Editorial Commentary

Testing two (of several) intravenous iron dosing strategies in hemodialysis

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Worldwide, over 2.6 million persons receive treatment for end-stage kidney disease (ESKD) and this number is expected to double by 2030 (1). Nearly all patients with ESKD develop anemia and the current standard of care is to treat with a combination of erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron (2). Patients on dialysis, and particularly those on hemodialysis, tend to have relatively low iron stores due to low dietary intake, poor gastrointestinal absorption of iron, and blood loss from hemodialysis, lab draws, vascular access procedures, and gastrointestinal hemorrhage. Estimated annual iron losses in patients receiving hemodialysis are 2 to 5 g per year (3). Furthermore, patients receiving dialysis typically require IV iron in order to respond adequately to ESAs (4) and to overcome the functional iron deficiency related to chronic inflammation, which is mediated largely through hepcidin, a liver-derived peptide that down-regulates duodenal iron absorption and macrophage iron release (5). Given safety concerns regarding high doses of ESAs (6-8) and changes in the payment structure for dialysis in the United States, IV iron has been more regularly prescribed, and often at relatively higher doses than in years past (9,10). However, the optimal dosing of IV iron in patients with ESKD remains unknown.

Potential adverse effects of IV iron include an increased risk of infection (11), atherothrombotic events (12), allergic reactions (including anaphylactoid reactions) (13), and nonallergic infusion reactions. The long-term effects to the bone marrow from excess iron supplementation are not known. Iatrogenic iron overload, which is associated with higher cumulative doses of IV iron, may be more common than previously recognized (14). Observational data suggest that the provision of IV iron might be associated with mortality and cardiovascular events among patients receiving hemodialysis (15-17). Kidney Disease: Improving Global Outcomes (KDIGO) provides guidelines regarding when to initiate IV iron based on serum ferritin concentrations and transferrin saturation (2). However, these guidelines (and others) do not provide an upper limit for ferritin or transferrin saturation. Although most dialysis units follow protocols for IV iron administration, these protocols are not standardized across centers and prescription patterns of IV iron are widely variable (9).

Earlier this year, in the *New England Journal of Medicine*, Macdougall and colleagues reported on the safety and efficacy of IV iron in patients receiving hemodialysis in the PIVOTAL trial (Proactive IV irOn Therapy in hemodiALysis patients) (18). In this prospective, multicenter, randomized, open-label trial, 2,141 patients on maintenance hemodialysis for <12 months were randomized 1:1 to "proactive, high-dose" versus "reactive, low-dose" strategies of IV iron sucrose for anemia. The proactive, high-dose iron arm delivered 400 mg of iron sucrose monthly unless the patient had a serum ferritin concentration ≥700 mcg/L or transferrin saturation ≥40%. The protocol for the reactive, low-dose iron arm obligated lower doses depending on ferritin and transferrin saturation but did not deliver iron sucrose if the ferritin was >200 mcg/L and the transferrin

saturation was >20%. Iron sucrose was temporarily held if the patient had an active infection that the study team considered to be a contraindication for IV iron; IV iron was restarted when investigators/treating physicians considered it to be safe. Laboratory results were monitored on a monthly basis. The dose of ESAs was selected by the clinician in order to maintain a target hemoglobin concentration between 10–12 g/dL.

Although PIVOTAL was an open label trial, the endpoints were blinded. The primary endpoint was time to the first event of nonfatal myocardial infarction or stroke, hospitalization for heart failure, or death. Patients were censored for loss to follow-up, kidney transplantation, or transfer to another dialysis modality (home hemodialysis or peritoneal dialysis). The investigators used conventional inferential analyses to compare the cumulative doses of IV iron, ESA dose requirements, and transfusion requirements between groups and Cox proportional hazards regression to determine the relative hazard (roughly equivalent to relative risk) of the primary composite and other secondary event-related endpoints.

Baseline characteristics of trial participants were generally well matched between groups. Patients were mostly male (65%) and white (79%), with a mean age of 63 years and a median duration of dialysis of five months. Almost half of the study participants had diabetes mellitus. Patients in the proactive, high-dose iron group were more likely to be current smokers, had higher baseline hemoglobin concentrations, and were less likely to use angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers or phosphate binders than patients in the reactive, low-dose iron group.

The median monthly dose of iron sucrose was 264 mg in the proactive, high-dose iron group and 145 mg in the reactive, low-dose iron group. On average, the 12-month cumulative dose of iron sucrose was 2,000 mg higher in the proactive, high-dose iron group. After a median follow-up time of 2.1 years, mean serum ferritin increased to roughly 650 mcg/L and transferrin saturation increased to roughly 27% in the proactive, high-dose iron group. In contrast, serum ferritin concentrations and transferrin saturation remained roughly similar to baseline values (200 mcg/L and 20%, respectively) in the reactive, low-dose iron group. The median monthly ESA dose was 19.4% lower in the proactive, high-dose iron group. Mean hemoglobin concentration rose more quickly in the proactive, high-dose iron group and these participants were less likely to receive blood transfusions than the reactive, low-dose iron group (rate ratio 0.78, 95% CI, 0.66–0.92).

The initial manuscript reported results of unadjudicated nonfatal myocardial infarctions and nonfatal hospitalizations for heart failure; these were amended in a formal correction (19). The proactive, high-dose iron strategy resulted in a lower incidence of the primary composite endpoint (29.3% versus 32.3%, P=0.04). When using methods to determine the hazard of recurrent events, the proactive, high-dose iron group had a lower rate of death, myocardial infarction, stroke, and hospitalization for heart failure (19.4 events per 100 patient-years) compared to the reactive, low-dose iron group (24.6 events per 100 patient-years; rate ratio 0.77, 95% CI, 0.66–0.92). There were no differences between groups in serious adverse events, vascular access thrombosis, infections, or health-related quality of life.

The results of PIVOTAL suggest that a proactive, high dose strategy of IV iron administration in patients new to hemodialysis appears to be safe, reduces the exposure to ESAs and blood transfusions, and is associated with a lower risk of death or major cardiovascular events. These findings contradict earlier observational reports that raised concern for higher rates of infection (20), cardiovascular events, and mortality with IV iron (15-17). This discrepancy can be explained at least in part by study design, as observational studies are subject to residual and unmeasured confounding; specifically, confounding by indication, since higher doses of IV iron (and ESAs) might be required in order to achieve targeted hemoglobin concentrations, particularly among patients with an activated pro-inflammatory state. PIVOTAL may also differ from past studies because of differences in the patient population. PIVOTAL was a single country trial (United Kingdom) of patients new to hemodialysis and may have limited generalizability to other populations, including patients of longer dialysis vintage.

The trial exhibits several important strengths. It was well powered for non-inferiority, so the conclusion vis-à-vis safety of the proactive, high dose iron strategy should be robust. Moreover, the proactive, high dose iron strategy appeared to be superior to the reactive, low dose strategy, and results were consistent across subgroups and in companion sensitivity analyses. However, several important questions remain unanswered.

The PIVOTAL trial intervention combined a “proactive” approach with a “high-dose” of IV iron administration. The investigators might have considered a trial comparing a proactive versus a reactive strategy of IV iron administration or a trial comparing a “high-dose” versus “low-dose” trial of IV iron; unfortunately, readers and the

nephrology community will be unable to disentangle the effects of the dual intervention. What PIVOTAL did not test was a "proactive, low-dose" strategy, which is often employed in United States dialysis programs (e.g., 50 mg iron sucrose weekly). Since the proactive, high-dose intermittent strategy appears to be as safe as a reactive, low-dose strategy, it would be of interest to compare "proactive, intermittent" to "proactive, maintenance" strategies of IV iron administration.

We should be mindful that while the proactive, high-dose strategy appeared safe, it was compared to a strategy in which ESA doses were roughly 20% higher. ESA use is thought to contribute to stroke and venous thromboembolic disease (as well as vascular access thrombosis). Comparing the proactive, high-dose strategy to another strategy in which ESA doses were similar and/or fewer patients received ESAs could help determine the optimal use of IV iron in patients receiving hemodialysis. PIVOTAL did not address the longer-term safety of the proactive, high-dose iron strategy and does not provide guidance with respect to the serum ferritin concentration or transferrin saturation above which IV iron should not be administered.

The PIVOTAL trial used iron sucrose in their protocol, but other strategies of iron dosing in patients receiving hemodialysis could consider alternative formulations of IV iron or recently introduced iron-containing phosphate binders. Ferric citrate coordination complex (FCCC) was approved in the United States in 2014 for the treatment of hyperphosphatemia; use of FCCC as a phosphate binder reduces the need for IV iron and ESAs (21). Future randomized controlled trials might compare IV iron to FCCC or to a combination of lower dose IV and oral iron.

In sum, PIVOTAL is the first randomized trial to provide reliable, highly informative guidance regarding safety and efficacy of alternative strategies of IV iron administration in patients receiving hemodialysis. We expect that additional randomized trials, some of which are underway, will further inform our approach to anemia management in patients with ESKD.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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