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Safety of Intravenous Iron in Hemodialysis Patients

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Abstract

Among end-stage renal disease patients maintained by hemodialysis, anemia has been managed primarily through erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron. Following concerns about the cardiovascular safety of ESAs and changes in the reimbursement policies in Medicare's ESRD program, the use of IV iron has increased. IV iron supplementation promotes hemoglobin production and reduces ESA requirements, yet there exists relatively little evidence on the long-term safety of iron supplementation in hemodialysis patients. Labile iron can induce oxidative stress and is also essential in bacterial growth, leading to concerns about IV iron use and risk of cardiovascular events and infections in hemodialysis patients. Existing randomized controlled trials provide little evidence about safety due to insufficient power and short follow-up; recent observational studies have been inconsistent, but some have associated iron exposure with increased risk of infections and cardiovascular events. Given the widespread use and potential safety concerns related to IV iron, well-designed large prospective studies are needed to assess to identify optimal strategies for iron administration that maximize its benefits while avoiding potential risks.

INTRODUCTION

Anemia, a common complication of end-stage renal disease (ESRD),[1] is associated with elevated morbidity, mortality, and healthcare costs.[2] A primary cause of anemia in ESRD is iron deficiency, particularly among patients requiring hemodialysis (HD). Iron deficiency can be classified into absolute iron deficiency and functional iron deficiency, each with multifactorial causes.[3] Absolute iron deficiency, or depleted iron stores, is frequently a result of blood loss, reduced intake, and impaired intestinal absorption of dietary iron.[3] Functional iron deficiency, or insufficient iron availability at the site of erythropoiesis despite adequate iron stores, can be caused by chronic inflammation associated with ESRD or elevated hepcidin levels.[3] Overall, HD patients lose an average of 1–2 g of iron per year, and some as much as 4–5 g per year.[4] Management of iron deficiency to meet the need for erythropoiesis is thus essential for optimal management of anemia in ESRD patients.

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Intravenous (IV) iron is an effective way to supplement iron and optimize erythropoiesis. Existing randomized controlled trials showed that supplementing erythropoiesis-stimulating agent (ESA) therapy with IV iron increases hemoglobin production and lowers ESA requirement.[5–6] Consequently, co-administration of ESAs and IV iron has become the primary management strategy for anemia in HD patients.[4] Subsequent to emerging evidence on the cardiovascular (CV) safety of ESAs[7–9] and changes in the reimbursement policies in Medicare's ESRD programs,[10] hemoglobin targets have decreased, allowing providers to reduce ESA dosing, decreasing potential risks associated with ESAs.[11,12] However, despite steadily falling hemoglobin levels, doses of IV iron rose from 210 mg per month in 2009–2010 to 280 mg per month in 2011, then back to a stable 200 mg per month in 2012–2013.[13,14] Consequently, ferritin levels in dialysis patients have generally been elevated, with many greater than 800 ng/mL.[13] The persistently high levels of ferritin raised concerns about appropriate use of iron.

Despite its established effectiveness, there have been concerns about the safety of IV iron supplementation. Unlike oral iron supplements, IV iron bypasses various homeostatic mechanisms that keep iron tightly regulated. Due to the association between labile iron and both induced oxidative stress and bacterial growth, elevated risks of CV events[15–17] and infection[18] have been a concern related IV iron use in HD patients. Hypersensitivity reactions have also been linked to the use of all iron formulations, though the reaction rates vary.[19] Unfortunately, the existing randomized controlled trials of IV iron are small and short-duration and therefore do not provide evidence on safety and long-term effects. Recent observational studies, primarily relying on cumulative iron exposure rather than clinical dosing patterns, have showed differing results.

Five forms of IV iron preparations have been approved for use in the United States (Table 1). These iron products are formulated with an iron oxyhydroxide core surrounded by a carbohydrate shell.[20] The sizes of the core and its surrounding carbohydrate shell differ among iron formulations, leading to different amount of labile iron being released.

In contemporary clinical practice, IV iron is either administered via bolus dosing, which provides frequent large doses over consecutive dialysis sessions, or via maintenance dosing, which provides small doses every one to two weeks to maintain iron stores. Decisions regarding when to use each dosing approach typically follow protocols established by dialysis clinics. These protocols provide treatment recommendations based on target levels of hemoglobin and observed iron status parameters - ferritin and transferrin saturation (TSAT).[21–24] A variety of dosing protocols exist in clinical practice, and they differ with respect to target levels of iron status parameters and dosing approach recommendations.[25–27] Optimal management strategies to administer IV iron have not been identified.

In this review, we comprehensively examine the recent epidemiologic evidence on the safety of IV iron use in HD patients, specifically focusing on hypersensitivity reactions, CV events, and infection.

IV IRON AND HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions have been a concerning complication of IV iron administration. First, and foremost, an anaphylactic reaction can be life-threatening if not immediately addressed. Second, the immediacy of the reaction that is experienced by the patient receiving the agent is traumatic for both patients and staff. However, it appears that the absolute incidence of adverse hypersensitivity reactions is low, especially with the use of newer agents.

Mechanism of Harm

All IV iron preparations can lead to hypersensitivity reactions, including anaphylaxis. Historically, occurrences of anaphylaxis were observed with high-molecular-weight iron dextran,[28] raising concerns regarding the safety of IV iron treatment. This product was in turn replaced by low-molecular-weight iron dextran and other non-dextran products and is no longer commercially available. Overall, anaphylactic reactions are rare in IV iron formulations other than high-molecular-weight iron dextran. Using data from the US FDA MedWatch programme (2001–2003), Chertow et al examined the frequency of adverse drug events related to the four older preparations. Compared to high-molecular-weight iron dextran, the rate of severe adverse reactions was much lower in low-molecular-weight iron dextran (3.3 versus 11.3 per million patients), or other non-dextran products (ferric gluconate: 0.9 per million patients; iron sucrose: 0.6 per million patients).[19] These rates were remarkably lower than those observed after their first release.

The mechanism of anaphylaxis associated with IV iron administration remains unknown. Immunological IgE- and IgG-mediated responses associated with the dextran component may explain the relative higher occurrence of anaphylactic reactions associated with high-molecule-weight iron dextran compared to other non-dextran preparations.[4,29] Among the other preparations, the activation of the complement system triggered by iron nanoparticles is likely to be involved.[29] As a consequence of complement activation, activation of mast cells and basophils increases, resulting in secretion products that potentially lead to hypersensitivity reactions.

Although the precise mechanism of hypersensitivity reactions to IV iron is unknown, the potential risk factors include asthma, mastocytosis, atopic status, and concurrent medications including beta blockers and angiotension-converting enzyme inhibitors.[4] Given the inability to predict hypersensitivity in patients using a serological evaluation, careful monitoring is needed when administering any IV iron product.

Epidemiologic Evidence

Due to the rarity of occurrence, evaluation of the hypersensitivity risk associated with iron formulations is challenging in randomized controlled trials and prospective observational studies; impractically large sample size would be needed to reach adequate statistical power. It is even more challenging to compare the risks among different iron formulations using these designs. Consequently, existing evidence base on IV iron and hypersensitivity reactions largely comprised of data from spontaneous reporting.[30–34] Excluding high-

molecular-weight iron dextran, the highest risk of anaphylaxis was observed in iron dextran, and no significant difference in risk was observed among other iron formulations including ferric gluconate, iron sucrose, and ferumoxytol. However, caution needs to be exercised when interpreting these results because data from voluntary reporting is prone to reporting bias.[35] Substantial under- or over-reporting and lack of verification makes them unfit for accurate estimation of incidence for a given adverse event.

Large observational studies can be used to examine the risk of such rare events. In a large cohort of 688,183 Medicare beneficiaries from 2003–2010, Wang et al reported higher incidence rate of anaphylaxis associated with incident exposure to iron dextran compared to other iron products combined (68 versus 24 per 0.1 million patients).[36] Following total iron repletion of 1 g administered within a 12-week period, the cumulative anaphylaxis risk was highest with iron dextran (82 per 0.1 million patients) and lowest with iron sucrose (21 per 0.1 million patients).

Despite the rarity of hypersensitivity events, physicians are required to inform patients about these risks before treatment,[37] and management tips have been provided for these adverse reactions.[4] A test dose is recommended for iron dextran. For other non-dextran formulations, administration with a relatively small dose and slow rate of infusion has been advised.[38]

IV IRON AND CV-RELATED RISK

Cardiovascular (CV) disease is the leading cause of death among HD patients. There have been theoretical concerns that IV iron may increase the risk of CV-related outcomes through inducing increased oxidative stress.[15–17]

Mechanism of Harm

With IV administration, iron is directly released into plasma, resulting in transient concentrations of labile plasma iron and formation of highly reactive free radicals,[39] damaging reactive oxygen species that attack membrane lipids and are associated with atherosclerosis. Excess free radicals could change the redox balance state to increase oxidative stress or at least exacerbate the level of oxidative stress present in HD patients.[39] Iron has been identified in atherosclerotic plaques, suggesting that IV iron may increase atherogenesis leading to CV deaths in HD patients.[40] Cell culture models and animal models have shown IV iron formulations induce oxidative stress and tissue inflammation.[41–43] However, no definite link has been established between iron treatment, oxidative stress, and CV risk.

Hepcidin, the important regulatory protein for iron, has also been hypothesized to mediate the effect of iron on CV-related risk by promoting iron accumulation in macrophages and subsequently atherosclerosis.[44] However, animal studies have shown conflicting results regarding the association of hepcidin level and the atherosclerosis process.[45–47] Recent clinical studies in HD patients found positive associations between increased level of hepcidin and arterial stiffness[48] and risk of CV events.[49]

Epidemiologic Evidence

Evidence from epidemiologic studies on IV iron and CV-related risk is inconclusive although early clinical studies indicated iron use with elevated risks of CV diseases[47] and mortality[50] in HD patients. Susantitaphong et al reviewed and meta-analyzed 24 single-armed studies and 10 parallel-arm randomized controlled trials and found no association between high IV iron doses and CV mortality (Table 2).[51] The completed studies were largely underpowered and generally evaluated outcomes that were not hard clinical end-points. They also had relatively short duration for follow-up.

A limited number of observational studies have evaluated the effect of IV iron on CV-related events and mortality in HD patients (Table 2), and the results are inconsistent. Iron doses greater than 400 mg/month[52] and 300 mg/month[53] were associated with higher CV mortality risk in two large cohort studies. Higher cumulative iron doses were also linked with higher CV events in a Japanese prospective cohort study, which examined a product not currently used in the United States.[54] Conversely, two recent retrospective studies of HD patients showed no association between large doses and short-term CV morbidity and mortality.[27,55] Similarly, no clear association has been established between IV iron and all-cause mortality. Higher doses were associated with increased risk of death in some studies,[52–54] but no association was found in others,[55,56] with a few demonstrated reduced risks at certain levels of dosing. [27,52,56] The conflicting data is partly due to the difficulty to separate the effect of iron overload from systemic inflammation on CV-related outcomes because serum ferritin level can be a marker for both conditions. Residual confounding by indication is likely another factor contributing to the inconsistency, as patients receiving larger amounts of iron may be at higher underlying CV risk.

Overall, despite theoretical concerns, it is unclear whether IV iron administration exacerbates atherosclerosis and leads to increased risk of CV diseases, the leading cause of death in the ESRD patients. Further research is needed to evaluate hard clinical end points, including myocardial infarction, stroke, and mortality. The possible mediating role of level of hepcidin and ferritin needs more thorough examination.

IV IRON AND INFECTION RISK

Patients on HD frequently experience infectious complications leading to hospitalization and death. There are concerns that IV iron may increase infection risk because of its effect on bacterial growth, host immunity, and clinical infection risk.

Mechanism of Harm

Iron is essential for bacterial growth. In iron-rich environments, bacteria can acquire iron from the blood stream by producing iron chelating siderophores or obtain iron from transferrin directly via transferrin receptor and use it to grow. Iron is also essential for proper host defense against infection. Iron overload has been linked with impaired neutrophil and T-cell functions, and subsequent immune dysfunction and increased Gram-positive bacteria growth in vitro.[57–59]

Epidemiological Evidence

As with CV risk, the few randomized controlled trials of IV iron were not large enough to evaluate infection risk. The Dialysis Patients' Response to Intravenous Iron with Elevated Ferritin (DRIVE) study randomized HD patients with TSAT ≤25% and ferritin 1,124–2,696 pmol/mL receiving high doses of epoetin alfa (>30,000 U per week) to ferric gluconate or no iron. In these patients, 1 g of IV iron did not increase the risk of infection and actually reduced number of serious adverse events compared with patients who received no iron over the 3-month period.[6] Another placebo-controlled trial in patients with heart failure (but not on dialysis) found no elevated risks of infection, hospitalization or mortality in patients who received IV iron therapy.[60]

Compared to oral iron supplements, IV iron showed increased risk of infection and CV events in a recent trial in non-dialysis patients with chronic kidney disease that had to be terminated early.[61] The results were considerably different from that of the Ferinject® assessment in patients with Iron deficiency anaemia and Non-Dialysis-dependent Chronic Kidney Disease (FIND-CKD) study that found no difference in infection risk across all three arms.[62] The discrepancy in the results may be partially caused by the single-center setting and greater loss to follow-up in the first study.

Several systematic reviews and meta-analyses performed to date are inconclusive. Early reviews published in 1999 found no evidence of an effect of iron and infection.[63–65] As more data accumulated, an updated review conducted by Ishida and Johansen suggested a potential link between iron and elevated infection risk.[66] Out of the 24 studies (published in and prior to 2013) included in the review, 12 studies showed an association of usage, dose-dependent risk or frequency-dependent risk between iron and infection or infection-related mortality, whereas the rest showed no association. Most of the 24 studies had small sample size and short follow-up duration. Many studies did not take into account of iron status parameters such as serum TSAT and ferritin levels, offering little information about the comparability of the patient groups across study groups. More than half of the studies (15/24) were carried out in other countries or in older cohorts in the United States, limiting generalizability of these results.

Two recent meta-analyses of randomized clinical trials also reported conflicting results. With both HD patients and non-HD patients with chronic kidney disease, Litton et al showed increased risk of infection comparing IV iron with either oral iron or no iron supplementation.[67] The other meta-analysis evaluated the safety of IV iron in HD patients with functional iron deficiency reported no association of iron use with infection risk, but only two studies were included in the analyses for this outcome.[51]

Cumulative Iron Exposure and Infection Risk

To date, a number of observational studies examined the effect of IV iron administration and risk of infection; most of them focused on cumulative iron exposures over a long period. Current data, however, give mixed signals. In the last five years, several observational studies with large population of HD patients have been published (Table 3). In a cohort of 14,078 dialysis patients in the United States, Miskulin et al examined the accumulated IV

iron dose over 1-, 3-, and 6-month rolling windows and found large associations between cumulative dose and infection-related outcomes, but these associations were very imprecise and included the null effect in all case.[27] Another study with 32,435 HD patients from 12 countries also reported non-statistically significant difference across dosage groups. However, infection-related mortality was elevated among patients receiving higher doses of IV iron over 4 months compared to 100–199 mg/month.[53] In another cohort of 9,544 incident HD patients, higher cumulative IV iron doses were not associated with infection-related hospitalizations.[68] Inadequate statistical power due to small sample sizes might have contributed to the inability to detect the difference in some of these studies.

To identify patient subgroups at higher risk, the effect of IV iron on risk of infection has also been evaluated in several studies. Catheters were found to be the leading risk factor of bacteremia in chronic HD patients.[69] Higher iron dose was also associated in patients with catheter-related sepsis than in patients without.[70] In recent work by our group comparing bolus dosing with maintenance dosing strategy in a large cohort of HD patients, highest risk of infection-related hospitalization was observed among patients with a catheter or history of recent infection.[71]

SAFETY OF IRON PROTOCOLS: TOWARDS MORE CLINICALLY-RELEVANT EFFECTS

Much of the existing research on iron has studied long-term cumulative exposure or shorter-term dose effects – exposures that do not align with treatment decisions made by clinicians. In contemporary clinical practice, IV iron is administered according to protocols, which recommend courses of treatment aimed at achieving target levels of hemoglobin and iron status parameters (ferritin and TSAT). Following availability of levels of these parameters, physicians make decisions about the iron administration approach (e.g., bolus dosing or maintenance dosing) for the next treatment course. A variety of dosing protocols exist in clinical practice, and they differ with respect to target levels of iron status parameters and administration approach recommendations.[24–27]

Little evidence is available regarding the safety and effectiveness of these dosing protocols in the literature. Clinical trials assessing the use of IV iron dosing protocols are lacking; existing large observational studies have focused on the effect of cumulative iron exposure over a long period, which do not align with the treatment decisions that physicians need to make regarding iron use.[72]

Existing studies have compared the safety of exposure to different administration approaches. Several studies consistently demonstrated short-term benefits of bolus iron administration on hemoglobin levels and iron status compared to more conservative maintenance dosing[73] or no iron.[6] No difference in CV risks was associated with either administration approach;[55,74] Elevated risk of infection was associated with bolus dosing approach. In a large cohort of 117,050 HD patients in the United States, our group compared bolus iron administration with maintenance dosing and found increased short-term risks of infection-related hospitalization or mortality (hazard ratio and 95% confidence interval: 1.08, 1.05–1.11).[71] In another study of 12,969 HD patients in the United States, Michels et

al reported lower mortality risk associated with maintenance dosing strategies compared with non-maintenance strategies.[75] It is worth noting that different definitions were used for administration strategies across these studies.

Altogether, the evidence concerning IV iron dosing protocols is lacking. The examination of cumulative exposures over a long time periods offers little clinically meaningful information to physicians with regard to treatment decisions, which concern more about the dosage, frequency, and timing of IV iron. Evaluation of different dosing protocols are needed to identify optimal strategies for iron treatment in HD patients.

CONCLUSION

Data have consistently demonstrated the effectiveness of IV iron treatment in management of anemia in the ESRD patients on HD. However, there remains considerable uncertainty about the best strategy for IV iron treatment of anemia management iron in ESRD patients. In particular, the dosage, frequency, and timing of IV iron use (target TSAT and ferritin levels) in HD patients are unknown. Given the increasing utilization of IV iron and data suggesting risk for some dosing practices in some patients, further research is needed to identify optimal dosing strategies that maximize the benefits of IV iron, while avoiding its potential risks.

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Table 1

IV iron formulations available in the United States

Generic Name	Brand Name (Manufacturer)	Approval Year	Test Dose Needed	Labeled Dosage for Iron Deficiency	IV administration time	Notes
High-molecule-weight iron dextran	DexFerrum (American Regent)	1954	Yes	1000 mg in 10 divided doses or total dose as a single IV infusion	Undiluted at an infusion rate not to exceed 50 mg (1mL)/min	Anaphylactic-type reactions and fatalities reported; resuscitation equipment and trained personnel necessary
Low-molecule-weight iron dextran	InFed (Watson)	1992	Yes	1000 mg in 10 divided doses or total dose as a single IV infusion	Undiluted at an infusion rate not to exceed 50 mg (1mL)/min	Anaphylactic-type reactions and fatalities reported; resuscitation equipment and trained personnel necessary
Ferric gluconate	Ferrlecit (Sanofi-Aventis); Nulecit (Watson)	1999	No	1000 mg in 8 divided doses (HD only)	60 minutes diluted in saline; undiluted IV push at 12.5 mg/min	Reactions to benzyl alcohol ingredient
Iron sucrose	Venofer (American Regent)	2000	No	1000 mg in 10 divided doses (HD); 1000 mg in 5 divided doses (NDD); 1000 mg in 2 doses of 300 mg and 1 dose of 400 mg (PD)	2–5 minutes undiluted or 15 minutes if diluted in saline (HD, NDD); 300 mg infused over 1.5 hours, 400 mg over 2.5 hours 14 days later, 400 mg infused over 2.5 hours 14 days later (PD)	7-day stability; anaphylactoid reactions
Ferumoxytol	Feraheme (AMAG)	2009	No	510 mg × 2 doses separated by 3 or 8 days	IV infusion diluted in saline or Dextrose Injection over 15+ minutes	MRI interaction for up to 3 mo; resuscitation equipment and trained personnel necessary. Anaphylactic-type reactions presenting with cardiac/ cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness
Ferric carboxymaltose	Injectafer (American Reagent)	2013	No	750 mg × 2 doses separated by at least 7 days (weighing ≥110 lb); 15 mg/kg body weight separated by at Least 7 days (weighing <110 lb)	Undiluted IV push at 100 (2mL) per minute, or diluted infusion over at least 15 minutes	Anaphylactic-type reactions presenting with shock, clinically significant hypotension, loss of consciousness, and/or collapse

Note: IV= intravenous; HD=hemodialysis; NDD=Non-hemodialysis dependent; PD=peritoneal dialysis

Table 2

Characteristics of epidemiological studies on IV iron and CV-related events among HD patients

First Author	Study Year	Country	Databases	N	Iron formulation	Exposures	Follow-up	HR (95% CI)	CV risk[f]
Kalantar-Zedeh 2005[52]	2001–2003	US	USRDS and DaVita	58,058	ferric gluconate, iron sucrose, iron dextran	<400 vs 0 mg/month	2 years	200–399: btw 0.5–0.6[e]	−
						≥400 vs 0 mg/month		≥400: btw 1.1–1.3	+
Kuo 2012[54]	2004–2005	Taiwan	Prospective study at Excelsior Renal Service Co	1,239	ferric chloride hexahydrate	40–800 vs 0 mg/6 months	12 months	1.7 (1.0–2.7)	+
						840–1600 vs 0 mg/6 months		3.5 (1.9–6.1)	+
						1640–2400 vs 0 mg/6 months		5.1 (3.0–9.7)	+
Kshirsagar 2013[55]	2004–2008	US	USRDS and DaVita	117,050	ferric gluconate, iron sucrose, iron dextran	bolus vs maintenance [a]	3 months	1.03 (0.99–1.07)	*
						high vs low (> 200 vs ≤ 200 mg/1 month)		0.99 (0.96–1.03)	*
Miskulin 2014[27]	2003–2008	US	USRDS and Dialysis Clinic Inc	14,078	all formulations[b]	vs >0–150/1 month vs >0–450/3 months vs >0–900/6 months	≤4 years	>350: 0.95 (0.70–1.29) >1050: 1.02 (0.74–1.41) >2100: 1.17 (0.76–1.79)	*
Susantitaphong 2014[51]	through Dec 2012	multi-country	24 single-arm studies and 10 parallel-arm RCTs	2,658	Multiple formulations[c]	NA	NA	NA	*
Bailie 2015[53]	2002–2011	12 countries	DOPPS	32,435	Multiple formulations[d]	average dose over 4 months (mg/month): 0, 1–99, 100–199 (reference), 200–299, 300–399, 400+	Median (IQR): 1.7 (1.0–2.4) years	increased risks with ≥300; ≥6 vs 1–2 mg/kg per month: 1.35 (1.12–1.62)	+

Note: IV=intravenous; CV=cardiovascular; HD=hemodialysis; US=the United States; USRDS=the United States Renal Data System; IQR=interquartile range; CI=confidence interval; HR=hazard ratio

[a] Bolus dosing: consecutive doses ≥ 100 mg exceeding 600 mg during one month; maintenance: all other iron doses during the month;

[b] No further explanation provided in the article;

[c] Iron sucrose, ferric gluconate, iron dextran, iron saccharate, iron polymaltose, iron oxide, ferrous colloid, ferumoxytol;

[d] Iron sucrose, ferric gluconate, iron dextran, iron saccharate, iron polymaltose, chondroitin sulfate iron complex, cideferron;

[e] Obtained from a figure in the article, the exact estimates were not available;

[f] Symbol representation: + = increased risk; − = decreased risk; * = no difference

Table 3

Characteristics of recent epidemiological studies on IV iron and infection among HD patients (2013–2016)

Author/Year	Study Year	Country	Databases	N	Population	Exposures	HR (95% CI)	Infection risk[d]
Brookhart 2013[71]	2004–2008	US	USRDS and DaVita	117,050	HD patients	bolus vs maintenance[a]; high vs low (> 200 vs ≤ 200 mg/1 month)	1.08 (1.05–1.11) 1.05 (1.02–1.08)	+
Miskulin 2014[27]	2003–2008	US	USRDS and Dialysis Clinic Inc.	14,078	HD patients	vs >0–150/1 month vs >0–450/3 months vs >0–900/6 months	>350: 1.26 (0.75–2.12) >1050: 1.69 (0.87–3.28) >2100: 1.59 (0.73–3.46)	*
Kuragano 2014[77]	2007–2009	Japan	multicenter-prospective	1,086	HD patients	cumulative weekly dose (vs no iron)	High: 5.22 (2.25–12.14); low: 1.78 (1.04–3.05)	+
Zitt 2014[78]	2000–2007	Austria	prospective	235	incident HD patients	yes vs no	0.31 (0.09–1.04)[b]	−
Bailie 2015[53]	2002–2011	12 countries	DOPPS	32,435	HD patients	average dose over 4 months (mg/month): 0, 1–99, 100–199 (reference), 200–299, 300–399, 400+	≥300: between 0.9–1.4[c]	*
Tangri 2015[68]	2003–2008	US	USRDS and Dialysis Clinic Inc.	9,544	incident HD patients	vs >0–150/1 month vs >0–450/3 months vs >0–900/6 months	>350: 0.91 (0.77–1.09) >1050: 1.08 (0.86–1.36) >2100: 1.26 (0.94–1.69)	*

Note: IV=intravenous; HD=hemodialysis; US=the United States; USRDS=the United States Renal Data System; HR=hazard ratio; CI=confidence interval

[a] Bolus dosing: consecutive doses ≥ 100 mg exceeding 600 mg during one month; maintenance: all other iron doses during the month;

[b] Outcome includes CV-related or sepsis-related mortality;

[c] Obtained from a figure in the article, the exact estimates were not available;

[d] Symbol representation: + = increased risk; − = decreased risk; * = no difference