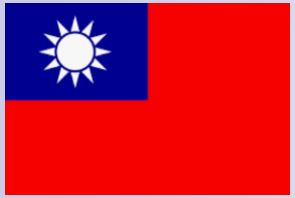

佛教慈濟醫療財團法人
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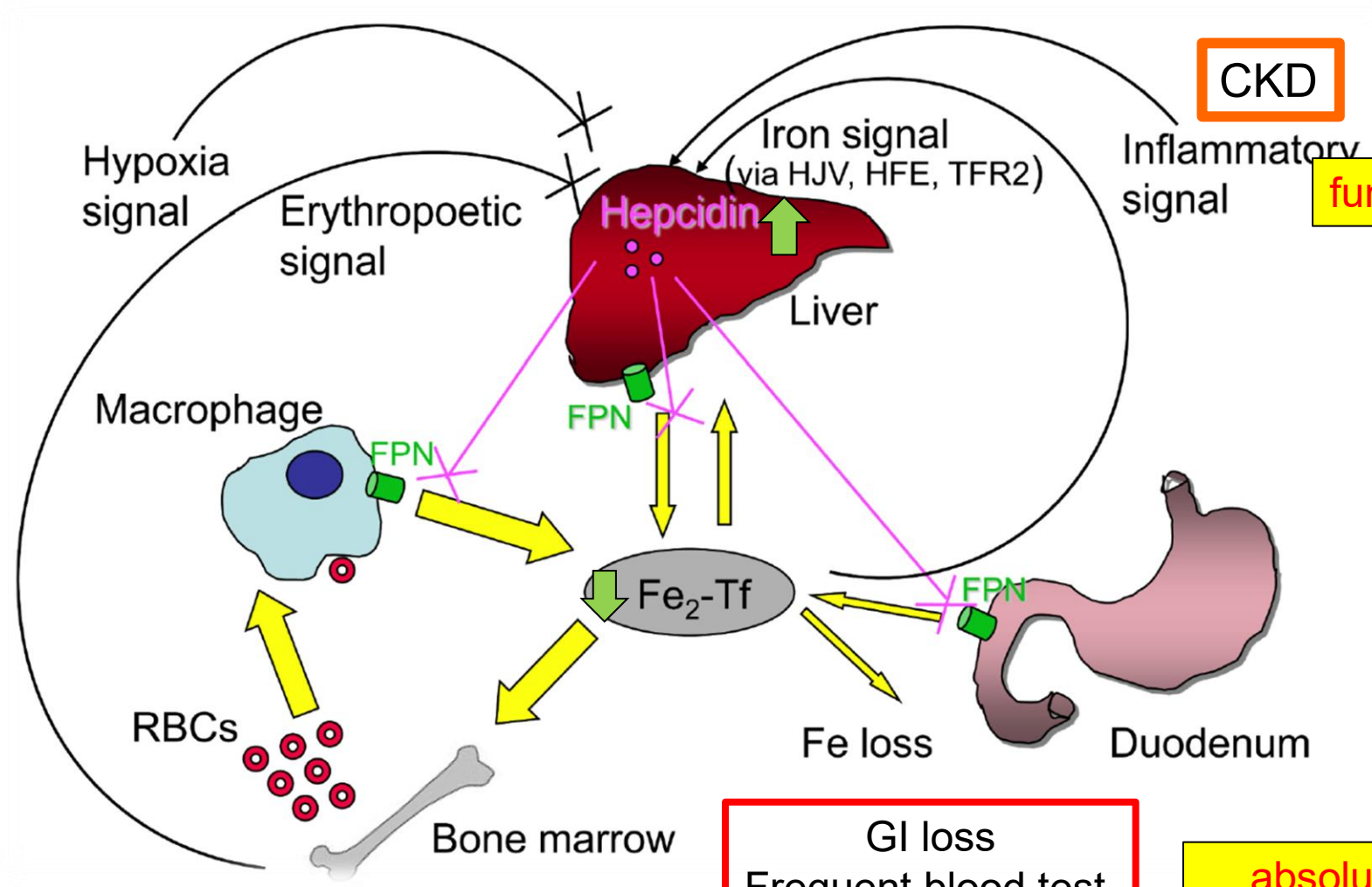
One Size Does Not Fit All: Redefining Iron Treatment in Renal Anemia

Professor Ko-Lin Kuo MD, PhD
Division of Nephrology, and Department of Research
Taipei Tzuchi Hospital

2025-12-05

Disordered iron balance in CKD



CKD

functional iron deficiency

GI loss
Frequent blood test

absolute iron deficiency

FPN: ferroportin

Babitt et al .*Am J Kidney Dis. 2010*

Anemia in CKD – Updating the Definitions of Two Iron States

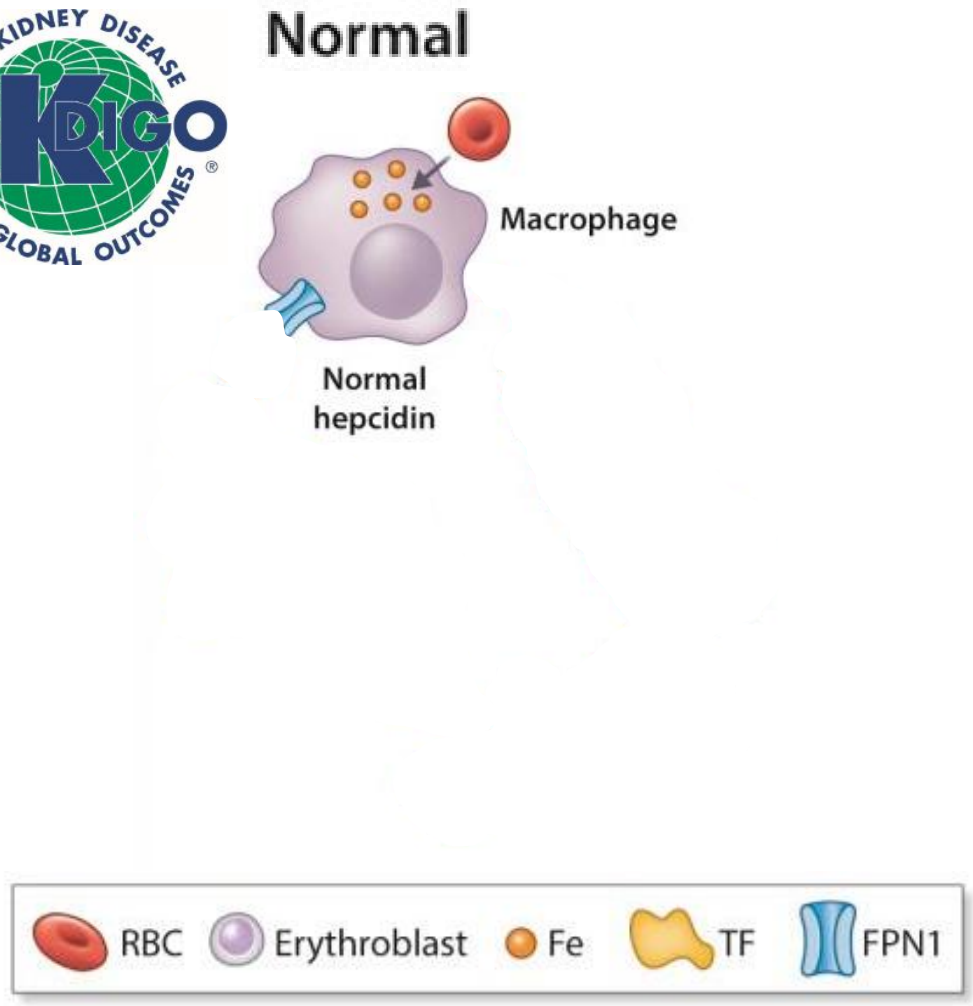


Figure 4 | Systemic movement of iron in different iron-related states.

Why 'One Size Fits All' No Longer Works

Table 1. Serum biomarkers for iron deficiency anemia in CKD

Name	Measures (U)	Relation to Iron Deficiency	Treatment Target[a]	Predicts Response to IV Iron	Sensitivity/ Specificity for Iron Deficiency[b]	Drawbacks
Ferritin	Level of ferritin in the blood (ng/dl)	Decreases (<100 ng/ dl diagnostic in nondialysis-	Uncertain[c]	Not reliable	<100 ng/dl: 35%/ 78%[31] <200 ng/dl: 41%/	Acute-phase reactant, elevations not solely related to iron status
		diagnostic in CKD)			27%[42]	
TSAT	Amount of iron bound to transferrin compared with total body stores (%iron/ TIBC)	Decreases (<20% diagnostic)	30%–50%	<30% Predictive	<20%: 63%/80%[21]	TIBC affected by inflammation and malnutrition
CHr	Absolute amount of Hg[illegible] re[illegible]	Not reflective of [illegible]	Not [illegible]	<29 pg predictive, [illegible]	57%/93%[31]	Time sensitive to [illegible]n of [illegible]tes
HRC%	Concentration of Hgb in RBCs (% relative Hgb content relative to RBC size)	Not reflective of stores	Not established	>6% predictive	82%/95%[31]	Must be measured within 6 h of collection
sTfR	Transferrin receptors shed from the RBC surface	May increase, can potentially note iron stores	Not established	>1.5 mg/L predictive	81%/71%[31]	Less reliable than CHr and HRC%, may rise in the setting of EPO
Hepcidin	Level of hepcidin in blood	Increases	Not applicable	Not reliable	Not applicable	—
Plasma NGAL	Level of NGAL in blood (ng/ml)	Increases	Not established	≤394 ng/ml	84%/50%[42]	—

TIBC, total iron binding capacity.
[a]Thresholds take into account current evidence and are recommended based on these data.
[b]Sensitivity/specificity measurements are best estimates, but comparisons across biomarkers are difficult because most studies were done in sample sizes of <100 patients and used different standards of comparison or diagnostic criteria (*e.g.*, bone marrow stores versus response to iron).
[c]Current recommendations 200–800 ng/dl and consider supplementation based on risk-benefit analysis for values ≥800 ng/m.

Traditional thresholds (TSAT, Ferritin) oversimplify biology

CHr (RET-He) and %HRC reflect real-time supply

Elizabeth Katherine Batchelor et al. JASN 2020;31:456-468

UK kidney association clinical practice guideline 2025

Guideline 2.2.2

We suggest that to define functional iron deficiency (FID) ("iron restricted erythropoiesis"), a TSAT < 20% in people with NDD-CKD or maintained on PD, and in those receiving HD be used. Normal or high serum ferritin values do not exclude iron deficiency, as it could be due to other causes such as infection or inflammation. (2B)

Rationale

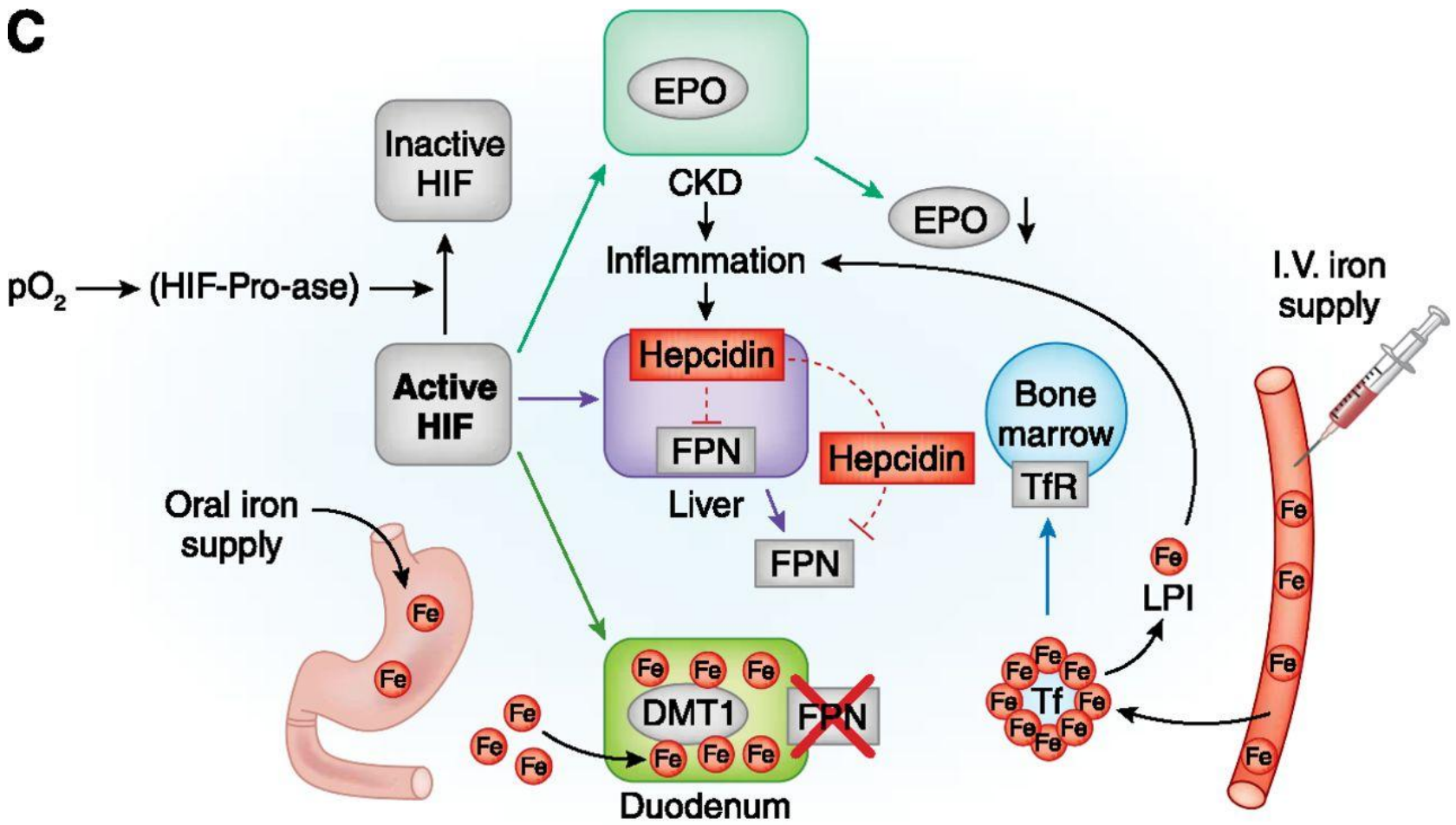
Iron is required for production of new red cells. Iron must be supplied to the erythropoietic tissue at an adequate rate, particularly if stimulated by ESA or HIF-PHI therapy.

•For people with CKD on dialysis (DD-CKD), percentage of **HRC > 6%,** or **CHr/RET-He < 31 pg** are ideal test to assess iron status.

•If these tests are not available or the person has thalassaemia or thalassaemia trait, a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 mcg/L) could be a suitable alternative

Bhandari *et al. BMC Nephrology* (2025)

Iron Therapy Challenges for CKD Anemia



FPN: ferroportin

Locatelli F et al. CJASN 11:1269–1280, 2016

Evidence for clinical benefits of iron administration

	Patients with CKD not on dialysis	Patients on dialysis
Reduction of congestive heart failure	Limited	Yes
Reduced occurrence of myocardial infarction	Limited	Yes
Improved quality of life	Not studied	Limited
Reduced occurrence of fatigue	Not studied	Limited
Improved cognitive function	Not studied	Limited
ESA dose reduction	Yes	Yes
Reduced blood transfusions	Not studied	Yes

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agents; RCT, randomized controlled trial.
Limited: data from retrospective, observational studies. Yes: supported by RCT data

Babitt et al. Kidney International 2021 99: 1280-1295

Evidence for increased risk of clinical harm with iron administration

	Patients with CKD not on dialysis	Patients on dialysis
Infections	Limited	No
Cardiovascular events	Limited	No
Diabetes	Limited	Limited
CKD progression	Limited	Not applicable
Anaphylaxis	Minimal	Minimal

CKD, chronic kidney disease; i.v., intravenous; RCT, randomized controlled trial.
No: supported by RCT data. Limited: data from retrospective, observational trials only. Minimal: overall minimal risk for contemporary i.v. iron formulations.

Babitt et al. Kidney International 2021, 99:1280-1295

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

Clinical Lessons from the PIVOTAL Trial

In patients recently started HD, a proactive, high-dose regimen of IV iron (relative to a reactive, low-dose regimen):

- Reduced the risk of the composite primary outcome of death or nonfatal CV events[1]
- Reduced the risk of MI and hospitalization for HF[1,3]
- Reduced ESA dose (19.4%) and transfusion rate (21%)[1]
- Does not cause an increased risk of infection risk[2]
- Does not cause an increased risk of stroke[4]

[1] Macdougall IC et al, NEJM 2019; 380(5): 447–458 [2] Macdougall IC et al, JASN 2020; 31: 1118–1127
[3] Jhund PS et al, JACC HF 2021; 9: 518–27 [4] Mark PB et al Kidney 360 2021; 2(11):p 1761-1769

2025 KDIGO CKD Anemia Guideline (Draft)

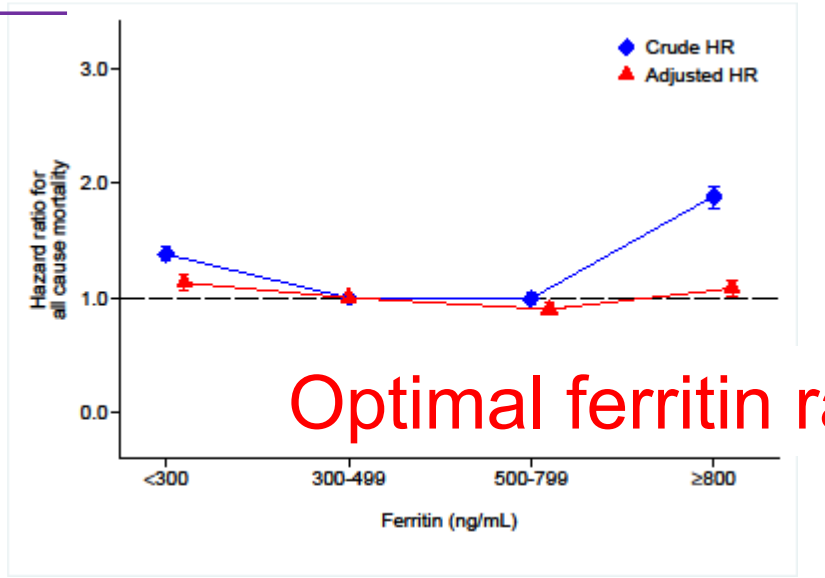
Recommendation 2.1: In people with anemia and CKD treated with hemodialysis (CKD G5HD), we suggest initiating iron therapy if ferritin ≤ 500 ng/ml (≤ 500 µg/l) and TSAT ≤30% (2D).

Practice Point 2.2: In people with CKD treated with iron, it is reasonable to withhold iron if ferritin ≥700 ng/ml (≥700 µg/l) or TSAT ≥40%.

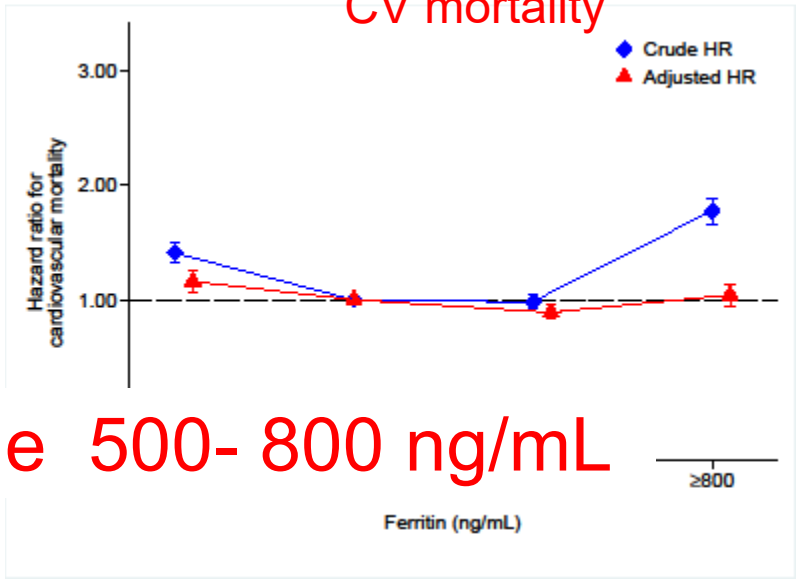
Ref: https://kdigo.org/wp-content/uploads/2024/11/KDIGO-2025-Anemia-in-CKD-Guideline_Public-Review-Draft_Nov42024.pdf

AIM-HD

All-cause mortality

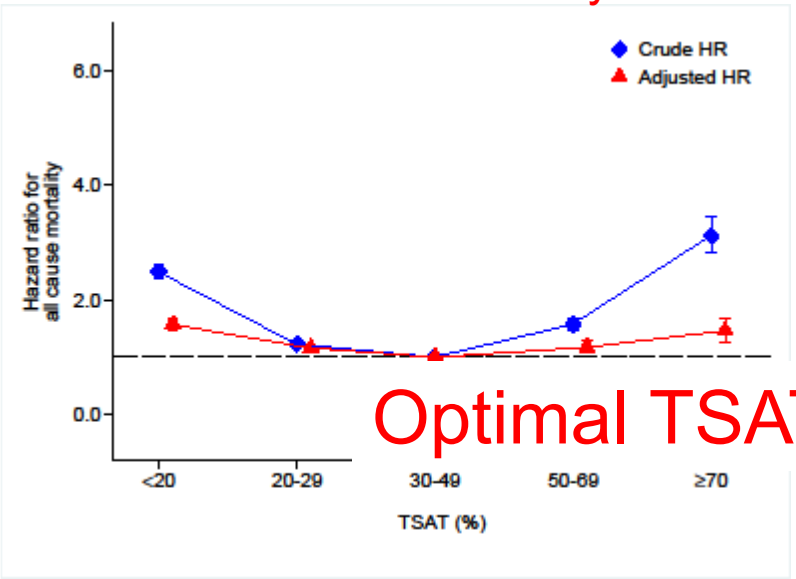


CV mortality

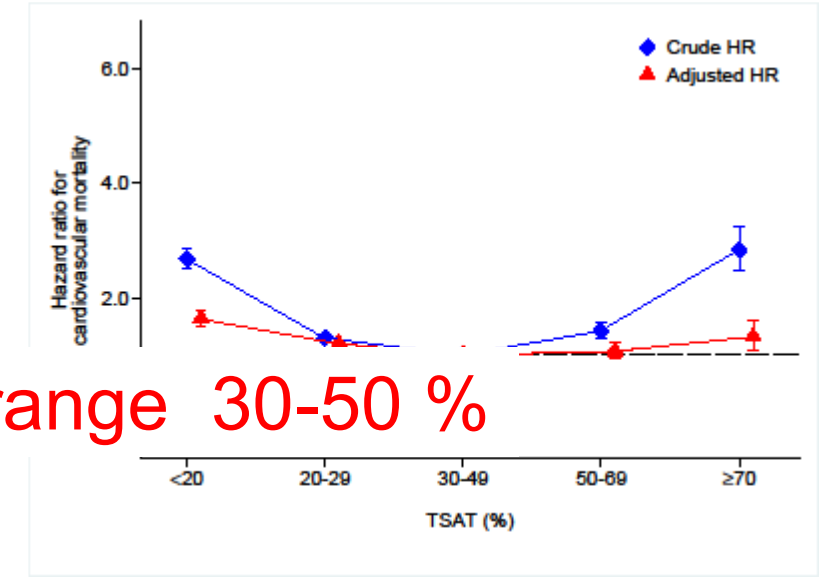


Optimal ferritin range 500- 800 ng/mL

All-cause mortality



CV mortality



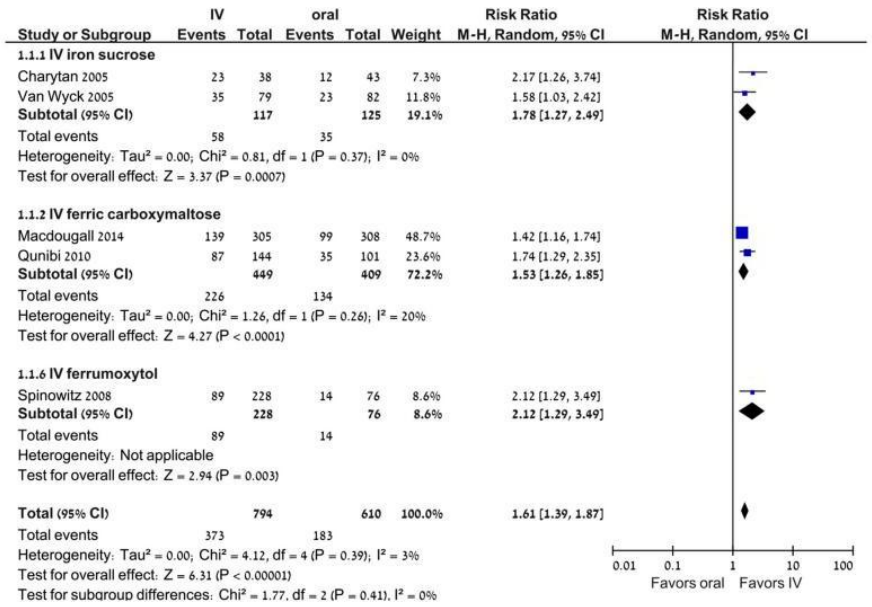
Optimal TSAT range 30-50 %

Kuo and Tarng et al. J Am Heart Assoc. 2018;7:e009206.

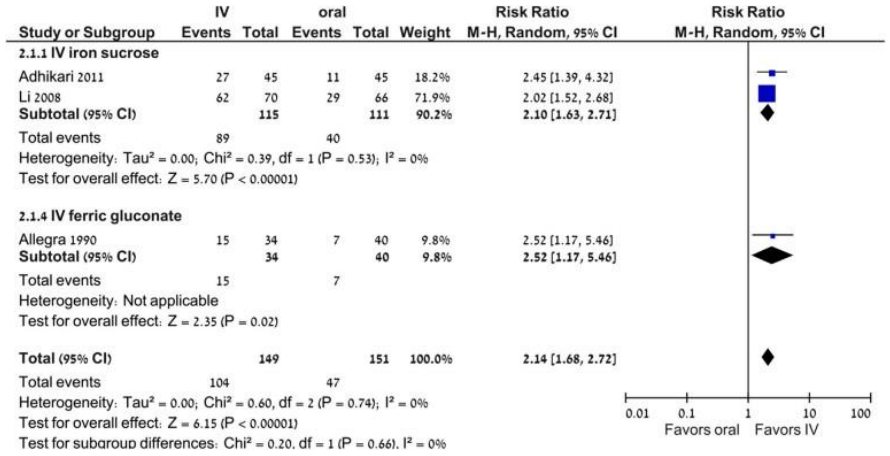
IV or oral iron supplementation in CKD

Percentage of patients reaching an elevation in Hb≧1 g/dL

CKD G3-G5



CKD G5D



Patients treated with IV iron were more likely to reach an Hb response

***American Journal of Kidney Diseases*, 2016**

Safety issues comparing IV vs oral iron

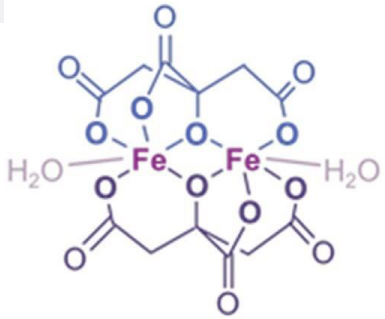
SAEs (REVOKE trial)

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
Str	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		

High incidence of SAEs (cardiac and infectious) in patients with IV iron replacement

Agarwal R. Kidney International (2015) 88, 905–914

Novel iron compounds – Ferric citrate

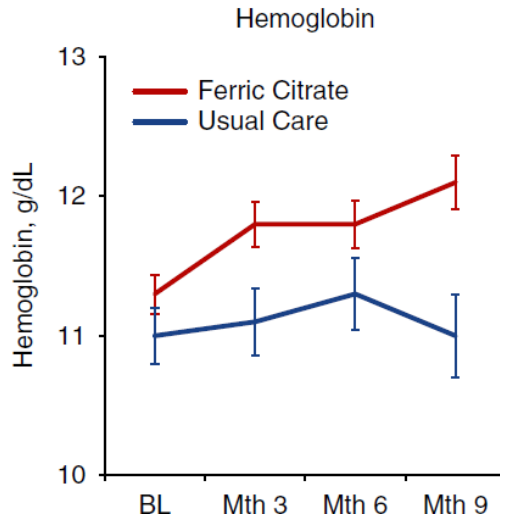


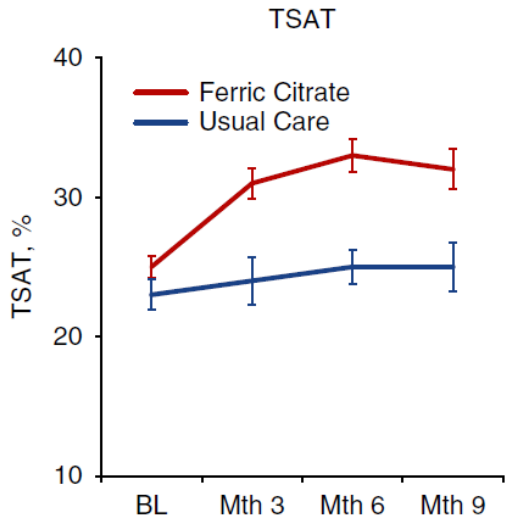
Mixture of ferric citrate coordination complexes (Auryxia^R, Fexeric^R, Riona^R, Nephoxil^R)

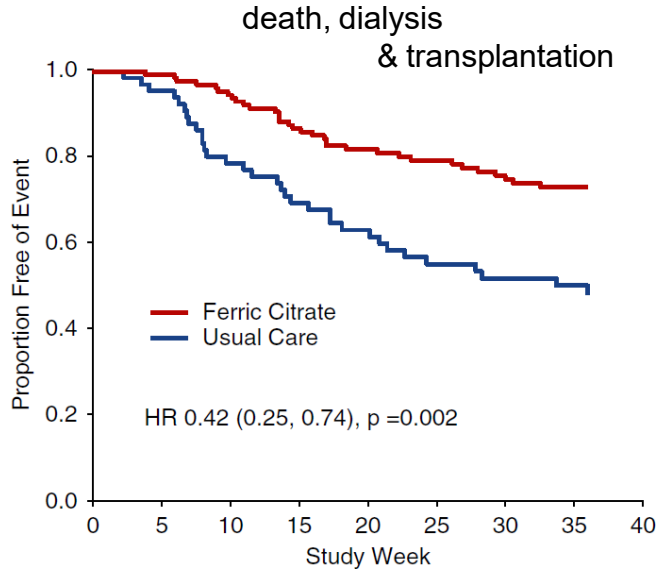
- binds phosphate
- releases iron

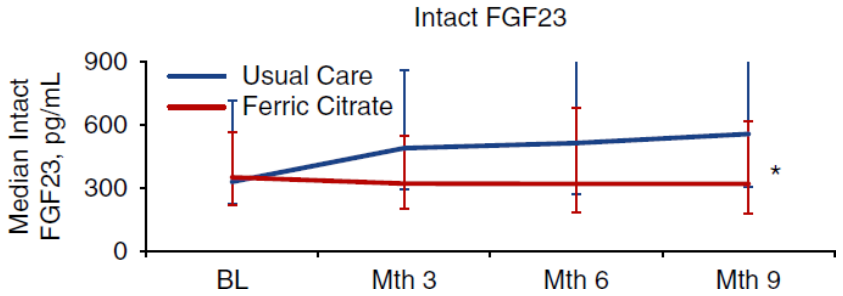
Ganz et al., *Drugs 2019*

N=203; eGFR ≤ 20ml/min x 1.73m^2 single center, open label trial, 2:1ferric citrate vs usual care









Block GA. J Am Soc Nephrol 2019

2025 KDIGO CKD Anemia Guideline (Draft)

Recommendation 2.2: In people with anemia and CKD G5HD in whom iron therapy is being initiated, we suggest using **IV Iron** rather than oral iron (2D).

Practice Point 2.1: In people with CKD G5HD in whom iron therapy is being initiated, administer **IV Iron using a proactive approach** to maintain stable iron status.

Recommendation 2.4: In people with anemia and **CKD not receiving hemodialysis** in whom iron is initiated, we suggest using either oral or IV iron based on the **person's values and preferences** (2D).

Practice Point 2.3: In people with CKD treated with oral iron, the choice between different formulations and dosing schedules is guided **by cost, individual patient preference, tolerability, and efficacy**.

Practice Point 2.4: In people with CKD treated with intravenous iron, the choice between different formulations is guided **by cost, individual preference, and recommended dosing schedules**.

Ref: https://kdigo.org/wp-content/uploads/2024/11/KDIGO-2025-Anemia-in-CKD-Guideline_Public-Review-Draft_Nov42024.pdf

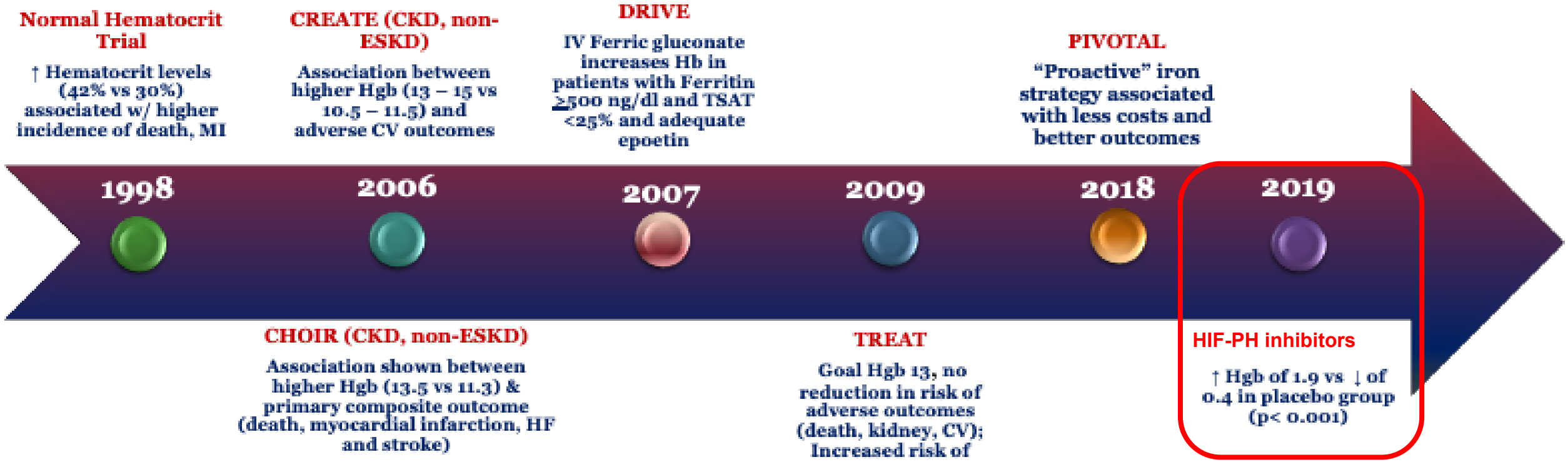
Special considerations in specific populations with CKD

	Specific Considerations
Peritoneal dialysis patients	Both ferric citrate and IV iron administration
Kidney transplant recipients	Caution with IV iron preparations (ferric carboxymaltose, saccharated iron oxide, and iron polymaltose): increased risk of hypophosphatemia
Hypothyroid patients	Caution regarding use of oral iron
Heart failure patients	Correction of iron deficiency with IV iron (ferric carboxymaltose): benefits in terms of intermediate endpoints (6 min walk test, quality of life, NYHA class) and hospitalization. IV iron lowers mortality risk (meta-analysis). Ongoing studies in heart failure patients with preserved ejection fraction, more common in CKD patients not on dialysis
Heart failure patients with reduced ejection fraction	Correction of iron deficiency has benefits independent of anemia
Patients with active infection	Caution about giving IV iron, particularly in those with Gram negative infections
Calciphylaxis patients	Caution in administering IV iron
Liver disease patients	No available data or consensus on iron administration
Children	Understudied area. Absence of RCTs on effects of iron administration on hard clinical outcomes. Results from small open-label and retrospective

CKD, chronic kidney disease; IV, intravenous; NYHA, New York Heart Association; RCTs, randomized controlled trials

Babitt et al. Kidney International 2021, 99: 1280-1295

How are iron kinetics affected in the era of HIF-PHIs ?



- MI: myocardial infarction
- CKD: chronic kidney disease
- ESKD: end-stage kidney disease
- Hgb: hemoglobin (g/dL)
- HF: heart failure
- DM: Diabetes mellitus
- VTE: venous thromboembolism
- HD: hemodialysis
- IV: intravenous

Clinical Kidney Journal

The impacts of hypoxia-inducible factor stabilizers on laboratory parameters and clinical outcomes in chronic kidney disease patients with renal anemia: a systematic review and meta-analysis

Hypoxia-inducible factor (HIF) stabilizer is a novel treatment of anemia in CKD. The present meta-analysis was conducted to extensively evaluate the impacts of HIF stabilizers on laboratory parameters and clinical outcomes.

Methods

Systematic search:
MEDLINE, Scopus, and Cochrane databases

Published and unpublished studies
2010 to March 2022

Outcomes:
- Hemoglobin and iron parameters
- Lipid and inflammatory profiles
- Clinical outcomes

Results

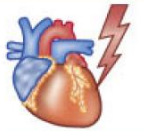
Forty-six studies with 27 338 patients were included in this study

Hemoglobin
Significantly increased Hb levels (MD 0.659 g/dL) compared with the control group (ESA or placebo)

Iron parameters
> Significantly decreased ferritin, TSAT, and hepcidin
> Significantly increased TIBC

Lipid profiles
Significantly decreased TC, LDL, HDL, and TG levels

AKI
RR 1.28 (1.00–1.64)
P = 0.04



MACE
RR 1.00 (0.94–1.07)
P = 0.71

Mortality
RR 0.91 (0.78–1.07)
P = 0.89

Conclusion: The present meta-analysis provided evidence that HIF-stabilizers increased hemoglobin and TIBC levels but reduced hepcidin, ferritin, TSAT, and lipid profiles in CKD patients with renal anemia.

Takkavatakarn et al.
Clinical Kidney Journal (2022)
email address
@CKJsocial

Clinical Kidney Journal, 2023, vol. 16, no. 5, 845–858

Roxadustat Reduced Monthly IV Iron Used vs Epoetin

Table 2. Prespecified efficacy end points, presented in hierarchical order

End Point (Analysis Set)	Roxadustat (*n*=1051)				Epoetin Alfa (*n*=1055)				Difference in LSM Changes (95% CI)/HR (95% CI)[c]	*P* Value for Superiority	NI *P* Value
	n	BL Value	Final Value	LSM Change/Adjusted LSM/Mean Monthly Value[a]/Event Rate[b]	*n*	BL Value	Final Value	LSM Change/Adjusted LSM/Mean Monthly Value[a]/Event Rate[b]			
Change in Hb from BL to mean during weeks 28–52, g/dl (ITT)	1003	10.01	10.78	LSM change: 0.77	1016	10.04	10.72	LSM change: 0.68	Difference in LSM changes: 0.09 (0.01 to 0.18)	–	<0.001[d]
Change in Hb from BL to mean during weeks 28–36, g/dl (PPS)	836	9.98	10.86	LSM change: 0.88	864	10.04	10.78	LSM change: 0.74	Difference in LSM changes: 0.14 (0.03 to 0.25)	–	<0.001[d]
Mean ch to we											–
Change value patier >ULN											–
Proportion of total time of interpolated Hb ≥10 g/dl from week 28–52[e] (ITT)	896	NA	NA	Adjusted LSM: 0.79	941	NA	NA	Adjusted LSM: 0.76	Difference in LSM: 0.03 (0.00 to 0.05)	–	<0.001[f]
Proportion of total time of interpolated Hb values between 10–12 g/dl from week 28–52[e] (ITT)	896	NA	NA	Adjusted LSM: 0.65	941	NA	NA	Adjusted LSM: 0.63	Difference in LSM: 0.02 (−0.01 to 0.05)	–	<0.001[f]
Mean monthly IV iron use during week 36 to EOS (ITT)	885	NA	NA	Mean monthly value: 58.71	920	NA	NA	Mean monthly value: 91.37	NA	<0.001	–
Event rate for first RBC transfusion (OT+3)	1048	NA	NA	Event rate: 6.0	1053	NA	NA	Event rate: 7.2	HR: 0.83 (0.64 to 1.07)	–	<0.001[g]

Mean monthly IV iron use from week 36 until EOS :

Roxadustat vs Epoetin alfa (58.71 mg versus 91.37 mg, P<0.001).

JASN 33: 850–866, 2022.

Roxadustat Reduced Monthly IV Iron Used vs Epoetin

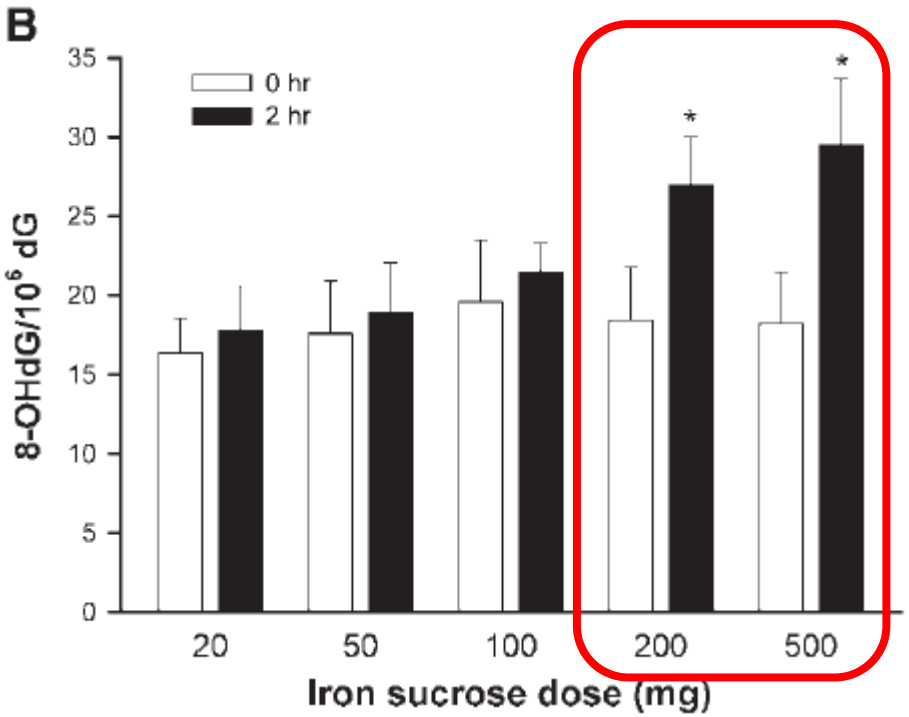
Table 2. Prespecified efficacy end points, presented in hierarchical order

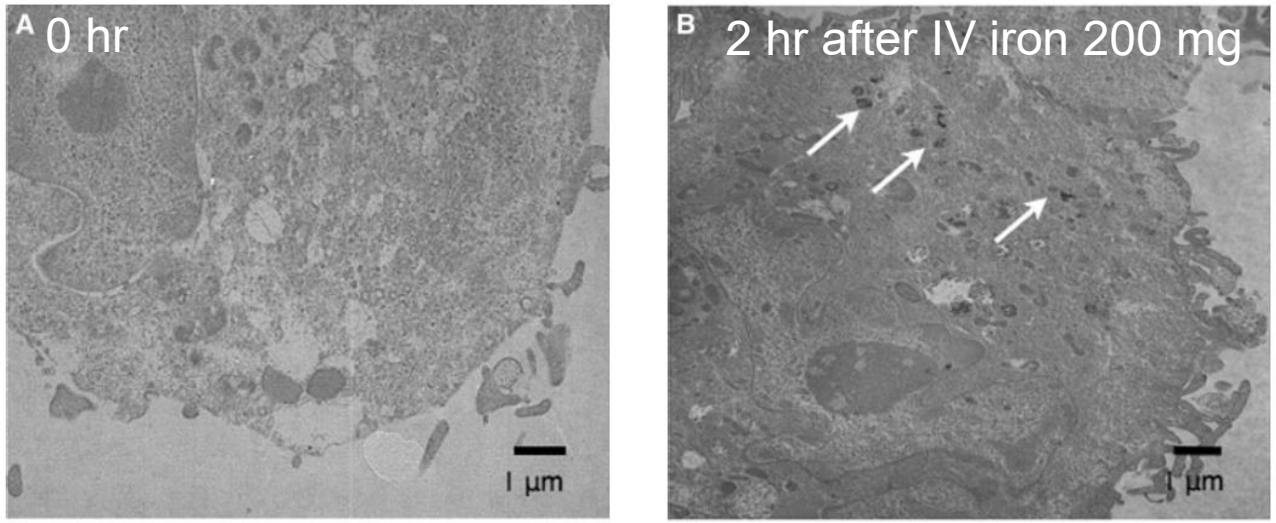
End Point (Analysis Set)	Roxadustat (*n*=1051)				Epoetin Alfa (*n*=1055)				Difference in LSM Changes (95% CI)/HR (95% CI)[c]	*P* Value for Superiority	NI *P* Value
	n	BL Value	Final Value	LSM Change/Adjusted LSM/Mean Monthly Value[a]/Event Rate[b]	*n*	BL Value	Final Value	LSM Change/Adjusted LSM/Mean Monthly Value[a]/Event Rate[b]			
Change in Hb from BL to mean during weeks 28–52, g/dl (ITT)	1003	10.01	10.78	LSM change: 0.77	1016	10.04	10.72	LSM change: 0.68	Difference in LSM changes: 0.09 (0.01 to 0.18)	–	<0.001[d]
Change in Hb from BL to mean during weeks 28–36, g/dl (PPS)	836	9.98	10.86	LSM change: 0.88	864	10.04	10.78	LSM change: 0.74	Difference in LSM changes: 0.14 (0.03 to 0.25)	–	<0.001[d]
Mean ch to we											–
Change value during weeks 28–52 in patients with BL hsCRP >ULN, g/dl (ITT)				0.80					0.20 (0.04 to 0.36)		–
Proportion of total time of interpolated Hb ≥10 g/dl from week 28–52[e] (ITT)	896	NA	NA	Adjusted LSM: 0.79	941	NA	NA	Adjusted LSM: 0.76	Difference in LSM: 0.03 (0.00 to 0.05)	–	<0.001[f]
Proportion of total time of interpolated Hb values between 10–12 g/dl from week 28–52[e] (ITT)	896	NA	NA	Adjusted LSM: 0.65	941	NA	NA	Adjusted LSM: 0.63	Difference in LSM: 0.02 (−0.01 to 0.05)	–	<0.001[f]
Mean monthly IV iron use during week 36 to EOS (ITT)	885	NA	NA	Mean monthly value: 58.71	920	NA	NA	Mean monthly value: 91.37	NA	<0.001	–
Event rate for first RBC transfusion (OT+3)	1048	NA	NA	Event rate: 6.0	1053	NA	NA	Event rate: 7.2	HR: 0.83 (0.64 to 1.07)	–	<0.001[g]

Does it have a meaningful impact on IV iron dose reduction?

JASN 33: 850–866, 2022.

IV Iron Sucrose Exacerbates Oxidative DNA Damage in Peripheral Blood Lymphocytes in HD Patients



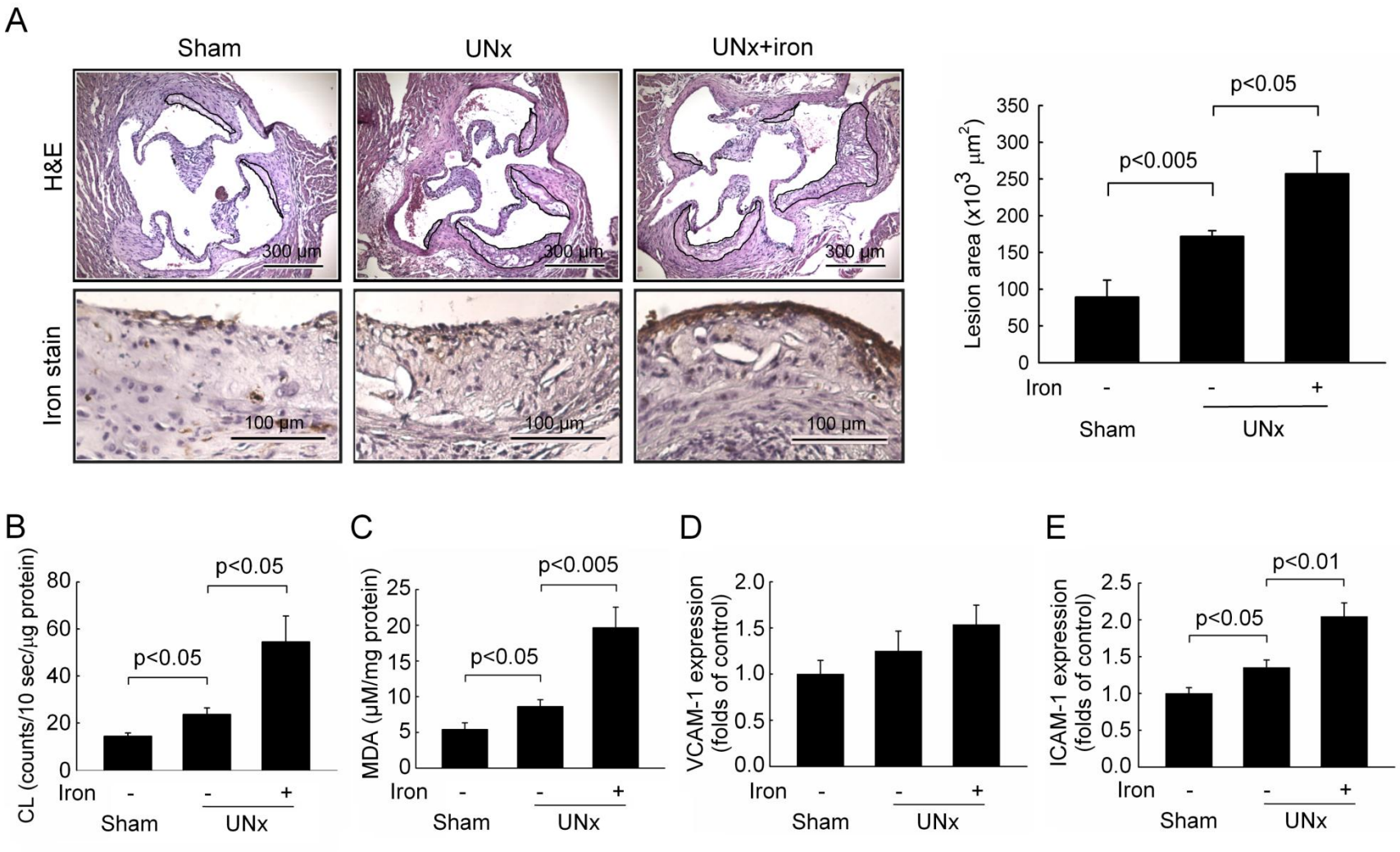


Lymphocytes treated with iron had distinct intracellular iron uptake (arrows)

8-OHdG: 8-Hydroxy 2'-deoxyguanosine

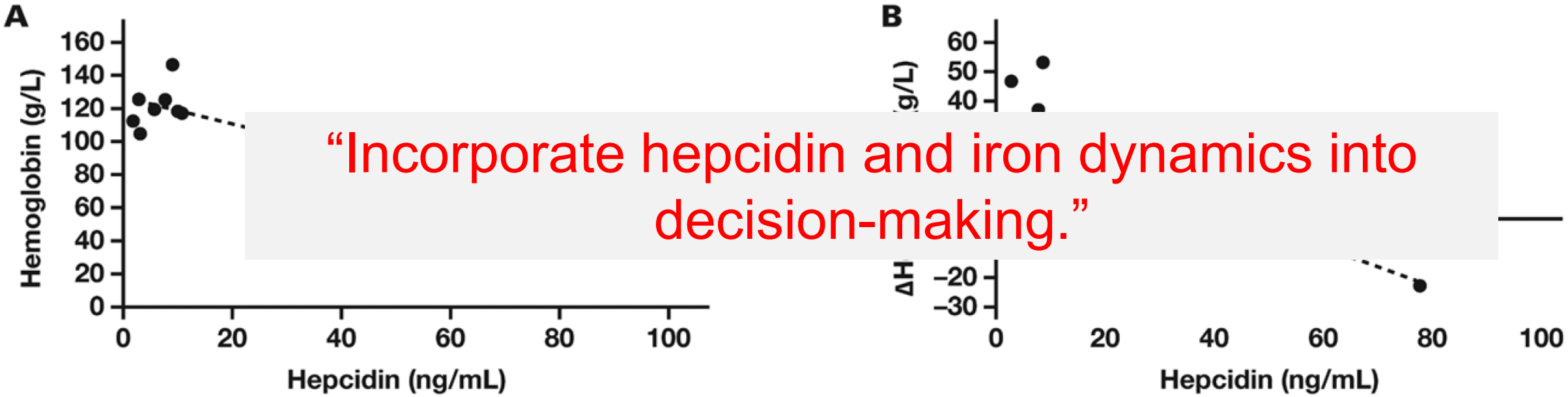
Kuo and Tarng et al J Am Soc Nephrol 2008; 19: 1817–1826

IP iron sucrose exacerbated lipid peroxidation and exacerbated atherosclerosis in uni-nephrectomized ApoE$^{-/-}$ mice



Kuo and Tarng et al. J Am Soc Nephrol 2014; 25 :2596-2606.

Lower hepcidin levels at 1 month were strongly correlated with Higher hemoglobin at 3 months (A) and Greater ΔHemoglobin (B) in HIF PHI treated patients



"Incorporate hepcidin and iron dynamics into decision-making."

Lab Med 2025. Online ahead of print.

Take Home Message

- Traditional markers such as **ferritin,** and **TSAT** are **insufficient alone** to assess iron stores or predict treatment response.
- **Dynamic biomarkers,** such as **CHr/RET-He, HRC %** or potentially **hepcidin**, to better reflect iron kinetics and the immediate effects of treatment.
- In the era of **HIF-PHIs**, which enhance iron metabolism, the optimal use of iron therapy—including **indications, dosing, and administration route** (IV vs. oral)—may need to be redefined compared with the rHuEPO era.
- A **personalized approach**—tailoring therapy by patient condition, treatment response, and iron metabolism—will be crucial to ensure **safety, efficacy, and sustainability.**

Thanks for your attentions