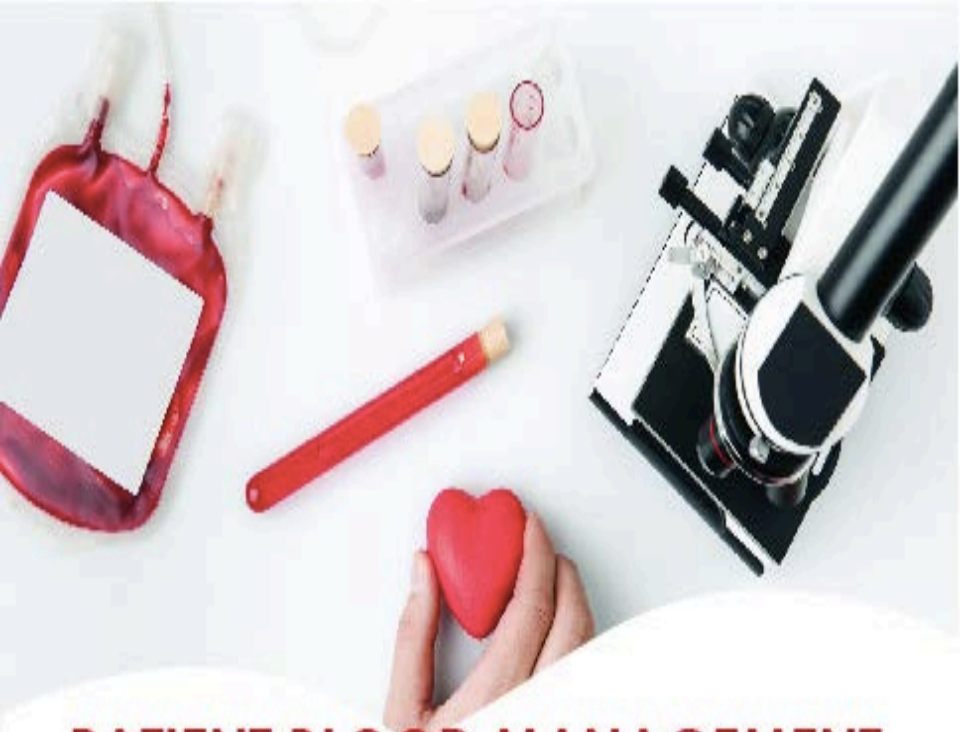


PATIENT BLOOD MANAGEMENT
dalla teoria alla pratica

T HOTEL Cagliari
29 Giugno 2018

Responsabile Scientifico
Marino Argiolas

VIFOR PHARMA

ESAs e ferro in emodialisi

Antonello Pani

Riccardo Cao

Struttura Complessa di Nefrologia e Dialisi
Azienda Ospedaliera G. Brotzu Cagliari

Patients opinion

"Once my doctor began treating my kidney disease, my greatest challenge was the constant exhaustion.
Fortunately, my doctor explained that anemia was causing my exhaustion and that people with serious illnesses, like kidney disease, may be at increased risk for anemia."

Alonso Mourning

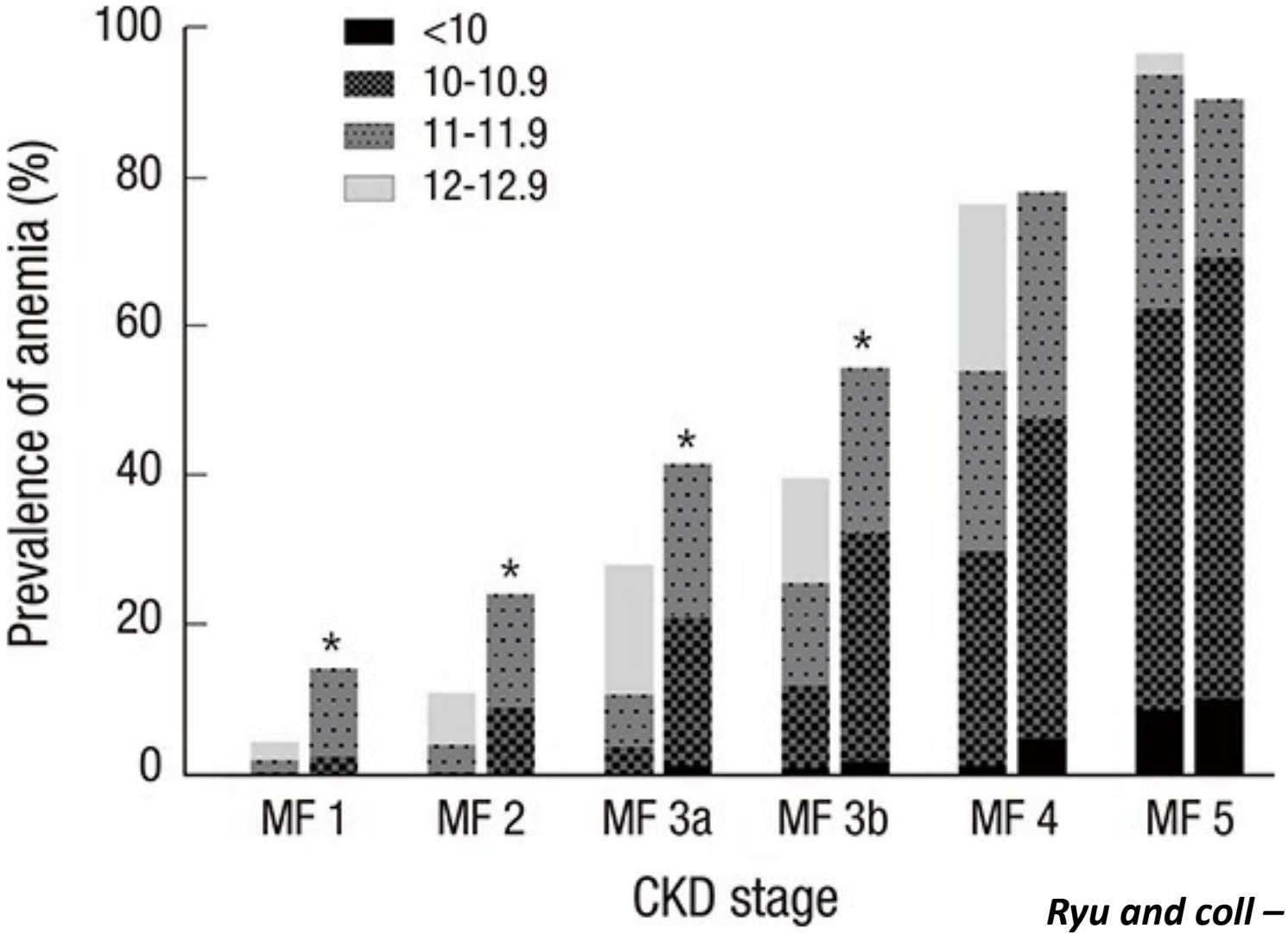
Historical Background

- Richard Bright (1836): first observed that anemia was a complication of renal failure.
- Robert Christison: further described renal anemia.
- Miyake (1977): purified and identified erythropoietin.
- Eschbach (Dec 2, 1985): first human use of EPO

Definitions

- Anemia is a condition in which the number of RBCs or their oxygen-carrying capacity is insufficient to meet physiologic needs, which vary by age, sex, altitude, smoking, and pregnancy status (WHO).
- For diagnosis and further evaluation Hb values according to NKF guidelines:
- Hb concentration
  - < 13.0 g/dl (o 130 g/l) in males and
  - < 12.0 g/dl (o 120 g/l) in females.

Burden of Anemia according to CKD stage

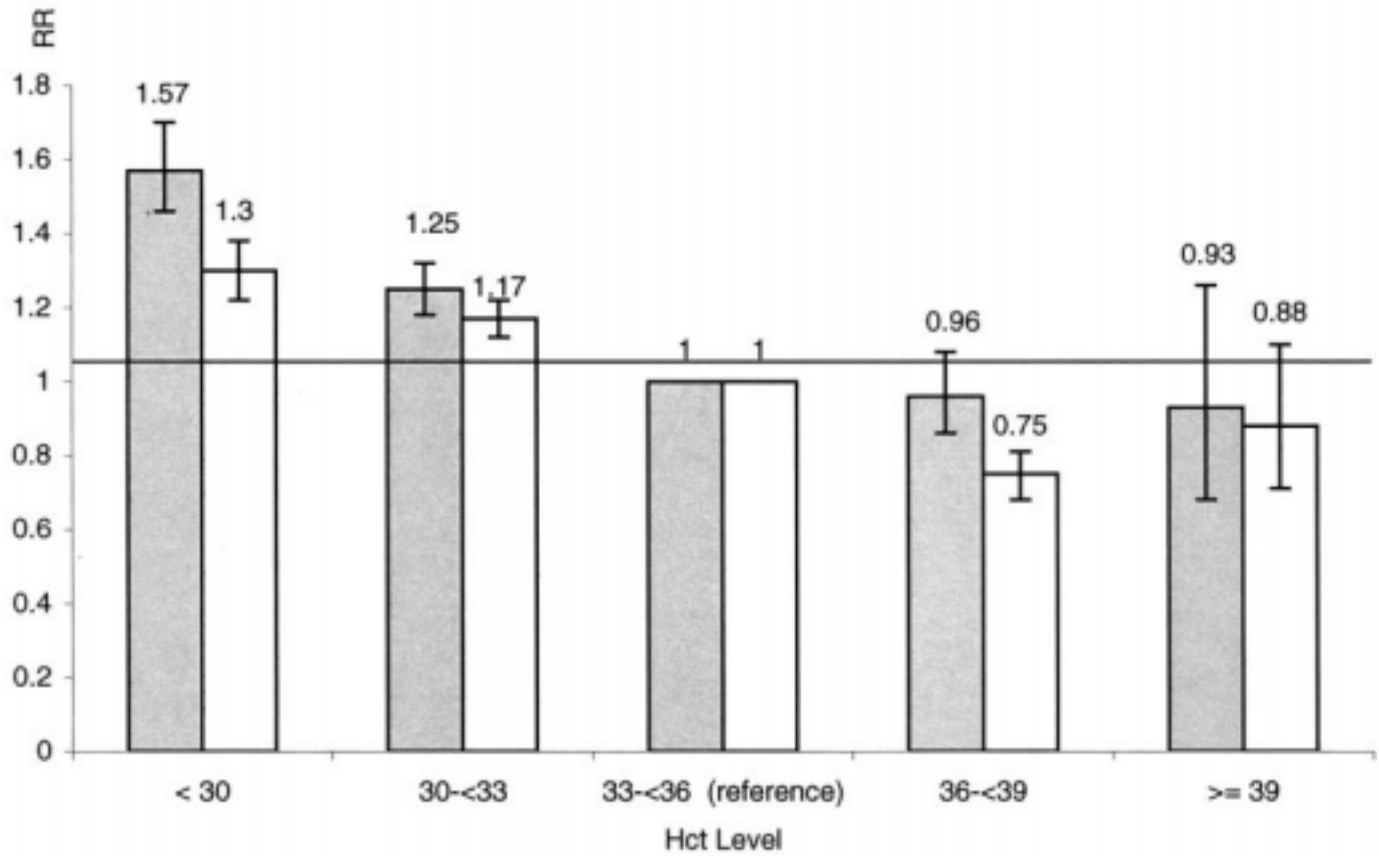


Ryu and coll – JKMS -2017

Death, Hospitalization, and Economic Associations among Incident Hemodialysis Patients with Hematocrit Values of 36 to 39%

ALLAN J. COLLINS,* SUYING LI,† WENDY ST. PETER,‡ JIM EBBEN,† TRICIA ROBERTS,† JENNIE Z. MA,§ and WILLARD MANNING‖
Hennepin County Medical Center and ‡College of Pharmacy, University of Minnesota, Minneapolis,

2001

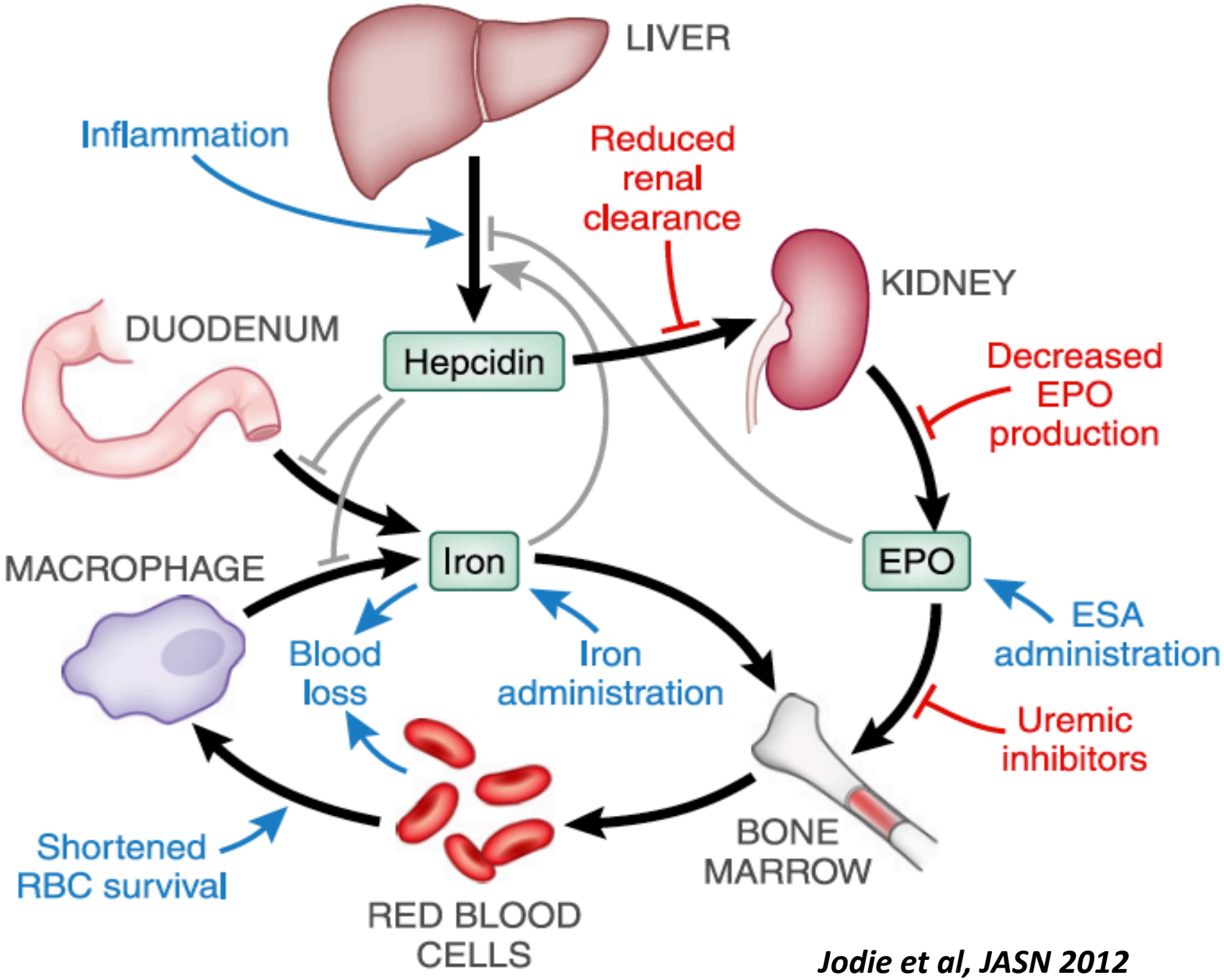


Relative risk for death (grey) and hospitalization for all causes in ESRD patients

Cautions in interpreting these results

Many studies that examined the relationship between Hb level and kidney function:

- Have been cross-sectional and not longitudinal in design.
- Described patients entered into clinical trials or seen by nephrologists, which are not a truly representative sample of patients with CKD.
- Included small numbers of patients with lower levels of kidney function.
- Used a great variety of methods to assess level of kidney function.
- Did not describe the cause of the anemia in patients with CKD.

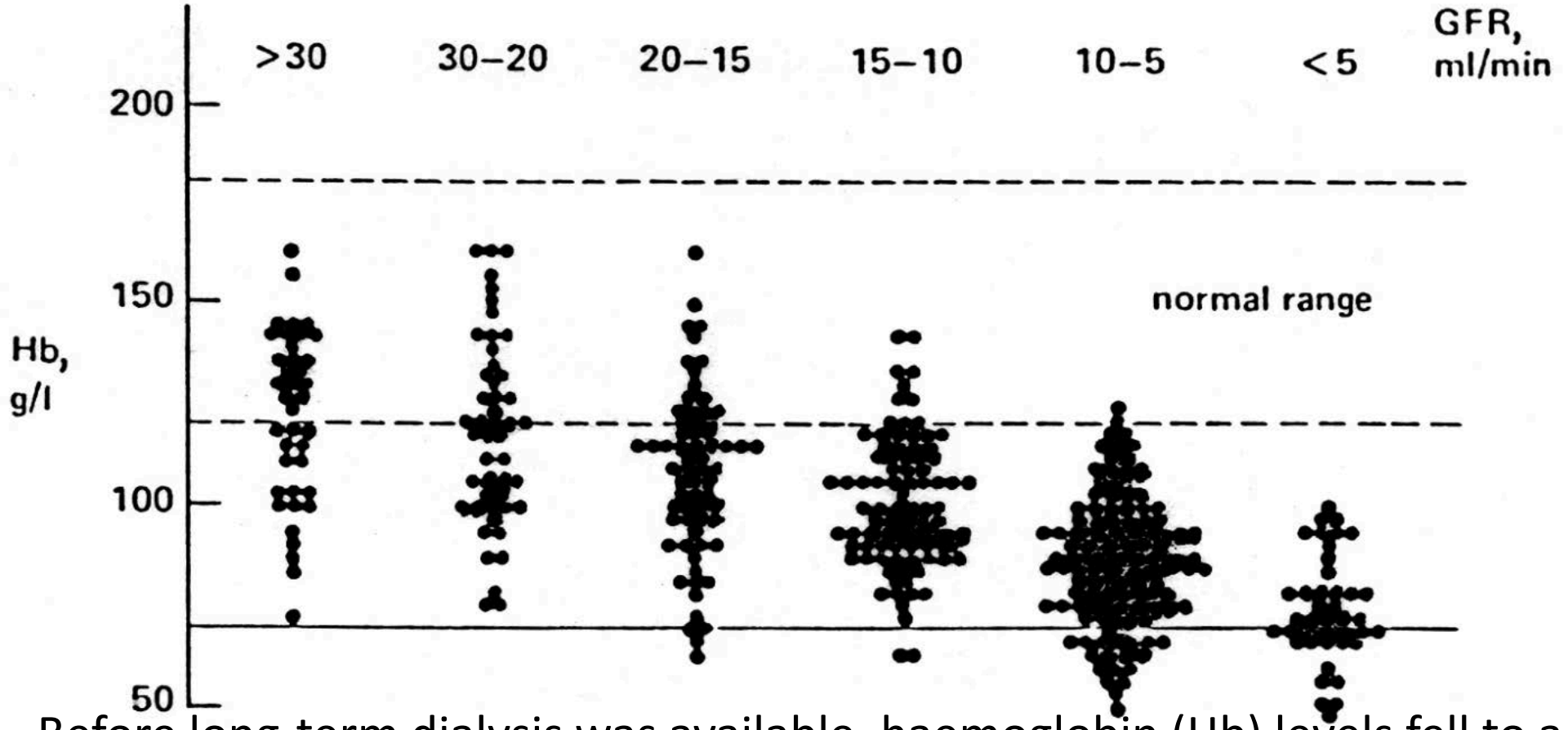


Jodie et al, JASN 2012

Causes of anemia in renal disease

- Relative EPO deficiency.
- Shortened RBC survival
- Bone marrow suppression.
- Other substrate deficiencies(B12 and folic acid)
- Iron deficiency.
- Blood loss

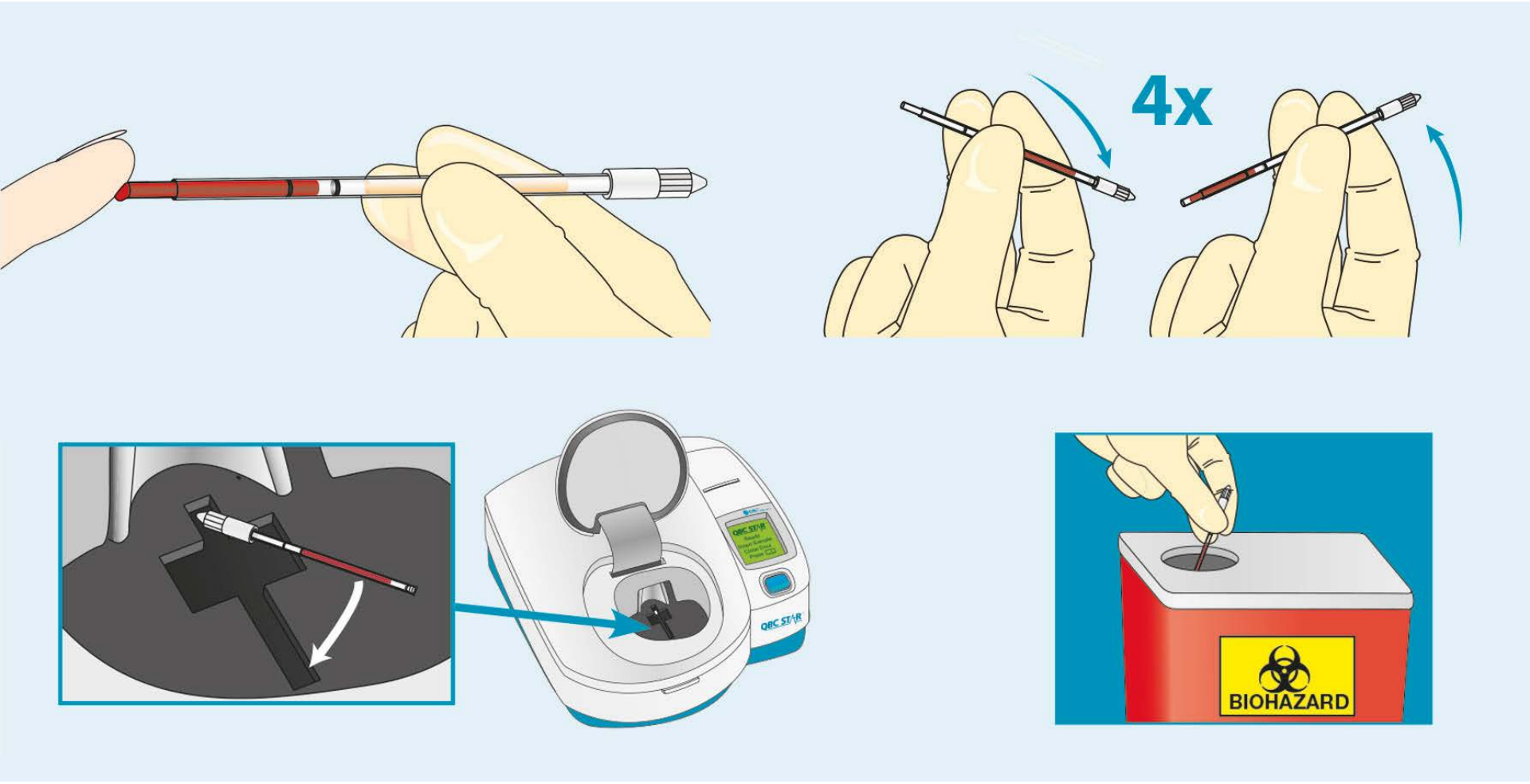
England 1965



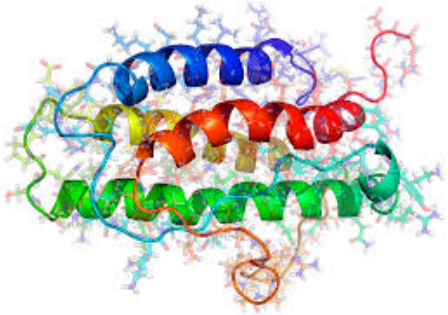
Before long-term dialysis was available, haemoglobin (Hb) levels fell to a mean of about 8 g/dl at a glomerular filtration rate (GFR) of 10ml/min, and about 7 g/dl at a GFR of 5, with a significant minority of patients running levels below 5 g/dl.

The anaemia of renal failure in a pre-dialysis and pre-EPO study. Mishra and Kerr, with permission.

Determinazione dell’ematocrito con capillare

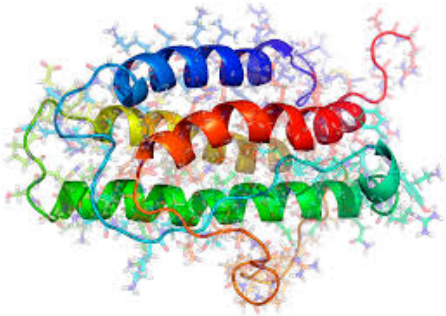


Erythropoietin



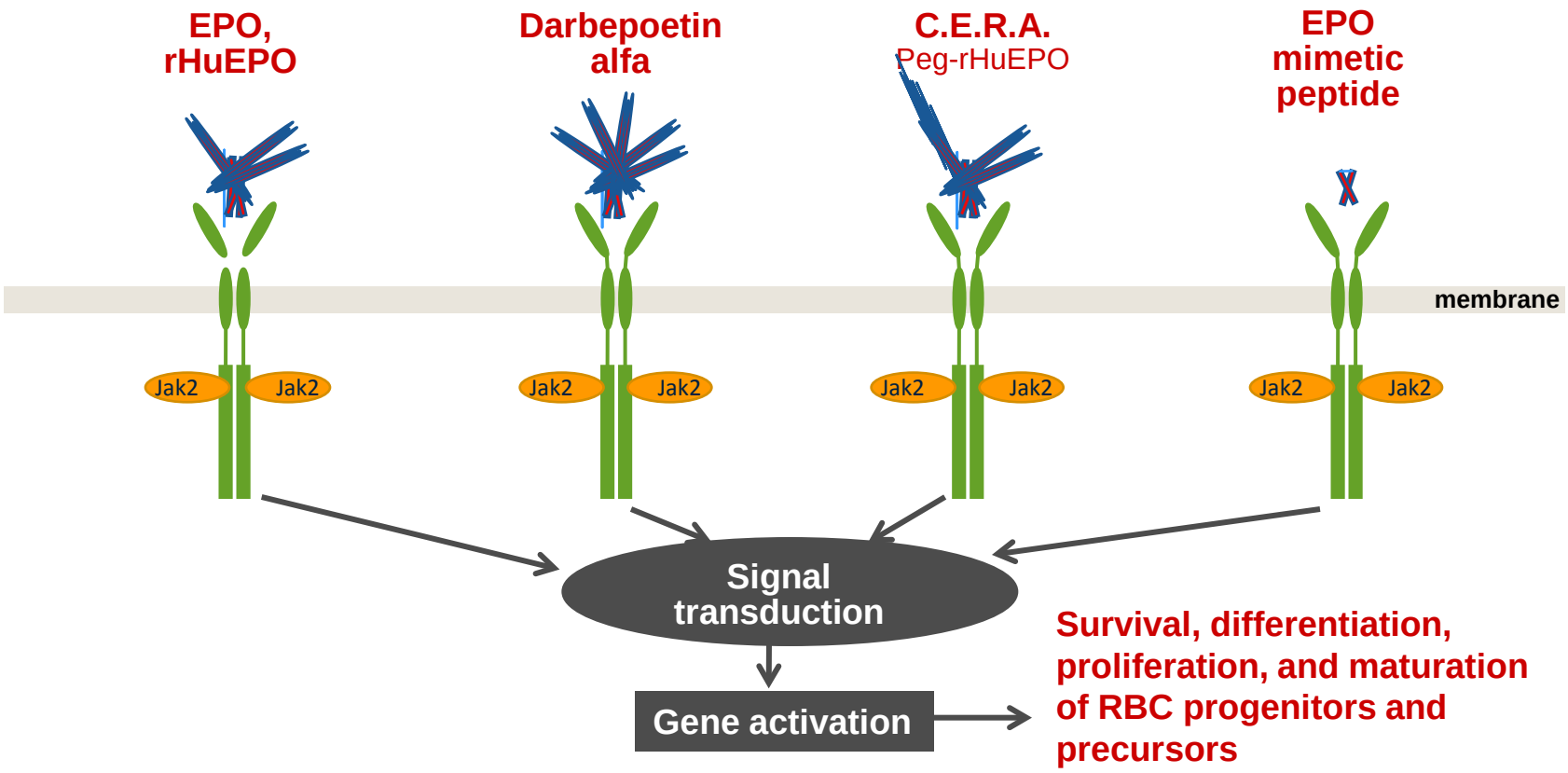
- “hemopoietine”
- 30.4 kDa glycoprotein hormone, plays a central role as a growth factor that sustains the survival of erythroid progenitor cells.
- Primary site of production is the liver in the fetus and kidneys after birth.
- Major sites of production-peritubular capillary endothelial cells and peritubular fibroblasts.

Erythropoietin



- Normal levels-10-30U/L
- 1 unit of EPO=erythropoietic effect in animals as occurs after stimulation with 5µmol of cobalt chloride.
- The EPO-receptor is a transmembrane receptor that belongs to the cytokine receptor superfamily.
- Receptor undergoes homodimerization after binding to EPO triggering downstream pathways(Ras/MAPk, JNK/MAPk, JAK/STAT and PI3.
- This activation promotes increased survival of precursor cells.

All ESAs act on the same target receptor

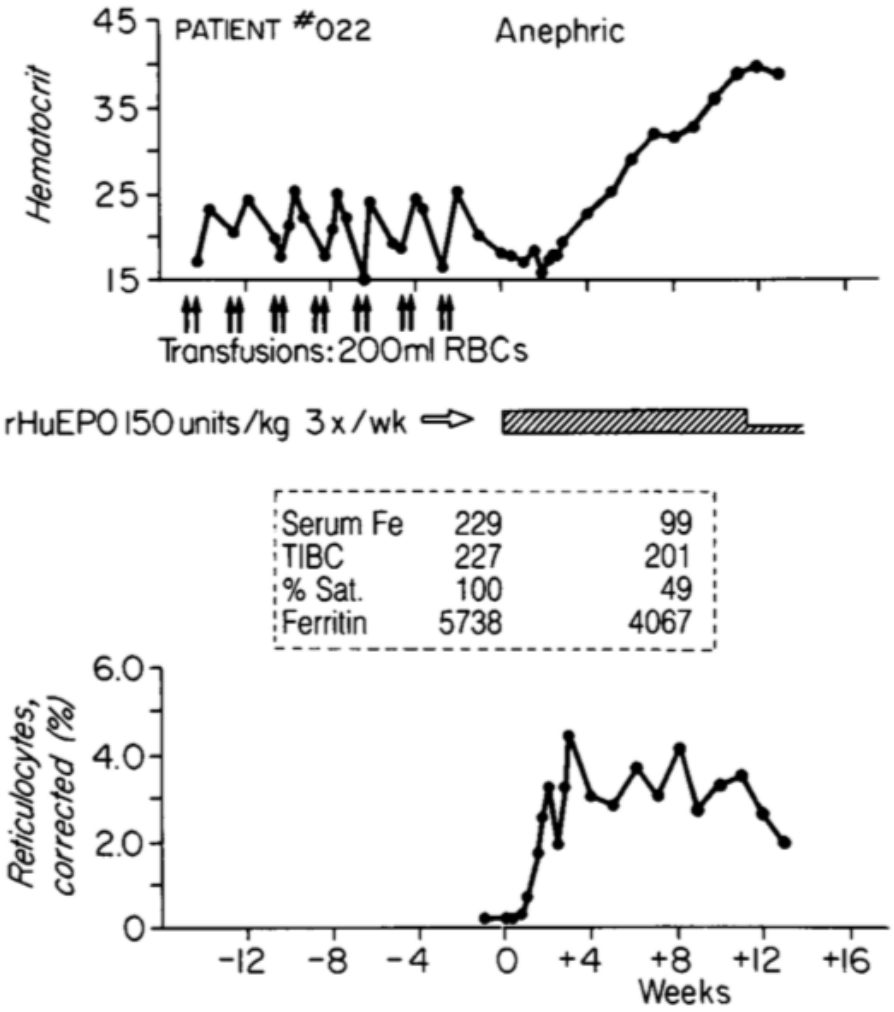


C.E.R.A., continuous erythropoietin
receptor activator; ESA, erythropoiesis-stimulating agent
EPO, erythropoietin; Jak, Janus Kinase; RBC, red blood cell

CORRECTION OF THE ANEMIA OF END-STAGE RENAL DISEASE WITH RECOMBINANT HUMAN ERYTHROPOIETIN

Results of a Combined Phase I and II Clinical Trial*

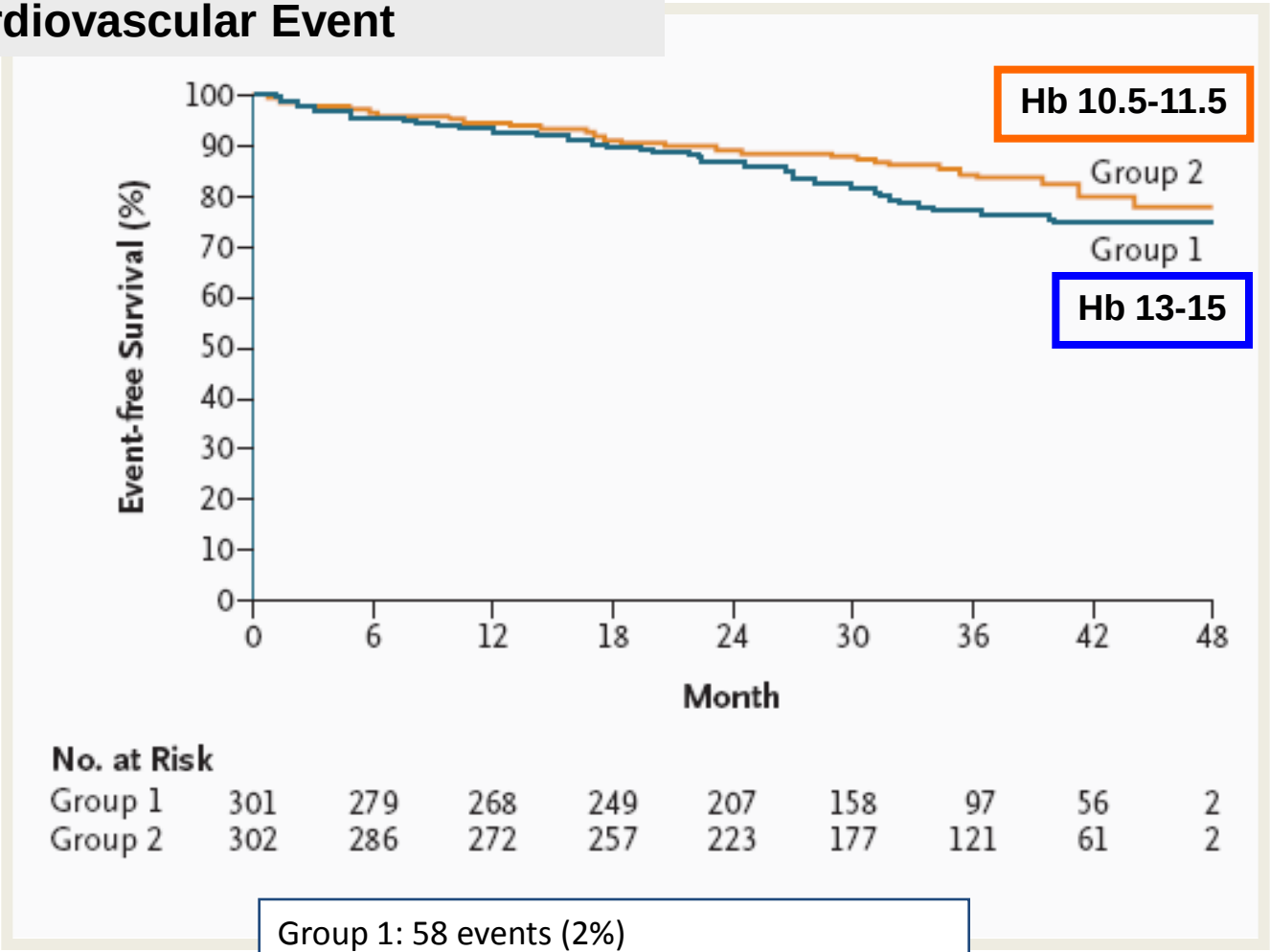
JOSEPH W. ESCHBACH, M.D., JOAN C. EGRIE, PH.D., MICHAEL R. DOWNING, PH.D., JEFFREY K. BROWNE, PH.D., AND JOHN W. ADAMSON, M.D.



1987

The Create study

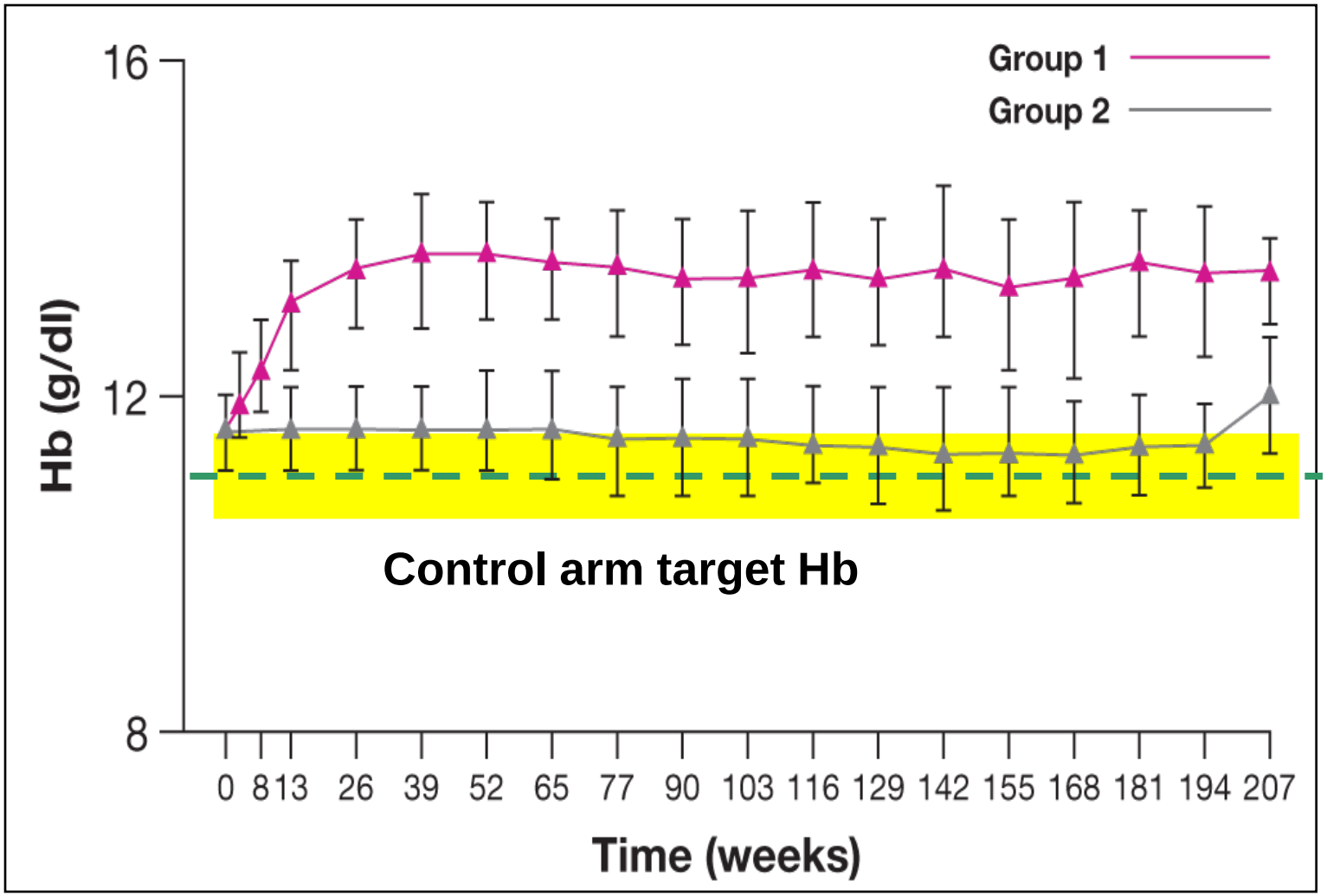
Time to the Primary End Point of a First Cardiovascular Event



Group 1: 58 events (2%)
Group 2: 47 events (1.5%)
HR 0.78; 95% CI 0.53 to 1.14; P = 0.20

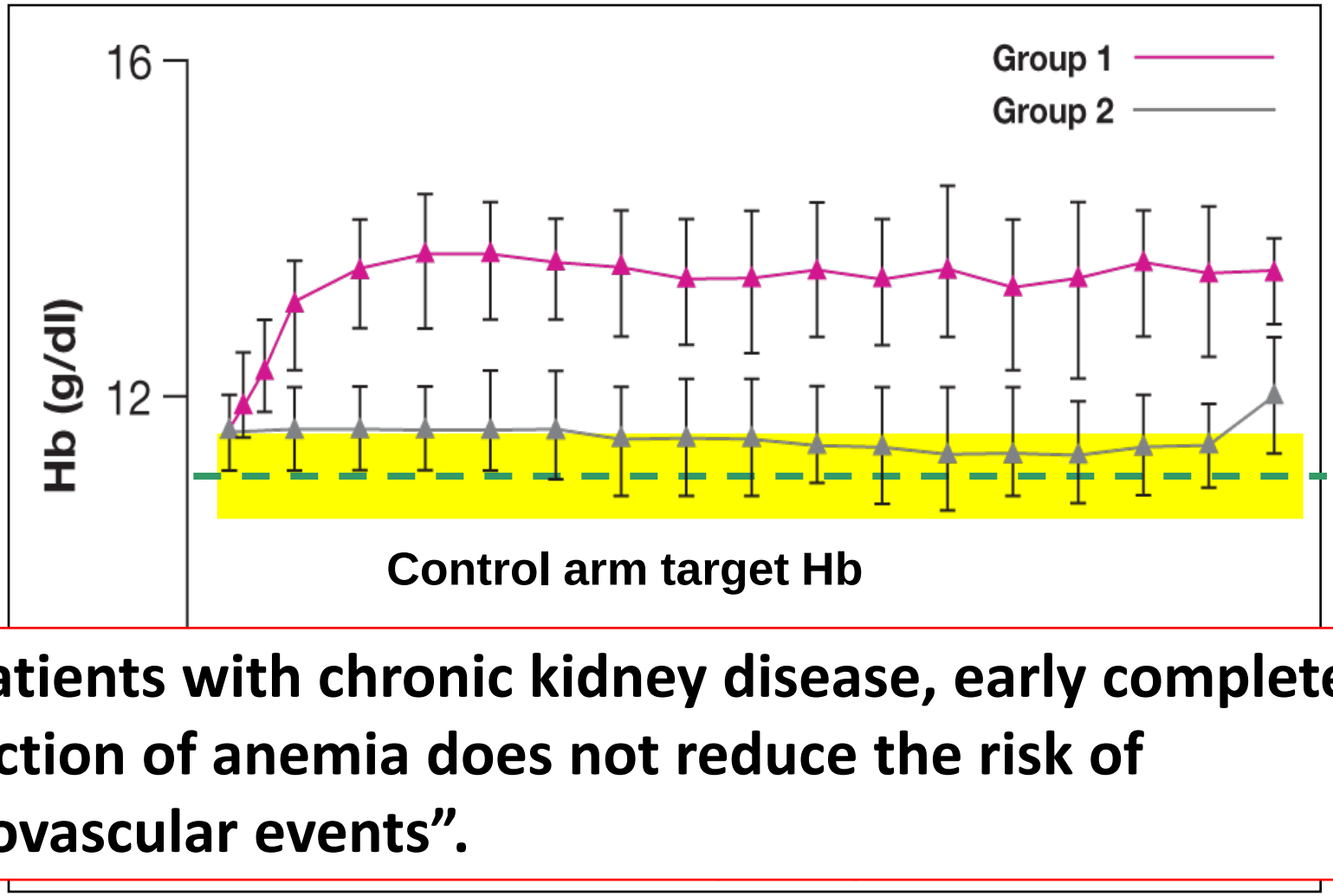
Drueke T, Locatelli F et al, N Engl J Med 2006

CREATE study: Hemoglobin levels over time



Drueke T, Locatelli F et al. N Engl J Med 2006; 355; n° 20, 2071-84

CREATE study: Hemoglobin levels over time



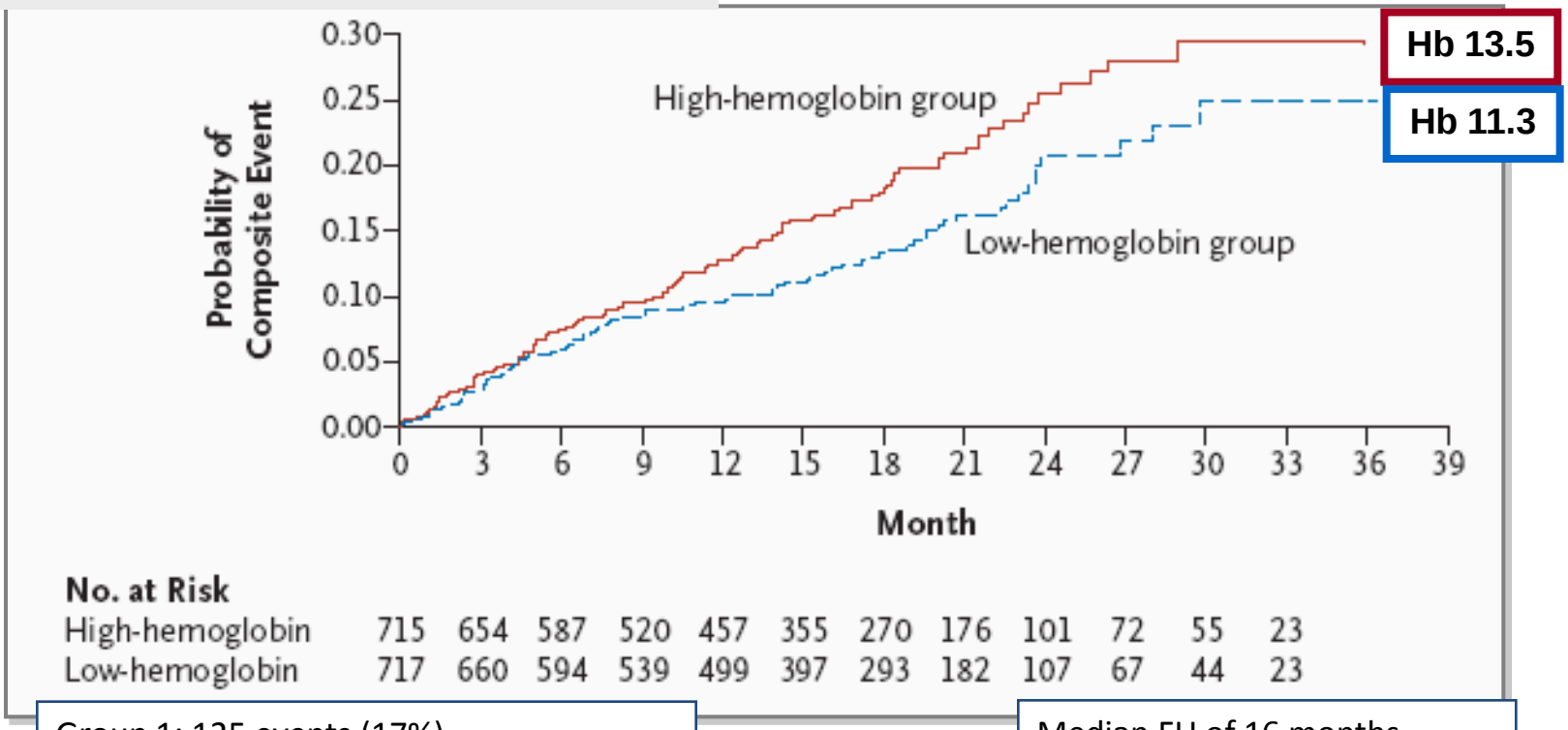
“In patients with chronic kidney disease, early complete correction of anemia does not reduce the risk of cardiovascular events”.

Drueke T, Locatelli F et al. N Engl J Med 2006; 355; n° 20, 2071-84

The CHOIR Trial

- 1432 CKD patients not on dialysis; half of them were diabetics

Primary Composite End-Point

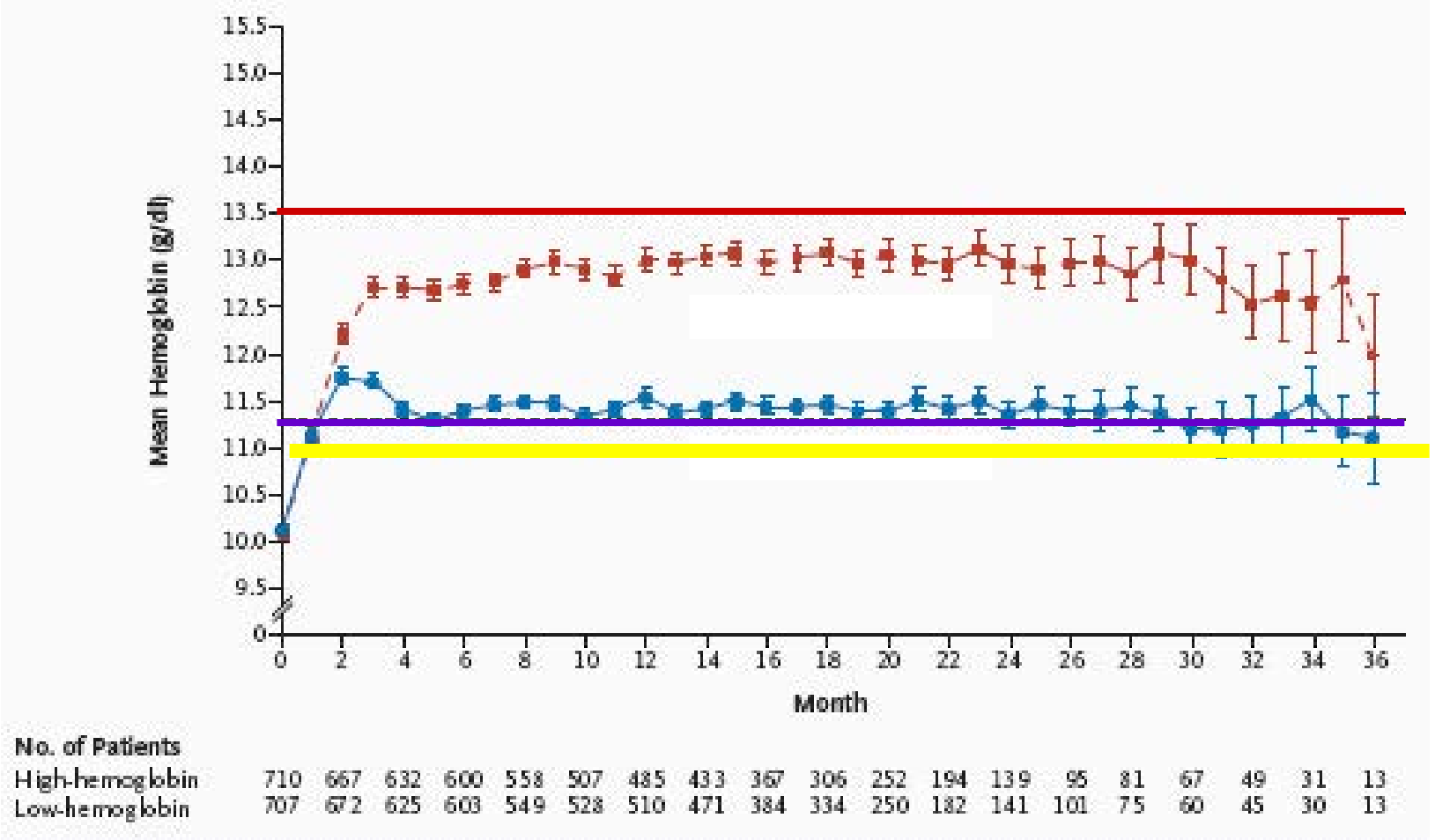


Group 1: 125 events (17%)
Group 2: 97 events (13%)
HR 1.34; 95% CI 1.03 to 1.74; P=0.03

Median FU of 16 months

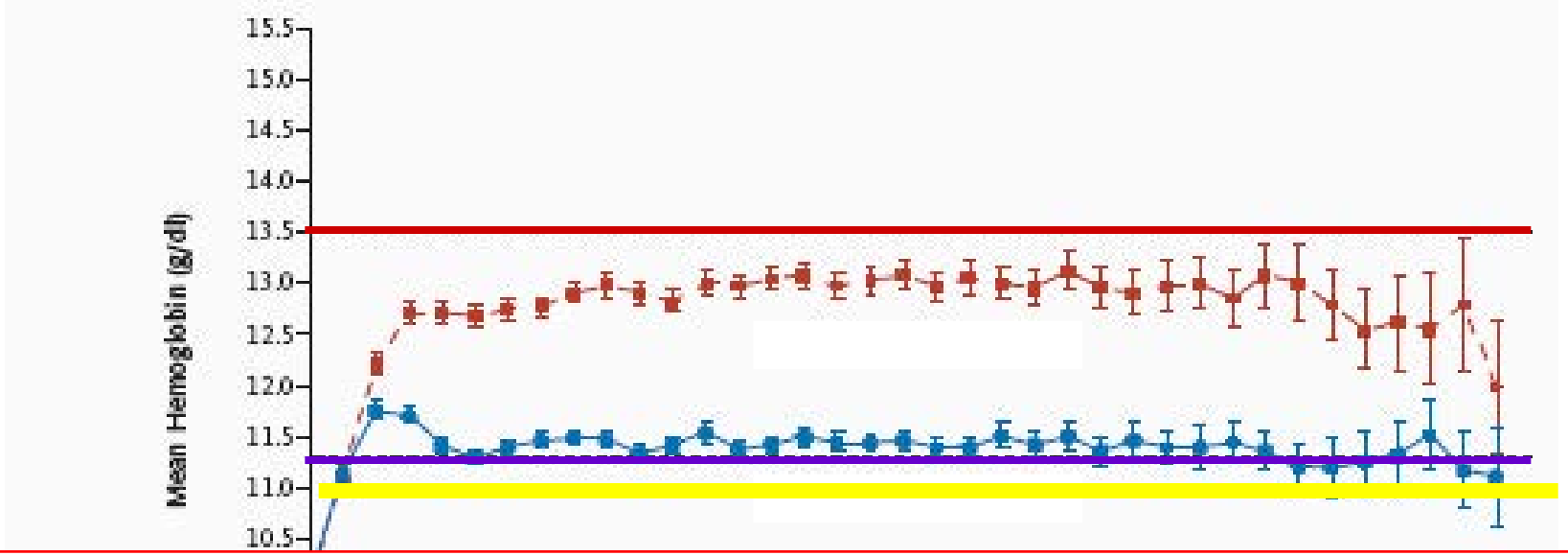
Singh et al, N Engl J Med 2006

CHOIR Study: an open label randomised study



Singh AK et al. N Engl J Med 2006; 355:2085- 98

CHOIR Study: an open label randomised study



"The use of a target hemoglobin level of 13.5 g per deciliter (as compared with 11.3 g per deciliter) was associated with increased risk and no incremental improvement in the quality of life **".**

Singh AK et al. N Engl J Med 2006; 355:2085- 98

ORIGINAL ARTICLE

The Treat Trial
NEJM 2009

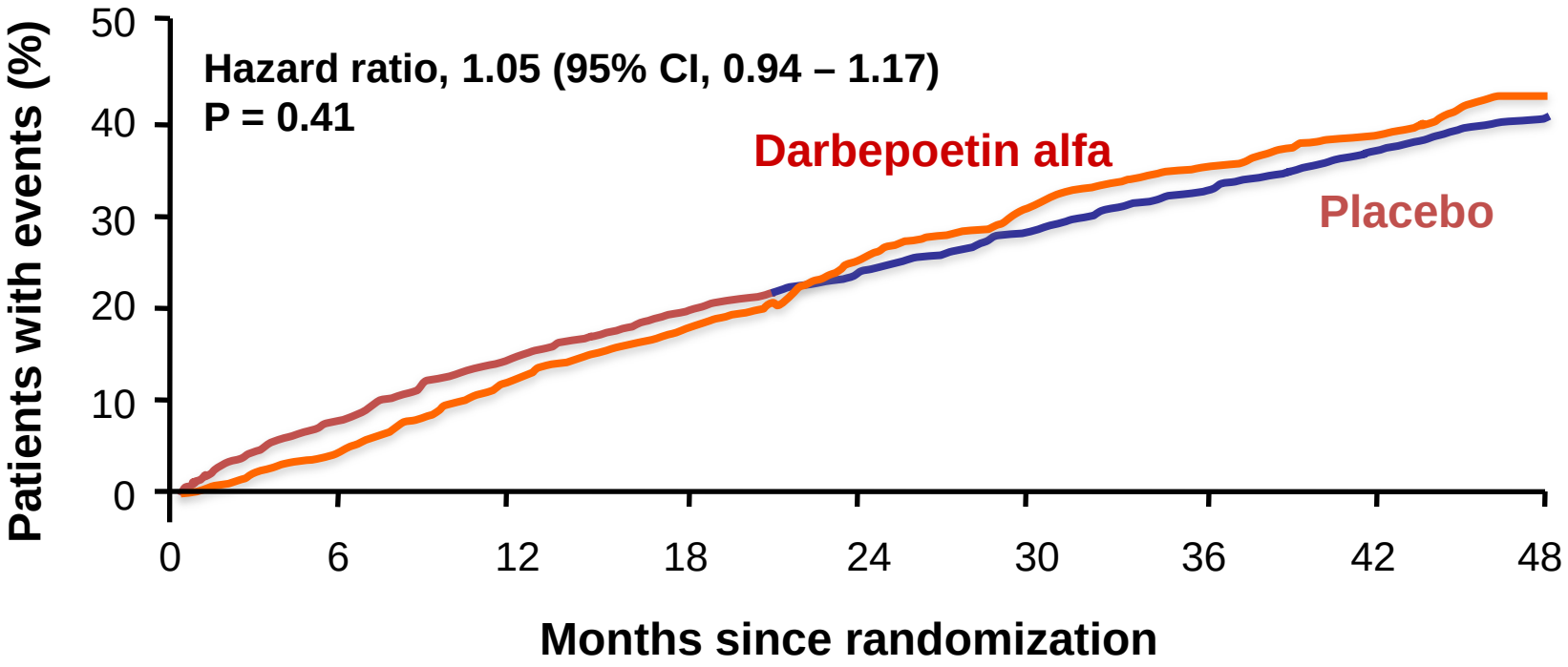
A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D., Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D., Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D., et al., for the TREAT Investigators*

- randomized, double-blind, placebo-controlled trial conducted at 623 sites in 24 countries.
- 4038 patients with diabetes, chronic kidney disease, and anemia, randomly assigned
  - 2012 patients to darbepoetin alfa to achieve an hemoglobin level of approximately 13 g per deciliter
  - 2026 patients to placebo, with rescue darbepoetin alfa when the hemoglobin level was less than 9.0 g per deciliter.
- The primary end points were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease.

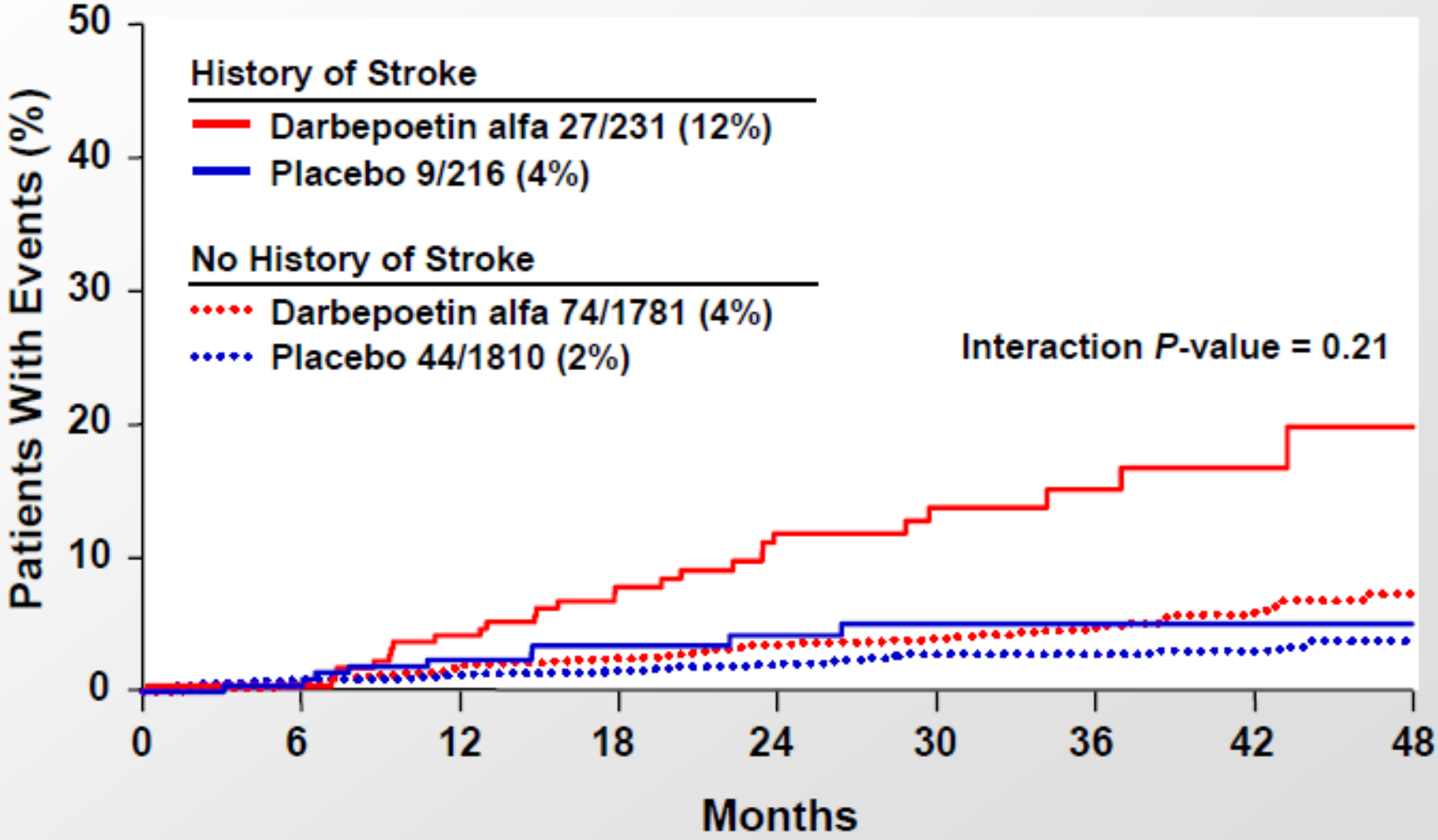
The TREAT Study

Cardiovascular composite end point (ITT)



Pfeffer MA et al. N Engl J Med 2009; 361:2019-32

Fatal and Nonfatal Stroke and History of Stroke (Post-hoc analysis)



Composite and Component End Points

End Point	Darbepoetin Alfa (N=2012)	Placebo (N=2026)	Hazard Ratio (95% CI)	P Value†
	number (percent)			
Primary end points				
Cardiovascular composite end point‡	632 (31.4)	602 (29.7)	1.05 (0.94–1.17)	0.41
Death from any cause	412 (20.5)	395 (19.5)	1.05 (0.92–1.21)	0.48
Myocardial infarction§	124 (6.2)	129 (6.4)	0.96 (0.75–1.22)	0.73
Stroke§	101 (5.0)	53 (2.6)	1.92 (1.38–2.68)	<0.001
Heart failure§	205 (10.2)	229 (11.3)	0.89 (0.74–1.08)	0.24
Myocardial ischemia	41 (2.0)	49 (2.4)	0.84 (0.55–1.27)	0.40
Renal composite end point (ESRD or death)	652 (32.4)	618 (30.5)	1.06 (0.95–1.19)	0.29
ESRD	338 (16.8)	330 (16.3)	1.02 (0.87–1.18)	0.83
Additional adjudicated end points				
Death from cardiovascular causes	259 (12.9)	250 (12.3)	1.05 (0.88–1.25)	0.61
Cardiac revascularization	84 (4.2)	117 (5.8)	0.71 (0.54–0.94)	0.02

ORIGINAL ARTICLE

The Treat Trial
NEJM 2009

A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D., Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D., Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D., et al., for the TREAT Investigators*

- The use of darbepoetin alfa (to achieve a higher Hb target) in patients with diabetes, chronic kidney disease, and moderate anemia who were not undergoing dialysis did not reduce the risk of either of the two primary composite outcomes (either death or a cardiovascular event or death or a renal event) and was associated with an increased risk of stroke.
- This risk may outweigh the potential benefits

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Darbepoetin Alfa and Chronic Kidney Disease

TO THE EDITOR: The TREAT study showed a neutral effect in aiming at a hemoglobin level of 13 g per deciliter as compared with a rescue value patients with chronic kidney disease and type 2 diabetes. The group with high levels of hemoglobin had more strokes and deaths related to cancer and mild improvement in quality of life. Should we stop treating our patients?

Should we stop treating our patients?

Locatelli, Del Vecchio, Casartelli N ENGL MED 362; 7 Feb 18, 2010

Darbepoetin Alfa and Chronic Kidney Disease

Nearly half these patients received darbepoetin alfa; this cannot be considered true "placebo"

control group than in the experimental group re-

of registry data, there is no evidence that we should stop treating anemia.

Given that the mean achieved hemoglobin level in the control group (10.6g per deciliter)… there is no evidence that we should stop treating anemia

Locatelli, Del Vecchio, Casartelli N ENGL MED 362; 7 Feb 18, 2010

KDIGO position statement

The current evidence, based on mortality data, for hemoglobin target levels intentionally aimed with ESA treatment in CKD patients treated indicates that:

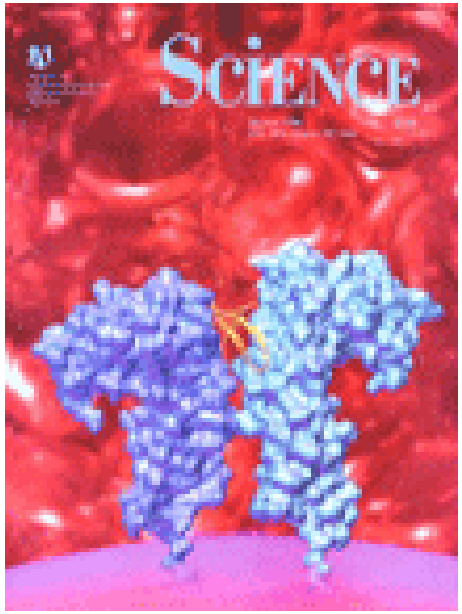
- levels of >13 g per 100 ml can be associated with harm,
- levels of 9.5–11.5 g per 100 ml are associated with better outcomes compared with >13 g per 100 ml
- for levels between 11.5 and 13 g per 100 ml, there is no evidence at this time for harm or benefit compared with higher or lower levels.

Locatelli – KI - 2008

Science The World's Leading Journal of Original Scientific Research, Global News, and Commentary.

Small Peptides as Potent Mimetics of the Protein Hormone Erythropoietin

Wrighton NC, Farrell FX, Chang R, Kashyap AK, Barbone FP, Mulcahy LS, Johnson DL, Barrett RW, Jolliffe LK, Dower WJ.



- Random phage display peptide libraries and affinity selective methods were used to isolate small peptides that bind to and activate the EPO receptor
- EPO mimetic peptide 1 (EMP1) was chosen
- This is a cyclic oligopeptide of 20 aminoacids, joined by a disulphide bridge between two cysteine residues

Science 1996 Jul 26;273(5274):458-64

AJKD AMERICAN JOURNAL OF KIDNEY DISEASES National Kidney Foundation

Am J Kidney Dis 2016; 67(1):133-142

New Treatment Approaches for the Anemia of CKD

Mario Bonomini, MD,[1] Lucia Del Vecchio, MD,[2] Vittorio Sirolli, MD,[1] and Francesco Locatelli, MD[2]

Not Directly Targeting the EPO Receptor

- HIF stabilizers
- Activin traps

Targeting the EPO Receptor

- EPO mimetic peptides
- EPO fusion proteins
- EPO-EPO dimers
- Antibody agonists to EPO receptor
- EPO gene therapy (TARGT EPO)
- Dimerization of EPO receptor intracellular domain with a CID

New erythropoiesis stimulating agents

Future directions

- HIF stabilizers

In-Depth Topic Review

American Journal of Nephrology

Am J Nephrol 2017;45:187–199
DOI: 10.1159/000455166

Published online: January 25, 2017

Targeting Hypoxia-Inducible Factors for the Treatment of Anemia in Chronic Kidney Disease Patients

Francesco Locatelli[a] Steven Fishbane[b] Geoffrey A. Block[c] Iain C. Macdougall[d]

[a]Department of Nephrology, Alessandro Manzoni Hospital, Lecco, Italy; [b]Department of Medicine, Hofstra Northwell School of Medicine, Great Neck, NY; [c]Denver Nephrologists, Denver, CO, USA; [d]Department of Renal Medicine, King's College Hospital, London, UK

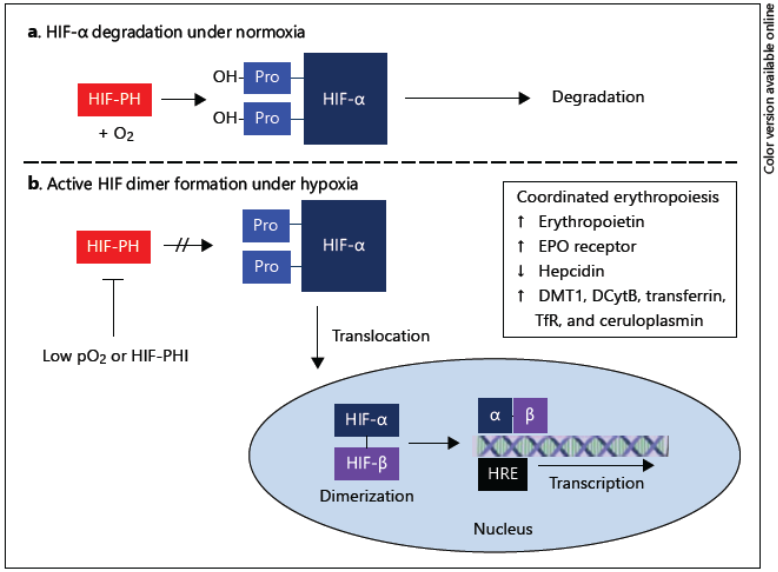


Fig. 2. a, b HIF activity under normoxic/hypoxic conditions and HIF-PHI inhibition, and its effects on erythropoiesis. DCytB, duodenal cytochrome B; DMT1, Divalent metal transporter 1; EPO, erythropoietin; HIF, hypoxia-inducible factor; HIF-PH, hypoxia-inducible factor-prolyl-4-hydroxylase domain; HRE, HIF-responsive element; Pro, proline.

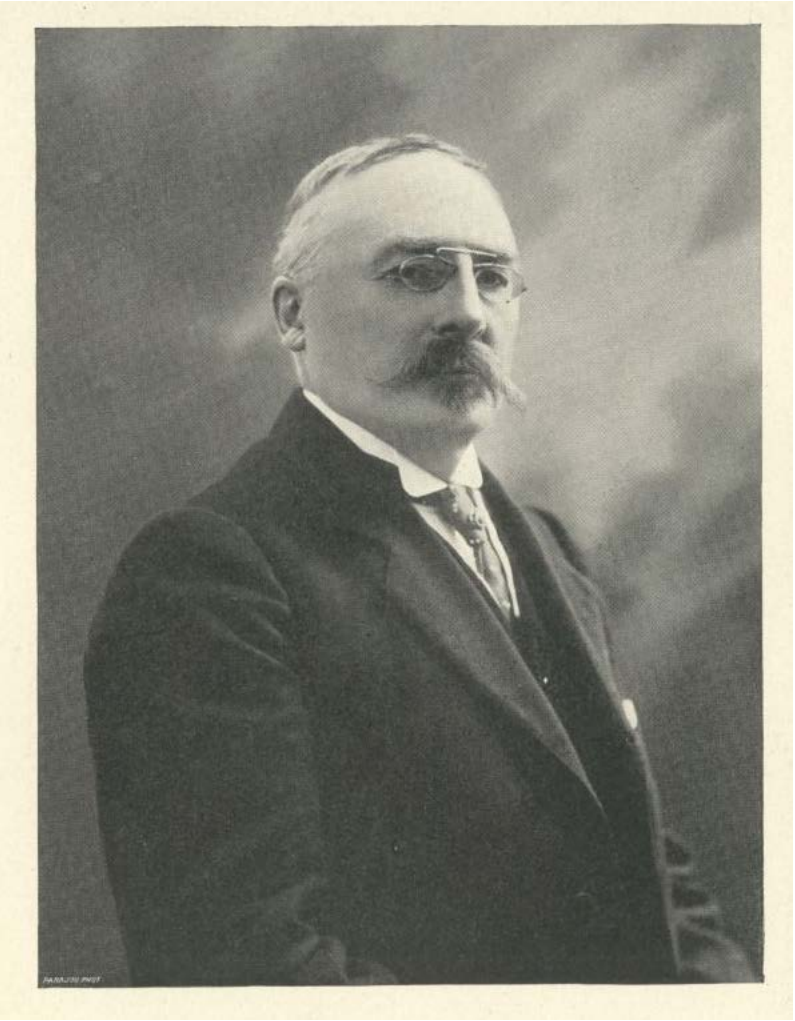
High-altitude physiology

At high altitude blood viscosity increase

Such change is due to an increase in red cells in the circulation

Mexico, Pico de Orizaba (5.610 m a.s.l.)

Paul Bert, 1870
La pression barometrique



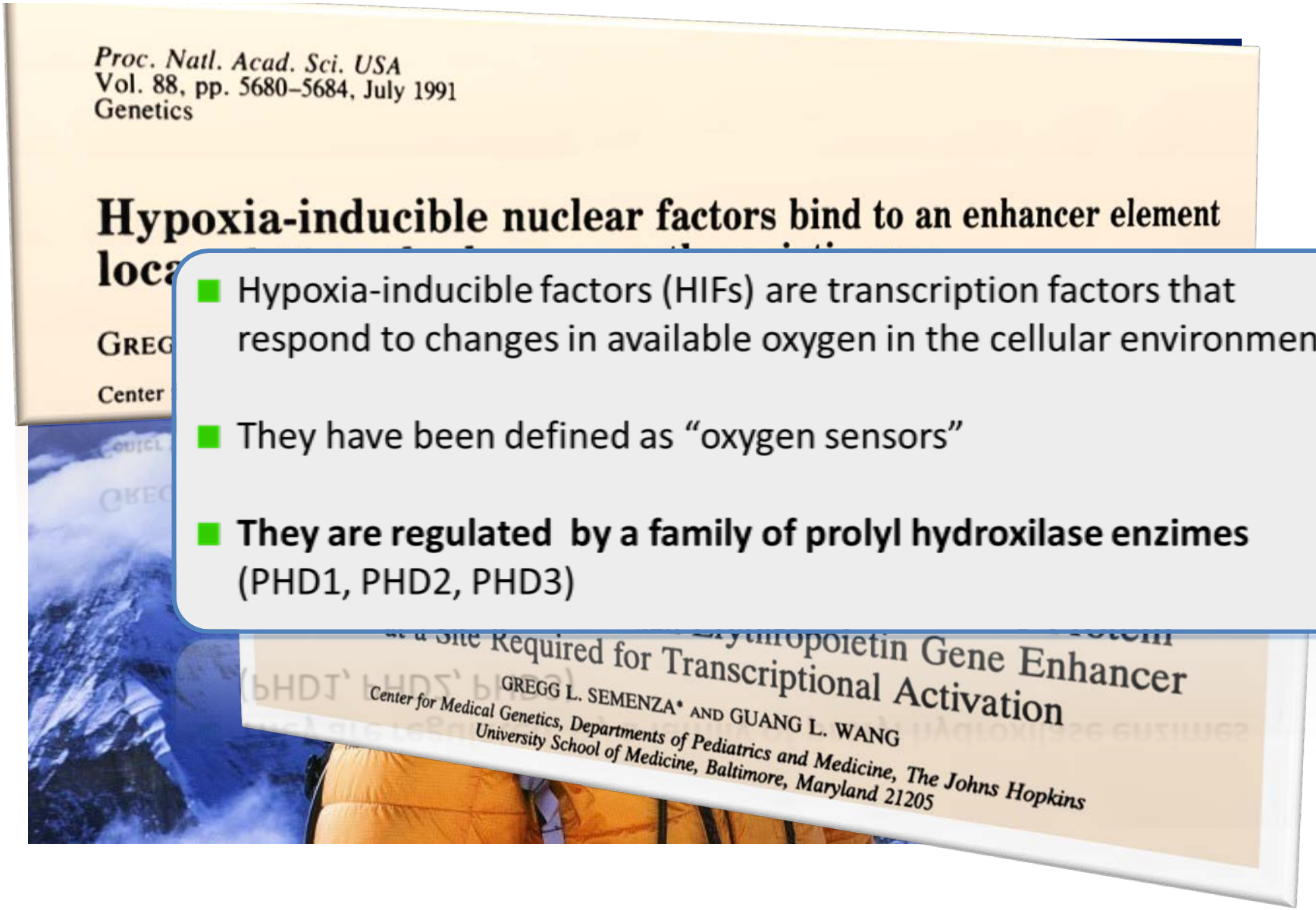
Professeur François-Gilbert Viault,
Professeur 'Anatomie Générale et d'Histologie à l'Université de Bordeaux, France

Expedition to the Peruvian Andes, 1890

Discovery:

Low oxygen partial pressure (pO2) induced increased erythropoiesis

HIF stabilizers



Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 5680–5684, July 1991
Genetics

Hypoxia-inducible nuclear factors bind to an enhancer element

GREG

Center

Required for Transcriptional Activation

GREGG L. SEMENZA* AND GUANG L. WANG

Center for Medical Genetics, Departments of Pediatrics and Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

- Hypoxia-inducible factors (HIFs) are transcription factors that respond to changes in available oxygen in the cellular environment
- They have been defined as “oxygen sensors”
- **They are regulated by a family of prolyl hydroxilase enzimes** (PHD1, PHD2, PHD3)

Hypoxia-Inducible Factor (HIF) Stabilizers

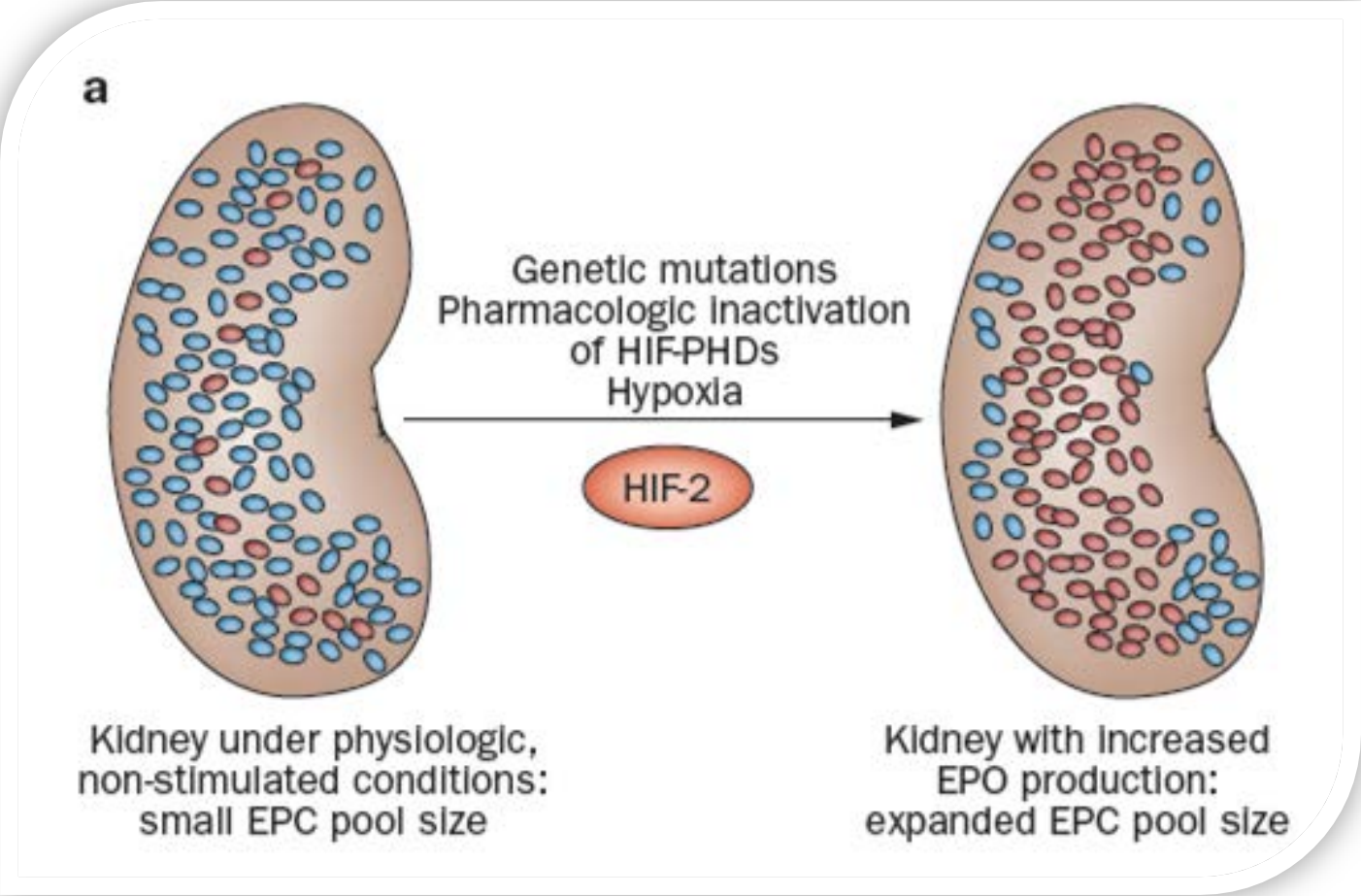
DRUG	COMPANY	STAGE OF CLINICAL DEVELOPMENT
FG-4592 (ROXADUSTAT)	FIBROGEN*	Phase II studies completed (ND CKD, HD, PD) **Phase III studies ongoing (ND CKD, HD, PD)**
AKB-6548 (VADADUSTAT)	AKEBIA THERAPEUTICS	Phase II studies completed (ND CKD) **Phase III studies ongoing (HD and ND-CKD, PRO$_2$TECT)**
GSK1278863	GLAXO SMITH KLINE	Phase IIa studies completed (ND CKD, HD) **Phase III studies ongoing, (ASCEND D and ASCEND ND)**
BAY 85-3934 (MOLIDUSTAT)	BAYER PHARMA	Phase IIb studies ongoing (ND CKD, HD) DIALOGUE studies
JTZ-951	AKROS PHARMA	Phase I study completed (HD)
DS-1093a	DAIICHI SANKYO	Phase I study completed (healthy and CKD stage 3-4 5D) STOP
ZYAN1	ZYDUS (INDIA)	Experimental studies in rats
JNJ-42905343	JOHNSON & JOHNSON	Experimental studies in rats

Phase 2 Punlished Studies

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

The size of the EPC pool is regulated in an oxygen-dependent manner and increases under hypoxic conditions



Koury MJ, Haase VH. Nat Rev Nephrol 2015Jul;11(7):394-410

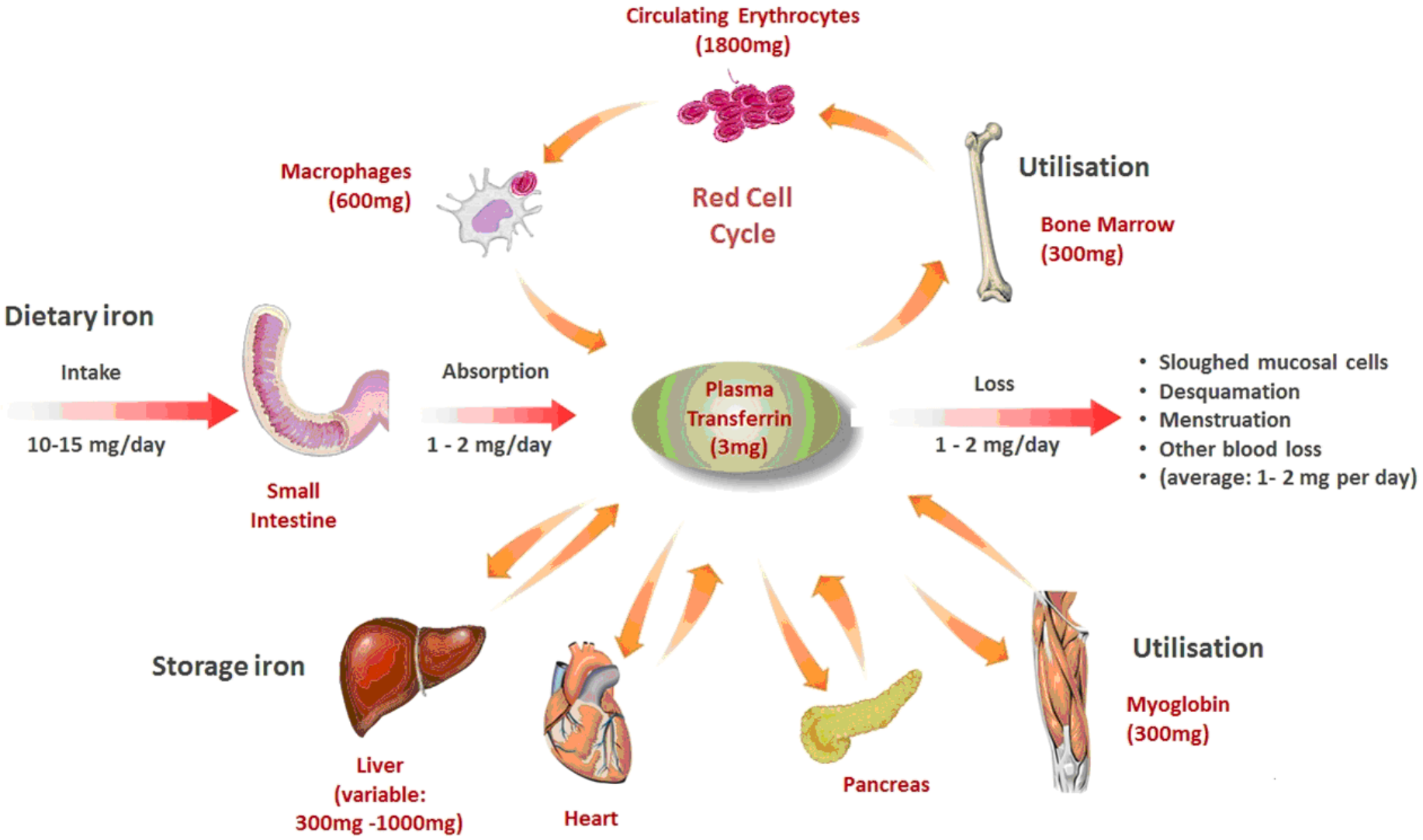
CLINICAL PRACTICE GUIDELINES FOR ANAEMIA IN ESRD

ESA

IRON

TRANSFUSIONs

Distribution of Iron in Adults



Causes of Absolute Iron Deficiency (1)

- Blood losses associated with:[1–3]
  - Laboratory tests and hospitalization
  - HD (from dialyzer and access)

	Healthy Patient	Non-dialysis CKD Patient	Hemodialysis Patient
Daily Blood Loss	0.83 ml/d	3.2 ml/d	5.0 ml/d
Annual Blood Loss	0.3 L/yr	1.2 L/yr	2–5 L/yr
Annual Iron Loss	0.1 g/yr	0.4 g/yr	1–2 g/yr to 4–5 g/yr

1. Sargent JA et al. Blood Purif 2004;22:112-113.
2. Rosenblatt SG et al. Am J Kidney Dis 1982;1:232-236.
3. Wizemann V et al. Kidney Int Suppl 1983;16:S218-S220.

Causes of Absolute Iron Deficiency (2)

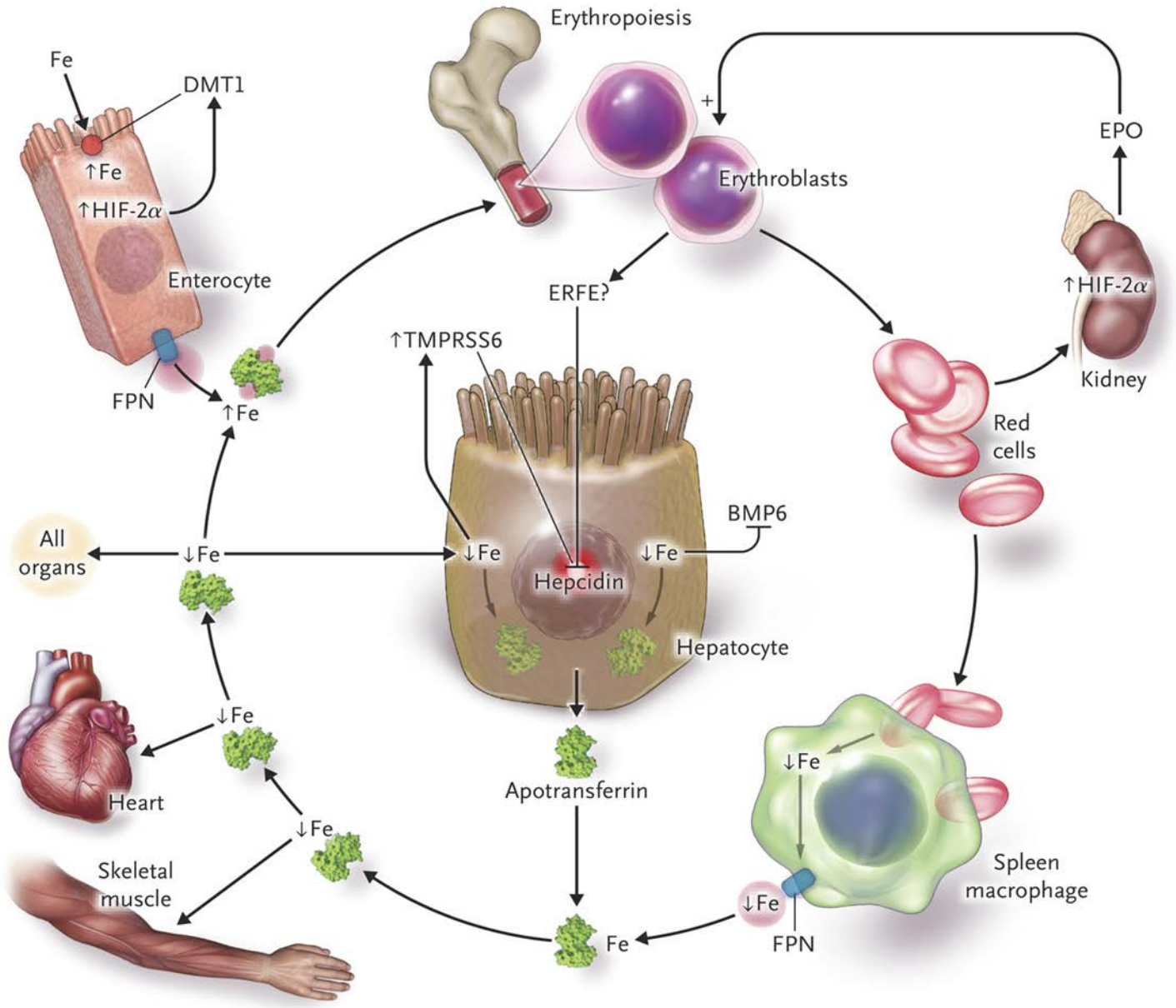
- GI losses due to anticoagulant or antiplatelet drugs.
- Reduced iron absorption due to medications (e.g., proton pump inhibitors and phosphate binders).
- Reduced iron absorption due to increased hepcidin levels.
- Reduced iron intake due to poor appetite, diet, and malnutrition.

Causes of Functional Iron Deficiency

- Inflammation results in:
  - Sequestration of iron within reticuloendothelial system (RES).
  - Reduced total iron binding capacity.
  - Lowered absolute amount iron available for erythropoiesis.

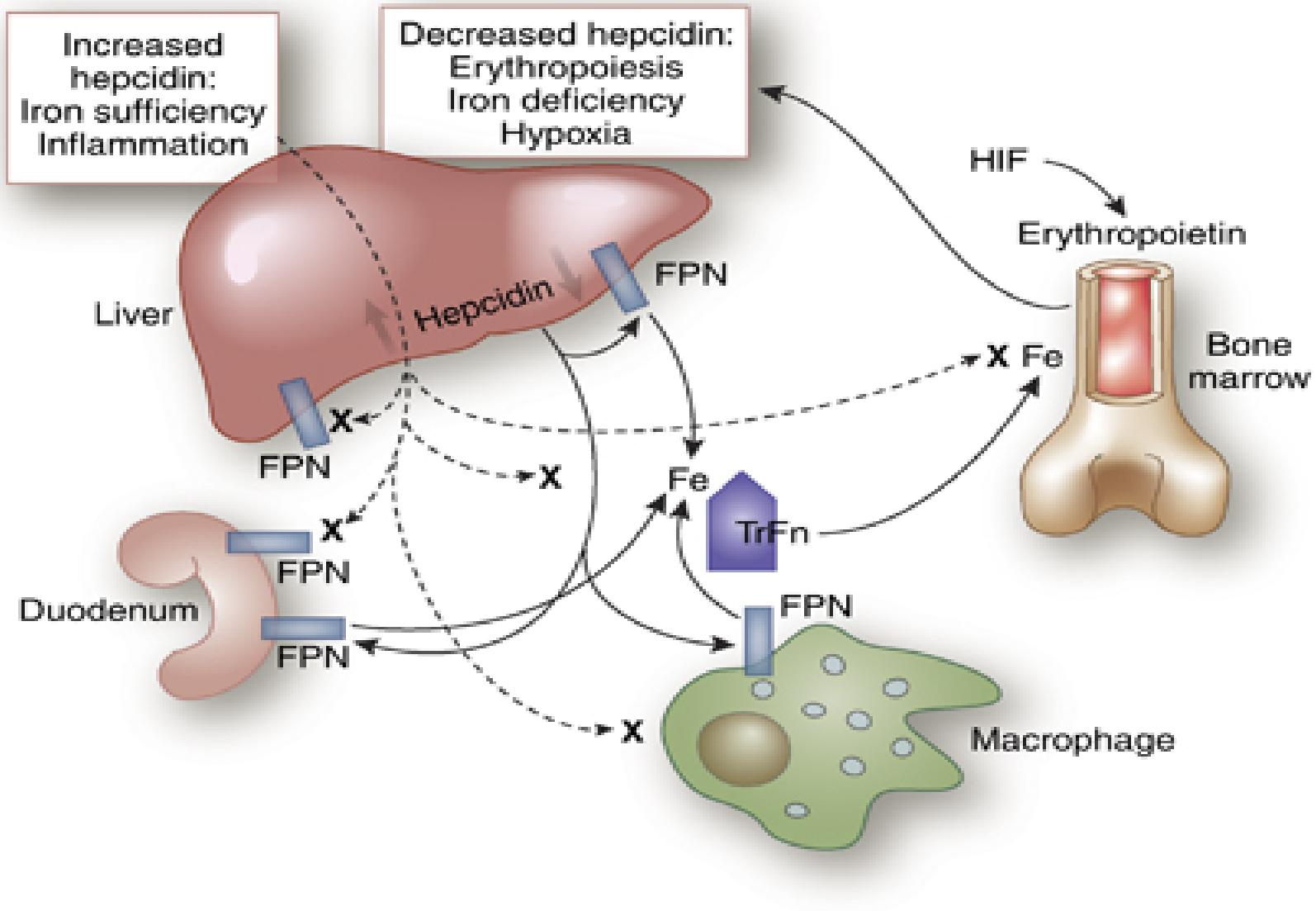
ESAs can create increased demand for iron and worsen iron availability in chronically inflamed patients.

Mechanisms of Adaptation to Iron Deficiency



Camaschella C. N Engl J Med 2015;372:1832-1843.

Role of Inflammation & Hepcidin in anemia in CKD



Measuring Iron Deficiency

- Both ferritin and TSAT have shortcomings when used to assess iron status.
- Ferritin 200 µg/l is frequently used as a cutoff value in dialysis patients.
- Although evidence is limited, TSAT <20% generally indicates absolute iron defiency.[1] However, TSAT >20% does not exclude this condition.
- In CKD patients, ferritin and TSAT should be used together.[1,2]
- Percentage of hypochromic red cells and reticulocyte Hb content can indicate inadequate iron supply, but the method is not practical for wide adoption.

1. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Int Suppl. 2012;2:279–335.
2. NICE Guideline No. 8, 2015.

Iron Therapy

- Oral formulations (sulfate, gluconate, fumarate, polysaccharide complex)
- Parenteral (iv) formulations (dextran, gluconate, sucrose, ferric carboxy maltose).
- Newer formulations are associated with significantly fewer side effects.
- The exact schedule for delivery needs to be optimized for each patient and there should be regular monitoring of Fe stores.
- Iv iron therapy should be guided by the iron status of the patient rather than empirical Rx. Approx 1000mg of Fe over 2-3 weeks is necessary to overcome the deficiency

Transfusions: lessons from TREAT

FDA U.S. Food and Drug Administration

The FDA calculated that for each five patients spared from transfusion, there was one additional stroke event

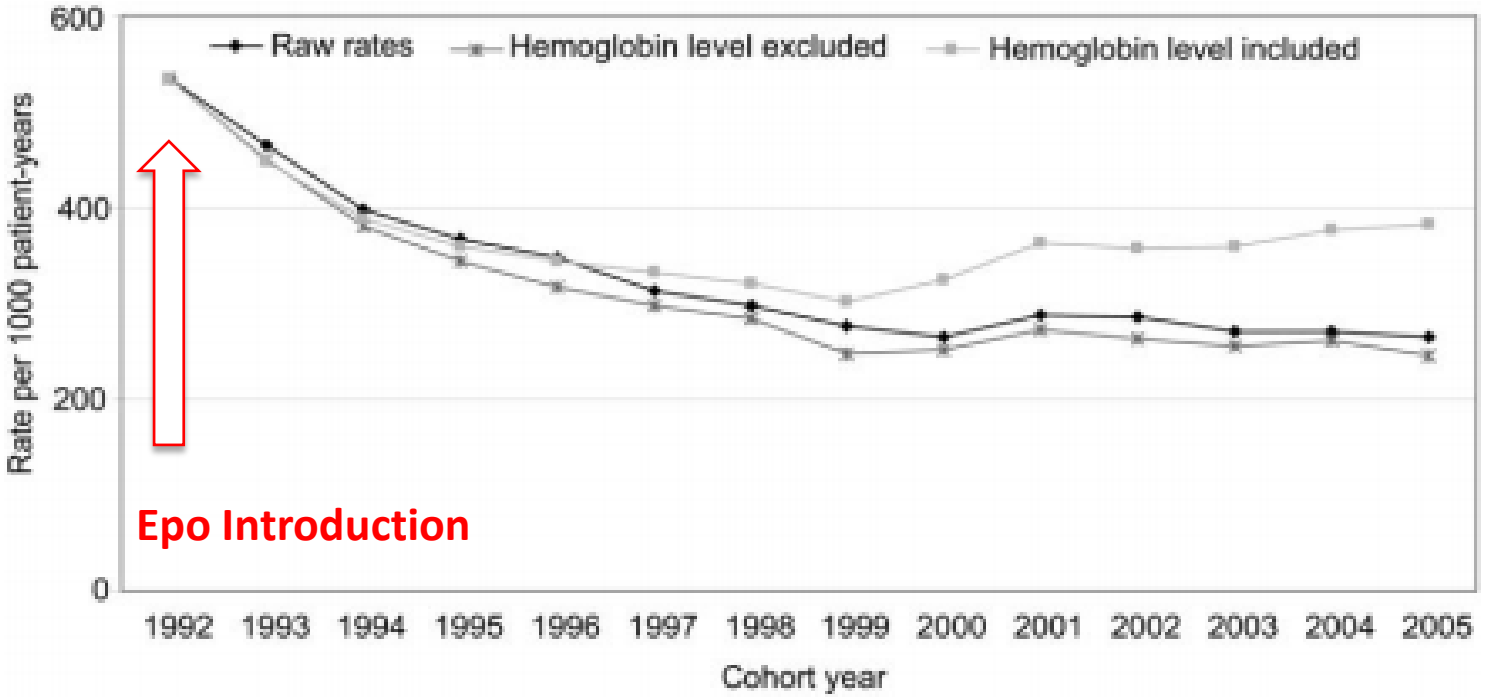
Lowering the labeled Hb target range would inevitably increase the risk for transfusion and with it the risk for allosensitization for future kidney transplant candidates

Wolfgang C. Winkelmayer. *J Am Soc Nephrol* 22: 1–2, 2011

Hassan I -AJKD - 2008

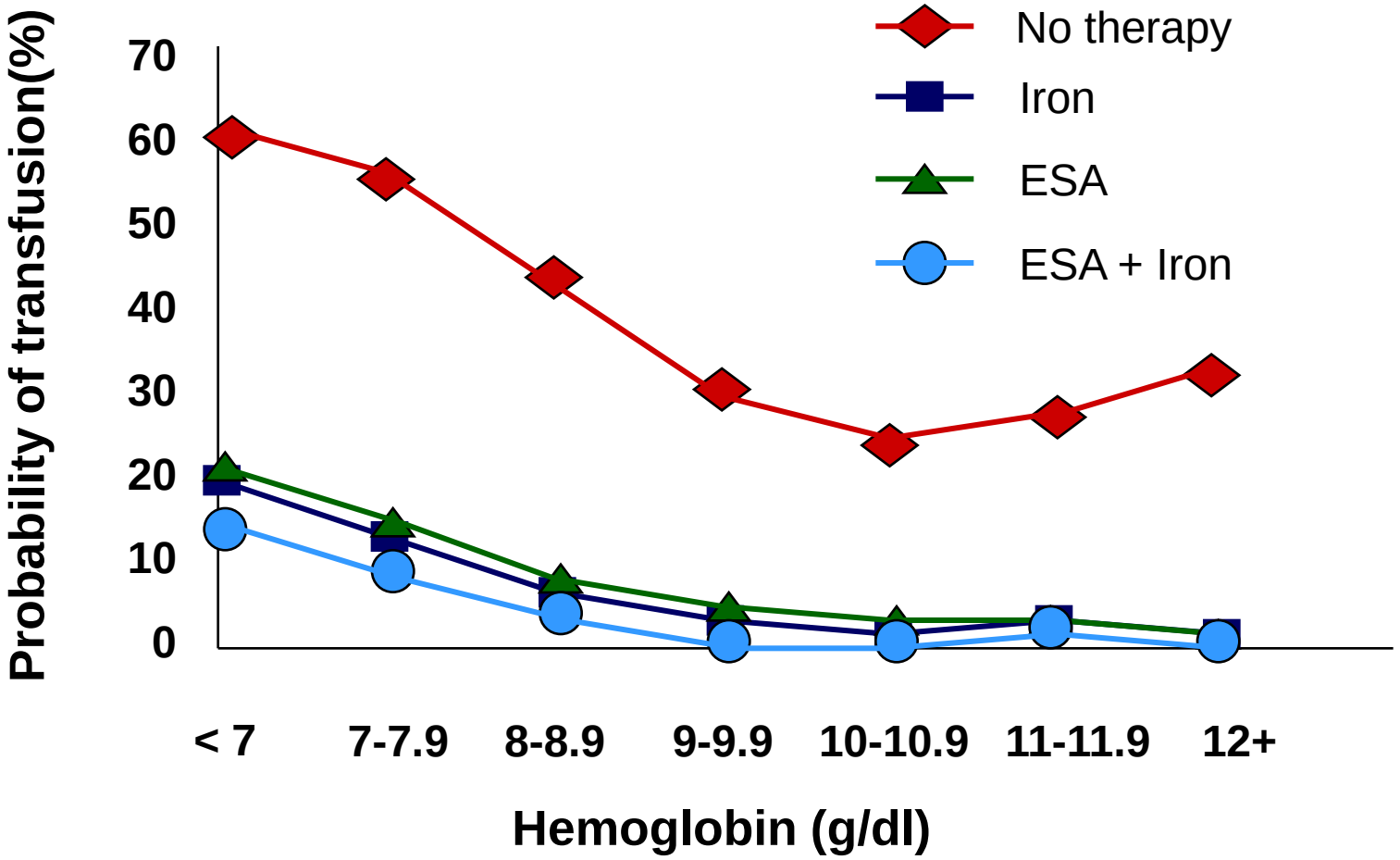
Temporal Trends in Red Blood Transfusion Among US Dialysis Patients, 1992-2005

Hassan N. Ibrahim, MD, MS,[1,2] Areef Ishani, MD, MS,[1,2] Robert N. Foley, MB,[1] Haifeng Guo, MS,[1] Jiannong Liu, PhD,[1] and Allan J. Collins, MD, FACP[1,2]



Transfusion events in hemodialysis patients decreased more than 2-fold from 1992 to 2005; most of the decrease occurred in the first 5 years after erythropoietin was introduced

Transfusion rates by Hb level according to the treatment status



Lawler ev et al *Clin J Am Soc Nephrol* 5: 667–672, 2010.

Never forget where we come from

Locatelli F, Del Vecchio L. Am J Nephrol 2010;31(6):557-60

The 'lucky 13' first chronic haemodialysis patients
Royal Free Hospital, January 1st 1965

Conclusions

- Anemia in CKD is multifactorial and plays critically contributes to patient's morbidity
- R-EPO introduction radically change anemia management and decreased more than 2-fold the transfusion burden
- The data on the upper limit of target Hb is conflicting but there is a trend towards a lower value.
- Newer agents both directly than indirectly targeting EPO receptor can represent the next step in anemia management in ESRD patients
- The analysis, prevention and treatment of iron deficiency is critical in anemia management, especially in ESRD patients.

Finding the magic formula for anemia treatment

A pinch of ESA…

A pinch of iron…

Mix everything together using wisdom


Grazie