see commentary on page 673

A randomized trial of intravenous and oral iron in chronic kidney disease

Rajiv Agarwal[1], John W. Kusek[2] and Maria K. Pappas[1]

[1]Indiana University School of Medicine and Richard L. Roudebush Veterans Administration Medical Center, Indianapolis, Indiana, USA and [2]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

Although iron is commonly used to correct iron deficiency anemia (IDA) in chronic kidney disease (CKD), its effect on kidney function is unclear. To assess this, we randomly assigned patients with stage 3 and 4 CKD and IDA to either open-label oral ferrous sulfate (69 patients to 325 mg three times daily for 8 weeks) or intravenous iron sucrose (67 patients to 200 mg every 2 weeks, total 1 g). The primary outcome was the between-group difference in slope of measured glomerular filtration rate (mGFR) change over two years. The trial was terminated early on the recommendation of an independent data and safety monitoring board based on little chance of finding differences in mGFR slopes, but a higher risk of serious adverse events in the intravenous iron treatment group. mGFR declined similarly over two years in both treatment groups (oral −3.6 ml/min per 1.73 m^2, intravenous −4.0 ml/min per 1.73 m^2, between-group difference −0.35 ml/min per 1.73 m^2; 95% confidence interval −2.9 to 2.3). There were 36 serious cardiovascular events among 19 participants assigned to the oral iron treatment group and 55 events among 17 participants of the intravenous iron group (adjusted incidence rate ratio 2.51 (1.56–4.04)). Infections resulting in hospitalizations had a significant adjusted incidence rate ratio of 2.12 (1.24–3.64). Thus, among non-dialyzed patients with CKD and IDA, intravenous iron therapy is associated with an increased risk of serious adverse events, including those from cardiovascular causes and infectious diseases.

Kidney International (2015) **88,** 905–914; doi:10.1038/ki.2015.163; published online 17 June 2015

KEYWORDS: adverse effects; anemia; chronic kidney disease; iron; randomized controlled trial

Correspondence: *Rajiv Agarwal, Indiana University and VAMC, 1481 West 10th Street, Indianapolis, Indiana 46202, USA. E-mail: ragarwal@iu.edu*

Received 5 March 2015; revised 31 March 2015; accepted 9 April 2015; published online 17 June 2015

It is estimated that there are ~8 million individuals in the United States with moderate-to-severe chronic kidney disease (CKD).[1] Anemia often occurs during moderate (stage 3) CKD, primarily from reduced erythropoietin production but also because of iron deficiency.[2] Enhanced erythropoiesis after therapy with recombinant human erythropoietin may lead to functional iron deficiency that often necessitates therapy with intravenous (IV) iron.[3] Although partial correction of anemia reduces the need for blood transfusions, toxicity due to the participation of elemental iron in causing cell damage and in generating oxidative stress has raised concern of potential health risks that remain incompletely understood.[4,5] There is a paucity of information on the safety of this therapy as only one-half of the randomized clinical trials of oral and IV iron in adults and children reported adverse events, and even fewer described those that were serious.[6]

Oxidative stress plays an important role in the pathogenesis and progression of CKD.[7,8] Iron increases biological markers of oxidative stress[9] in cell cultures,[10] animal models,[11] and among end-stage renal disease patients treated with hemodialysis.[12–14] Among patients with CKD not on dialysis, IV iron can generate oxidative stress and downstream effects such as endothelial damage and kidney injury.[15,16] Thus, iron-induced injury may lead to an accelerated course of renal[7] and cardiovascular disease.[17,18] Research recommendations emphasize the need to evaluate the long-term risks of IV iron therapy among CKD patients.[19]

We hypothesized that among patients with moderate-to-severe CKD and iron deficiency anemia (IDA), compared with oral iron, infusion of IV iron will result in greater decline in kidney function. We report here the primary results of the REVOKE (*r*andomized trial to *e*valuate intra*v*enous and *o*ral iron in chronic *k*idn*e*y disease).

RESULTS

Between 15 August 2008 and 20 October 2014, we randomized 136 subjects with iron deficiency anemia (IDA) and CKD not on dialysis to either oral iron sulfate or IV iron sucrose. The trial flow is shown in the Supplementary Appendix (Supplementary Figure S1 online).

The clinical characteristics of study participants at baseline are shown in Table 1. Of note, compared with the oral iron

Table 1 | Baseline characteristics of the study sample, overall and by treatment group assignment

Clinical characteristic	Oral iron ($n=69$)	Intravenous iron ($n=67$)	All subjects ($n=136$)
Age (years)	67.8 ± 11.5	63.2 ± 10.7	65.5 ± 11.3
Male sex, *n* (%)	54 (78.3%)	50 (74.6%)	104 (76.5%)
Blacks, *n* (%)	18 (26.1%)	27 (40.3%)	45 (33.1%)
Hispanic, *n* (%)	0 (0%)	2 (3%)	2 (1.5%)
Etiology of chronic kidney disease			
Diabetes mellitus, *n* (%)	30 (43.5%)	29 (43.3%)	59 (43.4%)
Hypertension, *n* (%)	20 (29%)	19 (28.4%)	39 (28.7%)
Ischemic kidney disease, *n* (%)	5 (7.2%)	3 (4.5%)	8 (5.9%)
Glomerulonephritis, *n* (%)	2 (2.9%)	4 (6%)	6 (4.4%)
Polycystic kidney disease, *n* (%)	1 (1.4%)	2 (3%)	3 (2.2%)
Other etiologies, *n* (%)	3 (4.3%)	6 (9%)	9 (6.6%)
Comorbid illnesses			
Diabetes mellitus, *n* (%)	54 (78.3%)	47 (70.1%)	101 (74.3%)
Cardiovascular disease, *n* (%)	43 (62.3%)	30 (44.8%)	73 (53.7%)
Hospitalized heart failure, *n* (%)	21 (30.4%)	16 (23.9%)	37 (27.2%)
Myocardial infarction, *n* (%)	17 (24.6%)	17 (25.4%)	34 (25%)
Coronary revascularization, *n* (%)	21 (30.4%)	15 (22.4%)	36 (26.5%)
Pacemaker or defibrillator, *n* (%)	7 (10.1%)	6 (9%)	13 (9.6%)
Stroke, *n* (%)	9 (13%)	6 (9%)	15 (11%)
Peripheral vascular disease, *n* (%)	12 (17.4%)	7 (10.4%)	19 (14%)
Hospitalized infectious disease, *n* (%)	34 (49.3%)	22 (32.8%)	56 (41.2%)
Skin (e.g., cellulitis), *n* (%)	11 (15.9%)	4 (6%)	15 (11%)
Bone (e.g., pyogenic arthritis, osteomyelitis), *n* (%)	6 (8.7%)	3 (4.5%)	9 (6.6%)
Lung (e.g., pneumonia), *n* (%)	16 (23.2%)	5 (7.5%)	21 (15.4%)
Sepsis, *n* (%)	6 (8.7%)	1 (1.5%)	7 (5.1%)
Urinary tract infections, *n* (%)	7 (10.1%)	5 (7.5%)	12 (8.8%)
Other infections, *n* (%)	3 (4.3%)	4 (6%)	7 (5.1%)
Gastrointestinal bleeding, *n* (%)	8 (11.6%)	3 (4.5%)	11 (8.1%)
Past RBC transfusion, *n* (%)	13 (18.8%)	12 (17.9%)	25 (18.4%)
Smoking, n *(%)*			
Never smoker, *n* (%)	13 (18.8%)	17 (25.4%)	30 (22.1%)
Past smoker, *n* (%)	44 (63.8%)	39 (58.2%)	83 (61%)
Active smoker, *n* (%)	12 (17.4%)	11 (16.4%)	23 (16.9%)
Medication use			
ACE inhibitor or ARB use, *n* (%)	45 (65.2%)	43 (64.2%)	88 (64.7%)
Statin use, *n* (%)	48 (69.6%)	44 (65.7%)	92 (67.6%)
Antiplatelet agent use, *n* (%)	47 (68.1%)	35 (52.2%)	82 (60.3%)
Erythropoietin agent use, *n* (%)	5 (7.2%)	6 (9%)	11 (8.1%)
Blood pressure			
Seated clinic systolic BP (mm Hg)	131.4 ± 21.9	129 ± 18.5	130.2 ± 20.3
Seated clinic diastolic BP (mm Hg)	63.2 ± 13.4	65.7 ± 12.4	64.4 ± 13
Proteinuria stratum			
High proteinuria stratum (≥3 g/g)	9 (13%)	9 (13.4%)	18 (13.2%)
Low proteinuria stratum (<3 g/g)	60 (87%)	58 (86.6%)	118 (86.8%)
Laboratory parameters			
Hemoglobin (g/dl)	10.5 ± 1	10.7 ± 1	10.6 ± 1
Transferrin saturation (%)	17.3 ± 6.7	17.4 ± 5.1	17.3 ± 5.9
Serum ferritin (ng/ml)	133 ± 155	173 ± 138	153 ± 148
Serum albumin (g/dl)	3.5 ± 0.5	3.5 ± 0.6	3.5 ± 0.5
Estimated GFR (ml/min per 1.73 m^2)	34.7 ± 10	34.3 ± 10.2	34.5 ± 10
Log urinary protein/creatinine (mg/mg)	− 0.9 ± 1.4	− 0.6 ± 1.5	− 0.7 ± 1.4

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; GFR, glomerular filtration rate; RBC, red blood cell.

group, the IV iron group was younger ($P=0.02$) and had less baseline cardiovascular disease ($P=0.04$) and past history of hospitalization due to infection ($P=0.05$). Overall, the mean hemoglobin concentration at baseline was 10.6 g/dl, transferrin saturation 17.3%, and serum ferritin 153 ng/ml. At baseline, erythopoiesis stimulating agents were used by only 8.1% of the participants. Mean measured glomerular filtration rate (mGFR) was 34.5 ml/min per 1.73 m^2 and proteinuria

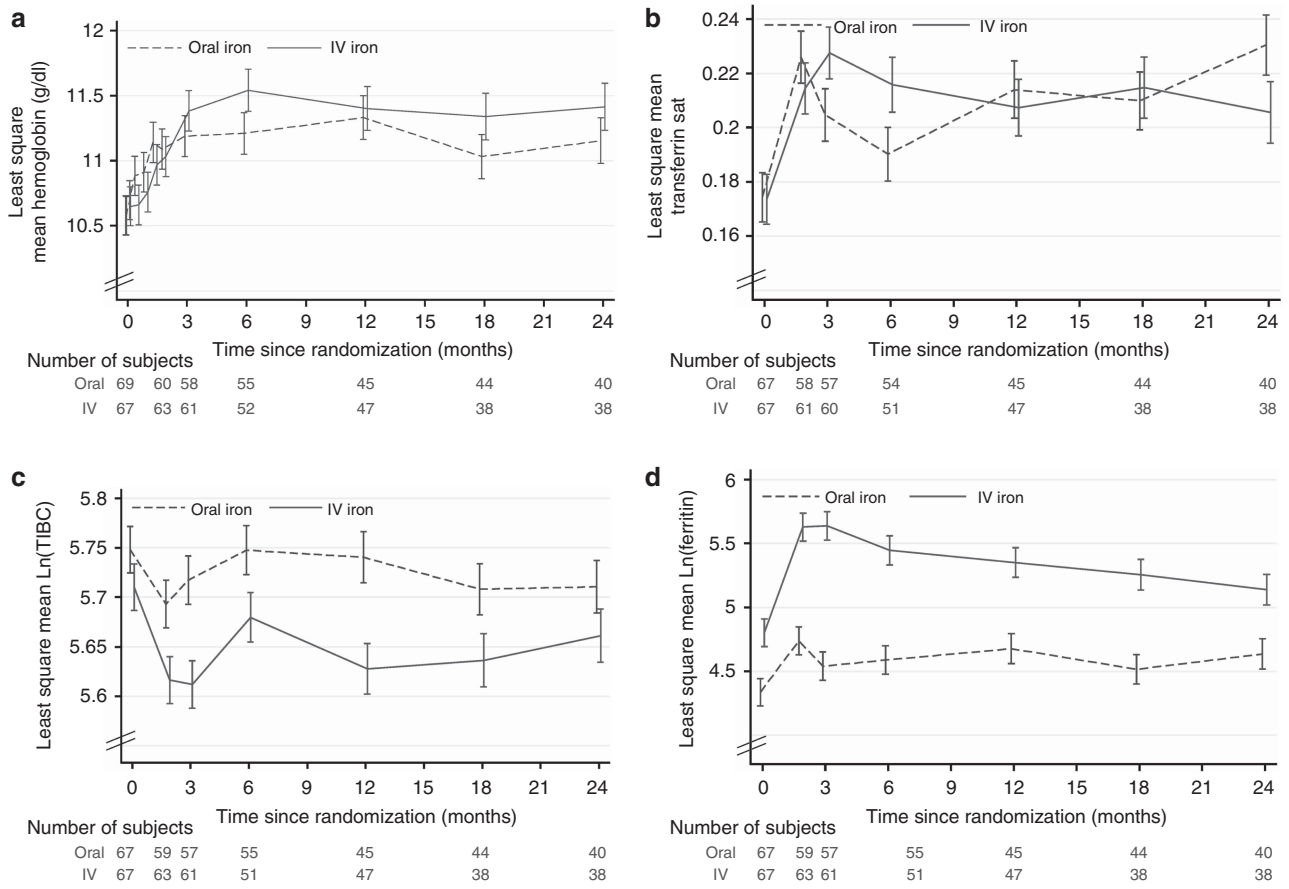

Figure 1 | Time course of hemoglobin and iron parameters. (**a**) Hemoglobin change from baseline to 3 months in the oral iron group was 0.61 g/dl and in the intravenous (IV) iron group was 0.69 g/dl (difference +0.08 (95% confidence interval (CI) −0.34 to 0.51, $P=0.72$). Differences at 6 months (0.22 g/dl, $P=0.3$), 12 months (−0.04 g/dl, $P=0.85$), and 24 months (0.15 g/dl, $P=0.56$) were also not statistically significant. (**b**) Transferrin saturation (sat) change from baseline to 3 months in the oral iron group was 0.03 and in the IV iron group was 0.05 (difference +0.024 (95% CI −0.004 to 0.052, $P=0.10$). Differences at 6 months (0.026, $P=0.08$), 12 months (−0.04 g/dl, $P=0.85$), and 24 months (−0.024 g/dl, $P=0.14$) were also not statistically significant. (**c**) Log total iron binding capacity (TIBC) change from baseline to 3 months in the oral iron group was −0.031 ($P=0.13$) and in the IV iron group was −0.098 ($P<0.001$) (difference −0.067 (95% CI −0.122 to −0.012, $P=0.02$). Differences in change from baseline at 6 months (−0.030, $P=0.31$), 12 months (−0.075 g/dl, $P=0.015$), and 24 months (−0.01, $P=0.74$) were small. (**d**) Log ferritin change from baseline to 3 months in the oral iron group was −0.20 ($P=0.01$) and in the IV iron group was 0.84 ($P<0.001$) (difference 0.63 (95% CI 0.41 to 0.85, $P<0.001$). Differences between groups in change from baseline at 6 months (0.39, $P=0.001$), 12 months (0.21 g/dl, $P=0.085$), and 24 months (0.04, $P=0.77$) diminished.

had a geometric mean of 0.5 g per g creatinine. The median follow up (interquartile range) of all participants was 24.0 months (11.0–24.3) and did not differ by treatment group assignment.

Hemoglobin control between groups and interventions to maintain hemoglobin

Figure 1a shows hemoglobin levels at baseline and over time in all participants. At baseline, mean hemoglobin was 10.5 g/dl in the oral iron group and 10.7 g/dl in the IV iron group. Hemoglobin levels improved over time in both groups, and no statistically significant difference between mean levels in the treatment groups was noted during follow-up.

Changes in transferrin saturation, total iron binding capacity, and serum ferritin are shown in Figure 1b–d. Serum ferritin concentration was significantly higher in the IV iron group only from baseline to 6 months.

Beyond the first 8 weeks of repletion therapy, IV iron administration was given to two subjects in the oral iron group (doses of 250 and 1000 mg), of which one was given during hospitalization. In contrast, 9 subjects in the IV iron group received additional IV iron at a median dose of 1729 mg (interquartile range 838–2000 mg). In comparison, oral iron was prescribed after the 8-week randomized treatment period to 7 subjects in the IV iron group for median of 20 days (interquartile range 12.3–20) and beyond the first 8 weeks to 36 subjects for a median of 60 days (interquartile range 30–to 90) (*P*-value for difference in medians = 0.001).

The average erythropoiesis-stimulating agent (ESA) use over the course of 2 years was similar in the two groups. In the oral iron group, 22 subjects required ESA for an average of 61 weeks (s.d. 39) with a geometric mean cumulative dose of darbepoetin of 483 μg. In the IV iron

group, 16 subjects required ESA for an average of 54 weeks (s.d. 41) with a geometric mean cumulative dose of darbepoetin of 614 μg.

In each group, 12 study participants received blood transfusions. Of those who needed packed red blood cell transfusions, the mean number of units needed over 2 years was 5.3 (range 2–20 units) in the oral group and 3.5 (range 1–7) in the IV group ($t=0.99$, $P=0.3$).

Early termination of the trial

The trial was stopped early on the unanimous recommendation of the data and safety monitoring board based on an increase in the serious adverse event rate in participants assigned to IV iron treatment compared with oral iron therapy and little difference in mGFR between treatment groups. Given the persisting signal of safety, but little chance of finding the projected difference in measured GFR between groups, they unanimously recommended termination of the trial.

Rate of decline in kidney function

Figure 2a shows the modeled iothalamate mGFR slopes in the two groups adjusted for baseline log urinary protein/creatinine ratio. Iothalamate GFR declined similarly over time in both groups (oral iron − 3.6 ml/min per 1.73 m^2 per year, IV iron –4.0 ml/min1.73 m^2 per year, and between-group difference − 0.35 ml/min per 1.73 m^2 per year; 95% confidence interval (CI) − 2.9 to 2.3, $P=0.79$). After additional adjustment for age, sex, black race, angiotensin-converting enzyme/angiotensin receptor blocker use, and cardiovascular disease, the rate of change in GFR became more similar between groups (oral iron − 3.8 ml/min per 1.73 m^2 per year, IV iron –3.9 ml/min per 1.73 m^2 per year, and between-group difference − 0.11 ml/min per 1.73 m^2 per year; 95% CI − 2.7 to 2.5, $P=0.94$; Figure 2b).

The small baseline difference in proteinuria was not statistically significant. There was significant increase in proteinuria over time ($P=0.04$) in both treatment groups, but there was no significant difference between groups (Supplementary Figure S2 online).

Results of kidney disease quality of life (KDQOL)

None of the domains of the KDQOL Questionnaire demonstrated any significant change over time or a significant interaction between treatment groups over time (Figure 3a–d).

Serious adverse events

Table 2 shows the serious adverse events between groups over the course of the trial. There were six deaths in the IV group and four in the oral iron group. A total of 104.5 patient-years (PY) of follow-up were obtained in the oral iron treatment group and 101 PY of follow up in the IV iron treatment group. Serious adverse events in the oral iron group occurred in 40 subjects who had 176 events (168.4/100 PY); in the IV iron group they occurred in 37 subjects who had 201 events

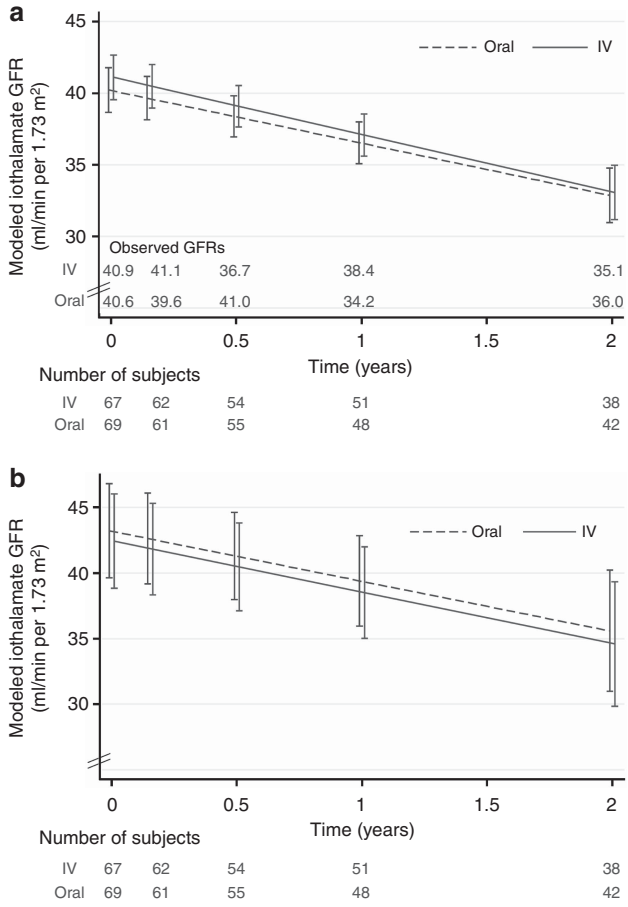

Figure 2 | Time course of change in measured glomerular filtration rate (GFR) using plasma iothalamate clearance. Plasma iothalamate clearances were measured at 5 time points over 2 years (baseline, 8 weeks, 6 months, 1 year, and 2 years). Error bars indicate one s.e. of the modeled mean at each time point. The numbers at the bottom of each of the figures denote the number of subjects with measurements in each of the two groups. Observed means for each group are shown just above the x axis and were similar to modeled means. (**a**) The modeled slopes over 2 years adjusted for baseline log urine protein/creatinine ratio. This was the primary end point of the study. Slope for oral iron − 3.6 ml/min per 1.73 m^2 per year, intravenous (IV) iron –4.0 ml/min per 1.73 m^2 per year, and between-group difference − 0.35 ml/min per 1.73 m^2 per year (95% confidence interval (CI) − 2.9 to 2.3, $P=0.79$). (**b**) A model further adjusted for age, sex, race, angiotensin-converting enzyme (ACE) or angiotensin receptor blocker (ARB) use, and cardiovascular disease. This was the secondary end point: slope for oral iron − 3.8 ml/min per 1.73 m^2 per year, IV iron –3.9 ml/min per 1.73 m^2 per year, and between-group difference 0.11 ml/min per 1.73 m^2 per year (95% CI − 2.7 to 2.5, $P=0.94$).

(199/100 PY), unadjusted incidence rate ratio (IRR) 1.18 (95% CI 0.97–1.45, $P=0.106$). Adjusted IRR was 1.60 (1.28–2.00), $P<0.0001$.

Serious adverse events due to infections in the oral iron group occurred 27 times in 11 subjects (25.8/100 PY); in the IV iron group they occurred 37 times in 19 subjects (36.6/100 PY; IRR 1.42 (95% CI 0.86–2.33, $P=0.17$). Adjusted IRR was 2.12 (1.24–3.64), $P<0.006$. Compared with the oral iron group, the incidence of lung and skin infections were increased between three- and fourfold in the IV iron group.

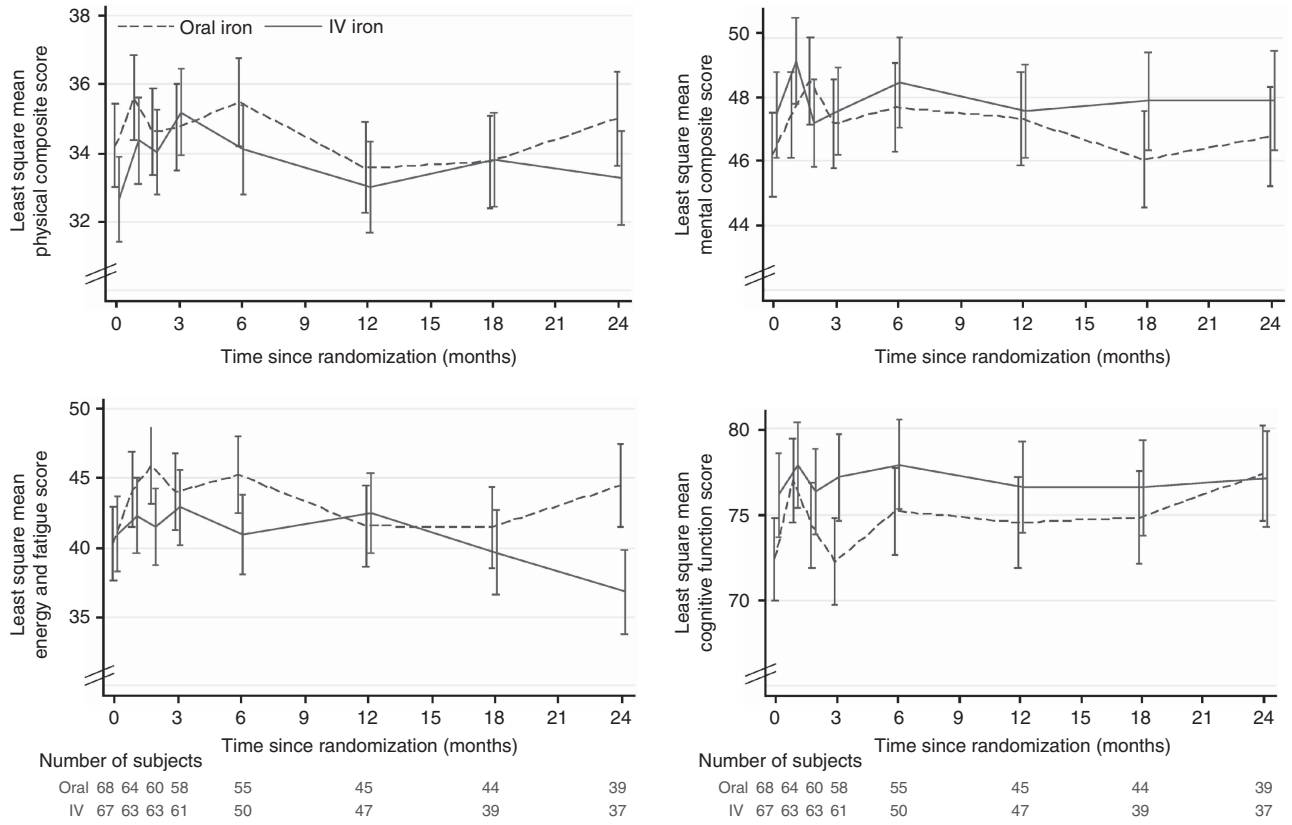

Figure 3 | Time course of kidney disease quality of life (KDQOL) by treatment group. Least square mean estimates of health-related quality of life scores are shown over time by two treatment groups. Error bars are 1 s.e.m. None of the comparisons were statistically different over time or between groups over time. Higher scores mean denote a higher health-related quality of life. Other domains of the KDQOL (data not shown) were also not significant.

Cardiovascular events in the oral iron group occurred 36 times in 19 subjects (34.4/100 PY); in the IV iron group they occurred 55 times in 17 subjects (54.4/100 PY; IRR 1.58 (95% CI 1.04–2.41, $P=0.033$). Adjusted IRR was 2.51 (1.56–4.04), $P<0.001$. Compared with the oral iron group, the incidence of hospitalized heart failure was increased approximately twofold in the IV iron group. Supplementary Figures S3–S5 online show that the distribution of the events was such that it was not one or two subjects in one group who influenced the outcomes.

Overall, gastrointestinal adverse events particularly diarrhea were more common among participants randomized to oral iron (Supplementary Table S1, Supplementary Appendix online). On the other hand, gout was more frequent among those randomized to IV iron.

DISCUSSION

Among anemic patients with iron deficiency and CKD enrolled in the REVOKE trial IV iron therapy, we failed to confirm that IV iron accelerates the decline in kidney function. However, IV iron was associated with an increased frequency of overall serious adverse events as well as cardiovascular and infectious complications. Specifically, IV iron administration was also associated with an increased incidence of the hospitalizations due to congestive heart failure, pneumonias, and serious skin infections (requiring administration of antibiotics in the hospital) that became apparent after adjustment for the more favorable clinical and demographic characteristics at baseline among participants assigned to IV iron therapy (younger age, lower prevalence of cardiovascular disease, and hospitalized infections). Treatment with either oral or IV iron-repletion therapy produced statistically and clinically significant improvements in hemoglobin that were sustained over the 24 months of the trial.

In a meta-analysis comparing randomized trials of oral with IV iron on hemoglobin response among patients with CKD not on dialysis, Rozen-Zvi *et al.*[20] reported six studies. Five of these six trials were of short term, 1–3 months, and compared with oral iron, the mean increase in hemoglobin with IV iron was 0.31 (95% CI 0.09–0.53) g/dl. However, one of the studies included in this meta-analysis was 6 months long and had a mean decline in hemoglobin of 0.52 g/dl associated with IV iron administration.[21] In the largest randomized clinical trial comparing IV with oral iron in iron-deficient anemic patients with CKD, the Ferinject assessment in patients with Iron deficiency anemia and Non-Dialysis-dependent Chronic Kidney Disease (FIND-CKD) investigators randomized 626 patients in 193 centers

Table 2 | Serious adverse events reported following randomization

Event type	Oral iron ($n=69$) Subjects (n)	Events (n)	Incidence rate (events/100 PY)	IV iron ($n=67$) Subjects (n)	Events (n)	Incidence rate (events/100 PY)	Incidence rate ratio, IV/oral (95% CI)	P	Adjusted incidence rate ratio, IV/oral (95% CI)	P
Overall SAEs	40	176	168.4	37	201	199	1.18 (0.97–1.45)	0.106	1.60 (1.28–2.00)	<0.0001
Infections	11	27	25.8	19	37	36.6	1.42 (0.86–2.33)	0.168	2.12 (1.24–3.64)	0.006
Skin	6	6	5.7	7	11	10.9	1.90 (0.70–5.13)	>0.2	3.79 (1.32–10.87)	0.013
Bone	2	7	6.7	3	4	4	0.59 (0.17–2.02)	>0.2		
Lung	4	4	3.8	8	11	10.9	2.85 (0.91–8.94)	0.073	4.35 (1.23–15.39)	0.022
UTI	3	5	4.8	3	5	4.9	1.03 (0.30–3.57)	>0.2	2.37 (0.60–9.34)	>0.2
Sepsis	1	2	1.9	5	5	4.9	2.59 (0.50–13.33)	>0.2	122.15 (0.89–16819.84)	0.056
Other	2	3	2.9	1	1	1	0.34 (0.04–3.32)	>0.2		
Cardiovascular	19	36	34.4	17	55	54.4	1.58 (1.04–2.41)	0.033*	2.51 (1.56–4.04)	<0.001
CHF	9	15	14.3	9	28	27.7	1.93 (1.03–3.62)	0.040*	2.07 (1.04–4.11)	0.038
Angina	2	2	1.9	2	2	2	1.03 (0.15–7.35)	>0.2		
MI	8	9	8.6	8	9	8.9	1.03 (0.41–2.61)	>0.2	1.25 (0.41–3.82)	>0.2
Stroke	0	0	0	2	2	2	2.0e+07 (0.00 -.)	>0.2		
Arrhythmia	4	4	3.8	4	5	4.9	1.29 (0.35–4.82)	>0.2		
PVD	1	2	1.9	2	3	3	1.55 (0.26–9.29)	>0.2		
Other	4	4	3.8	5	6	5.9	1.55 (0.44–5.50)	>0.2		
Renal	18	29	27.7	14	28	27.7	1.00 (0.59–1.68)	>0.2	1.39 (0.78–2.47)	>0.2
AKI	15	22	21	12	21	20.8	0.99 (0.54–1.80)	>0.2		
Hyperkalemia	5	6	5.7	2	4	4	0.69 (0.19–2.44)	>0.2		
Other	1	1	1	3	3	3	3.10 (0.32–29.84)	>0.2		
Cancer related	4	4	3.8	4	8	7.9	2.07 (0.62–6.87)	>0.2		
Other	31	69	66	25	61	60.4	0.91 (0.65–1.29)	>0.2		
PRBC transfusion	12	17	16.3	12	19	18.8	1.16 (0.60–2.22)	>0.2		
GI bleed	5	7	6.7	0	0	0	NA	NA		
Hyperglycemia	1	1	1	2	2	2	2.07 (0.19–22.82)	>0.2		
Hypoglycemia	3	5	4.8	0	0	0	NA	NA		
Diabetic retinopathy	1	2	1.9	1	5	4.9	2.59 (0.50–13.33)	>0.2		
Hypertensive crisis	1	1	1	3	5	4.9	5.17 (0.60–44.28)	0.134		
Urinary retention	2	3	2.9	2	3	3	1.03 (0.21–5.13)	>0.2		
Miscellaneous	21	33	31.6	20	27	26.7	0.85 (0.51–1.41)	>0.2		
ESRD	7	7	6.7	6	6	5.9	0.89 (0.30––2.64)	>0.2	1.04 (0.25–4.24)	>0.2
Death	4	4	3.8	6	6	5.9	1.55 (0.44–5.50)	>0.2	1.60 (0.28–9.07)	>0.2
CV related	2	2	1.9	2	2	2	1.03 (0.15–7.35)	>0.2		
Non-CV related	2	2	1.9	4	4	4	2.07 (0.38–11.30)	>0.2		

Abbreviations: AKI, acute kidney injury; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; ESRD, end-stage renal disease; GI, gastrointestinal; IV, intravenous; MI, myocardial infarction; NA, not available; SAE, serious adverse event; PRBC, packed red blood cell; PVD, peripheral vascular disease; PY, patient-years; UTI, urinary tract infection.

Oral iron exposure: 104.5 PY, and IV iron exposure: 101 PY. Adjustments for overall serious adverse events, cardiovascular events, renal events, AKI, hyperkalemia, and ESRD, death: age, sex, black race, stratum of proteinuria, baseline estimated glomerular filtration rate (GFR), diabetes, cardiovascular disease, tobacco use, systolic blood pressure (BP), statin use, antiplatelet therapy, angiotensin-converting enzyme (ACE) or angiotensin receptor blocker (ARB) use. Adjustments for CHF events: all the above adjustments except cardiovascular disease replaced by history of hospitalization for CHF. Adjustments for MI events: all the above adjustments except cardiovascular disease replaced by history of MI. Adjustments for infection events: all the above adjustments except dropped systolic BP, statin use, antiplatelet therapy, ACE or ARB use, and added history of hospitalized infection. Adjustments for skin infection events: all the adjustments for infection except that history of hospitalized infection replaced by prior history of hospitalized cellulitis. Adjustments for lung infection events: all the adjustments for infection except that history of hospitalized infection replaced by prior history of hospitalized pneumonia. Adjustments for urinary infection events: all the adjustments for infection except that history of hospitalized infection replaced by prior history of hospitalized UTI. Adjustments for sepsis events: all the adjustments for infection except that history of hospitalized infection replaced by prior history of hospitalized sepsis.

in a 1:1:2 ratio to ferric carboxymaltose targeting ferritin to high-level (400–600 ng/ml), lower-level (100–200 ng/ml), or oral iron with the primary end point of time to initiation of other anemia management (ESA, other iron therapy, or blood transfusion) or hemoglobin trigger of two consecutive values of <10 g/dl during weeks 8–52. The investigators reported the mean change in hemoglobin from baseline to 52 weeks as 1.0 g/dl in oral iron group, 0.9 g/dl when IV ferric carboxymaltose targeted ferritin to 100–200 ng/ml, and 1.4 g/dl ($P=0.26$) when IV ferric carboxymaltose targeted ferritin to 400–600 ng/ml ($P=0.014$).[22] Although statistically significant, the difference in hemoglobin of 0.4 g/dl between oral iron and high-dose IV iron observed in that study should be interpreted cautiously because the oral ferrous sulfate administration was only 100 mg twice daily that is much below the recommended intake of ferrous sulfate 325 mg three times daily used in our trial. Given the short duration of most of the clinical trials comparing oral with IV administration of iron, the long-term safety of these modes of administration of supplemental iron could not be assessed. Accordingly, guidelines have no recommendation on the preferred mode of iron administration in such patients.[19]

We showed that compared with oral iron-based therapy, IV iron therapy was associated with greater risk of infections and cardiovascular complications. Although assignment to the IV iron treatment group resulted in greater increments in both transferrin saturation and serum ferritin concentration, suggesting a better repletion of iron stores, there was little difference in mean hemoglobin increments in the long term. Overall, there was an increase in proteinuria noted, but between-group differences over time in baseline proteinuria were not observed. These findings confirm no increase in basal level of proteinuria over several weeks among patients receiving IV iron.[16]

The adverse events observed in our randomized trial are biologically plausible. Iron promotes growth of even common bacteria such as *Staphylococcus epidermidis*.[23] In addition, the inflammatory response to infection is enhanced[24,25] and phagocytic function of neutrophils has been shown to be impaired by iron.[26] Compared with oral iron, a greater iron saturation and a higher serum ferritin concentration were seen in the IV iron group that may increase the likelihood for the generation of free iron. Free iron induces the generation of the hydroxyl ion via the Haber–Weiss Fenton reaction, quenching of nitric oxide, and endothelial dysfunction, and may accelerate atherosclerosis.[27] Repeated administration of iron sucrose results in proteinuria after infusion;[16] if this results in impaired sodium handling by the kidney, it may explain excess heart failure hospitalizations seen in our study.

Our findings may not be generalizable to patients with kidney failure requiring hemodialysis or those with heart failure. As an example, among patients with heart failure randomized to either ferric carboxymaltose or placebo and followed for 6 months, cardiovascular disorders (sum of cardiac, vascular, and neuro disorders) were incident in 11.6/100 PY in the iron group and 25.6/100 PY in the placebo group.[28] This is in sharp contrast to 52.5 events/100 PY in the IV iron group and 33.5/100 PY in the oral group in our study. Infections were seen with an incidence of 1.4/100 PY in the iron group and none in the placebo group that again is in contrast to 36.6 events/100 PY in the IV iron group and 25.8/100 PY in the oral group in our study. In another study, of the heart failure patients with iron deficiency with or without anemia, 86% came from Russia, Ukraine, and Poland. Participants were randomized to ferric carboxymaltose or placebo and followed for 1 year and they had serious adverse event rate of approximately one-quarter of that reported in our study.[29] Because compared with the general population, patients with CKD are at elevated risk for cardiovascular and infectious illnesses, IV iron may exacerbate this risk.

Neither of the above studies was done in the CKD population. However, despite about a year-long trial, our safety data are difficult to compare with even the FIND-CKD study for several reasons.[22] First, they excluded patients whose CKD was progressing rapidly and they could reach end-stage renal disease within 12 months. Second, adverse events and serious adverse events are reported up to the point at which another anemia therapy was initiated and/or the randomized study medication was discontinued. In other words, if ESA was initiated or patient transfused, the study stopped reporting serious adverse events. Third, serious adverse events were reported if they occurred in $<1\%$ of the patients. Even so, the investigators reported serious adverse events in 25.3%, 24.0%, and 18.9% of patients in the high-ferritin IV iron, low-ferritin IV iron, and oral iron groups, respectively. Thus, compared with oral iron group, IV iron serious adverse event was between 27 and 34% higher. Fourth, multiple events within patients were not reported. In other words, multiple congestive heart failure events in one patient would only be reported once. REVOKE counted each event as a separate serious adverse event. In fact, the number of patients who had serious adverse events in REVOKE were similar between oral and IV iron groups. Indeed in our study, we found that exposure to IV iron increased the frequency—not the number of participants—with serious adverse events.

Although our results should not be extrapolated to hemodialysis patients, it is notable that among hemodialysis patients IV iron is being increasingly used.[30,31] This is presumably so in an effort to maintain hemoglobin concentration while sparing erythropoietin to reduce cost; this has provoked an increase in serum ferritin concentration and transferrin saturation. Our study raises the need for further research regarding the safety of this practice.

Among the trials conducted to date to evaluate the role of route of therapy to replenish iron, ours is the first to directly measure GFR and is one of the longest. In addition, randomizing a reasonably large number of subjects at one center with all adverse event ascertainments done by one investigator is a notable strength of this trial. There are limitations to consider including an open-label design, although this likely did not affect measurement of GFR or occurrence of all-cause

adverse events. Second, there were slight imbalances in the clinical and demographic characteristics of the treatment groups at baseline; however, they were less favorable (older age, more cardiovascular, and infectious disease history) among the oral iron group. Third, we did not have a placebo group. Thus, we did not study whether no iron is even safer than oral iron in this group of patients, but that would be considered unethical. Taken together, our findings raise the urgent need for long-term safety of IV iron in vulnerable populations such as CKD.

The primary question posed by our study as to whether IV iron accelerates the decline in GFR in patients with CKD was not conclusively answered; however, the likelihood of finding a 50% difference in mGFR at 2 years was very low. However, among patients with IDA and moderate-to-advanced CKD, compared with oral iron, IV iron sucrose appears to result in a higher risk for infections and cardiovascular complications over the long term. Oral iron may be the preferred initial mode of treatment for IDA in stage 3 and 4 CKD.

MATERIALS AND METHODS

The REVOKE was an open-label, parallel-group, active-control, single-center randomized trial designed to compare the safety and efficacy of an oral iron therapy with an IV iron treatment, each administered over the first 8 weeks after randomization. The study was conducted between August 2008 and November 2014 with study participants recruited from Eskenazi Hospital and the Veterans Administration Hospital, both located in Indianapolis, IN, USA. Initially constituted by the National Institutes of Health, an independent data and safety monitoring board reviewed the information on safety and study progress at least annually. During the latter part of the study, a new data and safety monitoring board was established by Indiana University. The study was approved by the Institutional Review Board of Indiana University and the Research and Development Committee of the Roudebush Veterans Administration Medical Center, Indianapolis. All study participants provided written informed consent.

Participants

Study participants were required to be at least 18 years of age, have an estimated GFR by the four-component MDRD (Modification of Diet in Renal Disease) formula of >20 and ≤ 60 ml/min per 1.73 m^2 using isotopic dilution mass spectrometry–calibrated creatinine,[32] anemia, and iron deficiency. Anemia was defined as blood hemoglobin concentration <12 g/dl and iron deficiency as either a serum ferritin concentration of <100 ng/ml or serum transferrin saturation of $<25\%$. Other exclusions are listed in the Supplementary Appendix online.

Study design

Randomization. Eligible participants were randomized in a 1:1 ratio, using permuted blocks, to either oral iron or IV iron using concealed opaque envelopes. The randomization sequence was computer generated by a statistician.

Study intervention

Iron deficiency was treated over 8 weeks beginning at the time of randomization for both treatment groups. Participants were seen at weeks 0, 2, 4, 6, and 8 after randomization. Those randomized to the IV iron group received iron sucrose 200 mg IV over 2 h at each of these 5 visits. Participants randomized to oral iron were counseled to take ferrous sulfate 325 mg three times daily for 8 weeks to provide at least the minimum dose of 200 mg elemental iron per day. Subsequently, in-person visits were conducted at 3, 6, 12, 18, and 24 months after randomization. The planned duration of the study was 24 months and mGFR was obtained at baseline, 8 weeks, 6 months, 12 months, and 24 months after randomization.

An interim medical history, review of a list of medications, and all adverse events related or unrelated to the randomized treatment were obtained at each in-person study visit.

Measurement of GFR

Plasma clearance of iothalamate was measured by administering an IV bolus of 5 ml of iothalamate meglumine (Conray 60, Malinkrodt, St Louis, MO) and sampling 2 ml of blood at 0, 5, 10, 20. 30, 45, 60, 90, 120, 150, 180, 240, and 300 min after injection. Iothalamate was measured by high-performance liquid chromatography. Plasma clearance was calculated using a two-pool model using validated pharmacokinetic software (Winnonlin, Princeton, NJ). Coefficient of variation for repeated measurement of plasma iothalamate clearance 3 days apart in the same subjects was 5.7%.[33]

Other measurements

Hemoglobin and serum chemistries were measured at biweekly intervals for the first 8 weeks after randomization and with every research visit thereafter. Iron stores were determined at baseline, 8 weeks, and then at every GFR visit thereafter. Quality of life was measured by the KDQOL instrument[34] at baseline, and periodic intervals thereafter. Proteinuria was estimated using measurements of urinary protein and creatinine before iron administration at baseline and at periodic intervals thereafter.

Anemia was managed by protocol using iron and ESA (see Supplementary Appendix online). Rescue therapy with additional iron therapy is also described in the Supplementary Appendix online.

Outcomes

The primary outcome was the difference between treatment groups in the slope of mGFR from baseline to 2 years adjusted for the log of baseline urinary protein/creatinine ratio. Further adjustment of the primary outcome was also made for age, sex, race (Black vs. non-Black), angiotensin-converting enzyme/angiotensin receptor blocker use, and the presence or absence of cardiovascular disease (all determined at baseline) and was a prespecified secondary outcome. Another secondary outcome was the between-group percent change in proteinuria from baseline to 8 weeks. Other outcomes were the difference between hemoglobin response between treatment groups and change in KDQOL.

Statistical analysis

We assumed a mean rate of decline in GFR of 4 ml/min per 1.73 m^2 per year in the oral iron group and a 50% greater decline in the IV iron group and a cumulative rate of dropout of 25%. We established a recruitment target of 100 patients for each treatment group with a minimum duration of follow-up of 2 years to achieve 82% power to detect our hypothesized difference in decline in kidney function at the 5% level of significance.

The analysis of the primary outcome was intention to treat, if the patient received at least one dose of the randomized drug (which was

the case for each subject). A linear mixed model was used with GFR as the outcome variable. Fixed effects were indicator variables for time (treated as a continuous variable), treatment, and their interaction. Random effects were subject and time with unstructured covariance; statistical inference was made using the maximum likelihood estimator. To avoid biasing the slopes we imputed GFR to be 10 ml/min per 1.73 m^2 in case of death or end-stage renal disease. The end-stage renal disease was defined as kidney transplantation or the receipt of dialysis for at least 30 days unless death occurred. Similar mixed models were used for analyzing the KDQOL domains and log transformed urine protein/creatinine ratio, except that time was treated as a categorical variable.

An adverse event was deemed serious if it resulted in hospitalization or a visit to the emergency room where an intervention was made to avert hospitalization. The nature and number of all serious adverse events was adjudicated by RA who was unaware of treatment assignment at the time of ascertainment. The duration of participation in the study per subject, which according to the trial design could be up to 24 months, was determined. The event rate was calculated by treatment group assignment. IRR by treatment was then determined along with the 95% CIs using the Poisson distribution assumption.

Adjudicated cardiovascular events included the following: myocardial infarction, stroke, hospitalization for congestive heart failure, hospitalized angina, arrhythmias, cardiac arrest, coronary revascularization, and peripheral vascular interventions. Adverse events reported are those during the course of 24 months of participation in the trial.

All analyses were conducted using Stata version 11.2 (Stata, College Station, TX). The *P*-values reported are two sided and taken to be significant at <0.05.

DISCLOSURE

RA served on a data safety monitoring board of a study sponsored by Amgen. He has also served as a consultant for Celgene, Takeda, Bayer, and Daiichi Sankyo. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

This study was supported in part by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (U01-DK71633) and Indiana Institute for Medical Research.

AUTHOR CONTRIBUTIONS

Rajiv Agarwal: literature search, study design, obtain funding, supervision of the study, data analysis, data interpretation, and writing. He was solely responsible for the decision to submit the manuscript and takes full responsibility for the accuracy and completeness of the reported data and analyses. Maria K Pappas: patient recruitment and study procedures, data collection, data entry, and summarizing data. John W Kusek: convening the data safety monitoring board and critical revision of the manuscript.

SUPPLEMENTARY MATERIAL

Figure S1. Disposition of the study participants.
Figure S2. Natural log of urine protein/creatinine ratio plotted over the course of the trial by drug assignment.
Figure S3. Distribution of single and multiple events over the course of the trial by drug assignment.
Figure S4. Distribution of infection events: Some events may be shown as a single dot due to simultaneous events such as cellulitis and pneumonia.
Figure S5. Distribution of cardiovascular events.

Table S1. Adverse events reported following randomization. Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

REFERENCES

1. Coresh J, Wei GL, McQuillan G *et al.* Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the third National Health and Nutrition Examination Survey (1988-1994). *Arch Intern Med* 2001; **161**: 1207–1216.
2. Fishbane S, Pollack S, Feldman HI. Iron indices in chronic kidney disease in the National Health and Nutritional Examination Survey 1988-2004. *Clin J Am Soc Nephrol* 2009; **4**: 57–61.
3. Nissenson AR, Strobos J. Iron deficiency in patients with renal failure. *Kidney Int Suppl* 1999; **69**: S18–S21.
4. Besarab A. Iron and cardiac disease in the end-stage renal disease setting. *Am J Kidney Dis* 1999; **34**: S18–S24.
5. Besarab A, Frinak S, Yee J. An indistinct balance: the safety and efficacy of parenteral iron therapy. *J Am Soc Nephrol* 1999; **10**: 2029–2043.
6. Albaramki J, Hodson EM, Craig JC *et al.* Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database Syst Rev* 2012; **1**: CD007857.
7. Haugen E, Nath KA. The involvement of oxidative stress in the progression of renal injury. *Blood Purif* 1999; **17**: 58–65.
8. Klahr S. Oxygen radicals and renal diseases. *Miner Electrolyte Metab* 1997; **23**: 140–143.
9. Agarwal R, Warnock D. Issues related to iron replacement in chronic kidney disease. *Semin Nephrol* 2002; **22**: 479–487.
10. Zager RA, Johnson AC, Hanson SY *et al.* Parenteral iron formulations: a comparative toxicologic analysis and mechanisms of cell injury. *Am J Kidney Dis* 2002; **40**: 90–103.
11. Shah SV. Role of iron in progressive renal disease. *Am J Kidney Dis* 2001; **37**: S30–S33.
12. Handelman GJ, Walter MF, Adhikarla R *et al.* Elevated plasma F2-isoprostanes in patients on long-term hemodialysis. *Kidney Int* 2001; **59**: 1960–1966.
13. Spittle MA, Hoenich NA, Handelman GJ *et al.* Oxidative stress and inflammation in hemodialysis patients. *Am J Kidney Dis* 2001; **38**: 1408–1413.
14. Salahudeen AK, Oliver B, Bower JD *et al.* Increase in plasma esterified F2-isoprostanes following intravenous iron infusion in patients on hemodialysis. *Kidney Int* 2001; **60**: 1525–1531.
15. Agarwal R, Vasavada N, Sachs NG *et al.* Oxidative stress and renal injury with intravenous iron in patients with chronic kidney disease. *Kidney Int* 2004; **65**: 2279–2289.
16. Agarwal R, Leehey DJ, Olsen SM *et al.* Proteinuria induced by parenteral iron in chronic kidney disease–a comparative randomized controlled trial. *Clin J Am Soc Nephrol* 2011; **6**: 114–121.
17. Drueke T, Witko-Sarsat V, Massy Z *et al.* Iron therapy, advanced oxidation protein products, and carotid artery intima-media thickness in end-stage renal disease. *Circulation* 2002; **106**: 2212–2217.
18. Becker BN, Himmelfarb J, Henrich WL *et al.* Reassessing the cardiac risk profile in chronic hemodialysis patients: a hypothesis on the role of oxidant stress and other non-traditional cardiac risk factors. *J Am Soc Nephrol* 1997; **8**: 475–486.
19. 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.
20. Rozen-Zvi B, Gafter-Gvili A, Paul M *et al.* Intravenous versus oral iron supplementation for the treatment of anemia in CKD: systematic review and meta-analysis. *Am J Kidney Dis* 2008; **52**: 897–906.
21. Stoves J, Inglis H, Newstead CG. A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. *Nephrol Dial Transplant* 2001; **16**: 967–974.
22. Macdougall IC, Bock AH, Carrera F *et al.* 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* 2014; **29**: 2075–2084.
23. Parkkinen J, von Bonsdorff L, Peltonen S *et al.* Catalytically active iron and bacterial growth in serum of haemodialysis patients after i.v. iron-saccharate administration. *Nephrol Dial Transplant* 2000; **15**: 1827–1834.
24. Zager RA, Johnson AC, Hanson SY. Parenteral iron therapy exacerbates experimental sepsis. Rapid communication. *Kidney Int* 2004; **65**: 2108–2112.

25. Zager RA, Johnson AC, Hanson SY *et al.* Parenteral iron compounds sensitize mice to injury-initiated TNF-alpha mRNA production and TNF-alpha release. *Am J Physiol Renal Physiol* 2005; **288**: F290–F297.
26. Sengoelge G, Kletzmayr J, Ferrara I *et al.* Impairment of transendothelial leukocyte migration by iron complexes. *J Am Soc Nephrol* 2003; **14**: 2639–2644.
27. Zheng H, Huang X, Zhang Q *et al.* Iron sucrose augments homocysteine-induced endothelial dysfunction in normal subjects. *Kidney Int* 2006; **69**: 679–684.
28. Anker SD, Comin CJ, Filippatos G *et al.* Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; **361**: 2436–2448.
29. Ponikowski P, van Veldhuisen DJ, Comin-Colet J *et al.* Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2014.
30. Miskulin DC, Zhou J, Tangri N *et al.* Trends in anemia management in US hemodialysis patients 2004-2010. *BMC Nephrol* 2013; **14**: 264.
31. Brookhart MA, Schneeweiss S, Avorn J *et al.* Comparative mortality risk of anemia management practices in incident hemodialysis patients. *JAMA* 2010; **303**: 857–864.
32. Levey AS, Coresh J, Greene T *et al.* Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145**: 247–254.
33. Agarwal R, Vasavada N, Chase SD. Liquid chromatography for iothalamate in biological samples. *J Chromatogr B Analyt Technol Biomed Life Sci* 2003; **785**: 345–352.
34. Hays RD, Kallich JD, Mapes DL *et al.* Development of the kidney disease quality of life (KDQOL) instrument. *Qual Life Res* 1994; **3**: 329–338.