

ORIGINAL ARTICLE

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

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ABSTRACT

BACKGROUND

Intravenous iron is a standard treatment for patients undergoing hemodialysis, but comparative data regarding clinically effective regimens are limited.

METHODS

In a multicenter, open-label trial with blinded end-point evaluation, we randomly assigned adults undergoing maintenance hemodialysis to receive either high-dose iron sucrose, administered intravenously in a proactive fashion (400 mg monthly, unless the ferritin concentration was $>700 \mu\text{g}$ per liter or the transferrin saturation was $\geq 40\%$), or low-dose iron sucrose, administered intravenously in a reactive fashion (0 to 400 mg monthly, with a ferritin concentration of $<200 \mu\text{g}$ per liter or a transferrin saturation of $<20\%$ being a trigger for iron administration). The primary end point was the composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death, assessed in a time-to-first-event analysis. These end points were also analyzed as recurrent events. Other secondary end points included death, infection rate, and dose of an erythropoiesis-stimulating agent. Noninferiority of the high-dose group to the low-dose group would be established if the upper boundary of the 95% confidence interval for the hazard ratio for the primary end point did not cross 1.25.

RESULTS

A total of 2141 patients underwent randomization (1093 patients to the high-dose group and 1048 to the low-dose group). The median follow-up was 2.1 years. Patients in the high-dose group received a median monthly iron dose of 264 mg (interquartile range [25th to 75th percentile], 200 to 336), as compared with 145 mg (interquartile range, 100 to 190) in the low-dose group. The median monthly dose of an erythropoiesis-stimulating agent was 29,757 IU in the high-dose group and 38,805 IU in the low-dose group (median difference, -7539 IU; 95% confidence interval [CI], -9485 to -5582). A total of 333 patients (30.5%) in the high-dose group had a primary end-point event, as compared with 343 (32.7%) in the low-dose group (hazard ratio, 0.88; 95% CI, 0.76 to 1.03; $P<0.001$ for noninferiority). In an analysis that used a recurrent-events approach, there were 456 events in the high-dose group and 538 in the low-dose group (rate ratio, 0.78; 95% CI, 0.66 to 0.92). The infection rate was the same in the two groups.

CONCLUSIONS

Among patients undergoing hemodialysis, a high-dose intravenous iron regimen administered proactively was noninferior to a low-dose regimen administered reactively and resulted in lower doses of erythropoiesis-stimulating agent being administered. (Funded by Kidney Research UK; PIVOTAL EudraCT number, 2013-002267-25.)

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*A complete list of the Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) investigators and committee members is provided in the Supplementary Appendix, available at NEJM.org.

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PATIENTS UNDERGOING MAINTENANCE hemodialysis usually have a negative iron balance owing to reduced absorption and increased blood loss.¹ The intravenous administration of iron has become standard care in the management of anemia, and large doses are increasingly used to reduce exposure to erythropoiesis-stimulating agents^{2,3} in order to reduce costs and mitigate concerns about potential risks, particularly because of cardiovascular toxic effects that have been observed in trials.^{4–8} However, intravenous iron therapy may cause harm by increasing the risks of infection, oxidative stress, vascular calcification, and atherothrombosis.^{9–13}

Rigorous scientific evaluation of the use of high doses of iron in patients undergoing hemodialysis has been limited, which has resulted in marked variation in its use among individual practitioners and across countries.³ We assessed first the noninferiority, and then the safety and efficacy, of a high-dose regimen of intravenous iron administered proactively, as compared with a low-dose regimen of intravenous iron administered reactively, in patients undergoing hemodialysis in the Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this prospective, randomized, open-label, blinded end-point,¹⁴ controlled trial at 50 sites in the United Kingdom. The trial protocol¹⁵ (available with the full text of this article at NEJM.org) was approved by the relevant health authorities and institutional review boards, and all the patients provided written informed consent. An independent data and safety monitoring committee performed regular safety surveillance. Data were entered into an electronic case-report form by the investigators (see the Supplementary Appendix, available at NEJM.org) and were analyzed at the Robertson Centre for Biostatistics, University of Glasgow, in the United Kingdom.

This was an academic investigator-led trial. The trial was funded by Kidney Research UK, which was supported by an unrestricted grant from Vifor Fresenius Medical Care Renal Pharma (which also provided iron sucrose for the trial, free of charge). Vifor Fresenius Medical Care Renal Pharma had no input into the trial design or

the data collection or analysis. However, the company was kept abreast of the progress of the trial by regular study reports and newsletters. No confidentiality agreements regarding the data were in place.

The initial draft of the manuscript was written by the first author and revised by all the authors. Medical writing assistance was provided by a professional medical writer, funded by Kidney Research UK (supported by Vifor Fresenius Medical Care Renal Pharma). The authors had access to the final trial results and take responsibility for the accuracy and completeness of the data, for the fidelity of the trial to the protocol, and for the decision to submit the manuscript for publication.

PARTICIPANTS

Adults with end-stage kidney disease in whom maintenance hemodialysis had been initiated no more than 12 months before the initial screening visit, who had a ferritin concentration of less than 400 μg per liter and a transferrin saturation of less than 30%, and who were receiving an erythropoiesis-stimulating agent were eligible to participate. Any iron therapy that had been prescribed previously was discontinued at the screening visit. The full eligibility criteria are provided in the protocol.

RANDOMIZATION, TREATMENT, AND FOLLOW-UP

Using a Web-based randomization system, we randomly assigned participants, in a 1:1 ratio, to receive a regimen of high-dose intravenous iron administered proactively or a regimen of low-dose intravenous iron administered reactively; patients were then evaluated monthly. Randomization was stratified according to vascular access (dialysis catheter vs. arteriovenous fistula or graft), diagnosis of diabetes (yes vs. no), and duration of hemodialysis treatment (<5 months vs. ≥ 5 months).

The ferritin concentration and transferrin saturation were measured monthly (usually during the first week of the month), and these values determined the monthly dose of iron sucrose to be administered intravenously during the subsequent week of hemodialysis (usually the second week of the month). In the high-dose group, 400 mg of iron sucrose per month, to be administered intravenously, was prescribed to the patients, with safety cutoff limits (ferritin concentration of 700 μg per liter or a transferrin

saturation of 40%) above which further intravenous iron administration was withheld pending repeat testing 1 month later. Patients in the low-dose group received a monthly dose of 0 mg to 400 mg of iron sucrose as required to maintain a minimum target ferritin concentration of 200 μ g per liter and a transferrin saturation of 20%, in line with accepted clinical guidelines (for details of the iron-dosing regimen, see the Supplementary Appendix). Iron therapy was temporarily withheld if the trial team identified an active infection that was deemed by the investigator to be sufficient to contraindicate the use of intravenous iron. Therapy was restarted when it was judged by the investigator to be safe to do so.

Clinicians selected the dose of erythropoiesis-stimulating agent that would be sufficient to maintain a hemoglobin level of 10 to 12 g per deciliter.¹⁶ Apart from the dose of erythropoiesis-stimulating agent, the trial teams treated patients according to standard practice.

TRIAL END POINTS

The primary end point was the composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death from any cause, assessed in a time-to-first-event analysis; definitions of the end-point events are provided in the Supplementary Appendix. The first secondary end point consisted of the components of the primary end point, including first and repeat events, which were analyzed as recurrent events. Other secondary efficacy end points included death from any cause; the composite of fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure; and each of the three subcomponents of that end point, all assessed in time-to-first-event analyses. An independent committee whose members were unaware of the trial-group assignments adjudicated these events according to prespecified criteria. Additional secondary efficacy end points included the dose of erythropoiesis-stimulating agent, the incidence of blood transfusion, and two quality-of-life measures (the European Quality of Life–5 Dimensions [EQ-5D] questionnaire and the Kidney Disease Quality of Life instrument).

Safety end points included vascular access thrombosis, hospitalization for any cause, and hospitalization for infection, each assessed in a time-to-first-event analysis, and the rate of episodes of infection. Laboratory tests, including the

hemoglobin level, serum ferritin concentration, and transferrin saturation, were assessed monthly. Data on serious adverse events were collected prospectively, and events were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 15.1. Data on nonserious adverse events, other than infection and vascular access thrombosis, were not collected.

STATISTICAL ANALYSIS

In the initial sample-size calculations, we assumed a 3-year event rate of 40% in the low-dose group and a 10% loss to follow-up (including loss to follow-up due to kidney transplantation). Thus, we estimated that a sample of 2080 patients who had 631 primary end-point events would provide the trial with 80% power to assess the noninferiority of high-dose iron to low-dose iron, with a noninferiority limit for the hazard ratio of 1.25.

Summary statistics are provided as numbers and percentages, as mean values with standard deviations, and as median values with interquartile ranges (25th to 75th percentile). Treatment effects were estimated as the effect in the high-dose group as compared with (or minus) the effect in the low-dose group, with adjustment for the stratification variables at randomization. The primary end point was analyzed first in terms of noninferiority in the intention-to-treat population, which included all the patients who had undergone randomization validly, with a supporting analysis in a per-protocol population that excluded patients with a major protocol violation. Analyses were censored at the date of kidney transplantation, withdrawal of consent, loss to follow-up, or transfer to home or peritoneal dialysis, whichever came first. Noninferiority was also assessed in a sensitivity analysis that included only patients who were currently receiving treatment, with data censored after patients discontinued the trial drug. The time-to-first-event analyses were conducted with the use of cause-specific Cox proportional-hazards models, including the stratification variables and the treatment variable. The noninferiority analysis tested the null hypothesis that the hazard ratio for the treatment effect was at least 1.25 against the alternative that the hazard ratio was less than 1.25, with a required one-sided significance level of 0.025. If noninferiority was established, a two-sided superiority test (Wald statistic) was carried out with no penalty regarding the P value.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Proactive, High-Dose Iron Regimen (N=1093)	Reactive, Low-Dose Iron Regimen (N=1048)
Age — yr	62.7±14.9	62.9±15.1
Male sex — no. (%)	710 (65.0)	688 (65.6)
Race — no. (%)†		
White	868 (79.4)	830 (79.2)
Black	93 (8.5)	97 (9.3)
Asian	96 (8.8)	89 (8.5)
Other	36 (3.3)	32 (3.1)
Median duration of dialysis treatment (IQR) — mo	4.9 (2.8–8.4)	4.8 (2.8–8.1)
Vascular access — no. (%)		
Dialysis catheter	449 (41.1)	428 (40.8)
Arteriovenous fistula or graft	644 (58.9)	620 (59.2)
Cardiovascular disease — no. (%)		
Atrial fibrillation	96 (8.8)	68 (6.5)
Heart failure	41 (3.8)	45 (4.3)
Hypertension	804 (73.6)	753 (71.9)
Hyperlipidemia	277 (25.3)	258 (24.6)
Peripheral vascular disease	92 (8.4)	95 (9.1)
Previous myocardial infarction	97 (8.9)	87 (8.3)
Previous stroke	85 (7.8)	91 (8.7)
Diabetes — no. (%)	494 (45.2)	456 (43.5)
Smoking status — no. (%)		
Current smoking	145 (13.3)	104 (9.9)
Former smoking	261 (23.9)	284 (27.1)
Never smoked	687 (62.9)	660 (63.0)
Weight — kg	81.3±21.0	82.9±20.9
Body-mass index‡	28.5±7.1	29.0±6.7
Blood pressure — mm Hg§		
Systolic	145±24	145±24
Diastolic	74±14	74±15
Hemoglobin — g/dl	10.6±1.4	10.5±1.4
Median serum ferritin concentration (IQR) — µg/liter	214 (132–305)	217 (137–301)
Median transferrin saturation (IQR) — %	20 (16–24)	20 (16–24)
Median C-reactive protein level (IQR) — mg/liter	6.0 (3.3–13.9)	7.0 (4.0–15.0)
Median dose of erythropoiesis-stimulating agent (IQR) — IU/wk¶	8000 (5000–10,000)	8000 (5000–12,000)
Primary cause of kidney failure — no. (%)		
Diabetic nephropathy	363 (33.4)	349 (33.5)
Glomerular disease	191 (17.6)	203 (19.5)
Hypertension	129 (11.9)	106 (10.2)
Tubulointerstitial disease	113 (10.4)	88 (8.4)
Renovascular disease	64 (5.9)	83 (8.0)
Polycystic kidney disease	62 (5.7)	55 (5.3)
Other	61 (5.6)	68 (6.5)
Unknown	110 (10.1)	96 (9.2)

* Plus-minus values are means ±SD. There were no significant differences between the two groups except for smoking status (P=0.03) and the hemoglobin level (P=0.04). Percentages may not total 100 because of rounding. IQR denotes interquartile range (25th to 75th percentile).

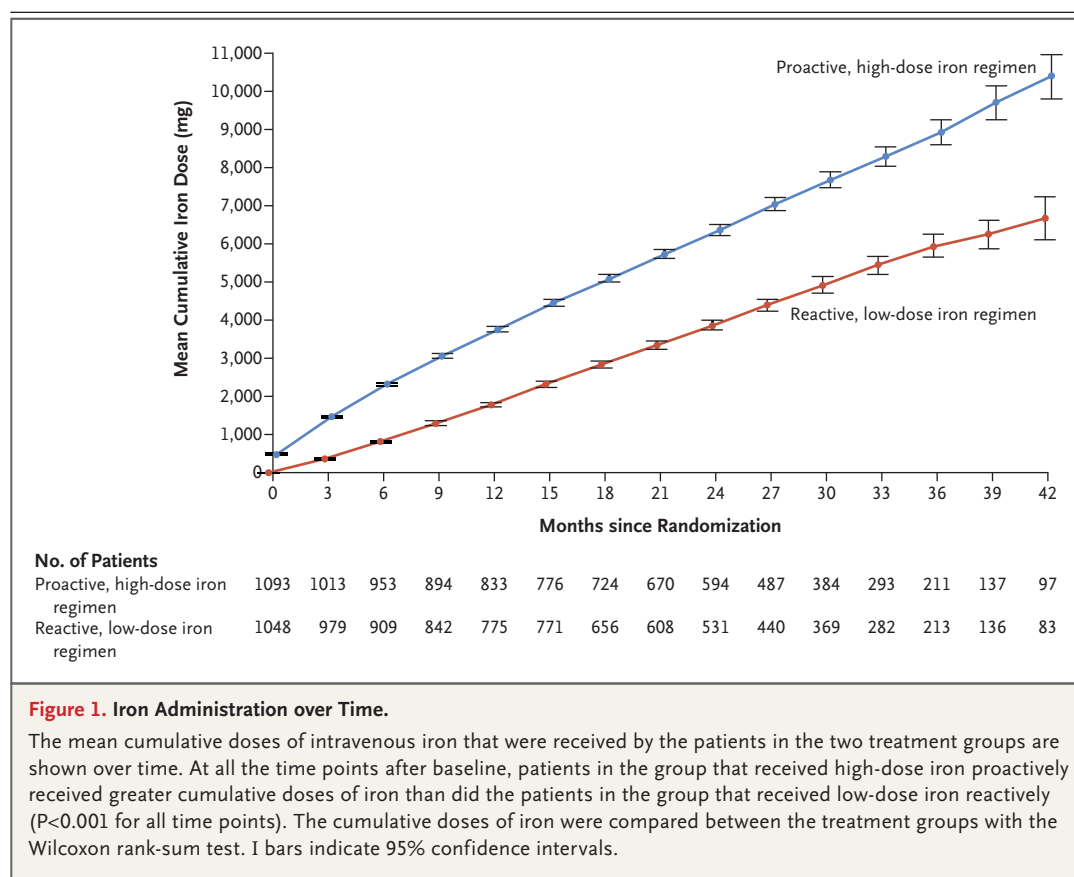
† Race was reported by the patients.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Blood-pressure measurements were taken before hemodialysis.

¶ For darbepoetin alfa and methoxy polyethylene glycol-epoetin beta, the weekly reported dose was multiplied by 200 to convert the units from micrograms to international units.

|| Tubulointerstitial disease included pyelonephritis, reflux nephropathy, and obstructive uropathy.



The incidence of death from any cause and a composite of myocardial infarction, stroke, or hospitalization for heart failure as recurrent events was analyzed with the use of the proportional-means model of Lin et al.¹⁷ and described in the form of mean frequency functions (method of Ghosh and Lin).¹⁸ Other statistical methods and details regarding statistical assumptions are described in the Supplementary Appendix. The results for the secondary end points are reported as point estimates and 95% confidence intervals with no adjustment for multiple comparisons, so the confidence intervals should not be used to infer definitive treatment effects. The cumulative doses of intravenous iron were compared between the treatment groups with the use of Wilcoxon rank-sum tests. The statistical analysis plan is available with the protocol at NEJM.org.

RESULTS

PATIENTS

The trial was conducted from November 2013 to June 2018. Of the 2589 patients who were screened

for entry into the trial, 448 did not meet the criteria for randomization. A total of 2141 patients were randomly assigned to a treatment group (1093 patients to the high-dose group and 1048 to the low-dose group) and constituted the intention-to-treat population (Fig. S1 in the Supplementary Appendix). Follow-up continued until June 6, 2018.

The characteristics of the patients at baseline were generally well balanced between the two treatment groups, except for smoking status ($P = 0.03$) and the hemoglobin level ($P = 0.04$) (Table 1). The prevalence of cardiovascular disease (a history of one or more of the following: myocardial infarction, stroke, heart failure, atrial fibrillation, or peripheral vascular disease) was 29.6% in the high-dose group and 28.2% in the low-dose group. With the exception of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers and phosphate binders, the use of medications at baseline was similar in the two groups (Table S1 in the Supplementary Appendix).

Excluding patients who died or underwent kid-

Table 2. Primary and Secondary End Points.*

End Point	Proactive, High-Dose Iron Regimen (N = 1093)	Reactive, Low-Dose Iron Regimen (N = 1048)	Estimated Treatment Effect (95% CI)	P Value
Primary composite end point†				
Event in the intention-to-treat population — no. (%)	333 (30.5)	343 (32.7)	0.88 (0.76 to 1.03)	<0.001‡
Event in the per-protocol population — no./total no. (%)	326/1080 (30.2)	339/1038 (32.7)	0.88 (0.75 to 1.02)	<0.001‡
Secondary efficacy end points				
Death from any cause and a composite of myocardial infarction, stroke, or hospitalization for heart failure as recurrent events — no. of events (rate per 100 patient-yr)	456 (20.6)	538 (26.1)	0.78 (0.66 to 0.92)§	—
Death from any cause — no. (%)	246 (22.5)	269 (25.7)	0.84 (0.71 to 1.00)	—
Fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure — no. (%)	179 (16.4)	192 (18.3)	0.85 (0.69 to 1.04)	—
Fatal or nonfatal myocardial infarction — no. (%)	105 (9.6)	121 (11.5)	0.79 (0.61 to 1.03)	—
Fatal or nonfatal stroke — no. (%)	40 (3.7)	38 (3.6)	0.98 (0.63 to 1.52)	—
Hospitalization for heart failure — no. (%)	56 (5.1)	77 (7.3)	0.66 (0.47 to 0.93)	—
Median monthly dose of erythropoiesis-stimulating agent (IQR) — IU¶	29,757 (18,673 to 48,833)	38,805 (24,377 to 60,620)	−7539 (−9485 to −5582)	—
Blood transfusion				
Any transfusion — no. (%)	198 (18.1)	226 (21.6)	0.79 (0.65 to 0.95)	—
Total no. of units transfused	967	1122	NA	—
No. of units transfused per yr	0.43±2.23	0.72±4.26	—	—
Least-squares mean change in EQ-5D quality-of-life health index score averaged over time**	−0.04±0.01	−0.05±0.01	0.01 (−0.01 to 0.02)	—
Least-squares mean change in KDQOL overall score averaged over time††	−4.77±0.65	−4.40±0.66	−0.37 (−1.88 to 1.13)	—
Secondary safety end points				
Vascular access thrombosis — no. (%)	262 (24.0)	218 (20.8)	1.15 (0.96 to 1.38)	0.12
Hospitalization for any cause — no. (%)	651 (59.6)	616 (58.8)	1.01 (0.90 to 1.12)	0.90
Hospitalization for infection — no. (%)	323 (29.6)	307 (29.3)	0.99 (0.82 to 1.16)	0.92

* All the analyses were conducted in the intention-to-treat population and are superiority analyses unless indicated otherwise. The widths of the confidence intervals for the secondary end points have not been adjusted for multiple comparisons, so the confidence intervals should not be used to infer definitive treatment effects. The estimated treatment effects are hazard ratios unless indicated otherwise. NA denotes not available.

† The primary end point was a composite of death from any cause, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

‡ The P value is for noninferiority. In the primary end-point analysis in the intention-to-treat population, $P = 0.11$ for superiority.

§ The treatment effect is a rate ratio.

¶ For darbepoetin alfa and methoxy polyethylene glycol-epoetin beta, the weekly reported dose was multiplied by 200 to convert the units from micrograms to international units. The treatment effect is the estimated difference between the group medians.

|| It was not possible to calculate a corresponding confidence interval for the number of units of blood transfused because of the high percentage of patients without an event.

== Plus-minus values for the least-squares mean change in scores are means with the standard error. The treatment effect is the estimated difference in the mean changes from baseline in the treatment groups as calculated with the use of a mixed-effects repeated-measures model. Scores on the European Quality of Life–5 Dimensions (EQ-5D) quality-of-life health index range from -0.594 to 1.0 , with higher scores indicating better quality of life. The EQ-5D analysis included data from 783 patients in the high-dose group and from 749 in the low-dose group.

†† Plus-minus values for the least-squares mean change in scores are means with the standard error. The treatment effect is the estimated difference in the mean changes from baseline in the treatment groups as calculated with the use of a mixed-effects repeated-measures model. Scores on the Kidney Disease Quality of Life (KDQOL) instrument range from 0 to 100 , with higher scores indicating better quality of life. The KDQOL analysis included data from 790 patients in the high-dose group and from 755 in the low-dose group.

ney transplantation, follow-up was incomplete for 162 patients (14.8%) in the high-dose group and for 175 (16.7%) in the low-dose group (Fig. S1 in the Supplementary Appendix). The median follow-up was 2.1 years, with a maximum follow-up of 4.4 years.

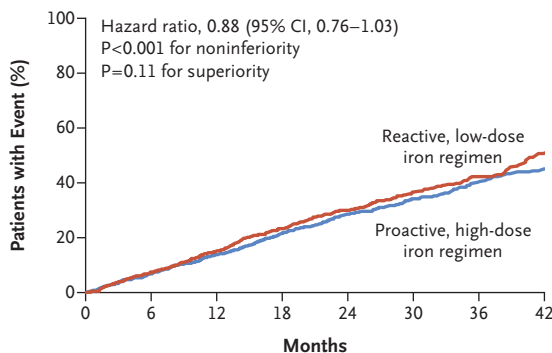
DOSES OF IRON AND ERYTHROPOIESIS-STIMULATING AGENTS

The cumulative doses of intravenous iron were greater in the high-dose group than in the low-dose group (Fig. 1). At month 12, the patients in the high-dose group had received a median of 2000 mg (95% confidence interval [CI], 1900 to 2100) more iron than the patients in the low-dose group. The median monthly dose of iron was 264 mg (interquartile range, 200 to 336) in the high-dose group and 145 mg (interquartile range, 100 to 190) in the low-dose group; the median difference in the monthly iron dose was 121 mg (95% CI, 114 to 129). The ferritin concentrations and transferrin saturation both increased from baseline rapidly with the high-dose regimen, as compared with the low-dose regimen (Figs. S2 and S3 in the Supplementary Appendix).

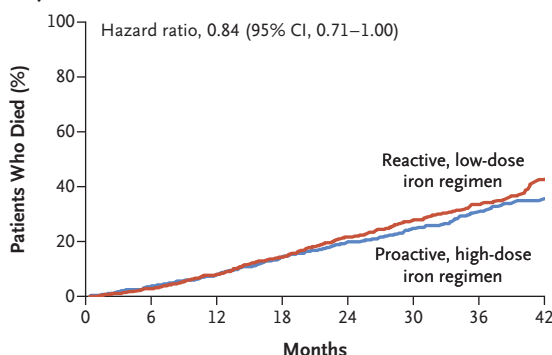
The cumulative dose of erythropoiesis-stimulating agent was lower in the high-dose group than in the low-dose group at all the postbaseline time points examined through 36 months (Fig. S4 in the Supplementary Appendix). The median monthly dose of erythropoiesis-stimulating agent was 19.4% lower in patients receiving the high-dose regimen (29,757 IU per month; interquartile range, 18,673 to 48,833) than in patients receiving the low-dose regimen (38,805 IU per month; interquartile range, 24,377 to 60,620) (median difference, -7539 IU per month; 95% CI, -9485 to -5582) (Table 2). Although patients in the two treatment groups had increases from baseline in the hemoglobin level over time, more rapid increases were observed in the high-dose group than in the low-dose group (Fig. S5 in the Supplementary Appendix). Plots of the median values and interquartile ranges of the above-mentioned laboratory tests are shown in Figures S6 through S10 in the Supplementary Appendix.

PRIMARY END POINT

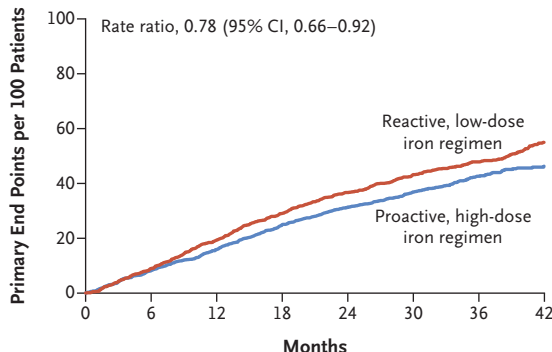
A primary end-point event occurred in 333 patients (30.5%) in the high-dose group, as compared with 343 (32.7%) in the low-dose group (hazard ratio, 0.88; 95% CI, 0.76 to 1.03; $P < 0.001$ for noninferiority).

A Primary Efficacy End Point**No. at Risk**

Reactive, low-dose iron regimen	1048	726	490	182
Proactive, high-dose iron regimen	1093	789	537	192

B Death from Any Cause**No. at Risk**

Reactive, low-dose iron regimen	1048	788	555	219
Proactive, high-dose iron regimen	1093	844	610	223

C Primary End-Point Components as Recurrent Events**No. at Risk**

Reactive, low-dose iron regimen	1048	788	551	219
Proactive, high-dose iron regimen	1093	844	609	192

Figure 2. Cumulative Incidence of the Primary Efficacy End Point, of Death from Any Cause, and of Death from Any Cause and a Composite of Cardiovascular Events as Recurrent Events.

Panel A shows the cumulative event rates for the primary efficacy end point (a composite of death from any cause, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure). Panel B shows the rates of death from any cause, and Panel C shows the rates of death from any cause and a composite of myocardial infarction, stroke, and hospitalization for heart failure as recurrent events plotted in the form of mean frequency functions with the use of the method of Ghosh and Lin.¹⁸ The hazard ratios (with 95% confidence intervals) and rate ratio (with the 95% confidence interval) were adjusted for the baseline stratification variables of vascular access, diabetes status, and duration of dialysis treatment.

priority; $P=0.11$ for superiority) (Fig. 2A and Table 2). Results were similar in the per-protocol population (hazard ratio, 0.88; 95% CI, 0.75 to 1.02; $P<0.001$ for noninferiority) and after the censoring of data from patients after they discontinued the trial drug. The effect of high-dose iron therapy on the primary end point was consistent across all the prespecified subgroups (vascular access, diabetes status, and duration of dialysis treatment), with no significant interactions observed (Fig. S11 in the Supplementary Appendix).

SECONDARY EFFICACY END POINTS

There were 246 deaths (22.5% of the patients) in the high-dose group and 269 (25.7%) in the low-dose group (hazard ratio, 0.84; 95% CI, 0.71 to 1.00) (Fig. 2B and Table 2), with consistent results observed across the prespecified subgroups (Fig. S11 in the Supplementary Appendix). The rates of fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure and the individual components of myocardial infarction and stroke were similar in the two treatment groups (Table 2). The rate of hospitalization for heart failure was lower in the high-dose group than in the low-dose group (hazard ratio, 0.66; 95% CI, 0.47 to 0.93).

Death and a composite of myocardial infarction, stroke, or hospitalization for heart failure as recurrent events occurred at a rate of 20.6 events per 100 patient-years in the high-dose group, as compared with 26.1 events per 100

Table 3. Serious Adverse Events.*

Event	Proactive, High-Dose Iron Regimen (N = 1093)	Reactive, Low-Dose Iron Regimen (N = 1048)
	no. of patients with event (%)	
Any serious adverse event	709 (64.9)	671 (64.0)
Infection or infestation	341 (31.2)	327 (31.2)
Injury, poisoning, or procedural complication	220 (20.1)	224 (21.4)
Cardiac disorder	154 (14.1)	165 (15.7)
General disorder or administration-site condition	159 (14.5)	129 (12.3)
Respiratory, thoracic, or mediastinal disorder	107 (9.8)	121 (11.5)
Gastrointestinal disorder	111 (10.2)	110 (10.5)
Surgical or medical procedure	117 (10.7)	102 (9.7)
Metabolism or nutrition disorder	95 (8.7)	116 (11.1)
Vascular disorder	90 (8.2)	104 (9.9)
Nervous system disorder	98 (9.0)	82 (7.8)
Renal or urinary disorder	34 (3.1)	48 (4.6)
Investigation†	33 (3.0)	44 (4.2)
Musculoskeletal or connective-tissue disorder	28 (2.6)	37 (3.5)
Neoplasm, benign, malignant, or unspecified, including cysts and polyps	27 (2.5)	27 (2.6)
Psychiatric disorder	21 (1.9)	26 (2.5)
Hepatobiliary disorder	23 (2.1)	18 (1.7)
Skin or subcutaneous-tissue disorder	22 (2.0)	14 (1.3)
Blood or lymphatic system disorder	14 (1.3)	17 (1.6)
Reproductive system or breast disorder	2 (0.2)	7 (0.7)
Eye disorder	2 (0.2)	6 (0.6)
Social circumstance‡	2 (0.2)	3 (0.3)
Immune system disorder	3 (0.3)	0
Congenital, familial, or genetic disorder	1 (0.1)	0
Ear or labyrinth disorder	0	1 (0.1)
Endocrine disorder	1 (0.1)	0

* Data are the numbers and percentages of patients who had a serious adverse event, according to *Medical Dictionary for Regulatory Activities*, version 15.1, system organ class.

† Investigation was defined as results of a laboratory test or other medical investigation that met the requirements for a serious adverse event.

‡ Social circumstance was defined as an event of medical relevance to the evaluation of other data (e.g., hospitalization for social reasons, such as general deterioration in health that led to an inability to function at home).

patient-years in the low-dose group (rate ratio, 0.78; 95% CI, 0.66 to 0.92) (Fig. 2C and Table 2). Patients in the high-dose group were less likely to receive blood transfusions than those in the low-dose group (hazard ratio, 0.79; 95% CI, 0.65 to 0.95). There were no significant between-group differences with regard to changes from baseline

in either the EQ-5D quality-of-life health index or the Kidney Disease Quality of Life overall score.

SAFETY

Vascular access thrombosis occurred in 262 patients (24.0%) in the high-dose group and in 218 (20.8%) in the low-dose group. The rates of hos-

pitalization for any cause and for infection were similar in the two treatment groups (Table 2). The rate of all episodes of infection in the high-dose group was 63.3 events per 100 patient-years, as compared with 69.4 events per 100 patient-years in the low-dose group (rate ratio, 0.91; 95% CI, 0.79 to 1.05).

Serious adverse events occurred in 709 patients (64.9%) in the high-dose group and in 671 (64.0%) in the low-dose group. The rates of the most common serious adverse events, analyzed according to MedDRA system organ class, were generally similar in the two treatment groups (Table 3). Infection was the most common noncardiovascular cause of death, and the rates were similar in the two treatment groups (Table S2 in the Supplementary Appendix).

OTHER END POINTS

High-dose iron administered proactively was associated with a small decrease in the platelet count over time, as compared with a small increase in the group that received low-dose iron administered reactively (Figs. S12 and S13 in the Supplementary Appendix). No significant between-group differences were observed with regard to the serum albumin concentration (Figs. S14 and S15 in the Supplementary Appendix).

DISCUSSION

In contrast to results from observational studies,¹⁹⁻²⁴ the results of this trial showed that the use of a high-dose intravenous iron regimen administered proactively was noninferior to the use of a low-dose intravenous iron regimen administered reactively and was not associated with higher risks of death, major adverse cardiovascular events, or infection. Furthermore, patients who received high-dose iron therapy had fewer blood transfusions and received lower doses of erythropoiesis-stimulating agents to maintain target hemoglobin levels than those in the low-dose group; patients in the high-dose group also had a faster increase in the hemoglobin level. In addition, high-dose iron administered proactively appeared to protect against recurrent events, including hospitalization for heart failure — a finding that is consistent with the results of placebo-controlled trials of intravenous iron therapy in patients with heart failure.²⁵⁻²⁸

The cardiovascular safety profile that is as-

sociated with the use of high-dose intravenous iron therapy to maintain a target hemoglobin level is notable, given the safety concerns about using higher doses of erythropoiesis-stimulating agents to elevate the hemoglobin level. We speculate that the dose-sparing effect of intravenous iron therapy on erythropoiesis-stimulating agents might contribute to the cardiovascular safety profile of high-dose iron therapy. It is also possible that iron replacement in patients with iron deficiency has direct cardiovascular benefits.

The absence of a greater risk of infection with the proactive, high-dose intravenous iron regimen is important, given studies that have suggested that iron might potentiate bacterial growth and infection.^{12,29-32} In our trial, the investigators were advised to discontinue iron therapy in patients during episodes of infection.

The most appropriate intravenous iron-replacement regimen in adults undergoing dialysis is unknown, which has resulted in different local, national, and international recommendations and practices. Observational studies have raised concern that monthly doses of 300 mg or more of intravenous iron are associated with poor outcomes.¹⁹⁻²¹ In the high-dose group of our trial, we used a monthly dose of 400 mg, with a per-protocol temporary discontinuation of treatment only if the ferritin concentration exceeded 700 μ g per liter or the transferrin saturation was 40% or higher. Patients in the high-dose group received approximately twice the amount of iron as those in the low-dose group over the first year of the trial and 83.5% more iron per month over the course of the trial. The median monthly dose of iron that was administered in the high-dose group was 264 mg, which is greater than the approximately 218-mg dose that was reported by the Dialysis Outcomes and Practice Patterns Study in the United States.³³ Given the absence of harm that was observed with the high-dose intravenous iron regimen in our trial, the safety and efficacy of even higher doses of iron might be explored in further trials.

The strengths of our trial include its size and long duration of follow-up, the collection and adjudication of important clinical events, and the limited exclusion criteria that allowed for the enrollment of a cohort of patients representative of those seen in routine clinical practice. Limitations of the trial include the restriction of the trial sites to a single country. Thus, the generalizability of

the trial findings to dialysis populations worldwide is unclear. The open-label nature of the trial may have potentially biased the rates of blood transfusion. Ongoing iron losses that have been associated with hemodialysis, combined with the iron-storage capacity of the reticuloendothelial system and the withholding of iron in patients with markedly elevated iron indexes (ferritin concentration of $>700 \mu\text{g}$ per liter or transferrin saturation of $\geq 40\%$), were expected to reduce the risk of overt toxic effects of iron in this population.¹ However, the safety of this high-dose iron regimen cannot be confirmed beyond the duration of the current trial. Finally, because quality-of-life data were missing for many patients, the interpretation of the effect of the iron dose with regard to these end points is limited.

In conclusion, this trial showed that, among patients undergoing hemodialysis, the use of a

high-dose regimen of intravenous iron administered proactively resulted in a significantly lower dose of erythropoiesis-stimulating agent and a lower incidence of blood transfusion than the use of a low-dose regimen administered reactively. Mortality and the incidence of nonfatal cardiovascular events and infections did not differ significantly between the two treatment groups.

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REFERENCES

- Wish JB, Aronoff GR, Bacon BR, et al. Positive iron balance in chronic kidney disease: how much is too much and how to tell? *Am J Nephrol* 2018;47:72-83.
- Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012;2:279-335.
- Baillie GR, Larkina M, Goodkin DA, et al. Variation in intravenous iron use internationally and over time: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2013;28:2570-9.
- Besarab A, Bolton WK, Browne JK, et al. 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* 1998;339:584-90.
- Coyne DW. The health-related quality of life was not improved by targeting higher hemoglobin in the Normal Hematocrit Trial. *Kidney Int* 2012;82:235-41.
- Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085-98.
- Pfeffer MA, Burdmann EA, Chen C-Y, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;361:2019-32.
- Drüeke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;355:2071-84.
- Macdougall IC, Bircher AJ, Eckardt KU, et al. Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int* 2016;89:28-39.
- Ganguli A, Kohli HS, Khullar M, Lal Gupta K, Jha V, Sakhuja V. Lipid peroxidation products formation with various intravenous iron preparations in chronic kidney disease. *Ren Fail* 2009;31:106-10.
- Del Vecchio L, Longhi S, Locatelli F. Safety concerns about intravenous iron therapy in patients with chronic kidney disease. *Clin Kidney J* 2016;9:260-7.
- Drakesmith H, Prentice AM. Hepcidin and the iron-infection axis. *Science* 2012;338:768-72.
- Neven E, De Schutter TM, Behets GJ, Gupta A, D'Haese PC. Iron and vascular calcification: is there a link? *Nephrol Dial Transplant* 2011;26:1137-45.
- Hansson L, Hedner T, Dahlöf B. Prospective Randomized Open Blinded End-point (PROBE) study: a novel design for intervention trials. *Blood Press* 1992;1:113-9.
- Macdougall IC, White C, Anker SD, et al. Randomized trial comparing proactive, high-dose versus reactive, low-dose intravenous iron supplementation in hemodialysis (PIVOTAL): study design and baseline data. *Am J Nephrol* 2018;48:260-8.
- National Institute for Health and Care Excellence (NICE). Chronic kidney disease: managing anaemia. June 3, 2015 (<https://www.nice.org.uk/guidance/ng8/resources/chronic-kidney-disease-managing-anaemia-pdf51046844101>).
- Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc B* 2000;62:711-30.
- Ghosh D, Lin DY. Nonparametric analysis of recurrent events and death. *Biometrics* 2000;56:554-62.
- Miskulin DC, Tangri N, Bandeen-Roche K, et al. Intravenous iron exposure and mortality in patients on hemodialysis. *Clin J Am Soc Nephrol* 2014;9:1930-9.
- Baillie GR, Larkina M, Goodkin DA, et al. Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality. *Kidney Int* 2015;87:162-8.
- 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* 2005;16:3070-80.
- Hougen I, Collister D, Bourrier M, et al. Safety of intravenous iron in dialysis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2018;13:457-67.
- 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* 2013;24:1151-8.
- Kshirsagar AV, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Brookhart MA. Intravenous iron supplementation practices and short-term risk of cardiovascular events in hemodialysis patients. *PLoS One* 2013;8(11):e78930.
- Dalal J, Katekhaye V, Jain R. Effect of ferric carboxymaltose on hospitalization and mortality outcomes in chronic heart failure: a meta-analysis. *Indian Heart J* 2017;69:736-41.

26. Anker SD, Kirwan BA, van Veldhuisen DJ, et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur J Heart Fail* 2018;20:125-33.
27. Qian C, Wei B, Ding J, Wu H, Wang Y. The efficacy and safety of iron supplementation in patients with heart failure and iron deficiency: a systematic review and meta-analysis. *Can J Cardiol* 2016; 32:151-9.
28. Cunha GJL, Rocha BML, Menezes Falcão L. Iron deficiency in chronic and acute heart failure: a contemporary review on intertwined conditions. *Eur J Intern Med* 2018;52:1-7.
29. Cassat JE, Skaar EP. Iron in infection and immunity. *Cell Host Microbe* 2013; 13:509-19.
30. Stefanova D, Raychev A, Deville J, et al. Hepcidin protects against lethal *Escherichia coli* sepsis in mice inoculated with isolates from septic patients. *Infect Immun* 2018;86(7):e00253-18.
31. Nairz M, Schroll A, Haschka D, et al. Genetic and dietary iron overload differentially affect the course of *Salmonella typhimurium* infection. *Front Cell Infect Microbiol* 2017;7:110.
32. Cross JH, Bradbury RS, Fulford AJ, et al. Oral iron acutely elevates bacterial growth in human serum. *Sci Rep* 2015;5: 16670.
33. US-DOPPS (Dialysis Outcomes and Practice Patterns Study) practice monitor: monthly IV iron dose received (90 day average), continuous (mg). April 2018 (https://www.dopps.org/DPM/Files/summaryIRON90DAY_overallTAB.htm).

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