

# 15th Budapest Nephrology School



**August 26-31, 2008**

**Semmelweis University, Budapest, Hungary**

## **Renal Anaemia**

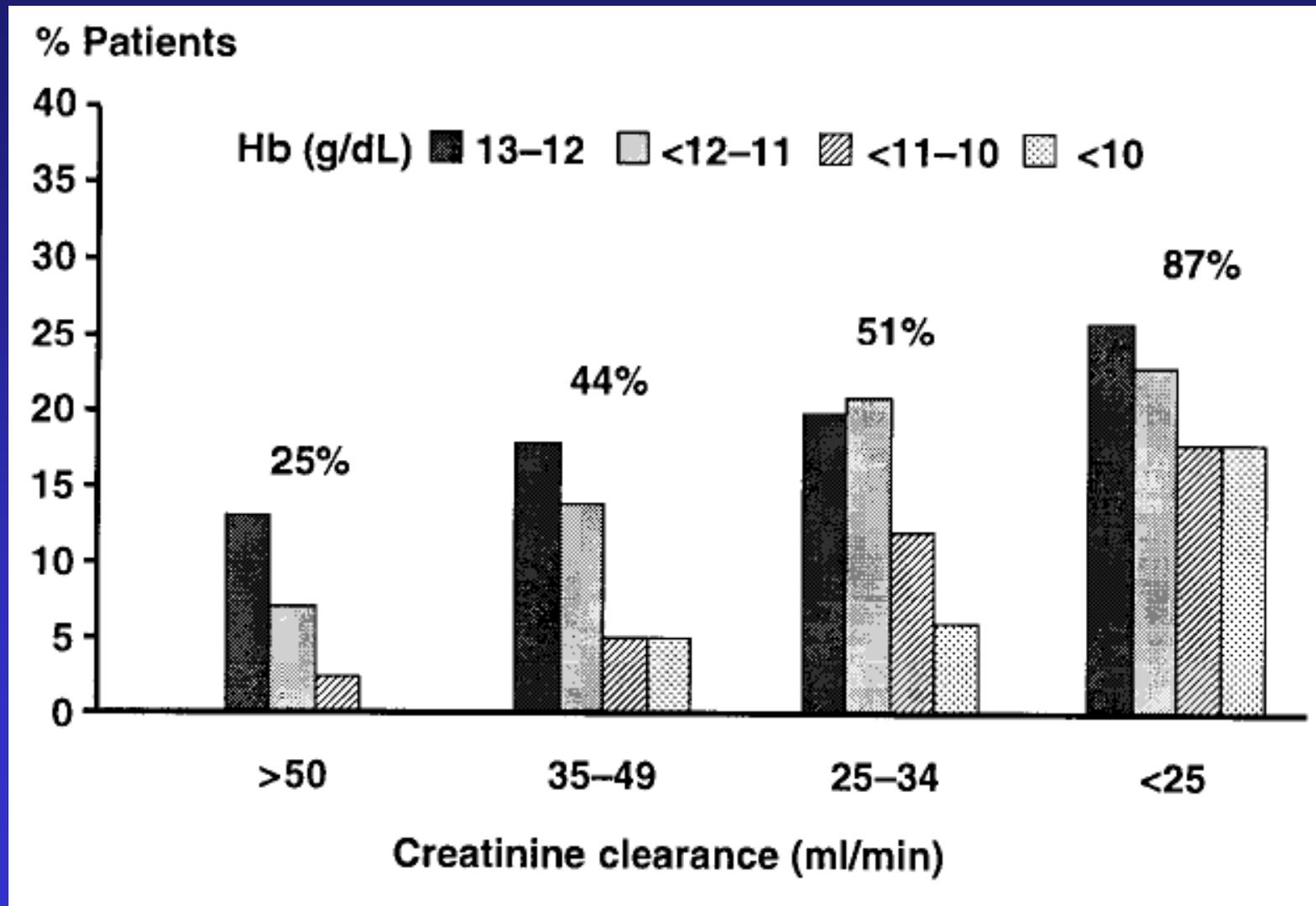
**(Target Hb and novel options in renal anaemia)**

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# Prevalence of anaemia by degree of renal function at baseline



# **Causes of anaemia secondary to chronic renal failure**

## **1. Decreased red cell survival**

- **External blood loss**
- **Decreased red cell survival within the circulation**

## **2. Decreased bone marrow stimulation**

- **Decreased erythropoietin production by failure kidneys**

## **3. Decreased bone marrow response**

# Erythropoiesis Stimulating Agents (ESA)

Half-life (h, mean  $\pm$  SEM)

	i.v.	s.c.
<b>CERA<sup>1</sup></b>	133 $\pm$ 9.83	137 $\pm$ 21.9
<b>Darbepoetin alfa<sup>2</sup></b>	25.3 $\pm$ 2.2	48.4 $\pm$ 5.2
<b>Epoetin beta<sup>3</sup></b>	8.8 $\pm$ 0.5	24.2 $\pm$ 2.6
<b>Epoetin alfa<sup>3</sup></b>	6.8 $\pm$ 0.6	19.4 $\pm$ 2.5

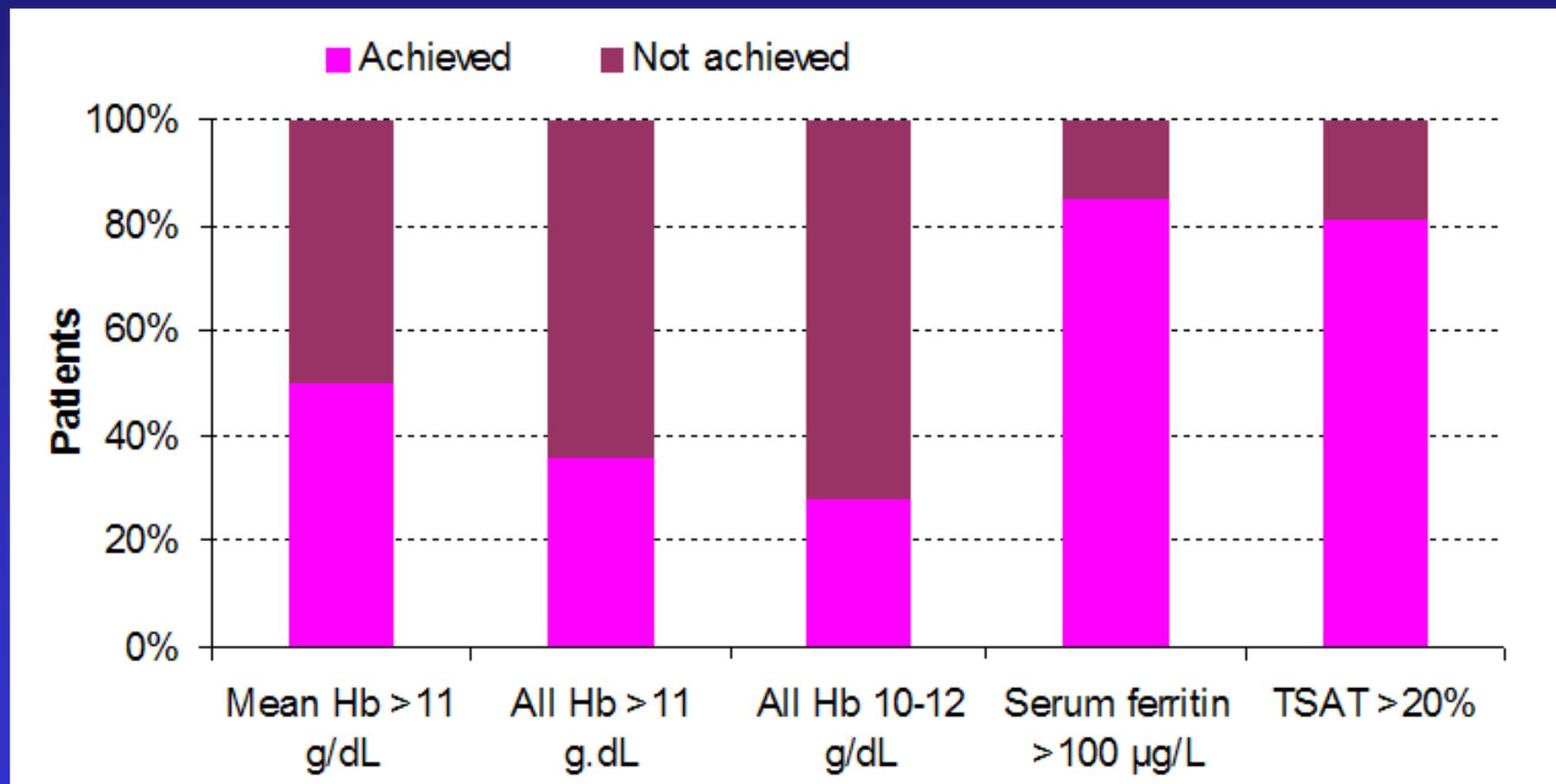
<sup>1</sup> from multiple dose studies

<sup>2</sup> Macdougall et al. *JASN* 1999

<sup>3</sup> Halstenson et al. *Clin Pharmacol Ther* 1991

## Treatment of renal anaemia remains suboptimal despite revised European Best Practice Guidelines (EBPG)

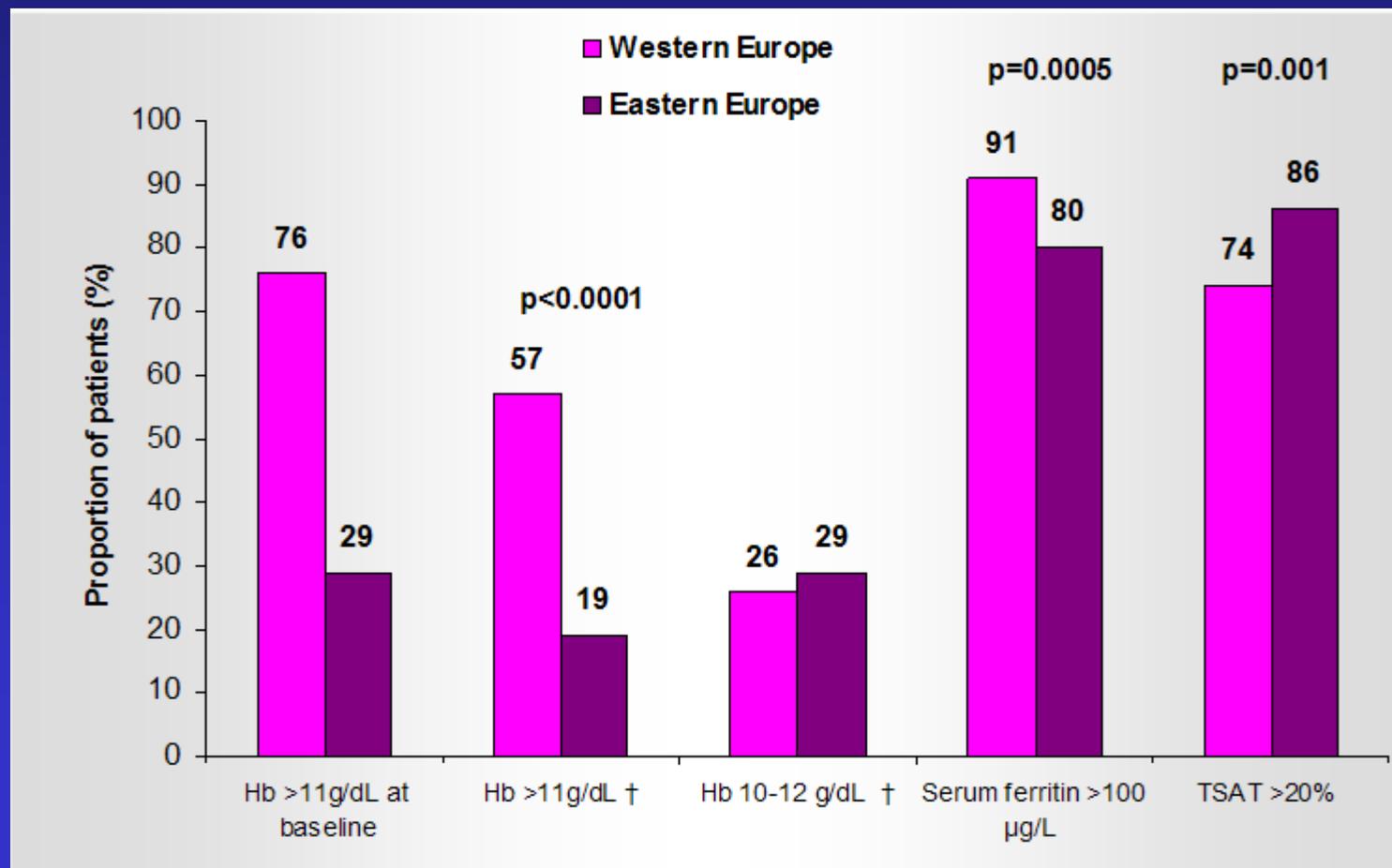
Francesco Locatelli<sup>1</sup>, Adrian Covic<sup>2</sup>, Iain C Macdougall<sup>3</sup> and Andrzej Wiecek<sup>4</sup>, on behalf of the ORAMA study group



Wiecek A et al., Renal Failure, 2008

# Treatment of renal anaemia: Comparison between Eastern and Western Europe with respect to the European Best Practice Guidelines (EBPG)

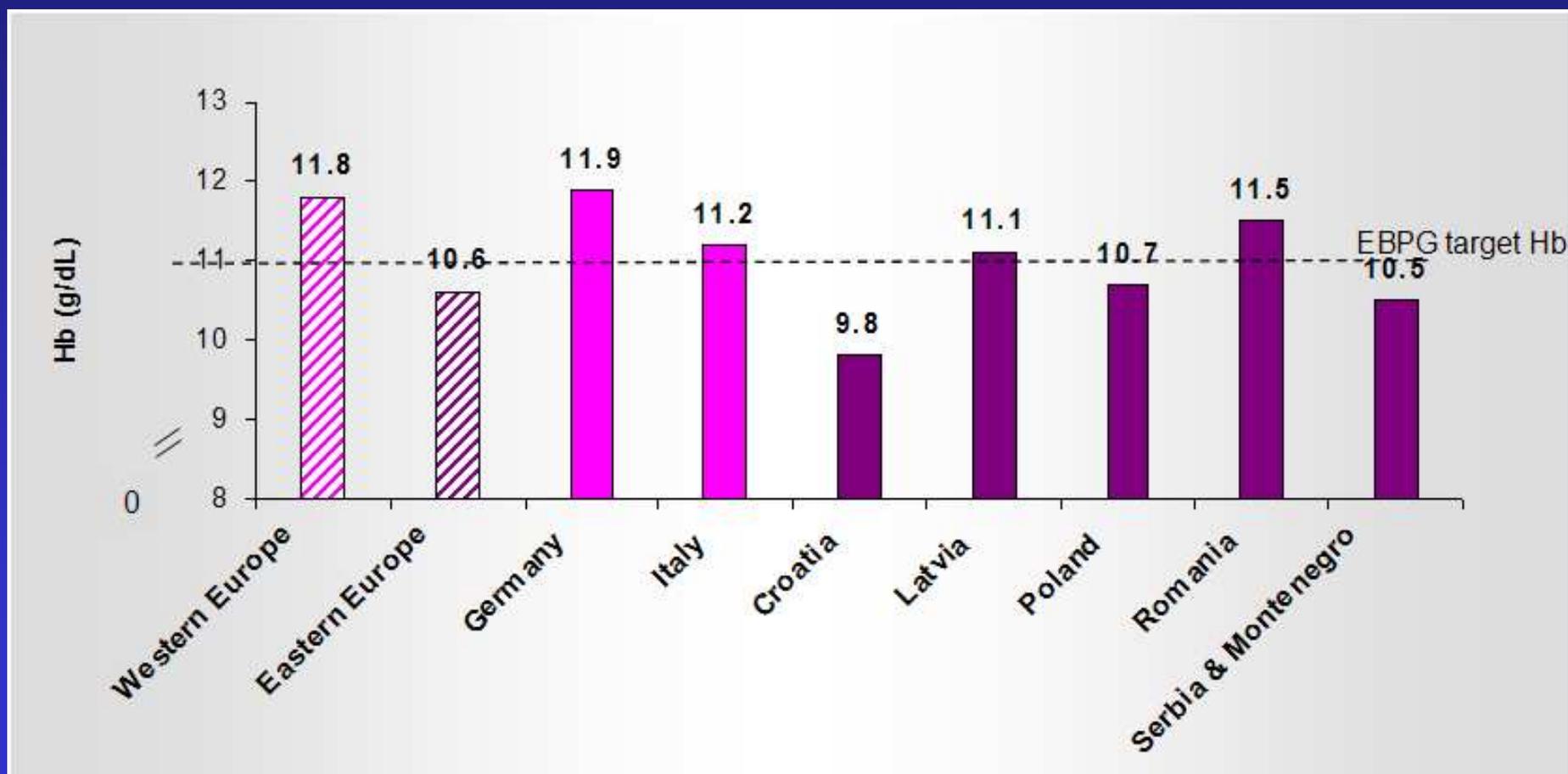
Andrzej Wiecek<sup>1</sup>, Adrian Covic<sup>2</sup>, Francesco Locatelli<sup>3</sup>, Iain C Macdougall<sup>4</sup>, on behalf of the ORAMA study group



Wiecek A et al., Renal Failure, 2008

# Treatment of renal anaemia: Comparison between Eastern and Western Europe with respect to the European Best Practice Guidelines (EBPG)

Andrzej Wiecek<sup>1</sup>, Adrian Covic<sup>2</sup>, Francesco Locatelli<sup>3</sup>, Iain C Macdougall<sup>4</sup>, on behalf of the ORAMA study group

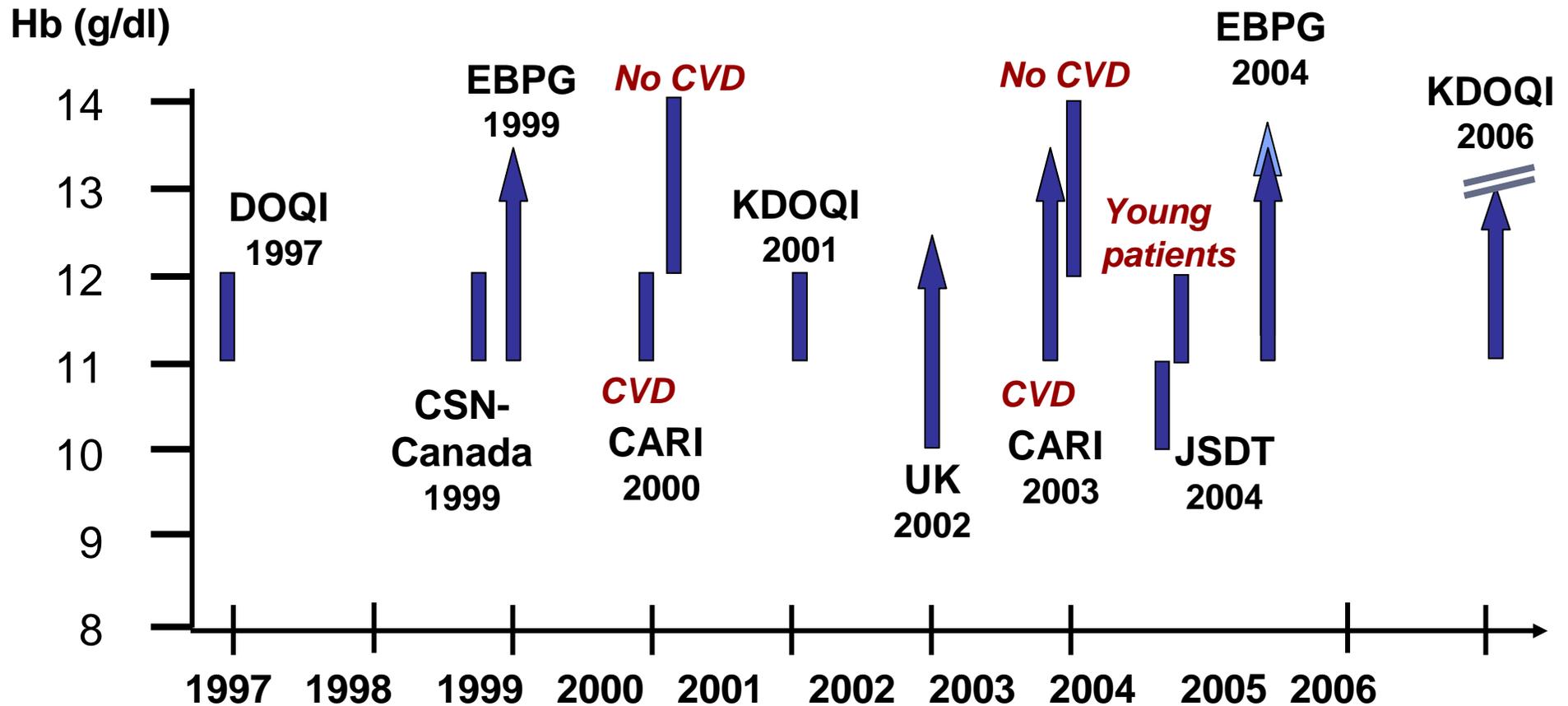


Wiecek A et al., Renal Failure, 2008

# Evidence in favor of a normal target hemoglobin

- Left ventricular hypertrophy
- Cognitive function
- Physical function
- Quality of life
- Mortality and morbidity

# Target Hb values in international guidelines



Locatelli et al. *Nephrol Dial Transplant* 2004;19(Suppl 2):1-43

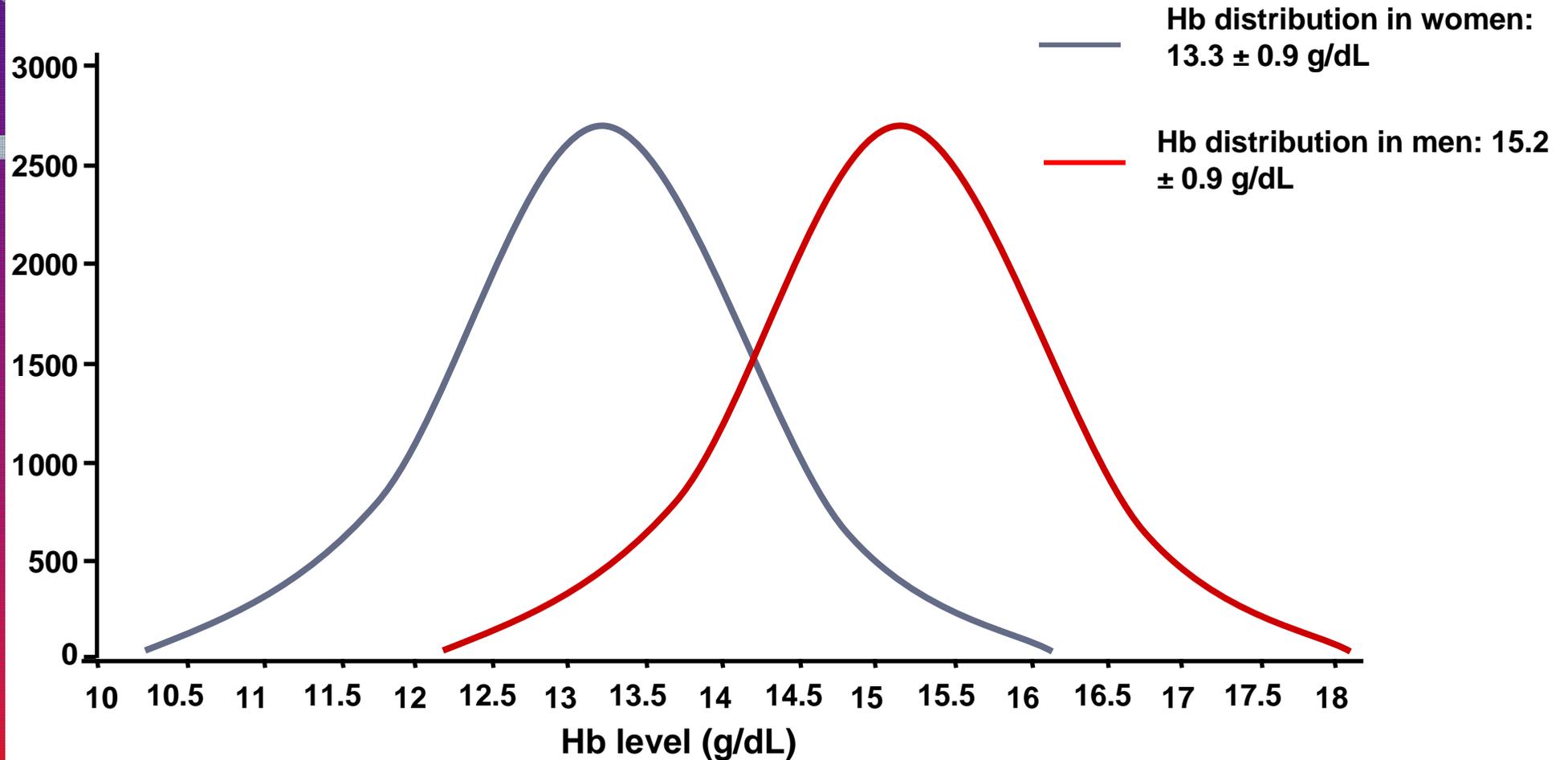
NKF-KDOQI. *AJKD* 2001;37(Suppl 1):S182-238; NKF-KDOQI. *AJKD* 2006;47(Suppl 3):S11-145

CARI. [www.cari.org.au/dialysis\\_bht Updating.php](http://www.cari.org.au/dialysis_bht Updating.php), 2005

Renal Association. [www.renal.org/Standards/Renal Standards\\_2002b.pdf](http://www.renal.org/Standards/Renal Standards_2002b.pdf), 2002

CSN. <http://csnscn.ca/local/files/guidelines/CSN-Guidelines-1999.pdf>, 1999

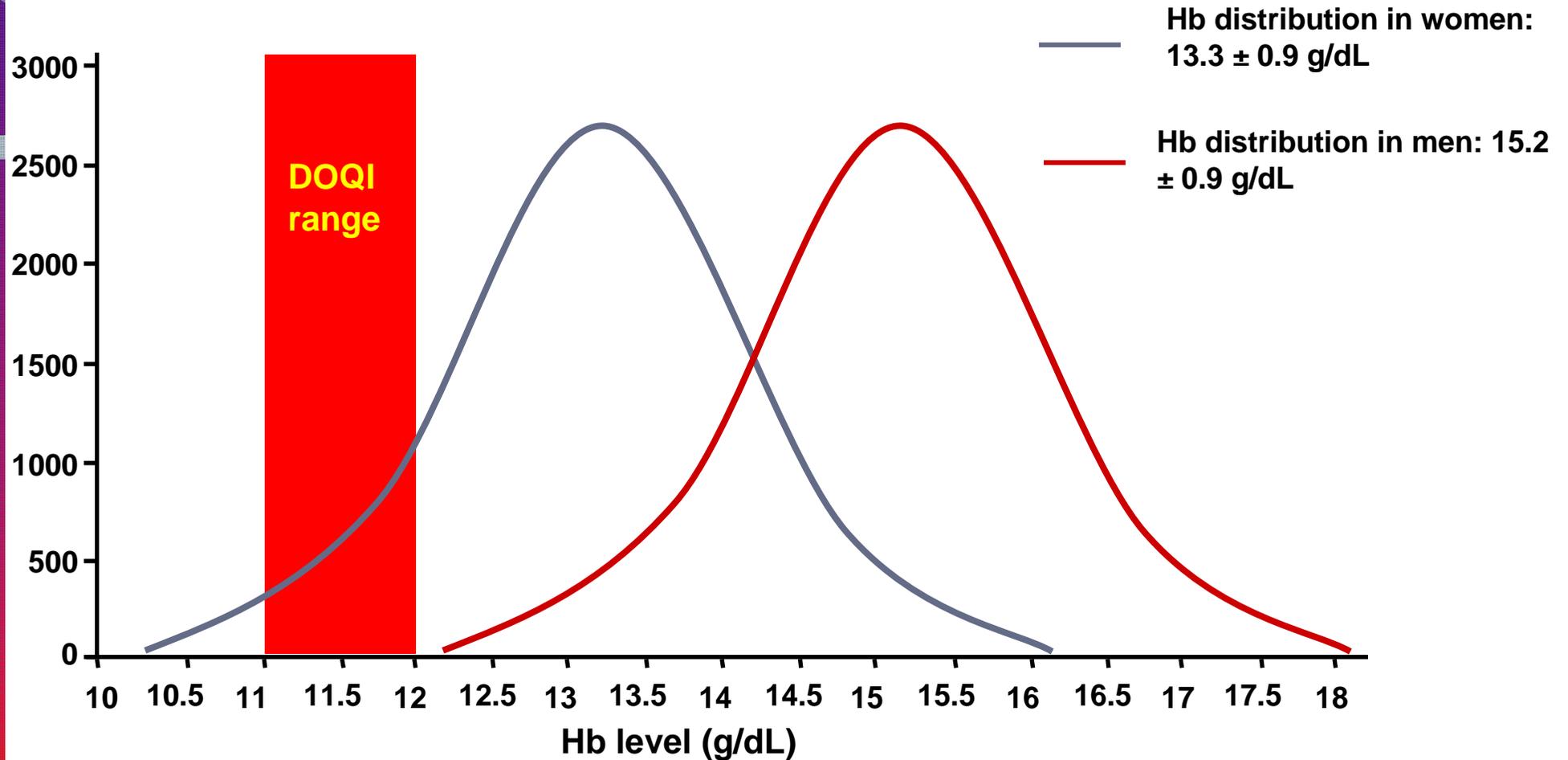
## Normal range of Hb with normal renal function



N=40,000 (NHANES III, 1988-1994)

Dallman et al. Iron Nutrition in health and disease. John Libbey & Co, London, 1996

# Target Hb in CKD patients versus normal Hb distribution



N=40,000 (NHANES III, 1988-1994)

Dallman et al. Iron Nutrition in health and disease. John Libbey & Co, London, 1996

## Optimal target Hb – a public debate

Phrommintikul A, Haas SJ, Elisk M et al.: **Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis.**

**Lancet, 2007,369**

Strippoli GF, Tognoni G, Navanethan SD, Nicolucci A, Craig JC.

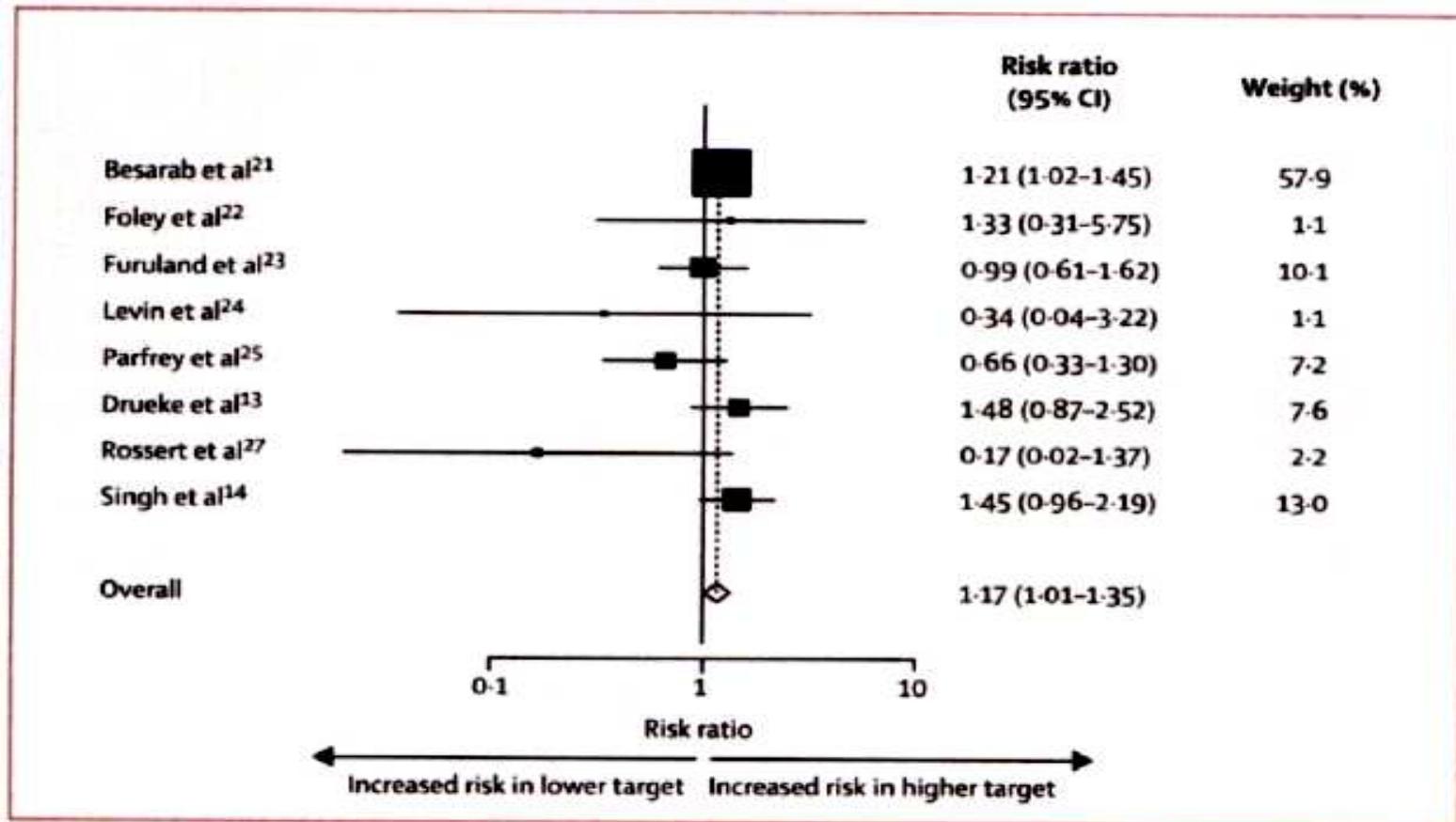
**Lancet, 2007,369**

**Haemoglobin targets: we were wrong, time to move on**

On the basis of the existing published trials, summarised by Phrommintikul and colleagues,<sup>4</sup> we contend that more trials of haemoglobin target concentrations in patients with chronic kidney disease are no longer required, should be stopped, or at least it should be made fully and publicly explicit what reasons grant their continuation. We say

this because of the rights of patients, and the credibility of the scientific nephrological community, after such a long history of contradictions. The question has been answered: higher haemoglobin target concentrations increase mortality via cardiovascular endpoints. Part rather than complete correction of anaemia is appropriate,

# Risk of all-cause mortality in the higher haemoglobin group compared with the lower haemoglobin group



**Figure 2: Risk of all-cause mortality in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)**

The Roger et al trial<sup>26</sup> is not reported because there were no deaths in either group.

# Risk of myocardial infarction in the higher haemoglobin group compared with the lower haemoglobin group

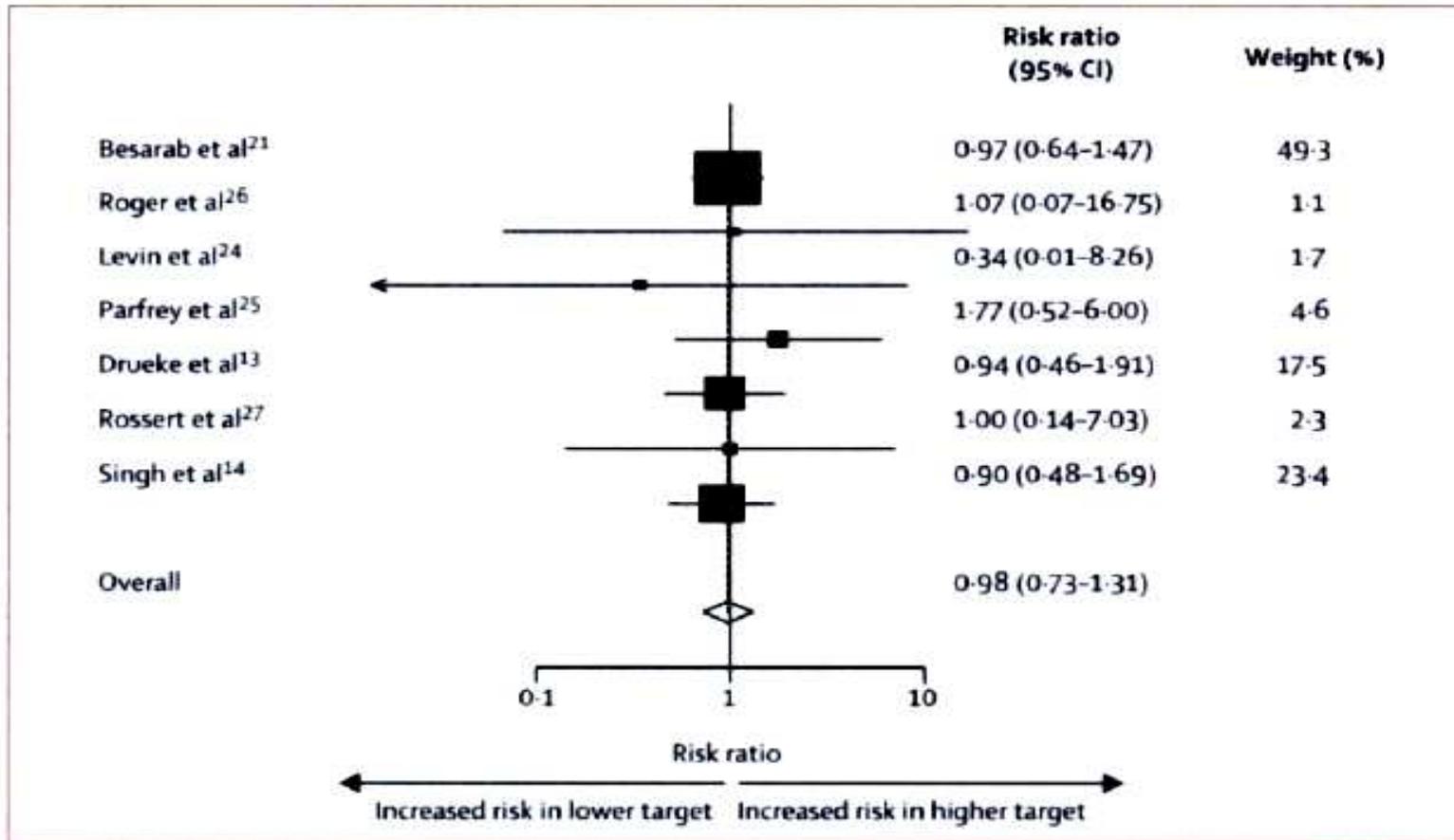


Figure 3: Risk of myocardial infarction in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

Phrommintikul A. et al. Lancet 2007, 369:381-388

# Risk of poorly controlled blood pressure in the higher haemoglobin group compared with the lower haemoglobin group

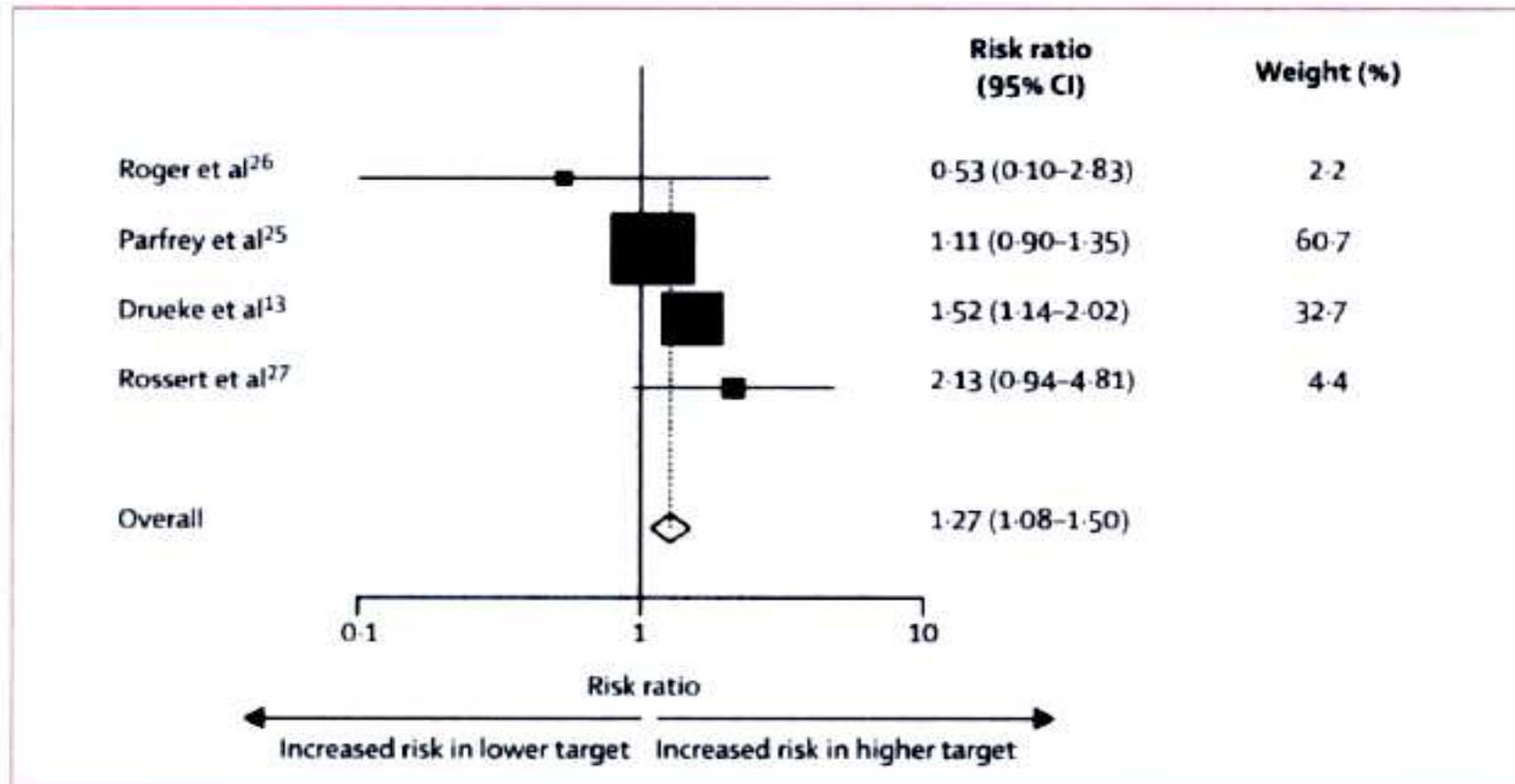


Figure 4: Risk of poorly controlled blood pressure in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

# Risk of arterio-venous access thrombosis in the higher haemoglobin target group compared with the lower haemoglobin target group

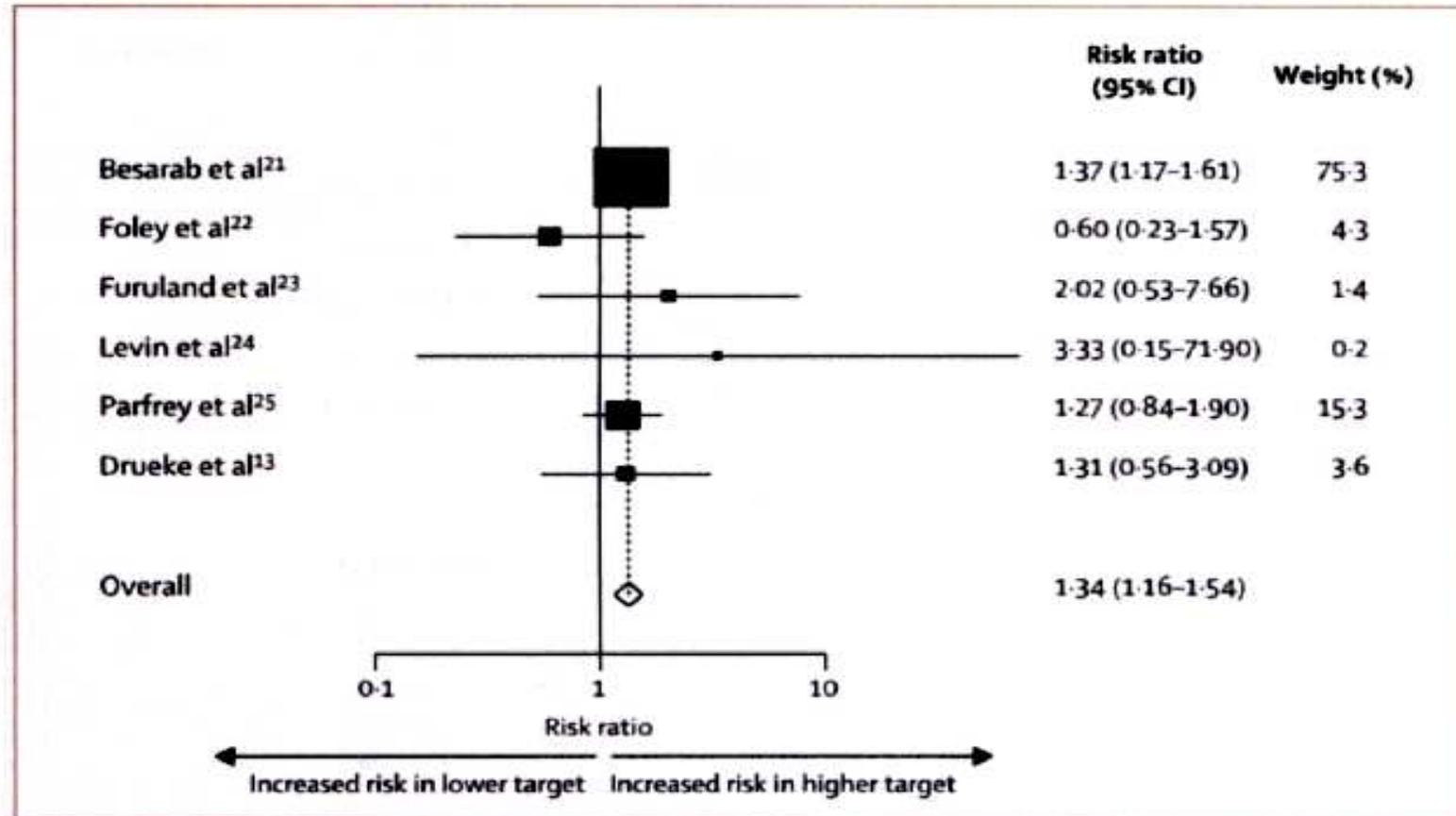
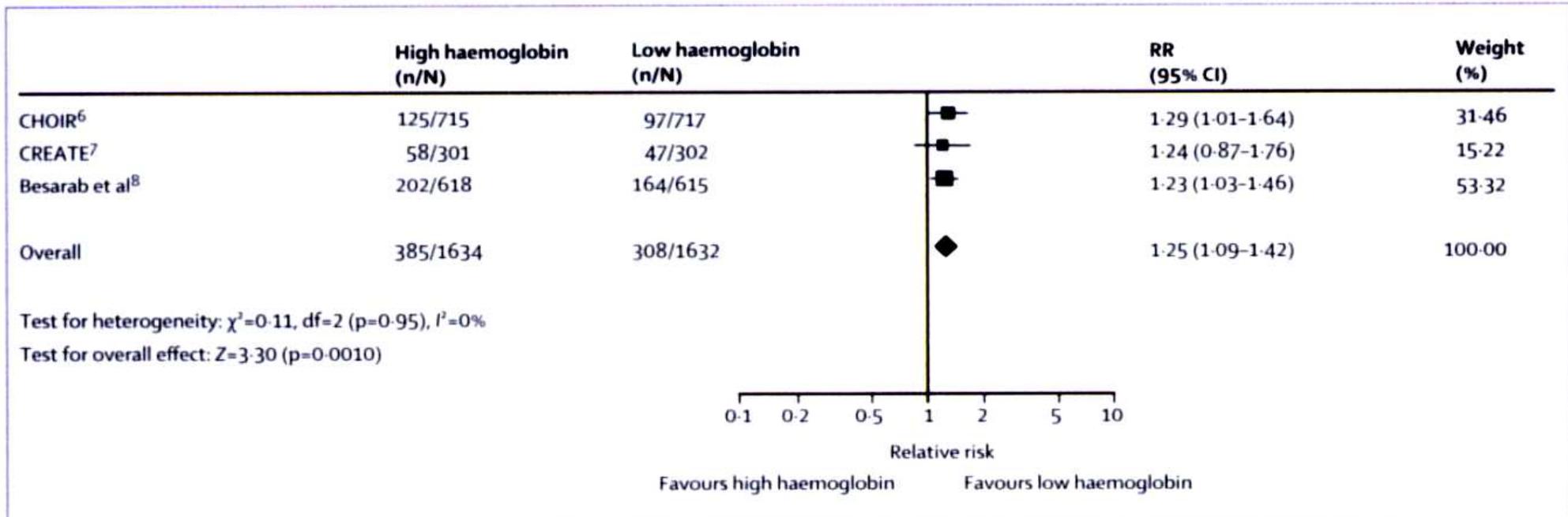


Figure 5: Risk of arteriovenous access thrombosis in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

Phrommintikul A. et al. Lancet 2007, 369:381-388

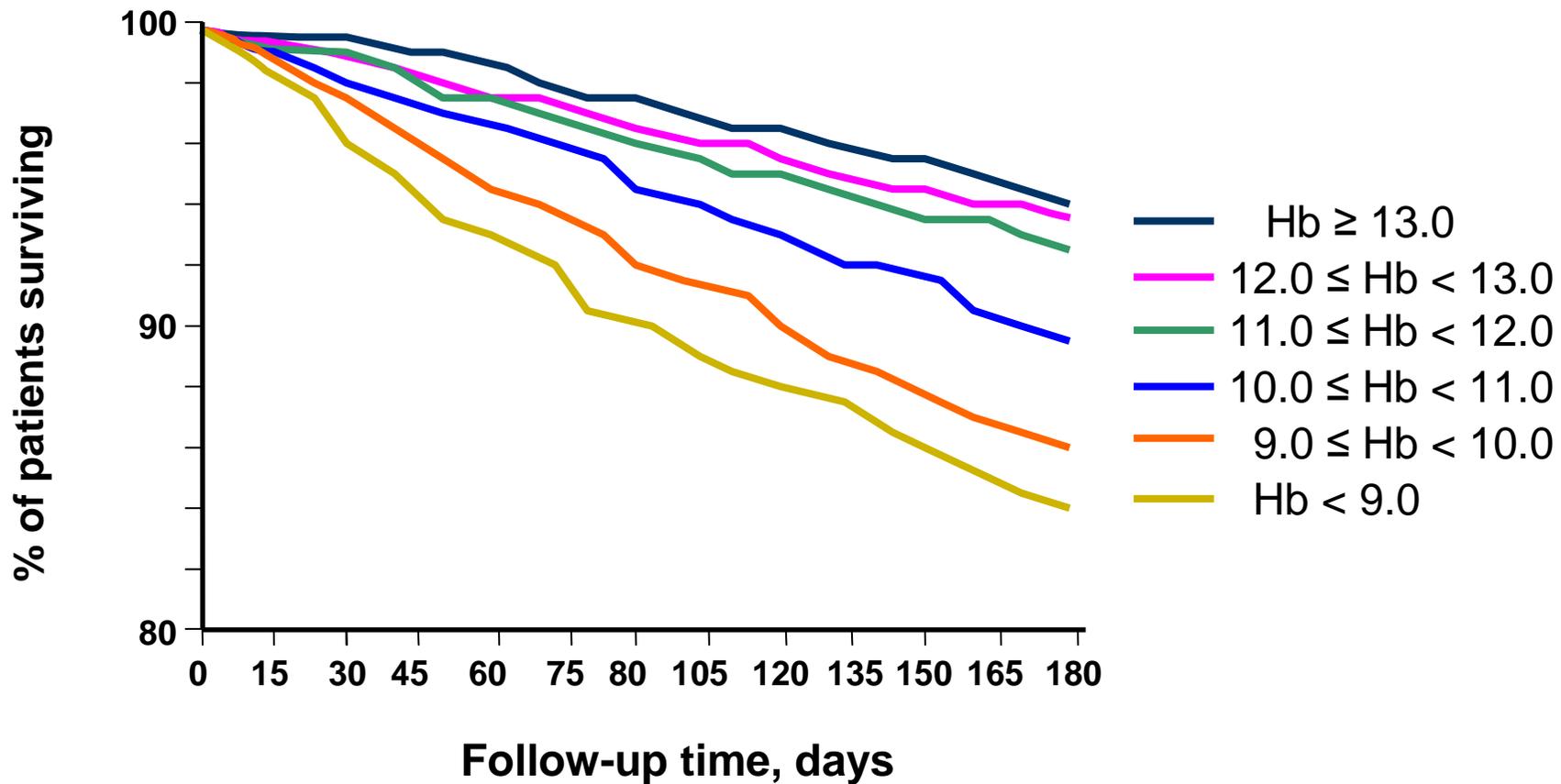
# Effect of different haemoglobin target concentrations on serious cardiovascular events



**Figure:** Effects of different haemoglobin target concentrations on serious cardiovascular events  
 RR=relative risk.

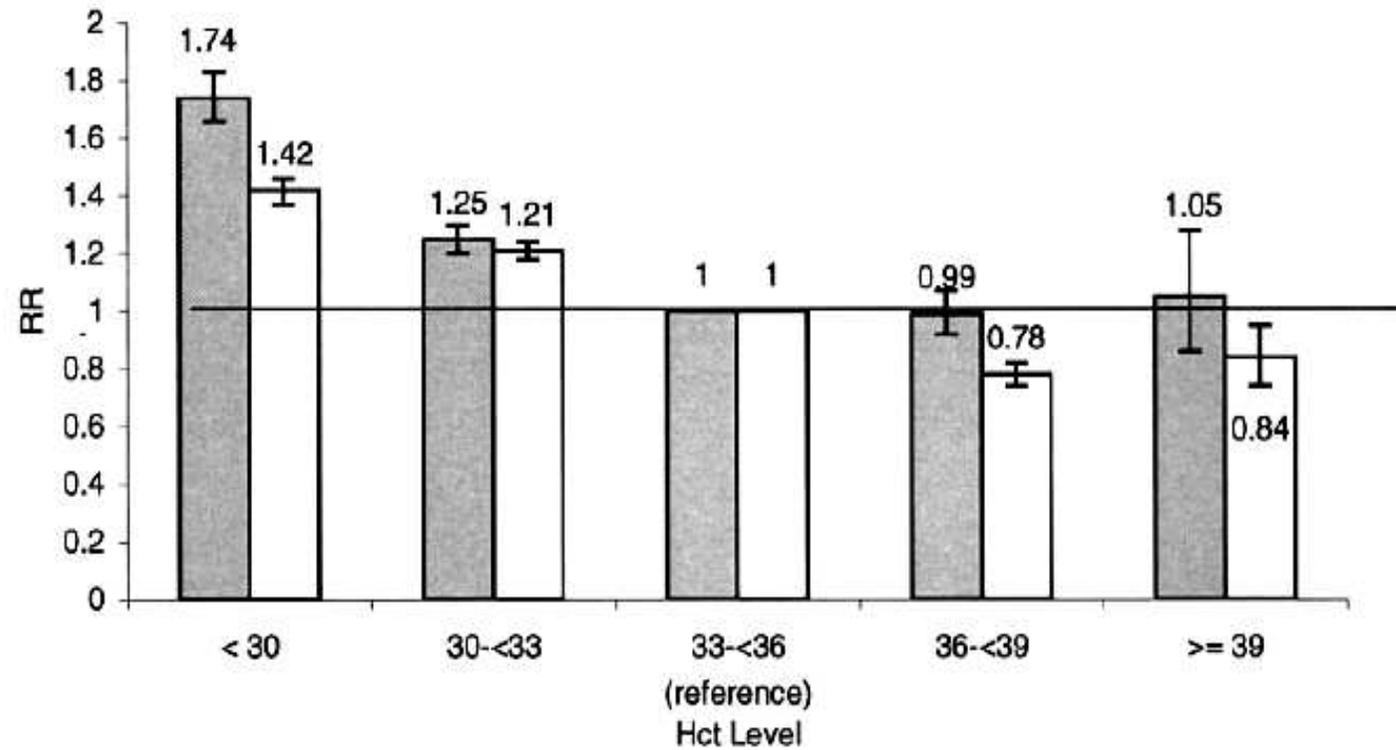
# Association between Hb values and prognosis

Fresenius Medical Care, North America (N=44,550)



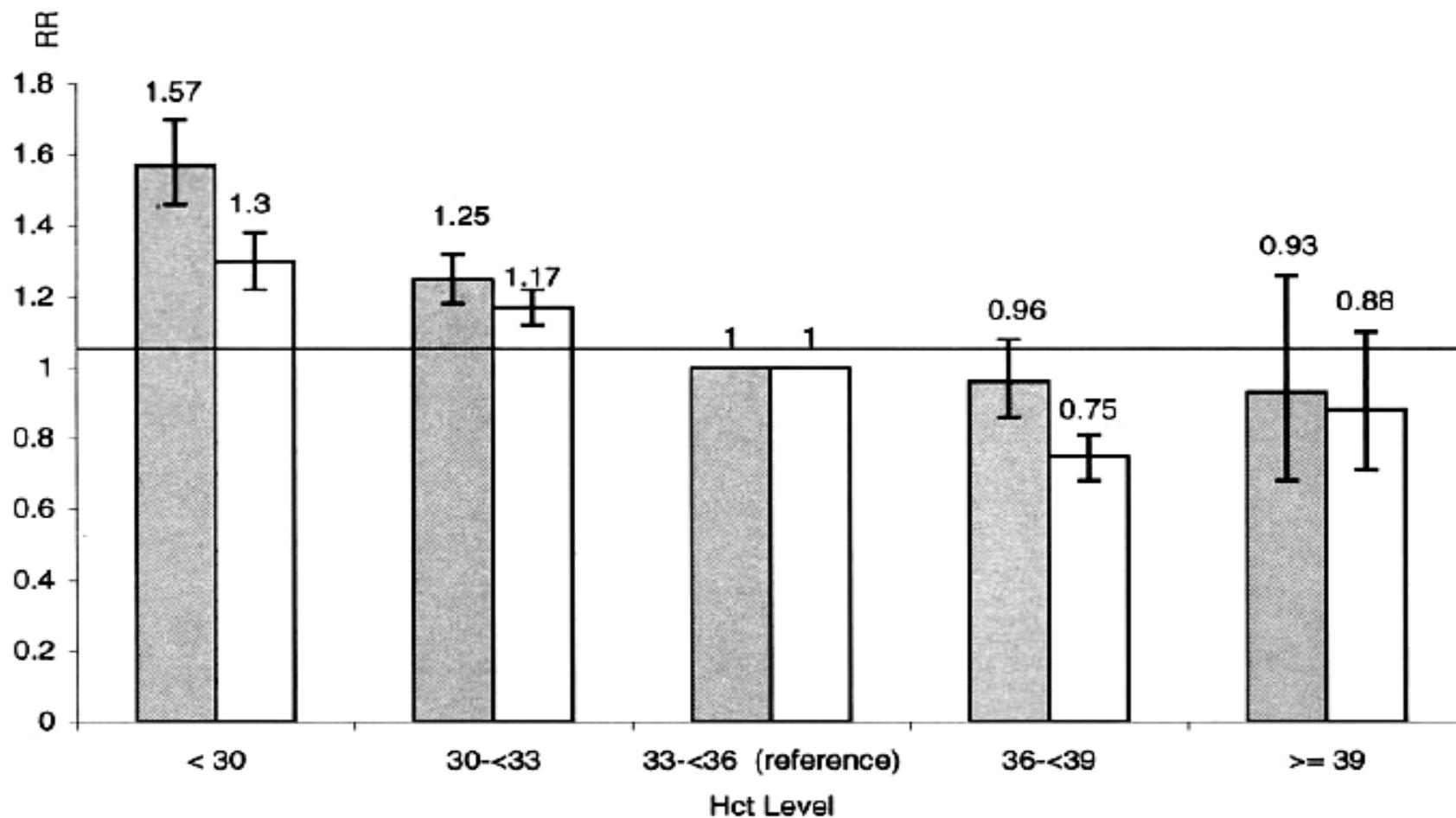
Ofsthun et al., *Kidney. Int.*, 2003;63:1908–1914

Relative risks (RR) of death (■) and hospitalization (□) from all causes [with 95% confidence intervals (CI)]. Hct, hematocrit.



**Collins A.J. et al. J Am Soc Nephrol 2001, 12:2465-2473**

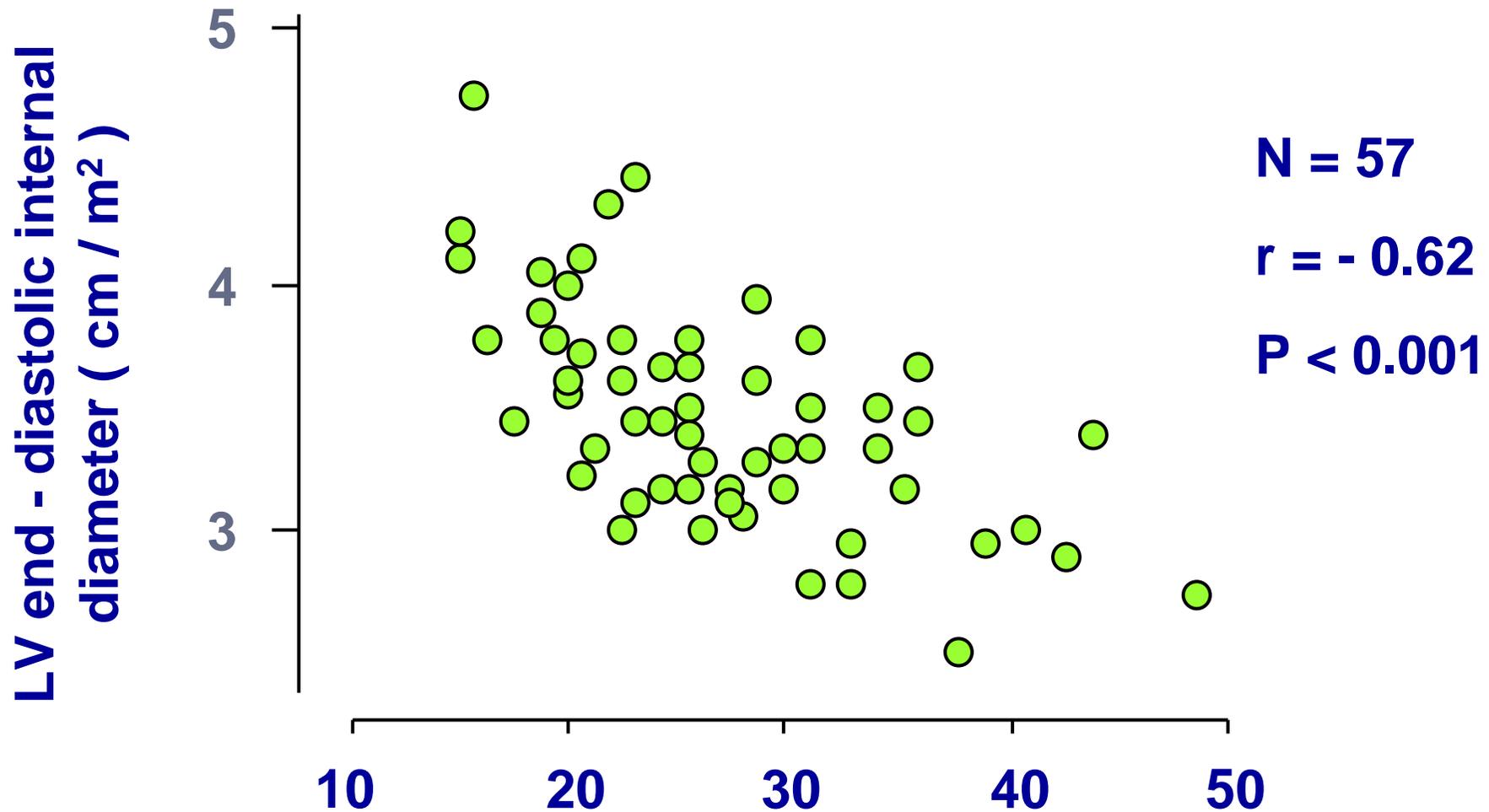
Relative risks (RR) of death (■) and hospitalization (□) from cardiac causes (with 95% CI). Hct, hematocrit.



**Collins A.J. et al. J Am Soc Nephrol 2001, 12:2465-2473**

# Uremic cardiomyopathy: an inadequate LVH

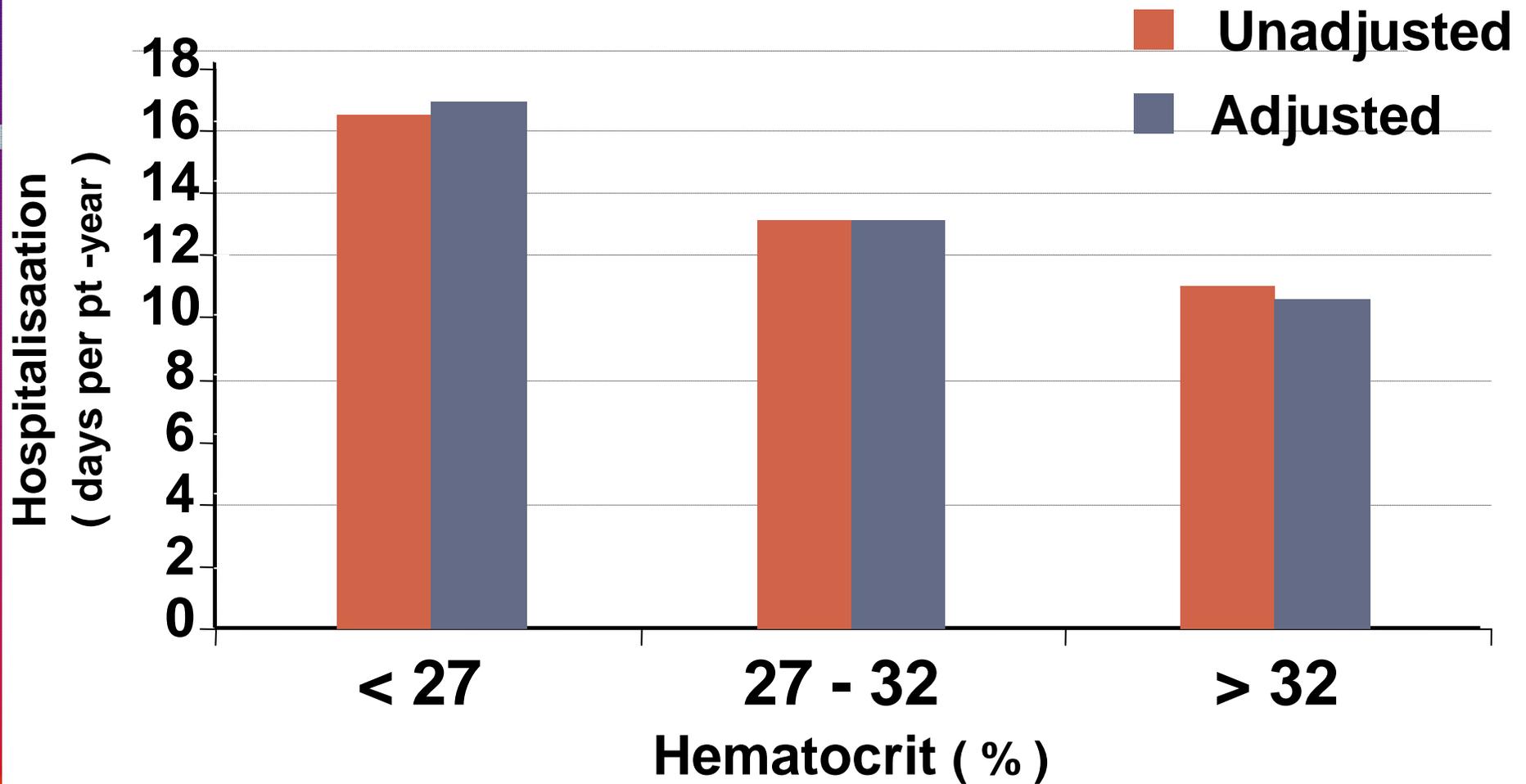
## Hematocrit and LV cavity diameter



London GM *et al.* *Kidney Int* 1987; 31: 973 - 80

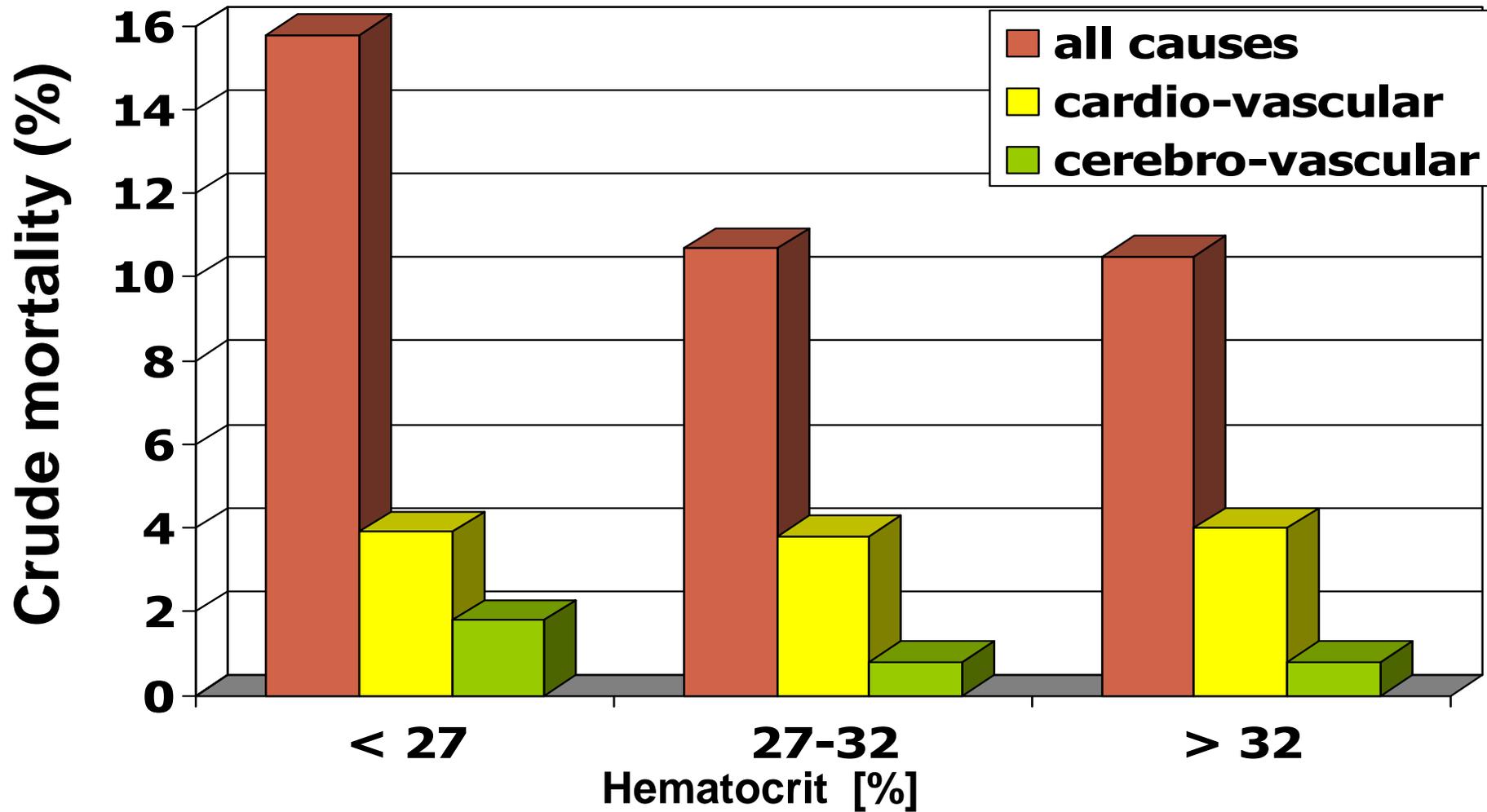
# ESRD PATIENT RISK FACTORS

## Anaemia and hospitalisation risk



Locatelli F. et al., Nephrol. Dial. Transplant., 1998; 13: 1642 - 1644

## Cause of death:

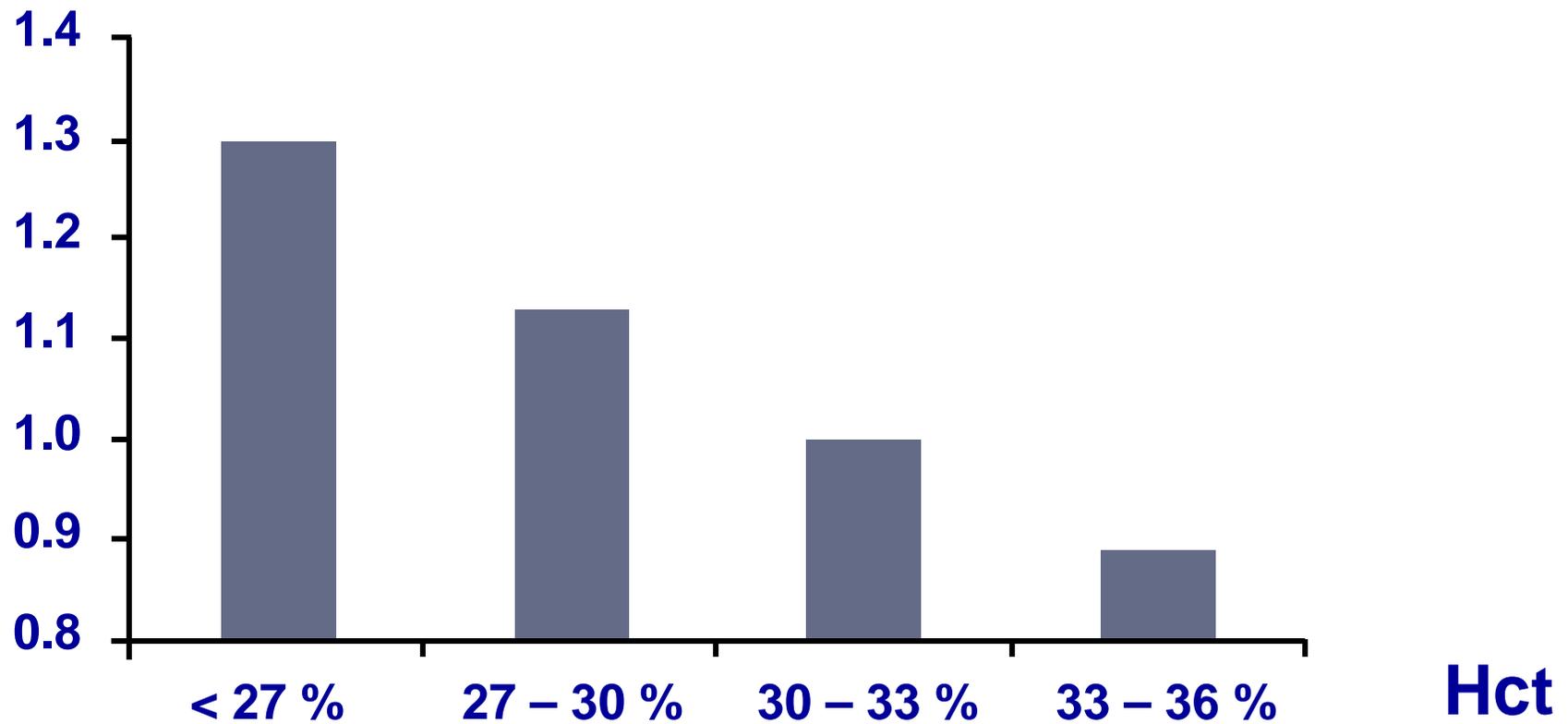


Locatelli F. et al., *Nephrol. Dial. Transplant.*, 1998, 13, 1642-1644

# US Observational Study

## Hospitalization risk and Hct in HD patients

### Relative risk

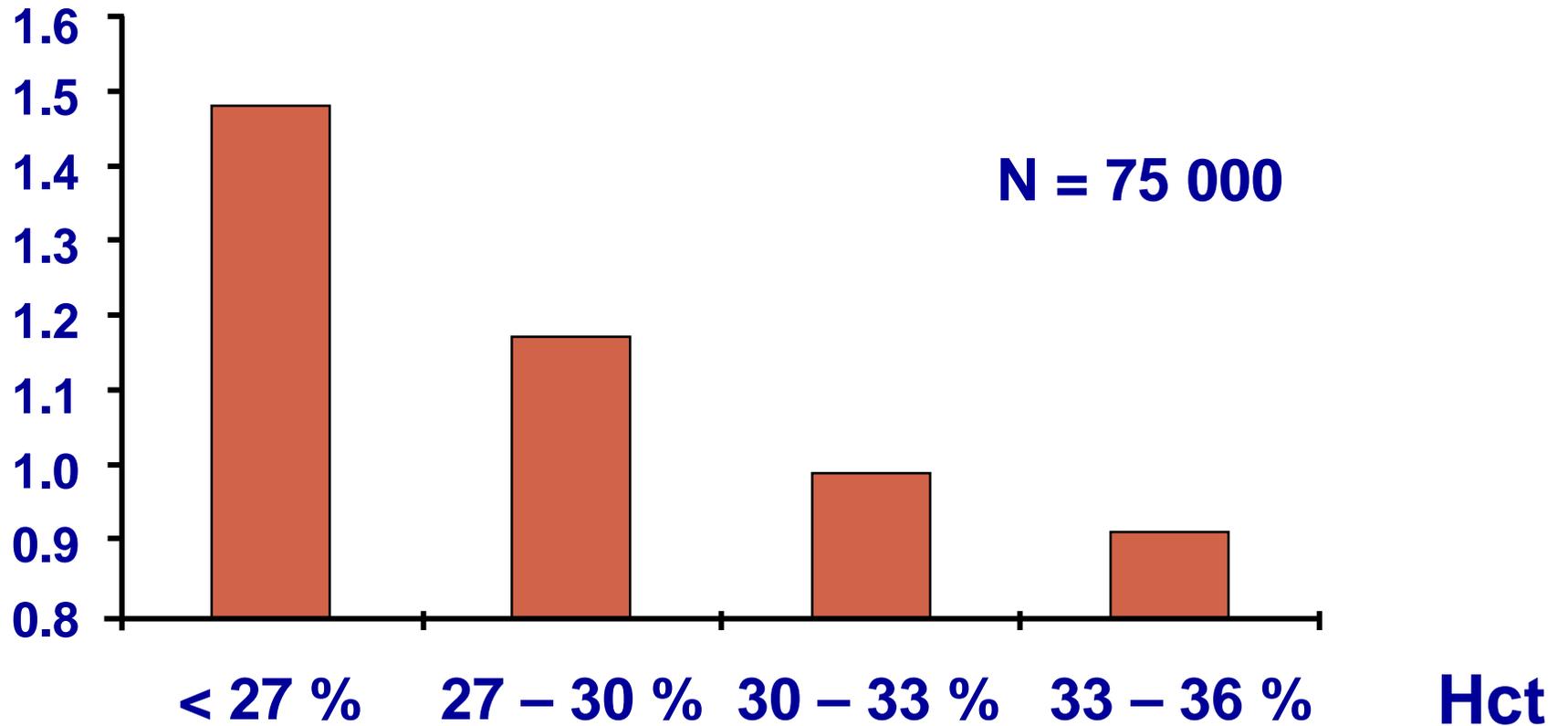


Xia et al., J. Am. Soc. Nephrol., 1999;10; 1309 - 1316

# US Observational Study

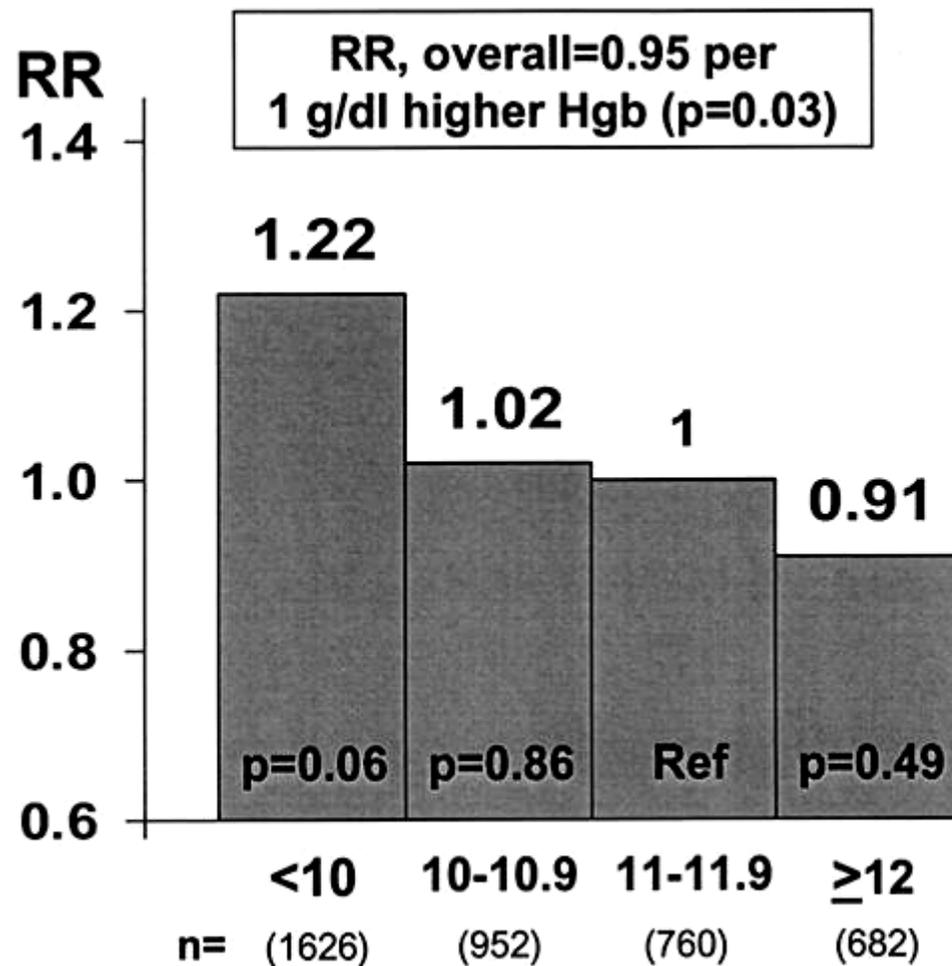
## Mortality risk and hematocrit in HD patients

Relative risk

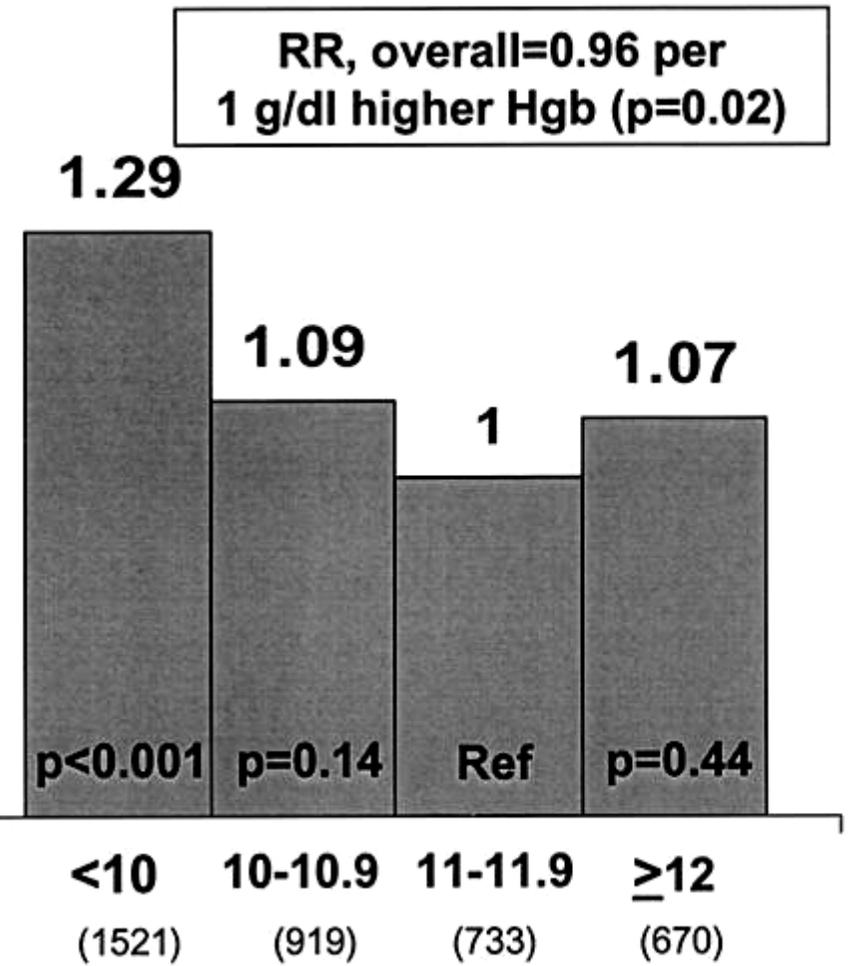


Ma J.Z. *et al.* J. Am. Soc. Nephrol., 1999; 10: 610

## Relative Risk of Death



## Relative Risk of Hospitalisation



**Haemoglobin (g/dl) at study entry**

Locatelli F. et al., *Nephrol. Dial. Transplant.*, 2004, 19: 121-132

# Observational trials: consistency, but limitations

**Consistency:** higher Hb values – better patient outcomes  
in many studies relationship extends into normal range

**Plausibility:** reduction in Hb → compensatory increase in CO,  
tissue ischemia

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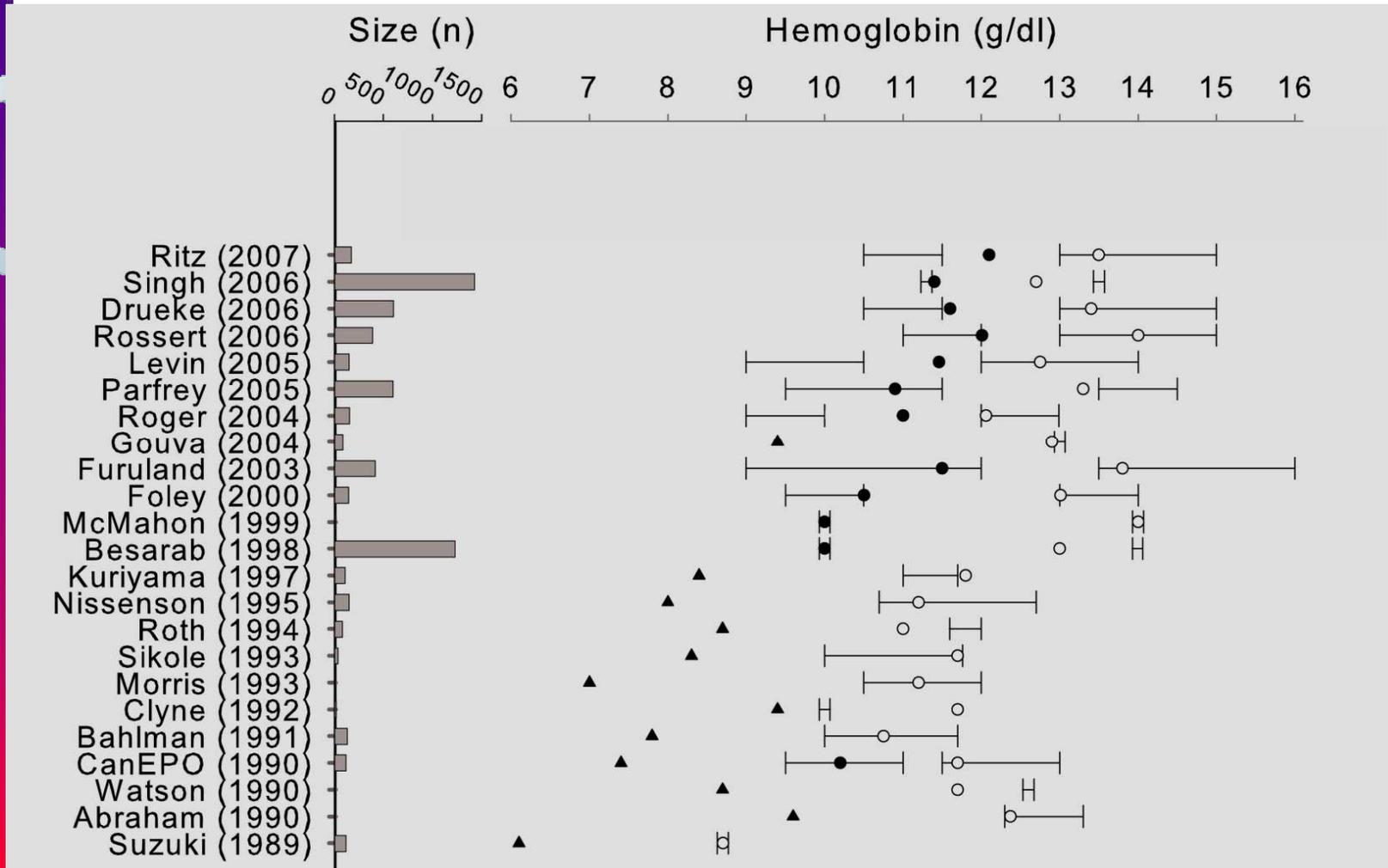
**Limitations:** Hb values can be influenced by many factors, including

- *inflammation,*
- *comorbid conditions,*
- *general quality and intensity of care,*
- *progression of kidney disease*

→ observational trials can **not** assess whether

- *relationship between Hb and prognosis is causal*
- *increasing the Hb levels improves outcomes*

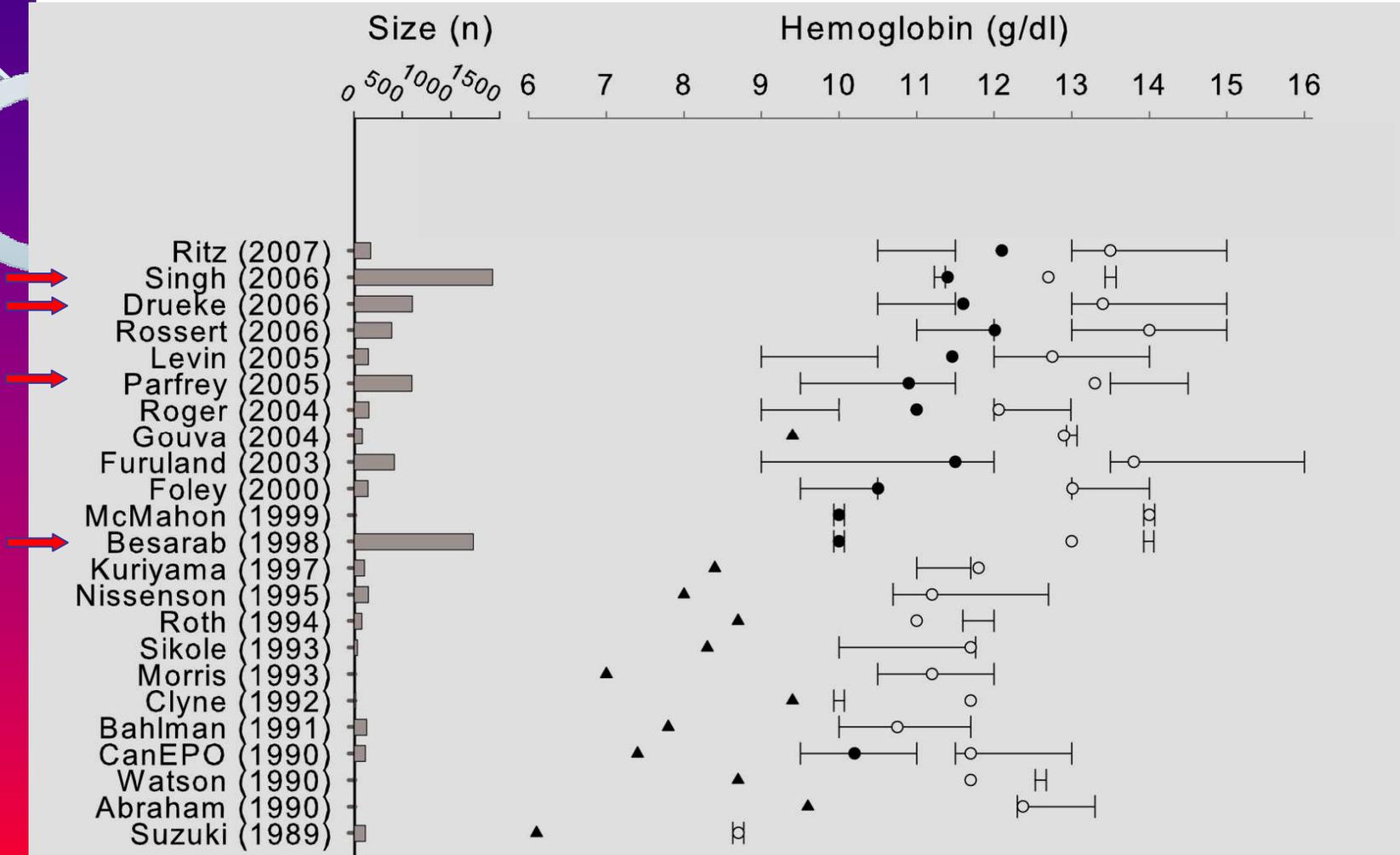
# Randomised clinical trials in anemia management



▲ Placebo/control mean Hb  
 ● Lower Hb arm: mean achieved Hb  
 ○ Higher Hb arm: mean achieved Hb  
 } Target range

Adapted and updated from  
 NKF-K/DOQI.  
 AJKD 2006; 47  
 (5 Suppl 3)

# Randomised clinical trials in anemia management



▲ Placebo/control mean Hb  
 ● Lower Hb arm: mean achieved Hb  
 ○ Higher Hb arm: mean achieved Hb  
 } Target range

Adapted and updated from NKF-K/DOQI. *AJKD* 2006; 47 (5 Suppl 3)

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

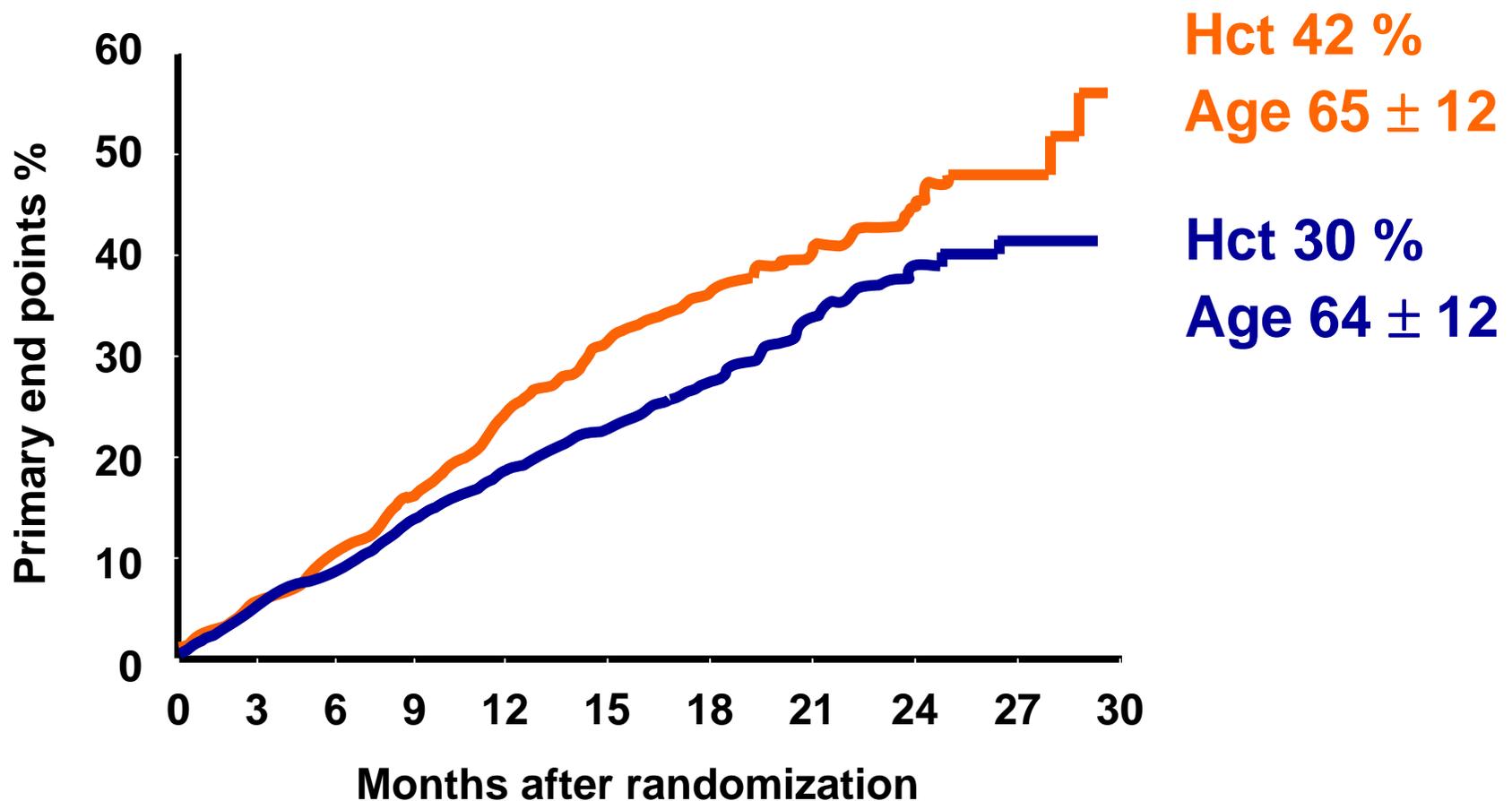
ANATOLE BESARAB, M.D., W. KLINE BOLTON, M.D., JEFFREY K. BROWNE, PH.D., JOAN C. EGRIE, PH.D.,  
ALLEN R. NISSENSON, M.D., DOUGLAS M. OKAMOTO, PH.D., STEVE J. SCHWAB, M.D., AND DAVID A. GOODKIN, M.D.

- Patients: 1233, HD, clinical evidence of CHF or IHD, hct 27-33 %
- Design: iv / sc Epoetin alfa High arm: target hct  $42 \pm 3$  % (= Hb 14)  
Low arm: target hct  $30 \pm 3$  % (= Hb 10)
- Primary EP: composite of death and 1st non-fatal MI (time to first event)
- Main results:
- study terminated early (futility, safety concerns)
  - more patients in the higher arm reached the endpoint (n.s.)
  - physical function score increased with hct
  - incidence of vascular access thrombosis higher in higher arm (243 vs 176;  $p=0.001$ )

**Besarab A et al., N. Engl. J. Med., 1998;339:584-590**

# Normal versus low haematocrit

Probability of death or first non - fatal myocardial infarction



Besarab A et al., N. Engl. J. Med., 1998 ; 339 : 584 - 590

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

2005

Patrick S. Parfrey,<sup>\*</sup> Robert N. Foley,<sup>†</sup> Barbara H. Wittreich,<sup>‡</sup> Daniel J. Sullivan,<sup>§</sup> Martin J. Zagari,<sup>‡</sup> and Dieter Frei,<sup>‡</sup> for the Canadian European Study Group

*<sup>\*</sup>Memorial University of Newfoundland, St. John's, Newfoundland, Canada; <sup>†</sup>Chronic Disease Research Group, Minneapolis, Minnesota; <sup>‡</sup>Ortho Biotech, Bridgewater, New Jersey; and <sup>§</sup>Johnson and Johnson, Pharmaceutical Research, LLC, Raritan, New Jersey*

- Patients: 596, recent HD initiation, no symptomatic heart disease, no left ventricular dilatation
- Design: iv / sc Epoetin alfa High arm: target Hb 13.5 – 14.5  
double-blind Low arm: target Hb 9.5 – 11.5
- Primary EP: left ventricular volume index (LVVI)
- Secondary EP: LVMI, de novo CHF, QOL, 6-min walking test
- Main results:
- changes in LVVI similar
  - only difference in secondary outcomes: improved SF-36 vitality score in the higher vs lower arm
  - adverse events similar, except rates of skeletal pain, surgery, and dizziness higher in lower arm; headache and cerebrovascular events higher in higher arm

**Parfrey PS et al., J. Am. Soc. Nephrol., 2005;16:2180-2189**

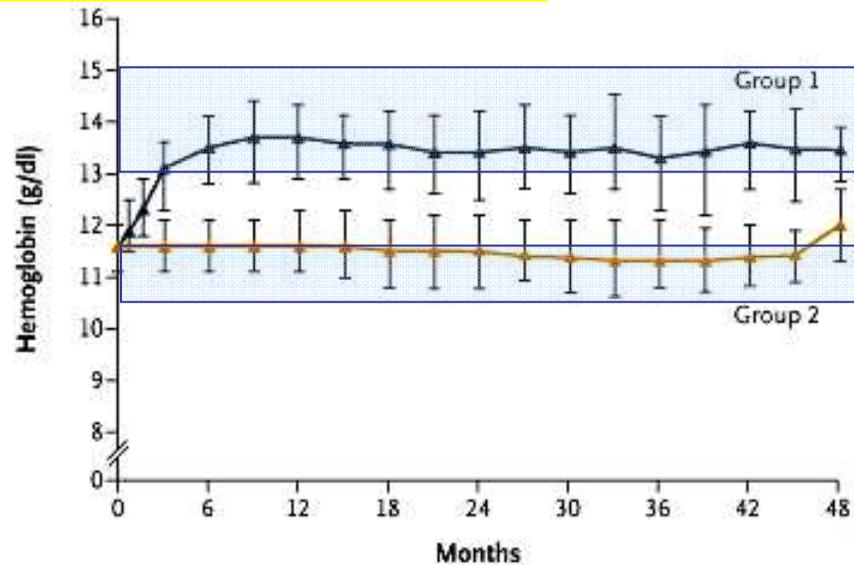
## Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia

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\*

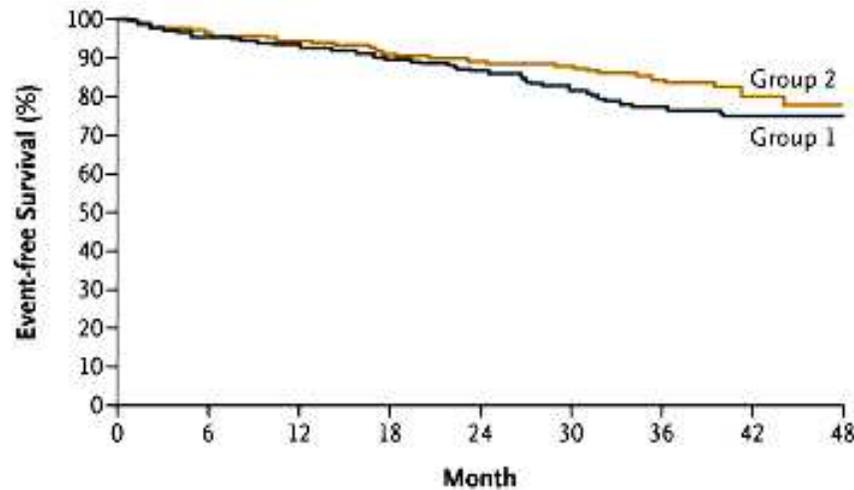
- Patients: 603, eGFR 15-35, Hb 11-12.5
- Design: sc Epoetin beta    High arm: target 13.0 – 15.0  
Low arm: when Hb < 10.5 → target 10.5 – 11.5
- Primary EP: composite of 8 CV events (time to first event)
- Secondary EP: change in LVMI, QOL, progression of CKD and others
- Main results:
- no difference in primary endpoint
  - improvement in QOL
  - time to dialysis shorter in higher arm

**Drüeke T B et al., N. Engl. J. Med., 2006;355:2071- 2084**

# CREATE trial



- Hb difference 1.9 / 1.7 / 1.5 g/dl
- starting dose 2000 IU/week
- mean weekly EPO dose:  
2000 vs 5000 IU



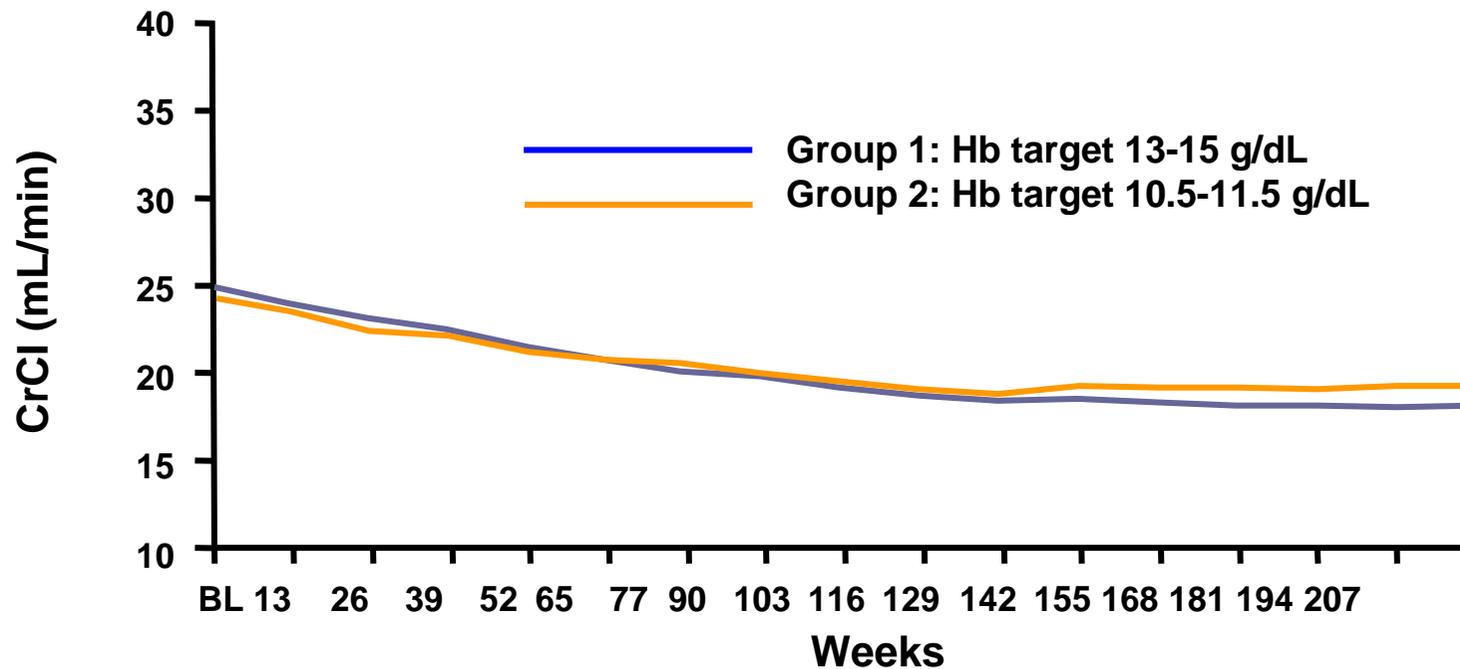
- no difference in CV events

No. 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

**Drüeke T B et al., N. Engl. J. Med., 2006;355:2071- 2084**

# CREATE trial

No significant impact on renal function with Hb correction to 13-15 g/dL



Drüeke TB et al., N. Engl. J. Med. 2006;355:2071-2084

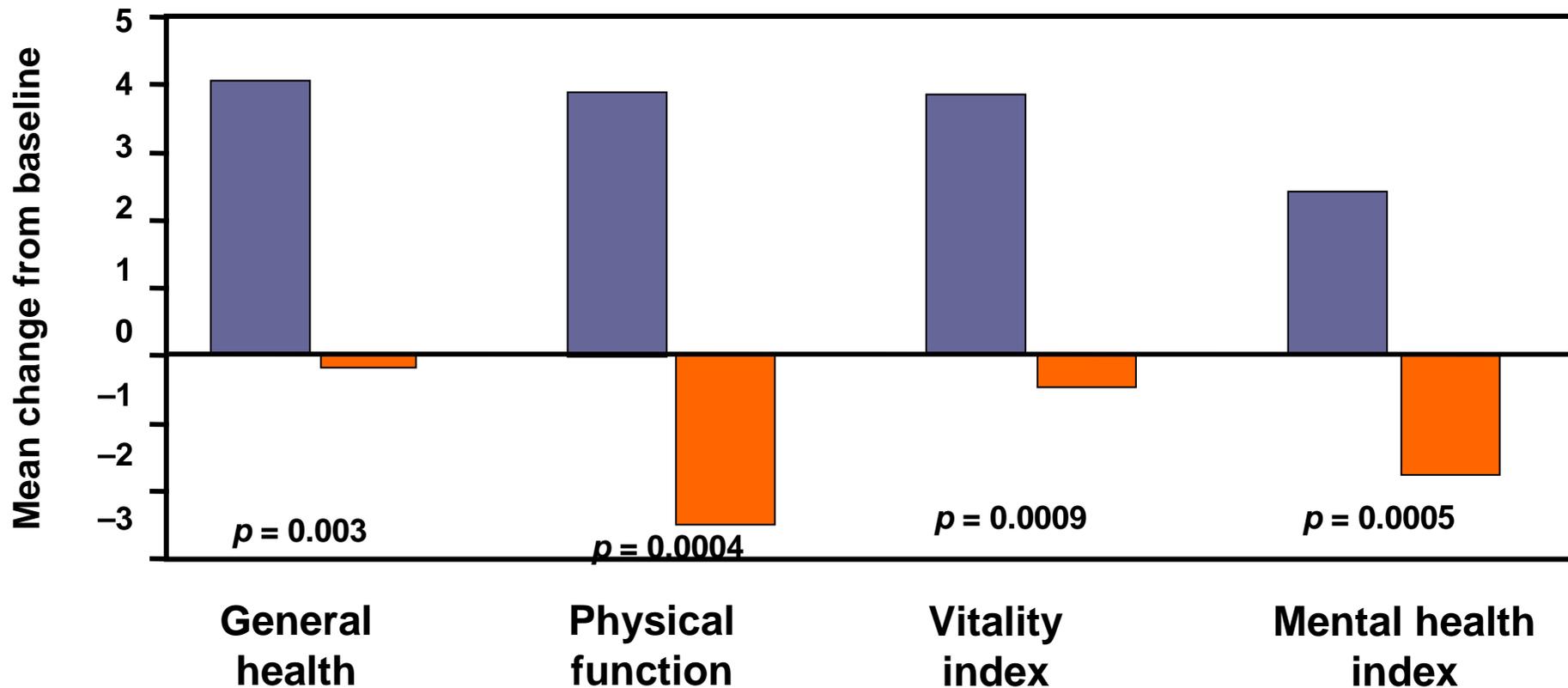
# CREATE trial

Significant QoL improvements with complete Hb correction

Target Hb

13.4 g/dL

11.5 g/dL



Drüeke TB et al., N. Engl. J. Med., 2006; 355: 2071-2084

## CREATE: Outcomes

- No differences in primary outcomes (CV events): 58 events (high Hb) vs 47 events (low Hb),  $p=0.2$
- No difference in LVMI change
- No difference in GFR and decline in GFR
- More patients started dialysis in high Hb group
- Improvement in QOL in high Hb group

A. Levin, *Nephrol. Dial. Transpl.*, 2007, 22, 309-312

## CREATE: Issues

- Primary outcomes:  
“Ultimately underpowered to demonstrate a difference between the groups” due to lower than expected event rate (6% vs 15%)
- New on dialysis:  
“This finding should not be over-interpreted”:
  - Non-protocolized nature of dialysis start
  - No difference in rate of decline of GFR or actual GFR at time of dialysis
  - Delayed dialysis start in lower Hb group due to open-label?

**A. Levin, Nephrol. Dial. Transpl., 2007, 22, 309-312**

## Interpretation of CREATE Results Limited by Inadequate Power

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

## CREATE: Conclusion

- “The CREATE study was ultimately underpowered to demonstrate a difference between the two groups, but did not describe harm to patients who were randomized to the higher Hb target arm.”

A. Levin, *Nephrol. Dial. Transpl.*, 2007, 22, 309-312

## 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\*

Patients: 1432, eGFR 15-50, Hb < 11

Design: sc Epoetin alfa High arm: target 13.5  
Low arm: target 11.3

Primary EP: composite of 4 CV events (time to first event)

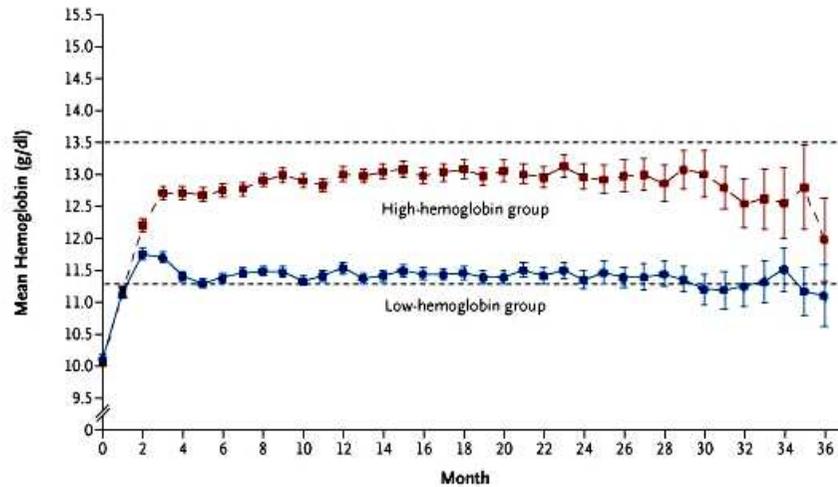
Secondary EP: change in QOL, RRT and others

Main results:

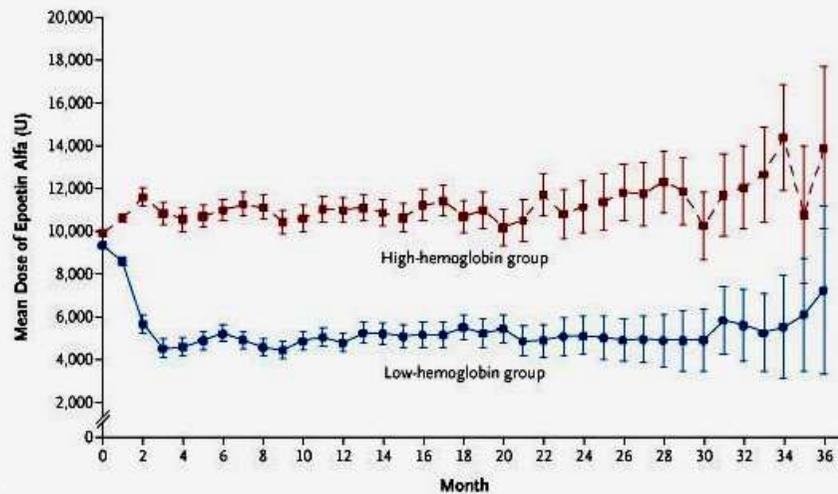
- study terminated early (futility, safety ?)
- more patients in the higher arm had at least one CV event
- no improvement in QOL
- trend towards a higher rate of progression to RRT

**Singh A K et al., N. Engl. J. Med., 2006;355:2085-98**

# CHOIR trial



No. of Patients	
High-hemoglobin	710 667 632 600 558 507 485 433 367 306 252 194 139 95 81 67 49 31 13
Low-hemoglobin	707 672 625 603 549 528 510 471 384 334 250 182 141 101 75 60 45 30 13



No. of Patients	
High-hemoglobin	709 693 659 623 578 530 500 452 370 310 258 189 132 97 79 65 52 27 11
Low-hemoglobin	707 691 655 621 577 549 526 479 393 333 262 189 141 95 73 54 43 27 12

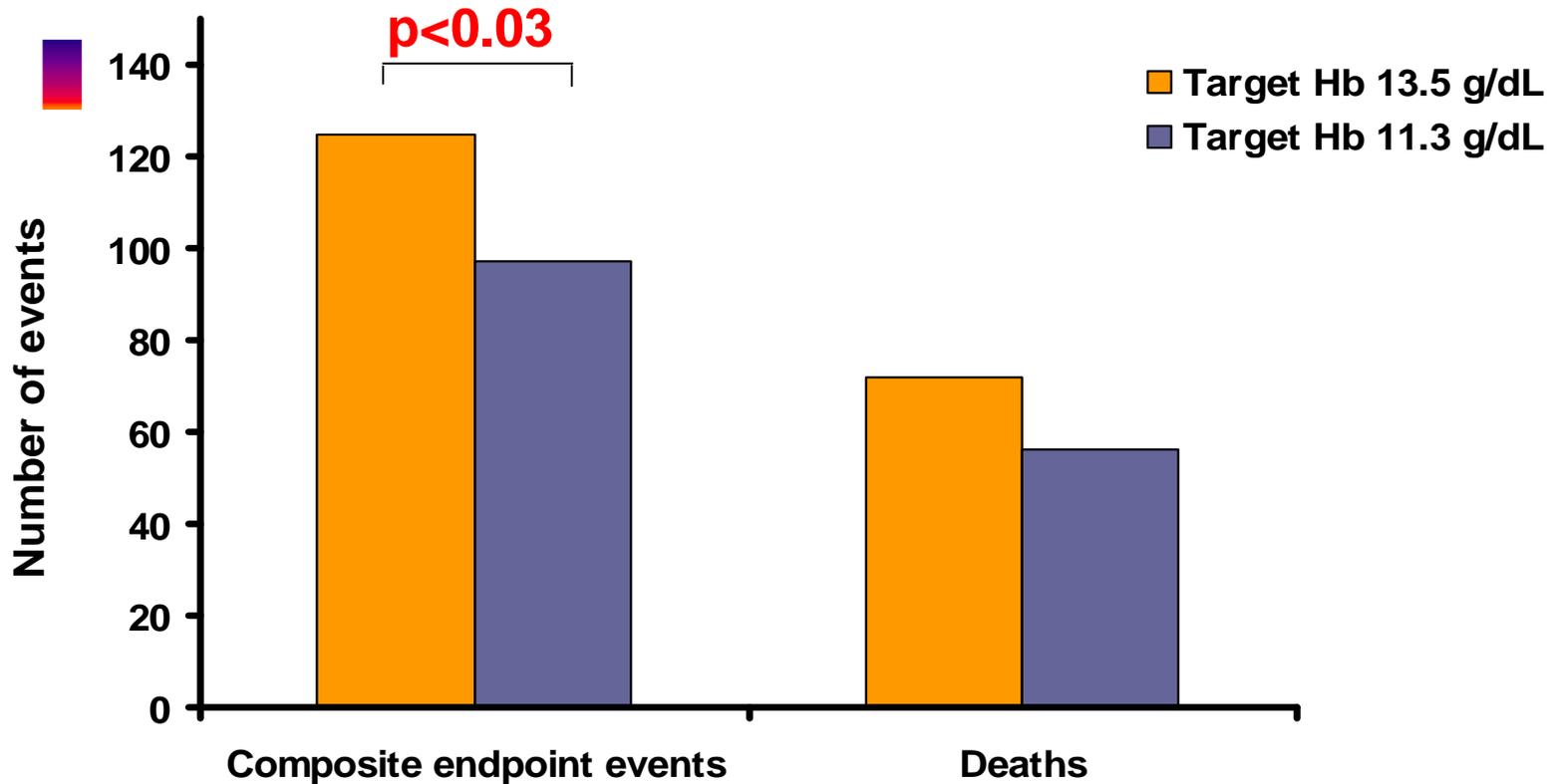
- Hb difference approx. 1.5 g/dl

- starting dose 10,000 IU/week  
 mean weekly EPO dose:  
 6,276 vs 11,215 IU

**Singh AK et al., N. Engl. J. Med., 2006; 355: 2085 - 2098**

# CHOIR: Increased Risk with Hb Correction to 13.5 g/dL in Non-Dialysis CKD Patients

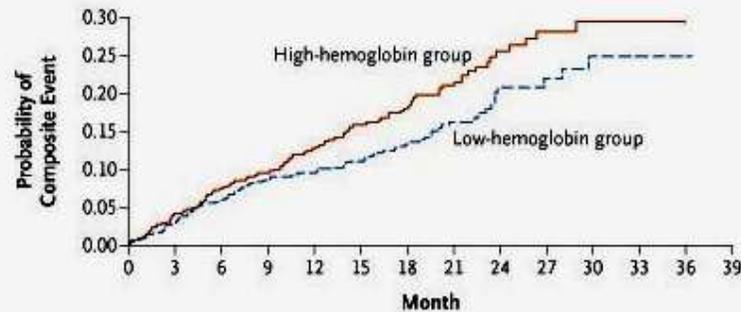
1,432 non-dialysis CKD patients from 130 US centres; comparing impact of Hb correction to 13.5 g/dL with correction to 11.3 g/dL on composite endpoint events (mortality, stroke, heart attack, hospitalisation) in patients on epoetin alfa therapy



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

# CHOIR trial

## A Primary Composite End Point

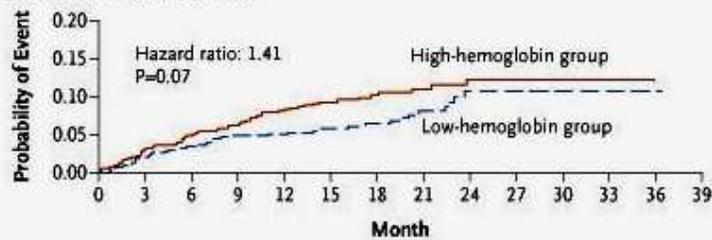


125 vs 97 events;  
 $p < 0.03$

### 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

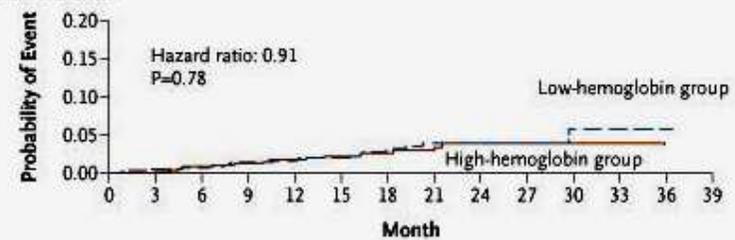
## B Hospitalization for CHF (without RRT)



### 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

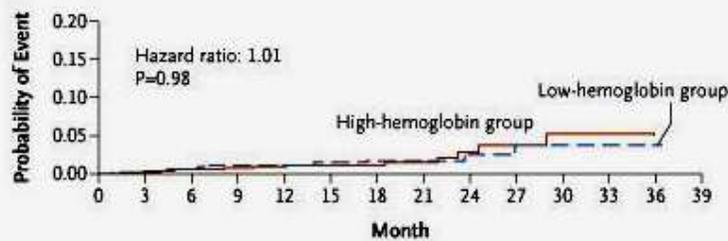
## C Myocardial Infarction



### 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

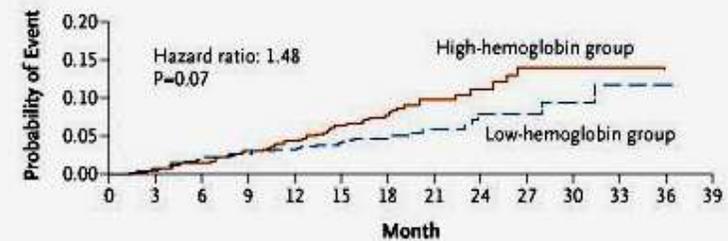
## D Stroke



### 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

## CHOIR: Outcomes

- Significant difference in primary end point (composite of death, MI, hospitalization for CHF, stroke):  
125 events (high Hb) vs 97 events (low Hb),  
 $p=0.03$
- No difference in QOL

A. Levin, *Nephrol. Dial. Transpl.*, 2007, 22, 309-312

## CHOIR: Conclusion

- “While the findings of CHOIR are indeed ‘true’, they may not be applicable to the population to whom the authors believe they should be applied; i.e. all patients with CKD”

A. Levin, *Nephrol. Dial. Transpl.*, 2007, 22, 309-312

## CHOIR: Issues

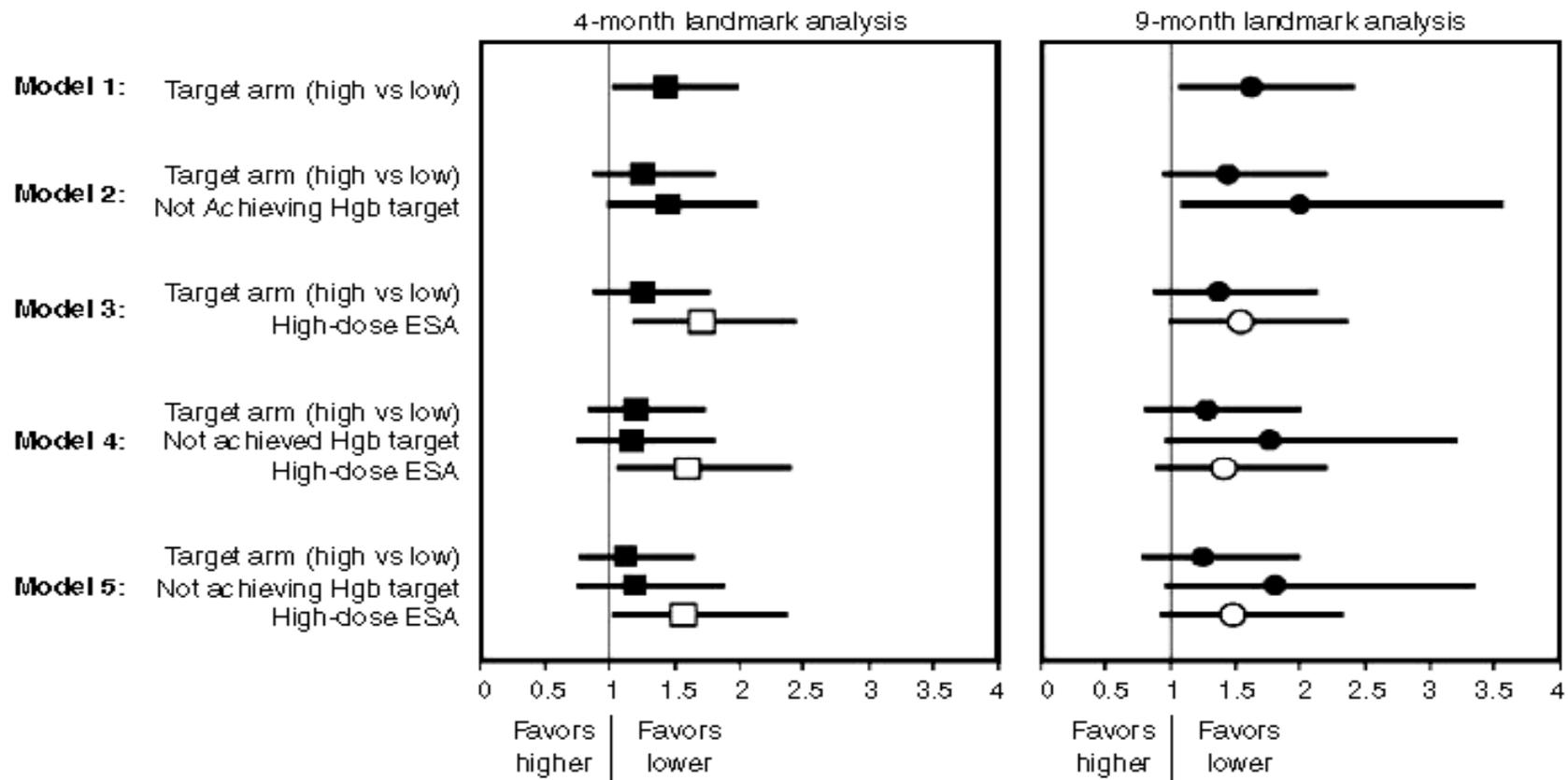
- Baseline imbalance (CABG and hypertension) may have impact on primary outcome measures
- "Of the original 1400 cohort, over half were lost"
- Against "recent trends in reporting RCTs", not all randomized patients were included in the analysis
- No demographic information regarding the 700 patients who completed the study
- Representation of the most unwell of all CKD patients and not representative of the majority? (<50% with iron use, 38% withdrawal rate, not able to reach target Hb values)
- "Lack of adherence to RCT convention" by stopping the trial not according to any usual stopping rule or suggestion of harm, but rather the suggestion of harm
- "Rigorous methodologists would suggest that p values of 0.03 are not significant when more than one analysis is planned"

Cox proportional hazards models for the primary composite endpoint of death, coronary heart failure hospitalization, stroke, or MI- CHOIR - Secondary analysis

Variable	Four-month landmark analysis N=1260		Nine-month landmark analysis N=1057	
	HR, 95% CI	P-value	HR, 95% CI	P-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>				
	N=1192		N=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

Szczech L., Kidney Int, advance online publication, 2 July 2008

Cox proportional hazards models for the primary composite endpoint of death, coronary heart failure hospitalization, stroke, or MI- CHOIR - Secondary analysis





## Definition of an inadequate response to epoetin treatment

An arbitrary definition of resistance to epoetin in either failure to attain the target Hb concentration while receiving more than 300 IU/kg/week (ca. 20000 IU/week) of epoetin subcutaneously or a continued need for such dosage to maintain the target

# Factors influencing anemia treatment and impacting EPO Dose in HD patients

## Factor

## Impact on EPO dose

- 
- ◆ Hemodialysis adequacy up to 100%
  - ◆ Hemodialysis quality / quantity up to 30%
  - ◆ Iron 20–70%
  - ◆ Inflammation 30–70%
  - ◆ Infection 30–70%

*Locatelli F et al., NDT 2004;19:121–132.*

*Hecking E, NDT 2004;19:100–107.*

*Richardson D, NDT 2002;17 Suppl 1:53–59.*

*Sitter T et al., NDT 2000;15:1207–1211.*

*Kato A et al., Nephron 2001;89(1):110–112.*

*Stenvinkel P, NDT 2002;17 Suppl 5:32–37.*

*Nitta K, Acta Haematol 2002;108:168–170.*



Secondary analysis of the CHOIR trial epoetin-a dose and achieved hemoglobin outcomes

- Our study demonstrates that patients achieving their target had better outcomes than those who did not; and among subjects who achieved their randomized target, no increased risk associated with the higher hemoglobin goal was detected



## The Optimal Hemoglobin in Dialysis Patients— A Critical Review

Ajay K. Singh\* and Steven Fishbane†

\*Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, and

†Division of Nephrology, Winthrop-University Hospital, Mineola, New York

The ideal study to define the hemoglobin target would be a large RCT with multiple treatment targets, perhaps hemoglobin levels of 9, 10, 11, 12, and 13 g/dl. Only such a study could fully elucidate the tradeoff of QoL benefit against risks at a meaningful spectrum of hemoglobin levels. However, very large sample sizes will be required in order to obtain adequate power. Lacking such a study, the current literature does not support an evidence-based guideline for specific upper or lower target hemoglobin levels.

**Singh A. and Fishbane S. *Seminars in Dialysis*. 2008;21(1):1-6**

# ACORD study: Methods

- Study design:
  - Randomized controlled trial
  - Target Hb: 13–15 g/dL (group 1) vs 10.5–11.5 g/dL (group 2)
- Inclusion criteria:
  - Diabetes mellitus type 1 or 2
  - Mild to moderate anemia
  - Chronic kidney disease stage 1 to 3
- Endpoints:
  - 1°: Change in left ventricular mass index (LVMI)
  - 2°: Echocardiographic variables, renal function, QOL, safety

**Ritz E. et al. Am. J. Kidney Dis., 2007; 49, 194-207**

## ACORD study: Results

- Hb: 13.5 g/dL (**group 1**) vs 12.1 g/dL (**group 2**),  $p < 0.001$
- LVMI: 112.3 g/m<sup>2</sup> vs 116.5 g/m<sup>2</sup>, ns
- Change in LVMI: greater numerical decrease in group 1, ns
- Change in CrCl: -5.5 mL/min vs -3.4 mL/min, ns
- Change in QOL (SF36): +5.33 vs -0.033,  $p = 0.04$
- Safety: No relevant differences

**Ritz E. et al. Am. J. Kidney Dis., 2007; 49, 194-207**

# ACORD study: Results

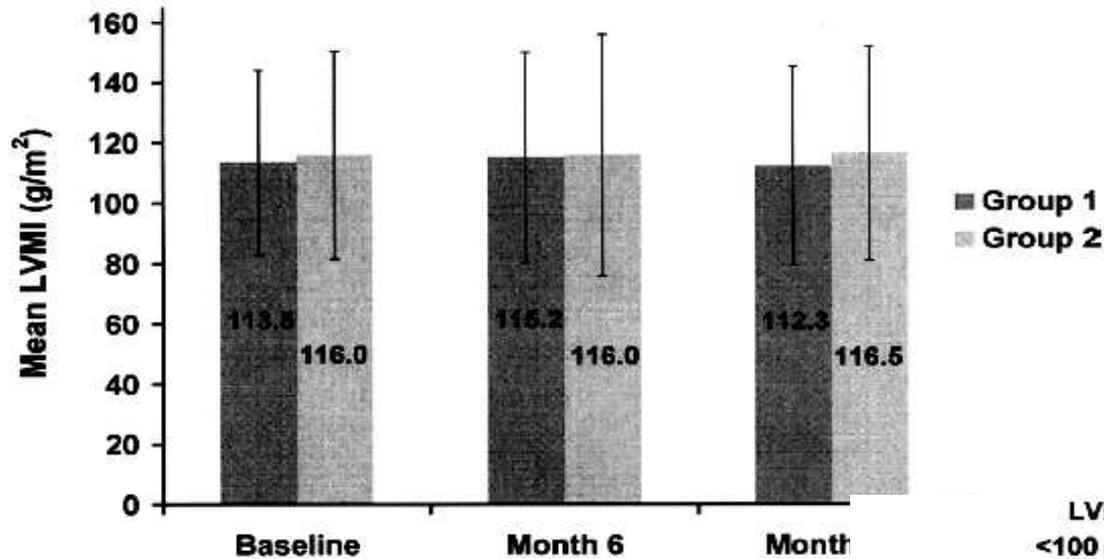


Figure 4. LVMI (mean ± SD) by treatment group.

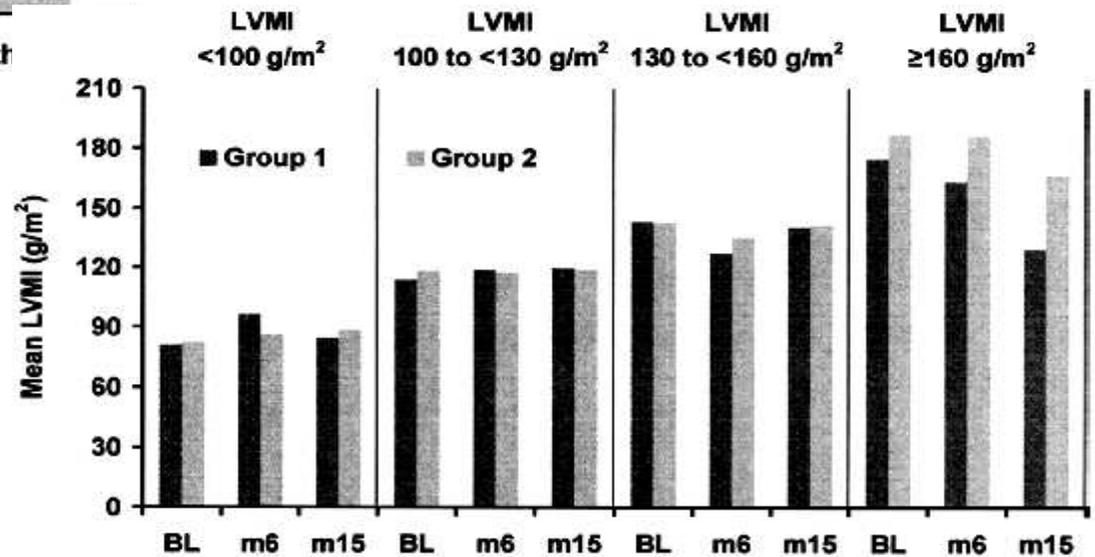


Figure 5. LVMI (mean ± SD) over time by degree of LVH at baseline. Abbreviation: BL, baseline.

## ACORD study: Conclusion

- Correction to an Hb target level of 13 to 15 g/dL does not decrease LVMI
- Normalization of Hb level prevented an additional increase in LVH, was safe and improved QOL

Ritz E. et al. Am. J. Kidney Dis., 2007; 49, 194-207

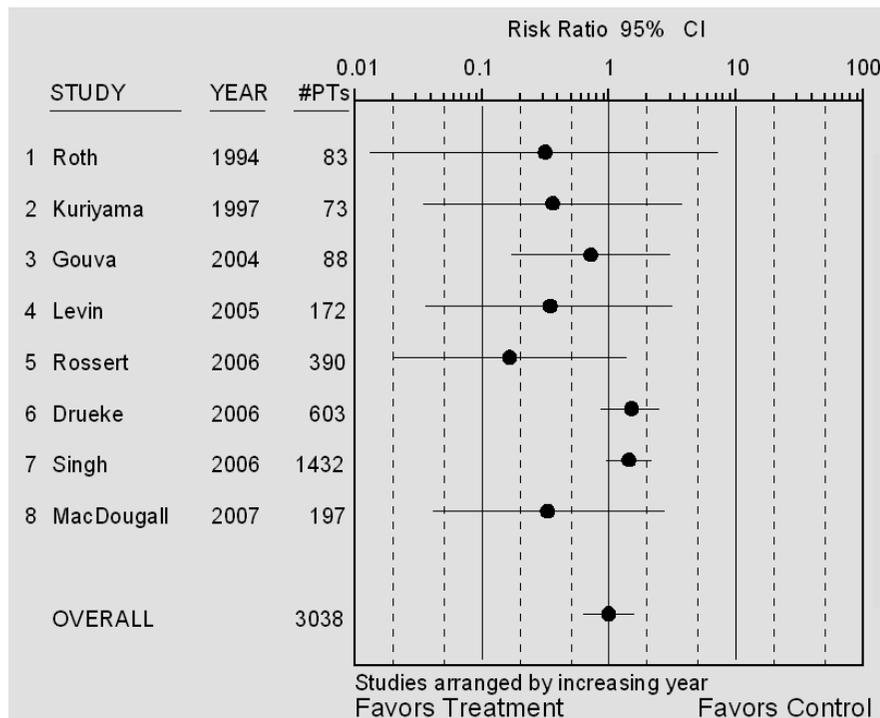
# Meta-analysis

## Non-dialysis CKD patients

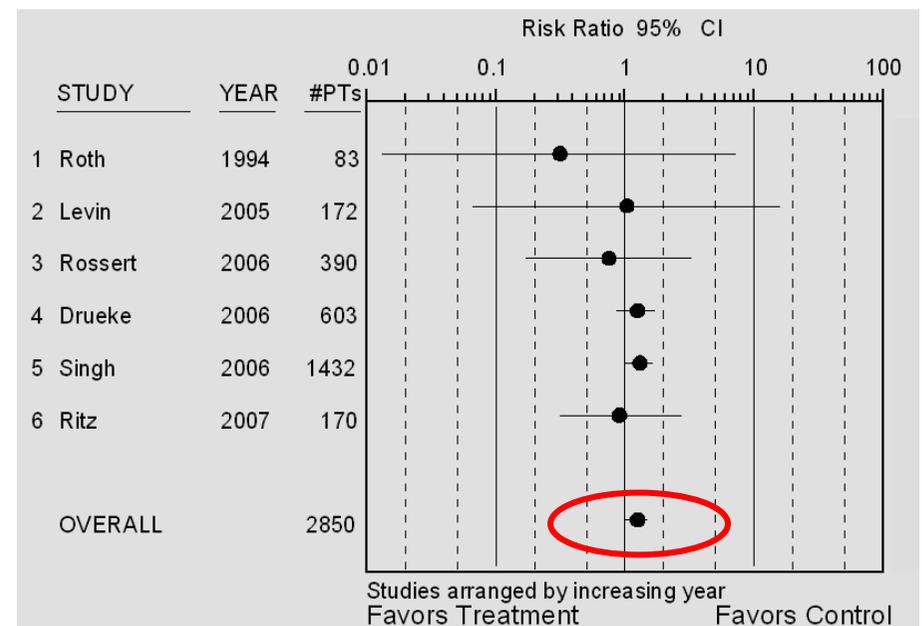
rel. mortality risk

rel. risk of adverse CV events

*for assignment to higher Hb target*



$Z = 0.04; 2p = 0.97$



$Z = 2.19; 2p = 0.029$

Adapted and from NKF-K/DOQI "Target Hb" 2007 update

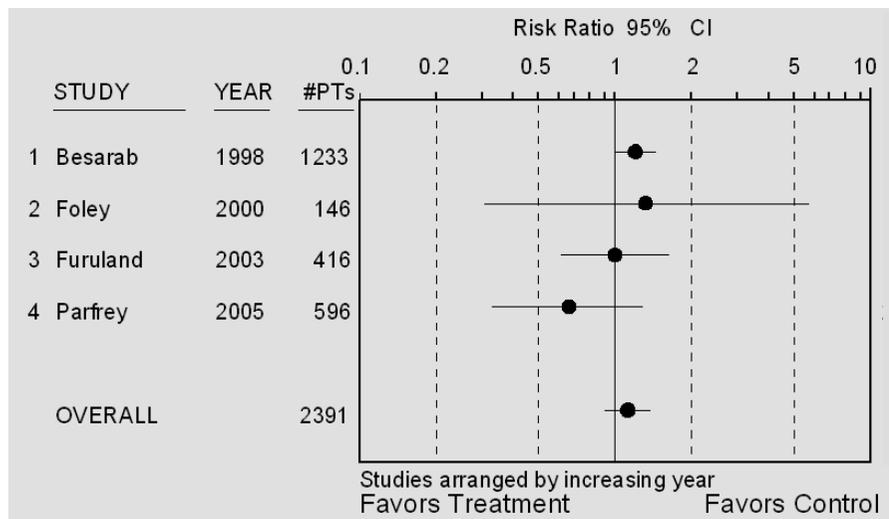
# Meta-analysis

## Dialysis CKD patients

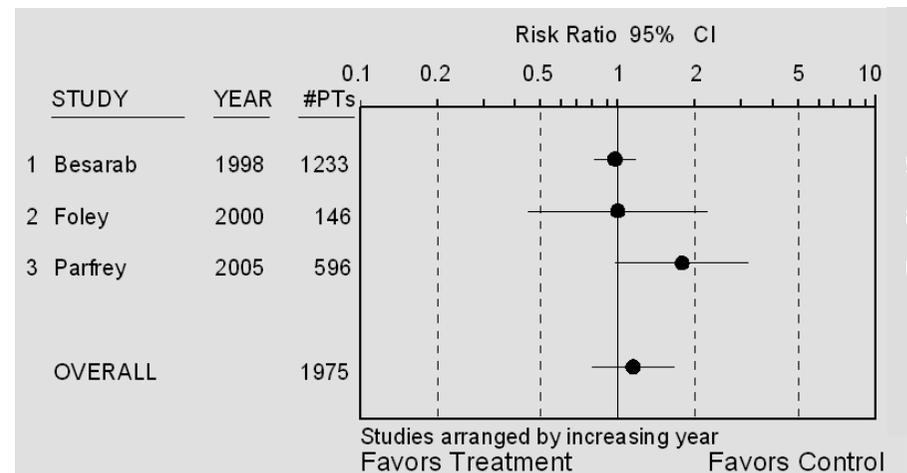
rel. mortality risk

rel. risk of adverse CV events

*for assignment to higher Hb target*



$Z = 1.04; 2p = 0.30$

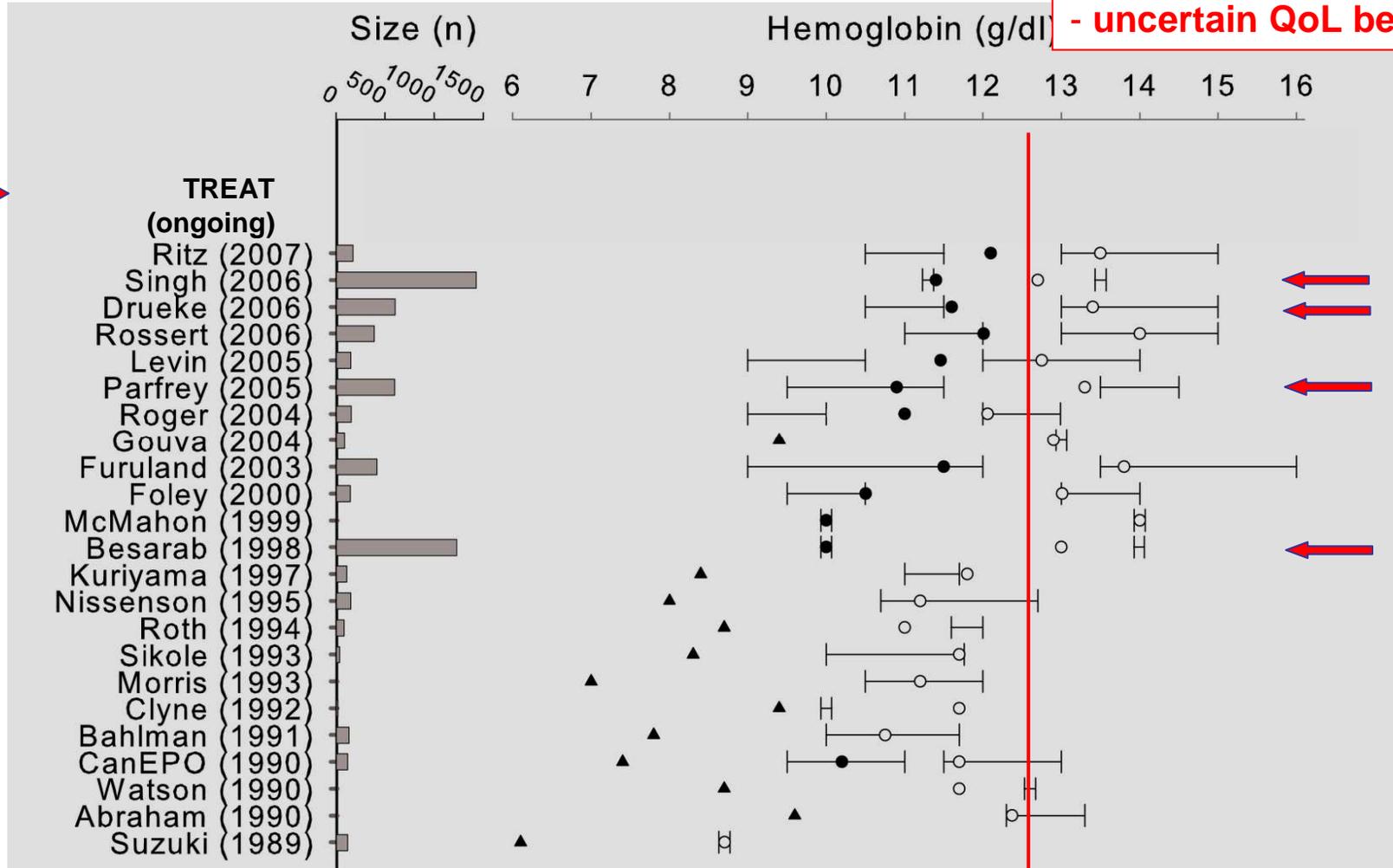


$Z = 0.69; 2p = 0.49$

**Adapted and from NKF-K/DOQI "Target Hb" 2007 update**

# What is the optimal target Hb ?

**Target > 13 g/dl:**  
 - risk for harm  
 - uncertain QoL benefit



▲ Placebo/control mean Hb  
 ● Lower Hb arm: mean achieved Hb  
 ○ Higher Hb arm: mean achieved Hb  
 } Target range

Adapted and updated from NKF-K/DOQI. *AJKD* 2006; 47 (5 Suppl 3)

# Clinical practice guidelines for anemia in chronic kidney disease: problems and solutions. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO)

Francesco Locatelli<sup>1</sup>, Allen R. Nissenson<sup>2</sup>, Brendan J. Barrett<sup>3</sup>, Rowan G. Walker<sup>4</sup>, David C. Wheeler<sup>5</sup>, Kai U. Eckardt<sup>6</sup>, Norbert H. Lameire<sup>7</sup> and Garabed Eknoyan<sup>8</sup>

The current evidence, based on mortality data, for hemoglobin target levels intentionally aimed with ESA treatment in CKD patients treated indicates that: **(1)**

- levels of >13 g per 100 ml can be associated with harm
- levels of 9.5–11.5 g per 100 ml are associated with better outcomes compared with >13 g per 100 ml
- for levels between 11.5 and 13 g per 100 ml, there is no evidence at this time for harm or benefit compared with higher or lower levels.

**Locatelli F et al. Kidney Int advance online publication, 2 July 2008**



**(2)**

**□ The relationship of the dose of ESA used and outcomes has not been examined adequately. Associations between the need for higher doses of ESA and poor outcomes could be surrogates for underlying comorbidities or toxicity.**

**□ Outcome studies of ESAs have heretofore based their interventional strategies on hemoglobin levels only, wherein the levels of hemoglobin achieved is equated with efficacy. There is a need to broaden the primary end points of clinical trials. Studies examining a given dose of ESA, as opposed to, or in combination with, that of an achieved hemoglobin target, are needed to evaluate resistance, nonresponsiveness, and ESA toxicity.**

**Locatelli F et al. *Kidney Int* advance online publication, 2 July 2008**



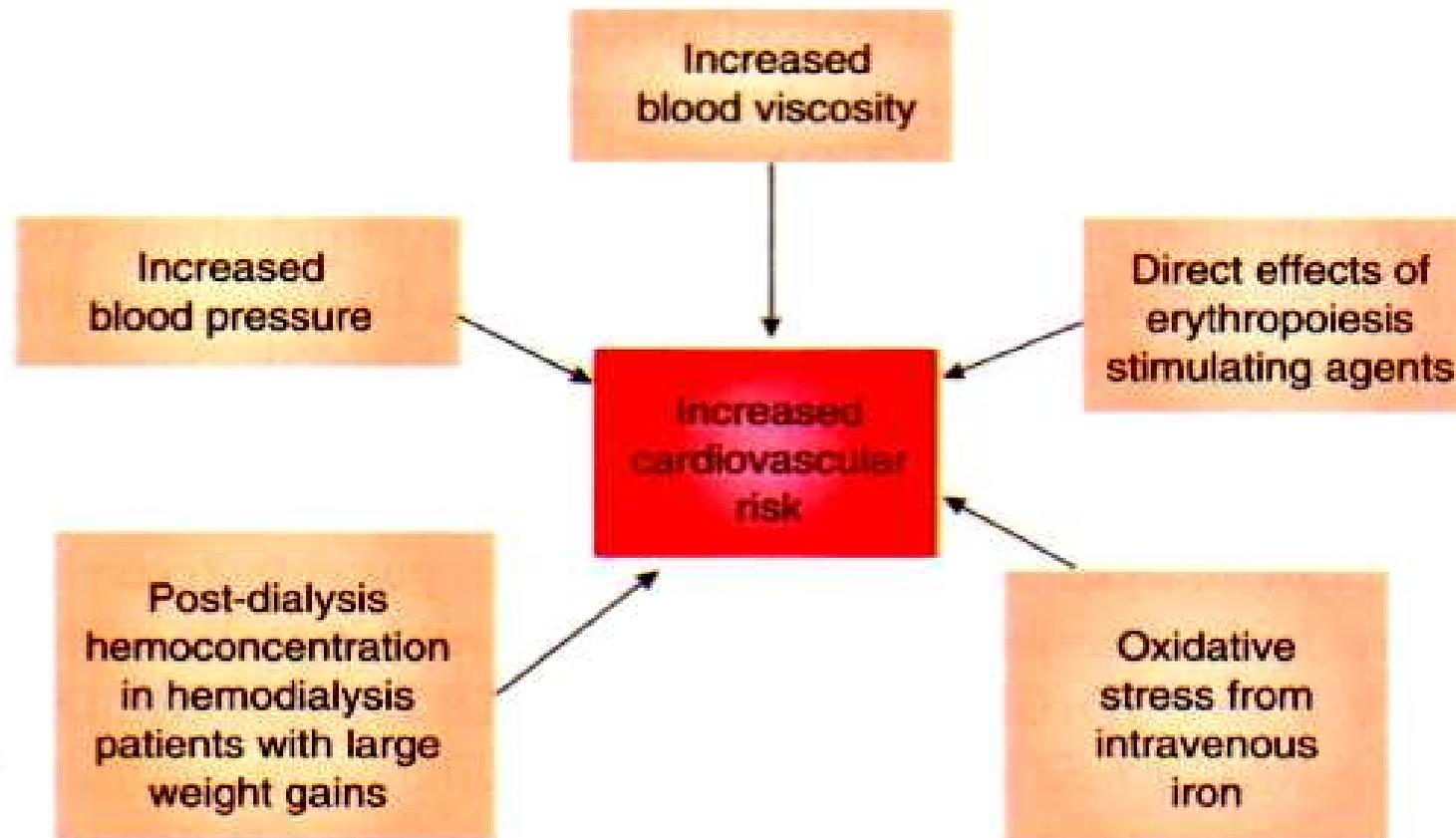
**(3)**

**The mechanisms of resistance to anemia correction remain poorly defined. A consistent definition of ESA resistance is crucial for future research**

**Based on anticipated results from key on-going studies, it is reasonable to plan for a start-up date no earlier than 2009, with an anticipated completion date of 2011.**

**Locatelli F et al. Kidney Int advance online publication, 2 July 2008**

## Potential mechanisms of increased cardiovascular risk with targeting of higher Hb levels with ESAs



Fishbane S and Nissenson AR., *Kidney Int.* 2007; 49: 806-813

# Ongoing Aranesp Studies Evaluating Hb Targets and Outcome

Study	Population	Target Hb	Planned patient number	Design	Aranesp Dose
TREAT <sup>42</sup> Amgen Global	<ul style="list-style-type: none"> <li>• CKD pts not yet on dialysis</li> <li>• Diabetes</li> </ul>	<ul style="list-style-type: none"> <li>• Aranesp: 13 g/dL</li> <li>• Placebo: rescue if Hb &lt; 9.0 g/dL</li> </ul>	4000	RCT, double-blind, placebo-controlled	0.75 mcg/kg/Q2W Double dose when stable and go to QM
RED-HF Trial <sup>43</sup> Amgen Global	<ul style="list-style-type: none"> <li>• HF (NYHA II to IV)</li> <li>• LVEF ≤ 35%</li> <li>• Hb 9 – 12 g/dL</li> </ul>	<ul style="list-style-type: none"> <li>• Aranesp: 13 g/dL, not to exceed 14.5 g/dL</li> </ul>	3400	RCT, double-blind, placebo-controlled	0.75 mcg/kg/Q2W Double dose when stable and go to QM

# TREAT in the context of CHOIR and CREATE studies

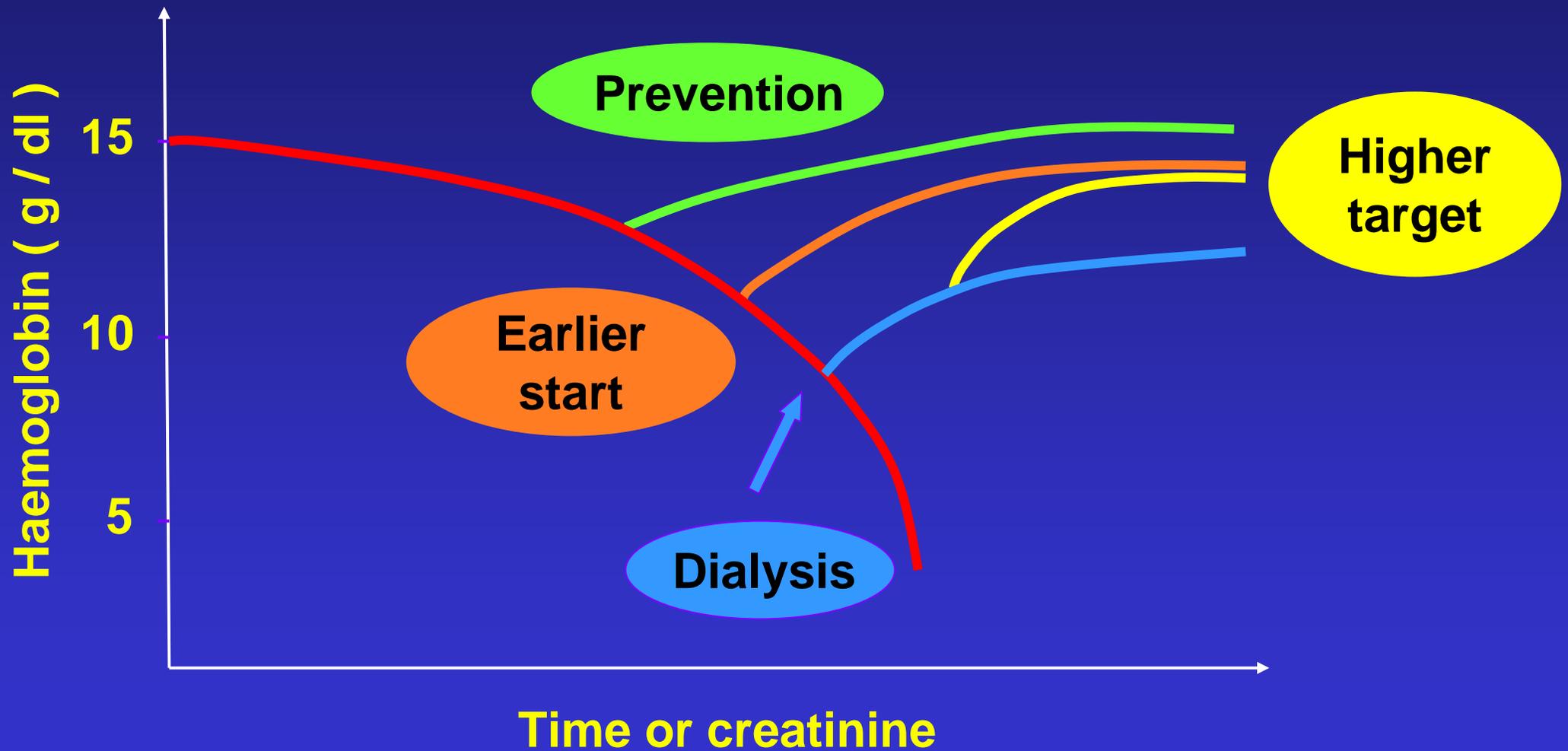
		CREATE <sup>1</sup> (N = 603)	CHOIR <sup>2</sup> (N = 1432)	TREAT (N = 4000)
Design		Randomized, <b>open-label</b>	Randomized, <b>open-label</b>	Randomized, double-blind, placebo controlled
Sponsor / Agent		Roche / NeoRecormon <sup>®</sup> (epoetin beta)	J&J / Procrit <sup>®</sup> (epoetin alfa)	Amgen / Aranesp <sup>®</sup> (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

## TREAT in context of CREATE and CHOIR studies

- Placebo-controlled double-blind study
- Event driven
- 4000 participants (vs. 605 CREATE, 1432 CHOIR)
- Type 2 diabetes with nephropathy
- TREAT has already enrolled and had more CV endpoints than CHOIR
- Data Safety and Monitoring Committee recommends continuation of TREAT

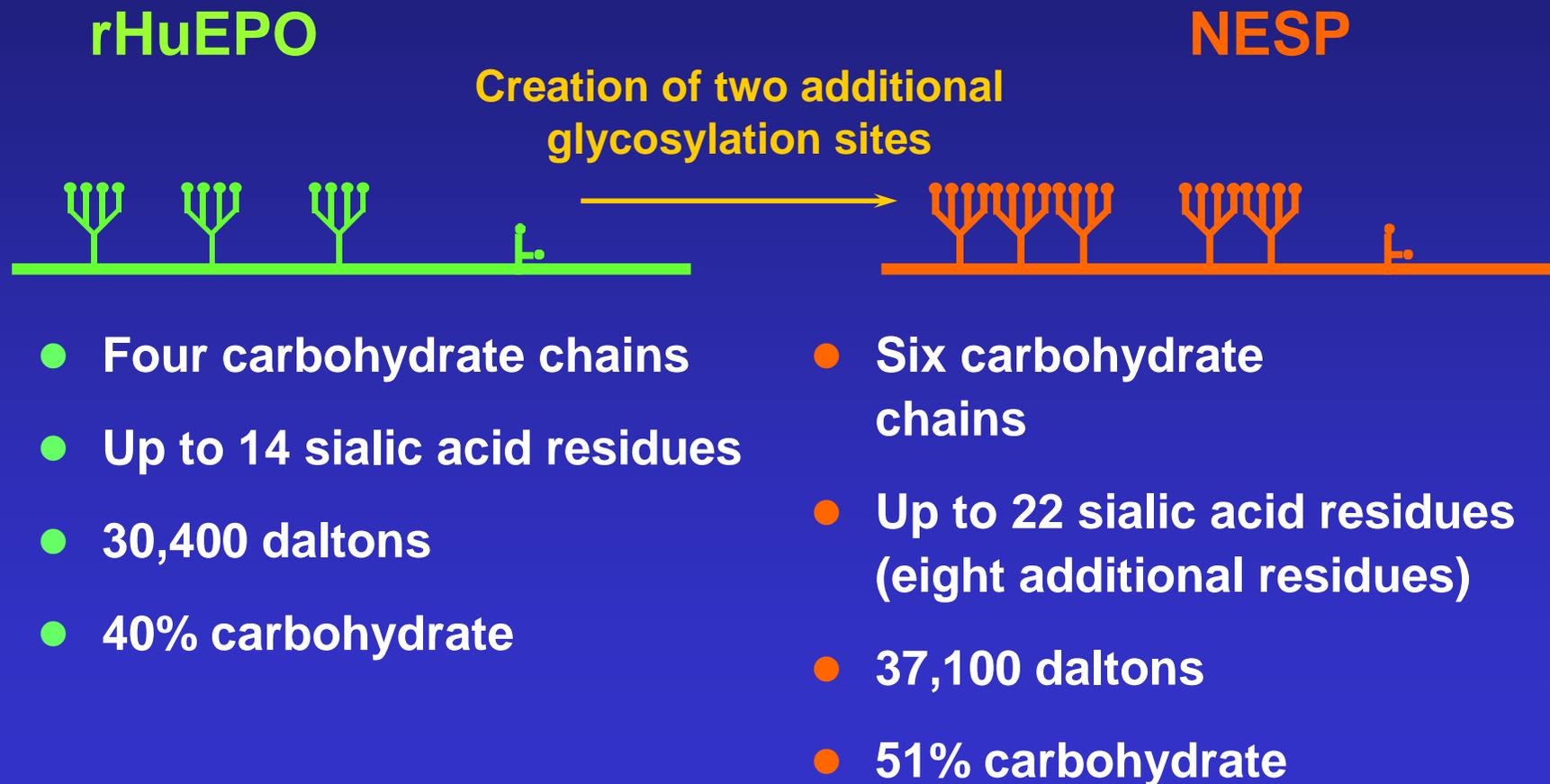
# Strategies for treating renal anemia



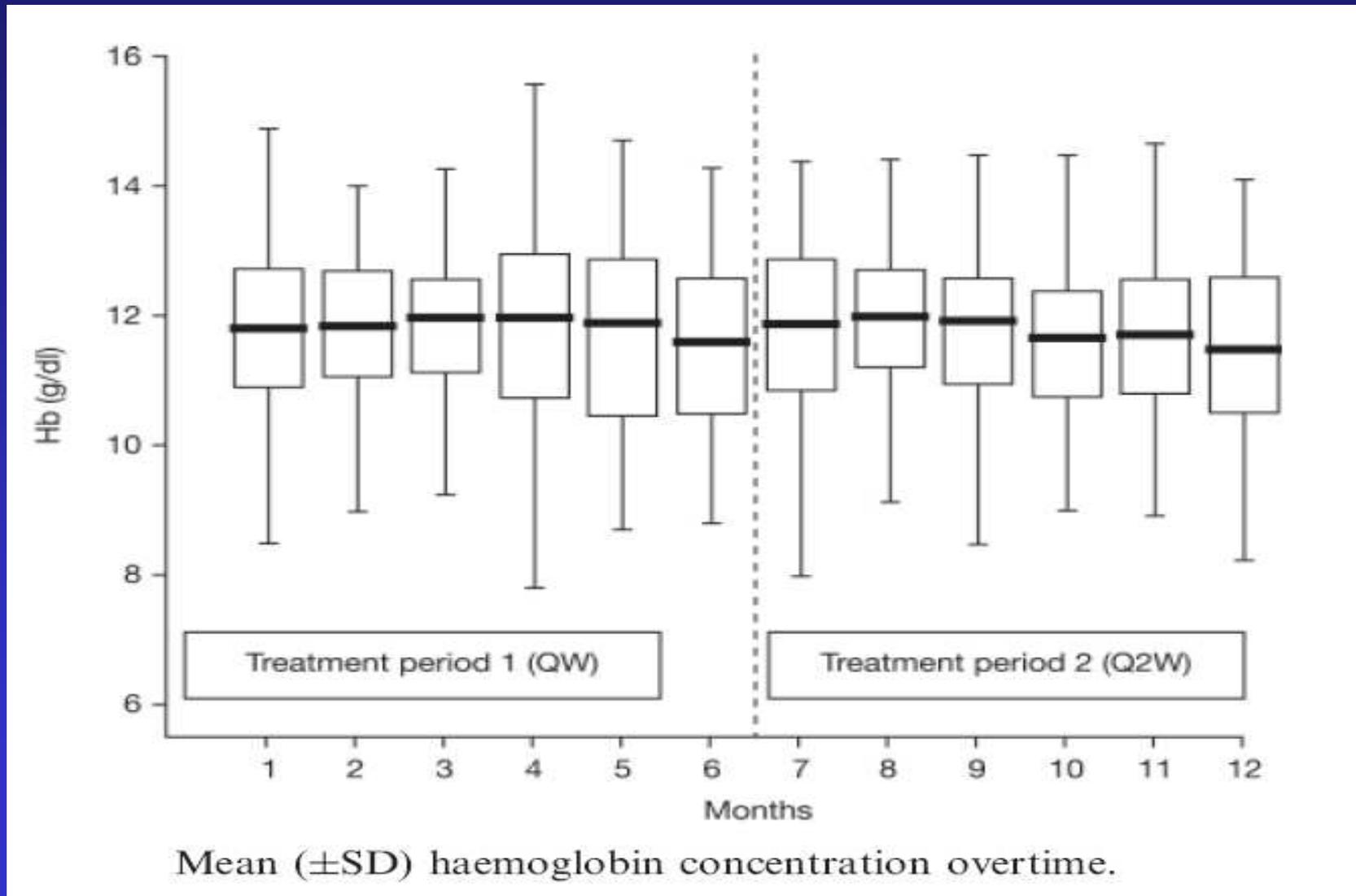
# **New options and the future of anaemia management in uraemic patients**

- **Polyglycated erythropoietins**
- **NESP (Novel Erythropoiesis Stimulating Peptides)**
- **CERA (Continuous Erythropoietin Receptor Activator)**
- **EPO-mimetics**
- **Inhibitors of prolyl hydroxylase (participating in HIF degradation) – FG-2216**
- **Gene therapy**

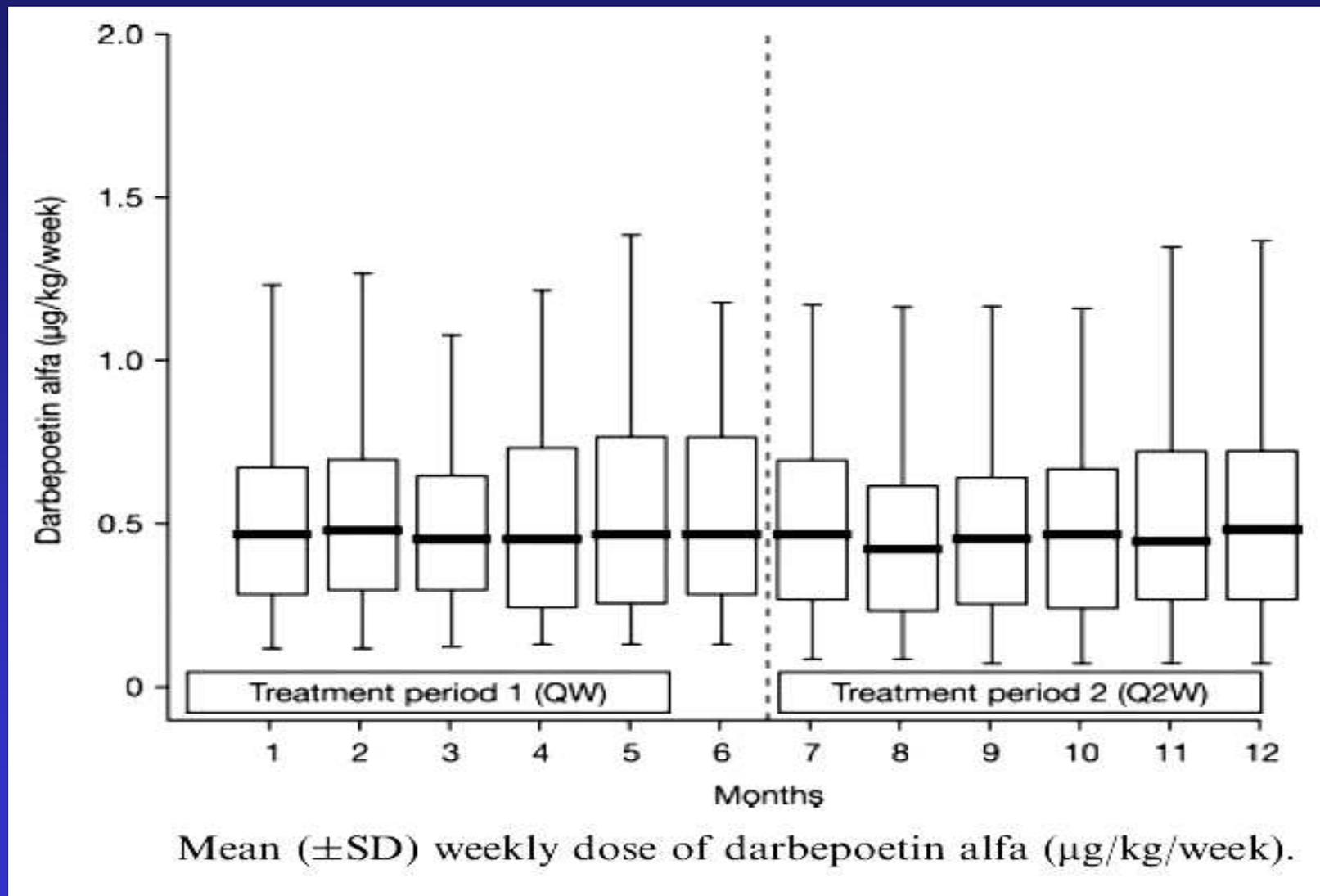
# Comparison of rHuEPO and NESP



# The efficacy of intravenous darbepoetin alfa administered once every 2 weeks in chronic kidney disease patients on haemodialysis



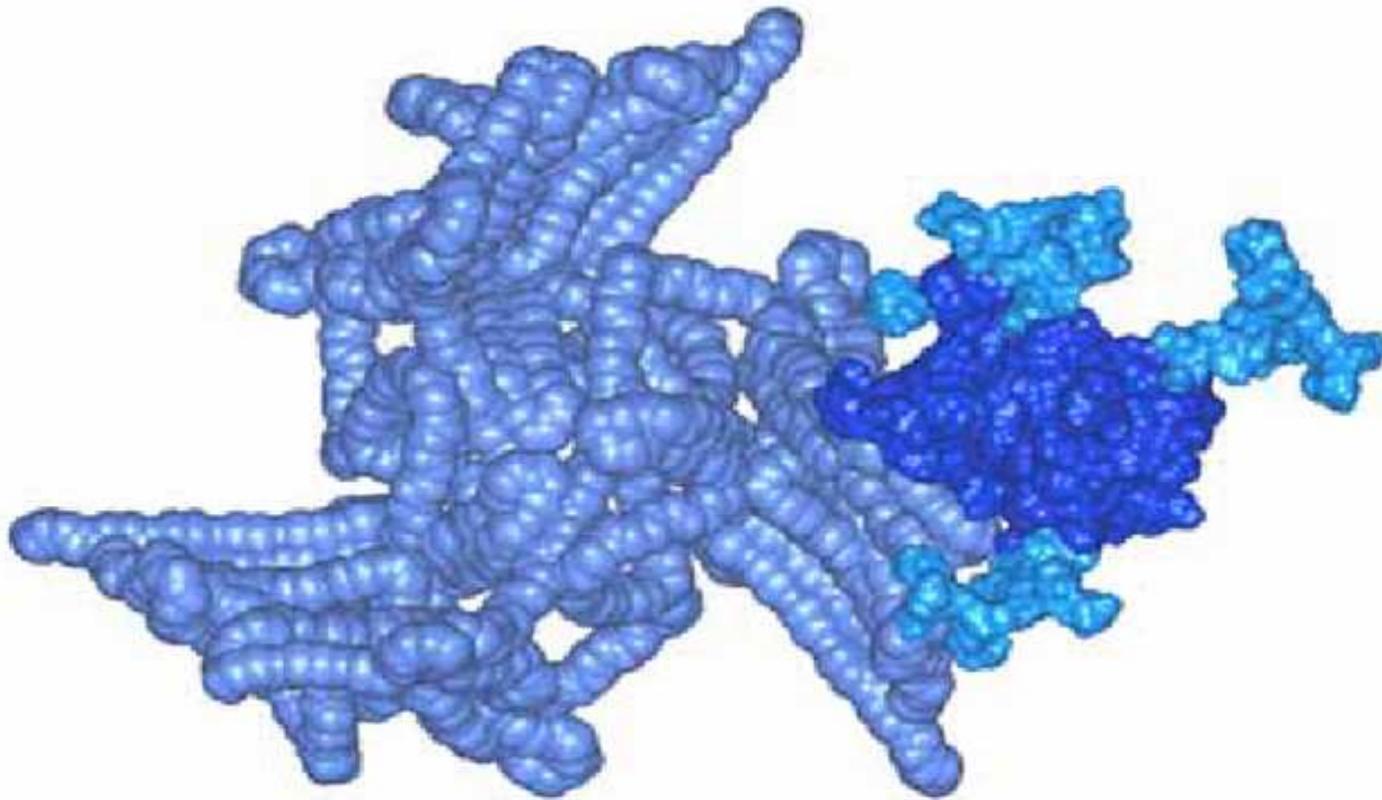
# The efficacy of intravenous darbepoetin alfa administered once every 2 weeks in chronic kidney disease patients on haemodialysis



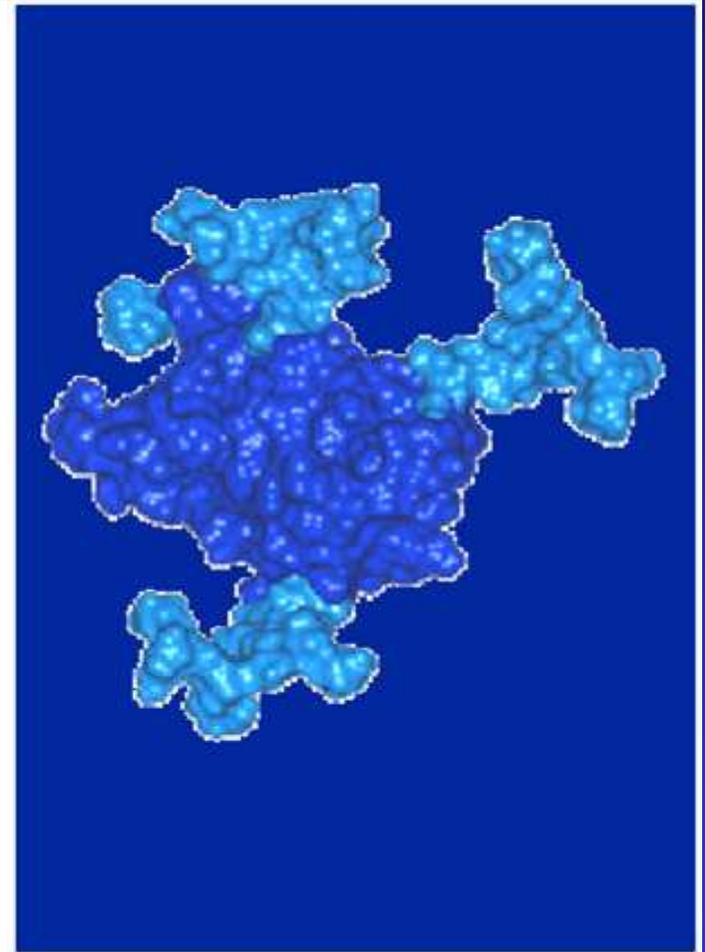
**CERA**

*Continuous Erythropoietin Receptor Activator*

# Comparison of EPO with CERA



**CERA**

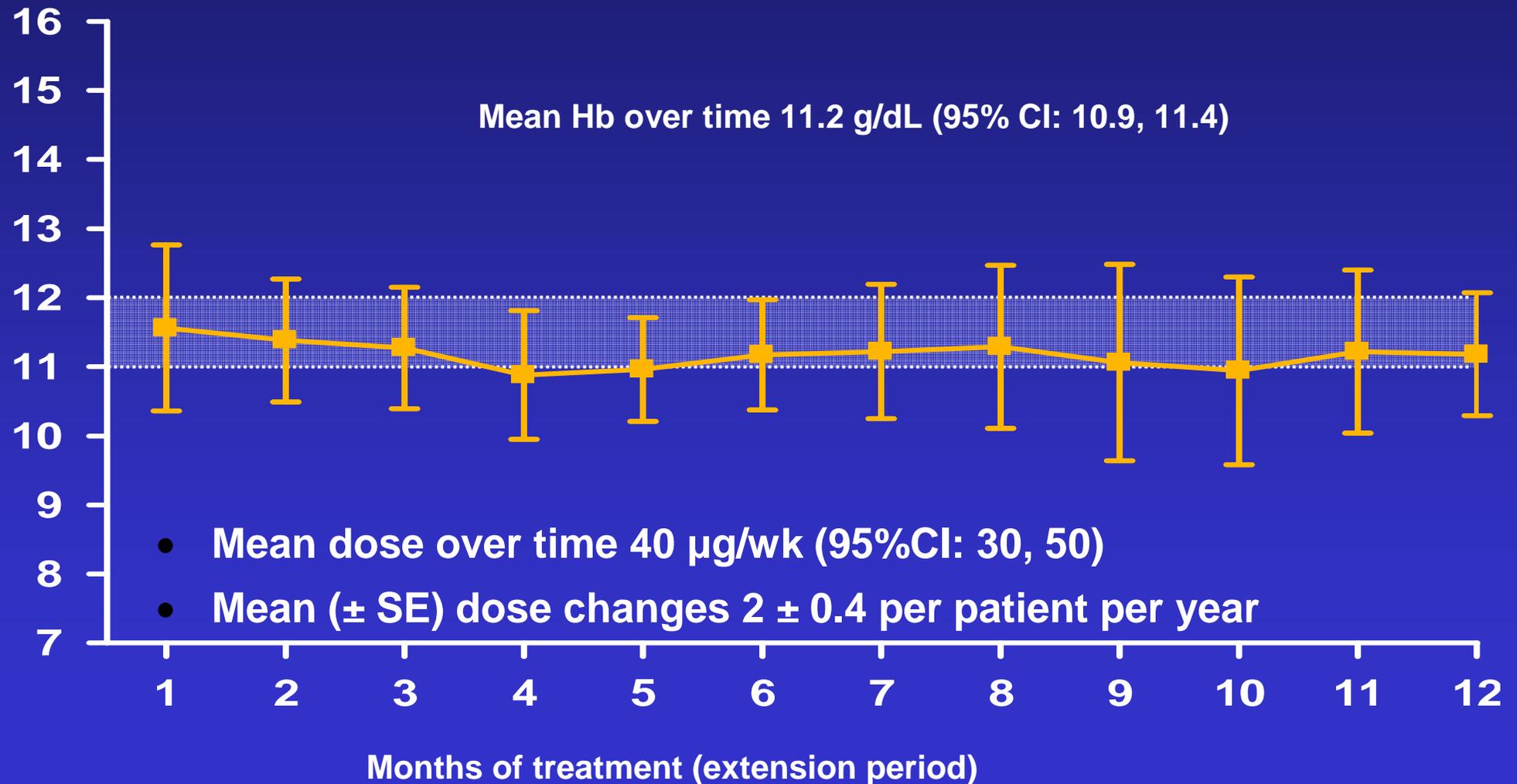


**EPO**

# CERA: Stable Activity Over Time

1x/4wk SC schedule, extension period, n=27  
(Safety population)

Hb (mean  $\pm$  SD, g/dL)

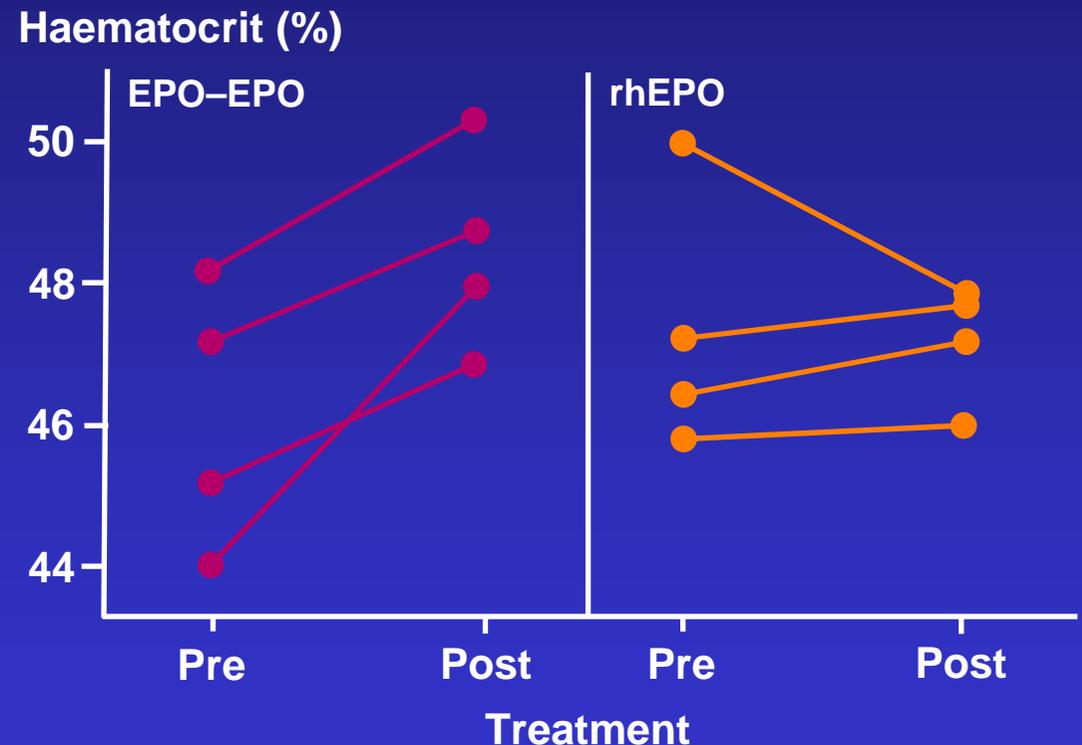


# Fusion proteins

## EPO–EPO fusion protein (EPO dimer, 17 amino acid linker)

- **3 x higher specific activity *in vitro* than rhEPO**
- **Greater haematopoietic activity in mice than rhEPO**
- **Remains in plasma longer than rhEPO**

*In vivo* efficacy of equal doses of EPO–EPO compared with rhEPO (300 IU/kg in mice)

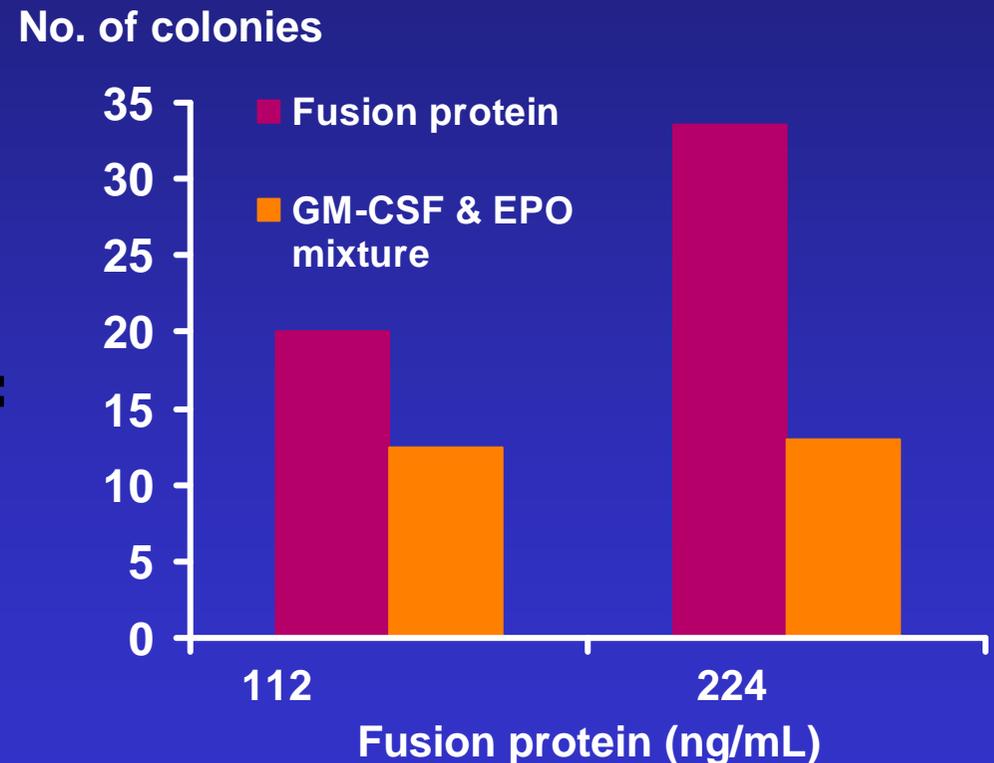


# Fusion proteins

## GM-CSF–EPO fusion protein

- **Burst forming unit-E requires at least one other factor (IL-3, IL-4, GM-CSF or *kit* ligand) + EPO**
- **GM-CSF upmodulates EPO receptors on progenitors: increases sensitivity to EPO**
- **Hybrid protein more efficient at inducing erythroid differentiation than mixture of GM-CSF and EPO**

Stimulation of BFU-E + CFU-GM colonies by fusion protein and equimolar mixture of GM-CSF and EPO



Coscarella et al 1997 (Menarini Ricerche SpA)

*Mary Ann Liebert,*

**Delivery of an erythropoietin-Fc fusion protein by inhalation in humans through an immunoglobulin transport pathway.**

[Dumont JA](#), [Bitonti AJ](#), [Clark D](#), [Evans S](#), [Pickford M](#), [Newman SP](#).

A novel drug delivery platform has been developed that utilizes a naturally occurring receptor known as the neonatal Fc receptor (FcRn). The receptor is specific for the Fc fragment of IgG and is expressed in epithelial cells where it functions to transport immunoglobulins across these cell barriers. It has been shown that FcRn is expressed in both the upper and central airways in non-human primates as well as in humans.

*Mary Ann Liebert,*

**Delivery of an erythropoietin-Fc fusion protein by inhalation in humans through an immunoglobulin transport pathway.**

[Dumont JA](#), [Bitonti AJ](#), [Clark D](#), [Evans S](#), [Pickford M](#), [Newman SP](#).

Pulmonary delivery of an erythropoietin- Fc fusion molecule (EpoFc) was previously demonstrated in non-human primates using this FcRn pathway. We have now conducted a phase I clinical study to test whether the FcRn pathway functioned similarly in man using human erythropoietin (Epo) fused to the Fc portion of human IgG1. The design was a three leg, non-randomized study conducted in healthy male volunteers with rising doses (3, 10, and 30 microg/kg) of the fusion protein targeted to the central lung regions. Using a target range of 10-30% vital capacity and 15 breaths per minute, approximately 70% of the lung-deposited dose of aerosolized EpoFc was delivered safely and effectively to the central lung regions.

*Mary Ann Liebert,*

**Delivery of an erythropoietin-Fc fusion protein by inhalation in humans through an immunoglobulin transport pathway.**

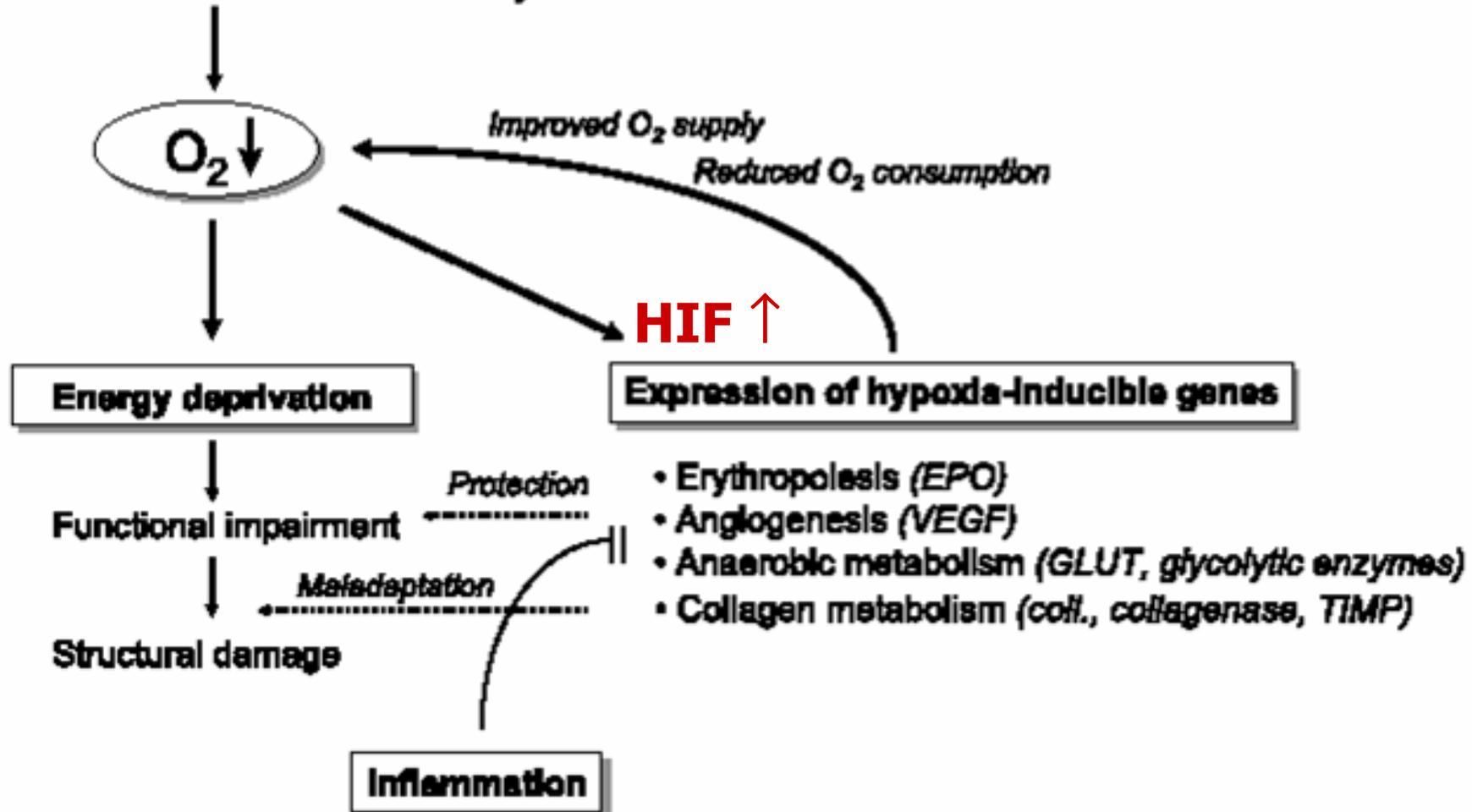
[Dumont JA](#), [Bitonti AJ](#), [Clark D](#), [Evans S](#), [Pickford M](#), [Newman SP](#).

## CONCLUSIONS

We showed dose-dependent concentrations of the fusion protein in the serum and an increase in circulating reticulocytes was evident in the highest dose group, thus demonstrating that large therapeutic molecules can be delivered to humans via the lung, with retention of biological activity, using the FcRn-mediated transport pathway

# Anemia

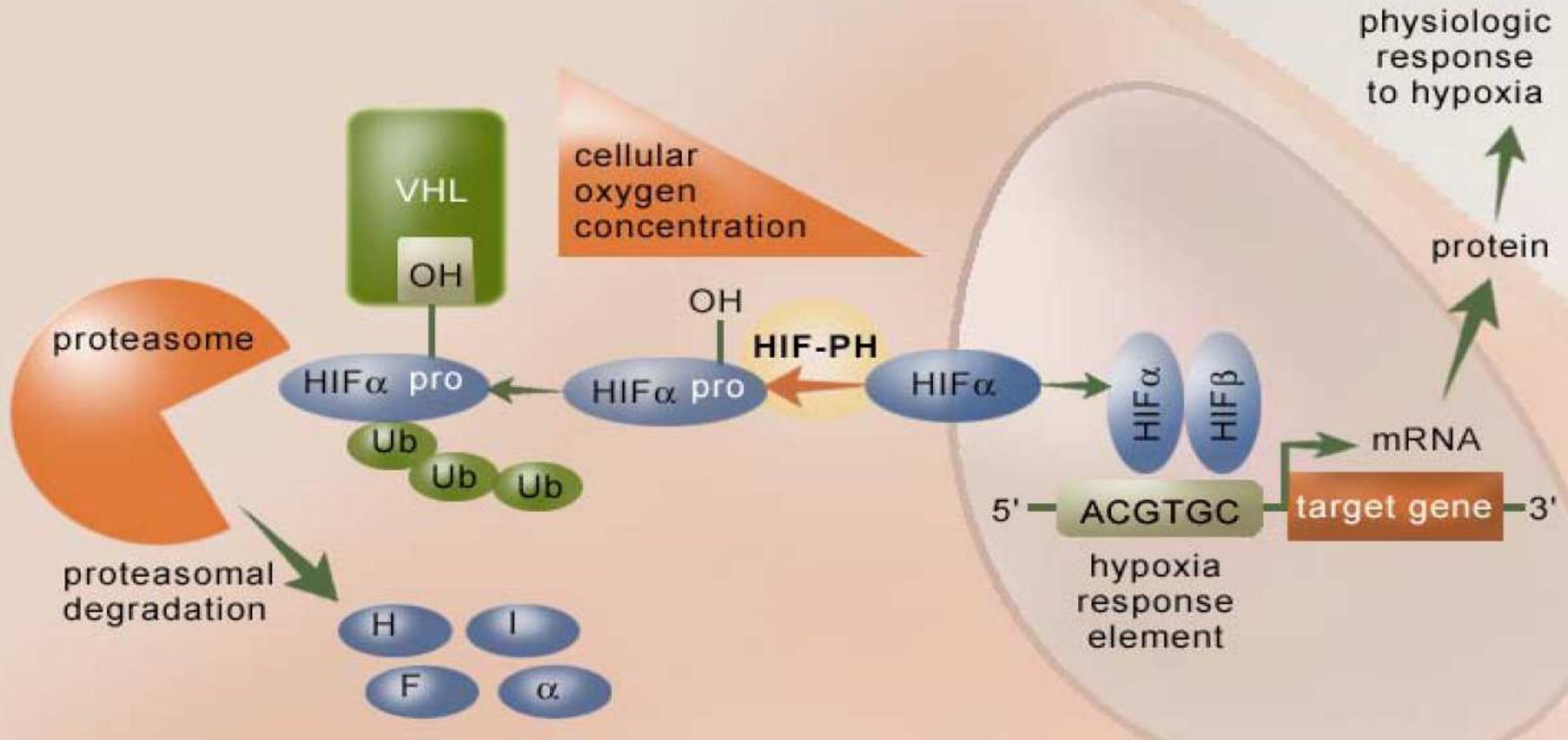
Vascular occlusion  
Vasoconstriction  
Reduced microvascular density



# Hypoxia-inducible Factor (HIF)

- **Regulates body's protective responses to low oxygen tension**
  - e.g., erythropoiesis in response to anemia
- **Transcription factor necessary for expression of erythropoietin (EPO)**
  - Several HIF isoforms with tissue-specific distributions and different target genes
- **Function and stability regulated by unique post-translational modification involving hydroxylation of proline amino acid residues**
  - Mediated by enzyme family of specific HIF-prolyl hydroxylases (HIF-PH)
- **Pharmacological inhibition of HIF-PH activates HIF, leading to HIF-dependent EPO expression**

# Cellular Oxygen Sensing Mechanism



# **FG-2216: Novel HIF-PH Inhibitor that Stimulates Erythropoiesis for the Treatment of Anemia**

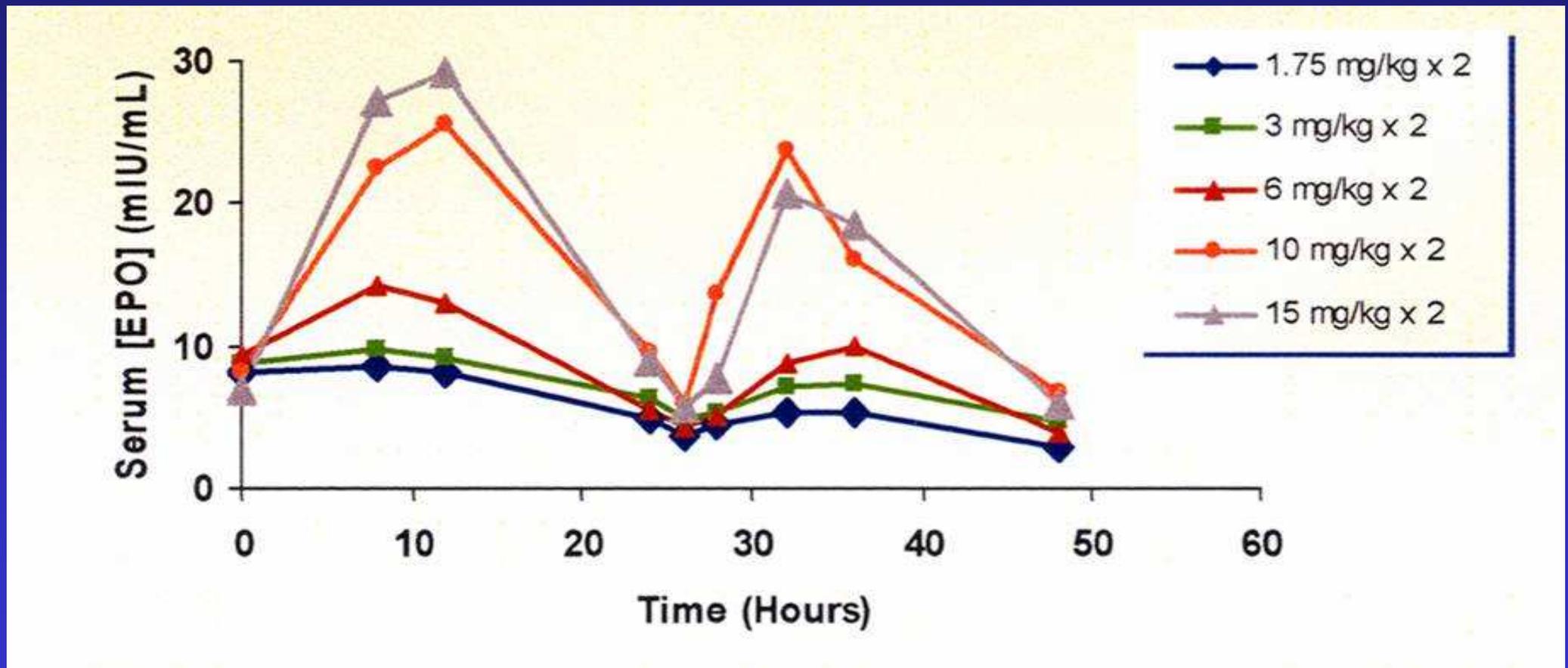
- **Orally bioavailable, small molecule inhibitor of hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) , FibroGen Inc., South San Francisco**
- **Coordinately regulates transcription of erythropoietin (EPO) gene, mobilization of iron and overcomes suppression of anti-erythropoietic cytokine effects**
  - **Improves iron absorption, transport, and bioavailability for heme synthesis, including reducing the expression of hepcidin to relieve block on iron bioavailability**
  - **Increases endogenous EPO and enhances sensitivity to EPO**
  - **Overcomes suppression of EPO production by TNF- $\alpha$  and IL-1b**
- **Corrects anemia in preclinical models of anemia including those with reduced renal function and mass, chemotherapy-induced anemia, and anemia of chronic disease**

# **FG-2216: Clinical Development**

- **Summary of Phase 1 clinical results in healthy subjects**
  - **Dose-dependent induction of EPO after single, oral dose of FG-2216**
  - **Provides first human proof of concept for inducing endogenous EPO and increasing hemoglobin (Hb) by a specific, orally active HIF-PH inhibitor**
  - **No serious adverse events (SAEs) up to 30 mg/kg administered for up to 4 weeks**
- **Ongoing Phase 2a dose-escalation studies in predialysis CKD patients**
  - **Anemic predialysis patients with advanced stage chronic kidney disease (CKD)**
    - **Patients with no previous exposure to rHuEPO ("rHuEPO-naïve")**
    - **Patients receiving continuous rHuEPO therapy for at least eight weeks prior to switching to dosing with FG-2216 ("rHuEPO-treated")**

# FG-2216 Dose-Related Induction of Endogenous Serum EPO

## No Desensitization in EPO Response Following repeated Dosing with FG-2216

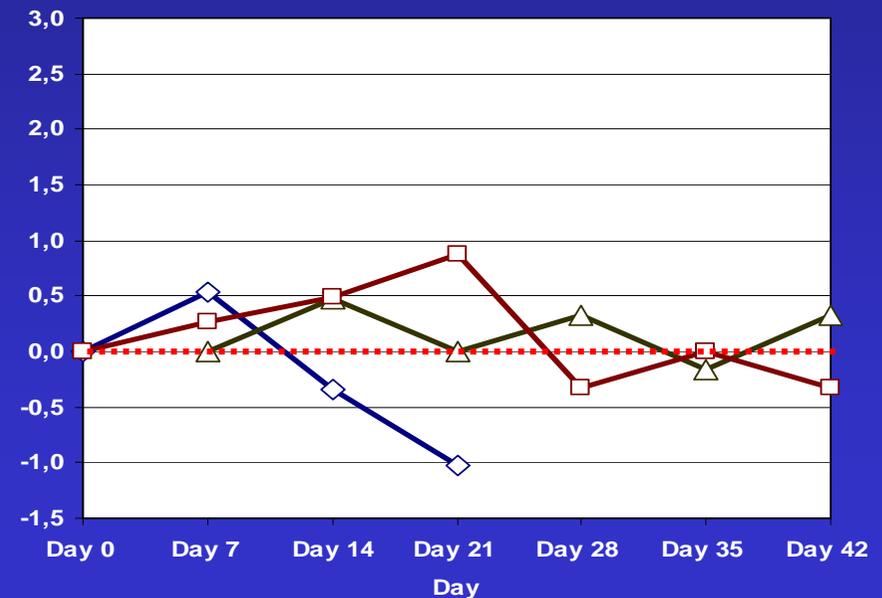
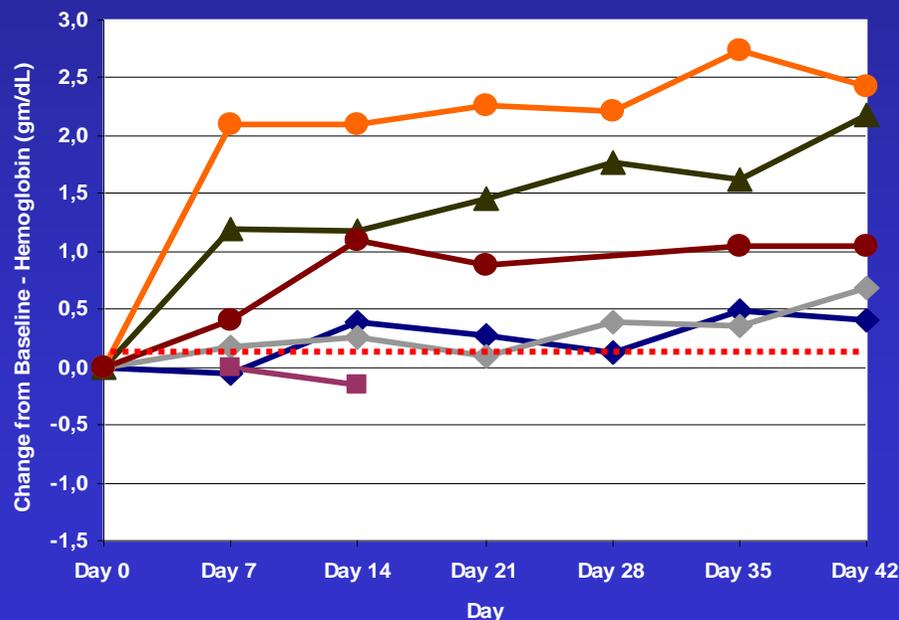


# Phase 2a (rHuEPO- naïve): Individual Hemoglobin Response to FG-2216 vs. Placebo – Change from Baseline

6 mg/kg group (first cohort, rHuEPO-naïve, predialysis patients)

Treatment Group	Mean Baseline Hb (g/dL)	Mean change from Baseline Hb (g/dL) Day 42* (or last value carried forward)
<b>FG-2216 (n=5)</b>	<b>9.6</b>	<b>1.9</b>
<b>Placebo (n=3)</b>	<b>9.8</b>	<b>-0.35</b>

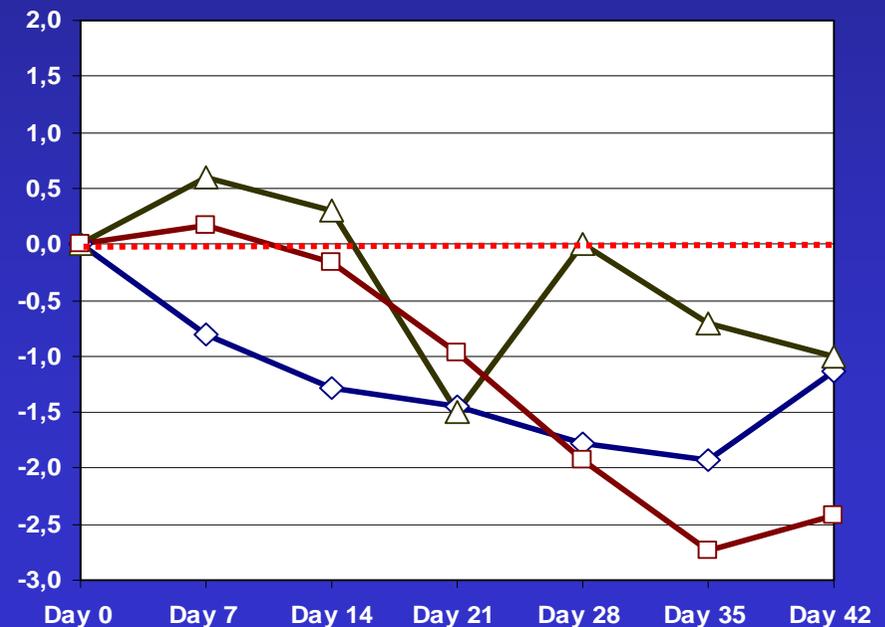
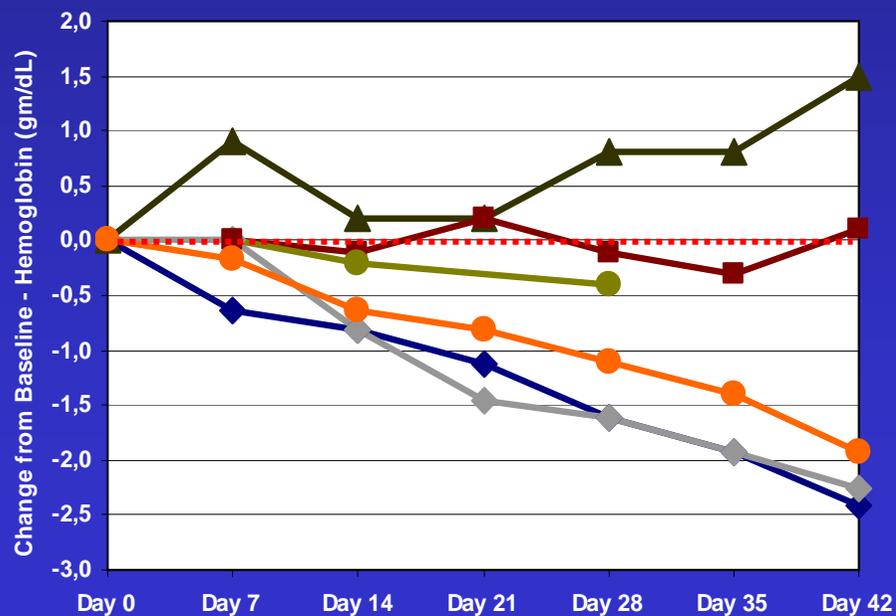
\*Difference between treatment and placebo group is statistically significant (Mann – Whitney rank sum test), p = 0.036



# Phase 2a (rHuEPO-treated): Individual Hemoglobin Response to FG-2216 vs Placebo – Change from Baseline

6 mg/kg group (first cohort, rHuEPO-treated, predialysis patients)

Treatment Group	Mean Baseline Hb (g/dL)	Mean change from Baseline Hb (g/dL) Day 42* (or last value carried forward)
<b>FG-2216 (n=6)</b>	<b>11.7</b>	<b>-0.9</b>
<b>Placebo (n=3)</b>	<b>11.5</b>	<b>-1.5</b>



# **FG-2216: Summary of Safety Results**

- **Phase 1 Studies: Normal Subjects**
  - n=72 treated with FG-2216
  - No SAEs
  - All AEs reported on FG-2216 treated subjects were mild and transient
  
- **Phase 2a Dose-Escalation Studies: CKD Patients**
  - n=14 treated with FG-2216
  - No Drug-Related SAEs
  - All AEs reported on FG-2216 treated patients have been mild and transient

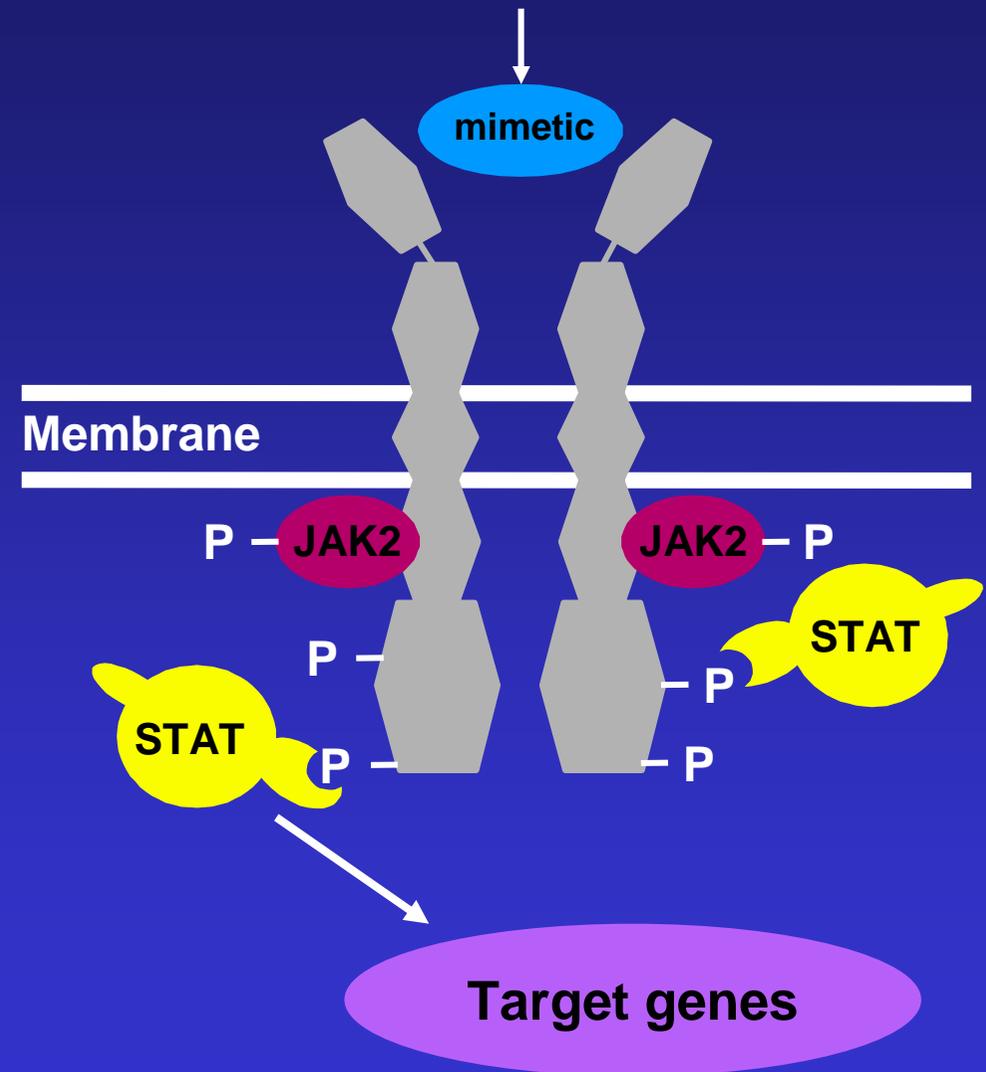
# Conclusions

- **The magnitude and rate of hemoglobin increases observed in patients treated with FG-2216 are likely to provide clinical benefit in treating anemia associated with chronic kidney disease**
- **FG-2216's novel mechanism of action – HIF stabilization - could provide in the future a convenient and cost-effective therapy for anemia than protein - based therapeutics**
- **Larger and long - term clinical trials are needed in order to document the safety profile and final clinical benefits of this new compound**

# EPO mimetics

## Rationale and strategy

- Both chains of the EPO receptor are needed
- Conformation of the EPO receptor in the dimer complex is flexible
  - suggests that a variety of molecules capable of dimerising the receptor may be able to act as EPO mimetics



# **AF37702 (Hematide™)**

## **Pegylated Peptide-Based Erythropoiesis-Stimulating Agent (ESA)**

- **AF37702 (Hematide™) is a synthetic dimeric peptide that is linked to polyethylene glycol (PEG)**
- **AF37702 (Hematide™) is an erythropoiesis agent (ESA) being developed by Affymax for the treatment of anemia associated with CKD or cancer**
- **The aminoacid sequence of AF37702 (Hematide™) is unrelated to that of EPO**
- **It is anticipated that AF37702 (Hematide™) may have several potential advantages over currently available EPO products**

# Background

## Hematide™

- ▶ Novel synthetic PEGylated peptide
- ▶ Binds to and activates the erythropoietin receptor
- ▶ Currently in Phase II clinical trials in anaemia of chronic kidney disease (CKD) and cancer

## Study Design

- ▶ Multi-centre, open-label, sequential dose-finding

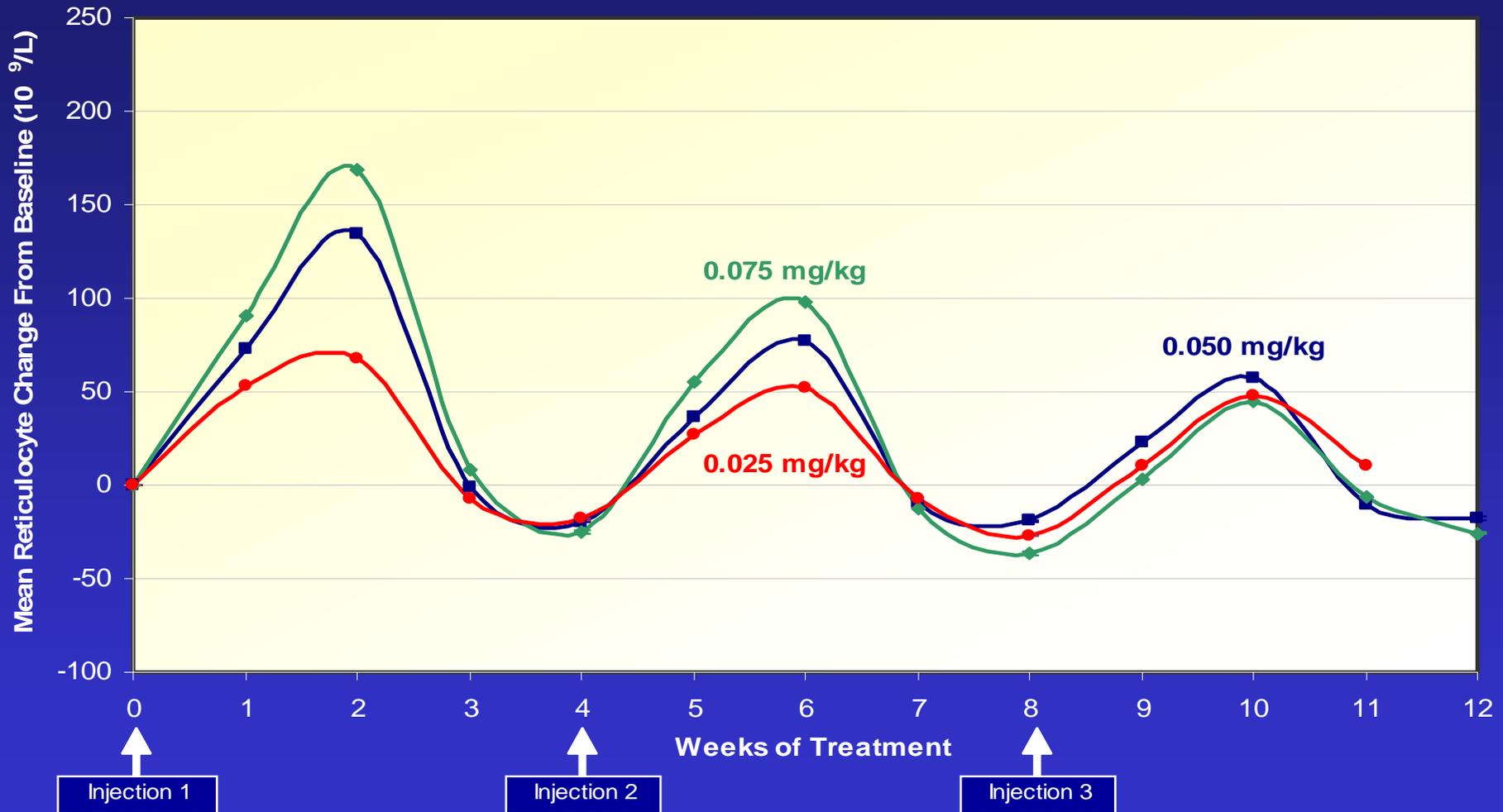
## Objective

- ▶ To evaluate the safety and pharmacodynamics of multiple doses of once-monthly (Q4W) subcutaneous (SC) Hematide

## Study Methods

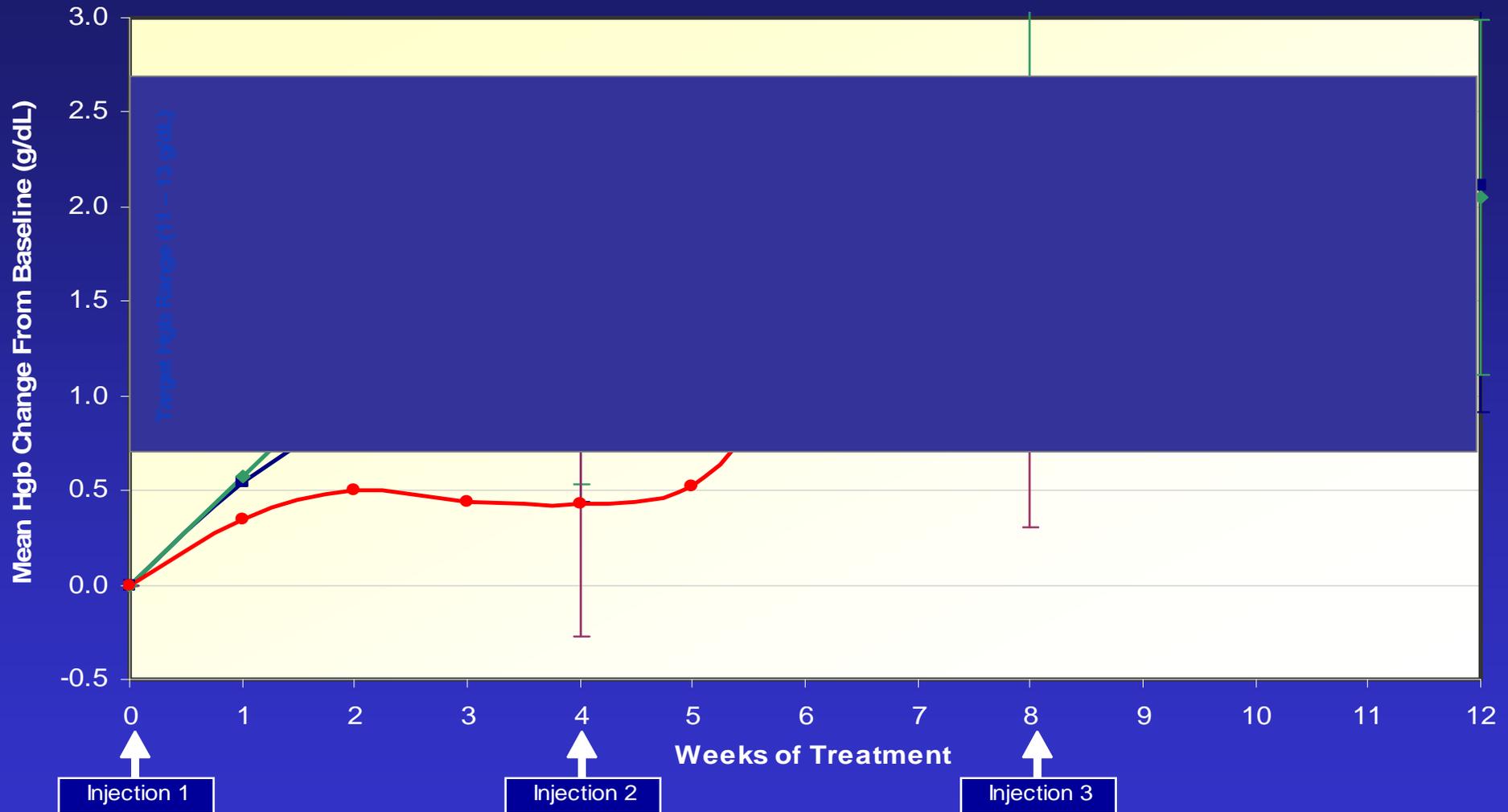
- ▶ Total of 60 erythropoiesis-stimulating-agent-naïve, pre-dialysis, CKD patients with anaemia (Hgb 9.0–10.9 g/dL)
- ▶ Enrolled into three dose cohorts
- ▶ Patients received up to six once-monthly SC doses
- ▶ Starting Hematide doses:
  - ▶ 0.025 mg/kg (n=15)
  - ▶ 0.050 mg/kg (n=30)
  - ▶ 0.075 mg/kg (n=15)
- ▶ Dose titration allowed after the first dose, based on haemoglobin (Hgb) levels
- ▶ *This study remains ongoing; further cohorts are being recruited*

## Hematide Mean Reticulocyte Change from Baseline (0–12 Weeks)



Andrzej Wiecek et al. Abstract # SP419 43rd ERA-EDTA Congress, July 15-18, 2006, Glasgow,

## Hematide Mean Hgb Change from Baseline (0–12 Weeks)



*Andrzej Wiecek et al. Abstract # SP419 43rd ERA-EDTA Congress, July 15-18, 2006, Glasgow,*

# Safety Results

## Adverse Events & Serious Adverse Events

- ▶ As of 26 Apr 2006, eleven (18%) patients reported 36 adverse events; all were assessed as not related to study drug
- ▶ No adverse event resulted in study withdrawal
- ▶ No injection site reaction was reported
- ▶ Eight serious adverse events were reported:

<i>H. pylori</i> gastritis	Haematoma
Ischaemic heart disease	Progression of CKD
Diabetic ketoacidosis	Peritonitis
Vomiting	Ankle fracture

- ▶ All serious adverse events were assessed as not related to study drug

## Conclusions

- ▶ Multiple monthly SC **Hematide** injections are well-tolerated
- ▶ Monthly **Hematide** 0.050 and 0.075 mg/kg dosing achieves correction of anaemia in 93% and 100% of patients by Week 8, respectively
- ▶ **Hematide** results in a sustained increase in Hgb (up to Week 22) when dosed monthly in patients with CKD
- ▶ Phase III **Hematide** studies are planned

# Conclusions

- **Renal anemia management is currently in a state of rapid development.**
- **New strategies for treating the anemia have emerged, particularly the concept of treating the condition earlier.**
- **We look forward to the results of pre-dialysis clinical trials.**
- **We can expect other erythropoietic substances to be available for therapeutic use.**

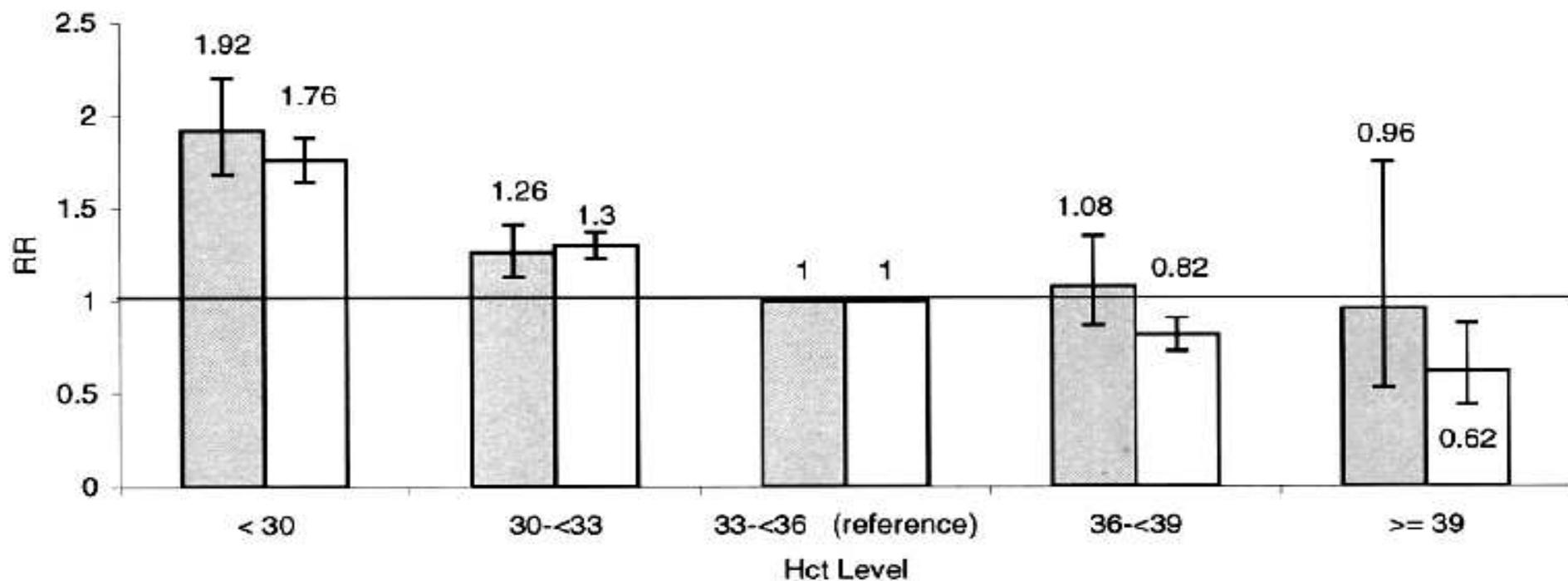
**Thank You for your attention !**

**A. Więcek**

**Katowice  
Poland**



Relative risks (RR) of death (■) and hospitalization (□) from infectious causes (with 95% CI). Hct, hematocrit.



Collins A.J. et al. J Am Soc Nephrol 2001, 12:2465-2473



**Primary results of the anemia correction in diabetes (ACORD)  
study**

Ritz E et al.

*Am J Kidney Dis* 2007;49:194-207



## TREAT: Status and Implications

- Ongoing double-blind, placebo-controlled trial
- Continuing after CREATE and CHOIR publication and DSMB review

“This should give confidence that the potential harm as described by the CHOIR authors has not been seen”

# Rationale to continue RED-HF™ Trial

- The treatment of anemia in heart failure is investigative and the optimal Hb concentration for patients with heart failure has not yet been determined.
- The RED-HF trial is fundamentally different from CHOIR and CREATE because of the study rationale, hypothesis, design, endpoints and patient population<sup>45</sup>
- The design of the RED-HF Trial was based on results from Amgen's phase 2 studies
  - In these studies evaluating the treatment of anemia with darbepoetin alfa in heart failure patients, treatment to a target Hb of  $14.0 \pm 1.0$  g/dL appeared to be well tolerated.<sup>47</sup>
  - The incidence of adverse events, including deaths, serious adverse events, and adverse events of special interest (cardiovascular and/or thrombotic events) was similar between the treatment arms.<sup>47</sup>
  - A pre-specified pooled analysis of the 2 largest phase 2 studies showed a trend towards reduced risk of all-cause mortality and heart failure hospitalization for treatment of anemia with darbepoetin alfa compared with placebo<sup>46</sup>
- The RED-HF Trial has been designed and powered to determine whether treatment of anemia with darbepoetin alfa improves clinical outcomes in patients with heart failure and anemia

**RED-HF™ Trial: Reduction of Events with Darbepoetin alfa in Heart Failure Trial**

# TREAT trial - ongoing

Patients: 4000, diabetic nephropathy (type 2 DM), eGFR 20-60, Hb < 11

Design: Double blinded, placebo controlled RCT

High arm: darbepoetin, target Hb 13 g/dl

Low arm: placebo, “rescue therapy” with darbepoetin, when Hb < 9 g/dl

Primary EP: all cause mortality and non-fatal CV events

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Individual physicians and national nephrological societies considered the trial as “unethical” because of the placebo arm !

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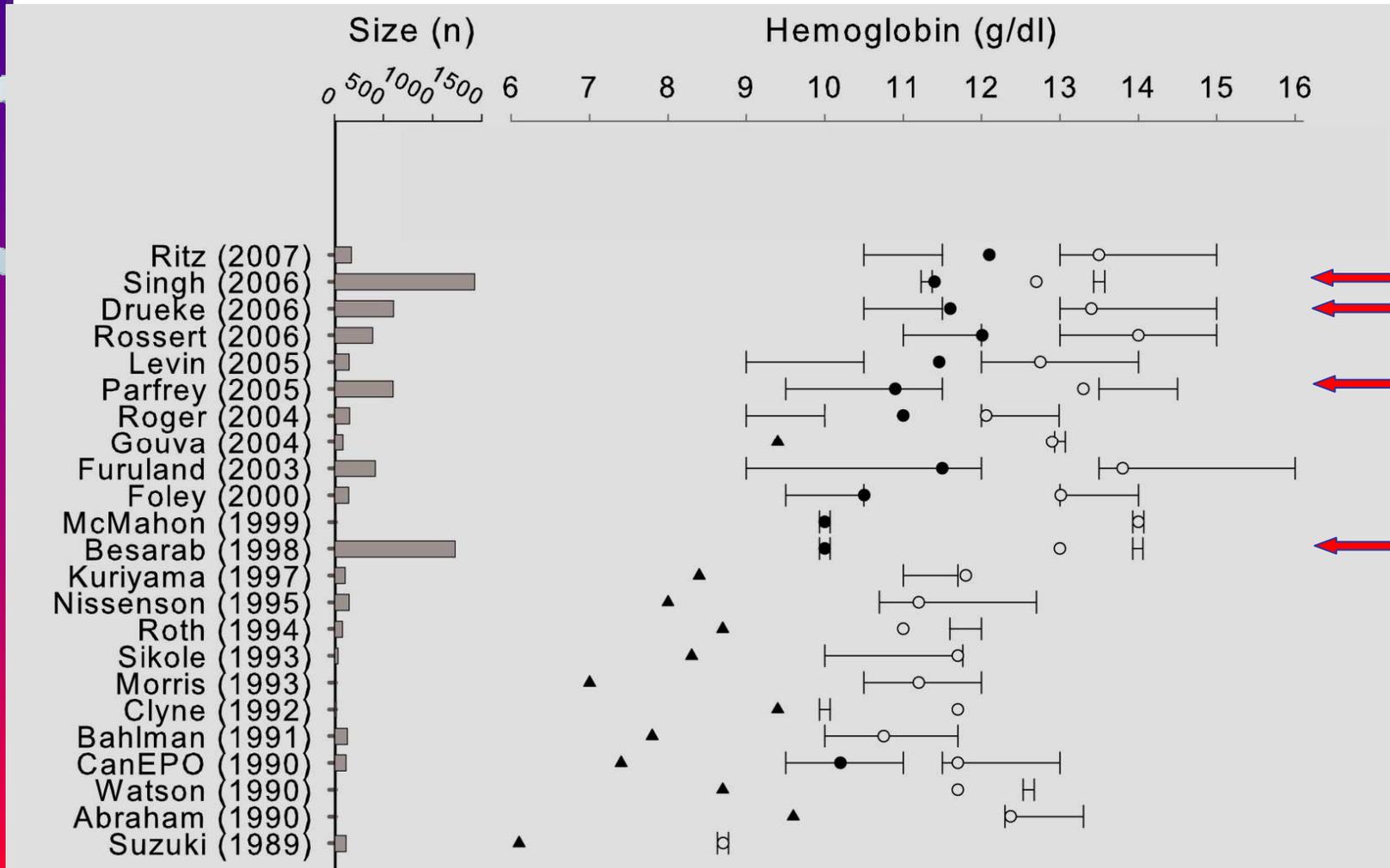
**Strippoli GF, Tognoni G, Navanethan SD, Nicolucci A, Craig JC. *Lancet* 369, 2007**

## Haemoglobin targets: we were wrong, time to move on

On the basis of the existing published trials, summarised by Phrommintikul and colleagues,<sup>4</sup> we contend that more trials of haemoglobin target concentrations in patients with chronic kidney disease are no longer required, should be stopped, or at least it should be made fully and publicly explicit what reasons grant their continuation. We say

this because of the rights of patients, and the credibility of the scientific nephrological community, after such a long history of contradictions. The question has been answered: higher haemoglobin target concentrations increase mortality via cardiovascular endpoints. Part rather than complete correction of anaemia is appropriate,

# RCTs

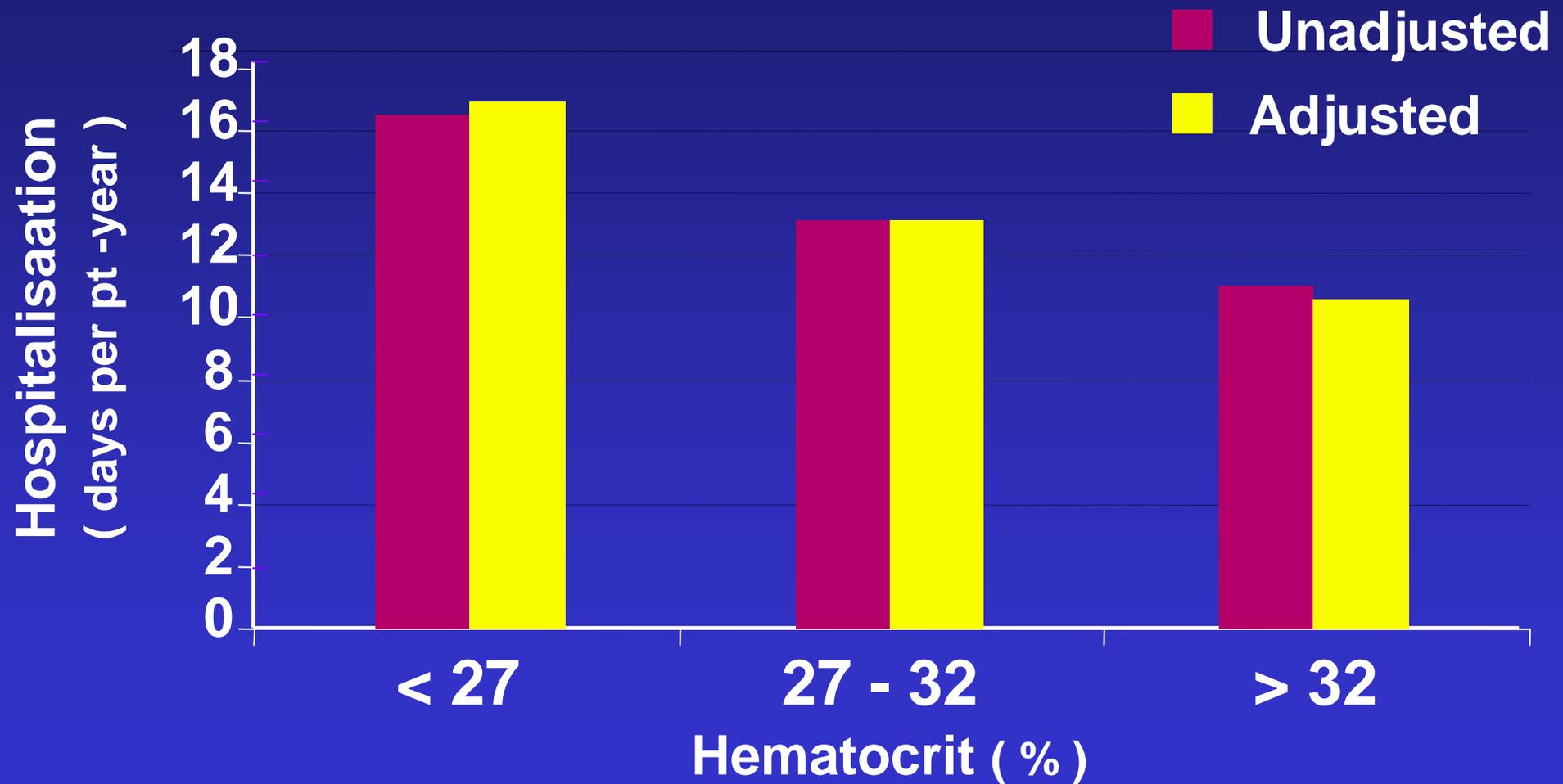


- ▲ Placebo/control mean Hb
- Lower Hb arm: mean achieved Hb
- Higher Hb arm: mean achieved Hb
- } | Target range

Adapted and updated from NKF-K/DOQI. *AJKD* 2006; 47 (5 Suppl 3)

# ESRD PATIENT RISK FACTORS

## Anaemia and hospitalisation risk

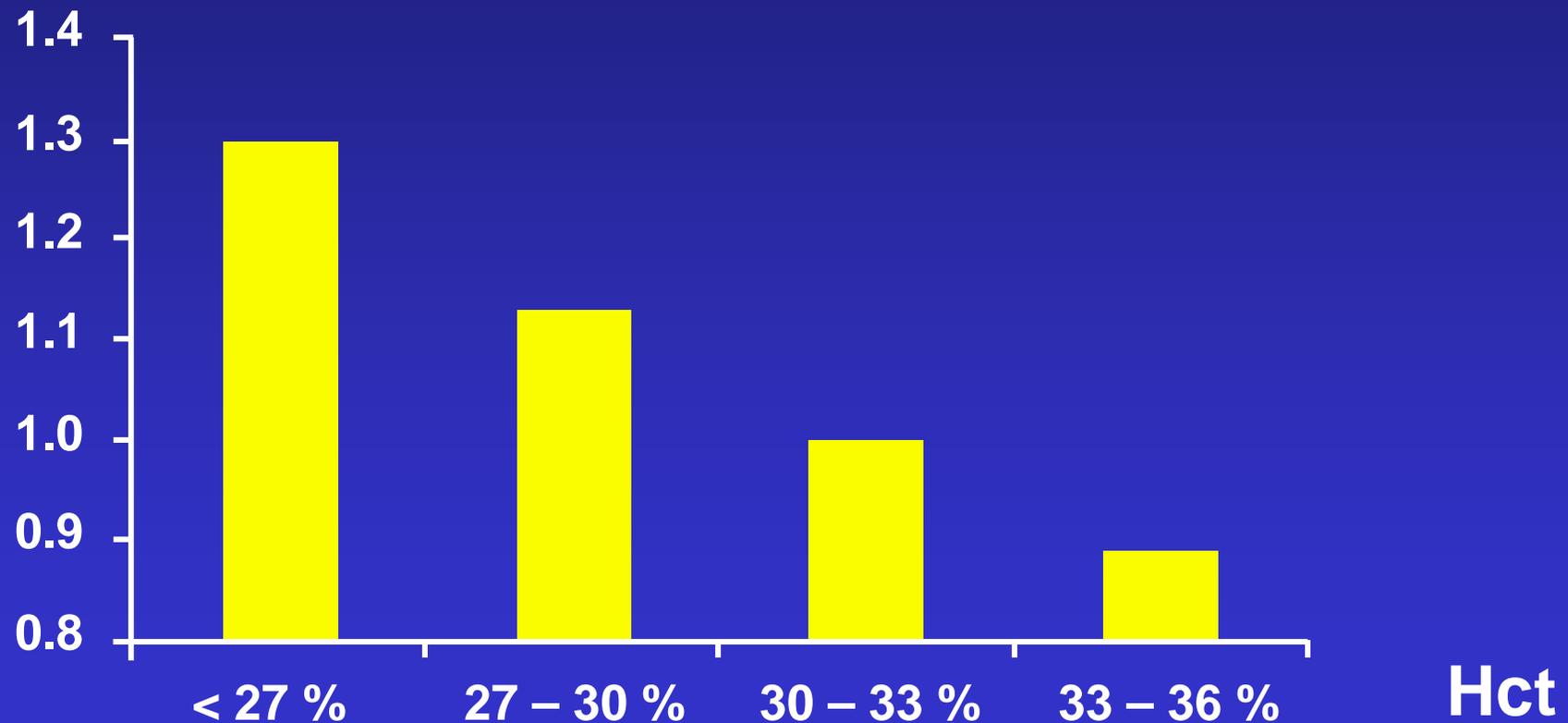


Locatelli F *et al* Nephrol Dial Transplant 1998; 13: 1642 - 4

# US Observational Study

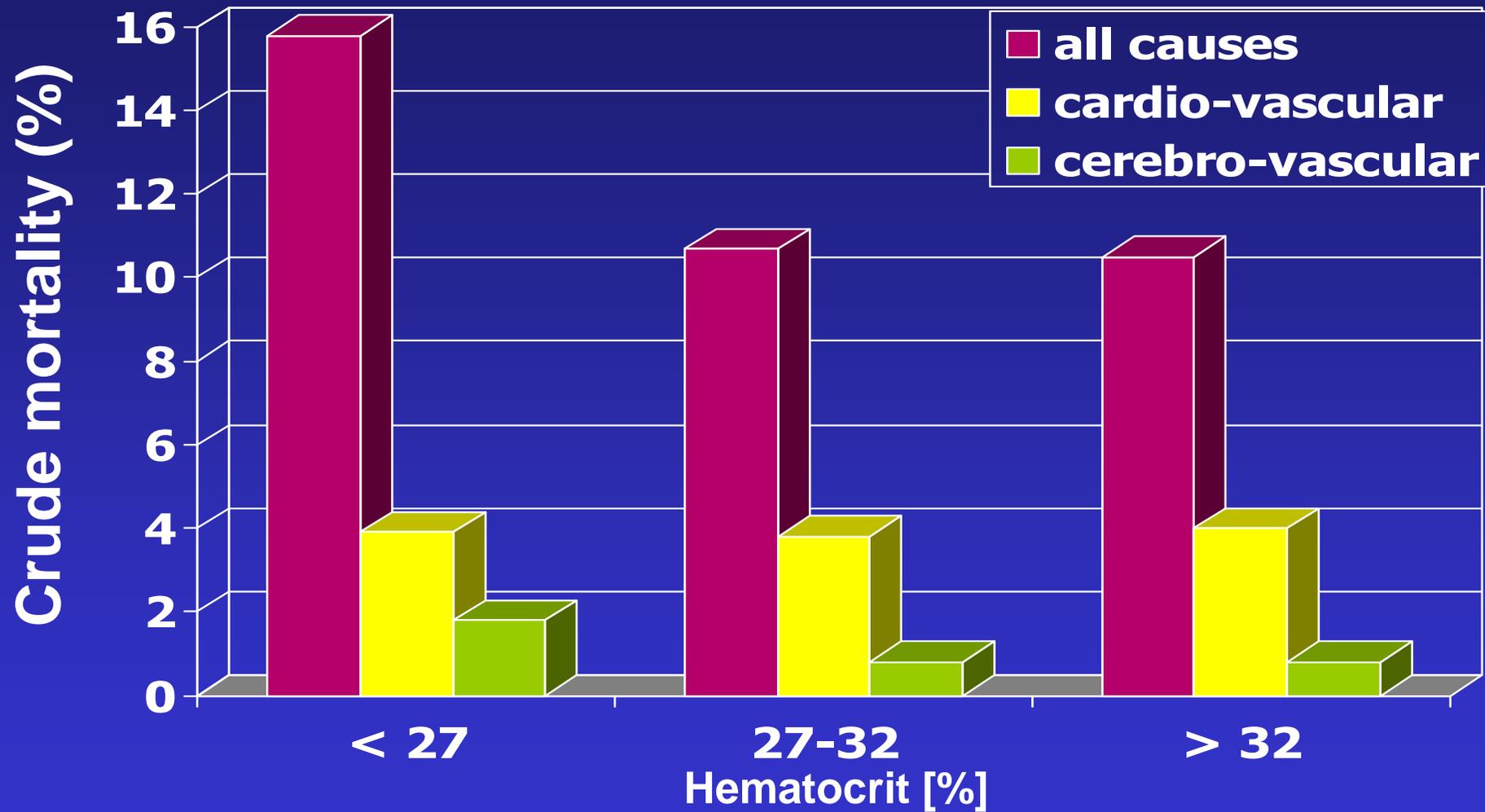
## Hospitalization risk and Hct in HD patients

Relative risk

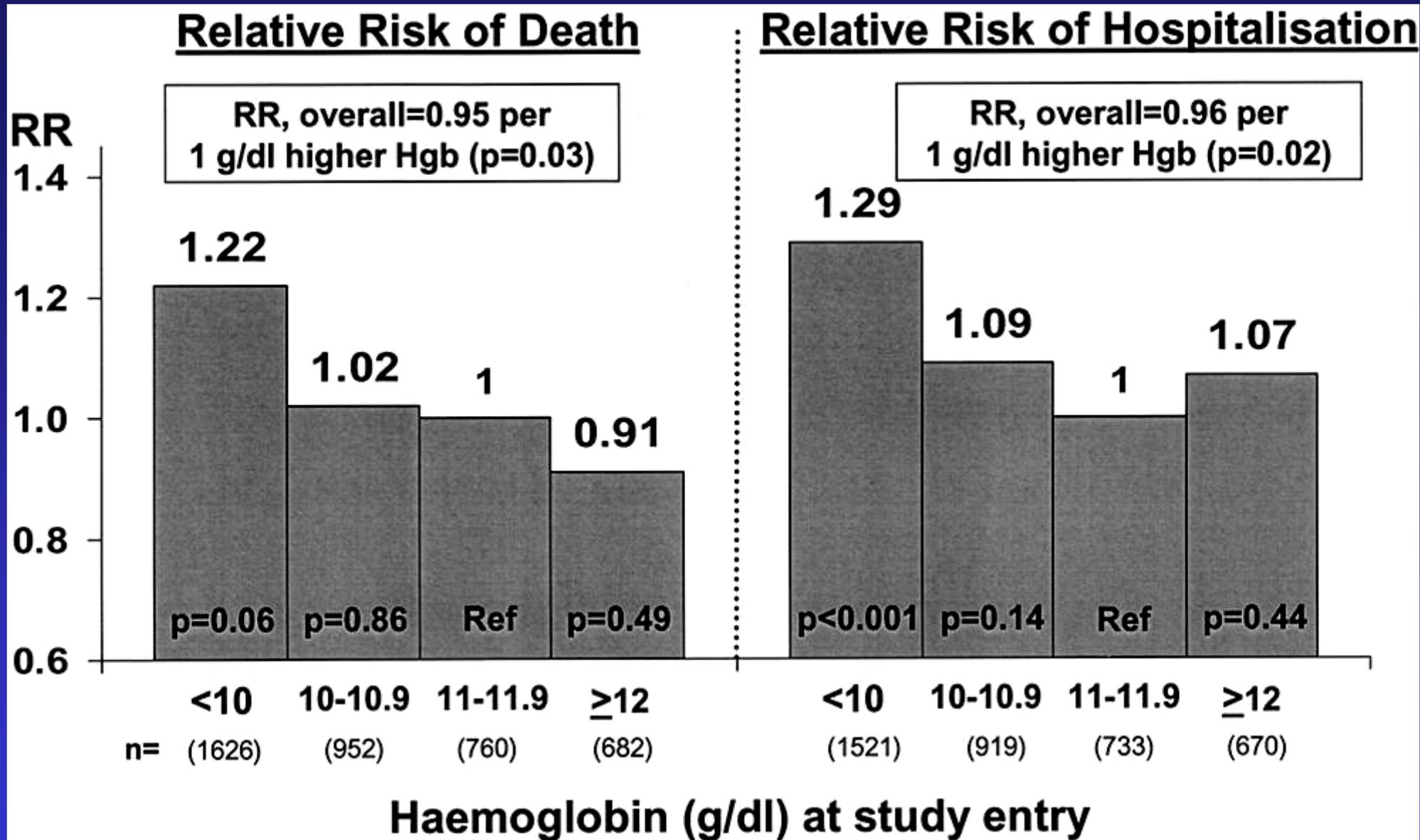


Xia *et al*, J Am Soc Nephrol 1999;10; 1309 - 16

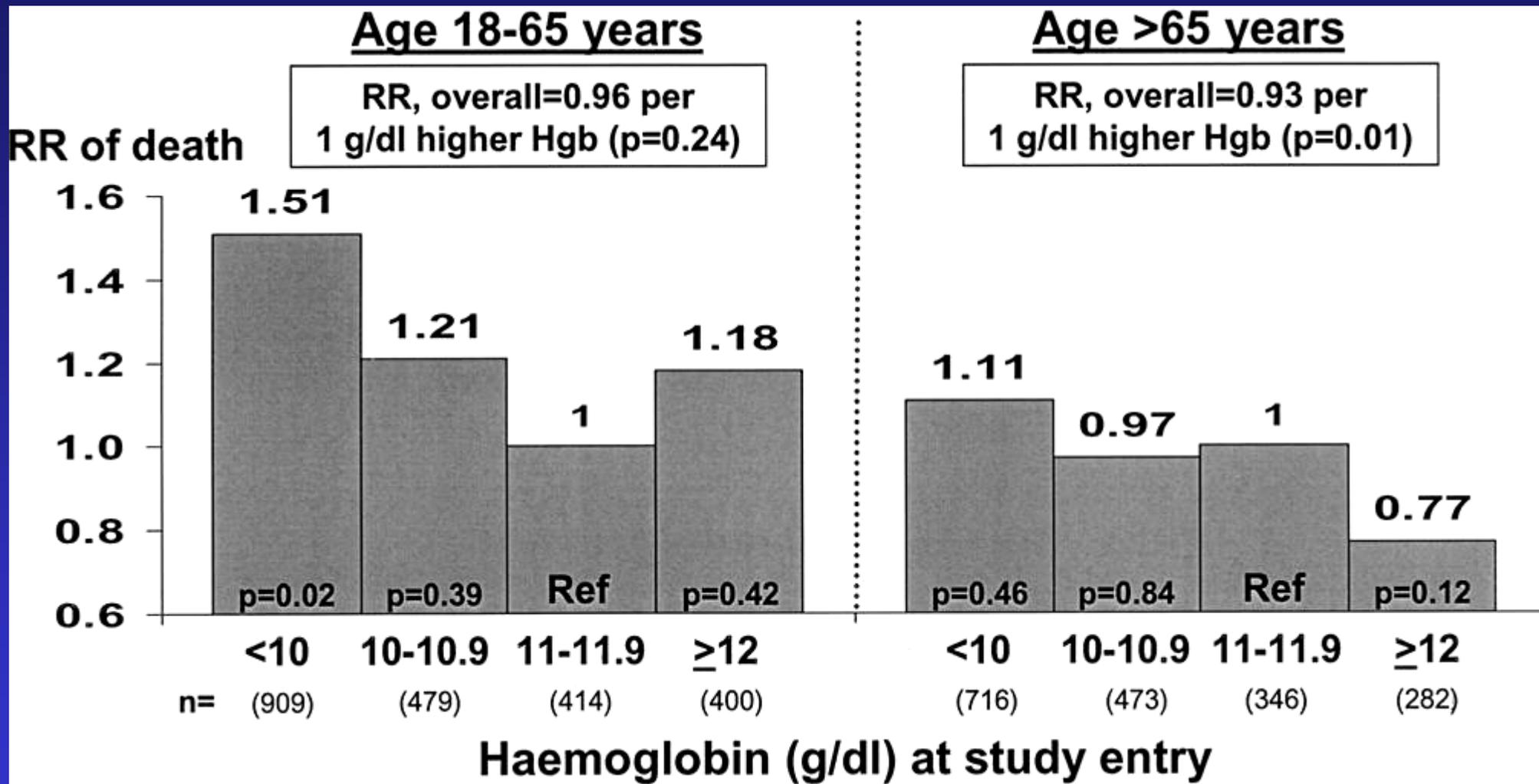
## Cause of death:



Locatelli F. et al.: NDT, 1998, 13, 1642-1644

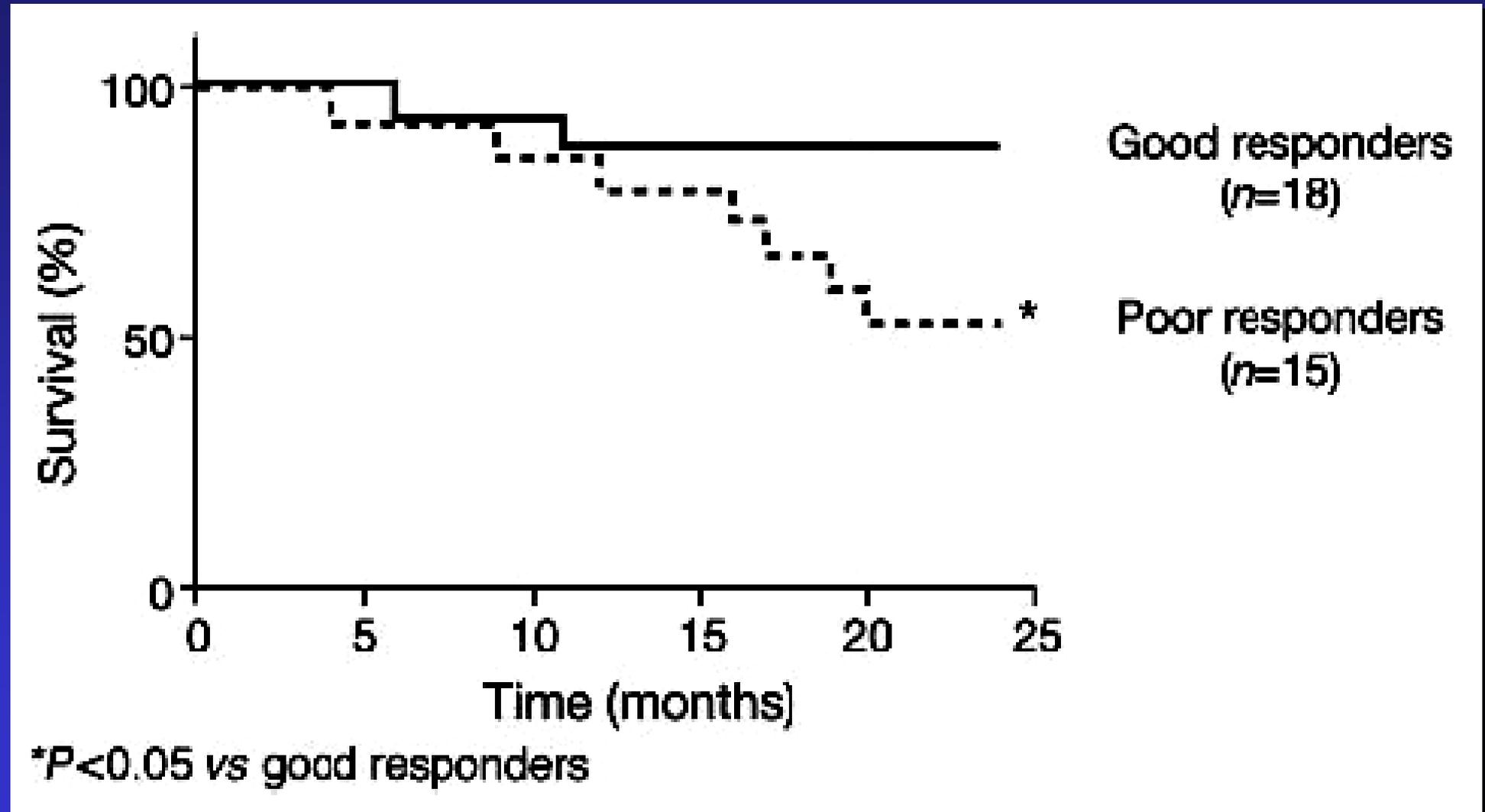


Locatelli F. et al.: Nephrol Dial Transplant (2004) 19: 121-132



Locatelli F. et al.: Nephrol Dial Transplant (2004) 19: 121-132

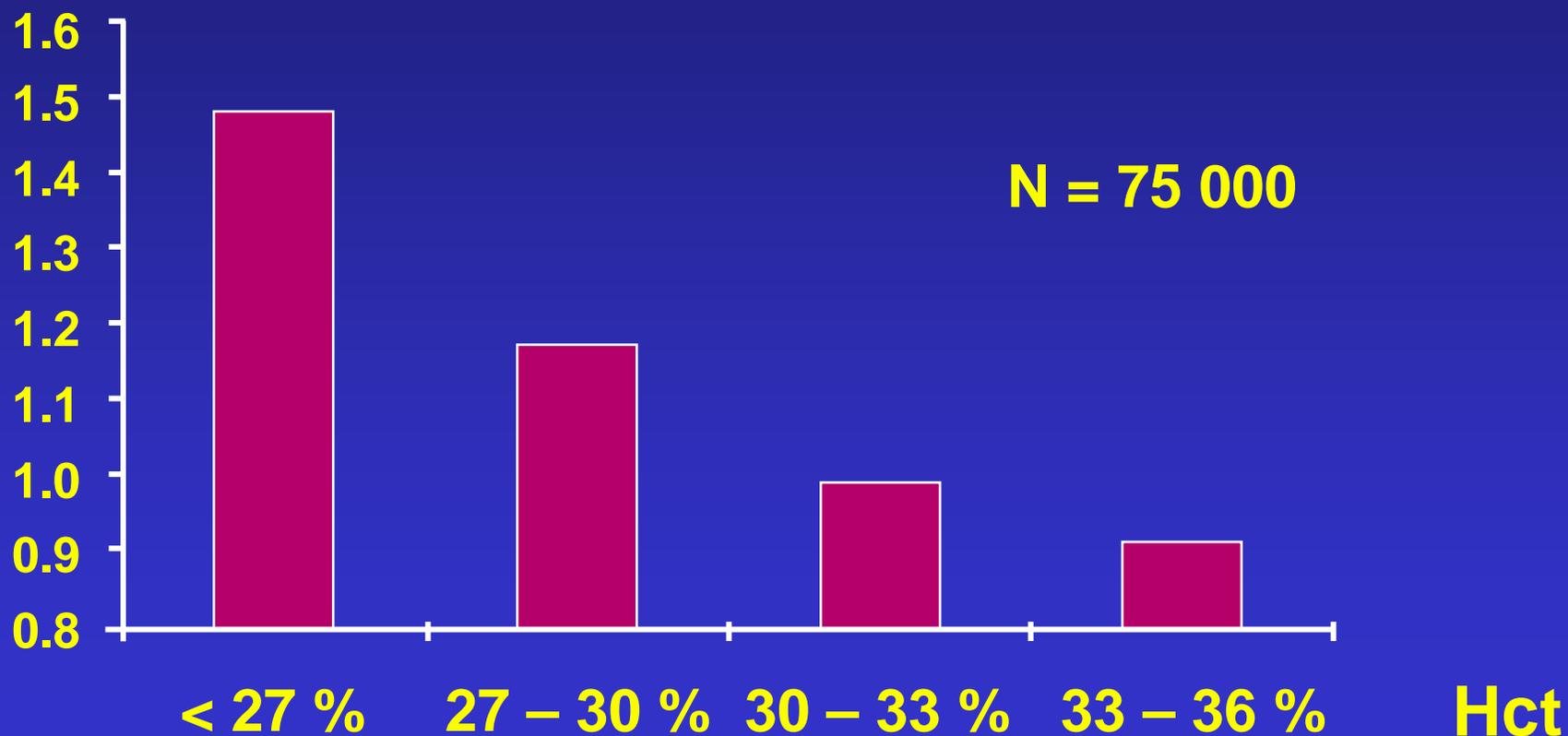
# Survival curve for good vs poor responders to epoetin.



# US Observational Study

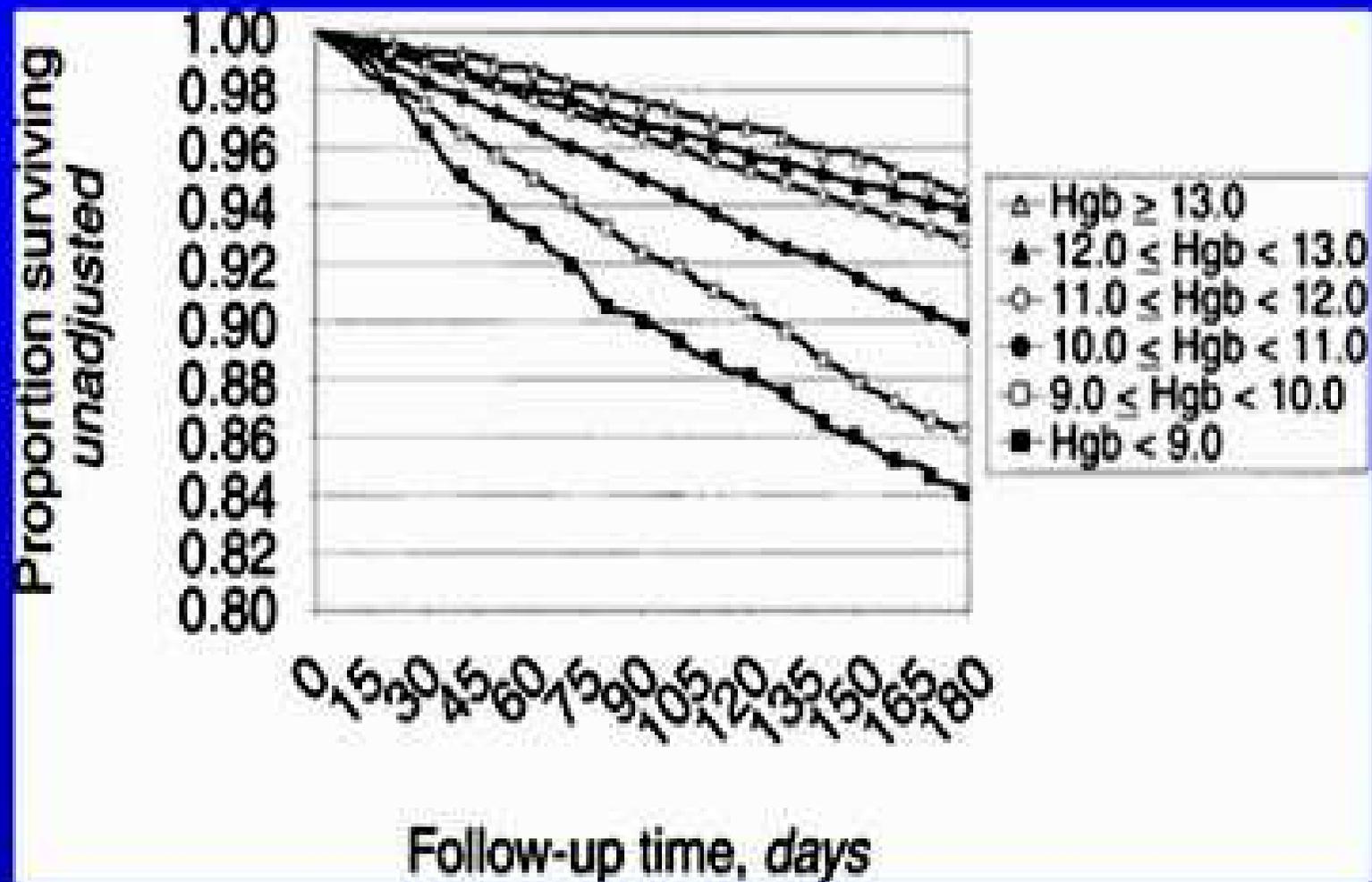
## Mortality risk and hematocrit in HD patients

### Relative risk



Ma JZ et al.: J Am Soc Nephrol 1999; 10: 610

## Higher Hgb and Survival in HD pts

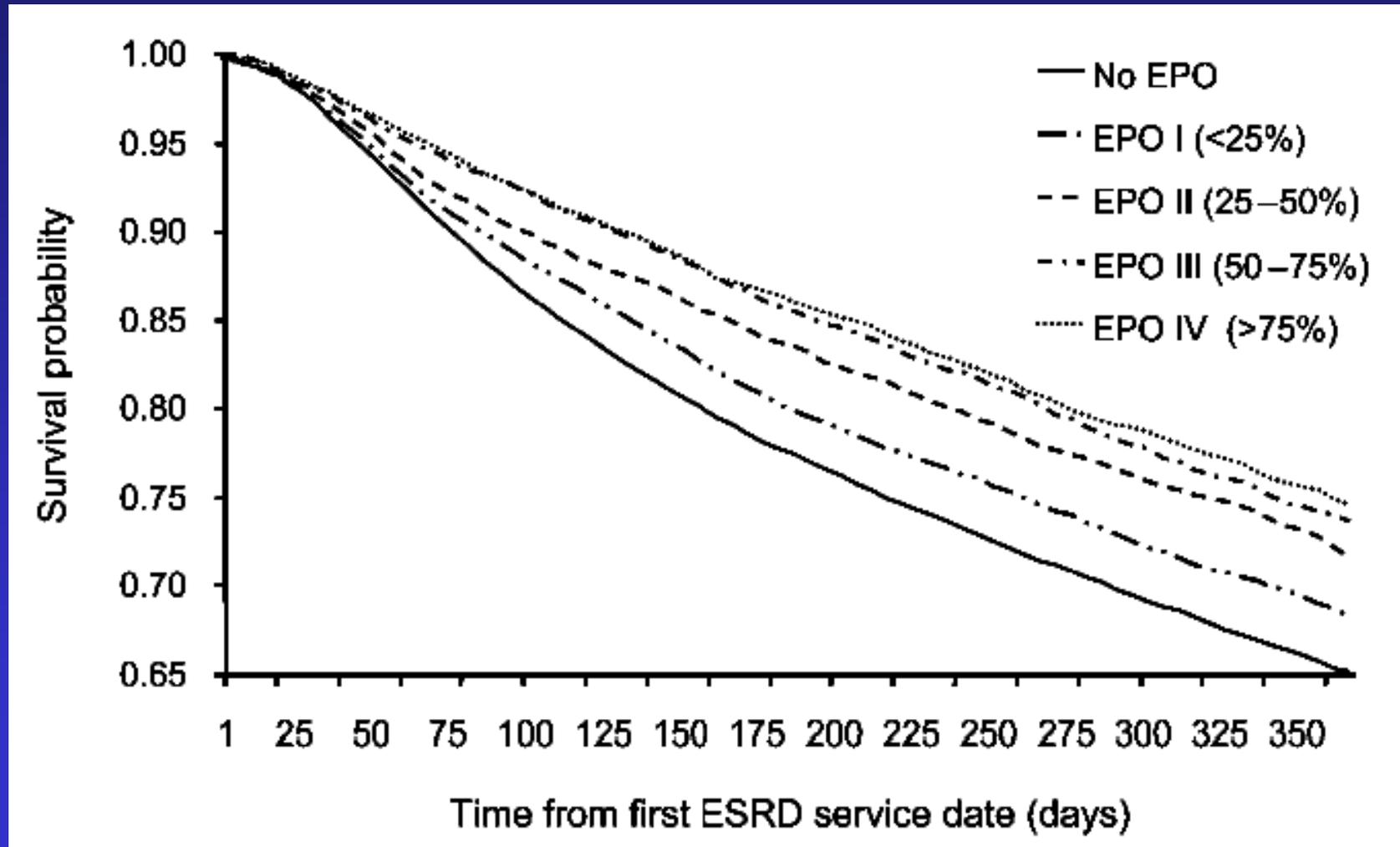


## Lowest Mortality Risk With Hb Maintained at 12-13 g/dL

Hb level g/dL	Hazard ratio for mortality over previous		
	1 month	3 months	6 months
<9	1.69	1.62	1.59
9 - <10	1.46	1.21	1.27
10 - <11	1.23	1.28	1.21
11 - <12	Ref	Ref	Ref
12 - <13	0.97	0.90	0.80
≥13	1.1	1.04	0.79
<i>p value</i>	<i>0.02</i>	<i>0.03</i>	<i>0.0001</i>

Robinson et al. Kidney Int (2005)

# One-year adjusted survival curves after initiation of dialysis in patients grouped according to level of epoetin use during the 2-year pre-dialysis period



**Collins A.J. Nephrol. Dial. Transplant. 2003 , 18, supp2; ii2-ii6**

# Importance of hemoglobin level in HD patients

**Recommended target hemoglobin of  $\geq 11$  g/dl leads to**

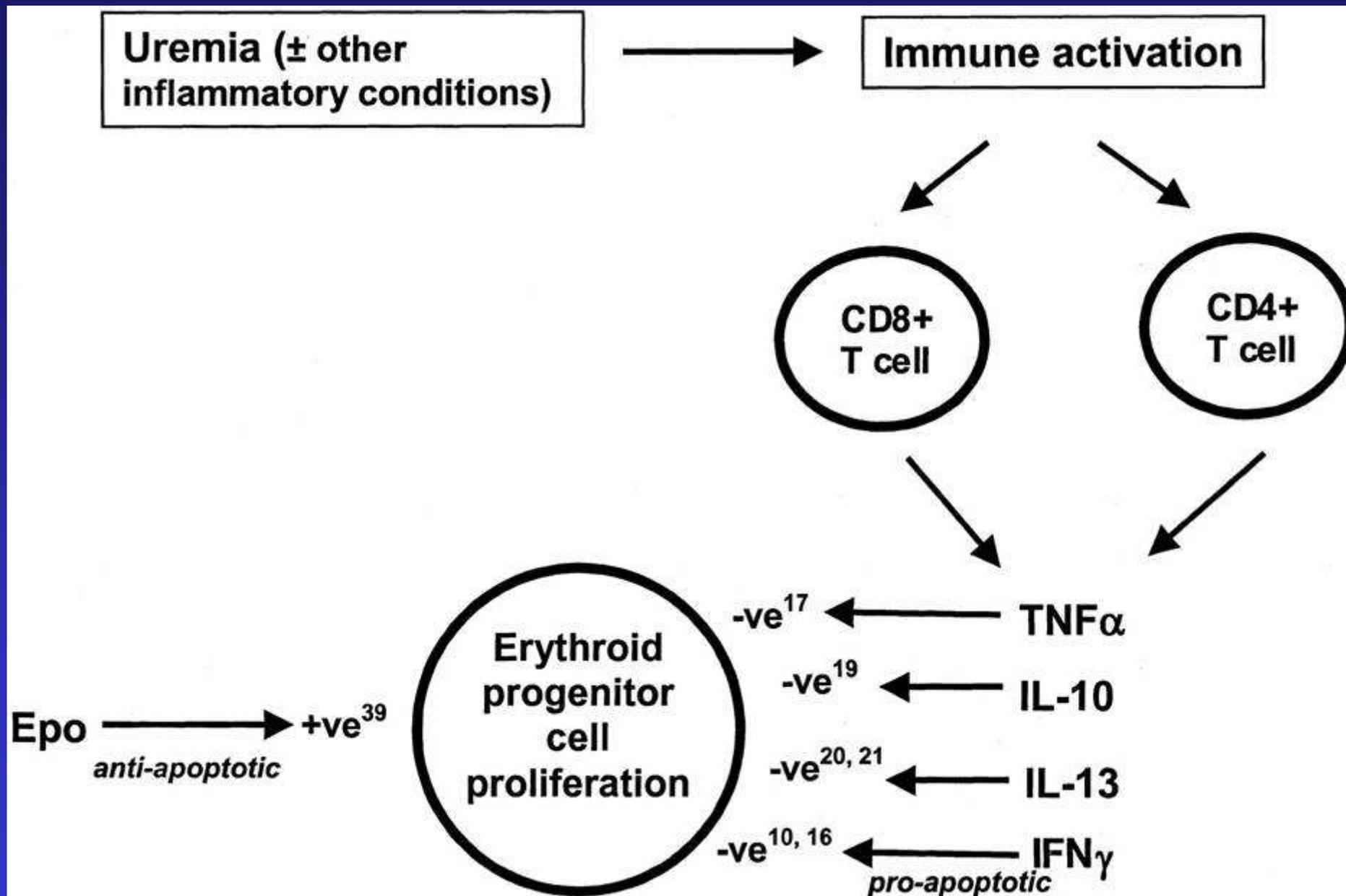
- Decreased risk of mortality (5% lower for every 1 g/dl)
- Decreased risk of hospitalization (4% lower for every 1 g/dl)
- Decreased risk of infections
- Increased quality of life

**Locatelli F et al., NDT 2004;19:121–132.**

## 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\*

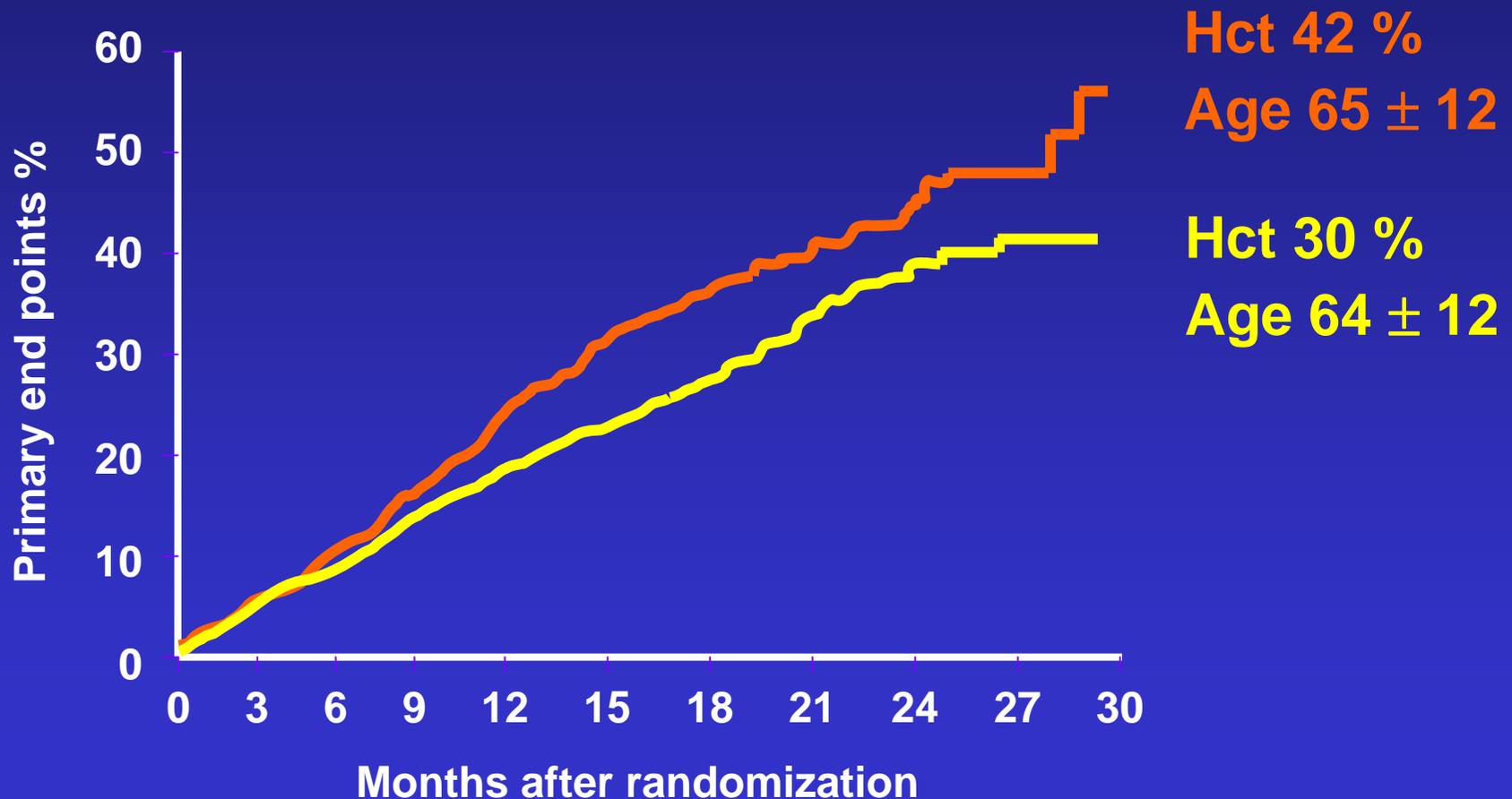
- Patients:** 603, eGFR 15-35, Hb 11-12.5
- Design:** sc Epoetin beta High arm: target 13.0 – 15.0  
Low arm: when Hb < 10.5 → target 10.5 – 11.5
- Primary EP:** composite of 8 CV events (time to first event)
- Secondary EP:** change in LVMI, QOL, progression of CKD and others
- Main results:**
- no difference in primary endpoint
  - improvement in QOL
  - time to dialysis shorter in higher arm



Cooper AC. et al.: J Am Soc Nephrol 2003, 14:1776-1784

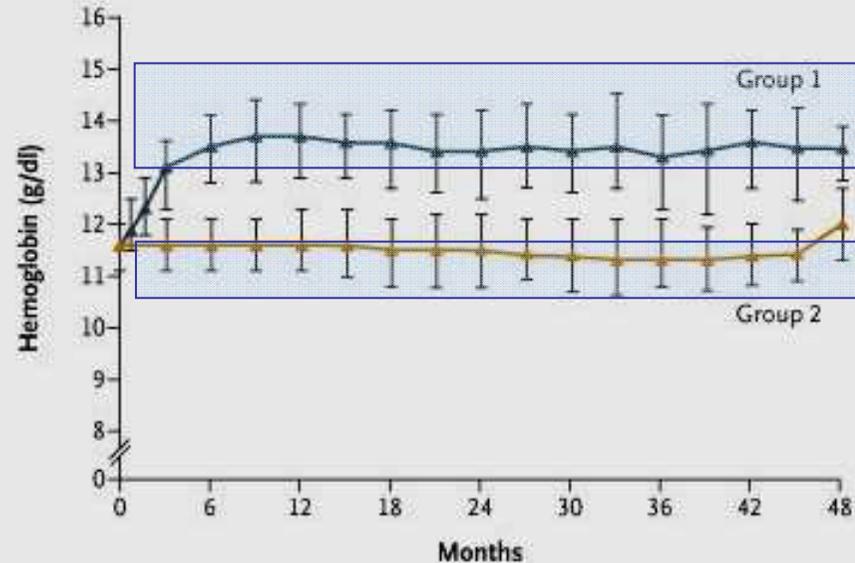
# Probability of death or first non - fatal myocardial infarction

## Normal versus low haematocrit

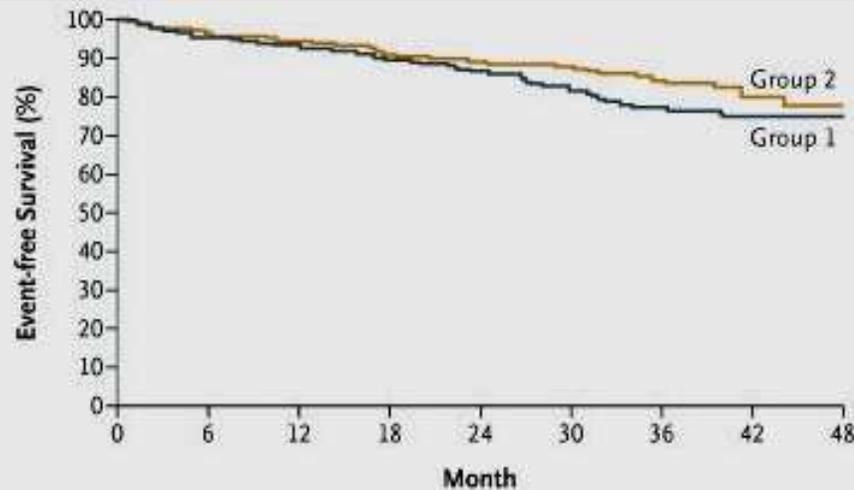


Besarab A et al. *N Engl J Med* 1998 ; 339 : 584 - 90

# CREATE trial



- Hb difference 1.9 / 1.7 / 1.5 g/dl
- starting dose 2000 IU/week
- mean weekly EPO dose:  
2000 vs 5000 IU



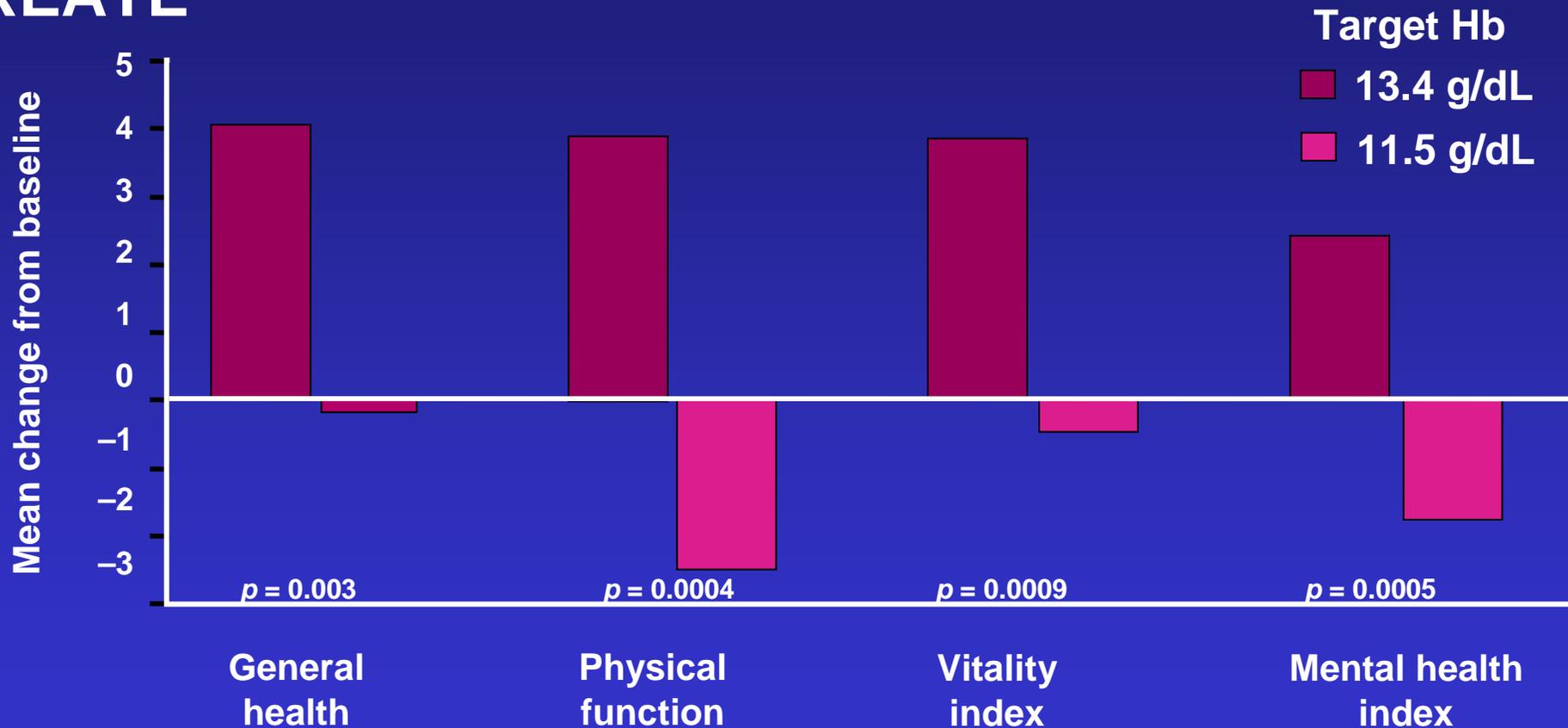
#### No. at Risk

Group 1	301	279	268	249	207	158	97	56	2
Group 2	302	286	272	257	223	177	121	61	2

- no difference in CV events

# Significant QoL Improvements with Complete Hb Correction

## CREATE



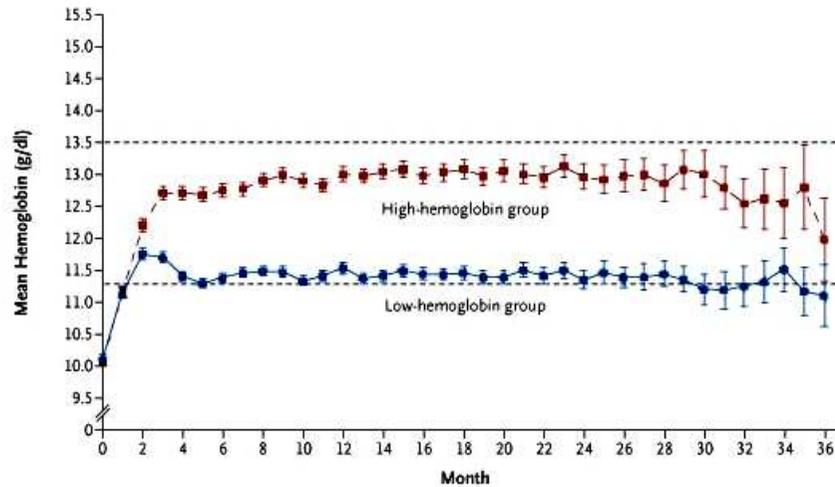
*Drueke T.B. et al. New Engl J Med 2006, 16, 2071-84*

## Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

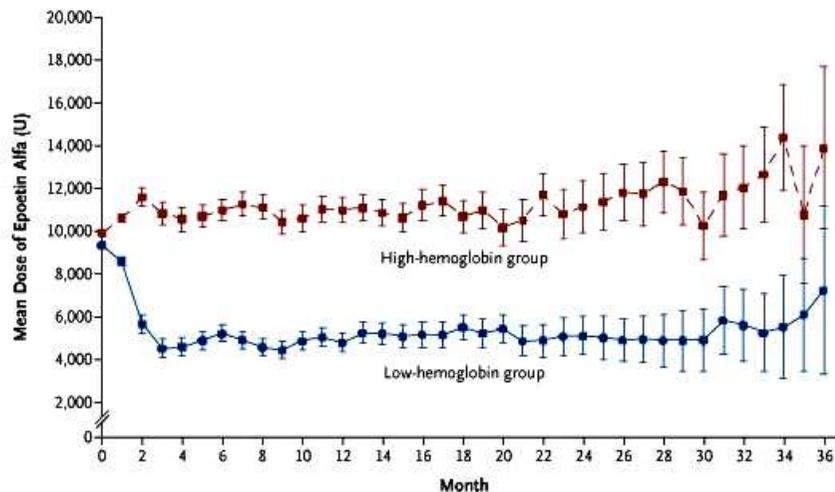
Ajay K. Singh, M.B., B.S., Lynda Szczech, M.D., Kezhen L. Tang, Ph.D.,  
Huiman Barnhart, Ph.D., Shelly Sapp, M.S., Marsha Wolfson, M.D.,  
and Donal Reddan, M.B., B.S., for the CHOIR Investigators\*

- Patients:** 1432, eGFR 15-50, Hb < 11
- Design:** sc Epoetin alfa High arm: target 13.5  
Low arm: target 11.3
- Primary EP:** composite of 4 CV events (time to first event)
- Secondary EP:** change in QOL, RRT and others
- Main results:**
- study terminated early (futility, safety ?)
  - more patients in the higher arm had at least one CV event
  - no improvement in QOL
  - trend towards a higher rate of progression to RRT

# CHOIR trial



No. of Patients	710	667	632	600	558	507	485	433	367	306	252	194	139	95	81	67	49	31	13
High-hemoglobin	710	667	632	600	558	507	485	433	367	306	252	194	139	95	81	67	49	31	13
Low-hemoglobin	707	672	625	603	549	528	510	471	384	334	250	182	141	101	75	60	45	30	13



No. of Patients	709	693	659	623	578	530	500	452	370	310	258	189	132	97	79	65	52	27	11
High-hemoglobin	709	693	659	623	578	530	500	452	370	310	258	189	132	97	79	65	52	27	11
Low-hemoglobin	707	691	655	621	577	549	526	479	393	333	262	189	141	95	73	54	43	27	12

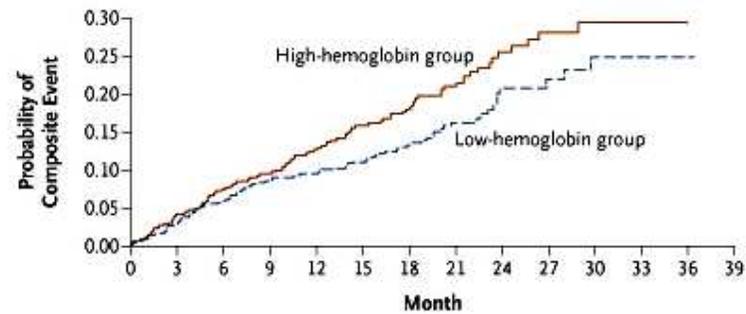
- Hb difference approx. 1.5 g/dl

- starting dose 10,000 IU/week  
 mean weekly EPO dose:  
 6,276 vs 11,215 IU

# CHOIR trial

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

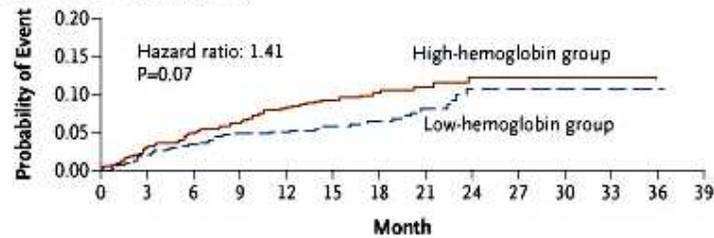
## A Primary Composite End Point



125 vs 97 events;  
 $p < 0.03$

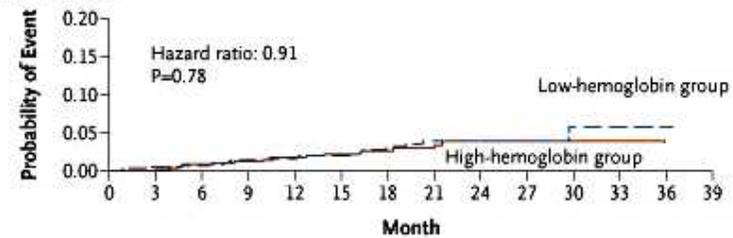
No. at Risk	
High-hemoglobin	715 654 587 520 457 355 270 176 101 72 55 23
Low-hemoglobin	717 660 594 539 499 397 293 182 107 67 44 23

## B Hospitalization for CHF (without RRT)



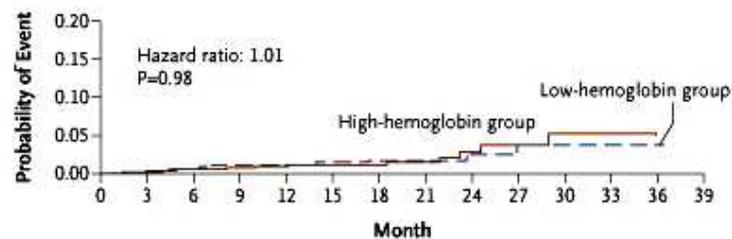
No. at Risk	
High-hemoglobin	715 656 591 523 461 359 273 179 102 73 56 23
Low-hemoglobin	717 663 596 544 504 402 299 187 111 70 45 24

## C Myocardial Infarction



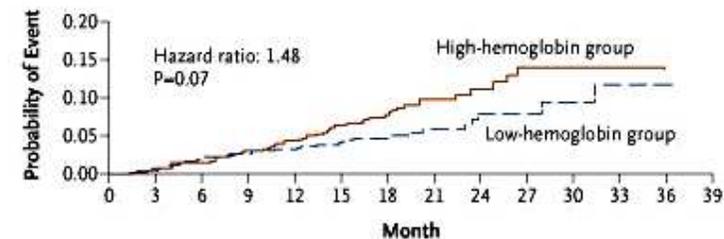
No. at Risk	
High-hemoglobin	715 674 612 543 487 387 295 193 113 79 59 25
Low-hemoglobin	717 672 609 560 520 415 307 192 115 73 49 26

## 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

# ACORD study: Methods

- **Study design:**
  - Randomized controlled trial
  - Target Hb: 13–15 g/dL (group 1) vs 10.5–11.5 g/dL (group 2)
- **Inclusion criteria:**
  - Diabetes mellitus type 1 or 2
  - Mild to moderate anemia
  - Chronic kidney disease stage 1 to 3
- **Endpoints:**
  - 1°: Change in left ventricular mass index (LVMI)
  - 2°: Echocardiographic variables, renal function, QOL, safety

# ACORD study: Results

- **Hb: 13.5 g/dL (group 1) vs 12.1 g/dL (group 2),  $p < 0.001$**
- **LVMI: 112.3 g/m<sup>2</sup> vs 116.5 g/m<sup>2</sup>, ns**
- **Change in LVMI: greater numerical decrease in group 1, ns**
- **Change in CrCl: -5.5 mL/min vs -3.4 mL/min, ns**
- **Change in QOL (SF36): +5.33 vs -0.033,  $p = 0.04$**
- **Safety: No relevant differences**

# ACORD study: Results

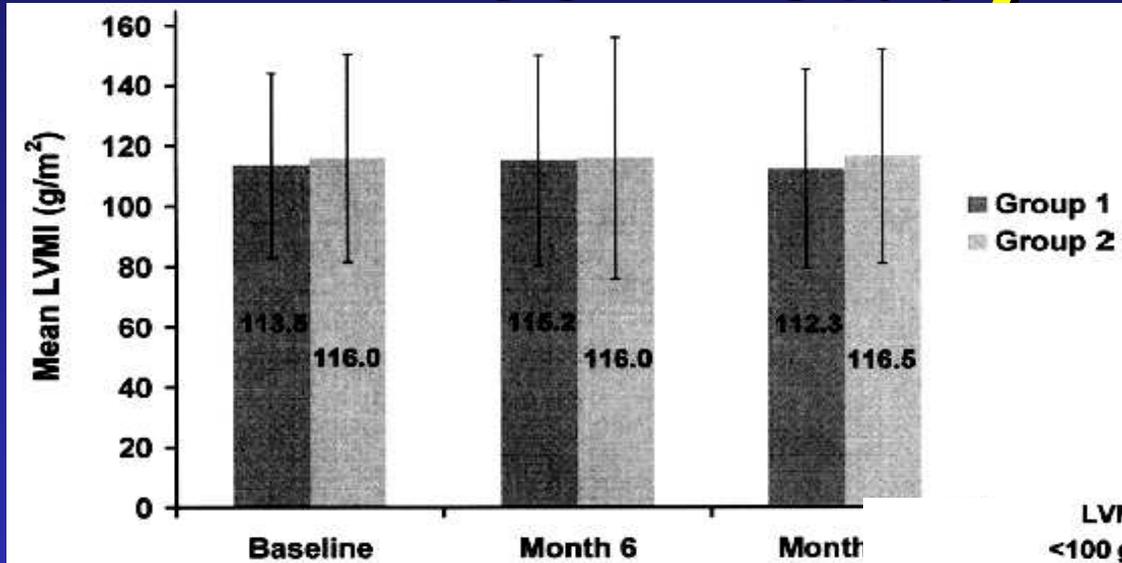
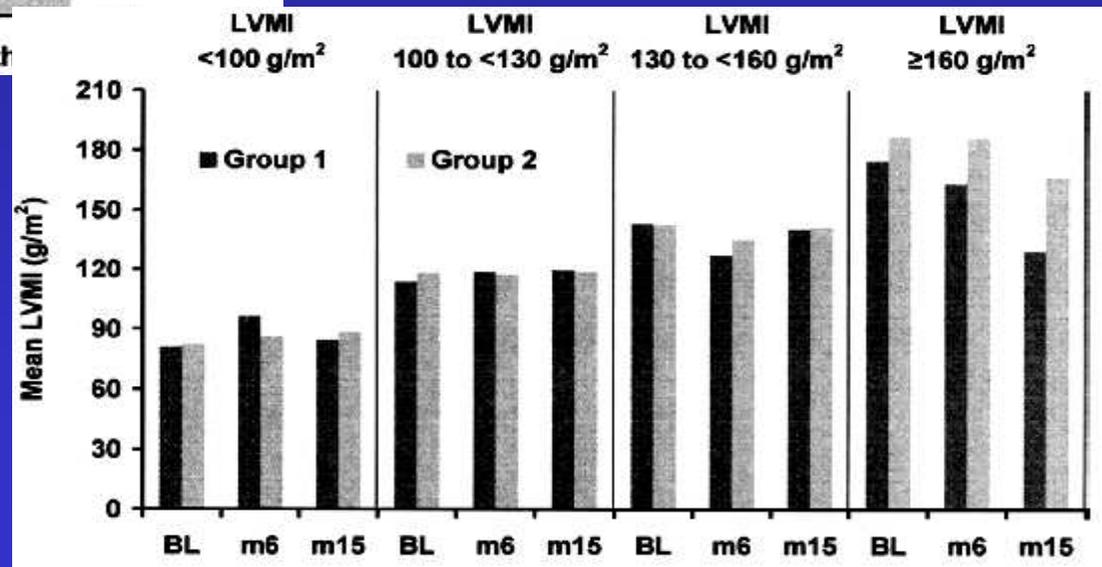
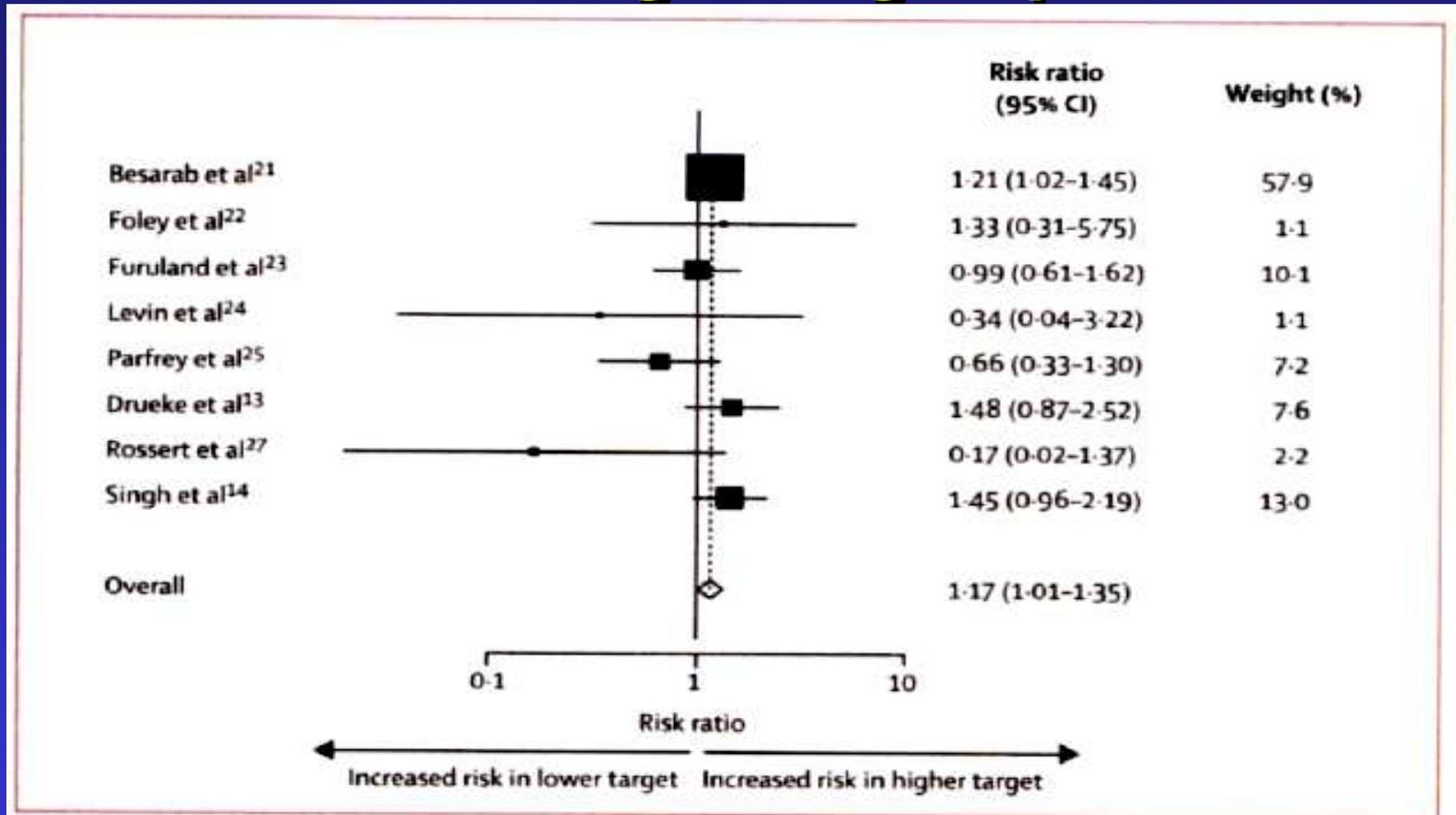


Figure 4. LVMI (mean ± SD) by treatment group.

Figure 5. LVMI (mean ± SD) over time by degree of LVH at baseline. Abbreviation: BL, baseline.



# Risk of all-cause mortality in the higher haemoglobin group compared with the lower haemoglobin group



**Figure 2: Risk of all-cause mortality in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)**

The Roger et al trial<sup>26</sup> is not reported because there were no deaths in either group.

# Risk of myocardial infarction in the higher haemoglobin group compared with the lower haemoglobin group

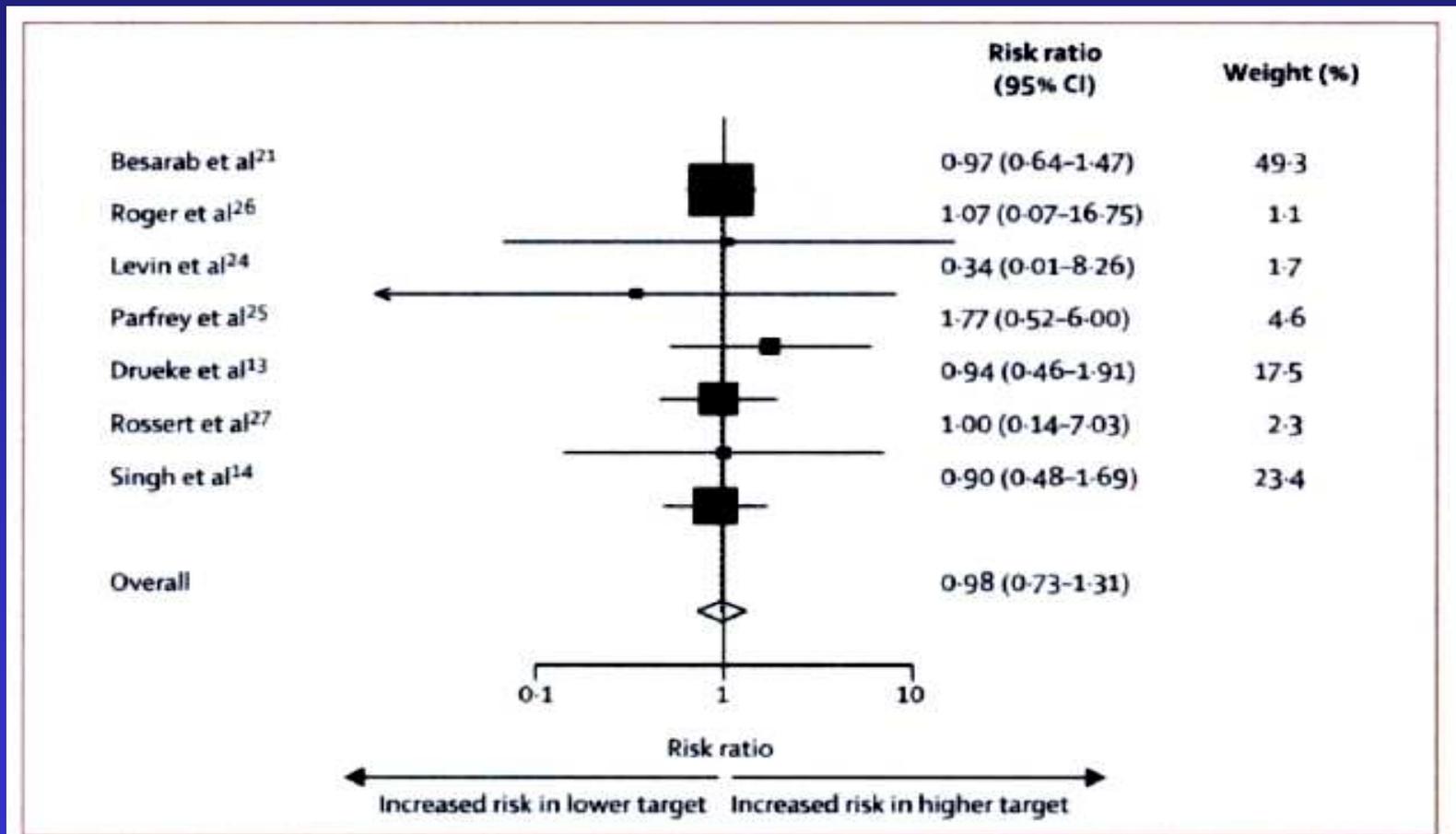


Figure 3: Risk of myocardial infarction in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

# Risk of poorly controlled blood pressure in the higher haemoglobin group compared with the lower haemoglobin group

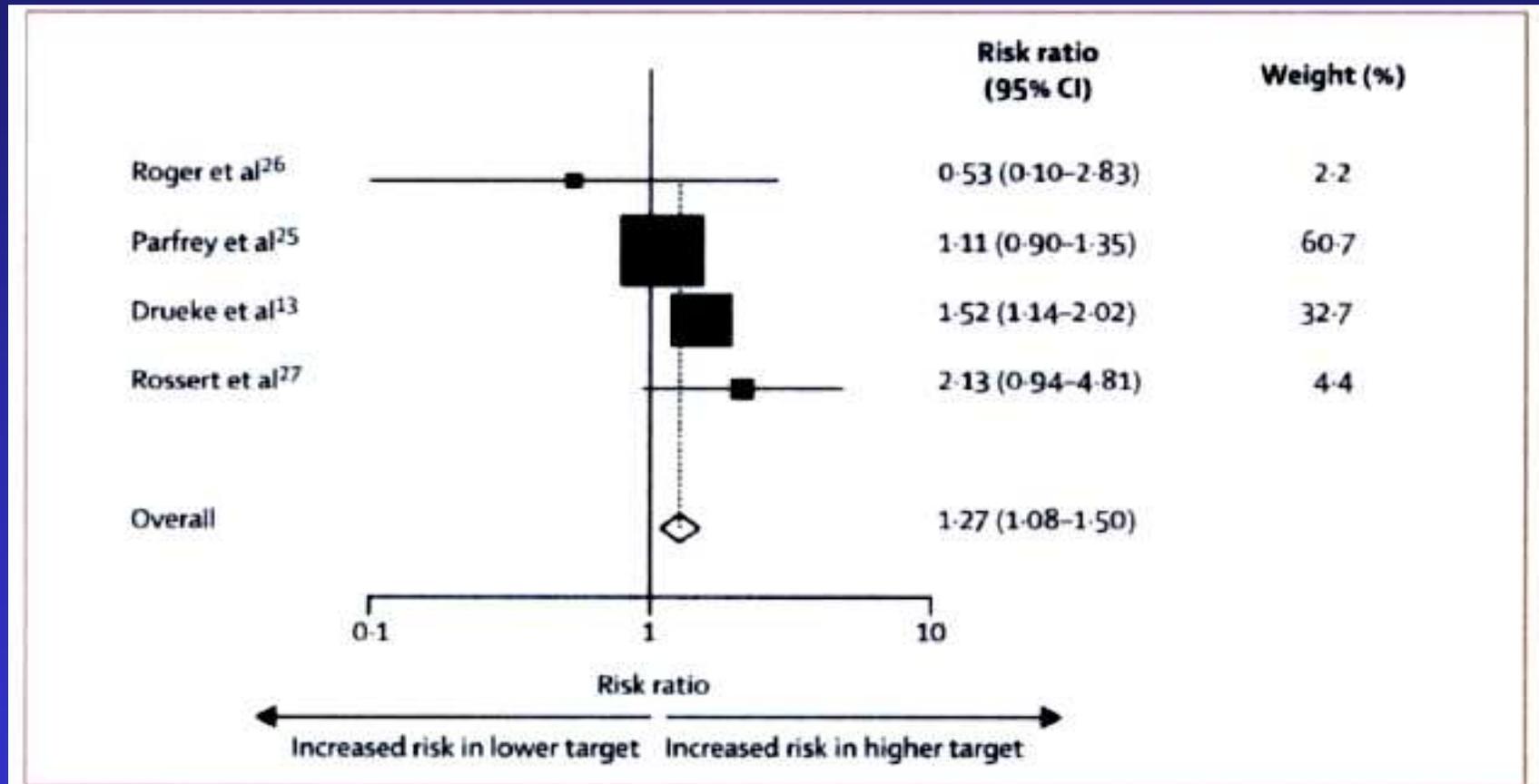
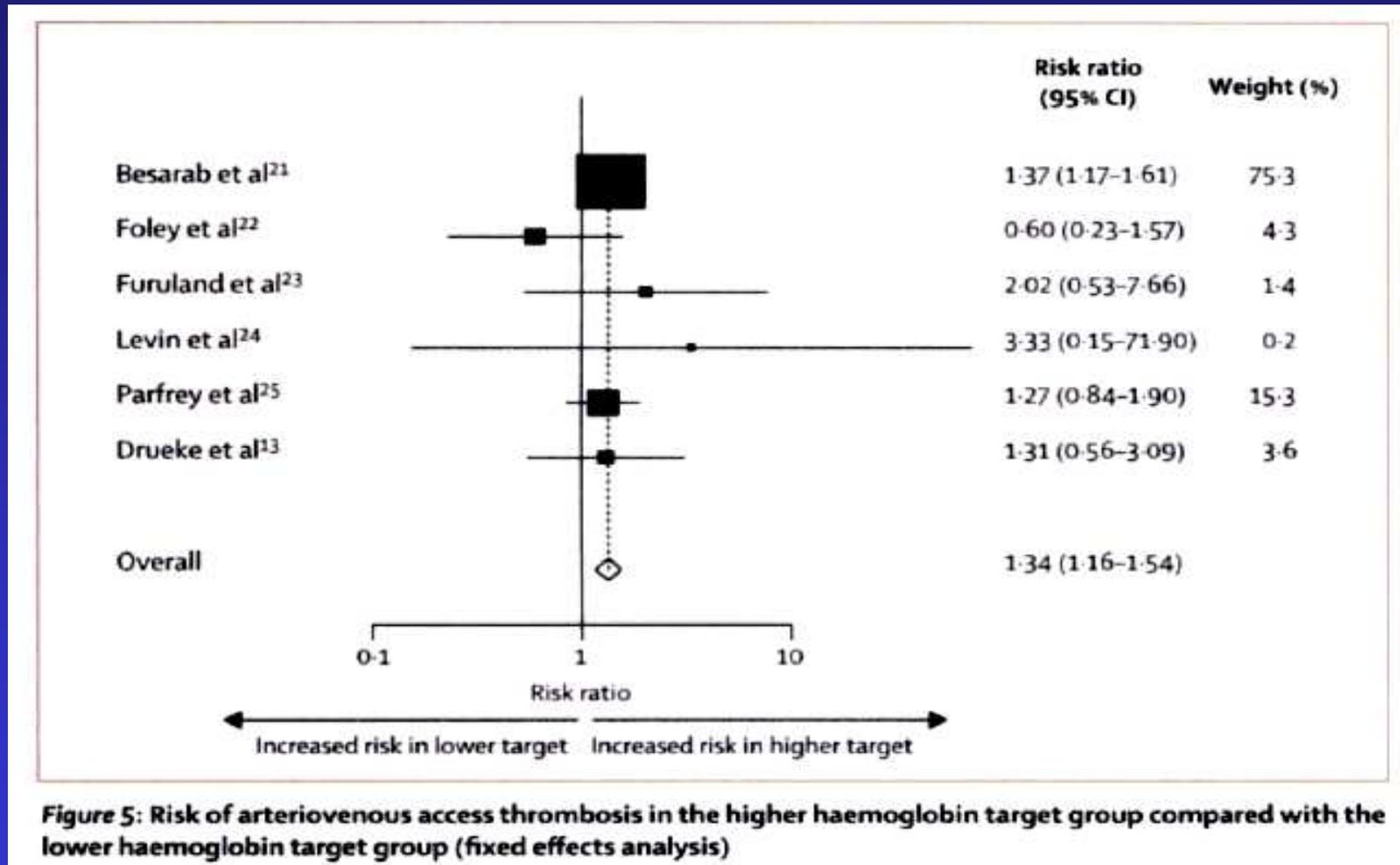


Figure 4: Risk of poorly controlled blood pressure in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

# Risk of arterio-venous access thrombosis in the higher haemoglobin target group compared with the lower haemoglobin target group



## Optimal target Hb – a public debate

Phrommintikul A, Haas SJ, Elisk M et al.: Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. *Lancet* 369, 2007

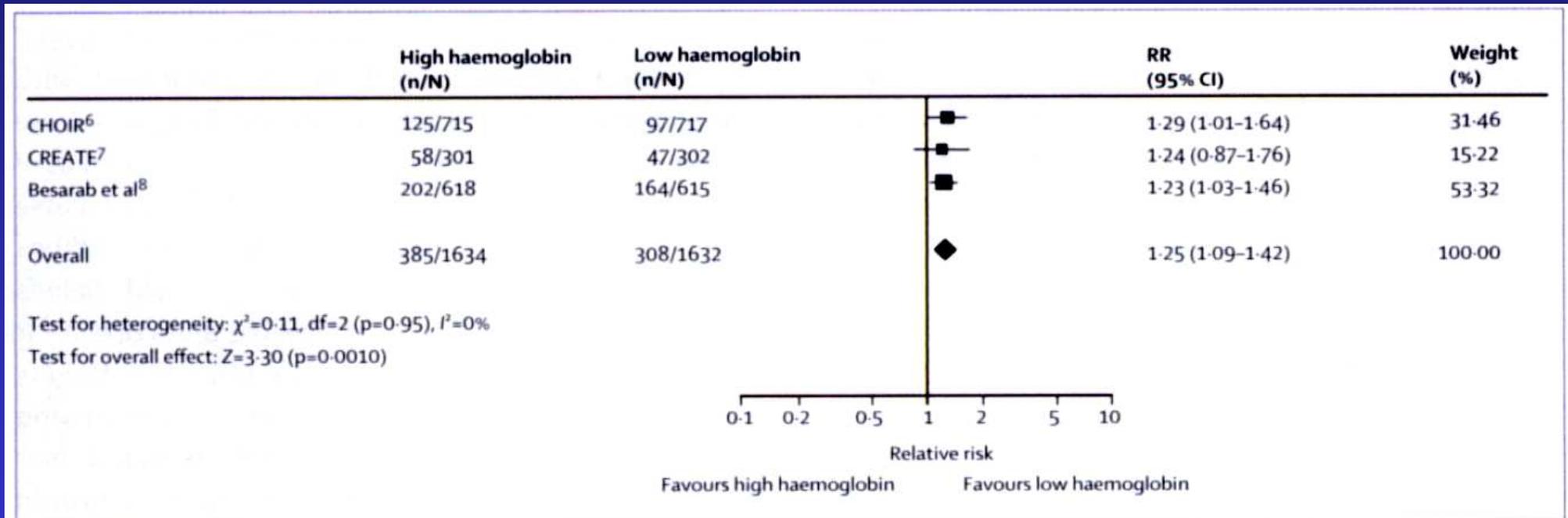
Strippoli GF, Tognoni G, Navanethan SD, Nicolucci A, Craig JC. *Lancet* 369, 2007

### Haemoglobin targets: we were wrong, time to move on

On the basis of the existing published trials, summarised by Phrommintikul and colleagues,<sup>4</sup> we contend that more trials of haemoglobin target concentrations in patients with chronic kidney disease are no longer required, should be stopped, or at least it should be made fully and publicly explicit what reasons grant their continuation. We say

this because of the rights of patients, and the credibility of the scientific nephrological community, after such a long history of contradictions. The question has been answered: higher haemoglobin target concentrations increase mortality via cardiovascular endpoints. Part rather than complete correction of anaemia is appropriate.

# Effect of different haemoglobin target concentrations on serious cardiovascular events

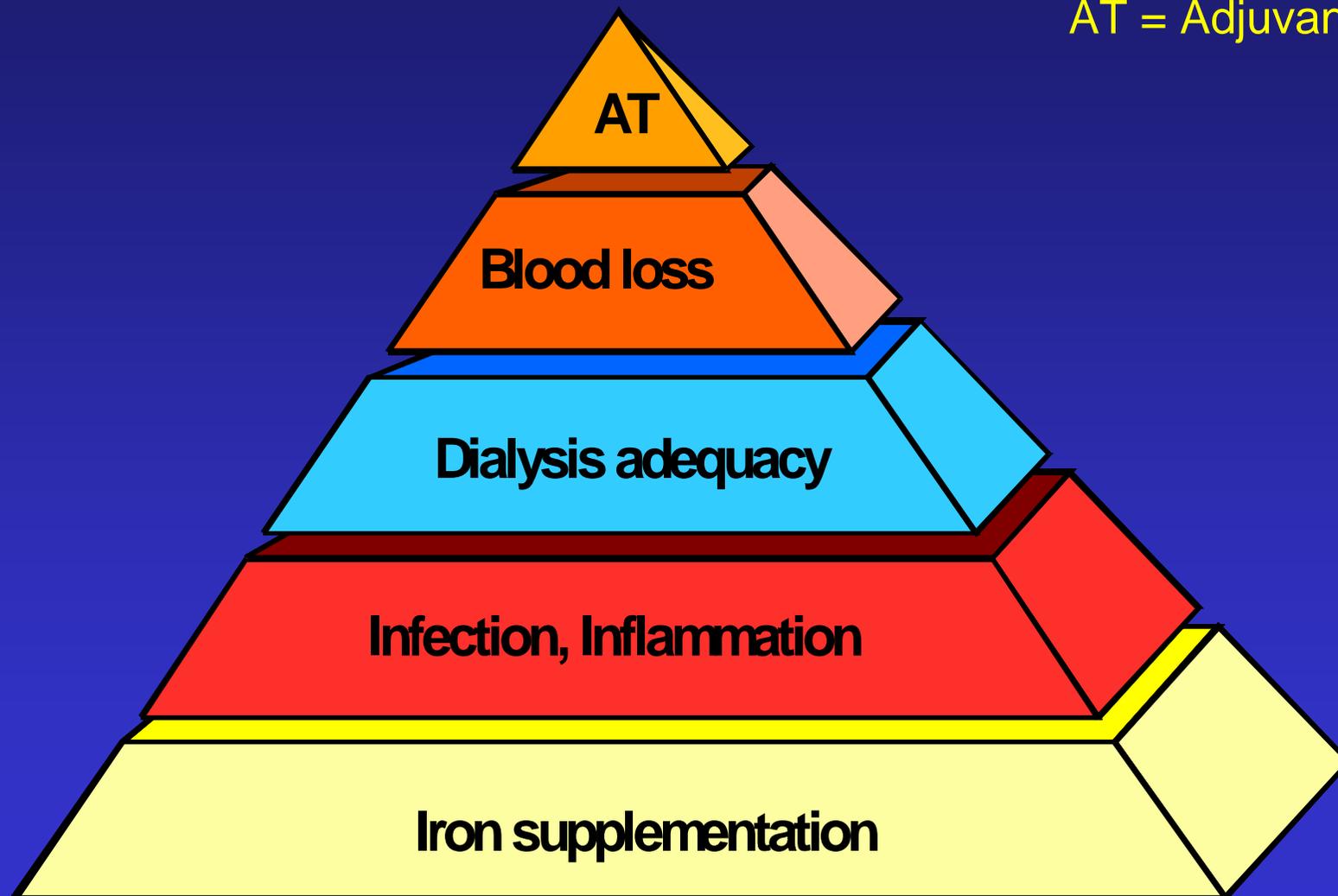


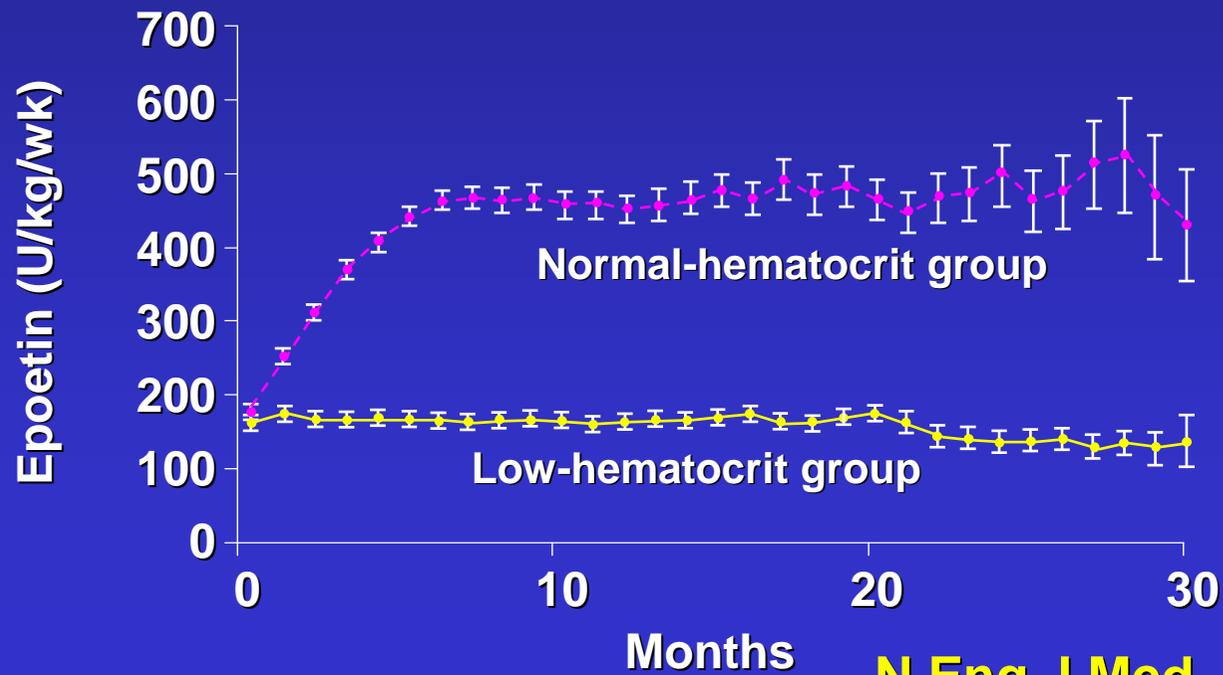
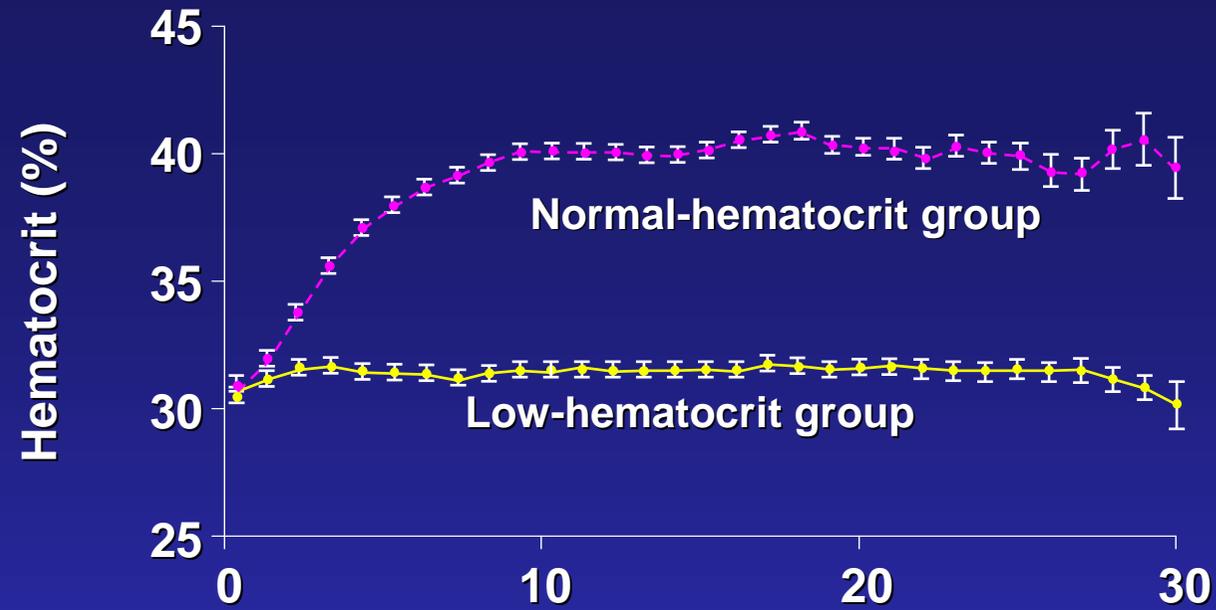
**Figure:** Effects of different haemoglobin target concentrations on serious cardiovascular events

RR=relative risk.

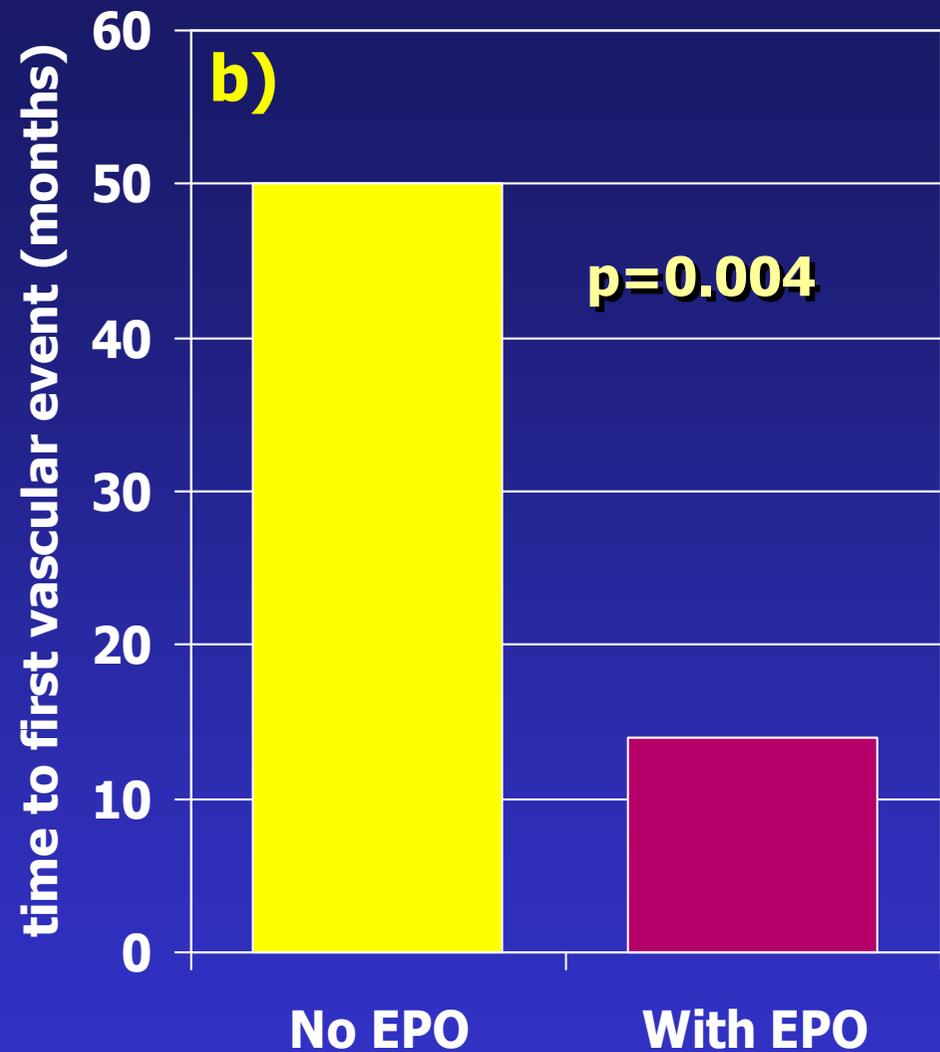
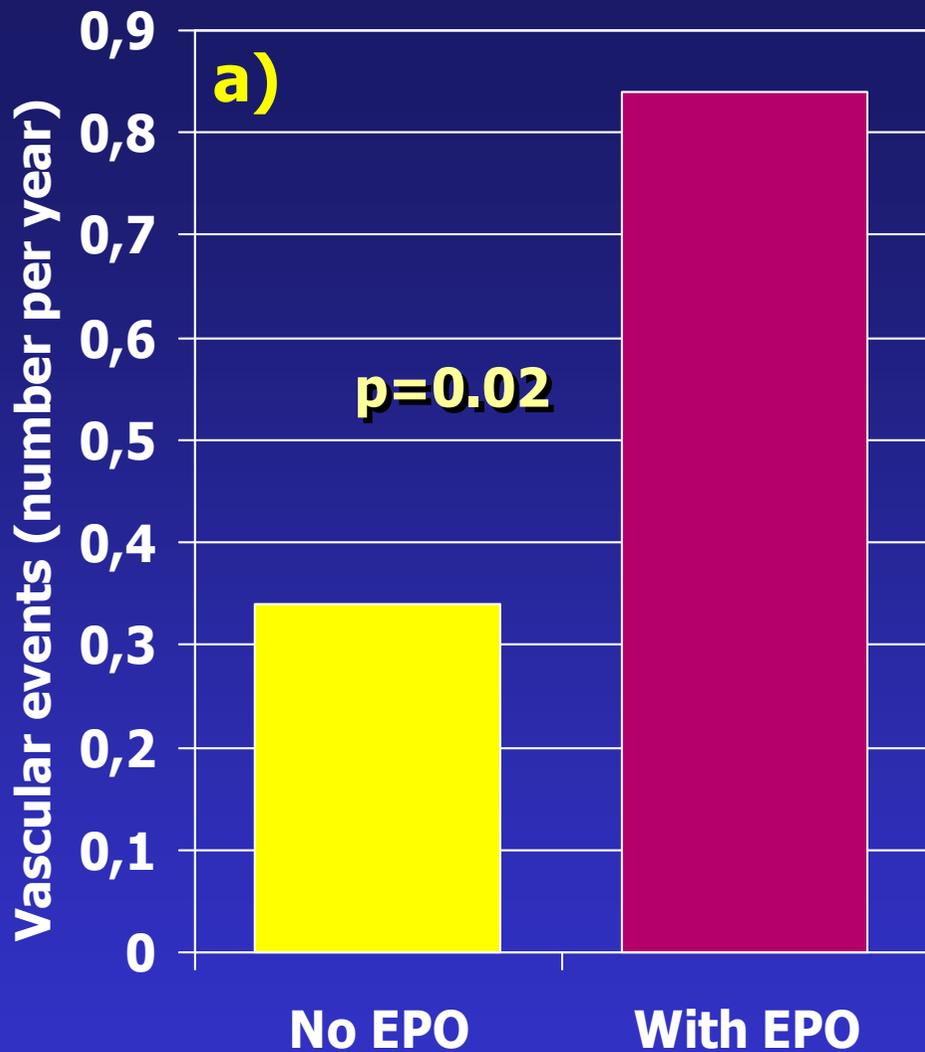
# Factors influencing anemia treatment

AT = Adjuvant therapy





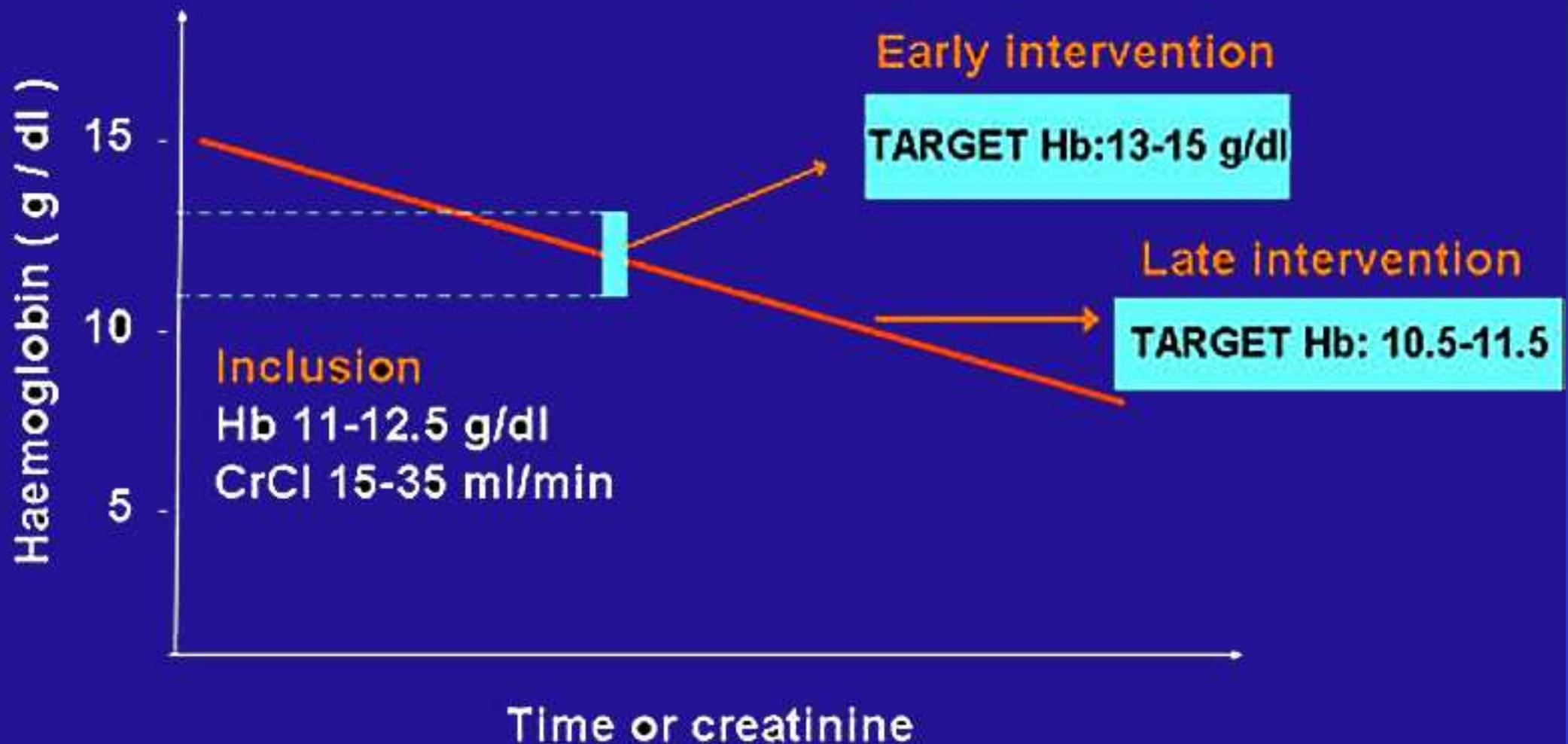
**Besarab A. et al.:**  
**N Eng J Med., 1998, 339, 584-590**



**Vascular events (a) and time to first vascular event (b) in diabetic patients on peritoneal dialysis not receiving EPO or receiving EPO therapy.**

**Waaken M., Zimmerman S.W.: Am J Kidney Dis (1998) 32: 488**

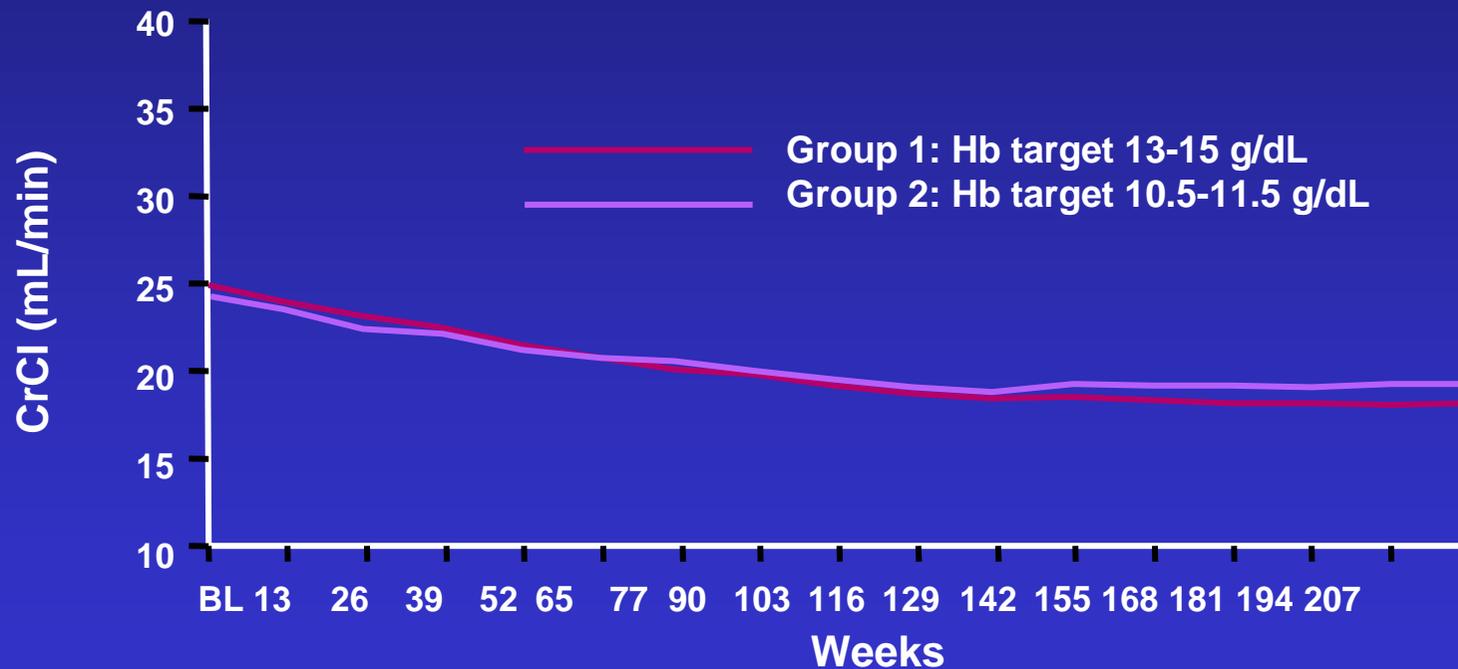
# Treatment initiation and target Hb levels for epoetin beta therapy in the CREATE trial



*Drueke T.B. et al. New Engl J Med 2006, 16, 2071-84*

# Negative Impact on Renal Function with Hb Correction to 13-15 g/dL

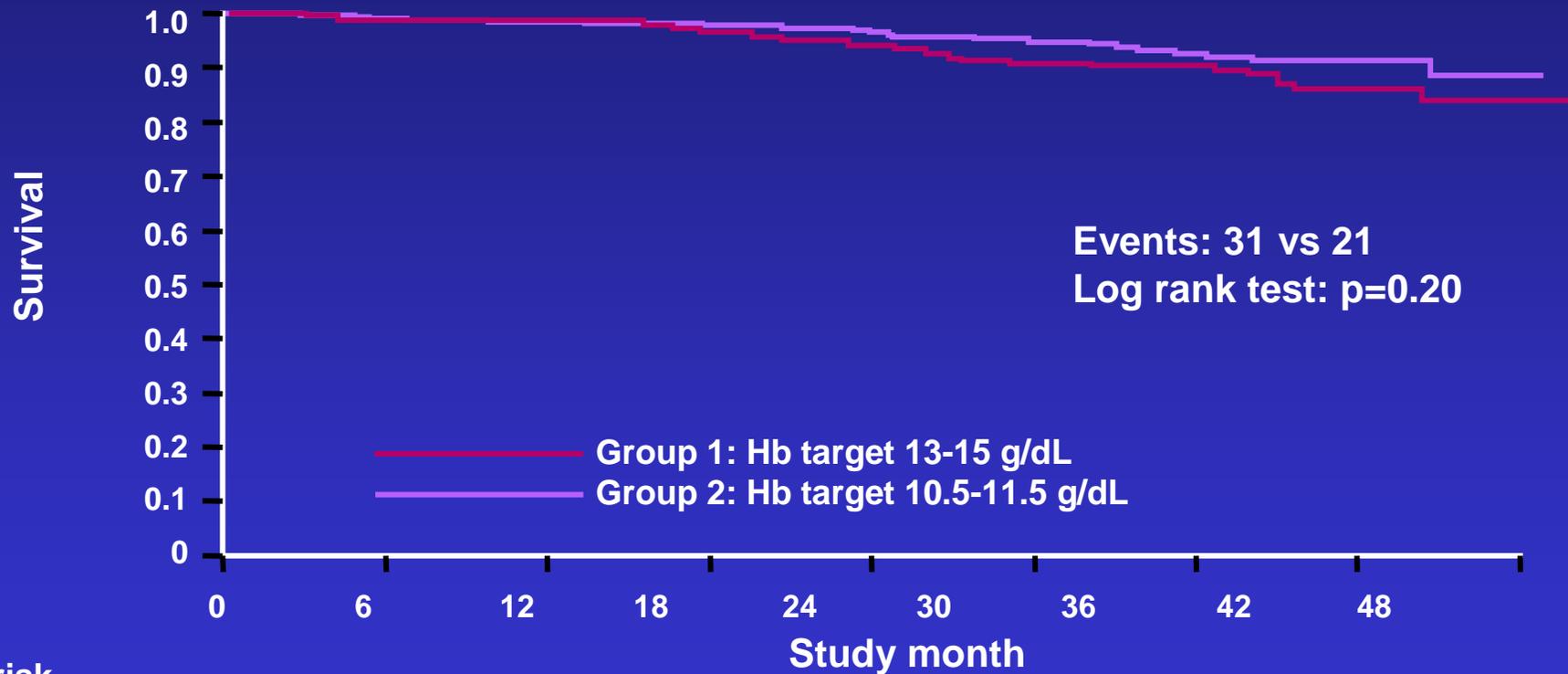
## CREATE



*Drueke T.B. et al. New Engl J Med 2006, 16, 2071-84*

# Negative Impact on Mortality with Hb Correction to 13-15 g/dL

## CREATE



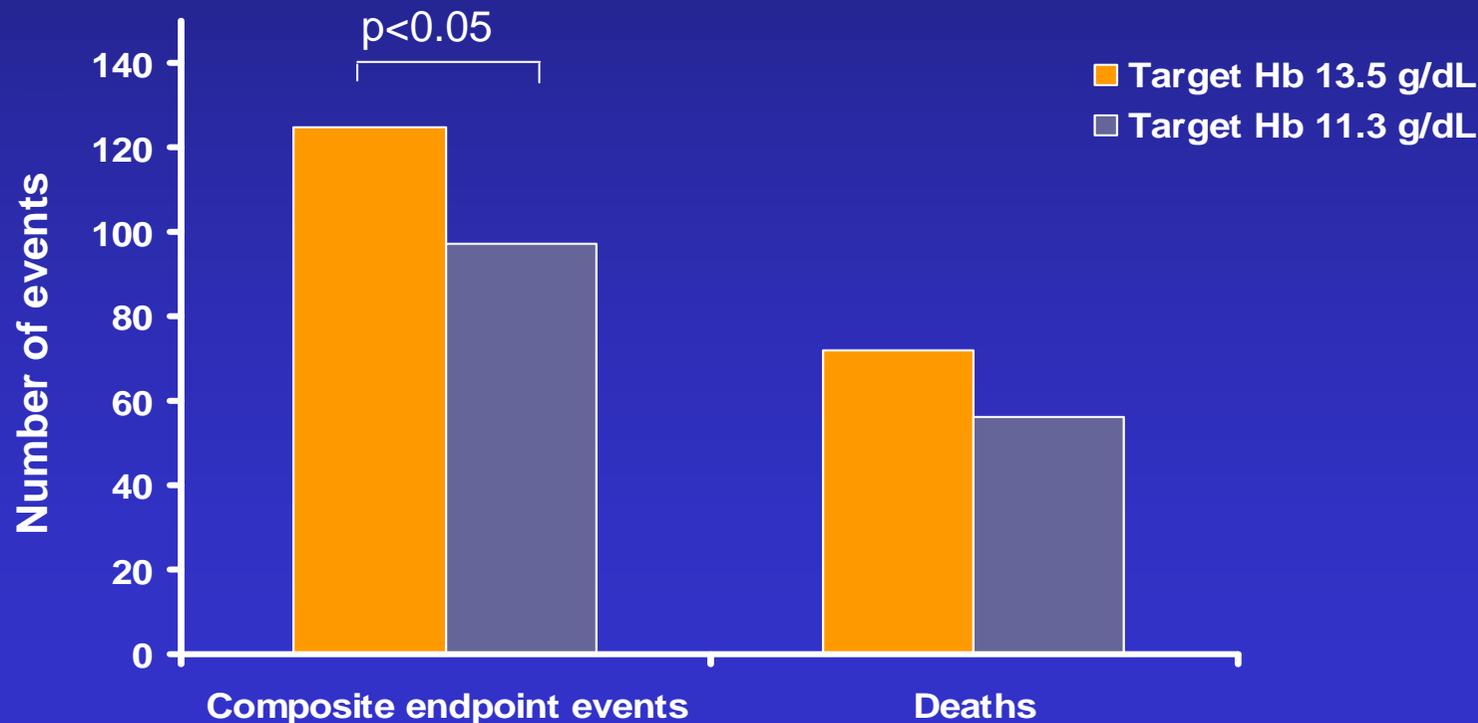
N at risk

Group 1	301	287	283	271	235	187	128	75	2
Group 2	302	297	290	280	253	201	140	78	4

*Drueke T.B. et al. New Engl J Med 2006, 16, 2071-84*

# Increased Risk with Hb Correction to 13.5 g/dL in Non-Dialysis CKD Patients

**CHOIR:** 1,432 non-dialysis CKD patients from 130 US centres; comparing impact of Hb correction to 13.5 g/dL with correction to 11.3 g/dL on composite endpoint events (mortality, stroke, heart attack, hospitalisation) in patients on epoetin alfa therapy



*Singh A.K. et al. New Engl J Med 2006, 16, 2085-98*

# Evidence Behind Target Hb >11 g/dL EBPG 2004

- Improvement in QoL      Abundant evidence (retrospective & prospective studies)
- Reduction in CV event rates      Some evidence based on small randomised controlled trials in ESRD patients
- Reduction in mortality      Correlation based on retrospective studies and registry data
- Slower CKD progression      No clear benefit based on randomised controlled trials

# Evidence Behind Target Hb >11 g/dL K/DOQI 2006

- Improvement in QoL Direct supporting evidence for benefit in dialysis patients; some benefit likely in non-dialysis patients
- Reduction in CV event rates Direct evidence for no benefit, or possible harm in dialysis patients; uncertainty in non-dialysis patients
- Reduction in mortality High quality supporting evidence for no benefit or possible harm in dialysis patients particularly with CVD; uncertainty in non-dialysis patients
- Slower CKD progression Low quality evidence suggesting no benefit, potential harm

# Evidence for Defining an Upper Hb Limit

**Hb correction to 13-15 g/dL**

**QoL**

Strong evidence for improvement

**CV morbidity**

Conflicting evidence

**Mortality**

Neutral to date

**CKD progression**

No evidence of effect

**CURRENTLY INCONCLUSIVE EVIDENCE  
FOR A SPECIFIC UPPER HAEMOGLOBIN LIMIT**

# **Causes of an inadequate response to epoetin treatment (1)**

**The most common cause  
of an incomplete response to epoetin  
is **absolute or functional iron deficiency****

# Absolute and functional iron deficiency

- ◆ **Absolute iron deficiency**

Deficit of total body iron store

Ferritin < 100 µg/l

- ◆ **Functional iron deficiency**

Failure of iron to reach proliferating erythroblasts despite sufficient iron stores

Ferritin > 100 µg/l

TSF < 20%

# Target levels of iron parameters in HD patients

## Recommendations

Parameter	Optimal	Acceptable
▪ Ferritin [ $\mu\text{g/l}$ ]	200–500	100–800
▪ Transferrin saturation [%]	30–40	20–50
▪ Proportion of hypochromic red blood cells [%]	< 2.5	< 10

# Iron Substitution

## Recommendations

- Intravenous iron substitution is mandatory due to the unavoidable blood losses in hemodialysis patients (1–4 l blood/year).
- HD patients should receive at least one i.v. iron administration every two weeks.
- Continuous high dose i.v. iron therapy (Ferritin > 1000 µg/L) could result in neutrophil inhibition.
- The higher the administered i.v. iron dose the slower the administration rate.

# Infection and Iron Sucrose North American Clinical Trial and USRDS

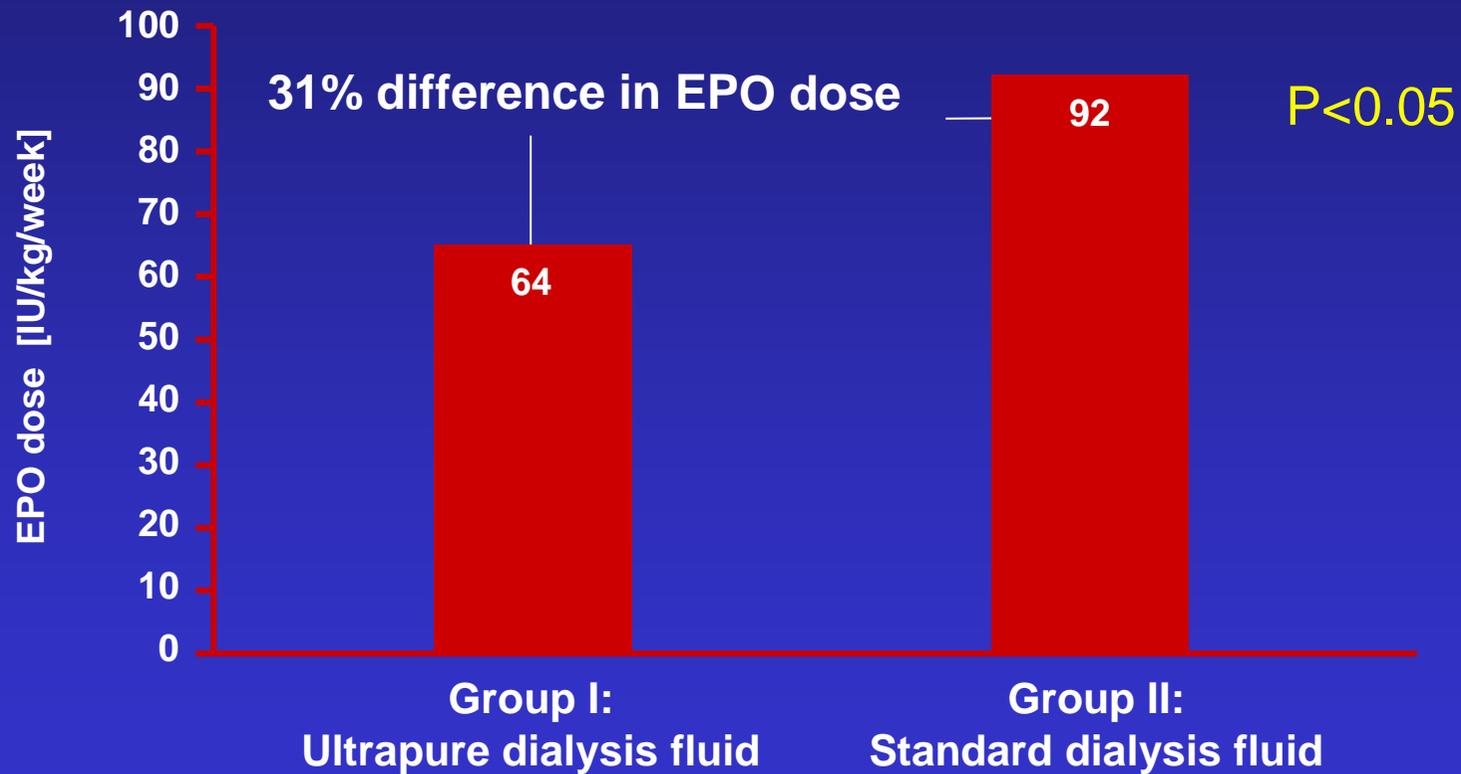
Hospitalization for Infection  
per 1,000 Patient Years



Aronoff, et al. Iron Sucrose in Hemodialysis Patients: Safety and Efficacy of Iron Replacement and Maintenance Therapy. Submitted.  
U.S. Renal Data System, USRDS 1999 Annual Data Report, p 92.  
U.S. Renal Data System, USRDS 2002 Annual Data Report: Atlas of End-Stage Renal Disease in the United States

# Hemodialysis quality / quantity

## Impact of dialysis fluid on EPO dose

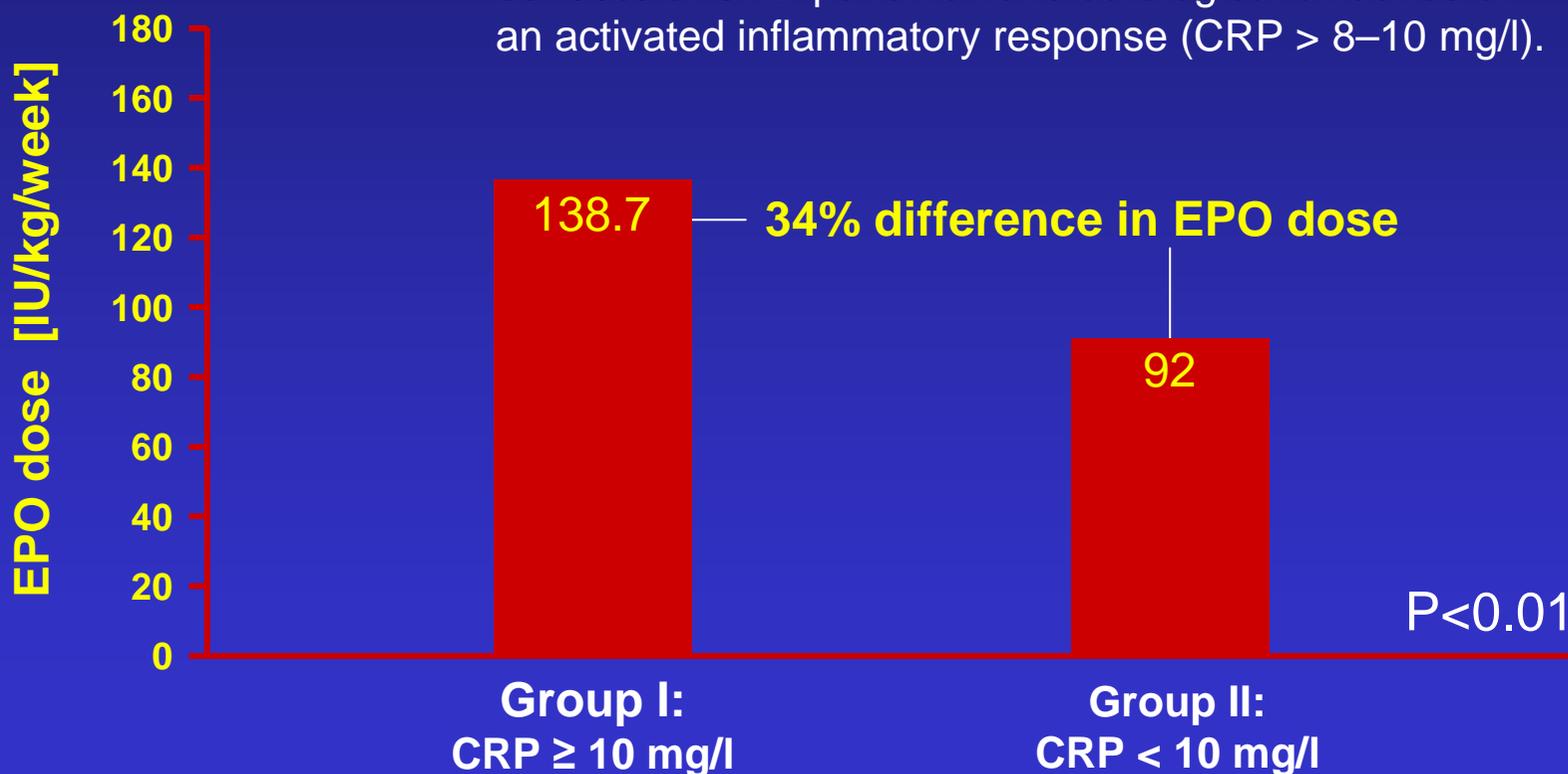


Sitter T et al., NDT 2000;15:1207–1211.

# Inflammation – Impact on anemia treatment

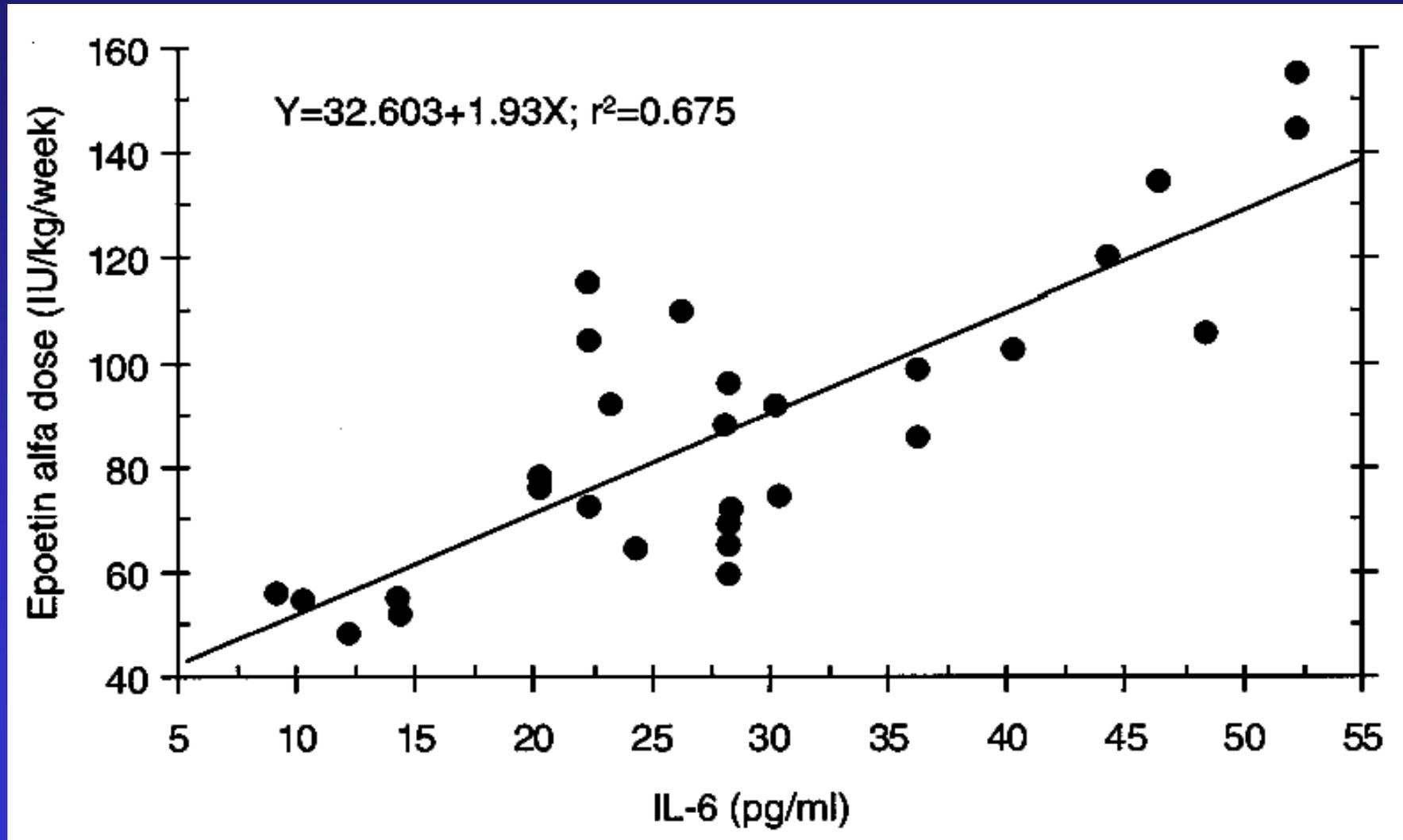
## Influence of CRP concentration on EPO dose

30–50% of CKD patients have serological evidence of an activated inflammatory response (CRP > 8–10 mg/l).



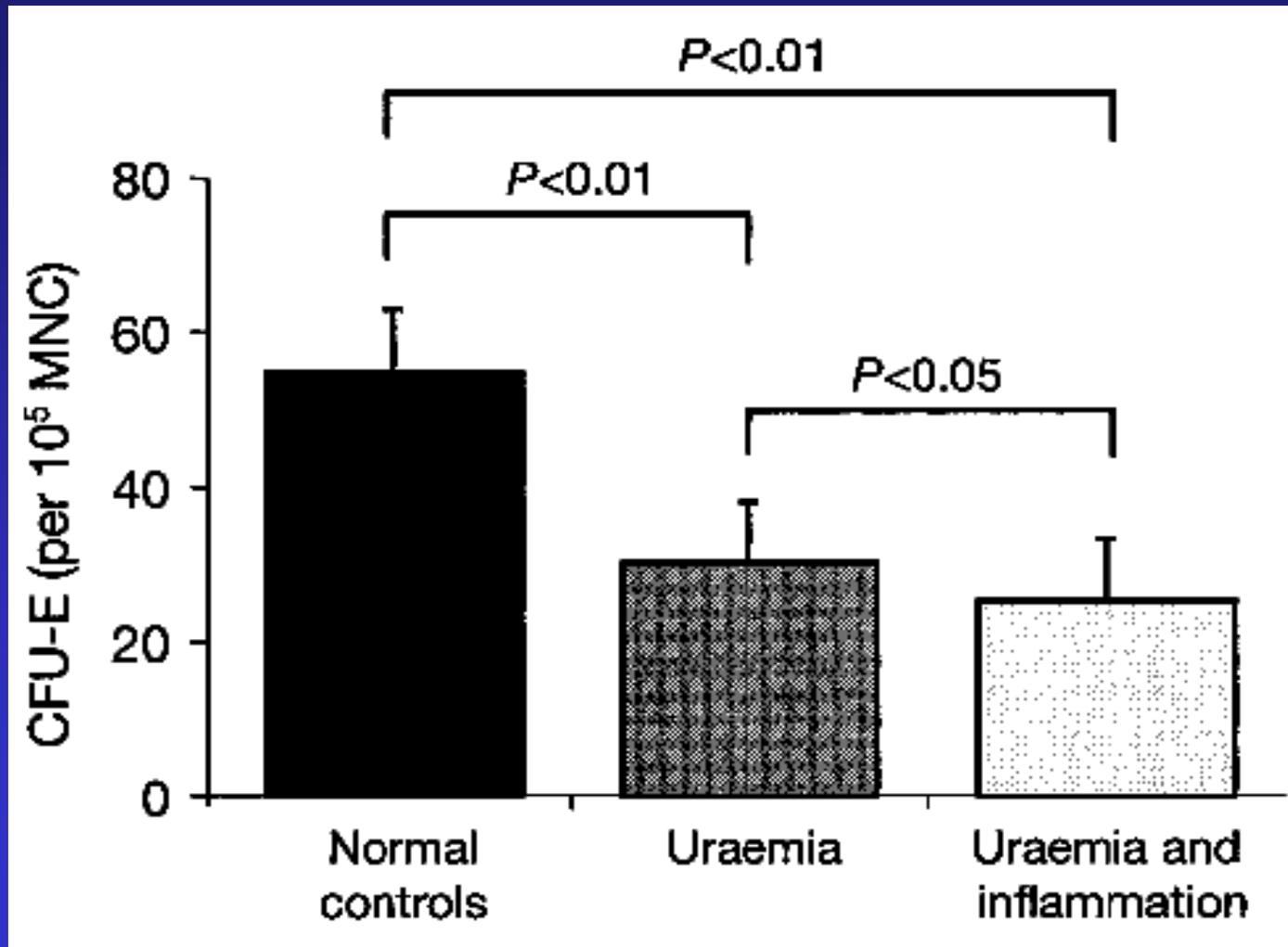
Stenvinkel P, NDT 2002;17 Suppl 5:32–37.  
Nitta K, Acta Haematol 2002;108;168–170.

# Correlation between inflammatory response (IL-6) and epoetin alfa dose



Richardson D. Nephrol Dial Transplant 2002, 17, suppl 1: 53-59

# Effect of uraemia and inflammation on erythropoiesis.



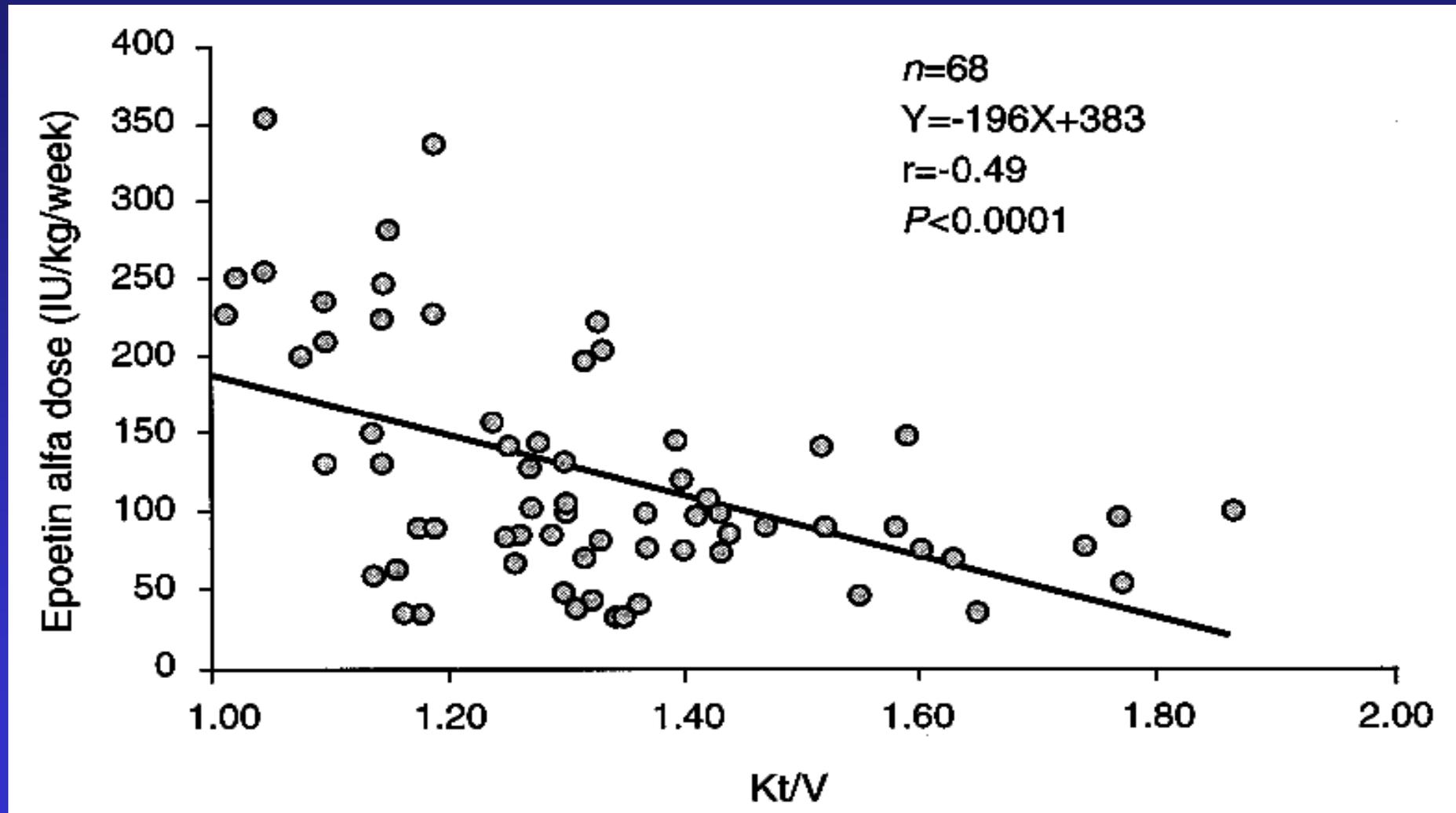
Allen DA. Et al. J Invest Med. 1999, 47: 204-211

# Infection

## Recommendations

- ◆ Iron supplementation should be stopped during documented infection since intravenous iron may also enhance bacterial growth.
- ◆ Patients with CRP  $> 20$  mg/l should be screened for silent infection of hemodialysis access grafts (visual control), paradontal disease or any low grade infection (diabetic foot ulcers).
- ◆ Elderly patients should be screened for urinary tract infection when Epoetin requirements increase.

# Correlation between dialysis adequacy (Kt/V) and epoetin alfa dose



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## PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

NICOLE CASADEVALL, M.D., JOELLE NATAF, M.D., BÉATRICE VIRON, M.D., AMIR KOLTA, M.D.,  
JEAN-JACQUES KILADJIAN, M.D., PHILIPPE MARTIN-DUPONT, M.D., PATRICK MICHAUD, M.D., THOMAS PAPO, M.D.,  
VALÉRIE UGO, M.D., IRÈNE TEYSSANDIER, B.S., BRUNO VARET, M.D., AND PATRICK MAYEUX, PH.D.

### ABSTRACT

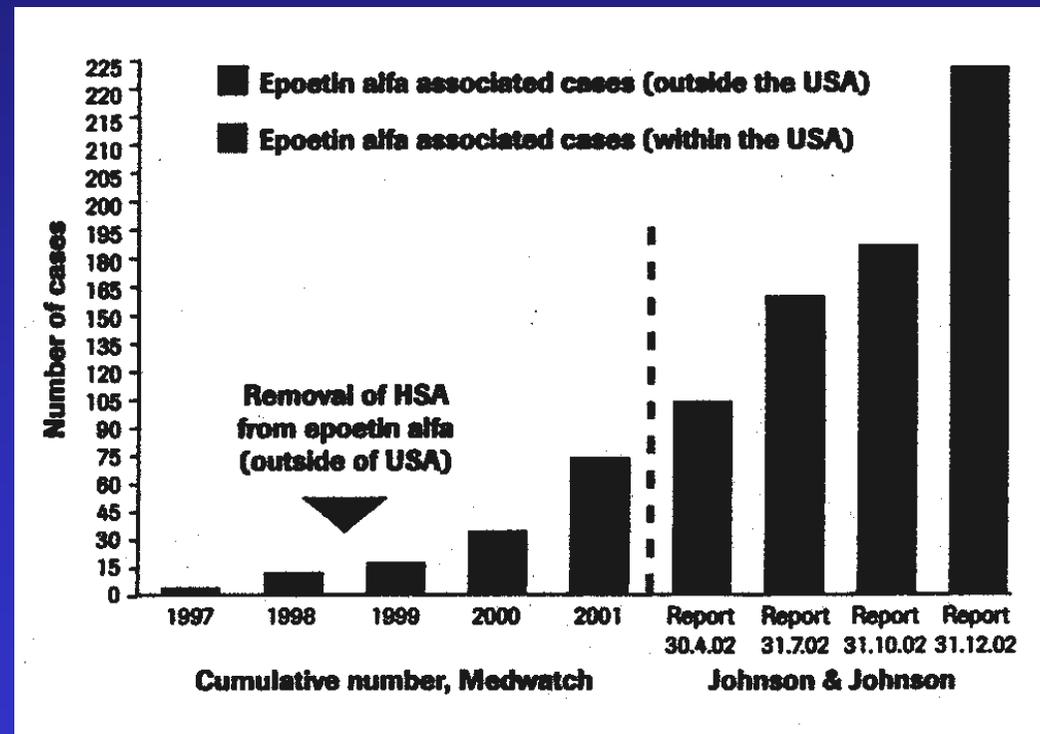
**Background** Within a period of three years, we identified 13 patients in whom pure red-cell aplasia developed during treatment with recombinant human erythropoietin (epoetin). We investigated whether there was an immunologic basis for the anemia in these patients.

**Methods** Serum samples from the 13 patients with pure red-cell aplasia were tested for neutralizing antibodies that could inhibit erythroid-colony formation by normal bone marrow cells in vitro. The presence of antierythropoietin antibodies was identified by means of binding assays with the use of radiolabeled intact, deglycosylated, or denatured epoetin.

level of erythropoiesis, as evidenced by the presence of erythroblasts in the bone marrow and reticulocytes in the blood.

The gene for human erythropoietin was cloned in 1985,<sup>3,4</sup> and recombinant human erythropoietin (epoetin) was approved for marketing in France in 1988 for the treatment of anemia in patients undergoing dialysis for chronic renal failure. Endogenous erythropoietin is a heavily glycosylated protein, and glycosylation is essential for its biologic activity. Endogenous erythropoietin and epoetin have different patterns of glycosylation, which involve primarily the sialic acid composition of oligosaccharide groups.<sup>5</sup> Epoetin alfa

# Cumulative incidence of suspected and confirmed PRCA cases associated with epoetin administration



## Incidence of antibody-mediated PRCA in patients with renal anaemia

The wording, number of cases, routes of administration and distribution information are as provided by the companies.

Company	No. of cases		Route	Patient experience years with product (highest possible incidence per 10,000 patient years)	Number of cases per country
	Sole use	Not sole use			
Ortho Biotech Eporex®	106 (+ 67 under investigation)	15	s.c.	1.7 million (1.11)	Not available
Roche Neorecormon®	5	3 – association cannot be ruled out	s.c	~650,000 (0.12)	England: 3 France: 1 Germany: 2 Spain: 1 Switzerland: 1
Amgen Epogen®	4	0	s.c.: 1 i.v.: 2 both: 1	2.4 million (0.02)	USA: 4
Amgen Aranesp®	0	3 – unlikely to be associated	s.c.: 1 both: 2	56,000 (0.5)	Germany: 1 Italy: 1 Netherlands: 1

*Locatelli F. et al.: Nephrol Dial Transplant , 2004*

# Concomitant Therapy

## Drugs possibly affecting Hb levels in HD patients

### Decrease Hb

Azathioprine

MMF

Antimetabolites

NSAIDs

### Increase Hb

Anti-TNF-alpha

Anticytokine Therapy

Talidomide

### No conclusive studies up to now

ACE-Inhibitors

Angiotensin-II blockers

Statins

# Summary

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## Approach

## Findings

---

### Gene therapy

- Increased EPO and haematocrit levels in recipient mice
- High variability

### Peptide EPO mimetics

- Agonist peptide family
- Inferior activity to epoetin
- Large molecular size

### Non-peptide EPO mimetics

- Small molecular size
- Low activity

### Modulators of receptor activity

- Inhibitors of haematopoietic cell phosphatase

# Summary

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## Approach

## Findings

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**Synthetic Erythropoiesis Protein (SEP)**

- Synthetic protein–polymer construct
- Longer half-life than epoetin

**Darbepoetin alfa**

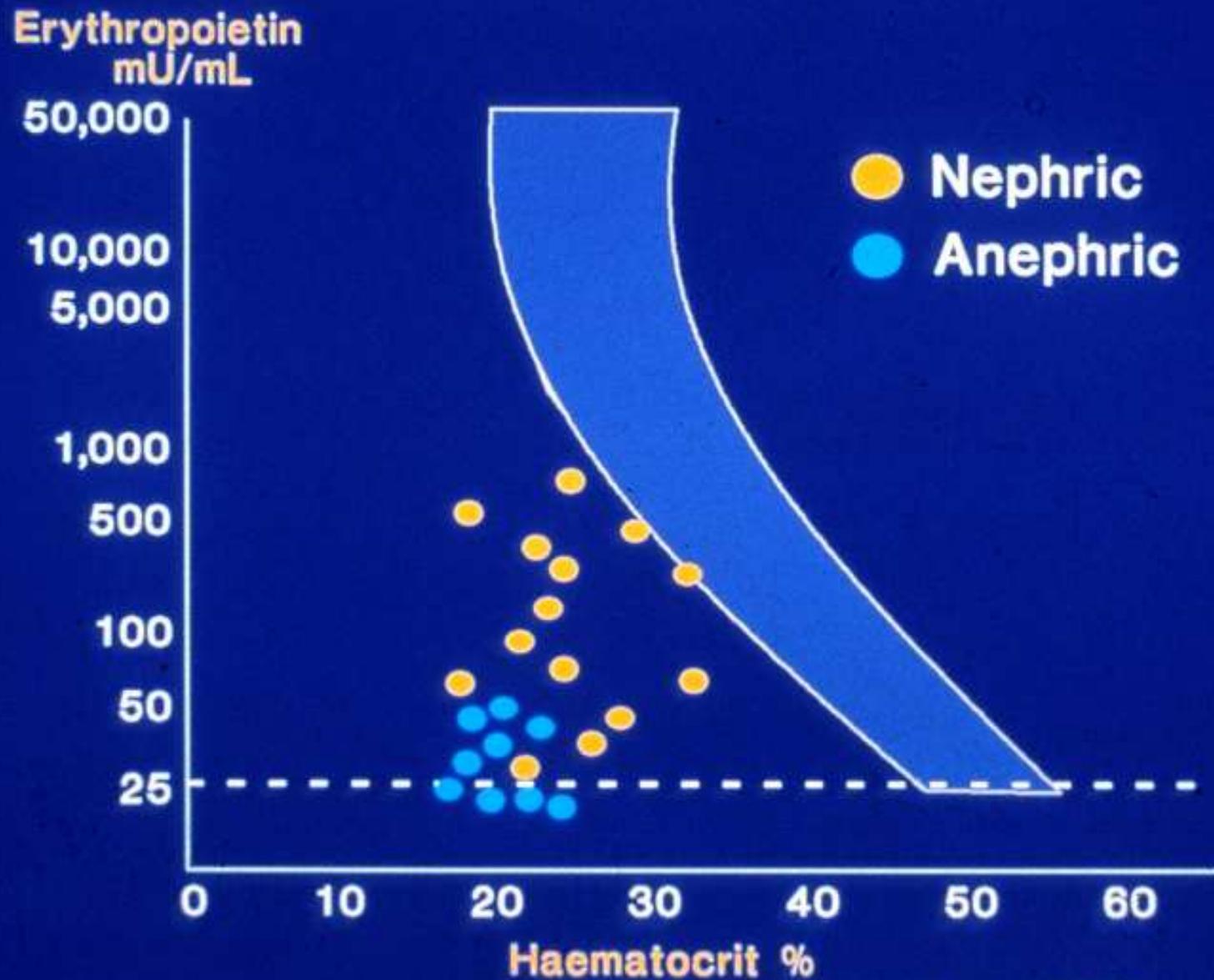
- Hyperglycosylated molecule
- Amino acid sequence of epoetin alfa altered to create carbohydrate attachment sites
- Longer half-life than epoetin

**and then . . .**

**Continuous Erythropoiesis Receptor Activator (CERA)**

- Innovative erythropoietic agent
  - Unique receptor binding characteristics
  - Longer half-life than epoetin
-

# Haematocrit vs Erythropoietin Level



Caro et al. 1979

# Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure

**Guideline I.1: Which patients should be evaluated and when should work-up begin?**

## **Recommendation**

**I. All patients with chronic anaemia associated with chronic kidney disease (CKD) should be investigated for possible treatment, irrespective of the stage of kidney disease and requirement for renal replacement therapy.**

**A work-up for a diagnosis of anaemia should be considered in patients with CKD when haemoglobin (Hb) concentration falls below the mean  $-2$  SD (i.e.  $<95\%$ ) Hb level of the normal population, adjusted for age and sex:**

- **$<11.5$  g/dl in adult female patients**
- **$<13.5$  g/dl in adult male patients**
- **$<12.0$  g/dl in adult male patients aged  $>70$  years.**

*(Evidence level B)*

# **Decreased bone marrow response to EPO stimulation in dialysis patients**

- **uraemic inhibitors („middle molecules“, polyamines, PTH, ribonuclease)**
- **iron deficiency**
- **inflammatory iron block (sepsis, inflammatory diseases, surgery and trauma- proinflammatory cytokines, hepcidine)**
- **aluminium excess/intoxication**
- **folate deficiency**
- **severe secondary hyperparathyroidism (osteitis fibrosa leads to decrease mass of erythropoietic marrow or myelofibrosis)**
- **physical inactivity**

# Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure

**Guideline I.2: What is the appropriate work-up to investigate anaemia in chronic kidney disease?**

## **Recommendation**

**I. An initial clinical and laboratory evaluation should be completed prior to considering the commencement of treatment with an erythropoiesis-stimulating agent (ESA) in patients with chronic kidney disease (CKD), to evaluate possible causes of anaemia superimposed on relative erythropoietin deficiency.**

*(Evidence level C)*

**Assessment of anaemia should involve laboratory measurement of the following parameters:**

- **haemoglobin (Hb) concentration—to assess the degree of anaemia**
- **red blood cell indices [mean corpuscular volume (MCV) and mean corpuscular Hb (MCH)]—to assess the type of anaemia**

## **Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure**

- **absolute reticulocyte count—to assess erythropoietic activity**
- **plasma/serum ferritin concentration—to assess iron stores**
- **functional iron available for erythropoiesis by the measurement of either:**
  - **percentage of hypochromic red blood cells (HRC)**
  - **plasma/serum transferrin saturation (TSAT)**
  - **reticulocyte Hb content (CHr)**
- **plasma/serum C-reactive protein (CRP)—to assess inflammation.**  
*(Evidence level B)*

**In patients on dialysis, the frequency and the received dose of dialysis should also be evaluated.**  
*(Evidence level C)*

## **Initial epoetin administration in dialysis patients**

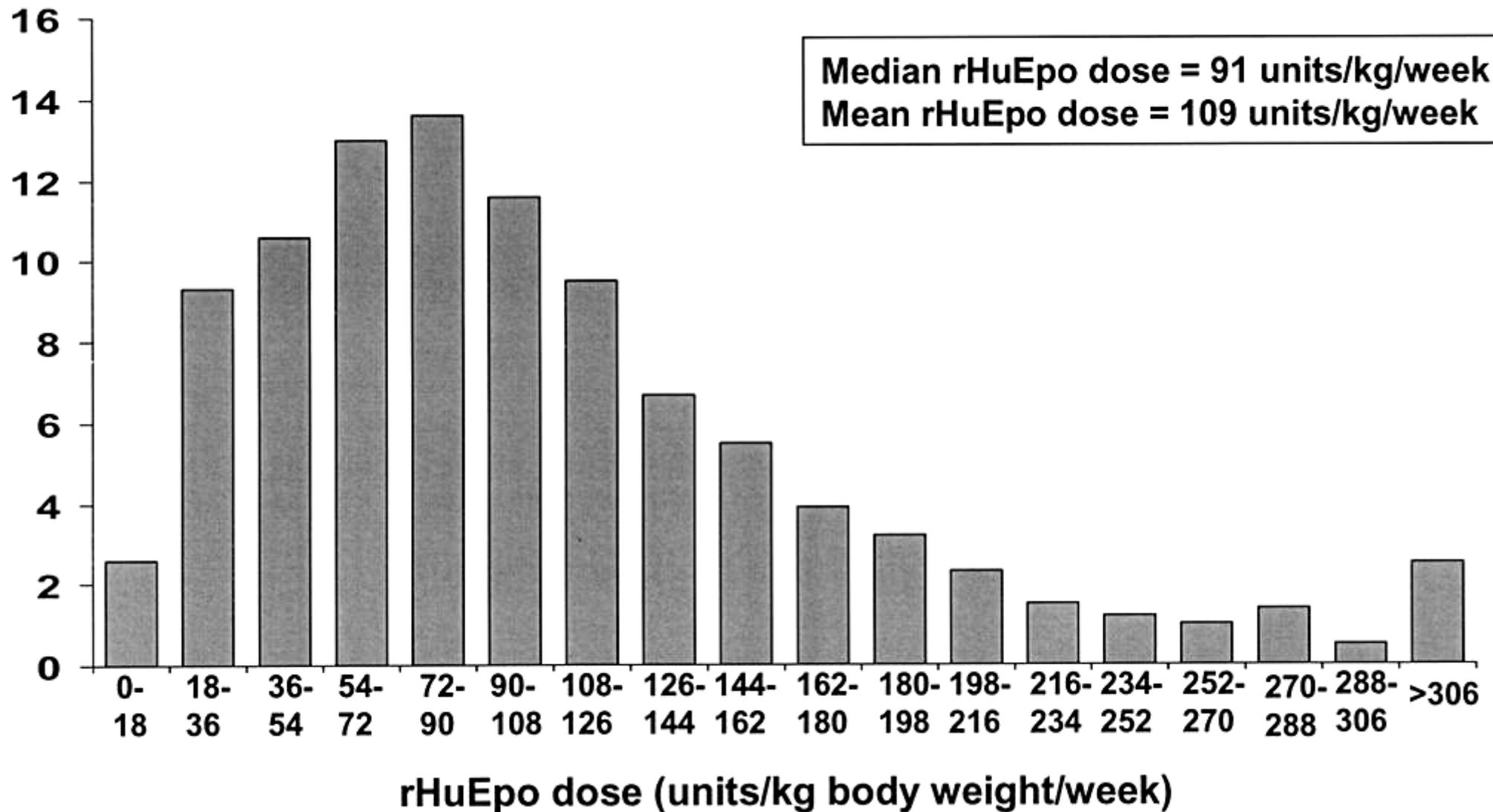
**The starting dose of ESA to correct renal anaemia may depend on several factors such as the degree and underlying cause of the anaemia.**

- In the correction phase, the starting dose for ESA – naive patients should normally be 20-30% higher than the maintenance dose.**

## **Route of epoetin administration**

- **Epoetin should normally be administered subcutaneously in predialysis and peritoneal dialysis patients – it is almost always more convenient, especially if self-administration is practiced.**

## Percent of patients



*Locatelli F. et al.: Nephrol Dial Transplant (2004) 19: 121-132*

**Table 2. Subgroup Meta-Analysis of Parallel Studies Comparing SC and IV Epoetin**

Study	SC (n)	Mean (SD)	IV (n)	Mean (SD)	WMD (95% CI random)	Weight (%)	WMD (95% CI random)
Comparison: weekly dose SC versus IV. Outcome: parallel studies (IU/kg/wk)							
Parallel studies with reported means and SD							
Boran et al <sup>22</sup>	18	86.00 (29.70)	18	172.00 (29.70)	←	11.9	-86.00 (-105.40--66.60)
Canaud et al <sup>24</sup>	16	110.70 (91.20)	18	129.60 (85.40)	—	7.9	-18.90 (-78.51--40.71)
Castro et al <sup>25</sup>	8	186.50 (24.33)	6	189.58 (20.75)	—	11.5	-3.08 (-26.74--20.58)
De Schoenmaker et al <sup>26</sup>	7	118.80 (21.00)	11	138.20 (14.10)	—	12.0	-17.40 (-35.05--0.25)
Kaufman et al <sup>2</sup>	107	95.10 (75.00)	101	140.30 (88.50)	—	11.6	-45.20 (-67.56--22.84)
Morsli et al <sup>31</sup>	10	104.00 (82.00)	10	156.00 (112.00)	←	5.6	-52.00 (-138.03--34.03)
Muirhead et al <sup>32</sup>	45	147.10 (113.50)	36	183.90 (129.40)	—	8.5	-36.80 (-90.53--16.93)
Parker et al <sup>34</sup>	27	33.00 (25.98)	27	132.00 (25.98)	←	12.2	-99.00 (-112.86--85.14)
Pelegri et al <sup>35</sup>	16	97.20 (51.30)	19	144.00 (79.50)	—	9.5	-46.80 (-90.50--3.10)
Virut et al <sup>41</sup>	24	84.00 (82.00)	25	112.00 (95.00)	—	9.4	-28.00 (-72.74--18.74)
Subtotal (95% CI)	278		271		◆	100.0	-44.57 (-71.76--17.37)
Test for heterogeneity chi-square = 88.15, <i>df</i> = 9, <i>P</i> < 0.00001							
Test for overall effect, <i>z</i> = 3.21, <i>P</i> = 0.001							
Total (95% CI)	278		271		◆	100.0	-44.57 (-71.78--17.37)
Test for heterogeneity chi-square = 88.15, <i>df</i> = 9, <i>P</i> < 0.00001							
Test for overall effect, <i>z</i> = 3.21, <i>P</i> = 0.001							

-100   -50   0   50   100  
Favors SC                      Favors IV

NOTE. Heterogeneity null hypothesis: there are no differences in treatment effect between trials.  
Abbreviations: WMD, weekly mean dose; CI, confidence interval; *df*, degrees of freedom.

# ESAM II

**8696 patients**

**4560 (52%) i.v.**  
**4136 (48%) s.c.**

**TSAT >20%**

**The effect of the route of administration (i.v. versus s.c.) on epoetin dose and hemoglobin concentration in hemodialysis patients**

**Jacobs C, Macdougall I.C, Horl W. H. J. Am Soc Nephrol 2003, 14, 769A-770A**

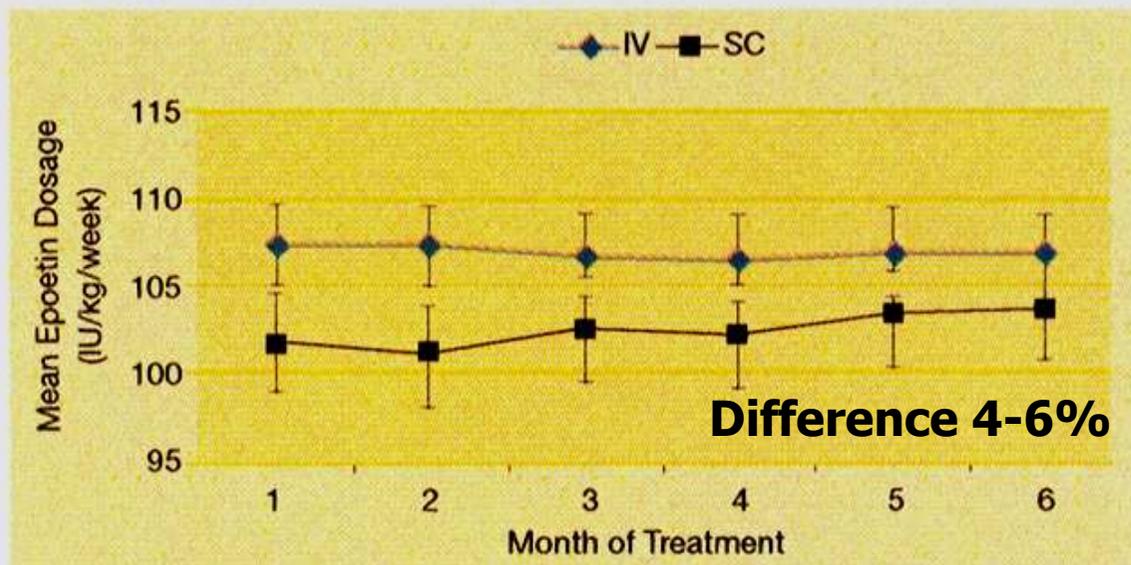


Figure 1. Mean monthly epoetin dosage (IU/kg/week) with 95% confidence intervals

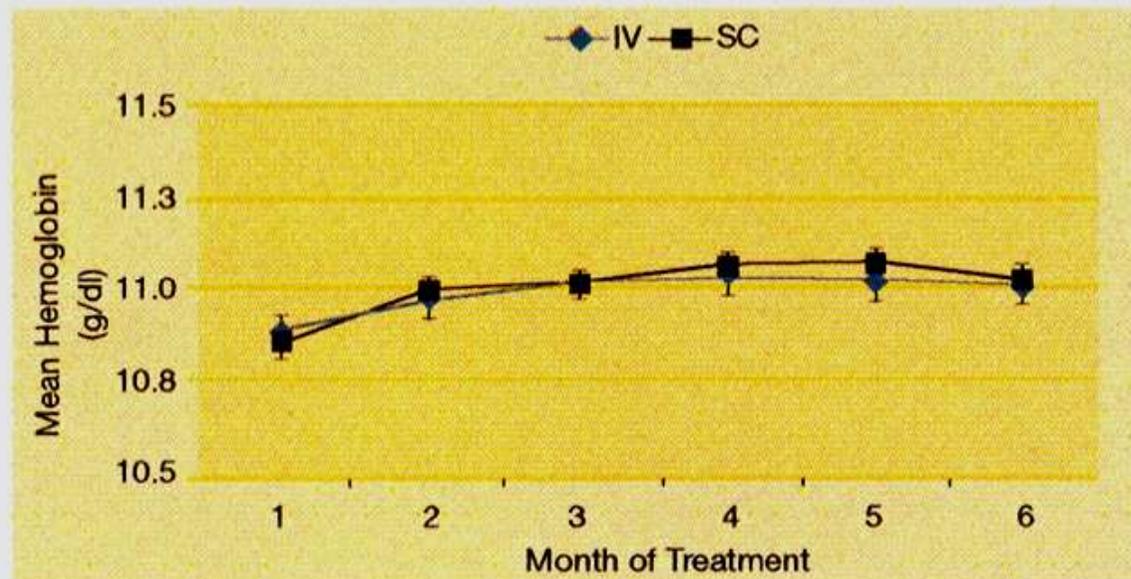


Figure 2. Mean monthly hemoglobin concentrations (g/dL) with 95% confidence intervals

# September 2002 – change of EPO route (from s.c. to i.v.)

Plasma ferritin: 200-500 ng/ml

% Hypochromic erythrocytes: <2,5%

**Table 1. Monthly haemoglobins and erythropoietin doses at Nottingham for haemodialysis patients (N=135) at baseline and three-month follow-up (December)**

	September (baseline)	October	November	December	p-value
Mean Hb (SD) g/dl	11.11 (1.40)	11.42 (1.45)	11.10 (1.58)	11.21 (1.39)	0.60
Mean epoetin alfa dose (SD) IU/week	10,416 (6485)	10,627 (6323)	11,153 (6776)	11,074 (6886)	0.09

**Dose difference after 3 months 5-6%**

**Erythropoetin: subcutaneous or intravenous dosing?**

**Fullerton L. et al. British Journal of Renal Medicine, 2002/2003, 7(4), 17-19**

# Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure

## Recommendation

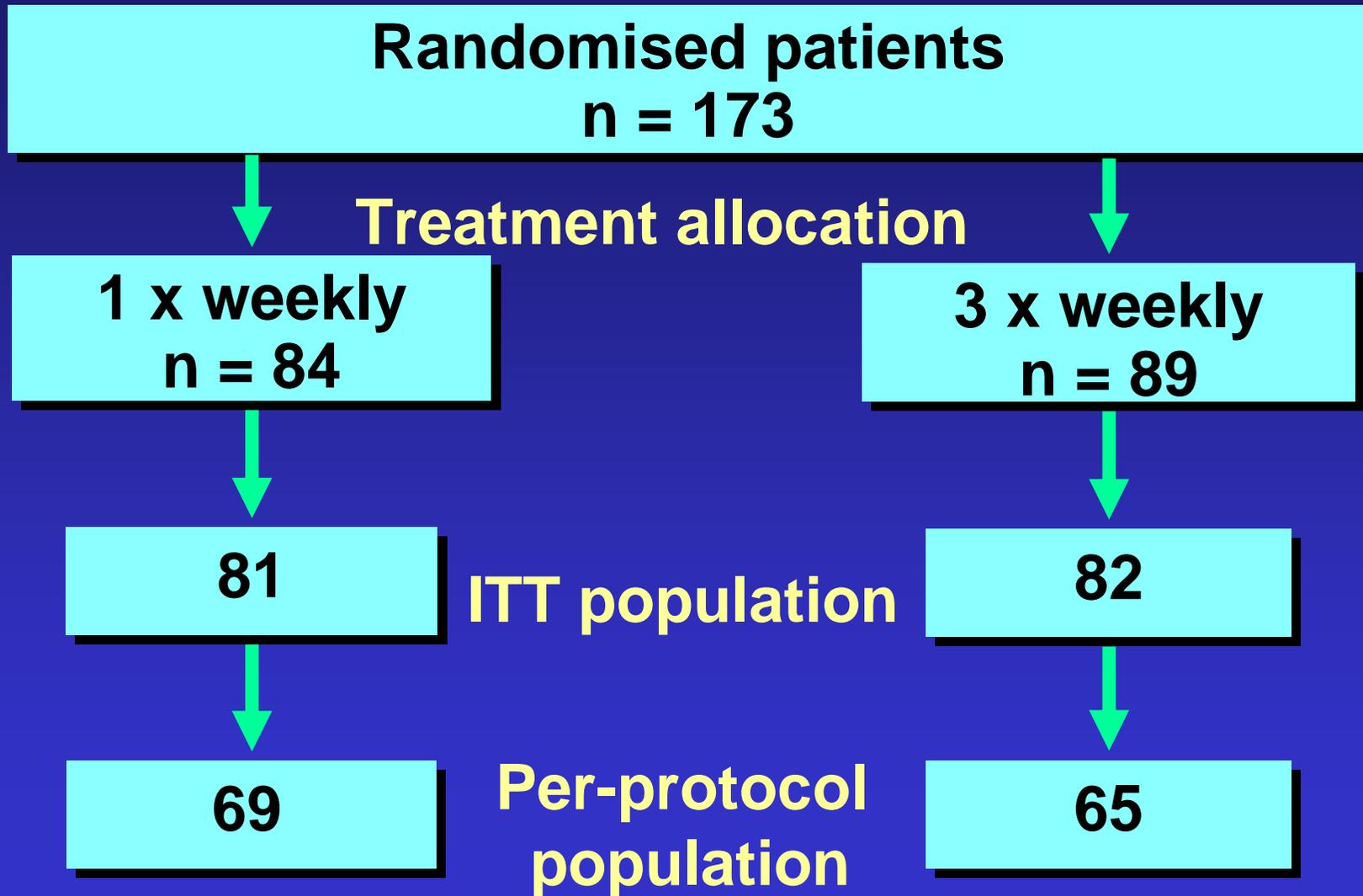
III. The frequency of administration of ESA is influenced by several factors including dose, route, treatment phase, type of ESA used and patient group being treated.

- In HD patients receiving i.v. epoetin alfa or epoetin beta, the drug should be given three times per week during both correction and maintenance phases. Evidence does not support the use of i.v. epoetin alfa or epoetin beta once weekly. However, the dosing frequency of epoetin beta may be reduced to once or twice weekly when administered s.c. in some HD patients.  
(*Evidence level A*)

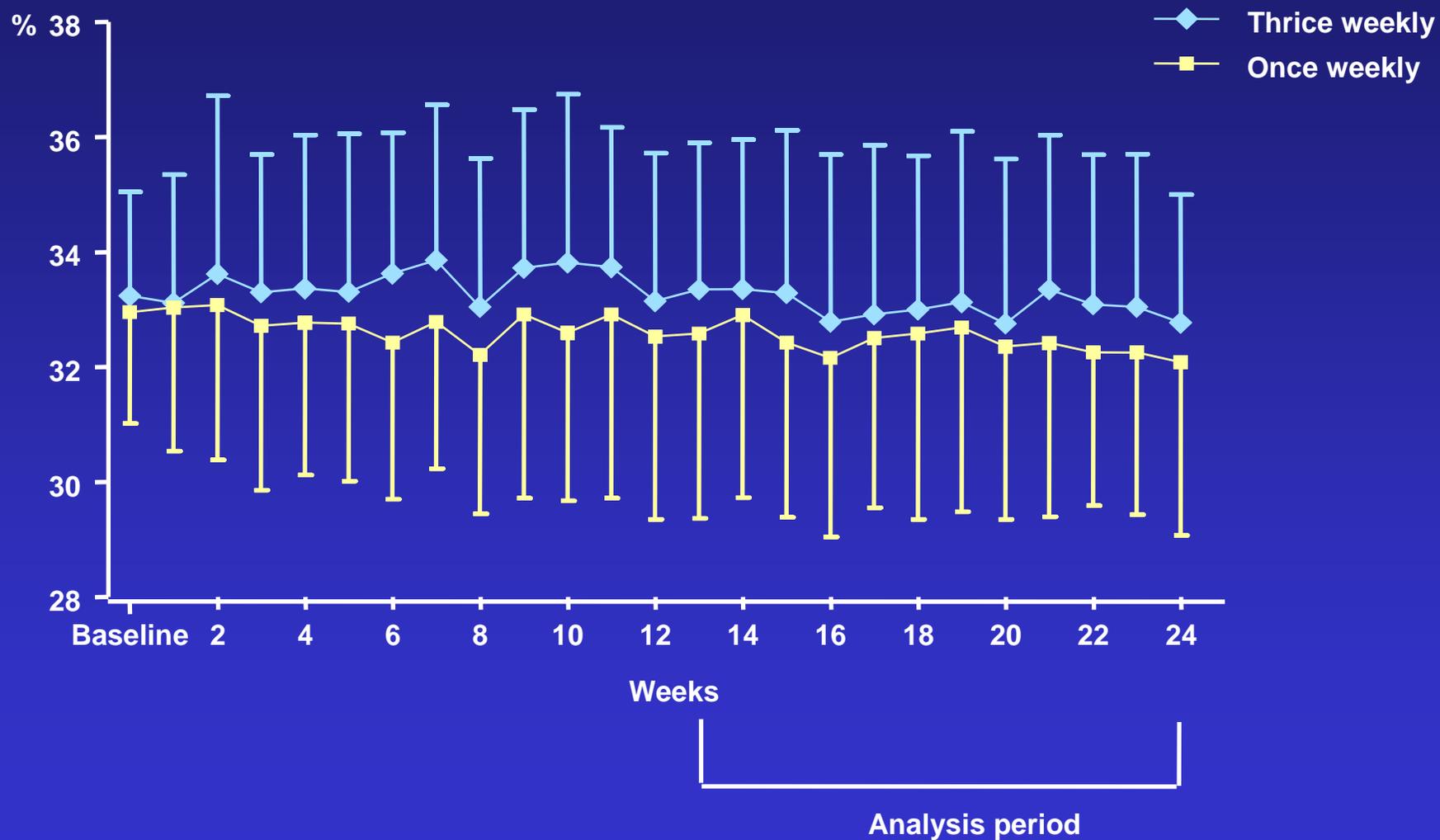
- In CKD, PD and transplant patients, epoetin beta can be given s.c. three times per week during the correction phase and once per week during the maintenance phase of treatment.  
(*Evidence level C*)
- During the correction phase, darbepoetin alfa should be given once per week either i.v. or s.c. in HD patients, and once per week s.c. in CKD, PD and transplant patients.  
(*Evidence level A*)
- During the maintenance phase, darbepoetin alfa can also be given less often (e.g. every 2–4 weeks) either s.c. or i.v. in selected patients.  
(*Evidence level C*)
- Darbepoetin alfa can be given once every 2 weeks either s.c. or i.v. to patients previously given s.c. epoetin alfa or beta once weekly.  
(*Evidence level B*)

Note: A table summarizing the information in this recommendation is provided at the end of this guideline.

# Patient allocation

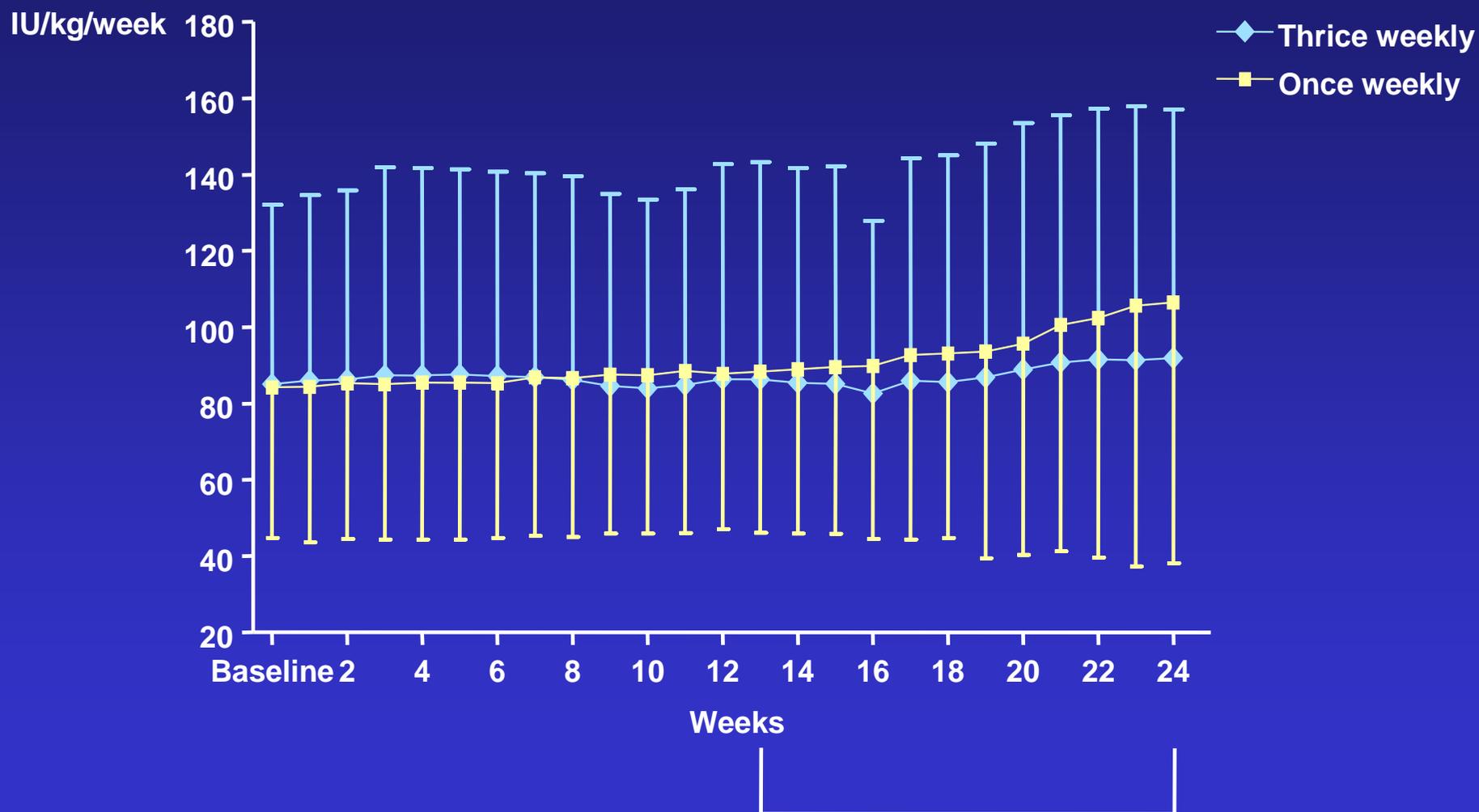


# Mean (SD) change over time: haematocrit per protocol analysis



Locatelli et al. *Am J Kidney Dis* 2002, 40, 1: 119-125

# Mean (SD) change over time: epoetin beta dose per protocol analysis



Analysis period

- **Once weekly SC epoetin beta is therapeutically equivalent to 3 times weekly treatment in maintaining a stable haematocrit**
- **No statistically significant dose increases required**
- **Once weekly epoetin beta has a similar tolerability profile to the 3 times weekly regimen**
- **Different dosing regimens (1x, 2x, 3x) provide the opportunity to individualise epoetin beta therapy according to specific needs**

# **Possible adverse effects of epoetin treatment**

- **hypertension**
- **vascular access thrombosis**

## **Other possible adverse effects of epoetin treatment**

- **seizures**
- **increase heparin dosage**
- **loss of dialyser clearance and hyperkalaemia**
- **antibodies direct against epoetin**

**increased blood  
viscosity**

**loss of hypoxic  
vasodilatation**

**activation of  
neurohumoral systems**

**EPO induced  
hypertension**

**↑ cell Ca<sup>2+</sup> uptake**

**↑ ET-1 release**

**direct vascular effect**

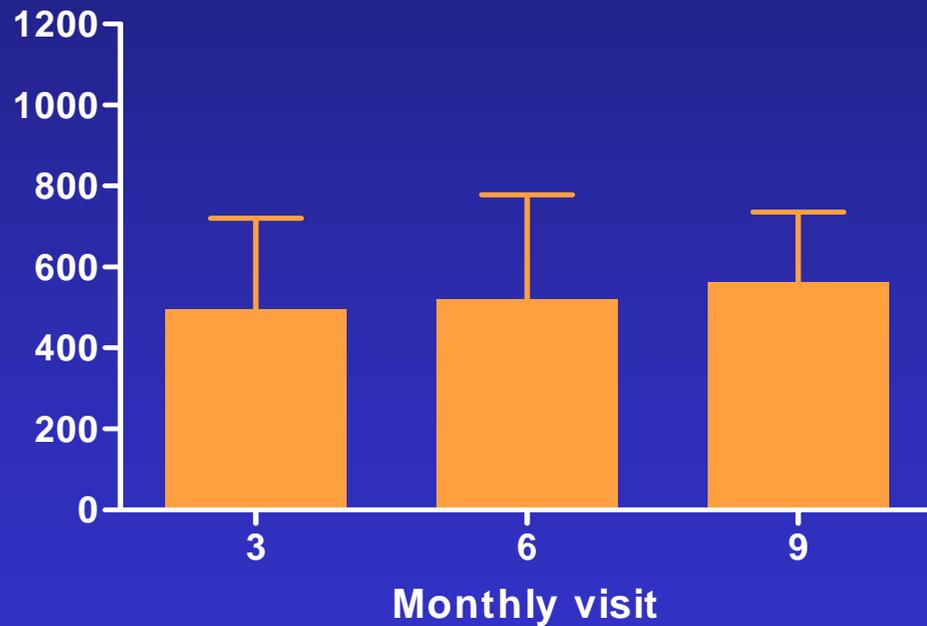
**mitogenic effect**

**platelet-dependent  
mechanism**

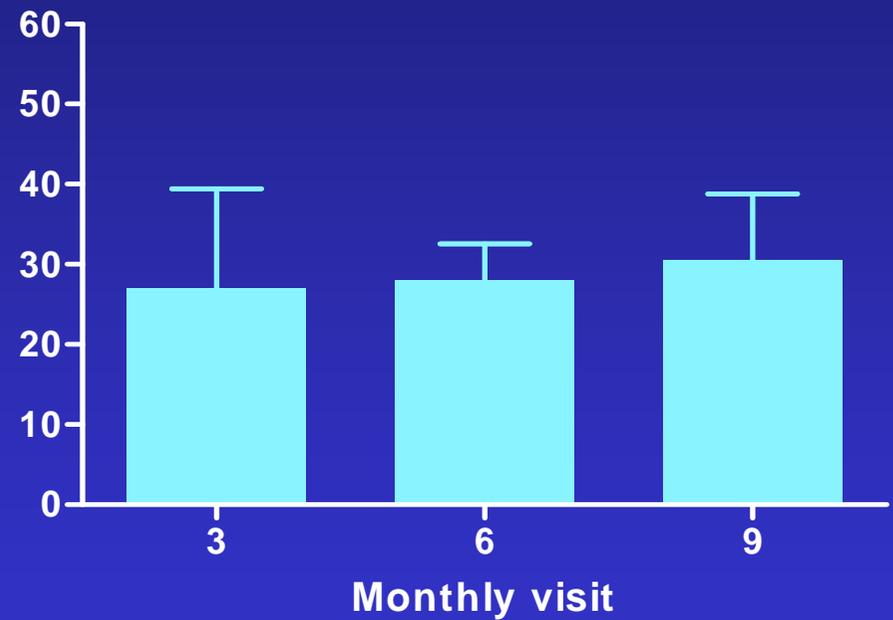
# CERA: Ferritin and TSAT Levels

1x/4wk SC schedule, extension period

Median ferritin (25th, 75th percentile; ng/mL)



Median TSAT (25th, 75th percentile; %)



# The Normal Hematocrit Trial

## Limitations and criticisms of the study

- Entry criteria required “high – risk cardiac patients”
- Increased mortality not due to the higher Hct *per se*
- Hct measured prior to HD session
- Hct less accurate marker of red cell mass than Hb
- Increased mortality not due to CV causes

Macdougall IC and Ritz E, Nephrol Dial Transplant 1998; 13: 3030

# **Metabolic adjuvants to epoetin therapy**

- **iv iron**
- **Folic acid**
- **Vit. B<sub>12</sub>**
- **Vit. B<sub>6</sub>**
- **Ascorbic acid (vit. C)**
- **Vit. D**
- **L-carnitine**
- **IGF-1 / IL-3**
- **Androgens**

# Iron dose and frequency of administration in HD patients

## Recommendations

- **Absolute iron deficiency** 30–50 mg Fe / HD  
or 1000 mg Fe in 6–10 weeks
- **Maintenance phase** 10–25 mg Fe Sucrose / HD  
or 1–3 x 20 mg Fe gluconate / week  
or 1 x 62,5 mg Fe gluconate / week  
or 1 x 100 mg Fe sucrose / 1–2 weeks  
or 1 x 100 mg Fe dextran\* /1–2 weeks
- **Hb correction phase** 150 mg of iron/Hb increase  
of 1 g/dl

\* low molecular weight dextran

# **Assessing and optimising iron stores**

**To achieve and maintain target Hb concentration (11 g/dl = haematocrit 33 %) sufficient iron should be administered to obtain the following in all patients:**

- **serum ferritin  $\geq 100 \mu\text{g/l}$**
- **hypochromic red cells  $< 10\%$  (or TSAT  $> 20\text{-}30\%$  or CHr  $> 29 \text{ pg/ml}$ )**

**In practice, to achieve the minimum criteria for Hb concentration it is necessary to have:**

- **serum ferritin 200-500  $\mu\text{g/l}$**
- **hypochromic red cells  $< 2.5\%$  (or TSAT of 30-40% or CHr  $\approx 35\%$ )**

# Cardiac Failure in ESRD

- Consistently associated with **poor survival**
- Already present in **40% patients at the start of dialysis therapy**

# Iron and Infection

Since:

- IV iron agents release catalytically active iron (2 -6%)
- Iron is required for bacterial growth
- Iron may inhibit phagocytosis
- Iron excess in promotes infection

Then:

Does IV iron therapy promote infection?

# Iron and Infection

**Risk of infection related to:**

- **Central venous catheters**
- **History of bacteraemia**
- **AV grafts**
- **Immunosuppression**
- **Not to ferritin levels**
- **Not to total dose of iv iron**

Hoen B, et al. EPIBACDIAL: Multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. JASN 9(5):869-76, 1998

## Safety of Parenteral Iron Life-Threatening Adverse Reactions



Fishbane S. Am J Kidney Dis 2003;41(S5):S18-S26.

## **Causes of an inadequate response to epoetin treatment (2)**

- **Chronic blood loss (gut, uterus)**
- **Infection/inflammation (access infections, surgical inflammation, tuberculosis, systemic lupus erythematosus, chronically rejecting allografts, AIDS)**
- **Hyperparathyroidism/osteitis fibrosa**
- **Aluminium toxicity**
- **Haemoglobinopathies (e.g. alpha and beta thalassaemias, sickle cell anaemia)**

# Inflammation

## Recommendations II

- ◆ In the presence of both, a high  $\text{Ca} \times \text{PO}_4$  product and high serum CRP level, patients should be screened and treated for calciphylaxis.
- ◆ Patients coming back from transplantation should be monitored carefully since rejected grafts may be a source of inflammation.
- ◆ In patients with failed renal allograft still in place or in patients with intravenous catheters a higher dose of Epoetin may be needed to correct anemia.

# Inflammation

## Recommendations I

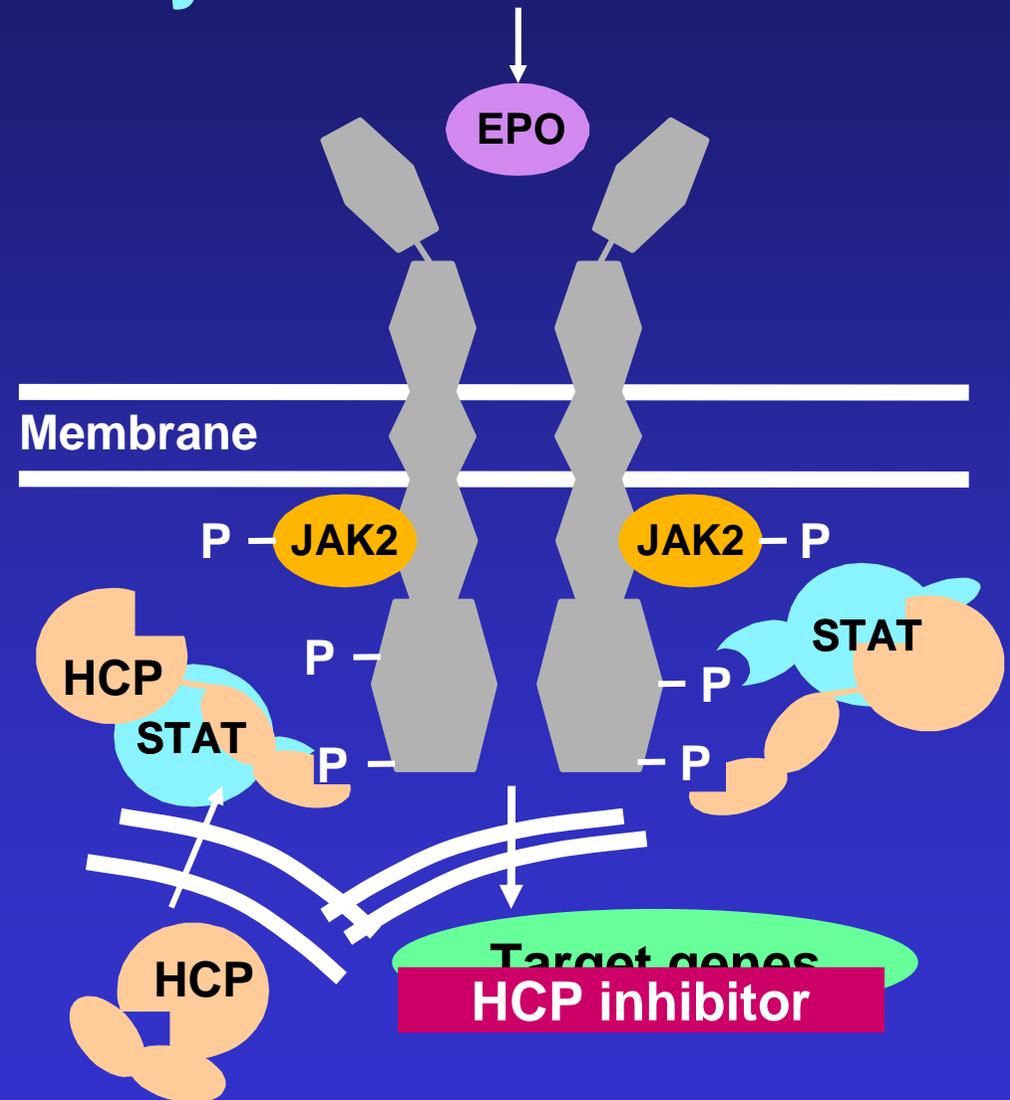
- ◆ CRP should be evaluated at least every 3 months.
- ◆ In patients with elevated CRP ( $> 5$  mg/l) biocompatibility of dialyzer membrane and hemodialysis fluid quality should be checked.
- ◆ If chronic inflammation persists, optimization of the dialysis protocol and dialysis dose should be aimed for.
- ◆ In patients with continuous rise in CRP and a past history of systemic disease causing renal failure, recurrence of the disease should be excluded

## **Causes of an inadequate response to epoetin treatment (3)**

- **Folate or vitamin B<sub>12</sub> deficiency**
- **Multiple myeloma, myelofibrosis**
- **Other malignancy**
- **Malnutrition**
- **Haemolysis**
- **Drug intake (e.g. high dose ACE inhibitor or AT<sub>1</sub> receptor antagonist therapy, immunosuppressive drugs)**
- **Inadequate dialysis**
- **Antierythropoietin antibodies**

# Modulators of receptor activity

- Haematopoietic cell phosphatase (HCP) is a negative regulator of the EPO signalling cascade
- It binds to phosphorylated EPO receptor and dephosphorylates JAK2, terminating signalling
- Inhibitors of HCP restore signalling and may enhance response to EPO



## **AF37702 (Hematide™)**

### **Pegylated Peptide-Based Erythropoiesis-Stimulating Agent (ESA)**

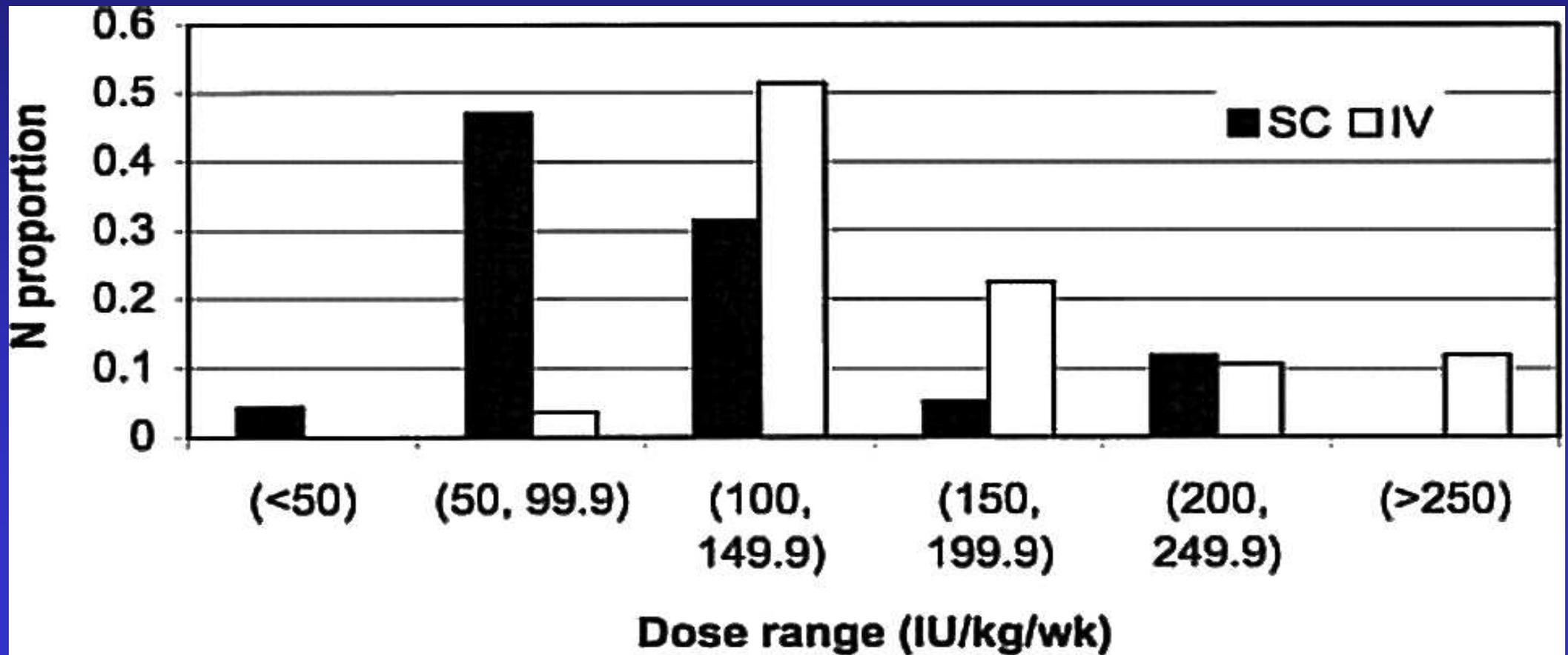
- **Preclinical evaluation of pegylated peptide-based ESA**
  - No detectable sequence identity to human erythropoietin (EPO)
  - Equal potency to natural EPO
  - Antibodies do not crossreact with recombinant human EPO
- **Pharmacokinetic data from rats, dogs, and monkeys**
  - Extended plasma half-life
    - Elimination half-life in monkey with 1.35-mg/kg dose, 58.4 hrs
      - Clearance rate, 0.96 mL/hr/kg
- **Erythropoietic activity detected in several models**
  - Efficacy equal in in vitro and in vivo models
- **This novel agent is a potent EPO receptor agonist with prolonged half-life and slow clearance**
  - Clinical trials forthcoming

**According to patient characteristics and preference, epoetin can be administered either subcutaneously or intravenously in patients on regular haemodialysis. Subcutaneous route will usually lead to lower doses of epoetin and in general this route is preferable**

**Eprex (Erypo) - only i.v.**

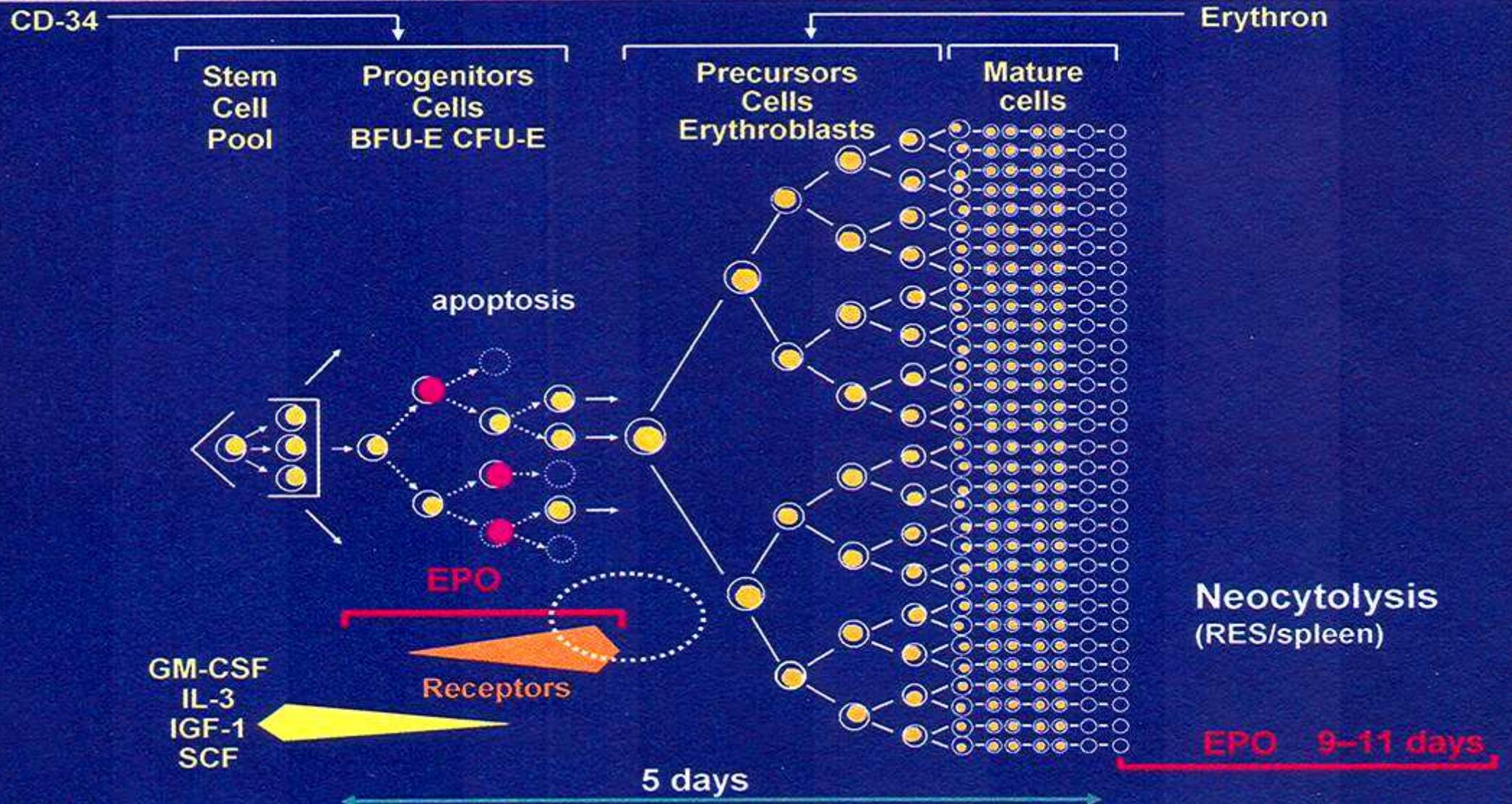
## Comparison of IV and SC dose

The average SC dose was  $113 \pm 43$  IU/kg/wk,  
and mean IV dose was  $161 \pm 46$  IU/kg/wk.



Besarab A. et al., Am .J. Kidney Dis., 2002, 40: 439-446

# Erythropoiesis



# ***Debate on the 'epidemic' of chronic kidney disease***

## ***The Reply***

**Chronic kidney disease is common: What do we do next?**

**Josef Coresh, Lesley A. Stevens and Andrew S. Levey**

**Nephrol Dial Transplant (2008) 23: 1122–1125**

- ***eGFR is a useful first step in CKD detection, evaluation and management, but not the last step.***
- **New equations should aim to decrease the bias in GFR estimation  $>60 \text{ ml/min/1.73 m}^2$  but estimation in this range is difficult. The MDRD study equation has been expressed in terms of standardized creatinine and its performance shown to improve after creatinine calibration compared to unstandardized creatinine. Major manufacturers have set 2008 as a target for calibrating their assays to isotope dilution mass spectrometry reference methods.**

- **The disparity between the prevalence of earlier stages of CKD and incidence of treated kidney failure across race and sex should not be taken as conclusive evidence for inaccuracies of the GFR estimating equations or inadequacy of the current GFR cutoff value.**
  - **Prevalence is not incidence and prevalence over-represents cases of longer duration and slower progression**
  - **Women may have a higher prevalence at earlier stages of CKD because they progress more slowly and have a lower mortality rate**
- **Defining 'healthy' in older individuals is problematic. The main rationale appears to be avoiding classification of a large number of elderly people as having CKD with limited treatments options. But Inadequate treatment for common diseases should be a challenge for future research rather than a reason for changing the definition of what is normal. Defining it as normal because it is common threatens to dismiss the urgent need for research in this topic.**

**Josef Coresh, Lesley A. Stevens and Andrew S. Levey  
Nephrol Dial Transplant (2008) 23: 1122–1125**

## Estimated glomerular filtration rate at baseline and changes of eGFR – ONTARGET study

	Ramipril	Telmisartan	Ramipril+ telmisartan	Telmisartan vs ramipril p	Ramipril+telmisartan vs ramipril p
eGFR, baseline	73.7 (19.3)	73.6 (19.9)	73.4 (19.5)	0.915	0.388
eGFR change baseline to 6 weeks	-2.14 (12.9)	-2.51 (13.2)	-4.01 (13.3)	0.070	<0.0001
eGFR change baseline to 2 years	-1.96 (15.1)	-3.05 (15.1)	-5.12 (15.7)	<0.0001	<0.0001
eGFR change 6 baseline to final	-2.82 (17.2)	-4.12 (17.4)	-6.11 (17.9)	<0.0001	<0.0001
eGFR change 6 weeks to final	-1.17 (17.1)	-2.06 (17.1)	-2.49 (17.4)	0.0032	<0.0001

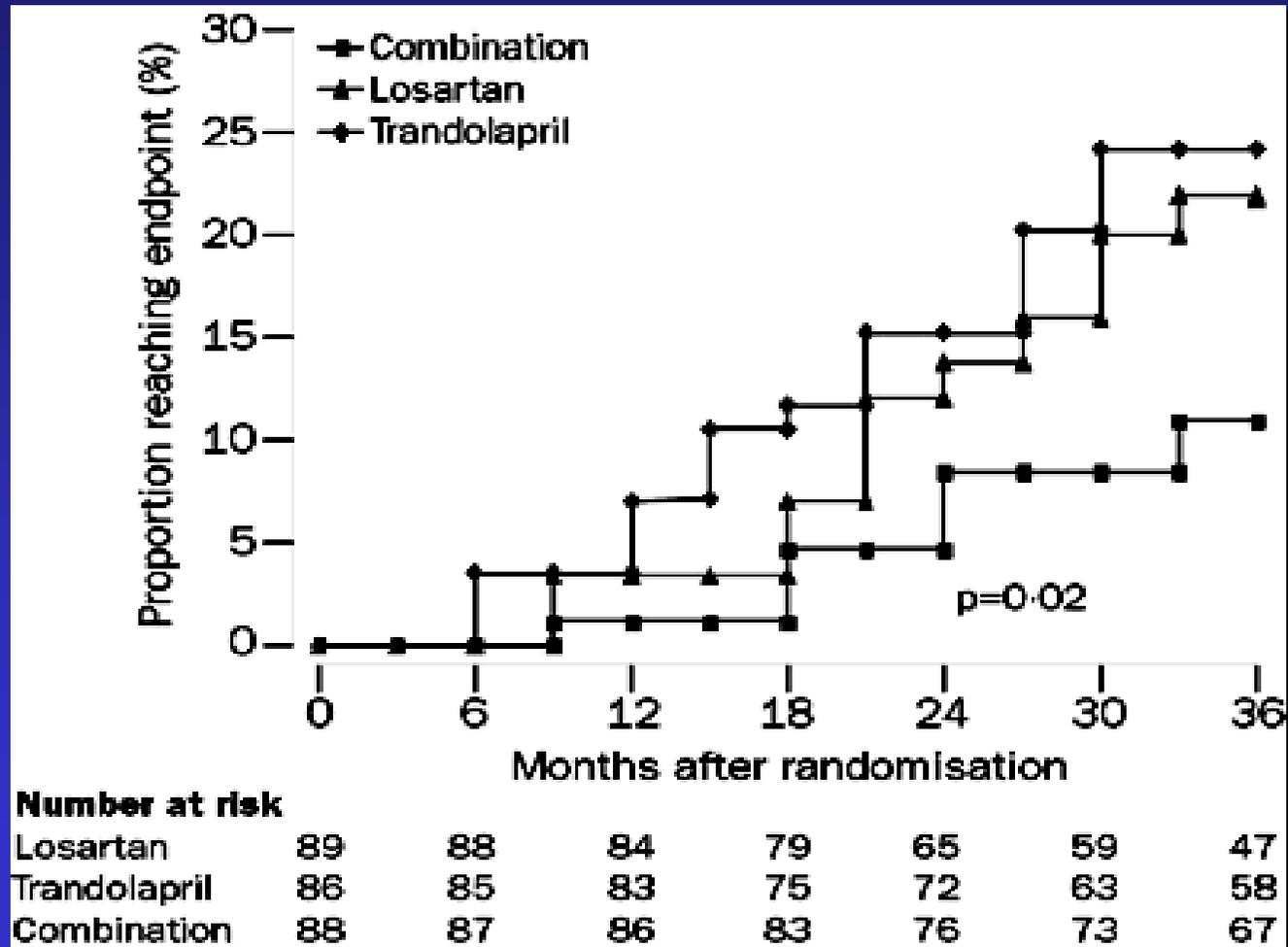
eGFR=estimated glomerular filtration rate (mL/min/1.73 m<sup>2</sup> [SD]). Number of participants with measurements=25551 at baseline, 24970 at 6 weeks, 22573 at 2 years, 19601 at study end.

# Incidence of primary and secondary renal outcomes and of its components- ONTARGET study

	Ramipril n (%)	Telmisartan n (%)	Ramipril+ telmisartan n (%)	Telmisartan vs ramipril HR (95% CI)	p	Ramipril+ telmisartan vs ramipril HR (95% CI)	p
All dialysis, doubling, death	1150 (13.4)	1147 (13.4)	1233 (14.5)	1.00 (0.92-1.09)	0.968	1.09 (1.01-1.18)	0.037
All dialysis and doubling	174 (2.03)	189 (2.21)	212 (2.49)	1.09 (0.89-1.34)	0.420	1.24 (1.01-1.51)	0.038
All dialysis	48 (0.56)	51 (0.60)	63 (0.74)	1.07 (0.72-1.58)	0.747	1.33 (0.92-1.94)	0.133
All death	1014 (11.8)	989 (11.6)	1065 (12.5)	0.98 (0.90-1.07)	0.641	1.07 (0.98-1.16)	0.144
Doubling	140 (1.63)	155 (1.81)	166 (1.95)	1.11 (0.88-1.39)	0.378	1.20 (0.96-1.50)	0.110
Acute dialysis	13 (0.15)	20 (0.23)	28 (0.33)	1.55 (0.77-3.11)	0.221	2.19 (1.13-4.22)	0.020
Chronic dialysis	33 (0.39)	31 (0.36)	34 (0.40)	0.94 (0.58-1.54)	0.817	1.05 (0.65-1.69)	0.854

Dialysis=at least one dialysis. Chronic dialysis=more than 2 months. Acute dialysis=2 months or less. Doubling=doubling of serum creatinine from baseline values. HR=hazard ratio. Reasons for acute dialysis were reported as severe infection (n=22), volume depletion (n=9), post-surgery (n=7), drugs (n=5), specific renal diseases (n=5), and other reasons (n=23). In three of 165 originally reported cases of dialysis,<sup>6</sup> detailed analysis revealed that no dialysis took place. In three of the 162 cases of dialysis, we got no information on duration of dialysis. Investigators could report several reasons for acute dialysis.

# COOPERATE – Combined therapy ARB i ACEI in non-diabetic nephropathy



Nakao N. et al. Lancet 2003; 361: 117-24

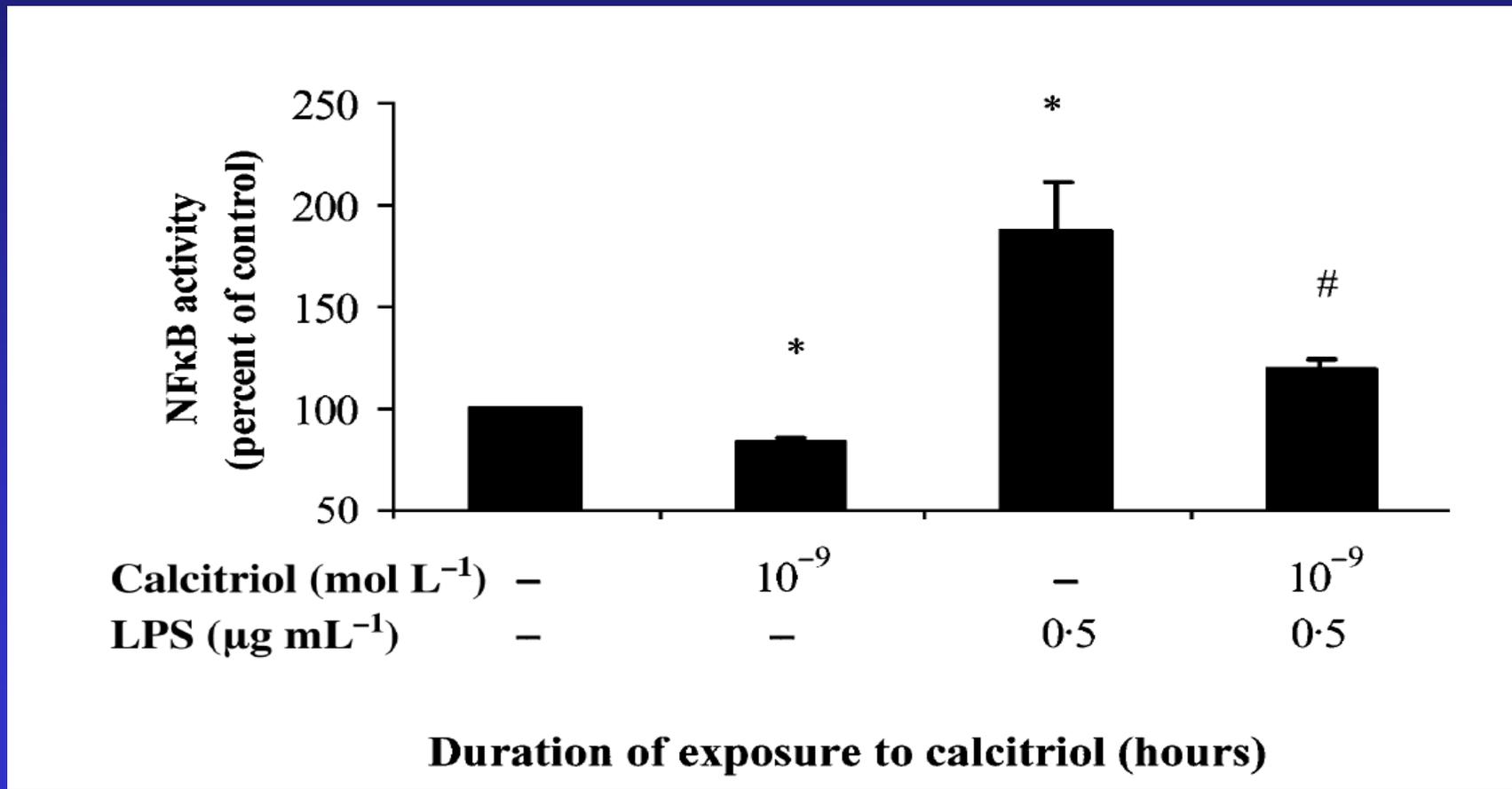
# The COOPERATE trial: a letter of concern

In the context of a meta-analysis,<sup>1</sup> we had reason to take an in-depth look at a study by Naoyuki Nakao and colleagues<sup>2</sup> published in *The Lancet* in 2003. We detected implausibilities of serious concern.

	Losartan (n=89)	Trandolapril (n=86)	Combination (n=88)	$\chi^2$ test
<b>Demographics</b>				
Sex (male)	48 (54%)	46 (53%)	47 (53%)	p=0.997
<b>Renal disease</b>				
Glomerular	58 (65%)	56 (65%)	57 (65%)	
Hypertension	15 (17%)	16 (19%)	15 (17%)	
Polycystic kidney disease	3 (3%)	5 (5%)	4 (5%)	
Unknown	13 (15%)	9 (10%)	12 (14%)	p=0.972
<b>ACE gene polymorphism</b>				
DD	9 (11%)	11 (13%)	10 (11%)	
ID	49 (49%)	41 (48%)	42 (48%)	
II	40 (40%)	34 (39%)	36 (41%)	p=0.9876

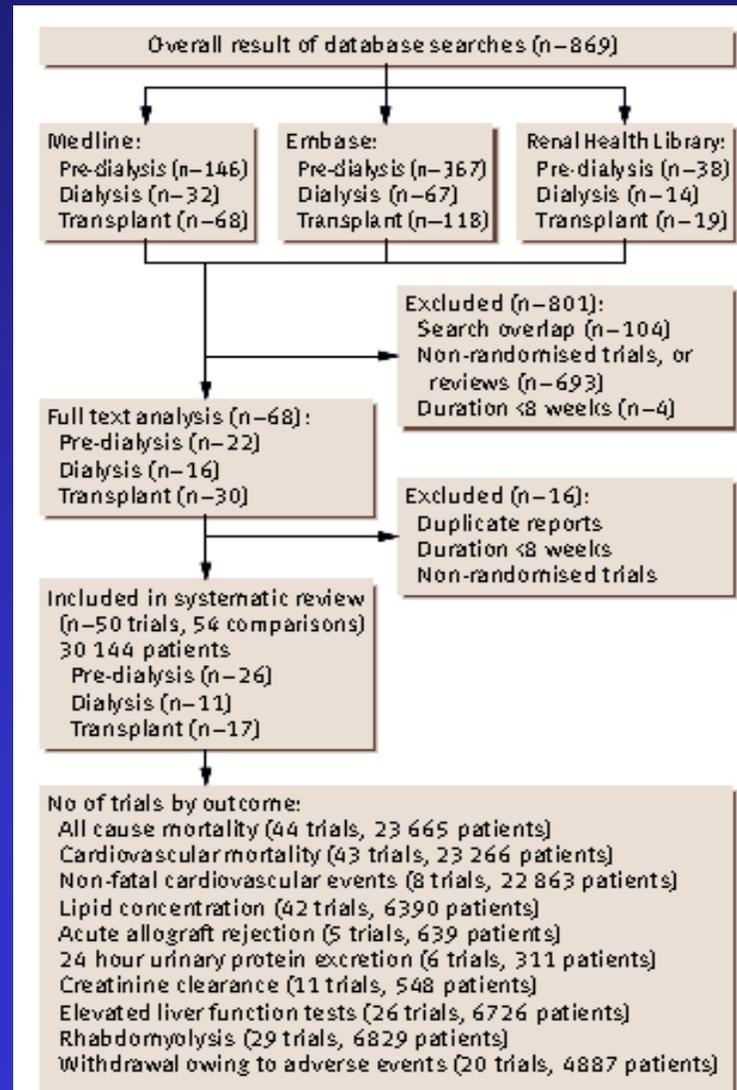
**Table:** Categorical variables from Nakao and colleagues' table 1

## Effect of calcitriol on NFκB pathway



Talmor Y et al. Eur J Clin Invest, 2008; 38: 548–554

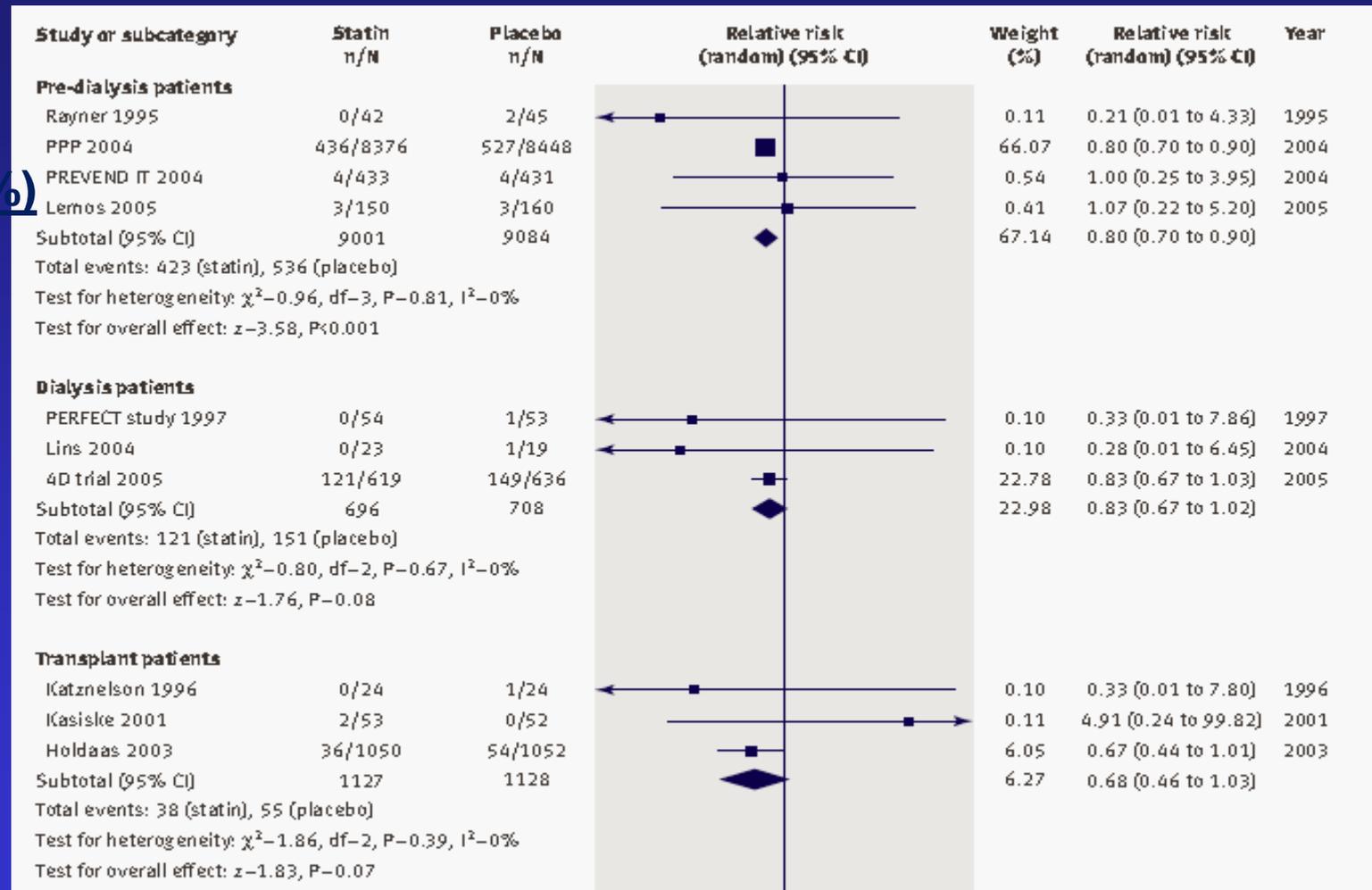
# Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials



*Strippoli G et al. BMJ  
2008;336;645-651*

# Effect of statins compared with placebo or no treatment on cardiovascular mortality in pre-dialysis, dialysis, and transplant patients

A significant (approximately 20%) reduction in the risk of cardiovascular mortality



# Recommended route and frequency of administration

Recommendation	Patient type			
	CKD stages 1–5 not on dialysis	HD	PD	Transplant
Recommended <b>route</b> of administration	s.c.	s.c. or i.v.	s.c.	s.c.
Recommended <b>frequency</b> of administration	EA: N/A EB: 1–3×/week DA: 1×/week	EA: 3×/week (i.v. <b>only</b> ) EB: 3×/week (i.v. or s.c.) DA: 1×/week (i.v. or s.c.)	EA: N/A EB: 3×/week DA: 1×/week	EA: N/A EB: 1–3×/week DA: 1×/week
Correction				
Maintenance	EA: N/A EB: 1–3×/week DA: 1×/week to 1×/2 weeks	EA: 3×/week (i.v. <b>only</b> ) EB: 1–3×/week (s.c.) EB: 2–3×/week (i.v.) DA: 1×/week to 1×/2 weeks (i.v. or s.c.)	EA: N/A EB: 1–3×/week DA: 1×/week to 1×/2 weeks	EA: N/A EB: 1–3×/week DA: 1×/week to 1×/2 weeks

EA = epoetin alfa; EB = epoetin beta; DA = darbepoetin alfa; N/A = not applicable because not licensed for use by this route. Supporting evidence levels can be found in Recommendations II and III.

## Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure

Locatelli F, Aljama P, Bárány P, Canaud B, Carrera F, Eckardt K-U, Hörl WH, Macdougall IC, Macleod A, Więcek A, Cameron S. Nephrol Dial Transplant 2004, 19 (suppl 2), ii16-ii31

## Recommendation

**II. Exact target Hb concentrations  $> 11$  g/dl should be defined for individual patients, taking gender, age, ethnicity, activity and co-morbid conditions into account. In HD patients, pre-dialysis Hb concentrations above 14 g/dl are not desirable due to the risks associated with the effects arising from post-dialysis haemoconcentration. (*Evidence level C*)**

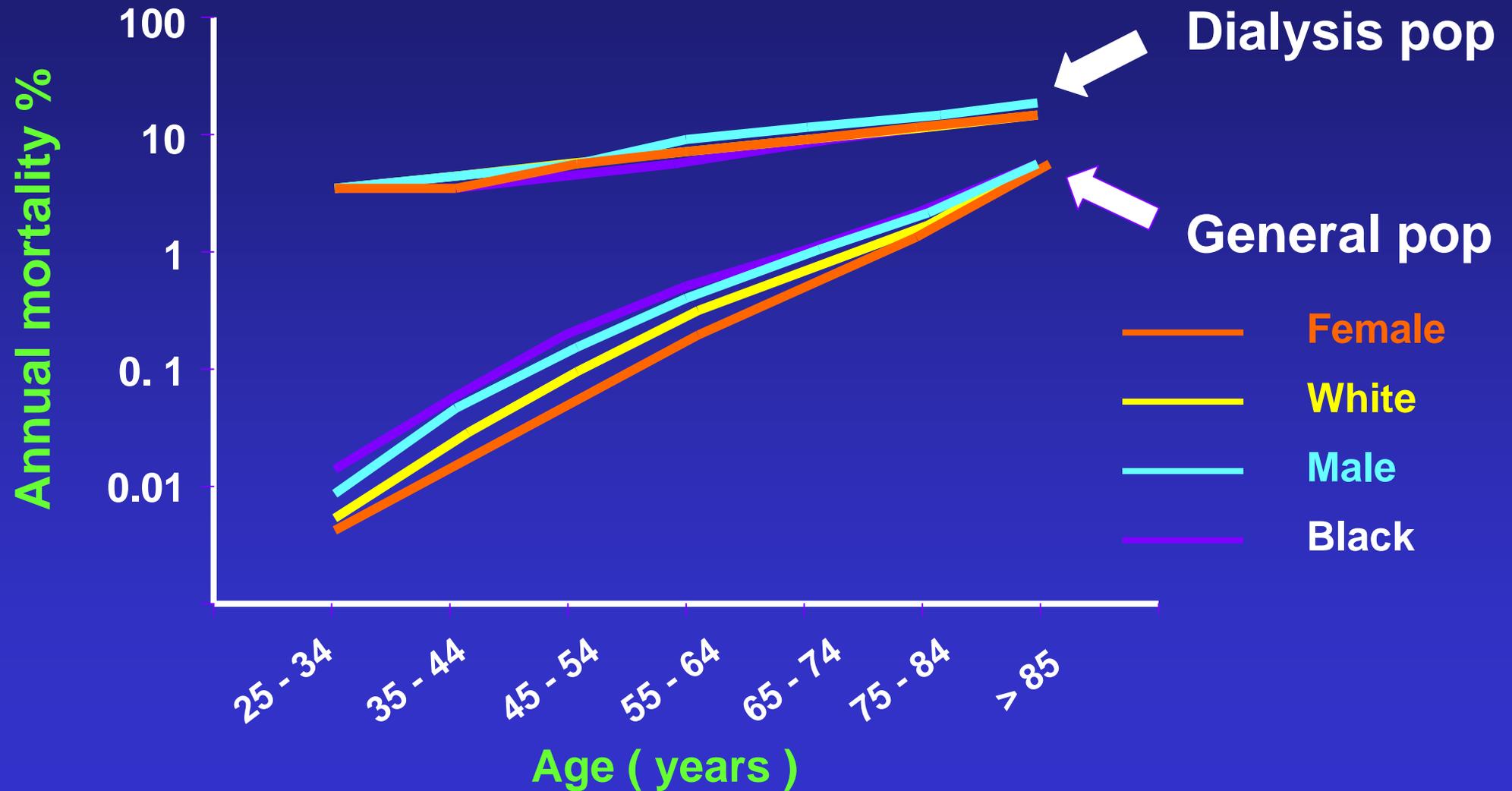
## Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure

### Recommendation

**III. The optimal target Hb concentration may vary in patients with significant co-morbidity:**

- **Hb concentrations >12 g/dl are not recommended for patients with severe cardiovascular disease [defined as class III and above of the New York Heart Association Classification of Congestive Heart Failure (Table 2, Appendix C)] unless continuing severe symptoms (e.g. angina) dictate otherwise.  
(Evidence level A)**
- **Until data become available, it seems prudent to recommend a cautious approach to raising Hb concentrations to levels >12 g/dl in patients with diabetes, especially with concurrent peripheral vascular disease.  
(Evidence level C)**
- **Patients with chronic hypoxaemic pulmonary disease may benefit from a higher Hb target.  
(Evidence level C)**

# Cardiovascular disease mortality in the USRDS



# Advances in the treatment with Erythropoiesis Stimulating Agents (ESA)

## Anaemia not related to CKD

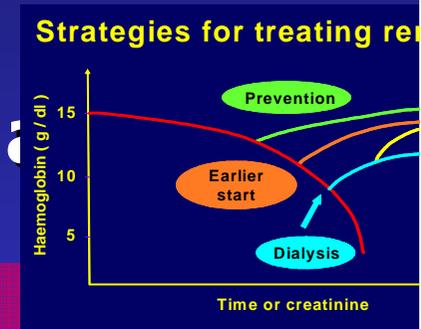
- **Old indications**
  - Cancer diseases
  - Chronic inflammation
  - Prematurity
  - Autologic blood transfusion
- **New indications**
  - Acute renal failure

## Anemia in CKD patients

1. New therapeutic options (prevention)
2. New drugs

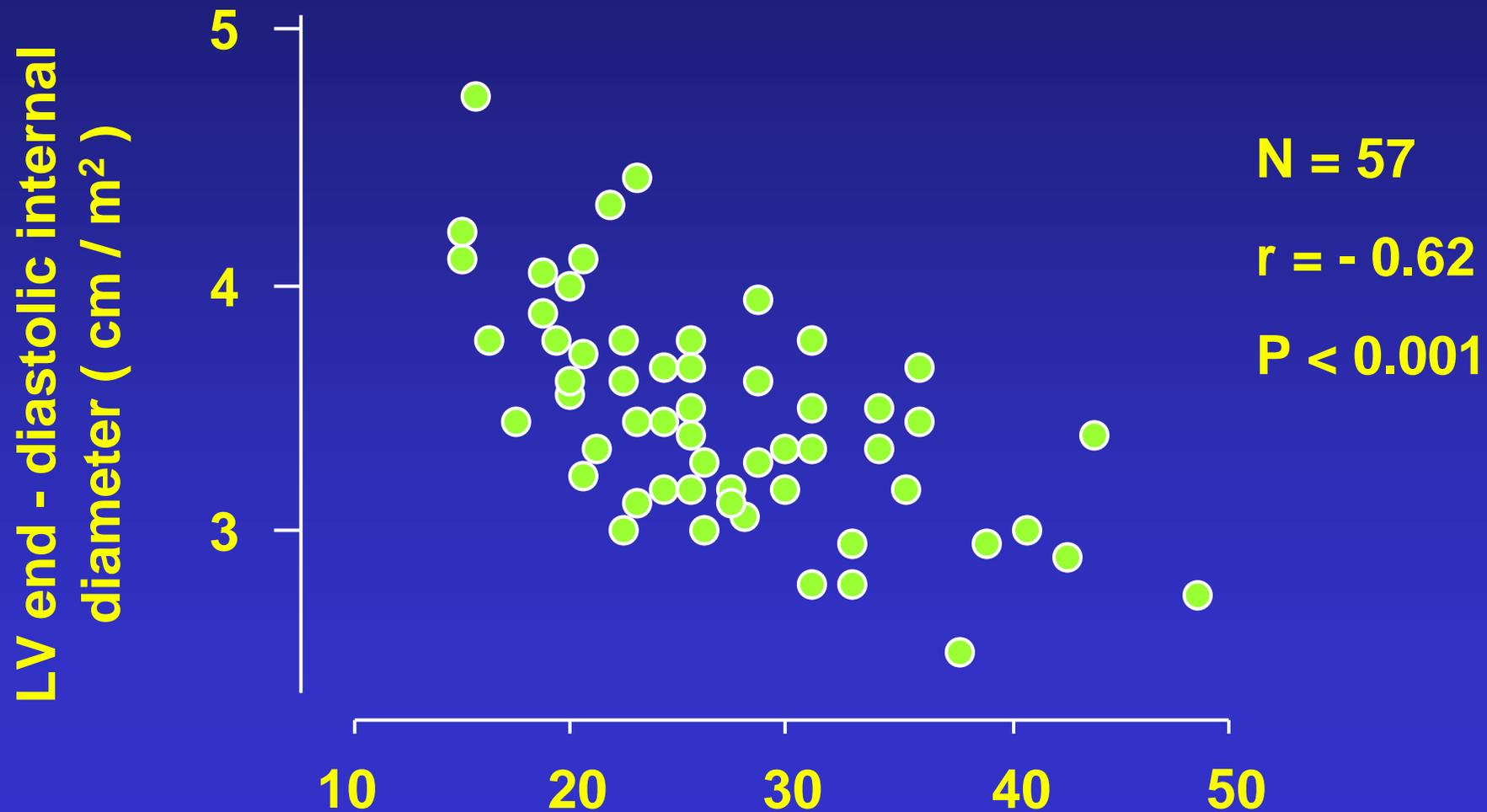
darbepoietin α  
CERA

- **New therapeutic concepts**

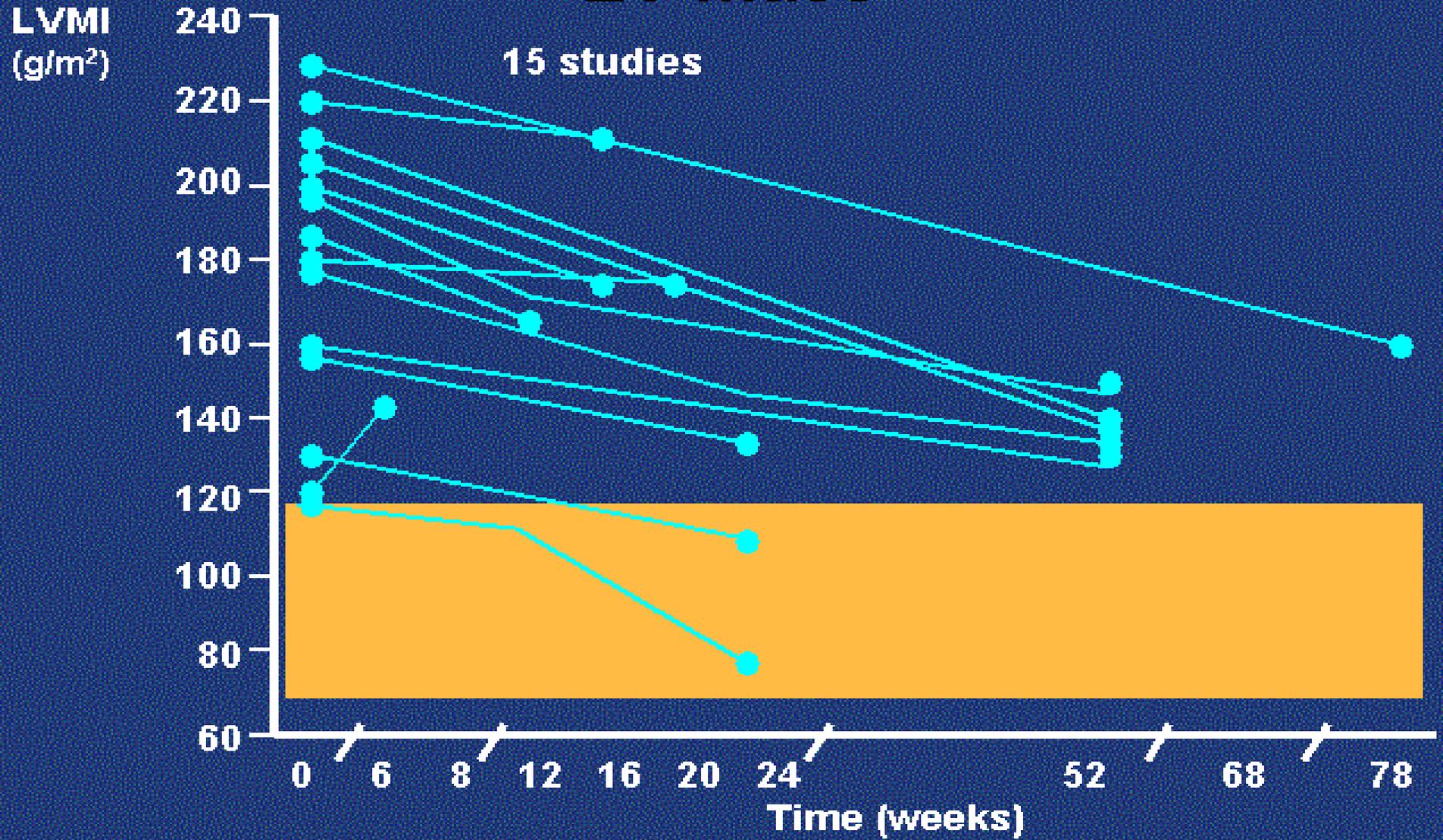


# Uremic cardiomyopathy: an inadequate LVH

## Hematocrit and LV cavity diameter

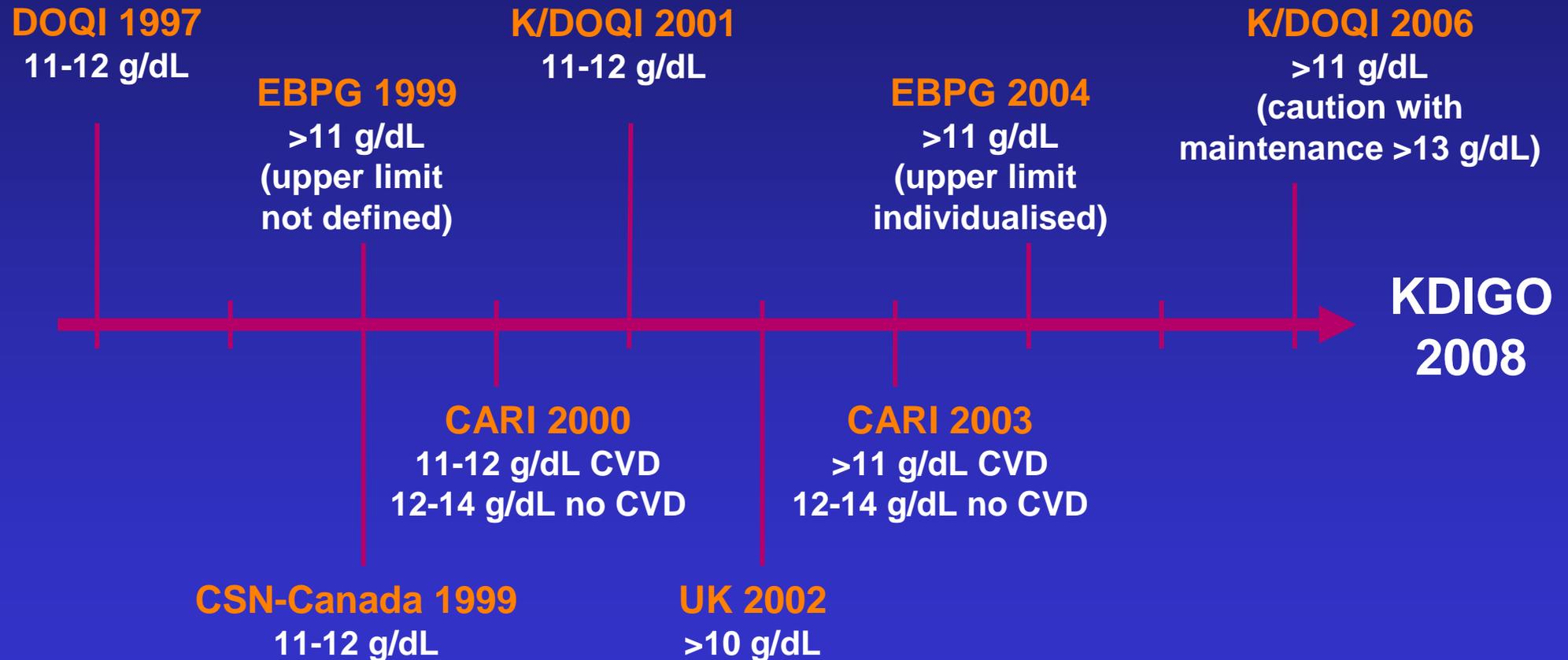


# Effect of partial anaemia correction on LV mass



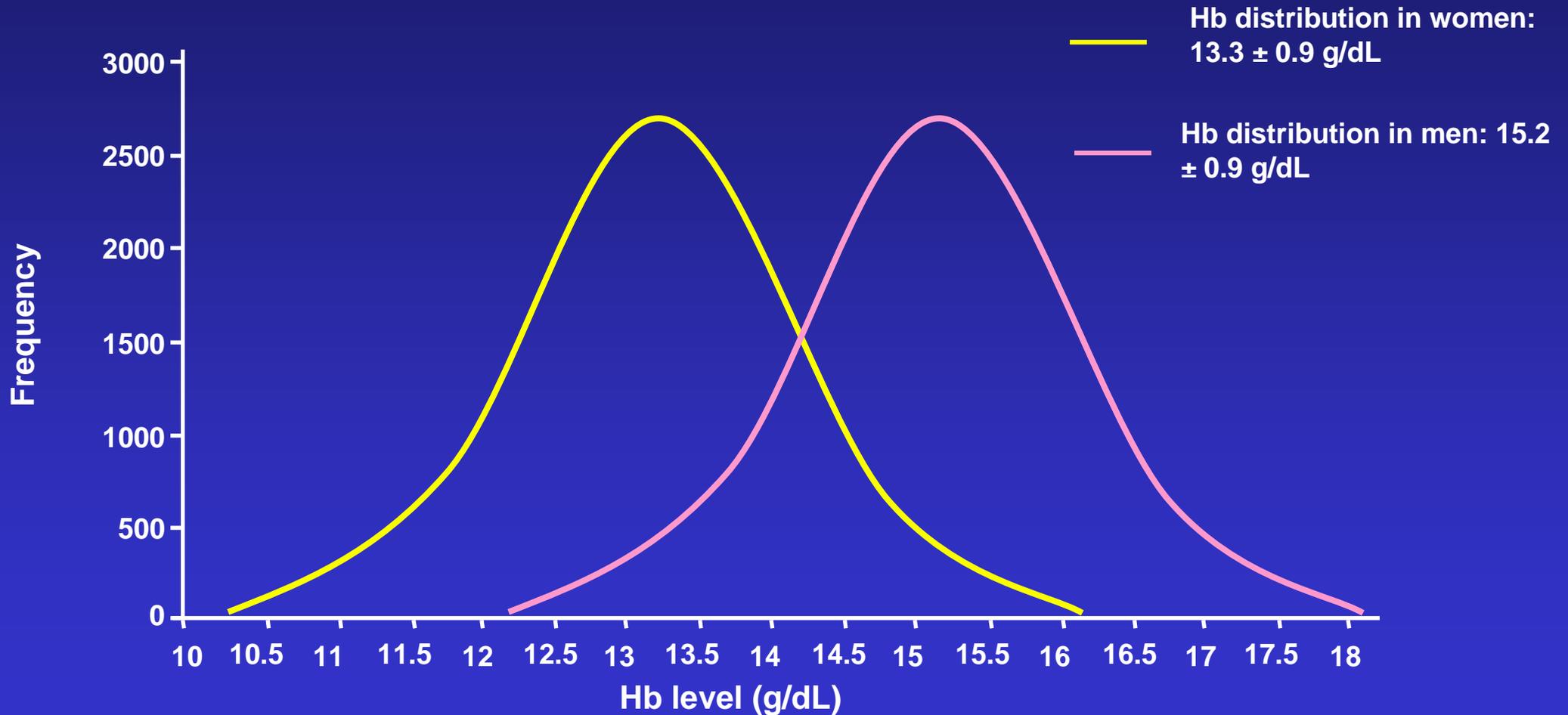
Radermacher J et al. Clin Nephrol 1995;44(Suppl 1):S56-60

# Target Hb in Anaemia Management Guidelines



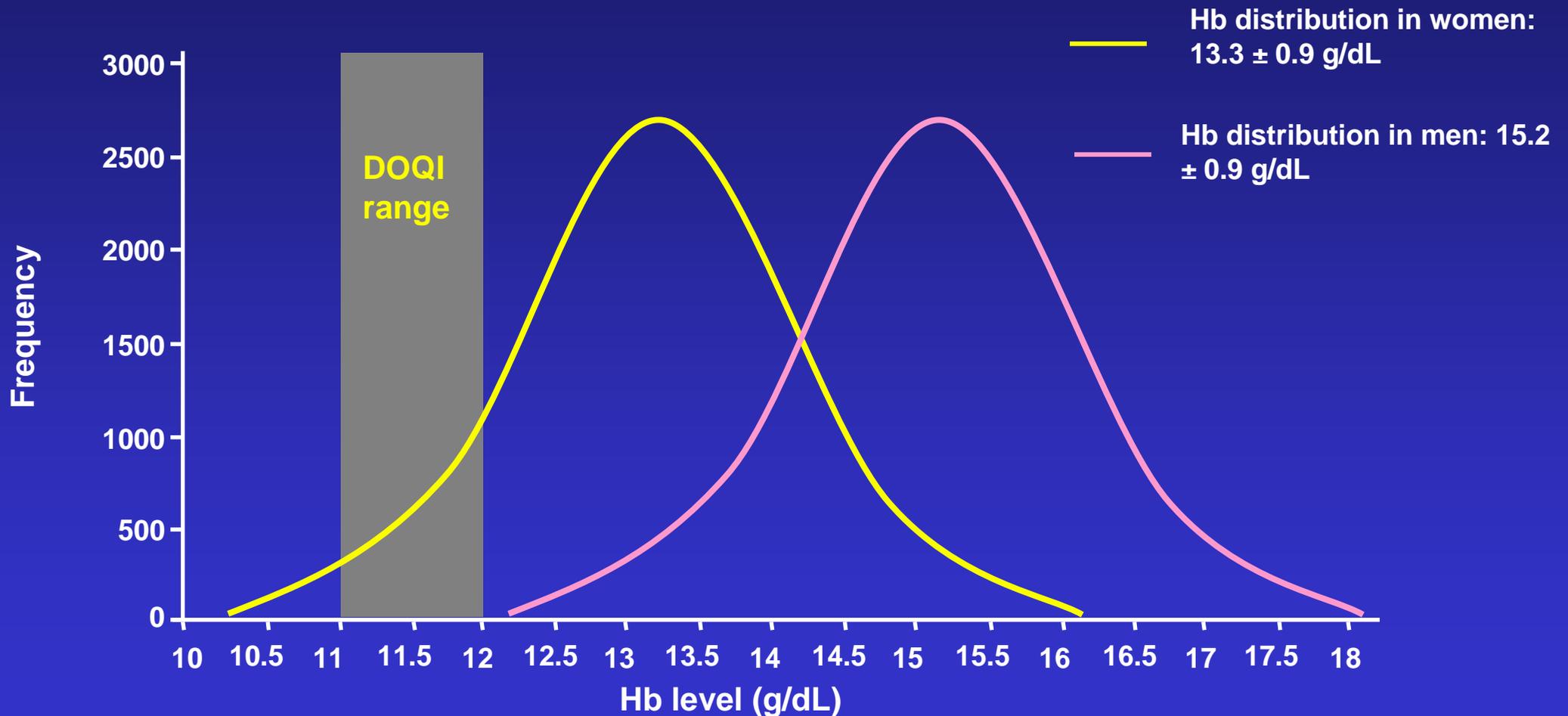
CVD=cardiovascular disease

# Normal Range of Hb With Normal Renal Function



N=40,000 (NHANES III, 1988-1994)

# Target Hb in CKD Patients Versus Normal Hb Distribution



N=40,000 (NHANES III, 1988-1994)

# Target Hb in Anaemia Management Guidelines

## Europe

European Best Practice Guideline (EBPG) of anaemia management in CKD <sup>1</sup>

- Only lower Hb limit
- Target Hb >11 g/dL

## US

National Kidney Foundation guideline of anaemia management in CKD (K/DOQI)<sup>2,3</sup>

- Lower and upper Hb limit
- Target Hb range 11-12 g/dL
  
- Lower Hb limit  $\geq 11$  g/dL (2006)
- Caution with maintaining Hb >13 g/dL

**1 Locatelli et al. *Nephrol Dial Transplant* 2004;19(Suppl 2):1-43**

**2 NKF-K/DOQ *AJKD* 2001;37(Suppl 1):S182-238**

**3 NKF-K/DOQI *AJKD* 2006; 47(Suppl 3): S11-145**



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## National Kidney Foundation Releases Anemia Guideline Update



**New recommendations based on months of analysis of six new randomized trials**

New York, NY  
August 30, 2007

After an extensive review of results from six new randomized controlled trials comparing risks and benefits of a range of target hemoglobins (Hb) in chronic kidney disease (CKD) patients, a National Kidney Foundation Kidney Disease Outcomes Quality Initiative™ (KDOQITM) work group is today issuing an official update of its 2006 Clinical Practice Guidelines on Anemia and CKD.

A key aspect of the update, which includes a new meta-analysis of all published trials, is its emphasis on clinical judgment and the needs of the individual patient receiving Erythropoiesis Stimulating Agent (ESA) therapy. In the new statements, the work group recommends what factors should be considered in selecting a Hb target and states that the selected Hb target should generally be in the range 11.0 to 12.0 g/dL. They point out that because of natural fluctuations, actual Hb results will vary widely from Hb targets.

Based on their analysis, the work group upgraded one of its opinion-based statements to an evidence-based guideline recommending that, in dialysis and non-dialysis CKD patients receiving Erythropoiesis Stimulating Agent (ESA) therapy, the Hb target should not be above 13.0 g/dL.

## Workgroup

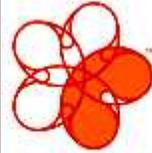
D. Van Wyck (Co-chair)  
K.-U. Eckardt (Co-chair)

J.W. Adamson  
J. S. Berns  
S. Fishbane  
R.N. Foley  
S. Ghaddar  
J.S. Gill  
K. Jabs  
H.H. Messner  
A.R. Nissenson  
G.T. Obrador  
J.C. Stivelman  
C.T. White

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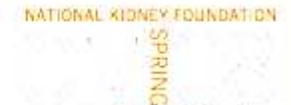
## The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI™)

### KDOQI™ News

- [National Kidney Foundation Releases Preliminary Anemia Guideline Update - New Evidence Spurs Re-examination of 2006 Recommendations](#)  
[Click here to download the complete Anemia Update, PDF \(2.38 MB\)](#)
- [Diabetes and Kidney Failure: A New Tool to Break the Cycle](#)
- [KDOQI Transparencies and COI policies](#)

## The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI™)

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI™) or KDOQI™ provides evidence-based



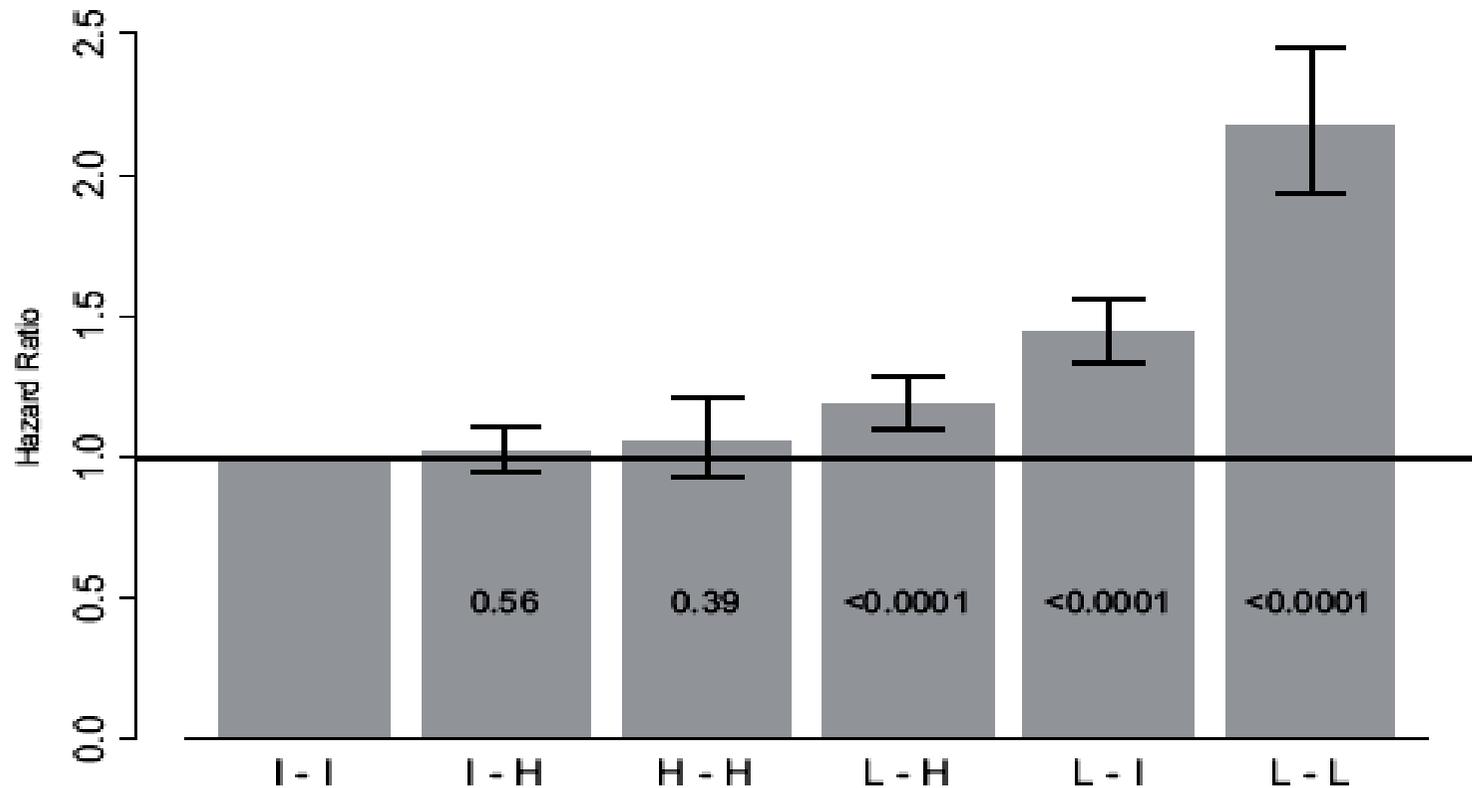
NATIONAL KIDNEY FOUNDATION  
SPRING  
Clinical Meetings  
**SAVE THE DATE!**  
April 2 - 6, 2008  
**Dallas, TX**



**GFR Calculator**

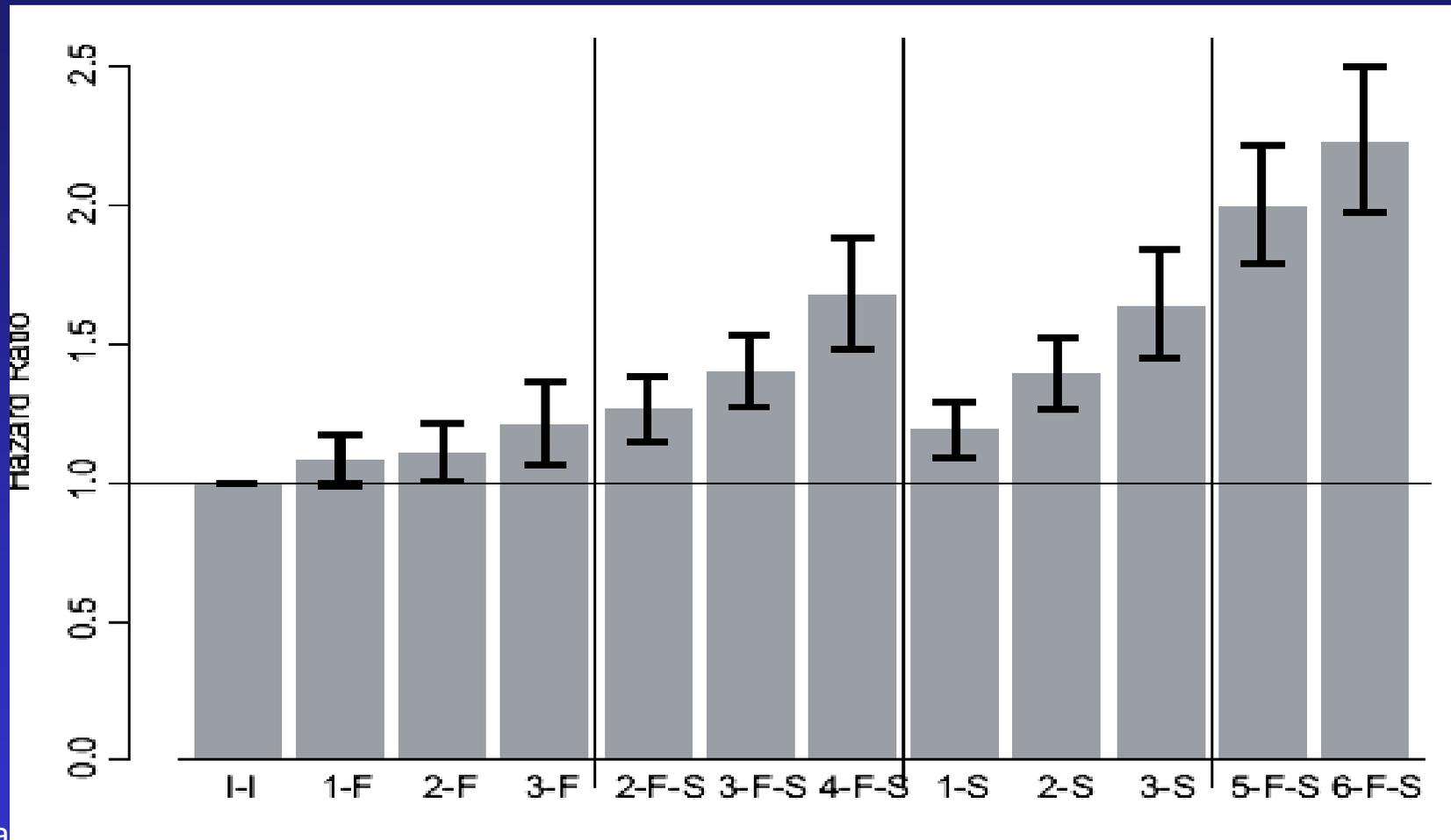


# Hemoglobin Level Variability: Associations with Mortality



Hemoglobin levels 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 categories seen in the 6-mo observation period. Each *P* value tests the corresponding variability group hazard ratio compared with the reference group (consistently intermediate).

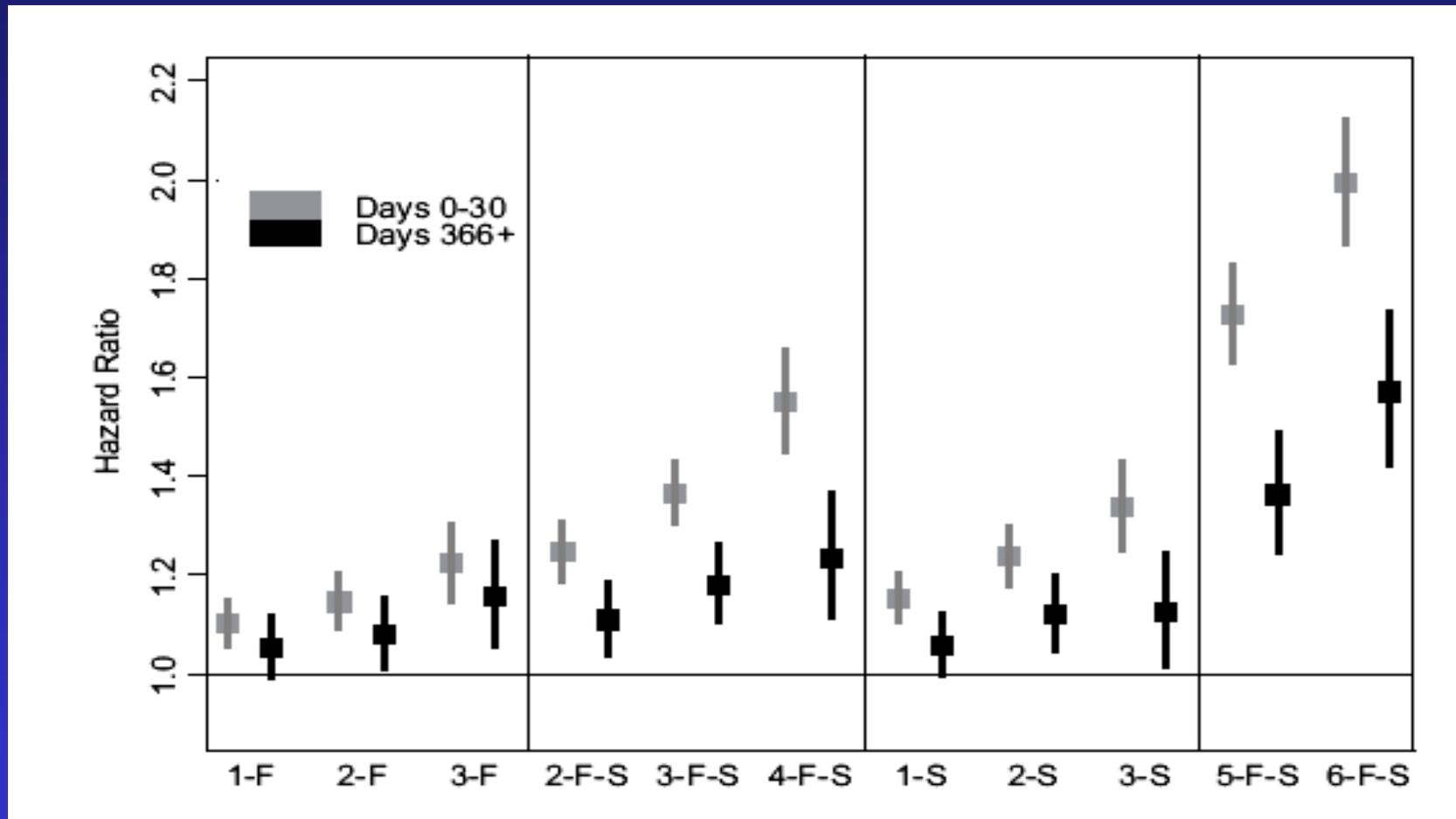
# Hemoglobin Level Variability: Associations with Mortality



Hemoglobin level variability is defined as the number of months with hemoglobin < 11 g/dl and first or second half of the 6-mo exposure period. For example, 2-F represents 2 mo with hemoglobin < 11 g/dl during the first 3 mo; 4-F-S represents 4 mo with hemoglobin < 11 g/dl during both the first and the second 3-mo periods. I-I, consistently intermediate (11 to 12.5 g/dl), represents the reference group.

**Gilbertson D. et al. Clin. J. Am. Soc. Nephrol., 2008 ;3: 133–138**

# Hemoglobin Level Variability: Associations with Mortality



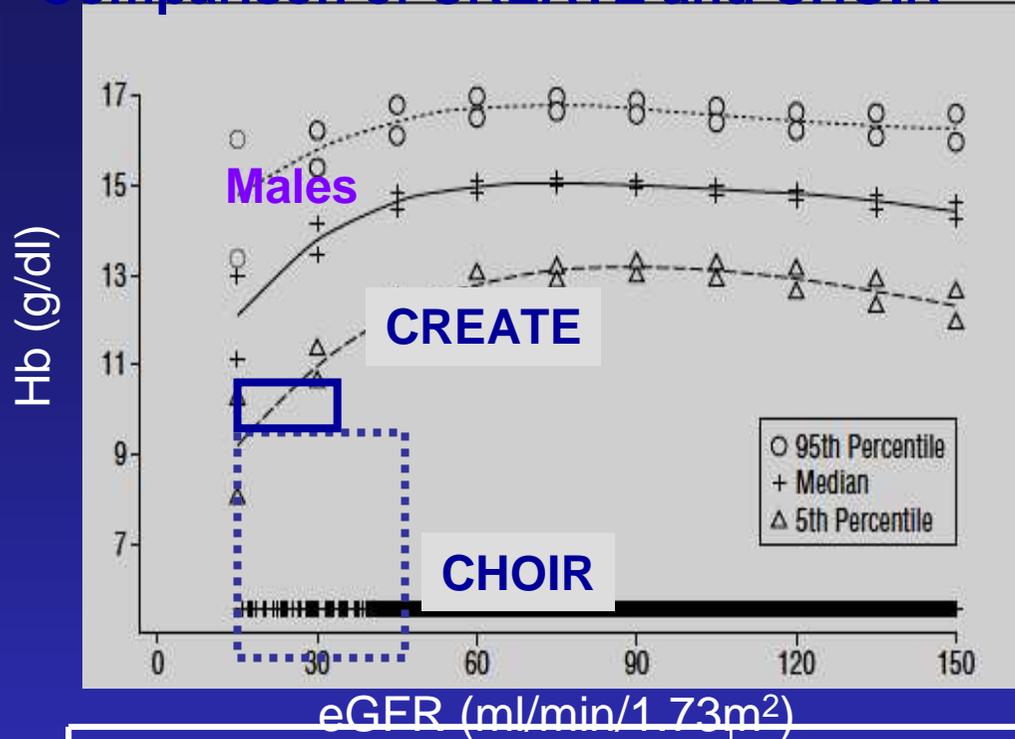
Interval Poisson model examining the change in hazard ratios over follow-up time. Number of months with hemoglobin 11 g/dl and first or second half of the 6-mo exposure period, as explained in Figure 2. I-I, consistently intermediate (11 to 12.5 g/dl), represents the reference group.

## KDOQI 2007 “Hb target update”

The Hb target is the intended aim of ESA therapy for the individual CKD patient. In clinical practice, achieved Hb results vary considerably from the Hb target.

1. In the opinion of the work group, selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events). (Clinical Practice RECOMMENDATION)
2. In the opinion of the work group, in dialysis and non-dialysis CKD patients receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL. (Clinical Practice RECOMMENDATION)
3. In dialysis and non-dialysis CKD patients receiving ESA therapy, the Hb target should not be above 13.0 g/dL. (Clinical Practice GUIDELINE - MODERATELY STRONG EVIDENCE)

## Comparison of CREATE and CHOIR



**Cross-sectional study in the US  
(NHANES III)**

	CREATE – baseline		CHOIR – baseline	
	Low arm	High arm	Low arm	High arm
<b>Age</b>	<b>58.8</b>	<b>59.3</b>	<b>66.3</b>	<b>66.0</b>
<b>DM as cause of CKD</b>	<b>21 %</b>	<b>20 %</b>	<b>51 %</b>	<b>47 %</b>
<b>Hypertension as cause of CKD</b>	<b>19 %</b>	<b>23 %</b>	<b>28 %</b>	<b>30 %</b>
<b>BP systolic</b>	<b>139</b>	<b>139</b>	<b>136</b>	<b>137</b>
<b>BP diastolic</b>	<b>80</b>	<b>79</b>	<b>71</b>	<b>72</b>

# **Lesson learned from CREATE and CHOIR**

**From an Editorial Comment by  
Adeera Levin**

***Nephrol Dial Transplant*  
2007;22:309-312**

# PROSPECTIVE STUDIES

STUDY	PUBLICATION	CONVERSION FACTOR	LENGTH OF THERAPY
Raymond et al.	ASN 2004, F-PO522	1:281 i.v 1:224 s.c	3 months
Giotta N et al.	ASN 2004, SU-PO434	1:246 i.v.	6 months
Roger et al.	Nephrology 2004; 9: 223	1:275 s.c vs i.v	3 months
Barril et al.	ASN 2004, SA-PO321	1:198 HD 1:190 CADO	6 months
Nissenson et al.	AJKD 2002; 40: 110	1:252 in the correction phase	6 months
Brunkhorst et al.	NDT 2004; 19: 1224	1:234 i.v. 1:214 s.c.	6 months
Tolman et al.	ASN 2004, MO-46	44% higher doses of erythropoietin beta than darbepoetin	9 months
Vanrenterghem et al.	Kidney Int 2002; 62: 2167	ca. 1:250 i.v.	12 months

## **Summary: CERA Clinical Profile**

- **CERA Phase II results (>1 year) indicate with extended administration intervals**
  - **a large number of patients are maintained within recommended ranges**
  - **keeping Hb in recommended ranges is achieved with few dose changes**
  - **overall, generally well tolerated**

**adverse events profile characteristic of this**

**Thank You for your attention !**

**A. Więcek**

**Katowice  
Poland**



## ERYTHROPOIESIS STIMULATING AGENTS (ESA)

Half-life (h, mean  $\pm$  SEM)

**i.v.**

**S.C.**

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<b>CERA<sup>1</sup></b>	133 $\pm$ 9.83	137 $\pm$ 21.9
<b>Darbepoetin alfa<sup>2</sup></b>	25.3 $\pm$ 2.2	48.4 $\pm$ 5.2
<b>Epoetin beta<sup>3</sup></b>	8.8 $\pm$ 0.5	24.2 $\pm$ 2.6
<b>Epoetin alfa<sup>3</sup></b>	6.8 $\pm$ 0.6	19.4 $\pm$ 2.5

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<sup>1</sup> from multiple dose studies

<sup>2</sup> Macdougall et al. *JASN* 1999

<sup>3</sup> Halstenson et al. *Clin Pharmacol Ther* 1991