# Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality

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**Intravenous (IV) iron is required for optimal management of anemia in the majority of hemodialysis (HD) patients. While IV iron prescription has increased over time, the best dosing strategy is unknown and any effect of IV iron on survival is unclear. Here we used adjusted Cox regression to analyze associations between IV iron dose and clinical outcomes in 32,435 HD patients in 12 countries from 2002 to 2011 in the Dialysis Outcomes and Practice Patterns Study. The primary exposure was total prescribed IV iron dose over the first 4 months in the study, expressed as an average dose/month. Compared with 100–199 mg/month (the most common dose range), case-mix-adjusted mortality was similar for the 0, 1–99, and 200–299 mg/month categories but significantly higher for the 300–399 mg/month (HR of 1.13, 95% CI of 1.00–1.27) and 400 mg/month or more (HR of 1.18, 95% CI of 1.07–1.30) groups. Convergent validity was proved by an instrumental variable analysis, using HD facility as the instrument, and by an analysis expressing IV iron dose/kg body weight. Associations with cause-specific mortality (cardiovascular, infectious, and other) were generally similar to those for all-cause mortality. The hospitalization risk was elevated among patients receiving 300 mg/month or more compared with 100–199 mg/month (HR of 1.12, 95% CI of 1.07–1.18). In light of these associations, a well-powered clinical trial to evaluate the safety of different IV iron-dosing strategies in HD patients is urgently needed.**

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Appropriate anemia management for hemodialysis (HD) patients is challenging. Optimal hemoglobin targets and strategies to balance erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron remain unclear. ESA doses in hemodialysis patients in the United States have decreased since the addition of a black box warning to the labeling and introduction of a bundled payment methodology, both in 2011.[1–7] IV iron use has concurrently increased, perhaps with the intent to reduce ESA-dosing requirements.[3–6] Administration of IV iron to HD patients complements ESA therapy, helps maintain target hemoglobin levels, and lowers ESA-dosing requirements.[8–11] However, IV iron use requires careful balance between intended clinical effect and uncertain risks of toxicities.[12,13] A number of authors have raised concerns regarding the potential for IV iron to cause oxidative stress and inflammation, endothelial dysfunction, and immune dysfunction, prompting calls for caution regarding the potential hazards of high exposures to IV iron.[1,14–17]

The few prior relevant observational studies produced conflicting results.[18–20] In a cohort of US patients who received hemodialysis during the mid-1990s, an analysis accounting for time-varying measures of iron administration found no significant association between iron use and all-cause mortality.[19] Another study of US HD patients treated in the early 2000s concluded that treatment with $>400$ mg/month was associated with elevated risk of all-cause mortality.[20] Analysis of data from Medicare's end-stage renal disease program found that centers using more IV iron in patients with lower hematocrits had lower mortality rates, whereas centers that used more iron in patients with higher hematocrits had elevated mortality risks.[18]

Those results may not be generalizable to other countries or current practice because they were limited to the United States when ESA and iron-dosing patterns were different from now and because other countries have other

iron preparations and dosing strategies.[21] Thus, an examination of the association of IV iron use with mortality in an international population, with a broader range of IV iron products and practices, is warranted. We hypothesized that the use of IV iron is safe at the most commonly administered doses in HD patients, but that the highest doses may increase all-cause-related, cardiovascular-related, and infection-related mortality.

## RESULTS

There were 6225 deaths among 32,435 patients. The median (interquartile range) follow-up time for mortality analyses was 1.7 (1.0–2.4) years, and the overall mortality rate was 0.11 per patient-year. Among causes of death, 35% were cardiovascular-related, 17% were infection-related, and 29% had another known cause of death.

Over a 4-month period, 32% of patients received no IV iron, and 10%, 19%, 17%, 6%, and 15% received average doses of 1–99, 100–199, 200–299, 300–399, and ⩾400 mg/month, respectively (Table 1). Of patients who received IV iron, the mean (s.d.) was 252 (189) mg/month. The most common dose was 200 mg/month (12% of patients). The most common preparations were as follows: iron sucrose (60%), sodium ferric gluconate (24%), iron polymaltose (11%), and iron dextran (2%) in Europe, Australia, and New Zealand; iron sucrose (71%), sodium ferric gluconate (20%), and iron dextran (8%) in North America; and iron saccharate (48%), chondroitin sulfate iron complex (35%), and cideferron (16%) in Japan. Of patients receiving IV iron, the mean (s.d.) number of doses per month over 4 months was 3.2 (2.4). Only 1.3% of patients were prescribed oral iron.

Patient demographics by IV iron dose categories, overall and by region, are shown in Table 1. Overall, 57–60% of patients were male and the mean age was 63–64 years. Higher IV iron doses were observed among patients with shorter time on dialysis, higher use of catheters for vascular access, higher body mass index, higher doses of ESA, higher prevalences of heart failure, diabetes, cancer, gastrointestinal bleeding, and peripheral vascular disease, as well as lower transferrin saturation (TSAT) values. IV iron doses were lowest in Japan. Within each region, body mass index differed little by iron dose categories.

The associations of all-cause mortality with IV iron dose are shown in Figure 1a and Table 2; Supplementary Figure online shows unadjusted Kaplan–Meier cumulative survival. Compared with the reference category of 100–199 mg/month (the most common dose range), the 0, 1–99, and 200–299 mg/month categories had similar hazard ratios (HRs) for all-cause mortality. Both the 300–399 mg/month and the ⩾400 mg/month categories had higher all-cause mortality (HR = 1.13, 95% confidence interval (CI) = 1.00–1.27 and HR = 1.18, 95% CI = 1.07–1.30, respectively). When IV iron dose was dichotomized, the HR for all-cause mortality was 1.12 (95% CI = 1.04–1.20) for IV iron dose ⩾300 mg/month compared with the 0 to <300 mg/month category. Instrumental variable analysis controlling for the same covariates and five indicators of facility practice demonstrated convergent validity: IV iron dose ⩾300 mg/month was associated with HR for all-cause mortality of 1.17 (95% CI = 0.96–1.41). This finding did not achieve statistical significance; instrumental variable analyses are often less precise than standard regression models.

Table 2 shows the effect of differing levels of adjustment on the association of categorical IV iron dose with all-cause mortality. For categories of IV iron dose ⩾300 mg/month, estimates were attenuated by the addition of albumin, hemoglobin, and ESA dose. Addition of TSAT, ferritin, and other variables had little effect on estimates.

Positive associations of IV iron dose ⩾300 mg/month with all-cause mortality were seen consistently in Europe in phases 2–4 and in North America in phases 3–4. The association of higher dose with elevated all-cause mortality was consistently seen regardless of dialysis vintage (<6, ⩾6 months); patient age (18–55, 56–65, 66–75, ⩾76 years); C-reactive protein level (<10, ⩾10 mg/l in countries where C-reactive protein is routinely measured); TSAT (<20, 20–39, ⩾40%, ferritin (<200, 200–499, ⩾500 ng/ml); IV iron dose frequency (average of <3, 3–<5, ⩾5, doses/month); and IV iron preparation (iron sucrose, sodium ferric gluconate, iron dextran in North America; iron sucrose, sodium ferric gluconate, and iron polymaltose in Europe, Australia, and New Zealand; iron saccharate and chondroitin sulfate iron complex in Japan). IV iron dose ⩾300 mg/month was positively associated with all-cause mortality in patients with a hemoglobin level of 10–12 g/dl (HR = 1.12, 95% CI = 1.02–1.22) and ⩾12 g/dl (HR = 1.25, 95% CI = 1.10–1.41), but not in patients with a hemoglobin level <10 g/dl (HR = 0.94, 95% CI = 0.80–1.10): overall interaction, $P = 0.05$. Patients with hemoglobin <10 g/dl comprised 20% of the total study population, and only 22% of this subset (4.5% of total patients) were in the ⩾300 mg/month category.

The patterns of associations of higher IV iron dose categories with higher HR of cardiovascular-related mortality, infection-related mortality, and noncardiovascular/non-infection-related mortality were generally similar to all-cause mortality (Figure 1b). Precision was limited because of fewer events compared with the all-cause mortality analysis, with only cardiovascular-related mortality at IV iron dose ⩾300 mg/month achieving statistical significance.

Normalizing average monthly IV iron doses to body weight showed that overall there was little difference in all-cause and cardiovascular-related mortality for dose categories from 0 to <6 mg/kg per month, but a higher risk at dose ⩾6 mg/kg per month (vs. 1- to 2-mg/kg per month: all-cause mortality, HR = 1.26, 95% CI = 1.13–1.40; and CV-related mortality HR = 1.35, 95% CI = 1.12–1.62). This pattern was not apparent for infection-related mortality (HR = 1.08, 95% CI = 0.83–1.40 for ⩾6 mg/kg per month vs. the 1 to 2-mg/kg per month category). The ⩾6-mg/kg per month category comprised 10% of patients.

Hospitalization risk was most clearly elevated at IV iron dose ⩾300 mg/month (vs. 100–199 mg/month: HR = 1.12, 95% CI = 1.07–1.18).