Clinical Kidney Journal

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Clinical Kidney Journal, 2021, vol. 14, no. 4, 1067–1076

doi: 10.1093/ckj/sfaa212
Advance Access Publication Date: 26 November 2020
CKJ Review

CKJ REVIEW

Intravenous iron therapy and the cardiovascular system: risks and benefits

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ABSTRACT

Anaemia is a common complication of chronic kidney disease (CKD). In this setting, iron deficiency is frequent because of the combination of increased iron needs to sustain erythropoiesis with increased iron losses. Over the years, evidence

Received: 22.4.2020; Editorial decision: 31.8.2020

has accumulated on the involvement of iron in influencing pulmonary vascular resistance, endothelial function, atherosclerosis progression and infection risk. For decades, iron therapy has been the mainstay of therapy for renal anaemia together with erythropoiesis-stimulating agents (ESAs). Despite its long-standing use, grey areas still surround the use of iron therapy in CKD. In particular, the right balance between either iron repletion with adequate therapy and the avoidance of iron overload and its possible negative effects is still a matter of debate. This is particularly true in patients having functional iron deficiency. The recent Proactive IV Iron Therapy in Haemodialysis Patients trial supports the use of intravenous (IV) iron therapy until a ferritin upper limit of 700 ng/mL is reached in haemodialysis patients on ESA therapy, with short dialysis vintage and minimal signs of inflammation. IV iron therapy has also been proven to be effective in the setting of heart failure (HF), where it improves exercise capacity and quality of life and possibly reduces the risk of HF hospitalizations and cardiovascular deaths. In this review we discuss the risks of functional iron deficiency and the possible benefits and risks of iron therapy for the cardiovascular system in the light of old and new evidence.

Keywords: anaemia, cardiovascular disease, chronic kidney disease, ferritin, heart failure, haemodialysis, iron

INTRODUCTION

Chronic kidney disease (CKD) is one of the fastest-growing causes of death worldwide and is predicted to be among the top five causes by 2040 [1]. Reversing this trend requires better prevention and treatment of CKD and possibly also of its complications, such as renal anaemia.

Before erythropoiesis-stimulating agents (ESAs) were available, repeated blood transfusions were required and iron overload was common. Following the introduction of ESAs, erythropoiesis remained suboptimal in some patients. Systemic inflammation and functional iron deficiency were the two most common causes of ESA resistance. Moreover, the combination of increased iron needs to sustain erythropoiesis with increased iron losses, resulting in a high prevalence of iron deficiency. Excessive ESA dosing to overcome ESA resistance was associated with adverse cardiovascular outcomes in clinical trials. Therefore, determining the optimal levels and strategy of iron supplementation is a key for preventing the potential adverse consequences of anaemia, ESA overdosing or iron overload. Based on the available but incomplete evidence, guidelines recommend a range of target values for iron parameters in response to iron supplementation [2, 3]. This review, which was planned as part of the activity of the European Renal and Cardiovascular Medicine Working Group, will focus on the risks of functional iron deficiency and iron therapy, the interaction of intravenous (IV) iron therapy with the cardiovascular system and CKD and how the recently published Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial testing different strategies of IV iron supplementation may change clinical practice [4].

THE PHYSIOLOGY OF IRON METABOLISM

Iron is the fourth most common element in the Earth's crust and the most abundant transition redox-active metal in our body. It has a dual property to either donate or accept electrons, thus it catalyses many cellular redox reactions. In the Fenton reaction, ferrous iron (Fe^{2+}) is oxidized by hydrogen peroxide (H_2O_2) to ferric iron (Fe^{3+}), yielding highly reactive hydroxyl radicals (HO•), while in the first step of the Haber–Weiss reaction, Fe^{3+} is reduced by superoxide ($•O_2^-$) into ferrous (Fe^{2+}) ion. Iron is essential for cell growth and survival, DNA synthesis and repair, mitochondrial function and inflammation regulation. It is also a prerequisite for haemoglobin (Hb) synthesis. However, excess free iron is toxic to cells due to its ability to catalyse free radical generation, leading to oxidative stress, dysfunctional lipid membranes and ultimately to cell death and organ damage.

In order to avoid plasma labile iron as much as possible, systemic iron balance needs to be tightly regulated by the pathways that supply, utilize, recycle and store iron. Specialized transport systems and membrane carriers have evolved in mammals to maintain iron in a soluble state that is suitable for circulation into the blood and transfer across cell membranes [5, 6]. Iron homoeostasis relies mainly on the control of iron efflux from duodenal enterocytes into the circulation and the recycling of senescent erythrocytes by macrophages through erythrophagocytosis.

Hepcidin is recognized as the 'master regulator' of iron homoeostasis. Originally considered to be an antimicrobial molecule, hepcidin is a 25amino acid peptide, which is primarily synthesized in hepatocytes. Its main action is to reduce the efflux of recycled iron from iron-exporting tissues (i.e. splenic and hepatic macrophages) as well as iron absorption from the gut [7, 8]. In particular, in reticulo-endothelial macrophages, hepcidin binds to the cellular iron export channel ferroportin, causing its internalization and subsequent degradation. In intestinal epithelial cells, hepcidin mainly acts by decreasing the protein levels of another iron channel, the apical divalent metal transporter 1 (DMT1) [7, 8]. *In vitro* studies suggest that hepatic hepcidin transcription is downregulated by iron deficiency, hypoxia and ineffective erythropoiesis. In such conditions, low hepcidin levels allow for iron absorption from intestinal cells and iron efflux from iron stores (macrophages, hepatocytes) into plasma, enabling iron to be used by bone marrow cells for erythropoiesis. In contrast, hepcidin is upregulated by inflammatory cytokines, bone morphogenetic proteins and iron. In situations of iron overload or increased inflammation, increased hepcidin results in decreased intestinal iron absorption and reduced efflux from iron stores [9, 10].

Hepcidin is upregulated by several inflammatory cytokines, including interleukin (IL)-6, IL-1α, IL-1β, and acute inflammatory stimuli such as lipopolysaccharide [11, 12]. This increase causes functional iron deficiency, considered as a major player in anaemia of chronic inflammatory disease. Patients with end-stage renal disease (ESRD) are a typical example of greatly elevated hepcidin levels [13] due to the inflammatory milieu accompanying uraemia.

Of note, both hepcidin and iron carriers such as ferroportin and DMT1 are expressed in the kidney and play important roles in the control of iron transport and accumulation [14]. Ferroportin is primarily located at the basal side and DMT1 at the apical side

of epithelial cells, mainly at the proximal tubule and thick ascending limb. Under normal conditions, only a small portion of transferrin is filtered through the glomerulus and reabsorbed via the proximal tubule, while hepcidin prevents the reabsorption of free iron present in the urine. When hepcidin is absent in the thick ascending limb, the iron is reabsorbed and sequestrated via DMT1 and ferritin or moves through ferroportin to the circulation to bind again with transferrin. In haemolysis, Hb is largely reabsorbed and degraded by the proximal tubule and iron is recycled again in the circulation [14].

Functional iron deficiency and positive iron balance

Functional iron deficiency is characterized by reduced iron availability despite adequate iron stores due to the sequestration of iron within the storage sites. It is often observed in patients with CKD and increased C-reactive protein levels; its presence is suggested by the coexistence of low transferrin saturation (TSAT) together with normal or high serum ferritin. However, due to the lack of an unequivocal gold standard, its true identification remains challenging.

Apart from being the cornerstone of anaemia of chronic disease and complicating many inflammatory diseases, recent observational studies suggest that functional iron deficiency per se is associated with increased risk of morbidity and mortality in various populations, including patients with heart failure (HF) and patients with CKD of various stages [15–18]. This is of importance because in patients with functional iron deficiency, IV iron administration might worsen cardiovascular disease or infections [2].

Following the publication of the Kidney Disease: Improving Global Outcomes (KDIGO) anaemia guidelines in 2012 [2], the use of iron has increased significantly. This went hand-in-hand with a progressive increase in serum ferritin levels, especially in the USA. In the USA, partially as a result of a new reimbursement policy for ESRD, mean serum ferritin levels have increased during the last decade, with 45.5% of the patients now having serum ferritin >800 ng/mL [19]. In Europe, and even more so in Japan, ESRD patients have in general lower ferritin levels [20]. In this regard, the mortality of ESRD patients is higher in the USA than in Japan and in many European countries, likely reflecting not only heterogeneous genetic and environmental characteristics, but also differences in the epidemiology of CKD, burden of comorbidities and anaemia treatment modalities, including different iron administration practices.

Several observational studies have related high ferritin levels with increased mortality in the non-dialysis (ND) [16, 17] and HD populations [18]. However, these studies suffer from the bias that ferritin is an inflammatory marker, possibly reflecting a higher comorbidity burden. Even with some inconsistency [21, 22], observational studies have also linked high IV monthly iron doses (>300–400 mg/month) with increased risk of death [23, 24].

In the pre-ESA era, iron overload and secondary haemochromatosis were important clinical issues. Today, HD patients who receive judicious doses of IV iron are likely to be in a state of positive iron balance without clinically relevant iron toxicity [25]. The concomitant use of ESAs, maintenance iron administration and the reticuloendothelial distribution of hepatic iron deposition likely minimize the potential for iron toxicity. However, iron overload is detected not only in inflamed patients, in whom inhibitory factors, like hepcidin, decrease iron release from reticulo-endothelial and hepatocyte stores, but also in those without signs of overt clinical infection [26].

Erythroferrone was first described in 2014 as an erythroid regulator of iron metabolism that mediates hepcidin suppression in conditions of increased erythropoiesis [27]. Recently, high erythroferrone levels have been found to be associated with an increased risk of death and cardiovascular complications [28]. Of note, treatment with ESAs amplified this relationship [28]. Considering that erythroferrone is a hepcidin suppressor, the pathogenic explanation of this observation remains unclear.

Existing terminology regarding iron status is inconsistent; the term ‘iron toxicity’ or ‘pathologic iron overload’ should be used to describe the adverse clinical consequences of iron therapy or disorders of iron metabolism. This implies that positive iron balance does not automatically lead to iron toxicity, nor it is a prerequisite for iron toxicity. The transition from positive iron balance to iron toxicity appears to be dependent on factors beyond the magnitude of body iron content and not necessarily the amount of iron administered. When ‘excess’ iron is predominately deposited in hepatocytes (i.e. parenchymal deposition), as might be observed in hereditary haemochromatosis due to mutations in the *HFE* gene, tissue damage is common, with iron deposition into Kupffer cells being a late finding. In contrast, when reticuloendothelial deposition of iron predominates, as is expected with IV iron administration, tissue damage is less frequent. Data from haemochromatosis patients suggest that a ‘spill over’ of iron from macrophages depends on both the speed and magnitude of iron accumulation. In the setting of CKD and IV iron therapy, iron would be expected to ‘spill over’ into hepatocytes if labile plasma iron (LPI) is present [27]. Clinically relevant concentrations of LPI would be expected if the iron-carrying capacity of transferrin is saturated. ESA treatment thus helps offset the increased hepcidin levels and iron loading within macrophages that can occur with IV iron therapy, supporting a synergistic relationship between therapies. Interestingly, a substantial number of HD patients have positive LPI after IV iron administration [29]; high ferritin and monthly iron doses were associated with positive LPI after IV iron. No statistical association was found between the patients having positive LPI and the type of administered iron molecule; however, only a low percentage of patients received iron molecules other than iron sucrose. Future studies should elucidate the clinical significance of LPI, especially focusing on its effect on cardiovascular morbidity and mortality and infectious complications.

Role of iron in vascular dysfunction

Given its interplay with oxygen, iron has a possible role in regulating arterial homoeostasis. Consequently, iron effects on two very common complications of CKD, namely pulmonary arterial hypertension (PAH) (Figure 1) and atherosclerosis (Figure 2), have been widely investigated. Indeed, cardiovascular disease is the leading cause of mortality in ESRD. In recent years, pulmonary hypertension has been recognized as a complication of ESRD and it is associated with a poor outcome [30].

The evidence coming from experimental animals is controversial, showing both a detrimental effect of iron overload on arterial function and improvement following iron administration. In rats, chronic administration of iron dextran induces endothelial dysfunction, increases free radical production and decreases nitric oxide (NO) bioavailability [31]. In turn, decreased NO levels lead to increased resistance of pulmonary arteries, causing right ventricular hypertrophy and vascular remodelling [32]. In another rat model, iron deficiency worsened PAH and produced medial hypertrophy, being reversed by iron

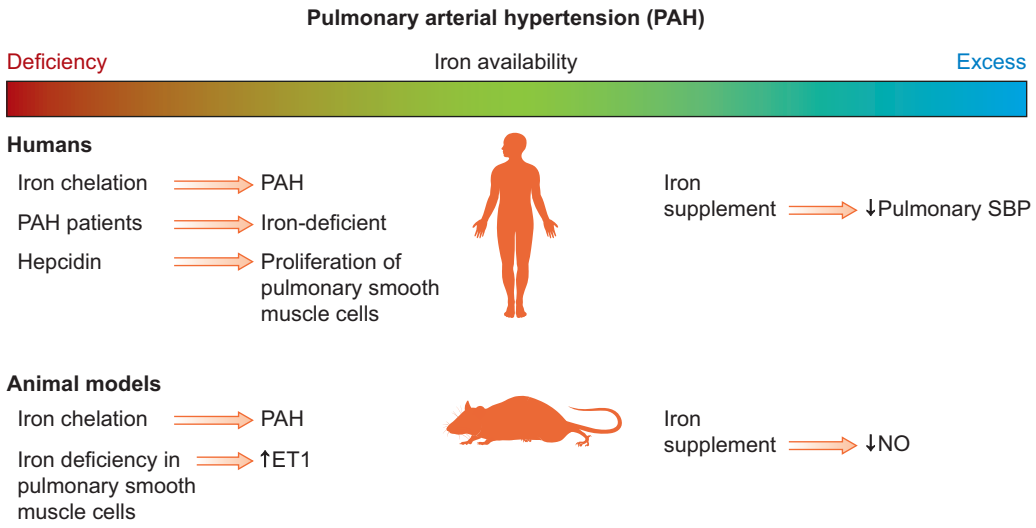

FIGURE 1: Iron and PAH. There is experimental and clinical evidence linking iron deficiency to PAH. In humans, iron chelation has been associated with PAH, while in PAH patients, iron deficiency was observed. In contrast, iron supplementation was associated with decreased pulmonary artery SBP. Additionally, hepcidin induced cultured pulmonary smooth muscle cell proliferation. In rats, iron deficiency was also associated with PAH and promoted endothelin-1 secretion by pulmonary smooth muscle cells. However, chronic administration of iron dextran was also potentially deleterious, decreasing nitrous oxide bioavailability.

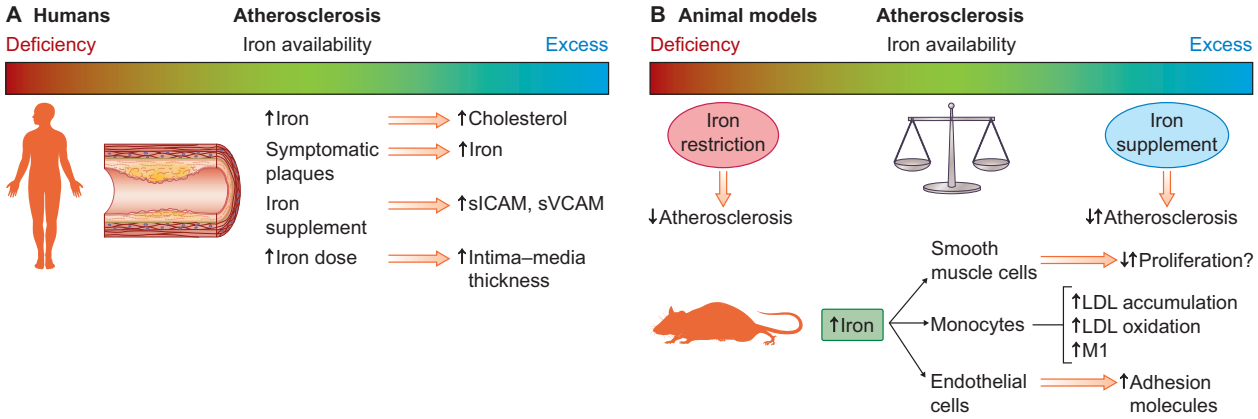

FIGURE 2: Iron and atherosclerosis. Iron availability has been linked to atherosclerosis. (**A**) In humans, iron excess or supplementation has been associated with increased serum levels of vascular adhesion molecules and increased intima–media thickness, while symptomatic atherosclerotic plaques are rich in iron. (**B**) In experimental animals, iron restriction was associated with milder atherosclerosis while there are inconclusive studies regarding the impact of iron supplementation on atherosclerosis. Increased iron availability had inconclusive effects on smooth muscle cell proliferation while it promoted LDL accumulation and oxidation as well as phenotypic changes in monocytes. In endothelial cells, increased iron availability increased the expression of adhesion molecules.

supplementation [33]. Interestingly, in animals with iron-deficient pulmonary vascular smooth muscle cells (VSMCs) but with otherwise normal circulating iron levels, PAH was probably induced by an increased production of endothelin-1 [34].

In healthy individuals, iron chelation promotes hypoxic vasoconstriction and increases pulmonary arterial pressure [35]. Abnormal iron handling has also been reported in several human conditions of PAH, with a significant percentage of patients being iron deficient [36]. To further support the role of iron in this condition, ferroportin has been found in human pulmonary artery smooth muscle cells. In this context, hepcidin increased proliferation of these cells, most likely by binding ferroportin and resulting in iron internalization and cellular retention [37]. On the other hand, iron supplementation can reduce pulmonary systolic blood pressure (SBP) during exercise in healthy individuals [38]. Overall, it seems that both low and high levels of iron could increase pulmonary arterial pressure by different mechanisms.

Regarding atherosclerosis, the evidence found in the literature is controversial. Iron can accumulate in the three main cell types associated with the formation of atheroma plaques, namely VSMCs, endothelial cells and macrophages [39]. Furthermore, iron loading in monocytes increased the oxidation and accumulation of low-density lipoproteins (LDLs) and the expression of scavenger receptors polarizing macrophages towards the pro-inflammatory M1 type [4]. In endothelial cells, iron loading induces an increase of adhesion molecules [vascular cell adhesion molecules (VCAMs), intercellular adhesion molecules (ICAMs) and selectin] [41]. Iron chelation has the opposite effect, decreasing the formation of foam cells [42]. In mice and rabbits, iron administration increases the extent of atherosclerosis, but it can also have a protective effect [46]. Conversely, iron restriction consistently decreased the extent of atheroma plaque both in mice and rabbits [47, 48]. In VSMCs, both iron administration and iron chelation have been shown to decrease VSMC growth [49, 50].

In humans, iron is associated with atherosclerosis. Indeed, it accumulates in atheroma plaques and correlates with cholesterol levels [51]. Also, symptomatic plaques show a higher iron content than the asymptomatic ones [52].

In CKD patients, iron sucrose administration increased soluble levels of adhesion molecules (sICAM, sVCAM) [43] and cumulative iron dose was correlated with increased intima–media thickness [53].

As already discussed, free iron is a cause of oxidative stress, possibly contributing to endothelial dysfunction and atherosclerosis progression [47].

The link between serum hepcidin and atherosclerosis

Malhotra *et al.* [54] addressed some of the remaining issues regarding the role of hepcidin in atherogenesis using genetically modified mice. Hepcidin inhibits iron release from macrophages via downregulation of the iron transporter ferroportin and increases intracellular iron stores. Mice with combined hepcidin and LDL receptor deficiency ($Hamp^{-/-}$, $Ldlr^{-/-}$) were protected from atherosclerosis observed in $Hamp^{+/+}$, $Ldlr^{-/-}$ mice after 21 weeks of high-fat diet and pro-inflammatory macrophages were reduced. These data are in agreement with previous studies in which pharmacological inhibition of hepcidin decreased foam cell formation and atherosclerosis [45]. However, although intracellular iron accumulation results in increased oxidized LDL retention, inflammatory signalling and intracellular reactive oxygen species generation, it is still uncertain whether inhibiting hepcidin would reduce human atherosclerosis. In a recent study, atherosclerosis plaque macrophages expressed hepcidin and this may be part of a vicious cycle implicating oxidized LDL cholesterol [55]. Thus oxidized LDL cholesterol increased hepcidin production by macrophages and iron retention while hepcidin or iron magnified macrophage Toll-like receptor 4 (TLR4)/nuclear factor κB (NF-κB) pathway activation and foaming triggered by oxidized LDL. However, studies in humans are scarce. Several human conditions are associated with increased levels of hepcidin. Thus higher hepcidin levels were associated with atherosclerotic plaques in non-alcoholic fatty liver disease patients [56] and in the general population [57] and with higher coronary artery calcium score in rheumatoid arthritis [58]. Furthermore, higher hepcidin levels are associated with cardiovascular events in HD patients [59]. However, and although recent clinical trials have shown the benefits of targeting inflammation in cardiovascular disease, the precise clinical impact of modifying iron homoeostasis needs further investigation.

Iron and the heart

Anaemia is a major contributor to reduced exercise tolerance and poorer quality of life in patients with HF irrespective of their renal function. However, iron deficiency has been associated with worse outcomes in patients with HF, independent of anaemia [60]. Moreover, IV iron supplementation but not anaemia correction by ESAs has a beneficial effect in HF. This suggests iron has direct actions on cardiac function.

There are several cellular mechanisms by which iron may improve cardiac function. Iron plays an important role in cellular oxygen storage (myoglobin) and cell metabolism, especially in tissues with a high energy demand, such as cardiomyocytes [61]. In animal experiments, induction of iron deficiency has been associated with the development of ventricular hypertrophy and systolic dysfunction, in which the sympathetic nervous system appears to play a role [61–63]. The corollary of these observations is that CKD, with its associated overactivity of the sympathetic nervous system and high prevalence of left ventricular hypertrophy, may be a setting where iron deficiency is a potentially modifiable target for treatment, as it can directly influence myocardial dysfunction. Cardiomyocytes from the explanted hearts of patients undergoing cardiac transplantation for HF show iron depletion and dysfunction of iron-dependent mitochondrial enzymes, again suggestive of a more direct effect of iron on cardiac tissue function [64]. Mice models specifically knocking out cardiomyocyte hepcidin develop fatal cardiomyopathy due to cellular iron deficiency despite normal systemic iron metabolism. This suggests cardiomyocyte hepcidin has a specific homoeostatic role in cardiac iron metabolism [65]. Iron replenishment may also benefit skeletal muscle function, an effect thought to contribute to the improvement in patient symptoms and general functional capacity with iron therapy in chronic HF.

Initial attempts to target anaemia in HF using a combination of IV iron sucrose and ESAs demonstrated improvements in functional status, triggering a number of studies examining treatment strategies for anaemia in HF [66]. Several randomized controlled trials showed that IV iron improves exercise capacity and quality of life [67, 68]. The same effect was not observed with oral iron [69]. IV iron also has benefits on exercise tolerance, documented by peak maximal oxygen consumption, New York Heart Association class or by 6-min walk test in patients with HF and reduced ejection fraction. In an individual patient data meta-analysis of four trials including 839 participants (504 assigned to IV iron), ferric carboxymaltose (FCM) was associated with fewer HF hospitalizations and lower cardiovascular mortality {rate ratio 0.59 [95% confidence interval (CI) 0.33–0.96]} [70].

It is reasonable to hypothesize that any benefit seen with IV iron on hospitalization for HF is merely due to increased Hb levels. However, this is not the case, as a relevant effect was not apparent when Hb was increased with ESA treatment. Indeed, the Reduction of Events by Darbepoetin Alfa in HF trial [71] did not show any benefit on the primary endpoint of all-cause mortality or HF hospitalization when aiming towards normal Hb levels with darbepoetin alpha.

Based on these data, the European Society of Cardiology guidelines recommend that all patients with HF undergo assessment of their iron status and that IV FCM should be considered in symptomatic patients primarily to improve exercise capacity and quality of life [72].

Until now, clinical trials have not tested the effect of IV iron on hard outcomes in patients with HF. Three large (>1000 patients) randomized controlled trials are currently ongoing. FerinjectAssessment in Patients With IRon Deficiency and Chronic HF 2 (NCT03036462; comparing FCM to placebo) and IV Iron Treatment in Patients With HF and Iron Deficiency: IRONMAN [NCT02642562; open-label iron (III) isomaltoside] enrol patients with HF and reduced ejection fraction, while the Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency(NCT02937454; comparing FCM to placebo) selects patients who have been stabilized following an episode of acute HF. The results of these clinical trials should inform whether IV iron improves outcomes for patients with HF and by inference should inform whether iron provides more direct cardiovascular benefit specific to myocardial performance in the setting of cardiac dysfunction.

IV iron therapy in CKD patients: current knowledge

In anaemic CKD patients, the goal of iron therapy is to correct absolute iron deficiency and to increase the Hb level to the desired target. Moreover, it is also intended to avoid transfusions, reduce anaemia-related symptoms and decrease ESA needs.

IV iron supplementation is considered the gold standard for patients on long-term HD. This is in line with the findings of a systematic review and meta-analysis by Shepshelovich *et al.* [73]: IV iron was superior to oral iron in patients with CKD Stage 5D and CKD Stages 3–5, with a significantly greater number of patients reaching an increase in Hb level >1 g/dL [relative risk (RR) 2.14 for CKDStage 5D and 1.61 for CKD Stages 3–5]. IV iron replacement was associated with a higher risk of treatment-related hypotension (RR 3.71) and fewer gastrointestinal adverse events (RR 0.43). The potential impact of IV iron on later vascular access availability in CKD Stages 3–5 was not addressed.

Nevertheless, the safety of IV iron at high doses is still a matter of debate. To answer this question, Hougen *et al.* [74] performed a systematic review of seven randomized controlled trials and 15 observational studies. No association was found between iron doses (>400 mg/month for most studies) and mortality or infection. Similarly, the observational studies included in the meta-analysis showed no association between higher IV iron dose (>200 mg/month for most studies) and several outcomes, including mortality infection, cardiovascular events and hospitalizations [74]. Of note, in the randomized trials, the mean follow-up period was rather short.

In addition, the frequency and duration of IV iron administration at different iron indices are still matters of debate. In 2007, the Dialysis Patients' Response to IV Iron with Elevated Ferritin study suggested that iron therapy may increase Hb levels and reduce ESA requirements in patients with serum ferritin levels >500 μg/L [75]. More recently, using clinical data from a large US dialysis provider, Li *et al.* [76] analysed a cohort of 13 249 HD patients ≥65 years of age. Compared with the reference strategy, more intensive iron treatment at moderate–high iron index levels were associated with higher risks of mortality and infection-related events.

Limited data exist for patients on peritoneal dialysis. Iron deficiency is a common observation in this population given the lack of easy vascular access and the low efficacy of oral iron. More sustained IV iron administration could be a therapeutic option to be implemented [77].

In ND-CKD patients, the selection of oral versus IV administration is less definite. The choice should take into account the severity of anaemia, availability of venous access, response to prior therapy, patient adherence and cost [78].

In recent years, three randomized trials compared the efficacy and safety of oral versus IV iron, with contrasting results. In the Randomized trial to Evaluate IV and Oral iron in CKD, 136 subjects at a single centre in the USA were randomized to receive open-label oral ferrous sulphate (325 mg tablets three times daily for 8 weeks) or IV iron sucrose (200 mg every 2 weeks); patients were followed for 2 years [79]. No difference was found in the primary outcome, i.e. between-group difference in slope of GFR change over 2 years.

The trial was terminated early because IV iron therapy was associated with a surprisingly higher risk of serious adverse events, including cardiovascular events and infection requiring hospitalizations. However, the study was not adequately powered to test these hard endpoints. These findings thus need careful interpretation. In another randomized trial, 351 iron-deficient ND-CKD patients were randomized 2:1 to either IV iron isomaltoside 1000 or iron sulphate (100 mg of elemental oral iron twice daily for 8 weeks) [80]. Isomaltoside 1000 was superior to oral iron sulphate in increasing Hb levels and was well tolerated. Instead, more patients stopped oral therapy due to side effects.

The Ferinjectassessment in patients with Iron deficiency anaemia and ND-dependent CKD (FIND-CKD) study was a 1-year, randomized, multicentre trial of 626 patients with ND-CKD, anaemia and iron deficiency without ESA therapy [81]. Patients were randomized (1:1:2) to high- or low-dose IV FCM or oral iron therapy (200 mg daily). The high-dose FCM group had a lower hazard ratio [HR 0.65 (95% CI 0.44–0.95), $P = 0.026$] of reaching the primary endpoint (the need for further iron therapy, ESA therapy and blood transfusions or two Hb levels <10 g/dL). Ferritin levels of ≥800 μg/L in the high-ferritin FCM group were not associated with an increase in serious adverse events.

These two trials suggest that for ND-CKD patients, the use of a more stable iron formulation (ferumoxytol, FCM and iron isomaltoside 1000) would be appropriate, reducing the number of iron infusions needed to achieve the same total dose.

The PIVOTAL trial: possible implications for clinical practice

The PIVOTAL trial is a prospective, multicentric, randomized controlled study that was conducted in the UK [4]. A total of 2141 patients undergoing HD for <12 months were randomized to either high-dose IV iron sucrose proactively (400 mg monthly, unless ferritin was >700 μg/L or TSAT ≥40%) or low-dose IV iron sucrose in a reactive fashion (0–400 mg monthly if ferritin was <200 μg/L or TSAT <20%). Over a median follow-up of 2.1 years, the patients in the high-dose group received a median monthly iron dose of 264 mg as compared with 145 mg in the low-dose group. High-dose proactive iron therapy met the criteria for superiority in reducing the risk of reaching the composite primary endpoint (non-fatal myocardial infarction, non-fatal stroke, hospitalization for HF or death) [HR 0.85 (95% CI 0.73–1.00), $P < 0.001$ for non-inferiority, $P = 0.04$ for superiority]. Furthermore, the patients in this group received a lower median monthly dose of ESA and had a lower transfusion rate and a lower HR to reach several secondary endpoints, including fatal or non-fatal acute myocardial infarction and hospitalization for HF. The infection risk and serious adverse events were similar in the two groups. This was recently expanded by a prespecified secondary analysis of the study [82], confirming identical infection rates in the two study arms.

Overall, these findings represent the first evidence supporting the safety and benefits of relatively high-dose IV iron therapy in HD patients on ESA therapy when targeting serum ferritin to 700 ng/mL in a proactive fashion. One point of reflection on the PIVOTAL trial is that, according to the trial design, the control group received a more conservative approach than that recommended by the KDIGO guidelines in 2012 [2]. This may possibly leave a gap in the knowledge of whether proactive IV iron therapy would have shown the same efficacy profile when compared with the actual standard of care. Table 1 summarizes current recommendations/suggestions on iron therapy in CKD and HF from major international bodies.

According to the scientific information available at the time, in 2013 the suggestions on iron therapy of the European Renal Best Practice (ERBP) were more cautious [3], indicating as an upper limit for IV iron treatment in adult CKD patients on ESA therapy a ferritin value of 500 ng/mL, especially in those with adequate TSAT values (>30%). A course of IV iron therapy could

Table 1. Comparison of indications for iron therapy between CKD and HF

Body	Year	Setting	Objective	ESA-treated versus untreated	Ferritin target		TSAT target		Maximum
					Start iron	Stop iron	Start iron	Stop iron	
KDIGO [2]	2012	All CKD stages	Hb increase or decrease in ESA dose	No difference	≤500 ng/mL	≤500 ng/mL (accepted ≤800 ng/mL in HD)	<30%	>30%	Higher ferritin levels in patients hyporesponsive to ESA or in whom discontinuation of ESA therapy is preferred
ERBP [3]	2013	ND-CKD	Correct absolute iron deficiency Hb increase or decrease in ESA dose	Different recommendation	ESA-naïve: <200 ng/mL ESA therapy: <300 ng/mL	ESA-naïve: >500 ng/mL ESA therapy: >500 ng/mL	ESA-naïve: <25% ESA therapy: <25%	≥30%	Not given
ERBP [3]	2013	CKDStage 5D	Correct absolute iron deficiency Increase Hb or decrease ESA dose	No difference	<300 ng/mL	≥500 ng/mL	<30%	≥30%	Higher serum ferritin levels in the presence of hyporesponsiveness to ESA or a risk:benefit ratio going against ESA use
European Society of Cardiology (ESC) [77]	2016	HF	Alleviate HF symptoms Improve exercise capacity and quality of life	Not applicable	<100 ng/mL or 100–299 ng/mL if TSAT <20%	≥300 ng/mL	<20%	≥20%	Not given

be considered in patients having higher serum ferritin levels in the presence of hyporesponsiveness to ESA or a risk:benefit ratio going against ESA use [3].

This new evidence implies a more certain upper range of ferritin level to aim at and not exceed with IV iron therapy. On the other hand, keeping patients not completely iron replete can cause them skip the full advantages of IV iron therapy. An update of the specific ERBP suggestions on this specific point has already been planned.

It should be remembered that the general applicability of these findings to everyday clinical practice is not automatic. Indeed, the patient population of the PIVOTAL trial [4] was selected for having a short dialysis vintage and few signs of inflammation. This represents a niche of the HD population, in whom a large percentage of patients have a higher burden of comorbidities, are inflamed and/or have functional iron deficiency. In this broader context, the long-term safety and efficacy of IV iron therapy remain a grey area in the knowledge. Moreover, the trial was performed in a single country (the UK), with a high percentage of patients being Caucasian. In other countries, iron needs could also depend on local extracorporeal circuit rinsing practices or protocols for anaemia management and IV iron dosing [83].

Considering that the PIVOTAL trial is the only trial at the moment with nonetheless a low generalizability, its evidence is insufficient to jump to final conclusions.

Other unanswered questions include the potential mechanisms by which high-dose iron therapy improved outcomes in the PIVOTAL trial. Was the benefit driven by increased Hb concentrations, larger iron stores or reduced ESA needs? Iron sucrose was used in the PIVOTAL trial. Would use of other, newer IV iron formulations such as FCM or iron isomaltoside have the same beneficial effects?

Finally, the median follow-up of the PIVOTAL trial is relatively short compared with the whole scenario of everyday clinical practice, where HD patients can be treated with IV iron for much longer periods, even decades.

CONCLUSIONS

It is now >30 years since the hypothesis that iron status could influence cardiovascular risk was first proposed. Accordingly, IV iron therapy has been associated with increased risks of atherothrombosis, vascular calcification, oxidative stress and infection, leading to the fear that excessive IV iron therapy could be associated with worse outcomes. The results of the PIVOTAL trial go a long way to allay these concerns [4]. The observed reduction in the primary composite endpoint is welcome reassurance that high-dose IV iron, targeting higher ferritin and TSAT concentrations than those recommended by most current guidelines, appears to be not only safe, but actually beneficial. The reduction in hospitalizations for HF and death observed in the PIVOTAL trial [4] is consistent with the findings of a meta-analysis of four trials testing IV iron in HF patients [70]. This is of particular interest considering that CKD patients with declining renal function are at high risk for HF as a consequence of uraemic cardiomyopathy [84]. This peculiar phenotype is characterized by increased left ventricular mass/hypertrophy, diastolic and systolic dysfunction and myocardial fibrosis.

For once we appear to have evidence of an intervention that can improve cardiovascular outcomes in HD patients. We must not be complacent, as further research is required into the mechanisms, generalizability (patients and preparations) and health economic implications (lower ESA and transfusion

needs, lower hospitalization rate, lower burden of comorbidities and deaths?).

Further research and clinical practice of IV iron therapy will also have to take into consideration the impact of inhibitors of the prolyl-hydroxylases domain, given that this new class of drugs decreases hepcidin levels and possibly improves iron utilization.

We must not rest on our laurels, but as Geoffrey Chaucer would have put it, 'Strike while the iron is hot!' .

ACKNOWLEDGEMENTS

We acknowledge Dr Alex Briggs for his contribution in language editing.

FUNDING

A.O.'s research is supported by PI19/00588, PI19/00815, DTS18/00032, ERA-PerMed-JTC2018 (KIDNEY ATTACK AC18/00064 and PERSTIGAN AC18/00071, ISCIII-RETIC REDinREN RD016/0009 FEDER funds, Sociedad Española de Nefrología, Fundacion Renal Iñigo Álvarez de Toledo (FRIAT), Comunidad de Madrid CIFRA2 B2017/BMD-3686.

CONFLICT OF INTEREST STATEMENT

L.D.V. was a member of advisory boards for DOC Pharma, Roche, Astellas and GlaxoSmithKline and an invited speaker at meetings supported by DOC Pharma, Roche, Astellas, Vifor Pharma and Mundipharma. She is national leader for the Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat–Non-Dialysis study supported by GlaxoSmithKline. R.E. has no financial or other relationships that might lead to a conflict of interest regarding this article. C.F. has no conflicts of interests to declare. J.M. was a member of an advisory board for Vifor Pharma. P.M. reports speaker honoraria from Vifor, AstraZeneca, Janssen, Napp, Novartis and Bristol-Myers Squibb, research grants from Boehringer Ingelheim and non-financial support from Pharmacosmos. A.O. is a consultant for Sanofi and has received speaker honoraria from Otsuka, Mundipharma, Amgen, Menarini, Fresenius Medical Care and Amicus. P.S. was an advisor for AstraZeneca, Bayer, Boehringer Ingelheim, Elpen Pharmaceuticals, Genesis Pharma and Menarini and has received speaker honoraria from Amgen, Boehringer Ingelheim, Innovis Pharma, Sanofi and Winmedica. J.M.V. has received speaker honoraria from Vifor Farma. F.M. has no conflicts of interest to declare. We declare that the contents presented in this article have not been published previously in whole or part.

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