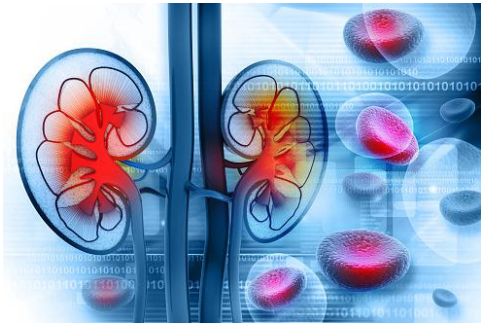
64th
Myanmar Medical Conference

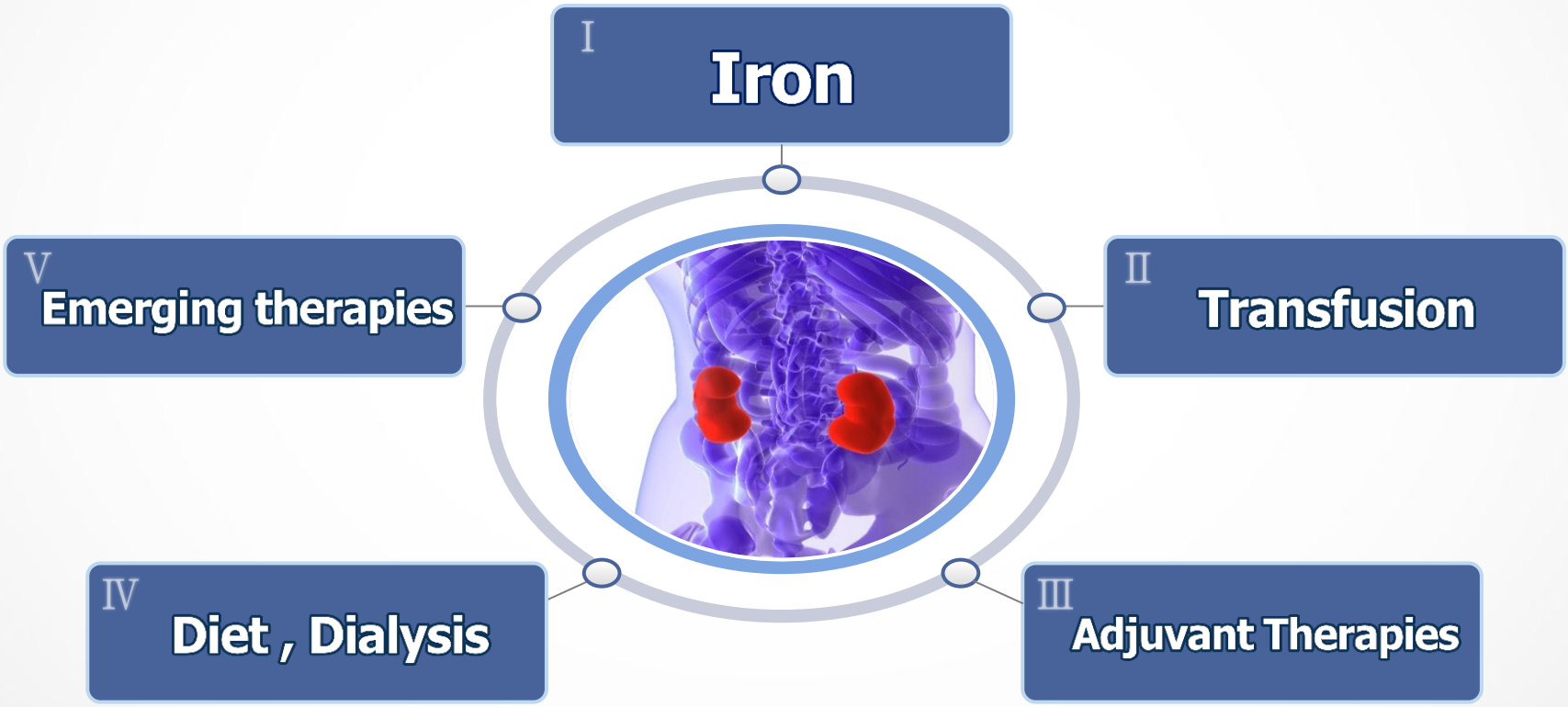
Role of Non-Erythropoietin Stimulating Agents in Renal Anemia



22-1-2018

Dr. Mya Htwe Nge
Consultant Nephrologist
Department of Nephrology
Yangon Specialty Hospital

Role of Non-ESA in Renal Anaemia



Common causes of Anemia in CKD

- Relative erythropoietin deficiency
- Iron deficiency
- Blood loss
- Reduced erythrocyte survival duration
- Inflammation
- Infection
- Underlying hematologic disease
- Hyperparathyroidism (dialysis patients)
- Hemolysis
- Nutritional deficits

Update on Anemia in ESRD and Earlier Stages of CKD: Core Curriculum 2018, AJKD

Benefits of Anemia Control

Benefits of Anemia Control

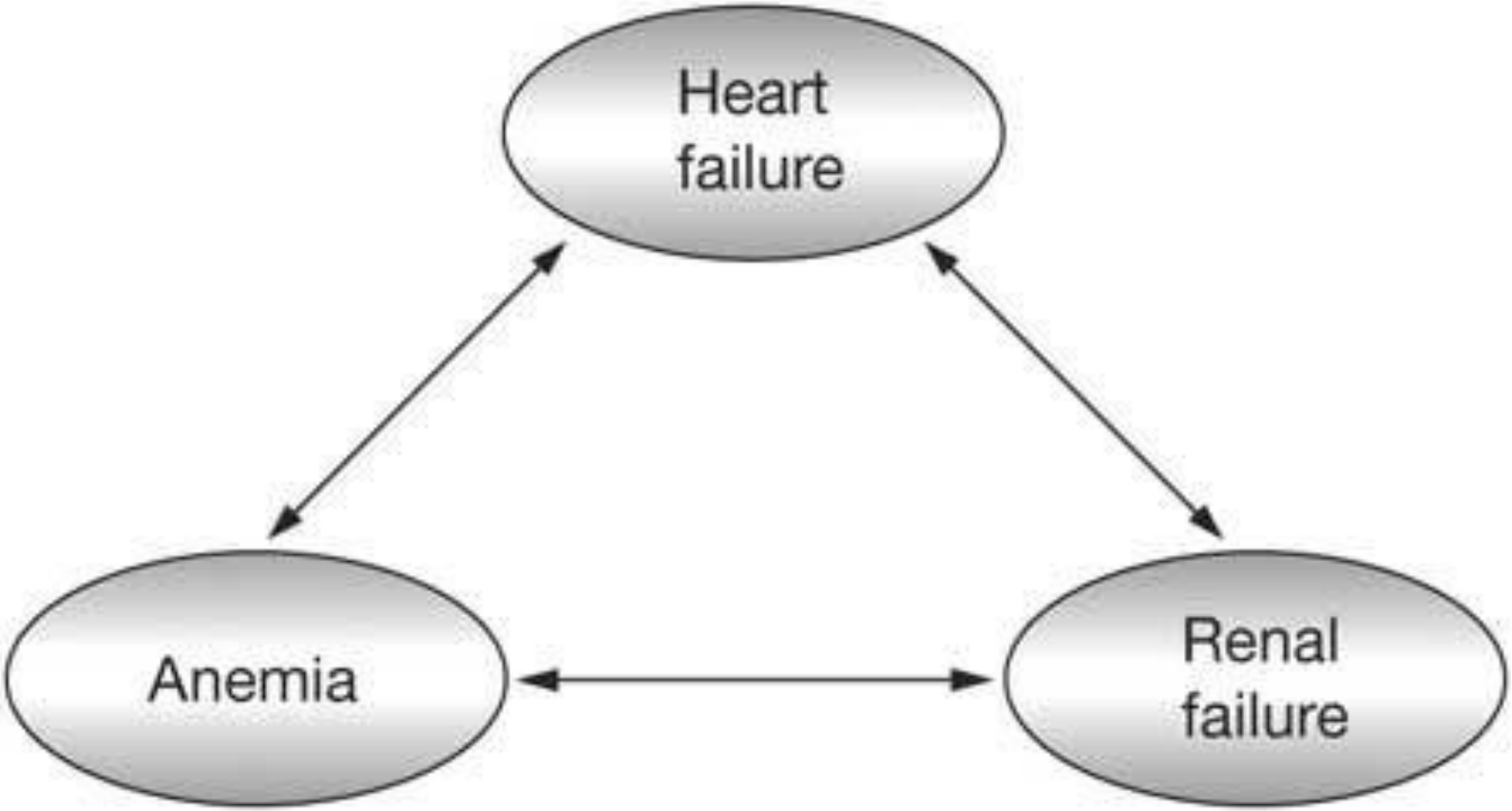
Improve

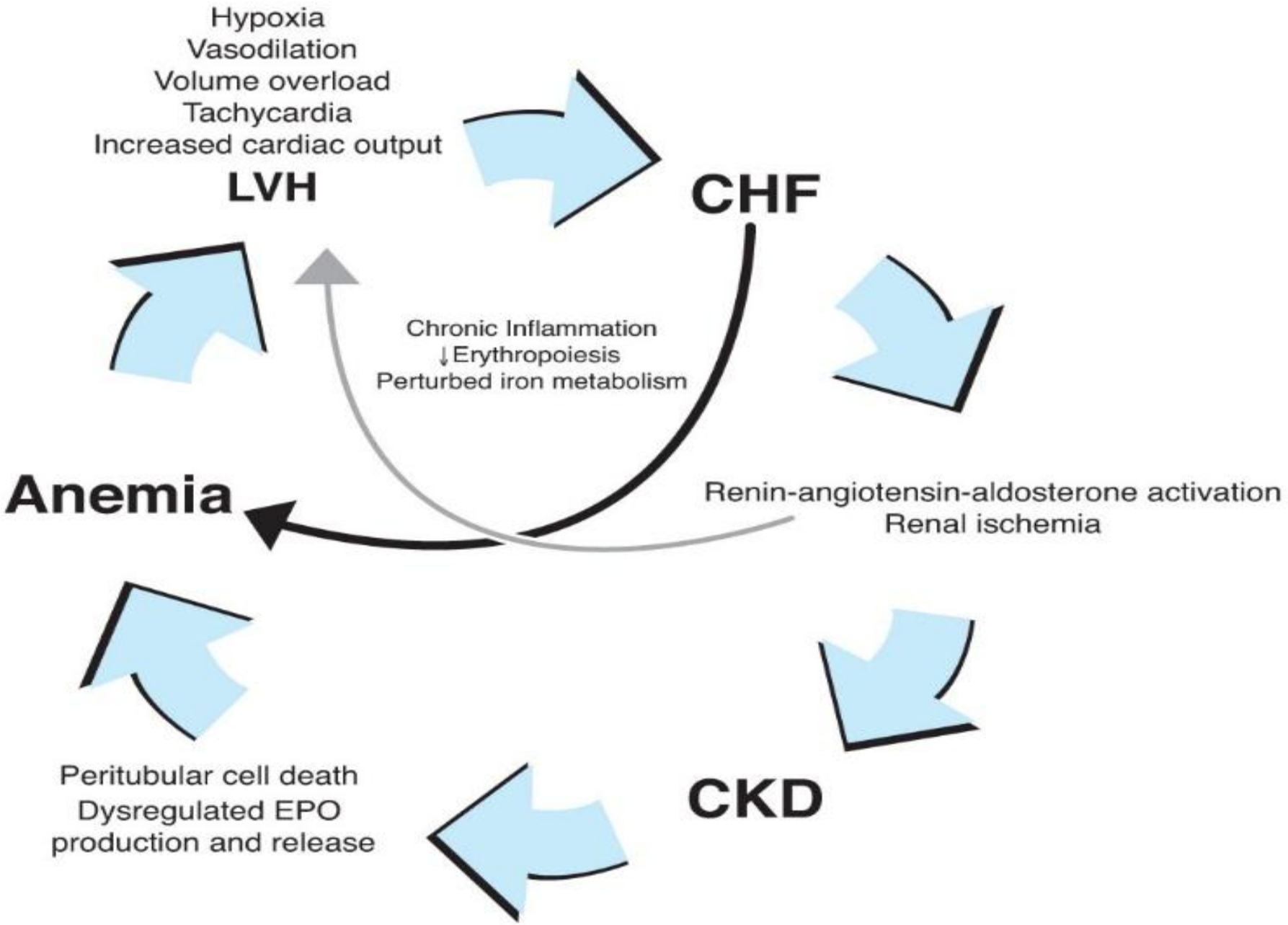
- Quality of life
- Exercise capacity
- Cognitive function
- Sleep patterns
- Sexual function
- Endocrine function
- Immune function
- Muscle function
- Nutrition
- Depression

Reduce

- Angina episodes
- LVH
- Hospitalizations
- Transfusion

Comprehensive Clinical Nephrology: Anemia in CKD: 5th Ed. (2015)


Heart failure
Anemia
Renal failure


Hypoxia
Vasodilation
Volume overload
Tachycardia
Increased cardiac output
LVH
CHF
Chronic Inflammation
↓Erythropoiesis
Perturbed iron metabolism
Anemia
Renin-angiotensin-aldosterone activation
Renal ischemia
CKD
Peritubular cell death
Dysregulated EPO
production and release

November 03, 2017

Anemia Raises ESRD Risk in Patients With Chronic Kidney Disease

Share this content:

In a study, end-stage renal disease was 31% more likely to develop in CKD patients with versus without anemia.

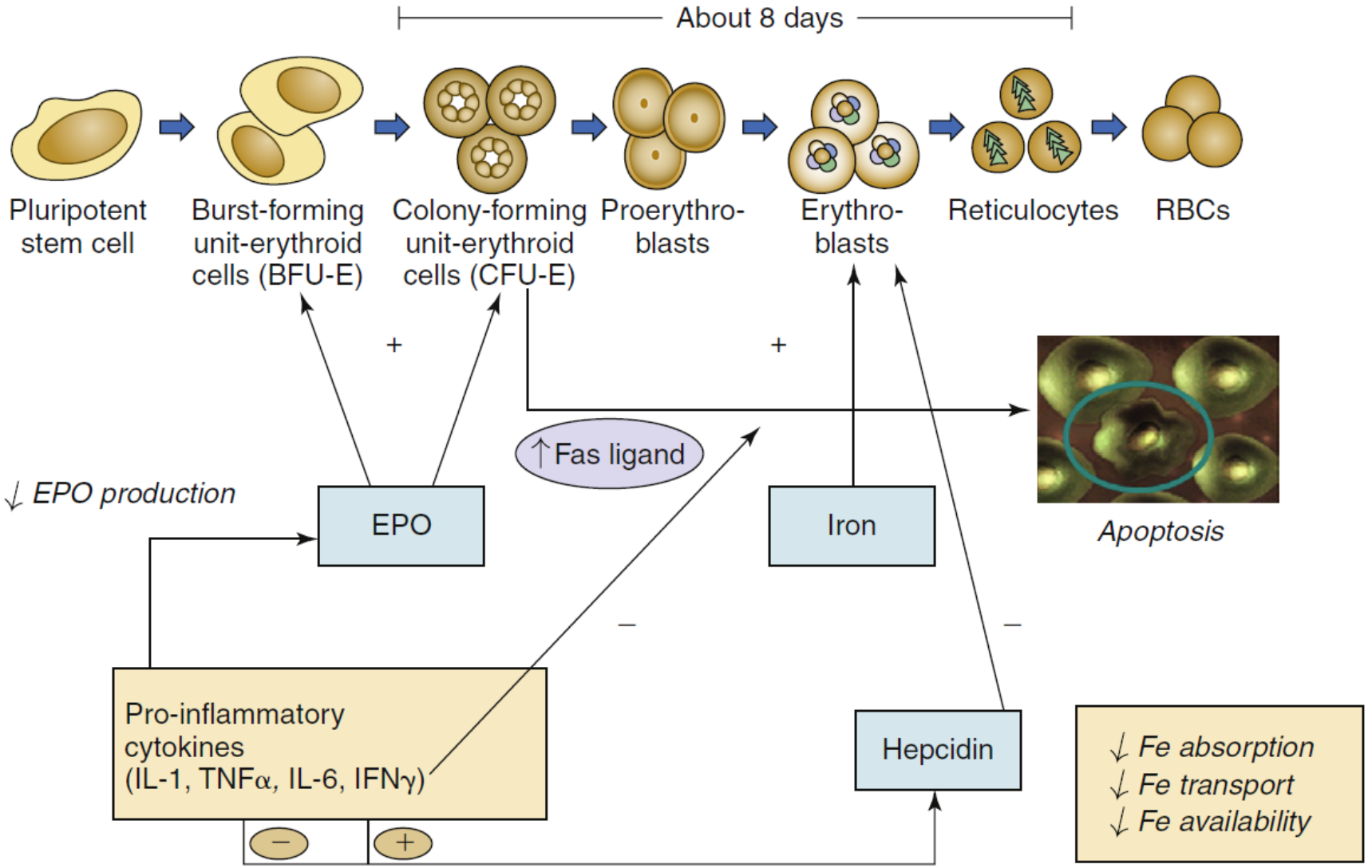
The following article is part of conference coverage from Kidney Week 2017 in New Orleans hosted by the American Society of Nephrology. *Renal & Urology News* staff will be reporting live on medical studies conducted by nephrologists and other specialists who are tops in their field in acute kidney injury, chronic kidney disease, dialysis, transplantation, and more. Check back for the latest news from Kidney Week 2017.

Evaluation of Anemia in CKD

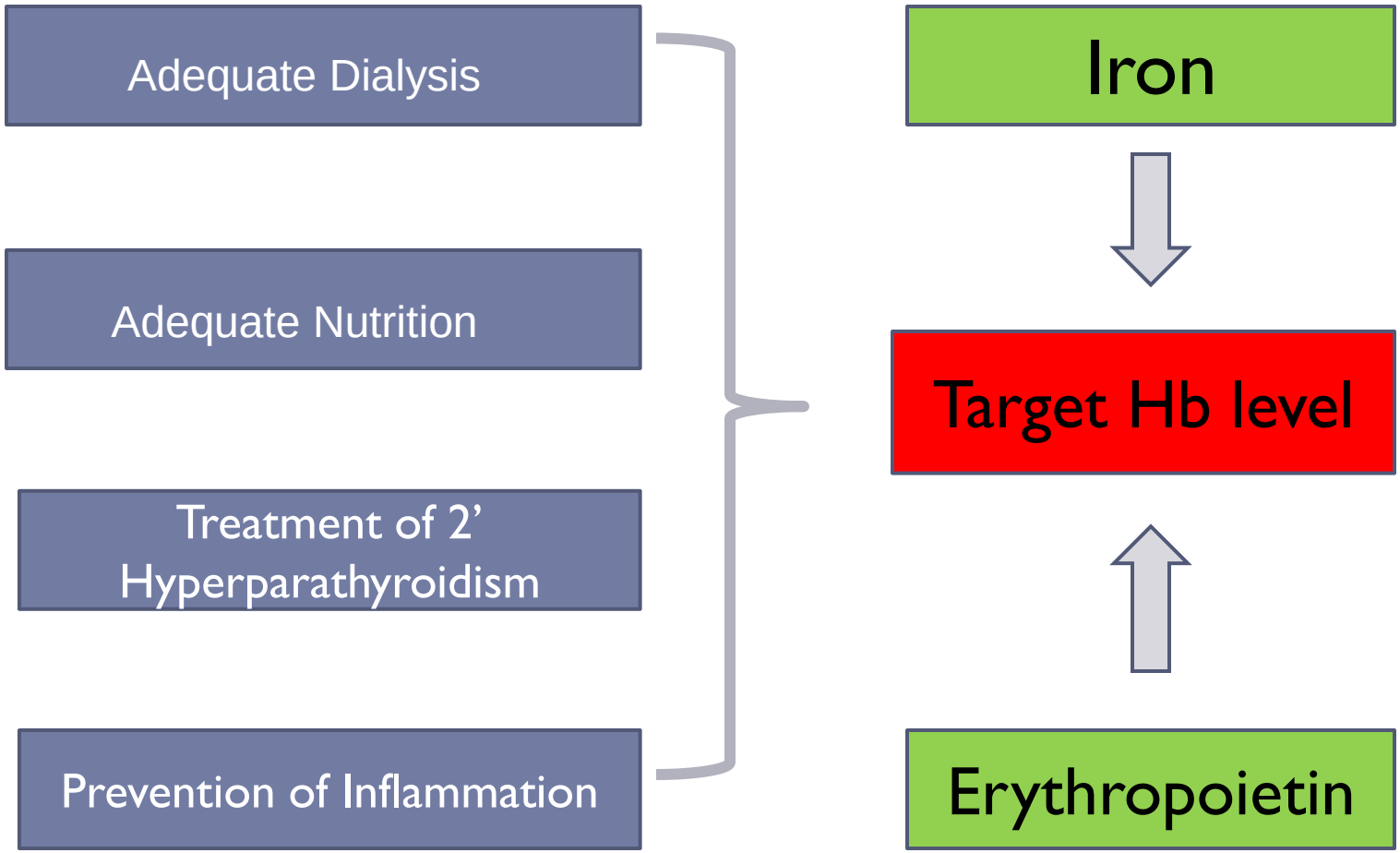
- Focused history and physical examination
- Blood testing
  - Complete blood cell count (including red blood cell indexes)
  - Reticulocyte count
  - Serum ferritin
  - Transferrin saturation
  - Folic acid
  - Vitamin B_{12}

Update on Anemia in ESRD and Earlier Stages of CKD: Core Curriculum 2018, AJKD

Erythropoiesis in chronic kidney disease



Treatment of Renal Anemia



Iron Therapy

Causes of Iron Deficieny in CKD

Absolute iron deficiency

- Low body iron stores – low serum ferritin
- **Reduced intake** - Poor appetite, Dietary restrictions
- **Increased iron loss** - GI bleeding, Multiple blood tests, Hemodialysis (may lose upto 2g/year through blood left in dialyser circuit)

Causes of Iron Deficiency in CKD

Absolute iron deficiency	Functional iron deficiency
• Low body iron stores – low serum ferritin • **Reduced intake** - Poor appetite, Dietary restrictions • **Increased iron loss** - GI bleeding, Multiple blood tests, Hemodialysis (may lose upto 2g/year through blood left in dialyser circuit)	• Common when ESA driven supraphysiological rate of erythropoiesis has outpaced the delivery of iron by transferrin • Normal or raised serum ferritin, low TSAT

Causes of Iron Deficiency in CKD

Absolute iron deficiency	Functional iron deficiency	Reticuloendothelial ('inflammatory') block
• Low body iron stores – low serum ferritin • **Reduced intake** - Poor appetite, Dietary restrictions • **Increased iron loss** - GI bleeding, Multiple blood tests, Hemodialysis (may lose upto 2g/year through blood left in dialyser circuit)	• Common when ESA driven supraphysiological rate of erythropoiesis has outpaced the delivery of iron by transferrin • Normal or raised serum ferritin, low TSAT	• Occurs with infection or inflammation • Iron is trapped in RE system & not released to transferrin for Hb synthesis • High CRP, raised ferritin, low TSAT

Iron therapy in CKD

Organization	Indication to iron therapy	Upper limits
KDIGO,[7] 2012	ESA-naïve and ESA therapy • Serum ferritin <500 ng/mL • TSAT <30%	Serum ferritin 500 ng/mL TSAT 30%

ERBP,[8] 2013	ESA-naïve
	• CKD-ND
	  • Serum ferritin <200 ng/mL
	  • TSAT <25%
	• CKD-5D
	  • Serum ferritin <300 ng/mL
	  • TSAT <25%
	ESA therapy
	• CKD all stages
	  • Serum ferritin <300 ng/mL
	  • TSAT < 30%
		Serum ferritin 500 ng/mL
		TSAT 30%
		Serum ferritin 500 ng/mL
		TSAT 30%

KDOQI,[13] 2013	• CKD all stages
	  • Serum ferritin <500 ng/mL
	  • TSAT <30%
		None (if high ferritin, weigh potential risks and benefits of persistent anaemia, ESA dosage, comorbid conditions, and health-related quality of life)

Canadian Guidelines,[14] 2013	• CKD all stages
	  • Serum ferritin <500 ng/mL
	  • TSAT <30%
		None

NICE,[11] 2015	• CKD all stages
	  • Serum Ferritin <200 ng/mL
	  • TSAT <20% (unless ferritin >800 ng/mL)
	  • %HRC less than 6% (unless ferritin
		Serum ferritin 500–800 ng/mL

CARI,[9] 2013	• Serum Ferritin <200 ng/mL • TSAT <20%	Serum Ferritin 1200 ng/mL TSAT 30%

Clinical practice guidelines on iron therapy: A critical evaluation: Hemodialysis International 2017; 21:S125–S131

Iron therapy in CKD

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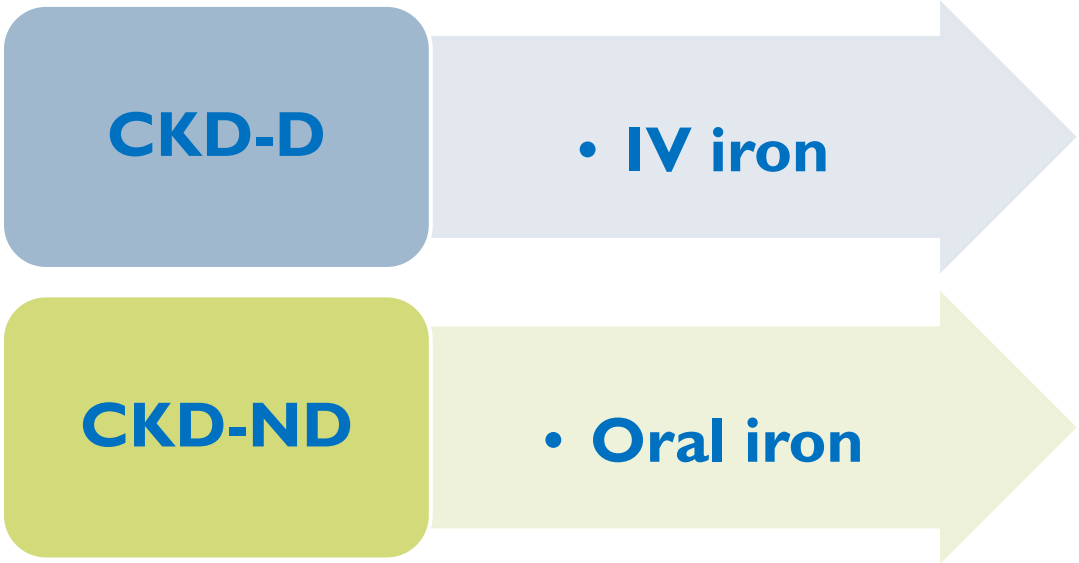
CARI,[9] 2013	• Serum Ferritin <200 ng/mL • TSAT <20%	Serum Ferritin 1200 ng/mL TSAT 30%

Use of iron to treat anemia in CKD

- suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy)



Route of iron administration in CKD ND

Based on

- severity of iron deficiency
- availability of venous access
- response to prior oral iron therapy
- side effects with prior oral or IV iron therapy
- patient compliance
- cost

Subsequent iron administration in CKD

Based on

- Hb responses to recent iron therapy
- Ongoing blood losses
- Iron status tests (TSAT & ferritin)
- Hb concentration
- ESA responsiveness & ESA dose in ESA treated patients, trends in each parameter
- Patient's clinical status

Iron Status (TSAT, Ferritin) Evaluation

Ferritin

- Cellular storage protein
- Marker of **storage iron**
- **Acute phase protein**
- Raised in inflammation & liver disease

TSAT (Tranferrin saturation)

- TSAT = (serum iron/TIBC) x 100
- Measure of **available iron**

Iron Status (TSAT, Ferritin) Evaluation

- **at least every 3 months** d/r ESA therapy, including the decision to start or continue iron therapy

- **more frequently**
  - when initiating or increasing ESA dose
  - when there is blood loss
  - when monitoring response after a course of IV iron
  - in other circumstances where iron stores may become depleted.

Markers of Iron Status in Chronic Kidney Disease Patients

Test	Recommended Range
Serum ferritin	100-500 µg/l (CKD) 200-500 µg/l (HD)
Transferrin saturation	20%-40%
Hypochromic red cells	<10%
Reticulocyte hemoglobin content (CHr)	>29 pg/cell
Serum transferrin receptor	Not established
Erythrocyte zinc protoporphyrin	Not established

Comprehensive Clinical Nephrology: Anemia in CKD: 5th Ed. (2015)

Cautions Regarding Iron Therapy

Initial dose

(IV iron dextran) - recommend

(IV non dextran iron) – suggest

patients - **monitored for 60 minutes after infusion**

resuscitative facilities (including medications) & **personnel** trained to evaluate & treat serious adverse reactions - available

Cautions Regarding Iron Therapy

Initial dose

(IV iron dextran) - recommend

(IV non dextran iron) – suggest

patients - **monitored for 60 minutes after infusion**

resuscitative facilities (including medications) & **personnel** trained to evaluate & treat serious adverse reactions - available

Avoid administering IV iron to patients with active systemic infections

IV Iron Toxicities

Immediate severe "anaphylactoid" reactions

Primarily with iron dextran

- Not IgE mediated
- May be direct release of mediators from mast cells

Other acute reactions — occur with all IV irons, some dose and rate of infusion related

- Arthralgias-myalgias
- Anaphylactoid reactions
- Hypotension
- Nausea, vomiting
- Urticaria
- Bronchospasm
- Chest, back, abdominal pain
- Death

Balancing Benefits and Risks of IV Iron Treatment

Risks

1. Anaphylaxis
2. Other risk have not been adequately addressed & excluded by published trials

Benefits

1. Reduced ESA dose
2. Correction of severe iron deficiency
3. Other benefits not well established

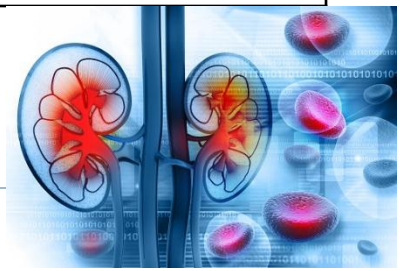
IV Iron Preparation

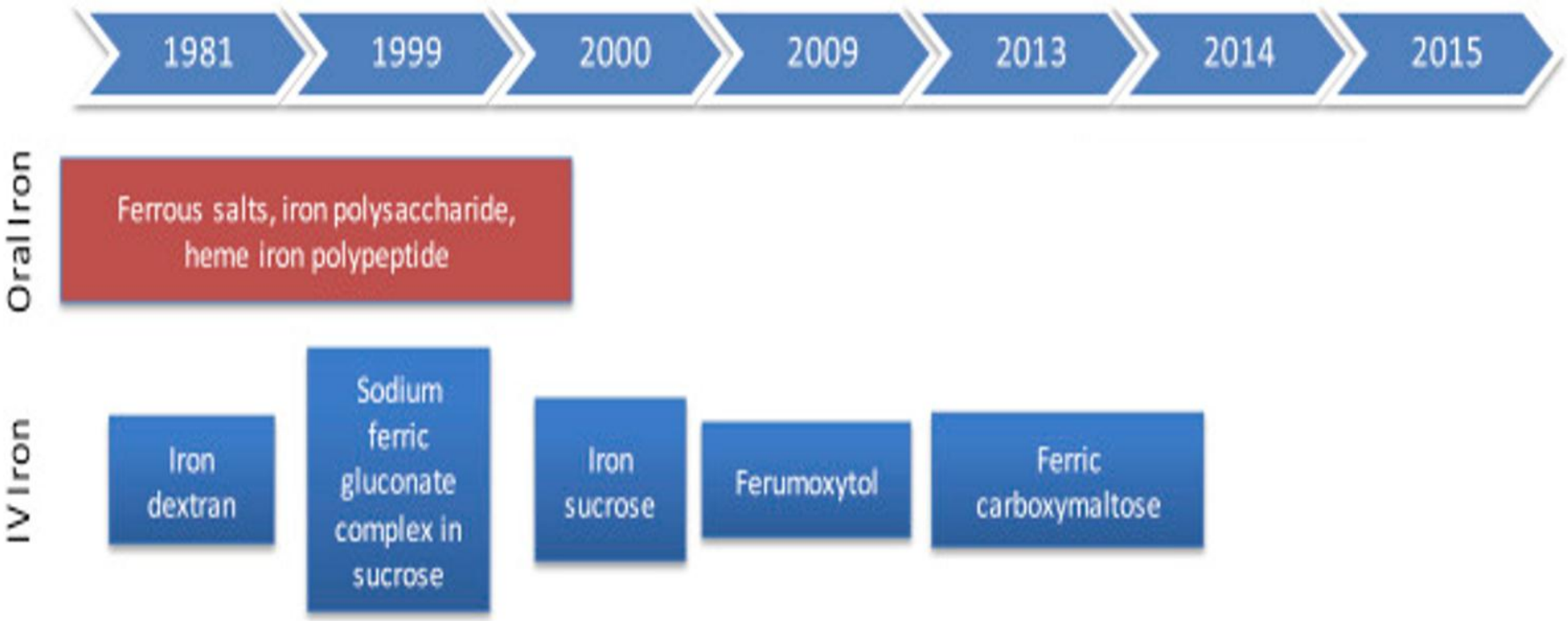
	Sodium ferric gluconate	Iron sucrose	Ferric carboxymaltose	Low molecular weight iron dextran	Iron isomaltoside 1000	Ferumoxytol
Trade name(s)	Ferrlecit[a]	Venofer[b]	Injectafer, Ferinject[c]	Cosmofer[d]	Monofer[e]	Feraheme[f]
Formulation	12.5 mg/mL in 5 mL single-use vial	20 mg/mL in 2.5 and 5 mL single-use vials and ampoules	50 mg/mL in 2, 10 and 20 mL single-use vials	50 mg/mL in 2, 5, and 10 mL single-use ampoules	100 mg/mL in 1, 2, 5, and 10 mL single-use vials/ ampoules	30 mg/mL in 17 mL as 510 mg single-use vial
Maximum single dosage [59, 60]	125 mg	200 mg	1000 mg (up to 200 mg in CKD-HD patients)	20 mg/kg	20 mg/kg	510 mg
Minimal administration time [59, 60]	10–60 min	10–30 min	15 min	4–6 h	15–30 min	15 min
Test dose required	No	No	No	Yes	No	No
FDA black box warning	No	No	No	Yes	NA (available in Europe only)	Yes

Oral iron supplements

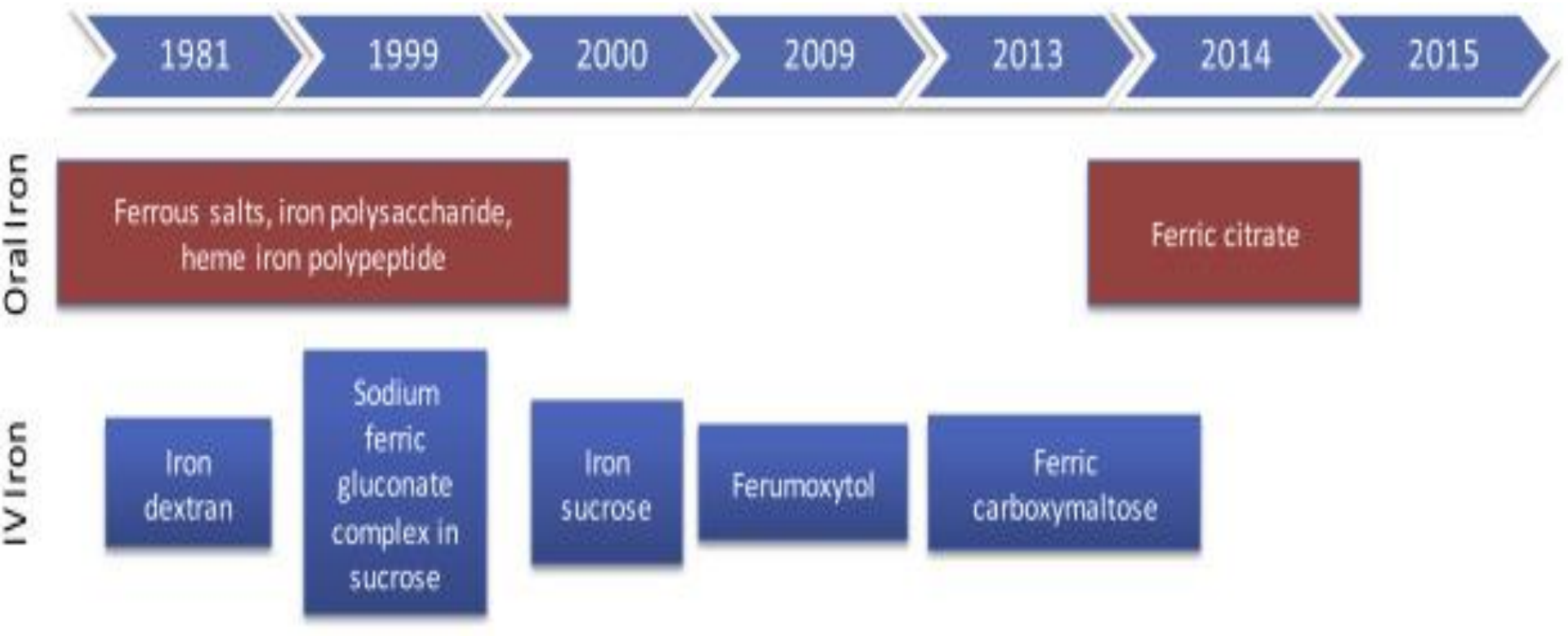
200 mg elemental iron / day

Compound	Dose	Content of ferrous iron
Ferrous Sulphate	200mg	60 mg
Ferrous Gluconate	300mg	35 mg
Ferrous Fumarate	200mg	65 mg
Colloidal Ferric hydroxide	200mg	100 mg




1981
1999
2000
2009
2013
2014
2015
Oral Iron
Ferrous salts, iron polysaccharide, heme iron polypeptide
IV Iron
Iron dextran
Sodium ferric gluconate complex in sucrose
Iron sucrose
Ferumoxytol
Ferric carboxymaltose

New option for Iron supplementation



Ferric citrate

- novel phosphate binder
- also supplies elemental iron
- orally
- potentially adherence enhancing strategy

- Ferric ion in ferric citrate combines with dietary phosphorus in GI tract
- excess ferric ions are reduced by bowel mucosa to ferrous iron and absorbed into systemic circulation

Anemia in chronic kidney disease: Pediatr Nephrol: published online 15 April 2017

Nephrol Dial Transplant (2016) 31: 1588–1594
doi: 10.1093/ndt/gfv268
Advance Access publication 3 July 2015

ndt
Nephrology Dialysis Transplantation

Full Reviews

Novel iron-containing phosphate binders and anemia treatment in CKD: oral iron intake revisited

Takeshi Nakanishi, Yukiko Hasuike, Masayoshi Nanami, Mana Yahiro and Takahiro Kuragano

Department of Internal Medicine, Division of Kidney and Dialysis, Hyogo College of Medicine, Nishinomiya, Japan

Correspondence and offprint requests to: Takeshi Nakanishi; E-mail address; t-nkns@hyo-med.ac.jp

Iron-based Binder Improves Phosphorus Levels in Dialysis Patients

Share this content:

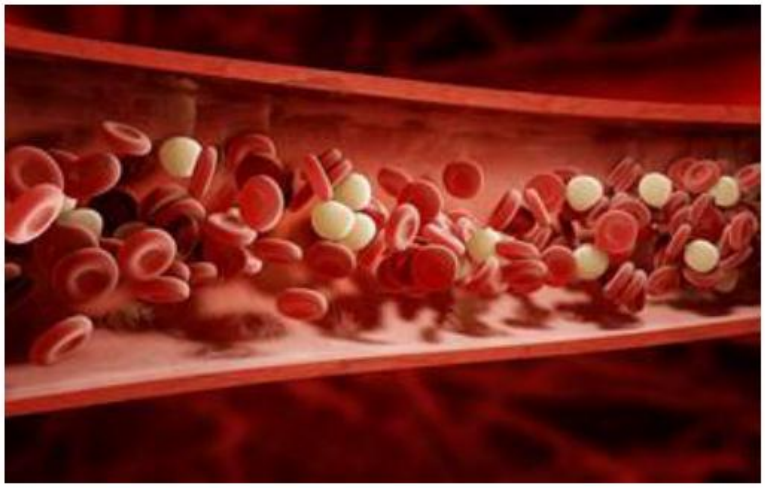
Sept 2014 - FDA approved - Phosphate binder in CKD-D

and anemia biomarker levels improved in a small group of real-world patients taking ferric citrate.

Natasha Persaud, Digital Content Editor

April 22, 2017

Ferric Citrate Modestly Improves Anemia, Study Confirms



Significantly more patients treated with ferric citrate increased their hemoglobin levels by 1 g/dL or more over 8 weeks.

ORLANDO, Fla. — The phosphate binder ferric citrate can partially raise hemoglobin levels in patients with non-dialysis dependent chronic kidney disease (NDD-CKD) and iron deficiency anemia, investigators confirmed at the National Kidney Foundation Spring Clinical Meetings.

November 08, 2017

NEWS IN BRIEF

Ferric Citrate Approved for Anemia in CKD Patients

Share this content:

Study results show that the phosphate binder was superior to placebo in raising hemoglobin levels in non-dialysis-dependent CKD patients with iron-deficiency anemia.

Nov 2017 - FDA approved — additional indication: IDA in CKD-ND

A new way of administering iron to HD patients?

Kidney International, Vol. 55 (1999), pp. 1891–1898

Dialysate iron therapy: Infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis

AJAY GUPTA, NEETA B. AMIN, ANATOLE BESARAB, SUSAN E. VOGEL, GEORGE W. DIVINE, JERRY YEE, and J. V. ANANDAN

Division of Nephrology, Department of Pharmacy Services, and Department of Bio... Detroit, Michigan, USA

Dialysate iron therapy: Infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis.

Background. Soluble iron salts are toxic for parenteral administration because free iron catalyzes free radical generation. Pyrophosphate strongly complexes iron and enhances iron transport between transferrin, ferritin, and tissues. Hemodialysis patients need iron to replenish ongoing losses. We evaluated the short-term safety and efficacy of infusing soluble ferric pyrophosphate by dialysate.

Methods. Maintenance hemodialysis patients receiving erythropoietin were stabilized on regular doses of intravenous

with prematuri... defects in cogn... ing childhood, ... [3–8]. Oral iro... primarily becau... trointestinal ad... ternative to th... parenterally fo... compounds are...

Hemodialysis International 2017; **21**:S104–S109

Scholarly Review

Ferric pyrophosphate citrate as an iron replacement agent for patients receiving hemodialysis

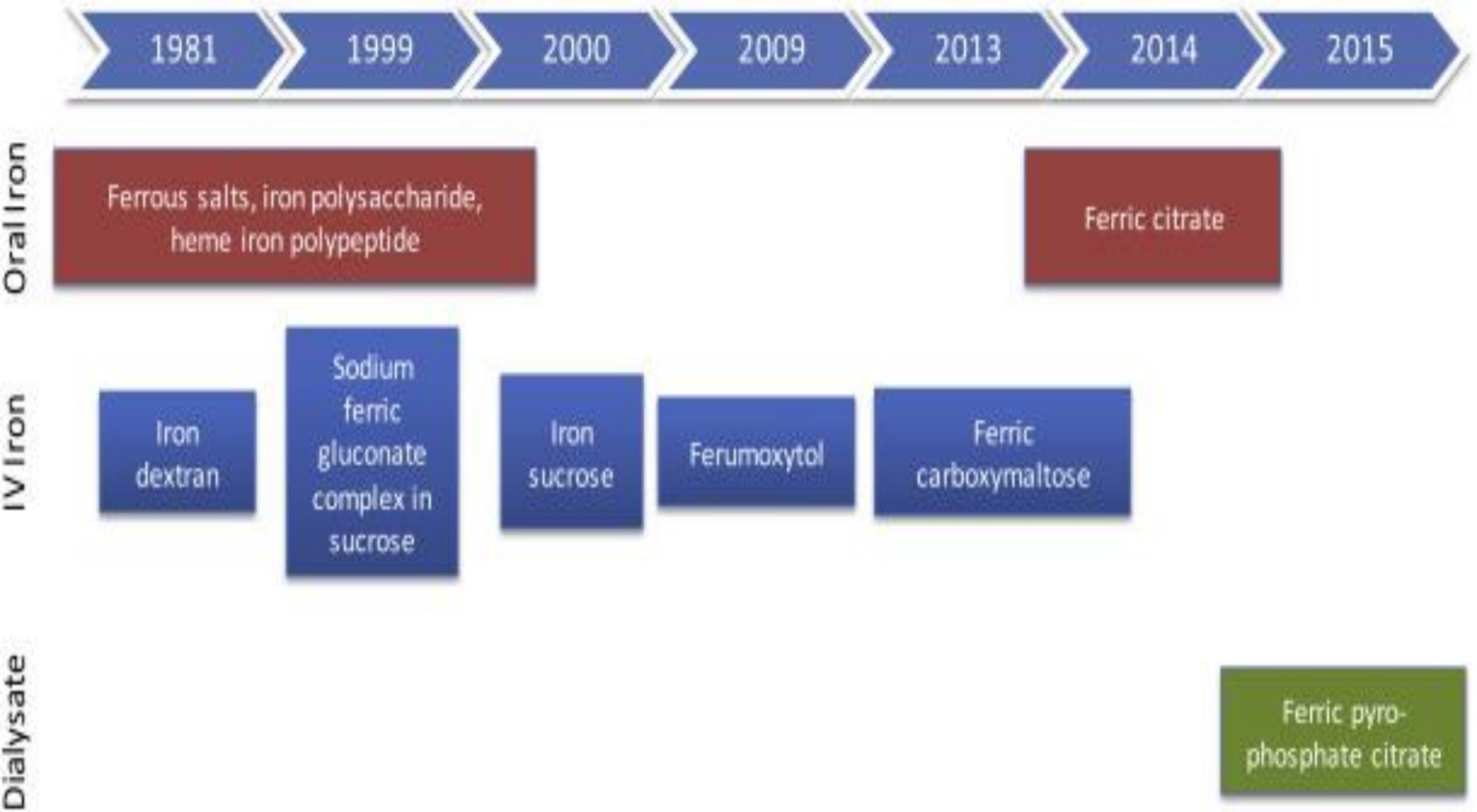
Steven FISHBANE, Hitesh H. SHAH

Division of Kidney Diseases and Hypertension, Department of Medicine, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra Northwell School of Medicine, Great Neck, New York, USA

Abstract

Treatment of anemia remains an integral component in the care of patients with end stage kidney disease receiving dialysis. Currently, both erythropoiesis stimulating agents and iron replacement agents remain important anemia management strategies for patients undergoing hemodialysis (HD). Ferric pyrophosphate citrate (FPC) was approved by the U.S. Food and Drug Administration in January 2015 as an iron replacement product in adult patients receiving long-term maintenance HD. FPC is administered to patients on HD through the dialysate. Multicenter randomized, placebo-controlled phase three clinical studies (CRUISE 1 and 2) have found dialysate FPC to maintain hemoglobin level and iron balance in patients receiving chronic HD. Adverse events were similar in both the dialysate FPC-treated and placebo groups. Another study showed a significant reduction in the prescribed erythropoietin-stimulating agents dose at the end of treatment in the dialysate FPC-treated group compared with placebo. These studies have shown that dialysate FPC is efficacious and well tolerated. In this article, we review clinical studies evaluating the efficacy and safety of FPC and also propose a protocol for iron replacement in HD units where dialysate FPC is to be used.

New option for Iron supplementation



Ferric pyrophosphate citrate

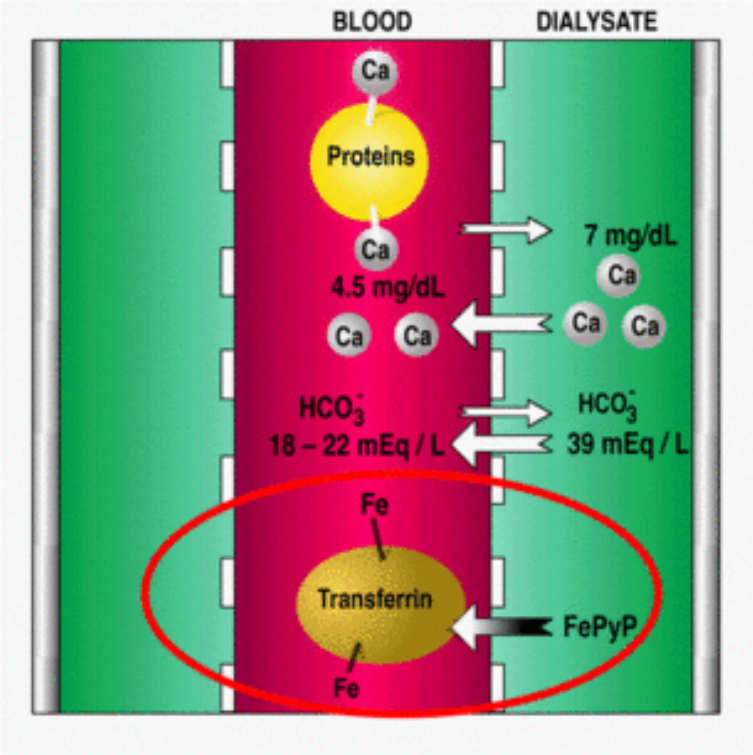
- novel, carbohydrate free, water-soluble, complex iron salt
- administered **via the dialysate**
- **approved by FDA in 2015**
- good efficacy and safety in adults on hemodialysis
- provides smaller amounts of iron over hours compared with supplementation IV, which may help avoid oxidative toxicity

Anemia in chronic kidney disease: Pediatr Nephrol: published online 15 April 2017

SFP Iron Delivered via Dialysate

- Iron-citrate-pyrophosphate complex: soluble, non-colloidal salt that is not conjugated with a sugar moiety.
- SFP is infused into the blood via dialysate over the course of the dialysis treatment
- SFP crosses the dialyzer membrane just like calcium and bicarbonate, entering the blood
- **SFP iron simply replaces the 5-7mg of iron that is lost during the dialysis treatment**
- SFP is the only iron in the world that can be delivered via dialysate

Inside Dialyzer Filter



ROCKWELL MEDICAL

Red Cell Transfusion

Red cell transfusion to treat anemia in CKD

Recommend - **avoiding, when possible**, red cell transfusions to minimize the general risks related to their use

In patients eligible for organ transplantation, we specifically recommend avoiding, when possible, red cell transfusions to **minimize the risk of allosensitization**

Table 5 | Estimated risk associated with blood transfusions per unit transfused

Adverse event	Estimated risk*
Immunological	
Fever/allergic reactions	1 in 100–200[a,b]
Hemolytic reaction	1 in 6000[b]
Transfusion-related acute lung injury (TRALI)	1 in 12,350[a]
Anaphylaxis	1 in 50,000[b]
Fatal hemolysis	1 in 1,250,000[a]
Graft versus host disease (GVHD)	Rare
Other	
Mistransfusion	1 in 14,000–19,000[c]

*United States data.
[a]Data from Carson JL *et al.*[212]
[b]Data from Klein.[213]
[c]Data from Klein HG *et al.*[214]

Table 6 | Estimated risk of transfusion-related infections per unit transfused

Potential transfusion-related risks	Estimated risk*
Hepatitis B	1 in 282,000–1 in 357,000[a]
West Nile virus	1 in 350,000[b]
Death from bacterial sepsis	1 in 1,000,000[b]
Hepatitis C	1 in 1,149,000[a]
Human immunodeficiency virus (HIV)	1 in 1,467,000[a]

*United States data.
[a]Data from Carson JL *et al.*[212]
[b]Data from Rawn J.[215]

suggest - benefits of red cell transfusions > risks in patients in whom :

- **ESA therapy - ineffective** (e.g., hemoglobinopathies, bone marrow failure, ESA resistance)
- **ESA risks > benefits** (e.g., previous or current malignancy, previous stroke)

We suggest that the decision to transfuse a CKD patient with non-acute anemia should not be based on any arbitrary Hb threshold, but should be determined by the occurrence of symptoms caused by anemia.

URGENT TREATMENT OF ANEMIA

Certain acute clinical situations

Suggest – transfusion (benefits > risks)

- **rapid correction of anemia is required to stabilize the patient's condition** (e.g., acute hemorrhage, unstable coronary artery disease)
- **rapid preoperative Hb correction is required**

Adjuvant Therapies

Adjuvant Therapies

Several agents have been investigated for a role in increasing efficacy of ESA's, allowing reduced doses:

- **L-carnitine**
- **Ascorbic acid**
- **Vitamin E**
- **Androgens**
- **Pentoxyfilline**

- Effects on [Hb] = inconsistent
- None have been shown to improve clinical outcomes
- **Use as ESA adjuvants = not recommended**

Adjuvant Therapies

- We recommend **not using androgens** as an adjuvant to ESA treatment.

- We suggest **not using adjuvants to ESA treatment including vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline**.

Androgen

Research Article

Meta-Analysis of Randomized Controlled Trials on Androgens versus Erythropoietin for Anaemia of Chronic Kidney Disease: Implications for Developing Countries

B. Adamu,[1] S. M. Ma'aji,[2] P. J. Erwin,[3] and I. M. Tleyjeh[4]

[1] *Nephrology Unit, Department of Medicine, Bayero University, Kano, PMB 3452, Nigeria*
[2] *Usmanu Danfodiyo University, Sokoto, PMB 2346, Nigeria*
[3] *Mayo Clinic College of Medicine, Rochester, MN 55905, USA*
[4] *King Fahad Medical City, Riyadh 11525, Saudi Arabia*

Correspondence should be addressed to B. Adamu, bappakano@yahoo.com

Received 25 February 2012; Revised 28 August 2012; Accepted 2 September 2012

Academic Editor: Li-Li Hsiao

Androgens which are relatively cheap were used in the treatment of anaemia in dialysis patients before the advent of Erythropoietin (EPO). However, there are concerns about their efficacy and side effects. *Aims*. To examine the efficacy and harms of androgens for the treatment of anaemia of chronic kidney disease (CKD) compared to EPO. *Settings and Design*. A systematic review and meta-analysis using an a priori protocol. *Methods and Materials*. We searched several databases for randomized controlled trials using the key terms anaemia, chronic kidney disease, and androgens, without language restrictions. We also searched reference lists of relevant articles. *Statistical Analysis Used*. Data was analyzed using Review manger 5 software. We summarized treatment effects as relative risks and mean differences, with 95% confidence intervals using a random-effect model. We tested for heterogeneity with Chi^2 and the I^2 statistics. *Results*. We identified four eligible trials involving 114 participants, majority (83.33%) of whom were males, mostly over 50 years of age. The pooled difference in mean haemoglobin between the nandrolone and EPO arms at the end of the trials was −0.11 (CI −0.80 to 0.58) which is not statistically significant. *Conclusions*. This meta-analysis revealed no difference between nandrolone and EPO for the treatment of anaemia of CKD in men over 50 years. Therefore, nandrolone can be used for the treatment of anaemia of CKD in this category of patients, in resource-limited countries. However, further studies are needed to determine the long-term safety of nandrolone in men over 50 years old, as well as its effectiveness and safety in females in general, and males less than 50 years of age.

Cochrane Library

Cochrane Database of Systematic Reviews

Androgens for the anaemia of chronic kidney disease in adults (Review)

Yang Q, Abudou M, Xie XS, Wu T

We found limited evidence to suggest that androgens may confer positive effects to increase Hb, HCT and serum albumin.

We were unable to determine if:

1. dose-effect relationships exist in relation to androgens and CKD-related anaemia in adults;
2. time-effect relationships exist in relation to androgens and CKD-related anaemia in adults;
3. androgens-erythropoietin relationships exist in relation to androgens and CKD-related anaemia in adults.

Androgen – Side Effects

- Acne
- Virilization
- Priapism
- Liver dysfunction
- Injection site pain
- Risk for peliosis hepatis
- Hepatocellular carcinoma

Vitamin - C

Kidney Research and Clinical Practice

journal homepage: http://www.krcp-ksn.com
Contents lists available at ScienceDirect

Original Article

The effect of intravenous ascorbic acid in hemodialysis patients with normoferritinemic ar

Dae Woong Kang, Chi Yong
Hyun Lee Kim*

Division of Nephrology, Department of Interna

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Effectiveness of Vitamin C in the Treatment of Anemia in Patients with Chronic Diseases: A Case Study

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Rec date: Dec 02, 2016; **Acc date:** Dec 19, 2016; **Pub date:** Dec 23, 2016

Research Article

Intravenous vitamin C can improve anemia in erythropoietin-hyporesponsive hemodialysis patients

Vit-C
enhances absorption of dietary iron,
contributes to mobilization of intracellular stored iron, and increases carnitine synthesis.

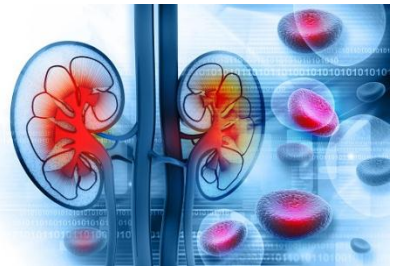
Caution should also be used, as **excessive vitamin C** ingestion can be associated with **renal oxalate deposition** and acute kidney injury

hyporesponsiveness in hemodialysis patients with hyperferritinemia of no obvious etiology.

sion of 1 participant because of bleeding). After 6 months, there were considerable increases

Determination of the **lowest effective dosages** and careful **monitoring of iron indices and plasma oxalate levels** are necessary, both to ensure the efficacy of high dose vitamin C, and to prevent any adverse effects of this treatment.

Vitamin - D



Evaluation of Effect of Vitamin D Deficiency on Anemia and Erythropoietin Hyporesponsiveness in Patients of Chronic Kidney Disease

N Nand[1], R Mittal[2]

Abstract

Background: The role of vitamin D deficien
in renal anemia has been documented. Hov
in India where the role of vitamin D supple
hyporesponsiveness to increased doses of
Hence this study.

Material and Methods: This study was conc
of CKD, on regular, twice weekly hemodialy
group A with deficient serum vitamin D leve
in group B with sufficient vitamin D levels (
cases were receiving erythropoietin in a dose

The effects of changing vitamin D levels on anemia in chronic kidney disease patients: A retrospective cohort review

Article *in* Clinical nephrology · July 2010

DOI: 10.5414/CNP74025 · Source: PubMed

Potential role of nutritional vitamin D supplementation in reducing hepcidin production is under active investigation, and ***vitamin D decreases hepcidin mRNA expression in vitro***

Suppression of Iron-Regulatory Hepcidin by Vitamin D

Justine Bacchetta,*†‡ Joshua J. Zaritsky,† Jessica L. Sea,* Rene F. Chun,* Thomas S. Lisse,* Kathryn Zavala,* Anjali Nayak,† Katherine Wesseling-Perry,† Mark Westerman,§ Bruce W. Hollis,‖ Isidro B. Salusky,† and Martin Hewison*

*Department of Orthopaedic Surgery, UCLA Orthopaedic Hospital, and †Department of Pediatrics, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California; ‡Centre de Référence des Maladies Rénales Rares, Institut de Génomique Fonctionnelle à l'Ecole Normale Supérieure de Lyon et Université de Lyon, Lyon, France; §Intrinsic Life Sciences, La Jolla, California; and ‖Departments of Pediatrics, Biochemistry, and Molecular Biology, Medical University of South Carolina, Charleston, South Carolina

ABSTRACT

The antibacterial protein hepcidin regulates the absorption, tissue distribution, and extracellular concentration of iron by suppressing ferroportin-mediated export of cellular iron. In CKD, elevated hepcidin and vitamin D deficiency are associated with anemia. Therefore, we explored a possible role for vitamin D in iron homeostasis. Treatment of cultured hepatocytes or monocytes with prohormone 25-hydroxyvitamin D or active 1,25-dihydroxyvitamin D decreased expression of hepcidin mRNA by 0.5-fold, contrasting the stimulatory effect of

Vitamin - E

REVIEW

DOES VITAMIN E HAVE A ROLE IN TREATMENT AND PREVENTION OF ANEMIA'S?

ABSTRACT

Vitamin E is a hi
and non-antioxida
acids in red blooc
shown that treat
precursors, enhan
trials have indica
decreasing the pre
the post-suppleme
low birth weight p
renal failure patie

RENAL FAILURE

http://informahealthcare.com/rnf
ISSN: 0886-022X (print), 1525-6049 (electronic)

Ren Fail, 2014; 36(5): 722–731

DOI: 10.3109/0886022X.2014.890858

informa healthcare

CLINICAL STUDY

Effects of vitamin E-coat
inflammation status in h
and meta-analysis

Shi-Kun Yang*, Li Xiao*, Bo Xu, Xiao-X

Department of Nephrology, The Second Xiangya

Abstract

Background: Vitamin E-coated dialyzer may have
status in hemodialysis (HD) patients. Therefore, w
anti-oxidation and anti-inflammatory effects o
Methods: The randomized controlled trials (RCTs
versus conventional dialyzer for HD patient
We screened relevant studies according to
meta-analyses using RevMan 5.1 software. *Res*
dialyzer therapy could significantly decrease the

Blood Purification

Blood Purif 2017;44:288–293
DOI: 10.1159/000478971

Vitamin E-Coated Dialyzer Inhibits Oxidative Stress

Shiho Yamadera[a] Yuya Nakamura[b, c] Masahiro Inagaki[d] Isao Ohsawa[c]
Hiromichi Gotoh[c] Yoshikazu Goto[c] Naoki Sato[b] Tatsunori Oguchi[b]
Yurika Gomi[b] Mayumi Tsuji[b] Yuji Kiuchi[b] Shinichi Iwai[a]

[a]Department of Healthcare and Regulatory Sciences, School of Pharmaceutics, Showa University, Shinagawa-ku, and [b]Department of Pharmacology, School of Medicine, Showa University, Shinagawa-ku, Tokyo, [c]Saiyu Soka Hospital, Soka City, Saitama-ken, and [d]Department of Chemistry, College of Arts and Sciences, Showa University, Fujiyoshida City, Yamanashi-ken, Japan

Blood Purification

Blood Purif 2017;43:338–345
DOI: 10.1159/000453442

Received: September 6, 2016
Accepted: November 15, 2016
Published online: March 2, 2017

Evaluation of the Impact of a New Synthetic Vitamin E-Bonded Membrane on the Hypo-Responsiveness to the Erythropoietin Therapy in Hemodialysis Patients: A Multicenter Study

Francesco Locatelli[a] Simeone Andrulli[a] Sara Maria Viganò[a] Massimo Concetti[b]
Sauro Urbini[c] Franca Giacchino[d] Roberto Broccoli[e] Filippo Aucella[f]
Maria Cossu[g] Paolo Conti[h] Laura Fattori[i] Giorgio Punzo[l] Daniela Angelini[j]
Marco Peruzzini[k] Salvatore Di Giulio[m] Marta Piroddi[n] Francesco Galli[n]

Conclusions: The ViE dialyzer can improve ESA response in HD patients. Changes in ERI during follow-up are independent from baseline ERI only in the ViE group.
Video Journal Club 'Cappuccino with Claudio Ronco' at http://www.karger.com/?doi=453442.

Carnitine

Clinical Study

Effects of Oral L-Carnitine Supplementation on Lipid Profile, Anemia, and Quality of Life in Chronic Renal Disease Patients under Hemodialysis: A Randomized, Double-Blinded, Placebo-Controlled Trial

Afsoon Ema
Asghar Ami
Hamed Bas
[1] Isfahan Kidney

L-Carnitine for Anemia in Hemodialysis Patients: A Last Resort

Jerry Yee

Some studies suggested that **L carnitine supplementation can prolong RBC lifespan and stimulate erythropoiesis by inhibiting apoptosis**

No large-scale randomized clinical trials evaluating whether supplementation is effective as an adjunctive treatment

tor in 1952 (2). It is the product of the multistep metab-olism of 6-N-trimethyllysine. Carnitine production

with regard to the beneficial effects of LC in the anemia of CKD. In CKD, erythrocyte, cellular free levels are

Pentoxifylline

originals

http://www.revistanefrologia.com

Effect of pentoxifylline on anaemia control in haemodialysis patients: retrospective observational case-control study

José M. Mora-Gutiérrez, Asunción Ferrer Nadal, Nuria García Fernández

Servicio de Nefrología. Hemodiálisis. Clínica Universic

Nefrologia 2013;33(4):524-31

doi:10.3265/Nefrologia.pre2013.Apr.11654

ABSTRACT

Introduction and objectives: Treatment of ar haemodialysis (HD) with iron and erythropoiesis-s agent (ESA) does not always lead to adequate control and has been associated with inflammatior inflammatory effect of pentoxifylline (PTX) may be in these cases. Our aim was to study the potentia PTX on anaemia in haemodialysis patients. Pat **method:** Retrospective observational case-control s patients (treated with PTX) and 18 controls (wi matched by age and sex) on HD (Clínica Unive

Pentoxifylline Improves Hemoglobin Levels in Patients with Erythropoietin-resistant Anemia in Renal Failure

ANGELA COOPER,*† ASHRAF MIKHAIL,* MARK W. LETHBRIDGE,† D. MICHAEL KEMENY,† and IAIN C. MACDOUGALL*

*Departments of *Renal Medicine and †Immunology, GKT School of Medicine, King's College Hospital, London, United Kingdom.*

Abstract. It was hypothesized that pentoxifylline might improve the response to recombinant human erythropoietin (rh-Epo) in anemic renal failure patients. Sixteen patients with ESRD and rh-Epo–resistant anemia, defined by a hemoglobin of <10.7 g/dl for 6 mo before treatment and a rh-Epo dose of ≥12,000 IU/wk, were recruited. They were treated with oral pentoxifylline 400 mg o.d. for 4 mo. *Ex vivo* T cell generation of tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) from the patients was assessed before treatment and 6 to 8 wk after therapy. A total of 12 of 16 patients completed the study. Before therapy, the 12 patients' mean hemoglobin concentration was 9.5 ± 0.9 g/dl. After 4 mo of pentoxifylline treatment, the mean hemoglobin concentration increased to 11.7 ± 1.0 g/dl ($P = 0.0001$). Baseline *ex vivo* T cell expression of TNF-α decreased from 58% ± 11% to 31% ± 23% ($P = 0.0007$) after therapy. Likewise, IFN-γ expression decreased from 31% ± 10% to 13% ± 10% ($P = 0.0002$). Pentoxifylline therapy may significantly improve the hemoglobin response in patients with previously rh-Epo–resistant anemia in renal failure. This may occur due to inhibition of proinflammatory cytokine production, which could interfere with the effectiveness of rh-Epo.

Pentoxifylline

RESEARCH ARTICLE

Pentoxifylline for Anemia in Chronic Kidney Disease: A Systematic Review and Meta-Analysis

Davide Bolignano[1]*, Graziella D'Arrigo[1], Anna Pisano[1], Giuseppe Coppolino[2]

Conclusions

There is currently no conclusive evidence supporting the utility of pentoxifylline for improving anemia control in CKD patients. Future trials designed on hard, patient-centered outcomes with larger sample size and longer follow-up are advocated.

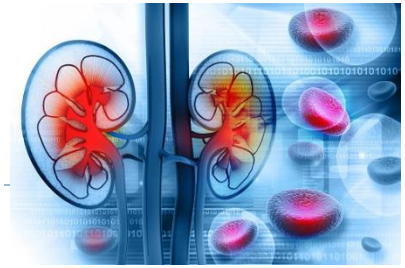
Background

Pentoxifylline (PTX) is a promising therapeutic approach for reducing inflammation and improving anemia associated to various systemic disorders. However, whether this agent may be helpful for anemia management also in CKD patients is still object of debate.

Study Design

Systematic review and meta-analysis.

Diet



Dietary Management

Sources of Heme iron (from animal sources)	Sources of Non-heme iron (from plants)
Lean meat	Nuts
Red meat	Beans
Sea food	Vegetables fortified grain products

Milk & milk products, tannins & caffeine inhibit iron absorption & should be avoided with iron rich sources of food.

Vitamin C can improve iron absorption & can be administered concomitantly with iron rich foods.

Dialysis

http://www.biomedcentral.com/1471-2369/15/155

BMC Nephrology

RESEARCH ARTICLE Open Access

Adequate hemodialysis improves anemia by enhancing glucose-6-phosphate dehydrogenase activity in patients with end-stage renal disease

Mahmoud Husni Ayesh (Haj Yousef)[1*], Ahnaf Bataineh[2], Elham Elamin[3], Yousef Khader[4], Khaldoon Alawneh[1] and Moha[illegible]d Rabab[illegible][1]

Adequate Hemodialysis

Abstract

Background: We conducted this study to determine the erythrocyte glucose-6-phosphate dehydrogenase (G6PD) activity level in patients with end-stage renal disease (ESRD) on maintenance hemodialysis (HD) and to determine the effect of hemodialysis adequacy on G6PD activity levels and its impact on anemia.

Methods: Eighty-two patients (48 men and 34 women) receiving regular hemodialysis for ESRD through arteriovenous fistulae for at least one year prior to the start of the study were enrolled in this study. G6PD activity levels were measured in all patients and the average Kt/V was used as a parameter of HD adequacy. Patients were divided into two groups according to Kt/V values. Group 1 included 45 patients with Kt/V≥1.2 (adequate HD), and group 2 included 37 patients with Kt/V<1.2 (inadequate HD). The average hemoglobin level and the weekly dose of an erythropoietin-stimulating agent, epoetin alpha (ESA), for each patient were calculated for one year.

Results: The mean (SD) erythrocyte G6PD activity for all patients on hemodialysis was 7.64 ± 1.85 U/g Hb. Patients who had received adequate hemodialysis had a significantly higher average erythrocyte G6PD (mean (SD) = 9.2 ± 0.7 U/g Hb) compared to patients who had inadequate hemodialysis (mean (SD) = 5.7 ± 0.7U/g Hb) (*P*-value <0.005). The mean hemoglobin concentration was significantly higher in patients with adequate hemodialysis compared to those with inadequate hemodialysis.

Conclusion: Our study demonstrated the beneficial effect of adequate hemodialysis in correcting anemia by enhancing the erythrocyte G6PD activity in patients.

J NEPHROL 2004; 17: 701-706

The effect of high-flux hemodialysis on renal anemia

Deniz Ayli[1], Meltem Ayli[2], Alper Azak[1], Cüneyt Yüksel[1], Gözde Petek Koşmaz[1], Gökhan Atilgan[1], Fatih Dede[1], Ekrem Abayli[1], Mine Çamlibel[3]

[1]Department of Nephrology, [2]Department of Hematology, Ankara Numune Education and Research Hospital, Ankara - Turkey
[3]Yaşam Di[illegible] Turkey

High-flux Hemodialysis

ABSTRACT: *Background:* Anemia is an important predictor of mortality and morbidity in patients with end-stage renal disease (ESRD) undergoing hemodialysis (HD). Erythropoietin (EPO) is an expensive drug, which increases the cost of therapy. In addition, anemia persists in 20-30% of cases despite EPO treatment. In this study, which depended on the idea that the clearance of moderate and high molecular weight erythropoiesis inhibitors leads to an improvement in terms of anemia, we aimed to investigate the effect of high-flux dialysis on anemia and EPO requirement in patients undergoing HD.

Methods: The study included 48 patients with ESRD on chronic HD treatment who could not reach the target hemoglobin (Hb) level, despite treatment with at least 200 IU/kg/week subcutaneous EPO. Patients were randomized into two groups and HD was performed with polysulphone low-flux dialyzer (Fresenius F6 HPS) or polysulphone high-flux dialyzer (Fresenius F60) for 6 months.

Results: Although the EPO doses were significantly lower ($p<0.001$) in the high-flux dialysis group, Hb levels showed a significant increase ($p<0.001$). In the low-flux dialysis group, Hb levels showed no significant increase, despite the steady increase in EPO doses. In the high-flux group, the reduction of beta$_2$-microglobulin (β_2-MG) and phosphorus levels during dialysis was significantly higher when compared to the low-flux group ($p<0.001$). During the follow-up period, while β_2-MG levels decreased significantly in the high-flux group ($p<0.05$), there was an increase in the low-flux group ($p<0.05$). Kt/V_{urea} values showed no significant difference throughout the study.

Conclusions: Our results suggest that high-flux dialysis use is effective and this can be an alternative method in terms of controlling renal anemia and reducing the cost of therapy. These beneficial effects of high-flux dialysis are probably mediated by the improved clearance of moderate and high molecular weight toxins.

Key words: *End-stage renal disease, Hemodialysis, Anemia, Erythropoietin, High-flux dialysis, Beta$_2$-microglobulin*

J Nephrol. 2004 Sep-Oct;17(5):693-700.

Ultrapure dialysate improves iron utilization and erythropoietin response in chronic hemodialysis patients - a prospective cross-over study.

Hsu PY[1], Lin CL, Yu CC, Chien CC, Hsiau TG, Sun TH, Huang LM, Yang CW.

Author information

Ultrapure Dialysate

Abstract

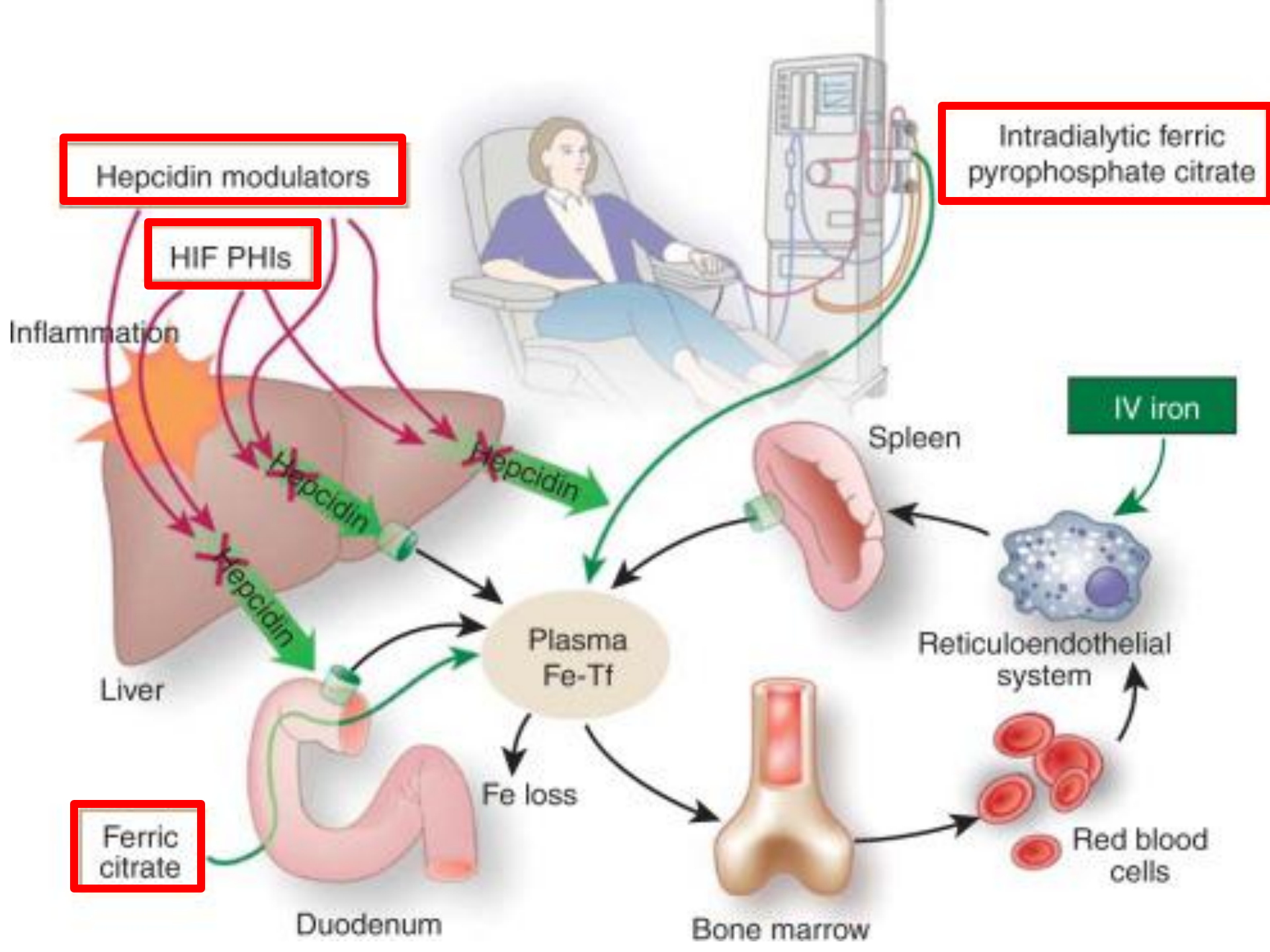
BACKGROUND: The impact of ultrapure dialysis on dialysate-related chronic inflammatory status and anemia in uremic patients on maintenance hemodialysis (HD) remains uncertain. We evaluated ultrapure dialysate effects on erythropoietin (EPO) response and inflammatory status in a prospective, randomized, cross-over study.

METHODS: Thirty-four HD patients were divided into two groups. One group was treated with conventional dialysate and the other group with ultrapure dialysate for 6 months and crossed over for another 6 months. Bacteria growth and dialysate endotoxin were examined. Parameters including C-reactive protein (CRP), recombinant human erythropoietin (rHuEPO) dose, ferritin, iron saturation and serum albumin were measured at the start, and at 6 and 12 months.

RESULTS: The endotoxin levels reduced significantly in the ultrapure dialysate by adding a dialysate ultrafilter. After a 6-month treatment with ultrapure dialysate, there were statistically significant differences in the systemic inflammation markers between both groups. Changing from conventional to ultrapure dialysis fluid significantly reduced CRP (7.01 +/- 5.059 to 4.461 +/- 3.754 mg/L, $p<0.05$), and resulted in reduced rHuEPO doses (12500 +/- 7060 to 10440 +/- 7050 U/month, $p<0.05$). Continuous conventional dialysate use was not associated with significant alternations in CRP (from 5.849 +/- 7.744 to 6.187 +/- 7.997 mg/L, $p=0.456$) and rHuEPO dose (14060 +/- 6210 to 15060 +/- 7250U/month, $p>0.05$). The ferritin level reduced significantly (422 +/- 183 to 272 +/- 162 mcg/L, $p<0.05$) in the ultrapure dialysate group. After another 6-month cross-over, the study parameters were reversed among the two groups indicating the beneficial effect of ultrapure dialysis.

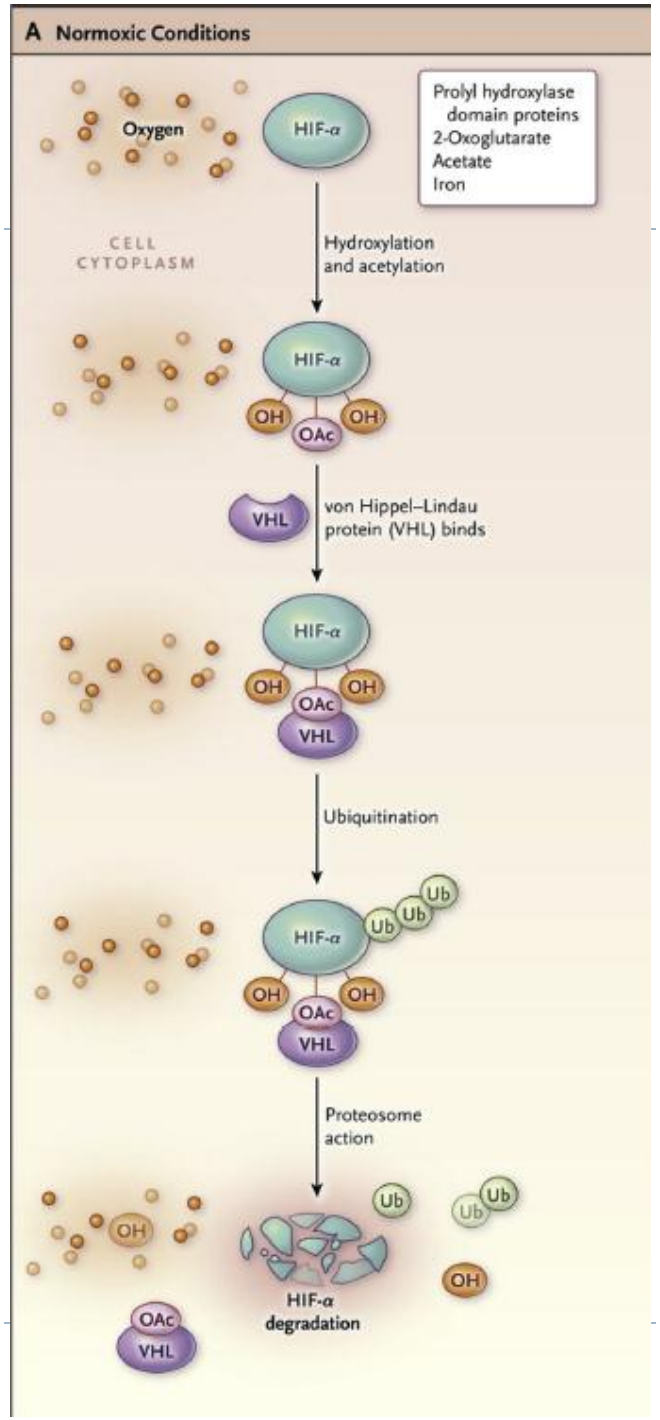
Emerging Therapies

- Hypoxia-inducible Factor Stabilizers
- Hepcidin Modulators


Hepcidin modulators
HIF PHIs
Inflammation
Intradialytic ferric pyrophosphate citrate
IV iron
Spleen
Hepcidin
Hepcidin
Hepcidin
Liver
Plasma Fe-Tf
Reticuloendothelial system
Fe loss
Ferric citrate
Duodenum
Bone marrow
Red blood cells

Emerging Therapies

- Hypoxia-inducible Factor Stabilizers
- Hepcidin Modulators


A Normoxic Conditions
Oxygen
HIF-α
Prolyl hydroxylase domain proteins
2-Oxoglutarate
Acetate
Iron
CELL CYTOPLASM
Hydroxylation and acetylation
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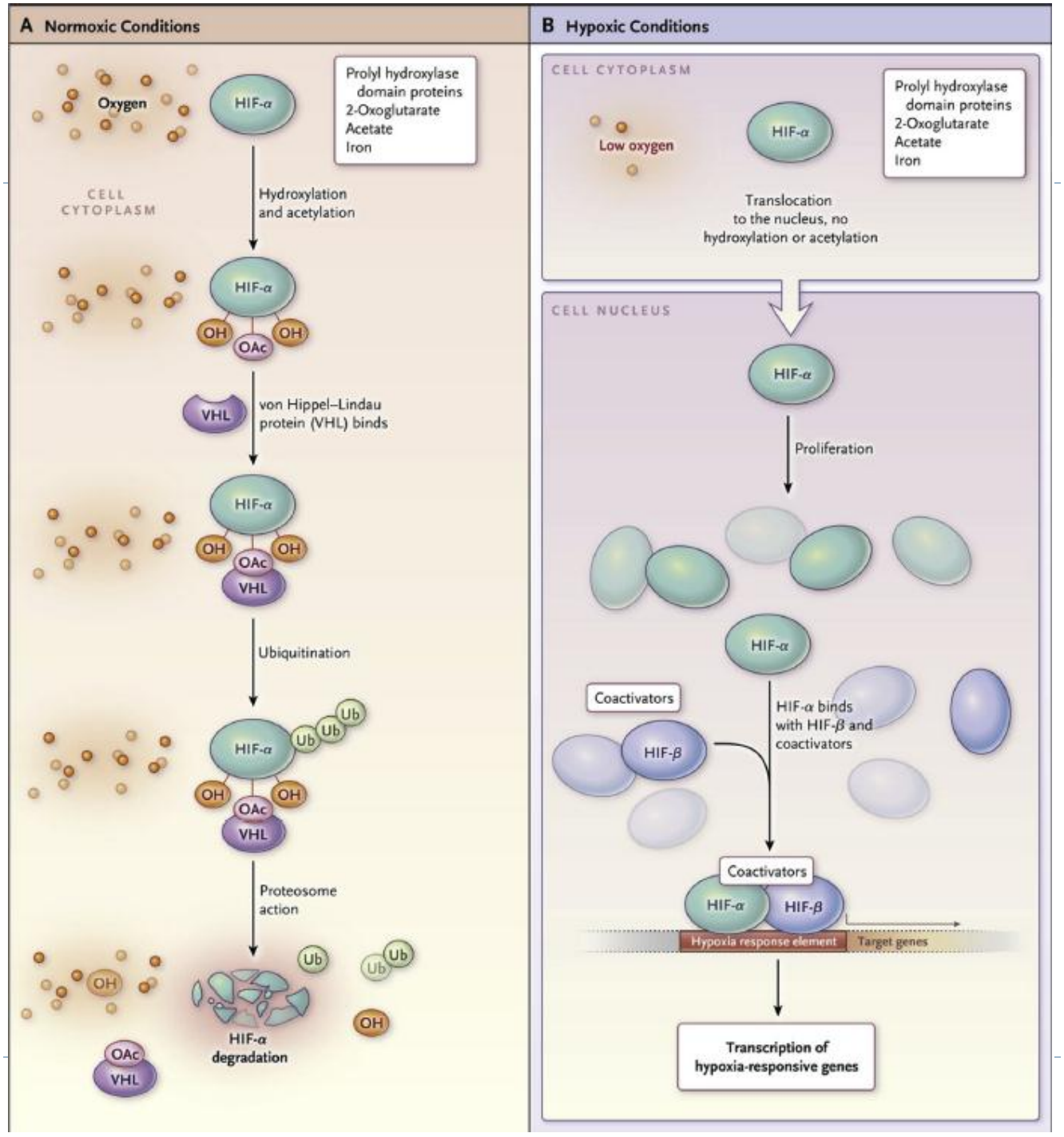
VHL
von Hippel–Lindau protein (VHL) binds
Ubiquitination
Ub
Proteosome action
HIF-α degradation


A Normoxic Conditions
Oxygen
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Prolyl hydroxylase domain proteins
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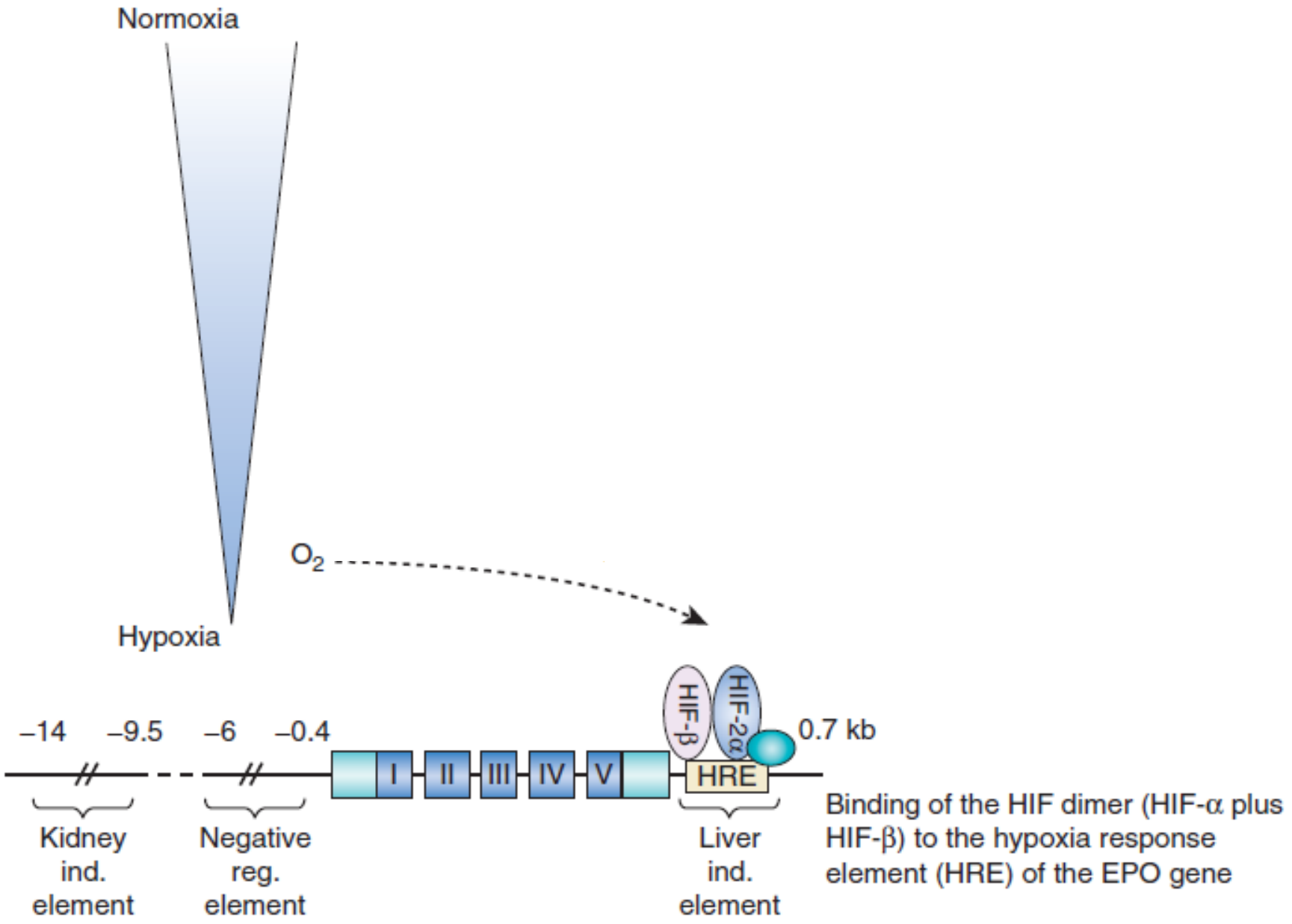
Acetate
Iron
CELL CYTOPLASM
Hydroxylation and acetylation
OH
OAc
VHL
von Hippel–Lindau protein (VHL) binds
Ubiquitination
Ub
Proteosome action
HIF-α degradation
B Hypoxic Conditions
CELL CYTOPLASM
Low oxygen
Translocation to the nucleus, no hydroxylation or acetylation
CELL NUCLEUS
Proliferation
Coactivators
HIF-β
HIF-α binds with HIF-β and coactivators
Hypoxia response element
Target genes
Transcription of hypoxia-responsive genes


Normoxia
Hypoxia
O_2
HIF-β
HIF-2α
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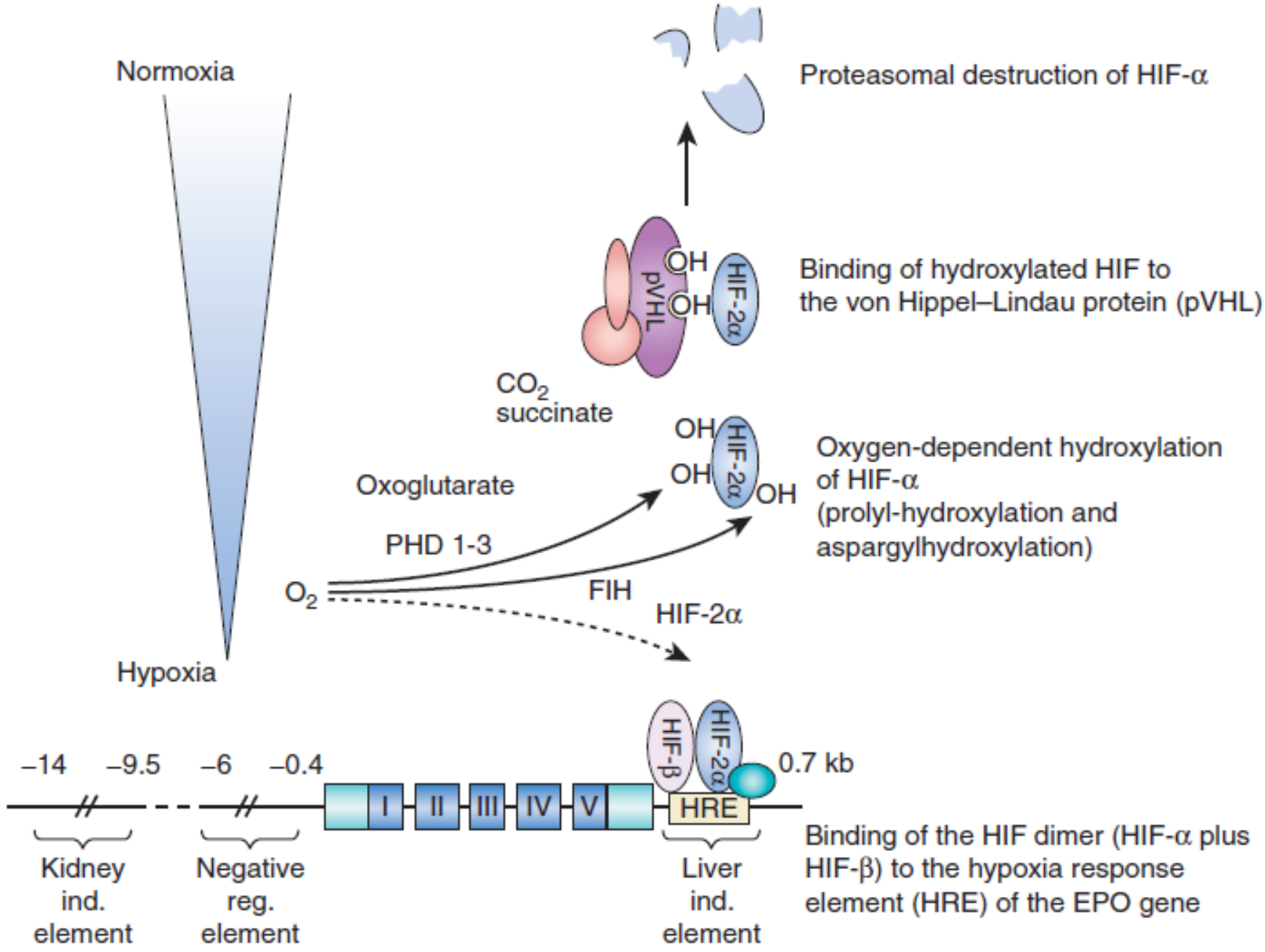
–9.5
–6
–0.4
I
II
III
IV
V
HRE
Kidney ind. element
Negative reg. element
Liver ind. element
Binding of the HIF dimer (HIF-α plus HIF-β) to the hypoxia response element (HRE) of the EPO gene


Normoxia
Hypoxia
Proteasomal destruction of HIF-α
OH
OH
pVHL
HIF-2α
Binding of hydroxylated HIF to the von Hippel–Lindau protein (pVHL)
CO_2
succinate
Oxoglutarate
PHD 1-3
O_2
FIH
HIF-2α
OH
OH
OH
HIF-2α
Oxygen-dependent hydroxylation of HIF-α (prolyl-hydroxylation and aspargylhydroxylation)
HIF-β
HIF-2α
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–0.4
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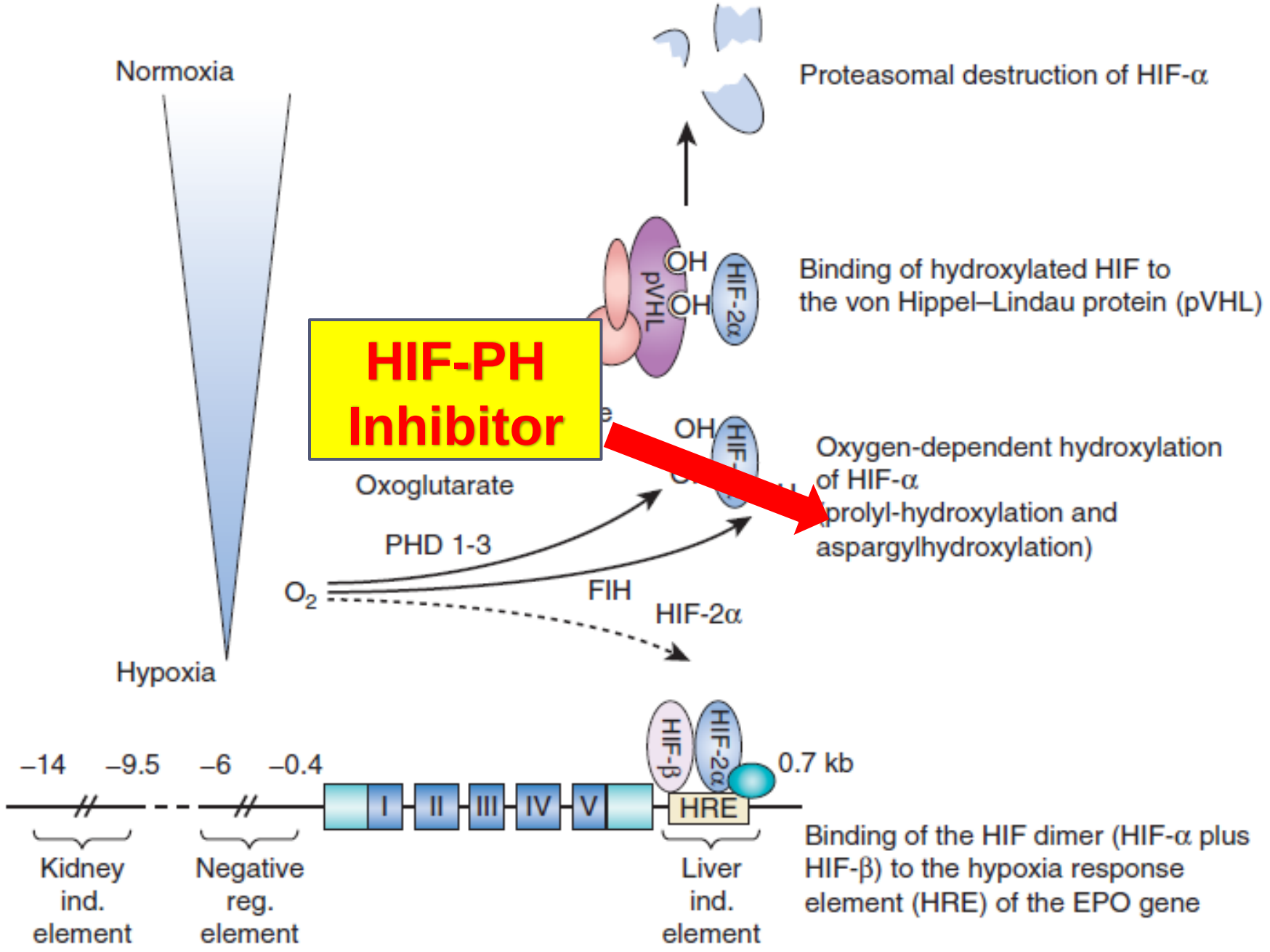
Normoxia
Hypoxia
Proteasomal destruction of HIF-α
Binding of hydroxylated HIF to the von Hippel–Lindau protein (pVHL)
pVHL
OH
OH
HIF-2α
HIF-PH Inhibitor
Oxoglutarate
PHD 1-3
O2
FIH
HIF-2α
Oxygen-dependent hydroxylation of HIF-α (prolyl-hydroxylation and aspargylhydroxylation)
HIF-β
HIF-2α
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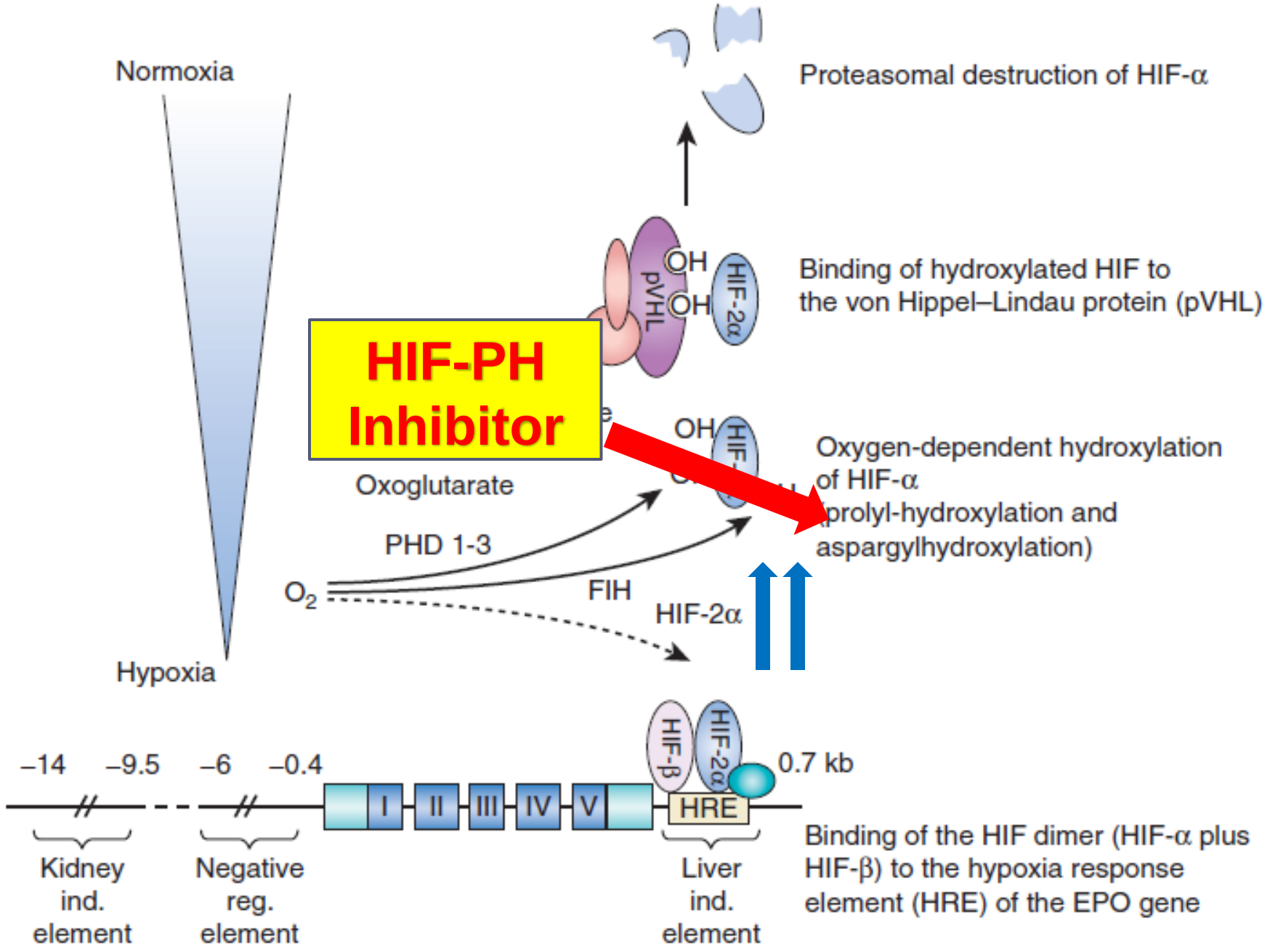
Binding of the HIF dimer (HIF-α plus HIF-β) to the hypoxia response element (HRE) of the EPO gene


Normoxia
Hypoxia
Proteasomal destruction of HIF-α
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pVHL
HIF-2α
Binding of hydroxylated HIF to
the von Hippel–Lindau protein (pVHL)
HIF-PH
Inhibitor
Oxoglutarate
PHD 1-3
O2
FIH
HIF-2α
Oxygen-dependent hydroxylation
of HIF-α
(prolyl-hydroxylation and
aspargylhydroxylation)
HIF-β
HIF-2α
–14
–9.5
–6
–0.4
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HRE
Kidney
ind.
element
Negative
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element
Liver
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Binding of the HIF dimer (HIF-α plus
HIF-β) to the hypoxia response
element (HRE) of the EPO gene

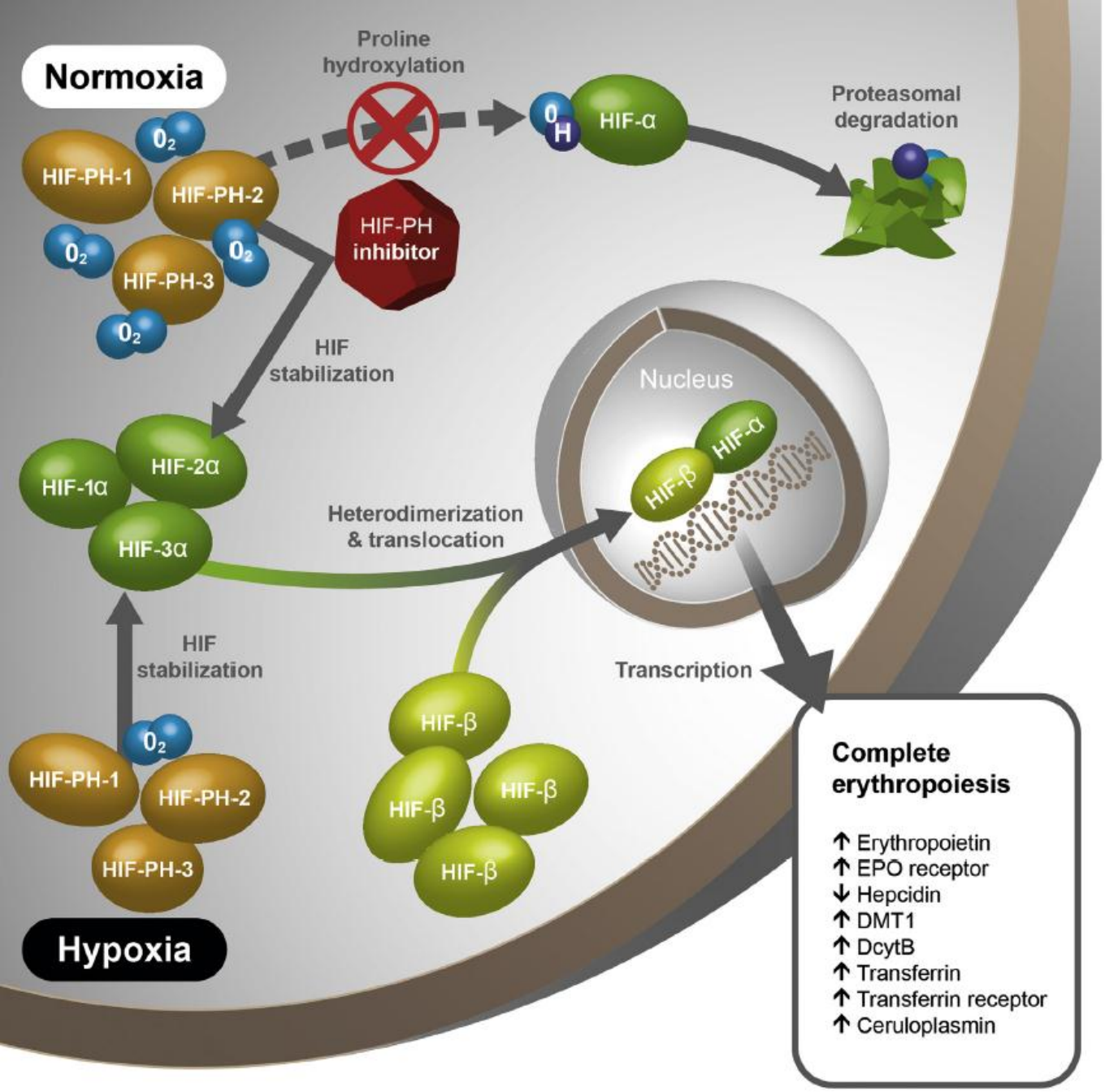


Fig:
Hypoxia-inducible factor (HIF) pathway.

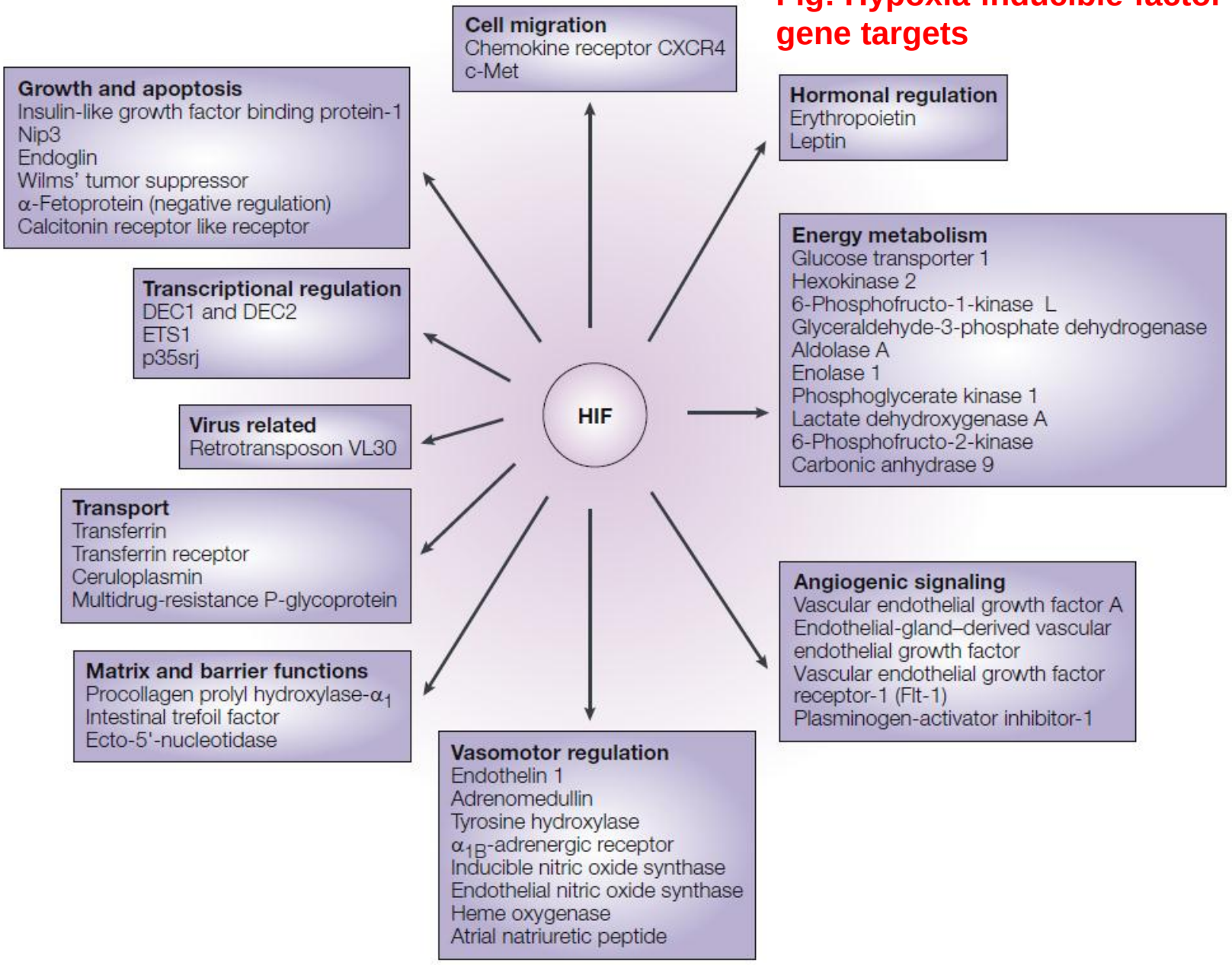
Abbreviations:
DcytB, duodenal cytochrome B;
DMT1, divalent metal transporter 1;
EPO, erythropoietin;
PH, prolyl hydroxylase

Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors: A Potential New Treatment for Anemia in Patients With CKD; Am J Kidney Dis. 2017;69(6):815-826

HIF stabilizers

- competitive inhibitors of HIF prolyl hydroxylases & asparagyl hydroxylase (enzymes involved in metabolism of HIF & its transcriptional activity)
- increase endogenous EPO production
- orally active
- currently being tested in Phase II & III clinical trials

Fig: Hypoxia-inducible factor (HIF) gene targets

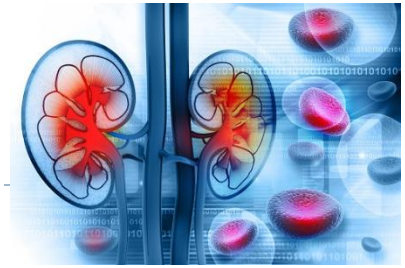


New options for the anemia of chronic kidney disease : Kidney International Supplements (2017) 7, 157–163

HIF stabilizers

Upregulate

- **EPO gene expression**
- expression of **other HIF target genes** including those coding for **enzyme & transporters involved in iron metabolism, angiogenesis, mitochondrial genesis**
- long-term consequences - not established & merit careful monitoring



Hypoxia-inducible factor stabilizers under development for treatment of anemia in chronic kidney disease

Company	Molecule	Drug name	Phase of development
FibroGen Astellas AstraZeneca	FG-4592	Roxadustat	Phase 3
GlaxoSmithKline	GSK 1278863	Daprodustat	Phase 3
Akebia	AKB-6548	Vadadustat	Phase 3
Bayer	BAY 85–3934	Molidustat	Phase 2/3
Japan Tobacco Inc	JTZ-951		Phase 1

New options for the anemia of chronic kidney disease : Kidney International Supplements (2017) 7, 157–163

Emerging Therapies

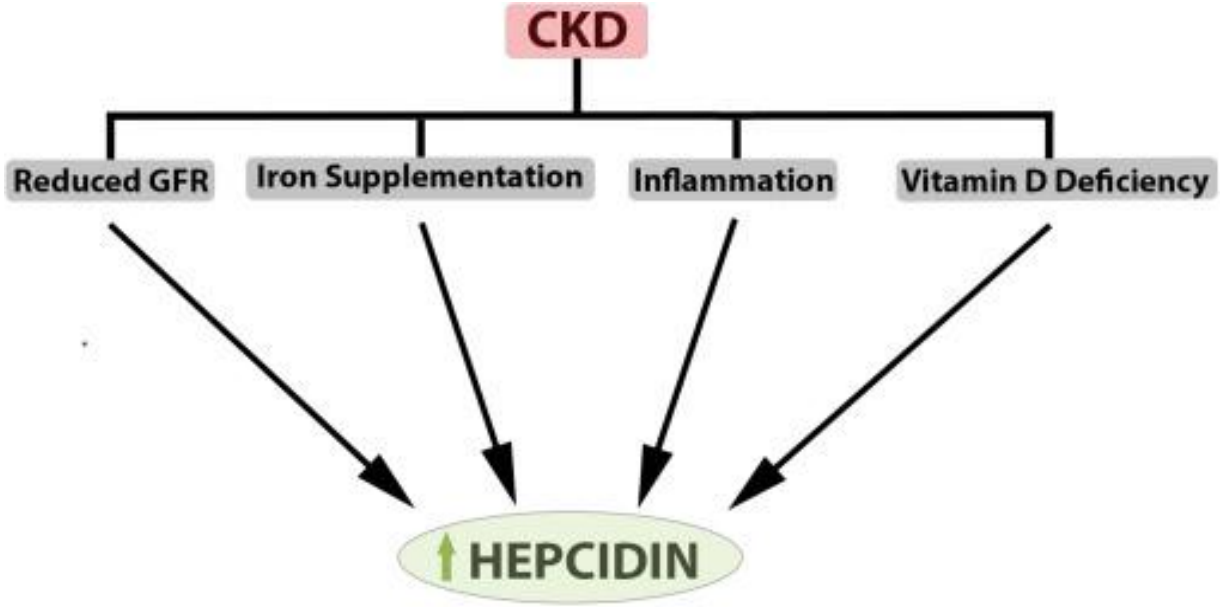
- Hypoxia-inducible Factor Stabilizers
- Hepcidin Modulators

25-amino acid peptide

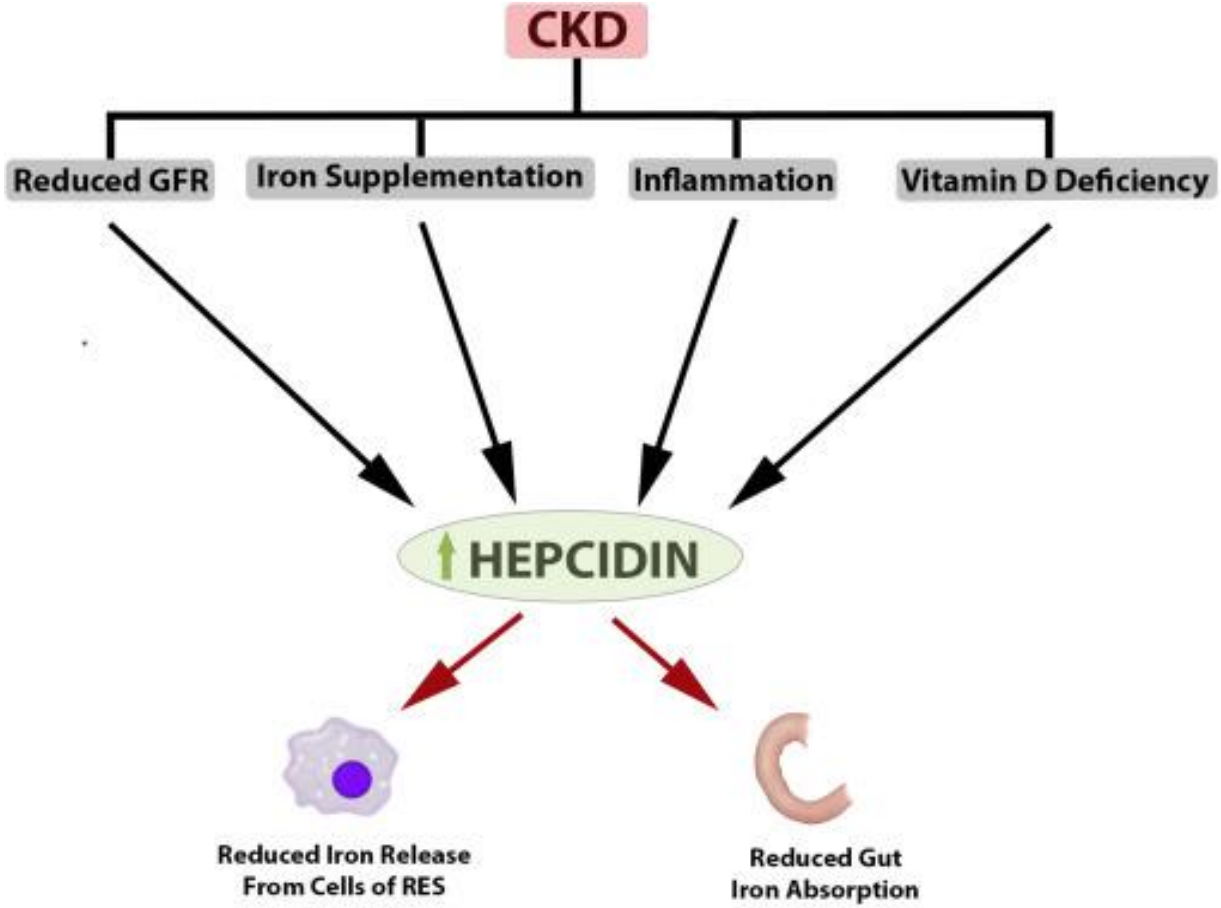
Iron regulatory protein

Produced by hepatocytes

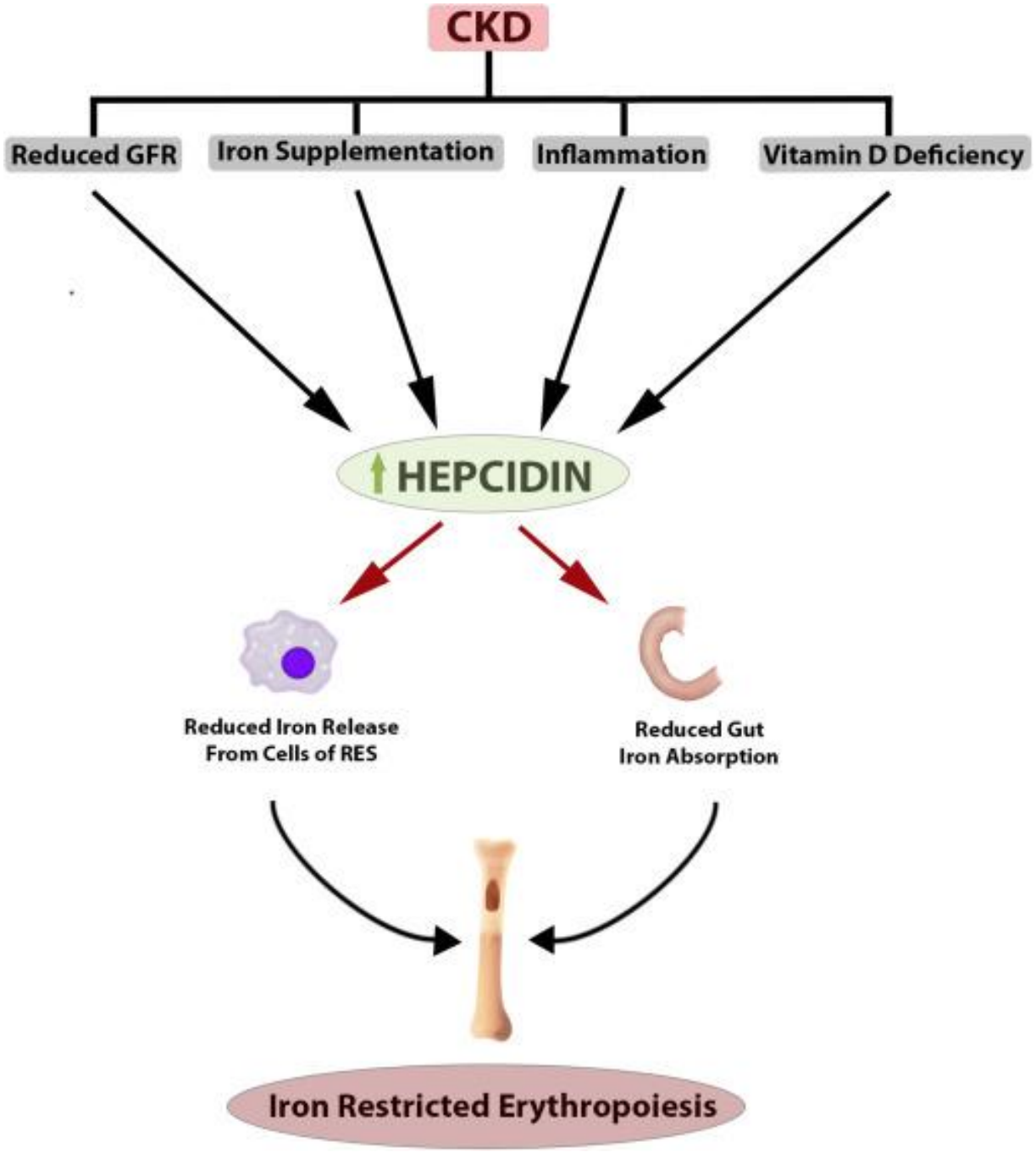
Iron metabolism & anemia in CKD: seminar in Nephrology: July 2016, p252-261



Iron metabolism & anemia in CKD: seminar in Nephrology: July 2016, p252-261



Iron metabolism & anemia in CKD: seminar in Nephrology: July 2016, p252-261



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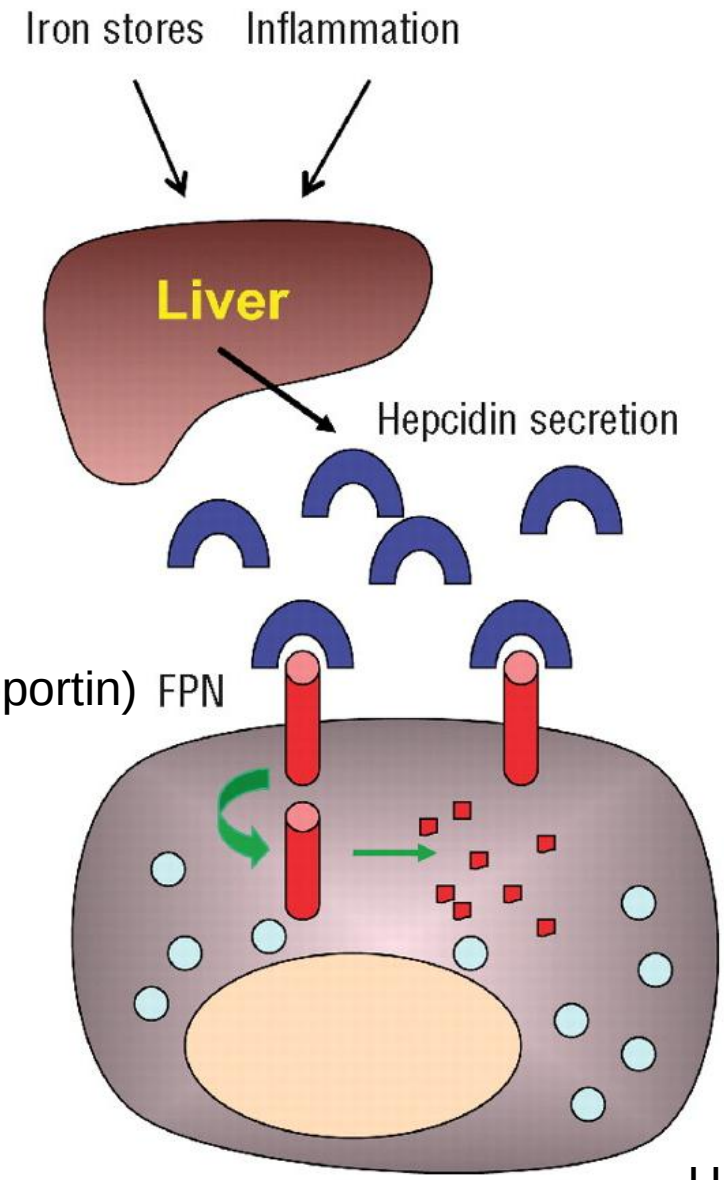
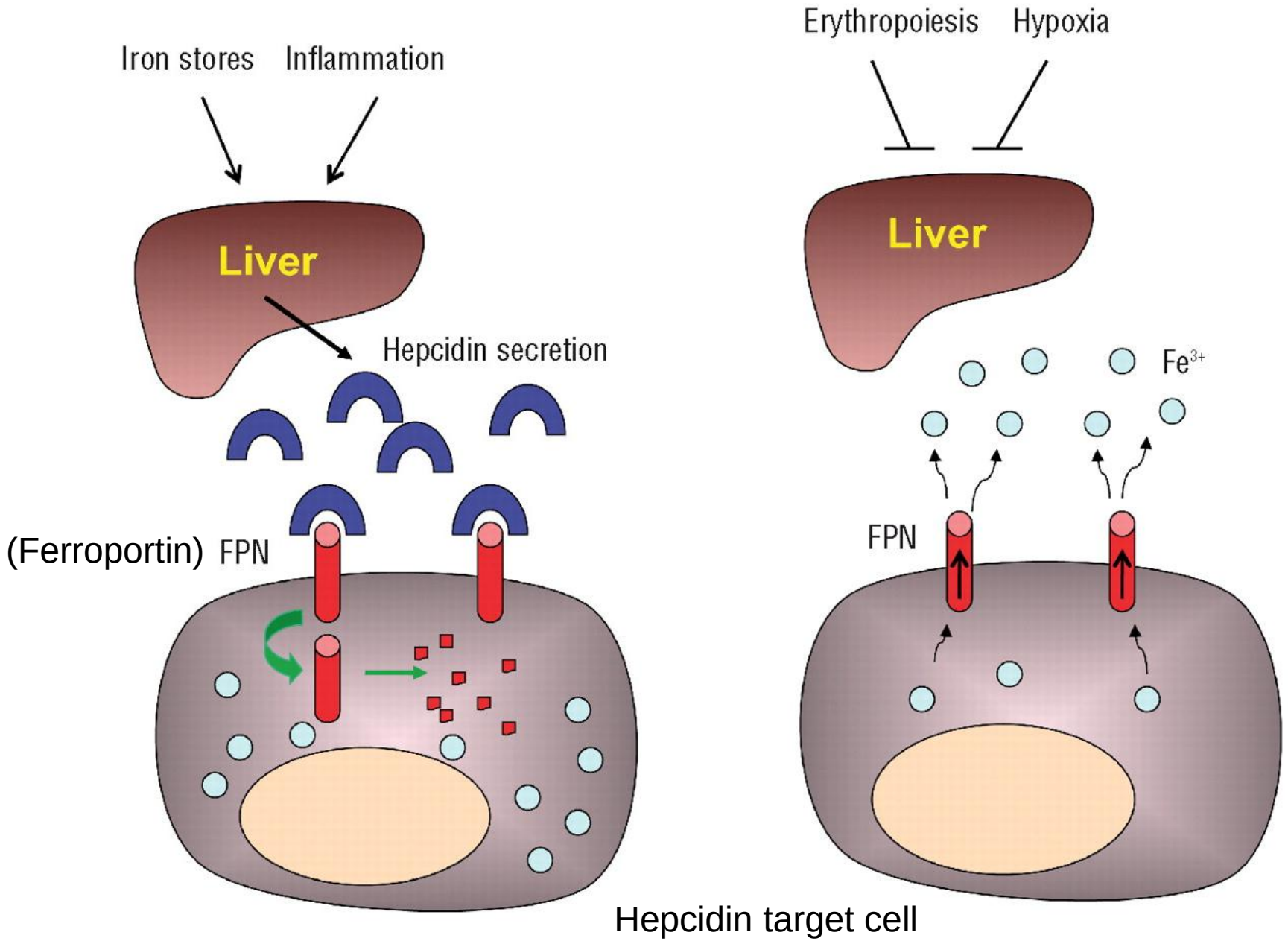


FPN (Ferroportin) = Iron Efflux channel


Iron stores
Inflammation
Liver
Hepcidin secretion
(Ferroportin) FPN
Erythropoiesis
Hypoxia
Liver
Fe3+
FPN
Hepcidin target cell

Hemodialysis International 2017; **21**:S37–S46

Scholarly Review

Role of hepcidin-ferroportin axis in the pathophysiology, diagnosis, and treatment of anemia of chronic inflammation

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Abstract

Anemia of chronic inflammation (ACI) is a frequently diagnosed anemia and portends an independently increased morbidity and poor outcome associated with multiple underlying diseases. The pathophysiology of ACI is multifactorial, resulting from the effects of inflammatory cytokines which both directly and indirectly suppress erythropoiesis. Recent advances in molecular understanding of iron metabolism provide strong evidence that immune mediators, such as IL-6, lead to hepcidin-induced hypoferremia, iron sequestration, and decreased iron availability for erythropoiesis. The role of hepcidin-ferroportin axis in the pathophysiology of ACI is stimulating the development of new diagnostics and targeted therapies. In this review, we present an overview of and rationale for inflammation-, iron-, and erythropoiesis-related strategies currently in development.

Key words: Anemia, inflammation, iron metabolism

Strategies for modulating hepcidin

- Anti-hepcidin antibodies
- Short interference RNA and anti-sense oligonucleotides
- Hepcidin-binding proteins
- Hepcidin-binding spiegelmeyers
- Hepcidin production inhibitors
- BMP6-HJV-SMAD pathway inhibitors
- IL-6 inhibitors
- Vitamin D
- Ferroportin agonists / stabilisers

What I would like to share from my learning:

Iron Therapy
- cornerstone in Mx of Renal Anemia

Red cell Transfusion
- avoid if possible

Adjuvant Therapies
- not routinely recommended

Dialysis – adequacy/ ultrapure dialysate
- better ESA response

Diet
- important in Anemia Mx

Ferric citrate
Ferric pyrophosphate citrate

Emerging Therapies
HIF stabilizers
Hepcidin modulators

Thank you