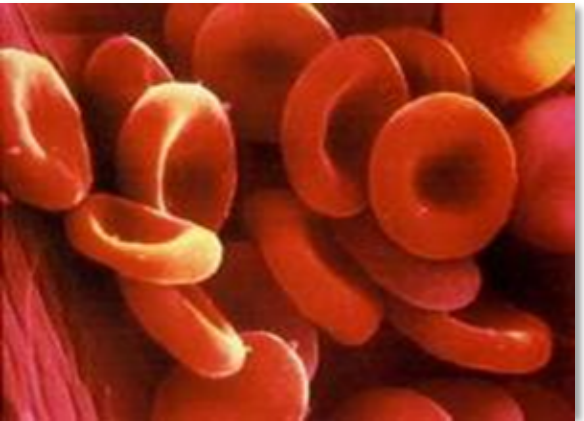
King's College Hospital NHS
NHS Foundation Trust

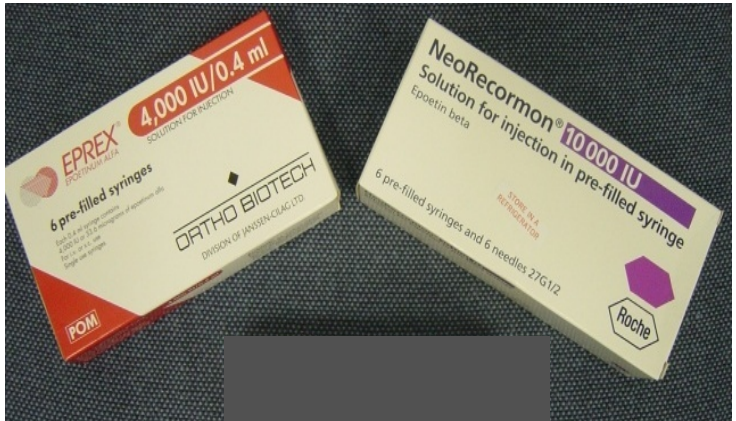
KING'S College LONDON

Management of CKD anaemia: the past, the present, and the future

Iain C. Macdougall

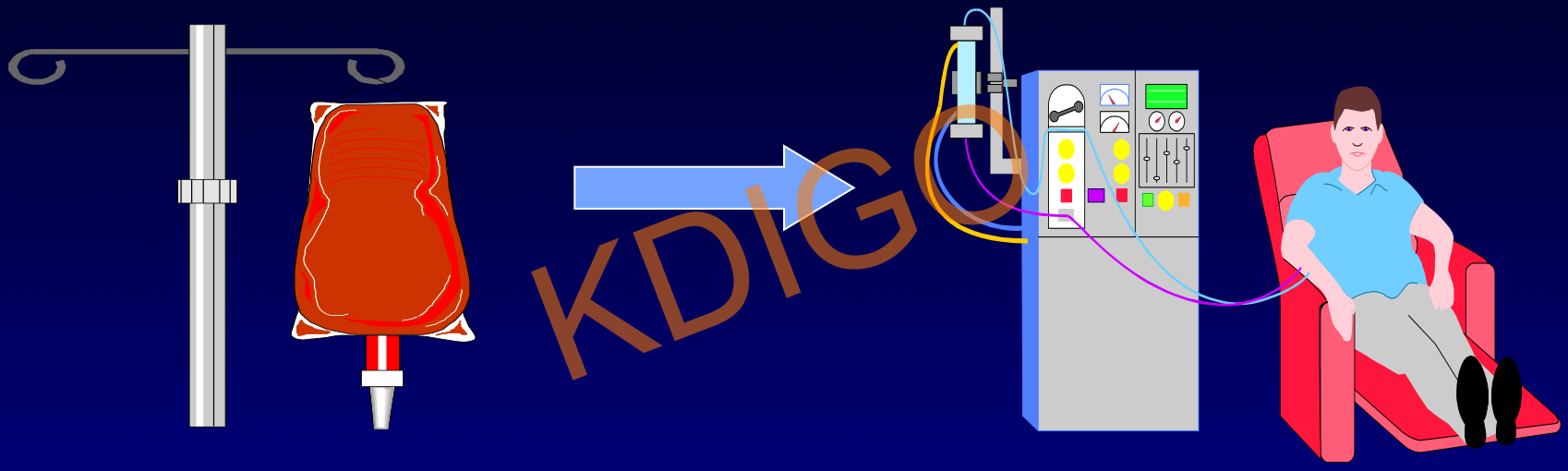
Consultant Nephrologist & Professor of Clinical Nephrology



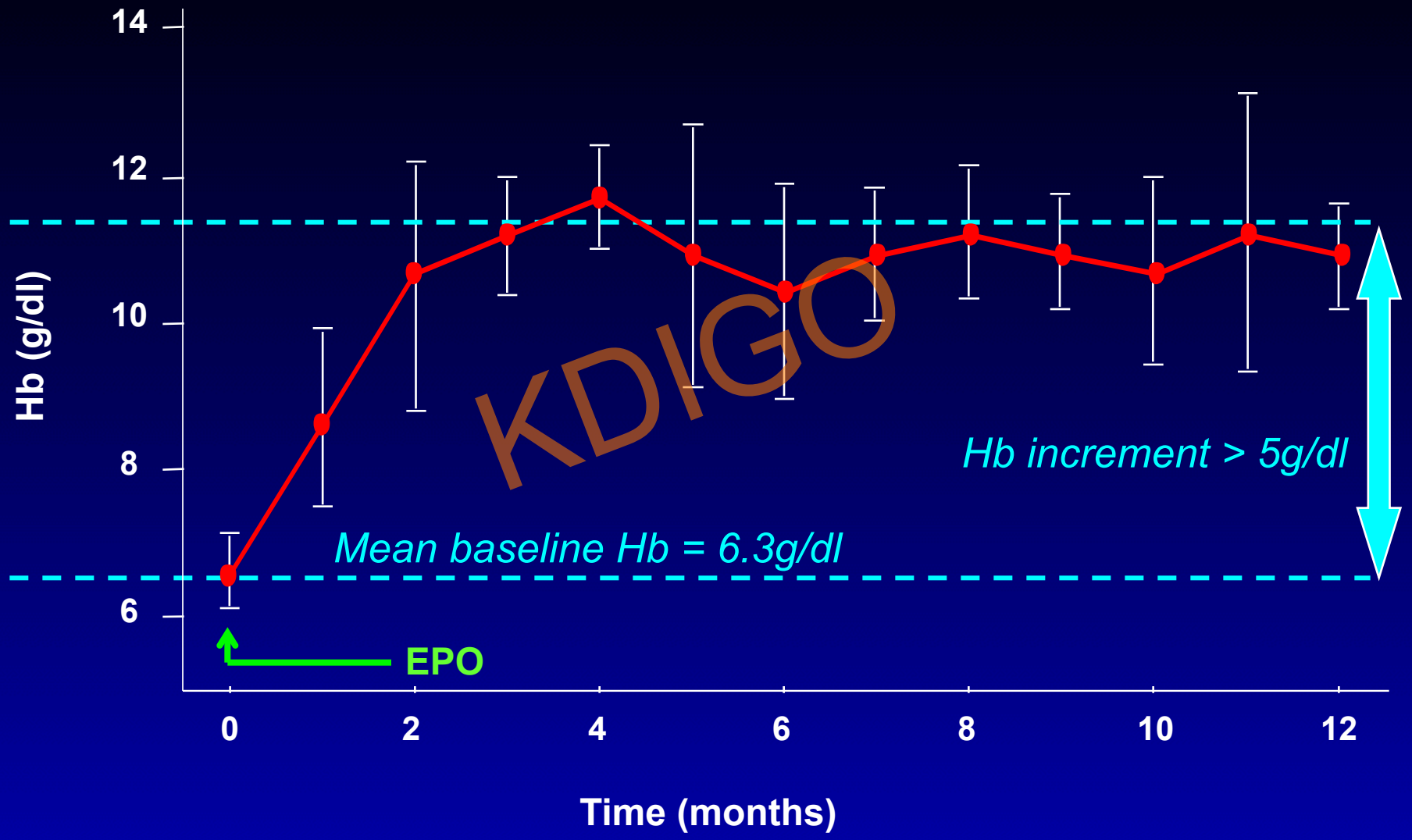


The past

Management of CKD anaemia prior to EPO



- Many dialysis patients had “top-up” transfusions every 2–4 weeks
- Effects transient
- Increased risk of infections, *esp. viral*
- Sensitisation to HLA antigens – transplantation problematic
- Iron overload



Macdougall et al., Lancet 1990; 335: 489-493.

Correction of anaemia - benefits

- ↑ quality-of-life
- ↑ exercise capacity
- ↓ cardiac output
- ↓ angina
- ↓ LVH
- ↓ bleeding tendency
- ↑ brain / cognitive function
- ↓ depression
- ↑ sleep patterns
- ↑ sexual function
- ↑ endocrine function
- ↑ immune function
- ↑ muscle metabolism
- ↓ hospitalisations
- ↓ transfusions
- ↑ nutrition

Canadian EPO Study Group

- Double-blind
- Randomised
- Placebo-controlled

- *Effect of EPO on:-*

quality-

of-life – *KDQ*

– *SIP*

–

exercise capacity

– *6-*

–

ss test

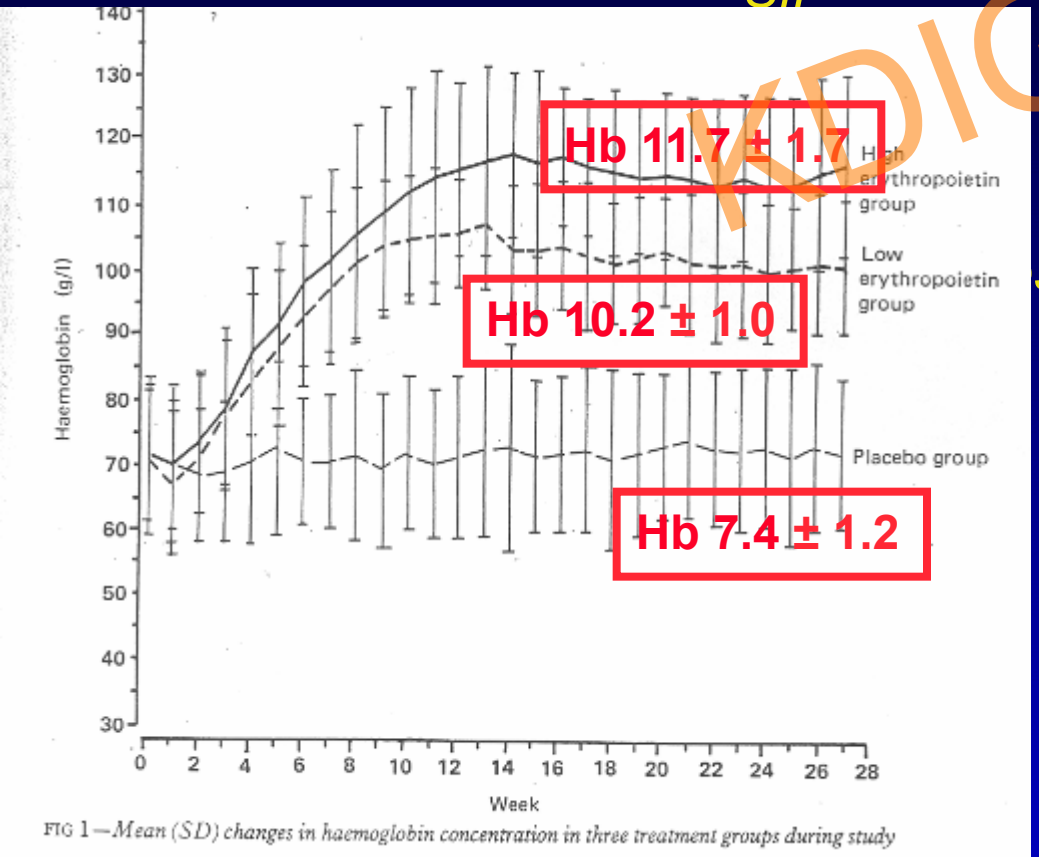


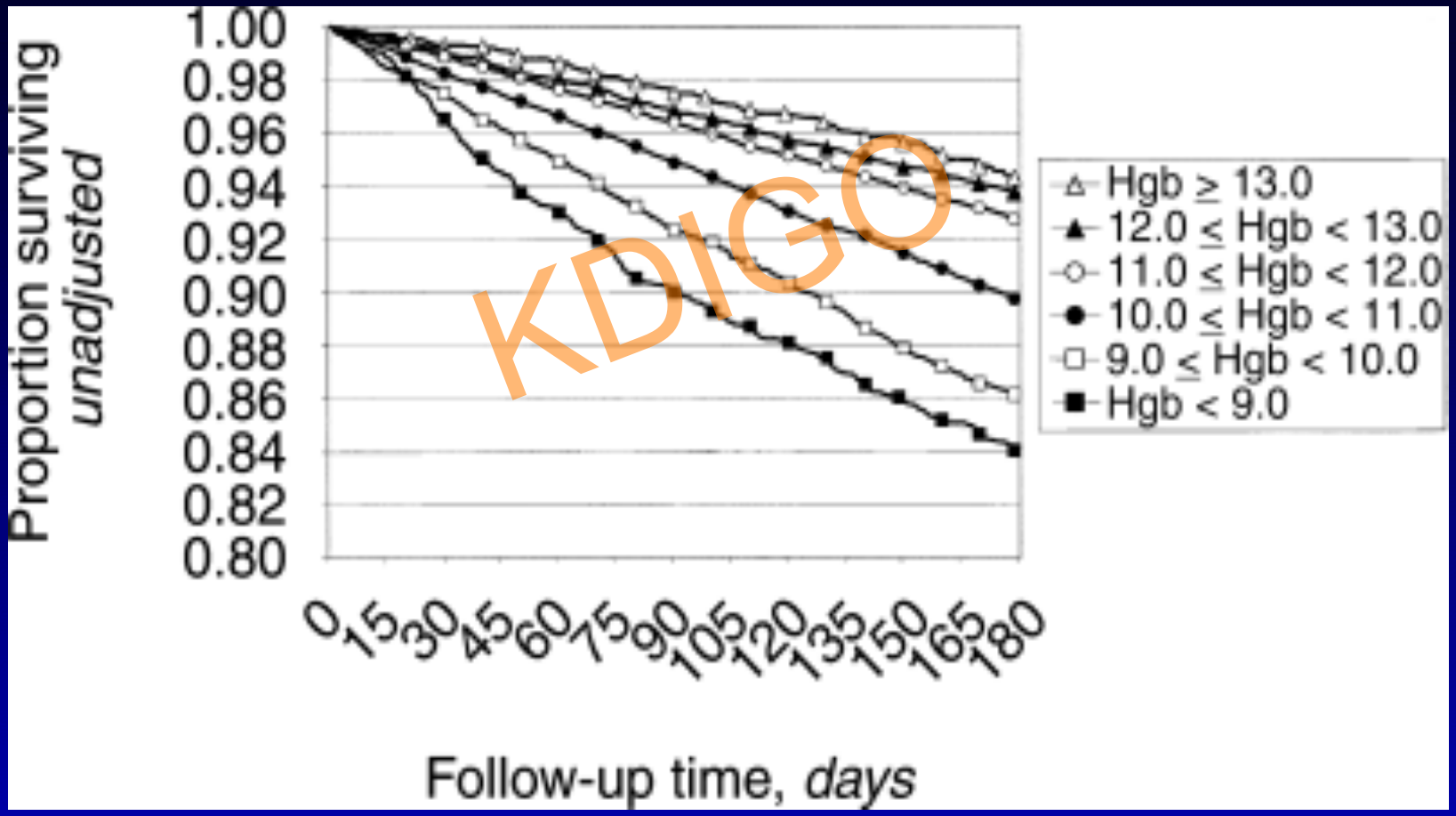
FIG 1—*Mean (SD) changes in haemoglobin concentration in three treatment groups during study*

- *118 HD pts. – Hb < 9g/dl*
- *EPO produced*
  - ↑ global & physical score
  - ↑ distance on stress test
  - ↑ diastolic BP
  - ↑ vascular access clotting

(11/78 vs. 1/40 placebo)

Hb predicts survival in observational studies

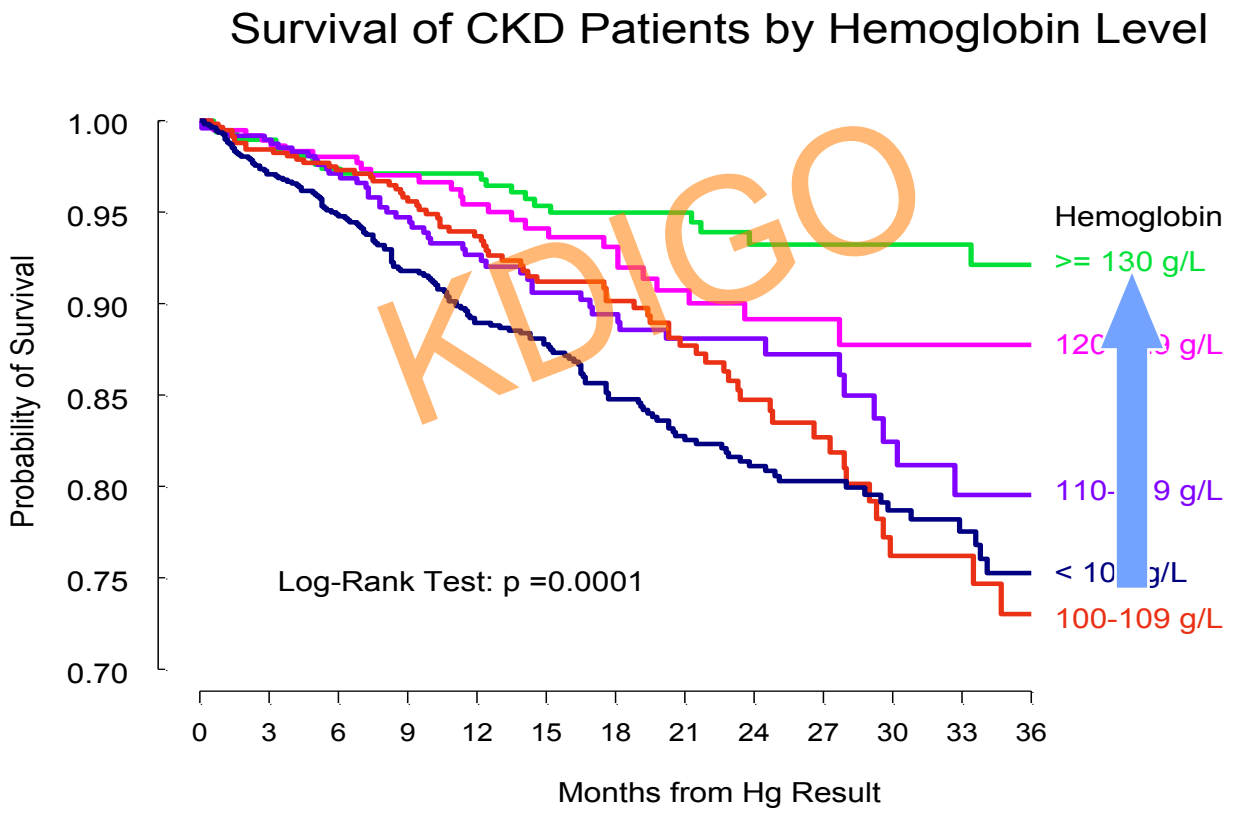
HD patients



Ofsthun et al, Kidney Int 2003; 63: 1908-1914.

Hb predicts survival in observational studies

ND-CKD patients



Levin A. et al, Nephrol Dial Transplant 2006; 21: 370-377.

And then the RCTs came along……

US Normal Hematocrit Trial

The New England Journal of Medicine

THE EFFECTS OF NORMAL AS COMPARED WITH LOW HEMATOCRIT VALUES IN PATIENTS WITH CARDIAC DISEASE WHO ARE RECEIVING HEMODIALYSIS AND EPOETIN

ANATOLE BESARAB, M.D., W. KLINE BOLTON, M.D., JEFFREY K. BROWNE, PH.D., JOAN C. EGRIE, PH.D., ALLEN R. NISSENSON, M.D., DOUGLAS M. OKAMOTO, PH.D., STEVE J. SCHWAB, M.D., AND DAVID A. GOODKIN, M.D.

ABSTRACT

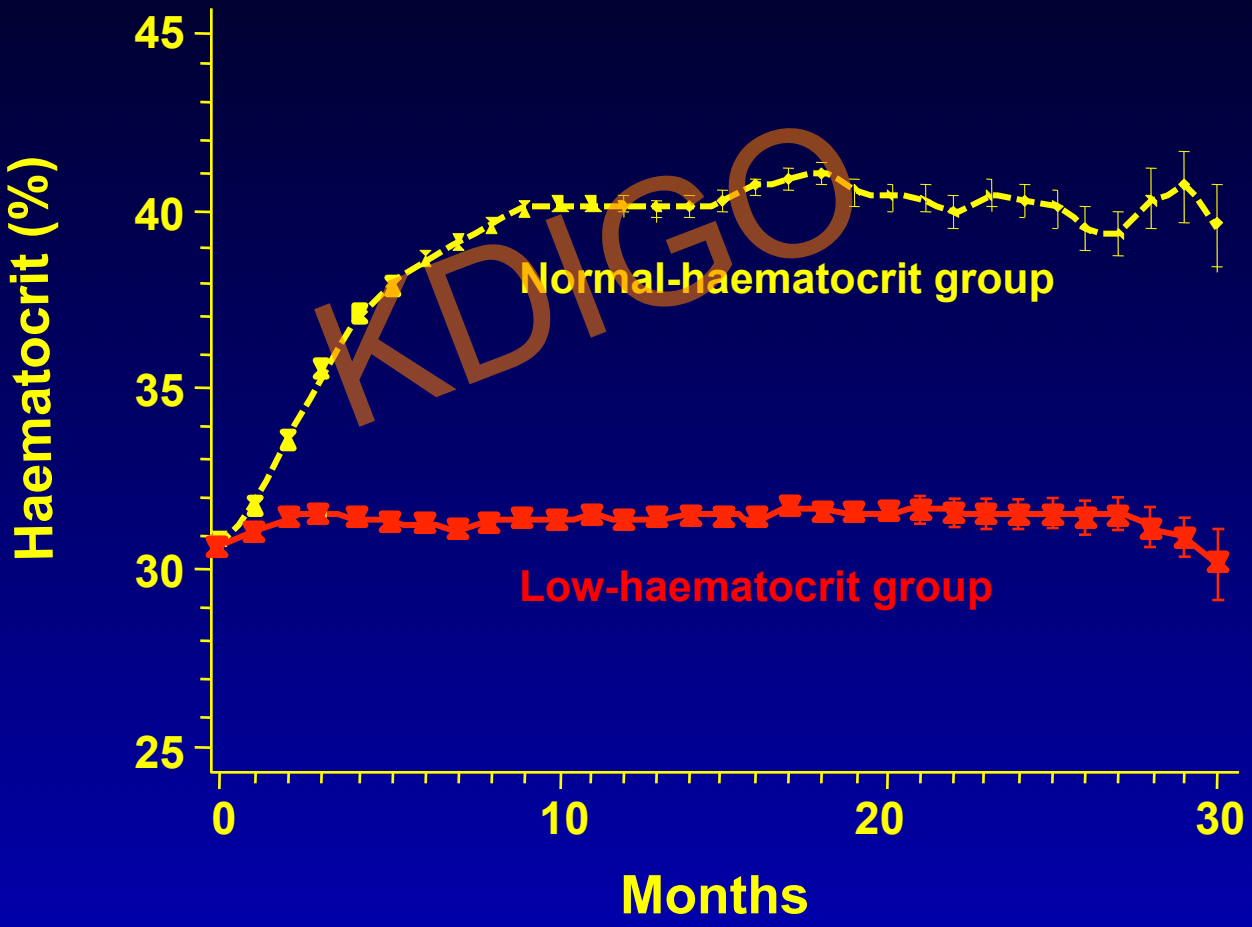
Background In patients with end-stage renal disease, anemia develops as a result of erythropoietin deficiency, and recombinant human erythropoietin (epoetin) is prescribed to correct the anemia partially. We examined the risks and benefits of normalizing the hematocrit in patients with cardiac disease who were undergoing hemodialysis.

Methods We studied 1233 patients with clinical evidence of congestive heart failure or ischemic heart disease who were undergoing hemodialysis: 618 patients were assigned to receive increasing doses of epoetin to achieve and maintain a hematocrit of 42 percent, and 615 were assigned to receive doses of epoetin sufficient to maintain a hematocrit of 30 percent throughout the study. The median duration of treatment was 14 months. The primary end point was the length of time to death or a first nonfatal myocardial infarction.

ation of this study, we found that 69 percent of the patients had hematocrits of 27 to 33 percent, 15 percent had values below 27 percent, and 16 percent had values above 33 percent (unpublished data). Yet the normal ranges for hematocrit values are 37 to 48 percent for women and 42 to 52 percent for men,[1] prompting the question of whether increasing the doses of epoetin would benefit patients who are undergoing hemodialysis. Cerebral oxygen delivery among patients with ischemic cerebrovascular disease, for example, is maximal when the hematocrit is 40 to 45 percent.[2]

Cardiac disease is the most common cause of death among patients who are regularly receiving dialysis.[3] Among these patients, partial correction of anemia reduces exercise-induced cardiac ischemia[4,5] and ameliorates the left ventricular hypertrophy[4,6-9] that predisposes patients to death and cardiac-related mor-

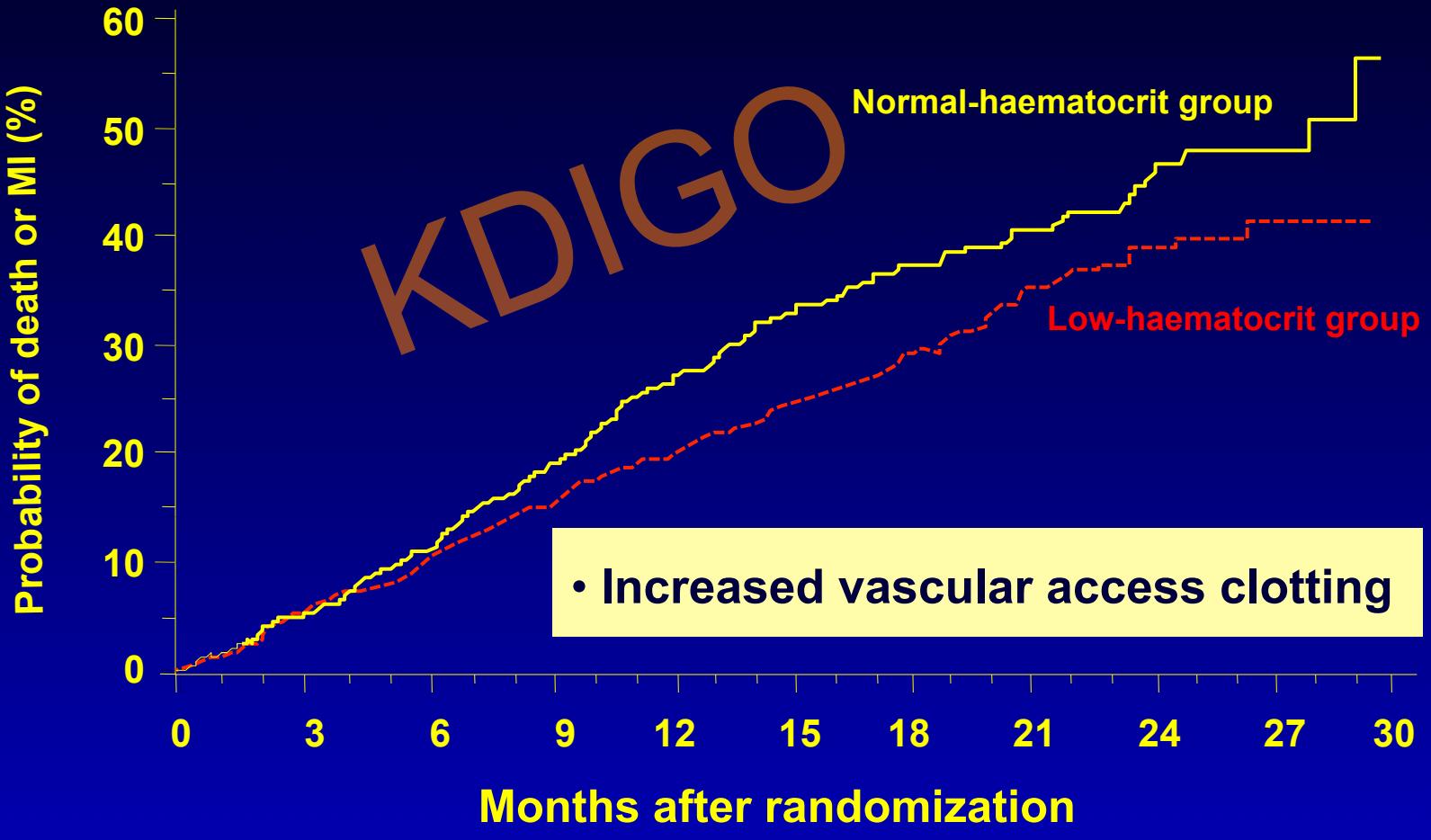
US Normal Hematocrit Trial



Besarab et al. NEJM 1998; 339: 584-90.

US Normal Hematocrit Trial

- *probability of death or first non-fatal MI*



Besarab et al. NEJM 1998; 339: 584-90.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2006 VOL. 355 NO. 20

Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia

Tilman B. Drüeke, M.D., Francesco Locatelli, M.D., Naomi Clyne, M.D., Kai-Uwe Eckardt, M.D., Iain C. Macdougall, M.D., Dimitrios Tsakiris, M.D., Hans-Ulrich Burger, Ph.D., and Armin Scherhag, M.D., for the CREATE Investigators*

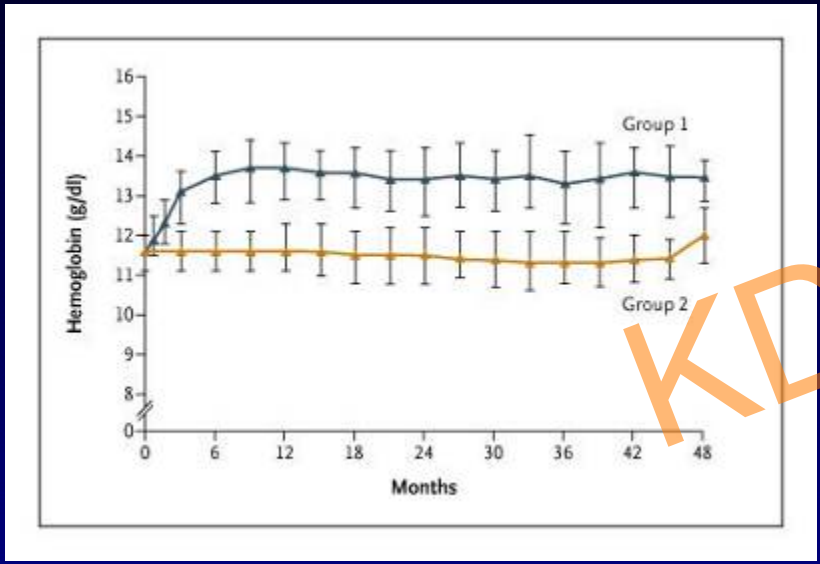
The NEW ENGLAND JOURNAL of MEDICINE

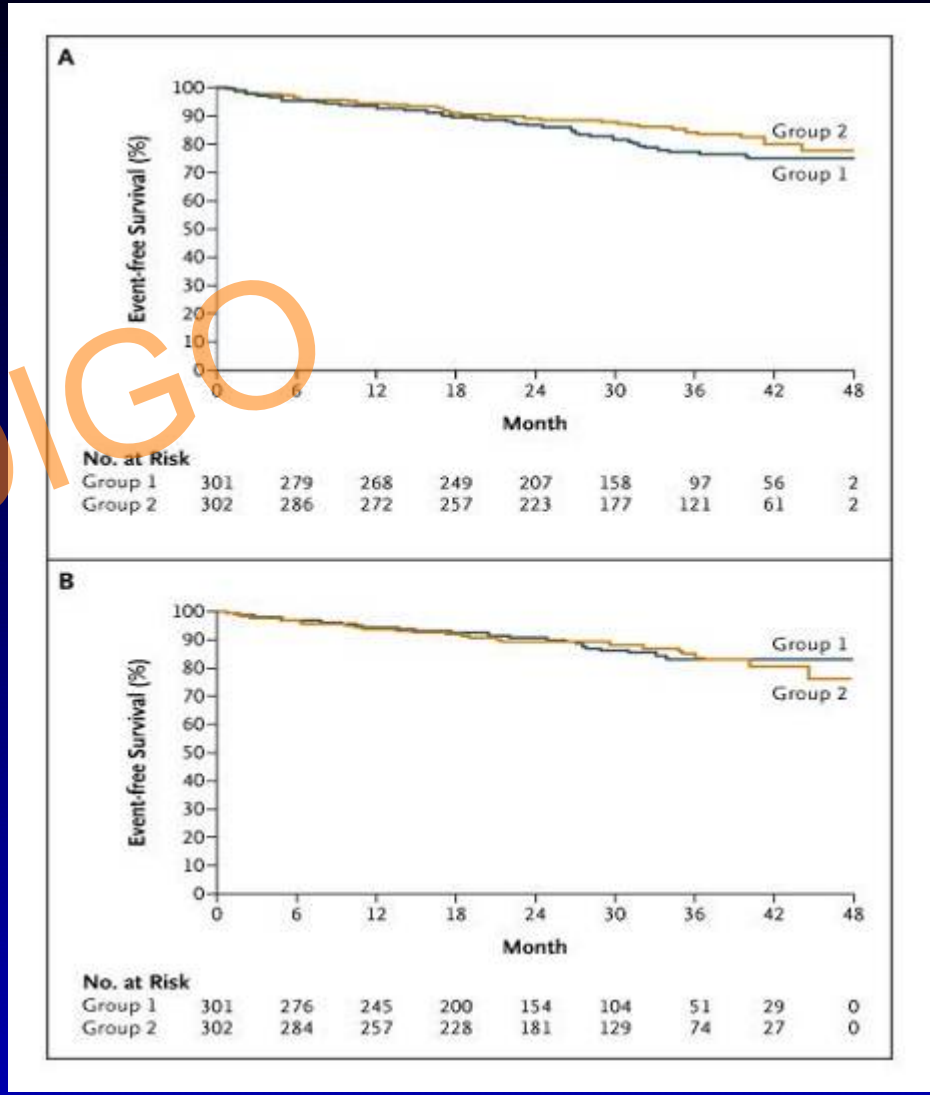
ORIGINAL ARTICLE

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

Ajay K. Singh, M.B., B.S., Lynda Szczech, M.D., Kezhen L. Tang, Ph.D., Huiman Barnhart, Ph.D., Shelly Sapp, M.S., Marsha Wolfson, M.D., and Donal Reddan, M.B., B.S., for the CHOIR Investigators*

CREATE Study





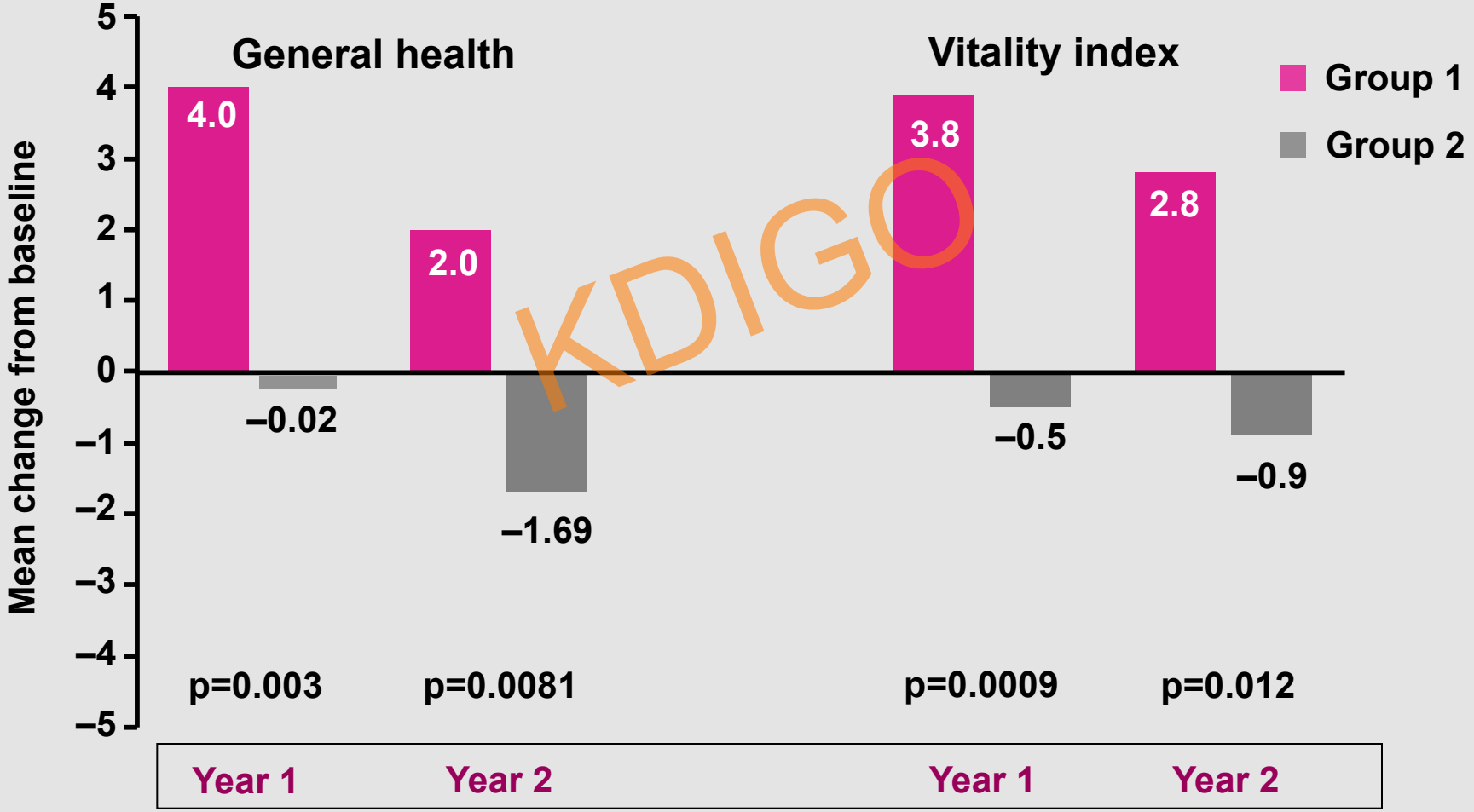
The NEW ENGLAND JOURNAL of MEDICINE

Drueke TB et al. N Engl J Med 2006;355:2071-2084.

Quality of life

General health and vitality index (SF-36)

CREATE study



CHOIR Study

- 1,432 non-dialysis CKD patients
- 130 US centres
- Treated with epoetin alfa

randomised

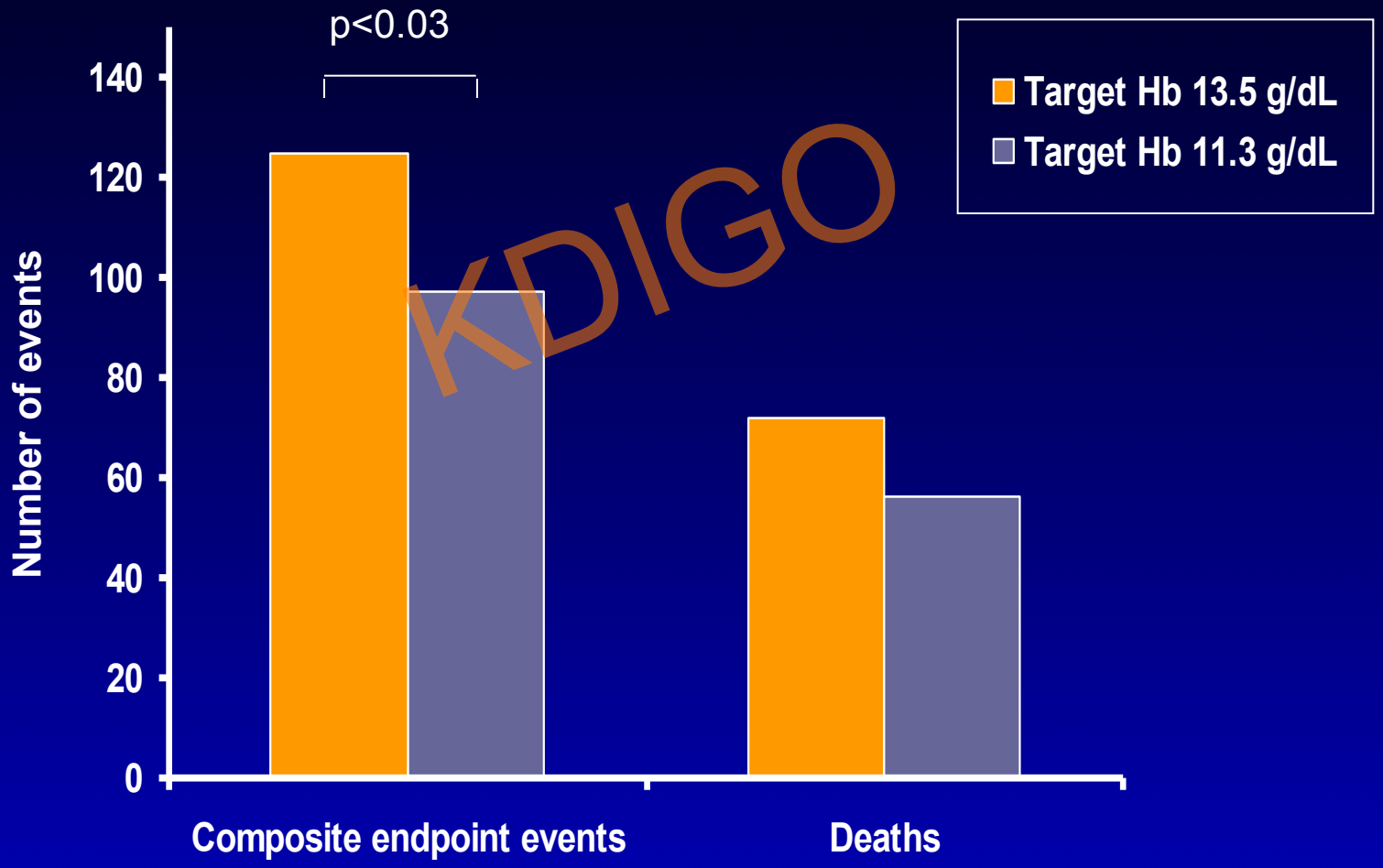
Hb 13.5 g/dl *Hb 11.3 g/dl*

- Composite end-point

(mortality, stroke, heart attack, hospitalisation)

Singh et al. NEJM 1998; 355: 2085-2098.

CHOIR Study



Singh et al. NEJM 1998; 355: 2085-2098.

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2009 Nov 19; 361: 2019-32.

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., John J.V. McMurray, M.D., Patrick Parfrey, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D., Ajay K. Singh, M.D., Scott D. Solomon, M.D., and Robert Toto, M.D., for the TREAT Investigators*

ABSTRACT

BACKGROUND

Anemia is associated with an increased risk of cardiovascular and renal events among patients with type 2 diabetes and chronic kidney disease. Although darbepoetin alfa can effectively increase hemoglobin levels, its effect on clinical outcomes in these patients has not been adequately tested.

METHODS

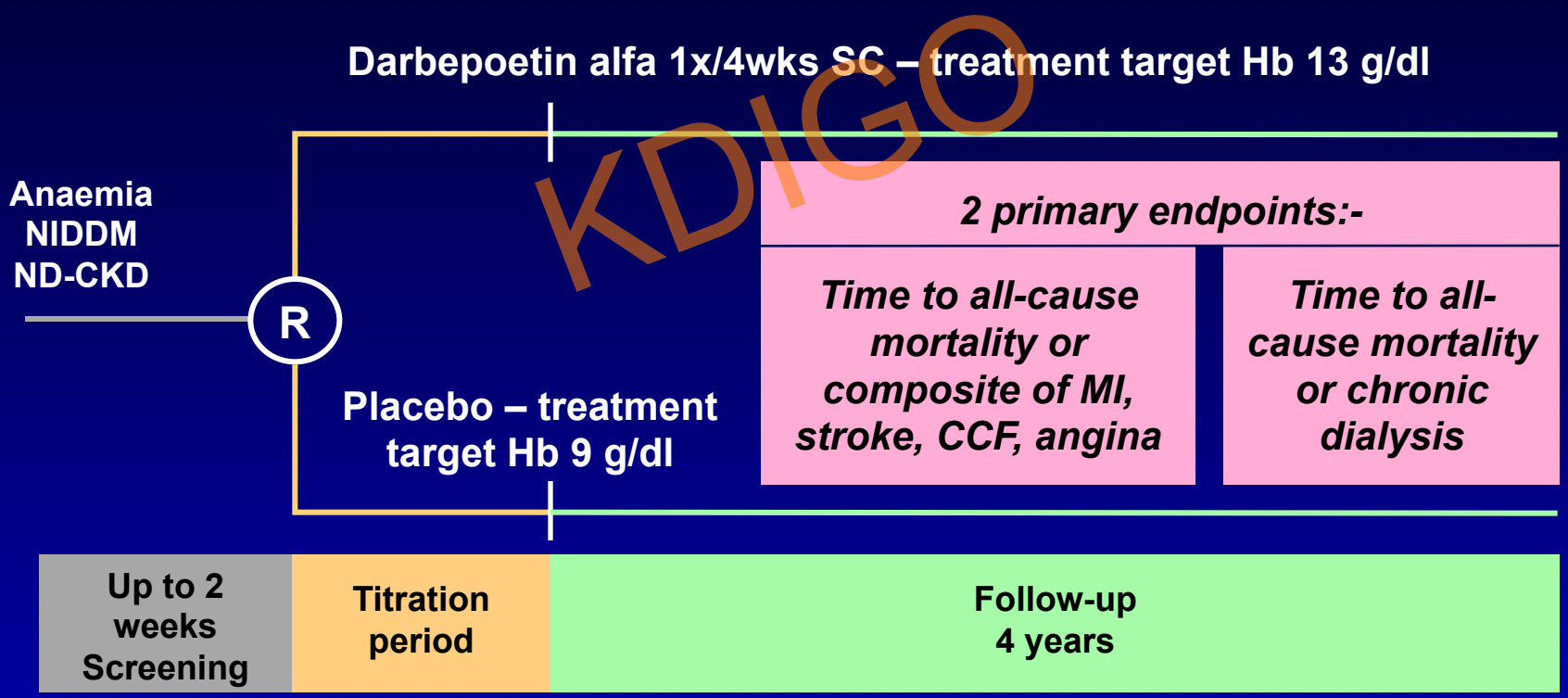
In this study involving 4038 patients with diabetes, chronic kidney disease, and anemia, we randomly assigned 2012 patients to darbepoetin alfa to achieve a hemoglobin level of approximately 13 g per deciliter and 2026 patients to placebo, with

The affiliations of the authors are listed in the Appendix. Address reprint requests to Dr. Pfeffer at the Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at mpfeffer@rics.bwh.harvard.edu.

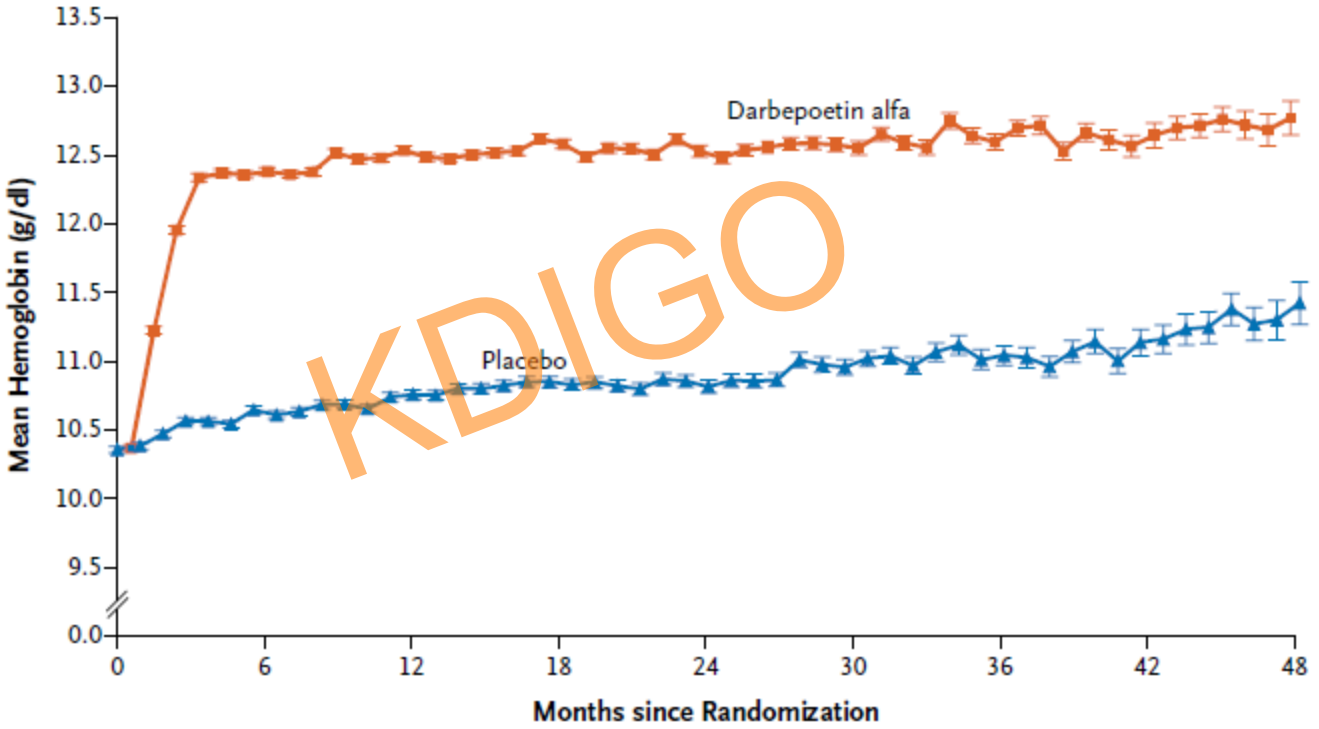
*The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) committees and teams are listed in the Appendix, and investigators and individual

The TREAT Study

Double-blind placebo controlled RCT: n = 4038



TREAT Study – Hb response



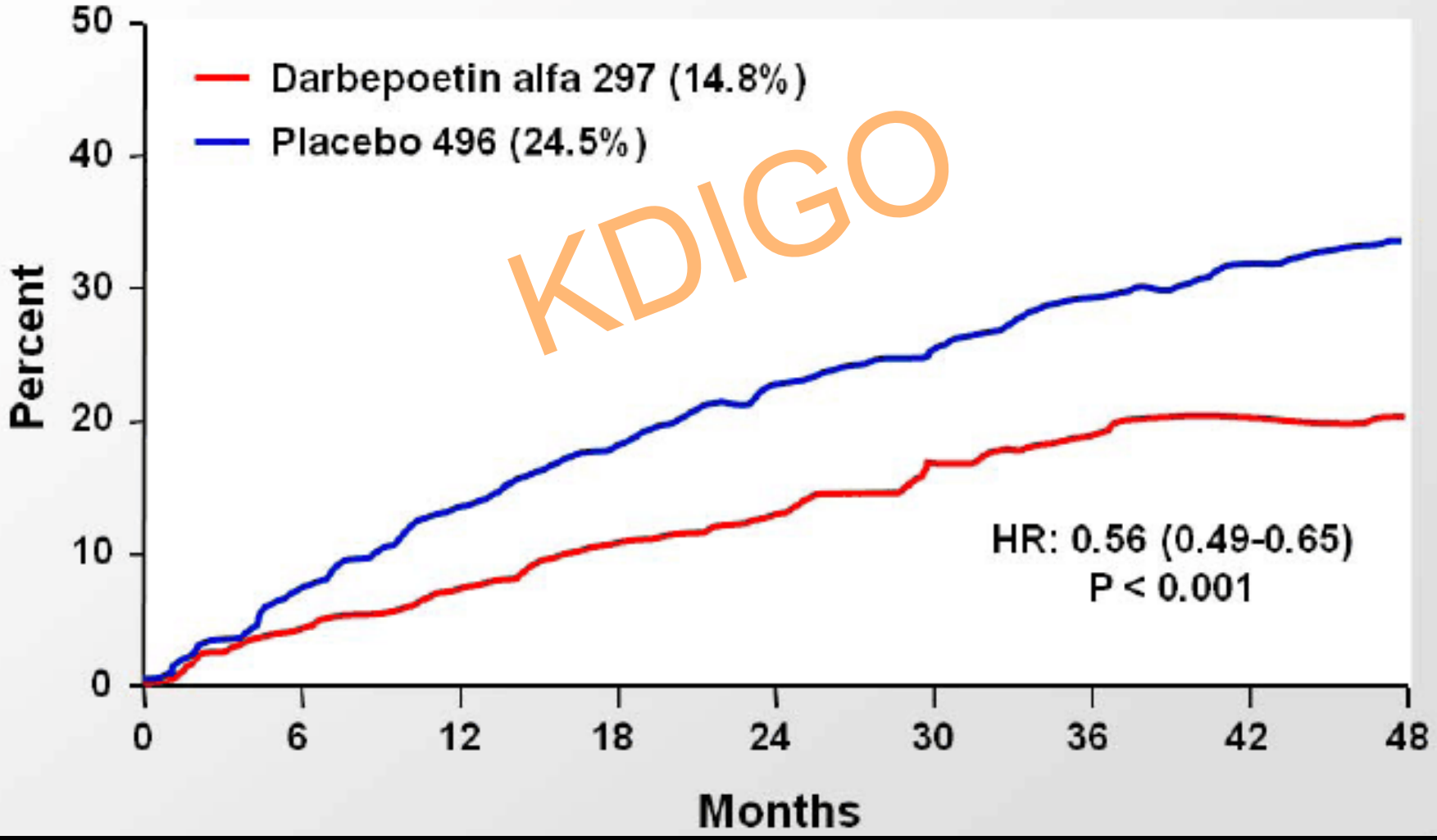
No. of Patients									
Darbepoetin alfa	2004	1768	1503	1300	946	635	404	253	97
Placebo	2019	1742	1460	1221	887	620	356	216	79

Figure 1. Mean Hemoglobin Levels through 48 Months among Patients Who Were Assigned to Receive Darbepoetin Alfa or Placebo.

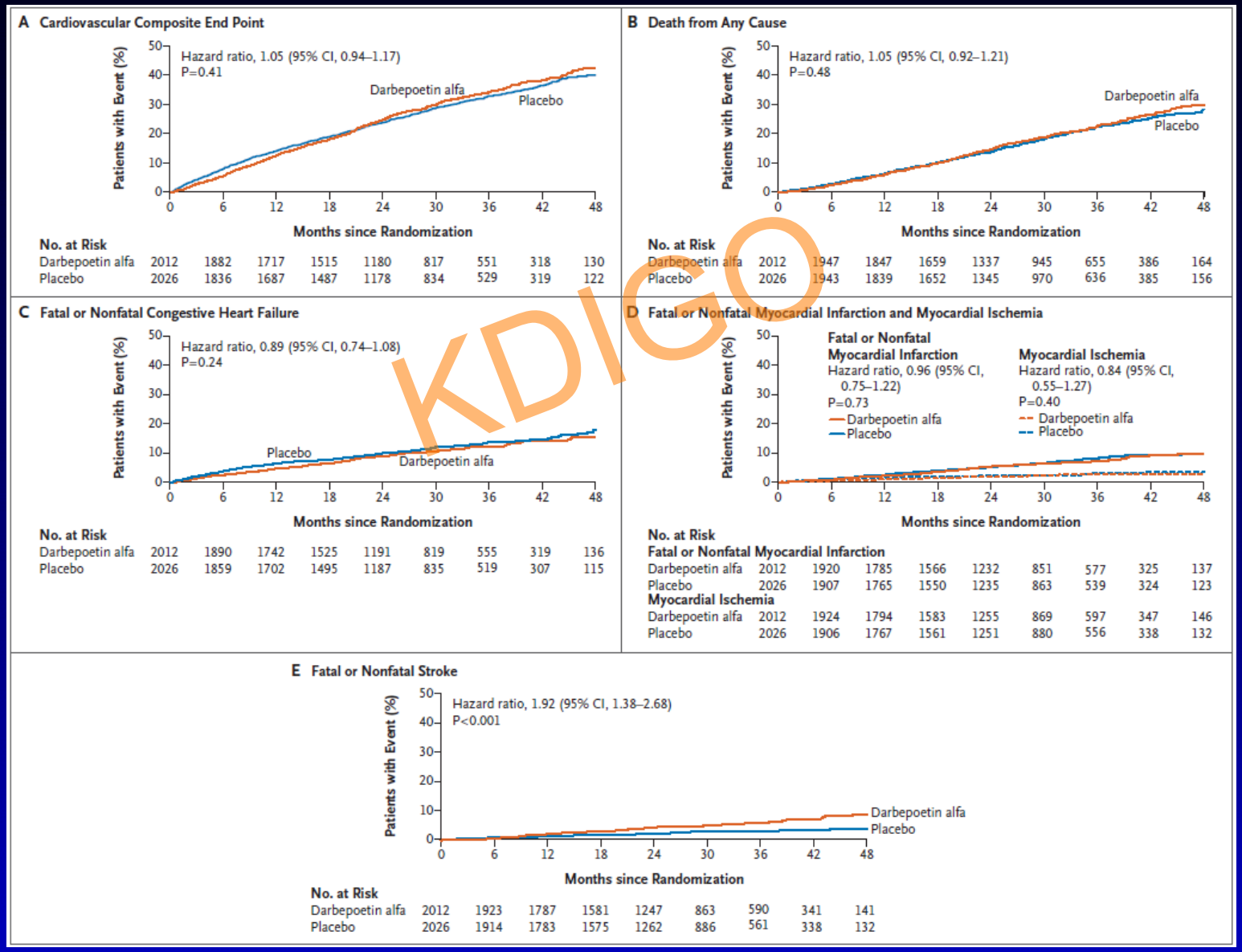
I bars represent standard errors.

Red Cell Transfusions

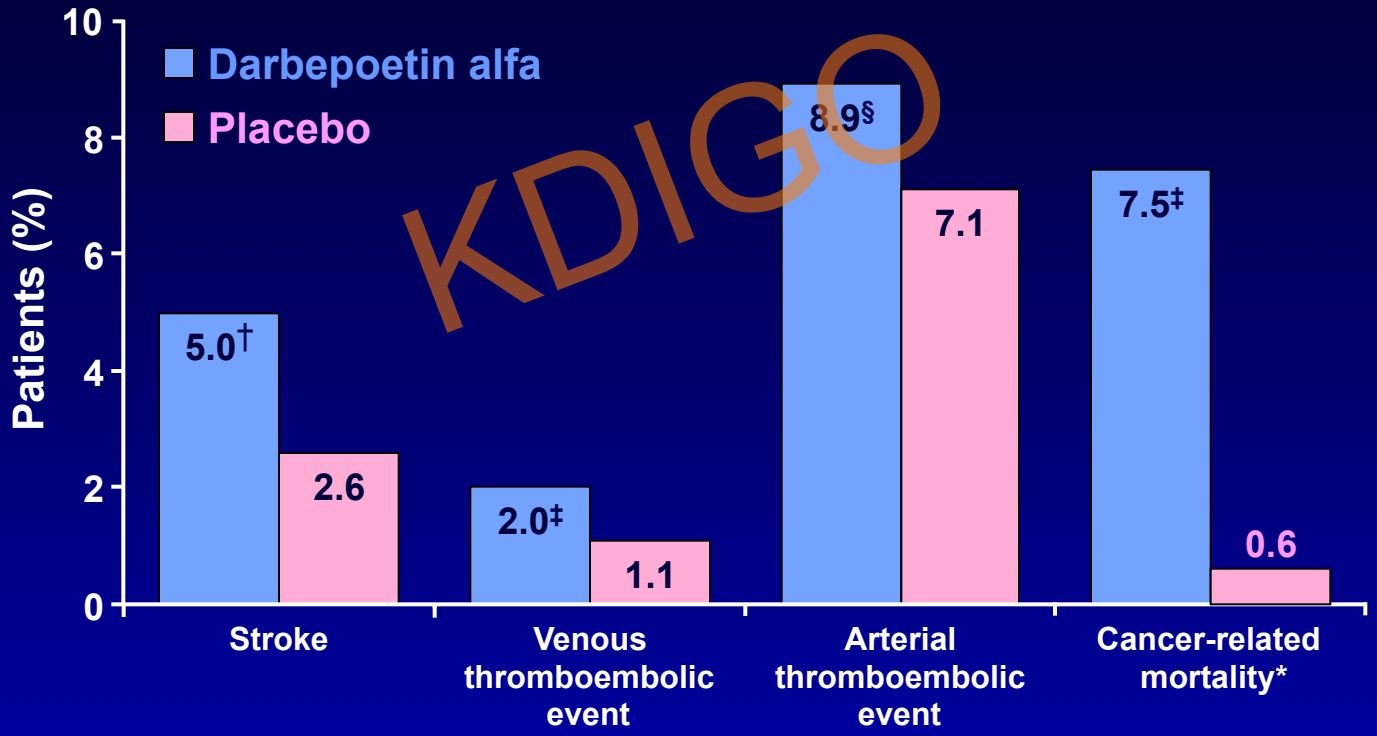
TREAT study



TREAT Study – CV Endpoints

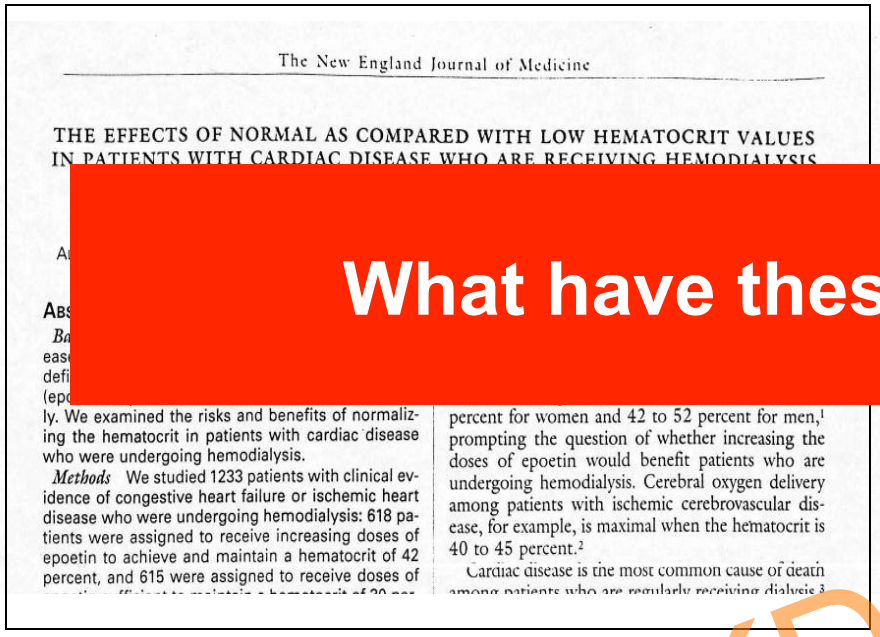


Safety Concerns in the TREAT Study



†, p<0.001 versus placebo
‡, p=0.02 versus placebo
§, p=0.04 versus placebo
*Amongst patients with a history of malignancy at baseline

Pfeffer MA et al. *N Engl J Med* 2009;361:2019–2032.


The New England Journal of Medicine

THE EFFECTS OF NORMAL AS COMPARED WITH LOW HEMATOCRIT VALUES IN PATIENTS WITH CARDIAC DISEASE WHO ARE RECEIVING HEMODIALYSIS

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doses of epoetin would benefit patients who are
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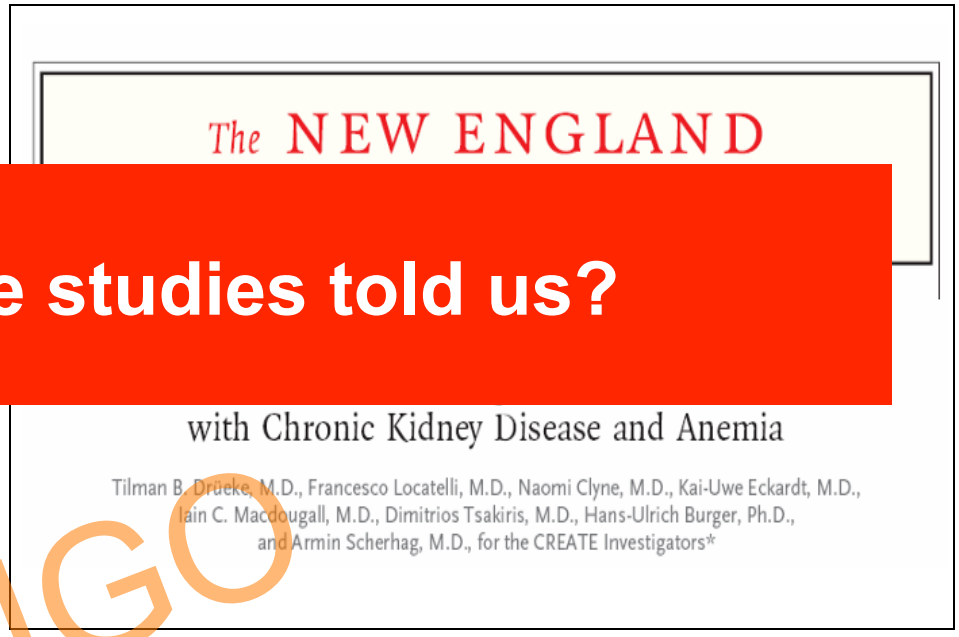
40 to 45 percent.[2]

Cardiac disease is the most common cause of death


The NEW ENGLAND

with Chronic Kidney Disease and Anemia

Tilman B. Drüeke, M.D., Francesco Locatelli, M.D., Naomi Clyne, M.D., Kai-Uwe Eckardt, M.D., Iain C. Macdougall, M.D., Dimitrios Tsakiris, M.D., Hans-Ulrich Burger, Ph.D., and Armin Scherhag, M.D., for the CREATE Investigators*

What have these studies told us?

KDIGO


The NEW ENGLAND JOURNAL of MEDICINE

Ajay K. Singh, M.B., B.S., Lynda Szczech, M.D., Kezhen L. Tang, Ph.D., Huiman Barnhart, Ph.D., Shelly Sapp, M.S., Marsha Wolfson, M.D., and Donal Reddan, M.B., B.S., for the CHOIR Investigators*


The NEW ENGLAND JOURNAL of MEDICINE

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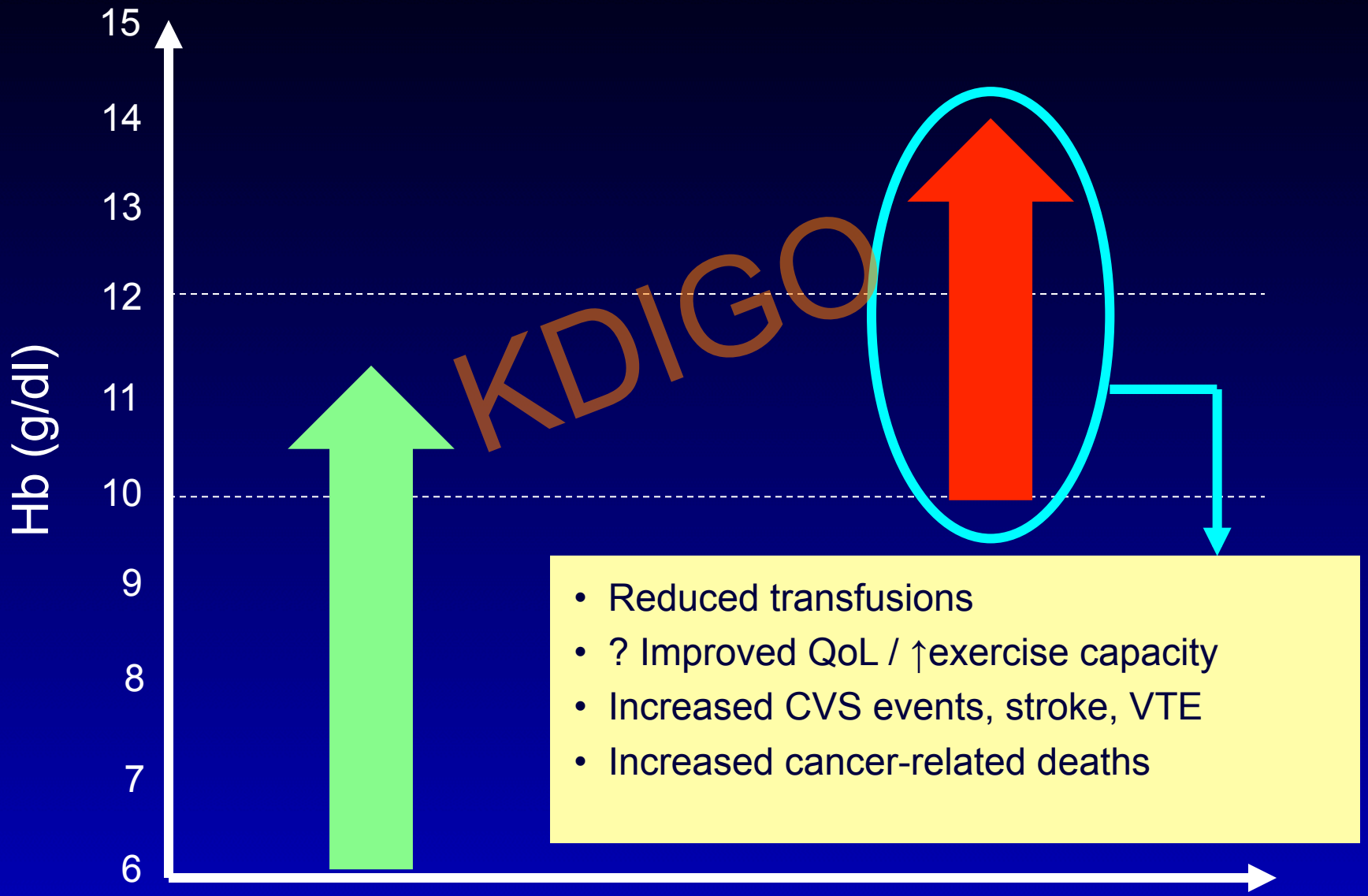
Hb should not be “normalized” by ESA therapy

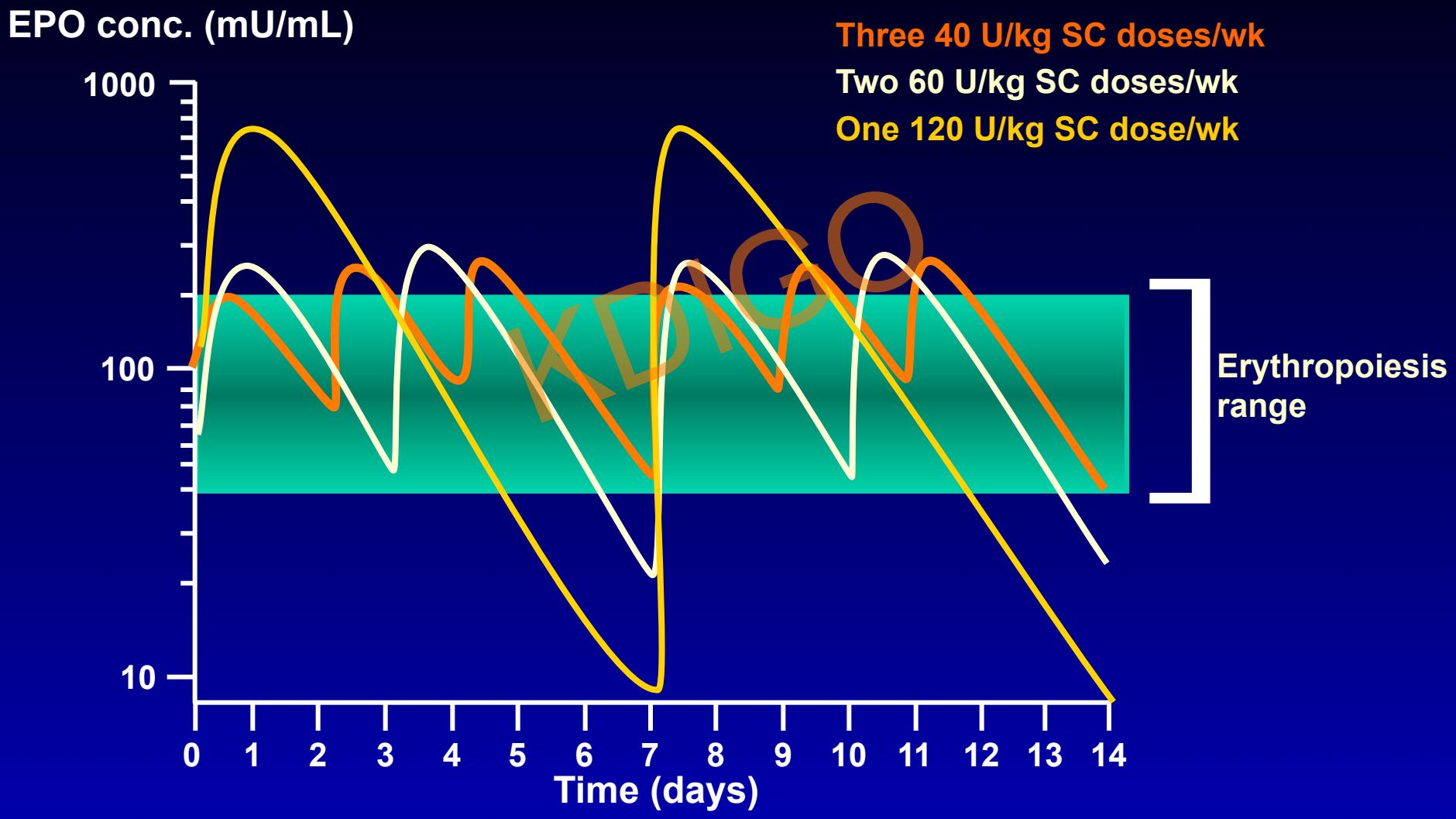
Besarab A et al. *N Engl J Med* 1998;339:584–590; Drüeke TB et al. *N Engl J Med* 2006;355:2071–2084; Singh AK et al. *N Engl J Med* 2006;355:2085–2098; Pfeffer MA et al. *N Engl J Med* 2009;361:2019–2032

Hb correction with ESA therapy



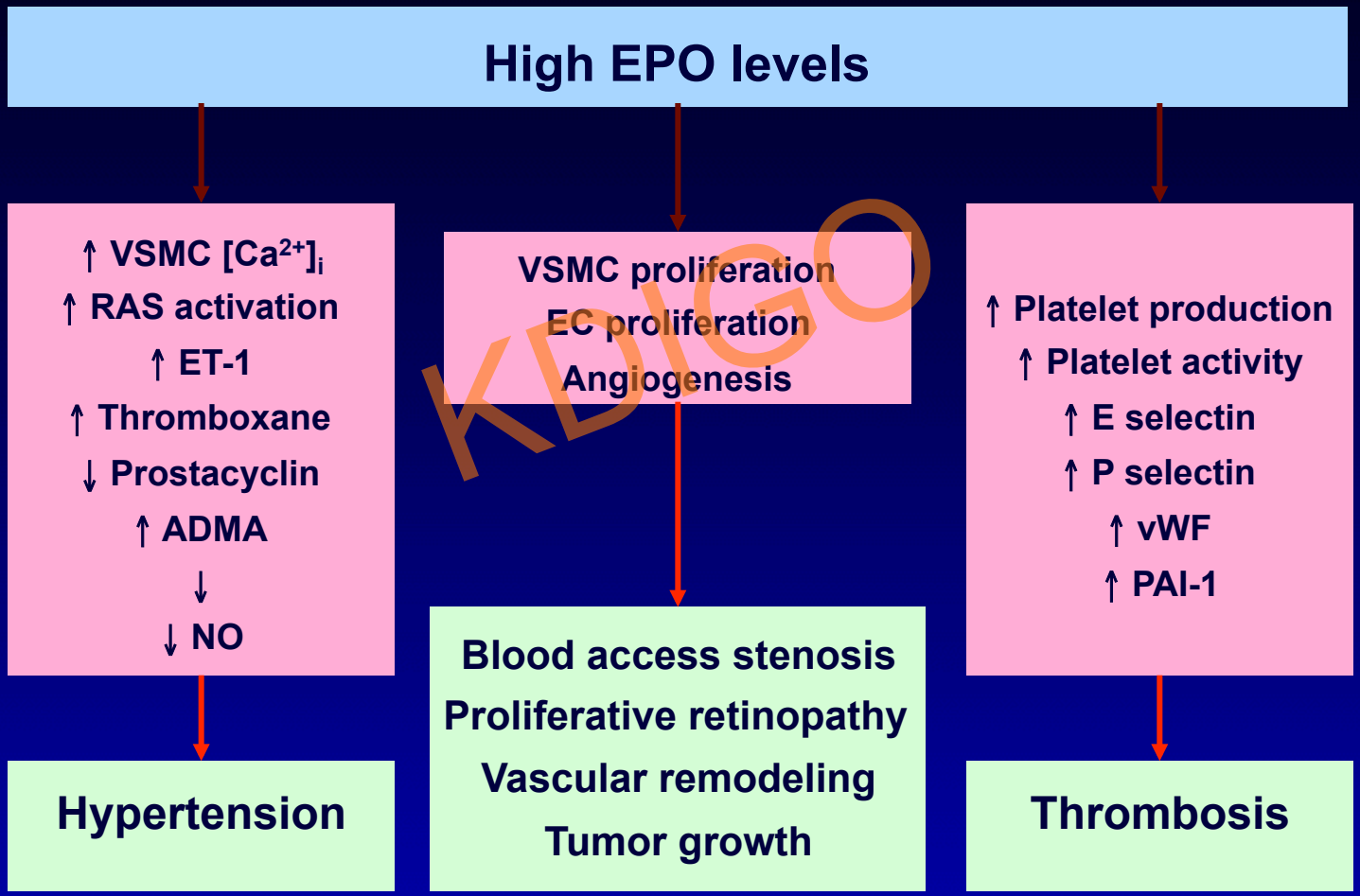
- Reduced transfusions
- ? Improved QoL / ↑exercise capacity
- Increased CVS events, stroke, VTE
- Increased cancer-related deaths

Is the CVS “harm” due to high EPO levels?



Besarab et al J Am Soc Nephrol 1992

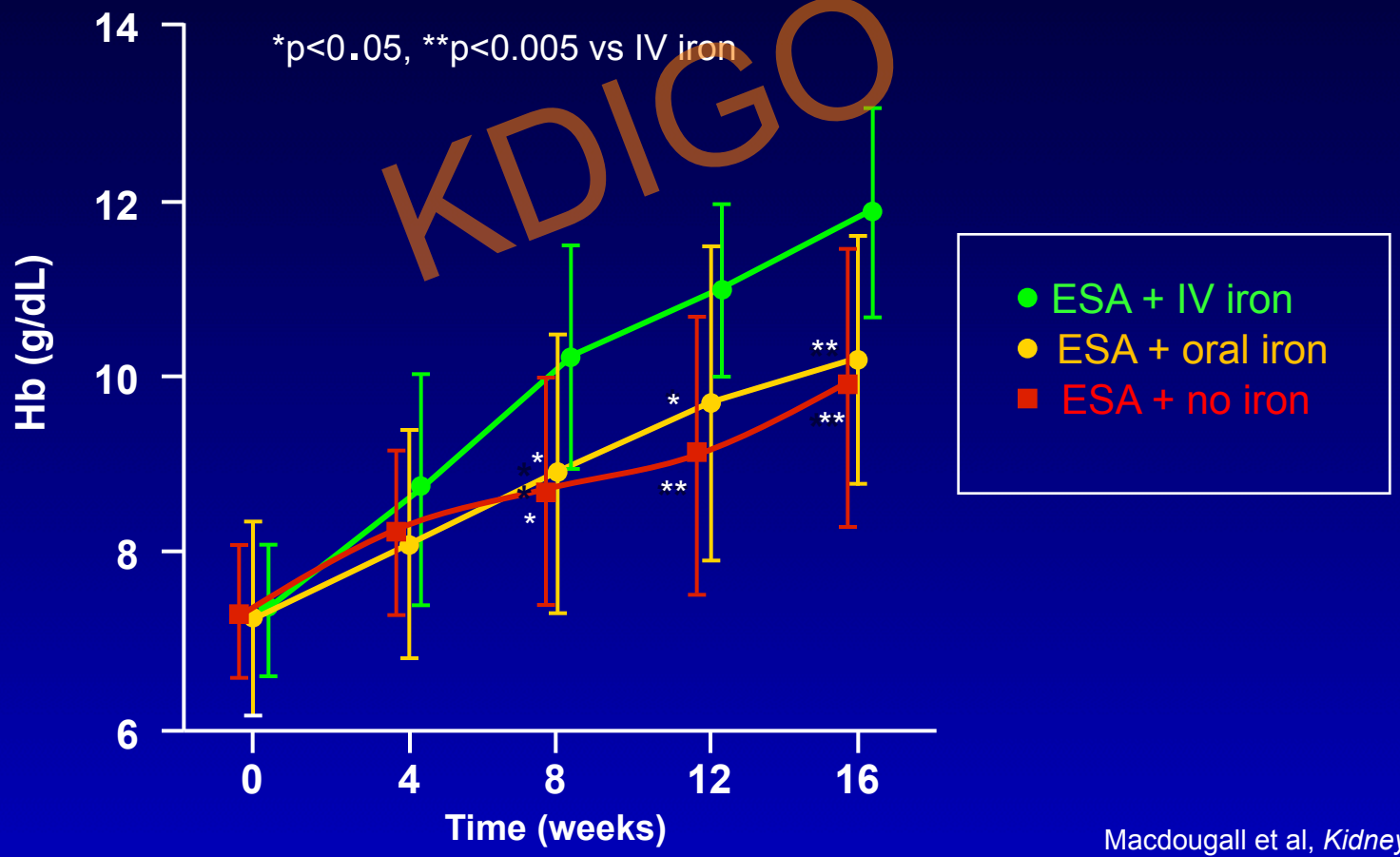
EPO has Non-erythropoietic Actions



Vaziri ND & Zhou X. Nephrol Dial Transplant 2009; 24: 1082–1088.

IV iron

Better Hb response with IV iron compared to oral or no iron



Macdougall et al, *Kidney Int* 1996.

Reduction in Recombinant Human Erythropoietin Doses by the Use of Chronic Intravenous Iron Supplementation

Steven Fishbane, MD, Gill L. Frei, MD, and John Maesaka, MD

● We have compared the efficacy of oral to intravenous iron for the chronic maintenance of iron stores in hemodialysis patients. Fifty-two hemodialysis patients with initial serum ferritin greater than 100 ng/mL and transferrin saturation greater than 15% were randomly assigned to one of two groups: those receiving oral iron therapy (n = 32) and those receiving intravenous iron dextran (100 mg twice weekly) (n = 20). At study completion (4 months), the mean hematocrit was significantly higher in the intravenous group than in the oral iron group

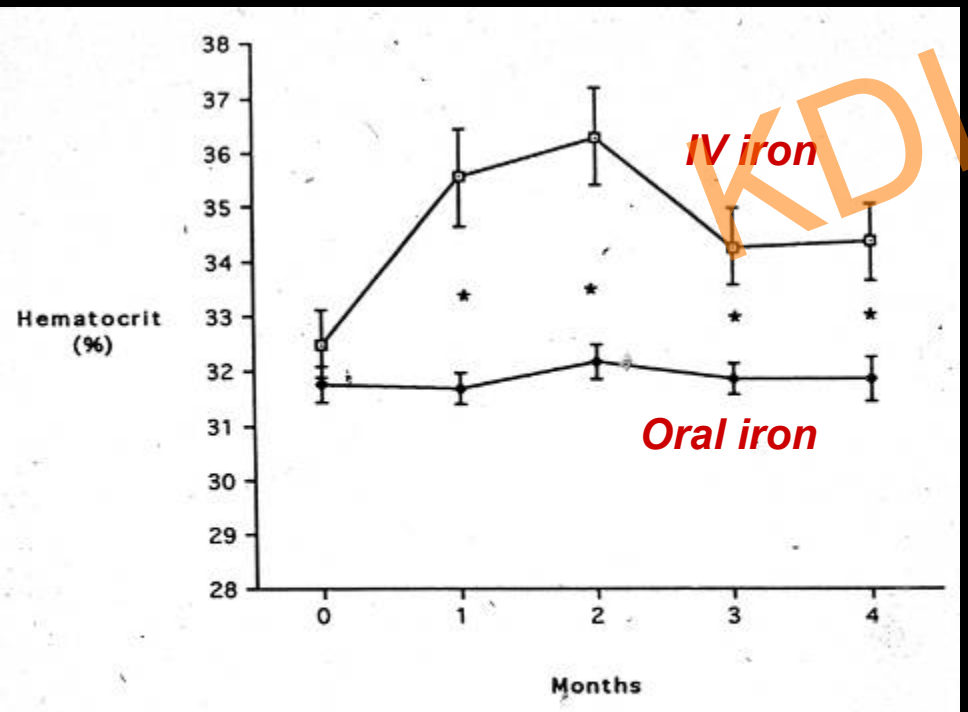


Fig 1. Mean hematocrit at every month of follow-up in the two study groups. Squares indicate the intravenous group; diamonds indicate the oral group. *$P < 0.05$.

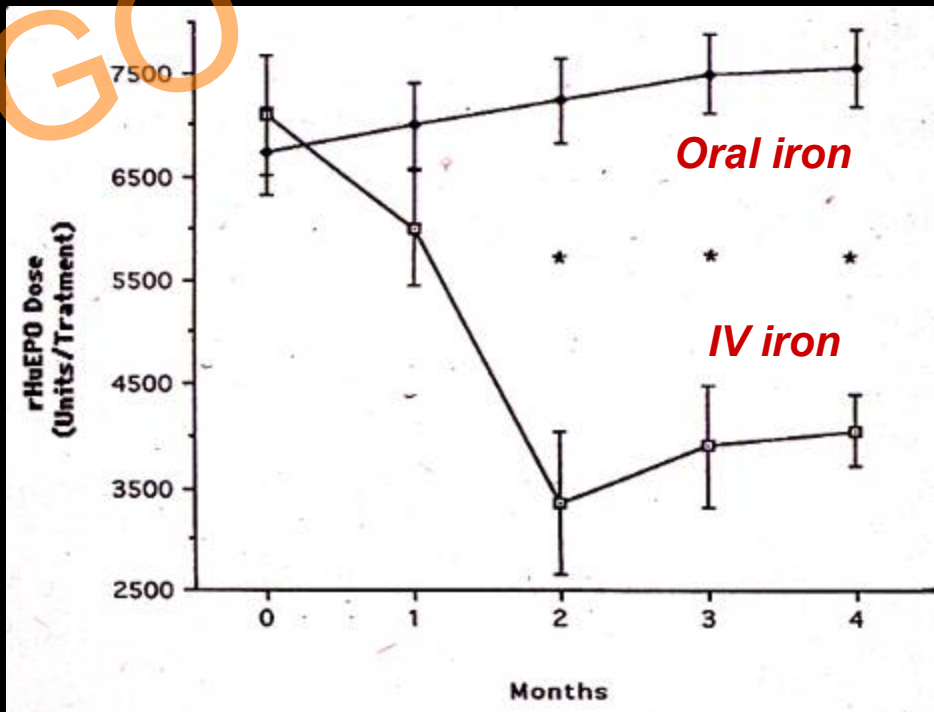


Fig 2. Mean rHuEPO dose at every month of follow-up in the two study groups. Squares indicate the intravenous group; diamonds indicate the oral group. *$P < 0.05$.

Concerns about IV iron

- Hypersensitivity reactions
- Oxidative stress
- Exacerbation of infections
- Iron overload

Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

OPEN

Iain C. Macdougall[1], Andreas J. Bircher[2], Kai-Uwe Eckardt[3], Gregorio T. Obrador[4], Carol A. Pollock[5,6], Peter Stenvinkel[7], Dorine W. Swinkels[8], Christoph Wanner[9], Günter Weiss[10], and Glenn M. Chertow[11]; for Conference Participants[12]

[1]Department of Renal Medicine, King's College Hospital, London, UK; [2]Allergy Unit, Dermatology Clinic, University Hospital Basel, Basel, Switzerland; [3]Department of Nephrology and Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [4]Universidad Panamericana School of Medicine, Mexico City, Mexico; [5]University of Sydney, Sydney, Australia; [6]Royal North Shore Hospital, Sydney, Australia; [7]Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska University Hospital, Stockholm, Sweden; [8]Department of Laboratory Medicine, Translational Metabolic Laboratory, Radboud University Medical Center, Nijmegen, the Netherlands; [9]Renal Division, University Hospital of Würzburg, Würzburg, Germany; [10]Department of Internal Medicine VI, Infectious Disease, Immunology, Rheumatology, Pneumology, Medical University of Innsbruck, Innsbruck, Austria; and [11]Division of Nephrology, Stanford University School of Medicine, Palo Alto, California, USA

Macdougall et al. *Kidney Int* 2016; 89 : 28-39.

Iron Management in CKD Conference

Steering Committee

Glenn Chertow, USA – Conference Co-Chair
Iain Macdougall, UK – Conference Co-Chair

Iron Overload Co-Chairs
Kai-Uwe Eckardt, *Germany* & Dorine Swinkels, *Netherlands*

Inflammation & Oxidative Stress Co-Chairs
Peter Stenvinkel, *Sweden* & Christoph Wanner, *Germany*

Iron & Infection Co-Chairs
Gregorio Obrador, *Mexico* & Günter Weiss, *Austria*

Hypersensitivity Reactions to IV Iron Co-Chairs
Andreas Bircher, *Switzerland* & Carol Pollock, *Australia*

The present

Current ESA and IV iron use

- Use ESA therapy to correct anaemia when Hb <10 g/dl (or 11 g/dl if symptoms)
- Aim for target Hb in range 10–12 g/dl; individualize
- Use lowest doses of ESA as possible
- Use supplemental iron to prevent iron deficiency and reduce ESA dose requirements – IV in HD; oral or IV 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 with IV iron

The future

Questions needing answers

- How much IV iron should be given to HD patients?
- What ferritin/TSAT targets are optimal in HD?

PIVOTAL

Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

- **UK multicentre prospective open-label 2-arm RCT of IV iron therapy in incident HD patients**

Lead investigator:	Iain Macdougall
Clinical Trial Manager:	Claire White
No of sites:	50
No. of patients:	2080
Commenced:	November 2013
Trial oversight:	Glasgow Clinical Trials Unit
Funder :	Kidney Research UK

This investigator-led clinical trial is supported through an unrestricted grant from
Vifor Fresenius Medical Care Renal Pharma

University of Glasgow

NHS Greater Glasgow and Clyde

THE RENAL ASSOCIATION founded 1950
UK Kidney Research Consortium : Renal Anaemia CSG

Kidney Research UK
Funding research to save lives

www.kidneyresearchuk.org
Registered Charity No: 252892 Registered Scottish Charity No. SC039245

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

Study design

Proactive IV iron arm – IV iron 400mg/month

(withhold if ferritin>700 ug/l; TSAT>40%)

Incident new HD patients (0-12 mths)

On ESA

R

Reactive – minimalistic IV iron arm
(give IV iron if ferritin<200 ug/l; TSAT<20%)

KDIGO

Primary endpoint

Time to all-cause mortality or composite of MI, stroke, HF hosp

Up to 4 weeks screening

Total study period approximately 4 years *(event-driven)* – 2 years recruitment; 2-4 years follow-up per patient

Sample size: 2080 patients

Kidney Research UK
Funding research to save lives

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

Primary endpoint

- Time to all-cause death or a composite of non-fatal cardiovascular events (MI, stroke, and HF hospitalisation)
  -- adjudicated by a blinded Endpoint Adjudication Committee

Secondary endpoints

- Incidence of all-cause death and a composite of myocardial infarction, stroke, and hospitalisation for heart failure as recurrent events.
- Time to (and incidence of) all-cause death
- Time to (and incidence of) composite cardiovascular event
- Time to (and incidence of) myocardial infarction
- Time to (and incidence of) stroke
- Time to (and incidence of) hospitalisation for heart failure
- ESA dose requirements
- Transfusion requirements
- EQ-5D QOL and KDQOL
- Vascular access thrombosis
- All-cause hospitalisation
- Infections; hospitalisation for infection

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

NETWORK OF SITES

King's College Hospital NHS
NHS Foundation Trust

England
Queen Elizabeth Hospital, Birmingham; Heartlands Hospital, Birmingham; Royal Free, London, King's College Hospital, London; Guy's & St Thomas', London; St Helier, Surrey; St George's, London; Royal Liverpool Hospital, University Hospital Aintree; Sheffield Teaching Hospital; Lister Hospital, Stevenage; Salford Royal Hospital, Manchester; Manchester Royal Hospital; Queen Alexandra Hospital, Portsmouth; Kent & Canterbury Hospital, Leicester General Hospital, Hull Royal Infirmary; Freeman Hospital, Newcastle; Churchill Hospital, Oxford; University Hospital of North Staffordshire, Stoke-on-Trent; Southmead Hospital, Bristol; Royal Cornwall Hospital; Nottingham City Hospital; Norfolk & Norwich Hospital; New Cross Hospital, Wolverhampton; Royal London Hospital; Wirral University Teaching Hospital; Royal Shrewsbury Hospital, Royal Devon & Exeter Hospital, Royal Preston Hospital, St James' Hospital, Leeds; Hammersmith Hospital, London; Royal Sussex Hospital, Brighton; Bradford Teaching Hospital; Coventry University Hospital; Southend University Hospital; Gloucestershire Royal Hospital; Derriford Hospital, Plymouth; Royal Berkshire, Reading

Wales
Morriston Hospital, Swansea; University Hospital, Cardiff

Scotland
Western Infirmary, Glasgow; Victoria Hospital, Kirkcaldy; Ninewells Hospital, Dundee; Royal Edinburgh Hospital

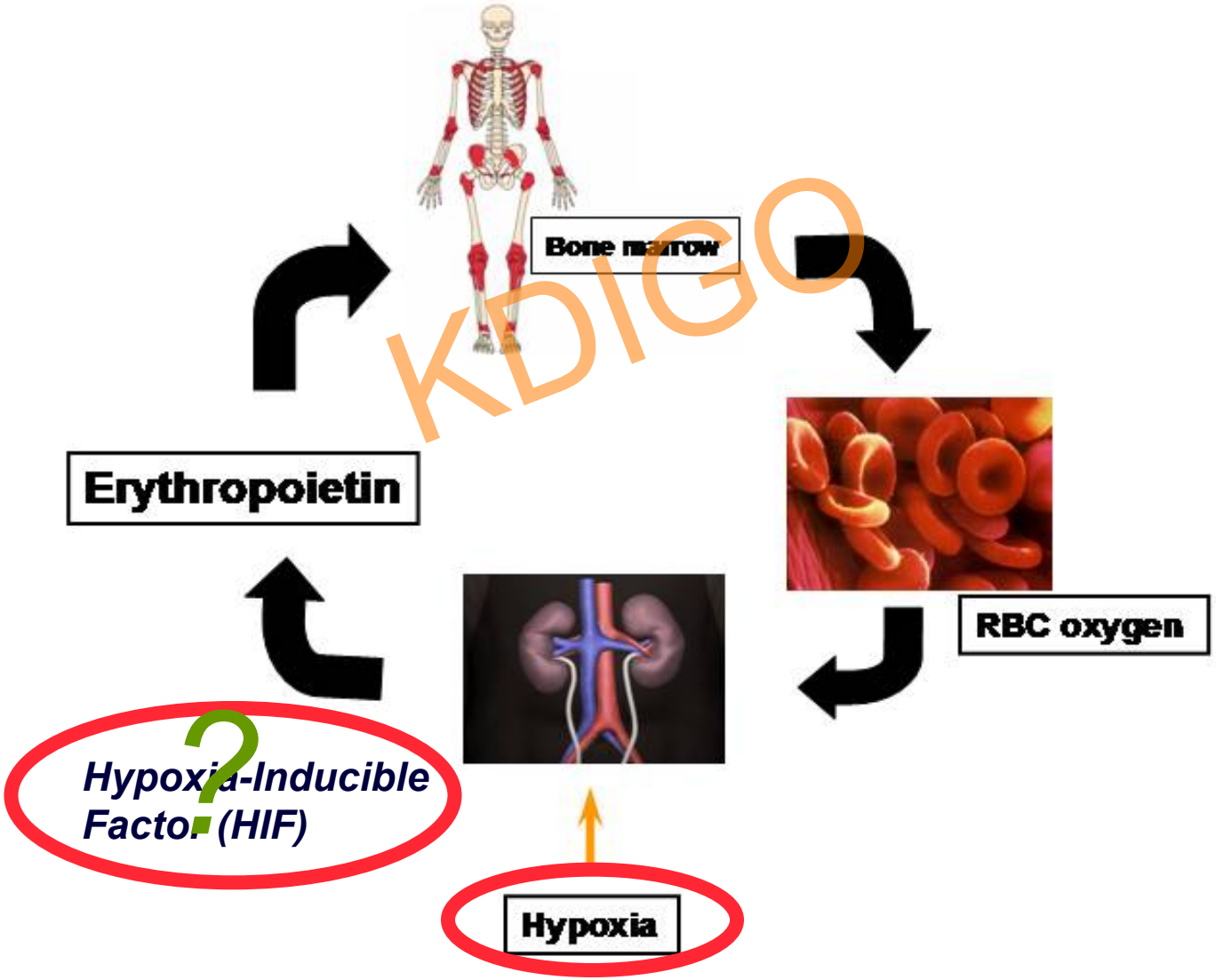
N. Ireland
Belfast City Hospital, Antrim Area Hospital;
Daisy Hill Hospital, Newry; Altnagelvin Hospital, Derry

Registered Charity No: 252892 Registered Scottish Charity No. SC039245

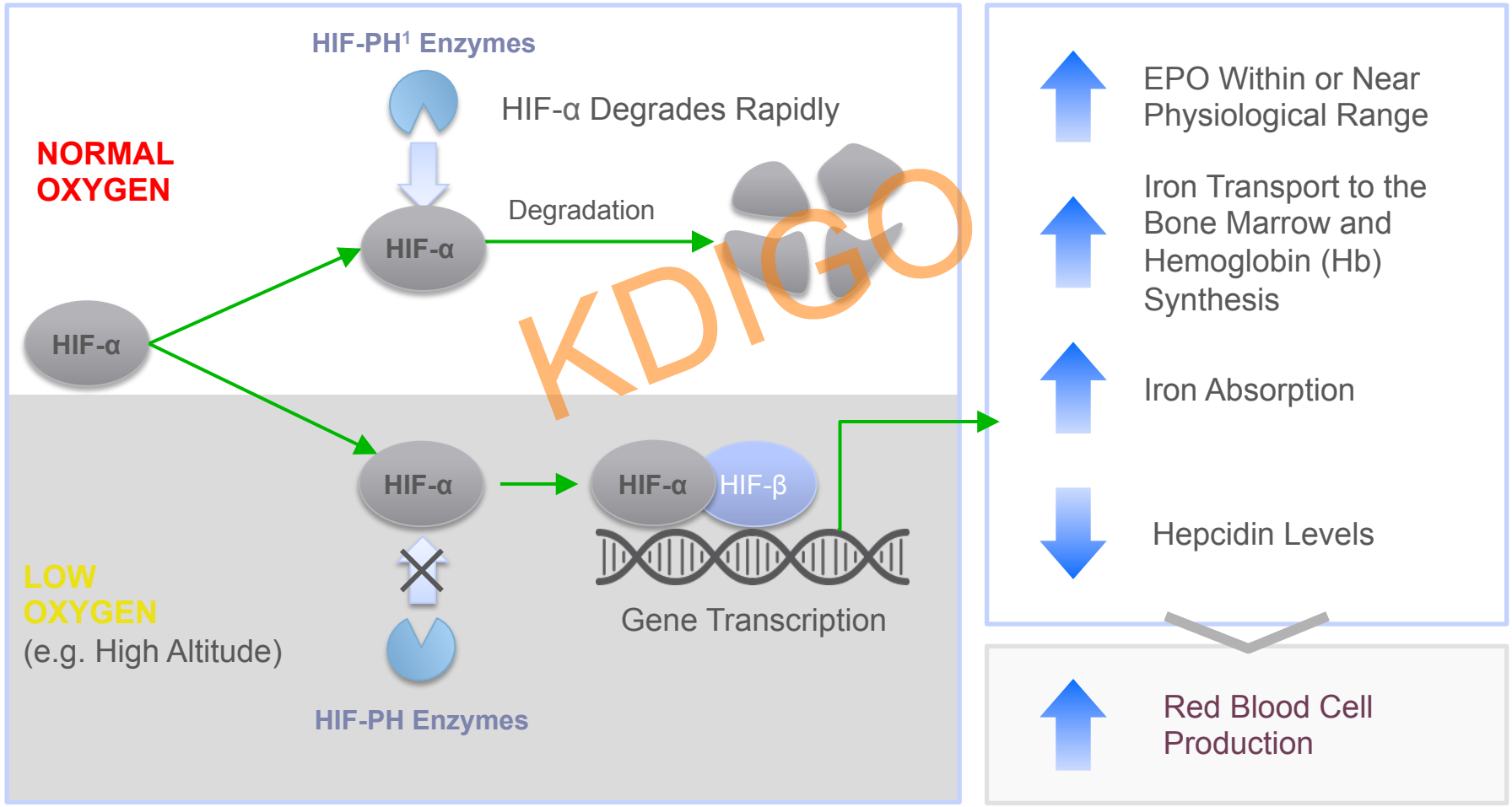
Kidney Research UK
Funding research to save lives

HIF stabilizers
– prolyl hydroxylase inhibitors

Regulation of erythropoietin



The physiology of hypoxia mediated through hypoxia inducible factor (HIF)



Slide courtesy of Dr. Lynda Szczech, Fibrogen Inc.

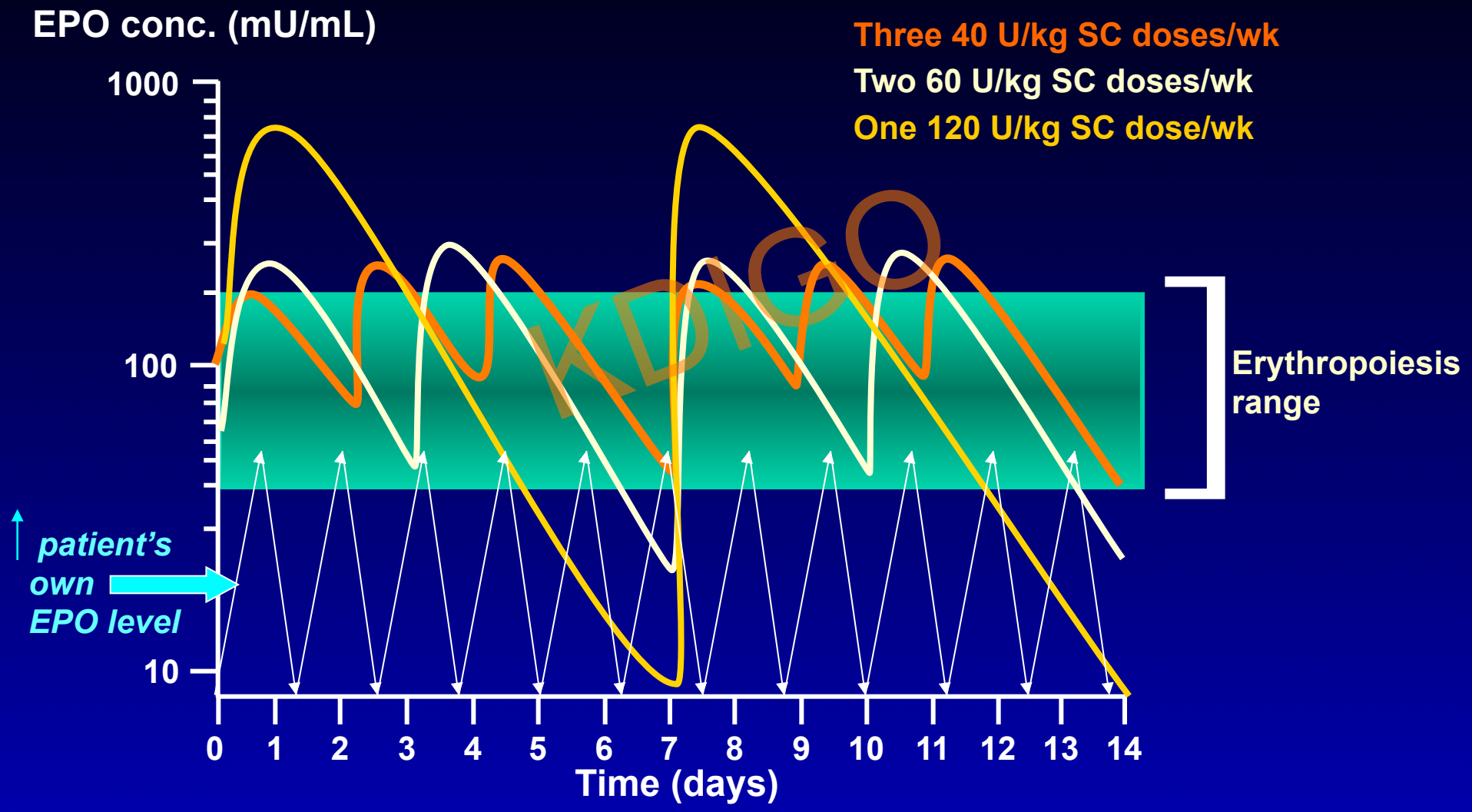
HIF stabilisers

- HIF is degraded by a prolyl hydroxylase enzyme
- Orally-active inhibitors of PH have been synthesised
- These drugs cause HIF levels to increase
- More HIF leads to more EPO

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 2

A new strategy



Besarab et al, J Am Soc

Nephrol Dial Transplant (2015) 30: 1665–1673
doi: 10.1093/ndt/gfv302
Advance Access publication 3 August 2015

ndt Nephrology Dialysis Transplantation

FASTTRACK *Original Article*

Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients

Anatole Besarab[1], Robert Provenzano[2], Joachim Hertel[3], Raja Zabaneh[4], Stephen J. Klaus[1], Tyson Lee[1], Robert Leong[1], Stefan Hemmerich[1], Kin-Hung Peony Yu[1] and Thomas B. Neff[1]

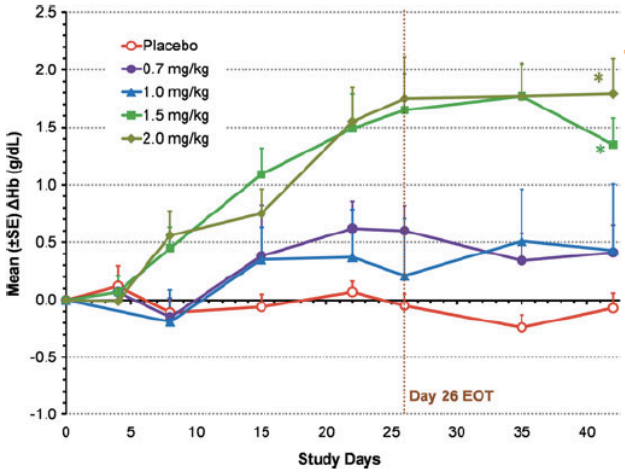


FIGURE 3: Mean change from BL in Hb (ΔHb) in TIW cohorts (EE population). Mean (SD) BL Hb was 10.1 (0.7) g/dL for roxadustat TIW subjects and 10.1 (0.6) g/dL for placebo subjects. Last-observation-carried-forward (LOCF) method was used to impute missing values. *P < 0.01 intergroup two-sample *t*-tests comparing roxadustat change from BL with placebo change from BL. End of treatment (EOT) for TIW was Day 26.

Original Report: Patient-Oriented, Translational Research

American Journal of Nephrology

Am J Nephrol 2017;45:380–388
DOI: 10.1159/000464476

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Published online: March 25, 2017

Clinical Trial of Vadadustat in Patients with Anemia Secondary to Stage 3 or 4 Chronic Kidney Disease

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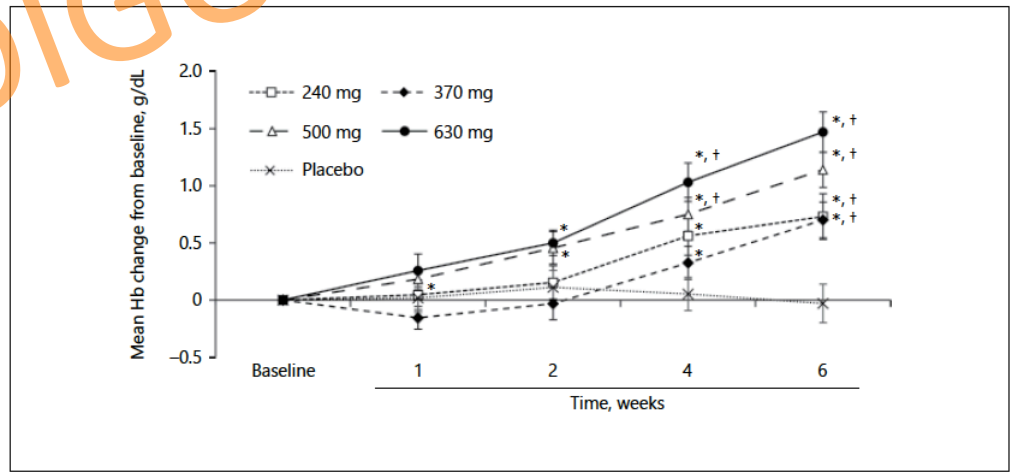
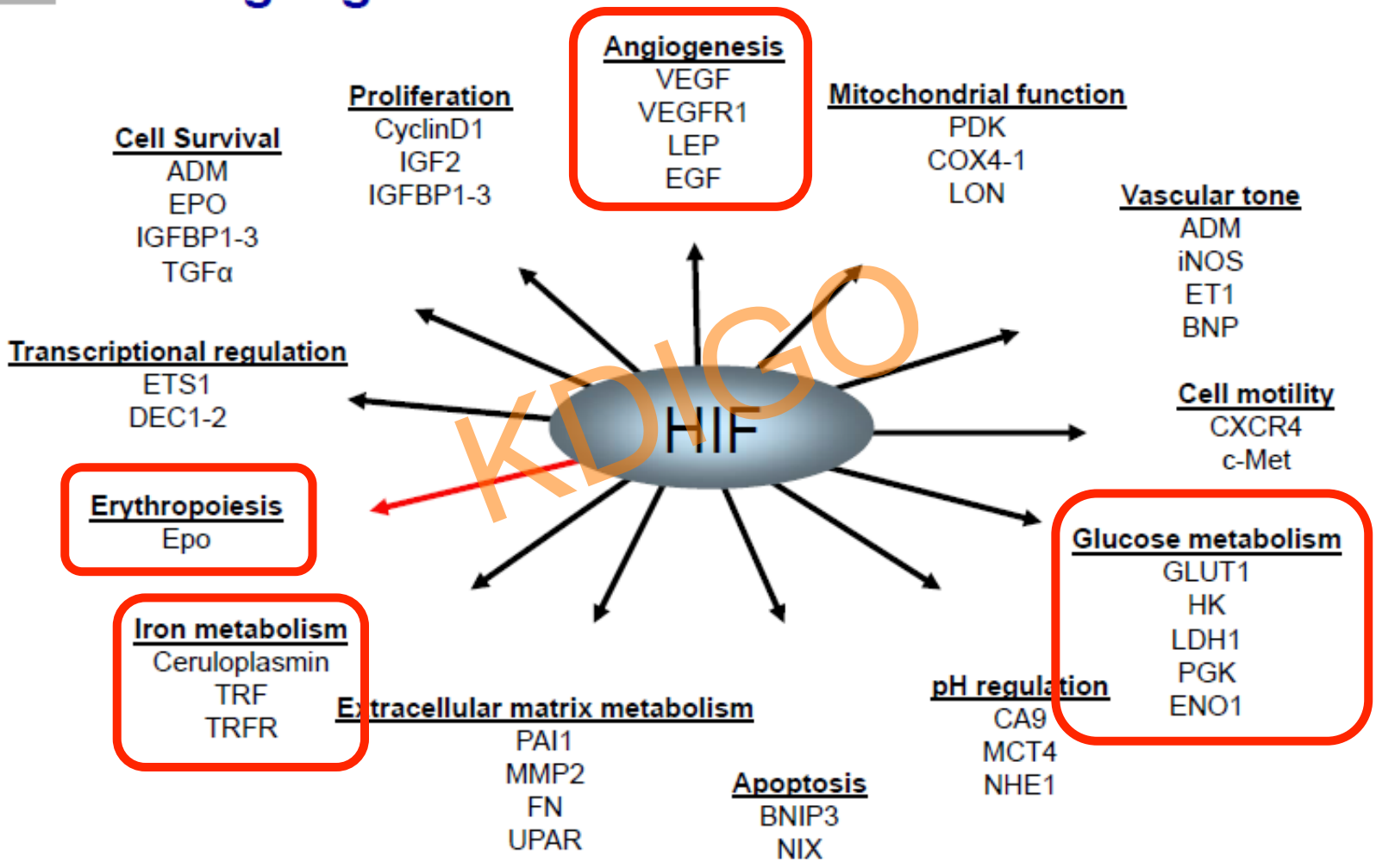


Fig. 2. Observed mean hemoglobin (Hb) concentration over the trial period during administration of vadadustat or placebo (modified intent to treat population). Data are expressed as the mean ± SEM Hb value at each time point. * $p < 0.05$ for comparisons with baseline. † $p < 0.05$ for comparisons with placebo.

HIF target genes



Adapted from Schofield & Ratcliffe, *Nat Rev Mol Cell Biol 2004*

Conclusions

- We have to accept that ESA therapy is not as safe as we thought 25 years ago
- Nevertheless, it keeps patients off blood transfusions and improves anaemic symptoms / quality-of-life
- IV iron can augment Hb response and reduce ESA doses
- However, there are potential concerns about IV iron's safety
- There are several 'new kids on the block', esp. HIF stabilizers