Nephrol Dial Transplant, 2024, **39**, 770–777
https://doi.org/10.1093/ndt/gfad250
Advance access publication date: 27 November 2023

TREATMENT STANDARD

Anaemia in CKD—treatment standard

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ABSTRACT

Anaemia is one of the most common complications of chronic kidney disease (CKD), having a significant impact on quality of life, and is also associated with a number of adverse clinical outcomes. Its pathogenesis is multifactorial, caused largely by an inadequate production of erythropoietin from the diseased kidneys, with iron deficiency, inflammation, shortened red cell lifespan and enhanced blood loss also being contributory factors. The management of this condition was transformed in the late 1980s by the advent of recombinant human erythropoietin (epoetin), and treatment paradigms have developed over the last three decades, largely focusing on a combination of epoetin or its analogues (erythropoiesis-stimulating agents; ESAs) along with iron supplementation, often administered intravenously due to increased hepcidin levels limiting iron absorption from the gut. Indeed, in patients with early CKD and iron deficiency, iron *per se* may be sufficient to improve the anaemia, delaying the need for ESA therapy. Other causes of anaemia should be excluded and corrected (if possible) before resorting to treatment with ESAs and iron. More recently, the hypoxia-inducible factor–prolyl hydroxylase inhibitors have entered the therapeutic arena; these are orally active agents that upregulate endogenous erythropoietin production as well as a number of iron-regulatory genes which may also enhance erythropoiesis. The latter drugs are highly efficacious, and may have advantages in inflammatory conditions causing resistance to conventional ESA therapy, but concerns exist regarding their safety, particularly in the longer term. This article reviews the current standards of treatment, as well as recent novel developments in the management of anaemia in CKD.

Keywords: anaemia, erythropoietin, HIF prolyl hydroxylase inhibitors, hypoxia-inducible factor, iron

'In a nutshell'

1. The balance between erythropoiesis-stimulating agents (ESAs) and iron supplementation has changed over the last few years, with less emphasis on ESAs and more on iron.
2. ESA therapy and a higher haemoglobin can exacerbate a number of adverse secondary outcomes, such as stroke and venous thromboembolism.
3. In contrast, liberal amounts of iron replacement, such as the doses used in the high-dose arm of the PIVOTAL trial—400 mg of intravenous iron sucrose per month with safety cut-offs of ferritin (700 µg/L) and transferrin saturation (40%)—would appear to improve a number of cardiovascular outcomes in dialysis patients, e.g. hospitalization for heart failure and possibly myocardial infarction.
4. Hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs) have recently been introduced as highly effective agents for the treatment of chronic kidney disease anaemia.
5. HIF-PHIs are orally active, and allow exposure to lower circulating levels of erythropoietin, but concerns exist regarding upregulation of other HIF-sensitive genes such as vascular endothelial growth factor, with the potential to enhance tumour production and growth, as well as to worsen diabetic proliferative retinopathy.

INTRODUCTION

Patients with chronic kidney disease (CKD) almost invariably develop a progressive and debilitating anaemia which, if untreated, usually culminates in a dependence on red cell transfusions. Data from the National Health and Nutrition Examination Survey (NHANES) in the USA [1] suggest that haemoglobin concentrations are generally well preserved in early renal insufficiency, but start to decline once the glomerular filtration rate (GFR) falls below 60 mL/min, and anaemia becomes highly prevalent in patients with a GFR below 30 mL/min. The vast majority of patients on dialysis require treatment for anaemia, with a few notable exceptions, e.g. when the cause of end-stage renal failure is polycystic kidney disease, since the cysts produce higher levels of erythropoietin compared with other causes of renal failure [2]. In

Received: July 28, 2023; Editorial decision: November 1, 2023
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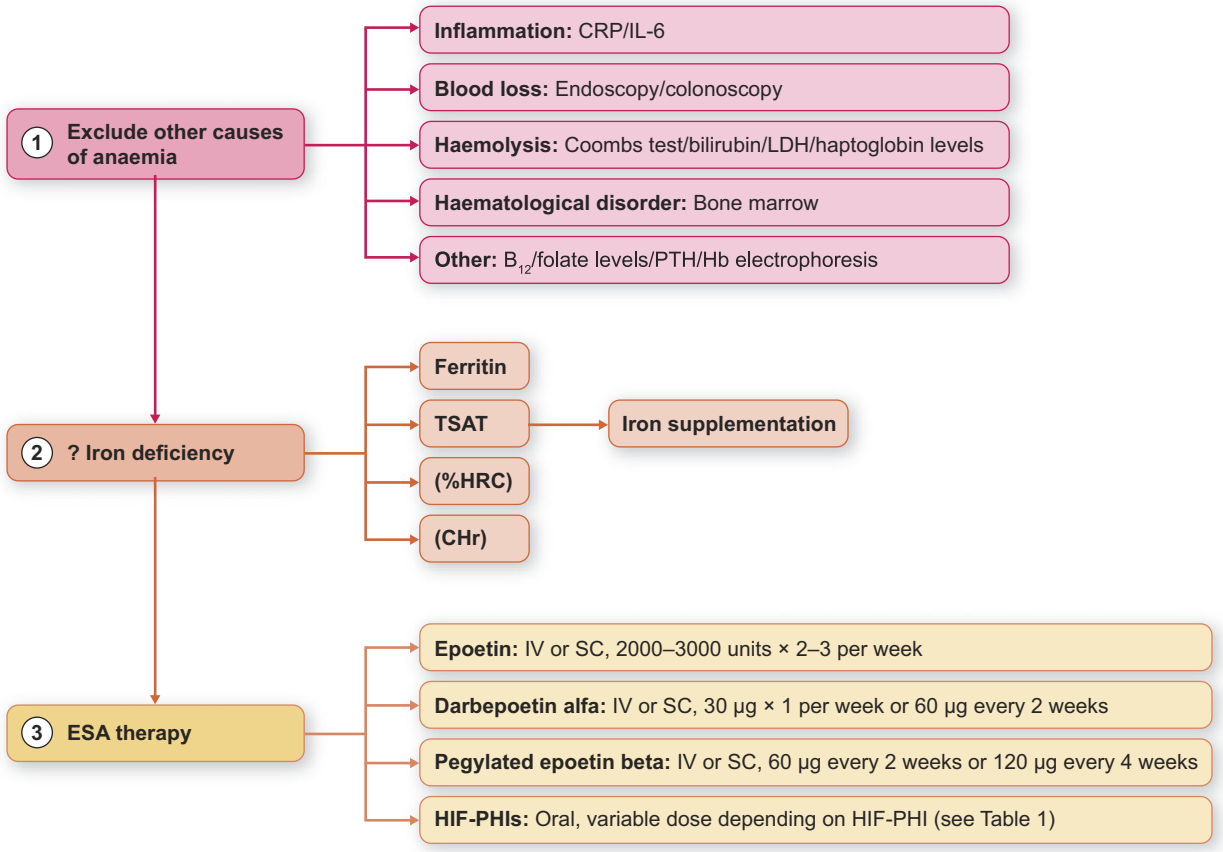

Figure 1: Stepwise algorithm depicting current standard-of-care treatment for CKD anaemia. CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase; PTH, parathyroid hormone; Hb, haemoglobin; %HRC, percentage of hypochromic red cells; CHr, reticulocyte haemoglobin content; ESA, erythropoiesis-stimulating agent; HIF-PHIs, hypoxia-inducible factor-prolyl hydroxylase inhibitors; IV, intravenous; SC, subcutaneous.

contrast, patients with diabetes as the cause of their CKD are often more anaemic for any given level of GFR compared with their non-diabetic counterparts [3]. As a practical point, if a patient's GFR is >60 mL/min then it is less likely that their anaemia is solely due to erythropoietin deficiency and other causes should be sought (see below).

Until the late 1980s when first-generation ESAs became available, it was commonplace for patients on dialysis to have haemoglobin concentrations of 5 or 6 g/dL and to require regular blood transfusions to avoid life-threatening complications of the severe anaemia. This, however, resulted in transfusional iron overload, in addition to sensitizing potential renal transplant recipients to HLA antigens, thus rendering subsequent transplantation more problematic. There were also potential problems with transfusion reactions and transmission of infectious agents, particularly viral.

Modern day management of CKD anaemia seeks to avoid these life-threatening complications, and the vast majority of patients can be effectively treated. The current standards of treatment and novel developments in the management of anaemia will be discussed below.

TREATMENT STANDARDS

The current management of CKD anaemia best incorporates a hierarchical stepwise approach involving three distinct strategies (Fig. 1; Table 1).

Exclusion of other causes of anaemia

Before embarking on treatment with iron or ESA therapy, it is important to exclude other contributory causes of anaemia, particularly those that are correctable, such as haematinic deficiencies (iron, vitamin B_{12} or folate), hypothyroidism, haemolysis, blood loss, primary bone marrow disorders and other haematological conditions (such as myeloma, myelodysplastic syndrome, etc.) [4]. To this end, a number of simple screening blood tests may be helpful.

Red cell indices

When the complete (or full) blood count is requested, the three major laboratory parameters that are reported are the haemoglobin concentration, the white cell count and the platelet count. However, modern day analysers provide accurate information on red cell morphology, notably the reticulocyte count, red cell size [mean cell volume (MCV)] and degree of haemoglobinization [mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC)], reticulocyte haemoglobin content (CHr), red cell distribution width (RDW) and percentage of hypochromic red cells (%hypoRBC). Each of these parameters can provide useful screening information for a number of conditions.

Reticulocyte count and indices

The normal absolute reticulocyte count is somewhere between 50 and 100 × 10^9/L to maintain a normal haemoglobin concentration. Reticulocyte counts <50 indicate low marrow

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Table 1: Drugs used in the management of CKD anaemia.

Drug name	Manufacturer/company	Route of administration, typical dosing schedule
Iron preparations		
Ferrous sulphate, ferrous fumarate, ferrous gluconate	Numerous generic companies	Oral, 200–300 mg once to thrice daily
Sucrosomial iron (SiderAL)	PharmaNutra	Oral, 30 mg/day up to 60 mg twice daily
Ferric citrate (Auryxia)	Akebia	Oral, initially 210 mg ×3/day
Iron sucrose (Venofer)	CSL Vifor, American Regent	IV bolus, 100–200 mg over 2–10 min
Sodium ferric gluconate (Ferrlecit)	Sanofi	IV bolus, 125 mg over 10 min
LMW iron dextran (CosmoFer; INFeD)	Pharmacosmos, Watson Pharmaceuticals	IV, 1000 mg/2 h; up to 20 mg/kg infusion over 4 h
Ferric carboxymaltose (Ferinject)	CSL Vifor, American Regent	IV, 500 mg over 6 min, or up to 1000 mg over 15 min
Ferric derisomaltose (Monofer)	Pharmacosmos	IV bolus, 500 mg over 2 min; up to 20 mg/kg IV infusion
Ferumoxytol (Feraheme)	AMAG Pharmaceuticals	IV, 510 mg over 15 min
ESA therapies		
Epoetin alfa	Multiple (including biosimilar versions)	IV or SC, 2000 units 2 or 3 times weekly
Epoetin beta	Multiple (including biosimilar versions)	IV or SC, 2000 units 2 or 3 times weekly
Darbepoetin alfa	Amgen	IV or SC, 30 µg once weekly or 60 µg every 2 weeks
Methoxypolyethylene glycol epoetin beta	Roche	IV or SC, 60 µg every 2 weeks or 120 µg once monthly
Roxadustat	FibroGen, Astellas, AstraZeneca	Oral, 70 mg thrice weekly
Vadadustat	Akebia	Oral, 300 (150–450) mg once daily
Daprodustat	GlaxoSmithKline	Oral, 2–4 mg once daily
Molidustat	Bayer	Oral, 50 (25–75) mg once daily
Enarodustat	Japan Tobacco Inc.	Oral, 2–6 mg once daily
Desidustat	Zydus Life Sciences	Oral, 125 (100–150) mg thrice weekly

erythropoietic activity, either due to inappropriately low circulating serum erythropoietin levels or due to marrow suppression caused by inflammation or primary bone marrow insufficiency. A reticulocyte count >100 indicates regenerative anaemia, and could be due to initiation of ESA treatment, but physicians should rule out bleeding and haemolysis.

The CHr is usually >29 pg/mL, and levels below this are usually due to iron deficiency.

Haematocrit

The haematocrit (or packed cell volume) represents the fraction of whole blood composed of red cells, as opposed to plasma, white cells, etc. In the past, this has been used as the outcome measure to describe anaemia in many clinical trials; however, the haematocrit is a relatively unstable analyte, and its measurement lacks precision, with no international standard in contrast to haemoglobin. Determination of haematocrit is also instrumentation-dependent since it is derived indirectly by automated analysers [4].

MCV

The normal MCV is between 77 and 100 fL, and values lower than this may be indicative of iron deficiency, an underlying haemoglobinopathy such as thalassaemia or sickle cell anaemia, aluminium intoxication (rare nowadays) or secondary to some drugs such as sirolimus.

Conversely, high MCV levels may be due to a number of causes, including vitamin B_{12} or folate deficiency, hypothyroidism, liver disease, alcohol intoxication, haemolytic anaemia, severe bleeding and myelodysplastic syndrome, or be secondary to some drugs such as azathioprine.

MCH, MCHC

A low MCH or MCHC may indicate longstanding iron deficiency, or an underlying haemoglobinopathy such as thalassaemia or sickle cell anaemia. A high MCH or MCHC has been described in haemolytic-uraemic syndrome.

RDW

The red cell distribution width describes the percentage variability in the volume of the red cell population. An increase in RDW may indicate a recent blood transfusion, or alternatively recent iron therapy correcting an underlying iron deficiency.

Other laboratory tests

Further laboratory tests may be indicated to screen for other causes of anaemia, such as low ferritin and transferrin saturation (TSAT) levels suggestive of iron deficiency, as well as low vitamin B_{12} and folate levels, and thyroid function tests to exclude hypothyroidism. A high reticulocyte count suggests an active marrow, and conditions such as haemolysis or occult blood loss should be considered. A screen for haemolysis may include a Coombs test, blood film, bilirubin level, lactate dehydrogenase level and haptoglobin levels, while if occult gastrointestinal blood loss is suspected, screening for faecal occult blood and/or endoscopy and colonoscopy may be indicated. Assessment of the degree of chronic inflammation may be helpful, and achieved by measuring the C-reactive protein or serum interleukin-6 level. Under-dialysis may also worsen the anaemia, which can improve by increasing the intensity of the dialysis prescription [5], and so measuring the Kt/V or urea reduction ratio may be indicated. Likewise, hyperparathyroidism exacerbates CKD anaemia [6], so serum PTH measurement may be helpful. In some ethnic minority patients in whom a haemoglobinopathy may be present, screening for thalassaemia or sickle cell anaemia by haemoglobin electrophoresis may be enlightening. Finally, if there is any suspicion of a primary bone marrow disorder, then a referral for haematological opinion and/or bone marrow examination may reveal the presence of myelodysplastic syndrome (particularly in elderly men) or haematological malignancy.

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Iron management

The most common cause of anaemia in CKD after erythropoietin insufficiency is iron deficiency, either absolute (where there is a lack of total body iron stores) or functional, when body stores are adequate but there is a failure to release the iron rapidly enough to the proliferating bone marrow [7]. Unfortunately, the tests for assessing iron deficiency in CKD are suboptimal, and usually rely on assessment of serum ferritin or transferrin saturation (TSAT). Measurement of the percentage of hypochromic red cells and/or CHr has been shown to be more discriminatory than the ferritin or TSAT [8], but neither test is widely available and the % hypochromic red cells needs to be measured on a fresh blood sample, which also limits its utility. Arbitrary cut-offs of serum ferritin have evolved over the years, with a value <30 µg/L strongly suggesting absolute iron deficiency. However, iron deficiency is common with ferritin levels up to 100 µg/L in non-dialysis CKD, and even 200 µg/L in dialysis patients. Likewise, TSAT levels <20% strongly suggest iron insufficiency [7]. Upper ferritin and TSAT limits for patients receiving IV iron are somewhat arbitrary, but may be around 600 µg/L in non-dialysis CKD and 800–1000 µg/L in dialysis patients. The mean ferritin levels reached in the higher ferritin arm of Ferinject® assessment in patients with Iron deficiency anaemia and Non-Dialysis-dependent Chronic Kidney Disease (FIND-CKD) (in non-dialysis CKD) [9] and in the high-dose arm of Proactive IV irOn Therapy in hemodiALysis patients (PIVOTAL) (in haemodialysis) [10] were around 500 µg/L and 650 µg/L, respectively. If iron deficiency is present (or suspected), then it is mandatory that this is corrected before ESA therapy is prescribed, for three reasons: (i) ESA therapy is much less effective in the presence of iron deficiency, requiring higher doses and incurring greater costs; (ii) iron supplementation would appear to be generally safer than ESAs; and (iii) many patients with iron deficiency will have a significant improvement in their anaemia with iron therapy without ESA therapy. This was shown fairly convincingly in the FIND-CKD study [9] in 626 non-dialysis CKD patients randomized to two different regimens of intravenous (IV) iron or oral ferrous sulphate in which there was a greater and faster increment in haemoglobin concentration with the higher ferritin target group of IV iron, but with significant increases in haemoglobin in all three groups. Iron supplementation before ESA therapy is, however, likely to be ineffective in advanced CKD and, in particular, dialysis patients since erythropoietin levels are by then usually too low to support adequate marrow erythropoietic activity, and concomitant ESA therapy will likely be required. The choice between oral and IV iron supplementation has been the subject of much debate [11], and remains a matter for physician and patient preference, but in general oral iron is less absorbed the more advanced the degree of renal impairment due to upregulation of hepcidin, which inhibits iron absorption from the gut [12], and IV iron becomes mandatory in the vast majority of dialysis patients.

ESA therapy

If other causes of CKD anaemia including iron deficiency have been excluded, then treatment with ESAs is indicated. These agents are highly effective in boosting the circulating erythropoietin levels and increasing marrow erythropoietic activity. First-generation agents consisted of recombinant human erythropoietin (epoetin), introduced in the late 1980s. Epoetin has a short half-life of 6–8 h and generally has to be administered two to three times a week for maximum effect. A second-generation molecule, initially called NESP (Novel erythropoiesis stimulating protein), and later darbepoetin alfa, was then created as a hyperglycosylated analogue of epoetin, which conferred greater metabolic stability, and a 3-fold longer half-life of over 25 h when injected intravenously [13]. This allowed less frequent darbepoetin dosing of once a week or once every 2 weeks. Subsequently, a pegylated form of epoetin beta was developed with a half-life of >130 h which allowed once-monthly dosing [14]. All agents are equally effective in correcting anaemia, administered either intravenously or subcutaneously, and are generally safe, but caution has to be exercised in over-correcting the haemoglobin to >12 g/dL to avoid possible cardiovascular toxicity, notably stroke and venous thromboembolism [15–18]. In addition, a very rare complication of all injectable ESAs is pure red cell aplasia, caused by the development of antibodies against the ESA which then cross-react with the patient's own endogenous erythropoietin, effectively shutting down all marrow erythropoietic activity.

Strategies for how to personalize treatments

For the individual patient, various decisions have to be made with regard to both iron management and ESA therapy.

Iron management

In non-dialysis patients with iron deficiency, the main decision is whether to prescribe oral or IV iron [11]. Oral iron has the advantage of being cheap and easy for the prescriber, but requires frequent and longer-term dosing to be effective, and may be poorly absorbed in advanced renal impairment. Furthermore, up to 60% of people taking oral iron supplements report gastrointestinal side-effects [19], resulting in poor adherence to therapy. IV iron is more effective in advanced CKD (and mandatory in dialysis patients when oral iron absorption is inadequate due to hepcidin upregulation) but requires facilities and staffing to administer, as well as the need for the patient to travel to the treatment centre. A further consideration regarding the use of IV iron in non-dialysis patients is the potential damage to veins which may subsequently be used for arteriovenous fistula creation. Doses of IV iron in non-dialysis and peritoneal dialysis patients may be around 1000 mg, repeated every few months as required, while doses in haemodialysis patients may be 100–200 mg once or twice a month. Ferritin and TSAT may be monitored every month in dialysis and every 3–4 months in non-dialysis and peritoneal dialysis patients.

ESA therapy

The pertinent decisions that have to be made for the individual patient starting ESA therapy are:

- When to start treatment (the 'trigger' haemoglobin concentration)
- What level of haemoglobin to aim for (the 'target' haemoglobin range)
- What type of ESA to use for the particular patient

International guidelines [4] suggest that ESA therapy should rarely (if ever) be initiated with a haemoglobin >10 g/dL since the benefit–risk ratio is likely to be unfavourable. If the haemoglobin is consistently <10 g/dL and/or the patient is symptomatic, then ESA therapy may improve quality of life and reduce the need for blood transfusions in the long-term. The benefits of ESA therapy when the haemoglobin is <9 g/dL are fairly compelling.

The 'target' haemoglobin for patients on ESA therapy has been the subject of much debate for over 20 years. Very strong evidence from several randomized controlled trials suggest that a haemoglobin >13 g/dL is harmful [15–18], and guidelines suggest an upper limit of 11.5 in the USA or 12.0 g/dL in Europe.

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Table 2: Worldwide availability of the HIF-PHIs.

Drug name	Brand name	Manufacturer	Phase 3 studies	Approval in the USA[a]	Approval in Europe[a]
Roxadustat	Evrenzo	FibroGen, Astellas, AstraZeneca	ANDES, ALPS, OLYMPUS, DOLOMITES (ND) PYRENEES, SIERRAS, HIMALAYAS, ROCKIES (DD)	No	Yes
Vadadustat	Vafseo	Akebia	PRO$_2$TECT (ND) INNO$_2$VATE (DD)	No	Dialysis only
Daprodustat	Jesduvroq	GlaxoSmithKline	ASCEND-ND (ND) ASCEND-D (DD)	Dialysis only (after 4 months)	Dialysis only
Molidustat[b]	Musredo	Bayer	MIYABI program—ND & DD		
Enarodustat[b]	Enaroy	Japan Tobacco Inc	SYMPHONY ND SYMPHONY HD		
Desidustat[c]	Oxemia	Zydus Life Sciences	DREAM-ND (ND) DREAM-D (DD)		

[a]As of July 2023.
[b]Approved in Japan.
[c]Approved in India.

However, the guidelines also stress the importance of individualizing the target haemoglobin [4, 20], accepting that (for example) it may be appropriate for some younger fit patients (or those with religious beliefs precluding blood transfusion) to have a target haemoglobin up to 12 g/dL, while for some older patients with a previous history of stroke, it may be preferable to maintain the haemoglobin around 10–11 g/dL.

The choice of ESA therapy between epoetin [IV or subcutaneous (SC), two to three times per week], darbepoetin alfa (IV or SC, once weekly or once every 2 weeks), pegylated epoetin beta (IV or SC, once every 2 weeks or once monthly) or a hypoxia-inducible factor–prolyl hydroxylase inhibitor (HIF-PHI; orally, once daily or thrice weekly) will depend on many factors, including cost, physician and patient preference, etc. All agents are highly and equally efficacious, although HIF-PHIs may be more effective in patients with inflammation resistant to conventional ESA therapy.

NEW DEVELOPMENTS IN THE MANAGEMENT OF CKD ANAEMIA

For over three decades, and as described above, the management of CKD anaemia has focused on a combination of an agent to stimulate erythropoiesis along with supplemental iron. The discovery of HIF in the early 1990s resulted in a completely novel approach to anaemia correction [21]. HIFs are oxygen-sensitive heterodimeric transcription factors that coordinate the response to hypoxia by increasing erythropoietin production in the kidneys and liver. Under normoxic conditions, prolyl hydroxylase enzymes hydroxylate the oxygen-regulated HIF-α subunit, thereby targeting it for proteasomal degradation [22]. In the presence of hypoxia, however, prolyl hydroxylation and degradation of HIF-α are inhibited, resulting in its cellular accumulation and formation of the HIF heterodimeric transcription factor [23, 24]. This HIF transcription factor complex then binds to the hypoxia-responsive element of the erythropoietin gene, causing an increase in erythropoietin production in both the kidneys and liver [25]. Understanding this pathway has allowed the pharmaceutical industry to develop inhibitors of the HIF prolyl hydroxylase enzyme which 'stabilize' HIF and thereby enhance endogenous erythropoietin production; this new class of drugs is termed 'hypoxia-inducible factor-prolyl hydroxylase inhibitors' (HIF-PHIs) or 'HIF stabilizers'. The levels of erythropoietin produced in patients treated with HIF-PHIs are substantially lower than those found in patients receiving epoetin injections, and it was therefore postulated that these new agents could have a reduced cardiovascular toxicity profile by avoiding the pleiotropic effects of high peak serum levels of erythropoietin [26].

Furthermore, since many of the iron regulatory genes such as transferrin and transferrin receptor are also HIF-sensitive and there is indirect downregulation of hepcidin, iron absorption and transport mechanisms may also be enhanced, potentially resulting in less need for supplemental iron [27]. HIF-PHIs may also theoretically be more effective in enhancing erythropoiesis and correcting anaemia in the presence of inflammation in patients who are resistant to conventional ESA therapy, but the evidence for this is sparse, and properly conducted clinical trials with this as an endpoint are needed to address this issue [28]. Finally, another major benefit of this new class of drugs is that they are orally active and avoid the need for frequent injections, as well as having greater stability at room temperature; this is, however, not an advantage for haemodialysis patients. Furthermore, drug–drug interactions are a limiting factor for these agents.

Worldwide, there are six HIF-PHIs that have completed phase 3 clinical trial programs (Table 2). The three front-runners are roxadustat, vadadustat and daprodustat, all of which underwent clinical trials in thousands of patients with both non-dialysis-dependent (NDD) and dialysis-dependent (DD) CKD [29–35].

Roxadustat was the first to complete its programme in 4277 NDD and 3880 DD patients [35]. There was undisputed efficacy in correcting anaemia and maintaining haemoglobin levels, and the main focus was on cardiovascular safety, with major adverse cardiovascular events (MACE) being the primary outcome measure for all trials [31–35]. In the initial primary analysis, the results were reassuring, with the primary composite endpoint of MACE in both NDD [hazard ratio (HR) 1.10, 95% confidence interval (CI) 0.96–1.27] and DD (HR 1.02, 95% CI 0.88–1.20) patients meeting non-inferiority with the comparator [35]. However, when the Food and Drug Administration (FDA) performed their own independent analysis of the data, they found HRs of 1.35 and 1.14, respectively, suggesting increased cardiovascular toxicity and, as a result, an FDA Advisory Committee voted against approval in the USA in July 2021 [36]. The European Medicines Agency, however, has approved roxadustat for use in CKD patients, although the files submitted to the European Medicines Agency (EMA) were different from those submitted to the FDA.

Vadadustat met non-inferiority for the MACE primary endpoint in the dialysis population (n = 3923) (HR 0.96, 95% CI 0.83–1.11)

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Table 3: Safety concerns with the HIF-PHIs.

- Thromboembolic complications
- Tumour growth/increased cancer risk
- Angiogenesis (VEGF)—cancer risk, worsening proliferative diabetic retinopathy
- Exacerbation of pulmonary arterial hypertension
- Worsening renal progression due to kidney fibrosis
- Increased infection risk, sepsis
- Immune dysregulation
- Enhanced progression of polycystic kidney disease
- Other side-effects, such as seizures, oesophageal/gastric erosions, hypothyroidism

[32] but did not achieve this in the NDD population ($n = 3476$) (HR 1.17, 95% CI 1.01–1.36) [31]. Vadadustat has been approved in Europe for the dialysis population, but not for non-dialysis patients, and has not been approved in the USA for any CKD modality.

For daprodustat, the MACE risk achieved non-inferiority for both NDD ($n = 3872$) [33] and DD ($n = 2964$) [34] populations in the prespecified intention-to-treat primary analysis, but did not achieve this in the NDD on-treatment secondary analysis [33], possibly due to protocol-specific issues in relation to event reporting. Daprodustat has been approved by both the FDA and the EMA for dialysis patients in the USA (after 4 months of treatment) and Europe, but not for non-dialysis patients. All three drugs have been approved in China and Japan.

Phase 3 trials for molidustat [37] and enarodustat [38] (in Japan), and desidustat [39] (in India) have been too small with insufficient power to generate meaningful information on cardiovascular safety. In summary, at best the HIF-PHIs do not appear to increase cardiovascular risk, but they also do not appear to reduce it, and there are concerns with the data and the analyses.

There are also quite a number of other theoretical concerns with this new class of drugs. In addition to erythropoietin and iron regulatory genes, there are several hundred other HIF-sensitive genes that are potentially upregulated [40]. These include, but are not limited to, increased vascular endothelial growth factor (VEGF), with the potential to exacerbate angiogenesis, enhance tumour growth and worsen diabetic retinopathy. Given the slow rate of progression of many cancers, it may take many years before we will know whether or not there is an increased cancer risk with the HIF-PHIs. Other potential adverse consequences of this new class of drugs are listed in Table 3.

The other recent major development in CKD management has been the recognition that IV iron is not as harmful as once thought, and indeed may confer previously unrecognized benefits. Observational data from both the Dialysis Outcomes and Practice Patterns Study (DOPPS) [41] and a cohort of 58 058 patients from DaVita dialysis clinics in the USA [42] both suggested an increase in cardiovascular mortality in haemodialysis patients exposed to greater doses of IV iron, and this was underpinned by data suggesting an increase in oxidative stress with IV iron, possibly accelerating atherogenesis [43]. Other concerns with IV iron included a possible predisposition to infections caused by increased bacterial growth [44] and reduced defence mechanisms against microorganisms due to impaired polymorphonuclear phagocytic function [45]. The PIVOTAL trial was conceived to investigate whether a more liberal high-dose proactive regimen of IV iron [400 mg of IV iron sucrose per month with safety cut-offs of ferritin (700 µg/L) and TSAT (40%)] would be more harmful than a restrictive low-dose regimen of 100–200 mg iron sucrose per month to maintain minimum ferritin and TSAT thresholds [10]. A total of 2141 haemodialysis patients were randomized to one of the two regimens, and the primary endpoint was a composite of all-cause mortality, myocardial infarction, stroke and hospitalization for heart failure. The results showed that the higher dose IV iron arm significantly reduced the risk of the primary outcome of death or non-fatal cardiovascular events, reduced the risk of myocardial infarction by 31% and hospitalization for heart failure by 33%, reduced the dose of ESA therapy by 19.4% and reduced the blood transfusion rate by 21% [10]. Importantly, there were no safety concerns and, in particular, no increased risk of infection [46] or hospitalization. Of note, also, many patients randomized to the low-dose iron arm remained relatively iron-deficient.

These data, along with data from multiple heart failure trials, suggest that previous concerns about IV iron were unfounded, and that IV iron may have positive benefits on the cardiovascular system, possibly via mechanisms independent of its effects on red cells and anaemia correction [47].

For additional information on both these developments, the reader may be interested in the reports of the two Controversies Conferences on CKD anaemia management organized by KDIGO, the first focusing on the role of iron [48], and the second on the role of the HIF-PHIs [49]. The report of a Scientific Workshop on HIF-PHIs sponsored by the National Kidney Foundation in the USA may also be of interest [50]. Finally, KDIGO are in the process of updating their 2012 Anemia Guideline, and the European Renal Best Practice position statement on the role of HIF-PHIs in CKD anaemia management will shortly be published [51].

SUMMARY

The anaemia associated with CKD is common, multifactorial in aetiology and easily managed in the vast majority of patients. Other causes of anaemia should be excluded and treated, particularly iron deficiency, since iron replacement may be enough *per se* to improve the haemoglobin. A serum ferritin <100 µg/L or a TSAT <20% should prompt consideration of iron therapy. If there is doubt about the presence of iron deficiency, then a trial of IV iron may be helpful, otherwise ESA therapy should be considered if the haemoglobin concentration is <10 g/dL (or there has been a clear downward trend over time if the haemoglobin is >10 g/dL). The choice of ESA between epoetin (IV or SC, two to three times per week), darbepoetin alfa (IV or SC, once weekly or once every 2 weeks), pegylated epoetin beta (IV or SC, once every 2 weeks or once monthly) or a HIF-PHI (orally, once daily or thrice weekly) will depend on many factors, including cost, physician and patient preference, etc. All agents are highly and equally efficacious, although HIF-PHIs may be more effective in patients with inflammation resistant to conventional ESA therapy. Previous optimism that HIF-PHIs (by exposing the patient to lower circulating levels of erythropoietin) would have less cardiovascular toxicity has not been realized, and there are a number of theoretical safety concerns, particularly increased risk of cancer progression in the long-term. Finally, many of the safety concerns regarding IV iron have been dispelled or lessened by the PIVOTAL trial, which also suggested that more liberal use of IV iron could have cardiovascular benefits beyond simply its effect on red cells.

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FUNDING

No funding was received in the preparation of this manuscript.

AUTHORS' CONTRIBUTIONS

This paper was written exclusively by I.C.M. with no input from a medical writer, and no involvement of the pharmaceutical industry.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

I.C.M. has received consultancy fees and honoraria from Vifor Pharma and GlaxoSmithKline. He was on the Trial Steering Committee for the ASCEND program as part of the clinical development of daprodustat.

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Received: July 28, 2023; Editorial decision: November 1, 2023
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