The Approach to the Management of Anemia in CKD

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Learning Objectives

- Identify iron deficiency anemia in patients with CKD
- Discuss key guideline recommendations for early intervention in iron deficiency in patients with CKD based on individualized patient circumstances
- Examine the data on use of ESA in patients with CKD
- Evaluate new opportunities for treatment of anemia in patients with CKD

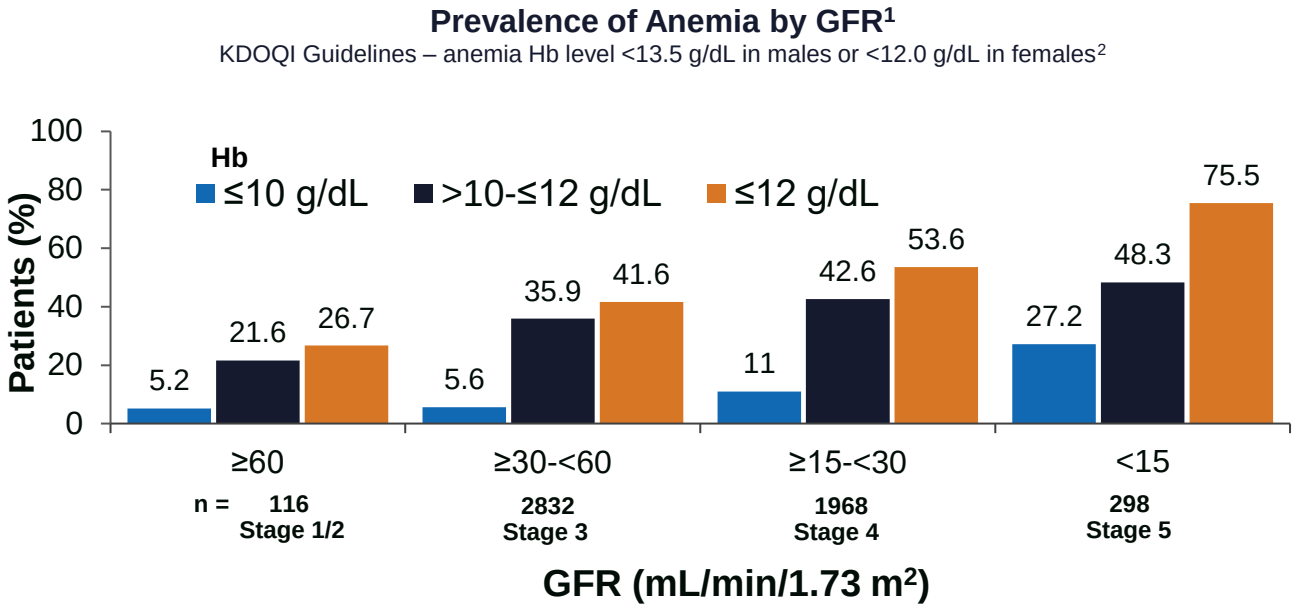
Chronic Kidney Disease is Common Among US Adults[1]

Fast Stats

- 15% of US adults—37 million people—are estimated to have CKD.*
- Most (9 in 10) adults with CKD do not know they have it.
- 1 in 2 people with very low kidney function who are not on dialysis do not know they have CKD.

1. https://www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html

Prevalence of Anemia by GFR



- Patients with CKD are more likely to die than to progress to renal replacement therapy with the highest risk in patients with multiple comorbidities, including anemia.[3,4]

If Not Effectively Managed, Anemia in CKD Can Contribute to the Risk of:[1-3]

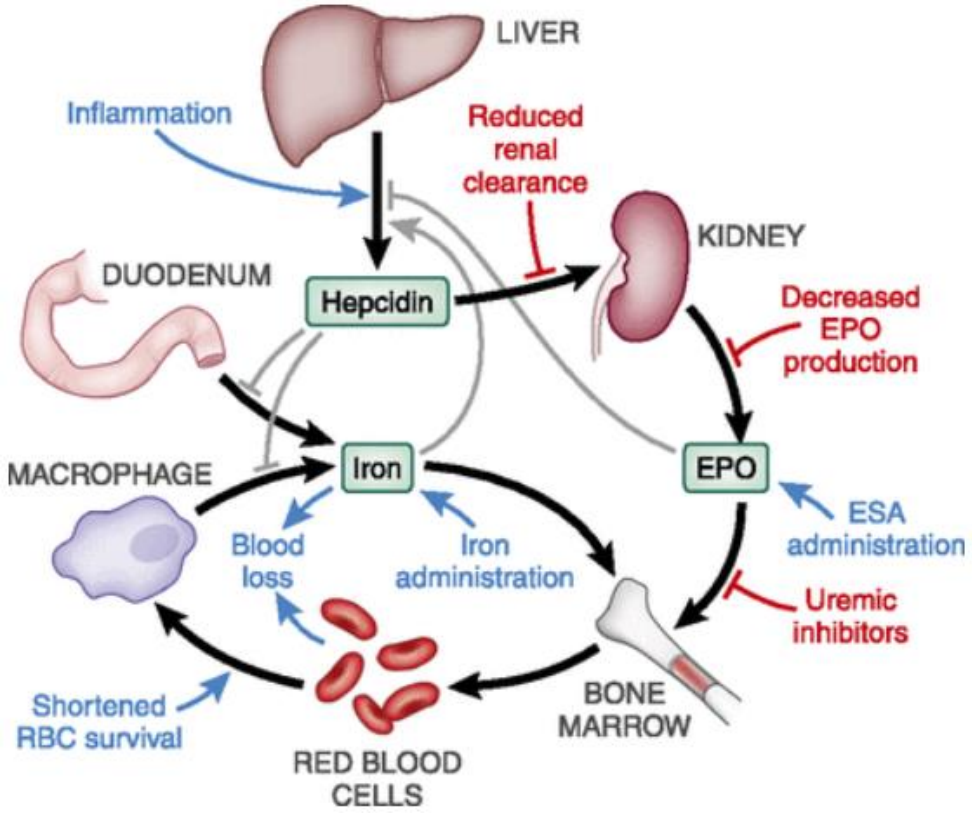
1. Thorp ML et al. *Nephrology (Carlton)*. 2009 Apr;14(2):240-6. 2. http://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_anemia/index.htm.
3. Abramson JL et al. *Kidney In*t. 2003 Aug;64(2):610-5.

Patients' Experience of Anemia in CKD: Results from a Recent Survey of 500 Patients in the US[1]

- Respondents attributed serious physical side effects to their anemia in CKD, including lack of energy (84%) and feeling ill (31%).
- People with anemia in CKD experience a strong negative emotional impact, notably sadness (41%) and nervousness about living with their condition (24%), and concern about their condition worsening (48%).
- Many respondents struggled to recall key information about their anemia in CKD; 63% of respondents didn't know or couldn't recall their Hb levels.
- Many patients did not correctly identify the symptoms of anemia. This included paleness (46%), headaches (69%) or difficulty breathing (66% in the US) as common symptoms associated with severe anemia in CKD.
- 53% of respondents felt more confident about the management of their condition after their doctor had spoken to them about treatment options.
- Respondents were most likely to look for information about anemia in CKD either online (52%) or on social media (32%).
  - However, only a minority of patients trusted information found online (21%) and via social media (14%) compared to other information sources.

1. https://www.astrazeneca.com/media-centre/articles/2018/survey-insights-help-deepen-our-understanding-of-patients-experience-of-anaemia-in-chronic-kidney-disease-to-address-this-critical-unmet-need04122018.html#!

Anemia in CKD is a Multifactorial Process[1]



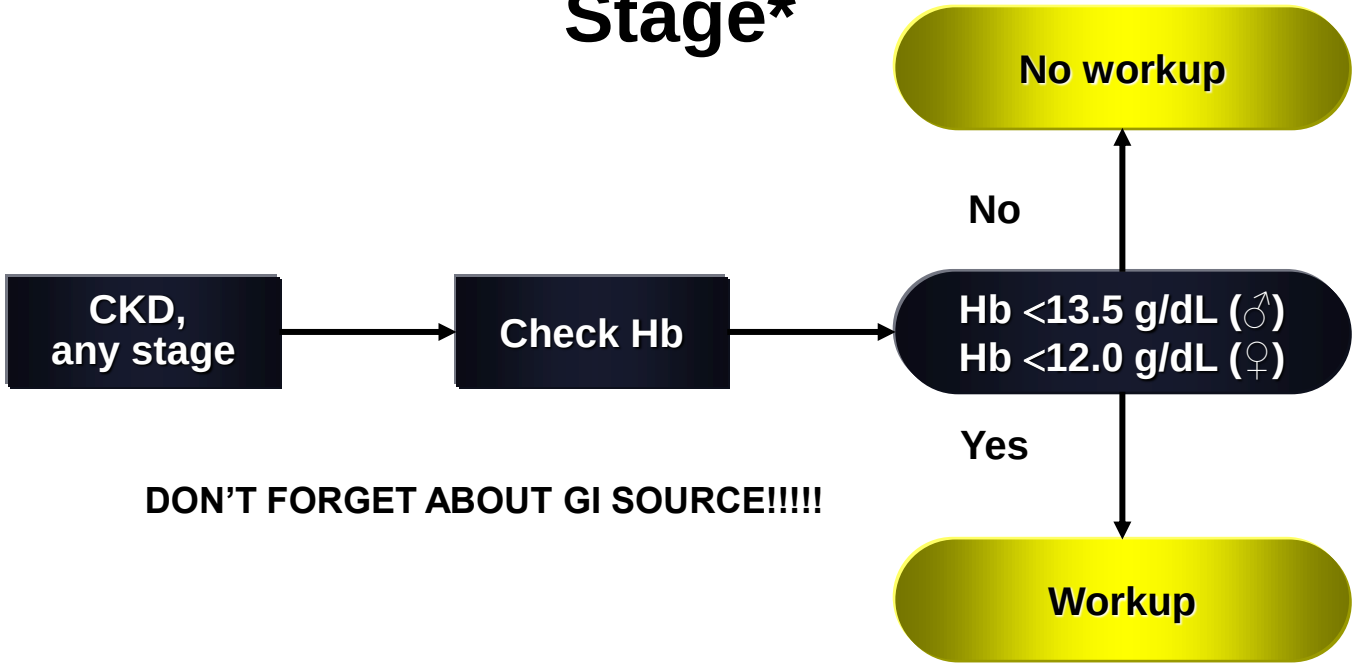
1. Babitt JL, Lin HY. *J Am Soc Nephrol*. 2012;23(10):1631-4.

Factors That Contribute to Anemia in CKD

- Predominant factor: ↓ endogenous EPO production by diseased kidneys
  - Biofeedback mechanism in response to ↓ blood oxygen-carrying capacity is impaired
- Other factors:
  - Shortened lifespan of red blood cells (70-80 days)
  - Chronic blood loss due to bleeding abnormalities
  - Nutritional factors leading to malnutrition and vitamin deficiencies
  - Iron deficiency is especially common

NKF. *Am J Kidney Dis*. 2006;47(suppl 3):S1-S146.

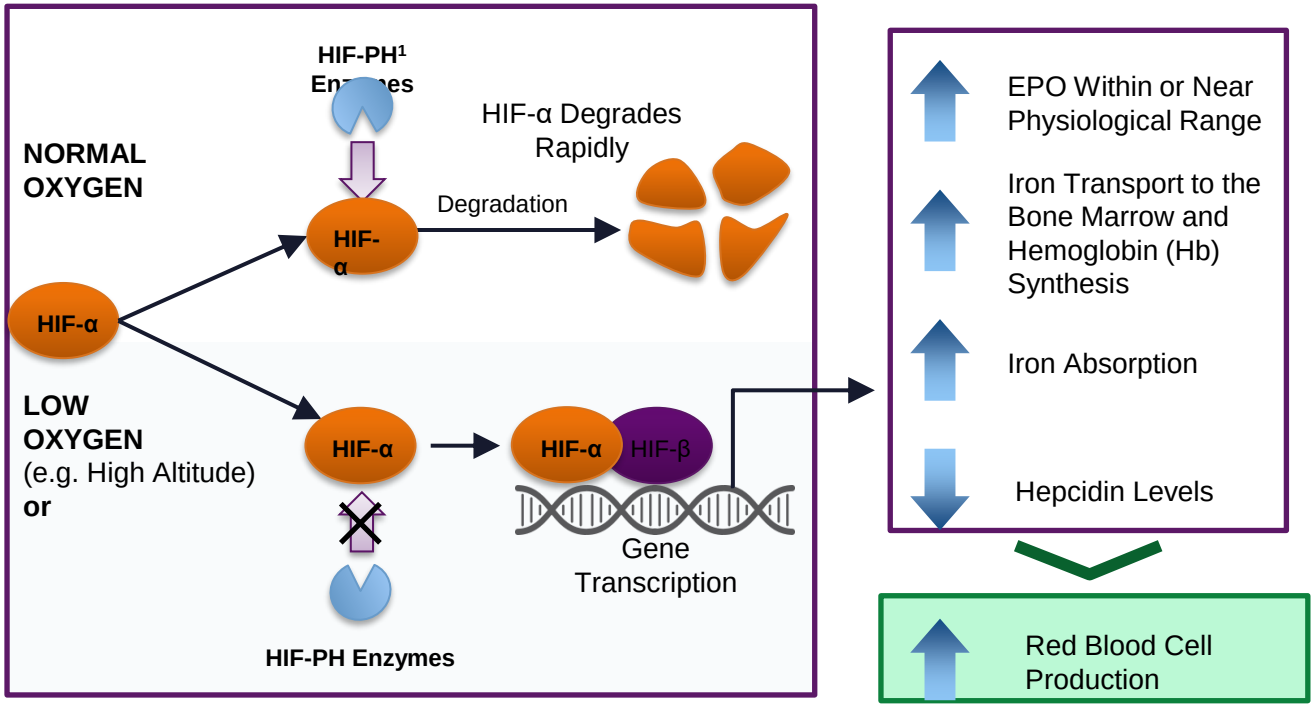
Hb Levels Should Be Evaluated in ALL CKD Patients, Regardless of Stage*



*Note that these are screening recommendations, not treatment recommendations.

Modified from National Kidney Foundation. *Am J Kidney Dis*. 2006;47(suppl 3):S1-S146 (A).

Natural Pathway to Increase Red Blood Cell Production



Iron Deficiency

- Anemia in chronic kidney disease (CKD) is quite common, with iron deficiency being a key culprit.
- Occurs once glomerular filtration rate (GFR) drops to ≤60 mL/min/1.73 m2.
- Prevalence of anemia in CKD increases with worsening kidney function.
- Etiology of anemia in CKD is multifactorial
  - Relative erythropoietin deficiency being common feature
  - Other factors that cause the bone marrow less responsive to erythropoietin play an important role,
    - Most notably iron deficiency and inflammation.

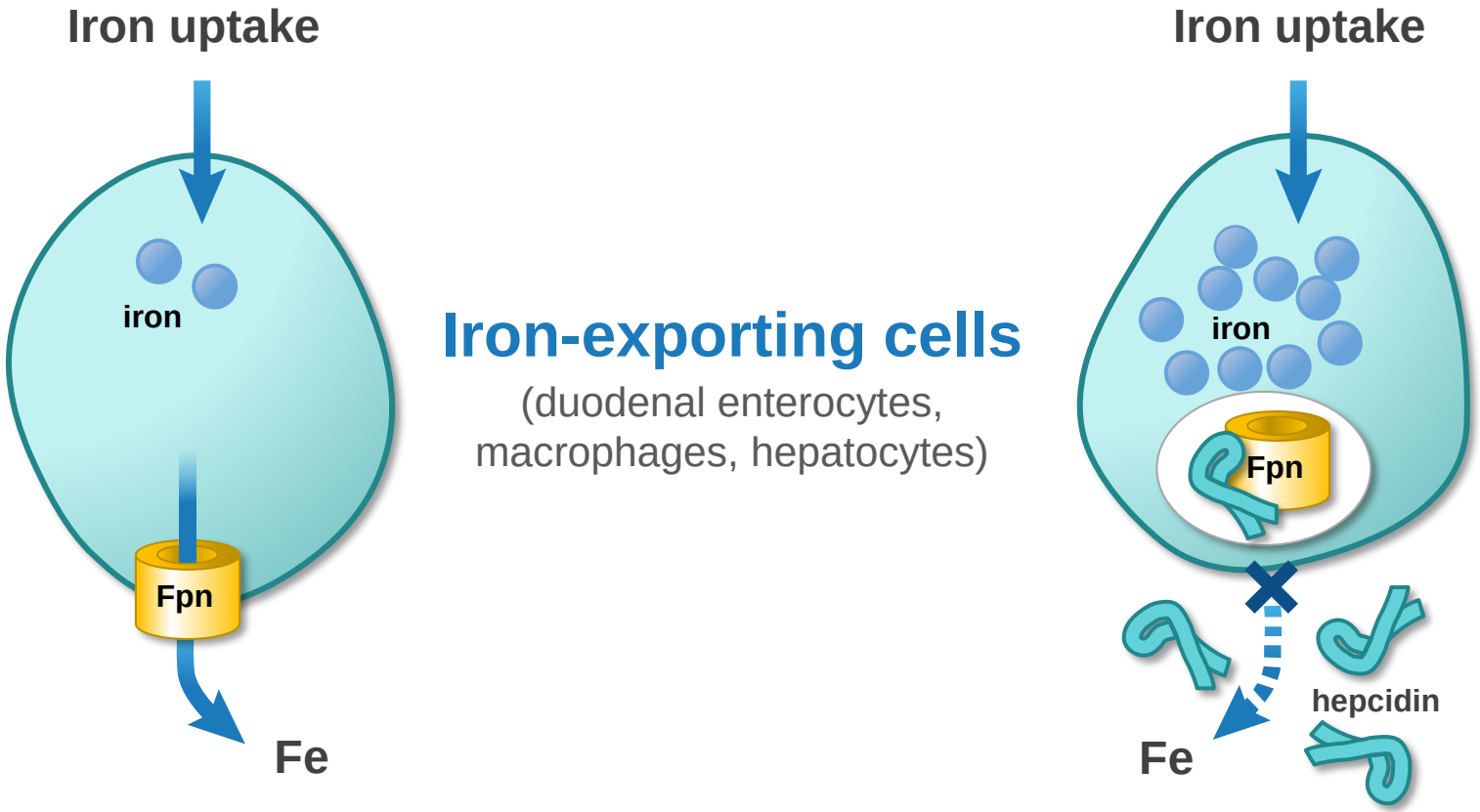
Diagnosis of Iron Deficiency

- Diagnosis of ID anemia in patients with CKD can be complex and impacted by confounding factors and test accuracy:
  - Many patients with CKD may have anemia of chronic disease which is mediated in part by upregulation of hepcidin by inflammatory cytokines. Hepcidin levels are usually increased in this patient population. o
- Diagnostic tests should be able to detect both types of ID.
- Measurement of iron stores in the bone marrow is “gold standard”
  - Rarely performed in patients with CKD due to its invasive nature.
  - saturday

Diagnosis of ID

- Commonly used tests that should be ordered include:
  - Serum iron
  - Total iron-binding capacity (TIBC)
  - Serum ferritin
  - Calculation of the percent transferrin saturation (TSAT)
  - Determination of the percentage of hypochromic red blood cells (RBCs)

Ferroportin and Hepcidin: Key Factors in Iron Regulation[1]

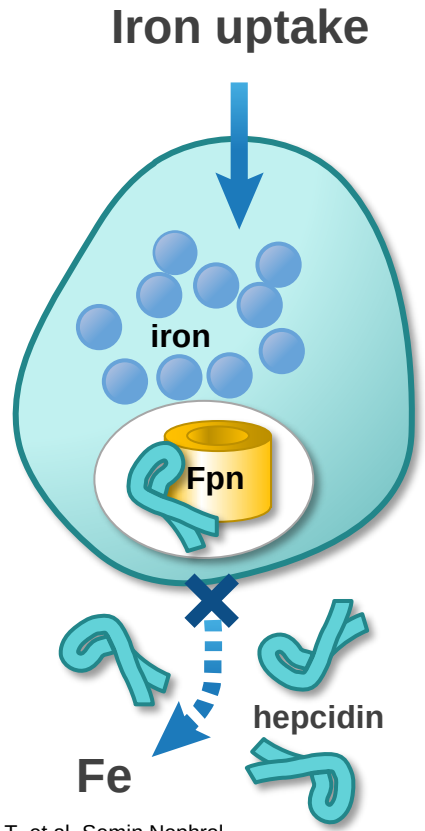


1. Ganz T. J Am Soc Nephrol. 2007;18:394-400.

Adults with CKD Exhibit Significantly Increased Serum Hepcidin Levels[1-4]

Factors Contributing to the Increased Hepcidin Expression Observed in CKD

- Chronic inflammation
- Infections
- IV iron therapy
- Reduced renal clearance of hepcidin



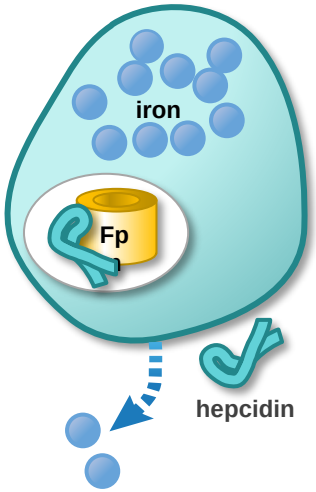
1. Zaritsky J, et al. Clin J Am Soc Nephrol. 2009;4:1051-1056; 2. Zaritsky J, et al. Clin J Am Soc Nephrol. 2010;5:1010-1014; 3. Ganz T, et al. Semin Nephrol. 2016;36:87-93; 4. Zumbrennen-Bullough K, et al:. Nephrol Dial Transplant. 2014;2:263-273.

Means of Overcoming the Hepcidin Blockade Associated With CKD[1,2]

Iron Export From Macrophages

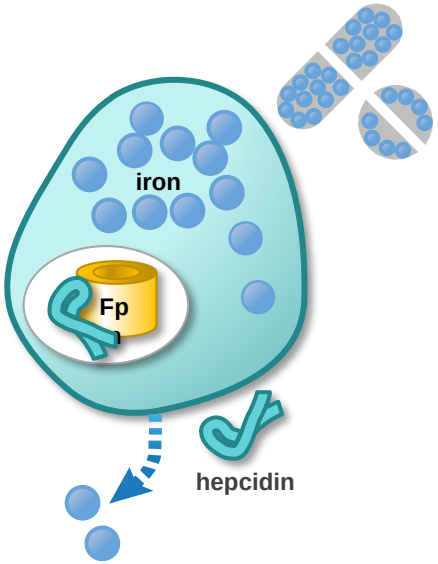
CKD

Increased hepcidin results in reduced ferroportin-mediated iron export (hepcidin block)



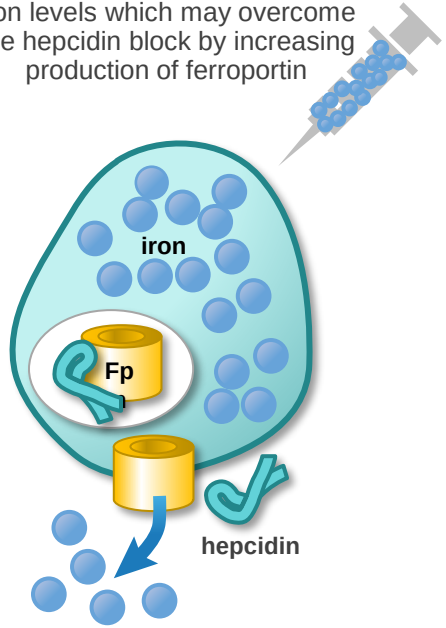
CKD + Oral Iron

Iron absorption from oral iron may be inadequate to overcome the hepcidin block



CKD + IV Iron

IV iron results in high intracellular iron levels which may overcome the hepcidin block by increasing production of ferroportin



1. McDonagh T, et al. Eur J Heart Fail. 2015;17:248-262; 2. Aapro M et al. Ann Oncol. 2012;23:1954-1962

The Consequences of High Levels of Intracellular Iron Required to Overcome "Hepcidin Blockade"

- High serum ferritin levels
- Potential for iron overload and organ dysfunction
- Potential increased risk for infection
  - Impairment of host defenses
  - Stimulation of pathogen growth
- Potential oxidative effect of administered IV iron on vascular endothelium
  - Vascular injury
  - Accelerated atherosclerosis

Intravenous versus Oral Iron in CKD[1]

Risks of IV iron

- Inflammation
- Oxidative stress
- Cytotoxicity
- Endothelial dysfunction
- Anaphylaxis
- Hemosiderosis
- Bacterial infections
- Cardiovascular events
- Mortality

Benefits of IV iron

- Better bioavailability
- Rapid efficacy
- No compliance issue
- Greater Hb increase
- Reduced ESA needs
- Reduced transfusion needs

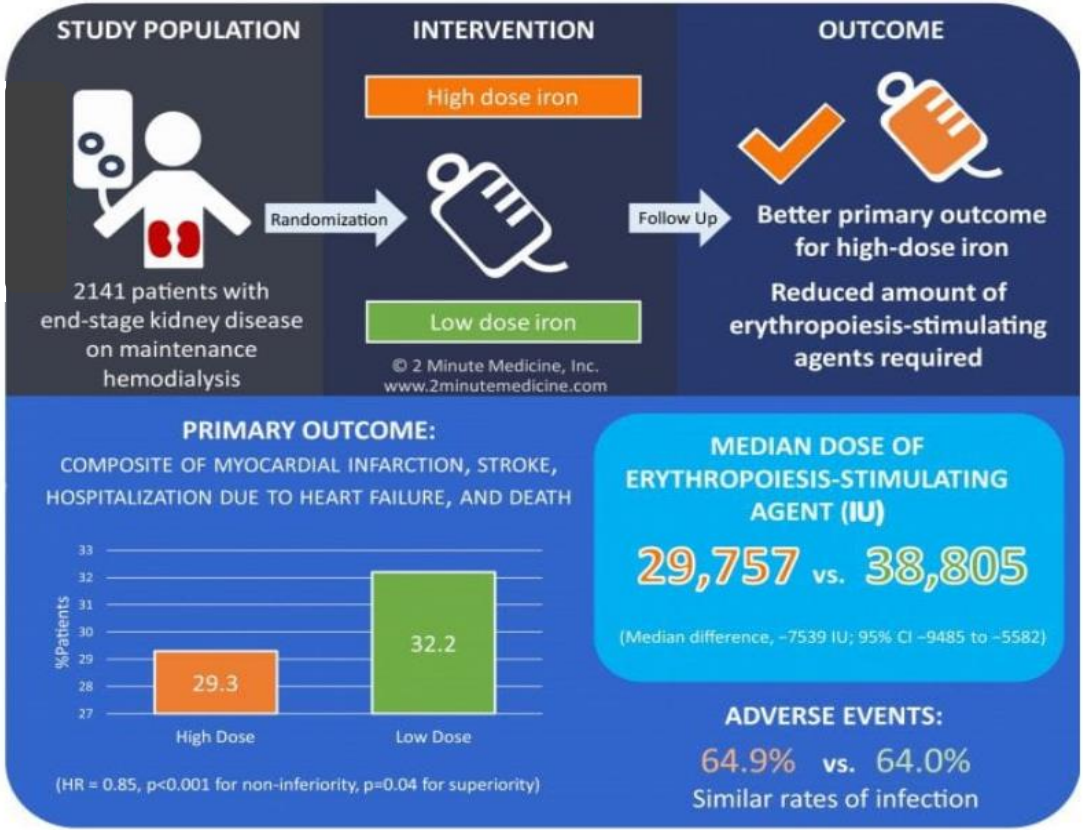
1. Drüeke TB, Massy ZA. *Kidney Int*. 2015 Oct;88(4):673-5.

Clinical Implications of Supplemental Iron Use

- Addresses iron deficiency
- IV iron easy to administer and usually well tolerated in HD patients
- Replaces ongoing iron losses in HD patients

- Oral iron often poorly tolerated and ineffective
- IV iron inconvenient in non-HD CKD patients
- Acute reactions to IV iron
- Long term safety issues (eg. CV toxicity; infection risk; iron overload)

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis: PIVOTAL Trial[1]



1. Macdougall IC et al. *N Engl J Med.* 2019 Jan 31;380(5):447-458

Anemia in Chronic Kidney Disease

Development of ESA deficiency

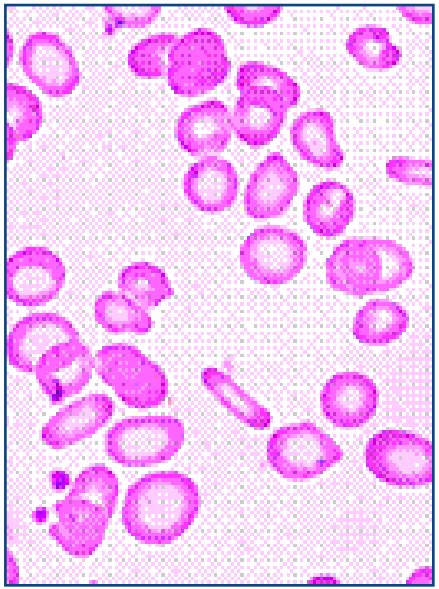
Relative in stage 3-4

85-90% in stage 5 and ESRD

Iron deficiency

Blood losses (vary with modality)

Sequestration



Published Randomized Controlled Trials in CKD: The Bottom Line

Study	N	Study Population	Hb (g/dL) or Hct(%) Target	CV Outcome	Quality of Life
Besarab. *N Engl J Med*. 1998	1233	HD + CHF/CAD	30 42	No benefit	Improved?
Foley. *Kidney Int.* 2000	146	HD - CHF/CAD	9.5-10.5 13-14	No benefit	Improved
Roger. *J Am Soc Nephrol*. 2004	155	Stage 3-4	9-10 12-13	No benefit	No difference
Parfrey. *J Am Soc Nephrol*. 2005	596	HD - CHF/CAD	9.5-11.5 13.5 -14.5	No benefit	Improved
Levin. *Am J Kidney Dis*. 2005	172	Stage 2-5	9-10.5 12-14	No benefit	Improved
Singh. *N Engl J Med.* 2006	1432	Stage 3-4	10.5-11 13-13.5	No benefit	No difference
Drüeke. *N Engl J Med.* 2006	603	Stage 3-4	10.5-11.5 13-15	No benefit	Improved

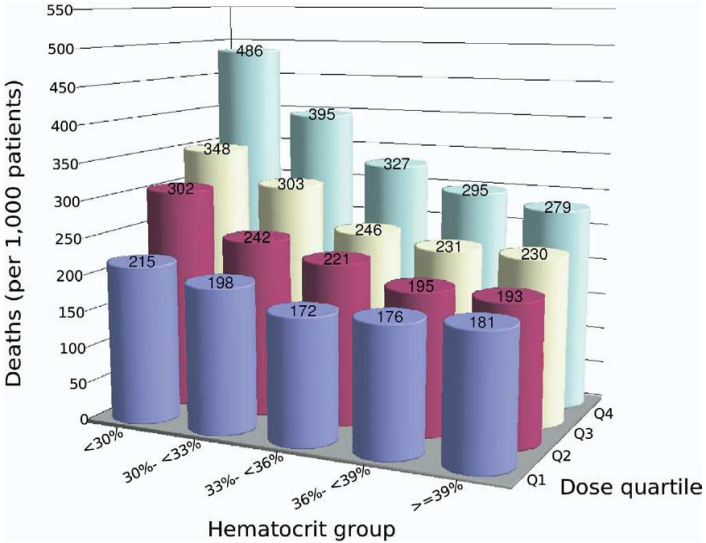
Epoetin Requirements Predict Mortality in HD Patients

Study objective: Examine the relationship between epoetin dose requirements and mortality

Retrospective cohort study using US Renal Data System administrative claims data from 2000-2001

N= 94,569 prevalent HD patients in 2000 and 2001.

Cox proportional hazard regression analysis (adjusted for baseline variables) and a 5-knot cubic regression spline were used to model the dose response relationship between epoetin and all-cause mortality.



Unadjusted 1-year mortality rates by hematocrit group according to epoetin dose quartile.

Zhang, Y., et al. American J of Kidney Dis Vol.44, No. 5 (Nov), 2004: p. 866

Erythropoiesis-Stimulating Agents (ESAs): Time for Reevaluation

Paradigm shift

"The trials raise major concerns regarding the use of ESAs to increase Hbg concentrations in patients with CKD above a level intended solely to avert the need for erythrocyte transfusions. "

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

JANUARY 21, 2010

Erythropoiesis-Stimulating Agents — Time for a Reevaluation

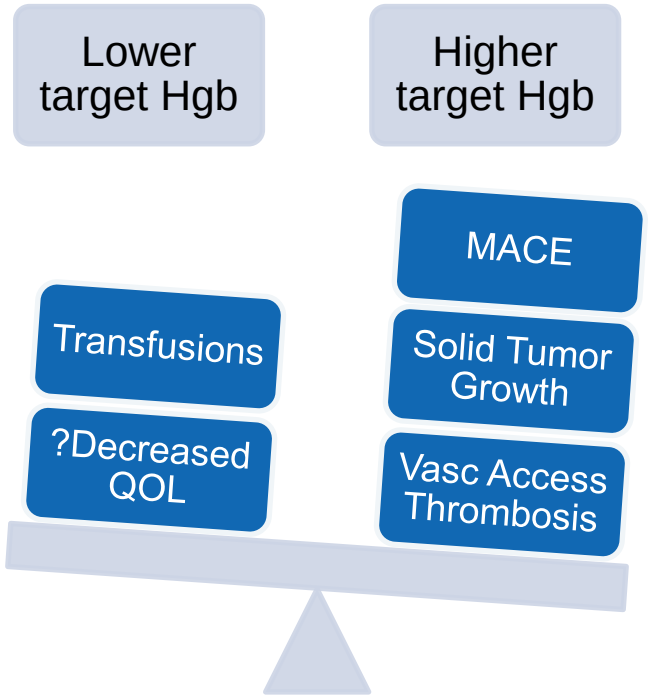
Ellis F. Unger, M.D., Aliza M. Thompson, M.D., Melanie J. Blank, M.D., and Robert Temple, M.D.

Epoetin alfa was approved in 1989 by the Food and Drug Administration (FDA) for the treatment of anemia associated with chronic kidney disease "to elevate or maintain the red blood cell level . . .

therapy were enrolled and randomly assigned either to receive increasing doses of epoetin alfa to reach and maintain a "normal" hematocrit value of 42±3% or to continue epoetin alfa therapy to

Source: Unger et al. NEJM Vol. 362, #3; 2010

Balancing Risk vs. Benefit of ESA Therapy



Proposed Mechanisms for CV Events at Higher Target Hgb Levels and ESA doses: Which is Responsible?

- Since randomization of the RCTs was by target Hgb level, only the target Hgb level can be considered cause and effect
- Higher ESA doses are highly associated with adverse events in secondary analyses
  - Patients who achieved higher target Hgb levels at low ESA doses had fewer adverse events than patients who required high ESA doses to achieve lower target Hgb levels
  - This is highly confounded by comorbidities that may lead to ESA resistance and poorer outcomes

Proposed Mechanisms for CV Events at Higher Target Hgb Levels and ESA doses: Other Contributing Factors

- Increased blood viscosity due to higher Hgb level
- Improved platelet function at higher Hgb levels (more margination)
- Thrombocytosis due to ESA-induced functional iron deficiency
- Hypertension
  - Increased RBC volume
  - Decreased peripheral vasodilation at higher Hgb levels
  - Effect of ESAs on vascular smooth muscle (increased endothelin, angiotensin, impaired endothelium dependent relaxation and altered calcium homeostasis)

Pharmacologic Blood Levels of EPO Have Off-target Effects[1]

- Peak serum EPO level is 600 mU/mL following IV injection of 30 units/kg EPO; EPO level is 4-24 mU/mL in patients with normal Hgb levels
- At high blood levels EPO may have paracrine effects on non-erythroid receptors in heart, brain, CNS and vasculature which are cytoprotective but also trophic
- Repetitive stimulation and resetting of cardiac growth signals could disorder cardiac modeling, increase vulnerability to stress, or impair the ability of higher Hgb to diminish left ventricular hypertrophy

1. Fishbane S, et al: *CJASN* 2007;2:1274-1282.

Clinical Implications of ESA Use

- Reproduces deficient native hormone
- Effective in most patients
- Well tolerated in most patients
- 30 years experience
- IV administration invisible to HD patients

- SC administration in non-HD patients
- Long-term cardiovascular events
- ESA resistance
- Do not address iron mobilization disorders

Balancing Risk vs. Benefit of ESA Therapy[1,2]

Since the institution of the PPS (bundled payment) for dialysis and the FDA ESA label change in 2011:

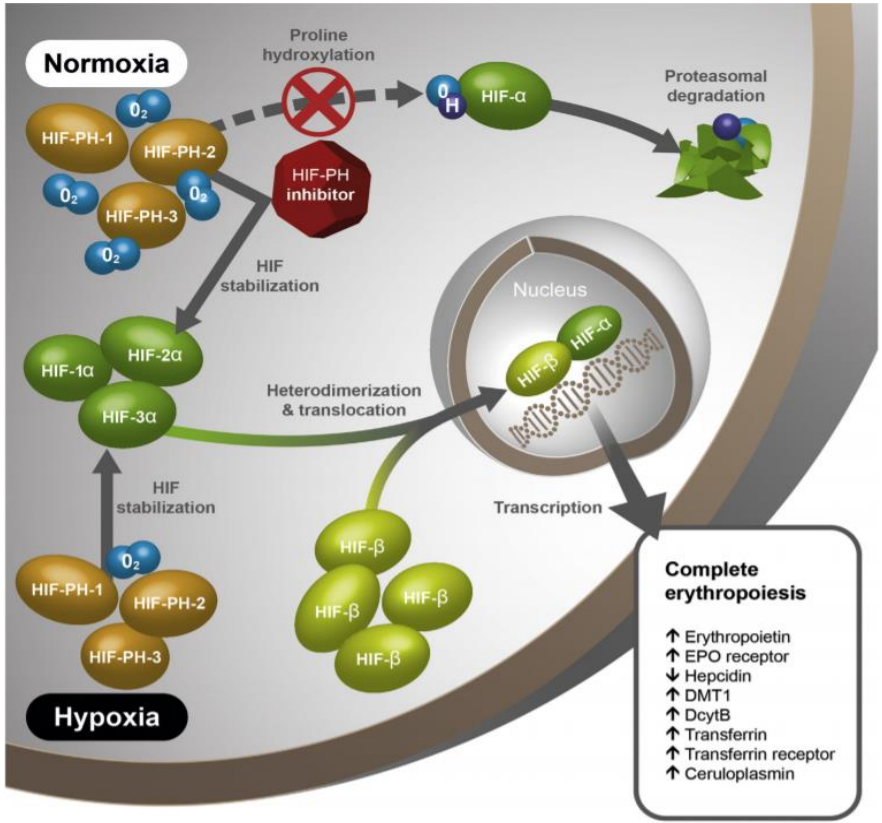
- **Average ESA doses have decreased around 40%**
- **Mean Hgb levels have decreased from 11.5 to 10.8 g/dL (DOPPS)**
- **Observed rates of stroke, VTE and heart failure have decreased[1]**
- **Transfusion rates have increased from around 2.7% to 3.0% (DOPPS)**
- **The increase in transfusions is primarily among patients receiving multiple transfusions who are less likely to be transplant candidates[2]**

Is this an acceptable trade-off?

What about quality of life?

1. Chertow GM et al. *J Am Soc Nephrol*. 2016;27: 3129-3138. 2. Hirth RA et al. *Am J Kidney Dis*. 2014;64:616-621.

Pharmacologic Inhibition of HIF-PH to Selectively Activate HIF-Dependent Erythropoiesis[1]



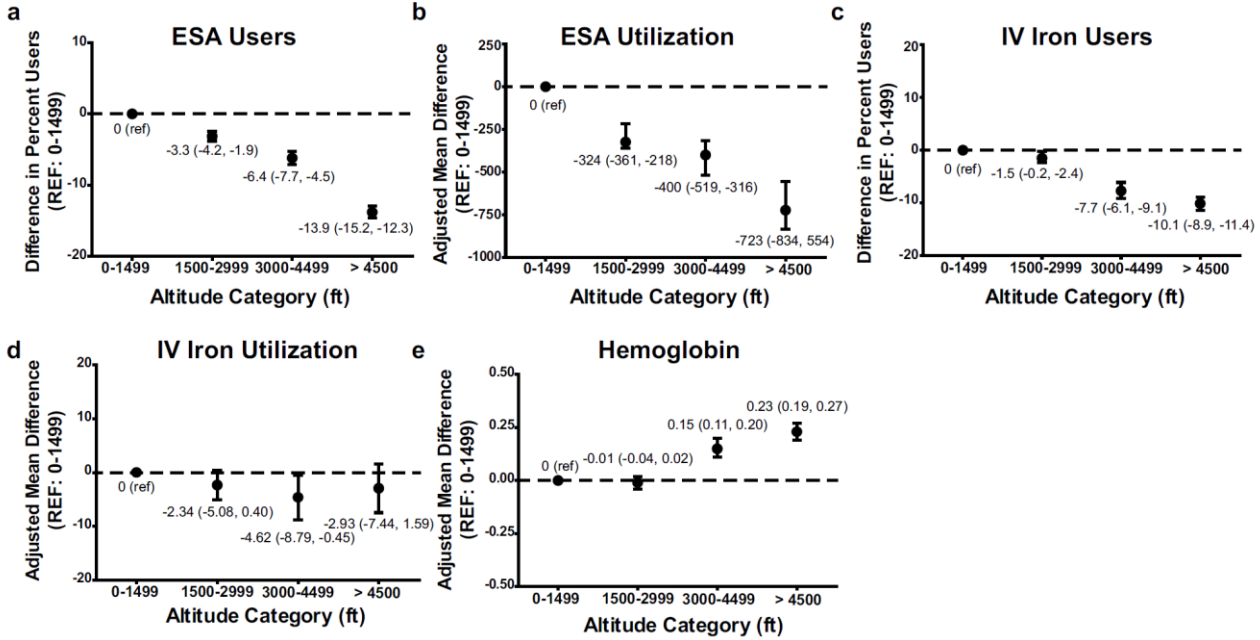
1. Gupta N, Wish JB. *Am J Kidney Dis.* 2017 Jun;69(6):815-826

Physiopathology

- The mechanism to compensate hypoxia by an increase in erythropoiesis is still preserved in failing kidneys
- However, EPO expression is regulated to inadequately low levels because of high oxygen concentration in renal interstitial cells due to reduced oxygen consumption in failing kidneys
- HIF-PH, might be suited for the induction of endogenous EPO by mimicking hypoxia and could potentially be a beneficial therapeutic agent for anemia.

Source: Investigator's Brochure Bay 89-3534 .Data on File

Effect of Altitude on Anemia, ESA Use, Iron Use and Mortality



Sibbel, J Neph 2016

Characteristics of HIF-PH Inhibitors Under Development in the US

Generic Name	Investigational Name	Sponsor	Half Life	Dosing Frequency	Investigational Status
Roxadustat	FG-4592	FibroGen, Astellas & AstraZeneca	12-13 hr	3x weekly	Phase 3
Vadadustat	AKB-6548	Akebia/Keryx & Otsuka	4.5 hr	Daily	Phase 3
Daprodustat	GSK-1278863	Glaxo-SmithKline	4 hr	Daily	Phase 3

Roxadustat Global Phase 3 Studies

DD-CKD Studies	N	Population, Comparator	Results
HIMALAYAS	1,043	Incident dialysis vs epoetin-α	Non-inferior to ESA
SIERRAS	741	Stable/incident dialysis vs epoetin-α	Superior to ESA
ROCKIES	2,133	Stable/incident dialysis vs epoetin-α	Superior to ESA
PYRENEES	838	Stable dialysis vs epoetin-α or darbepoetin	Not available
NDD-CKD Studies	**N**	**Population, Comparator**	**Results**
ANDES	922	Nondialysis vs placebo	Superior to placebo
OLYMPUS	2,781	Nondialysis vs placebo	Superior to placebo
ALPS	597	Nondialysis vs placebo	Superior to placebo

Pooled MACE/MACE+		
Patient population	**N**	**Results**
Nondialysis-dependent	>4,300	No clinically-meaningful difference between roxadustat and placebo
Incident dialysis	1,500	Better outcomes observed in patients on roxadustat than those on epoetin alfa
Dialysis-dependent	~4,000	No clinically-meaningful difference between roxadustat and epoetin alfa

Vadadustat Phase 3 Program for the Treatment of Anemia Due to CKD

RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, NON-INFERIORITY PHASE 3 CARDIOVASCULAR OUTCOMES STUDIES

Non-dialysis dependent (NDD) N = up to 3700		Dialysis dependent (DD) N = up to 3600	
PROTECT CORRECTION	PROTECT CONVERSION	INNOVATE CORRECTION / CONVERSION	INNOVATE CONVERSION
Not ESA Treated	ESA Treated	New-Onset Dialysis*	ESA Treated
Vadadustat vs Darbepoetin Alfa	Vadadustat vs Darbepoetin Alfa	Vadadustat vs Darbepoetin Alfa	Vadadustat vs Darbepoetin Alfa

Primary Efficacy Endpoint: Change in hemoglobin (Hb) from baseline
Primary Safety Endpoint: Major Adverse Cardiovascular Events (MACE)

*≤16 weeks of dialysis treatment, with or without prior ESA treatment

Daprodustat: Global Phase 3 Registration Program[1]

- **ASCEND-D** (Anaemia Studies in CKD: Erythropoiesis via a Novel PHI Daprodustat-Dialysis) will enroll ~3,000 dialysis dependent patients with anemia associated with CKD switching from an ESA. Recruitment has completed, and results are anticipated in 2020

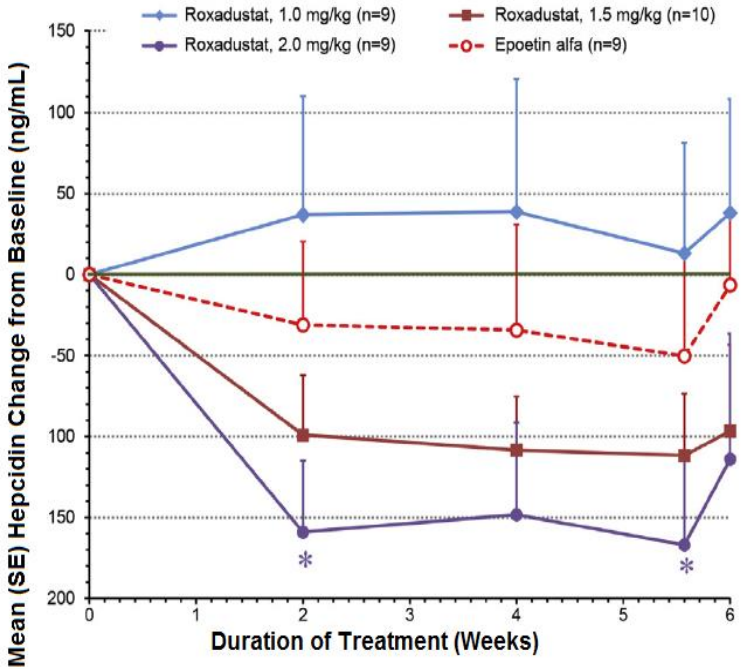
- **ASCEND-ND** (Anaemia Studies in CKD: Erythropoiesis via a Novel PHI Daprodustat-Non-Dialysis) will enroll ~4,500 non-dialysis dependent patients with anemia associated with CKD, and will include patients either switching from or naive to an ESA. Recruitment remains ongoing and results are anticipated in 2020.

For both studies, the co-primary endpoints are time to first occurrence of MACE and mean change in Hgb between the baseline and efficacy period (mean over Weeks 28-52).

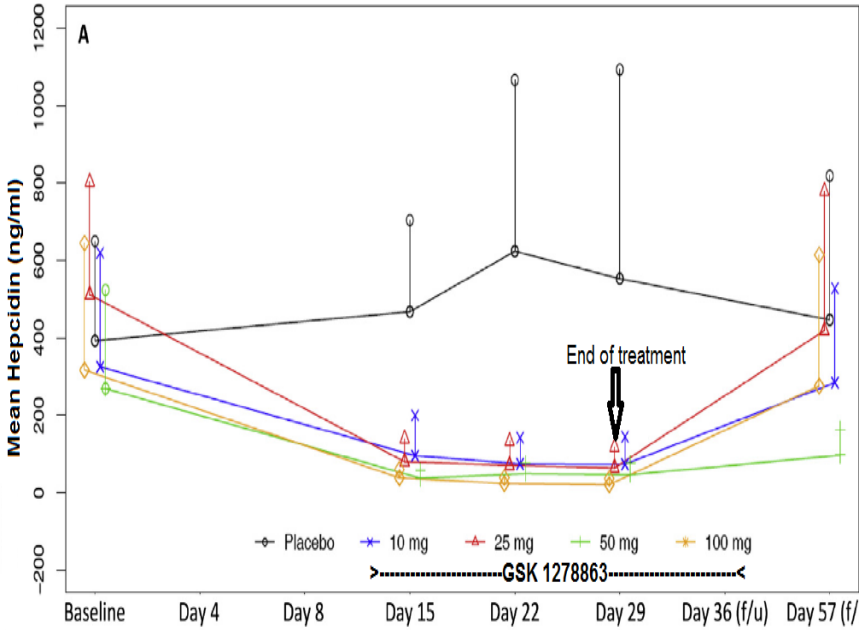
1. https://www.gsk.com/en-gb/media/press-releases/gsk-announces-positive-phase-3-results-for-daprodustat-in-patients-with-anaemia-associated-with-chronic-kidney-disease/

Roxadustat and Daprodustat: Effects on Hepcidin

Roxadustat lowers hepcidin in a dose dependent manner in dialysis patients[1]

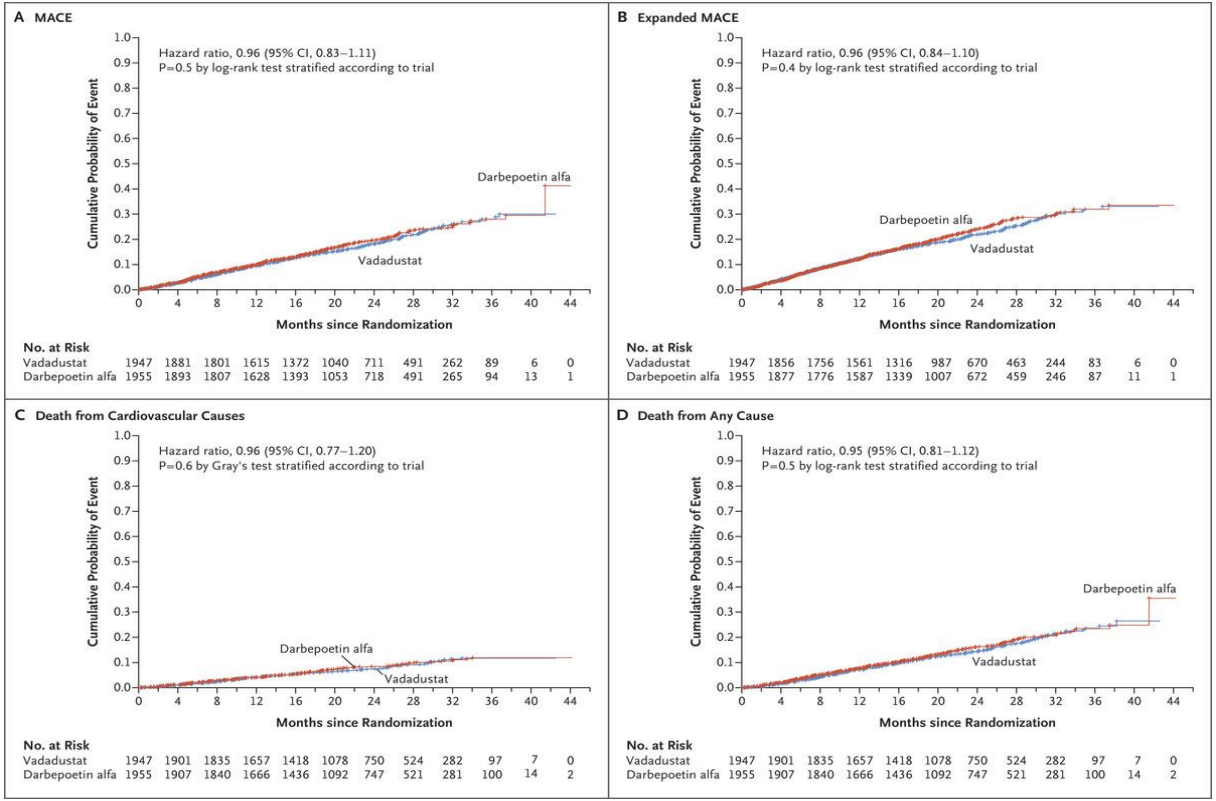


Daprodustat lowers hepcidin in CKD patients[2]



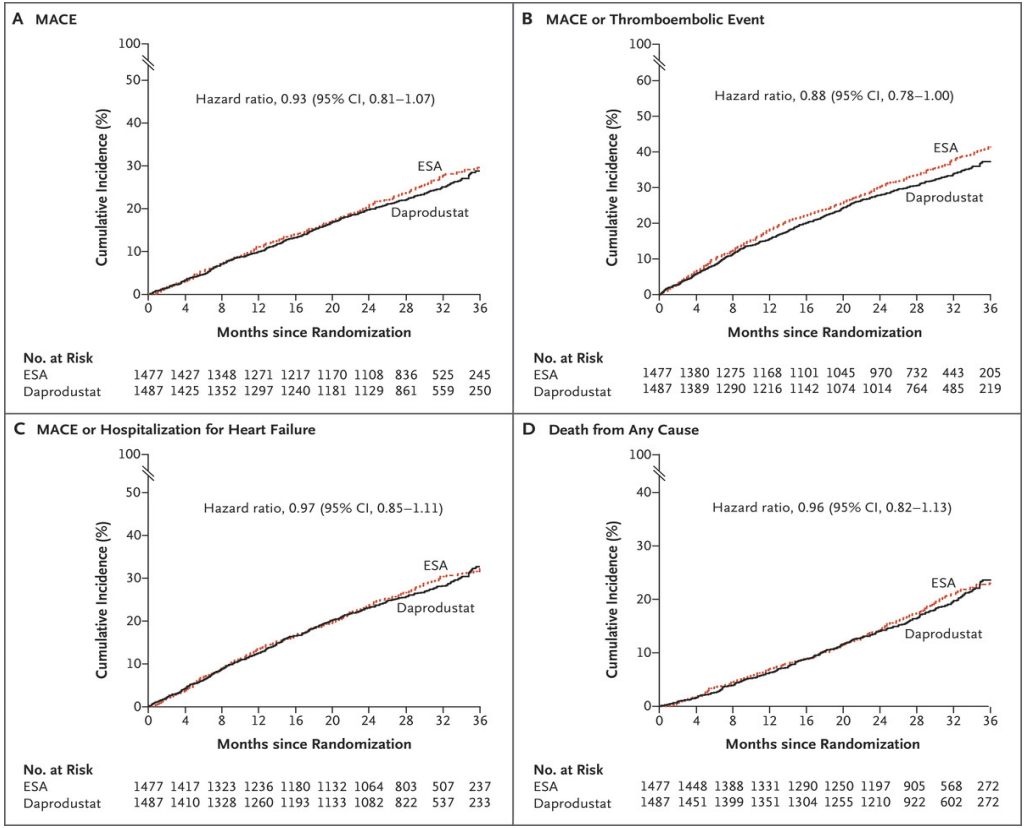
1. Provenzano R et al. *Am J Kidney Dis*. 2016 Jun;67(6):912-24. 2. Brigandi RA et al. *Am J Kidney Dis*. 2016 Jun;67(6):861-71

MACE, Expanded MACE, Death from Cardiovascular Causes, and Death from Any Cause in the Pooled Safety Population of the Two Trials



K Eckardt et al. N Engl J Med 2021;384:1601-1612

Kaplan–Meier Plots of Time to First Occurrence of Adjudicated Cardiovascular Events and Death from Any Cause (Intention-to-Treat Population)



AK Singh et al. N Engl J Med 2021;385:2325-2335.

Dustat Phase 3 Findings, FDA Action

Drug	Safety	Efficacy	FDA action
Roxadustat	• Hazard ratio for MACE with roxadustat: 1.10 (95% CI, 0.96-1.27), demonstrating noninferiority per authors	Mean Hb change of 1.9 g/dL in roxadustat group vs 0.2 g/DL, regardless of rescue therapy	Did not approve (August 2021) in part due to concerns about risk of thrombotic events
Vadadustat	• First MACE in 22.0% of vadadustat group vs 19.9% of darbepoetin alfa group (HR, 1.17) – noninferiority **not** met • SAEs: 65.3% vs 64.5% (ESA-untreated), 58.5% vs 56.6% (treated)	Mean between-group difference in change in Hb was 0.05 g/dL (ESA-untreated) and -0.01 g/dL (treated); met noninferiority	Did not approve (March 30, 2022) in part due to MACE in non-dialysis patients
Daprodustat	• First MACE in 19.5% vs 19.2%, respectively (met noninferiority) • Similar % of adverse events in groups • More cancer death/tumor progression or recurrence in daprodustat group (3.7% vs 2.5%; RR, 1.47; *P*=.04)	Mean Hb change 0.74 g/dL in daprodustat group vs 0.66 g/dL in darbepoetin alfa group (met noninferiority)	Accepted application, April 2022

Singh AK et al. *N Engl J Med*. 2021;385(25):2325-2335. Chertow GM et al; PRO2TECT Study Group. *N Engl J Med*. 2021;384(17):1589-1600. Provenzano R et al. *Clin J Am Soc Nephrol*. 2021;16(8):1190-1200.
Akebia. https://ir.akebia.com/news-releases/news-release-details/akebia-therapeutics-receives-complete-response-letter-fda. HCPLive, https://www.hcplive.com/view/fda-committee-recommends-against-roxadustat-approval-cdk.
FibroGen, https://investor.fibrogen.com/news-releases/news-release-details/fibrogen-receives-complete-response-letter-fda-roxadustat-anemia

Pharmacokinetic properties of Daprodustat, Roxadustat, and Vadadustat

Compound	Effective Daily Oral Doses in Phase 2 Trials	Dosing Schedule	Half-Life, h	Plasma EPO, IU/L	Metabolism
Daprodustat (GSK-12278863)	5-25 (also examined 50 and 100 mg)	1×/d	~1-7	24.7[a] and 34.4[b]	CYP2C8 with minor CYP3A4
Roxadustat (FG-4592, ASP1517)	0.7-2.5 mg/kg	3×/wk	12-15	113[c] and 397[d]	CYP2C8
Vadadustat (AKB-6548, MT-6548)	150-600 mg	1×/d (3×/wk)	4.7-9.1	32	NR

Wish, JB et al. Am J Kidney Dis. 78(5):709-718.

HIF Stabilizers: Safety Concerns

- Potential upregulation of several hundred other hypoxia sensitive genes, including those involved in:
  - Glucose regulation
  - Angiogenesis
  - Extracellular matrix production
  - Cell proliferation and survival
- Elevation of liver enzymes
- Fatal hepatic necrosis in a patient

Conclusions

- Managing anemia in patients with CKD is complex.
- Iron metabolism is an important consideration and requires careful assessment.
- EPO dosing and Hgb targets have changed with increased clinical experience
- HIF stimulators offer an opportunity to overcome functional iron deficiency and enhance erythropoiesis in a more physiologic way