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HEART AND KIDNEY IN FOCUS

CLINICAL CASES
IRON DEFICIENCY AND ANAEMIA

CHRONIC KIDNEY DISEASE & IRON DEFICIENCY ANAEMIA

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KIDNEY DISEASE – A RISING BURDEN

The worldwide burden of kidney disease is rising,[1,2] but public awareness remains relatively low compared with other conditions, such as heart disease and cancer.[3,4]

Chronic kidney disease (CKD) is defined as **kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73m^2 for 3 months or more**, irrespective of cause.[5] CKD (stage 3–5) has an estimated prevalence of **7% in England (patients aged ≥35 years)[6] and 4.5% in Ireland**.[7]

CKD prevalence increases with age and it is reported to be **13.9% (stage 3–5) among people aged ≥60 years** in the community in the UK.[6,8] **Table 1** provides some key facts and figures for CKD in the UK and Ireland.

Table 1. Chronic kidney disease in numbers – UK and Ireland.

The UK[9,10]	Ireland[11,12]
• Around 3 million people have CKD. • Around 63,000 people are being managed for stage 5 CKD. • There are almost 30,000 people on dialysis. • Approximately 3000 kidney transplants take place every year (with ~5000 people still waiting). • There are 71 adult and 13 paediatric renal centres in the UK.	• Twenty per cent of adults aged over 45 years in Ireland have CKD. • Approximately 2,300 patients require dialysis. • Total end-stage kidney disease population is approximately 5,000 patients. • More than 250,000 HD treatments are delivered every year, accounting for 20% of all day case attendances at HSE hospitals each year. • There were approximately 139 kidney transplants in 2021. • There are 14 major hospitals with renal services in Ireland.

IRON DEFICIENCY AND ANAEMIA ARE COMMON IN CKD

Among non-dialysis (ND) patients with CKD (stages 3–5), up to ~70% are anaemic (Figure 1).[13]
A large scale, cross-sectional US multicentre study reported that anaemia (defined as Hb ≤12 g/dL) was present in many patients with reduced glomerular filtration rate (<60 mL/min/1.73m^2, CKD stages 3–5) (**Figure 1A**).[13] Among the analysed patient population (n = 5222), women were 2.2 times more likely to have Hb ≤12 g/dL than men.[13]

The NHANES III study (2007–2010) found that iron deficiency was common across all stages of ND-CKD (3–5) with a prevalence of 60–70%.[14-17] Iron deficiency was defined as: absolute, when there is a deficiency of total body iron stores; and functional, when there are ample or increased total body iron stores, but with sequestration of iron in the reticuloendothelial system, with inadequate iron supply for erythropoiesis.[15]

An epidemiological study in America, the PRE-dialysis Survey on Anaemia Management (**PRESAM**), reported that 61% of new dialysis patients (n = 1997, between the period 1999–2000) (**Figure 1B**) had either absolute iron deficiency (38.6%) or functional iron deficiency (21.6%).[16] A recent study found the prevalence of anaemia with functional iron deficiency to be 36.9% in CKD patients on HD, where FID was defined as >200 ng/dL.[18]

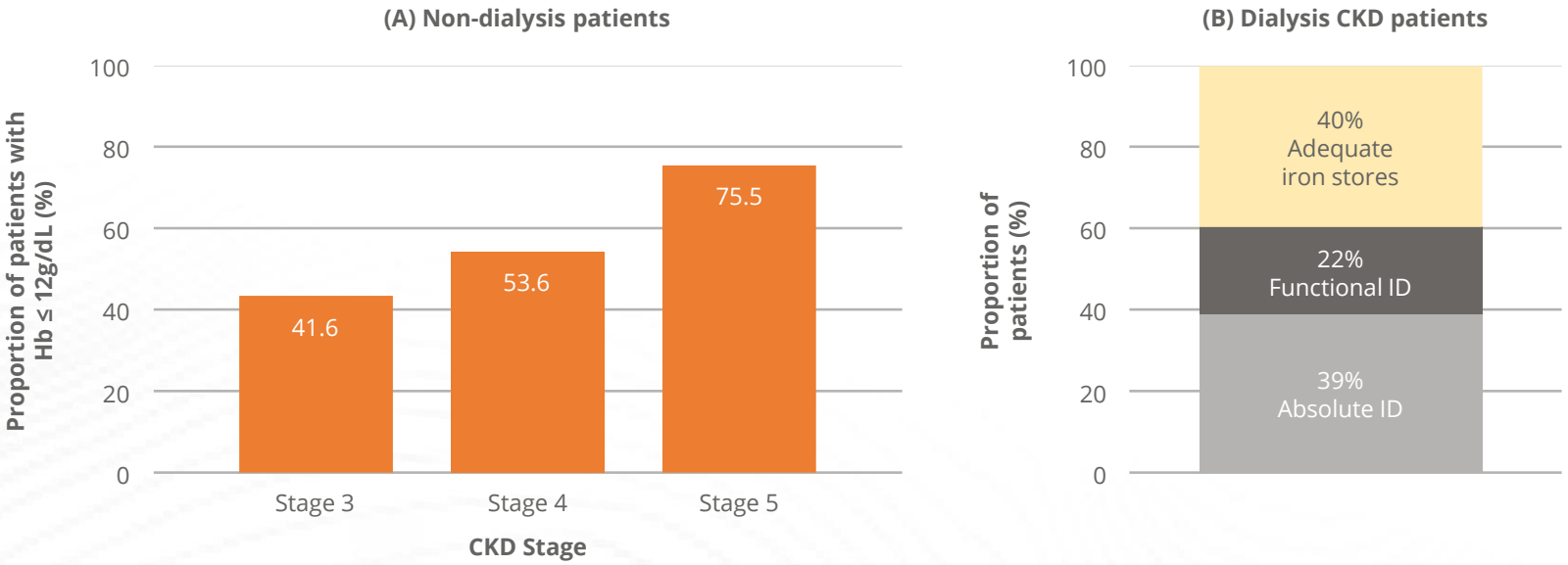


Figure 1. Prevalence of anaemia and iron deficiency in (A) ND-CKD patients where anaemia was defined as ≤12 g/dL and (B) new dialysis patients, where iron status was calculated as either adequate iron stores: serum ferritin ≥100 µg/L + transferrin saturation ≥20%; functional iron deficiency: serum ferritin 100 µg/L + transferrin saturation <20%; absolute iron deficiency: serum ferritin <100 µg/L. Adapted from McClellan et al (2004) and Valderrábano et al (2003).[13,16]

CKD, chronic kidney disease; ID, iron deficiency; ND-CKD, non-dialysis chronic kidney disease; TSAT, transferrin saturation.

SYMPTOMS AND IMPACT OF ANAEMIA IN CKD

Symptoms attributable to anaemia in CKD include:[19,20]

Tiredness | **Shortness of breath** | **Lethargy** | **Palpitations**

The KDIGO Clinical Practice Guideline for Anaemia in CKD states that anaemia in patients with stable CKD should be evaluated independently of CKD in order to identify any reversible process contributing to the anaemia.[21]

Data from observational studies have shown that anaemia in CKD is associated with poorer outcomes including reduced QoL,[22–26] increased risks of coronary heart disease, stroke, progression to end-stage renal disease (ESRD) and mortality.[22–26]

Other outcomes associated with anaemia in CKD include increased risk of hospitalisation, cardiovascular disease, and cognitive impairment.[27]

THE MECHANISMS OF IRON DEFICIENCY AND ANAEMIA IN CKD ARE MULTIFACTORIAL AND COMPLEX

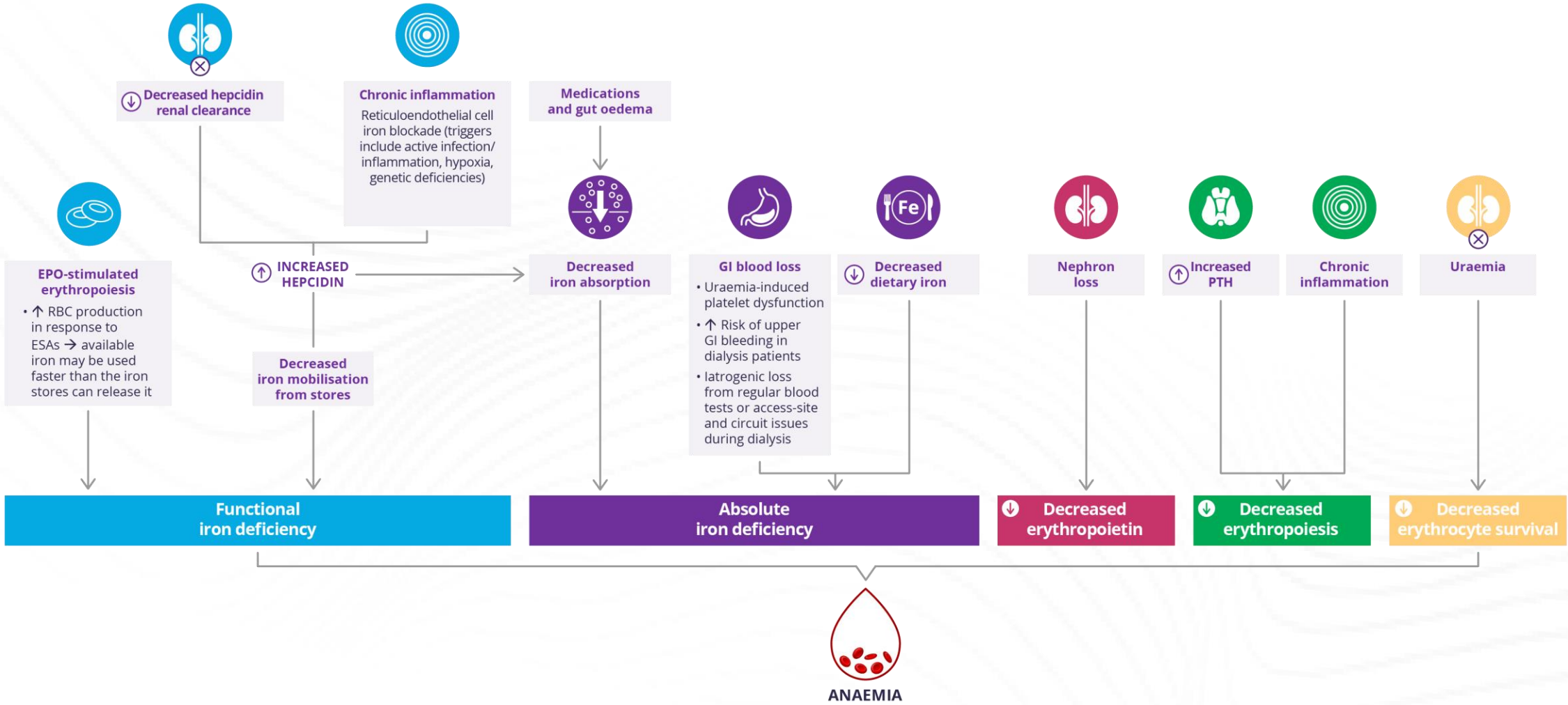


Figure 2. Anaemia in CKD is a multifactorial process.[27–29]

CKD, chronic kidney disease; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; GI, gastrointestinal; ID, iron deficiency; PTH, parathyroid hormone; RBC, red blood cell.

RECOMMENDED THRESHOLDS FOR DIAGNOSIS OF IRON DEFICIENCY AND ANAEMIA

Diagnostic criteria of iron deficiency and anaemia in CKD vary between different clinical guidelines, which are summarised in **Table 2**.

Table 2. Recommended thresholds for the diagnosis of iron.

Professional association	Year	Definition of anaemia (Hb, g/dL)	Recommended iron deficiency threshold values			Additional considerations
			Serum ferritin (µg/L)	TSAT (%)	Additional tests	
KDIGO[21]	2012	<13 (men); <12 (women)	No recommendation	No recommendation	• Full blood count • Absolute reticulocyte count • Serum vitamin B12/folate levels	N/A
NICE (NG203)[20]	2021	<11 and symptomatic	<100†	<20	• % HRC (>6%) • Retic.Hb (<29pg)	If % HRC and Retic.Hb tests are not available, use a combination of TSAT <20 and serum ferritin <100 µg/L
UK Renal Association[30]	2020	<11 and symptomatic	<100†‡	<20†	• % HRC (>6%)† • Retic.Hb (<29pg)† • Absolute reticulocyte count if indicated	N/A

†Based on the definition of iron repletion in the guideline. ‡Unless serum ferritin is >800 µg/L.

Retic.Hb, reticulocyte haemoglobin content; Hb, haemoglobin; HRC, hypochromic red blood cells; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute for Health and Care Excellence; TSAT, transferrin saturation.

Additional tests to diagnose and monitor iron deficiency

- **Percentage of hypochromic RBC** reflects iron availability in the preceding 2–3 months, making it a sensitive long-term time-averaged functional parameter.[27]
- **Reticulocyte Hb** content is an indicator of whether iron is incorporated into reticulocytes within 3–4 days after starting iron administration, and can therefore serve as a functional parameter that may be useful in guiding iron and ESA therapy.[27]

EXAMPLES OF TRIALS FOR TREATMENT OF ANAEMIA AND IRON DEFICIENCY ANAEMIA IN CKD

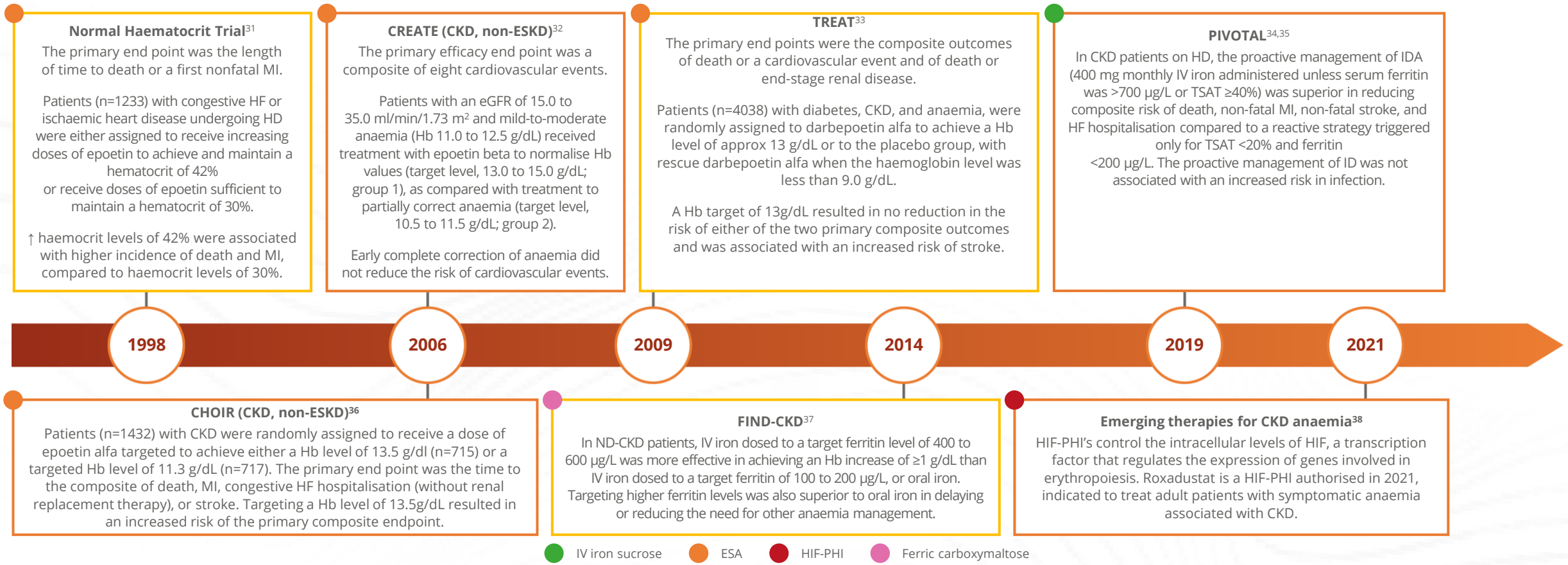


Figure 3. Examples of trials evaluating treatment options in anaemia and iron deficiency anaemia in patients with CKD. Adapted from Besarab et al (1998), Drüeke et al (2006), Evrenzo PI (2022), Pfeffer et al (2009), Macdougall et al (2014), Macdougall et al (2019), MacDougall et al (2020), and Singh et al (2006).[31–38]

CKD, chronic kidney disease; CV, cardiovascular; ESA, erythropoiesis stimulating agent; ESKD, end-stage kidney disease; Hb, haemoglobin; HD, haemodialysis; HF, heart failure; HIF, hypoxia-inducible factor; IV, intravenous; MACE, major adverse cardiovascular event; MI, myocardial infarction; ND, non-dialysis; PHI, prolyl hydrolase inhibitor; TSAT, transferrin saturation; VTE, venous thromboembolism.

Of note, a prespecified secondary analysis of the PIVOTAL trial also demonstrated no increase in risk of infections with IV iron in dialysis patients maintaining a ferritin level of ~600–700 µg/L.[35]

TREATMENT OF ANAEMIA IN CKD – ESA THERAPY CONSIDERATIONS

Iron supplementation is recommended in patients with CKD and IDA to replete iron stores and to help achieve and maintain target Hb:[20,21,30,39,40]

- before considering or when starting ESAs
- during maintenance ESA therapy
- before the initiation of HIF-PHIs

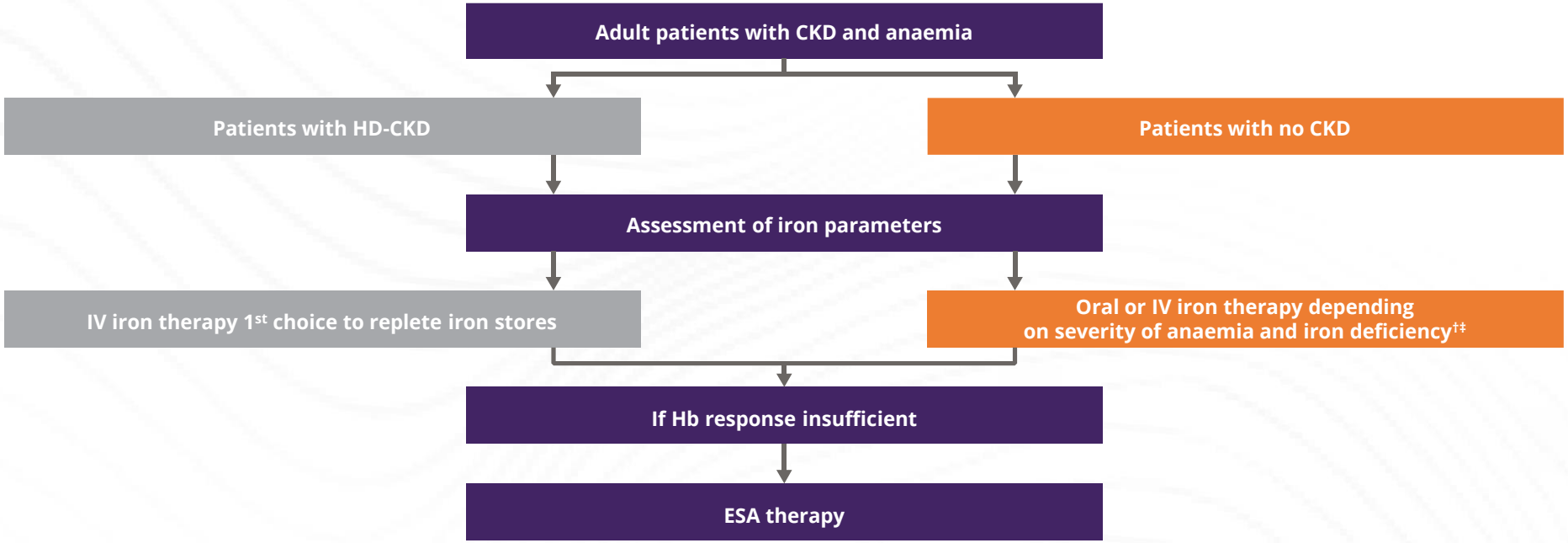
Table 3. Initiation of ESA and iron status.

Professional association	Considerations when initiating ESA therapy in patients with CKD
KDIGO[21,39]	Address all correctable causes of anaemia (including iron deficiency and inflammatory status) prior to initiation of ESA therapy
NICE (NG203)[20]	ESA therapy should not be initiated in the presence of absolute iron deficiency without also managing the iron deficiency
UK Renal Association[30]	Patients should be iron replete to achieve and maintain target Hb whether receiving ESAs or not

ESA, erythropoiesis-stimulating agent; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute for Health and Care Excellence.

TREATMENT OF ANAEMIA IN CKD WITH IRON THERAPY – IRON REPLETION

A simplified algorithm for the treatment of iron deficiency in CKD patients with anaemia is summarised in **Figure 4**.[20,21,30] This algorithm was recommended before HIF-PHI came on the market which now offers another treatment option for anaemia in iron-replete subjects.



Continued iron therapy should be based on careful consideration of the following:[21]

- An integrated assessment of Hb responses
- Iron status tests
- ESA dose/responsiveness
- Ongoing blood losses, and
- Clinical status

Available data are limited to recommend long-term IV dosing strategies.

Figure 4. Simplified algorithm for the treatment of anaemia in CKD using iron repletion based on the iron status and stages of CKD.[20,21,30]

†KDIGO guidelines recommend a 1–3 month trial of oral iron therapy in patients with ND-CKD. ‡NICE recommends a trial of oral iron before offering IV iron therapy in patients with ND-CKD who are not on ESA. If they are intolerant of oral iron or target Hb levels are not reached within 3 months, offer IV iron therapy; for patients receiving ESA offer oral iron only if: IV iron therapy is contraindicated, or the person chooses not to have IV iron therapy. Carry out routine monitoring of iron stores to prevent iron overload using serum ferritin at intervals of 1 to 3 months.

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; HD, haemodialysis; HIF-PHI, hypoxia-inducible factor prolyl hydrolase inhibitor; IV, intravenous; ND, non-dialysis.

MAXIMUM RECOMMENDED THRESHOLDS FOR IRON REPLETION

Choice of oral or IV iron depends on a number of factors, including the stage of CKD or modality of renal replacement therapy, as well as healthcare professionals' and patients' preferences.[41,42] **In HD patients, there is less debate** about whether to use IV iron; instead, **the focus has been on its dosing and timing** of administration.[43] **Table 4** shows the recommended upper limits for TSAT and ferritin levels.

Table 4. Recommended maximum TSAT and ferritin threshold values

Professional association	Year	(Hb, g/dL)	Upper limit for iron therapy ND-CKD		Upper limit for iron therapy HD-CKD		Monitor response to iron therapy
			Serum ferritin (µg/L)	TSAT (%)	Serum ferritin (µg/L)	TSAT (%)	
KDIGO[21]	2012	Increase in Hb	<500 µg/L	<30%	–	–	Every 3 months (monthly in patients on HD)
NICE (NG203)[20]	2021	–	<800 µg/L	–	<800 µg/L	–	Every 3 months (1–3 months in patients on HD)
UK Renal Association[30]	2020	10–12 g/dL	<800 µg/L[†]	>20%	Recommend proactive high-dose IV iron sucrose 400 mg every month (or equivalent) should be given unless ferritin >700 µg/L or TSAT >40%	TSAT >40%	Every 1–3 months

[†]To prevent ferritin levels exceeding 800 µg/L, review the dose of iron when serum ferritin levels Reach 500 µg/L.[30]

CKD, chronic kidney disease; Hb, haemoglobin; HD, haemodialysis; HF, heart failure; IV, intravenous; KDIGO, Kidney Disease: Improving Global Outcomes; MI, myocardial infarction; ND, non-dialysis; NICE, National Institute for Health and Care Excellence; TSAT, transferrin saturation.

For ND-CKD patients, the **FIND-CKD study** indicated that IV iron dosed to a target ferritin level of 400 to 600 µg/L was more effective in achieving an Hb increase of ≥1 g/dL than IV iron dosed to a target ferritin of 100 to 200 µg/L, or oral iron.[37] The higher dose of IV iron was also superior to oral iron in delaying or reducing the need for other anaemia management.[37]

The **PIVOTAL study** demonstrated, in an HD-CKD population, that proactive management of IDA (400 mg monthly IV iron administered unless serum ferritin was >700 µg/L or TSAT ≥40%) was superior to a reactive strategy (triggered only for TSAT <20% and ferritin <200 µg/L) in reducing the composite primary endpoint (non-fatal MI, non-fatal stroke, hospitalisation for HF, or death from any cause, assessed in a time-to-first-event analysis).[34]

The following case studies have been selected to reflect on the diagnosis, treatment initiation and dosing, and treatment goals in the management of CKD patients (ND and HD) for iron deficiency and anaemia.

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Ferinject® (ferric carboxymaltose)

Prescribing Information - Ireland
For full prescribing information refer to the Summary of Product Characteristics (SmPC)
Active Ingredient: Ferric carboxymaltose (50mg/mL)
Presentation: Dispersion for injection/infusion. Available as a 2mL vial (as 100mg of iron), 10mL vial (as 500mg of iron) and 20mL vial (as 1000mg of iron).
Indication: Treatment of iron deficiency when oral iron preparations are ineffective or cannot be used or if there is a clinical need to deliver iron rapidly. The diagnosis must be based on laboratory tests.
Dosage and Administration: The posology of Ferinject follows a stepwise approach:
Step 1: Determination of the iron need:
The individual iron need for repletion using Ferinject is determined based on the patient's body weight and haemoglobin (Hb) level, using the simplified table in the SmPC. Two doses may be required to replenish the total iron need.
Step 2: Calculation and administration of the maximum individual iron dose(s):
Based on the total iron need determined, the appropriate dose(s) of Ferinject should be administered:
In adults and adolescents aged 14 years and older, the maximum single dose is 15 mg iron/kg body weight (for administration by intravenous injection) or 20 mg iron/kg body weight (for administration by intravenous infusion) and the maximum recommended cumulative dose of Ferinject is 1,000 mg of iron (20 mL Ferinject) per week.
In children and adolescents aged 1 to 13 years, the maximum single dose is 15 mg iron/kg body weight, and the maximum recommended cumulative dose of Ferinject is 750 mg of iron (15 mL Ferinject) per week.
In all cases, if the total iron need is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose.
Administration rates for intravenous injection using undiluted dispersion:
For iron doses of 100mg to 200mg, there is no prescribed administration time. For doses >200mg to 500mg, Ferinject should be administered at a rate of 100mg iron/min. For doses >500mg to 1,000mg, the minimum administration time is 15 min.
Administration of intravenous drip infusion:
For iron doses of 100mg to 200mg, there is no prescribed administration time. For doses >200mg to 500mg, Ferinject should be administered in a minimum of 6 mins. For doses >500mg to 1,000mg, the minimum administration time is 15 mins.
Ferinject must only be diluted in 0.9% m/V NaCl but should not be diluted to concentrations less than 2 mg iron/mL.
Step 3: Post-iron repletion assessments
Contraindications: Hypersensitivity to Ferinject or any of its excipients. Known serious hypersensitivity to other parenteral iron products. Anaemia not attributed to iron deficiency. Iron overload or disturbances in utilisation of iron.
Special warnings and precautions: Parenterally administered iron preparations can cause potentially fatal anaphylactic reactions. The risk is enhanced for patients with known allergies, a history of severe asthma, eczema or other atopic allergy, and in patients with immune or inflammatory conditions. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). Ferinject should only be administered in the presence of staff trained to manage anaphylactic reactions where full resuscitation facilities are available (including 1:1000 adrenaline solution). Each patient should be observed for 30 minutes following administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Symptomatic hypophosphataemia leading to osteomalacia and fractures requiring clinical intervention has been reported. Patients should be asked to seek medical advice if they experience symptoms. Serum phosphate should be monitored in patients who receive multiple administrations at higher doses or long-term treatment, and those with existing risk factors. In case of persisting hypophosphataemia, treatment with ferric carboxymaltose should be re-evaluated. In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Careful monitoring of iron status is recommended to avoid iron overload. There is no safety data on the use of single doses of more than 200mg iron in haemodialysis-dependent chronic kidney disease patients. Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that treatment with Ferinject is stopped in patients with ongoing bacteraemia. In patients with chronic infection a benefit/risk evaluation has to be performed. Caution should be exercised to avoid paravenous leakage when administering Ferinject. The efficacy and safety of Ferinject has not been investigated in children below 1 year of age. Ferinject is therefore not recommended for use in children in this age group.
Special Populations: In adults and adolescents aged 14 years and older, a single maximum daily dose of 200 mg iron should not be exceeded in haemodialysis-dependent chronic kidney disease patients.
In children aged 1 to 13 years with chronic kidney disease requiring haemodialysis, the efficacy and safety of Ferinject has not been investigated. Ferinject is therefore not recommended for use in children aged 1 to 13 years with chronic kidney disease requiring haemodialysis.
A careful risk/benefit evaluation is required before use during pregnancy. Ferinject should not be used during pregnancy unless clearly necessary and should be confined to the second and third trimester. Foetal bradycardia may occur during administration of parenteral irons, as a consequence of hypersensitivity. The unborn baby should be carefully monitored during administration to pregnant women.
Undesirable effects: Common (≥1/100 to <1/10): Hypophosphataemia, headache, dizziness, flushing, hypertension, nausea, injection/infusion site reactions. Rare (≥1/10,000 to <1/1,000): Anaphylactic reactions. Frequency not known: Kounis syndrome, hypophosphataemic osteomalacia. Please consult the SmPC in relation to other undesirable effects
Legal category: POM
MA Number: PA0949/004/001
Date of Authorisation: 19.07.2007
MA Holder: Vifor France, 100-101 Terrasse Boieldieu, Tour Franklin La Défense 8, 92042 Paris La Défense Cedex, France

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Date of preparation: 06/2023

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Email: MedicalInfo_UK@viforpharma.com

Venofer® (iron sucrose)

Prescribing Information - Ireland
For full prescribing information refer to the Summary of Product Characteristics (SmPC)
Active ingredient: Iron sucrose (20 mg/mL)
Presentation: Solution for injection/infusion. Available as a 5 mL vial (as 100 mg of iron).
Indication: Treatment of iron deficiency where there is a clinical need for a rapid iron supply, in patients who cannot tolerate oral iron therapy or who are non-compliant, in active inflammatory bowel disease where oral iron preparations are ineffective, and in chronic kidney disease when oral iron preparations are less effective. The diagnosis of iron deficiency must be based on appropriate laboratory tests.
Dosage and Administration: The total cumulative dose of Venofer, equivalent to the total iron deficit (mg), must be individually determined for each patient, based on haemoglobin level and body weight and calculated with the Ganzoni formula. The total single dose must not exceed 200 mg of iron given not more than three times per week.
Administration for intravenous drip infusion:
Venofer must be diluted only in sterile 0.9% m/V sodium chloride solution up to a maximum dilution of 1 mg/mL. For iron doses of 50 mg, minimum infusion time is 8 minutes. For doses of 100 mg, minimum infusion time is 15 minutes. For doses of 200 mg, the minimum administration time is 30 min.
Intravenous injection: Venofer may be administered by slow intravenous injection at a rate of 1 mL undiluted solution per minute and not exceeding 10 mL Venofer (200 mg iron) per injection.
Administration into dialysis machine: Venofer may be administered during a haemodialysis session directly into the venous line of the dialysis machine under the same conditions as for intravenous injection.
Contraindications: Hypersensitivity to Venofer or any of its excipients. Known serious hypersensitivity to other parenteral iron products. Anaemia not attributed to iron deficiency. Iron overload or disturbances in utilisation of iron.
Special warnings and precautions: Parenterally administered iron preparations can cause potentially fatal anaphylactic/anaphylactoid reactions. The risk is enhanced for patients with known allergies, a history of severe asthma, eczema or other atopic allergy, and in patients with immune or inflammatory conditions. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction).
Venofer should only be administered in the presence of staff trained to manage anaphylactic reactions where full resuscitation facilities are available (including 1:1000 adrenaline solution). Each patient should be observed for 30 minutes following administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Careful monitoring of iron status is recommended to avoid iron overload. Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that treatment with Venofer is stopped in patients with ongoing bacteraemia. In patients with chronic infection a benefit/risk evaluation has to be performed. Caution should be exercised to avoid paravenous leakage when administering Venofer.
Special populations: The use of Venofer has not been studied in children. A careful risk/benefit evaluation is required before use during pregnancy. Venofer should not be used during pregnancy unless clearly necessary and should be confined to the second and third trimester. Foetal bradycardia may occur during administration of parenteral irons, as a consequence of hypersensitivity. The unborn baby should be carefully monitored during administration to pregnant women.
Undesirable effects Common (≥1/100 to <1/10): Dysgeusia, hypotension, hypertension, nausea and injection/infusion site reactions. Frequency not known: Anaphylactoid/anaphylactic reactions and Kounis syndrome. Please consult the SmPC in relation to other undesirable effects.
Legal category: POM
MA Number: PA 949/001/002
Date of Authorisation: 11.09.2009
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Additional information is available on request

Adverse events should be reported. Reporting forms and information can be found at http://www.hpra.ie/homepage/about-us/report-an-issue
Adverse events should also be reported to Vifor Pharma UK Ltd. Tel: +44 1276 853633
Email: medicalinfo_UK@viforpharma.com