Innovations in the Treatment of CKD-Related Anemia: Focus on Improving Patient-Centered Outcomes

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- Historical Background: Anemia of CKD
- Current Landscape of CKD-related Anemia Management in the US and Globally
- Discovery and Innovation: the HIF Pathway

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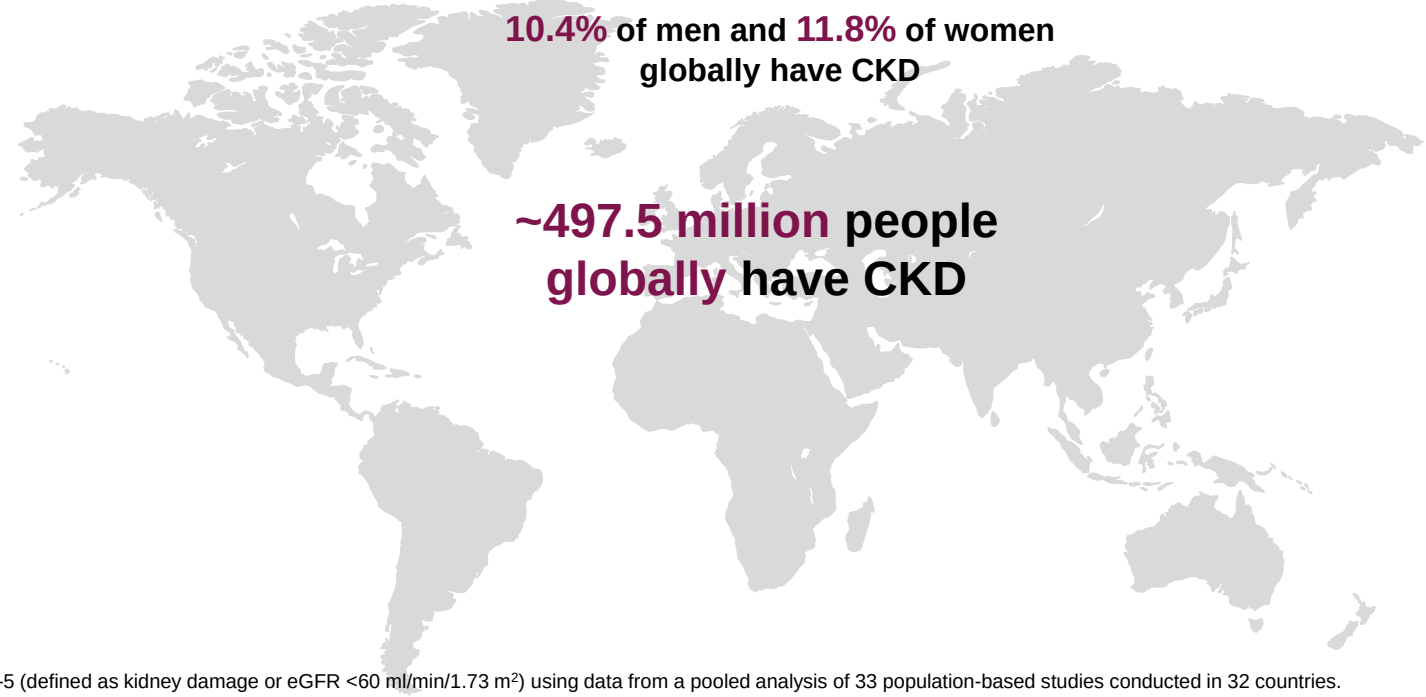
CKD: a global health concern

Global prevalence of CKD (age ≥20 years) in 2010[a]

10.4% of men and 11.8% of women globally have CKD



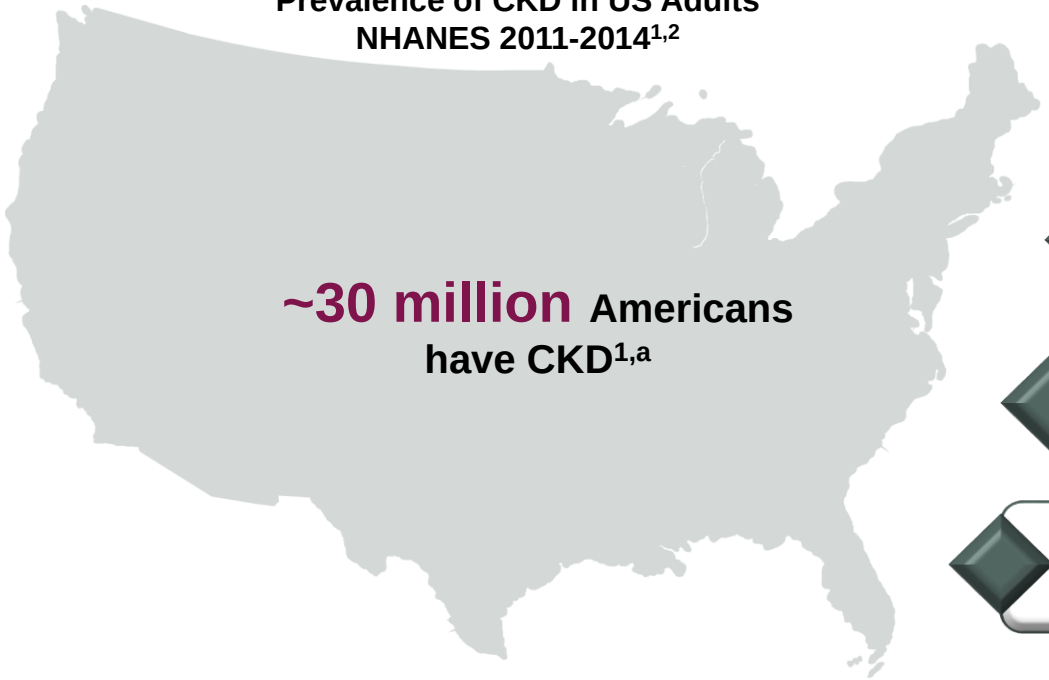
~497.5 million people globally have CKD

[a]CKD stages 1-5 (defined as kidney damage or eGFR <60 ml/min/1.73 m^2) using data from a pooled analysis of 33 population-based studies conducted in 32 countries.
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

Mills KT et al. *Kidney Int.* 2015;88:950–957.

CKD prevalence in the US

Prevalence of CKD in US Adults NHANES 2011-2014[1,2]



~30 million Americans have CKD[1,a]

- **14.8%** of US adults have CKD:[2,b]
  13.0% men and **16.5%** women
- Prevalence increases with age:[2,b]
  32.6% in those ≥60 years of age
- Comorbidities are common:[2,b,c]
  40% with diabetes mellitus
  40% with CV disease
- In US Medicare patients, cost of CKD in 2015 was **$55.8 billion**:[3]
  per patient per year cost was **$22,228**

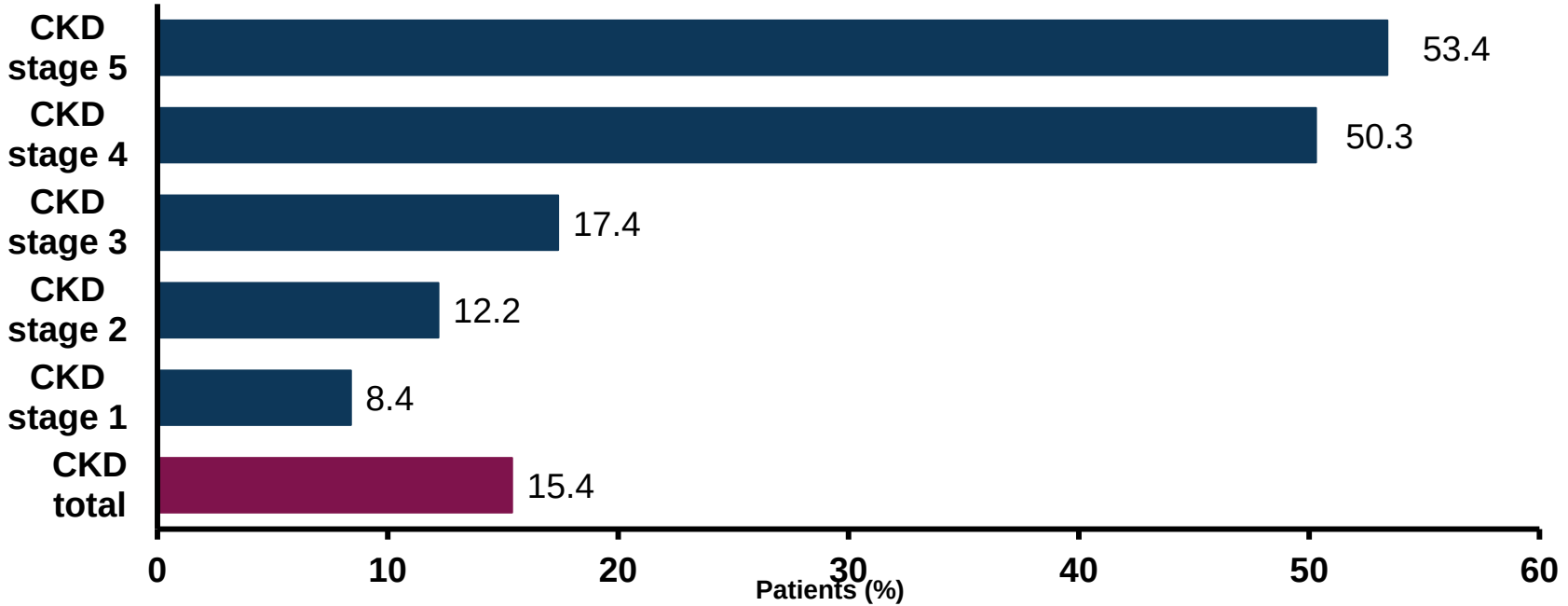
[a]CKD stages 1–5 among US adults ≥18 years using data from the 2011–2014 NHANES and the CKD-EPI equation. These estimates are subject to variability and do not account for persistence of albuminuria or creatinine as indicated by the KDIGO recommendations. Estimates by sex, race, or ethnicity were age-adjusted using the 2000 US standard population; [b]CKD stages 1-5 (defined as either eGFR <60 ml/min/1.73 m^2 CKD-EPI or ACR ≥30 mg/g) among US adults ≥20 years of age using data from 2011-2014 NHANES; [c]self-reported.
ACR = albumin-to-creatinine ratio; CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; CV = cardiovascular; eGFR = estimated glomerular filtration rate; KDIGO = Kidney Disease Improving Global Outcomes; NHANES = National Health and Nutrition Examination Survey.

1. Center for Disease Control. National chronic kidney disease fact sheet, 2017. https://www.cdc.gov/kidneydisease/pdf/kidney_factsheet.pdf. Accessed September 21, 2018; 2. United States Renal Data System. 2017 Annual Data Report. https://www.usrds.org/2017/view/v1_01.aspx. Accessed September 21, 2018;
3. United States Renal Data System. 2017 Annual Data Report. https://www.usrds.org/2017/view/v1_06.aspx. Accessed September 21, 2018.

Anemia frequency in CKD increases with disease severity

Prevalence of anemia by CKD stage in the US

Cross-sectional analysis of patients with CKD from NHANES >18 years of age in 2007–2008 and 2009–2010 (N=2125)



Anemia was defined as serum hemoglobin ≤12 g/dL in women and ≤13 g/dL in men and stages of CKD were defined in accordance with the recommendations of the National Kidney Foundation.

CKD = chronic kidney disease; NHANES = National Health and Nutrition Examination Survey.

Stauffer M et al. *PLoS One.* 2014. http://dx.doi.org/10.1371/journal.pone.0084943. Accessed September 25, 2018.

Patient-Centered Care:
Fatigue is a major issue and concern among patients with CKD

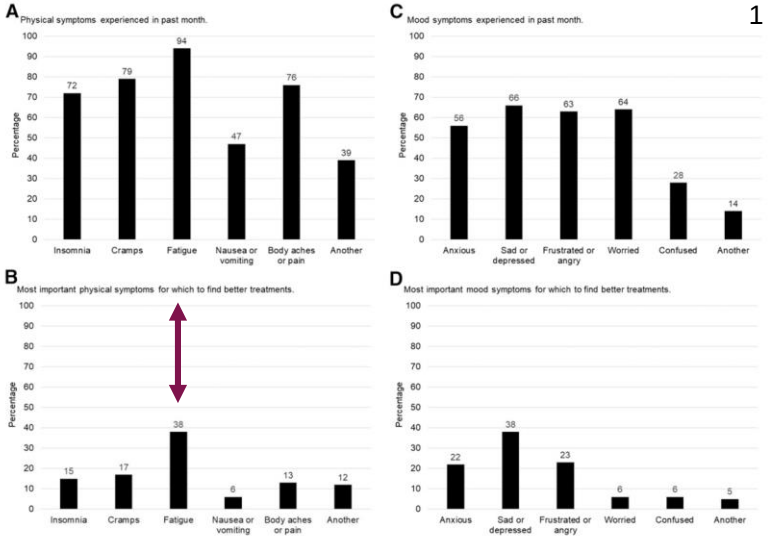


Figure 3. | Survey responses captured physical and mood symptoms experienced by patients and the most important physical and mood symptoms for which to find better treatments. (A) displays physical symptoms experienced in the past month. (B) displays the most important physical symptoms for which to find better treatments. (C) displays mood symptoms experienced in the past month. (D) displays the most important mood symptoms for which to find better treatments.

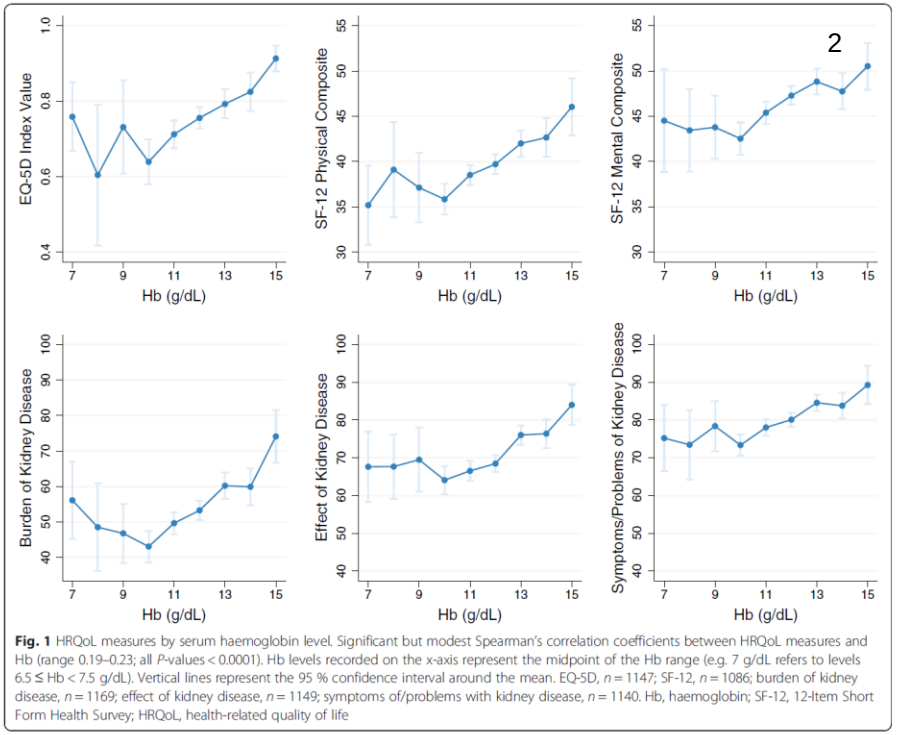


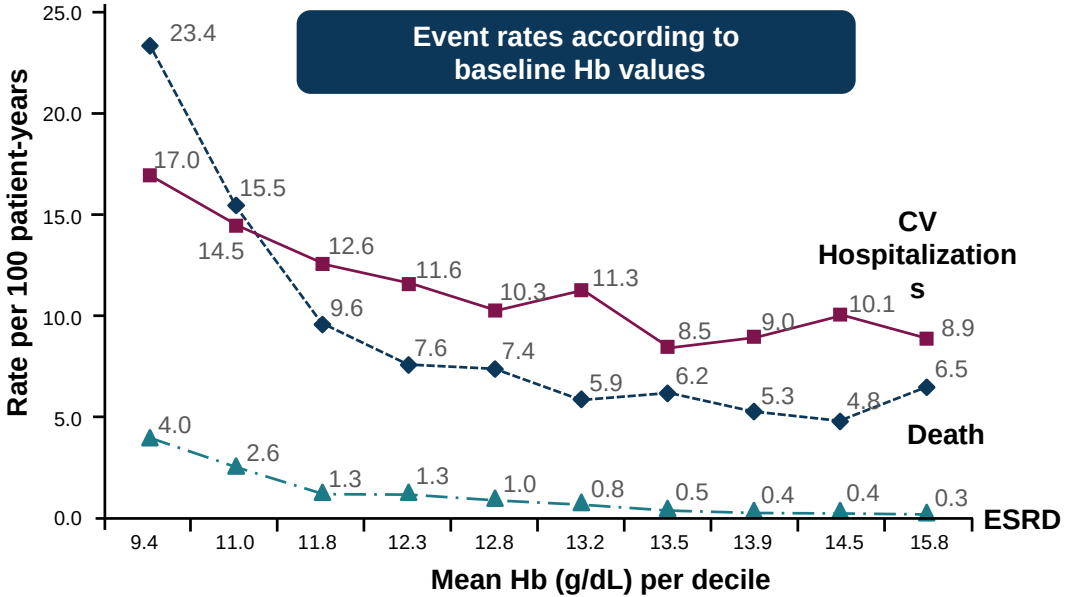
Fig. 1 HRQoL measures by serum haemoglobin level. Significant but modest Spearman's correlation coefficients between HRQoL measures and Hb (range 0.19–0.23; all *P*-values < 0.0001). Hb levels recorded on the x-axis represent the midpoint of the Hb range (e.g. 7 g/dL refers to levels 6.5 ≤ Hb < 7.5 g/dL). Vertical lines represent the 95 % confidence interval around the mean. EQ-5D, *n* = 1147; SF-12, *n* = 1086; burden of kidney disease, *n* = 1169; effect of kidney disease, *n* = 1149; symptoms of/problems with kidney disease, *n* = 1140. Hb, haemoglobin; SF-12, 12-Item Short Form Health Survey; HRQoL, health-related quality of life

1. Flythe J et al. Symptom Prioritization among Adults Receiving In-Center Hemodialysis. CJASN 2018; 13:735-745.
2. Eriksson D et al. Cross-sectional survey in CKD patients across Europe describing the association between quality of life and anemia. BMC Nephrol 2016; 17: 1-10

Association between severity of CKD-related anemia and increased risk of mortality, CV hospitalization, and ESRD

Risk of mortality, CV hospitalizations, and ESRD in patients with CKD by baseline Hb level

Retrospective cohort study of patients with CKD stage 3 or 4 (eGFR <60 and ≥15 mL/min/m^2)[a] age ≥20 years from a US HMO database enrolled between January 1997-December 2004 and followed up to June 30, 2005 (N=5885)



- In this population, compared with nonanemic patients, patients with the lowest Hb (<10.5 g/dL) had:[b]
  - **2-fold** increase in risk of CV hospitalization
  - **5-fold** increase in risk of death
  - **5-fold** increase in progression of ESRD

Patients treated with erythropoietin stimulating agents or blood transfusions before the index hemoglobin were excluded from the analysis.

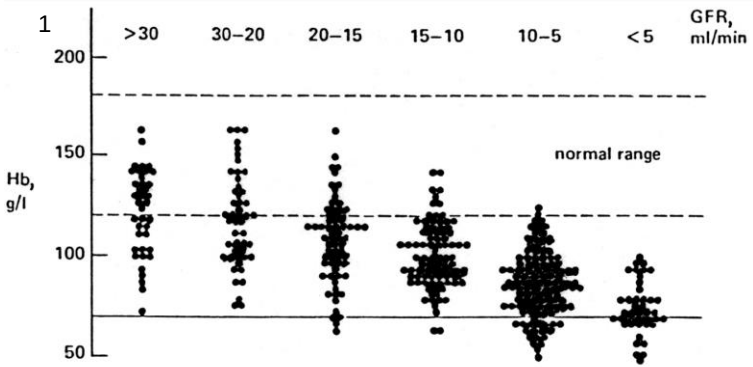
[a]GFR estimated using MDRD equation; [b]The hazard ratios adjusted for significant variables including time-varying eGFR and Hb in patients with Hb <10.5g/dl vs >12.5 g/dl were 2.18 for CV hospitalization, 5.27 for all-cause mortality, and 5.46 for ESRD (p<0.0001) for all comparisons.

CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; ESRD = end-stage renal disease; Hb = hemoglobin; HMO = health maintenance organization; MDRD = Modification of Diet in Renal Disease.

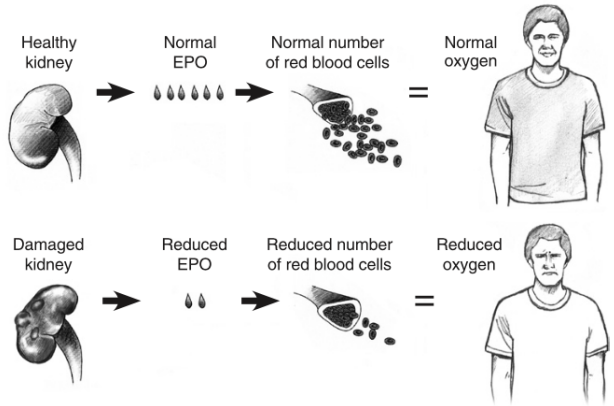
Thorp ML et al. *Nephrology.* 2009;14:240–246.

CKD-Related Anemia

1



2



1. Misra and Kerr
2. NIH Publication No. 14–4619 May 2014
3. Adamson JW. Am Soc Hem; 50 Years in Hematology 2008;Ch 1:

Impact of EPO Introduction on Hematocrit (Hct) in ESRD

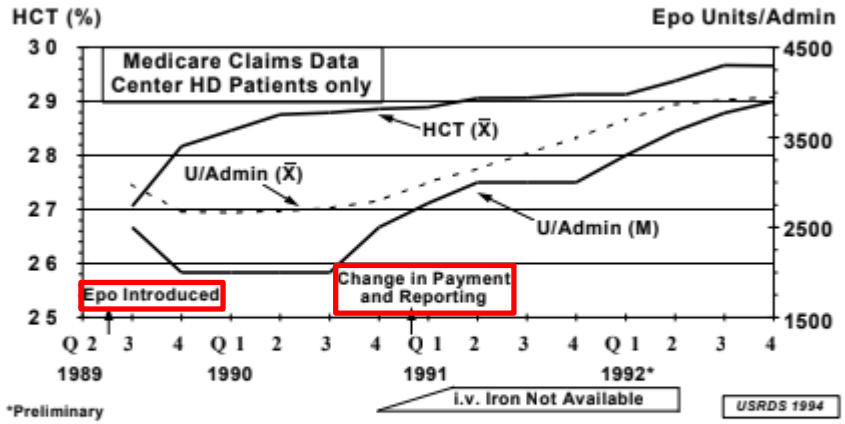


Figure V-21

Average Patient Hematocrit and EPO Dose by Quarter, 1989-1992. X-Bar is the mean. M is the median. U is EPO units. Admin. is administration Center hemodialysis patients only. Before 1/1/91, EPO dose was reported as the last dose in the billing period. After 1/1/91, reported dose was calculated by HCFA as the average over the billing period. From the Quarterly Dialysis Records (See Technical notes, Chapter XV, for details of the Quarterly Dialysis Records File.)

USRDS Annual Data Report 1994, Ch 5: 76

December 1990:
Omnibus Budget Reconciliation Act:
reimbursement for EPO per unit dosage

Increased risk of mortality and CV events with ESAs at higher Hb targets in patients with CKD anemia

NHCT[1]

- 1265 patients with DD-CKD with CHF or ischemic heart disease
- high Hb (14 g/dL) vs low Hb (10 g/dL)[a]

Increased risk of death/non-fatal MI

RR 1.28
(95% CI 1.069-1.56)

- Open-label, prospective
- 1° composite EP: Death, non-fatal MI
- Median follow-up: 14 months[2]

CHOIR[3]

- 1432 patients with NDD-CKD (eGFR 15-50 mL/min/1.73 m^2)
- high Hb (13.5 g/dL) vs low Hb (11.3 g/dL)[a]

Increased risk of death/MI/hCHF/stroke

HR 1.34
(95% CI 1.03-1.74; p=0.03)

- Open-label, prospective
- 1° composite EP: Death, MI, stroke, CHF
- Median follow-up: 16 months

CREATE[4]

- 603 patients with NDD-stage 3/4 CKD (eGFR 15-35 mL/min/1.73 m^2)
- high Hb (13-15 g/dL) vs low Hb (10.5-11.5 g/dL)

With higher targets

Trend of increased risk of mortality[c]

RR 1.48
(95% CI 0.87-2.52)[6]

- Open-label, parallel-group
- 1° composite EP: CV events[b]
- Mean duration: 3 years

TREAT[5]

- 4038 patients with T2DM NDD-CKD (eGFR 20-60 mL/min/1.73 m^2)
- high Hb (13 g/dL; ESA) vs low Hb (9 g/dL; placebo + rescue ESA)

Increased risk of fatal or non-fatal stroke[c]

HR 1.92
(95% CI 1.38-2.68; p<0.001)

- Randomized, double-blind, placebo-controlled
- 1° composite EPs: (1) Death, MI or hospitalization for MI, stroke, CHF; (2) death or end-stage renal disease
- Median follow-up: 29.1 months

Please note that it is inappropriate to make direct comparisons between the studies as the study design, demographics and other criteria were different.

[a]Study was terminated early; [b]Sudden death, MI, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalization for ≥24 hours or prolongation of hospitalization, complication of peripheral vascular disease (amputation or necrosis), or cardiac arrhythmia resulting in hospitalization for ≥24 hours; [c]Secondary EP.

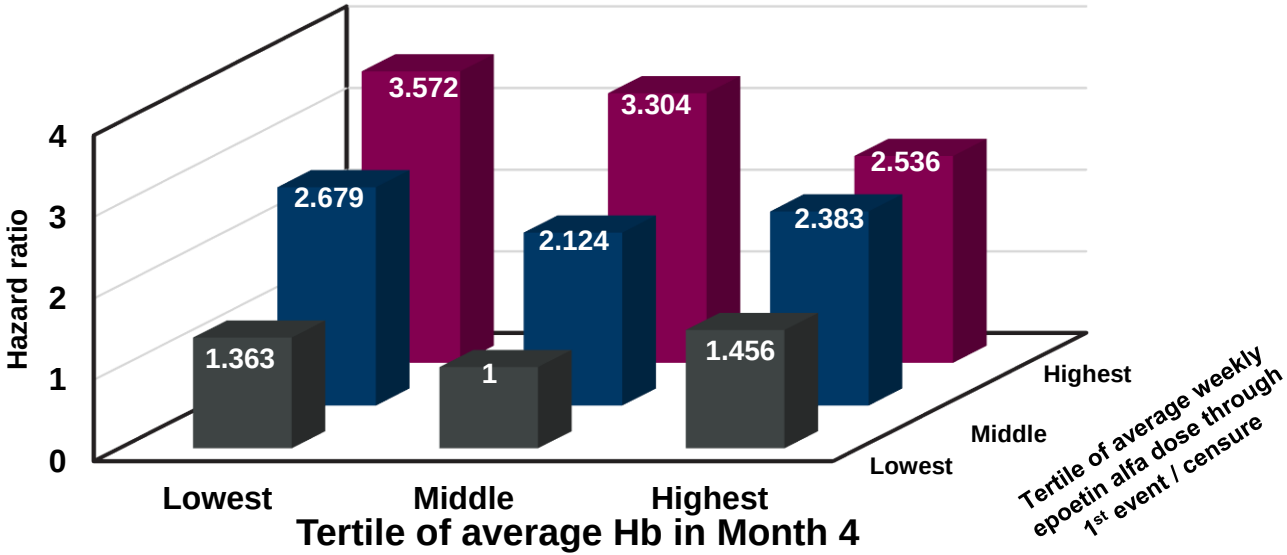
CHF = congestive heart failure; CHOIR = Correction of Hemoglobin and Outcomes in Renal Insufficiency; CKD = chronic kidney disease; CREATE = Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta; DD, dialysis-dependent; eGFR = estimated glomerular filtration rate; EP = endpoint; ESA = erythropoiesis-stimulating agent; Hb = hemoglobin; hCHF = hospitalization for CHF; HCT = hematocrit; HD = hemodialysis; HR = hazard ratio; MI = myocardial infarction; NDD = nondialysis-dependent; NHCT = Normal Hematocrit Cardiac Trial; RR = risk ratio; T2DM = Type 2 diabetes mellitus; TREAT = Trial to Reduce Cardiovascular Events with Aranesp Therapy.

1. Epogen Prescribing Information, Amgen Inc, July 2018; 2. Besarab A et al. *N Engl J Med.* 1998;339:584–590; 3. Singh A et al. *N Engl J Med.* 2006;355:2085–2098; 4. Drüeke T et al. *N Engl J Med.* 2006;355:2071–2084; 5. Pfeffer M et al. *N Engl J Med.* 2009;361:2019–2032; 6. Phrommintikul A et al. *Lancet.* 2007;369:381-388.

High ESA doses rather than high Hb concentrations were associated with poor outcomes

Risk for the composite endpoint of death, heart failure hospitalization, stroke, or MI according to Hb achieved at 4 months and long-term maintenance dose of ESA received [1]

Post-hoc analysis of the CHOIR study to evaluate the relationship of ESA dose exposure, Hb achieved and outcomes (N=1224)



Irrespective of Hb achieved, the relative risk in the highest epoetin alfa dose tertile was significantly increased, when compared to the lowest risk group of middle Hb tertile and lowest dose tertile (HR range, 2.536 to 3.572; p<0.05)

The middle tertile is set as referent. The x-axis represents average Hb in month 4, and the z-axis represents the average weekly dose of epoetin alfa received prior to the first event or time of censure. Average Hb tertiles were (g/dl): lowest ≤ 11.5, middle >11.5 to <12.7, highest ≥ 12.7. Average weekly erythropoietin dose tertiles prior to first event were (1,000 units): lowest <5,164, middle 5,164–10,095, highest >10,095.

CHOIR = Correction of Hemoglobin and Outcomes in Renal Insufficiency; CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; Hb = hemoglobin; HR = hazard ratio; ICU = intensive care unit; MI = myocardial infarction.

McCullough PA et al. *Am J Nephrol.* 2013;37:549–558.

Selected Recommendations for Exogenous Supplemental Therapies

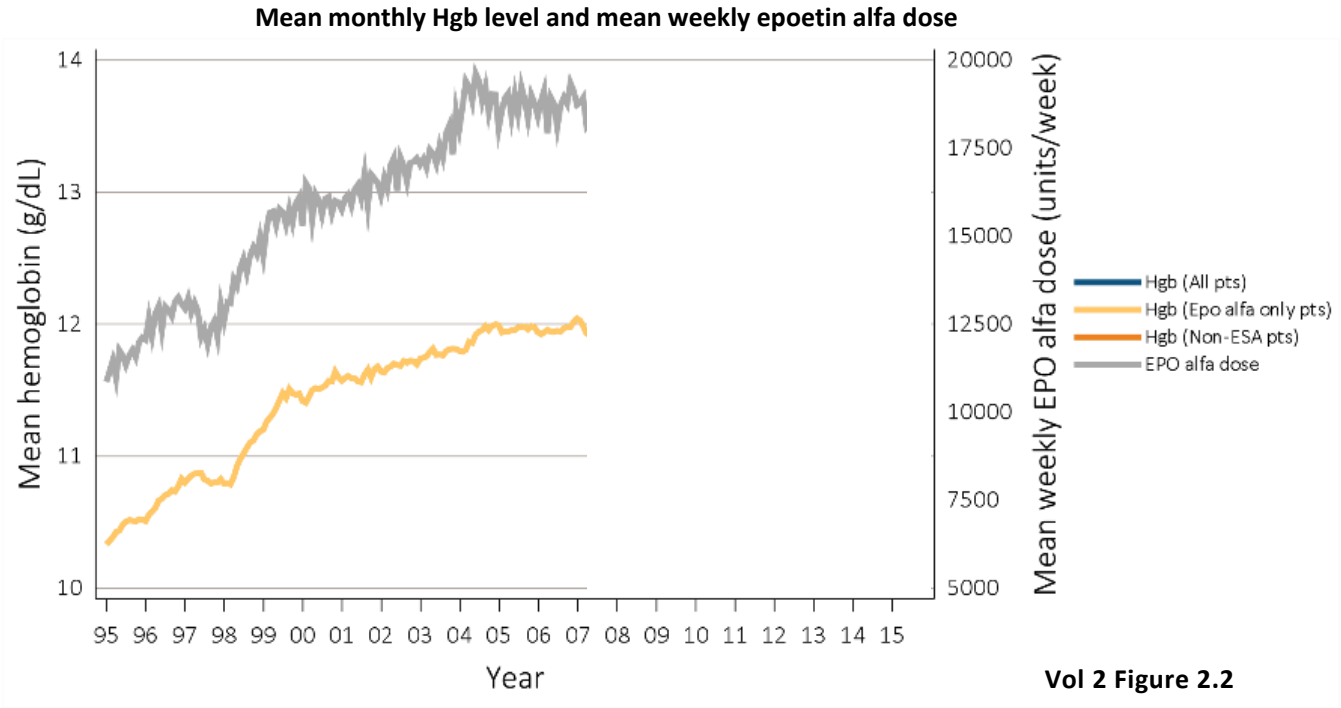
	KDIGO[1]	NKF-KDOQI[2] (Commentary on KIDIGO 2012)
ESA	• Initiate ESA in DD patients: – Hb 9 to 10 g/dL • Initiate ESA in NDD patients: – Hb <10 g/dL[a] • Target Hb levels: – Hb 11.5 g/dL	• Initiate ESA: – Hb <10 g/dL • Target Hb levels: – Hb 11 g/dL
Evaluation of ESA hyporesponsiveness	• No increase in Hb after the first month of ESA treatment • Suggest avoiding repeated escalation in ESA dose beyond double the initial weight-based dose	• No increase in Hb after ≥2 months of ESA treatment
Iron	• Trial of iron (oral or IV) recommended if TSAT is ≤30% and ferritin ≤500 ng/ml • Not recommended for routine use in patients with serum ferritin consistently ≥500 ng/ml • Avoid administering IV iron to patients with active systemic infections	• Trial of IV iron can be considered if TSAT is low (≤30%) even if ferritin is above 500 ng/ml) • Insufficient evidence upon which to base a recommendation for an upper ferritin limit above which IV iron must be withheld • Avoid high-molecular weight iron dextran • No recommendation regarding the use or avoidance of IV iron in the setting of infection; more evidence needed
Oral iron	• NDD patients: no clearly defined advantage or preference for IV compared to oral iron • DD patients: IV iron preferred	• NDD patients: IV iron may be superior but more research is needed
Transfusion	• Consider its use when ESA is ineffective or in patients with high potential for ESA risks	• Agreement with KDIGO recommendations

to ESA therapy and the presence of symptoms attributable to anemia.

DD = dialysis dependent; ESA = erythropoietin stimulating agent; Hb = hemoglobin; IV = intravenous; KDIGO = Kidney Disease: Improving Global Outcomes; NDD = non-dialysis dependent; NKF-KDOQI = National Kidney Foundation–Kidney Disease Outcomes Quality Initiative; TSAT = transferrin saturation.

1. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. *Kidney Int Suppl.* 2012;2:279-335. http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-Anemia%20GL.pdf. Accessed October 13, 2018. 2. Kliger AS et al. *Am J Kidney Dis.* 2013;62:849-859.

Temporal Changes in Hgb Levels and EPO-alfa Doses among Adult HD patients on dialysis ≥90 days



Vol 2 Figure 2.2

Mean Monthly Hgb level and Mean weekly EPO-α dose (averaged over a month), Medicare claims, 1995-2015

Data Source: Special analyses, USRDS ESRD Database.

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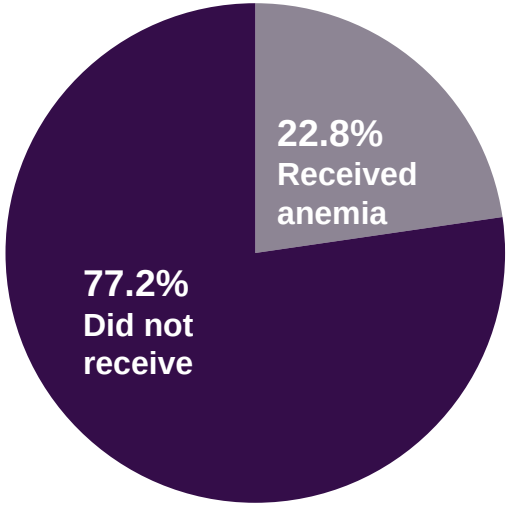
CKD-related anemia remains untreated in most

Proportion of patients with CKD anemia, predominately NDD, who reported treatment for anemia within the previous 3 months[1,a]

Cross-sectional analysis of patients with CKD >18 years of age from NHANES in 2007–2010; 410/2125 CKD patients had anemia



Decision to initiate treatment requires complex considerations including:[2]

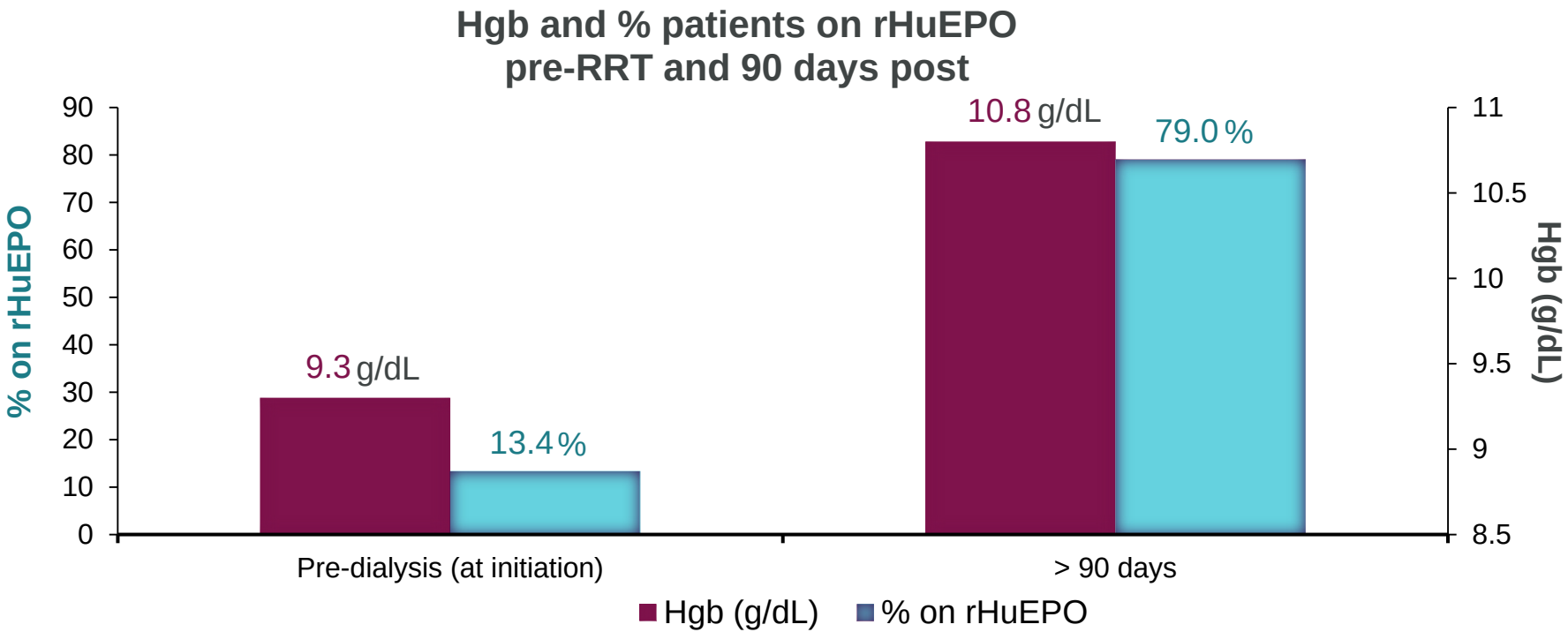
- Presence and severity of anemia symptoms
- Rate of Hb decline
- Risks versus benefits of treatment
- Patient tolerance and adherence
- Cost

[a]Survey weighted to the US Population; Anemia was defined as serum hemoglobin ≤12 g/dL in women and ≤13 g/dL in men and stages of CKD were defined in accordance with the recommendations of the National Kidney Foundation.

CKD = chronic kidney disease; Hb = hemoglobin; NDD = non-dialysis dependent; NHANES = National Health and Nutrition Examination Survey.

1. Stauffer ME et al. *PLoS One*. 2014; 2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. *Kidney Int Suppl*. 2012;2:283-287. https://dx.doi.org/10.1038/kisup.2012.41. Accessed November 1, 2018.

Anemia Management in the US (USRDS 2018): HD Only

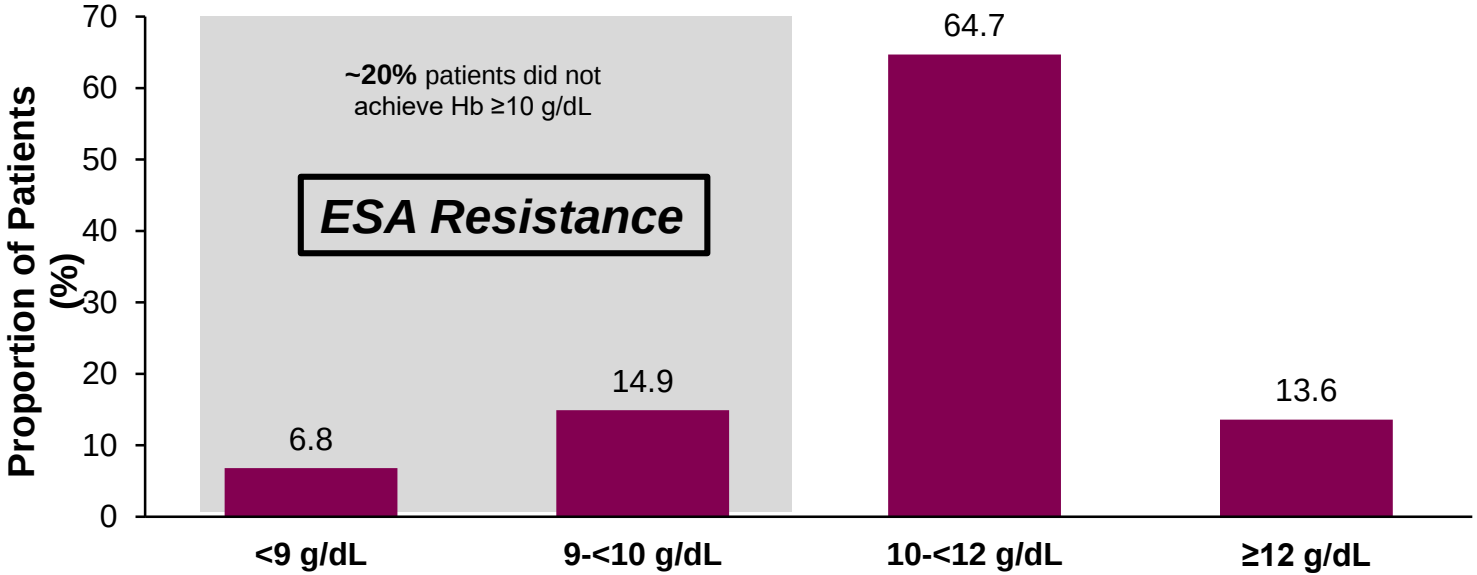


USRDS 2018, Ch 1 & 2.

Patients with CKD anemia remain a clinical challenge even in the ESRD arena

Distribution of Hb levels among CKD patients on HD

Data from CROWNWeb, May 2016; USRDS 2017 Annual Report



CKD = chronic kidney disease; CROWNWeb = Consolidated Renal Operations in a Web-Enabled Network; Hb = hemoglobin; HD = hemodialysis; USRDS = United States Renal Data System.

United States Renal Data System. 2017 Annual Data Report. https://www.usrds.org/2017/download/v2_c02_ClinCare_17.pdf. Accessed September 21, 2018.

Inflammation increases as renal function declines

Plasma levels of inflammatory biomarkers and acute phase proteins according to eGFR

Data from the Chronic Renal Insufficiency Cohort study between June 2003 and September 2008 (N=3939)

Biomarker (median, IQR)	eGFR (ml/min per 1.73 m^2)					p-value[a]
	>60 (n=412)	50-59 (n=754)	40-79 (n=1042)	30-39 (n=967)	<30 (n=764)	
Acute Phase Protein						
hs-CRP (mg/L)	1.9 (0.9, 4.2)	2.5 (1.0, 6.8)	2.7 (1.1, 6.0)	2.8 (1.2, 7.1)	2.8 (1.1, 7.1)	<0.001
Fibrinogen (g/L)	3.5 (3.0, 4.1)	3.9 (3.3, 4.5)	4.0 (3.4, 4.7)	4.2 (3.5, 5.0)	4.5 (3.8, 5.4)	<0.001
Albumin (g/dL)	4.1 (3.8, 4.3)	4.0 (3.8, 4.3)	4.0 (3.7, 4.2)	3.9 (3.6, 4.2)	3.9 (3.6, 4.2)	<0.001
Cytokines						
IL-1β (pg/mL)	0 (0, 0.7)	0 (0, 0.9)	0.2 (0, 1.3)	0.3 (0, 1.4)	0.4 (0, 2.0)	<0.001
IL-1RA (pg/mL)	605.3 (312.6, 1262.8)	636.6 (350.3, 1340.3)	698.7 (389.6, 1529.8)	805.9 (448.8, 1642.6)	850.5 (426.6, 1771.6)	<0.001
IL-6 (pg/mL)	1.2 (0.7, 2.1)	1.6 (1.0, 2.6)	1.8 (1.2, 2.9)	2.2 (1.3, 3.5)	2.4 (1.5, 3.9)	<0.001
TNF-α (pg/mL)	1.4 (1.0, 2.1)	1.7 (1.2, 2.6)	2.1 (1.5, 2.9)	2.5 (1.8, 3.5)	3.0 (2.2, 4.1)	<0.001
TGF-β (pg/mL)	11.3 (6.3, 19.4)	10.1 (5.8, 16.6)	11.4 (6.8, 18.2)	11.2 (6.9, 18.1)	10.6 (6.4, 17.5)	0.01

[a]p-values <0.001 were significant after Bonferroni correction for multiple comparisons.

IL-6 = interleukin-6; IL-β = interleukin-1β; IL-1RA = interleukin-1 receptor antagonist; eGFR = estimated glomerular filtration rate; hs-CRP =high-sensitivity C-reactive protein; IQR = interquartile range; TGF = transforming growth factor; TNF = tumor necrosis factor.

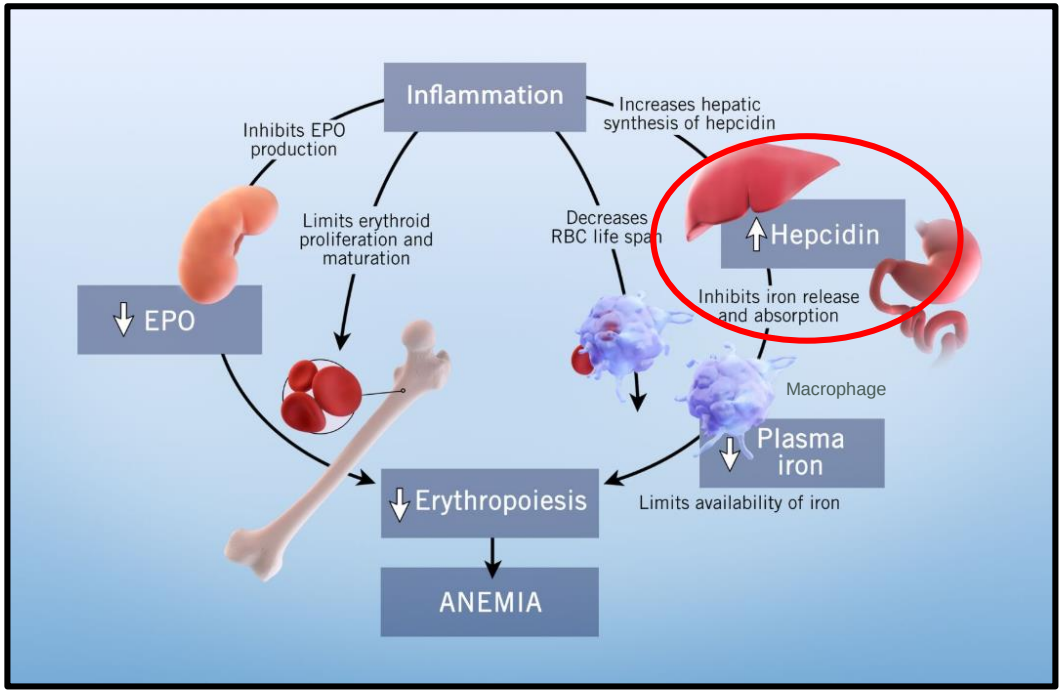
Gupta J et al. *Clin J Am Soc Nephrol*. 2012;7:1938-1946.

Inflammation suppresses erythropoiesis via multiple mechanisms

CHRONIC INFLAMMATION

Elevated inflammatory Cytokines[1]

- Suppresses endogenous erythropoietin production[1,2]
- Impairs proliferation and differentiation of erythroid progenitors[1]
- Decreases lifespan of RBC[1]
- **Increases hepcidin levels leading to reduced iron availability[1]**



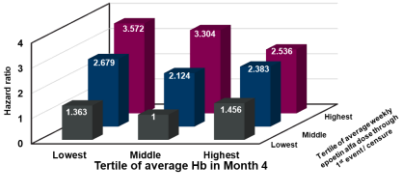
RBC = red blood cell.

1. Brugnara C et al. Hematologic aspects of kidney disease. 2016: 1875-1911; 2. Faquin et al. *Blood.* 1992;79:1987-94 .

ESA Resistance: unresponsive

Definition of ESA Resistance:

- Inability to achieve or maintain a desired Hb concentration using a maximum dose of 450 units/kg per week IV ESA or 300 units/kg per week SQ ESA[1]
- 2 consecutive hemoglobin measurements, 10 g/dL (every other week) with contemporaneous ESA dose > 7,700 U/treatment [2]
- Affects ~12-20% of the dialysis-dependent CKD population (ESRD) [2-3]
- **Characterized by higher CRP, Hepcidin, Ferritin, and PTH levels and IV Iron use** [2,5,6]
- **ESA resistance is associated with increased mortality** [2-8]



1 Administration of epoetin. NKF-DOQI Clinical Practice Guidelines for Anemia of Chronic Renal Failure. Am J Kidney Dis. 2001; 37 (Suppl 1):S207.
2 Luo J, Jensen DE, Maroni B, Brunelli SM. Spectrum and Burden of Erythropoiesis-Stimulating Agent Hyporesponsiveness among Contemporary Hemodialysis Patients. Am J Kidney Dis 2016; 68: 763-771
3 United States Renal Data System. 2017 Annual Data Report; Data from CROWNWeb, May 2016
4 Bradbury BD et al. Impact of elevated C-reactive protein levels on ESA dose and responsiveness. NDT 2009; 24:919-925.
5 Szczech LA, Barnhart HX, Inrig JK et al. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. Kidney Int. 2008;74(6):791.
6 Petrulienė Pet a. Hepcidin serum levels and resistance to recombinant human erythropoietin therapy in hemodialysis patients. Medinina 2017; 53: 90-100
7 Bradbury BD et al. Effect of Epoetin alfa dose changes on Hb and mortality in hemodialysis patients with Hb levels persistently below 11 g/dL. Clin J Am Soc Nephrol. 2009;4(3):630-637.
8 Kilpatrick RD, Critchlow CW, Fishbane S et al. Greater epoetin alfa responsiveness is associated with improved survival in hemodialysis patients. Clin J Am Soc Nephrol. 2008;3(4):1077-1083.

Rethinking CKD Anemia

CKD anemia is a serious disease that is associated with morbidity, mortality and reduced QoL

- Anemia is a common and anticipated consequence of CKD[1,2]
- CKD anemia is an independent risk factor associated with increased mortality and risk of CV events[3,4]
- Anemia is associated with fatigue and lower HRQoL[5]

Exogenous replacement therapies are an incomplete solution for erythropoiesis and have serious CV risk

- Replacing endogenous erythropoietin with ESAs was a medical innovation over transfusion that helped many patients with CKD anemia[6]
- Today, CV risks of ESAs prevent many patients with CKD anemia from being treated adequately with ESAs[6]
- Oral iron has been associated with poor tolerability; IV iron has been associated with increased risk of CV events and infection[6-9]

CKD anemia is more than an erythropoietin and iron deficiency

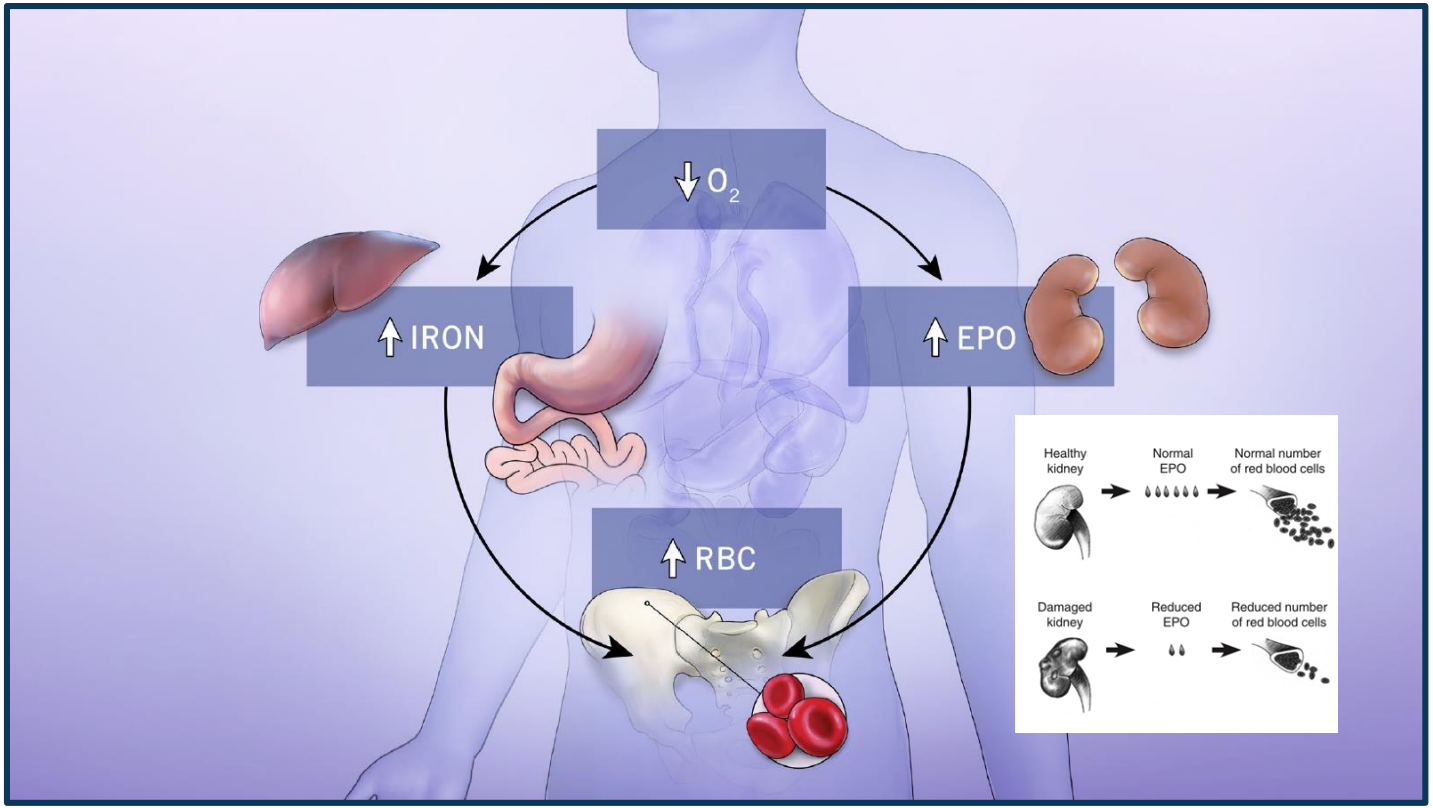
- Potential contributing causes of CKD anemia include progressive inflammation* associated with advancing CKD[10]
- Increased hepcidin levels, impaired GI iron absorption & mobilization of existing iron stores (Fe Dysmetabolism)[10,11]

1. Li Y et al. *Medicine.* 2016; http://dx.doi.org/10.1097/MD.0000000000003872. Accessed October 31, 2018; 2. Stauffer M et al. *PLoS One.* 2014. http://dx.doi.org/10.1371/journal.pone.0084943. Accessed September 25, 2018; 3. Collins AJ. *Adv Stud Med*. 2003;3:S194-S197; 4 Thorp ML et al. *Nephrology.* 2009;14:240–246; 5. Eriksson D et al. Cross-sectional survey in CKD patients across Europe describing the association between quality of life and anemia. BMC Nephrol 2016; 17: 1-10 6. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. *Kidney Int Suppl.* 2012;2:279-335; http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-Anemia%20GL.pdf. Accessed October 31, 2018; 7. Cancelo-Hidalgo et al. *Curr Med Res Opin.* 2013;29:291-303; 8. Bailie GR et al. *Kidney Int.* 2015;87:162-168; 9. Litton E et al. BMJ. 2013. http://dx.doi.org/10.1136/bmj.f4822. Accessed November 12, 2018; 10. Gupta J et al. Inflammation and progression of CKD: the CRIC study. Clin J Am Soc Nephrol. 2012;7:1938-1946. 11. Brugnara C et al. Hematologic aspects of kidney disease. 2016: 1875-1911. 12. Petrulienė Pet a. Hepcidin serum levels and resistance to recombinant human erythropoietin therapy in hemodialysis patients. Medinina 2017; 53: 90-100

Innovations in the Treatment of CKD-Related Anemia: Directed at Improving Patient-Centered Outcomes

- Historical Background: Anemia of CKD
- Current Landscape of CKD-related Anemia Management in the US and Globally
- **Discovery and Innovation: the HIF Pathway**

Normal regulation of erythropoiesis

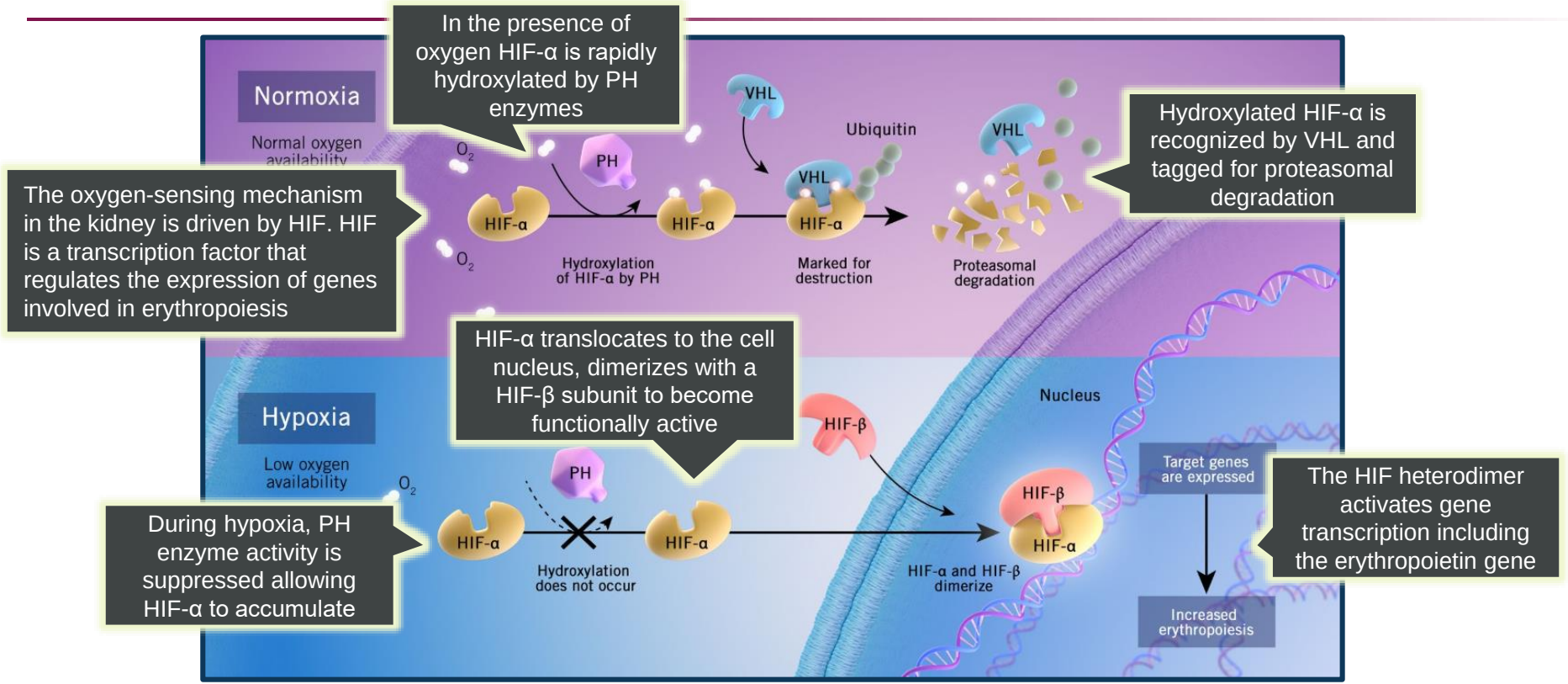


EPO = erythropoietin; RBC = red blood cell.

Koury M et al. *Nat Rev Nephrol.* 2015;11:394–410.

NIH Publication No. 14–4619 May 2014

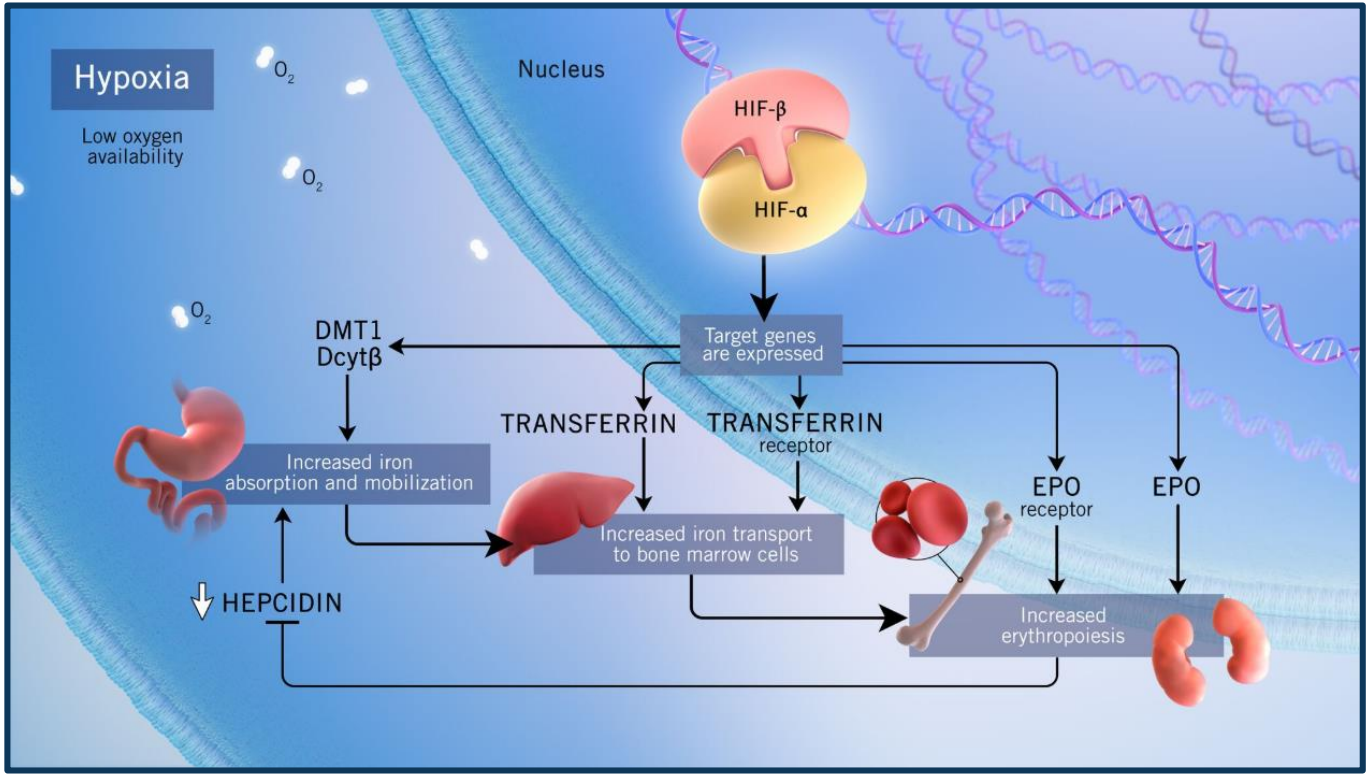
Physiologic erythropoietin production is regulated by the HIF pathway



HIF = hypoxia inducible factor; PH = prolyl-hydroxylase; VHL = von Hippel-Lindau protein.

Haase VH. *Blood Rev*. 2013;27:41-53.

Transient activation of the HIF pathway mediates a cascade of factors favorable to enhanced erythropoietic activity

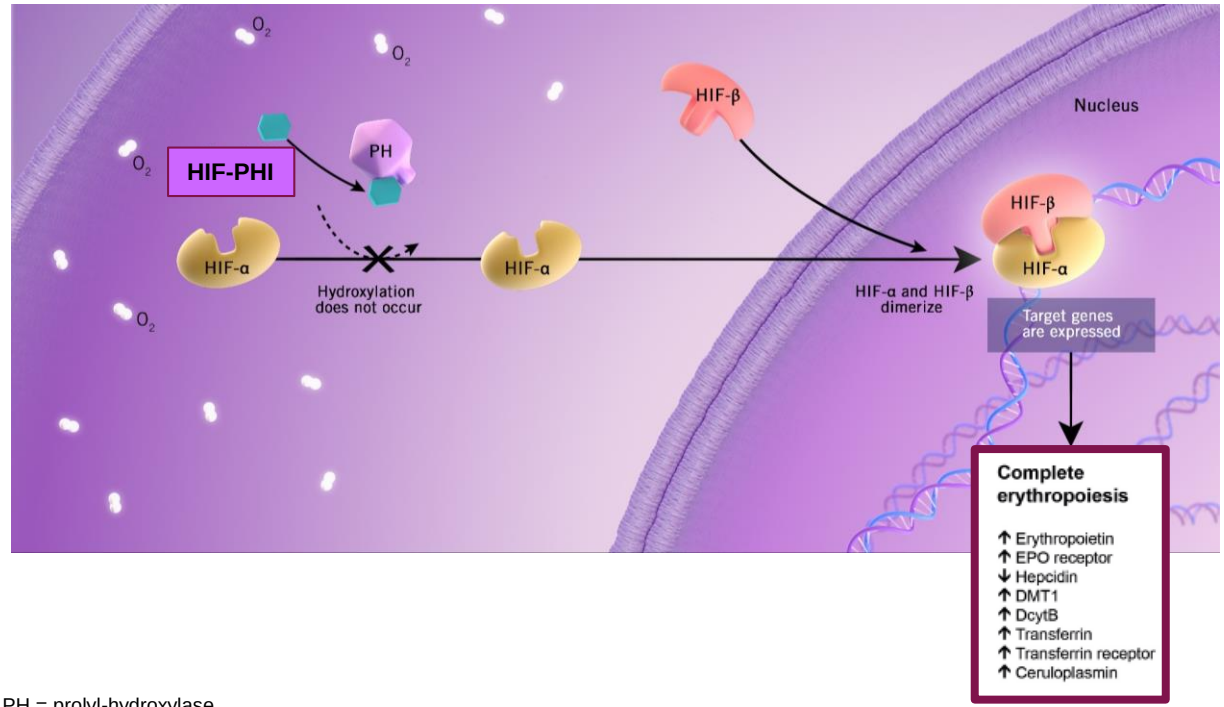


DMT1 = divalent metal transporter-1; DYCTβ = duodenal cytochrome β reductas; EPO = erythropoietin; HIF = hypoxia-inducible factor; PH = prolyl-hydroxylase.

1. Dev S et al. *Hemodial Int.* 2017;21(Suppl 1):S6-S20; 2. Koury MJ et al. *Nat Rev Nephrol*. 2015;11:394-410; 3. Coyne DW et al. *Kidney Int Suppl.* 2017;7:157-163.

Development of Inhibitors of HIF-prolyl hydroxylases (PH) to treat CKD-related anemia

- Oral agents that induce **rapid and reversible activation of HIF-α and elevate erythropoietin levels**



CKD = chronic kidney disease; HIF = hypoxia inducible factor; PH = prolyl-hydroxylase.

Gupta N, Wish JB. Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors: a Potential New Treatment for Anemia in Patients with CKD. Am J Kidney Dis 2017; 69: 815-826.

Hypoxia-Inducible Factor (HIF) Prolyl Hydroxylase Inhibitors

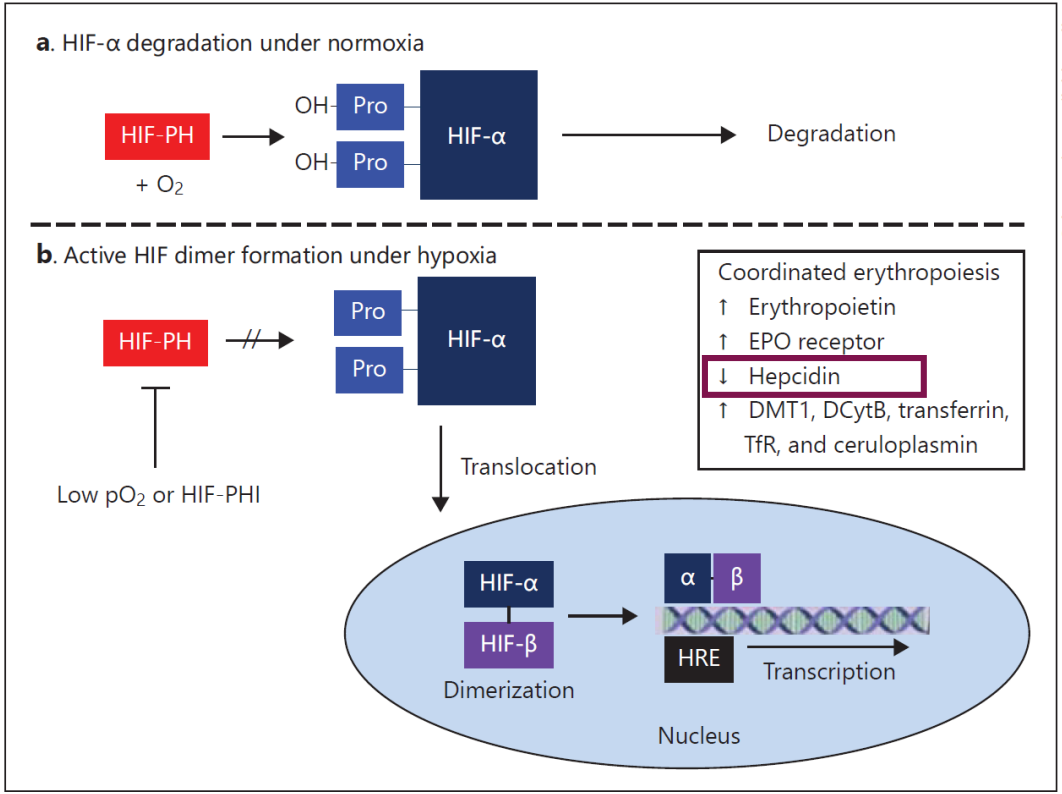
Table 1. Characteristics of HIF-PH Inhibitors Under Development

Generic Name	Investigational Name	Sponsor	Half-Life, h	Dosing Frequency	Investigational Status
Roxadustat	FG-4592	FibroGen, Astellas, & AstraZeneca	12-13	3×/wk	Phase 3
Vadadustat	AKB-6548	Akebia	4.5	Daily	Phase 3
Daprodustat	GSK-1278863	GlaxoSmithKline	4	Daily	Phase 2 (US) Phase 3 (Japan)
Molidustat	BAY 85-3934	Bayer	NA	Daily	Phase 2

Abbreviations: HIF-PH, hypoxia-inducible factor prolyl hydroxylase; NA, not available (data not published).

Gupta N, Wish JB. Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors: a Potential New Treatment for Anemia in Patients with CKD. Am J Kidney Dis 2017; 69: 815-826.

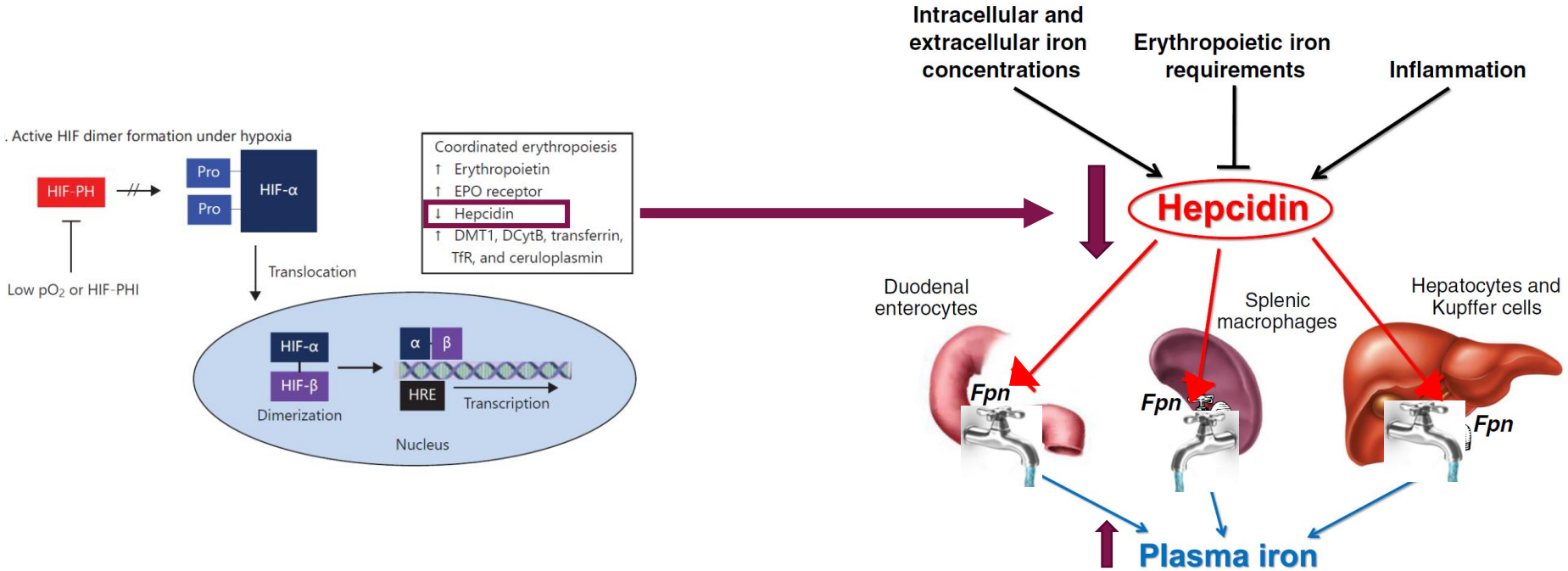
Hypoxia-Inducible Factor (HIF) Prolyl Hydroxylase Inhibitors: *Mechanism of Action*



DCytB = duodenal cytochrome B
DMT1 = Divalent metal transporter
HIF-PH, hypoxia-inducible factor-prolyl-4-hydroxylase domain
Pro = proline.

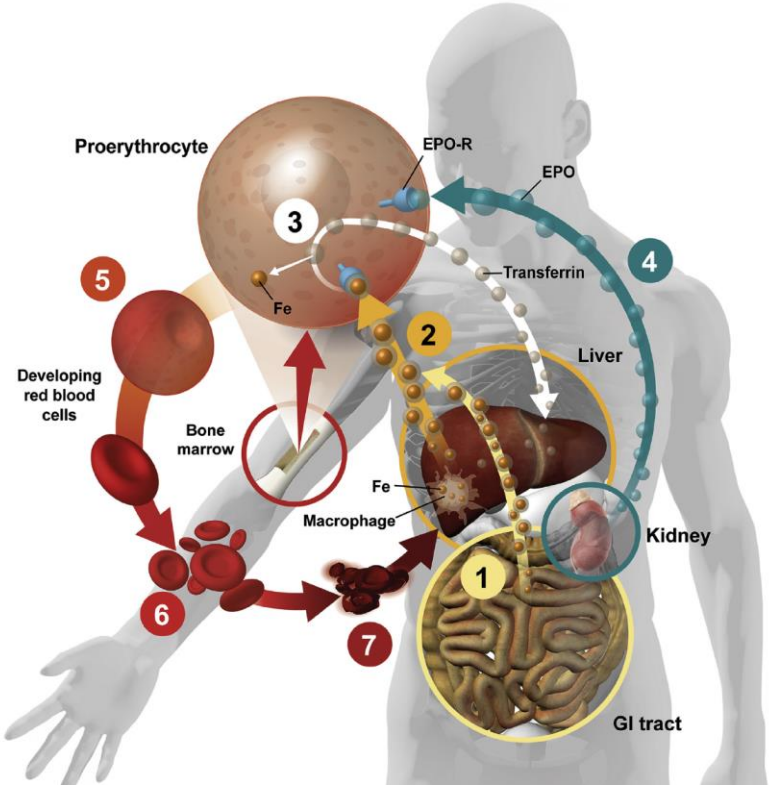
Locatelli F, Fishbane S, Block GA, Macdougall IC. Targeting Hypoxia-Inducible Factors for the Treatment of Anemia in Chronic Kidney Disease Patients. Am J Nephrol 2017;45:187–199.

Hypoxia-Inducible Factor (HIF) Prolyl Hydroxylase Inhibitors: *Mechanism of Action*



Ganz T, Nemeth E. Hepcidin and iron homeostasis. Biochimica et Biophysica Acta 2012; 1823: 1434–1443

Hypoxia-Inducible Factor (HIF) *Prolyl Hydroxylase Inhibitors: Mechanism of Action*

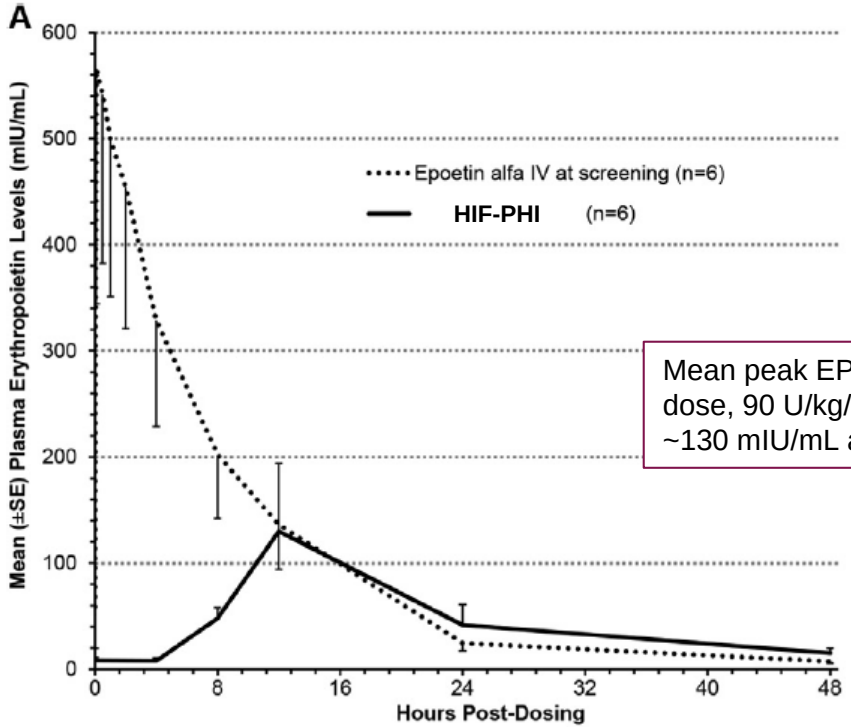


Erythropoietic Effects:

- **Upregulated DMT1 and Dcytβ: ↑GI Fe**
- **Upregulated Transferrin and TfR: ↑ Fe Transport to BM**
- **Indirectly inhibits Hepcidin: ↑ Ferroportin & RES Fe release**
- **Upregulated endogenous EPO and EPO-R**
- **Promotes RBC maturation**

Gupta N, Wish JB. Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors: a Potential New Treatment for Anemia in Patients with CKD. Am J Kidney Dis 2017; 69: 815-826.

Endogenous EPO levels 0 to 48 hours following exogenous administration of epoetin alfa vs HIF-PHI treatment within the same participants



Mean peak EPO levels in participants receiving epoetin alfa (median dose, 90 U/kg/wk) were ~700 mIU/mL compared to a peak of levels of ~130 mIU/mL at 12 hrs in participants receiving a mean HIF-PHI dose.

Provenzano R et al. Am J Kidney Dis. 67(6):912-924.

Innovations in the Treatment of CKD-Related Anemia: Directed at Improving Patient-Centered Outcomes

Summary and Conclusions

- Anemia is a common and anticipated consequence of CKD
  - Independent risk factor associated with increased mortality and risk of CV events
  - Systemic literature review demonstrated untreated CKD-related anemia is associated with reduced Qol and increased HRUs
- ESAs were a medical breakthrough in the management of CKD anemia, but are an incomplete solution and have serious CV risk
- Advances in understanding of the physiology and pathophysiology of CKD-related anemia have occurred in the past decade, specifically the central role of HIF in providing a coordinated erythropoietic response
- Development of HIF-PHIs, many in or having completed Phase III trials, offer the potential to improve patient-centered outcomes in CKD

Thank You!

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& Health Sciences
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