Kronik Böbrek Yetmezliğinde Optimum Anemi Tedavisi

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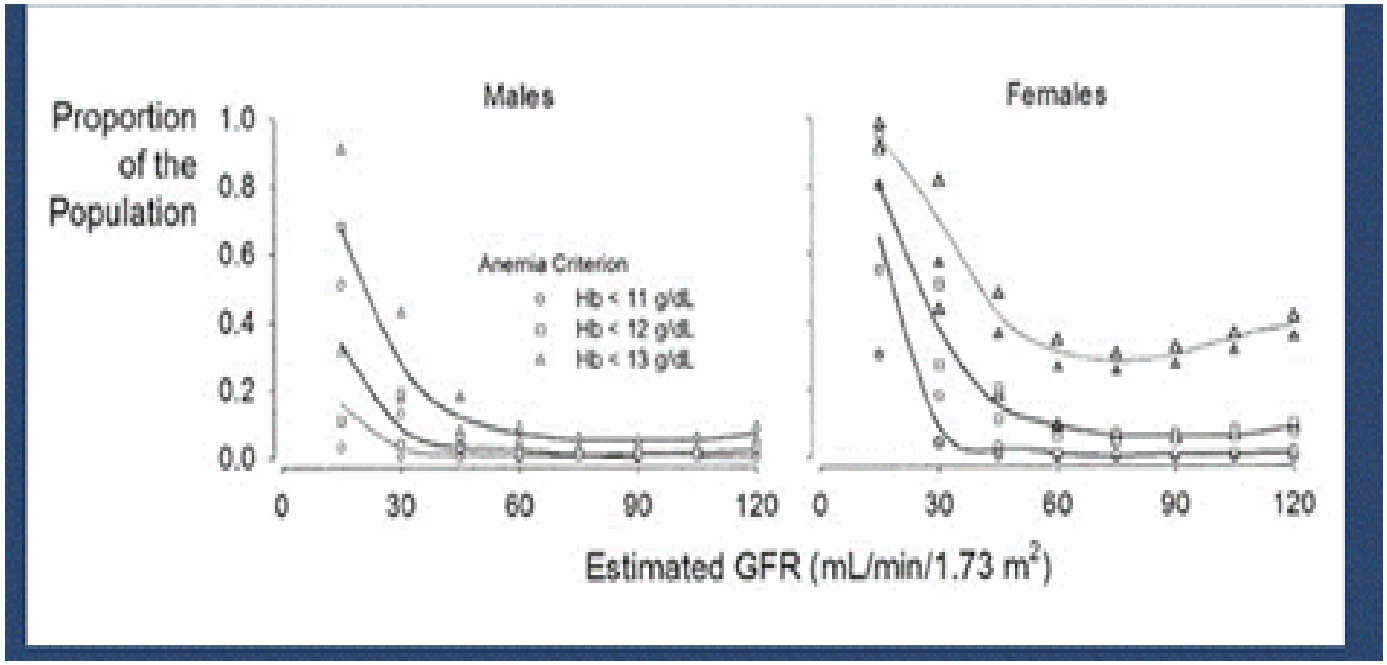
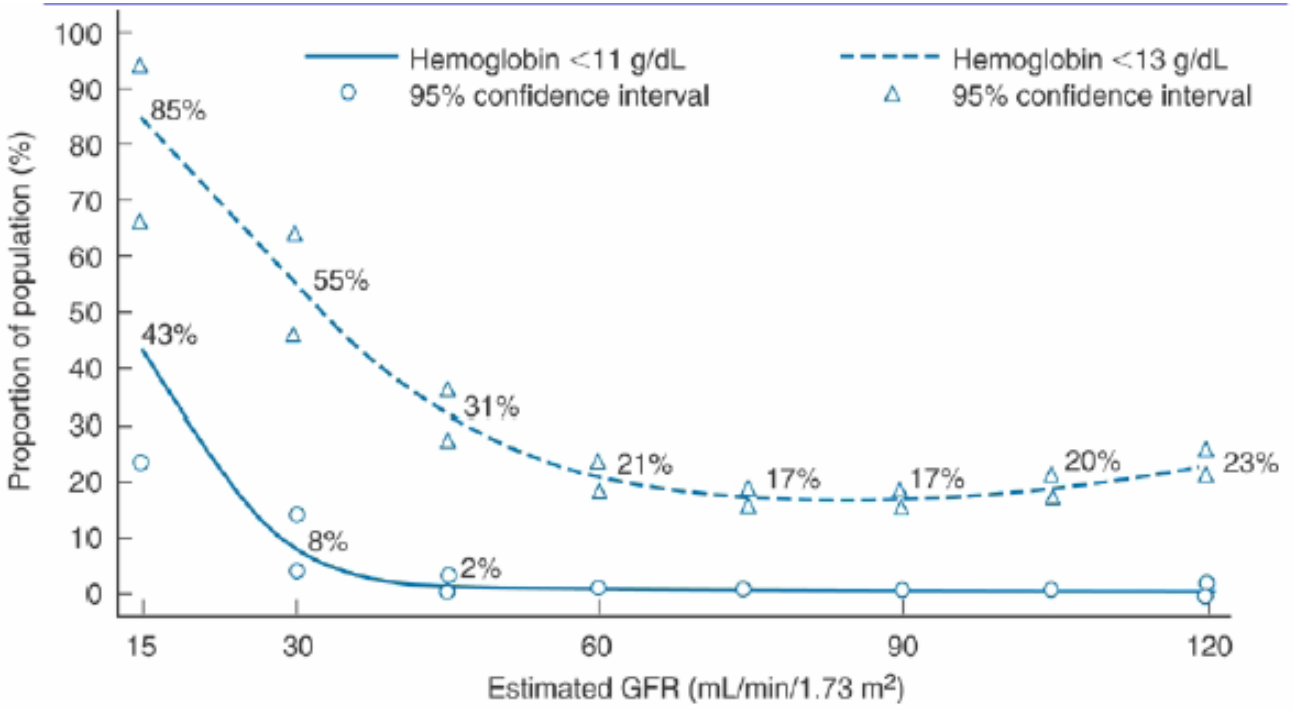
Anemi prevalansı

- Anemi, KBH'da erken dönemde gelişir
- GFR<30 ml/dk şiddetli anemi sıktır



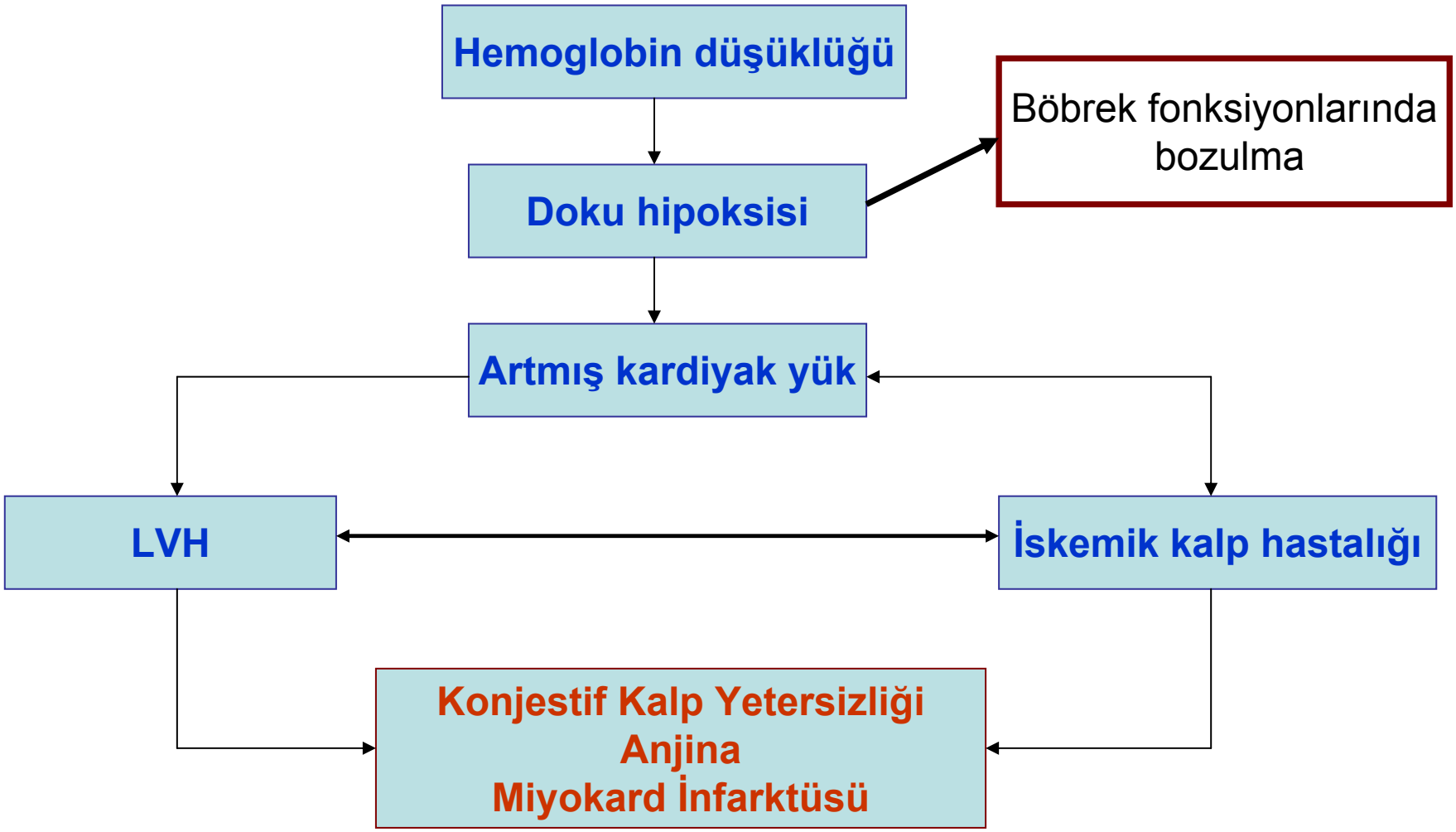
Astro et al. Arch Intern Med, 2002

Kronik Böbrek Yetersizliği ve Anemi



K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative.
Am J Kidney Dis 39 (2) [suppl 1]: 1-246, 2002

Aneminin kardiyak sonucu



Metivier et al. NDT 2000

Anemi - Mortalite

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Reduced Kidney Function and Anemia as Risk Factors for Mortality in Patients With Left Ventricular Dysfunction

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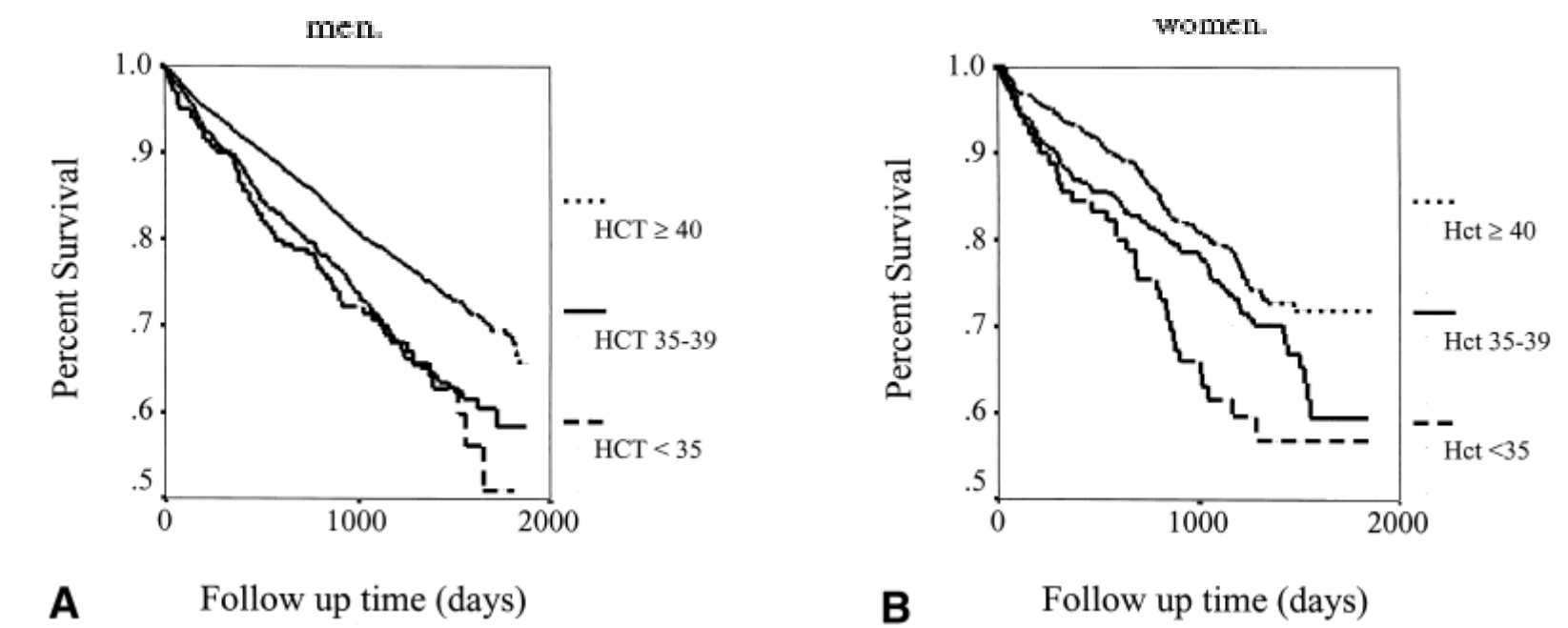
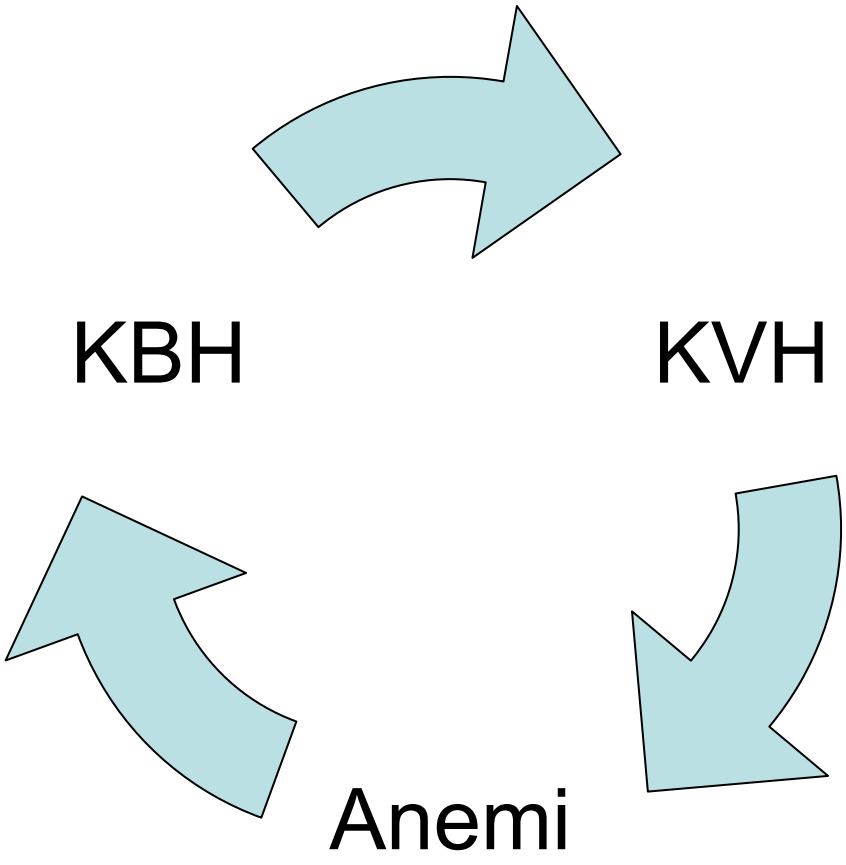
Marvin A. Konstam, MD,* Deeb N. Salem, MD,* Andrew S. Levey, MD,‡ Mark J. Sarnak, MD‡
Boston, Massachusetts



Hematokritte % 3 azalma ile mortalitede % 7 artma

Kardiyorenal Sendrom



Anemi Tedavisinin Yararları

- Kalp dışı
  - Yaşam kalitesi artar
  - Egsersiz kapasitesi artar
  - Kognitif fonksiyonlar iyileşir
  - Cinsel fonksiyonlar iyileşir
  - İmmün cevap düzelir
  - İştah, beslenme düzelir
  - Kanamaya eğilim azalır
  - Uyku düzeni normalleşir
- Kalp ile ilgili
  - Kalp debisi azalır
  - LVH azalır
  - Angina azalır

- Anemi düzeltilmeli mi?
  - Hipertansiyon erken tanı ve tedavisinin yararları konusunda güçlü kanıtlar var
  - Aneminin düzeltilmesinin yararları konusunda kanıt az
- Anemi hızlı mı düzeltilmeli?
  - Kronik hiponatremi, malign hipertansiyon

Anaemia management in patients with chronic kidney disease: a position statement by the Anaemia Working Group of European Renal Best Practice (ERBP)

Appendix: summary of recommendations

	EBPG 2004	KDOQI 2006/2007	ERBP: anaemia group position, 2008
Definition of anaemia	Hb <11. 5 in women Hb <13.5 in men ≤70 years Hb <12 in men >70 years	Hb <12 in females Hb <13.5 in males	Hb <12 in females Hb <13.5 in males
Haemoglobin target	Hb >11 g/dl; Hb >14 g/dl not desirable (>12 g/dl in CVD)	[a]Generally Hb 11–12 g/dl, target Hb should not be >13 g/dl	Generally Hb 11–12 g/dl target Hb should not be >13 g/dl
Targets for iron therapy	TSAT (%) Lower limit: 20 Target: 30–50 Ferritin (ng/ml) Lower limit: 100 Target 200–500	TSAT (%) Lower limit: ≥20 Ferritin Lower limit: 100 in non-HD, 200 in HD Do not routinely exceed 500	TSAT (%) Lower limit: ≥20 Ferritin Lower limit: 100 in non-HD, 200 in HD Do not routinely exceed 500

Non-diyaliz KBH

Yüksek risk diyaliz

Table 1. Design characteristics for anemia RCTs

	Normal Hematocrit	CREATE	CHOIR	TREAT
Design	randomized, open-label	randomized, open-label	randomized, open-label	randomized, double-blind
Sponsor/agent	Amgen/Epogent® (epoetin-α)	Amgen/Aranesp® (darbepoetin-α)	J&J/Procrit® (epoetin-α)	Amgen/Aranesp® (darbepoetin-α)
Dosing	unclear	2,000 weekly	initiate 10,000 weekly when stable go to bi-weekly	0.75 mcg/kg/Q2W double dose when stable and go to monthly
Dosing frequency	3 times weekly on dialysis	de novo to weekly	de novo to weekly to bi-weekly	de novo to bi-weekly to monthly
Hb target(s), g/l	arm 1 9–11 arm 2 13–15	13.0–15.0 10.5–11.5	13.0 placebo (rescue for Hb <9.0)	13.0 placebo (rescue for Hb <9.0)
Regions	USA	global	USA	global
Inclusion criteria				
Hb, g/l	9–11.0	11.0–12.5	<11.0	≤11.0
eGFR/CrCl	ESRD	15–35	15–50	20–60
Diabetes	≈ 44%	≈ 25%	48.5%	100%

The NEW ENGLAND JOURNAL of MEDICINE

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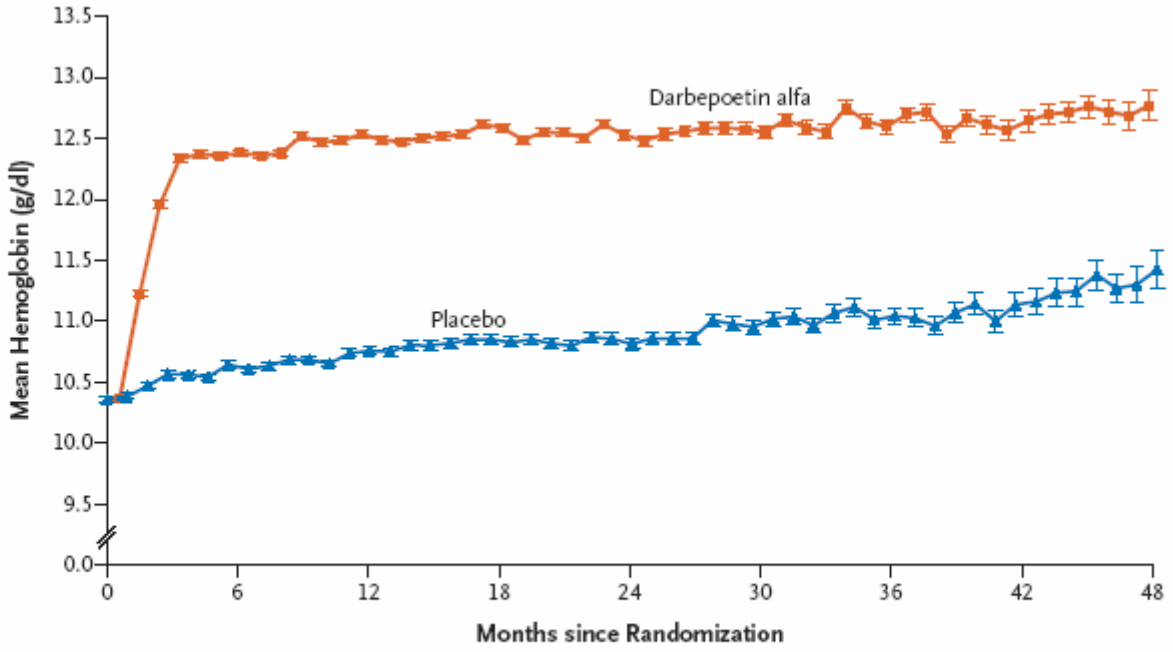
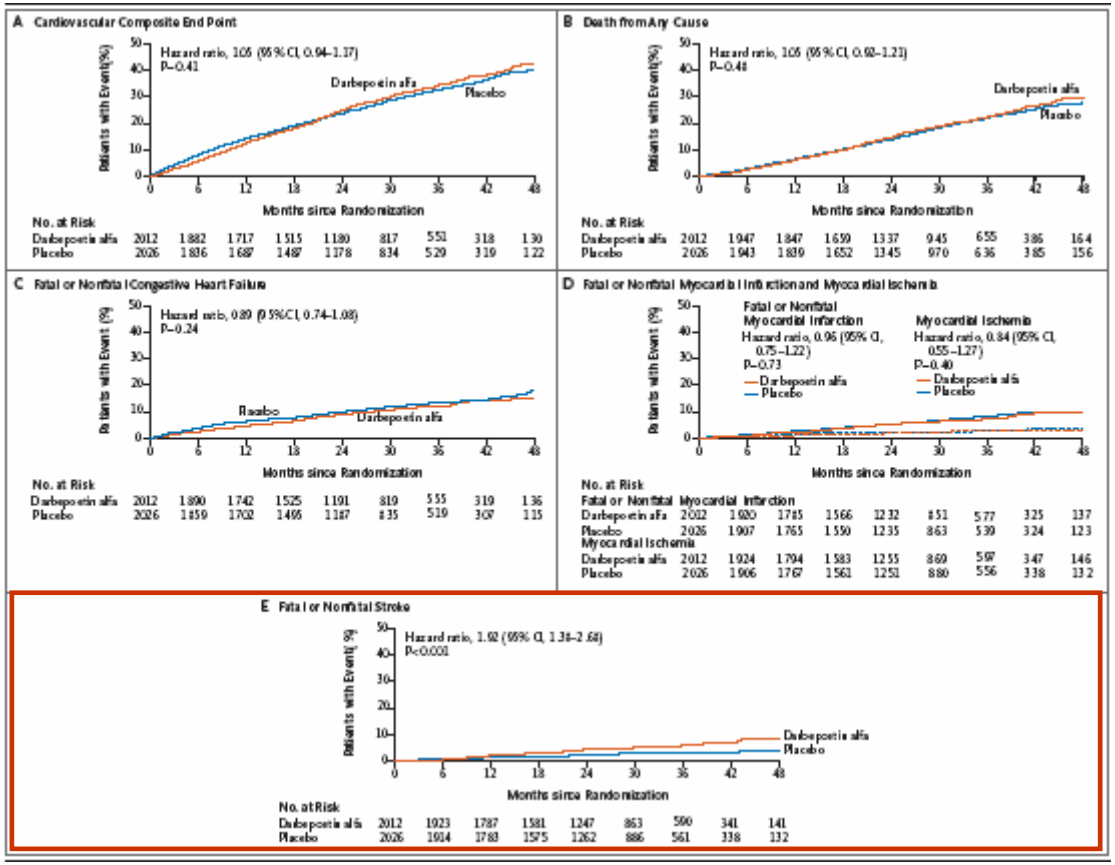
A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D., Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D., Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D., John J.V. McMurray, M.D., Patrick Parfrey, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D., Ajay K. Singh, M.D., Scott D. Solomon, M.D., and Robert Toto, M.D., for the [illegible] Investigators*

TREAT



No. of Patients									
Darbepoetin alfa	2004	1768	1503	1300	946	635	404	253	97
Placebo	2019	1742	1460	1221	887	620	356	216	79



Yüksek hemoglobin kolunda risk artışı

ESA Tedavisi

- Eritropoetin tedavisinin amaçları
  - Kan transfüzyonu ihtiyacını ortadan kaldırmak
  - Ciddi aneminin komplikasyonlarını önlemek
  - Yaşam kalitesini artırmak

ESA Tedavisi

Hb konsantrasyonu sürekli 11 gr/dl'nin altında olan ve diğer anemi nedenleri dışlanan kronik böbrek hastalıklı bütün hastalara eritropoezi stimüle eden ajanlar verilmelidir

- Eritropoetin alfa
- Eritropoetin beta
- Darbepoetin alfa

ESA Tedavisi – Genel Prensipler

- Yanıt; doza bağımlıdır, hastalar arasında önemli farklar vardır
- Yanıt; uygulama yolu ile ilişkilidir.
  - sc > iv (ihtiyaç %30 daha az)
  - Darbepoetin ile daha az önemli
- Yanıt; yetersiz demir, kemik iliği fibrozu, infeksiyon, inflamasyon, yetersiz diyaliz ile sınırlanabilir

ESA Tedavisi

- Hematolojik
  - Aneminin parsiyel düzeltilmesi ile LVH'da gerileme
  - Sistemik vasküler dirençte düzelme
  - Egsersiz ilişkili kardiyak iskemide düzelme
- Non-hematolojik
  - Üremik bulgularda azalma (cinsel fonk, kortizol metz..)
  - Yaşam kalitesinde artma (zindelik, uyku..)
  - Kognitif fonksiyonlarda ve serebral kan akımında artma

ESA Tedavisi

- Demir durumu değerlendirilmeden EPO başlanmamalı
    - 100 mg Fe-sukroz ile Hb 0.5-0.6 gr artar.
  – EPO idamesinde Fe tedavisi sürdürülmeli
- Hemoglobin X Hematokrit
  – Hematokritte Lab değişkenliği daha fazla

ESA Tedavisi

- Başlangıç dozu
  - 50-300 U/kg 3/hf
    - 100 U/kg 3/hf iv Hedefe ulaşma: % 90
    - 50 U/kg 3/hf iv Hedefe ulaşma: % 70

    - FDA: 50-100 U/kg 3/hf
    - K/DOQI öneri yok, bireysel

ESA – yetersiz yanıt

- Standart bir tanımı yok
- Uygun ESA dozlarına rağmen Hb<11 gr/dl
  - Maksimum doz: 300 IU/kg/hafta (sc)
    450 IU/kg/hafta (iv)
  - Süre: 6 ay

ESA – yetersiz yanıt

- Demir Eksikliği
- İnflamasyon
- Gizli Kanama
- Diğerleri

ESA – Yan Etki

- Sık görülenler
  - Hipertansiyon
  - Baş ağrısı (% 15)
  - Grip benzeri sendrom (% 5)
- Kardiyovasküler etkiler
- Saf eritroid aplazi

ESA – destekleyici tedavi

- L-karnitin
- Askorbik asit
- Androjenler
- Pentoksifilin
- Statinler

Demir tedavisi

- Daha düşük ESA dozları ile hedefe ulaşma

- Enfeksiyon riski
- Oksidatif stres
- KV Hastalık

“ DEMİR DURUMUNUN DOĞRU TAYİNİ ÖNEMLİ ”

Drueke T, Witko-Sarsat V, Massy Z, et al. **Iron therapy, advanced oxidation protein products, and carotid artery intima-media thickness in end-stage renal disease**. Circulation. 2002;106:2212–2217

Kuo KL, Hung SC, Wei YH, Tarng DC. **Intravenous iron exacerbates oxidative DNA damage in peripheral blood lymphocytes in chronic hemodialysis patients**. J Am Soc Nephrol. 2008;19:1817–1826

Hedef Değerler

		EBPG 2004	K/DOQI 2006/2007	ERBP 2008
Demir Tedavi Hedefleri	TSAT % Alt sınır Hedef	 20 30-50	 ≥ 20	 ≥ 20
	Ferritin ng/ml Alt sınır Hedef	 100 200-500	100 (non-HD) 200 (HD) < 500	100 (non-HD) 200 (HD) < 500

Demir Parametreleri

	TSAT %	Ferritin ng/ml
Mutlak demir eksikliği	< 20	< 100
Fonksiyonel demir eksikliği	< 20	> 500 ↓
İnflamatuvar hastalıklar	< 20	> 500 ↑

Yüksek CRP
Düşük/düşen Alb

Diğer demir indeksleri

- Hipokromik eritrosit yüzdesi
  - TSAT ve Ferritine göre daha duyarlı
  - <%2.5 : Normal
  - >% 10: Demir yetersiz eritropoez
  - ESA tedavisi esnasında %50'ye çıkabilir
  - Özel cihaz gerektirir (flow sitometri)
- Retikülosit hemoglobin içeriği
  - <29 (<32): Demir yetersiz eritropoez
  - TSAT ve ferritine göre kemik iliğinde demir varlığının direkt göstergesi

Demir Parametreleri

Demir eksikliğinin değerlendirilmesinde
“kemik iliği demirinin ölçümü”
altın standart olarak düşünülmesine rağmen,
testin doğruluğunu vurgulayan çok az
çalışma vardır

Table 1. Sensitivity and Specificity of Iron Measures for Detecting Functional Iron Deficiency in Patients With CKD

Reference	Patients	Iron Measures	Sensitivity (%)	Specificity (%)
Stancu et al[8]	CKD	BM iron (−)	65	65
Domrongkitchaiporn et al[20]	PD	BM iron (−)	25	80
		Ferritin <100 ng/mL	13	100
		TSAT <20%	20	100
Fishbane et al[28]	HD	Ferritin <100 ng/mL	48	75
		TSAT <21%	81	63
Tessitore et al[29]	HD	Ferritin <100 ng/mL	35	78
		TSAT <19%	59	78
Mittman et al[30]	HD	Ferritin <100 ng/mL	38	53
		TSAT <20%	50	60
		CHr <28 pg	78	71
Tarng et al[31]	HD	CHr <28 pg	78	87
Tarng et al[32]	HD	TfR-F >0.6	90	79

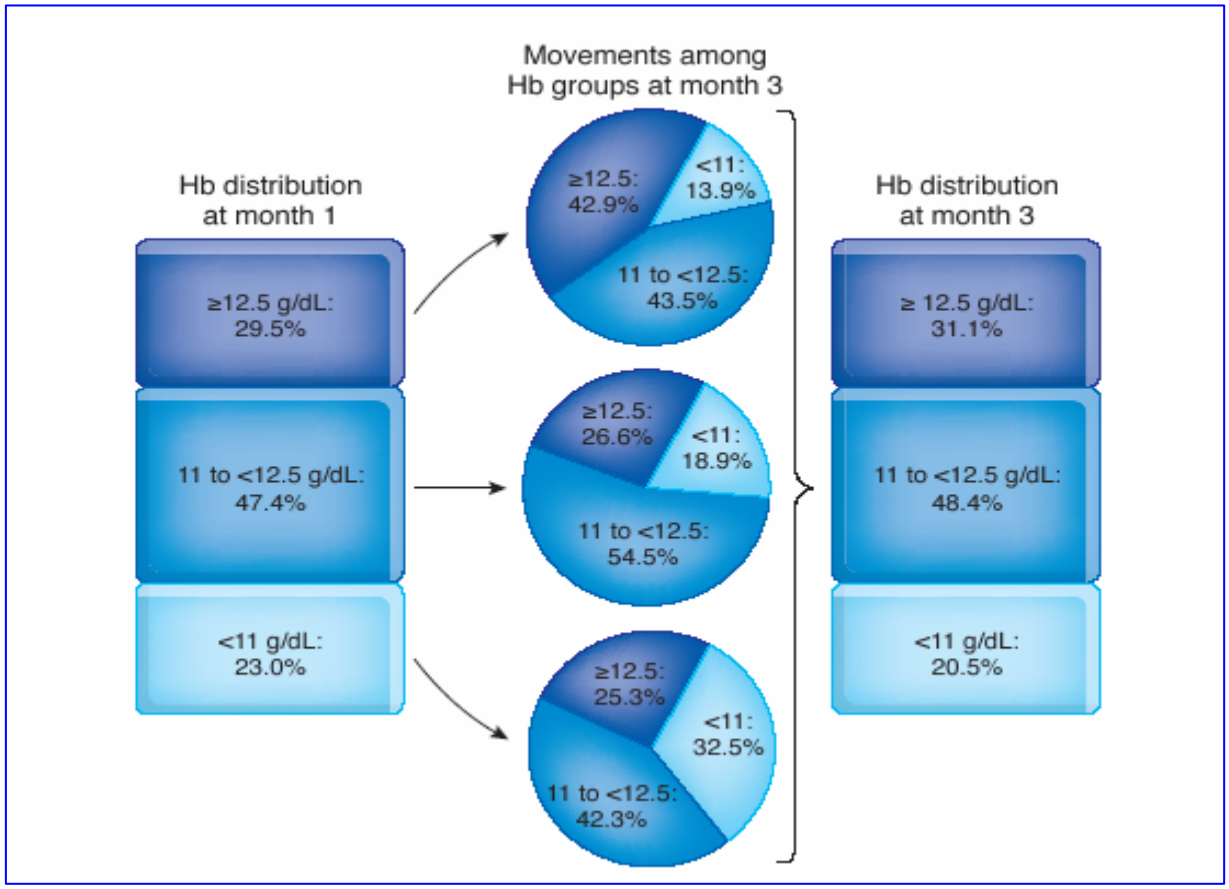
Note: Erythropoietic response to iron therapy is used as the gold standard for the diagnosis of functional iron deficiency.

Tarng DC, AJKD 2010

- Fonksiyonel demir eksikliğini gösteren “tek güvenilir kriter”
  - Demir tedavisine alınan eritropoietik yanıt
  - Ferritin>500 olduğu halde demir tedavisine yanıt veren hastalar var

“Mekanik protokollere dikkat”

Hemoglobin dalgalanması



United States Renal Data System: United States Renal Data System 2006 Annual Data Report Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States. *Am J Kidney Dis* 49:1–296, 2007

Hb düzeyini 11-12 gr/dl aralığında tutmak en iyisi gibi görünüyor,
Ancak…

Table 1. Distribution of 137 ND-CKD patients according to the pattern of individual Hb variability during the 1st year of ESA therapy (modified from [9])

Hb, g/dl[1]	Prevalence, %	
Constantly at 11–13	9.5	
Constantly >13	0.7	
Constantly <11	4.4	
Fluctuating from 11–13 to <11	48.9	% 85.3
Fluctuating from 11–13 to >13	16.0	
Fluctuating from <11 to >13	20.4	

[1] To convert into SI units (g/l), multiply by 10.

Nicola LD. Nephron Clin Pract 2010

Kontrolsüz Hb morbiditeyi artırır

En düşük hospitalizasyon/ko-morbiditeye sahip hedef Hb

Hb	Hospital Admission, %	Admission for Infection, %	Average LOS, days	Average Comorbidity, n
Low	69.2	29.5	12.7	2.4
Target	25.3	6.2	1.9	1.1
High	29.8	7.4	2.2	1.2
LAL	51.1	17.6	6.5	1.8
LAH	33.5	9.3	2.8	1.3
HA	54.0	17.7	6.4	1.8

LOS = length of hospital stay

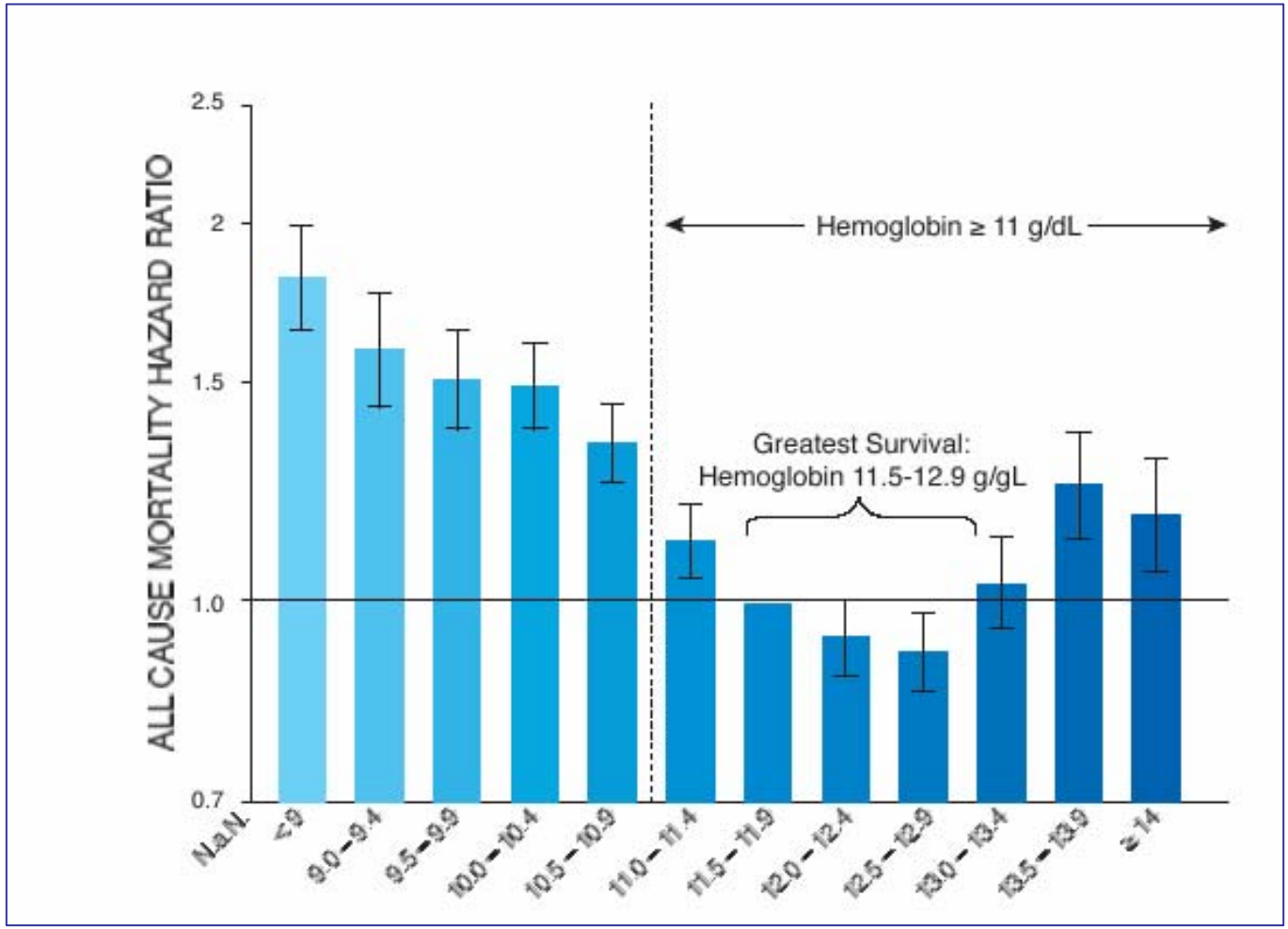
LAL = low-amplitude fluctuation with low Hb

LAH = low-amplitude fluctuation with high Hb

HA = high-amplitude fluctuation

Ebben et al. *Clin J Am Soc Nephrol.* 2006;1:1205-1210.

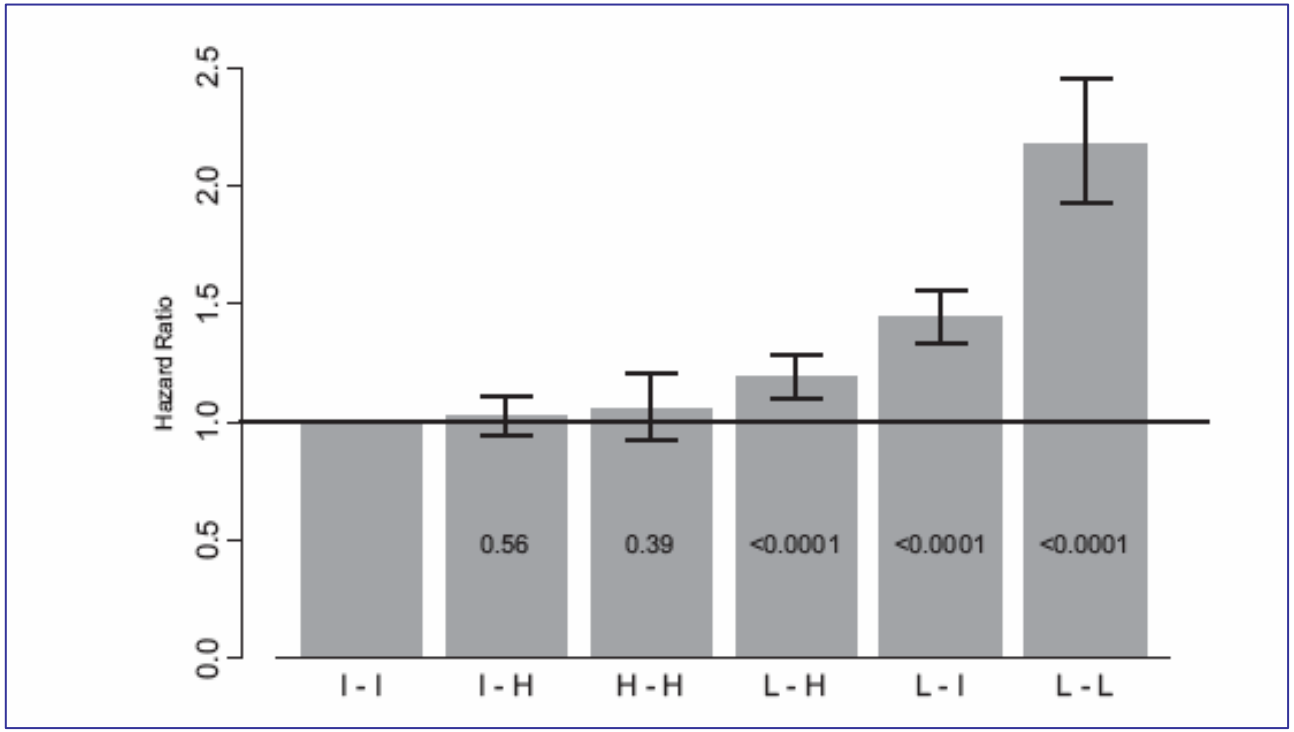
Hemoglobin dalgalanması



Regidor DL, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J, Greenland S, Kalantar-Zadeh K: Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol* 17: 1181–1191, 2006

Hb dalgalanması mortalite ile birliktedir

Dirençli/geçici düşük Hb düzeyleri ve yüksek değişkenlik ile ölüm riski artar



Low: <11 gr/dl

Intermediate: 11-12.5

High: >12.5 gr/dl

Gilbertson, JASN 2008

Hb dalgalanmasının nedenleri

- Demir eksikliği
- İdame tedavisini ihmal ederek yapılan “yükle ve bekle” tedavisi
- Hastanın ESA tedavisine bireysel yanıtı
- İnflamasyon / enfeksiyon
- Diğer: Hospitalizasyon, kanama, HPT, PRCA, ilaçlar,İDKA

Hb değişkenliğini azaltma stratejileri

- Daha sık Hb kontrolü (haftada/2 haftada bir)
- ESA dozunda ince ayar
- Preemptif ESA ayarı
  - Hedef Hb düzeylerinde oynamalar
  - Enfeksiyon, inflamasyon, kanama, hospitalizasyon
- HPT, Demir eksikliği, enfeksiyon, inflamasyon tedavisi
- ESA- demir uygunsuzluğuna dikkat

Bireyselleştirilmiş Tedavi

- Hb: 10.5 gr/dl
- Kendini iyi hissediyor
- Aktif bir hayatı var

Tedavi başlamak için
acele etme

- Hb: 11.5 gr/dl
- Yorgunluk, çabuk yorulma
- Nefes darlığı

Trombotik riski 2.plana at
Tedavi başla
Daha yüksek değeri hedefle

Yaşam Kalitesi / Kardiyak fonksiyonlar !..

TREAT Versus Treatment: A Patient's View of a Scientific Interpretation

Alexander Prisant

AJKD Volume 55, Issue 3, **Pages A31-A32 (March 2010)**

Some have questioned the value of newer strategies like darbepoetin for the treatment of anemia in patients with late-stage chronic kidney disease (CKD). As one of those patients twice over (my first bout was treated with a kidney transplant which is now failing), I feel that it is relevant to consider studies like TREAT from the patient's view, particularly in conditions like anemia which can impact patients' well-being independent of "hard" outcomes such as incident-free longevity.

Beyond CKD, I have severe cardiovascular disease: coronary artery disease with 2 separate 3-vessel coronary artery bypass grafting procedures, advanced heart failure with a profoundly enlarged heart, an ejection fraction of 15%, and an ocular stroke that took half my vision, all of which is related to a lifelong history of CKD. Indeed, when I was born my father was told I would not live 24 hours due to significant bilateral ureteral obstruction. Yet somehow I was among the first to survive bilateral nephrostomies and to be saved by an experimental miracle drug—aureomycin, an early tetracycline antibiotic. At age 51, I was fortunate to receive a kidney transplant at Stanford University. I then survived intracranial posttransplant lymphoproliferative disorder through radiation—refusing to end immunosuppression. (Please understand that some otherwise rational and educated patients would rather save their transplant than their lives.) Currently, my glomerular filtration rate (GFR) is 15 mL/min in my transplanted kidney, and my life depends on maintaining a fine balance between perfusing the kidney while protecting the heart from a relentless tendency towards fluid overload.

I am an active, type A personality, and none of these medical impediments has truly slowed me down—except anemia, which in recent years had forced me toward retirement and had prevented me from virtually all exercise, even walking 30 minutes per day to protect my heart. It was the anemia that seemed to promote a rapid decline in cardiac function leading to severe shortness of breath, expectoration of bloody fluid, and increased angina. For more than a year, I have followed a strict protocol of darbepoetin, 100 μg subcutaneously every other week, along with my dozen other medications.

- In September 2009, my hemoglobin was over 12 g/dL for the first time in more than 5 years. While my wife suffers endless, nonlethal back pain, I am symptom free and feel great, despite a persistently low ejection fraction and a GFR that hovers in a range where many patients are considered for dialysis. I can again exercise 3 times weekly and after 8 years, my angina is virtually gone. My cardiologist cleared me for an expedition to South America in November—the last inhabited continent my wife and I had not visited—a trip which completed one of my life goals

In recent months articles and editorials have presented varied physician views on an issue with broad ramifications, ever more relevant, in our transitional medical age:

- treat the patient as an individual, or treat in line with the latest empirical study
- Quality of Life : hard clinical end-points

Gelecekteki Tedavi Yaklaşımları

- Protein bazlı ESA
  - Epoetin (alfa
  - Darbepoetin
  - CERA
  - SEP
  - EPO füzyon proteinleri
- Küçük moleküllü ESA
  - Peptit bazlı (hematide)
  - Peptit bazlı olmayan
- Diğer
  - HIF stabilizerleri, GATA, HCP inhibitörleri
  - EPO gen tedavisi

(Continuous erythropoietin receptor activator)
Yarı ömrü daha uzun (130 saat)
Etkinlik benzer

Sentetik- pegile EPO
≡ EPO-mimetik
Yarı ömrü 24 saat
3-4 haftada bir, etkin
PRCA'da önemli