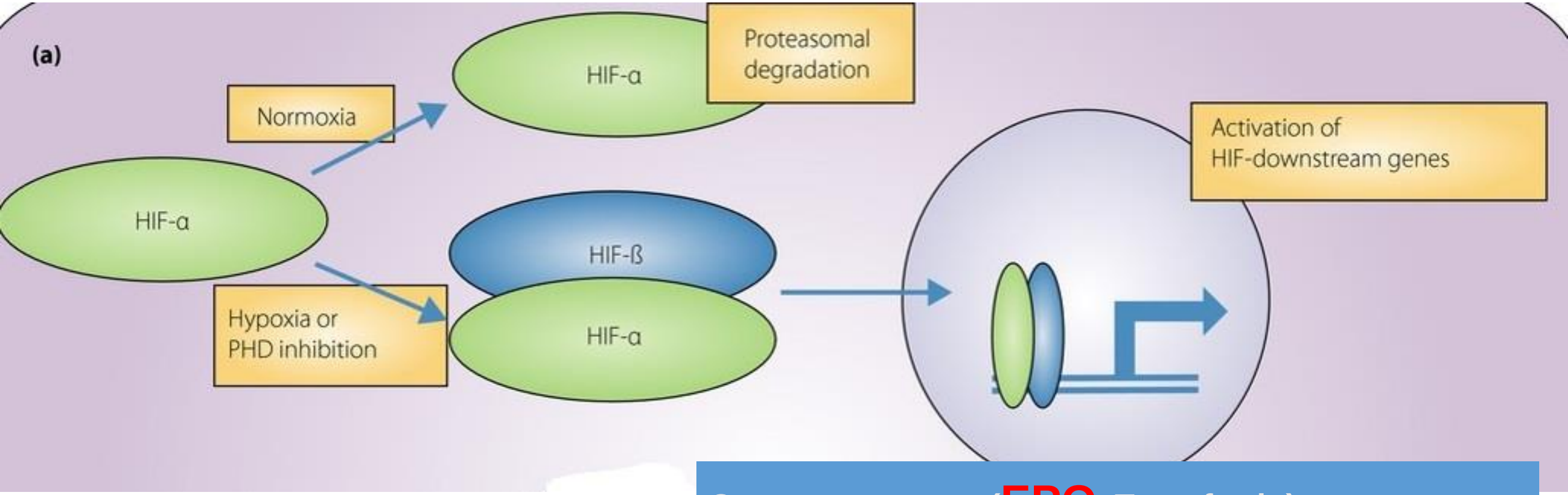
HKSN/APSN CME course

Anemia in CKD

Masaomi Nangaku

Division of Nephrology and Endocrinology
the University of Tokyo Graduate School of Medicine

Cellular responses against anemia and hypoxia



Oxygen transport (**EPO**, Transferrin)

Vascular regulation (VEGF, adrenomedullin, HO-1)

Glucose uptake and glycolysis (Glut-1, Aldolase A)

Anti-oxidative enzymes (SODs, catalase)

Hirakawa, Nangaku, et al. J Diabetes Investig 2017

High altitude training: 'Altitude Doping'

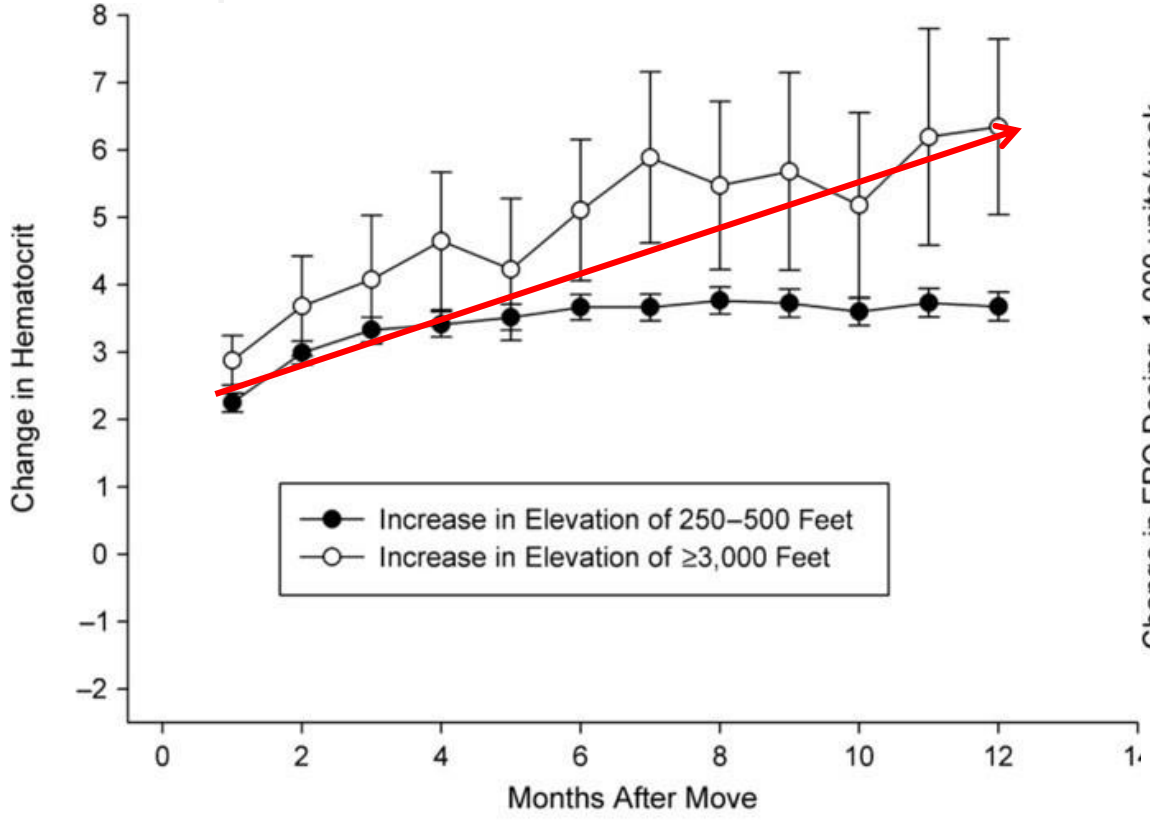
It's the legal version of blood doping.
Instead of taking drugs to stimulate the production of red blood cells, many endurance athletes spend time in the thin air of high altitudes.

The body responds to the thin air at high altitudes by producing proteins in the HIF family.
HIF stimulates the production of red blood cells and builds capillaries to deliver more oxygen to the muscles.

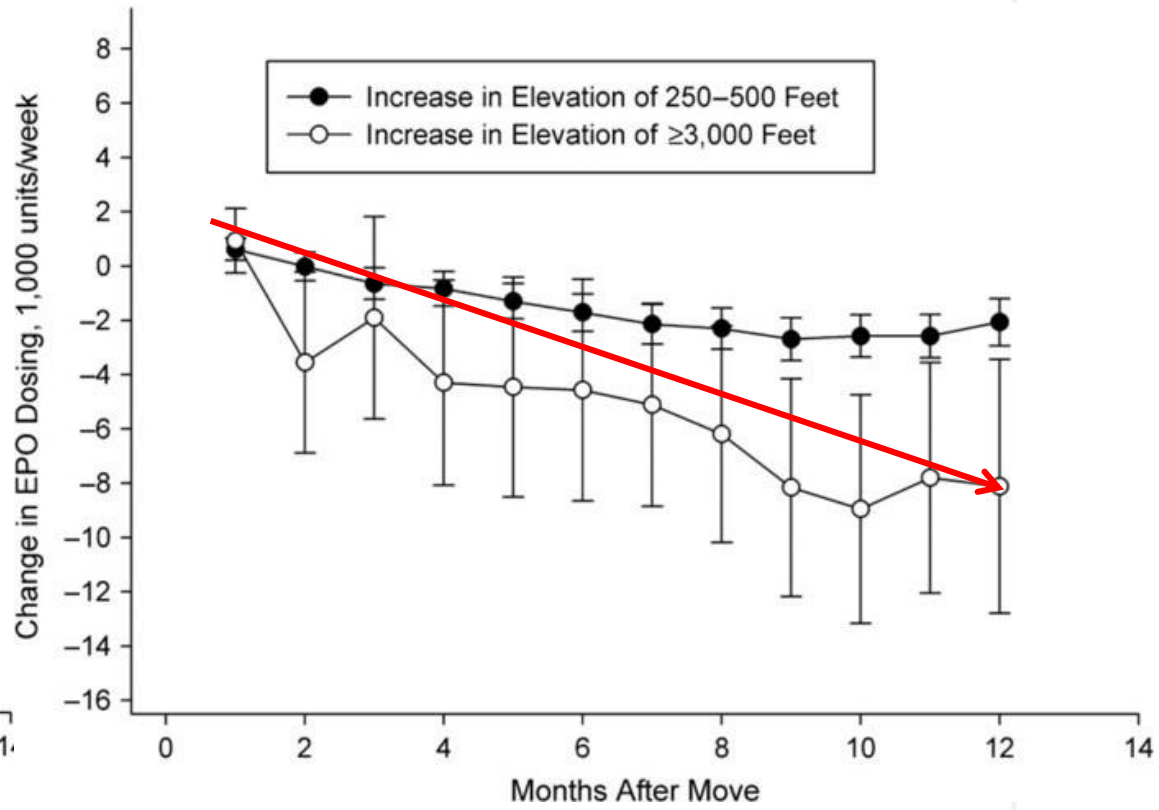
Helen Fields. Science 2010

altitude-induced hypoxia reduces erythropoietin requirements in HD patients

change in Hct

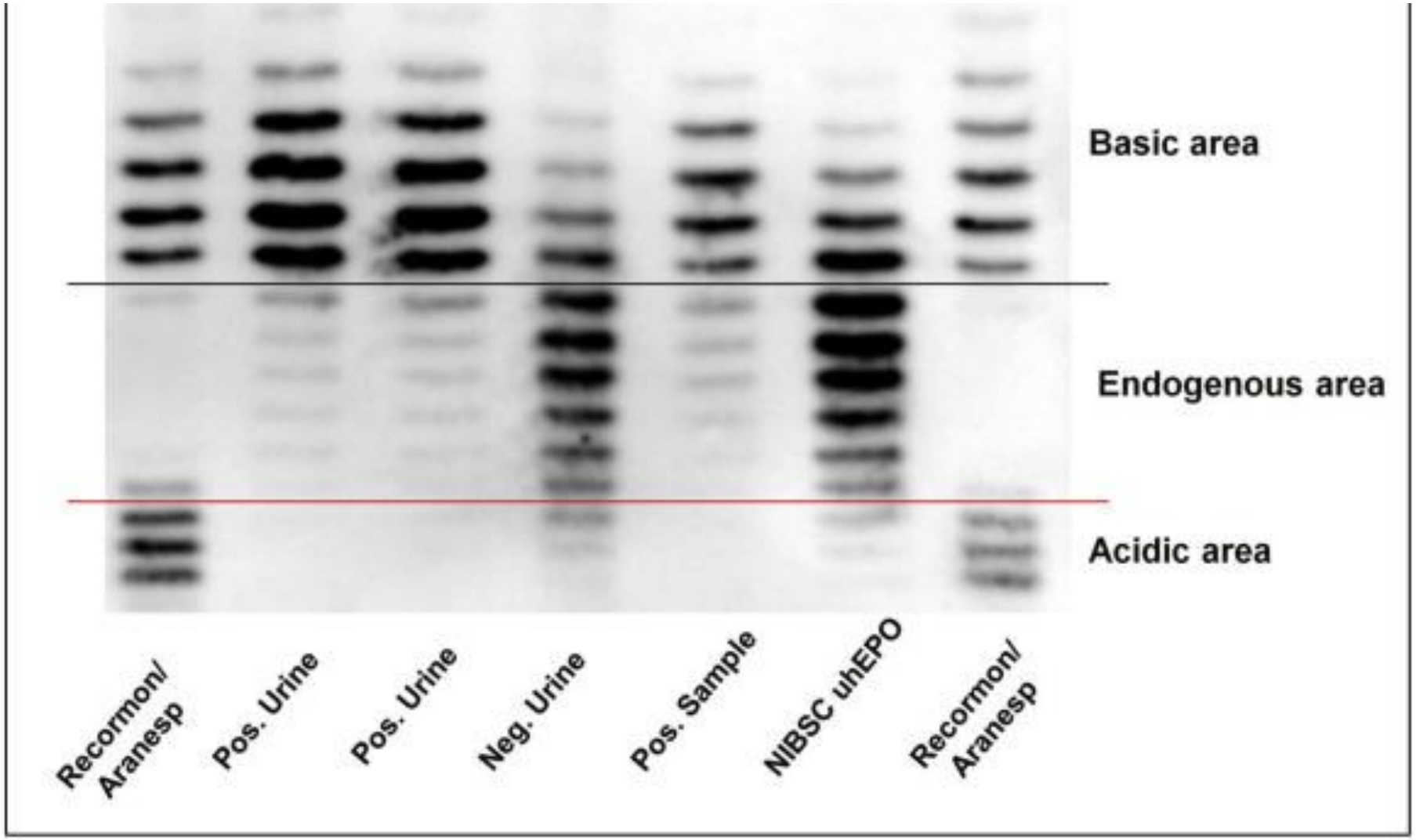


change in EPO dosing



Brookhart et al. Am J Epidemiol 2011

isoelectric focusing analysis of urine to detect recombinant ESA

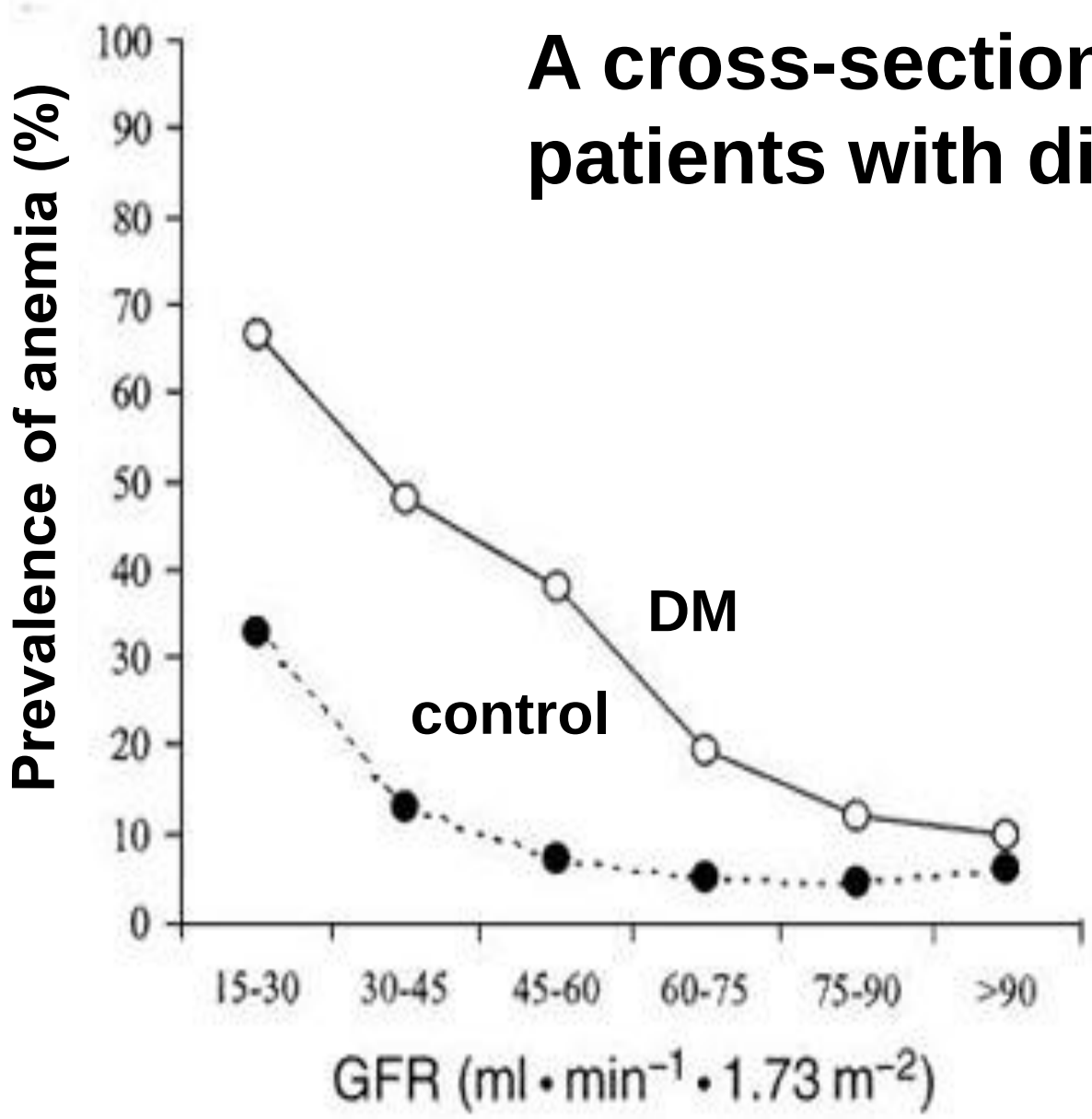


Salamin et al. Mol Cell Endocrinol 2017

ESA in CKD

Anemia is more prevalent in DKD

A cross-sectional survey of 820 patients with diabetes



Thomas et al.
Diabetes Care 2003

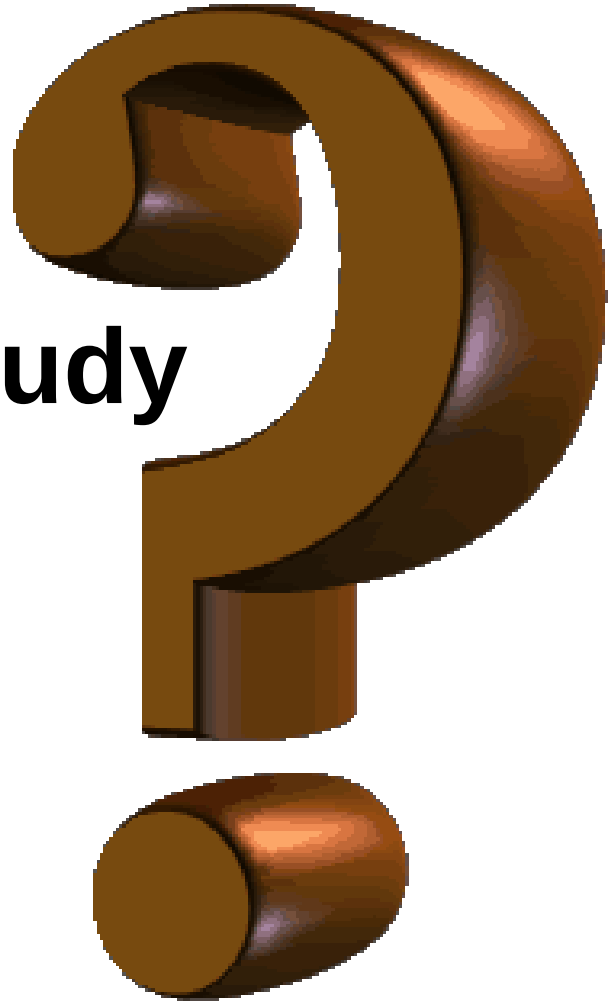
The phase II StUdy of BArdoxolone methyl in patients with chronic KIdney disease and type 2 diabetes;

TSUBAKI study

ASN Kidney Week press briefing on Friday, Nov 3
Presentation at the session of Late Breaking Clinical Trial (High-Impact Clinical Trials) Saturday, Nov 4

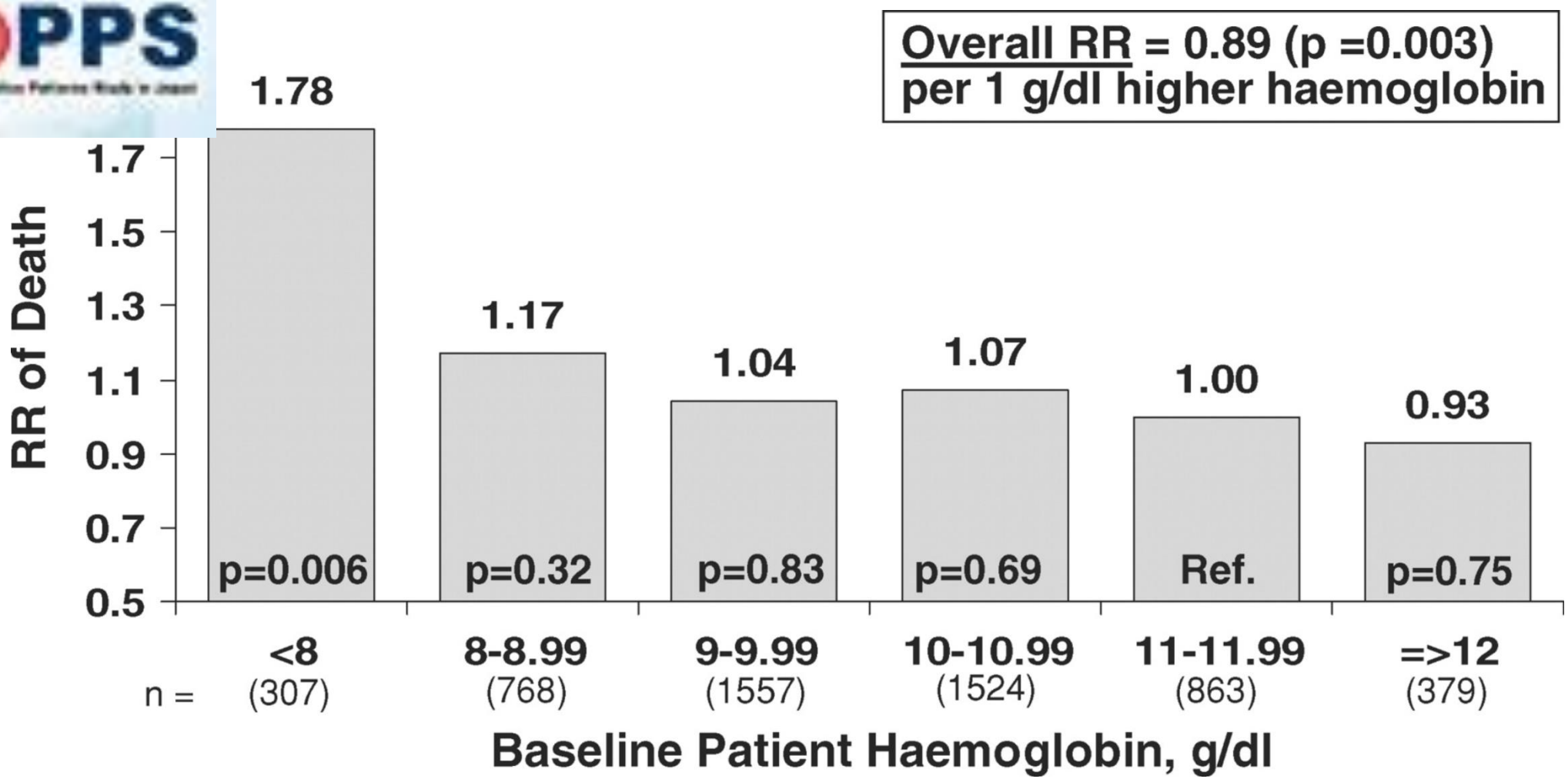
Target hemoglobin of anemia in CKD

Observational study



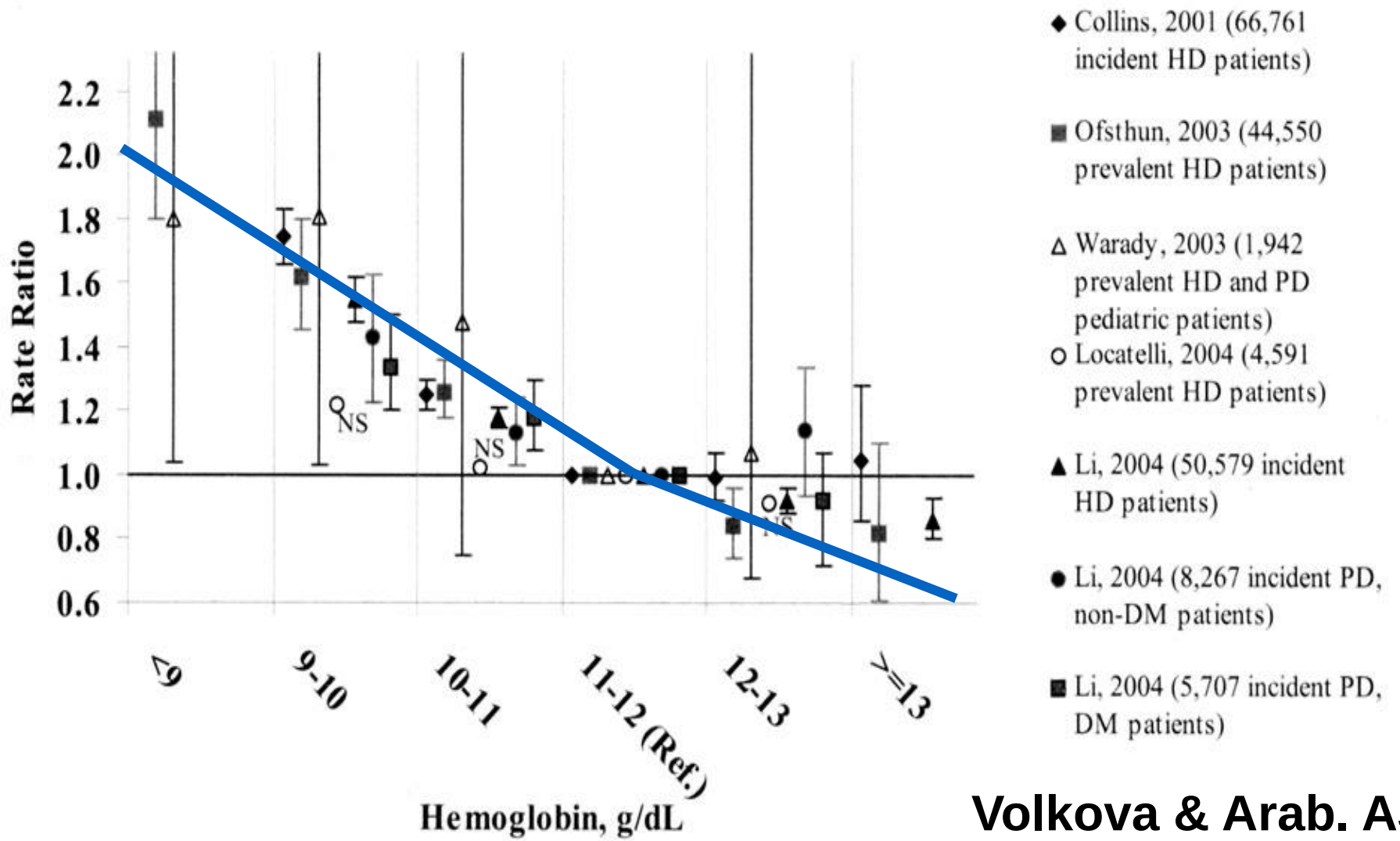
Interventional study

Baseline patient hemoglobin levels and subsequent mortality risk: J-DOPPS



Akizawa et al. NDT 2008

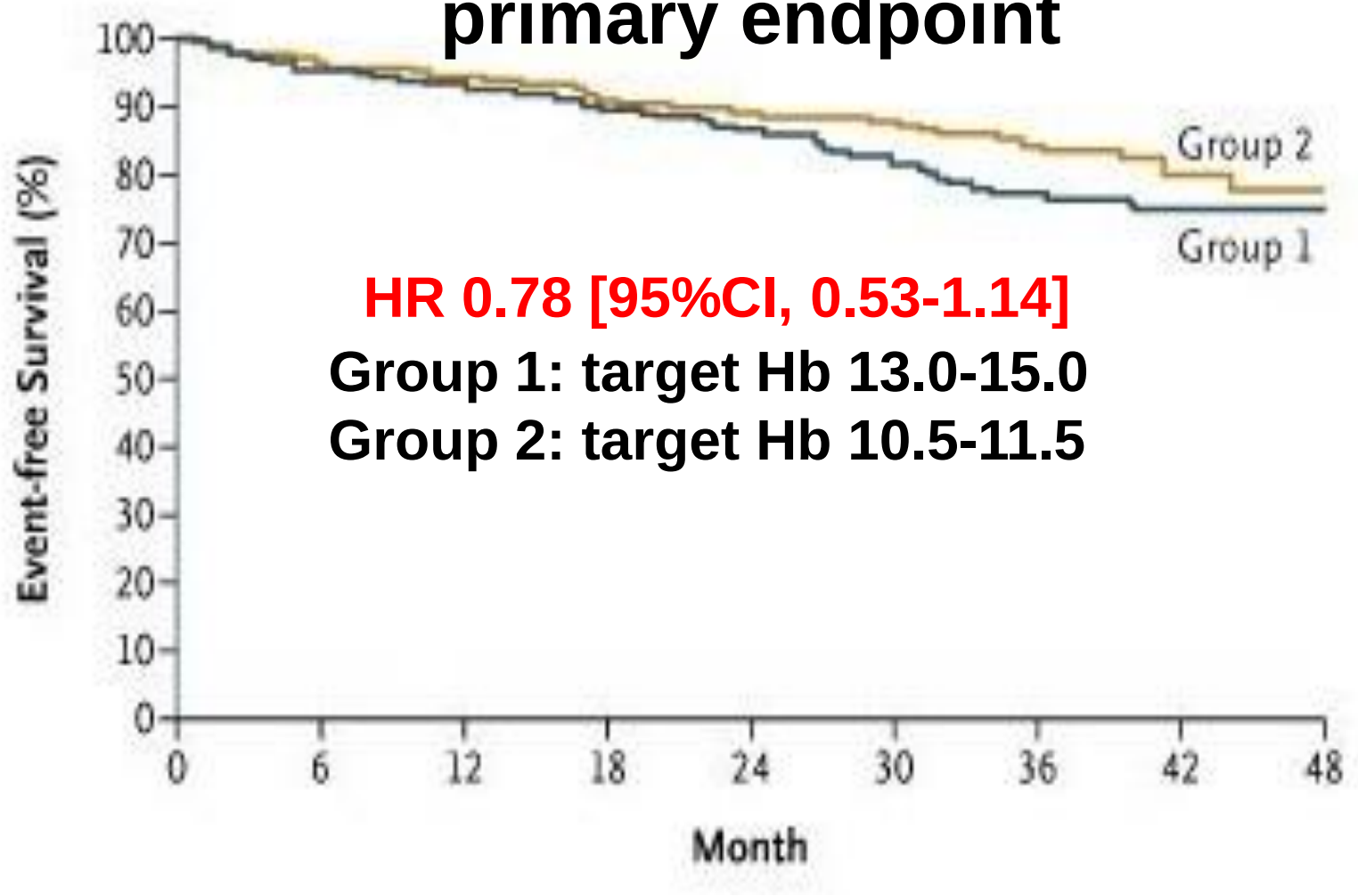
Anemia and prognosis of CKD patients meta-analysis



Volkova & Arab. AJKD 2006

Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)

primary endpoint



HR 0.78 [95%CI, 0.53-1.14]

Group 1: target Hb 13.0-15.0

Group 2: target Hb 10.5-11.5

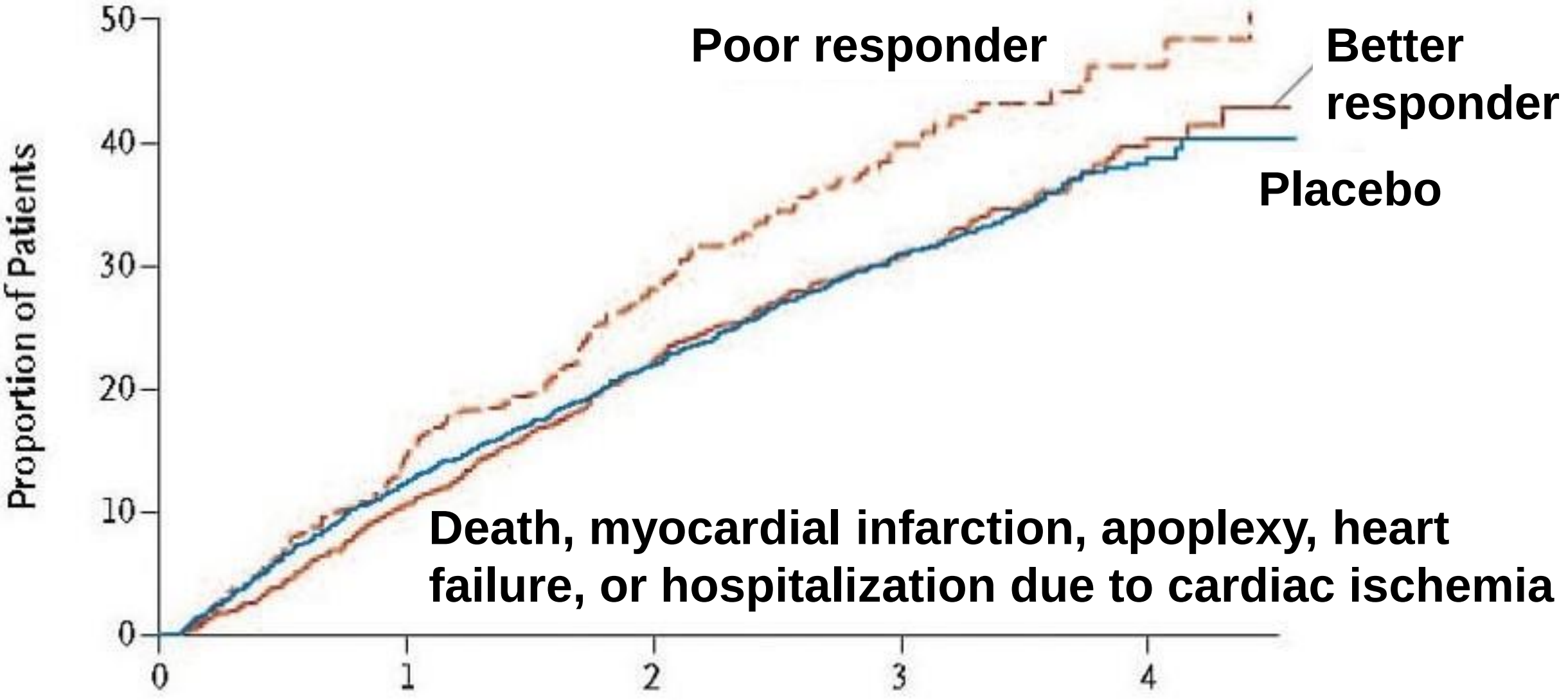
Drueke et al. N Engl J Med 2006

TREAT study

Endpoint	Darbepoetin alfa N = 2012	Placebo N = 2026	HR (95% CI)	*P*-value
CV Composite	632 (31.4)	602 (29.7)	1.05 (0.94-1.17)	0.41
Death	412 (20.5)	395 (19.5)	1.05 (0.92-1.21)	0.48
Heart Failure	205 (10.2)	229 (11.3)	0.89 (0.74-1.08)	0.24
MI	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
Myocardial Ischemia	41 (2.0)	49 (2.4)	0.84 (0.55-1.27)	0.40
Renal Composite	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

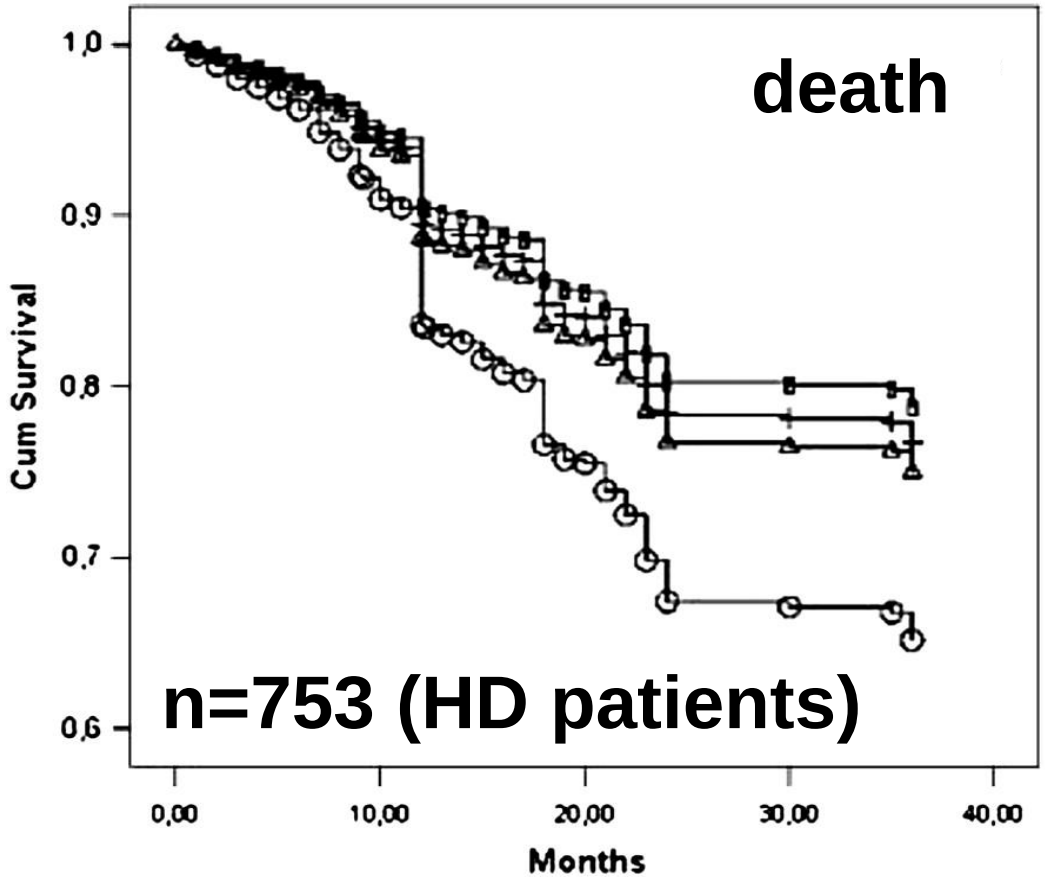
Pfeffer et al. N Engl J Med 2009

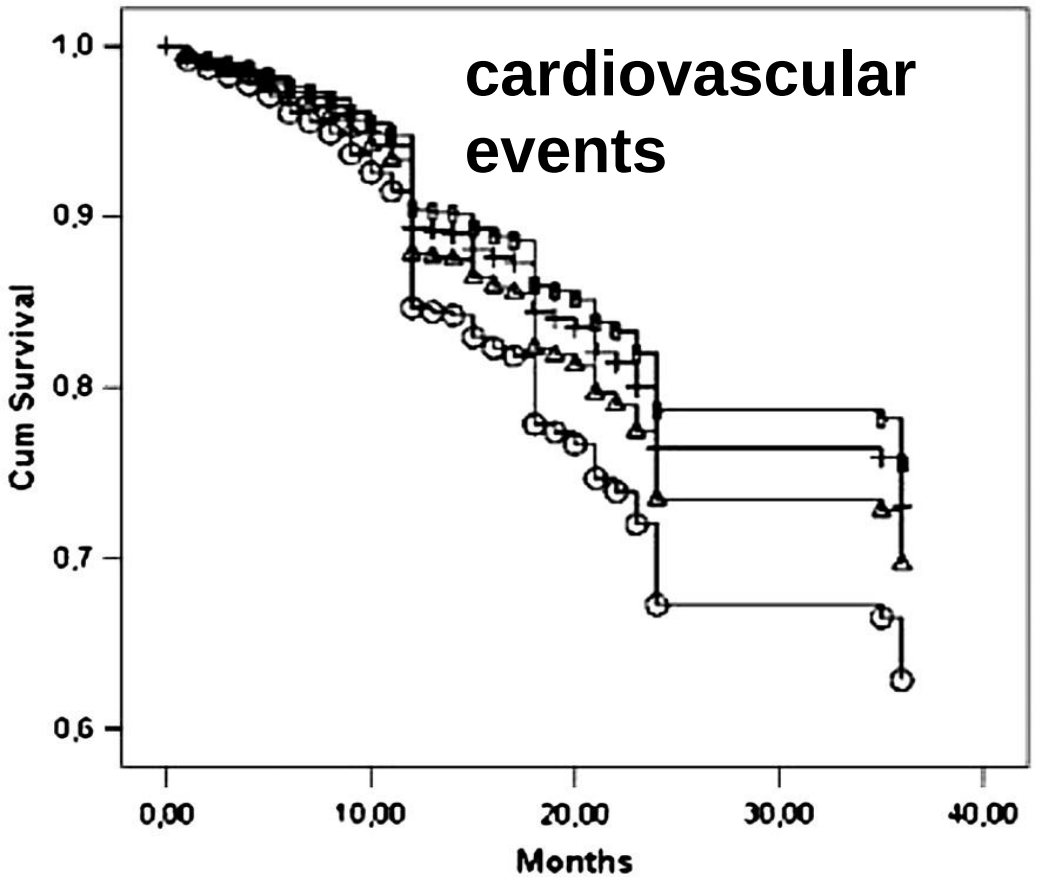
ESA hyporesponsiveness: TREAT study



Solomon et al. N Engl J Med 2010

EPO hyporesponsiveness : RISCAVID study





ESAs resistance index (ERI): the weekly ESAs dose / kgBW / Hb (g/dL)

Panichi et al. Nephrol Dial Transplant 2011

Erythropoietin hyporesponsiveness in Japanese HD patients: possible role of statins

a Association between statin prescription and subsequent ESA hyporesponsiveness by increasing levels of adjustment

Outcome	Statin Rx	Number of patients	Number of events, *n* (%)	OR (95% CI)			
				model 1[b]	model 2[c]	model 3[d]	model 4[e]
Hgb <10 g/dL	+	585	66 (11.3)	0.88 (0.67–1.13)	0.86 (0.65–1.14)	0.85 (0.64–1.13)	0.87 (0.66–1.15)
ESA dose[a] >6,000 units/week	–	3,017	394 (13.1)				

ESA, erythropoiesis-stimulating agent; Hgb, hemoglobin.
[a] Mircera doses were converted to darbepoetin doses using a 1.2:1 ratio, and darbepoetin doses were converted to epoetin doses using a 250:1 ratio.
[b] Model 1: adjusted for DOPPS phase and accounting for facility clustering.
[c] Model 2: adjusted for model 1+ age, gender, vintage, 11 summary comorbidities and post dialysis weight.
[d] Model 3: adjusted for model 2+ Kt/V, treatment time, hospitalization in past 3 months.
[e] Model 4: adjusted for model 3+ CRP, albumin, TSAT, ferritin.

b Association between statin prescription and subsequent ESA resistance index by increasing levels of adjustment

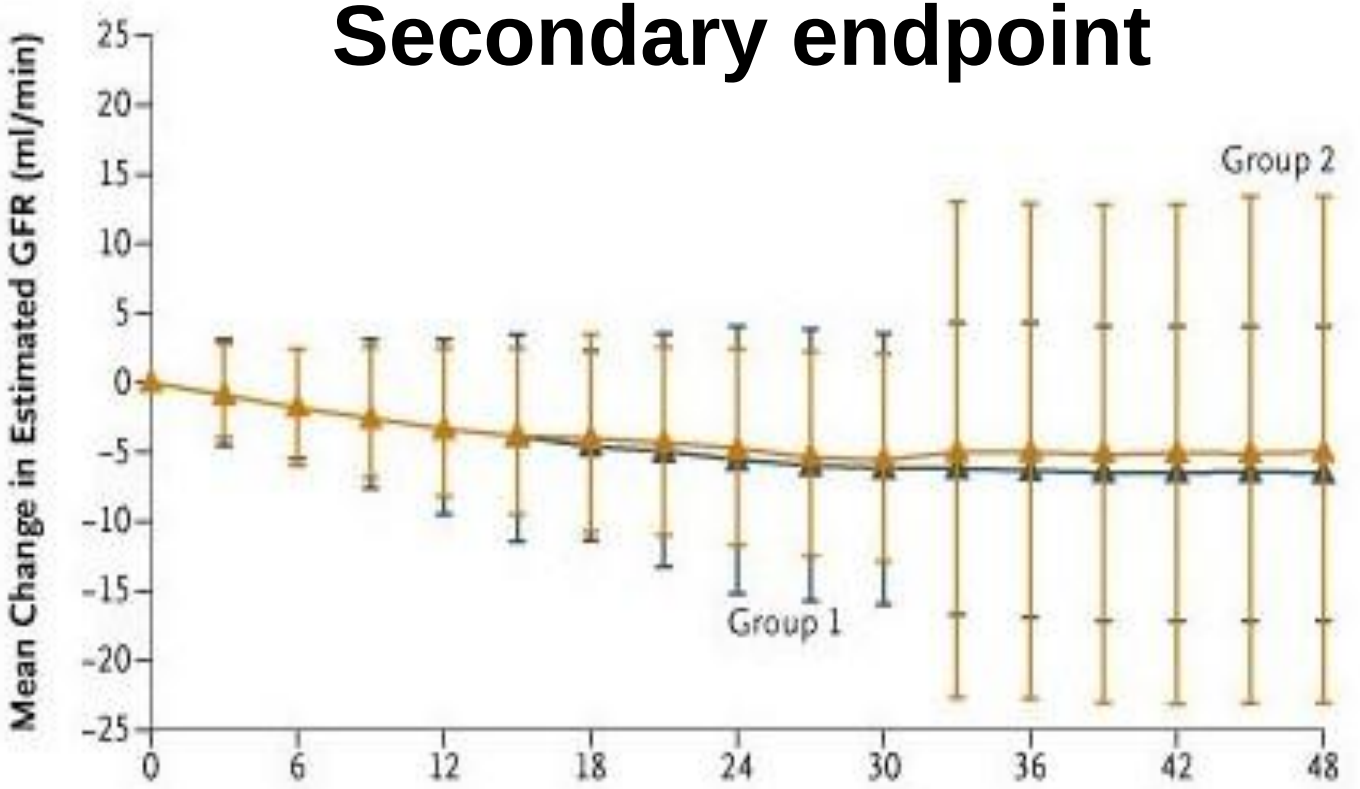
Outcome	Statin Rx	Number of patients	Average ERI	Ratio of means (95% CI)			
				model 1[b]	model 2[c]	model 3[d]	model 4[e]
logERI[a,f]	+	585	10.1	0.92 (0.87–0.97)	0.95 (0.90–1.00)	0.94 (0.89–0.99)	0.94 (0.89–0.99)
	–	3,017	10.7				

ESA, erythropoiesis-stimulating agent; ERI, ESA resistance index.
[a] Mircera doses were converted to darbepoetin doses using a 1.2:1 ratio, and darbepoetin doses were converted to epoetin doses using a 250:1 ratio.
[b] Model 1: adjusted for DOPPS phase and accounting for facility clustering.
[c] Model 2: adjusted for model 1+ age, gender, vintage, 11 summary comorbidities and post dialysis weight.
[d] Model 3: adjusted for model 2+ Kt/V, treatment time, hospitalization in past 3 months.
[e] Model 4: adjusted for model 3+ CRP, albumin, TSAT, ferritin.
[f] ERI = ESA/(dry weight × Hgb).

Hasegawa, Nangaku et al. Am J Nephrol 2017

Kidney outcome in CREATE

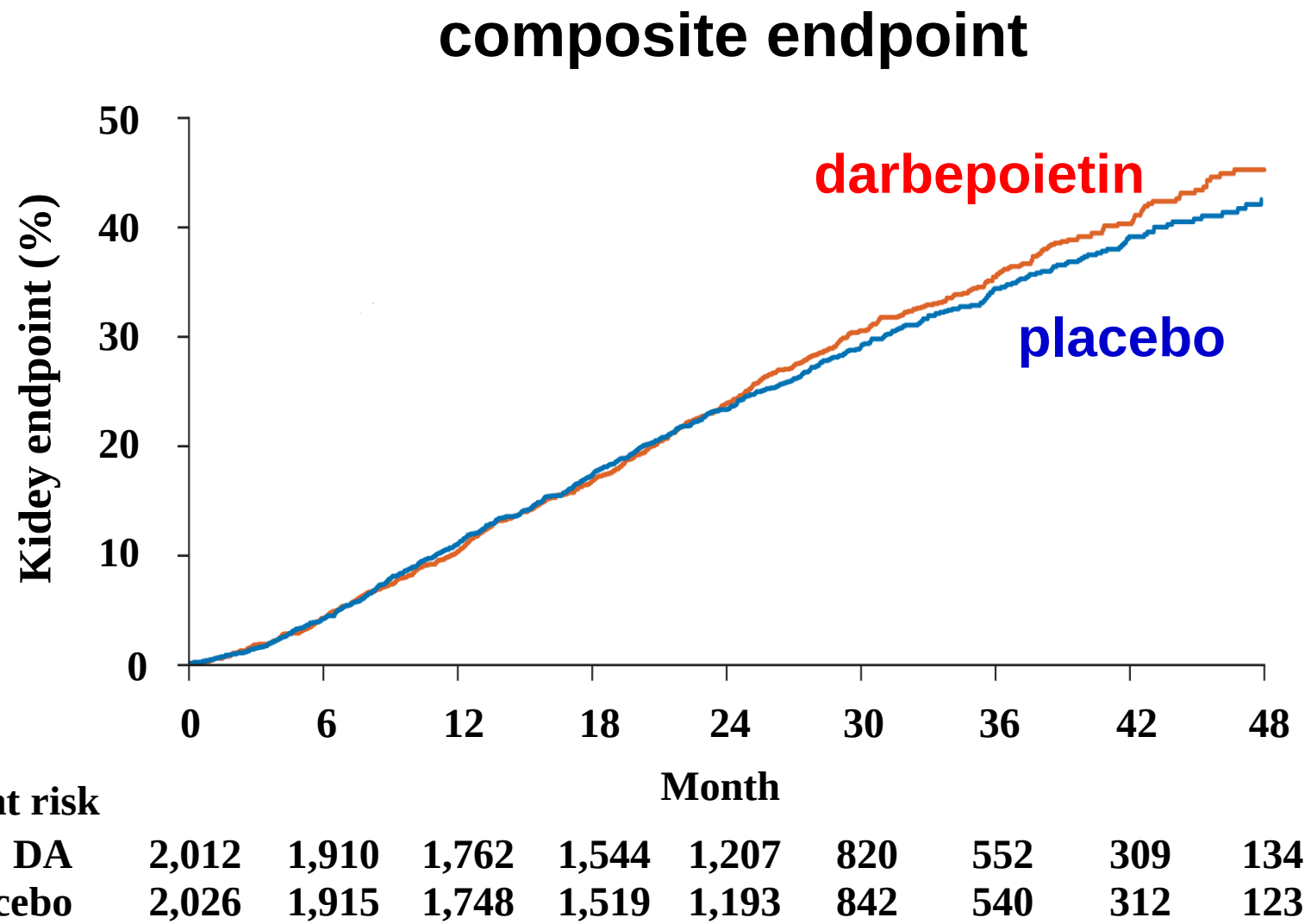
Secondary endpoint



No. at Risk									
Group 1	299	287	287	287	287	287	287	288	289
Group 2	298	293	293	293	293	293	293	293	293

Drueke et al. N Engl J Med 2006

Kidney outcome in TREAT



Pfeffer et al. N Engl J Med 2009

Therapeutic Apheresis and Dialysis

A21 study

Therapeutic Apheresis and Dialysis 2012; 16(6):529–540
doi: 10.1111/j.1744-9987.2012.01082.x

High Target Hemoglobin With Erythropoiesis-Stimulating Agents Has Advantages in the Renal Function of Non-Dialysis Chronic Kidney Disease Patients

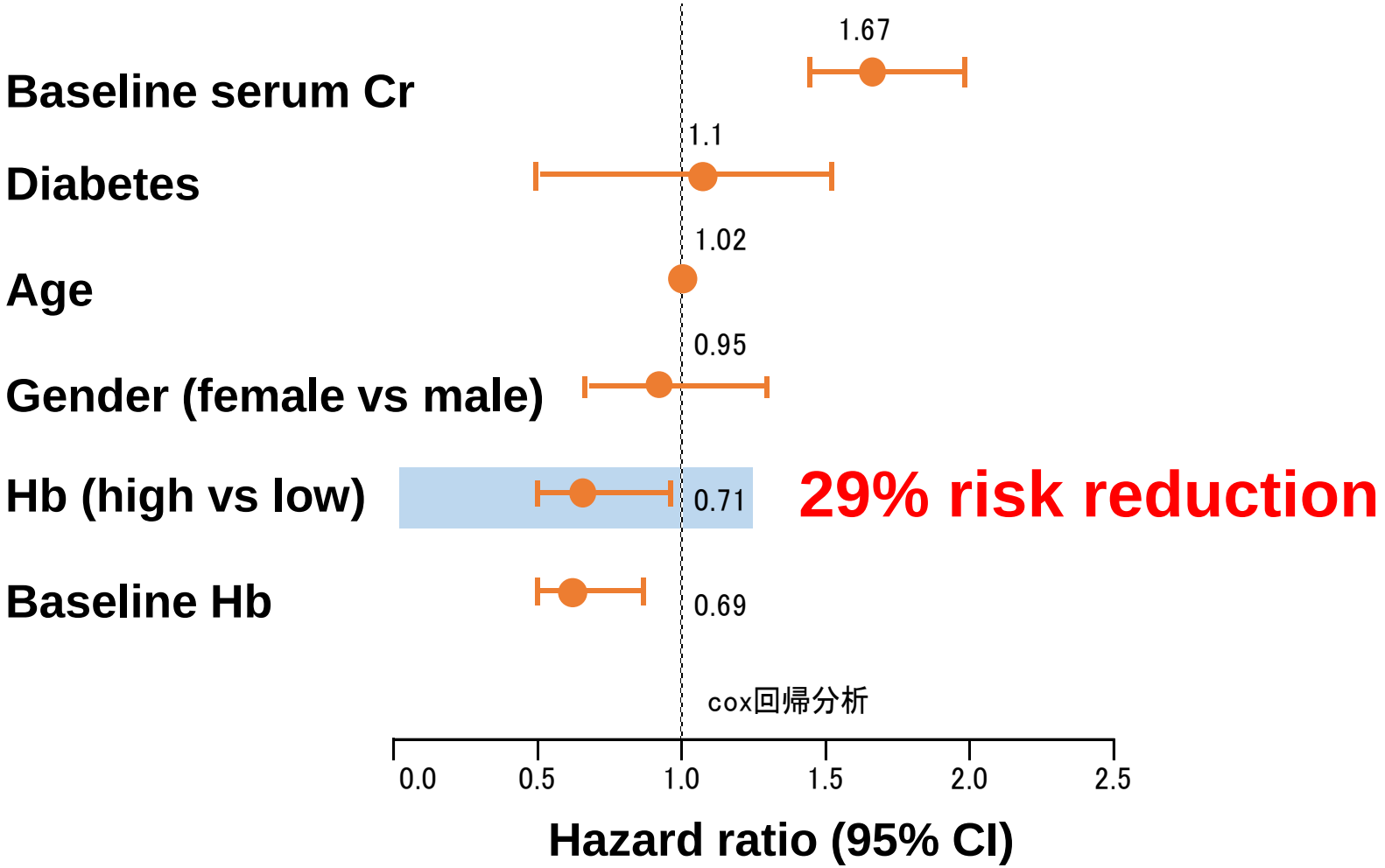
Yoshiharu Tsubakihara,[1] Fumitake Gejyo,[2] Shinichi Nishi,[4] Yasuhiko Iino,[5] Yuzou Watanabe,[8] Masashi Suzuki,[3] Akira Saito,[9] Takashi Akiba,[6] Hideki Hirakata,[10] and Tadao Akizawa[7]

Trial design	**Multi-center, randomized, open-labelled trial**
subject	**Non-HD CKD patients** **Hb <10.0 g/dL, serum creatinine 2.0 – 6.0 mg/dL**
	high Hb group（target Hb 11.0–13.0 g/dL）treated with darbepoietin [*n* = 161] **low Hb group （target Hb 9.0–11.0 g/dL）treated with epoetin-alpha [*n* = 180]** **Fe supplementation to keep TSAT>20% and ferritn >100 ng/mL**

Tsubakihara et al. Ther Apher Dial 2012

Risks of kidney events

Cox proportional hazards model adjusted by age, sex, and randomization factors



Tsubakihara et al. Ther Apher Dial 2012

No differences in adverse effects (cardiovascular) between the high Hb group and the low Hb group

TABLE 2. *Cardiovascular events considered as adverse*

Preferred term (MedDRA/J Version 8.1)	Number of patients (%)	
	High Hb group ($n = 161$)	Low Hb group ($n = 160$)
Hypertension	22 (13.7)	11 (6.9)
Blood pressure increased	17 (10.6)	37 (23.1)
Chest pain	6 (3.7)	–
Blood pressure decreased	5 (3.1)	1 (0.6)
Cardiomegaly	4 (2.5)	5 (3.1)
Palpitations	4 (2.5)	1 (0.6)
Orthostatic hypotension	3 (1.9)	1 (0.6)
Retinal vein occlusion	3 (1.9)	–
Lacunar infarction	2 (1.2)	2 (1.3)
Myocardial infarction	2 (1.2)	1 (0.6)
Arteriovenous fistula occlusion	2 (1.2)	1 (0.6)
Chest discomfort	2 (1.2)	–
Myocardial ischemia	2 (1.2)	–
Angina pectoris	2 (1.2)	–
Pulmonary congestion	2 (1.2)	–
Atrial fibrillation	1 (0.6)	2 (1.3)
Tachycardia	1 (0.6)	2 (1.3)
Cardiac failure congestive	1 (0.6)	2 (1.3)
Cerebellar infarction	1 (0.6)	–
Cerebral infarction	1 (0.6)	–
Cardiac failure	–	2 (1.3)
Cerebral ischemia	–	2 (1.3)
Bradycardia	–	1 (0.6)
Cardiac failure chronic	–	1 (0.6)
Heart rate increased	–	1 (0.6)
Pulse abnormal	–	1 (0.6)
Mitral valve incompetence	–	1 (0.6)
Fat embolism	–	1 (0.6)
Procedural hypertension	–	1 (0.6)

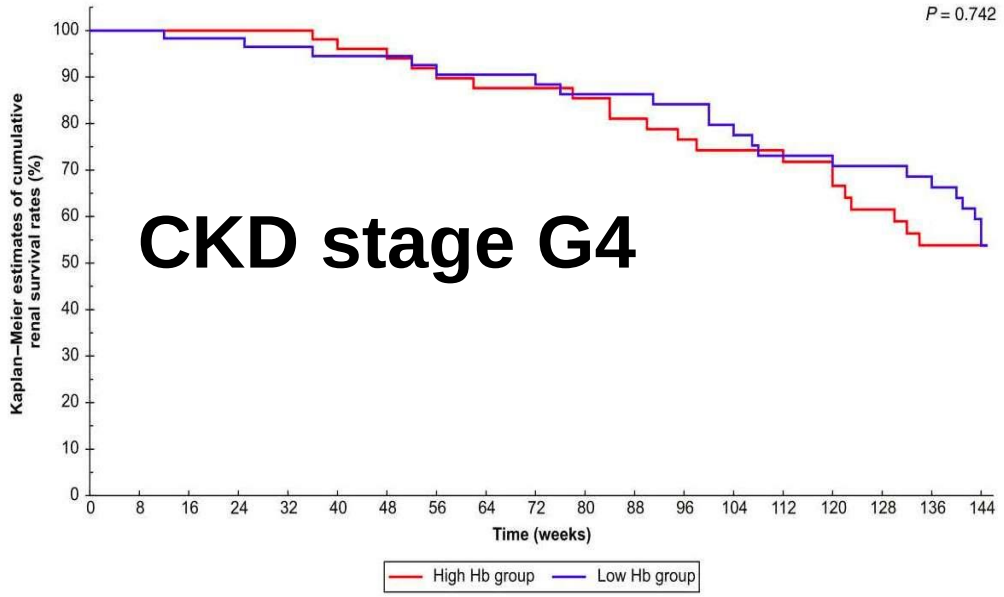
events
high Hb group 63（39.1%）
low Hb group 60（37.5%）

Mainly hypertension

Tsubakihara et al.
Ther Apher Dial 2012

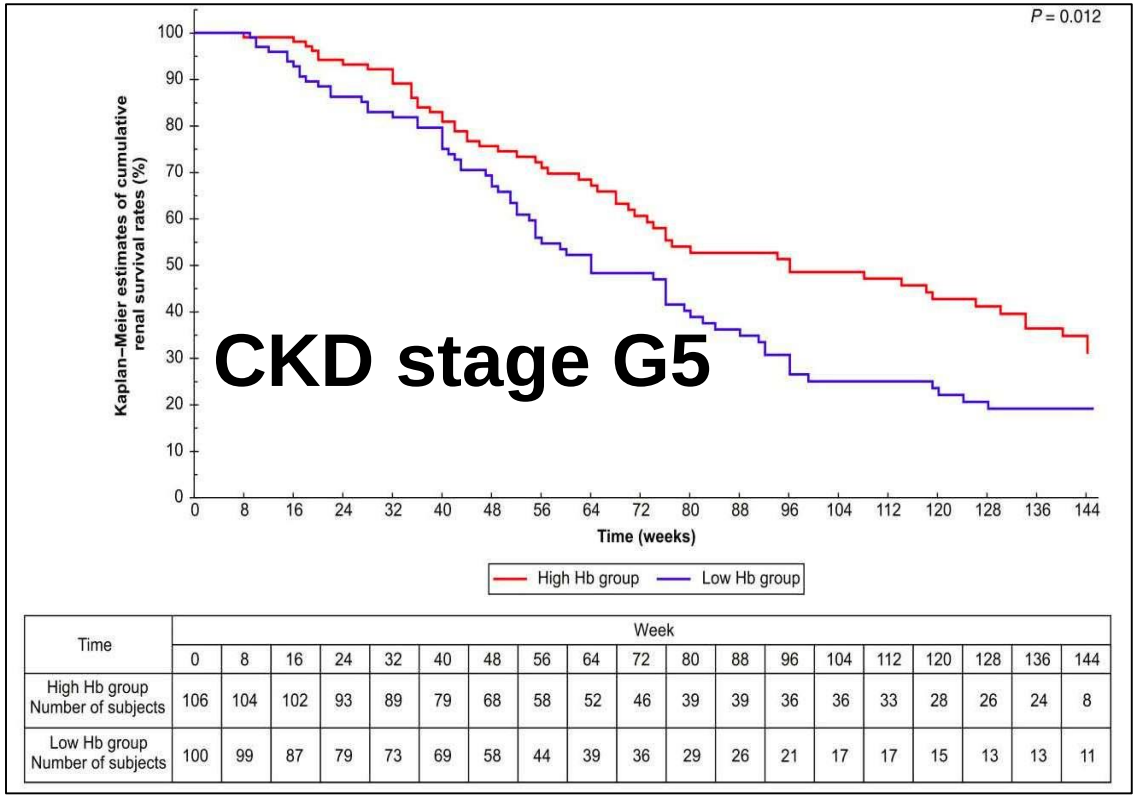
post-hoc analysis

a



CKD stage G4

Time	Week																		
	0	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144
High Hb group Number of subjects	55	54	54	53	52	47	46	42	41	41	39	36	34	31	29	27	24	21	13
Low Hb group Number of subjects	60	59	58	54	50	48	48	45	43	42	41	40	39	35	33	32	31	29	20



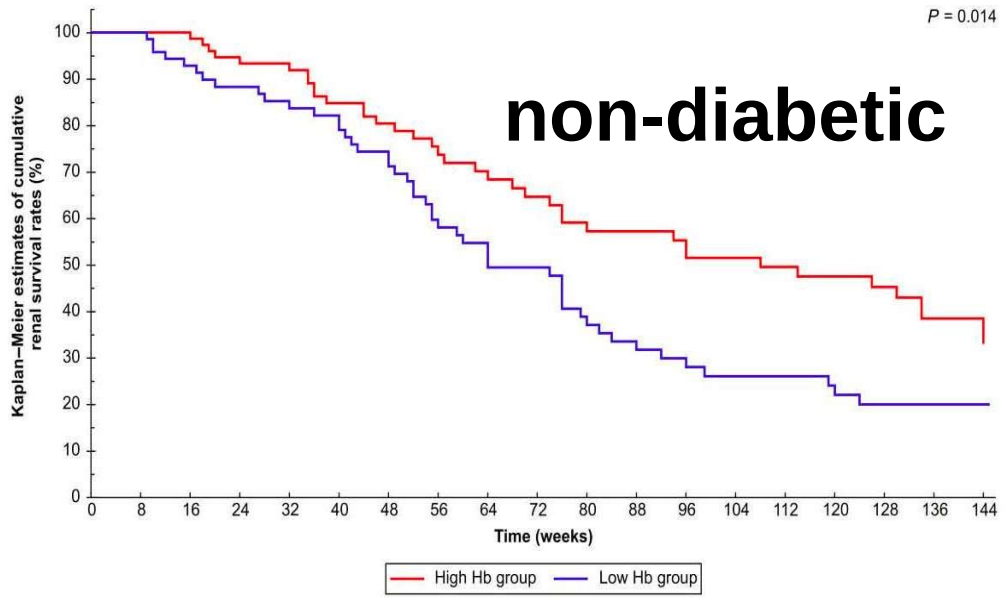
CKD stage G5

Time	Week																		
	0	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144
High Hb group Number of subjects	106	104	102	93	89	79	68	58	52	46	39	39	36	36	33	28	26	24	8
Low Hb group Number of subjects	100	99	87	79	73	69	58	44	39	36	29	26	21	17	17	15	13	13	11

Tsubakihara et al. Ther Apher Dial 2015

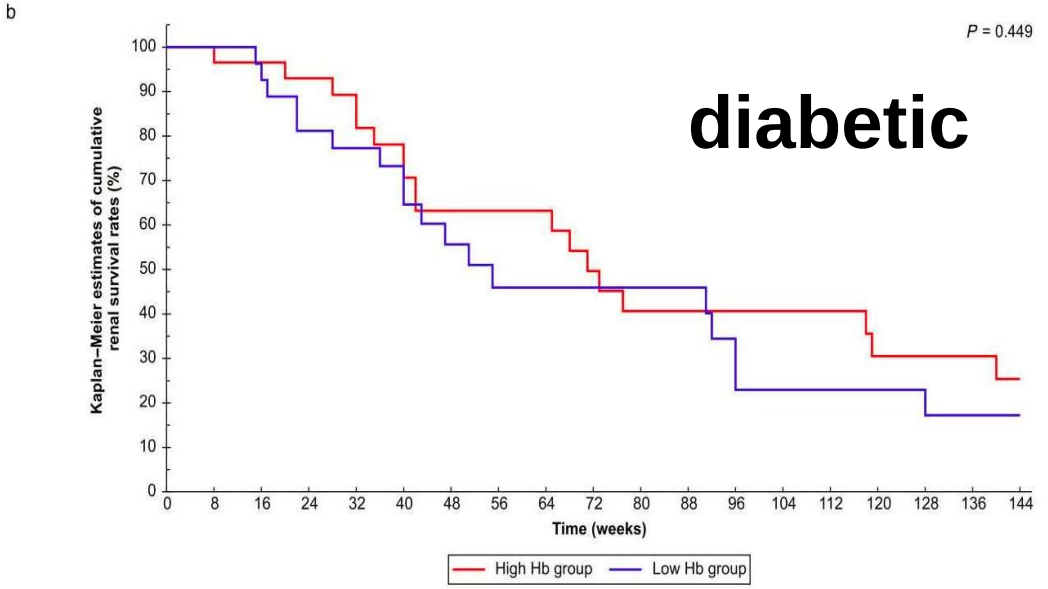
post-hoc analysis

a



Time	Week																		
	0	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144
High Hb group Number of subjects	76	76	75	68	65	59	51	42	38	35	30	30	28	28	25	22	20	18	6
Low Hb group Number of subjects	72	71	63	57	54	52	46	35	30	30	21	18	15	13	13	11	10	10	8

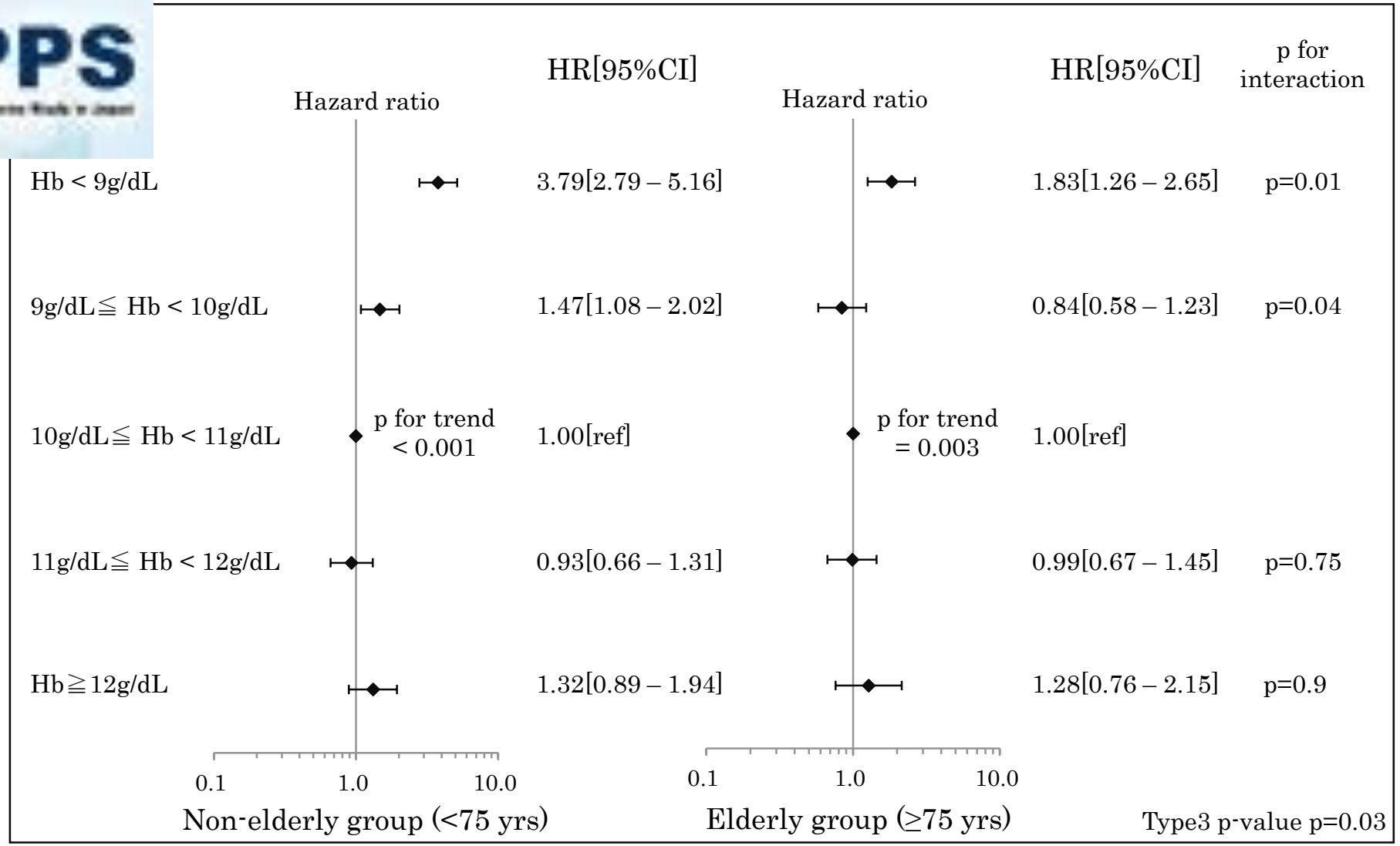
b



Time	Week																		
	0	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144
High Hb group Number of subjects	30	28	28	26	23	20	18	16	14	11	9	9	8	8	8	6	6	6	1
Low Hb group Number of subjects	28	28	25	22	19	16	12	9	9	8	8	8	5	5	5	5	3	3	2

Tsubakihara et al. Ther Apher Dial 2015

Elderly people are more tolerant to low Hb levels



Hanafusa, Nangaku et al. Nephrol Dial Transplant 2014

treatment of anemia in CKD: ESA

JSDT
Guideline of anemia in CKD 2015

Target Hb level and criterion for initiation of treatment of renal anemia

In adult HD patients, the target Hb levels to be maintained are in the range of 10–12 g/dL in the blood samples collected at the beginning of the week of HD. (1C)

Target Hb level and criterion for initiation of treatment of renal anemia

In adult CKD patients in the predialysis phase, the target Hb levels to be maintained are in the range of 11–13 g/dL. (2C)

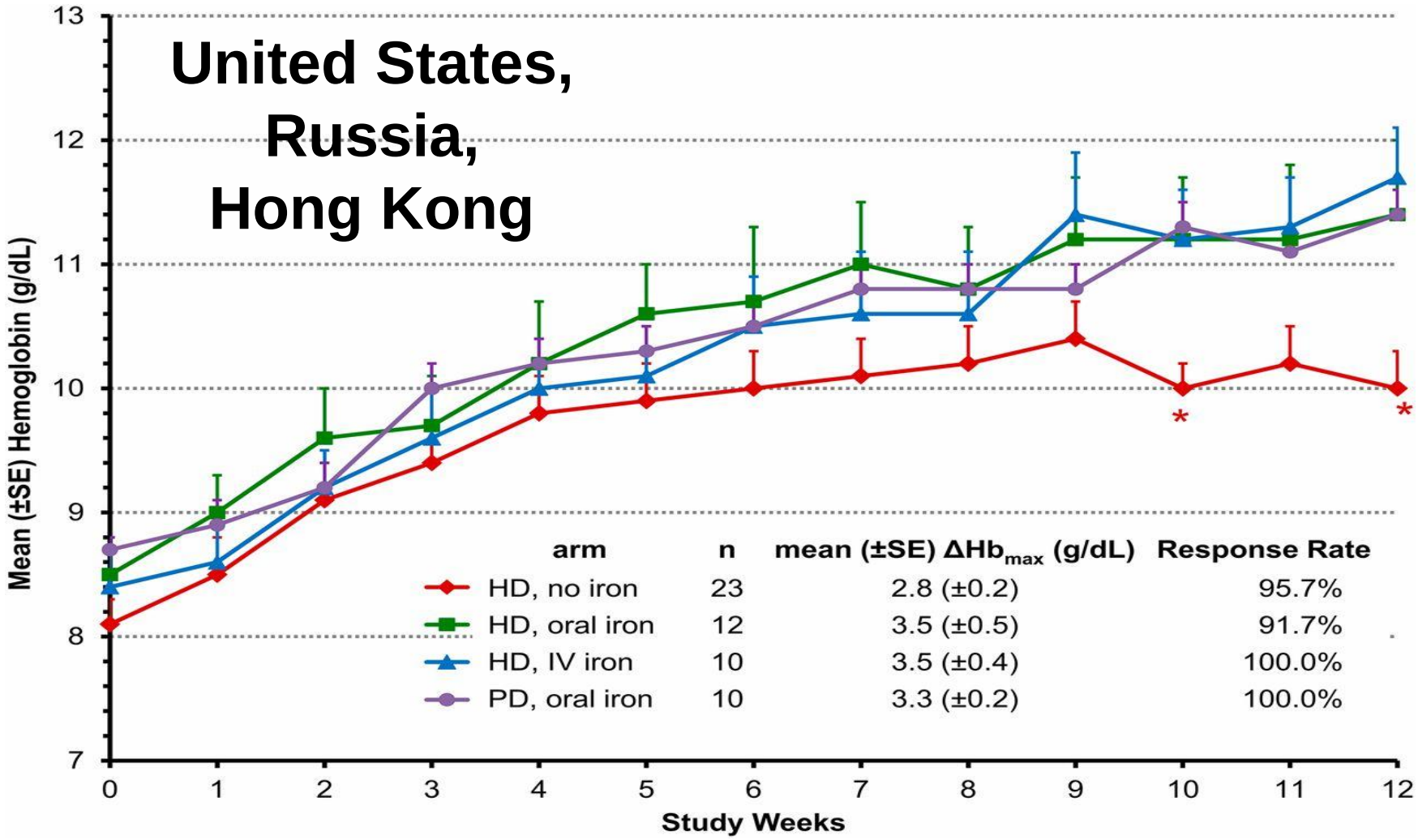
However, if the patient has a history of serious CVD or complications, or if it is medically necessary, dose reduction or the discontinuation of medication should be considered when the Hb level exceeds 12 g/dL. (not graded)

Target Hb level and criterion for initiation of treatment of renal anemia

In the actual treatment of HD, PD, and CKD patients in the predialysis phase, it is recommended to determine the target Hb levels according to the pathological conditions of individual patients by refering to the values provided above. (1C)

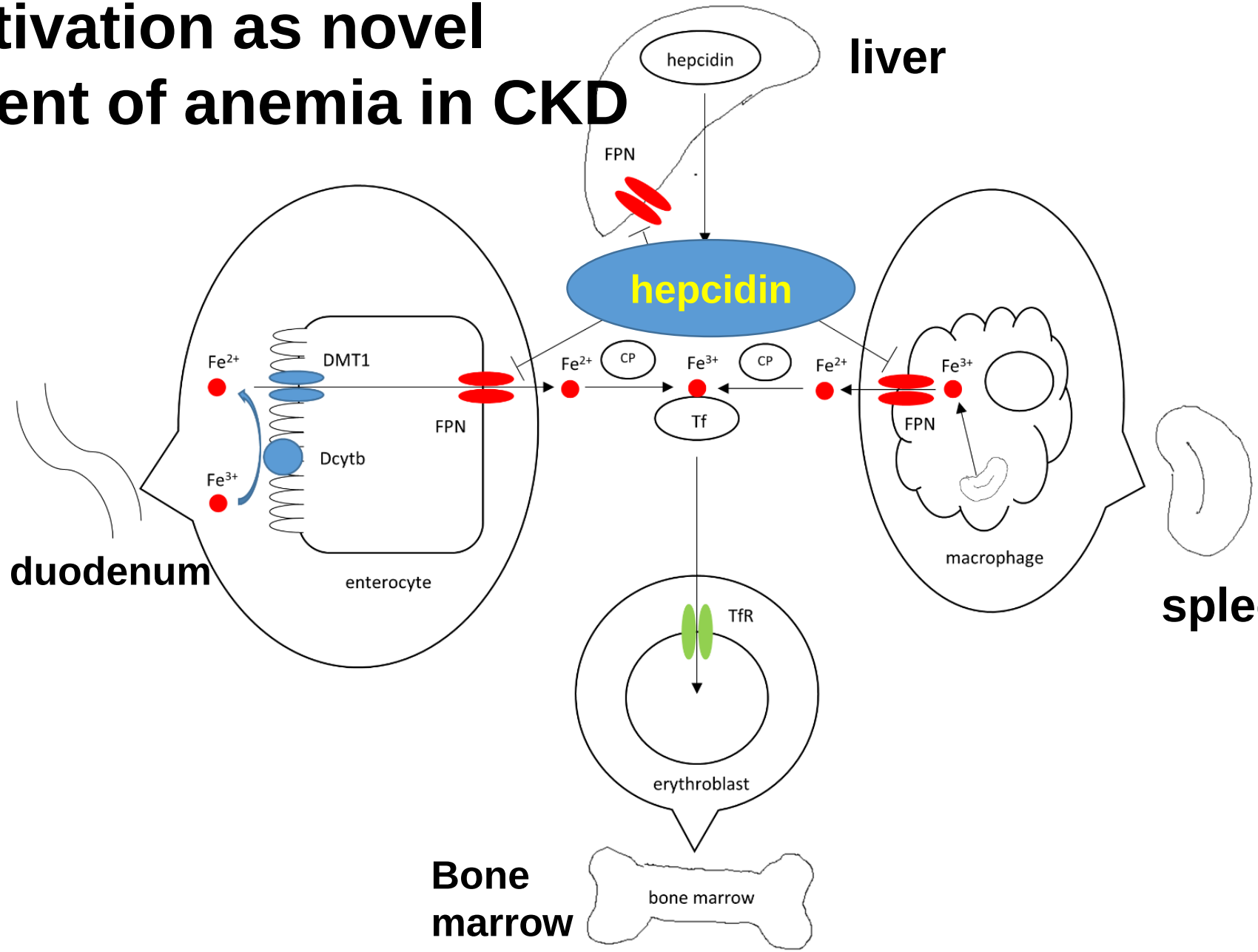
Novel ally for treatment of anemia in CKD: HIF activator (PHD inhibitor)

roxadustat in HD patients: hemoglobin



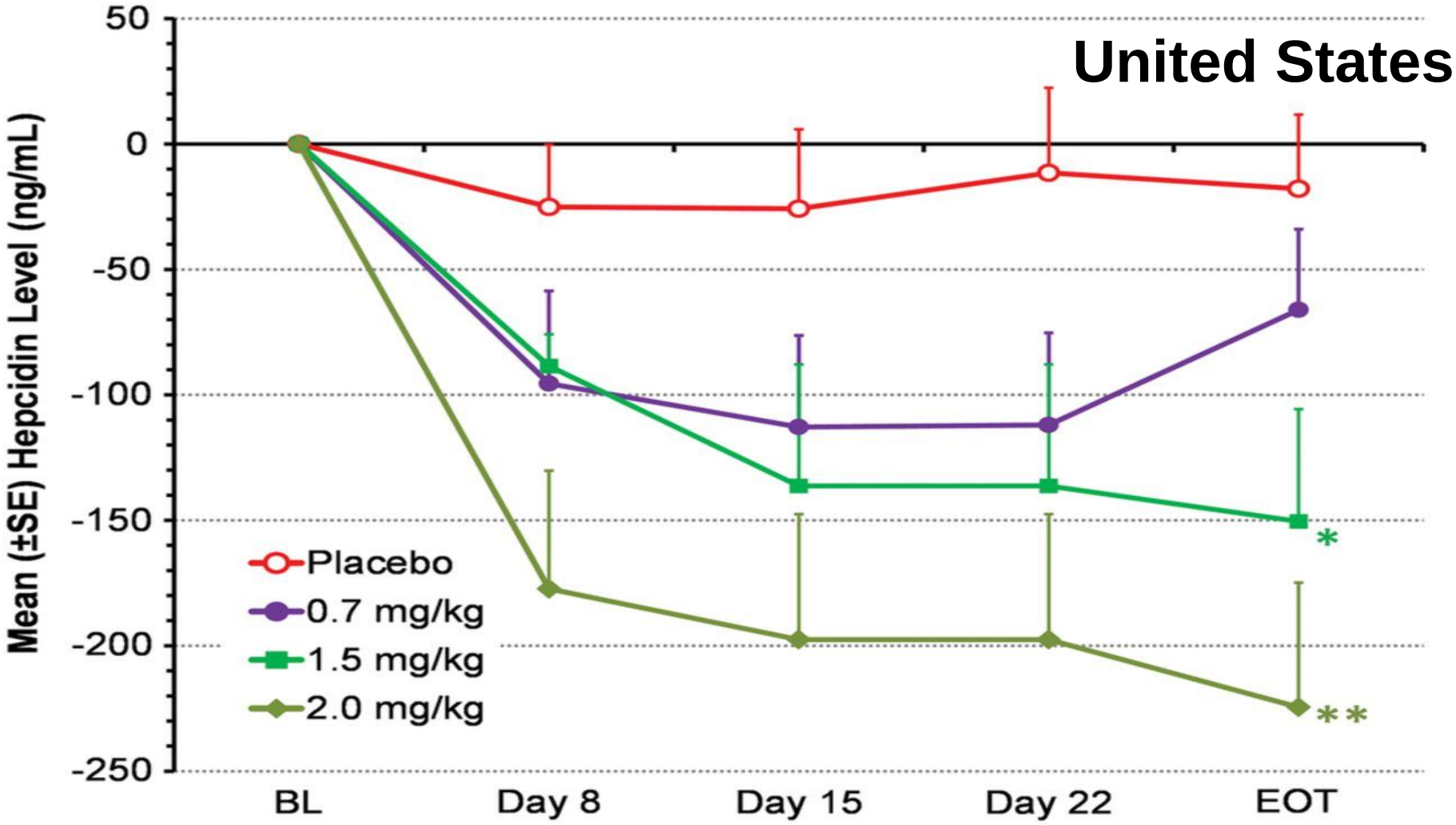
Besarab et al. JASN 2016

HIF activation as novel treatment of anemia in CKD



Sugahara, Tanaka T, Nangaku. Kidney Int 2017

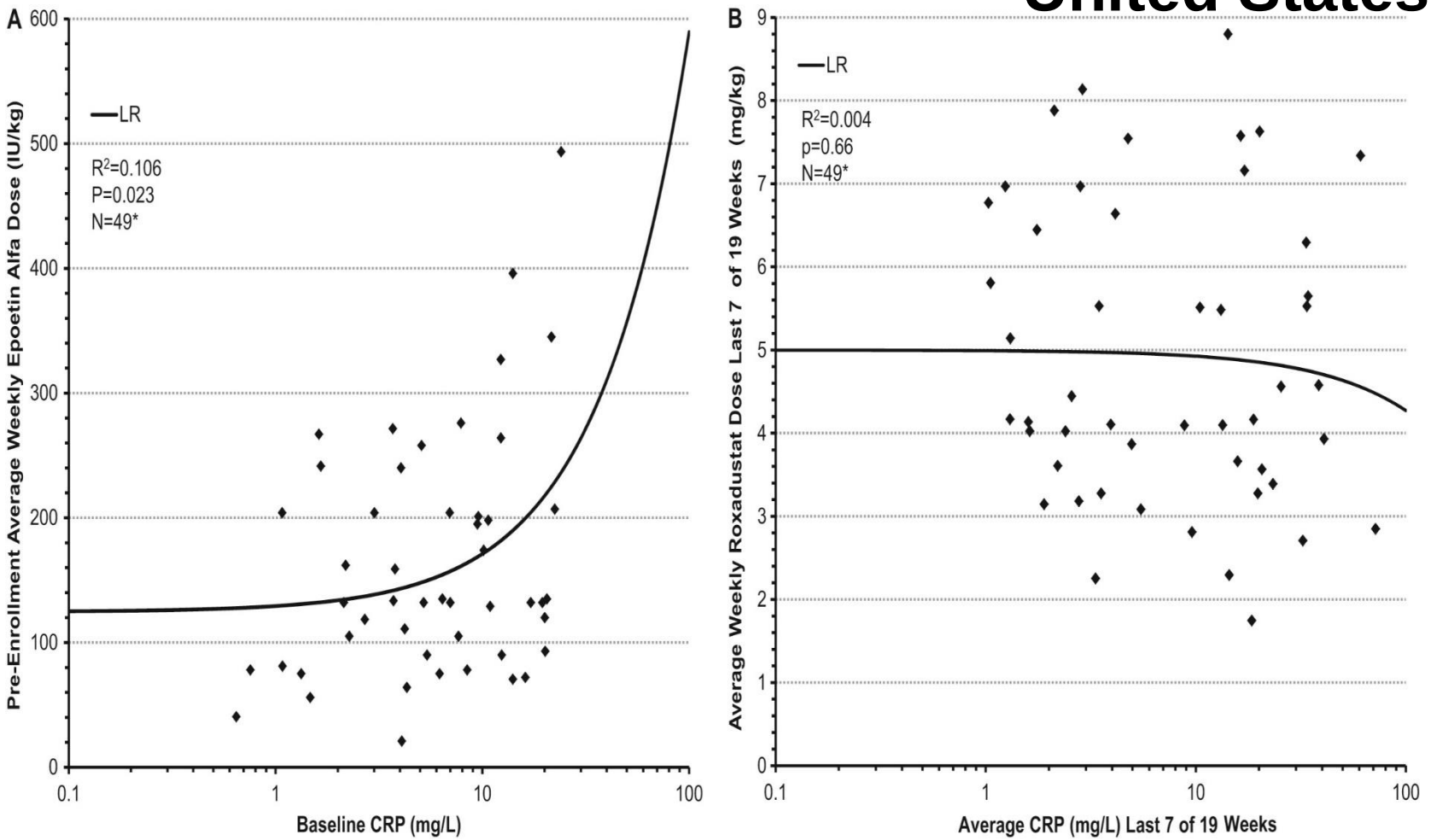
Phase 2a study of roxadustat in subjects with anemia and CKD (G3 or G4): hepcidin levels



Besarab et al. Nephrol Dial Transplant 2015

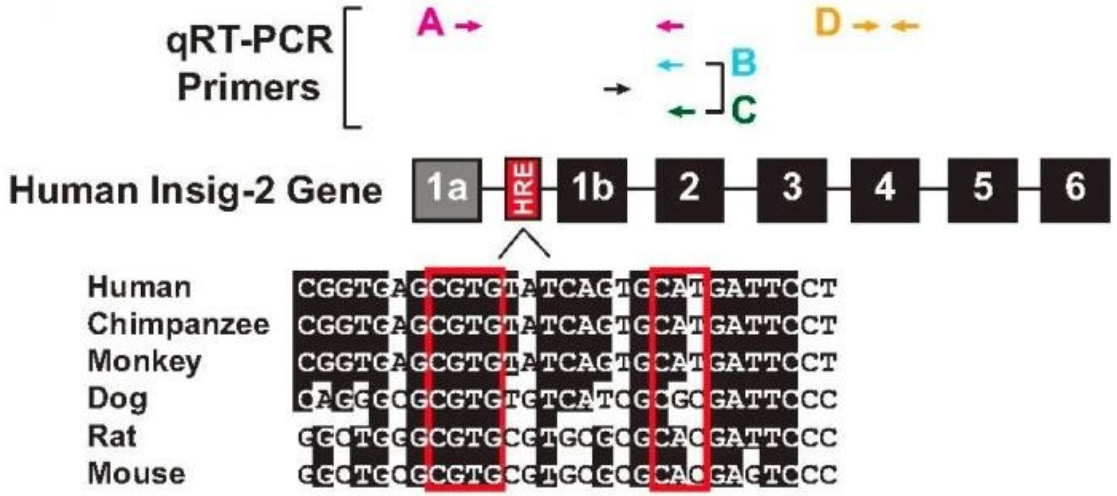
roxadustat maintenance dose requirements were independent of baseline CRP levels

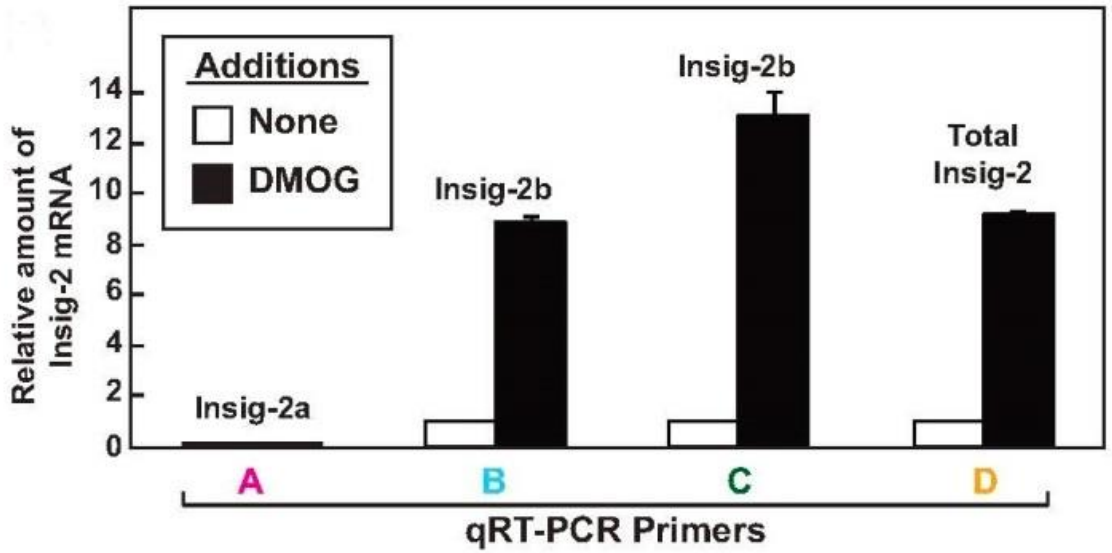
United States

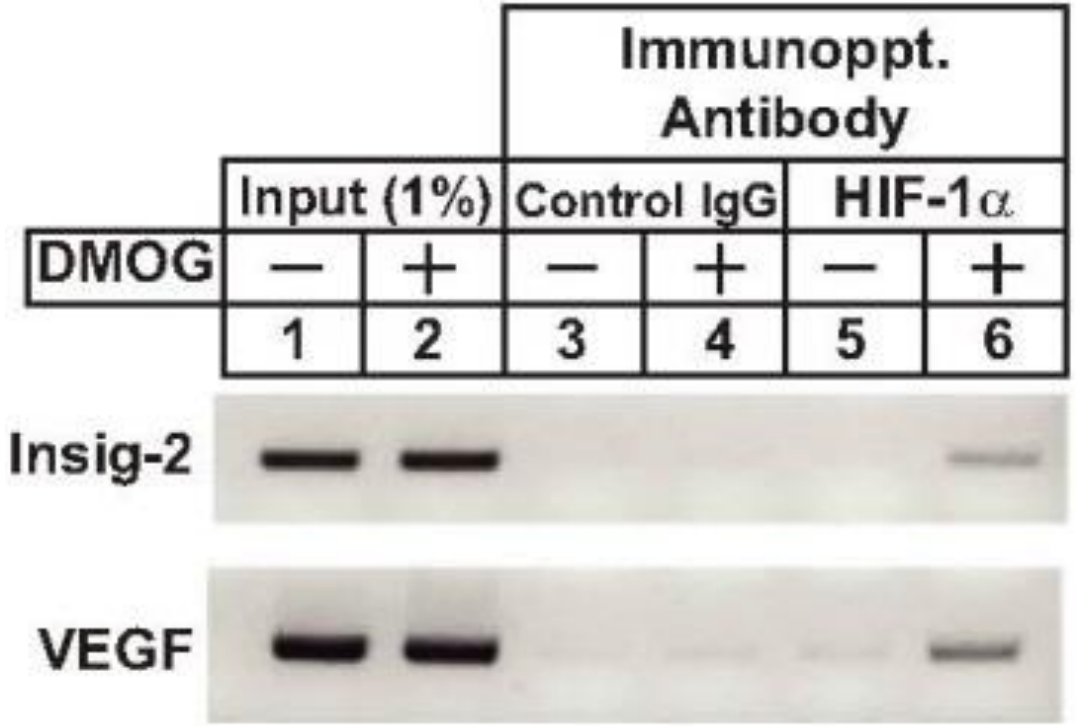


Provenzano et al. AJKD 2016

HIF-1 activates insulin-induced gene 2 (Insig-2) transcription

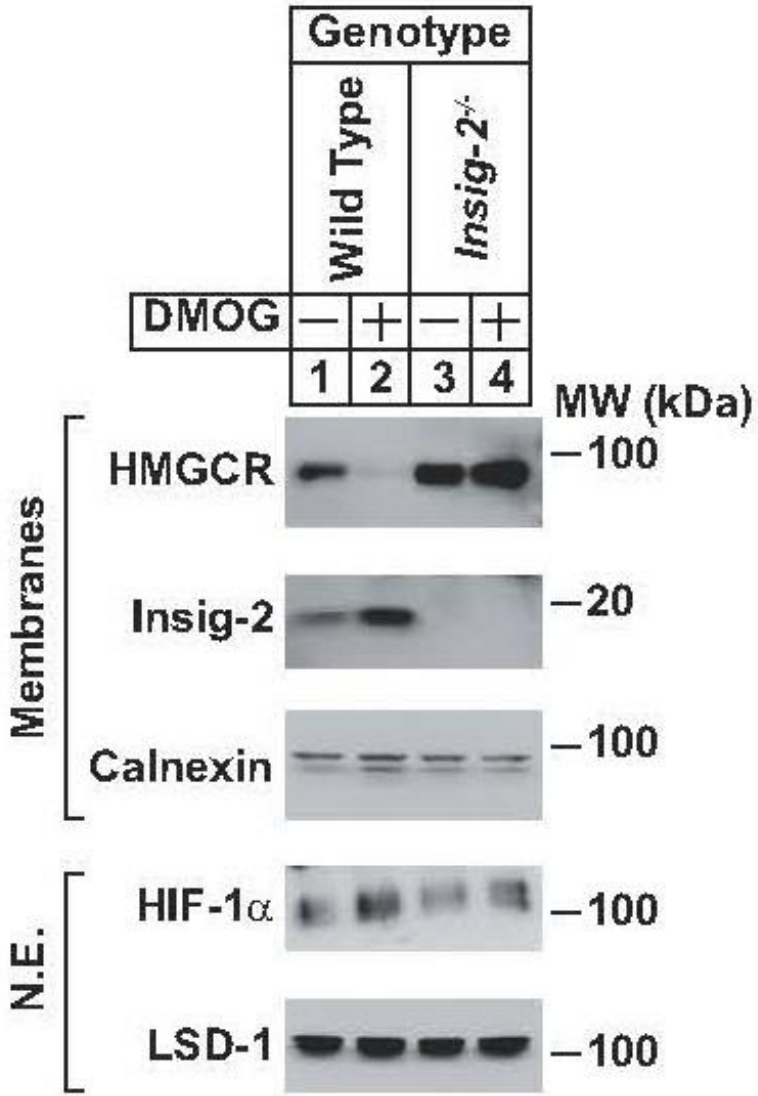


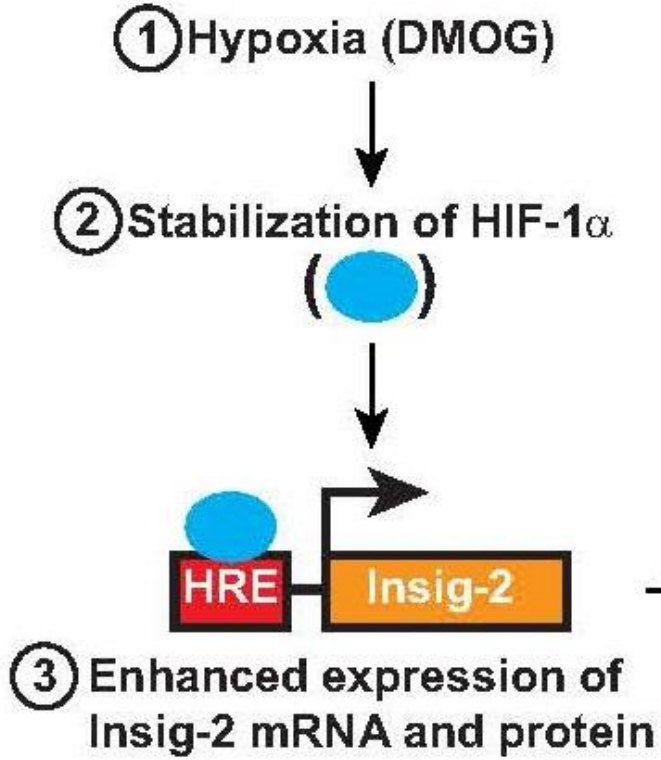


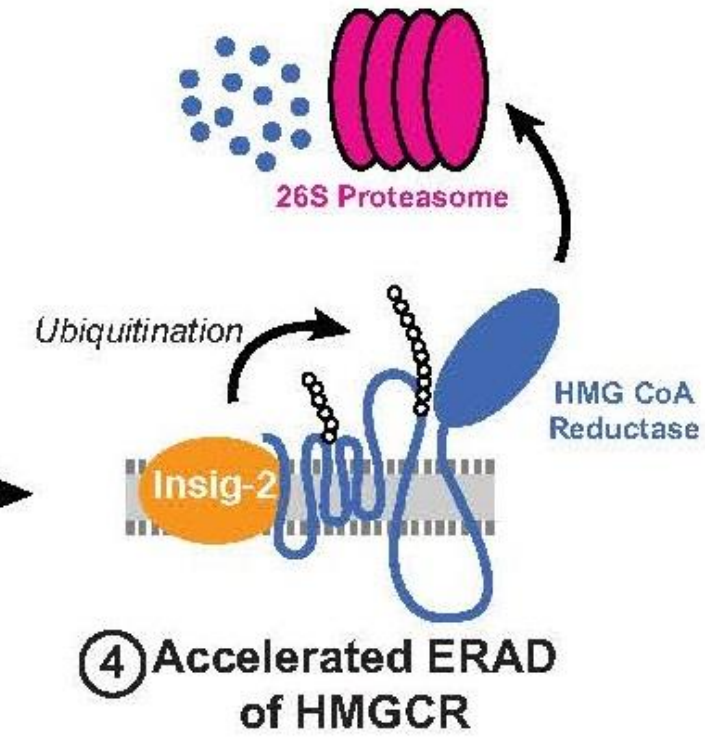


Hwang et al. J Biol Chem 2017

HIF-1 activates Insig-2 transcription for degradation of HMG-CoA reductase in the liver

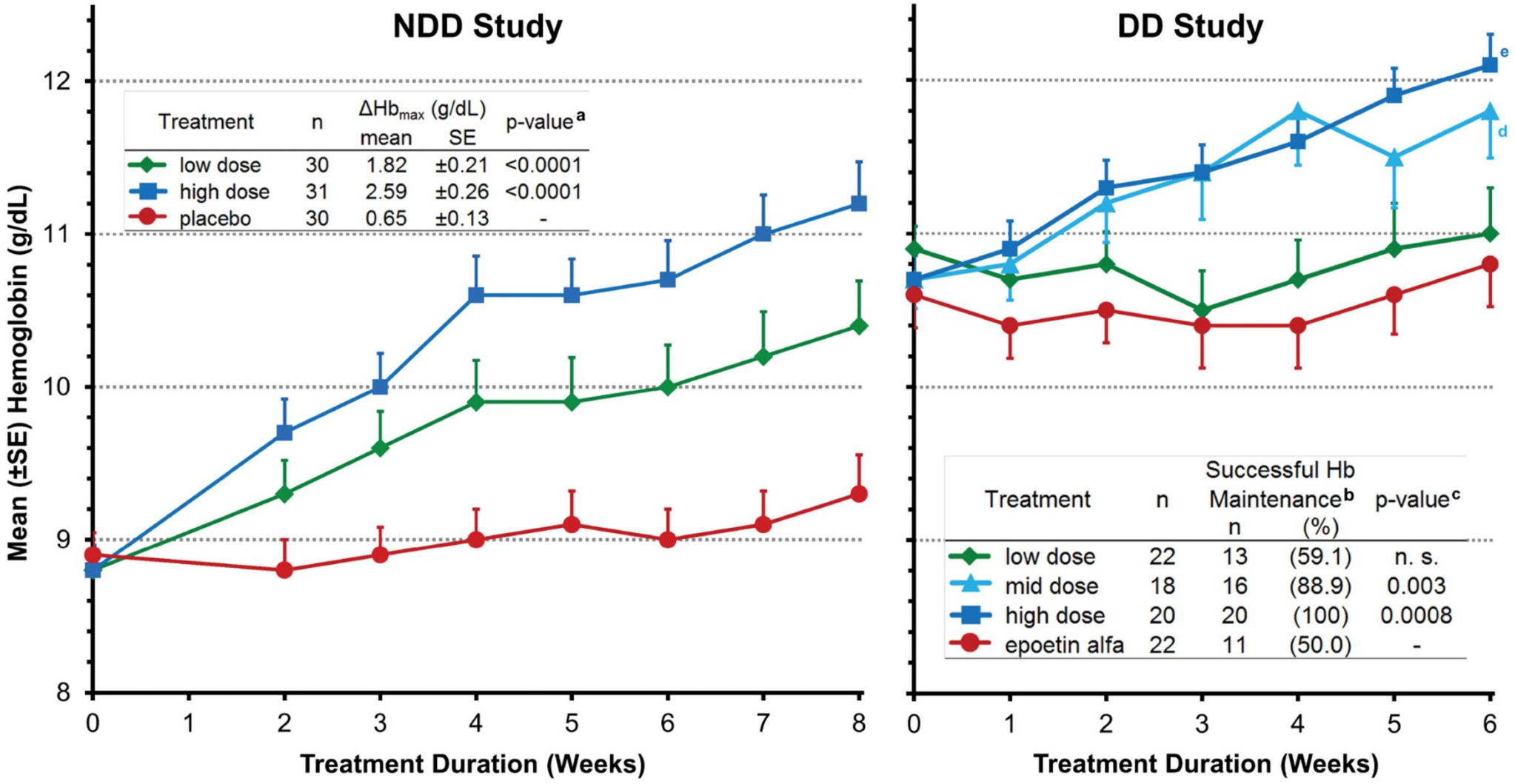






Hwang et al. J Biol Chem 2017

phase 2 studies of roxadustat for treatment of anemia in China



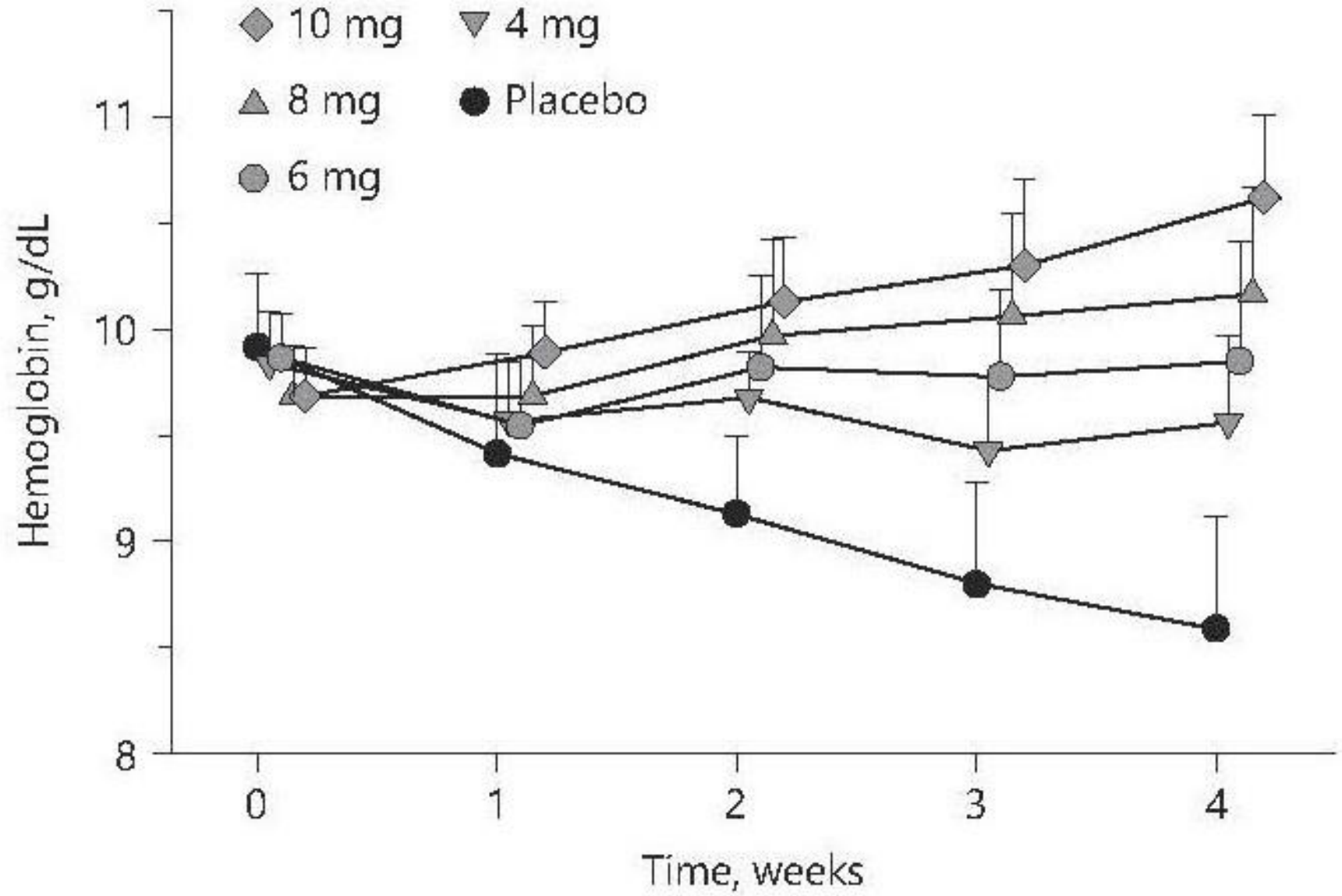
Nan Chen, Jiaqi Qian, Jianghua Chen, Xueqing Yu, Changlin Mei, Chuanming Hao et al. NDT 2017

decreases from baseline for the lipid parameters in the roxadustat groups

	NDD study			DD study			
	Placebo	roxadustat low	roxadustat high	rhEPO	roxadustat low	roxadustat mid	roxadustat high
Total chol (mg/dL)	8.0 (±30.0)	-31.7 (±25.3)	-35.6 (±37.5)	18.3 (±24.32)	-11.1 (±31.31)	-13.1 (±31.64)	-15.8 (±48.63)
LDL-chol (mg/dL)	4 (±25.5)	-22.4 (±19.4)	-32.0 (±33.5)	-5.0 (±15.3)	-25.0 (±20.2)	-23.4 (±20.6)	-25.8 (±27.6)

Nan Chen, Jiaqi Qian, Jianghua Chen, Xueqing Yu, Changlin Mei, Chuanming Hao et al. NDT 2017

effects of daprodustat on anemia in Japanese HD patients



Akizawa, Nangaku et al. Am J Nephrol 2017

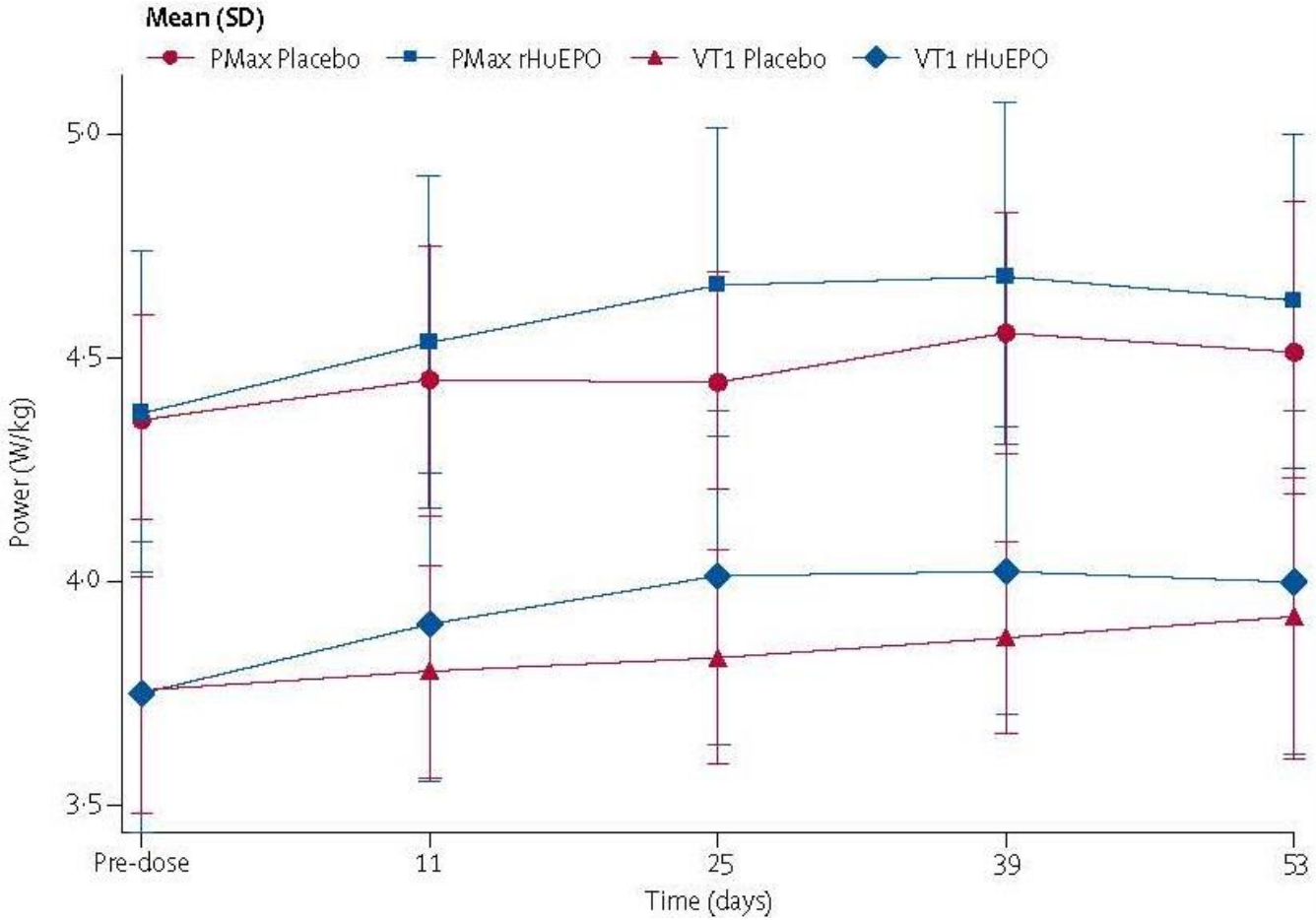
decreases from baseline for the lipid parameters at week 4 in the daprodustat groups

		Placebo	Daprodustat			
			4 mg	6 mg	8 mg	10 mg
Total Chol (mmol/L)	Baseline 95% CI	3.8 (3.5, 4.2)	4.0 (3.7, 4.5)	3.9 (3.6, 4.4)	3.7 (3.3, 4.2)	3.9 (3.6, 4.2)
	Week 4 CFB 95% CI	5.3 (-0.6, 11.6)	-7.4 (-12.2, -2.3)	-10.8 (-15.3, -6.0)	-9.0 (-14.9, -2.7)	-14.6 (-19.8, -9.0)
LDL-C (mmol/L)	Baseline 95% CI	2.0 (1.7, 2.3)	2.2 (1.9, 2.5)	2.1 (1.8, 2.4)	1.9 (1.6, 2.3)	2.1 (1.8, 2.4)
	Week 4 CFB 95% CI	4.8 (-10.4, 22.5)	-11.1 (-17.2, -4.7)	-10.8 (-17.2, -4.0)	-12.5 (-18.8, -5.7)	-17.3 (-24.3, -9.6)

Akizawa, Nangaku et al. Am J Nephrol 2017

Effects of erythropoietin on cycling performance of well trained cyclists: a double-blind, randomised, placebo-controlled trial

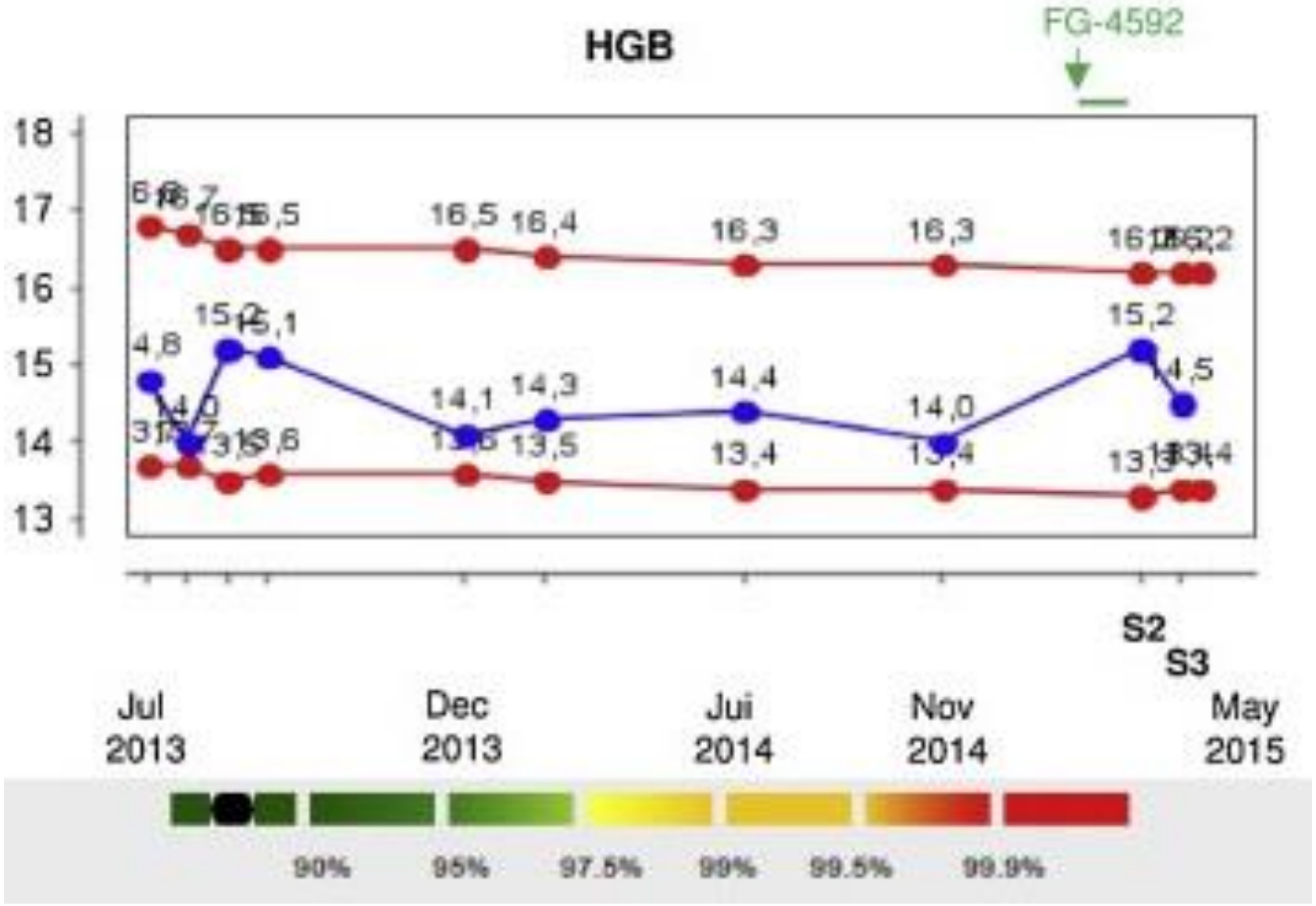
Jules A A C Heuberger, Joris I Rotmans, Pim Gal, Frederik E Stuurman, Juliëtte van 't Westende, Titiaan E Post, Johannes M A Daniels, Matthijs Moerland, Peter L J van Veldhoven, Marieke L de Kam, Herman Ram, Olivier de Hon, Jelle J Posthuma, Jacobus Burggraaf, Adam F Cohen



EPO enhanced performance in a maximal exercise test leading to exhaustion, but did not improve submaximal exercise test or road race performance.

Lancet Haematol 2017

first case of doping with PHD inhibitor, FG-4592



Buisson et al. J Pharm Biomed Anal 2016

Appropriate target Hb of ESA, iron supplementation, and PHD inhibitor as a novel treatment modality