Canadian Society of Nephrology/
Société canadienne de néphrologie
CSN/SCN

ANEMIA MANAGEMENT OF CKD: a 21st Century Approach

The meeting will start shortly.

In the meantime, here are some Zoom tips:

You will be automatically muted and your camera is off

Click on “Q&A” to ask the panelists questions

If you have technical issues, please use the chat.

THIS MEETING IS BEING RECORDED

Technical Questions?

Text or call

Dr. Robert Provenzano

Dr. Provenzano is the Chief Medical Officer, Nephrology Practice Solutions, a national kidney care management company; and Vice President of Medical Affairs at DaVita Kidney Care. Dr. Provenzano is also a Clinical Professor of medicine at Wayne State University in Detroit, where he earned his medical degree.

Dr. Provenzano completed his Nephrology fellowship at Henry Ford Health System and served as the Chief of the nephrology, hypertension, and transplantation at St. John Hospital & Medical Center in Detroit, MI.

Anemia Management of CKD: a 21st Century Approach

R. Provenzano, MD, FACP, FASN

Associate Professor of Clinical Medicine, Wayne State University School of Medicine

Canadian Society of Nephrology

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Disclosures

Consulting Fees:

AstraZeneca, DaVita, FibroGen, Rockwell Medical

Speakers' Bureaus:

AstraZeneca

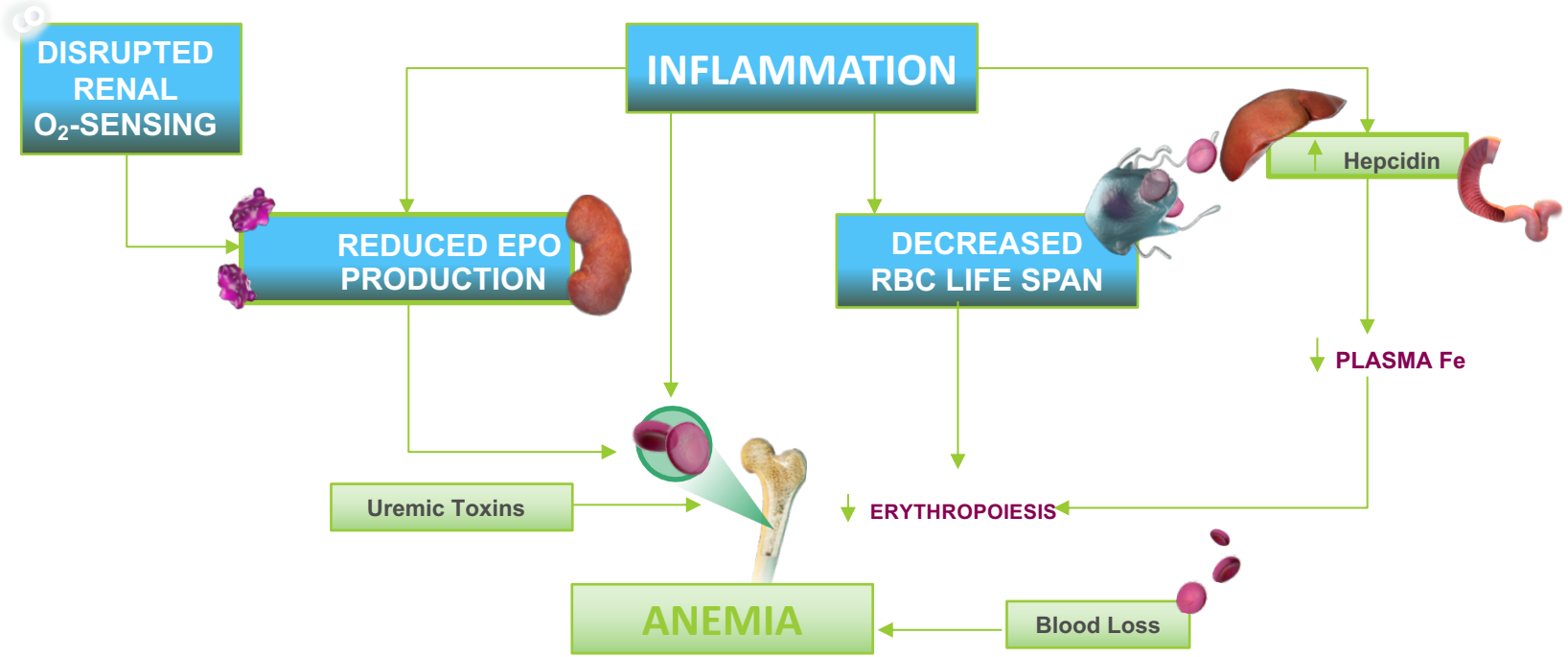
Learning Objectives

- Articulate the pathogenic mechanisms involved in anemia associated with CKD, including the roles of inflammation, hepcidin, and the HIF pathway
- Interpret outcomes from clinical trials evaluating the use of HIF-PHIs to treat anemia in patients with CKD
- Discuss the potential place of HIF-PHIs in the management of anemia in patients with CKD

The Pathogenesis of Anemia in CKD

Etiology of CKD Anemia Is Multifactorial in Nature [1-4]

CKD Pathophysiology Involves Several Processes

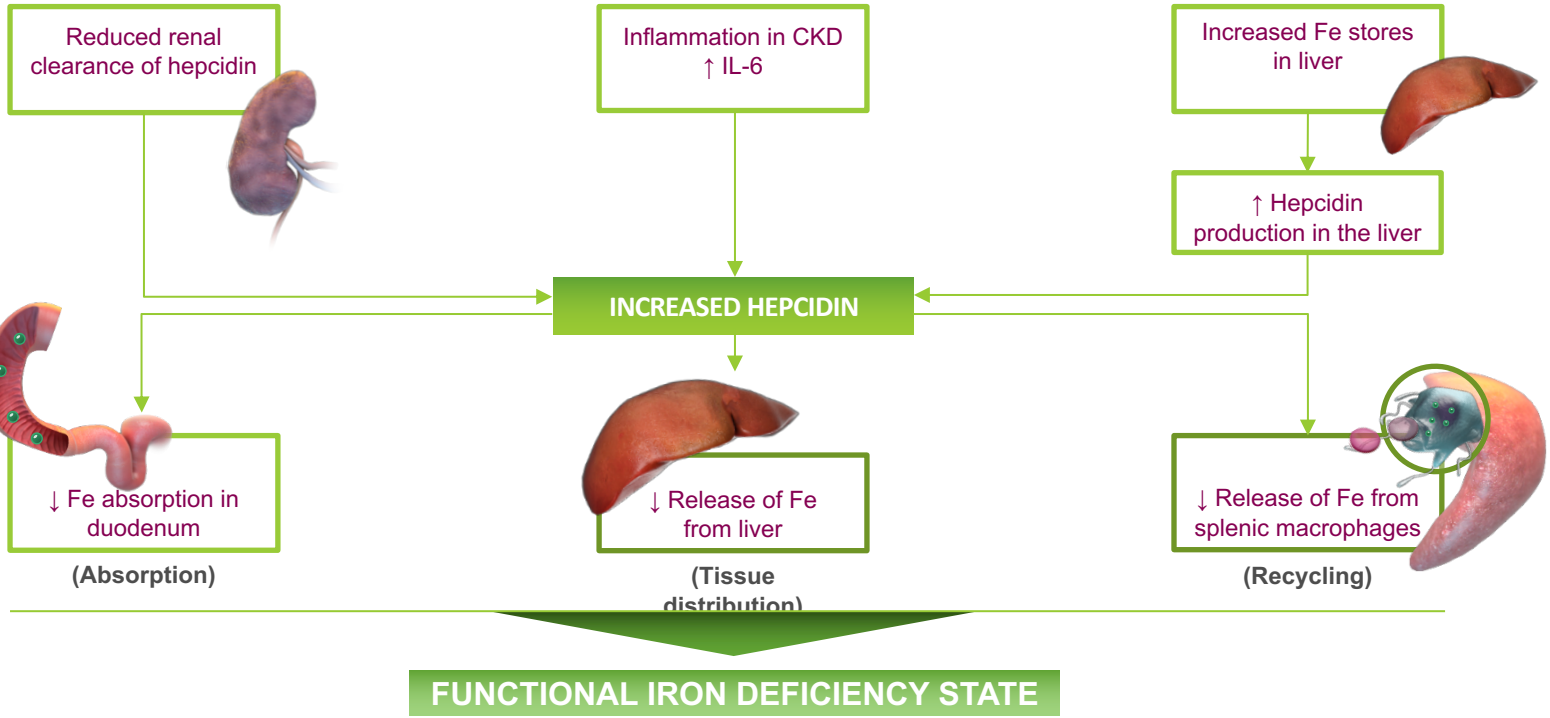


Hepcidin

- Hepcidin discovered in 2000
  - Peptide produced by liver
  - Key regulator of iron metabolism, use, recycling, and transport
  - Levels affected by iron stores, inflammation states, and EPO
- Hepcidin has been associated with anemia in CKD and resistance to ESA therapy
- Increased hepcidin in CKD
  - Caused by inflammation and reduced renal clearance
  - Leads to reduced circulating iron levels and impaired iron transport

1. Locatelli F, et al. *Am J Nephrol*. 2017;45(3):187-199. 2. Gaweda AE. *Hemodial Int*. 2017;21:S21-S27. 3. Atkinson MA, et al. *Pediatr Nephrol*. 2015;30(4):635-643.

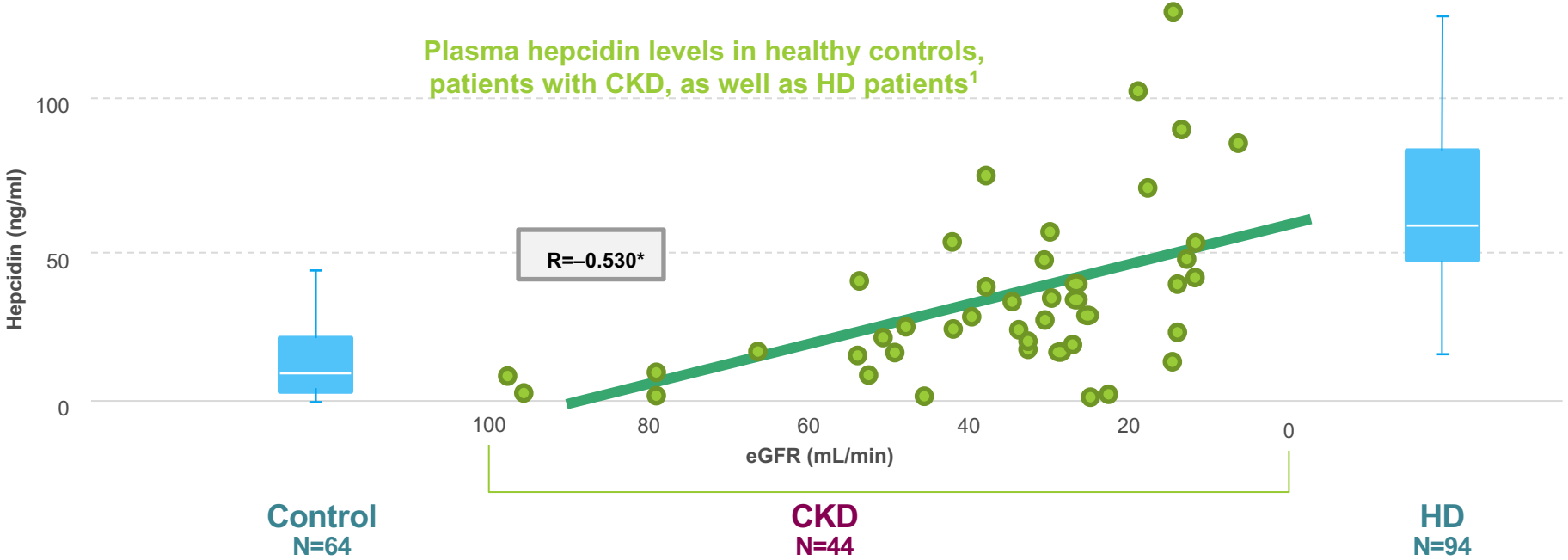
Hepcidin Regulates Iron Metabolism and Hepcidin Levels Are Often Elevated in CKD[1-3]



CKD = chronic kidney disease; Fe = iron; IL-6 = interleukin 6.

1. Babitt JL, et al. *J Am Soc Nephrol*. 2012;23:1631-1634. 2. Bergamaschi et al. *Haematologica*. 2009;94:1631-1633. 3. Kim YL. *Kidney Res Clin Pract*. 2012;31:1-3.

Hepcidin Levels Increase as CKD Progresses to ESRD



- Hepcidin is a main cause of functional iron deficiency and iron-restricted erythropoiesis[2]
- Following HIF stimulation, hepcidin levels significantly decrease[2]

Functional Iron Deficiency Following ESA Treatment

- Impaired response to ESA in patients with CKD and anemia
- Result of iron-restricted erythropoiesis
  - Elevated hepcidin levels
  - Increased iron demand

Locatelli F, et al. *Am J Nephrol*. 2017;45(3):187-199.

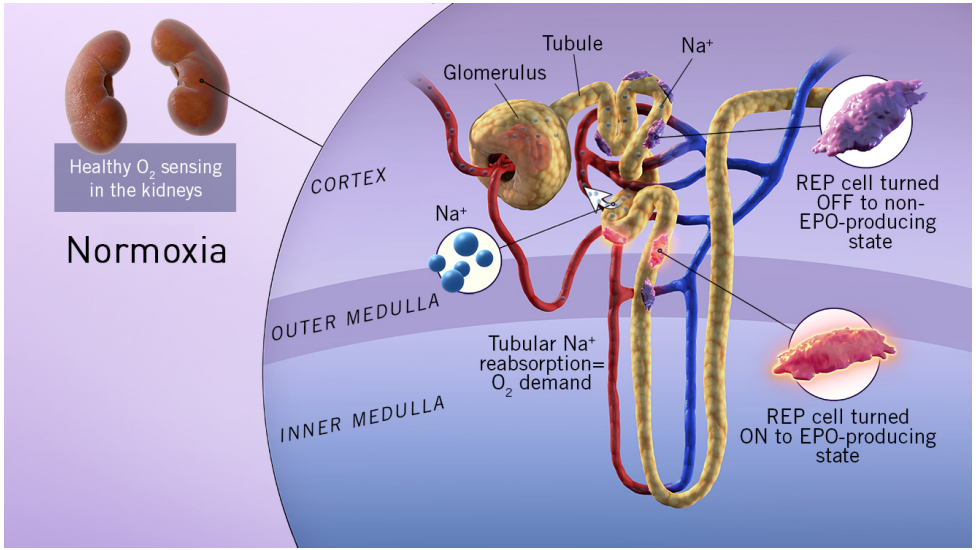
The HIF Pathway

- Hypoxia-inducible factors (HIF)
  - Family of oxygen-sensitive proteins that regulate the cell's transcriptional response to hypoxia
  - Response to hypoxia may be blunted in patients with CKD due to decreased renal tubular oxygen consumption
- Central regulator of erythropoiesis in response to hypoxia
  - EPO production
  - **Indirect suppression of hepcidin** by promotion of erythropoiesis
  - Augmentation of enteric iron absorption and transport
  - Mobilization of endogenous iron stores to erythroid marrow

Locatelli F, et al. *Am J Nephrol*. 2017;45(3):187-199.

The Kidneys Are the Key Oxygen Sensors of the Body That Lead to Increased Erythropoiesis

Healthy kidneys respond to changes in blood oxygenation levels to control erythropoiesis[1,2]



- Kidneys have a high oxygen demand, largely driven by tubular sodium reabsorption[3,4]
- The high oxygen demand is matched closely by the supply of oxygen[5,6]
- Any slight decrease in oxygen supply—such as in anemia—results in hypoxia[5-7]
- Hypoxia is sensed by REP cells[1,2]

Na^+=sodium ion; REP=renal erythropoietin-producing.

1. Wenger RH, Hoogewijs D. *Am J Physiol Renal Physiol.* 2010;298(6):F1287-F1296. **2.** Pan X, et al. *PLoS One.* 2011;6(10):e25839. **3.** Halperin ML, et al. *Clin J Am Soc Nephrol.* 2006;1(5):1049-1053. **4.** Lassen NA, et al. *Acta Physiol Scand.* 1961;51:371-384. **5.** Singh P, et al. *Brenner & Rector's the Kidney.* 10th ed. Philadelphia, PA: Elsevier; 2016:122-143. **6.** Donnelly S. *Am J Kidney Dis.* 2001;38(2):415-425. **7.** Brugnara C, Eckardt KU. *Brenner & Rector's the Kidney.* 10th ed. Philadelphia, PA: Elsevier; 2016:1875-1911.

The Kidneys Are the Key Oxygen Sensors of the Body That Lead to Increased Erythropoiesis

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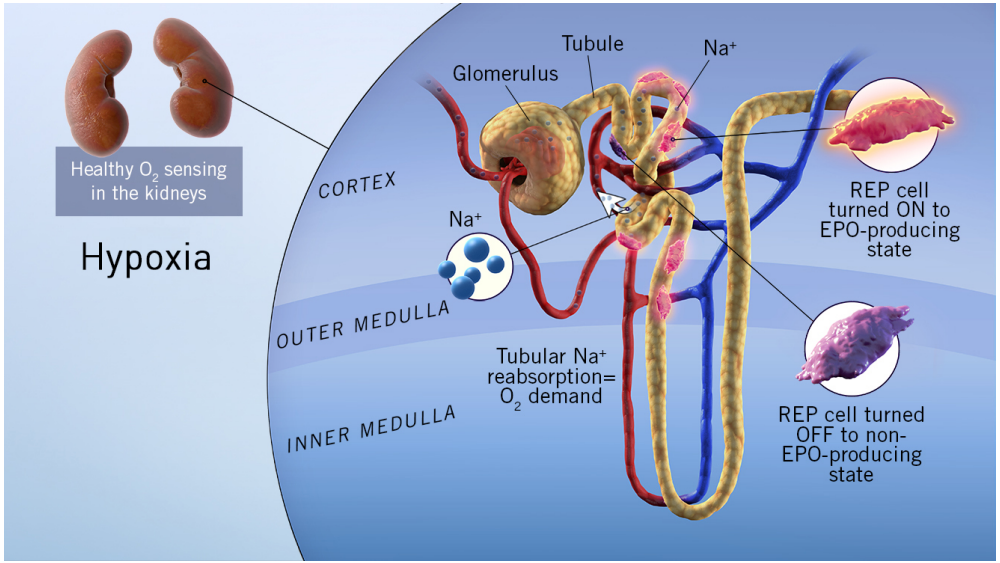
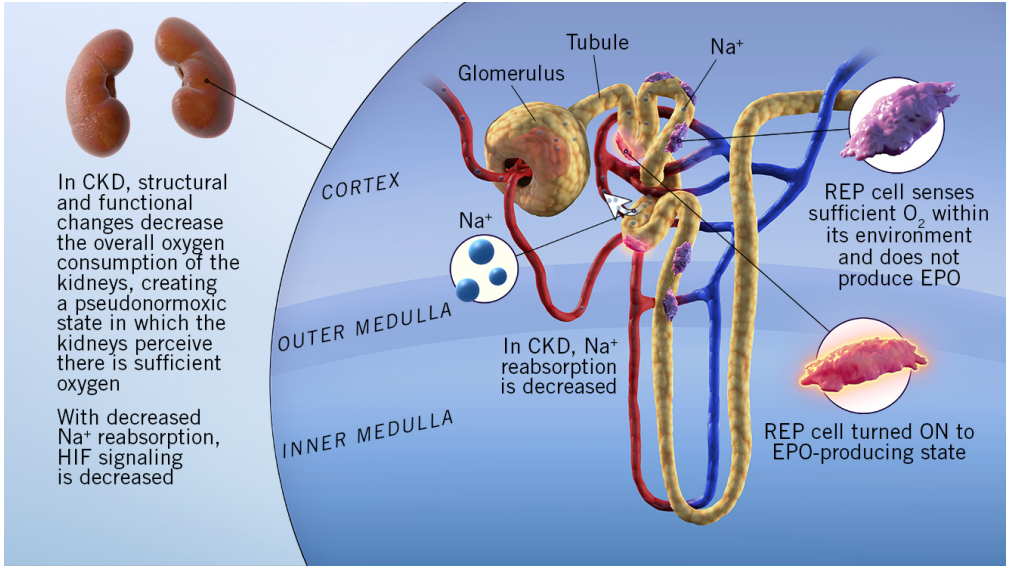


- REP cells are located in the cortex and outer medulla[1,2]
- In healthy kidneys, REP cells respond to hypoxia by producing EPO[1,2]
  - In normoxia, most REP cells are turned off and do not produce EPO[1,2]
  - In hypoxia, most REP cells are turned on and produce EPO[1,2]

1. Wenger RH, Hoogewijs D. *Am J Physiol Renal Physiol.* 2010;298(6):F1287-F1296. **2.** Pan X, et al. *PLoS One.* 2011;6(10):e25839.

In CKD, the Change in Oxygen Consumption Disrupts HIF Signaling

CKD progressively impairs the ability of the kidneys to recognize low blood oxygenation and the need for increased EPO production[1-5]

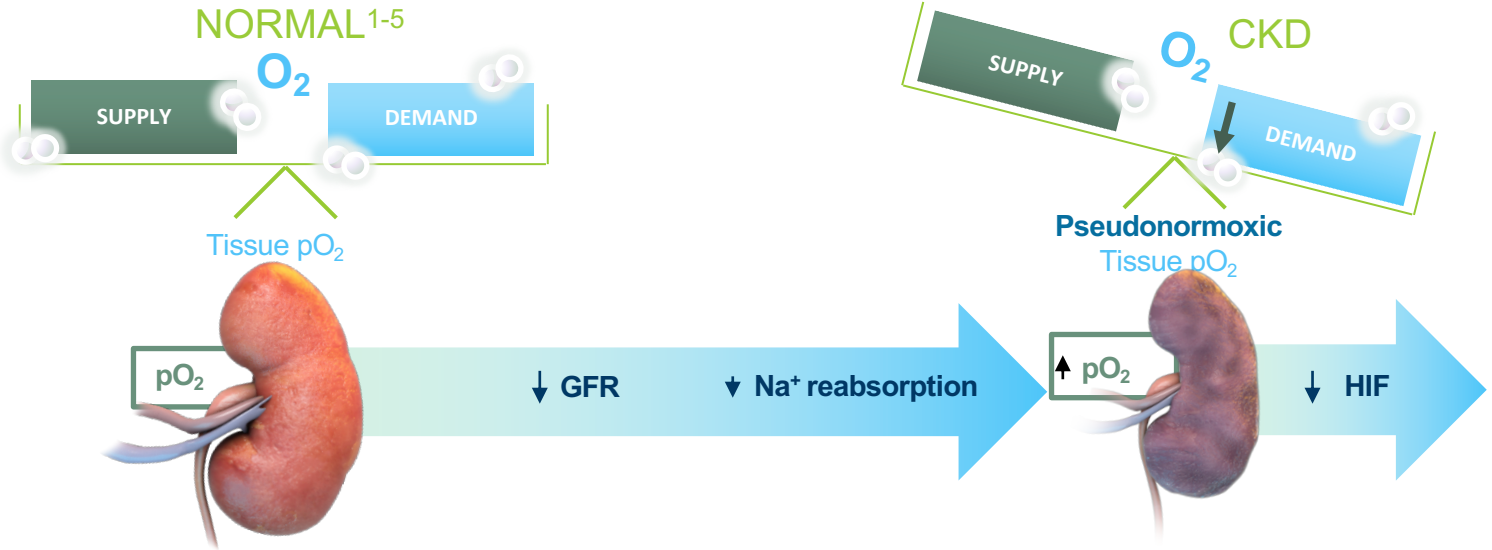


- As GFR declines, the kidneys consume less oxygen due to decreased tubular sodium transport[3,5,6]
- REP cells sense sufficient oxygen to meet the kidneys' needs *despite low Hb levels*[1,5]
- HIF signaling is reduced resulting in[1,5,6]:
  - Decreased EPO production
  - Insufficient erythropoiesis to correct Hb levels
  - Worsening anemia and decreased oxygen delivery to the rest of the body

1. Brugnara C, Eckardt KU. *Brenner & Rector's the Kidney.* 10th ed. Philadelphia, PA: Elsevier; 2016:1875-1911. **2.** Wenger RH, Hoogewijs D. *Am J Physiol Renal Physiol.* 2010;298(6):F1287-F1296. **3.** Singh P, et al. *Brenner & Rector's the Kidney.* 10th ed. Philadelphia, PA: Elsevier; 2016:122-143. **4.** Donnelly S. *Am J Kidney Dis.* 2001;38(2):415-425. **5.** Locatelli F, et al. *Am J Nephrol.* 2017;45(3):187-199. **6.** Halperin ML, et al. *Clin J Am Soc Nephrol.* 2006;1(5):1049-1053.

The Kidney's Ability to Elicit an Erythropoietic Response to Hypoxia Is Impaired in CKD[1]

- Causes include:
  - Disrupted oxygen sensing in the kidney due to a pseudonormoxic state[2]
  - Reduced number of REP cells available to elicit a hypoxic response[2]



Emerging Agents Targeting HIF

Understanding HIF/PHDs

- Inhibition of HIF prolyl-4-hydroxylase domains (HIF-PHD) prevents the degradation of HIF-α
  - Stimulates EPO synthesis by creating a pseudo-hypoxic environment
  - Improves iron absorption
  - Improves mobilization of storage iron
  - Indirectly reduces hepcidin levels

HIF-PHD

- HIF-PHD 1
- HIF-PHD 2
- HIF-PHD 3

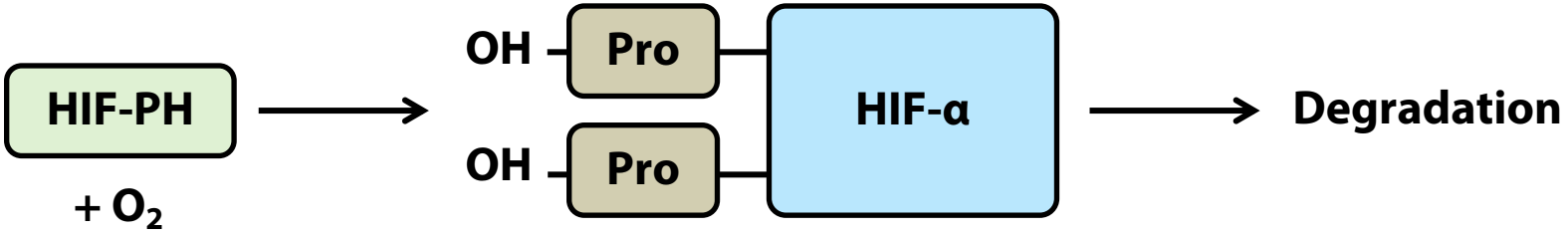
HIF-α

- HIF-1α
- HIF-2α
- HIF-3α

Locatelli F, et al. *Am J Nephrol*. 2017;45(3):187-199.

HIF Intracellular Distribution: Normoxia

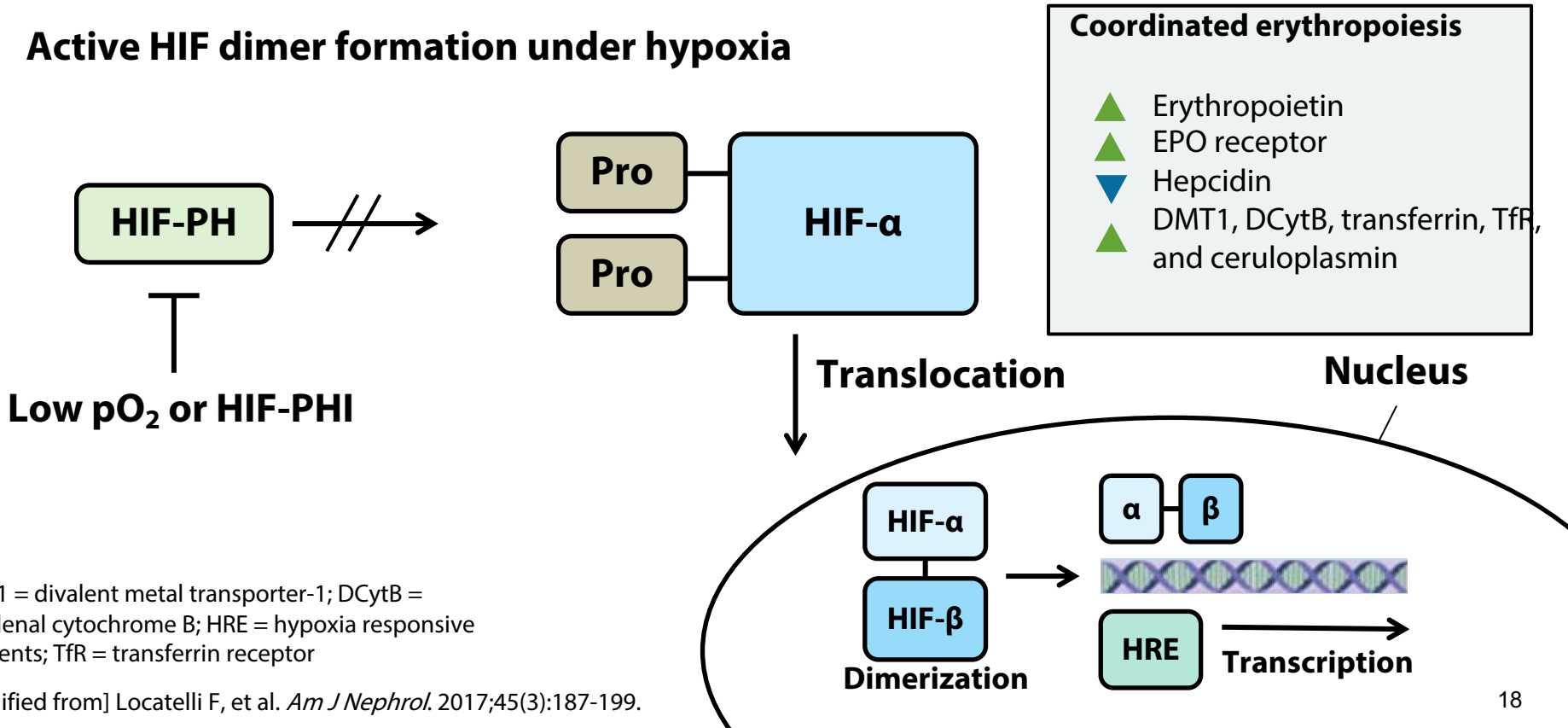
HIF-α degradation under normoxia



HIF = hypoxia-inducible factor; HIF-PH = HIF prolyl-4-hydroxylase domain; Pro = proline

Locatelli F, et al. *Am J Nephrol*. 2017;45(3):187-199.

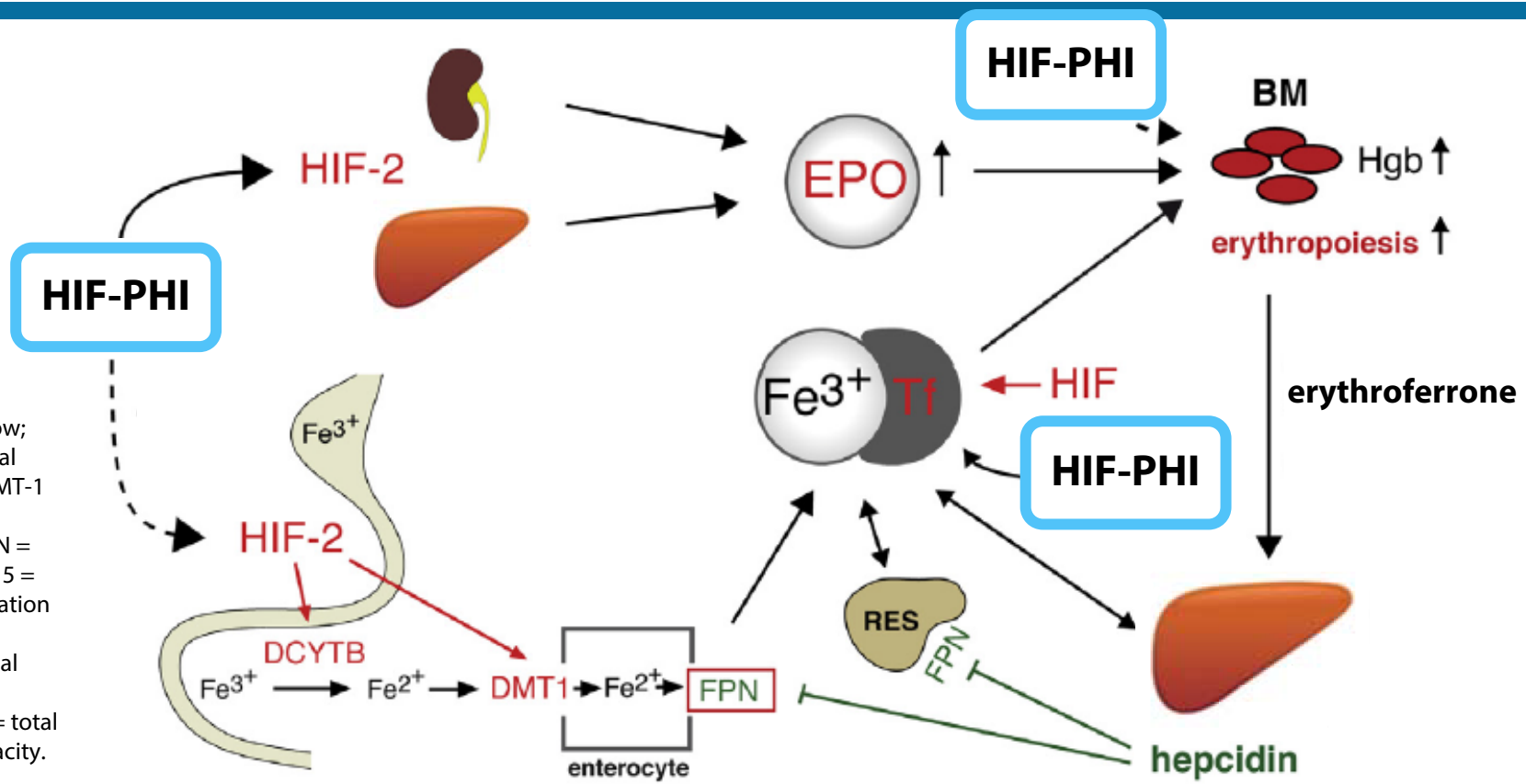
HIF Intracellular Distribution: Hypoxia



DMT1 = divalent metal transporter-1; DCytB = duodenal cytochrome B; HRE = hypoxia responsive elements; TfR = transferrin receptor

[Modified from] Locatelli F, et al. *Am J Nephrol*. 2017;45(3):187-199.

HIF-PHIs: Overview of Potential/Known Mechanisms

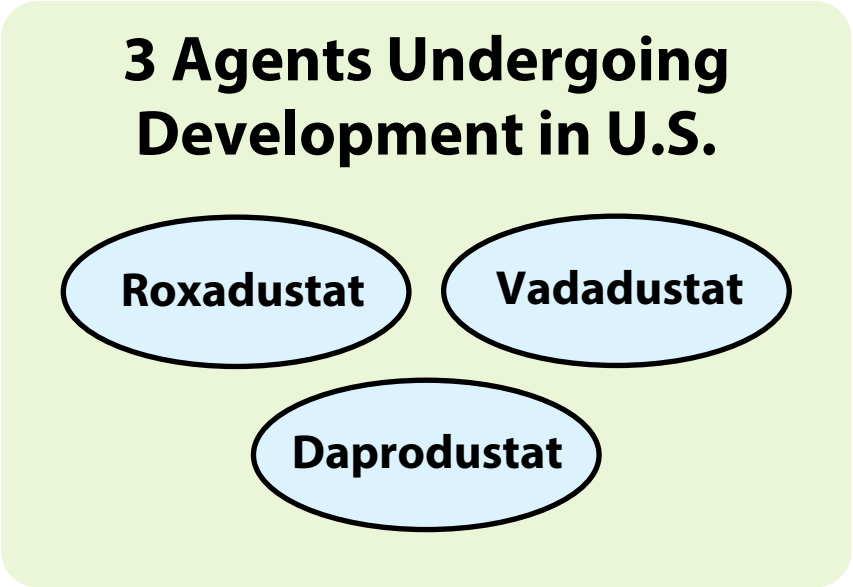


BM = bone marrow; DCYTB = duodenal cytochrome b; DMT-1 = divalent metal transporter-1; FPN = ferroportin; GDF15 = growth differentiation factor 15; RES = reticuloendothelial system; TF = transferrin; TIBC = total iron binding capacity.

Sanghani NS and Haase VH. *Adv Chronic Kidney Dis*. 2019;26(4):253-266.

HIF-PHIs

- Orally-administered
- Reversible
  - HIF transcriptional activity returns to baseline between doses



1. Sanghani NS and Haase VH. *Adv Chronic Kidney Dis*. 2019;26(4):253-266 2. Pergola PE, et al. *Kidney International.* 2016. 90, 1115–1122.
3. Kaplan JM, et al. *Int. J. Mol. Sci*. 2018, 19, 389.

HIF-PHIs: Pharmacologic Profiles

	Roxadustat	Vadadustat	Daprodustat
Effective Daily Oral Doses in Phase II Trials	0.7-2.5 mg/kg	150-600 mg	5-25 mg (50 and 100 mg also examined)
Dosing Schedule	3x weekly	Daily (3x weekly)	Daily (3x weekly)
Half-Life (hours)	12-15	4.7-9.1	~1-7
Plasma EPO (IU/L)	113 and 397, 130	32	24.7 and 34.4, 82.4
Metabolism	CYP2C8	NR	CYP2C8 with minor CYP3A4
Rel. Activity, IC50 for PHD2 (μM)	PHD1,2,3 equally, 0.027	PHD3>PHD1>PHD2, 0.029	PHD3>PHD1>PHD2, 0.067

CYP = cytochromeP450; IC50 = half maximal inhibitory concentration; NR = Not reported/Not published

Sanghani NS and Haase VH. *Adv Chronic Kidney Dis*. 2019;26(4):253-266.

HIF-PHIs: Phase II Trials in DD-CKD

	Study	n	Duration (weeks)	Comp.	Ferritin	TIBC	Hepcidin	VEGF	Chol.
Roxadustat	Provenzano et al.	54 (part 1) and 90	6 or 19*	rhEPO	↓	↑ (part 1†)	↓†	NR	↓
	Besarab et al.	60	12	None	↓†	↑†	↓†	NR	NR
	Chen et al.	87	6	rhEPO	↓	↑†	↓	NR	↓†
Vadadustat	Haase et al.	94	16	None	↓	↑†	↓†	No chg.	No chg.
Daprodustat	Holdstock et al.	82	4	rhEPO	↓	↑	No chg. (5 mg)	No chg.	↓
	Brigandi et al.	83	4	Placebo	↓	↑	↓ (10 mg, 25 mg)	Lg. variation	No chg.
	Akizawa et al.	97	4	Placebo	↓	↑	↓	No chg.	↓
	Meadowcroft et al.	216	24	Placebo	↓	↑	↓	No chg.	No chg.

*Two-part study: first part was a 6-week dose ranging study and second part was a 19-week treatment study with various starting doses and titration adjustments.
†Denotes statistically significant values reported for the end of treatment in one or several dose cohorts or for the combined analysis of all dosing groups.
Comp = active comparator group; DD-CKD = dialysis-dependent CKD; no chg = no change.

Sanghani NS and Haase VH. *Adv Chronic Kidney Dis*. 2019;26(4):253-266.

HIF-PHIs: Phase II Trials in NDD-CKD

	Study	n	Duration (weeks)	Comp.	Ferritin	TIBC	Hepcidin	VEGF	Chol.
Roxadustat	Besarab et al.	116	4	Placebo	↓	↑†	↓†	NR	NR
	Provenzano et al.	145	16-24	None	↓†	↑†	↓†	NR	↓†
	Chen et al.	91	6	Placebo	↓†	↑†	↓†	NR	↓†
Vadadustat	Pergola et al.	210	20	Placebo	↓†	↑†	↓†	No chg.	No chg.
Daprodustat	Martin et al.	93	6	Placebo	↓†	↑†	↓†	No chg.	No chg.
	Holdstock et al.	72	4	Placebo	↓	↑	↓	No chg.	↓
	Brigandi et al.	70	4	Placebo	↓	↑	↓	Lg. variation	NR
	Besarab et al.	116	4	Placebo	↓	↑†	↓†	NR	NR

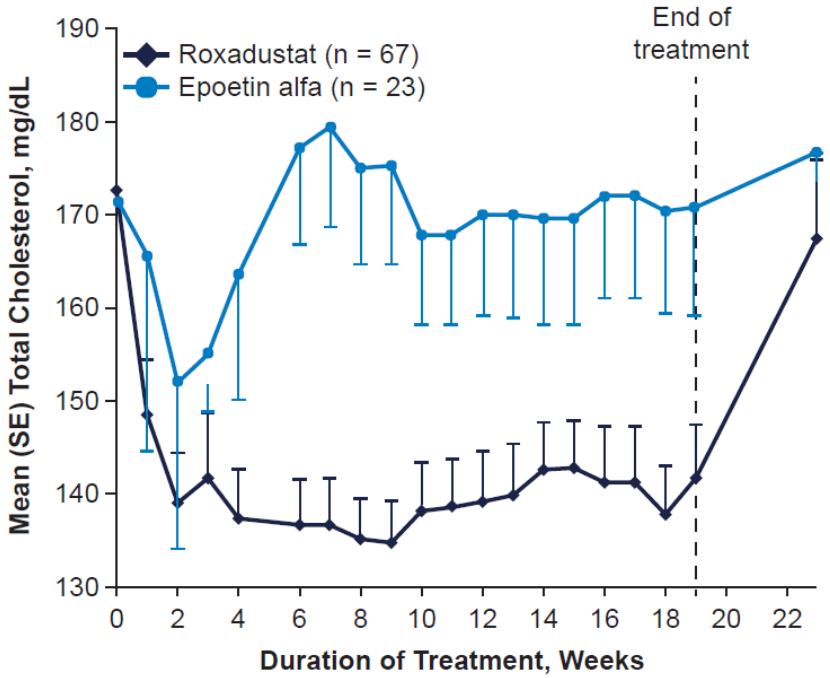
†Denotes statistically significant values reported for the end of treatment in one or several dose cohorts or for the combined analysis of all dosing groups.

NDD-CKD = non-dialysis-dependent CKD

Sanghani NS and Haase VH. *Adv Chronic Kidney Dis*. 2019;26(4):253-266.

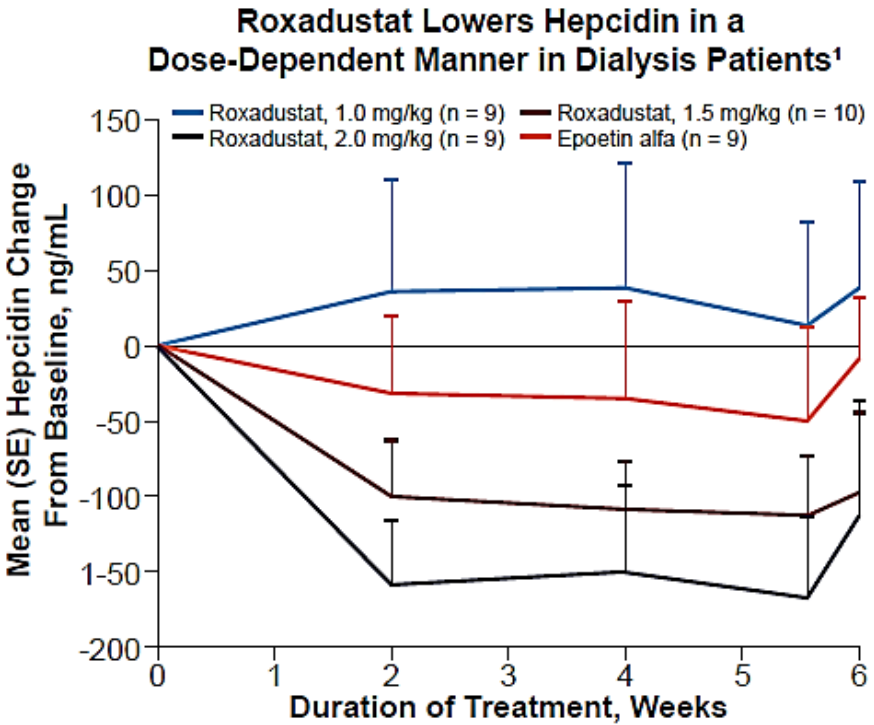
Roxadustat and Cholesterol[1]

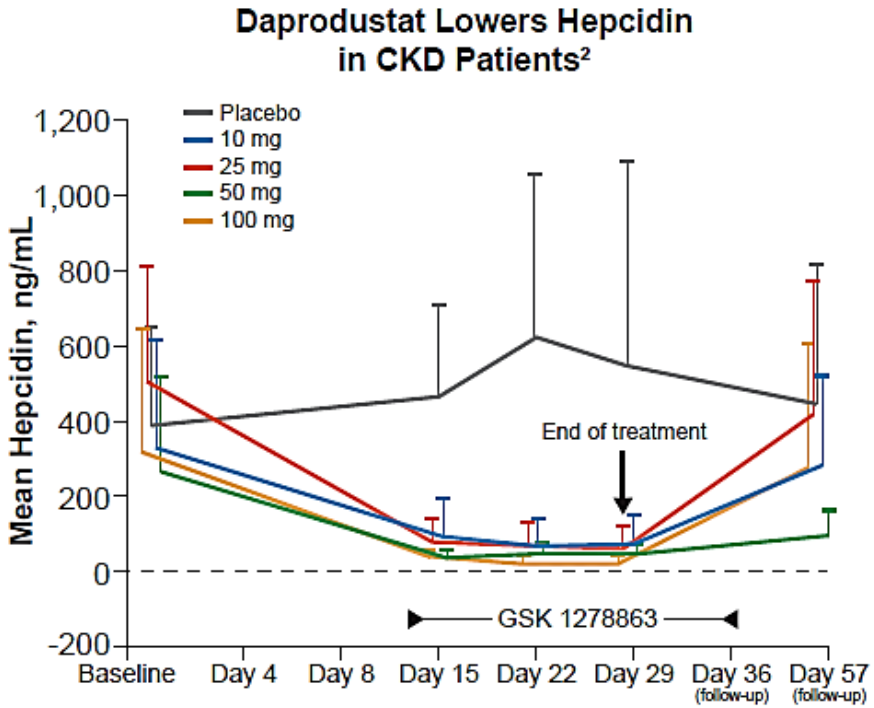
- **Roxadustat Lowers Total Cholesterol in Dialysis Patients**



1. Provenzano R et al. *Am J Kidney Dis*. 2016;67:912-924.

Roxadustat and Daprodustat: Effects on Hepcidin





1. Provenzano R et al. *Am J Kidney Dis*. 2016;67:912-924. 2. Brigandi RA et al. *Am J Kidney Dis*. 2016;67:861-871.

HIF-PHIs: Major Named Phase III Trials and Status

	Trial Name	NCT	n	Patient Population	Comp.	Duration (weeks)	Status
Roxadustat	PYRENEES	NCT02278341	838	Stable DD-CKD	Epoetin alfa, darbepoetin alfa	52+	Completed
	ROCKIES	NCT02174731	2133	Stable DD-CKD	Epoetin alfa	52+	Completed
	SIERRAS	NCT02273726	741	Stable DD-CKD	Epoetin alfa	52+	Completed
	HIMALAYAS	NCT02052310	1043	Incident DD-CKD	Darbepoetin alfa	52+	Completed
	ALPS	NCT01887600	597	NDD-CKD	Placebo	52+	Completed
	ANDES	NCT01750190	922	NDD-CKD	Placebo	52+	Completed
	OLYMPUS	NCT02174627	2781	NDD-CKD	Placebo	52+	Completed
	DOLOMITES	NCT02021318	616	NDD-CKD	Darbepoetin alfa	104	Completed

Sanghani NS and Haase VH. *Adv Chronic Kidney Dis*. 2019;26(4):253-266. US National Library of Medicine: Clinicaltrials.gov. Accessed 22 July 2020.

HIF-PHIs: Major Named Phase III Trials and Status

	Trial Name	NCT	n	Patient Population	Comp.	Duration (weeks)	Status
Vadadustat	$INNO_2VATE$	NCT02865850	369	Incident DD-CKD	Darbepoetin alfa	52+	Completed
		NCT02892149	3554	Stable DD-CKD	Darbepoetin alfa	52+	Completed
	PRO_2TECT	NCT02680574	1752	NDD-CKD on rhEPO	Darbepoetin alfa	52+	Completed
		NCT02648347	1761	NDD-CKD rhEPO-naïve	Darbepoetin alfa	52+	Completed
Daprodustat	ASCEND-D	NCT02879305	2964	Stable DD-CKD	Epoetin alfa, darbepoetin alfa	52+	Active
	ASCEND-ID	NCT03029208	300 (est)	Incident DD-CKD	Darbepoetin alfa	52	Active
	ASCEND-TD	NCT03400033	407	Stable DD-CKD	Epoetin alfa	52	Completed
	ASCEND-ND	NCT02876835	4500 (est)	NDD-CKD + rhEPO naïve	Darbepoetin alfa	52+	Active
	ASCEND-NHQ	NCT03409107	600 (est)	NDD-CKD rhEPO naïve	Placebo	28	Active

Sanghani NS and Haase VH. *Adv Chronic Kidney Dis*. 2019;26(4):253-266. US National Library of Medicine: Clinicaltrials.gov. Accessed 22 July 2020.

ASN 2019 Kidney Week: Cardiovascular Safety of Roxadustat Confirmed in Pooled Analyses[1]

Population, Comparator	MACE	MACE+	All-Cause Mortality	Conclusion
NDD (n = 4,270) placebo	HR = 1.08 (95% CI, 0.94-1.24)	HR = 1.04 (95% CI, 0.91-1.18)	HR = 1.06 (95% CI, 0.91-1.23)	Risk of MACE, MACE+, and all-cause mortality in roxadustat patients comparable with placebo
ID (n = 1,526) EPO	HR = 0.70 (95% CI, 0.51-0.96)	HR = 0.66 (95% CI, 0.50-0.89)	HR = 0.76 (95% CI, 0.52-1.11)	Those taking roxadustat had 30% ↓ risk of MACE and 34% ↓ risk of MACE+ compared with those taking EPO, with a trend toward ↓ all-cause mortality for roxadustat, relative to EPO
DD (n = 3,880) EPO	HR = 0.96 (95% CI, 0.82-1.13)	HR = 0.86 (95% CI, 0.74-0.98)	HR = 0.96 (95% CI, 0.79-1.17)	No ↑ risk of MACE and all-cause mortality and a ↓ risk of MACE+ compared with EPO

1. Provenzano R et al. American Society of Nephrology Kidney Week 2019 (ASN 2019). Abstract FR-OR131.

ASN 2019 Kidney Week: Other Benefits of Roxadustat in Pooled Analyses of Phase 3 Global Studies

Slower eGFR decline observed in NDD patients

- In patients with baseline eGFR ≥15 mL/min/1.73 m^2, with a treatment difference of 1.62 mL/min/1.73 m^2 in eGFR change at 12 months from the baseline ($P < .0001$), or a reduction by 38% in eGFR decline in the roxadustat arm relative to the placebo arm

Improvements in quality of life measures in NDD patients

- Statistically significant improvements from baseline to week 12 in quality of life endpoints, including SF-36 vitality subscale ($P = .0002$), SF-36 physical functioning subscale ($P = .0369$), FACT-AN anemia subscale ($P = .0012$), FACT-AN total score ($P = .0056$), and EQ-5D-SL VAS score ($P = .0005$) when comparing roxadustat with placebo in CKD patients not on dialysis

Efficacy regardless of inflammation status

- Mean achieved Hb levels and roxadustat dose requirements were not impacted by baseline CRP levels in multiple phase 3 studies, including in SIERRAS study, which is reflective of US dialysis practice under current ESA labeling restrictions
  - in SIERRAS, roxadustat dose requirements remained stable over time, while epoetin alfa dose requirements increased by 57% over 52 weeks in the epoetin alfa arm

1. Provenzano R al. ASN 2019. Abstract TH-OR021. 2. Charytan C et al. ASN 2019. Abstract SA-PO227. 3. Fishbane S et al. ASN 2019. Abstract TH-OR022. 4. Esposito C et al. ASN 2019. Abstract SA-PO225. 5. Coyne D et al. ASN 2019. Abstract SA-PO228. 6. Fishbane S et al. ASN 2019. Abstract TH-OR023. 7. https://fibrogen.gcs-web.com/news-releases/news-release-details/fibrogen-announces-new-roxadustat-data-presented-2020-era-edta

ASN 2020 Kidney Week: Roxadustat Pooled Global Phase 3 Study Oral Presentations

TH-OR02: Detailed analysis of pooled DD studies in terms of efficacy, TEAEs, and CV events

TH-OR03: Response not influenced by baseline iron status in NDD

TH-OR04: No increase in neoplasm vs. placebo in NDD or vs. ESA in DD

TH-OR05: Efficacy irrespective of baseline iron or inflammatory status; IV iron and rescue lower than placebo in NDD

TH-OR06: Decreased IV iron use vs. epoetin in DD

TH-OR09: Adverse events higher post-transfusion vs. overall f/u in NDD and DD, in roxa and comparator group

ASN 2020 Kidney Week: Roxadustat Pooled Global Phase 3 Study Poster Presentations (1)

PO0256: Decreased RBC transfusion vs. placebo in NDD (P<0.0001) and vs. ESA in DD (P<0.046)

PO0257, PO0262: Improved iron parameters vs. placebo in NDD

PO0258: Improved HRQOL vs. placebo in NDD

PO0259: Decreased IV iron use, MACE and MACE+ vs epoetin alfa in incident DD in all subgroups examined

PO0260: Increased efficacy vs. placebo in NDD in all subgroups examined, greatest if Hb<8 or eGFR<10

PO0261, PO0268: Risk of transfusion 4 fold greater for Hb<10 vs. >10 in NDD, 5 fold greater in DD

ASN 2020 Kidney Week: Roxadustat Pooled Global Phase 3 Study Poster Presentations (2)

PO0263, PO0265: Hb response in NDD and DD is independent of inflammatory status

PO0267: No increase in retinopathy vs. placebo in NDD and vs. ESA in DD

PO1031, PO1032: Efficacy and safety in NDD and DD comparable in diabetic and non-diabetic subjects

PO2111, PO2112: Efficacy unrelated to presence of heart failure in NDD and DD

PO2113: Lowering of LDL, TC, and TG in NDD and DD vs. comparator in all subgroups examined

PO2114: No effect on BP vs. comparator in NDD and DD

PO2625, PO2656: MACE, MACE+, and CV component lowest when achieved Hb >10 (including 10-11, 11-12, and >12) in NDD and DD

Summary of Roxadustat Global Phase 3 Studies[1-7]

DD-CKD Studies	Population, Comparator	Efficacy Results
HIMALAYAS	N = 1,043, incident dialysis vs EPO	Superior to EPO
SIERRAS	N = 741, stable dialysis vs EPO	Superior to EPO
ROCKIES	N = 2,133, stable/incident dialysis vs EPO	Superior to EPO
PYRENEES	N = 836, stable dialysis vs EPO or darbepoetin	Superior to ESA
NDD-CKD Studies	**Population, Comparator**	**Efficacy Results**
ALPS	N = 594, nondialysis vs placebo	Superior to placebo
ANDES	N = 922, nondialysis vs placebo	Superior to placebo
OLYMPUS	N = 2,781, nondialysis vs placebo	Superior to placebo
DOLOMITES	N = 616, nondialysis vs darbepoetin	Non-inferior to ESA

1. Provenzano R al. ASN 2019. Abstract TH-OR021. 2. Charytan C et al. ASN 2019. Abstract SA-PO227. 3. Fishbane S et al. ASN 2019. Abstract TH-OR022.
4. Esposito C et al. ASN 2019. Abstract SA-PO225. 5. Coyne D et al. ASN 2019. Abstract SA-PO228. 6. Fishbane S et al. ASN 2019. Abstract TH-OR023.
7. https://fibrogen.gcs-web.com/news-releases/news-release-details/fibrogen-announces-new-roxadustat-data-presented-2020-era-edta

Vadadustat Top-Line Phase 3 Global Data: DD

- Topline data from two INNO$_2$VATE studies (DD-CKD) announced May 5, 2020
  - **Vadadustat met primary efficacy endpoint** of non-inferiority to darbepoetin alfa in mean Hb change by 24-36 weeks (primary evaluation period) and 40-52 weeks (secondary evaluation period)
  - Non-inferior safety outcomes to darbepoetin alfa

Available at: https://ir.akebia.com/node/10876/pdf.

Vadadustat Top-Line Phase 3 Global Data: NDD

- Topline data from phase 3 PRO$_2$TECT (NDD-CKD) announced Sept. 3, 2020
  - **Vadadustat met primary efficacy endpoint** of non-inferiority darbepoein alfa in mean Hb change by 24-36 weeks (primary evaluation period) and 40-52 weeks (secondary evaluation period)
  - **Vadudstat did not meet the primary safety endpoint** vs. darbepoetin defined as time to first occurrence of MACE event (HR 1.17, 95% CI 1.01-1.36, prespecified NI margin upper bound 1.25)

https://www.prnewswire.com/news-releases/akebia-therapeutics-announces-top-line-results-from-its-pro2tect-global-phase-3-program-of-vadadustat-for-treatment-of-anemia-due-to-chronic-kidney-disease-in-adult-patients-not-on-dialysis-301123808.html

Potential Utility of HIF-PHIs in Clinical Practice

HIF-PHIs: Clinical Benefits

- Correction and/or maintenance of Hb is associated with lower plasma EPO levels compared to ESA
- Lowering of hepcidin levels and beneficial effects on iron metabolism
- Potential anti-inflammatory effects
- Potential benefits in ESA-resistant patients
- Potential protection from ischemic events

Sanghani NS and Haase VH. *Adv Chronic Kidney Dis*. 2019;26(4):253-266.

HIF-PHIs: Potential Disadvantages and Safety Concerns

- Potential pro-tumorigenic effects
- Neuroendocrine tumor development
- Pulmonary hypertension
- Pro-angiogenic effects negatively impacting retinal diseases or cancer development
- Thromboembolic complications
- CKD progression (the role of HIF in renal fibrogenesis is controversial, cell type- and context-dependent), renal and liver cyst progression in PKD
- Effects on autoimmune diseases are not clear
- Effects on underlying infectious processes is unclear
- Adverse metabolic effects such as hyperglycemia and hyperuricemia
- Hyperkalemia (reported in phase II/III studies)
- Adverse effects in patients with chronic hepatitis

Sanghani NS and Haase VH. *Adv Chronic Kidney Dis*. 2019;26(4):253-266.

Summary

Summary

- ESA therapy revolutionized treatment of anemia in CKD
  - US FDA recommends conservative dosing due to cardiovascular risks
  - Hyporesponsiveness
    - Requires higher ESA doses (and greater risk of AEs)
- Hepcidin associated with anemia in CKD and resistance to ESA
  - Increased hepcidin in CKD is caused by inflammation and reduced renal clearance and leads to reduced circulating iron levels and impaired iron transport.

Summary cont'd

- HIF pathway: regulator of EPO in response to hypoxia
- Inhibitors of HIF-PHD (HIF-PHIs)
  - Stimulate EPO synthesis, improve iron metabolism, and indirectly reduce hepcidin, which increases mobilization of iron stores
  - Three agents currently undergoing development in United States
    - Roxadustat
    - Vadadustat
    - Daprodustat

Acknowledgments

Jay B. Wish, MD
Professor of Clinical Medicine, IU School of Medicine

Question & Answer

Primary manuscripts

Study No, Name	Study Description	Journal
001 OLYMPUS	Roxadustat vs Pbo in NDD-CKD	JASN
002 ROCKIES	Roxadustat vs ESA in DD-CKD	JAMA
060 ANDES	Roxadustat vs Pbo in NDD-CKD	Kidney Int Reports
063 HIMALAYAS	Roxadustat vs ESA in New DD-CKD	NDT
064 SIERRAS	Roxadustat vs ESA in DD-CKD	AJKD
608 ALPS	Roxadustat vs Pbo in NDD-CKD	NDT
610 DOLOMITES	Roxadustat vs ESA in NDD-CKD	Kidney Int
613 PYRENEES	Roxadustat vs ESA in DD-CKD	Kidney Int

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