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The present and future of anaemia management in CKD patients

Prof. Andrzej Wiecek

Department of Nephrology, Transplantation and Internal Medicine

Medical University of Silesia, Katowice, Poland

e-mail: awiecek@sum.edu.pl

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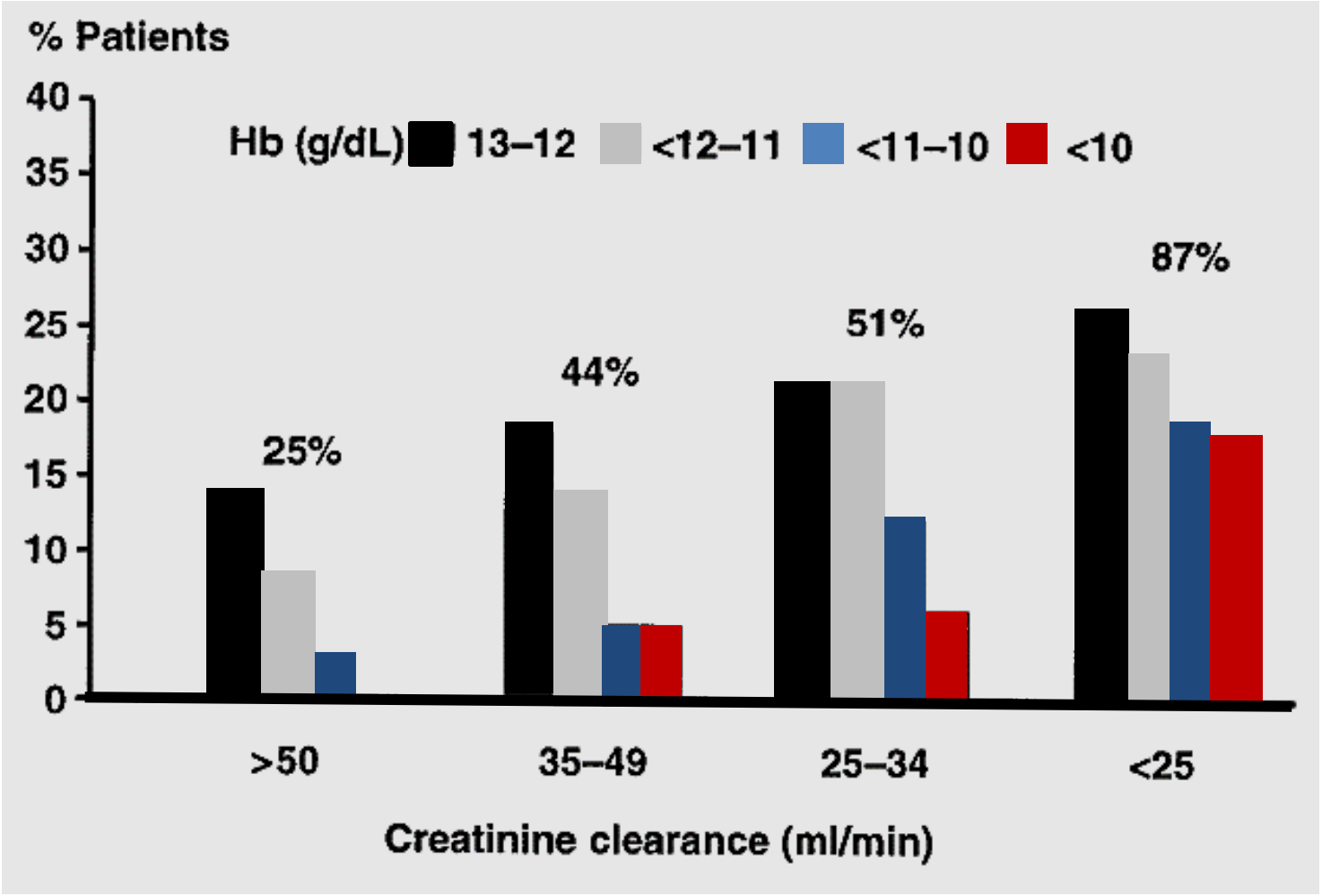
Prevalence of anaemia in patients with chronic kidney disease



Levin A., Nephrol. Dial. Transplant., 2001, 16, suppl 2: 7-11

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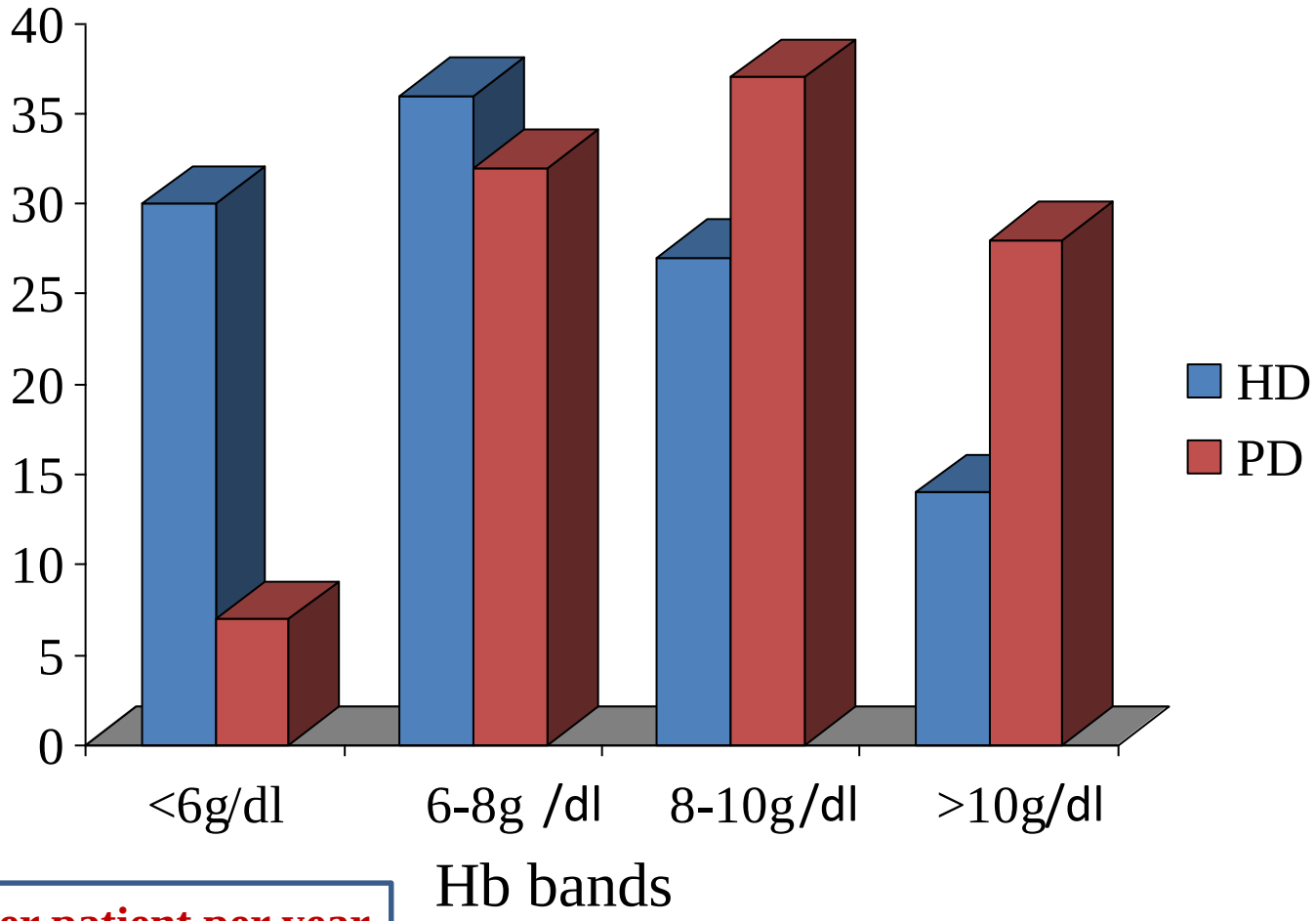
Distribution of Hb concentrations in haemodialysis and PD patients in 1984



~ 3 units blood per patient per year

Courtesy of dr Ch. Winearls, Oxford, UK

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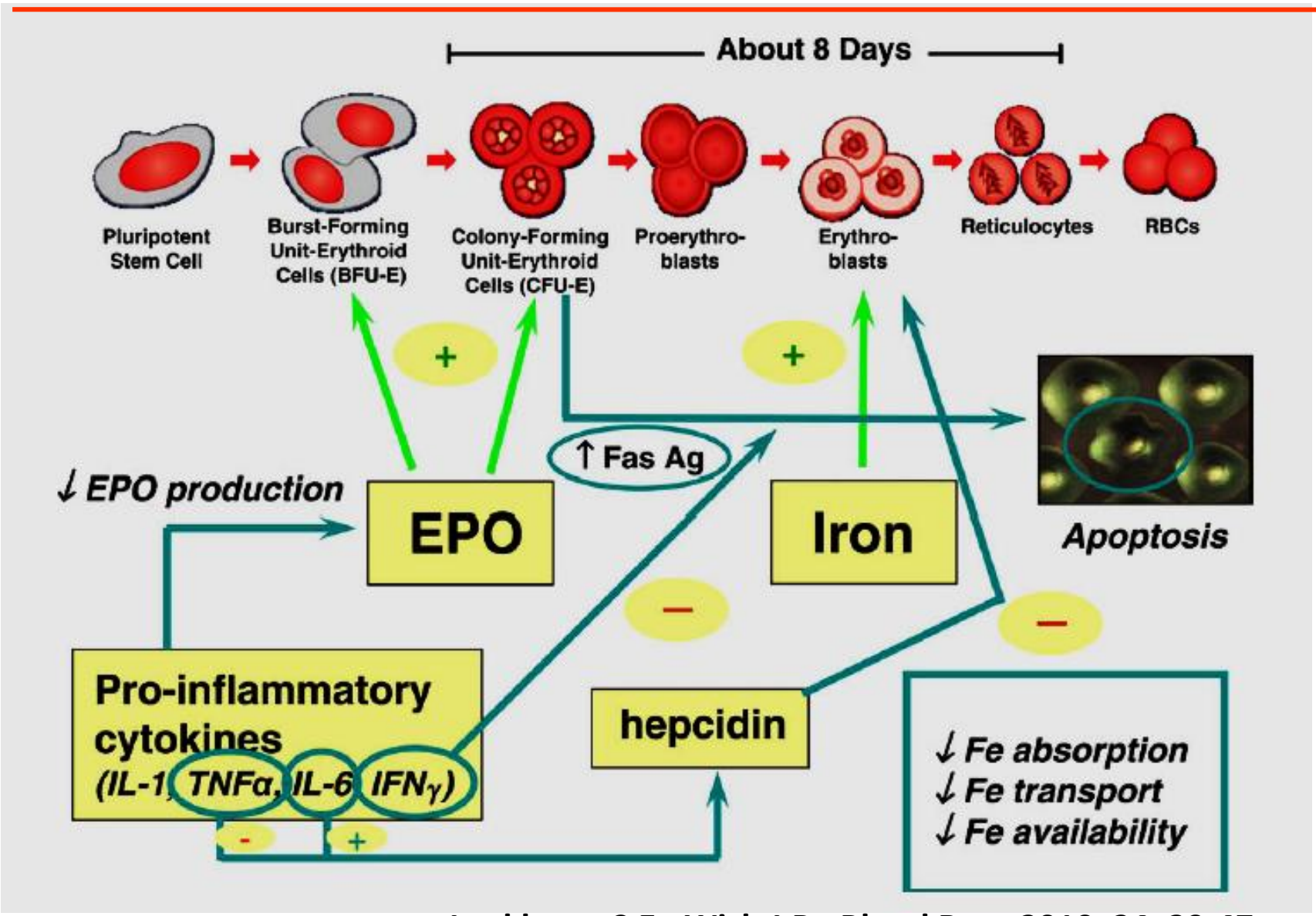
Erythropoiesis in chronic kidney disease



Lankhorst C.E., Wish J.B., Blood Rev., 2010, 24, 39-47

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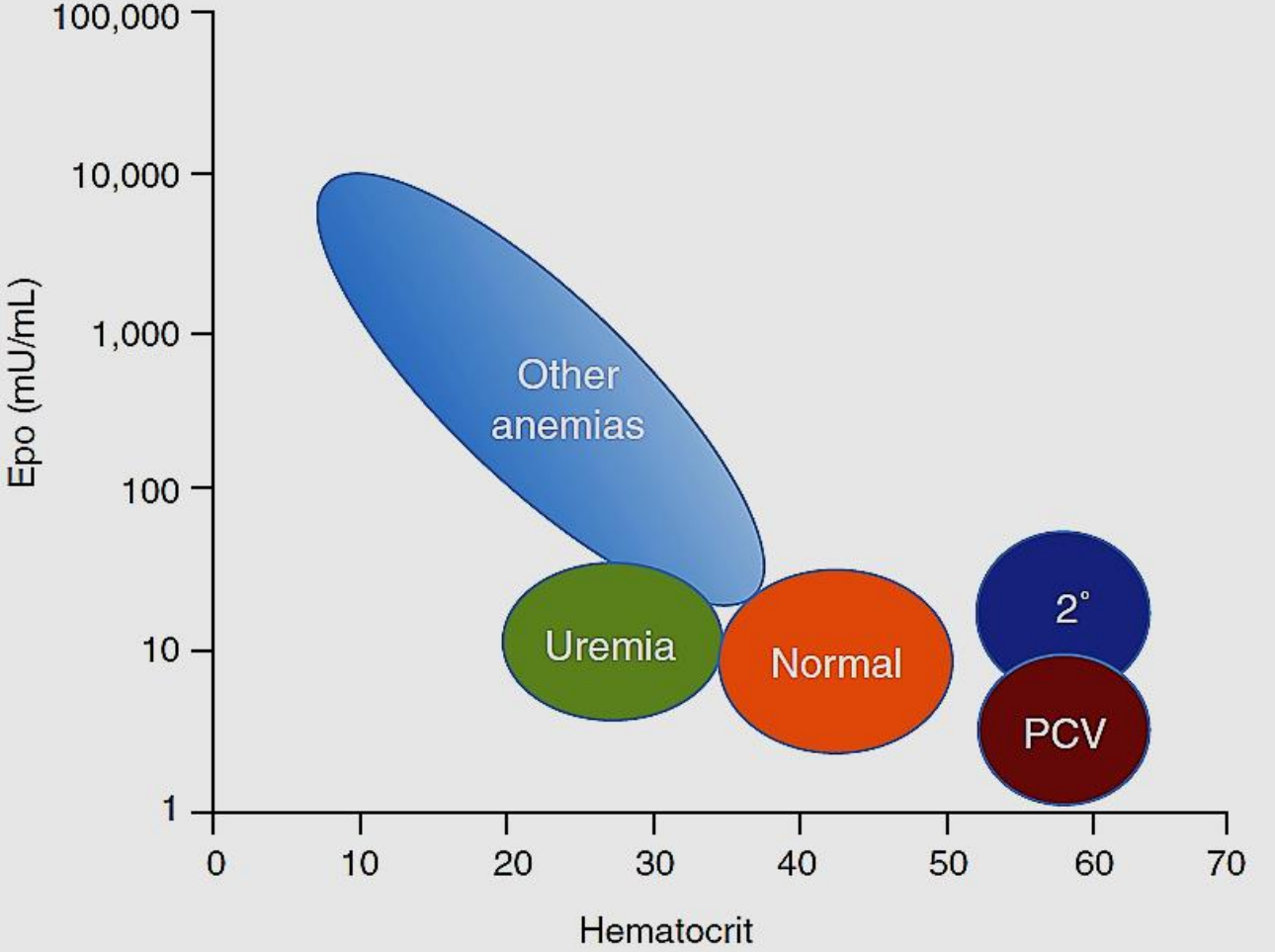
Plasma erythopoietin (EPO) levels in patients with different types of and degrees of anaemia and in those with primary or secondary erythrocytosis



Bunn H.F., Cold Spring Harb. Perspect. Med. 2013; 3: a011619

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Currently available Erythropoiesis Stimulating Agents (ESAs)

Table 1. Currently Available Erythropoiesis-Stimulating Agents

Agent	Active Compound	Manufacturing Process	Year Licensed
Epoetin alfa/beta (Epogen, Eprex, Erypo, NeoRecormon)	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene–transfected CHO cells	1989 (Epogen, in US); 1990 (Eprex/ Erypo/NeoRecormon, in Europe)
Epoetin delta (Dynepo)	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene–transfected human cells	2006 (outside of US); product withdrawn by Shire in 2009
"Biosimilar" epoetins (Binocrit, Hexal, Retacrit, Silapo, Eporatio)	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene–transfected CHO cells	2009 onward
Nonapproved or locally approved "copy" epoetins	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene-transfected human cells	Available in many countries outside of US and Europe, eg, India, China, Thailand, Argentina, Brazil
Darbepoetin alfa (Aranesp)	Hyperglycosylated recombinant human EPO analogue	Recombinant DNA technology; mutated EPO cDNA–transfected CHO cells	2001 (both US and Europe)
C.E.R.A. (Mircera)	Pegylated recombinant human EPO analogue		2009 (outside of US only)
Omontys (Peginesatide)	**Syntetic and pegylated EPO- mimetic**	**Syntetic EPO**	**2012 only for HD (USA)**

Macdougall I. C., Am. J. Kidney Dis., 2012, 59, 444 - 451

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2009

2013

Macdougall I. C., Am. J. Kidney Dis., 2012, 59, 444 - 451

Current ESA and iv iron use

- Use ESA therapy to control anaemia when Hb <10.0 g/dl or < 11.0 g/dl if symptoms)
- Aim for target Hb in range 10.0 -12.0 g/dl; individualize
- Do not exceed intentionally 13.0 g/dl
- Use lowest doses of ESA as possible
- Use supplemental iron to prevent iron deficiency and reduce ESA dose requirements – i.v in HD; oral or i.v. in ND - CKD
- Aim for ferritin > 100 ug/l and TSAT >20%
- Upper limit of ferritin not clear; do not actively exceed 800 ug/l

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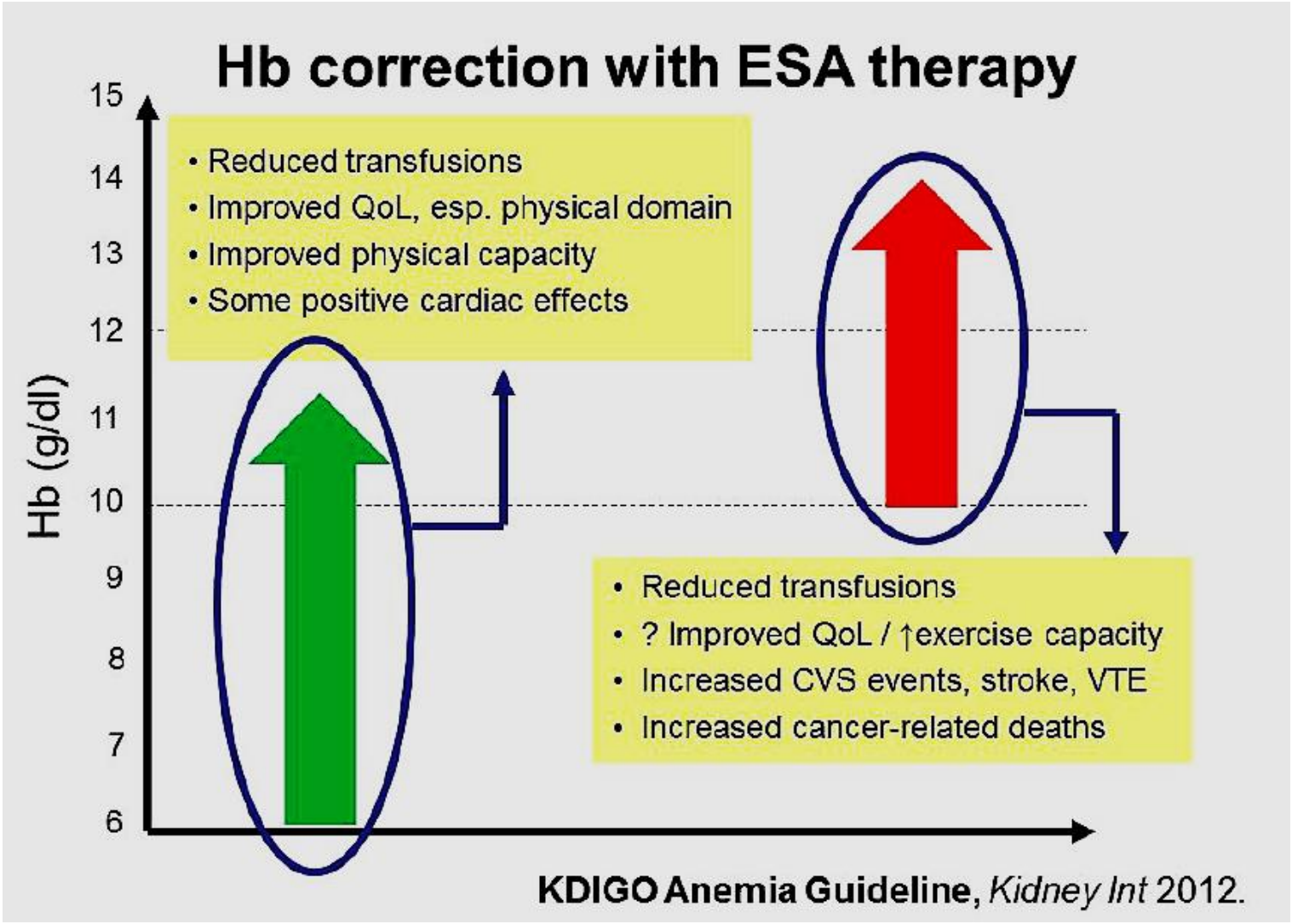
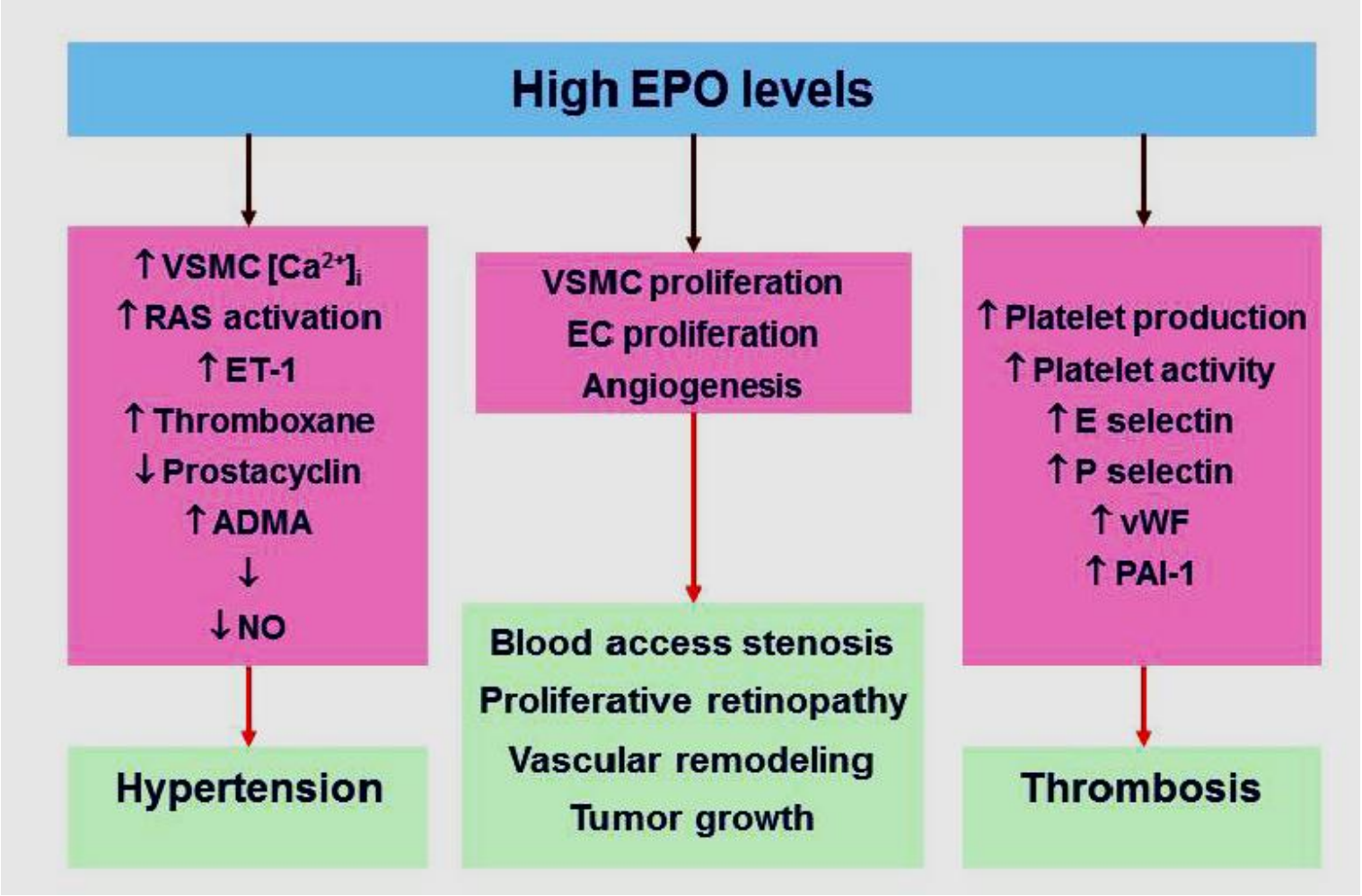
Clinical consequences of anaemia treatment in CKD patients



What we know about treatment of anaemia in CKD patients in 2017?

- Generally well tolerated
- Treatment increases Hb and reduces need for blood transfusions
- Higher Hb concentration obtained with higher ESAs doses may lead to increased the risk of adverse events (predominantly CV events)
- Probably improves patients' quality of life
  - Relationships for most subscales particularly vitality, exercise capacity is sigmoid
    - major increases occur between 7 to 9 -10 g/dl Hb
    - Effects of Hb levels is off at 9-11 g/dl Hb
    - In most studies no added benefit at higher Hb except for "vitality" or "fatigue" that are measurable up to 13 g/dl

EPO has non-erythropoietic actions



Vaziri N.D. and Zhou X., Nephrol. Dial. Transplant., 2009, 24, 1082-1088

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Why we need a new ESAs ?

Available ESAs are very effective drugs, however:

- recombinant ESAs are still expensive
- recombinant ESAs require cold storage
- recombinant ESAs are administered by the parenteral route
- high recombinant ESAs doses may increase cardiovascular risk
- recombinant ESAs may cause PRCA

New treatment strategies are needed

with a better safety profile than existing ESAs

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New strategies under development to stimulate erythropoiesis

Not Directly Targeting the EPO Receptor

- HIF stabilizers
  - FG-4592 (Roxadustat)
  - AKB-6548
  - GSK1278863
  - BAY 85-3934 (Molidustat)
  - JTZ-951
  - DS-1093a
- Activin traps
  - Sotatercept (ACE-011)
  - Luspatercept (ACE-536)
  - LY2157299

Targeting the EPO Receptor

- EPO mimetic peptides
  - Centocor molecules: CNTO 528, CNTO 530, CNTO 531
  - AplaGen GmbH: AGEM400(HES)
  - Peginesatide[a]
- EPO fusion proteins
  - EPO-EPO dimers
  - EPO-CPT
  - EPO-$(CPT)_3$
  - Albumin-EPO
  - EPO-hyFc (Genexine GX-E2)
- Antibody agonists to EPO receptor
  - Mouse monoclonal IgG
  - Ab12 molecule
  - Ab12.6 (Abbott Laboratories ABT-007) molecule
- EPO gene therapy (TARGT EPO)
- Dimerization of EPO receptor intracellular domain with a CID

Bonomini M. et al., Am. J. Kidney Dis., 2016, 67, 133-142

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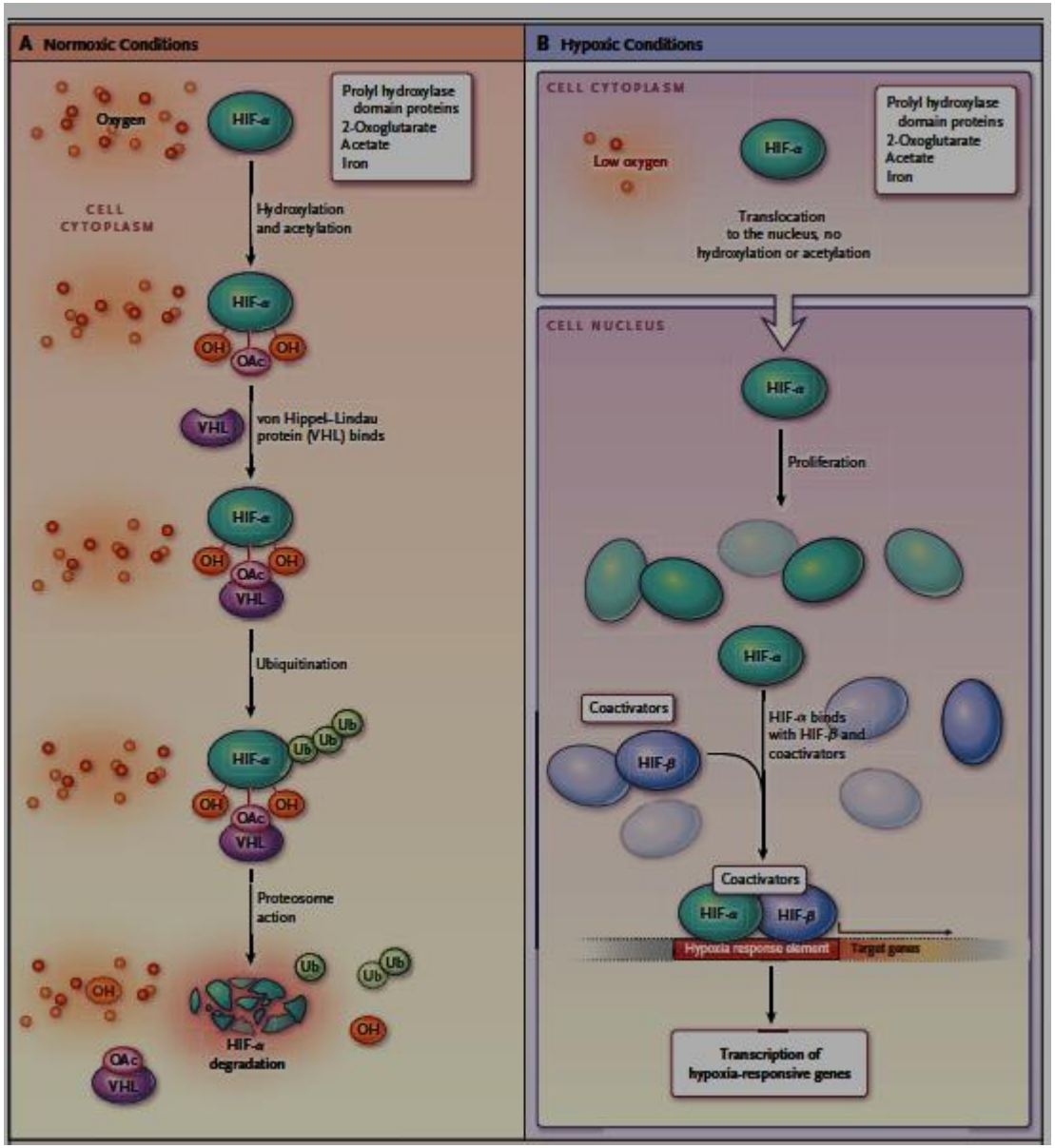
Role of Hypoxia-Inducible Factor α (HIF- α) under normoxic and hypoxic conditions



West J.B., N. Engl. J. Med., 2017, 376, 1965-1971

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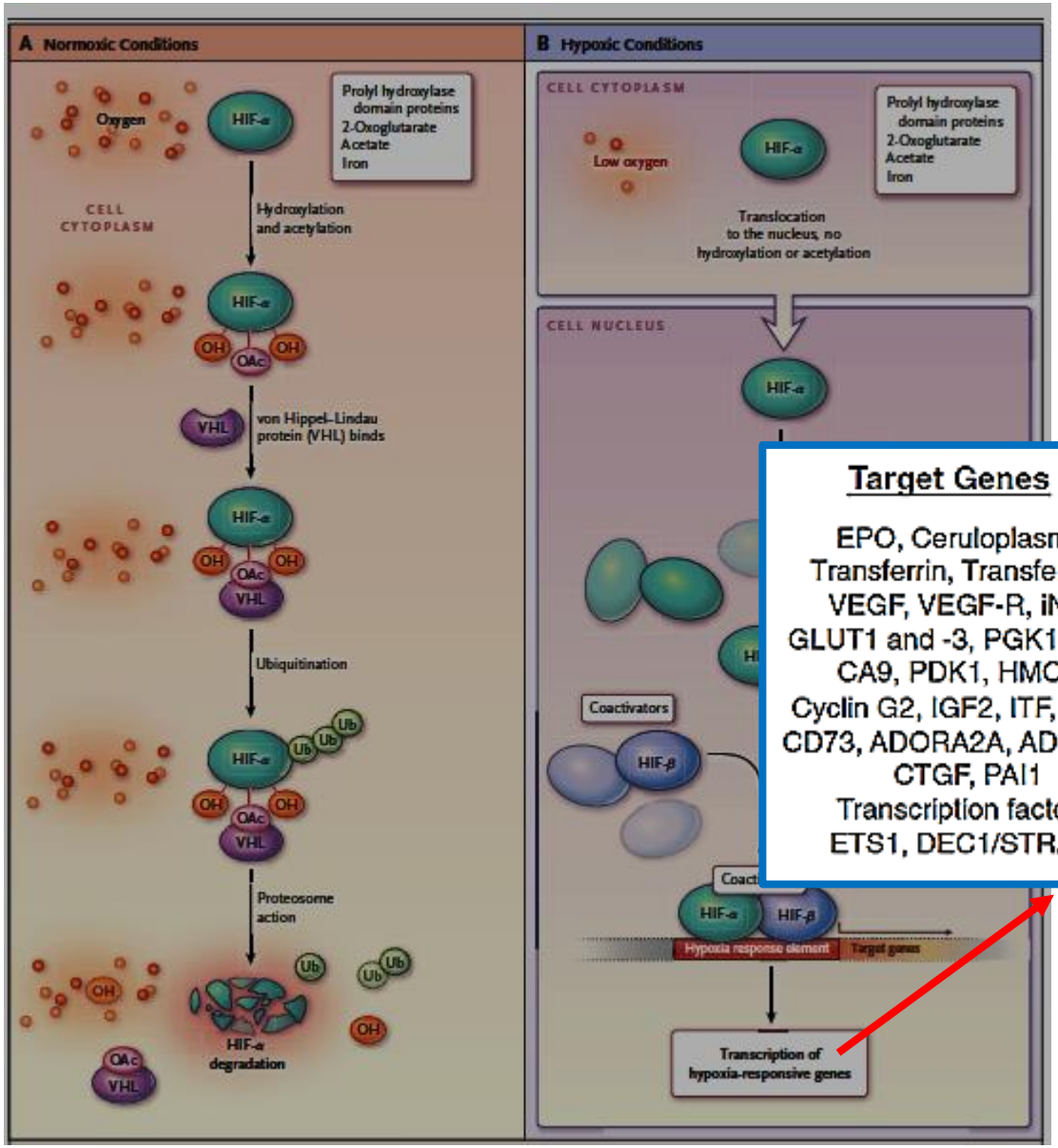
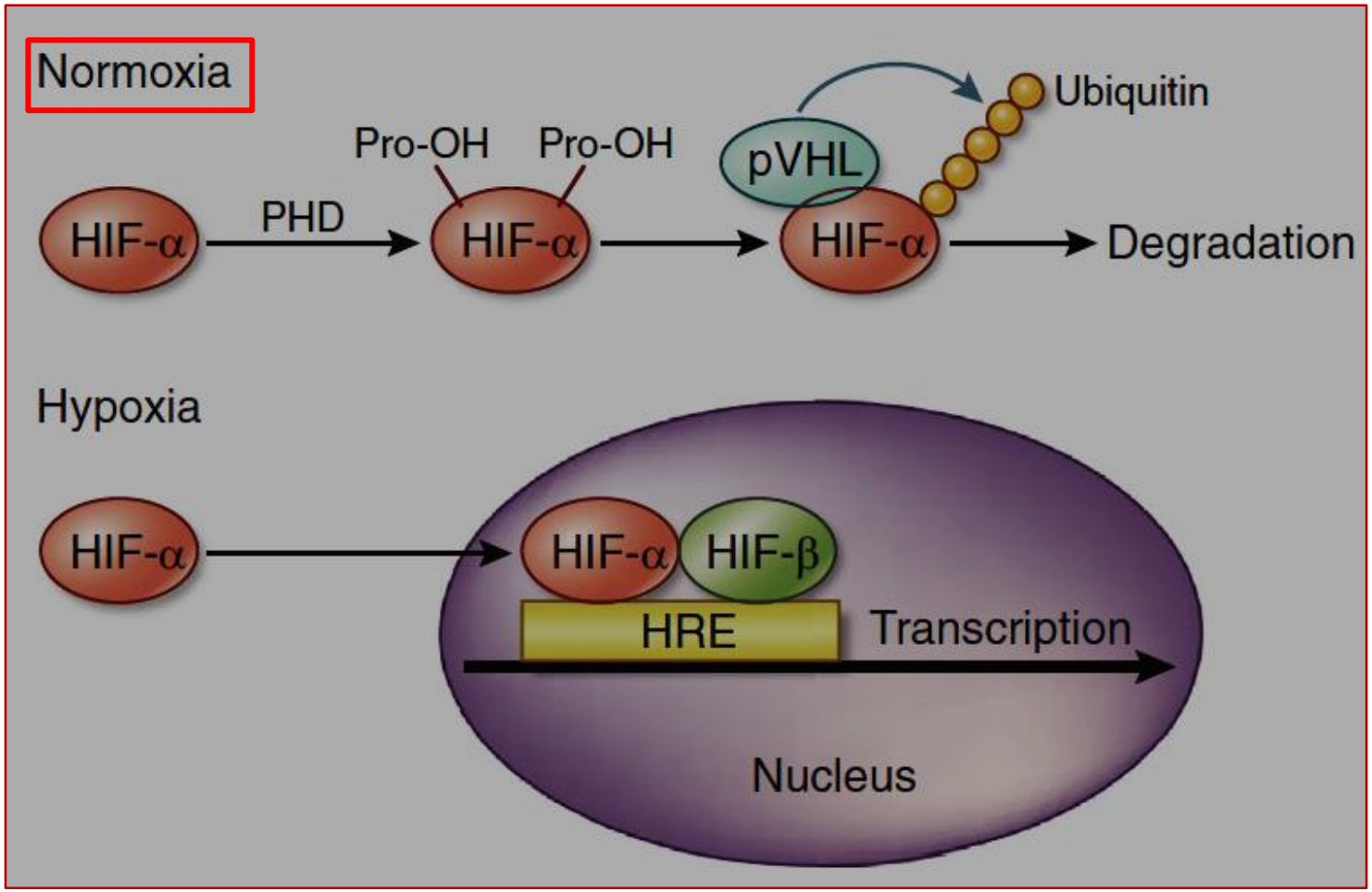


Target Genes	Adaptation to Hypoxia
EPO, Ceruloplasmin, Transferrin, Transferrin R	Erythropoiesis / Iron metabolism
VEGF, VEGF-R, iNOS	Angiogenesis / Vasculogenesis
GLUT1 and -3, PGK1, LDHα, CA9, PDK1, HMOX1	Metabolic adaptation / Glycolysis
Cyclin G2, IGF2, ITF, MDR1	Mitochondrial function
CD73, ADORA2A, ADORA2B	Proliferation / Cell survival
CTGF, PAI1	Cellular barrier function
Transcription factors: ETS1, DEC1/STRA13	Extracelluar matrix production
	Cell migration

West J.B., N. Engl. J. Med., 2017, 376, 1965-1971

Prolyl hydroxylase domain - hypoxia-inducible factor (PHD-HIF) oxygen - sensing system



Sugahara M. et al., Kidney Int. 2017., 92, 306-312

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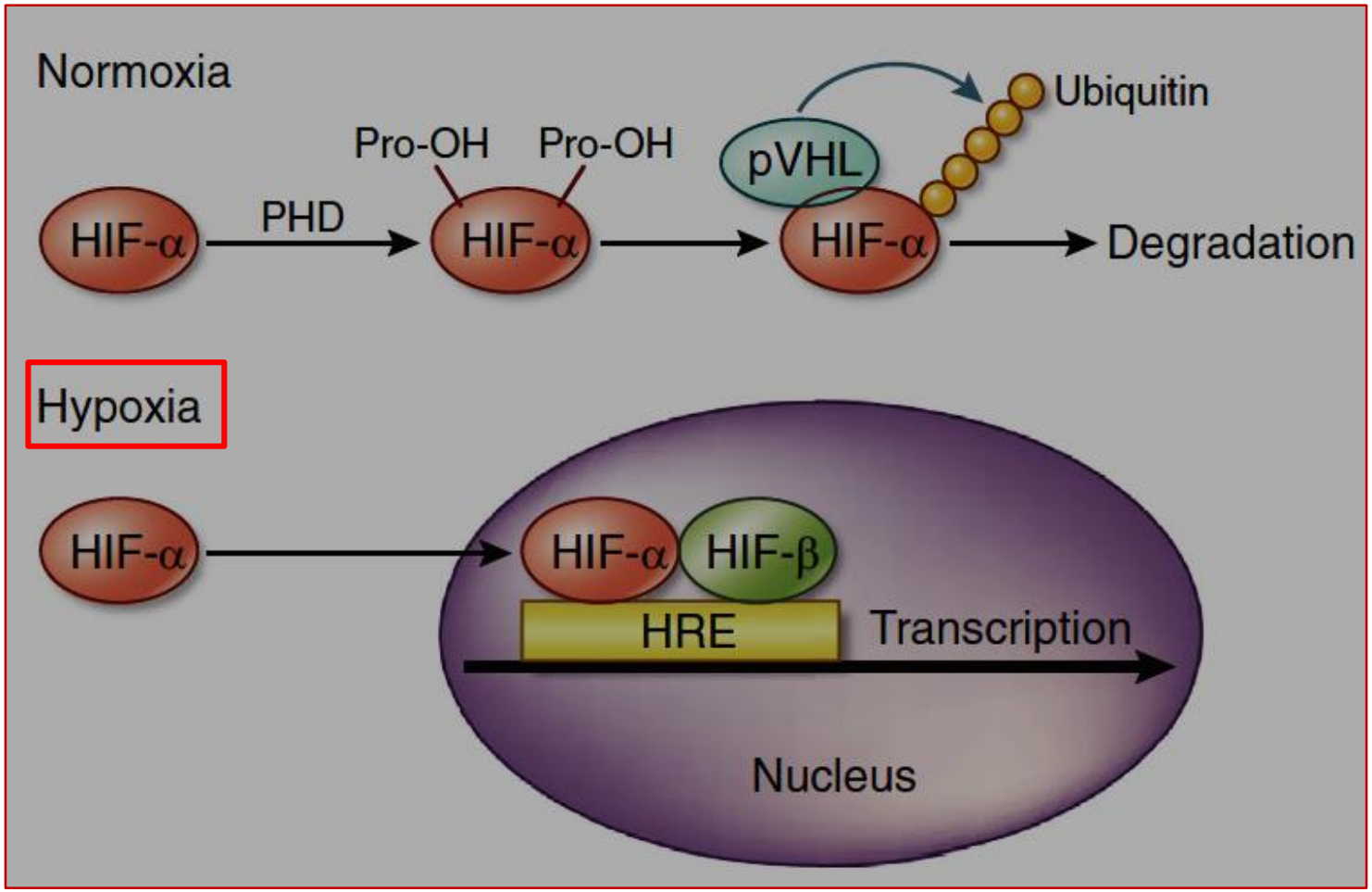

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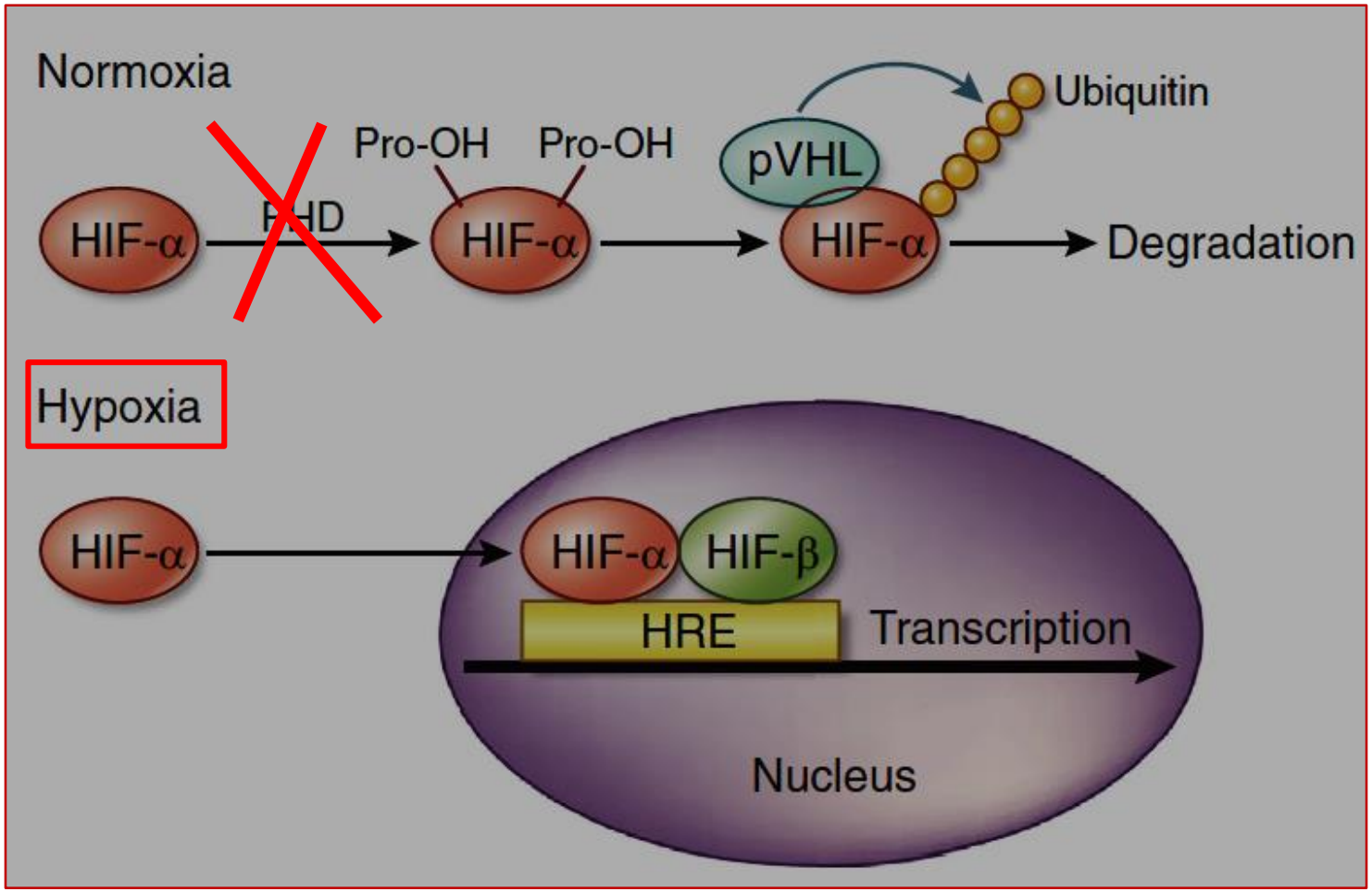

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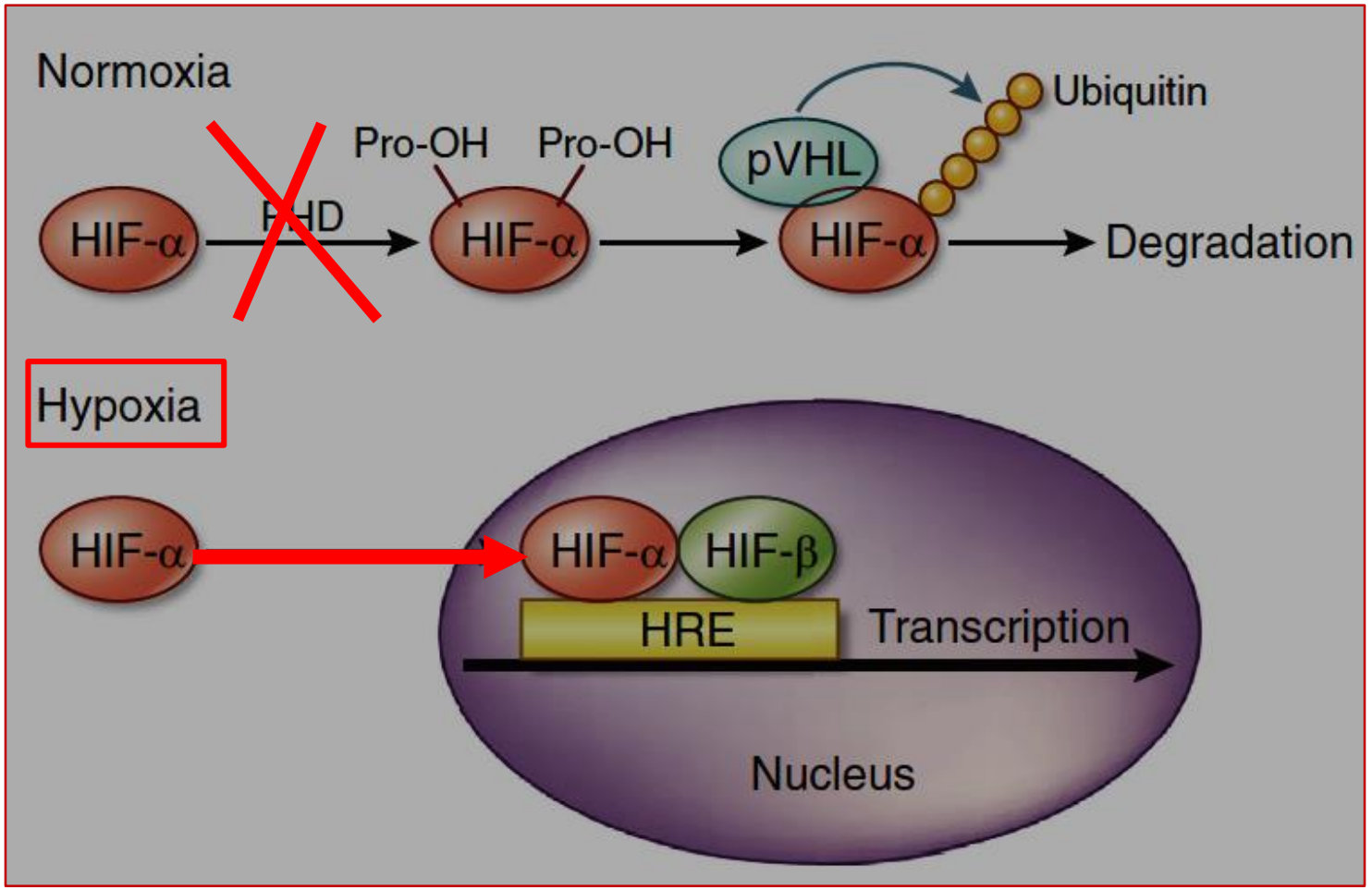

Sugahara M. et al., Kidney Int. 2017., 92, 306-312

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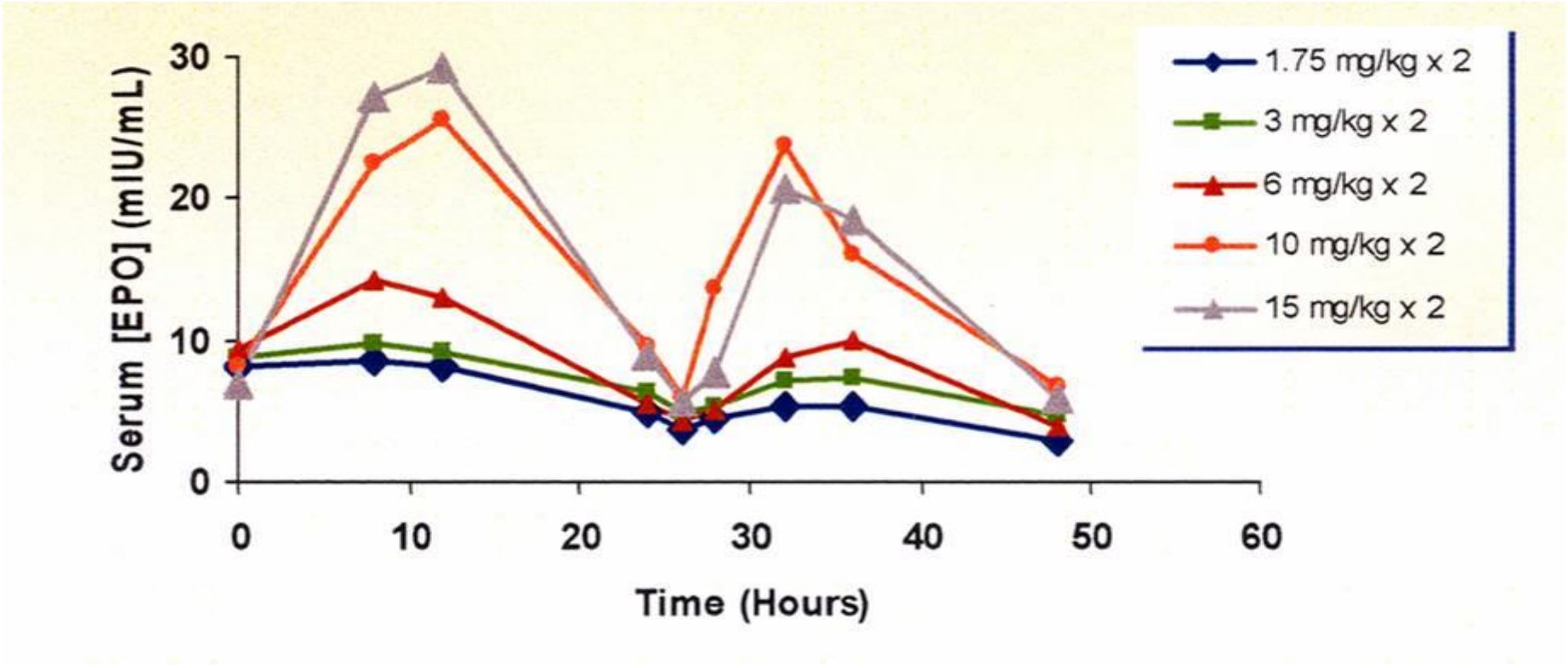
Dose-related induction of endogenous serum EPO after FG-2216 p.o.



No desensitization in EPO response following repeated dosing with FG-2216

Urquilla P et al.: J Am Soc Nephrol 2004; 15: 546A

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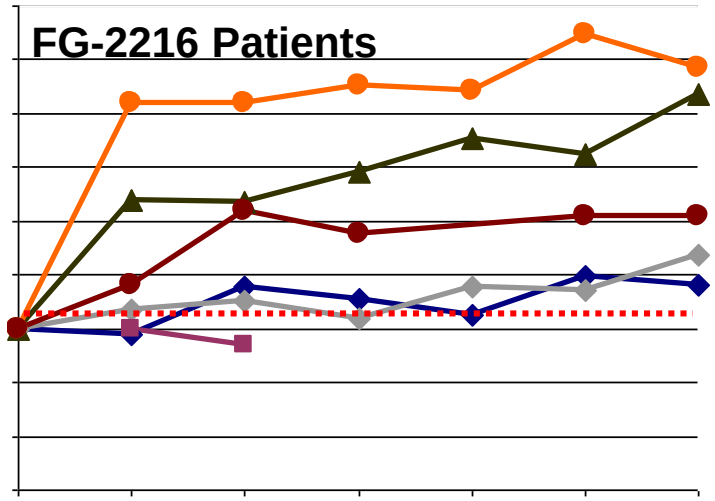
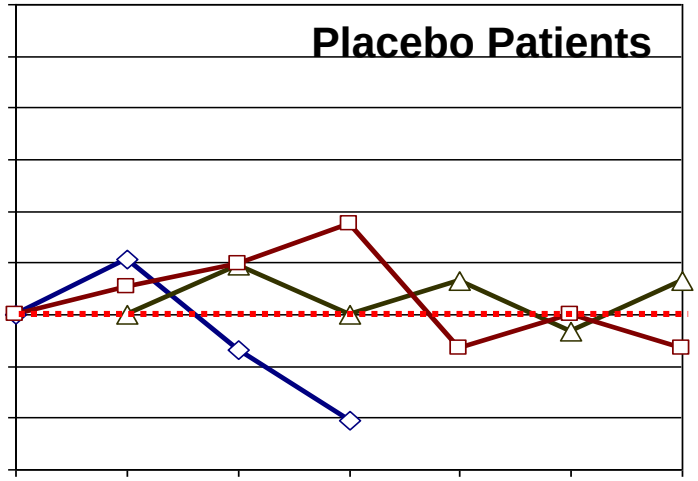
Phase 2a (rHuEPO- naïve): Individual haemoglobin response to FG-2216 vs. Placebo – change from baseline

6 mg/kg group (first cohort, rHuEPO-naïve, predialysis patients)

Treatment Group	Mean Baseline Hb (g/dL)	Mean change from Baseline Hb (g/dL) Day 42* (or last value carried forward)
FG-2216 (n=5)	9.6	1.9
Placebo (n=3)	9.8	-0.35

*Difference between treatment and placebo group is statistically significant (Mann – Whitney rank sum test), p = 0.036



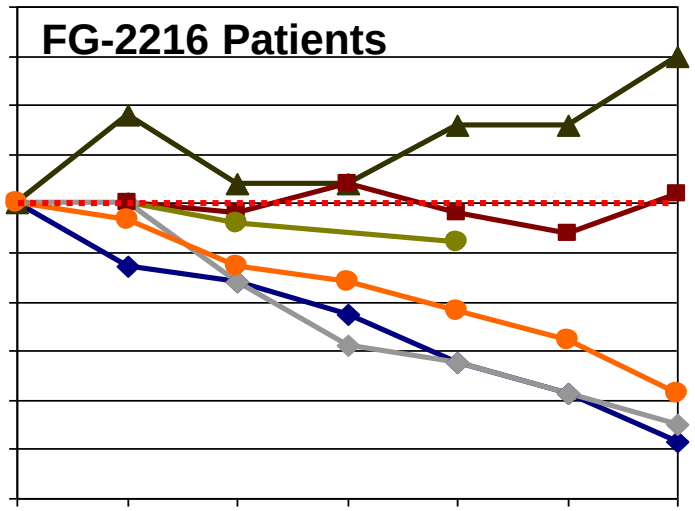


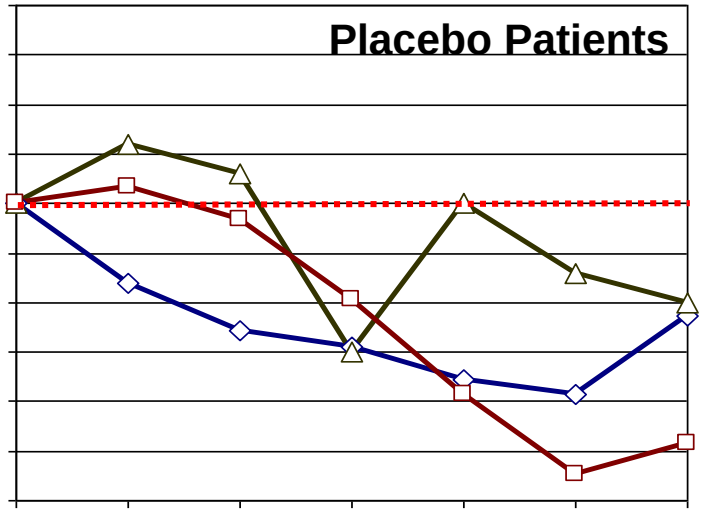
Wiecek A et al.: XLII ERA-EDTA Annual Congress June 2005, Istambul, Turkey

Phase 2a (rHuEPO-treated): Individual haemoglobin response to FG-2216 vs Placebo – change from baseline

6 mg/kg group (first cohort, rHuEPO-treated, predialysis patients)

Treatment Group	Mean Baseline Hb (g/dL)	Mean change from Baseline Hb (g/dL) Day 42* (or last value carried forward)
FG-2216 (n=6)	11.7	-0.9
Placebo (n=3)	11.5	-1.5





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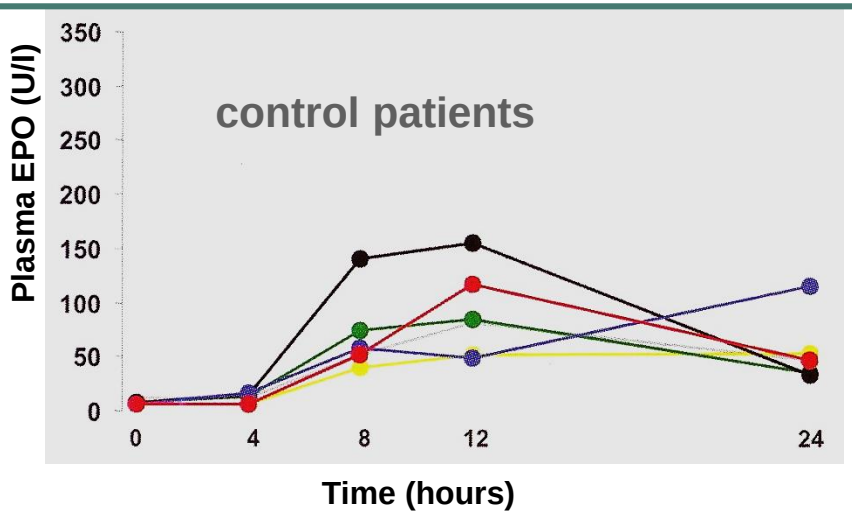
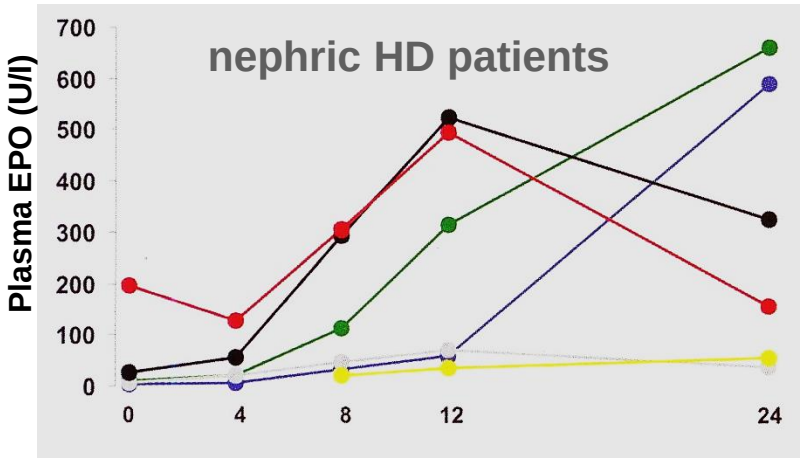
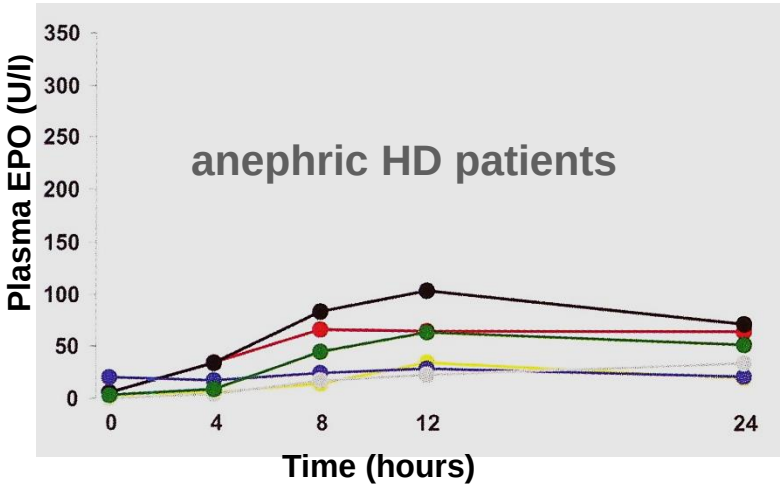
FG-2216 increases plasma-EPO levels in healthy controls and in HD patients with and without remaining renal tissue

24-hour kinetics of plasma EPO levels after a single dose of FG-2216







Bernhardt et al. Am. J. Soc. Nephrol., 2010; 21:2151-2156

HIF PHIs in development

Company	Molecule	Drug name	Phase of development
FibroGen Astellas Astra Zeneca	FG-4592	Roxadustat	Phase 3
GSK	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

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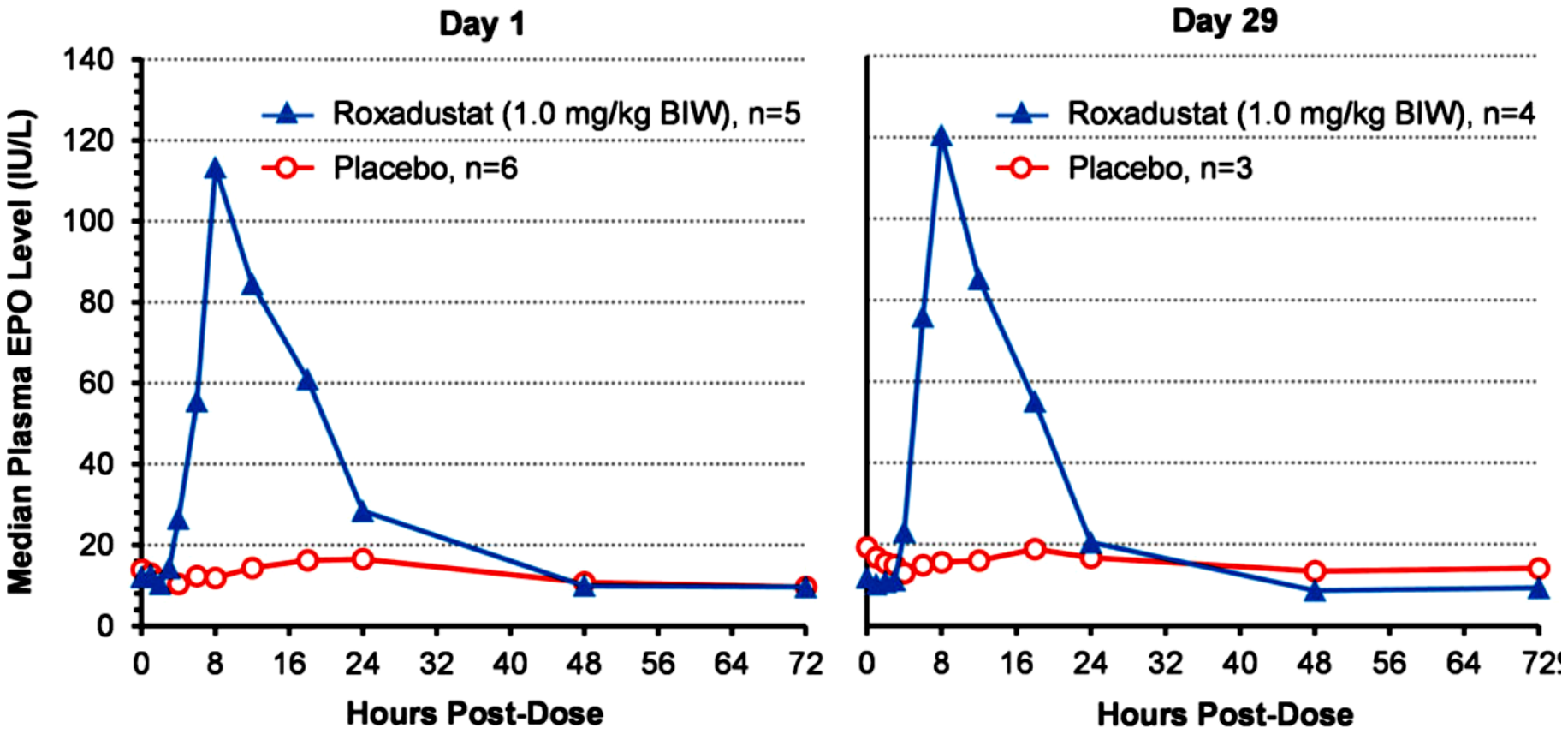
Changes in plasma EPO levels on first and final days of treatment with FG-4592 (Roxadustat) or placebo in non dialyzed CKD patients



No desensitization in EPO response following repeated dosing with FG-4592

Besarab A. et al. Nephrol. Dial. Transplant., 2015, 30: 1665–1673

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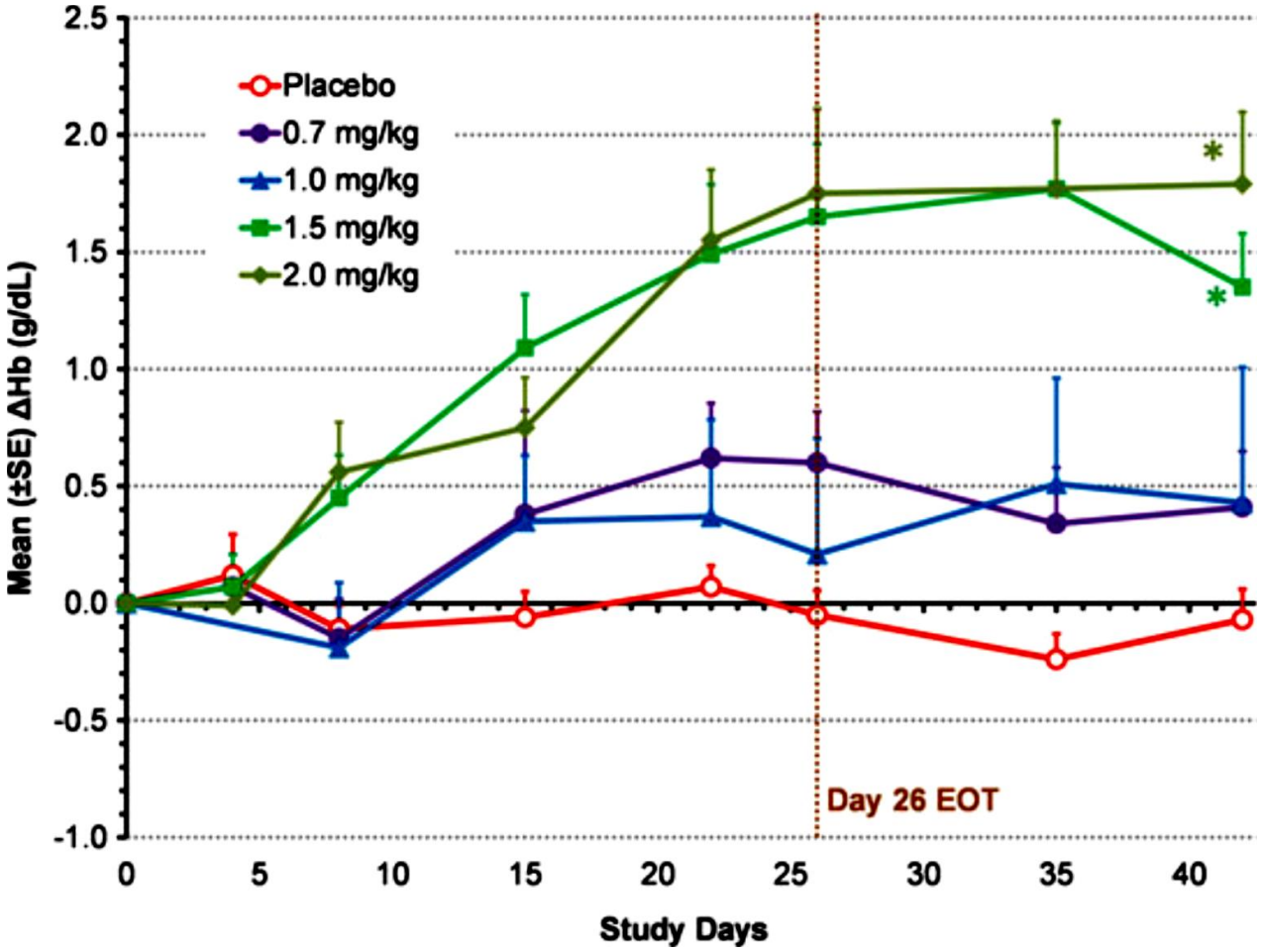
Mean change from baseline in Hb (ΔHb). CKD patients (non dialyzed) treated with different doses of FG 4562 (Roxadustat)



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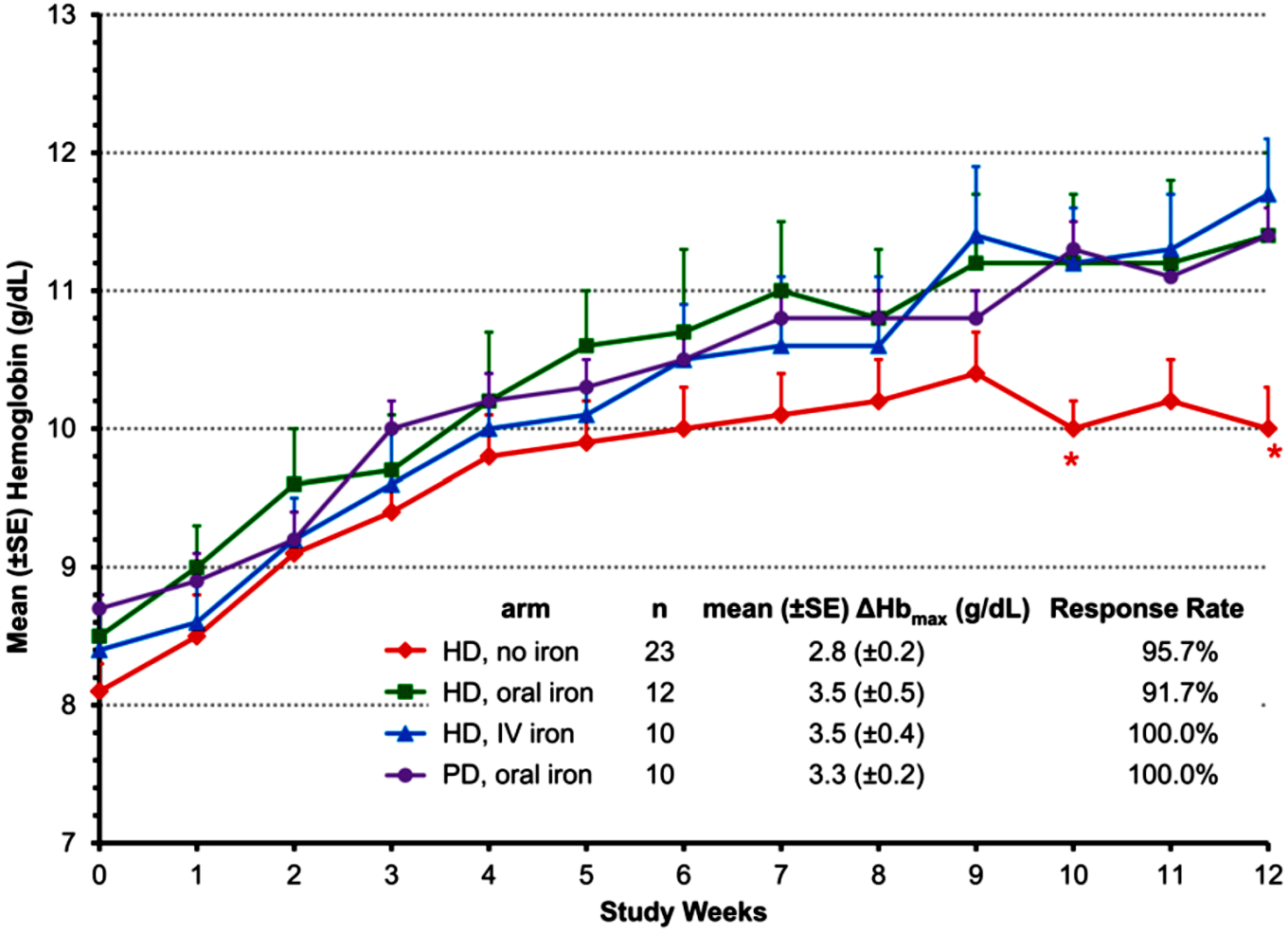
Mean hemoglobin levels over time in HD and PD patients treatd with Roxadustat (FG-4592) given orally



Besarab A. et al., J. Am. Soc. Nephrol.,2016, 27: 1225–1233

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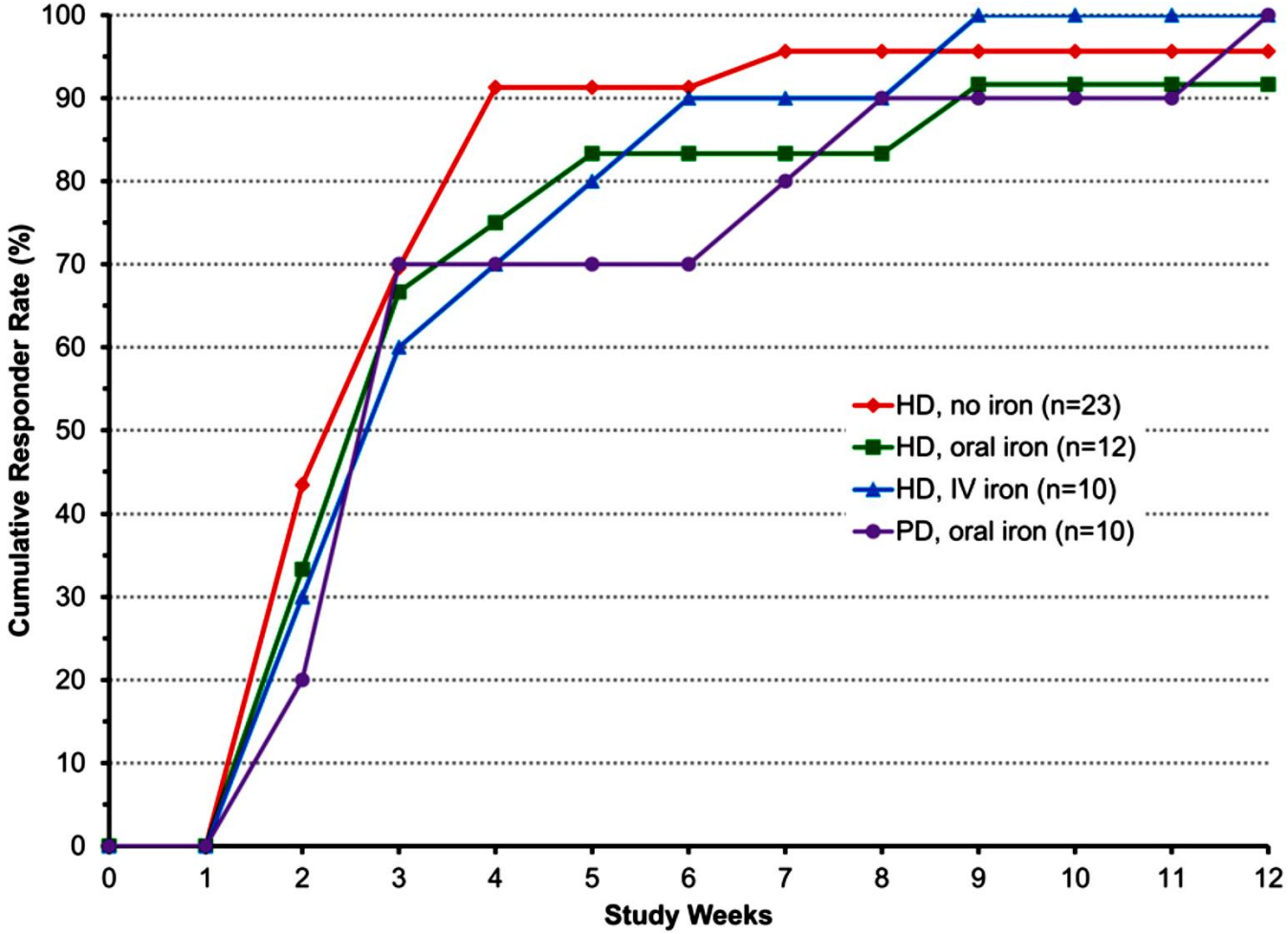
Cumulative Hb responses in HD and PD patients treated with Roxadustat (FG-4592) given orally



Besarab A. et al., J. Am. Soc. Nephrol.,2016, 27: 1225–1233

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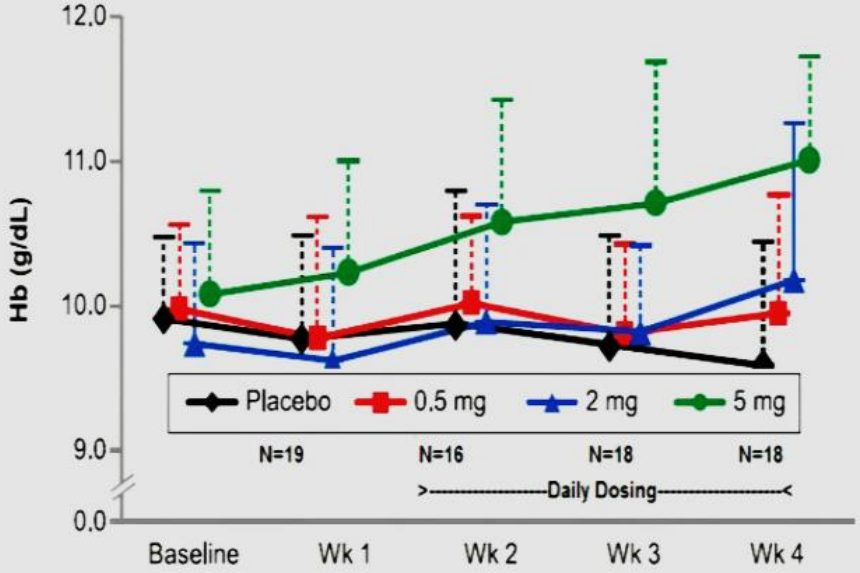
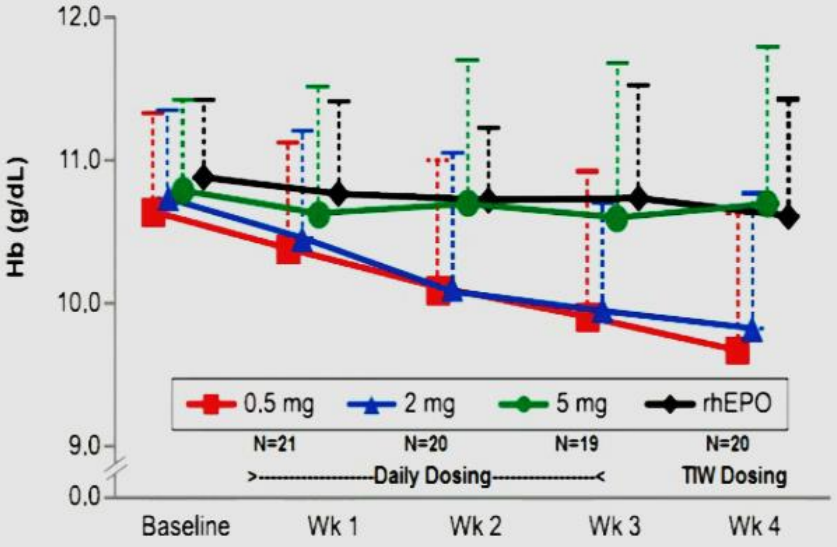
Effect of Daprodustat (GSK1278863) on blood haemoglobin concentration in CKD patients

Hemoglobin



GSK1278863 (Daprodustat) increases hemoglobin at 5 mg daily in CKD Patients
(Holdstock L, J Am Soc Nephrol, 27: 1234, 2016)



GSK1278863 (Daprodustat) is equally effective at maintaining hemoglobin as EPO at 5 mg daily dose in Dialysis Patients (Holdstock L, J Am Soc Nephrol, 27: 1234, 2016)

Holdstock L. et al., J. Am.Soc. Nephrol., 2016, 27, 1234 - 1244

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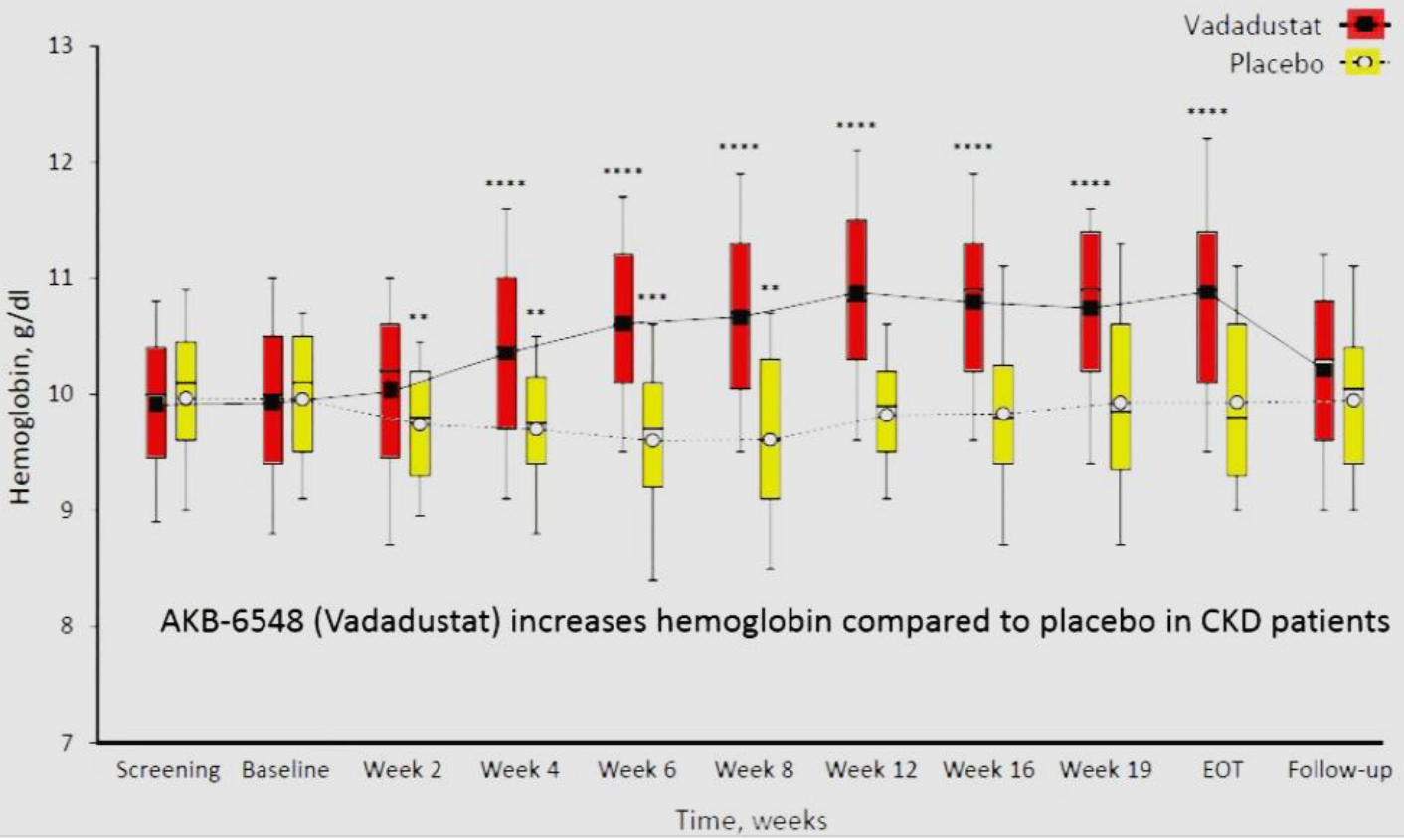
Effect of Vadadustat (AKB-6548) on blood Hb concentration in CKD patients

Hemoglobin



Pergola P.E. et al. Kidney Int., 2016, 90, 1115-1122

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Medical need for HIF-stabilizers - *pro*

- HIF inhibitors are orally - active (could provide in the future a more convenient and cost-effective therapy for anaemia of chronic kidney disease than protein - based therapeutics)

- They may stimulate erythropoiesis with much lower EPO levels (given some concerns about clinical outcomes arising from use of ESAs that cause supraphysiologic circulating EPO levels, use of agents producing transient, more physiologic increases in endogenous EPO may have significant benefit in the treatment anaemia in patients with CKD)

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Medical need for HIF-stabilizers - *contra*

- Potential and unpredictable adverse effects (rare development of severe liver toxicity)
- Several other (hundreds?) genes are also activated (e.g. VEGF)
- Larger and long - term clinical trials are needed (in order to document the safety profile and final clinical benefits of these new compounds)

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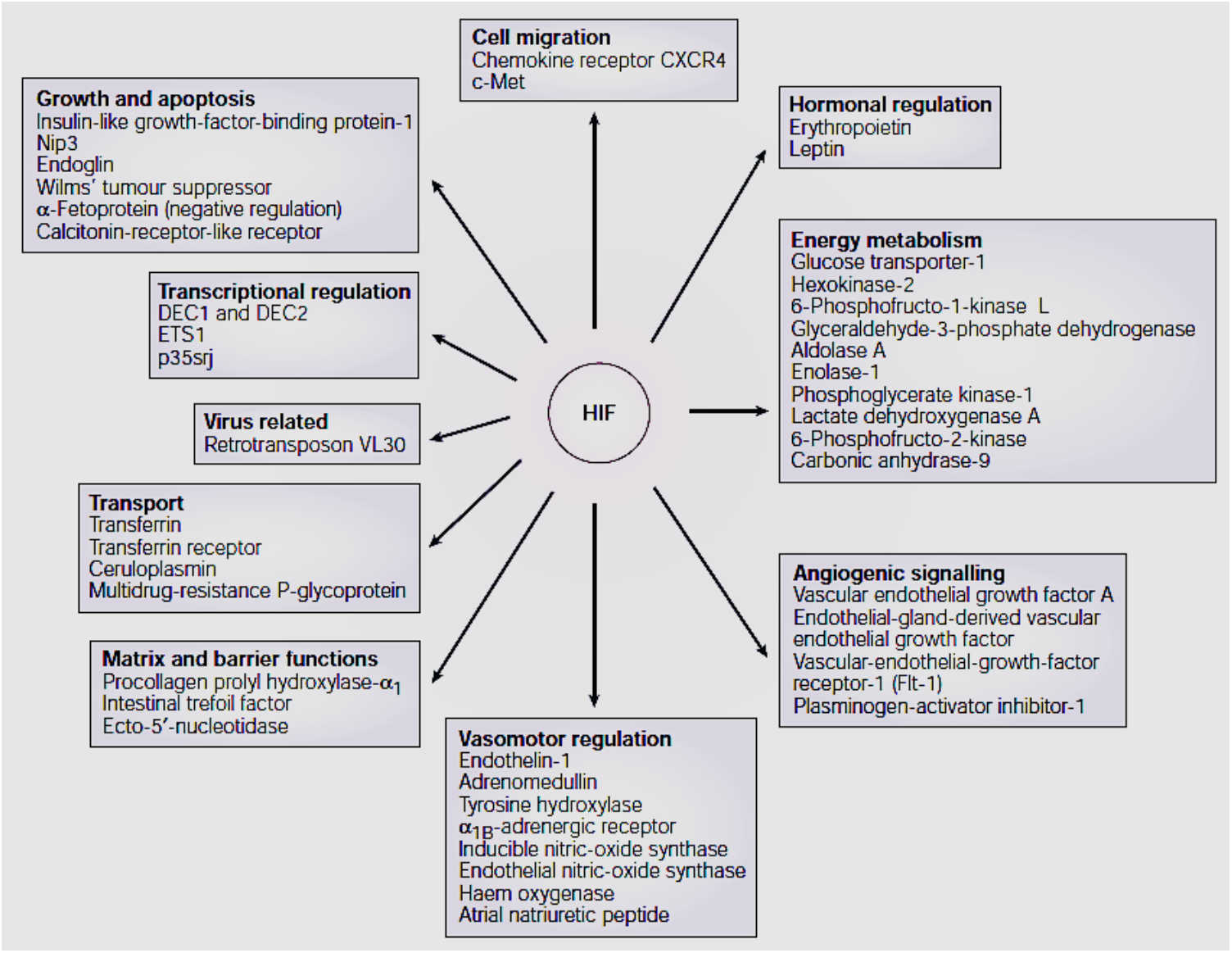
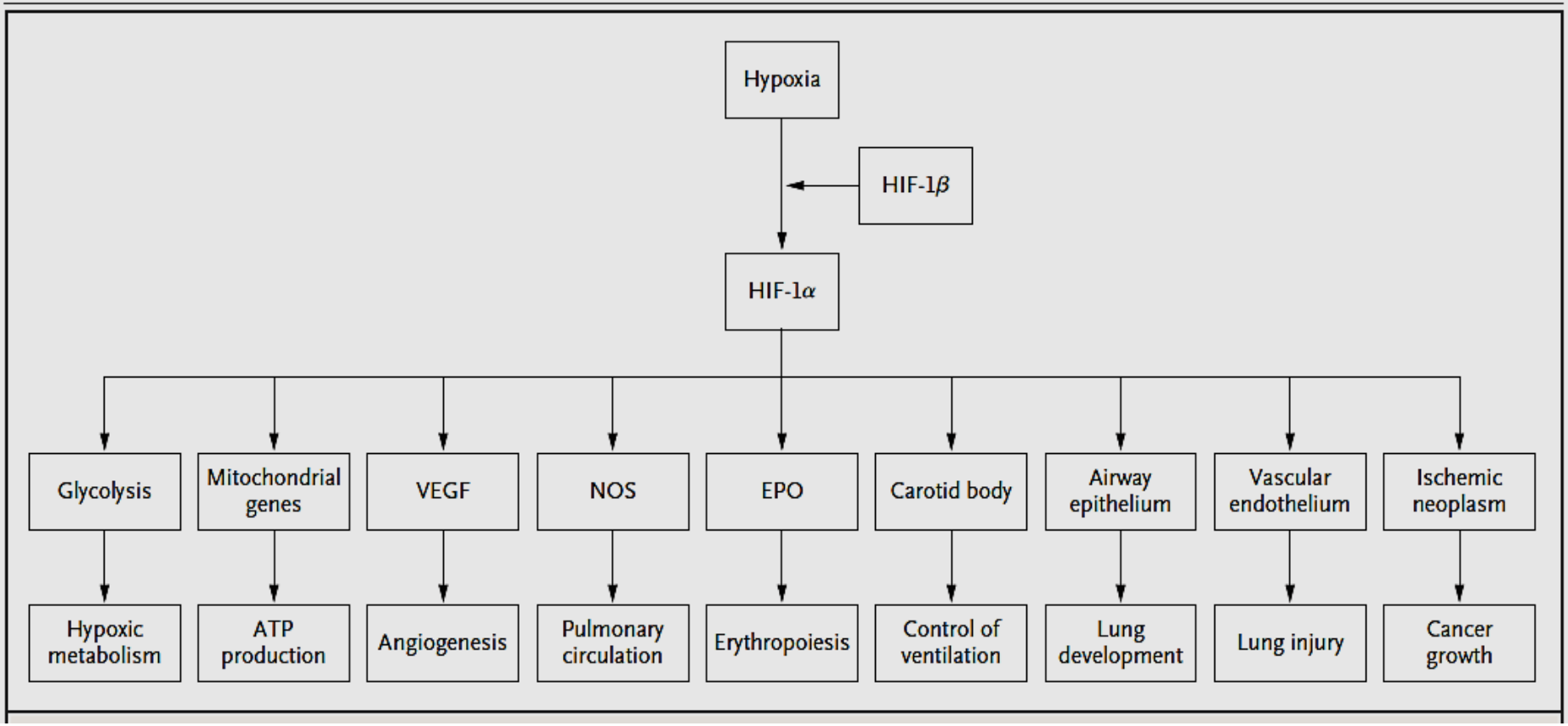
Direct transcriptional targets of HIF



Schofield C.J., Ratcliffe P.J., Nature Rev. Mol. Cell Biol., 2004, 5, 343 - 354

Leading European Nephrology

The spectrum of physiological responses to HIF 1α



West J.B., N. Engl. J. Med., 2017, 376, 1965-1971

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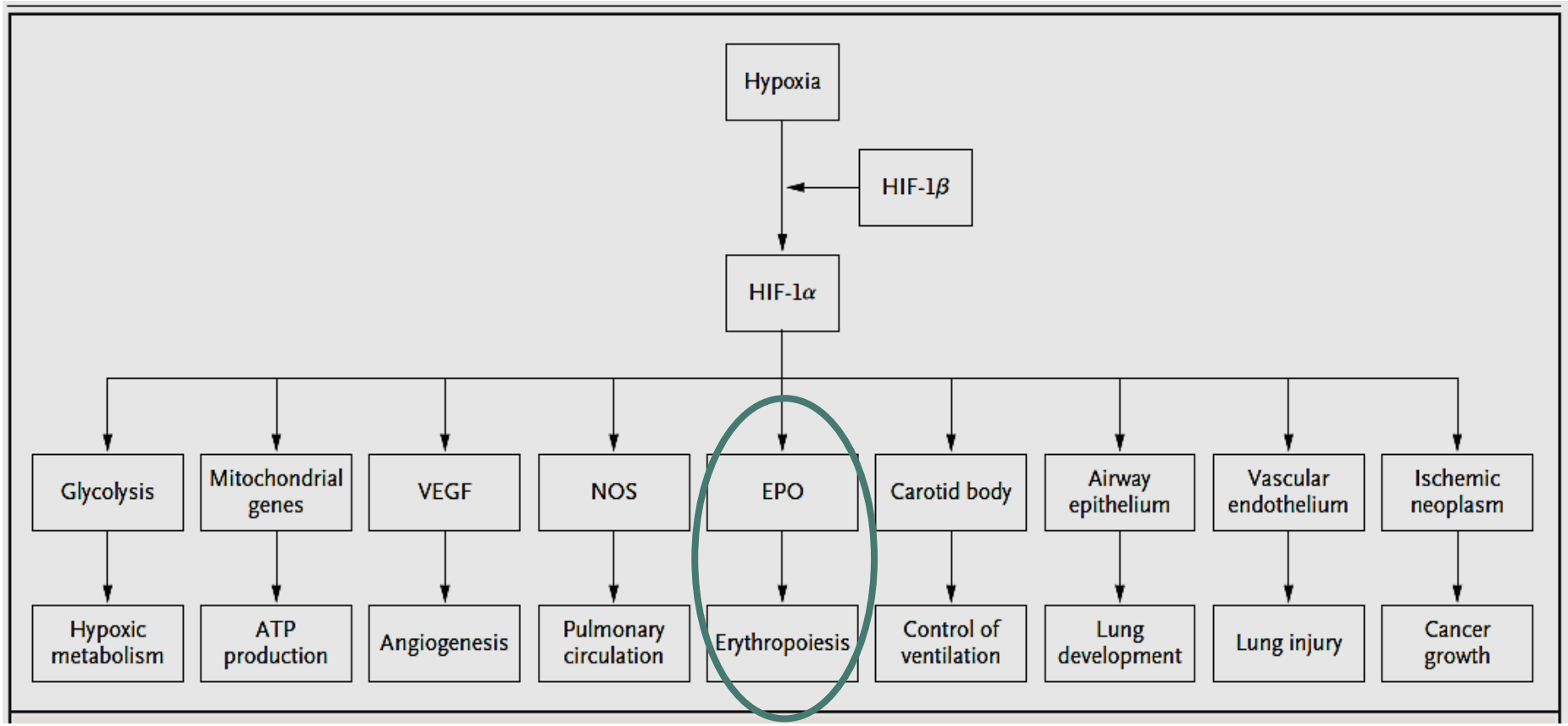
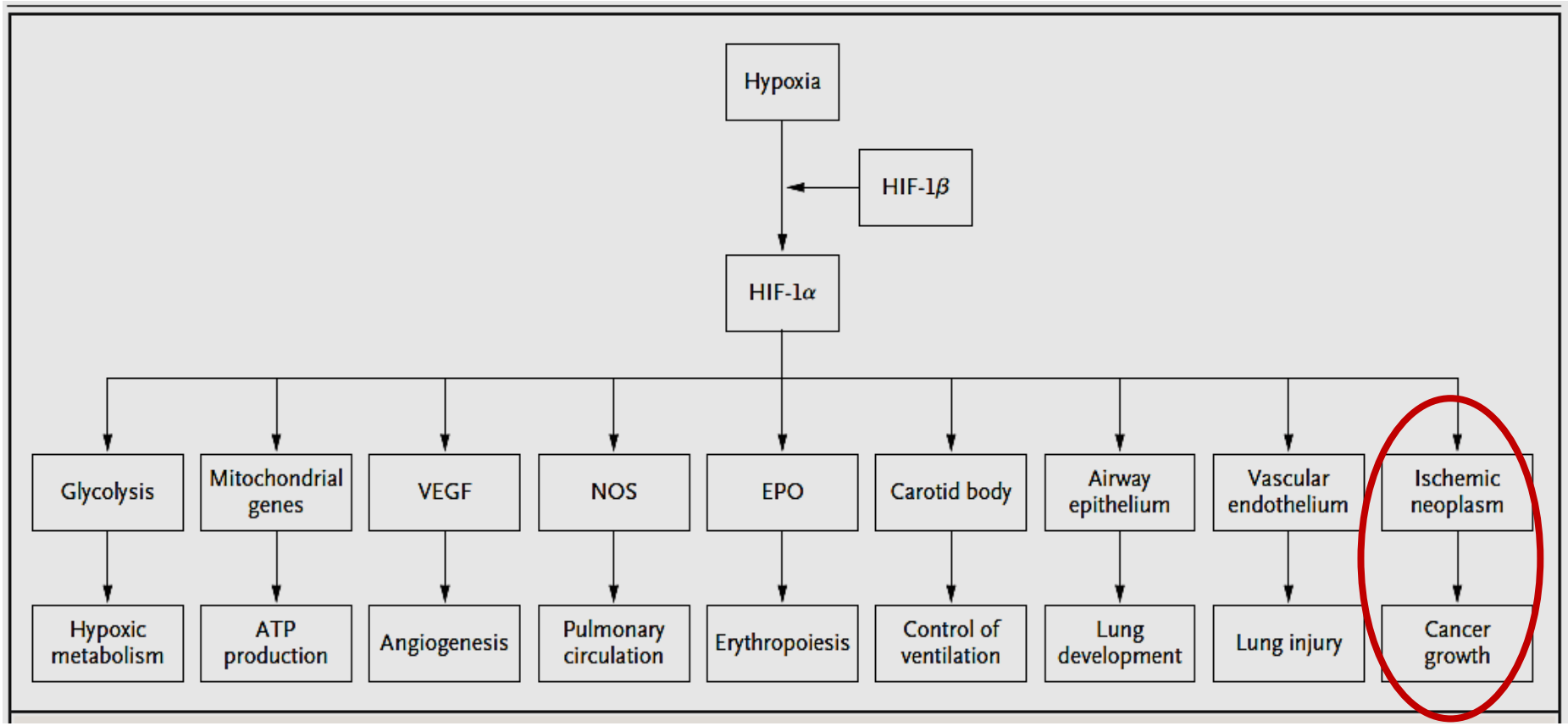


West J.B., N. Engl. J. Med., 2017, 376, 1965-1971

The spectrum of physiological responses to HIF 1α



West J.B., N. Engl. J. Med., 2017, 376, 1965-1971

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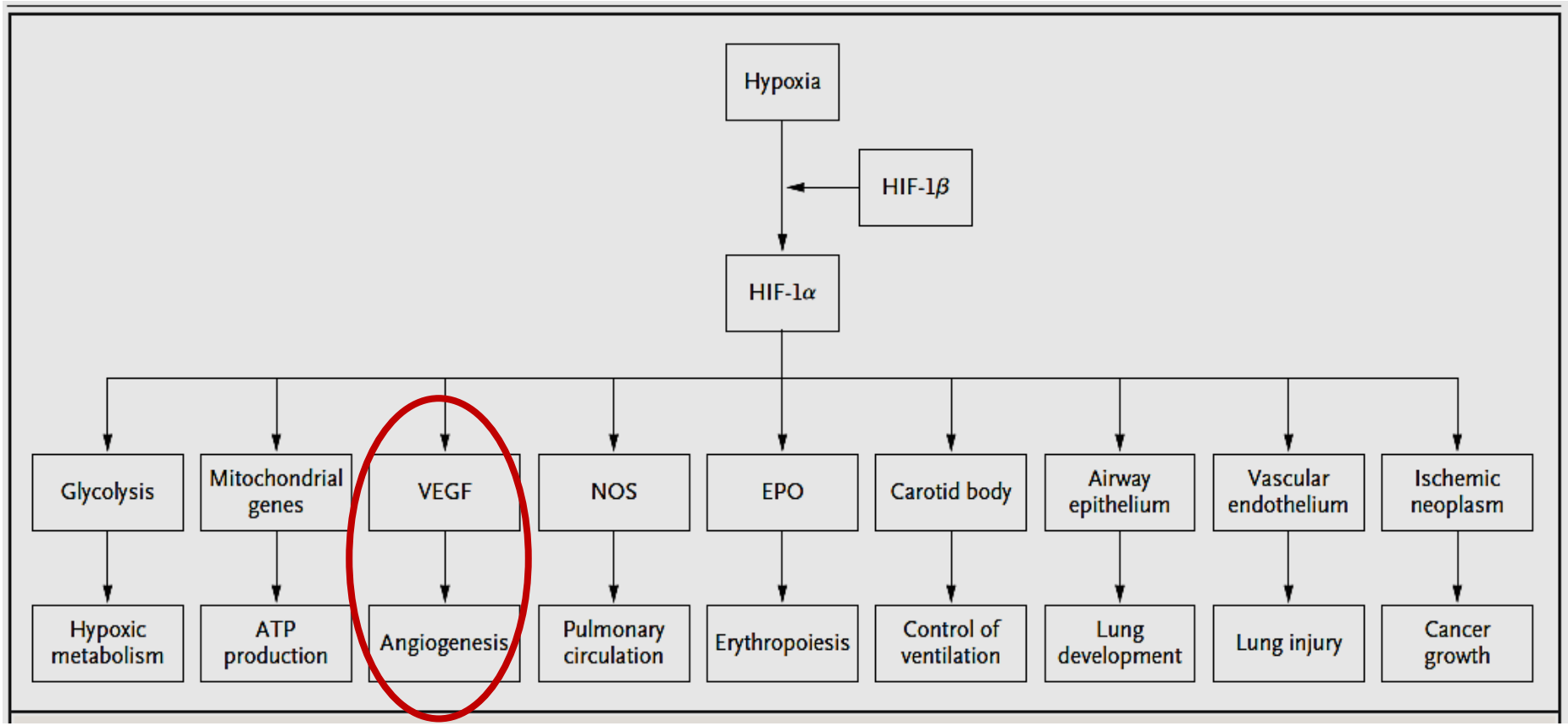
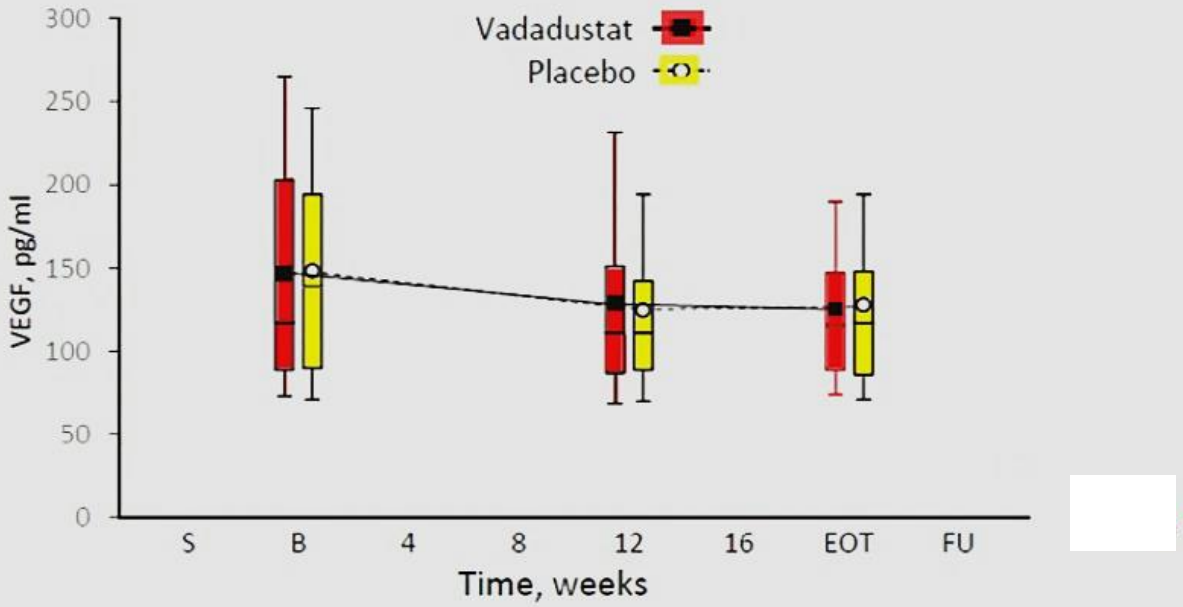


West J.B., N. Engl. J. Med., 2017, 376, 1965-1971

Leading European Nephrology

Plasma levels of VEGF after 12 weeks and at the end of the trial in CKD patients treated with Vadadustat

AKB-6548 (Vadadustat) and VEGF

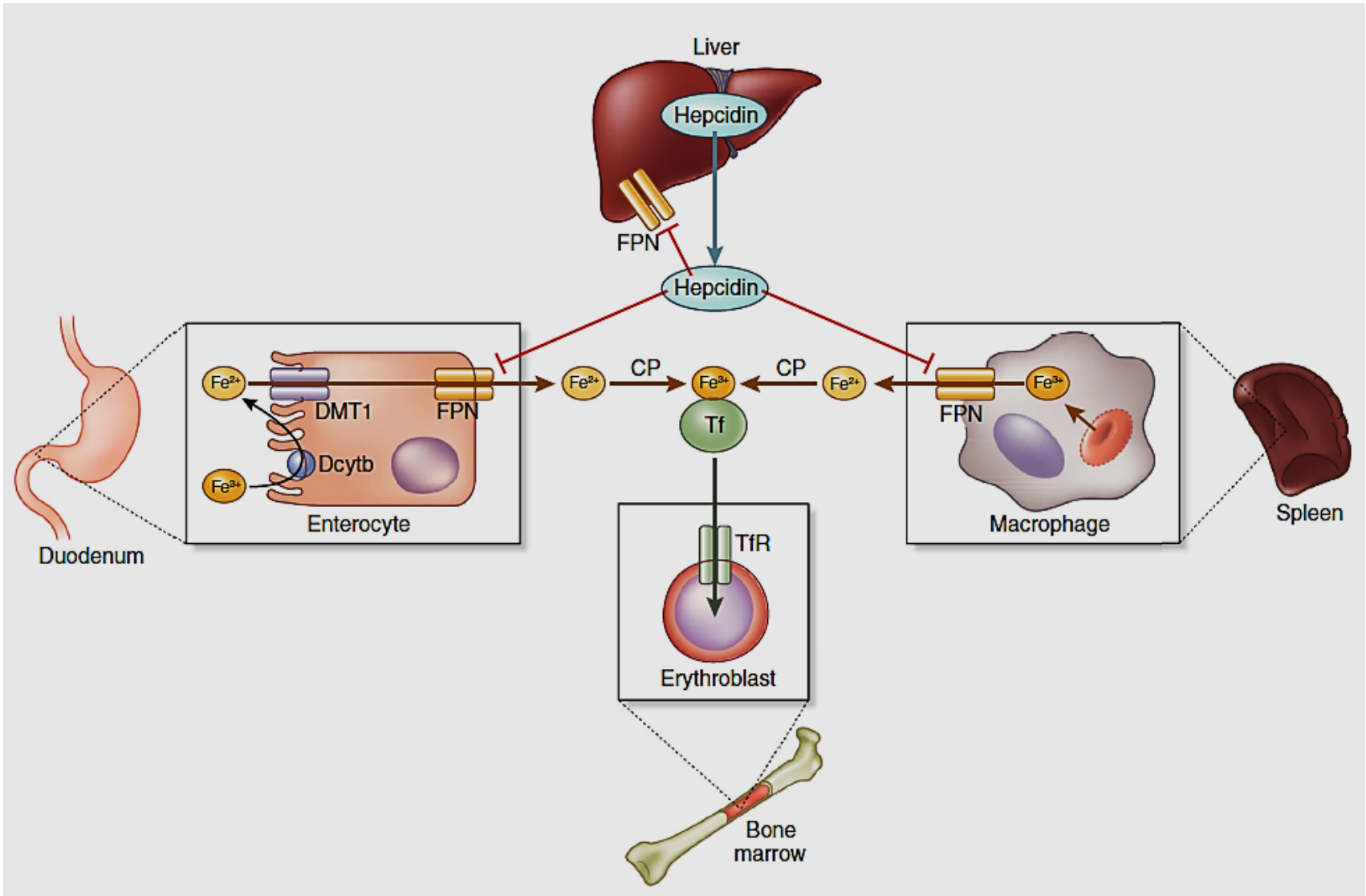


VEGF concentrations do not meaningfully differ between Vadadustat and Placebo

Pergola P.E. et al. Kidney Int., 2016, 90, 1115-1122

Leading European Nephrology

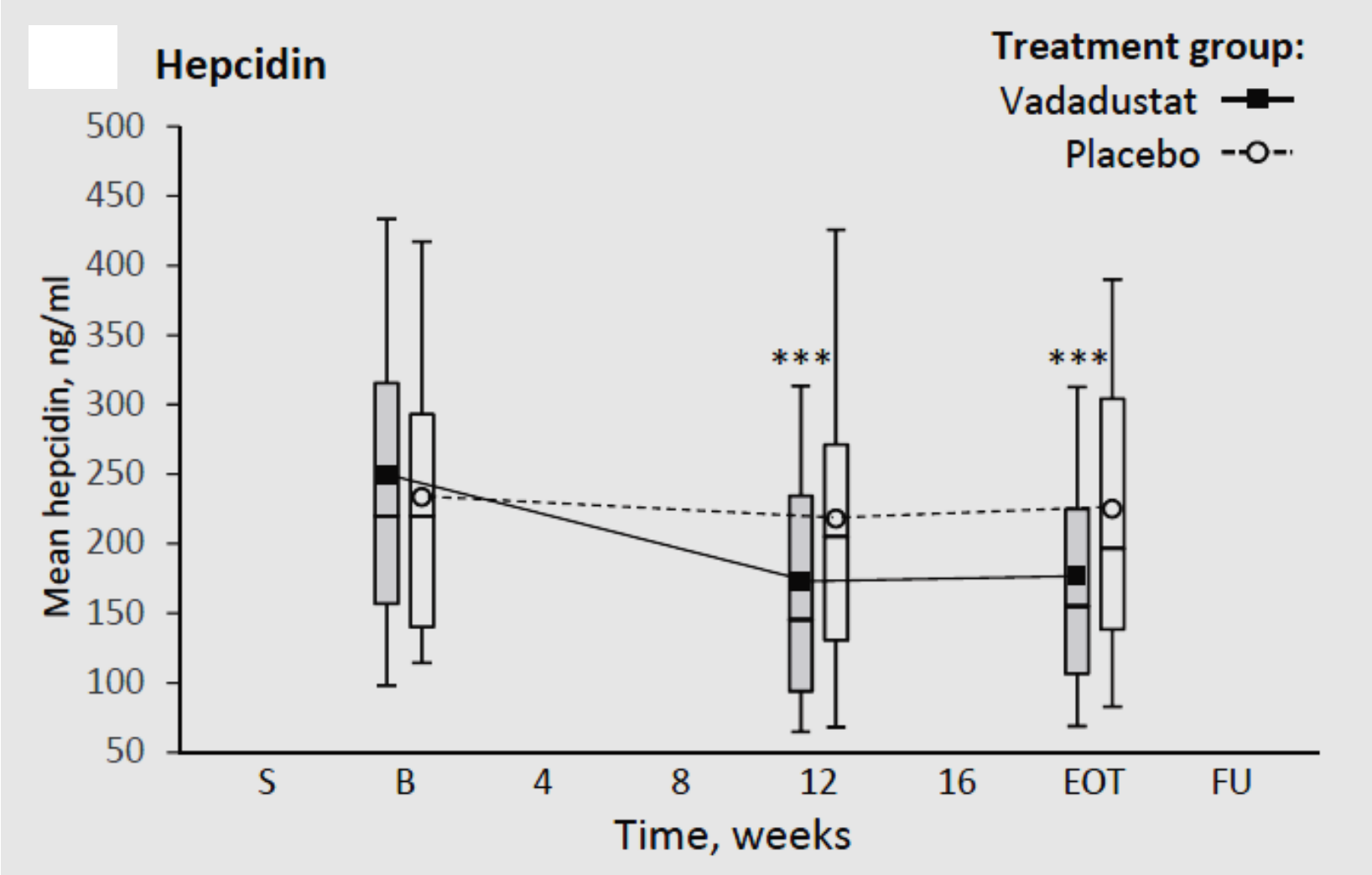
Role of hepcidin in the iron metabolism



Sugahara M. et al., Kidney Int. 2017., 92, 306-312

Leading European Nephrology

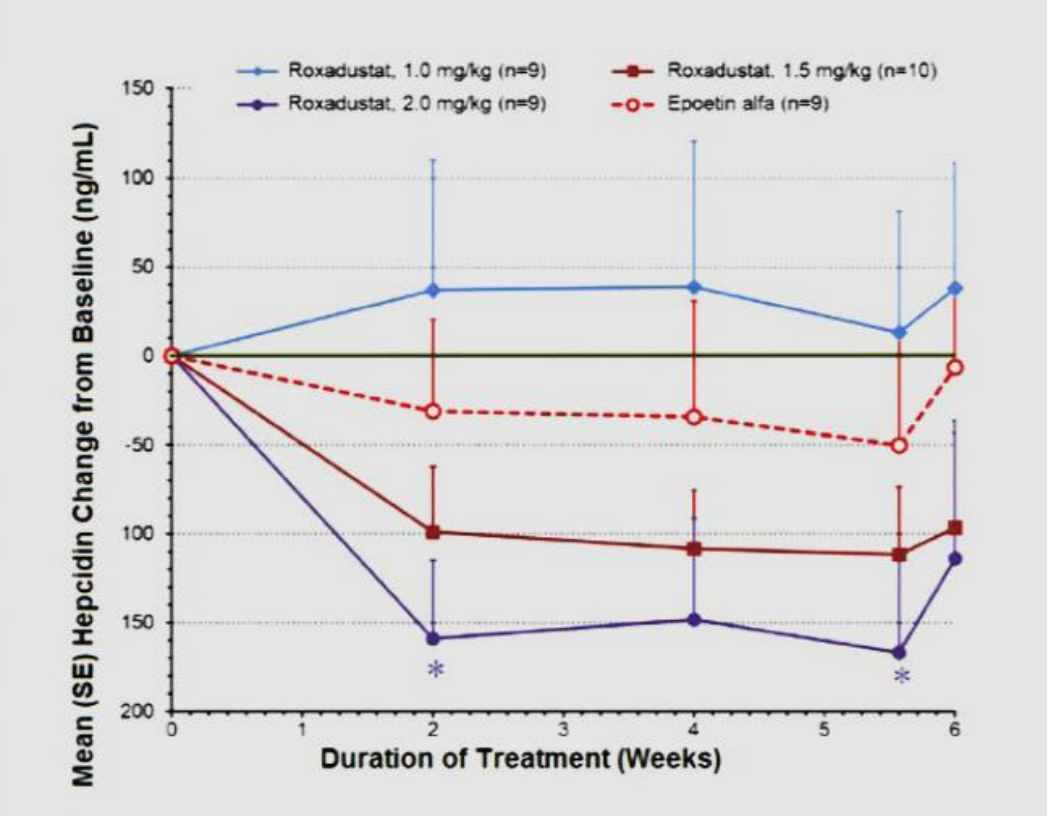
Plasma levels of hepcidin after 12 weeks and at the end of the trial in CKD patients treated with Vadadustat



Pergola P.E. et al. Kidney Int., 2016, 90, 1115-1122

Leading European Nephrology

FG-4592 (Roxadustat) lowers plasma hepcidin concentration in a dose dependent manner in dialysis patients

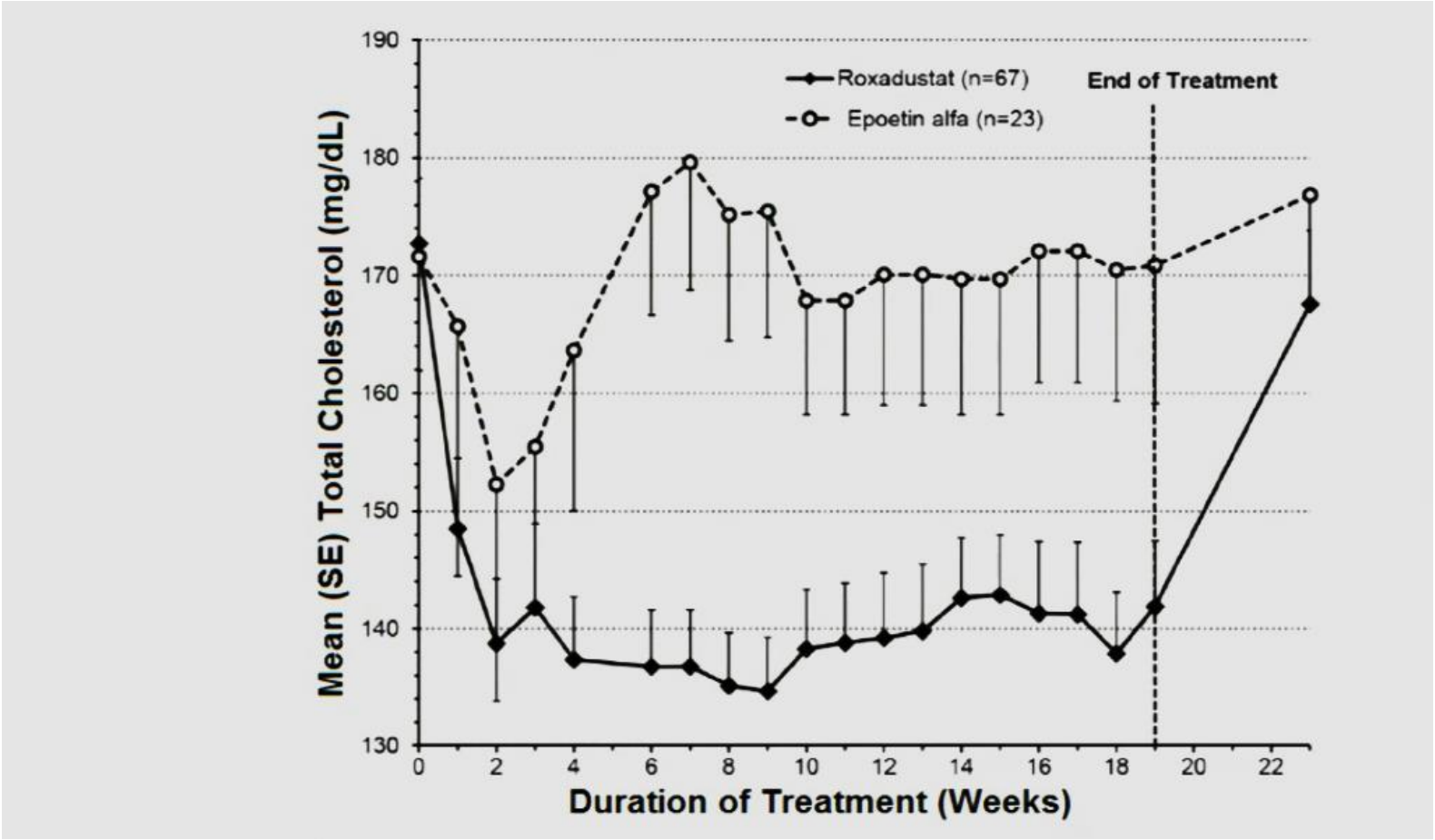


Mean (SE) hepcidin change from baseline

Unpublished data

Leading European Nephrology

FG-4592 (Roxadustat) lowers serum total cholesterol concentration in dialysis patients



FG-4592 (Roxadustat) lowers serum total cholesterol concentration in dialysis patients

Unpublished data

Leading European Nephrology

GSK1276833 (Daprodustat) lowers serum total cholesterol and LDL cholesterol in a dose dependent manner in CKD patients

Analyte	Parameter	Non-Dialysis Study			
			GSK1278863		
		Placebo (N=19)	0.5 mg (N=16)	2 mg (N=18)	5 mg (N=18)
Total cholesterol (mmol/L)	n	19	16	17	18
	Baseline	4.1	4.5	3.9	4.2
	95% CI	3.7, 4.6	3.8, 5.2	3.4, 4.6	3.6, 5.0
	n	15	12	16	17
	CFB at 4 weeks	-3.8%	-3.8%	-6.2%	-7.4%
	95% CI	-7.7, 0.4	-9.5, 2.3	-13.4, 1.6	-16.0, 2.1
LDL-c (mmol/L)	n	19	16	17	18
	Baseline	2.1	2.3	2.0	2.2
	95% CI	1.8, 2.5	1.9, 2.8	1.6, 2.4	1.8, 2.7
	n	15	12	16	17
	CFB at 4 weeks	-3.3%	-2.9%	-7.5%	-13.9%
	95% CI	-10.7, 4.8	-10.3, 5.2	-16.4, 2.3	-22.8, -3.9

Brigandi R et al., Am. J. Kidney Dis. 2016, 67, 861, Supplement table 4

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Brigandi R et al., Am. J. Kidney Dis. 2016, 67, 861, Supplement table 4

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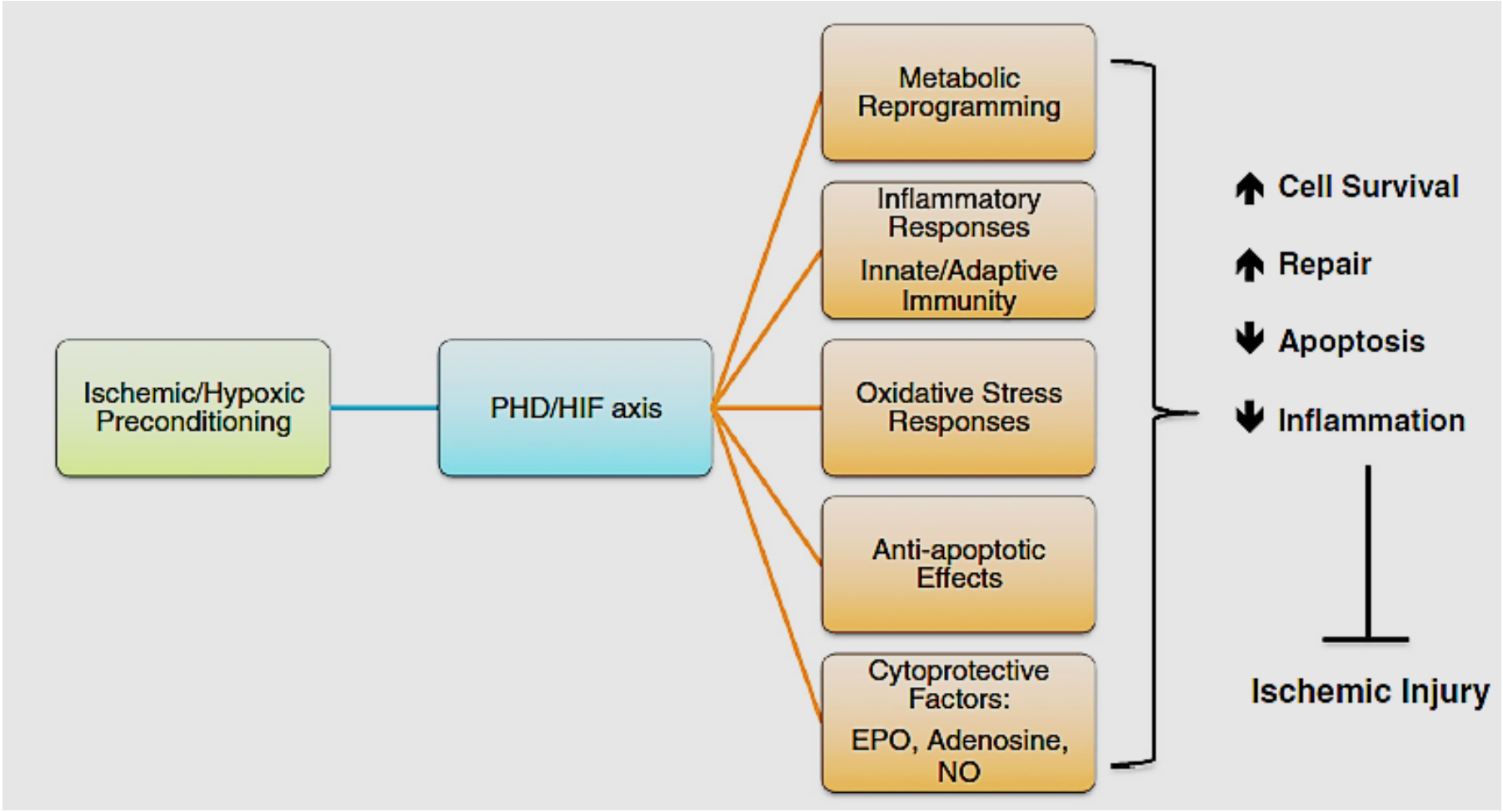
Molecular mechanisms implicated in PHD/HIF mediated renoprotection



Kapitsinou P.P., Haase V.H., Am. J. Physial., 2015, 309, F821 - 834

Leading European Nephrology

New strategies under development to stimulate erythropoiesis

Targeting the EPO Receptor

- EPO mimetic peptides
  - Centocor molecules: CNTO 528, CNTO 530, CNTO 531
  - AplaGen GmbH: AGEM400(HES)
  - Peginesatide[a]
- EPO fusion proteins
  - EPO-EPO dimers
  - EPO-CPT
  - EPO-$(CPT)_3$
  - Albumin-EPO
  - EPO-hyFc (Genexine GX-E2)
- Antibody agonists to EPO receptor
  - Mouse monoclonal IgG
  - Ab12 molecule
  - Ab12.6 (Abbott Laboratories ABT-007) molecule
- EPO gene therapy (TARGT EPO)
- Dimerization of EPO receptor intracellular domain with a CID

Bonomini M. et al., Am. J. Kidney Dis., 2016, 67, 133-142

Leading European Nephrology

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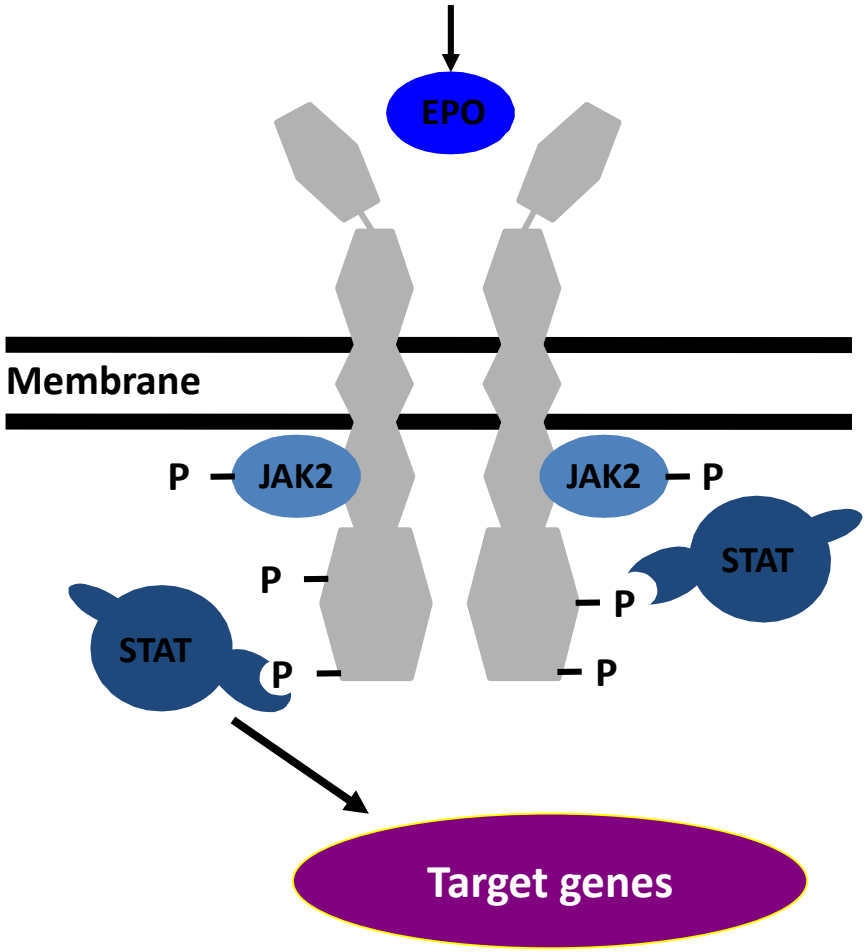
Bonomini M. et al., Am. J. Kidney Dis., 2016, 67, 133-142

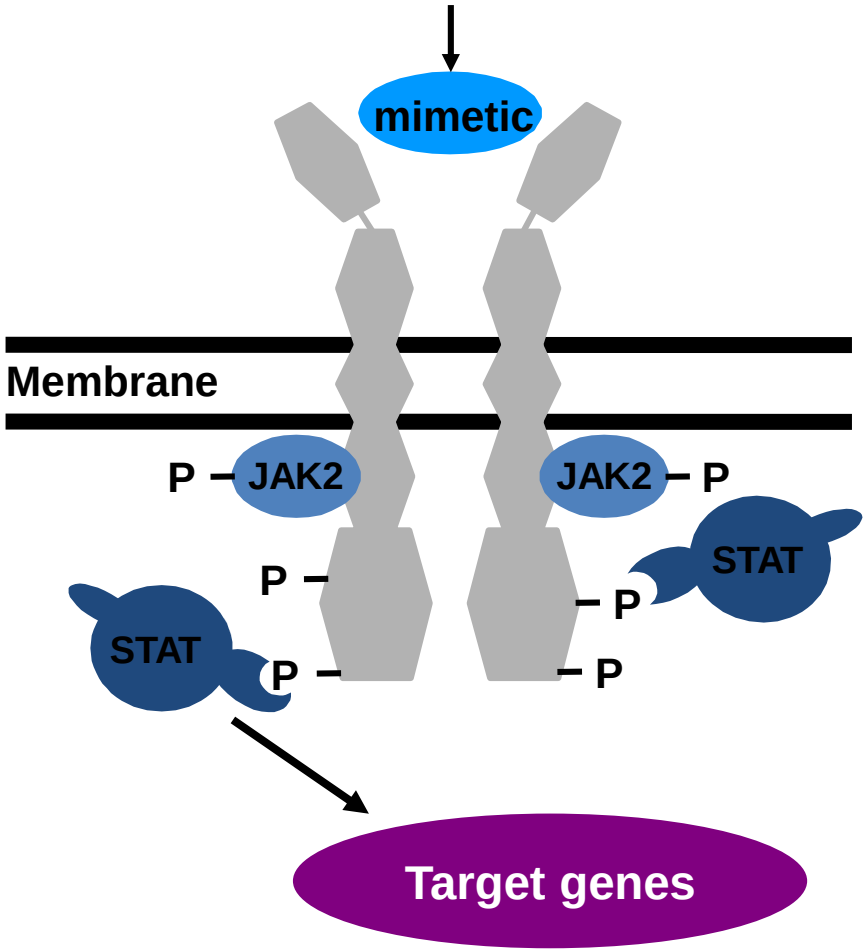
EPO receptor activation

- EPO binding leads to dimerisation of EPO receptor
- JAK2 (tyrosine kinase) is autophosphorylated
- JAK2 phosphorylates EPO receptor, creating docking sites for several signalling proteins
- Signalling proteins translocate to nucleus and activate transcription (STAT5)



EPO mimetics - rationale and strategy

- Both chains of the EPO receptor are needed
- Conformation of the EPO receptor in the dimer complex is flexible
  - suggests that a variety of molecules capable of dimerising the receptor may be able to act as EPO mimetics



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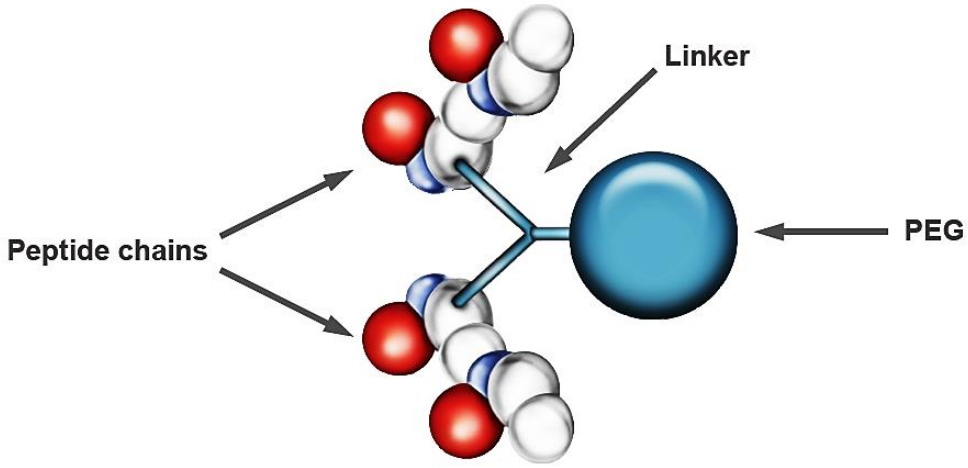
Background – Peginesatide

(formerly known as Hematide™)



Peginesatide

Omontys, (Affymax + Takeda)

- Synthetic, PEGylated investigational, peptide-based erythropoiesis-stimulating agent (ESA)
- Binds to and stimulates the EPO receptor
- No structural homology with EPO
- Approved by the FDA for the treatment of anemia due to CKD in patients on dialysis (2012)

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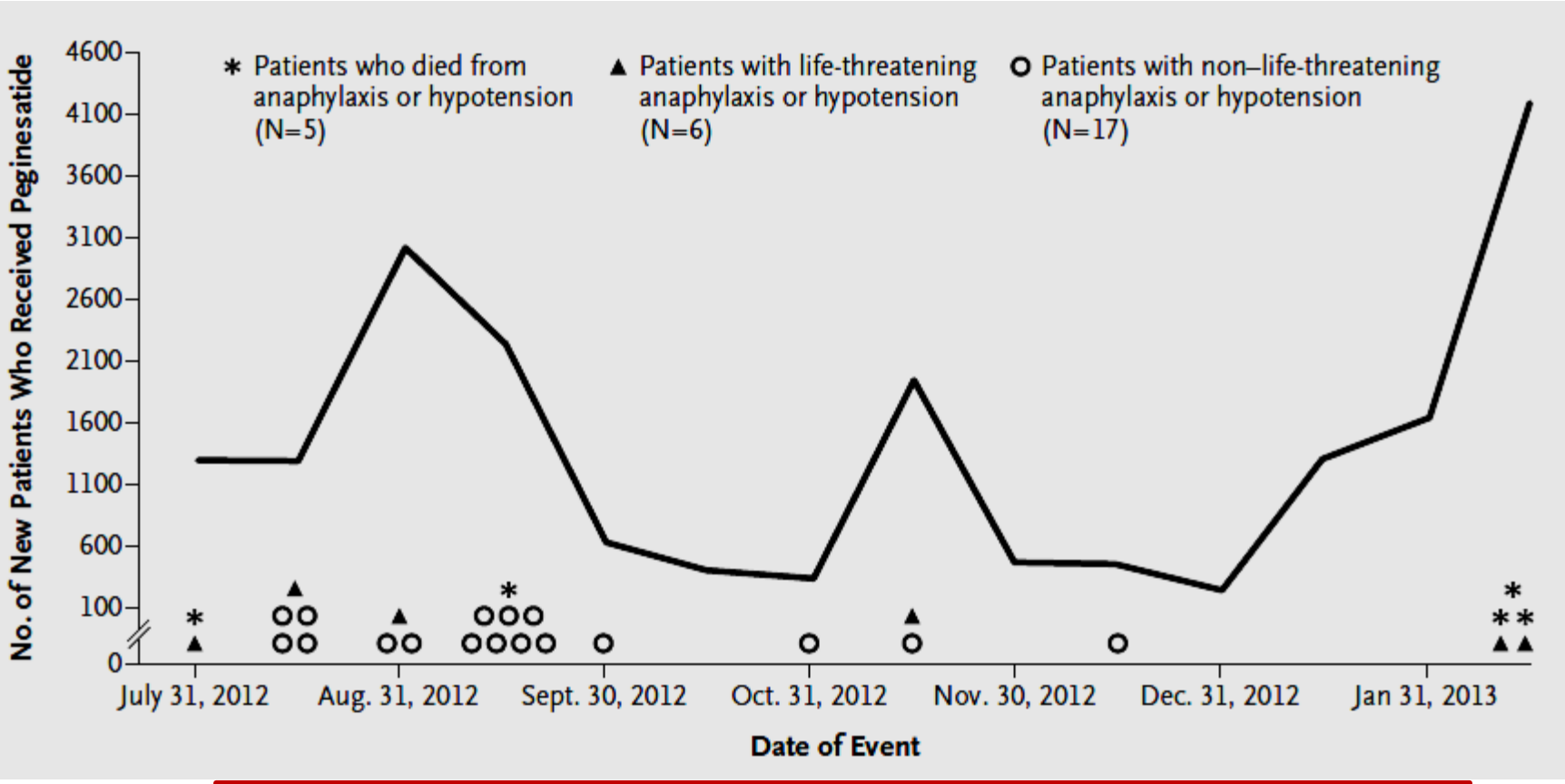
Fatal, life-threatening, and non–life-threatening occurrences of anaphylaxis and hypotension in patients who received a first dose of peginesatide



Deaths and life-threatening and non–life-threatening events were reported to the Food and Drug Administration

Bennet Ch. et al., N. Engl. J. Med., 2014, 370; 2055 - 2056

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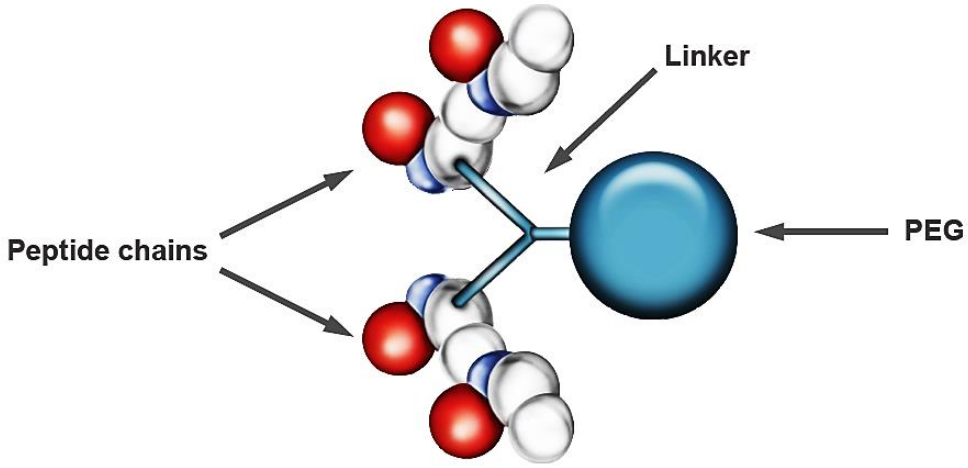
(formerly known as Hematide™)



Peginesatide

Omontys, (Affymax + Takeda)

Withdrawn from the market (2013)!

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Bonomini M. et al., Am. J. Kidney Dis., 2016, 67, 133-142

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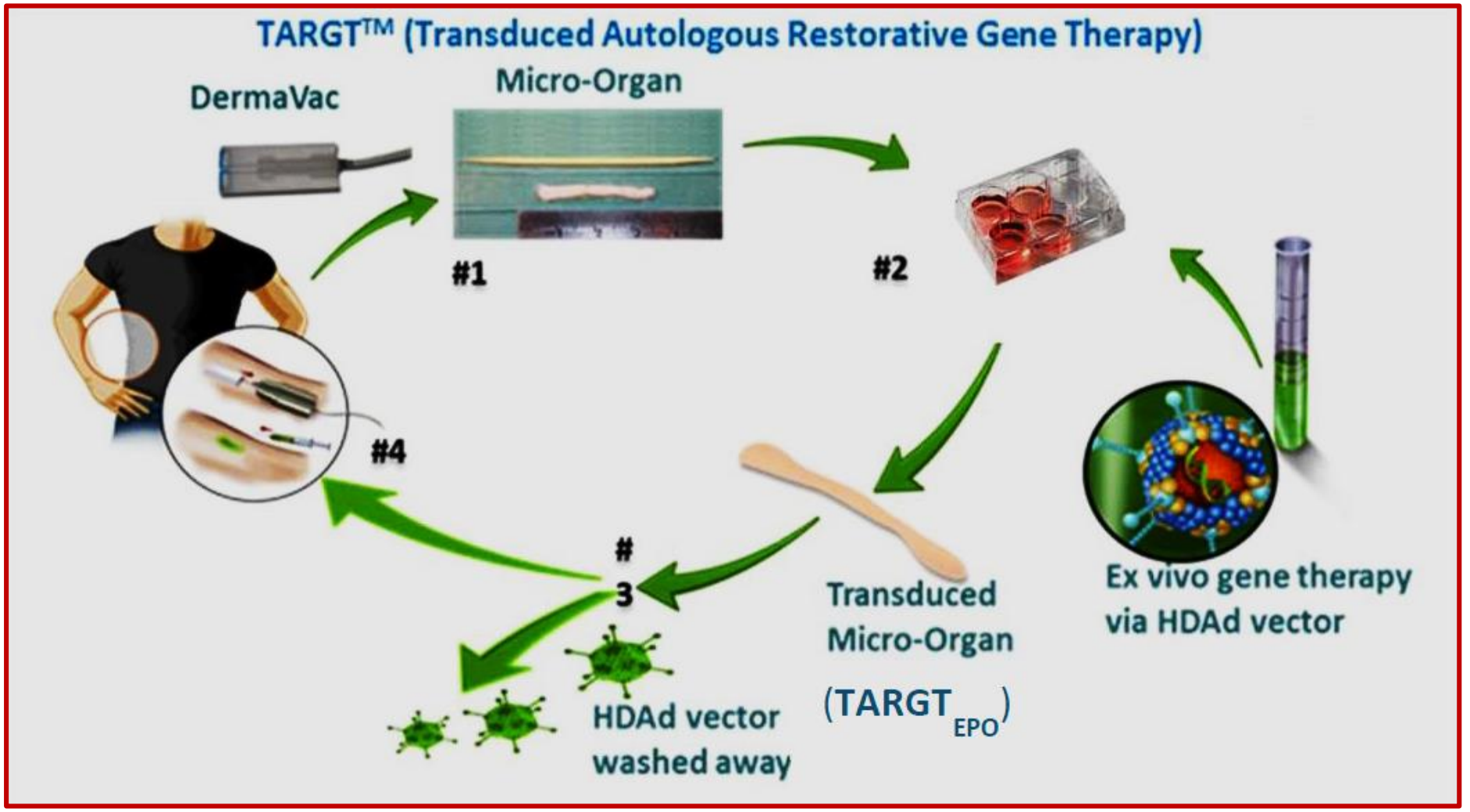
Erythropoietin Bio-pomp

(EPODURE currently TARGTepo - Medgenics)



West J. B., N. Engl. J. Med., 2017, 376, 1965-1971

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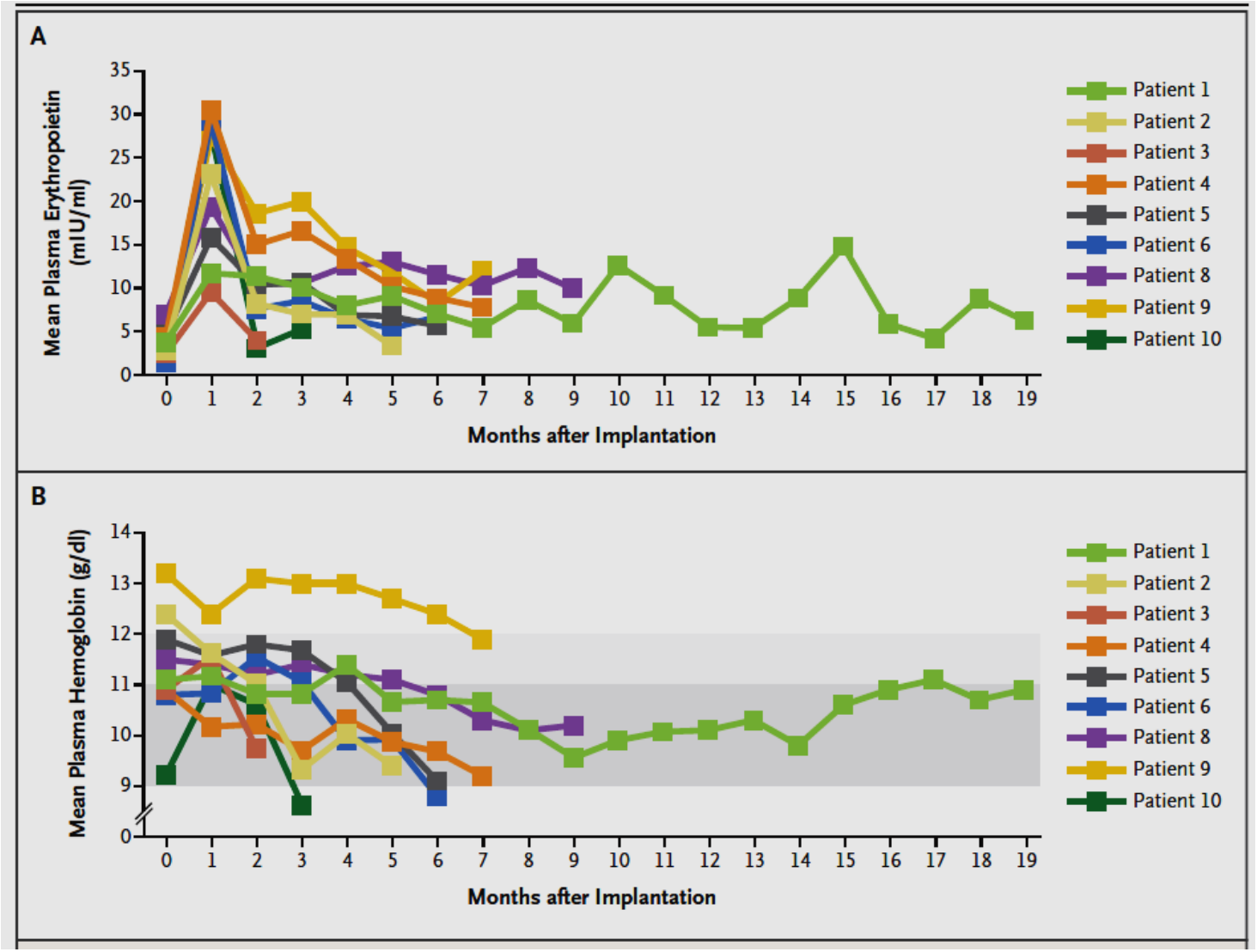
Levels of erythropoietin and haemoglobin after implantation of TARGTepo in patients with ESKD



Blum S. et al., N. Engl. J. Med., 2017; 376: 189-191

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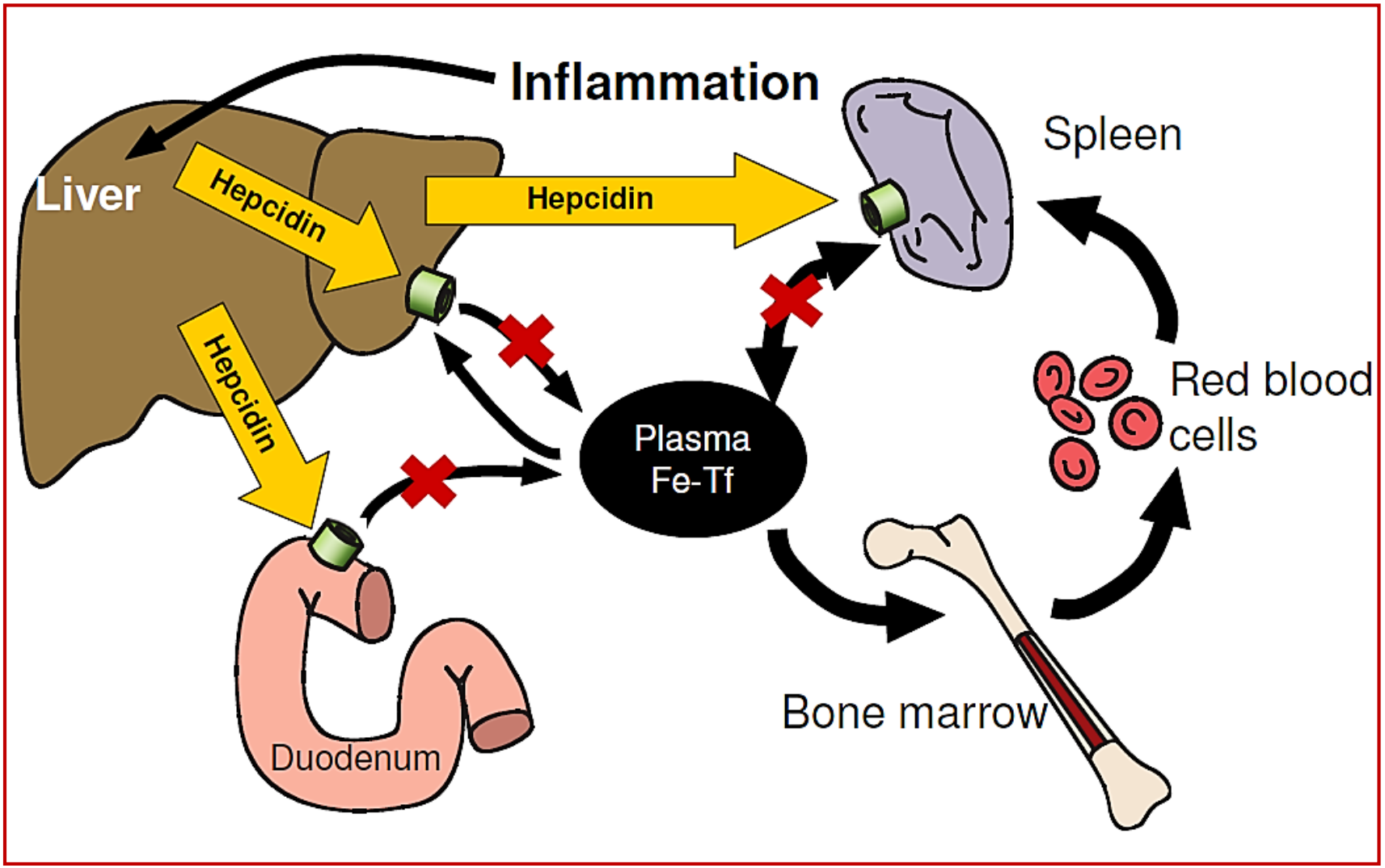
Regulation of hepcidin by inflammation



Ganz T., J. Am. Soc. Nephrol., 2007;18: 394–400

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

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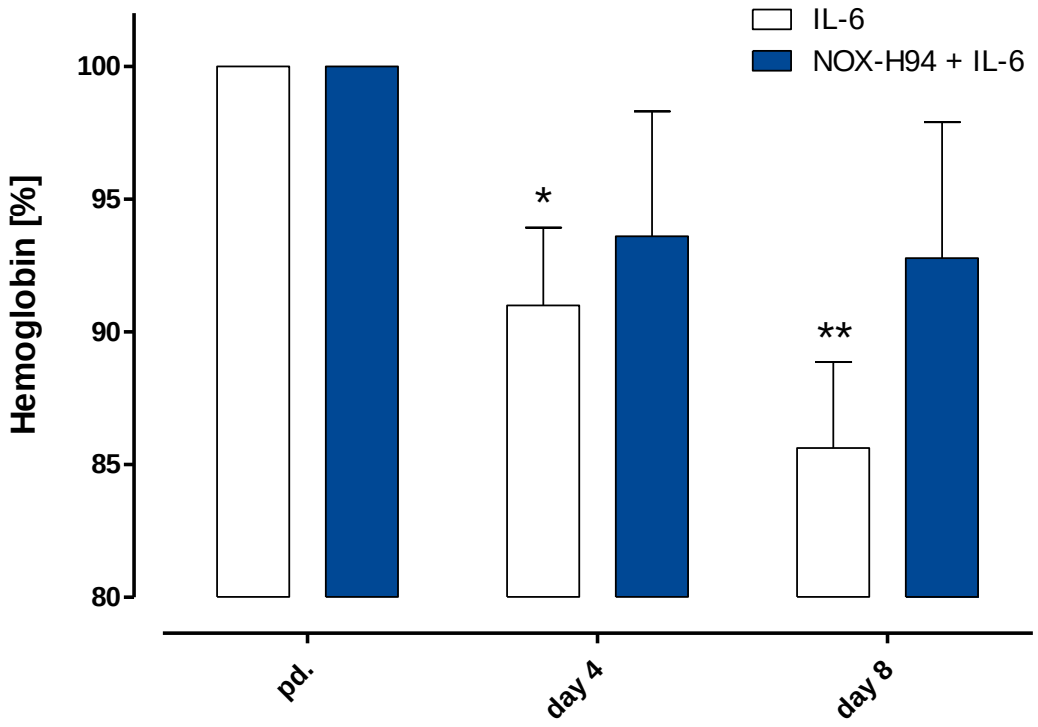
Effect of hepcidin inhibitor (NOX-H94) on haemoglobin in IL-6 Induced anaemia

Daily s.c. human IL-6 injections induce anaemia through endogenous hepcidin; cynomolgus monkey model:



data:
- IL-6 every other day, 0.3 µg/kg
- mean+SEM, n=4
- baseline corrected for the individual animals

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British Journal of Pharmacology

British Journal of Pharmacology (2016) **173** 1580–1588

NOX-H94

RESEARCH PAPER

Safety, pharmacokinetics and pharmacodynamics of the anti-hepcidin Spiegelmer lexaptepid pegol in healthy subjects

Correspondence Kai Riecke, NOXXON Pharma AG, Max-Dohrn-Straße 8-10, 10589 Berlin, Germany. E-mail: clinic@noxxon.com

Received 4 June 2015; **Revised** 11 January 2016; **Accepted** 11 January 2016

M Boyce[1], S Warrington[1], B Cortezi[1], S Zöllner[2], S Vauléon[2], D W Swinkels[3], L Summo[2], F Schwoebel[2] and K Riecke[2]

[1]*Hammersmith Medicines Research, London, UK,* [2]*NOXXON Pharma AG, Berlin, Germany, and* [3]*Hepcidinanalysis.com, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands*

BACKGROUND AND PURPOSE

Anaemia of chronic disease is characterized by impaired erythropoiesis due to functional iron deficiency, often caused by excessive hepcidin. Lexaptepid pegol, a pegylated structured L-oligoribonucleotide, binds and inactivates hepcidin.

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Anti-hepcidin Spiegelmer Lexaptepid = NOX-H94 in healthy subjects

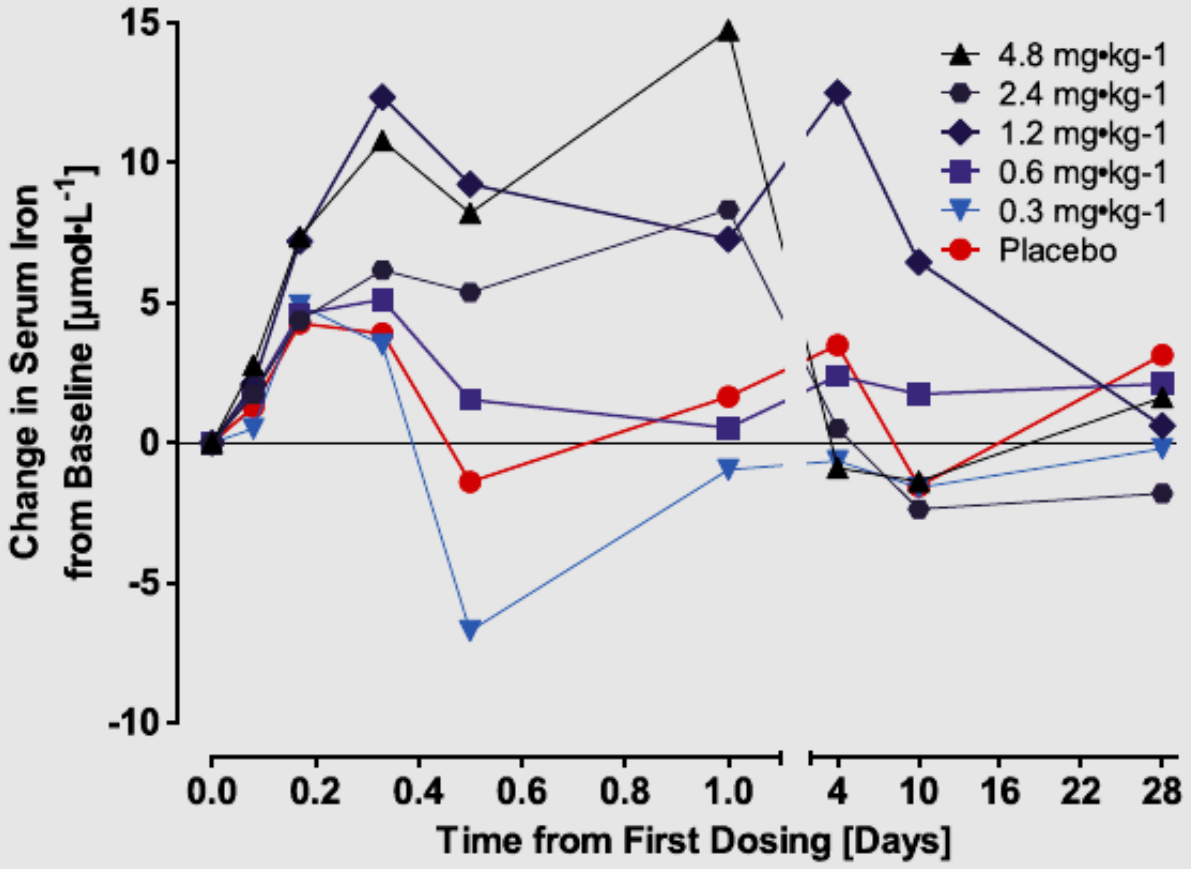

Figure 5

Serum iron profiles after single i.v. doses of lexaptepid.

Boyce M. et al., British Journal of Pharmacology, 2016, 173, 1580–1588

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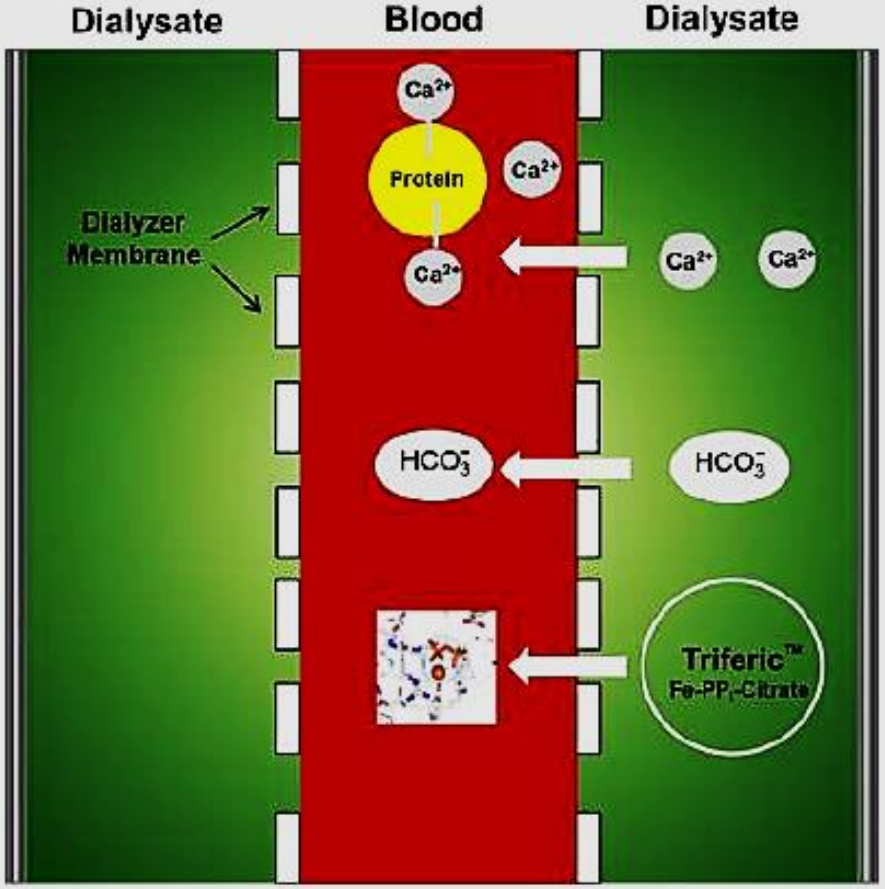
Iron delivered via dialysate

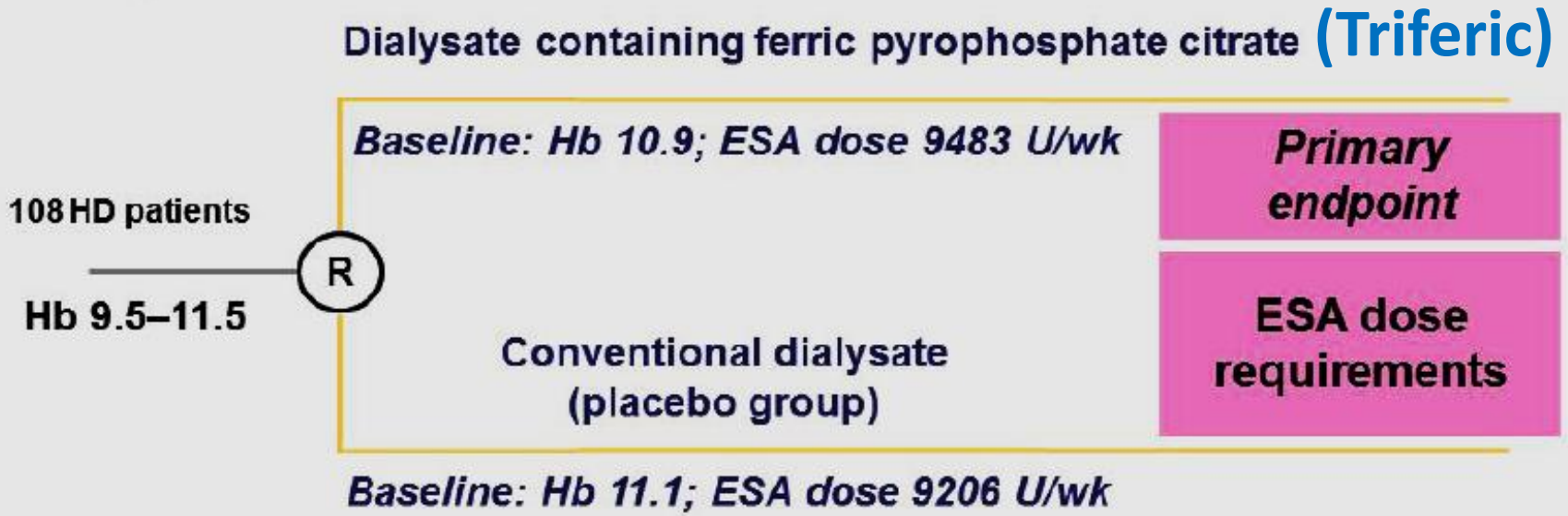
- Soluble and non-colloidal iron salt, not conjugated with a sugar moiety
- Iron- citrate- pyrophosphate
- MW ~1000 Da, similar to vitamin B_{12}
- Added to bicarbonate concentrate
- Crosses the dialyzer during the haemodialysis treatment and binds immediately to apotransferrin, largely bypassing the RE system



Gupta A. et al., Kidney Int., 2015, 88, 1187-1194

PRIME Study

- **Prospective, randomised, placebo-controlled, double-blind trial**
- **Study duration = 9 months**



Gupta A. et al., Kidney Int., 2015, 88, 1187-1194

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PRIME Study – 35% ESA dose reduction vs. placebo

	Triferic N=52		Placebo N=51	
	U/wk (SD)	% Change from Baseline	U/wk (SD)	% Change from Baseline
Hgb g/dL Baseline	11.0		11.1	
Hgb g/dL EoT	10.4	-5.1	10.5	-5.8
Prescribed ESA Dose U/wk (SD) Baseline	9483 (5414)		9206 (5500)	
Prescribed ESA Dose U/wk (SD) EoT	9871 (7523)	7.3 (67.66)	12,628 (13,967)	37.3 (106.9)
LS mean (SE) % Change from Baseline	4.9 (12.1)		39.8 (12.2)	
95% CI LS mean	-19.1, 28.8		15.7, 64.0	
LS mean difference from Placebo	-35.0 (17.20)			
95% CI LS mean difference	-69.1, -0.8			
P-value	0.045			

Gupta A. et al., Kidney Int., 2015, 88, 1187-1194

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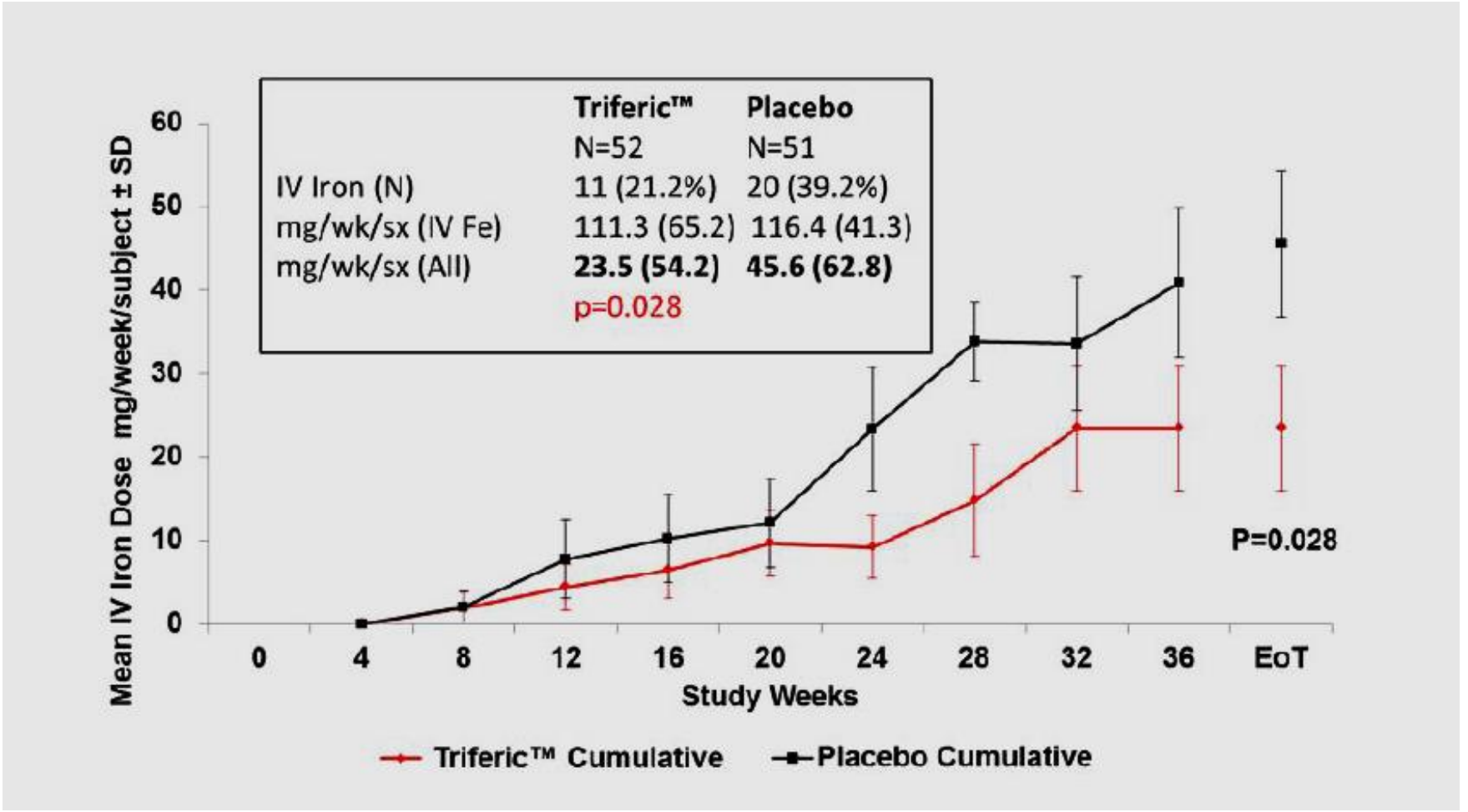
PRIME Study – Triferic reduces i.v. iron requirements by 48%



Gupta A. et al., Kidney Int., 2015, 88, 1187-1194

Summary

- Current treatment of anaemia in patients with CKD will certainly change in the future
- First new drug on the market will be most probably one of the HIF stabilizers (phase 3 of clinical trials)
- New drugs in the anaemia management in CKD patients will improve the compliance and the clinical benefits of such therapy
- The key to CKD anaemia management will be still individualization of the potential benefits (reducing blood transfusions and anaemia-related symptoms) against the risks of harm

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Nephrology

Andrzej Więcek
Katowice