Title

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ORIGINAL ARTICLE

Association of oral iron replacement therapy with kidney failure and mortality in CKD patients

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ABSTRACT

Background. Oral iron is the predominant route of iron replacement (IRT) but its benefits and safety are unclear in patients with chronic kidney disease (CKD).

Methods. We examined the association of oral IRT vs no IRT with end-stage kidney disease (ESKD) and mortality in a national cohort of US Veterans. We identified 17 413 incident new users of oral IRT with estimated glomerular filtration rates <60 mL/min/1.73 m^2 and 32 530 controls who did not receive any IRT during 2004–18. We used propensity score–overlap weighting to account for differences in key baseline characteristics associated with the use of oral IRT. We examined associations using competing risk regression and Cox models.

Results. In the cohort of 49 943 patients, 1616 (3.2%) patients experienced ESKD and 28 711 (57%) patients died during a median follow-up of 1.9 years. Oral IRT was not associated with ESKD [subhazard ratio (HR) (95% confidence interval, CI) 1.00 (0.84–1.19), $P = .9$] and was associated with higher risk of all-cause mortality [HR (95% CI) 1.06 (1.01–1.11), $P = .01$]. There was significant heterogeneity of treatment effect for mortality, with oral IRT associated with higher mortality in the subgroups of patients without congestive heart failure (CHF), anemia or iron deficiency. In patient with blood hemoglobin <10 g/dL oral IRT was associated with significantly lower mortality.

Conclusion. Oral IRT was associated with lower mortality only in patients with anemia. In patients without anemia, iron deficiency or CHF, the risk–benefit ratio of oral IRT should be further examined.

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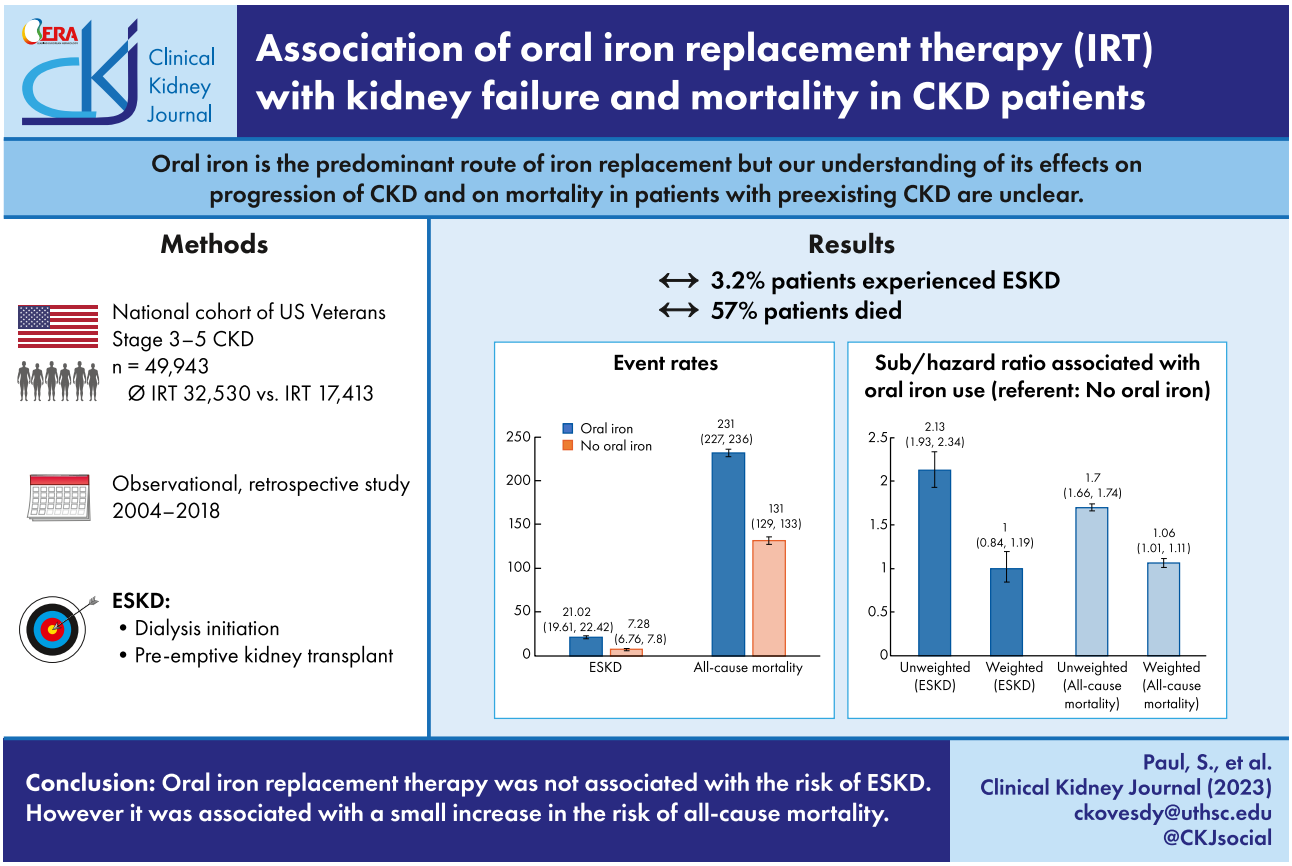
GRAPHICAL ABSTRACT



Keywords: chronic kidney disease, dialysis, end-stage kidney disease, iron replacement, mortality

INTRODUCTION

Chronic kidney disease (CKD) is a leading cause of death and affects approximately 850 million people worldwide [1]. Patients with CKD experience multiple abnormalities that contribute to the high morbidity and mortality associated with decreased kidney function. Anemia is one of the most common complications that affects individuals with CKD, with a prevalence ranging from 7% to >50% in advanced stages of disease [2]. The etiology of anemia in CKD is complex, with decreased erythropoetin production, erythropoetin hyporesponsiveness, and absolute and functional iron deficiency all contributing to its development.

Iron is an essential component of hemoglobin for erythropoiesis and it is also involved in numerous other physiologic processes. CKD is associated with multiple disturbances in iron homeostasis resulting in inadequate iron supply. Iron deficiency independent of anemia has been associated with poor cardiac outcomes, progression of CKD, increased hospitalizations and mortality in patients with non-dialysis-dependent CKD and those with congestive heart failure (CHF) [3–6]. Evidence suggests that iron replacement therapy (IRT) is effective in the correction of iron deficiency anemia in patients with CKD but its effect on clinical outcomes remains unclear [7]. It has been postulated that intravenous IRT could induce oxidative stress which could theoretically lead to higher risk of cardiovascular disease, infection, CKD progression, other organ damage and mortality [7, 8]. Oral IRT may thus seem more desirable, and evidence suggests that oral IRT is also effective in increasing hemoglobin levels and ferritin levels in CKD, albeit less effectively than parenteral IRT [9–11]. However, recently there have been reports of potentially harmful effects of oral IRT, due to deleterious changes in the gut microbiome such as increased risk of gut inflammation, constipation and diarrhea resulting in increased production and absorption of uremic toxins, which have been linked to adverse renal and cardiovascular outcomes [12–14].

There are limited data about the effects of oral IRT on progression of CKD and on mortality in patients with preexisting CKD. To better understand the benefits and risks of oral IRT, we examined the association of oral IRT with the incidence of end-stage kidney disease (ESKD) and all-cause mortality in patients with pre-existing CKD in a large national cohort of US Veterans. We hypothesized that oral IRT is associated with lower incidence of ESKD and all-cause mortality in patients with pre-existing CKD.

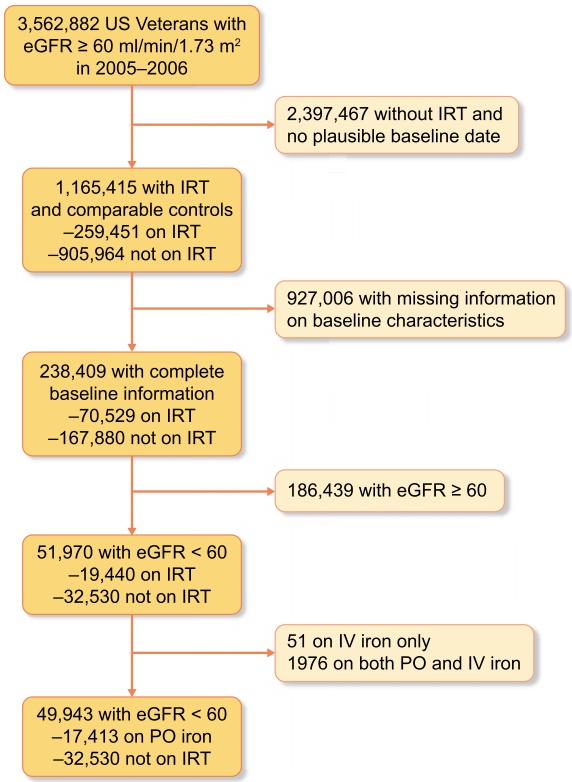


Figure 1: Flow chart of cohort creation.

MATERIALS AND METHODS

Cohort definition

We examined data from US Veterans included in the Therapeutic Interventions in Chronic Kidney Disease (TRI-CKD) study, a historic cohort of 3 562 882 patients with estimated glomerular filtration rates (eGFRs) ≥60 mL/min/1.73 m^2 recorded from 1 October 2004 through 30 September 2006, with longitudinal follow-up until 30 September 2019 [15]. From this cohort we identified incident new users of oral IRT who had eGFR <60 mL/min/1.73 m^2 at the time of starting IRT and a comparator group of untreated patients with similar characteristics at a randomly selected date. Figure 1 shows the flow chart of patient selection. From the parent cohort we excluded 2 397 467 patients who were never exposed to IRT during subsequent follow-up, and whose randomly generated baseline date was not matched to the baseline date of treated patients. Among the remaining 1 165 415 patients, we identified 259 451 incident new users of IRT, and 905 964 patients with baseline dates within the same 180-day periods as the treated patients but who did not receive such therapy. We then excluded 927 006 patients with missing information about key characteristics at baseline and 186 439 patients with baseline eGFRs of ≥60 mL/min/1.73 m^2. Finally, due to the very low number of patients receiving exclusively intravenous iron products among the remaining patients (<0.1%) we excluded 51 patients who received intravenous iron alone and 1976 patients who received a combination of intravenous and oral iron. Our final study sample thus consisted of 49 943 patients with eGFR <60 mL/min/1.73 m^2 at baseline, of whom 17 413 (35%) were treated with oral IRT and 32 530 (65%) were untreated.

Data collection

We obtained information about baseline demographic characteristics, comorbidities, medications, vital signs and laboratory variables from the Veterans Affairs (VA) Corporate Data Warehouse (CDW) [16]. Medication data were extracted from the DEcision Support System (DSS) National Data Extracts' outpatient and inpatient pharmacy files and from Medicare Part D files [17]. Information about medications received from non-VA sources was obtained from non-VA medication files in CDW (including over the counter medications, herbal supplements, VA-prescribed medications filled at non-VA pharmacies, and medications prescribed by providers outside the VA). We defined baseline medication use as the presence of at least one outpatient dispensation of ≥30 days during the 365 days prior to the baseline date. Comorbidities were identified from the VA Inpatient and Outpatient Medical SAS Datasets based on the presence of International Classification of Disease (ICD)-9 and ICD-10 diagnostic and procedure codes and Current Procedural Terminology (CPT) codes, as well as from Centers for Medicare and Medicaid Services (CMS) Data files. We used the presence of at least one inpatient or at least two outpatient codes recorded prior to the baseline date to define a comorbid condition. We calculated the Charlson Comorbidity Index (CCI) using the Deyo modification for administrative data sets [18]. Laboratory data was obtained from the VA LabChem files [19] and eGFR was estimated from the 2009 Chronic Kidney Disease Epidemiology Collaboration equation [20]. We collected information about urine protein–creatinine ratio (UPCR), urine albumin–creatinine ratio (UACR) and urine dipstick protein from the DSS National Data Extracts Laboratory Results file and the VA LabChem file in the CDW. We converted UPCR and urine dipstick protein to UACR using the conversion equations by Sumida *et al.* [21] and categorized the resulting UACR values as <30 mg/g, 30–<300 mg/g or ≥300 mg/g.

Exposure and outcomes

We used an incident new user design to define treatment exposure. Patients were considered incident new users if they received a dispensation of ≥30 days of any form of oral IRT, preceded by no dispensation of the same during the 365 days prior to this while having a record of VA pharmacy enrollment.

Our co-primary outcomes were ESKD, defined as the initiation of dialysis or pre-emptive kidney transplant identified from the US Renal Data System (USRDS) [22], and all-cause mortality identified from the VA Vital Status Files [23]. We followed patients until the occurrence of any of the above outcomes, last recorded VA encounter date or end of follow-up (30 September 2019 for mortality or 30 June 2018 for ESKD).

We analyzed associations of oral IRT with outcomes using an intention-to-treat (ITT)-like design where the treatment exposure at cohort entry is carried forward irrespective of future treatment status. We compared patients newly starting oral IRT with untreated patients with a baseline date within the same 180-day period to mitigate any non-contemporaneous control bias. We started follow-up for treated patients on the date of receiving the first oral iron prescription, and for untreated patients on a randomly assigned date that was computer-generated based on the start dates in the treated group (modeling elapsed time from cohort entry to start of treatment), in order to adjust for the otherwise systematically unequal lengths of follow-up in the treated and untreated groups. We only retained untreated patients with randomly

assigned start dates occurring before a recorded outcome or their censoring date.

Statistical analysis

We described data as number (%) for categorical variables and mean ± standard deviation or median (25th–75th percentile), as appropriate, and compared characteristics between exposed and unexposed patients using standardized differences. We calculated cumulative incidence rates per 1000 patient-years overall and stratified by treatment status. We examined the association of oral IRT (vs no IRT) with ESKD in competing risk regression models (with mortality as the competing event) using the Fine and Gray method [24] and with all-cause mortality using Cox proportional hazard models. We calculated propensity scores (PS) from baseline characteristics using logistic regression models, using as predictors the 180-day baseline time period, patient baseline age, sex, race, ethnicity, marital status, insurance type, military service connectedness, income, baseline use of medications [erythropoiesis stimulating agents, renin–angiotensin-aldosterone system inhibitors (RAASi), potassium-sparing diuretics and mineralocorticoid receptor antagonists, thiazide diuretics, loop diuretics, other blood pressure–lowering agents, proton pump inhibitors, non-steroidal anti-inflammatory agents (NSAIDs) and opioid analgesics], comorbidities (diabetes mellitus, myocardial infarction, peripheral- and cerebrovascular disease, CHF and the CCI), body mass index, systolic and diastolic blood pressure, and baseline eGFR, UACR, hemoglobin, total iron saturation (TSAT) and serum ferritin. We used a PS-overlap weighting method [25, 26] to account for differences in baseline characteristics between treated and untreated patients. This weighting scheme makes observations with a substantial probability for either treatment (based on the PS model) more influential and smoothly down-weights patients in the tails of the PS distribution, thus mitigating undue influence of patients in either treatment that were unlikely candidates for the respective other treatment (without the need to exclude them altogether based on arbitrary cut-off values). We examined heterogeneity of treatment effects from key baseline characteristics such as typical treatment indications for iron therapy (e.g. low hemoglobin level, iron deficiency or heart failure) in subgroup analyses with the calculation of multiplicative interaction terms, using the same statistical approach as detailed above.

Analyses were conducted using Stata MP version 17.1 (StataCorp, College Station, TX, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The study was approved by the Institutional Review Boards of the Memphis and Long Beach VA Medical Centers, with exemption from informed consent.

RESULTS

Patients were overall 74 ± 10 years old, 97% were male, 14% were African American and 57% had diabetes (Table 1). The baseline eGFR, blood hemoglobin, TSAT and serum ferritin levels were 49 mL/min/1.73 m^2 (40–55), 12.0 ± 2.1 g/dL, 20% (13–28) and 110 µg/L (49–226), respectively. Patients starting oral IRT had a higher prevalence of comorbid conditions, were more likely to be African American and to be treated with various medications, and had lower eGFR, blood hemoglobin, TSAT and serum ferritin levels (Table 1). The baseline characteristics of patients receiving and not receiving IRT were similar after PS weighting (all standardized differences <0.1, Table 1).

Association of IRT with ESKD and all-cause mortality

A total of 1613 (3.2%) patients experienced ESKD [event rate, 95% confidence interval (CI) 11.13/1000 patient-years (10.6, 11.7)] and 28 711 (57%) patients died [event rate, 95% CI 159.9/1000 patient-years (158.05, 161.75)] during a median follow-up of 1.9 years. Event rates and unadjusted subhazard and hazard ratios for ESKD and mortality, respectively, were higher in patients receiving oral IRT (Table 2), but the risk was attenuated after PS weighting, with no significant association observed between IRT and ESKD, and a small albeit statistically significant association seen between oral IRT and all-cause mortality (Table 2). The association of oral IRT with ESKD was consistent in all examined subgroups, but we observed significant heterogeneity of treatment effect for all-cause mortality, with interactions noted for CHF, serum ferritin, TSAT and blood hemoglobin levels (Fig. 2). In patients with CHF, with blood hemoglobin <10 g/dL, with TSAT <20% or with serum ferritin <100 µg/L, oral IRT was associated with lower mortality or showed no significant association with mortality, while in patients with no CHF, with blood hemoglobin ≥10 g/dL, with TSAT ≥20% or with serum ferritin ≥100 µg/L, oral IRT was associated with significantly higher all-cause mortality (Fig. 2).

DISCUSSION

In this study, we investigated whether oral IRT was associated with incident ESKD and mortality in a large national cohort of US Veterans. We found that in the overall cohort oral IRT was not associated with higher incidence of ESKD and was associated with a small increase in the risk of all-cause mortality. There was significant heterogeneity of treatment effect concerning all-cause mortality, with an association with higher mortality limited to patients with no CHF, anemia or iron deficiency. In patients with anemia oral IRT was associated with significantly lower mortality, while in patients with CHF and low iron storage, oral IRT showed no association with mortality.

To our knowledge, this study is one of the first to examine the association of oral iron therapy with relevant clinical outcomes in a large cohort of patients with non-dialysis-dependent CKD. Clinical trials found that oral IRT was effective in increasing absolute hemoglobin concentration in patients with CKD [27–30] but could not provide definitive conclusions about its effect on clinical end points such as progression of CKD or mortality, due to inadequate sample size and length of follow-up. Despite a lack of certainty about the effects on mortality and kidney failure, a positive effect of IRT could be implied based on benefits such as correction of anemia and iron deficiency, and improvement in the quality of life of patients with CHF [31]. While the most common indication for IRT in CKD is iron deficiency anemia, we found that many patients with normal iron stores and/or hemoglobin levels above the ranges recommended for therapy received IRT. The biologic significance of iron extends beyond its role as a building block for red blood cells [32], as suggested among others by experimental studies which found that iron deficiency, independent of anemia, causes functional impairment of skeletal muscle [33, 34], and iron supplementation improves muscle performance and functionality in hospitalized patients [35]. This raises the possibility that IRT could be applied for broader indications, and may explain why we detected its use in non-anemic/non–iron deficient patients.

Notwithstanding putative benefits of IRT in patients who could derive a physiologic benefit (e.g. patients suffering from

Table 1: Baseline characteristics of the overall cohort and of patients receiving oral iron replacement and not receiving iron replacement.

	All ($n = 49\,943$)	No iron therapy ($n = 32\,530$)	Oral iron therapy ($n = 17\,413$)	Standardized difference before PS weighting	Standardized difference after PS weighting
Age (years)	74 ± 10	75 ± 10	73 ± 10	–0.111	0
Sex (male)	48 562 (97)	31 693 (97)	16 869 (97)	–0.033	0
Race				0.148	0
White	39 717 (80)	26 540 (82)	13 177 (76)		
African American	7036 (14)	4156 (13)	2880 (17)		
Others	3190 (6.4)	1834 (5.6)	1356 (7.8)		
Ethnicity (Hispanic)	2389 (4.8)	1420 (4.4)	969 (5.6)	0.055	0
Marital status				0.170	0
Single	3340 (6.7)	2004 (6.2)	1336 (7.7)		
Married	26 871 (54)	18 414 (57)	8457 (49)		
Divorced	12 029 (24)	7316 (23)	4713 (27)		
Widowed	6681 (13)	4229 (13)	2452 (14)		
Unknown	1022 (2)	567 (1.7)	455 (2.6)		
Service connected	23 042 (46)	14 601 (45)	8441 (49)	0.072	0
Insurance type				0.118	0
None	9095 (18)	5499 (17)	3596 (21)		
Medicare	36 454 (73)	23 973 (74)	12 481 (72)		
Other	4394 (8.8)	3058 (9.4)	1336 (7.7)		
Income[a]	16 600 (5664–33 876)	16 840 (4044–33 876)	16 200 (8164–33 228)	–0.112	0
Erythropoiesis-stimulating agent	455 (1)	157 (0.5)	298 (1.7)	0.118	0
RAAS inhibitors	31 919 (64)	20 250 (62)	11 669 (67)	0.099	0
Thiazide diuretics	16 468 (33)	10 806 (33)	5662 (33)	-0.015	0
Other antihypertensives	32 440 (65)	20 161 (62)	12 279 (71)	0.181	0
Loop diuretics	16 114 (32)	8733 (27)	7381 (42)	0.331	0
Potassium-sparing diuretics	5216 (10)	3032 (9.3)	2184 (13)	0.103	0
Mineralocorticoid receptor antagonists	4413 (8.8)	2499 (7.7)	1914 (11)	0.114	0
Proton pump inhibitors	20 782 (42)	12 184 (38)	8598 (49)	0.242	0
NSAIDs	20 235 (41)	11 867 (37)	8368 (48)	0.236	0
Opioids	14 059 (28)	8227 (25)	5832 (34)	0.181	0
Diabetes mellitus	28 566 (57)	17 840 (55)	10 726 (62)	0.137	0
Myocardial infarction	10 277 (21)	6248 (19)	4029 (23)	0.096	0
Peripheral vascular disease	13 639 (27)	8354 (26)	5285 (30)	0.104	0
Cerebrovascular disease	12 235 (25)	7583 (23)	4652 (27)	0.079	0
CHF	16 209 (33)	9319 (29)	6890 (40)	0.232	0
CCI	4.5 ± 2.9	4.2 ± 2.8	5 ± 2.9	0.293	0
Body mass index (kg/m^2)	29 ± 6	29 ± 5.8	29 ± 6.3	–0.024	0
Systolic blood pressure (mmHg)	130 ± 20	130 ± 19	130 ± 21	–0.036	0
Diastolic blood pressure (mmHg)	70 ± 12	71 ± 11	69 ± 12	–0.153	0
eGFR[a] (mL/min/1.73 m^2)	49 (40–55)	50 (42–56)	47 (36–54)	–0.336	0
CKD stage				0.349	0
3a	31 860 (64)	22 065 (44)	9795 (20)		
3b	12 808 (26)	8082 (16)	4726 (9.5)		
4	4132 (8.3)	1988 (4.0)	2144 (4.3)		
5	1143 (2.3)	395 (0.8)	748 (1.5)		
UACR (mg/g)				–0.244	0
<30	35 325 (71)	24 139 (74)	11 186 (64)		
30–<300	9129 (18)	5578 (17)	3551 (20)		
≥300	5489 (11)	2813 (8.6)	2676 (15)		
Ferritin[a] (µg/L)	110 (49–226)	123 (64–233)	77 (26–210)	–0.087	0
TSAT[a] (%)	20 (13–28)	24 (18–31)	13 (9–18)	–0.955	0
Hemoglobin (g/dL)	12.0 ± 2.1	12.7 ± 1.9	10.6 ± 1.7	–1.163	0

Results are presented as number (%) for categorical, means ± standard deviation for numerical and median (25th percentile–75th percentile) for skewed ([a]) covariates. Standardized difference was calculated after PS weighting.

Table 2: Event rates, (sub)hazard ratios and 95% confidence intervals of outcomes associated with oral iron replacement, compared with no oral iron replacement.

	ESKD					All-cause mortality				
		Crude (un-weighted) models		PS overlap weighted models			Crude (un-weighted) models		PS overlap weighted models	
	Event rate per 1000 PY (95%CI)	SHR (95% CI)	P-value	SHR (95% CI)	P-value	Event rate per 1000 PY (95% CI)	HR (95% CI)	P-value	HR (95% CI)	P-value
Oral iron ($N = 17\,413$)	21.02 (19.61, 22.42)	2.13 (1.93, 2.34)	<.0001	1.00 (0.84, 1.19)	0.9	231.47 (227.34, 235.68)	1.70 (1.66, 1.74)	<.0001	1.06 (1.01, 1.11)	.01
No oral iron ($N = 32\,530$)	7.28 (6.76, 7.8)	Referent		Referent		131.38 (129.41, 133.37)	Referent		Referent	

PS, propensity score; PY, patient-years; SHR, subhazard ratio; HR, hazard ratio; ESKD, end stage kidney disease.

iron deficiency, or those with CHF and myocardial dysfunction), administering iron could also have unintended negative consequences. Iron mass balance is regulated in the body by controlling absorption, but there is no mechanism to actively enhance iron excretion. Epidemiological and experimental studies have shown an association with iron overload and atherosclerosis [36–40]. Iron binds to circulating transferrin, and an excess of catalytic iron (i.e. iron that is not bound to transferrin) can trigger iron-dependent oxidative stress, and can accelerate disease progression by producing lipid oxidation, protein oxidation, inflammation and endothelial dysfunction [41, 42]. While these mechanisms have been invoked primarily in the case of parenteral iron administration where the protective effect of diminished enteral absorption is bypassed, we cannot exclude its relevance when oral administration results in a relative increase in iron stores beyond what is needed physiologically, especially when IRT is used in non-anemic/non-iron deficient patients. More recent findings also suggest that oral iron, which has traditionally been considered free of the concerns attributed to parenteral iron, could also be deleterious through its effects on gut homeostasis, by altering the gut microbiome either directly or indirectly causing constipation [12, 13, 43–46]. These effects of oral iron could increase gut inflammation and gut permeability, resulting in increased production and absorption of uremic toxins, contributing to increased cardiovascular events and mortality [12, 14, 46]. Our findings that oral IRT was associated with lower mortality in patients with anemia, and with higher mortality in patients without firm indications for iron replacement (like anemia, iron deficiency or CHF), suggest that the balance of risks and benefits may tilt in the favor of IRT when a definitive indication exists, but also that in patients without such indication(s) oral IRT may not be completely benign. Definitive answers to these questions would require randomized controlled clinical trials.

Our study is notable for the large number of analyzed patients, for being nationally representative and for having detailed information on key confounders. Our study also has limitations that should be acknowledged. Our cohort consisted of mostly male US Veterans, and hence it is unclear whether conclusions apply to females or to non-Veterans. We examined oral iron therapy alone, and it is unclear whether similar results would apply to parenteral iron therapy. The observational and retrospective design makes the results prone to confounding; while we accounted for major known confounders, residual confounding remains possible from unmeasured characteristics such as inflammation. In our attempt to create comparable groups of treated and untreated patients, we excluded many individuals, and thus our conclusions should be limited to patients with characteristics similar to those included in our analyses.

CONCLUSIONS

In this large national cohort of patients with CKD, oral IRT was not associated with the risk of ESKD. Oral IRT was associated with lower mortality in those with anemia. In patients with no CHF, with higher hemoglobin and with adequate iron stores, oral IRT was associated with higher all-cause mortality. The efficacy and safety of IRT should be tested in clinical trials.

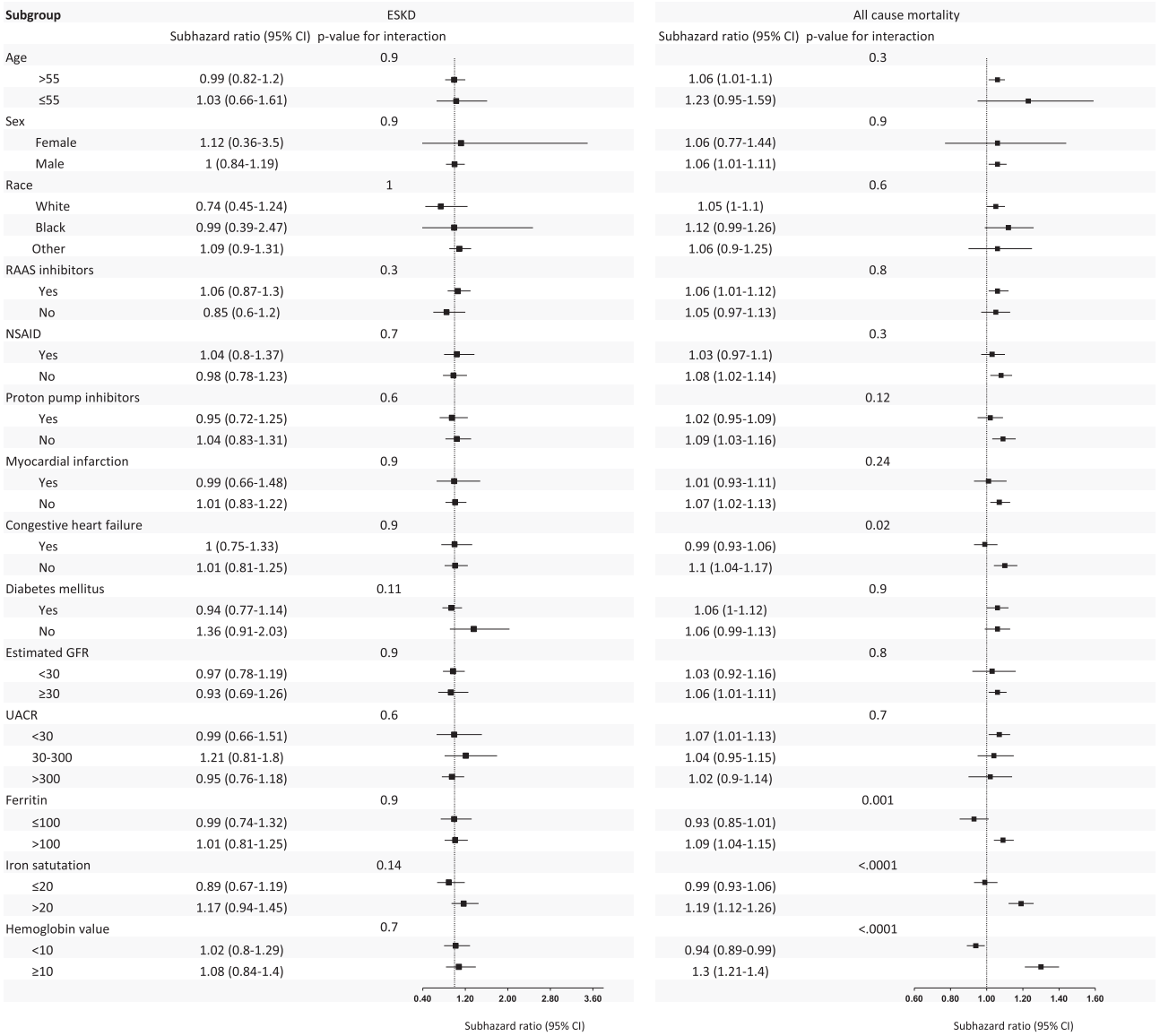


Figure 2: Forest plot of (sub)hazard ratios and 95% CIs for ESKD and all-cause mortality associated with oral iron replacement therapy in propensity score weighted analyses.

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CONFLICT OF INTEREST STATEMENT

C.P.K. has been a consultant for Abbott, Akebia, AstraZeneca, Bayer, Boehringer Ingelheim, Cara Therapeutics, CSL Vifor, CSL Behring, GSK, Pharmacosmos, ProKidney, Rockwell, Takeda and Tricida. C.M.R. has received honoraria from Ardelyx, AstraZeneca, Fresenius, Nutricia, Otsuka, Reata and Roche. K.K.-Z. has received honoraria and/or support from Abbott, Abbvie, ACI Clinical (Cara Therapeutics), Akebia, Alexion, Amgen, Ardelyx, ASN (American Society of Nephrology), AstraZeneca, Aveo, BBraun, Chugai, Cytokinetics, Daiichi, DaVita, Fresenius,

Genentech, GSK, Haymarket Media, Hofstra Medical School, IFKF (International Federation of Kidney Foundations), ISH (International Society of Hemodialysis), International Society of Renal Nutrition & Metabolism (ISRNM), JSDT (Japanese Society of Dialysis Therapy), Hospira, Kabi, Keryx, Kissei, Novartis, Novo-Nordisk, OPKO, NIH (National Institutes of Health), NKF (National Kidney Foundations), Pfizer, Regulus, Relypsa, Resverlogix, Dr Schaer, Sandoz, Sanofi, Shire, VA (Veterans Affairs), Takeda, Vifor, UpToDate and ZS-Pharma. The other authors declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

VA policies prevent the sharing of identifiable data with outside investigators. Sharing of de-identified data is allowed after obtaining appropriate approvals.

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