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Understanding Anemia in Patients with CKD: From Diagnosis to Data on Emerging Agents

Supported by an educational grant from Akebia Therapeutics, Inc. and Otsuka America Pharmaceutical, Inc.

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Learning Objective 1

Review pathophysiology and signs and symptoms of anemia in patients with CKD.

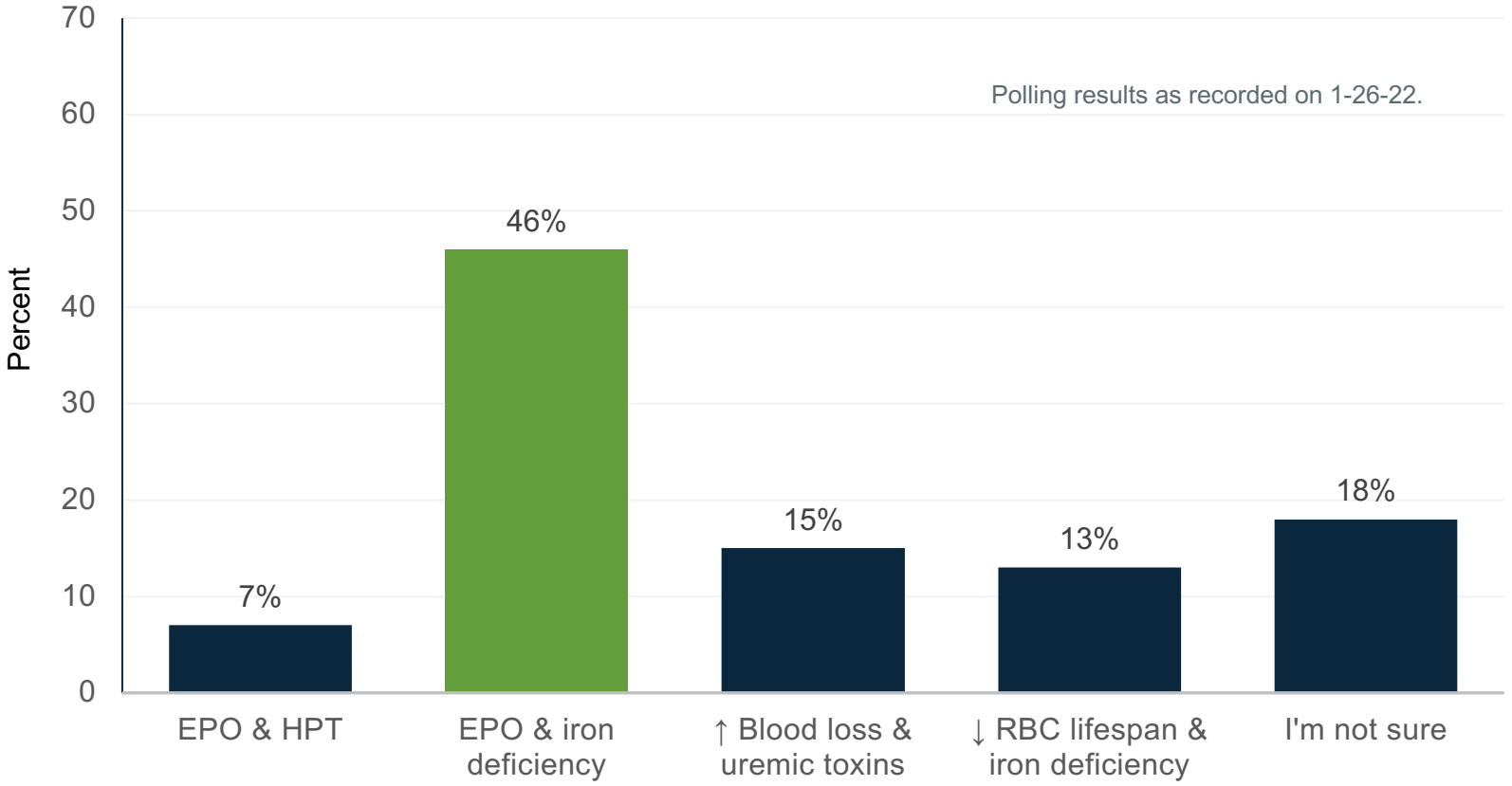
Audience Response

Which of the following factors contribute most to anemia in CKD?

A. Epoetin and hyperparathyroidism
B. Epoetin and iron deficiency
C. Increased blood loss and uremic toxins
D. Shortened RBC lifespan and iron deficiency
E. I’m not sure

CKD = Chronic kidney disease. RBC = Red blood cells.

Which of the following factors contribute most to anemia in CKD?



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Symptoms of Anemia in CKD

May include:

- Fatigue or tiredness
- Shortness of breath
- Unusually pale skin
- Weakness
- Body aches
- Chest pain
- Dizziness

U.S. Department of Health and Human Services. National Institute of Diabetes and Digestive and Kidney Diseases Website. 2020. https://www.niddk.nih.gov/health-information/kidney-disease/anemia. Accessed January 14, 2022.

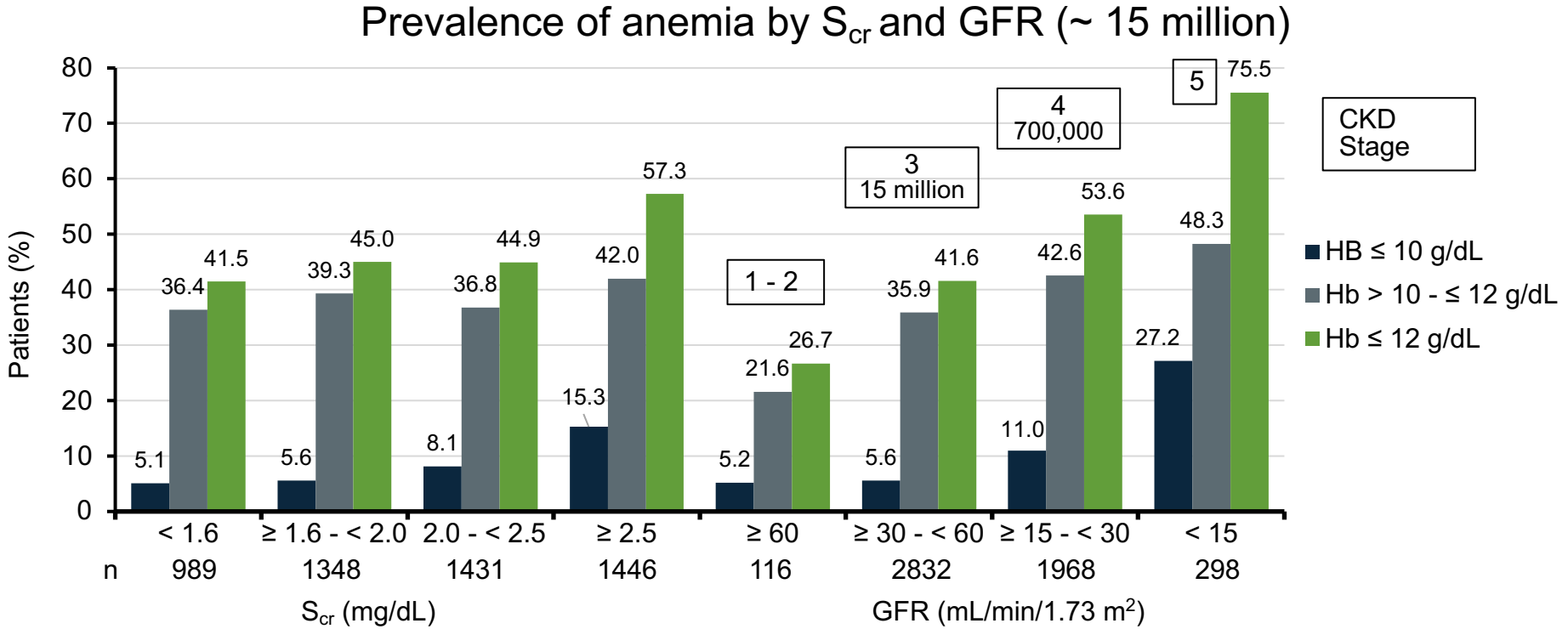
Symptoms of Anemia in CKD

May include:

- Fatigue or tiredness
- Shortness of breath
- Unusually pale skin
- Weakness
- Body aches
- Chest pain
- Dizziness
- Fainting
- Fast or irregular heartbeat
- Headaches
- Sleep problems
- Trouble concentrating
- Decrease in appetite

U.S. Department of Health and Human Services. National Institute of Diabetes and Digestive and Kidney Diseases Website. 2020. https://www.niddk.nih.gov/health-information/kidney-disease/anemia. Accessed January 14, 2022.

Anemia in CKD and Relationship to Stage of CKD



EPO = Erythropoietin. g/dL = Grams per deciliter. GFR = Glomerular filtration rate. mL/min/1.73 m^2 = Milliliters per minute. S_{cr} = Serum creatinine. Hb = Hemoglobin.

McClellan W, et al. *Curr Med Res Opin.* 2004;20(9):159:1501–1510.

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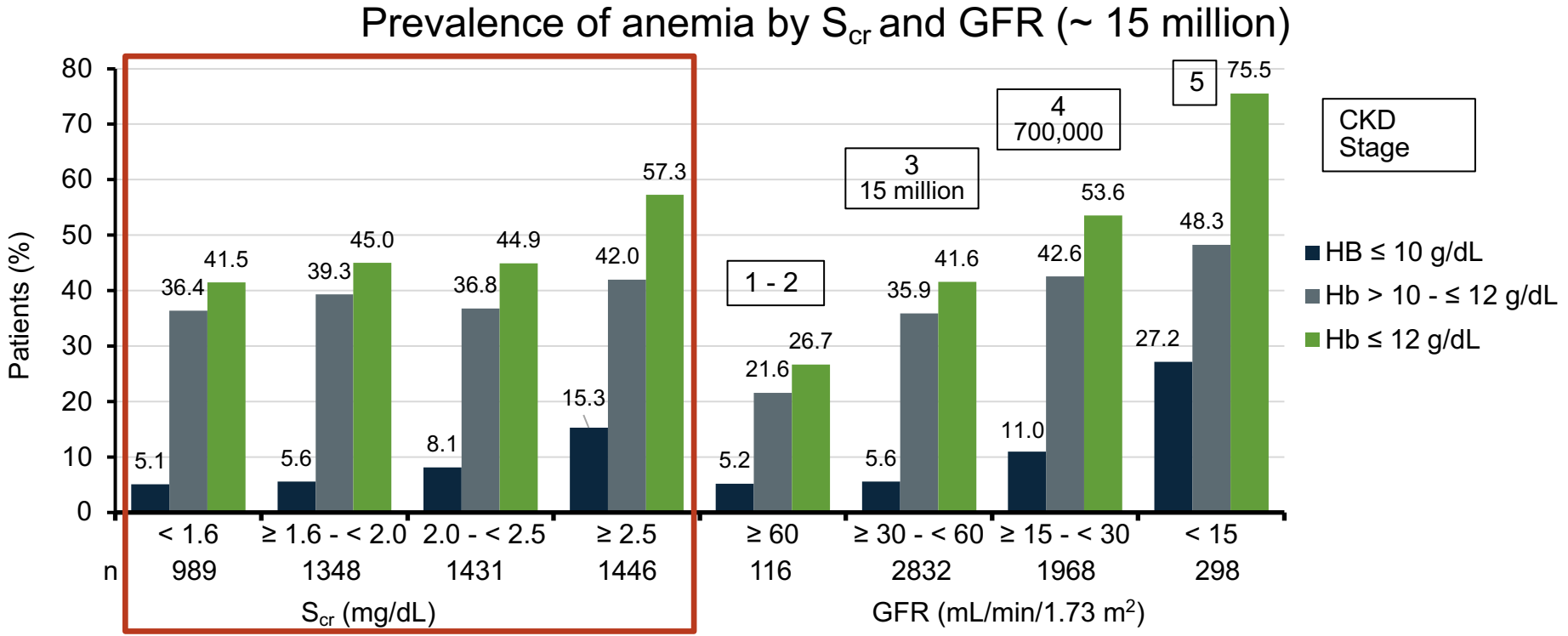

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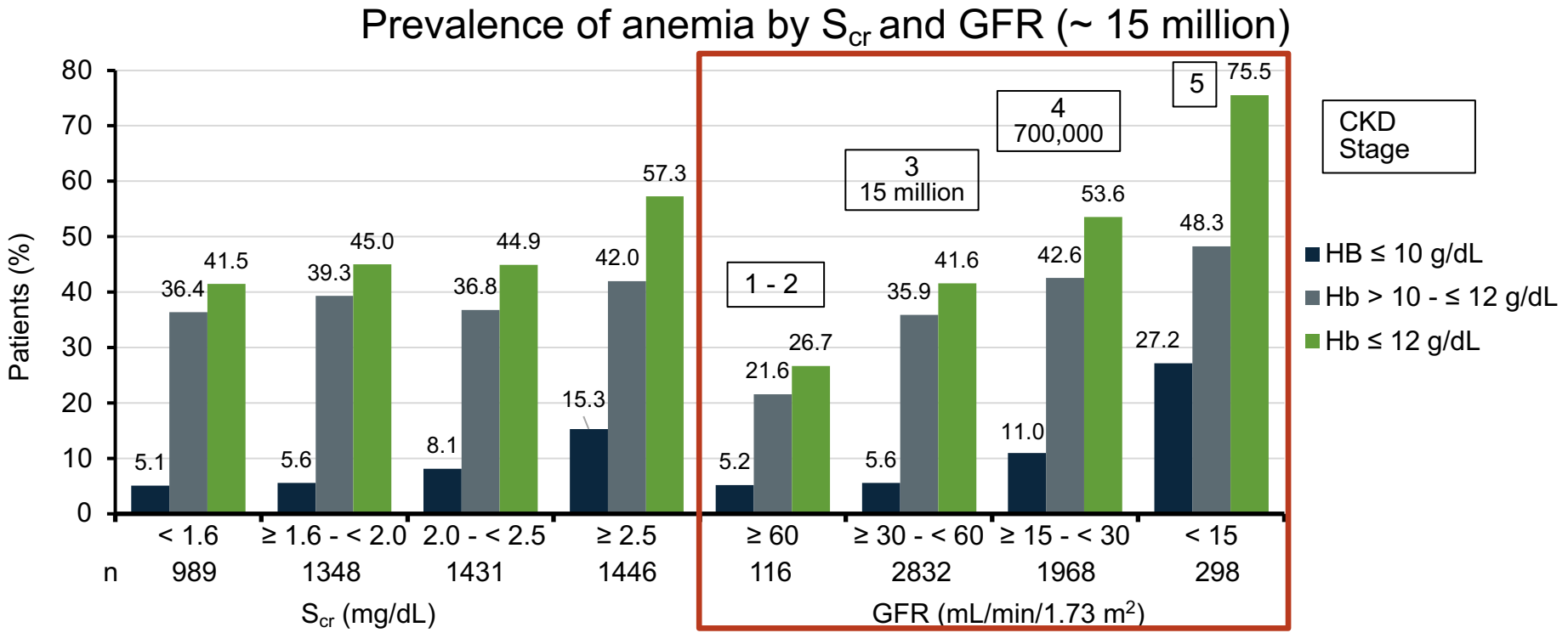

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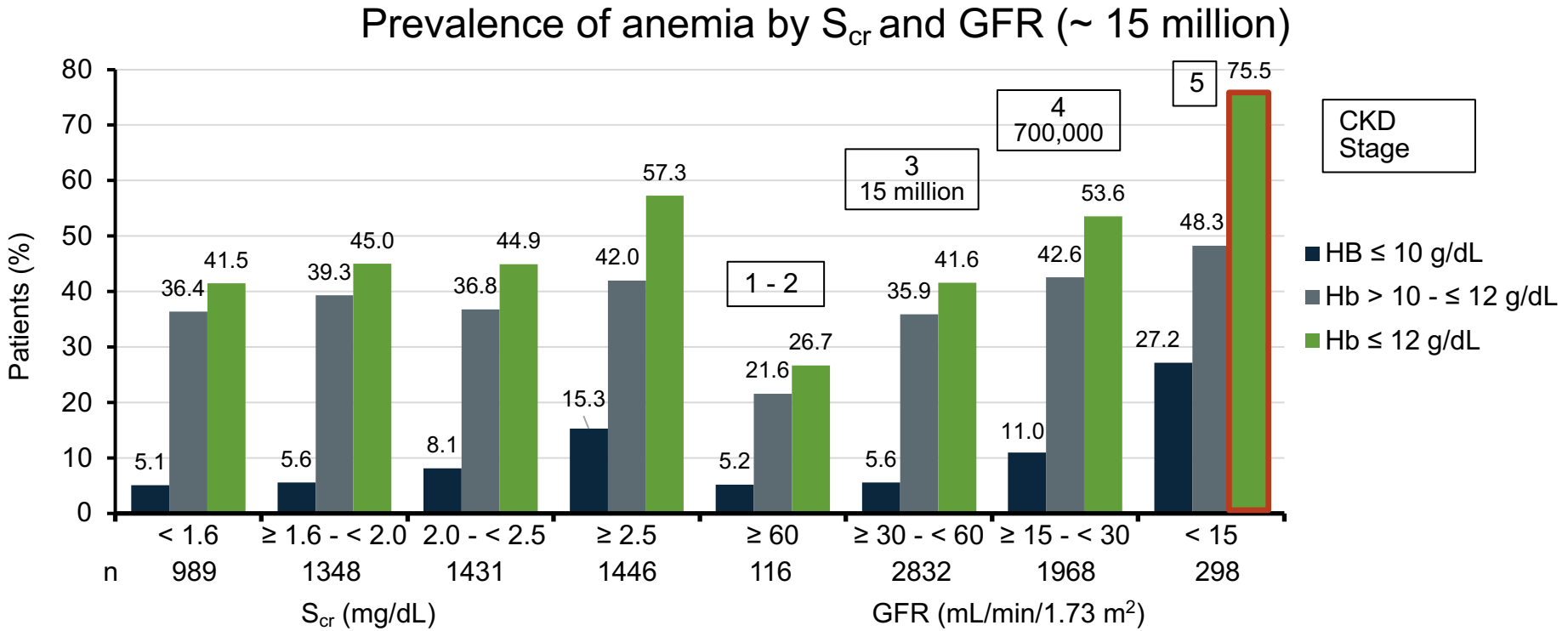

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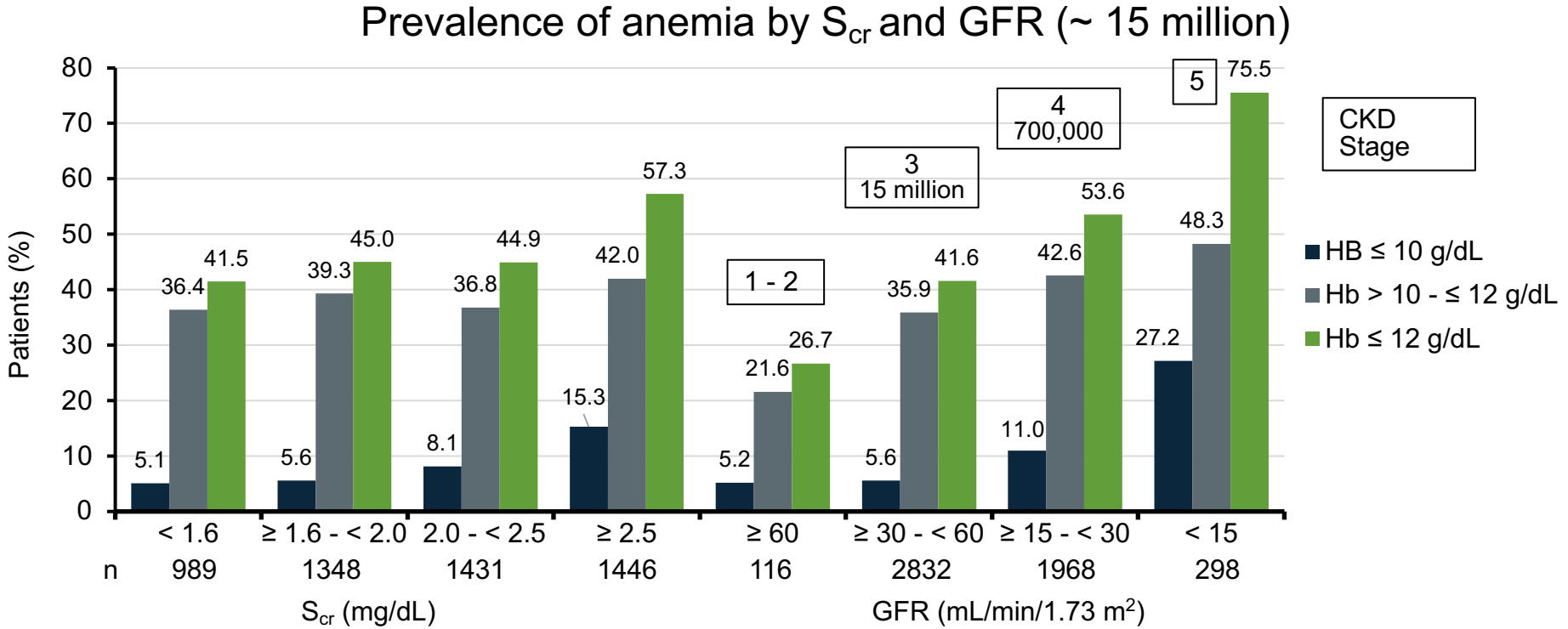

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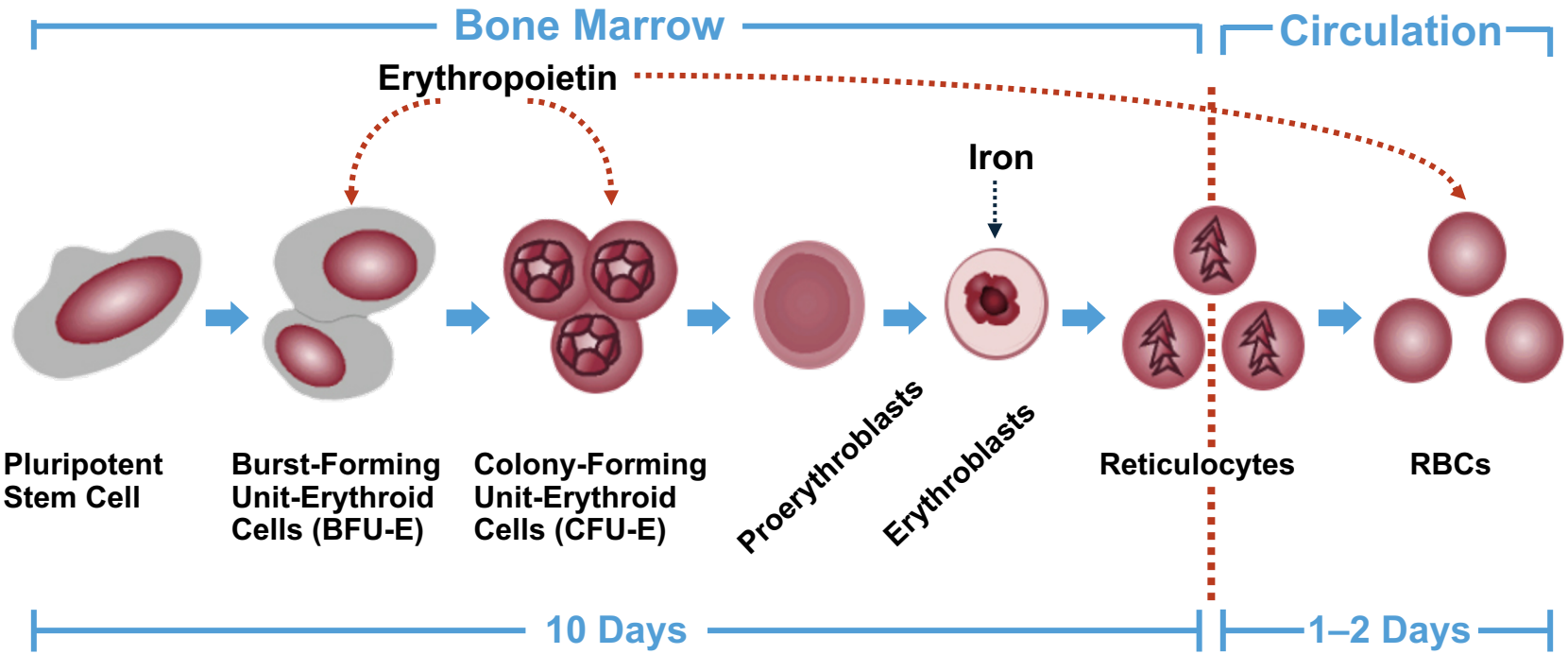
Normal Red Blood Cell Production



Steinberg MH, et al. Chapter 33: Pathobiology of the human erythrocyte and its hemoglobins. In: *Hematology: Basic Principles and Practice*. 7th ed. 2018;447-457.

Factors That Contribute to Anemia in CKD

- The big two:
  1. Epoetin deficiency
  2. Iron deficiency

Portolés J, et al. *Front Med.* 2021;8:64296. Tanaka M, et al. *Ther Apher Dial.* 2018;22(3):242-245.

Factors That Contribute to Anemia in CKD

- The big two:
  1. Epoetin deficiency
  2. Iron deficiency
- Other contributors:
  - Shortened RBC lifespan
  - Increased blood loss
  - Uremic toxins/inadequate dialysis
  - Hyperparathyroidism

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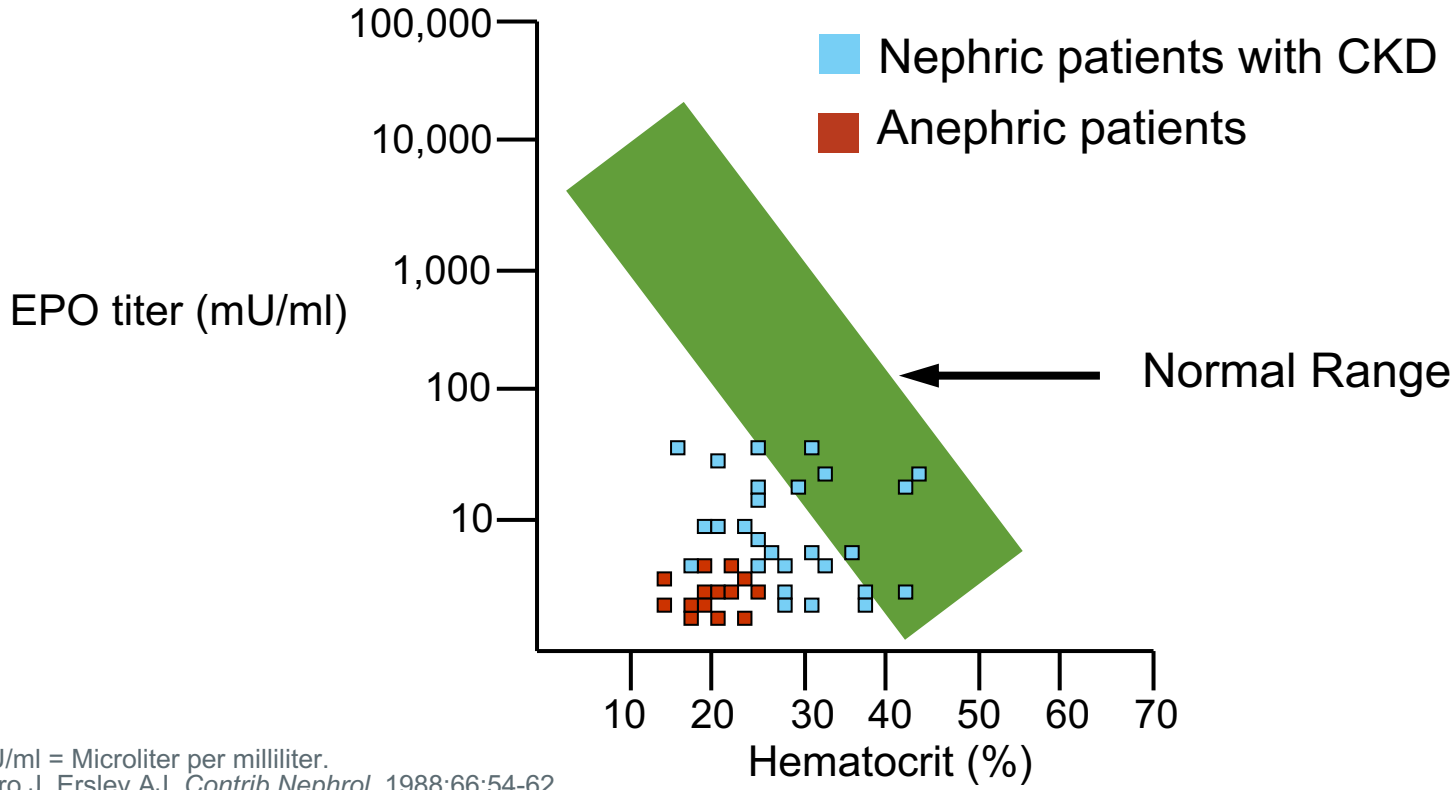
Anemia of CKD is Primarily Due to Insufficient EPO Production



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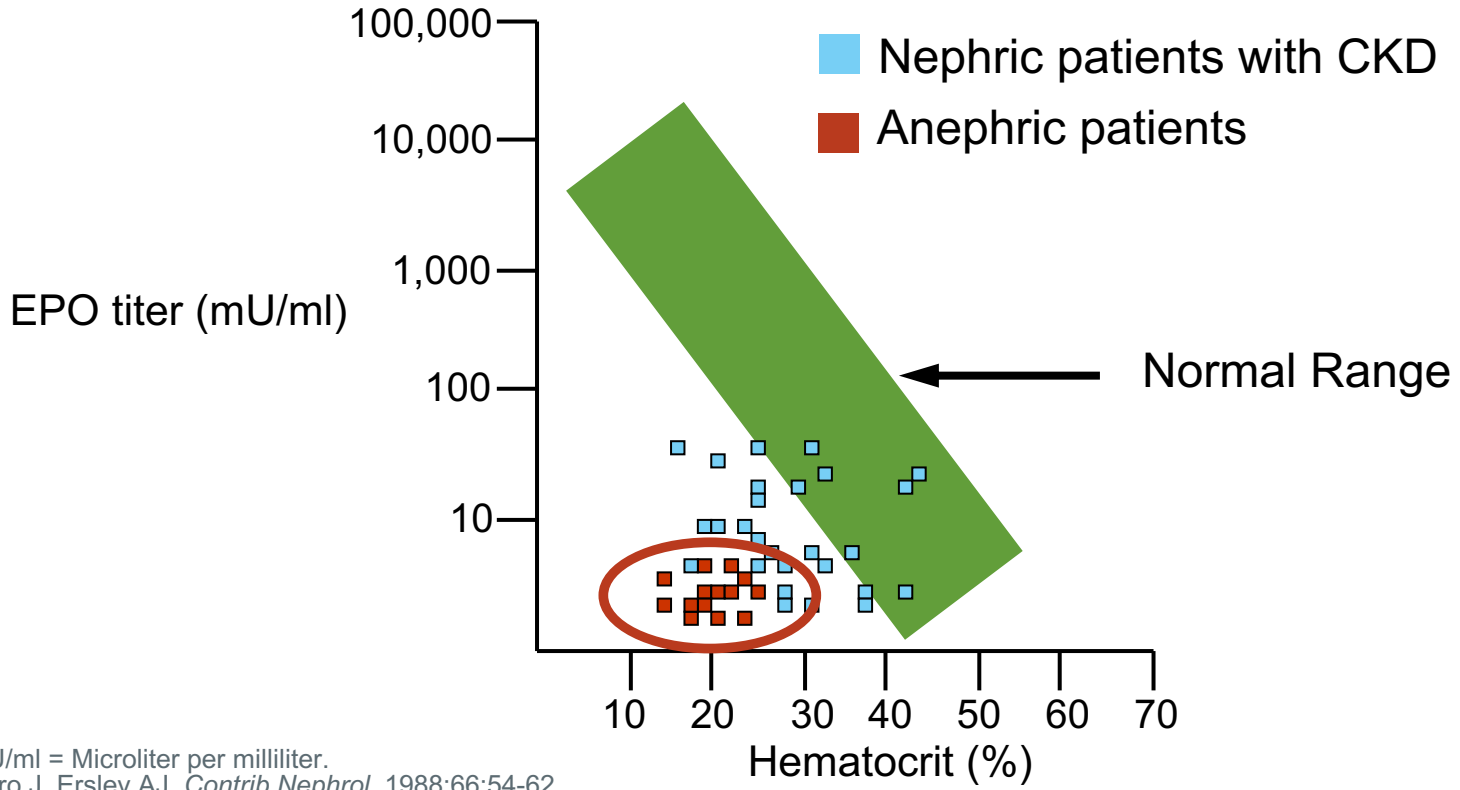

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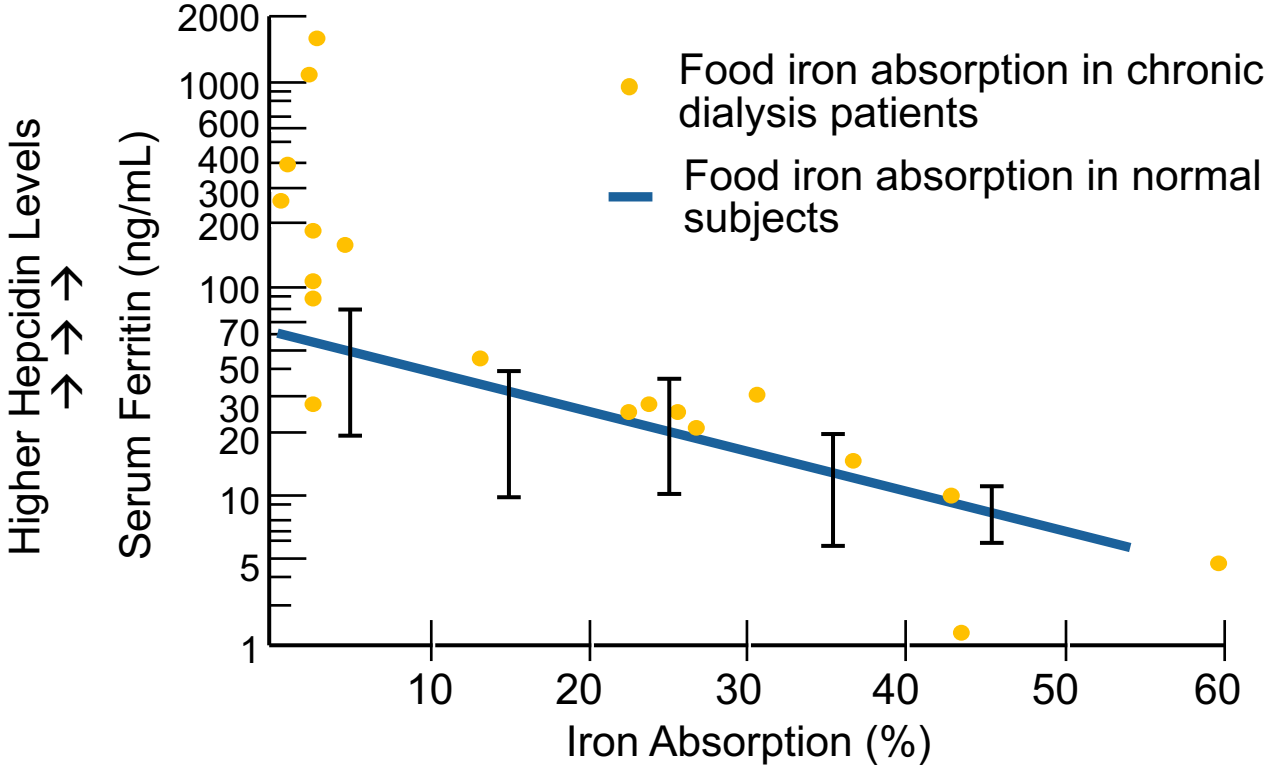
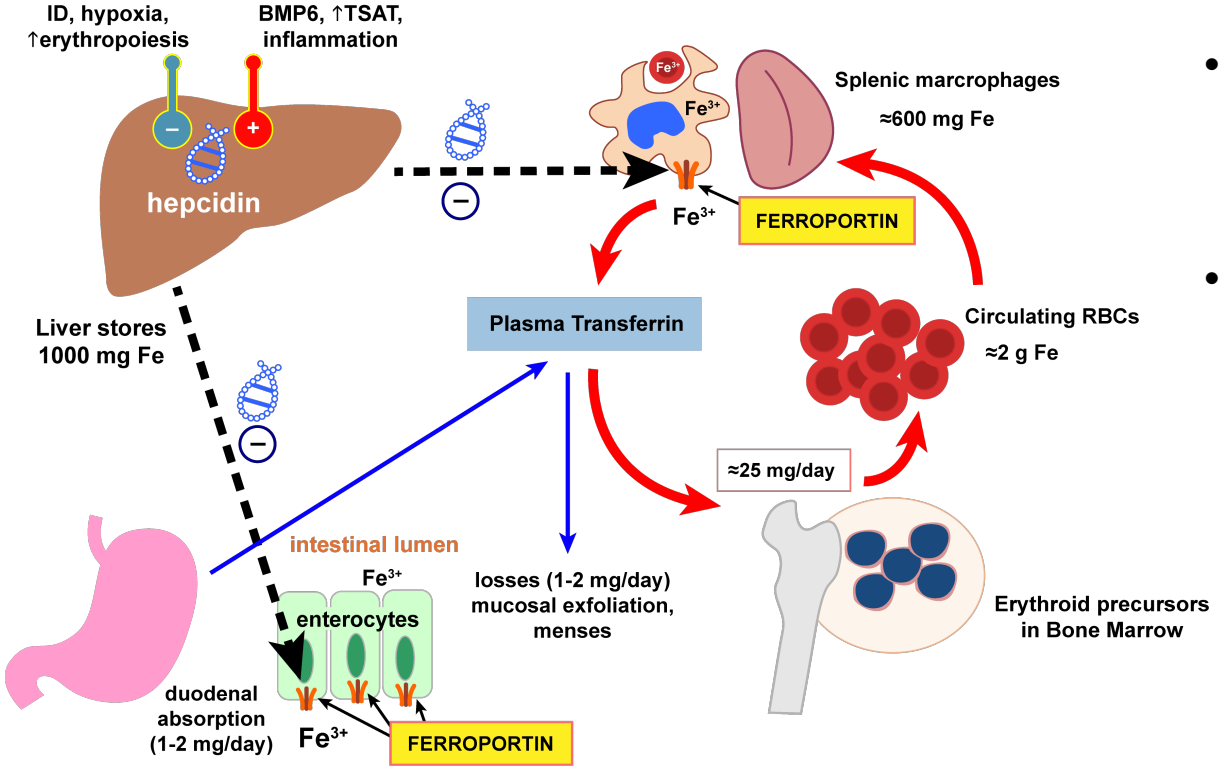
Relationship of Food Iron Absorption to Serum Ferritin Levels



Ng/mL = Nanograms per milliliter.

Eschbach JW, et al. *Ann Intern Med.* 1977;87(6):710-713.

Role of Hepcidin in Iron Balance and Iron Deficiency in CKD



- In CKD, hepcidin dysregulation contributes to iron deficiency anemia
- Hepcidin levels increase in CKD because:
  - Hepcidin cleared by kidneys
  - Inflammation (IL-6) stimulates hepcidin production

BMP6 = Bone morphogenetic protein-6. Fe = Iron. ID = Iron deficiency. Mg/day = milligrams per day. TSAT = Transferrin saturation.

Ganz T. *N Engl J Med.* 2019;381:1148-1157; Girelli D, et al. *Int J Hematol.* 2018;107:16-30.

Faculty Discussion

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Director, Chromalloy American Kidney Center
Division of Nephrology
Washington University School of Medicine
St. Louis, MO

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Learning Objective 2

Implement evidence-based recommendations for the use of iron supplementation and ESAs for anemia in patients with CKD.

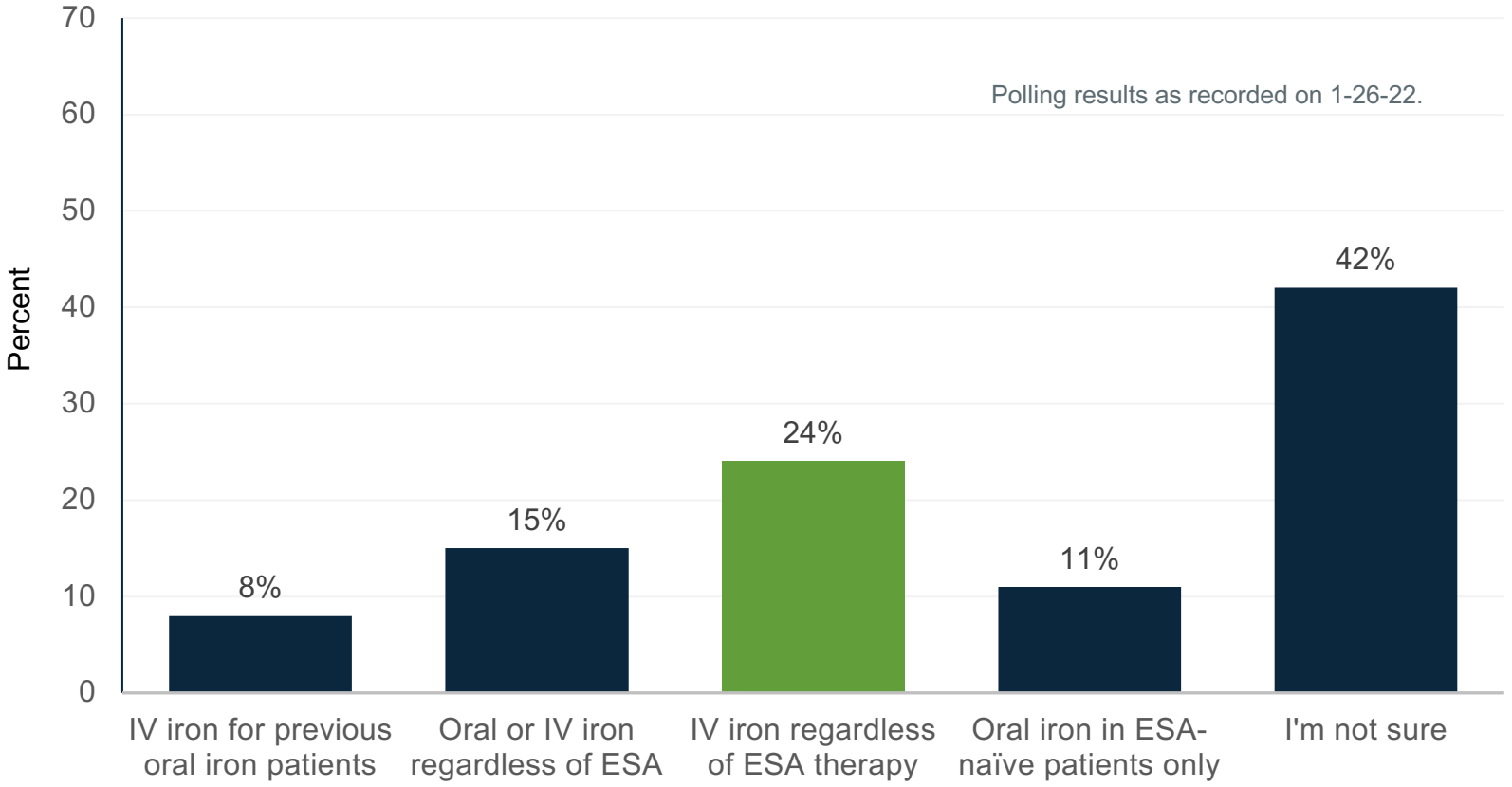
Audience Response

According to KDIGO guidelines for iron in patients with DD-CKD, which of the following is recommended?

A. Intravenous (IV) iron only in patients previously on oral iron
B. Oral or IV iron regardless of ESA therapy
C. Trial of IV iron regardless of ESA therapy
D. Trial of oral iron in ESA-naive patients only
E. I'm not sure

DD = Dialysis-dependent. ESA = Erythropoiesis stimulating agents. KDIGO = Kidney Disease Improving Global Outcomes.

According to KDIGO guidelines for iron in patients with DD-CKD, which of the following is recommended?



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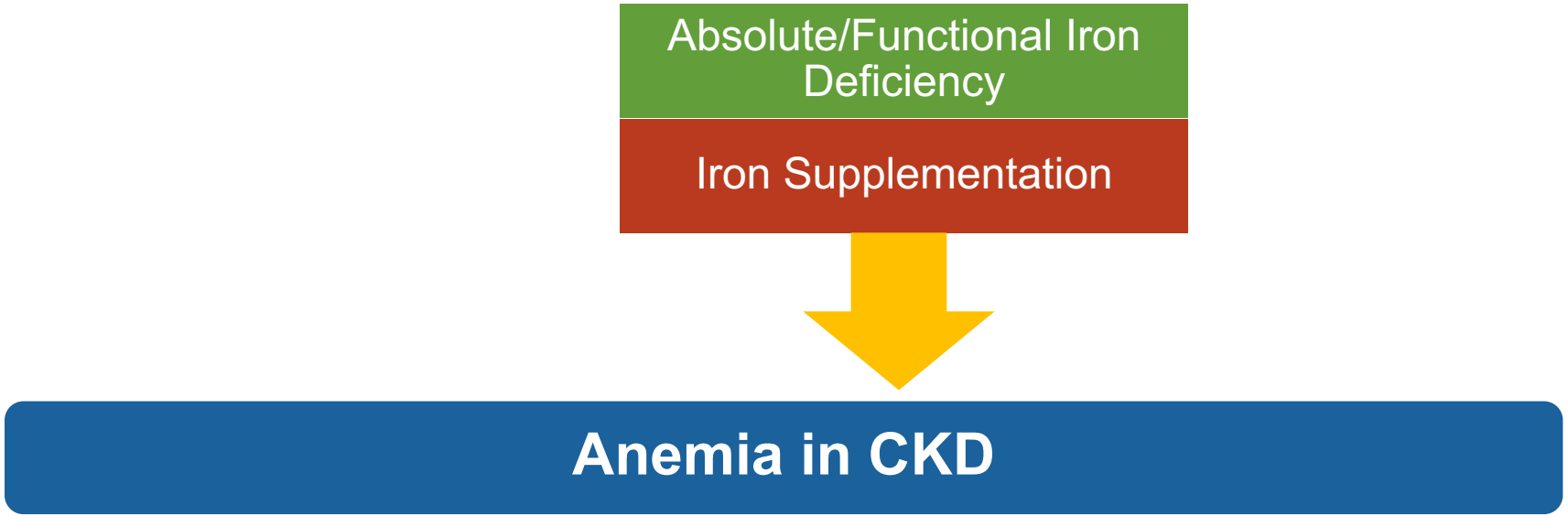
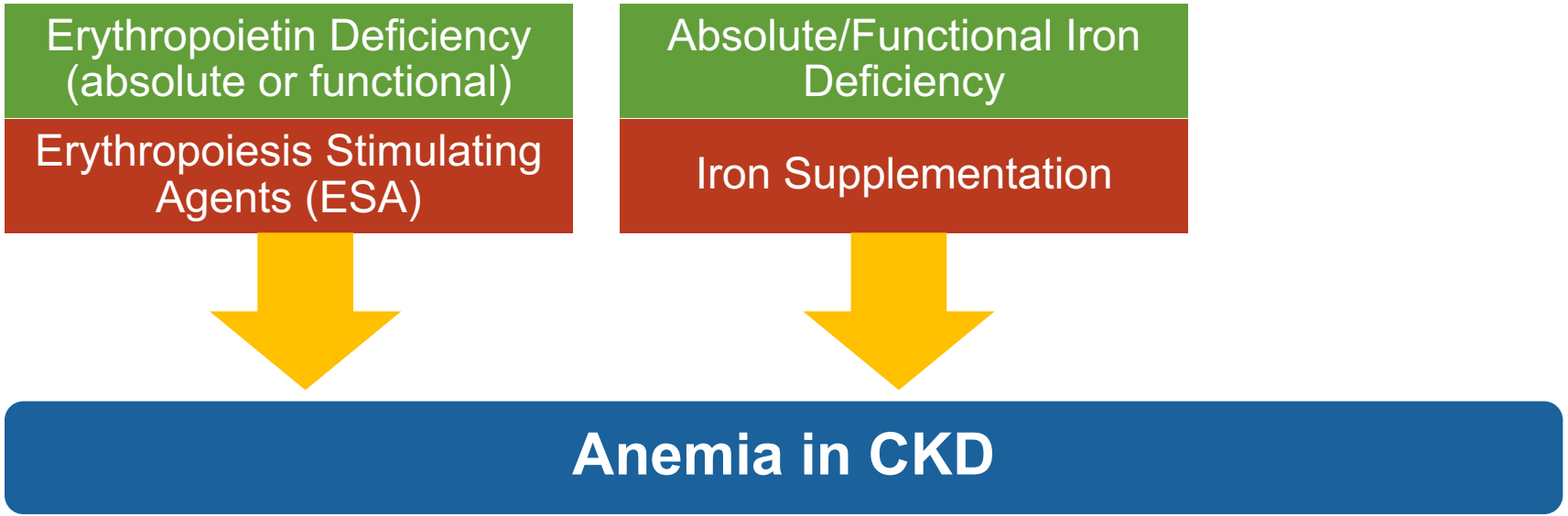
Current Treatments for Anemia in CKD



McMurray JJV, et al. *Kidney Int Suppl.* 2012;2(4):279-335.

Current Treatments for Anemia in CKD



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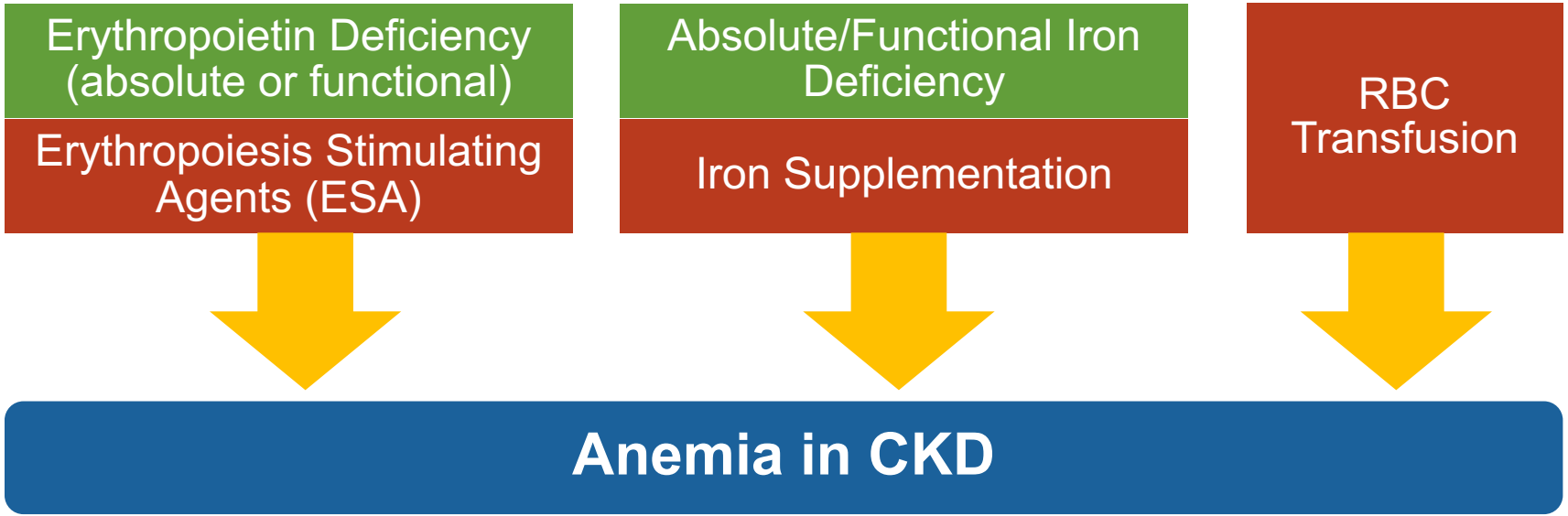

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Benefits and Risks of IV Iron Therapy

Potential Benefits

- Avoid or minimize
  - Blood transfusions
  - ESA therapy
  - Anemia-related symptoms

CV = Cardiovascular.

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Benefits and Risks of IV Iron Therapy

Potential Benefits

- Avoid or minimize
  - Blood transfusions
  - ESA therapy
  - Anemia-related symptoms

Risk of Harms

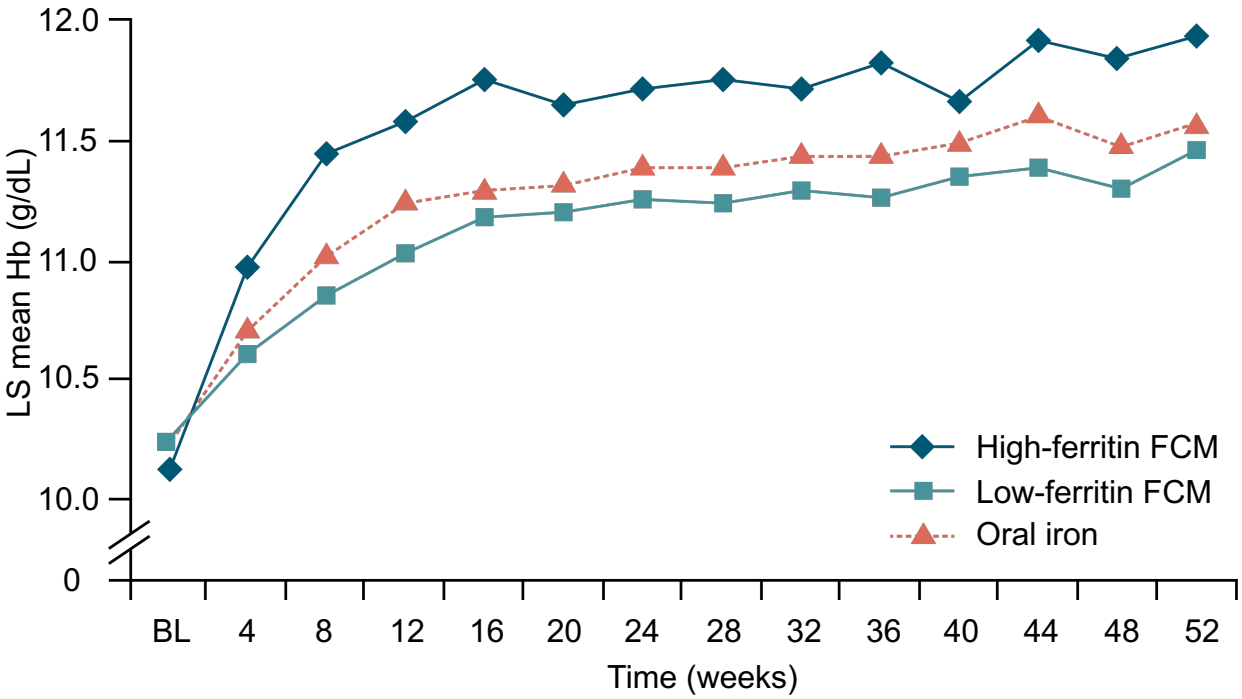
- Anaphylactoid and other acute reactions
- Oxidative stress
- Unknown long-term risks
  - Mortality
  - CV events
  - Infections
  - Tissue depositions

CV = Cardiovascular.

McMurray JJV, et al. *Kidney Int Suppl.* 2012;2(4):279-335.

Ferinject® Assessment in Patients With Iron Deficiency Anemia and Non-Dialysis-Dependent CKD (FIND-CKD)

- 626 CKD patients with anemia (Hb 9-11 g/dL)
- Ferritin <100 ng/mL; or TSAT <20% and ferritin <200 ng/mL
- Randomized to oral iron (100 mg BID PO) vs. IV iron (lower or higher dose)
- Oral iron was as good as low dose IV iron and almost as good as high dose IV iron

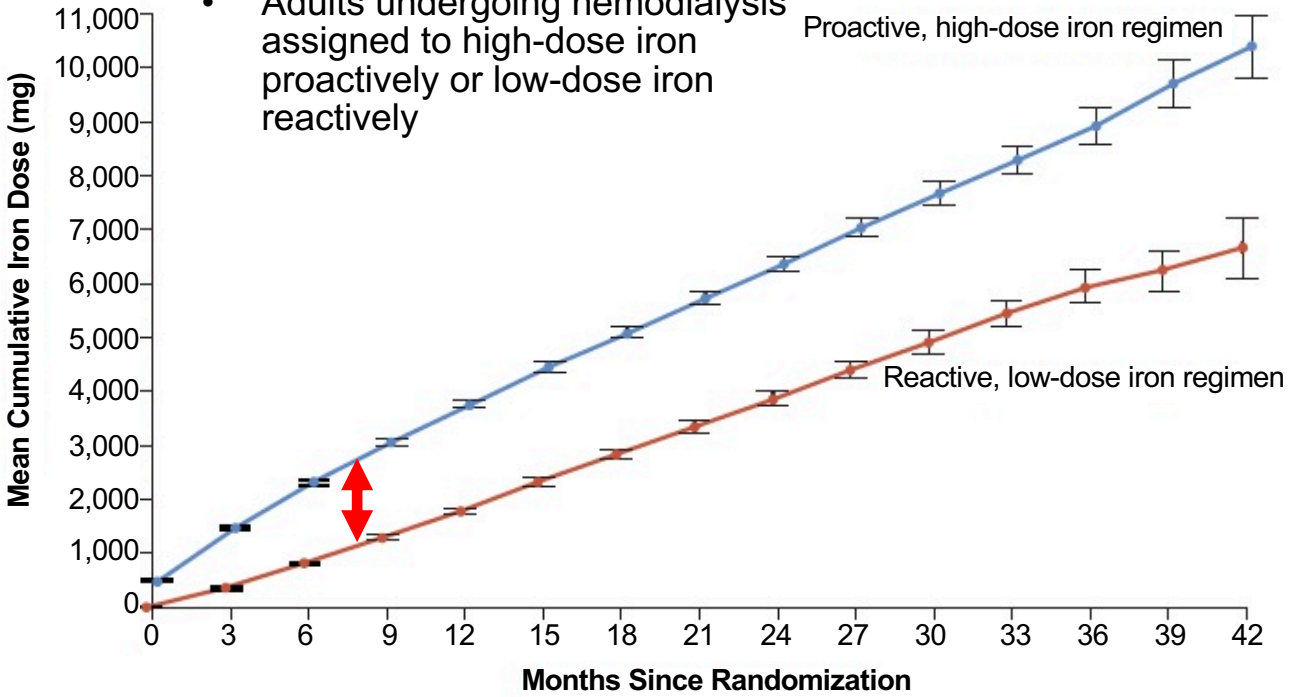


BID = Twice a day. BL = Baseline. g/dL = Grams per deciliter. FCM = Ferric carboxymaltose. Hb = Hemoglobin. LS = Least squares. Ng/mL = Nanograms per milliliter. PO = By mouth.

Macdougall IC, et al. *Nephrol Dial Transplant*. 2014;29(11):2075-2084.

PIVOTAL Trial in CKD-DD: IV Iron in Patients on Maintenance Hemodialysis

- Adults undergoing hemodialysis assigned to high-dose iron proactively or low-dose iron reactively

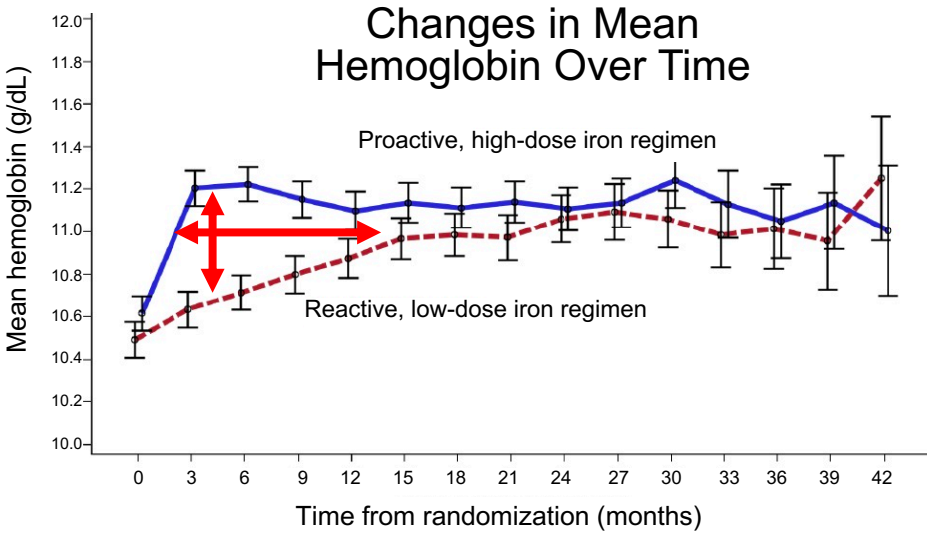


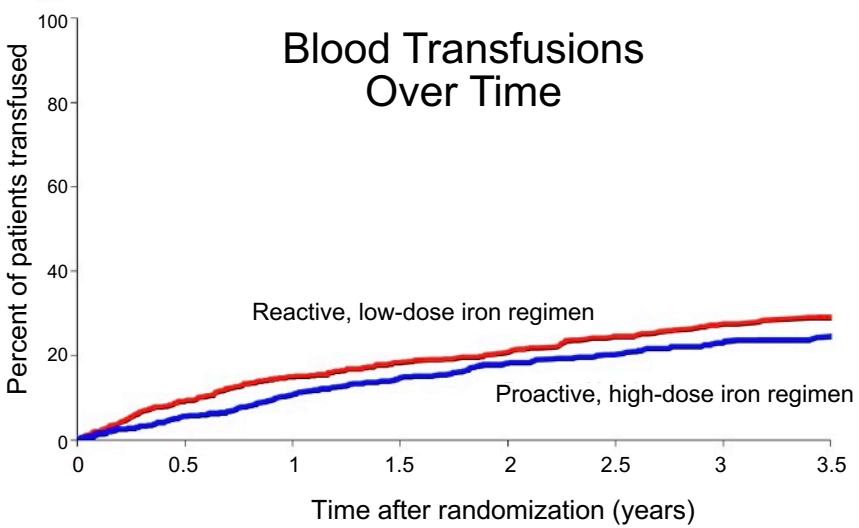
- 1st year: proactive arm rec'd ~ 3.8 grams of IV iron
- 1st year: reactive arm rec'd ~ 1.8 grams of iron
- After 1st year, average monthly iron was ~ 200 mg/month vs. ~ 165 mg/month

PIVOTAL = **P**roactive **IV** ir**O**n **T**herapy in haemodi**AL**ysis patients

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

PIVOTAL Trial: Changes in Hemoglobin, Blood Transfusions



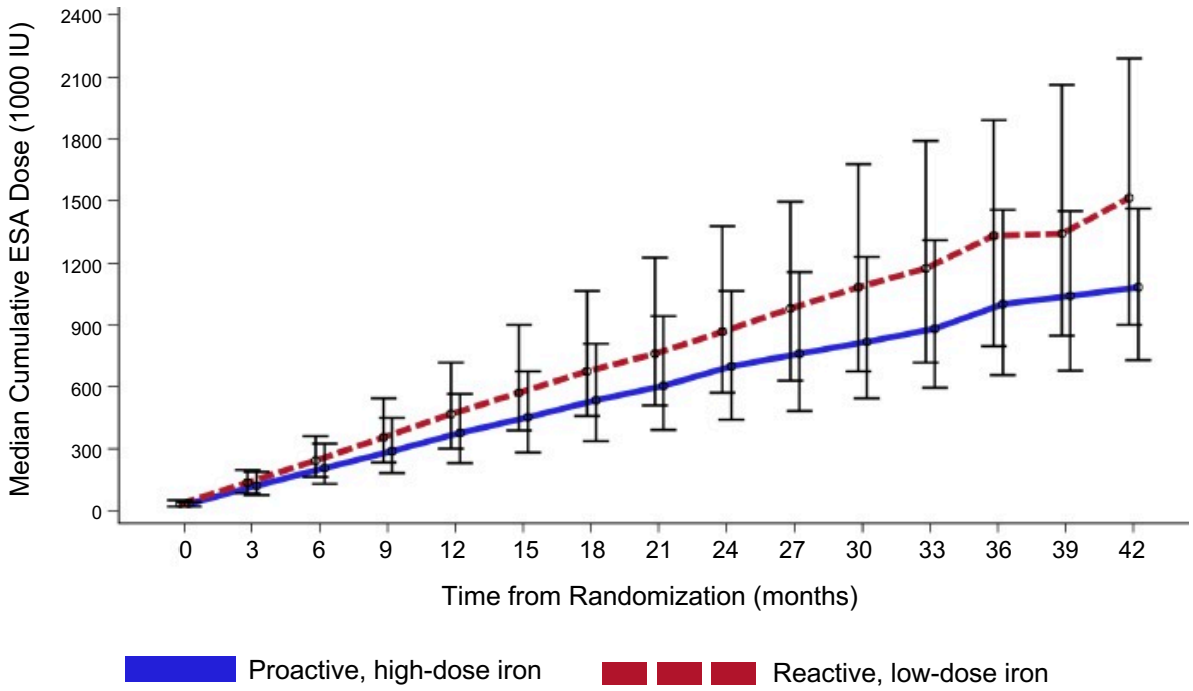


- During the first year, the proactive iron arm increased hemoglobin more than a reactive iron policy and led to fewer transfusions

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

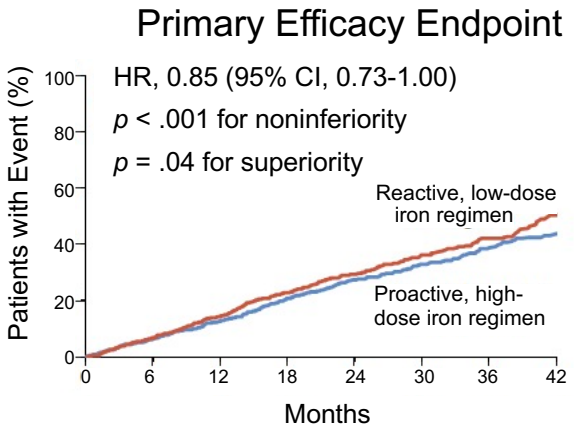
PIVOTAL Trial: Median Cumulative ESA Dose Exposure

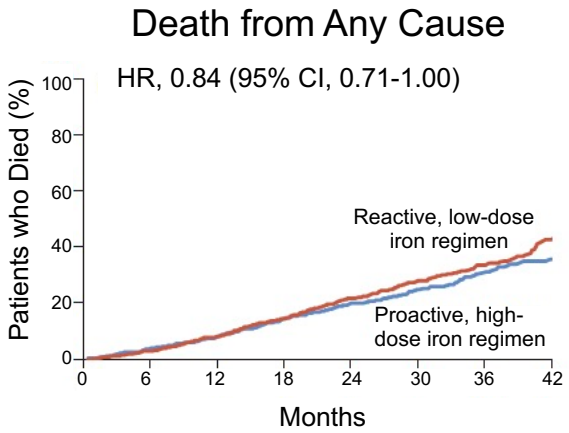
- Iron loading then maintenance iron decreases ESA exposure
- Less EPO is associated with fewer CV events, HF admissions, and deaths.

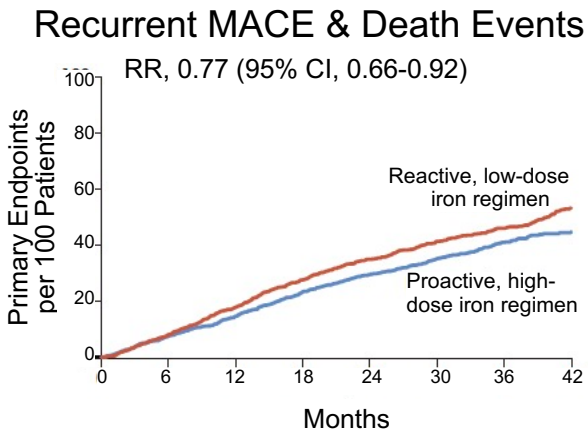


HF = Heart failure. IU = International units.
Macdougall IC, et al. *N Engl J Med*. 2019;380:447-458.

PIVOTAL Trial: IV Iron in Patients Undergoing Maintenance Hemodialysis







Proactive, high-dose iron Reactive, low-dose iron

- IV iron loading and maintaining high iron stores is safe, beneficial, and less costly
- “The infection rate was the same in the two groups”

CI = Confidence interval. HR = Hazard ratio. MACE = Major adverse cardiovascular event. RR = Rate ratio.

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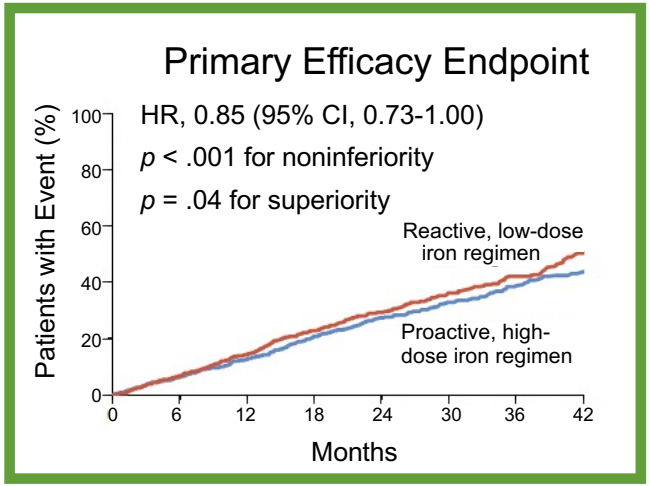

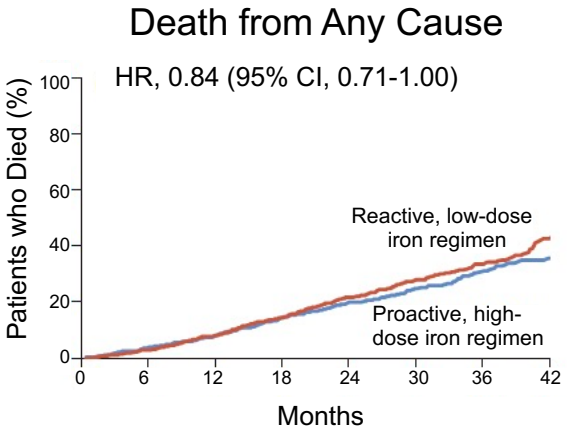

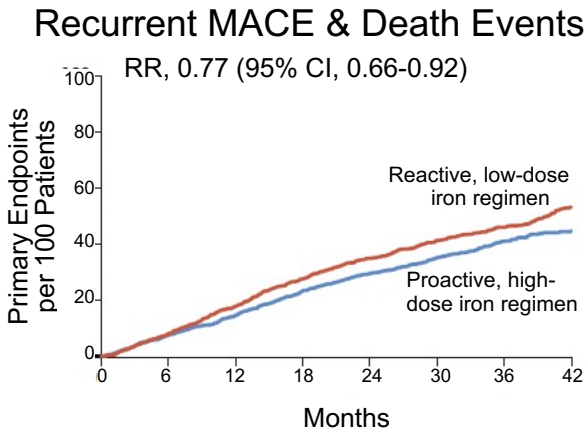

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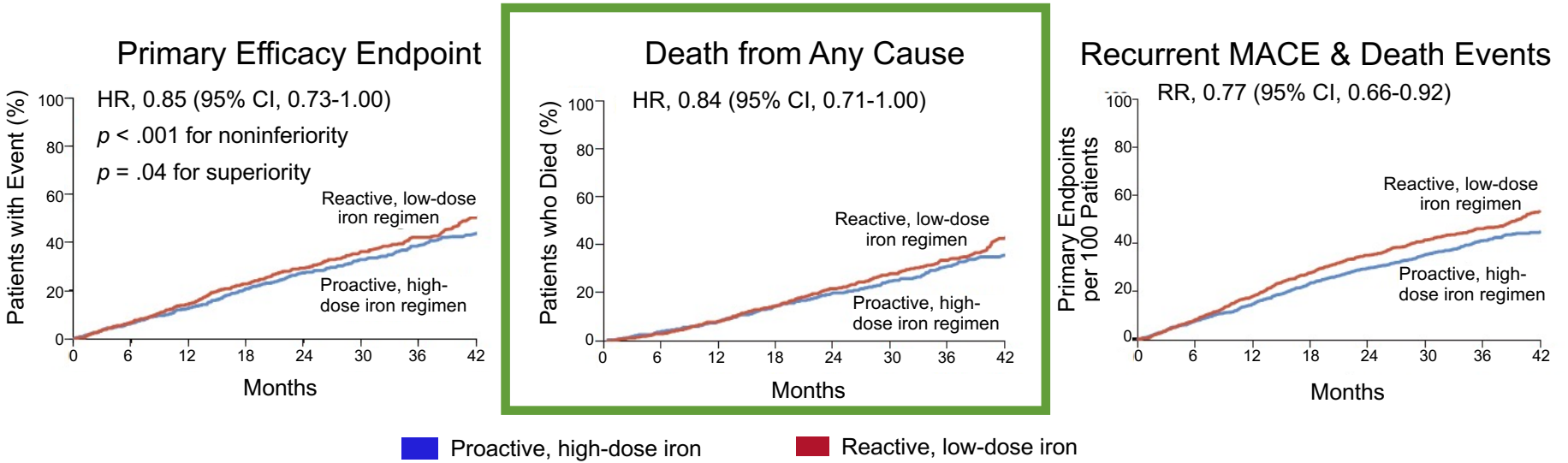

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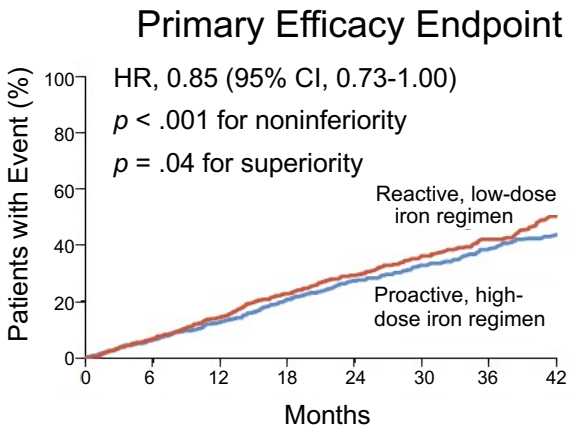

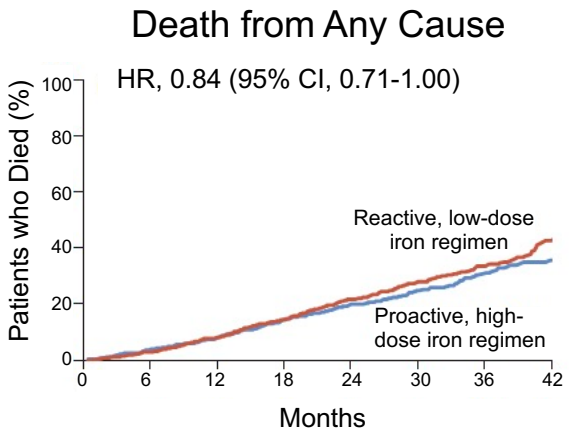

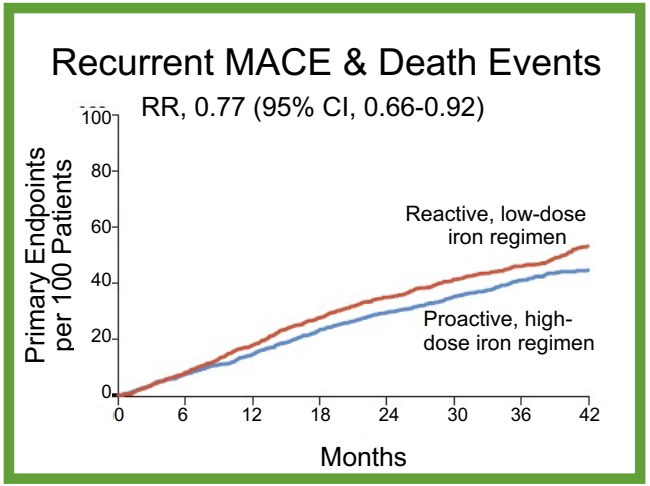

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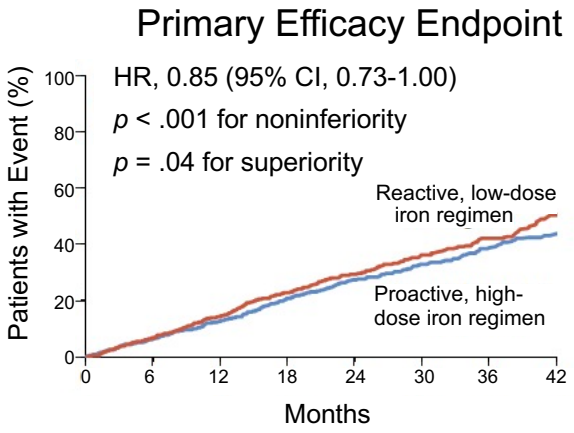

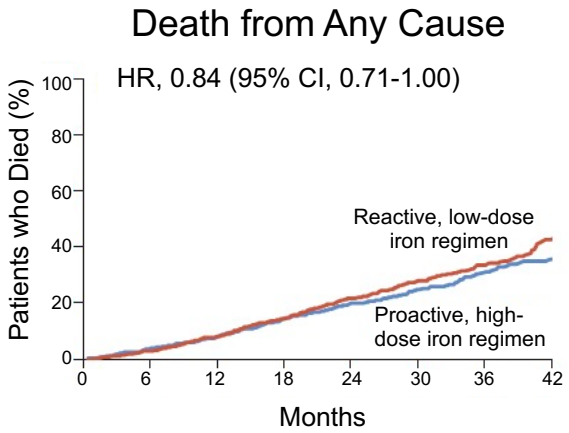

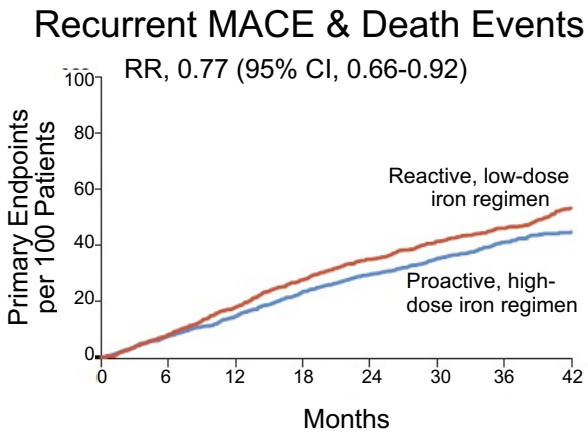

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KDIGO Clinical Practice Guideline: Iron

- Balance potential benefits of avoiding/minimizing transfusions, ESA therapy, and anemia-related symptoms against risks of therapy
- CKD-DD: trial of IV iron regardless of ESA therapy
- CKD-NDD: oral or IV iron depends on severity of iron deficiency and experience with prior iron therapy

NDD = Non-dialysis dependent.

McMurray JJV, et al. *Kidney Int Suppl.* 2012;2(4):279-335.

KDIGO Clinical Practice Guideline: ESAs

- Address all correctable causes of anemia prior to initiation of ESA therapy
- Balance potential benefits of reducing RBC transfusions and anemia-related symptoms against risk of harm in individual patients
- Individualize decision to treat based on rate of fall of Hb concentration, prior response to iron therapy, risk of needing transfusion, risk related to ESA therapy, presence of symptoms attributable to anemia

McMurray JJV, et al. *Kidney Int Suppl.* 2012;2(4):279-335.

Faculty Discussion

CME OUTFITTERS

Bruce S. Spinowitz, MD

Associate Director, Nephrology
Vice Chairman, Medicine
New York-Presbyterian Queens
Professor of Clinical Medicine
Weill Cornell Medical College
New York, NY

CME OUTFITTERS

Learning Objective 3

Appraise the safety and efficacy, as well as the PK and PD profiles of emerging HIF-PHIs for DD- and NDD-CKD.

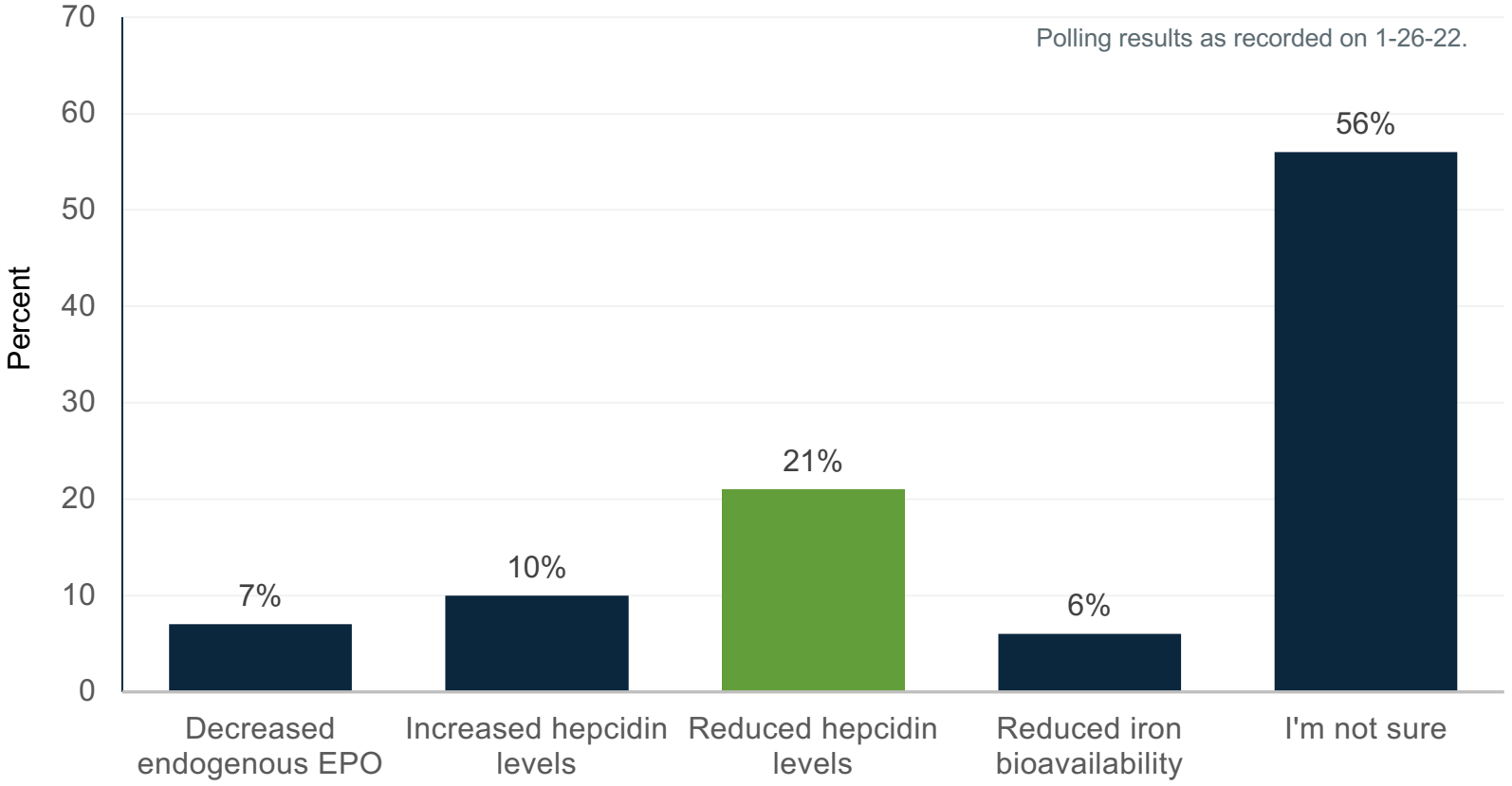
Audience Response

Which of the following is associated with HIF-PHI therapy?

A. Decreased production of endogenous EPO
B. Increased hepcidin levels
C. Reduced hepcidin levels
D. Reduced iron bioavailability
E. I'm not sure

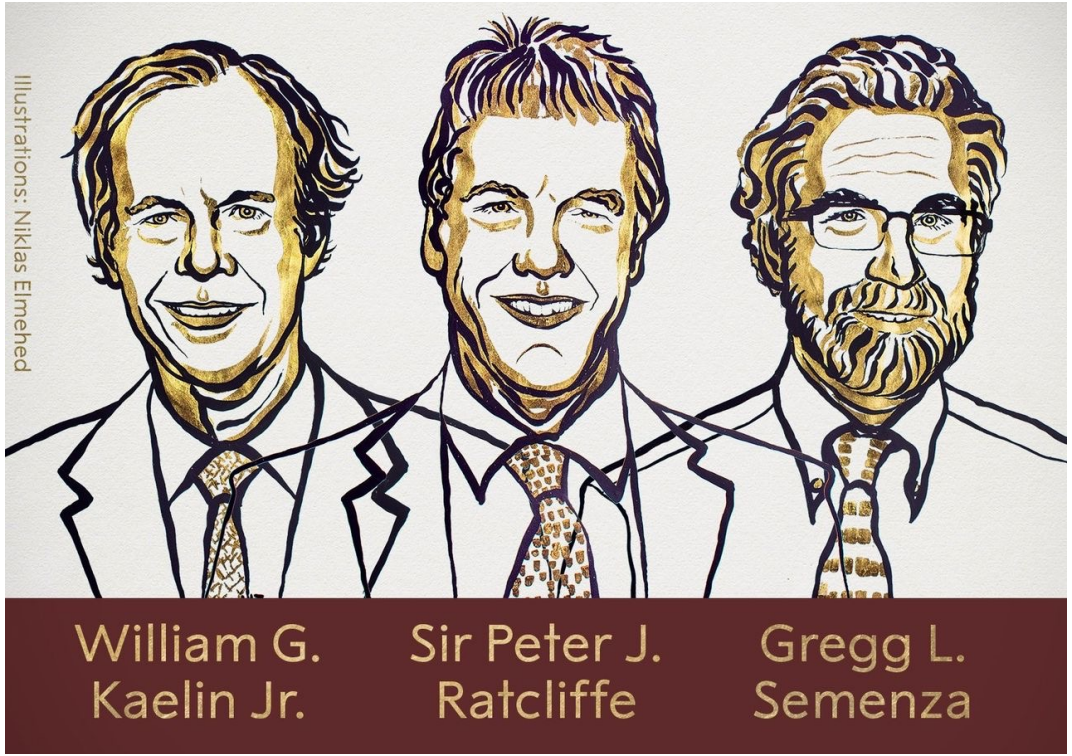
HIF-PHI = hypoxia-inducible factor prolyl hydroxylase inhibitors.

Which of the following is associated with HIF-PHI therapy?



CME OUTFITTERS

The Nobel Prize in Physiology or Medicine 2019

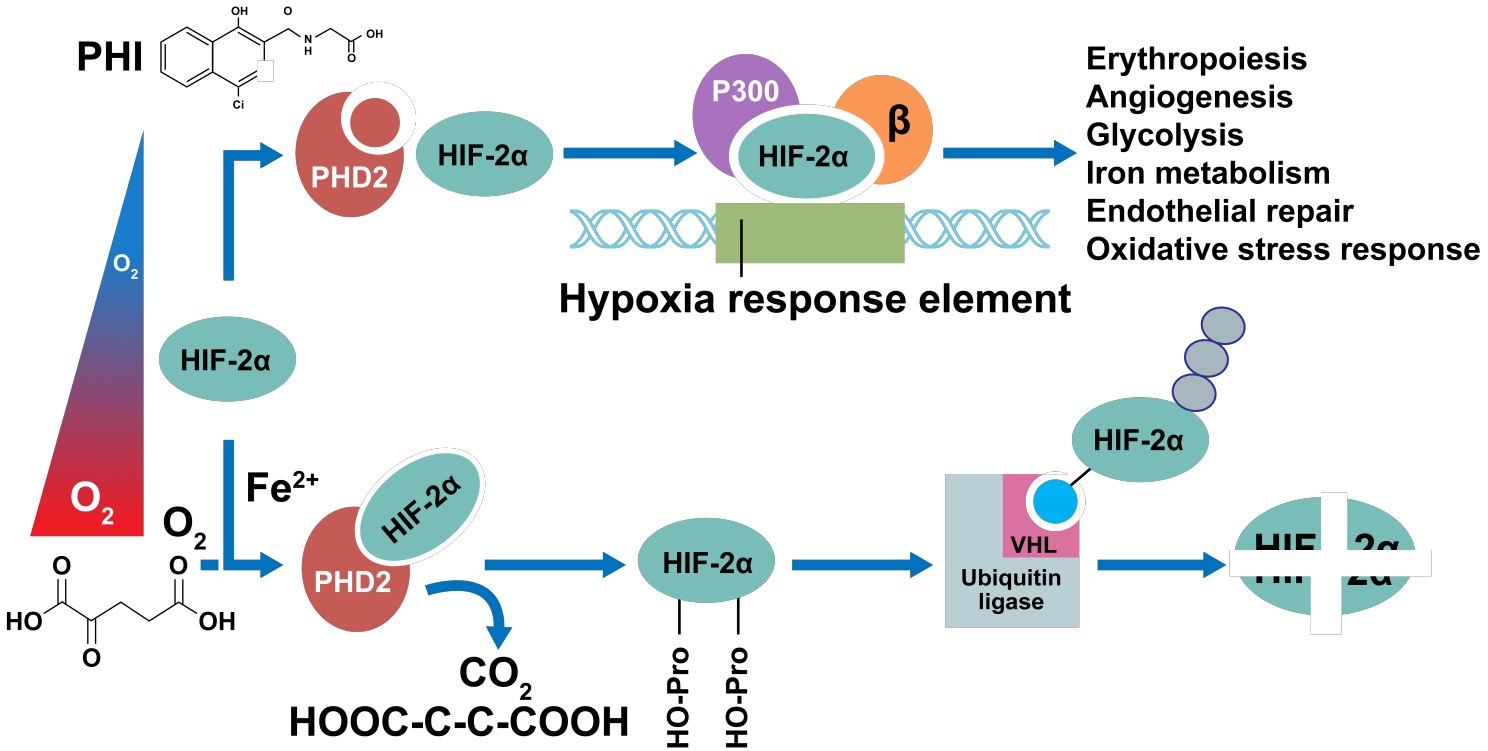


"…for their discoveries of how cells sense and adapt to oxygen availability"

The Nobel Assembly at Karolinska Institutet

Adapted from the official announcement of laureates. Nobel Prize Institute. 2019. Illustration by Niklas Elmehed.

Control of Erythropoietin Production by the HIF Pathway and PHD Enzymes



PHD = Prolyl hydroxylase domain. PHI = Prolyl hydroxylase domain-containing enzyme inhibitors. VHL = von Hippel-Lindau.
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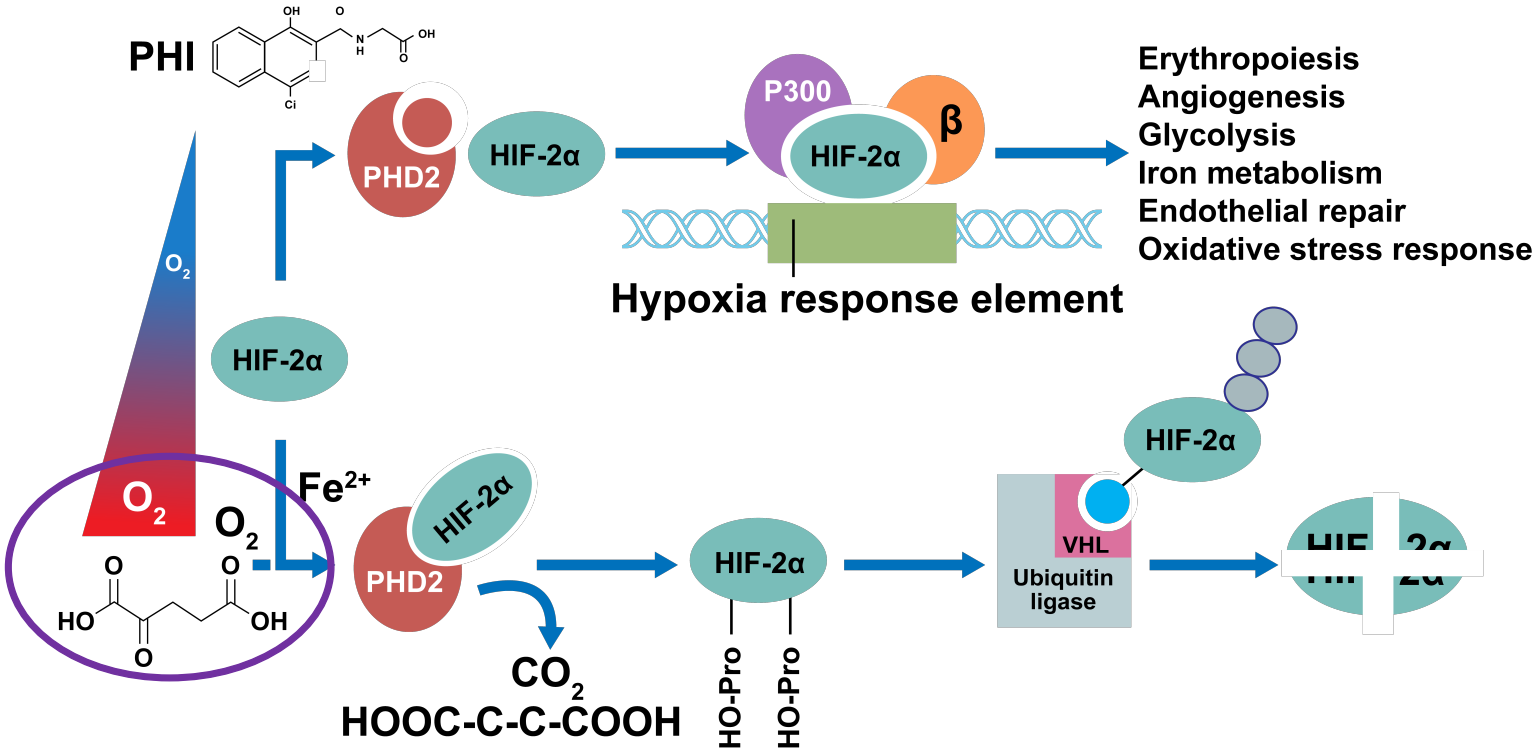

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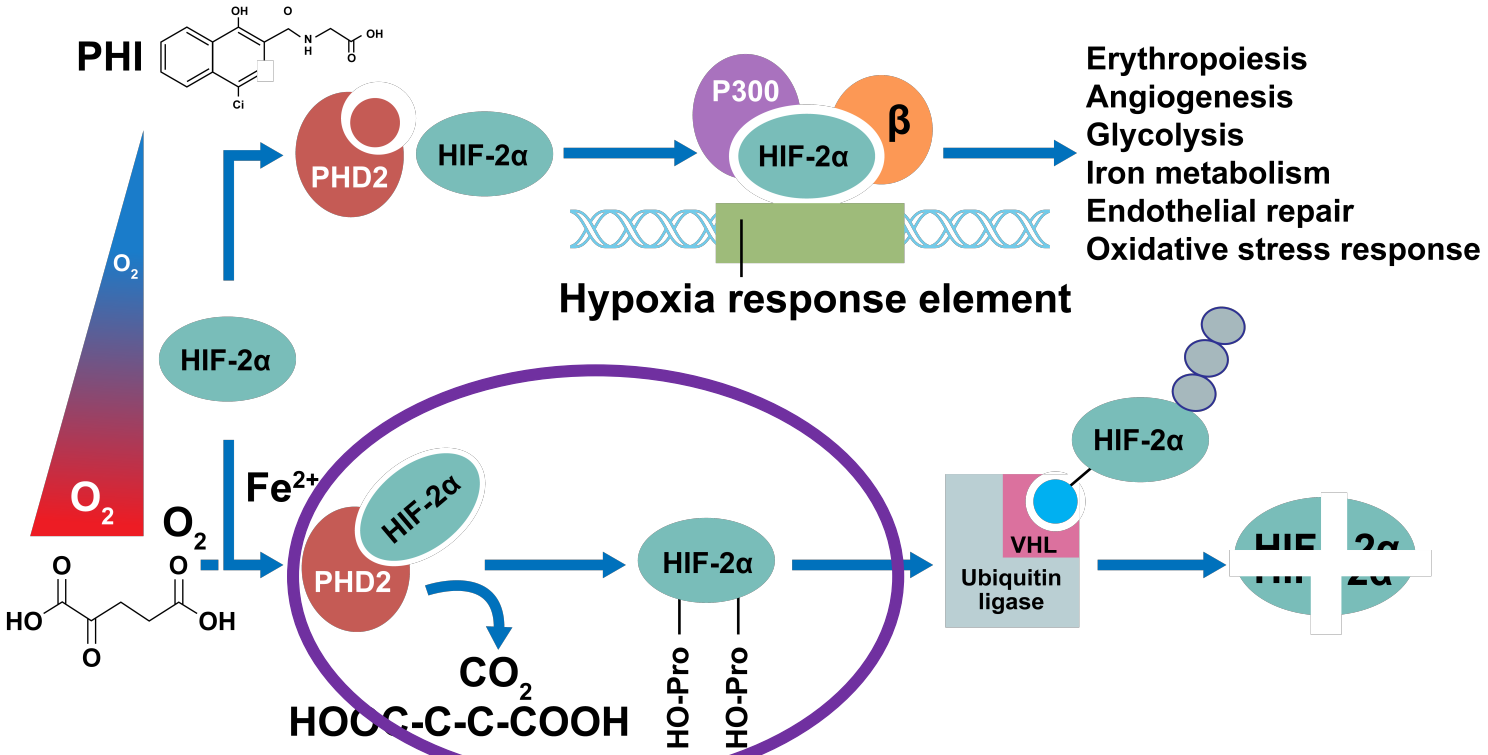

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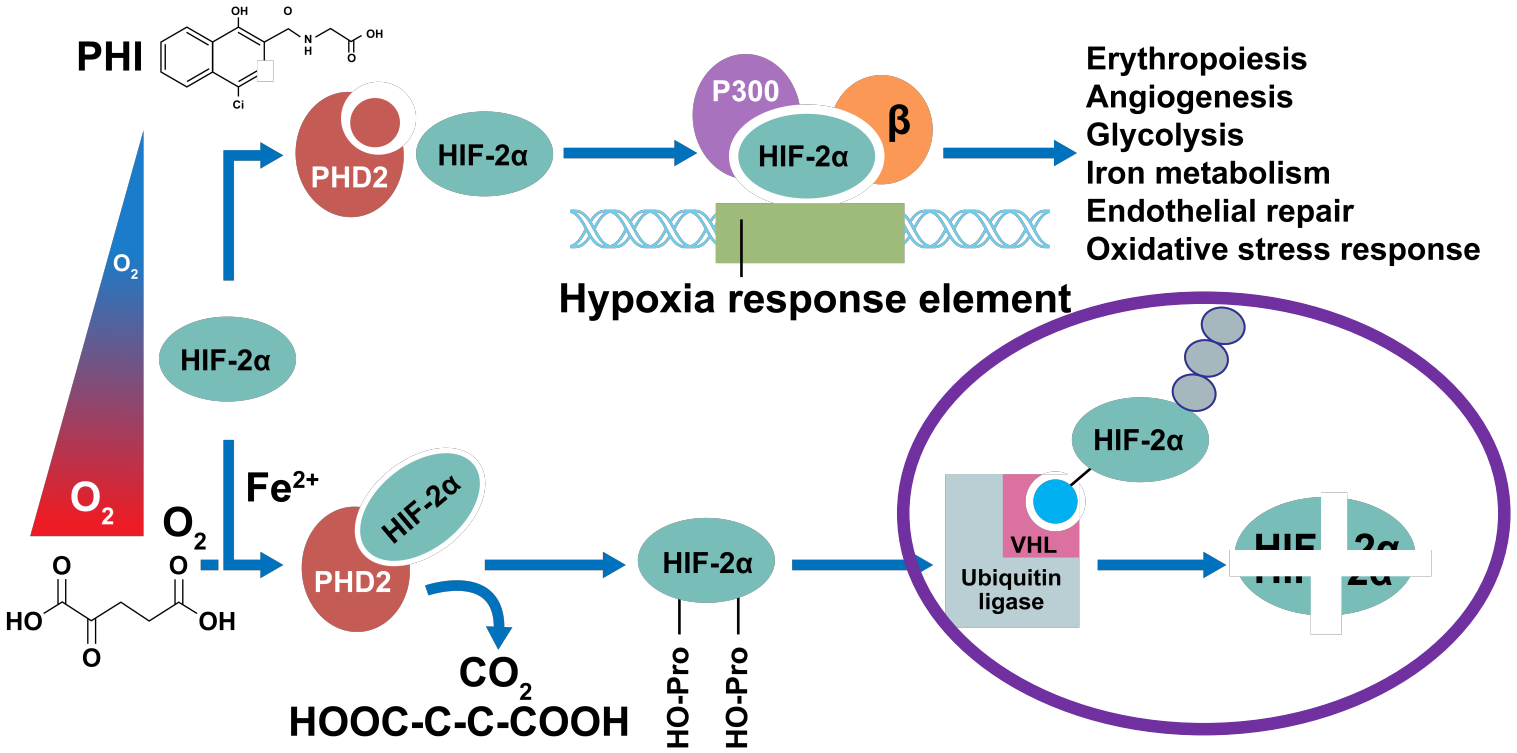

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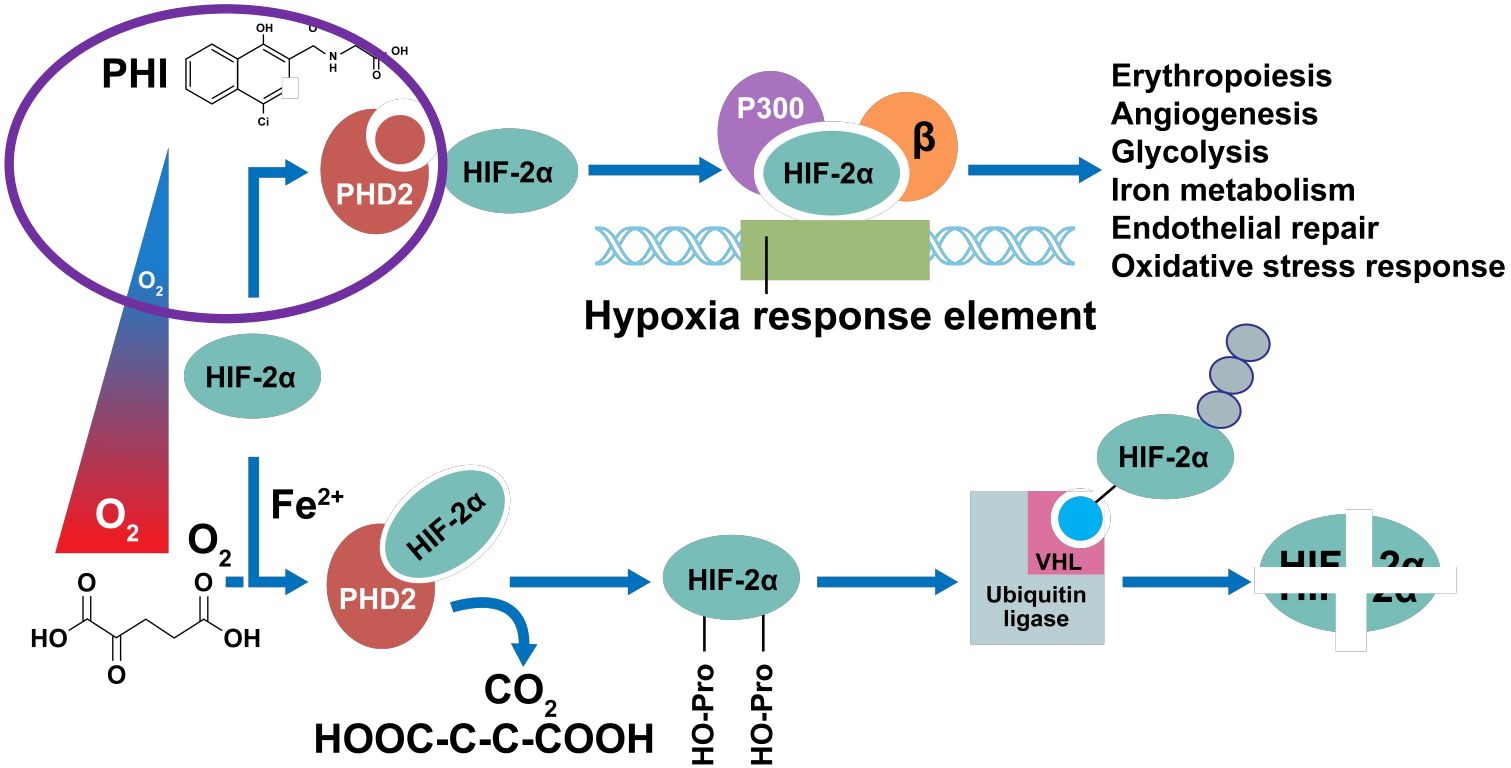

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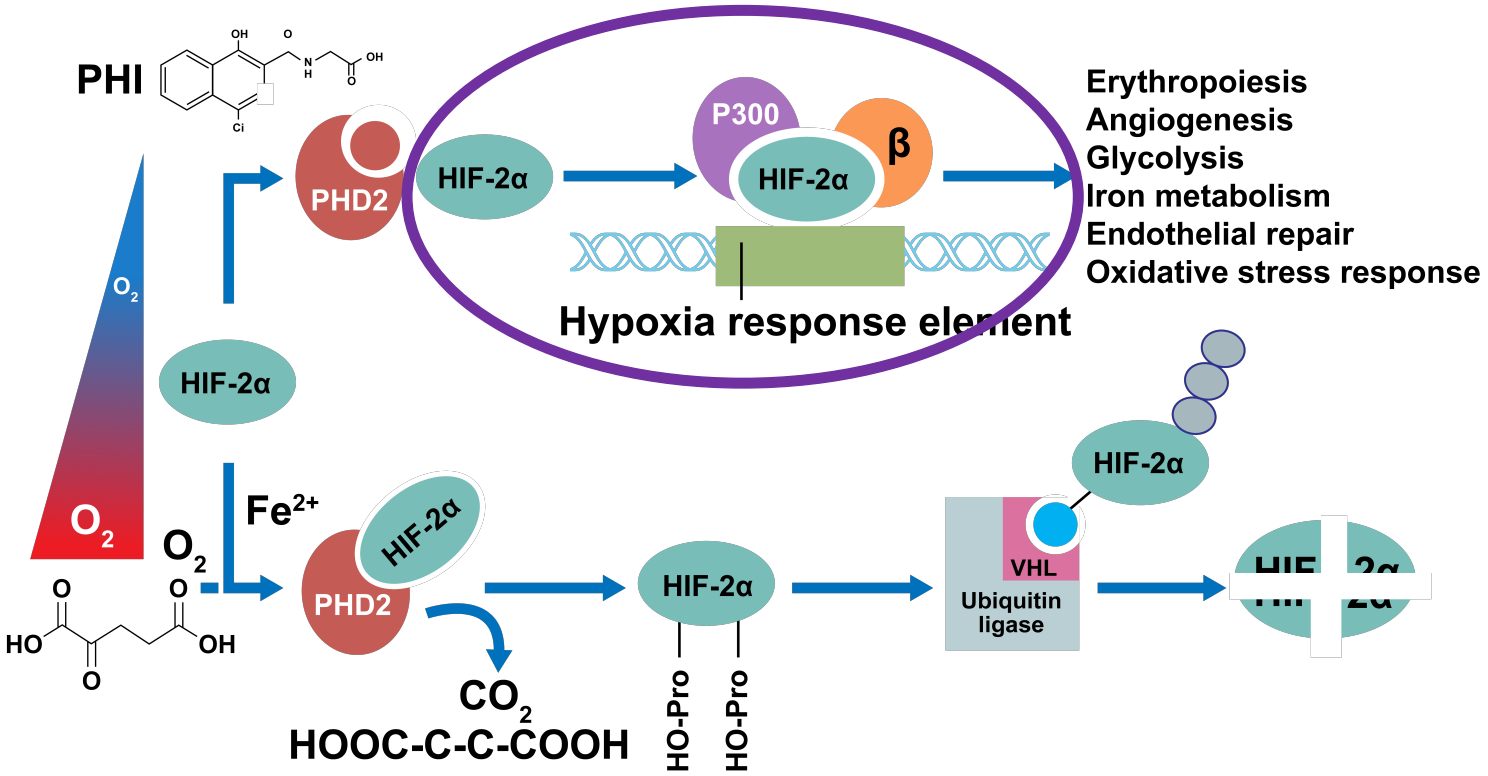

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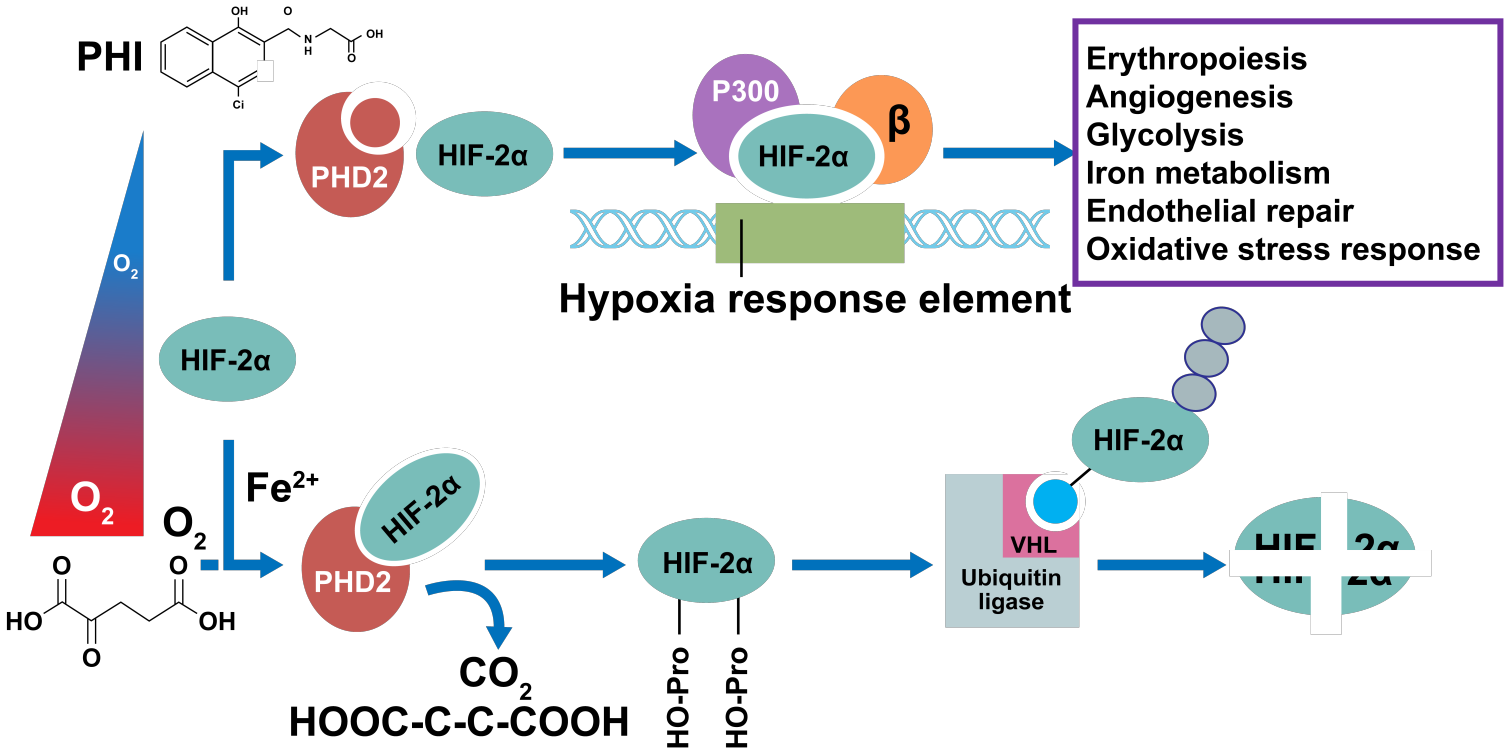

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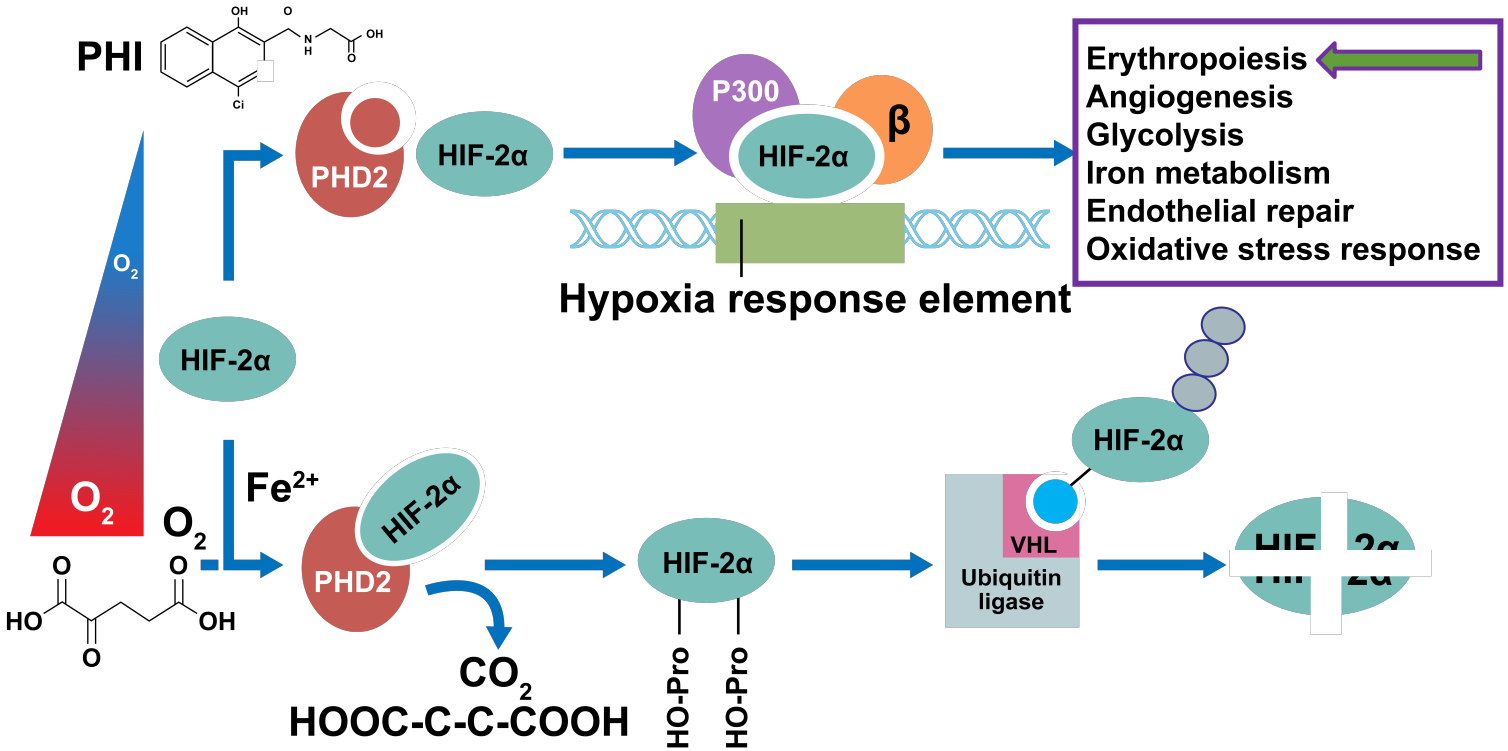

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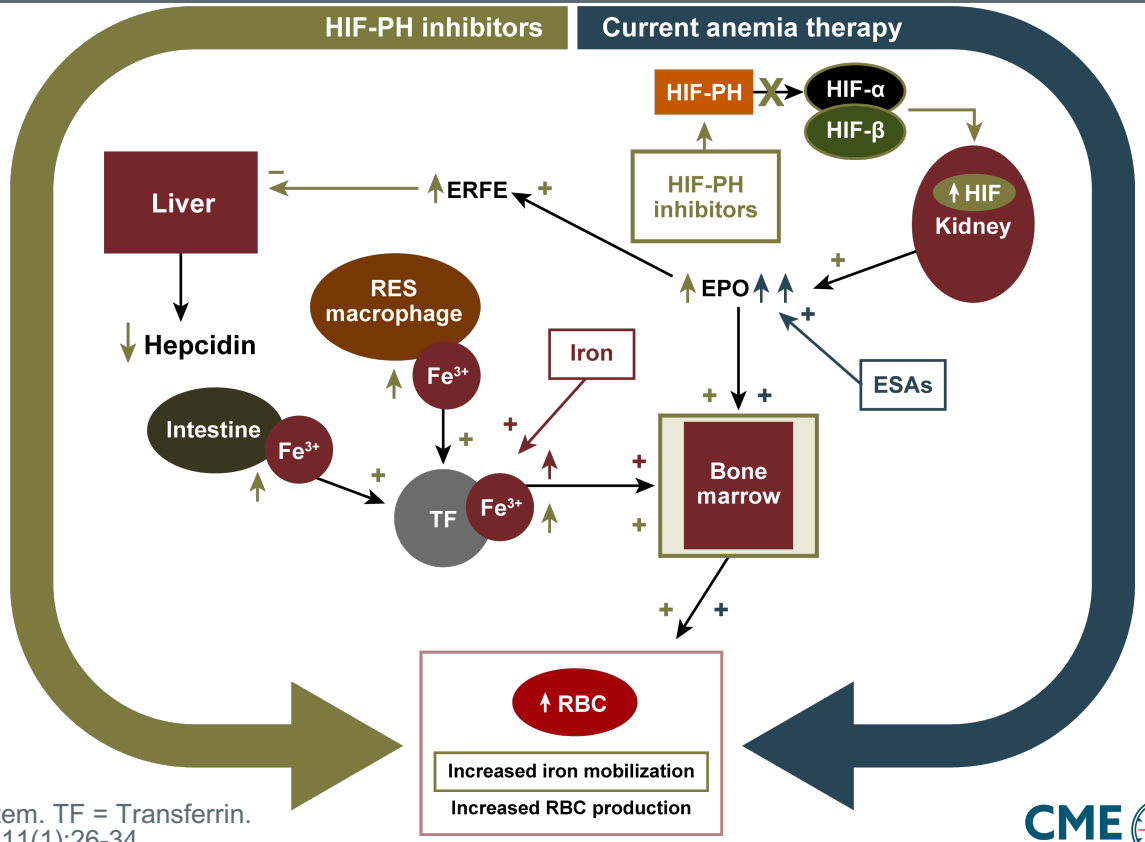
Effect of HIF-PHIs on Management of Anemia in CKD

- Oral HIF-PHIs
- Suppresses hepcidin and promotes iron bioavailability



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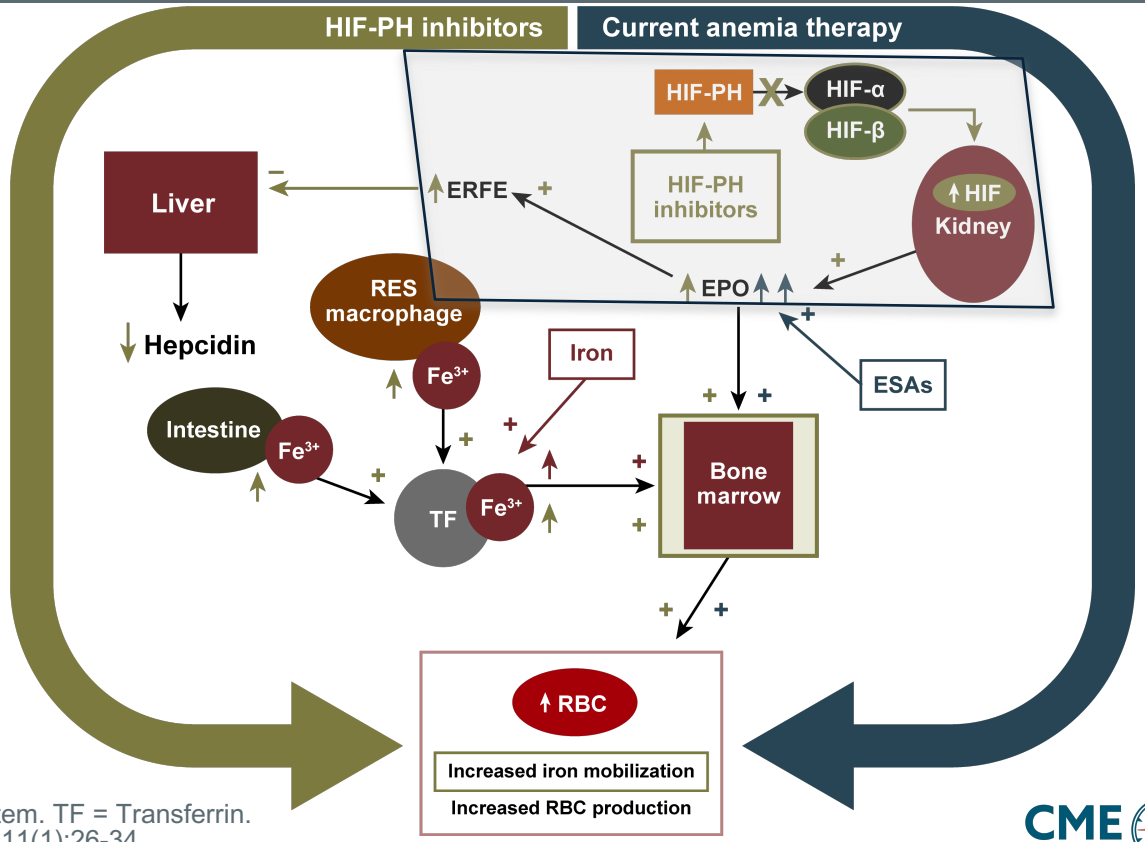

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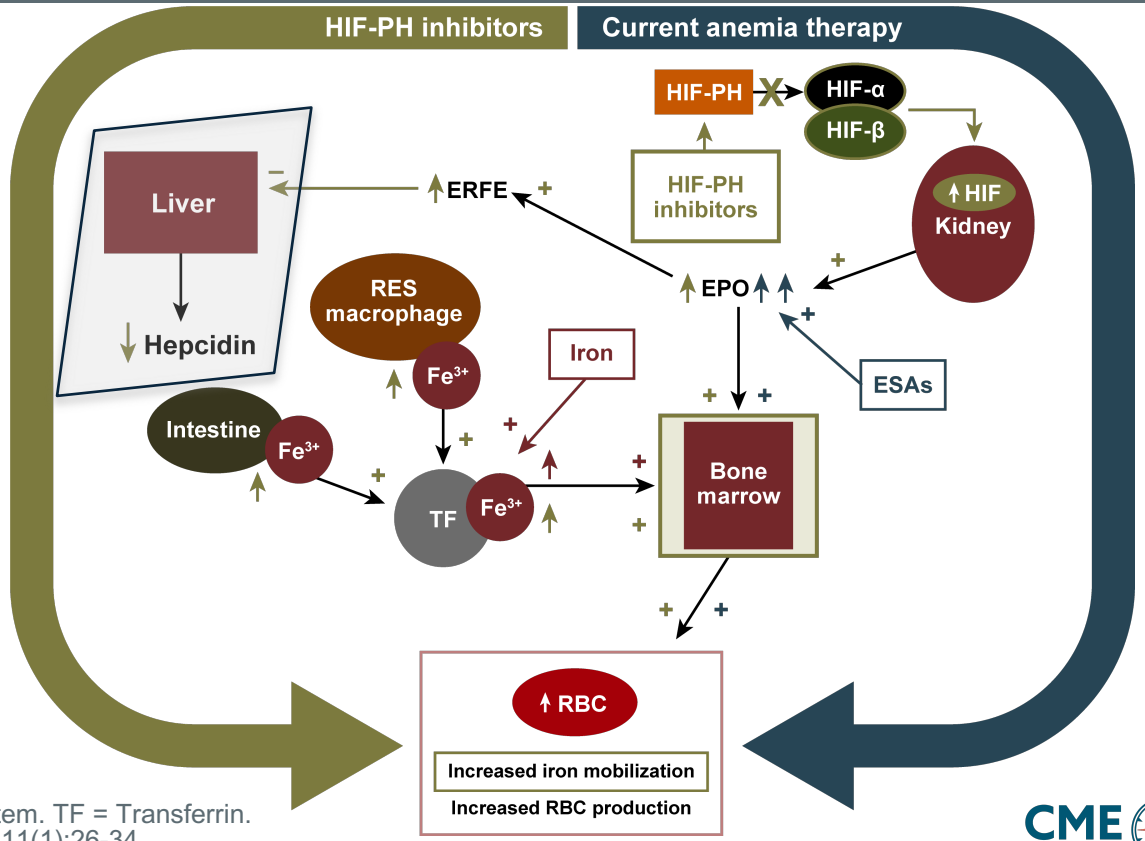

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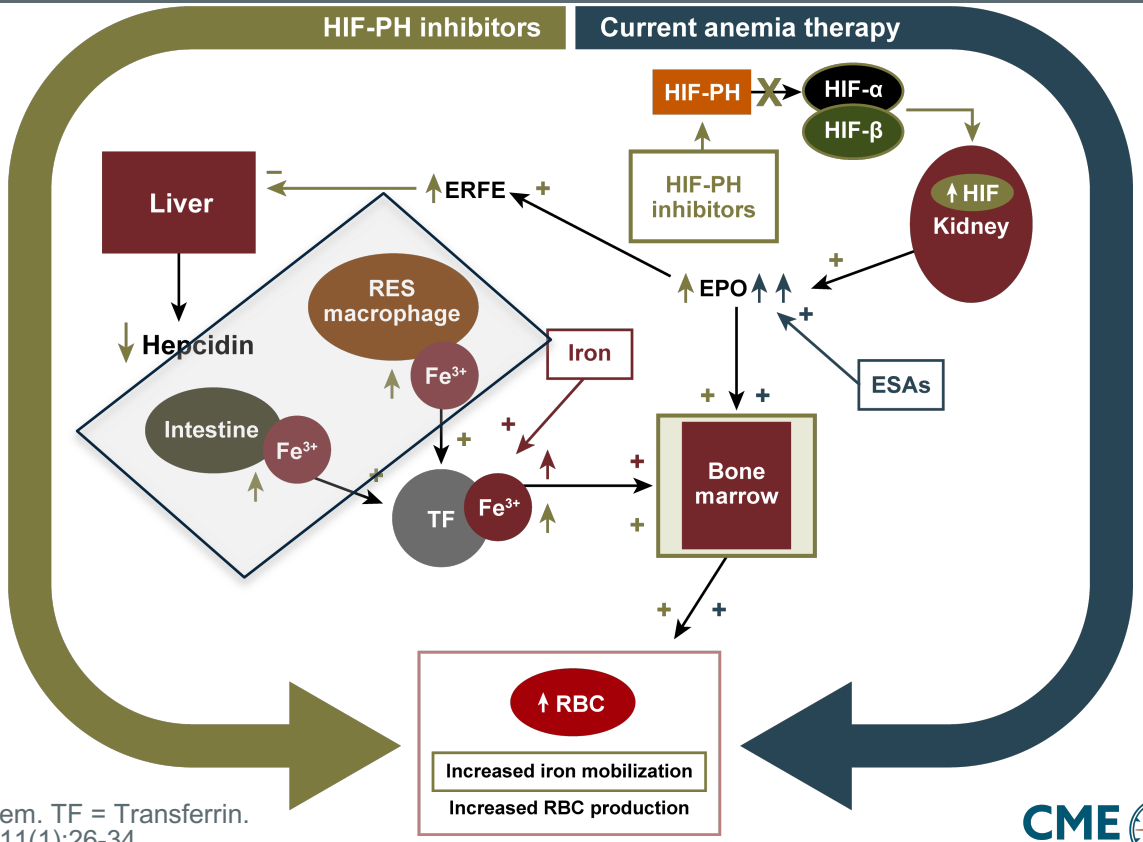

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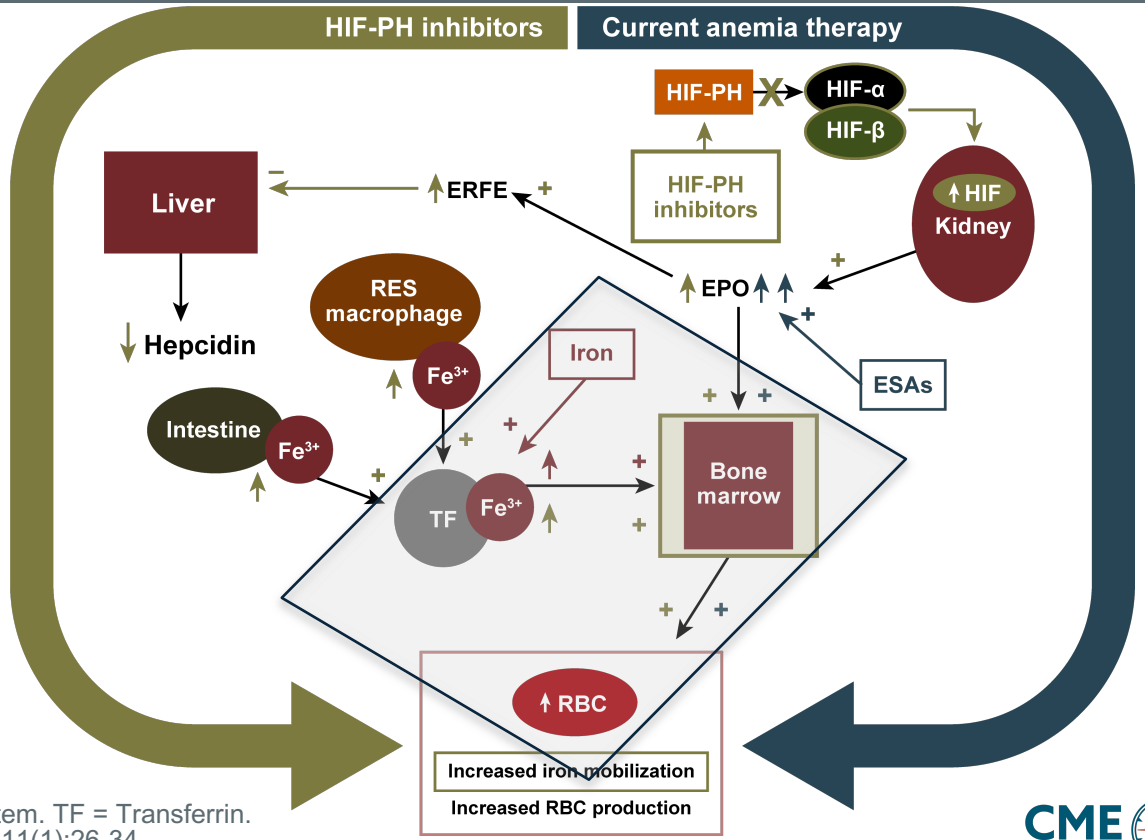

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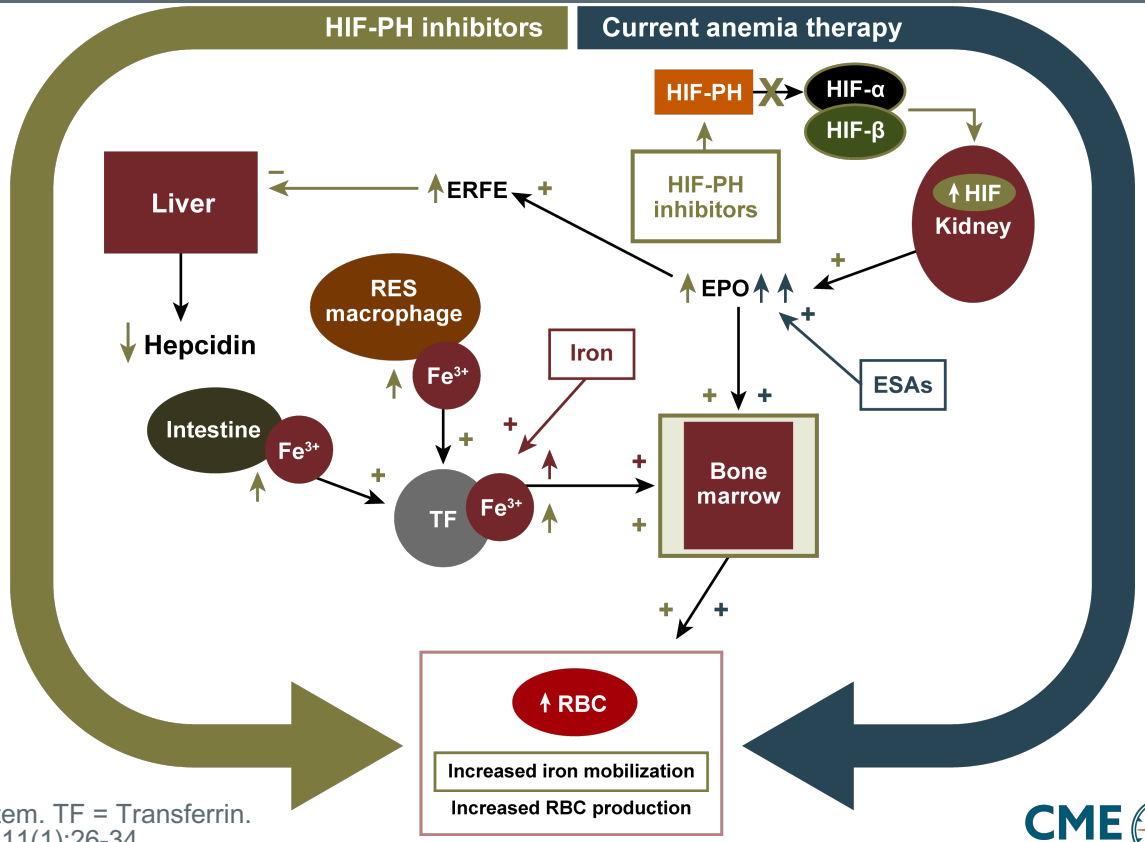

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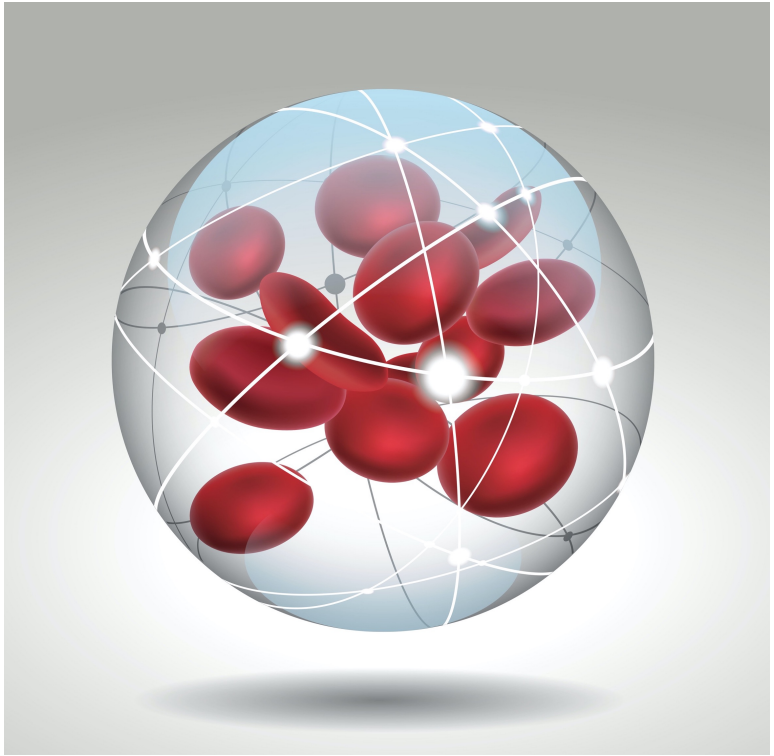
Current Status of HIF-PHI Development

- Several HIF-PHIs in various stages of development



Current Status of HIF-PHI Development

- Roxadustat
  - Currently approved in China, Japan, Chile, South Korea
  - FDA Cardiovascular and Renal Drugs Advisory Committee voted on July 15, 2021, against approval due to safety issues
  - Additional clinical trial on safety in both NDD and DD patient populations requested by FDA

FDA = U.S. Food and Drug Administration. PDUFA = Prescription Drug User Fee Amendment.

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- Daprodustat
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Phase 3 Clinical Trials of HIF-PHIs Safety and Efficacy Data Published

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PYRENEES	DD-CKD ES-treated	Epoetin or darbepoetin	838	52-104
Vadadustat				
INNO$_2$VATE	Incident DD-CKD Prevalent DD-CKD	Darbepoetin Darbepoetin	369 3554	52 52
PRO$_2$TECT	NDD-CKD ESA-naïve NDD-CKD ESA-treated	Darbepoetin Darbepoetin	1751 1725	52 52

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ASCEND-ID	Incident DD-CKD	Darbepoetin	330	52
ASCEND-TD	HD, daprodustat administered 3 times weekly	Epoetin or placebo	407	52
ASCEND-D	HD	Epoetin	2964	52
ASCEND-NHQ	NDD-CKD	Placebo	600	28
ASCEND-ND	NDD-CKD	Darbepoetin	6000	52
Molidustat				
MIYABI HD-C	HD ESA-naïve	None	25	24
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MIYABI-PD	PD	None	51	36
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MIYABI ND-M	NDD-CKD ESA-treated	Darbepoetin	164	36
Enarodustat				
SYMPHONY-HD	HD	Darbepoetin	173	24
SYMPHONY-ND	NDD-CKD ESA-naïve and ESA-treated	Darbepoetin	216	24
Desidustat				
DREAM-D	DD-CKD ESA-treated	Epoetin	392	24
DREAM-ND	NDD-CKD	Darbepoetin	588	24

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Clinical Trials.gov.

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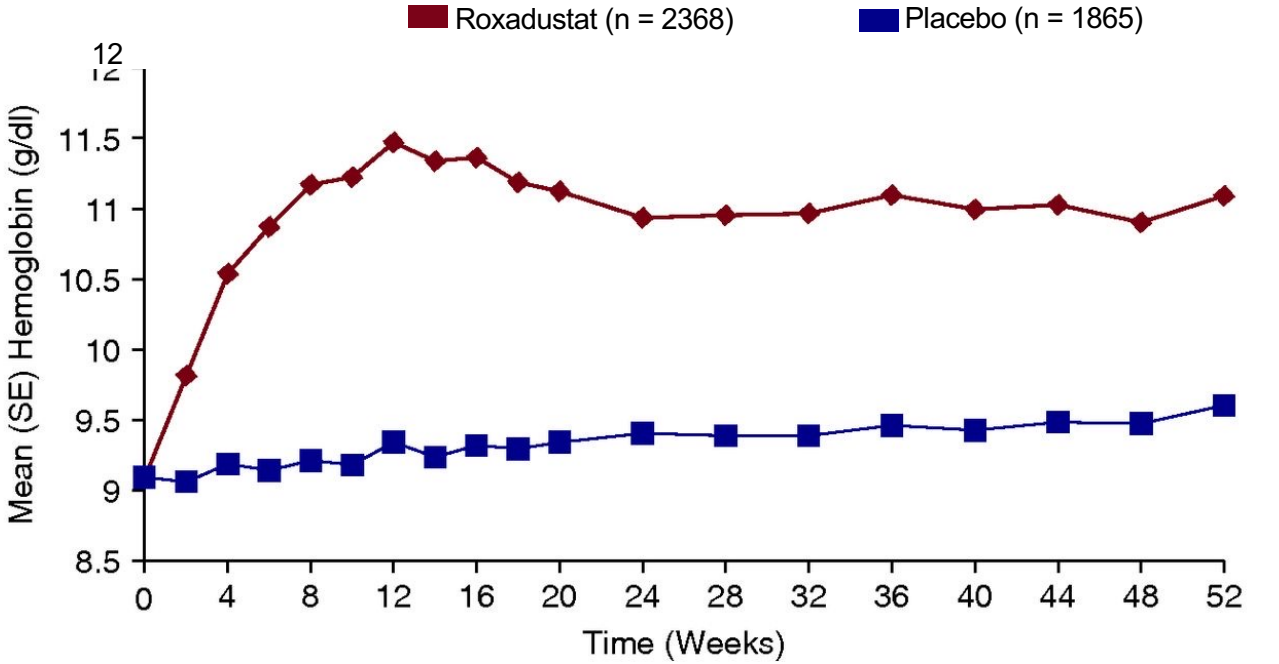
HIF-PHI Efficacy

- Hemoglobin efficacy versus placebo or ESA
- Transfusion reduction
- Avoidance of salvage therapy
  - (Transfusion, IV Iron, or ESA)

Roxadustat

Pooled NDD Studies: Mean (± SE) Hb (g/dL) Over Time Up to Week 52



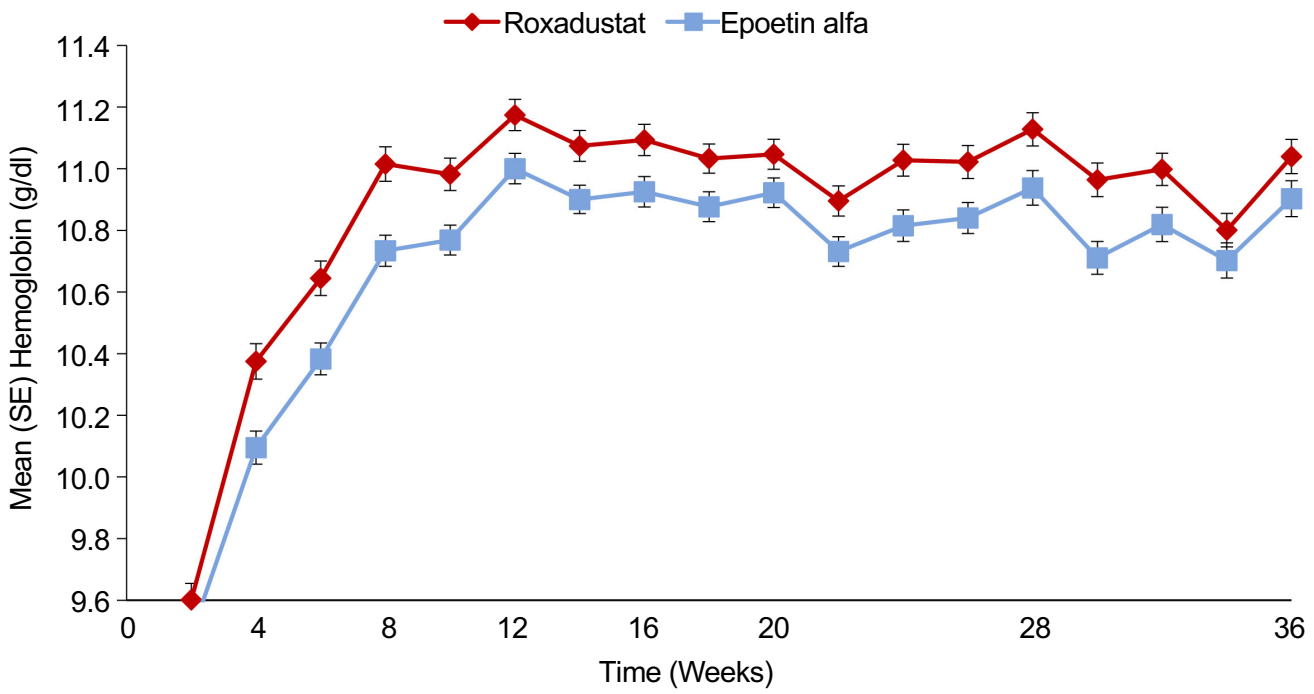
Averaged over Weeks 28-52	
Difference (95% CI)	1.72 (1.65, 1.79)
p value	< .001

Mean change from baseline in Hb (g/dL)

SE = Standard error.

Provenzano R, et al. *Clin J Am Soc Nephrol.* 2021;16(8):1190-1200.

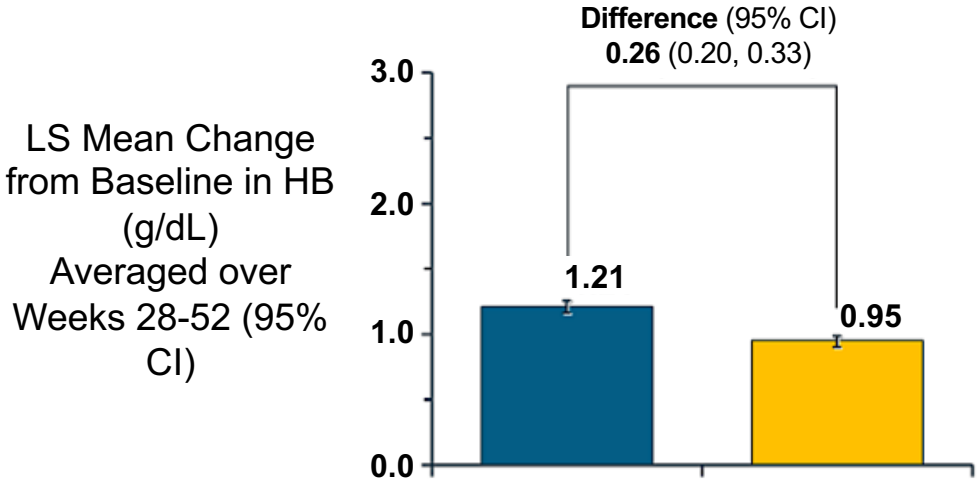
Hemoglobin Levels by Treatment Arm ID-DD



ID = incident dialysis.

Provenzano R, et al. *Kidney Int Rep.* 2020;6(3):613-623.

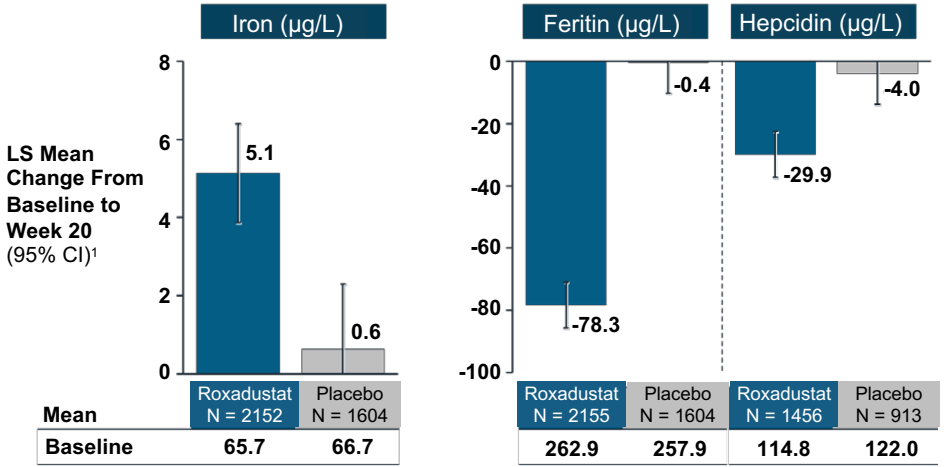
Pooled DD Studies: Change in Hb from Baseline to Mean Over Weeks 28-52



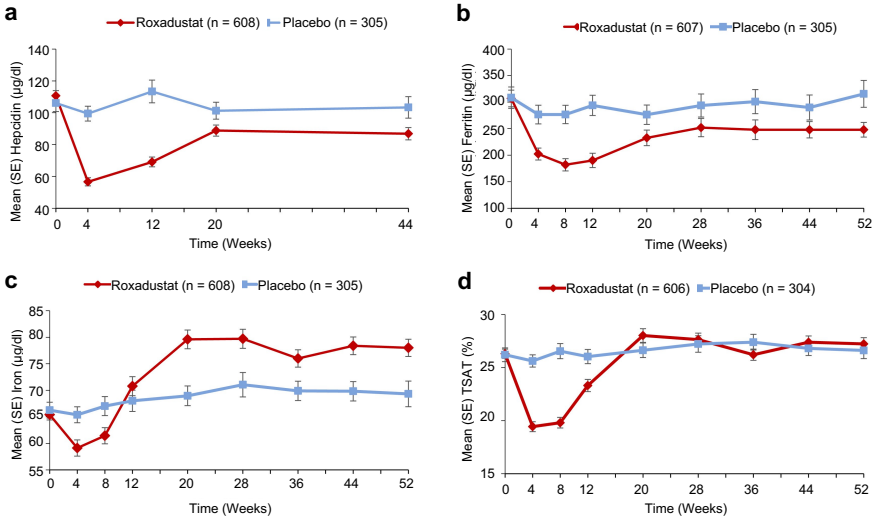
Mean Hb (g/dL)	Roxadustat	Epoetin alfa
Baseline	9.63	9.66
Week 28-52 (averaged)	10.85	10.65

U.S. Food and Drug Administration (FDA) Advisory Committees. FDA Website. 2021. CRDAC-20210715-FibroGen_Backgrounder-1.pdf. Accessed January 25, 2022.

NDD: Roxadustat Effect on Iron Parameters and Hepcidin

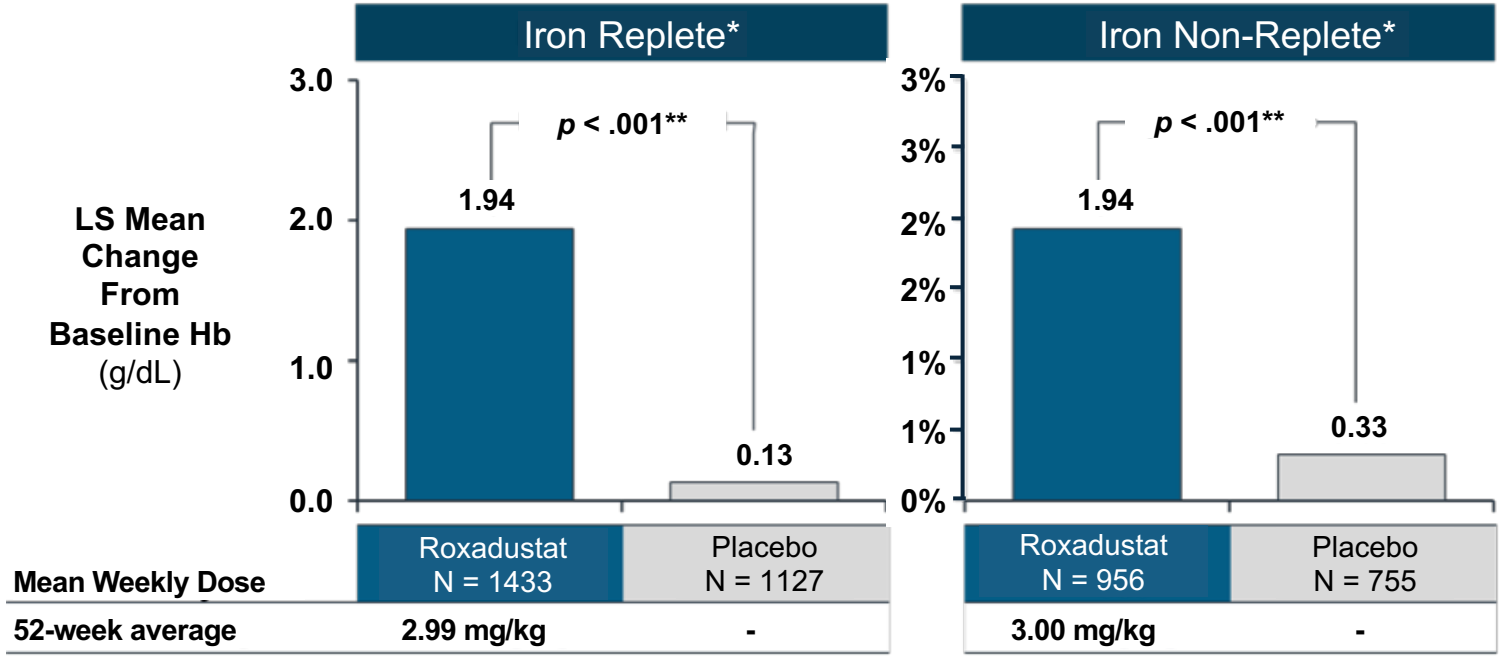


Levels (Full Analysis Set)[2]



1. U.S. Food and Drug Administration (FDA) Advisory Committees. FDA Website. 2021. CRDAC-20210715-FibroGen_Backgrounder-1.pdf. Accessed January 25, 2022. 2. Coyne DW, et al. *Kidney Int Rep.* 2020;6(3):624-635.

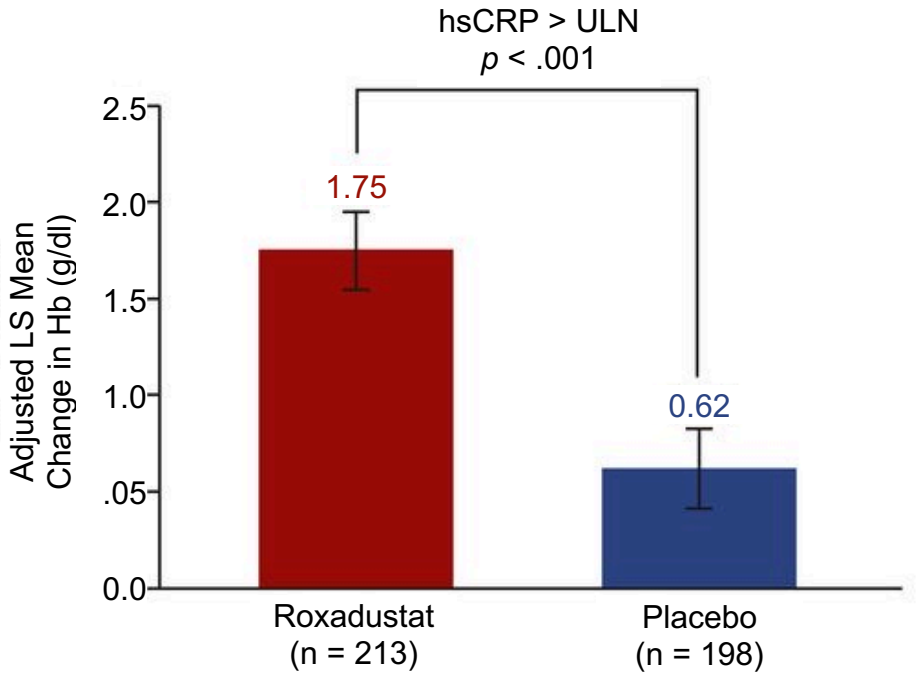
Pooled NDD: Change from Baseline in HB Levels Iron Replete vs. Iron Non-Replete* at Baseline



* Iron replete was defined as TSAT ≥ 20% and ferritin ≥ 100 ng/mL; mean change from baseline to mean of Weeks 28-52. ** *p*-value not controlled for multiplicity.

U.S. Food and Drug Administration (FDA) Advisory Committees. FDA Website. 2021. CRDAC-20210715-FibroGen_Backgrounder-1.pdf. Accessed January 25, 2022.

ITT Analysis Set: Hb Change from Baseline (NDD) Averaged Weeks 28-52, Patients with Elevated hsCRP at Baseline

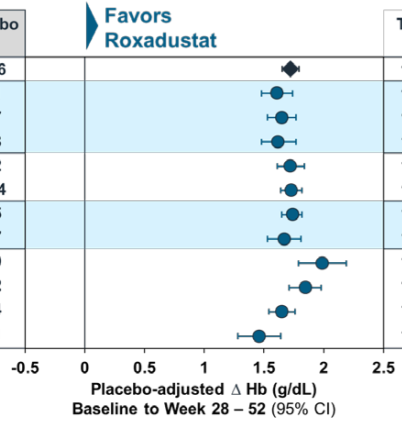


hsCRP = High-sensitivity C-reactive protein. ULN = Upper limit of normal.
Fishbane S, et al. *J Am Soc Nephrol.* 2021;32(3):737-755.

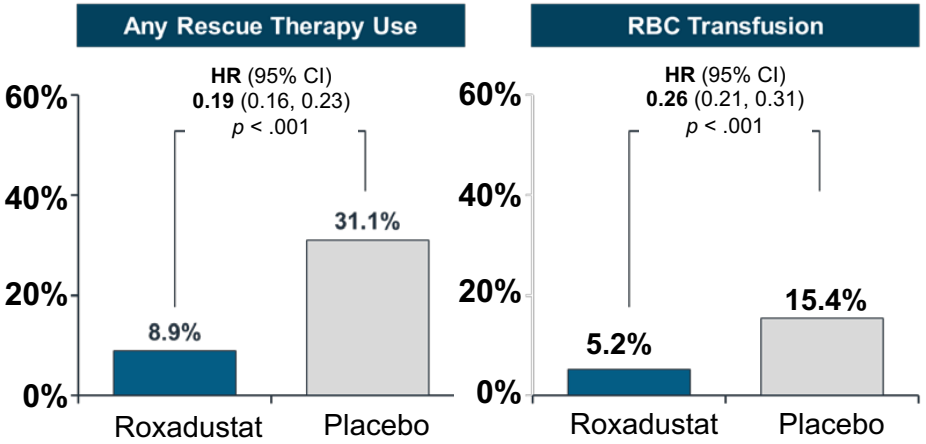
Efficacy: Reducing Transfusions, IV Iron Use and ESA Treatment in CKD-ND Patients

Pooled NDD Studies: Roxadustat Treatment Effect by Subgroup

	Roxa N	Placebo N	Treatment Effect (95% CI)	P-value vs Placebo
Pooled NDD	2391	1886	**1.72** (1.65, 1.79)	**< 0.001**
US	552	441	**1.61** (1.48, 1.74)	**< 0.001**
Europe	597	447	**1.65** (1.53, 1.77)	**< 0.001**
Other	1242	998	**1.62** (1.48, 1.77)	**< 0.001**
Male	974	832	**1.72** (1.61, 1.84)	**< 0.001**
Female	1417	1054	**1.73** (1.64, 1.82)	**< 0.001**
CRP ≤ ULN	1222	855	**1.74** (1.65, 1.82)	**< 0.001**
CRP > ULN	526	357	**1.67** (1.53, 1.82)	**< 0.001**
eGFR < 10*	481	359	**1.99** (1.79, 2.19)	**< 0.001**
eGFR 10 - < 15*	526	452	**1.85** (1.71, 1.98)	**< 0.001**
eGFR 15 - < 30*	954	724	**1.65** (1.54, 1.76)	**< 0.001**
eGFR ≥ 30*	430	351	**1.46** (1.28, 1.64)	**< 0.001**



Percent of Patients in First 52 Weeks



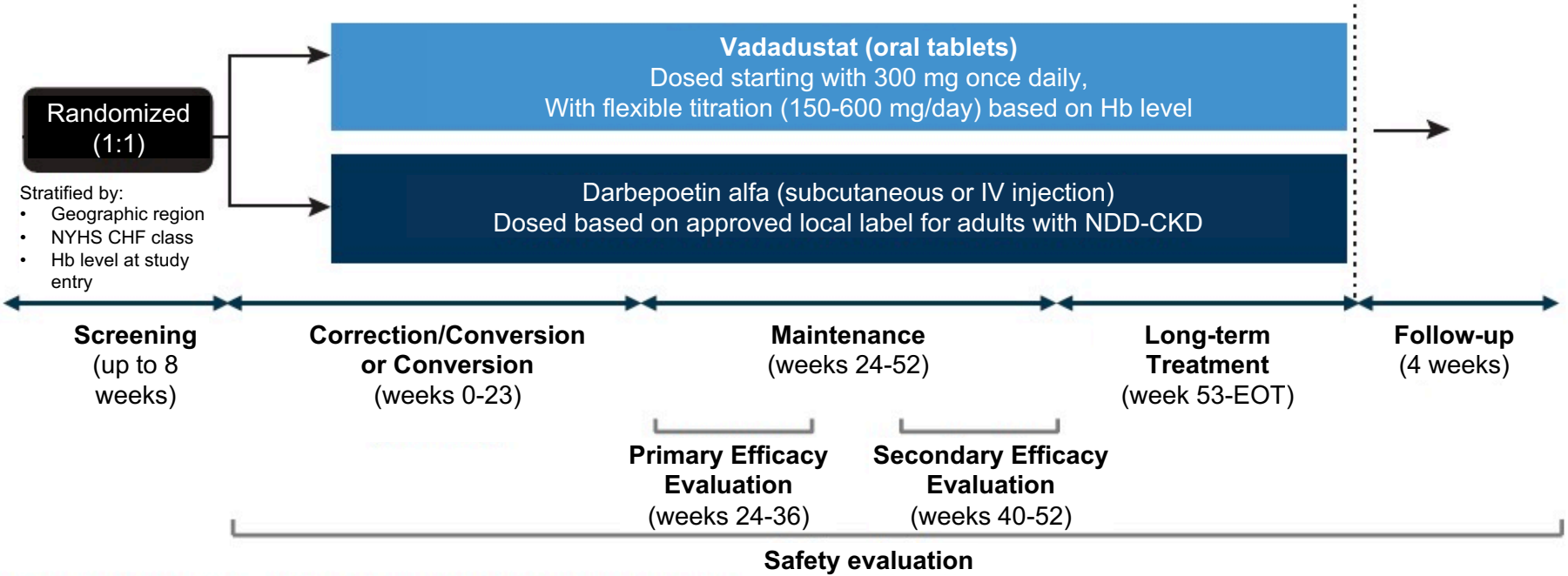
* mL/min/1.73 m^2. ***p*-value not controlled for multiplicity.

U.S. Food and Drug Administration (FDA) Advisory Committees. FDA Website. 2021. https://www.fda.gov/media/150728/download. Accessed January 25, 2022.

CME OUTFITTERS

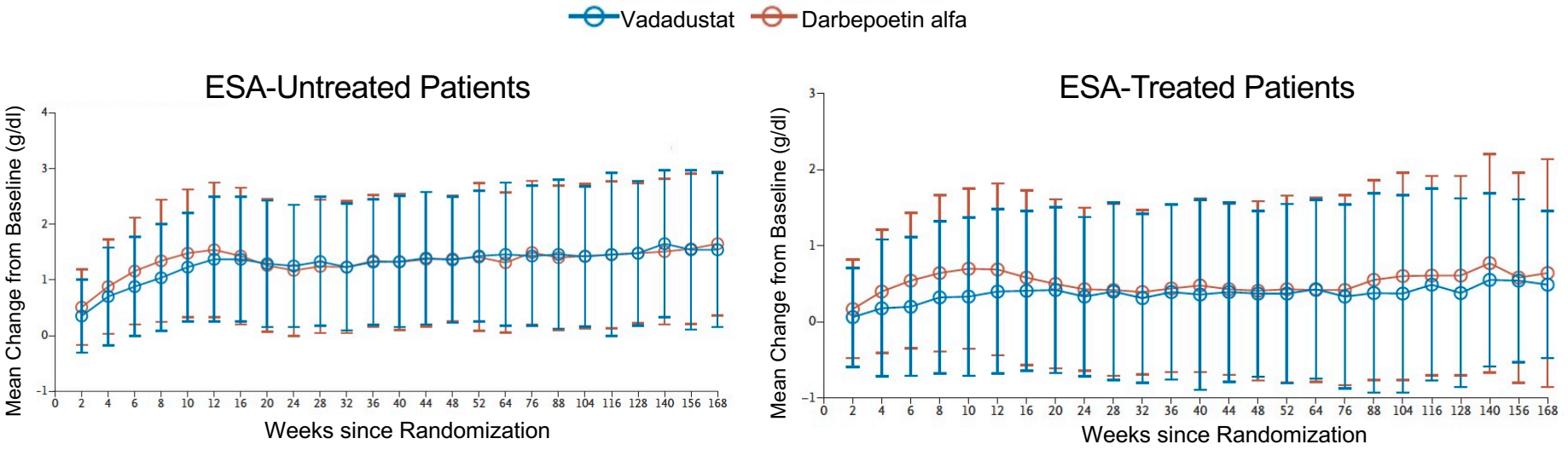
Vadadustat

PRO$_2$TECT (NDD): Study Design



CHF = Congestive heart failure. EOT = End of treatment. NYHA = New York Heart Association.
Chertow GM, et al. *N Engl J Med.* 2021;384:1589-1600.

PRO$_2$TECT: Hemoglobin Concentration in ESA-Untreated and ESA-Treated Patients

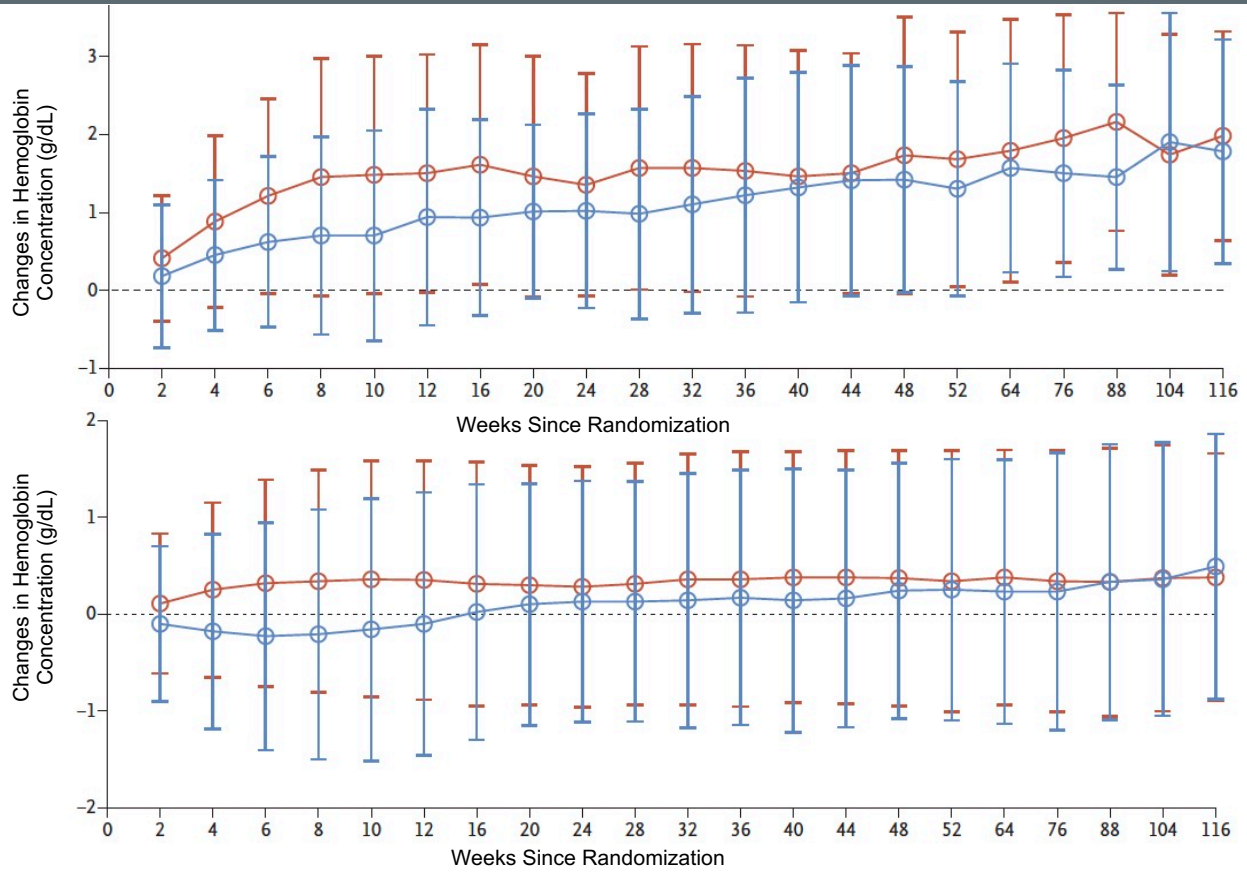


Chertow GM, et al. *N Engl J Med.* 2021;384:1589-1600.

Mean Changes in Hb Concentrations in Incident DD-CKD Trial and Prevalent DD-CKD Trial

Incident DD-CKD Trial →

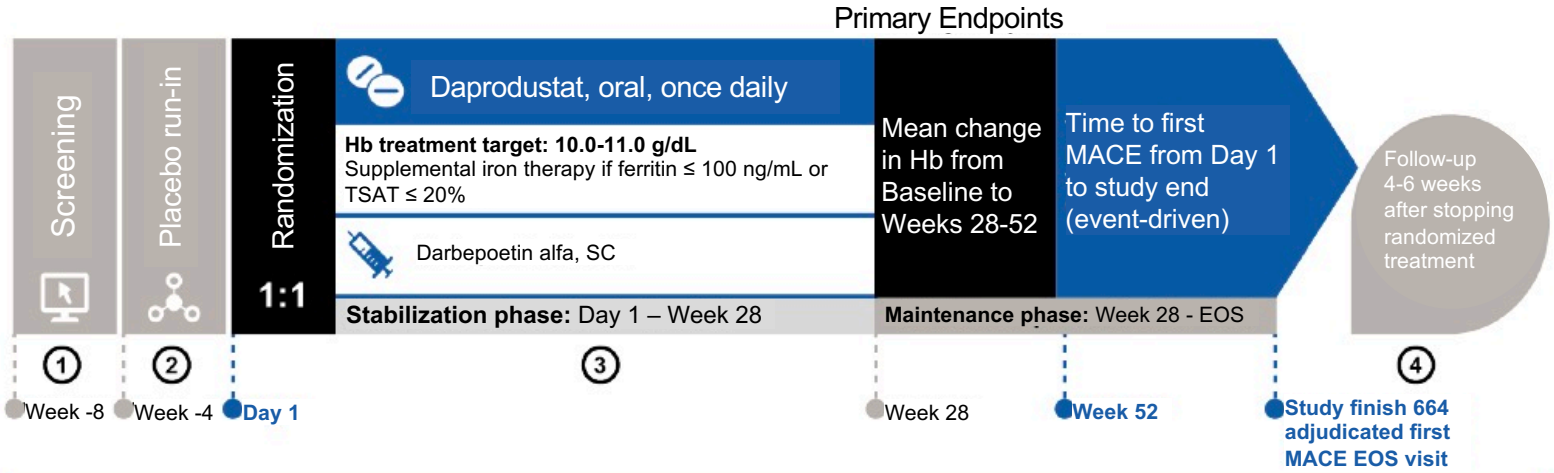
Prevalent DD-CKD Trial →



Eckardt K-U, et al. *N Engl J Med.* 2021;384(17):1601-1612.

Daprodustat

ASCEND-ND Study Design



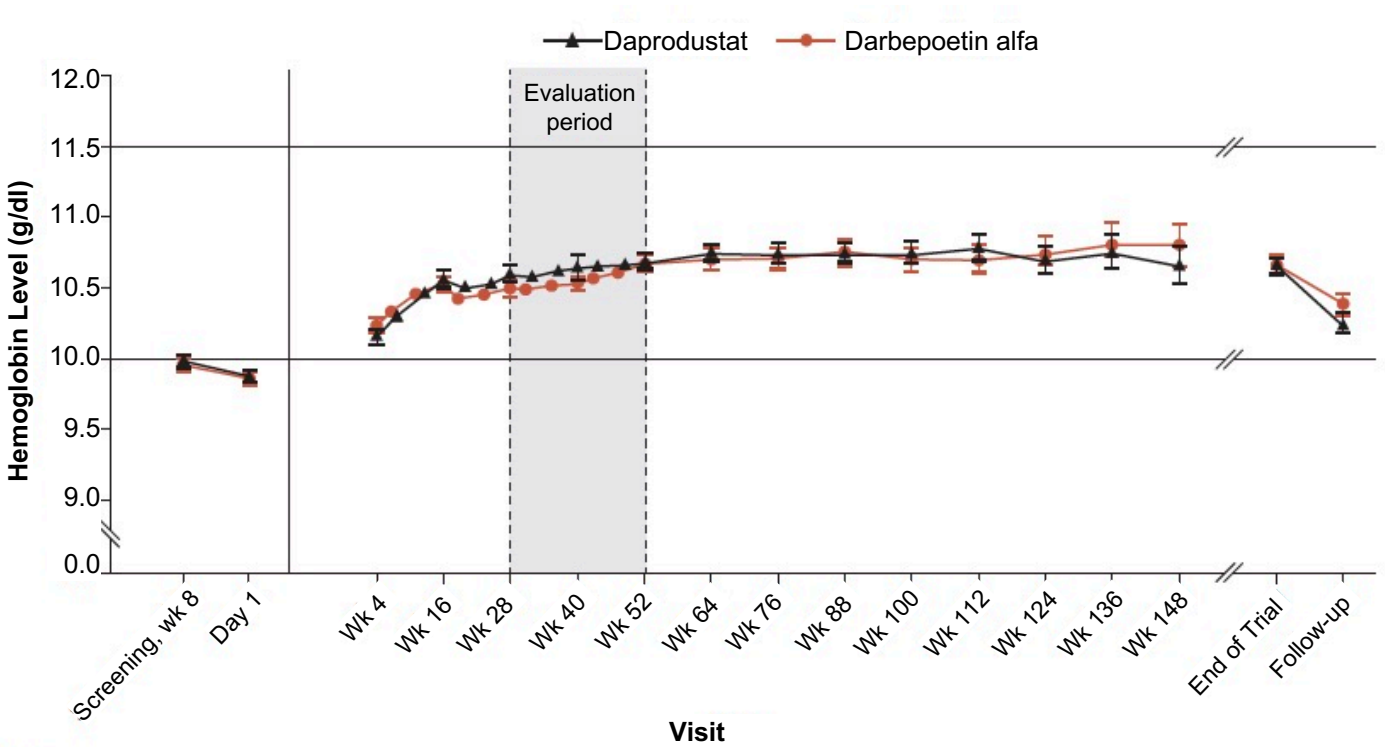
Study Periods

1. **Screening:** Determine eligibility
2. **Placebo run-in:** Establish adherence to daprodustat placebo tablets and study procedures
3. **Treatment:** Includes *stabilization phase* to titrate randomized treatment to achieve the Hb target and *maintenance phase* to assess long-term safety and efficacy
4. **Follow-up:** Assess safety post-treatment

ASCEND-ND = Anaemia Study in CKD: Erythropoiesis via a Novel prolyl hydroxylase inhibitor Daprodustat -- Non-Dialysis. EOS = End of study. SC = Subcutaneous injection.

Perkovic V, et al. *Nephrol Dial Transplant.* 2021 December 2. [Epub ahead of print].

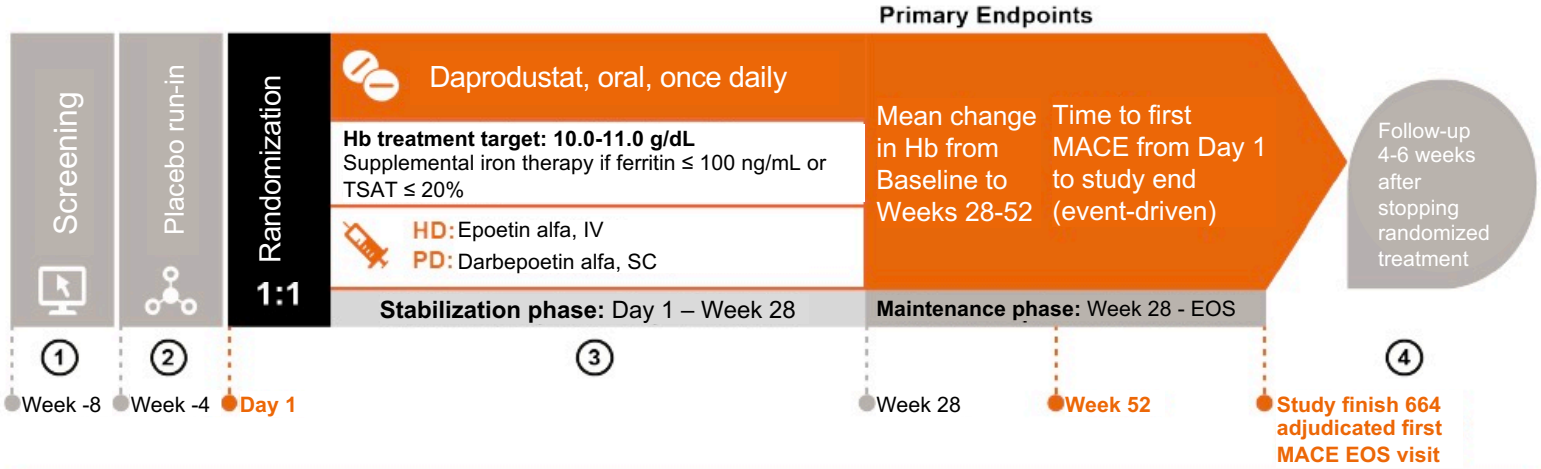
ASCEND-ND: Hemoglobin Level According to Visit (ITT Population)



ITT = Intention to treat.
ASCEND-ND = Anaemia Study in CKD: Erythropoiesis via a Novel prolyl hydroxylase inhibitor Daprodustat − Non-Dialysis.
Singh AK, et al. *N Engl J Med.* 2021;385:2313-2324.

CME OUTFITTERS

ASCEND-D: Study Design



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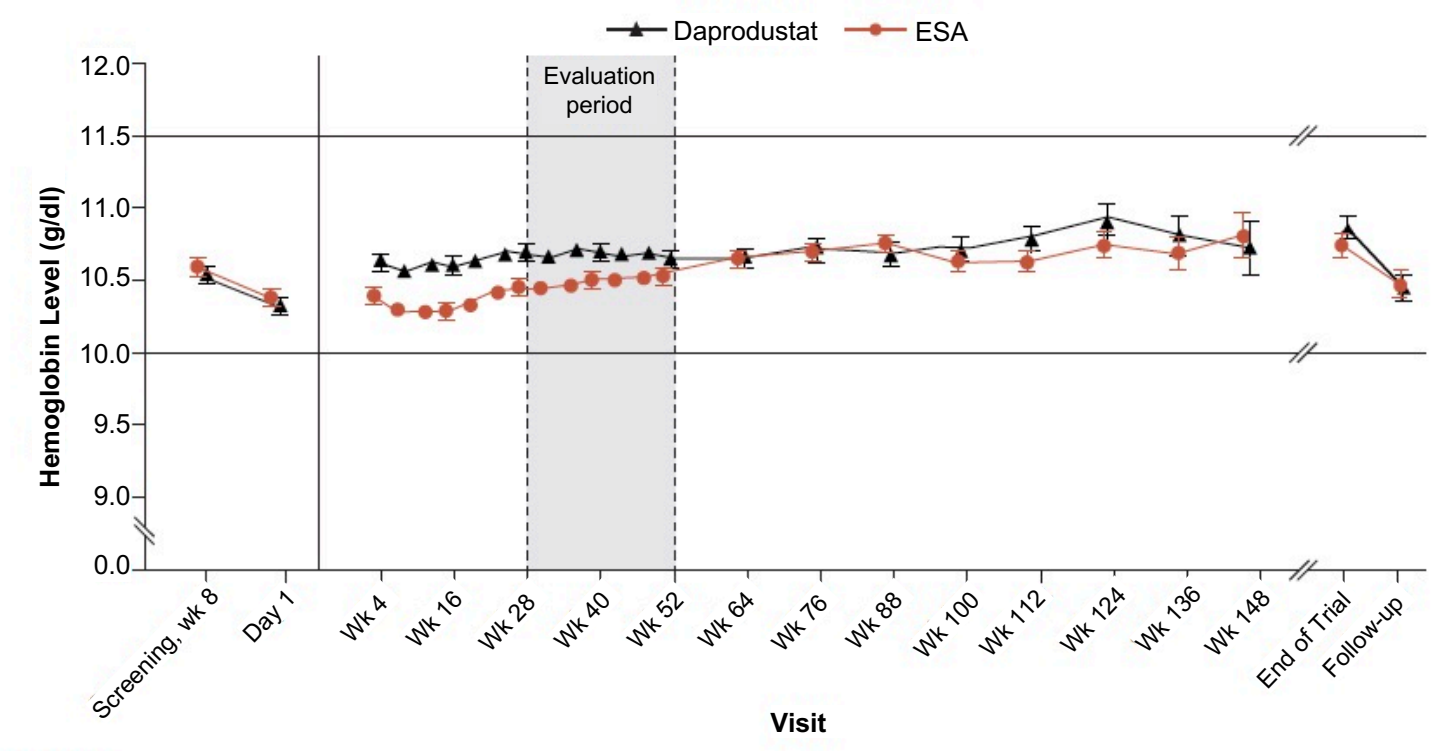
ASCEND-D = Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat − Dialysis).
Singh AK, et al. *N Engl J Med*. 2021;385:2325-2335.

ASCEND-D: Hemoglobin Level According to Visit (Intention-to-Treat Population)



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

Summary: Efficacy of HIF-PHIs

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- HIF-PHIs increase transferrin levels (TIBC), and iron usually increases proportionately; **therefore, TSAT doesn't change, but more iron is available**
- There might be an IV iron-sparing effect
- The superior efficacy of HIF-PHIs in the inflamed patient (**ESA hypo-responders**) remains to be convincingly demonstrated

Faculty Discussion

Safety of HIF-PHIs

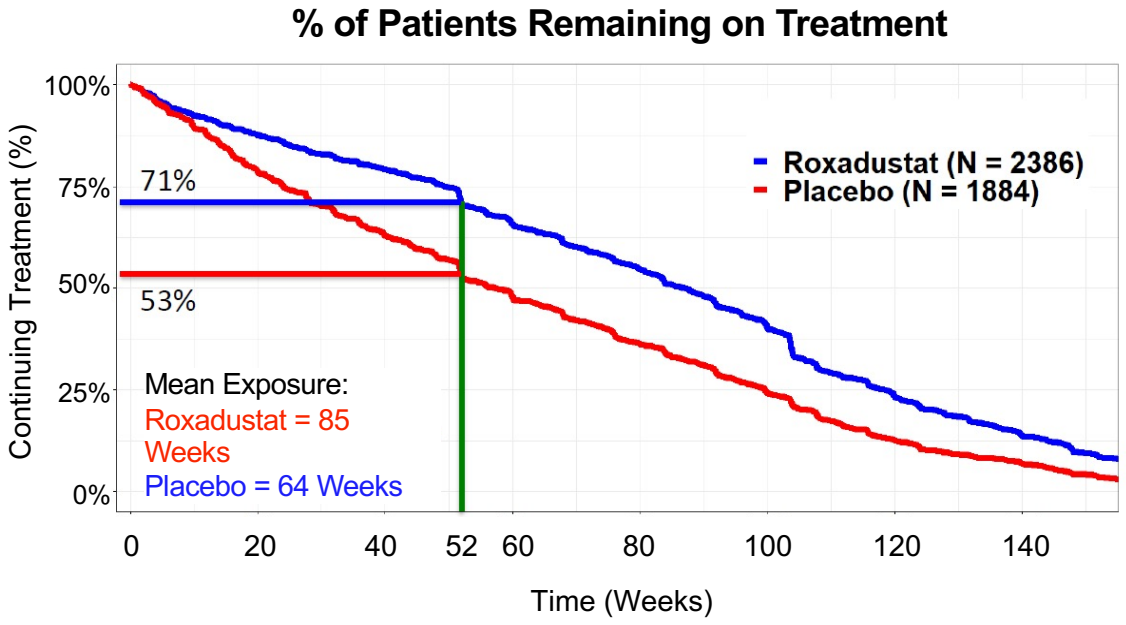
MACE Outcome Summary

HIF-PHI	NDD or DD	Primary Analysis HR (95% CI)	Sensitivity Analysis HR (95% CI)
Roxadustat	NDD	1.10 (0.96, 1.27) OS	1.35 (1.11, 1.70) OT + 7
Roxadustat	DD	1.02 (0.88, 1.20) OT + 7	1.14 (1.00, 1.30) OS: FDA
Vadadustat	NDD	1.17 (1.01, 1.36) OS	NR
Vadadustat	DD	0.96 (0.83, 1.11) OS	NR
Daprodustat	NDD	1.03 (0.89, 1.19) OS	1.40 (1.17, 1.66) OT + 28
Daprodustat	DD	0.93 (0.81, 1.07) OS	0.96 (0.81, 1.14) OT + 28

MACE = major adverse cardiac events; OS = On study; OT = On treatment.

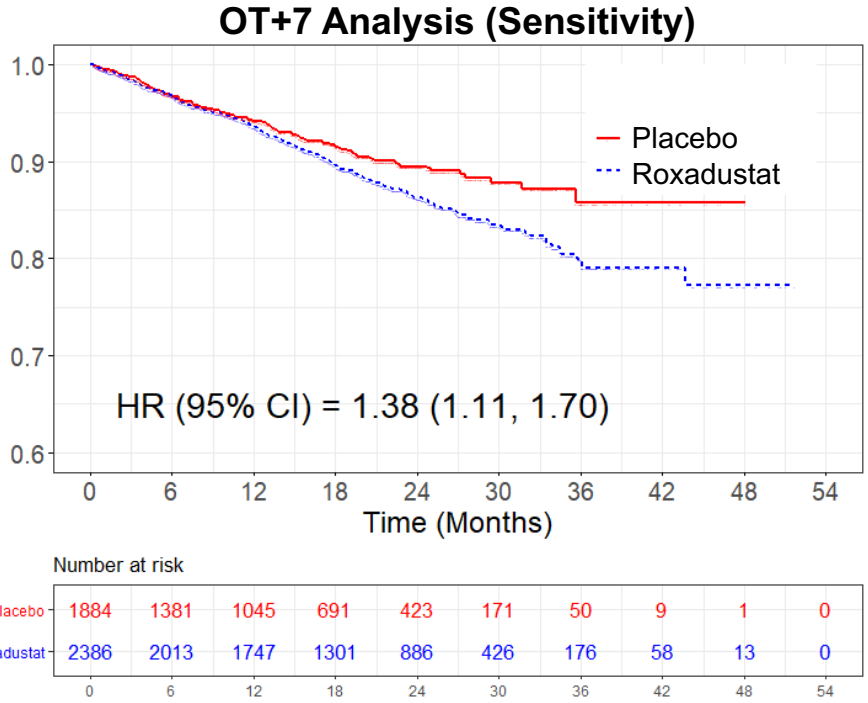
CKD-ND Patients: Major Adverse Cardiovascular Events (MACE) with Roxadustat versus Placebo

- Roxadustat: 3 trials vs placebo: roxadustat 2391 vs. placebo 1886 patients
  - Placebo patients far more likely to drop out
  - Patients could continue on treatment when they started dialysis
    - Roxadustat patient start HD, Hb at goal, continues on roxadustat during very high-risk 1st 6-months on HD
    - Placebo patient starts HD, Hb is low, starts ESA and is off treatment



U.S. Food and Drug Administration (FDA) Advisory Committees. FDA Website. 2021. CRDAC-20210715-FibroGen_Backgrounder-1.pdf. Accessed January 25, 2022.

The FDA Decided On-Treatment + 7 Day (OT+7) was an Appropriate Sensitivity Analysis for the Roxadustat versus Placebo NDD Trials



On-Study Analysis: HR (95% CI) = 1.10 (0.96, 1.27)

- No significant risk of MACE relative to placebo

OT+7 Analysis: HR (95% CI) = 1.38 (1.11, 1.70)

- Suggests increased risk while receiving assigned treatment
- Interpretation complicated by differential exposure

The FDA's own statement

Exposure to drug, but mostly exposure to dialysis!

OT+7 = On-treatment and within 7 days of last dose of study medication.

U.S. Food and Drug Administration (FDA) Advisory Committees. FDA Website. 2021. CRDAC-20210715-FibroGen_Backgrounder-1.pdf. Accessed January 25, 2022.

Serious and AEs, DD Pooled Studies (OT+7)

Serious Adverse Events, DD Pooled Studies (OT+7)

	Events, N (%) Roxadustat N = 1940	Events, N (%) ESA N = 1940	Events (per 100 PY) Roxadustat 3315 P-Y	Events (per 100 PY) ESA 3744 P-Y	Absolute Δ Risk (per 100 P-Y)	Relative Risk Based on P-Y
Thombotic Events						
Thrombosis	241 (12.42)	201 (10.36)	7.27	5.37	1.90	1.4
Device/shunt thrombosis	121 (6.24)	94 (4.85)	3.65	2.51	1.14	1.5
Deep vein thrombosis (term)	24 (1.24)	7 (0.36)	0.72	0.19	0.53	3.9
Miscellaneous						
Hypoglycemia FDA	29 (1.49)	25 (1.29)	0.87	0.67	0.20	1.3
Gastroenteritis	27 (1.39)	16 (0.82)	0.81	0.43	0.38	1.9
Seizure FDA	26 (1.34)	19 (0.98)	0.78	0.51	0.27	1.6
Pancreatitis FDA	20 (1.03)	11 (0.57)	0.60	0.29	0.31	2.1
Adverse Drug Reactions Known for ESAs						
Systemic hypertension FDA	89 (4.59)	110 (5.67)	2.68	2.94	-0.26	0.9
Myocardial infarction FDA	88 (4.54)	85 (4.38)	2.65	2.27	0.38	1.2
Peripheral edema FDA	5 (0.26)	2 (0.1)	0.15	0.05	0.10	2.8
Angina	27 (1.39)	30 (1.55)	0.81	0.80	0.01	1.0
Rash FDA	2 (0.1)	2 (0.1)	0.06	0.05	0.01	1.1

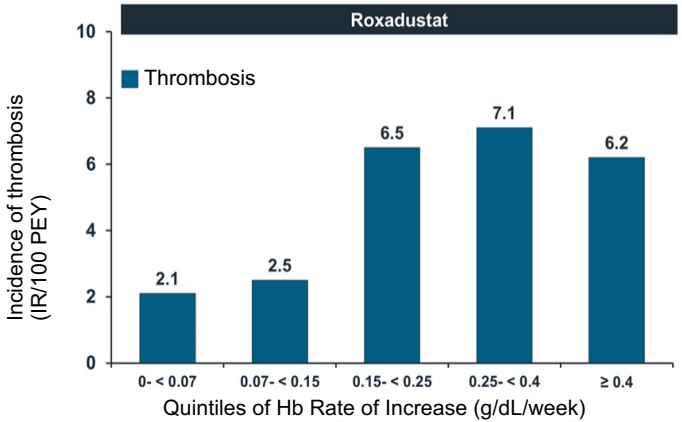
All Adverse Events, DD Pooled Studies (OT+7)

	Events, N (%) Roxadustat N = 1940	Events, N (%) Epoetin alfa N = 1940	Events (per 100 PY) Roxadustat 3315 P-Y	Events (per 100 PY) Epoetin alfa 3744 P-Y	Risk Difference (per 100 P-Y)	Relative Risk Based on P-Y
Thombotic Events						
Device/shunt thrombosis	271 (13.97)	228 (11.75)	8.17	6.09	2.08	1.34
Thrombosis	392 (20.21)	344 (17.73)	11.82	9.19	2.63	1.29
Deep vein thrombosis (term)	29 (1.49)	19 (0.98)	0.87	0.51	0.36	1.72
Gastrointestinal						
Vomiting FDA	161 (8.3)	134 (6.91)	4.86	3.58	1.28	1.36
Gastroenteritis	86 (4.43)	68 (3.51)	2.59	1.82	0.77	1.43
Miscellaneous						
Headache FDA	198 (10.21)	157 (8.09)	5.97	4.19	1.78	1.42
Hypotension FDA	230 (11.86)	199 (10.26)	6.94	5.32	1.62	1.31
Fatigue FDA	115 (5.93)	97 (5)	3.47	2.59	0.88	1.34
Pruritus FDA	103 (5.31)	85 (4.38)	3.11	2.27	0.84	1.37
Adverse Drug Reactions Known for ESAs						
Systemic hypertension FDA	365 (18.81)	367 (18.92)	11.01	9.80	1.21	1.12
Dyspnea FDA	129 (6.65)	150 (7.73)	3.89	4.01	-0.12	0.97
Peripheral edema FDA	98 (5.05)	95 (4.9)	2.96	2.54	0.42	1.16
Myocardial infarction FDA	91 (4.69)	87 (4.48)	2.74	2.32	0.42	1.18
Rash FDA	67 (3.45)	53 (2.73)	2.02	1.42	0.60	1.43
Seizure FDA	45 (2.32)	33 (1.7)	1.36	0.88	0.48	1.54

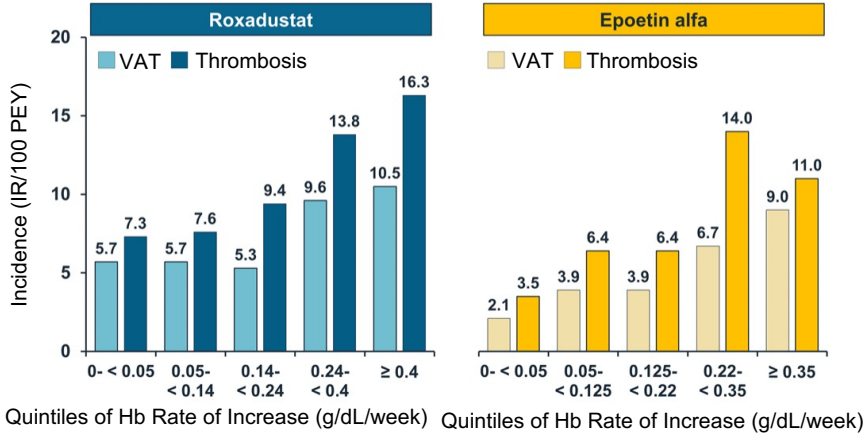
Adverse events denoted by “term” are individual preferred terms. All others are queries. FDA = FDA query. P-Y = Patient-year.

U.S. Food and Drug Administration (FDA) Advisory Committees. FDA Website. 2021. CRDAC-20210715-FDA_Slides_0-1.pdf. Accessed January 25, 2022.

NDD: Thrombosis AEs Increased with Increasing Hb Rate of Rise in Patients Using Roxadustat



NDD: Thrombosis and VAT Increased with Increasing Hb Rate of Rise



Phase 3 Dosing vs. Proposed Dosing

Phase 3 Dosing

1. Target Hb: **10.5 – 12.0** g/dL
2. Starting doses
   - ESA untreated
     - **70** mg TIW in patients < 70 kg
     - **100** mg TIW in patients 70+ kg
   - ESA conversion

Epoetin Alfa (IU/Week)	Roxadustat Start Dose (mg/dose TIW)
< 5000	**70**
5000 to 7999	**100**
8000 to 16000	**150**
> 16000	**200**

3. No restriction on consecutive dose increases in patients not responding

Proposed Dosing

1. Target Hb: **10.0 – 11.0** g/dL
2. Starting doses
   - ESA untreated
     - **40** mg TIW in patients < 70 kg
     - **50** mg TIW in patients 70+ kg
   - ESA conversion

Epoetin Alfa (IU/Week)	Roxadustat Start Dose (mg/dose TIW)
< 5000	**40**
5000 to 7999	**50**
8000 to 16000	**70**
> 16000	**100**

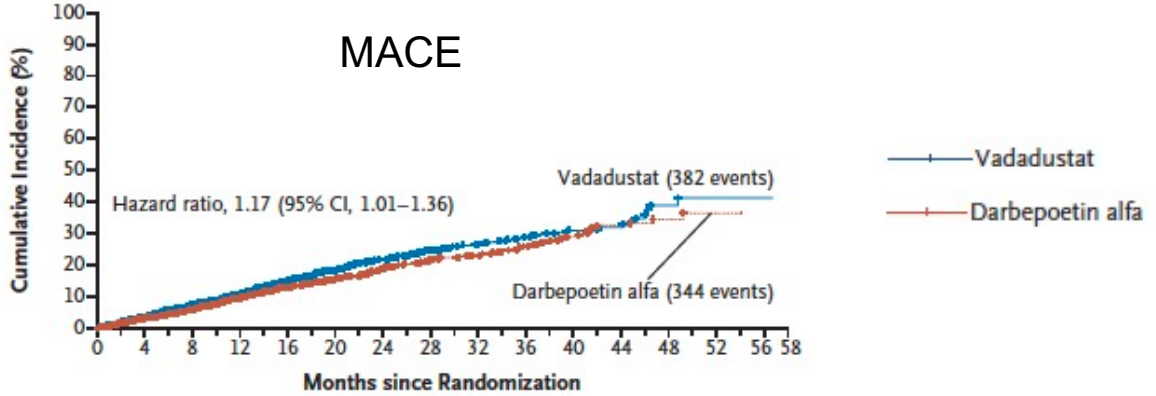
3. No more than 3 consecutive dose increases in patients not responding

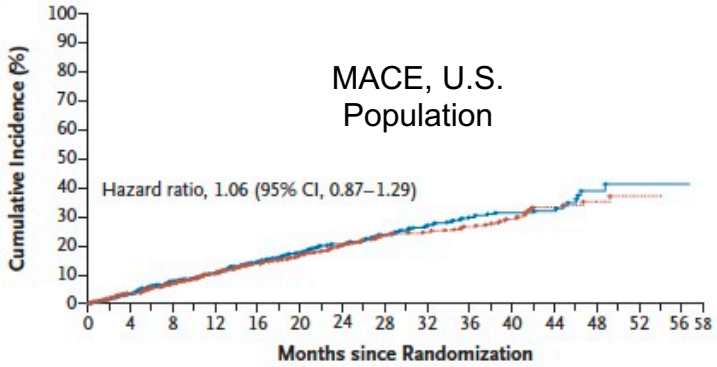
VAT = Vascular access thrombosis.

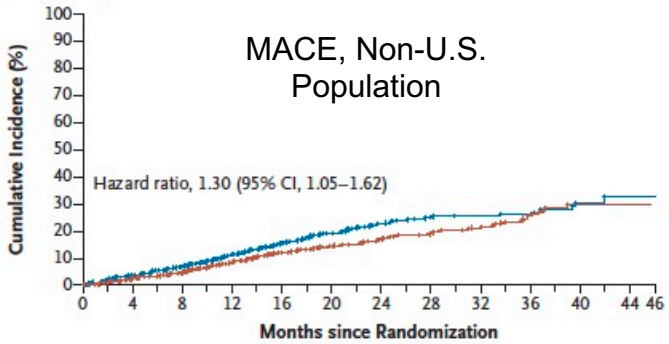
U.S. Food and Drug Administration (FDA) Advisory Committees. FDA Website. 2021. CRDAC-20210715-FDA_Slides_0-1.pdf. Accessed January 25, 2022.

Vadadustat in Patients with Anemia and CKD-NDD

- Cumulative incidences of a first adjudicated MACE (composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke)







Chertow GM, et al. *N Engl J Med.* 2021;384:1589-1600.

CME OUTFITTERS

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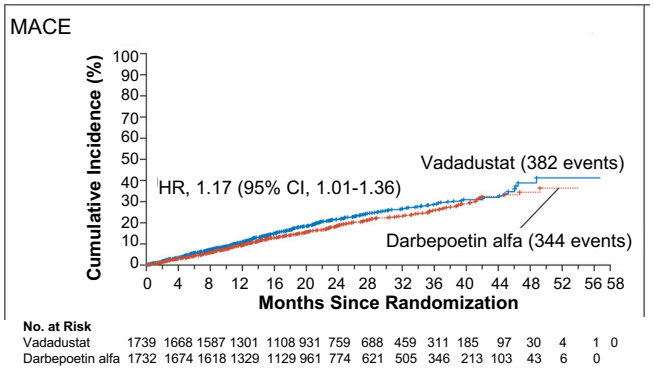
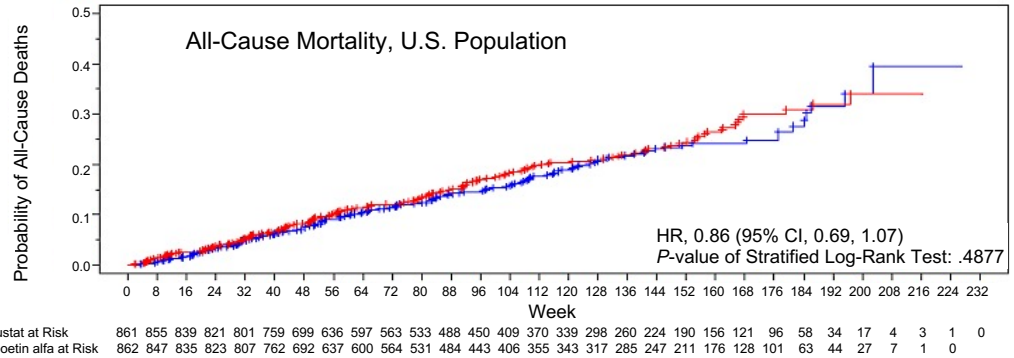
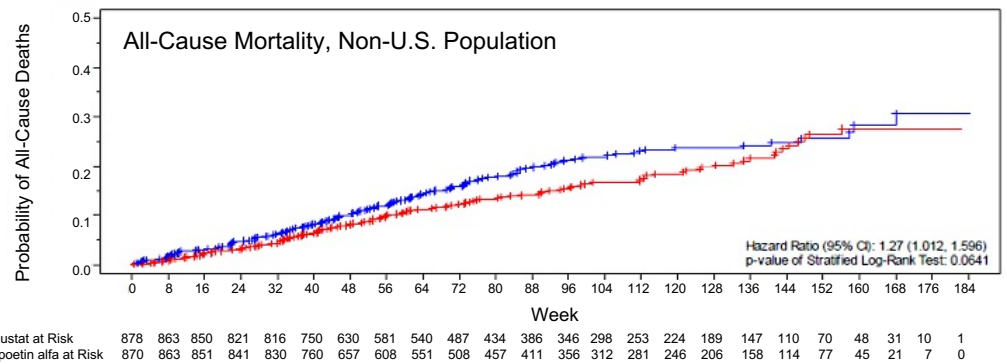




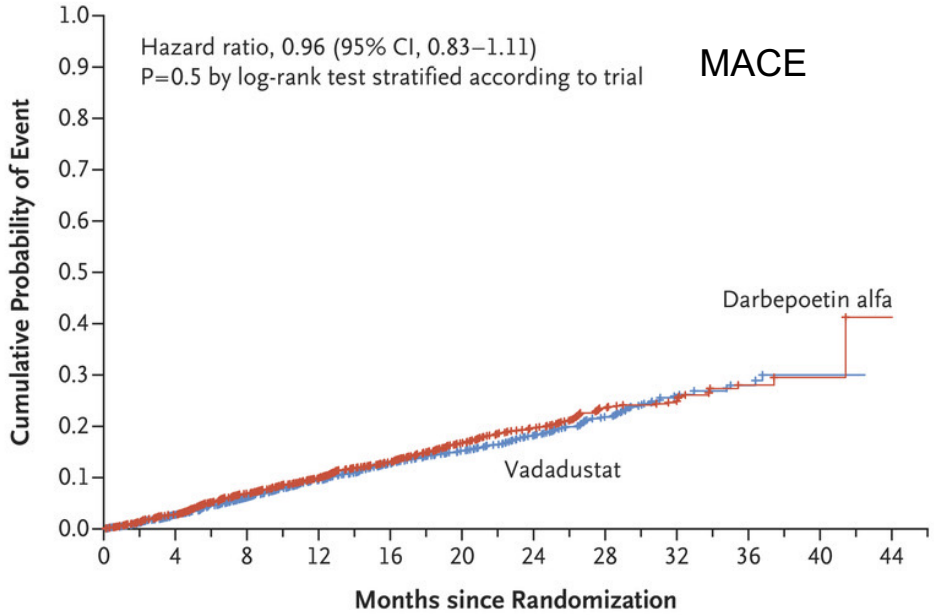


Age as a Continuous Variable

Chertow GM, et al. *N Engl J Med.* 2021;384:1589-1600.

Vadadustat in Patients with Anemia and CKD-DD

- Cumulative incidences of a first adjudicated MACE (composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke)

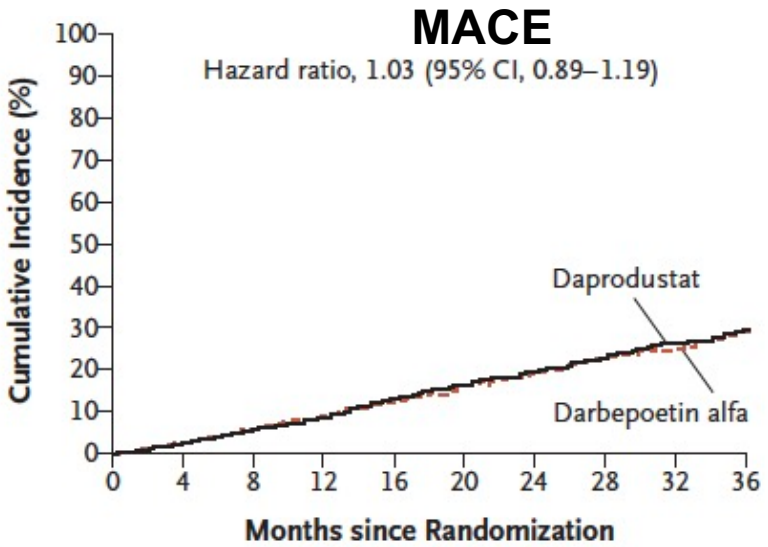


Eckardt K-U, et al. *N Engl J Med.* 2021;384(17):1601-1612.

Daprodustat: CKD-NDD

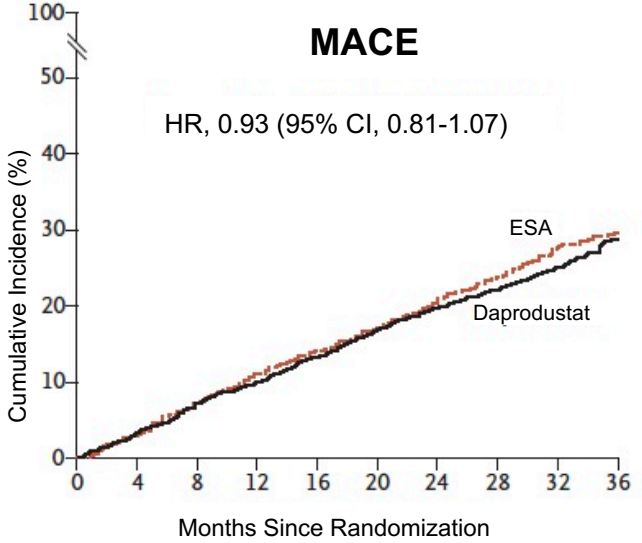
- Primary analysis - On Study - ITT
- Noninferior (< 1.25 upper limit CI)

Primary cardiovascular outcome	No. (%)		No. (%)	
MACE	378 (19.5)	464	371 (19.2)	441
Death from any cause	252 (13.0)	301	259 (13.4)	298
Nonfatal myocardial infarction	96 (5.0)	125	91 (4.7)	116
Nonfatal stroke	30 (1.5)	38	21 (1.1)	27



Singh AK, et al. *N Engl J Med.* 2021;385:2313-2324.

ASCEND-D: MACE (Time to First Occurrence) ITT Population



Forest Plot of Hazard Ratio of Time to 1st Occurrence of Adjudicated MACE

Analysis	Treatment	No. of Patients/ Total No.	HR (95% CI)
Primary: First occurrence MACE	Daprodustat ESA	374/1487 394/1477	0.93 (0.81, 1.07)
Supportive: First occurrence on-treatment MACE	Daprodustat ESA	255/1482 271/1474	0.96 (0.81, 1. 14)

Primary Cardiovascular Outcome – no. (%)

MACE	374 (25.2)	455	394 (26.7)	514	HR, 0.93 (0.81-1.07) $p < .001$
Death from any cause	244 (16.4)	294	233 (15.8)	300	– –
Nonfatal myocardial infarction	101 (6.8)	126	126 (8.5)	170	– –
Nonfatal stroke	29 (2.0)	35	35 (2.4)	44	– –

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

Safety of Daprodustat vs Darbepoetin in CKD-NDD

- Potential safety signals
  - **Cancer-related death or tumor progression or recurrence**
    - 3.7% daprodustat vs. 2.5% darbepoetin (unadjusted *p* = .04)
  - **Esophageal or gastric erosions**
    - 3.6% daprodustat vs. 2.1% darbepoetin (unadjusted *p* = .005)
    - LDL cholesterol lowering by daprodustat was not significantly greater than darbepoetin
- **And in the CKD-DD population…**
  - CA-related deaths were not higher with daprodustat (3.2% vs. 3.5% with ESA)
  - Esophageal/gastric ulcers were not higher with daprodustat (4.0% vs. 5.5% with ESA)
  - LDL cholesterol lowering by daprodustat was not significantly greater than darbepoetin

Summary

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- The long-term safety of HIF-PHIs needs further exploration
- HIF-PHIs have been approved for treating CKD-related anemia in numerous countries, but not in the U.S.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

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SMART Goals

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Specific, Measurable, Attainable, Relevant, Timely

- Recognize signs and symptoms of anemia in patients with CKD
- Implement current guidelines for optimizing management of anemia by addressing decreased availability of iron and decreased levels of erythropoietin
- Stay current with new developments regarding the use of HIF-PHIs for dialysis-dependent and non-dialysis-dependent CKD

CME Outfitters

AFTER THE SHOW

Questions & Answers

Recorded January 26, 2022.

CME OUTFITTERS

Understanding Anemia in Patients with CKD: From Diagnosis to Data on Emerging Agents

Supported by an educational grant from Akebia Therapeutics, Inc. and Otsuka America Pharmaceutical, Inc.

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