Interplay between iron and inflammatory processes

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Disclosure of Interests

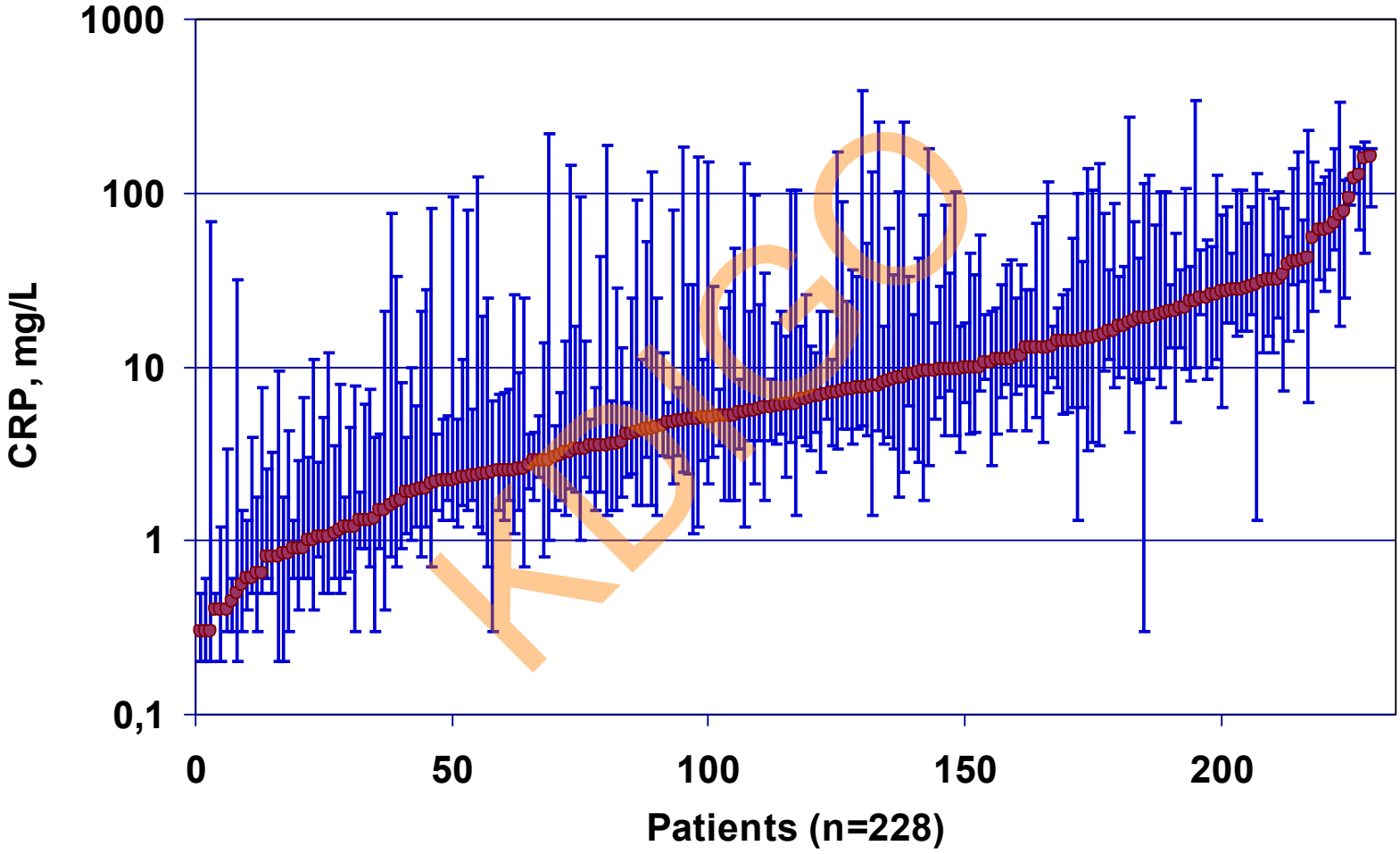
Nothing to declare except participation in several clinical trials of anti-anemic drugs.

My topics

- Inflammation, ESA resistance and functional iron deficiency
- Iron markers
  - Predictors of response to iron?
  - Correlation to inflammation
- Hepcidin and inflammation in CKD
- Associations with mortality in CKD patients
- Treatment with iron

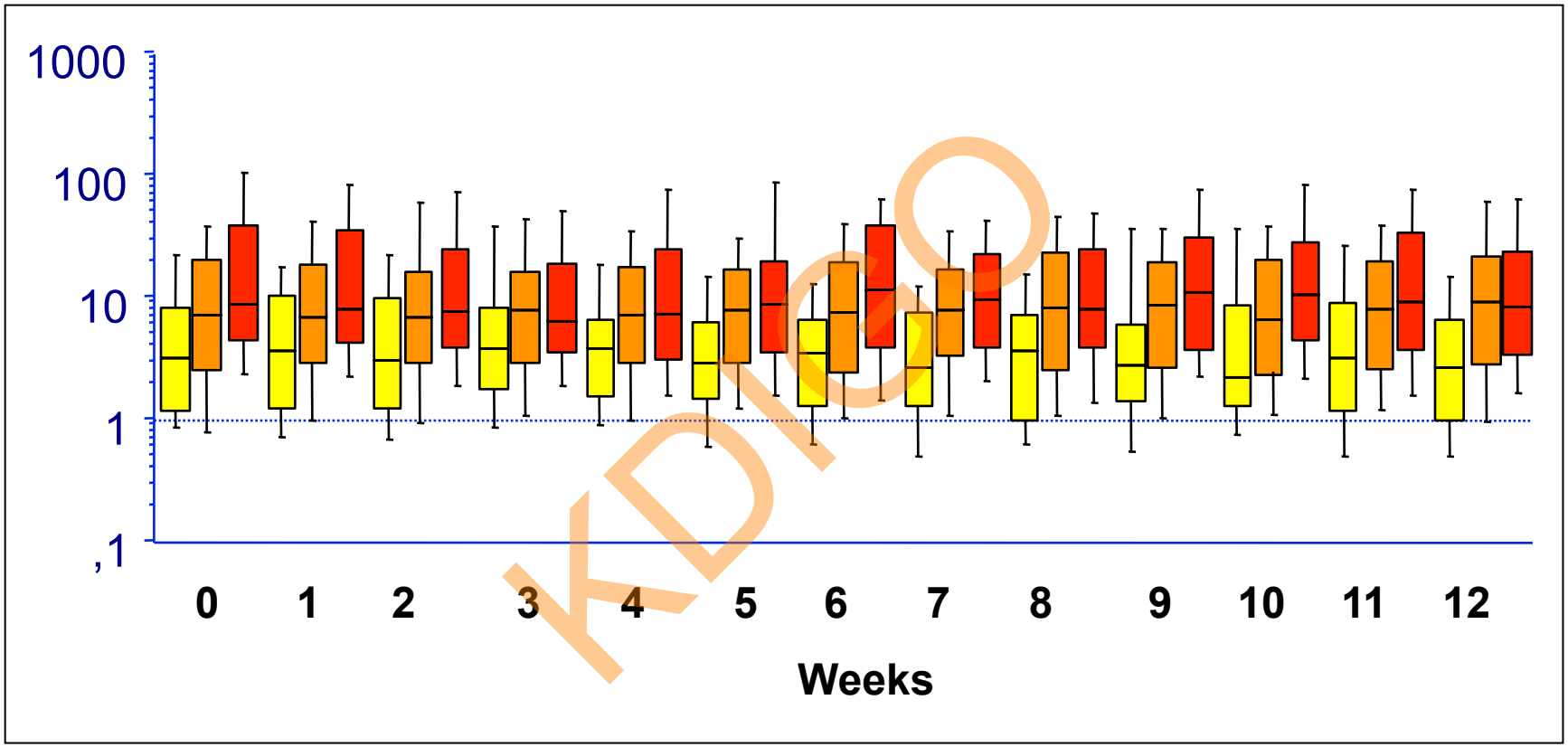
CRP Variation in Hemodialysis Patients Over Three Months

the MIMICK study



Snaedal *et al*. Am J Kidney Dis 2009 Jun;53(6):1024-33

CRP are higher in HD patients with comorbidity



p-value <0.01 all weeks except no 3

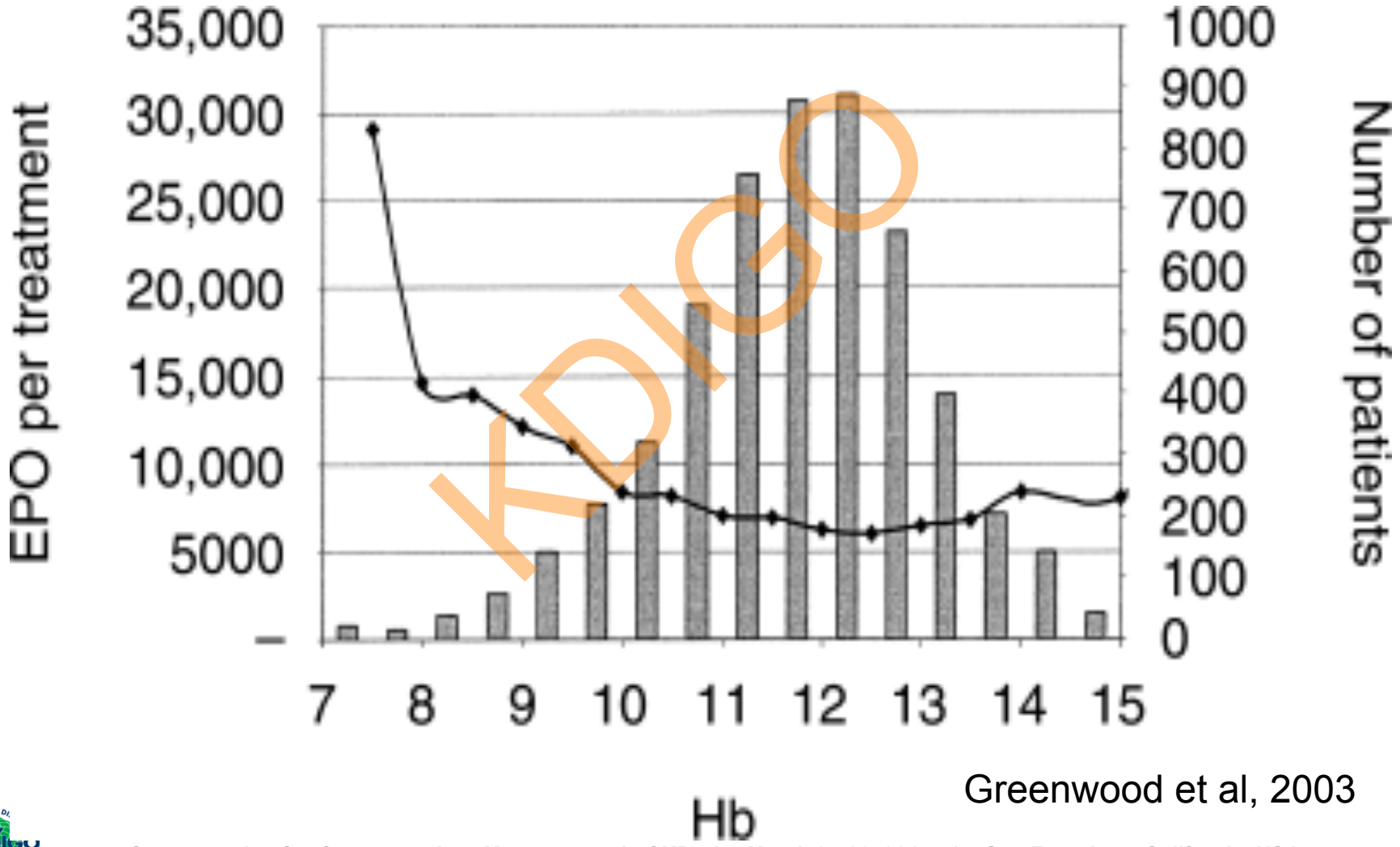
Low risk n=43

Medium risk n=129

High risk n=56

Snaedal *et al*. Am J Kidney Dis 2009 Jun;53(6):1024-33

Anemia in *epoetin-treated* dialysis patients



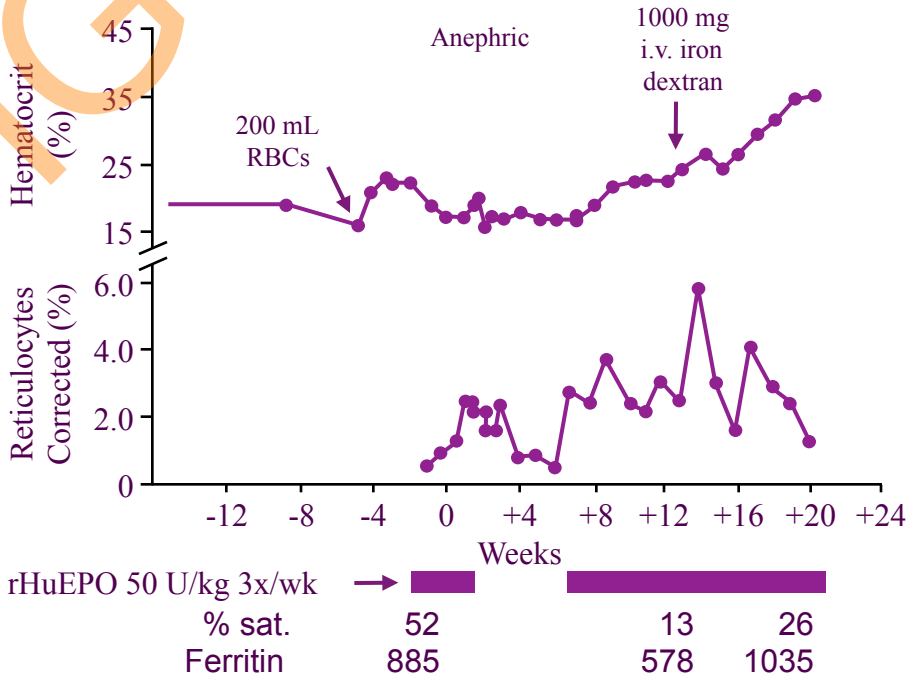
Greenwood et al, 2003

Functional Iron Deficiency Was Described Early in Epoetin-treated CKD5D Patients

- Combined Phase I and II trial data for recombinant human erythropoietin (rHuEPO) in 25 HD patients with anemia
- rHuEPO administration induced a fall in TSAT and serum iron levels

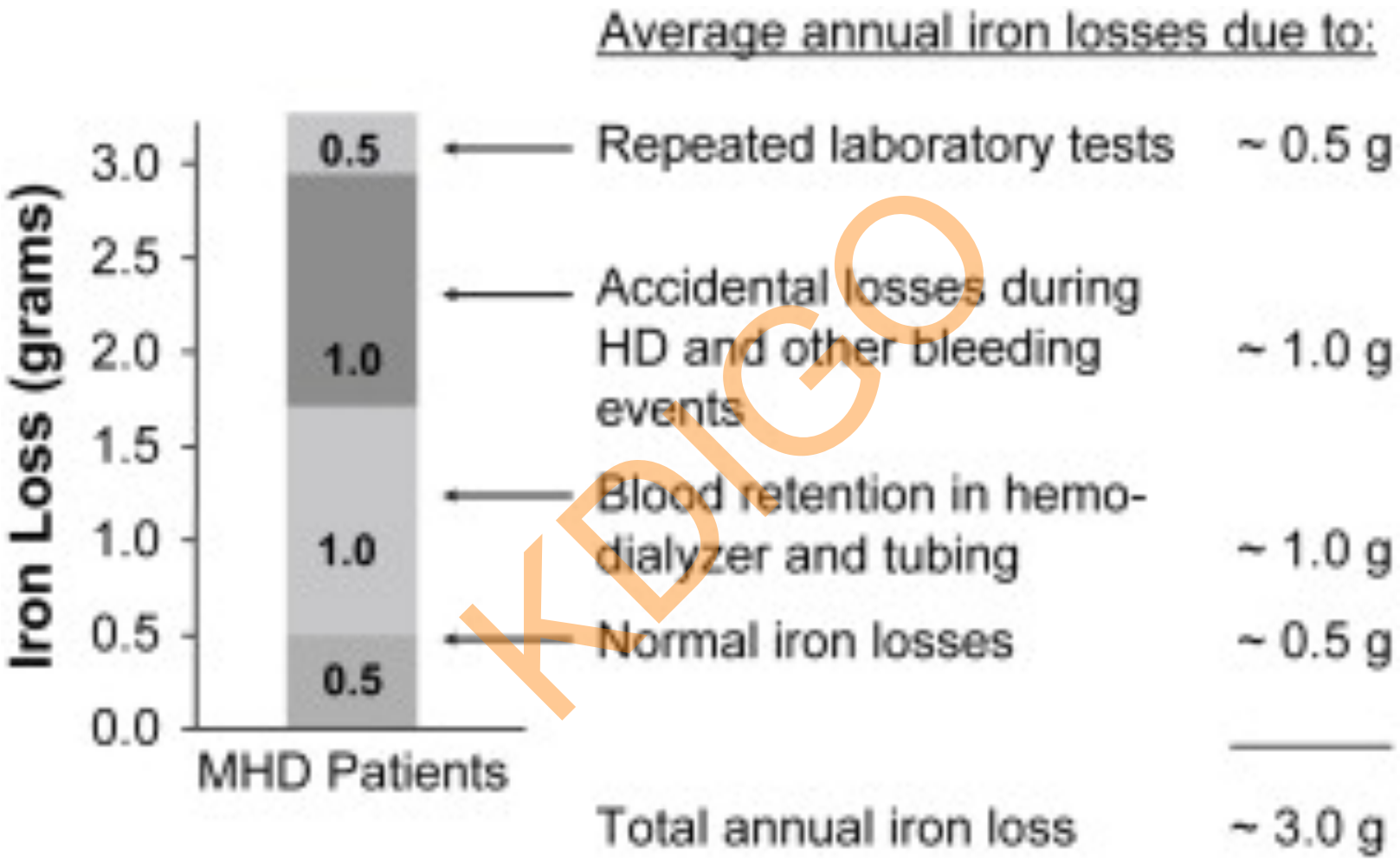
Dr. Joseph Eschbach
1933–2007

'One of the clinical features seen with this form of treatment was a state of functional iron deficiency'



Eschbach JW et al. *N Engl J Med* 1987;316:73–78

Estimated annual loss of iron in hemodialysis patients



Kalantar-Zadeh et al. Advances in Chronic Kidney Disease, Volume 16, Issue 2, 2009, 143 - 151

NECOSAD study

- inadequate EPO response in 3,6 % of the pts:
  - (*1*) hemoglobin less than 9.7g/dL,
  - (*2*) serum ferritin greater than or equal to 200 g/L, and
  - (*3*) EPO dose greater than or equal to 14,000 IU/week.

Table 2. Possible causes[a] for inadequate erythropoietin (EPO) response of selected patients[b] ($N = 57$) /1677, 3,6 %

Causes for inadequate EPO response	Total number of patients
Infection/inflammation	41
Blood loss	16
Hyperparathyroidism/aluminum toxicity	10
Hemoglobinopathy	2
Folate/vitamin B_{12} deficiency	1
Multiple myeloma/myelofibrosis/ myelodysplastic syndrome	6
Malnutrition	5
Hemolysis	0
Inadequate dialysis	2
Pure red cell aplasia	1
Malignancy	7
Graft/shunt problems	14
Operation	8
Suspected noncompliance	9
Medication (≥bone marrow suppress)	4
Unknown	2

[a] Adjusted according to the categorization of the National Kidney Foundatio Dialysis Outcome and Quality Investigation (2002).

[b] Some patients fall in more than one category (i.e., there is more than or possible cause for their inadequate EPO response).

Kidney Int. 2005 Sep;68(3):1215-22. Kharagjitsingh AV, et al; NECOSAD Study Group.

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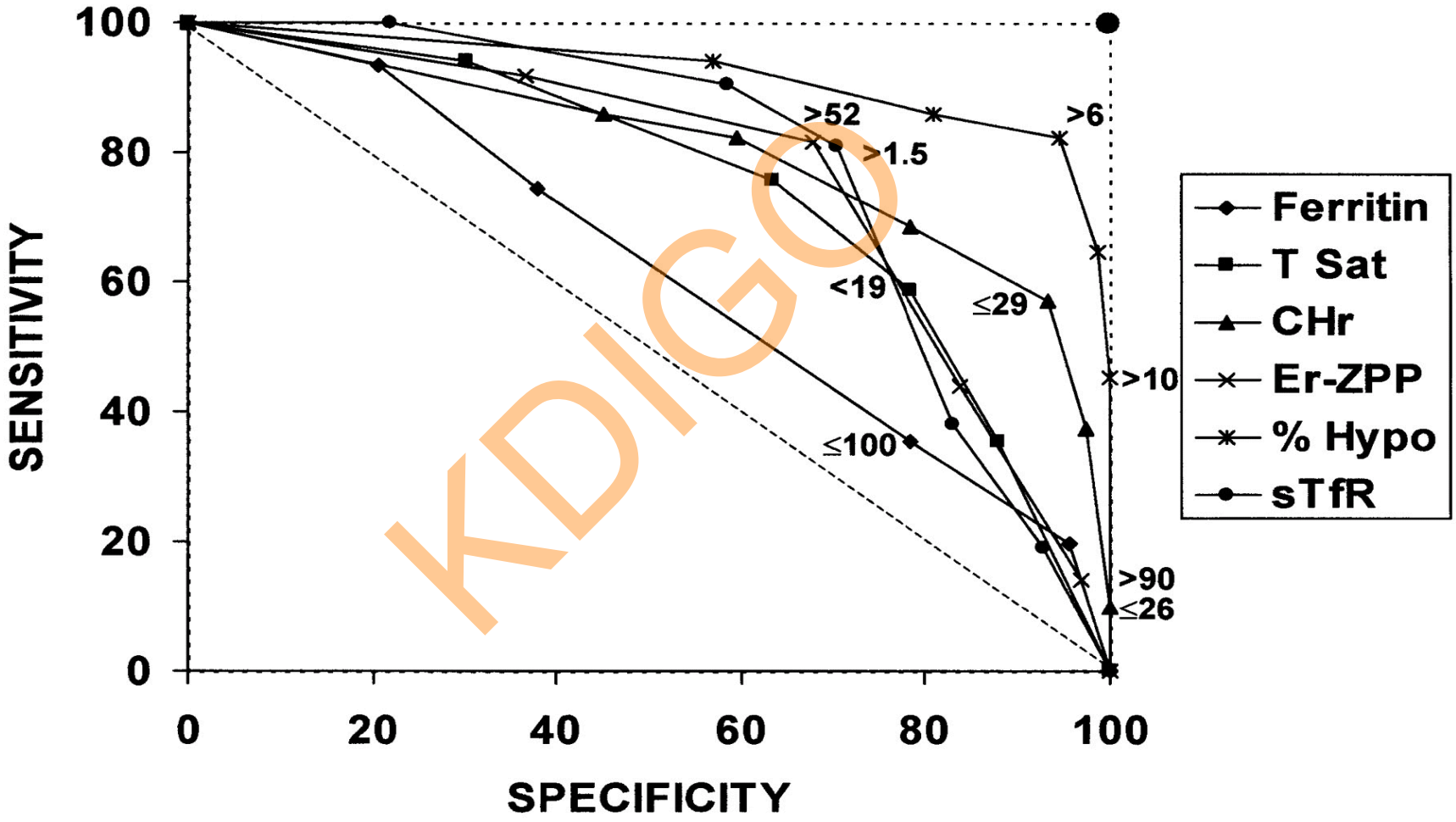
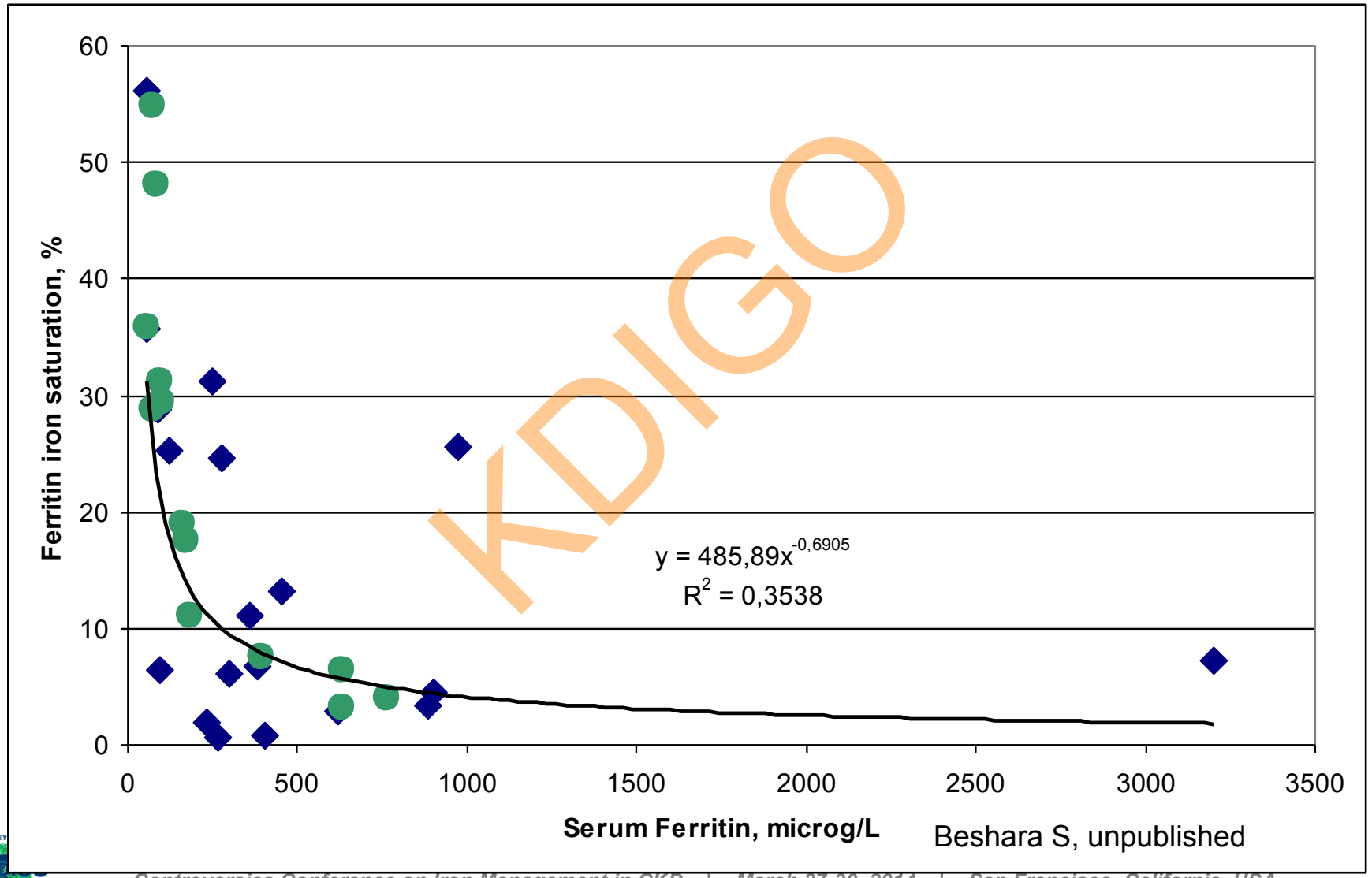
Poor prediction of ESA response by iron markers



Tessitore et al. Nephrol Dial Transplant. 2001 Jul;16(7):1416-23.

Ferritin iron content (%) in CKD 2-5 patients (green) and dialysis patients (blue).



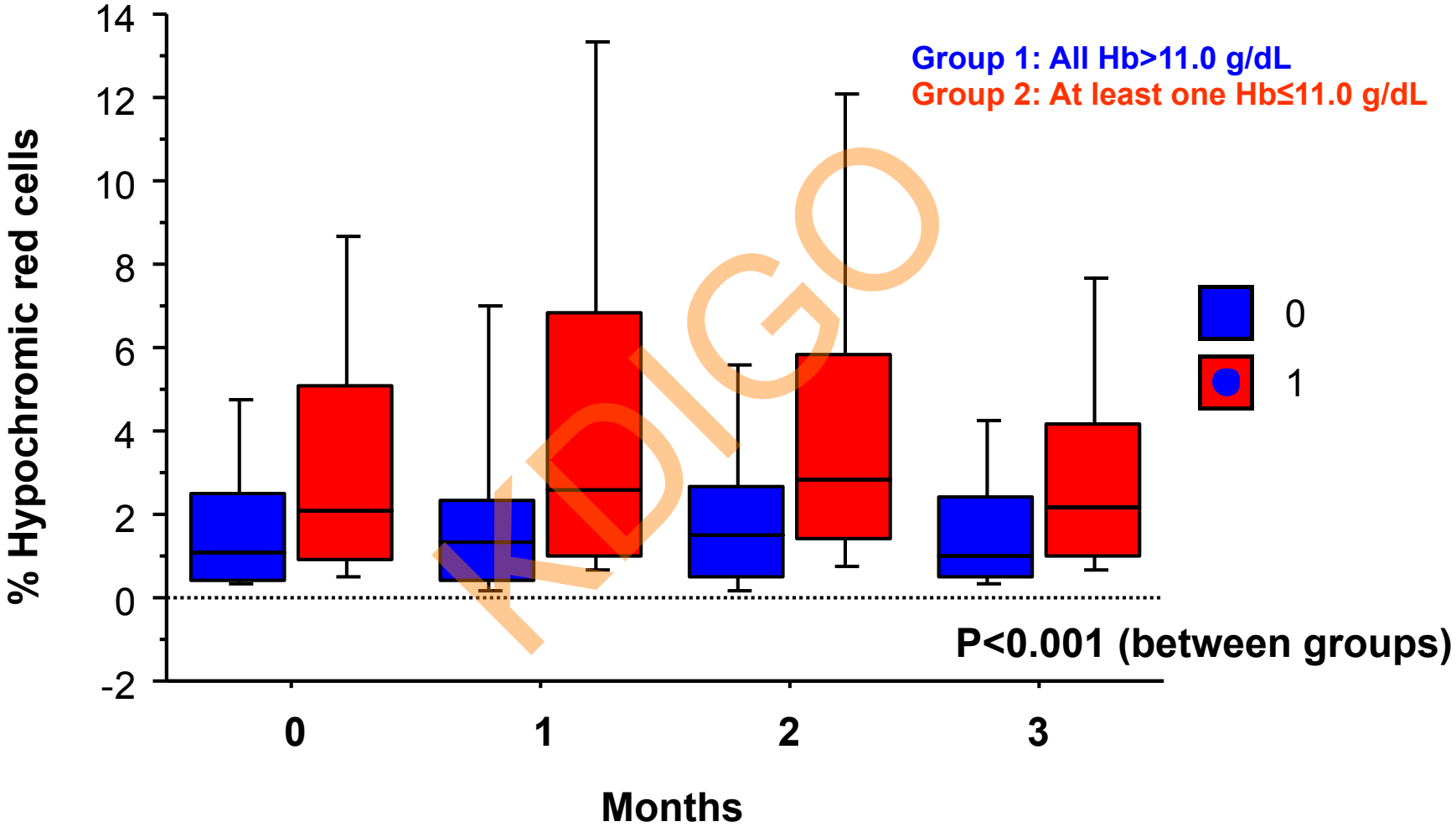
Biomarkers for Assessing and Managing Iron Deficiency Anemia in Late-Stage Chronic Kidney Disease

- …all currently available laboratory biomarkers of iron status (either newer or classical markers) do not have an ideal predictive ability when used singly to determine iron deficiency as defined by a response to iron challenge test.
- … there is insufficient evidence to determine the test performance of the combinations of newer biomarkers, or combinations of newer and classical biomarkers, for diagnosing iron deficiency.
- …it may be that CHr and %HYPO have better predictive ability for a response to IV iron treatment than classical markers (TSAT <20 or ferritin <100 ng/mL) in HD CKD patients.

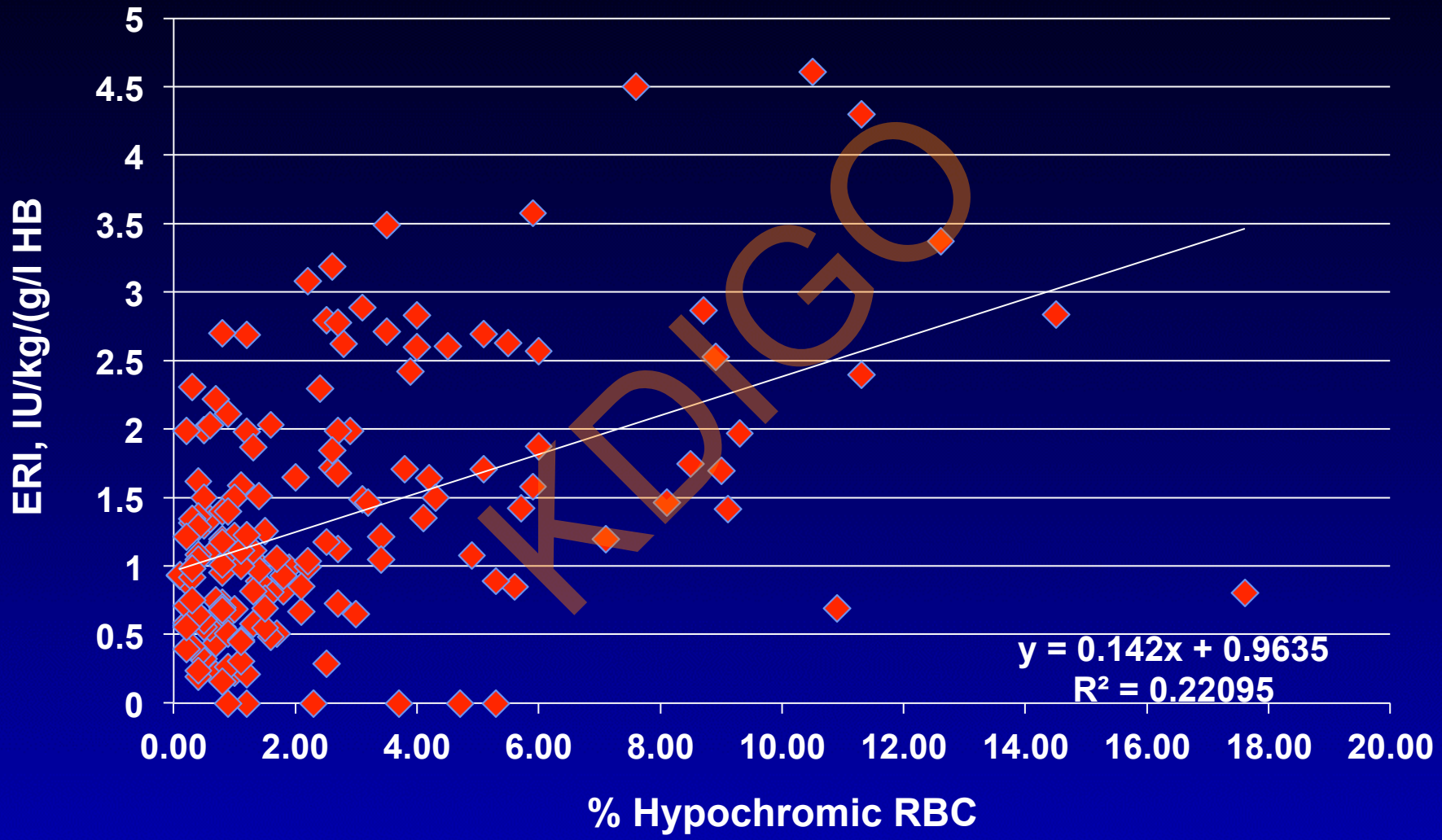
Chung M, et al. Comparative Effectiveness Review No. 83. Prepared by the Tufts Evidence-based Practice Center

Hemoglobin Groups and Hypochromic Red Cells

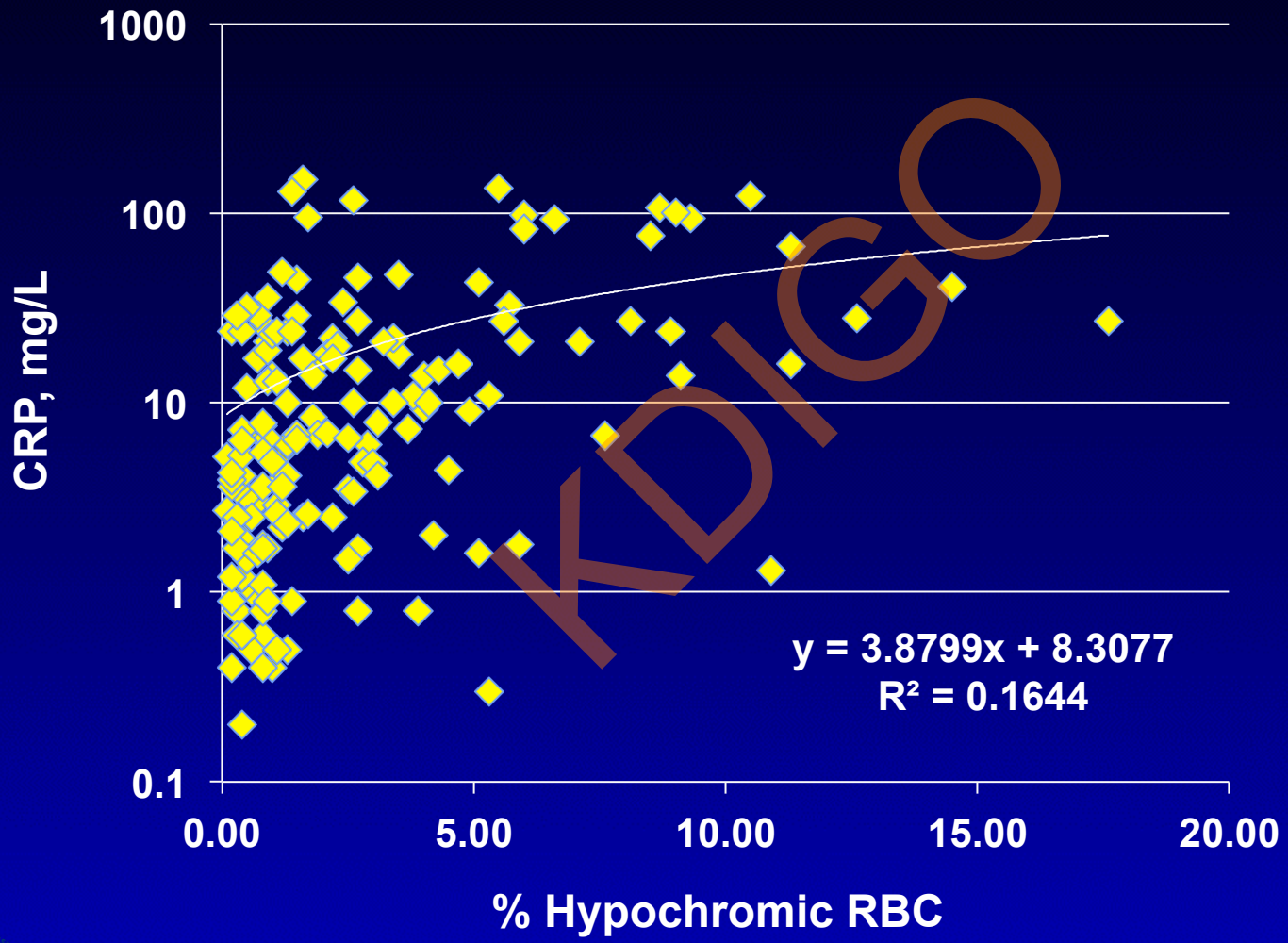
the MIMICK study (unpublished)



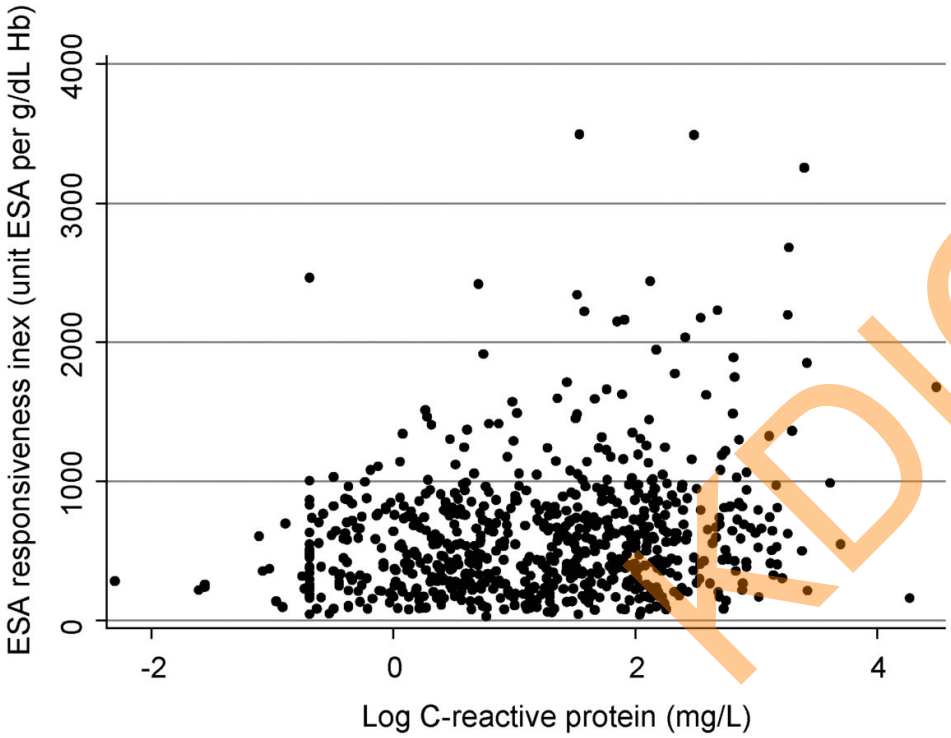
Relationship hypochromic RBC – ESA resistance in HD patients

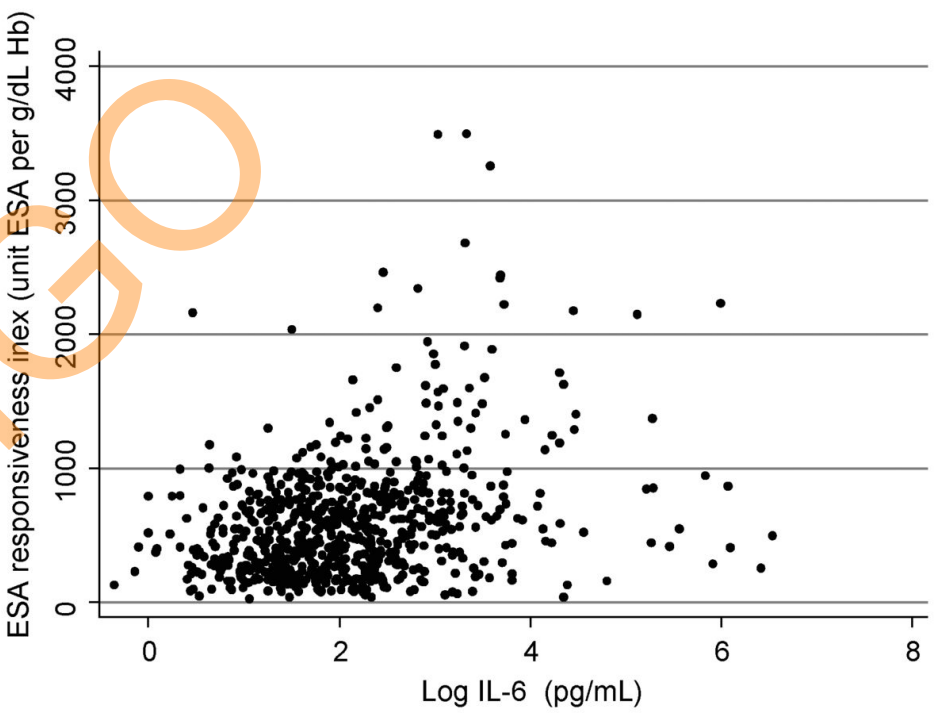


Relationship hypochromic RBC – CRP in HD patients



Association between two inflammatory markers (CRP, IL-6) and epoetin resistance in 754 hemodialysis patients.





Rattanasompattikul M et al. Nephrol. Dial. Transplant. 2013;28:1936-1945

My topics

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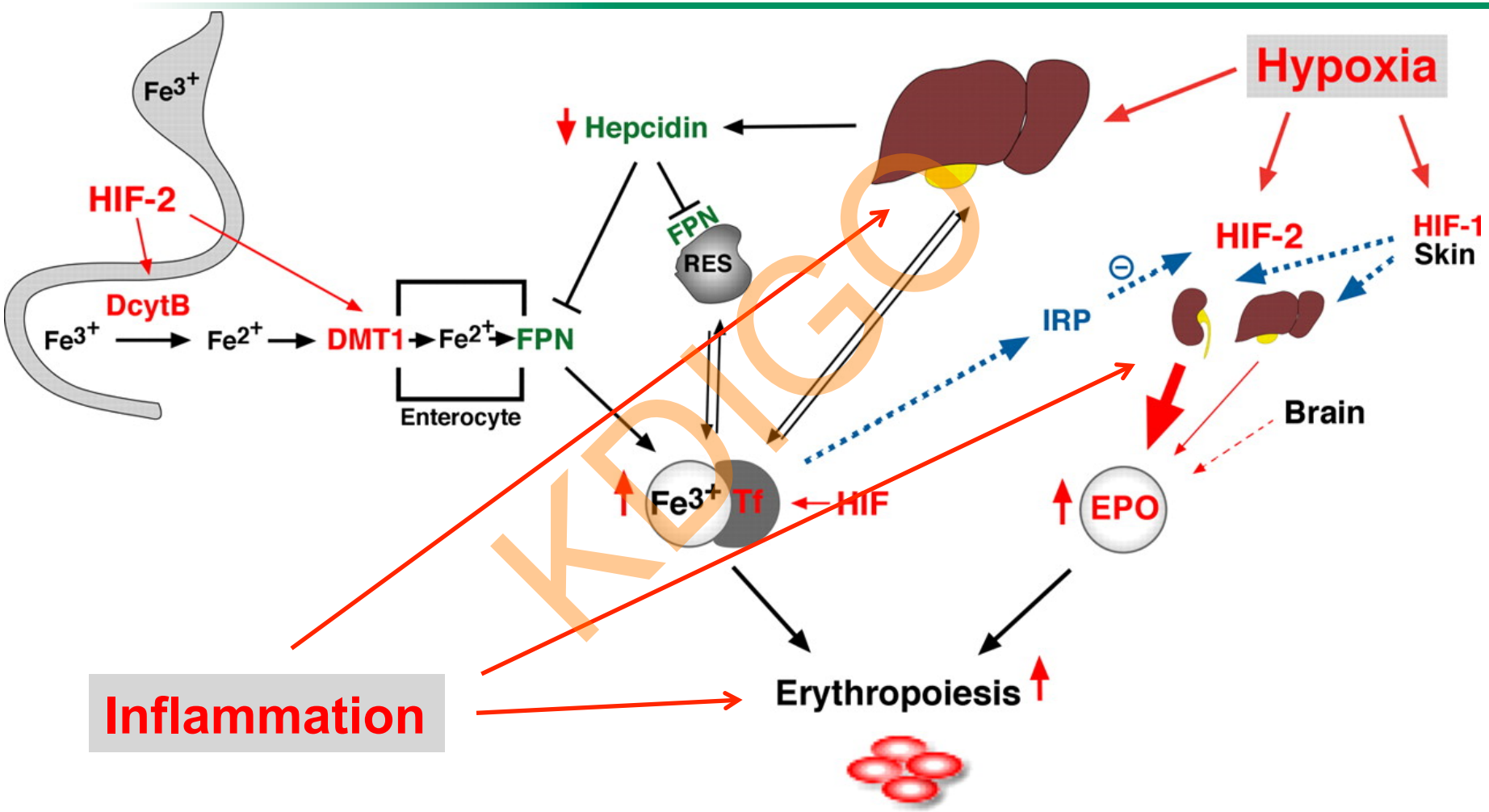
Systemic Inflammation – Effects on Erythropoiesis

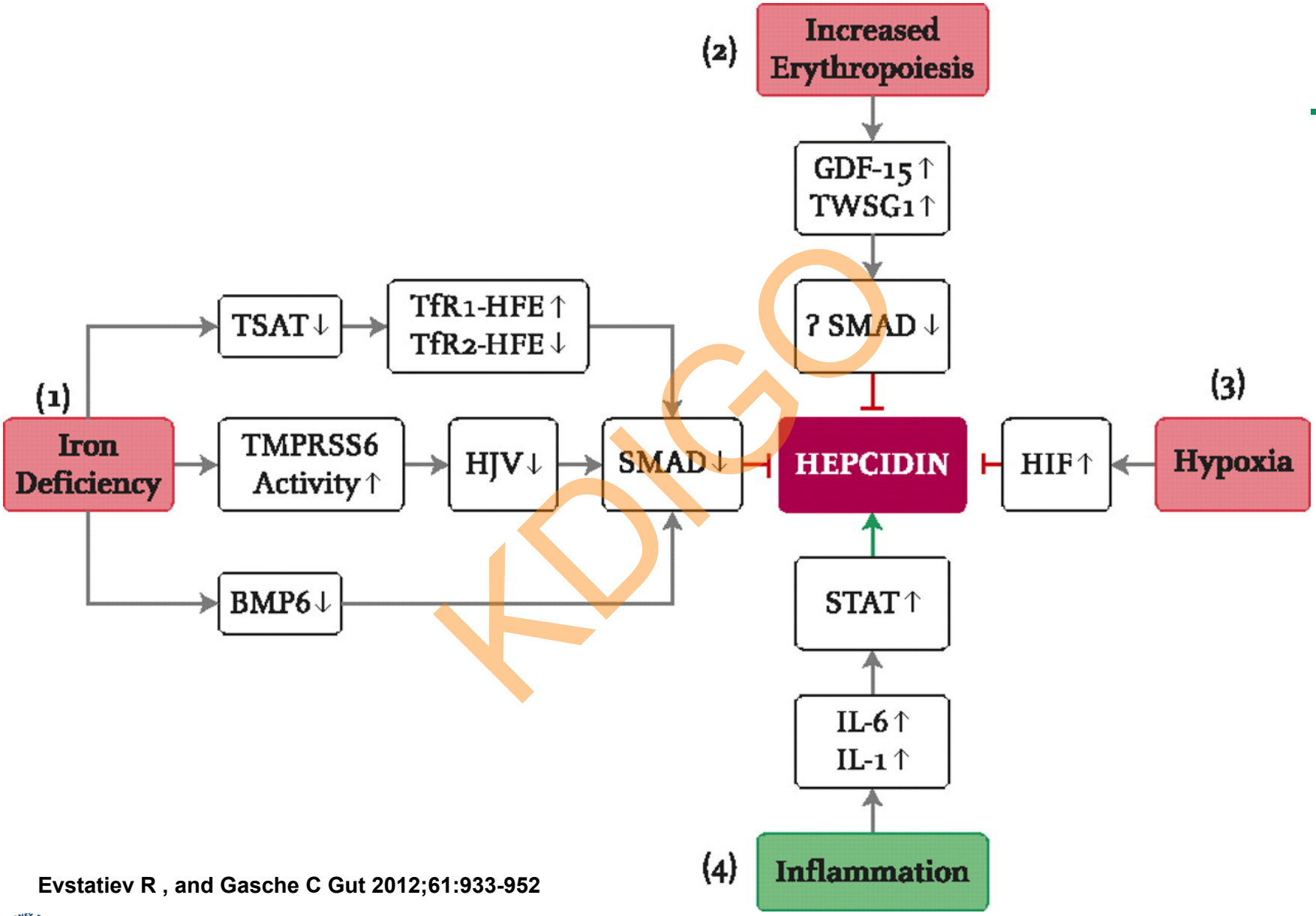
- Decreased endogenous erythropoietin production
- Suppression of erythropoiesis
  - decreased erythropoietin sensitivity
- Shortened erythrocyte survival
- Impaired iron utilization

Hypoxia and inflammation interplay: coordinates EPO synthesis with iron metabolism.



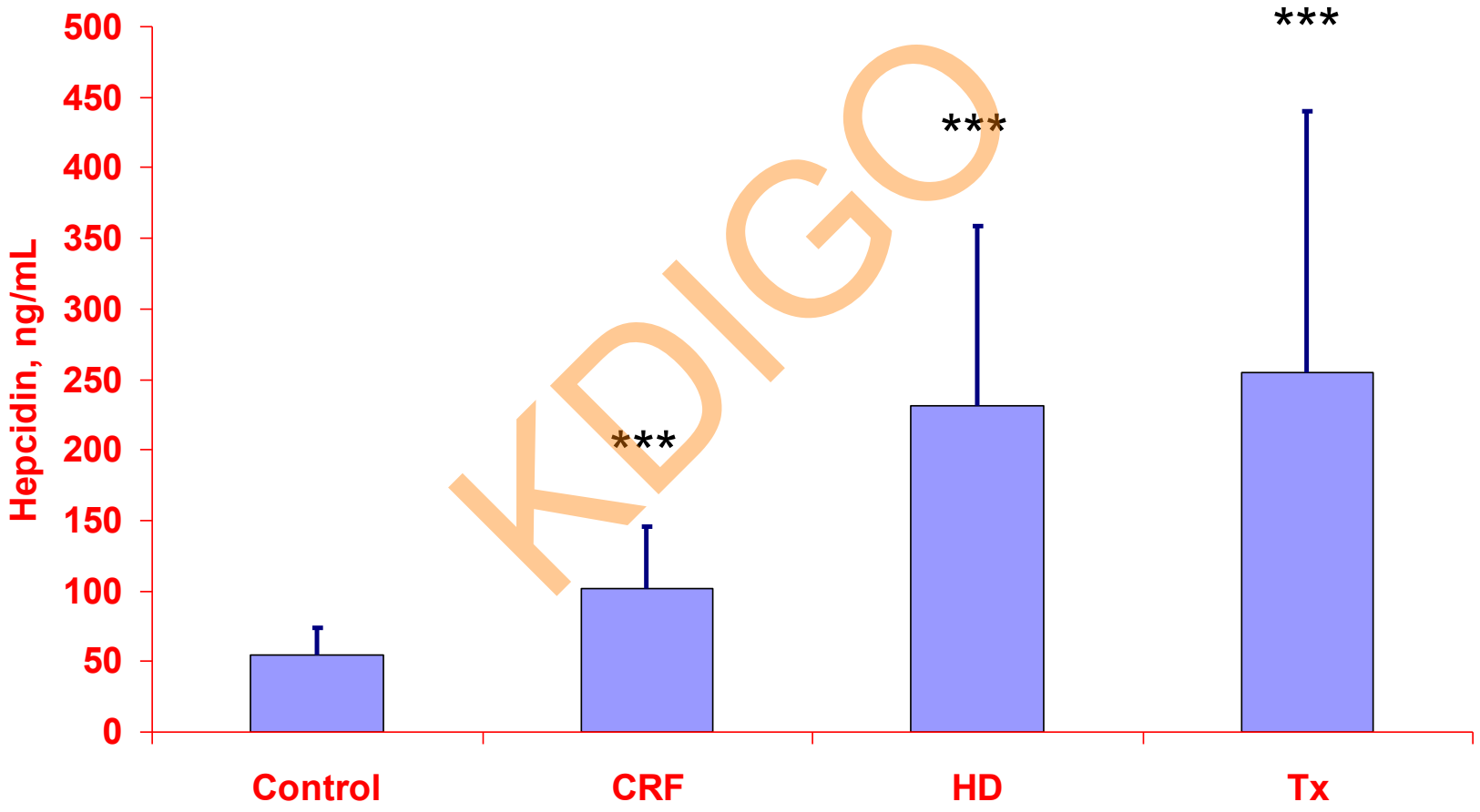
Modified from Haase V H Am J Physiol Renal Physiol 2010;299:F1-F13

Regulation of hepcidin synthesis.

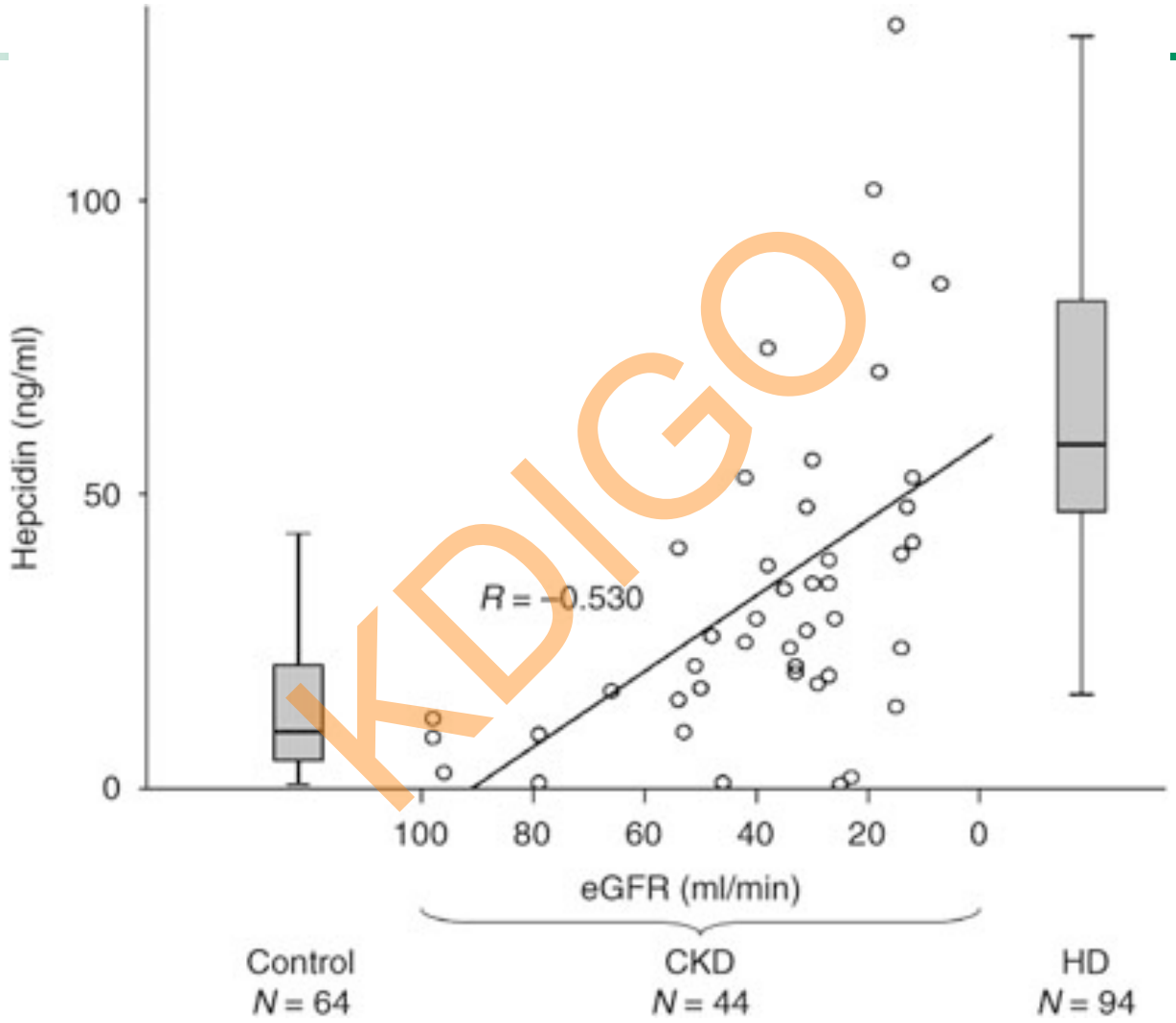


Evstatiev R , and Gasche C Gut 2012;61:933-952

Hepcidin levels in CKD patients

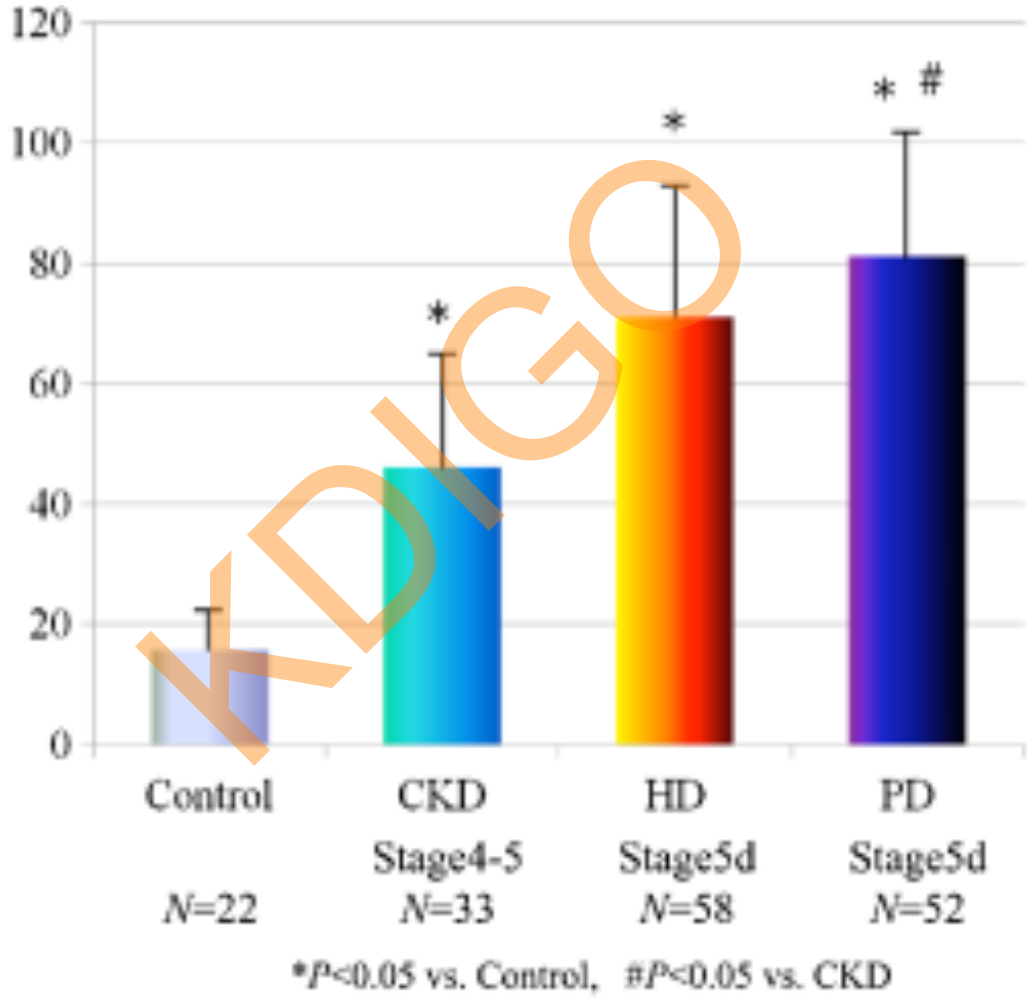


Malyszko et al. Am. J. Hematol. 81:832–837, 2006

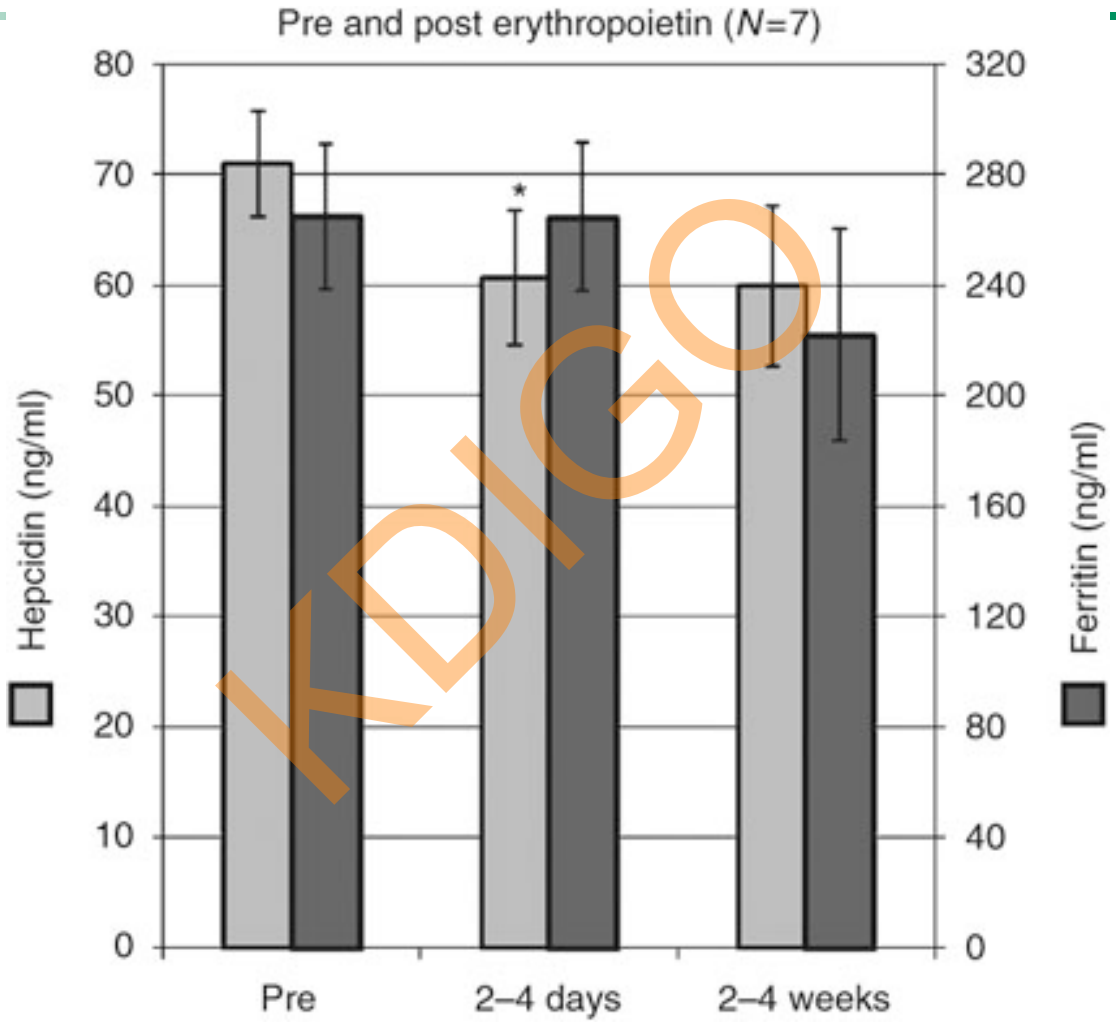


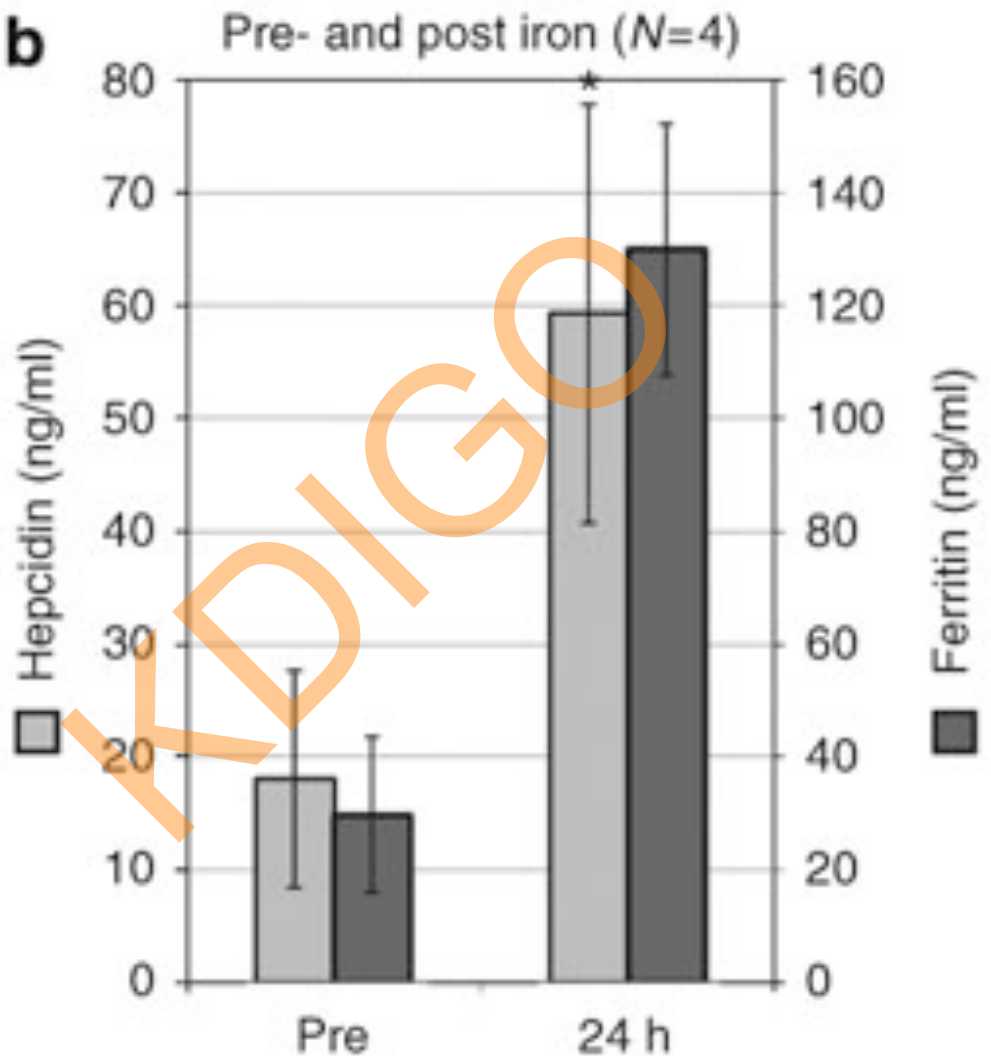
Ashby et al. *Kidney International*. 2009;75(9):976–981.

Serum hepcidin-25 levels in healthy controls and chronic kidney disease (CKD) patients



Tsuchiya and Nitta. **Therapeutic Apheresis and Dialysis** Volume 17, Issue 1, pages 1-8,


Pre and post erythropoietin (N=7)
Hepcidin (ng/ml)
Ferritin (ng/ml)
80
70
60
50
40
30
20
10
0
320
280
240
200
160
120
80
40
0
*
Pre
2–4 days
2–4 weeks



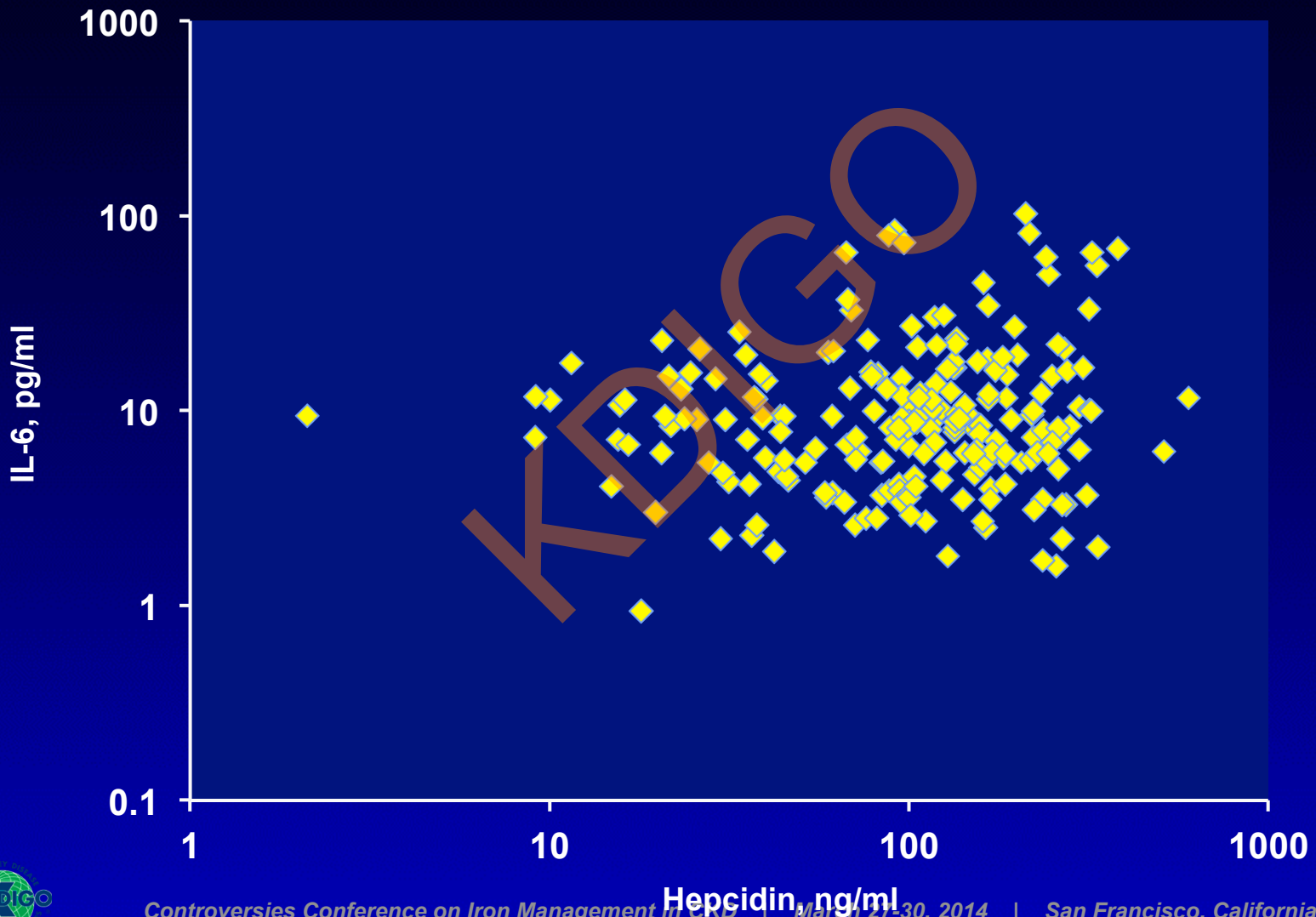
Ashby et al. *Kidney International*. 2009;75(9):976–981.

Anemia and inflammatory variables according to hepcidin tertile groups

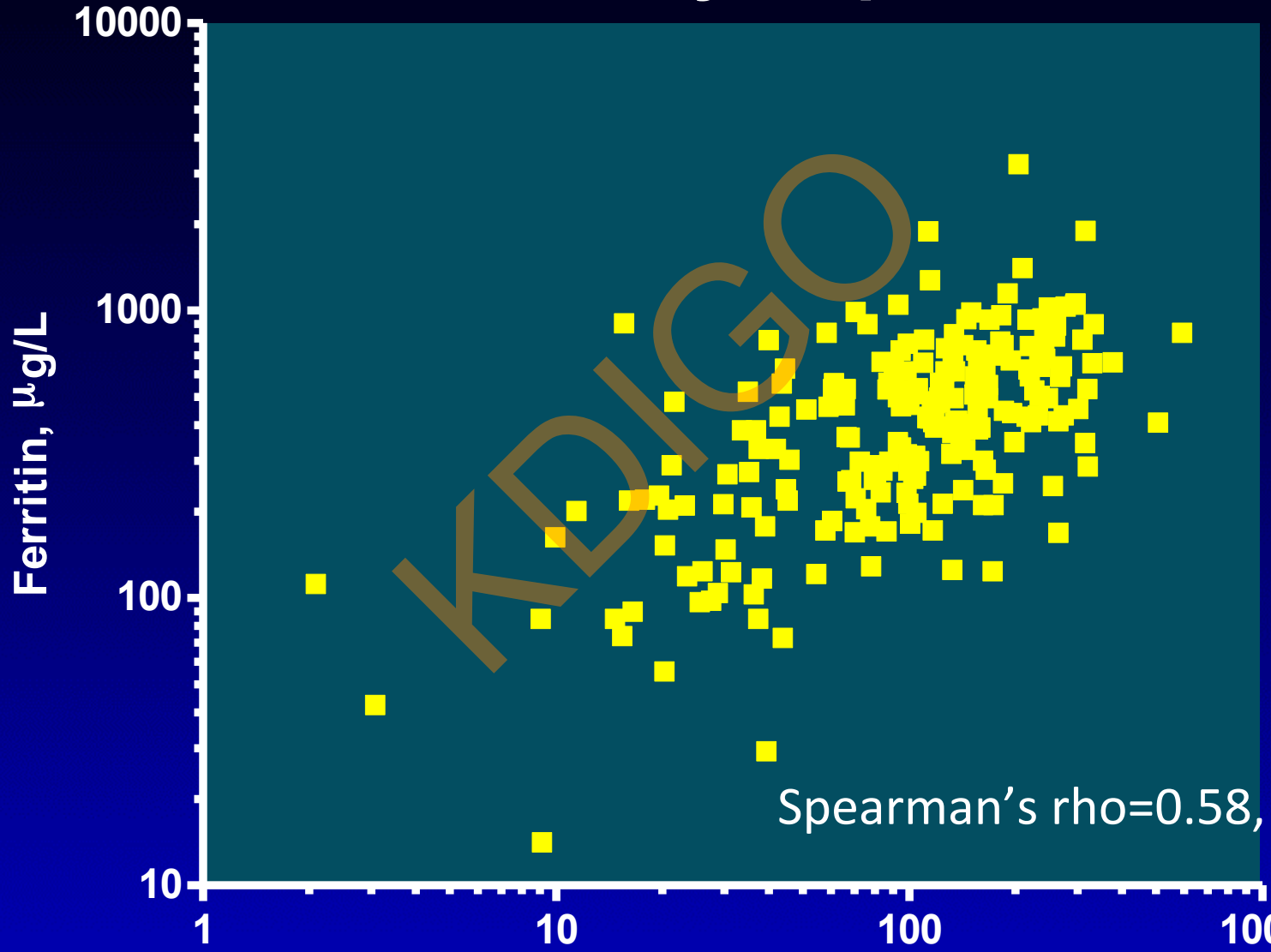
	Tertile 1	Tertile 2	Tertile 3	p
Hep, ng/ml	38 (22-61)	110 (96-129)	221 (170-267)	
Hb, g/dL	11.9 (10.9-12.7)	11.8 (11.0-12.7)	12.0 (11.3-12.7)	0.7
Ferritin, g/L	216 (120-380)	422 (296-610)	630 (427-834)	<0.001
Hypochromic RBC, %	1.6 (0.75-4.1)	1.1 (0.5-2.7)	1.3 (0.8-4.0)	0.12
CRP, mg/L	6.4 (2-18)	6.3 (2.6-19)	7.4 (3.0-24.3)	0.5
IL-6, pg/ml	8.7 (4.7-14.5)	8.8 (5.5-25.7)	8.2 (5.5-47.7)	0.8
ESA, IU/kg per week	168(106-240)	119, (71-265)	121 (78-209)	<0.05

MIMICK study, ASN poster 2011

Relationship p-hepcidin – IL-6 in hemodialysis patients

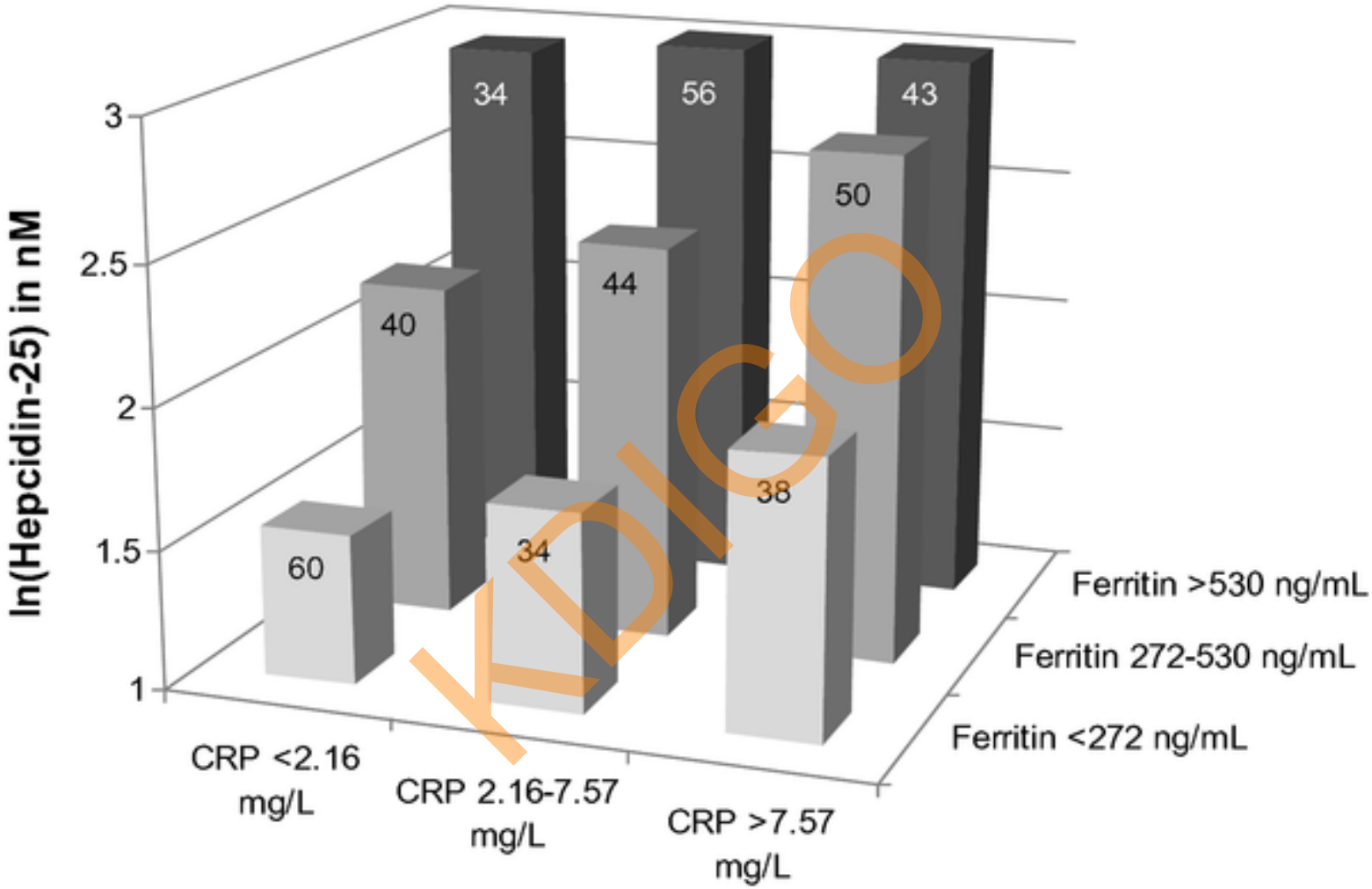


Relationship p-hepcidin – p-ferritin in hemodialysis patients



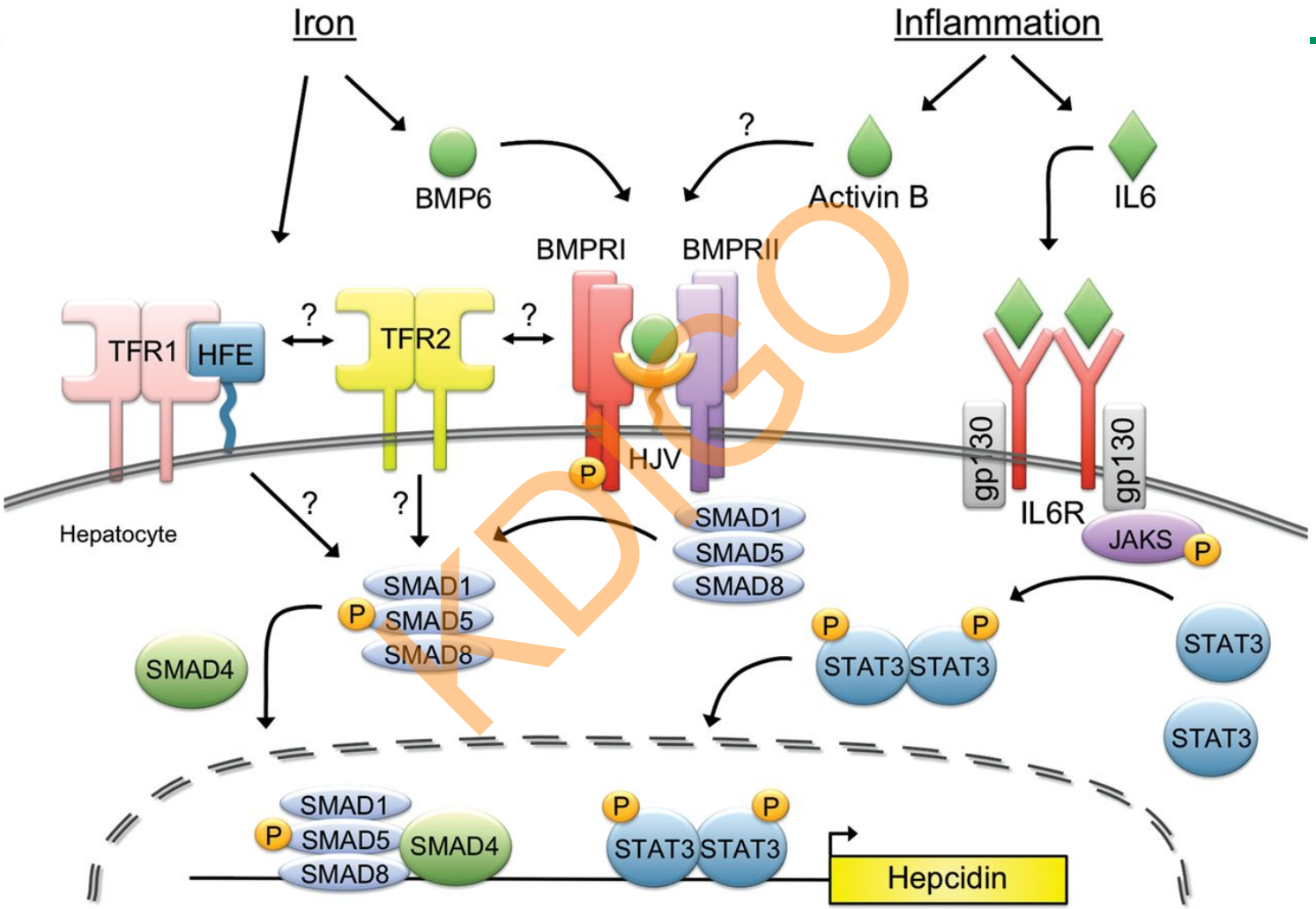
MIMICK study, ASN poster 2011

Relationship between ferritin, hsCRP and hepcidin-25.



van der Weerd NC, Grooteman MPC, Bots ML, van den Dorpel MA, et al. (2012) Hepcidin-25 in Chronic Hemodialysis Patients Is Related to Residual Kidney Function and Not to Treatment with Erythropoiesis Stimulating Agents. PLoS ONE 7(7): e39783.

Molecular regulation of hepcidin by iron and inflammation.



Zumbrennen-Bullough K , and Babitt J L Nephrol. Dial. Transplant. 2014;29:263-273

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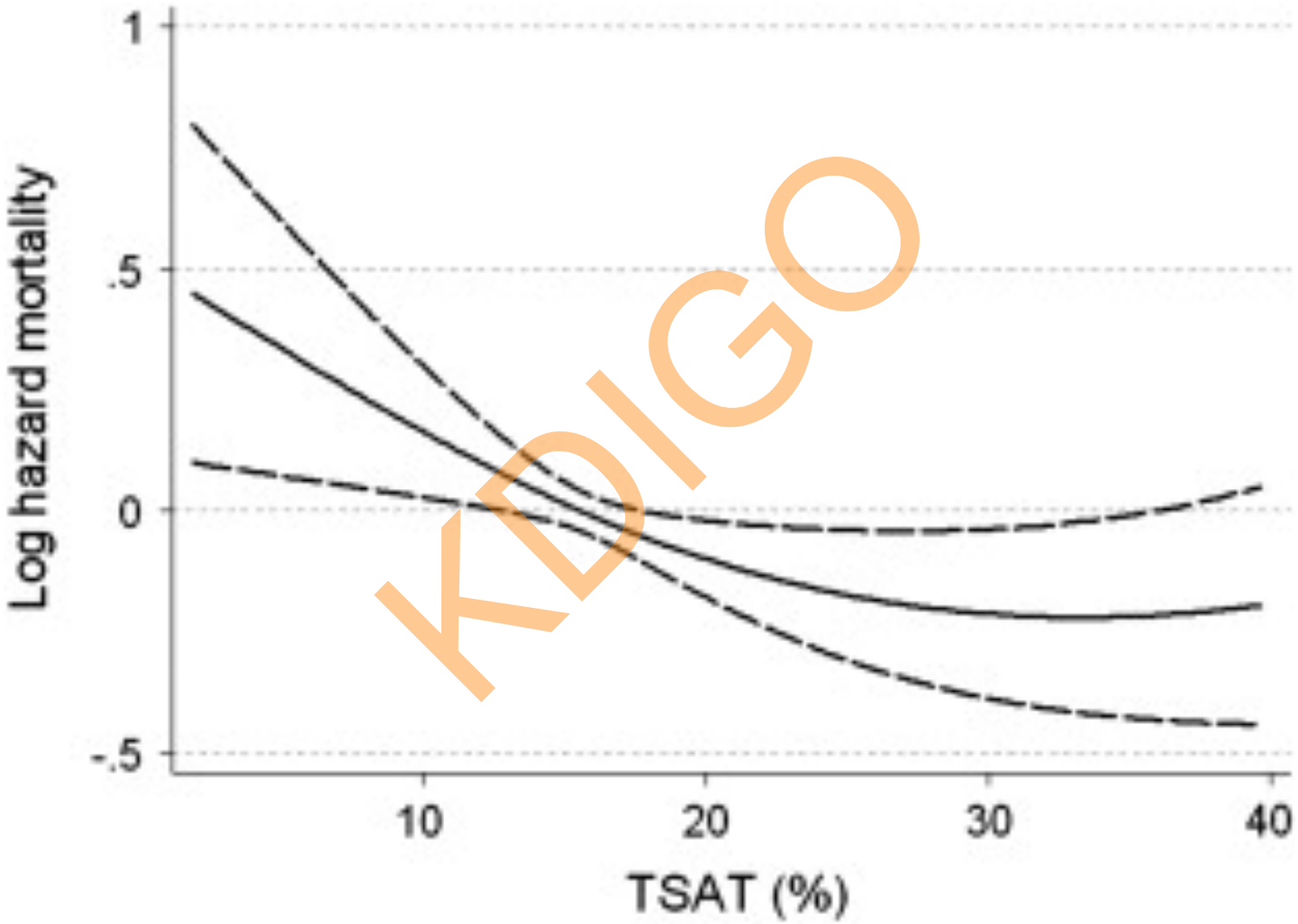
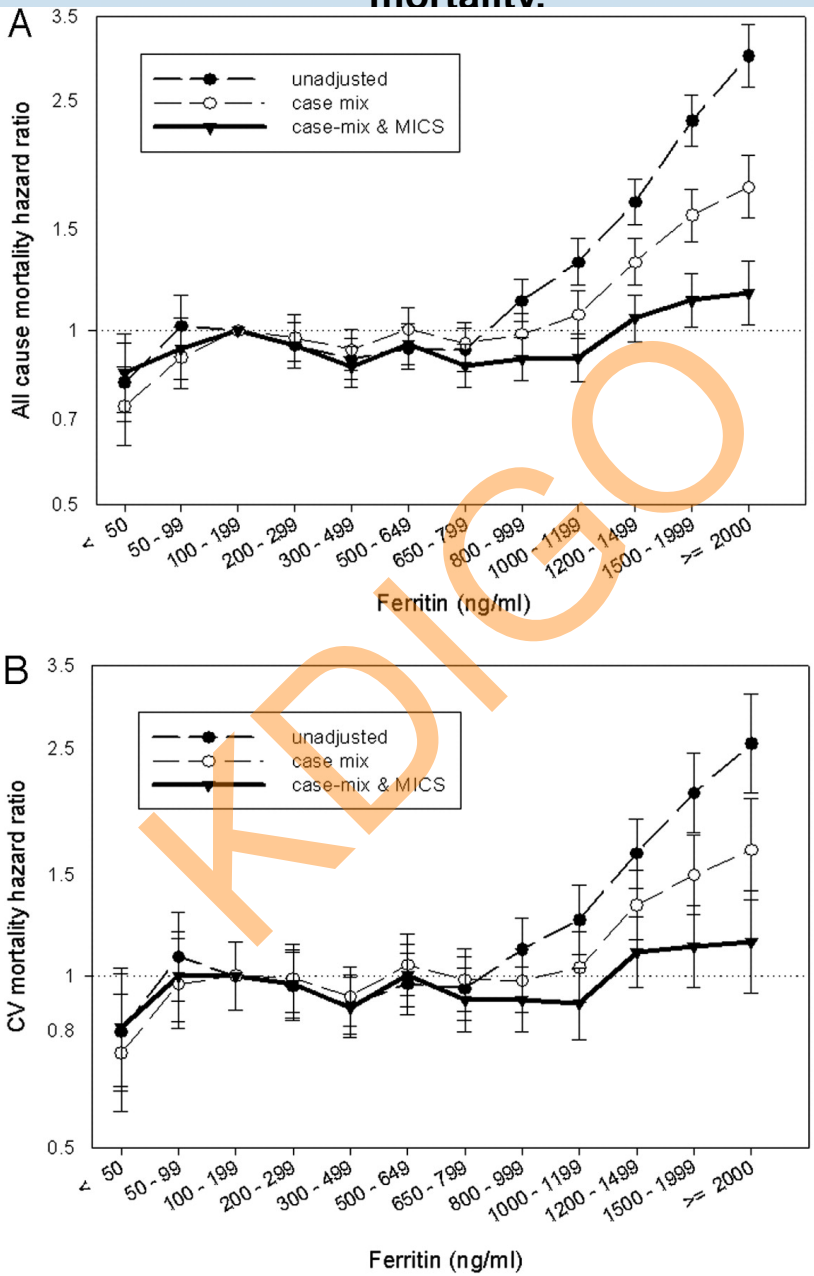
All-cause mortality associated with transferrin saturation (TSAT) ratio in patients with moderate and advanced non–dialysis-dependent chronic kidney



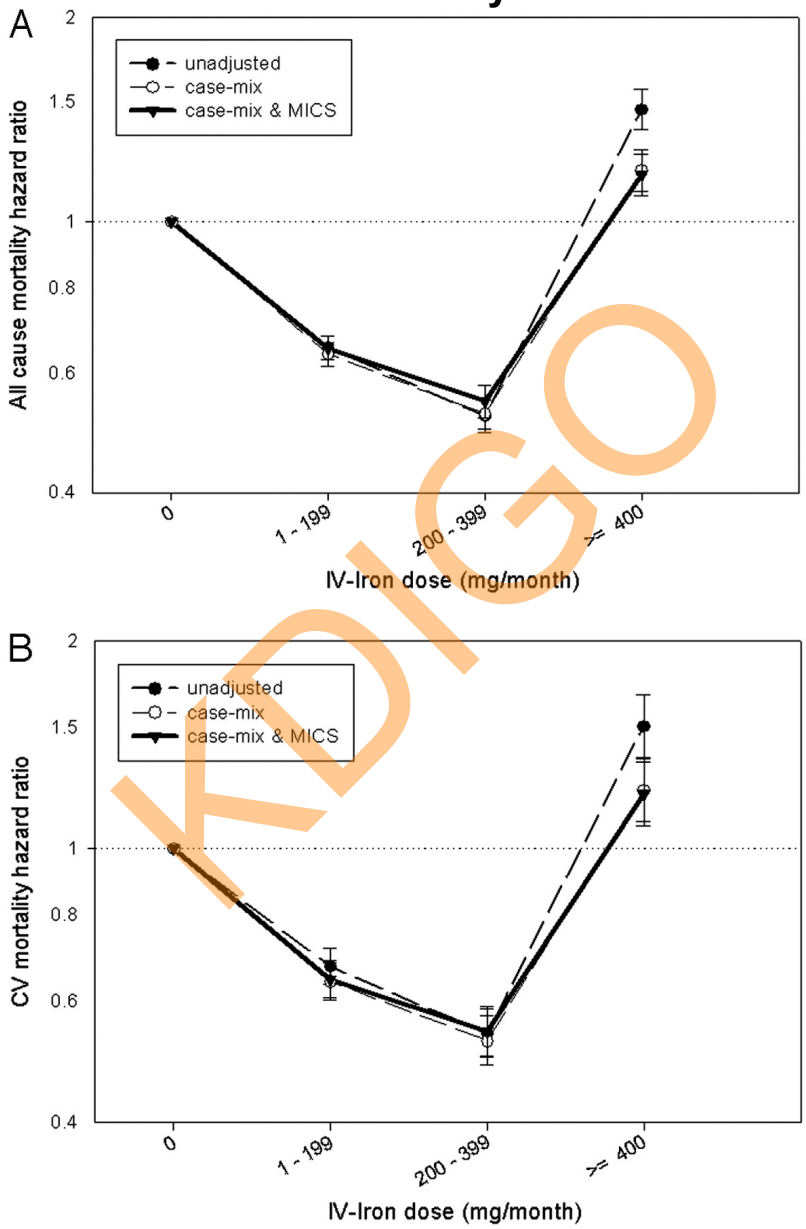
Kovesdy. Advances in Chronic Kidney Disease, Volume 16, Issue 2, 2009, 109 - 116

Association between serum ferritin and all-cause (top) and cardiovascular (CV; bottom) mortality.



Kalantar-Zadeh K et al. JASN 2005;16:3070-3080

Association between administered intravenous iron and all-cause (top) and CV (bottom) mortality.



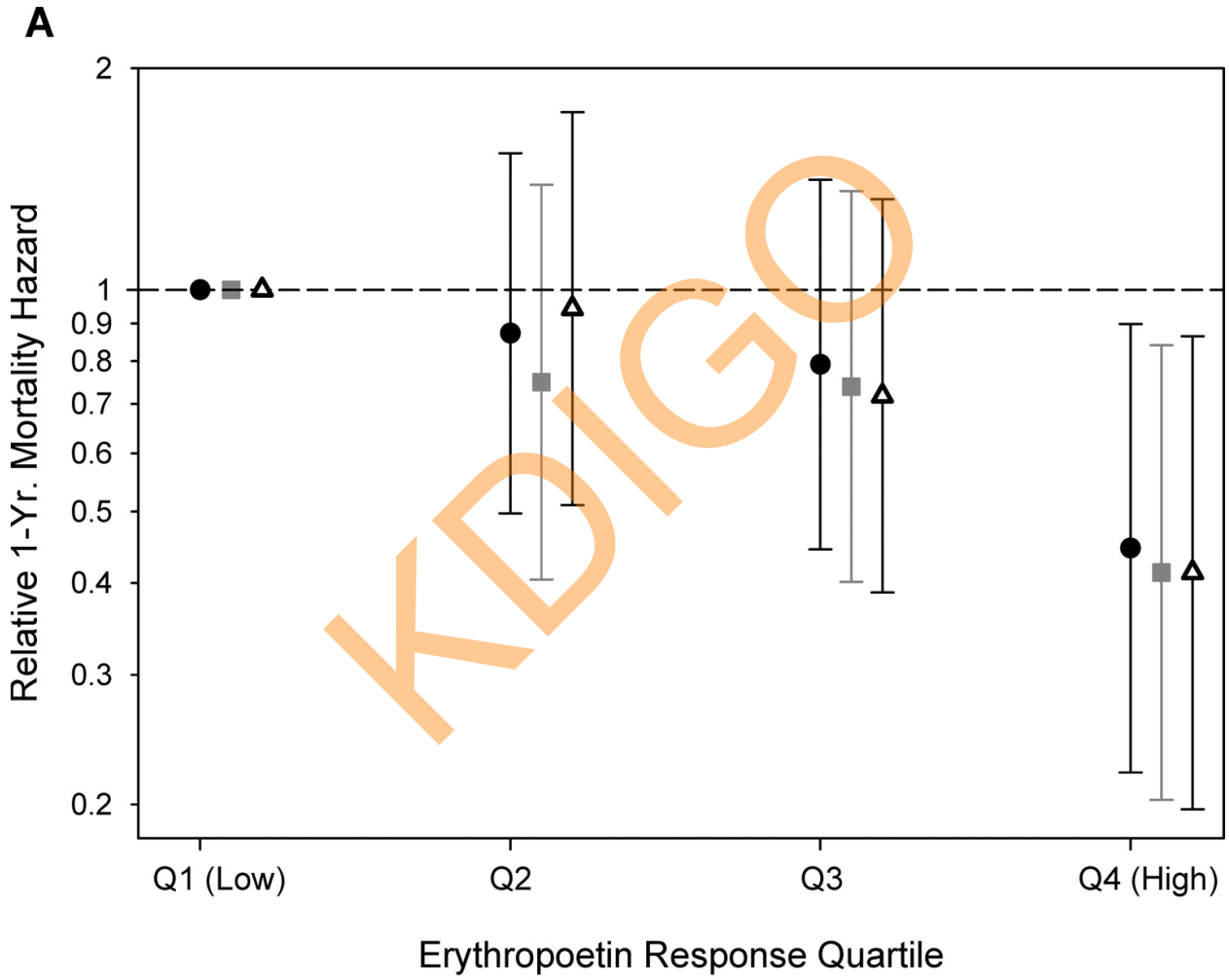
Kalantar-Zadeh K et al. JASN 2005;16:3070-3080

Table 3. Results of weighted multivariable model for the probability of mortality as a function of iron administered during the prior 6 mo

Variable	Category	Adjusted[a]	
		Hazard Ratio (95% CI)	*P* value
Iron (mg)[b]	None	Ref.	0.78
	> 0 to 700	1.04 (0.91–1.19)	
	> 700 to 1000	1.00 (0.87–1.14)	
	> 1000 to 1800	0.96 (0.84–1.09)	
	> 1800	1.04 (0.90–1.21)	

Feldman et al. J Am Soc Nephrol 15: 1623–1632, 2004

Epoetin Responsiveness Predicts Survival in the Normal Hematocrit Study. Association between epoetin response quartile, and all-cause 1-yr mortality assessed using a Cox proportional hazard model.



Kilpatrick R D et al. CJASN 2008;3:1077-1083

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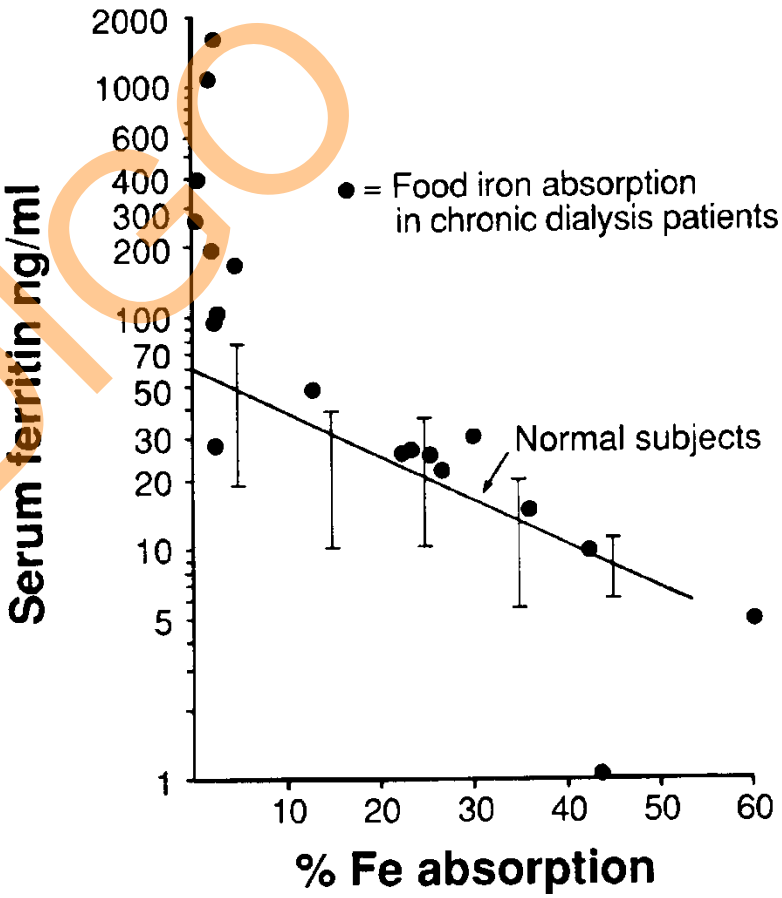
Oral iron is often not effective in CKD

Poor absorbtion

- **Inflammation – high hepcidin**
- **Interaction with other drugs**

•Intolerance

- **GI-symptoms**

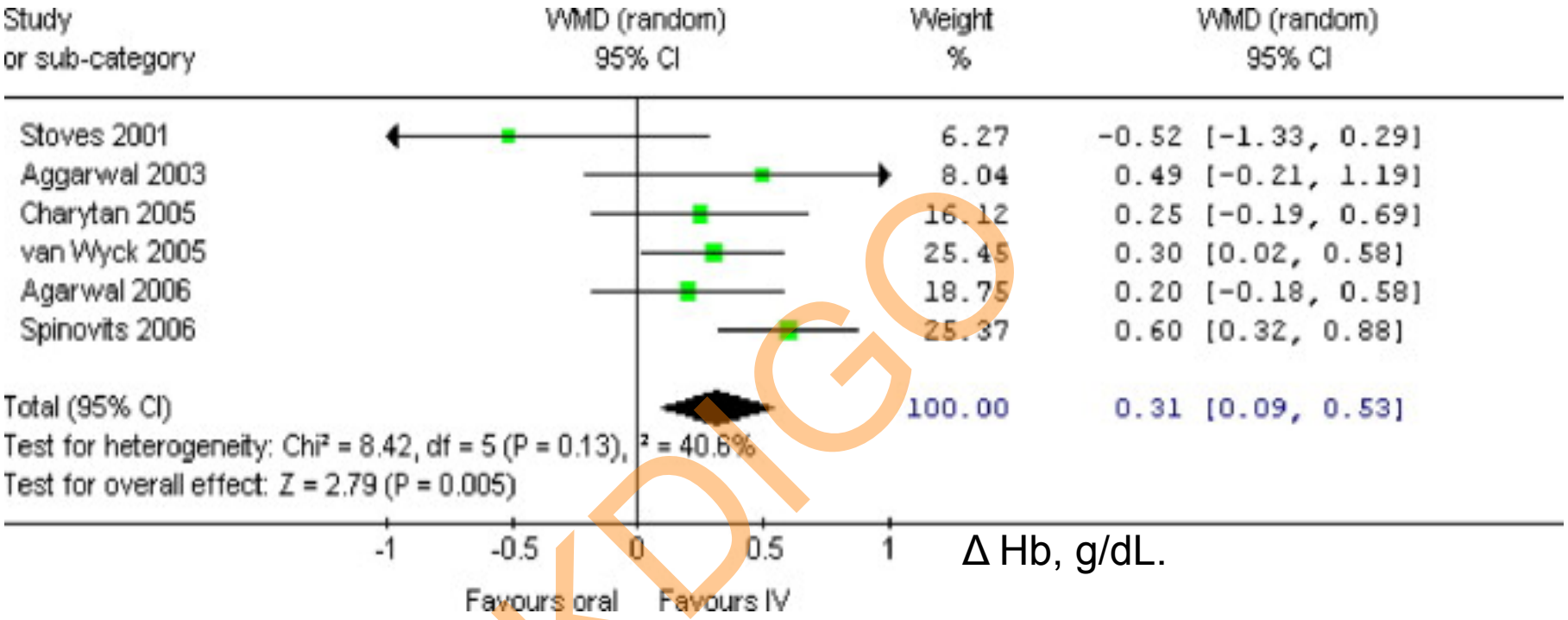


Treatment schedules IV iron

- Intermittent (triggered by threshold levels of ferritin and /or TSAT)
  1. Low dose – 10 doses of 100 mg during 3-4 weeks
  2. High dose - 500-1000 mg total dose infusion

- Continuous (depending on response)
  1. Low dose – 10-200 mg*1-3 per 7-28 days
  2. High dose - 1000 mg every third month

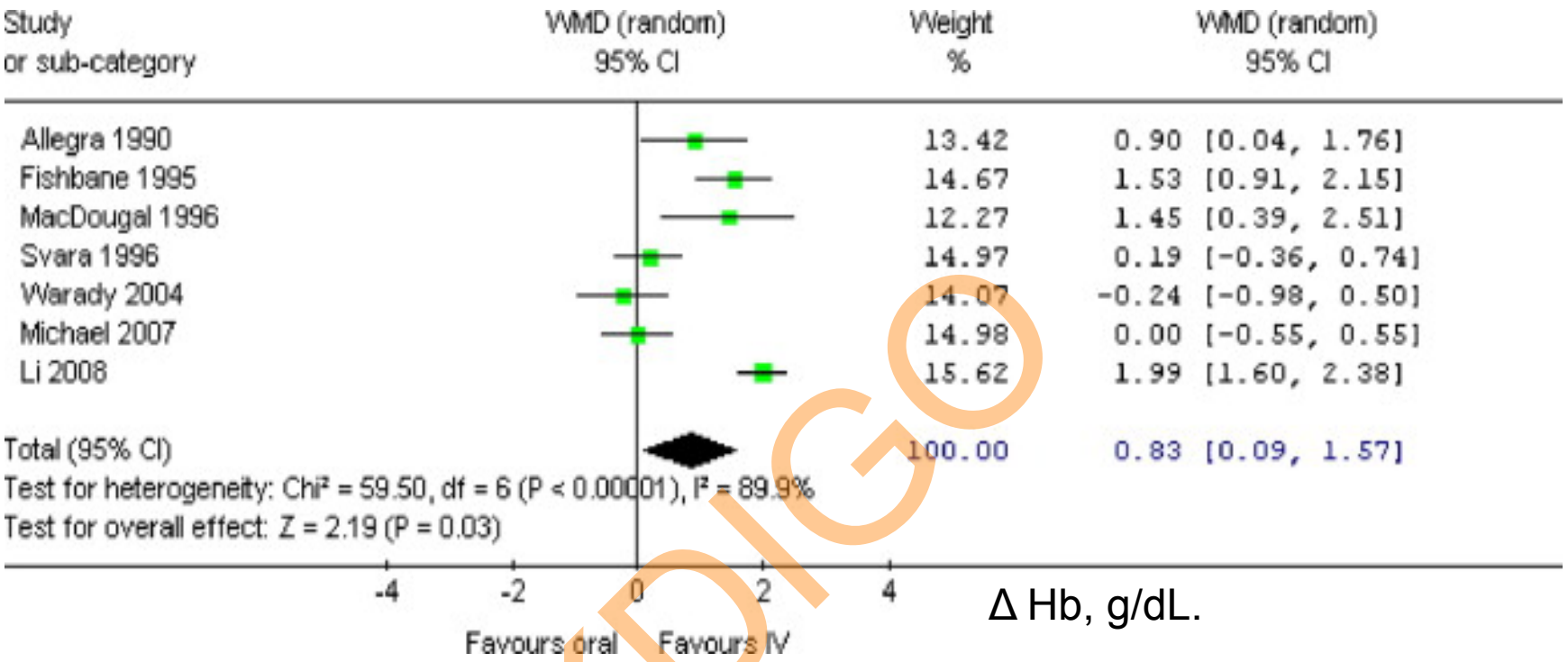
Intravenous Versus Oral Iron Supplementation for the Treatment of Anemia in CKD: Systematic Review and Meta-analysis



Hemoglobin (Hb) level or change from baseline for trials comparing intravenous (IV) iron versus oral iron in patients with chronic kidney disease (CKD) not on dialysis therapy.

The IV iron arm included 421 patients and the oral iron arm included 281 patients.

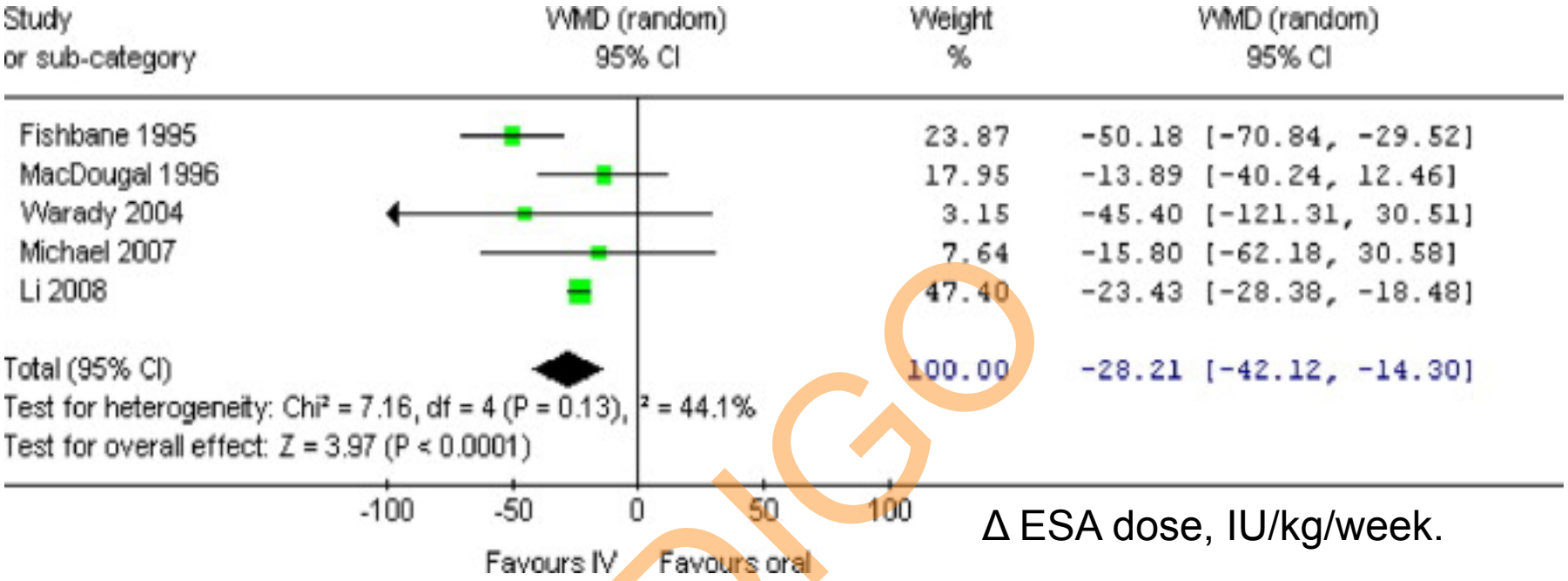
Rozen-Zvi et al, American Journal of Kidney Diseases Volume 52, Issue 5 2008 897 - 906



Hemoglobin (Hb) level or change from baseline for trials comparing intravenous (IV) iron versus oral iron in dialysis patients.

The IV iron arm included 215 patients and the oral iron arm included 205 patients. Serum Hb may be converted from g/dL to g/L by multiplying by 10.

Rozen-Zvi et al, American Journal of Kidney Diseases Volume 52, Issue 5 2008 897 - 906

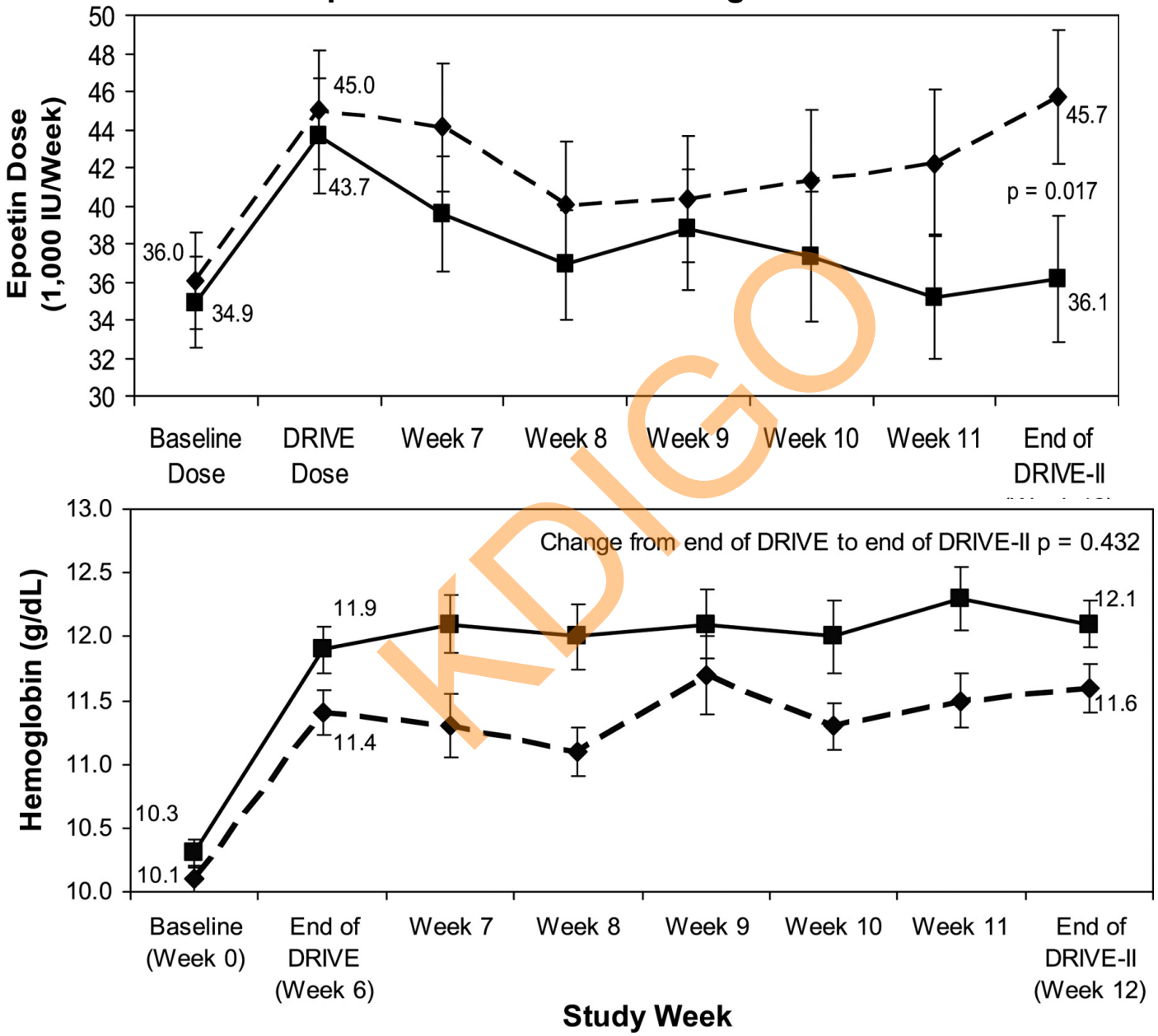


Erythropoiesis-stimulating agent (ESA) dose or change from baseline at end of study for trials comparing intravenous (IV) iron versus oral iron in dialysis patients.

The IV iron arm included 152 patients and the oral iron arm included 156 patients. Abbreviation: CI, confidence interval.

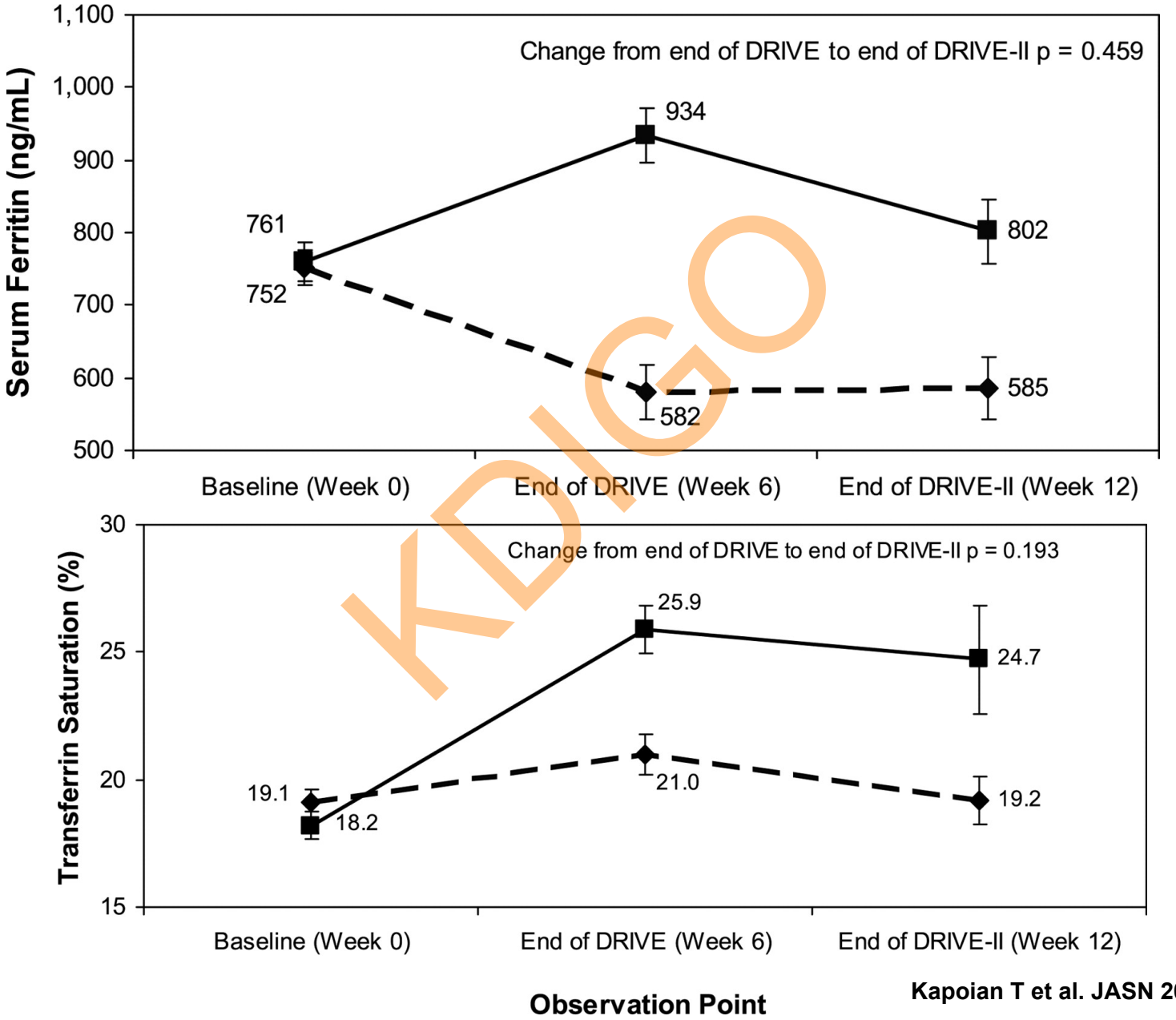
Rozen-Zvi et al, American Journal of Kidney Diseases Volume 52, Issue 5 2008 897 - 906

Epoetin dose and Hb throughout DRIVE-II.



Kapoian T et al. JASN 2008;19:372-379

Serum ferritin at baseline, end of DRIVE (wk 6), and end of DRIVE-II (wk 12).

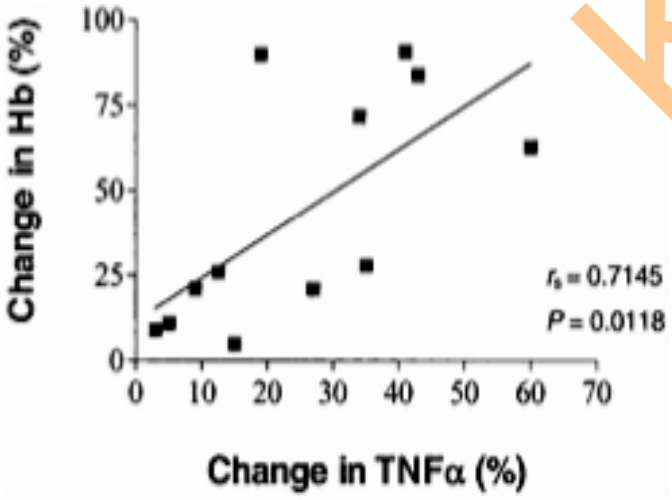


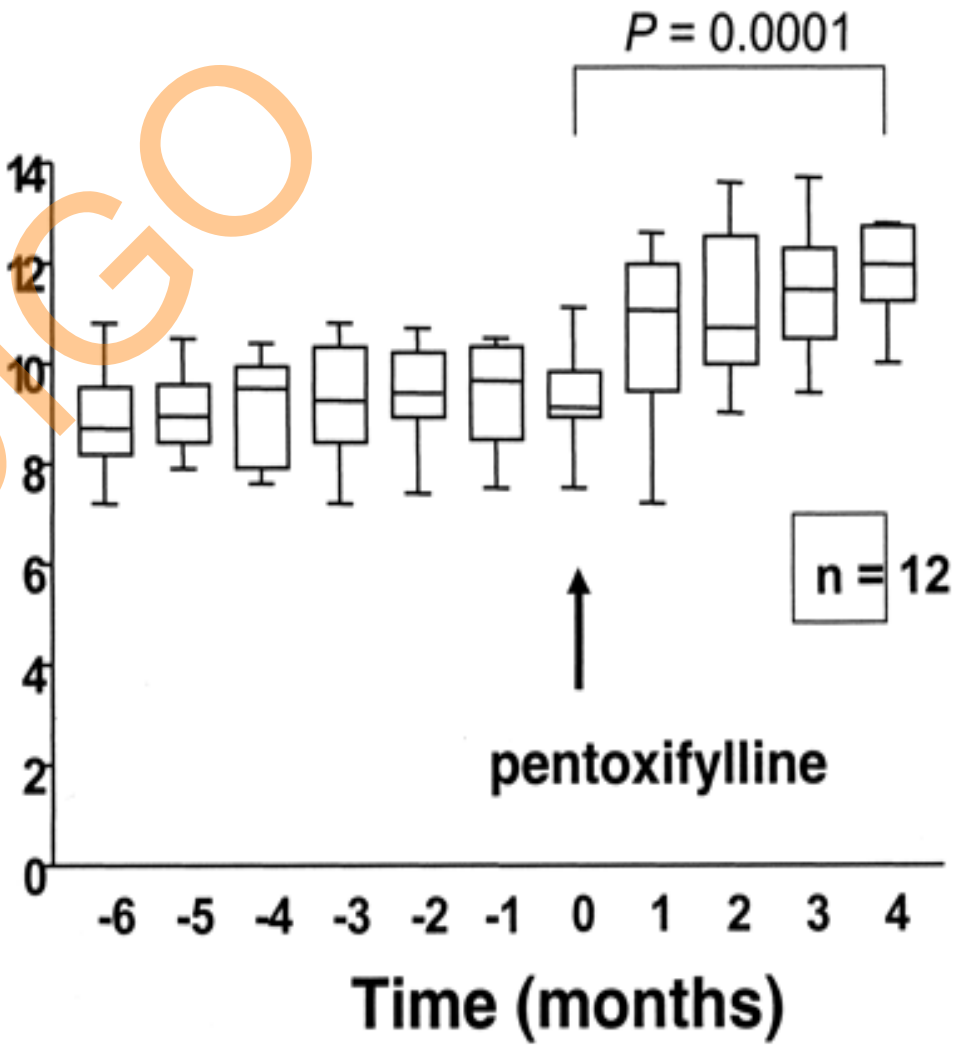
Kapoian T et al. JASN 2008;19:372-379

Pentoxifylline Improves Hemoglobin Levels in Patients with Erythropoietin-resistant Anemia in Renal Failure

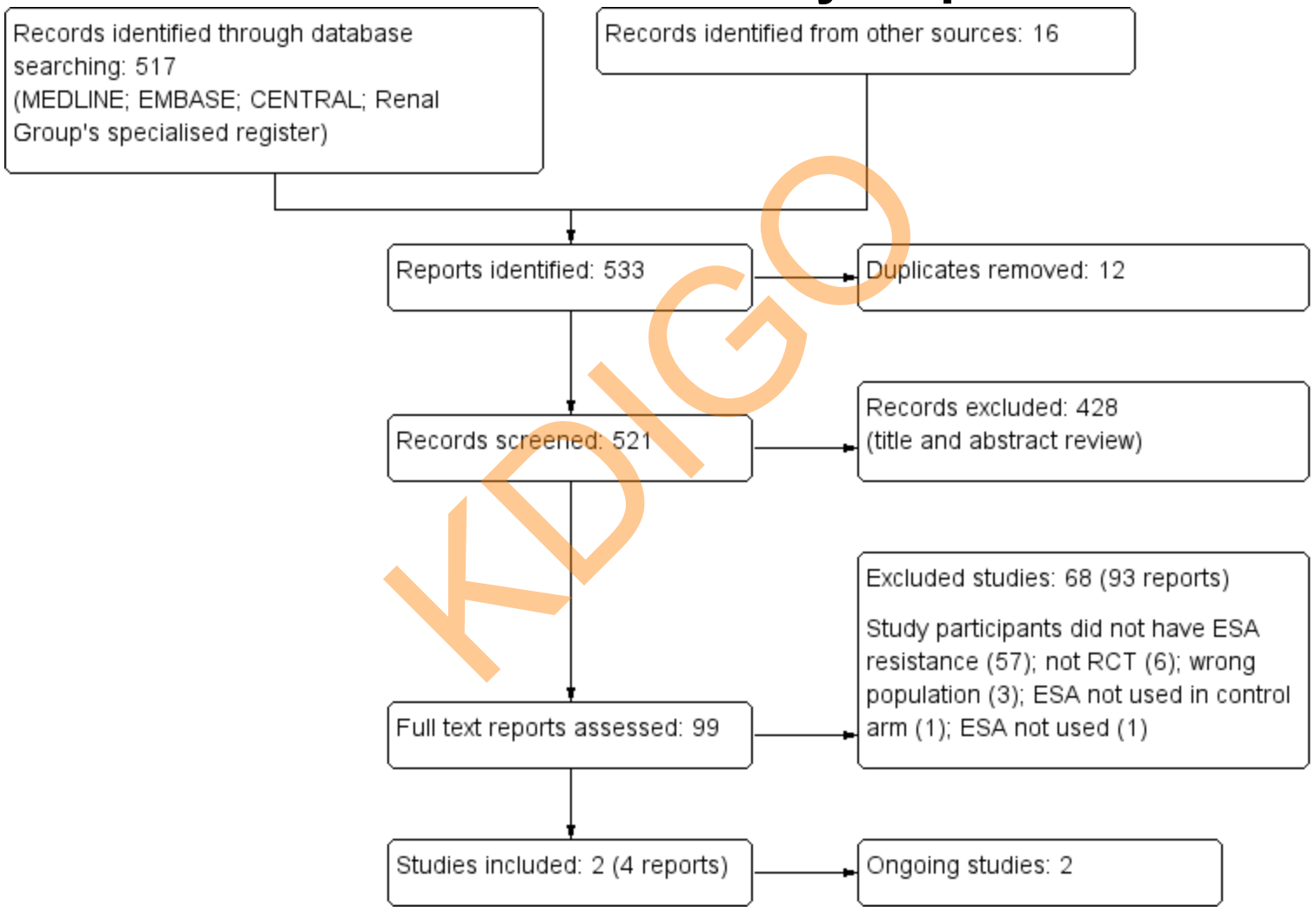
ANGELA COOPER,*† ASHRAF MIKHAIL,* MARK W. LETHBRIDGE,†
D. MICHAEL KEMENY,† and IAIN C. MACDOUGALL*
*Departments of *Renal Medicine and †Immunology, GKT School of Medicine, King's College Hospital, London, United Kingdom.*

- 16 ESRD patients with EPO-resistant anemia treated with pentoxifylline for 4 months.
- Baseline *ex vivo* T cell expression of IFN-γ and TNF-α decreased.



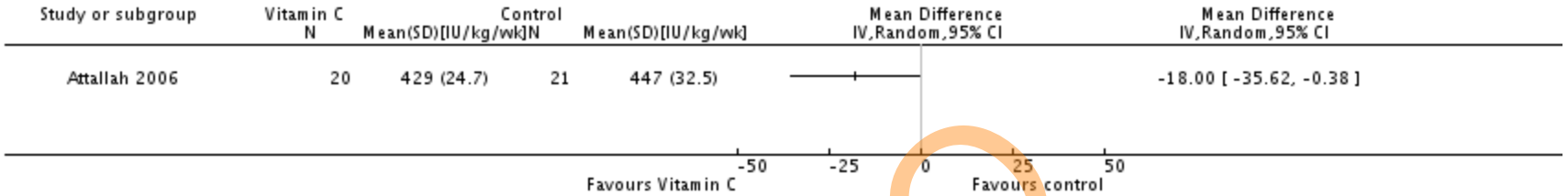


Cochrane review: Interventions for erythropoietin-resistant anaemia in dialysis patients

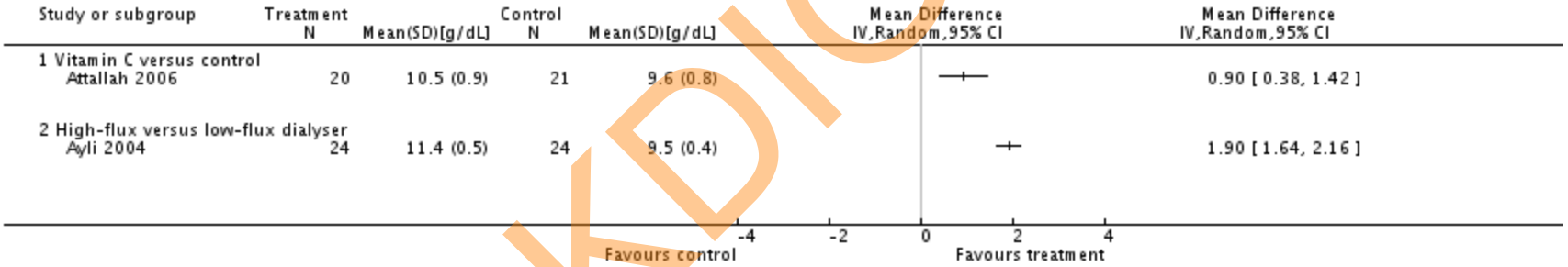


Badve et al. Cochrane Database Syst Rev. 2013 Aug

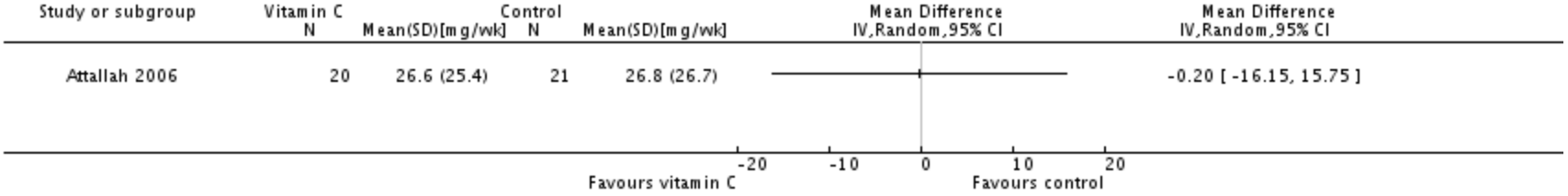
Review: Interventions for erythropoietin-resistant anaemia in dialysis patients
Comparison: 3 ESA and IV iron doses
Outcome: 1 EPO dose



Review: Interventions for erythropoietin-resistant anaemia in dialysis patients
Comparison: 2 Haematology and biochemistry results
Outcome: 1 Haemoglobin



Review: Interventions for erythropoietin-resistant anaemia in dialysis patients
Comparison: 3 ESA and IV iron doses
Outcome: 2 IV Iron



Summary

- Inflammation is highly prevalent with large inter- and intraindividual variation in CKD patients.
- Inflammation has several effects on erythropoiesis and is one important regulator of hepcidin
- Inflammation, functional iron deficiency and ESA hyporesponsiveness are linked to comorbidity and mortality
- None of the currently available laboratory biomarkers of iron status is a reliable predictor for iron response in CKD patients
- CKD patients have high hepcidin levels which contribute to anemia, functional iron deficiency as well as ESA and oral iron hyporesponsiveness .
- The optimal treatment of anemia in CKD patients with inflammatory-induced functional iron deficiency and hyporesponse is not established. Long-term safety of different treatment schedules have not been adequately evaluated in clinical trials.

thank you!