

# Current Controversies in Anemia: Target Hemoglobin levels and Outcomes

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*Dallas, Texas*

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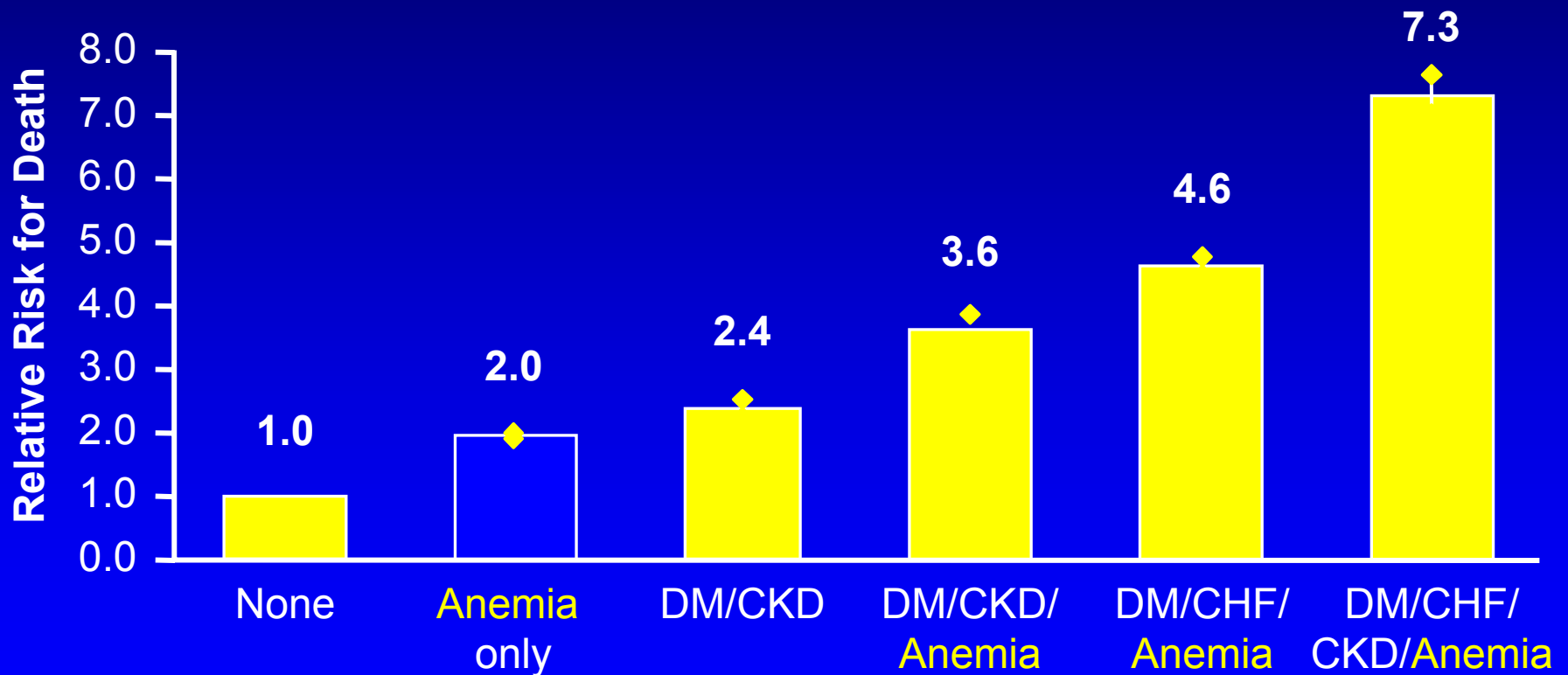
- Evidence for treatment to increase Hb
  - improves quality of life...but
  - Improved cardiovascular and renal outcomes remain elusive
- Current hemoglobin target and Treatment
  - 11-12 g/dl
  - Not to exceed 13 g/dl
- Future
  - New ESA dosing and target trials
  - Novel therapeutics (e.g. HIF modulation)

Evidence

# Anemia is a Risk Factor for Morbidity and Mortality

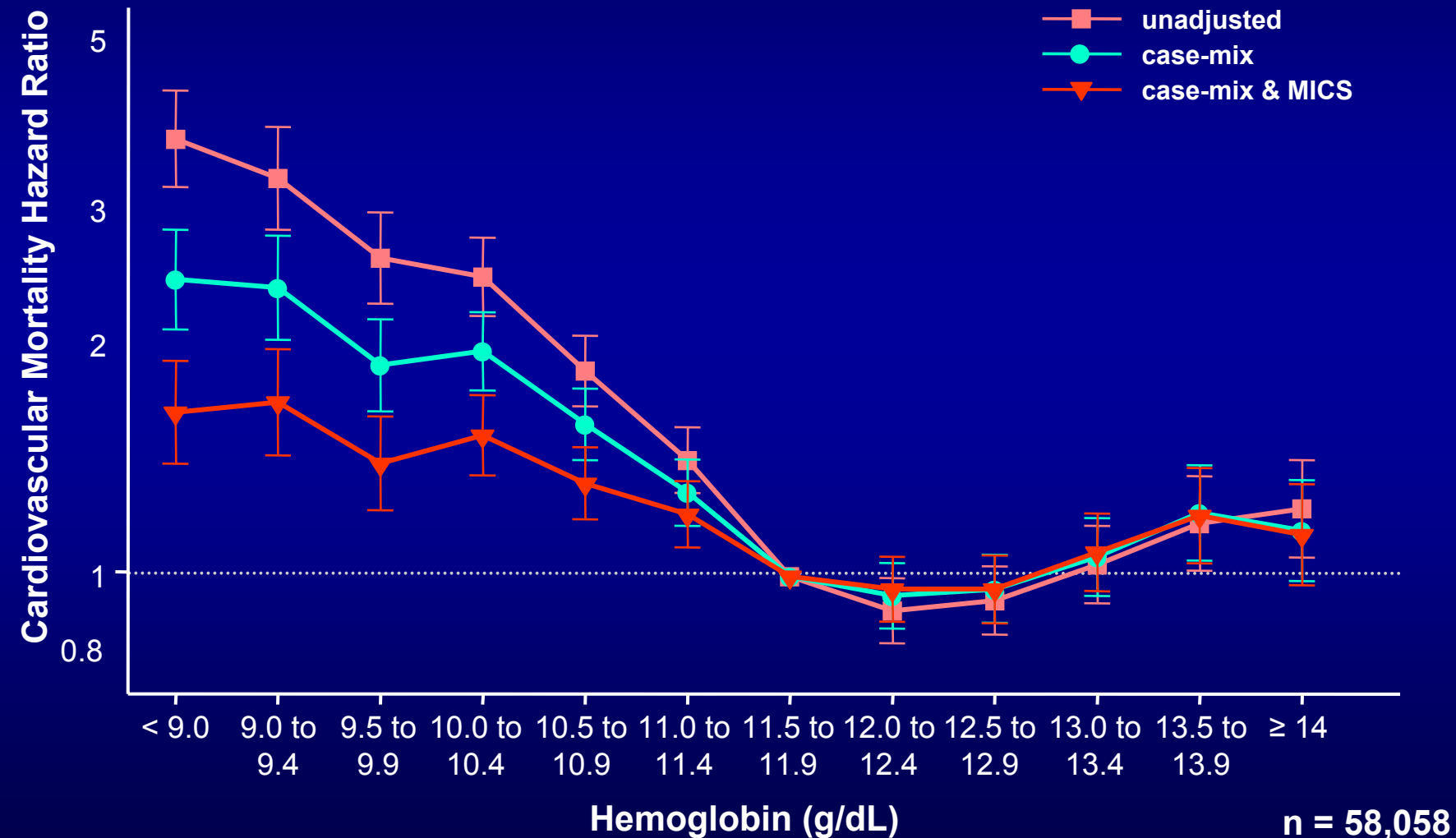
# Anemia Significantly Impacts Mortality in CKD Patients

Medicare sample (5%), follow-up from 1996 to 1997 of enrollees aged  $\geq 65$  yo, adjusted for age, sex, and race



DM=diabetes mellitus; CHF=congestive heart failure.  
Collins et al. *Adv Stud Med.* 2003;3:S14-S17.

# Cardiovascular Death in Hemodialysis Patients



# HCT/Hb in Observational Studies

- Hgb levels decrease in sick patients
- This fact hopelessly intertwines Hgb level with outcomes
- No multivariate technique could ever truly indicate the causal relationship between Hgb and outcomes
- RCTs can definitely determine the effect of treatment with ESAs
- Now that RCT literature base has expanded, there is no reason for anyone to do another observational study of Hgb and outcomes

# Association Between Hemoglobin Exposure Parameters and Mortality

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Exposure	HR (95% CI)
Absolute level of Hb (g/dl)	0.81 (0.77 to 0.84)
Temporal trend in Hb (g/dl/mo)	0.51 (0.44 to 0.59)
Hemoglobin variability	
Per 0.5 g/dl	1.15 (1.10 to 1.20)
Per 0.75 g/dl	1.24 (1.16 to 1.32)
Per 1.0 g/dl	1.33 (1.22 to 1.45)
Per 1.5 g/dl	1.53 (1.35 to 1.75)

# Published Randomized Controlled Trials of Anemia Therapy and Cardiac Disease in Chronic Kidney Disease

Study	N	Design	Study Population	HCT/Hb Target	Primary Outcome	Follow-up (mos)
Besarab <i>NEJM</i> 339:1998	1233	Open Label	HD + CHF/CAD	30 42	Death, MI	29
Foley <i>KI</i> 58:2000	146	Open Label	HD - CHF/CAD	9.5-10.5 13-14	LVMI LVVI	12
Roger <i>JASN</i> 15:2004	155	Open Label	Stage 3-5	9-10 12-13	Δ LVMI	24
Parfrey <i>JASN</i> 16:2005	596	Double Blind	HD - CHF/CAD	9.5-11.5 13.5 -14.5	LVVI	22
Levin <i>AJKD</i> 46:2005	172	Open Label	Stage 2-5	9-10.5 12-14	LVMI	22.6
Singh <i>NEJM</i> 355: 2006	1432	Open Label	Stage 4-5	11-11.5 13-13.5	Death, CV event	16
Druecke <i>NEJM</i> 355: 2006	603	Open Label	Stage 4-5	11-11.5 13-15	Death, CV event	36

**Total 4337**

# Published Randomized Controlled Trials in Chronic Kidney Disease: Bottom Line

Study	Population	Hb Target	CV Outcome	Quality of Life
Besarab <i>NEJM</i> 339:1998	HD + CHF/CAD	30 42	No benefit	? Improved
Foley <i>KI</i> 58:2000	HD - CHF/CAD	9.5-10.5 13-14	No benefit	Improved
Roger <i>JASN</i> 15:2004	Stage 3-5	9-10 12-13	No benefit	Improved
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Levin <i>AJKD</i> 46:2005	Stage 2-5	9-10.5 12-14	No benefit	Improved
Singh <i>NEJM</i> 355: 2006	Stage 4-5	11-11.5 13-13.5	Worse in High Hb	No difference
Druecke <i>NEJM</i> 355: 2006	Stage 4-5	11-11.5 13-15	No benefit	Improved

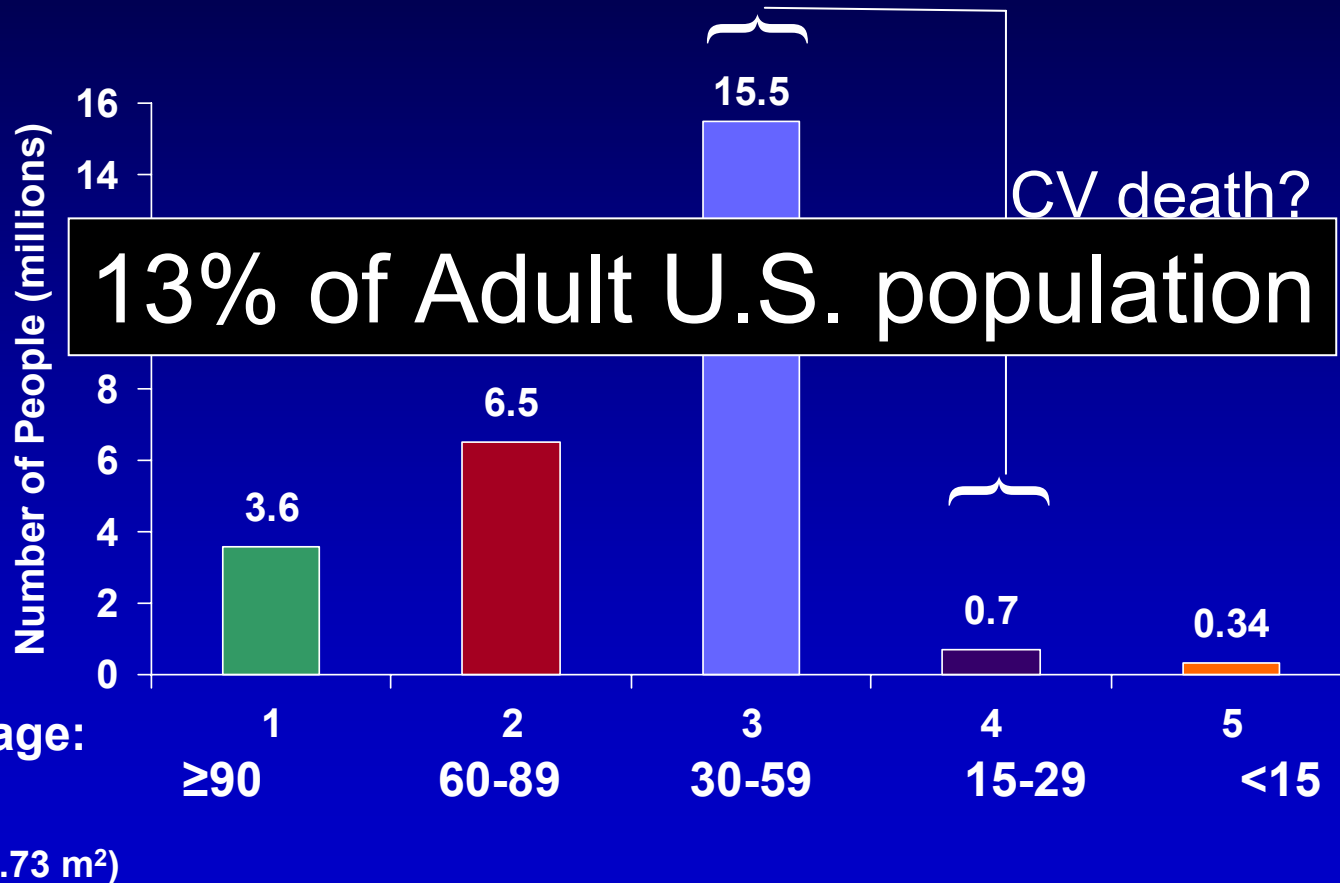
# Published Randomized Controlled Trials of Anemia Therapy and CV Outcomes in Chronic Kidney Disease

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ASB 2002		Blind				
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Total 3268

# Prevalence of Chronic Kidney Disease in the United States by Stage

Cross-Sectional Data (NHANES 1999-2004)



CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

\*On dialysis.

Coresh J et al. *JAMA*. 2007;298:2038-2047; USRDS, 2007.

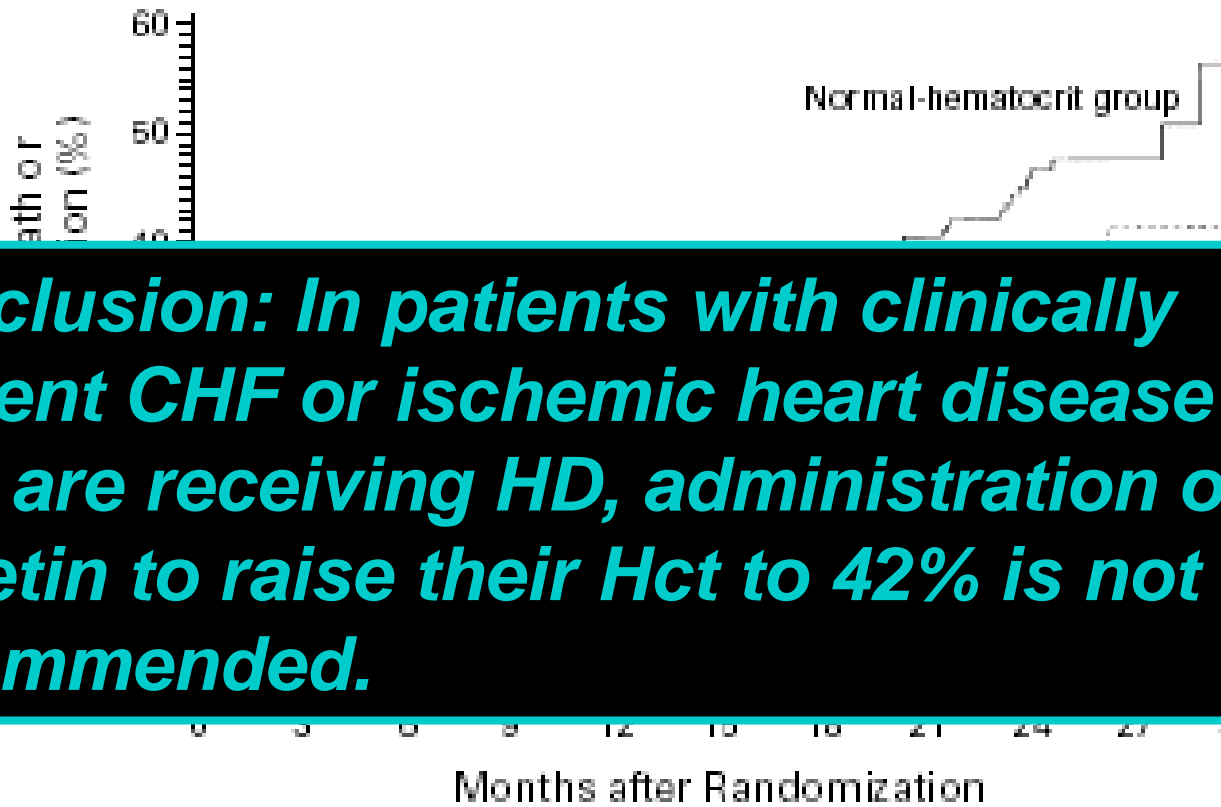
# Normalization of Hematocrit in Hemodialysis Patients with CHF or CAD

- **Design:** 1233 patients CHF or CAD on Hemodialysis randomized to Epoetin and Hematocrit of 42 or 30 %, median follow up 14 mos.
- **Primary end point:** time to death or first nonfatal MI
- **Results:**

Hematocrit Group	Death	Nonfatal MI
Normal	183	19
Low	150	14

RR: 1.3; 95% CI, 0.9 to 1.9  
Both groups: Mortality rate decreased with increasing Hct

# Normal Hematocrit Study



**Conclusion: In patients with clinically evident CHF or ischemic heart disease who are receiving HD, administration of epoetin to raise their Hct to 42% is not recommended.**

## No. AT RISK

Normal hematocrit	618	540	476	416	353	269	186	124	69	26
Low hematocrit	615	537	485	434	391	292	216	131	80	20

# Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) Objective:

Determine the impact of **degree** of anemia correction on mortality and CV morbidity in patients with CKD (Stage 3-4) not on dialysis

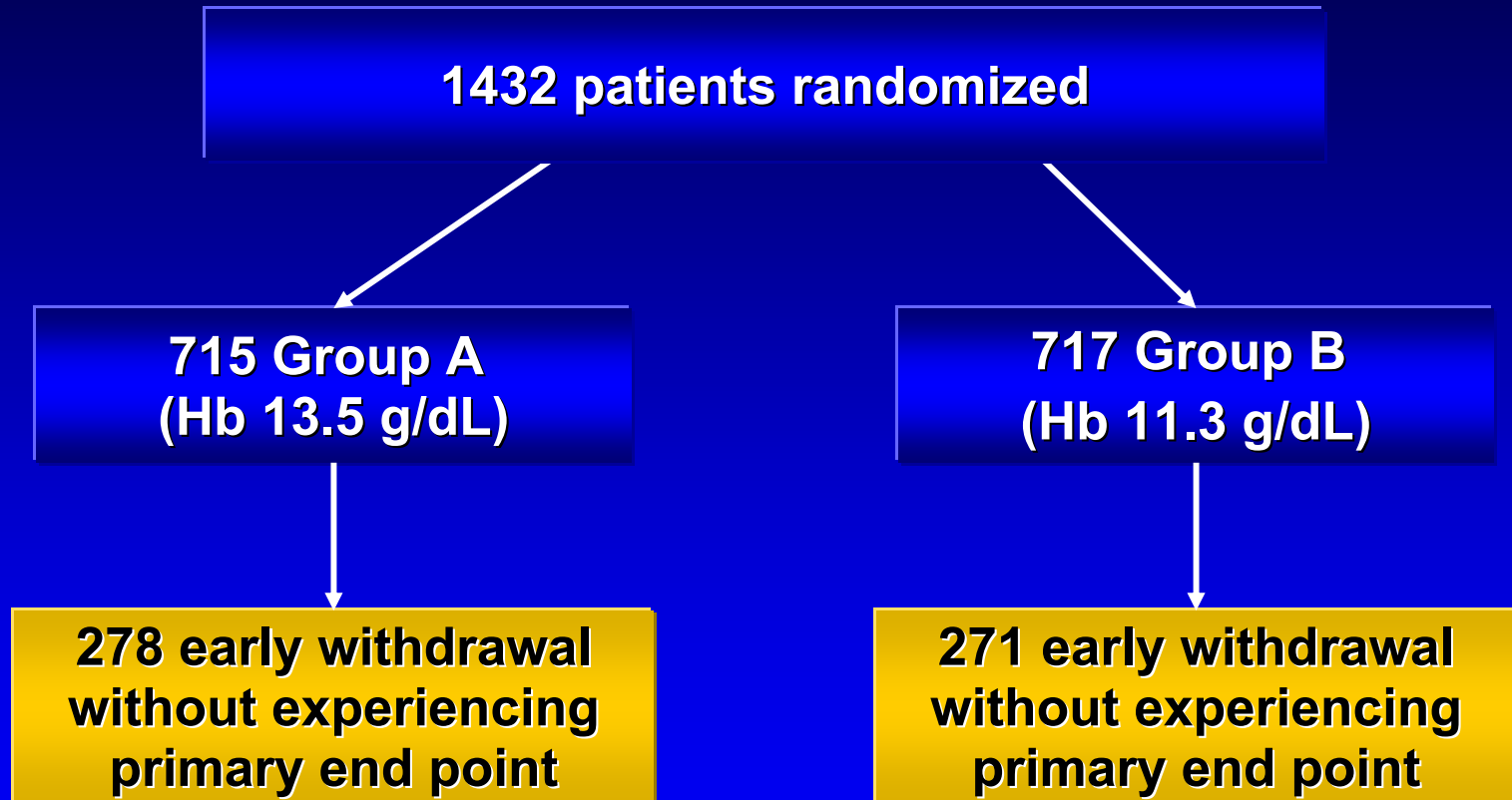
# CHOIR General Design Characteristics

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Design	Randomized, open-label
Primary end point	Time to all-cause mortality or MI, CVA, HF
Erythropoietic agent	Epoetin alfa
Dosing frequency	de novo to QW to Q2W
Hb target(s) (g/dL)	
Arm 1	13.5 (13-13.5)
Arm 2	11.3 (10.5-11)
Regions/countries	US
No. centers	130

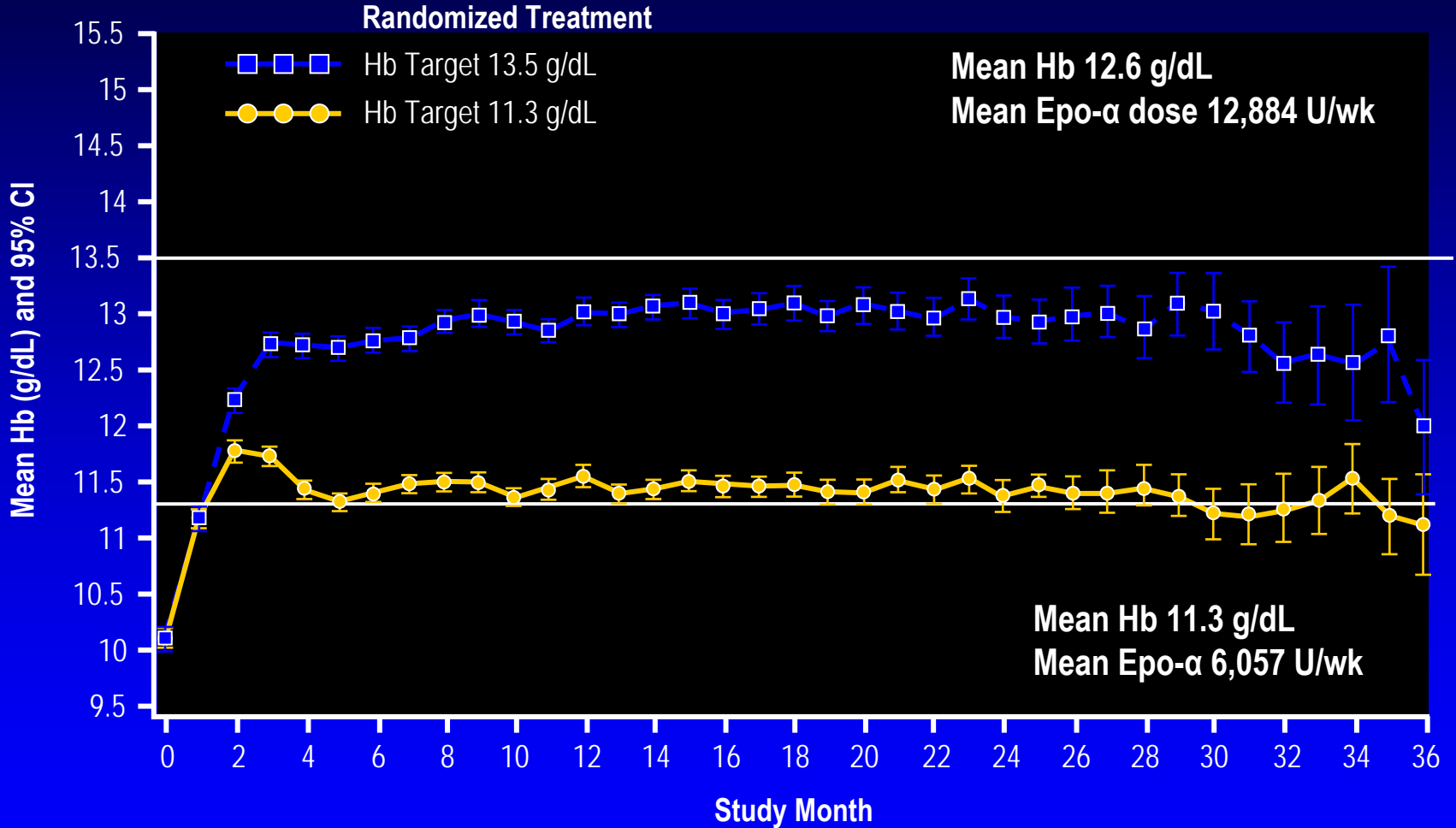
# Correction of Hb and Outcomes in Renal Insufficiency (CHOIR)

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**DSMB stopped study May 2005 for futility (not a stopping rule)**

# Mean Monthly Hb Levels



N

Hb 13.5	710	667	632	600	558	507	485	433	367	306	252	194	139	95	81	67	49	31	13
Hb 11.3	707	672	625	603	549	528	510	471	384	334	250	182	141	101	75	60	45	30	13

# CHOIR Outcomes: Mortality and CV Morbidity

End Point	# Events		HR (95% CI)	P Value
	Hb 13.5	Hb 11.3		
Composite Primary	125	97	1.34 (1.03, 1.74) <sup>a</sup>	.03
Secondary				
All-cause mortality	107	78	1.41 (0.97, 2.05)	.07
Major morbidity	178	134	1.19 (0.94, 1.49)	.15
Stroke	59	47	1.23 (0.83, 1.84)	.33
Heart failure	64	47	1.41 (0.97, 2.05)	.07
ESRD	155	134	1.19 (0.94, 1.49)	.15
CV hospitalization	233	197	1.23 (1.01, 1.48)	.03

**Conclusion: The use of a target hemoglobin level of 13.5 g/dL (as compared with 11.3 g/dL) was associated with increased risk and no incremental improvement in the quality of life**

<sup>a</sup>Time for KM curves to separate: ~6-8 months.  
Singh et al. *N Engl J Med.* 2006;355(20):2085-2098 (A).

# CHOIR Study Issues

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- Different at baseline
  - Coronary artery bypass grafts
    - High-Hb group 17% vs low-Hb group 14%, ( $P=.03$ )
  - HTN high
    - High-Hb group 95% vs low-Hb group 92% ( $P<.02$ )
- Over half were lost in each group
  - Dialysis start in about half
  - Remainder withdrawn for various reasons
  - High doses of epoetin alfa compared with CREATE
    - CREATE 5000 to 6000 units
    - CHOIR 11,000 units
- Final analysis: “CHOIR is a RCT of 700 patients, who did not achieve target Hb values of 13.5 g/dL (median was 12.8 g/dL) despite receiving 11,000 units of epoetin alfa”

# Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE) Trial Objective

Determine the impact of **early vs late** anemia correction on mortality and CV morbidity in patients with CKD (Stage 3-4) not on dialysis

# Correction of Renal Anemia CREATE Studies

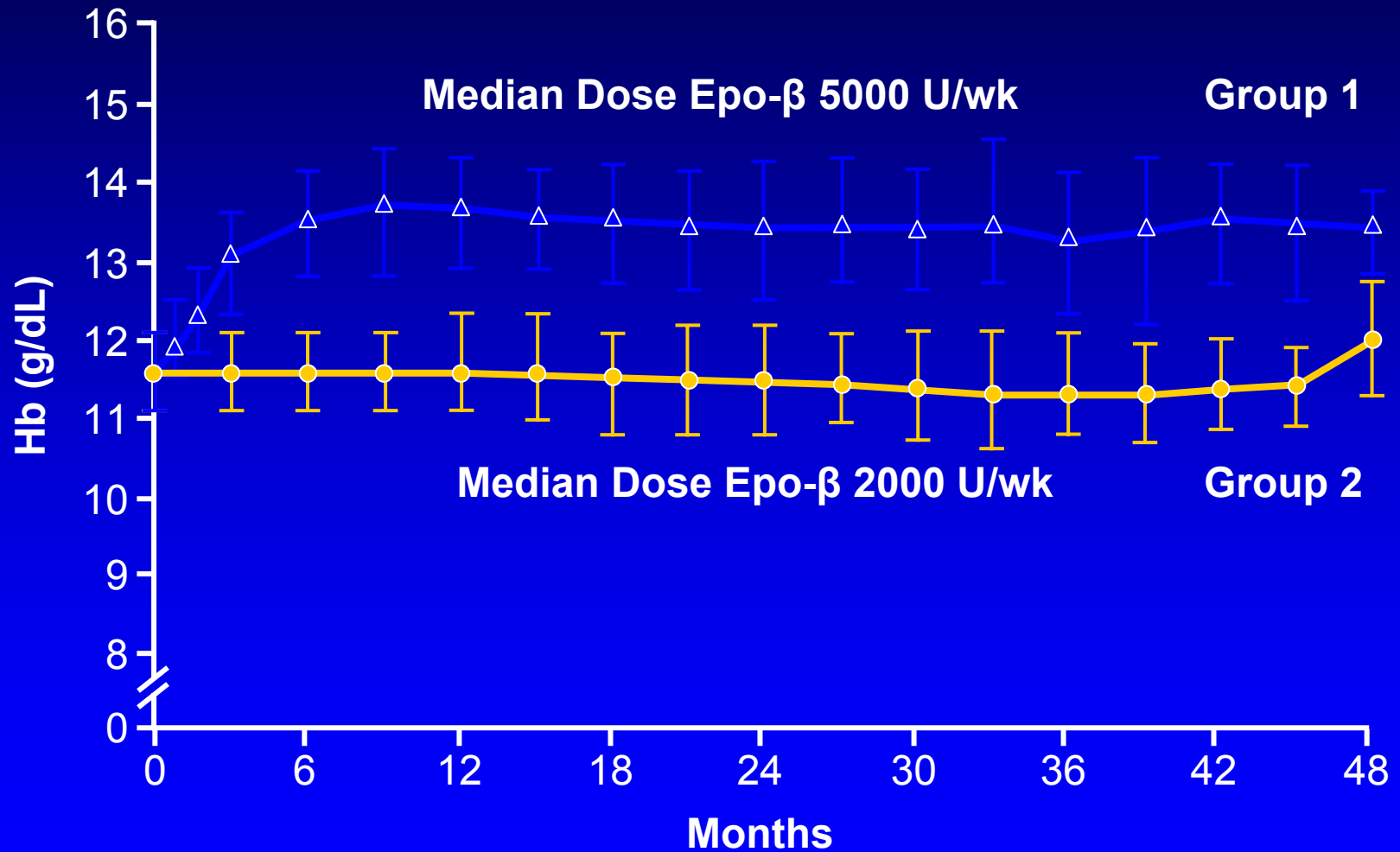
CREATE <sup>1</sup> (N=603)	
Design	Randomized, open-label
Primary end point	Time to CV event: SD, MI, CVA, TIA, HF, angina, arrhythmia, PVD
Sponsor/agent	Roche/NeoRecormon <sup>®</sup> (epoetin beta)
Dosing	2000 QW
Dosing frequency	<i>De novo</i> to QW
Hb target(s), g/dL	
Group 1	13.0-15.0
Group 2	10.5-11.5 <sup>a</sup>
Regions/countries	EU, Mexico, China, Taiwan, Thailand, Russia, Turkey, Greece
No. centers	94

SD=sudden death; CVA=cerebrovascular accident; TIA=transient ischemic attack; HF=heart failure.

<sup>a</sup>Treatment starts when Hb <10.5 g/dL.

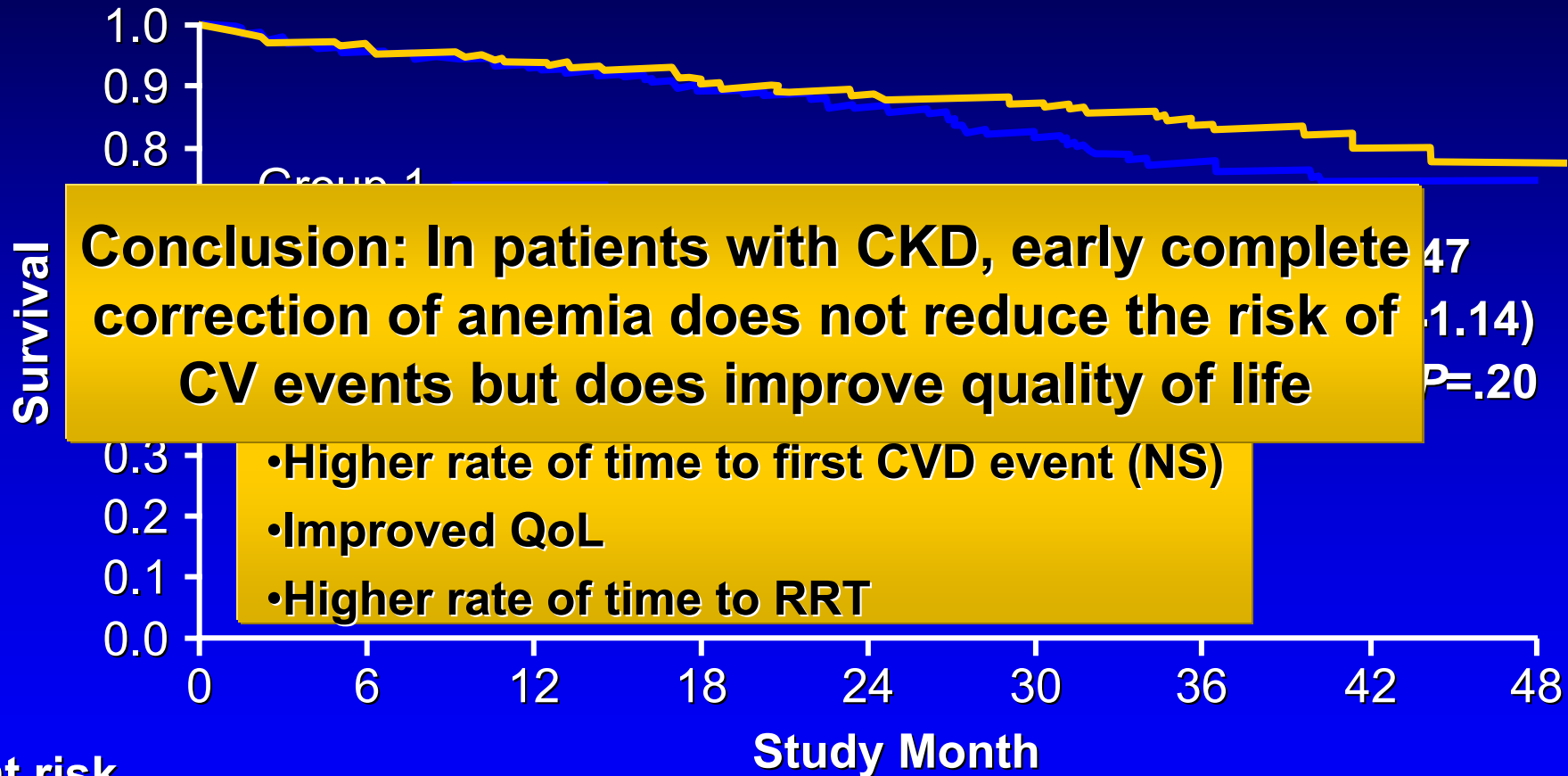
Drüeke et al. *N Engl J Med.* 2006;355(20):2071-2084.

# CREATE HB Level



# Primary End Point

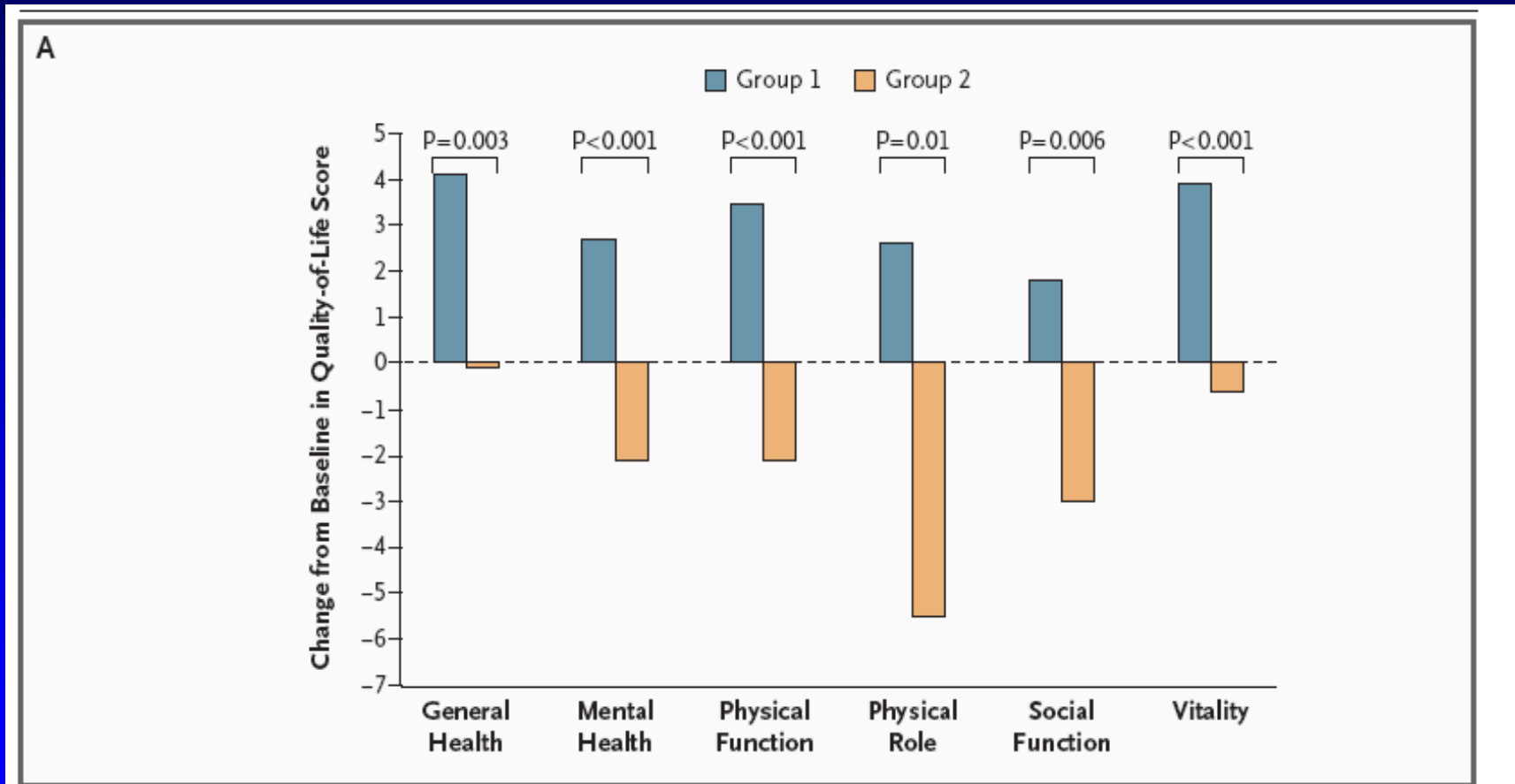
## Time to first CV events (105 events)



n at risk

	0	6	12	18	24	30	36	42	48
Group 1	301	279	268	249	207	158	97	56	2
Group 2	302	286	272	257	223	177	121	61	2

# Higher Hb and Quality of Life in the Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE) Trial



# Interpretation of CREATE Results Limited by Inadequate Power

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- Patients in the higher target Hb group (13 to 15 g/dL) were NOT found to have a statistically significant higher risk of the composite primary end point
- The results of the CREATE study were strongly influenced by an overall low CV event rate (6% vs 15% anticipated)

# Summary 1: Outcomes Trials of ESA Treatment of CKD Associated Anemia

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- Cardiovascular Outcomes Trials in ~ 3300 with a total of 703 events
- Quality of Life benefit
- No Cardiovascular Benefit
- Small number of study participants compared to overall CKD population

# Current Target and Treatment

# Benefits of Treatment With Erythropoiesis-Stimulating Agents (ESAs)

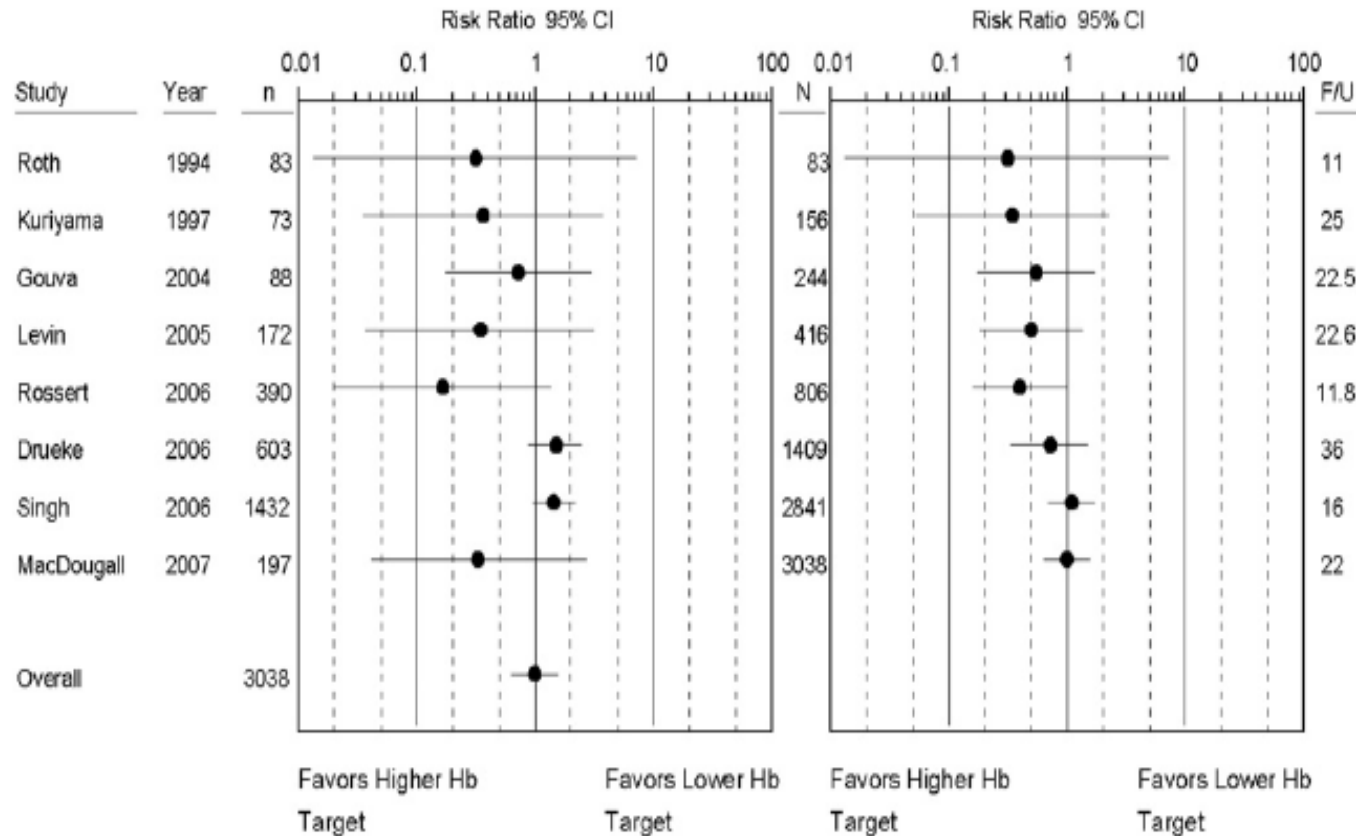
- Treatment with ESAs to achieve partial correction of Hb levels is associated with
  - Improved quality of life
  - Reduced Transfusions

# 2007 KDOQI Update to Clinical Practice Guideline Recommendations: ESA Use

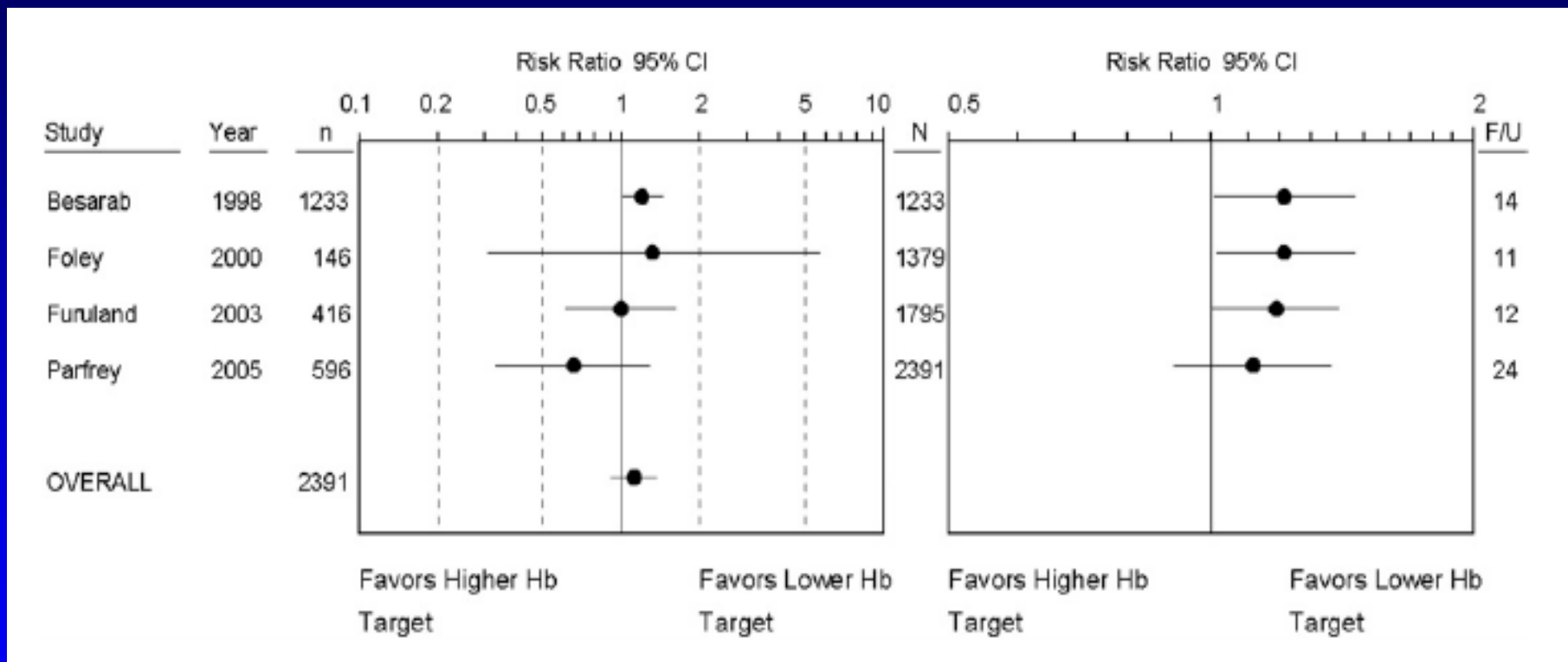
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- **Hb target and Hb level should be individualized**
- **Consider potential benefit and potential harm**
- **Hb target range for dialysis and non-dialysis CKD patients**
  - **11.0 to 12.0 g/dL**
  - **should not be > 13.0 g/dL**

# Relative Mortality Risk For Assignment To Higher Hb Treatment Targets In Patients With **Non-dialysis CKD**



# Relative mortality risk for assignment to higher Hb treatment target in patients disease undergoing dialysis



# ESA Safety Label Change

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- FDA Prescribing Changes (March 9, 2007)
- Review of 5 studies using ESAs reaching Hb of 12 g/dL
- Increased the risk for death and for serious CV events when administered to target a Hb of >12 g/dL
- Increased risk of arterial and venous thromboembolic events, including MI, stroke, congestive heart failure, and hemodialysis graft occlusion.
- Rate of Hb rise of >1 g/dL over 2 weeks may also contribute to these risks

MI=myocardial infarction. Aranesp® (darbepoetin alfa) [package insert]. Thousand Oaks, CA: Amgen, Inc.; 2007 (A); Procrit® (epoetin alfa) [package insert]. Raritan, NJ: Ortho Biotech Products, LP; 2007 (A); Epogen® (epoetin alfa) [package insert]. Thousand Oaks, CA: Amgen, Inc.; 2007 (A). US Food and Drug Administration. <http://www.fda.gov/cder/drug/infopage/RHE/qa.htm>. Accessed on May 1, 2007.

# Target Hemoglobin

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- Practice guidelines for binary processes are easy
  - Warfarin in A Fib
  - ACEI in CHF
  - Aspirin post MI etc.
- Practice guidelines for continuous variables like Hgb target are very hard

# Target Hemoglobin

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- Evidence for a Hgb target would ideally come from a large RCT with several targets:
  - Hgb 8,9,10,11,12,13                      impractical
- Without such studies only relative boundaries can be defined:
  - CHOIR -Some target level at or below 13.5 g/dL is clearly harmful
  - CREATE- Some target level at or below 13-15 may be harmful
  - NHCS- Some level at or below 14 g/dL is harmful

# Guidelines

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- Hb target reflects a tradeoff between QOL benefit and safety risk
- Can there be any evidence based guidelines for Hb target?
- What should the target Hgb be?

# What Should the Hb Target be?

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- CHOIR tested Hgb 11.3 g/dL vs. 13.5 g/dL
  - Achieved level in higher group 12.6 g/dL
- Does this mean 11.3 g/dL is optimal?
  - No

# What Should We (What I) Do Now

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- FDA recommendations compel one to target Hb  $\leq$  12 g/dL, but the high goals achieved in CHOIR and CREATE were  $\sim$ 12.6 and  $\sim$ 13.6 g/dL, respectively
- No new information in CKD patients since CHOIR and CREATE...TREAT is ongoing
- Talk to colleagues and patients about FDA warning
- Target Hb 12 g/dL
- Look forward to more information from FDA and TREAT results
- Continue to minimize use of blood transfusions

# ESA Dose Adjustments

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- Adjust dose for each patient to achieve and maintain the Hb level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL
- If the Hb is approaching 12 g/dL, the dose should be reduced by ~25%
  - If the Hb continues to increase, temporarily withhold doses until Hb begins to decrease, then reinstate dose ~25% lower than previous dose
- If the Hb increases by more than 1 g/dL in a 2-week period, the dose should be decreased ~25%

Aranesp<sup>®</sup> (darbepoetin alfa) [package insert]. Thousand Oaks, Calif: Amgen, Inc.; 2007 (A);  
Procrit<sup>®</sup> (epoetin alfa) [package insert]. Raritan, NJ: Ortho Biotech Products, LP; 2007 (A);  
Epogen<sup>®</sup> (epoetin alfa) [package insert]. Thousand Oaks, Calif: Amgen, Inc.; 2007 (A).

# Summary 2: Target Hb and ESA Use in Anemia of Chronic Kidney Disease

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- ESA safe and effective for treating anemia when used “appropriately”
- Individualize target Hb and Hb level
- Anemia Guidelines generally recommend
  - target Hb range 11-12 g/dL
  - Not to exceed 13 g/dl
- Additional studies are needed to improve treatment decisions

# The Future

# Is There a Future for Discovery in Anemia of Chronic Kidney Disease?

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- Determine whether dose of ESA or level of Hb is important in adverse side effects
- Determine optimal (safest and most efficacious) Hb target and ESA dose for individual patient
- Discover new mechanisms of anemia
- Discover new ways to manage anemia
  - Iron absorption
    - Better iron products
  - Inflammation
    - Heparin
    - HIF and others

Trial to Reduce CV Events With  
Aranesp<sup>®</sup> (darbepoetin alfa) Therapy  
(TREAT)

# TREAT Hypothesis

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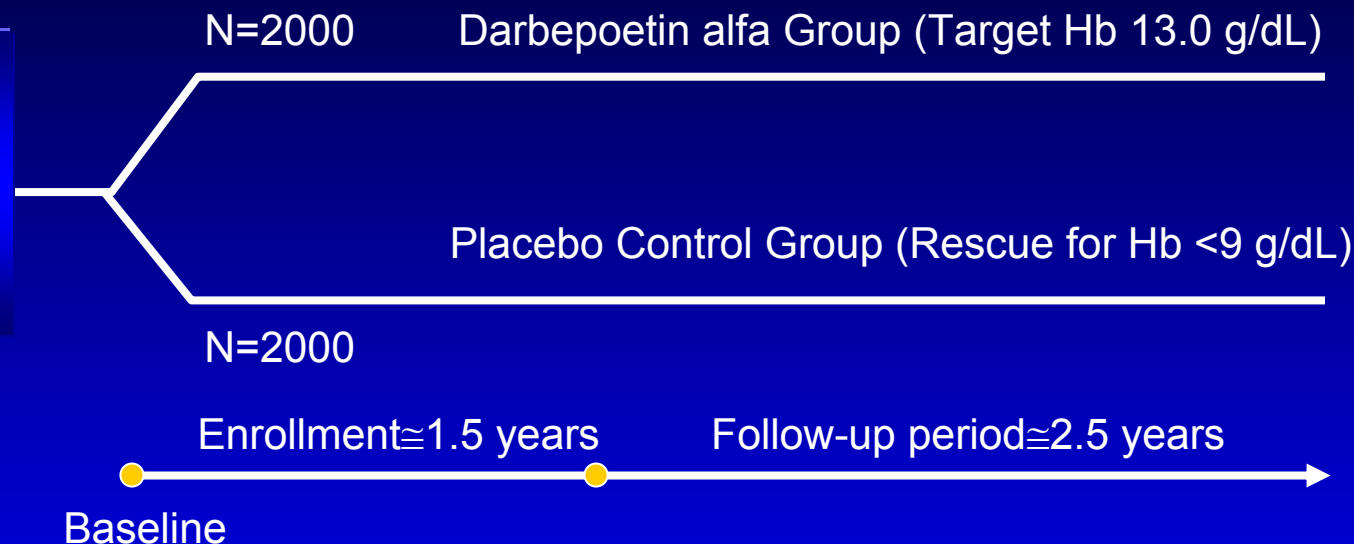
Treatment of anemia with darbepoetin alfa  
in subjects with CKD and type 2 diabetes  
mellitus decreases mortality and CV morbidity

# TREAT Study Design

## A Phase 3 Clinical Trial

### Study Population

- Hb  $\leq 11$  g/dL
- GFR 20-60 mL/min/1.73 m<sup>2</sup>
- Type 2 diabetes mellitus



### Primary End Point

- Composite event rate comprising all-cause mortality and CV events
  - Myocardial ischemia
  - Myocardial infarction
  - Congestive HF
  - Cerebrovascular accident

### Secondary End Points

- Time to ESRD or all-cause mortality (key 2<sup>o</sup> end point)
- Time to
  - All-cause mortality
  - CV mortality
  - Myocardial ischemia
  - MI
  - CVA
  - Congestive HF
  - ESRD
- Rate of decline in eGFR relative to baseline
- Change in patient-reported fatigue

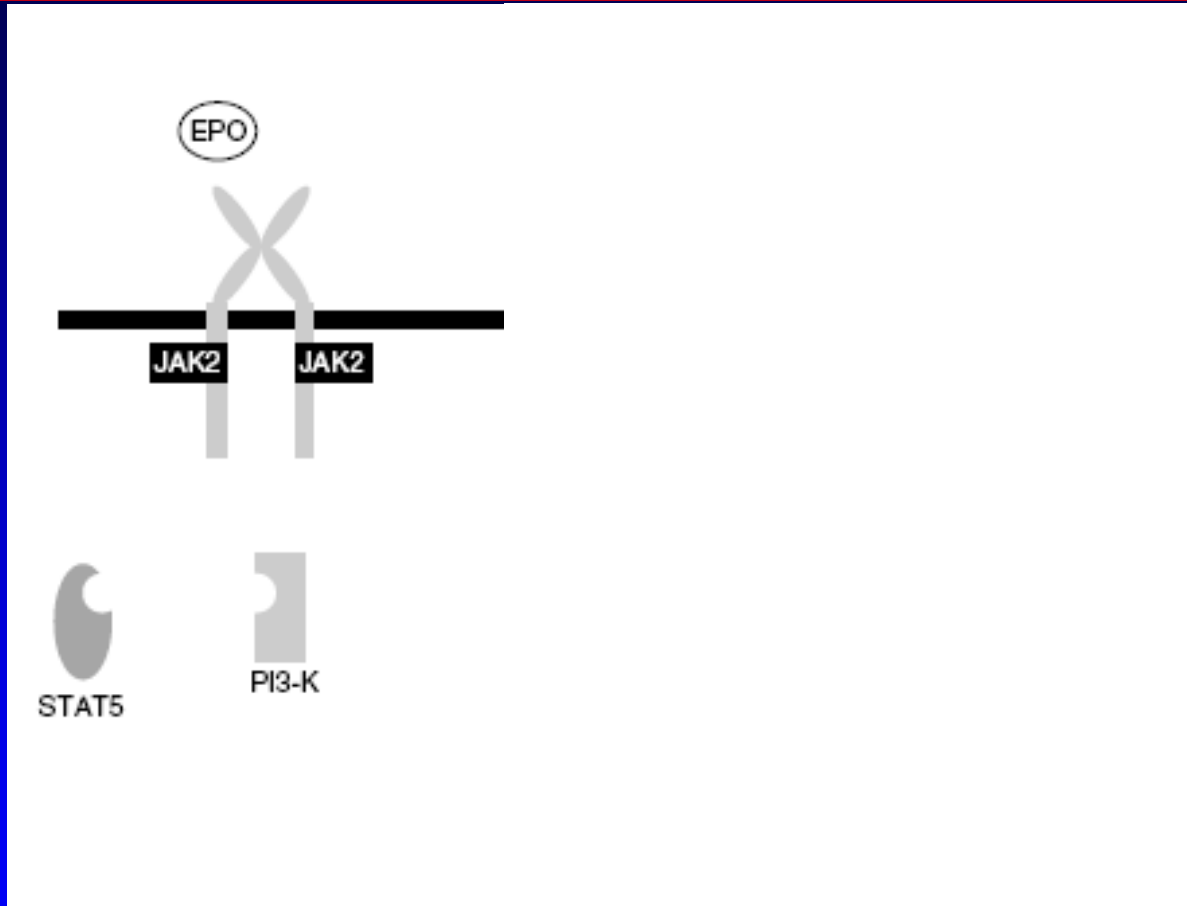
Mix et al. *Am Heart J.* 2005;149(3):408-413.

# Effects of ESAs

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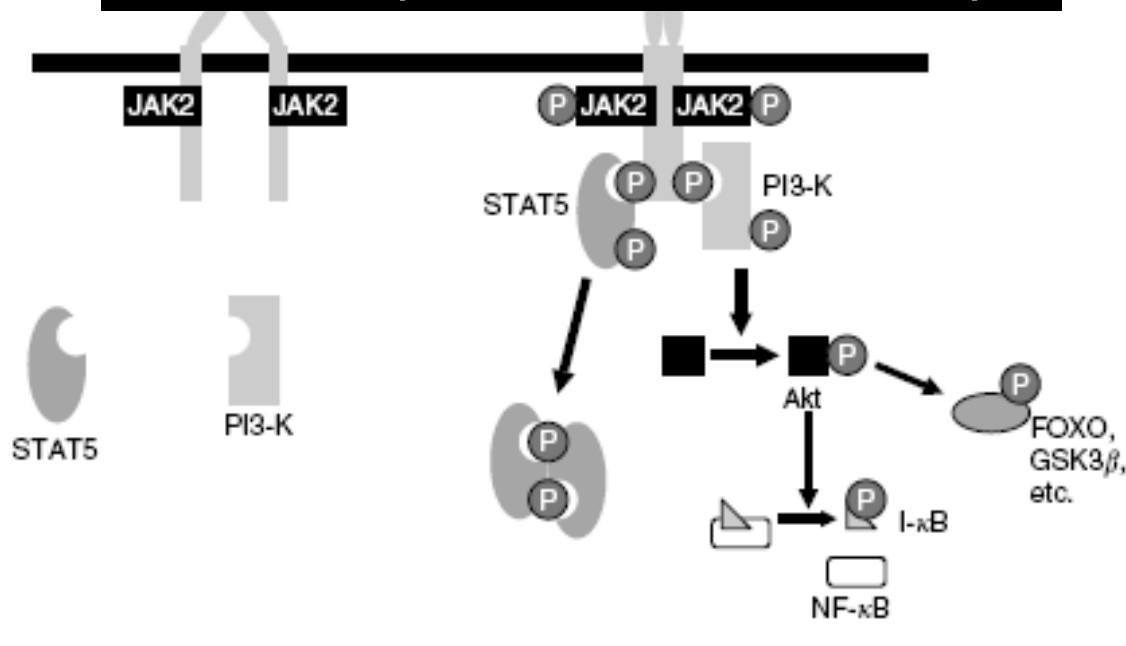
- Modulate broad array of cellular processes
  - progenitor stem cell development
  - cellular integrity, and angiogenesis.
- Pleiotropic effect in CNS, CVS and Kidney
- Randomized controlled do not negate renoprotective effects of EPO.
- Patients with CKD benefit from early recognition and appropriate correction of anemia with ESA.

# Major intracellular signals activated by Erythropoietin

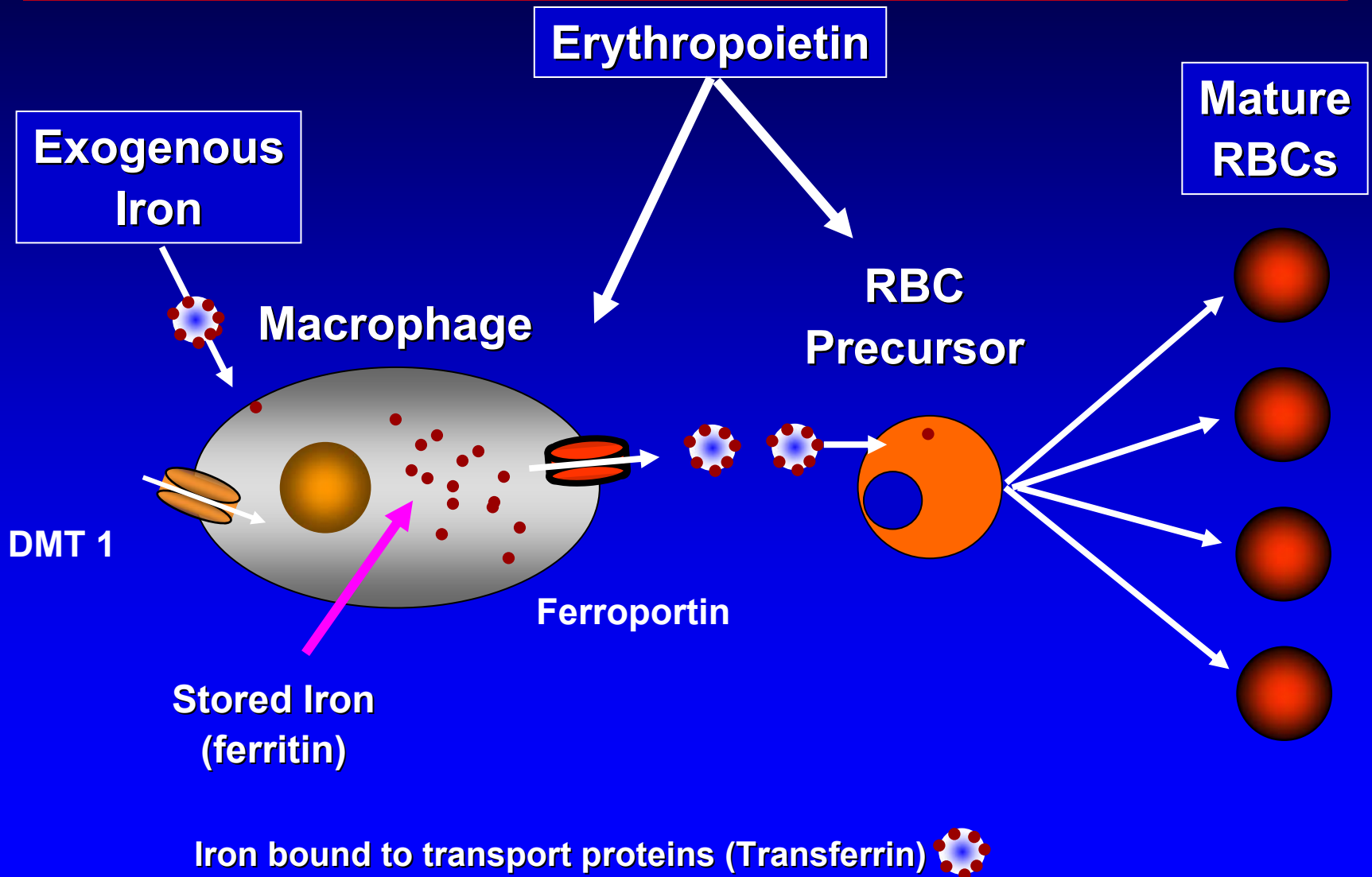


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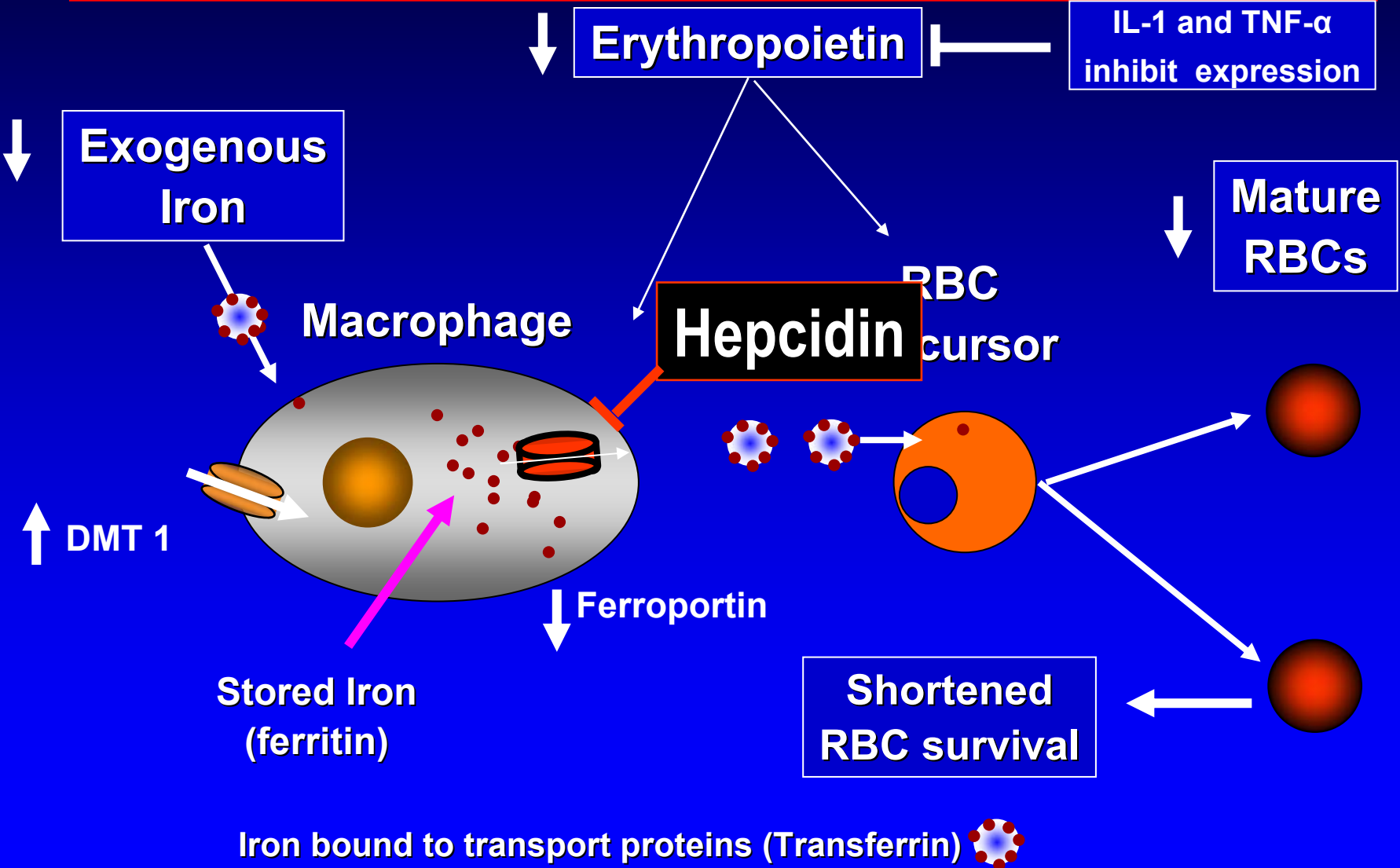
Red blood cell differentiation,  
proliferation and  
survival (inhibition of apoptosis)



# Iron Transport and Storage



# Iron Transport and Storage in Chronic Inflammation (CKD)



# Regulation of Systemic Iron Homeostasis

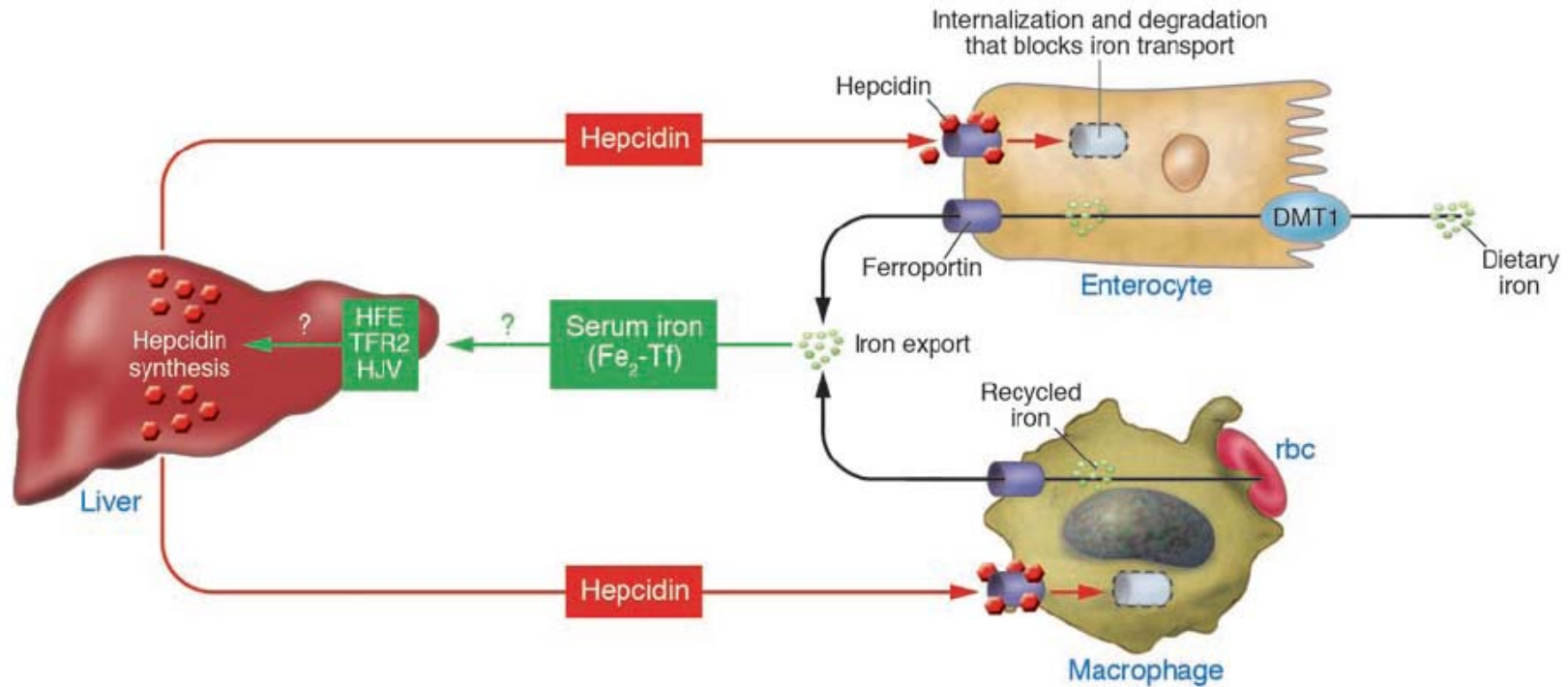


Figure 1

# Hypoxia Inducible Factor 1

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- Transcription factor activated by low O<sub>2</sub>
- Uregulates EPO gene via hypoxia response element (HRE)
- First discovered HRE motif was first identified as a 50-bp sequence in the 3-flanking region of the human erythropoietin (*EPO*) gene
- HIF-1 is hydroxylated by prolyl hydroxylase enzymes enabling interaction with pVHL, substrate recognition component of an E3-ubiquitin ligase complex that targets HIF-1 for degradation
- In absence of oxygen, prolyl hydroxylase activity is inhibited, stabilization and nuclear translocation of the HIF-1-subunit, enabling it to bind to HIF-1 and form transcriptionally active HIF-1

# Possible Future Treatment Options for CKD-Related Anemia

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- Erythropoietin-mimetic peptides
  - long duration of action that allows for once monthly dosing
- Hypoxia-Inducible Factor (HIF) Stabilizer
  - first oral therapy for the treatment of anemia in CKD
- Anti-inflammatory drugs?
- Heparin antagonists?

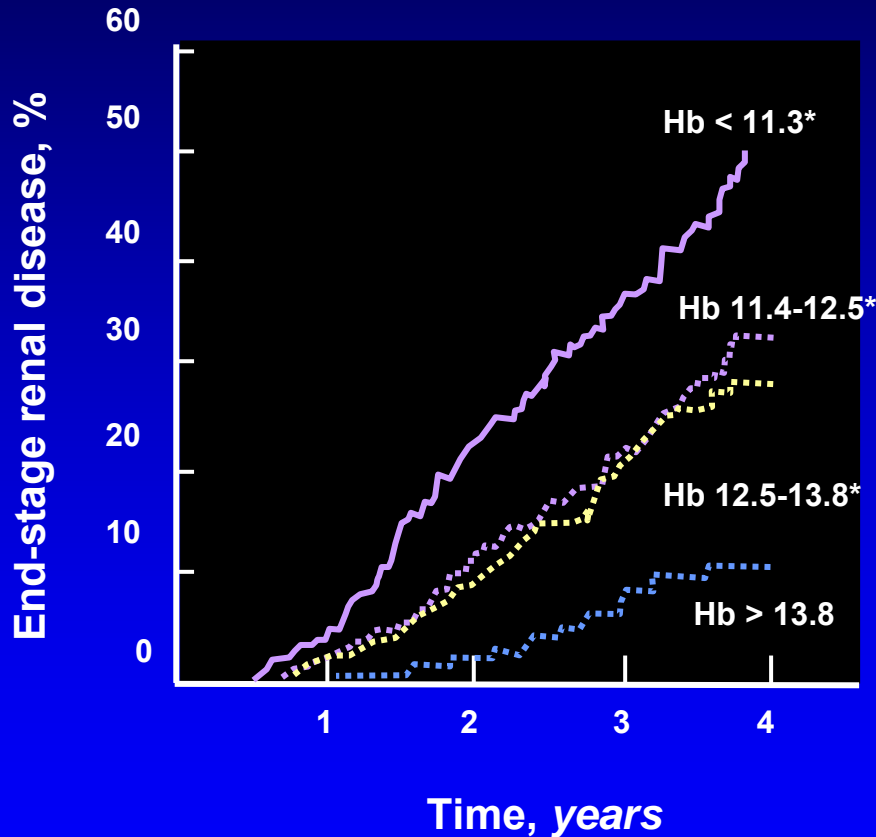
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- Evidence for treatment to increase Hb
  - improves quality of life...but
  - Improved cardiovascular and renal outcomes remain elusive
- Current hemoglobin target and Treatment
  - 11-12 g/dl
  - Not to exceed 13 g/dl
- Future
  - New ESA dosing and target trials
  - Novel therapeutics (e.g. HIF modulation)

Back Up

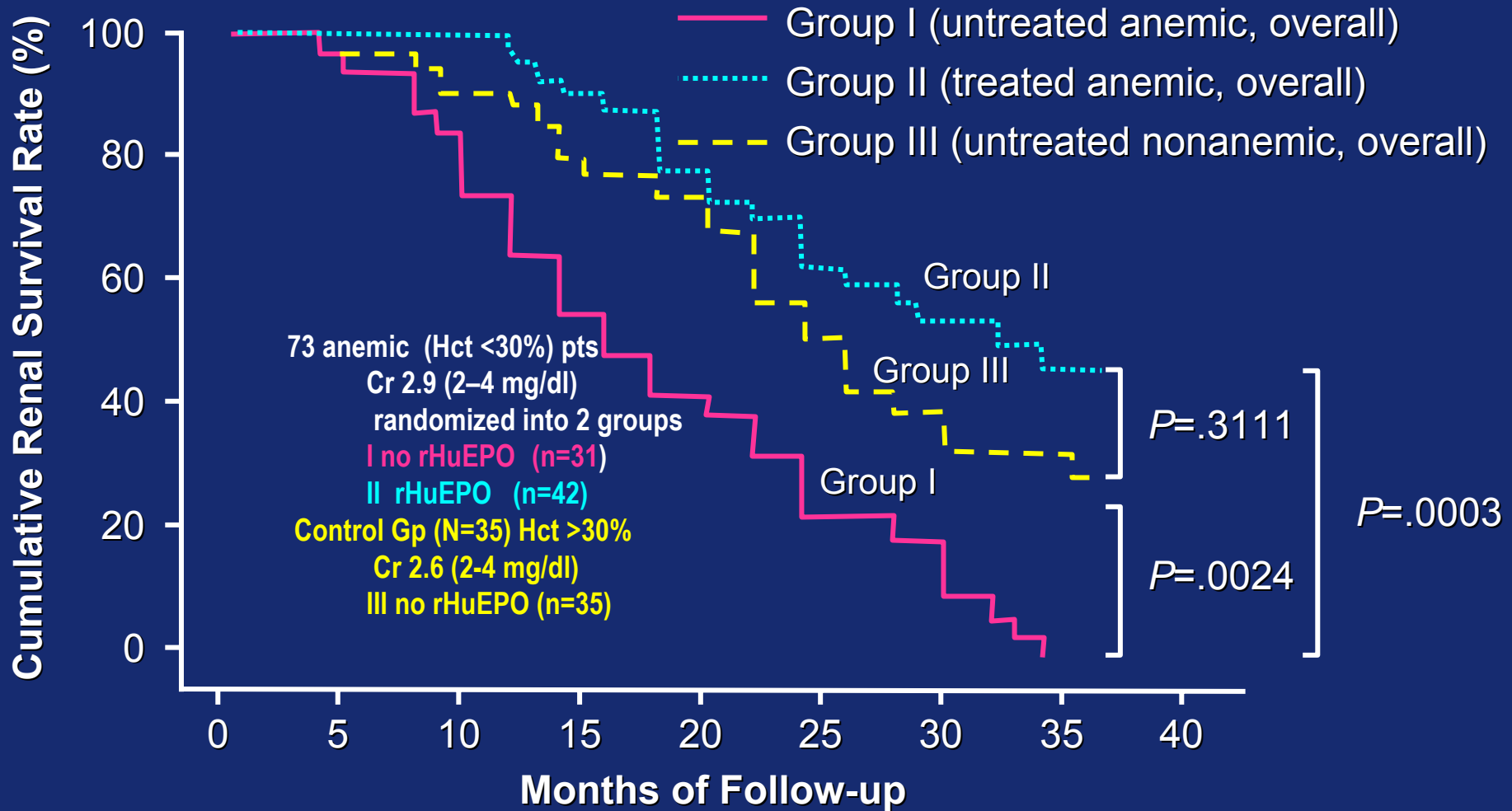
# Hemoglobin Predicts ESRD in Type 2 Diabetics with Nephropathy: RENAAL Trial (N=1513)



Hb g/dl	Adjusted HR*	P value
< 11.3	1.99	0.001
11.3-12.5	1.61	0.02
12.5-13.8	1.85	0.002
> 13.8	1.00	-

\* Age, gender, GFR, Race, Proteinuria, CV disease, A1c, lipids, BP, Ca, P, albumin

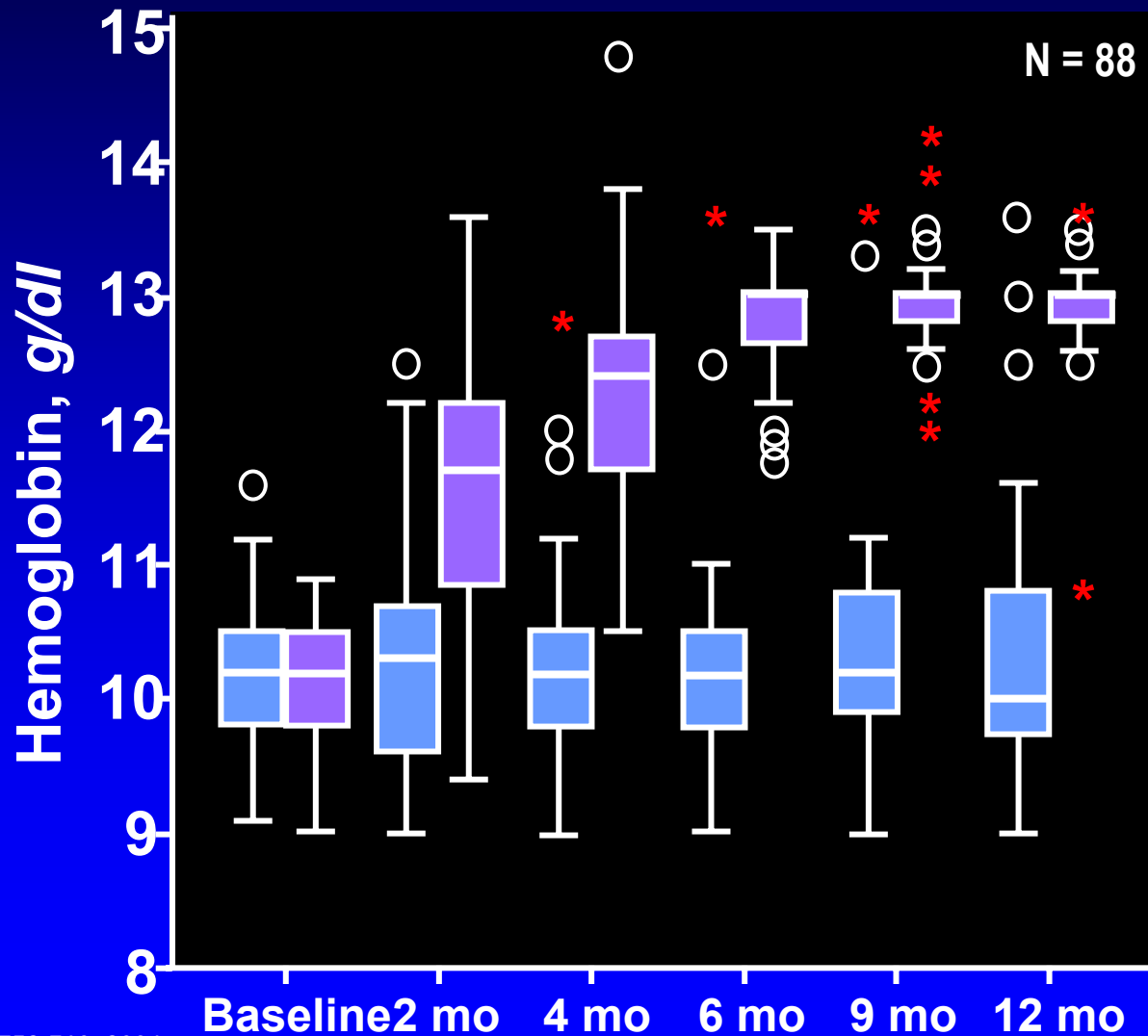
# Randomized Controlled Trial of EPO treatment delays progression of CKD



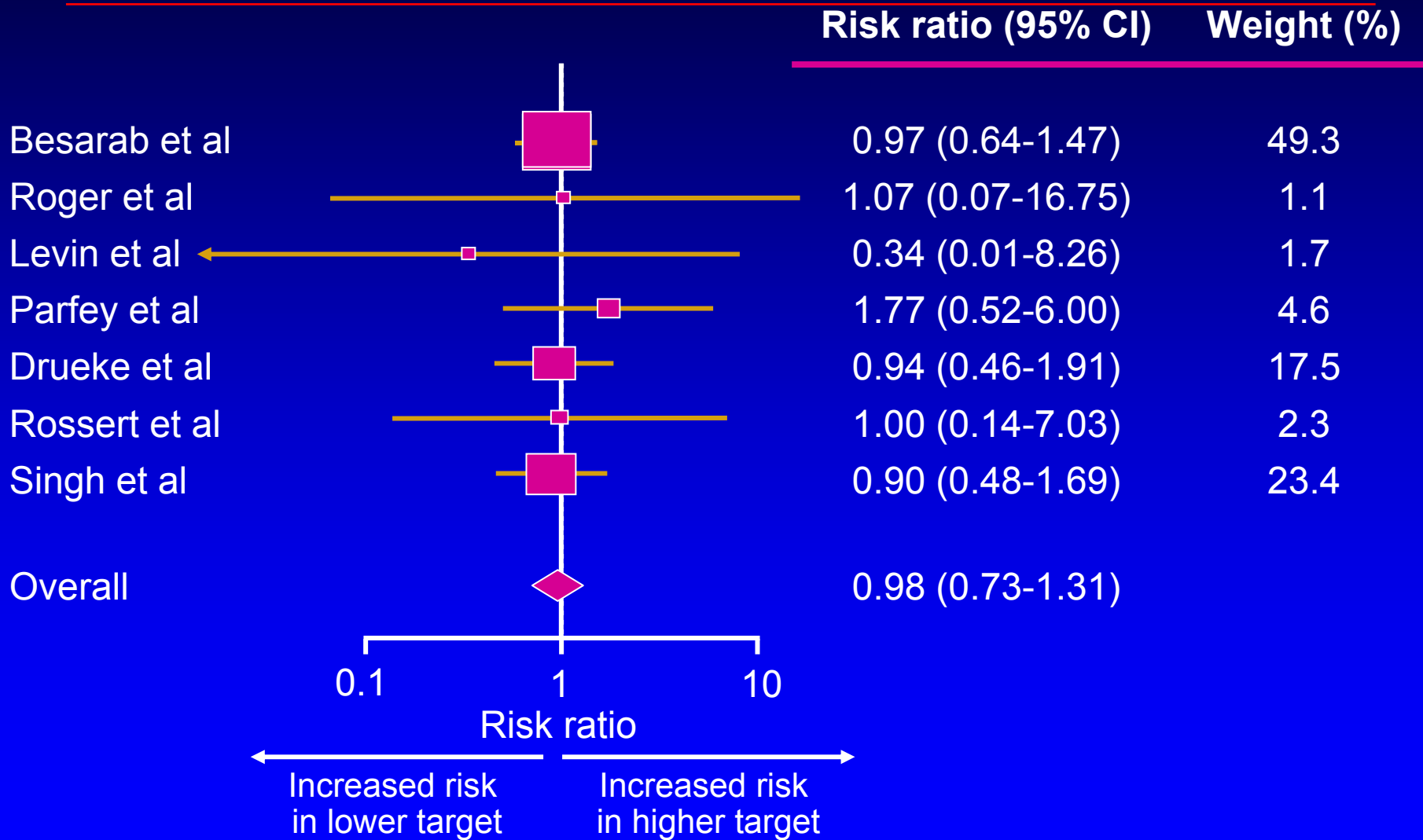
N=108

Kuriyama . *Nephron*. 1997;77:176-185.

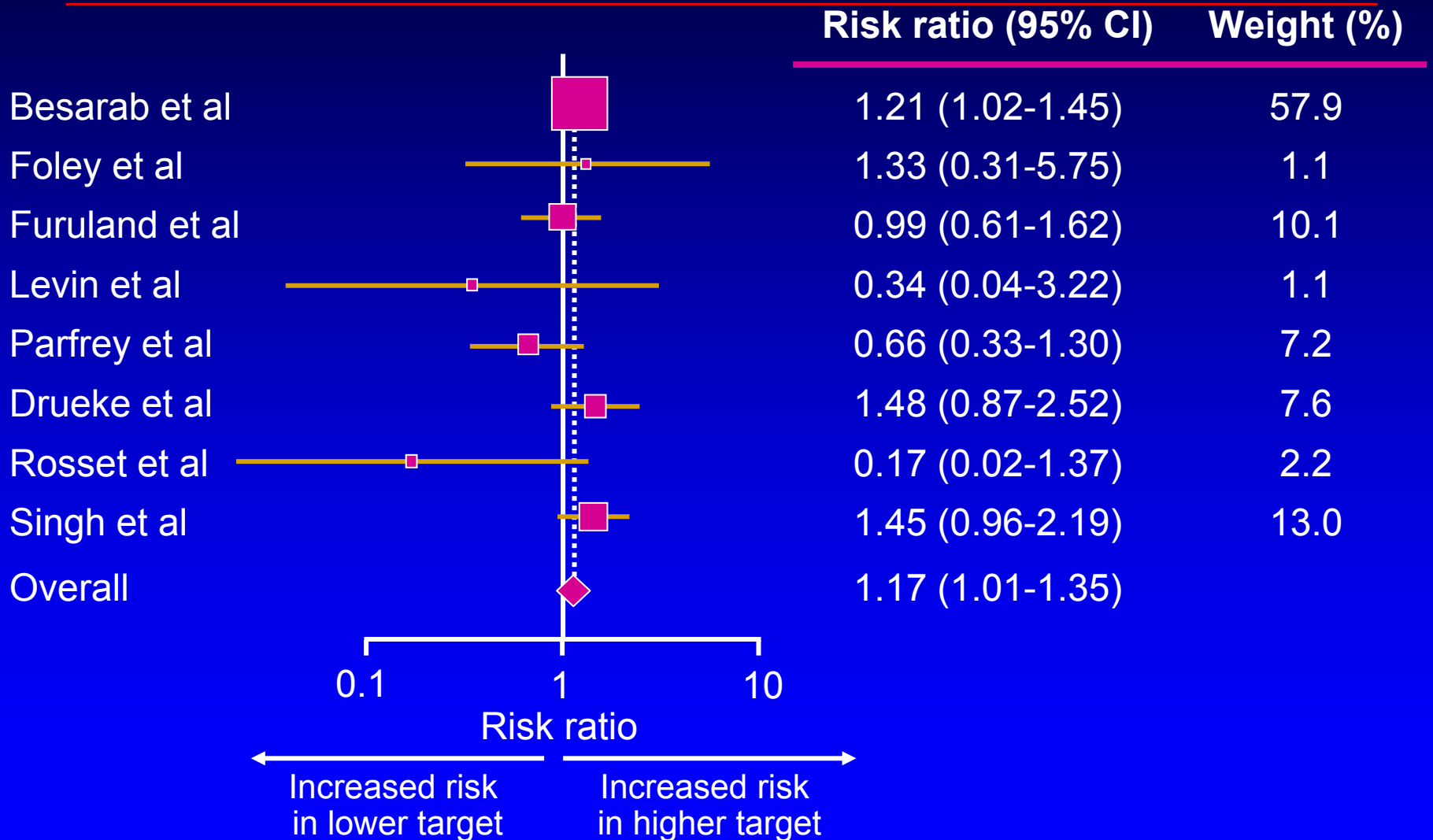
# Differences in Achieved Hb with Early (■) vs Late (□) Treatment of Anemia in CKD



# Risk of Myocardial Infarction; Higher Hb vs Lower Hb (Fixed Effects Analysis)



# Risk of All-Cause Mortality; Higher Hb vs Lower Hb (Fixed Effects Analysis)



# ESA Safety Label Change

## FDA Prescribing Changes (March 9, 2007)

- Use lowest dose of ESA that will increase Hb concentration to lowest level to avoid the need for RBC transfusion
- ESAs increased risk for death and serious CV events when administered to target an Hb of >12 g/dL

Aranesp<sup>®</sup> (darbepoetin alfa) [package insert]. Thousand Oaks, CA: Amgen, Inc.; 2007 (A); Procrit<sup>®</sup> (epoetin alfa) [package insert]. Raritan, NJ: Ortho Biotech Products, LP; 2007 (A); Epogen<sup>®</sup> (epoetin alfa) [package insert]. Thousand Oaks, CA: Amgen, Inc.; 2007 (A).  
US Food and Drug Administration. <http://www.fda.gov/cder/drug/infopage/RHE/qa.htm>. Accessed on May 1, 2007.

# FDA Public Advisory March 9, 2007: Erythropoiesis-Stimulating Agents

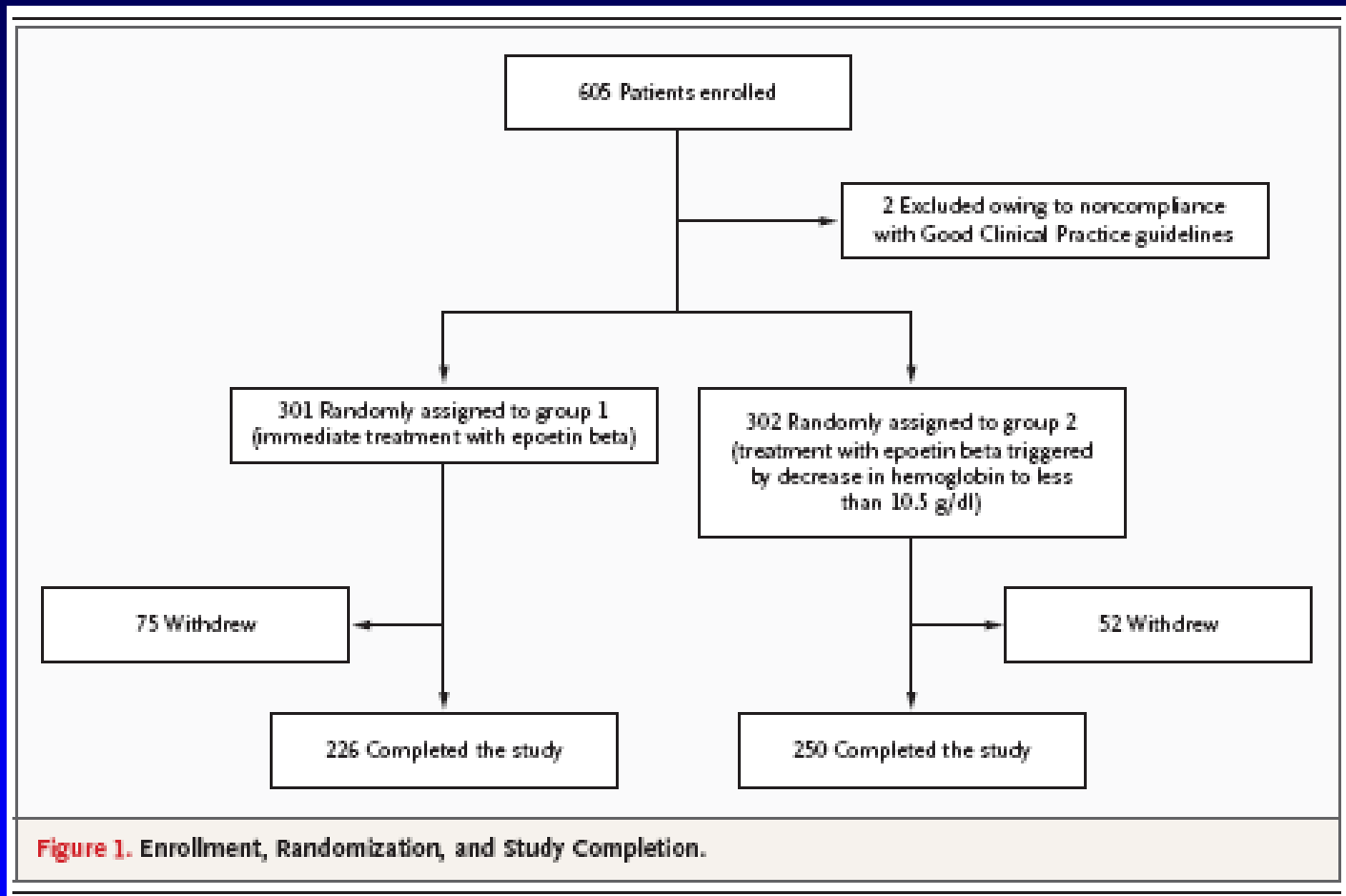
- The FDA today issued a public health advisory outlining new safety information, including revised product labeling about ESAs, widely-used drugs for the treatment of anemia.
- The drugs affected by the safety update are darbepoetin alfa (Aranesp) and epoetin alfa (Epogen and Procrit).
- FDA and manufacturers agreed on revised product labeling that includes updated warnings, new boxed warning, and modifications to dosing instructions.
- New boxed warning advises physicians to monitor hemoglobin and to adjust the ESA dose to maintain the lowest hemoglobin level needed to avoid the need for blood transfusions. Physicians and patients should carefully weigh the risks of ESAs against transfusion risks.

# Summary 2: KDOQI Guidelines 2006

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- Evidence-based guideline recommends Hb should be  $\geq 11$  g/dL in all CKD patients
- CPR cites insufficient evidence to maintain Hb  $\geq 13$  g/dL in patients receiving ESA therapy
- HD-CKD goal for serum ferritin  $> 200$  ng/mL
- CPR cites insufficient evidence for routine use of iron when serum ferritin  $> 500$  ng/mL
- Evidence-based guideline recommends IV as route of iron administration in HD-CKD

# CREATE Patient Accounting



# CREATE Baseline Characteristics

**Table 1. Demographic and Baseline Characteristics.\***

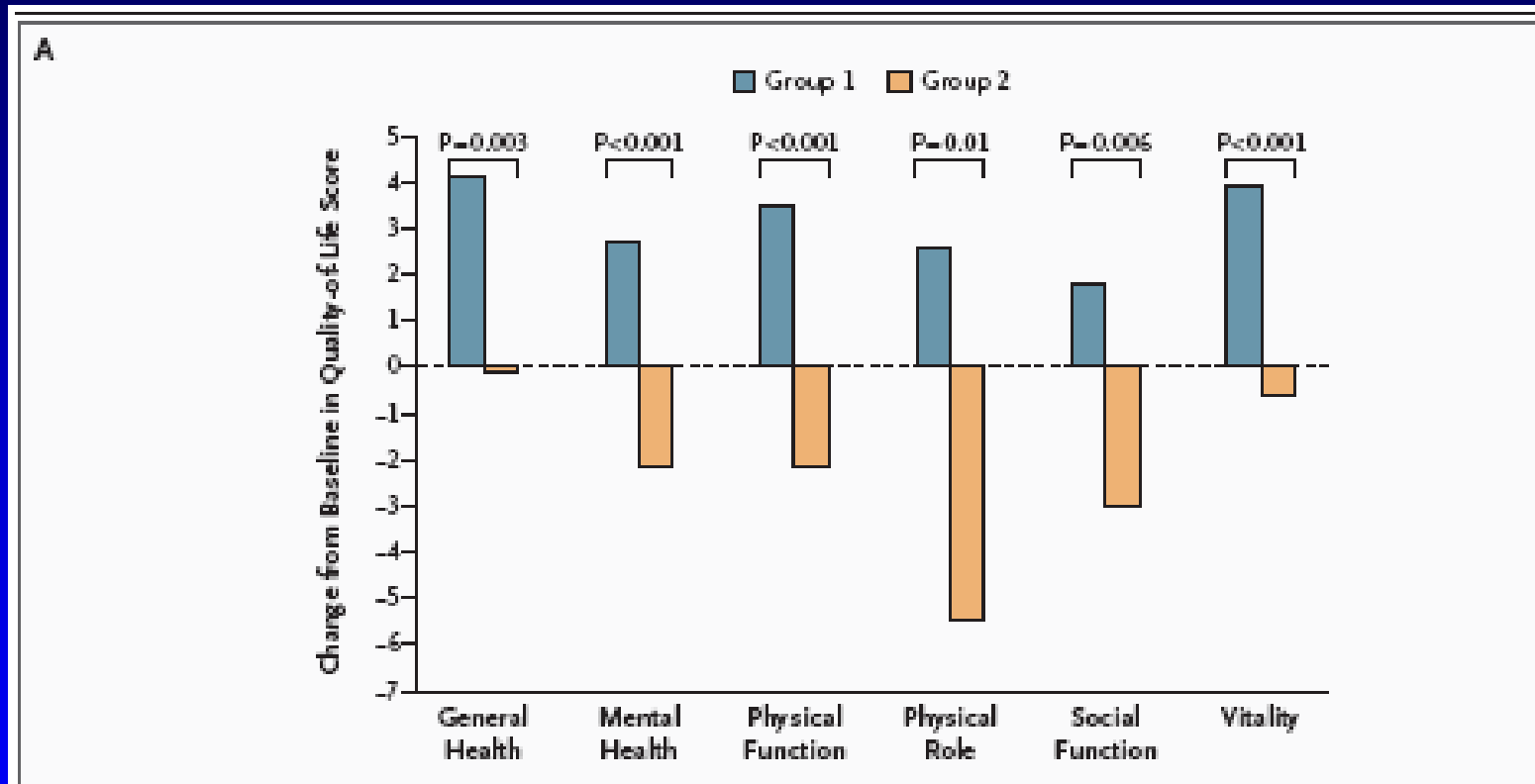
Characteristic	Group 1 (N=301)	Group 2 (N=302)	P Value
Weight (kg)	74.7±15.6	71.8±14.2	0.05
Body-mass index	26.6±4.5	26.2±4.8	0.42
Age—yr	59.3±14.6	58.8±13.7	0.36
Male sex—no. (%)	171 (57)	154 (51)	0.16
Estimated GFR—ml/min†	24.9±6.3	24.2±6.0	0.30
Cause of chronic kidney disease—no. of patients (%)			
Glomerulonephritis	62 (21)	71 (24)	0.43
Hypertensive renal disease	69 (23)	57 (19)	0.23
Diabetic nephropathy	61 (20)	63 (21)	0.91
Polycystic kidney disease	37 (12)	39 (13)	0.88
Pyelonephritis	22 (7)	21 (7)	0.92
Interstitial nephritis	22 (7)	16 (5)	0.35
Other	52 (17)	56 (19)	0.74
Unknown	15 (5)	15 (5)	0.94
Diabetes mellitus—no. of patients (%)			
Insulin-dependent	13 (4)	10 (3)	0.58
Dyslipidemia—no. of patients (%)			
Hypertension—no. of patients (%)‡	275 (91)	269 (89)	0.38
Blood pressure—mm Hg			
Systolic	139±17	139±16	0.87
Diastolic	79±10	80±9	0.28
Receipt of at least one antihypertensive agent—no. of patients (%)‡			
Angiotensin converting-enzyme inhibitors	152 (51)	142 (47)	0.39
Angiotensin II-receptor blockers	57 (19)	66 (22)	0.41
Beta-blockers	130 (43)	102 (34)	0.02
Calcium-channel blockers	155 (52)	156 (52)	0.97
Alpha-blockers	50 (17)	41 (14)	0.32
Loop diuretics	145 (48)	127 (42)	0.13
Thiazide or other diuretic	27 (9)	28 (9)	0.96

# CREATE Baseline Characteristics cont'd

**Table 1. (Continued.)**

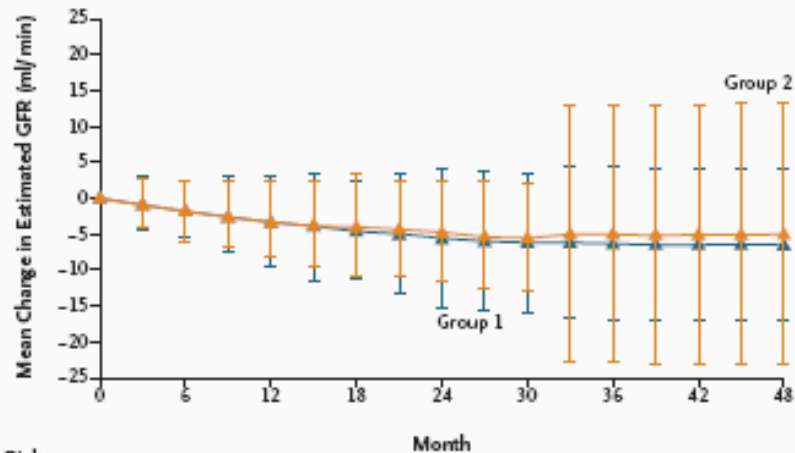
Characteristic	Group 1 (N= 301)	Group 2 (N= 302)	P Value
Preexisting cardiovascular disease — no. of patients (%)§	280 (93)	278 (92.1)	0.71
Chronic heart failure	93 (33)	87 (31)	0.61
Previous myocardial infarction	3 (1)	4 (1)	0.85
Cerebrovascular disease	10 (4)	6 (2)	0.37
Coronary artery disease	9 (3)	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	

# CREATE Quality of Life



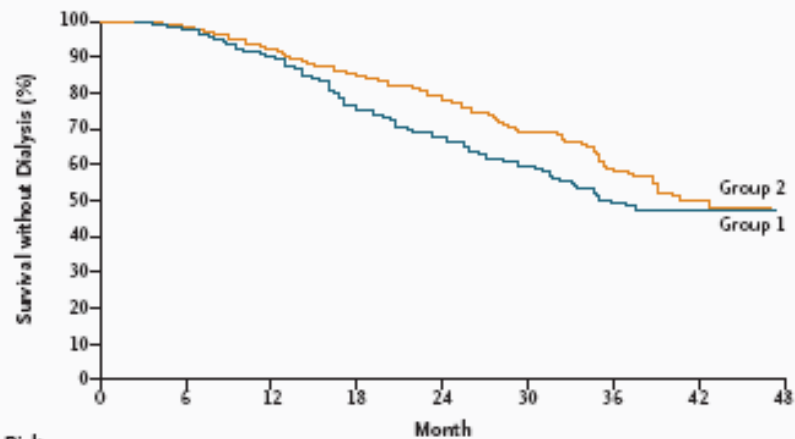
# CREATE: Renal Outcomes

B



No. at Risk		Month								
Group 1	299	287	287	287	287	287	287	288	289	
Group 2	298	293	293	293	293	293	293	293	293	

C



No. at Risk		Month								
Group 1	301	281	255	211	162	115	62	35	0	
Group 2	302	293	269	243	199	138	82	33	0	

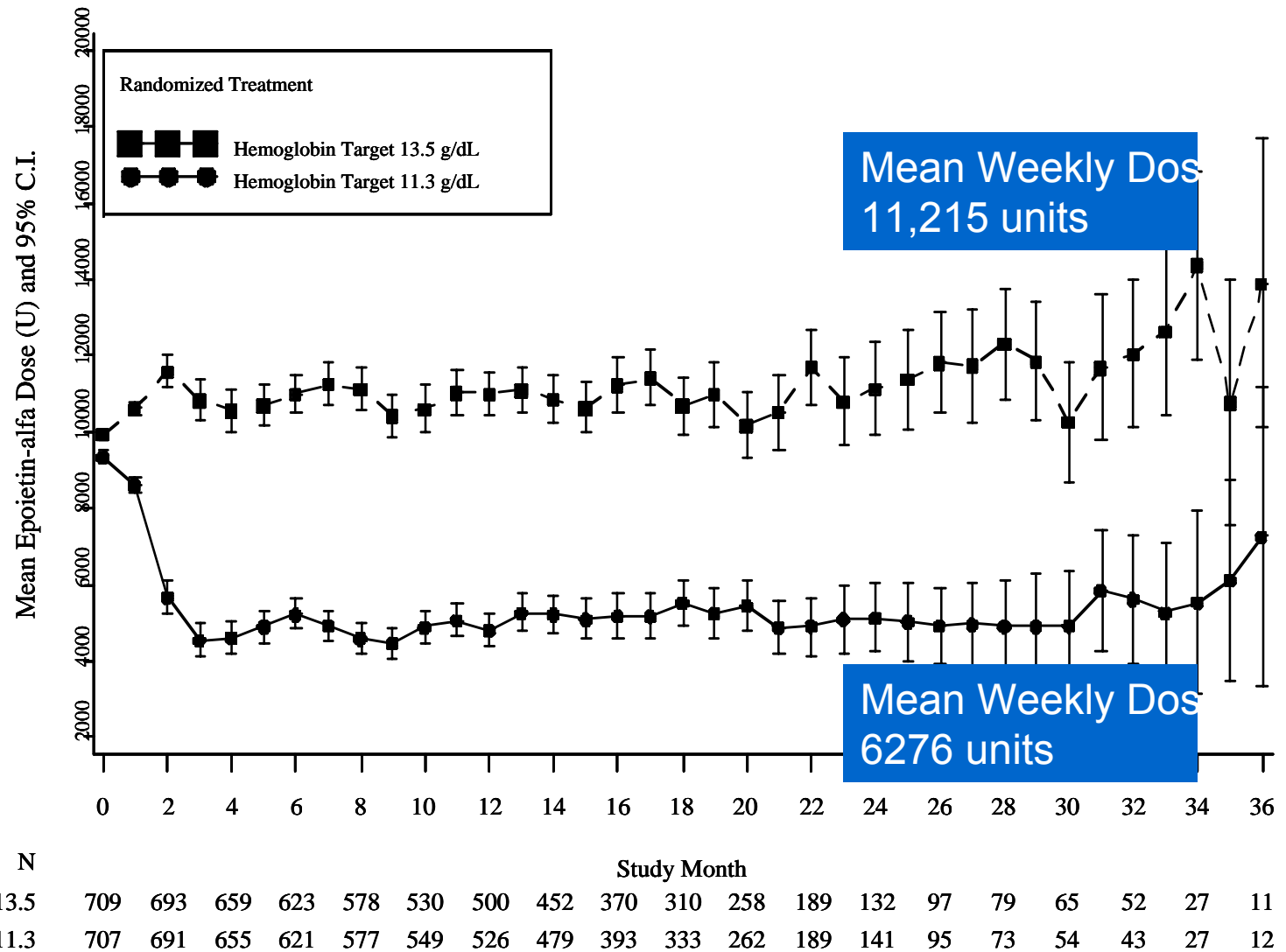
# CHOIR Outcomes: Hb and Procrit Dose

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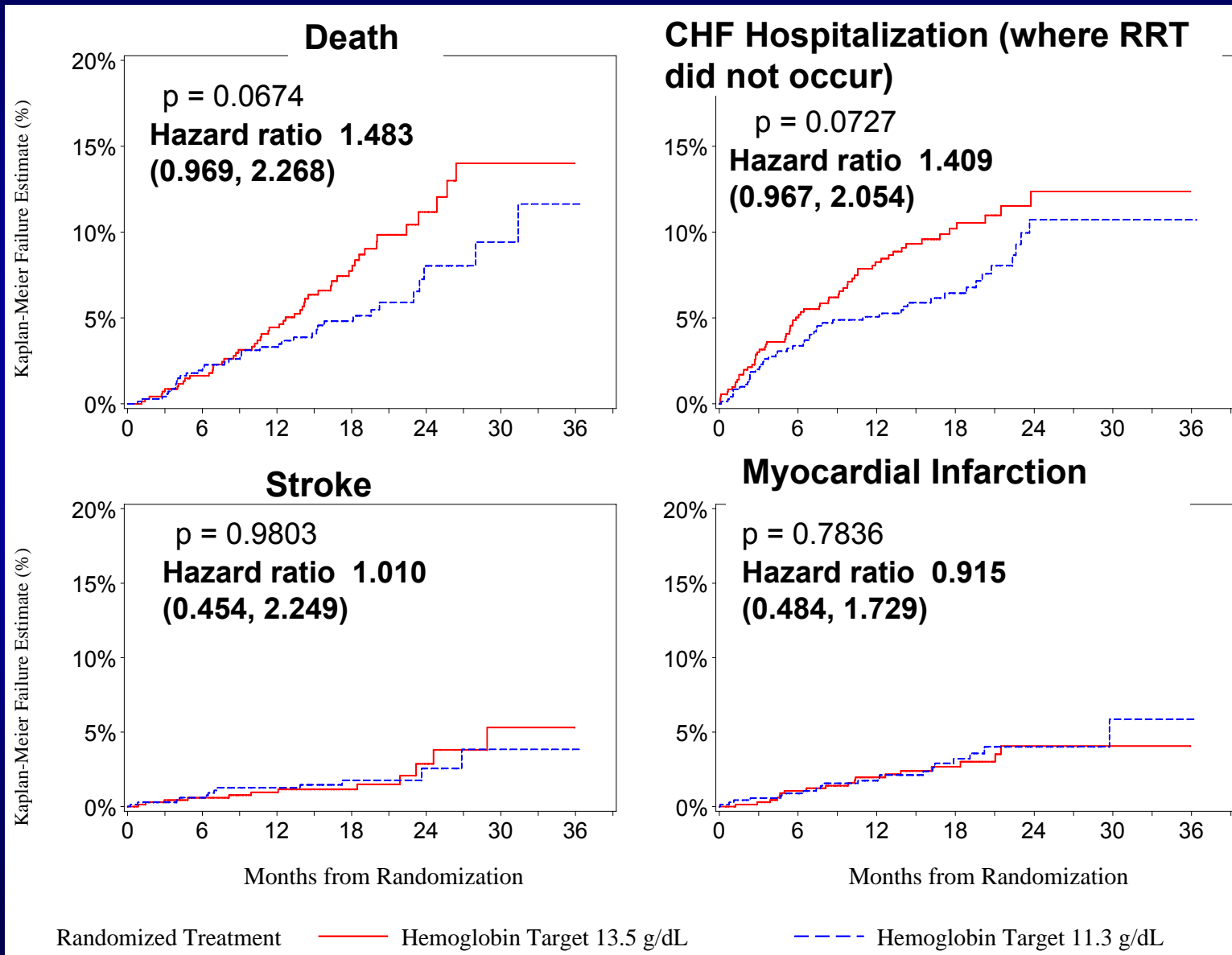
Parameter	Hb 13.5		Hb 11.3	
	Baseline	EOS	Baseline	EOS
Hb (g/dL)	~10	13	~10	11
Procrit dose (units)	10,000	20,000	10,000	10,000

EOS = End of Study

# Mean Weekly Doses of Epoetin alfa



# Components of the Primary Endpoint

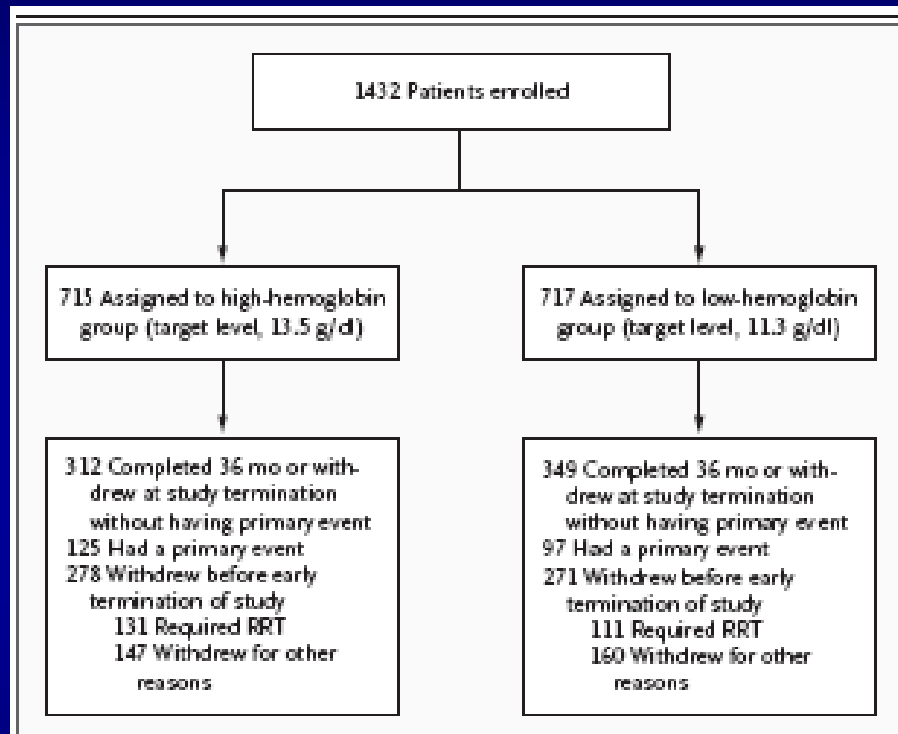


# CHOIR Secondary Endpoints

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

End Point	High-Hemoglobin Group (N=715) no. of patients (%)	Low-Hemoglobin Group (N=717) no. of patients (%)	Hazard Ratio (95% CI)		P Value†
<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

# CHOIR Patient Accounting



**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.

# Hb as a Risk Factor for Progression of Chronic Kidney Disease

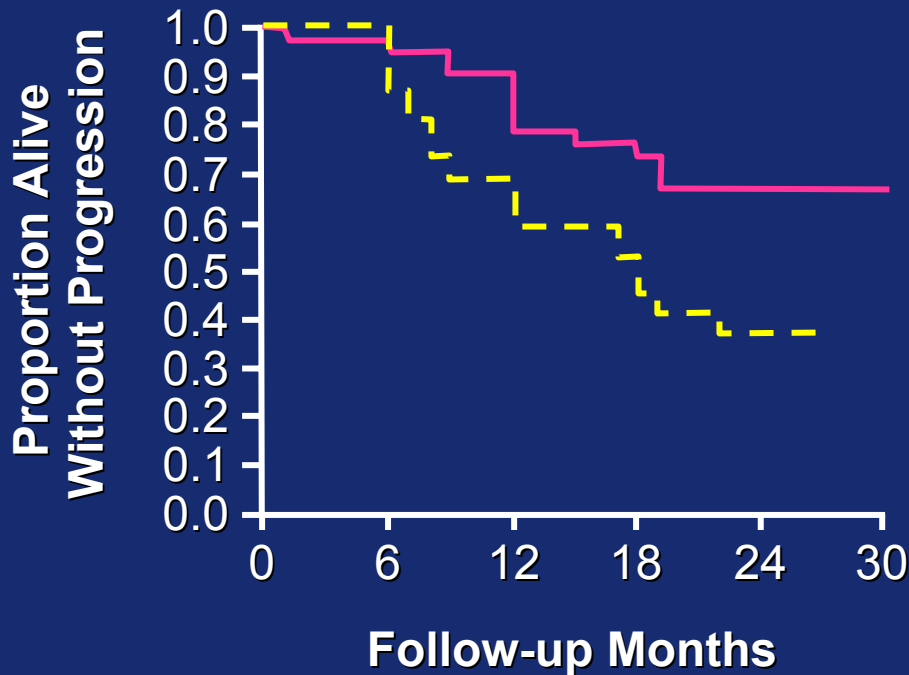
Observational Studies

# Effect of Increasing Hb on Progression of Chronic Kidney Disease

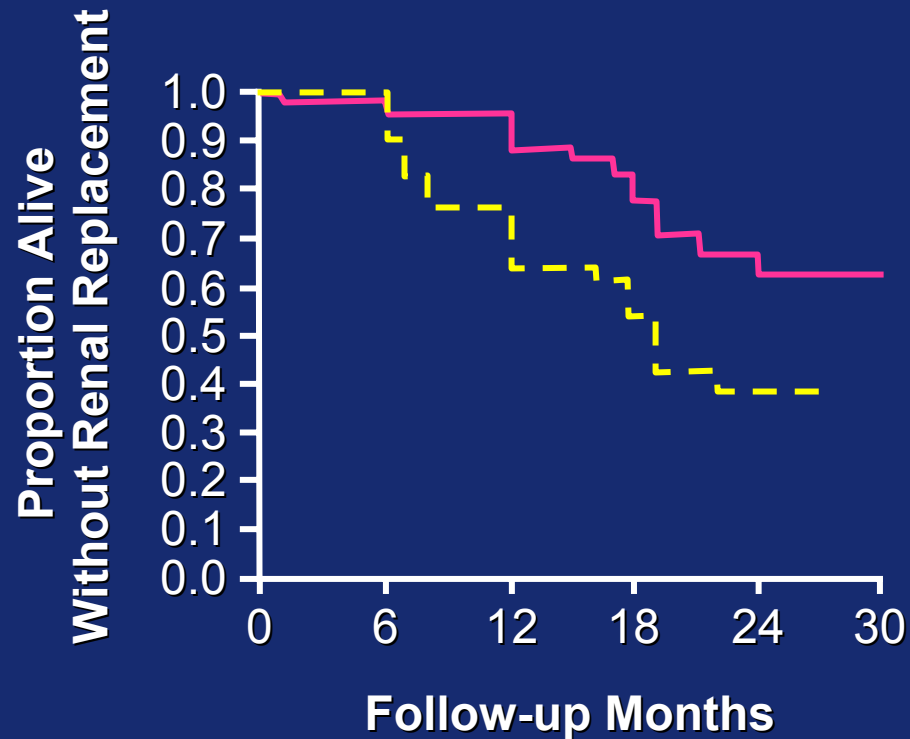
Clinical Trials

# K-M Plots for Doubling of Creatinine, ESRD, or Death (A), and ESRD or Death (B): Early (Broken Line) vs Deferred (Solid Line) Erythropoietin Treatment

**A** Log-rank  $P=.0078$



**B** Log-rank  $P=.011$



— Deferred      - - - Early

N=88

Gouva. *Kidney Int.* 2004;66:753-760.

# Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE): General Design Characteristics

Design		Randomized, open-label
Sponsor / Agent		Roche / Neorecormon <sup>®</sup> (epoetin beta)
Dosing Frequency		De novo to QW
Hb Target(s), g/dL	Arm 1	13-15
	Arm 2	10.5-11.5*
Regions/Countries		EU, Mexico, China, Taiwan, Thailand

\* Treatment starts when Hb <10.5 g/dL

# CREATE Baseline Characteristics

Hb	11.0 – 12.5
eGFR/CrCl*	15-35
Diabetes	No (~20%)
Hb (g/dL)	11.6
eGFR/CrCl (ml/min)	24.5

# CREATE Endpoints

<p>Primary Endpoint</p>	<ol style="list-style-type: none"><li>1. Change in LVMI: baseline to 1 year</li> <li>2. Time to:<ul style="list-style-type: none"><li>- Sudden death</li><li>- MI (fatal, non-fatal)</li><li>- Stroke (fatal, non-fatal)</li><li>- Heart failure (acute)</li><li>- Angina (hosp &gt;24 hrs)</li><li>- Arrhythmias (hosp &gt;24 hrs)</li><li>- PVD (necrosis, amputation)</li></ul></li></ol>
<p>Secondary Endpoints</p>	<ul style="list-style-type: none"><li>- All-cause mortality</li><li>-- CV mortality</li><li>- CHF (change in NYHA class)</li><li>- CV interventions</li><li>- Hospitalization</li><li>- LV growth and systolic fxn</li><li>- <b>Progression of CKD</b></li><li>- Nutritional status</li><li>- QOL</li></ul>

# CREATE: Renal Outcome

Total Study Duration (months)		48
Median Follow-up (years)		2.5
Hb Achieved (g/dL)	Arm 1	13.49
	Arm 2	Unknown ('stable')
Composite Primary Event Rate (% per year)		5.8
HR (95% CI) Composite Primary Endpoint		1.22 (0.83, 1.79) - estimated
# ESRD Events Observed	Arm 1	127
	Arm 2	111
HR (p value) Time to ESRD		1.32 (p = 0.034)

# Conclusion: Anemia and Kidney Disease Progression in CKD including ESRD

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- Observational studies: anemia is a risk factor for kidney disease progression
- Clinical Trials: Treating anemia with erythropoietin decreases progression of kidney disease in some not others
- More studies to confirm (TREAT and others)

# How Higher Hemoglobin Prolongs Life for Patients with Renal Disease

- Rationale:
  - Higher Hb improves O<sub>2</sub> delivery
  - (Erythropoietin cardio and neuroprotective)
- Only observational data indicate higher hemoglobin associated with longer survival
- Proof from clinical trials in CKD and ESRD lacking
- Additional CV and Renal outcomes trials needed

### 3 Anemia Outcome CKD Trials: CREATE, CHOIR, TREAT

#### *TREAT Objectives are Fundamentally Different*

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- **CREATE** (Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin beta) – *Completed*
  - Determine the impact of early vs late anemia correction on mortality and cardiovascular morbidity in patients with CKD
- **CHOIR** (Correction of Hemoglobin and Outcomes In Renal insufficiency) – *Terminated Early*
  - Determine the impact of degree of anemia correction on mortality and cardiovascular morbidity in patients with CKD
- **TREAT** (Trial to Reduce Cardiovascular Events with Aranesp<sup>®</sup> Therapy) – *Enrolling*
  - Determine the impact of anemia therapy (yes/no) on mortality and cardiovascular morbidity in patients with CKD and type 2 diabete

# Key Inclusion Criteria and Baseline Characteristics

	<b>CREATE<sup>1</sup></b> (N = 603)	<b>CHOIR<sup>2</sup></b> (N = 1432)	<b>TREAT</b> (N = 4000)
<b>Inclusion</b>			
Hb (g/dL)	11.0 – 12.5	<11.0	≤11.0
eGFR/CrCl*	15-35	15-50	20-60
Diabetes	No (~25%)	No (48.5%)	Yes (100%)
<b>Baseline Characteristics</b>			
Hb (g/dL)	11.6	10.1	-
eGFR/CrCl*	24.5	27.0	-

\* mL/min/1.73m<sup>2</sup>

1. Drüeke TB et al *N. Engl. J. Med.* 2006;355:2071-84

2. Singh AK et al *N. Engl. J. Med.* 2006;355:2085-98

# Primary Endpoint

<b>CREATE<sup>1</sup></b> (N = 603)	<b>CHOIR<sup>2</sup></b> (N = 1432)	<b>TREAT</b> (N = 4000)
<p>Time to composite of: First CV event</p> <ul style="list-style-type: none"><li>— Sudden death</li><li>— MI (fatal, non-fatal)</li><li>— Stroke (fatal, non-fatal)</li><li>— Transient ischemic attack</li><li>— Acute heart failure</li><li>— Angina (hosp &gt;24 hrs)</li><li>— Arrhythmias (hosp &gt;24 hrs)</li><li>— PVD (necrosis, amputation)</li></ul>	<p>Time to composite of:</p> <ul style="list-style-type: none"><li>— All-cause mortality or</li><li>— CV morbidity<ul style="list-style-type: none"><li>- MI</li><li>- Stroke</li><li>- Hospitalization for heart failure [No coincident initiation of RRT]</li></ul></li></ul>	<p>Time to composite of:</p> <ul style="list-style-type: none"><li>—All-cause mortality or</li><li>—CV morbidity<ul style="list-style-type: none"><li>- MI</li><li>- Stroke</li><li>- Heart failure</li><li>- Hosp for acute myocardial ischemia</li></ul></li></ul>

1. Drüeke TB et al *N. Engl. J. Med.* 2006;355:2071-84

2. Singh AK et al *N. Engl. J. Med.* 2006;355:2085-98

# TREAT in the Context of CHOIR and CREATE Studies

		<b>CREATE<sup>1</sup></b> (N = 603)	<b>CHOIR<sup>2</sup></b> (N = 1432)	<b>TREAT</b> (N = 4000)
Design		Randomized, <b>open-label</b>	Randomized, <b>open-label</b>	Randomized, double-blind, placebo controlled
Sponsor / Agent		Roche / NeoRecormon® (epoetin beta)	J&J / Procrit® (epoetin alfa)	Amgen / Aranesp® (darbepoetin alfa)
Dosing		2,000 QW	Initiate 10,000 QW When stable go to Q2W	0.75 mcg/kg/Q2W Double dose when stable and go to QM
Dosing Frequency		<i>De novo</i> to QW	<i>De novo</i> to QW to Q2W	<i>De novo</i> to Q2W to QM
Hb Target(s), g/dL	Arm 1	13.0-15.0	13.5	13.0
	Arm 2	10.5-11.5*	11.3	<b>Placebo</b> (Rescue for Hb <9.0)
Regions/Countries		EU, Mexico, China, Taiwan, Thailand, Russia, Turkey, Greece	US	US, EU, CAN, AU, LA, RUS
# Centers		94	130	~700
Censor at RRT		Unknown	<b>Yes</b>	No

\* Treatment starts when Hb <10.5 g/dL

1. Drüeke TB et al *N. Engl. J. Med.* 2006;355:2071-84

2. Singh AK et al *N. Engl. J. Med.* 2006;355:2085-98

# Key Inclusion Criteria and Baseline Characteristics

	<b>CREATE<sup>1</sup></b> (N = 603)	<b>CHOIR<sup>2</sup></b> (N = 1432)	<b>TREAT</b> (N = 4000)
<b>Inclusion</b>			
Hb (g/dL)	11.0 – 12.5	<11.0	≤11.0
eGFR/CrCl*	15-35	15-50	20-60
Diabetes	No (~25%)	No (48.5%)	Yes (100%)
<b>Baseline Characteristics</b>			
Hb (g/dL)	11.6	10.1	-
eGFR/CrCl*	24.5	27.0	-

\* mL/min/1.73m<sup>2</sup>

1. Drüeke TB et al *N. Engl. J. Med.* 2006;355:2071-84

2. Singh AK et al *N. Engl. J. Med.* 2006;355:2085-98

# Primary Endpoint

<b>CREATE<sup>1</sup></b> (N = 603)	<b>CHOIR<sup>2</sup></b> (N = 1432)	<b>TREAT</b> (N = 4000)
<p>Time to composite of: First CV event</p> <ul style="list-style-type: none"><li>— Sudden death</li><li>— MI (fatal, non-fatal)</li><li>— Stroke (fatal, non-fatal)</li><li>— Transient ischemic attack</li><li>— Acute heart failure</li><li>— Angina (hosp &gt;24 hrs)</li><li>— Arrhythmias (hosp &gt;24 hrs)</li><li>— PVD (necrosis, amputation)</li></ul>	<p>Time to composite of:</p> <ul style="list-style-type: none"><li>— All-cause mortality or</li><li>— CV morbidity<ul style="list-style-type: none"><li>- MI</li><li>- Stroke</li><li>- Hospitalization for heart failure [No coincident initiation of RRT]</li></ul></li></ul>	<p>Time to composite of:</p> <ul style="list-style-type: none"><li>—All-cause mortality or</li><li>—CV morbidity<ul style="list-style-type: none"><li>- MI</li><li>- Stroke</li><li>- Heart failure</li><li>- Hosp for acute myocardial ischemia</li></ul></li></ul>

1. Drüeke TB et al *N. Engl. J. Med.* 2006;355:2071-84

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# Primary Endpoint

<b>CREATE<sup>1</sup></b> (N = 603)	<b>CHOIR<sup>2</sup></b> (N = 1432)	<b>TREAT</b> (N = 4000)
<p>Time to composite of: First CV event</p> <ul style="list-style-type: none"><li>— Sudden death</li><li>— MI (fatal, non-fatal)</li><li>— Stroke (fatal, non-fatal)</li><li>— Transient ischemic attack</li><li>— Acute heart failure</li><li>— Angina (hosp &gt;24 hrs)</li><li>— Arrhythmias (hosp &gt;24 hrs)</li><li>— PVD (necrosis, amputation)</li></ul>	<p>Time to composite of:</p> <ul style="list-style-type: none"><li>— All-cause mortality or</li><li>— CV morbidity<ul style="list-style-type: none"><li>- MI</li><li>- Stroke</li><li>- Hospitalization for heart failure [No coincident initiation of RRT]</li></ul></li></ul>	<p>Time to composite of:</p> <ul style="list-style-type: none"><li>—All-cause mortality or</li><li>—CV morbidity<ul style="list-style-type: none"><li>- MI</li><li>- Stroke</li><li>- Heart failure</li><li>- Hosp for acute myocardial ischemia</li></ul></li></ul>

1. Drüeke TB et al *N. Engl. J. Med.* 2006;355:2071-84

2. Singh AK et al *N. Engl. J. Med.* 2006;355:2085-98

# Effect of Hemoglobin Level in Patients with Asymptomatic Cardiomyopathy

Hemodialysis

Foley et al

Kid Int 2000

# Normalization of Hb in ESRD Patients with LVH and LV Dilatation

- **Design:** 146 HD patients with LVH or LV dilation randomized to epoetin-alpha to achieve Hb 10 or 13.5 g/dL for 48 wks
- **Primary outcomes:**  $\Delta$  LV mass index and  $\Delta$  in cavity volume

**Conclusion:** Normalization of Hb a) does not regress established LV hypertrophy or LV dilation b) does improve quality of life.

treatment

- correlation between Hb and LV volume index ( $P = 0.009$ )
- improvement in fatigue ( $P = 0.009$ ) and depression ( $P = 0.02$ )

Double-Blind Comparison of Full and Partial Anemia  
Correction in Incident Hemodialysis Patients without  
Symptomatic Heart Disease

Hemodialysis

Parfrey et al

JASN 2005

# Canadian-European Normalization Study

	Lower (9.5 to 11.5 g/dl)	Higher (13.5 to 14.5 g/dl)	Between Group	
			Effect <sup>a</sup>	P
LVVI (ml/m <sup>2</sup> ; n [mean ± SD])				
baseline	300 (68.6 ± 21.1)	296 (68.8 ± 20.9)		
week 24	254 (70.6 ± 21.7)	255 (69.4 ± 22.4)		
week 48	222 (70.4 ± 25.5)	223 (67.5 ± 23.4)		
week 96	160 (68.5 ± 25.2)	170 (66.7 ± 26.1)		

**Conclusion: Normalization of Hb does not have a beneficial effect on cardiac structure when compared to partial correction in CKD patients on dialysis.**

week 24	233 (416 ± 133)	242 (407 ± 141)
---------	-----------------	-----------------

<b>% change from baseline (n [Est ± SE])</b>	<b>237 (26 ± 9)</b>	<b>249 (32 ± 9)</b>	<b>6.6</b>	<b>0.4462</b>
<b>Congestive heart failure (N; n [%])</b>	<b>300 (12 [4%])</b>	<b>296 (11 [4%])</b>		<b>0.8687</b>

No

Effects of Early and Late Intervention with  
Epoetin on Left Ventricular Mass among  
Patients with Chronic Kidney  
Disease (Stage 3 or 4)

Roger et al

JASN 2004

# Hemoglobin Normalization and LVH in CKD

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- **Study Design:** Randomized open-label parallel group
- **Study Population:** 155 CKD patients
  - Ccr 15-50 ml/min
  - Hb 11-12 g/dL
- **Intervention:** SC epoietin alpha to maintain [Hb] between
  - 12 - 13 g/dL (group A)
  - 9 - 10 g/dL (group B).
- **Primary Outcome:** Development of LVH
- **Follow up:** 2 yr or until required dialysis;

# Results and Conclusion

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- **RESULTS:**

- Group A Hb ~ 12.5, Group B Hb ~ 11.0 g/dl

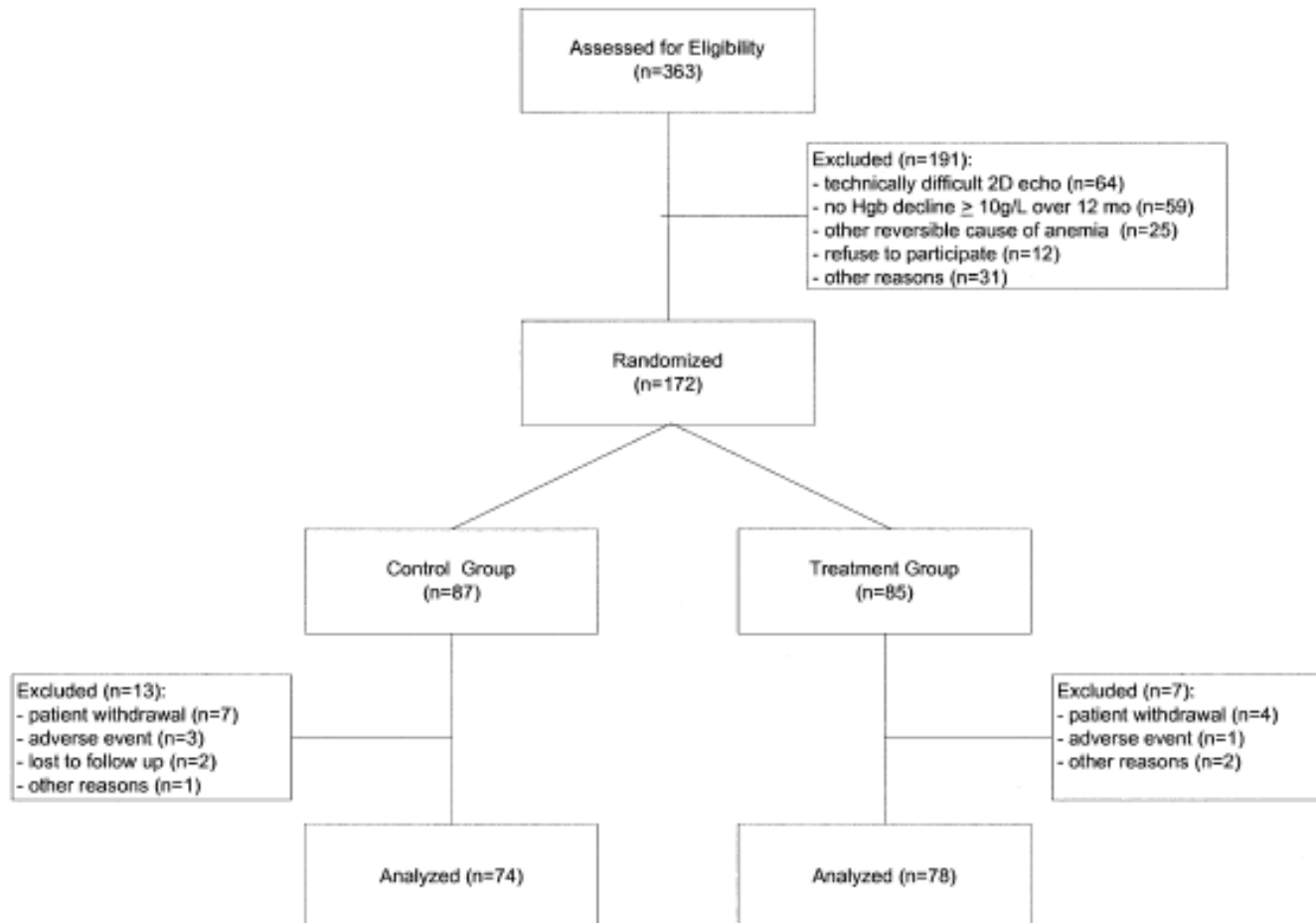
***Conclusion: Maintenance of [Hb] above 12 g/dL, compared with 9 - 10 g/dL, had similar effect on LVMI and did not affect development or progression of LVH***

- No significant difference in BP
- No significant difference in decline in renal function

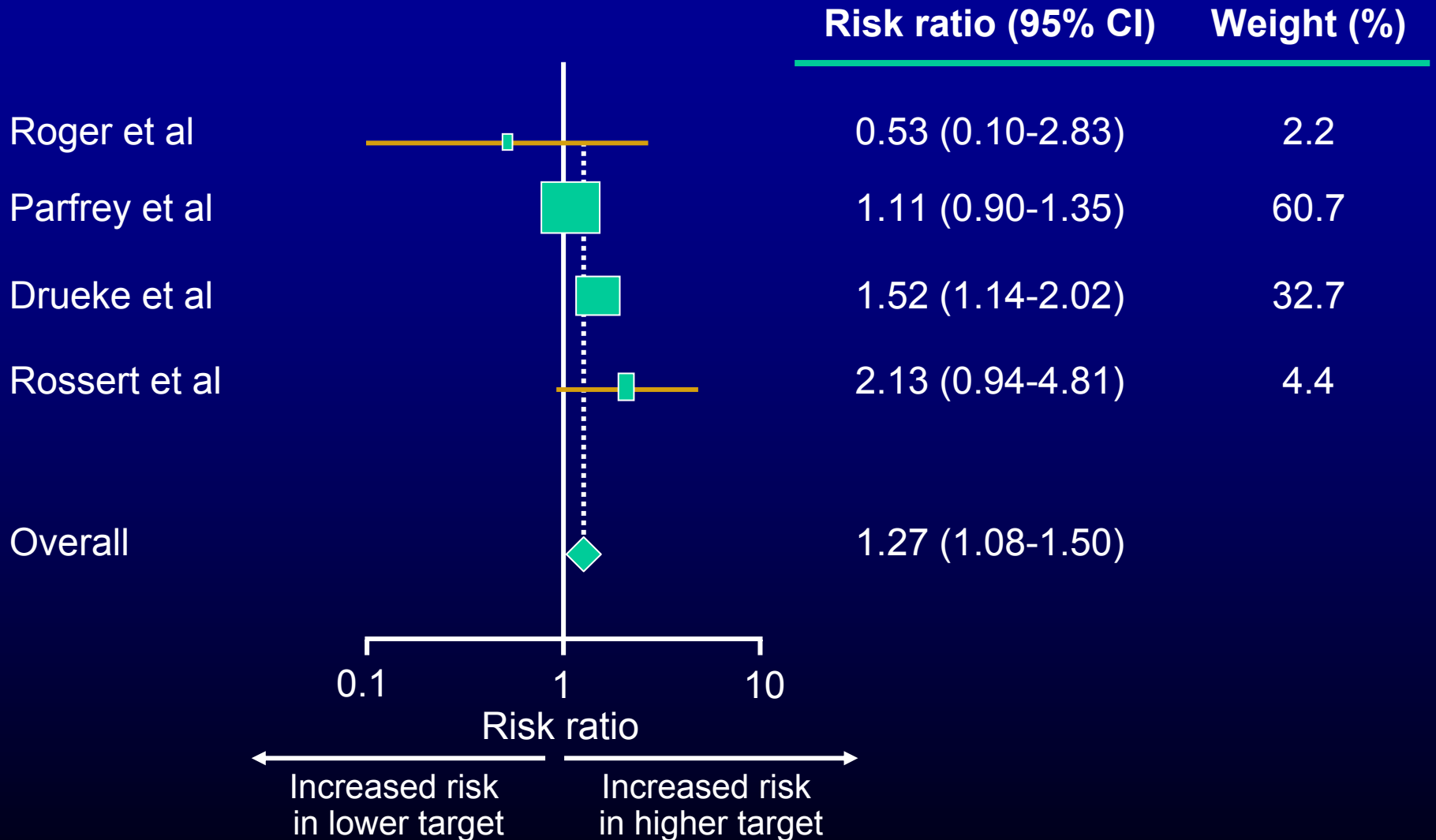
Canadian Randomized Trial of Hemoglobin  
Maintenance to Prevent or Delay Left  
Ventricular Mass Growth in Patients With  
Chronic Kidney Disease

Levin et al  
AJKD 2005

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



# Risk of Poorly Controlled Blood Pressure; Higher Hb vs Lower Hb (Fixed Effects Analysis)



# Risk of Arteriovenous Access Thrombosis; Higher Hb vs Lower Hb (Fixed Effects Analysis)

