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...
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 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 (Fe²⁺) is oxidized by hydrogen peroxide (H₂O₂) to ferric iron (Fe³⁺), yielding highly reactive hydroxyl radicals (HO•), while in the first step of the Haber–Weiss reaction, Fe³⁺ is reduced by superoxide (O₂⁻) into ferrous (Fe²⁺) 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 ef- flux 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 ef-flux 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 ef-flux 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 anemia 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 is it 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 predominantly 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
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 induced proliferation of cultured pulmonary smooth muscle cells. However, chronic administration of iron dextran was also potentially deleterious, decreasing nitrous oxide bioavailability.

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 [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−/−, Ldr−/−) were protected from atherosclerosis observed in Hamp+/+, Ldr−/− 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-kB (NF-kB) pathway activation and foamaging 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 homeostasis 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 homeostatic 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. Ferrinject Assessment 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 Shesheblovich 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 CKD Stage 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 sucrose in increasing Hb level and was well tolerated. Instead, more patients stopped oral therapy due to side effects.

The Ferinject assessment 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 (ferumoxytrol, FCM and 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

| ESA-treated versus untreated | Ferritin target | TSAT target | Start iron | Stop iron | Objective |
|-----------------------------|----------------|-------------|------------|-----------|-----------|
| ESA-naive: <25% | <500 ng/mL | Not applicable | <30% | Not given | Hb increase or decrease in ESA dose |
| ESA-naive: >30% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >50% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >70% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >90% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >95% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >98% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >100% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >105% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >110% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >120% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >150% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >200% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >300% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >400% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >500% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >600% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >700% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >800% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >900% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |
| ESA-naive: >1000% | >500 ng/mL | Not applicable | No difference | No difference | Correct absolute iron deficiency |

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'.

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**CONFLICT OF INTEREST STATEMENT**

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**REFERENCES**

1. Foreman KJ, Marquez N, Dolgert A et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. Lancet 2018; 392: 2052–2090
2. Kidney Disease: Improving Global Outcomes Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2012; 2: 279–335
3. Locatelli F, Bárány P, Covic A et al. Kidney Disease: Improving Global Outcomes guidelines on anemia management in chronic kidney disease: a European Renal Best Practice position statement. Nephrol Dial Transplant 2013; 28: 1346–1359
4. Macdougall IC, White C, Anker SD et al. Intravenous iron in patients undergoing maintenance hemodialysis. N Engl J Med 2019; 380: 447–458
5. Ganzi T. Systemic iron homeostasis. Physiol Rev 2013; 93: 1721–1741
6. Frazer DM, Anderson GJ. The regulation of iron transport. Biofactors 2014; 40: 206–214
7. Nemeth E, Tuttle MS, Powelson J et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science 2004; 306: 2090–2093
8. Brasse-Lagnel C, Karim Z, Letteron P et al. Intestinal DMT1 cotransporter is down-regulated by hepcidin via proteasome internalization and degradation. Gastroenterology 2011; 140: 1261–1271
9. Macdougall IC, Malyszko J, Hider RC et al. Current status of the measurement of blood hepcidin levels in chronic kidney disease. Clin J Am Soc Nephrol 2010; 5: 1681–1689
10. Sato M, Hanafusa N, Tsuchiya K et al. Serum ferritin and mortality: findings from the USA, Japan and European dialysis outcomes and practice patterns study. Nephrol Dial Transplant 2013; doi: 10.1093/ndt/gfs192
11. Sato M, Hanafusa N, Tsuchiya K et al. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. Blood 2003; 101: 2461–2463
12. Cho ME, Hansen JL, Peters CB et al. An increased mortality risk is associated with abnormal iron status in diabetic and non-diabetic veterans with predialysis chronic kidney disease. Kidney Int 2019; 96: 750–760
13. Awan AA, Walther CP, Richardson PA et al. Prevalence, correlates and outcomes of absolute and functional iron deficiency anemia in nondialysis-dependent chronic kidney disease. Nephrol Dial Transplant 2019; doi: 10.1093/ndt/gfs192
14. Sato M, Hanafusa N, Tsuchiya K et al. Impact of transferrin saturation on all-cause mortality in patients on maintenance hemodialysis. Blood Purif 2019; 48: 158–166
15. US-DOPPS Practice Monitor. Serum ferritin (most recent), death rates and outcomes of absolute and functional iron deficiency anemia in nondialysis-dependent chronic kidney disease. Nephrol Dial Transplant 2019; doi: 10.1093/ndt/gfs192
16. Sato M, Hanafusa N, Tsuchiya K et al. Impact of transferrin saturation on all-cause mortality in patients on maintenance hemodialysis. Blood Purif 2019; 48: 158–166
17. Karaboyas A, Morgenstern H, Pisoni RL et al. Administration of parenteral iron and mortality among hemodialysis patients. J Am Soc Nephrol 2004; 15: 1623–1632
18. Miskulin DC, Tangri N, Bandeen-Roche K et al. Intravenous iron exposure and mortality in patients on hemodialysis. Clin J Am Soc Nephrol 2014; 9: 1930–1939
Intravenous iron therapy and the cardiovascular system

23. Kalantar-Zadeh K, Regidor DL et al. Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol 2005; 16: 3070–3080

24. Bailie GR, Larkina M, Goodkin DA et al. Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality. Kidney Int 2015; 87: 162–168

25. Wish JB, Aronoff GR, Bacon BR et al. Positive iron balance in chronic kidney disease: how much is too much and how to tell? Am J Nephrol 2018; 47: 72–83

26. Rostoker G, Griuncelli M, Loridon C et al. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: a MRI study. Am J Med 2012; 125: 991–999

27. Kautz L, Jung G, Valore EV et al. Identification of erythroferrone as an erythroid regulator of iron metabolism. Nat Genet 2014; 46: 678–684

28. Spoto B, Kakkar R, Lo L et al. Serum erythroferrone levels associate with mortality and cardiovascular events in hemodialysis and in CKD patients: a two cohorts study. J Clin Med 2019; 8: 523

29. Bnaya A, Shavit L, Malyszko JS et al. Labile plasma iron levels in chronic hemodialysis patients treated by intravenous iron supplementation. Ther Apher Dial 2019; 24: 416–422

30. Schoeneng NC, Argula RG, Klings ES et al. Prevalence and mortality of pulmonary hypertension in ESRD: a systematic review and meta-analysis. Lung 2020; 198: 535–545

31. Marques VB, Nascimento TB, Ribeiro RF et al. Chronic iron overload in rats increases vascular reactivity by increasing oxidative stress and reducing nitric oxide bioavailability. Life Sci 2015; 143: 89–97

32. Bertoli SR, Marques VB, Rossi EM et al. Chronic iron overload induces vascular dysfunction in resistance pulmonary arteries associated with right ventricular remodeling in rats. Toxicol Lett 2018; 295: 296–306

33. Cotroneo E, Ashke A, Wang L et al. Iron homeostasis and pulmonary hypertension: iron deficiency leads to pulmonary vascular remodeling in the rat. Circ Res 2015; 116: 1680–1690

34. Lakhal-Littleton S, Crosby A, Frise MC et al. Intracellular iron deficiency in pulmonary arterial smooth muscle cells induces pulmonary arterial hypertension in mice. Proc Natl Acad Sci USA 2019; 116: 13122–13130

35. Smith TG, Balanos GM, Croft QP et al. The increase in pulmonary arterial pressure caused by hypoxia depends on iron status. J Physiol 2008; 586: 5999–6005

36. Ruiter G, Lankhorst S, Boonstra A et al. Iron deficiency is common in idiopathic pulmonary arterial hypertension. Eur Respir 2011; 37: 1386–1391

37. Ramakrishnan L, Pedersen SL, Toe QK et al. The hepcidin/ferrititin axis modulates proliferation of pulmonary artery smooth muscle cells. Sci Rep 2018; 8: 12972

38. Cheng HY, Frise MC, Curtis MK et al. Intravenous iron delivers a sustained (8-week) lowering of pulmonary artery pressure during exercise in healthy older humans. Physiol Rep 2019; 7: e14164

39. Vinchi F, Muckenthaler MU, Silva MC et al. V. Atherogenesis and iron: from epidemiology to cellular level. Front Pharmacol 2014; 5: 94

40. Kraml PJ, Klein RL, Huang Y et al. Iron loading increases cholesterol accumulation and macrophage scavenger receptor I expression in THP-1 mononuclear phagocytes. Metabolism 2005; 54: 453–459

41. Kartikasari AE, Georgiou NA, Visseren FL et al. Endothelial activation and induction of monocyte adhesion by nontransferrin-bound iron present in human sera. FASEB J 2006; 20: 353–355

42. Saeed O, Otsuka F, Polavarapu R et al. Pharmacological suppression of hepcidin increases macrophage cholesterol efflux and reduces foam cell formation and atherosclerosis. Arterioscler Thromb Vasc Biol 2012; 32: 299–307

43. Kuo KL, Hung SC, Lee TS et al. Iron sucrose accelerates early atherogenesis by increasing superoxide production and upregulating adhesion molecules in CKD. J Am Soc Nephrol 2014; 25: 2596–2606

44. Marques VB, Veal MAS, Mageski JGA et al. Chronic iron overload intensifies atherosclerosis in apolipoprotein e deficient mice: role of oxidative stress and endothelial dysfunction. Life Sci 2019; 233: 116702

45. Vinchi F, Porto G, Simmelbauer A et al. Atherosclerosis is aggravated by iron overload andameliorated by dietary and pharmacological iron restriction. Eur Heart J 2020; 41: 2681–2695

46. Kirk EA, Heinecke JW, LeBoeuf RC. Iron overload diminishes atherosclerosis in apoE-deficient mice. J Clin Invest 2001; 107: 1545–1553

47. Lee TS, Shiao MS, Pan CC et al. Iron-deficient diet reduces atherosclerotic lesions in apoE-deficient mice. Circulation 1999; 99: 1222–1229

48. Zhang WJ, Wei H, Frei B. The iron chelator, desferrioxamine, reduces inflammation and atherosclerotic lesion development in experimental mice. Exp Biol Med (Maywood) 2010; 235: 633–641

49. Mueller PP, May T, Perz A et al. Control of smooth muscle cell proliferation by ferrous iron. Biomaterials 2006; 27: 2193–2200

50. Porreca E, Ucchino S, Di Febbo C et al. Antiproliferative effect of desferrioxamine on vascular smooth muscle cells in vitro and in vivo. Arterioscler Thromb 1994; 14: 299–304

51. You SA, Archacki SR, Angheloiu G et al. Proteomic approach to coronary atherosclerosis shows ferritin light chain as a significant marker: evidence consistent with iron hypothesis in atherosclerosis. Physiol Genomics 2003; 13: 25–30

52. Gustafsson H, Hallbeck M, Norell M et al. Fe(III) distribution varies substantially within and between atherosclerotic plaques. Magn Reson Med 2014; 71: 885–892

53. Druèke T, Witko-Sarsat V, Massy Z et al. Ferritin, a significant marker: evidence consistent with iron hypothesis in atherosclerosis. J Clin Investig 1999; 104: 2681–2695

54. Malhotra R, Wunderer F, Barnes HJ et al. Hepcidin deficiency protects against atherosclerosis. Arterioscler Thromb Vasc Biol 2011; 31: 1386–1391

55. Xiao L, Luo G, Guo X et al. Iron loading increases cholesterol accumulation and macrophage scavenger receptor I expression in THP-1 mononuclear phagocytes. Metabolism 2005; 54: 453–459

56. Abdel-Khalek MA, El-Barbary AM, Essa SAM et al. Iron deficiency is associated with right ventricular remodeling in rats. J Physiol 2011; 39: 178–187

57. Xiaol L, Luo G, Guo X et al. Macrophage iron retention aggravates atherosclerosis: evidence for the role of autocrine formation of hepcidin in plaque macrophages. Biochim Biophys Acta Mol Cell Biol Lipids 2020; 1865: 268–277

58. Valenti L, Swinkels DW, Burdick L et al. Serum ferritin levels are associated with vascular damage in patients with nonalcoholic fatty liver disease. Nutr Metab Cardiovasc Dis 2011; 21: 568–575

59. Galesloot TE, Holewijn S, Kiemenev LA et al. Serum hepcidin is associated with presence of plaque in postmenopausal women of a general population. Arterioscler Thromb Vasc Biol 2011; 34: 446–451
59. van der Weerd NC, Grooteman MPC, Bots ML et al. Hepcidin-25 is related to cardiovascular events in chronic haemodialysis patients. Nephrol Dial Transplant 2013; 28: 3062–3071
60. Jankowska EA, Rozentryt P, Witkowska A et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J 2010; 31: 1872–1880
61. Zhabyeyev P, Oudit GY. Unraveling the molecular basis for cardiac iron metabolism and deficiency in heart failure. Eur Heart J 2017; 38: 373–375
62. Maeder MT, Khammy O, dos Remedios C et al. Myocardial and systemic iron depletion in heart failure implications for anemia accompanying heart failure. J Am Coll Cardiol 2011; 58: 474–480
63. Dong F, Zhang X, Culver B et al. Dietary iron deficiency induces ventricular dilation, mitochondrial ultrastructural aberrations and cytochrome c release: involvement of nitric oxide synthase and protein tyrosine nitration. Clin Sci (Lond) 2005; 109: 277–286
64. Melenovsky V, Petrik J, Mracek T et al. Myocardial iron content and mitochondrial function in human heart failure: a direct tissue analysis. Eur J Heart Fail 2017; 19: 522–530
65. Vela D. Balance of cardiac and systemic hepcidin and its role in heart physiology and pathology. Lab Invest 2018; 98: 315–326
66. Silverberg DS, Wexler D, Blum M et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol 2000; 35: 1737–1744
67. Jankowska EA, Tkaczyszyn M, Suchocki T et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. Eur J Heart Fail 2016; 18: 786–795
68. van Veldhuisen DJ, Ponikowski P, van der Meer P et al. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. Circulation 2017; 136: 1374–1383
69. Lewis GD, Malhotra R, Hernandez AF et al. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. JAMA 2017; 317: 1958–1966
70. Anker SD, Kirwan BA, van Veldhuisen DJ et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. Eur J Heart Fail 2018; 20: 125–133
71. Swedberg K, Young JB, Anand IS et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. N Engl J Med 2013; 368: 1210–1219
72. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18: 891–975
73. Shepshelovich D, Rozen-Zvi B, Avni T et al. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. Am J Kidney Dis 2016; 68: 677–690
74. Hougen I, Collister D, Bourrier M et al. Safety of intravenous iron in dialysis: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2018; 13: 457–467
75. Coyne DW, Kapoian T, Suki W et al. Ferric gluconate is highly efficacious in anaemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) Study. J Am Soc Nephrol 2007; 18: 975–984
76. Li X, Cole SR, Kshirsagar AV et al. Safety of dynamic intravenous iron administration strategies in hemodialysis patients. Clin J Am Soc Nephrol 2019; 14: 728–737
77. Mitsopoulos E, Lysitiska A, Patenakis P et al. Efficacy and safety of a low monthly dose of intravenous iron sucrose in peritoneal dialysis patients. Int Urol Nephrol 2020; 52: 387–392
78. Roger SD. Practical considerations for iron therapy in the management of anaemia in patients with chronic kidney disease. Clin Kidney J 2017; 10: 19–115
79. Agarwal R, Kusew JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney Int 2015; 88: 905–914
80. Kalra PA, Bhandari S, Saxena S et al. A randomized trial of iron isomaltoside 1000 versus oral iron in non-dialysis dependent chronic kidney disease patients with anaemia. Nephrol Dial Transplant 2016; 31: 646–655
81. Macdougall IC, Bock AH, Carrera F etal. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. Nephrol Dial Transplant 2014; 29: 2075–2084
82. Macdougall IC, Bhandari S, White C et al. Intravenous iron dosing and infection risk in patients on hemodialysis: a prespecified secondary analysis of the PIVOTAL trial. Clin J Am Soc Nephrol 2020; 31: 1118–1127
83. Robinson BM, Larkina M, Bieber B et al. Evaluating the effectiveness of IV iron dosing for anaemia management in common clinical practice: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). BMC Nephrol 2017; 18: 330
84. Wanner C, Amann K, Shoji T. The heart and vascular system in dialysis. Lancet 2016; 388: 276–284