dosage to maintain hemoglobin level between 100 and 120 g/L was significantly decreased in the high dose iron arm (52,129.03 ± 23,810 vs. 45,760 ± 20,978.71, $P \leq 0.02$) [(3)].

Another study also compared ESA requirements in Thai people receiving haemodialysis prescribed regular low dose iron (100 mg/month, n=40) and regular high dose iron (200 mg/month, n=39). Similarly, this showed reduced ESA requirements, to maintain a desirable Hb level of 100-120 g/L, in those patients on the high dose iron regiment. The mean monthly ESA dose at month 12, was 35,706 ± 21,637 IU in the 100-mg IV iron group compared with 26,382 ± 14,983 IU in the 200-mg IV iron group ($P = 0.03$). No significance was seen between the two groups when looking at the death rate, cardiovascular events, blood transfusions or EQ-5D quality of life measurements [(4)].

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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

Treatment of anaemia in CKD with ESA can be expensive [1], takes time to work and carries a small but significant risk to the patient. It is therefore reasonable, as with any therapy, to treat only those who are expected to benefit in the time frame that therapy is being considered. For example, people with severe sepsis/inflammation/acute bleeding are unlikely to respond.

People with a very short life expectancy (days or weeks) are not likely to survive long enough for therapy to provide benefit in terms of an increase in Hb. The clinician and patient should agree on a therapeutic plan and, at an appropriate time, review whether therapy is providing enough benefit to continue treatment.

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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

In determining target Hb guidelines it is important to assess potential benefits (in terms of possible improved survival, improvement in health-related quality of life (HRQoL) and avoidance of transfusion requirement and hospitalisation) vs. potential harms (increased mortality, increased risk of vascular events).

Although several studies have shown that higher Hb targets could be associated with improvements in both physical and mental health domains [1], the HRQoL benefits of higher Hb targets diminish over time [1]. In addition, there is no apparent Hb threshold above which there is definitively a quality-of-life improvement in the higher Hb treatment arms.

Besarab et al [2] reported a study of normalisation of haemoglobin in 1233 prevalent people with receiving HD with high cardiovascular risk on haemodialysis. Normalisation of haemoglobin showed no benefit in risk reduction but did show an improvement in quality of life. The treatment arm showed a trend towards increased risk of death or cardiac event (183 deaths and 19 myocardial infarcts, producing 202 primary events, compared to 164 events (150 deaths, 14 myocardial infarcts) and vascular access (39% versus 29%) and the trial was terminated before completion on the grounds that the study was unlikely to show benefit from normalisation.

Two trials evaluated the effect of ESA on people not yet receiving dialysis – CHOIR [3] and CREATE [4]. outcome of the CHOIR trial showed no benefit of higher Hb outcome in people with NDD-CKD (eGFR 15-50ml/min/1.73m^2) randomised to Hb of 113 g/L vs. 135 g/L. Higher outcome target Hb had an increased risk (using composite endpoints of death, myocardial infarction, or hospitalisation for congestive cardiac failure) and no incremental improvement in quality of life [3]. The limitation of this trial is that, compared with the group assigned to the lower Hb treatment target, the higher Hb target group showed at baseline a statistically greater proportion of patients with a history of hypertension and coronary artery bypass graft. A report posted by the trial sponsor [5] indicates that patients assigned to the higher Hb treatment arm also had a significantly greater severity of congestive heart failure (CHF) at baseline. The results of a multivariate analysis, included in this report, indicate that after adjustment for baseline conditions (CHF by National Health and Nutrition Examination Survey CHF score, atrial fibrillation/flutter, serum albumin level, reticulocyte count, and age), the relationship between treatment assignment and primary composite outcome events is no longer statistically significant (HR, 1.24; 95% confidence interval [CI], 0.95 to 1.62; p = 0.11 compared with the unadjusted HR of 1.34; 95% CI: 1.03 to 1.74; p = 0.03) (6). A secondary analysis of the CHOIR trial suggested that higher doses of epoetin α, rather than target Hb per se, were associated with an increased risk of death, myocardial infarction, congestive heart failure or stroke compared with lower epoetin doses, and with poorer outcomes [6]. Another secondary analysis of the CHOIR trial found that, among patients with diabetes mellitus, the percentage of people reaching the primary end point of death, myocardial infarction, congestive heart failure or stroke within 3 years was similar in the high and low haemoglobin arms of the trial (24.8% versus 24.7%, respectively; p = 0.249). By contrast, among patients without diabetes mellitus at baseline, 36.4% of participants randomised to the higher Hb target had reached the primary end point after 3 years compared with 24% of those randomised to the lower haemoglobin target (HR 1.70; 95% CI: 1.03–2.81; p= 0.04). Individuals without diabetes mellitus randomised to the higher haemoglobin target had a significantly greater risk of reaching the primary end point after 3 years than individuals with diabetes mellitus randomised to the lower haemoglobin target [7].

The CREATE [4] trial reported that early correction of anaemia to normal Hb (130-150 g/L vs. 105-115 g/L) did not reduce risk of cardiovascular events. Indeed, the hazards ratio for primary endpoints of death from any cause or death from cardiovascular disease consistently (but not significantly) favoured the lower haemoglobin target group. The trend to increase in events appeared to occur after initiation of dialysis but there was no difference in endpoints after censoring of data from patients who started dialysis. Quality of life was significantly better in the higher Hb outcome group. Although GFR was not significantly different between the two groups, more people started kidney replacement therapy earlier in the higher Hb outcome group (p =0.03) with the difference apparent from 18 months. An important limitation of this trial is that the event rate was much lower than predicted; thus, the power to detect a difference in event rates was decreased [4].

Other important limitation (s) of these trials is that important subgroups of participants enrolled in large trials, such as young adults, people returning to dialysis after failed kidney transplant, or people with chronic lung disease were not identified or assessed in any of these trials.

Further analysis of outcome of high target Hb was performed by the KDOQI team [8]. An Evidence Review Team analysed all data from randomised controlled trials of anaemia management in NDD-

CKD, including, CHOIR, CREATE and other studies. Combining mortality outcomes from eight studies involving 3038 subjects with CKD (the CHOIR and CREATE trials contributed most of the weight to the analysis) revealed no difference between the higher and lower Hb target [7], but combining adverse cardiovascular events from six studies involving 2850 subjects showed an increased risk among the patients assigned to the higher Hb targets (a RR of 1.24, 95% CI: 1.02–1.51) [8], although it is worth noting that the CHOIR and CREATE trials also contributed most of the weight to the analysis. Among dialysis patients, combining mortality (four studies, 2391 subjects) or cardiovascular outcomes (three studies, 1975 subjects) showed no statistically significant difference between the higher and lower Hb level with The US Normal Haematocrit Trial [2] contributing most of the weight to the analysis.

In the TREAT trial [9], 4038 people with diabetes, chronic kidney disease not on dialysis, and anaemia, were randomly assigned in a 1:1 ratio to darbepoetin α, to achieve Hb level of approximately 130 g/L or to placebo, with rescue darbepoetin α when the haemoglobin level was less than 90 g/L. The primary end points were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalisation for myocardial ischaemia) and of death or end-stage kidney disease. After a median follow up of 29 months, there was no difference between the two arms in the primary outcome of death, cardiovascular event or end stage kidney disease. Fatal or nonfatal stroke occurred in 101 participants assigned to darbepoetin α and 53 participants assigned to placebo (HR, 1.92; 95% CI: 1.38 to 2.68; p <0.001). The investigators concluded that for many involved in clinical decision making this risk of prescribing an ESA in this population will outweigh the potential benefits [9].

Data from observational studies have, however, not shown increased hazard risk among people who achieved higher Hb. In one study, data from people receiving haemodialysis in the UK Renal Registry from 1999 to 2005 were analysed for the relative risk of death at different Hb concentrations. Hb concentrations above the reference range (100–110 g/L) consistently showed a 35% lower relative risk of death, while people with haemoglobin below 100 g/L had a 28% higher mortality. The greatest mortality was seen in people with haemoglobin <90 g/L (73% increased risk of death, although due to the small numbers, this was not statistically significant). On the other hand, the lowest death rate was seen in people with haemoglobin levels between 120 and 139 g/L (64% reduced mortality) [10].

The effect of cumulative ESA dose was also reported in another retrospective study [11]. In this study, which looked at data from Medicare's end-stage kidney disease program between 1999 and 2007, different US dialysis centres annual anaemia management practice were characterised by estimating their typical use of ESAs and intravenous iron in people receiving haemodialysis within 4 hematocrit categories. Monthly mortality rates were assessed using Cox proportional hazards regression to correlate centre-level patterns of ESA and iron use with 1-year mortality risk in 269,717 people on incident haemodialysis. Monthly mortality rates were highest in people with haematocrit less than 30% (mortality, 2.1%) and lowest for those with haematocrit of 36% or higher (mortality, 0.7%). After adjustment for baseline case-mix differences, dialysis centres that used larger ESA doses in people with haematocrit less than 30% had lower mortality rates than centres that used smaller doses (highest vs. lowest dose group: HR, 0.94; 95% CI: 0.90-0.97). Centres that administered iron more frequently to people with haematocrit less than 33% also had lower mortality rates (highest vs. lowest quintile, HR, 0.95; 95% CI: 0.91-0.98). However, centres that used larger ESA doses in people with haematocrit between 33% and 35.9% had higher mortality rates (highest vs. lowest quintile, HR,

1.07; 95% CI: 1.03-1.12). More intensive use of both ESAs and iron was associated with increased mortality risk in people with haematocrit of 36% or higher [11].

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 using EQ5D index, Visual Analogue Scale (VAS), and the KD-QoL (Physical Component Score (PCS) and Mental Component Score (MCS)). The mean baseline EQ5D index and VAS scores were 0.68 and 60.7; 33.7 (PCS) and 46.0 (MCS). Female sex, higher BMI, diabetes mellitus, history of myocardial infarction, stroke or heart failure were associated with significantly worse EQ5D index and VAS. CRP and transferrin saturation (TSAT) were associated with QoL. Hemoglobin was not an independent predictor of QoL. TSAT was an independent predictor of PCS. CRP was associated with most aspects of QoL. Impaired functional status was associated with mortality. Quality of life was impaired in people starting hemodialysis. CRP was a consistent independent predictor of the majority of QoL scores. TSAT ≤20% was associated with worse physical component scores of QoL [12].

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 [13].

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[14].

The findings of all the above studies have made it difficult to define a safe target Hb in CKD patients treated with ESA. As a result, target Hb in this patient group has been the subject of extensive debate in the literature:

- KDIGO suggests that for adults receiving dialysis, ESA therapy could be used to avoid having the Hb concentration fall below 90 g/L by starting ESA therapy when the haemoglobin is between 90– 100 g/L [15].
- The Anaemia Working Group of ERBP expressed its view that Hb values of 110-120 g/L should be generally sought in the CKD population without intentionally exceeding 130 g/L In low-risk patients (i.e., in younger patients with very few comorbidities). In those with ischaemic heart disease with worsening ischaemic symptoms associated with anaemia, or in those in whom a clear benefit on quality of life can be foreseen, the start of ESA therapy could be considered at higher Hb values but not exceeding 120 g/L. In high-risk patients, including those with asymptomatic ischaemic heart disease, treatment initiation with ESA should be started at Hb values between 90 and 100 g/L to maintain a Hb value ~100 g/L during maintenance therapy [16].
- NICE guidelines on managing anaemia in people with CKD suggest maintaining the “aspirational” Hb range between 100 and 120 g/L for adults [17]. 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 [17].

- The health economics of anaemia therapy using ESAs has been subject to a NICE systematic review [17] which concludes that treating to a target Hb 100-120 g/L is cost effective in HD patients [17]. Table 1 summarises the mean Hb data for prevalent UK dialysis patients from the 24th (2020) UK Renal Registry Reports [18].
- The Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2007) notes that using ESAs to achieve Hb levels greater than 120 g/L is associated with an increased risk of death and serious cardiovascular events in people with CKD. The MHRA advises that Hb levels greater than this should be avoided, and that patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of the symptoms of anaemia. Use of ESAs to achieve Hb levels greater than 120 g/L is not consistent with UK marketing authorisations for ESAs. Informed consent should be obtained and documented [19].

Table 1: Hb data for UK prevalent people receiving HD [15].

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

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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. [1, 2] 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 [2, 3].

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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

For initiation of ESA therapy, several points are to be considered:

- Type(s) of licensed ESAs available
- Initial ESA dose
- ESA dose adjustment: dose required for Hb correction vs. maintenance.
- Route of ESA administration
- Frequency of ESA administration that best fit patient requirements and achieve maximal convenience
- Monitoring for the anticipated response in terms of Hb rise, rate of Hb rise, possible adverse effect (e.g. hypertension).

In general, the aim of initial ESA therapy is to achieve a rate of increase in Hb levels of 10 to 20 g/L per month. This rate of rise is considered safe as evidenced from interventional trials on people who are ESA naïve [1-3]. In CKD patients with initial Hb levels less than target range, these trials have shown the mean initial rate of Hb level increase to be in the range of 7 to 25 g/L in the first 4 weeks. This rate of Hb increase is affected by the population, iron status, initial ESA dose, and the frequency and route of ESA administration.

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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. Subcutaneous administration of short-acting ESA preparations may be preferred in people receiving haemodialysis due to improved ESA efficacy at the EPO receptor, allowing for smaller doses to be used. However, convenience and choice may favour intravenous (IV) administration in people on HD. (2B)

Rationale

In the outpatient setting, SC administration is the only routinely feasible route of administration for non-HD CKD patients. For HD patients, either SC or IV administration is feasible. Among short-acting ESAs, subcutaneous administration is associated with approximately 30% reduction in dose requirements compared to that of IV administration for the same target Hb outcome. This has been proven in a large multi-centre RCT on people on long term HD who had their haematocrit maintained within target range while on epoetin α either via SC or IV route. Participants were then randomised to IV or SC route. Upon randomisation, ESA doses were first decreased to allow haematocrit levels to decrease to less than target range. Doses were titrated upward to again achieve target haematocrit levels, and then were adjusted to maintain haematocrit in the target range during a 26-week maintenance phase. Among 107 people who completed the trial, those assigned to SC route showed 27% lower ESA doses than those assigned to IV administration [(1)]. However, not all participants showed a dose decrease after conversion from IV to SC, and some patients showed a dose increase. Among long-acting agents, efficacy of SC administration appears to be equivalent to that of IV route at the examined dosing frequencies [(2-5)].

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patients treated by haemodialysis or peritoneal dialysis: a randomized trial. Am J Kidney Dis 2007; 50(6):989-1000.

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

The frequency of ESA administration should be determined by the CKD treatment setting and the class of ESA. Maximum efficacy is achieved by using the dosing intervals that are ESA class specific. In people receiving HD prescribed SC short-acting ESA therapy, ESA efficacy is maximal when the drug is given thrice weekly. Short-acting ESA efficacy decreases and dose requirement increases, when the dosing frequency is extended from thrice-weekly to once-weekly administration [(1)]. Increasing the time interval between dosages of long-acting ESAs could also result in an increase in dose requirements [(2)]. Doses and dosing intervals should be tailored to each individual person's response to therapy. Use of algorithms may assist in optimising therapy [(3)].

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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. (1A)

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

The NICE Guidelines for anaemia management in chronic kidney disease recommend an "aspirational" Hb of 100-120 g/L. It is anticipated that if a population Hb distribution is centred on this outcome with a mean of 110 g/L, then 85% of the population will have Hb > 100 g/L [(1)].

In people receiving HD, withholding ESA doses for Hb levels greater than the target range is associated with subsequent downward Hb excursions often to levels less than target Range [(2)]. The time between withholding ESA doses and return of Hb to target range is variable and unpredictable. In HD patients with Hb values greater than 140 g/L, the median time for Hb to return to 120 g/L or less after withholding of a SC-administered ESA is 7-9 weeks. The difference between withholding long and short acting ESAs on the rate of Hb reduction is not significant [(3)].

ESA dose adjustment may be higher during initiation (or titration after switching between different ESAs) than maintenance phases of ESA therapy. In a randomized double-blind trial comparing a short-acting ESA with a long-acting ESA in people on haemodialysis previously receiving epoetin α, dose adjustments were made in 25% increments or decrements of the baseline dose, aiming to maintain individual Hb concentrations within a range of 90 to 130 g/L [(4)]. Approximately 70% of patients required dose adjustment in the 20-week titration period, and 50% required dose adjustment during the 8-week maintenance period.

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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. (2C)

Rationale

In the TREAT trial, there was an increased risk of stroke in the high ESA group (HR 1.92; 95% CI 1.38–2.68): 5.0% of the high Hb group had a stroke compared to 2.6% in the placebo group (P<0.001).

Venous thrombo-embolic events occurred significantly more frequently in the high Hb arm (2.0%) compared to the placebo arm (1.1%, P=0.02) [(1)].

A post-hoc analysis of TREAT trial showed that: 7.4% of those with a history of malignancy at baseline died from cancer in the ESA arm compared to 0.6% in the placebo arm (P=0.002) [(2)].

In a meta-analysis comparing possible adverse events related to ESA therapy, The higher Hb concentrations in ESA treated people with NDD-CKD increased risk for stroke (RR 1.51, 95% CI: 1.03–2.21), hypertension (RR 1.67, 95% CI: 1.31–2.12), and vascular access thrombosis (RR 1.33; 95% CI: 1.16–1.53), and possibly the risk of death (RR 1.09; 95% CI: 0.99–1.20), serious cardiovascular events (RR 1.15, 95% CI: 0.98–1.33) or ESRD (RR 1.08; 95% CI: 0.97–1.20). [(3)] However, the risk of stroke was independent of Hb level or dose of ESA suggesting other factors such as iron deficiency [(4)].

Patients with neoplasia who received ESA in randomised clinical trials had an increased risk of tumor progression and reduced overall survival compared with study controls [(5)].

The MHRA advised that r-HuEPOs should not be given to people with cancer who do not fulfil the criteria in the authorised cancer indications, and that patients should be monitored closely to ensure that the lowest approved dose of r-HuEPO is used to adequately control of symptoms of anaemia [(5)].

The joint guideline from the American Society of Clinical Oncology and the American Society of Haematology [(6)] recommends using ESA therapy with great caution in people with active malignancy, particularly when cure is the anticipated outcome.

NICE evaluated the efficacy and safety of ESA in treating anaemia in people with cancer receiving chemotherapy [(7)]. Although NICE researchers identified 23 randomised controlled trials evaluating the effectiveness and safety of erythropoiesis-stimulating agents (ESAs) for treating cancer treatment-related anaemia, NICE assessment focused only on trials that evaluated ESAs at a starting dose reflecting the current license (Hb <100 g/L). In total 16 studies were included in the analysis of the outcome related to anaemia and 7 trials in the outcome related to overall survival. NICE analysis of available trials concluded that erythropoiesis-stimulating agents are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy. ESAs were effective in increasing haemoglobin concentrations, improving haematological responses, reducing the need for blood transfusions and improving health-related quality of life, but that it could not assume that ESA treatment either prolonged or shortened survival compared with treatment without an ESA [(7)].

References

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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 for people with unstable Hb, out of target Hb level, anticipated Hb drop due to blood loss/haemolysis, infection or suboptimal dialysis. The response to ESA therapy varies widely between different patient groups and individuals within those groups. In addition, 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 (ongoing anaemia) and overtreatment (rapidly rising Hb/hypertension or polycythaemia) may be avoided [1-3].

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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. (1A)

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). (2C)

Rationale

Extensive publications are available on the topic of resistance to ESA therapy including the Revised European Best Practice Guidelines [1] which defines ESA resistance as above. Failure to respond at an earlier stage in therapy should however raise suspicion of ESA resistance.

Comparison of the individual Hb outcome achieved and the dose of ESA used can provide a useful way of highlighting individuals that are ESA resistant during local unit audit [2, 3]. ESA therapy is efficacious in most people. However, many conditions and treatment variables can cause or explain apparent resistance to ESA therapy. Adequate investigation and management of these underlying conditions is crucial in achieving satisfactory outcome haemoglobin values as well as requiring therapy in their own right.

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 [4].

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 [5].

References

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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 (1A):

- 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/µl
- High serum ferritin

Guideline 3.15.1
We recommend that all ESA therapy should be stopped in people who develop ESA induced PRCA. (1A)

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

Anti-erythropoietin antibody associated pure red cell aplasia (PRCA) is a very rare cause of resistance characterised by

- transfusion dependency
- low reticulocyte count (<1%)
- lack of proerythroid progenitor cells in the bone marrow
- neutralising anti-erythropoietin antibodies [1].

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 [2], and 0.02 per

10,000 patient-years of intravenous exposure [3]. Nevertheless, most reported cases of anti-erythropoietin antibody-associated PRCA have occurred in people with CKD who have received the drug subcutaneously [4,5,6].

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 [5].

PRCA is specifically characterized by the following clinical features [6]:

- 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 [7].

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 [8].
    - People with suspected ESA induced PRCA who test positive using binding antibodies should have the diagnosis confirmed with the definitive testing for neutralising antibodies [9].

There are several tests that can be used. These include:

- radioimmunoprecipitation assay
- electrochemiluminescence bridging enzyme-linked immunosorbent assay
- surface plasmon resonance-based immunoassay.

The most validated test is the radioimmunoprecipitation assay. This test is very sensitive and can detect the presence of high-affinity anti-EPO IgG at concentrations as low as 10 ng/ml. This test is not currently available within NHS but can be organised with the industry as a part of post-marketing pharmacovigilance arrangement with the PRCA Rare Disease Group.

ESA induced PRCA is an immune mediated process. While spontaneous remissions after cessation of EPO therapy have been reported, immunosuppressive therapy is usually needed in most cases [10]. One study evaluated 170 CKD patients who developed epoetin-associated PRCA [11]. Of the 34 people who received epoetin after the onset of PRCA, 56% recovered epoetin responsiveness; the highest rate of epoetin responsiveness was observed among those who had no detectable anti-erythropoietin antibodies at the time of epoetin administration (89%). The study also reported that the highest recovery rates were among those treated with immunosuppressive therapy, particularly a combination of cyclophosphamide and prednisone [11]. Other options such as rituximab, danazol or even plasma exchange may be considered.

Verhelst et al [12] 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. In addition, if epoetin therapy is to be reconsidered for these people, only the intravenous rather than the subcutaneous route should be considered for drug administration.

ESA induced PRCA is now part of RaDaR, the UK rare disease registry [13].

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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 [1]. 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.

References

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4. Treatment of Anaemia with HIF-PHI Agents (Guidelines 4.1-4.9)

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/1.73m^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)

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. (2C)

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. (2C)

Rationale

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. These oxygen-responsive heterodimeric transcription factors, known as HIFs (hypoxia-inducible factors), are integral to the cellular response to hypoxia, orchestrating a cascade of events that influence vital physiological functions [(1)]. HIFs are particularly noteworthy for their role in managing oxygen homeostasis through their involvement in the production of endogenous erythropoietin (EPO) and iron regulation within the body [(1-3)].

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 [(1-2)]. 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 [(1-3)].

Erythroferrone (ERFE) is the main erythroid regulator of hepcidin. When erythropoietin is released from the kidney it stimulates the production of new red blood cells and also increases the synthesis of ERFE in bone marrow erythroblasts. Increased ERFE then suppresses hepcidin synthesis, thereby mobilizing cellular iron stores for use in heme and haemoglobin synthesis. The mechanism by which hepcidin is decreased by HIF-PHI therapy has been attributed primarily to increased production of erythroferrone due to increased haematopoiesis [(4)]. Hepcidin is a peptide hormone that modulates the levels of ferroportin – an iron-export channel found on the surface of cells in the duodenum, liver, and macrophages. Hepcidin's inhibitory action on ferroportin suppresses both intestinal iron absorption and iron release from macrophages, thereby influencing the overall iron balance in the body [(5)]. The connection between HIFs and hepcidin is significant; systemic activation of HIFs prompts an increase in endogenous EPO production and iron utilisation by erythroblasts. This intricate interaction subsequently downregulates hepcidin production in the liver, promoting enhanced intestinal iron absorption and mobilisation from iron stores [(6-9)]. This orchestrated interplay forms a sophisticated regulatory network that maintains iron homeostasis, ensuring optimal functioning of various biological processes.

In the presence of oxygen, prolyl hydroxylase enzymes hydroxylate the oxygen-regulated HIF-α subunit, thereby targeting it for proteasomal degradation [(10)]. HIF-PHI therapy stimulates erythropoiesis primarily by upregulating endogenous EPO production, thereby 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 [(11-14)].

When there is a reduction of blood oxygen levels, prolyl hydroxylation and degradation of HIF-α subunits are inhibited, resulting in its cellular accumulation and dimerisation with the HIF-β subunits and this heterodimer acts as the transcription factor for the EPO gene [(15-16)]. Prolyl hydroxylation can be pharmacologically inhibited by oral HIF-PHI therapy [(17-18)], which stimulates erythropoiesis, largely by increasing endogenous EPO production from increased transcription of EPO genes.

Phase three trials have confirmed the efficacy and safety of this class of drug. Currently, Roxadustat and Vadadustat are available and approved in the UK by NICE. Roxadustat should be considered in people with CKD not on dialysis but can be continued when the person progresses to dialysis therapy based on NICE guidance. The drug can be used in people receiving dialysis according to the SmPC but this has not been reviewed by NICE for this purpose (from increased transcription of EPO genes). Vadadustat is recommended, within its marketing authorisation, as an option for treating symptomatic anaemia caused by chronic kidney disease in adults having maintenance dialysis based on NICE guidance.

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 [19, 20]. Others suggest no significant change in health-related quality of life measures or functional health scores [10-13].
"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

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Rationale for Treatment with HIF-PHI Agents (Guidelines 4.1-4.9)

Published trials confirm that the six HIF-PHI agents with data are superior to placebo and non-inferior to ESAs in increasing and maintaining haemoglobin (Hb) concentration among people with NDD-CKD and DD-CKD [1-33]. Large, randomised trials have demonstrated that Roxadustat [8-19], Vadadustat [20-23], and Daprodustat [1-7] 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 [24-33]. 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 [34-40]. 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 [41]. A total of 26 trials were included in this recent analysis with over 24, 000 participants. The average length of follow-up was 16.5 months (range 6-42 months) and the mean baseline eGFR ranged from 15.9-22.1 ml/min/1,73m^2. The mean age was 67.1 years (range 48-72 years). 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) [41].

Roxadustat, the first in class HIF-PHI to receive NICE guidance and SmPC recommendation has a half-life of around 15 hours in people with CKD, is orally bioavailable, leads to an increase in EPO levels after oral administration and lasts for up to 48 hours post-dose administration. Its efficacy and safety have been examined in eight randomised controlled trials involving 9600 patients [8-19].

The results of trials that included people treated with haemodialysis (HD) and peritoneal dialysis (PD) and single-arm trials among patients treated with PD [19] have shown that HIF-PHI therapy is at least as effective among those receiving PD versus HD.

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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

Current targets which aim for partial correction of Hb are based on clinical trials conducted more than a decade ago [1-3]. These landmark trials compared higher versus lower Hb targets achieved using ESAs, in which major adverse cardiovascular events (MACE), mortality, and thrombotic events were more common among people assigned to the higher of the Hb targets [1-3]. In addition, one trial comparing a high Hb target with placebo (and a conservative rescue strategy) in people with NDD-CKD and diabetes found an increased rate of strokes [4]. 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.

For people with symptomatic anaemia associated with non-dialysis dependent chronic kidney disease at the time of treatment initiation, HIF-PHI therapy is recommended by NICE [5] as a treatment option and is comparable to ESA therapy. NICE recommends that the choice between a HIF-PHI and ESA should be made in discussion with the individual.

In determining target Hb guidelines it is important to assess potential benefits (such as possible improved survival, improvement in health-related quality of life (HRQoL) and avoidance of transfusion requirement and hospitalisation) vs. potential harms (increased mortality and vascular events) and patient choice [6, 7].

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 [8]. They also reported no evidence of increased cardiovascular safety or mortality risk when compared with ESA's [8] 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 of less than 100 g/L. [5].

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.

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 [9].

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 [10]. 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 has a recommended Hb range of 100- 110 g/L. The two RCTs, INNO$_2$VATE 1 (n 369) and 2 (n=3554), on pooled analysis showed non inferiority to darbepoetin

alpha during 52 weeks follow up [11, 12]. The population consisted of 60% US and 40% non-US where the trail Hb ranges were 80 to 110 g/L and 90 to 120 g/L in non-US participants. Overall MACE HR; was 0.96 with 95% CI: 0.83-1.11 and for the US participants only it was HR 1.0 with 95% CI; 0.84-1.18. The current SmPC recommends a Hb target range of 100-110 g/L [13]. The comparative 100 patient year data for vadadustat versus ESA therapy respectively were myocardial infarction 2.9 vs 2.9; Vascaulr access thrombosis 4.8 vs 3.9; stroke 1.1 vs 1.4; DVT 0.5 vs 0.6; PE 0.2 vs 0.3.

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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 100-120g/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 for Guidelines 4.4-4.6

Currently only 1 HIF-PHI 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. Compared with ESA these drugs work as well for anaemia management [1, 2]. NICE has therefore recommended that HIF-PHI can be used as an alternative to ESA for people with NDD-CKD stages 3 to 5, especially if they find self-injecting difficult or painful or rely on others to give them their injections. 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. Clinicians with expertise in this field have indicated that the decision whether to stop treatment depends on how well anaemia is managed. They stated that they would titrate the dose down if Hb levels reached approximately 125 g/L so that Hb levels stay within a “presumed safe range” (that is, between 100 g/L and 120 g/L) rather than stopping treatment completely.

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 hours 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 hours 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 or 130 g/L in most studies [3-20]. 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.

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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 retinopathy. (1D)

Guideline 4.7.5
We recommend caution in people with a history of thrombotic events following the SmPC for contra-indications. (1A)

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. (2C)

Rationale for certain specific groups (Guidelines 4.7)

Malignancy

Hypoxia inducible factor-1 alpha (HIF-1α) is a key transcription factor in tumour progression [(1)]. HIF-1α inhibitors are currently used in cancer treatment [(1)]. Genetic HIF activation is a central mechanism of tumorigenesis in people with the von Hippel-Lindau (VHL) disease and clear cell renal carcinomas [(2)]. 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) [(3)]. 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) [4]. *Post hoc* analyses that accounted for differential dosing frequency attenuated this observed risk [4]. 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 [5].

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. It has been postulated that cyst formation is related to chloride-dependent fluid secretion into the cyst lumen [6].

Hypertension

Pre-clinical studies in healthy rats and rats with CKD demonstrated that HIF-PHI therapy generate significant dose-dependent blood-pressure lowering effects [7, 8]. 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 [9]. 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 [10]. One relatively large study, the SYMPHONY-ND study which compared enarodustat 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%) [11]. Other NDD-CKD trials have not shown increased risk of eye disease with HIF-PHI therapy [12, 13, 14, 15].

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%) [16]. 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) [17].

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 [8, 18]. The underlying mechanisms are complex and may be related to the rapid rate of rise in Hb for roxadustat. [19] In

addition, the impact of HIF-PHI on iron metabolism (upregulation of transferrin, [20] or interference of the coagulation system (increased expression of plasminogen activator inhibitor) may contribute to thrombotic risk [21]. Roxadustat showed an excess risk of thrombosis in both NDD-CKD (versus ESA) and DD-CKD (versus placebo) trials [22]. Vascular access thrombosis occurred in 1.5 versus 0.9/100 patients years and DVT was 0.7 versus 0.2/100 patients years [23]. A pooled analysis of roxadustat trials demonstrated higher risks were associated with the rate of Hb rise [24]. Lower doses of roxadustat, may lead to a slower rate of Hb rise, and thus ameliorate thrombosis risk while maintaining efficacy. Thrombotic risk with vadadustat were not noted in published data [25]. Daprodustat trials have not reported a significant excess risk of thrombosis compared with active comparator although there was a numerical increased risk of vascular access thrombosis (2.1% versus 1.5%) [4, 25, 26].

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 (14 trials) [3].

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. [27, 28] 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 are 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 [29]. As with all drugs, there is a risk for drug-drug interactions with the use of HIF-PHI therapy, particularly in combination with other oral agents.

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 Vadadustat 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 [3]. 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) (30). 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 [26, 27]. 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 [18, 19].

Roxadustat was previous reviewed by the FDA for its potential use in CKD [29, 31]. Data submitted included 3 separate trials comparing Roxadustat with placebo that were pooled for meta-analyses in the NDD-CKD (n = 4270) population [32]. A fourth study comparing roxadustat to darbepoetin alfa was analysed separately (DOLOMITES) [33]. The pooled analyses for roxadustat did not have prespecified agreed (FDA) noninferiority margins [32, 33]. Further this risk was accentuated during on-treatment sensitivity analyses (as opposed to intention-to-treat analysis). This analysis was suggested by the FDA to minimise the effect of including unexposed person-times or events that may not be affected by the intervention [18]. When assessing events occurring while people were on treatment and for one week after discontinuation (on-treatment + 7 days analyses), 277 (7.2%) events were recorded in the roxadustat arm compared with 131 (5.6%) events in the placebo arm (HR 1.38; 95% CI: 1.11-1.70). However, there was higher dropout rates in the placebo compared to roxadustat arms, with potential for bias that may have disadvantaged roxadustat [33].

Three studies of roxadustat compared to ESA involving people receiving dialysis (N=3880) were meta-analysed [33]. 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) [29].

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 [35]. ~~S~~everal contributing factors may impact this risk, including treatment non-responsiveness, and converting stable ESA treated people receiving dialysis.

In the case of non-responsiveness, treatment with roxadustat should not be continued beyond 24 weeks after the start of treatment. 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."

In a published analysis of the four roxadustat trials in the DD-CKD population [8], MACE and MACE+ in the on-treatment plus 7 day analyses showed different results in incident vs. prevalent dialysis patients, noted similar risk of MACE (HR 0.83; 95% CI: 0.61-1.13) and nominally lower risk of MACE+ (HR 0.76; 95% CI: 0.57-1.00) among incident dialysis patients treated with roxadustat, whereas roxadustat was less favourable for MACE (HR 1.18; 95% CI: 1.00-1.38) and all-cause mortality (HR 1.23; 95% CI: 1.02-1.49) in prevalent dialysis patients [33].

Pooled results from two randomized trials involving NDD-CKD persons in which vadadustat was compared with darbepoetin alfa were analysed [19]. 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 [25]. 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 [34]. 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) [34].

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) [24]. 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 [24].

Daprodustat was evaluated in randomised, open-label, phase 3 trial, in patients with DD-CKD subjects using the active comparator of epoetin alfa if they were receiving haemodialysis or darbepoetin alfa if they were receiving peritoneal dialysis [5]. A total of 2964 patients underwent randomization. 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.

Overall meta-analyses have reassured the short-term safety of these drugs in comparison to ESA therapy. Natale et al [30] found not difference in MACE and MACE+; similar to those from Takkavatakarn et al [37]. A meta-analysis limited to only non-dialysis and active comparator (9 studies with 9470 people) there was no difference in CV outcomes [3].

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 [38]. 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).

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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. (2C)

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.

5. 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. (1A)

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. (2C)

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

CKD results in chronic anaemia, the degree of which usually reflects the severity of CKD. As with any chronic anaemia, patients tend to deal with this by various compensatory mechanisms. Blood transfusion is rarely an acute requirement except in emergencies such as acute blood loss, acute haemolysis or severe sepsis/inflammation. Hence the risk benefit ratio of the intervention needs to be analysed before prescribing a red blood cell transfusion to treat anaemia in people with chronic kidney disease.

The potential risks associated with blood transfusion include transfusion reactions, iron overload and transfusion acquired infections. In the presence of severe chronic anaemia, transfusion may lead to congestive cardiac failure, particularly in the elderly. A review of transfusion outcome in people with acute coronary artery syndromes revealed a greater mortality rate in transfusion recipients [(1)]. Another review suggested that treatment of mild to moderate anaemia resulted in increased mortality [(2)]. Also transplant recipient sensitisation may occur following transfusion resulting in longer transplant register waiting times and difficulty in finding a cross match negative donor. A study from Ireland looking at causes of sensitisation of potential allograft recipients showed that the level of sensitisation increased with the number of units of blood transfused and also demonstrated a direct relationship between degree of sensitisation and waiting time for transplantation [(3)]. Blood transfusions can induce antibodies to histocompatibility leukocyte antigens that can reduce the success of kidney transplantation; thus transfusions generally should be avoided in patients awaiting a kidney transplant [(2)].

The use of ESAs can greatly reduce the need for red blood cell transfusions in people with anaemia of CKD when target Hb concentrations are achieved and maintained [(4-5)]. Since the introduction of ESAs and reduction in routine blood transfusion in people with anaemia and CKD, sensitisation has markedly reduced [(6)]. With the advent of new immunosuppressant regimens after 1995, the use of pre-transplantation transfusion have been rendered largely obsolete [(7)]. The K-DOQI anaemia guideline recommends that no single Hb concentration justifies or requires transfusion and the target Hb recommended for chronic anaemia management should not serve as a transfusion trigger [(8)]. NICE agrees that there are clinical reasons to minimise blood transfusion in anaemia of CKD and if blood transfusion is essential the relevant haematology guidelines should be followed (e.g. the British Society for Haematology (BSH) guidelines https://b-s-h.org.uk/guidelines/guidelines) [(8)]. In hospitalised patients who are haemodynamically stable, the need for transfusion is directed by symptoms and the Hb values. Whilst one study suggested that a value in CKD patients of <70 g/L or <80 g/L in post-operative surgical patients or pre-existing cardiac disease should prompt transfusion, transfusion should be based on patient assessment and policies set by local transfusion guidelines [(9)].

Hepatitis E virus (HEV) is a RNA virus and has 4 genotypes: the one commonly found in the UK is genotype 3. The most common route of infection in the UK is from eating raw or undercooked meat (particularly pork products) and shellfish; however, HEV can be transmitted via blood transfusion and solid organ transplantation. Incidence of HEV in the UK has been increasing considerably since 2011. It was estimated that as many as 100,000 persons may suffer acute infections each year and that less than 1 in 100 will have any illness at all. The majority of people who become infected with HEV have no symptoms and the infection clears completely within a couple of months. HEV may pose a risk of harm to immunocompromised patients who may be unable to clear the infection, which may then become persistent, potentially leading to chronic inflammation of the liver and cirrhosis. The UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) recommends that immunocompromised /immunosuppressed patients should receive HEV negative blood components [10]. All blood components in the UK are HEV tested. However, neither irradiated components nor CMV negative components (unless the patient is a neonate or pregnant), are required.

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6. 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. (2C)

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 1) [1-3].

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 [3].
2. Immunosuppressive medications: Mycophenolate and azathioprine are myelosuppressive agents. Calcineurin inhibitors may cause anaemia by microangiopathic haemolysis [4-8]. OKT3 may also cause haemolytic uraemic syndrome (HUS) [9-10]. Tacrolimus has also been associated with anaemia [11-13]. It may interfere with post erythropoietin receptor binding intracellular signalling and may occasionally cause HUS [13-14].
3. Angiotensin converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) use: ACE inhibition has been linked with anaemia [3, 15]. Its pathogenesis is multifactorial and may include inhibition of endogenous EPO production, production of an erythropoiesis-inhibiting protein [16] and inhibition of angiotensin II mediated stimulation of erythrocyte precursors [17].
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 [18-19].
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 [20-22].
8. Rejection episodes: Acute rejection may cause reduced endogenous EPO production [23]. 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 [24].
The prevalence of red cell transfusions early post-transplant is high, averaging 40% in reported series [25]. 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 [25]. 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 [26-28]. 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 [25]. Endogenous EPO is sustained from 28 days post-transplant in the setting of primary graft function [29]. 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 [30, 31]. 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 [3]. 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 [25, 32]. 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 [32]. 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 [33]. 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, $P < 0.001$) [34].

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% ($p<0.001$) [35].

Gafter-Gvili et al. assessed 266 people and found that 51.3% experienced early PTA and 36.6% experiences late PTA. The study found that there was higher mortality after 4 years in those who experienced early PTA, which processed 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) [36].

Scechter et al. [33] 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 <11g/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) [33].

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 [37, 38]. 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 [39, 40]. Studies in the early post-transplant period did not show significant adverse events including delayed graft function or hypertension [41, 42]. Studies in the late transplant period have shown increased incidence of hypertension [43, 44]. 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 [45].

In another prospective study that assessed the effect of correction of anaemia on progression of kidney Insufficiency in people with a kidney transplant; 128 people from 17 centres in France treated with ESA were randomised to full correction of anaemia (haemoglobin values130–150 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 of people reaching end-stage kidney disease and the number of 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 decrease of kidney function and reduces the number of grafts lost [46].

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 [47].

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 significant increase in the vitality and mental health domains of the medical outcomes short form health survey [48].

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 [41, 42]. Similarly, studies in late post-transplant period have shown efficacy of ESA in these people [43, 44, 49, 50].

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/1.73m^2) of epoetin beta versus control [51].

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Table 1. Causes of post-transplant anaemia

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

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 resports 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 [1-2]. The numbers of people treated are too small to currently make any specific recommendations of use of HIF-PHI in people with a kidney transaplant [1-2]. In the recent published studies from Asia, there were approximately 73 patients in the 4 studies from Asia [3-6]. 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.

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Special Populations (Guidelines 7.1-7.3)

Guideline 7.1 - Malignancy:
We suggest treating symptomatic anaemia in people with CKD and cancer in those with a Hb <100 g/L. (2B)

Rationale

- Iron replacement may be used to improve haemoglobin response, and reduce RBC transfusions, for patients receiving ESA with or without iron deficiency. If patients are receiving cardiotoxic chemotherapy, iron must NOT be administered on the same day.
- ESAs may be offered to patients, on active treatment for cancer (chemotherapy), whose cancer treatment is not curative.
- If a person has an active cancer, NOT having chemotherapy treatment, DO NOT give ESA's.
- If a person had a previous cancer which is deemed cured, then there are no concerns for giving ESA's.

Guideline 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 recommendation on HIF-PHI therapy. (not graded)

Rationale

ESA should be considered in people with MDS with low risk MDS and symptomatic anaemia and Hb <100g/L. If a person with MDS does not respond to ESA therapy within 8-12 weeks then Haematologists should consider commencing G-CSF.

Guideline 7.3 - Pregnancy:
We recommend that pregnant and post-partum women with CKD are given parenteral iron, if indicated, from the second trimester onwards and if the benefit is judged to outweigh the potential risk for both the mother and the foetus according to SmPC guidance. (1C)

Guideline 7.3.1
We recommend that ESA therapy during pregnancy may be continued unless there is a major contra-indication (e.g., hypertension or thrombosis risks). (2C)

Rationale

During pregnancy, plasma volumes become higher than the increase in red blood cell mass, which leads to lower observed haemoglobin levels. The lower reference limit for haemoglobin concentrations in pregnancy is 110 g/L in the first trimester, 105 g/L in the second trimester and 100 g/L in the post-partum period [1, 2], with values <85 g/L associated with an estimated 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 [3]. There are no data to guide the optimum target haemoglobin for women with CKD in pregnancy [4].

The most common cause of anaemia in pregnancy is iron deficiency, which is estimated to affect greater than 40% of pregnancies [5]. 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) [2].

Pregnant women are normally offered oral iron in the first instance if Hb is below target value, however IV iron is offered if they cannot tolerate oral iron or the Hb has not responded to oral therapy [2, 6]. Parenteral iron is considered safe in pregnancy and breastfeeding [7-10], although there is a paucity of safety data on exposure in the first trimester. It is important to review the SmPC for each pregnant person as foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. The unborn baby should be carefully monitored during intravenous administration of parenteral irons to pregnant women.

Recent reviews have commented that ESA therapy are considered safe in pregnancy, as they are large molecules which is unlikely to cross the placenta [11, 12]. They are also considered safe during lactation. Often twice to three times the use dose is required during pregnancy to achieve the desired haemoglobin target.

These recommendations are consistent with Guideline 4.6.1 of the UKKA pregnancy in CKD guidelines which states that “We recommend pregnant women with CKD are given parenteral iron if indicated”.

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New Therapies for Consideration in the future

Several new areas of drug development are ongoing including inhibitors of hepcidin production or action, anti-interleukin-6 specific antibodies (Ziltivekimab), anti-inflammatory biologicals, and activin receptor ligand traps [1].

A phase 1/2, placebo-controlled trial examined the effects of intravenous ziltivekimab every 2 weeks for 12 weeks vs placebo, in 61 people on haemodialy sis with a single nucleotide polymorphism of the *TMPRSS6* gene (putatively increases susceptibility to IL-6–mediated inflammatory effects). Ziltivekimab led to a significantly greater reduction of high-sensitivity C-reactive protein and ESA usage and ESA resistance index. There was also an increased serum iron, total iron binding capacity, transferrin saturation, and serum albumin [2]. Future trials may define its benefit.

PRS080#022, a PEGylated (polyethylene glycol bound) anticalin protein, antagonizes hepcidin with picomolar affinity [3]. Two first-in-human randomised, double-blind phase 1 trials of PRS-080#22; a single intravenous infusion of placebo or PRS-080#22 was administered to 48 healthy volunteers (phase 1a) and 24 patients on hemodialysis (phase 1b) at different doses (0.08-16 mg/kg for the phase 1a study and 2-8mg/kg for the phase 1b study) in successive dosing cohorts. This led to a dose dependent reduction in serum hepcidin levels, mobilisation of serum iron with increased serum iron concentration and transferrin saturation. There was impact on ferritin or haemoglobin. This drug was safe and effective but further clinical studies are needed.

Neutralising hepcidin with a monoclonal antibody (mAb) may prevent ferroportin internalization, restore iron efflux from cells, and allow transferrin-mediated iron transport to the bone marrow. A multi-centre, phase 1 study evaluated the safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of a fully humanized mAb (LY2787106) with high affinity for hepcidin in cancer patients with anaemia [4]. Thirty-three patients with hepcidin levels ≥5 ng/mL received LY2787106 either every 3 weeks (19 patients, dose range 0.3–10 mg/kg) (part A) or weekly (14 patients, dose 10 mg/kg) (part B). Consistent dose-dependent increases in serum iron, and transferrin saturation were seen at the 3 and 10 mg/kg dose levels, typically peaking within 24 h after LY2787106 administration and returning to baseline by day 8. LY2787106 resulted in transient iron mobilization, thus supporting the role of hepcidin in iron regulation [4].

Haemojuvelin (HJV), encoded by the HEF2 gene, a glycosylphosphatidylinositol-linked membrane-associated protein (expressed in liver, skeletal muscle and heart), binds to bone morphogenic proteins (BMPs) and enhances their effectiveness to activate the BMP-SMAD (small mothers against decapentaplegic) signalling pathway to stimulate hepcidin transcription in hepatocytes [5, 6].

Currently animal data is available suggesting that BMP6 is a key endogenous regulator of hepcidin [7, 8]. Deletions in genes encoding the ligand BMP6, the BMP coreceptor HJV, the BMP Type I receptors ALK2 and ALK3, or the intracellular signalling molecule SMAD4 [9-11], all independently resulted in inappropriately suppressed hepcidin expression and tissue iron overload. Recent studies examining te use of anti-haemojuvelin antibodies have demonstrated improvements in anaemia [12]. Pre-clinical models have clearly shown that anti-HJV antibodies have the potential to modulate hepcidin and improve Hb in inflammatory and non-inflammatory conditions [13]. A recent phase 1b/2a multi-center, open-label clinical trial of DISC-0974, a monoclonal antibody (mAB) targeting hemojuvelin, in

people with myelofibrosis or chronic kidney disease is ongoing (NCT05320198). Initial findings have shown a dose-dependent decreases in hepcidin across all treated patients. These reductions in hepcidin corresponded to dose-dependent increases in serum iron.

Aptamers are synthetic single-stranded oligonucleotides that bind ligands with high affinity, representing a novel class of oligonucleotide structures suitable for blocking purposes [14]. Spiegelmers are mirror image aptamers. Spiegelmers are attractive therapeutic agents and NOX-H94 is a polyethylene glycol conjugated (PEGylated) spiegelmer that targets and binds to human hepcidin [15]. The first human trial is currently underway [15, 16].

A study characterizing the molecular mechanism of ferroportin disease with parenchymal iron overload and resistance to hepcidin, the thiol form of Cys326 in ferroportin was found to be essential in hepcidin–ferroportin interaction. An antiferroportin mAb which binds to the extracellular loop of ferroportin, can block the hepcidin–ferroportin interaction, while maintaining ferroportin function [17]. This strategy would promote ferroportin activity and allow continuous iron influx, potentially preventing iron-restrictive erythropoiesis due to hepcidin excess. Human studies are awaited.

SGLT2 inhibitors have been shown to increase Hb in people with chronic kidney disease and/ or heart failure [18-23]. The increased Hb in people treated with SGLT2 inhibitors seems to be independent of diuretic use or as a result of intravascular volume depletion causing haemoconcentration [24, 25]. Data suggest that SGLT2 inhibitor administration is associated with transient increases in serum EPO concentrations (30%–40%), an increase in reticulocyte counts or haematocrit levels [26] and a decrease in ferritin and hepcidin, indicating erythropoietic stimulation [27-30]. However, more information is needed to better understand the mechanisms of action underlying these effects and their clinical relevance.

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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 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.

Patient Information leaflet for Anaemia of Chronic Kidney Disease (CKD)

Patient Information Sheet:
One of the kidney's main jobs is to help make red blood cells. The kidneys make a hormone called erythropoietin that is a signal for the body to make red blood cells.

If your kidneys don't work as well as they should, they make less erythropoietin, so fewer red blood cells are made. Iron levels in the body are usually low in people with advanced kidney disease.

The medical term for this condition is Anaemia of Chronic Kidney Disease. It means a low amount of red blood cells in the body caused by long-term kidney disease.

People with anaemia often feel tired and short of breath, but there can be other symptoms.

We treat anaemia with medicines including iron tablets and iron injections. We also use ESA (also called EPO) injections and other medication (HIF-PHI) that help make erythropoietin and help make iron work better in the body.

Guideline 1 - Evaluation of anaemia – Baseline investigations
Subjects with chronic kidney (CKD) disease who develop anaemia need initial investigations in the form of blood tests to:

1. Assess the severity of anaemia
2. Assess the cause of anaemia: some subjects with CKD could develop anaemia due to causes other than kidney disease: such as bleeding, iron & vitamin deficiency or many other causes. It is important to perform all the required tests before concluding that the anaemia is due to CKD.

Guideline 2.1 - Treatment of Anaemia with Iron therapy:
Iron is one of the building blocks of red cell formation by the body. Therefore correction of iron deficiency is an important initial step in the treatment of anaemia of CKD.

Guideline 2.2 - Treatment of Anaemia with Iron Therapy - Initiation of ESA/HIF-PHI and Iron Status:

- There are several specific blood tests arranged regularly through the kidney clinic to ensure the adequacy of iron stores in the body of subjects with CKD, and to assess how easily these iron stores are utilized by the body to correct anaemia.
- Many subjects could have their anaemia corrected by receiving iron therapy only.
- Therefore, it is important to ensure that people with CKD have adequate iron stores prior to considering the initiation of other drugs like ESA or HIF-PHI.

Guideline 2.3 - Treatment of Anaemia with Iron therapy - Route of Administration
Oral iron tablets are effective in correcting iron deficiency in the majority of CKD subjects with anaemia.

Intravenous iron:

- Intravenous iron (Iron injection given by a drip into the vein, IV iron), is usually needed when iron tablets are not effective or not tolerated by subjects with CKD.
- IV iron is widely used to correct iron deficiency among people receiving haemodialysis.
- IV iron is also given routinely to people before starting on ESA of HIF-PHI therapy to make this treatment more effective.

- There are different preparations of IV iron. Some preparations are given in a small dose at frequent intervals, others are given as large dose infused over few hours.
- People receiving large dose iron infusions will not require frequent treatment unlike those receiving small dose preparations.
- Small dose, more frequent IV iron is suitable for people receiving In Centre Haemodialysis, while large dose, less frequent preparations are suitable for people with CKD not receiving dialysis or those receiving peritoneal dialysis.

Guideline 2.4 - Treatment of Anaemia with Iron therapy – safety and Upper limit for iron therapy.

- Iron treatment, particularly IV iron, is not without risks, they are administered guided by the value of iron level in the blood.
- There are several tests available to assess iron level in the blood and body.
- The commonest test is “serum Ferritin”.
- Usually the aim of treatment with iron is to achieve serum ferritin level between 500-700 mcg/L.
- IV iron treatment should be withheld in the presence of any active infection. It should also be avoided in people with active Hepatitis C virus infection, in some people with chronic liver disease and those with hereditary liver conditions.
- To ensure safe treatment with IV iron, people will need regular blood tests (every 1-3 months) to monitor iron level and the response to treatment.

Guideline 3. Treatment with Erythropoiesis Stimulating Agents

- The aim of treatment of CKD with ESA preparations is to improve quality of life and reduce/avoid the need for blood transfusion.
- Like intravenous iron, ESA therapy is not without risks. The doctor will discuss the risk benefit ratio with the receipient/their carer before initiating this treatment.
- There are different ESA preparations; ome are short acting preparations, needing to be administered more than once weekly, other are longer acting preparations given less frequently (weekly or monthly).
- ESA preparations are given by injection: either into the vein (IV) or under the skin (subcutaneous, SC). Although SC injection allows lower dose of the drug to produce the desired effect, the choice and route of ESA administration is determined by several factors, such as the availability of the preparation in the local hospital, the availability of access for IV administration and choice of the recipient.
- It will be helpful if the recipient/carer discuss the need for the drug (a shared decision), available options and risk benefit ratio of treatment with the health care professional prior to starting therapy.
- Overcorrection of anaemia using ESA therapy could be harmful with adverse effects on the heart and blood pressure. Therefore, treatment with ESA aims to achieve and maintain haemoglobin level between 100 and 120 g/L in adults, and slightly lower in children younger than 2 years old.
- To achieve and maintain this target Hb range, people receiving ESA therapy will need regular blood testing to assess the response to treatment and allow adjustment of ESA dose according to Hb level.
- ESA therapy is not without risks. Therefore, ESA therapy is a shared decision (balancing benefits and risks) and should be used cautiously/ avoided in people with history of stroke, or in people with certain malignancies.
- Blood pressure needs to be monitored regularly in people receiving ESA, and if needed, blood pressure should be controlled with medications according to local guidelines.
- Very rarely, people may become immune against ESA therapy, as a result they become severely anaemic and do not respond to any ESA drugs. People who develop this condition should stop

receiving ESA therapy. They may require regular blood transfusions until they are treated to regain their ability to respond to ESA therapy.

Guideline 4 - Treatment of Anaemia – HIF-PHI Agents

HIF-PHI are newly introduced medications that are now licensed to treat anaemia in CKD subjects. They are administered in the form of oral tablets. They act on a system in the body that is activated when the level of oxygen in the blood is low. When activated, the body produces more red blood cells. This could be partly through the production of more erythropoietin and partly through better use of available iron for blood cell production.

HIF-PHI tablets activate this system, regardless of the oxygen level in the blood. As a result, more red blood cells are produced and anaemia is corrected.

- Like ESA, HIF-PHI treatment is dependent on the amount of iron in the body. Therefore, it is important to treat iron deficiency in any person before prescribing HIF-PHI therapy.
- Treatment with HIF-PHI should continue if and when the person is unwell for any other reason. During any illness, like surgery or chest infection, anaemia in subjects with CKD could get worse, so treatment of anaemia should continue during acute illness unless there is a reason to stop the drug.
- Overcorrection of anaemia using HIF-PHI therapy could be harmful with adverse effects on the heart and blood pressure. Therefore, treatment with HIF-PHI therapy aims to achieve and maintain haemoglobin level between 100 and 120 g/L in adults.
- To achieve and maintain this target Hb range, people receiving HIF-PHI therapy will need regular blood testing to assess the response to treatment and allow adjustment of HIF-PHI dose according to Haemoglobin level.
- HIF-PHII therapy is not without risks. Therefore, this therapy should be used cautiously/ avoided in people with history of stroke or in people with certain malignancies.
- Blood pressure needs to be monitored regularly in people receiving HIF-PHI, and if needed, blood pressure should be controlled with medications according to local guidelines.
- HIF-PHI therapy should be avoided in people with active malignancy, those with history of epilepsy, history of blood clots and subjects with autosomal dominant polycystic kidney disease.

Guideline 5: Blood Transfusion in people with Anaemia of CKD

- Whenever possible, people on the transplant waiting list should avoid receiving blood transfusions to avoid/ reduce the risks of rejection when they receive their transplant.
- Blood transfusion, if needed, should be decided based on each person's requirements, rather than guided by the blood test results only.
- People with suppressed immune system, due to kidney transplant or due to any other medical condition, and those on the transplant waiting list should receive blood that is negative for hepatitis E virus.

Guideline 6.0 Peri-transplant and Post Transplant Anaemia

- Kidney transplant recipients may develop anaemia due to a variety of causes.
- It is important to investigate and identify the cause of anaemia prior to considering treatment with iron, ESA or HIF-PHI.
- If indicated, transplant recipients can be treated with iron, ESA or HIF-PHI as per the guidelines for people with CKD not on dialysis.

Guideline 7.0 Special Populations

- Symptomatic people with CKD and cancer may be treated with Iron & ESA therapy as per the guidelines for people with CKD not on dialysis.
- Pregnant subjects with CKD who develop anaemia may be treated with ESA therapy. They may be treated with IV iron from the second trimester.
- Pregnant subjects may continue ESA therapy during pregnancy.