Trials in Anemia: Implications for Care 2010

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Objectives

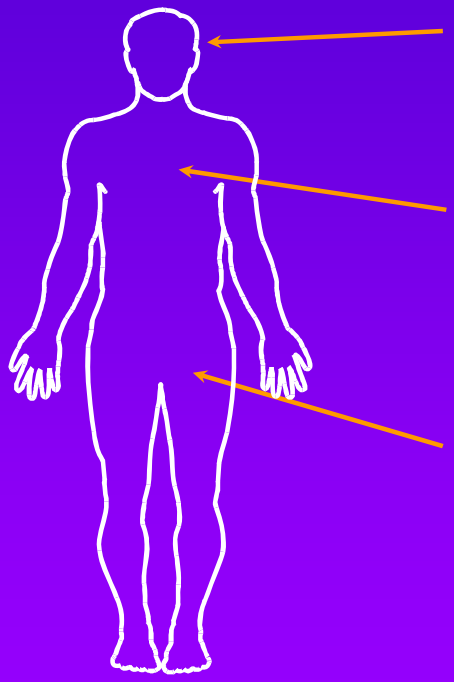
- To examine current understandings from clinical trials in anemia in CKD patients
  - Or….What have we really learned after 20 years of research in anemia therapy ?

The Context

- Observational studies
- Interventional studies in different populations
  - Dialysis
  - CKD

What we do know…..

Anemia Is Associated with Many Adverse Sequelae



Cognitive function
- confusion[1]
- impaired cognition[6]

Cardiovascular
- cardiac enlargement[2,3]
- angina[1,5]
- Palpitations[5]

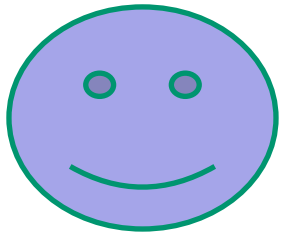
Progression of CKD

Quality of Life
- reduced exercise capacity[4]
- impaired libido/impotence

[1]Hoffbrand AV et al. *Essential Hematology.*1993. [2]Levin A et al. *Am J Kidney Dis.* 1999;34:125-134. [3]Foley RN et al. *Am J Kidney Dis.* 1998;28:53-61. [4]Mayer G et al. *Kidney Int*. 1998;34:525-528. [5]Mackie MJ et al. In: Edwards CRW et al, eds. *Davidson's Principles and Practice of Medicine*, 1995. [6]Nissenson AR. *Am J Kidney Dis*. 1992;20:21-24. [7]Schaefer RM et al. *Contrib Nephrol*. 1989;76:273-81.

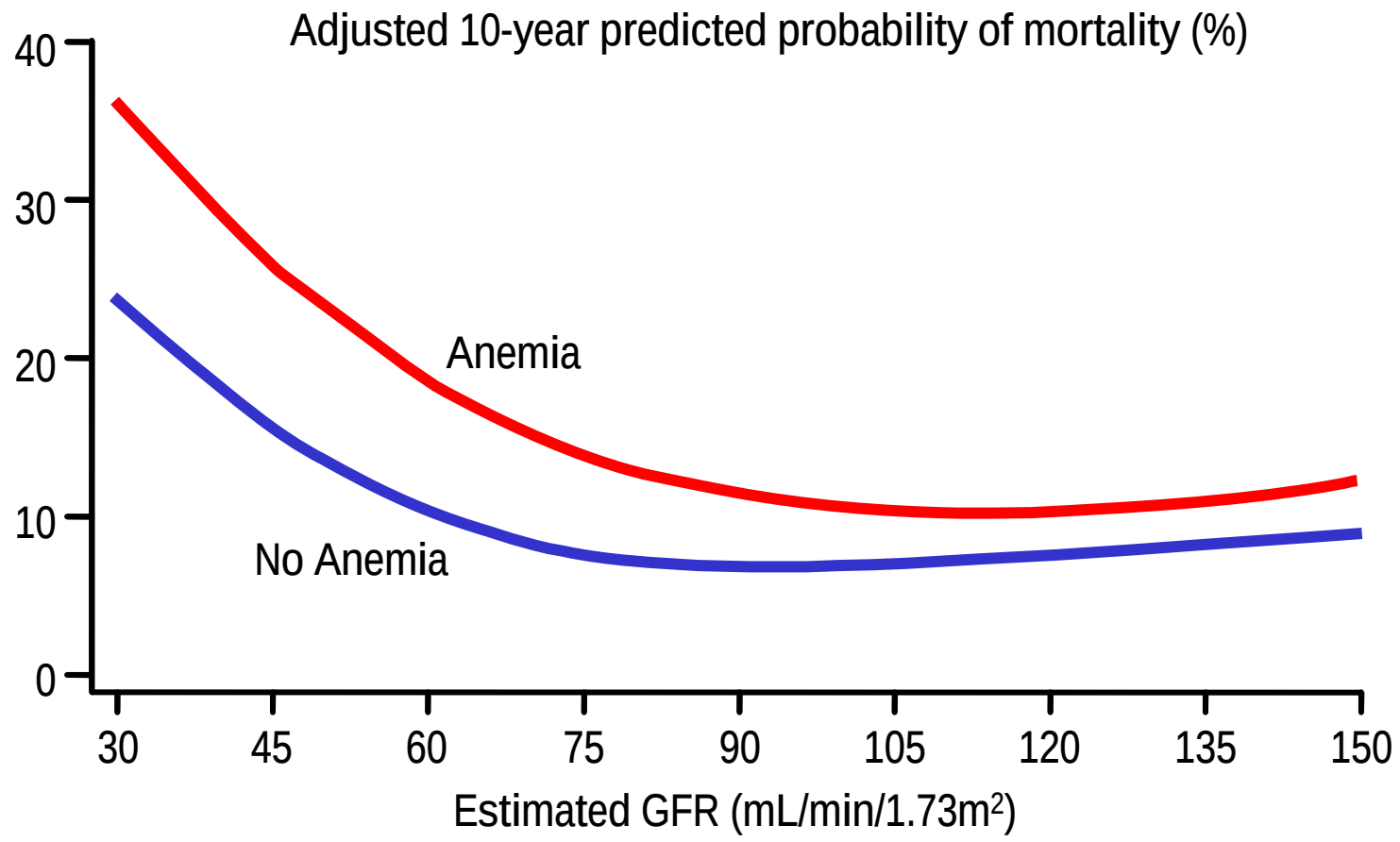
Multiple Observations in multiple populations that higher Hgb leads to better outcomes..

- Those patients with high Hgb do better
  - <120 g/L consistent cut point
- Observational studies, no treatment groups
  - Geriatric patients
  - Oncology patients
  - Cardiac patients
  - Kidney patients



Hb and All-Cause Mortality in CKD

By GFR and anemia - 10 year ARIC



Anemia defined as Hb <13.5 g/dL in men, <12 g/dL in women

Astor, AHA 2004

Cardiac Pts

Anemia as a Risk Factor for Kidney Function Decline in Individuals With Heart Failure†

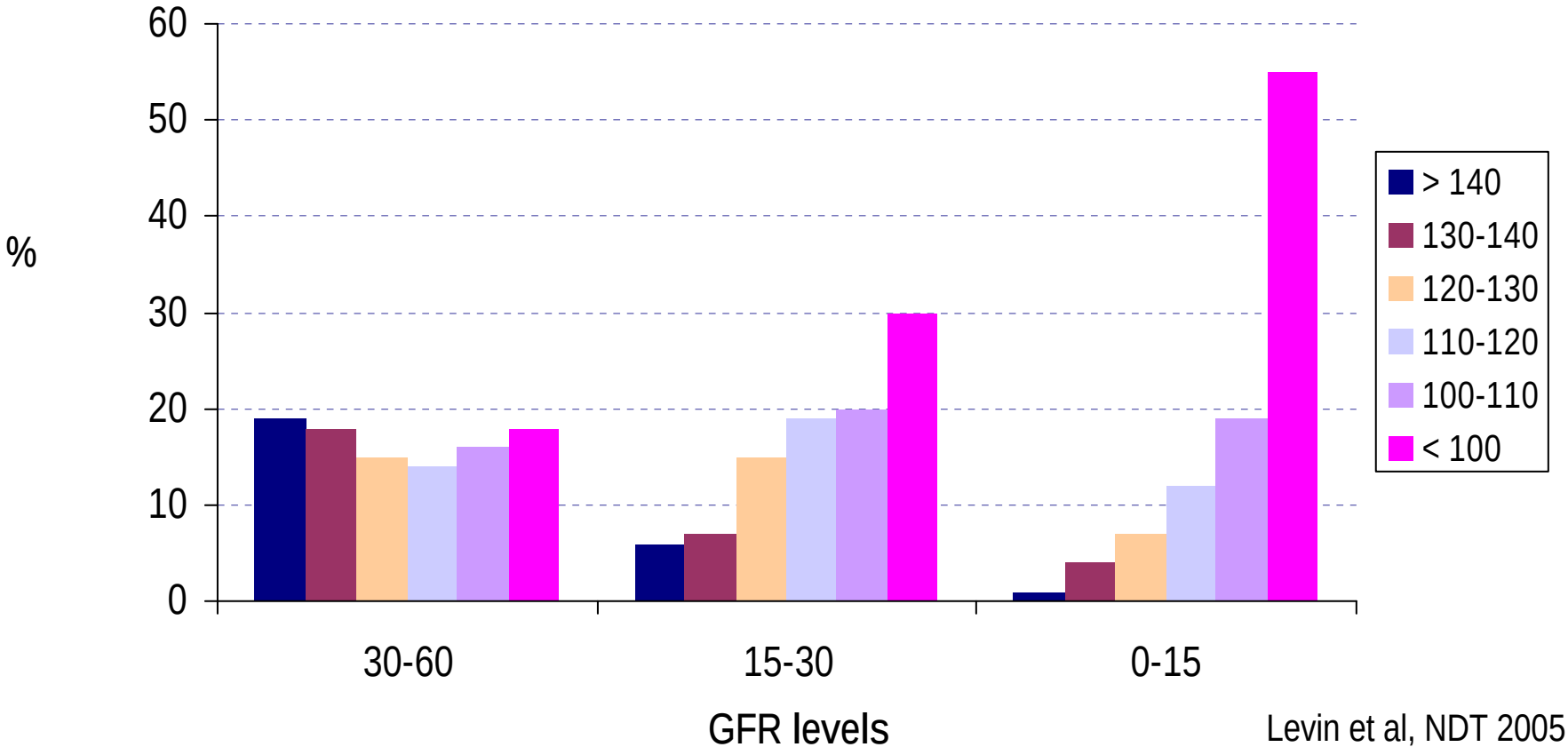
Nisha Bansal, MD[a], Hocine Tighiouart, MS[b], Daniel Weiner, MD[a], John Griffith, PhD[b], Panagiotis Vlagopoulos, MD[a], Deeb Salem, MD[c], Adeera Levin, MD[d], and Mark J. Sarnak, MD[a,*]

Table 2
Study outcomes stratified by the presence or absence of anemia

Study Outcomes	Nonanemic	Anemic	p Value
All-cause mortality	22%	34%	<0.001
Decrease in GFR ≥ 6 ml/min/ 1.73 m^2 per yr	25%	32%	0.002
Doubling of serum creatinine	2%	4%	0.01
Increase in creatinine of 0.5 mg/dl	14%	21%	<0.001

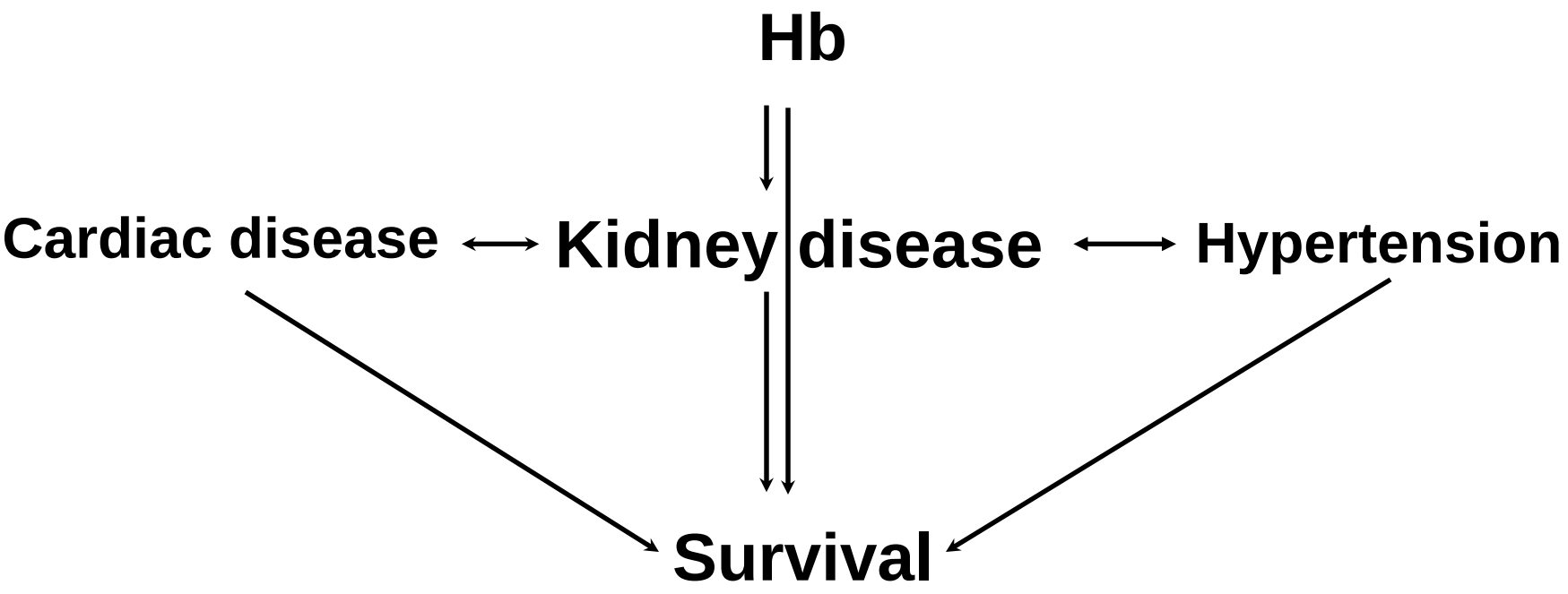
Hgb Falls as GFR declines ….
but there is significant heterogeneity at each CKD stage

N= 3028 CKD Patients in BC Canada, referred to nephrologists, prior to initiation of anemia therapy



Levin et al, NDT 2005

Simple Understanding

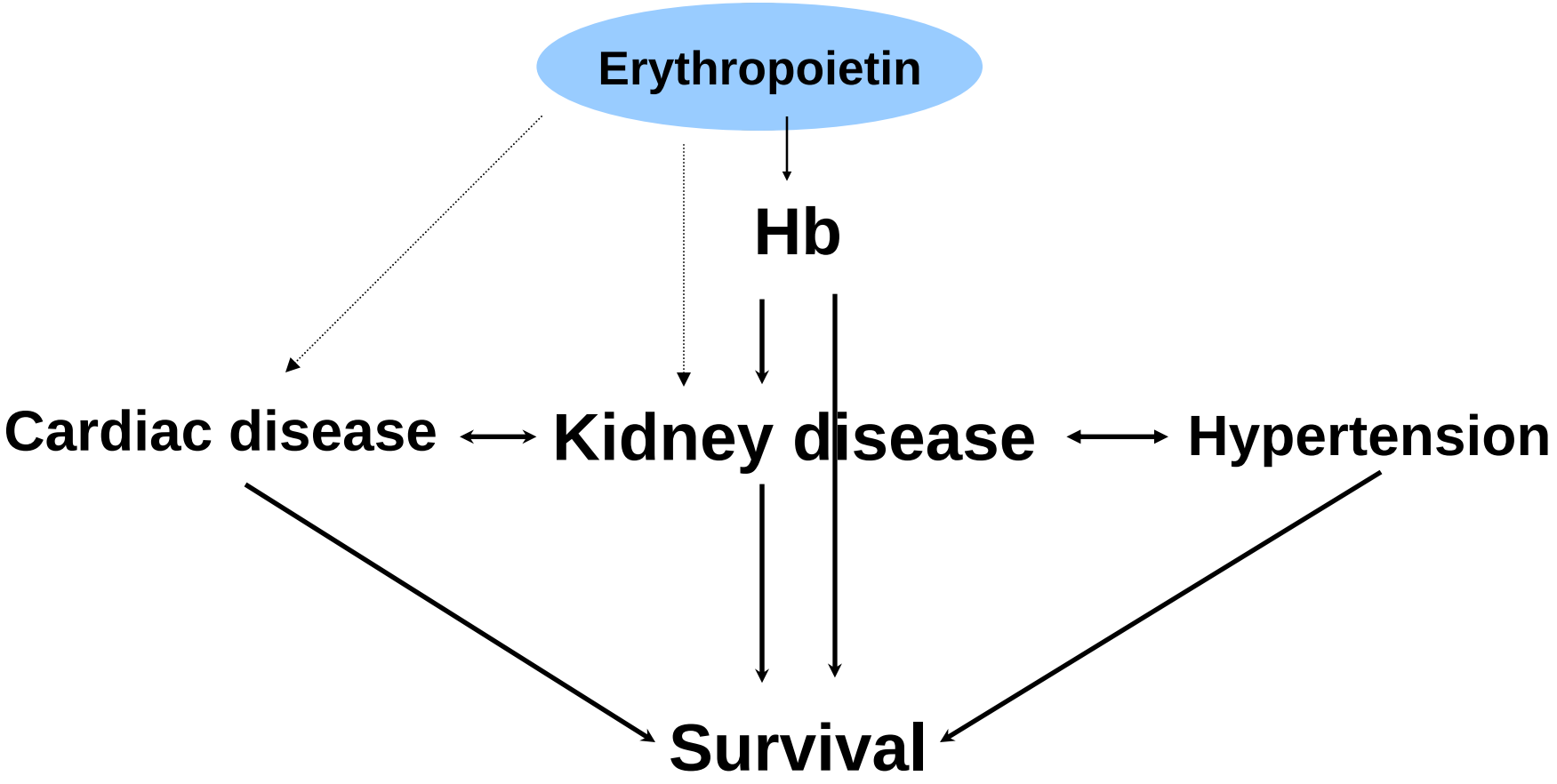


Strong Association in observational studies: Hgb and CV outcomes

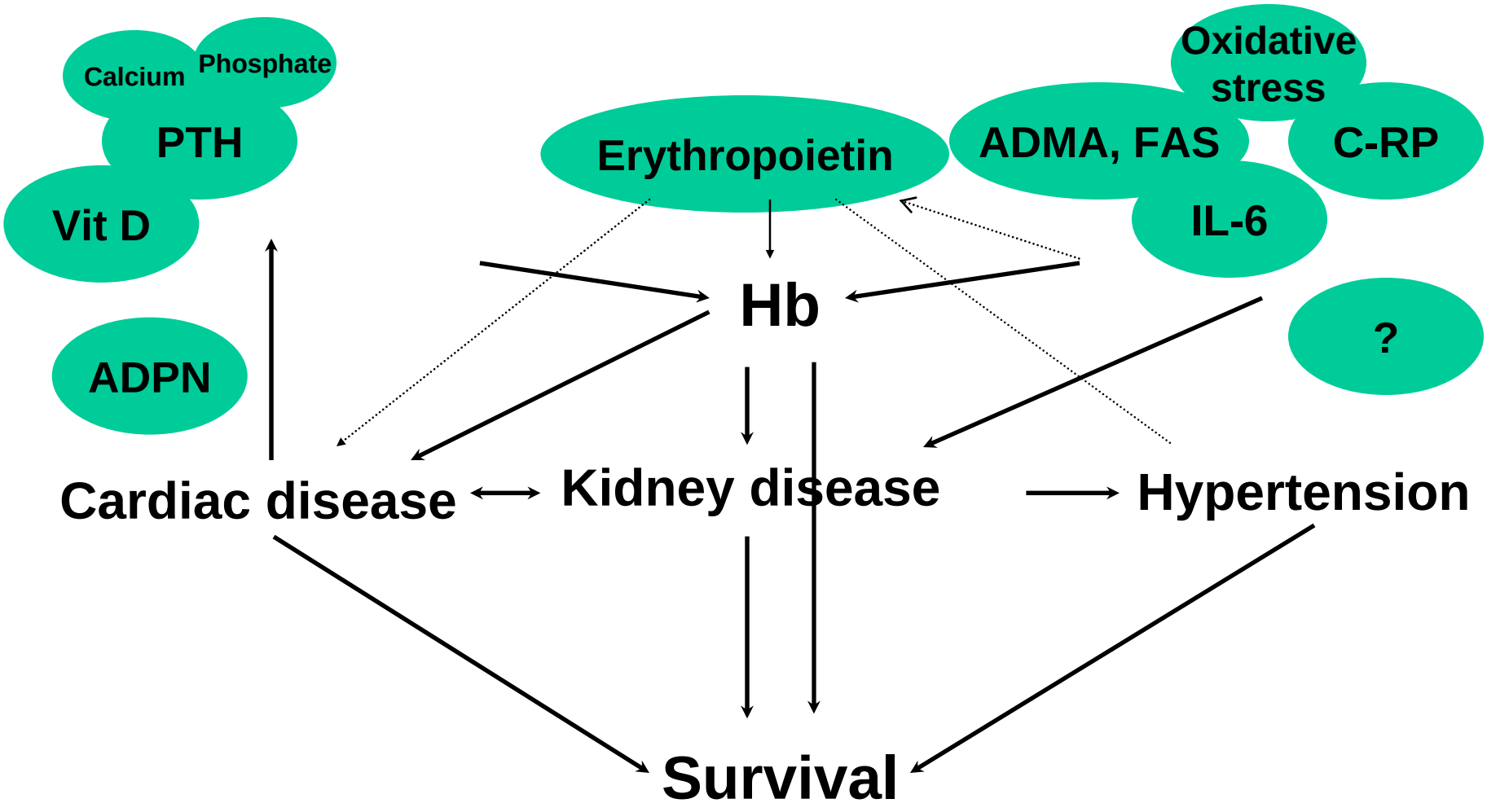
Potential Explanations:

1. ↓ Hgb = marker of cardiac function/ inflammation
2. ↓ Hgb associated with other risk factors
3. ↓ Hgb = risk factor for cardiac ischemia?
4. ↓ Hgb = cause of cardiac remodelling

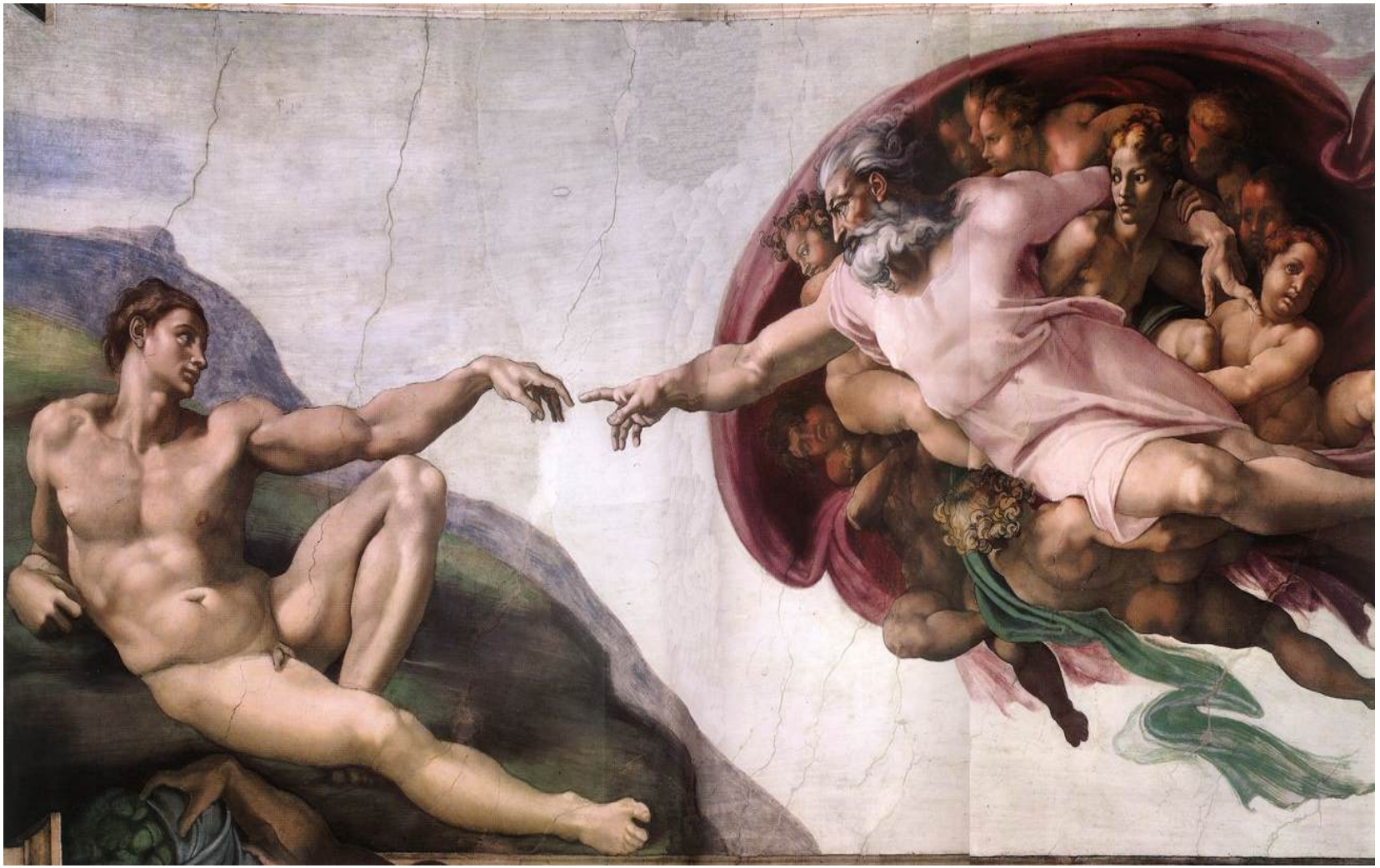
Increasing Complexity



Complex Interactions



Then, there was erythropoietin….



Erythropoietin effects: beyond Hb

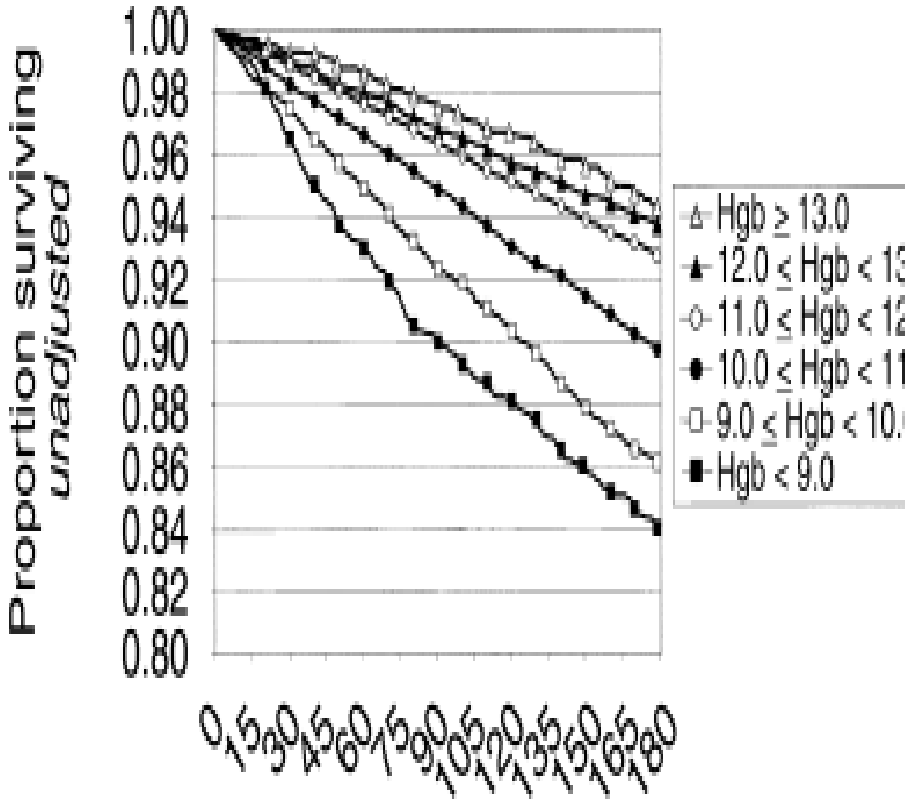
- Increase Hb and RBC survival
- Erythropoietin ~ effects on different organs/ systems
  - angiogenisis (Ribatti, 1999),
  - neuronal cells, (Cerami, 2000 PNAC)
  - renal endothelial, epithelial and tubular cells (Westenfelder KI ‘99, Nemoto ‘01)
  - myocardial cells (Parsa, JCI 2003)
- Factors in cell differentiation, proliferation, anti-apoptosis
  - EPO receptor: super-family of cytokine receptors ~ TNF
  - Signal transduction to 3 common cell survival pathways
    - PI3K, ERK1/2-MAPK, and JAK- Stat 5

Erythropoietin Hormone

- Early Randomized Control Trials
  - prove efficacy and safety
- Studies to corroborate and extend knowledge
  - Observational
  - Controlled

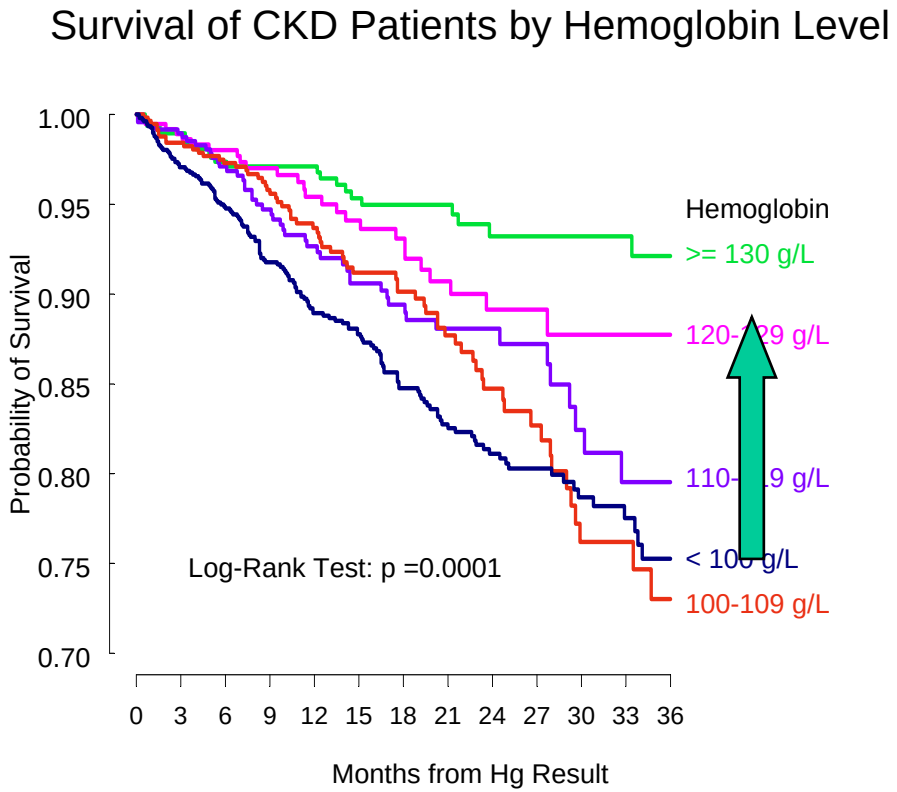
Hgb predicts survival in observational studies

Hb in HD pts + ESA



Ofsthun et al KI, 2003 63 (1908-1914)

Hb prior to Dialysis, No ESA



Levin et al, NDT 2005

The Trials

The question of the 1990's

- Since lower Hb is consistently associated with poor outcomes, does raising Hb to normal levels improve outcomes?

Unique features of Hb Trials

- Difficult to blind
- Non placebo
- Co-interventions vary between arms
  - ESA dose, iron therapy, antihypertensive agents)
  - Vary in intensity
- Outcomes
  - CV events, survival
  - LVH, Quality of life

Key learnings

- Increasing doses in sick patients may not lead to improved outcomes
- Increasing doses in sick patients may do harm

- Well patients do not require high doses of ESA to achieve ‘target’ Hb of ? Any level

Dialysis populations are too late in the continuum of disease

- Focus on non dialysis patients

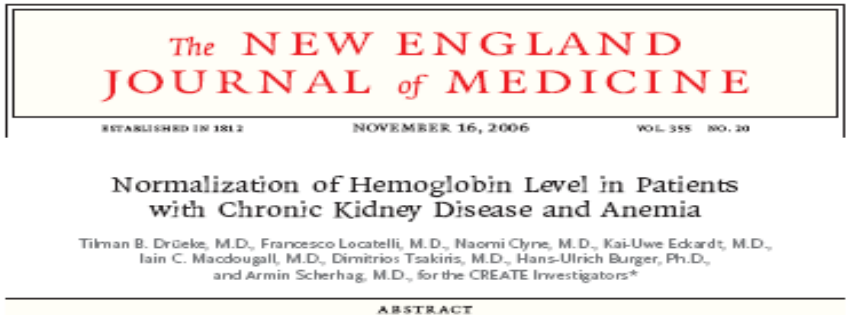
Recent studies in non dialysis pts

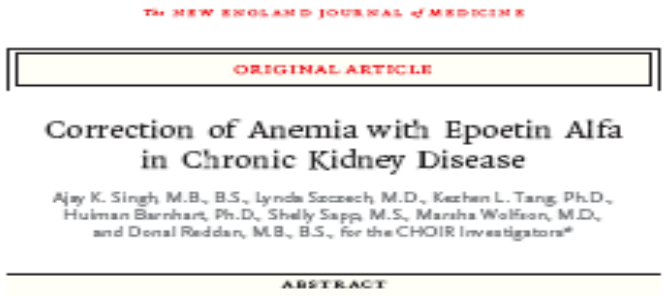
- Does normal Hgb in CKD improve CVD outcomes?
  - Surrogate measures (LVMI)
  - CV events
- Roger et al Australian RCT N= 150
- Levin et al Canadian RCT N= 150
- MacDougall UK RCT N= 138

- Drueke et al European RCT N = 600
- Singh et al US RCT N= 1400
- Pfeffer et al International RCT N = 4000

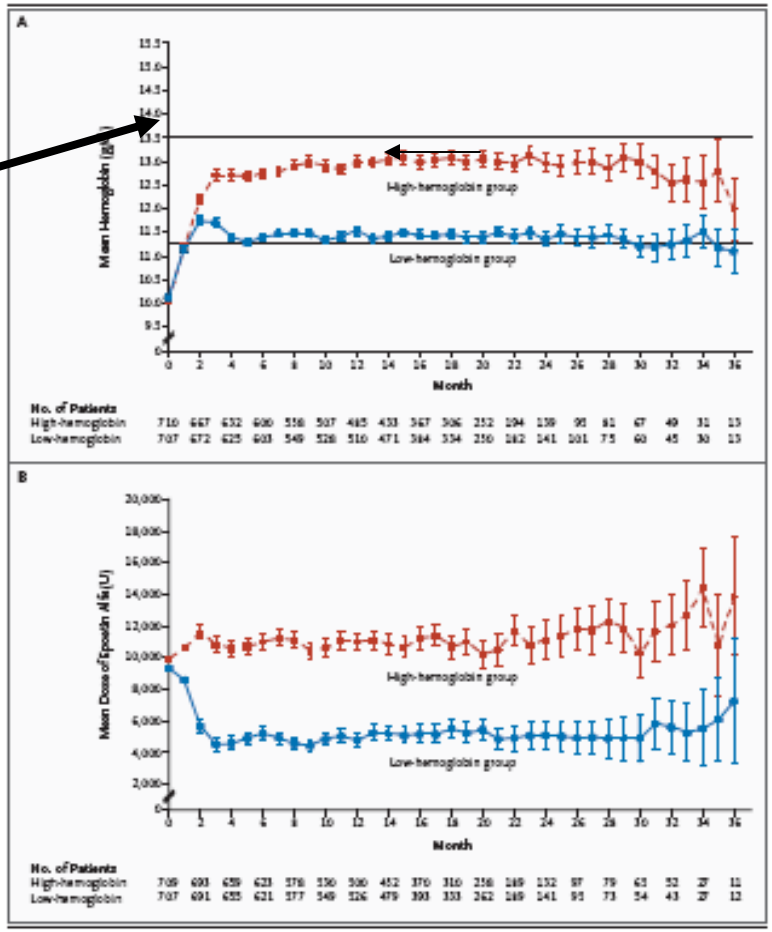
Controversy persists despite large trials: Methodology and remaining myths

- CREATE
  - Well done RCT N= 600
  - EPO dose ~ 5000 u/wk
  - Duration 36 m
  - Underpowered for event rate observed
  - No difference in adverse events observed (6 vs 15%)
- CHOIR
  - RCT with significant drop out N= 1400—700
  - Duration 16 m
  - EPO doses > 3x vs other studies (11K u/wk); non achievement of Hgb target despite this
  - Imbalance in key factors at baseline
  - Suggestion of harm
  - ? Results and conclusions





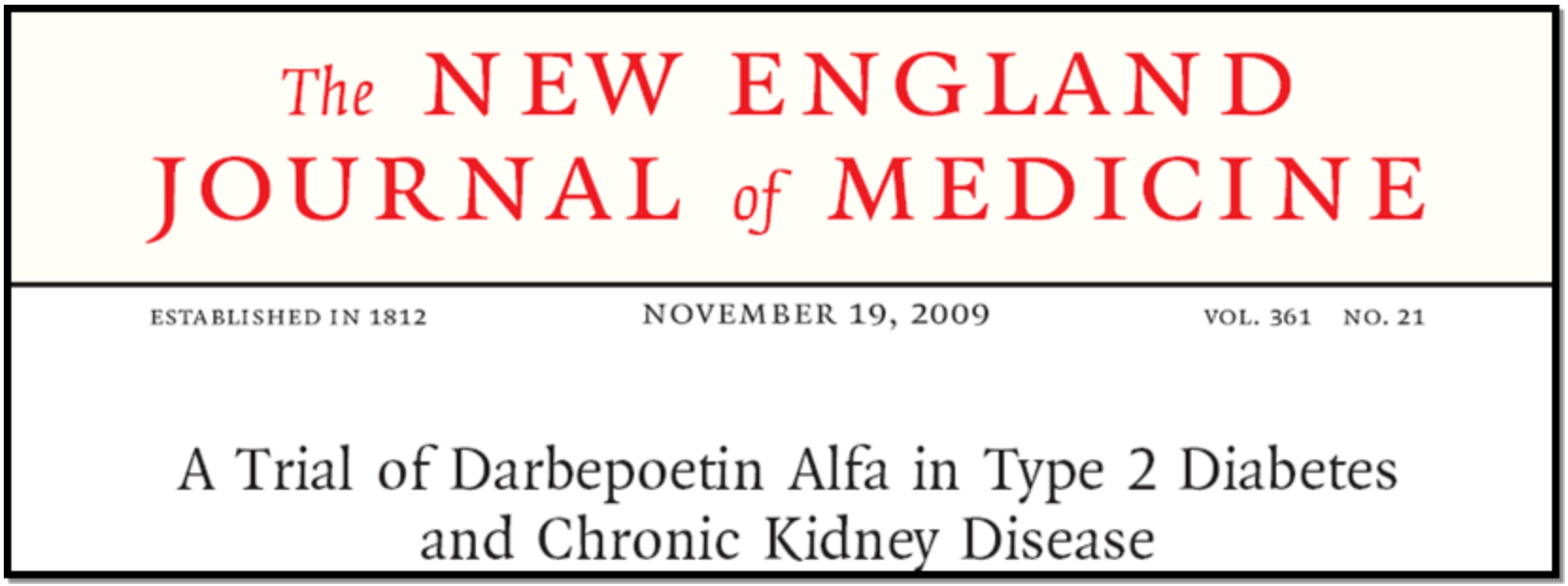
- High Hgb group only reached 12.8
  - Target 13.5
- Median doses EPO 11,000
- Quality of Life
  - unchanged



was examined; the difference between the two groups persisted (hazard ratio, 1.28; 95% CI, 1.07 to 1.54; P=0.007). Results similar to those in the primary analysis were observed when hospitalization for congestive heart failure with renal replacement therapy was included in the composite end point (hazard ratio for the high-hemoglobin group vs. the low-hemoglobin group, 1.37; P=0.02). In addition, the results comparing all hospitalizations for congestive heart failure (including those involving renal replacement therapy) in the two groups were similar to the results of hospitalization for congestive heart failure in the primary end point (hazard ratio, 1.44; P=0.04).

TREAT

TRIAL TO REDUCE CARDIOVASCULAR EVENTS WITH ARANESP THERAPY



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 19, 2009 VOL. 361 NO. 21

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

Randomized, double-blinded, placebo-controlled, 623 sites, 24 countries, enrolled 2004-2007

>4000 pts

Type II DM, CKD with GFR 20-60 ml/min (MDRD)

Hgb <110 g/l, Tsat > 15%

Hypothesis

Trial to Reduce Cardiovascular Events with Aranesp Therapy

In patients with type 2 diabetes, chronic kidney disease not requiring dialysis, and concomitant anemia, raising hemoglobin with darbepoetin alfa would lower the rates of death, cardiovascular morbidity and end-stage renal disease.

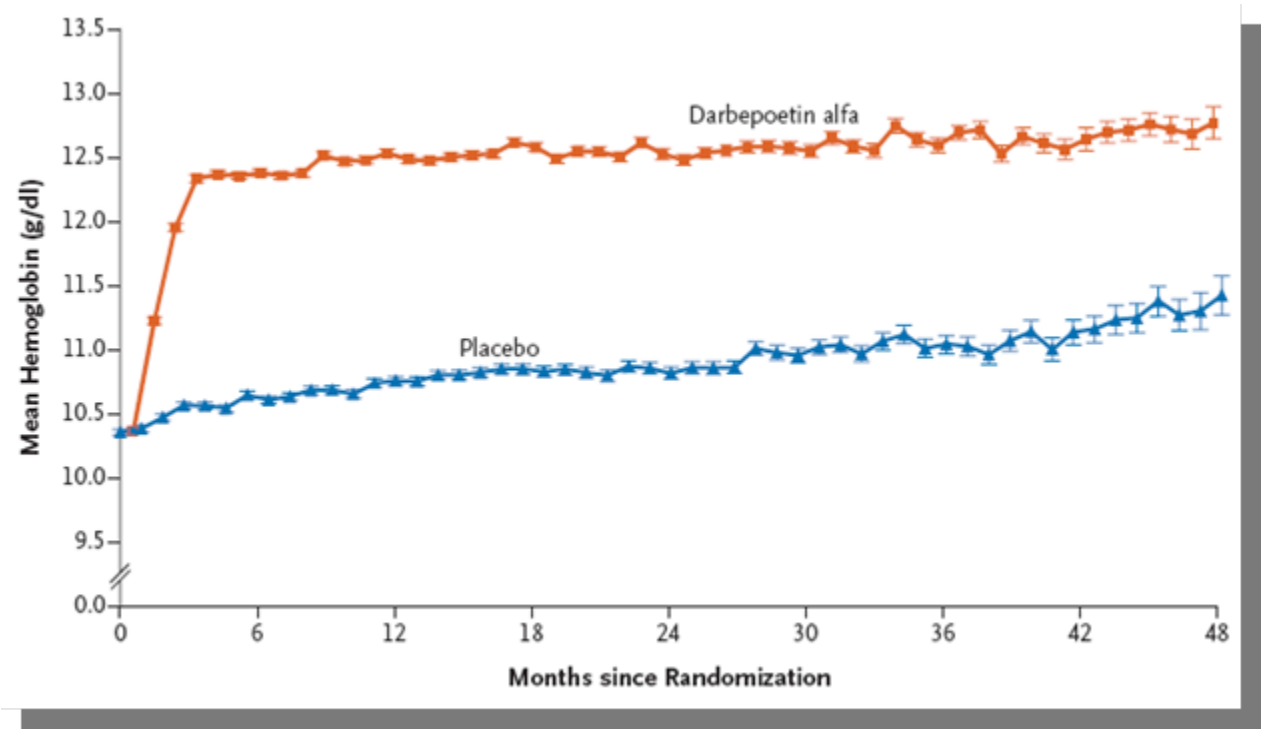
Outcomes

- Adjudicated by committee blinded to randomization and hemoglobin level at time of assessment

- Primary outcomes
  - Time to composite of any cause death or CV event (MI, CHF, CVA, hospitalization)
  - Time to composite of any cause death or ESRD

- Secondary outcomes
  - All components of primary outcomes
  - Time to death
  - CV deaths
  - Rate of GFR decline
  - Changes in patient-reported QoL outcomes using FACT-Fatigue and other

Achieved Hb



125 g/L

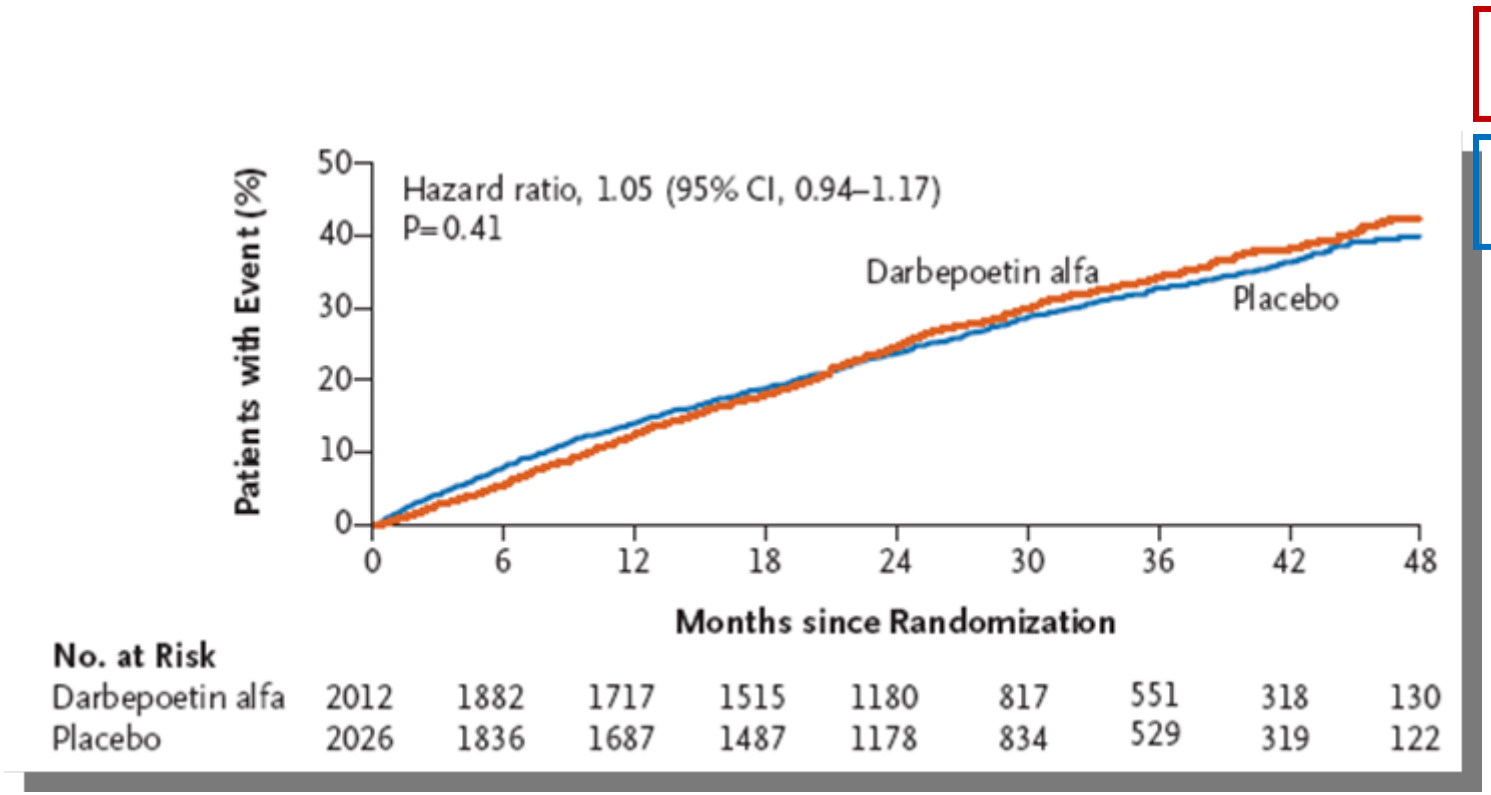
- Median monthly dose 176 ug
- Less transfusions

106 g/L

- Median monthly dose 0 ug
- 46% received at least one rescue dose
- More pts received IV iron

Primary Outcome

Composite CV outcome: death or nonfatal CV event, ns

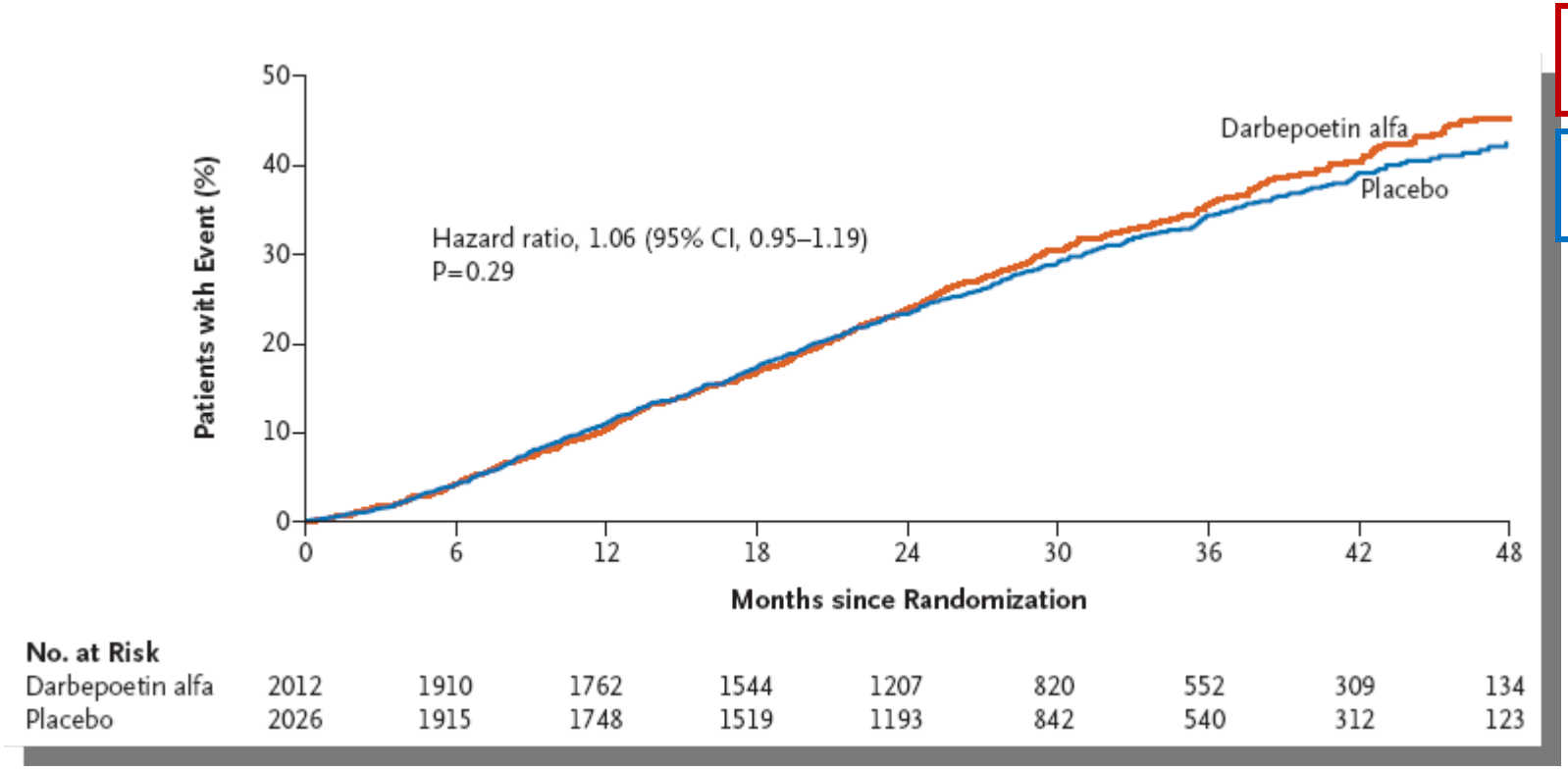


31.4%

29.7%

Primary Outcome

Composite renal outcome: death or ESRD



32.4%

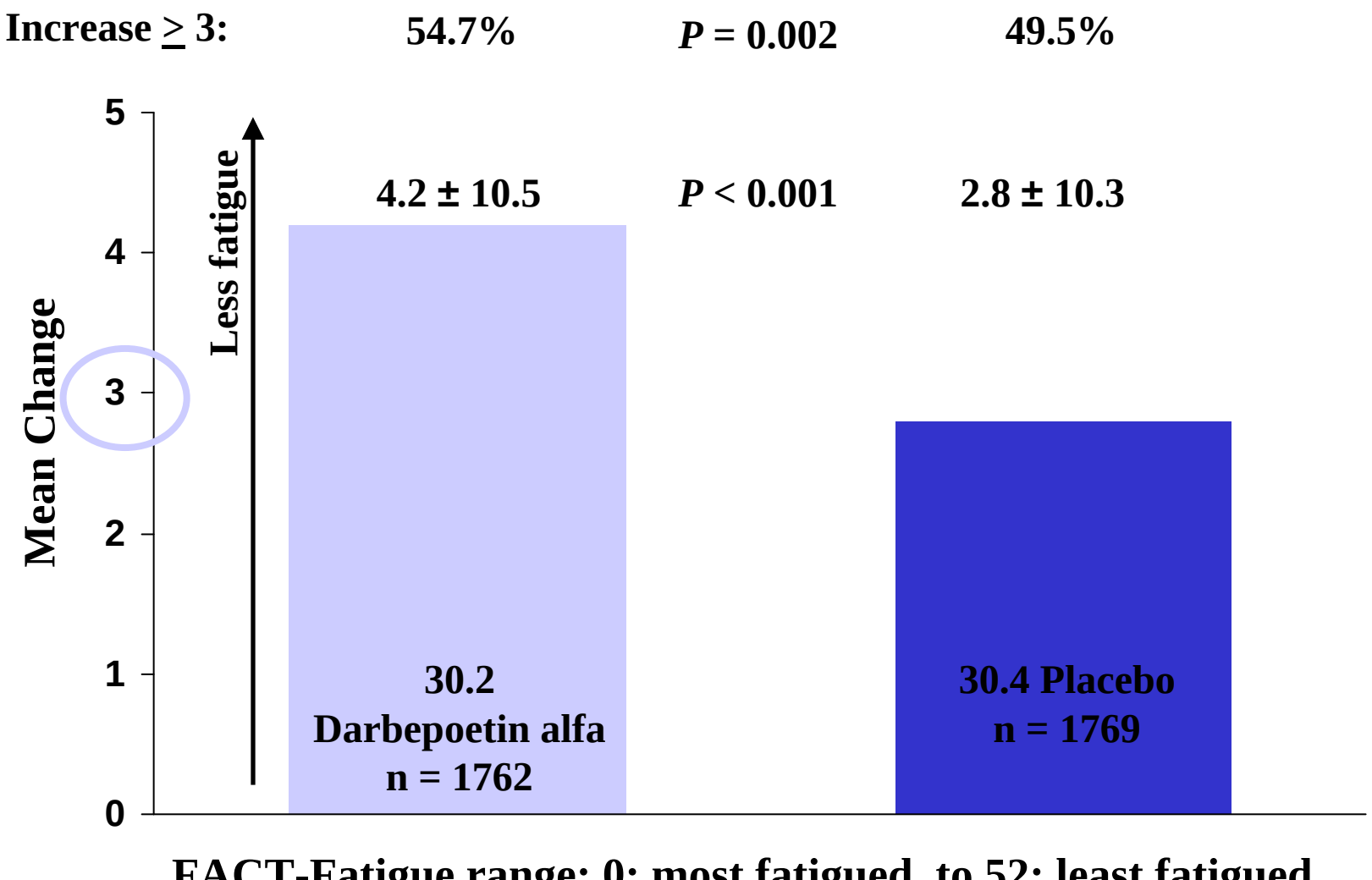
30.5%

ESRD occurred in ~ 16% of all pts

Primary Composite and Component Endpoints

Endpoint	Darbepoetin alfa N = 2012	Placebo N = 2026	HR (95% CI)	*P*-value
CV Composite	632 (31.4)	602 (29.7)	1.05 (0.94-1.17)	0.41
Death	412 (20.5)	395 (19.5)	1.05 (0.92-1.21)	0.48
Heart Failure	205 (10.2)	229 (11.3)	0.89 (0.74-1.08)	0.24
MI	124 (6.2)	129 (6.4)	0.96 (0.75-1.22)	0.73
Stroke	101 (5.0)	53 (2.6)	1.92 (1.38-2.68)	<0.001
Myocardial Ischemia	41 (2.0)	49 (2.4)	0.84 (0.55-1.27)	0.40
Renal Composite	652 (32.4)	618 (30.5)	1.06 (0.95-1.19)	0.29
ESRD	338 (16.8)	330 (16.3)	1.02 (0.87-1.18)	0.83

Patient Reported Outcomes
FACT-Fatigue Score at 25 Weeks



FACT-Fatigue range: 0: most fatigued, to 52: least fatigued

Other Outcomes of Interest

	Darbepoetin alfa	Placebo	*P*-value
SBP	134 (126-143)	134 (126-143)	NS
DBP	73 (67-78)	71 (65-77)	<0.001
ATE	178 (8.9%)	144 (7.1%)	0.04
VTE	41 (2.0%)	23 (1.1%)	0.02
Revasc	84 (4.2%)	117 (5.8%)	0.02

VTE: Venous Thromboembolic events
ATE: Arterial Thromboembolic events (in part adjudicated as endpoints)
Revasc: Cardiac revascularization

Malignancy in TREAT

	Darbepoetin alfa	Placebo	P-value
Overall			
Cancer-related AE	139/2012 6.9%	130/2026 6.4%	0.53
Deaths in patients with cancer	53/139 38%	50/130 38%	n.s.
Deaths attributed to cancer	39/2012 1.9%	25/2026 1.2%	0.08
Subgroup: Baseline ☑ History of malignancy (n = 348)			
All cause mortality	60/188 31.9%	37/160 23.1%	0.13
Deaths attributed to cancer	14/188 7.4%	1/160 0.6%	0.002

TREAT : Conclusions

- Treatment of diabetic CKD patients with Aranesp to target Hgb of 130 g/L, when compared to placebo and Aranesp rescue at Hgb <90 g/L, showed:
  - No reduction in composite CV outcome
  - No reduction in composite renal outcome
  - Increased risk of stroke
  - Increased risk of thromboembolic disease
  - Increased risk of death from pre-existent cancer
  - No significant improvement in most QoL measures
  - But: less number transfusions and improved fatigue

IN THE LITERATURE

TREAT: Implications for Guideline Updates and Clinical Care

American Journal of Kidney Diseases,

targets. Guideline groups, such as KDIGO, should ensure that patient-centered outcomes remain the focus of the guideline commentary: messages for the updates need to be clear and succinct, refraining from too much conjecture. The data are clearer now than they have been for decades: anemia therapy aimed at high hemoglobin targets does not change clinically meaningful outcomes, such as cardiovascular events, death, or time to dialysis therapy. Although therapy may impact positively on specific aspects of quality of life, it also may confer risks.

Levin and Beaulieu 2010

Relationship between Epoetin Alfa Dose and Mortality: Findings from a Marginal Structural Model

Ouhong Wang,* Ryan D. Kilpatrick,* Cathy W. Critchlow,* Xiang Ling,*
Brian D. Bradbury,* David T. Gilbertson,† Allan J. Collins,† Kenneth J. Rothman,‡§ and
John F. Acquavella*

Higher dose predicts poor outcome

Multiple studies confirm this

- HD pts
- CKD pts

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Erythropoietic Response and Outcomes in Kidney Disease and Type 2 Diabetes

Scott D. Solomon, M.D., Hajime Uno, Ph.D., Eldrin F. Lewis, M.D., M.P.H., Kai-Uwe Eckardt, M.D., Julie Lin, M.D., M.P.H., Emmanuel A. Burdmann, M.D., Ph.D., Dick de Zeeuw, M.D., Ph.D., Peter Ivanovich, M.D., Andrew S. Levey, M.D., Patrick Parfrey, M.D., Giuseppe Remuzzi, M.D., Ajay K. Singh, M.D., Robert Toto, M.D., Fannie Huang, M.S., Jerome Rossert, M.D., Ph.D., John J.V. McMurray, M.D., and Marc A. Pfeffer, M.D., Ph.D., for the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) Investigators

Responsiveness to ESA in initial phase predicts long term outcome

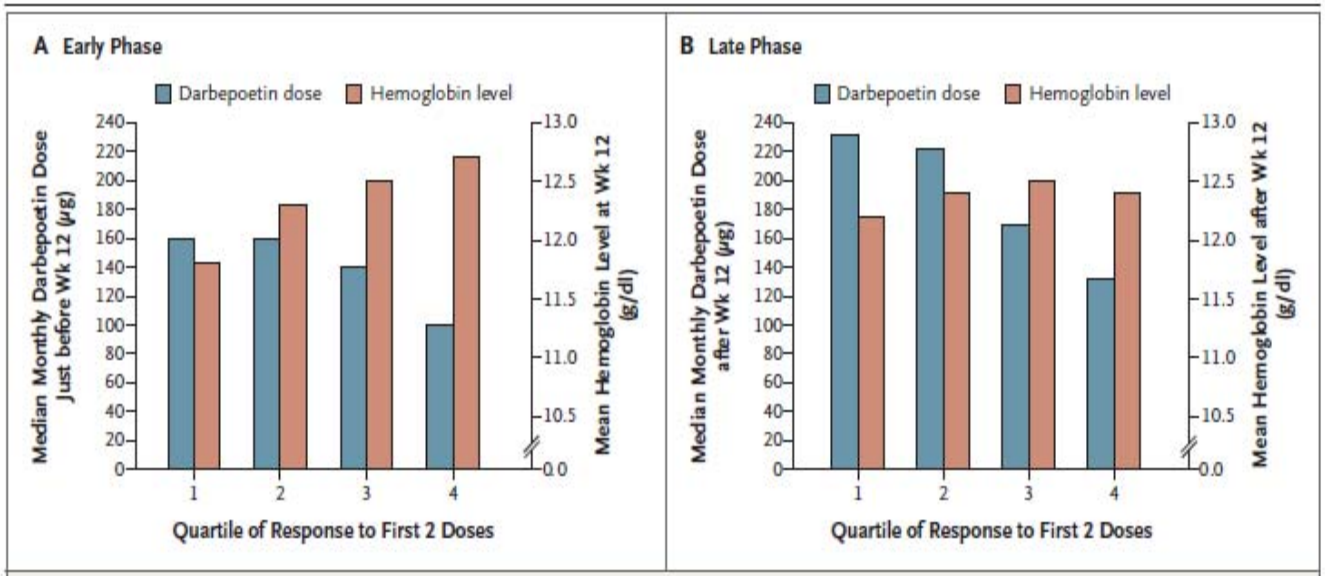
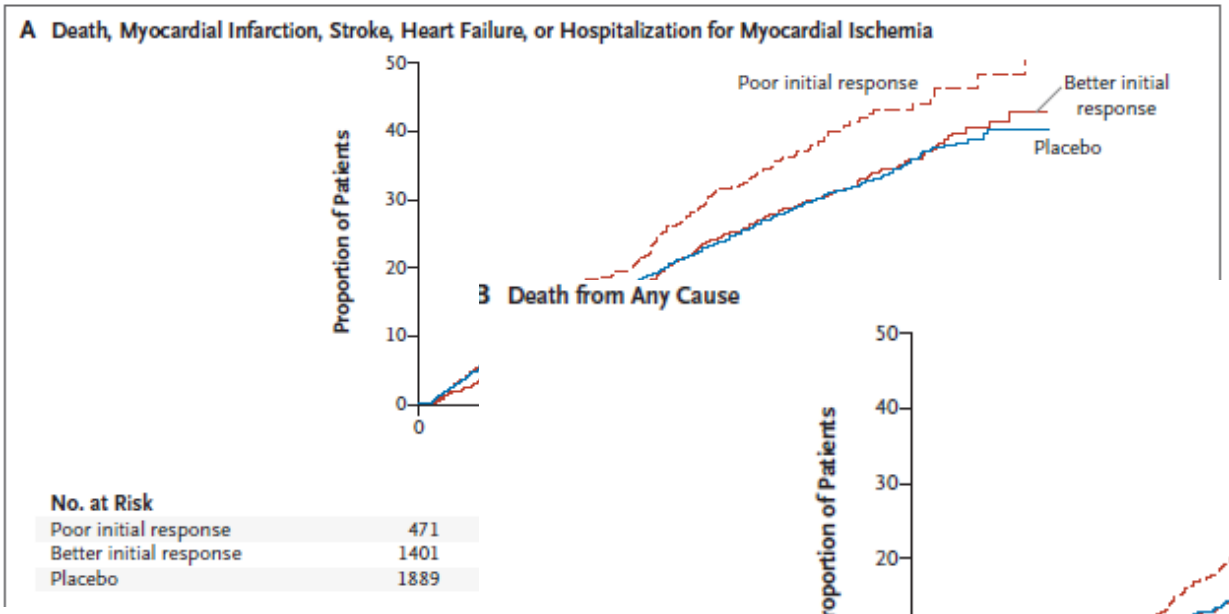
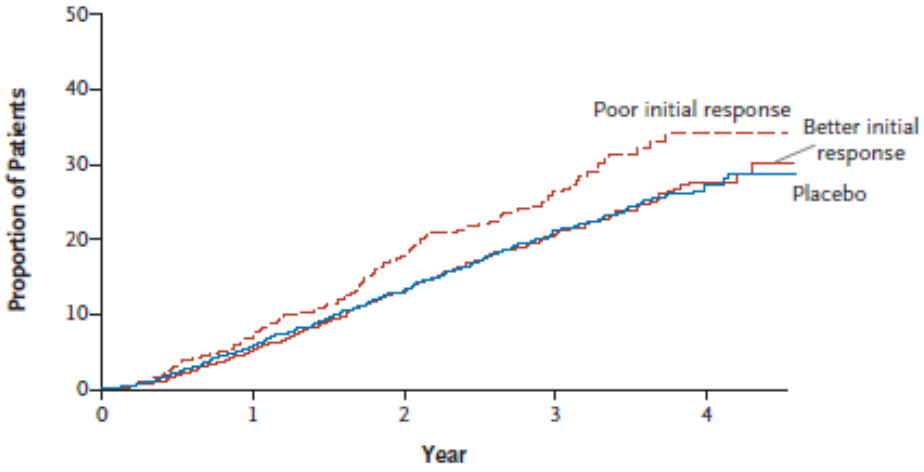


Figure 1. Association between Hemoglobin Level and Dose of Darbepoetin Alfa, According to the Level of Response to the First Two Doses.
Panel A shows the mean hemoglobin level at week 12 and the median monthly dose of darbepoetin alfa received before week 12, according to quartile of change in hemoglobin level (response) after the first two weight-based doses. Panel B shows the mean hemoglobin level after week 12 and the median monthly darbepoetin alfa dose during the trial after week 12, according to quartile of response after the first two weight-based doses.

Table 2. Rate of End Points and Adjusted Hazard Ratios.*

	Placebo (N=1889)	Poor Response (N=471)	Better Response (N=1401)	Adjusted Hazard Ratio (95% CI)†
	rate per 100 patient-yr (95% CI)			
Cardiovascular composite	12.3 (11.3–13.4)	16.3 (14.0–18.9)	12.4 (11.2–13.6)	1.31 (1.09–1.59)
Death from any cause	7.5 (6.8–8.3)	9.9 (8.3–11.9)	7.5 (6.7–8.5)	1.41 (1.12–1.78)
Stroke	1.0 (0.8–1.4)	2.3 (1.6–3.4)	2.0 (1.6–2.6)	1.26 (0.78–2.02)





Key learnings

- Increasing Hb in sick individuals may not lead to improved outcomes

- High doses of ESA in sick patients may do harm
  - Poor responders ~ harm
  - Good responders~ benefit / no harm

- Iron raises Hb in CKD patients without apparent adverse effects

Some caveats

- One size does not fit all
  - The CKD population is too heterogeneous to apply one particular target to and expect a predictable outcome
- Anemia is a marker of underlying disease burden, rather than an absolute target for intervention
- Focus should shift away from tight therapeutic range hemoglobin targets and consider ESA exposure as a potential harm: dissociate dose from target Hb

Practical Implications of current knowledge

- Identify and treat iron depletion in CKD patients
- Thresholds for starting ESA should be ~100 or lower and individual symptoms taken into account
- A history of thrombotic events or malignancy should reduce enthusiasm for ESA, or for dose acceleration

Perspective :
Asking the right questions