

**Thursday, October 21, 2021**

**4:00 p.m. to 4:45 p.m.**

Tennessee Academy of Family Physicians  
72<sup>nd</sup> Annual Scientific Assembly  
The Park Vista Doubletree Hotel, Gatlinburg, Tennessee  
October 19-22, 2021

**“Anemia”**

**JERRY MULLERSMAN, M.D., PHD, MPH**

**Presentation Objectives:**

- 1) Review the general mechanisms underlying the development of anemia.
- 2) Examine the types of anemia most commonly afflicting subpopulations of adults.
- 3) Consider diagnostic and therapeutic approaches to anemia in various situations.

# ANEMIA

Jerald Mullersman, MD, PhD, MPH

# Definition of Anemia

Often thought of as a hemoglobin level more than 2 standard deviations below the mean for a patient, taking into account the person's age and sex

# Hgb Values Below Which Anemia Exists at Sea Level

<b>Age, Years</b>	<b>Hb, g/dL</b>
<b>Both Sexes</b>	
1–2	11
3–5	11.2
6–11	11.8
<b>Females</b>	
12–15	11.9
16–69	12
≥70	11.8
<b>Males</b>	
12–15	12.6
16–19	13.6
20–49	13.7
50–69	13.3
≥70	12.4

from Elghetany and Banki, “Erythrocytic Disorders” (2021)

# Broad Categories of Anemia

- Loss or Accelerated Destruction of Erythrocytes
- Impaired Synthesis of Erythrocytes

# Commonly Used Laboratory Tests

- Hct/Hgb
- Red cell indices
  - MCV
  - MCHC
  - RDW
- Morphology on smear
- Reticulocyte count
- Bone marrow aspirate/biopsy
- Iron-related studies on serum and bone marrow
- B12/folate levels
- DAT
- Occult blood
- Erythropoietin level

# Some Examples of Loss or Destruction

- Bleeding
- Hemolytic anemia
  - Immune-mediated
  - Hemoglobinopathy
  - G6PD deficiency
  - Microangiopathic
- Parasitic infection

# Some Examples of Impaired Synthesis

- Iron deficiency
- Chronic Kidney Disease (CKD)
- Chronic Inflammation
- Viral infection
- Myelodysplasia or other neoplasia in bone marrow
- B12/folate deficiency
- Porphyria



# Typical Treatments for Loss or Destruction

- Iron supplementation
- Transfusion
- IVIg/corticosteroids
- Anti-malarial or other anti-parasitic medications

# Typical Treatments for Impaired Synthesis

- Iron supplementation
- Transfusion
- B12/folate supplementation
- Erythropoietin or related medication

# Erythropoietin as Treatment – Brief History

- First purified in 1977
- A partial amino acid sequence permitted cloning of the EPO gene
- Epogen (recombinant erythropoietin) approved by FDA in 1989
- Hypoxia-inducible factor (HIF) is a hypoxia-responsive transcription factor that regulates the EPO gene
- Erythropoietin is given by injection because of large molecular weight

# Erythropoietin as Treatment – Approved Uses

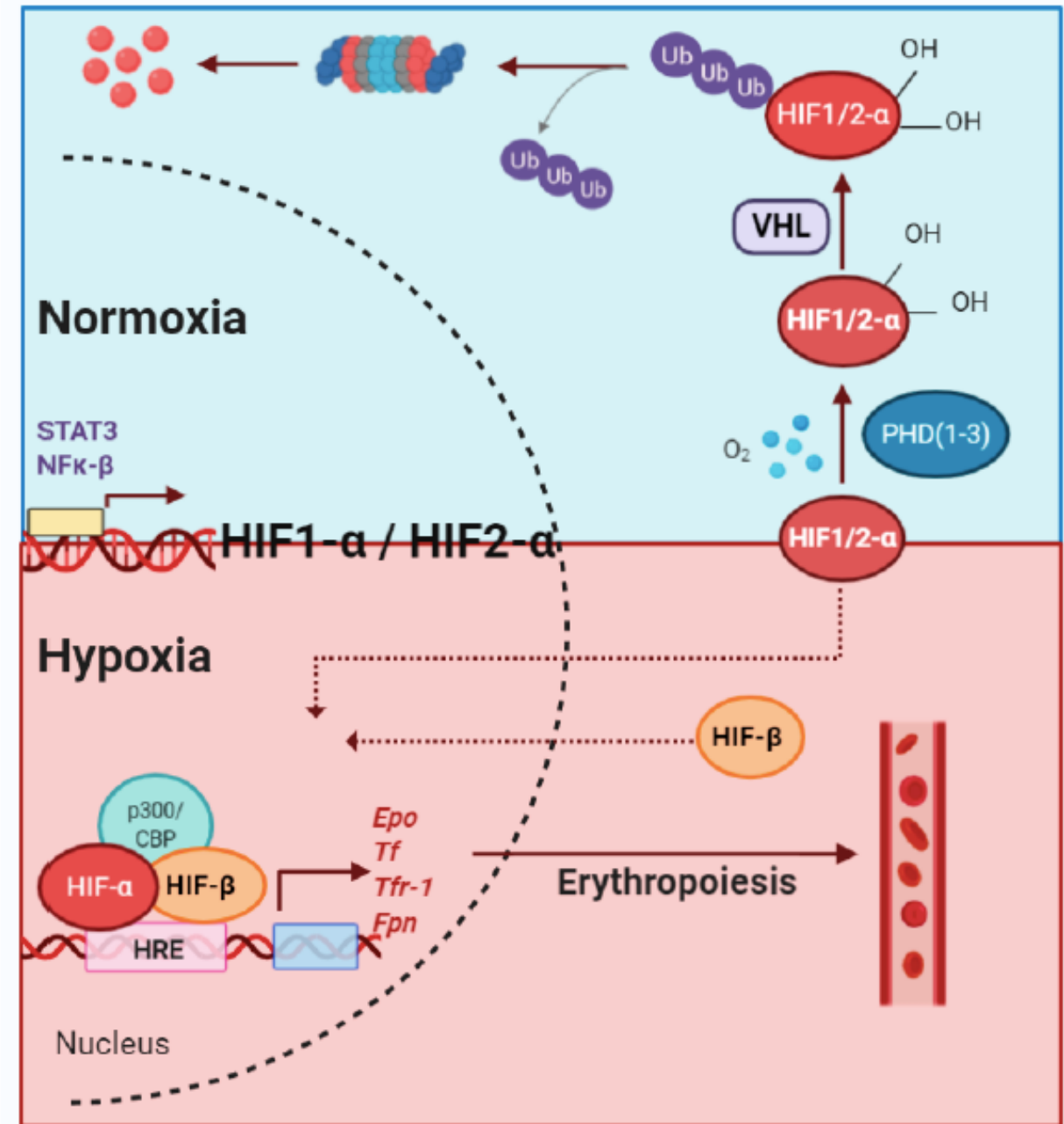
- Anemia of CKD
- Chemotherapy-induced anemia
- Anemia due to therapy for HIV with zidovudine
- Reduction of allogeneic RBC transfusions for certain surgeries

# Erythropoietin as Treatment – Boxed Warning

Increased risk of:

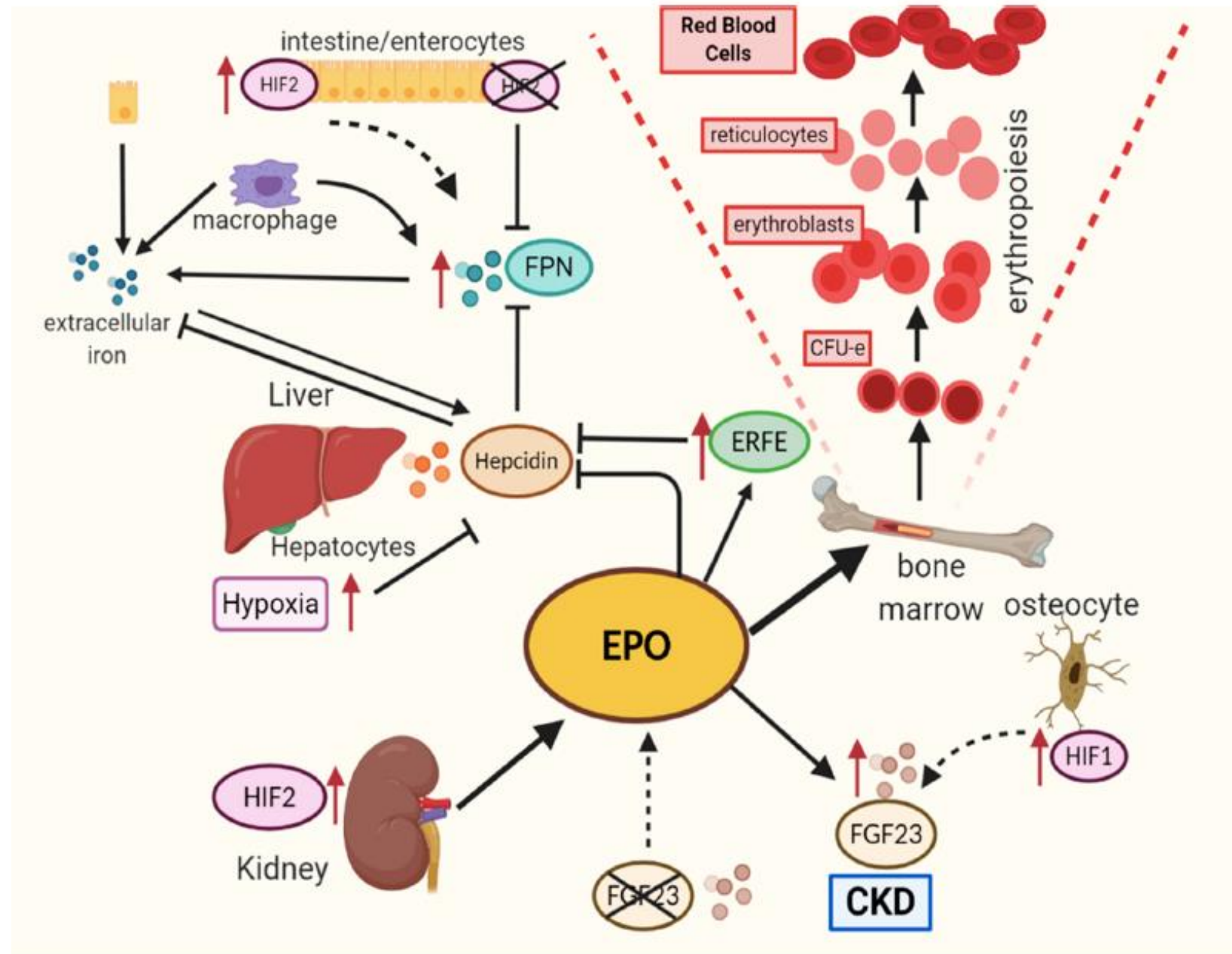
- Death
- Myocardial infarction
- Stroke
- Venous thromboembolism
- Thrombosis of vascular access
- Tumor progression or recurrence

# HIF Prolyl Hydroxylase and Hypoxia



from Watts et al, "Hypoxia Pathway Proteins...", Int J Mol Sci (2020)

# Regulation of Erythropoiesis by Hypoxia Pathway Proteins



from Watts et al, "Hypoxia Pathway Proteins...", Int J Mol Sci (2020)

# Inhibitors of HIF Prolyl Hydroxylase (HIF-PHIs)

- This is a new class of orally bioavailable drugs that reduce the ubiquitin-mediated degradation of HIF
- HIF-PHIs promote the transcription of the wide array of genes involved in response to hypoxia, including EPO and various genes involved in iron metabolism



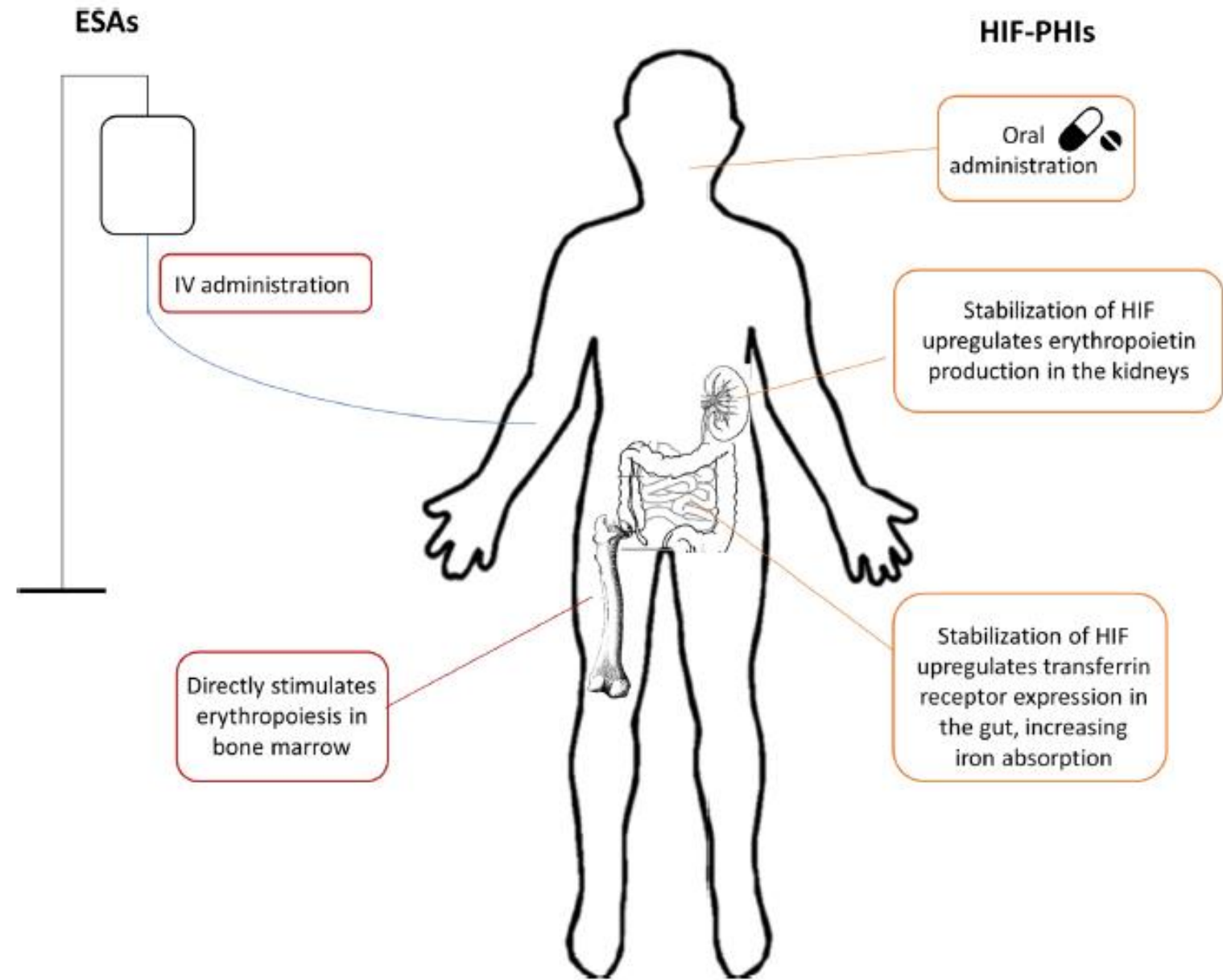
## Some HIF-PHIs with Clinical Trials

- Daprodustat – approved in Japan
- Desidustat
- Enarodustat – approved in Japan
- Moludistat
- Roxadustat – approved in Japan, China, Chile, South Korea
- Vadadustat – approved in Japan

# Some Pros and Cons of ESAs versus HIF-PHIs

- ESAs
  - Pros
    - Reduce requirement for RBC transfusion
    - May lessen fatigue & improve HR-QOL
  - Cons
    - Requirement for higher doses may increase risk of CV AEs
    - Often need supplemental iron
- HIF-PHIs
  - Pros
    - Non-inferior to ESAs in raising/maintaining hemoglobin level
    - Oral administration
    - May reduce need for supplemental iron
  - Cons
    - Risks relative to tumor growth and other issues not well established

# ESAs versus HIF-PHIs



from Hanna et al, "Burden of Anemia in Chronic Kidney Disease..." Adv Ther (2021)

# Recent Developments at FDA

- FDA's Cardiovascular and Renal Drugs Advisory Committee (CRDAC) reviewed data related to approval of Roxadustat in July 2021
- CRDAC voted against approval of the drug for the treatment of anemia due to CKD because of safety concerns
- FDA decision pending as of 30 Aug 2021

# Selected References

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