Anemia and Cardiovascular Disease:

The Good, The Bad, The Ugly

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Disclosures

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Relation between Renal Dysfunction and Cardiovascular Outcomes after Myocardial Infarction

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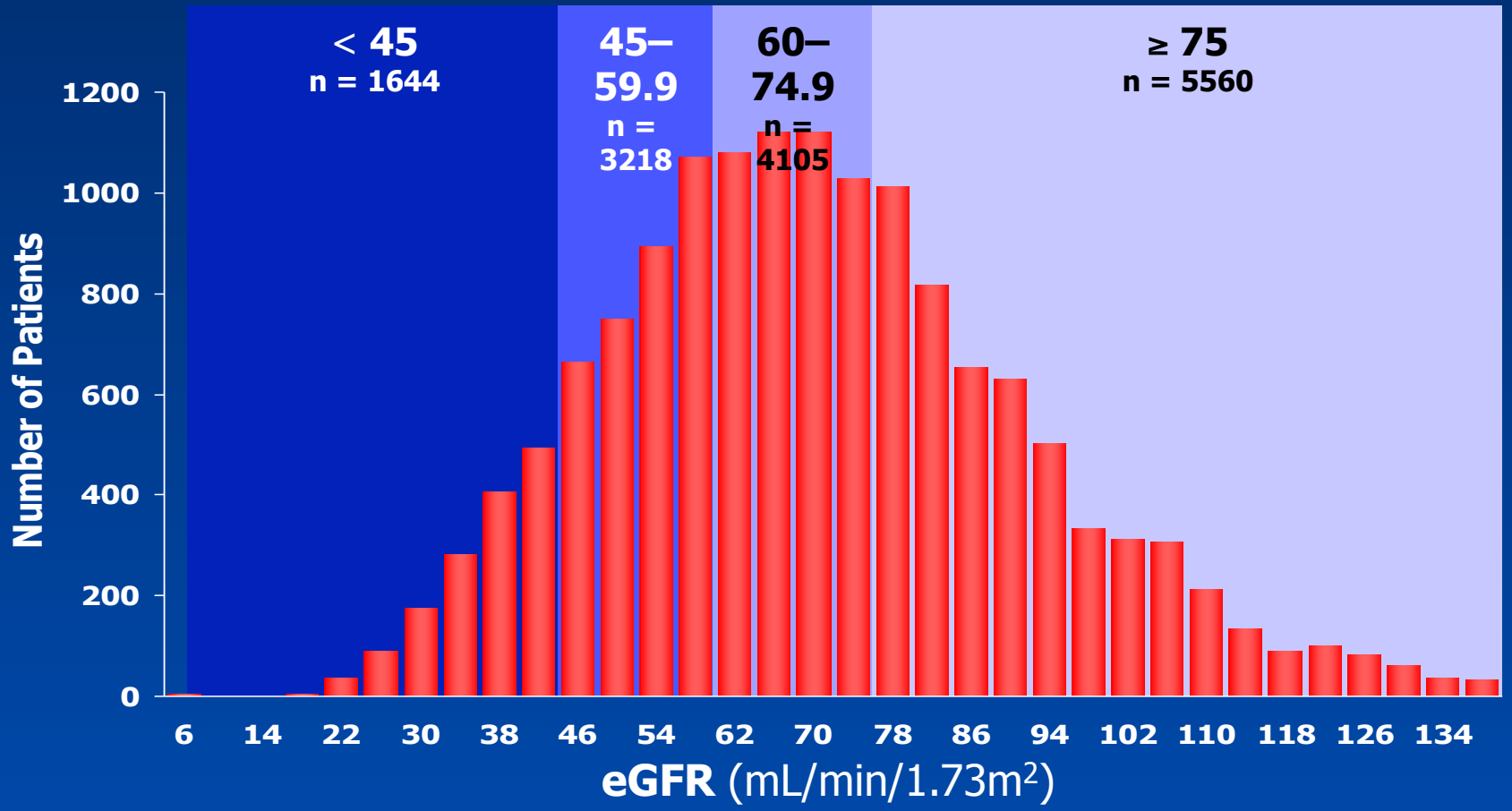
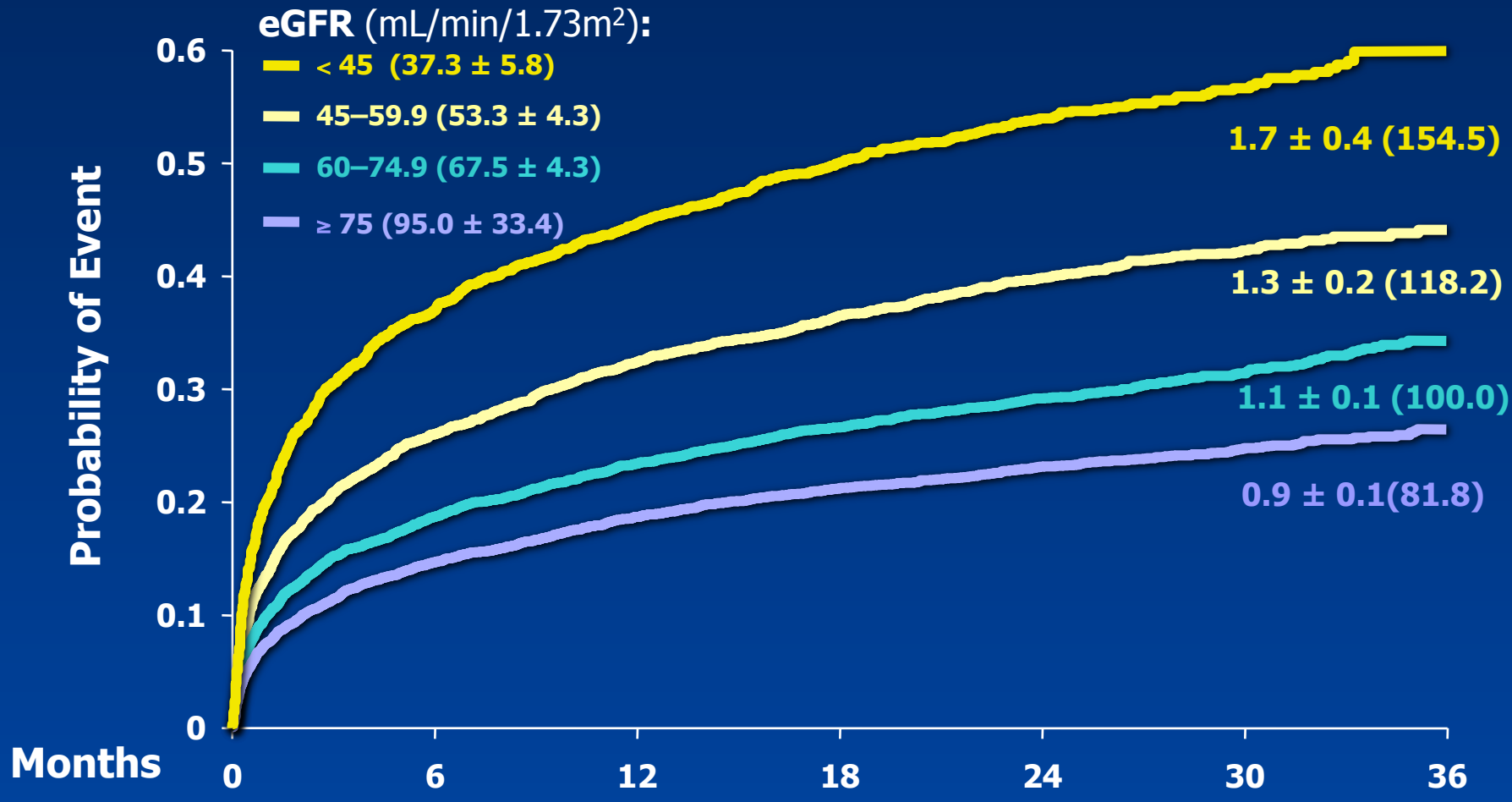
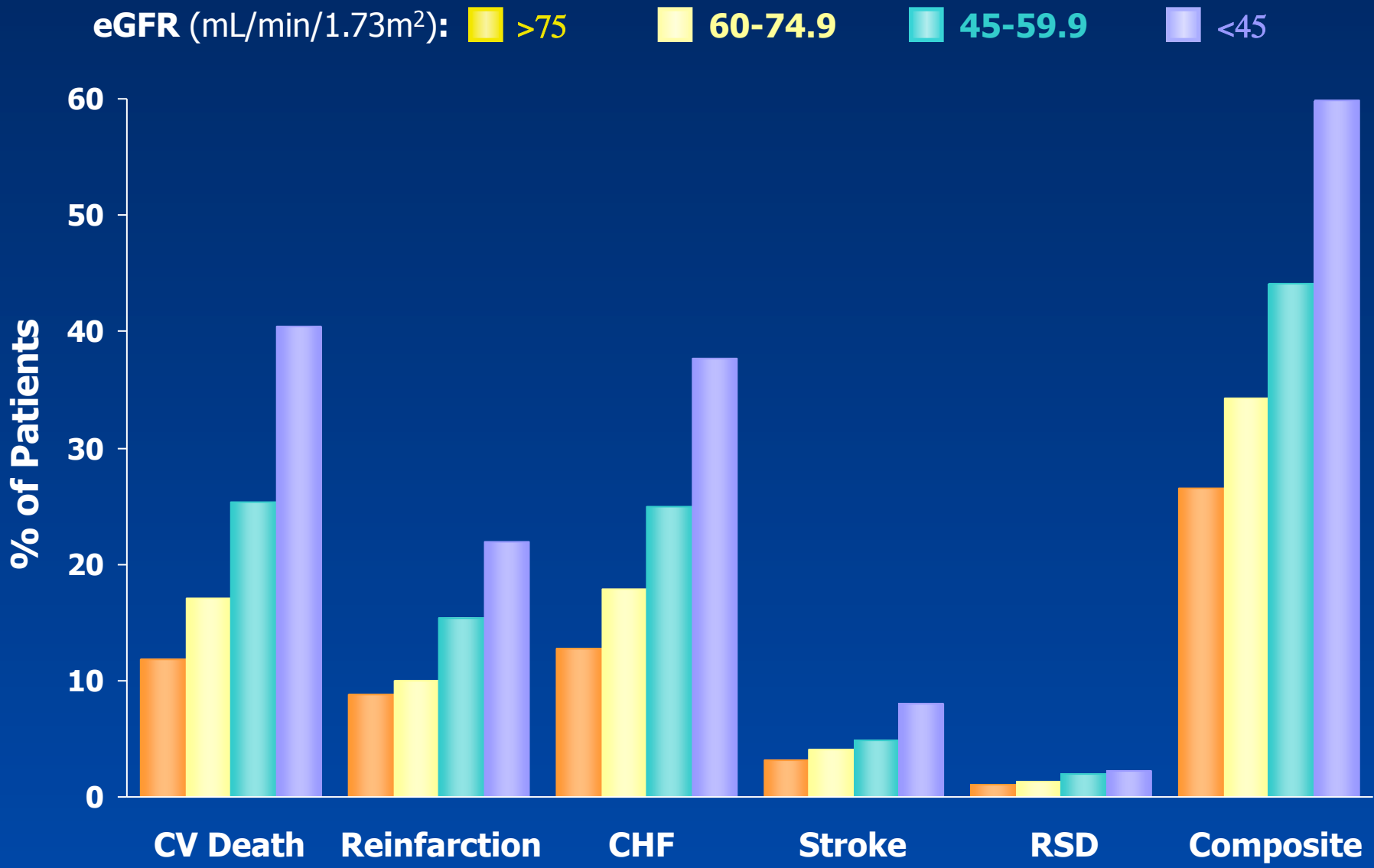


CV Death, MI, HF, RSD, or Stroke by Renal Function

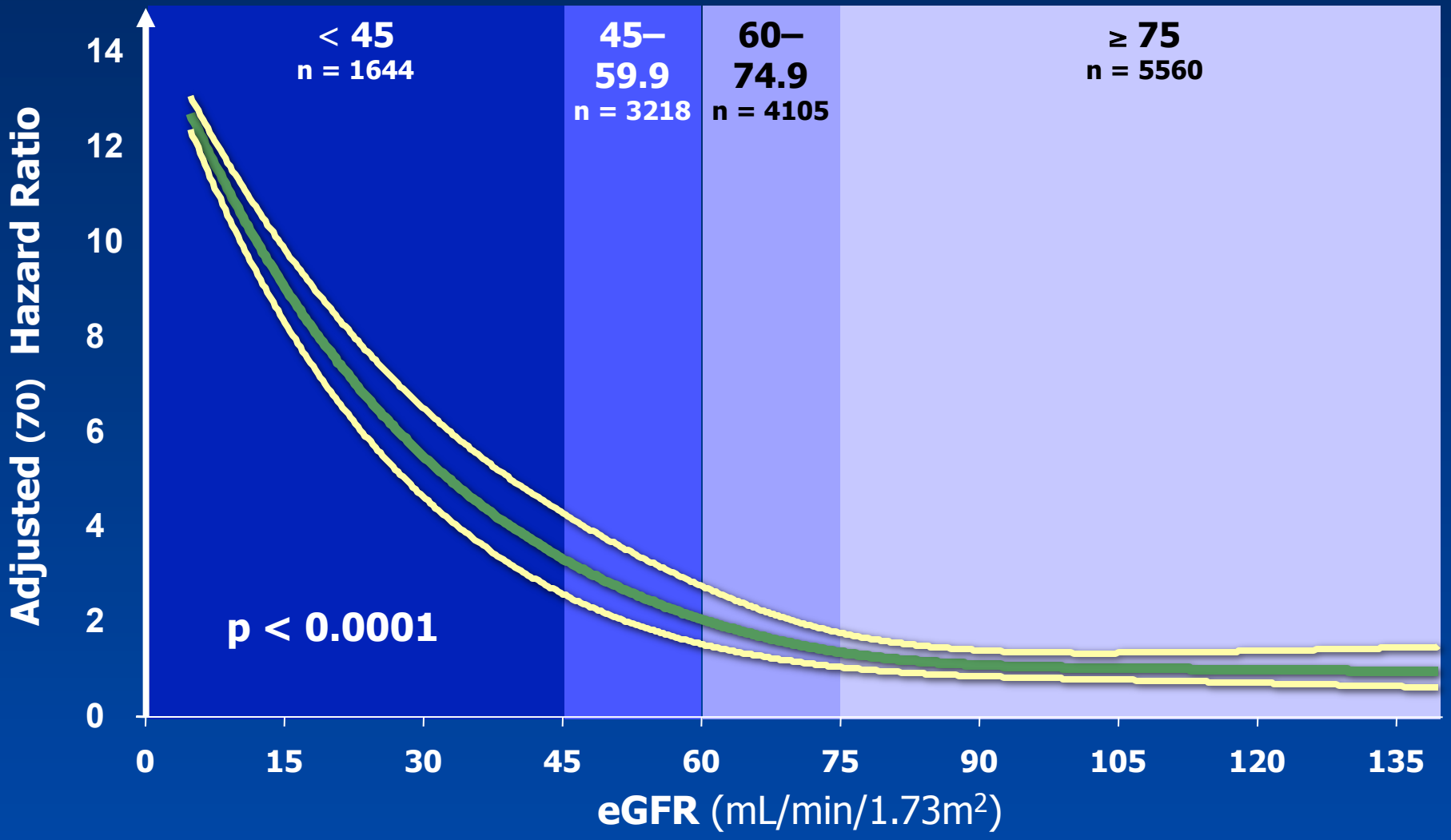


Months	0	6	12	18	24	30	36
≤ 45	1644	1029	894	776	469	220	40
45–59.9	3218	2365	2143	1953	1177	646	148
60–74.9	4105	3314	3106	2893	1900	973	233
≥ 75	5560	4719	4472	4200	2804	1593	438

Cardiovascular Events



Spectrum of Risk (CV events)



Anavekar NS et al NEJM 2004; 351:1285

VALIANT CKD

- Mean eGFR in VALIANT:

  67

- % of patients with eGFR < 60:

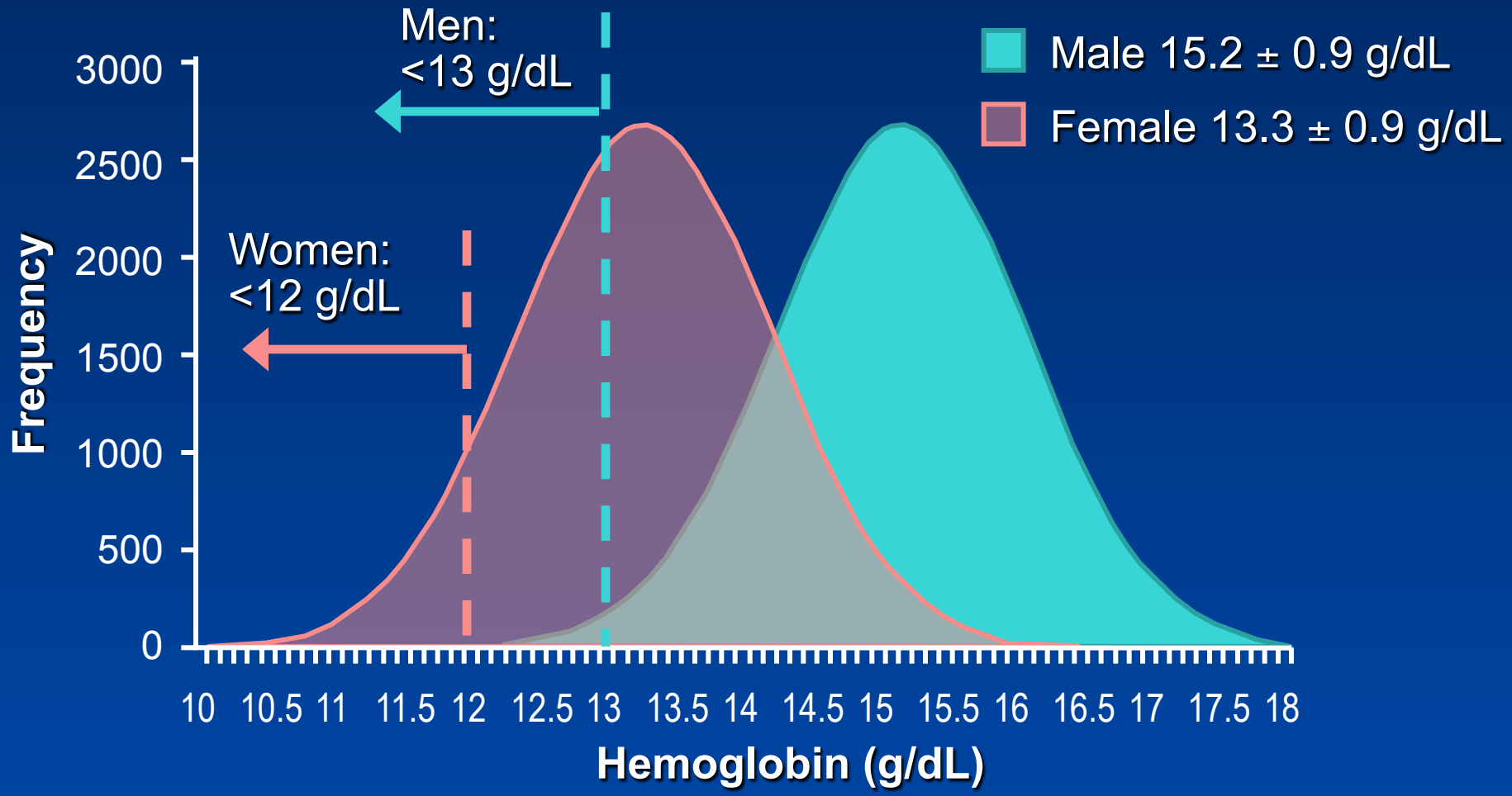
  33%

- Total # of patients going on to ESRD: 14

/14,703 = < 0.1%

Anemia and CV Risk

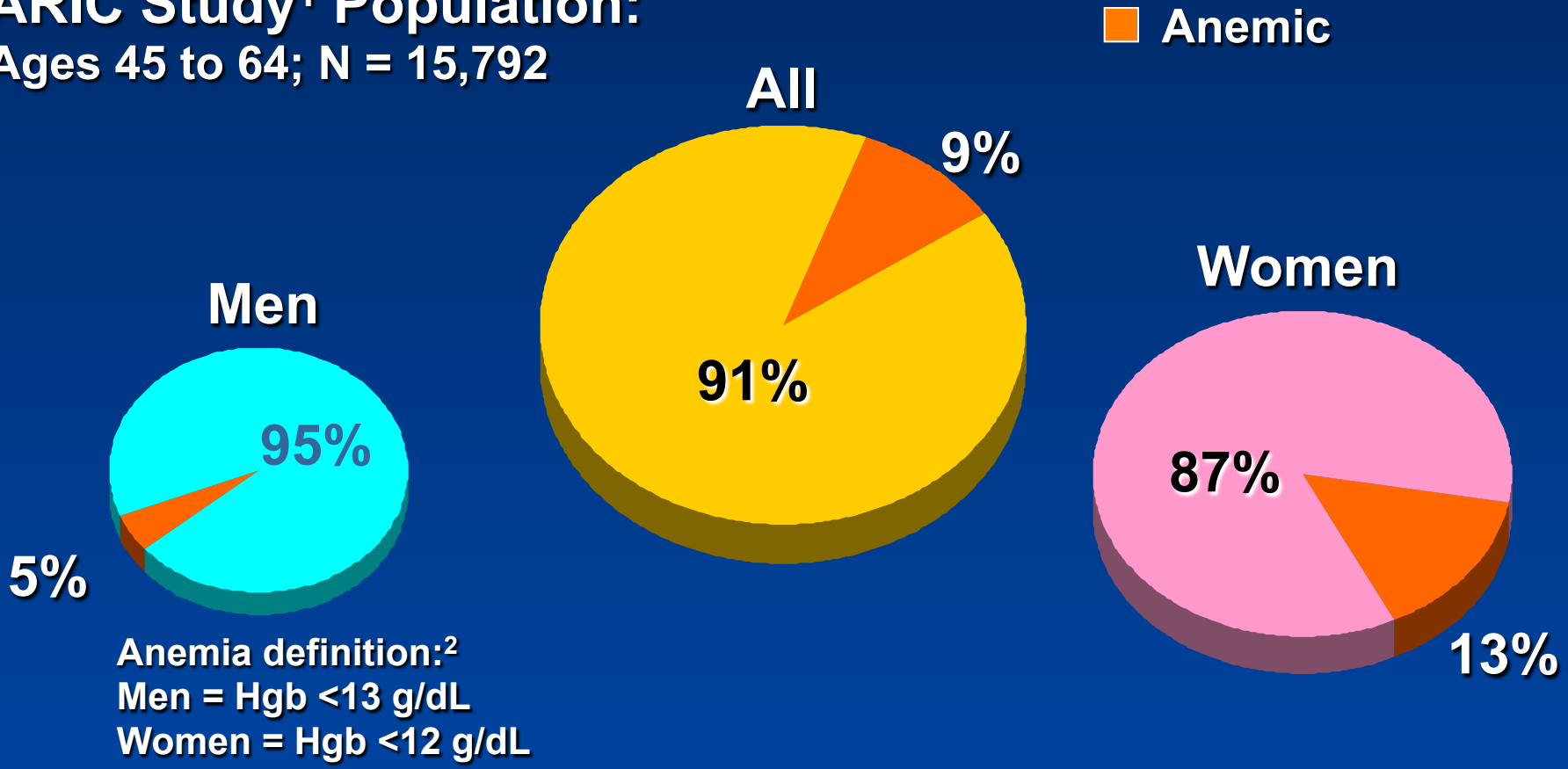
World Health Organization (WHO) Anemia Definition[1]



1. World Health Organization. Geneva, Switzerland; 2001. 2. Dallman et al. In: *Iron Nutrition in Health and Disease*. London, UK: John Libbey & Co; 1996:65-74.

Based on WHO Definition, 9% of Adults Have Anemia: ARIC Study*

ARIC Study[1] Population:
Ages 45 to 64; N = 15,792



Anemia definition:[2]
Men = Hgb <13 g/dL
Women = Hgb <12 g/dL

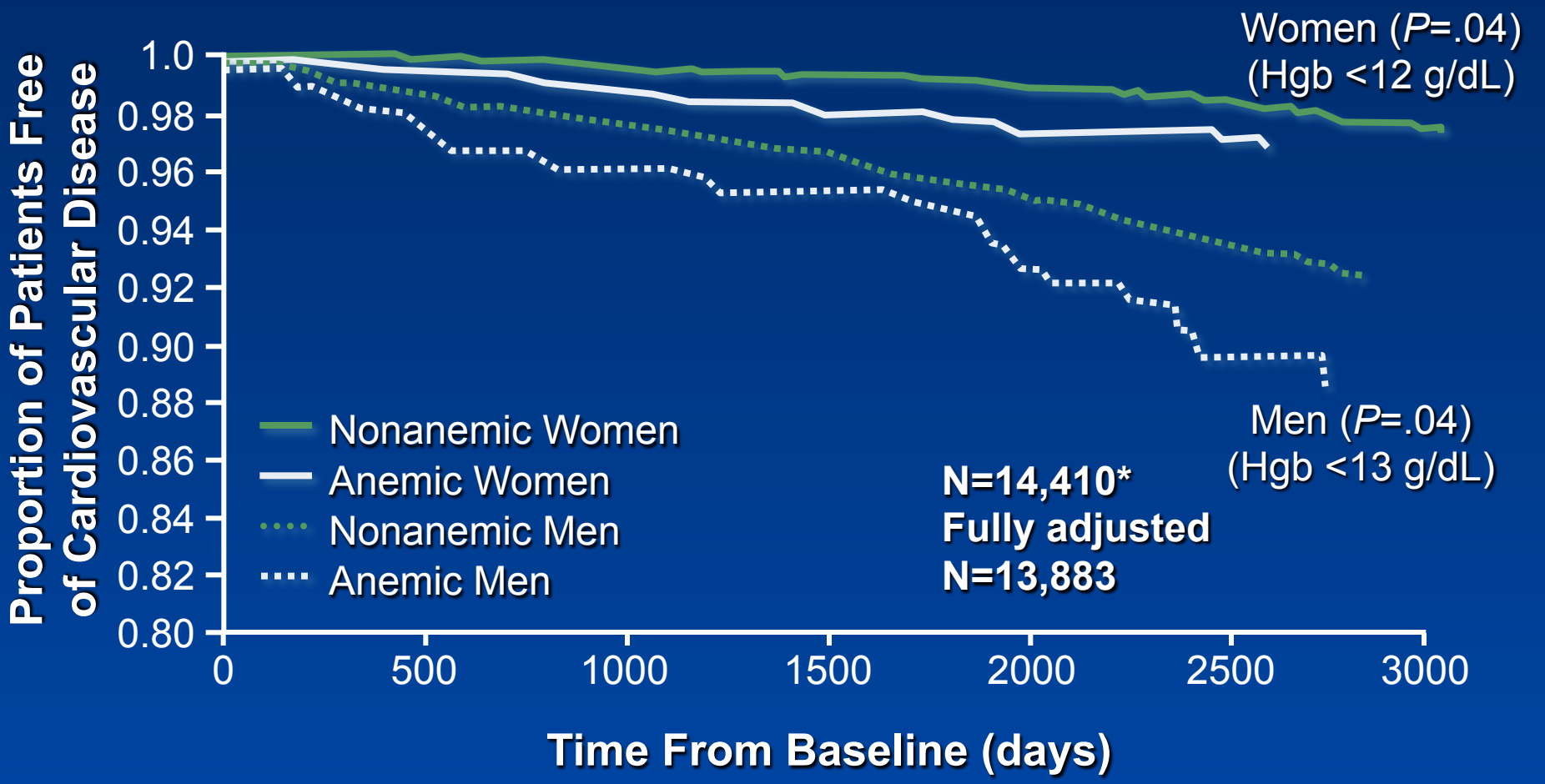
*The Atherosclerosis Risk in Communities (ARIC) study enrolled subjects in 4 US communities: Forsyth County, NC; Jackson, Miss; Minneapolis, Minn; and Washington County, Md.

1. Sarnak et al. *J Am Coll Cardiol*. 2002;40:27-33. 2. World Health Organization. Geneva, Switzerland; 2001.

Causes of Anemia in CVD

- Normally, bone marrow generates ~ 200 billion new cells per day to match the cells lost or removed from circulation.
- The expected compensatory response to anemia is a heightened rate of erythropoiesis.
- Failure to demonstrate a compensatory response signifies slowed or defective erythropoiesis.
- Most common cause of defective erythropoiesis in CAD population is chronic kidney disease (even mild CKD).

Anemia and Increased Cardiovascular Disease ARIC Study

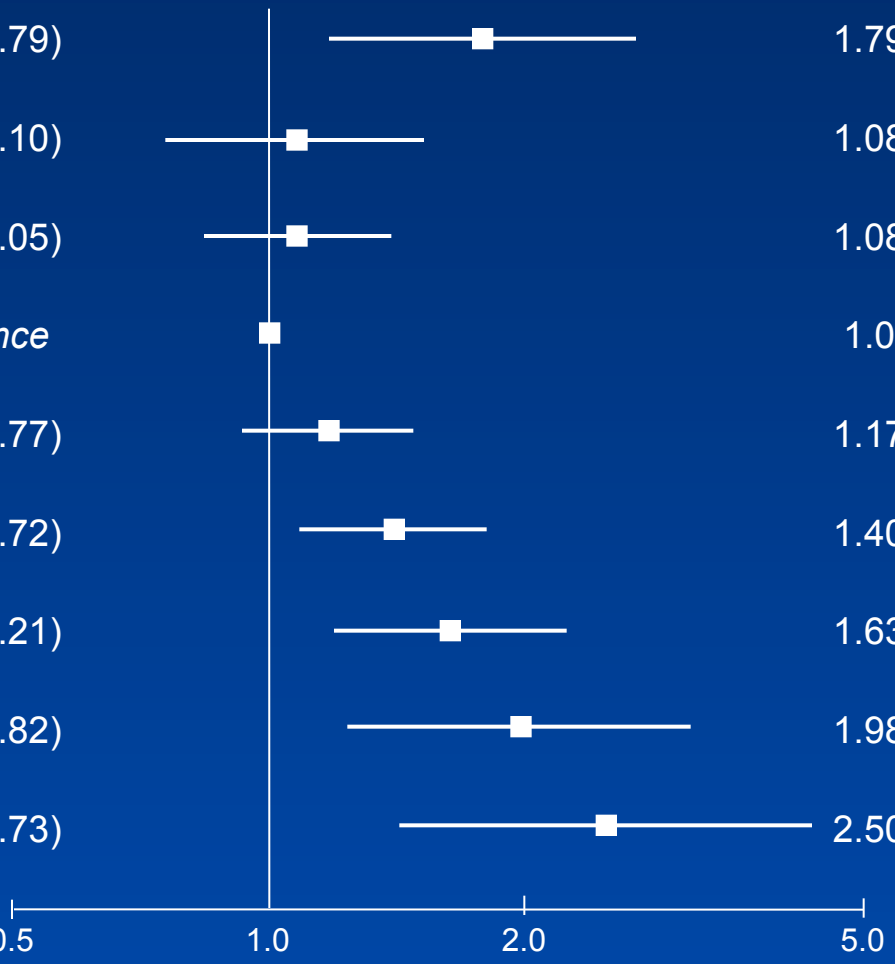


*Patients with hemoglobin levels. Sarnak et al. *J Am Coll Cardiol.* 2002;40:27-33.

Anemia and CV Death in ACS

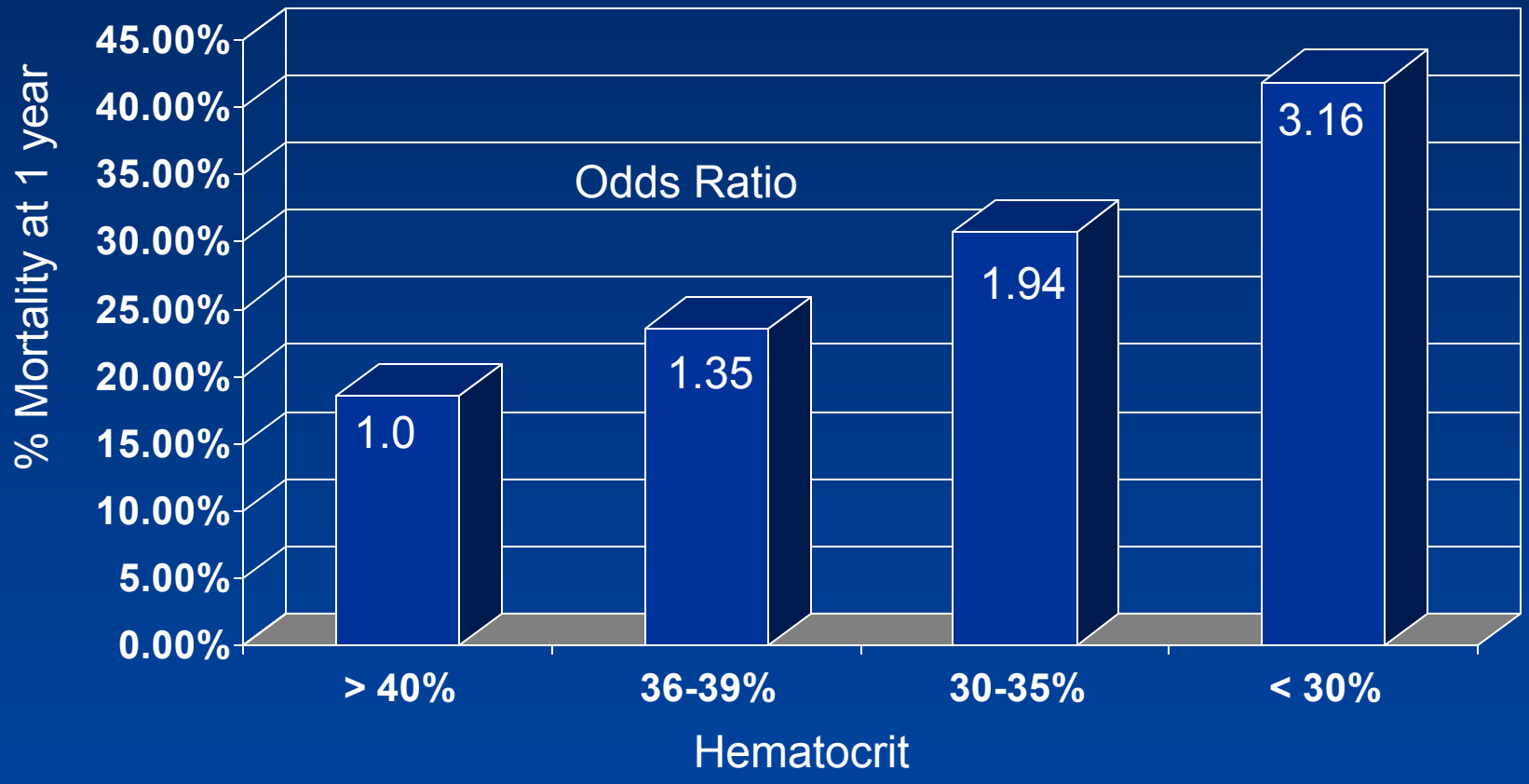
OR & 95% CI for CV Death by 30 d

Hgb (g/dl) value	n	*Unadjusted* OR	(95% CI)	*Adjusted for Baseline Characteristics* OR	(95% CI)	P
>17	968	1.27	(0.90-1.79)	1.79	(1.18-2.71)	0.007
16-17	2783	0.85	(0.65-1.10)	1.08	(0.78-1.52)	0.637
15-16	5702	0.86	(0.70-1.05)	1.08	(0.84-1.39)	0.5302
14-15	6926	1.0	*reference*	1.0	*reference*	
13-14	5077	1.47	(1.22-1.77)	1.17	(0.93-1.47)	0.175
12-13	2502	2.22	(1.82-2.72)	1.40	(1.09-1.80)	0.009
11-12	962	3.29	(2.57-4.21)	1.63	(1.19-2.24)	0.003
10-11	288	3.97	(2.71-5.82)	1.98	(1.24-3.15)	0.004
<10	191	5.07	(3.32-7.73)	2.50	(1.42-4.39)	0.001



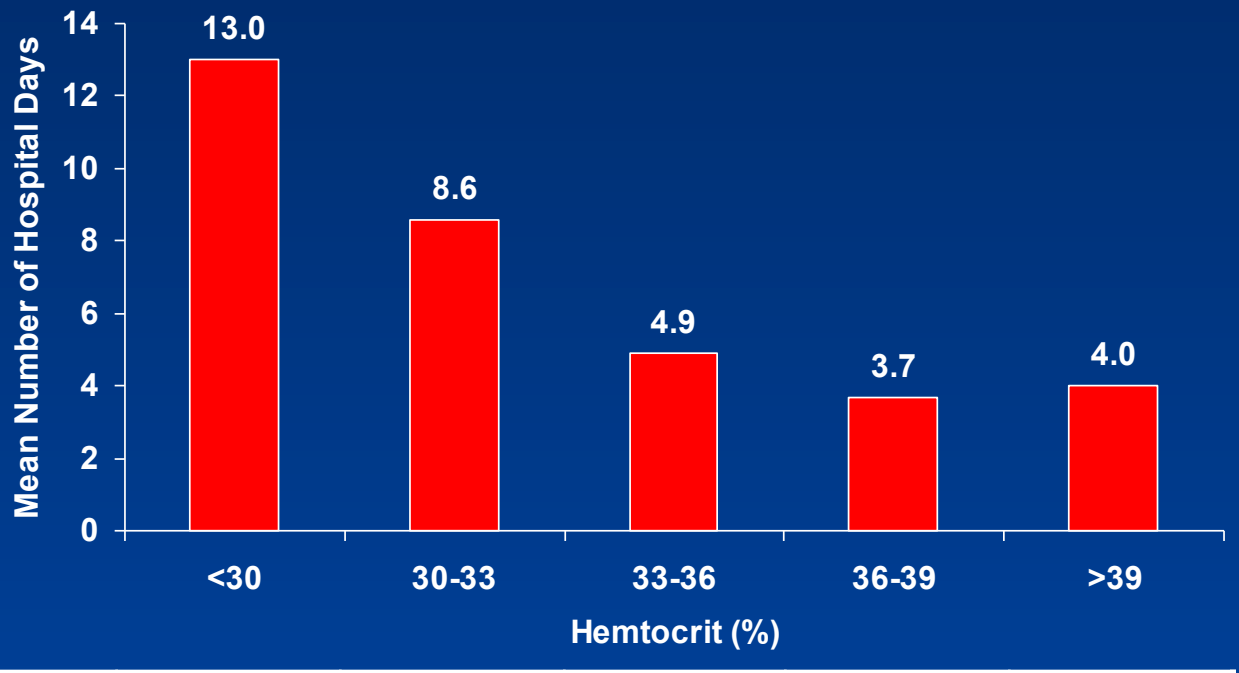
Sabatine et al. Circulation 2005

Acute MI: Higher Hematocrit is Associated with Lower Risk of Death



Langston, Kid Int 2003, 64:1398-1405
Retrospective cohort of 709 Medicare patients admitted to community hospitals for acute MI
Odds Ratio Adjusted for age, sex, race, kidney function and cardiovascular co-morbidities
4% decrease in one year risk of death per 1% increase in hematocrit

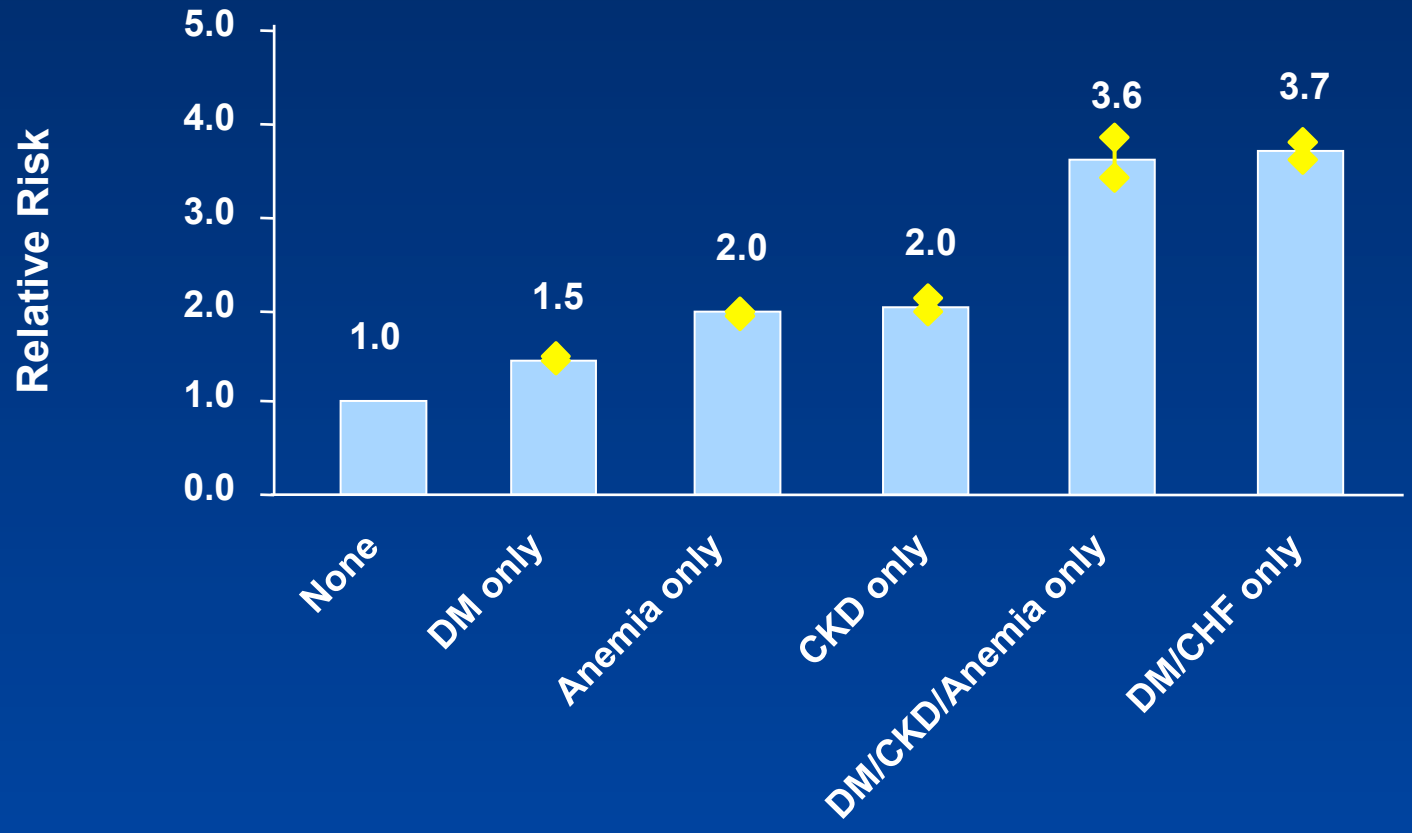
ESRD - USRDS: Higher Hematocrit is Associated with Fewer Hospital Days



N	4,308	11,558	22,192	10,265	2,256

Li & Collins, Kid Int 2004, 65:626-633
50,579 incident HD patients in the US between Jan 98 – Dec 1999
Follow-up 2.5 yrs (hospitalization) and 3.0 yrs (mortality)
Unadjusted data

Anemia, Diabetes and CKD Have Similar Impact on Mortality



Collins, AJ. *Adv Stud in Med.* 2003;3(3C):S14-S17.

Anemia and CKD are Risk Factors for Mortality

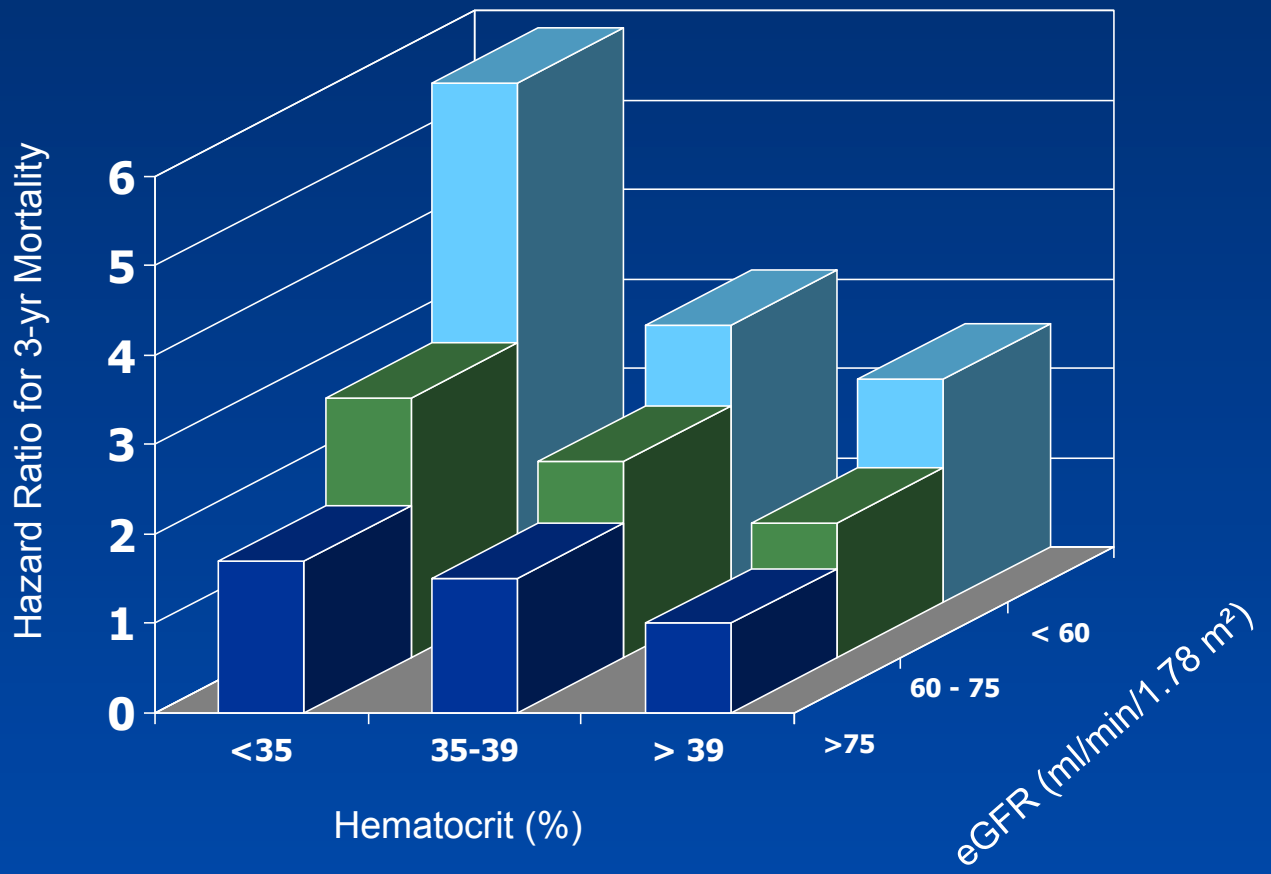
	Unit Change	RR (95% CI)
Hematocrit	1% decrease	1.06 (1.04–1.08)
GFR	10 mL/min decrease	1.06 (1.03–1.10)

Retrospective analysis of 6,635 patients – SOLVD database

Al-Ahmad A, et al. *J Am Coll Cardiol*. 2001;38(4):955-962.

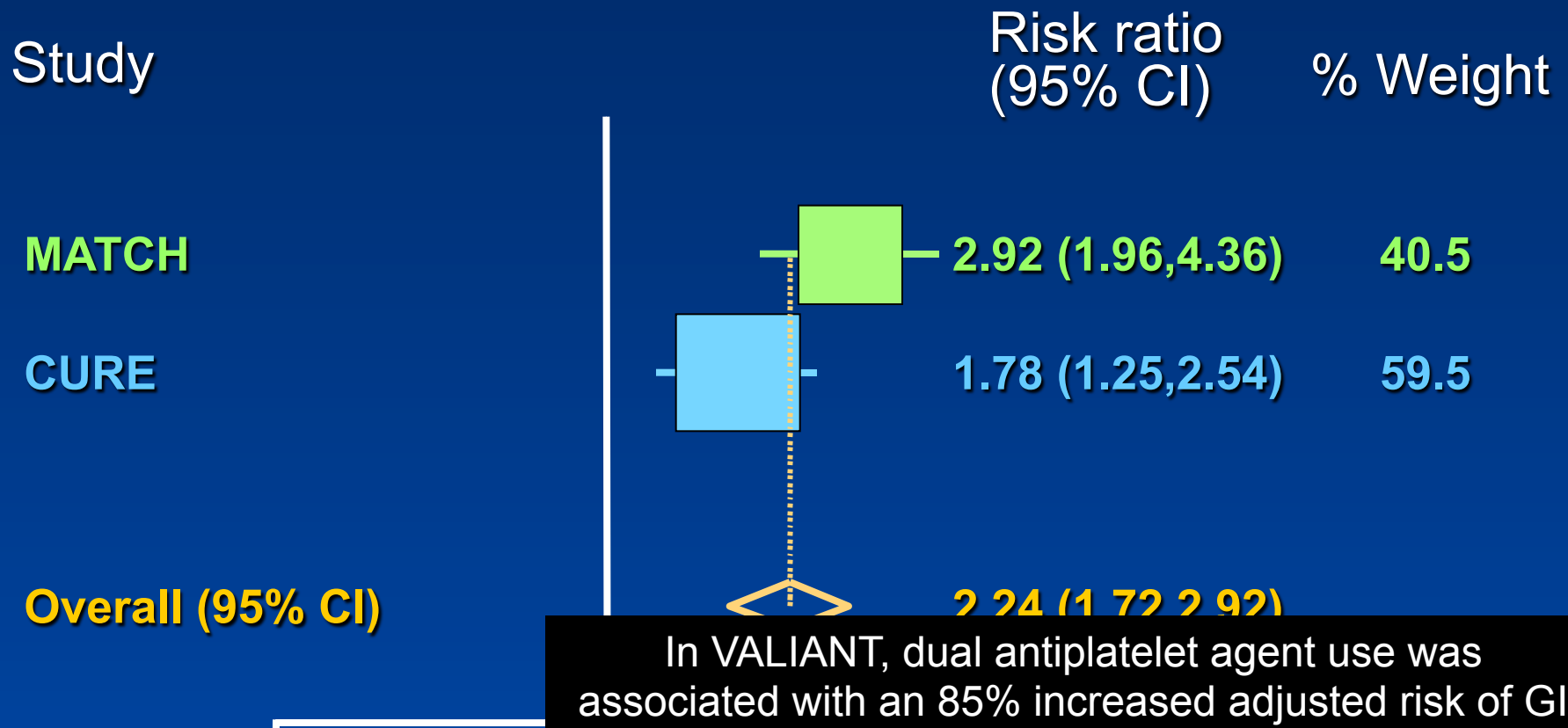
Double Jeopardy of Renal Insufficiency and Anemia in Patients Undergoing Percutaneous Coronary Interventions

Hitinder S. Gurm, MD, A. Michael Lincoff, MD, Neil S. Kleiman, MD, Dean J. Kereiakes, MD, James E. Tcheng, MD, Herbert D. Aronow, MD, MPH, Arman T. Askari, MD, Danielle M. Brennan, MS, and Eric J. Topol, MD



Gurm et al. Am J Cardiol 2004;94:30-4.

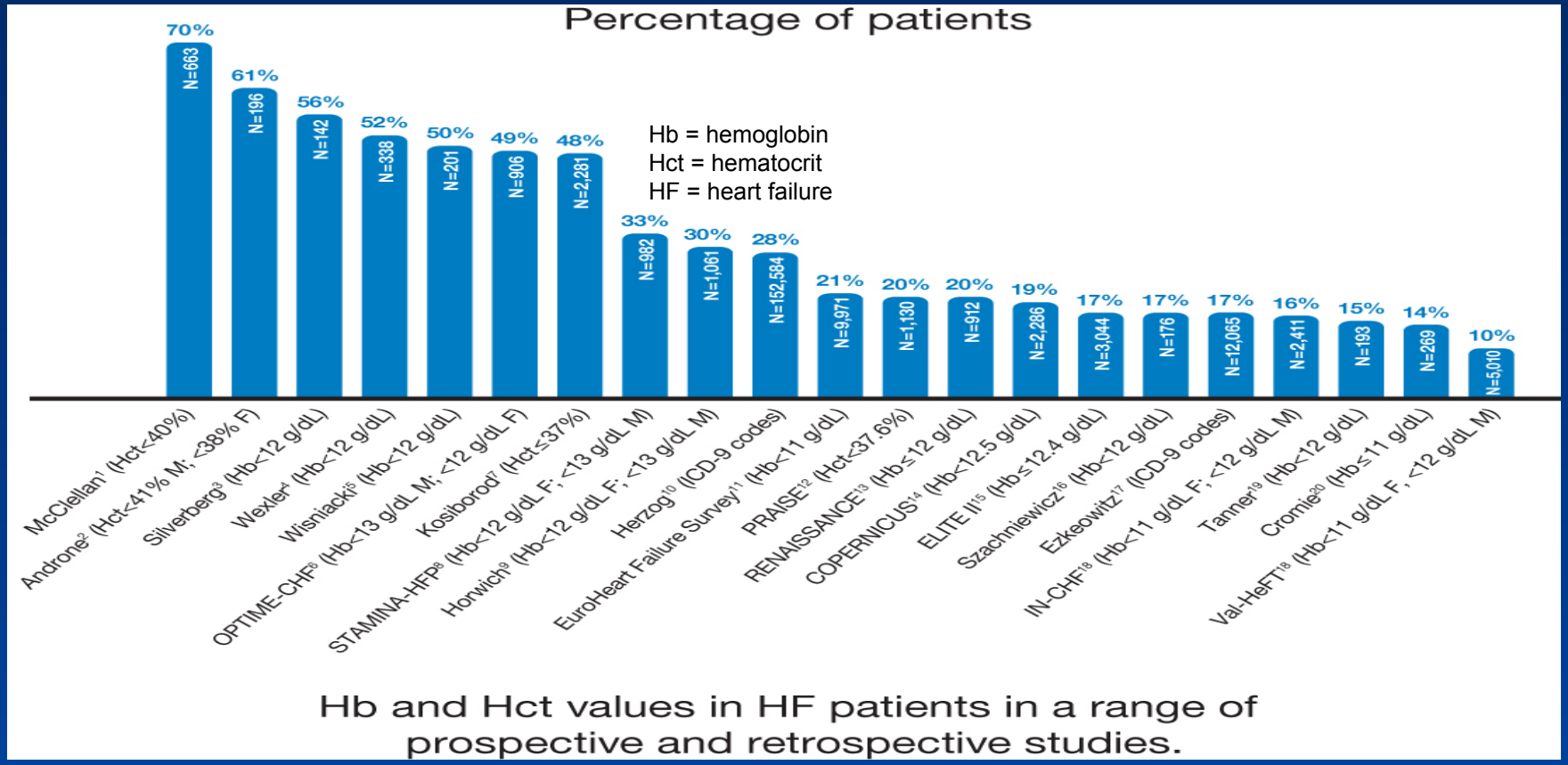
Dual Antiplatelet Agents Increase Risk of GI Bleeding in Cardiac Patients



In VALIANT, dual antiplatelet agent use was associated with an 85% increased adjusted risk of GI bleeding (each 10 points of reduced eGFR increased GI bleeding risk by 20%)

ANEMIA IN HF

Anemia In Patients With Heart Failure

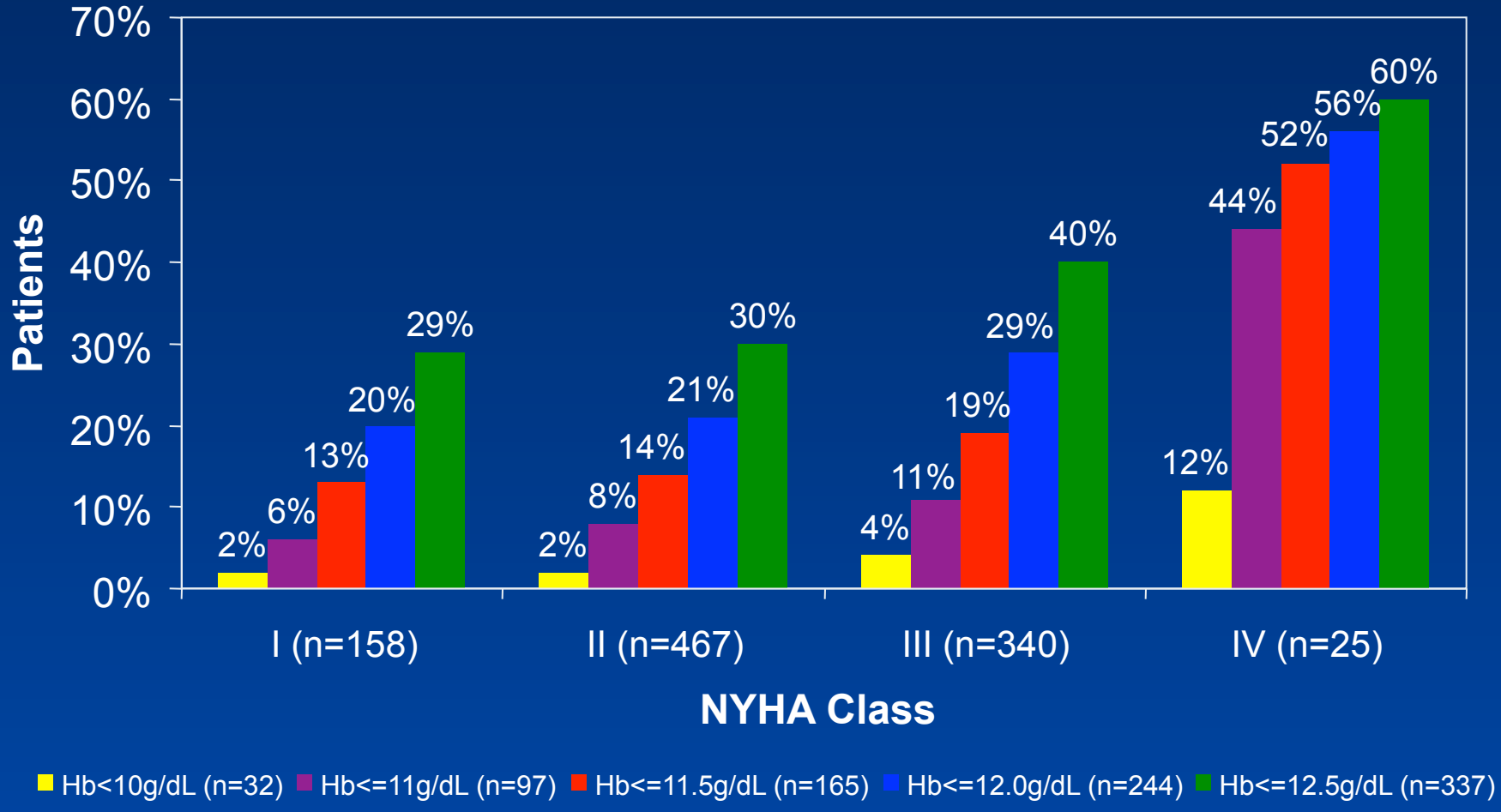


Hb and Hct values in HF patients in a range of prospective and retrospective studies.

The prevalence of anemia in heart failure patients is approximately:

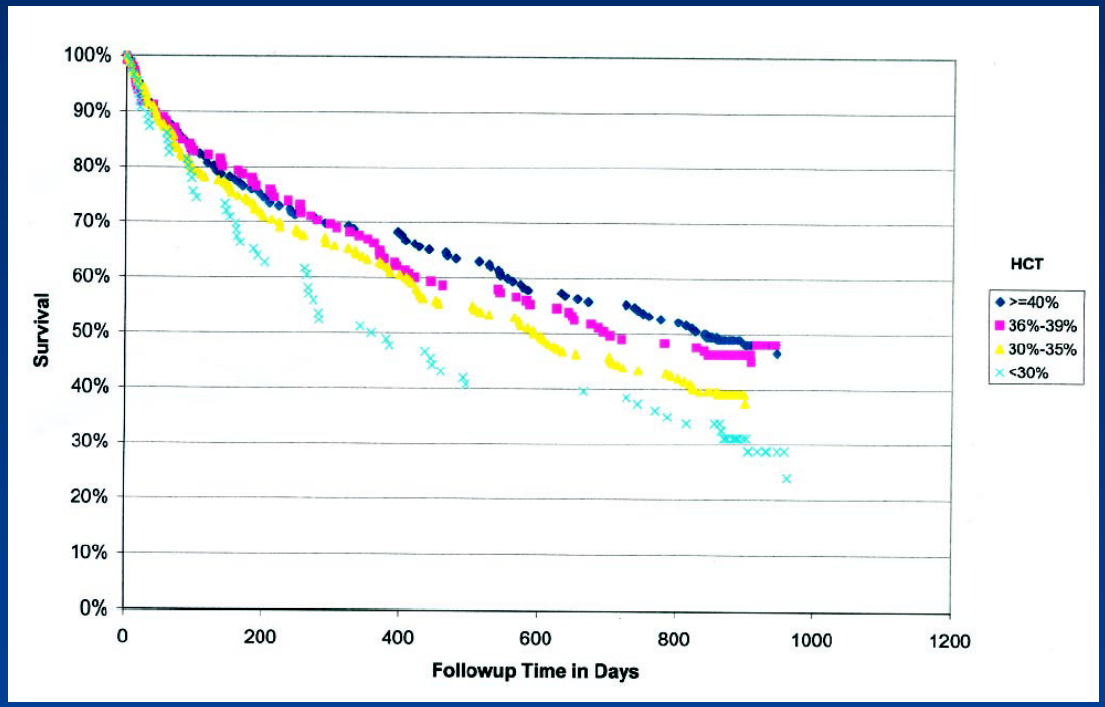
- 30% for Inpatients
- 20% for Outpatients

The Prevalence of Anemia and The Severity Of Heart Failure



Source: STAMINA Registry – 45 General Cardiologist sites, n=673, 12 Academic sites (incl. HF Specialists), n=337

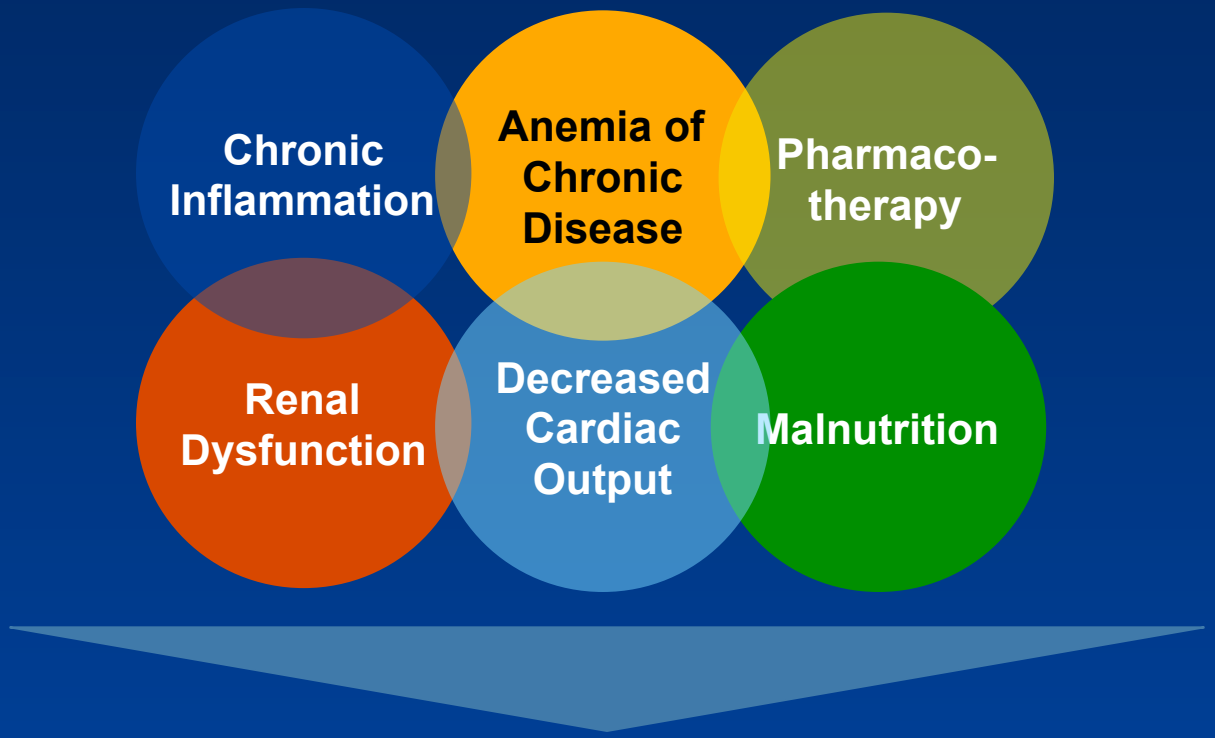
Heart Failure: Higher Hematocrit is Associated with Lower Risk of Death



Hematocrit	%	1 Year Mortality	OR
> 40%	30.3%	31.3%	1.0
36 - 39%	22.9%	33.8%	1.08
30 – 35%	33.2%	36.7%	1.17
< 30%	13.6%	50.0%	1.60

McClellan, JASN 2002, 13:1928-36
Retrospective cohort of 655 Medicare patients admitted to community hospitals for heart failure
Adjusted for age, sex, race, kidney function and cardiovascular co-morbidities
2.4% decrease in one year risk of death per 1% increase in hematocrit

The Etiology of Anemia in Heart Failure is Likely Multifactorial



Bone marrow dysfunction

Abnormal iron homeostasis (uptake, release, utilization)

Intravascular fluid imbalance (hemodilution)

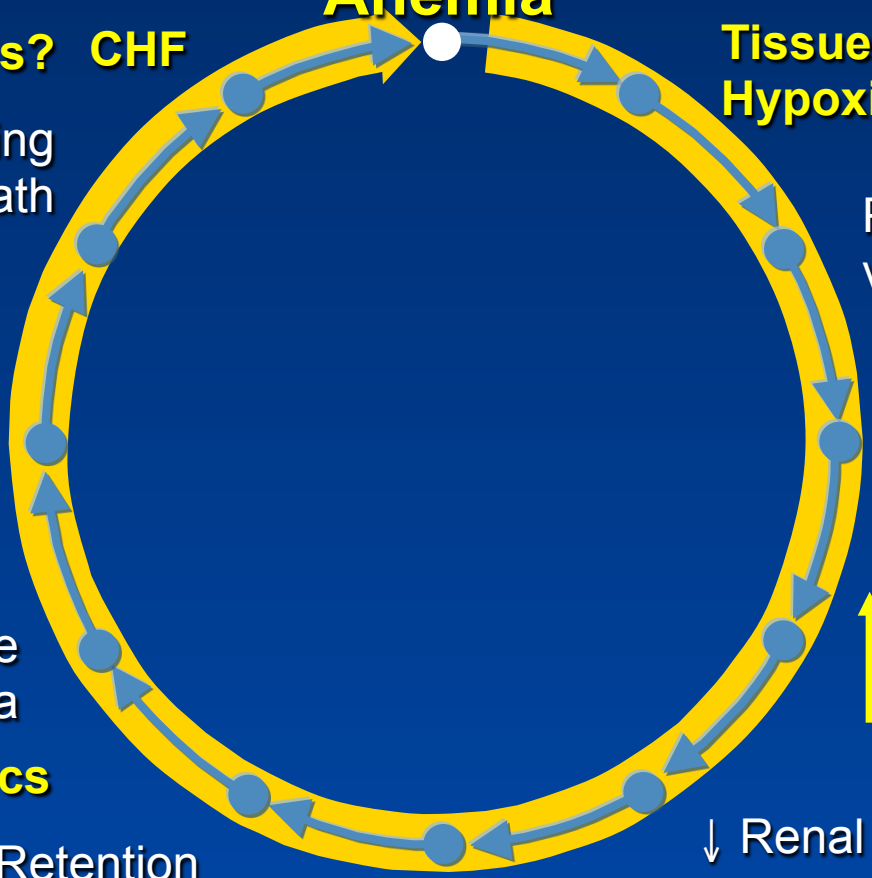
EPO deficiency or resistance

Causes of Anemia in HF

↓ Cardiac Output	• Impaired renal perfusion, leading to impaired renal function, decreased EPO production and anemia[1] • Impaired bone marrow perfusion leading to impaired function and anemia[1]
Cytokines	• TNF and other inflammatory cytokines may cause bone marrow suppression, interfere with the action of EPO and the cellular release and utilization of iron[2]
Iron Deficiency	• Edematous GI may diminish absorption of iron • Chronic aspirin therapy may lead to blood loss
ACE inhibitors	• Down-regulation of EPO by angiotensin-converting enzyme (ACE) inhibitors[3]
Dilutional	• Plasma volume expansion[4]

[1]Chatterjee et al. *Eur J Heart Fail*. 2000;2:393-398. [2]Silverberg et al. *J Am Coll Cardiol*. 2000;35(7)1737-44. [3]Volpe et al. *Am J Cardiol.* 1994;74:468-473. [4]Androne et al. *Circulation.* 2003;107:226-229.

Pathophysiology of Anemia in CHF



Anemia
Tissue Hypoxia
↓ Blood pressure
Activation of SNS
↓ Renal blood flow
↑ Renin Angiotensin Aldosterone ADH
Increased Retention
↑ Diuretics
↑ Plasma volume … Edema
↑ LV Mass
↑ LV diameter
Remodeling LVH … cell death
Apoptosis?
CHF
↑ Inflammation
↓ Exercise
Peripheral vasodilation

Adapted from Okonko & Anker. *J Cardiac Failure*. 2004;10(suppl):S5-S9.

Patients with Anemia Have Worse Heart Failure: Val-HeFT Database

Baseline Variables	No Anemia (n = 3857)	Anemia (n = 1145)	P-value
Age ≥65 yrs %	62±11	66 ±11	<0.001
NYHA III-IV %	36	45	<0.001
History of PND %	8	11	<0.001
SBP (mmHg, mean±SD)	124.2±18	122.6±18	<0.001
Edema (%)	23	38	<0.001
GFR (ml/min/1.73m^2)	60±15	52 ±17	<0.001
MLHFQ score (mean±SD)	31±23	35±24	<0.001
Background therapy, %			
Diuretics	84	91	<0.001
Digoxin	66	70	0.02
Serum Albumin (g/L, mean±SD)	4.2±0.3	4.0±0.4	<0.001
CRP (pg/mL, mean±SD)	5.7±8.9	8.9±12.9	<0.001
BNP (pg/mL, mean±SD)	162±210	242±276	<0.001
LVEF % (mean±SD)	**27±7**	**26±7**	**0.21**
LVIDd/BSA cm/m2 (mean±SD)	**3.6±0.5**	**3.7±0.5**	**0.09**

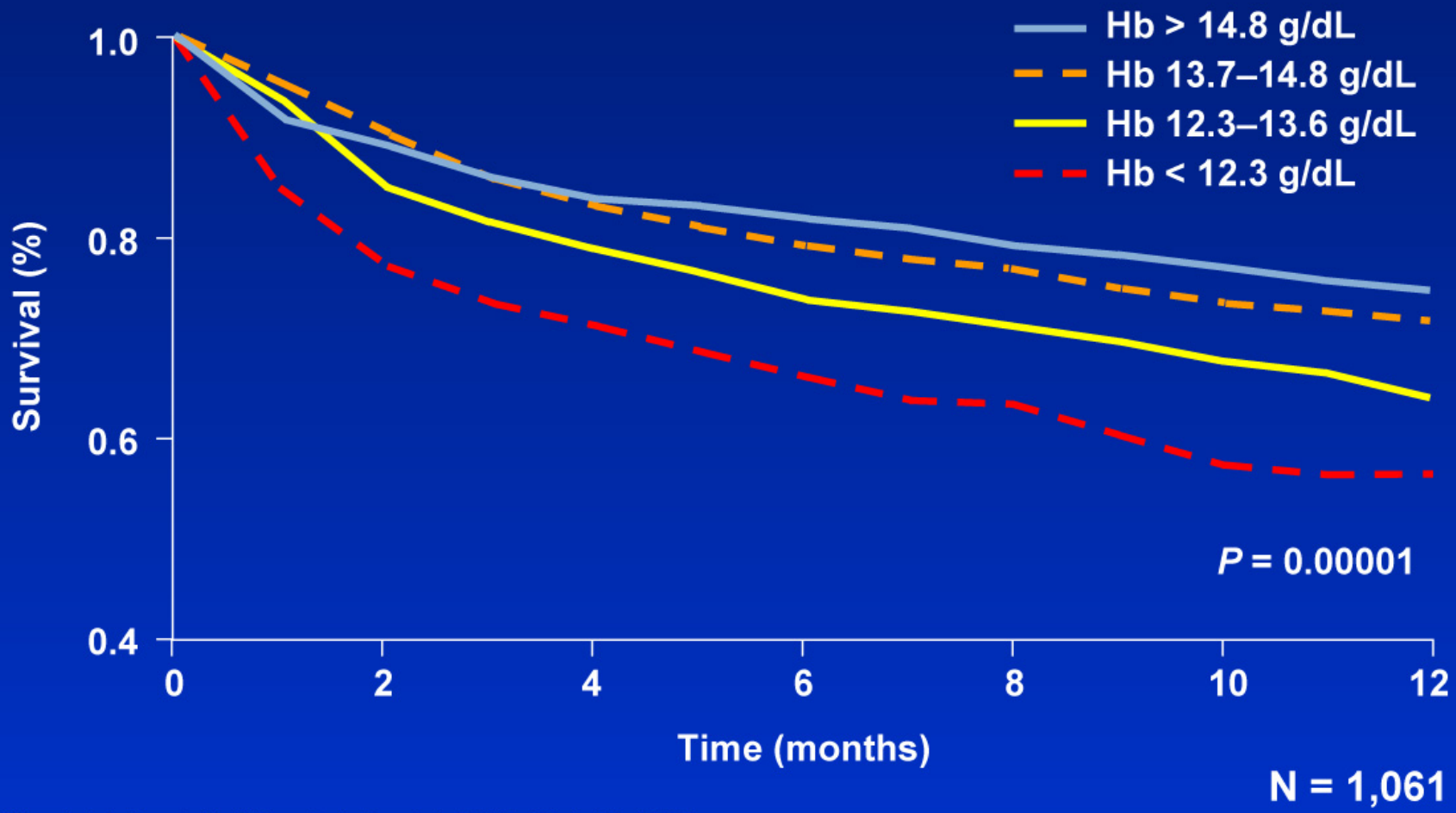
Anand et al 2005, Circulation ;112:1121-1127

Anemia is Associated with Increased Risk for Hospitalization in Heart Failure Patients

Study	Design	N	Anemia Risk Assessment	Limitations
Alexander[1]	Retrospective cohort study of a population based HF database	90,316	Anemia was an independent risk factor of 1-year rehospitalization (RR 1.162; 95% CI: 1.134 to 1.191)	no confirmation of the HF diagnosis; undercounts of minorities and biased results.
Polanczyk[2]	Prospective, single center, observational study	205	Anemia was an independent predictor of 3-month rehospitalization (p=0.002)	Too small of a population to resolve a small difference in readmission rates; role of confounding variables due to lack of control
OPTIME-CHF[3]	Retrospective chart review	906	Anemia was an independent predictor of 60-day death or rehospitalization (odds ratio of 0.89 per 1 g/dL increase in hemoglobin; 95% CI: 0.82 to 0.97)	Anemia may have been caused by hemodilution in hospitalized patients
Kosiborod[4]	Retrospective chart review	2,281	Patients had 2% higher risk of 1-year rehospitalization for every 1% lower hematocrit (95% CI: 1.01 to 1.03; p=0.0002)	Lack of data on transfusions or other treatments for anemia; study generalizability to non-study population
COPERNICUS[5]	Randomized, double blind, placebo controlled trial	2,286	Anemia was an independent risk factor for 1-year morbidity (HF hospitalization) and mortality outcomes	-

[1]Alexander M, et al. *Am Heart J.* 1999;137:919-927
[2]Polanczyk CA, et al. *J Card Failure.* 2001;7:289-298
[3]Felker GM, et al. *Am J Cardiol.* 2003;92:625-628
[4]Kosiborod M, et al. *Am J Med.* 2003;114:112-119
[5]Anker SD, et al. *J Am Coll Cardiol.* 2004;43(suppl A):Abstract 842-2

Hemoglobin and Mortality in Heart Failure Patients

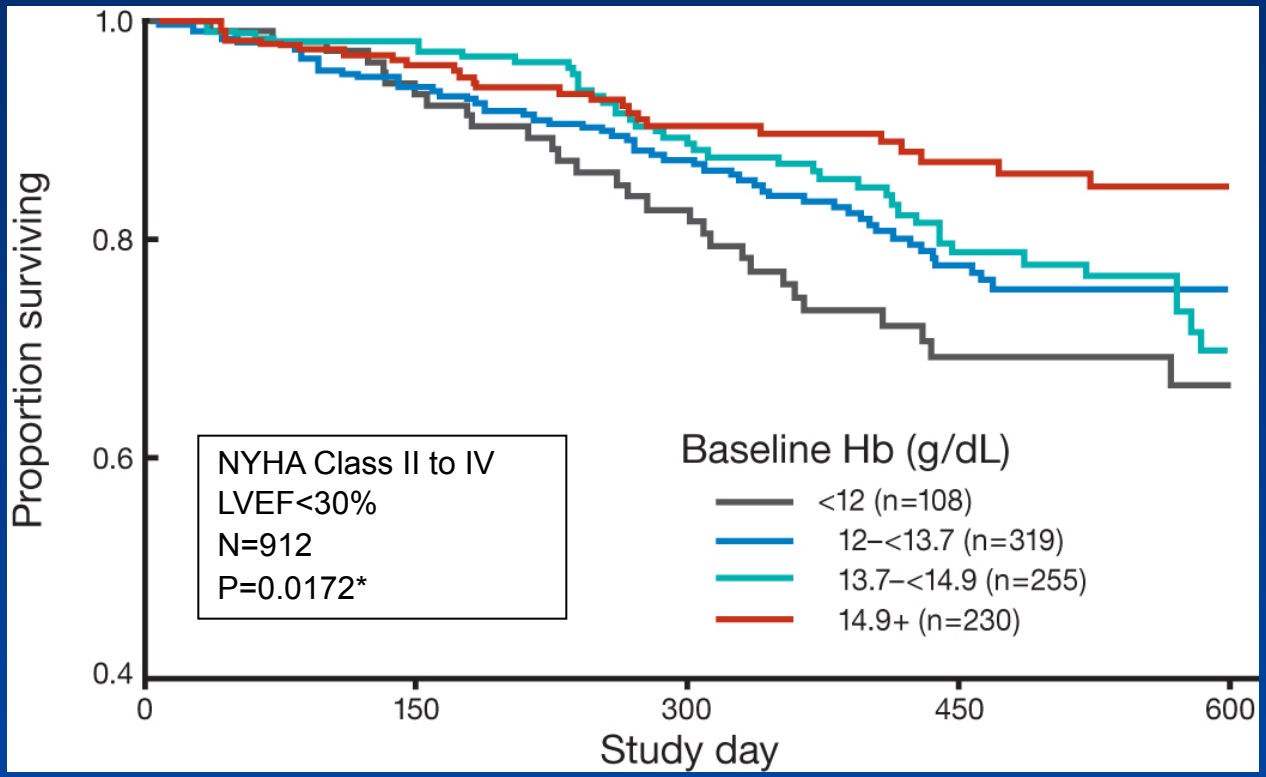


Horwich TB, et al. *J Am Coll Cardiol*. 2002;39:1780-1786.

Anemia and Mortality In Heart Failure Patients: RENAISSANCE

RENAISSANCE Study[1]

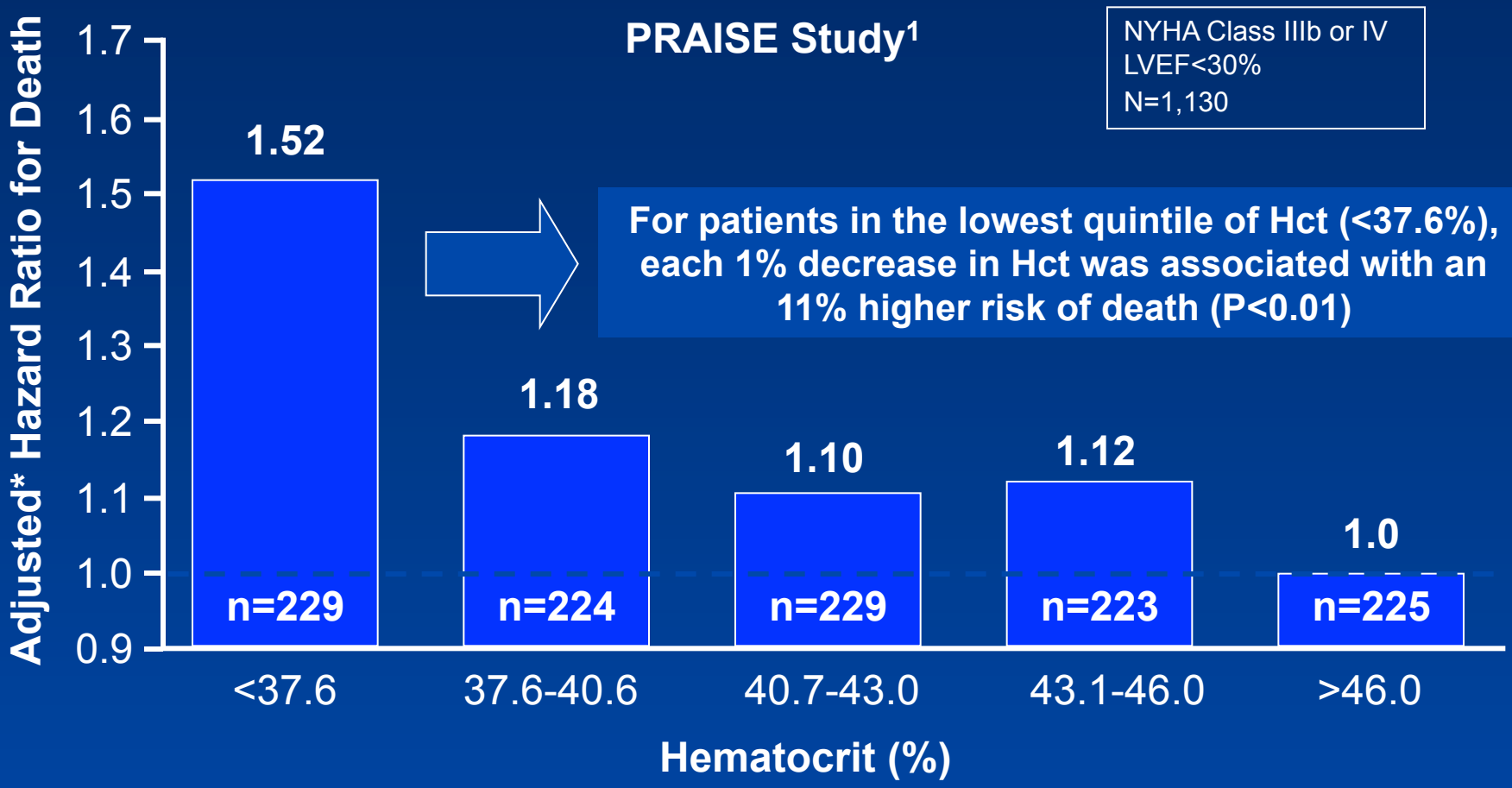
Kaplan-Meier Survival Curve by Baseline Hb Concentration



*Log-rank test; 1-year mortality was 28% in anemic subjects (Hb<12 g/dL) vs. 16% in non-anemic subjects

[1]Anand et. al., *Circulation*. 2004;110:149-154

Anemia and Mortality In Heart Failure Patients: PRAISE



*Adjusted for age, gender, diabetes, smoking, heart failure etiology, EF, NYHA Class, systolic BP, WBC count & serum creatinine

[1]Mozaffarian et al. *J Am Coll Cardiol.* 2003;41:1933-1939

Severity Of Anemia and the Risk For Death Or Heart Failure Hospitalization

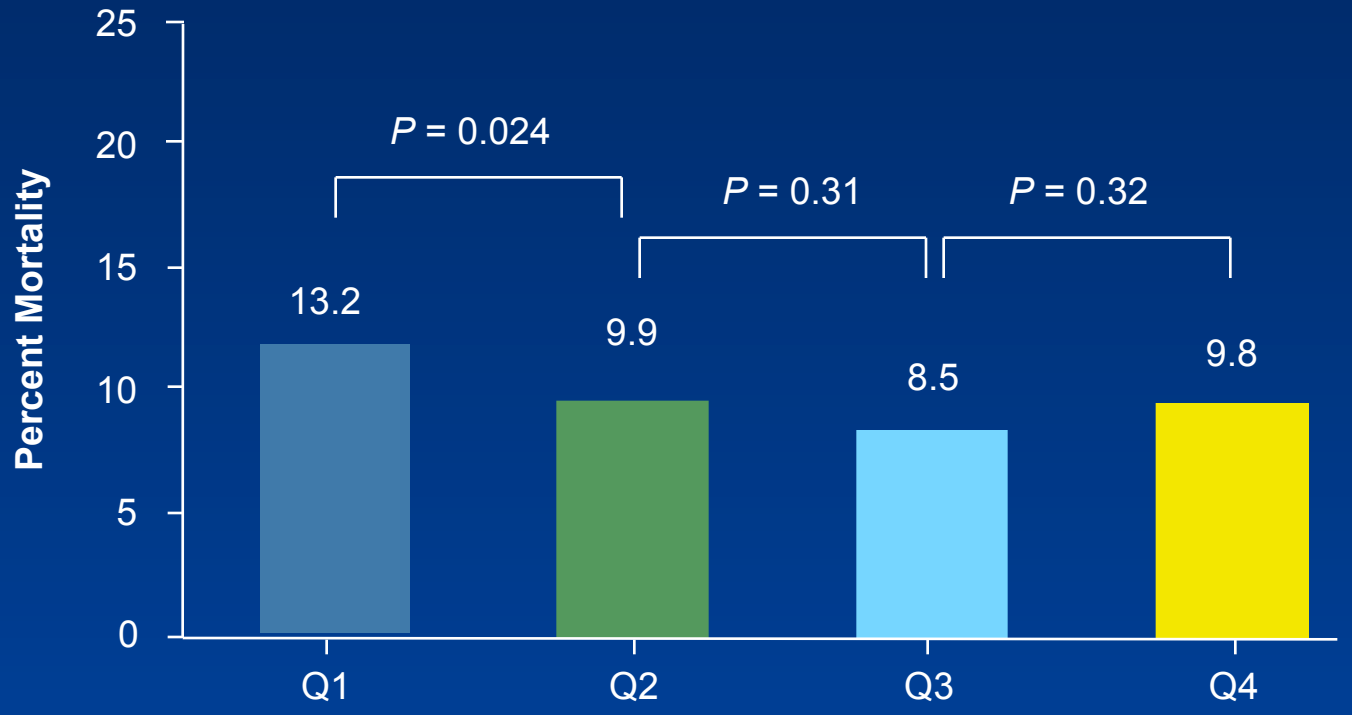
COPERNICUS Study[1]

Hemoglobin (g/dL)	1-Year Death or HF Hospitalization Kaplan-Meier Event Rates (%)	N
<11	46.6	115
11 to <12.5	36.1	315
12.5 to <13.5	30.5	432
13.5 to <15	31.9	834
15 to 16.5	26.5	463
>16.5	25.5	127

N=2,286; LVEF<25%; severe HF with dyspnea or fatigue at rest or on minimal exertion

[1]Anker SD, et al. *J Am Coll Cardiol.* 2004;43(suppl A):Abstract 842-2

Worsening of Hb from Baseline to 12 Months was Associated with Increased Mortality in Val-HeFT



Quartile change in Hgb, g/dL	< - 0.8	> - 0.8 to < -0.1	> - 0.1 to < + 0.5	≥ + 0.5
Mean change in Hgb, g/dL	- 1.66	- 0.47	+ 0.15	+ 1.11
Mean BL Hgb, g/dL	14.24	13.92	13.71	13.30
Mean 12 month Hgb, g/dL	12.58	13.44	13.86	14.40
Number of patients	950	991	937	1028

Anand et al 2005, Circulation ;112:1121-1127

CHARM Programme

3 component trials comparing candesartan to placebo in patients with symptomatic heart failure

CHARM Alternative	CHARM Added	CHARM Preserved
n=2028	n=2548	n=3025
LVEF ≤40% ACE inhibitor intolerant	LVEF ≤40% ACE inhibitor treated	LVEF >40% ACE inhibitor treated/not treated

Primary outcome for each trial: CV death or CHF hospitalisation

Primary outcome for Overall Programme: All-cause death

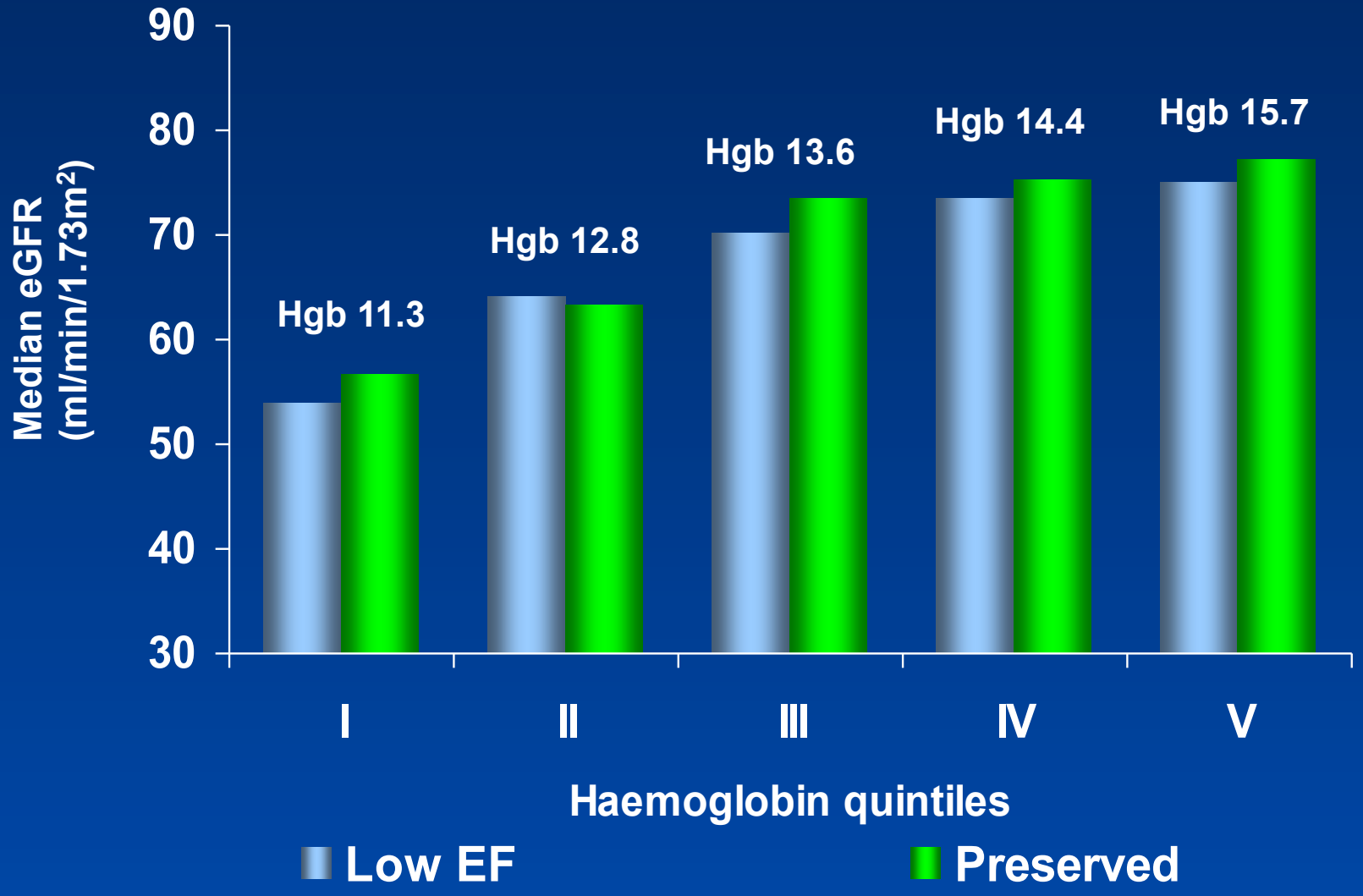
Relevant exclusions

- Serum creatinine ≥ 265 µmol/l (3 mg/dl)
- Known bilateral RAS
- Haemoglobin/anaemia NOT specifically mentioned

Baseline characteristics

	Alternative	Added	Preserved	Overall
n=2028	n=2548	n=3023	n=7599	
Mean age (years)	67	64	67	66
Women (%)	32	21	40	32
NYHA class (%)				
II	48	24	60	45
III	49	73	38	52
IV	3	3	2	3
Mean LVEF	30	28	54	39
Medical history (%)				
myocardial infarction	61	56	44	53
diabetes	**27**	**30**	**28**	**28**
hypertension	50	48	64	55
atrial fibrillation	25	26	29	27

Median eGFR and Haemoglobin quintiles



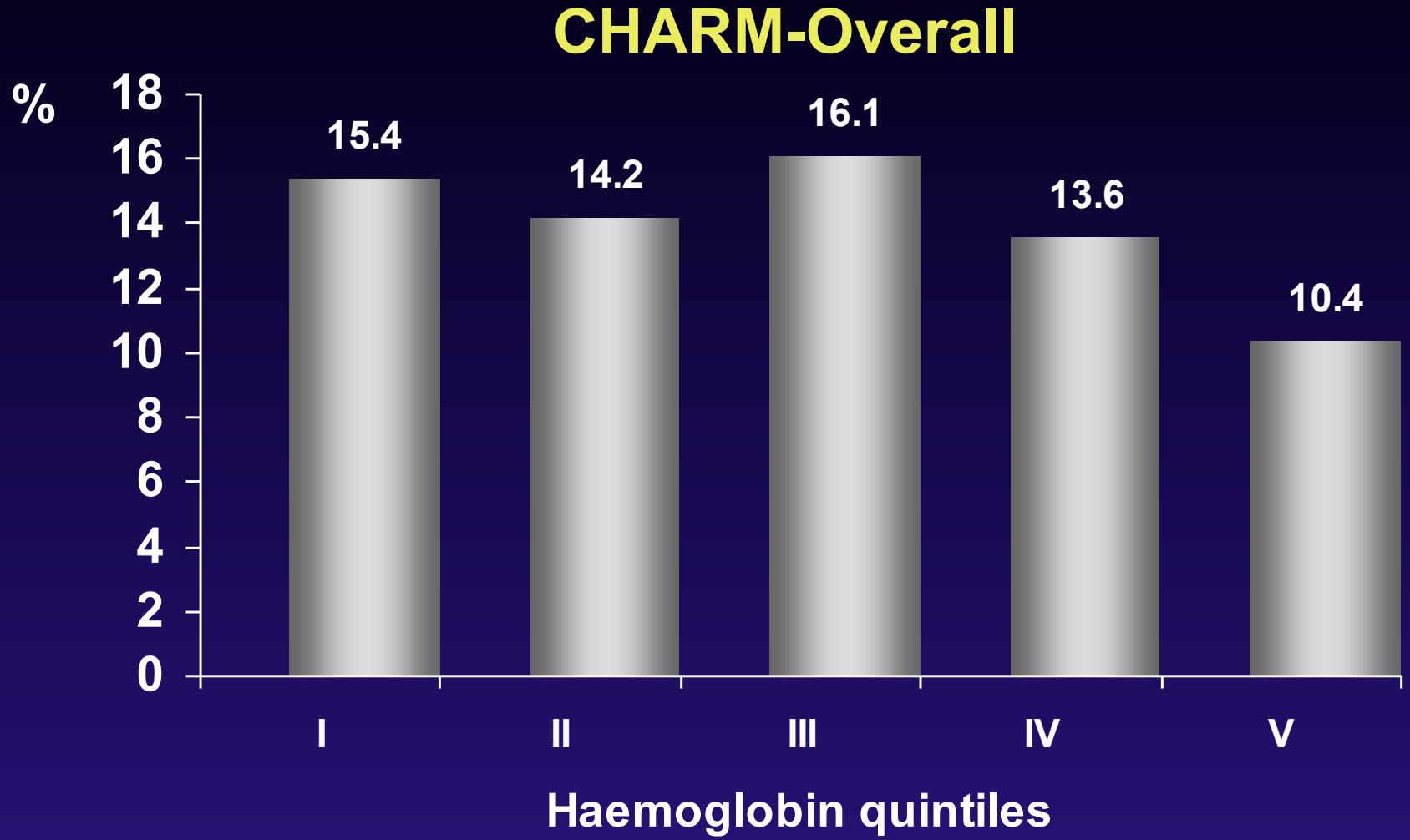
O'Meara et al. CHARM Investigators. Circulation 2006

CHARM anemia independent of GFR

Measurement	All Patients		
	Anemia (n=677)	No Anemia (n=1976)	*P**
eGFR, mL · min^{-1} · 1.73 m^{-2}			
Mean	60.5	75.0	<0.001
eGFR ≥90, %	11.7	24.8	<0.001
eGFR ≥60, %	44.9	70.5	<0.001
eGFR <30, %	9.0	1.7	<0.001

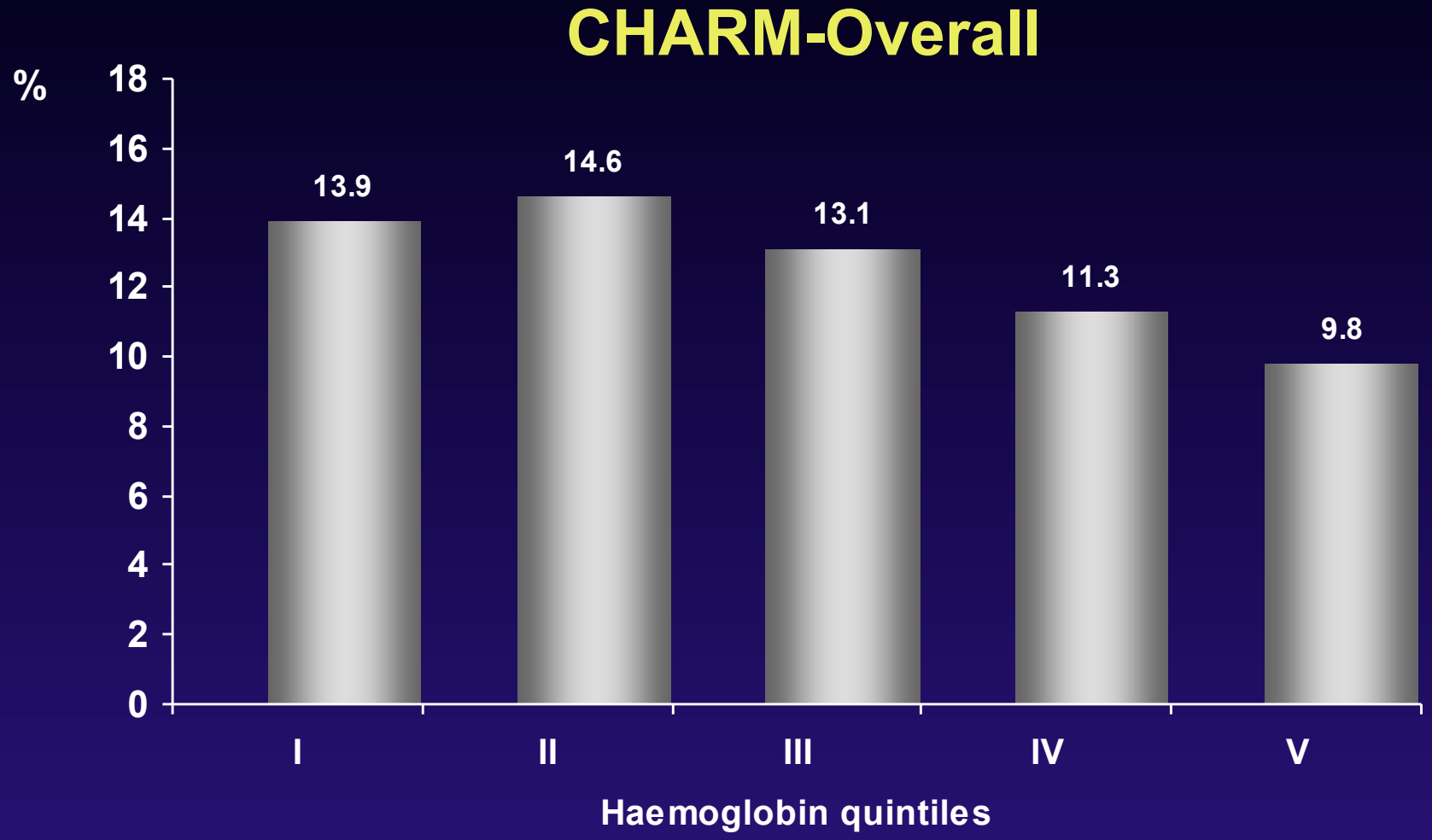
O'Meara et al. CHARM Investigators. Circulation 2006

Relationship between haemoglobin and ECG LVH



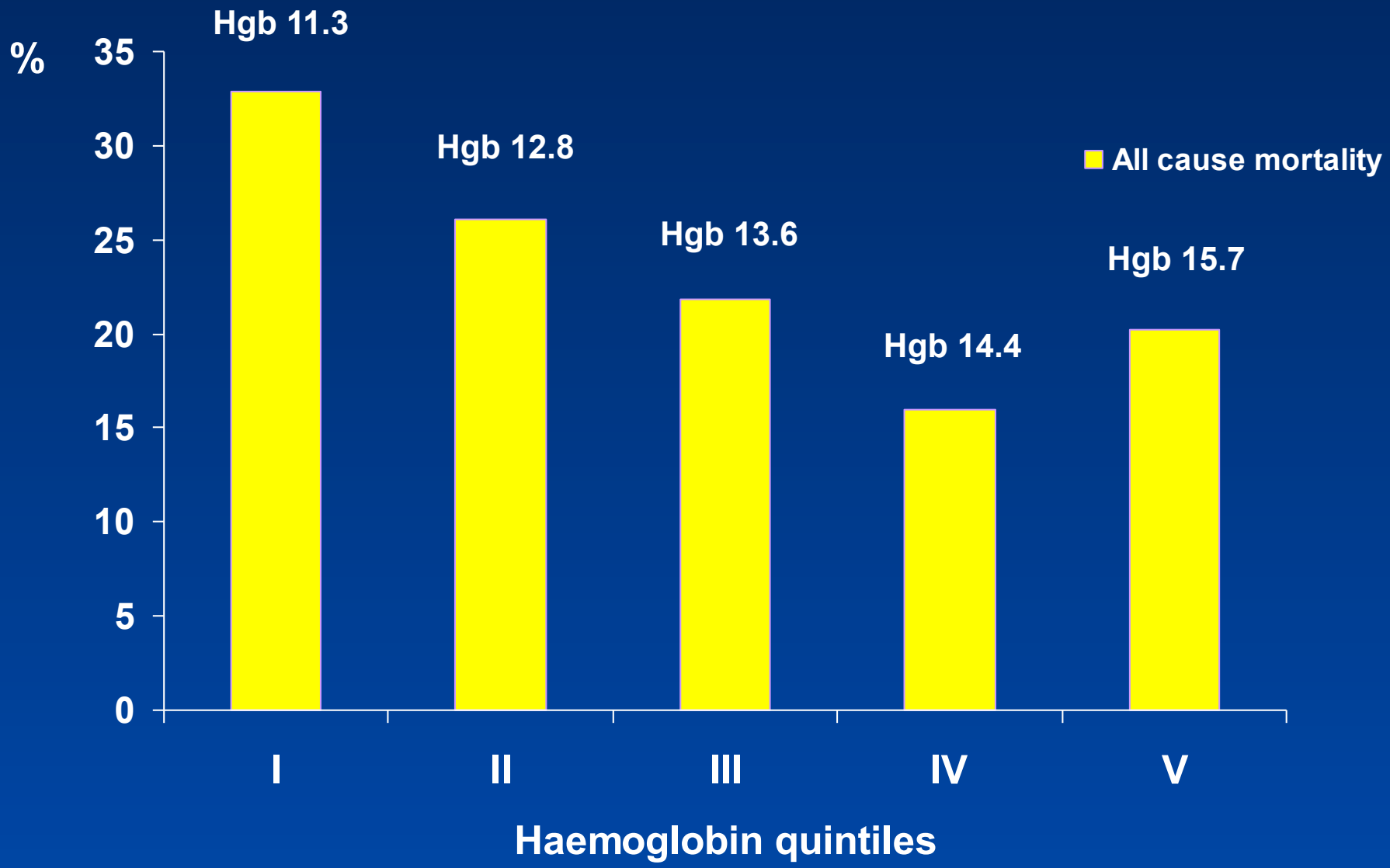
O'Meara et al. CHARM Investigators. Circulation 2006

Relationship between haemoglobin and radiological cardiomegaly



O'Meara et al. CHARM Investigators. Circulation 2006

Hemoglobin and Mortality



O'Meara et al. CHARM Investigators. Circulation 2006

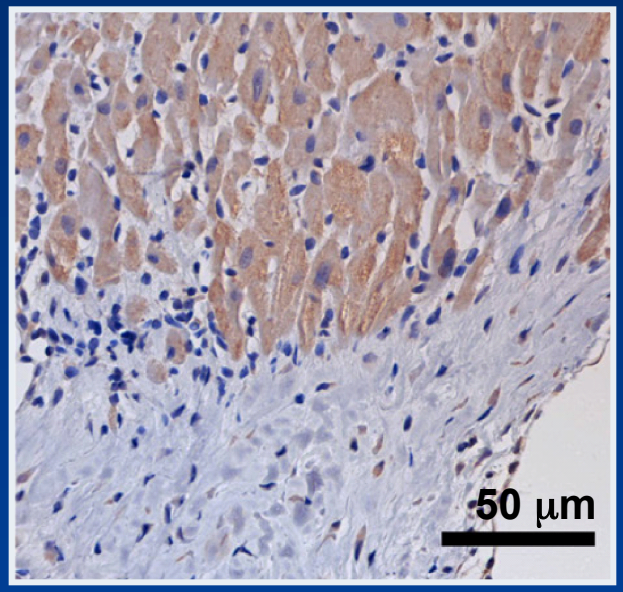
Rationale for Anemia Correction

Potential Benefits of Treating Anemia in CVD

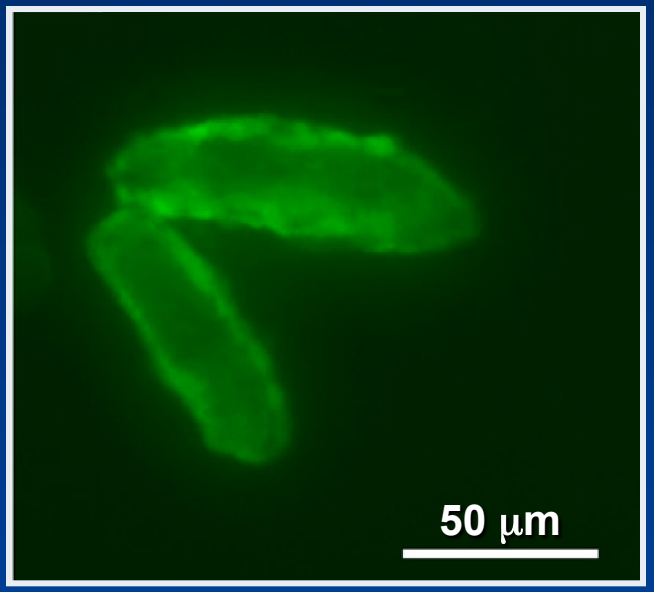
- Improved oxygen delivery
- Improved exercise tolerance
- Attenuate adverse remodeling
- Improved QoL
- Antiapoptotic?
- Decrease in hosp./death?

Adapted from Felker and O' Connor *J Am Coll Cardiol*. 2004;44:959-966.

Erythropoietin Receptors are Present on *Adult* Cardiac Myocytes



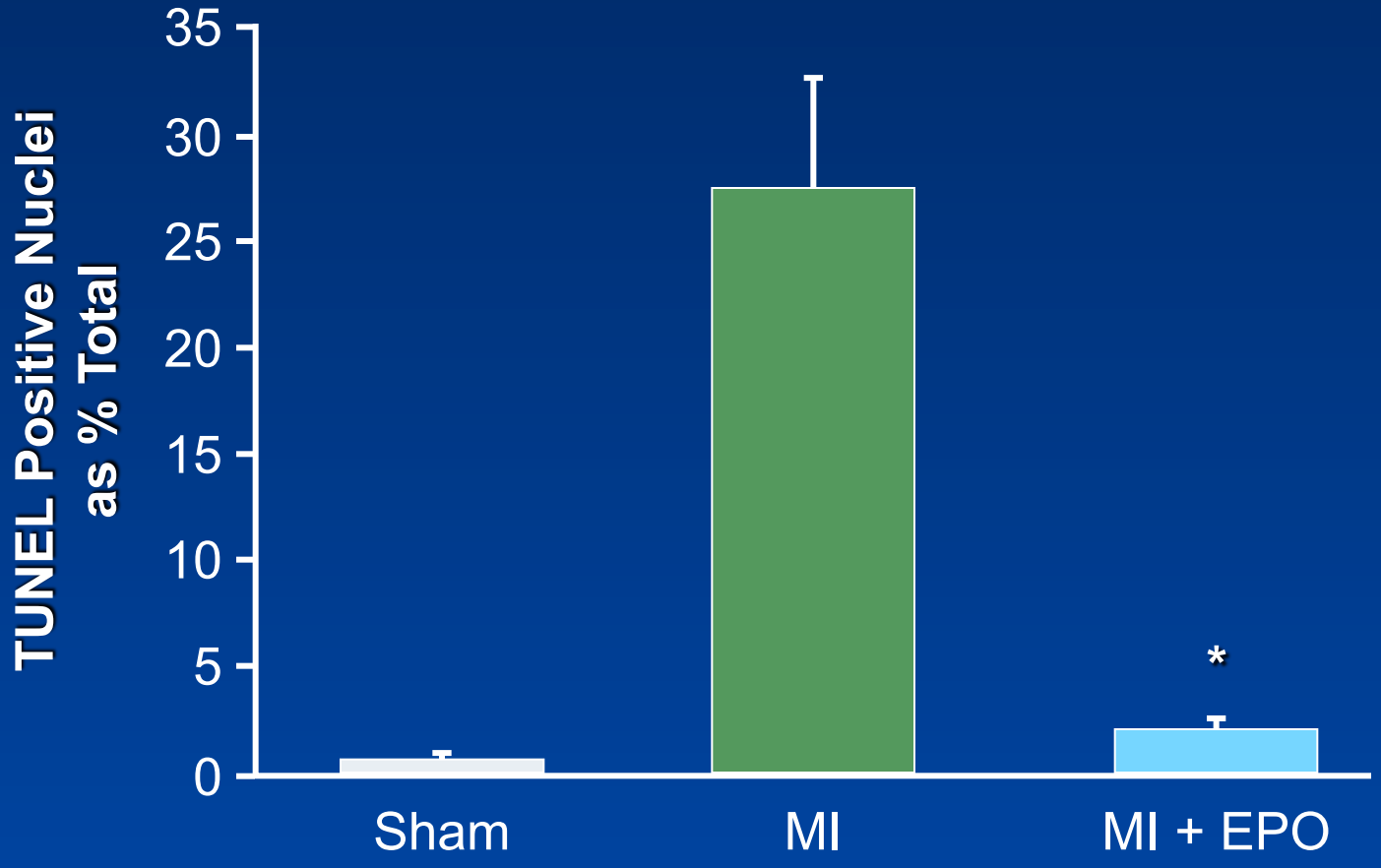
EPOR protein in adult rat heart sections using immuno-histochemistry



EPOR protein in isolated adult rat cardiac myocytes visualized by fluorescence microscopy

Wright et al. 2004. FASEB.

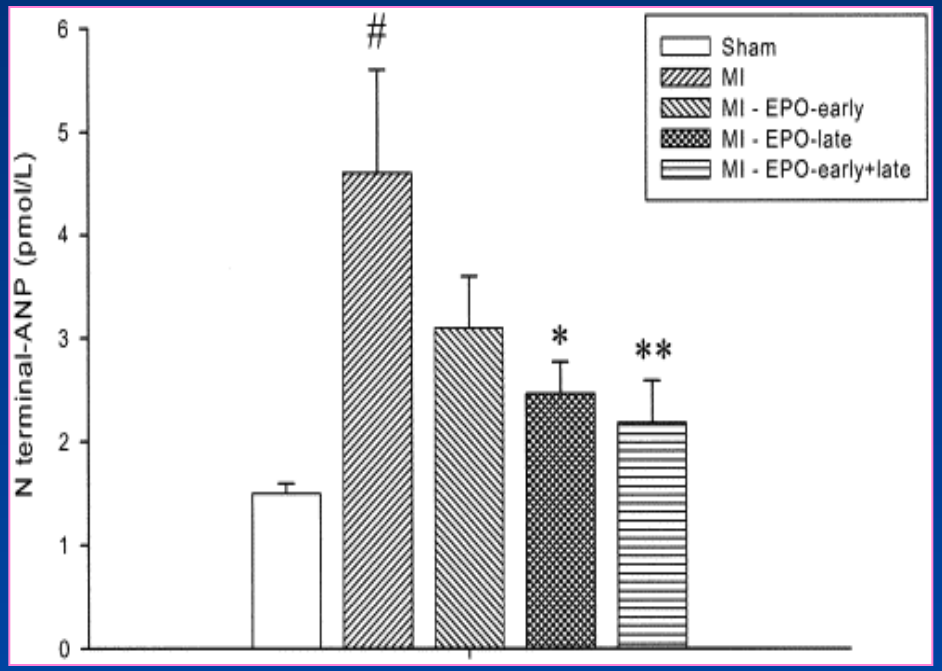
EPO Administered at time of LAD Ligation Reduces Myocyte Apoptosis



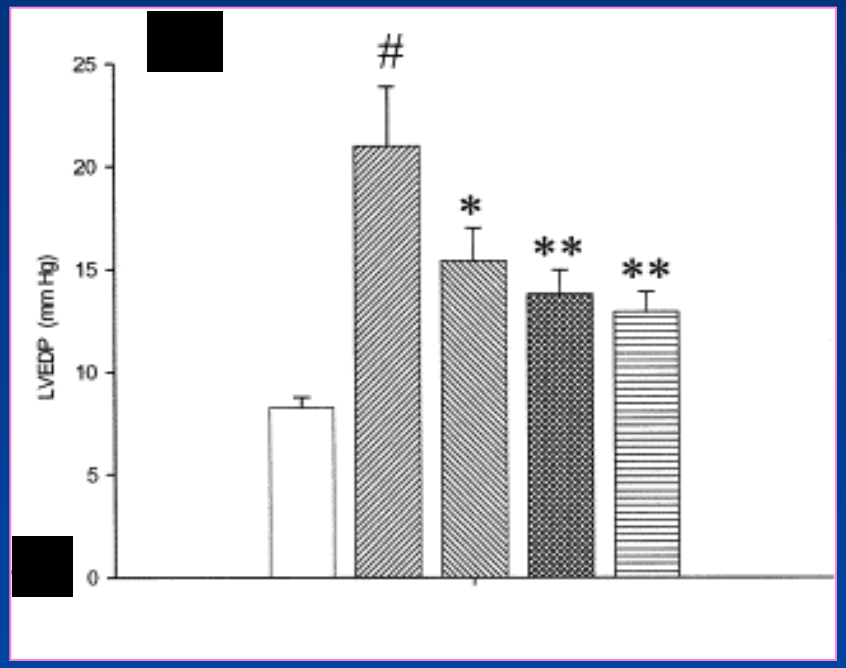
Tramontano et al. *Biochem Biophys Res Commun*. 2003;308:990-994.

Effect of EPO on Cardiac Function in Rats Post-MI

N-terminal ANP plasma levels (pmol/L)



LVEDP (mmHg)



*p <0.05 vs MI; **p <0.01 vs MI; #p <0.01 vs sham

Van der Meer P, et al. JACC 2005

Clinical Trials of Anemia Correction with Erythropoeitin

Studies Evaluating The Effect Of Treatment Of Anemia With Recombinant Human Erythropoietin (rHuEPO) In Heart Failure Patients

Study	N	Mean changes in selected endpoints	P Value
Silverberg et al. 2000[1] • No control group • Not blinded	26	NYHA class (3.66 → 2.66) LVEF (27.7% → 35.4%) Number of hospitalizations/patient (2.72 → 0.22)	<0.05 <0.001 <0.05
Silverberg et al. 2001[2] • Randomized control group • Not blinded, no placebo	32	NYHA class (3.8 → 2.2; 3.5 → 3.9 for control) LVEF (30.8% → 36.3%; 28.4% → 23.0% for control) Hospital days (13.8 → 2.9; 9.9 → 15.6 for control)	<0.0001 <0.013 <0.03
Silverberg et al. 2003[3] • No control group • Not blinded	179	NYHA class (3.90 → 2.54) LVEF (34.9% → 38.7%) Number of hospitalizations/patient (2.90 → 0.12) Fatigue, shortness of breath VAS (8.76 → 2.75)	<0.05 <0.05 <0.05 <0.05
Mancini et al. 2003[4] • Randomized, placebo controlled • Single blinded	23	Hb (11.0 ± 0.6 →14.3 ± 1.2 g/dL; 10.9 ± 1.1→11.5±1.3 g/dL for control Peak VO_2 (11± 0.8 → 12.7 ± 2.8 ml/kg/min; 10.0±1.9 → 9.5 ± 1.6 ml/kg/min for control) Exercise Duration (590 ± 107→ 657±119 sec; 542 ± 115→ 459 ±172 sec for control) 6-min walk (1187 ± 279→1328 ± 254 ft; 929 ± 356 → 1052 ± 403 ft for control) MLHFQ (9 point decrease for EPO; 10 point increase for control)	<0.0001 <0.05 <0.004 <0.05 <0.04
Silverberg et al. 2005[5] • No control group • Not blinded	78	NYHA class (3.7 → 2.5) LVEF (33.3% → 36.9%) Number of hospitalizations/patient (2.7 → 0.7)	<0.01 <0.01 <0.01

[1] *J Am Coll Cardiol*. 2000;35(7):1737-1744
[2] *J Am Coll Cardiol*. 2001;37(7):1775-1780
[3] *Nephrol Dial Transplant*. 2003;18:141-146
[4] *Circulation*. 2003;107:294-299
[5] *Kidney Blood Press Res*. 2005;28:41-47

Congestive Heart Failure (CHF) and CKD: Clinical Benefit of Anemia Correction

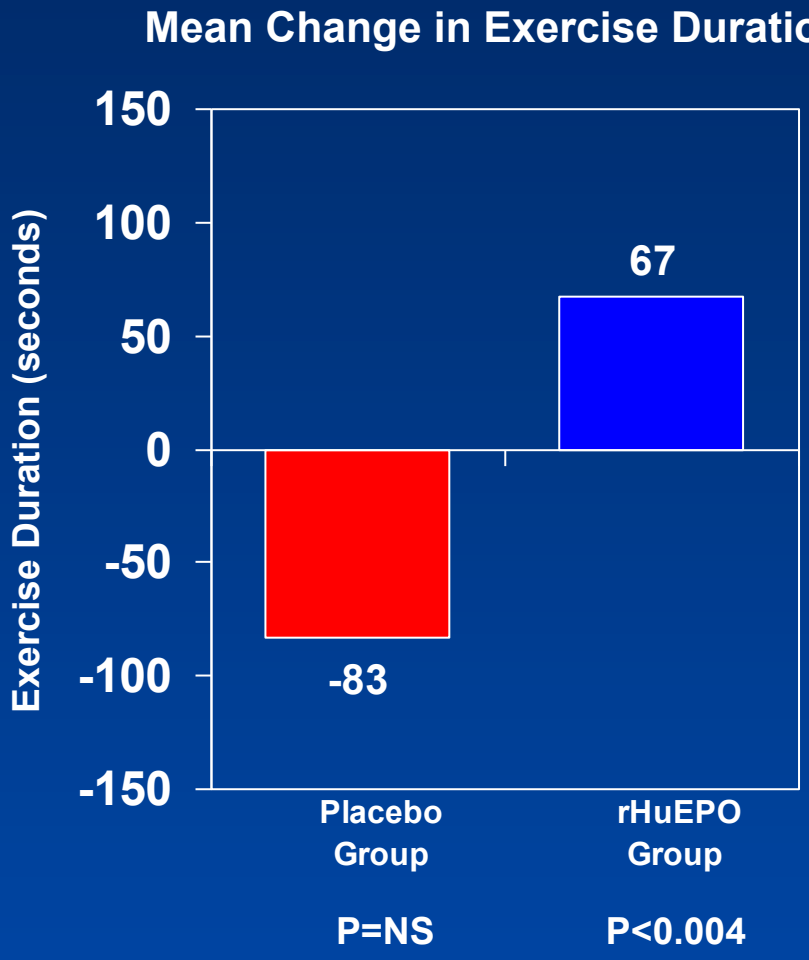
126 Anemic Patients With Resistant CHF

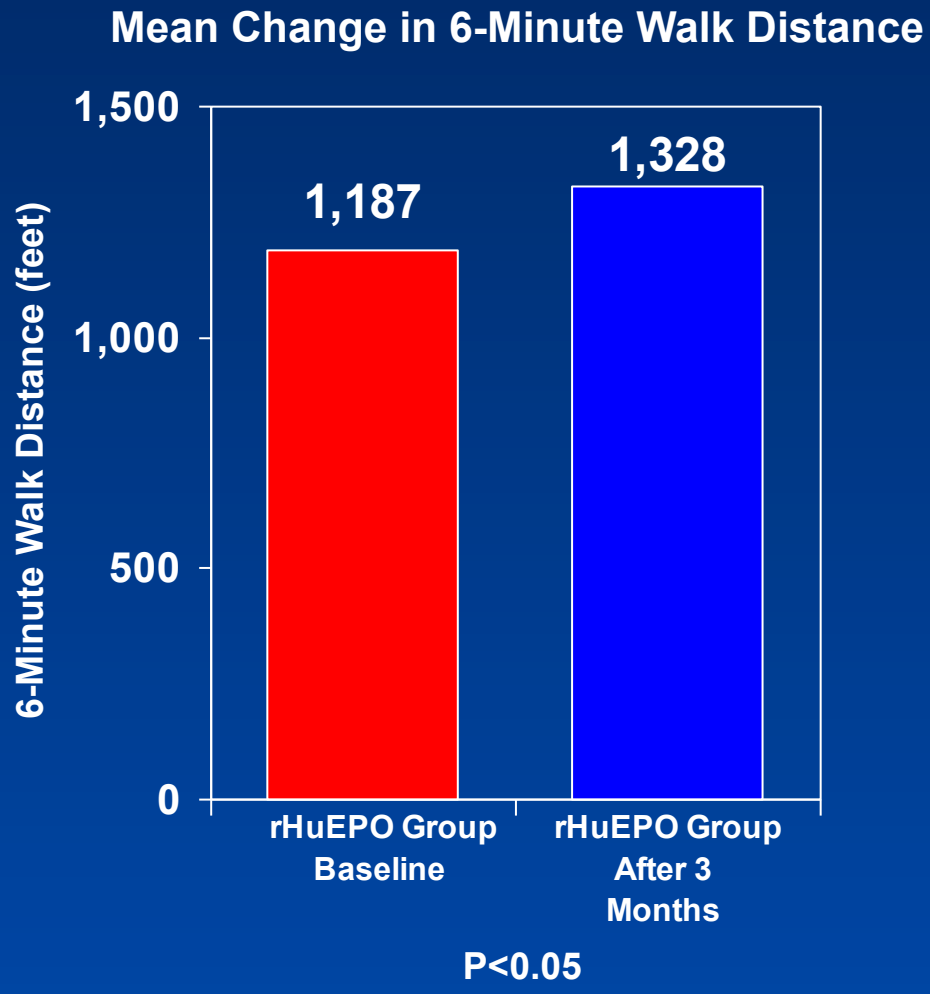
	Before	After
Hemoglobin (g/dL)*	10.3	13.1*
Serum creatinine (mg/dL)	2.4	2.3
GFR (mL/min/month)*	-0.95	0.27*
NYHA class (0–4)*	3.8	2.7*
Fatigue/SOB index (0–10)*	8.9	2.7*
Hospitalizations*	3.7	0.2*
Systolic BP (mmHg)	132	131
Diastolic BP (mmHg)	75	76

Statistical difference following anemia correction $p < 0.05$
NYHA = New York Heart Association

Silverberg DS, et al. *Peritoneal Dial Int.* 2001;21(suppl 3):S236-S240.

Effect of Treatment Of Anemia With rHuEPO On Exercise Duration And 6-Minute Walk…

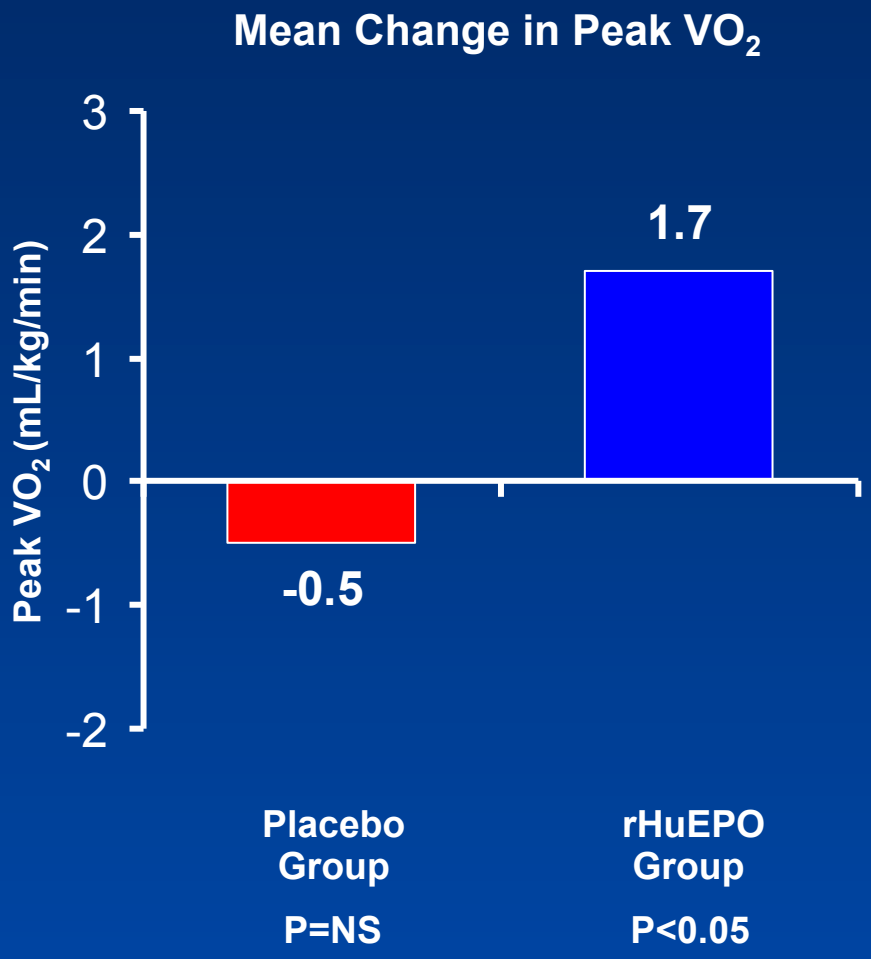


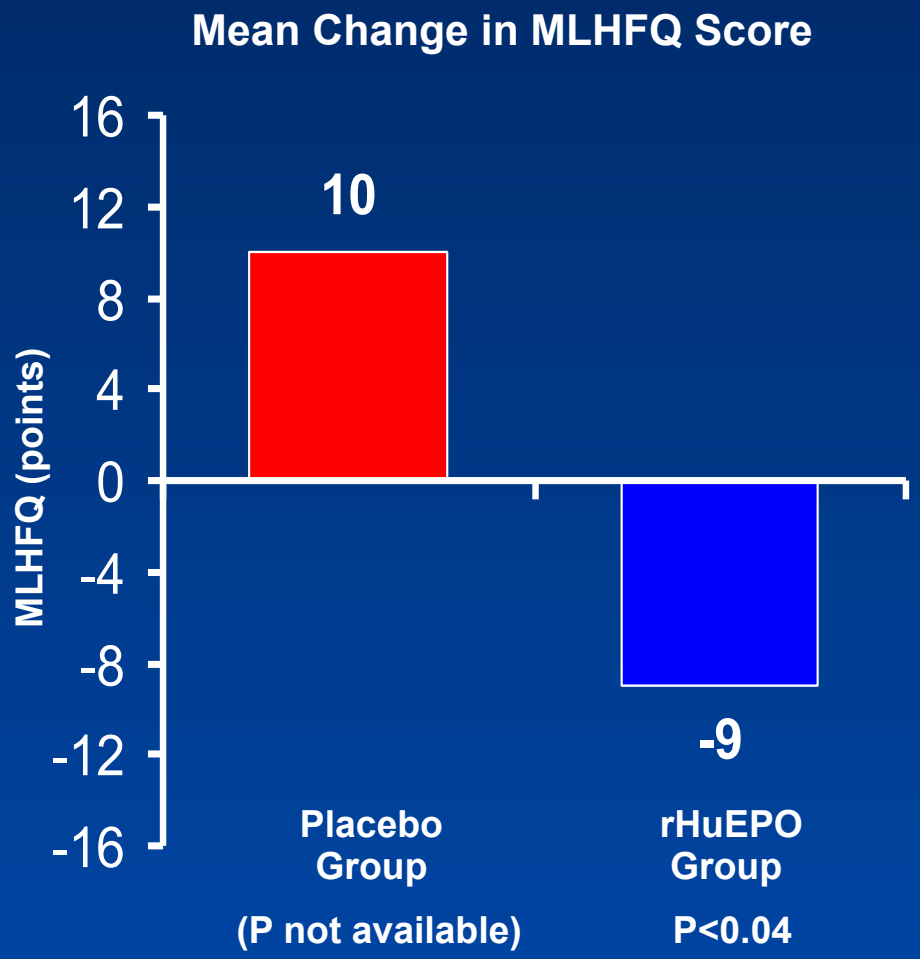


Randomized, placebo-controlled, single-blinded study; N=23 (n=8 for placebo group, n=15 for EPO group)

Mancini et al. Circulation. 2003;107:294-299.

…As Well As Peak VO_2 And Quality Of Life In Heart Failure Patients





Randomized, placebo-controlled, single-blinded study; N=23 (n=8 for placebo group, n=15 for EPO group)

Mancini et al. *Circulation.* 2003;107:294-299.

Pooled Analysis of HF Anemia Trials

	Placebo n=209	**Darbepoetin alfa n=266**	
		Outcomes hazard ratio (95% CI)	**p value**
Composite endpoint		0.67 (0.44, 1.03)	0.064
HF-related hospitalization		0.66 (0.40, 1.07)	0.091
All-cause mortality		0.76 (0.39, 1.48)	0.418

Abraham W. ESC 2006

Pooled Analysis of HF Anemia Trials

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Abraham W. ESC 2006

Potential Benefits and Risks of Treating Anemia in HF

Potential Benefits

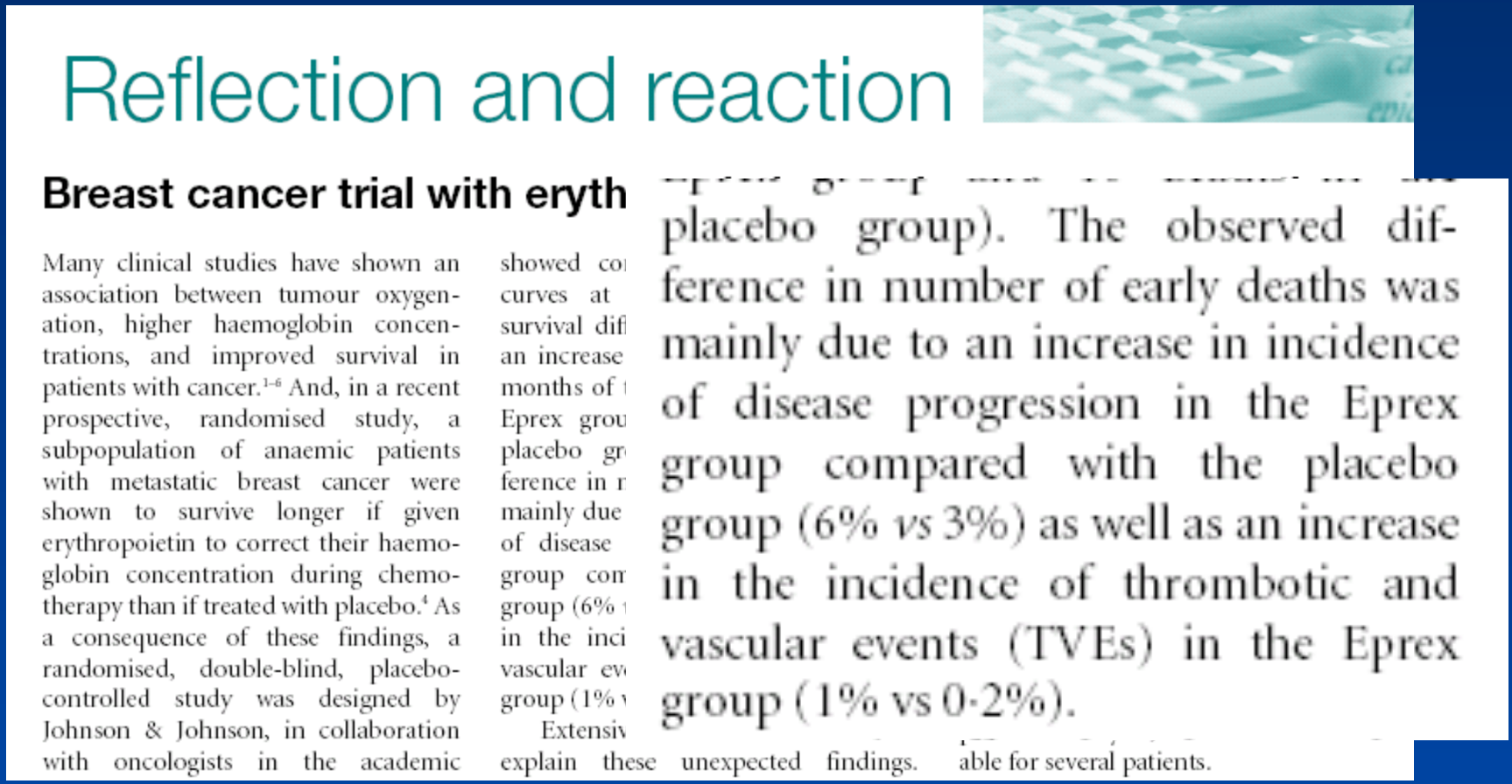
- Improved oxygen delivery
- Improved exercise tolerance
- Attenuate adverse remodeling
- Improved QoL
- Antiapoptotic?
- Decrease in hosp./ death?

Potential Risks

- Increased thrombosis
- Platelet activation
- Hypertension
- Endothelial activation

Adapted from Felker and O' Connor *J Am Coll Cardiol*. 2004;44:959-966.

Recent Oncology Publications Raised Concern Regarding VTE Risk in EPO-Treated Patients



Reflection and reaction

Breast cancer trial with eryth

Many clinical studies have shown an association between tumour oxygenation, higher haemoglobin concentrations, and improved survival in patients with cancer.[1-6] And, in a recent prospective, randomised study, a subpopulation of anaemic patients with metastatic breast cancer were shown to survive longer if given erythropoietin to correct their haemoglobin concentration during chemotherapy than if treated with placebo.[4] As a consequence of these findings, a randomised, double-blind, placebo-controlled study was designed by Johnson & Johnson, in collaboration with oncologists in the academic

showed co
curves at
survival dif
an increase
months of
Eprex grou
placebo gr
ference in r
mainly due
of disease
group con
group (6%
in the inci
vascular ev
group (1%
Extensiv

explain these unexpected findings.

placebo group). The observed difference in number of early deaths was mainly due to an increase in incidence of disease progression in the Eprex group compared with the placebo group (6% *vs* 3%) as well as an increase in the incidence of thrombotic and vascular events (TVEs) in the Eprex group (1% vs 0·2%).

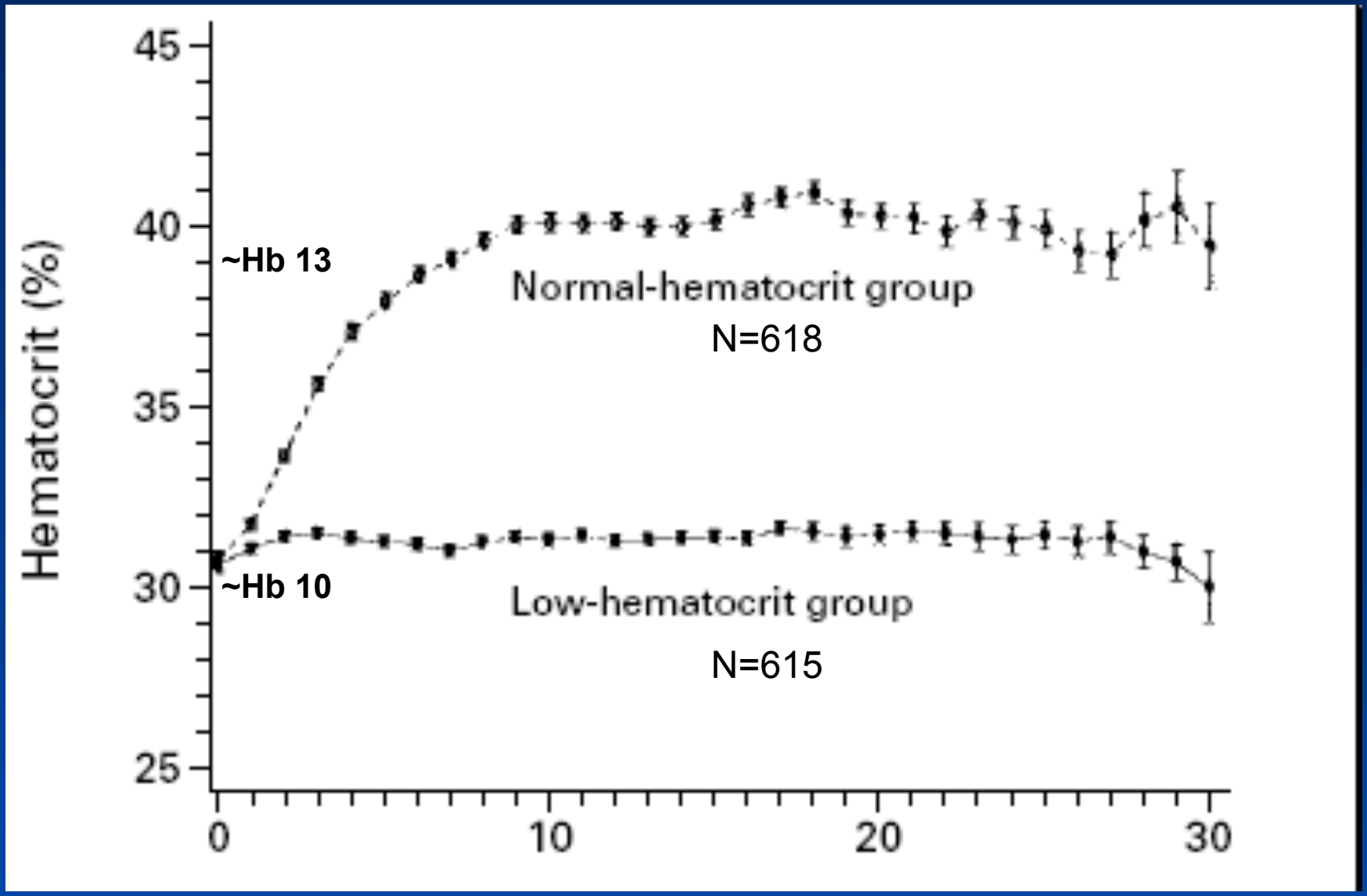
able for several patients.

The Lancet Oncology 2003;4:459-460.

Treatment of Anemia with Erythropoietin Stimulating Agents (ESAs): What We Know

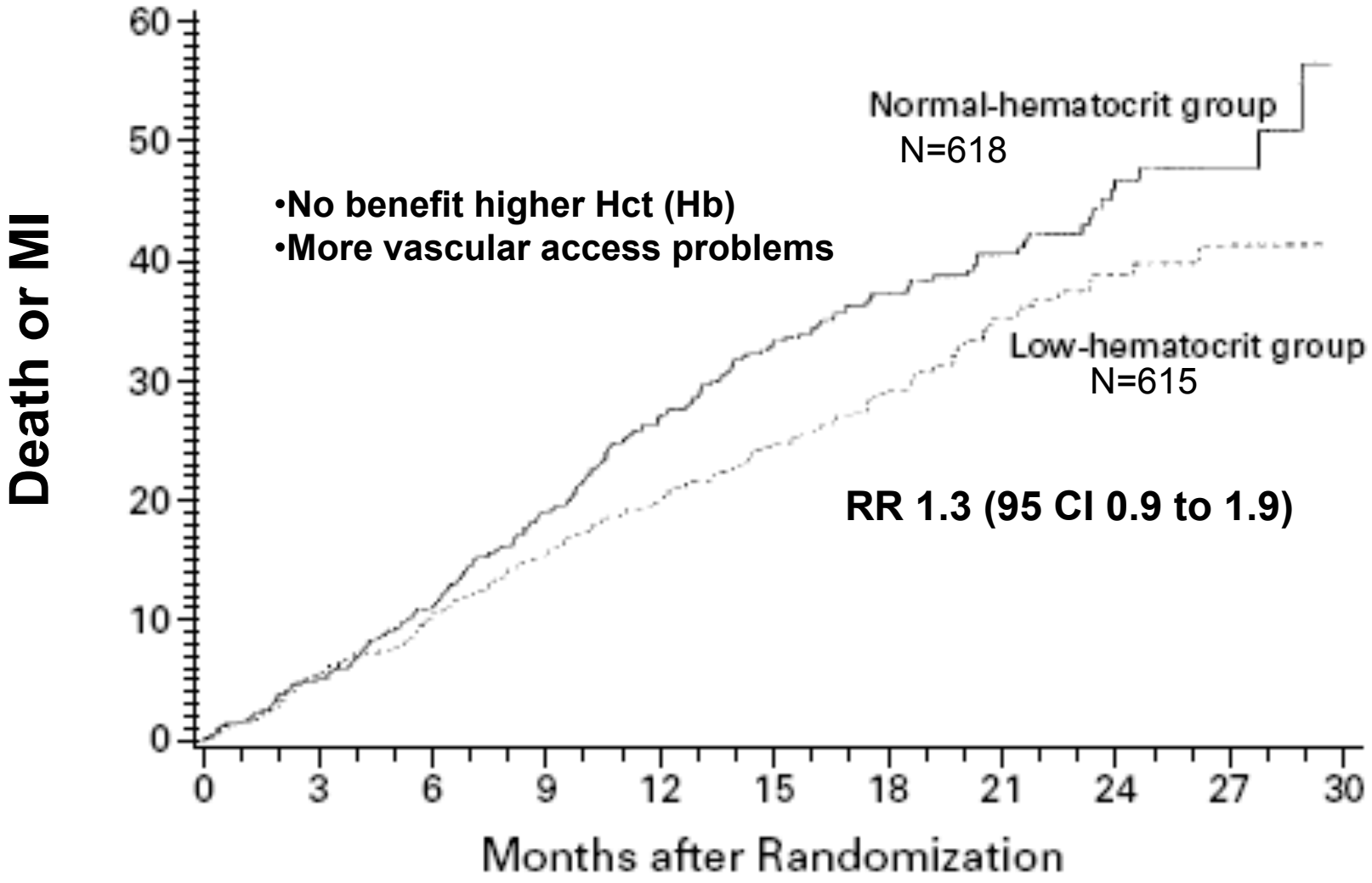
	Dialysis	CKD
Improvements		
Hb	✓	✓
Reduces Transfusion	✓	+/-
Quality of Life	✓	+/-
CV Outcomes	no	3 RCTs

Normal Hematocrit Dialysis Trial



Besarab et al,New Engl J Med 1998

Normal Hematocrit Dialysis Trial



Besarab et al,New Engl J Med 1998

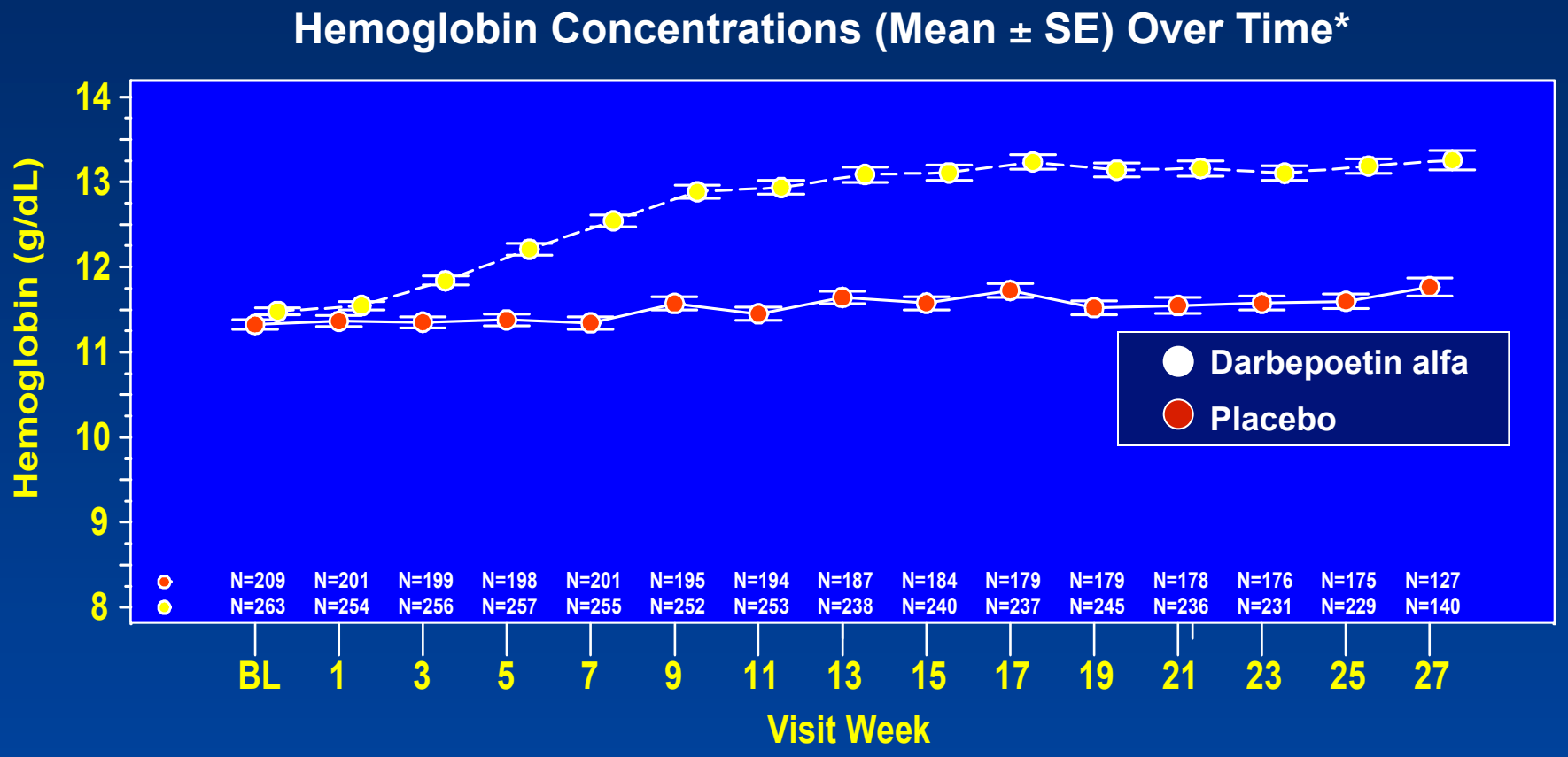
Current NKF/ KDOQI Guidelines for Anemia Correction

- **In patients with CKD, Hb should be 11.0 g/dL or greater (*MODERATELY STRONG RECOMMENDATION)***
  - **Observational data that patients with lower Hb do worse**
  - **Assocation between anemia and LVH**
  - **Improvement in QOL with anemia correction to 11-12 g/dL**
- **In the opinion of the Work Group, there is insufficient evidence to recommend routinely maintaining Hb levels at 13.0 g/dL or greater in ESA-treated patients.**

3 RCTs Designed to Address Whether Anemia Correction in CKD May Improve CV Morbidity and Mortality

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

Pooled Efficacy Results:
Hemoglobin Response in Studies 170 and 171



*For subjects in study 170 who stayed on study longer than 27 weeks, the Hb concentration remained stable throughout the study

General Design Differences

		CREATE	CHOIR	TREAT
Design		Randomized, open-label	Randomized, open-label	Randomized, double-blind, controlled
Sponsor / Agent		Roche / Neorecormon® (epoetin beta)	J&J / Procrit® (epoetin alfa)	Amgen / Aranesp® (darbepoetin alfa)
Dosing		2,000 QW	Initiate 10,000 QW When stable go to Q2W	0.75mcg/kg/Q2W Double dose when stable and go to QM
Dosing Frequency		De novo to QW	De novo to QW to Q2W	De novo to Q2W to QM
Hb Target(s), g/L	Arm 1	130-150	135	130
	Arm 2	105-115*	113	Rescue for Hb <90
Regions/Countries		EU, Mexico, China, Taiwan, Thailand	US	US, EU, CAN, AU, LA, RUS
# Centers		Unknown	130	~700
Censor at RRT		Unknown	Unknown	No

* Treatment starts when Hb <10.5 g/dL

Key Inclusion Criteria and Baseline Characteristics

	CREATE (N = 472)[a, c, d]	CHOIR (N = 963 - 1141)[a, b]	TREAT (N = 348 - 441)[a]
Inclusion			
Hb (g/L)	110 – 125	<110	≤110
eGFR/CrCl*	15-35	15-50	20-60
Diabetes	No (~20%)	No (48.5%)	Yes (100%)
Baseline Characteristics			
Hb (g/L)	116	101	-
eGFR/CrCl*	24.5	27.0	-

[a] Study population sample w/ available data
[b] Abstracts, 2004 ASN, St. Louis, MO
[c] MacDougall et al. NDT 2003;18[suppl 2]:ii13-ii16
[d] www.theKidney.org

* TREAT, CHOIR: mL/min/1.73m^2

* CREATE: mL/min

European Best Practice Guideline 4: Comments Regarding Initiation of rHuEPO

- "There is widespread agreement that symptoms usually begin when the Hb is <11 g/dL."
- "There is abundant evidence, including data from randomized studies, that quality of life, CV morbidity, exercise capacity, endocrine, immune and sexual function, and hospitalization rates, are all improved in pre-dialysis patients if the Hb is increased from lower levels to >10-11 g/dL."
- "Prospective data suggesting mortality can be diminished by increasing the Hb concentration are, as yet, lacking."

Nephrol Dial Transpl 1999;14(Suppl 5):11-13.

Study Endpoints

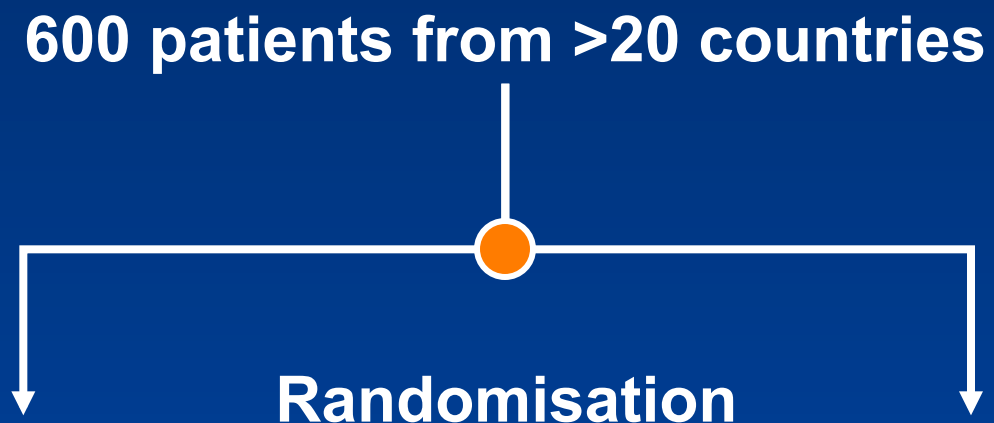
	CREATE	CHOIR	TREAT
Primary Endpoint	1. Change in LVMI: baseline to 1 year 2. Time to: - Sudden death - MI (fatal, non-fatal) - Stroke (fatal, non-fatal) - Heart failure (acute) - Angina (hosp >24 hrs) - Arrhythmias (hosp >24 hrs) - PVD (necrosis, amputation)	Time to all-cause mortality or CV morbidity: - MI - Stroke - Heart failure Hospitalization -Unplanned hospitalization for heart failure [No coincident initiation of RRT] with administration of IV inotrope, diuretic, vasodilator	Time to all-cause mortality or CV morbidity: - MI - Stroke - Heart failure - Hosp for acute myocardial ischemia
Secondary Endpoints	- All-cause mortality - CV mortality - CHF (change in NYHA class) - CV interventions - Hospitalization - LV growth and systolic fxn - Progression of CKD - Nutritional status - QOL	-All Cause Mortality -CHF Hospitalization -MI -CVA -RRT -CV Hospitalization -Incident CHF -All cause Hospitalization -Change from baseline for Hct/ Hb, eGFR, Fe stores -HRQOL	Time to each of: - ESRD or all-cause mortality - ESRD - CV mortality - Components of 1^{o} endpoint Change in pt-reported fatigue: baseline to wk 25 Change in eGFR

CREATE: Study design

Primary study objectives: To investigate the effects of early epoetin beta treatment to normal target haemoglobin (Hb) values compared to partial anaemia correction on cardiovascular (CV) events

Hg 11-12.5

eGFR 15-35



High target Hb (13–15 g/dl)

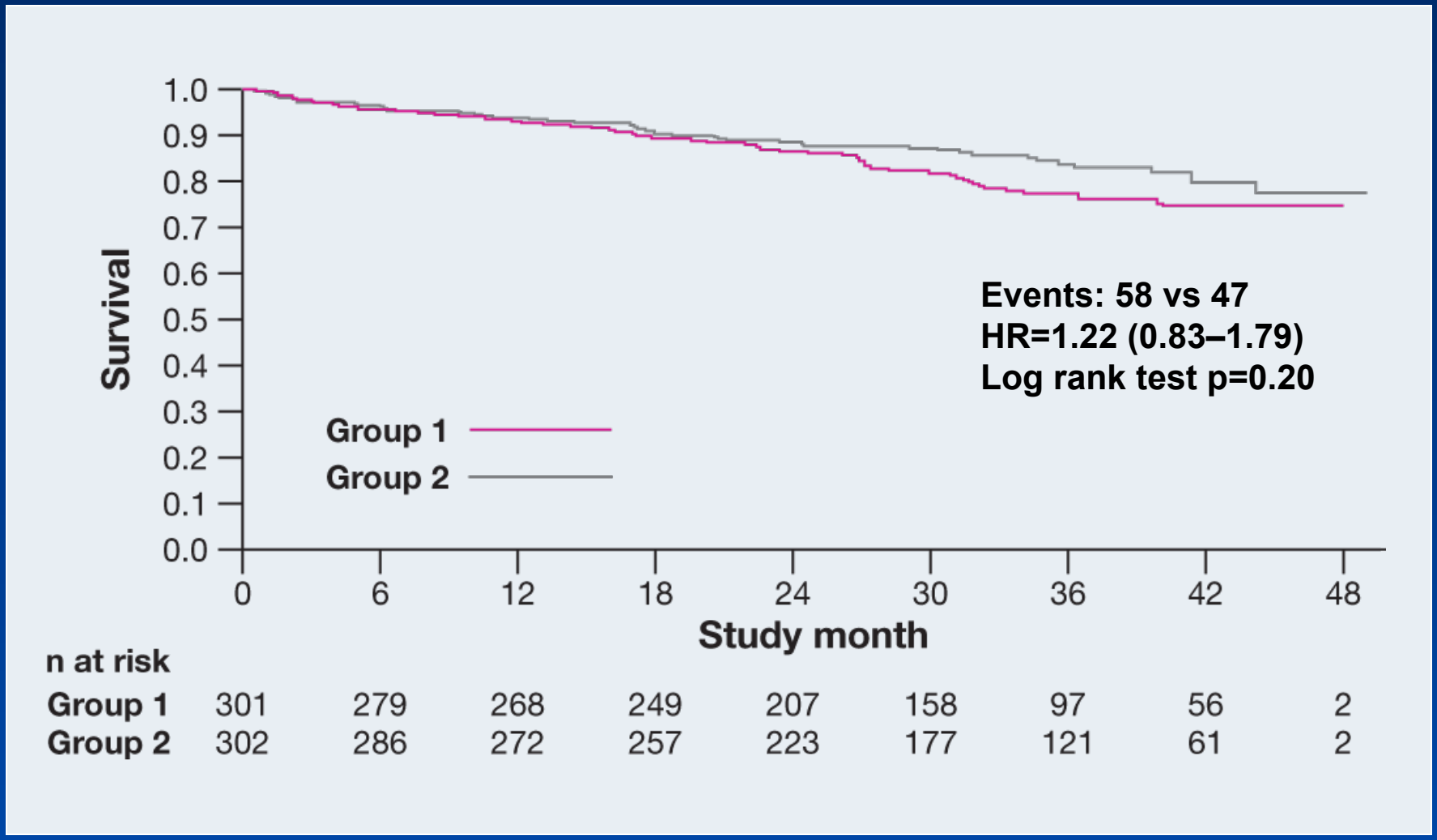
Standard target Hb (10.5–11.5 g/dl)

Group 1

Group 2

Primary endpoint

Time to first CV events (105 events)

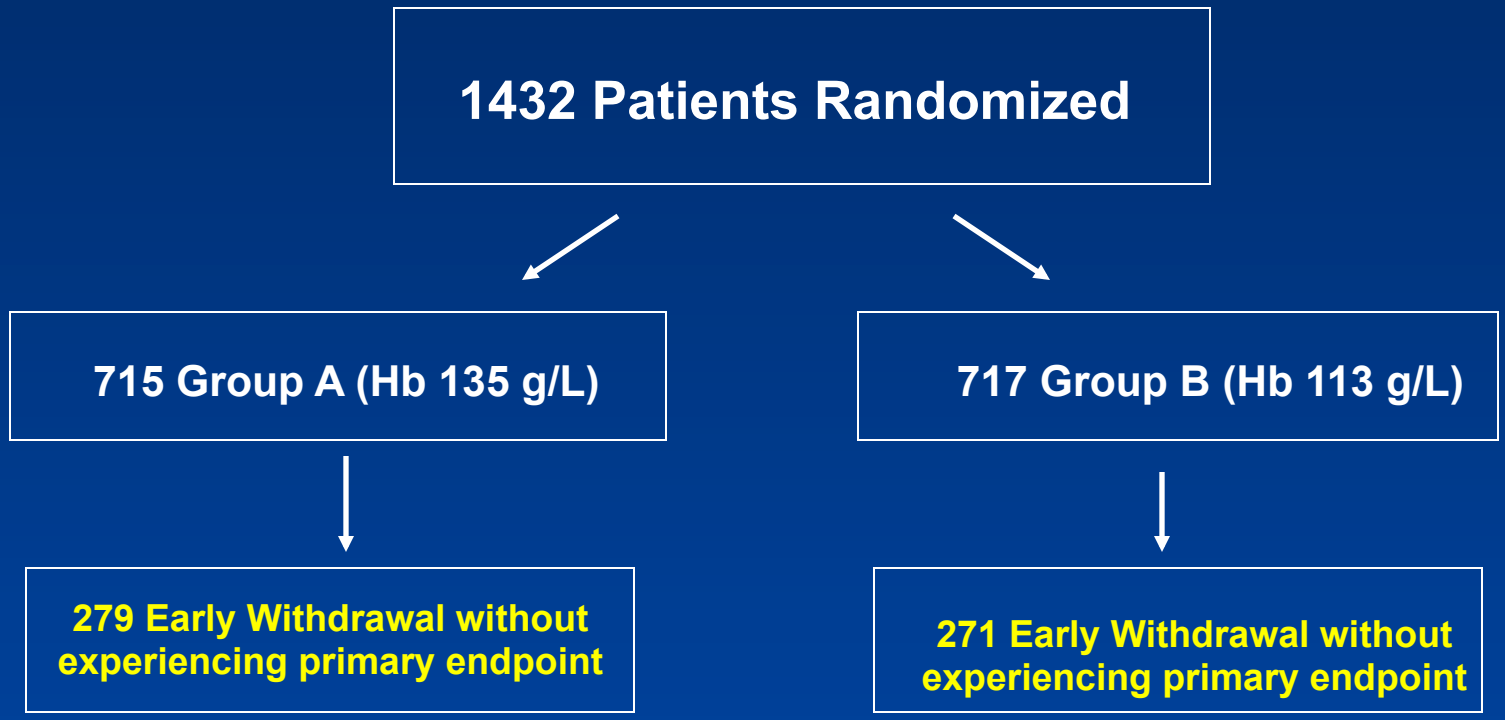


Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE)

		CREATE[a]
Reason for Stopping		Last subject followed 2 years
Duration Enrollment (months)		Unknown
Total Study Duration (months)		48
Median Follow-up (years)		2.5
Hb Achieved (g/L)	Arm 1	135
	Arm 2	Unknown ('stable')
Composite Primary Event Rate (% per year)		5.8
# Composite Primary Events Observed	**Arm 1**	**58**
	Arm 2	**47**
HR (95% CI) Composite Primary Endpoint		**1.22 (0.83, 1.79) - estimated**
# ESRD Events Observed	**Arm 1**	**127**
	Arm 2	**111**
HR (p value) Time to ESRD		**1.32 (p = 0.034)**
Secondary Endpoints		Improved QOL (p = 0.003) in higher Hb arm, but clinical significance uncertain; no difference in other 2ndarys

[a] www.theKidney.org

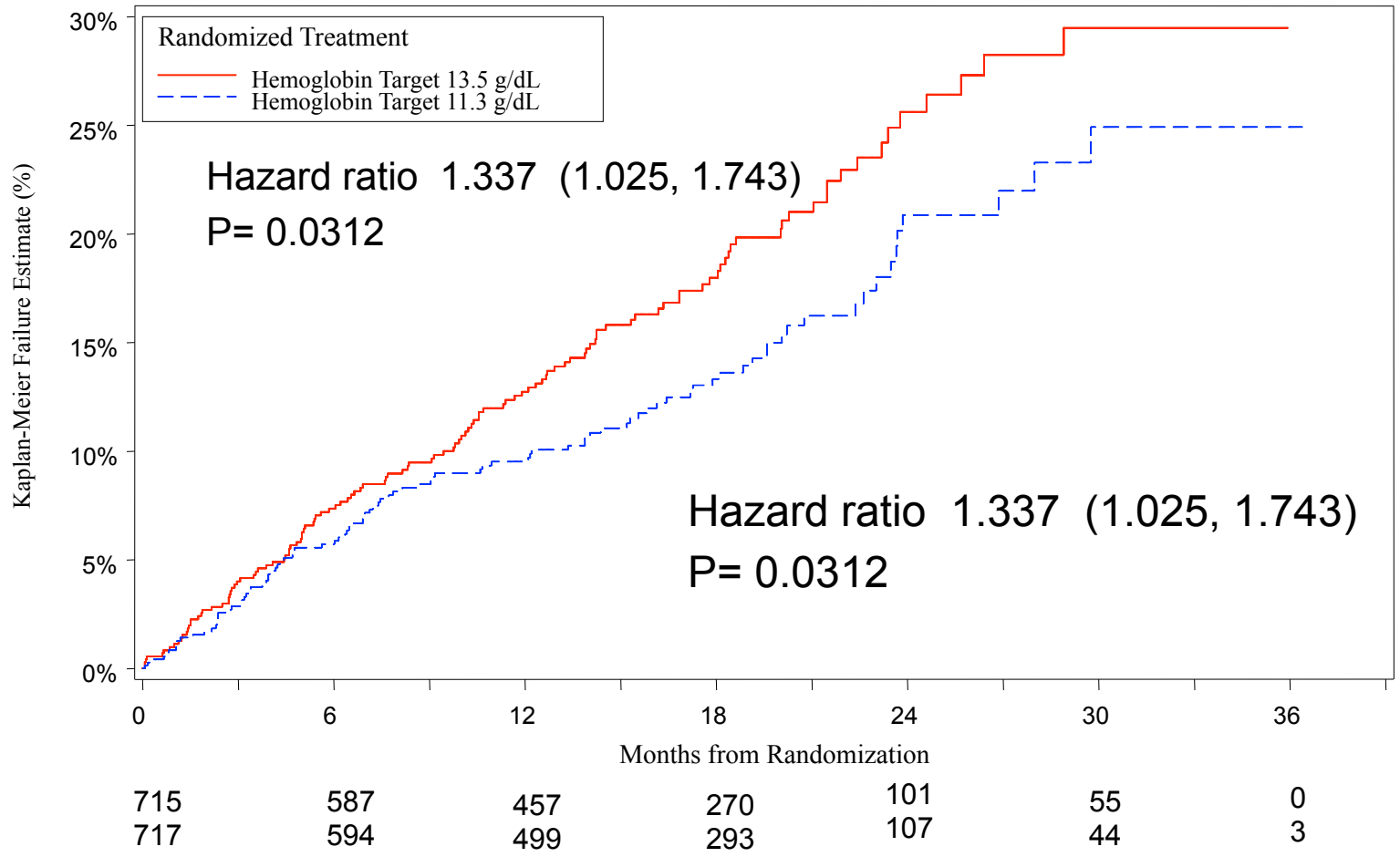
Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)



DSMB Stopped Study May 2005 for Futility (not a stopping rule)
Results Released April 2006 at NKF meeting

Singh A et al. *NEJM 2006*

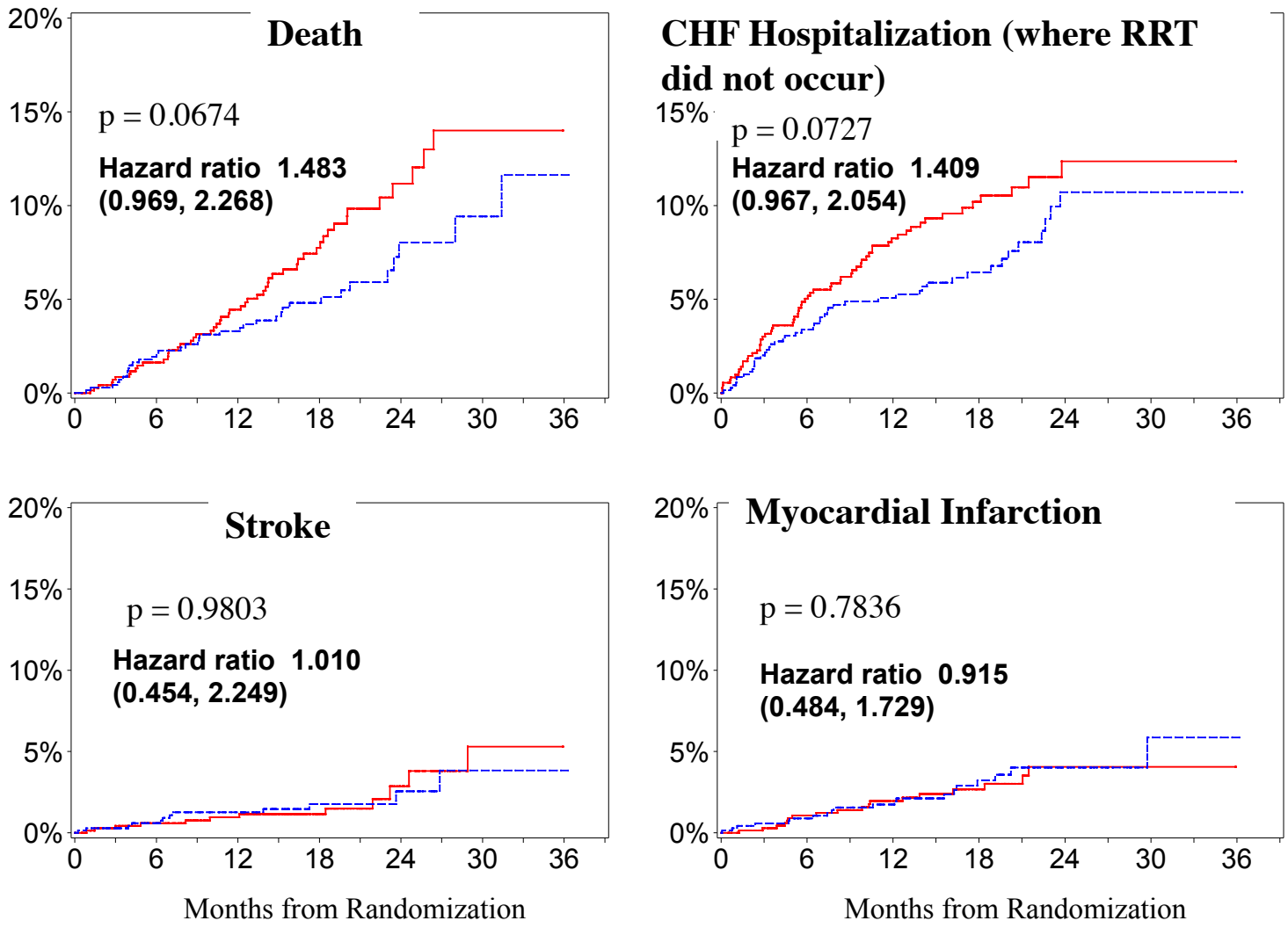
Kaplan-Meier Plot of the Time to the Primary Composite Event between Randomization and Termination: ITT Population



Primary Composite Endpoint:
Death, MI, CHF hosp (no RRT) and/or stroke

Singh A et al. *NEJM 2006*

Components of the Primary Endpoint



Singh A et al. *NEJM 2006*

CHOIR Outcomes: Mortality and CV Morbidity

Endpoint	# Events		HR (95% CI)	p-value
	Hb 135	Hb 113		
Composite Primary	**125**	**97**	**1.337 (1.025, 1.743)***	**0.0312**
Secondary				
All-cause death	52	36	1.483 (0.969, 2.268)	0.0674
CV death	26	22		?
MI	18	20	0.915 (0.484, 1.720)	0.78
Stroke	12	12	1.010 (0.454, 2.249)	0.9803
Heart Failure	64	47	1.409 (0.967, 2.054)	0.0727
Time to ESRD	?	?	1.186 (0.941, 1.495)	?
Cardiovascular hospitalization	?	?	1.225 (1.0131, 1.448)	
Composite primary event rate	17.5%	13.5%		
KM – 3yr event rate	29.5%	24.9%		

* Time for KM curves to separate: ~ 6-8 months

Singh A et al. *NEJM 2006*

CHOIR Results

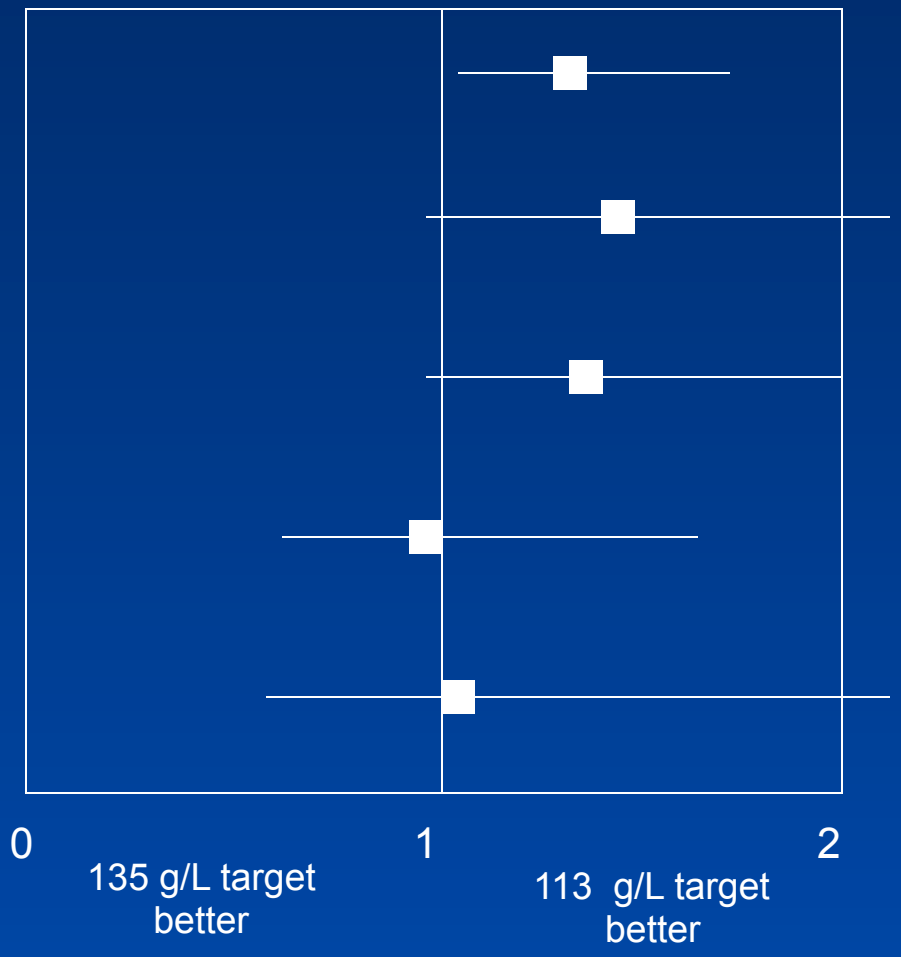
Primary Composite Endpoint

Death

CHF Hospitalization

Myocardial Infarction

Stroke

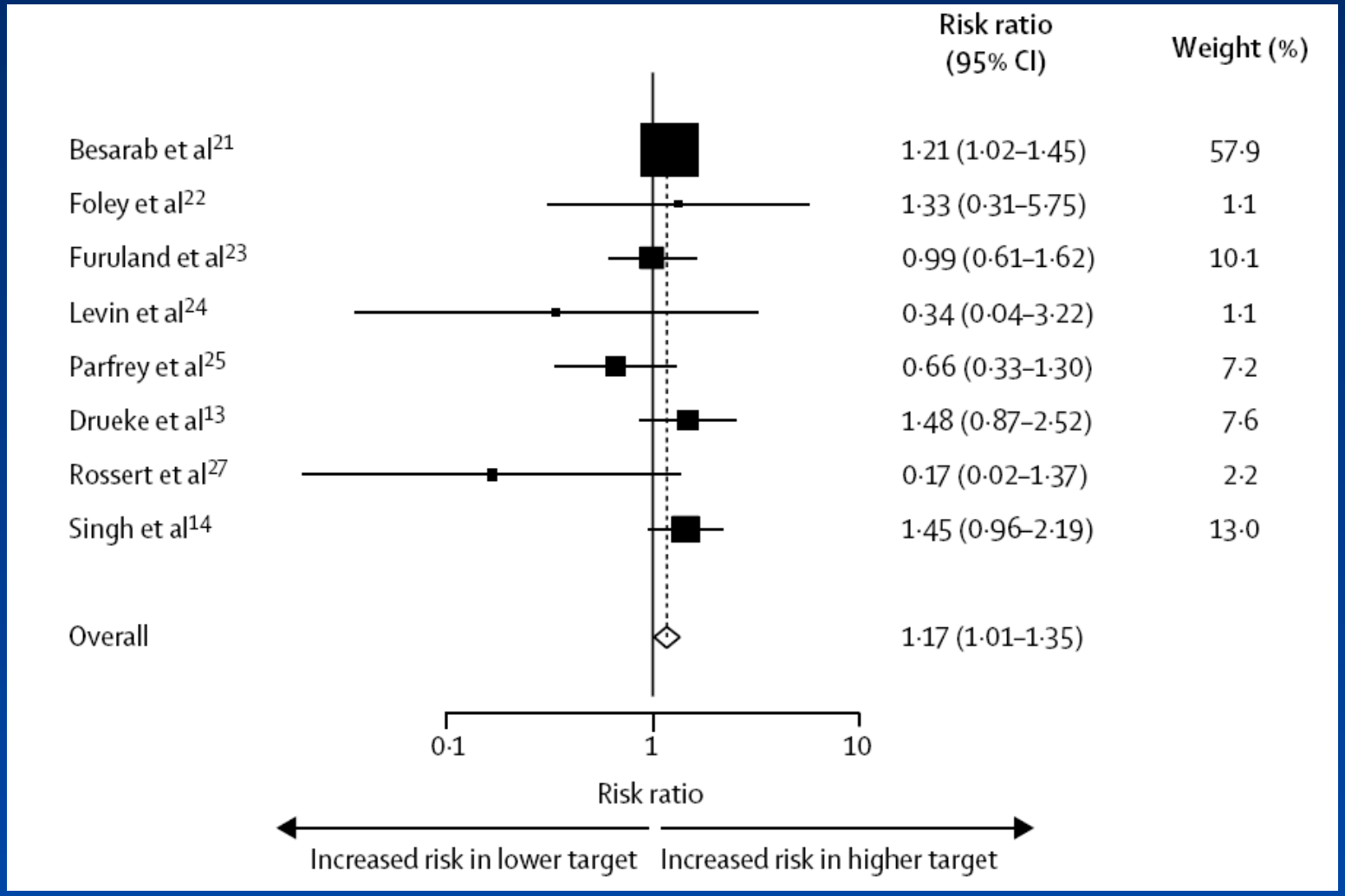


Singh A et al. *NEJM 2006*

Cause of Death in CHOIR

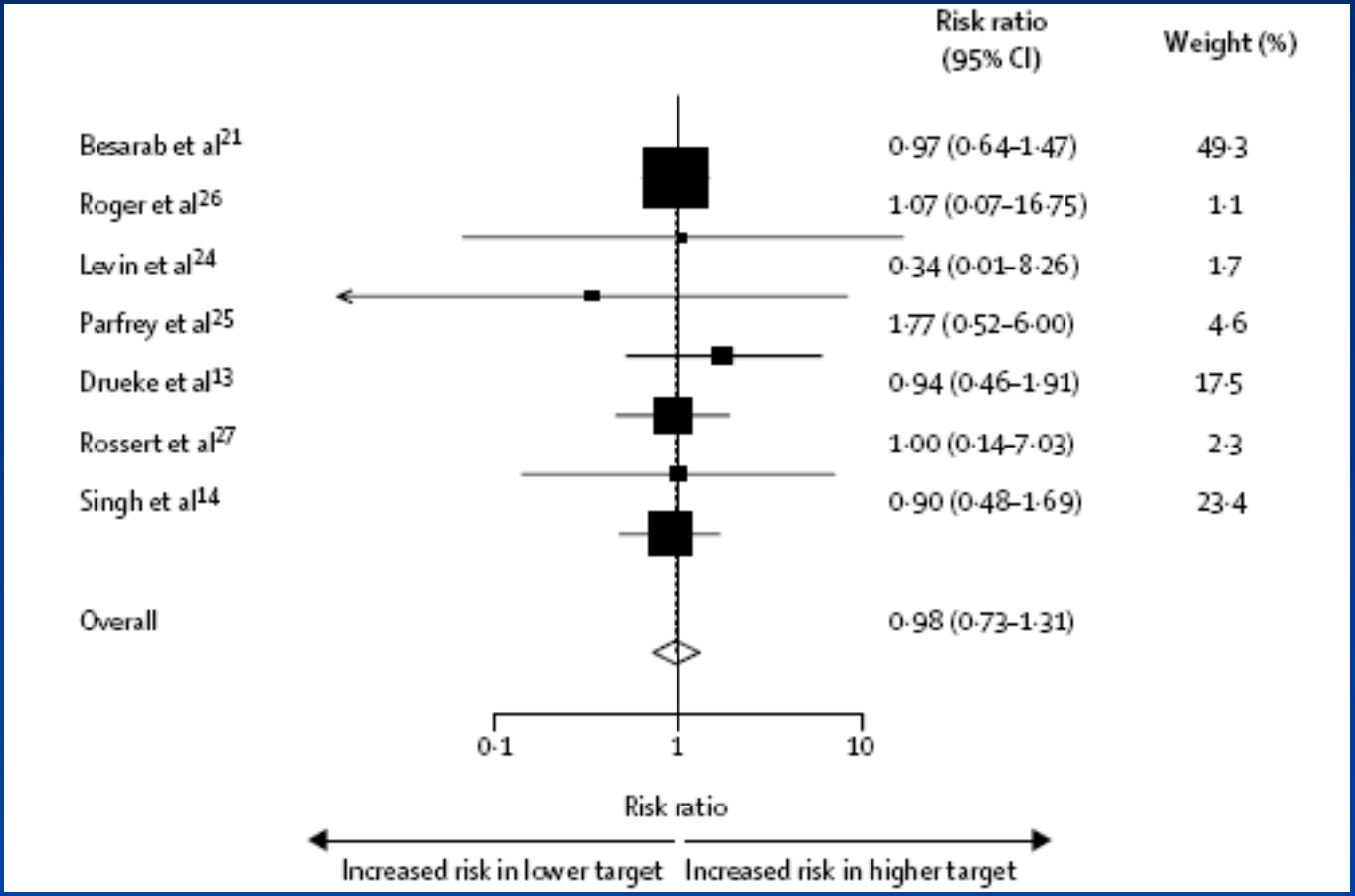
	Hb 135 g/L	Hb 113 g/L
Deaths	52	36
Causes		
Cardiovascular	26	22
Thrombotic	0	2
ESRD	2	0
Sepsis	5	0
Other	19	12

Metaanalysis: Mortality



Lancet 2007

Metaanalysis: MI

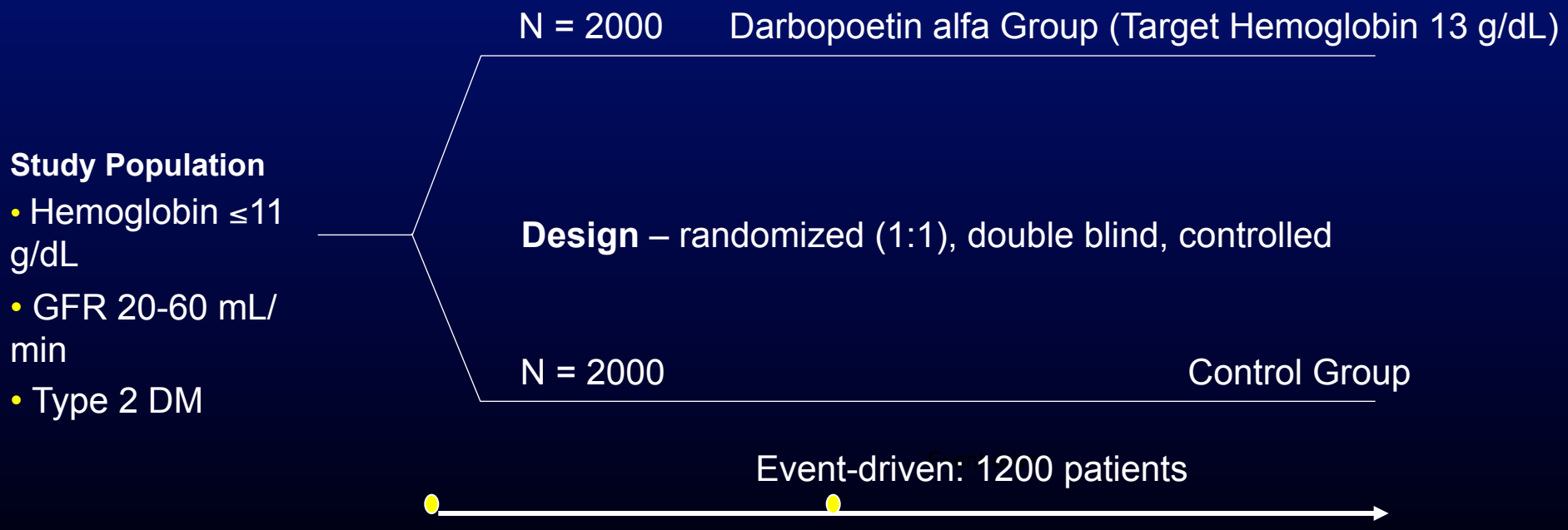


Lancet 2007

TREAT: Trial to Reduce Cardiovascular Events with Aranesp® (Darbepoetin alfa) Therapy

Hypothesis:

Treatment of anemia with darbopoetin alfa reduces the risk of mortality and nonfatal cardiovascular events in patients with CKD and type 2 diabetes



CHOIR vs. TREAT: Subject Exposure

Study	N	Median (Pt-months)	Total (Pt-years)	Events
TREAT*	**3225**	**13**	**3346.6**	**362**
CHOIR	1432	16	~1900**	222

TREAT almost 2x greater overall exposure to study drug than CHOIR

* Based on 01-Mar-2007 Oracle Clinical Database

** Crude estimate: 1432 patients x (16 months / 12 months/year) = 1900 patient-years

Cleveland Functional Electrical Stimulation Center, Cleveland VA Medical Center, Cleveland, OH, USA (DMT)

and upper arm control using an implantable controller. *Am J Hand Surg* 2002; **27**: 265–76.

Haemoglobin targets: we were wrong, time to move on

s page 381

Anaemia occurs in nearly all patients with moderate-to-severe chronic kidney disease. The most widely used treatment options are erythropoiesis-stimulating agents (eg, Epogen, Procrit, and Aranesp), with an economic burden of US$10 billion in sales worldwide in 2006, and $2 billion Medicare expenditure for dialysis patients in 2006 in the USA alone.[1] Administration of erythropoietin rapidly increases haemoglobin

www.thelancet.com Vol 369 February 3, 2007

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Why do some still recommend the continuation of existing trials of haemoglobin targets?[9–12] What justification could there be for ethics committees, and for the relevant steering committees and data and safety monitoring committees, to continue randomisation or treatment in haemoglobin target trials? One such trial is the Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT), due to enrol

frey, M.D., Hans-Henrik Parving, M.D., Guiseppe Remuzzi, M.D., Ajay K. Singh, M.D., Scott D. Solomon, M.D., and Robert Toto, M.D.

NEJM 2007

2007

Unanswered Question in Anemia Rx

- What Targets?
- Which Patients?

FDA Issues New Warnings on Anemia Drugs

FDA Issues New Warnings for Doctors to More Carefully Prescribe Widely Used Anemia Drugs

Red blood cells are shown in this graphic. Federal health officials issued stern new warnings Friday for doctors to more carefully prescribe widely used anemia drugs that can increase the risk of death and other serious problems in patients with cancer and kidney disease. At issue are drugs sold under the brand names Procrit, Epogen and Aranesp. These drugs are genetically engineered versions of a natural protein, erythropoietin, that increases the number of red blood cells

WASHINGTON Mar 9, 2007 (AP)— Federal health officials issued stern new warnings Friday for doctors to more carefully prescribe widely used anemia drugs that can increase the risk of death and other serious problems in patients with cancer and kidney disease.

At issue are drugs sold under the brand names Procrit, Epogen and Aranesp. These drugs are genetically engineered versions of a natural protein, erythropoietin, that increases the number of red blood cells.

Uncertainty in the Treatment of Anemia in Chronic Kidney Disease

Marc A. Pfeffer, MD, PhD, FACC,* Scott D. Solomon, MD,*
Peter Ivanovich, MD,† Ajay K. Singh, MD,* John J. V. McMurray, MD‡

*Department of Medicine, Brigham and Women's Hospital, Boston, MA; †Department of Medicine, Jesse Brown Veterans Administration and Northwestern University, Chicago, IL; ‡Department of Cardiology, Western Infirmary, Glasgow, UK

Anemia is a readily identifiable surrogate associated with …high rates of adverse clinical outcomes. Because ESP can raise hematocrit, it is imperative to definitively determine the risk: benefit ratios of these available therapies…. To accept a benefit based on the existing data may be exposing patients to an expensive therapy that is either ineffective or may even contribute to adverse outcome. On the other hand, to accept harm based on existing data may deny patients the ability to improve their prognosis as well as quality of life.

Rev Cardiovasc Med 2005

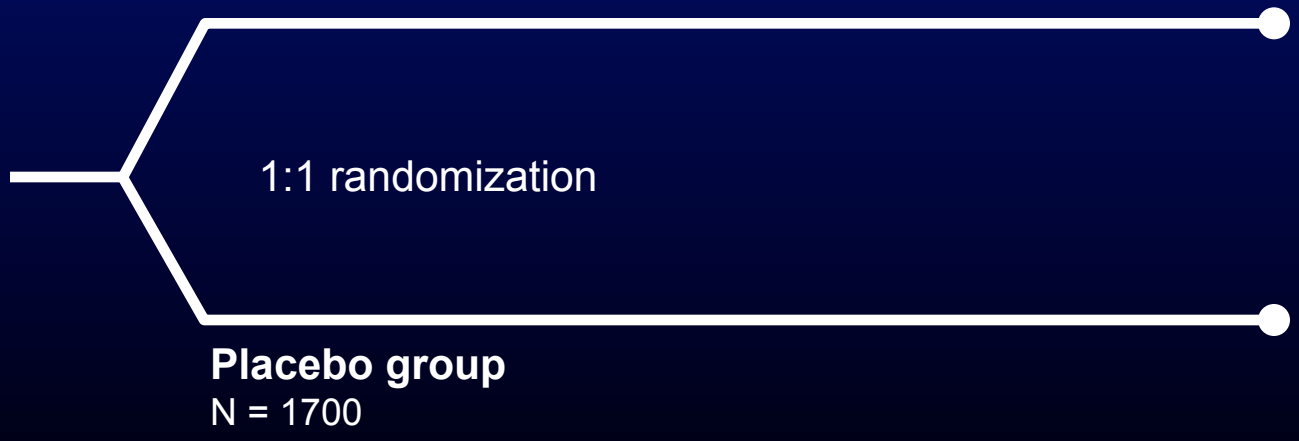
RED-HF Trial: Hypothesis and Study Design

Hypothesis:

Treatment of anemia with darbepoetin alfa in subjects with symptomatic left ventricular systolic dysfunction and anemia decreases the risk of all-cause mortality or hospital admission for worsening HF

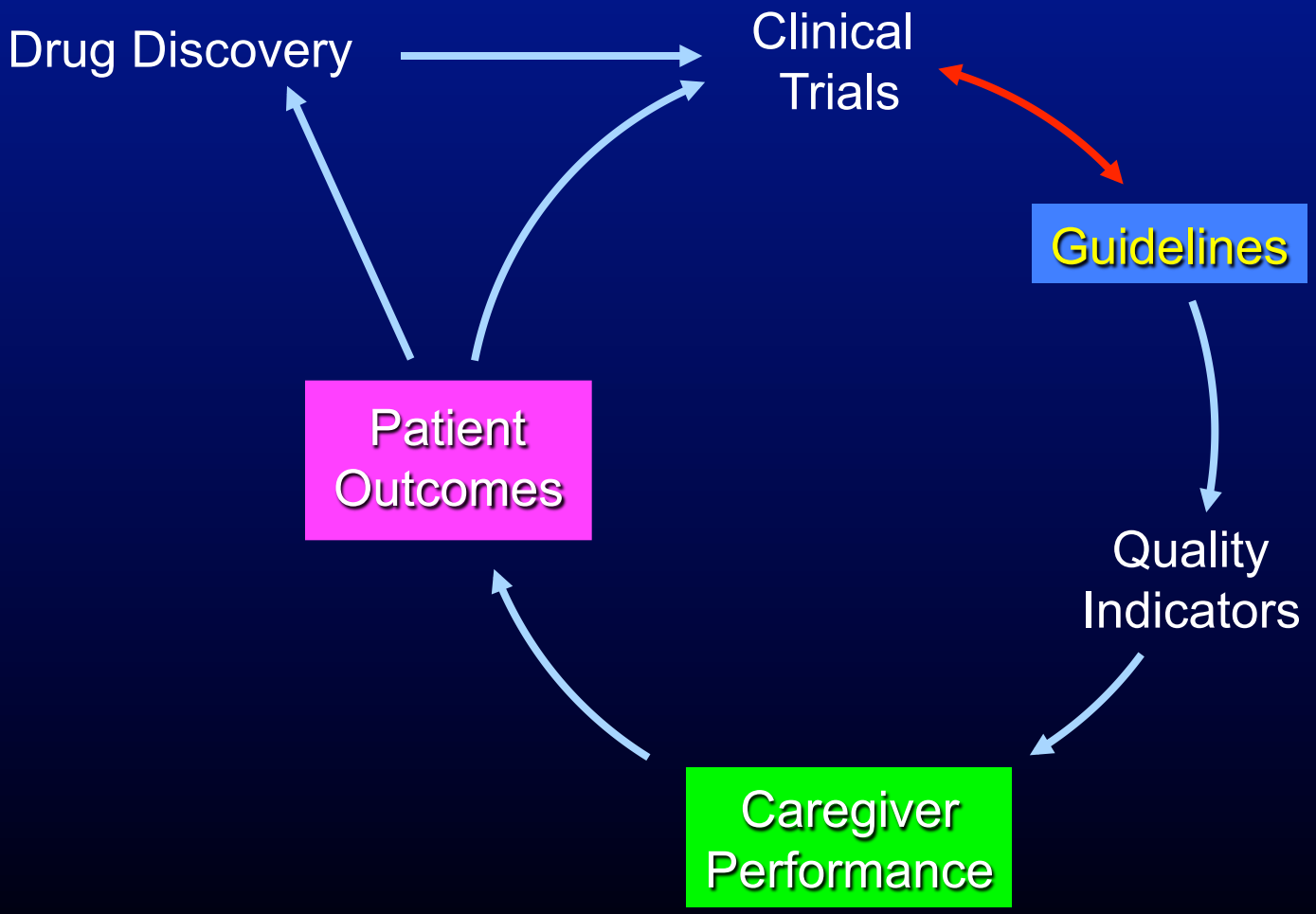
Study Population

- Hb 9 to 12 g/dL
- LVEF ≤ 35%
- NYHA Class II to IV



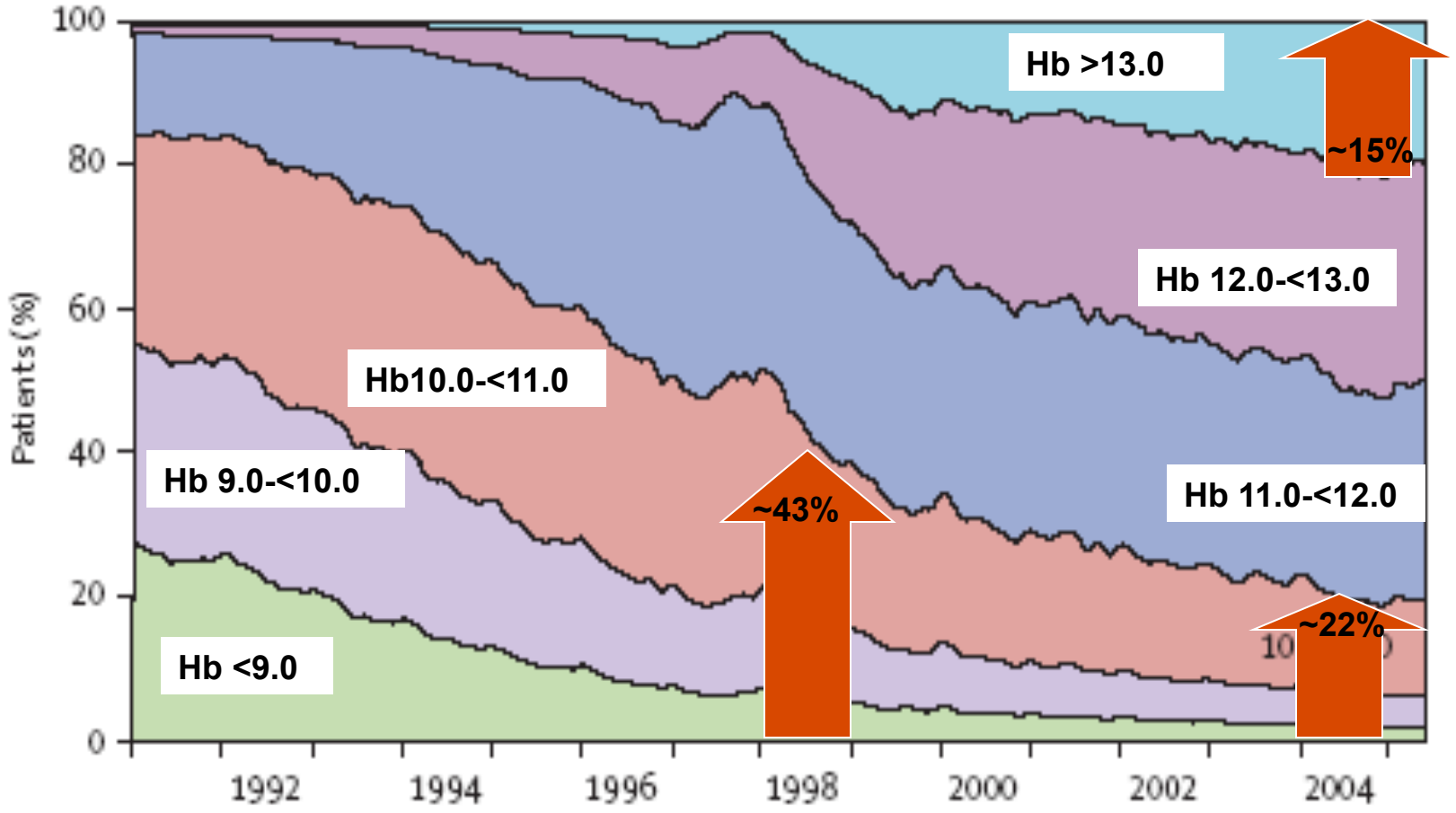
Young JB, et al J Cardiac Failure 2006;(Suppl 1):6:S77.

Randomized Controlled Trials Play A Critical Role in Advancing Patient Care Through Guidelines



Califf, R et al *JACC* 2002;40(11):1895-1901

Monthly Hemoglobin (Hb) of US Dialysis Patients



Hb level 11 g/dL a CMS Performance Measure

Steinbrook, Lancet 2006;368:2191.

Randomized Controlled Trials Have Driven the Evolution of Guidelines in Cardiology

ACC/AHA Guidelines for Management of Acute MI: Beta Blockade

- 1990 – Beta blockers are first recommend for targeted patients (reflex tachycardia, systolic hypertension, persistent angina, no signs of heart failure)[1]
- 1996 – Guidelines include 'non ST MI' patients in the highest level recommendation[2]
- 1999 – Patients with 'moderate LV failure' are moved from the class III (potentially harmful) to the class IIb (potentially useful) level recommendation[3]
- 2001 – Beta blockers are a highest-level recommendation for all post-MI patients[4]

[1] Gunnar RM, et al. *Circulation* 1990;82(2):664-707

[2] Ryan TJ, et al. *Circulation* 1996;94(9):2341-2350

[3] Ryan TJ, et al. *Circulation* 1999;100(9):1016-30

[4] Smith CC, et al. *Circulation* 2001;104(13):1577-9

ACC = American College of Cardiology
AHA = American Heart Association
MI = myocardial infarction
LV = left ventricular

Negative Results From Randomized Controlled Trials Evolve The Practice of Medicine

- Secondary prevention of cardiovascular disease with estrogens[1]
- Prophylaxis against ventricular dysrhythmia in the peri-myocardial infarction setting with lidocaine[2]
- Prophylaxis against pre-eclampsia with calcium supplementation[3]

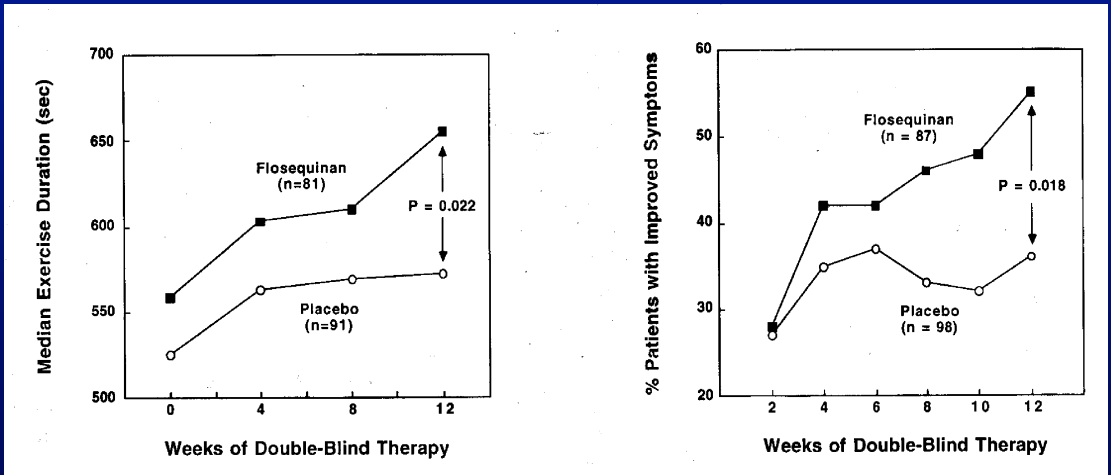
[1] Hulley S, et al. *JAMA* 1998;280(7):605-613.
[2] Sadowski ZP, et al. *American Heart Journal* 1999;137(5):792-798.
[3] Levine RJ, et al. *NEJM* 1997;337(2):69-76.

Patients who are deficient in X do not necessarily benefit from repleting X

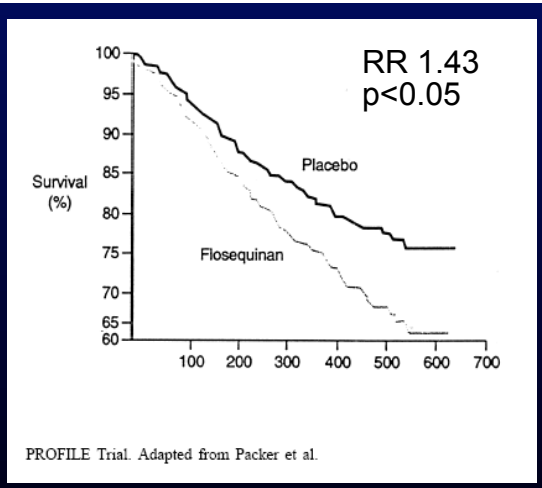
- Hormone Replacement Therapy
  - Reduced Estrogen associated with increased risk of
    - Heart Disease
    - Bone Loss
  - Observational Suggested Benefits of HRT
  - Randomized Trials suggested harm with HRT
- Thyroid Replacement
  - Just enough – good
  - Too much - bad

Beneficial Impact on HRQOL Does Not Always Extrapolate to Other Health Outcomes

Improvement in: Exercise duration[1] Heart failure symptoms[1]



Decreased survival[2]



HRQOL = health-related quality of life

[1] Packer M, et al. JACC 1993; 22(1):65-72.
[2] Packer M, et al. (abstract) Circulation 1993;88(Suppl):I-301.
[2] Van Veldhuisen DJ, et al. International Journal of Cardiology 2001;80(1):19-27.

Anemia Management Guidelines State that Additional Data Are Needed

- National Kidney Foundation[1]:
  - "Additional studies are needed to clarify the relationship between Hgb/Hct and outcomes in CKD patients, particularly those with heart disease."

- European Best Practice Guidelines:
  - "Prospective data suggesting mortality can be diminished by increasing the Hb concentration are, as yet, lacking."[2]

  - "…no prospective data have yet shown an improvement in survival in any single group of patients treated with erythropoiesis-stimulating agents."[3]

[1] *Am J Kid Dis* 2001;1(Suppl 1):S182-S238.

[2] *Nephrol Dial Transpl* 1999;14(Suppl 5):11-13.

[3] *Nephrol Dial Transplant* 2004;19(Suppl 2):ii6-ii15.

Conclusions

- Anemia is a risk factor for adverse outcome in patients with CKD and CVD
- Correction of anemia with ESPs may offer benefits to some patients in some clinical circumstances, although degree of correction is hotly debated
- Nevertheless, the potential for harm has been demonstrated with anemia correction in the CKD population
- We should be cautious until we have results from ongoing major clinical trials in anemia correction to reduce CV risk

The definition of equipoise

Trials of Anemia Targets in CKD

- **CHOIR study**
  - **1432 subjects recruited, diabetic and nondiabetic CKD patients**
  - **Epoetin-alfa**
  - **130 centers, US only**
  - **Hb 13.5 g/dL vs 11.3 g/dL**
  - **Study stopped by Data and Safety and Monitoring Board**
- **CREATE study**
  - **Approximately 603 subjects**
  - **Epoetin-beta**
  - **100 centers. 22 countries**
  - **Study reported data at European Renal Association/European Dialysis and Transplant Association conference**
- **TREAT study**
  - **4000 subjects with CKD and type 2 diabetes**
  - **Darbepoietin**
  - **700 centers, 26 countries**
  - **Placebo-controlled with rescue arm: Hb 9.0 g/dL vs 13.0 g/dL**
  - **Enrollment under way**

CHOIR = American Correction of Hemoglobin and Outcomes in Renal Insufficiency; CREATE = Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin-beta; TREAT = Trial to Reduce Cardiovascular Events with Aranesp® Therapy.

CHOIR Study Design

- Open label, Randomized Controlled Trial
- 130 sites randomized 1432 subjects in US
- 3 years duration
    - Median f/u 16 months
- Study population
    - Hb < 11 g/dl
    - Age ≥ 18
    - Steady-state GFR ≥ 15 ml/min and ≤ 50 ml/min
- Primary Endpoint: Composite event
    - Death
    - Myocardial infarction
    - Stroke
    - CHF hospitalization (excluding RRT)

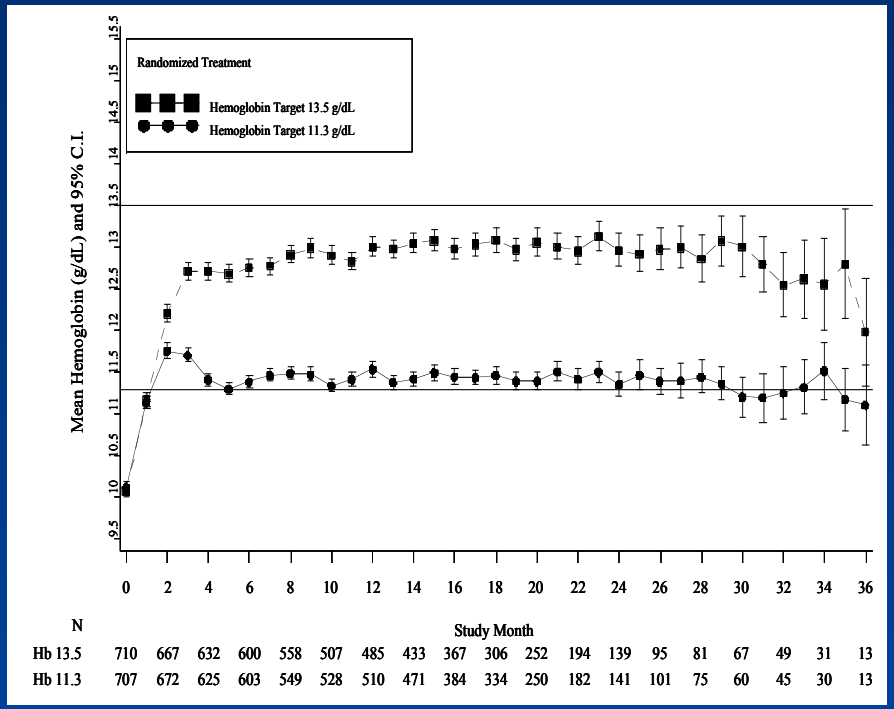
Singh et al In press

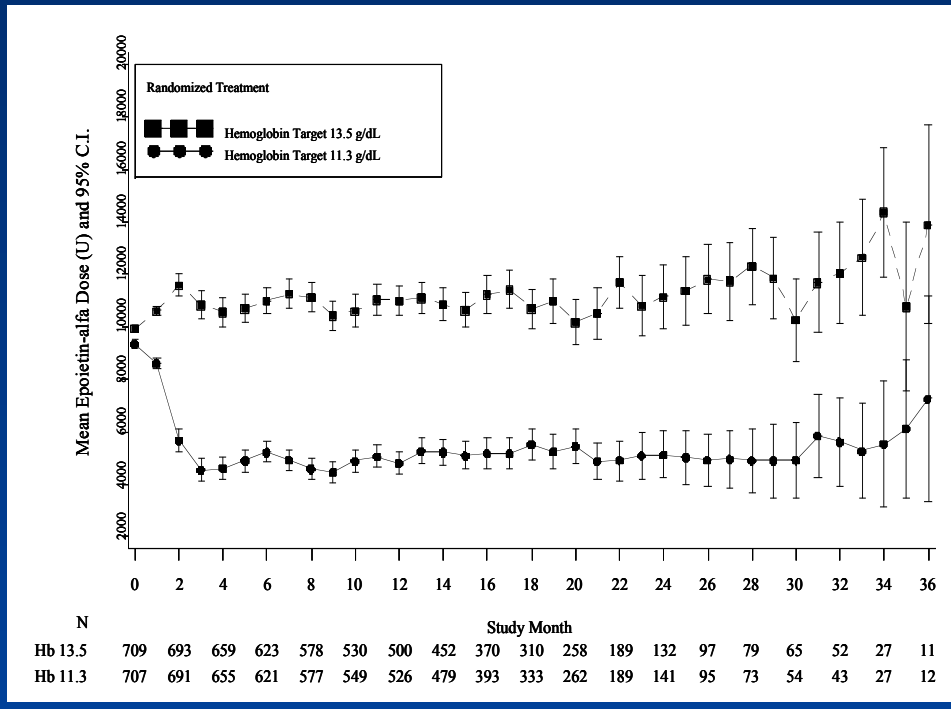
Baseline Characteristics

	Group A Hb 13.5 g/dL	Group B Hb 11.3 g/dL
Age	66	66.3
Gender (male) %	43.8	45.9
Race (Black) %	28.6	29.3
Ethnicity (Hispanic) %	12.5	13.5
Smoking %	47.5	44.6
BMI	30.4	30.4
Hematocrit (%)	31.4	31.4
Transferrin Saturation (%)	25.2	24.6
Creatinine Clearance (mL/ min)	36.	37.1
Etiology of CKD		
Diabetes %	46.8	50.8
Hypertension %	29.9	27.5

Singh et al In press

Hemoglobin and Epoetin alfa over Time



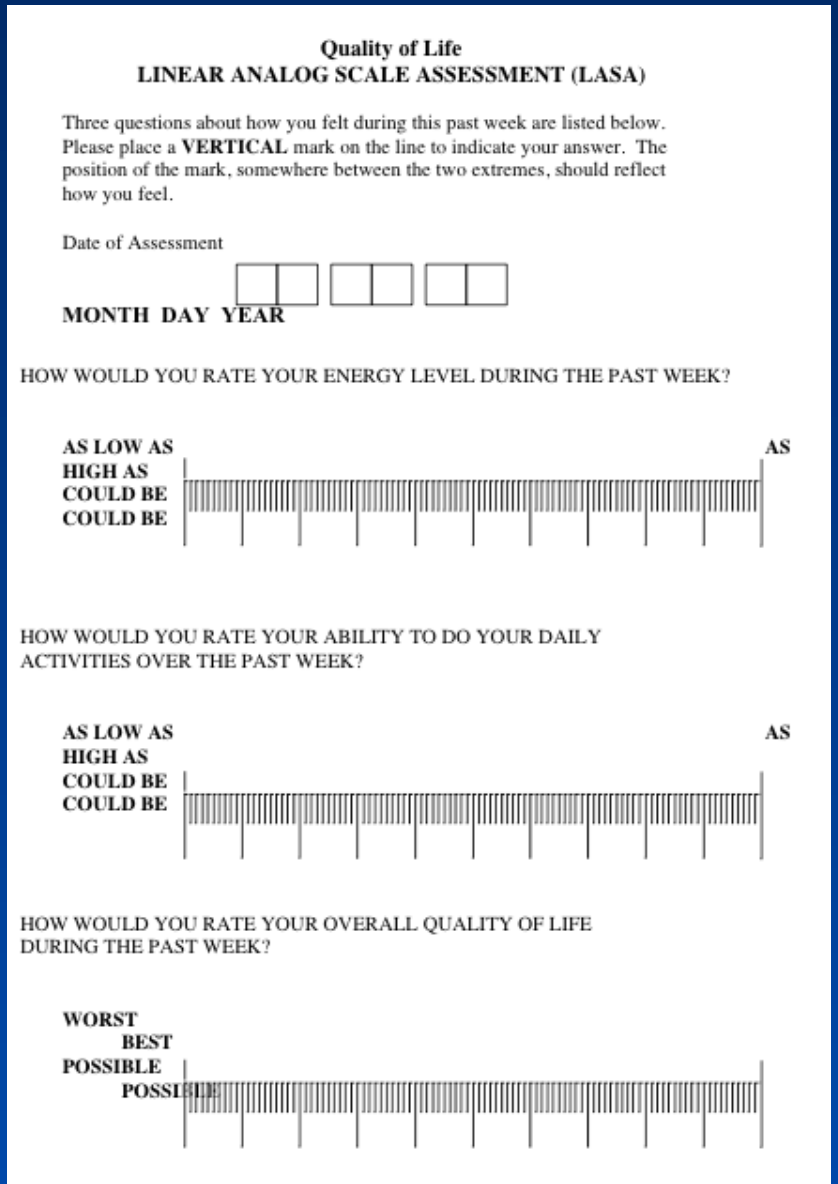


Singh et al In press

CHOIR: QOL

- 3 instruments
  - LASA
  - KDQ
  - SF-36
- Limitations
  - Open label
  - Subjective

CHOIR QOL: LASA



Quality of Life
LINEAR ANALOG SCALE ASSESSMENT (LASA)

Three questions about how you felt during this past week are listed below. Please place a **VERTICAL** mark on the line to indicate your answer. The position of the mark, somewhere between the two extremes, should reflect how you feel.

Date of Assessment

MONTH DAY YEAR

HOW WOULD YOU RATE YOUR ENERGY LEVEL DURING THE PAST WEEK?

AS LOW AS
HIGH AS
COULD BE
COULD BE ... **AS**

HOW WOULD YOU RATE YOUR ABILITY TO DO YOUR DAILY ACTIVITIES OVER THE PAST WEEK?

AS LOW AS
HIGH AS
COULD BE
COULD BE ... **AS**

HOW WOULD YOU RATE YOUR OVERALL QUALITY OF LIFE DURING THE PAST WEEK?

WORST
POSSIBLE ... **BEST POSSIBLE**

Longitudinal Analysis

High vs. Low

	Difference	P value
Energy Level	**0.0798**	**0.350**
Ability in DL	**0.1356**	**0.233**
Overall QOL	**-0.001**	**0.991**

CHOIR KDQ: Fatigue

Week	High Hb 13.5 g/dL	Low Hb 12.3 g/dL	Difference betw'n gp	P value	N at risk (High,Low)
0					663,656
24	0.9	0.8	0.1		456,447
48	0.9	0.8	0.1		364,389
72	0.7	0.7	0.0		54,76
96	0.7	0.5	0.2		62,79
120	0.6	0.5	0.1		9,11
144	-0.7	0.2	-0.9		3,7
Final	0.6	0.6	0.0	0.664	536,536

Longitudinal Analysis

	High Gp	Low Gp	Difference	P value
Estimate	**0.0275**	**0.0248**	**0.0027**	**0.527**
SD	**0.0031**	**0.003**		

CHOIR QOL: Vitality

Week	High Hb !3.5 g/dL	Low Hb 12.3 g/dL	Difference betw' n gp	P value	N at risk (High,Low)
0					684,676
24	14.9	12.1	2.8		493,481
48	13.9	10.9	3.0		395,416
72	7.8	10.6	-2.8		55,78
96	11.4	8.5	2.9		71,83
120	4.1	5.0	0.9		9,11
144	-13.3	13.1	26.4		3,7
Final	10.0	8.2		0.577	579,577

Longitudinal Analysis

	High Gp	Low Gp	Difference	P value
Estimate	0.3778	0.3527	0.0251	0.701
SD	0.0468	0.0455		

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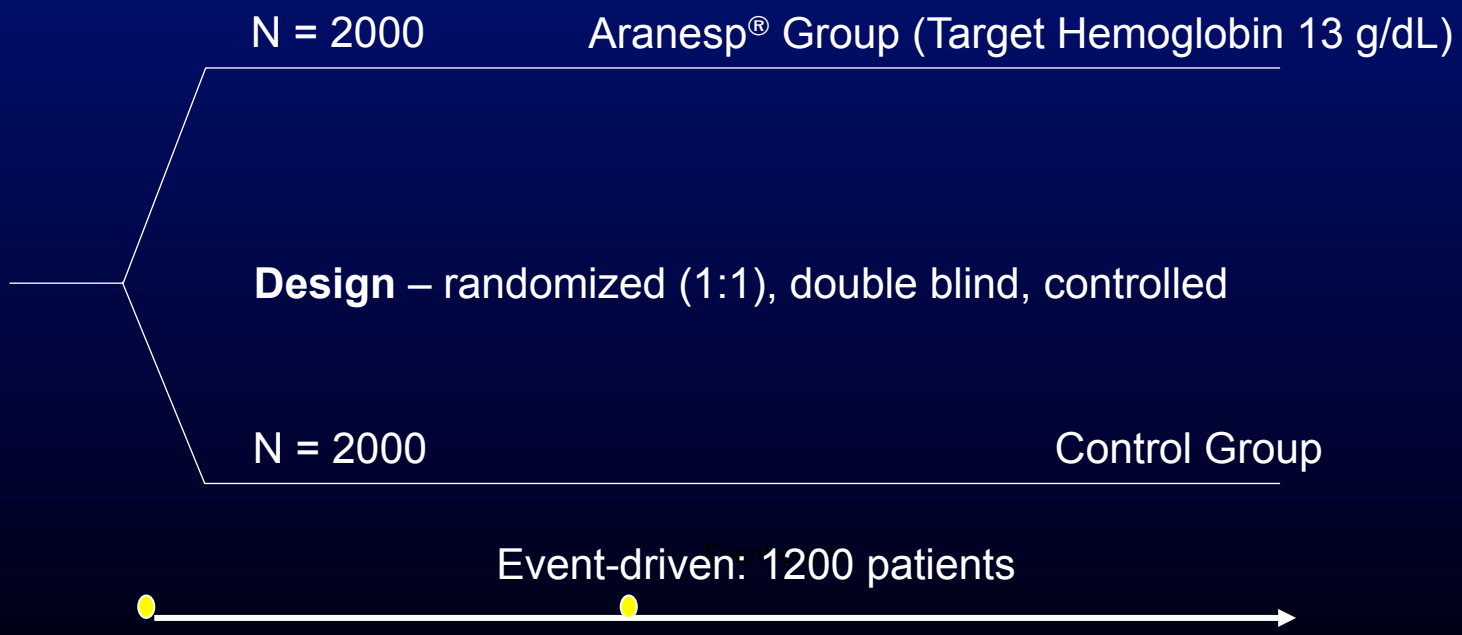

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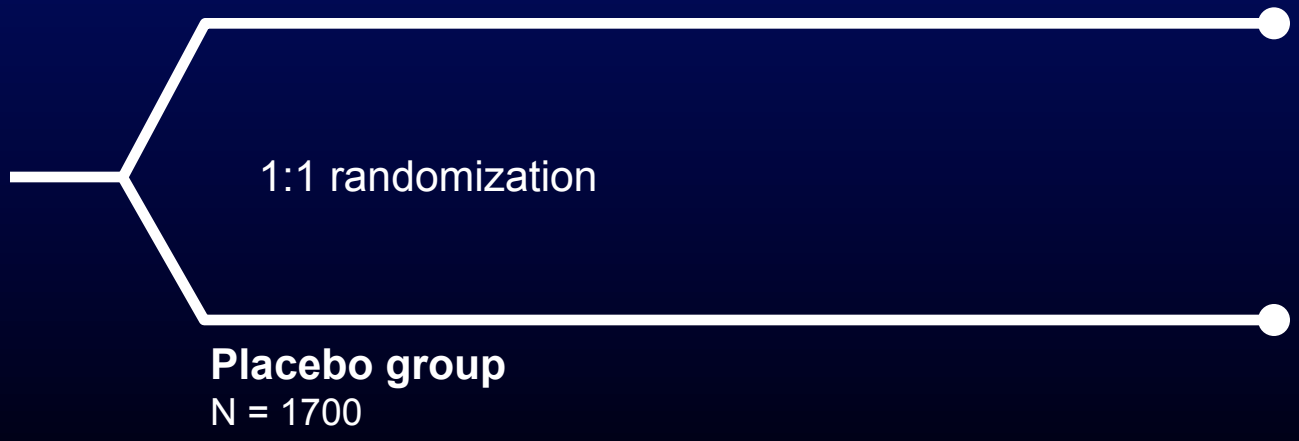

Young JB, et al J Cardiac Failure 2006;(Suppl 1):6:S77.

FDA Black Box Warning
March 9 2007

WARNINGS: Erythropoiesis-Stimulating Agents

Use the lowest dose of ESA that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion (see DOSAGE AND ADMINISTRATION).

ESAs increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

Cancer Patients: Use of ESAs

- Shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL,
- Increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated in this population.