

2014

Considerations and Challenges in Defining Optimal Iron Utilization in Hemodialysis

D. M. Charytan

A. B. Pai

C. T. Chan

D. W. Coyne

A. M. Hung

*See next page for additional authors*Follow this and additional works at: <https://academicworks.medicine.hofstra.edu/articles> Part of the [Nephrology Commons](#)

Recommended Citation

Charytan D, Pai A, Chan C, Coyne D, Hung A, Kovesdy C, Fishbane S. Considerations and Challenges in Defining Optimal Iron Utilization in Hemodialysis. . 2014 Jan 01; 26(6):Article 2273 [p.]. Available from: <https://academicworks.medicine.hofstra.edu/articles/2273>. Free full text article.

This Article is brought to you for free and open access by Donald and Barbara Zucker School of Medicine Academic Works. It has been accepted for inclusion in Journal Articles by an authorized administrator of Donald and Barbara Zucker School of Medicine Academic Works. For more information, please contact academicworks@hofstra.edu.

Authors

D. M. Charytan, A. B. Pai, C. T. Chan, D. W. Coyne, A. M. Hung, C. P. Kovesdy, and S. Fishbane

JASN

J Am Soc Nephrol. 2015 Jun; 26(6): 1238–1247.
Published online 2014 Dec 26. doi: [10.1681/ASN.2014090922](https://doi.org/10.1681/ASN.2014090922)

PMCID: PMC4446883
PMID: [25542967](https://pubmed.ncbi.nlm.nih.gov/25542967/)

Considerations and Challenges in Defining Optimal Iron Utilization in Hemodialysis

[David M. Charytan](#),^{✉*} [Amy Barton Pai](#),^{†‡} [Christopher T. Chan](#),^{*§} [Daniel W. Coyne](#),^{*||} [Adriana M. Hung](#),^{¶**} [Csaba P. Kovesdy](#),^{¶††} and [Steven Fishbane](#)^{*‡‡}, on behalf of the Dialysis Advisory Group of the American Society of Nephrology

*Renal Division and

¶Nephrology Division, Departments of Medicine and

†Pharmacy Practice, Brigham & Women's Hospital, Boston, Massachusetts;

‡Albany College of Pharmacy and Health Sciences, Albany, New York;

§Toronto General Hospital, University Health Network, Ontario, Canada;

||Washington University, Saint Louis, Missouri;

**Vanderbilt University Medical Center, Nashville, Tennessee;

††University of Tennessee Health Science Center, Memphis, Tennessee; and

‡‡Hofstra North Shore-LIJ School of Medicine, Great Neck, New York

✉Corresponding author.

Correspondence: Dr. David M. Charytan, Renal Division, Brigham & Women's Hospital, 1620 Tremont Street, Third Floor, Boston, MA 02115. Email: dcharytan@partners.org

Copyright © 2015 by the American Society of Nephrology

Abstract

[Go to:](#)

Trials raising concerns about erythropoiesis-stimulating agents, revisions to their labeling, and changes to practice guidelines and dialysis payment systems have provided strong stimuli to decrease erythropoiesis-stimulating agent use and increase intravenous iron administration in recent years. These factors have been associated with a rise in iron utilization, particularly among hemodialysis patients, and an unprecedented increase in serum ferritin concentrations. The mean serum ferritin concentration among United States dialysis patients in 2013 exceeded 800 ng/ml, with 18% of patients exceeding 1200 ng/ml. Although these changes are broad based, the wisdom of these practices is uncertain. Herein, we examine influences on and trends in intravenous iron utilization and assess the clinical trial, epidemiologic, and experimental evidence relevant to its safety and efficacy in the setting of maintenance dialysis. These data suggest a potential for harm from increasing use of parenteral iron in dialysis-dependent patients. In the absence of well powered, randomized clinical trials, available evidence will remain inadequate for making reliable conclusions about the effect of a ubiquitous therapy on mortality or other outcomes of importance to dialysis patients. Nephrology stakeholders have an urgent obligation to initiate well designed investigations of intravenous iron in order to ensure the safety of the dialysis population.

Keywords: dialysis, ESRD, anemia, erythropoietin

Patients with ESRD receive numerous therapeutic interventions, yet the clinical benefits are often questionable. The gold-standard proof of efficacy and safety is a properly planned and conducted randomized controlled trial (RCT). Such trials are largely unavailable for hard clinical end points in patients with ESRD, in whom most interventions are implemented based on extrapolation of results of observational data, RCTs performed in other populations (*e.g.*, treatment of hypertension or diabetes), or

RCTs demonstrating improvement in intermediate or surrogate end points, such as biochemical abnormalities (*e.g.*, hemoglobin, parathyroid hormone, or phosphorous).

Applying treatments without the benefit of conclusive evidence from RCTs is defensible. After all, lack of proof of efficacy does not equal proof of lack of efficacy, and one can easily justify treatment based on favorable observational data or compelling pathophysiologic links between the abnormalities and adverse clinical outcomes. For decades, treatment in ESRD was shaped by this model of thinking, under the assumption that the balance of risks and benefits would surely justify the interventions in question.

More recently, several RCTs suggested that erythropoiesis-stimulating agent (ESA) use could be harmful and failed to confirm prior observational studies and cross-sectional analyses that had consistently shown improved patient outcomes with higher achieved hemoglobin, thereby refuting widely held beliefs about the benefits of anemia therapy.^{1,4} The prospect of an entire generation of patients with ESRD being exposed to potentially harmful effects of high-dose ESA had a chilling effect, with swift regulatory action and consequent changes in clinical practice.² The cautionary tale of ESA therapy has spotlighted other ESRD interventions lacking sufficient RCT-based evidence of hard clinical benefits. Phosphate binder use, secondary hyperparathyroidism therapies, novel arteriovenous fistula cannulation techniques, and changes in duration and dose of dialytic technique have been implemented based on epidemiologic studies or clinical trials powered on unvalidated surrogate end points and beliefs that their benefits would outweigh theoretical risks. However, questions about efficacy^{6,8} and safety² will persist until dispelled by proper evidence from RCTs.

Among the many treatments applied to correct biochemical abnormalities without proper evidence, use of intravenous iron (IVI) for anemia is particularly important because its use in ESRD is rising and nearly universal,¹⁰ and it epitomizes clinical equipoise based on equally plausible arguments suggesting potential benefits and harm in the absence of definitive evidence from RCTs. Given the failure of RCTs to confirm observational associations in the area of anemia, use of observational evidence and surrogate end points to develop guideline statements is questionable and cannot adequately assure the safety of the IVI use now dominant in the United States dialysis population.

In this article, we describe the background upon which IVI use has become ubiquitous, the pros and cons of its application, and most importantly, why the practice of IVI use in ESRD more so than ever demands well powered and properly conducted RCTs.

Secular Trends

[Go to:](#)

The introduction of epoetin in 1989 led to dramatic declines in transfusions and to higher hemoglobin values in dialysis patients.^{11,12} Mean hemoglobin increased from 9.6 g/dl in 1991 to 10.8 g/dl by 1997. The 1997 guidelines by the Dialysis Outcomes Quality Initiative (now the Kidney Diseases Outcomes Quality Initiative [KDOQI]) recommended IVI to support a hemoglobin between 11 and 12 g/dl, maintain ferritin between 100 and 800 ng/ml, and transferrin saturation (TSAT) between 20% and 50%.¹³ Both the 1997 and 2001 guidelines were opinion based given the absence of RCT evidence on long-term safety of targeting higher hemoglobin and ferritin with ESAs or IVI.^{13,14} However, they were a necessary attempt to guide practice given imperfect data and, as described below, were associated with increased use of IVI.

Mean hemoglobin in hemodialysis patients increased from 11.0 g/dl in 1998 to 12.0 g/dl in 2005.¹¹ Mean ferritin was only 302 ng/ml in 1993, and 36% of patients had evidence of iron deficiency as evidenced by serum ferritin <100 ng/ml.¹⁵ By 2001, when KDOQI raised the lower ferritin threshold further to 200 ng/ml, mean ferritin had risen to 526 ng/ml (Figure 1).^{14,16} Mean ferritin reached 586 ng/ml in 2007 with 22% of patients >800 ng/ml.¹⁶ Subsequently, between 2006 and 2010, hemodialysis patients saw modest declines in mean hemoglobin and ESA doses, whereas transfusion rates were unchanged.^{17,19}

These changes were spurred by several factors: reexamination of ESA safety issues first raised by the 1998 Normal Hematocrit Trial^{1,20}; the Correction of Hemoglobin and Outcomes in Renal Insufficiency trial, which demonstrated that targeting a higher hemoglobin with ESA was associated with increased risk of death and cardiovascular events³; a 2007 US Food and Drug Administration (FDA) advisory recommending more conservative ESA use; several analyses suggesting that higher ESA doses *per se* mediated risk^{21,23}; and finally the 2009 Trial to Reduce Cardiovascular Events With Aranesp Therapy, which reported that ESAs did not reduce cardiovascular events or deaths but increased thrombotic risks, and possibly the risk in patients with cancer—a finding highlighted by the results of several oncology trials.^{2,24}

More recently in 2011, the US Centers for Medicare and Medicaid Services instituted a partially capitated payment system for dialysis services that included both ESAs and IVI, which were previously separately billable.²⁵ This provided financial incentives for dialysis providers to reduce utilization of high-cost items like ESAs by increasing use of lower-cost IVI.²⁶ Concurrently, the US FDA revised the ESA label, cautioning against starting ESAs in patients with hemoglobin >10 g/dl, eliminating the 10–12 g/dl hemoglobin target, and recommending the lowest ESA dose necessary to avoid transfusion.^{5,27}

These events were associated with declines in mean hemoglobin and ESA doses, increased transfusions, increased IVI use, and increased iron stores.^{18,28} Data from the Dialysis Outcomes and Practice Patterns Study Practice Monitor showed a decrease in hemoglobin from 11.5 to 11.0 g/dl between August 2010 and December 2011, and to 10.9 g/dl by December 2013.²⁹ Mean weekly ESA dose declined from 19,700 to 10,800 U between August 2010 and December 2013.²⁹ Conversely, mean ferritin increased from 640 to 826 ng/ml from August 2010 to January 2012 and remained stable through December 2013.²⁹ Similarly, the percentage of patients with ferritin >1200 ng/ml increased from 8.6% to 18% of patients.²⁹

Iron Deficiency

[Go to:](#)

Iron is an essential component of hemoglobin, myoglobin, and other enzymes involved in oxidation and reduction.³⁰ Absolute iron deficiency has been associated with wide-ranging systemic effects including fatigue, glossitis, restless legs, and pica and may affect stamina in the absence of overt anemia. Most significantly, sufficient iron availability during development of nascent reticulocytes is necessary for complete hemoglobinization of red blood cells.

Iron deficiency will occur in most hemodialysis patients due to ongoing blood losses from the dialysis circuit, gastrointestinal tract, laboratory testing, and procedures.¹⁴ In addition, inflammation increases hepcidin, thereby reducing intestinal iron absorption and release of iron from stores—a process possibly antagonized by secretion of erythroferrone, a recently identified hormone that appears to suppress hepcidin secretion.^{31,33} Trials have thus repeatedly shown oral iron to be ineffective at treating iron deficiency in the setting of hemodialysis,³⁴ which appears to be due to hepcidin-mediated blockade of iron absorption, ongoing iron losses, and poor patient tolerance. Consequently, guidelines have repeatedly recommended IVI in hemodialysis patients^{13,14,23}—a recommendation consistent with trials demonstrating that administration of IVI increases hemoglobin and reduces ESA dose requirements,^{22,35,36} although whether increasing hemoglobin or reducing ESA dose improves quality of life or reduces morbidity and mortality is unknown.

Assessment of Iron Stores

[Go to:](#)

Ferritin and TSAT, the currently recommended tests to assess iron status in dialysis patients,³⁷ have limitations that make diagnosis of iron deficiency or overload challenging. Ferritin is a positive and transferrin is a negative acute phase reactant.³⁸ This is relevant because inflammation is highly prevalent in the dialysis population.³⁹ Ferritin, a marker of intracellular iron stores, also has sex differences and

important interpersonal variability,⁴⁴ whereas transferrin, the major iron-binding protein in circulation, is affected by protein-energy wasting as well as diurnal variation.

Studies have shown that the sensitivity of the lower TSAT limit of <20% is low (59%–88%).^{41, 43} Similarly, at a cut-off of ≤ 100 ng/ml, the sensitivity of ferritin is 35%–48% (validated against a functional definition of increasing hemoglobin and/or decreasing ESA dose).^{41, 43} At ≤ 200 ng/ml, sensitivity is only 41% (validated against bone marrow biopsy).⁴² Thus, current indices perform poorly—only half of the patients who will respond to additional IVI have a ferritin <100 and a TSAT $\leq 20\%$, functional iron deficiency, or reticuloendothelial blockade. This may explain why people with normal values of TSAT or higher ferritin levels (500–1200 ng/ml) still respond to IVI.³⁵

Ferritin's utility to detect iron overload faces similar challenges. Most hemodialysis patients receiving ESA and IVI supplementation have excessive hepatic iron on magnetic resonance imaging.^{44, 45} In a study that closely followed guidelines for ESA administration and iron supplementation, 80% of the patients had excessive iron in the liver on magnetic resonance imaging and 30% had severe liver iron overload.⁴⁵ A 2009 study including 96 hemodialysis patients using bone marrow biopsy showed that most patients with ferritin levels of >500 ng/ml had higher levels of C-reactive protein and an increased content of bone marrow iron.⁴⁶ In short, the most widely used indices to assess iron stores are currently insufficient to reliably distinguish patients likely to benefit from IVI from those with iron overload. Measurement of bone marrow, hepatic, or myocardial iron stores may provide a means of distinguishing individuals likely to benefit from additional IVI from those likely to be harmed. Similarly, serum hepcidin levels could help to distinguish individuals likely to benefit from IVI versus those in whom alternative approaches (*e.g.*, treatment of inflammation) are likely to be safer or more effective. To date, the reproducibility and clinical utility of these tools for preventing IVI complications remain theoretical and are yet to be established in clinical studies.

Benefits of IVI

[Go to:](#)

It should be noted that the introduction of ESAs and IVI was broadly welcomed by the nephrology community because the requirement for frequent transfusion in the pre-ESA era was associated with important downsides, including iron overload, infections (especially hepatitis C), pretransplant sensitization, and the occasional inability to safely transfuse highly immunized patients. However, whether IVI treatment itself results in improved health is largely unknown. RCTs have not sufficiently evaluated patient-centered outcomes such as mortality, hospitalization, or quality of life. By contrast, surrogate end points such as hemoglobin or ESA dose have been extensively studied. There has also been some limited evaluation of IVI for its effect on restless legs syndrome and other patient symptoms.⁴⁷

With respect to hemoglobin response and ESA dose reduction, the literature is rich and consistent in finding treatment to be efficacious. The first published RCT comparing intravenous and oral iron in hemodialysis patients found a 46% ESA dose reduction with intravenous therapy.⁴⁸ Subsequent studies have been very consistent in finding that regular (often weekly) doses of IVI reduce ESA requirements, although there is less literature on peritoneal dialysis. Largely unanswered questions remain regarding how much iron to administer, the optimal dosing regimen, and targets for iron status tests.

One important trial was the Dialysis Patients' Response to IVI with Elevated Ferritin (DRIVE) study.³⁵ This study broke new ground by testing the efficacy of IVI when administered to individuals with serum ferritin >500 ng/ml and TSAT $\leq 25\%$ and allowed enrollment of individuals with ferritin between 800 and 1200 ng/ml, a level typically used to exclude enrollment in previous IVI trials.^{49, 50} Randomization to IVI resulted in an increase in hemoglobin compared with placebo. A follow-up observational study of DRIVE participants demonstrated that IVI led to a significant reduction in ESA dose requirements and the cost of anemia management.^{36, 51} The study extended previous knowledge by suggesting that IVI treatment improves erythropoietic response to ESA therapy even with fairly high baseline ferritin, but the small

number of participants ($n=134$) and short duration preclude the ability to make definitive safety conclusions.

It is clear that raising ferritin and TSAT with IVI reduces ESA doses and lowers costs, and it is possible that increasing hemoglobin levels with more IVI and fewer ESAs improves outcomes. However, this has not yet been tested in clinical trials, and improving hemoglobin levels in this manner may not actually be beneficial. For example, increasing hemoglobin levels did not improve clinical outcomes in ESA treatment studies (except in the treatment of severe anemia). By contrast, secondary analyses of trial data suggest that higher ESA doses are associated with adverse cardiovascular outcomes,⁵² suggesting that using IVI to reduce ESA doses could have important cardiovascular benefits. Although untested in a nephrology setting, a recent cardiology study may be helpful in this regard. The Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure study randomized 459 patients with congestive heart failure to treatment with intravenous ferric carboxymaltose or placebo.⁵³ After 24 weeks, improvements were found in measures of functional status and quality of life in the IVI group. There was no significant difference in mortality, but there was a trend toward fewer heart failure hospitalizations ($P=0.08$). Findings were similar in the recent Cardiac Compass with Optivol to Negate Future Inpatient Re-Admissions through Monitoring in HF Patients study, which randomized 304 patients with heart failure to ferric carboxymaltose or placebo and demonstrated significant reductions in heart failure hospitalization (hazard ratio, 0.39; 95% confidence interval [95% CI], 0.19 to 0.82; $P=0.01$).⁵⁴ Extrapolation of these findings to hemodialysis patients is difficult, but it does support the potential for important clinical benefits from IVI in the hemodialysis population.

In summary, IVI-induced ESA dose reduction and hemoglobin increase may improve health outcomes, but the putative benefits remain speculative and untested in RCTs. Until the effect of IVI in hemodialysis on mortality, cardiovascular events, hospitalizations, quality of life, or other outcomes is better understood, whether IVI treatment is actually beneficial will remain unknown. A study currently recruiting in the United Kingdom (Proactive IV Iron Therapy in Haemodialysis Patients [PIVOTAL]) is powered for a primary end point of time to all-cause death or a composite of nonfatal cardiovascular events and may prove helpful in this regard. The PIVOTAL study will recruit 2080 patients from >50 sites and will compare the effect of a proactive high-dose with a reactive low-dose regimen of iron sucrose in ESA-treated hemodialysis patients with ferritin <400 $\mu\text{g/L}$ and TSAT <30%.⁵⁵ With a primary end point of time to death or a composite of nonfatal cardiovascular events and secondary end points that include infection and infectious hospitalizations, it is expected that the results will provide crucial insights into the true clinical benefits of IVI in the setting of hemodialysis.

Pharmacology of IVI

[Go to:](#)

Early IVI compounds were formulated as inorganic iron oxyhydroxide complexes but were highly toxic with high incidences of severe hypotension.⁵⁶ Currently available formulations surround the iron oxyhydroxide core with carbohydrate shells of different sizes and polysaccharide branch characteristics and are considered nanoparticles (Table 1).^{57, 58}

Pharmacokinetic analysis of IVI complexes is limited by difficulties in distinguishing IVI formulations from endogenous iron without radiolabeling. Nevertheless, the carbohydrate shell clearly determines the relative uptake by endothelial and lymphatic cells as well as the reticuloendothelial system (RES).⁵⁸ This results in longer plasma residence times with higher doses, especially with larger molecular weight formulations.^{59, 60} Thus, doses above the RES capacity will remain circulating until the concentration falls below the capacity limit, at which point the pharmacokinetics become linear or concentration independent. Given their complexity, these agents have not been sufficiently studied with regard to comparative biodistribution, metabolic fate, and potential extracellular and intracellular toxicity.

In Vitro Safety Signals

[Go to:](#)

The transient release of labile iron directly into plasma (*i.e.*, before metabolism by RES) is more likely with smaller carbohydrate shells and results in transient concentrations of labile plasma iron and formation of highly reactive free radicals such as the hydroxyl radical that uniquely limits the maximum dose that can be administered with each formulation (Table 2).^{61,63} Not surprisingly, IVI formulations have been shown to induce oxidative stress, inflammation and cellular toxicity, pro-oxidant cell signaling, tissue inflammation, cellular iron deposition, and cytotoxicity in cell culture models, animal models, and acutely in human participants^{63,67} with more labile compounds inducing more toxicity than those with larger carbohydrate shells.^{68,69} IVI has also been associated with immune dysfunction, augmentation of bacterial growth, and increased Gram-positive bacteria growth *in vitro*.^{67,69,71} Taken collectively, these studies underscore the need for comprehensive clinical and translational investigations to evaluate the effect of differences in formulation, pharmacokinetic, and pharmacodynamic characteristics and to determine whether repeated induction of oxidative stress from IVI has long-term sequelae.

Safety Signals in Clinical Trials

[Go to:](#)

Although well powered studies of sufficient duration are not yet available, examination of previously reported studies, even without the power or duration of necessary follow-up, provide at least a cursory understanding for whether any safety signal is present with IVI treatment. The easiest adverse effect of IVI to assess is anaphylaxis, because of its immediacy and severity. The most helpful study in this regard was reported by Michael *et al.* A total of 2534 hemodialysis patients were directly observed after double-blind exposure to intravenous sodium ferric gluconate (SFGC) or placebo.⁵⁰ One patient in each of the SFGC and placebo groups experienced anaphylactoid reactions. Additional cases with characteristics possibly consistent with anaphylaxis occurred in 0.4% of intravenous SFGC-treated patients and 0.1% of placebo-treated patients. The results suggest that there is a relatively low rate of anaphylaxis with nondextran irons and that the reactions are generally easily managed. Relatively large, but nonrandomized, clinical trials are consistent with a similar safety profile for iron sucrose therapy,⁴⁹ although this and other studies have been less helpful for assessing anaphylaxis due to the lack of placebo controls, direct observation, under-reporting, or use of inappropriate data sources to assess end points.

It is more difficult to assess long-term safety although some information on end-organ effects, cardiovascular events, and infection risk can be gleaned from available clinical trials, with the understanding that they were underpowered or had insufficient duration of follow-up for reliable conclusions. For example, in the recently reported Ferinject assessment in patients with Iron Deficiency Anemia and Non-Dialysis-Dependent Chronic Kidney Disease (FIND-CKD) study, 626 patients with predialysis CKD were treated with intravenous ferric carboxymaltose (with a high and low ferritin target) or oral iron for 52 weeks. The percentage of deaths, myocardial infarctions, and infections was not significantly different between oral iron-treated and IVI-treated patients. However, the study was not powered for safety.⁷² Similarly, a 2008 meta-analysis comparing IVI to oral iron by Rozen-Zvi *et al.* included seven dialysis studies,³⁴ but only one had >100 patients and none had treatment periods >6 months. The authors noted additionally that data related to safety (mortality rate) were sparse. Finally, the 6-week DRIVE trial and its 6-week follow-up DRIVE II trial randomized only 57 participants with ferritin >800 ng/ml.^{35,36} Taken together, we would conclude that the clinical trial literature on IVI in hemodialysis has insufficient patients followed for an insufficient length of time to fully assess the long-term safety of IVI treatment, particularly when used in individuals with serum ferritin >800 ng/ml.

Safety Signals in Epidemiology Studies

[Go to:](#)

Observational studies provide an important alternative to RCTs for assessing the safety of IVI, despite a greater susceptibility to confounding and bias. A 2002 study by Feldman *et al.* used the US Renal Data System (USRDS) Dialysis Morbidity and Mortality Studies waves 1, 3, and 4 to analyze the safety of IVI. Among 10,169 patients, those with bills submitted for >10 vials of iron dextran over a 6-month period

were found to have increased risks of death (adjusted relative risk, 1.11; 95% CI, 1.00 to 1.24) and hospitalization (adjusted relative risk, 1.12; 95% CI, 1.01 to 1.25) than those without any submitted bills.⁷³ A subsequent analysis of 32,566 Fresenius Inc. hemodialysis patients by the same authors did not confirm an association between IVI dose and risk of death after adjusting for time-varying measures of iron treatment and fixed and time-varying measures of morbidity,⁷⁴ whereas a study by Kaysen *et al.* of 59,840 prevalent hemodialysis patients found that use of IVI was associated with a 22% reduction in mortality.⁷⁵

More recently, Kalantar-Zadeh *et al.* studied 58,058 DaVita Inc. dialysis patients. For patients who received <400 mg of IVI per month, the risk for death was found to be lower compared with patients with no IVI administered. By contrast, doses >400 mg per month were associated with increased risks of death.⁷⁶ Subsequently, Kshirsagar *et al.* studied 117,050 hemodialysis patients. No association was found between dose of IVI and short-term risk of myocardial infarction, stroke, or death.⁷⁷ By contrast, a much smaller observational study found dose-related increases in risks of cardiovascular events and death with intravenous ferric chloride hexahydrate—a product not currently in use in the United States.⁷⁸

The relationship between IVI and infection is another area of interest. Previously published studies have had mixed results. A prospective observational study by Hoen *et al.* followed 988 hemodialysis patients from 19 French centers for 6 months. There were 51 episodes of bacteremia, but no association with either IVI dosing or serum ferritin concentration was detected.⁷⁹ Brookhart *et al.* recently used DaVita data to study 117,050 hemodialysis patients. Patients with higher compared with lower doses had a slightly but significantly greater risk of infection-related hospitalization or death (hazard ratio, 1.05; 95% CI, 1.02 to 1.08), whereas individuals with the combination of high serum ferritin and high iron saturations at baseline had the highest risk of infection-related hospitalizations. Brookhart *et al.* also found that compared with maintenance therapy, bolus treatment was associated with a greater risk of infection (risk difference, 25 additional events per 1000 patient-years; 95% CI, 16 to 33).⁸⁰

On balance, these studies have conflicting signals and do not establish a clear relationship between IVI dosing and mortality. Better studies of the associations of outcomes, particularly infection, with dose and pattern of administration are clearly needed. Dose-related safety information is particularly necessary given that the above studies analyzed data partly or wholly predating contemporary increases in serum ferritin and iron utilization.²⁹ For example, >75% of participants in the study by Brookhart *et al.* had baseline ferritin <700 ng/ml.⁸⁰ To our knowledge, the long-term effect of IVI administration to patients with elevated baseline serum ferritin levels upon surrogate markers of atherosclerosis, immune function, inflammation, and vascular reactivity also remain unstudied. However, a recent study in which 19 of 21 (90.5%) long-term dialysis patients with serum ferritin >1000 ng/ml had evidence of increased oxidative stress as well as splenic and hepatic tissue iron overload⁴⁴ suggests caution.

Clinical Ramifications

[Go to:](#)

As reviewed above, clinical trials have failed to study the long-term consequences of contemporary IVI utilization,⁸¹ whereas epidemiologic studies raise questions regarding effects on mortality, cardiovascular outcomes, infections, and tissue deposition, and *in vitro* experiments support the notion that IVI exacerbates oxidative stress, inflammation, and endothelial dysfunction.^{78, 82} Despite clear clinical ramifications, data remain insufficient to make firm recommendations regarding the maximum single, weekly, or cumulative dose of IVI or to support a particular limit of iron indices above which iron administration is clearly contraindicated. Given current levels of exposure to IVI, these data raise the possibility of large-scale harm to dialysis patients from current practices. However, it remains unclear whether reducing IVI use would actually improve cardiovascular or infectious outcomes or conversely whether it would potentially increase transfusion rates, thereby resulting in harm. In short, there is compelling public health rationale for prioritizing a judicious examination of risk versus benefits of IVI.

The escalating trends in IVI use should also make one consider the pressures that drive changes in prescribing behavior in dialysis care. Guidelines and clinical judgements driven by ESA trials have stimulated decreased ESA with broader utilization of IVI for ESA sparing. Coupled with payment pressures (particularly given beliefs that because adverse events associated with IVI are rare, high-dose IVI would be innocuous⁸³), these concerns have driven practices that have not undergone proper safety evaluation. These factors are especially prominent with IVI, but they are hardly unique and are arguably broadly representative of the influences on ESRD care.

The case of IVI thus appears to represent an undesirable paradigm in which initial studies and an imperfect evidence base without appropriate RCTs and guideline-based practices (potentially not appropriate for individual patients) have converged with financial incentives to dialysis units, Medicare quality parameters, and the potential for rapid adoption given the dominance of large and medium dialysis organizations to quickly drive drug utilization well beyond the space in which the risk versus benefit ratio has been adequately defined. Caution is needed, especially (although not exclusively) in anemia management, in which recent definitive RCTs had divergent results from earlier, encouraging observational studies.^{1,4,84} Performing the needed studies to define best practices may represent an opportunity to not only redefine utilization of IVI but to also transform the overall model of ESRD care.

Recommendations

[Go to:](#)

There is considerable uncertainty regarding whether contemporary patterns of IVI utilization result in improved patient-level outcomes and not just an improvement in anemia. Although analysis of large databases provides the best means of detecting rare adverse effects of IVI,⁸⁵ the current situation provides urgent justification for ESRD stakeholders to fund the large RCTs designed to provide gold-standard answers to basic safety questions about a widely used therapy.

The highest priority should be given to RCTs, like the PIVOTAL study,⁵⁵ that are designed to compare the effect of conservative and liberal strategies of IVI administration, to compare the safety of bolus and maintenance dosing strategies, and to understand the utility of standard or novel biomarkers of iron stores for detecting iron deficiency and avoiding iron overload and iron-related morbidity in hemodialysis ([Table 3](#)). These trials must be powered to detect differences in mortality, cardiovascular events, infections, and hospitalizations. Given the larger size of the hemodialysis population as well as the greater losses of blood and higher utilization of iron in hemodialysis compared with peritoneal dialysis, priority should be given to studies of the hemodialysis population. Nevertheless, similar considerations apply peritoneal dialysis, and studies in this population may also be necessary.

The joint influences of inadequate studies, practice guidelines, the delivery of care in large organizations, and strong financial incentives to these organizations have at times driven dialysis care in directions that may have harmed generations of patients with ESRD. Changes in iron utilization represent yet another predictable outcome of those influences. The uncertain safety presents the nephrology community with a critical opportunity to demand RCTs with patient-level outcomes and to ensure that there is adequate science in this and other areas of dialysis practice to make evidence-based practice the primary determinant of our treatment algorithms and to fully realize our ethical and professional obligations to provide safe and effective care to our patients.

Disclosures

[Go to:](#)

D.M.C. reports consulting fees from Keryx Biopharmaceuticals, research and clinical support from Medtronic, and expert witness fees from Fresenius. A.B.P. reports consulting fees from Keryx. C.T.C. is a consultant for Baxter Global and Intelomed. D.W.C. reports consulting fees and/or research funding from Keryx Biopharmaceuticals, Rockwell Medical, Fresenius North America, Hospira, Fibrogen, GlaxoSmithKline, and AbbVie, and is involved in suits related to the overuse and abuse of ESAs, IVI, and

vitamin D in dialysis patients. C.P.K. reports consulting fees from Amgen. S.F. reports consulting and research funding from Keryx Biopharmaceuticals and consulting and research funding from Rockwell Inc.

Acknowledgments

[Go to:](#)

We thank Kristen Ward, Jan Deane, and Jay Wish from ESRD Network 11 for their assistance in obtaining the annual mean ferritin data.

The authors acknowledge support from the National Institutes of Health (grants DK096189, HL11831402, and DK100772 to D.M.C.; U01-FD004889 to A.B.P.; R01-DK091288 to C.T.C.; and R01-DK096920 and U01-DK102163 to C.P.K.), the Baxter CEC grant program (to C.T.C.), and the US Department of Veterans Affairs Office of Clinical Science Research and Development (Career Development Award CDA2-031-09S to A.M.H.).

The opinions expressed in this article are those of the authors and are not necessarily the opinions of their institutions or of all of the members of the American Society of Nephrology (ASN). The members of the ASN's Dialysis Advisory Groups and Communication Committee reviewed this article before submission.

The following individuals were members of the ASN Dialysis Advisory Group at the time of writing this article: Gregory L. Braden (Springfield, MA), Christopher T. Chan (Toronto, ON, Canada), David M. Charytan (Boston, MA), Michael J. Fischer (Chicago, IL), Jennifer E. Flythe (Chapel Hill, NC), Vanessa Grubbs (San Francisco, CA), LaTonya Hickson (Rochester, MN), Adriana M. Hung (Nashville, TN), Frank Hurst (Silver Spring, MD), Timmy C. Lee (Birmingham, AL), Mark Lukaszewski (Washington, DC; ASN staff), Rajnish Mehrotra (Seattle, WA; Advisory Group Chair), Timothy W. Meyer (Palo Alto, CA), Sharon M. Moe (Indianapolis, IN; ASN Council Liaison), Amy Barton Pai (Albany, NY), Jeffrey Perl (Toronto, Ontario), Shuvo Roy (San Francisco, CA), Michael J. Somers (Boston, MA), John Stivelman (Seattle, WA), Isaac Teitelbaum (Denver, CO), and Leslie Wong (Cleveland, OH).

Footnotes

[Go to:](#)

Published online ahead of print. Publication date available at www.jasn.org.

References

[Go to:](#)

1. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 339: 584–590, 1998 [PubMed: 9718377]
2. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJ, Parfrey P, Parving HH, Remuzzi G, Singh AK, Solomon SD, Toto R, TREAT Investigators : A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 361: 2019–2032, 2009 [PubMed: 19880844]
3. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D, CHOIR Investigators : Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 355: 2085–2098, 2006 [PubMed: 17108343]
4. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A, CREATE Investigators : Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 355: 2071–2084, 2006 [PubMed: 17108342]
5. US Food and Drug Administration: US FDA drug safety communication: Modified dosing recommendations to improve the safe use of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease, 2011. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm>. Accessed June 11, 2014

6. Suki WN, Zabaneh R, Cangiano JL, Reed J, Fischer D, Garrett L, Ling BN, Chasan-Taber S, Dillon MA, Blair AT, Burke SK: Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 72: 1130–1137, 2007 [PubMed: 17728707]
7. Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Floege J, Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW, Mix TC, Moe SM, Trotman ML, Wheeler DC, Parfrey PS, EVOLVE Trial Investigators : Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 367: 2482–2494, 2012 [PubMed: 23121374]
8. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, Mujais S, Mexican Nephrology Collaborative Study Group : Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol* 13: 1307–1320, 2002 [PubMed: 11961019]
9. Nesrallah GE, Cuerden M, Wong JH, Pierratos A: Staphylococcus aureus bacteremia and buttonhole cannulation: Long-term safety and efficacy of mupirocin prophylaxis. *Clin J Am Soc Nephrol* 5: 1047–1053, 2010 [PMCID: PMC2879300] [PubMed: 20413438]
10. Hirth RA, Turenne MN, Wheeler JR, Nahra TA, Sleeman KK, Zhang W, Messana JA: The initial impact of Medicare’s new prospective payment system for kidney dialysis. *Am J Kidney Dis* 62: 662–669, 2013 [PubMed: 23769138]
11. US Renal Data System : USRDS 2008 Annual Data Report: Atlas of End Stage Renal Disease in the United States, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2008
12. Coyne DW, Brennan DC: Seeking safe and efficacious anemia management. *Semin Dial* 22: 590–591, 2009 [PubMed: 19744148]
13. National Kidney Foundation–Dialysis Outcomes Quality Initiative : NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. *Am J Kidney Dis* 30[Suppl 3]: S192–S240, 1997 [PubMed: 9339151]
14. KDOQI : IV. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: Update 2000. *Am J Kidney Dis* 37[Suppl 1]: S182–S238, 2001 [PubMed: 11229970]
15. US Renal Data System : USRDS 1996 Annual Data Report, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1996
16. US Centers for Medicare and Medicaid Services: 2008 Annual Report, End Stage Renal Disease Clinical Performance Measures Project, Baltimore, MD, US Department of Health and Human Services, US Centers for Medicare and Medicaid Service Office of Clinical Standards and Quality, 2008
17. Freburger JK, Ng LJ, Bradbury BD, Kshirsagar AV, Brookhart MA: Changing patterns of anemia management in US hemodialysis patients. *Am J Med* 125: 906.e9–914.e9, 2012 [PubMed: 22938926]
18. Collins AJ, Monda KL, Molony JT, Li S, Gilbertson DT, Bradbury BD: Effect of facility-level hemoglobin concentration on dialysis patient risk of transfusion. *Am J Kidney Dis* 63: 997–1006, 2014 [PubMed: 24315770]
19. Thamer M, Zhang Y, Lai D, Kshirsagar O, Cotter D: Influence of safety warnings on ESA prescribing among dialysis patients using an interrupted time series. *BMC Nephrol* 14: 172, 2013 [PMCID: PMC3751481] [PubMed: 23927675]
20. Coyne DW: The health-related quality of life was not improved by targeting higher hemoglobin in the Normal Hematocrit Trial. *Kidney Int* 82: 235–241, 2012 [PMCID: PMC3388517] [PubMed: 22437411]

21. US Food and Drug Administration: Public Health Advisory: Erythropoiesis-Stimulating Agents (ESAs): Epoetin alfa (marketed as Procrit, Epogen), Darbepoetin alfa (marketed as Aranesp), 2007. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm054721.htm>. Accessed March 19, 2007
22. Susantitaphong P, Alqahtani F, Jaber BL: Efficacy and safety of intravenous iron therapy for functional iron deficiency anemia in hemodialysis patients: A meta-analysis. *Am J Nephrol* 39: 130–141, 2014 [PubMed: 24513913]
23. Kidney Disease Improving Global Outcomes: KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int* 2: 279–335, 2012
24. Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, Zwahlen M, Clarke MJ, Weingart O, Kluge S, Piper M, Napoli M, Rades D, Steensma D, Djulbegovic B, Fey MF, Ray-Coquard I, Moebus V, Thomas G, Untch M, Schumacher M, Egger M, Engert A: Erythropoietin or Darbepoetin for patients with cancer—meta-analysis based on individual patient data. *Cochrane Database Syst Rev* (3): CD007303, 2009 [PubMed: 19588423]
25. Centers for Medicare & Medicaid Services, HHS : Medicare Program; end-stage renal disease prospective payment system. Final rule. *Fed Regist* 75: 49029–49214, 2010 [PubMed: 20712086]
26. Weiner DE, Winkelmayr WC: Commentary on ‘The DOPPS practice monitor for U.S. dialysis care: Update on trends in anemia management 2 years into the bundle’: Iron(y) abounds 2 years later. *Am J Kidney Dis* 62: 1217–1220, 2013 [PubMed: 24267389]
27. Epogen: Epogen Package Insert. US Food and Drug Administration, June 24, 2011
28. Fuller DS, Pisoni RL, Bieber BA, Port FK, Robinson BM: The DOPPS practice monitor for U.S. dialysis care: Update on trends in anemia management 2 years into the bundle. *Am J Kidney Dis* 62: 1213–1216, 2013 [PubMed: 24140369]
29. Arbor Research Collaborative for Health : DOPPS Practice Monitor, Ann Arbor, MI, Arbor Research Collaborative for Health, 2014
30. Ganz T, Nemeth E: Heparin and disorders of iron metabolism. *Annu Rev Med* 62: 347–360, 2011 [PubMed: 20887198]
31. Ganz T: Systemic iron homeostasis. *Physiol Rev* 93: 1721–1741, 2013 [PubMed: 24137020]
32. Coyne DW: Heparin: Clinical utility as a diagnostic tool and therapeutic target. *Kidney Int* 80: 240–244, 2011 [PubMed: 21677632]
33. Kautz L, Jung G, Valore EV, Rivella S, Nemeth E, Ganz T: Identification of erythroferrone as an erythroid regulator of iron metabolism. *Nat Genet* 46: 678–684, 2014 [PMCID: PMC4104984] [PubMed: 24880340]
34. Rozen-Zvi B, Gaftor-Gvili A, Paul M, Leibovici L, Shpilberg O, Gaftor U: Intravenous versus oral iron supplementation for the treatment of anemia in CKD: Systematic review and meta-analysis. *Am J Kidney Dis* 52: 897–906, 2008 [PubMed: 18845368]
35. Coyne DW, Kapoian T, Suki W, Singh AK, Moran JE, Dahl NV, Rizkala AR, DRIVE Study Group : Ferric gluconate is highly efficacious in anemic 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* 18: 975–984, 2007 [PubMed: 17267740]

36. Kapoian T, O'Mara NB, Singh AK, Moran J, Rizkala AR, Geronemus R, Kopelman RC, Dahl NV, Coyne DW: Ferric gluconate reduces epoetin requirements in hemodialysis patients with elevated ferritin. *J Am Soc Nephrol* 19: 372–379, 2008 [PMCID: PMC2396742] [PubMed: 18216316]
37. Kidney Disease Improving Global Outcomes : KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease: Summary of recommendation statements. *Kidney Int Suppl* 2: 283–287, 2012
38. Gabay C, Kushner I: Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 340: 448–454, 1999 [PubMed: 9971870]
39. Hung A, Pupim L, Yu C, Shintani A, Siew E, Ayus C, Hakim RM, Ikizler TA: Determinants of C-reactive protein in chronic hemodialysis patients: Relevance of dialysis catheter utilization. *Hemodial Int* 12: 236–243, 2008 [PubMed: 18394058]
40. Canavese C, Bergamo D, Ciccone G, Longo F, Fop F, Thea A, Martina G, Piga A: Validation of serum ferritin values by magnetic susceptometry in predicting iron overload in dialysis patients. *Kidney Int* 65: 1091–1098, 2004 [PubMed: 14871430]
41. Fishbane S, Kowalski EA, Imbriano LJ, Maesaka JK: The evaluation of iron status in hemodialysis patients. *J Am Soc Nephrol* 7: 2654–2657, 1996 [PubMed: 8989744]
42. Kalantar-Zadeh K, Höffken B, Wunsch H, Fink H, Kleiner M, Luft FC: Diagnosis of iron deficiency anemia in renal failure patients during the post-erythropoietin era. *Am J Kidney Dis* 26: 292–299, 1995 [PubMed: 7645533]
43. Tessitore N, Solero GP, Lippi G, Bassi A, Faccini GB, Bedogna V, Gammara L, Brocco G, Restivo G, Bernich P, Lupo A, Maschio G: The role of iron status markers in predicting response to intravenous iron in haemodialysis patients on maintenance erythropoietin. *Nephrol Dial Transplant* 16: 1416–1423, 2001 [PubMed: 11427634]
44. Ghoti H, Rachmilewitz EA, Simon-Lopez R, Gaber R, Katzir Z, Konen E, Kushnir T, Girelli D, Campostrini N, Fibach E, Goitein O: Evidence for tissue iron overload in long-term hemodialysis patients and the impact of withdrawing parenteral iron. *Eur J Haematol* 89: 87–93, 2012 [PubMed: 22435497]
45. Rostoker G, Griuncelli M, Loridon C, Couprie R, Benmaadi A, Bounhiol C, Roy M, Machado G, Jankiewicz P, Drahi G, Dahan H, Cohen Y: Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: A MRI study. *Am J Med* 125: 991.e1–999.e1, 2012 [PubMed: 22998881]
46. Rocha LA, Barreto DV, Barreto FC, Dias CB, Moysés R, Silva MR, Moura LA, Draibe SA, Jorgetti V, Carvalho AB, Canziani ME: Serum ferritin level remains a reliable marker of bone marrow iron stores evaluated by histomorphometry in hemodialysis patients. *Clin J Am Soc Nephrol* 4: 105–109, 2009 [PMCID: PMC2615700] [PubMed: 18842949]
47. Sloand JA, Shelly MA, Feigin A, Bernstein P, Monk RD: A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. *Am J Kidney Dis* 43: 663–670, 2004 [PubMed: 15042543]
48. Fishbane S, Frei GL, Maesaka J: Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. *Am J Kidney Dis* 26: 41–46, 1995 [PubMed: 7611266]
49. Aronoff GR, Bennett WM, Blumenthal S, Charytan C, Pennell JP, Reed J, Rothstein M, Strom J, Wolfe A, Van Wyck D, Yee J, United States Iron Sucrose (Venofer) Clinical Trials Group : Iron sucrose in hemodialysis patients: Safety of replacement and maintenance regimens. *Kidney Int* 66: 1193–1198, 2004 [PubMed: 15327417]

50. Michael B, Coyne DW, Fishbane S, Folkert V, Lynn R, Nissenson AR, Agarwal R, Eschbach JW, Fadem SZ, Trout JR, Strobos J, Warnock DG, Ferrlecit Publication Committee : Sodium ferric gluconate complex in hemodialysis patients: Adverse reactions compared to placebo and iron dextran. *Kidney Int* 61: 1830–1839, 2002 [PubMed: 11967034]
51. Pizzi LT, Bunz TJ, Coyne DW, Goldfarb DS, Singh AK: Ferric gluconate treatment provides cost savings in patients with high ferritin and low transferrin saturation. *Kidney Int* 74: 1588–1595, 2008 [PubMed: 19034302]
52. Szczech LA, Barnhart HX, Inrig JK, Reddan DN, Sapp S, Califf RM, Patel UD, Singh AK: Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney Int* 74: 791–798, 2008 [PMCID: PMC2902279] [PubMed: 18596733]
53. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P, FAIR-HF Trial Investigators : Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 361: 2436–2448, 2009 [PubMed: 19920054]
54. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD, CONFIRM-HF Investigators : Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency [published online ahead of print August 31, 2014]. *Eur Heart J* 10.1093/eurheartj/ehu385 [PMCID: PMC4359359]
55. EU Clinical Trials Register: Proactive IV Iron Therapy for Haemodialysis Patients (PIVOTAL), 2013. Available at: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002267-25/GB>. Accessed June 27, 2014
56. Danielson BG: Structure, chemistry, and pharmacokinetics of intravenous iron agents. *J Am Soc Nephrol* 15[Suppl 2]: S93–S98, 2004 [PubMed: 15585603]
57. Jahn MR, Andreasen HB, Futterer S, Nawroth T, Schunemann V, Kolb U, Hofmeister W, Munoz M, Bock K, Meldal M, Langguth P: A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer), a new intravenous iron preparation and its clinical implications. *Eur J Pharm Biopharm* 78: 480–491, 2011 [PubMed: 21439379]
58. Duncan R, Gaspar R: Nanomedicine(s) under the microscope. *Mol Pharm* 8: 2101–2141, 2011 [PubMed: 21974749]
59. Pai AB, Nielsen JC, Kausz A, Miller P, Owen JS: Plasma pharmacokinetics of two consecutive doses of ferumoxytol in healthy subjects. *Clin Pharmacol Ther* 88: 237–242, 2010 [PubMed: 20592725]
60. Henderson PA, Hillman RS: Characteristics of iron dextran utilization in man. *Blood* 34: 357–375, 1969 [PubMed: 5804025]
61. Cabantchik ZI: Labile iron in cells and body fluids: Physiology, pathology, and pharmacology. *Front Pharmacol* 5: 45, 2014 [PMCID: PMC3952030] [PubMed: 24659969]
62. Pai AB, Boyd AV, McQuade CR, Harford A, Norenberg JP, Zager PG: Comparison of oxidative stress markers after intravenous administration of iron dextran, sodium ferric gluconate, and iron sucrose in patients undergoing hemodialysis. *Pharmacotherapy* 27: 343–350, 2007 [PubMed: 17316146]
63. Balakrishnan VS, Rao M, Kausz AT, Brenner L, Pereira BJ, Frigo TB, Lewis JM: Physicochemical properties of ferumoxytol, a new intravenous iron preparation. *Eur J Clin Invest* 39: 489–496, 2009 [PubMed: 19397688]

64. Zager RA, Johnson AC, Hanson SY, Wasse H: Parenteral iron formulations: A comparative toxicologic analysis and mechanisms of cell injury. *Am J Kidney Dis* 40: 90–103, 2002 [PubMed: 12087566]
65. Toblli JE, Cao G, Oliveri L, Angerosa M: Assessment of the extent of oxidative stress induced by intravenous ferumoxytol, ferric carboxymaltose, iron sucrose and iron dextran in a nonclinical model. *Arzneimittelforschung* 61: 399–410, 2011 [PubMed: 21899208]
66. Lim CS, Vaziri ND: The effects of iron dextran on the oxidative stress in cardiovascular tissues of rats with chronic renal failure. *Kidney Int* 65: 1802–1809, 2004 [PubMed: 15086920]
67. Fishbane S, Mathew A, Vaziri ND: Iron toxicity: Relevance for dialysis patients. *Nephrol Dial Transplant* 29: 255–259, 2014 [PubMed: 24166458]
68. Johnson AC, Becker K, Zager RA: Parenteral iron formulations differentially affect MCP-1, HO-1, and NGAL gene expression and renal responses to injury. *Am J Physiol Renal Physiol* 299: F426–F435, 2010 [PMCID: PMC2928522] [PubMed: 20504881]
69. Gupta A, Zhuo J, Zha J, Reddy S, Olp J, Pai A: Effect of different intravenous iron preparations on lymphocyte intracellular reactive oxygen species generation and subpopulation survival. *BMC Nephrol* 11: 16, 2010 [PMCID: PMC2933673] [PubMed: 20716362]
70. Parkkinen J, von Bonsdorff L, Peltonen S, Gronhagen-Riska C, Rosenlof K: Catalytically active iron and bacterial growth in serum of haemodialysis patients after i.v. iron-saccharate administration. *Nephrol Dial Transplant* 15: 1827–1834, 2000 [PubMed: 11071973]
71. Barton Pai A, Pai MP, Depczynski J, McQuade CR, Mercier RC: Non-transferrin-bound iron is associated with enhanced *Staphylococcus aureus* growth in hemodialysis patients receiving intravenous iron sucrose. *Am J Nephrol* 26: 304–309, 2006 [PubMed: 16809897]
72. Macdougall IC, Bock AH, Carrera F, Eckardt KU, Gaillard C, Van Wyck D, Roubert B, Nolen JG, Roger SD, FIND-CKD Study Investigators : 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* 29: 2075–2084, 2014 [PMCID: PMC4209879] [PubMed: 24891437]
73. Feldman HI, Santanna J, Guo W, Furst H, Franklin E, Joffe M, Marcus S, Faich G: Iron administration and clinical outcomes in hemodialysis patients. *J Am Soc Nephrol* 13: 734–744, 2002 [PubMed: 11856779]
74. Feldman HI, Joffe M, Robinson B, Knauss J, Cizman B, Guo W, Franklin-Becker E, Faich G: Administration of parenteral iron and mortality among hemodialysis patients. *J Am Soc Nephrol* 15: 1623–1632, 2004 [PubMed: 15153574]
75. Kaysen GA, Müller HG, Ding J, Chertow GM: Challenging the validity of the EPO index. *Am J Kidney Dis* 47: 166, 2006 [PubMed: 16377397]
76. Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG: Time-dependent associations between iron and mortality in hemodialysis patients. *J Am Soc Nephrol* 16: 3070–3080, 2005 [PubMed: 16033854]
77. Kshirsagar AV, Freburger JK, Ellis AR, Wang L, Winkelmayr WC, Brookhart MA: Intravenous iron supplementation practices and short-term risk of cardiovascular events in hemodialysis patients. *PLoS ONE* 8: e78930, 2013 [PMCID: PMC3815308] [PubMed: 24223866]
78. Kuo KL, Hung SC, Lin YP, Tang CF, Lee TS, Lin CP, Tarng DC: Intravenous ferric chloride hexahydrate supplementation induced endothelial dysfunction and increased cardiovascular risk among hemodialysis patients. *PLoS ONE* 7: e50295, 2012 [PMCID: PMC3515606] [PubMed: 23227165]

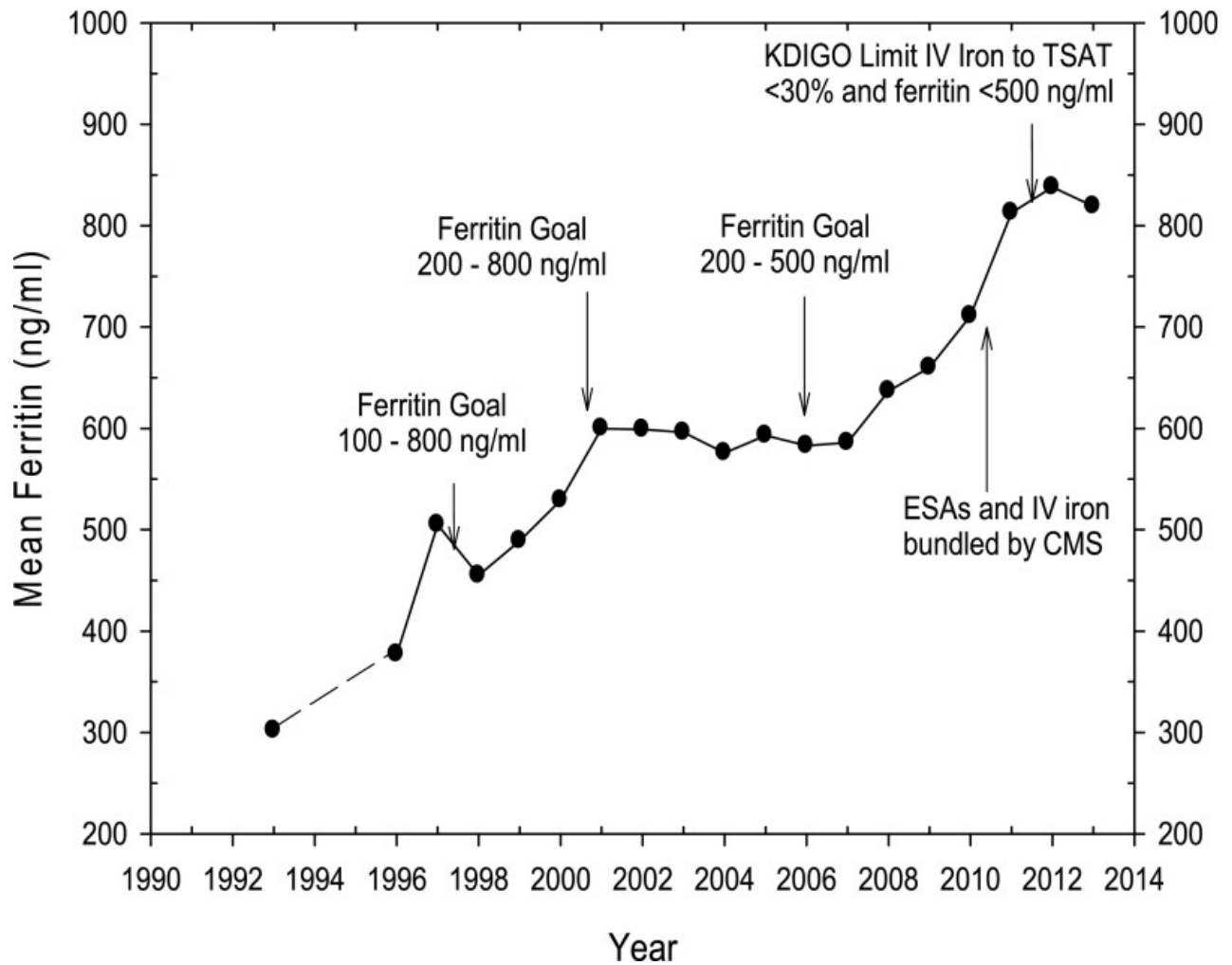
79. Hoen B, Paul-Dauphin A, Hestin D, Kessler M: EPIBACDIAL: A multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J Am Soc Nephrol* 9: 869–876, 1998 [PubMed: 9596085]
80. Brookhart MA, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Kshirsagar AV: Infection risk with bolus versus maintenance iron supplementation in hemodialysis patients. *J Am Soc Nephrol* 24: 1151–1158, 2013 [PMCID: PMC3699831] [PubMed: 23787911]
81. Kliger AS, Foley RN, Goldfarb DS, Goldstein SL, Johansen K, Singh A, Szczech L: KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. *Am J Kidney Dis* 62: 849–859, 2013 [PubMed: 23891356]
82. Kuo KL, Hung SC, Wei YH, Tarng DC: Intravenous iron exacerbates oxidative DNA damage in peripheral blood lymphocytes in chronic hemodialysis patients. *J Am Soc Nephrol* 19: 1817–1826, 2008 [PMCID: PMC2518435] [PubMed: 18495964]
83. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J: Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant* 21: 378–382, 2006 [PubMed: 16286429]
84. Foley RN, Parfrey PS, Morgan J, Barré PE, Campbell P, Cartier P, Coyle D, Fine A, Handa P, Kingma I, Lau CY, Levin A, Mendelssohn D, Muirhead N, Murphy B, Plante RK, Posen G, Wells GA: Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 58: 1325–1335, 2000 [PubMed: 10972697]
85. Charytan C, Bernardo MV, Koch TA, Butcher A, Morris D, Bregman DB: Intravenous ferric carboxymaltose versus standard medical care in the treatment of iron deficiency anemia in patients with chronic kidney disease: A randomized, active-controlled, multi-center study. *Nephrol Dial Transplant* 28: 953–964, 2013 [PubMed: 23222534]
86. Renal Network of the Upper Midwest Inc : Elab 2011 National and Trend Report, Saint Paul, MN, Renal Network of the Upper Midwest Inc, 2011
87. Auerbach M, Winchester J, Wahab A, Richards K, McGinley M, Hall F, Anderson J, Briefel G: A randomized trial of three iron dextran infusion methods for anemia in EPO-treated dialysis patients. *Am J Kidney Dis* 31: 81–86, 1998 [PubMed: 9428456]
88. Rodgers GM, Auerbach M, Cella D, Chertow GM, Coyne DW, Glaspy JA, Henry DH: High-molecular weight iron dextran: A wolf in sheep's clothing? *J Am Soc Nephrol* 19: 833–834, 2008 [PubMed: 18369084]
89. Auerbach M, Ballard H: Clinical use of intravenous iron: Administration, efficacy, and safety. *Hematology Am Soc Hematol Educ Program* 2010: 338–347, 2010 [PubMed: 21239816]
90. Folkert VW, Michael B, Agarwal R, Coyne DW, Dahl N, Myirski P, Warnock DG, Ferrlecit Publication Committee : Chronic use of sodium ferric gluconate complex in hemodialysis patients: Safety of higher-dose (> or =250 mg) administration. *Am J Kidney Dis* 41: 651–657, 2003 [PubMed: 12612989]
91. Hollands JM, Foote EF, Rodriguez A, Rothschild J, Young S: Safety of high-dose iron sucrose infusion in hospitalized patients with chronic kidney disease. *Am J Health Syst Pharm* 63: 731–734, 2006 [PubMed: 16595812]
92. Macdougall IC, Strauss WE, McLaughlin J, Li Z, Dellanna F, Hertel J: A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD. *Clin J Am Soc Nephrol* 9: 705–712, 2014 [PMCID: PMC3974353] [PubMed: 24458078]
93. Schiller B, Bhat P, Sharma A: Safety and effectiveness of ferumoxytol in hemodialysis patients at 3 dialysis chains in the United States over a 12-month period. *Clin Ther* 36: 70–83, 2014

[PubMed: 24315802]

94. Onken JE, Bregman DB, Harrington RA, Morris D, Buerkert J, Hamerski D, Iftikhar H, Mangoo-Karim R, Martin ER, Martinez CO, Newman GE, Qunibi WY, Ross DL, Singh B, Smith MT, Butcher A, Koch TA, Goodnough LT: Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: The REPAIR-IDA trial. *Nephrol Dial Transplant* 29: 833–842, 2014 [PubMed: 23963731]

Figures and Tables

[Go to:](#)

Figure 1.

Trends in mean serum ferritin over time. Data sources include the ESRD Core Indicators Project, the USRDS, the Dialysis Outcomes Practices Patterns Study, the Network 11 ELab Project, and the Medicare Clinical Performance Measure Reports.^{13, 15, 16, 86} IV, intravenous.

Table 1.

Physiochemical characteristics and pharmacokinetics of IVI formulations

Properties	Ferumoxytol	Ferric Carboxy Maltose	Iron Dextran	Iron Sucrose	Ferric Gluconate
Molecular mass (D)	731,000	150,000	410,000	252,000	200,000
Carbohydrate shell	Polyglucose sorbitol carboxymethylether	Carboxymaltose	Dextran polysaccharide	Sucrose	Gluconate, loosely associated sucrose
Median shell/particle diameter (nm)	26.3	23.1	12.2	8.3	8.6
Properties	Ferumoxytol	Ferric Carboxy Maltose	Iron Dextran	Iron Sucrose	Ferric Gluconate
Relative catalytic iron release	+		++	+++	
Relative stability of elemental iron within the carbohydrate shell	High	High	High	Medium	Low
Relative osmolality	Isotonic	Isotonic	Isotonic	Hypertonic	Hypertonic
Administration (iv push) rates	30 mg/s	Bolus push	50 mg (1 ml)/min	Approximately 20 mg/min	12.5 mg/min
$t_{1/2}$ (h)	Approximately 15	7–12	5–20	6	Approximately 1

D, daltons; nm, nanometer; iv, intravenous.

Table 2.

FDA approval and dosing of currently approved IVI formulations

Drug (Trade Name)	Year Approved	Test Dose Necessary	Maximum Approved Single Dose	Off-Label Dosing	Iron Repletion Dose	Miscellaneous
Low molecular weight iron dextran ⁸⁷ (InFed)	1992	25 mg over 15–30 min	100 mg over 30 s	1 g over 4–6 h	1 g	Equipment to respond to anaphylaxis required
High molecular weight iron dextran ^{88 89}	1996	25 mg over 15–30 min	100 mg over 30 s	1 g over 4–6 h	1 g	Not available in Europe; use discouraged due to high incidence of reactions
Sodium ferric gluconate ⁹⁰ (Ferrelicit)	1999	No	125 mg iv push over 10 min	250 mg iv push over 15 min	125 mg at each hemodialysis session×8	
Generic: Nulecit	2011					
Iron Sucrose ⁹¹ (Venofer)	2000	No	200 mg iv push over 2–5 min	300 mg iv over 1 h	100 mg iv at 10 consecutive or 200 mg iv at 5 consecutive hemodialysis sessions	—
Ferumoxytol ^{92 93} (Feraheme)	2009	No	510 mg iv push over <1 min	—	510 mg×2 doses over 2 different visits	—
Ferric carboxymaltose (Injectafer ⁹⁴ Ferinject)	2013	No	750 mg slow push or infusion over 15 min	—	750 mg×2 over 1 wk	

Dashed-lines indicate non-applicable items.

Table 3.

Research recommendations

Comparison	Priority	Recommended Design	Major End points
Conservative versus liberal dosing strategies	+++	RCT	Mortality, infection, nonfatal CV end points
Bolus versus maintenance dosing	+++	RCT	Mortality, infection, nonfatal CV end points
High versus low ferritin threshold for IVI administration	+++	RCT	Mortality, infection, nonfatal CV end points, end-organ damage
Ferritin versus TSAT versus novel iron biomarkers	+	TRS, RCT, or PCS	Iron overload, end-organ damage
ESA sparing versus IVI sparing versus hemoglobin sparing strategies	++	RCT	Mortality, infection, nonfatal CV end points, quality of life
IVI versus standard or novel oral iron formulations	+	TRS, RCT	Mortality, infection, nonfatal CV end points, quality of life, anemia, ESA dose
Comparison of IVI formulation/brand	+	RCT	Mortality, infection, nonfatal CV end points, anemia end points, ESA dose
Comparison	Priority	Recommended Design	Major End points

TRS, translational research study; PCS, prospective cohort study; CV, cardiovascular.

Articles from Journal of the American Society of Nephrology : JASN are provided here courtesy of **American Society of Nephrology**