

**Adverse Effects of Epoetin:
What is the the evidence?
What are the potential mechanisms?**

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Disclosure

I have been a consultant, received honoraria and grant support from manufacturers of

ESAs

Amgen*

Ortho

Adventis

Hoffman La Roche

Affymax

Fibrogen

Iron

Rockwell International

Watson Pharma*

American Regent*

Advanced Magnetics

* denotes speaker's board

Adverse Effects of Epoetin: truth or speculation

Is it true?

Who is at risk?

(all patients?)

(Hyporesponsive patients?)

(Related to Hb achieved?)

How is it mediated?

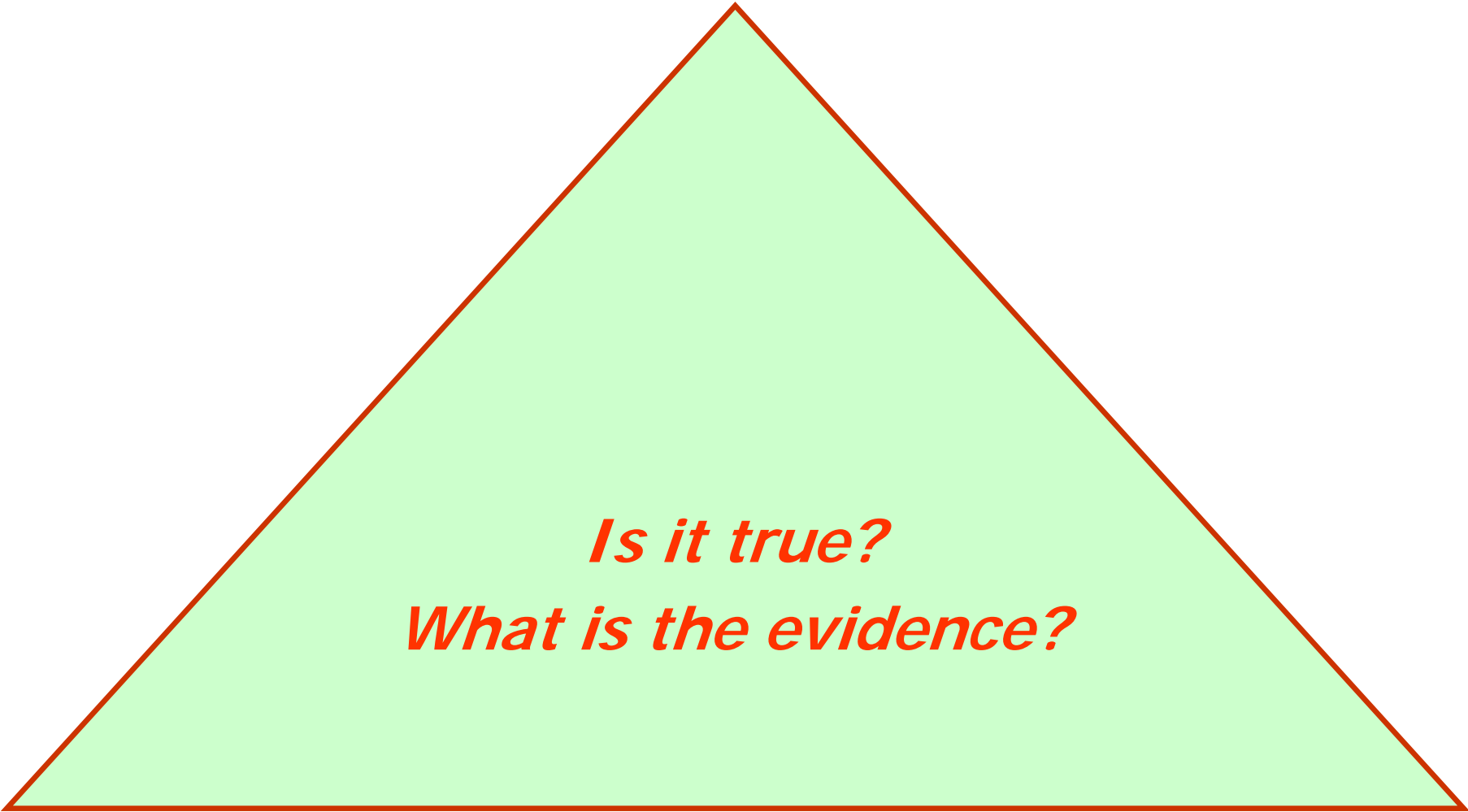
(dose dependent direct effects on

non-erythropoietic receptors)

(via an increase in Hb?)

(Indirectly via other mechanisms?)

Adverse Effects of Epoetin: truth or speculation



Is it true?
What is the evidence?

Evidence

- Evidence is a fact or body of facts on which a proof, belief, or judgment is based
- Evidence is not certainty
- Evidence may be weak or strong
- May be obtained through experience, observational research, or experimental trial (RCT)
- Must be relevant to the understanding of the problem in a patient or to the clinical decisions (diagnostic, therapeutic, or care-oriented) made about that patient.

Best Evidence

- Hierarchy adopted by USA and Canadian Task Forces on Preventive Services
 - Well designed (and executed) RCTs
 - Observational analytical studies (preferably prospective cohort)
 - Multiple observational time series (descriptive studies)
 - Consensus and expert opinions by authorities or experts
 - Personal anecdotal experience

Best Evidence: considerations

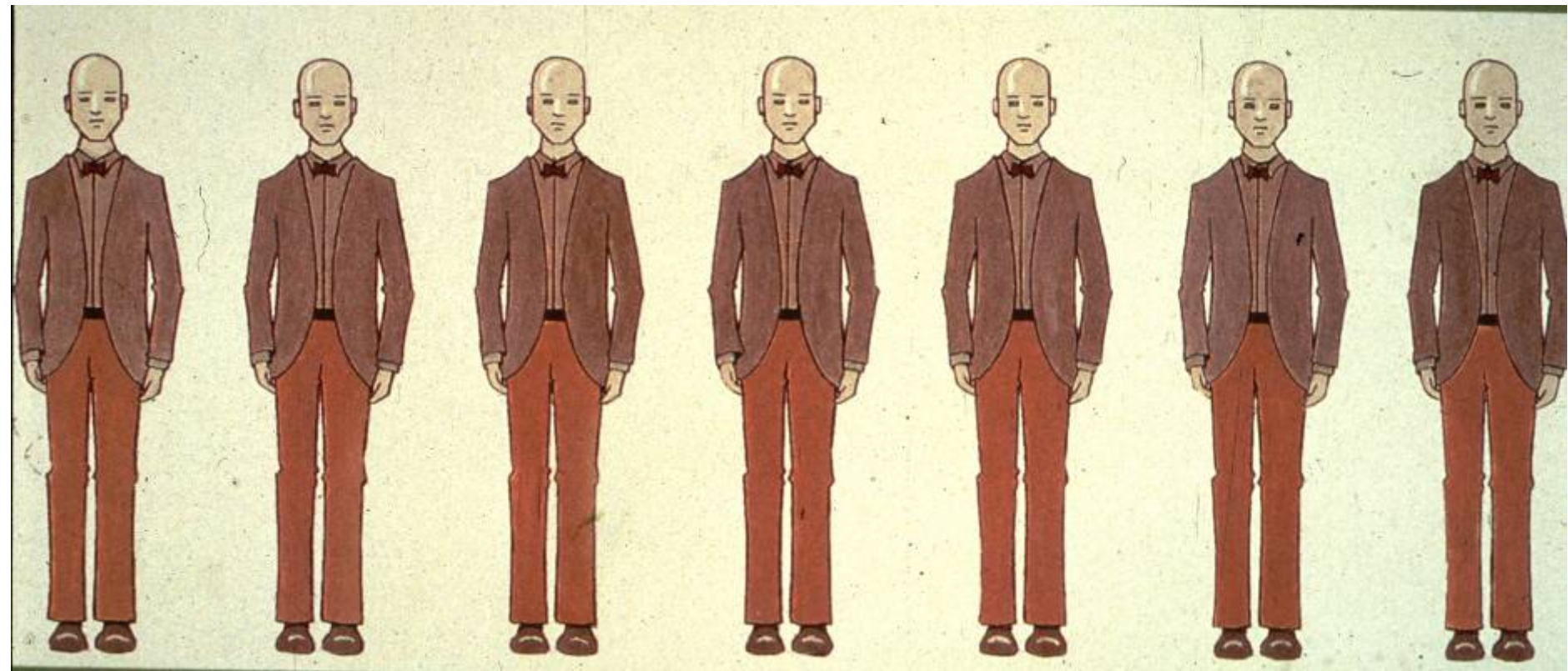
- Best does not = RCT
- Quality can be equal among the hierarchy of evidence

Integrating best evidence into the physician-patient interaction

- Finding a common ground with a patient
 - Explaining to them the rationale as their physician
 - Listening to their views
 - Making sense from both points of view
 - Reaching a mutually acceptable agreement about what to do.

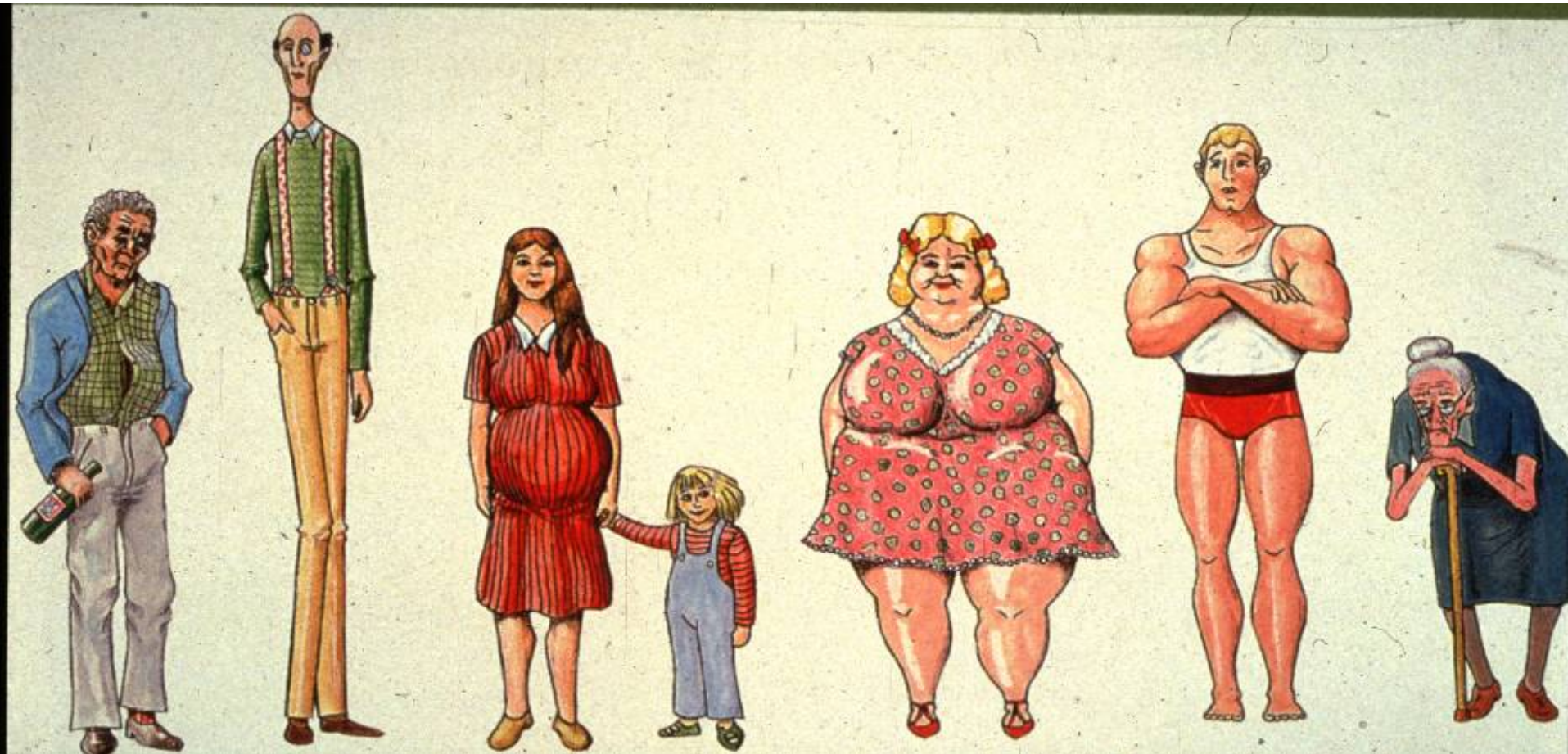
One Size fits All

Courtesy of Dr. Gilbert Debray



We know we must individualize

Courtesy of Dr. Gilbert Debray



In medicine we treat an individual and we take pains to individualize the patient

Two well randomized cohorts of patients will include individual subjects with different genotype/phenotype.

The same rules will be applied to all subjects in each cohort.

Outcome analyses consider that genotype/phenotype is the same for all included subjects

Results clearly show that outcomes of therapy within the cohort vary: some benefit, some are harmed.

One cohort has a better benefit /risk ratio. We then generalize findings to all subjects in a cohort

The problem is to identify who in each cohort is at risk for an adverse or for a favourable effect/



↑
?

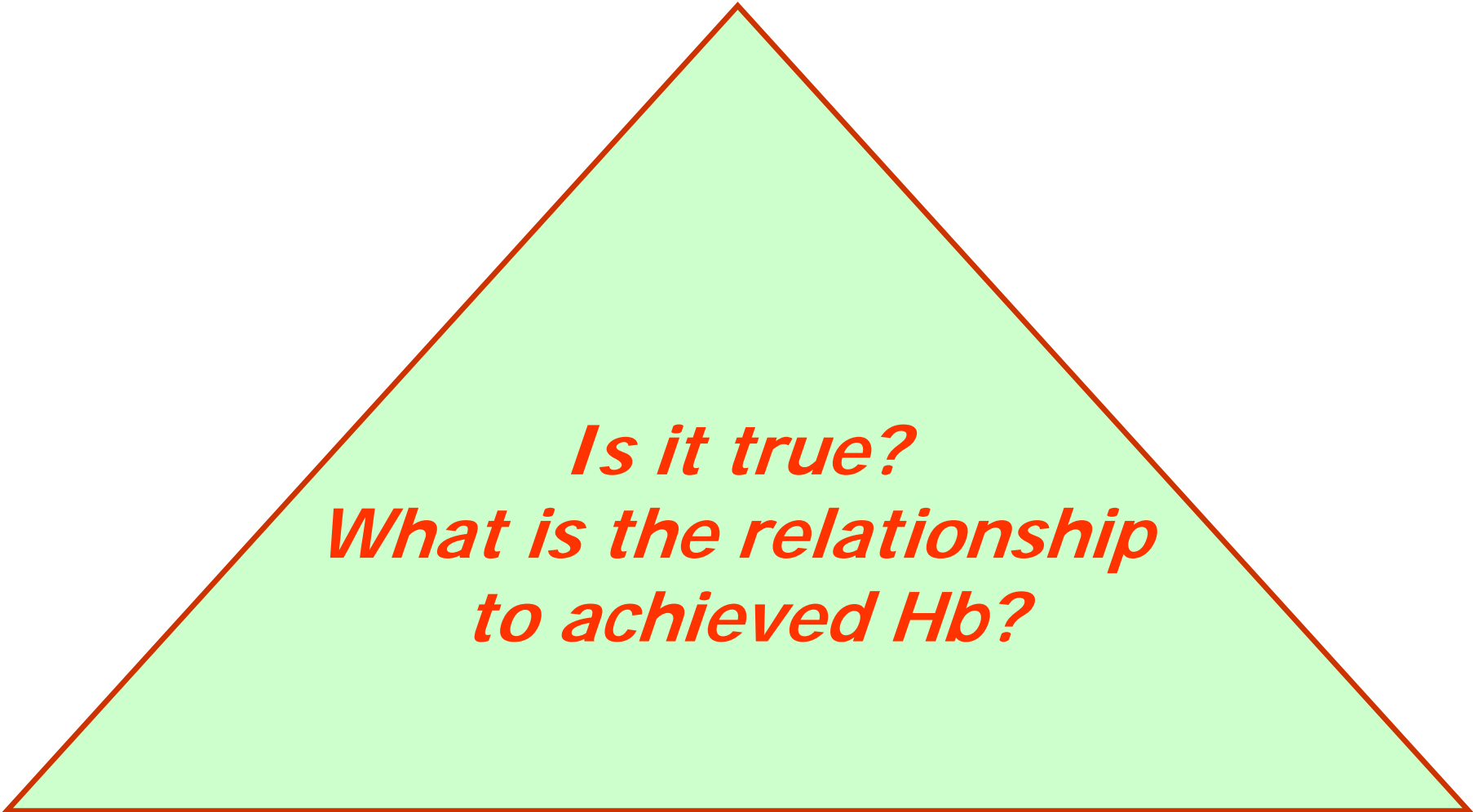
↑

↑
?

The ugly “truth” about EBM

- No “evidence” that the practice of EBM results in better clinical outcomes and benefits to patients (no RCT)
- EBM is prone to many interpretation, applications, and uses.
 - These are like books of faith.

Adverse Effects of Epoetin: truth or speculation

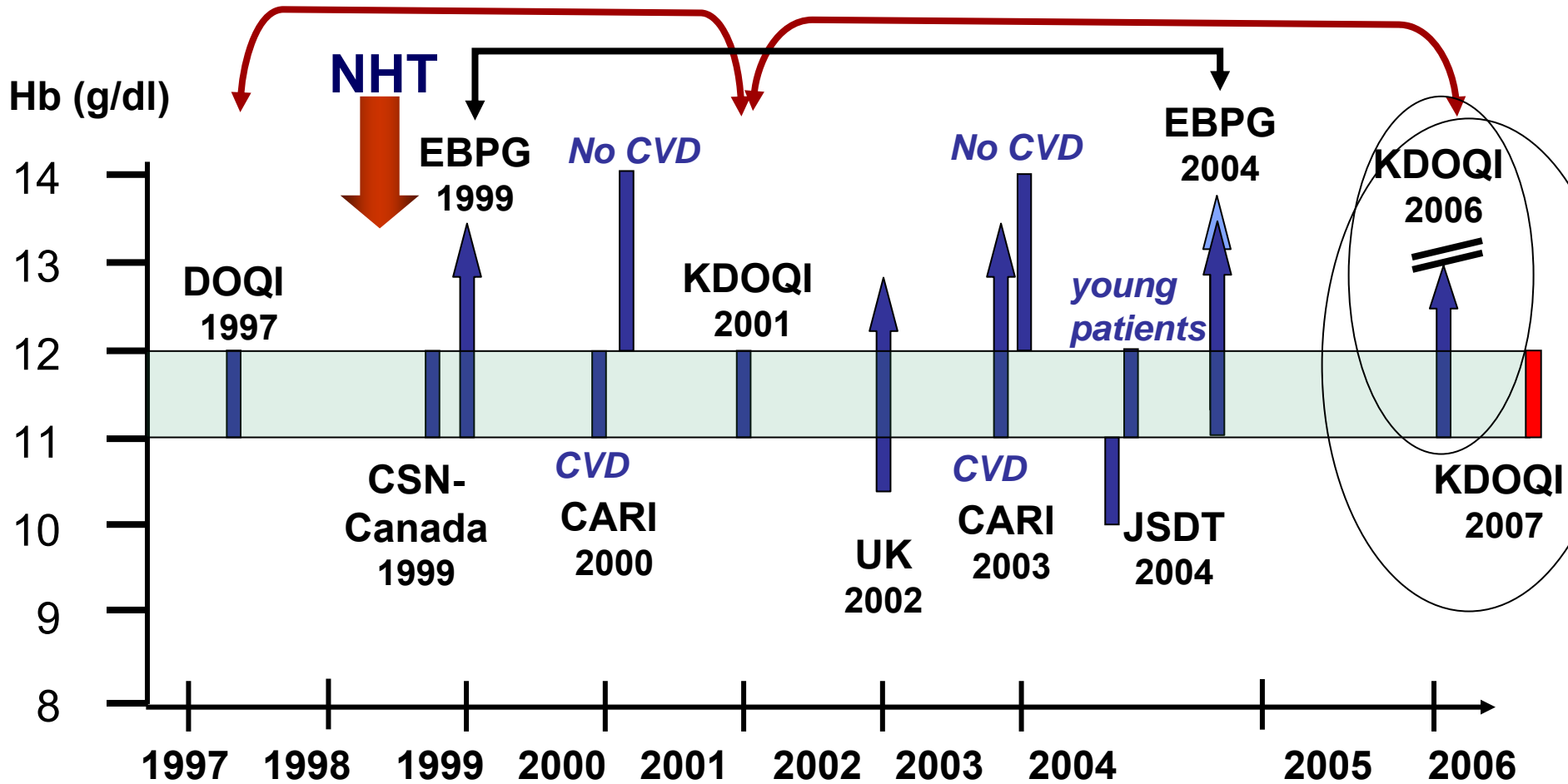


*Is it true?
What is the relationship
to achieved Hb?*

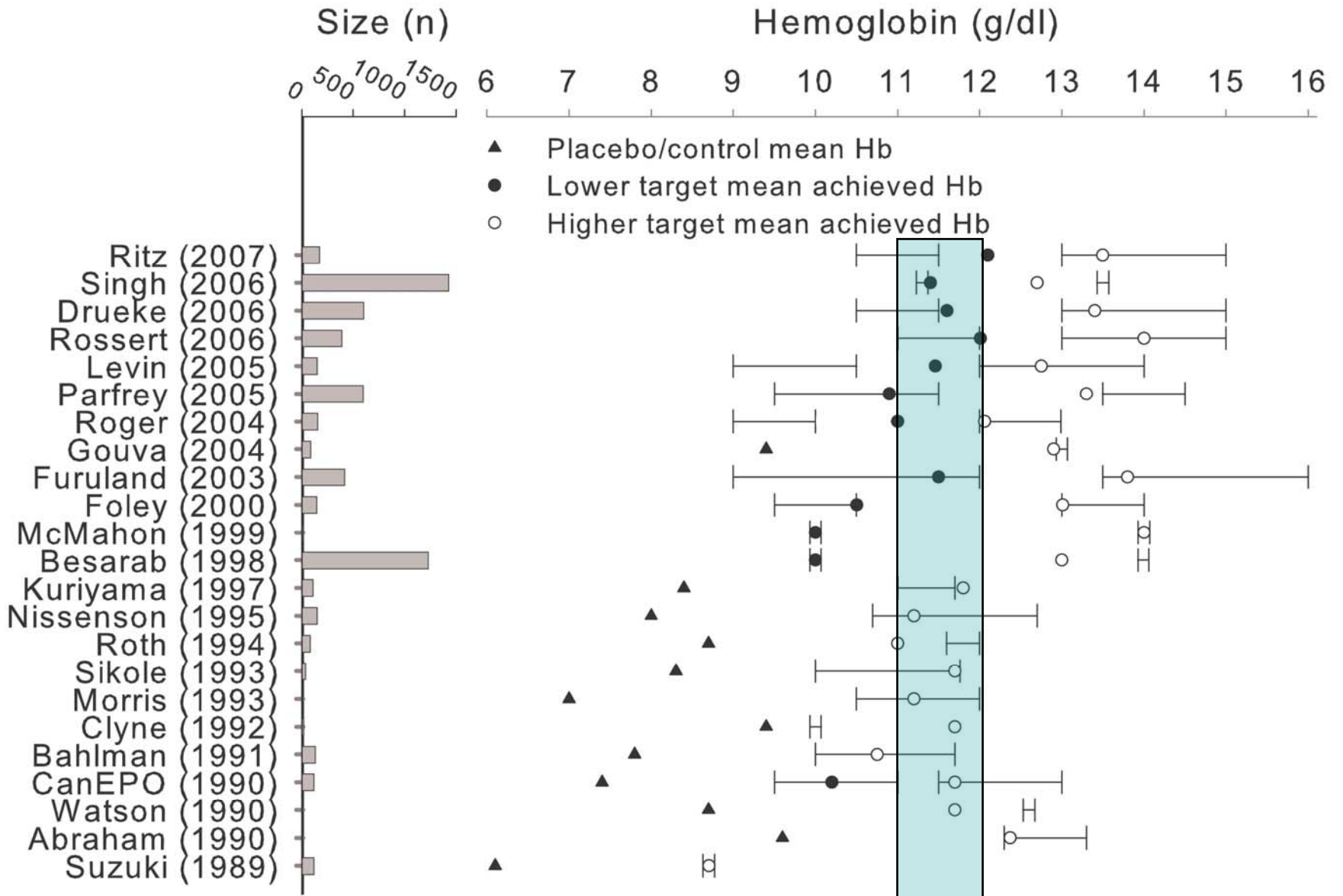
Target Hemoglobin in Patients with CKD –

Searching for the truth for
more than a decade!!

Target Hb Values in International Guidelines

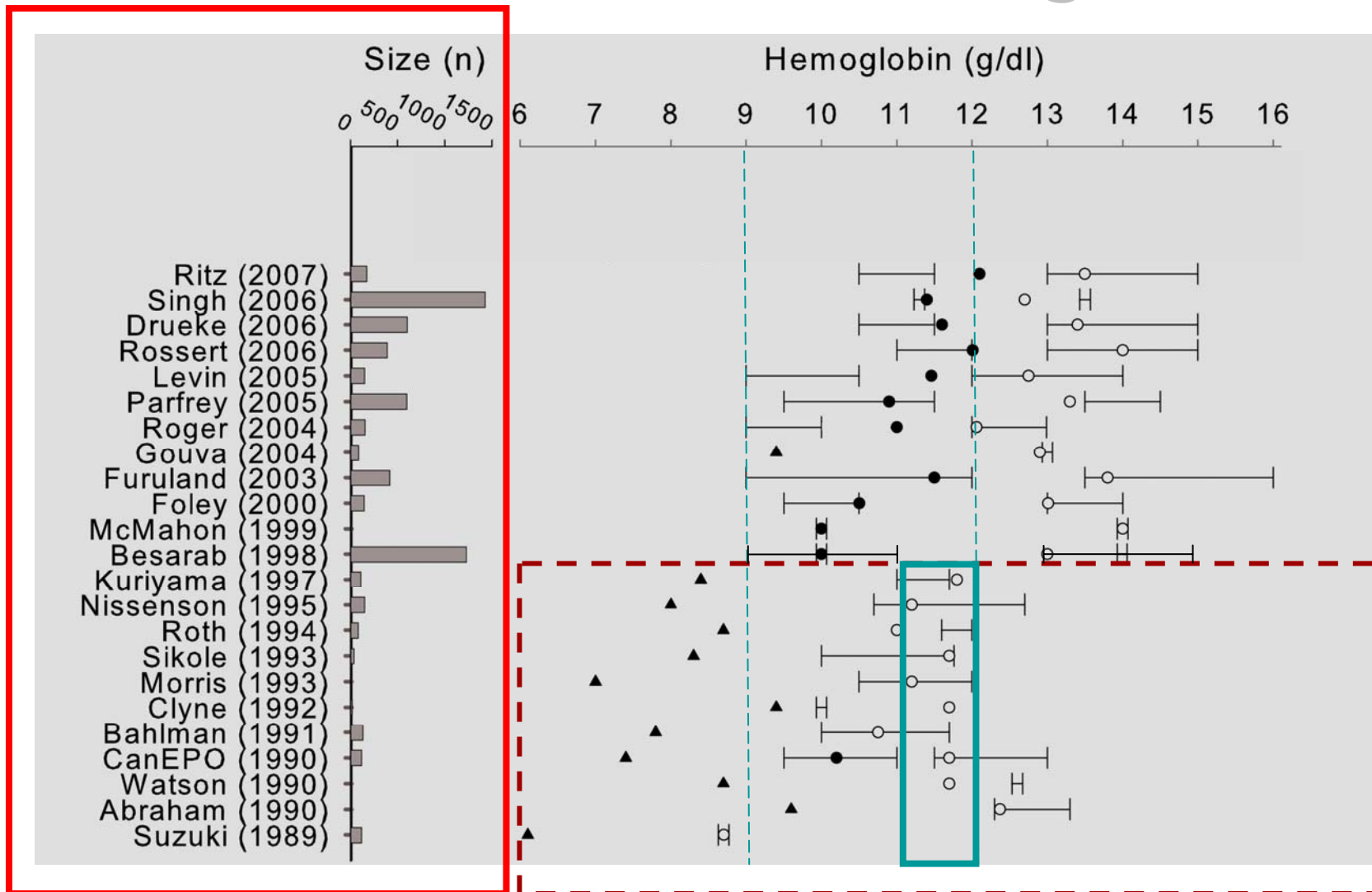


Rationale: 2.1.2



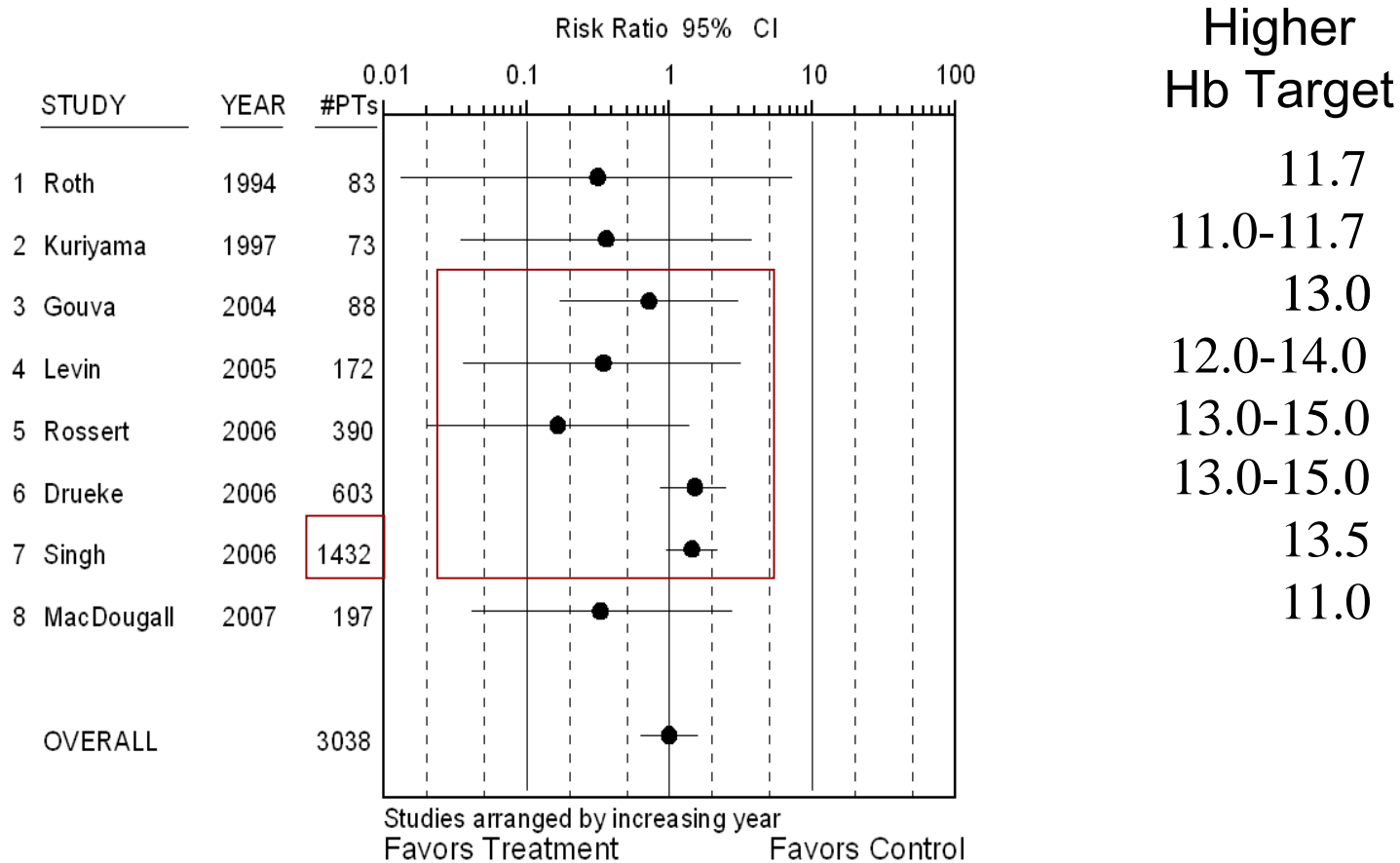
Courtesy Dr. D. VanWyck

RCTs in Anemia Management



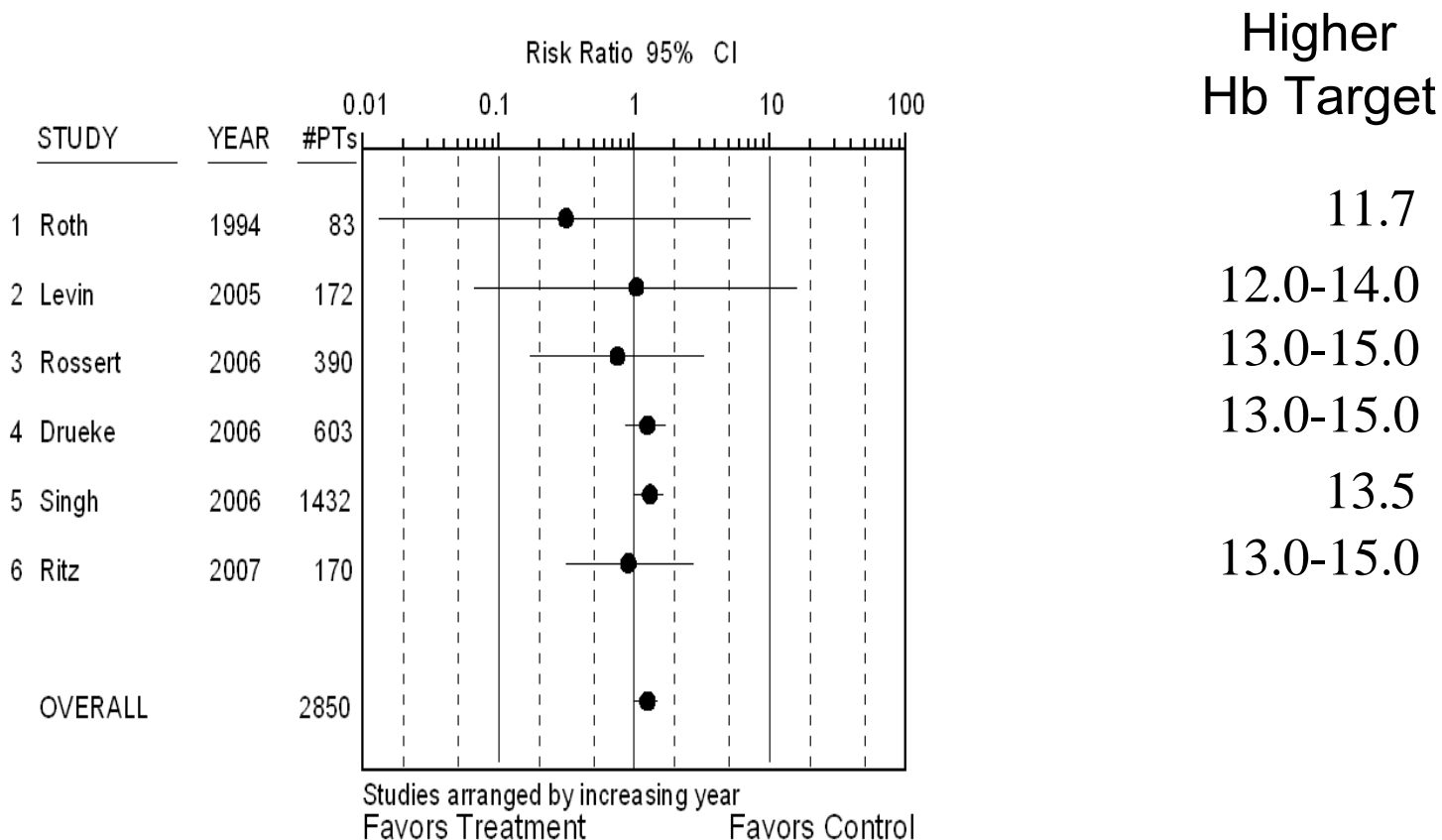
- ▲ Placebo/control mean Hb
- Lower Hb arm: mean achieved Hb
- Higher Hb arm: mean achieved Hb

Relative *mortality* risk for assignment to higher treatment targets: Non-Dialysis-CKD



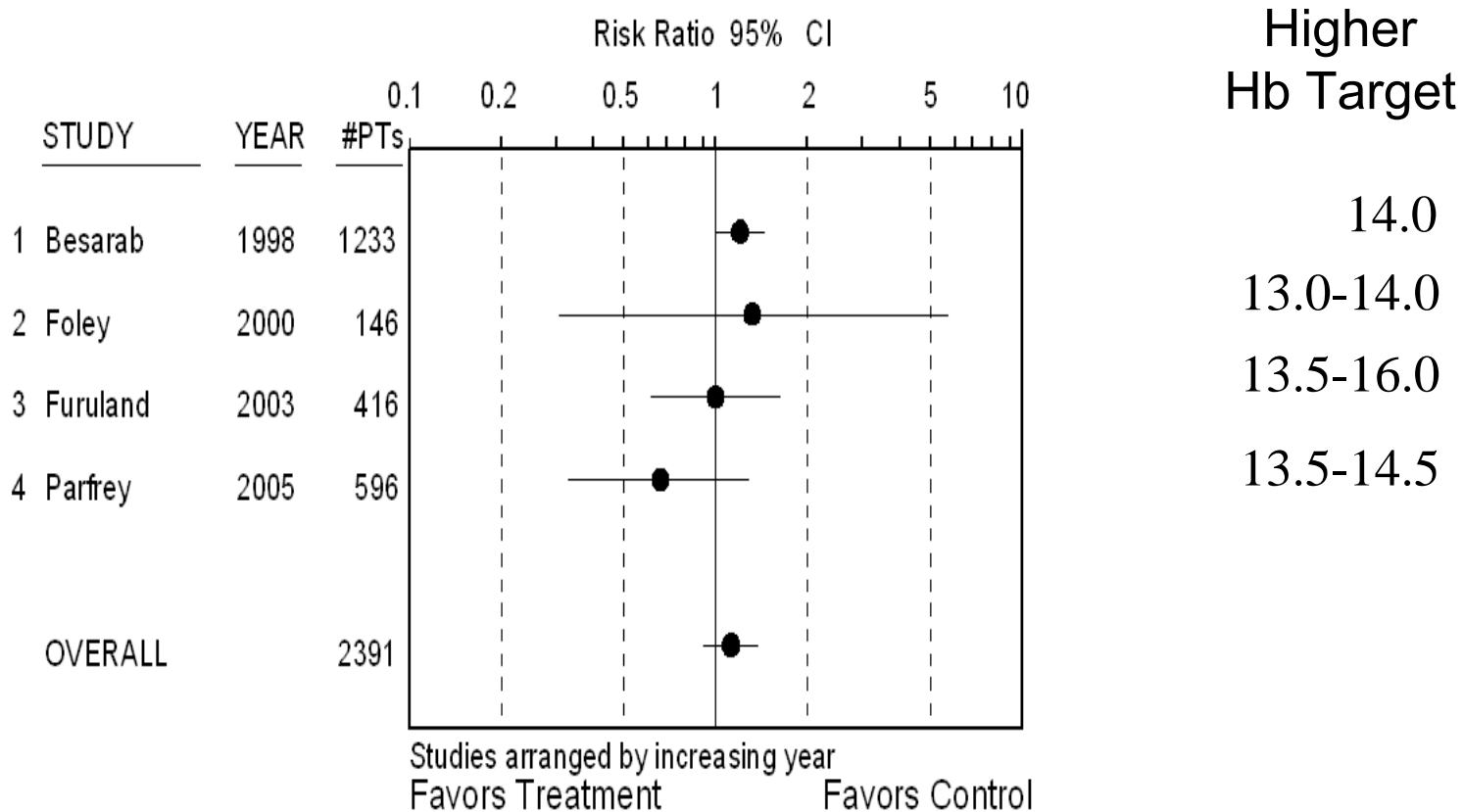
Relative Risk: 1.02, 95% CI 0.63-1.61

Relative risk of cardiovascular events for assignment to higher targets: Non-dialysis CKD



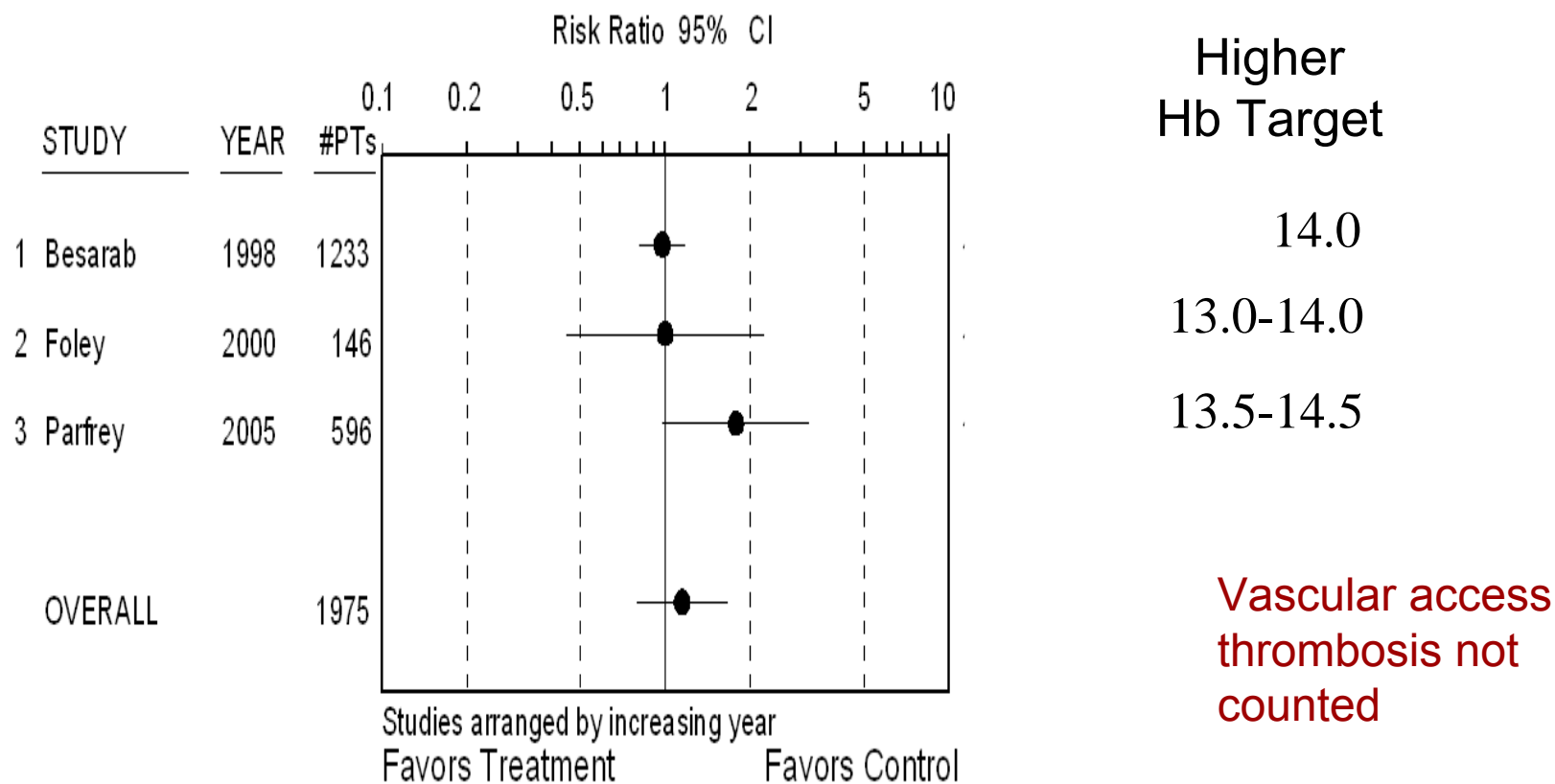
Relative Risk: 1.24, 95% CI 1.02-1.51

Relative *mortality* risk for assignment to higher treatment targets: Dialysis CKD



Relative Risk: 1.12, 95% CI 0.91-1.37

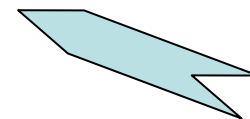
Relative risk of cardiovascular events for assignment to higher targets: Dialysis CKD



Relative Risk: 1.14, 95% CI 0.79-1.64

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.
 - 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)
 - 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)
 - 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)



This was an opinion based recommendation in 2006

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

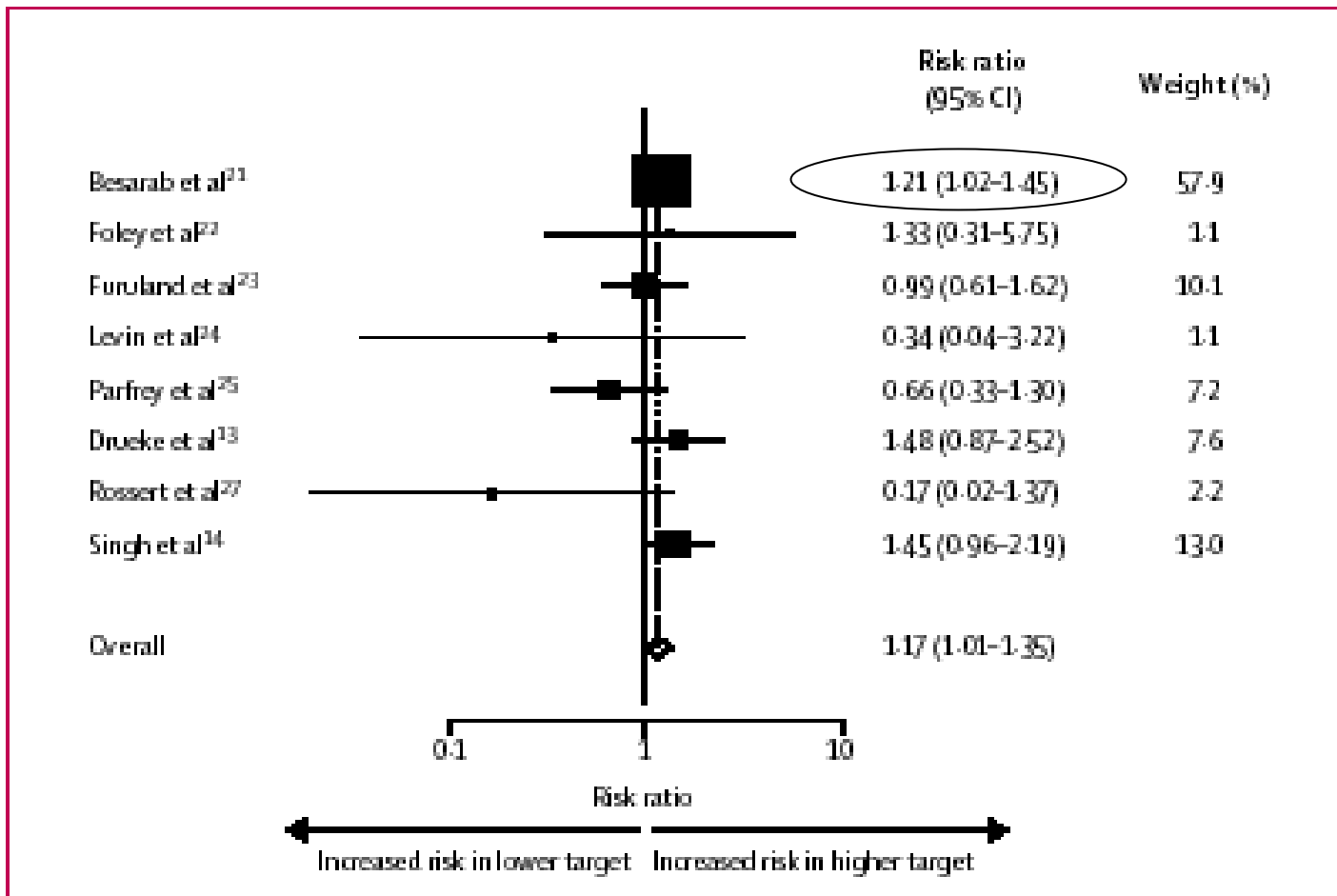
On the basis of the existing published trials, summarised by Phrommintikul and colleagues,⁴ we contend that more trials of haemoglobin target concentrations in patients with chronic kidney disease are no longer required, should be stopped, or at least it should be made fully and publicly explicit what 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,

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



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



**FDA Public Health Advisory
Erythropoiesis-Stimulating Agents (ESAs)
Epoetin alfa (marketed as Procrit, Epogen), Darbepoetin alfa
(marketed as Aranesp)**

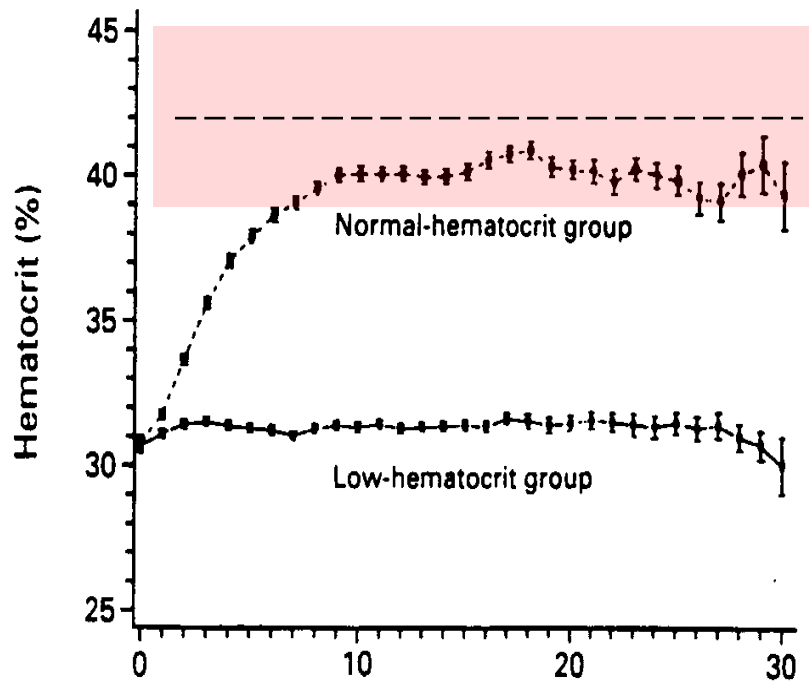
- **All ESAs have the same mechanism of action**
- **New product labeling to include a new boxed warning, updated warnings, and a change to the dosage and administration sections for all ESAs.**
- **For all patients:**
 - **Use the lowest dose possible to gradually increase the hemoglobin concentration to avoid the need for transfusion.**
 - **Measure hemoglobin twice a week for 2 to 6 weeks after any dosage adjustment to ensure that hemoglobin has stabilized in response to the dose change.**
 - **Withhold the dose of the ESA if the hemoglobin increase exceeds 12 g/dL or rises by 1g/dL in any 2 week period**
- **Essentially sets a Ceiling and a Floor to avoid transfusion**

Hb < 8.5 g/dL

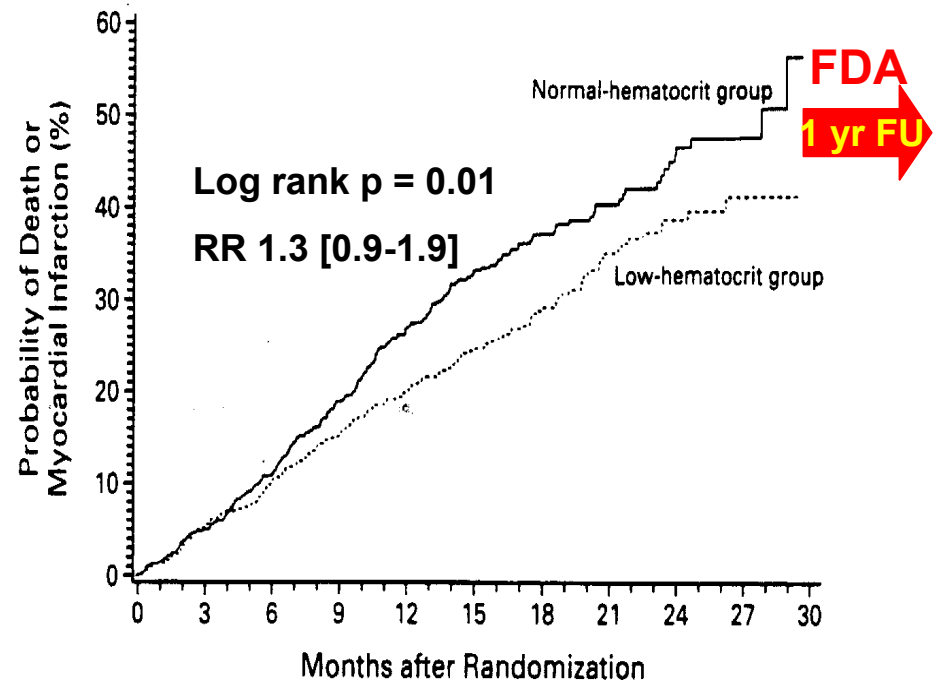
Impractical

Normal vs Low hematocrit in patients with cardiac disease receiving Hemodialysis and Epoetin (N Hct Trial a.k.a. Besarab Trial)

Data Set as of 3/31/1996



Data Set as of 6/24/1996



“Concern about safety at the **3rd interim analysis** prompted the independent DSMB to recommend that the study be stopped ,, [even though primary outcome] ... did not reach the pre-specified stopping boundary corresponding to an overall 5% level of significance (O’Brien-Fleming)”

GRAFT THROMBOSIS, $p < 0.001$

Death and/or AMI endpoint, RR 0.9-1.9, p NS [log rank p value required to stop for futility or harm/benefit $p=0.00088$]. If analysis performed 6/24/1996, RR of death 1.28 (0.92-1.78)

Normal Hematocrit Study: Completed Study

Normal Hematocrit Primary Endpoint Components: Final Study Report

Component	High Hct n = 634	Low Hct n = 631
Primary endpoint deaths	208 (32.8%)	173 (27.4%)
Total deaths	221 (34.9%)	185 (29.0%)
Non-fatal MI	20 (3.2%)	16 (2.5%)

* Log rank test of event free survival

P<0.01*

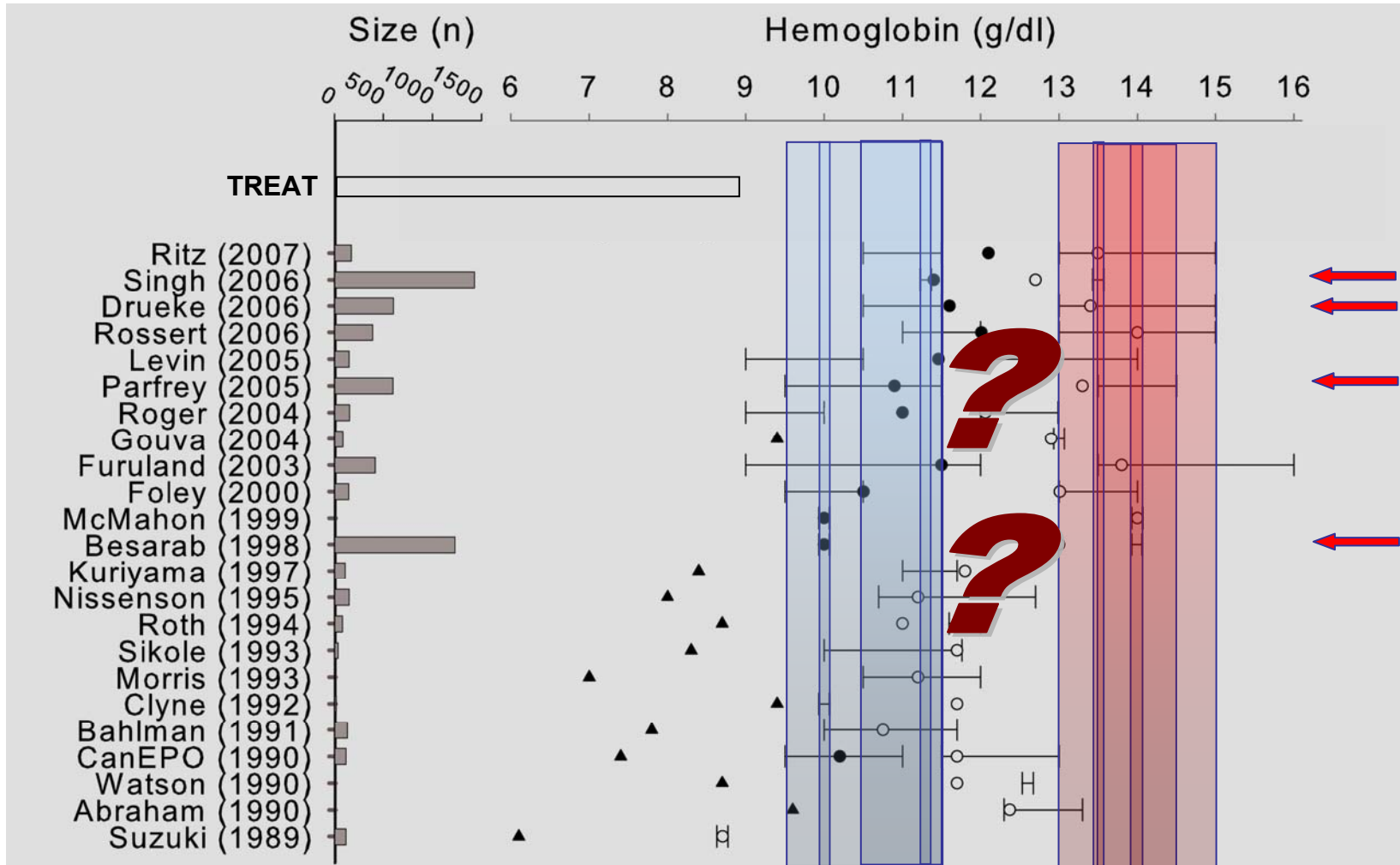
Source: FDA Briefing Document, CDRAC 2007

Normal Hematocrit Study

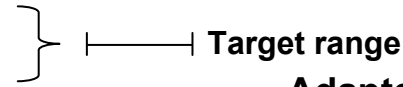
Results: Components of Primary Endpoint

	Target		RR	95% CI
	42% (Normal Hct) N = 634	30% (Low Hct) N = 631		
Death	221 (35%)	185 (29%)	1.19	1.01 to 1.40
Non-fatal MI	20 (3.2%)	16 (2.5%)	1.24	0.65 to 2.38
Either	241 (38%)	201 (32%)	1.19	1.03 to 1.39

What should be the Target Hb ?

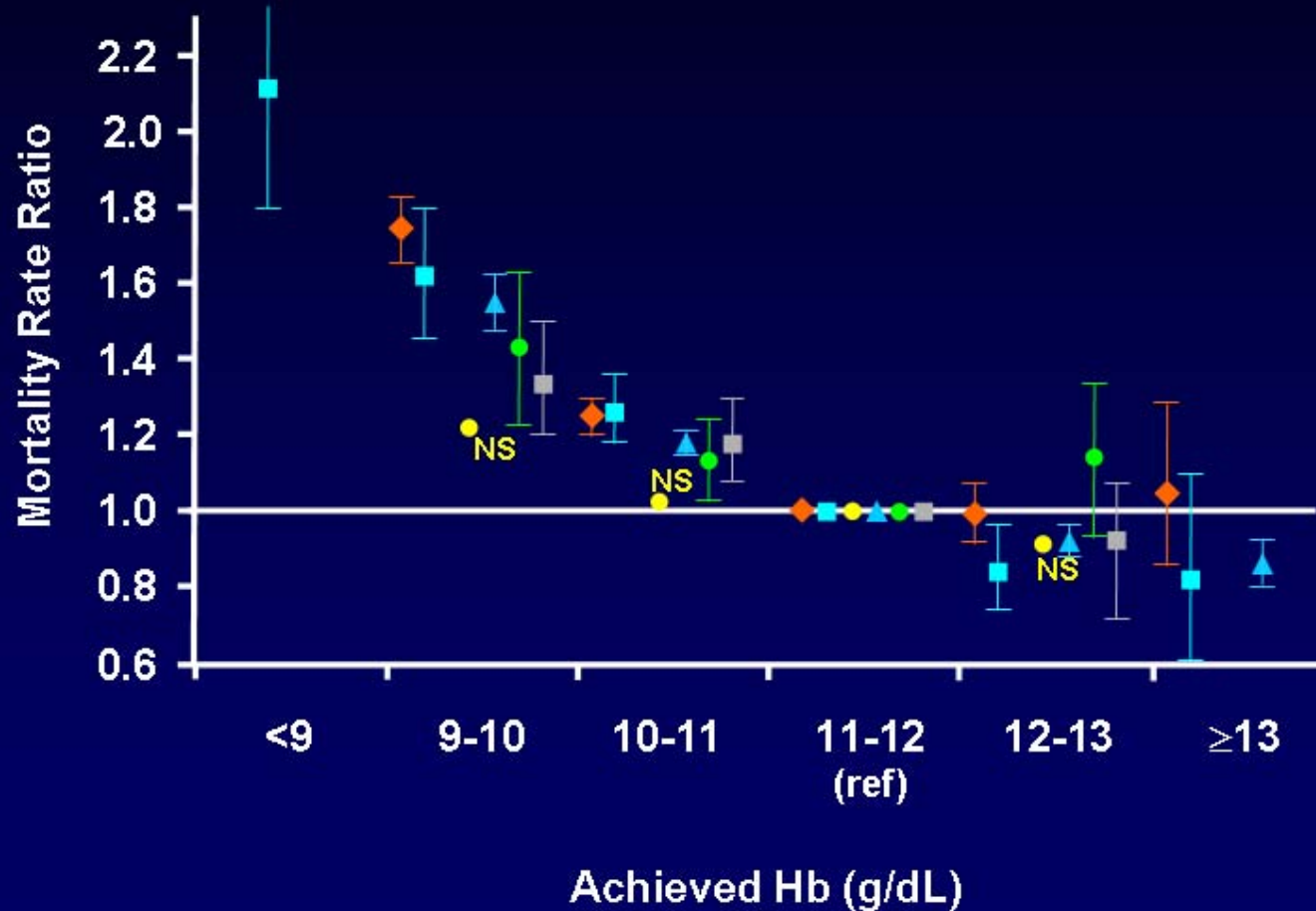


- ▲ Placebo/control mean Hb ▲
- Lower Hb arm: mean achieved Hb
- Higher Hb arm: mean achieved Hb



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

Achieved Hb and Outcomes in Comprehensive Clinical Practice Data

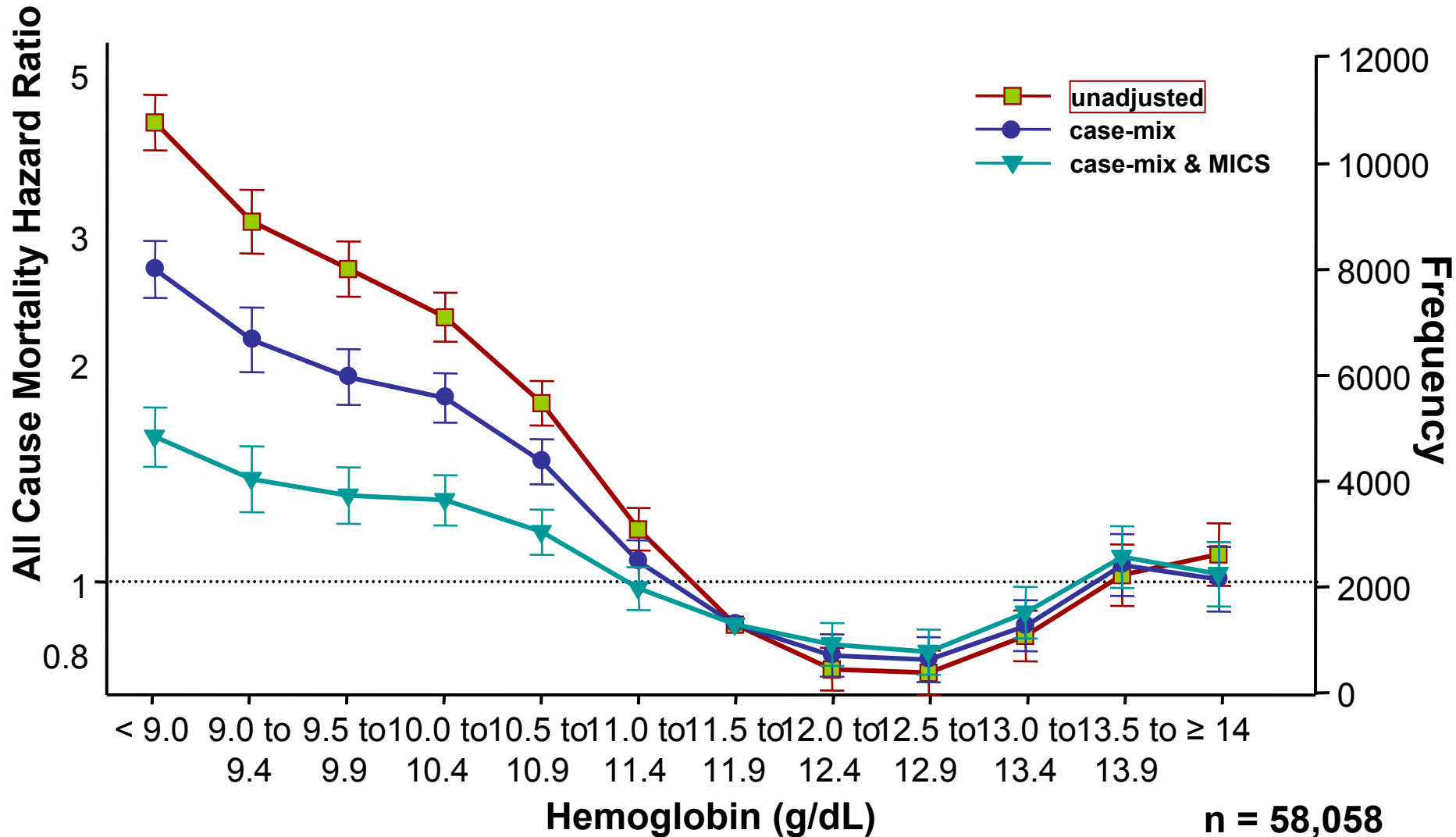


- ◆ Collins, 2001 (66,761 incident HD patients)
- Ofsthun, 2003 (44,550 prevalent HD patients)
- Locatelli, 2004 (4,591 prevalent HD patients)
- ▲ Li, 2004 (50,579 incident HD patients)
- Li, 2004 (8,267 incident PD, non-DM patients)
- Li, 2004 (5,707 incident PD, DM patients)

95% CI; NS=not significant

Adapted from: Volkova & Arab, *AJKD* 2006.

All-Cause Death in All Patients (Incident & Prevalent)

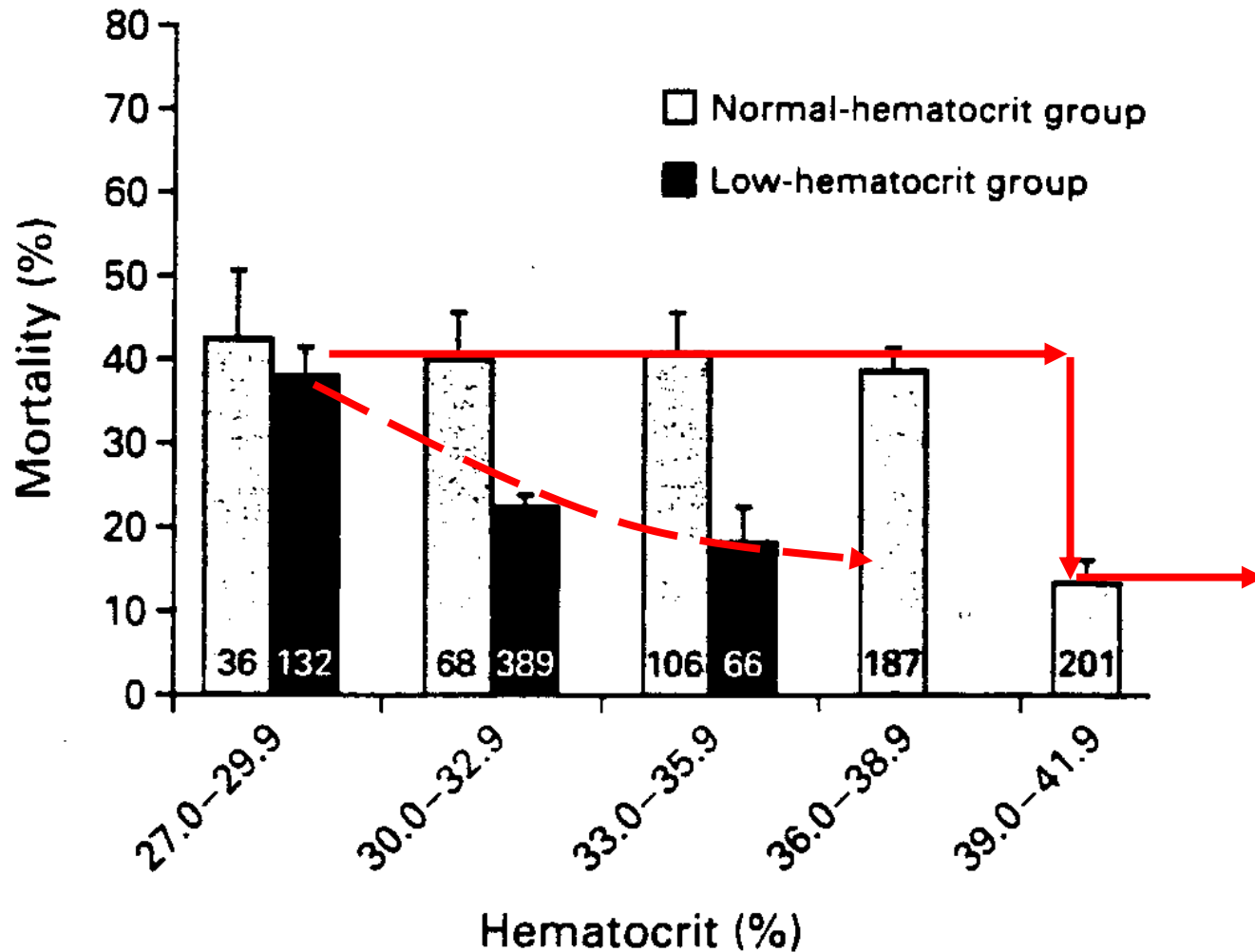


Adverse Effects of Epoetin: truth or speculation



Post hoc analyses

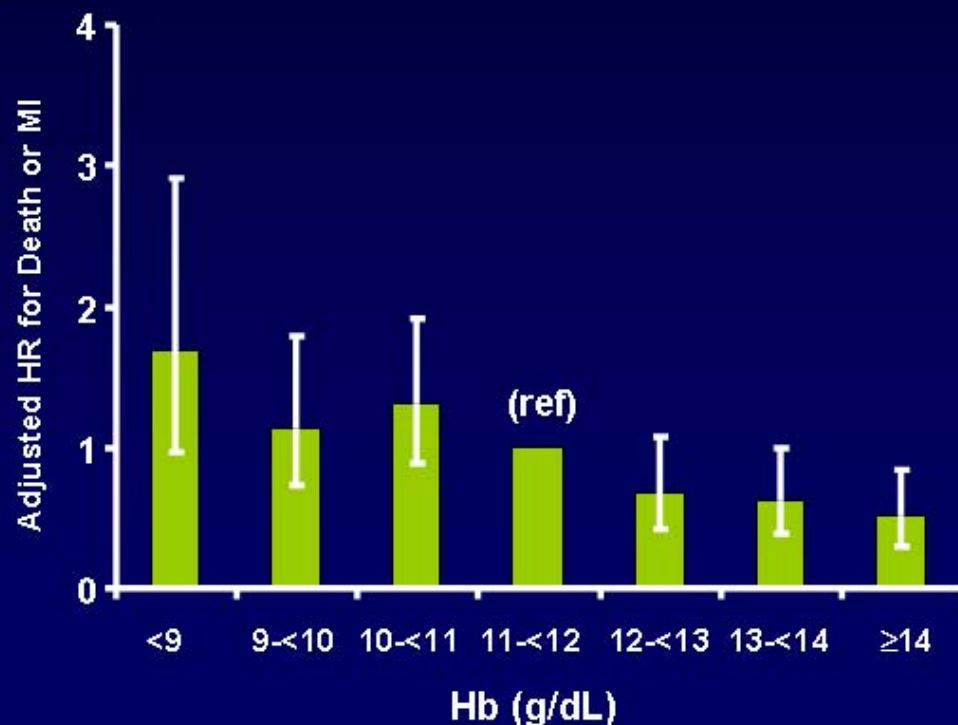
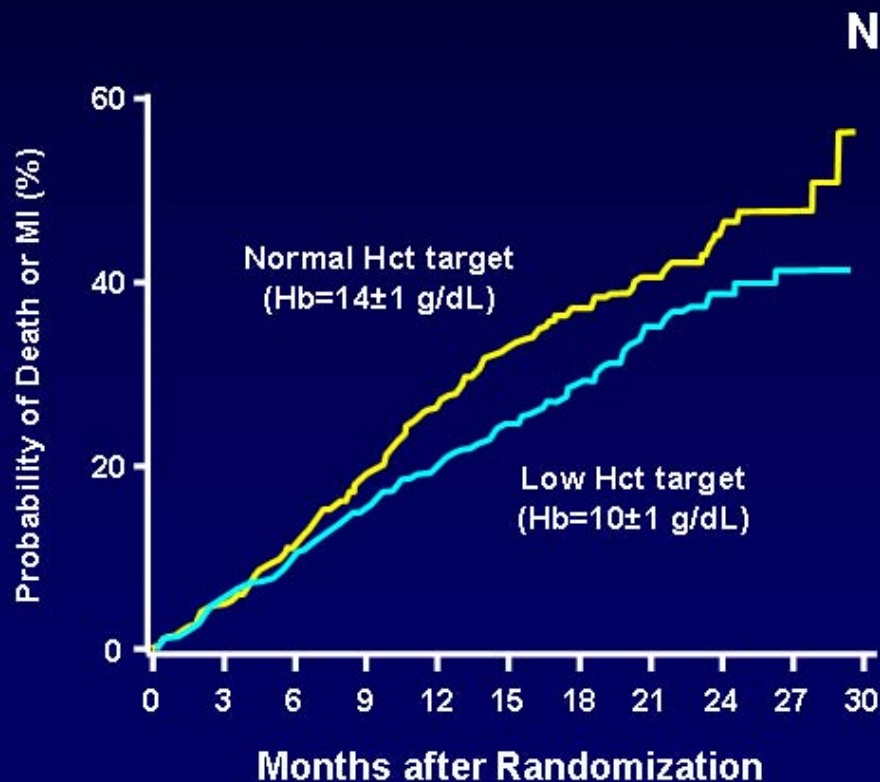
Mean (\pm SE) Mortality Rate as a function of the Average hematocrit value in the normal-hematocrit and low-hematocrit groups. Normal-Hematocrit Trial



Apparent Paradox of Targeted vs Achieved Hb

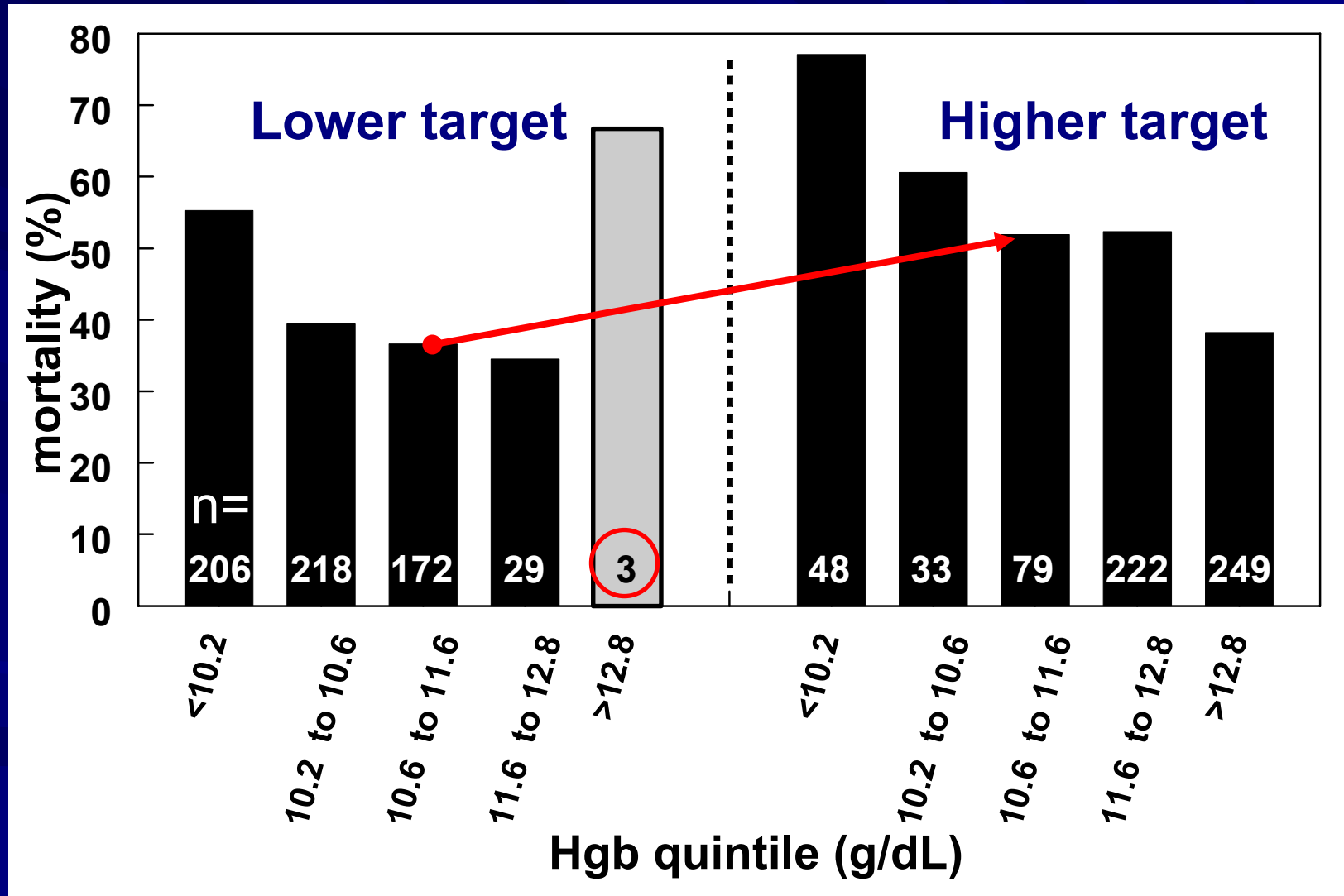
- Evidence suggests **targeting** high Hb results in greater risk

- Patients **achieving** a higher Hb exhibit better clinical outcomes



Normal Hematocrit Study:

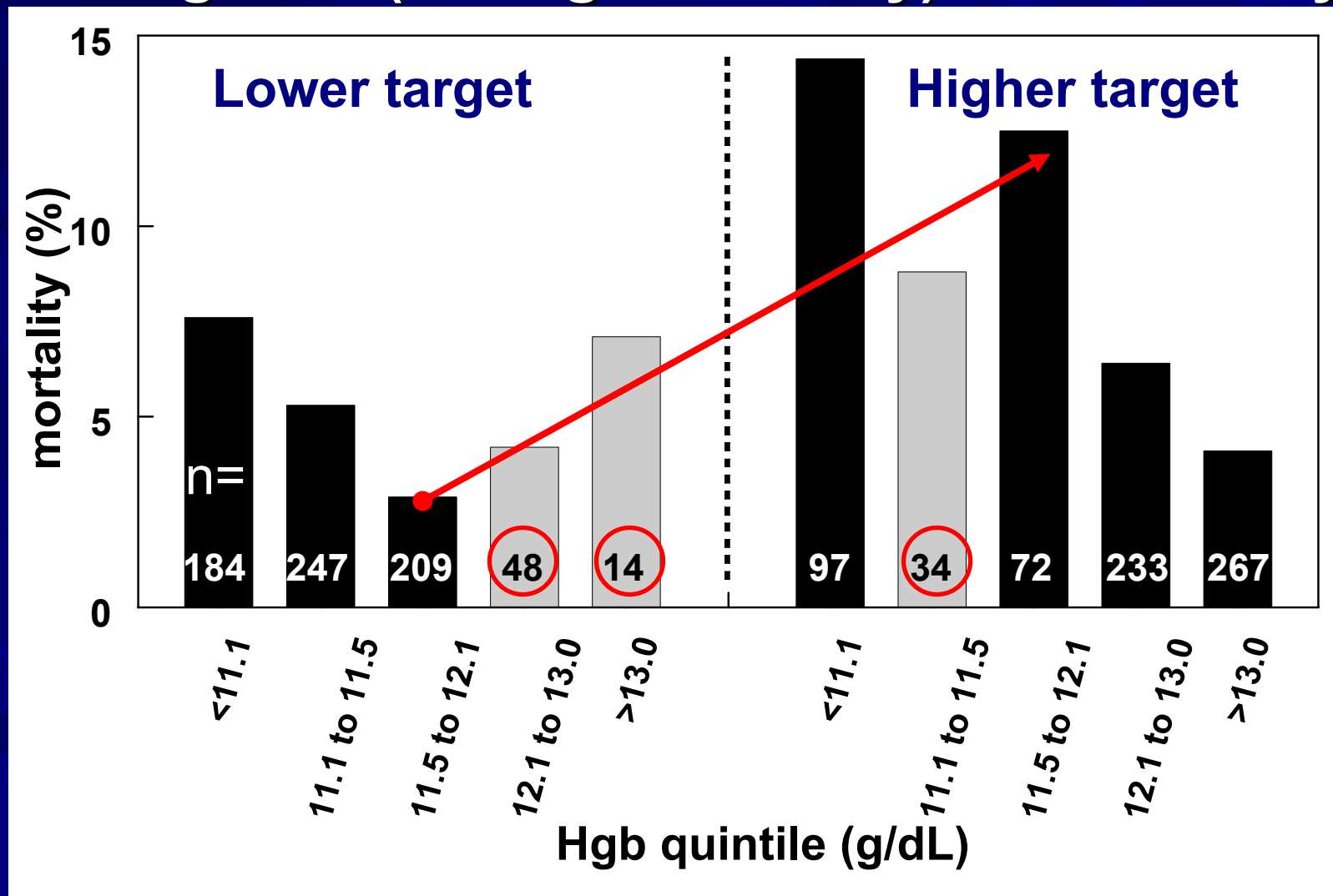
- Negative Association Between Mean Hemoglobin (throughout study) and Mortality:



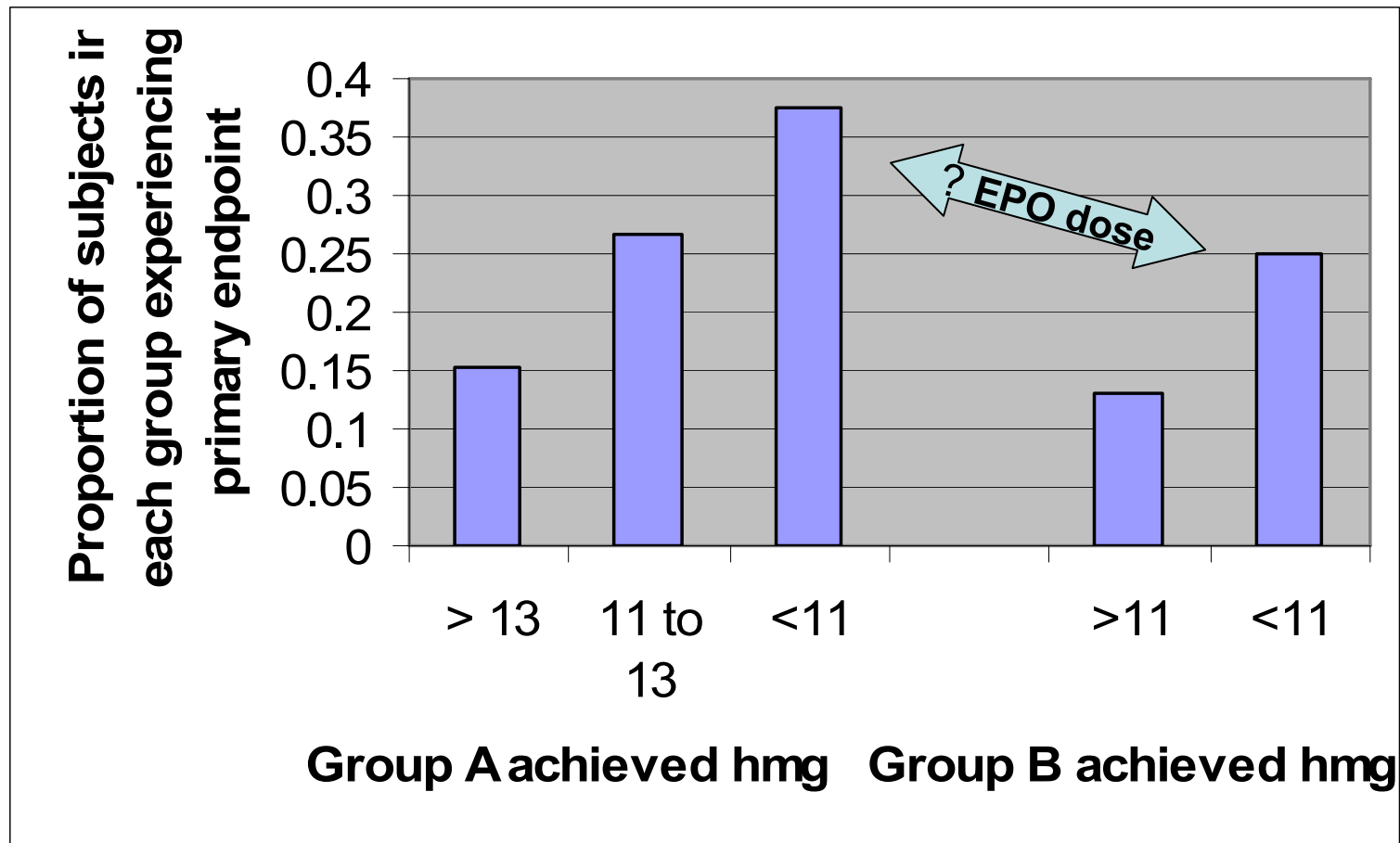
FDA analysis of data collected through 7/5/97

CHOIR Study Results

- Negative Association Between Mean Hemoglobin (throughout study) and Mortality:



Proportion of subjects in each group experiencing primary endpoint



CHOIR Summary

- A target of 13.5 gm/dL is associated with worse outcomes as compared to a target of 11.3 gm/dL.
- Subject's achieving their desired hemoglobin target, irrespective of target, had better outcomes than those not achieving their target.
- Among subjects who achieve their desired target, increased risk associated with the higher goal could not be detected.
- High dose epoetin-alfa among subjects who do not achieve their target hemoglobin were associated with worse outcomes. The association between high dose and poorer outcomes may be the mechanism by which the results of the CHOIR ITT showed a target of 13.5 gm/dL caused greater risk.

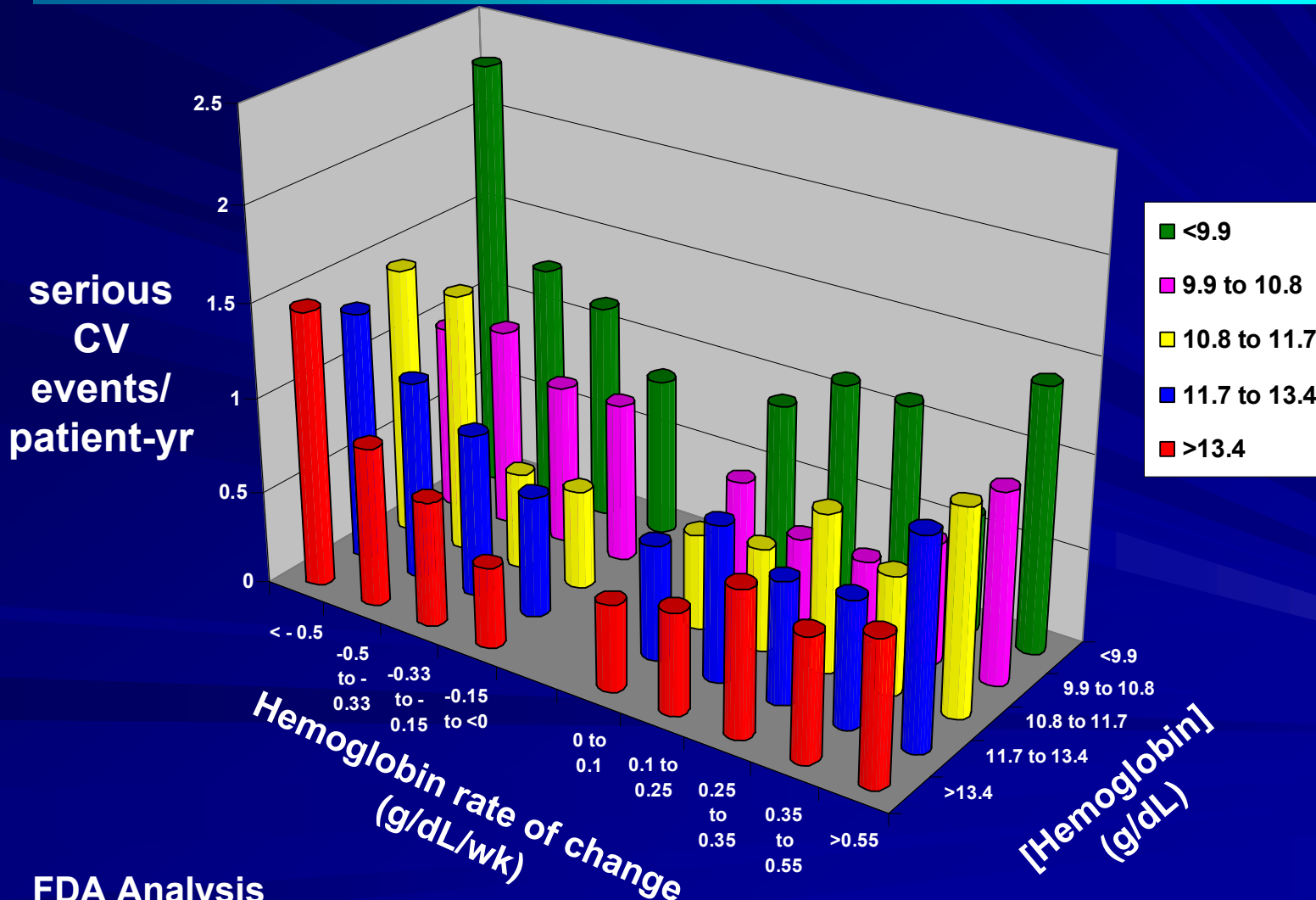
Szczech, Sapp, Singh, Reddan, and Barnhart.
Presented at ASN meeting November 2007.

Post hoc analyses of the RTCs suggest

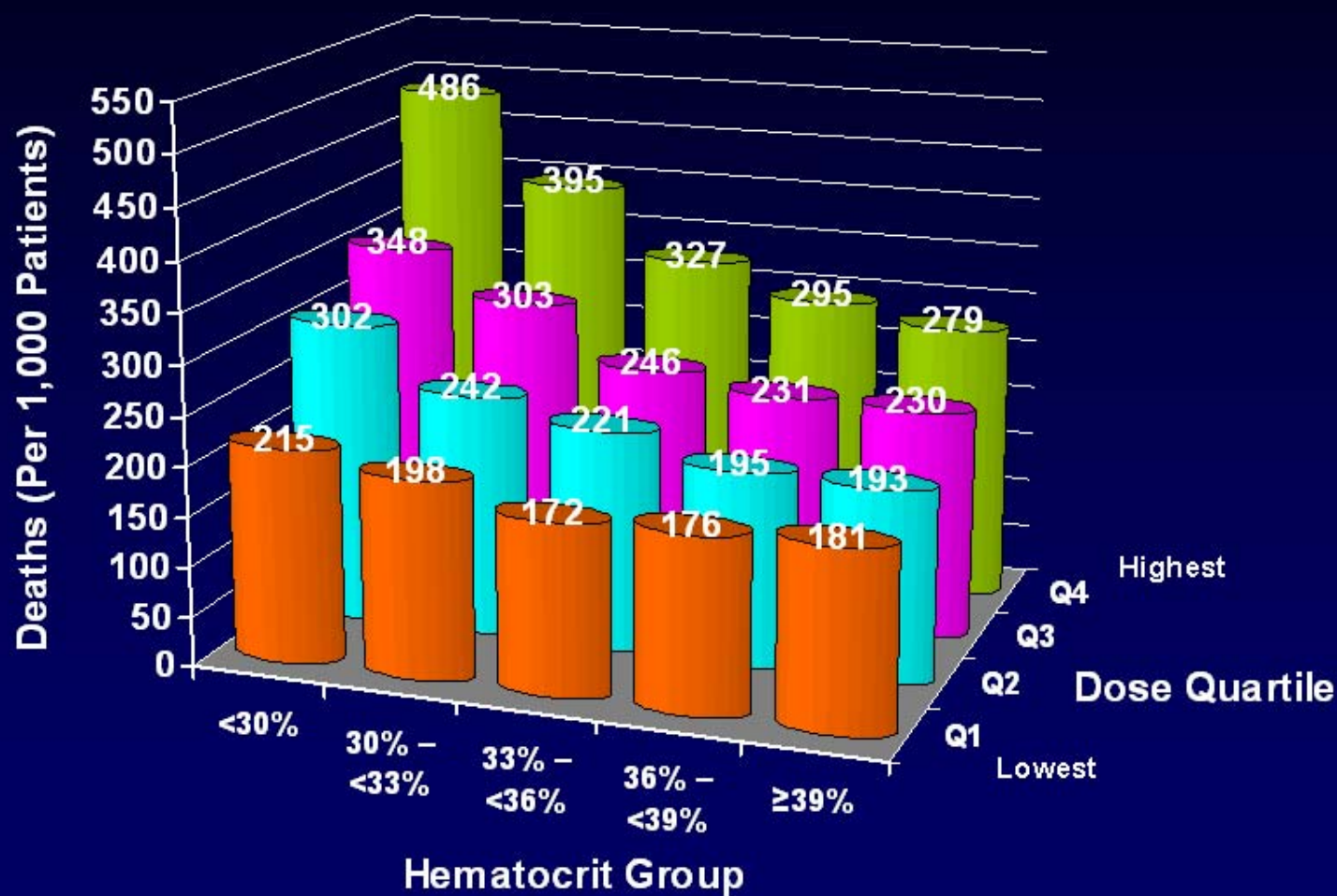
- **Mortality and Cardiovascular Events are related to**
 - Hb achieved
 - Dose of EPO used.
 - Change in Hb
 - decreasing → increased risk,
 - increasing → less risk;
 - U shaped

Normal Hematocrit Study:

“Dynamic” Analysis of Relations Between Serious Cardiovascular Events, Prevailing Hemoglobin, and Preceding Hemoglobin Rate of Change



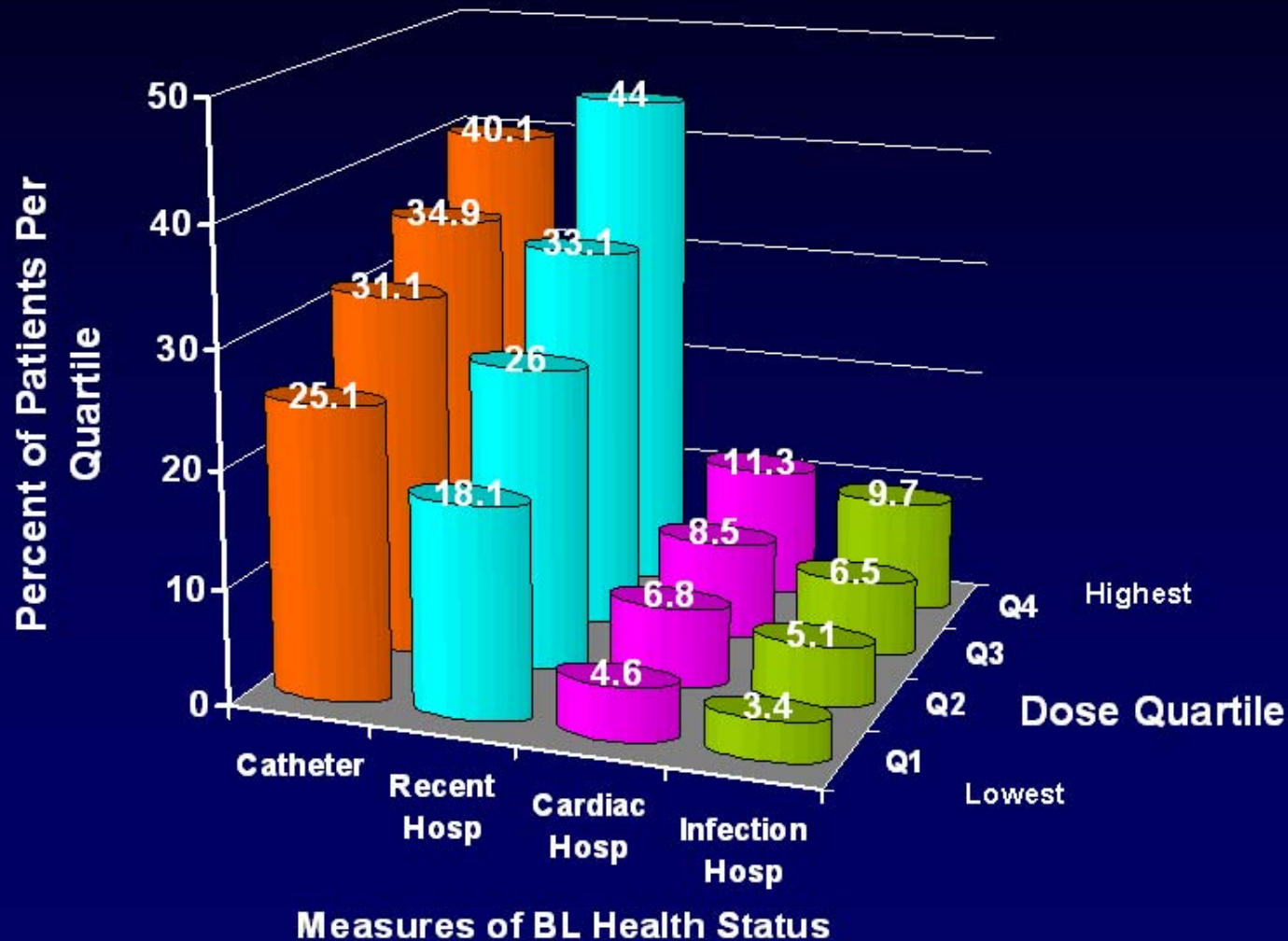
Greater ESA Dose is Associated with Mortality in an Unadjusted Analysis



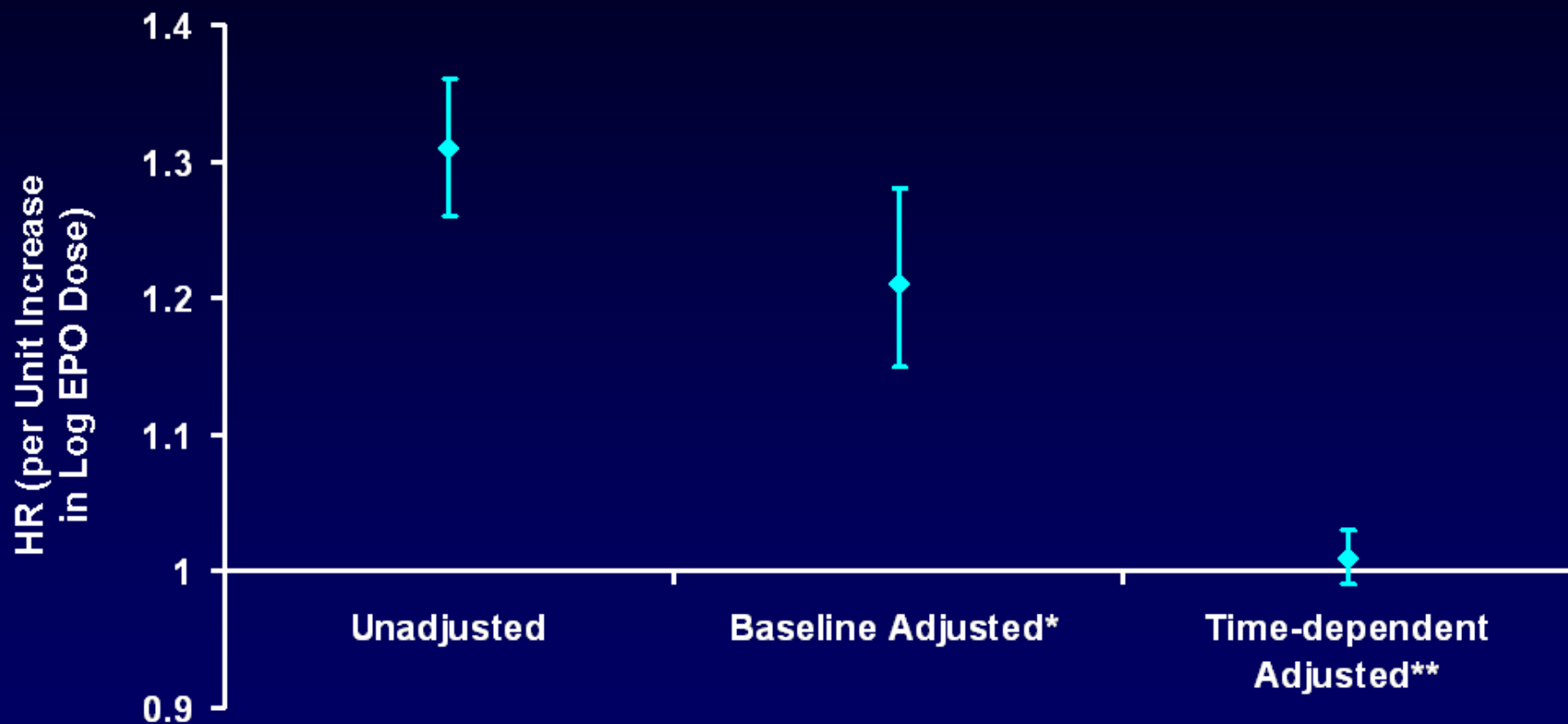
Zhang, *Am J Kidney Dis*, 2004.

Dose quartiles: Q1, 1388 to 7905 U/week; Q2, >7905 to 13,377 U/week; Q3, >13,377 to 22,068 U/week; Q4, >22,068 U/week

Greater Dose Requirements Correlate with Measures of Poor Health Status at Baseline



Association Between ESA Dose and Mortality Attenuated with Adjustment for Confounding



FMC-NA (N=22,955, 95% CI), In Press (*Am J Kidney Disease*)

*Dose at baseline adjusted for baseline Hb and health status.

**Time dependent dose adjusted for baseline health status and time-dependent Hb.

Adverse Effects of Epoetin: truth or speculation

Its true.

Who is at risk?

(all patients?

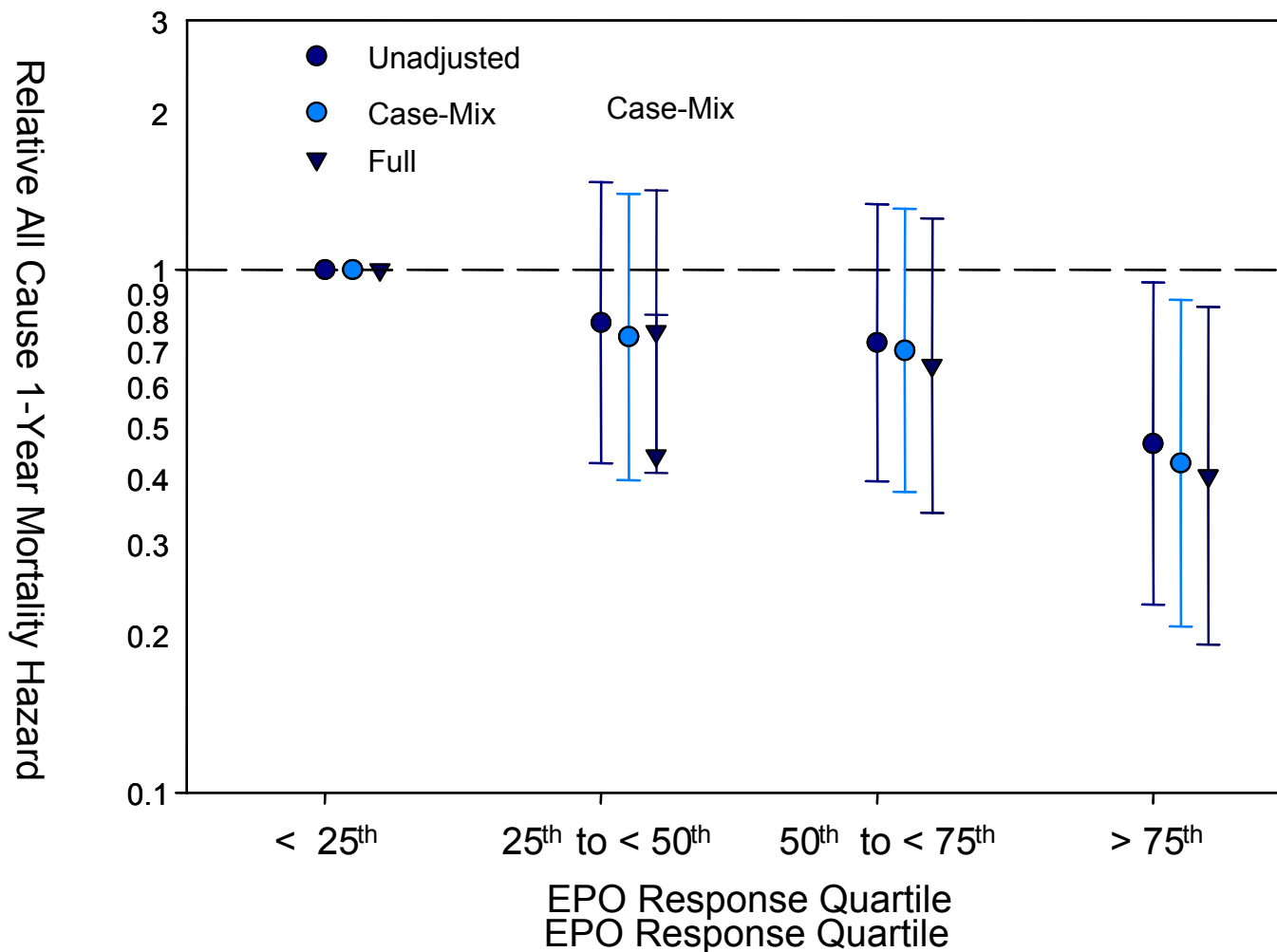
Hyporesponsive patients?)

Prospective Evaluation of ESA- Responsiveness (Normal HCT Study)

- **618 patients randomized to “normal” hemoglobin target**
 - **117 patients experienced a decrease in hemoglobin, despite a “50% increase in Epoetin alfa dose”**
 - **297 patients experienced no change or an increase in hemoglobin**

FDA exploratory analysis
(required 6 data points)

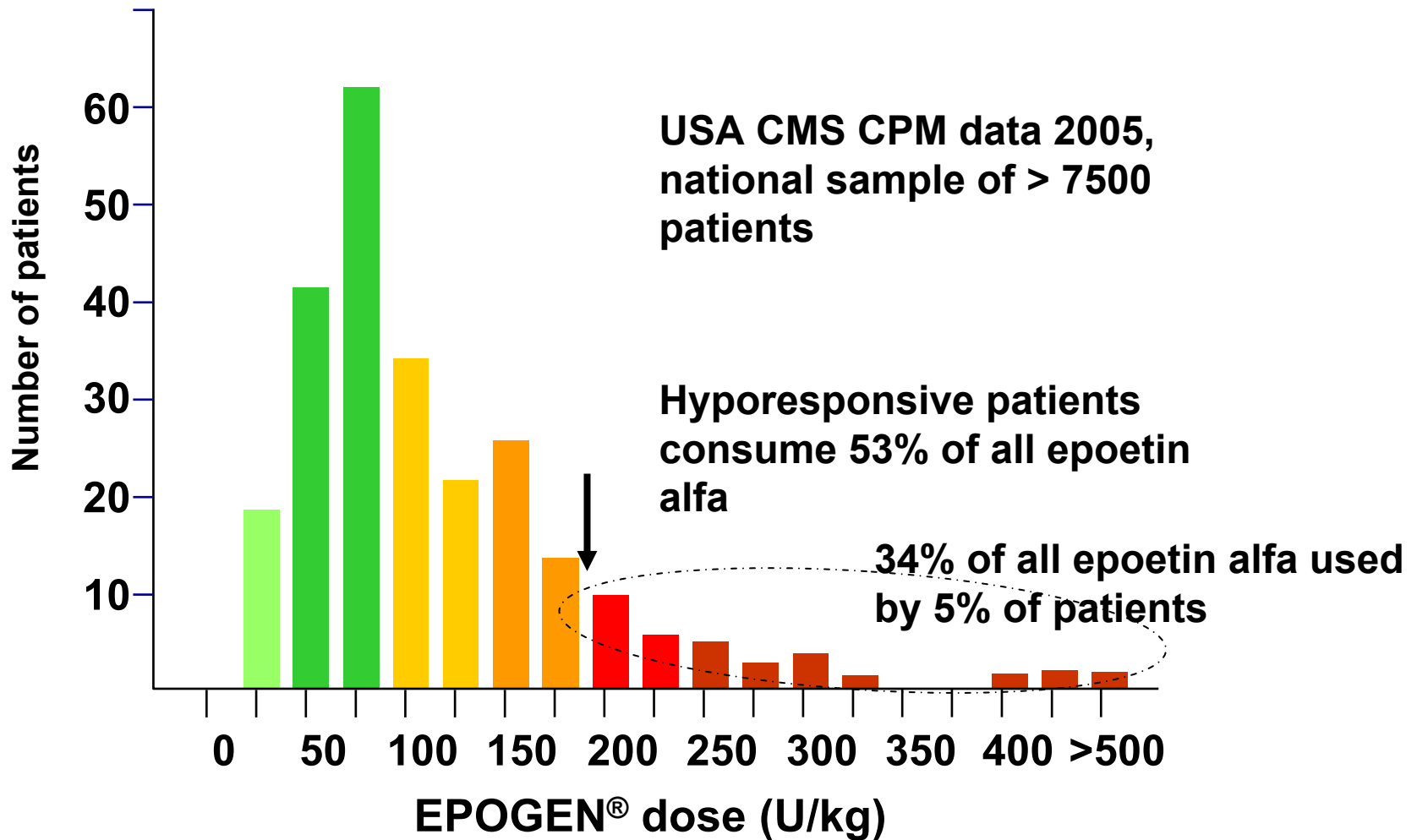
Crude and adjusted hazard ratio estimates for the association between EPO response and one year mortality



The ESA Hyporesponsive Patient

- **Definitions vary**
- **Represents approximately 30-40% of dialysis patients**
- **Characterized by markers of the acute phase response (low serum albumin, elevated CRP, elevated ferritin)**
- **Guidelines caution treating with iron if serum ferritin > 500 ng/ml; therefore, in order to raise Hgb > 11 g/dL, patients treated with high doses of epoetin**

Dose Requirements Vary Among Patients



Adverse Effects of Epoetin: truth or speculation

If true?

Who is at risk?

How is it mediated?

*(dose dependent direct effects on
non-erythropoietic receptors)*

(via an increase in Hb?)

(Indirectly via other mechanisms?)

Observed Effects = thrombosis

- **Cardiovascular Events**
 - Acute non-fatal myocardial infarction
 - Vascular access thrombosis
 - Cerebrovascular accidents (stroke)
- **Vascular shear stress**
- **Platelets and coagulation**

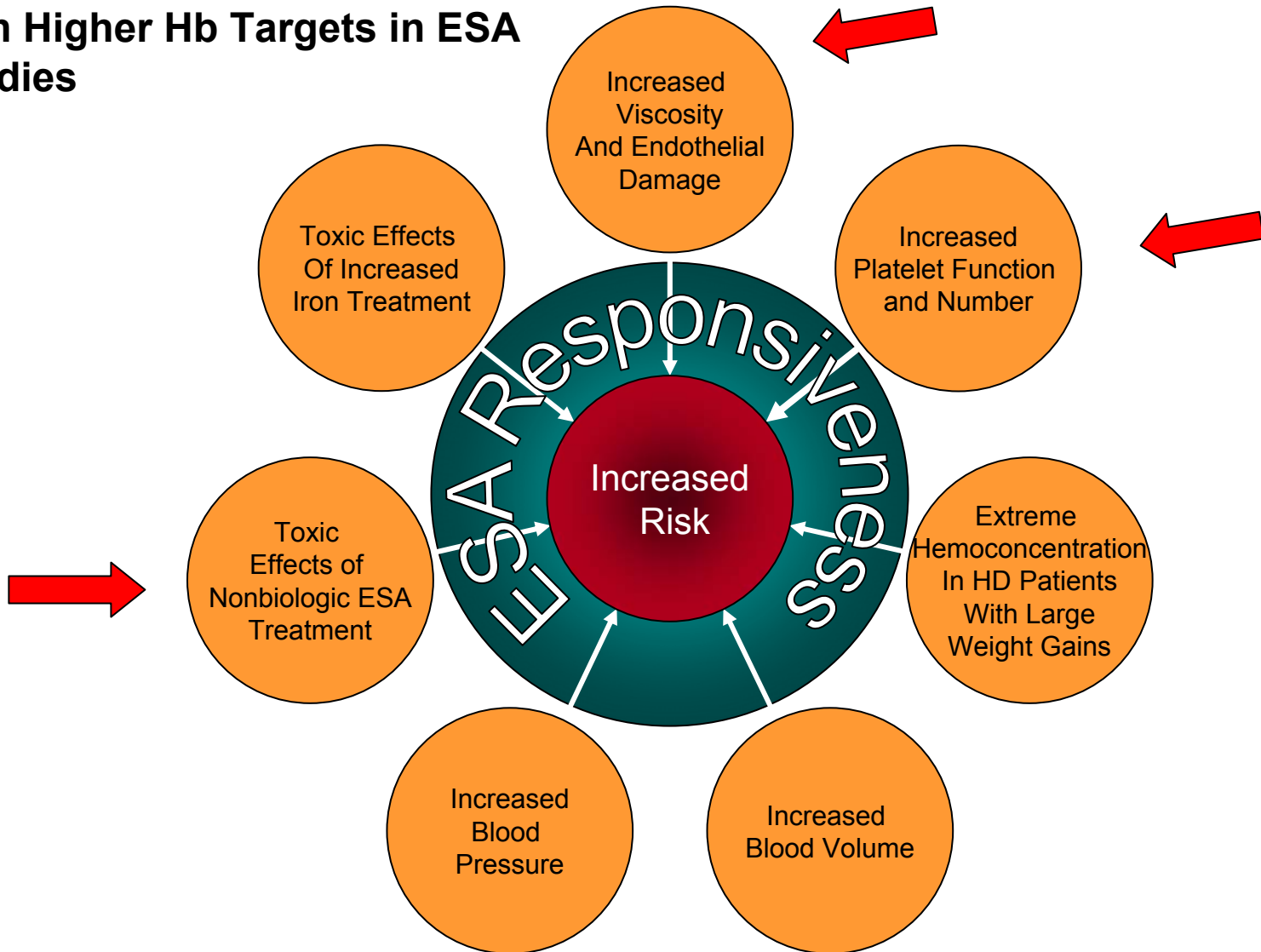
BMJ 1990;300:573

NEJM 1998;339:584

J Am Soc Nephrol 16:2180-2189, 2005

Kidney Int 58:1325-1335, 2000

Potential Mechanisms for Increased Cardiovascular Risk with Higher Hb Targets in ESA Studies



Vascular Wall Shear Stress

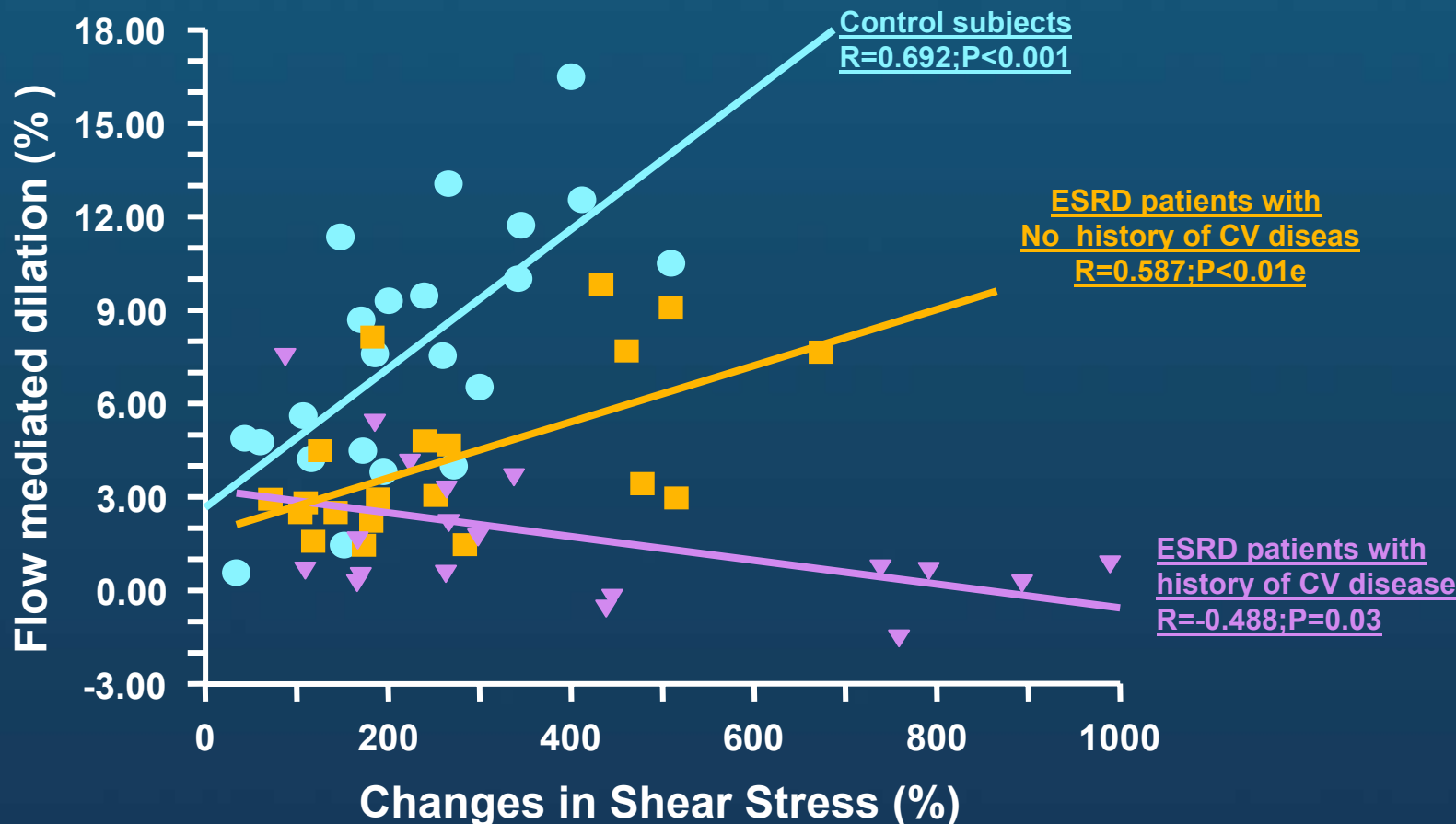
- Anemia produces vasodilatation
- Restoration toward “normal” Hb increases viscosity and wall shear stress on the vascular endothelium
- Vascular endothelium is already abnormal in advanced CKD
- Increased shear stress can produce endothelial injury/alter endothelial function increasing risk for thrombosis
- Certain patients may be more susceptible
 - We currently do not know the characteristics of such patients.

Vascular Wall Shear Stress

- Patients with kidney disease and atherosclerosis frequently have multiple areas of unstable atherosclerotic plaque and/or ulcerations that are vulnerable to increased viscosity associated shear stress
- Even the relatively small increases in blood viscosity as Hb rises above 13 g/dL may have an accentuated harmful effect when vascular disease is present.
- During fluid removal, changes in Hct and viscosity/shear stress in HD patients occur over hrs and not weeks as in normal's.
- Patients with cardiovascular disease may respond to shear stress changes differently from those without CV disease

ESRD Pts with Hx of CVD Have Paradoxical Vasoconstriction to Increased Shear Stress

Dysfunctional microcirculatory endothelium extrapolates to risk with increased viscosity



Shear Stress, Microparticles, and Coagulation

- Changes in shear stress on endothelial cells is associated with release of microparticles into the circulation.
- Circulating microparticles are associated with a variety of disorders characterized by coagulopathy [HIT, TTP, PNH, SCD] as well as vascular and cardiovascular diseases¹
- Shed membrane microparticles with procoagulant potential are produced by human atherosclerotic plaques²
- Shear induced apoptosis could be a critical determinant of plaque thrombogenicity after plaque rupture.

1. Piccin A et al. Circulating microparticles: pathophysiology and clinical implications. Blood Rev. 2007 May;21(3):157-71

2. Mallat Z, et al. Shed membrane microparticles with procoagulant potential in human atherosclerotic plaques: a role for apoptosis in plaque thrombogenicity. Circulation. 1999;99(3):348-53

Platelets and their function during ESA treatment

The prolonged bleeding time of anemic azotemic patients corrects to normal as hematocrit is increased above 30%, whether by transfusion¹ or ESA²

- Hemodynamic effect from increased RBC # (Hb)
- Transient increase in platelet count
 - direct effect on megakaryocytes (which have erythropoietin receptors) resulting in increased platelet count
- Sustained improvement in platelet function.
 - Increased platelet adhesiveness.

1. Fernandez F, et al. Low hematocrit and prolonged bleeding time in uraemic patients: effect of red cell transfusion. Br J Haematol 1985;59:139–148

2. Moia M, et al. Improvement in the haemostatic defect of uraemia after treatment with recombinant human erythropoietin. Lancet. 1987 Nov 28;2(8570):1227-9

Hemodynamic effects of Red blood cell

- During non anemic blood flow conditions, red cell axial migration occurs leaving a plasmatic zone at the vessel wall into which platelets are dispersed.
 - Shearing forces are maximal in this zone and promote platelet activation.
 - Platelets that concentrate at the vessel wall can be activated if vascular injury occurs by contact with vessel wall constituents. ¹
 - Increased Hb/HCT reduce the width of the plasmatic zone which in turn
 - **increases probability of platelet activation**
 - **Increases platelet-platelet contact and platelet-vessel wall interaction, particularly when the platelet count is raised as well.**
 - **Increases the likelihood of the initiation of thrombus formation²**
 - Mechanisms best worked out for polycythemic states² but might be active at lower Hb levels in CKD
1. **Livio M, et al. Uraemic bleeding: role of anaemia and beneficial effect of red cell transfusions. Lancet. 1982 Nov 6;2(8306):1013-5**
 2. **Pearson TC . Hemorheologic considerations in the pathogenesis of vascular occlusive events in polycythemia vera Semin Thromb Hemost. 1997;23(5):433-9**

Platelets and their function during ESA treatment

- Epo reverses “uremic” platelet dysfunction independently of Hct/Hb¹
- EPO increases platelet number by 10-20%²
- EPO, even in normals, increases platelet reactivity³:
 - thrombin-receptor-activating peptide increased alpha-granule secretion and occurs at EPO doses of 100-500 U/kg in normals.
 - Manifested as release of P-selectin from both endothelial and alpha granules
 - Increased circulating E-selectin by > 100% noted. Reflects endothelial activation and release.
- Maximum platelet aggregation in ESRD patients increases during EPO therapy before Hb increases⁴
- These effects occurs in vivo and are procoagulant

1. Tang WW, et al. Am J Nephrol 1998;18:263

2. Jelkmann W. Physiol Rev 1992;72:449 Kaupke CJ et al. JASN 1993;3:1672

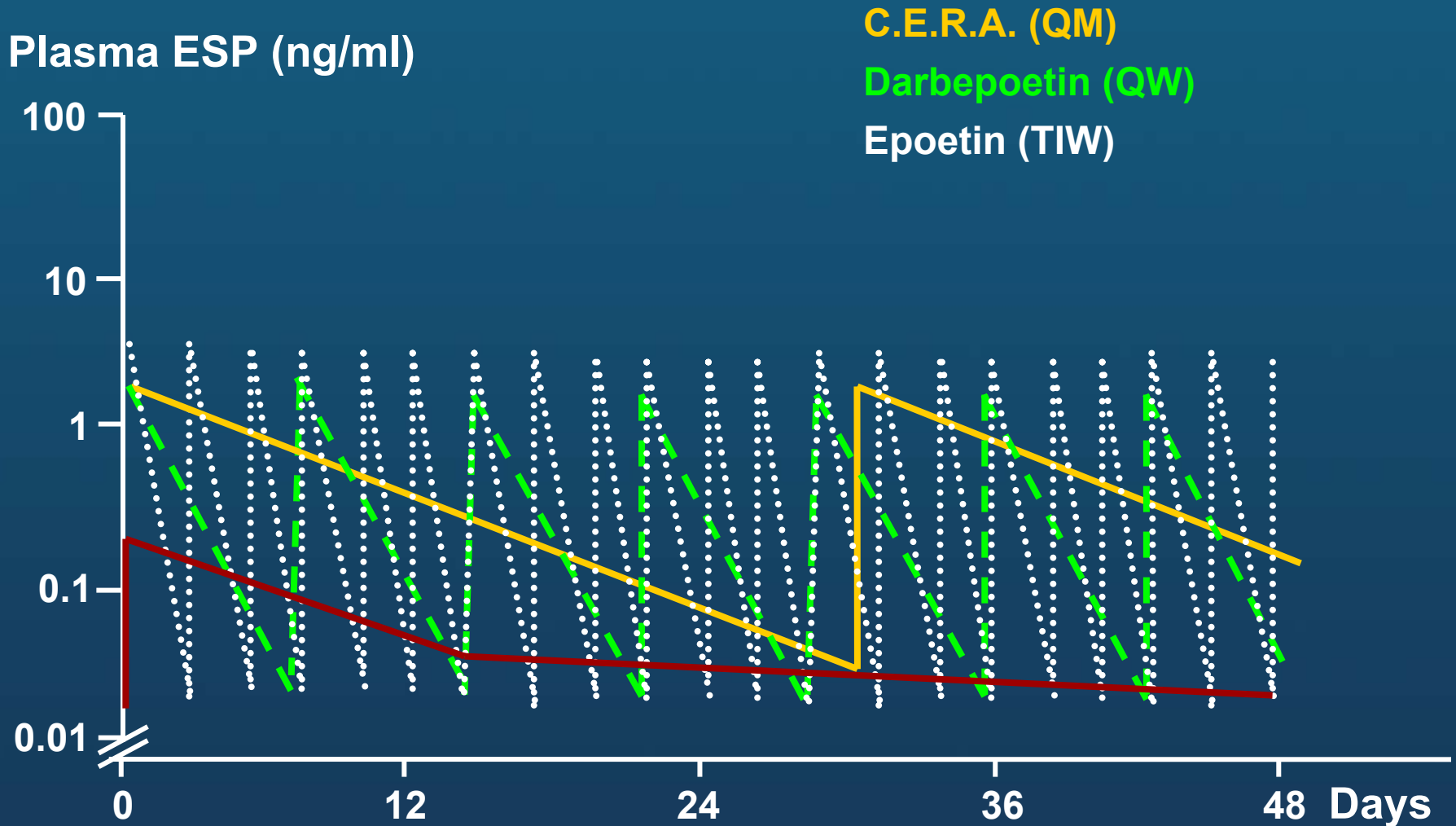
3. Stohlawetz PJ et al. Blood 2000;95:2983

4 Sayinalp N. Thrombosis Research 1998;90:195

Platelets and their function during ESA treatment

What about Iron deficiency?

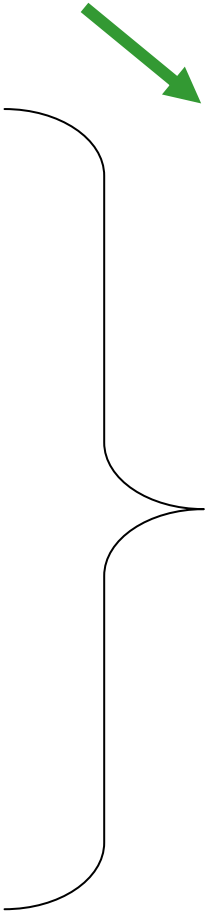
Representation of the Plasma Levels of Erythropoietic Proteins*



*estimated values based on 6000 IU epoetin / week

Tissues expressing Epo receptors and the problem of specificity

- Bone marrow BFU, CFU
- Liver
- Endothelial cells
- Splenic Macrophages
- Vascular Myocytes
- Central Nervous system
- Cardiocytes
- Tumor cells
- Uterus
- Testicular cells



**[homo dimeric
high affinity]:
desired effects
occurring at Epo
levels < 1000
mU/mL (<10 ng/mL)**

**[hetero dimeric
low affinity]: effects
may be desired or
undesired and
occur at high Epo
concentrations > 10
ng/mL)**

High ESA levels

- The minimal effective exogenous dose required to mimic or augment the paracrine functions of erythropoietin in some organs (brain, heart, endothelium) is higher than that needed for treatment of anemia¹
- At high EPO levels, cytoprotective effects can be offset by undesired procoagulant and vasoactive actions
 - Endothelin release
 - NO release and transport
- At repeatedly attained or sustained high levels, cardiovascular hemostasis may be adversely affected

Coleman TR et al. Cytoprotective doses of erythropoietin or carballyated erthropoietin have markedly different procoagulant and vasoactive activities. Proc Natl Acad Sci 2006; 103-5965-70

Summary

- Adverse effects of EPO converge on processes that are procoagulant and alter endovascular function.
- These effects are both Hb/Hct (RBC number) dependent and independent
- Some effects only occur at high EPO levels (dose)
- **In a patient with a susceptible genotype/phenotype who is hyporesponsive, these effects may lead to adverse outcomes**

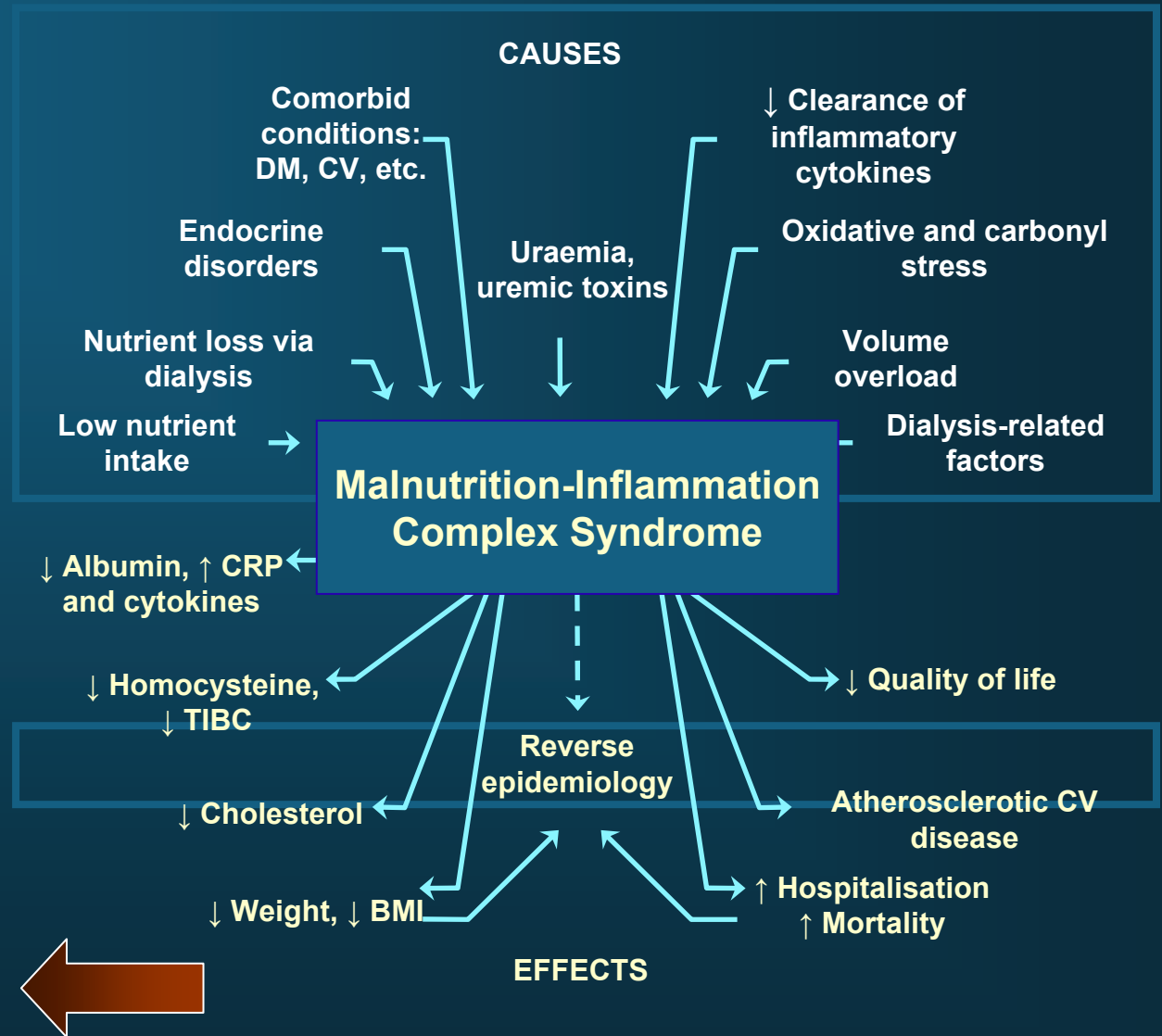
Treatment of the Individual

- Research Evidence must be integrated with
 - clinical circumstances;
 - clinical setting;
 - patients values, preferences, expectations, and ultimately patients choices;

Thank You

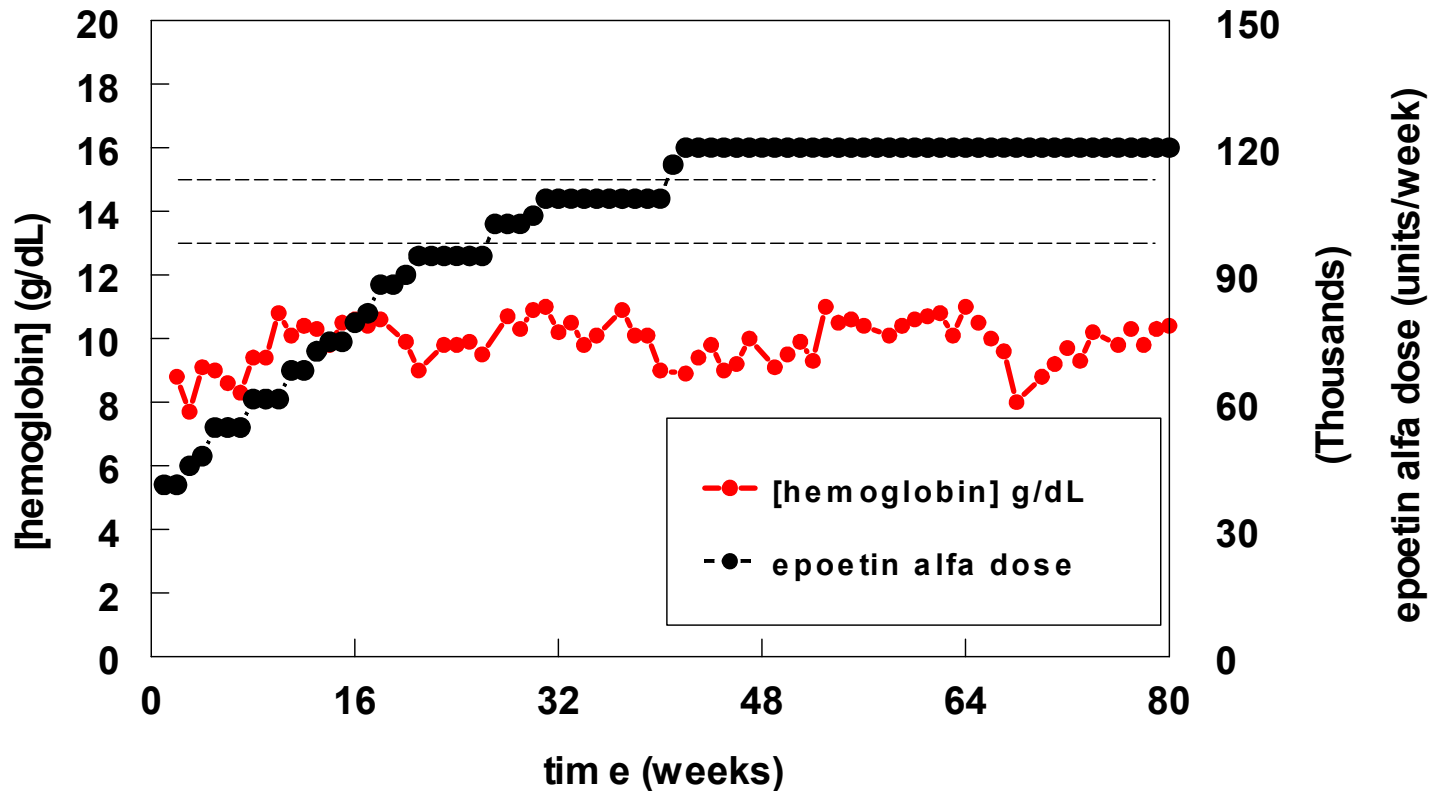
Hb Stability:

- MICS



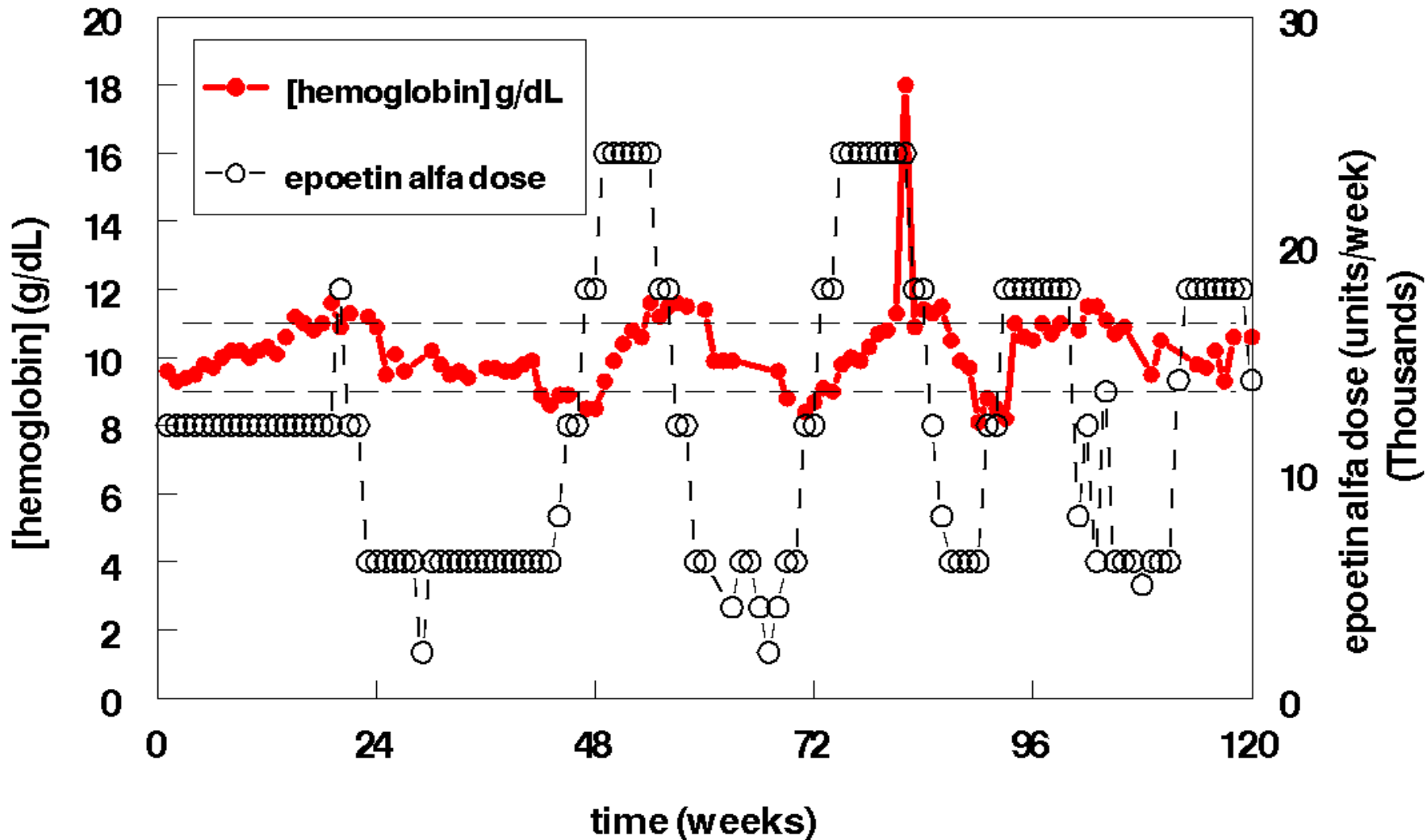
Hypo-responsive anaemia

ESA-Hyporesponsiveness in a Single Patient:

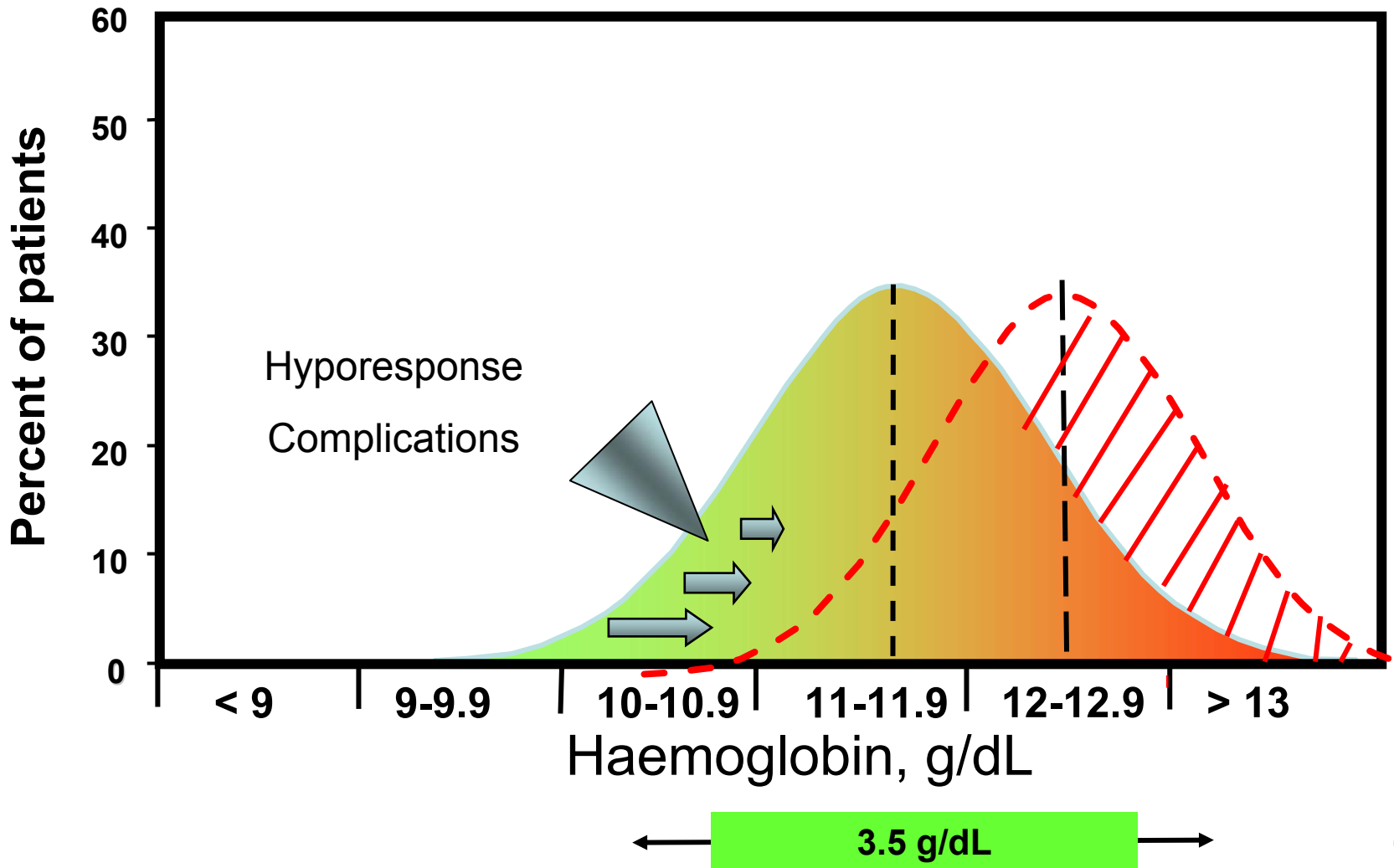


Key Unanswered Question: whether less responsive patients or those with specific risk factors would experience fewer cardiovascular events if attempts were not made to raise their hemoglobin to some “ideal” target.

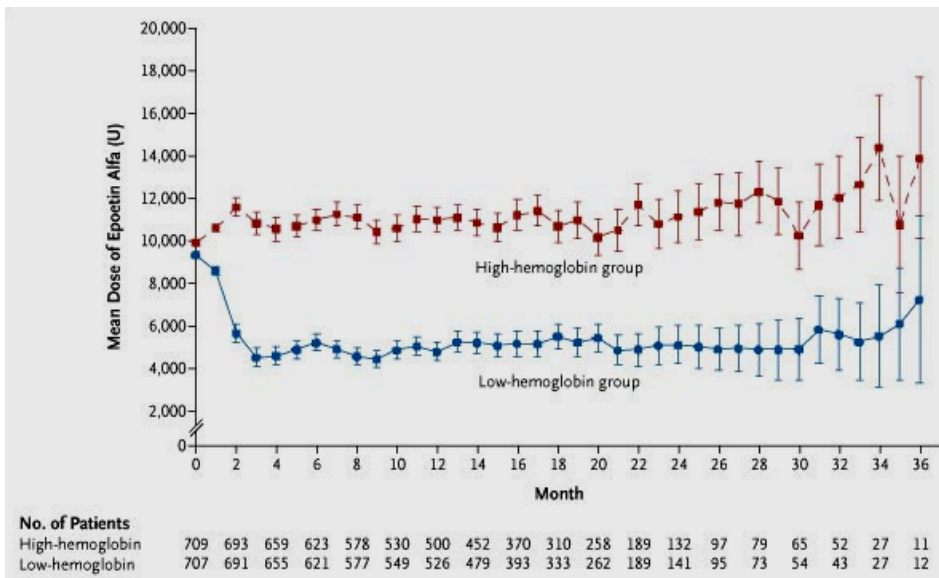
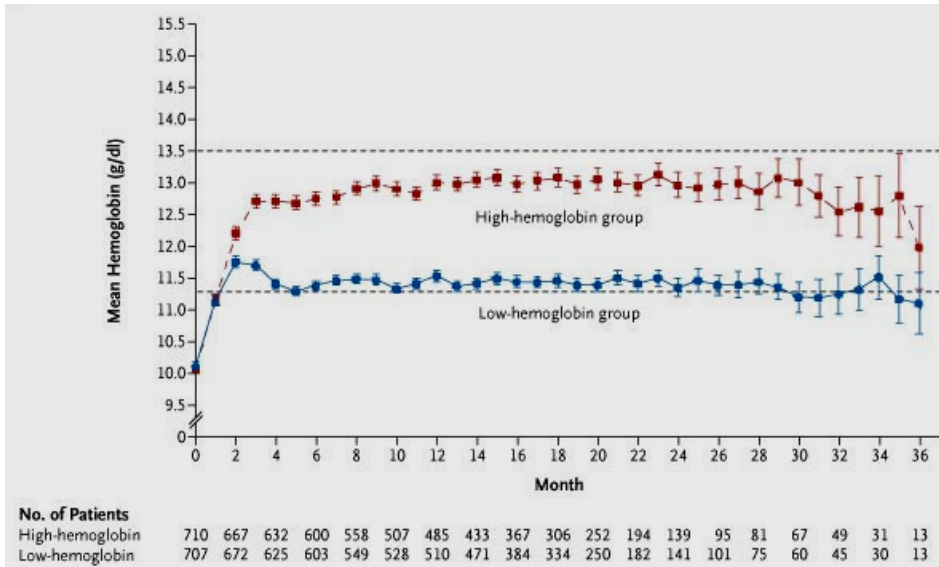
Dose Optimization Challenges: Cycling in a Subject from the Normal Hematocrit Study



Treating Hyporesponders will Increase the Mean!



CHOIR Trial



- Hb difference ~ 1.5 g/dl
- Withdrawal rate high (38.3%)
- Imperfect randomization: high Hb group had more HTN, freq of CABG)

„DSMB recommended.. study be terminated.. even though neither the efficacy or futility boundaries had been crossed, **BECAUSE** the conditional power of benefit for the high-hemoglobin group by the scheduled end of study was less than 5%...“

- starting dose 10,000 IU/week
- mean weekly EPO dose:
6,276 vs 11,215 IU
- In CREATE :
2,000 vs 5,000 IU 70

Number of subjects achieving targets

