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**Proactive high-dose IV iron is preferred therapy in ESKD patients: PRO**

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**Key Points:**
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**Abstract:**
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Proactive high-dose IV iron is preferred therapy in ESKD patients: PRO

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Proactive intravenous (IV) iron is preferred management in patients with end-stage kidney disease (ESKD) because it is a necessity in these patients due to pathophysiologic changes in iron regulation as outlined below. Outcome trials indicate the benefits and safety of proactive iron in ESKD and other populations.\textsuperscript{1, 2} The hypothesized harms from IV iron have not materialized, or are easily avoided.\textsuperscript{3, 4}

Normally, intestinal iron absorption increases during iron deficiency or increased erythropoiesis, and is minimized when iron stores are replete.\textsuperscript{5} Hemochromatosis can be from genetic disorders, transfusions, or excessive IV iron. No physiologic mechanisms eliminate excess iron, but hemodialysis-related blood loss leads to mean iron losses of 2.0-2.4g/year.\textsuperscript{1} Iron deficiency can be absolute or functional (also called iron-restricted erythropoiesis).\textsuperscript{5}

For 25 years some have hypothesized that IV iron in ESKD can exacerbate infections, cause or accelerate cardiovascular disease, and damage the heart and liver via overload.\textsuperscript{4, 6} But valid tests of these hypotheses are largely randomized trials, and the PIVOTAL trial is definitive that proactive iron use is superior to a conservative iron strategy and demonstrates no evidence of these hypothesized harms.\textsuperscript{1}

Under normal conditions, serum hepcidin regulates iron availability.\textsuperscript{5} Low hepcidin levels permit higher intestinal absorption and storage iron release to maintain transferrin saturation (TSAT; serum iron/total iron binding capacity). High hepcidin levels minimize intestinal iron absorption and impair storage iron release, leading to a lower TSAT.

Hepcidin levels are high in ESKD for reasons unrelated to iron status. Hepcidin is cleared by the kidneys, and consequently increases as kidney function declines. Inflammation - common in ESKD - upregulates hepcidin expression via the cytokine interleukin-6.\textsuperscript{5} Administration of IV iron may raise hepcidin further. Inflammation increases ferritin, rendering ferritin a poor predictor of iron status. A study correlating bone marrow iron content to ferritin in ESKD patients found just 12% of the ferritin variability could be ascribed to iron content, and patients with little or no marrow iron had ferritin ranging from <100ng/ml to >1000ng/ml.\textsuperscript{7} Although hepcidin lowers serum iron, TIBC also tends to fall in ESKD. Consequently TSAT poorly correlates with iron stores in ESKD.

Guidelines have dealt with the poor predictive value of ferritin and TSAT in patients with ESKD by increasing cut-off’s for diagnosis of iron deficiency and recommending use of other criteria to assess iron needs when ferritin is high, but these are pragmatic changes that routinely miscategorize an individual’s iron status.

In patients with ESKD, ESA-stimulated erythropoiesis can quickly exceed iron availability. Depending on prior iron stores, this will result in overt iron deficiency or iron-restricted erythropoiesis because high hepcidin levels prevent the appropriate physiologic responses.

IV iron products are cleared by the reticuloendothelial system, largely in the liver and spleen, where the carbohydrate shell is metabolized and iron stored as ferritin or exported to circulating transferrin, raising TSAT. IV iron bypasses the hepcidin blockade and can resolve iron-restricted erythropoiesis, lowering ESA dose requirements.\textsuperscript{8} Thus, ESA and IV iron are natural competitors: if you provide IV iron, you will
use less ESA, as shown in the PIVOTAL trial where ESA doses were 24% lower with proactive iron, and transfusions less frequent.\textsuperscript{1}

Major concerns about IV iron safety largely started with post hoc analyses of the Normal Hematocrit Trial (NHT) which showed increased deaths in ESKD patients randomized to an ESA-driven normal hemoglobin (13-15g/dL) or 9-11g/dL.\textsuperscript{6} The trial was stopped early in 1996 due to the primary endpoint – myocardial infarction and death - being higher in the high target arm. Before publication, in 1997 an ASN abstract using Medicare claims data correlated use of IV iron to increased mortality in ESKD patients, and a presentation of the abstract’s results was distributed to US nephrologists by the ESA manufacturer. In 1998, the NHT’s published results adjusted virtually all statistical reporting for the trial’s premature termination.\textsuperscript{6} The authors reported a high hemoglobin target showed a trend toward harm (relative risk 1.3, 95% confidence intervals (CI) 0.9 to 1.9), but improved quality of life and reduced transfusions. Surprisingly, deaths were not associated with higher ESA doses, and higher hemoglobin associated with better survival.\textsuperscript{6}

The 1998 NHT publication speculated higher IV iron use may have accounted for the adverse outcomes, provided several post hoc analyses to support this, and cited the 1997 ASN abstract as further evidence.\textsuperscript{6} Thus a trial sponsored by an ESA manufacturer had moved suspicion from higher hemoglobin targets and ESA to IV iron. But IV iron was not the problem.

Only in 2006 was a second outcomes trial of ESA in chronic kidney diseases published, showing a normal hemoglobin target (13.5g/dL) increased cardiovascular events and death compared to a lower target. In 2009, a double-blind outcomes trial randomized diabetics to ESA targeting hemoglobin to 13.0 g/dL or placebo. It showed no benefit from ESA, and significant harm. In both these trials, IV iron use was low and unrelated to the adverse outcomes.

In 2007, the FDA disclosed the NHT’s unadjusted statistical results showed randomization to normal hemoglobin had increased “the risk for the primary end point (risk ratio 1.28, 95% CI 1.06–1.56; \textit{P}=0.0112)”\textsuperscript{9} and mortality (\textit{p}=0.0188).\textsuperscript{9} An FDA analysis of the NHT data found a strong relationship of higher ESA dose to higher mortality. Finally, in 2012, I obtained the NHT’s clinical report filed with the FDA in 1996.\textsuperscript{9} Targeting higher hemoglobin did not improve quality of life (\textit{p}=0.88), and significantly increased hospitalizations and thrombotic events. The report stated IV iron use in the NHT was only 12-14\% at baseline and fell to 9-10\% at 1 year.

To lower ESA use, use IV iron proactively, but avoid iron overload by stopping iron if TSAT is >40-50\%. Too much IV iron can cause hemochromatosis, and would likely resemble transfusional iron overload, where “it is generally accepted that transfusion of more than 15 to 20 units of RBCs...can cause clinically significant iron overload.”\textsuperscript{10} A unit of blood contains ~250 mg of iron, therefore >3.8-5.0 grams of excess iron would be significant.\textsuperscript{10} But hemodialysis patients may use a gram of iron correcting their anemia, then lose the equivalent of 8-10 units of blood/year (2.0-2.4 grams of iron).\textsuperscript{1} To develop iron overload, a patient would need to receive >5.8-6.2g of iron in a year (and possibly >7.4g) while having only usual blood losses. In transfusional iron overload “a TSAT below (45\% for men, 40\% for women) is good evidence that the patient does not have iron overload, even if the ferritin is elevated.”\textsuperscript{10}
Magnetic resonance imaging studies in ESKD to assess iron load purportedly show mild to severely elevated iron in the liver and spleen, where IV iron is taken up. The scans rarely show any cardiac iron deposition, but it should in clinically significant hemochromatosis. A severely iron overloaded hemodialysis patient who stopped IV iron should require years to lose sufficient blood to normalize stores, yet scans indicate resolution in months, indicating overestimation of true iron stores.

The PIVOTAL trial is definitive to assess cardiovascular events, infections and death related to proactive iron use. It randomized 2141 ESKD patients on dialysis for <1 year to proactive iron (400 mg of iron sucrose monthly if monthly determined TSAT was <40% and ferritin <700ng/ml), or conservative IV iron (0-400 mg of IV iron monthly to maintain TSAT at 20% and ferritin 200ng/ml). After median follow-up of 2.1 years, the primary endpoint of first nonfatal myocardial infarction, nonfatal stroke, heart failure hospitalization and death was significantly reduced by proactive iron (hazard ratio, 0.85; 95% CI, 0.73 to 1.00; P<0.001 for noninferiority; P = 0.04 for superiority), and in a recurrent-events analysis, the proactive iron was even more impressive (rate ratio, 0.77; 95% CI, 0.66 to 0.92). Infection rates were not different between arms.

These results are supported by a meta-analysis of four placebo-controlled, double-blind trials of IV iron in patients with heart failure (44% also had kidney disease) demonstrating substantial cardiovascular outcome benefits and safety. Compared to placebo-treated patients, patients receiving a mean dose of 1679 mg of IV iron had significantly lower rates of recurrent CV hospitalizations and CV mortality (rate ratio 0.59; P =0.009), reduced recurrent HF hospitalizations and CV mortality (rate ratio 0.53; P =0.011), and all-cause mortality (rate ratio 0.60; P =0.009).

How much iron is proactive? New ESKD patients targeted to ferritin >700ng/ml received about ~300mg/month the first year to raise hemoglobin and replete stores, then ~200mg/month to maintain that goal. Should we stop proactive iron in ESKD if the ferritin is >700ng/ml? Some recommend that, but as shown in a randomized trial of IV iron versus no iron in ESKD patients requiring high ESA doses, ferritin had no predictive value over a 500-1200ng/ml range, and IV iron significantly increased hemoglobin, lowered ESA doses, reduced serious adverse events (post hoc), and did not increase infections.

Whatever ferritin limit you choose (I use 1200ng/ml), use proactive iron but stop it if TSAT is >40-50% for patient safety and to avoid iron overload. Consider a 1g trial of IV iron in patients on high ESA doses with ferritin above your limit if hemoglobin is below target and TSAT <25%. 

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