Use of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors for the Treatment of Anemia in Chronic Kidney Disease: What HIF?

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Pharmacist Learning Objectives

1. Identify the place in therapy of erythropoiesis-stimulating agents (ESA) for the treatment of anemia of chronic kidney disease (CKD) in patients undergoing hemodialysis (HD)
2. Recognize the black box warning associated with erythropoiesis-stimulating agents (ESA)
3. Describe the effects of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI) on erythropoietin, hepcidin, and iron
4. Summarize current literature comparing the use of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI) to erythropoiesis-stimulating agents (ESA) for the treatment of anemia of chronic kidney disease (CKD) in patients undergoing hemodialysis (HD)
5. Given a patient case, select an appropriate treatment regimen for a patient with anemia of chronic kidney disease (CKD) undergoing hemodialysis (HD)

Pharmacy Technician Learning Objectives

1. Recognize two generic erythropoiesis-stimulating agents (ESA)
2. Recognize the black box warning associated with erythropoiesis-stimulating agents (ESA)
3. Recall the randomized controlled trial that evaluated the use of daprodustat in patients with anemia of chronic kidney disease (CKD) undergoing dialysis
4. Given a patient case, recognize the benefits of using hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) for the treatment of anemia of chronic kidney disease (CKD) in patients undergoing hemodialysis (HD)

Abbreviations

Abbreviation	Meaning	Abbreviation	Meaning
ACR	Albumin to Creatinine Ratio	**KDIGO**	Kidney Disease Improving Global Outcomes
BUN	Blood Urea Nitrogen	**LVH**	Left Ventricular Hypertrophy
CHF	Congestive Heart Failure	**MBD**	Mineral and Bone Disorder
CI	Confidence Interval	**MI**	Myocardial Infarction
CKD	Chronic Kidney Disease	**ND**	Non-Dialysis
CVA	Cerebrovascular Accident; Stroke	**NYHA**	New York Heart Association
DD-CKD	Dialysis-Dependent CKD	**PD**	Peritoneal Dialysis
DILI	Drug-Induced Liver Injury	**PHD**	Prolyl Hydroxylase Domain; Prolyl Hydroxylase Enzyme
DM	Diabetes Mellitus	**PO**	By Mouth; Oral
EPO	Erythropoietin (endogenous)	**PRCA**	Pure Red Cell Aplasia
ESA	Erythropoiesis Stimulating Agent	**QoL**	Quality of Life
ESRD	End Stage Renal Disease	**RBC**	Red Blood Cell
GERD	Gastroesophageal Reflux Disease	**RCT**	Randomized Controlled Trial
GFR	Glomerular Filtration Rate	**RR**	Risk Ratio
GIB	Gastrointestinal Bleed	**RRT**	Renal Replacement Therapy
HD	Hemodialysis	**SMD**	Standardized Mean Difference
HF	Heart Failure	**SubQ**	Subcutaneous
Hgb	Hemoglobin	**T2DM**	Type 2 Diabetes Mellitus
HIF-PHI	Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor	**TEAE**	Treatment-Emergent Adverse Event
HR	Hazard Ratio	**TIBC**	Total Iron Binding Capacity
HTN	Hypertension	**TIW**	Three times weekly
IDA	Iron Deficiency Anemia	**TSAT**	Transferrin Saturation
IV	Intravenous	**VTE**	Venous Thromboembolism

Introduction: Chronic Kidney Disease (CKD)[1-2]

- Longstanding, progressive deterioration of kidney function[1-2]
  - Renal dysfunction (structural or functional abnormalities) must be present for ≥3 months to be considered chronic
  - Classified based on glomerular filtration rate (GFR); albuminuria due to CKD is further classified by the albumin to creatinine ratio (ACR)

Stage	GFR (mL/min/1.73 m^2)
G1	≥90
G2	60-90
G3a	45-60
G3b	30-44
G4	15-29
G5	<15

Table 1: CKD Classification by GFR

Category	Albumin to creatinine ratio (mg/g)
A1	<30
A2	30-300
A3	>300

Table 2: Albuminuria Classification by ACR

- Dialysis (i.e., hemodialysis, peritoneal dialysis) usually initiated when[1]
  - Patient has uremic symptoms (nausea, vomiting, pericarditis, etc.)
  - There is difficulty controlling fluid overload, electrolyte imbalances (e.g., hyperkalemia) or acidosis with current lifestyle and medication interventions
- Etiology[1,3]
  - Diabetic nephropathy and hypertensive nephrosclerosis are the most frequent causes
  - Glomerulonephritis
  - Urinary tract obstructions, nephrolithiasis
  - Recurrent kidney infections
- Epidemiology[1,4-5]
  - Approximately 14.9% of people in the United States have CKD as of 2018
  - Minority populations have a higher risk of development due to prevalence of diabetes mellitus and hypertension

Population at Risk	Statistics
Black or African American	35% of people with CKD in the United States 11-13% diagnosed with diabetes mellitus (DM) 6x more likely to get CKD from hypertension (HTN) than white Americans 4x as likely to develop renal failure as white Americans
Hispanic or Latino	Number of people with CKD increased by >70% since 2000 12-13% diagnosed with DM; 25% aged ≥45 years diagnosed with DM 22.5% diagnosed with HTN 1.3x more likely to be diagnosed with CKD than white Americans
Asian American	19% diagnosed with HTN
American Indian	14.7% diagnosed with DM; 30% diagnosed with HTN 2x more likely to have DM (and die from DM) compared to white Americans 1.2x more likely to be diagnosed with CKD compared to white Americans
Alaska Native	
Hawaiian Native	6x more likely to die from diabetes compared to white Americans
Other Pacific Islander	19% diagnosed with HTN

Table 3: Minority Populations and Complications Associated with Diabetes Mellitus, Hypertension, and Chronic Kidney Disease

- Morbidity and Mortality[6]
  - Responsible for 1.2 million deaths worldwide in 2017 (12th leading cause of death)
  - 35.8 million disability-adjusted life years in 2017

Anemia of Chronic Kidney Disease[7-9]

- "Most common complication of CKD"
- Hemoglobin (Hgb) less than 13 g/dL in men, or less than 12 g/dL in women

Anemia of Chronic Disease[7]

Decline in renal function → Decreased erythropoietin (EPO) production → Decreased production of RBCs

- Red blood cells (RBCs) are same size (normocytic) and with normal color (normochromic)
- Red blood cells are underproduced by the bone marrow due to **decreased EPO** (hypoproliferative)
- Starts to develop when GFR < 60 mL/min/1.73 m^2; as renal function declines, anemia worsens

Iron Deficiency Anemia[7-9]

- Patients with CKD suffer from both absolute and functional iron deficiency anemia (IDA)
- Absolute – reduced or absent iron stores in bone marrow, liver, and spleen
    - Loss of blood during hemodialysis
    - Impaired dietary iron absorption
    - Gastrointestinal bleeding (GIB)
- Functional – normal iron stores, however iron is being used elsewhere and is unavailable for erythropoiesis
    - **Hepcidin** – Peptide hormone produced by liver that regulates iron absorption and metabolism
        - Regulated by iron stores, hypoxia, **inflammation**, and erythropoiesis
        - Renally eliminated → accumulates in renal dysfunction
    - Ferroportin – transport protein responsible for uptake of iron
        - Found in enterocytes – iron absorption in the duodenum and proximal jejunum
        - Found in reticuloendothelial cells (e.g., macrophages) – iron absorption from senescent RBCs and recycling for new RBCs
        - Bound and degraded by hepcidin → **decreased iron absorption**

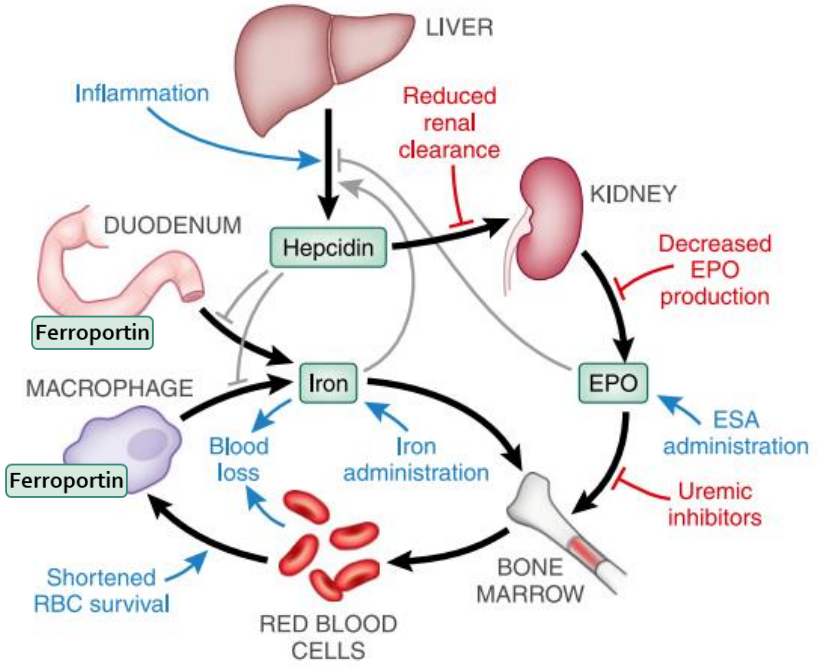


Figure 1: Pathophysiology of Anemia of CKD

Outcomes of Anemia of CKD[8-11]

Reduced Quality of Life (QoL)	Development of Left Ventricular Hypertrophy	Increased risk of adverse renal and cardiovascular outcomes	Increased mortality

Guideline Recommendations for the Treatment of Anemia of Chronic Kidney Disease[12-14]

Definition of Anemia[12-14] (*Table 4)*

	2012 Kidney Disease Improving Global Outcomes (KDIGO)	2015 Japanese Society for Dialysis Therapy: Guidelines for Renal Anemia in CKD	2021 National Institute for Health and Care Excellence (NICE) Guidelines on Chronic Kidney Disease: Assessment and Management
Hemoglobin	Male: <13 g/dL Female: <12 g/dL	Male: Age <60: <13.5 g/dL Age 60-69: <12.0 g/dL Age ≥70: <11.0 g/dL Female: Age <60: <11.5 g/dL Age 60-69: <10.5 g/dL Age ≥70: <10.5 g/dL	Adult, children, young people: <11 g/dL Less than 2 years old: <10.5 g/dL

Iron Evaluation and Administration[12-14] *(Table 5)*

	2012 Kidney Disease Improving Global Outcomes (KDIGO)	2015 Japanese Society for Dialysis Therapy: Guidelines for Renal Anemia in CKD	2021 National Institute for Health and Care Excellence (NICE) Guidelines on Chronic Kidney Disease: Assessment and Management
Not on Iron or ESA	- Hemodialysis (HD): IV iron - Non-dialysis (ND): 1-3 months PO iron if both: a) Desire to increase Hgb without starting ESA b) TSAT ≤30%, ferritin ≤500 ng/mL	- Iron therapy prior to ESA therapy if ferritin level <50 ng/mL - HD: IV iron - ND, PD: PO iron	- HD: Trial IV iron; offer PO iron if IV is contraindicated or personal choice - ND: Trial PO iron prior to IV iron; offer IV iron if after 3 months goal Hgb levels are not reached
On ESA but not Iron	- HD: IV iron - ND: 1-3 months PO iron if both: a) Desire to increase Hgb or decrease in ESA dose b) TSAT ≤30%, ferritin ≤500 ng/mL	- Iron therapy for those on ESA and cannot maintain Hgb level, when ferritin <100 ng/mL and TSAT <20% - Do not administer iron that targets serum ferritin ≥300 ng/mL	- Offer IV iron regardless of dialysis status - Reserve PO iron for those with contraindications to IV iron, or personal choice
Evaluation	- TSAT, ferritin at baseline and every 3 months during ESA therapy* - More frequent monitoring when: a) Initiating or increasing ESA dose (e.g., weekly) b) Blood loss c) Monitoring response after IV iron d) Other situations of iron store depletion	- TSAT, ferritin for iron indices - At least monthly on iron - At least every 3 months while not on iron	- TSAT, ferritin for iron indices - No earlier than 1 week after IV iron - HD: Every 1-3 months - ND: Every 3 months Maximum iron levels in anemia of CKD: - Ferritin should not be >800 ng/mL; review when ~500 ng/mL

*Iron deficiency: TSAT ≤20% and ferritin ≤100 ng/mL (ND, PD) or ≤200 ng/mL (HD)

Erythropoiesis Stimulating Agent Evaluation and Administration[12-14] (*Table 6*)

	2012 Kidney Disease Improving Global Outcomes (KDIGO)	2015 Japanese Society for Dialysis Therapy: Guidelines for Renal Anemia in CKD	2021 National Institute for Health and Care Excellence (NICE) Guidelines on Chronic Kidney Disease: Assessment and Management
Initiation	- HD: Hgb 9-10 g/dL*; may use to avoid Hgb falling below 9 g/dL - ND: Hgb <10 g/dL and assessed: a) Rate of fall of Hgb, symptoms of anemia b) Prior response to iron therapy c) Risk of needing transfusion, ESA administration *May be started in patients with Hgb ≥10 g/dL as some have improvements in quality of life at higher concentrations (Not graded)	- HD: Hgb <10 g/dL - ND, PD: Hgb <11 g/dL	- Hgb <11 g/dL, regardless of dialysis status
Maintenance	- Do NOT maintain Hgb above 11.5 g/dL - Do NOT intentionally increase Hgb ≥13 g/dL	- HD: 10-12 g/dL - ND, PD: 11-13 g/dL* *If ND patient has previous history of CVD or other complication, reduce dose and/or discontinue ESA when Hgb >12 g/dL	- Between 10-12 g/dL - Keep rate of Hgb increase between 1-2 g/dL per month - Monitor every 2-4 weeks during ESA induction, then every 1-3 months for maintenance - AVOID Hgb >12 g/dL due to risk of death and serious adverse CV events
Administration	- HD: IV or subcutaneous (SubQ) - ND, peritoneal dialysis (PD): SubQ preferred	- HD: IV - ND, PD: SubQ	- Consider the following: a) patient population (HD vs ND, PD) b) Pain of injection, frequency of administration c) Patient lifestyle and preferences, cost d) Efficacy (SubQ vs IV, short-acting vs long-acting)
Hypo-responsiveness	- Do not go beyond double the original ESA dose - Treat specific causes of poor response (iron stores, blood loss, etc.)	- Patient is more likely to have poor prognosis - Weigh ESA side effects: hypertension, thromboembolism, pure red cell aplasia (PRCA)	- Treat specific/other causes of anemia (intercurrent illness, chronic blood loss, PRCA) - Considered resistant if Hgb range not achieved despite large doses of IV or SubQ ESA, or continued need to administering high doses of ESAs

Complications of Red Blood Cell Transfusions[15]

Transfusion-associated infections	Iron overload	Allosensitization •Building antibodies to attack future RBCs	Febrile non-hemolytic reactions	**Kidney transplant rejection**

Erythropoiesis Stimulating Agents: Pharmacotherapy[16-21]

- Recombinant versions of EPO that stimulate production of red blood cells in the bone marrow

- Efficacy
  - Reduces the need for blood transfusions
  - Improves symptoms of fatigue

Name	Epoetin alfa (Epogen, Procrit, Retacrit)		
Indications	Anemia secondary to CKD Chemotherapy-induced anemia Antiretroviral-induced anemia (zidovudine)	**Adverse Effects**	Edema, hypertension, diarrhea, injection site thrombosis, pruritus, myalgia, fatigue, seizures Rare: pure red cell aplasia
Dose (Anemia of CKD)	- Dialysis: **50-100 units/kg IV 3 times a week** - Non-dialysis: 50-100 units/kg IV or SubQ once weekly, or 10,000-20,000 units IV or SubQ every other week	**Black Box Warning**	Increased risk of myocardial infarction (MI), stroke (CVA), venous thromboembolism (VTE), and mortality when targeting Hgb >11 g/dL Increased risk of cancer recurrence
Monitoring	- Baseline Hgb and weekly - Initiate when Hgb <10 g/dL - Reduce dose or halt therapy if Hgb approaches/exceeds 11 g/dL (dialysis) or 10 g/dL (ND); Hgb should raise no faster than 1 g/dL every 2 weeks - Iron: TSAT >20% and ferritin >100 ng/mL for adequate iron stores	**Pearls**	- In ND patients, consider only using if Hgb decline would result in RBC transfusion - Administer iron if low stores or patient is ESA hyporesponsive
Elimination	Renal (minimal): **$T_{1/2}$ = 3-14 hr in CKD** Metabolized by hepatic galactose receptors		

Table 7: Epoetin alfa Drug Information

Name	Darbepoetin (Aranesp)		
Indications	Anemia secondary to CKD Chemotherapy-induced anemia	**Adverse Effects**	Cough, dyspnea, edema, hypertension, diarrhea, injection site thrombosis, myalgia, fatigue, seizures Rare: pure red cell aplasia
Dose (Anemia of CKD)	- Dialysis: **0.45 mcg/kg IV or SubQ once weekly** or 0.75 mcg/kg every 2 weeks - ND: 0.45 mcg/kg IV or SubQ once every 4 weeks	**Black Box Warning**	Increased risk of MI, CVA, VTE, and mortality Increased risk of cancer recurrence
Monitoring	- Baseline Hgb and weekly - Initiate when Hgb <10 g/dL - Reduce dose or halt therapy when Hgb approaches/exceeds 11 g/dL (dialysis) or 10 g/dL (ND); Hgb should raise no faster than 1 g/dL every 2 weeks - Iron: TSAT >20% and ferritin >100 ng/mL for adequate iron stores	**Pearls**	- If desired response is not achieved at 12 weeks despite dose titrations, further dose increases will likely not be beneficial - Administer iron if low stores or patient is ESA hyporesponsive
Elimination	Renal (minimal): **$T_{1/2}$ = 46 hr** Metabolized by hepatic galactose receptors		

Table 8: Darbepoetin Drug Information

Landmark Studies Evaluating ESAs[19-21] (*Table 9*)

Trial	CHOIR	TREAT
Agent	Epoetin alfa, high Hgb goal 13.5 g/dL, low Hgb goal 11.3 g/dL	Darbepoetin, Hgb goal 13 g/dL
Population	N=1432 Patients with CKD	N=4038 Patients with T2DM, CKD, and anemia
eGFR	15-50 mL/min/1.73 m^2	20-60 mL/min/1.73 m^2
Baseline Hgb	<11 g/dL	≤11 g/dL
Median follow-up	16 months	29.1 months
Primary Outcomes	- **Composite** of death, MI, hospitalization for congestive heart failure (CHF) without renal replacement therapy (RRT), or CVA: HR 1.34 (P=0.03)	- Death or cardiovascular event: HR 1.05 (P=0.41) - Death or end-stage renal disease: HR 1.06 (P=0.29)
Secondary Outcomes	- Hospitalization for **CV causes**: HR 1.23 (P=0.03) - Hospitalization for **any cause**: HR 1.18 (P=0.03)	- **Stroke**: HR 1.92 (P<0.001, NNH 40) - **Cancer-related death**: 14/188 darbepoetin vs 1/160 placebo (P=0.002)
Other Notes	- Goal Hgb of 13.5 g/dL offered no additional quality of life benefit - High Hgb group did not achieve 13.5 g/dL (only got to 12.6 g/dL) - This study established the **ESA black box warning**	- No increased risk of cardiovascular composite outcome, but increased incidence of stroke - Improvement in fatigue symptoms based on FACT-Fatigue symptom score: 54.7% vs 49.5% (P=0.002)

New Kid on the Block: Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors (HIF-PHIs)[22-26]

Roxadustat | **Vadadustat** | **Daprodustat** | Enarodustat | Molidustat | Desidustat

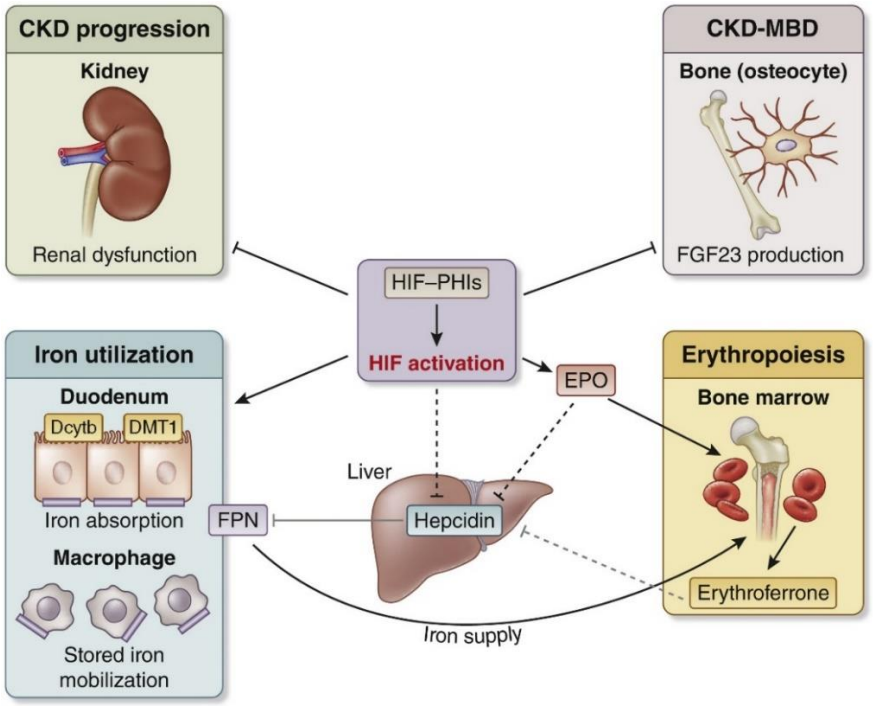


Figure 2: Possible Effects of HIF-PHIs[23]

Normal Pathophysiology of HIF[22]

- **Hypoxia-Inducible Factor (HIF)**
  - Heterodimeric protein with α and β subunits that activates EPO gene transcription when hypoxia is detected in the body
  - Also activates gene transcription associated with iron uptake and transport
  - Stimulates endogenous EPO production in the liver and kidney, and increased iron availability
- **Prolyl Hydroxylase Domains (PHDs)**
  - Prolyl-hydroxylase enzymes that hydroxylase the HIF-α subunit
    - Hydroxylation results in HIF degradation
    - Requires oxygen to perform function
  - PHD1, PHD2, and PHD3 isoforms

Normoxia - Adequate Oxygen Status

- PHD binds to HIF and activates degradation of protein
- EPO production and iron uptake normal

Hypoxia - Low Oxygen Status

- PHD expression reduced, HIF protein stabilized
- HIF induces gene transcription of EPO and iron regulation
- EPO and iron uptake ramped up

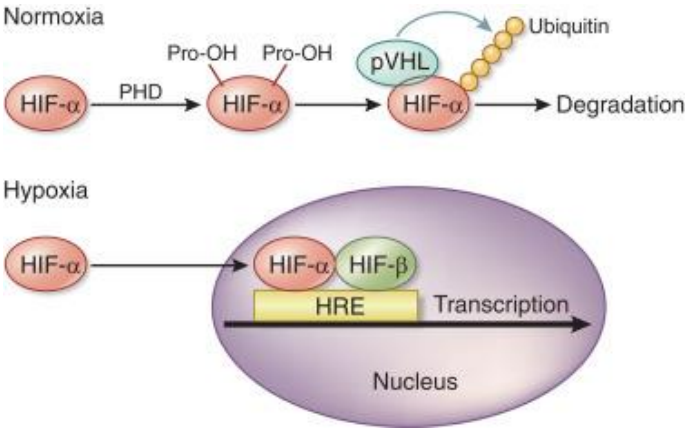


Figure 3: Normal Physiology of HIF and PHD[23]

Mechanism of action of HIF-PHIs[23]

- Reversible inhibitor of PHDs
- Stabilizes HIF proteins HIF-1α and HIF-2α
- Increases HIF-regulated gene expression

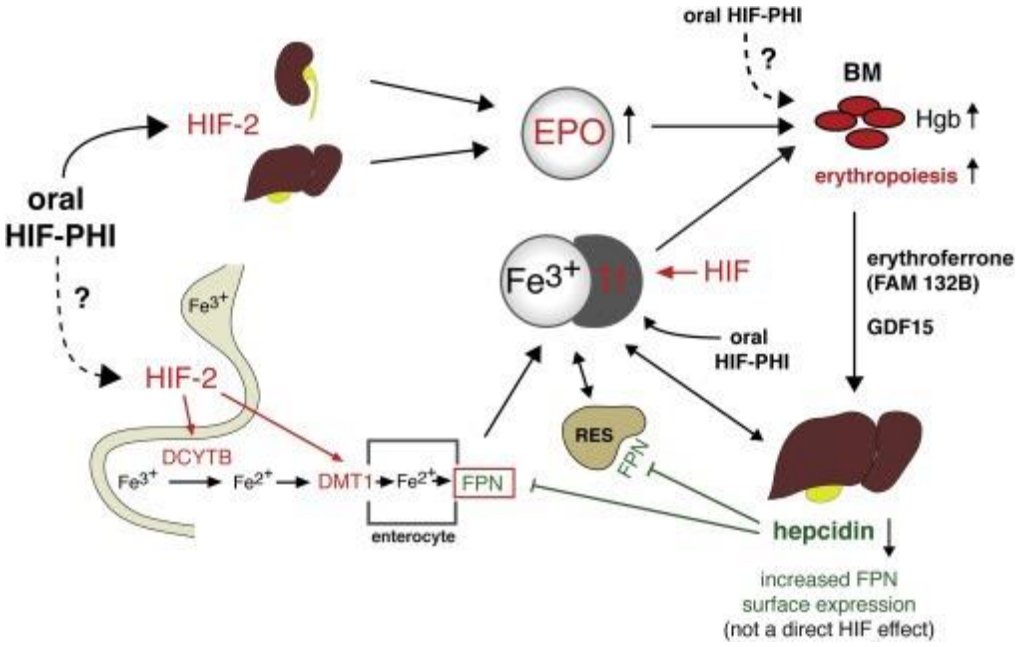


Figure 4: Mechanism of Action of HIF-PHIs[24]

Effects of HIF-PHIs[23,25]

- **Erythropoietin** – enhanced endogenous production via HIF-mediated gene transcription
- **Iron** – enhanced absorption and mobilization via decrease in hepcidin and maintained expression of ferroportin
- **Hepcidin** – decreased production due to perceived hypoxic state and erythropoiesis
- **Cholesterol** – hypothesis that because of the perceived hypoxic state, low density lipoprotein receptor expression is increased, and lipid uptake is enhanced for overall lowering of cholesterol

Pharmacokinetics at a Glance[26]

Roxadustat	Vadadustat	Daprodustat
• CYP2C8 (major) • Glucuronidation, glucosidation	• No CYP metabolism • UGT1A9 (major)	• CYP2C8, 3A4 (minor) • No Phase II metabolism

Controversy: Food and Drug Administration Disapproval[27-35]

Japan	Europe	United States
☐ Roxadustat - Approved 2019	☐ Roxadustat - Approved 2021	☐ Roxadustat - **Rejected** 2021
☐ Vadadustat - Approved 2020	☐ Vadadustat - **Pending**	☐ Vadadustat - **Rejected** 2022
☐ Daprodustat - Approved 2020	☐ Daprodustat - Approved 2022	☐ Daprodustat - **Pending**

Question: What place in therapy should HIF-PHIs have for the treatment of anemia of CKD, in the context of hemodialysis, in the United States?

Table #10: The efficacy of Roxadustat for the treatment of anemia in dialysis dependent chronic kidney disease patients: an updated systematic review and meta-analysis of randomized clinical trials		
Objective	To investigate the efficacy and safety of roxadustat for anemia in dialysis-dependent CKD patient	
Methods		
Study design	Updated systematic review and meta-analysis of 10 randomized controlled trials (RCTs)	
Study Selection	• Registered with Preferred Reporting for Systematic Review and Meta-Analysis (PRISMA) and Cochrane Handbook for Systematic Reviews of Interventions • Utilized PubMed, EMBASE, Scopus, Web of Science, Cochrane Central, and Google Scholar • Timeframe: Time of inception to July 2021 • Studies were included with the following parameters: - **Population:** Diagnosed with CKD and on dialysis - **Intervention:** Roxadustat - **Comparator:** ESA or placebo - **Outcome:** Change in hemoglobin level and iron utilization parameters • Studies were excluded if: - Observational - Non-randomized - No comparator group • Search protocol: (Roxadustat OR ASP1517 OR FG4592 OR "FG-4592") AND (kidney OR renal) AND (Anemia)	
Data Extraction	• Each RCT abstracted for: first author, published date, country, study design, phase, study period, number of patients, age, gender, and roxadustat dose	• Three reviewers independently extracted data using Microsoft Excel • Discrepancies resolved through discussion • Two reviewers performed meta-analysis; results reviewed by two separate authors
Outcomes	**Primary** • Changes in hemoglobin level • Iron utilization parameters: ferritin, serum iron, TSAT, TIBC, transferrin, hepcidin, Hgb in reticulocytes	**Secondary** • Treatment-emergent adverse effects (TEAEs) • Serious adverse events
Statistical Analysis	• Outcomes of interest used Mantel-Haenszel method: risk ratios for dichotomous outcomes, standardized mean difference (SMD) for continuous outcomes • Heterogeneity estimated with Cochran's Q Test: fixed-effects model for low heterogeneity ($P<0.10$, $I^2<50\%$), random-effects model for high heterogeneity ($P\geq0.10$, $I^2\geq50\%$) • Sensitivity analysis based on removing one RCT at a time • Publication bias assessed with Egger regression test	

Results	
Study Characteristics	

Study	Country (n of sites)	Population Characteristics	Roxadustat Dose	Study Duration
Akizawa et al. 2020	Japan (58)	N=301; age ~65±11 yr; male ~70%; dialysis >12 weeks	70 or 100 mg TIW	24 weeks
Charytan et al. 2021	USA (76)	N=741; age ~58±13 yr; male ~50-60%; dialysis 2 weeks to 4 months	70-200 mg TIW	52 weeks
Chen et al. 2017	China (8)	N=96; age ~50±10 yr; male 60.8% ROX, 95.1% rhEPO; dialysis ≥4 months	Weight based (1.1-2.3 mg/kg TIW)	6 weeks
Chen et al. 2019	China	N=304; age ~50±12 yr; male ~60%; dialysis ≥4 months	100 mg (BW 45 to <60 kg) or 120 mg (BW ≥60 kg)	26 weeks
Provenzano et al. 2016	USA	N=90; age ~57±12 yr; male ~61-67%; dialysis ≥4 months	Weight based (1.0-2.0 mg/kg TIW)	19 weeks
Provenzano et al. 2021	USA	N=1,043; age ~54±15 yr; male ~60%, dialysis 2 weeks to 4 months	70 or 100 mg TIW	52 weeks
NCT02278341 (PYRENEES) 2019	Worldwide (150)	N=836; age ~61±13 yr; male ~57%; dialysis ≥4 months	100, 150, or 200 mg	104 weeks
Hou et al. 2021	China	N=129; age ~48±12 yr; male ~56%; dialysis ≥12 months	100 mg (BW 45 to <60 kg) or 120 mg (BW ≥60 kg)	24 weeks
NCT01888445 2018	Japan (28)	N=127; age ~61±8 yr; male ~72%; dialysis 2-5 weeks	50, 70, or 100 mg TIW	24 weeks
NCT02174731 (ROCKIES) 2020	18 Countries (197)	N=2,101; age ~54±15 yr; male ~60%; dialysis 2 weeks to 4 months	N/A	4 years

BW: body weight, rhEPO: recombinant human erythropoietin, ROX: roxadustat, TIW: three times weekly, yr: year

Outcomes

Study	Change in Hemoglobin, SMD (g/dL) [95% CI]	Change in Serum Iron, SMD (µmol/L) [95% CI]	Serious Adverse Events Risk Ratio [95% CI]
Akizawa et al. 2020	-0.56 [-0.81, -0.30]	0.35 [0.12, 0.58]	1.43 [0.87, 2.35]
Charytan et al. 2021	0.25 [0.10, 0.39]	0.22 [0.04, 0.39]	0.98 [0.88, 1.09]
Chen et al. 2017	0.59 [0.09, 1.09]	0.08 [-0.41, 0.57]	---
Chen et al. 2019	0.19 [-0.05, 0.43]	0.48 [0.22, 0.74]	1.42 [0.72, 2.80]
Provenzano et al. 2016	0.00 [-0.49, 0.49]	0.27 [-0.22, 0.76]	1.44 [0.65, 3.23]
Provenzano et al. 2021	0.17 [0.05, 0.29]	0.21 [0.07, 0.36]	1.06 [0.93, 1.22]
NCT02278341 (PYRENEES) 2019	0.23 [0.09, 0.36]	---	1.13 [0.98, 1.30]
Hou et al. 2021	1.49 [1.08, 1.90]	0.40 [0.02, 0.79]	1.00 [0.09, 10.72]
NCT01888445 2018	0.01 [-0.44, 0.46]	---	2.47 [0.60, 10.24]
NCT02174731 (ROCKIES) 2020	0.07 [-0.02, 0.16]	---	1.00 [0.93, 1.08]
Total	0.21 [0.02, 0.39]	0.27 [0.18, 0.36]	1.04 [0.99, 1.10]
Heterogeneity	I^2=89%	I^2=0%	I^2=2%

CI: confidence interval, I^2: Iota-squared (heterogeneity), SMD: Standardized Mean Difference

Other Outcomes of Note:

- Treatment Emergent Adverse Effects (TEAEs): RR 1.03 [1.01, 1.05], driven by ROCKIES study (weight 40.6%); all other studies included did not find statistical significance
- Gastrointestinal adverse effects: RR 1.40 [1.04, 1.88], driven by ROCKIES (weight 18.0%), Charytan et al. (weight 18.1%), and Provenzano et al. 2021 (weight 16.4%); I^2=79%
- Cardiovascular adverse effects: RR 1.03 [0.90, 1.18], driven by ROCKIES study (weight 49.1%)

Conclusions and Evaluation

Author's Conclusions

Roxadustat is associated with increased Hgb levels and improved iron utilization parameters. Specifically, roxadustat increases levels of TIBC, serum iron, and transferrin, and decreases levels of hepcidin. Roxadustat is associated with higher TEAEs, but no difference in serious adverse effects.

Critique

Strengths

- Only included randomized controlled trials
- Focused on dialysis-dependent CKD patients
- Multiple nationalities represented in the trials provided
- Reported both efficacy (Hgb, iron) and safety (TEAEs, cardiovascular adverse events)
- Weighed studies to proportion significance

Limitations

- Mostly open label trials (9 out of 10)
- Various roxadustat doses in each study
- Different follow up periods in each study
- Long-term data is still needed; only one Phase 4 study included
- Did not evaluate outcomes of IV/PO iron use between roxadustat and the comparator
- Did not list hemoglobin initiation or target goals from each study

FDA Reasoning

Roxadustat has adequate efficacy compared to ESAs, however the safety events pose a greater risk than benefit. Specifically, there is an increased risk of death, MACE, VTE, vascular access thrombosis, and seizures, based on 4 studies reviewed.

Takeaway Summary

Roxadustat is a reasonable alternative to ESAs for the treatment of anemia of CKD in patients on HD. Although there were more treatment-emergent adverse effects reported with roxadustat use, the rate of serious adverse events was not statistically significant, which included cardiovascular adverse effects. The 10 RCTs analyzed show no increased risk of that described by the FDA (e.g., MACE).

Table #11: Safety and Efficacy of Vadadustat for Anemia in Patients Undergoing Dialysis (INNO$_2$VATE)		
Objective	To evaluate the safety and efficacy of vadadustat compared to darbepoetin alfa for the treatment of anemia in patients undergoing hemodialysis or peritoneal dialysis	
Methods		

Study design	• Pooled analysis of two phase 3, randomized, open-label, active-controlled, event-driven trials
	• United States, Europe, other regions
	• Trial periods: correction or conversion period (weeks 0-23), maintenance period (weeks 24-52), long-term treatment period (week 53 until end of treatment), and safety follow-up period (4 weeks)
	  ○ Primary evaluation period (weeks 24-36)
	  ○ Secondary evaluation period (weeks 40-52)	

Population	**Inclusion Criteria**
	• ≥18 years old
	• Have CKD and undergoing dialysis (≥12 weeks prevalent DD-CKD)
	• Limited ESA exposure for incident DD-CKD, ESA exposure required for prevalent DD-CKD (at least 1 dose in last 8 weeks)
	• Serum ferritin ≥100 ng/mL, TSAT ≥20%
	• Hemoglobin
	  ○ Incident DD-CKD trial: 8-11 g/dL
	  ○ Prevalent DD-CKD trial
	  ▪ United States: 8-11 g/dL
	  ▪ Other countries: 9-12 g/dL
		Exclusion Criteria
		• Received red-cell transfusion in previous 8 weeks
		• Anemia not caused by CKD
		• Uncontrolled hypertension
		• Recent cardiovascular event

Intervention	• 1:1 ratio of vadadustat or darbepoetin alfa
	  ○ Vadadustat (PO): 300 mg daily, maximum 600 mg daily (doses of 150, 450, 600 mg available)
	  ○ Darbepoetin alfa (SubQ or IV): Based on previous dose or product label dosing
	• Stratified based on location, NYHA classification, and hemoglobin concentration at trial entry
	  ○ Incident DD-CKD: <9.5 vs ≥9.5 g/dL
	  ○ Prevalent DD-CKD: <10 vs ≥10 g/dL
	• Target Hgb level
	  ○ United States: 10-11 g/dL
	  ○ Other countries: 10-12 g/dL
	• Could use ESAs as rescue therapy starting week 6 if symptoms worsened and Hgb <9.5 g/dL (temporarily discontinued treatment agent at that time; double dose of darbepoetin alfa used)	

Outcomes	**Efficacy** Mean change in hemoglobin from baseline to average concentration during primary evaluation and secondary evaluation periods **Safety** <u>Primary</u>: First occurrence of an adjudicated major adverse cardiovascular event (MACE), pooled across the two studies <u>Secondary:</u> • First occurrence of "expanded MACE" (MACE plus hospitalization for HF or VTE except vascular access failure), pooled across the two studies • Composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction	
Statistical Analysis	• Upper bound of 95% confidence interval set at 1.25 for primary safety end point • Lower bound of 95% confidence interval set at -0.75 g/dL for primary efficacy end point • Cox regression model to analyze time to first MACE event • Covariates: baseline hemoglobin, location, New York Heart Association (NYHA) Class, sex, age (≤65 or >65 years), race, CVD, DM	

Results

Baseline characteristics

Characteristic N=3,923 patients	Incident DD-CKD Trial		Prevalent DD-CKD Trial	
	Vadadustat (N=181)	Darbepoetin alfa (N=188)	Vadadustat (N=1777)	Darbepoetin alfa (N=1777)
Age, yr	56.5±14.8	55.6±14.6	57.9±13.9	58.4±13.8
Male, no. (%)	107 (59.1)	113 (60.1)	990 (55.7)	1004 (56.5)
Racial Group, no. (%)				
White	129 (71.3)	143 (76.1)	1135 (63.9)	1096 (61.7)
Black	38 (21.0)	35 (18.6)	432 (24.3)	444 (25.0)
Asian	12 (6.6)	8 (4.3)	76 (4.3)	99 (5.6)
Hispanic Ethnic Group, no. (%)	71 (39.2)	66 (35.1)	682 (38.4)	674 (37.9)
Hemodialysis, no. (%)	158 (87.3)	169 (90.0)	1652 (93.0)	1633 (91.0)
Disease History, no. (%)				
DM	105 (58)	96 (51.1)	971 (54.6)	998 (56.2)
CVD	69 (38.1)	73 (38.8)	868 (48.8)	932 (52.4)
Hemoglobin, g/dL, Mean (SD)	9.4±1.1	9.2±1.1	10.6±0.9	10.2±0.8
<9.5 g/dL	94 (51.9)	99 (52.7)	---	---
≥9.5 g/dL	87 (48.1)	89 (47.3)	---	---
<10.0 g/dL	---	---	620 (34.9)	619 (34.8)
≥10.0 g/dL	---	---	1157 (65.1)	1158 (65.2)
Baseline Iron Use, no. (%)				
PO Iron Only	19 (10.5)	9 (4.8)	123 (6.9)	118 (6.6)
IV Iron Only	92 (50.8)	110 (58.5)	911 (51.3)	853 (48.0)
IV and PO Iron	18 (9.9)	13 (6.9)	83 (4.7)	85 (4.8)

Outcomes

Primary

Pooled Outcome	Vadadustat (N=1947)	Darbepoetin alfa (N=1955)	HR (95% CI)
Cumulative Probability of a First MACE, no. (%)	355 (18.2)	377 (19.3)	0.96 (0.83-1.11)
All-cause Mortality	253 (13.0)	253 (12.9)	---
Nonfatal MI	76 (3.9)	87 (4.5)	---
Nonfatal Stroke	26 (1.3)	37 (1.9)	---

Incident DD-CKD	Vadadustat (N=181)	Darbepoetin alfa (N=188)	HR (95% CI)
MACE, no. (%)	22 (12.3)	24 (12.9)	0.97 (0.536-1.761)

Prevalent DD-CKD	Vadadustat (N=1777)	Darbepoetin alfa (N=1777)	HR (95% CI)
MACE, no. (%)	333 (18.8)	353 (20.0)	0.96 (0.828-1.117)

Secondary

Incident DD-CKD

Parameter	Vadadustat	Darbepoetin alfa	Mean Difference	95% CI
Change in Hgb, g/dL				
Week 24-36	1.26±0.11	1.58 ±0.11	-0.31±0.11	-0.53 to -0.10
Week 40-52	1.42±0.13	1.50±0.14	-0.07±0.13	-0.34 to 0.19
Within goal Hgb, %				
Week 24-36	43.6%	56.9%	---	---
Week 40-52	39.8%	41.0%	---	---
RBC Transfusion, %				
Week 24-36	1.3%	1.3%	---	---
Week 40-52	2.4%	0.7%	---	---

Prevalent DD-CKD

Parameter	Vadadustat	Darbepoetin alfa	Mean Difference	95% CI
Change in Hgb, g/dL				
Week 24-36	0.19±0.03	0.36±0.03	-0.17±0.03	-0.23 to -0.10
Week 40-52	0.23±0.04	0.41±0.03	-0.18±0.04	-0.25 to -0.12
Within Goal Hgb, %*				
Week 24-36	49.2%	53.2%	---	---
Week 40-52	44.3%	50.9%	---	---
RBC Transfusion, %				
Week 24-36	2.0%	1.3%	---	---
Week 40-52	2.0%	1.9%	---	---

*Based on country-specific target

- Similar changes in mean serum concentration of hepcidin, ferritin, and TSAT between vadadustat and darbepoetin
- Fewer patients on vadadustat required rescue therapy with ESA compared to darbepoetin (prevalent DD-CKD: 27.6% vs 30.2% weeks 0-23)

Safety

N=1,947 vadadustat, N=1,955 darbepoetin alfa

Event	Incident DD-CKD		Prevalent DD-CKD	
	Vadadustat (N=179)	Darbepoeitin alfa (N=186)	Vadadustat (N=1768)	Darbepoeitin alfa (N=1769)
Any serious adverse event	49.7%	56.5%	55.0%	58.3%
Any drug-related adverse events	3.9%	2.7%	9.6%	3.8%
Any serious drug-related adverse events	0.6%	2.2%	1.6%	1.5%
Vascular access thrombosis	3.4%	5.4%	6.0%	4.4%

- Common adverse events with vadadustat in prevalent DD-CKD (≥10%): HTN, diarrhea, pneumonia

Conclusions and Evaluation

Author's Conclusions

Oral vadadustat is noninferior compared to darbepoetin alfa in patients with CKD who are undergoing dialysis.

Critique

Strengths

- Randomized controlled trial
- Diverse populations; specified Hispanic ethnicity
- Majority of patients were on prevalent DD-CKD
- Included hemoglobin baseline and targets for United States
- Reported both efficacy (Hgb) and safety (MACE)

Limitations

- Open-label
- Vadadustat had standardized initial dose whereas darbepoetin alfa was titrated base on patient's prior doses or dosing protocol
- Rescue therapy with ESA could skew results
- Included baseline iron use, but not changes thereafter
- Long-term studies still needed for further safety and efficacy analysis

FDA Reasoning

Vadadustat associated with increased risk of MACE and drug-induced liver injury (DILI). Increased risk of thromboembolic events (vascular access thrombosis in dialysis)

Takeaway Summary

Vadadustat is a reasonable alternative to darbepoetin alfa for the treatment of anemia of CKD in HD patients. No increased incidence of MACE nor DILI were noted in prevalent DD-CKD patients; the events posed by the FDA were reported in the PRO_2TECT trials in patients not on dialysis; as the same was not seen in dialysis patients, vadadustat should still be considered for patients on dialysis. As for vascular access thrombosis, further analysis will be needed to assess if a 1.6% increased incidence constitutes a greater risk vs benefit.

Table #12: Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis (ASCEND-D)		
Objective	To determine the efficacy and safety of daprodustat compared to ESAs	
Methods		
Study design	• Multicenter, multinational, open-label, phase 3 randomized controlled trial conducted from 11/23/16 – 8/10/2018 • 431 centers in 35 countries • Stratified by type of dialysis, geographic region, and participation in ambulatory substudy monitoring blood pressure	
Population	**Inclusion Criteria** • Chronic kidney disease • Dialysis ≥ 90 days • Received ESA for ≥6 weeks • Hgb 8.0-12.0 g/dL → 8.0-11.5 g/dL after 4-week run-in period • Ferritin ≥100 ng/mL and TSAT >20%	**Exclusion Criteria** • Anemia unrelated to CKD, a recent cardiovascular event, or current/recent cancer (within 2 years) • Kidney transplant • Active GI bleeding, or clinically significant GI bleed ≤4 weeks before screening • ACS, CVA, TIA ≤4 weeks before screening • New York Heart Association (NYHA) Class IV Heart failure • Uncontrolled hypertension

Intervention	• 1:1 ratio of daprodustat or injectable ESA
	  ○ Daprodustat: 4-12 mg daily (according to ESA dose); stepped changes from 1-24 mg
	  ○ Injectable ESA according to previous ESA dose
	  ▪ IV epoetin alfa for patients on HD
	  ▪ SubQ darbepoetin alfa for patients on PD
	• Maintain hemoglobin 10.0-11.0 g/dL	

Outcomes	**Primary (non-inferiority)** 1. Mean change in hemoglobin level from baseline to the average during the primary evaluation period (week 28-52) 2. First occurrence of an adjudicated major adverse cardiovascular event (MACE): a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke **Secondary (superiority)** • Average monthly dose of intravenous iron administered from baseline to week 52 • First occurrence of a MACE • First occurrence of a MACE or thromboembolic event • First occurrence of a MACE or hospitalization for heart failure	
Statistical Analysis	• Enroll 3000 patients for 945 adjudicated first MACEs for a noninferiority margin of 1.20 • COVID-19 adjustment: noninferiority margin changed to 1.25 • 90% power maintained despite revised trial size of 664 target number of events • Change in hemoglobin noninferiority margin set at -0.75 g/dL • Intention-to-treat • One-sided α 0.025 • Secondary superiority analysis performed if noninferiority established for the two primary outcomes • Holm-Bonferroni method to adjust for multiplicity	

Results

Baseline characteristics

Characteristic (N=2964)	Daprodustat (N=1487)	ESA (N=1477)
Median age (IQR), yr	58 (48-67)	59 (47-68)
Male, no. (%)	851 (57.2)	847 (57.3)
Race, no. (%)		
White	995 (66.9)	982 (66.5)
Black*	228 (15.3)	233 (15.8)
Asian	176 (11.8)	181 (12.3)
Hemodialysis, no. (%)	1316 (88.5)	1308 (88.6)
Coexisting Condition		
Coronary artery disease	347 (23.3)	344 (22.6)
Heart failure	267 (18.0)	254 (17.2)
Myocardial infarction	122 (8.2)	135 (9.1)
Stroke	96 (6.5)	110 (7.4)
Hypertension	1366 (91.9)	1373 (93.0)
Thromboembolic event	273 (18.4)	242 (16.4)
Diabetes	615 (41.4)	617 (41.8)
Labs		
Median hemoglobin (IQR), g/dL	10.4 (9.7-11.1)	10.5 (9.8-11.1)
Median total iron (IQR), µmol/L	13 (10-16)	13 (10-16)
Median LDL (IQR), mg/dL	81.9 (61.0-103.1)	81.1 (61.0-103.9)
Intravenous Iron		
Patients receiving therapy (%)	64.3	63.8
Median Dose (IQR), mg/month	100 (0-217.4)	97.1 (0-217.4)
ESA Hyporesponsiveness, no. (%)	183 (12.3)	180 (12.2)

*Post-hoc analysis showed 39.0% of patients in United States were Black

Outcomes

Primary Outcome Non-Inferiority	Daprodustat (N=1487)	ESA (N=1477)	Treatment Effect (95% CI)	P-Value
Change in hemoglobin level from baseline to week 28-52, g/dL	0.28±0.02	0.10±0.02	Mean adjusted difference, 0.18 (0.12-0.24)	<0.001
MACE, No. (%)	374 (25.2)	394 (26.7)	HR, 0.93 (0.81-1.07)	<0.001
Death from any cause	244 (16.4)	233 (15.8)	---	---
Nonfatal MI	101 (6.8)	126 (8.5)	---	---
Nonfatal CVA	29 (2.0)	35 (2.4)	---	---

Secondary Outcome, No. (%) Superiority	Daprodustat (N=1487)	ESA (N=1477)	Treatment Effect (95% CI)	P-Value
MACE	374 (25.2)	394 (26.7)	HR, 0.93 (0.81-1.07)	---
MACE or thromboembolic event	497 (33.4)	543 (36.8)	HR, 0.88 (0.78-1.00)	---
MACE or hospitalization for heart failure	425 (28.6)	433 (29.3)	HR, 0.97 (0.85-1.11)	---
Death from any cause	244 (16.4)	233 (15.8)	HR, 0.96 (0.82-1.16)	---
Adjusted monthly IV iron dose from baseline to week 52, mg, Mean (SD)	90.8±3.3	99.9±3.3	Mean difference, -9.1 (-18.4 to 0.2)	---

- Daprodustat decreased hepcidin levels and increased TIBC more compared to ESAs
- Patients hyporesponsive to ESAs required less IV iron in the daprodustat arm compared ESAs, and more often maintained target Hgb levels on daprodustat
- Rapid rise in Hgb (>2 g/dL in 4-week period) was similar between daprodustat and ESAs

Safety

Adverse Effect, No. (%)	Daprodustat (N=1482)	ESA (N=1474)
All TEAEs	1307 (88.2)	1252 (84.9)
Hypertension	243 (16)	1252 (85)
Dialysis hypotension	141 (10)	110 (7)
Hyperkalemia	91 (6)	89 (6)
Esophageal or gastric erosions	60 (4)	81 (5.5)
Arteriovenous fistula thrombosis	85 (6)	98 (7)
All Serious TEAEs	773 (52.2)	748 (50.7)
Pneumonia	86 (6)	81 (5)
Arteriovenous fistula thrombosis	36 (2)	57 (4)

Conclusions and Evaluation

Author's Conclusions

Daprodustat is an effective treatment for anemia of CKD for patients undergoing hemodialysis or peritoneal dialysis.

Critique

Strengths

- Randomized controlled trial
- Representation of Black Americans
- Evaluated rise in hemoglobin along with overall change
- Daprodustat was titrated based on previous doses of ESA therapy
- Evaluated patients with ESA hyporesponsiveness
- Reported both efficacy (change in Hgb, iron use) and safety (MACE, VTE)
- Provided additional on-treatment analysis

Limitations

- Open-label
- Did not specify ethnicities
- Did not use darbepoetin in HD patients, nor epoetin in PD patients
- Initiation Hgb criteria not fully applicable to USA patients (i.e., upper limit of Hgb 12 g/dL)

FDA Reasoning

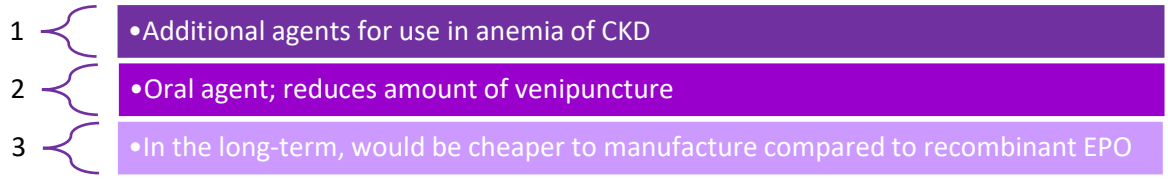
To Be Determined by February 1st, 2023

Takeaway Summary

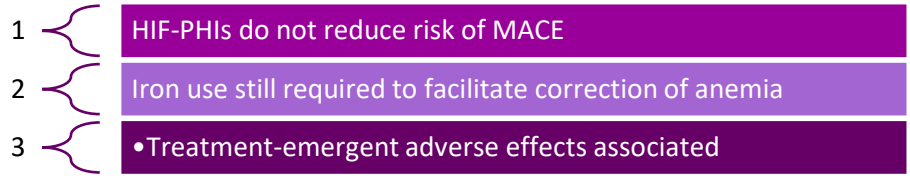
Daprodustat is a reasonable alternative to ESAs in patients with anemia of CKD on HD. The incidence of MACE was comparable to that of ESAs and numerically did not confer additional risk (HR 0.93). Previous concerns for gastric events and increased thrombosis risk were not seen in this trial. Patients who were hyporesponsive to ESAs further saw a decreased need for IV iron while on daprodustat, adding an additional benefit to using this HIF-PHI.

Summary

- Final Statements
  - Current guideline recommendations for the treatment of anemia of CKD include iron, ESAs, and RBCs
    - Consensus is that iron be utilized first, then consider ESAs after a risk/benefit analysis
    - Depending on the guideline, initial hemoglobin values to administer agents slightly differ
    - Goal is to avoid RBC transfusion due to myriad of consequences
  - Oral HIF-PHIs endogenously increase EPO
    - Shown to increase hemoglobin levels in patients with anemia of CKD comparable to that of ESAs
    - Side effect profiles vary slightly between agents, but are overall tolerable
- My recommendation
  - **Daprodustat** shows the most evidence for use compared to ESAs, and should be approved by the FDA
    - Studies included change in hemoglobin, MACE events, and safety parameters
    - Included parameters previously not seen in studies conducted on roxadustat and vadadustat
      - Rate of rise in hemoglobin
      - Initial daprodustat dose based on prior ESA dose
      - Effects on ESA hyporesponsive patients
  - **Roxadustat** and **vadadustat** are also reasonable alternatives compared to ESAs, however further data will be needed to gain the FDA's approval
    - Safety data for roxadustat (targeting hemoglobin level of 10.0-11.0 g/dL rather than 10.5-12 g/dL)
    - Application for vadadustat specifically in DD-CKD patients (exclude non-dialysis patients)
- Benefits



- Limitations



- Questions remaining[22,39]
  - Are there long-term benefits towards iron absorption and metabolism?
    - Longest study of 4 years found no difference compared to ESAs
    - Hepcidin levels and other inflammatory markers decreased (e.g., C-reactive protein), but iron utilization was not different between HIF-PHIs and ESAs except in cases of ESA hyporesponsiveness
  - What other pleotropic effects can be seen with HIF-PHIs?[22]
    - Current literature shows conflicting evidence for benefits vs detriments
    - Need more studies to specifically focus on cholesterol effects to gather conclusions on potential LDL-reducing effects
    - HIF-2α has data indicating its pathophysiologic association with gastroesophageal reflux disease (GERD); HIF-PHIs may not be appropriate for patients with similar conditions[39]

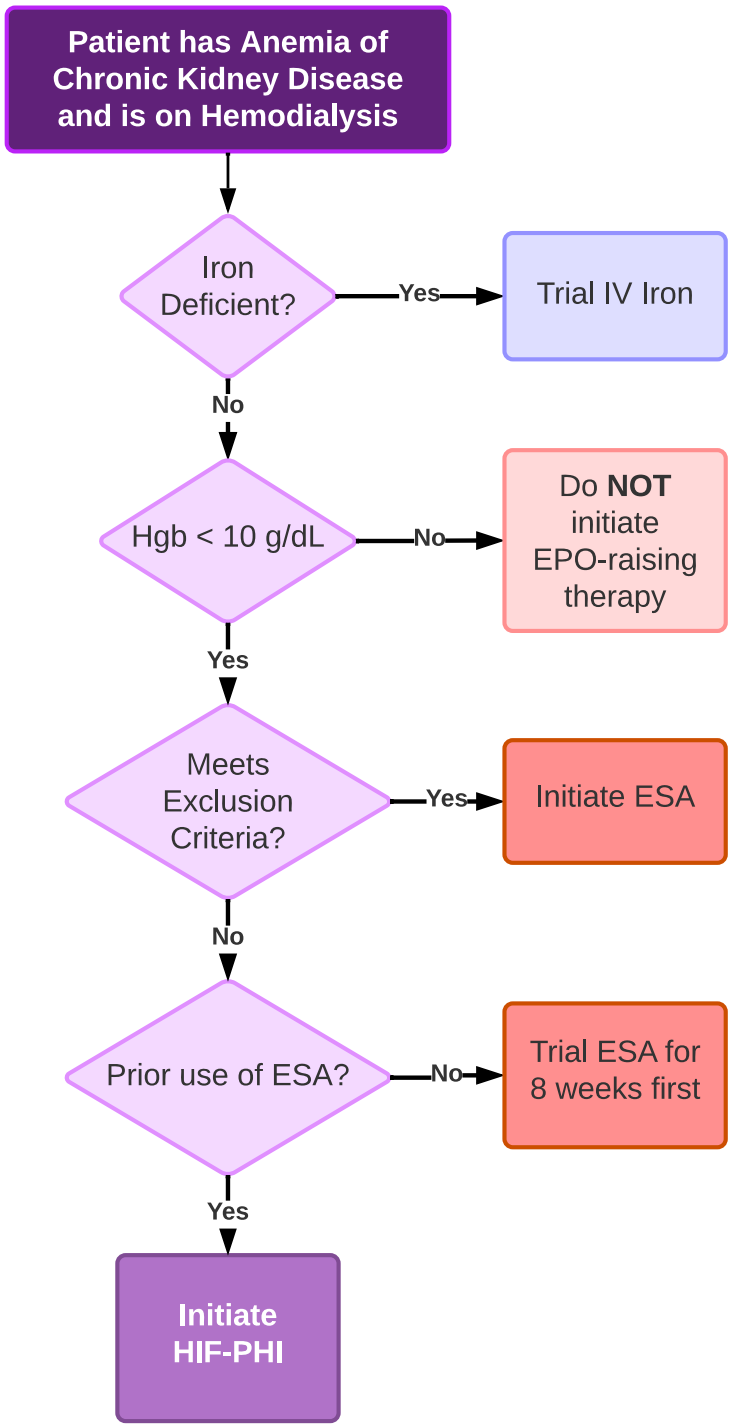
Treatment Algorithm

Anemia:
- Male: Hgb < 13 g/dL
- Female: Hgb < 12 g/dL

Iron Deficiency in HD:
- TSAT < 20%
- Ferritin < 200 ng/mL

Exclusions
- Use of gemfibrozil (roxadustat, daprodustat)

Pleotropic risk Precautions
- History of Barrett's esophagitis or uncontrolled gastroesophageal reflux disease
- Hyperlipidemia
- Fibrosis (hepatic, renal)



Strong recommendation

Daprodustat

Moderate recommendation

Vadadustat

Roxadustat

Abbreviations

- **EPO** - erythropoeitin
- **ESA** - erythropoesis-stimulating agents (epoetin alfa, darbepoetin)
- **HIF-PHI** - Hypoxia-inducible factor prolyl hydroxylase inhibitor
- **TSAT**- transferrin saturation

Resources for Pharmacists

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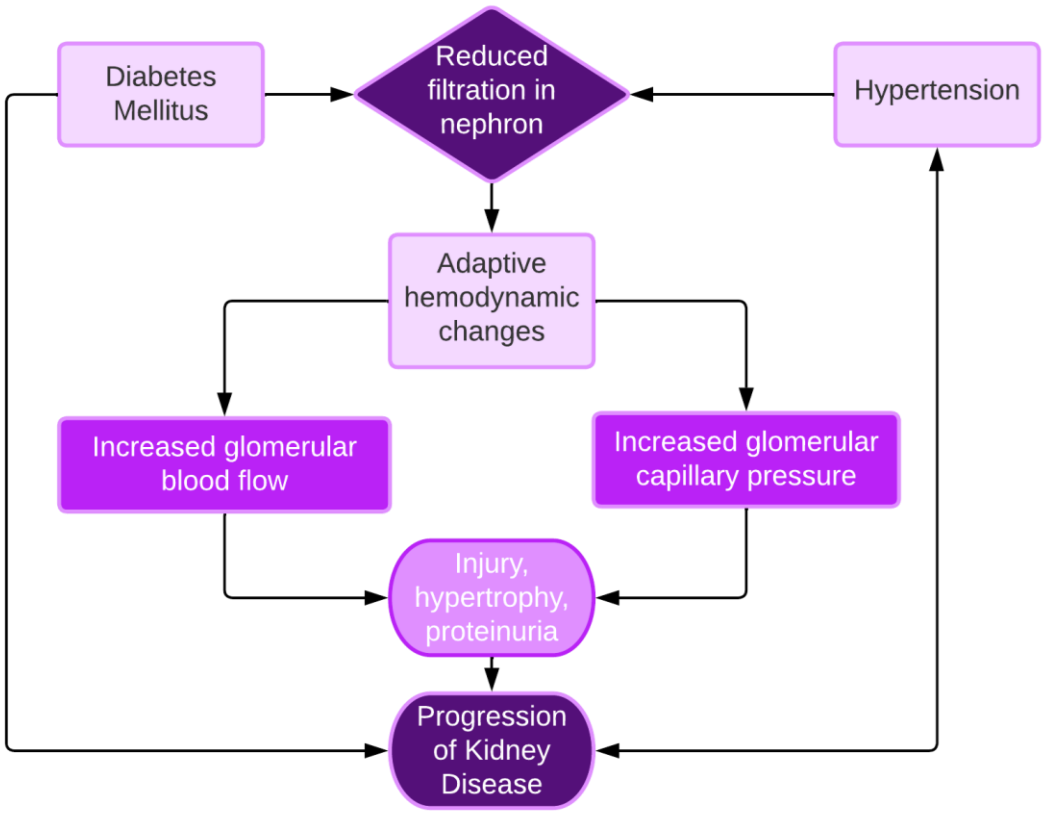
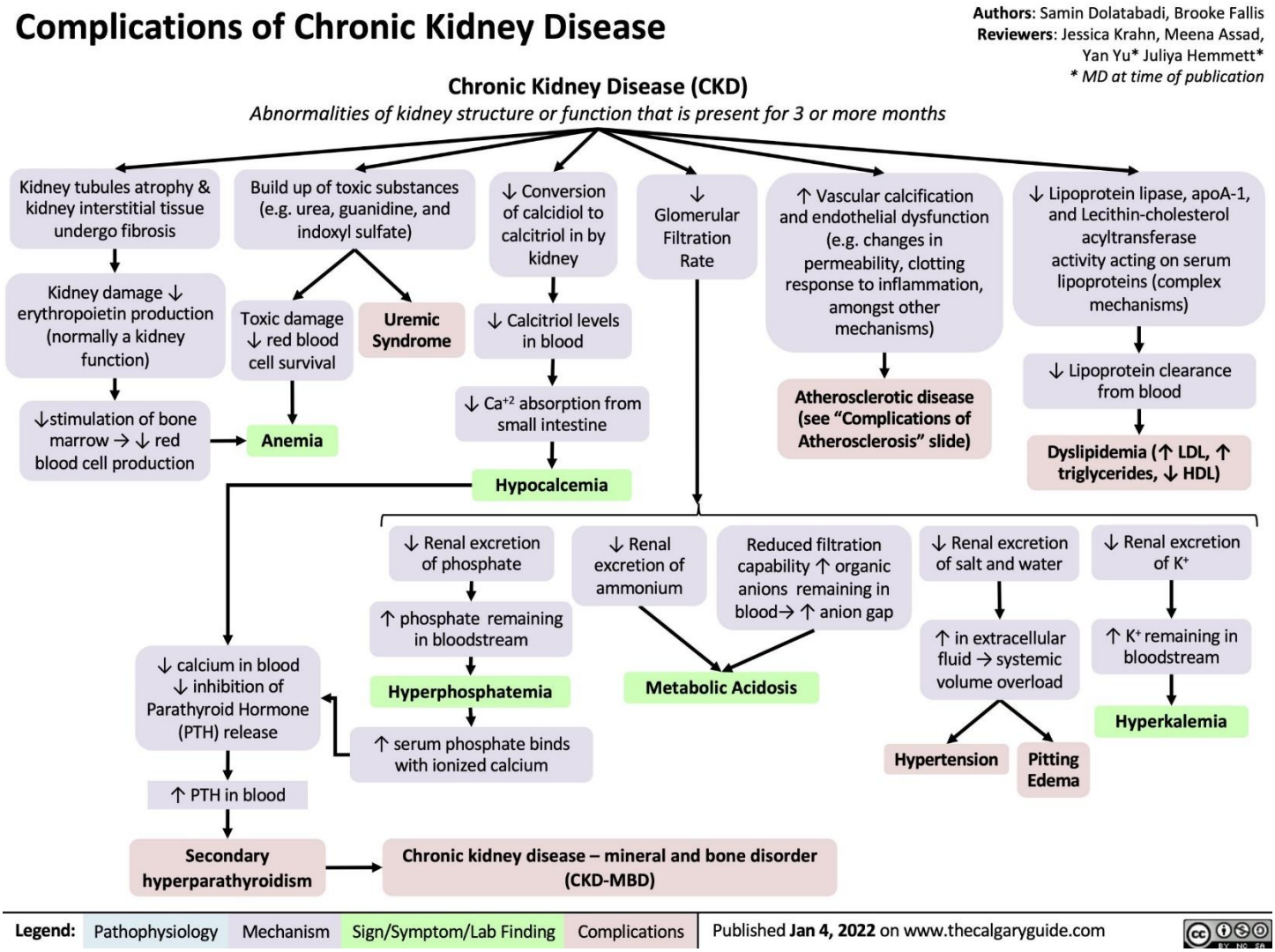
Appendix

General Pathophysiology of Chronic Kidney Disease[1-3]



Complications of Chronic Kidney Disease[1,3]

Electrolyte Abnormalities	Mineral and Bone Disorder (MBD)	Need for Dialysis	Anemia
•Hyperkalemia •Hyperphosphatemia •Hyper- or hypocalcemia •Elevated blood urea nitrogen (BUN)	•High levels of phosphate bind with calcium → low calcium in blood •Increased parathyroid (PTH) release → secondary hyperparathyroidism	•End Stage Renal Disease (ESRD) •Start considering when CKD Stage 4-5 •Other considerations •Signs/symptoms of renal failure (pruritus, electrolyte imbalance) •Uncontrolled hemodynamics •Cognitive impairment •Malnutrition	•Reduced erythropoietin production •Released stimulation of red blood cell production



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Iron Parameters[40]

Parameter	Measure and Clinical Significance	Normal Range	
		Men	Women
Serum Iron	- Measure of circulating iron that is bound to transferrin and ferritin - Necessary to make hemoglobin for RBCs	70-175 mcg/dL	50-170 mcg/dL
Transferrin **Transferrin Saturation (TSAT)**	- Delivers iron to various tissues in the body - Percent of iron bound to transferrin	20-50%	
Ferritin	- Measure of iron stores in body - Blood protein that contains iron and is stored in liver, spleen, skeletal muscles, and bone marrow (small amount in blood)	24-336 mcg/L	11-307 mcg/L
Total (or Transferrin) Iron Binding Capacity (TIBC)	- Measure of the capacity of transferrin to bind iron - High TIBC means low levels of iron	250-450 mcg/dL	

Potential Pleotropic Effects of HIF-PHIs[22,39,41-42]

Beneficial	Detrimental
• Ischemic disease mitigation • Quells inflammation • Tissue injury/infection healing • Lipid reduction • Mucosal protection	• Chronic renal fibrosis • Exacerbated inflammation • Hepatic fibrosis • Lipid production • Gastroesophageal reflux disease