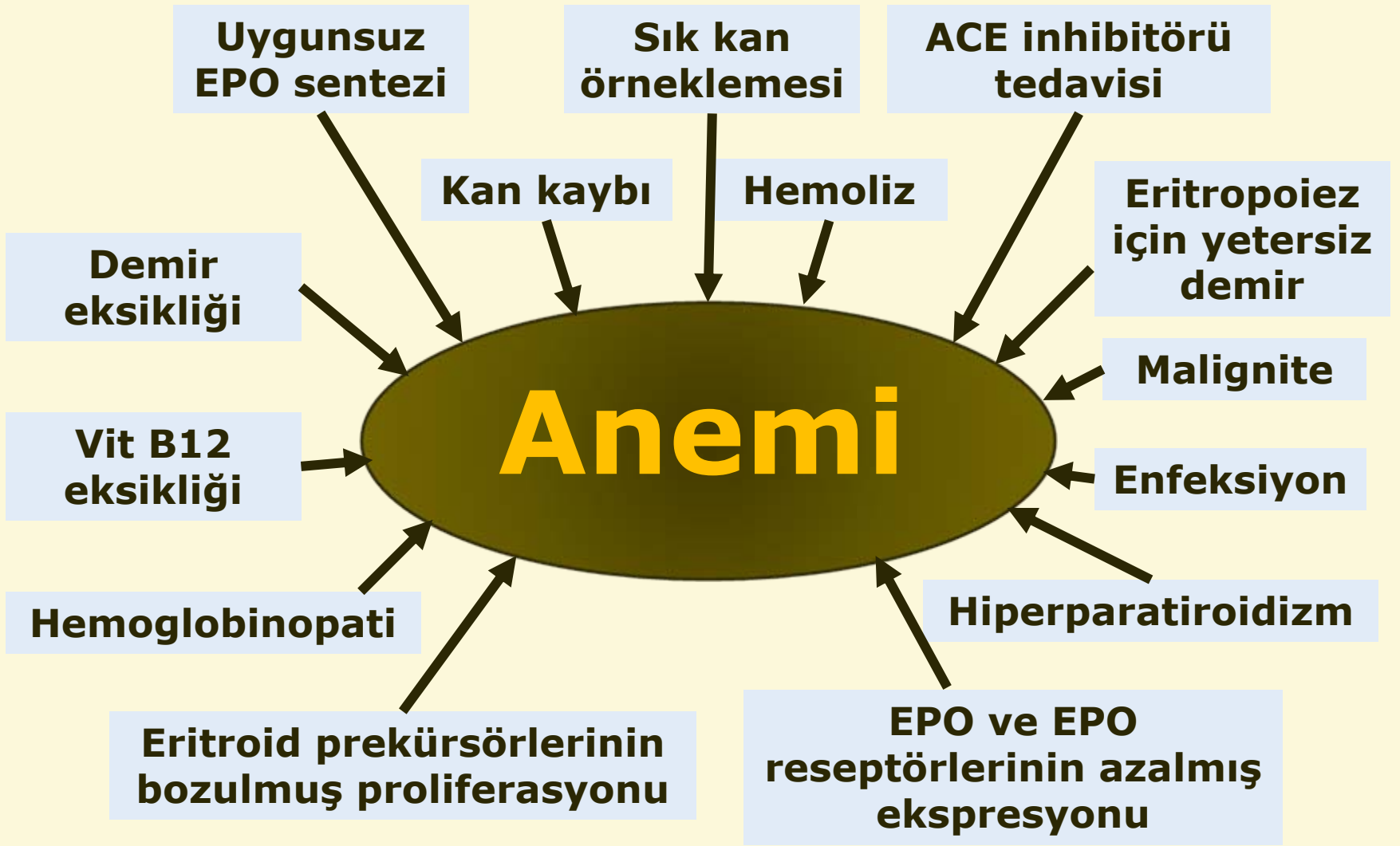


# **PREDİYALİZ ANEMİ**

**Dr. Sim Kutlay**

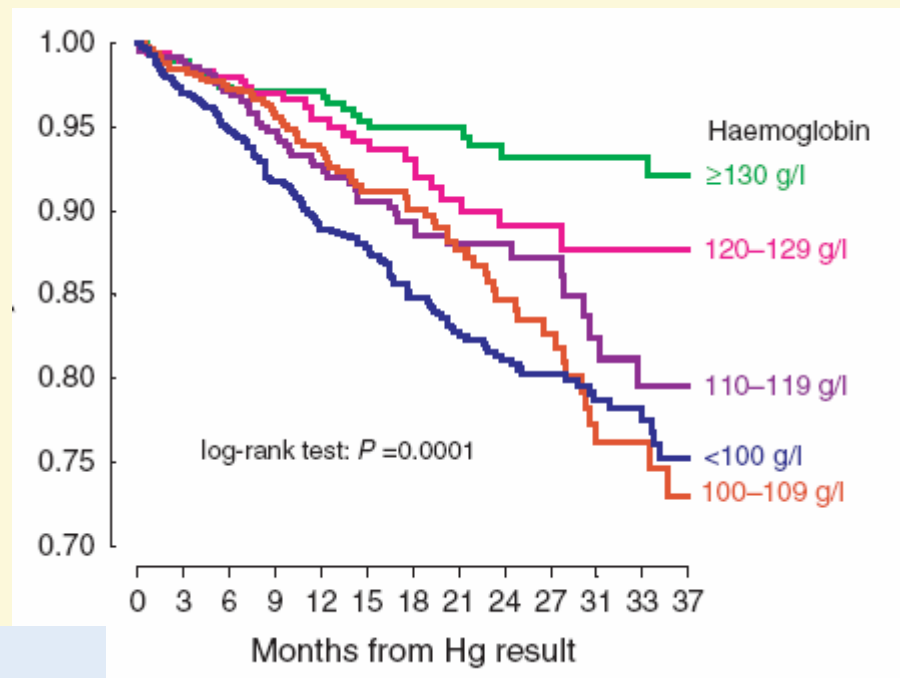
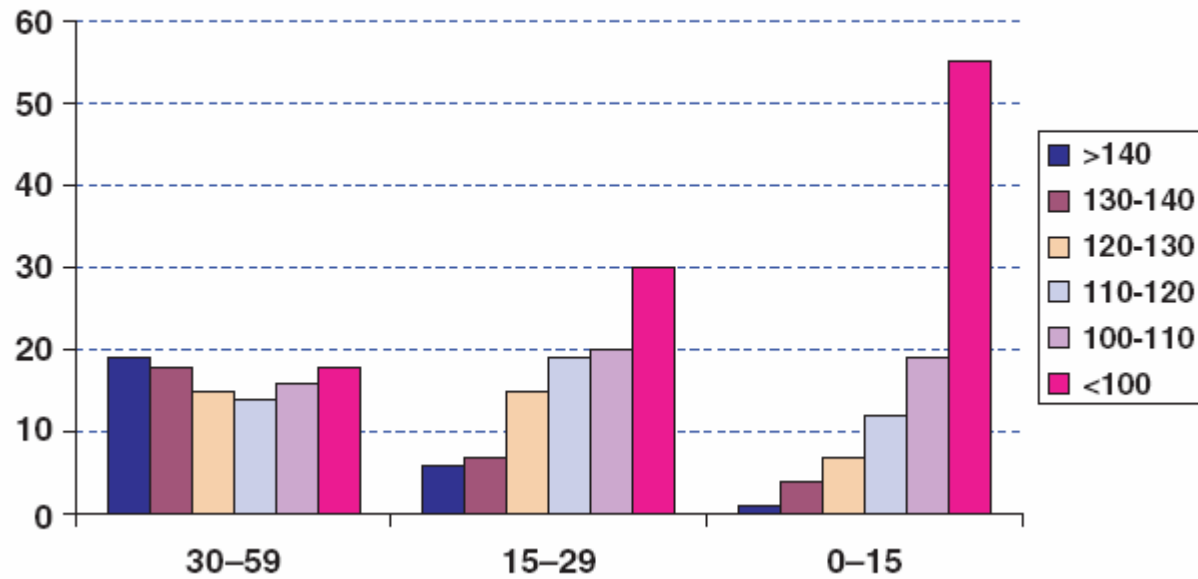


*Coyne DW, Seminars in Dialysis, May 2008*

## KBH'nın çeşitli evrelerinde anemi izlemi

Evre	GFR (ml/dk/1.73m <sup>2</sup> )	Önerilen Hb izlemi
1	≥90	Yıllık
2	60-80	Yıllık
3 (ESA almayan)	30-59	Yıllık
3 (ESA alan)	30-59	En az ayda bir; stabil doz alıyorsa 3 ayda bir
4	15-29	Evre 3 gibi
5 (diyalize girmeyen)	<15	

### Haemoglobin at time of referral prior to dialysis predicts survival



Variable	Risk Ratio	95% CI		P-value
Age (5 years)	1.318	1.146	1.516	0.0001
Female vs male gender	0.824	0.701	0.968	0.0187
Diabetes	1.492	1.261	1.766	0.0001
eGFR (5 ml/min)	0.891	0.851	0.933	0.0001
Hgb $\geq$ 140 g/l*	1.00			
Hgb 130–139 g/l	0.992	0.568	1.731	0.9766
Hgb 120–129 g/l	1.126	0.673	1.884	0.6523
Hgb 110–119 g/l	1.500	0.926	2.430	0.0997
Hgb 100–109 g/l	1.770	1.104	2.838	0.0177
Hgb <100 g/l	1.904	1.197	3.027	0.0065

Variable	eGFR: 30–59 ml/min				eGFR: 15–29 ml/min				eGFR: <15 ml/min			
	Risk ratio	95% CI		P-value	Risk ratio	95% CI		P-value	Risk ratio	95% CI		P-value
Age (5 years)	1.582	1.014	2.468	0.0434	1.101	0.899	1.347	0.3524	1.581	1.271	1.966	0.0001
Female vs male gender	0.433	0.224	0.837	0.0128	0.825	0.651	1.047	0.1133	0.907	0.713	1.153	0.4259
Diabetes	0.847	0.436	1.644	0.6227	1.685	1.310	2.166	0.0001	1.480	1.155	1.898	0.0020
eGFR (5 ml/min)	1.216	1.027	1.439	0.0230	0.840	0.727	0.971	0.0183	1.062	0.860	1.313	0.5757
Haemoglobin (10 g/l)	0.812	0.714	0.924	0.0015	0.861	0.806	0.920	0.0001	0.914	0.844	0.990	0.0281

# **Diyalize Girmeyen KBH'lılarda Demir Eksikliği Nedenleri**

- **Kan kaybı**
  - **Gastrointestinal sistem**
  - **Menstruel kan kaybı**
  - **Tekrarlayıcı kan örneklemesi**
  - **İdrarla kan kaybı (nadir)**
  - **Cerrahi kan kaybı**
- **Artmış demir kullanımı**
  - **ESA tedavisi**
- **Malabsorpsiyon**
  - **Fonksiyonel aklorhidri**
  - **Etkileşime giren ilaçlar (ör. Fosfat bağlayıcılar)**
  - **Kronik atrofik gastrit**
- **Diyetteki yetersizlik**
- **Bu faktörlerin kombinasyonu**

# Iron Indices in Chronic Kidney Disease in the National Health and Nutritional Examination Survey 1988–2004

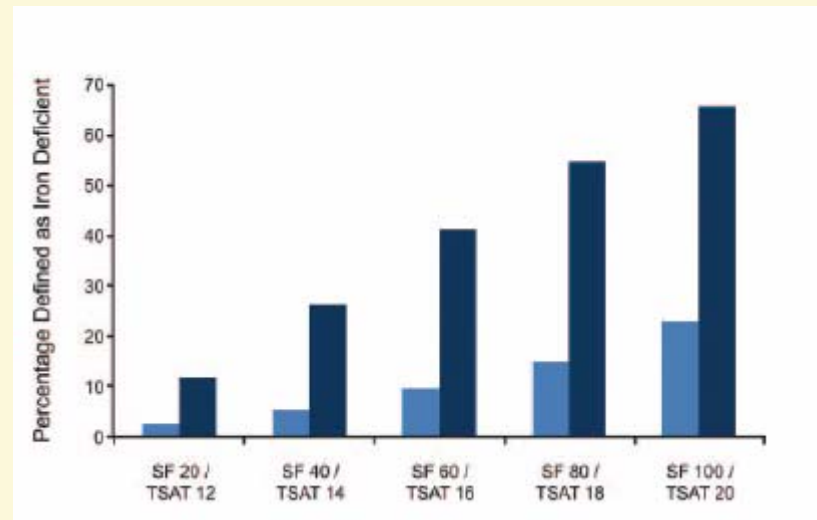
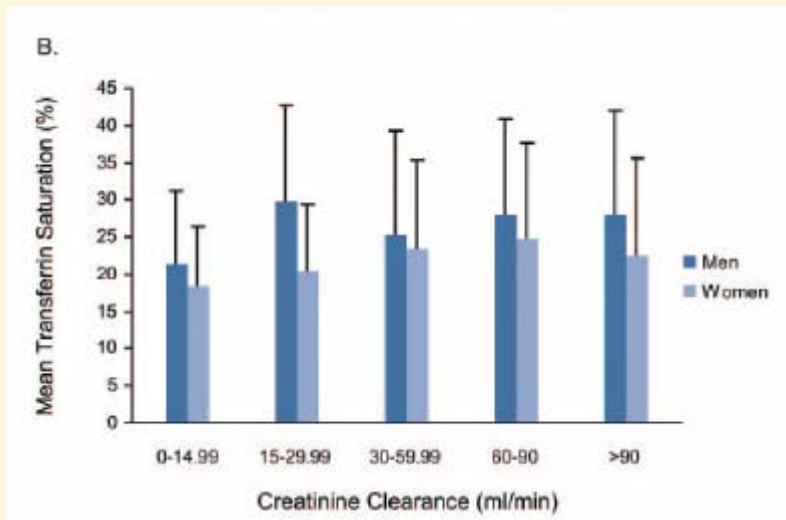
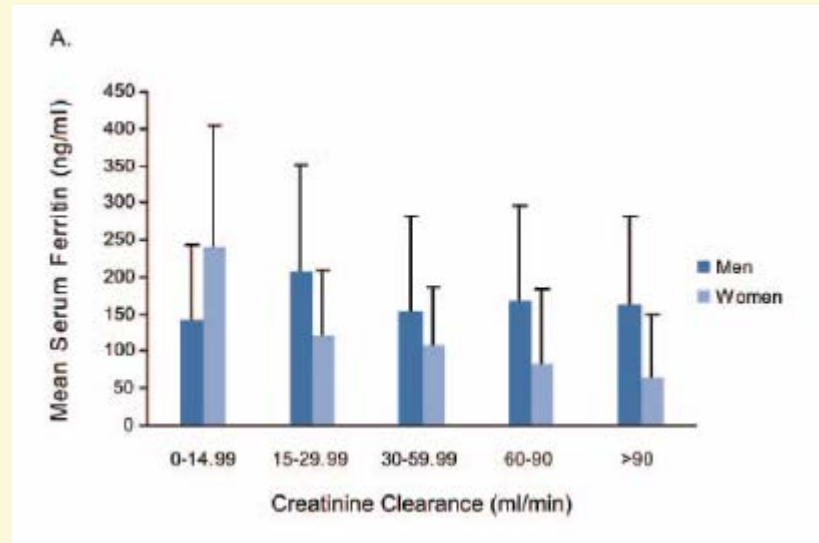
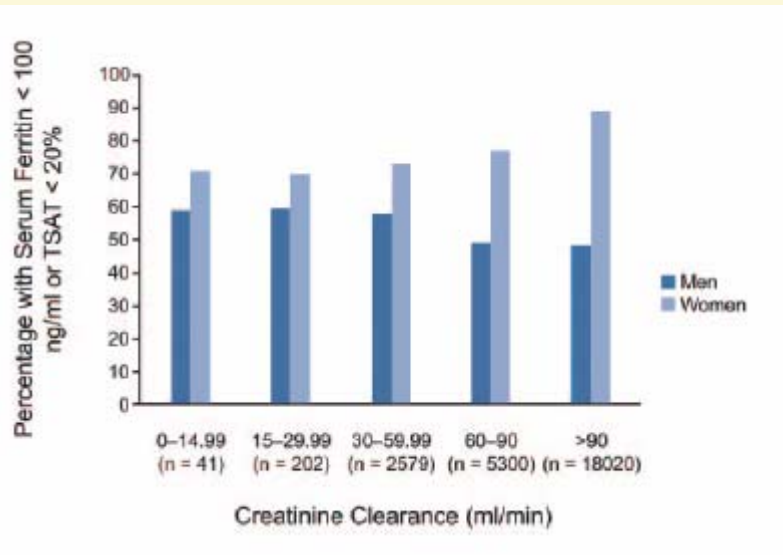
Steven Fishbane,\* Simcha Pollack,<sup>†</sup> Harold I. Feldman,<sup>‡</sup> and Marshall M. Joffe<sup>§</sup>

*\*Winthrop University Hospital, Mineola, New York; <sup>†</sup>Department of Computer Information Systems and Decision Sciences, St. John's University, Jamaica, New York; <sup>‡</sup>Renal Electrolyte and Hypertension Division, Department of Medicine, and <sup>§</sup>Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania*

**Background and objectives:** Anemia is a common and early complication of nondialysis chronic kidney disease (CKD). One contributing factor is iron deficiency, which may be particularly problematic during erythropoietin replacement therapy. The aim of this study was to examine the prevalence of iron deficiency in nondialysis CKD.

**Design, setting, participants, & measurements:** The National Health and Nutritional Examination Survey (NHANES) data for NHANES III (1988 to 1994) and subsequent NHANES 2-yr datasets, 1999 to 2000, 2001 to 2002, and 2003 to 2004 were analyzed for individuals >18 yr old.

**Results:** It was found that low levels of iron tests [either serum ferritin < 100 ng/ml or transferrin saturation (TSAT) < 20%] were present in most patients with reduced creatinine clearance (CrCl). The percentage of low iron tests was higher among women than men, present in 57.8 to 58.8% of men and 69.9 to 72.8% of women ( $P < 0.001$ ). With declining levels of CrCl, in



# KBH Hastalarında Demir Tedavisi için NKF-KDOQI Anemi Kılavuzları

1. Aneminin ilk değerlendirilmesinin bir parçası olarak serum ferritin ve TSAT'ın (veya CHr) ölçülmesi (Kılavuz 1.2).
2. Başlangıçtaki ESP tedavisi sırasında her ay, stabil ESP tedavisinde en az 3 ayda bir demir profilinin çıkarılması (Kılavuz 3.2.1).
3. Demir profilinin Hb düzeyi ve ESP dozu ile birlikte yorumlanması (Kılavuz 3.2.2).
4. ESP tedavisi boyunca serum ferritini  $>100\text{ng/ml}$  ( $\mu\text{g/L}$ ) ve TSAT'ı  $>20\%$  (veya CHr'yi  $>29\text{ pg}$ )'da tutacak dozda yeterli demir verilmesi (Kılavuz 3.2.3).
5. Serum ferritini  $>500\text{ ng/ml}$  ( $\mu\text{g/L}$ ) ise rutin olarak IV demir verilmesini önermemize yetecek veri henüz yoktur (Kılavuz 3.2.4).
6. Demir verilmesi oral veya IV olabilir (Kılavuz 3.2.5).
7. IV demir dekstran dozu uygulanırken hem personel hem de ilaç açısından anafilaksiye müdahale için hazır olunmalıdır (Kılavuz 3.2.6).

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

*Benaya Rozen-Zvi, MD,<sup>1</sup> Anat Gafter-Gvili, MD,<sup>2</sup> Mical Paul, MD,<sup>3</sup> Leonard Leibovici, MD,<sup>4</sup> Ofer Shpilberg, MD,<sup>2</sup> and Uzi Gafter, MD, PhD<sup>1</sup>*

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**Background:** Iron supplementation is essential for the treatment of patients with anemia of chronic kidney disease (CKD). It is not clear which is the best method of iron administration.

**Study Design:** Systematic review and meta-analysis. A search was performed until January 2008 of MEDLINE, Cochrane Central Register of Controlled Trials, conference proceedings in nephrology, and reference lists of included trials.

**Setting & Population:** Patients with CKD (stages III to V). We included dialysis patients and patients with CKD not on dialysis therapy (hereafter referred to as patients with CKD).

**Selection Criteria for Studies:** We included all randomized controlled trials regardless of publication status or language.

**Intervention:** Intravenous (IV) versus oral iron supplementation.

**Outcomes Measures:** Primary outcomes assessed: absolute hemoglobin (Hb) level or change in Hb level from baseline. We also assessed all-cause mortality, erythropoiesis-stimulating agent requirement, adverse events, ferritin level, and need for renal replacement therapy in patients with CKD.

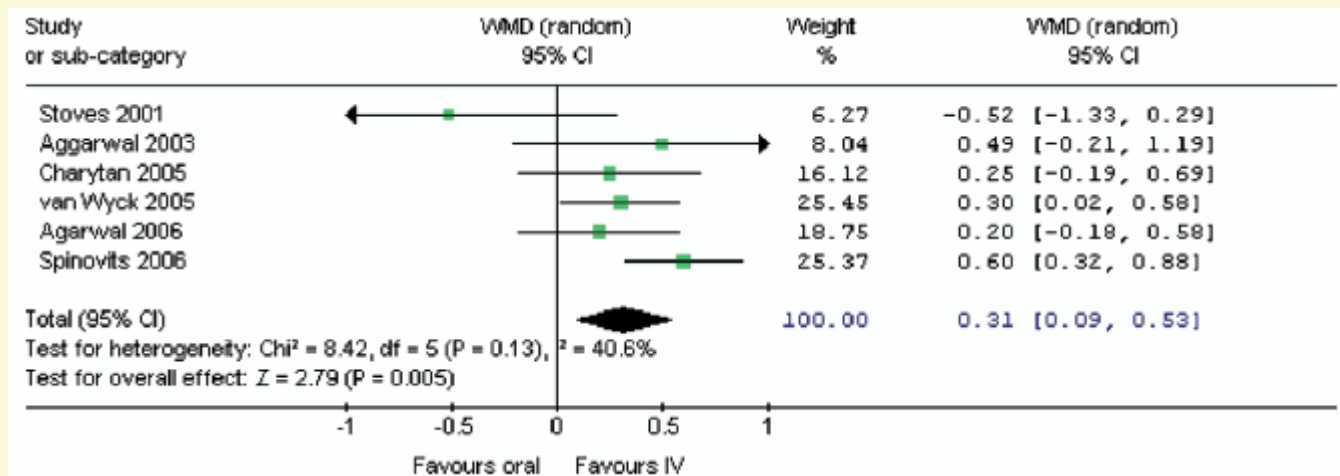
**Results:** 13 trials were identified, 6 including patients with CKD and 7 including dialysis patients. Compared with oral iron, there was a significantly greater Hb level in dialysis patients treated with IV iron (weighted mean difference, 0.83 g/dL; 95% confidence interval, 0.09 to 1.57). Meta-regression showed a positive association between Hb level increase and IV iron dose administered and a negative association with baseline Hb level. For patients with CKD, there was a small but significant difference in Hb level favoring the IV iron group (weighted mean difference, 0.31 g/dL; 95% confidence interval, 0.09 to 0.53). Data for all-cause mortality were sparse, and there was no difference in adverse events between the IV- and oral-treated patients.

**Limitations:** There was significant heterogeneity between trials. Follow-up was limited to 2 to 3 months.

**Conclusions:** Our review shows that patients on hemodialysis therapy have better Hb level response when treated with IV iron. For patients with CKD, this effect is small.

*Am J Kidney Dis* 52:897-906. © 2008 by the National Kidney Foundation, Inc.

Study	Renal Function (mL/min)	Men (%)	Duration of Dialysis (mo)	Baseline TSAT (%) / Ferritin (ng/mL) / Hb (g/dL)	ESA Use (%)	Dose Change	Baseline ESA Dose	Allocation Generation/Concealment	Time of Included Hb Measurement
<b>Patients with CKD</b>									
Van Wyck et al 2005 <sup>36*</sup>	GFR 30.4	32.9		16.4/92.6/10.2	40.5	No	NR	B/B	Day 42
Charytan et al 2005 <sup>33</sup>	GFR 28.5	37.1		16.7/103.8/10.1	37.8	No	NR	B/B	Day 42
	NR	39.6		16.6/125/9.8	100	No	2,000 U SC d 1, 8, 15, 22, 29, 36		
Agarwal et al 2006 <sup>34†</sup>	GFR 31.8	44.4		17.2/72.5/10.5	None	—	—	A/A	Day 43
	GFR 30.4	38.5		17.9/66.4/10.7					
Aggarwal et al 2003 <sup>35</sup>	CCr 13	65		59.8/181.4/5.8	100	No	2,000 U × 2 wk	A/B	2 mo
	CCr 18.6	80		63.6/180.3/6.3					
Stoves et al 2001 <sup>38†</sup>	GFR 14‡	45.5		NR/100‡/9.9	100	Yes	2,000 U × 3 wk	A/A	2 mo
	GFR 12‡	65.2		NR/74‡/9.7					
Spinowitz et al 2006 <sup>37†</sup>	NR	41.2		11.3/146.1/9.96	25.9	No	NR	B/B	Day 35
		31.6		10.1/143.5/9.96	23.7	No	NR		



# Diyalize Girmeyen KBH'lılarda Oral veya IV Demir: 4 Randomize Kontrollü Çalışma

Çalışma	Hasta sayısı	Doz	Bazal Hb (g/dL)	Sonlanım
Aggarwal ve ark.	40	Oral:FS günde 3 kez 200 mg; IV: elementer demir, ayda 2 kez 100 mg ; hepsi 2000 IU EPO aldı	Oral : 6.26 ± 1.0 IV: 5.83 ± 0.60	Eş zamanlı kullanımda IV demir oralden daha iyiydi. Oral grupta 3. ayda Hb 8.94 ± 1.17 g/dl (p=0.001) iken IV grupta 10.05 ± 0.90 g/dl (p=0.001) idi.
Stoves ve ark.	45	Oral:FS günde 3 kez 200 mg; IV: IS her ay 300 mg	Oral : 9.7 (9.3-10.2) IV: 9.9 (9.2-10.6)	IV demir üstün değildi. Hb yanıtında belirgin fark yoktu: Altıncı ayda (12.2[10.6-12.8] karşın 12.5 [11.6-13.3] g/dl).
Charytan ve ark.	96	Oral:FS günde 3 kez 325 mg; IV: IS her hafta 5 doz 200 mg	Oral : 9.7 (0.8) IV: 9.8 (0.6)	IV ve oral demir arasında belirgin fark yoktu.
Van Wyck ve ark.	182	Oral:FS 56 gün boyunca günde 3 kez 325 mg; IV: IS 14 güne bölünerek 1 g	Oral : 10.1 IV: 10.2	IV grubunda orale göre primer sonlanıma ulaşanların oranı (% 44.3'e karşı % 28, p=0,0344) ve 42. günde ortalama Hb artışı (07'ye karşı 0.4 g/dl; p=0.0298) daha yüksekti.

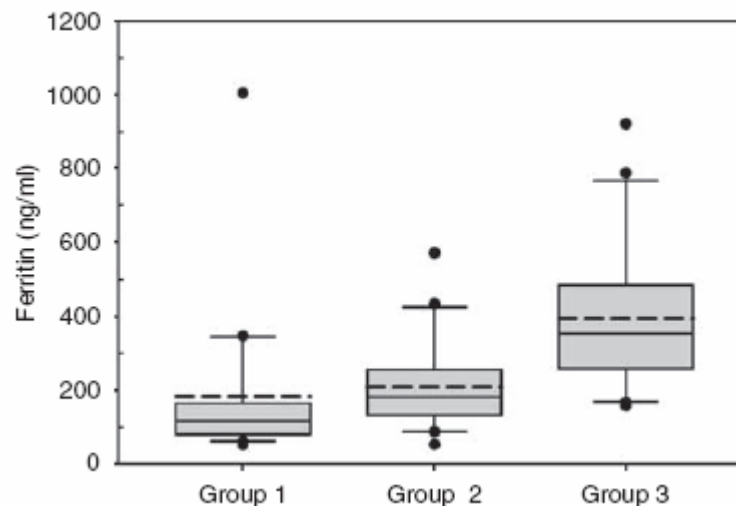
# Variability of ferritin measurements in chronic kidney disease; implications for iron management

Bradley A. Ford<sup>1</sup>, Daniel W. Coyne<sup>2</sup>, Charles S. Eby<sup>1,2</sup> and Mitchell G. Scott<sup>1</sup>

<sup>1</sup>Department of Pathology and Immunology, Washington University, St Louis, Missouri, USA and <sup>2</sup>Department of Medicine, Washington University, St Louis, Missouri, USA

Serum ferritin levels are a proxy measure of iron stores; existing guidelines for managing anemia in hemodialysis patients suggest that serum ferritin concentrations should be maintained at >200 ng/ml. The KDOQI recommendations further state there is insufficient evidence advocating routine intravenous iron when ferritin levels exceed 500 ng/ml. Here we determined the interassay differences and short-term intraindividual variability of serum ferritin measurements in patients on chronic hemodialysis to illustrate how these

Patients on chronic hemodialysis undergo routine laboratory assessment of their hematologic and iron status that includes measurement of serum ferritin and transferrin saturation.<sup>1-3</sup> For chronic kidney disease (CKD) patients on hemodialysis taking erythropoiesis-stimulating agents, the 2006 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines and Clinical Practice Recommendations suggest that iron status be assessed at least once every 3 months. The KDOQI practice recommendations



**Table 1 | Relationships between different ferritin immunoassays**

Ferritin method		Deming regression equation	95% confidence interval of slope	95% confidence interval of intercept	Mean % difference <sup>a</sup>	p <sup>b</sup>
x	y					
Siemens Centaur	Beckman	y=0.87x+4.1	(0.80; 0.95)	(-50.6; 58.8)	-12.8	<0.001
Siemens Centaur	Ortho Vitros Eci	y=0.89x-6.2	(0.84; 0.95)	(-46.1; 33.8)	-13.4	<0.001
Siemens Centaur	Siemens Dimension RxL	y=0.91x+30.7	(0.80; 1.00)	(-47.9; 109.3)	-1.7	0.50
Siemens Centaur	Roche Elecsys	y=1.10x+27.8	(1.03; 1.17)	(-22.4; 78.0)	15.1	<0.001
Siemens Centaur	Abbott Architect	y=1.18x-42.0	(1.05; 1.31)	(-133.3; 49.2)	8.8	0.002
Beckman Access	Abbott Architect	y=1.36x-48.2	(1.21; 1.51)	(-142.2; 45.8)	21.6	<0.001

<sup>a</sup>Mean % difference calculated by method of Bland and Altman.<sup>3,2</sup>

<sup>b</sup>P calculated from two-tailed t-test with null hypothesis that the mean percent difference is equal to zero.

**Table 2 | Predicted values obtained with each assay at current and historical KDOQI cutoffs<sup>a</sup>**

Assay	Ferritin (ng/ml)	Ferritin (ng/ml)	Ferritin (ng/ml)
Siemens Centaur	200	500	800
Beckman Access	178	439	700
Ortho Vitros Eci	172	439	706
Siemens Dimension RxL	212	486	759
Roche Elecsys 2010	194	548	902
Abbott Architect	224	632	1040

KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

<sup>a</sup>Values shown are the predicted values from the Deming regression equations in Table 1, assuming values of 200, 500, and 800 were obtained using the Siemens Centaur method.

## GELECEKTE CEVAP VERMEMİZ GEREKEN SORULAR...

# DEMİR

Prediyaliz dönemdeki  
anemik demir  
profilinin netleşmesi

Oral ya da IV  
replasman tercihinin  
netleşmesi

Ferritin ölçüm  
yöntemlerinin  
standardizasyonu

KBH'da ferritin  
düzeyini kullanmak  
yararlı mı değil mi?

	<b>Hasta</b>	<b>Hedef</b>	<b>Ort Hb</b>	<b>Primer sonlanım</b>	<b>Primer sonlanım p değeri (HR)</b>
<b>NHS 1998</b>	1265	Düşük 9.0-11.0	10.0	Ölüm+MI	Düşük Hb lehine p=0.001 (HR=1.28)
		Yüksek 13.0-15.0	13.0		
<b>LVVI 2005</b>	596	Düşük 9.5-11.5	10.8	LVVI'da değişiklik	Gruplar arasında fark yok p=0.87
		Yüksek 13.5-14.5	13.1		
<b>CHOIR 2006</b>	1432	Düşük 11.1-11.5	11.3	Ölüm+MI + inme + KKY hos	Düşük kol lehine p=0.03 (HR=1.34)
		Yüksek 13.1-14.0	12.6		
<b>CREATE 2006</b>	603	Düşük 0.5-11.5	11.5	Ölüm+MI + KKY + inme + TIA + aritmi + amputasyon...	Düşük kol lehine ama p=0.2 (HR=0.78)
		Yüksek 13.0-15.0	13.4		

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

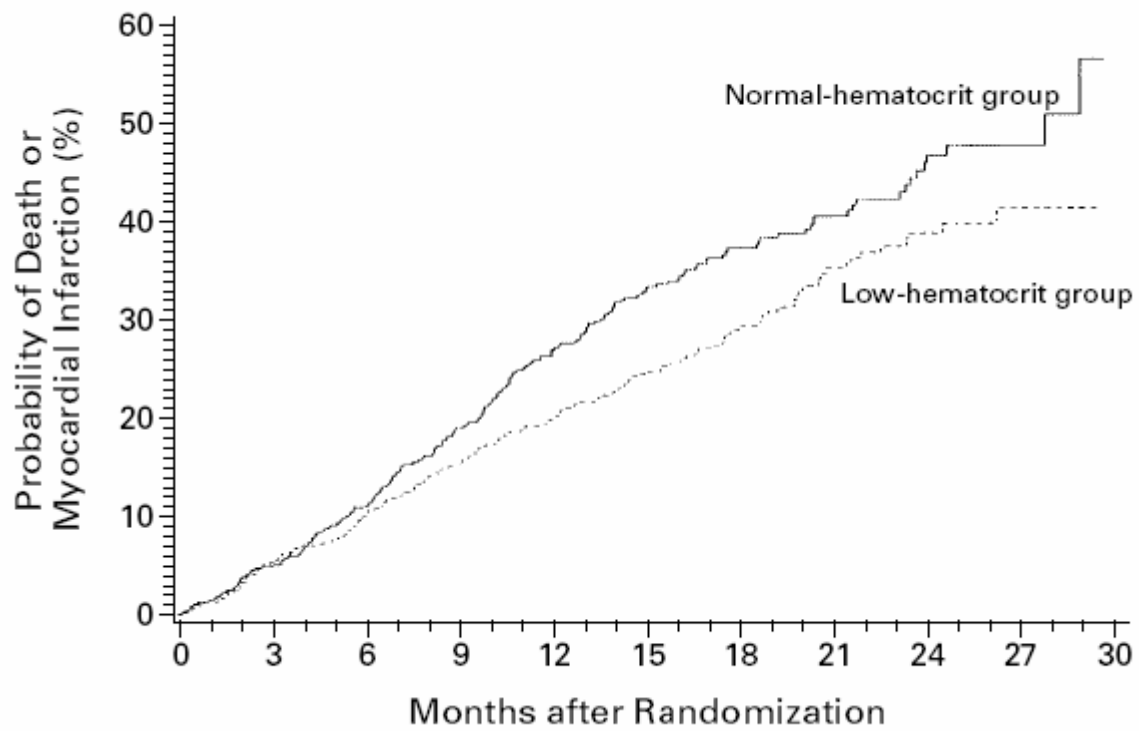
ANATOLE BESARAB, M.D., W. KLINE BOLTON, M.D., JEFFREY K. BROWNE, PH.D., JOAN C. EGRIE, PH.D.,  
ALLEN R. NISSENSON, M.D., DOUGLAS M. OKAMOTO, PH.D., STEVE J. SCHWAB, M.D., AND DAVID A. GOODKIN, M.D.

**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

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,<sup>1</sup> 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.<sup>2</sup>



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\*

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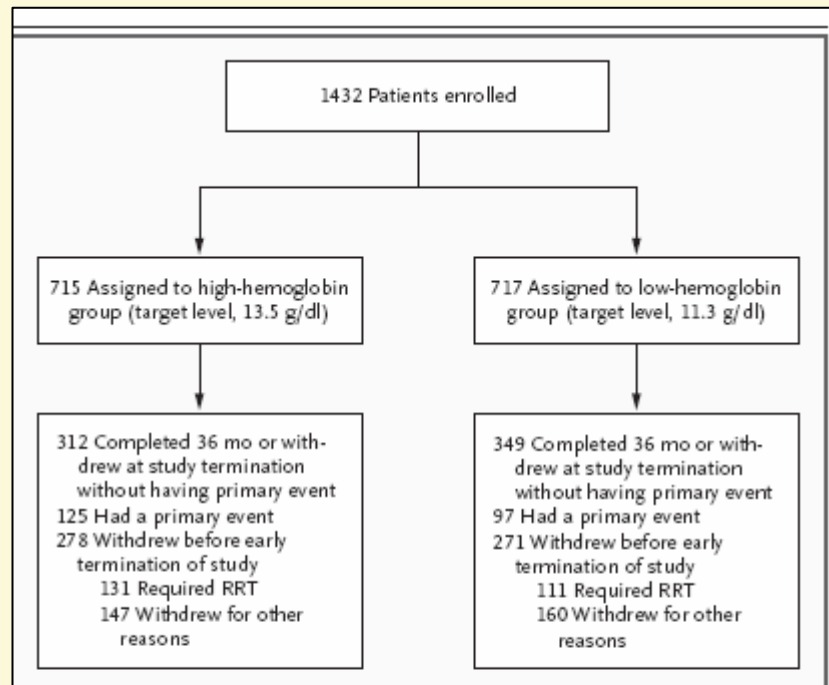
ABSTRACT

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**BACKGROUND**

Anemia, a common complication of chronic kidney disease, usually develops as a consequence of erythropoietin deficiency. Recombinant human erythropoietin (epoetin alfa) is indicated for the correction of anemia associated with this condition. However, the optimal level of hemoglobin correction is not defined.

From the Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston (A.K.S.); the Renal Division, Duke University Medical Center (L.S., D.R.), Duke Clinical Research Institute (L.S., S.S.), and the Department of Biostatistics and



**Figure 1. Enrollment and Outcomes.**

A total of 1432 patients were enrolled; 715 were assigned to the high-hemoglobin group (with a target level of 13.5 g per deciliter), and 717 were assigned to the low-hemoglobin group (with a target level of 11.3 g per deciliter). In addition to the stated reasons for withdrawal from the study, other reasons included a request from a patient, an investigator, or the study sponsor; pregnancy; an adverse event; a protocol violation; or a loss to follow-up. RRT denotes renal replacement therapy.

**Table 1.** Baseline Characteristics of the Patients.\*

Characteristic	High-Hemoglobin Group (N=715)	Low-Hemoglobin Group (N=717)
Age (yr)	66.0±14.3	66.3±13.5
Female sex (%)	56.2	54.1
Race (%)		
White	62.3	61.1
Black	28.6	29.3
American Indian or Alaskan Native	0.1	0.4
Asian or Pacific Islander	3.4	3.2
Other	5.6	6.0
Hispanic ethnic background (%)	12.5	13.5
History of smoking tobacco (%)	47.5	44.6
Cause of chronic kidney disease (%)		
Diabetes	46.8	50.8
Hypertension	29.9	27.5
Other	23.3	21.6
Cardiovascular history (%)		
Hypertension	95.8	93.2†
Myocardial infarction	16.4	15.0
CABG	17.4	13.5‡
PCI	10.9	11.9
Congestive heart failure	24.4	22.9
Atrial fibrillation	9.4	8.6
Stroke	9.8	10.0
Peripheral vascular disease	16.4	16.4
Myocardial infarction, stroke, CABG, PCI, or amputation of a lower limb	36.3	34.5
Body-mass index	30.4±7.7	30.4±7.5
Blood pressure (mm Hg)		
Systolic	136.7±19.7	135.6±20.0
Diastolic	71.6±11.6	70.9±11.2
Mean arterial	93.3±12.1	92.5±12.0

**Table 1. (Continued.)**

	High-Hemoglobin Group (N=715)	Low-Hemoglobin Group (N=717)
Hemoglobin (g/dl)	10.1±0.9	10.1±0.9
Hematocrit (%)	31.4±2.9	31.4±2.9
Transferrin saturation (%)	25.2±11.8	24.6±10.1
Ferritin (ng/ml)	167.8±157.2	179.2±171.5
Creatinine clearance (ml/min/1.73 m <sup>2</sup> ) <sup>§</sup>	36.7±17.0	37.1±17.9
GFR (ml/min) <sup>¶</sup>	27.0±8.7	27.3±9.1
Albumin (g/dl)	3.7±0.5	3.8±0.5
Ratio of total protein to creatinine in urine	1.6±2.3	1.5±2.3
Medications (%)		
ACE inhibitor only	35.7	37.8
ARB only	29.7	26.8
Combination of ACE inhibitor and ARB	8.3	9.6
Beta-blocker (including labetalol)	46.9	47.7
Platelet aggregation inhibitor (excluding heparin)	42.8	45.0
HMG CoA reductase inhibitor	52.8	52.3
Iron		
Intravenous	2.6	1.6
Oral	26.5	26.7
Unknown route	3.1	1.6

\* Plus-minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. Race and ethnic group were assigned by the investigators. Cardiovascular history was reported either by the patient or by chart review. CABG denotes coronary-artery bypass grafting, PCI percutaneous coronary intervention, ACE angiotensin-converting enzyme, ARB angiotensin II-receptor blocker, and HMG CoA 3-hydroxy-3-methylglutaryl coenzyme A.

† P=0.03 for the comparison with the high-hemoglobin group.

‡ P=0.05 for the comparison with the high-hemoglobin group.

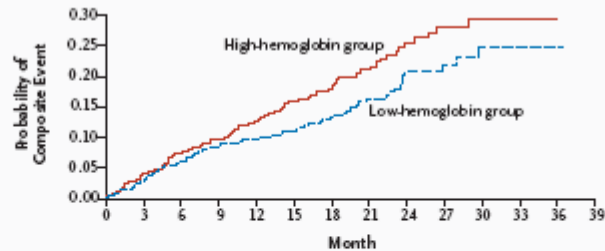
§ The rate was calculated with the use of the Cockcroft-Gault formula.

¶ The GFR was calculated according to the MDRD formula.



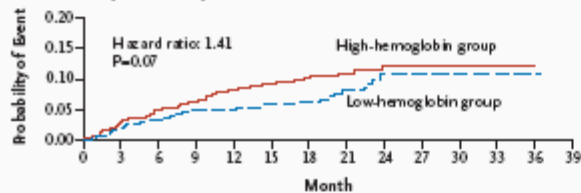
**A**

**Primary Composite End Point**



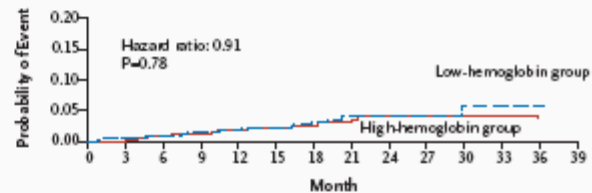
No. at Risk	
High-hemoglobin	715 654 587 520 457 355 270 176 101 72 55 23
Low-hemoglobin	717 660 594 539 499 397 293 182 107 67 44 23

**B Hospitalization for CHF (without RRT)**



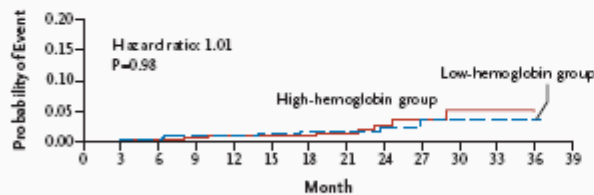
No. at Risk	
High-hemoglobin	715 656 591 523 461 359 273 179 102 73 56 23
Low-hemoglobin	717 663 596 544 504 402 299 187 111 70 45 24

**C Myocardial Infarction**



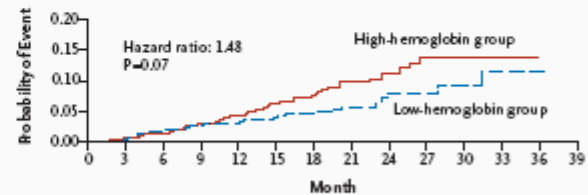
No. at Risk	
High-hemoglobin	715 674 612 543 487 387 295 193 113 79 59 25
Low-hemoglobin	717 672 609 560 520 415 307 192 115 73 49 26

**D Stroke**



No. at Risk	
High-hemoglobin	715 672 611 543 487 386 295 195 113 79 59 25
Low-hemoglobin	717 675 608 559 518 414 306 193 115 72 48 25

**E Death**



No. at Risk	
High-hemoglobin	715 675 614 545 490 389 297 196 114 80 60 25
Low-hemoglobin	717 676 610 564 523 418 310 195 117 74 49 26

**Table 2. Secondary End Points.\***

End Point	High-Hemoglobin Group (N=715) no. of patients (%)		Low-Hemoglobin Group (N=717)		P Value†
			Hazard Ratio (95% CI)		
<b>Clinical results</b>					
Components of the primary end point‡					
Death	52 (7.3)	36 (5.0)	1.48 (0.97–2.27)		0.07
Hospitalization for congestive heart failure (without renal replacement therapy)	64 (9.0)	47 (6.6)	1.41 (0.97–2.05)		0.07
Myocardial infarction	18 (2.5)	20 (2.8)	0.91 (0.48–1.73)		0.78
Stroke	12 (1.7)	12 (1.7)	1.01 (0.45–2.25)		0.98
Renal replacement therapy					
Any renal replacement therapy§	155 (21.7)	134 (18.7)	1.19 (0.94–1.49)		0.15
Hospitalization for renal replacement therapy	99 (13.8)	81 (11.3)	1.25 (0.93–1.68)		0.13
Hospitalization					
Cardiovascular causes	233 (32.6)	197 (27.5)	1.23 (1.01–1.48)		0.03
Any cause	369 (51.6)	334 (46.6)	1.18 (1.02–1.37)		0.03
	High-Hemoglobin Group		Low-Hemoglobin Group		P Value¶
	Baseline	Change from Baseline‖	Baseline	Change from Baseline**	
<b>Quality of life‡‡</b>					
LASA score					
Energy	38.1±23.7	16.6±28.6	38.2±23.1	15.5±28.6	0.67
Activity	40.8±25.9	15.0±39.9	42.5±25.8	13.3±29.8	0.98
Overall quality of life	46.3±26.2	11.2±29.7	46.1±25.4	11.9±28.1	0.46
KDQ total score	20.3±5.8	1.6±5.6	20.6±6.0	1.1±5.6	0.26
SF-36 score					
Physical function	41.9±28.2	3.2±24.0	42.4±27.3	2.1±23.3	0.49
Physical role	31.9±38.9	6.4±40.7	32.5±39.2	7.5±43.2	0.32
Pain	57.8±28.5	0.4±28.1	58.0±27.1	2.4±26.7	0.15
General health	41.3±20.1	3.0±19.2	42.6±20.1	1.8±17.8	0.87
Vitality	35.2±22.6	10.0±23.8	36.6±22.4	8.2±20.6	0.58
Social function	63.7±29.5	1.3±33.1	63.7±29.0	3.5±28.7	0.16
Emotional role	57.2±43.6	0.8±48.3	57.4±43.3	5.9±48.1	0.01
Mental health	69.6±19.5	1.7±18.5	70.2±20.1	2.4±18.2	0.31

**Table 3. Adverse Events.\***

Adverse Event	High-Hemoglobin Group (N= 686)	Low-Hemoglobin Group (N= 688)	P Value†
	<i>no. of patients (%)</i>		
Any event	607 (88.5)	589 (85.6)	0.11
Thrombovascular event			
Any event	126 (18.4)	120 (17.4)	0.65
Any clinically relevant event‡	74 (10.8)	82 (11.9)	0.51
Any serious adverse event	376 (54.8)	334 (48.5)	0.02
Any serious adverse event associated with epoetin alfa§	10 (1.5)¶	3 (0.4)‖	0.05
Serious adverse events**			
Congestive heart failure	77 (11.2)	51 (7.4)	0.02
Myocardial infarction	10 (1.5)	19 (2.8)	0.09
Gastrointestinal hemorrhage	18 (2.6)	18 (2.6)	0.99
Chest pain	23 (3.4)	16 (2.3)	0.25
Cellulitis	16 (2.3)	11 (1.6)	0.33
Pneumonia	32 (4.7)	28 (4.1)	0.59
Renal failure	95 (13.8)	73 (10.6)	0.07

## İki hemoglobin hedefine ulaşmak için Epoetin Alfa kullanılan CHOIR çalışmasındaki klinik sonuçlar

Sonlanım	Hb 13.5 d/dl (n=715)	Hb 11.3 g/dl (n=717)	Hazard ratio (% 95 CI)	P
Kompozit olaylar (ölüm, inme, MI, KKY)	125 (% 17.5)	97 (% 13.5)	1.34 (1.03-1.74)	0.03
Ölümler	52 (% 7.3)	36 (% 5.0)	1.48 (0.97-2.27)	0.07
KKY için hospitalizasyon	64 (% 9.0)	47 (% 6.6)	1.41 (0.97-2.05)	0.07

*Singh AK, Am J Kidney Dis, December 2008*

## CHOIR alıřmasındaki seilmiř kt olaylar

<b>Kt olay</b>	<b>Hb 13.5 g/dl (n=686)</b>	<b>Hb 11.3 g/dl (n=688)</b>	<b>P</b>
ESA ile herhangi bir ciddi kt olay	10 (%1.5)	3 (%0.4)	0.05
Ciddi kt olay:KKY	77 (%11.2)	51 (%7.4)	0.02

*Singh AK, Am J Kidney Dis, December 2008*

# 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\*

### ABSTRACT

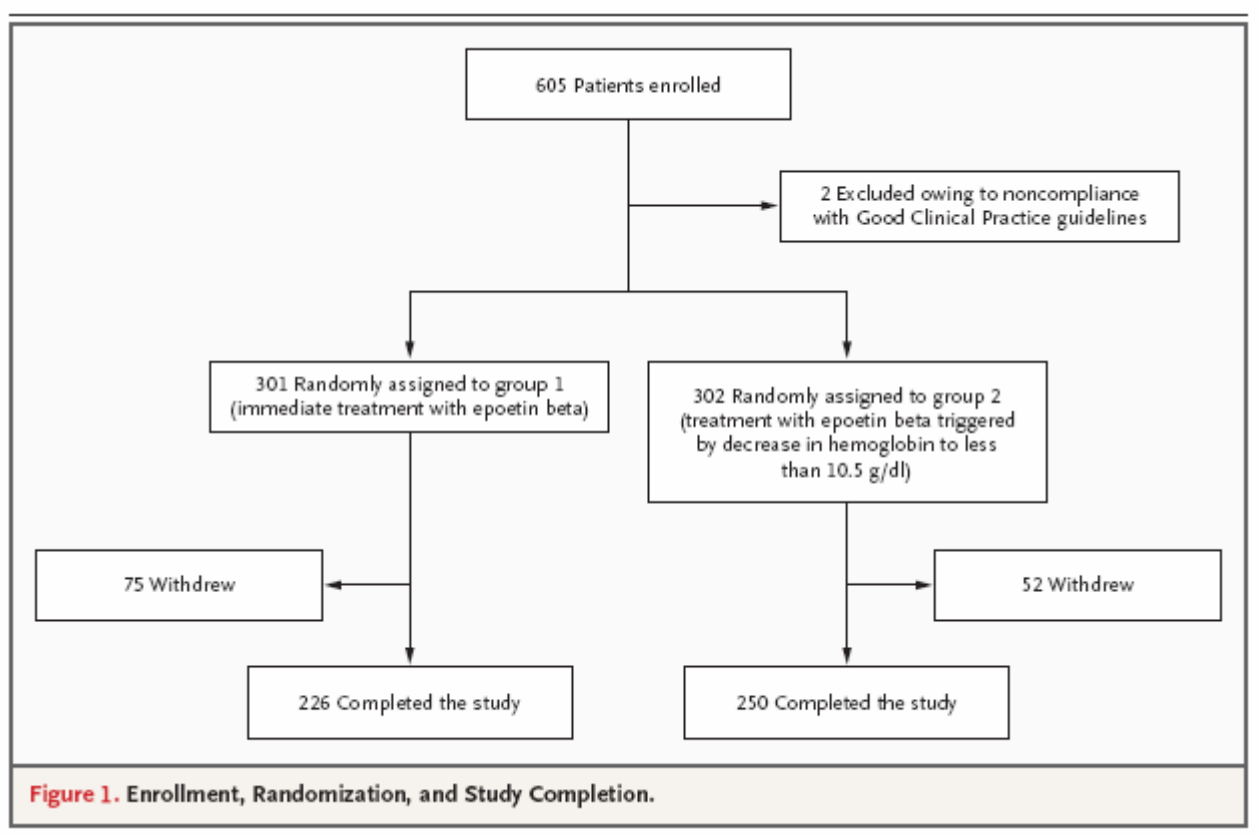
#### BACKGROUND

Whether correction of anemia in patients with stage 3 or 4 chronic kidney disease improves cardiovascular outcomes is not established.

#### METHODS

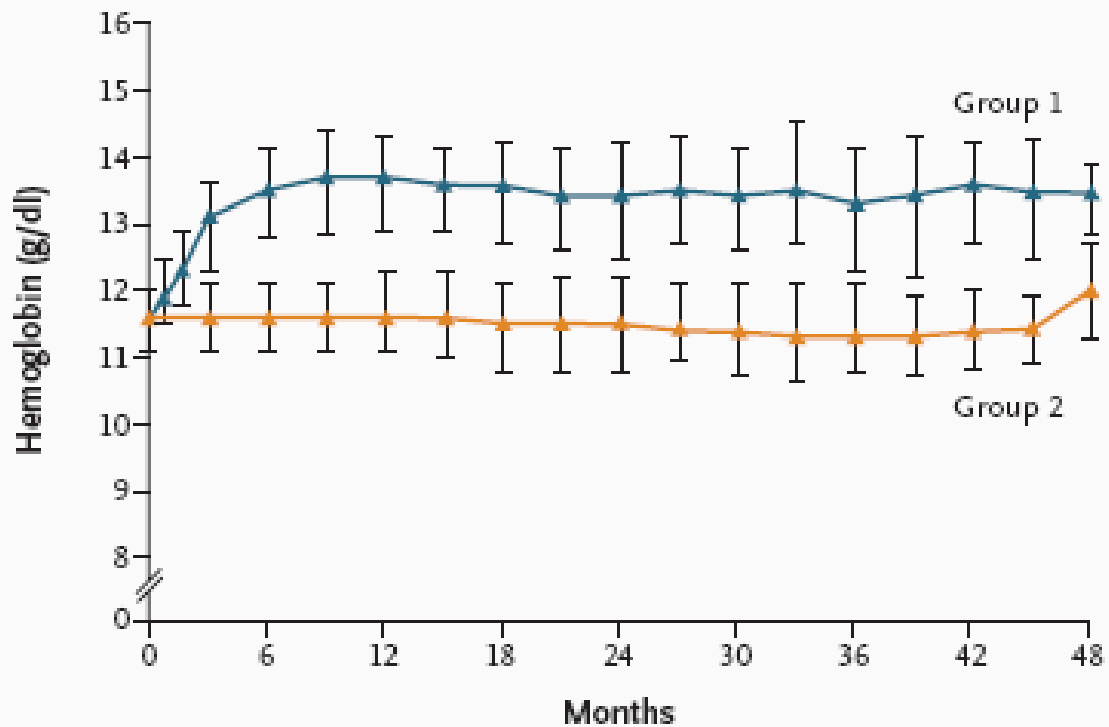
We randomly assigned 603 patients with an estimated glomerular filtration rate (GFR) of 15.0 to 35.0 ml per minute per 1.73 m<sup>2</sup> of body-surface area and mild-to-moderate anemia (hemoglobin level, 11.0 to 12.5 g per deciliter) to a target hemoglobin value in the normal range (13.0 to 15.0 g per deciliter, group 1) or the subnormal range (10.5 to 11.5 g per deciliter, group 2). Subcutaneous erythropoietin (epoetin beta) was initiated at randomization (group 1) or only after the hemoglobin level fell below 10.5 g per deciliter (group 2). The primary end point was a composite of eight cardiovascular events; secondary end points included left ventricular mass index, quality-of-life scores

From Inserm Unité 507 and Assistance Publique-Hôpitaux de Paris, Necker Hospital, Division of Nephrology, Paris (T.B.D.); the Department of Nephrology and Dialysis, Ospedale A. Manzoni, Lecco, Italy (F.L.); the Department of Nephrology, University Hospital Lund, Lund, Sweden (N.C.); the Department of Nephrology and Hypertension, University of Erlangen-Nürnberg, Erlangen, Germany, and the First Medical Clinic, Mannheim University Hospital, University of Heidelberg, Heidelberg, Germany (K.-U.E.); the Department of Renal Medicine, King's College Hospital, London (I.C.M.); the Depart-



**Table 1. (Continued.)**

<b>Characteristic</b>	<b>Group 1 (N= 301)</b>	<b>Group 2 (N= 302)</b>	<b>P Value</b>
Preexisting cardiovascular disease — no. of patients (%)§	280 (93)	278 (92.1)	0.71
Chronic heart failure	93 (33)	87 (31)	0.61
Previous myocardial infarction	3 (1)	4 (1)	0.85
Cerebrovascular disease	10 (4)	6 (2)	0.37
Coronary artery disease	9 (3)	10 (4)	0.91
Peripheral vascular disease	6 (2)	5 (2)	0.88
NYHA class — no. of patients (%)			
0	167 (55)	149 (49)	0.14
I	37 (12)	43 (14)	0.52
II	53 (18)	44 (15)	0.34
Echocardiographic variables			
Left ventricular volume — ml			
Mean	67.7±19.2	65.1±19.2	0.17
Median	64.0	62.7	
Left ventricular mass index — g/m <sup>2</sup>			
Mean	120.3±35.0	118.0±34.3	0.44
Median	116.0	113.0	
Hemoglobin — g/dl	11.6±0.6	11.6±0.6	0.89
Serum ferritin — ng/ml			
Mean	174.4±148.3	189.4±157.7	0.56
Median	131.1	128.3	
Transferrin saturation — %			
Mean	25.6	38.1	0.59
Median	23.9	25.1	



**Figure 2.** Median Hemoglobin Levels in the Intention-to-Treat Population during the Study.

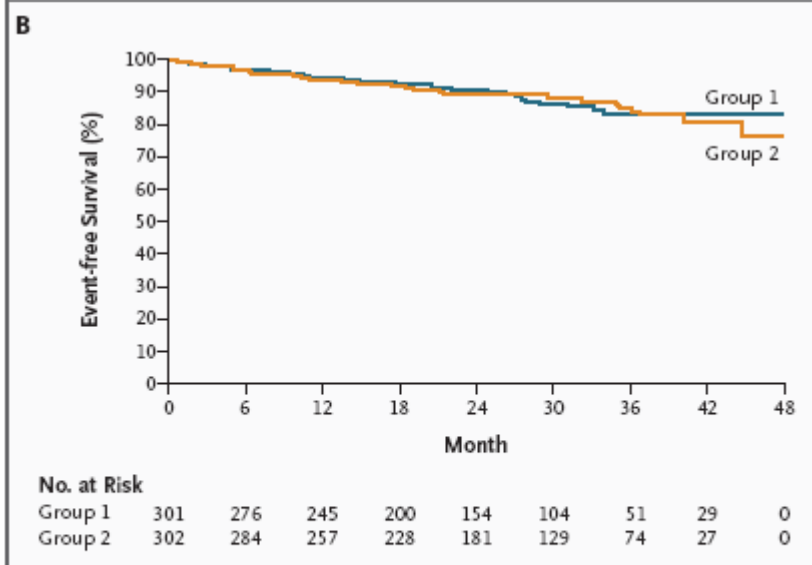
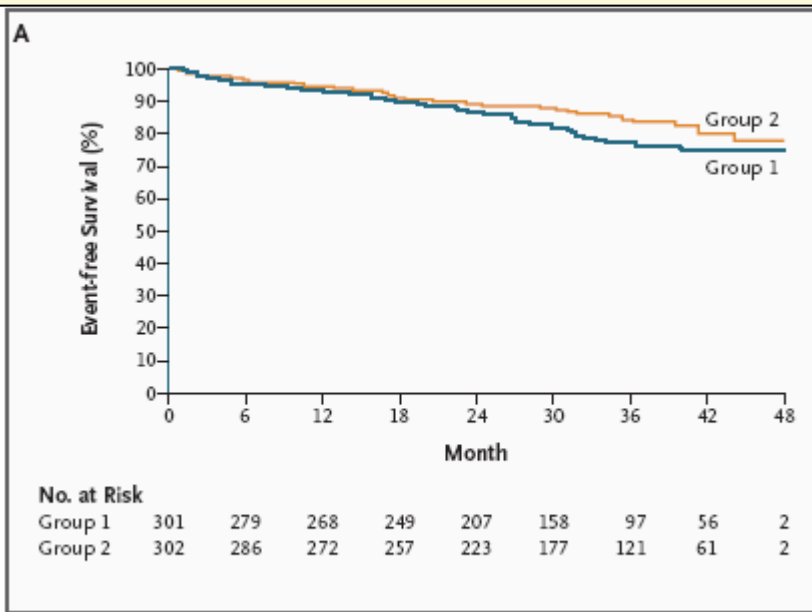
I bars indicate standard deviations.

**Table 2. Summary of the Most Frequent Adverse Events and Other Relevant Adverse Events.\***

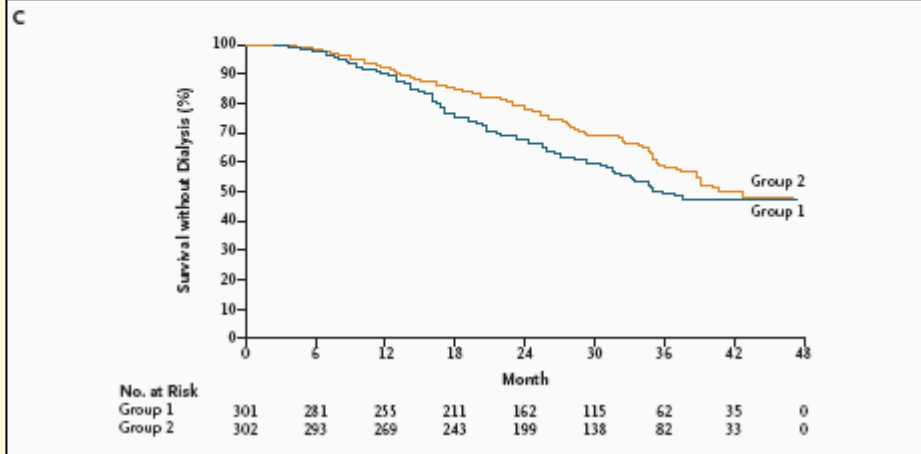
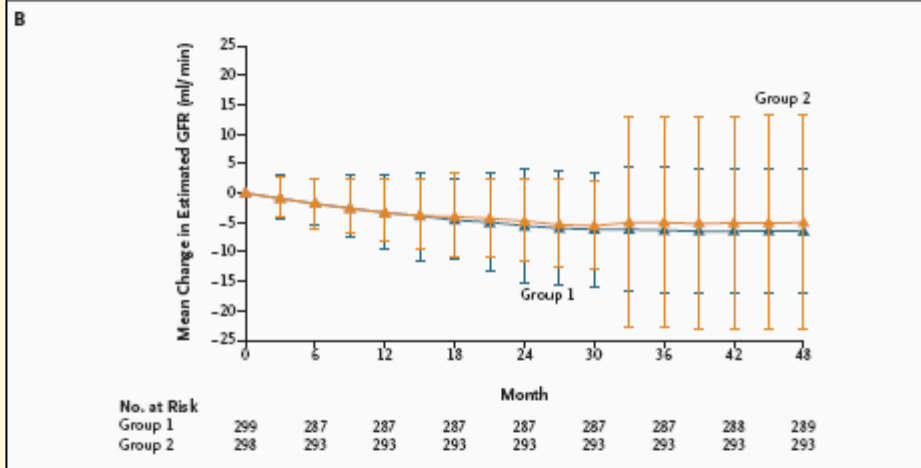
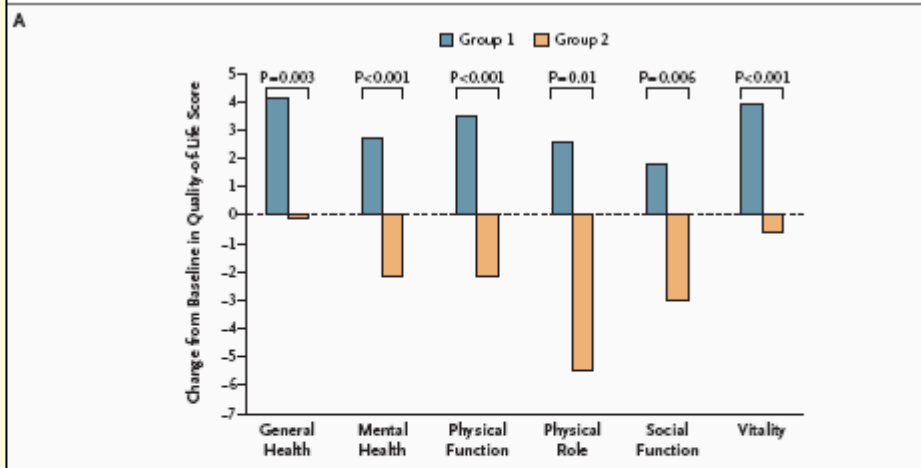
Adverse Event	Group 1 (N= 300)	Group 2 (N= 302)	P Value
	<i>no. of patients (%)</i>		
<b>Most frequent adverse events</b>	279 (93)	273 (90)	0.28
Cardiac disorders	73 (24)	70 (23)	0.78
Acute cardiac failure	13 (4)	23 (8)	0.11
Arrhythmia	18 (6)	16 (5)	0.78
Myocardial infarction	14 (5)	15 (5)	0.94
Angina pectoris	16 (5)	7 (2)	0.07
Progression of chronic kidney disease	166 (55)	163 (54)	0.77
Vascular disorders	135 (45)	89 (29)	<0.001
Hypertension†	89 (30)	59 (20)	0.005
Hypotension	14 (5)	17 (6)	0.66
Peripheral vascular disorder	17 (6)	8 (3)	0.08
Nervous system disorders	77 (26)	53 (18)	0.02
Headache	31 (10)	16 (5)	0.03
Dizziness	19 (6)	14 (5)	0.41
Infections	168 (56)	165 (55)	0.77
Urinary tract infection	28 (9)	35 (12)	0.40
Nasopharyngitis	24 (8)	23 (8)	0.92
Upper respiratory tract infection	17 (6)	28 (9)	0.11
Influenza	26 (9)	12 (4)	0.02
Pneumonia	15 (5)	14 (5)	0.91
Bronchitis	26 (9)	22 (7)	0.58
Gastrointestinal disorders	119 (40)	104 (34)	0.20
Diarrhea	26 (9)	25 (8)	0.92
Constipation	24 (8)	19 (6)	0.46
Nausea	16 (5)	14 (5)	0.76
Vomiting	15 (5)	15 (5)	0.94

**Table 2. (Continued.)**

<b>Adverse Event</b>	<b>Group 1 (N=300)</b>	<b>Group 2 (N=302)</b>	<b>P Value</b>
	<i>no. of patients (%)</i>		
<b>Metabolic and nutritional disorders</b>	111 (37)	106 (35)	0.66
Hyperkalemia	30 (10)	31 (10)	0.97
Hypercholesterolemia†	25 (8)	22 (7)	0.69
Gout	15 (5)	16 (5)	0.94
Hypoglycemia	16 (5)	5 (2)	0.02
<b>Musculoskeletal and connective-tissue disorders</b>	87 (29)	98 (32)	0.38
Back pain	25 (8)	32 (11)	0.38
Arthralgia	21 (7)	19 (6)	0.79
Pain in arms, legs, hands, or feet	18 (6)	16 (5)	0.77
Muscle cramp	9 (3)	16 (5)	0.19
<b>General disorders</b>	86 (29)	77 (25)	0.41
Asthenia	17 (6)	17 (6)	0.95
Peripheral edema	22 (7)	12 (4)	0.09
Fatigue	14 (5)	18 (6)	0.54
<b>Skin and subcutaneous-tissue disorders</b>	61 (20)	47 (16)	0.14
Pruritus	27 (9)	18 (6)	0.18
<b>Respiratory, thoracic, or mediastinal disorders</b>	50 (17)	47 (16)	0.75
Cough	20 (7)	16 (5)	0.53
<b>Psychiatric disorders</b>	35 (12)	38 (13)	0.78
Insomnia	12 (4)	23 (8)	0.07
<b>Blood and lymphatic disorders</b>	12 (4)	24 (8)	0.05
<b>Referral for unplanned investigations</b>	45 (15)	30 (10)	0.07
Increased blood pressure	21 (7)	13 (4)	0.18
<b>Other relevant adverse events</b>			
Cerebrovascular accident	8 (3)	5 (2)	0.48
Transient ischemic attack	5 (2)	2 (<1)	0.34
<b>Arteriovenous fistula</b>			
Thrombosis	12 (4)	8 (3)	0.42
Complication	8 (3)	3 (1)	0.17



**Figure 3.** Time to the Primary End Point of a First Cardiovascular Event before (Panel A) and after (Panel B) Censoring of Data on Patients at the Time of Initiation of Dialysis.



## CREATE çalışmasında istatistiksel anlamlılığa ulaşmış sekonder sonlanımlar

<b>Sonlanım</b>	<b>Hb 13.0-15.0 g/dl</b>	<b>Hb 10.5-11.5 g/dl</b>	<b><i>P</i></b>
Vasküler hastalıklar	135/300 (%45)	89/302 (%29)	<0.001
Hipertansiyon	89/300 (%30)	59/302 (%20)	0.005
Diyalize ilerleme	127/301	111/302	0.03

*Singh AK, Am J Kidney Dis, December 2008*

# Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis



Arintaya Phrommintikul, Steven Joseph Haas, Maros Elsik, Henry Krum

## Summary

**Background** Recombinant human erythropoietin is commonly used for treatment of anaemia. Our aim was to determine whether targeting different haemoglobin concentrations with such treatment is associated with altered all-cause mortality and cardiovascular events in patients with anaemia caused by chronic kidney disease.

**Methods** We did a meta-analysis of randomised controlled clinical trials that were identified in medical databases and trial registration websites. Trials were eligible for inclusion if they assessed the effects of targeting different haemoglobin concentrations in patients with anaemia caused by chronic disease who were randomly assigned to treatment with recombinant human erythropoietin, recruited at least 100 patients, and had a minimum follow-up of 12 weeks.

**Findings** We analysed nine randomised controlled trials that enrolled 5143 patients. There was a significantly higher risk of all-cause mortality (risk ratio 1.17, 95% CI 1.01–1.35;  $p=0.031$ ) and arteriovenous access thrombosis (1.34, 1.16–1.54;  $p=0.0001$ ) in the higher haemoglobin target group than in the lower haemoglobin target group in the fixed effects model without heterogeneity between studies. There was a significantly higher risk of poorly controlled blood pressure (1.27, 1.08–1.50;  $p=0.004$ ) in the higher haemoglobin target group than in the lower target haemoglobin group with the fixed effects model; however, this was not significant in the random effects model (1.31, 0.97–1.78;  $p=0.075$ ). The incidence of myocardial infarction was much the same in the two groups.

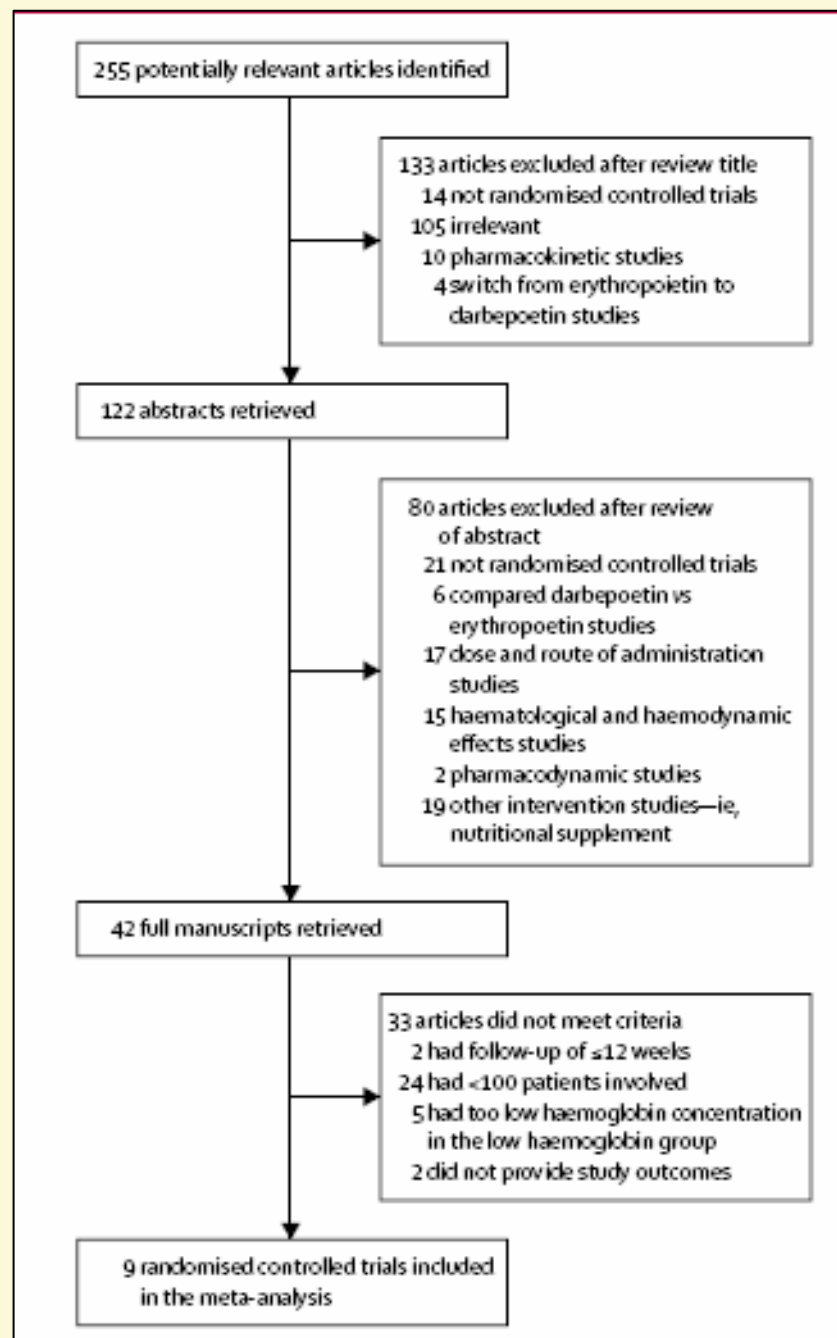
**Interpretation** To target higher haemoglobin concentrations when treating patients with anaemia caused by chronic kidney disease with recombinant human erythropoietin puts such patients at increased risk of death. Current guidelines do not include an upper limit for the target haemoglobin concentration; such an upper limit should be considered in future recommendations.

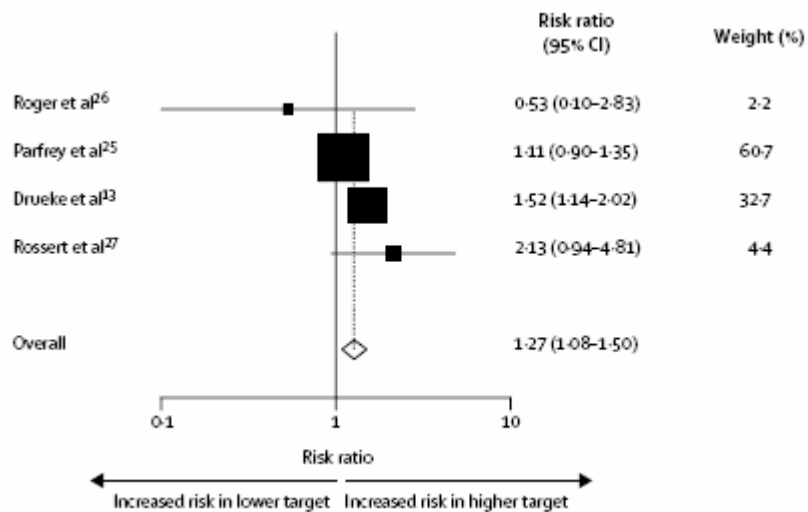
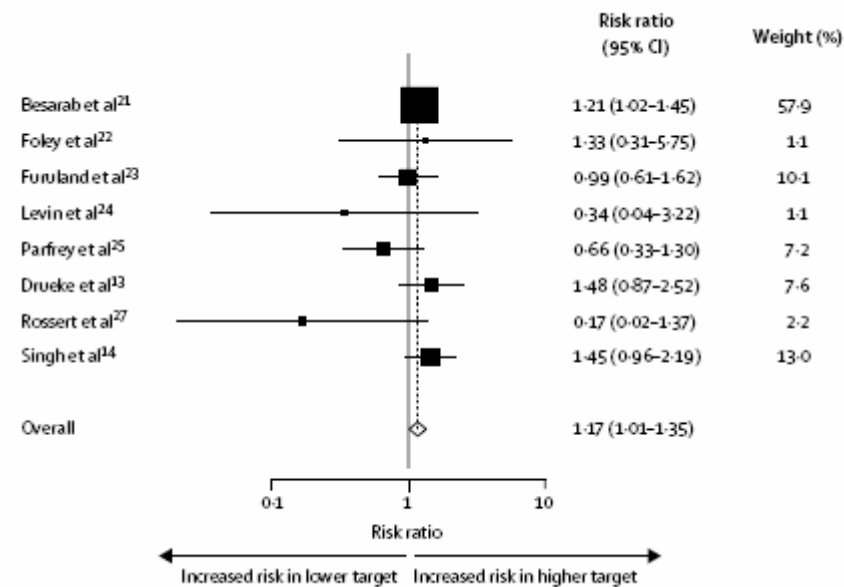
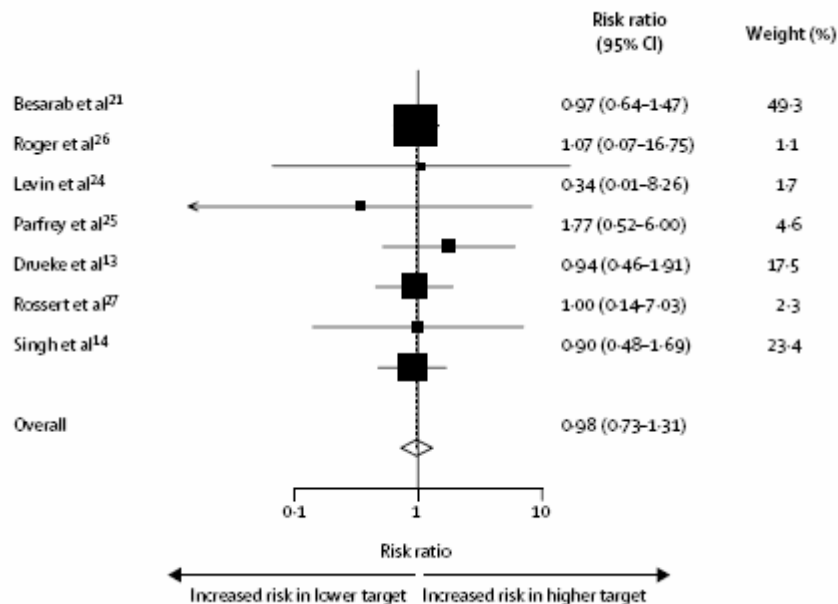
*Lancet* 2007; 369: 381–88

See [Comment](#) page 346

NHMRC Centre of Clinical Research Excellence in Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University, Alfred Hospital, Melbourne, Australia (A Phrommintikul MD, S J Haas BPharm, M Elsik FRACP, Prof H Krum FRACP); and Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (A Phrommintikul)

Correspondence to: Prof Henry Krum, NHMRC Centre of Clinical Research Excellence in Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University, Alfred Hospital, Central and Eastern Clinical School, Melbourne VIC 3004, Australia [henry.krum@med.monash.edu.au](mailto:henry.krum@med.monash.edu.au)





**CREATE VE CHOIR'DAN  
ALDIĐIMIZ DERSLER**

# Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)

Etiklik sorunu

Plasebo kontrollü

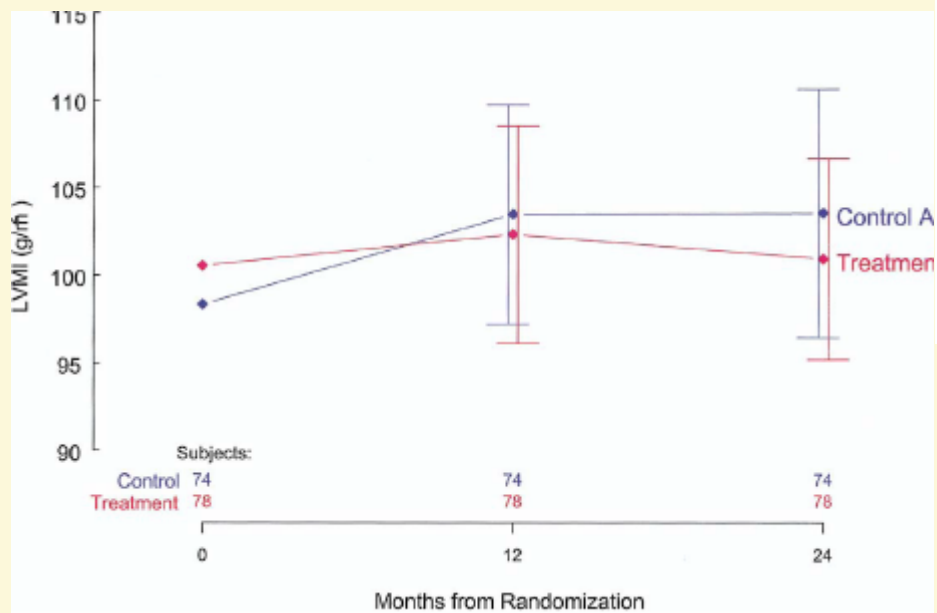
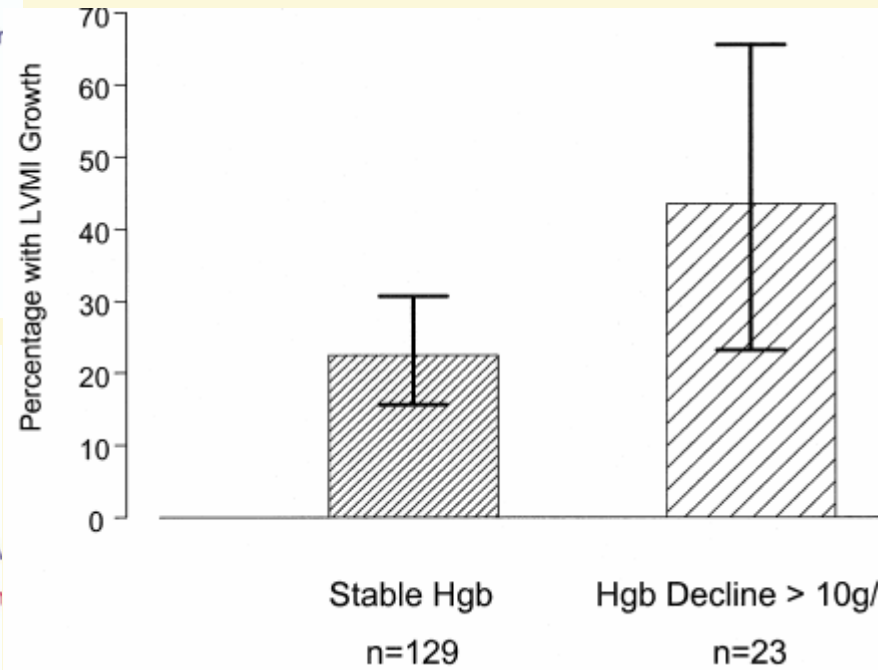
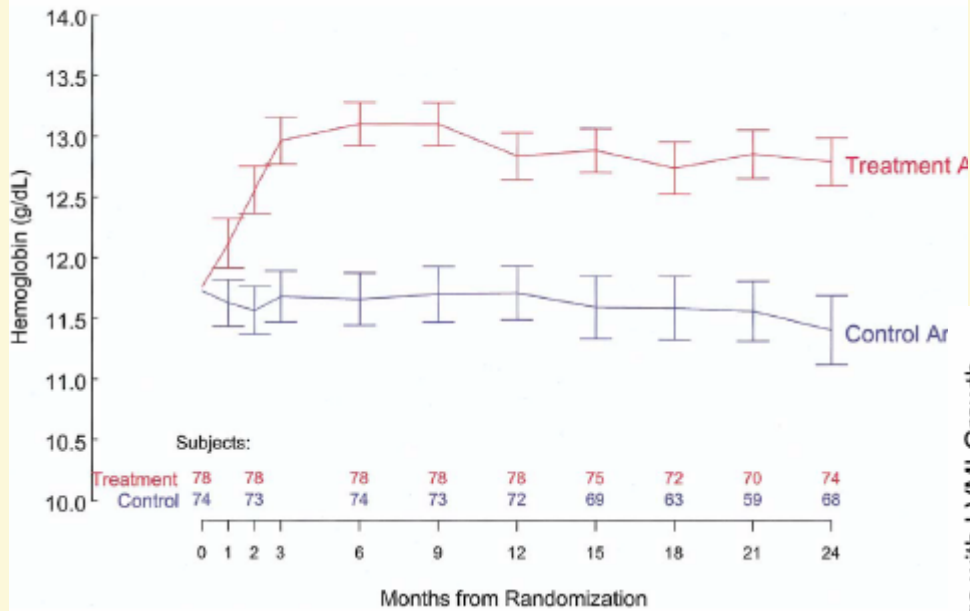
KDIGO 2011 Kılavuzu

## Canadian Randomized Trial of Hemoglobin Maintenance to Prevent or Delay Left Ventricular Mass Growth in Patients With CKD

Adeera Levin, MD, Ognjenka Djurdjev, MSc, Christopher Thompson, MD, Brendan Barrett, MD, Jean Ethier, MD, Euan Carlisle, MD, Paul Barre, MD, Peter Magner, MD, Norman Muirhead, MD, Sheldon Tobe, MD, Paul Tam, MD, Jose Arturo Wadgymar, MD, Joanne Kappel, MD, David Holland, MD, Vincent Pichette, MD, Ahmed Shoker, MD, George Soltys, MD, Mauro Verrelli, MD, FRCOC, and Joel Singer, PhD

• **Background:** This randomized clinical trial is designed to assess whether the prevention and/or correction of anemia, by immediate versus delayed treatment with erythropoietin alfa in patients with chronic kidney disease, would delay left ventricular (LV) growth. Study design and sample size calculations were based on previously published Canadian data. **Methods:** One hundred seventy-two patients were randomly assigned. The treatment group received therapy with erythropoietin alfa subcutaneously to maintain or achieve hemoglobin (Hgb) level targets of 12.0 to 14.0 g/dL (120 to 140 g/L). The control/delayed treatment group had Hgb levels of  $9.0 \pm 0.5$  g/dL ( $90 \pm 5$  g/L) before therapy was started: target level was 9.0 to 10.5 g/dL (90 to 105 g/L). Optimal blood pressure and parathyroid hormone, calcium, and phosphate level targets were prescribed; all patients were iron replete. The primary end point is LV growth at 24 months. **Results:** One hundred fifty-two patients were eligible for the intention-to-treat analysis: mean age was 57 years, 30% were women, 38% had diabetes, and median glomerular filtration rate was 29 mL/min (0.48 mL/s; range, 12 to 55 mL/min [0.20 to 0.92 mL/s]). Blood pressure and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use were similar in the control/delayed treatment and treatment groups at baseline. Erythropoietin therapy was administered to 77 of 78 patients in the treatment group, with a median final dose of 2,000 IU/wk. Sixteen patients in the control/delayed treatment group were administered erythropoietin at a median final dose of 3,000 IU/wk. There was no statistically significant difference between groups for the primary outcome of mean change in LV mass index (LVMI) from baseline to 24 months, which was  $5.21 \pm 30.3$  g/m<sup>2</sup> in the control/delayed treatment group versus  $0.37 \pm 25.0$  g/m<sup>2</sup> in the treatment

TRIAL OF ANEMIA CORRECTION IN CKD



## LV Büyüme modeli:

**Düşük bazal LVMI, düşük bazal Hb ve ileri yaş ile LV büyümesi arasındaki (randomizasyon koluna bakmaksızın) bağımsız ilişkiler**

<b>Değişken</b>	<b>Odds Ratio</b>	<b>%95 CI</b>	<b>P</b>
0 ay LVMI (/10g/m <sup>2</sup> )	0.749	0.621-0.905	0.0027
Yaş (/10y)	1.357	1.029-1.788	0.0305
Hb (/1.0 g/dl)	0.580	0.344-0.977	0.0408
Randomizasyon kolu (kontrol=1, tedavi=2)	0.619	0.282-1.355	0.2299

*Levin ve ark, Am J Kidney Dis, November 2005*

## LV Büyüme modeli:

**Düşük bazal LVMI, ileri yaş, cinsiyet ve çalışma süresinde Hb düzeyinde düşme ile LV büyümesi arasındaki bağımsız ilişki**

<b>Değişken</b>	<b>Odds Ratio</b>	<b>%95 CI</b>	<b>P</b>
0 ay LVMI (/10g/m <sup>2</sup> )	0.780	0.642-0.949	0.0128
Yaş (/10y)	1.398	1.051-1.860	0.0216
Cinsiyet (kadın v erkek)	2.285	0.978-5.338	0.0562
Diabet	2.186	0.965-4.950	0.0608
0-24 ay Hb değişimi (/1.0g/dl)	0.689	0.493-0.961	0.0285

*Levin ve ark, Am J Kidney Dis, November 2005*

## **FDA'NIN ESA KULLANIMINA İLİŞKİN BİLGİ DEĞİŞİKLİĞİ, Mart 2007**

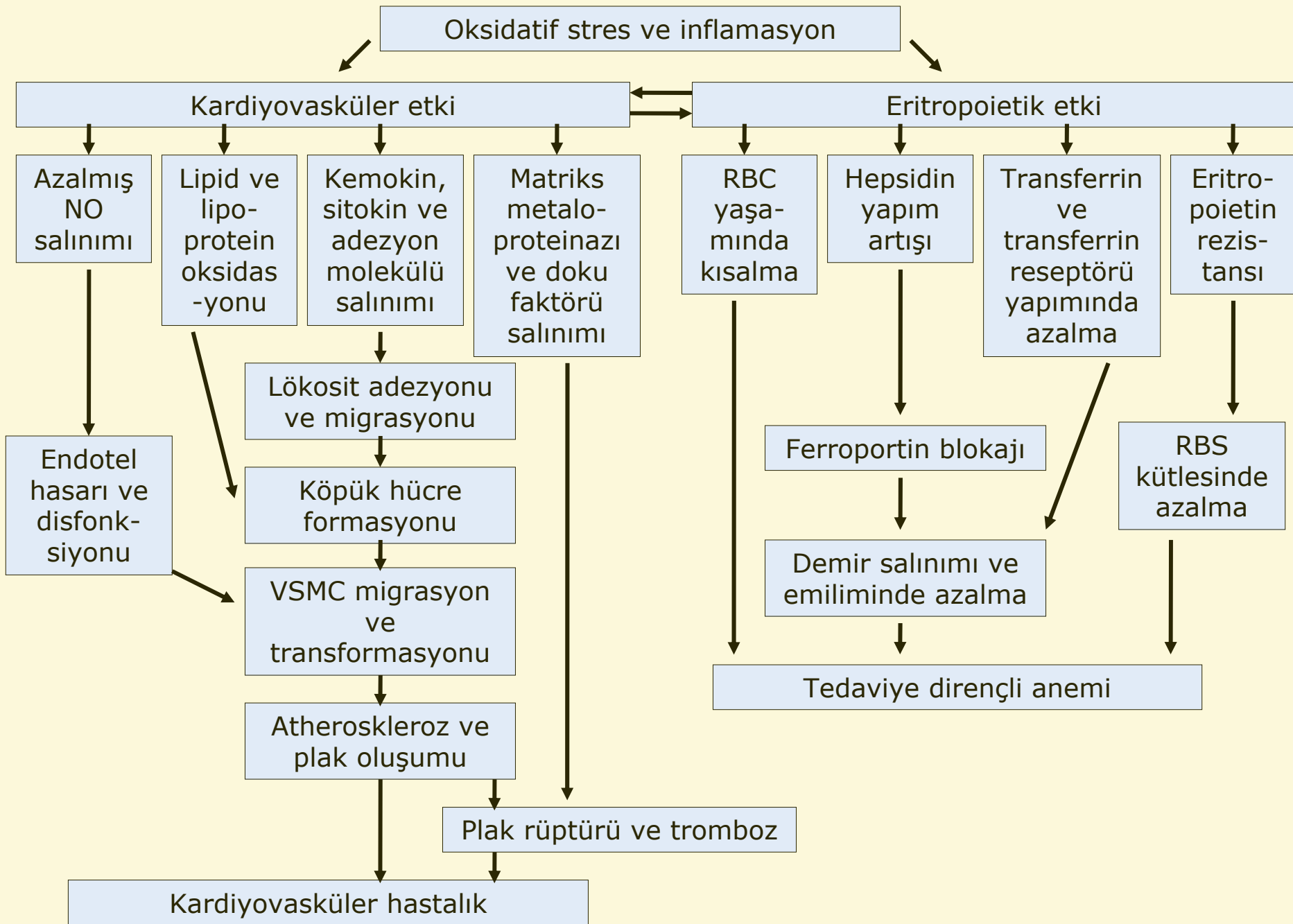
- “Hemoglobin konsantrasyonunu eritrosit transfüzyonu yapma gereksinimini ortadan kaldıracak en düşük değere yavaş yavaş yükseltecek en düşük doz (Aranesp/EPOGEN/PROCRIT) kullanılmalıdır”.
- “Hedef hemoglobin değeri 12 g/dl'den daha yüksek seçilirse eritropoiez stimule edici ajanlar (ESA) ölüm ve ciddi kardiyovasküler olay risklerini artırmaktadır”.
- Hemoglobin değeri 12 g/dl'nin üzerine çıkmışsa ESA dozu azaltılmak yerine iptal edilmelidir.

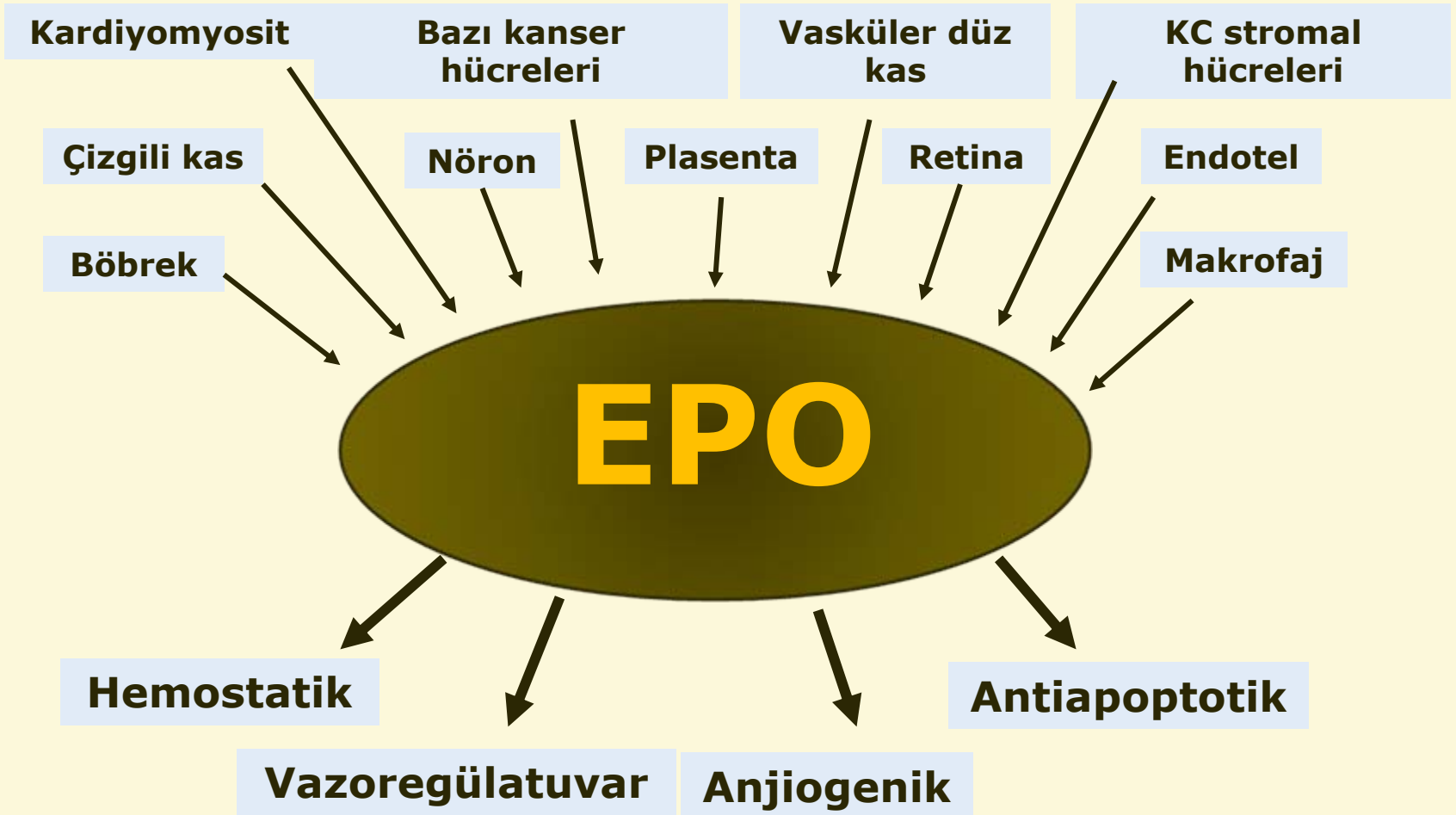
## **REVİZE EDİLMİŞ NKF KDOQİ ANEMİ KILAVUZLARI, 2007**

**2.1.1.** Her hastada ESA başlanacak Hb düzeyi ve hedef Hb düzeyine olası yararlar (yaşam kalitesinde yükselme ve transfüzyonu önleme gibi) ve zararlar (yaşamı tehdit eden kötü olay riski gibi) dikkate alınarak karar verilmelidir (Klinik Pratik ÖNERİ).

**2.1.2.** ESA tedavisi alan diyalize giren ya da girmeyen KBH hastalarında seçilen hedef Hb düzeyi genelde 11.0-12.0 g/dl arasında olmalıdır (Klinik Pratik ÖNERİ).

**2.1.3.** ESA tedavisi alan diyalize giren ya da girmeyen KBH hastalarında seçilen hedef Hb düzeyi 13.0 g/dl'nin üzerinde olmamalıdır (Klinik Pratik KILAVUZ – ORTA DERECEDE GÜÇLÜ KANIT).





*Vaziri ND et al, Nephrol Dial Transplant, Nov 2008*

## Yüksek EPO düzeyleri

**VSMC (Ca<sup>++</sup>)i yükselme**  
**RAS aktivitesinde yükselme**  
**ET-1 yükselme**  
**Tromboksanda yükselme**  
**Prostasiklinlerde azalma**  
**ADMA'da yükselme**  
**NO'da azalma**

**Hipertansiyon**

**VSMC proliferasyonu**  
**EC proliferasyonu**  
**Anjiogenez**

**Vasküler yol stenozu**  
**Proliferatif retinopati**  
**Vasküler remodelling**  
**Tümör büyümesi**

**Trombosit üretiminde artma**  
**Trombosit aktivitesinde artma**  
**E selektinde artma**  
**P selektinde artma**  
**v WF'de artma**  
**PAI-1'de artma**

**Tromboz**

# Secondary analysis of the CHOIR trial epoetin- $\alpha$ dose and achieved hemoglobin outcomes

Lynda A. Szczech<sup>1,2</sup>, Huiman X. Barnhart<sup>2,3</sup>, Jula K. Inrig<sup>1,2</sup>, Donal N. Reddan<sup>1,4</sup>, Shelly Sapp<sup>2,3</sup>, Robert M. Califf<sup>5</sup>, Uptal D. Patel<sup>1,2</sup> and Ajay K. Singh<sup>6</sup>

<sup>1</sup>Department of Medicine, The Renal Division, Duke University Medical Center, Durham, North Carolina, USA; <sup>2</sup>Duke Clinical Research Institute, North Carolina, Durham, USA; <sup>3</sup>Department of Biostatistics and Bioinformatics, Duke University, Durham, North Carolina, USA; <sup>4</sup>Department of Medicine, University College Galway, Galway, Ireland; <sup>5</sup>Duke Translational Research Institute, Durham, North Carolina, USA and <sup>6</sup>The Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

Trials of anemia correction in chronic kidney disease have found either no benefit or detrimental outcomes of higher targets. We did a secondary analysis of patients with chronic kidney disease enrolled in the Correction of Hemoglobin in the Outcomes in Renal Insufficiency trial to measure the potential for competing benefit and harm from achieved hemoglobin and epoetin dose trials. In the 4 month analysis, significantly more patients in the high-hemoglobin compared to the low-hemoglobin arm were unable to achieve target hemoglobin and required high-dose epoetin- $\alpha$ . In unadjusted analyses, the inability to achieve

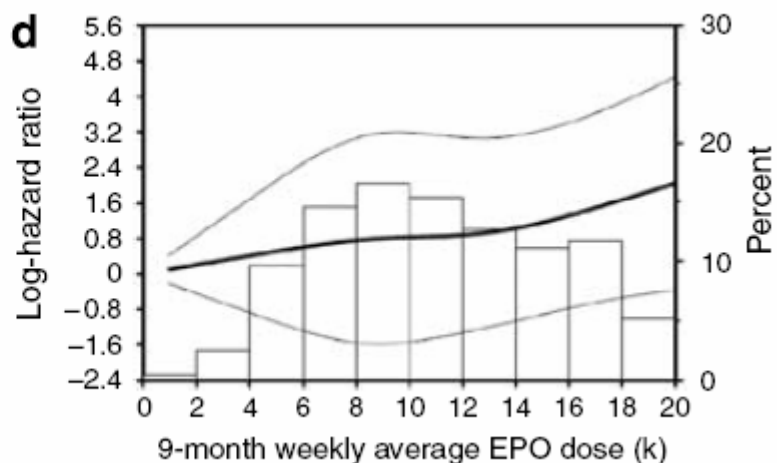
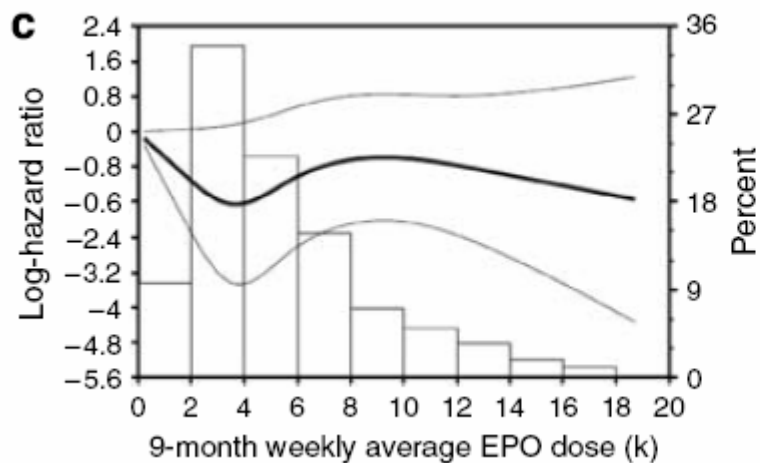
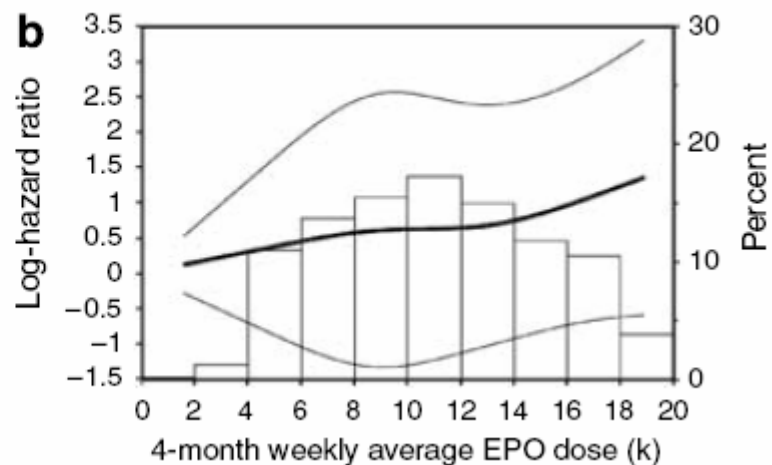
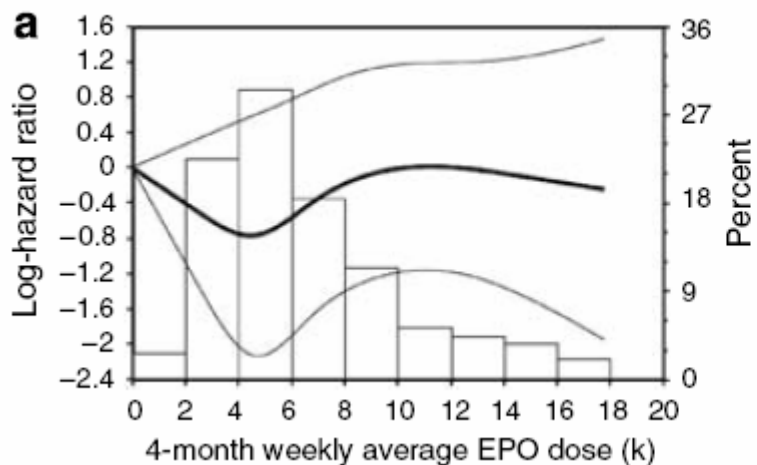
Recombinant erythropoietin revolutionized the care of patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD)<sup>1,2</sup> reducing blood transfusions and complications like iron overload. Although initial therapy was aimed at partial anemia correction, observational studies suggested that treatment with erythropoietin-stimulating agents (ESA) to higher targets was associated with improved survival.<sup>3,4</sup> Three randomized trials of anemia correction in CKD and ESRD patients, however, failed to demonstrate a benefit of higher hemoglobin targets.<sup>5-8</sup> In fact, the final analyses of one trial unexpectedly demonstrated harm among

**Table 1 | Baseline characteristics of subjects<sup>a</sup>**

	Four-month landmark analysis population			Nine-month landmark analysis population		
	High-hemoglobin group (N=627)	Low-hemoglobin group (N=633)	P-value	High-hemoglobin group (N=519)	Low-hemoglobin group (N=538)	P-value
Age, year	65.9 (14.2)	66.6 (13.2)	0.37	65.7 (14.3)	66.4 (13.2)	0.41
Female sex (%)	56.5%	54.0%	0.39	57.4%	54.1%	0.28
Race (%)			0.74			0.53
White	62.7%	61.6%		63.5%	60.8%	
Black	28.0%	29.5%		28.6%	30.5%	
American-Indian or Alaskan Native	0.2%	0.5%		0.2%	0.6%	
Asian or Pacific Islander	3.7%	2.8%		3.1%	2.2%	
Other	5.4%	5.5%		4.6%	5.9%	
Hispanic ethnic background (%)	12.3%	13.1%	0.67	12.6%	13.4%	0.69
History of smoking tobacco (%)	46.6%	43.8%	0.31	45.1%	43.3%	0.57
Cause of CKD (%)			0.50			0.66
Diabetes mellitus	46.4%	49.7%		45.8%	48.6%	
Hypertension	30.2%	28.3%		30.9%	29.1%	
Other	23.4%	22.1%		23.3%	22.3%	
<i>Cardiovascular history (%)</i>						
Hypertension	95.8%	92.9%	0.03	95.2%	92.4%	0.07
Myocardial infarction	14.8%	14.6%	0.92	14.6%	13.6%	0.66
CABG	17.9%	13.2%	0.03	16.7%	12.5%	0.05
PCI	9.4%	10.8%	0.43	9.6%	10.9%	0.50
Congestive heart failure	22.0%	20.7%	0.58	21.0%	18.9%	0.41
Atrial fibrillation	8.1%	8.8%	0.66	8.2%	7.8%	0.81
Stroke	9.5%	9.0%	0.74	9.8%	9.2%	0.75
Lower-extremity amputation	3.2%	2.8%	0.71	3.2%	2.5%	0.53
MI, CABG, or PCI	26.3%	25.0%	0.59	26.1%	23.7%	0.37
Body Mass Index (kg/m <sup>2</sup> )	30.5 (7.8)	30.4 (7.5)	0.85	30.5 (7.6)	30.7 (7.7)	0.69
GFR (ml/min/m <sup>2</sup> )	27.1 (8.7)	27.6 (9.1)	0.30	27.5 (8.7)	28.3 (9.1)	0.14
Baseline hemoglobin (g/100 ml)	10.1 (0.86)	10.1 (0.85)	0.78	10.1 (0.85)	10.1 (0.84)	0.28
Week 3 hemoglobin (g/100 ml)	10.7 (0.94)	10.6 (0.94)	0.10	10.7 (0.95)	10.6 (0.94)	0.50
Baseline albumin (g/10 ml)	3.8 (0.51)	3.8 (0.46)	0.35	3.8 (0.47)	3.8 (0.45)	0.94
Baseline phosphorus (mg/100 ml)	4.1 (0.73)	4.1 (0.74)	0.36	4.1 (0.73)	4.0 (0.73)	0.12
Baseline cholesterol (mg/100 ml)	184.6 (50.2)	183.5 (47.9)	0.70	184.5 (48.9)	183.9 (47.7)	0.83
Ratio of total protein/creatinine in urine	1.5 (2.10)	1.4 (2.10)	0.36	1.3 (1.84)	1.2 (1.84)	0.38
Ferritin (ng/ml)	167.8 (157.2)	178.5 (173.1)	0.25	165.9 (158.1)	172.5 (157.0)	0.50
Transferrin saturation (%)	25.3 (11.7)	24.6 (10.1)	0.29	25.2 (11.8)	24.7 (10.2)	0.43
Transferrin saturation <20% (%)	36.1%	33.9%	0.40	36.1%	33.9%	0.44
<i>Medications (%)</i>						
ACE inhibitor or ARB	75.8%	75.3%	0.84	77.5%	76.8%	0.80
Beta blocker	45.0%	47.9%	0.30	44.9%	47.7%	0.36
HMG CoA reductase inhibitor	52.3%	53.0%	0.79	54.4%	55.0%	0.85
<i>Iron</i>						
Intravenous	2.9%	1.8%	0.18	3.1%	2.1%	0.28
Oral	27.1%	25.8%	0.60	26.8%	24.1%	0.32
Not specified	3.4%	1.6%	0.04	3.3%	2.4%	0.06

**Table 3 | Cox proportional hazards models for the primary composite endpoint of death, coronary heart failure hospitalization, stroke, or MI**

Variable	Four-month landmark analysis <i>N</i> =1260		Nine-month landmark analysis <i>N</i> =1057	
	HR, 95% CI	<i>P</i> -value	HR, 95% CI	<i>P</i> -value
<i>Model 1</i>				
Target arm (high vs low)	1.44, 1.05–1.97	0.02	1.62, 1.09–2.40	0.02
<i>Model 2</i>				
Target arm (high vs low)	1.26, 0.89–1.78	0.20	1.44, 0.95–2.18	0.09
Not achieving hemoglobin target	1.46, 1.00–2.13	0.05	1.99, 1.12–3.55	0.02
<i>Model 3</i>				
Target arm (high vs low)	1.26, 0.90–1.75	0.18	1.37, 0.89–2.11	0.15
High-dose ESA	1.71, 1.20–2.43	0.003	1.54, 1.00–2.35	0.05
<i>Model 4</i>				
Target arm (high vs low)	1.21, 0.85–1.71	0.29	1.28, 0.82–2.00	0.27
Not achieving hemoglobin target	1.17, 0.76–1.79	0.47	1.76, 0.97–3.20	0.06
High-dose ESA	1.60, 1.08–2.38	0.02	1.40, 0.90–2.19	0.13
<i>Model 5</i>				
	<i>N</i> =1192		<i>N</i> =1016	
Target arm (high vs low)	1.17, 0.81–1.68	0.41	1.25, 0.80–1.97	0.33
Not achieving hemoglobin target	1.21, 0.78–1.89	0.39	1.80, 0.97–3.34	0.06
High-dose ESA	1.57, 1.04–2.36	0.03	1.48, 0.94–2.32	0.09
Self-reported hypertension	0.94, 0.48–1.85	0.86	0.66, 0.32–1.37	0.27
Previous CABG	2.44, 1.70–3.49	<0.01	1.75, 1.08–2.86	0.02
Use of IV iron	0.47, 0.12, 1.90	0.29	0.36, 0.05, 2.63	0.32



# **Hemoglobinde Dalgalanma**

# Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin

**STEVEN FISHBANE and JEFFREY S. BERNIS**

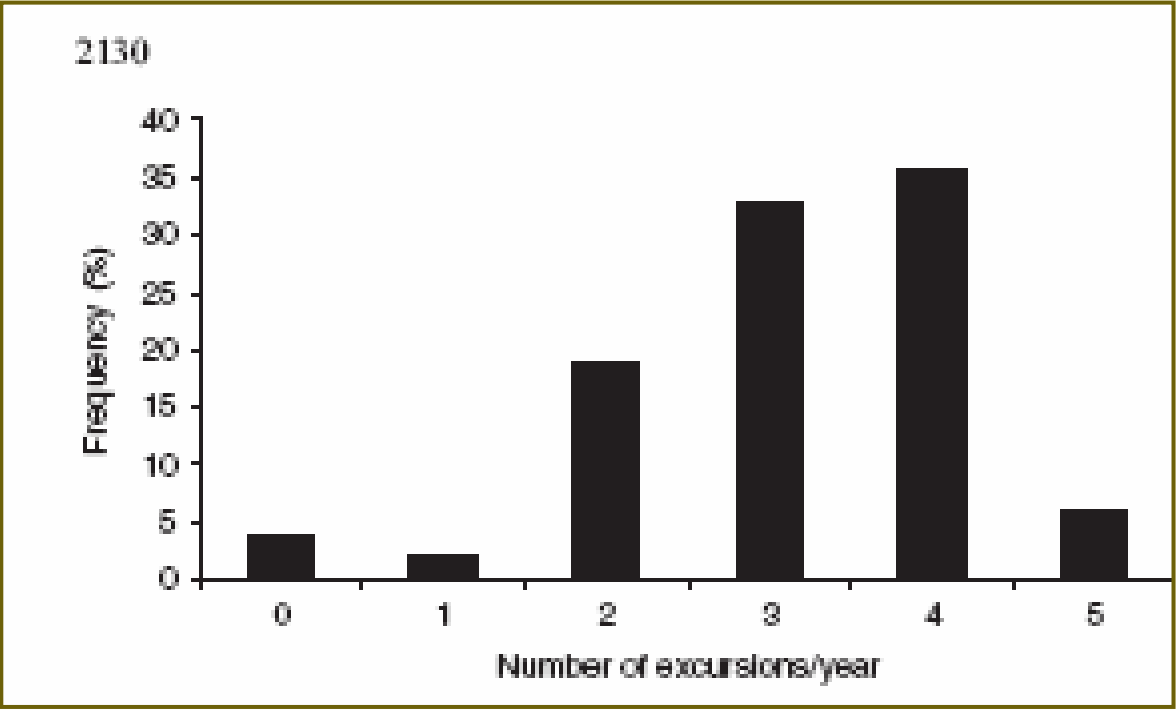
*Winthrop-University Hospital, Mineola, New York; and Renal, Electrolyte, and Hypertension Division, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania*

## **Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin.**

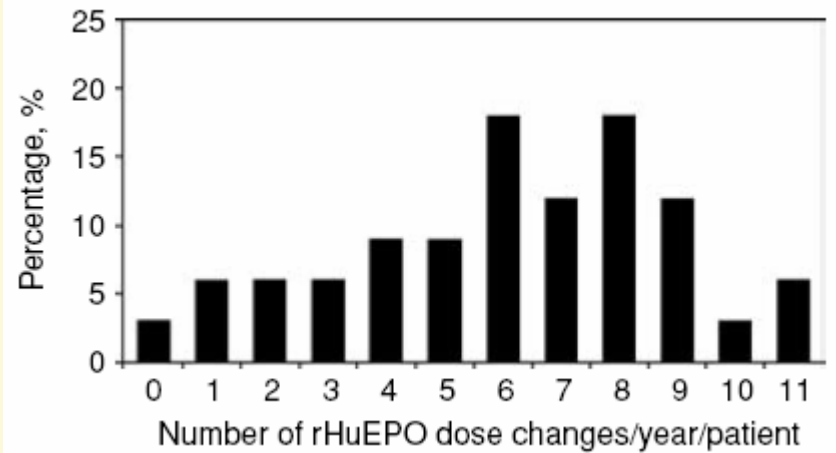
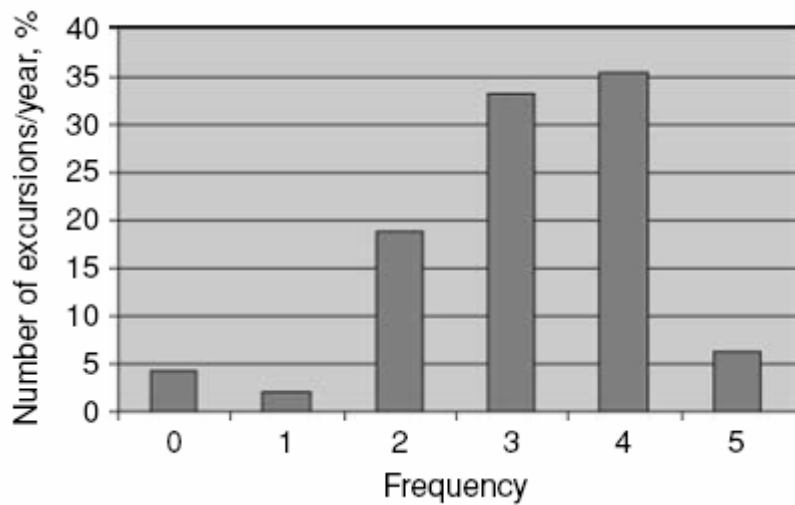
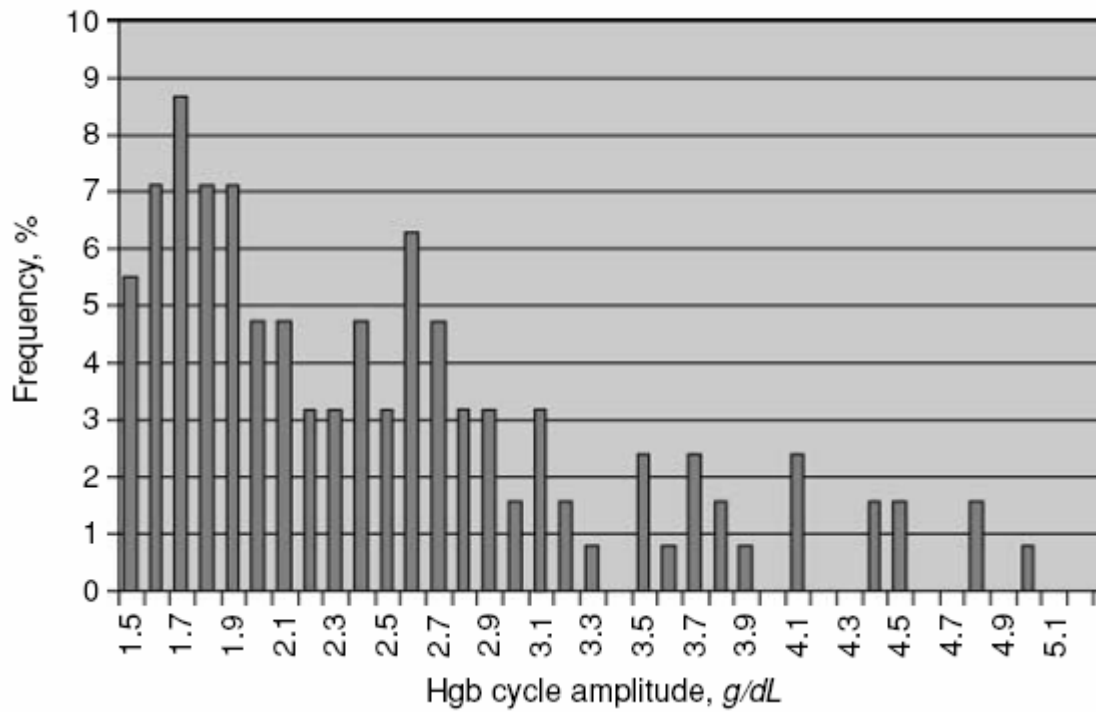
*Background.* Treatment with recombinant human erythropoietin (rHuEPO) has been a major advance for the management of anemia in patients on hemodialysis. Therapy, however, is often observed to be associated with recurrent cyclic fluctuations in hemoglobin levels. The purpose of this analysis was to describe the phenomenology of hemoglobin cycling during rHuEPO treatment.

*Methods.* Data were analyzed for 281 hemodialysis patients treated at Winthrop-University Hospital Dialysis Centers be-

a great advance in the management of this problem [2, 3]. Treatment to achieve partial correction of patients' hemoglobin level results in improved quality of life [4] and is associated with reduced risk for mortality [5] and hospitalization [6]. However, therapy with rHuEPO is quite different than biologic erythropoietic processes; treatment involves short, intermittent, non-physiologic bursts of plasma EPO availability which do not directly coincide either temporally or in mag-



*Fishbane S et al, Kidney International, 2005*



# **Hemoglobin Dalgalanmasına Etki Eden Faktörler**

- **ESA uygulama pratikleri**
- **Hastalık ve hospitalizasyon**
- **Sıvı Dengesi**
- **Demir statusu ve tedavisi**

**Klinik önemi ?**

# Hemoglobin Level Variability: Associations with Mortality

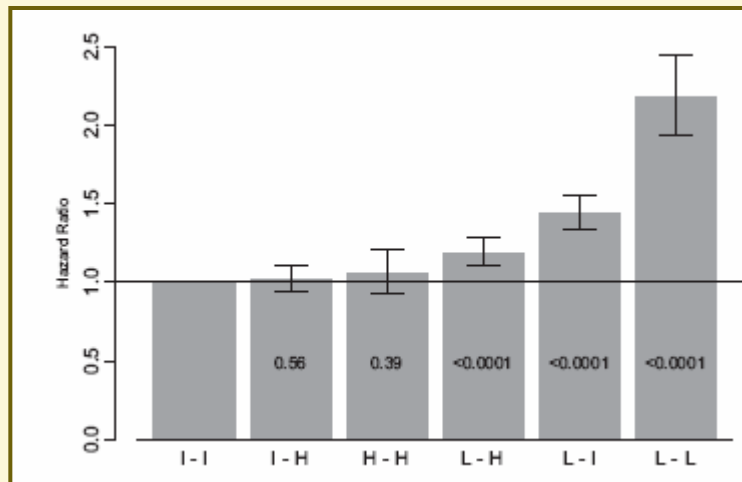
David T. Gilbertson,\* James P. Ebben,\* Robert N. Foley,\*<sup>†‡</sup> Eric D. Weinhandl,\*  
Brian D. Bradbury,<sup>§</sup> and Allan J. Collins\*<sup>†‡</sup>

\*Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, Minnesota; <sup>†</sup>Hennepin County Medical Center, Minneapolis, Minnesota; <sup>‡</sup>University of Minnesota, Minneapolis, Minnesota; and <sup>§</sup>Department of Epidemiology, Amgen, Inc., Thousand Oaks, California

**Background/objectives:** Awareness of hemoglobin level variability in dialysis patients is increasing, as is interest in its potential implications. In this retrospective, national study of associations between the degree of hemoglobin level variability in the first 6 mo of 2004 and subsequent mortality rates in the following 6 mo, 159,720 hemodialysis patients receiving epoetin therapy were studied. **Design, setting, participants, measurements:** Monthly hemoglobin values were categorized as low (L; < 11 g/dl), intermediate (I; 11 to 12.5 g/dl), and high (H; >12.5 g/dl). Variability groups were classified on the basis of the lowest and highest hemoglobin categories seen during the 6-mo observation period: low-low (L-L), 1.4%; intermediate-intermediate (I-I), 6.0%; high-high (H-H), 2.3%; low-intermediate (L-I), 18.3%; intermediate-high (I-H), 31.7%, and low-high (L-H), 40.2%.

**Results:** On multivariate analysis, adjusted hazards ratios for subsequent mortality events were as follows: I-I, 1.0 (reference category); I-H, 1.02 (95% confidence interval [CI] 0.95 to 1.11); H-H, 1.06 (95% CI 0.93 to 1.21); L-H, 1.19 (95% CI 1.10 to 1.28); L-I, 1.44 (95% CI 1.33 to 1.56), and L-L, 2.18 (95% CI 1.93 to 2.45). Persistently and transiently low hemoglobin levels and highly variable hemoglobin levels were associated with increased risk of death; transiently and persistently high hemoglobin levels were not associated with increased risk of death. Bayesian modeling indicated that  $\geq 3$  mo with hemoglobin levels <11 g/dl may be associated with of increased risk of death.

**Conclusions:** Number of months with hemoglobin values below the target range, rather than hemoglobin variability itself, may be the primary driver of increased risk of death. Further research is needed to distinguish cause from effect and to understand the underlying mechanisms.



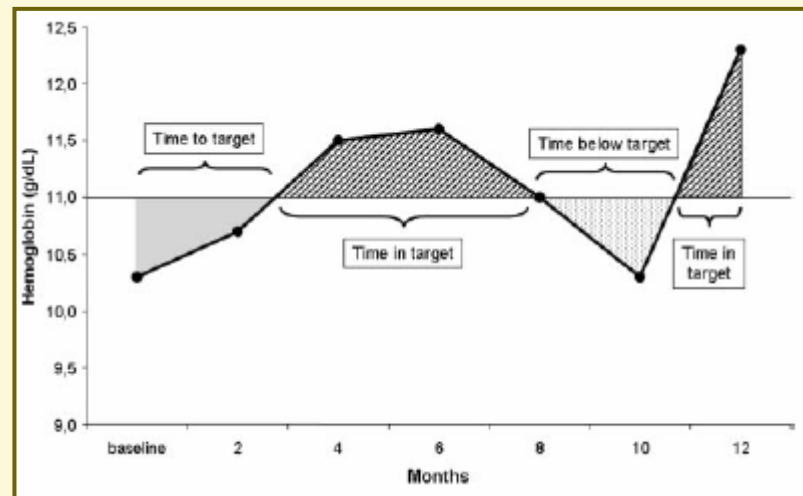
# Stability of Target Hemoglobin Levels during the First Year of Epoetin Treatment in Patients with Chronic Kidney Disease

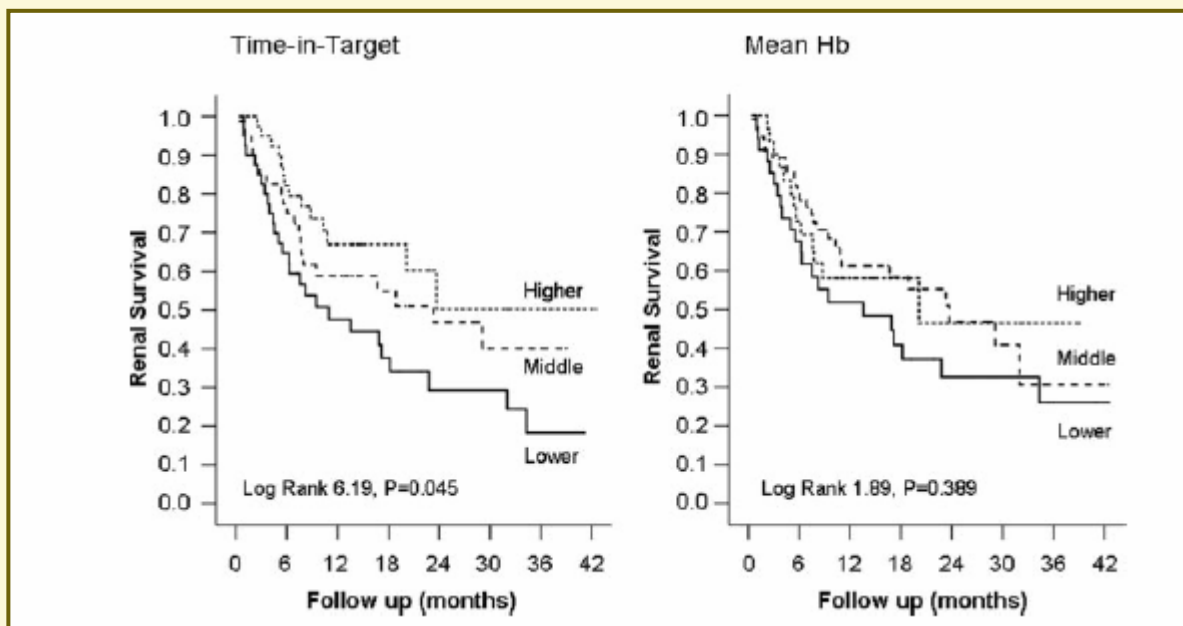
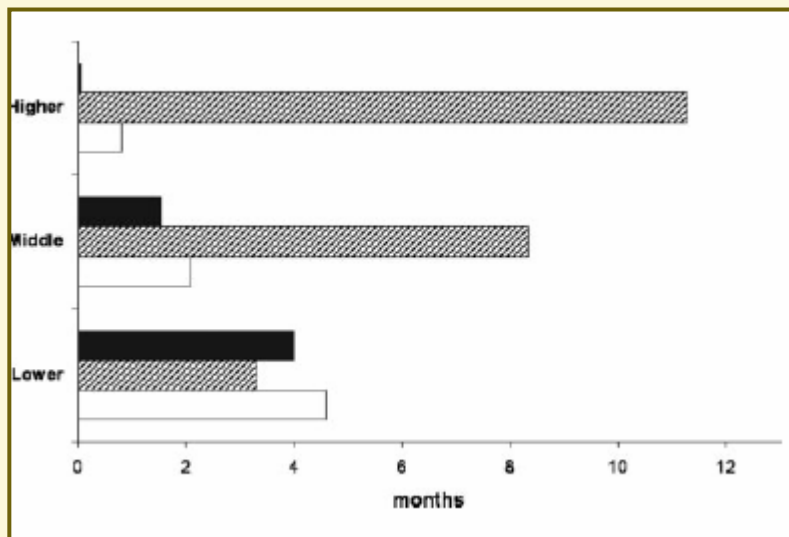
Luca De Nicola,\* Giuseppe Conte,\* Paolo Chiodini,<sup>†</sup> Bruno Cianciaruso,<sup>‡</sup> Andrea Pota,<sup>‡</sup> Vincenzo Bellizzi,<sup>§</sup> Giuseppina Tirino,\* Deborah Avino,\* Fausta Catapano,\* and Roberto Minutolo\*

*\*Nephrology Division and <sup>†</sup>Department of Biostatistics, Second University of Naples-Santa Maria del Popolo degli Incurabili Hospital-Azienda Sanitaria Locale Napoli 1, and <sup>‡</sup>Department of Nephrology, University Federico II, Naples, and <sup>§</sup>Nephrology Division, County Hospital, Solofra, Italy*

**Background and Objectives:** Instability of hemoglobin levels during epoetin therapy is a new problem in hemodialysis. We evaluated extent and correlates of time in target, that is, the time spent with hemoglobin  $\geq 11$  g/dl during the first year of epoetin and its association with renal survival.

**Design, Setting, Participants, & Measurements:** Data were collected in 917 visits for 12.0 mo in 119 patients with chronic kidney disease; thereafter, patients started renal survival analysis for 10.1 mo. At baseline, hemoglobin was  $10.0 \pm 0.8$  g/dl and GFR was  $22.1 \pm 14.2$  ml/min per  $1.73$  m<sup>2</sup>.





Nicola LD et al, Clin J Am Soc Nephrol, Nov 2007

# Hemoglobin Dalgalanmasında Cevaplanması Gereken Sorular

1. Klinik önemi nedir ?
2. Tek bir hemoglobin değeri mi, 3-6 aylık hemoglobin ortalaması mı ?
3. Demirde dalgalanmanın sonuçları ?
4. Hemoglobinde aşırı hızlı yükselmenin (overshoot) önemi ?
5. Non-eritropoietik hücrelerde dalgalanmanın etkileri ?

ABD Saėlık Hizmetleri Arařtırma ve Kalite Ajansı  
bir tedavi pratiėi kılavuzunu

“fiziksel veya mental hastalık veya hasarı  
iyileřtirmeye ynelik prosedr ve pratikleri neren  
bir kılavuz”

olarak tanımlamaktadır.





**“The young physician starts life with 20 drugs for each disease, and the old physician ends life with one drug for 20 diseases.”**

*William Osler*