复旦大学 中国红十字会
華山醫院

Iron Supplement in CKD Patients in China

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Contents

- Consensus on anemia management in CKD patients in China
- Anemia control in CKD patients in China
- Hepcidin and iron homeostasis in CKD

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Recommendations for Use of Iron Supplementation in Patients with CKD

2.1.1: When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). *(Not Graded)*

Recommendations for Use of Iron Supplementation in Patients with CKD

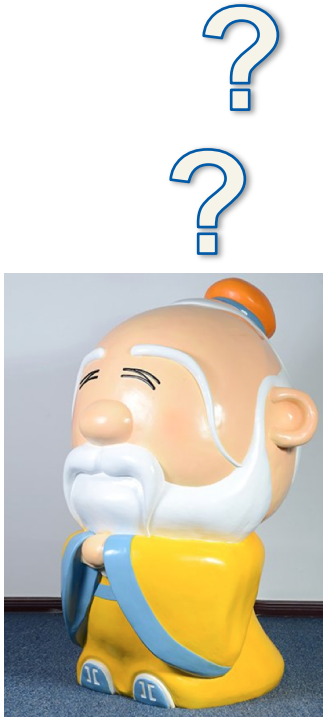
2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral

- **Limitation in current iron status assessment**
- **Long term safety concerns on i.v. iron**
- **…**

2.1.

in ESA dose is desired*** and

- TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 µg/l)



*Based on patient symptoms and overall clinical goals, including avoidance of transfusion, improvement in anemia-related symptoms, and after exclusion of active infection.

***Based on patient symptoms and overall clinical goals including avoidance of transfusion and improvement in anemia-related symptoms, and after exclusion of active infection and other causes of ESA hyporesponsiveness.

Consensus on Iron supplement in CKD Patients in China

- Criteria for iron supplement in CKD
  - CKD anemic patients not on ESA or iron
    - TSAT <30%; Ferritin <500ug/L: a trial of IV iron (ND-CKD, trial 1-3 months of oral iron, switch to IV iron if no effect)
  - CKD anemic patients are on ESA but not iron
    - An increase in Hb or reduction of ESAs are desired and TSAT <30%; Ferritin <500ug/L: trial of IV iron (ND-CKD, trial 1-3 months of oral iron, switch to IV iron if no effect)
  - If ferritin > 500 ug/L, we recommend no IV iron. However, if increase of ESAs does not improve anemia and acute infection excluded, you may try IV iron.

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Consensus on Iron supplement in CKD Patients in China

- Iron supplement and dosages
  - ND-CKD or PD: oral iron first, or if needed IV Iron.
  - HD： preferably IV iron
  - Oral Iron: 200mg/day, reevaluate in 1-3 months. If not reached the goal or not tolerant, switch to IV iron
  - IV iron: (1) HD patients, IV iron; Initiation: 1000mg, if ferritin ≤500ug/L and TSAT≤30%, repeat; (2) Maintenance： 100mg/1-2 weeks， depends on response, iron status, Hb, ESA etc.
  - If TSAT ≥50% and/or ≥800ug/L, stop iv iron for 3 months. If TSAT and ferritin ≤50% and ≤800ug/L respectively, resume IV iron at reduced does by 1/3-1/2.

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Intravenous Iron Sucrose in Chinese Hemodialysis Patients with Renal Anemia

Han Li Shi-xiang Wang

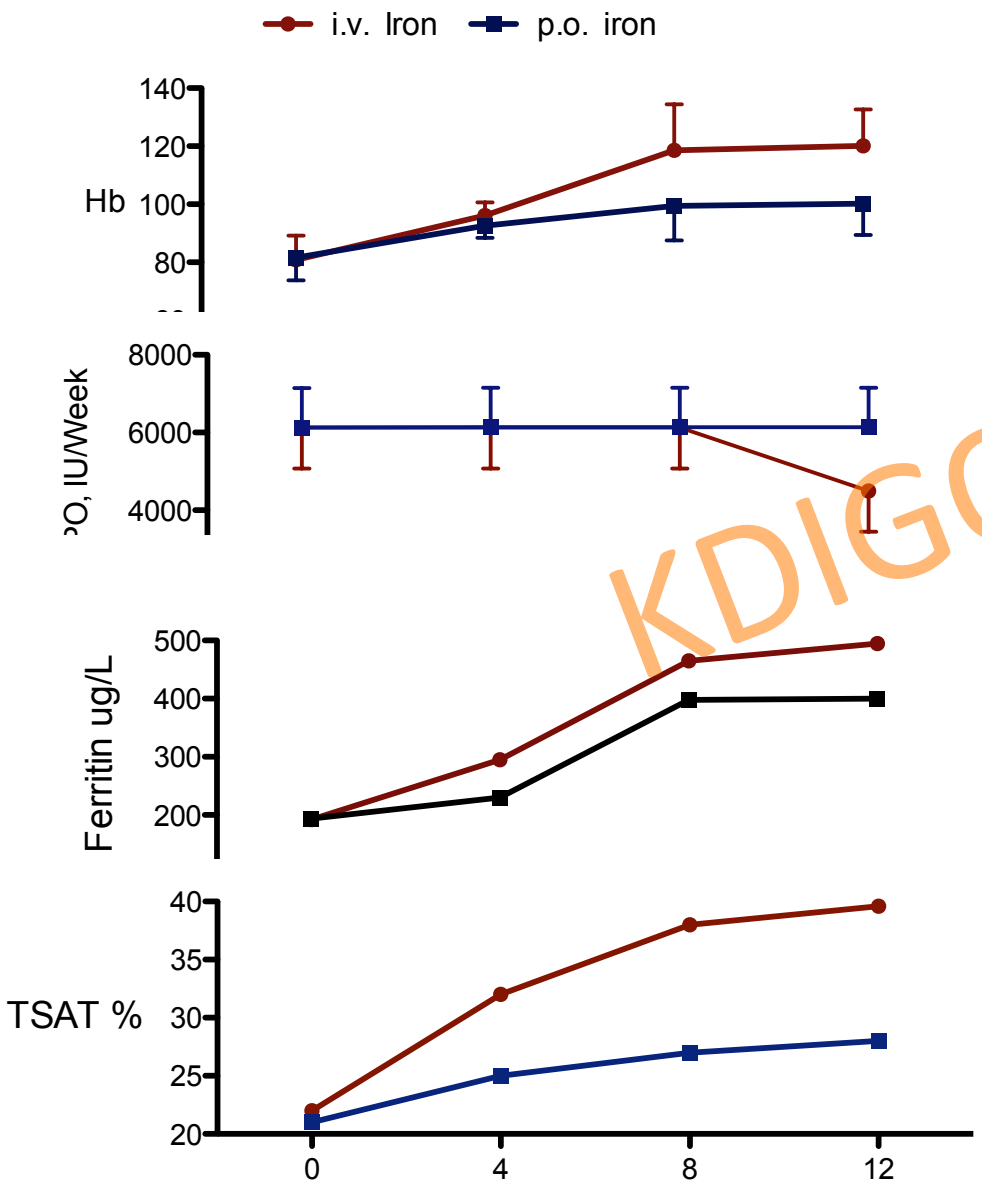
Blood Purification Center, Beijing Chaoyang Hospital, Capital University of Medical Sciences, Beijing, China

Item	i.v. group (n = 70)	p.o. group (n = 66)
Age, years	53.6 ± 13.8	54.9 ± 12.6
Sex ratio, male/female	31/39	26/40
Duration of hemodialysis, months	37.6 ± 37.4	35.9 ± 33.1
Dialysis frequency, times/week	2.8 ± 0.4	2.7 ± 0.4
EPO dosage, U/kg/week	118 ± 34	119 ± 25
iPTH, ng/ml	188.7 ± 65.5	192.4 ± 59.6
Scr, μmol/l	979.8 ± 286.2	982.5 ± 273.6
BUN, mmol/l	25.9 ± 7.6	25.5 ± 7.0
Hb, g/l	80.9 ± 8.3	81.6 ± 7.8
Hct, %	22.1 ± 2.3	23.1 ± 2.8
SF, μg/l	192.6 ± 154.4	194.7 ± 158.4
TSAT, %	22.3 ± 12.4	21.3 ± 16.8
Folic acid, μg/l	15.6 ± 7.3	16.1 ± 5.2
Vitamin B_{12}, ng/l	738.2 ± 397.4	751.2 ± 417.8
CRP, mg/l	1.8 ± 1.2	1.9 ± 1.1

Beijing Chaoyang Hospital

- maintenance hemodialysis,
- Hb concentration 60–90 g/l
- ferritin (SF) <500 ng/ml
- TSAT < 30%

Han Li & Shi-Xiang Wang Blood Purif 2008;26:151–156



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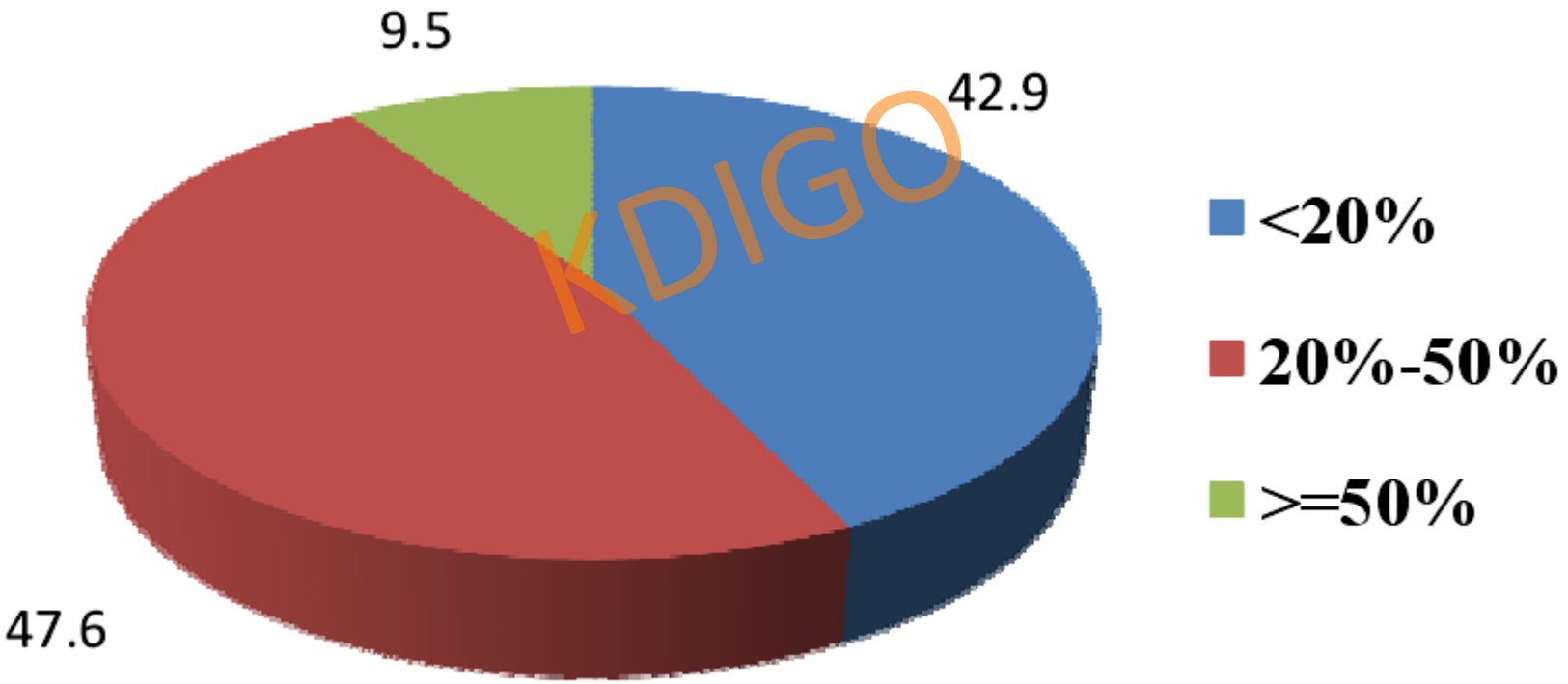
China Dialysis Patients Hb≥100g/L

	2012		2013		2014		2015	
	mean	%	mean	%	mean	%	mean	%
Hb (g/L)	97	47.92%	99	50.25%	101	55.41%	102	57.31%

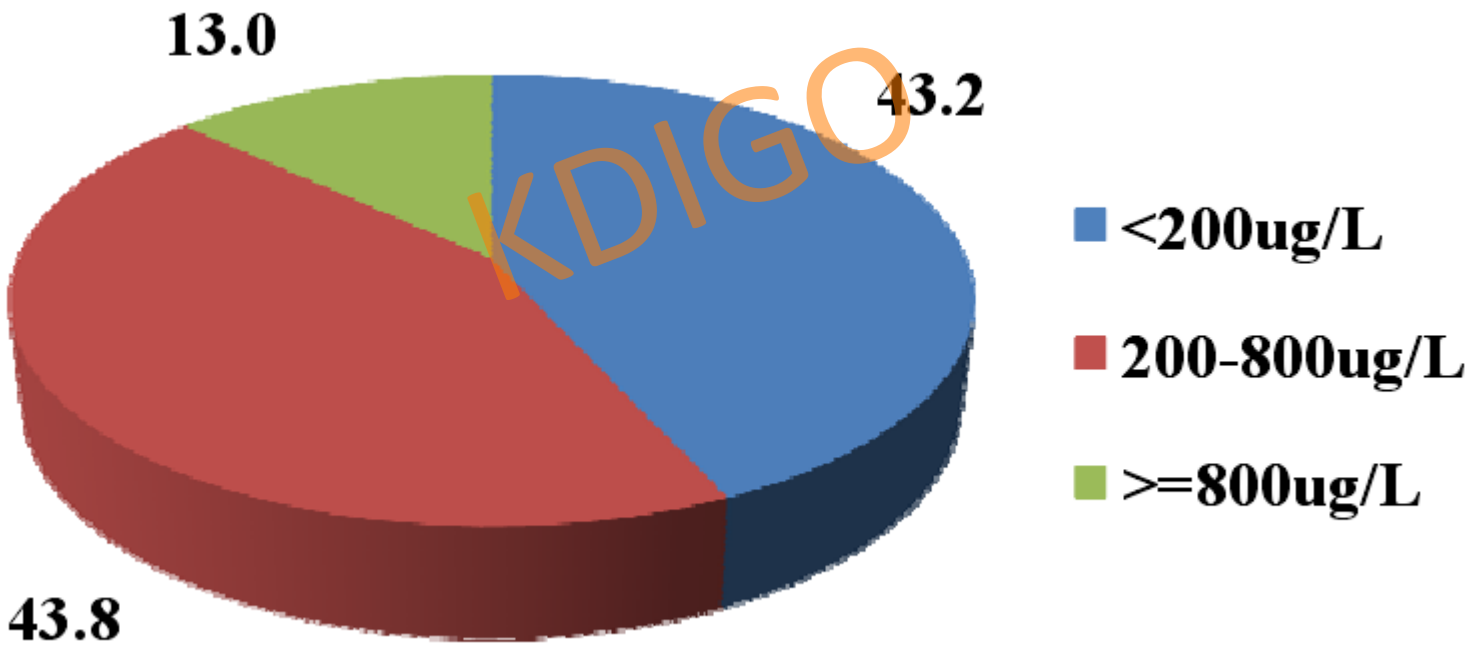
China Dialysis Registry provided by Dr. Cai G

2012 China Maintenance Dialysis Patients TSAT



China Dialysis Registry

2012 China Maintenance Dialysis Patients Serum Ferritin



China Dialysis Registry

Anemia Management in the China Dialysis Outcomes and Practice Patterns Study（DOPPS）

(Beijing, Shanghai and Guangzhou)

Measure	China (n = 1,379)	Japan (n = 1,586)	North America (n = 5,100)
Patient characteristics			
Age, years	59.4±14.6	64.7±12.0	62.9±15.1
Female, %	46.6	37.3	44.5
Vintage, years	4.8±4.6	8.5±7.5	4.0±4.2
Urine output >1 cup/day, %[a]	62.0	50.8	46.7
Body mass index, kg/m^2	21.9±3.5	21.1±3.3	28.5±7.0
Standardized, Kt/V[b]	2.03±0.41	2.14±0.25	2.25±0.26
Sessions per week	2.76±0.55	2.96±0.21	2.98±0.24
Comorbidities, %			
Cardiovascular disease[c]	60.6	60.7	72.0
Diabetes	24.0	35.3	61.2
Cancer	4.3	11.2	13.1
GI bleeding	2.5	5.2	5.8
Hepatitis B infection	8.6	2.5	1.2
Hepatitis C infection	12.0	8.4	3.7

Zuo et al Blood Purif 2016;42:33–43

Causes of ESRD

Anemia Management in the China DOPPS

Measure	China (n = 1,379)	Japan (n = 1,586)	North America (n = 5,100)
Cause of ESRD, %			
Diabetes	20.2	31.7	42.5
Glomerular disease	46.1	44.8	11.3
Polycystic kidney disease	5.3	4.8	2.7
Other	28.5	18.6	43.6

Zuo et al Blood Purif 2016;42:33–43

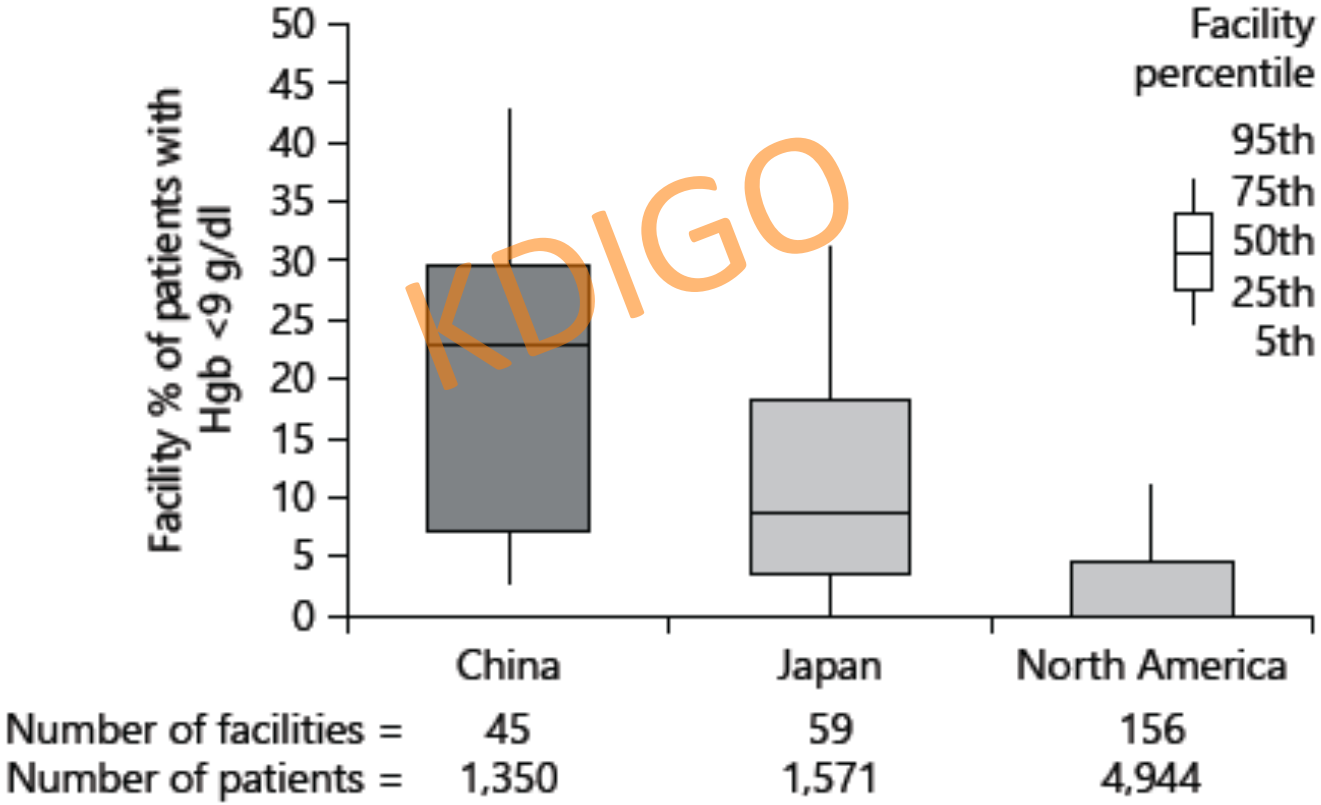
Hb and Iron Status

(Anemia Management in the China DOPPS)

Measure	China (n = 1,379)	Japan (n = 1,586)	North America (n = 5,100)
Hgb, g/dl	10.5±2.0	10.4±1.2	11.5±1.2
Hgb categories, g/dl, %			
<8	12.0	2.7	0.6
8–<9	9.0	7.6	2.1
9–<10.0	15.9	24.1	6.6
10.0–12.0	41.7	58.5	60.4
>12.0	21.4	7.1	30.3
TSAT, %	31.2±15.2	24.2±10.7	29.3±12.4
TSAT categories, ng/ml, %			
<20	24.2	37.7	20.2
20–29	30.1	36.9	38.0
30–49	33.5	22.5	34.9
≥50	12.1	2.9	6.8
Ferritin	417±428	157±222	648±444
Ferritin categories, mg/l, %			
<200	40.7	75.4	12.2
200–499	33.6	19.7	30.1
500–799	16.1	3.3	28.6
≥800	9.6	1.6	29.1

Zuo et al Blood Purif 2016;42:33–43

Distribution of Facility Percentage of Patients with Hgb <9 g/dl by Region



Zuo et al Blood Purif 2016;42:33–43

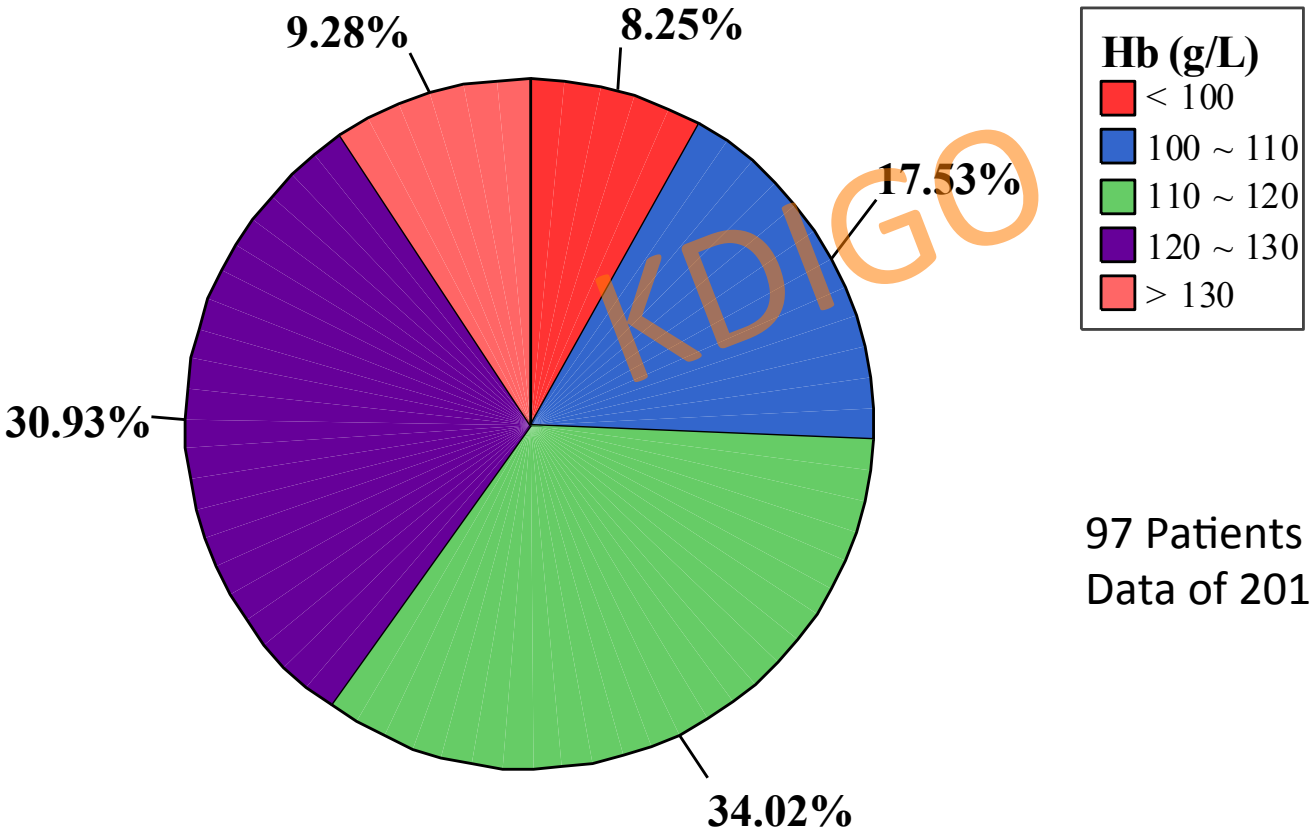
Iron and ESA Use

(Anemia Management in the China DOPPS)

Measure	China (n = 1,379)	Japan (n = 1,586)	North America (n = 5,100)
Medication prescribed[d], %			
ESA	92.6	79.6	81.4
IV iron	37.2	21.9	58.2
ESA origin[e]			
Domestic	89.3	–	–
Non-domestic	10.7	–	–
ESA type, %			
Epoetin[f]	100	52.5	86.6
Pegylated epoetin	0	0	0
Darbepoetin	0	47.5	13.4
Other	0	0	0
ESA route, IV, %	50.8	100	97.3
EPO equivalent dose (EPO + darbepoetin), IV, ›	9.0 (6.0–10.0)	4.0 (2.0–6.0)	12.0 (6.0–24.6)

Zuo et al Blood Purif 2016;42:33–43

Anemia Control in PD Patients in Huashan Hospital



97 Patients from Shanghai city
Data of 2015.6 – 2016.6

Unpublished data

Anemia Control in PD Patients in Huashan Hospital

Hb (g/L)	< 100	100 ~110	110 ~ 120	120 ~ 130	>130
Ferritin (ng/mL)	188 (154,454)	250 (170,298)	239 (157,347)	211 (107,305)	143 (129,184)
TSAT (%)	25.0 ± 4.1	28.7 ± 8.1	30.8 ±7.3	31.2 ± 7.6	33.7 ± 8.0
EPO (1000xU/mo)	40.0 (32.5,55)	30.0 (30,40)	25 (20,35)	20 (15,20)	10 (10,20)
Iv iron (mg/year)	400 (125,1275)	200 (0,750)	200 (0,400)	0 (0,225)	0 (0,300)

Iv Iron use: 47.4%
Oral iron: 2.1%
EPO: 97%

Zhu T et al Unpublished data

Heterogeneity in Anemia Management in CKD Patient in China

- Insurance coverage or reimbursement cap
- Practice pattern of physician (two-times weekly hemodialysis is more commonly practiced in China)
- Different ESAs

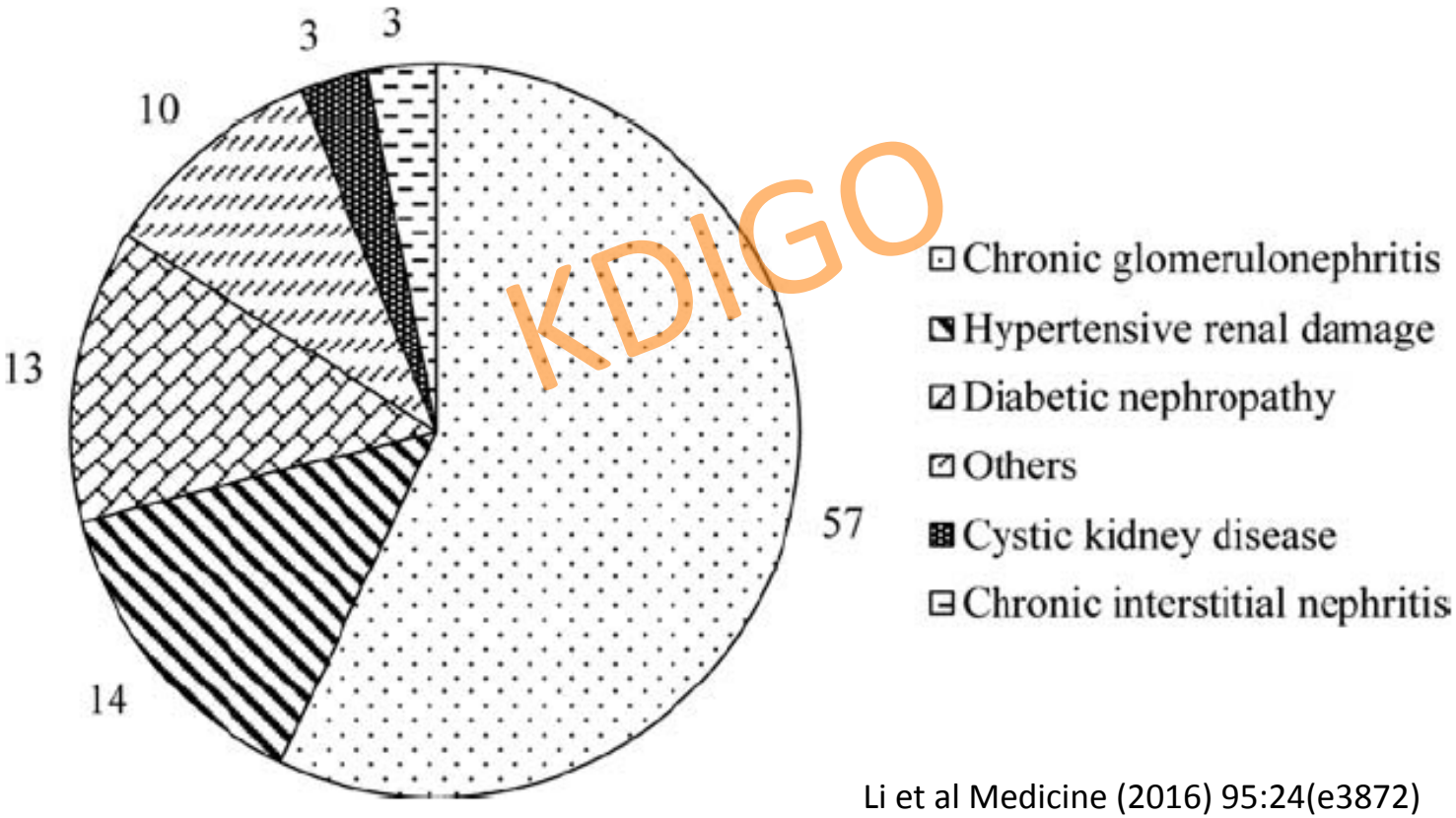
Zuo et al Blood Purif 2016;42:33–43

Anemia in Patients with Non-dialysis Chronic Kidney Disease in Shanghai Area

Variable	Overall	eGFR, mL/min/1.73 m^2				
		Stage 1, eGFR ≥90	Stage 2, 90 > eGFR ≥60	Stage 3, 60 > eGFR ≥ 30	Stage 4, 30 > eGFR ≥ 15	Stage 5, eGFR <15
N	2420	642	440	509	341	488
Age, y	54.51 ± 16.95	44.52 ± 16.48	54.98 ± 15.64	59.12 ± 15.44	59.31 ± 15.33	59.52 ± 15.43
BMI	23.47 ± 4.39	23.37 ± 4.32	24.44 ± 5.33	23.76 ± 4.46	22.92 ± 4.17	22.67 ± 3.41
Male	1297 (53.6%)	315 (49.1%)	256 (58.2%)	314 (61.7%)	189 (55.4%)	223 (45.7%)
Female	1123 (46.4%)	327 (50.9%)	184 (4.18%)	195 (38.3%)	152 (44.6%)	265 (54.3%)
SBP, mm Hg	135.18 ± 29.95	124.47 ± 17.54	132.97 ± 23.12	138.34 ± 41.26	139.34 ± 21.88	144.92 ± 34.32
DBP, mm Hg	80.78 ± 24.46	77.33 ± 10.46	79.71 ± 11.35	83.89 ± 14.41	81.67 ± 13.13	82.38 ± 14.35
Hypertension	1086 (45.5%)	182 (28.9%)	175 (40.5%)	244 (48.3%)	192 (56.8%)	293 (60.8%)
History of smoking	504 (21.1%)	123 (19.2%)	107 (24.5%)	105 (21.0%)	86 (25.5%)	83 (17.6%)
Hb, g/dL	126.33 ± 13.56	137.39 ± 15.05	138.09 ± 15.59	124.80 ± 21.77	110.74 ± 19.02	104.23 ± 26.64
Ferritin, ng/mL	180.83 ± 144.86	147.82 ± 128.71	193.67 ± 130.87	176.32 ± 135.97	188.03 ± 153.51	184.77 ± 140.62
Transferrin saturation, %	27.11 ± 10.54	29.40 ± 12.68	34.19 ± 12.54	17.09 ± 10.41	28.19 ± 16.62	25.58 ± 12.46

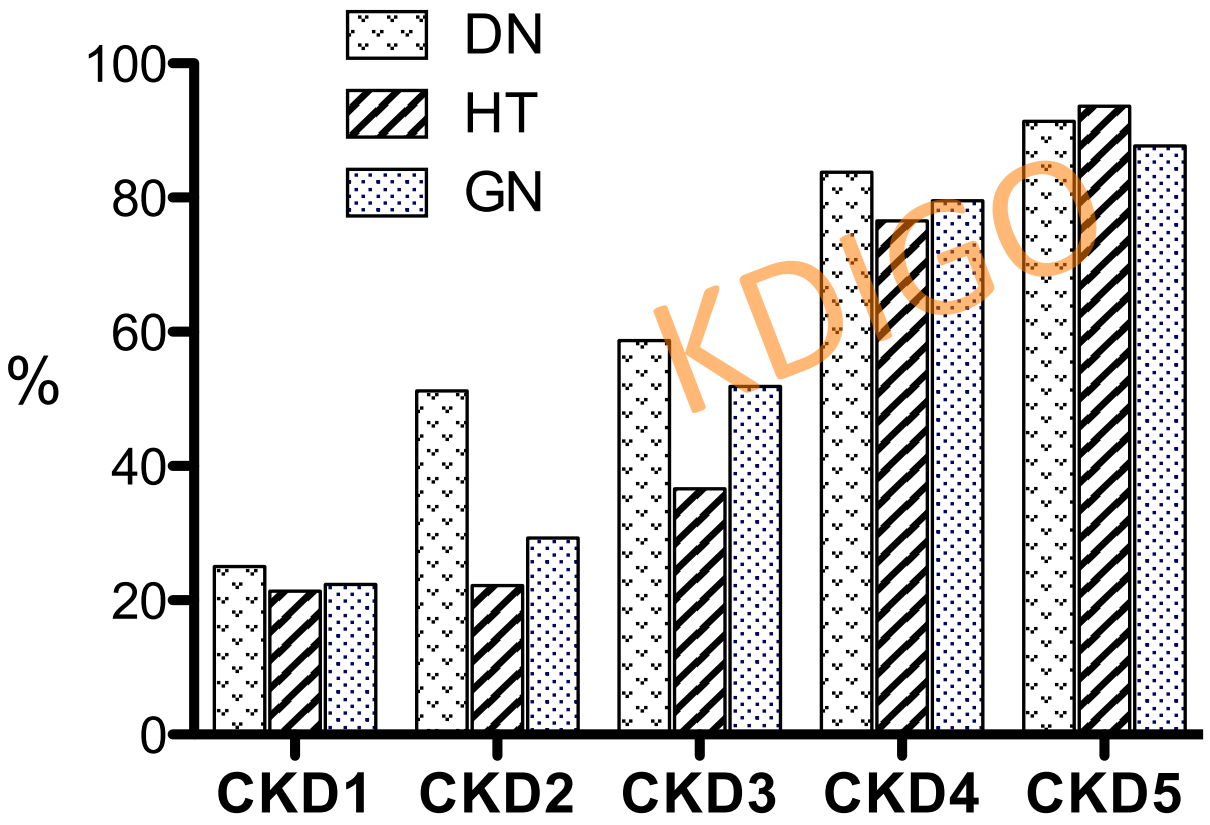
Li et al Medicine (2016) 95:24(e3872)

Underlying Diseases of CKD



Li et al Medicine (2016) 95:24(e3872)

Anemia in Pre-dialysis CKD



Anemia defined as a Hb of 13.0 g/dL in men and 12.0 g/dL in women

Modified from Li et al Medicine (2016) 95:24(e3872)

Iron Status in Patients with Non-dialysis Chronic Kidney Disease in Shanghai Area

Variable		Total (%)	eGFR, mL/min/1.73 m^2 Stage 1, eGFR ≥90 (% of patients)	Stage 2, 90 > eGFR ≥60 (% of patients)	Stage 3, 60 > eGFR ≥30 (% of patients)	Stage 4, 30 > eGFR ≥15 (% of patients)	Stage 5, eGFR <15 (% of patients)
Ferritin level, ng/mL	≤100	29.7 (319)	47.1 (49)	20.0 (36)	44.0 (60)	26.9 (69)	26.5 (105)
	101–200	24.1 (272)	35.3 (39)	30.0 (32)	16.0 (51)	25.0 (58)	25.0 (92)
	201–500	46.1 (436)	17.6 (44)	83.3 (44)	40.0 (79)	48.1 (101)	48.5 (168)

Li et al Medicine (2016) 95:24(e3872)

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Variable		Total (%)	eGFR, mL/min/1.73 m^2 Stage 1, eGFR ≥90 (% of patients)	Stage 2, 90 > eGFR ≥60 (% of patients)	Stage 3, 60 > eGFR ≥30 (% of patients)	Stage 4, 30 > eGFR ≥15 (% of patients)	Stage 5, eGFR <15 (% of patients)
Ferritin level, ng/mL	≤100	29.7 (319)	47.1 (49)	20.0 (36)	44.0 (60)	26.9 (69)	26.5 (105)
	101–200	24.1 (272)	35.3 (39)	30.0 (32)	16.0 (51)	25.0 (58)	25.0 (92)
	201–500	46.1 (436)	17.6 (44)	83.3 (44)	40.0 (79)	48.1 (101)	48.5 (168)
Transferrin saturation, %	≤20	41.0 (344)	41.2 (39)	20.0 (31)	42.3 (59)	36.2 (78)	43.4 (137)
	20–30	36.9 (318)	29.4 (34)	40.0 (34)	50.0 (68)	48.9 (79)	30.3 (103)
	>30	22.1 (323)	29.4 (52)	40.0 (51)	7.7 (58)	14.9 (60)	26.2 (102)

Li et al Medicine (2016) 95:24(e3872)

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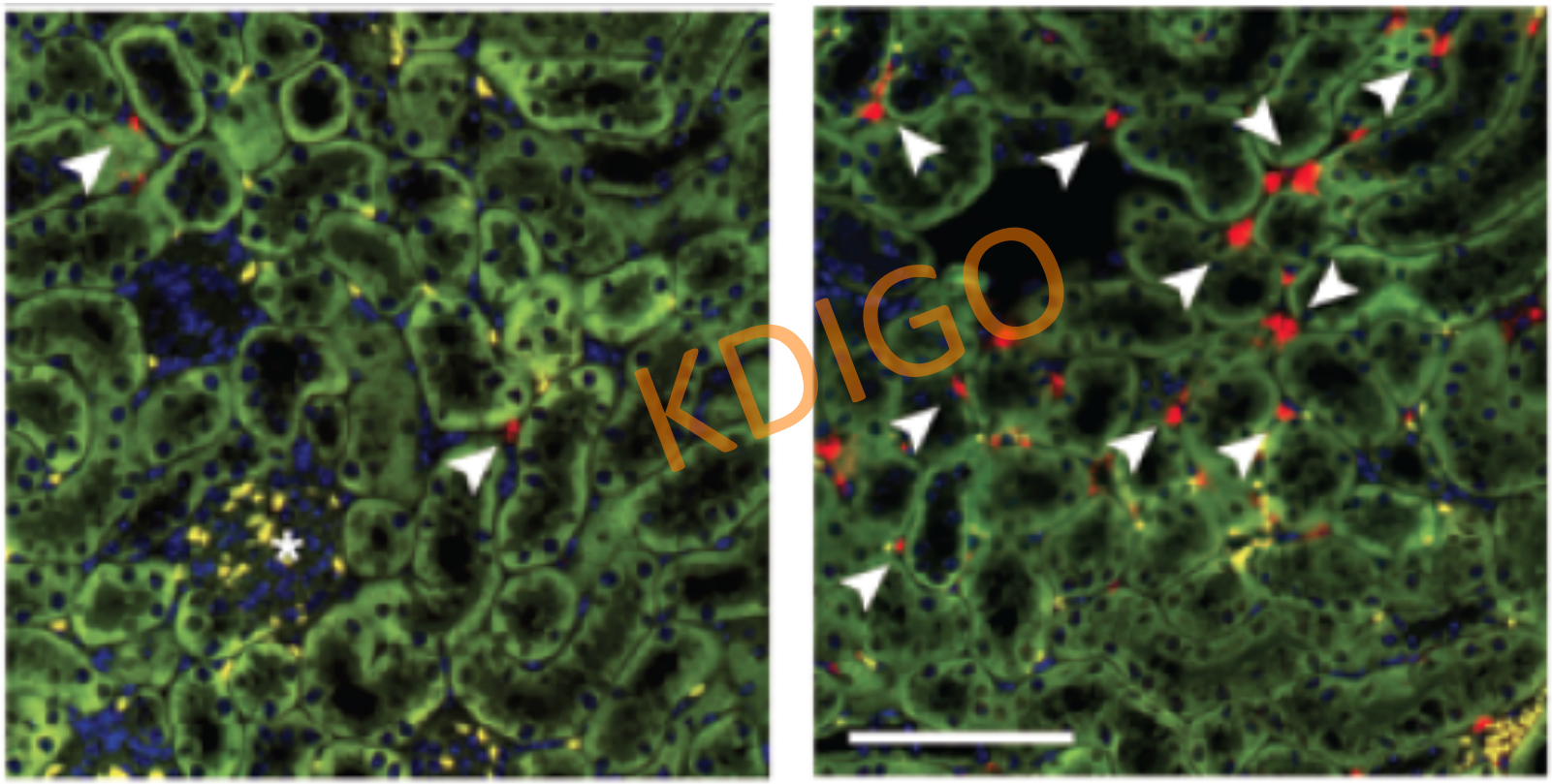
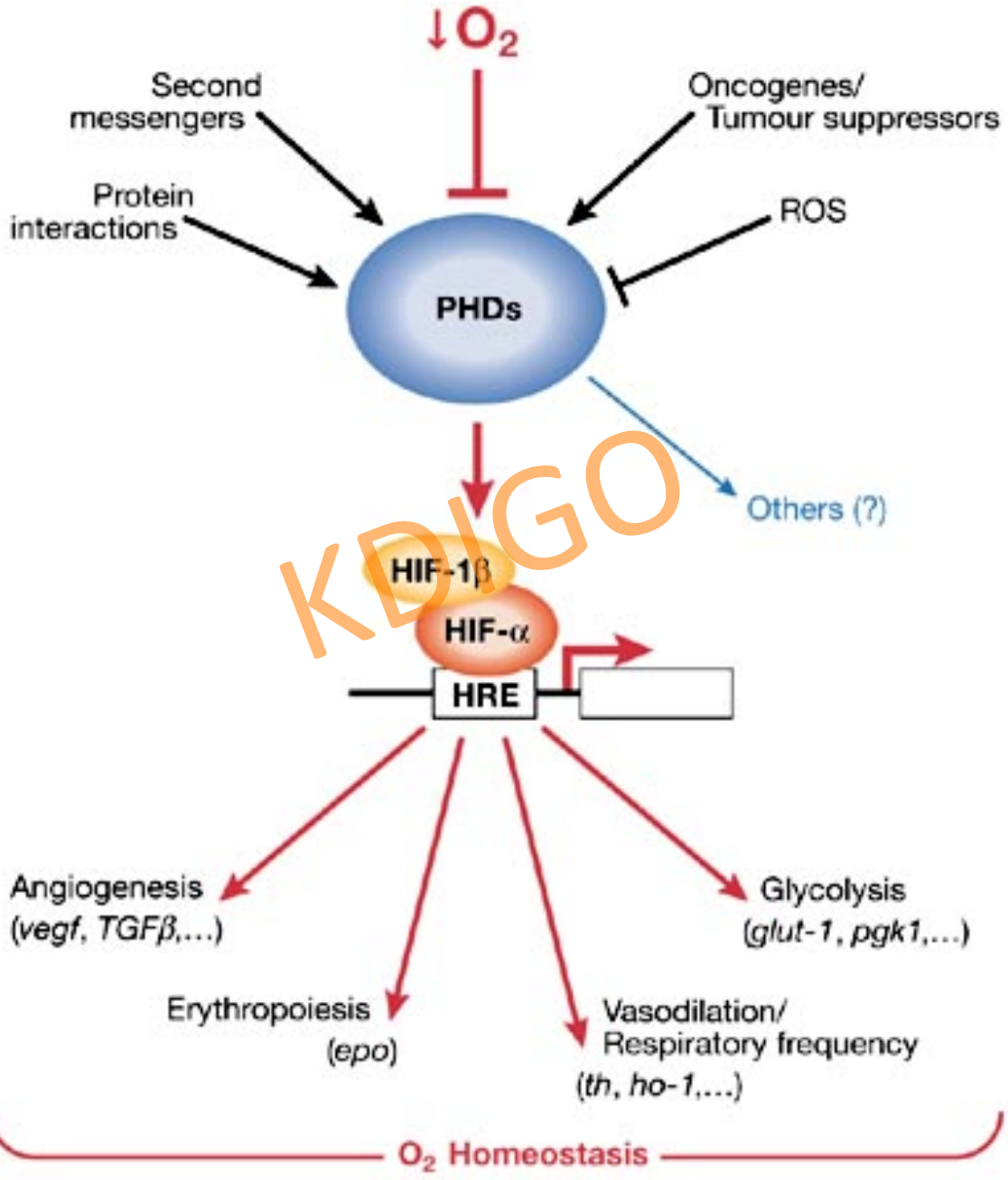
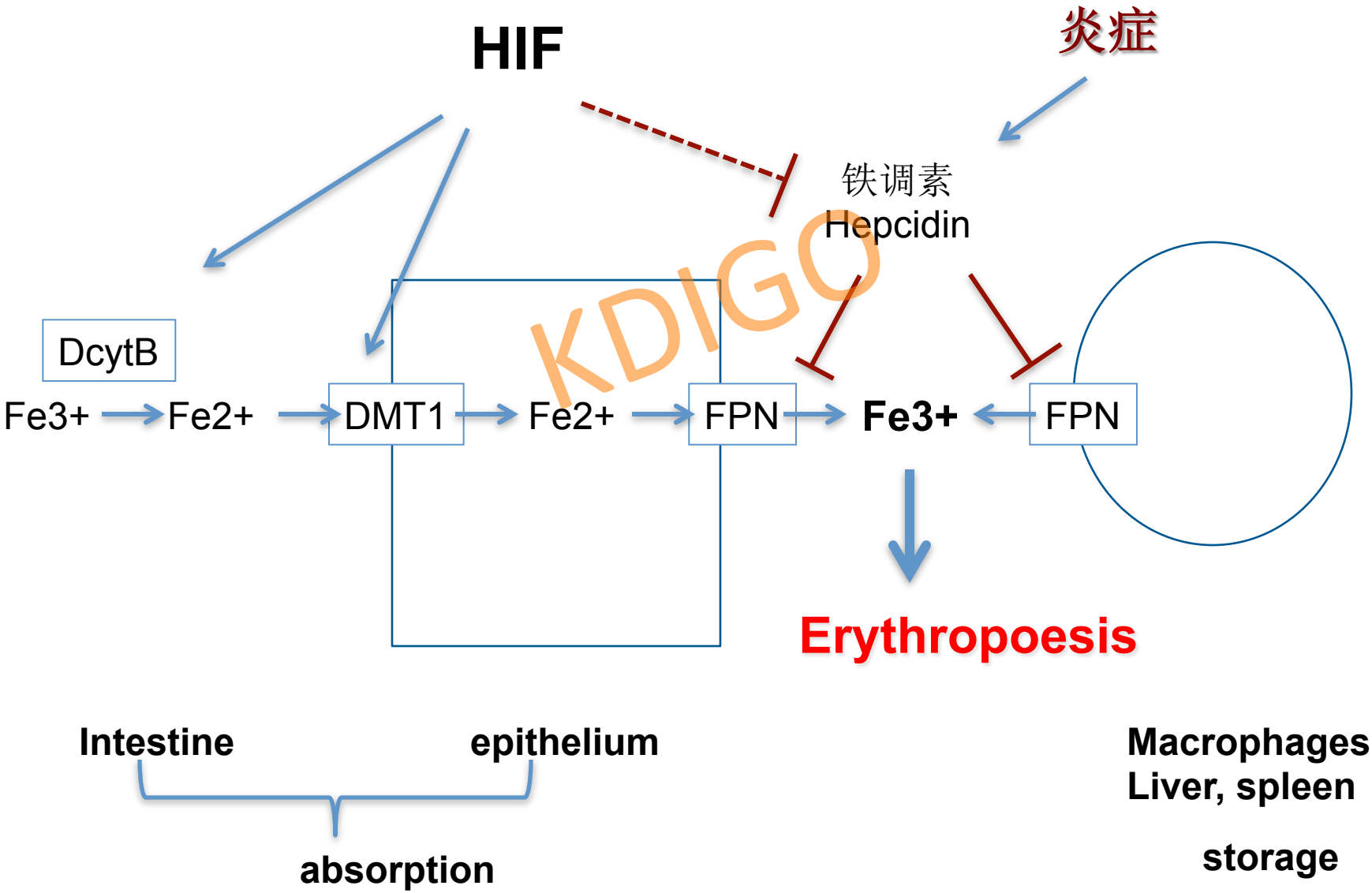
The kidney is the physiologic source of EPO in the adult



Farsijani et al J Clin Invest. doi:10.1172 2016


↓O2
Second messengers
Oncogenes/ Tumour suppressors
Protein interactions
ROS
PHDs
Others (?)
HIF-1β
HIF-α
HRE
Angiogenesis (vegf, TGFβ,...)
Glycolysis (glut-1, pgk1,...)
Erythropoiesis (epo)
Vasodilation/ Respiratory frequency (th, ho-1,...)
O2 Homeostasis

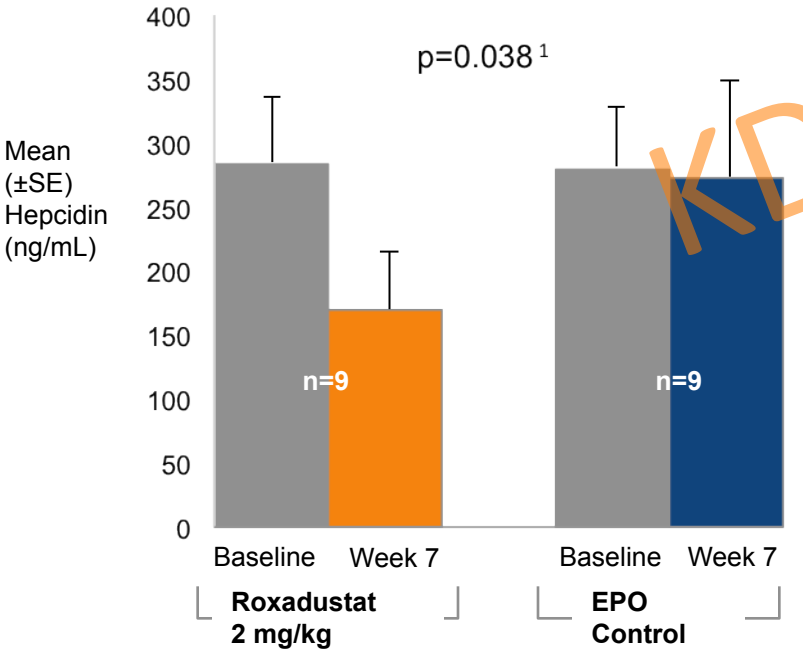
Iron Absorption and Storage



Roxadustat Reduces Hepcidin

Decreased Hepcidin Improves Iron Availability and Reduces ESA Resistance

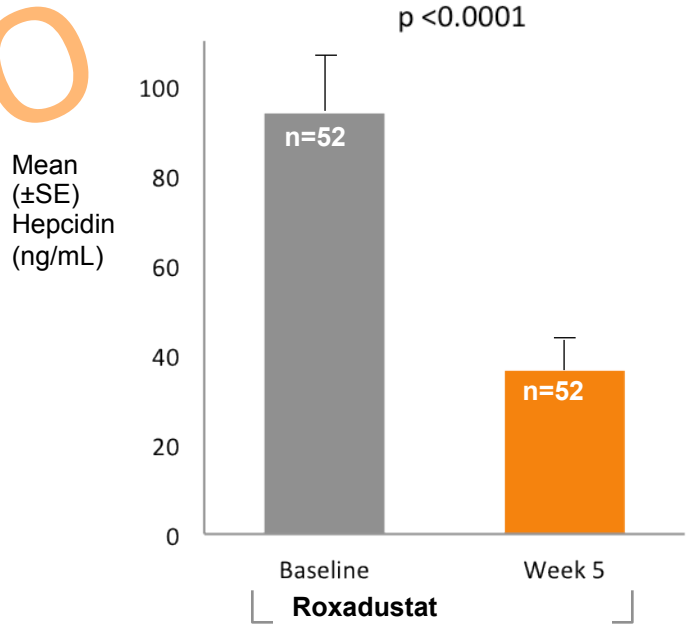
CKD-DD Patients Previously Treated with EPO and Randomized (Study 040a) (Conversion, previously on ESA)



¹ p-value: change in hepcidin level at Week 7 from baseline in roxadustat vs EPO

Source: Provenzano et al. 2016, Clin J Am Soc Nephrol (in press) doi: 10.2215

CKD-DD Newly Initiated Dialysis (Study 053, ESA naive)

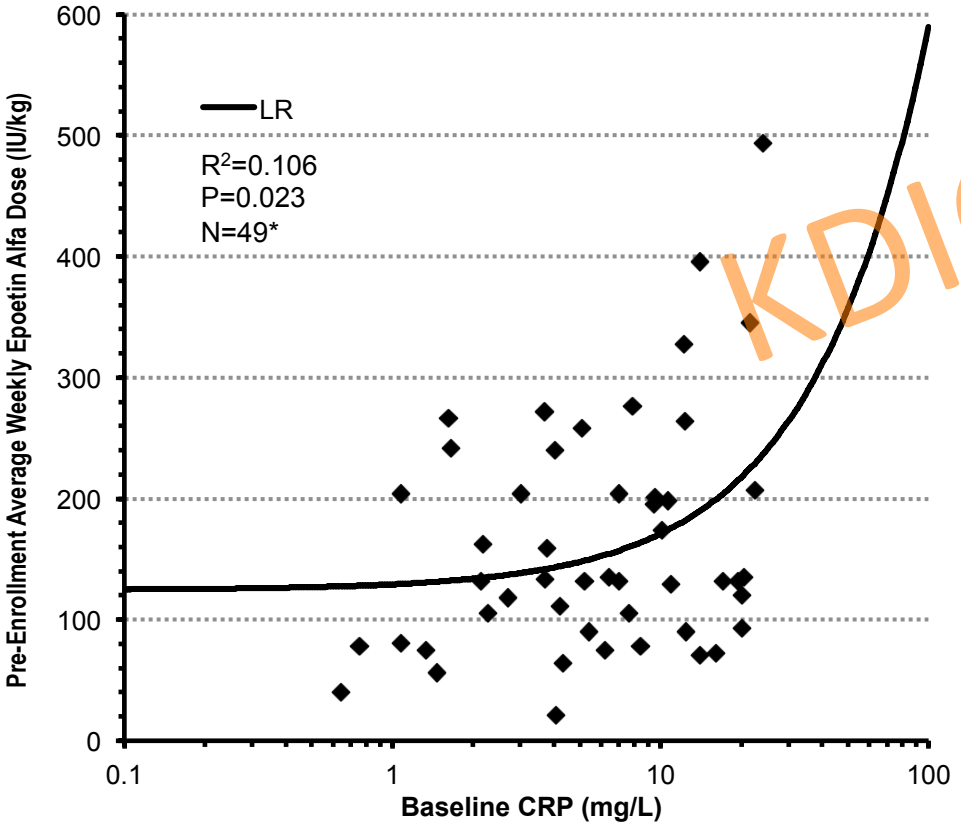


Source: Besarab et al (2016) J Am Soc Nephrol. 27:1225-1233

Higher ESA but NOT Roxadustat Doses Required in Presence of Inflammation

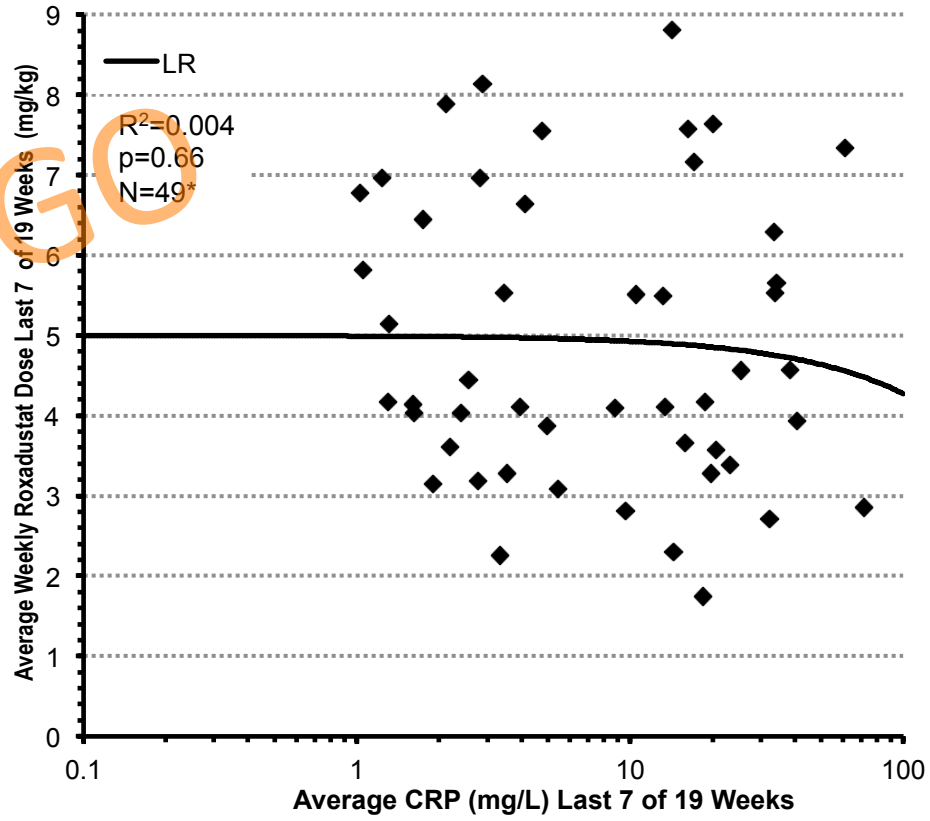
Study 040B: Epoetin Alfa Arm

- EPO dose requirement vs CRP



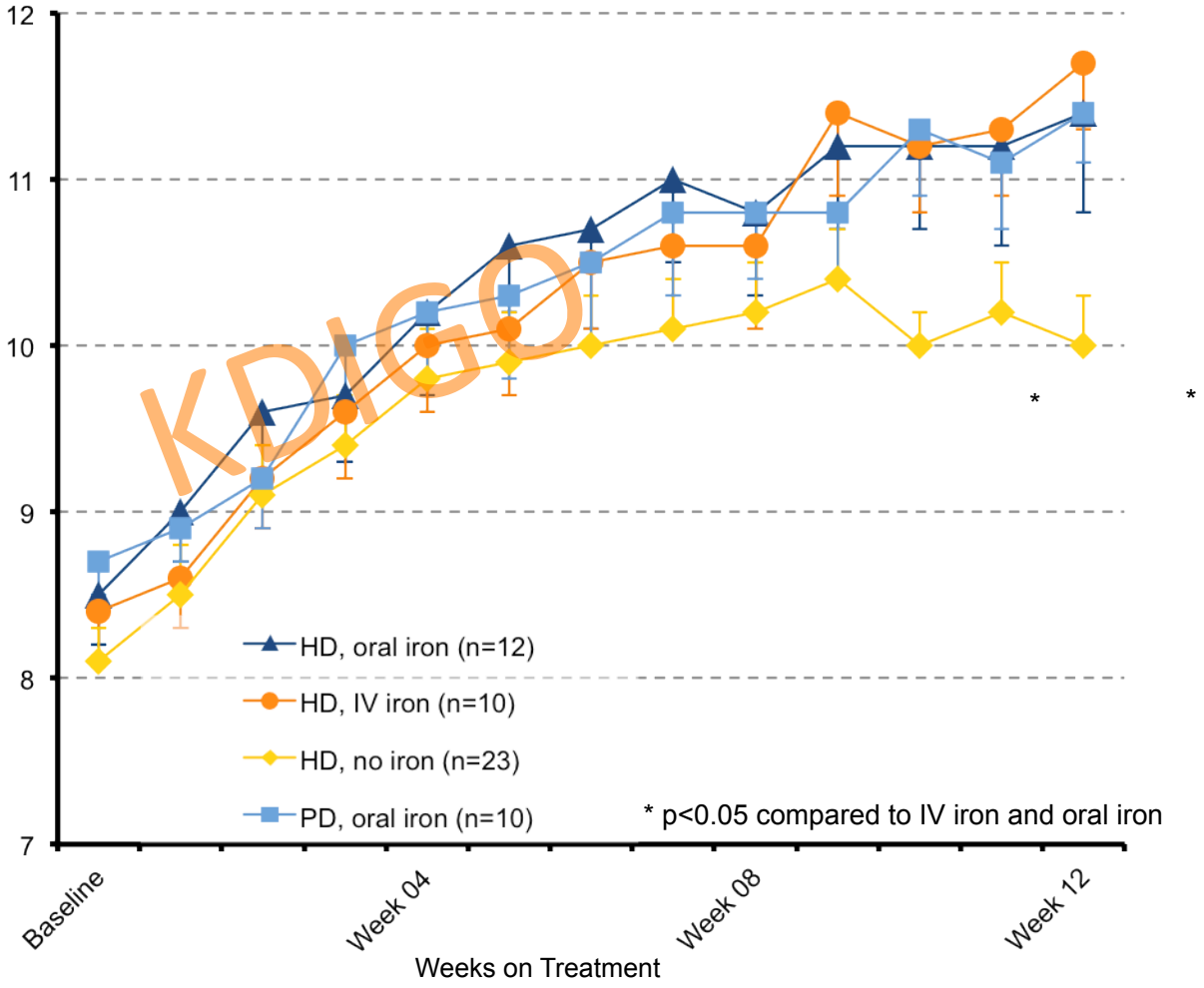
Study 040B: Roxadustat Arm

- Roxa dose requirement vs baseline CRP



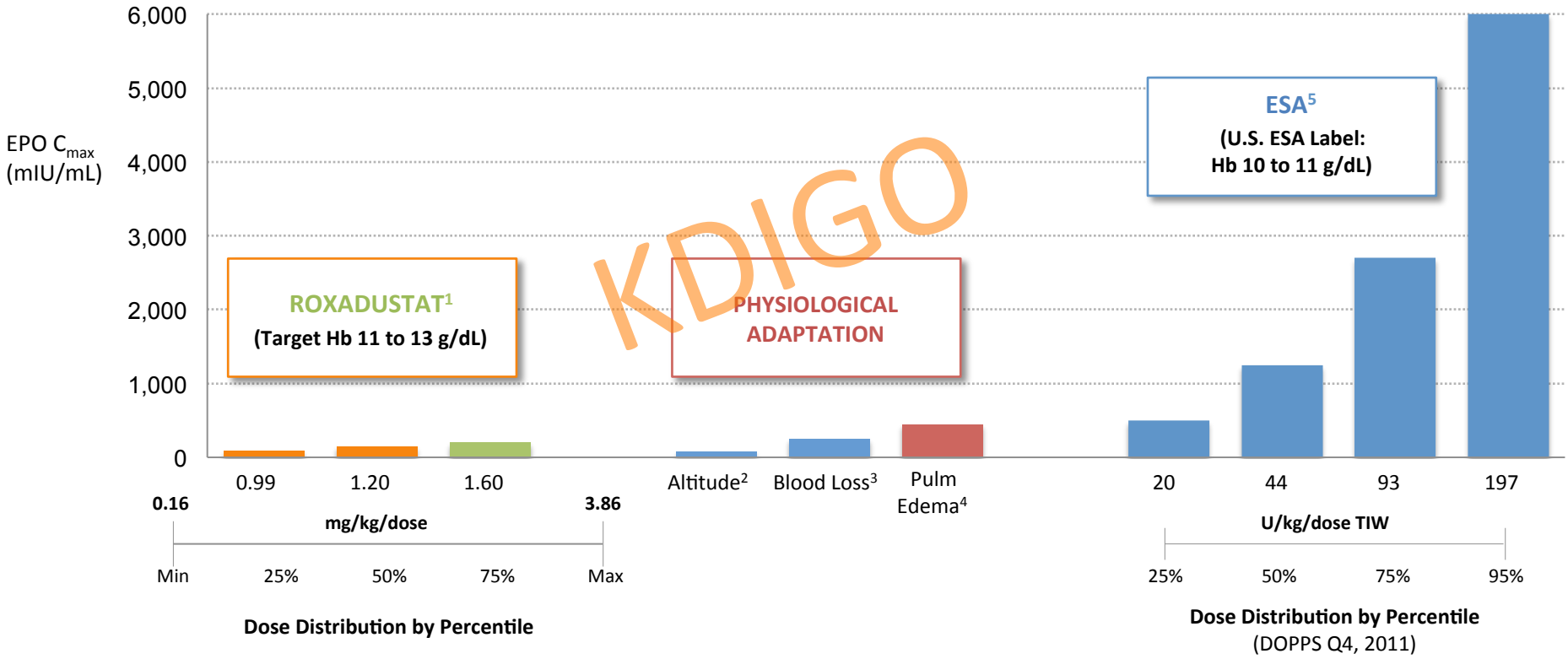
Source: Provenzano et al. 2016, Clin J Am Soc Nephrol (in press) doi: 10.2215

PHI Corrects Anemia in Newly Initiated Dialysis Patients without IV Iron



Source: Besarab et al (2016) J Am Soc Nephrol. 27:1225-1233

PHI Achieves Target Hb within or near Physiologic EPO C_{max} Levels



[1] C_{max} data for roxadustat estimated for a subset of 243 patients who achieved Hb response and were dosed at expected therapeutic doses.
[2] Milledge & Cotes (1985) J Appl Physiol 59:360.
[3] Goldberg et al. (1993), Clin Biochem 26:183, Maeda et al. (1992) Int J Hematol 55:111.
[4] Kato et al. (1994) Ren Fail 16:645.
[5] Based on Flaherty et al. (1990) Clin Pharmacol Ther 47:557.

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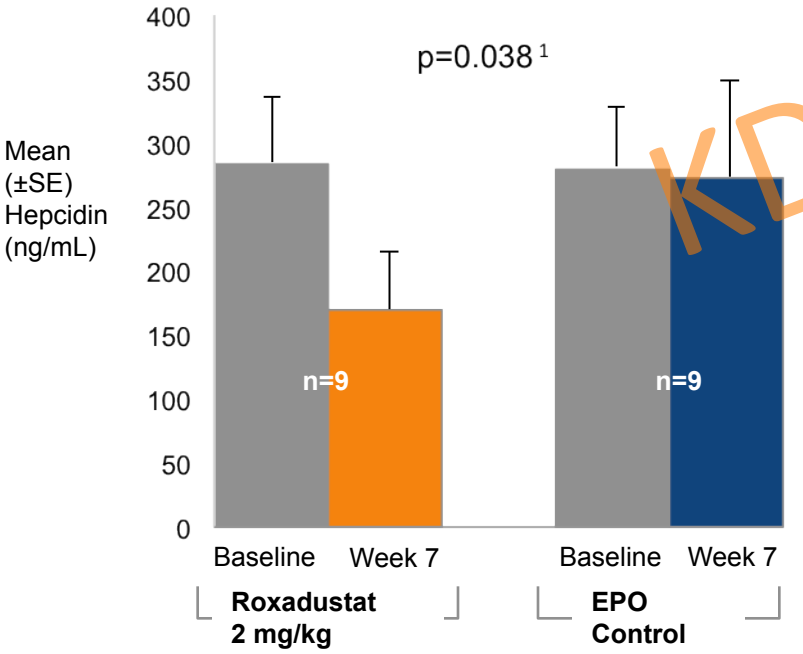

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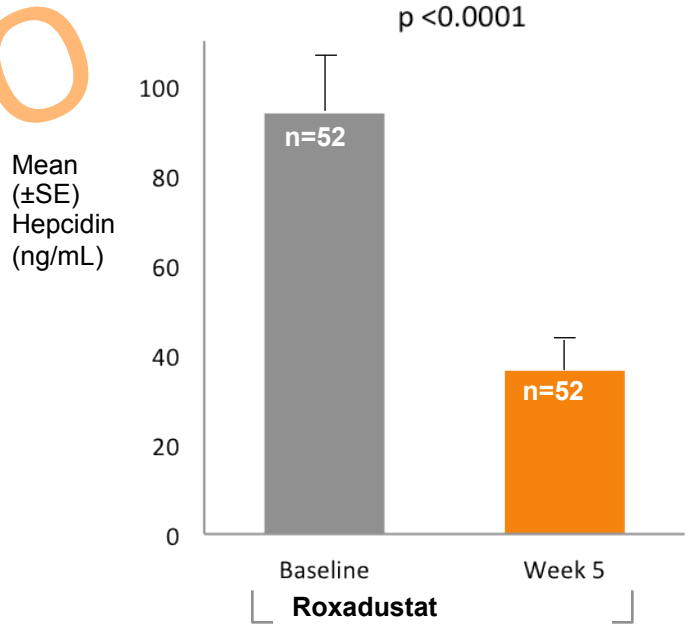

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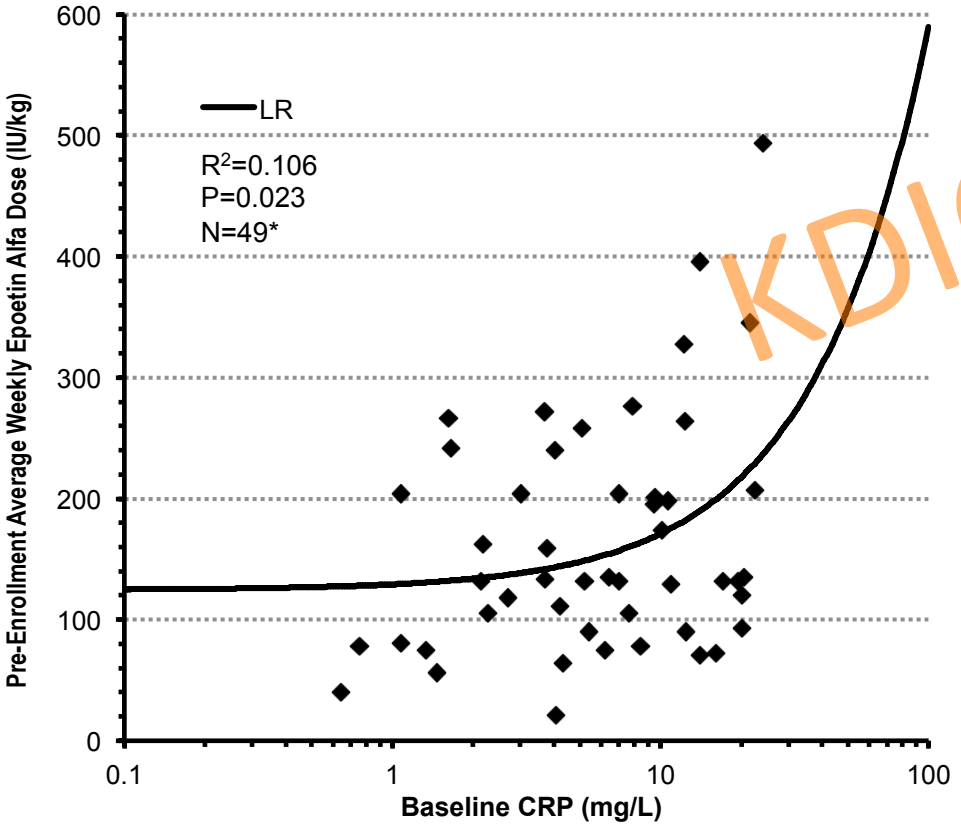
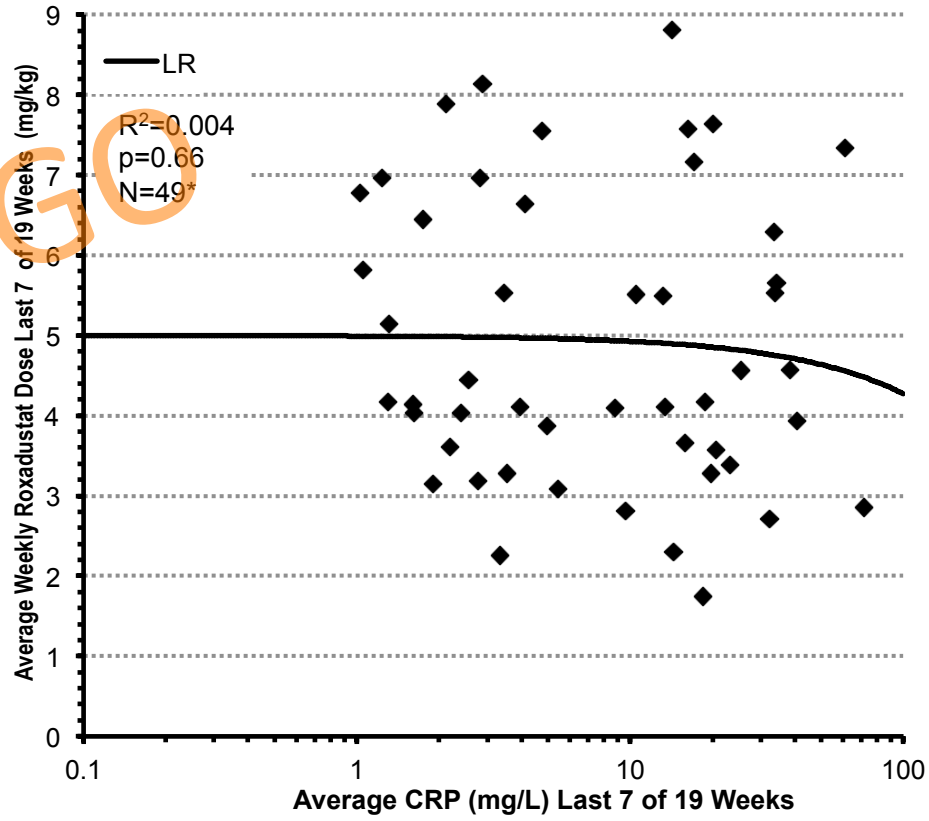
Study 040B: Epoetin Alfa Arm

- EPO dose requirement vs CRP



Study 040B: Roxadustat Arm

- Roxa dose requirement vs baseline CRP



Source: Provenzano et al. 2016, Clin J Am Soc Nephrol (in press) doi: 10.2215

Contents

- Consensus on anemia management in CKD patients in China
- Anemia control in CKD patients in China
- Hepcidin and iron homeostasis in CKD

Thank You for Your Attention