The Evolving Roles of Iron Treatment, ESAs, and HIF-PHIs Towards Successful Anemia Treatment

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Disclosures

- CareDX grant

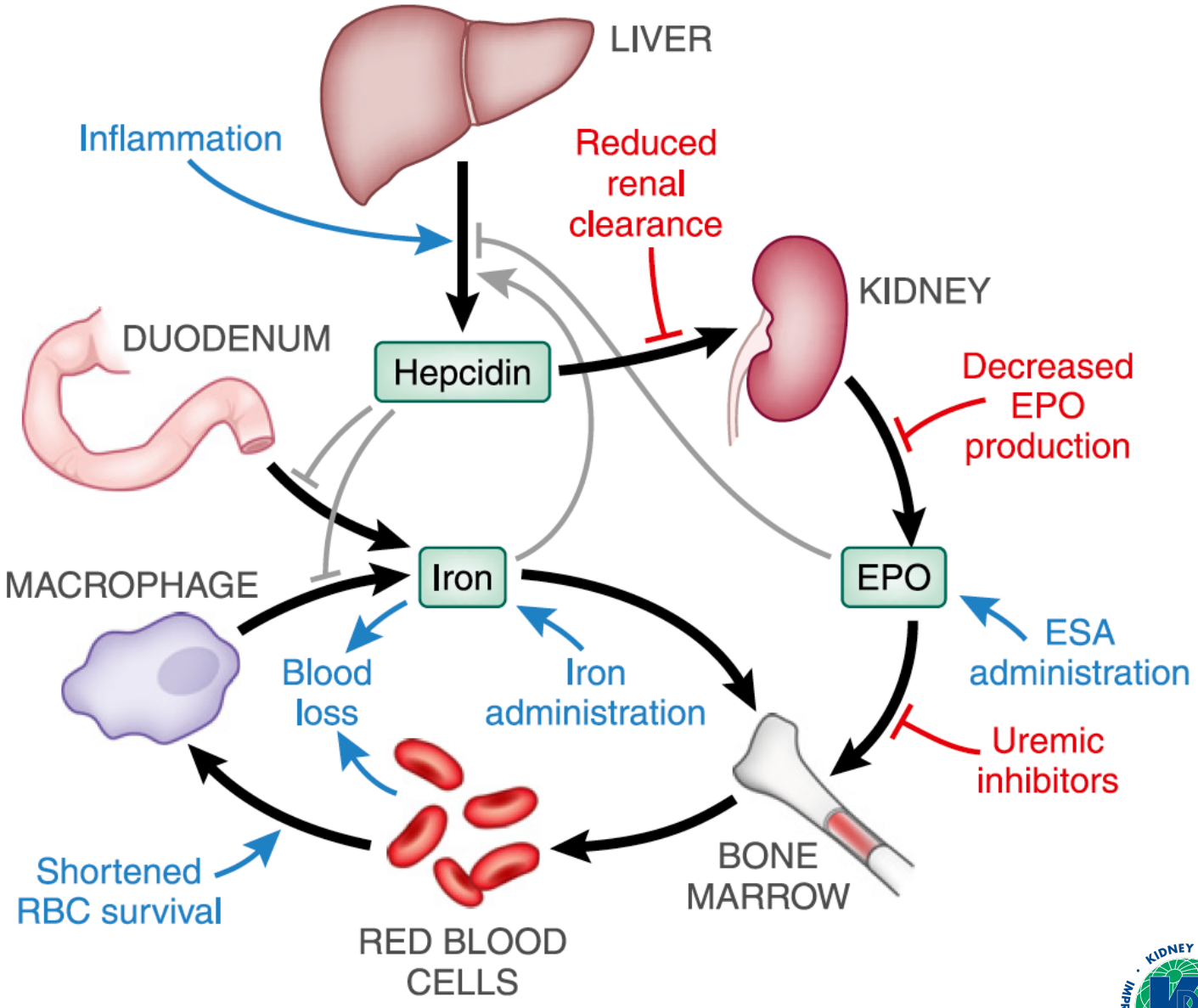
Prevalence of anemia in CKD

20-65% of patients with kidney disease have anemia

Associated with increased risk of:

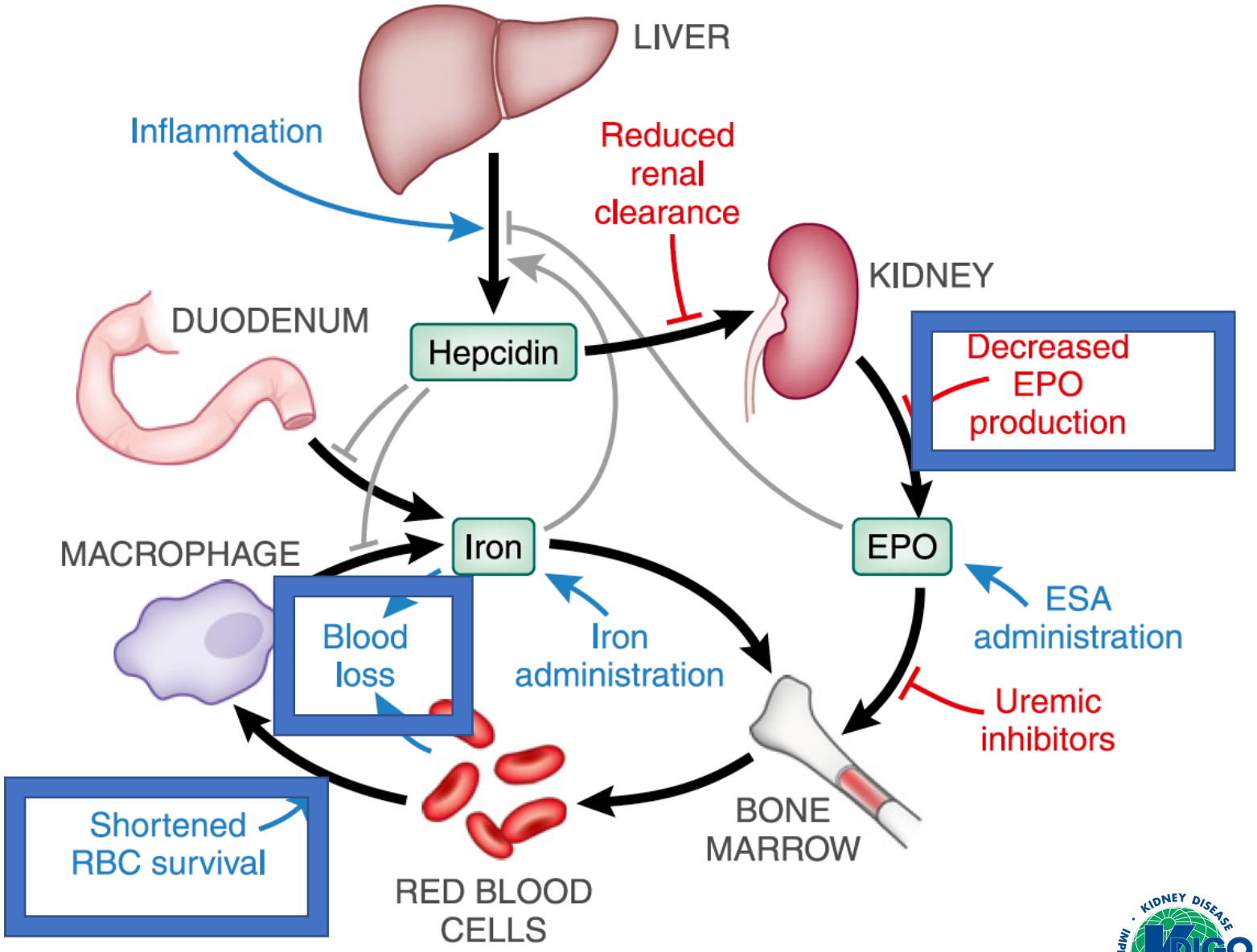
- hospitalizations
- cardiovascular disease
- mortality

Anemia in CKD



Babitt J, JASN 2012

Anemia in CKD



Babitt J, JASN 2012

Iron deficiency in CKD

Absolute iron deficiency

- Deficit of total body iron
- Blood loss, impaired dietary absorption, use of ESAs which depletes iron stores, phlebotomy

Functional iron deficiency

- Low transferrin saturation but normal to high ferritin
- Deficiency of circulating iron that limits erythropoiesis

Options for anemia management in CKD

IV or oral iron	HIF stabilizers (proyl hydroxylase inhibitors)	Erythropoietin stimulating agents (ESAs)
Transfusions	? SGLT II inhibitors	? Other newer agents

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KDIGO 2012 guidelines on iron in anemia

TREATMENT WITH IRON AGENTS

2.1.1: When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). *(Not Graded)*

2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):

- an increase in Hb concentration without starting ESA treatment is desired* and
- TSAT is $\leq$30% and ferritin is $\leq$500 ng/ml ($\leq$500 µg/l)

2.1.3: For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):

- an increase in Hb concentration** or a decrease in ESA dose is desired*** and
- TSAT is $\leq$30% and ferritin is $\leq$500 ng/ml ($\leq$500 µg/l)

KDIGO 2012

Table 2 | Evidence for clinical benefits of iron administration

	Patients with CKD not on dialysis	Patients on dialysis
Reduction of congestive heart failure	Limited[60,61]	Yes[62]
Reduced occurrence of myocardial infarction	Limited[63]	Yes[62]
Improved quality of life	Not studied	Limited[64]
Reduced occurrence of fatigue	Not studied	Limited[64]
Improved cognitive function	Not studied	Limited[64]
ESA dose reduction	Yes[65]	Yes[65]
Reduced blood transfusions	Not studied	Yes[62]

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

Babbitt J et al, 2022 KI

ORIGINAL ARTICLE

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

Iain C. Macdougall, M.D., Claire White, B.Sc., Stefan D. Anker, M.D., Sunil Bhandari, Ph.D., F.R.C.P., Kenneth Farrington, M.D., Philip A. Kalra, M.D., John J.V. McMurray, M.D., Heather Murray, M.Sc., Charles R.V. Tomson, D.M., David C. Wheeler, M.D., Christopher G. Winearls, D.Phil., F.R.C.P., and Ian Ford, Ph.D., for the PIVOTAL Investigators and Committees*

- Multi-center open-label trial
- Adults on HD were assigned to receive high-dose iron proactively or low-dose iron reactively.

Macdougall I, *NEJM* 2019

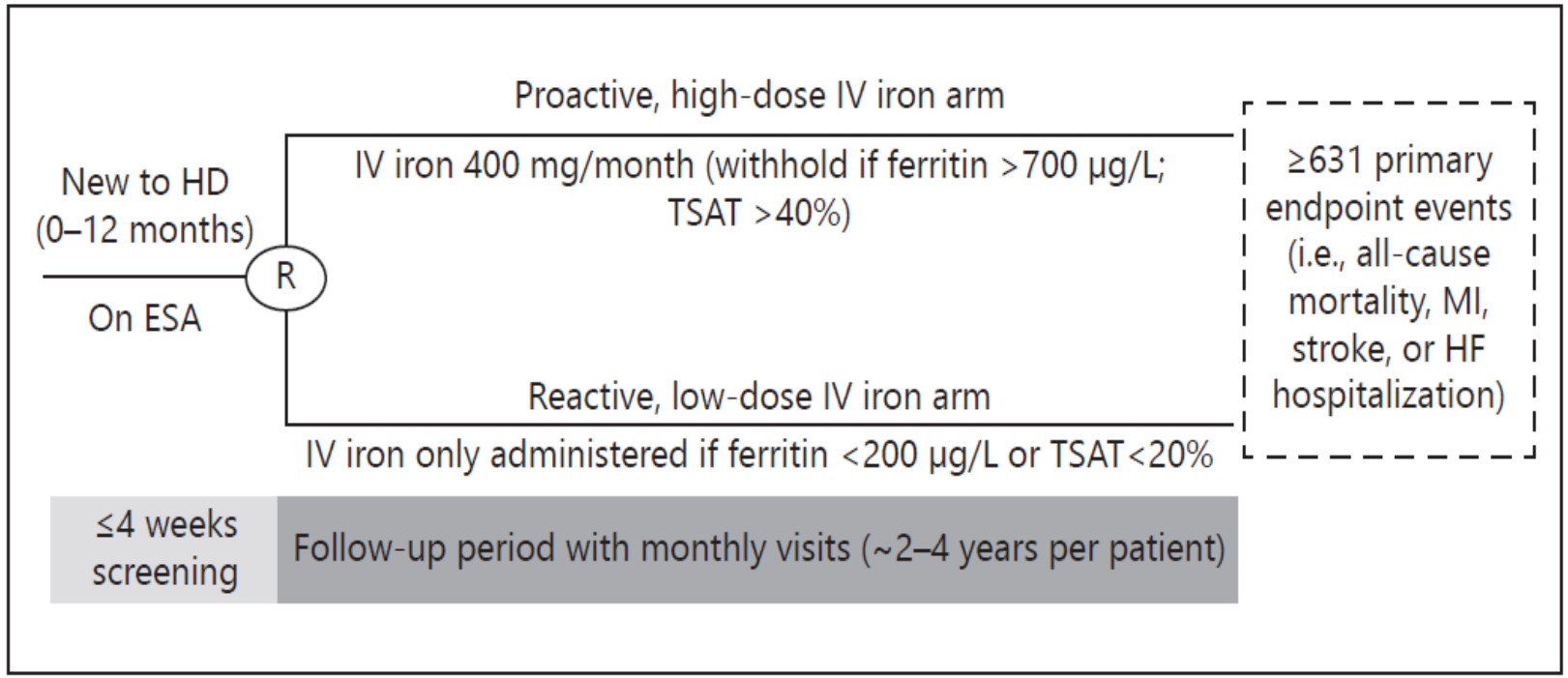


Fig. 1. PIVOTAL trial design. ESA, erythropoiesis-stimulating agents; HD, hemodialysis; HF, heart failure; IV, intravenous; MI, myocardial infarction; TSAT, transferrin saturation.

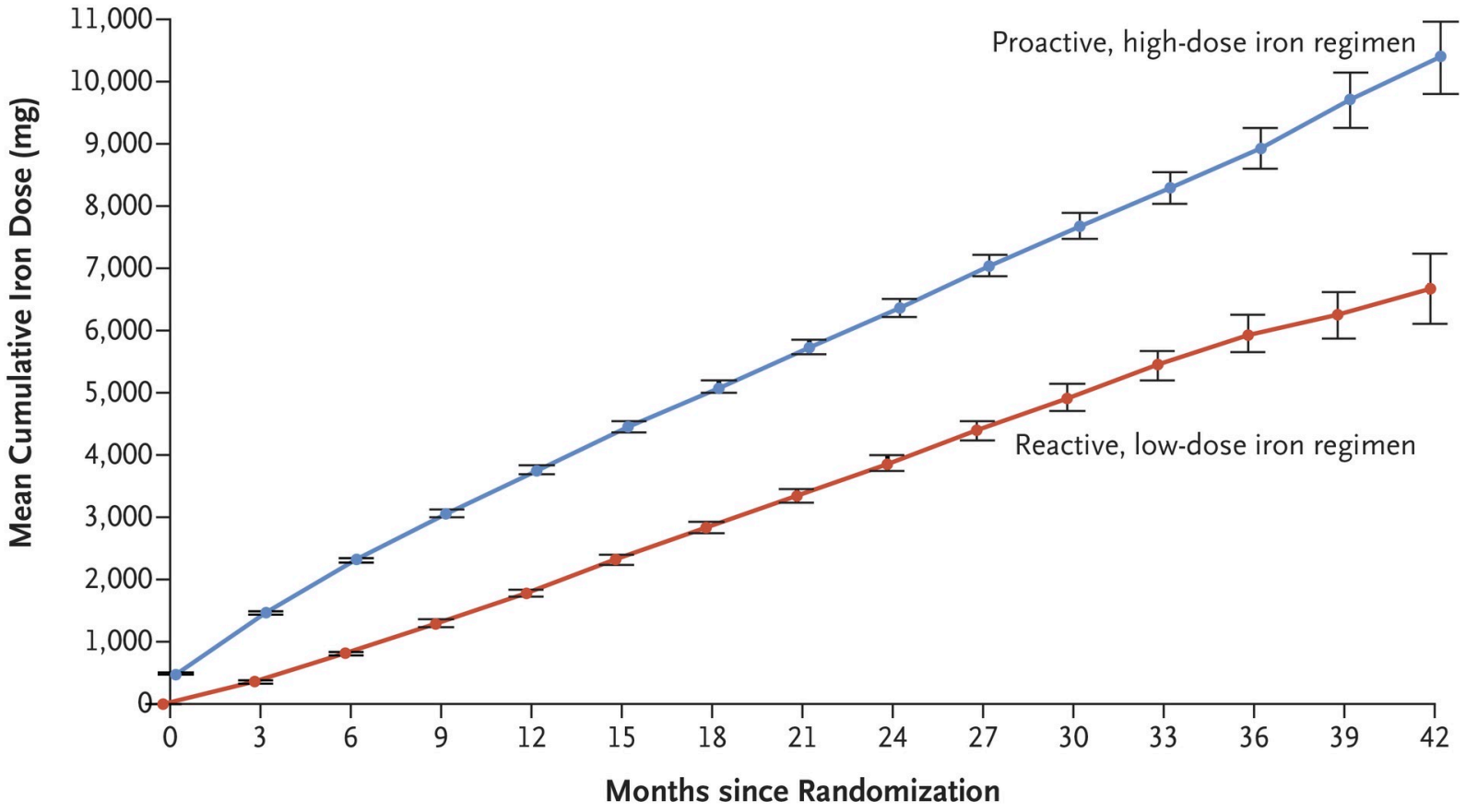
Am J Nephrol 2018;48:260–268
DOI: 10.1159/000493551

PIVOTAL Trial

Macdougall I, *NEJM* 2019

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Proactive, High-Dose Iron Regimen (N = 1093)	Reactive, Low-Dose Iron Regimen (N = 1048)
Age — yr	62.7±14.9	62.9±15.1
Male sex — no. (%)	710 (65.0)	688 (65.6)
Race — no. (%)†		
White	868 (79.4)	830 (79.2)
Black	93 (8.5)	97 (9.3)
Asian	96 (8.8)	89 (8.5)
Other	36 (3.3)	32 (3.1)
Median duration of dialysis treatment (IQR) — mo	4.9 (2.8–8.4)	4.8 (2.8–8.1)
Vascular access — no. (%)		
Dialysis catheter	449 (41.1)	428 (40.8)
Arteriovenous fistula or graft	644 (58.9)	620 (59.2)
Cardiovascular disease — no. (%)		
Atrial fibrillation	96 (8.8)	68 (6.5)
Heart failure	41 (3.8)	45 (4.3)
Hypertension	804 (73.6)	753 (71.9)
Hyperlipidemia	277 (25.3)	258 (24.6)
Peripheral vascular disease	92 (8.4)	95 (9.1)
Previous myocardial infarction	97 (8.9)	87 (8.3)
Previous stroke	85 (7.8)	91 (8.7)
Diabetes — no. (%)	494 (45.2)	456 (43.5)

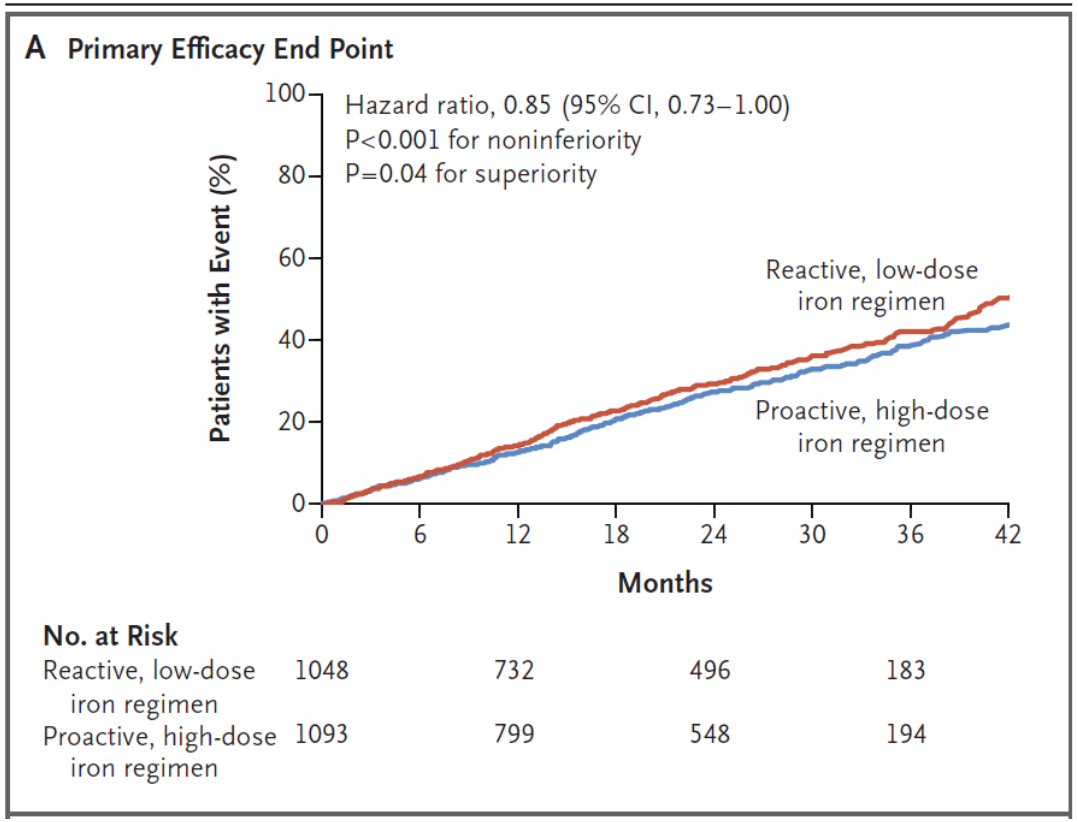


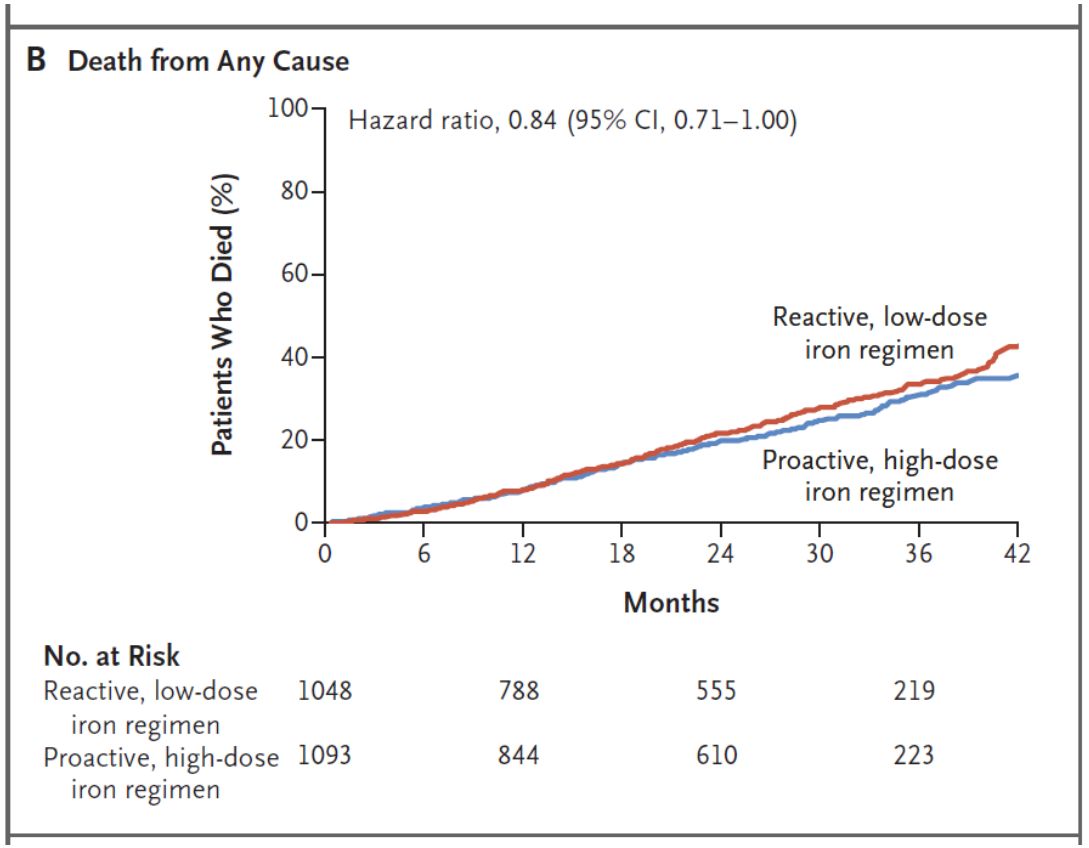
No. of Patients															
Proactive, high-dose iron regimen	1093	1013	953	894	833	776	724	670	594	487	384	293	211	137	97
Reactive, low-dose iron regimen	1048	979	909	842	775	771	656	608	531	440	369	282	213	136	83

Macdougall IC et al. N Engl J Med 2019;380:447-458

Macdougall I, *NEJM* 2019

PIVOTAL Trial





Macdougall I, *NEJM* 2019

Is iron a risk factor for infection?

Iron during infection

2.4: Avoid administering IV iron to patients with active systemic infections. (*Not Graded*)

KDIGO 2012

Risk of infection with iron administration in CKD

Non-transferrin bound iron may increase the risk for bacterial infections

Infection rates similar in PIVOTAL though retrospective observational studies have suggested that more intensive IV iron administration (at doses greater than those in PIVOTAL) increase risk of mortality

Table 3. Serious Adverse Events.*

Event	Proactive, High-Dose Iron Regimen (N = 1093)	Reactive, Low-Dose Iron Regimen (N = 1048)
	no. of patients with event (%)	
Any serious adverse event	709 (64.9)	671 (64.0)
Infection or infestation	341 (31.2)	327 (31.2)

Macdougall I, *NEJM* 2019

Treatment with oral iron

Drawbacks of oral iron

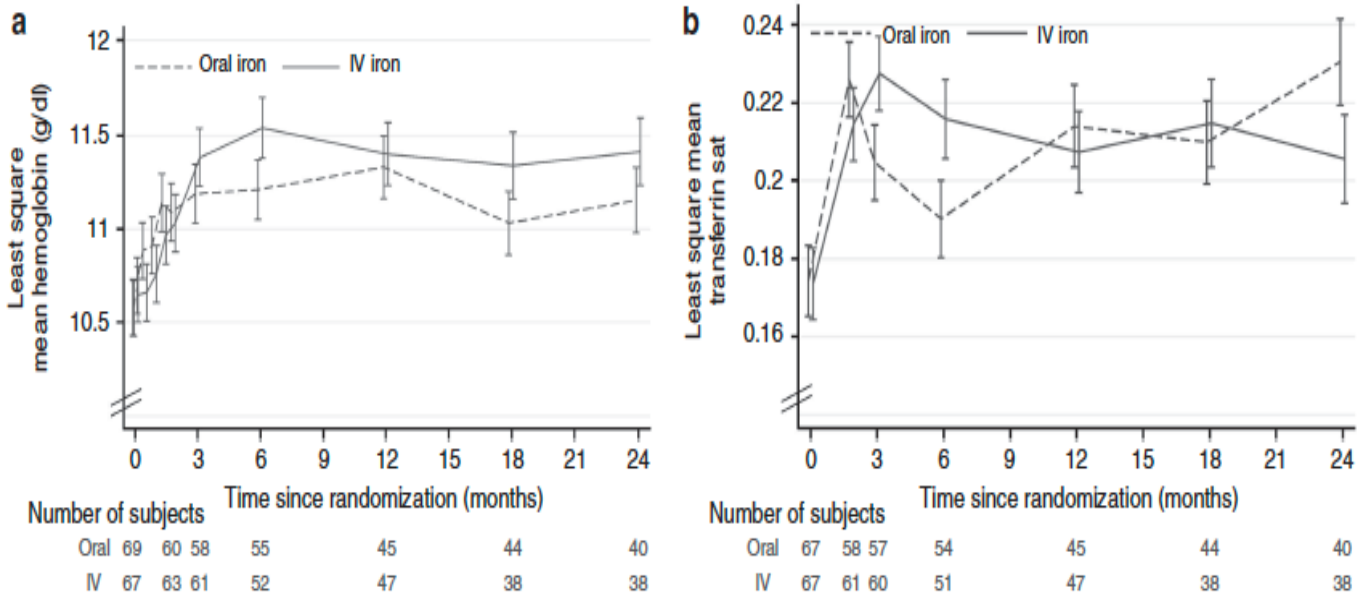
- GI intolerance
- Poor absorption due to elevated hepcidin

Advantages of oral iron

- Non-invasive
- Less hypersensitivity than IV formulation

REVOKE Trial

- Randomized assignment to oral versus IV iron in ND-CKD for outcome of change in kidney function
- Trial terminated early due to 2-fold increase in infections in the IV group



Agarwal R, KI, 2015

Iron formulations

Table 1. List of Oral Iron Agents Used for Treating Anemia in Patients With CKD

Agent	Elemental Iron per Tablet	Total Salt Content per Tablet	Recommended Dosage
Ferric citrate or FC (Auryxia)	210 mg	1 g	3 tablets a day (630 mg elemental iron) with meals for IDA in CKD
Ferric citrate hydrate or FCH (Riona)	45 mg	250 mg	500 mg × 3 times a day for hyperphosphatemia in CKD
Ferric citrate (Nephoxil)	105 mg	500 mg	N/A
Ferric maltol (Feraccru)	30 mg	30 mg	30 mg twice daily
Ferrous sulfate (generic)	65 mg	325 mg	1000 mg/d (200 mg/d elemental iron) for IDA in CKD
Ferrous fumarate (Ferro-Sequels; Slow FE, Apo-Ferrous Gluconate)	106 mg	325 mg	600 mg/d (200 mg/d elemental iron) for IDA in CKD
Ferrous gluconate (Fergon)	37.5 mg	325 mg	1600 mg/d (200 mg/d elemental iron) for IDA in CKD
Liposomal iron (Ferrolip)	30 mg	30 mg	30 mg/d (for IDA)
Heme iron polypeptide (Proferrin)	12 mg	12 mg	3 or 4 tablets/d (for IDA in CKD)

Abbreviations: CKD, chronic kidney disease; IDA, iron deficiency anemia; N/A, not available.

IV versus oral iron and treatment target?

- FIND-CKD trial
- 56-week, open-label, multicentre prospective trial of 626 patients with non-dialysis-dependent CKD not on ESAs
- Patients randomized (1:1:2) to intravenous (IV) ferric carboxymaltose (FCM), targeting a higher (400–600 µg/L) or lower (100–200 µg/L) ferritin or oral iron therapy.
- Primary end point was time to initiation of other anemia management (ESA, other iron therapy or blood transfusion) or Hb <10 g/dL during Weeks 8–52.

Macdougall I, NDT, 2014

FIND-CKD Trial

Table 3. Adverse events and serious adverse events (safety population)

Event	High-ferritin FCM ($n = 154$)	Low-ferritin FCM ($n = 150$)	FCM total ($n = 304$)	Oral iron ($n = 312$)
Any adverse event, *n* (%)	126 (81.8)	129 (86.0)	255 (83.9)	255 (81.7)
Gastrointestinal disorders	32 (20.8)	38 (25.3)	70 (23.0)	128 (41.0)
Diarrhoea	15 (9.7)	11 (7.3)	26 (8.6)	45 (14.4)
Constipation	2 (1.3)	5 (3.3)	7 (2.3)	37 (11.9)
Nausea	9 (5.8)	7 (4.7)	16 (5.3)	15 (4.8)
Dyspepsia	2 (1.3)	3 (2.0)	5 (1.6)	17 (5.4)
Infections	51 (33.1)	51 (34.0)	102 (33.6)	95 (30.4)
Urinary tract infection	18 (11.7)	10 (6.7)	28 (9.2)	17 (5.4)
Nasopharyngitis	13 (8.4)	10 (6.7)	23 (7.6)	16 (5.1)
Influenza	4 (2.6)	8 (5.3)	12 (3.9)	7 (2.2)

Macdougall I, NDT, 2014

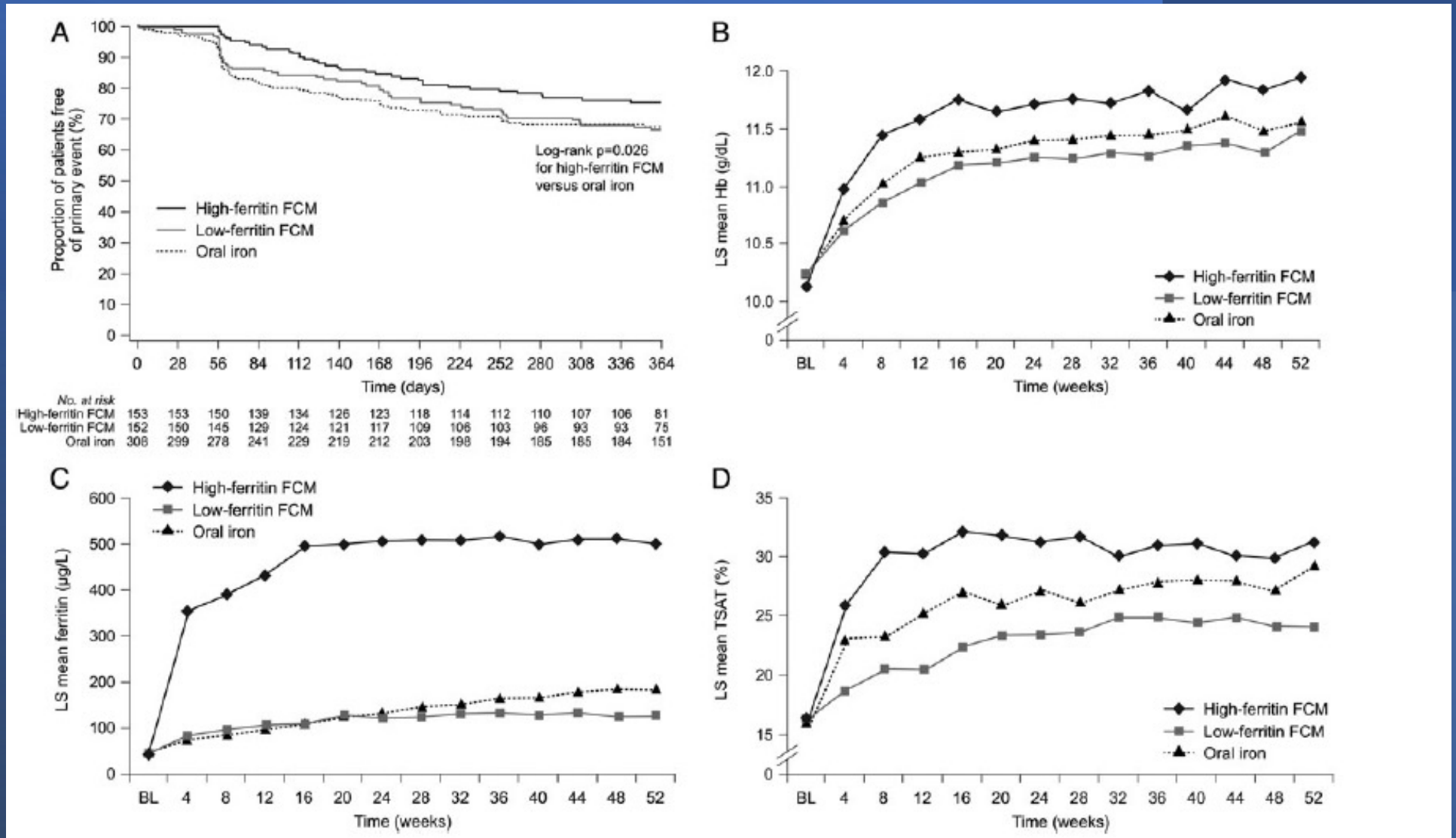


FIGURE 2: (A) Time to initiation of other anaemia management or Hb trigger (Kaplan–Meier estimates) and LS mean locally measured observed values over time for (B) Hb (C) ferritin and (D) TSAT according to treatment group (ITT population). Measurements of Hb, ferritin and TSAT were included up to the point at which other anaemia therapy was initiated (with or without cessation of randomized study drug) and/or the patient discontinued the study. BL, baseline; FCM, ferric carboxymaltose.

Macdougall I, NDT, 2014

Summary of the evolving data on iron treatment

- In ND-CKD, targeting ferritin 400-600 led to delays or reduction in the need for other treatment using IV ferric carboxymaltose compared with oral iron without notable adverse reactions (which differs from prior studies)
- A high-dose intravenous iron regimen administered proactively may be superior to a low-dose regimen administered reactively and resulted in lower doses of erythropoiesis-stimulating agent being administered

Continued gaps in iron's role in anemia

What are the optimal parameters to target and when to withhold iron therapy

Head-to-head comparisons of different IV formualtions

What are the hard outcomes in association with iron use?

Options for anemia management in CKD

IV or oral iron

HIF stabilizers (proyl hydroxylase inhibitors)

Erythropoietin stimulating agents (ESAs)

Transfusions

? SGLT II inhibitors

? Other newer agents

HIF-PHIs

Gained approval in Europe

Gained approval in Asia

Has not received approval in the US

HIF-PHIs

- HIF-PHIs stimulates erythropoietin production in the liver and kidneys.
- In the presence of oxygen, prolyl hydroxylase enzymes hydroxylate HIF, thereby targeting it for subsequent proteasomal degradation which can be inhibited by oral HIF-PHIs
- Pre-clinical studies have also shown that HIF activation is associated with a reduction in hepcidin concentration, enhanced intestinal iron absorption, and increased iron availability for erythropoiesis.
- Effects beyond erythropoiesis and iron metabolism including
  - cellular differentiation and growth
  - vascular homeostasis and hemodynamics
  - inflammation and cellular metabolism

Overview of Efficacy of HIF-PHIs

- Efficacy similar to ESAs
- Reduce need for transfusions and rescue therapy during the trials

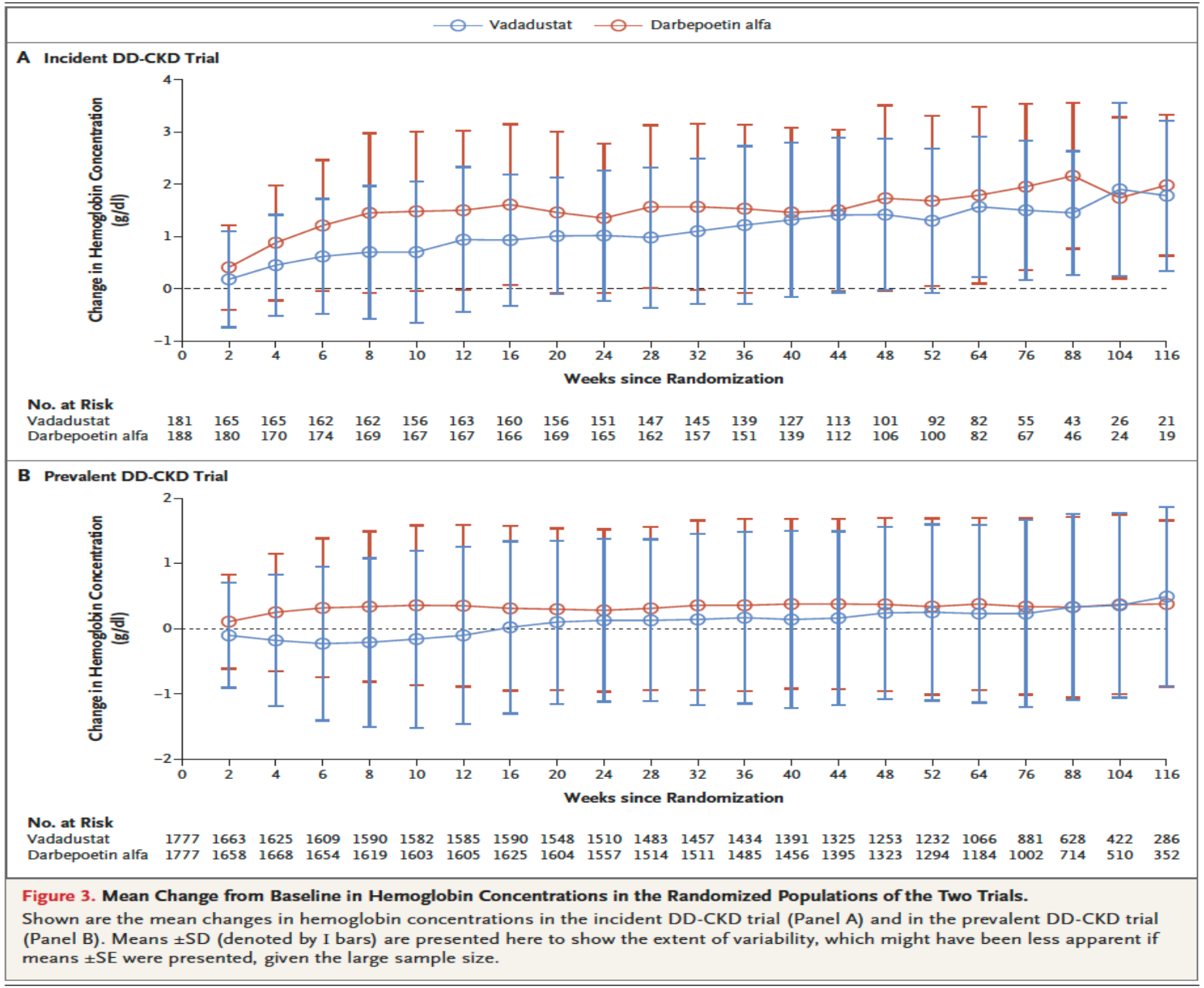
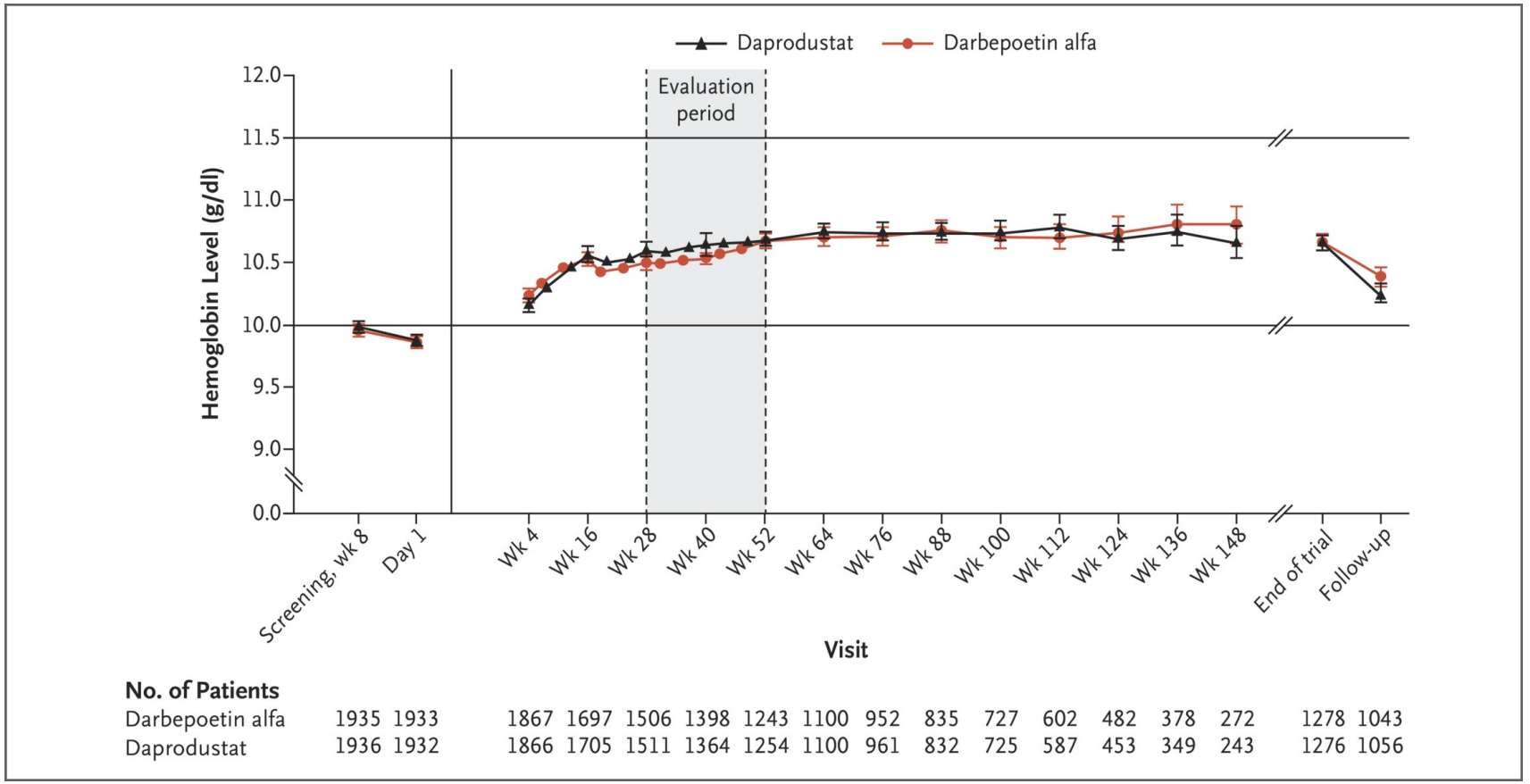


Figure 3. Mean Change from Baseline in Hemoglobin Concentrations in the Randomized Populations of the Two Trials.
Shown are the mean changes in hemoglobin concentrations in the incident DD-CKD trial (Panel A) and in the prevalent DD-CKD trial (Panel B). Means ±SD (denoted by I bars) are presented here to show the extent of variability, which might have been less apparent if means ±SE were presented, given the large sample size.

Eckardt K, NEJM 2021

Hemoglobin Level, According to Visit (Intention-to-Treat Population)



The NEW ENGLAND JOURNAL of MEDICINE

HIF-PHIs efficacy

- Efficacy similar in both peritoneal and hemodialysis

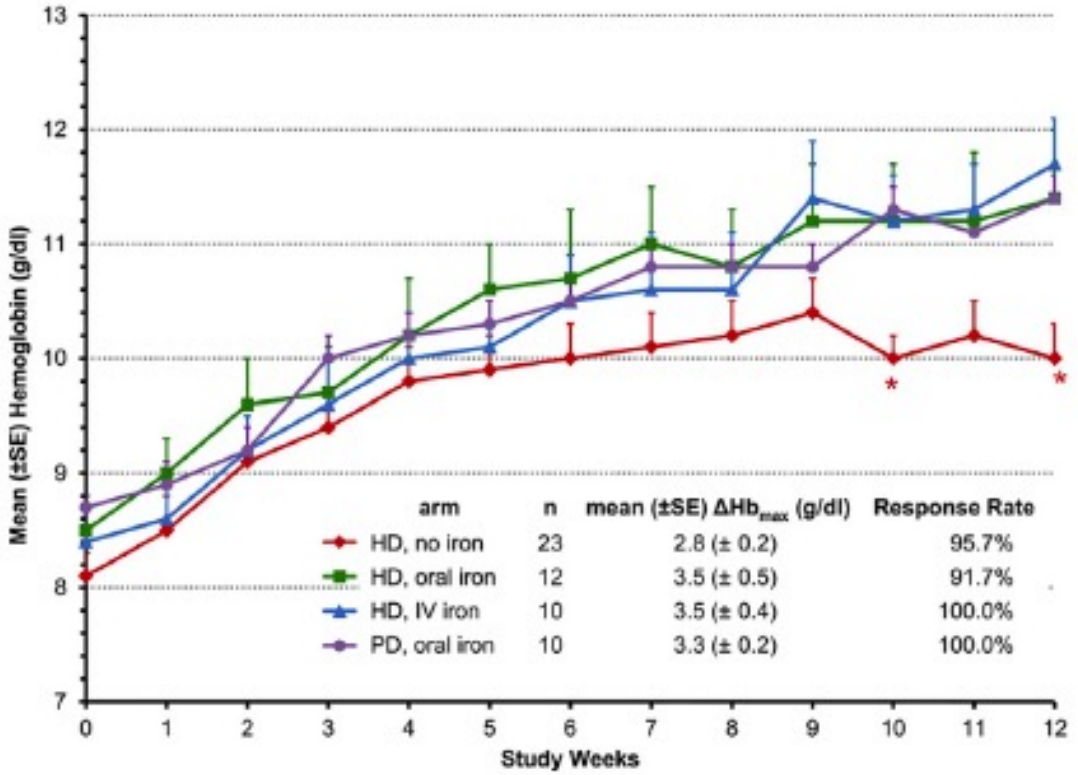


Figure 6 | Mean change in hemoglobin with the HIF stabilizer, roxadustat, in dialysis patients. Patients on hemodialysis and/or peritoneal dialysis were given oral roxadustat, with oral iron, i.v. iron, or no iron supplementation. The change in mean hemoglobin ± SE is shown by study week. *$P < 0.05$ in comparisons between the no-iron cohort to the pooled-iron cohorts. Hb, hemoglobin; HD, hemodialysis; PD, peritoneal dialysis. Reprinted with permission from Besarab A, Chernyavskaya E, Motylev I, et al. Roxadustat (FG-4592): correction of anemia in incident dialysis patients. *J Am Soc Nephrol.* 2016;27:1225–1233. Copyright © American Society of Nephrology.

Coyne D, KI Supp, 2017

Difference between the HIF-PHIs

- Roxadustat appears to have the fastest response
- No head-to-head trials of HIF-PHIs

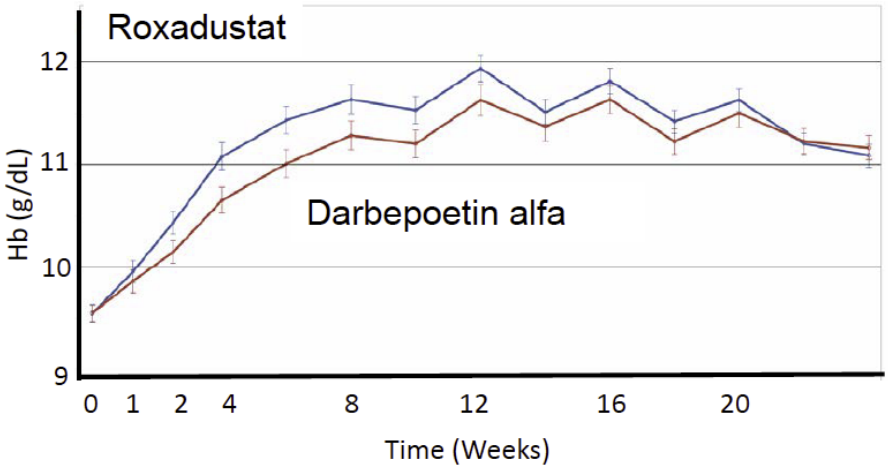
Efficacy Endpoint: Study 610 (Hemoglobin Response Rate)

Primary endpoint: % hemoglobin responders during the first 24 weeks of treatment.

- Note that hemoglobin increases more rapidly in the roxadustat group before 4 weeks

	Roxadustat N=286	Darbepoetin alfa N=272
Number (%) responders	256 (89.5%)	213 (78.0%)
95% Confidence Interval (CI)	(85.4%, 92.8%)	(72.6%, 82.8%)
Difference of proportions (roxadustat – darbepoetin)	11.5%	
95% CI of difference	(5.7%, 17.4%)	

www.fda.gov



Targets for hemoglobin correction

3.4.1: For adult CKD ND patients with Hb concentration $\geq$10.0 g/dl ($\geq$100 g/l), we suggest that ESA therapy not be initiated. (*2D*)

3.4.2: For adult CKD ND patients with Hb concentration $<$10.0 g/dl ($<$100 g/l) we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia. (*2C*)

3.4.3: For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when the hemoglobin is between 9.0–10.0 g/dl (90–100 g/l). (*2B*)

3.4.4: Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl (100 g/l). (*Not Graded*)

KDIGO 2012

Targets for hemoglobin correction

ESA MAINTENANCE THERAPY

3.5.1: In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD. (*2C*)

3.5.2: Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl (115 g/l) and will be prepared to accept the risks. (*Not Graded*)

3.6: In all adult patients, we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l). (*1A*)

KDIGO 2012

Does use of HIF-PHIs decrease the need for iron?

- Protocols differed across trials and very difficult to interpret
- Often left up to investigator discretion in terms of whether to give iron

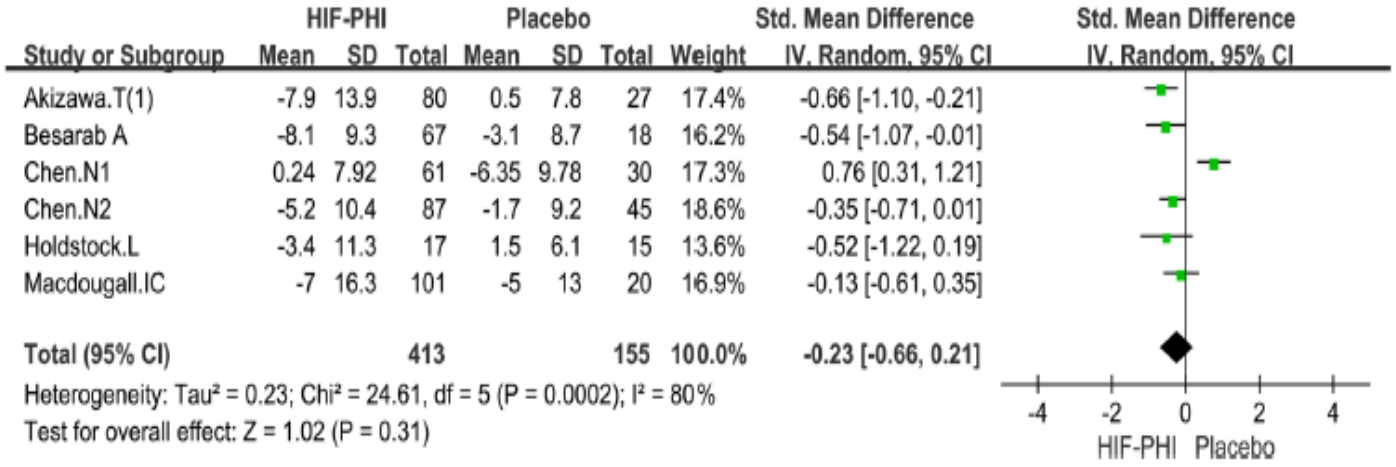


Fig. 6 Forest plots for comparisons of ΔTSAT. *HIF-PHI* hypoxia-inducible factor prolyl hydroxylase inhibitor, *ΔFerritin* change in ferritin level from baseline

Zhang S, Int J of Urology and Nephrology, 2021

Asia Pacific Society of Nephrology Recommendations on HIF-PHI use

- Consider using as alternatives to ESA
- Iron status should be evaluated before HIF-PHI are used and correction of iron occur (ferritin > 100 ng/mL and TSAT > 20%)

Possible scenarios when to use HIFs

Those who wish to avoid injections (CKD-ND)

Target Hb cannot be achieved with recommended dose of ESA (hyporesponsiveness) – can consider conversion to HIF

Cost-benefit –likely to vary by region/nation and bundling versus not

Cautions with HIF-PHIs

- Screen for tumor and retinal lesions before use of HIF
- Follow size of renal cysts
- Caution in those with history of pre-existing ischemic heart disease, cerebrovascular disease, or peripheral vascular disease
- Monitor liver function after starting
- Early referral to ophthalmology if vision changes
- Post-marketing surveillance will be very important