Safety concerns about intravenous iron therapy in patients with chronic kidney disease

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Abstract

Anaemia in chronic kidney disease (CKD) is managed primarily with erythropoiesis-stimulating agents (ESAs) and iron therapy. Following concerns around ESA therapy, intravenous (IV) iron is being administered more and more worldwide. However, it is still unclear whether this approach is safe at very high doses or in the presence of very high ferritin levels. Some observational studies have shown a relationship between either high ferritin level or high iron dose and increased risk of death, cardiovascular events, hospitalization or infection. Others have not been able to confirm these findings. However, they suffer from indication biases. On the other hand, the majority of randomized clinical trials have only a very short follow-up (and thus drug exposure) and are inadequate to assess the mortality risk. None of them have tested the role of different iron doses on hard end points. With the lack of clear evidence coming from well-designed and large-scale studies, several data suggest that excessive iron therapy may be toxic in several aspects, ranging from iron overload to tissue damage from labile iron. A number of experimental and clinical data suggest that either excessive iron therapy or iron overload may be a possible culprit of atherogenesis. The process seems to be mediated by oxidative stress. Iron therapy should also be used cautiously in the presence of active infections, since iron is essential for bacterial growth. Recently, the European Medicines Agency officially raised concerns about rare hypersensitivity reactions following IV iron administration. The balance has been in favour of benefits. In several European countries, this has created a lot of confusion and somewhat slowed the run towards excessive use. Altogether, IV iron remains a mainstay of anaemia treatment in CKD patients. However, in our opinion, its excessive use should be avoided, especially in patients with high ferritin levels and when ESA agents are not contraindicated.

Key words: anaphylaxis, atherosclerosis, chronic kidney disease, iron, safety

Introduction

After the publication of the Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) study [1], the integrated use of iron and erythropoiesis-stimulating agents (ESAs) has received growing attention in order to use the lowest dose of ESA and start it as late as possible. Indeed, it was found that intravenous (IV) iron therapy can improve anaemia even in patients without iron deficiency [2, 3] and that it may postpone or avoid the start of ESAs compared with oral iron in patients with chronic kidney disease (CKD) not on dialysis [4]. On the wave of these findings, in 2012 the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on anaemia management suggested a wider use of iron therapy and higher values of ferritin and transferrin saturation levels at which iron therapy should be started or stopped [5] (Table 1).

Oral iron is cheap and easy to administer. However, in CKD patients its gastrointestinal tolerability is often poor and absorption may be suboptimal through the blockade of ferroportin expression, the protein in charge of iron absorption in the bowel. For this reason, IV iron is needed in many cases to obtain
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In individual patients.

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have analysed the association between IV iron and mortality with conflicting results. Among these, the Dialysis

Outcomes and Practice Patterns Study (DOPPS) analysed associa-

tions between IV iron dose and clinical outcomes in > 30 000 HD

patients [14]. By considering a cumulative iron exposure of 4

months, significantly higher mortality and hospitalization risks

were found in the patients receiving ≥ 300 mg/month compared

with lower cumulative doses. Conversely, data from the DaVita

database in the USA showed only a trend towards increased mor-

tality in those receiving > 400 mg of IV iron/month [15].

A number of reasons can explain discrepancies among stud-

ies. The main one is the big confounder of treatment indications:

the sicker the patient, the more likely iron therapy is needed.

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with poor survival only in those using IV iron inappropraitely

in the patients with high haematocrit levels [17].

Another possibility is that patients with comorbidities are

more likely to have functional iron deficiency because of high

haptocrit levels blocking iron from utilization for erythropoiesis.

Table 1. Indications for iron therapy in CKD patients

| Organization      | When to start                                      | When to stop                                     |
|-------------------|---------------------------------------------------|-------------------------------------------------|
| KDIGO [5]         | ESA naive                                         | Serum ferritin ≥ 500 ng/mL                       |
|                   | • Serum ferritin < 500 ng/mL                      | TSAT ≥ 30%                                      |
|                   | • TSAT < 30%                                       |                                                 |
|                   | ESA therapy                                       |                                                 |
|                   | • Serum ferritin < 500 ng/mL                      |                                                 |
|                   | • TSAT < 30%                                       |                                                 |
| ERBP [6]          | ESA naive                                         | Serum ferritin ≥ 500 ng/mL                       |
|                   | • CKD-ND                                          | TSAT ≥ 30%                                      |
|                   | • Serum ferritin < 200 ng/mL                      |                                                 |
|                   | • TSAT < 25%                                       |                                                 |
|                   | • CKD-5D                                          |                                                 |
|                   | • Serum ferritin < 300 ng/mL                      |                                                 |
|                   | • TSAT < 25%                                       |                                                 |
| KDOQI [7]         | CKD all stages                                    | None if high ferritin, weigh potential risks and benefits of persistent anaemia, ESA dosage, comorbid conditions and health-related quality of life |
| Canadian Guidelines [8] | CKD all stages                                         | None                                                   |
|                   | • Serum ferritin < 500 ng/mL                      |                                                 |
|                   | • TSAT < 30%                                       |                                                 |
| NICE [9]          | CKD all stages                                    | Serum ferritin 500–800 ng/mL                    |
|                   | • Serum ferritin < 100 ng/mL                      |                                                 |
|                   | • TSAT < 20% (unless ferritin > 800 ng/mL)        |                                                 |
|                   | • HRC < 6% (unless ferritin > 800 ng/mL)          |                                                 |

CKD-ND, non-dialysis CKD.

Iron repletion, significant increases in haemoglobin (Hb) values

and/or savings in ESA dose. While IV administration seems to

be the most effective route, especially in haemodialysis (HD)

patients, a trial of oral iron may still be recommended in most

non-dialysis CKD patients as a first option.

Even if the KDIGO recommendations are not fully accepted [6],
significant changes in everyday clinical practice have occurred

especially in the USA, with a trend towards lower Hb levels and

ESA doses and higher IV iron and blood transfusion use. In

many cases, obtained ferritin levels are much higher than

those suggested by KDIGO guidelines [2] or European Renal Best

Practice (ERBP) [6]. These very high ferritin levels are not only
due to excessive iron therapy, but also to inflammation and to
decreased ESA use in recent years while maintaining similar

iron doses. Their persistence for very long periods calls their

safety aspects into question. This is also in the light of the fact

that differing from oral administration, IV iron bypasses physio-

logical defences to overload in the bowel and remains unused in

the case of functional iron de

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IV iron and patient outcome

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Another possibility is that patients with comorbidities are

more likely to have functional iron deficiency because of high

haptocrit levels blocking iron from utilization for erythropoiesis.
In this setting, IV iron may enhance oxidative stress and atherosclerosis or cause iron overload. The selection of either prevalent or incident HD patients may also be important.

Regrettably, observational studies cannot sort out between possibilities, especially when testing all-cause mortality as a hard end point.

Data from clinical trials on hard end points are scarce. The Ferinject® assessment in patients with Iron deficiency anaemia and Non-Dialysis-dependent Chronic Kidney Disease (FIND-CKD) study evaluated whether IV ferric carboxymaltose compared with oral iron could delay and/or reduce ESA use in 626 CKD patients not on dialysis [4]. According to the safety analysis, mortality was similar between treatment groups during the 12-month follow-up. However, the study was not adequately powered for testing hard end points.

Recently, a meta-analysis of 2658 patients from 24 single-arm studies and 10 randomized clinical trials did not demonstrate an increased risk of adverse events including infections, cardiac events and mortality [18]. Of note, these data were obtained from an exploratory analysis restricted to only two randomized clinical trials (359 analysable patients). The median duration of IV iron administration was 16 weeks, ranging from 2 to 96 weeks. However, even when the sample size of clinical trials is put together in a meta-analysis, it remains largely insufficient to test hard end points.

Ad hoc prospective studies are needed to overcome the majority of the biases of observational studies. In this regard, the results of the Proactive IV On Therapy for HaemodiALysis patients (PIVOTAL) study are awaited [19]. This is a large, open-label, randomized trial aimed at comparing the effect of a proactive high-dose versus a reactive low-dose IV iron therapy on hard end points in more than incident HD patients. The duration of the trial is event driven and is planned to be 2–3 years. Unfortunately, even this well-designed randomized trial may have insufficient statistical power to test hard end points.

Given the strong biases of observational studies and the lack of clinical trials with adequate sample size and follow-up, safety concerns of iron therapy other than hard end points may become a good starting point for reflection and warning towards excessive iron use.

**Excessive IV iron and the risk of iron overload**

According to the Dialysis Outcomes and Practice Patterns Study (DOPPS) Practice Monitor, serum ferritin levels have progressively increased in recent years in the USA, with nearly 40% of the HD population having ferritin levels >800 ng/mL [20]. The increase in mean IV iron dose (from 210 mg/month in 2009–10 to a peak of 280 mg/month in 2011, then back to 200 mg/month in 2013) combined with lower ESA doses accounted for 46% of the increase in ferritin over time [21]. In the absence of changes in reimbursement policies, similar trends in therapeutic practices have also occurred also in some European countries [22].

High ferritin levels have been related to poor survival in both non-dialysis [23] and dialysis [15] patients, but the ferritin levels at which mortality risk increases is still matter of debate [24]. As for iron therapy, observational studies have the confounding bias that serum ferritin is also a marker of inflammation, and thus of comorbidity. When selecting only patients with polycystic kidney disease (who usually have a low comorbidity burden), mortality was significantly related only with ferritin levels ≥1200 ng/mL in a fully adjusted model [25].

Only a few studies have tested the more important question, i.e. whether the administration of iron to patients with high ferritin levels may translate into iron overload or any kind of harm. The Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) trial [25], found that IV iron was effective in increasing Hb levels and reducing ESA doses in 134 patients with serum ferritin between 500 and 1200 ng/mL and transferrin saturation (TSAT) <25%. The rates of infections, cardiac adverse events and deaths were similar between the IV iron and control groups. However, the study was not powered to provide information about iron overload and long-term safety.

According to an old autopsy study, serum ferritin did not always correlate with bone marrow iron stores but correlated with hepatosplenic siderosis [26]. After the introduction of ESA in clinical practice, significant iron overload has become less evident. However, it may still be substantial in inflamed patients in whom inhibitory factors, like hepcidin, decrease iron release from reticulo-endothelial and hepatocyte stores [27]. Indeed, HD patients with very high ferritin levels have a mean liver iron concentration similar to that of patients with untreated idiopathic haemochromatosis [28]. Unfortunately, it is difficult to discriminate whether the iron detected in the liver is deposited within parenchymal hepatocytes or safely stored within reticulo-endothelial cells. Of note, elevated levels of non-transferrin bound iron (NTBI), which corresponds to iron that is not bound to transferrin and does not correspond to heme or ferritin iron, may be potentially responsible for cellular damage both at the cellular surface and at the intracellular level [29].

Keeping in mind this limitation, studies with non-invasive measurements of hepatic iron content suggest signs of iron overload in HD patients [30–33].

Ghoti et al. [33] analysed the iron content in 21 HD patients with serum ferritin >1000 ng/mL and several comorbidities. The majority had increased iron deposition in both the liver and spleen. Pancreatic deposition was less frequent. However, preliminary data suggest that iron overload may cause insulin resistance in HD patients [34, 35]. Differing from haemochromatosis and secondary haemosideroses, the heart is not significantly involved [33].

Canavesi et al. [31] showed signs of mild to moderate liver iron overload in 28 of 40 dialysis patients treated with IV iron. As expected, serum ferritin was significantly higher in those with moderate iron overload (482 ± 246 ng/mL) compared with those without (245 ± 183 ng/mL). However, the study was criticized for selecting patients with iron overload [36]. According to a more recent study, mild to severe hepatic iron overload was observed by magnetic resonance imaging (MRI) in a substantial percentage of 119 HD patients with a low comorbidity burden who were treated with IV iron [32]. MRI also revealed spleen anomalies (a sign of secondary haemosiderosis) in several patients. Following iron discontinuation, iron content fell quickly in patients with iron overload [31, 34].

Whether iron overload detected by non-invasive measurements translates into clinically meaningful harm is still an open question, also considering that with these techniques the cut-off ferritin value for moderate to severe iron overload [31, 34] is lower than the suggested upper limit to not be generally exceeded when administering iron therapy (Table 1) [6].

**Infection risk**

Iron is essential for bacterial growth, especially for intracellular microorganisms. The human body has developed mechanisms of defence for withholding iron from microorganisms. Transferrin and lactoferrin sequester iron, providing a form of non-specific immunity. Some bacteria can compete for iron by producing
iron chelators (siderophores) or directly acquire iron from transferrin by a membrane-bound transferrin receptor. When IV iron is given despite oversaturation of iron-binding proteins, free iron may enhance bacterial growth [37]. In vitro and in vivo studies have also shown that iron excess could also impair neutrophil and T-cell function, impairing host resistance [38, 39].

Few data exist relating IV iron administration and infection risk in CKD patients [40–42]. In 12 HD patients with central vein catheters, the administration of IV iron sucrose was followed by the release of NTBI and more frequent signs of bacterial growth in half of them (especially in those with TSAT >30%) [43]. Teehan et al. [44] found that HD patients receiving IV iron despite replenished iron indices are at increased risk for bacteraemia. In a retrospective cohort study of HD patients, Brookhart et al. [45] compared the safety of iron bolus dosing (100 mg in at least two consecutive treatments) to maintenance dosing (low-dose administration every 1–2 weeks to maintain iron stores). Patients receiving the bolus were at higher risk of infection than those on a maintenance dose, especially if they had a central vein catheter or had had a recent infection. Similarly, the DOPPS study showed a trend towards an increased infection-related mortality in prevalent HD patients treated with > 300 mg of IV iron [14]. A meta-analysis of 24 clinical trials also found an increased risk of infection with IV iron compared with oral or no iron treatment [46]. Conversely, a prospective observational study of 985 patients failed to demonstrate a relationship between infection and serum ferritin or IV iron dosing [47]. Of note, the frequency and the amount of iron administered were significantly higher in those who developed bacteraemia than in those who did not.

Altogether, the evidence relating IV iron with increased infection risk is scarce, mainly because of the heterogeneity of the studies and bias in treatment indications. Nevertheless, we agree with the KDIGO guidelines [5], which suggest not administering IV iron during active systemic infections.

The link between IV iron, oxidative stress and atherosclerosis

CKD patients experience accelerated atherosclerosis leading to excessive cardiovascular death; oxidative stress may be a pathogenic mediator. IV iron has been identified as a possible culprit influencing oxidative stress [48]. Free iron is a potent oxidizing agent leading to the formation of reactive oxygen species (ROS) [49, 50]. ROS can rise to lipid radicals, contributing to endothelial dysfunction and atherogenesis. Given that the rate of release of labile iron varies among iron formulations, the potential for causing oxidative stress may vary as well [51]. Despite theories, the link between iron therapies, oxidative stress and atherosclerosis is far from clear. Kuo et al. [52] demonstrated that therapy with iron sucrose accelerates early endothelial damage and subsequent atherosclerosis in mice with renal dysfunction. They also found that circulating mononuclear cells from CKD patients who have received iron sucrose produced higher levels of intracellular superoxide than untreated ones. However, these findings have recently been questioned, since these effects of iron sucrose may occur with the use of the iron sucrose similar, Fe-Back, but not with the originator [53].

Iron has been found in advanced human atherosclerotic plaques [54]. Free Hb and iron may be important in plaque destabilization following intra-plaque haemorrhage [55]. However, this does not translate necessarily in to causality. Moreover, elevated levels of iron contribute to the extent of protein, but not lipid, oxidation in advanced human lesions [56].

Some years ago, Sullivan et al. [57] hypothesized a key role of hepcidin in promoting iron accumulation in macrophages and then atherosclerosis. Experimental studies have shown that hepcidin overexpression promotes plaque destabilization [58]. Conversely, in a mouse model of selective iron overload in macrophages, Kautz et al. [59] were unable to demonstrate an increased expression of hepatic hepcidin at any stage of the atherosclerosis progression or an increase in atherosclerotic plaque size in relation to elevated macrophage iron. Data about the role of iron in the transition of vascular muscular smooth cells are also controversial [60].

Some years ago, Drüeke et al. [61] showed that cumulative iron dose was positively related to carotid intimal-media thickness in HD patients < 60 years of age. More recently, van der Weerd et al. [62] found a positive relationship between hepcidin levels and fatal and non-fatal CV events in 405 HD patients who were included in the CONvective TRAnsport Study (CONTRAST). Of note, in human hereditary haemochromatosis, which is caused by hepcidin deficiency, there is no increased incidence of cardiovascular disease [51].

Epidemiological data are controversial. The DOPPS showed that HD patients receiving high IV iron doses had a higher risk of cardiovascular death [14]. Conversely, other observational studies [16, 63], a randomized clinical trial [4] and a meta-analysis [17] have not been able to demonstrate the same association.

Altogether, despite pathogenic hypotheses, the evidence linking IV iron therapy, oxidative stress and cardiovascular disease is still limited. Data from randomized clinical trials testing the risk of cardiovascular events following differing schedules of IV iron therapy are awaited [20].

IV iron and anaphylactic reactions

Following a national review of IV iron molecules by the French Medicines Agency, in 2013 the EMA officially raised concerns about rare hypersensitivity reactions following IV iron administration [64]. Despite the rarity of these events, physicians are now required to better and fully inform patients about IV iron risks and put in place adequate resuscitation measures in the unlikely event that this occurs. Since it was not possible to discriminate the risk of the single molecule, this caution is to be applied to all iron molecules.

Historically, IV iron use has been associated with rare but potentially fatal adverse events and undesirable side effects. These reactions have been reported in several safety studies and with all the IV iron molecules (Table 2), even if they seem to be more rare with the new iron molecules (excepting for ferumoxylt, see below). All iron molecules share an iron core and a carbohydrate shell that minimizes the release of the bioactive iron. However, they differ in the size of the core and the, type and density of the surrounding carbohydrate [65]. The larger the carbohydrate shell, the lower the labile iron that is released.

Both IgG- and IgE-mediated responses are likely to be involved in immunological reactions to iron dextran [66, 67], but data about IgE-mediated reactions are less convincing [60]. Complement activation-related pseudo-allergy is likely the most common mechanism of acute hypersensitivity reactions provoked by the other IV iron molecules [68], similar to those occurring following IV vancomycin administration [59].

Starting from the early years, reactions, including anaphylaxis, were noted with high molecular weight (HMW) iron dextran (Imferon®) [69]. In 1991, it was replaced by a safer low molecular weight (LMW) iron dextran (InFeD®). In 1996, a second HMW iron dextran, Dexferrum®, entered the US market. This coincided with
a rise in reported adverse events [70, 71]. At the end of the 1990s, sodium ferric gluconate and iron sucrose became available. According to data from the US Food and Drug Administration (FDA), a rate of approximately 94 adverse drug events per million doses of IV iron was described [72]. HMW iron dextran had significantly higher rates of life-threatening reactions versus LMW iron dextran or other non-dextran iron products. Others showed no significant difference in toxicity between LMW iron dextran and iron sucrose [73, 74]. More recently, Wysowski et al. [75] found that allergic reactions are possible with all four parenteral iron molecules (Dexferrum, INFeD, iron gluconate and iron sucrose); it is difficult to discriminate which product has the largest risk.

According to a recent report by the FDA [76], 79 cases of anaphylactic reactions have been reported with ferumoxytol since its approval in 2009; 18 patients died despite the proper use of therapies and emergency resuscitation measures [76]. In nearly half of the cases, reactions occurred during the first administration. A boxed warning has been added to the label recommending not to administer ferumoxytol in patients with a history of allergy to IV iron and carefully consider administration in those with a history of multiple drug allergies.

Unfortunately, retrospective reports about iron safety are based on voluntary reporting and are biased by unclear definitions of hypersensitivity reactions. Moreover, the use of IV iron molecules varies across countries and over time [77]. Conversely, prospective observational studies and randomized clinical trials do not have adequate statistical power to study very rare drug-related adverse events and, more importantly, to compare the rate of one molecule with another. Because of their novelty, newer iron molecules, like ferumoxytol, may be subject to overreporting. Very recently, a systematic review assessed the safety of IV iron by obtaining data from 103 trials that were published between 1965 and 2013 [78]. Overall, 35 severe infusion reactions were reported for 9223 patients without any death. Compared with oral iron or placebo, serious infusion reactions were more frequent with IV iron (relative risk (RR) 2.47 (95% CI 1.43–4.28)), particularly with iron gluconate; the other iron molecules were not associated with a statistically significant increased risk of severe infusion reactions. LMW and HMW iron dextran were not included in the analysis.

Wang et al. [79] analysed all the anaphylactic reactions following IV iron administration in Medicare patients in the USA. They found that the incidence rate of anaphylaxis at first exposure was higher for iron dextran (68/100 000 persons) than for other iron molecules for (24/100 000 persons for iron sucrose, gluconate and ferumoxytol combined). The same held true during subsequent IV iron administrations.

Altogether, the risk of a hypersensitivity reaction following IV iron is low. The recent EMA recommendations on IV iron administration have sensitized nephrologists to the possible negative consequences of severe reactions occurring in the absence of adequate organization for in-hospital emergencies. This has somewhat reduced the prescription of IV iron in several settings, such as in non-HD patients or in those who receive HD outside the hospital (home dialysis, limited-assistance centres [80]).

### Monitoring and regulating IV iron therapy

Serum ferritin, combined with either transferrin saturation or total iron-binding capacity, is the most widely used marker to assess iron stores. While suboptimal, since they are influenced by inflammation and nutritional status, they are cheap and easily available worldwide. Alternative iron markers have been proposed, such as Hb content in reticulocytes, percentage of hypochromic red blood cells, erythrocyte zinc protoporphyrin, soluble transferrin receptor, and labile iron. However, the performance of these biomarkers for diagnosing iron deficiency or overload is considered insufficient compared with classical (and in general cheaper) markers for everyday clinical practice [81].

Serum hepcidin is the key regulator of iron metabolism [82]. It has a good relationship with ferritin levels but also shares some of its limitations. As for serum ferritin, it is influenced by inflammation and its synthesis is not necessarily reduced by iron deficiency, excepting for substantial absolute deficiency (where, it should be noted, ferritin levels work well) [83]. In addition, its capability to predict bone marrow iron stores [84] and ESA response [85] is limited. At present, its dosing is used mainly for experimental and not clinical purposes.

Some years ago, the superconducting quantum interference device and quantitative computed tomography were proposed as non-invasive methods to test iron stores [86]. More recently, liver MRI has been used to measure iron overload in CKD patients, but it is expensive and not easily accessible to everybody.

Interestingly, serum ferritin is the only marker with discriminatory capacity in receiver operating characteristics curves analysis to detect iron overload with liver MRI [33].

Unfortunately, current evidence is unable to sort out the critical ferritin level at which iron-deficient erythropoiesis becomes systemic iron overload or at which IV iron can cause harm. While it is widely accepted to not routinely exceed ferritin values of 500–800 ng/mL during iron therapy, current guidelines or position papers give different suggestions on the topic (Table 1), sometimes also influenced by economic considerations [7]. Moreover, as testified by mean ferritin values in the HD population,
these ferritin values are often exceeded during iron therapy in everyday clinical practice.

Considering that the benefits of IV iron in terms of Hb increase and decreased ESA doses become less evident for TSAT values ≥30% and high ferritin values, we do believe that there is no need to use high doses of IV iron therapy, especially in CKD patients who are not on dialysis or in those who are ESA naive [6].

Conclusions

Following concerns about ESA therapy, iron therapy has expanded. However, excessive IV iron use, combined with blood transfusions, may expose patients to iron overload. More subtle safety concerns may also be related to IV iron, such as worsening of atherosclerosis and oxidative stress and increased risk of infection. Labile iron may also cause parenchymal damage by itself.

In the absence of clear evidence about safe values of serum ferritin and transferrin saturation that should not be exceeded with iron therapy or safe cumulative iron doses, physicians should consider wisely which is the best treatment option for their patient. Starting from clinical and laboratory data, possible risks and benefits of both ESA and iron therapy should be balanced as options to achieve a more suitable Hb level. The task is complex, especially in inflamed patients with functional iron deficiency, since they are more likely to possibly develop iron overload in the long-term and be victims of subtle damage caused by labile iron unbound to serum transferrin.

Conflict of interest statement

F.L. is or has been a member of an advisory board and/or speaker at meetings supported by Akebia, Amgen, Janssen, GSK, Fibrogen, Astellas, Keryx, Roche and Pharmacosmos. L.D.V. was a member of an advisory board of Astellas and received honoraria from Takeda.

We also declare that the results presented in this article have not been published previously in whole or part, except in abstract format.

References

1. Pfeffer MA, Burdmann EA, Chen CY et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009; 361: 2019–2032
2. Stancu S, Barsan L, Stanciu A et al. Can the response to iron therapy be predicted in anemic nondialysis patients with chronic kidney disease? Clin J Am Soc Nephrol 2010; 5: 409–416
3. Stancu S, Stanciu A, Zugravu A et al. Bone marrow iron, iron indices, and the response to intravenous iron in patients with non-dialysis-dependent CKD. Am J Kidney Dis 2010; 55: 639–647
4. Macdougall IC, Beck AH, Carrera F et al. 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.
5. 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
6. Locatelli F, Bárány P, Covic A et al. Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. Nephrol Dial Transplant 2013; 28: 1346–1359
7. Kliger AS, Foley RN, Goldfarb DS et al. KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. Am J Kidney Dis 2013; 62: 849–859
8. Moist LM, Troyanov S, White CT et al. Canadian Society of Nephrology commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. Am J Kidney Dis 2013; 62: 860–873
9. http://www.nice.org.uk/guidance/ng8 (9 December 2015, date last accessed)
10. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001833.jsp&mid=WCOb01ac058004d5c1 (26 January 2015, date last accessed)
11. Feldman HI, Santanna J, Guo W et al. Iron administration and clinical outcomes in hemodialysis patients. J Am Soc Nephrol 2002; 13: 734–744
12. Feldman HI, Joffe M, Robinson B et al. Administration of parenteral iron and mortality among hemodialysis patients. Am Soc Nephrol 2004; 15: 1623–1632
13. Kuragano T, Matsumura O, Matsuda A et al. Association between hemoglobin variability, serum ferritin levels, and adverse events/mortality in maintenance hemodialysis patients. Kidney Int 2014; 86: 845–854
14. Bailie GR, Larkina M, Goodkin DA et al. Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intra venous iron doses and mortality. Kidney Int 2015; 87: 162–166
15. Kalantar-Zadeh K, Regidor DL, McAllister CJ et al. Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol 2005; 16: 3070–3080
16. 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: 1390–1393
17. Brookhart MA, Schneeweiss S, Avorn J et al. Comparative mortality risk of anemia management practices in incident hemodialysis patients. JAMA 2010; 303: 857–864
18. Susantitaphong P, Alqahtani F, Jaber BL. Efficacy and safety of intravenous iron therapy for functional iron deficiency anaemia in hemodialysis patients: a meta-analysis. Am J Nephrol 2014; 39: 130–141
19. https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002267-25/GR#F (15 April 2015, date last accessed)
20. Fuller DS, Pisoni RL, Bieber BA et al. The DOPPS practice monitor for U.S. dialysis care: update on trends in anemia management 2 years into the bundle. Am J Kidney Dis 2013; 62: 1213–1216
21. Karaboyas A, Zee J, Morgenstern H et al. Understanding the recent increase in ferritin levels in United States dialysis patients: potential impact of changes in intravenous iron and erythropoiesis-stimulating agent dosing. Clin J Am Soc Nephrol 2015; 10: 1814–1821
22. Evans M, Sutorp MM, Bellocq R et al. Trends in haemoglobin, erythropoietin-stimulating agents and iron use in Swedish chronic kidney disease patients between 2008 and 2013. Nephrol Dial Transplant 2015; doi:10.1093/ndt/gfv298
23. Kovesdy CP, Estrada W, Ahmadzadeh S et al. Association of markers of iron stores with outcomes in patients with non-dialysis-dependent chronic kidney disease. Clin J Am Soc Nephrol 2009; 4: 435–441
24. Hatamizadeh P, Ravel V, Lukowsky LR et al. Iron indices and survival in maintenance hemodialysis patients with and without polycystic kidney disease. Nephrol Dial Transplant 2013; 28: 2889–2898
25. Coyne DW, Kapoian T, Sukk W et al. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum...
64. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001833.jsp&mid=WC0b01ac058004d5c1 (26 January 2015, date last accessed)

65. Bircher AJ, Auerbach M. Hypersensitivity from intravenous iron products. *Immunol Allergy Clin North Am* 2014; 34: 707–723

66. Zinderman C, Landow L, Wise R. Anaphylactoid reactions to dextran 40 and 70: reports to the United States Food and Drug Administration, 1969 to 2004. *J Vasc Surg* 2006; 43: 1004–1009

67. Novey HS, Pahl M, Haydik I et al. Immunologic studies of anaphylaxis to iron dextran in patients on renal dialysis. *Ann Allergy* 1994; 72: 224–228

68. Rampton D, Folkersen J, Fishbane S et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. *Haematologica* 2014; 99: 1671–1676

69. Hamstra RD, Block MH, Schocket AL. Intravenous iron dextran in clinical medicine. *JAMA* 1980; 243: 1726–1731

70. Fletes R, Lazarus JM, Gage J et al. Suspected iron dextran-related adverse drug events in hemodialysis patients. *Am J Kidney Dis* 2001; 37: 743–749

71. Rodgers GM, Auerbach M, Cella D et al. High-molecular weight iron dextran: a wolf in sheep’s clothing? *Am Soc Nephrol* 2008; 19: 833–834

72. Chertow GM, Mason PD, Vaage-Nilsen O et al. On the relative safety of parenteral iron formulations. *Nephrol Dial Transplant* 2004; 19: 1571–1575

73. Moniem KA, Bhandari S. Tolerability and efficacy of parenteral iron therapy in haemodialysis patients: a comparison of preparations. *Transfus Altern Transfus Med* 2007; 1: 1–7

74. Sav T, Tokgoz B, Sipahioglu MH. Is there a difference between allergic potencies of the iron sucrose and low molecular weight iron dextran? *Ren Fail* 2007; 29: 423–426

75. Wysowski DK, Swartz L, Borders-Hemphill BV et al. Use of parenteral iron products and serious anaphylactoid-type reactions. *Am J Hematol* 2010; 85: 650–654

76. http://www.fda.gov/Drugs/DrugSafety/ucm440138.htm (15 April 2015, date last accessed)

77. Bailie GR, Clark JA, Lane CE et al. Hypersensitivity reactions and deaths associated with intravenous iron preparations. *Nephrol Dial Transplant* 2005; 20: 1443–1449

78. Avni T, Bieber A, Grossman A et al. The safety of intravenous iron preparations: systematic review and meta-analysis. *Mayo Clin Proc* 2015; 90: 12–23

79. Wang C, Graham DJ, Kane RC et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. *JAMA* 2015; 314: 2062–2068

80. Rivera R, Guido D, Del Vecchio L et al. The Lombardy Section of Italian Society of Nephrology. Impact of European medicines agency recommendations for hypersensitivity reactions on intravenous iron prescription in haemodialysis centres of the Lombardy region. *J Nephrol* 2015; in press

81. Chung M, Moorthy D, Hadar N et al. Biomarkers for Assessing and Managing Iron Deficiency Anemia in Late-Stage Chronic Kidney Disease. Report no. 12(13)-EHC140-EF. Rockville, MD: Agency for Healthcare Research and Quality (US), 2012

82. Nemeth E, Valore EV, Territo M et al. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. *Blood* 2003; 101: 2461–2463

83. Mercadel L, Metzger M, Haymann JP et al. The relation of hepcidin to iron disorders, inflammation and hemoglobin in chronic kidney disease. *PloS One* 2014; 9: e99781

84. Bârsan L, Stanciu A, Stancu S et al. Bone marrow iron distribution, hepcidin, and ferroportin expression in renal anemia. *Hematology* 2015; 20: 543–552

85. Costa E, Swinkels DW, Laarakkers CM et al. Hepcidin serum levels and resistance to recombinant human erythropoietin therapy in haemodialysis patients. *Acta Haematol* 2009; 122: 226–229

86. Fischer R, Harmatz PR. Non-invasive assessment of tissue iron overload. *Hematol Am Soc Hematol Educ Program* 2009: 215–221