Practical Guidance for Treating iron deficiency patients with chronic kidney disease

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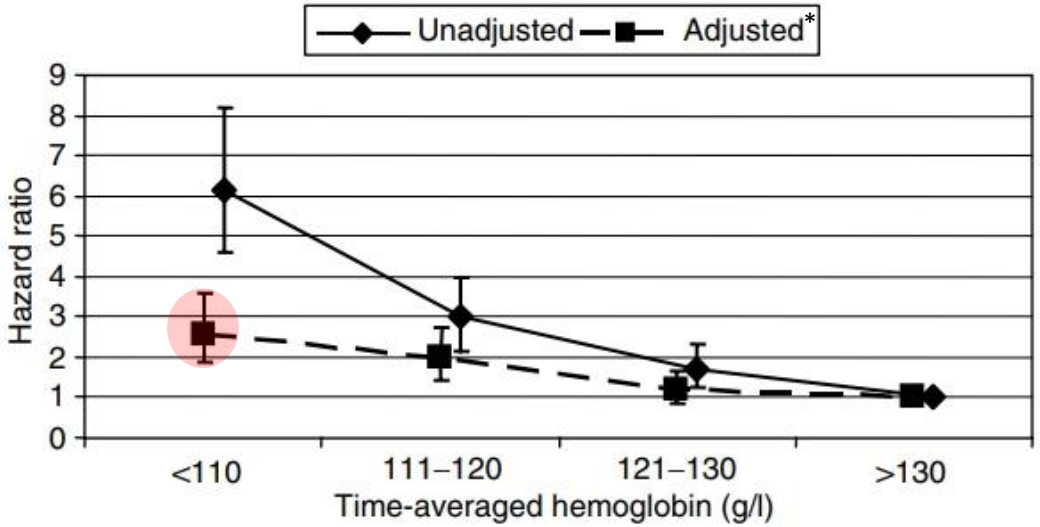
Anemia and CKD

- **Anemia: Very well-known risk factor of all-cause mortality in CKD patients**

	Composite (*N*=440)	Death before dialysis (*N*=245)	Dialysis (*N*=195)
<110 g/l (*N*=174)	138 (79.3%)	68 (39.0%)	70 (40.2%)
111–120 g/l (*N*=216)	139 (64.3%)	74 (34.2%)	65 (30.0%)
121–130 g/l (*N*=201)	86 (42.8%)	50 (24.9%)	36 (17.9%)
>130 g/l (*N*=262)	77 (29.4%)	53 (20.2%)	24 (9.2%)

[a]Data presented as number (% of total).

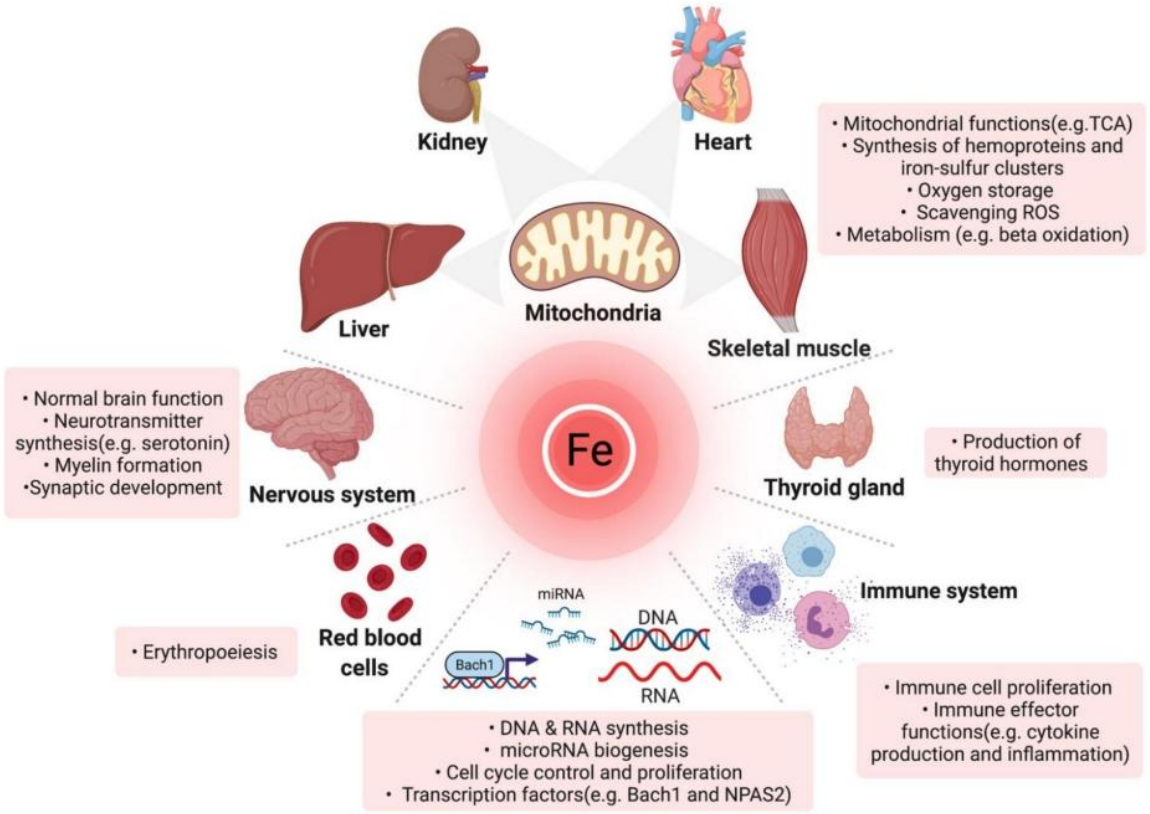


*after adjustment for age, race, DM, ASCVD, BMI, smoking status, MAP, estimated GFR, serum albumin, blood cholesterol, and 24-h urine protein

Kovesdy CP, et al. Kidney Int. 2006;69;560-4

Iron deficiency in CKD patients

- **Iron deficiency anemia (IDA)** vs. **Iron deficiency *without* anemia**
  - The physiological role of iron extends well **beyond hematopoiesis**
  - Iron deficiency causes functional impairment in ***energy-demanding tissues*** (muscles, ***myocardium***, and ***renal tubules***)
    : they usually ***precede*** the decline in erythropoiesis



	Normal	Negative iron balance	Iron-deficient erythropoiesis	Iron-deficiency anemia
Iron stores				
Erythron iron				
Marrow iron stores	1-3+	0-1+	0	0
Serum ferritin (μg/L)	50-200	<20	<15	<15
TIBC (μg/dL)	300-360	>360	>380	>400
SI (μg/dL)	50-150	NL	<50	<30
Saturation (%)	30-50	NL	<20	<10
Marrow sideroblasts (%)	40-60	NL	<10	<10
RBC protoporphyrin (μg/dL)	30-50	NL	>100	>200
RBC morphology	NL	NL	NL	Microcytic/ hypochromic

Alnuwaysir RIS, et al. J Clin Med. 2022:11;125
Harrison's Internal Medicine 19th edition.

Iron deficiency in CKD patients

- **Iron deficiency in CKD patients**

  - **Over 50% of CKD patients affected**
  - Leads to anemia, fatigue, cardiovascular risk, cognitive impairment, etc.
  - Contributes to ESA resistance and poor outcomes
  - **Traditional view from nephrologists:**

    focusing on correcting anemia using ESA and iron supplantation (but *Hb not too high)*

    iron deficiency 'per se' has rarely been regarded as an independent therapeutic target

Alnuwaysir RIS, et al. J Clin Med. 2022:11;125

Does iron deficiency alone affects the health of CKD patients?

- **Evidence from heart failure studies**

  : correction of iron deficiency is important irrespective of anemia

  - **Impact of iron deficiency *vs*. anemia**

    Jankowska et al.: ID alone > anemia alone in predicting ***poor exercise capacity***
    Comín-Colet et al.: ID (not anemia) ***independently ↓ QoL***
    Klip et al., Martens et al.: ID → ***40%↑ mortality;*** *anemia alone → not significant*

  - **IV iron therapy (esp. ferric carboxymaltose)**

    FAIR-HF, CONFIRM-HF, EFFECT-HF: ***↑exercise tolerance, QoL***
    AFFIRM-AHF: 26% ***↓ HF hospitalization, independent of Hb***
    IRONOUT-HF: ***IV but not oral iron effective***

- **In CKD population?**

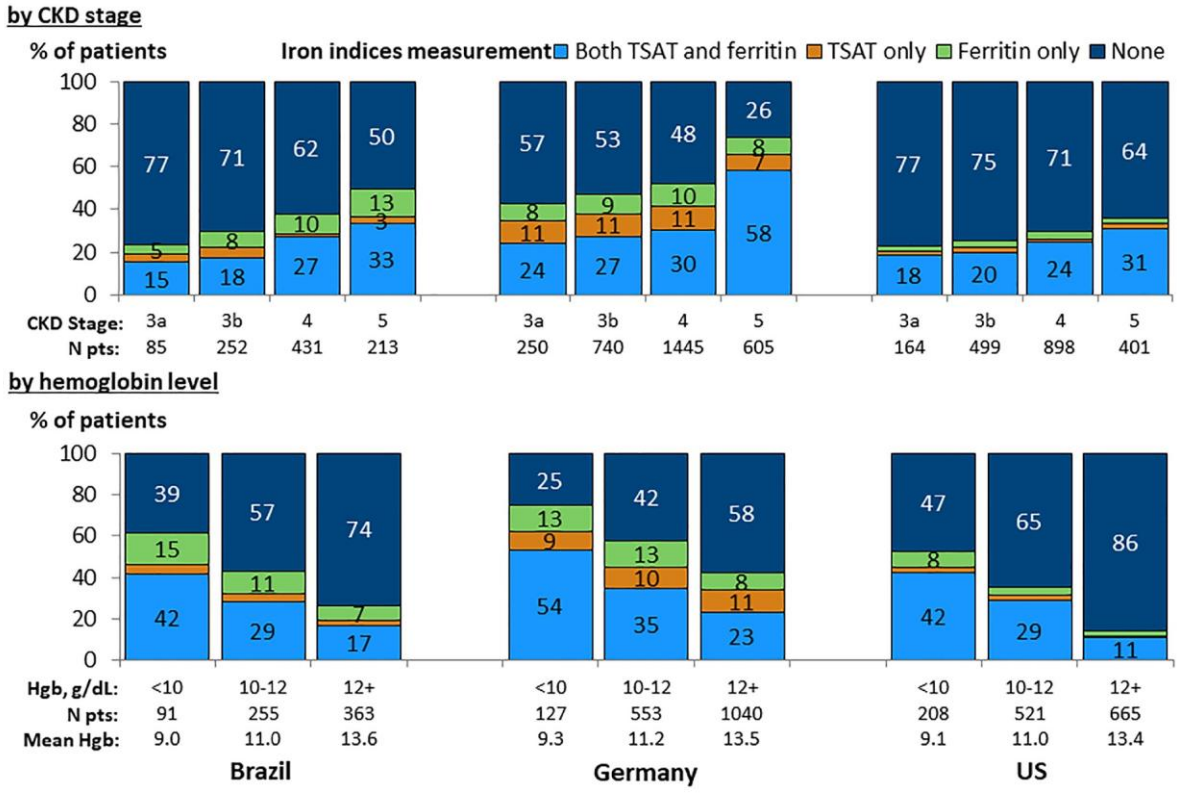
  - probable to possible.
  - but not yet defined.

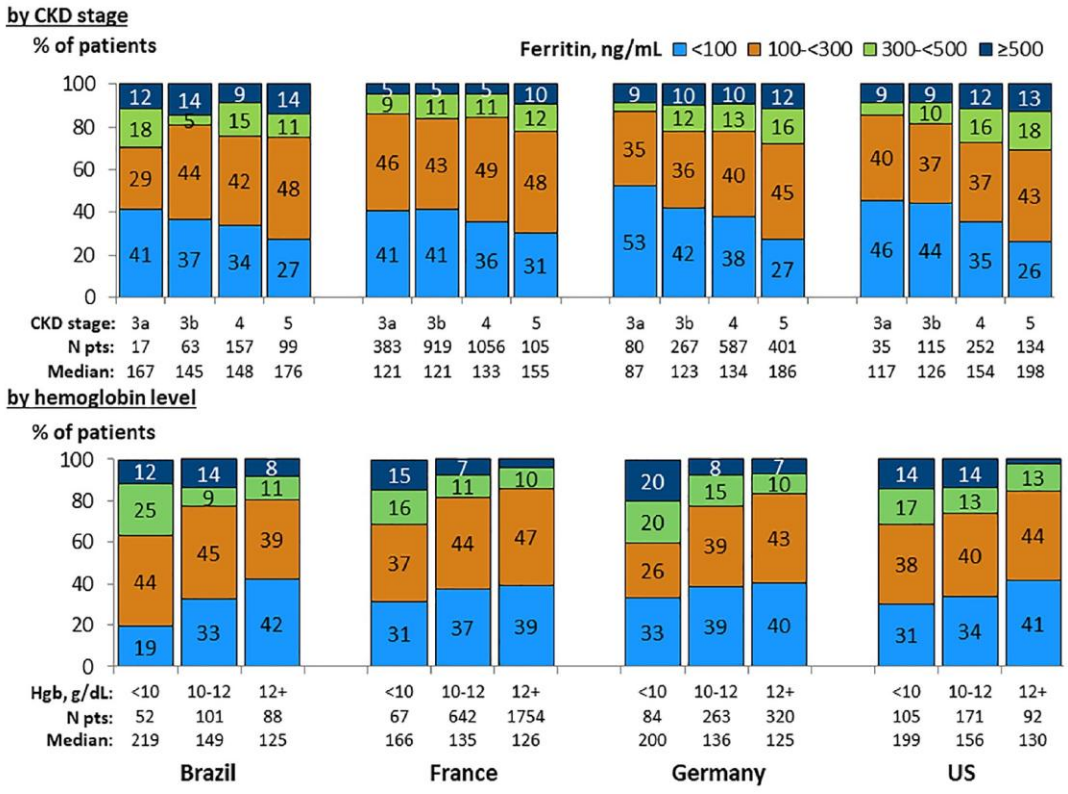
Jankowska EA, et al. J Card Fail. 2011;17:899-906
Comín-Colet J, et al. Eur J Heart Fail. 2013;15:1164-72
Klip IT, et al. Am Heart J. 2013;165:55-82
Martens P, et al. Acta Cardiol. 2018;73:115-23
(FAIR-HF) Anker SD, et al. N Engl J Med. 2009;361:2436-48
(CONFIRM-HF) Ponikowski P, et al. Eur Heart J. 2015;36:657-68
(EFFECT-HF) van Veldhuisen dJ, et al. Circulation. 2017;136:1374-83
(AFFIRM-AHF) Ponikowski P, et al. Lancet. 2020;396:1895-904
(IRONOUT-HF) Lewis GD, et al. JAMA. 2017;317:1958-66

Does iron deficiency alone affects the health of CKD patients?

- **Iron deficiency in CKD patients**

  - Underrecognized
  - Significant proportion of CKD patients have iron deficiency, irrespective of anemia

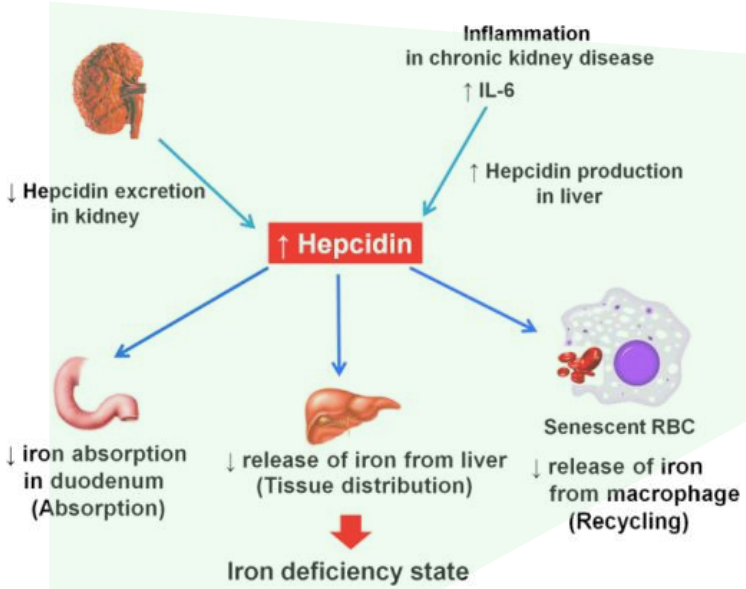


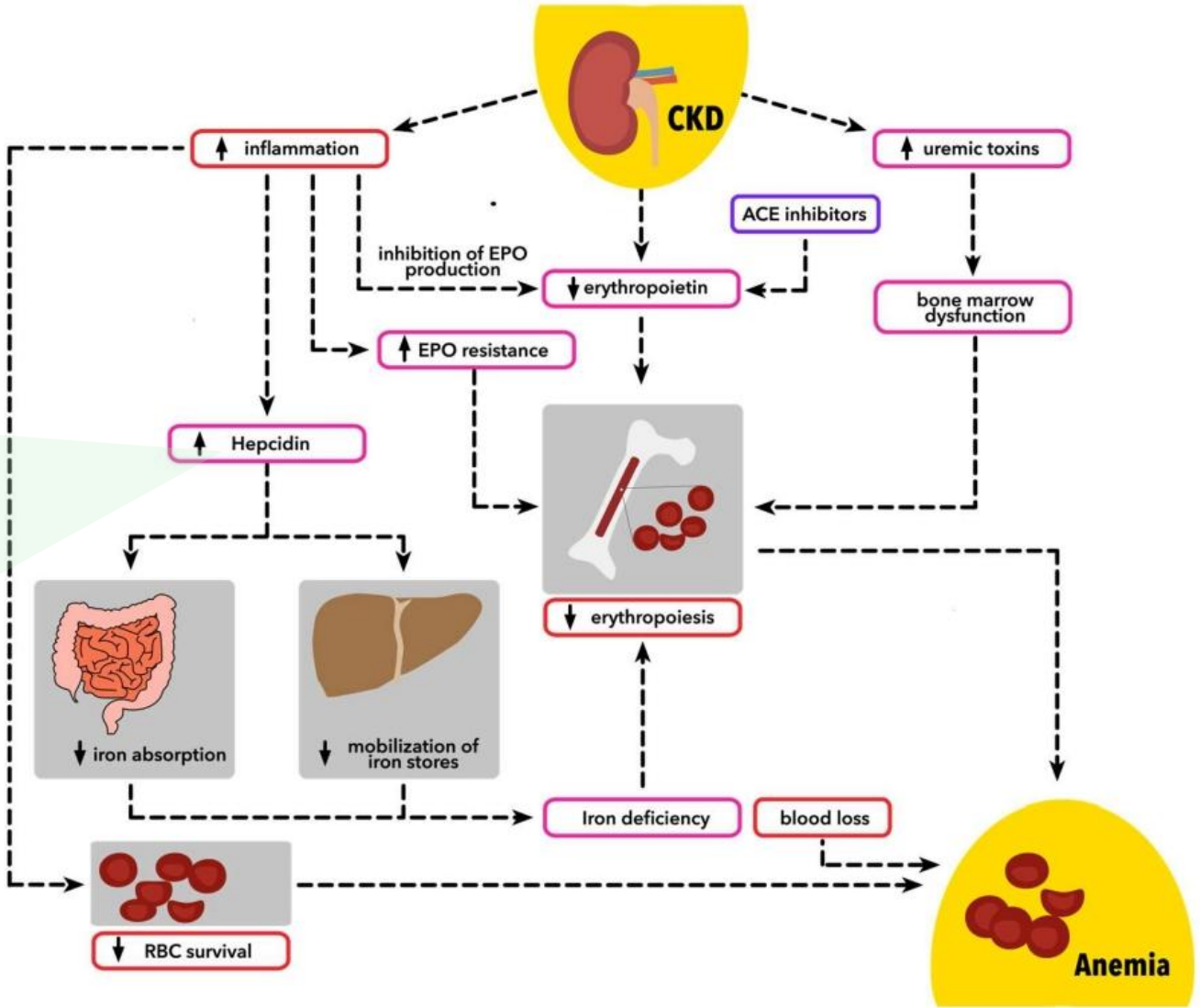


Wong MMY, et al. Clin Kidney J. 2020;13:613-24

Pathophysiology of anemia in CKD

- **Mechanisms in CKD**
  - Multifactorial
  - Two main findings
    - *1) Decrease of EPO*
    - *2) Increase of hepcidin (=functional iron deficiency)*





Badura K, et al. Biomedicines. 2024;12:1191

Terminologies for iron deficiency

Old terms	New terms (2025)	Definition/typical pattern	Meaning and reasons for change
Absolute iron deficiency	**Systemic iron deficiency**	Low ferritin (<100 ND / <200 HD) *AND* Low TSAT (< 20 %)	- ***true depletion*** - depleted total body iron - ***Tx. Strategy: replace iron to replenish stores (either oral or IV)***
Functional iron deficiency	**Iron-restricted erythropoiesis (IRE)**	Ferritin normal or high *AND* Low TSAT (< 20 %)	- utilization block -iron present but ***unavailable for erythropoiesis*** -iron trapped in stores due to ***hepcidin-driven ferroportin inhibition*** ***- Tx. Strategy: to bypass the hepcidin block (IV > oral)***

DRIVE study: IV iron for anemic HD patients with *high ferritin & low TSAT*

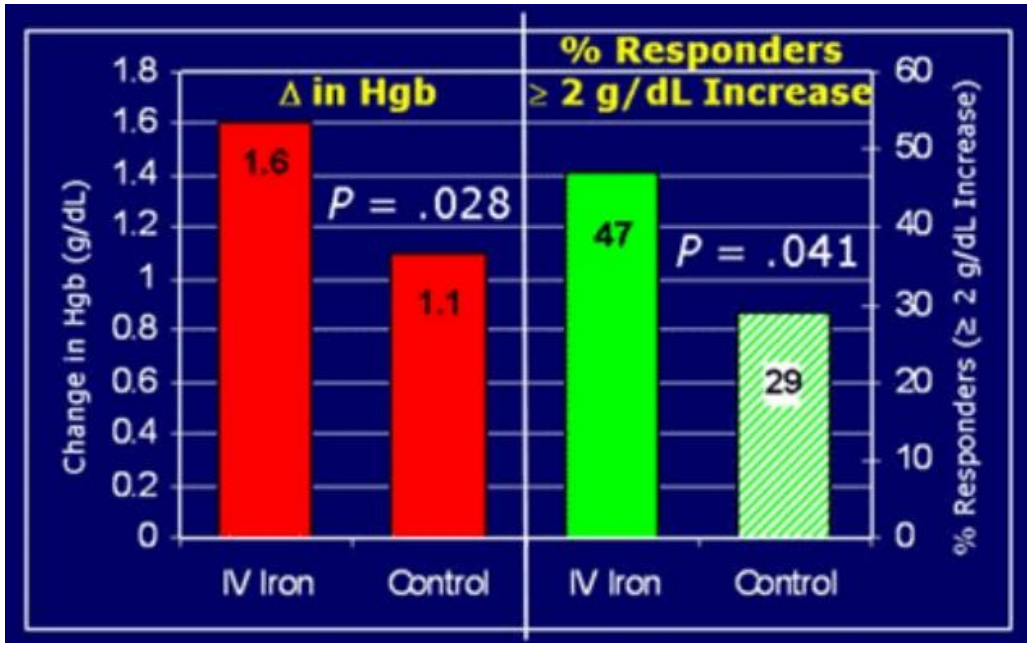
- **A prospective, randomized, controlled, parallel-group, multicenter clinical trial**

  - **Major inclusion criteria**
    - **Serum ferritin 500-1200 ng/mL and TSAT ≤ 25%**
    - Hb ≤ 11.0 g/dL
    - Receiving epoetin dose ≥ 225 IU/kg/week or ≥ 22,500 IU/week
    - ≤ 125 mg of IV iron per week in any of the 4 weeks prior to screening

  - **Patients are randomized in a 1:1 ratio to receive**
    - IV iron group: 1 g of ferric gluconate (125 mg x 8 HD sessions)
    - Control group: no IV iron

  - **Results & significance**
    - IV iron effective **even with ferritin 500–1200 µg/L**

    → Evidence for treating IRE (functional ID) with high ferritin



Coyne, DW, et al. J Am Soc Nephrol. 2007;18:975-84

Oral vs. IV iron

▪ Formulation of iron for CKD patients

Route	Pros	Cons	Typical use
Oral	Easy, inexpensive	Poor absorption, GI upset	Earlier CKD
Intravenous	Rapid retention, bypasses hepcidin block	Need IV access, cost	CKD 3-4, dialysis, with ESA use

▪ Conventional oral iron

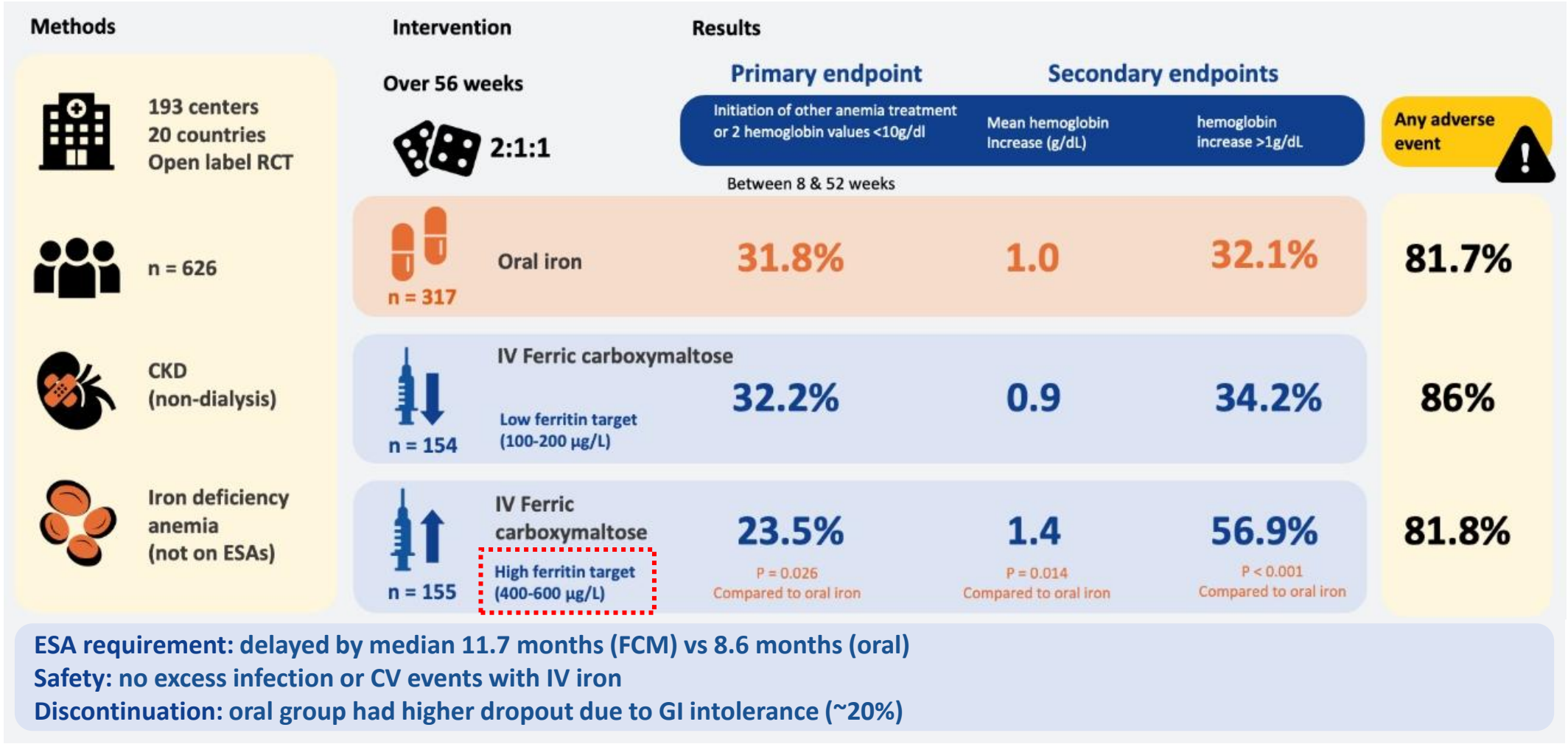
- Ferrous sulfate, ferrous fumarate, ferrous gluconate,…
- Absorbed in duodenum through DMT1 (divalent metal transporter-1)
- **Blocked when hepcidin suppresses ferroportin**
  : ***leading to markedly reduced absorption in inflammation or CKD (absorption rate 5~15%)***

∴ CKD and other chronic inflammatory condition (=functional ID): oral iron is largely ineffective*

* ferric maltol or sucrosomial iron: use hepcidin-independent absorption pathways, offering better tolerability and modest efficacy in early CKD

FIND-CKD (2014): high dose FCM *vs.* low dose FCM *vs.* oral iron

- IV iron is superior to oral formulation in *NON*-dialysis CKD patients
- Targeting a higher ferritin level would be more beneficial

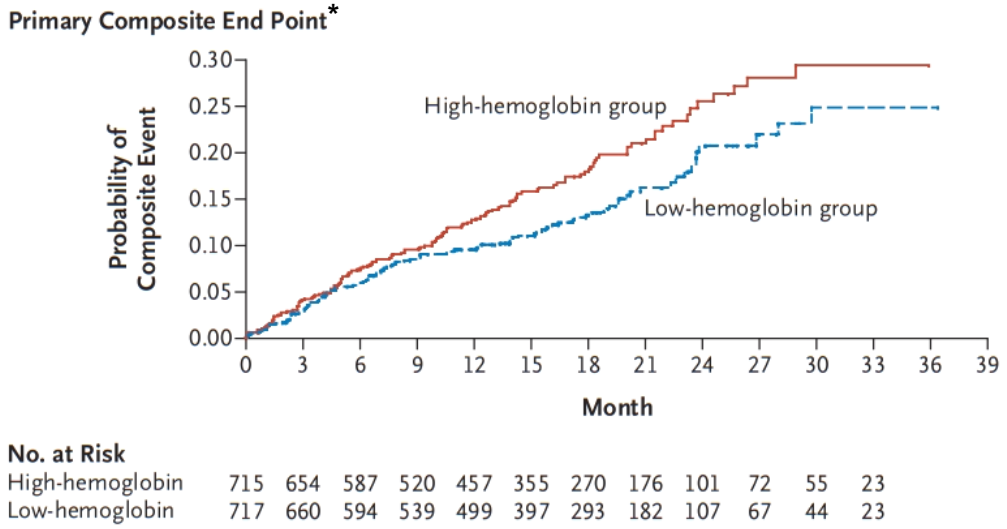


Macdougall IC, et al. Nephrol Dial Transplant. 2014;29:2075-84

In CKD patients: Is correction of anemia enough? Correction of ID?

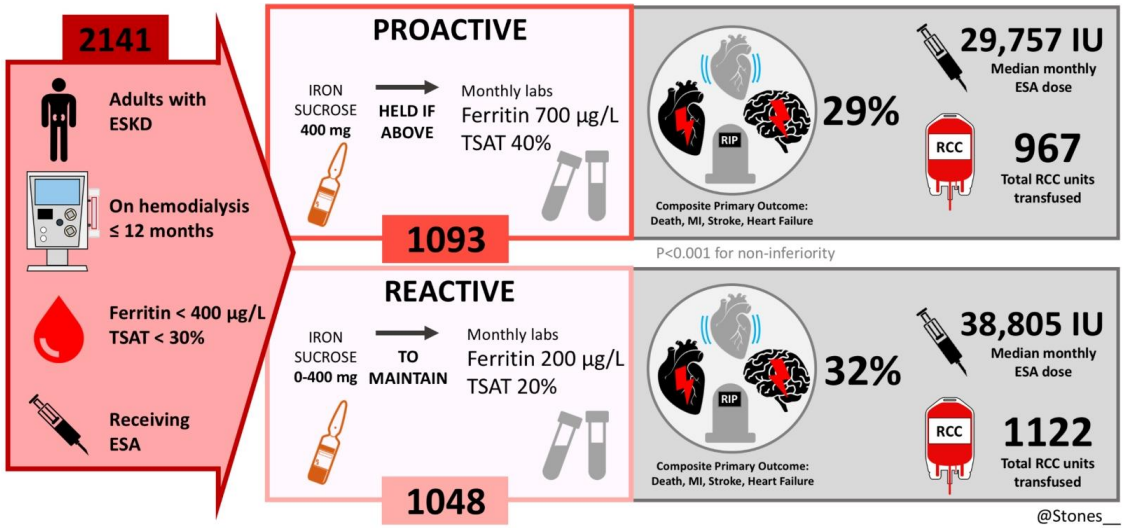
- **Treatment implication of iron replacement to CKD patients with ID?**

· Focusing on EPO stimulation (*i.e.*, ESA)
- Proven clinical benefit
- But multiple studies consistently suggest that **high Hb levels (*e.g.* around 13) would rather be detrimental** to patients



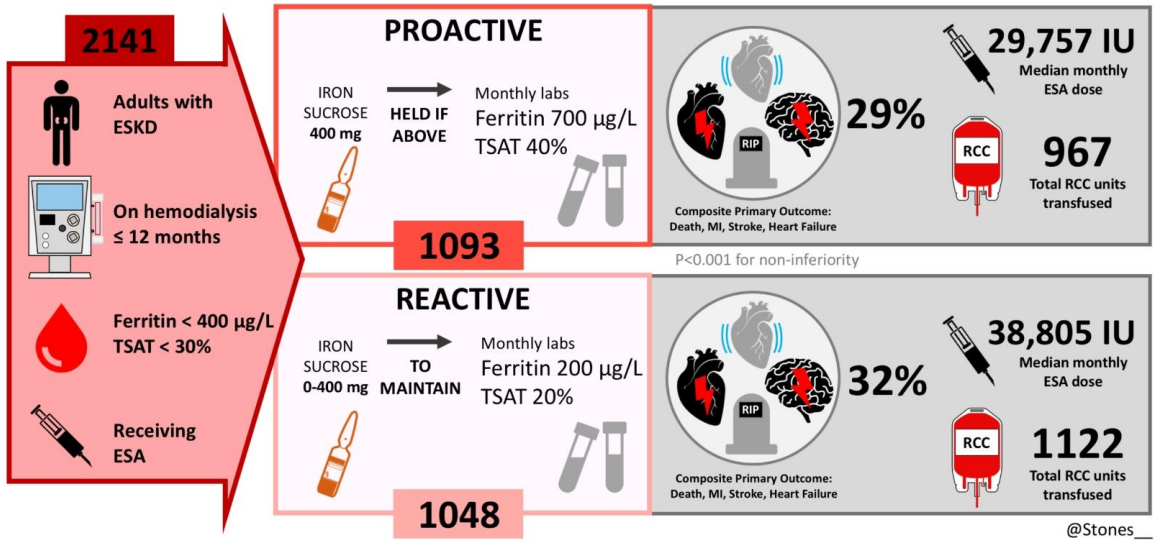
*Primary endpoint: a composite of death, MI, hospitalization for CHF, and stroke

· Focusing on evasion of hepcidin (*i.e.*, I.V. iron)
- Proven clinical benefit
- Especially when applied proactively (PIVOTAL trial)



(Left) Singh AK, et al. N Engl J Med. 2006:355:2085-98
(Right) Macdougall IC, et al. N Engl J Med. 2019;380:447-58
Visual abstract: a courtesy of Dr. Sinead Stoneman (@Stones_)

Phase 3 PIVOTAL (Proactive IV IrOn Therapy in HaemodiALysis Patients) study



Category	Proactive Group	Reactive Group
Approach	Regular, scheduled IV iron (**preventive**)	IV iron when deficient (**as-needed**)
Dose	**400 mg IV iron / month**	**100 mg / week (0–400 mg / month), if needed**
Continue criteria	**Ferritin < 700 µg/L & TSAT < 40 %**	**Start if Ferritin < 200 µg/L or TSAT < 20 %**
Hold criteria	**Ferritin ≥ 700 µg/L or TSAT ≥ 40 %**	**Ferritin ≥ 200 µg/L or TSAT ≥ 20 %**

Key results of the PIVOTAL study

Outcome	Result
Primary composite (death, MI, stroke, HF hospitalization)	HR 0.85 (95% CI 0.73–1.00, $p = 0.04$) — favoring proactive group
ESA dose	↓ 19%
Transfusions	↓ 24%
Infection risk	No significant difference

- Proactive, higher-dose IV iron safely reduces CV events, ESA use, and transfusions in HD patients.
- Established ferritin 700 µg/L and TSAT 40% as safe upper limits: the direct evidence base for KDIGO 2025 updates.

Macdougall IC, et al. N Engl J Med. 2019;380:447-58
Visual abstract: a courtesy of Dr. Sinead Stoneman (@Stones_)

Phase 3 PIVOTAL trial

- **Dose and frequency of IV iron: evidence and insights from PIVOTAL trial**

: Sufficient dose with low frequency (*e.g.,* 400 mg/mo) is better than small dose with high frequency (100 mg/wk),

In terms of

- *Hepcidin kinetics*

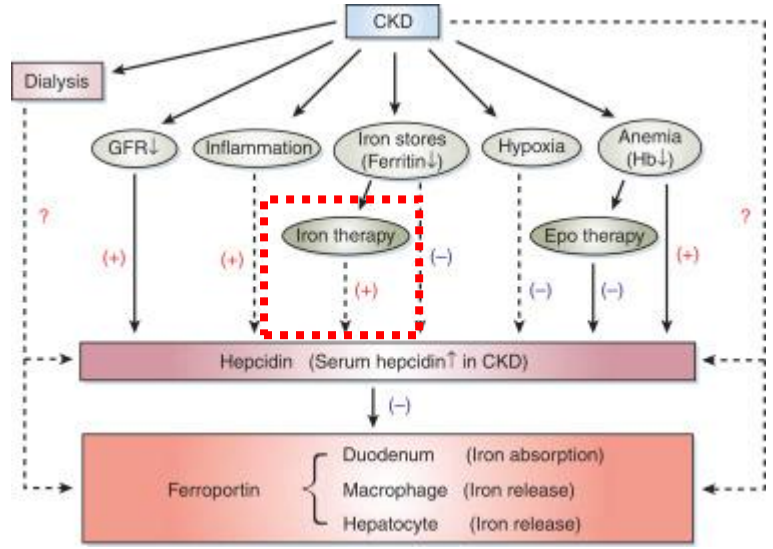
small, frequent dose: repeated hepcidin spikes → ↓iron absorption & utilization
sufficient, intermittent doses: hepcidin stabilized → effective erythropoiesis

- *Iron storage & utilization*

small, frequent dose: less effective
sufficient, int. dose: stable iron storage in the RES → gradual release to the BM

- *Practicality, cost and safety*

small, frequent dose: labor intensive, more visit, more chance of side effects
sufficient, int. dose: more beneficial



Hamada Y, et al. Kid Int. 2009;75:873-4

Iron therapy in CKD 2025 updates

- **Definition of iron deficiency (ID)**

	Diagnostic threshold	Meaning
ID in non-dialysis CKD	Ferritin <100 µg/L ***or*** TSAT <20%	Absolute iron deficiency
ID in dialysis-dependent CKD	Ferritin <200 µg/L ***or*** TSAT <20%	Functional or absolute deficiency
Functional ID / IRE	Ferritin ≥100 (ND) / ≥200 (HD/PD) ***but*** TSAT <20%	Iron stores OK, but utilization impaired

Iron therapy in CKD 2025 updates

- **Definition of iron therapy <u>initiation</u> threshold (When to treat?; KDIGO draft 2025)**

Patients	Iron therapy initiation criterion	Meaning
CKD G3-G4ND, G5PD	Ferritin <100 ***and*** TSAT <40%, ***or*** Ferritin 100–300 **and** TSAT <25%	A newly specified dual-criterion approach adopting a more liberal TSAT cut-off
CKD G5 HD	Ferritin ≤ 500 ng/mL ***and*** TSAT ≤ 30%	Previously accepted threshold maintained; proactive IV iron therapy recommended based on the PIVOTAL trial

Iron therapy in CKD 2025 updates

- **Definition of iron therapy <u>discontinuation</u> threshold (When to stop?; KDIGO draft 2025)**

Patients	Iron therapy withhold criterion	Meaning
CKD treated with iron (any stage, both dialysis and non-dialysis)	ferritin ≥700 ng/ml ***or*** TSAT ≥40%	Clearly defines the points at which iron therapy should be withheld and re-evaluated

Iron therapy in CKD 2025 updates

- **Key differences: KDIGO 2012 vs. 2025 (draft)**

Aspect	KDIGO 2012	KDIGO 2025 (Draft)	Change / Implication
Conceptual clarity	One combined cut-off (Ferritin <500, TSAT <30%) used both for initiation and target → confusion	Separate criteria for **diagnosis**, **initiation**, and **withholding**	Clear 3-step framework
Initiation threshold	Ferritin <500, TSAT <30%	HD: ≤500/≤30%; ND/PD: <100/ <40% or 100–300/<25%	**More liberal TSAT range**, esp. in non-dialysis CKD
Withholding threshold	Not clearly defined	Withhold if Ferritin ≥700 or TSAT ≥40%	**Safety ceiling clarified**
Guideline tone	Conservative : fear of overload	Proactive : optimize iron availability	**Encourages proactive IV iron and more frequent re-evaluation**
Evidence base	Expert consensus, limited trials	Strong RCT data (*PIVOTAL, FIN D-CKD, DRIVE*)	Evidence-driven

Practical considerations in iron management (KDIGO 2025-based)

▪ Monitoring & Timing

- Test for anemia at referral, regularly during F/U, and when symptoms suggest anemia
- Evaluated with CBC, reticulocyte, ferritin and TSAT
- At least: annually for CKD G3, twice a year for CKD G4, every 3 months for CKD G5 or G5D
- Consider more frequent testing after ESA or HIF-PHI initiation, or clinical deterioration/change

▪ Route of iron therapy

- Oral iron: early CKD (G3–G4) with low hepcidin, only mild ID
- IV iron: iron-restricted erythropoiesis, ESA use, dialysis, or poor oral tolerance
- For HD patients: adopt a proactive, high-dose, low-frequency strategy

▪ When to pause or reassess

- Ferritin ≥700 µg/L or TSAT ≥40% → withhold iron and re-evaluate, and resume once values fall below these limit
- Temporarily stop iron during active systemic infection or acute inflammatory state
- Consider checking serum phosphate periodically

Practical considerations in iron management (KDIGO 2025-based)

- **For HIF-PHI users**

- Alternative for ESA
- Correct iron first, use only after iron status optimization
- Monitor closely: HIF-PHIs suppress hepcidin and enhance iron mobilization, which may reduced iron requirements initially, but regular monitoring of ferritin/TSAT is essential to prevent iron depletion
- Long-term safety uncertain yet

- **For transplant recipients**

- Manage anemia as CKD
- Prefer IV iron: MMF and tacrolimus can decrease GI absorption of oral iron
- avoid HIF-PHI until more evidence available

Proposed algorithm for iron replacement in CKD patients (KDIGO 2025-based)

Step 1. Evaluate baseline

Measure Hb, reticulocytes, ferritin, TSAT

Systemic iron deficiency (absolute ID)

ND: Ferritin<100 & TSAT<20%

HD: Ferritin<200 & TSAT<20%

Iron-restricted erythropoiesis (IRE; functional ID)

Ferritin ≥100(ND)/≥200(HD) & TSAT<20%

Step 2. Decide initiation threshold & route

Non-dialysis/PD (start if any):

· Ferritin<100 & TSAT <40%

· Ferritin 100-300 & TSAT <25%

Route: oral or IV (shared decision, IV favored if with a strong IRE feature)

HD, start if

· Ferritin<500 & TSAT<30%

Route: IV (Proactive, high-dose, low-frequency)

Step 3. Monitoring & adjustment

ND/PD: at least every 3 months / HD: more frequently

Hold or re-evaluate if Ferritin ≥ 700 or TSAT ≥ 40%

Future research & evolving questions in this field

- **Non-anemic iron deficiency**

- Role of iron therapy in CKD patients with normal Hb?
- Needs for RCTs analogues to HF studies (FAIR-HF-style for CKD)

- **Combination approaches**

- Interaction of IV iron with HIF-PHI and ESA: optimal sequencing? dose synergy? safety?

- **Biomarker refinement**

- validation of Ret-Hb, CHr, %Hypo RBCs as reliable monitoring tool
- non-invasive indicators for early functional ID

- **Patient-centered outcomes**

- QoL, fatigue, cognitive and physical function – endpoints beyond Hb response

Take-Home Messages: iron therapy in CKD

- **Iron deficiency is common and clinically important in CKD**
  - even in patients without anemia or with only mild anemia (probable to possible)

- **IV iron therapy, esp. when used proactively, improves Hb, reduces ESA use, and lowers CV events**
  - supported by evidences from PIVOTAL and FIND-CKD

- **KDIGO 2025 introduces a clearer 3-step (diagnose → initiate → withhold) with updated thresholds**
  - more evidence-based and easier to apply in clinical practice

- **Ferritin ≥700 µg/L or TSAT ≥40% marks the point for hold therapy and re-evaluate**
  - a relatively liberal threshold that still ensures safety

- **Future focus: earlier correction of ID in non-anemic CKD, individualized treatment strategies, and patient-centered outcomes beyond Hb response**