Renal anemia: theory and evidence

Masaomi Nangaku
Division of Nephrology and Endocrinology the University of Tokyo Graduate School of Medicine, Japan

COI disclosure

presenter : Masaomi Nangaku

I have the following relationships to disclose.

Potential Financial Conflicts of Interest

(1) Employment: No

(2) Stock ownership or options: No

(3) Patent royalties/licensing fees: No

(4) Research funding: Kyowa-Hakko-Kirin, Astallas, Chugai, Takeda, Tanabe-Mitsubishi, Dainippon-Sumitomo, Boehringer, Novartis, Daiichi-Sankyo, Kowa, MSD, Torii, Kureha

(5) Honoraria: Kyowa-Hakko-Kirin, Astallas, Chugai, Takeda, Tanabe-Mitsubishi, Dainippon-Sumitomo, Boehringer, Novartis, Daiichi-Sankyo, Kowa, MSD, Pfiser, Astra Zeneca, Bayer, Ono, Shionogi, Eisai, Otsuka, Mochida, Alexion, Sanofi

(6) Manuscript fees: Kyowa-Hakko-Kirin, Chugai, Novartis

(7) Advisory board: Kyowa-Hakko-Kirin, Astallas, Chugai, JT, GSK, Takeda, Tanabe-Mitsubishi

Wolfgang Amadeus Mozart

1756 born

1784~ hypertension, nasal bleeding, headache

1791~ depression, personality change, anemia, the taste of death on their tongues

1791.5.12 Death of uremia at the age of 35

EDITORIAL REVIEW

Did Mozart Die of Kidney Disease? A Review From the Bicentennial of His Death[1]

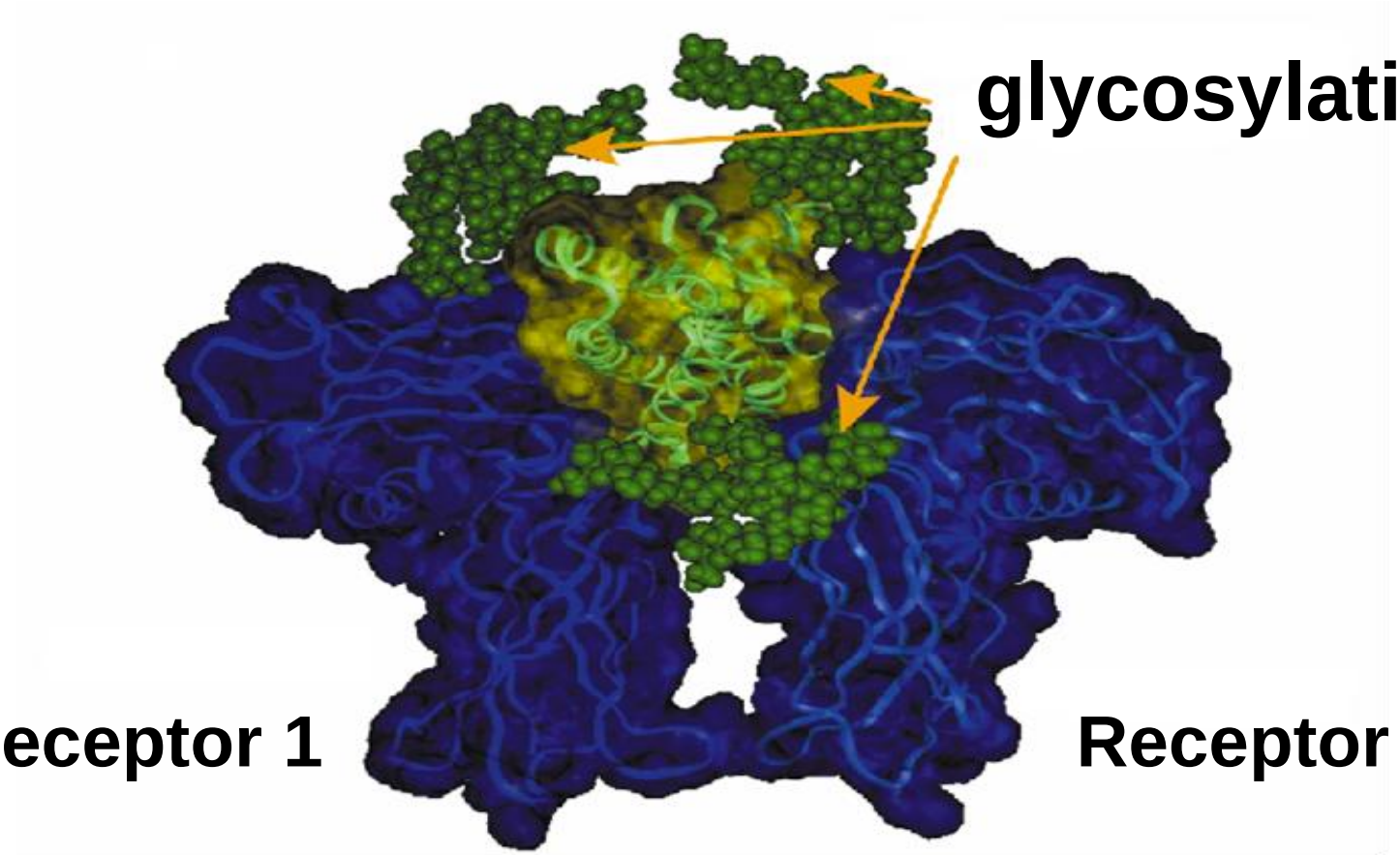
Edward N. Guillery[2]

E.N. Guillery, Division of Pediatric Nephrology, Department of Pediatrics, University of Iowa Hospitals and Clinics, Iowa City, IA.

(J. Am. Soc. Nephrol. 1992; 2:1671–1676)

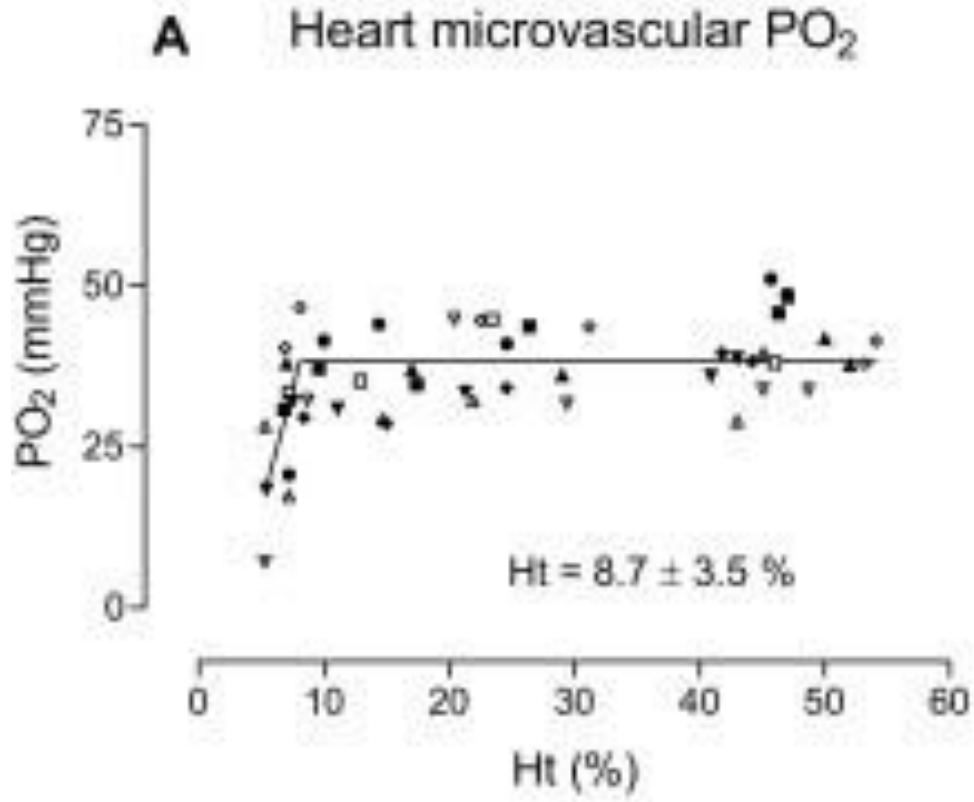
and wrote that Mozart required a "night jacket which he could put on frontways, since on account of his swollen condition he was unable to turn in bed" (1). Mozart said to her "Why, I have already the taste of death on my tongue." Cold poultices were placed on Mozart's "burning head," which, it seemed to Haibel, caused him to become unconscious, in which state

erythropoietin



Heart, kidney, and intestine have different tolerances for anemia

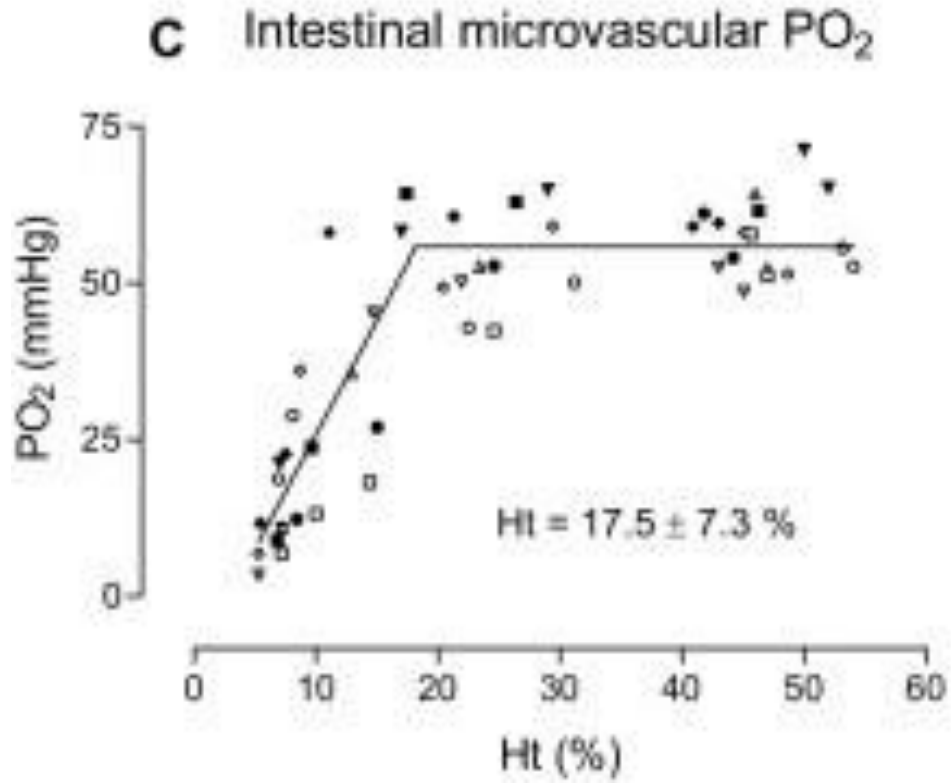
cardiac μPO_2 (40 ± 6 mm Hg at baseline) decreased only in the ultimate stage of the experiment at Ht of 8.7 ± 3.5%



van Bommel et al. Transl Res 2008

Heart, kidney, and intestine have different tolerances for anemia

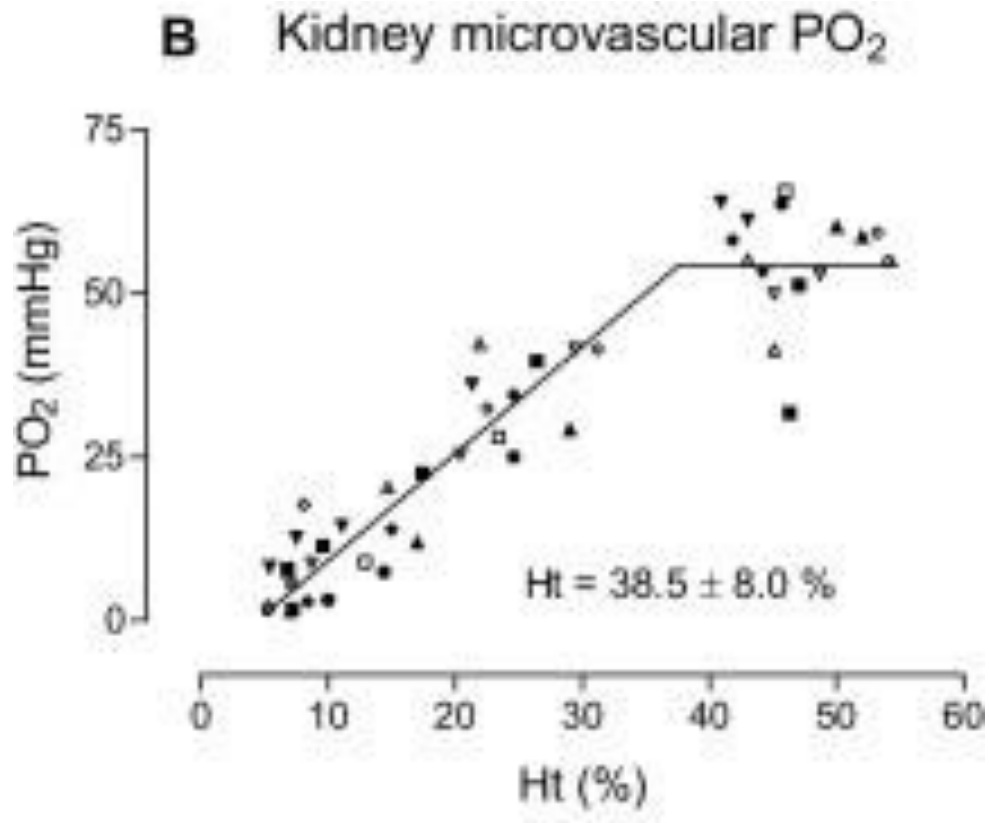
intestinal μPO_2 (59 ± 6 mm Hg at baseline) did not start to decrease until Ht reached 17.4 ± 7.1%



van Bommel et al. Transl Res 2008

Heart, kidney, and intestine have different tolerances for anemia

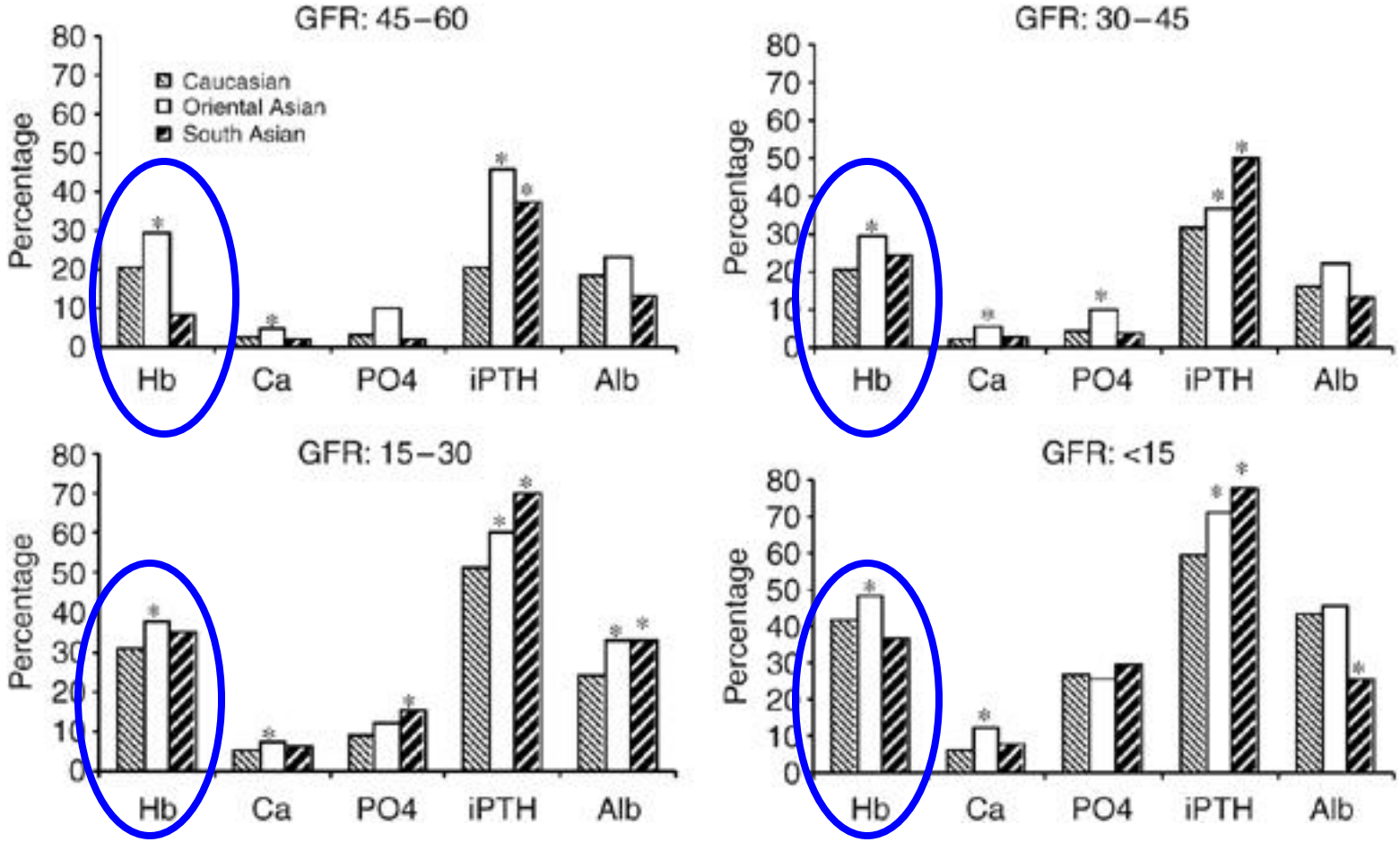
renal μPO_2 (56 ± 10 mm Hg at baseline) started to decrease at a Ht of 38.5 ± 8.6%



van Bommel et al. Transl Res 2008

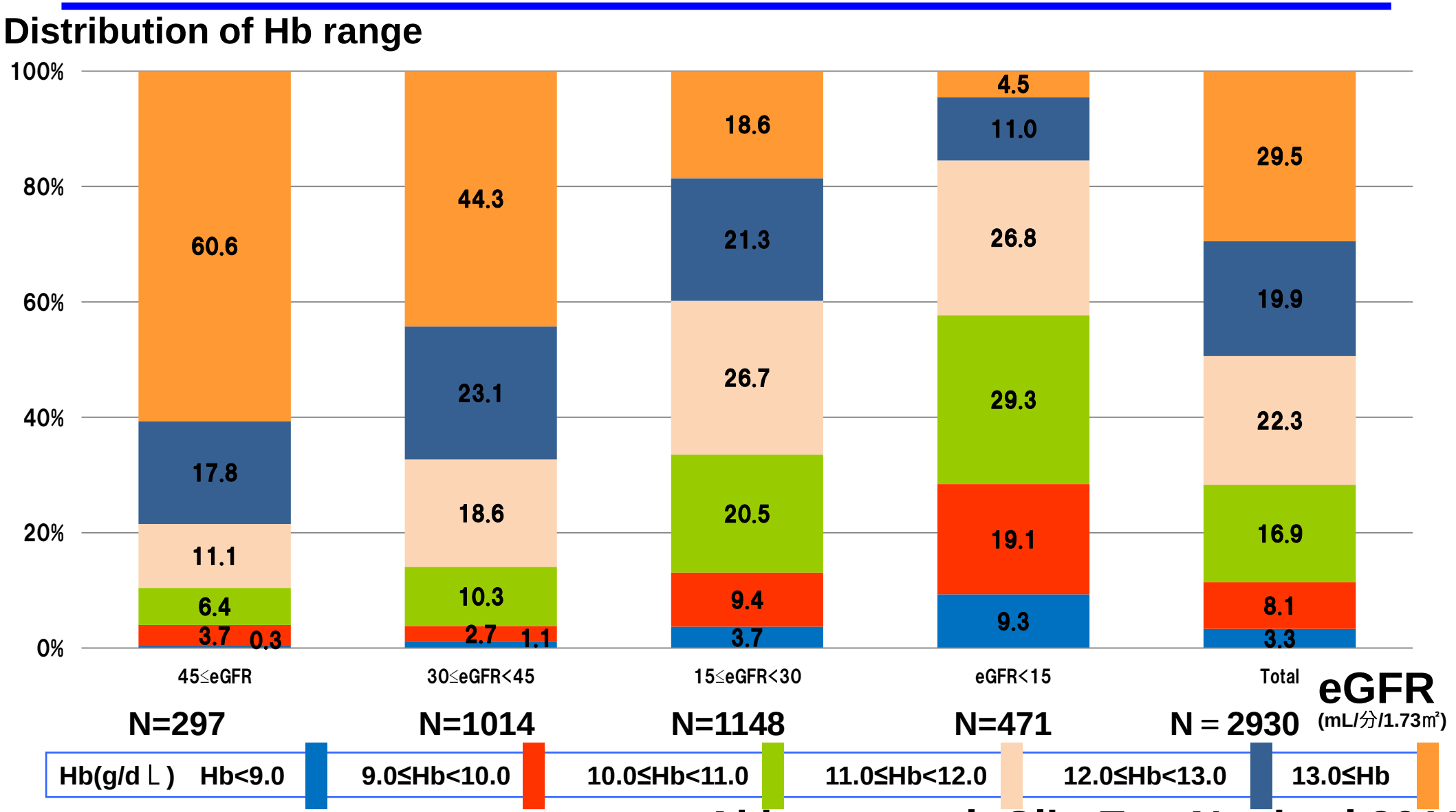
Oriental Asians tend to develop renal anemia compared with other races

Observational cross-sectional study (n=5,322)



Barbour et al. Kidney Int 2008

Distribution of Hb range based on eGFR CKD-JAC



Akizawa et al. Clin Exp Nephrol 2011

Case 63-year-old male

【History】

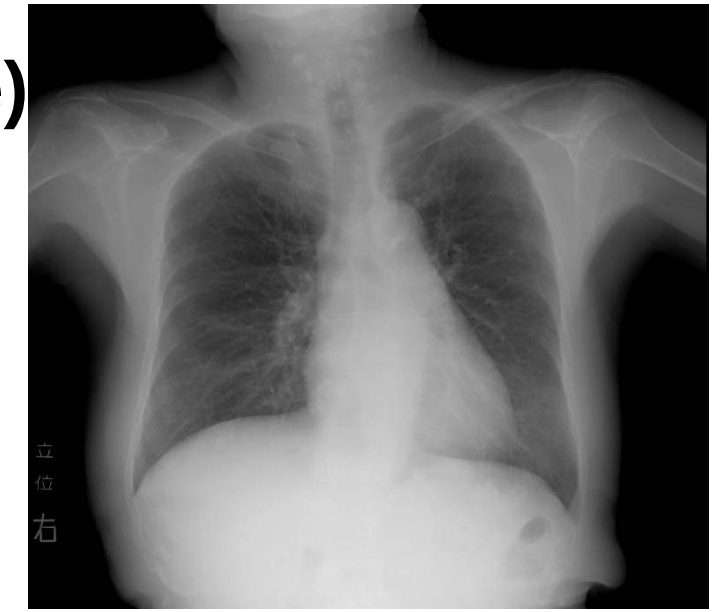
1993 Diagnosed as diabetes mellitus

1999 Started insulin treatment

The control of HbA1c was around 7-8%, and her kidney function deteriorated.

2007 Admission on foot for the evaluation of the IHD

149cm, 42.7kg (BMI 19.2), BT 36.8℃,
BP 160/92mmHg, PR 82/min, SpO2 98%(room air)
Chest Xp: CTR 47.6%　CPAngle sharp
ECG: ST elevation at V2,V3 (no change)



Hb 8.9 (MCV 96, MCH 33, MCHC 34),
WBC 5600 (Seg 75%, Mono 8%, Lymph 14%),
Plt 200,000
BUN 40 mg/dL　Cr 3.1 mg/dL　eGFR 17.1 ml/min/1.73m^2
Na 131　K 4.2　Cl 94　cCa 9.1 mg/dL　iP 3.8 mg/dL
Fe 63 μg/dL　TIBC 165 μg/dL　ferritin 333 ng/ml

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BP 160/92mmHg, PR 82/min, SpO2 98%(room air)
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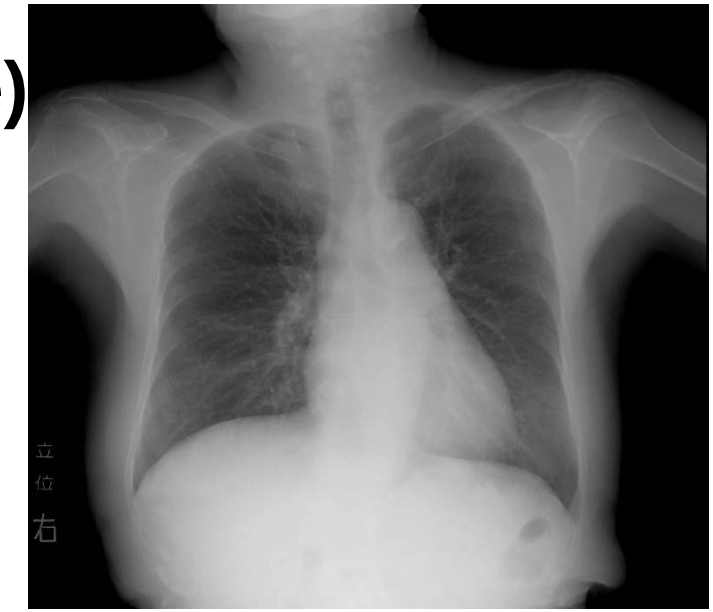

Hb 8.9 (MCV 96, MCH 33, MCHC 34),
WBC 5600 (Seg 75%, Mono 8%, Lymph 14%),
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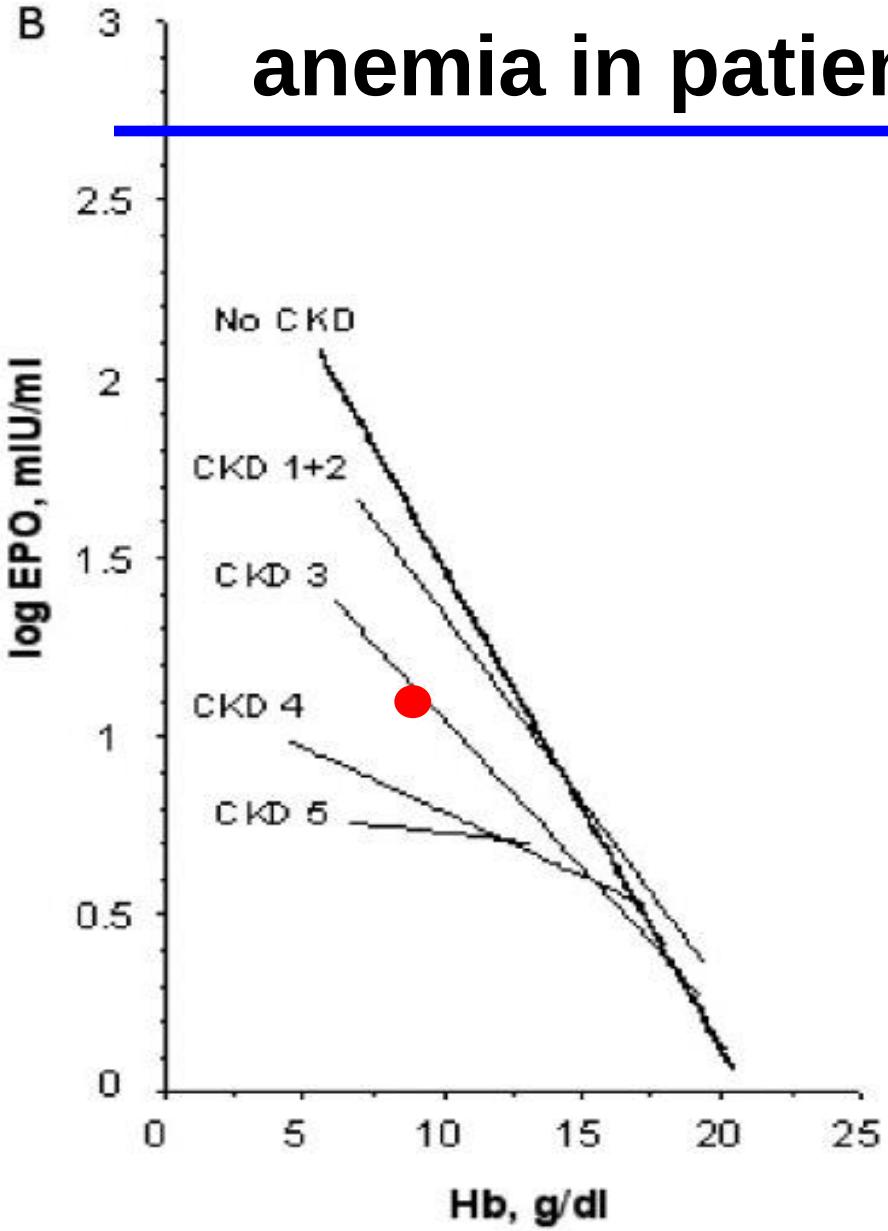
BUN 40 mg/dL　Cr 3.1 mg/dL　eGFR 17.1 ml/min/1.73m^2
Na 131　K 4.2　Cl 94　cCa 9.1 mg/dL　iP 3.8 mg/dL
Fe 63 μg/dL　TIBC 165 μg/dL　ferritin 333 ng/ml
EPO 14.1 mIU/mL (normal range: 8.0 ~ 36.0)

Serum EPO concentrations and responses to anemia in patients with or without CKD



This case

EPO 14.1 mIU/ml

Log_{10} 14.1 = 1.15

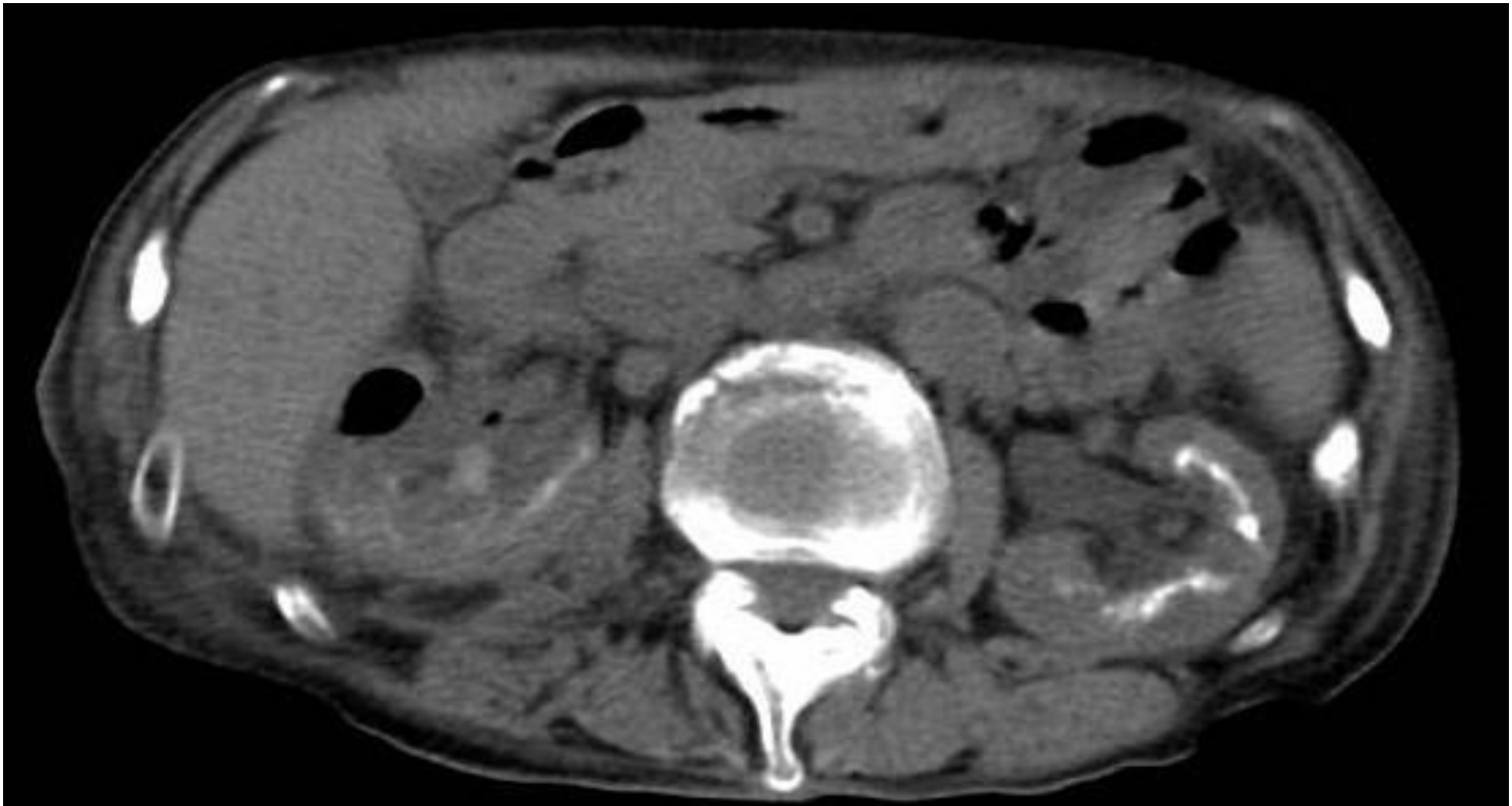
Hb 8.8g/dl

Artunc & Risler. Nephrol Dial Transplant 2007

Case 72-year-old female

CKD due to medullary sponge kidney

Diagnosis was made at the age of 50



Referred from the urology department to investigate a cause of anemia

s> dyspnea, no abdominal discomfort or abnormal bowel movements
o> BP 90/56
Hb 5.4 (MCV 90.2, MCH 29.5, MCHC 32.7),
WBC 6100 (Band 2, Seg 55, Mono 4, Lymph 39),
Plt 141000
BUN 26.9 mg/dL Cr 1.92 mg/dL eGFR 20.6 ml/min./1.73m^2
Na 140 K 4.0 Cl 112 cCa 9.0 mg/dL iP 4.8 mg/dL
CRP 1.43
Fe 121 μg/dL TIBC 151 μg/dL ferritin 344 ng/mL

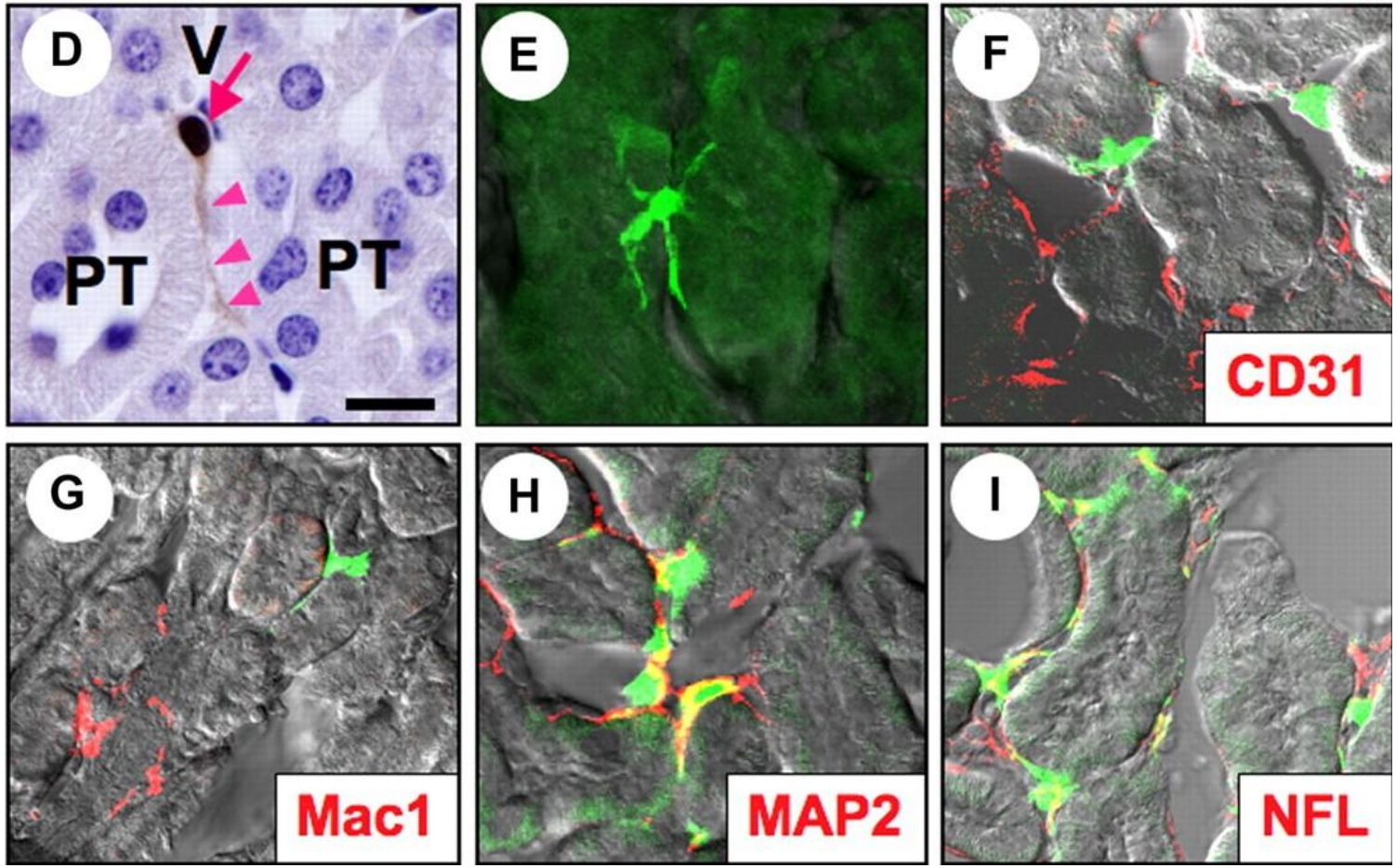
EPO 27.7 mU/ml (8.0-36.0)
vitamin B12 218 pg/ml (233-914)
folate 2.5 pg/ml (3.6-12.9)

Bone marrow aspiration
Normoplastic marrow NCC 93000/µl, MgK 60/µl micromegakaryocyte, a decrease in erythroblasts, abnormal nuclear division
=> Diagnosis: MDS RCMD (refractory cytopenia with multi-lineage dysplasia)

Mechanisms of EPO production and its disturbance

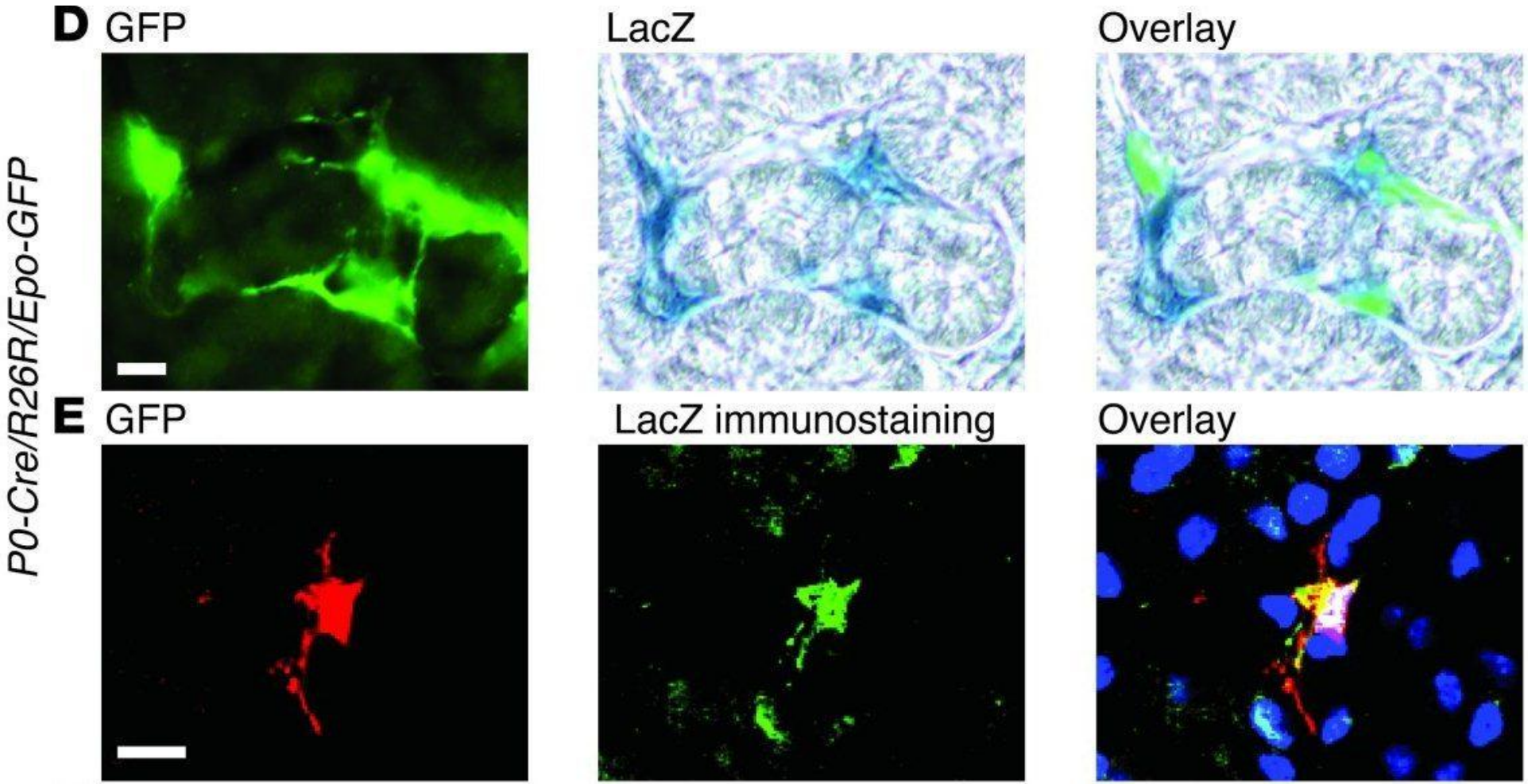
Identification of EPO producing cells

transgenic mice expressing GFP under the control of a 180-kb mouse *Epo* gene locus



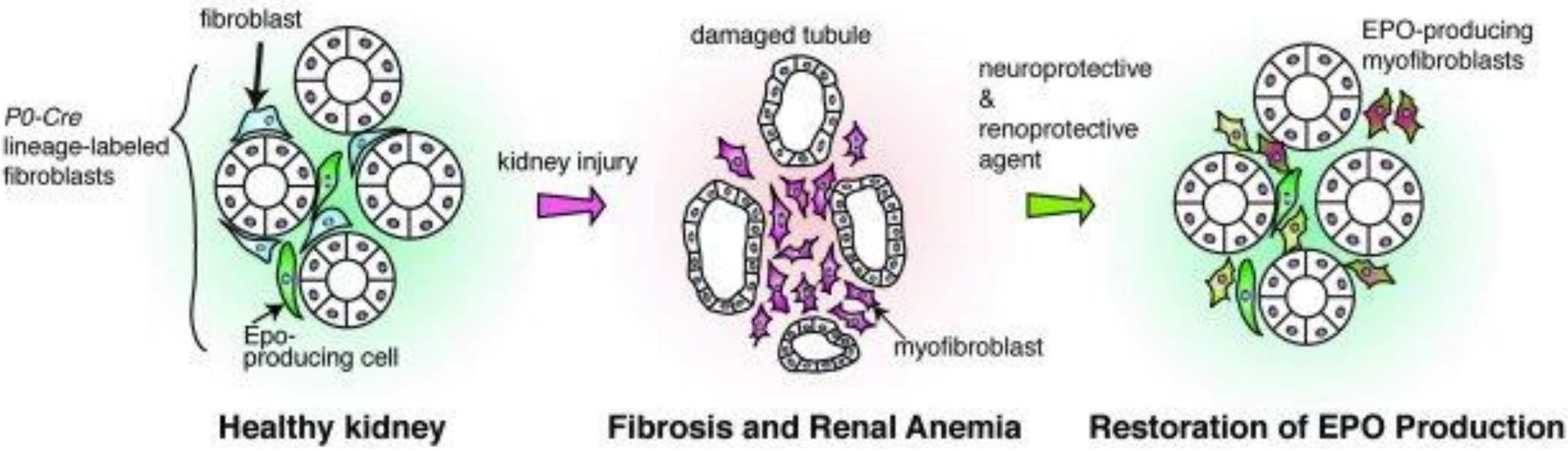
Obara et al. Blood 2008

EPO producing cells contribute to fibrosis of the kidney



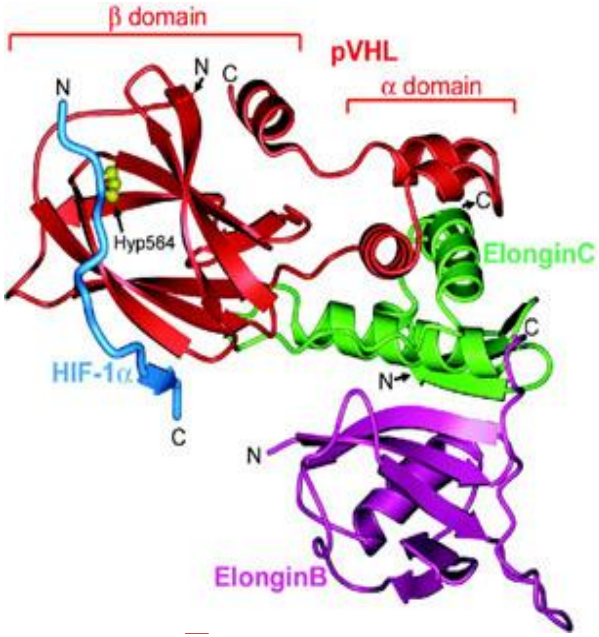
Asada et al. J Clin Invest 2011

EPO producing cells contribute to fibrosis of the kidney

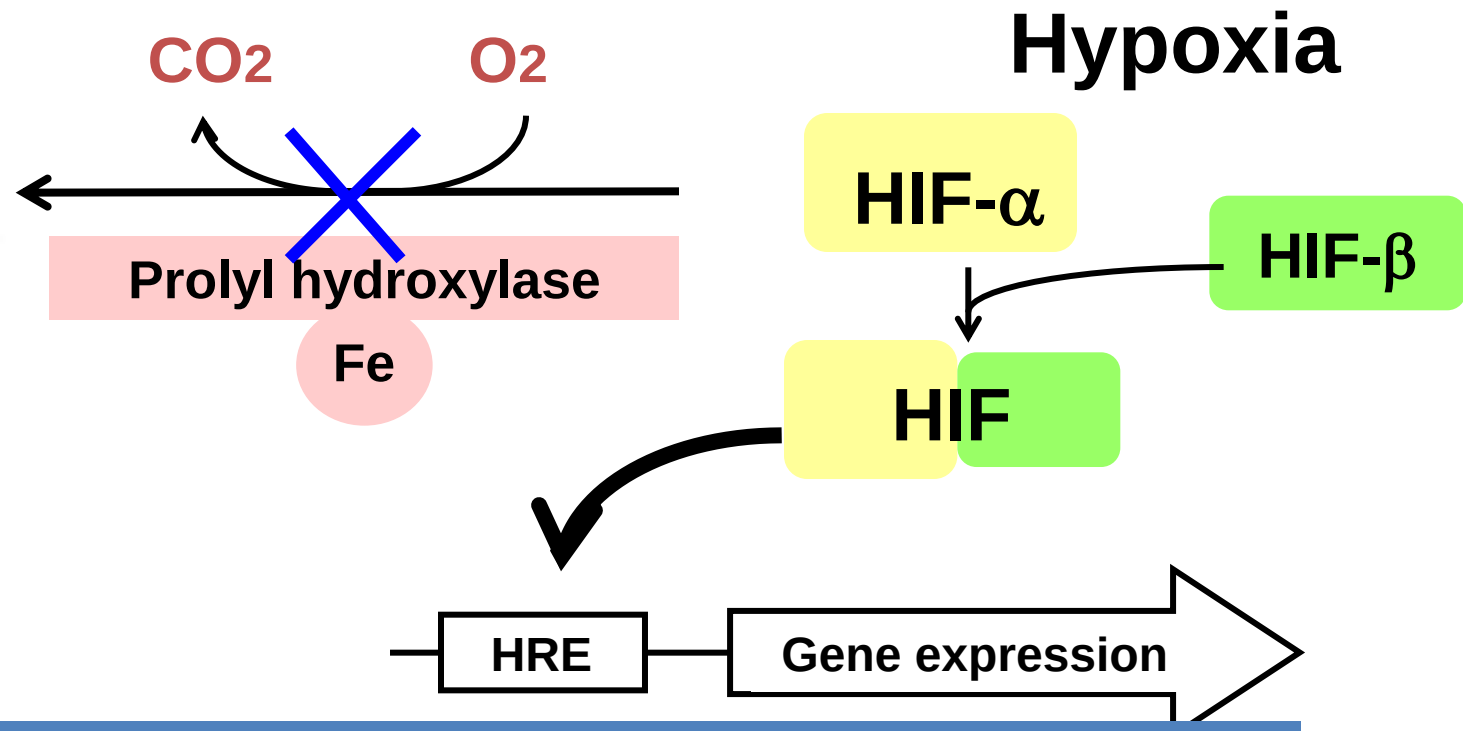


Asada et al. J Clin Invest 2011

Cellular responses against hypoxia



(Min et al. Science 2002)



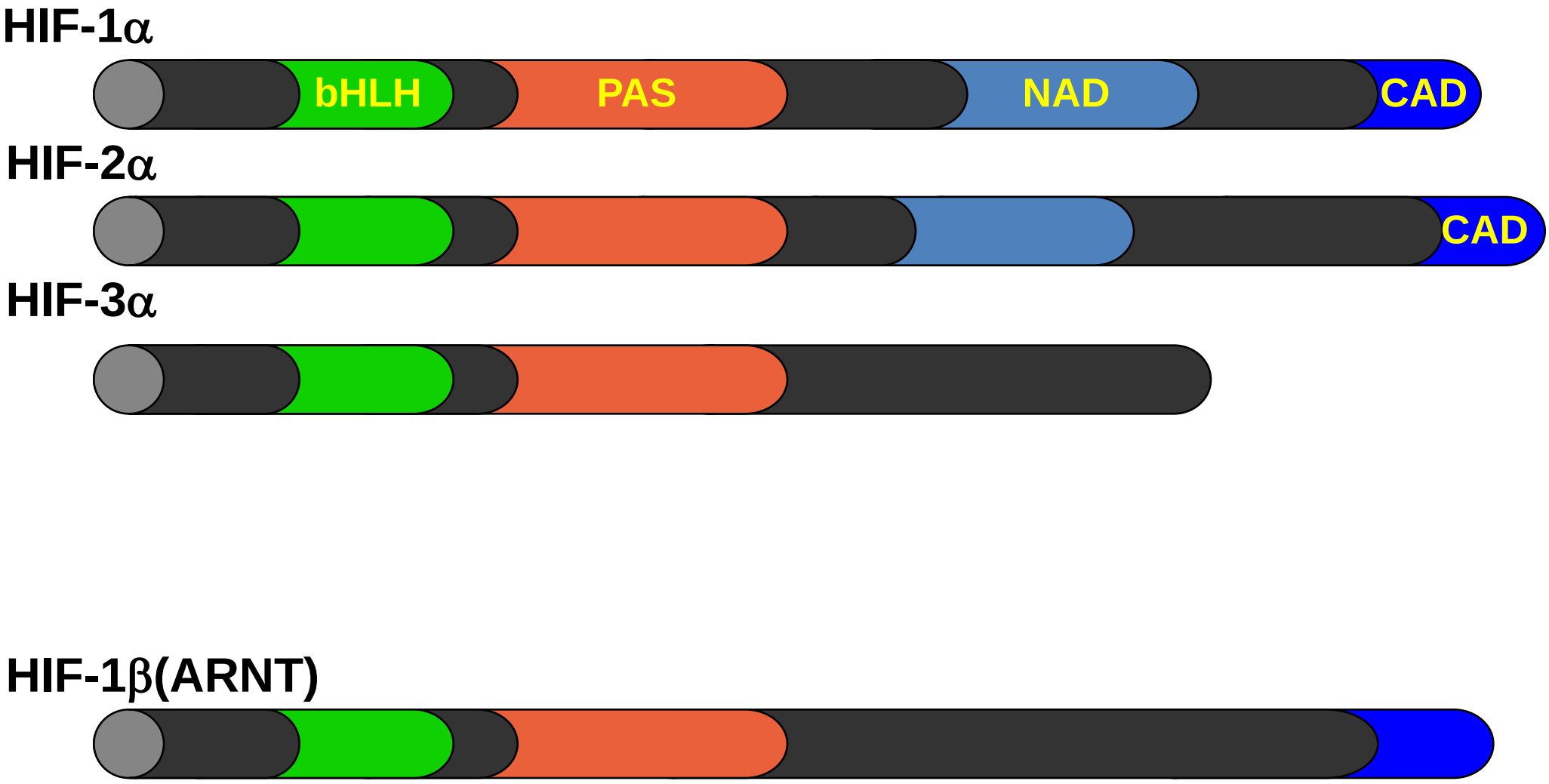
Oxygen transport (EPO, Transferrin)

Vascular regulation (VEGF, adrenomedullin, HO-1)

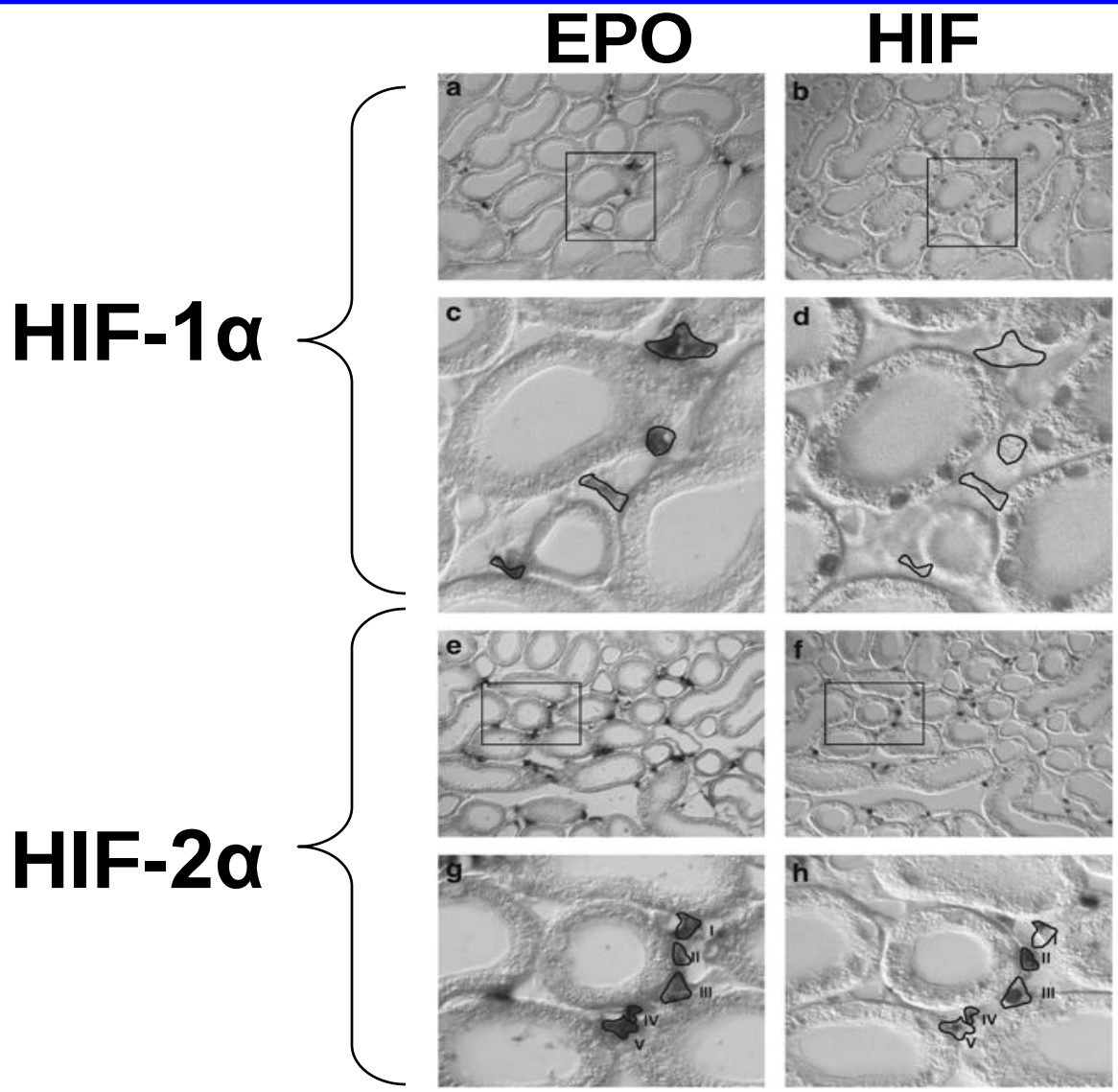
Glucose uptake and glycolysis (Glut-1, Aldolase A)

Anti-oxidative enzymes (SODs, catalase)

Mimura & Nangaku. Nature Rev Nephrol 2010

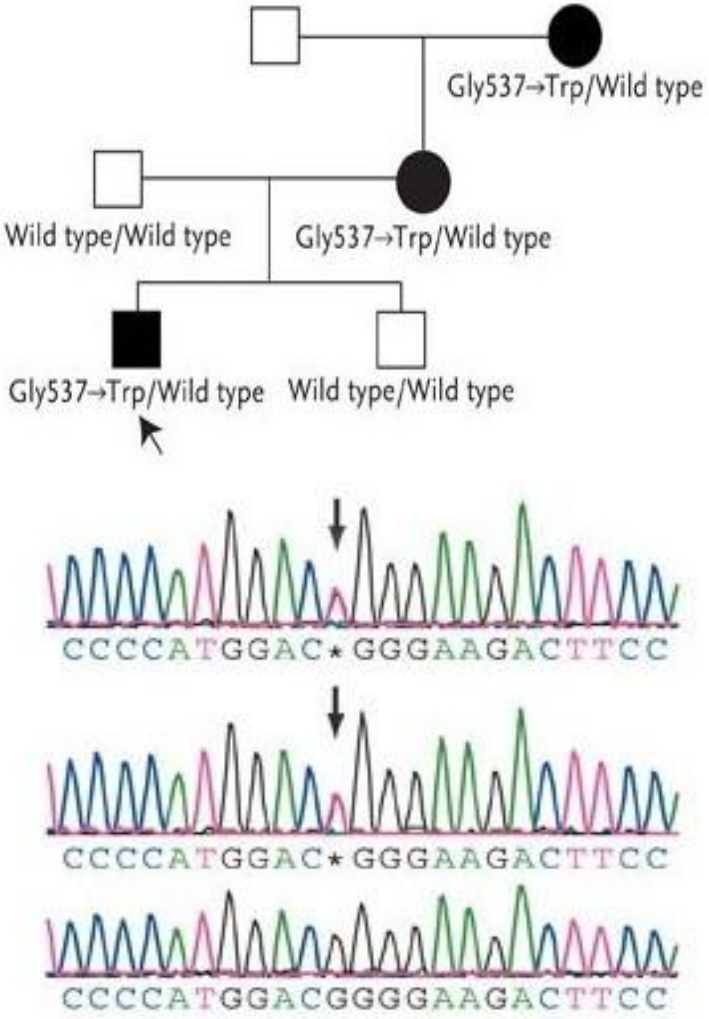

HIF-1α
bHLH
PAS
NAD
CAD
HIF-2α
CAD
HIF-3α
HIF-1β(ARNT)

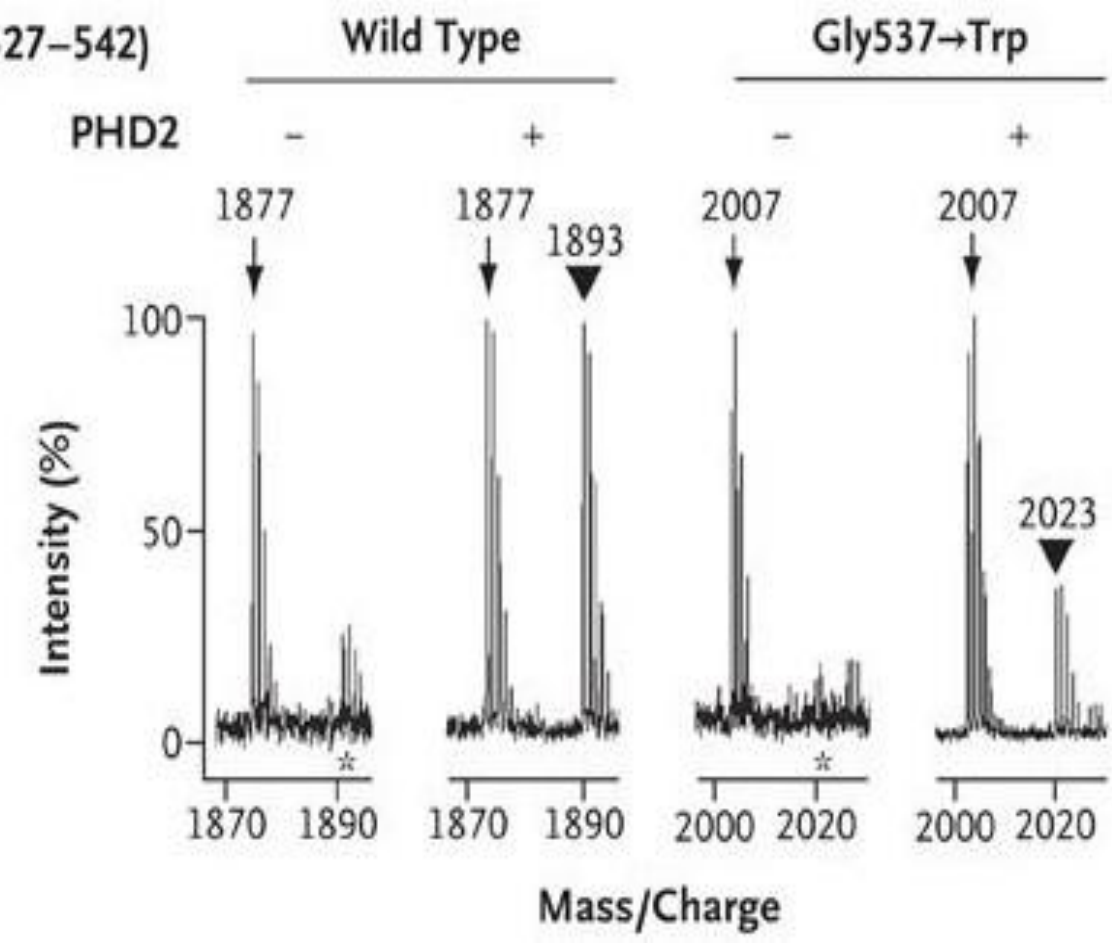
EPO mRNA colocalizes with HIF-2α in the interstitial cells, but not with HIF-1α



Paliege et al. Kidney Int 2010

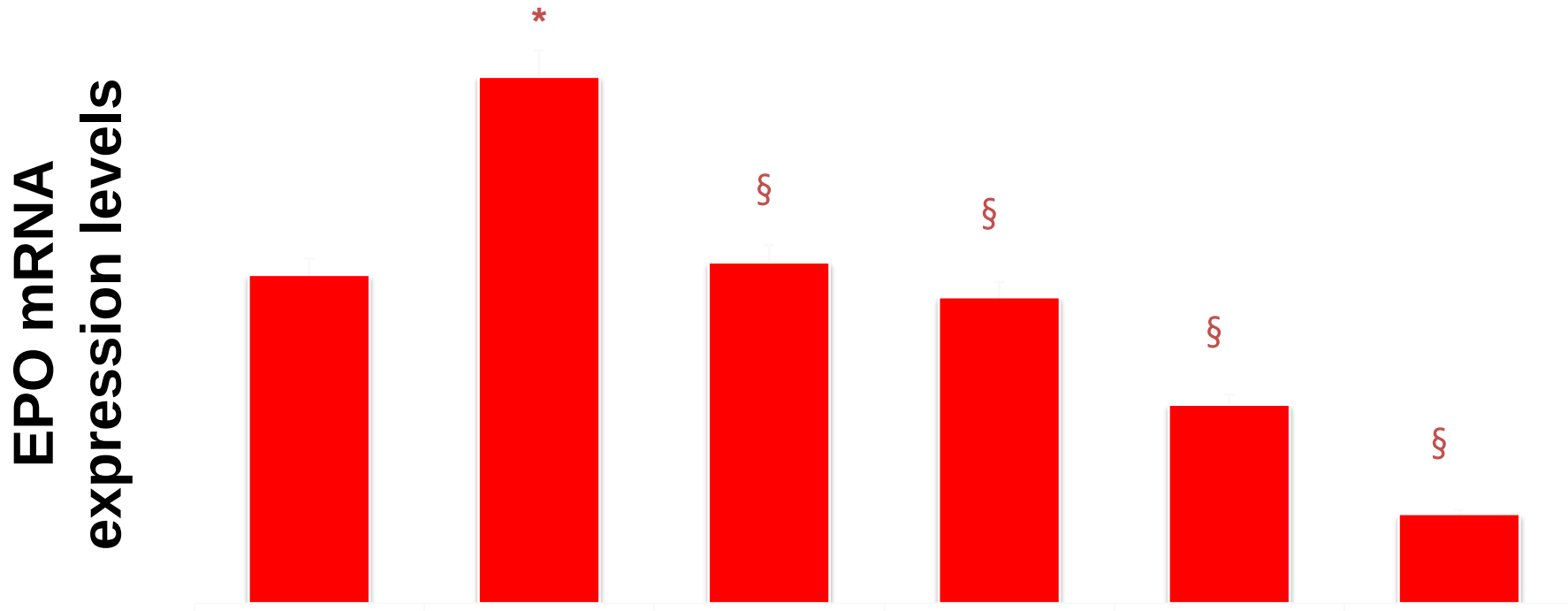
HIF-2α gain-of-function mutation is a cause of familial polycythemia





Percy et al. N Engl J Med 2008

Suppression of EPO expression by indoxyl sulfate: *in vitro*

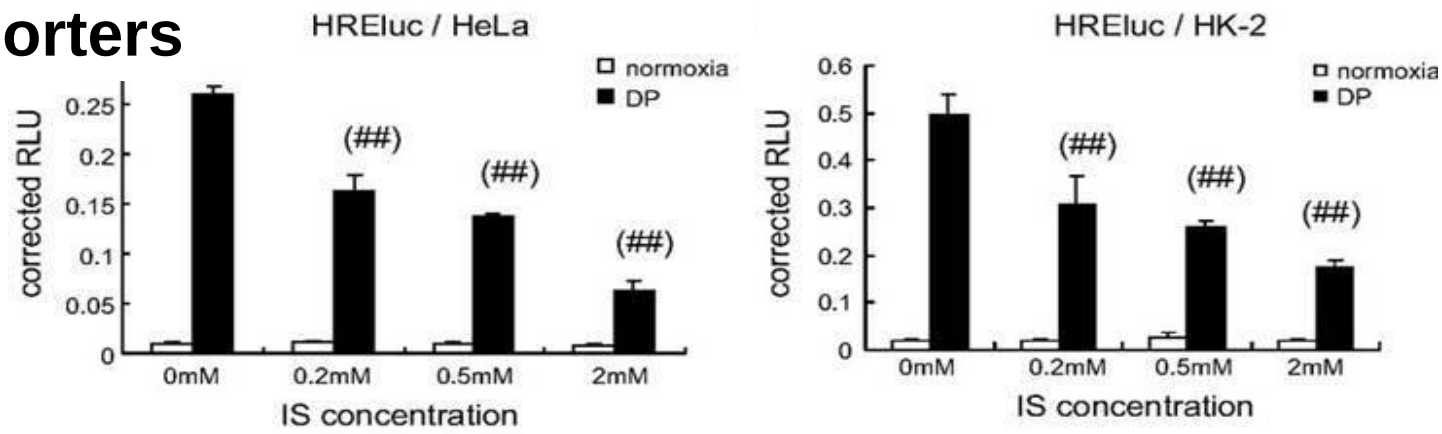


$CoCL_2$ (100μM)	-	+	+	+	+	+
Indoxyl sulfate (mM)	-	–	0.5	1.0	2.5	5.0

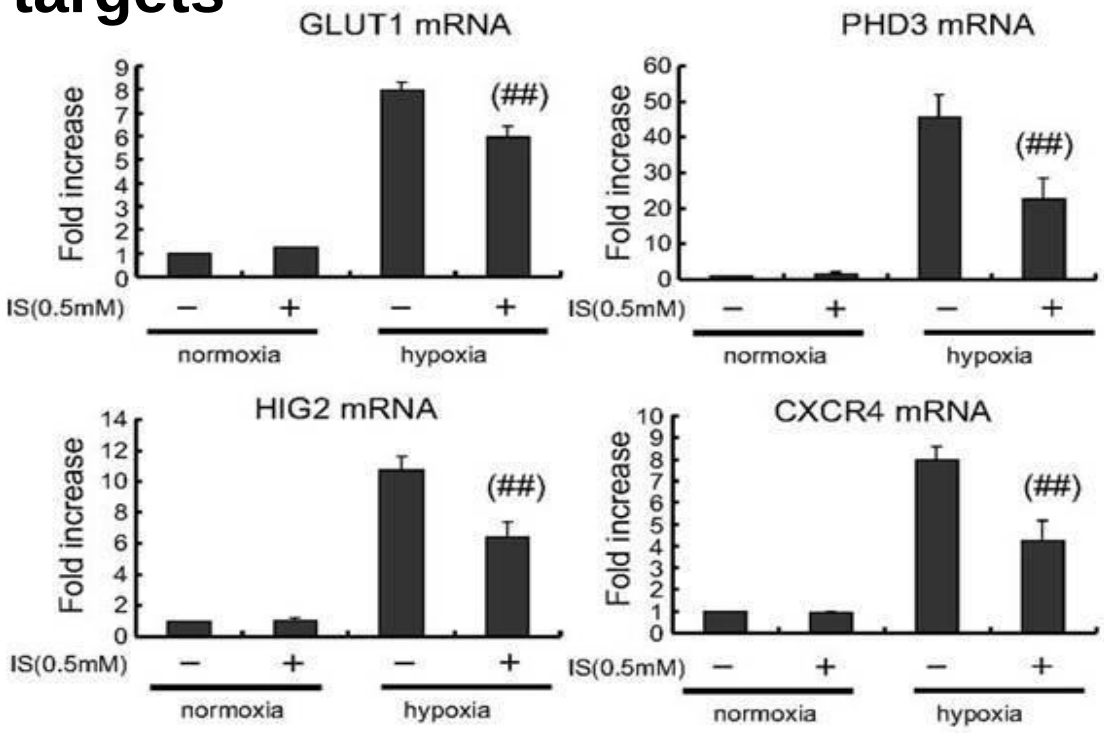
Chiang, Nangaku, Inagi et al. Lab Invest 2011

indoxyl sulfate inhibits HIF activity

reporters



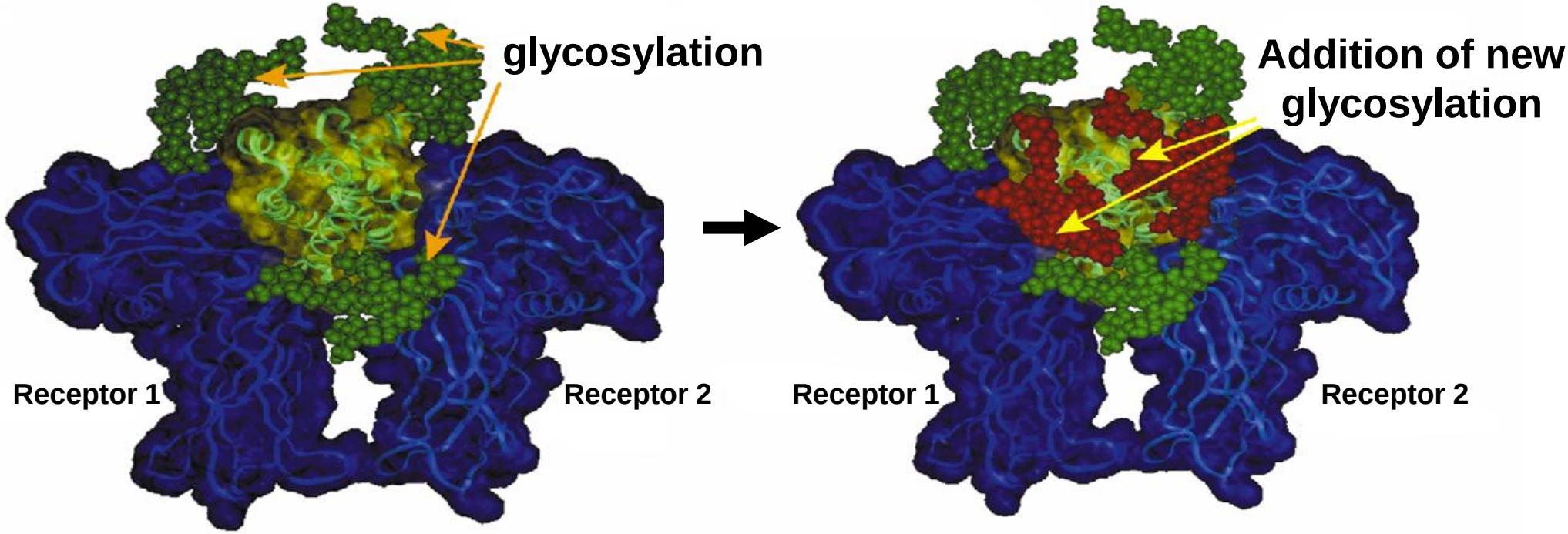
HIF targets



IS: indoxyl sulfate

Tanaka, Nangaku et al. FASEB J 2013

Long-acting EPO
darbepoetin /
Novel Erythropoiesis Stimulating Protein

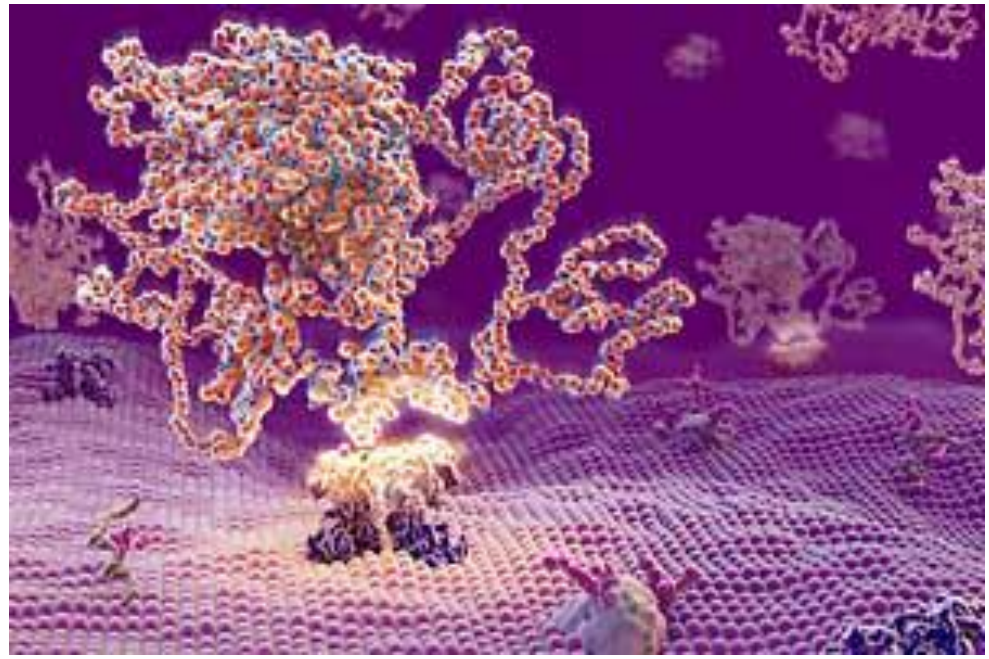


Australia, Hong Kong, Japan, Korea, Malaysia, New Zealand, Philippines, Singapore, Taiwan, Thailand

Long-acting EPO

Mircera /

Methoxy polyethylene glycol-epoetin beta



Australia, Bangladesh, Cambodia, Hong Kong, Japan, Korea, India, Indonesia, Malaysia, Myanmar, Nepal, New Zealand, Pakistan, Philippines, Singapore, Sri Lanka, Taiwan, Thailand, Vietnam

Biosimilar recombinant EPO induces the production of neutralizing antibodies

Table 1 | Patients' characteristics and issues related to the use of biosimilar r-HuEpo and laboratory results

	Anti-r-HuEpo positive	Anti-r-HuEpo negative	*P*
Numbers of patients (cases)	23	7	—
Gender, male/female (case/case)	13/10	3/4	0.526
Age, years ± s.d.	61.1 ± 21.4	52.8 ± 4.8	0.784
CKD status, cases (%)			0.647
Predialysis	8 (34.8)	2 (28.6)	
Hemodialysis	14 (60.9)	4 (57.1)	
Peritoneal dialysis	1 (4.3)	1 (14.3)	
Etiology of CKD, cases (%)			0.393
Diabetic nephropathy	5 (26.1)	3 (42.9)	
Chronic glomerulonephritis	3 (13.0)	0	
Unknown	14 (60.9)	4 (57.1)	
r-HuEpo exposure duration, months ± s.d. (range in months)	12.1 ± 7.8 (3–36)	22.3 ± 19.8 (6–60)	0.001*
r-HuEpo dose, U/kg/week ± s.d.	149 ± 82	171 ± 91	0.991
Hb before LOE, g/dl ± s.d.	10.8 ± 1.6	11.4 ± 0.7	0.458
Hemoglobin by the time of LOE, g/dl ± s.d.	5.6 ± 0.9	7.3 ± 0.7	<0.001*
Reticulocytes, cell/mm^3 ± s.d.	5978 ± 1217	13,128 ± 3,456	<0.001*
Serum ferritin, ng/ml ± s.d.	368.6 ± 83.1	370.3 ± 93.7	0.967
Transferring saturation, % ± s.d.	28.3 ± 6.6	28.8 ± 5.2	0.821
Serum folate, pg/ml ± s.d.	12.8 ± 4.5	12.5 ± 4.3	0.526

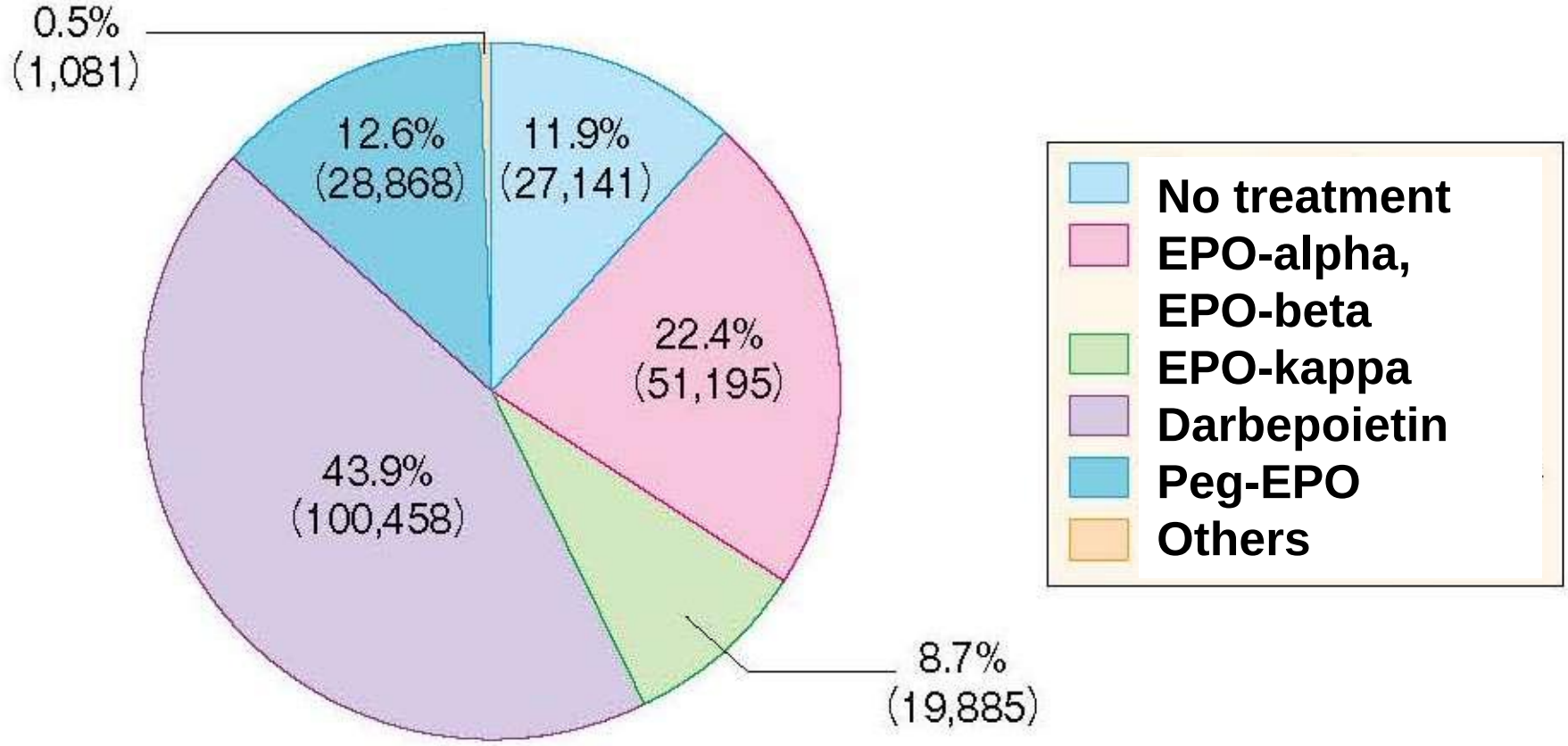
n = 30 patients with CKD treated with biosimilar Epo and who developed a sudden loss of efficacy

Praditpornsilpa et al. Kidney Int 2011

How the Japanese dialysis patients are treated

Database of JSDT

Ratios of various ESAs



Hb levels of the Japanese dialysis patients

Database of JSDT

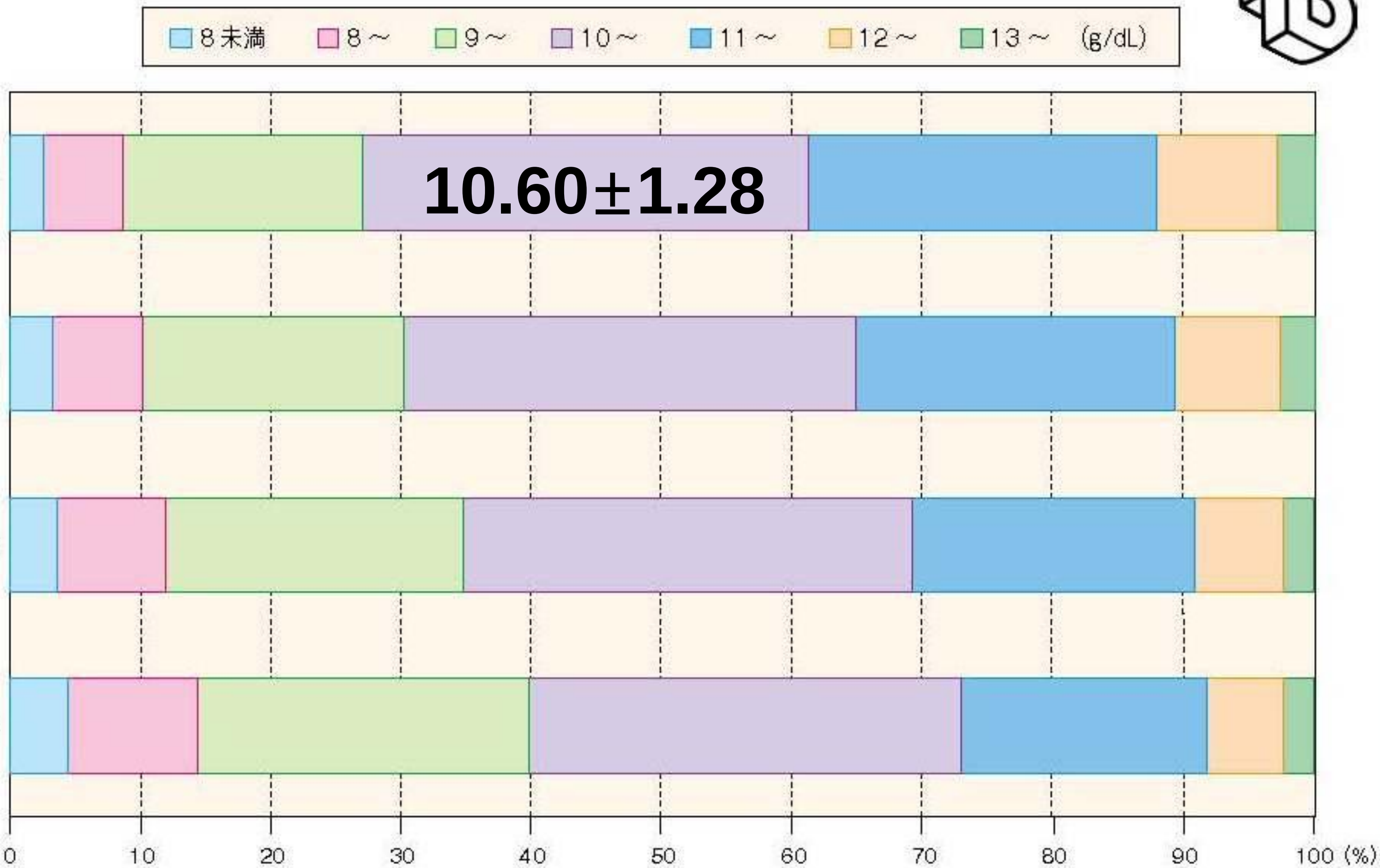
year

2012

2010

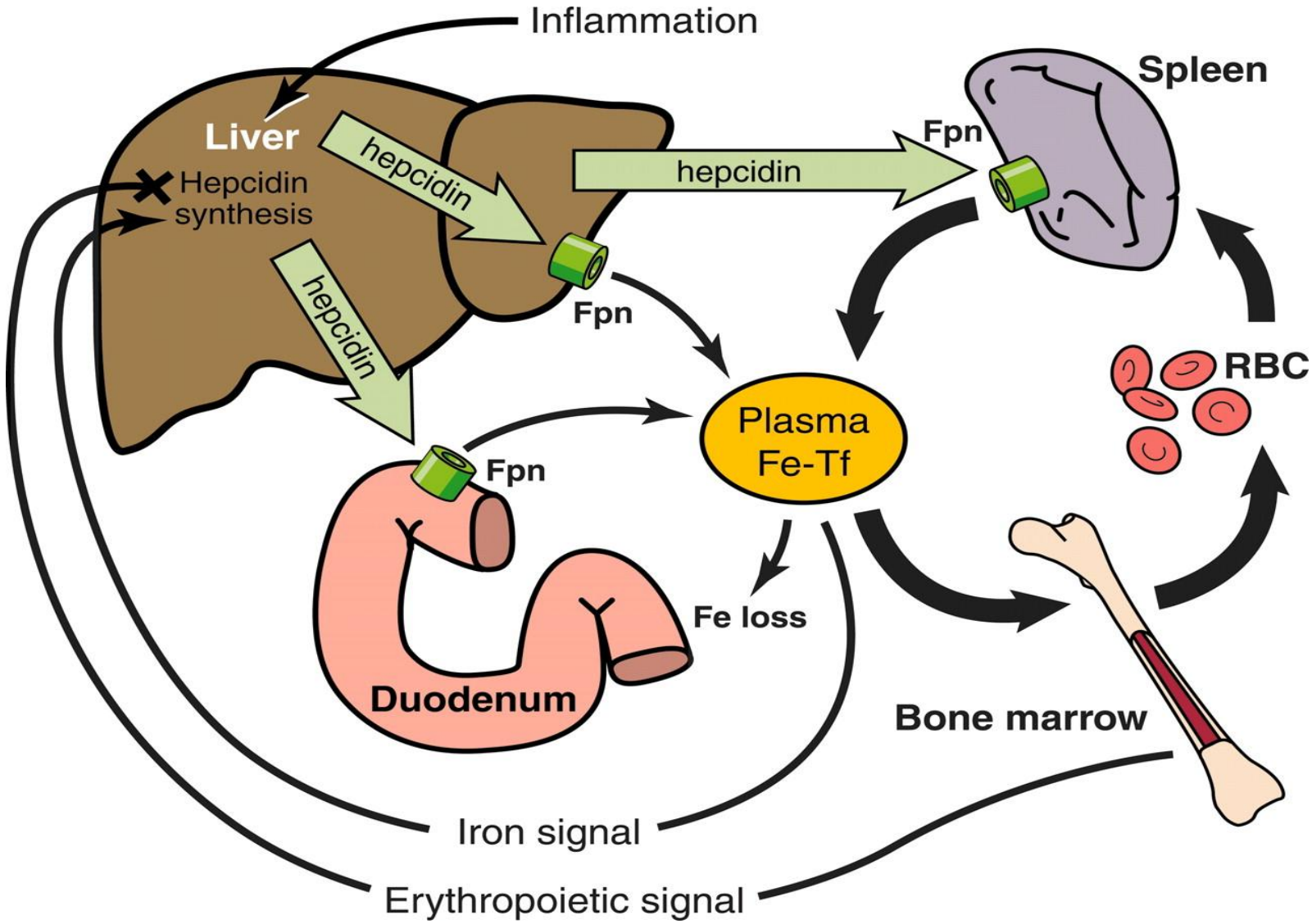
2008

2006



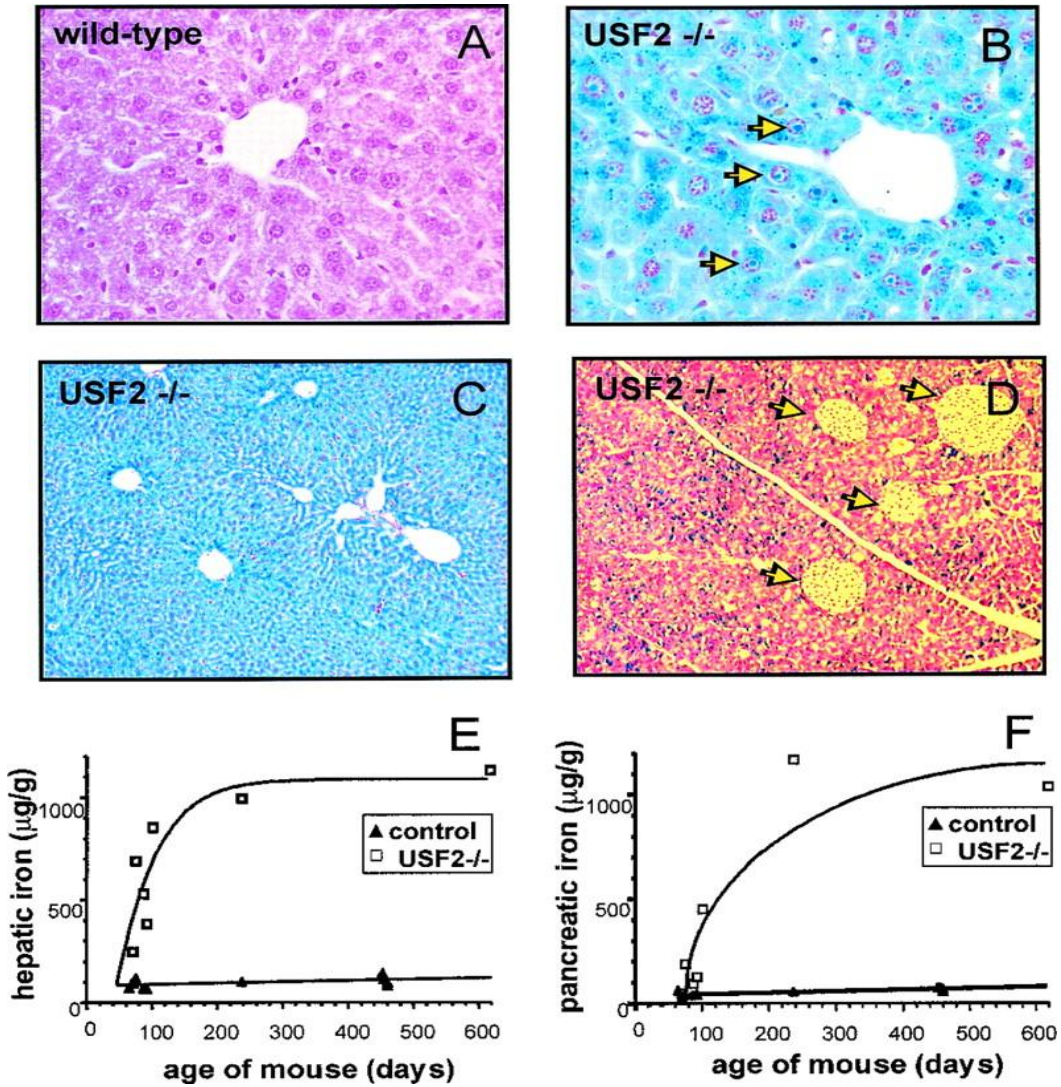

IRON

Iron homeostasis



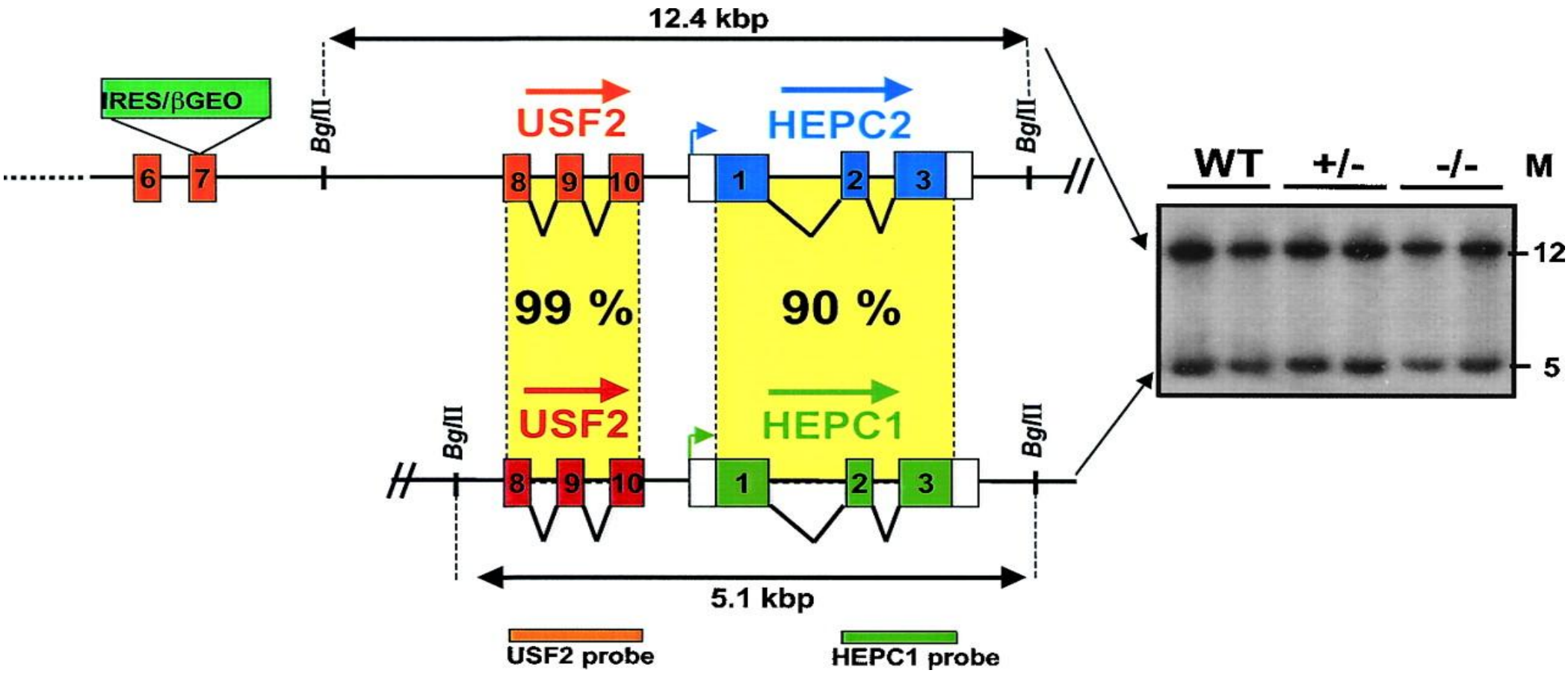
Ganz. J Am Soc Nephrol 2007

Iron deposition in USF2-KO mice



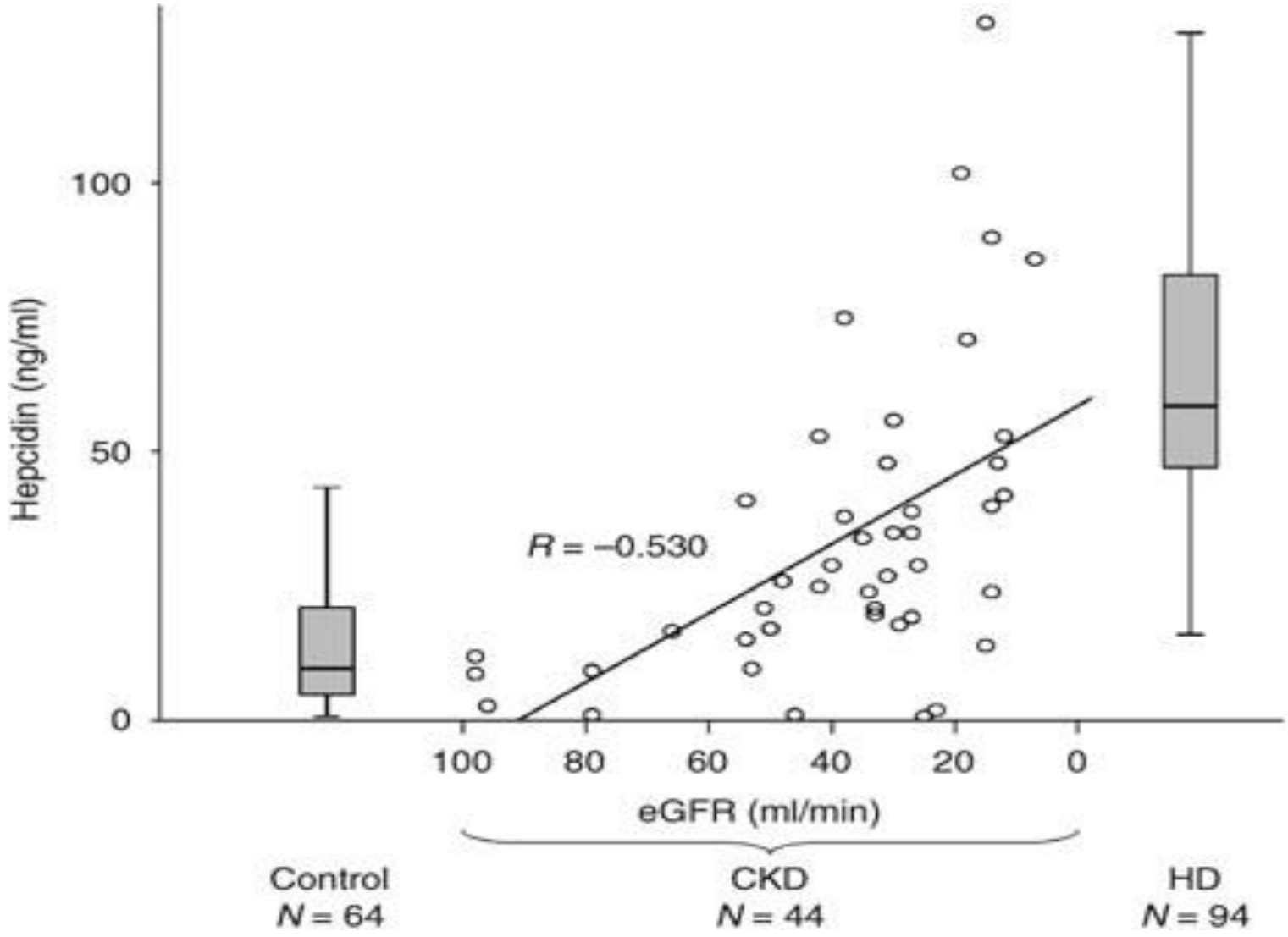
Nicolas et al. Proc Natl Acad Sci 2001

Hepcidin was also knocked out in USF2-KO mice



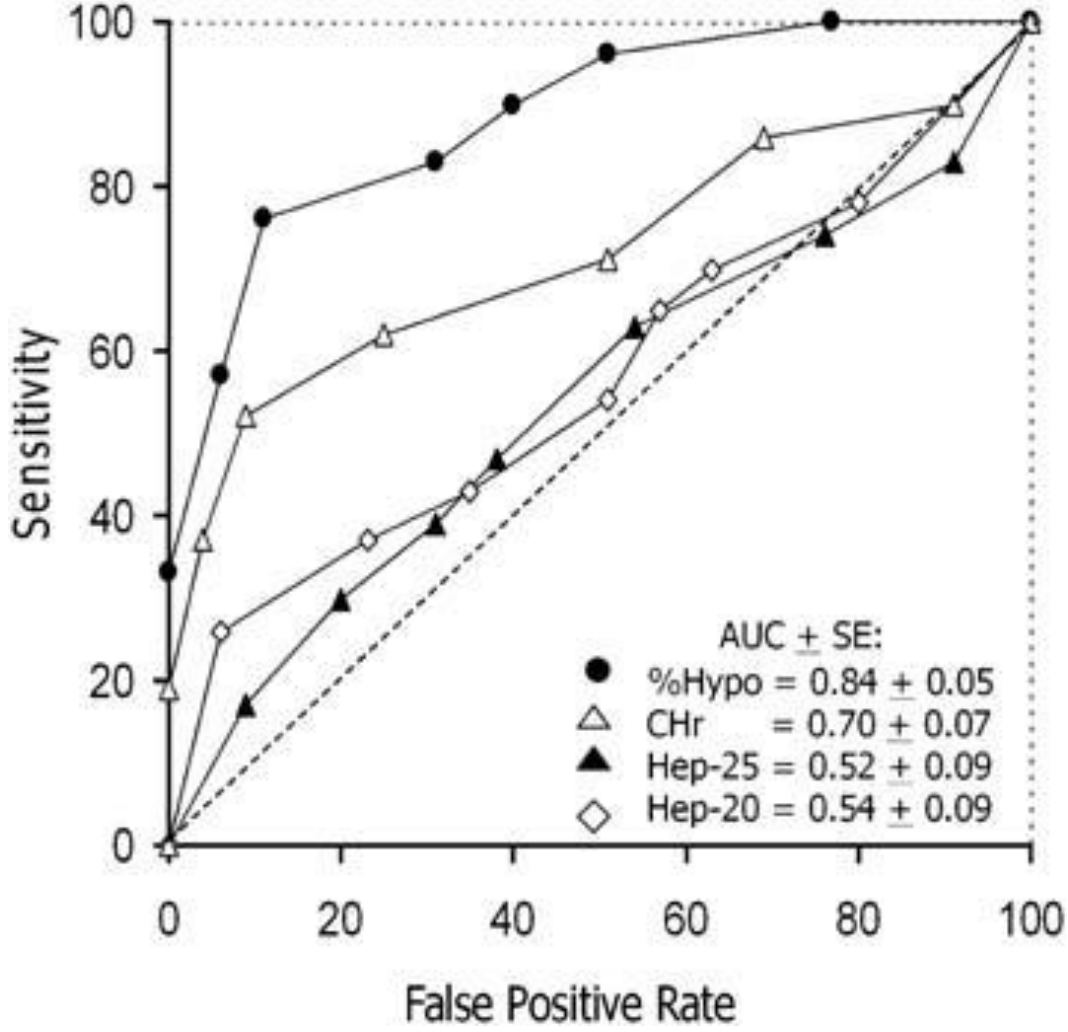
Nicolas et al. Proc Natl Acad Sci 2001

hepcidin is increased in CKD patients



Ashby et al. Kidney Int 2009

hepcidin does NOT predict iron responsiveness

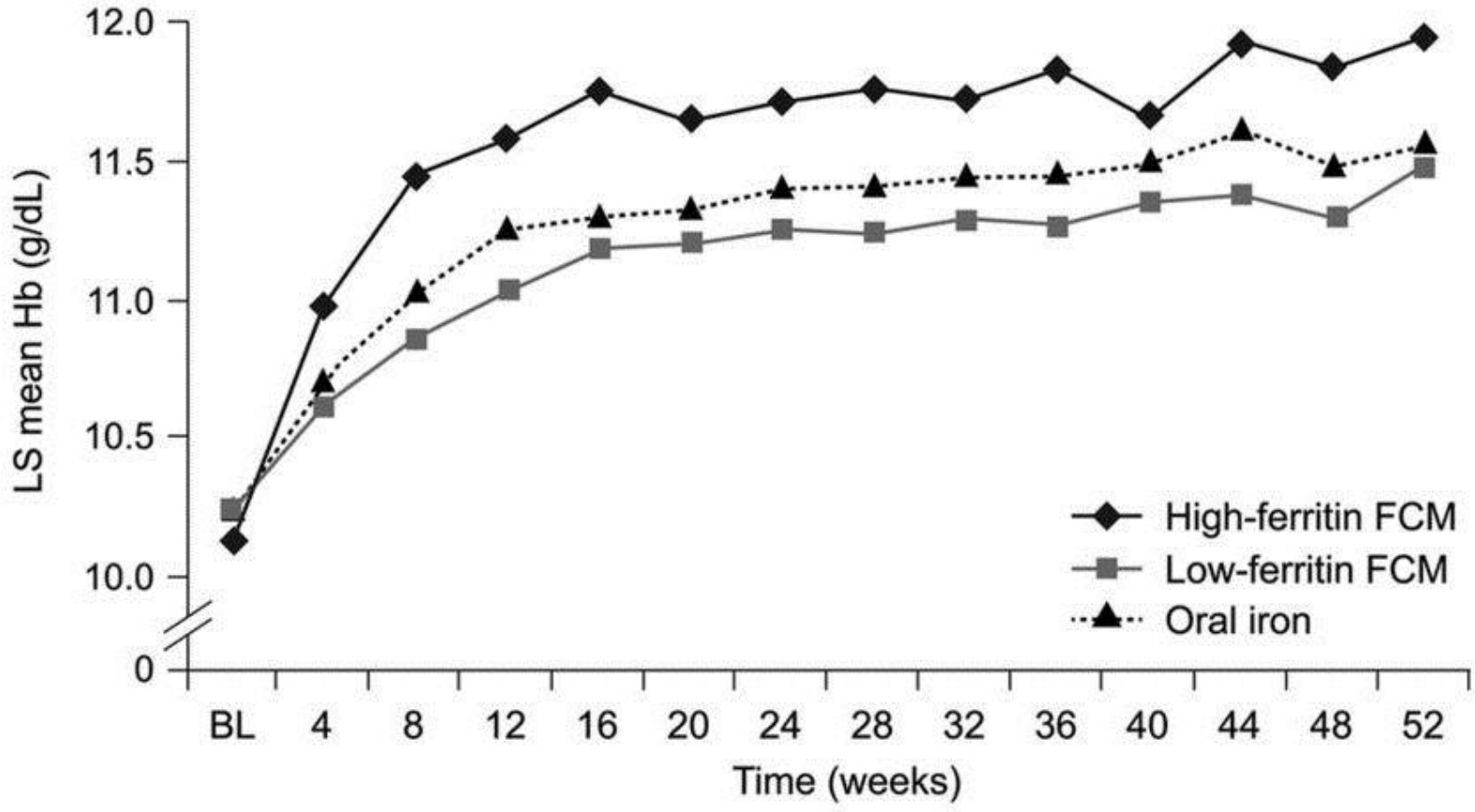


Diagnostic accuracy for iron responsiveness by ROC curve analysis

%Hypo:
% of hypochromic RBC
CHr:
reticulocyte Hb content

Tessitore et al. Nephrol Dial Transplant 2010

FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with CKD and iron deficiency anemia



Macdougall et al. Nephrol Dial Transplant 2014

NICE Anaemia Management in CKD 2011

People receiving ESA maintenance therapy should be given iron supplements to keep their:

serum ferritin levels between 200 and 500 µg/l in both HD and non-HD patients, and either

– TSAT above 20% (unless ferritin is greater than 800 µg/l) or

– percentage hypochromic red cells (%HRC) less than 6% (unless ferritin is greater than 800 µg/l).

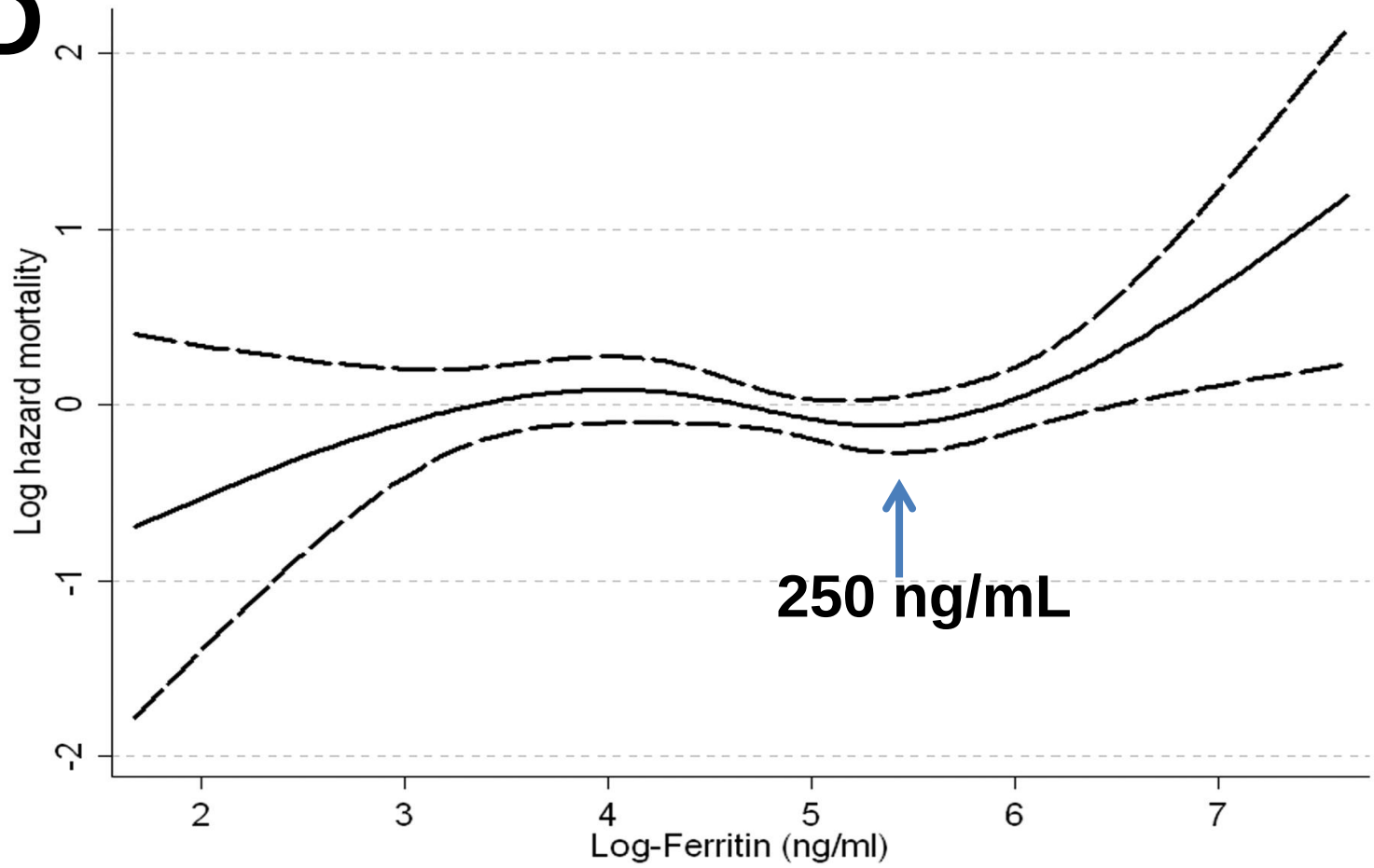
KDIGO Clinical Practice Guideline for Anemia in CKD 2012

For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of iron therapy

if an increase in Hb concentration without starting ESA treatment is desired and TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 mg/l)

Multivariable adjusted log-hazards of all-cause mortality associated with levels of natural-log-transformed serum ferritin concentration

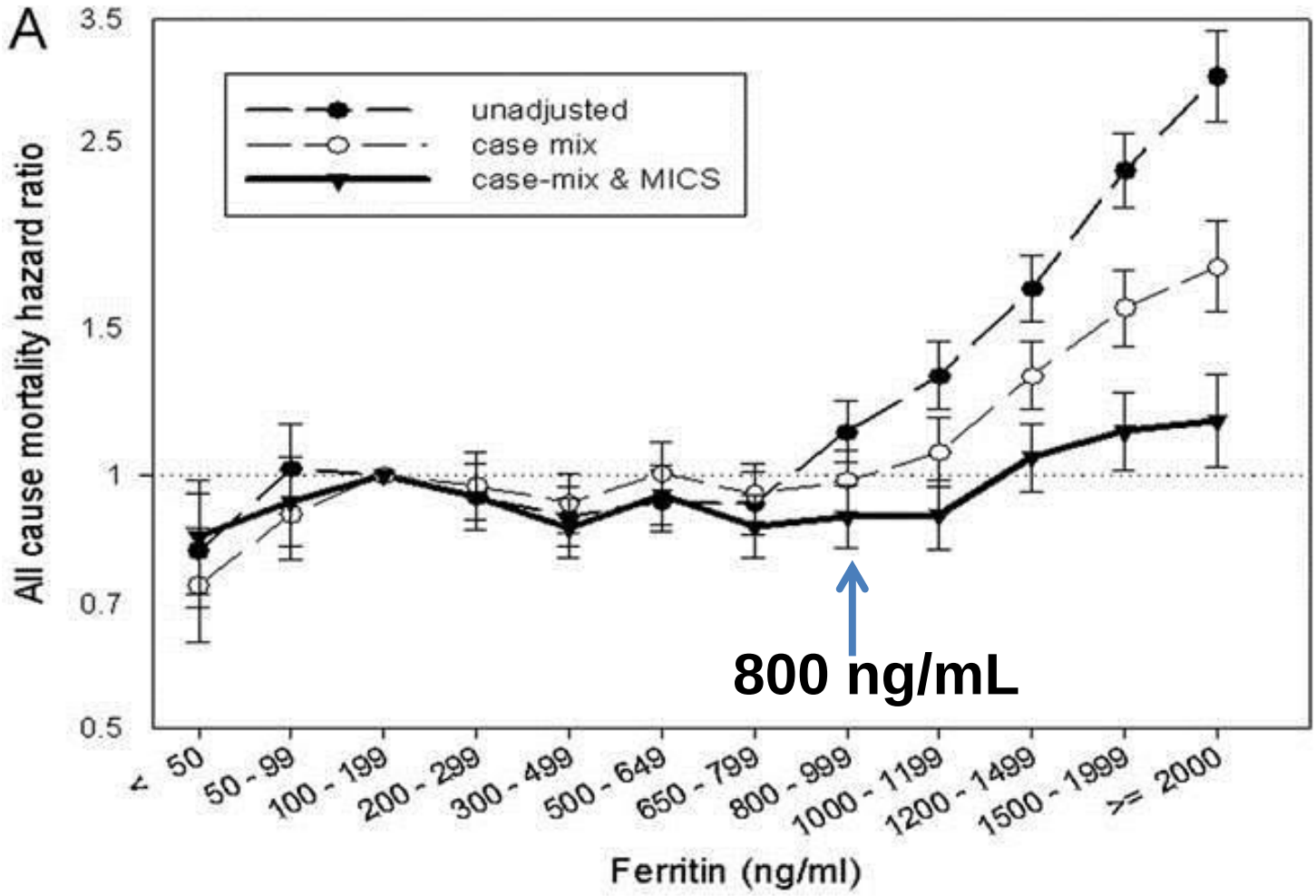
non-HD



Kovesdy et al. CJASN 2009

Association between serum ferritin and all-cause mortality

HD

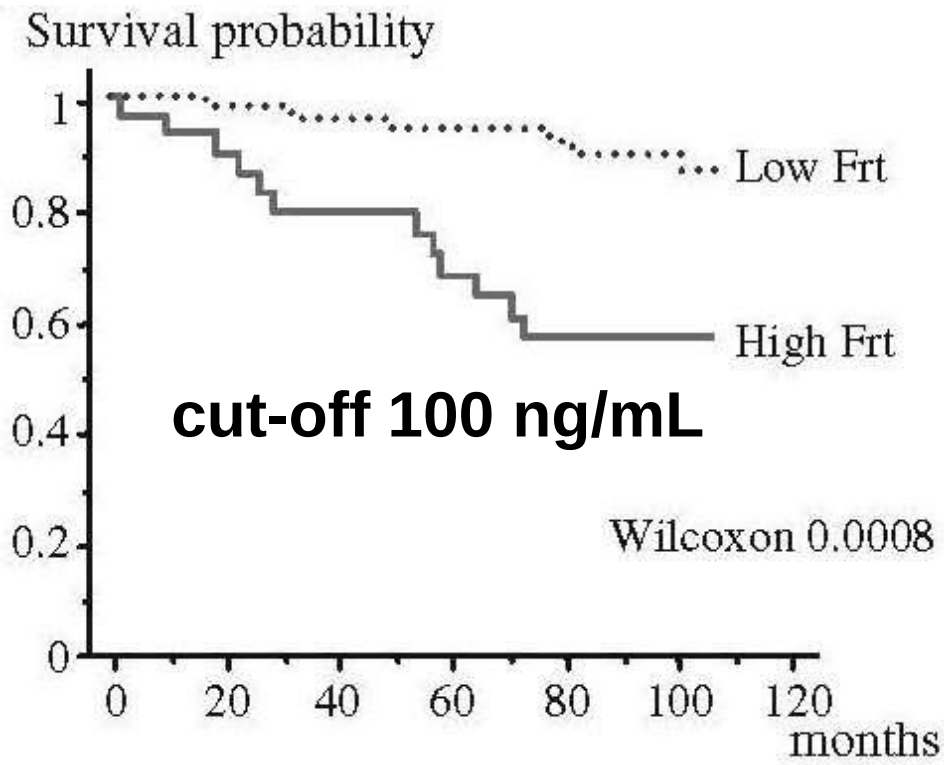


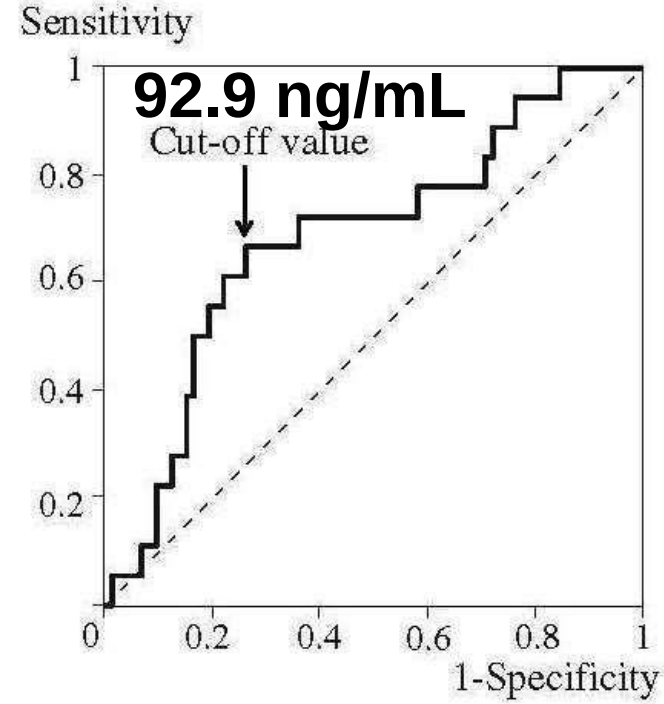
Kalantar-Zadeh et al. JASN 2005

Association between high risk of death with high serum ferritin levels

the Nishinomiya Study

HD





Cut-off value of ferritin	92.9 ng/ml
Sensitivity	0.667
Specificity	0.736
Area under the curve	0.683
P value	0.017
95%CI	0.543 - 0.822

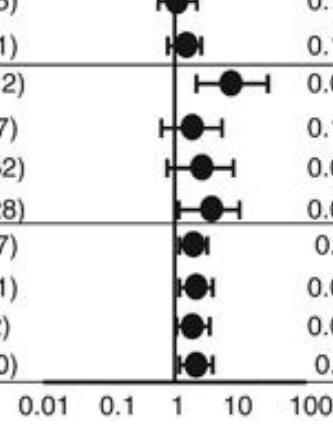
Hasuike et al. Clin Exp Nephrol 2010

Association between adverse events with high serum ferritin levels (>100 ng/mL) and with high-amplitude ferritin fluctuations

Treatment for Renal Anemia on Prognosis (TRAP) study

HD

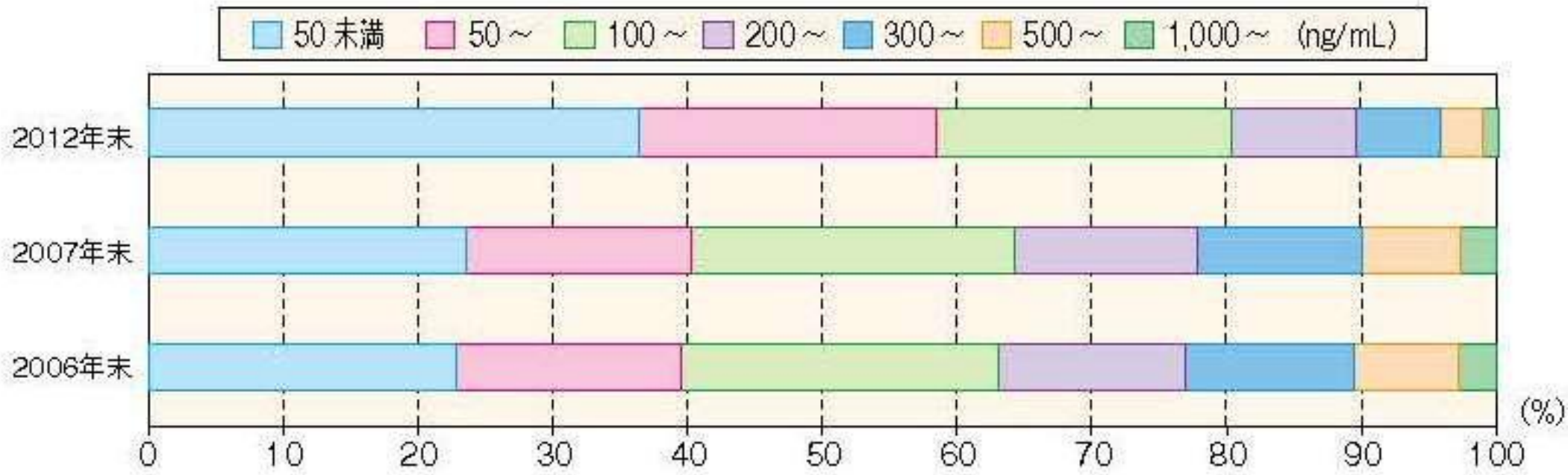
Event	Ferritin fluctuation	Hazard ratio (95% CI)		*P*-value
	Low	1		
Cerebro-cardio vascular disease	L-H	1.53	(0.58–4.02)	0.389
	High	2.22	(1.07–4.63)	0.033
	H-L	2.16	(0.9–5.23)	0.086
	HA	1.77	(0.74–4.27)	0.201
Infectious disease	L-H	1.38	(0.94–2.01)	0.096
	High	1.76	(1.29–2.4)	<0.001
	H-L	1.57	(1.09–2.28)	0.016
	HA	1.2	(0.84–1.72)	0.31
Hospitalization	L-H	1.59	(1.10–2.28)	0.013
	High	0.85	(0.57–1.25)	0.403
	H-L	1.08	(0.71–1.65)	0.711
	HA	1.32	(0.91–1.91)	0.141
Death	L-H	6.18	(1.99–19.12)	0.002
	High	2.28	(0.70–7.47)	0.174
	H-L	3.15	(0.86–11.52)	0.083
	HA	3.75	(1.15–12.28)	0.029
All events	L-H	1.43	(1.09–1.87)	0.01
	High	1.32	(1.02–1.71)	0.035
	H-L	1.35	(1.01–1.82)	0.043
	HA	1.38	(1.05–1.80)	0.02



Kuragano et al. Kidney Int 2014

Serum ferritin of the Japanese dialysis patients

Database of JSDT



New anemia guideline: JSN & JSDT

Iron supplementation should be started in patients with serum ferritin ≤50 ng/mL in patients NOT treated with ESA.

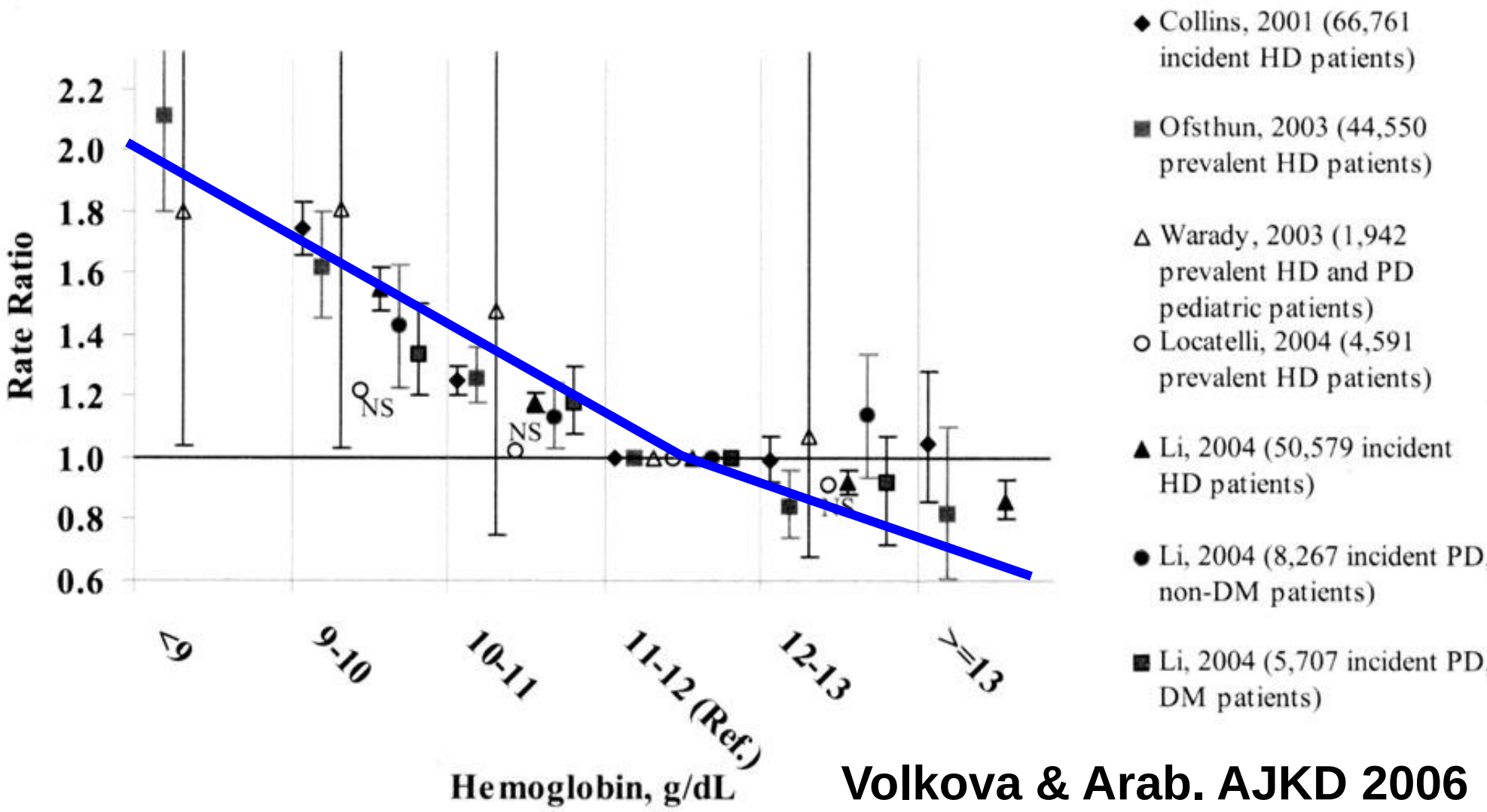
Iron supplementation should be started in patients with TSAT ≤20 % or serum ferritin ≤100 ng/mL in patients treated with ESA.

Serum ferritin should not exceed 300 ng/mL or 500 ng/mL.

Target Hb

Epidemiological studies showed correlation between high Hb and good prognosis

Anemia and prognosis of CKD patients meta-analysis

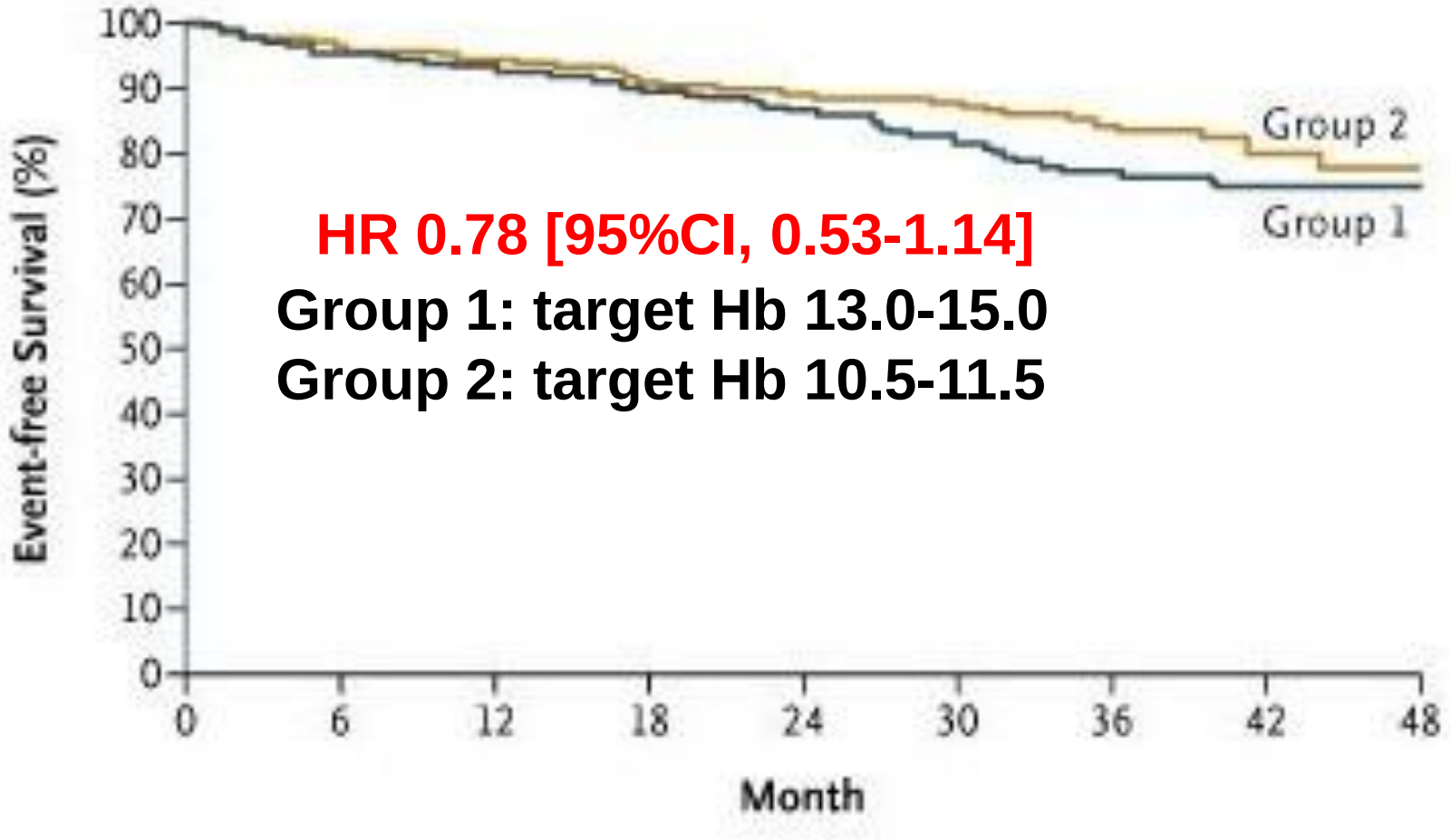


Volkova & Arab. AJKD 2006

Prospective trials showed that high Hb does not necessarily improve cardiovascular outcome

CREATE: primary endpoint

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



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: Composite and Component End Points

Table 2. 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

* ESRD denotes end-stage renal disease.
† P values have not been adjusted for multiple comparisons.
‡ A patient may have had multiple cardiovascular events of different types. The cardiovascular composite end point reflects only the first occurrence of any of the components.
§ This category includes both fatal and nonfatal events.

Pfeffer et al. N Engl J Med 2009

Difference of cardiovascular events between Japan and Western countries

A21 trial

秋澤忠男 et al. 腎と透析. 2014

Past history	AMI (%)	CABG (%)	PAD (%)
High Hb group	5.6	0.6	6.2
Low Hb group	3.1	0.6	3.8

CHOIR

Past history	AMI (%)	CABG (%)	PAD (%)
High Hb group	16.4	17.4	16.4
Low Hb group	15.0	13.5	16.4

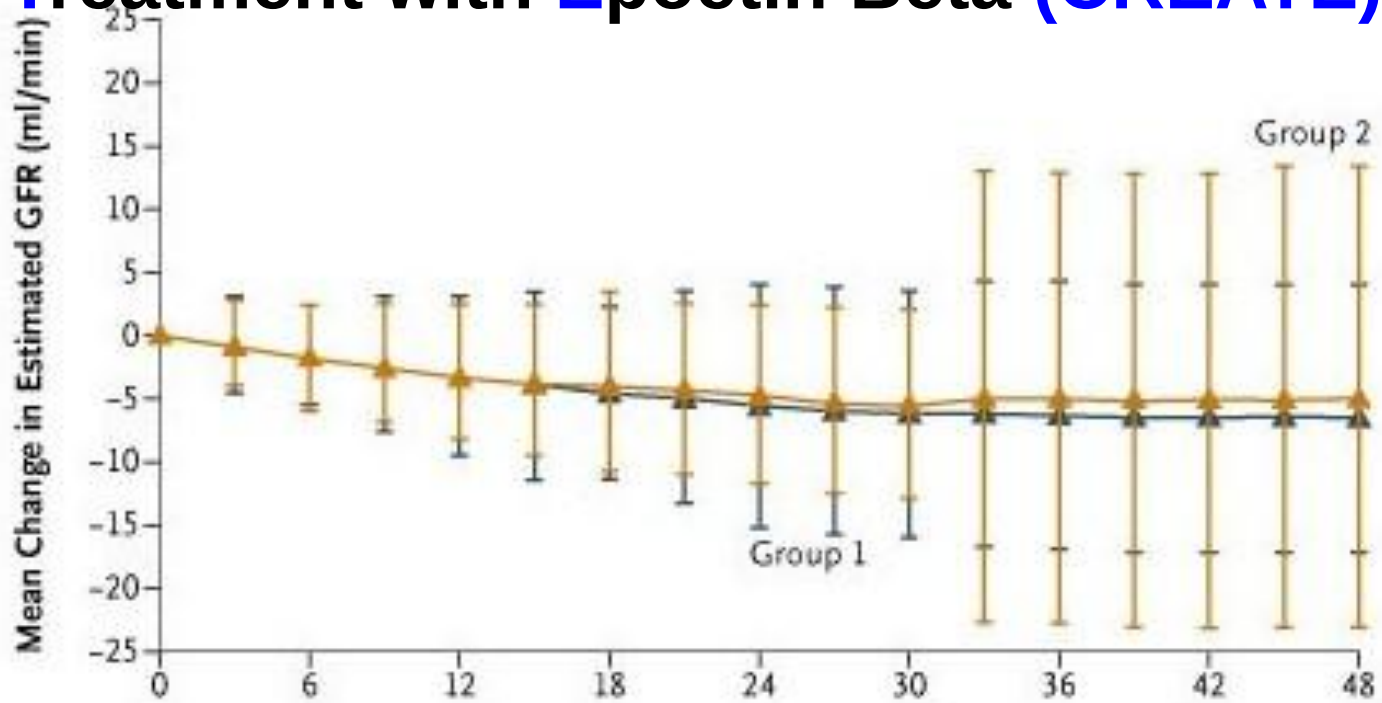
Difference of cardiovascular events between Japan and Western countries

	Cardiovascular events (/1000 person・year)	apoplexy (/1000 person・year)
CHOIR	51.7	5.4
CREATE	58.0	7.2
TREAT	76.4	9.5
A21	15.6	2.1
Gonryo (G3-5)	21.8	8.6

Renal outcome in prospective trials

CREATE: secondary endpoint

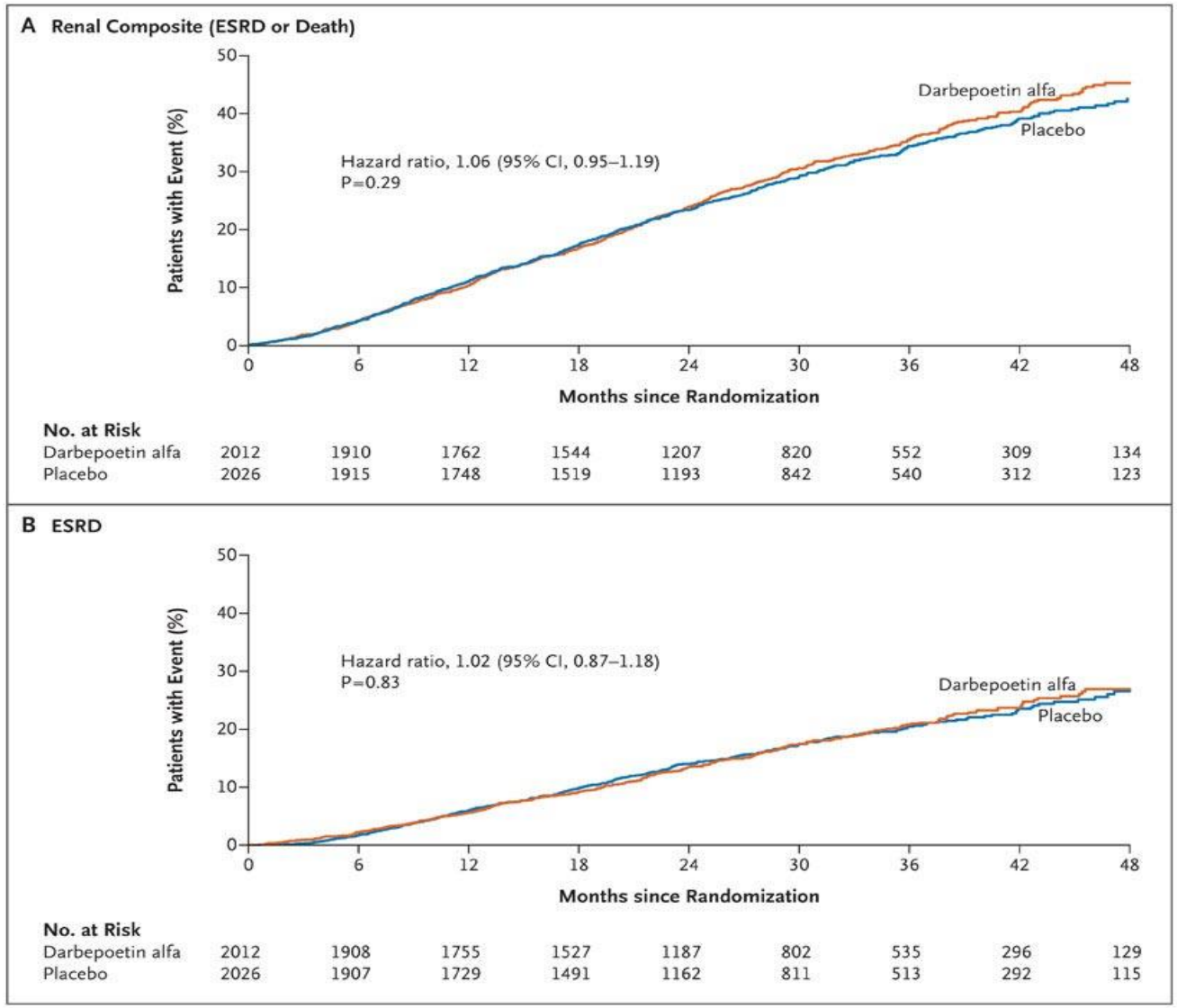
Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)



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

TREAT: secondary endpoint of renal outcomes



Pfeffer et al. N Engl J Med 2009

Difference of kidney outcomes between Japan and Western countries

Incident dialysis

	eGFR (mL/min/1.73m²)	reason
A21	5.16	uremia
CREATE	12	heart failure/ volume overload
USRDS	11.1	heart failure/ volume overload

秋澤 忠男 et al. 腎と透析. 2014

A21 STUDY

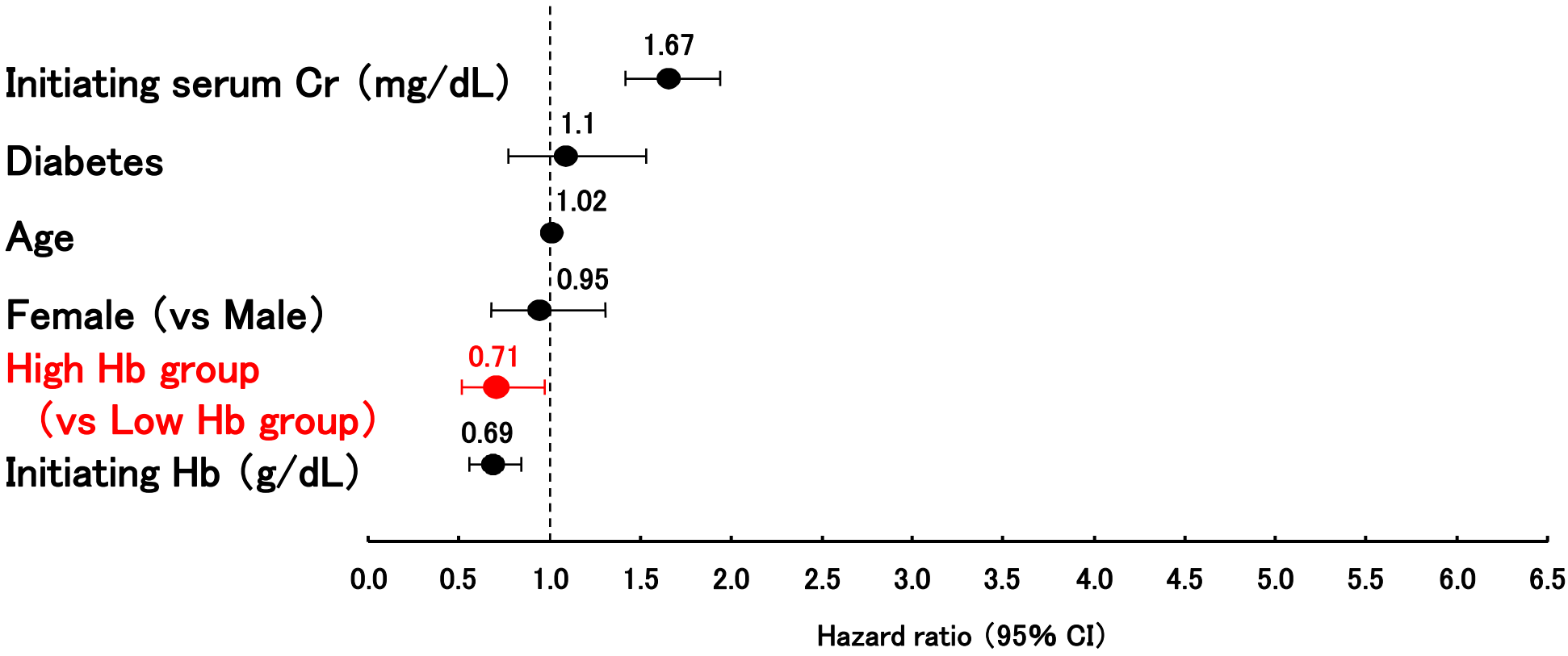
Design	Multi-center, prospective, randomized, open-labeled trial
	CKD patients (Age ≥ 20) Hb ＜10.0 g/dL, serum Cr : 2.0～6.0 mg/dL
	High Hb group（target Hb11.0～13.0g/dL）: treated with darbepoietin Low Hb group（target Hb 9.0～11.0g/ dL ）: treated with EPO Iron is supplemented to keep transferrin saturation > 20% and ferritin > 100 ng/mL

Primary endponit

✓ Time to doubling of serum Cr, incident dialysis, kidney transplantation, or death

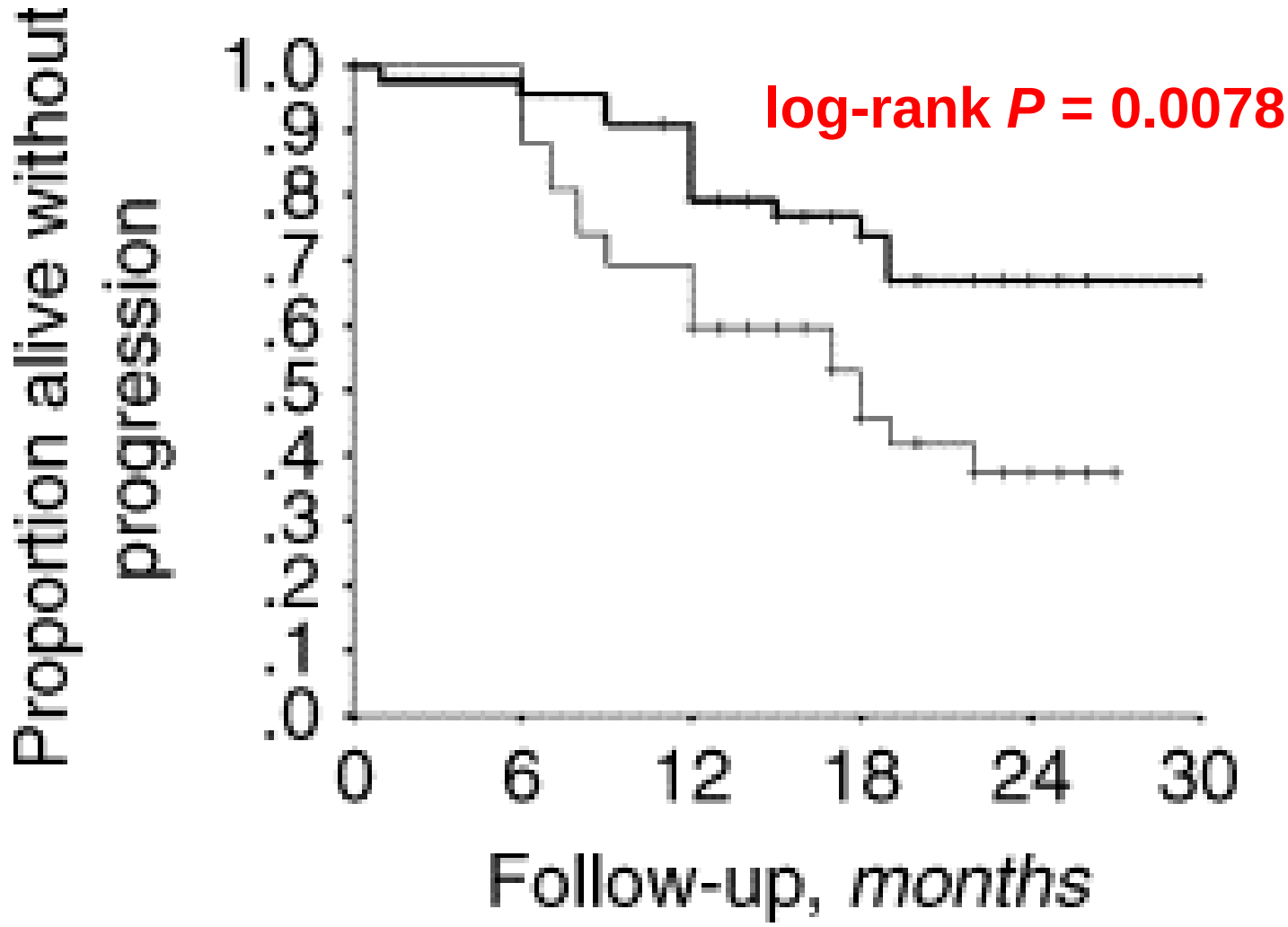
Tsubakihara et al. Ther Apher Dial 2012

Hazard ratio of renal survival



Tsubakihara et al. Ther Apher Dial 2012

Gouva trial : primary endpoint



Gouva et al. Kidney Int 2004

		JSDT(2008)	NICE (2011)	KDIGO(2012)	ERBP(2013)
non-HD	Start	11		10	10 (9~12 according to risks)
	Target	11~13	10~12	~11.5	~12
	Upper limit	13 (12 for those with severe cardiovascular complications)		13	13
HD	Start	10 (11 for young and active)		9~10	10 (9~12 according to risks)
	Target	10~11 (11~12 for young and active)	10~12	~11.5	~12
	Upper limit	12 (13 for young and active)		13	13

New anemia guideline: JSN & JSDT

Target Hb should be 11~13 g/dL for non-HD CKD patients and PD patients, and 10~12 g/dL for HD patients, respectively.

Target Hb should be individualized based on the personal conditions of the patient.

ESA hyporesponsiveness

The NEW ENGLAND JOURNAL of MEDICINE 2010

ORIGINAL ARTICLE

Erythropoietic Response and Outcomes in Kidney Disease and Type 2 Diabetes

Scott D. Solomon, M.D., Hajime Uno, Ph.D., Eldrin F. Lewis, M.D., M.P.H., Kai-Uwe Eckardt, M.D., Julie Lin, M.D., M.P.H., Emmanuel A. Burdmann, M.D., Ph.D., Dick de Zeeuw, M.D., Ph.D., Peter Ivanovich, M.D., Andrew S. Levey, M.D., Patrick Parfrey, M.D., Giuseppe Remuzzi, M.D., Ajay K. Singh, M.D., Robert Toto, M.D., Fannie Huang, M.S., Jerome Rossert, M.D., Ph.D., John J.V. McMurray, M.D., and Marc A. Pfeffer, M.D., Ph.D., for the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) Investigators

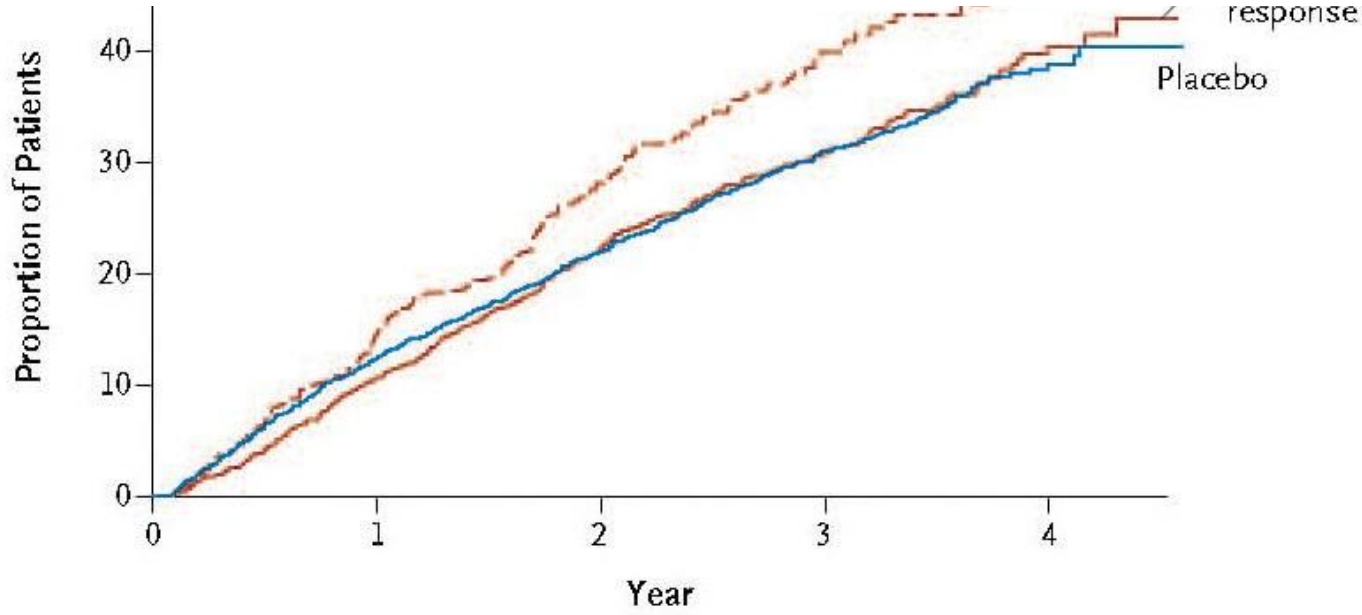
Based on changes of Hb during the 1st month

Poor response

Better response

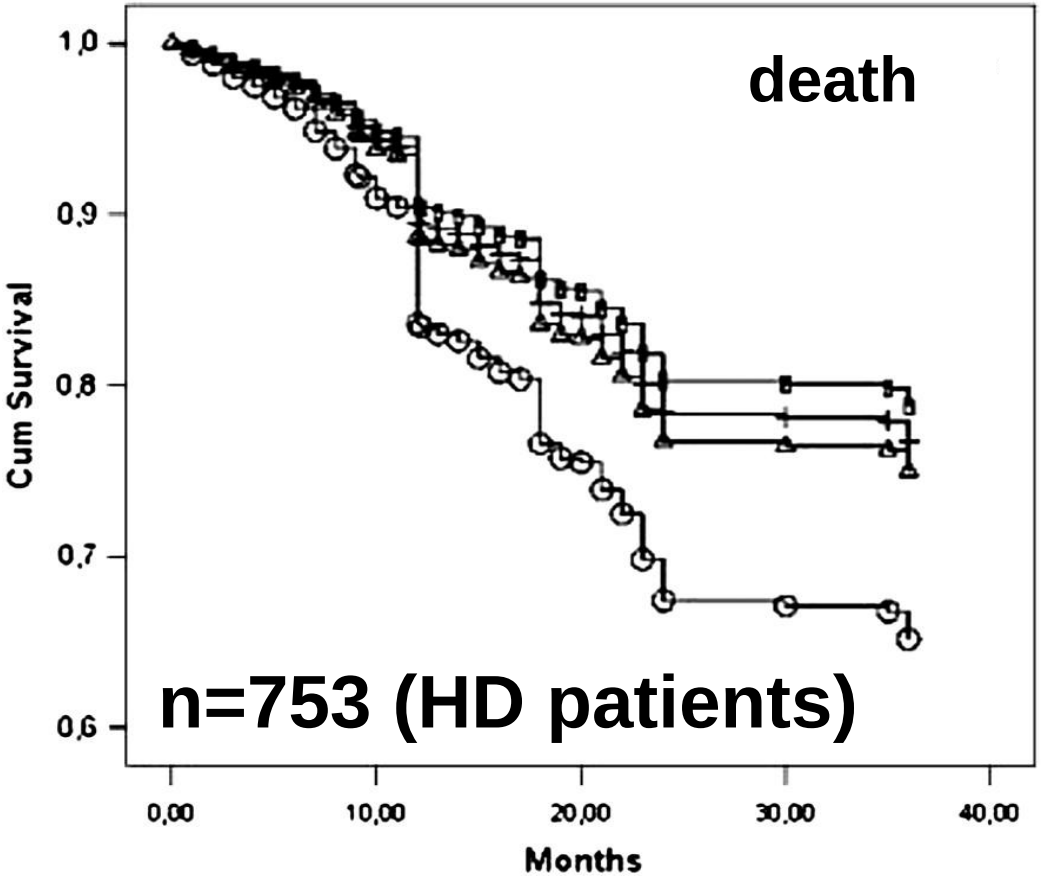
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Hb change (%)	<2	2 to <8	8 to <15	≥15
Median (g/dl) (interquartile range)	-0.2 (-0.7 to 0.0)	0.5 (0.4 to 0.7)	1.2 (1.0 to 1.4)	2.0 (1.7 to 2.6)

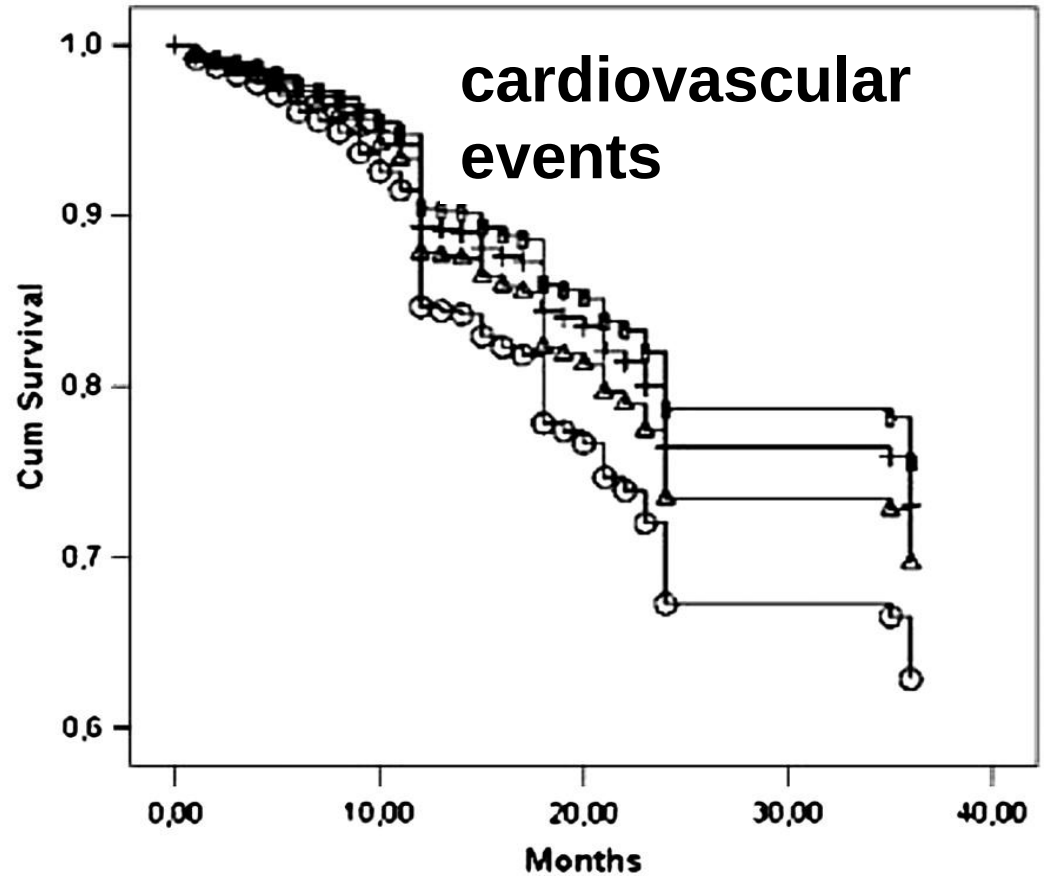
Death, myocardial infarction, apoplexy, heart failure, or hospitalization due to cardiac ischemia



No. at Risk					
Poor initial response	471	394	272	125	30
Better initial response	1401	1234	854	408	94
Placebo	1889	1611	1138	514	117

EPO hyporesponsiveness : RISCAVID study

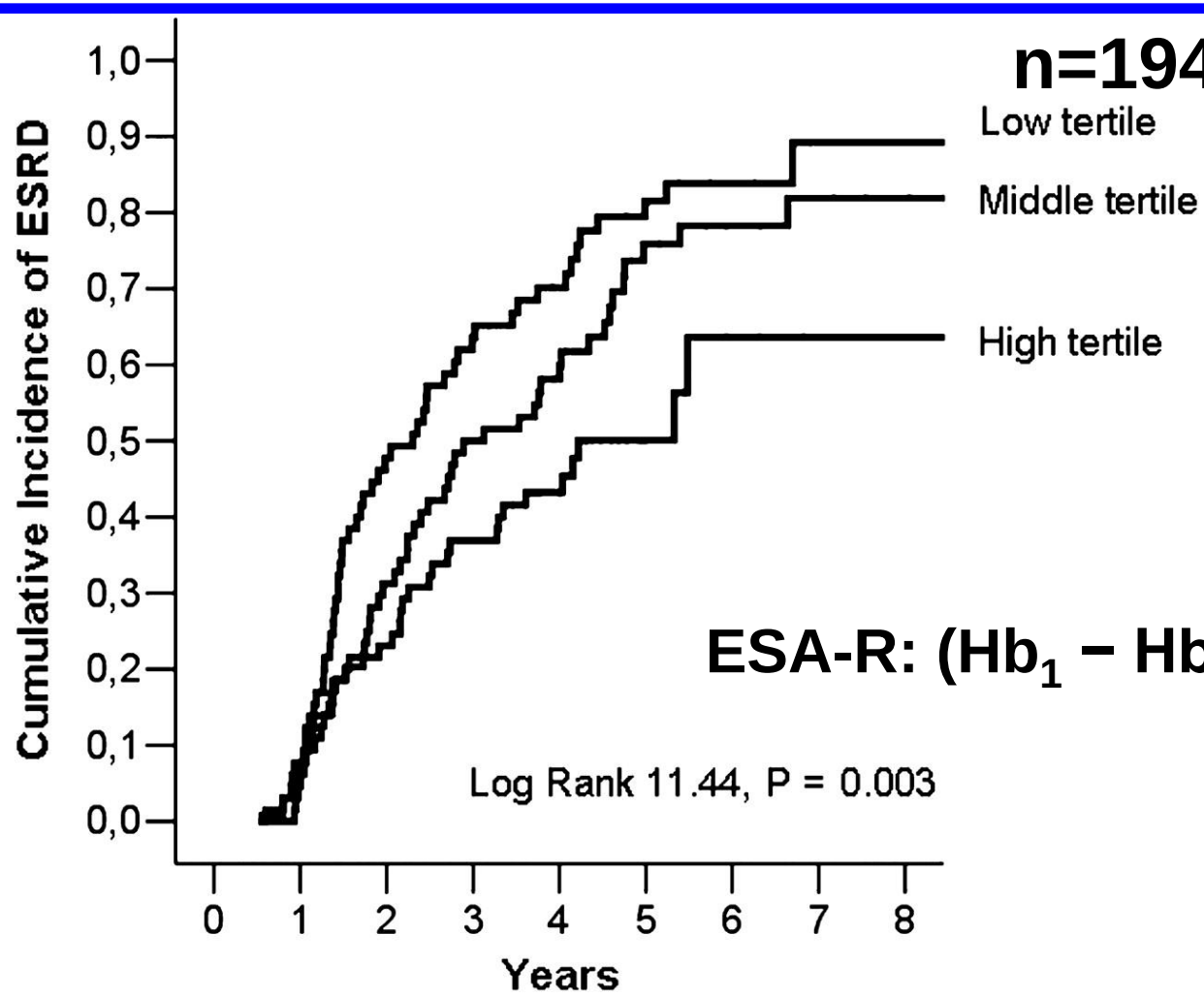




ESAs resistance index (ERI): the weekly ESAs dose / kgBW / Hb (g/dL)

Panichi et al. Nephrol Dial Transplant 2011

EPO hyporesponsiveness and risk of ESRD



n=194 (non-HD)

ESA-R: ($Hb_1 - Hb_0$)/time/ESA

Minutolo et al. Nephrol Dial Transplant 2012

New anemia guideline: JSN & JSDT

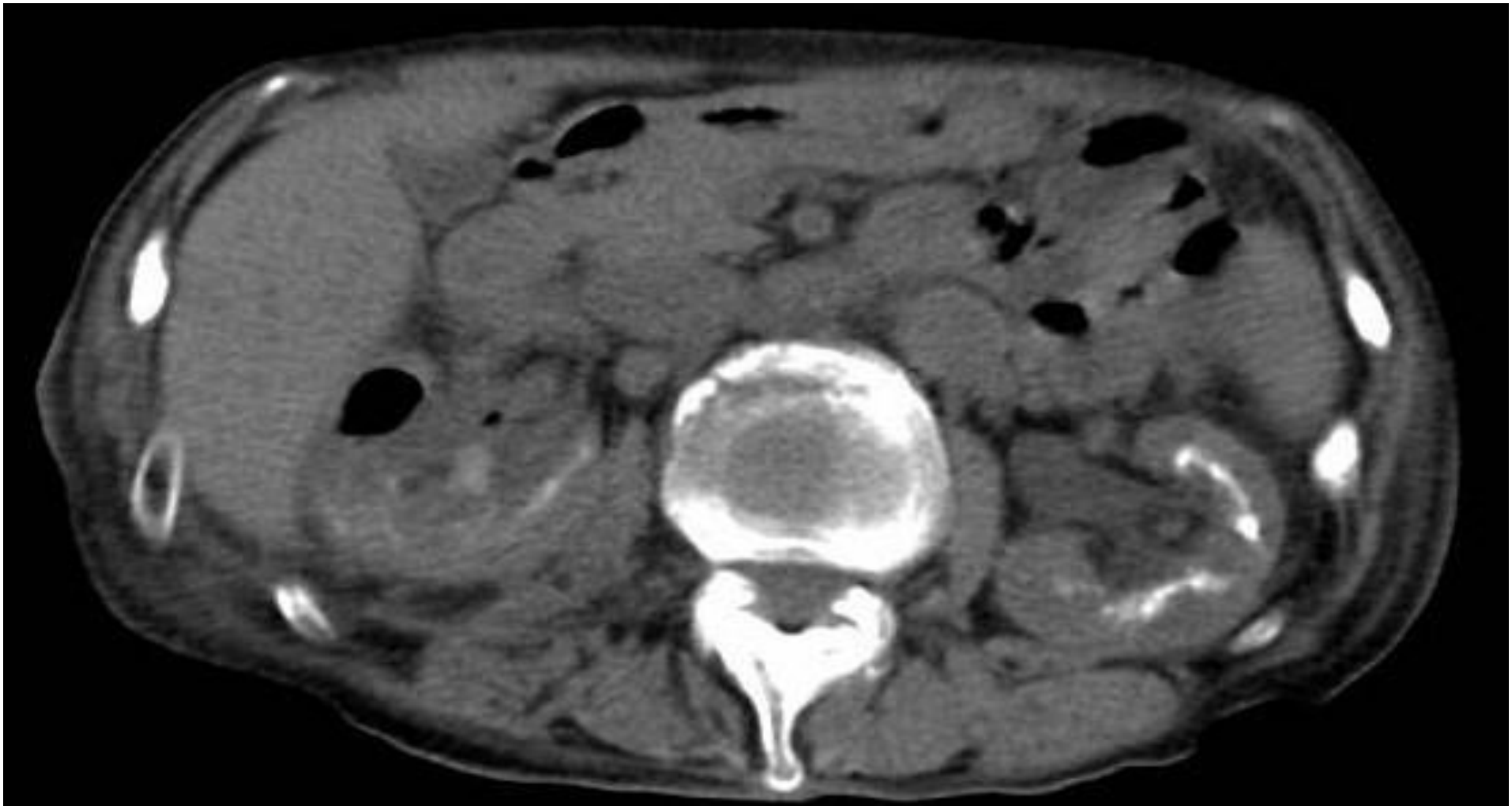
The definition of "ESA hyporesponsiveness" remains unclear.

Failure of achievement of target Hb with the dose of ESA approved by the administration authorities or the government suggests "ESA hyporesponsiveness".

A cause of "ESA hyporesponsiveness" should be investigated before increasing the dose of ESA.

Case 72-year-old female

CKD due to medullary sponge kidney with renal anemia and MDS



Clinical management of myelodysplastic syndromes: Japanese Society of Hematology guideline

40–60,000 U of EPO (once to three times per week) (grade A) is recommended

Clinical management of myelodysplastic syndromes: update of SIE, SIES, GITMO practice guidelines

Fixed, rather than weight-adjusted, weekly subcutaneous doses of 60–80,000 U of EPO (once-a-week or subdivided in two doses) (grade A) or 300 μg darbepoetin (once-a-week) should be used (grade B) for at least 12 weeks, possibly more than 20 (grade B).

Santini et al. Leuk Res 2010

ESAs are not associated with increased risk of thrombosis in patients with MDS

Variables	Unadjusted model 12-week exposure window (n=212) ORs	95% CI		12-week exposure window (n=212) ORs	95% CI		Adjusted model 8-week exposure window (n=234) ORs	95% CI		4-week exposure window (n=246) ORs	95% CI	
ESA use	1.368	0.757	2.472	1.209	0.603	2.426	1.236	0.636	2.402	1.312	0.721	2.388
RBC				4.598	2.29	9.229	6.712	3.126	14.41	5.194	2.429	11.106
Catheterization				6.465	2.373	17.615	21.499	4.576	101	13.274	2.986	59.006

Note: 12 weeks (or 4 weeks) in the comparator and hazard periods with a 24-week gap.

Smith et al. Haematologica 2012

Anemia treatment should be individualized based on the personal conditions of the patient.

日本腎臓学会は腎臓学研究の進歩と知識の普及、国民への還元を目的としています。

一般社団法人 日本腎臓学会 Japanese Society of Nephrology

APSN