Clinical Significance of Anemia in HF and its Treatment

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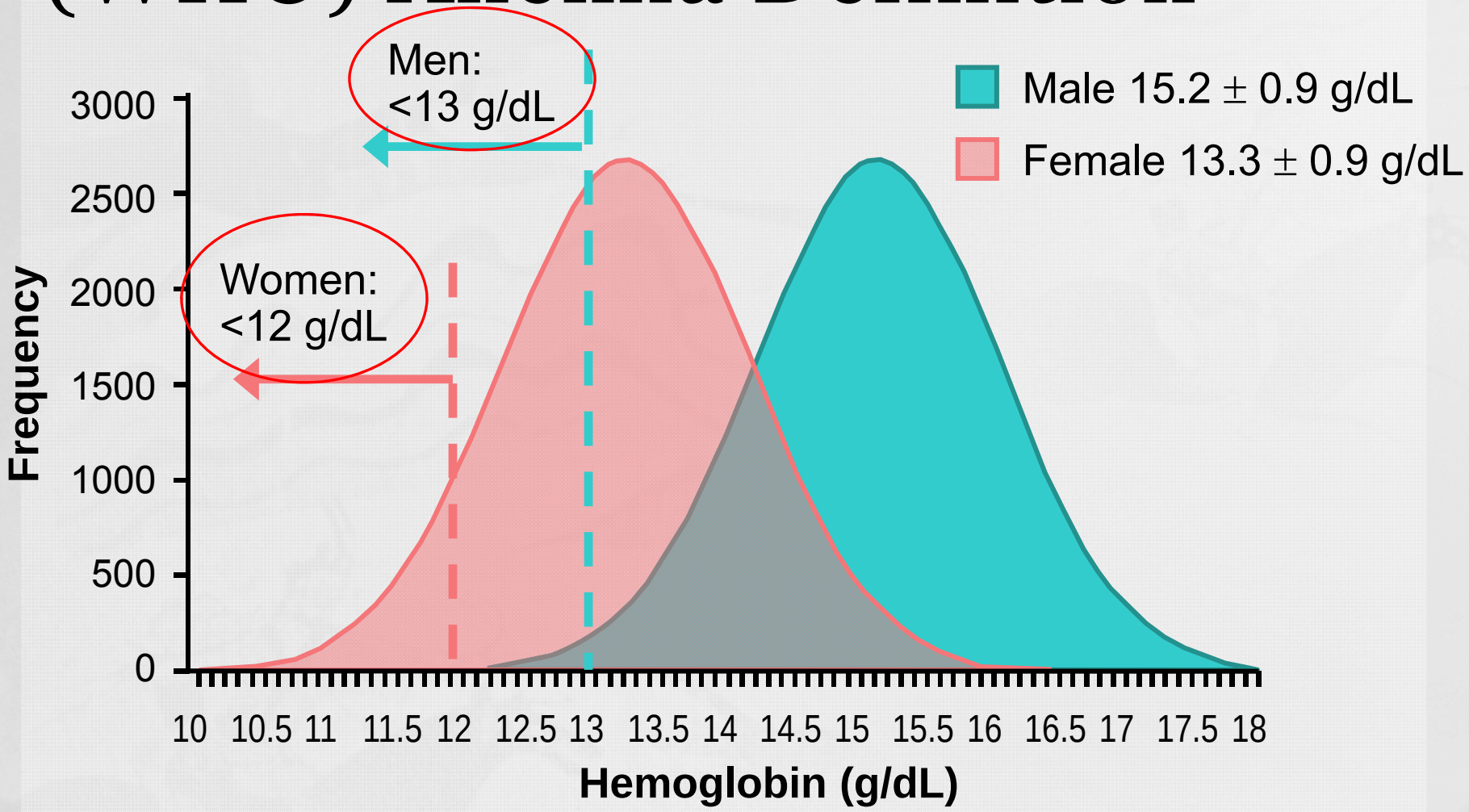
World Health Organization (WHO) Anemia Definition[1]



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.

Scope of the problem

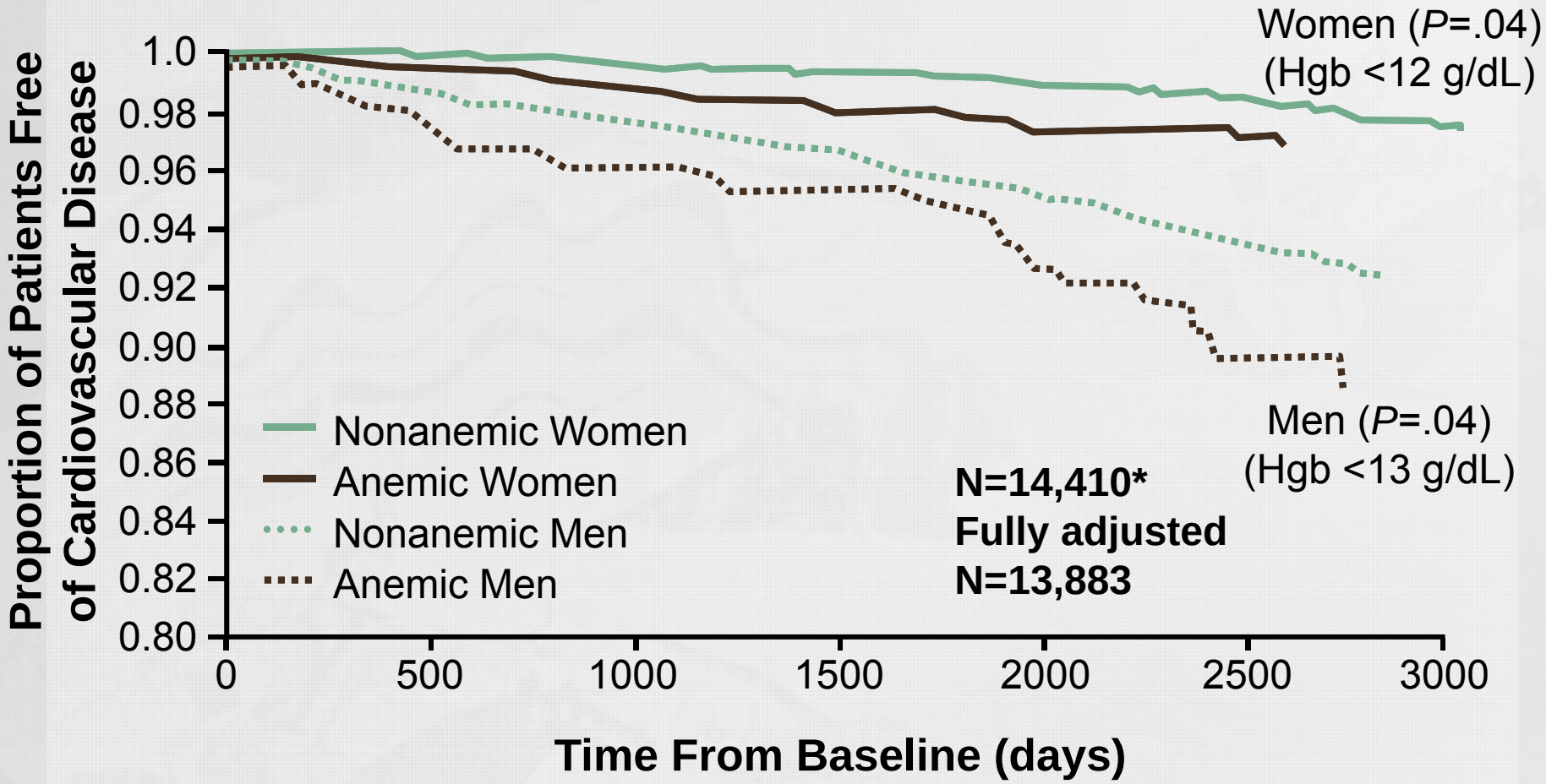
1. Prevalence of Anemia in HF patients is from 4% to 55%.
2. Wide variation is due to
    1. difference in population studied
    2. definition of anemia used
3. Most accepted definition:

Hb <13g/dl in males , <12g in females.

Risk Factors

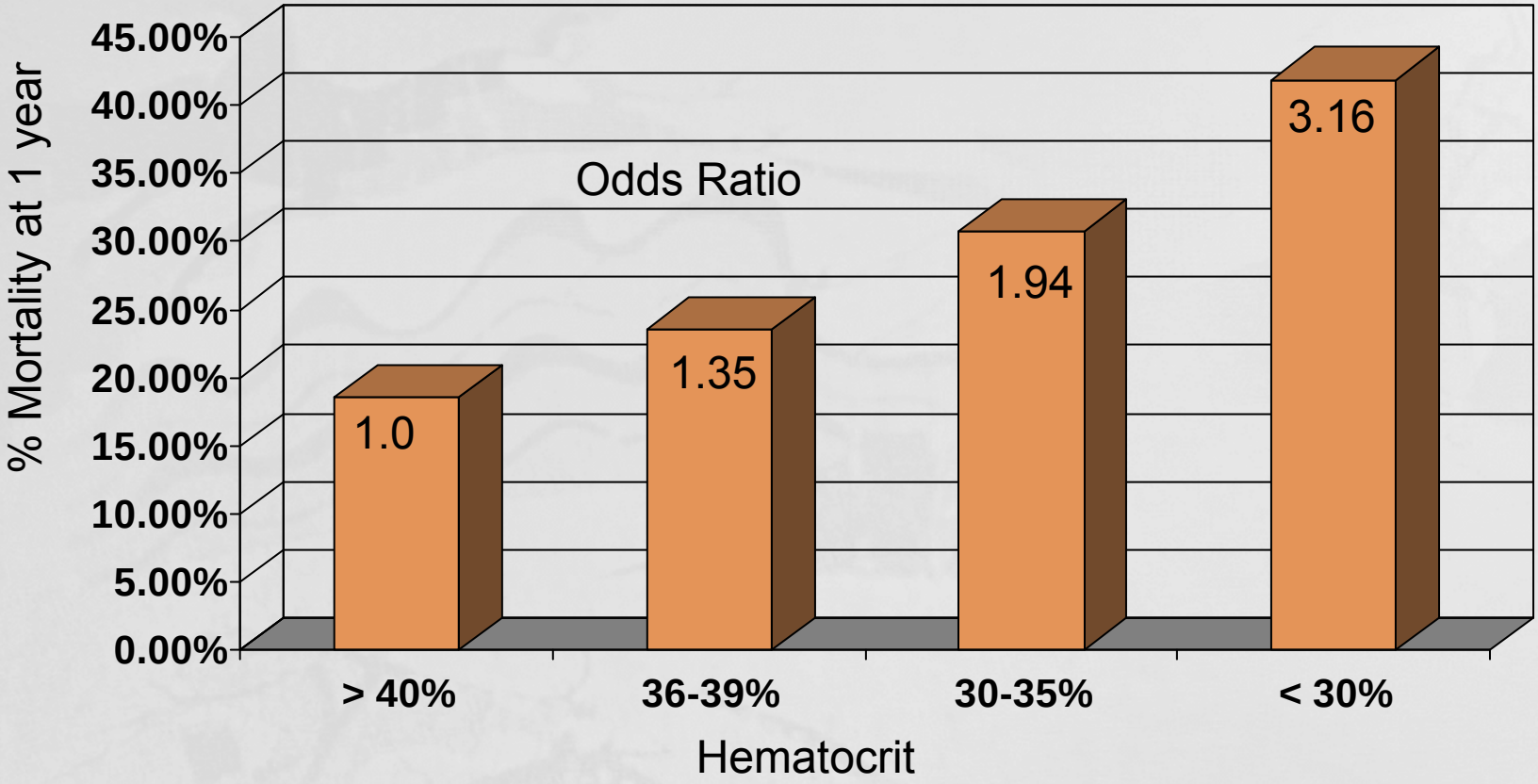
1. Increasing age
2. Female gender
3. Chronic kidney disease
4. Decreased body mass index
5. Use of ACE inhibitors
6. Increased jugular venous pressure
7. Lower-extremity edema

Anemia and Increased Cardiovascular Disease ARIC Study



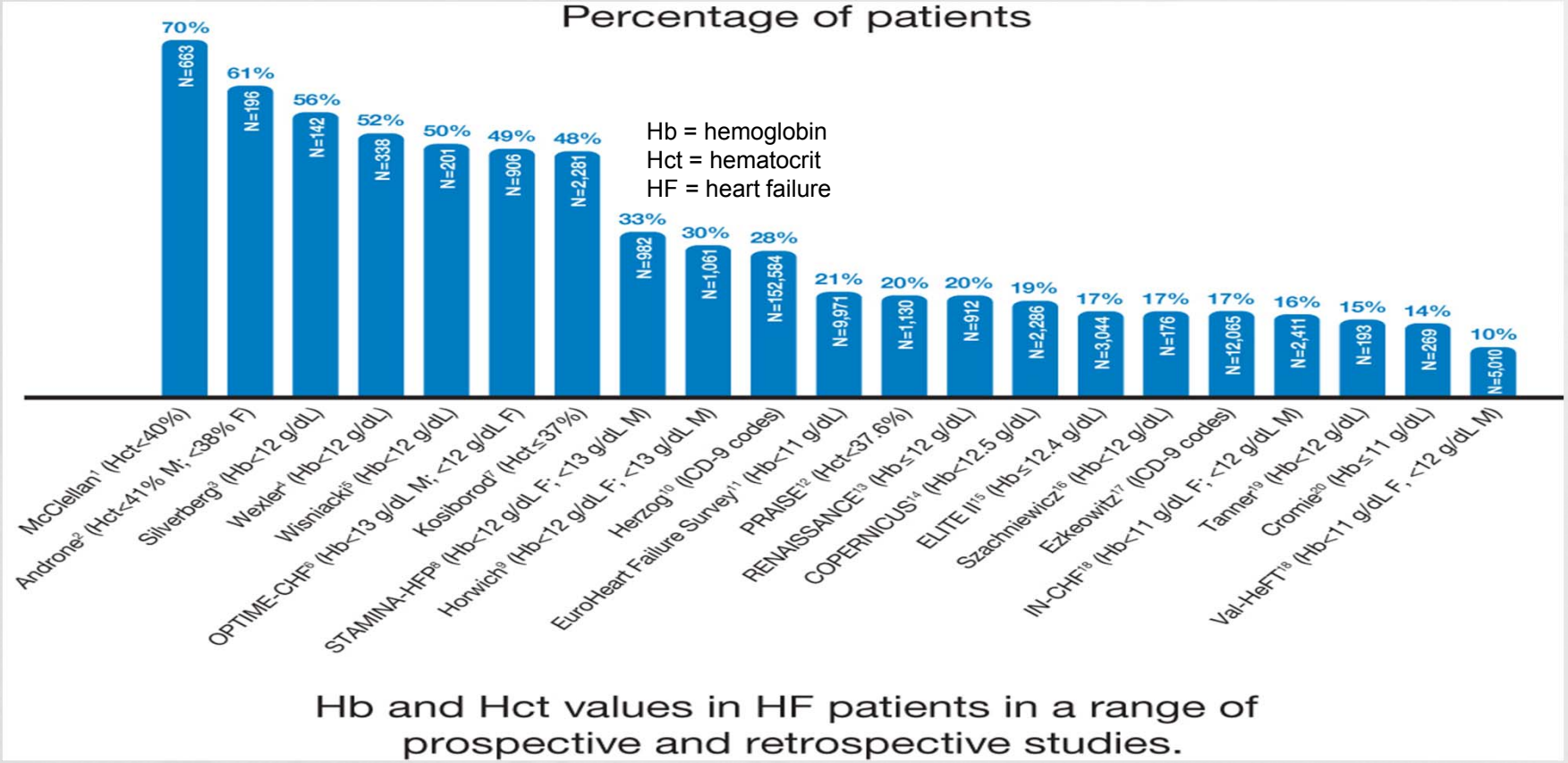
*Patients with hemoglobin levels. Sarnak et al. *J Am Coll Cardiol.* 2002;40:27-33.

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

Anemia In Patients With Heart Failure

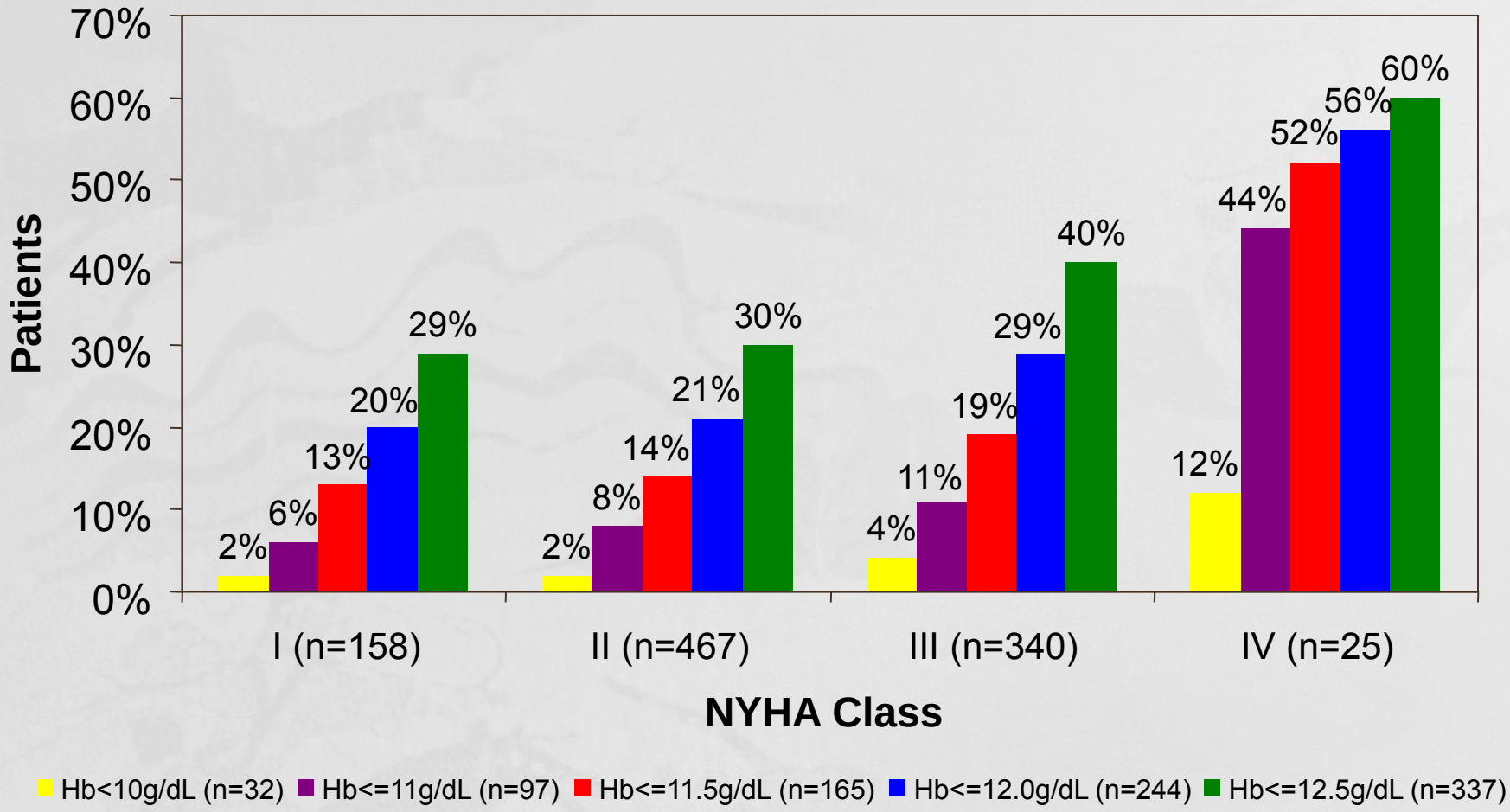


Hb and Hct values in HF patients in a range of prospective and retrospective studies.

The prevalence of anemia in heart failure patients is approximately:

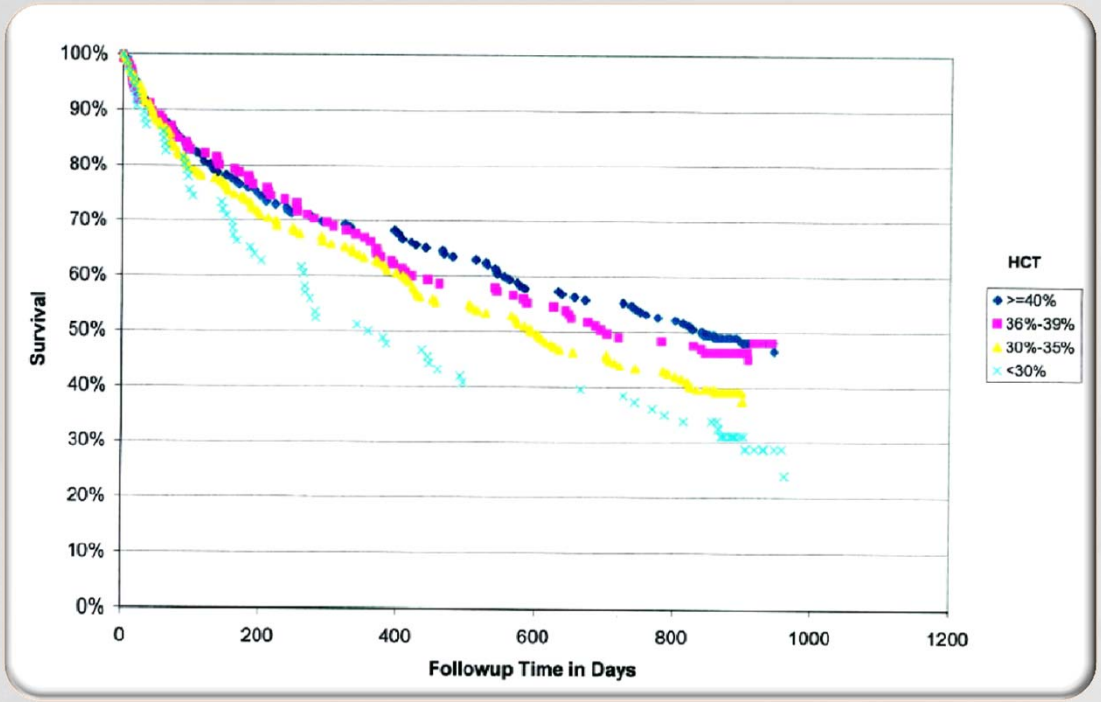
- 30% for Inpatients
- 20% for Outpatients

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

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

Causes of Anemia in HF

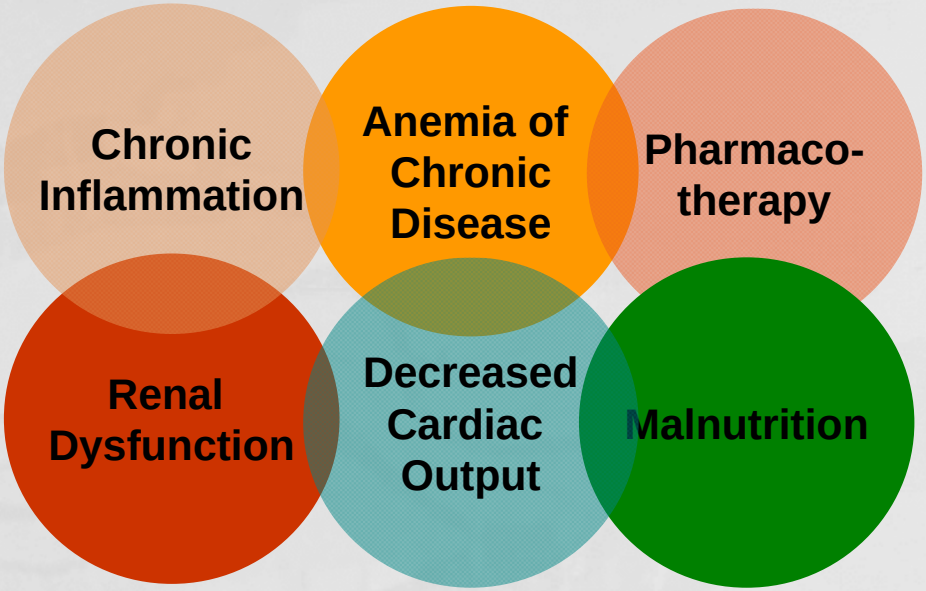
↓ Cardiac Output	• Impaired renal perfusion, leading to impaired renal function, decreased EPO production and anemia[1] • Impaired bone marrow perfusion leading to impaired function and anemia[1]
Cytokines	• TNF and other inflammatory cytokines may cause bone marrow suppression, interfere with the action 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.

Etiology

- Relative erythropoietin deficiency
- Resistance to erythropoiesis
- Nutrition deficiency (e.g., iron, folate, vit. B12)
- Malabsorption secondary to edema of GI mucosa
- Limited availability of iron for erythropoiesis
- Elevation of inflammatory cytokines
- Hemodilution
- Drugs (e.g., ACEi, ARB, aspirin)

The Etiology of Anemia in Heart Failure is Likely Multifactorial



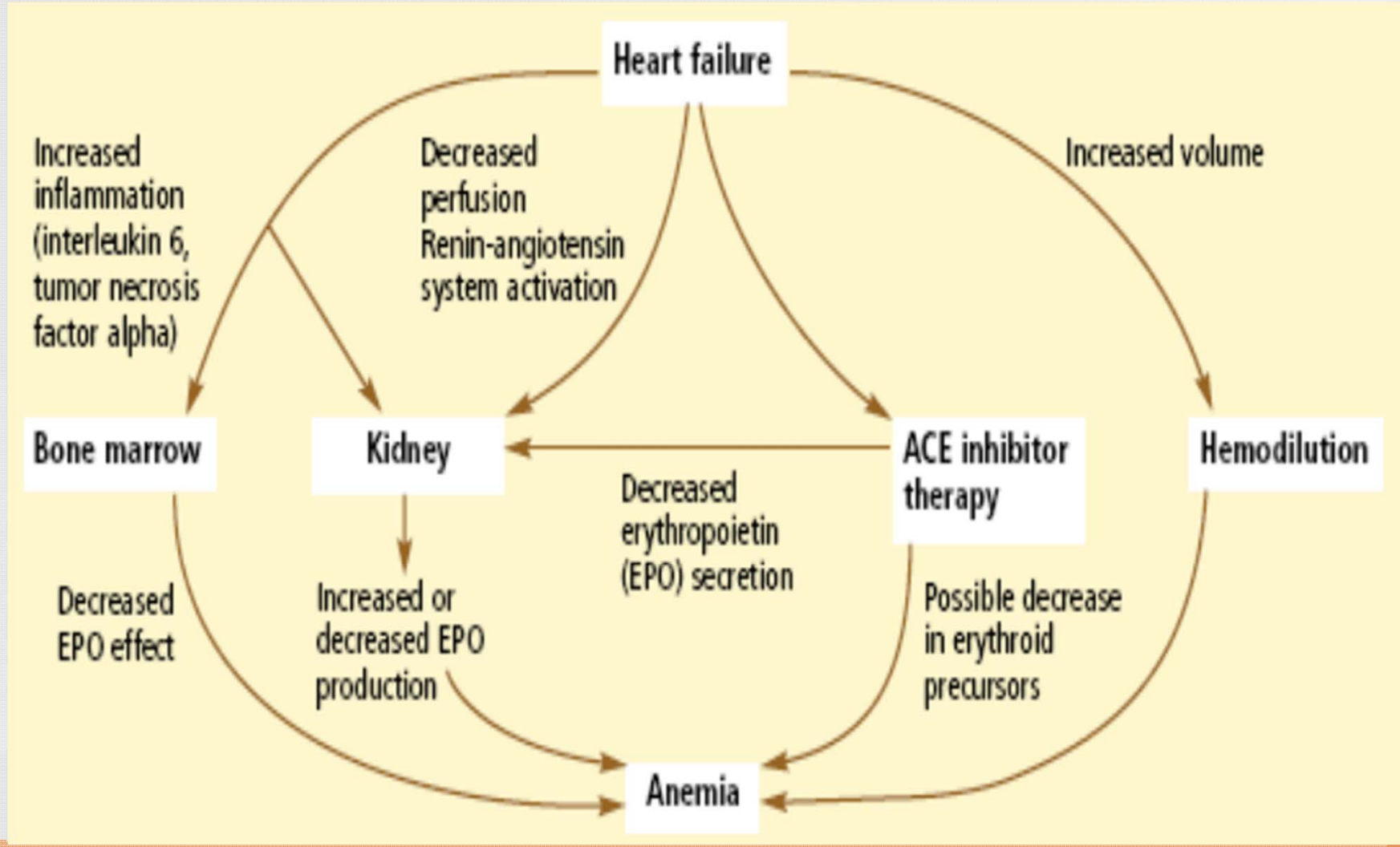
Bone marrow dysfunction

Abnormal iron homeostasis (uptake, release, utilization)

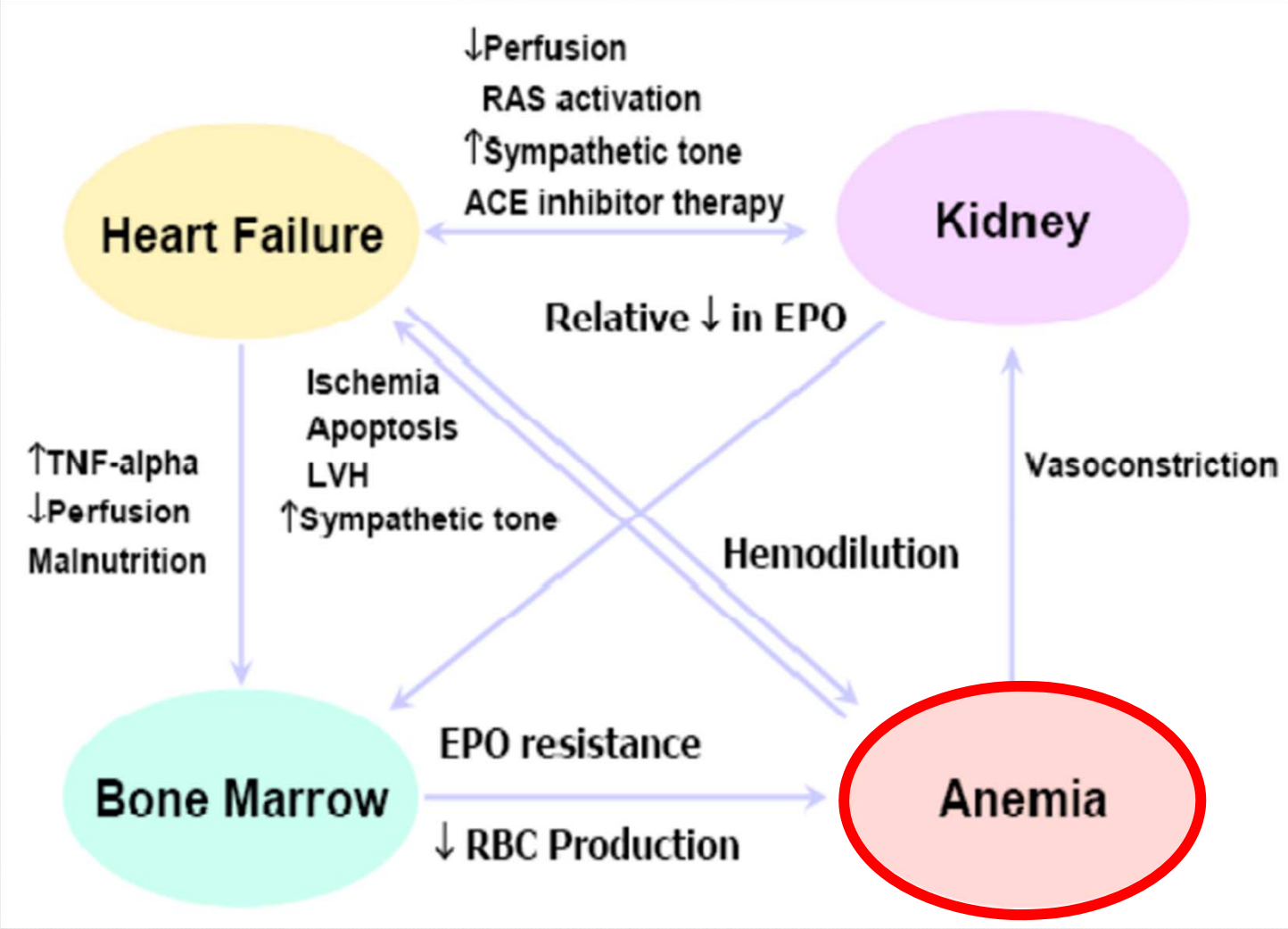
Intravascular fluid imbalance (hemodilution)

EPO deficiency or resistance

Anemia in heart failure is likely multifactorial



Anemia in heart failure is likely multifactorial



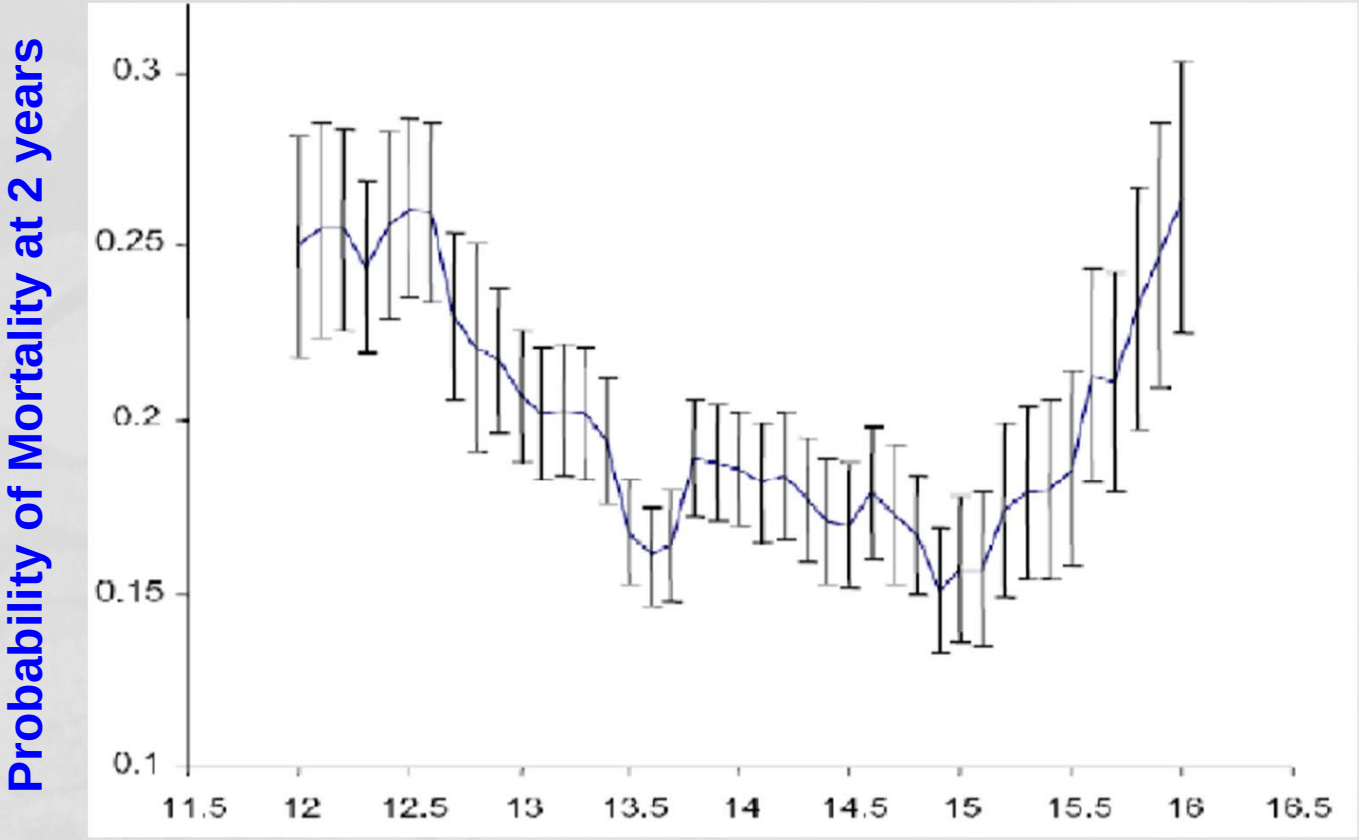
Consequences of Anemia

1. Independent risk factor for development of symptomatic CHF.
2. Statistically significant increased mortality.
3. poor exercise tolerance even after controlling for ejection fraction, age, and renal function.
4. reducing oxygen-carrying capacity, forcing the heart to adapt by increasing its rate and stroke volume.

Consequences of Anemia

Investigator	Profile	Association
Al-Ahmad *et al.*[1] SOLVD	Anemic patients were more likely to be older, women, non-white, NYHA class III or IV, and diabetic	A 1% lower Hct was associated with a 1.027 (95% CI: 1.015, 1.038) higher relative risk for mortality; anemia and low GFR were found to be independent risk factors for predicting morbidity and mortality in heart failure
McClellan *et al.*[2]	Anemic patients were more likely to be older	Compared with individuals with an Hct ≥40%, the RR (95% CI) at 1 year for anemic patients was 1.08 (.79–1.47) for Hct 36–39%;1.17 (0.89–1.54) for Hct 30–35%; 1.60 (1.19–2.16) for Hct ≤30%
Mozaffarian *et al.*[3] PRAISE	Higher Hct was associated with younger age, male gender, more prevalent smoking, slightly lower EF, and higher blood pressure	Over a range of Hct between 25.4 and 37.5, each 1% decrease in Hct was associated with a 11% higher risk of death (HR 1.11, 95% CI: 1.02–1.20, p<0.01) and an 8% higher risk of pump failure deaths (HR 1.08, 95% CI:1.05–1.12) Compared with the highest quintile (46.1–58.8%), the patients in the lowest quintile (25.4–37.5%) had a 52% higher risk of death
Horwich *et al.*[4]	Anemic patients were more likely to be women, in NYHA class IV, have lower albumin, lower BMI, impaired renal function, lower blood pressure, higher heart rate, and higher right-sided pressures	On univariate analysis, each 1g/dl decrease in Hgb was associated with a 16% increased risk of death; on multivariate analysis, each 1 gm decrease in Hgb was associated with a 13% increased risk of mortality (RR 1.1, CI: 1.045–1.224)
Ezekowitz *et al.*[5]	Anemia was more common in older patients, in women, and in patients who were hypertensive or had chronic renal insuffiency	1 and 5 year mortality was 38 and 59% in patients with anemia, respectively, compared with 27% and 50% for those without anemia (p<0.0001); Cox proportional hazard ratios for mortality in anemic patients was 1.34 (1.24–1.46)
Kalra *et al.*[6]	Anemic patients were more likely to be older, and have higher creatinine, lower peak VO_2, and severe symptoms; no significant difference in LVEF between the patients who were and were not anemic	Peak VO_2 decreased significantly with decreasing Hgb levels; R: 0.41, p<0.014; hemoglobin was an independent predictor of peak VO_2 max, independent of age, EF, and serum creatinine

Consequences of Anemia



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

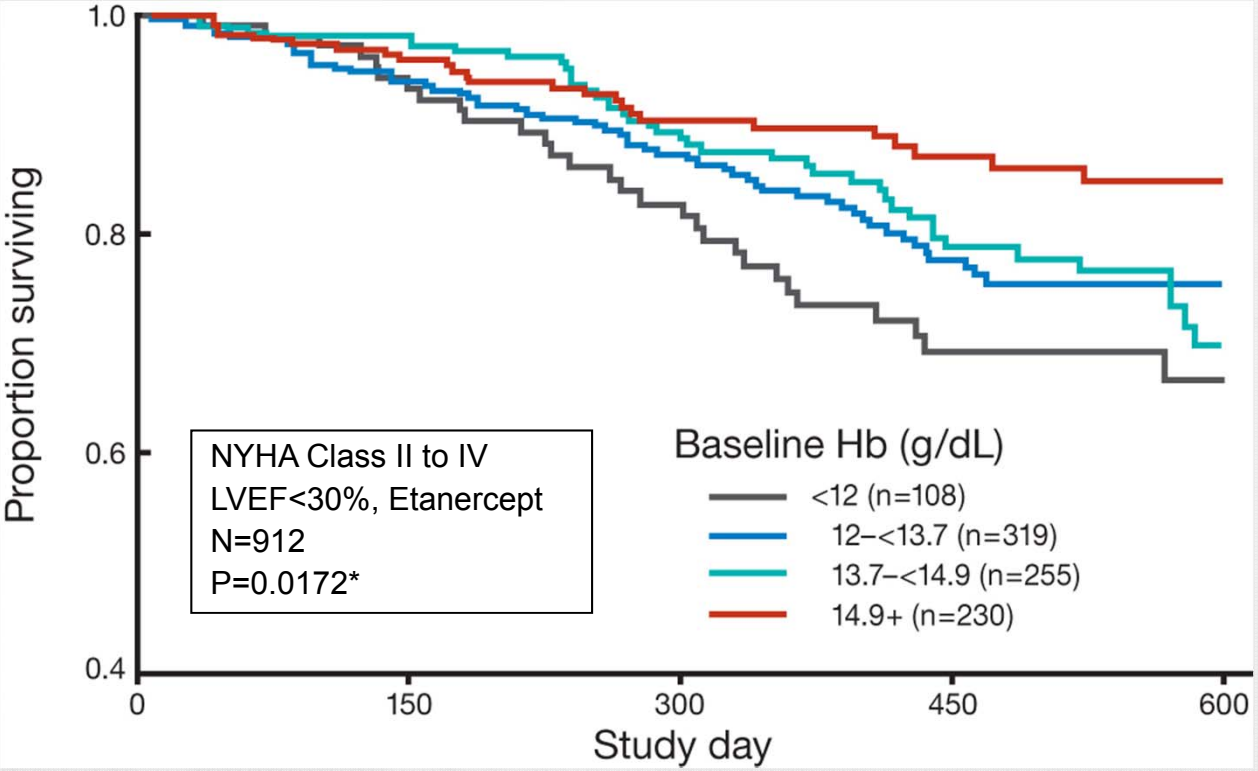
Study	Design	N	Anemia Risk Assessment	Limitations
Alexander[1]	Retrospective cohort study of a population based HF database	90,316	Anemia was an independent risk factor of 1-year rehospitalization (RR 1.162; 95% CI: 1.134 to 1.191)	no confirmation of the HF diagnosis; undercounts of minorities and biased 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

Anemia and Mortality In Heart Failure Patients: RENAISSANCE

RENAISSANCE Study[1]

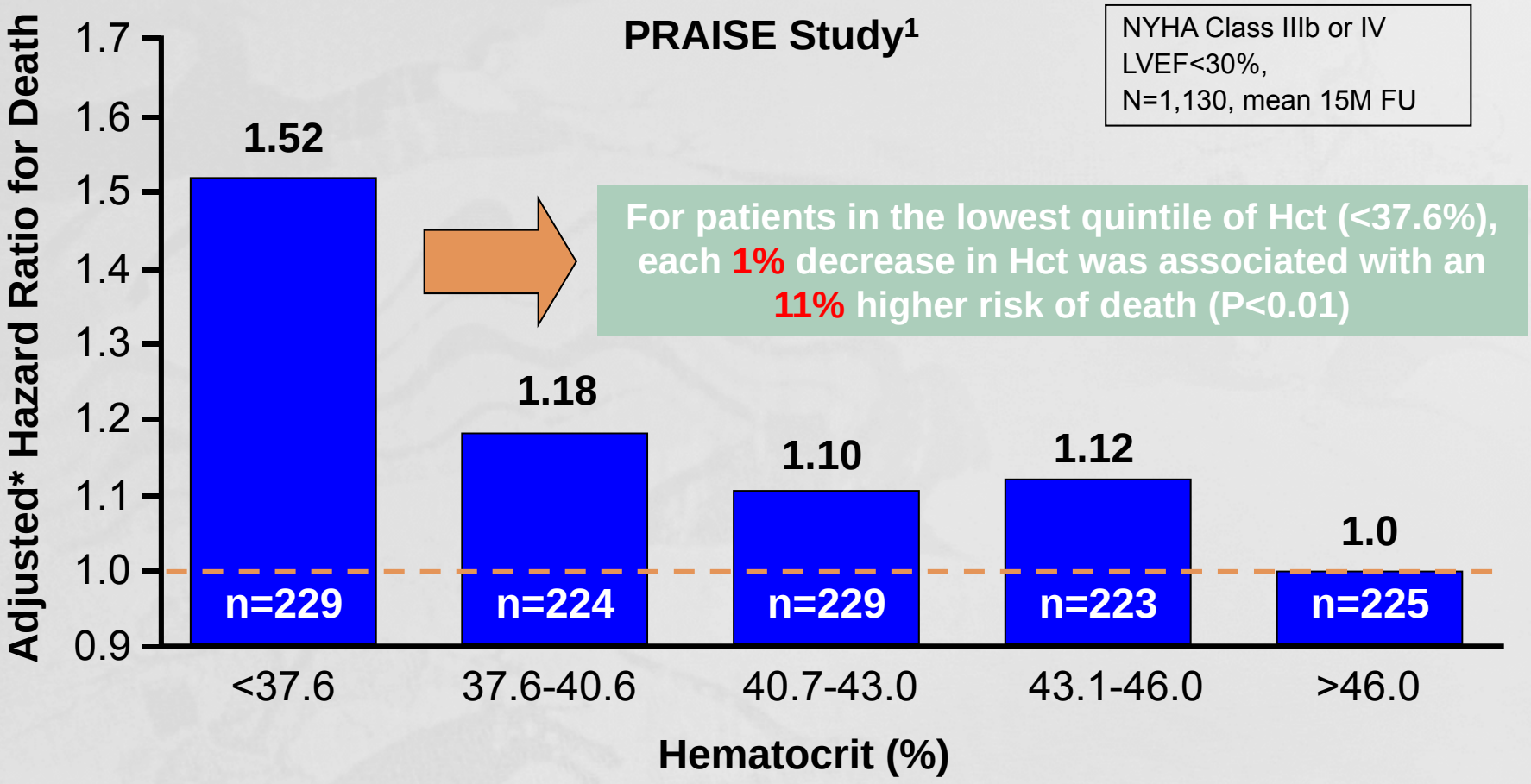
Kaplan-Meier Survival Curve by Baseline Hb Concentration



*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

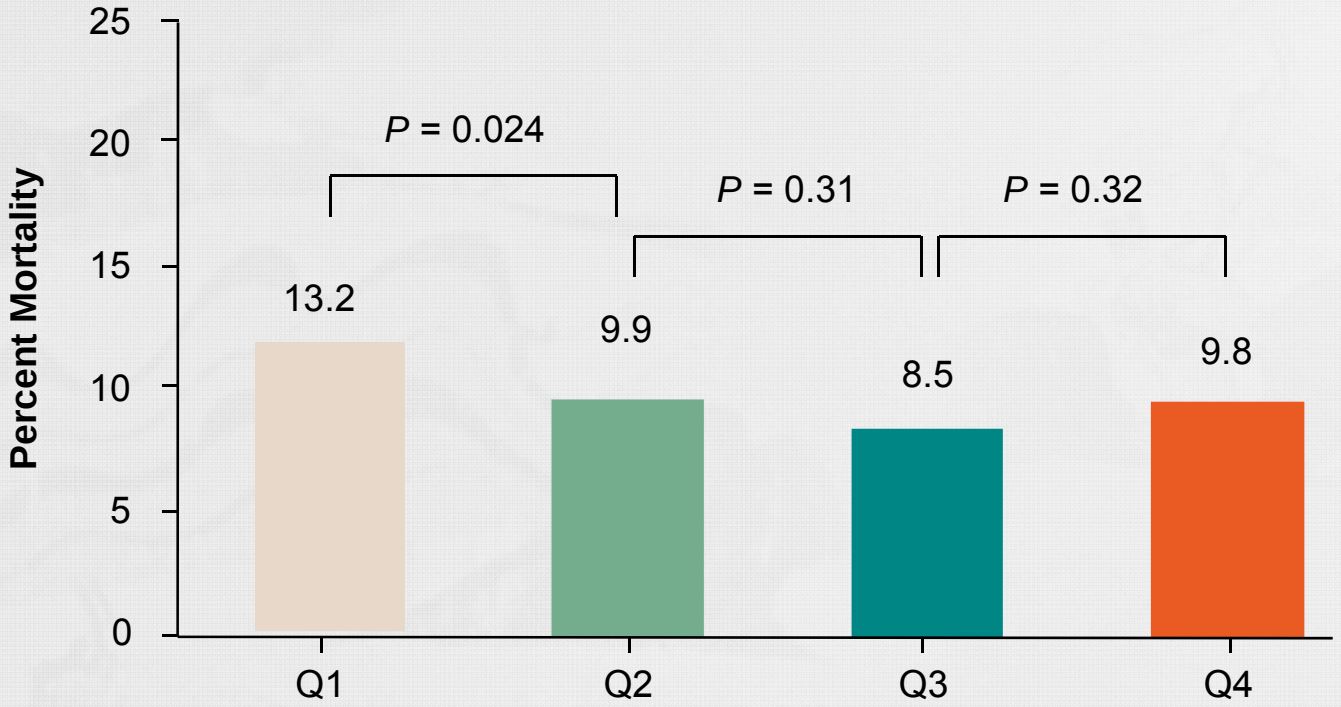
COPERNICUS Study[1]

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

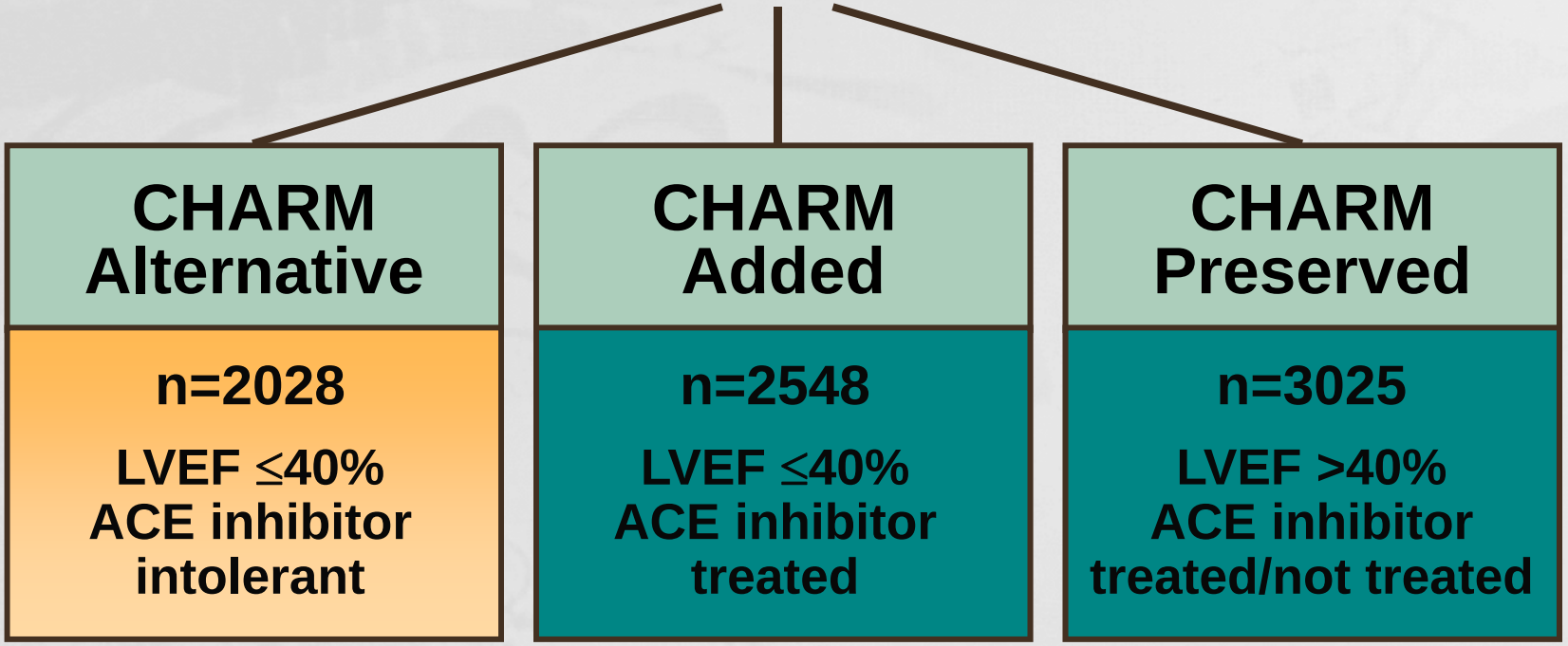


Quartile change in Hgb, g/dL	< - 0.8	> - 0.8 to < -0.1	> - 0.1 to < + 0.5	≥ + 0.5
Mean change in Hgb, g/dL	- 1.66	- 0.47	+ 0.15	+ 1.11
Mean BL Hgb, g/dL	14.24	13.92	13.71	13.30
Mean 12 month Hgb, g/dL	12.58	13.44	13.86	14.40
Number of patients	950	991	937	1028

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

CHARM Programme

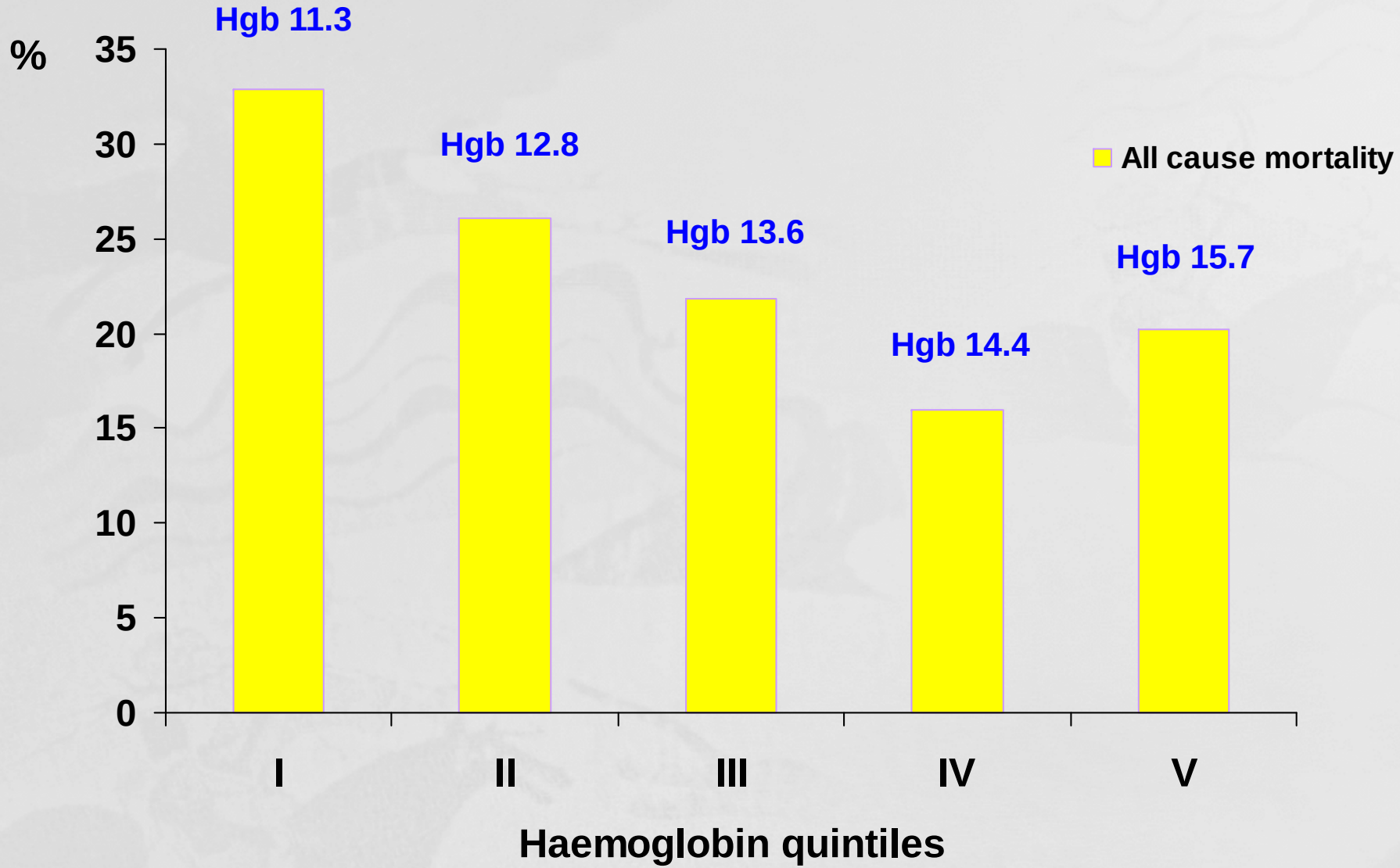
3 component trials comparing candesartan to placebo in patients with symptomatic heart failure



Primary outcome for each trial: CV death or CHF hospitalisation

Primary outcome for Overall Programme: All-cause death

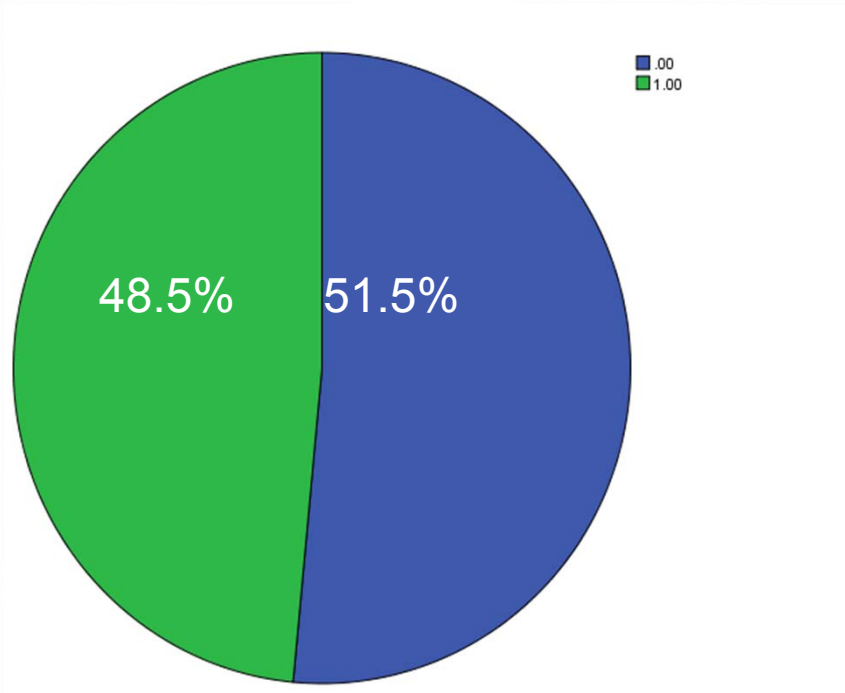
Hemoglobin and Mortality



O'Meara et al. CHARM Investigators. Circulation 2006

Anemia in KorHF registry

		Frequency	Percent	Valid %
Valid	Normal	1638	51.2%	51.5%
	Anemia	1543	48.2%	48.5%
	Total	3181	99.4%	100%
Missing	System	19	0.6%	
Total		3200	100.0	



Anemia in KorHF registry

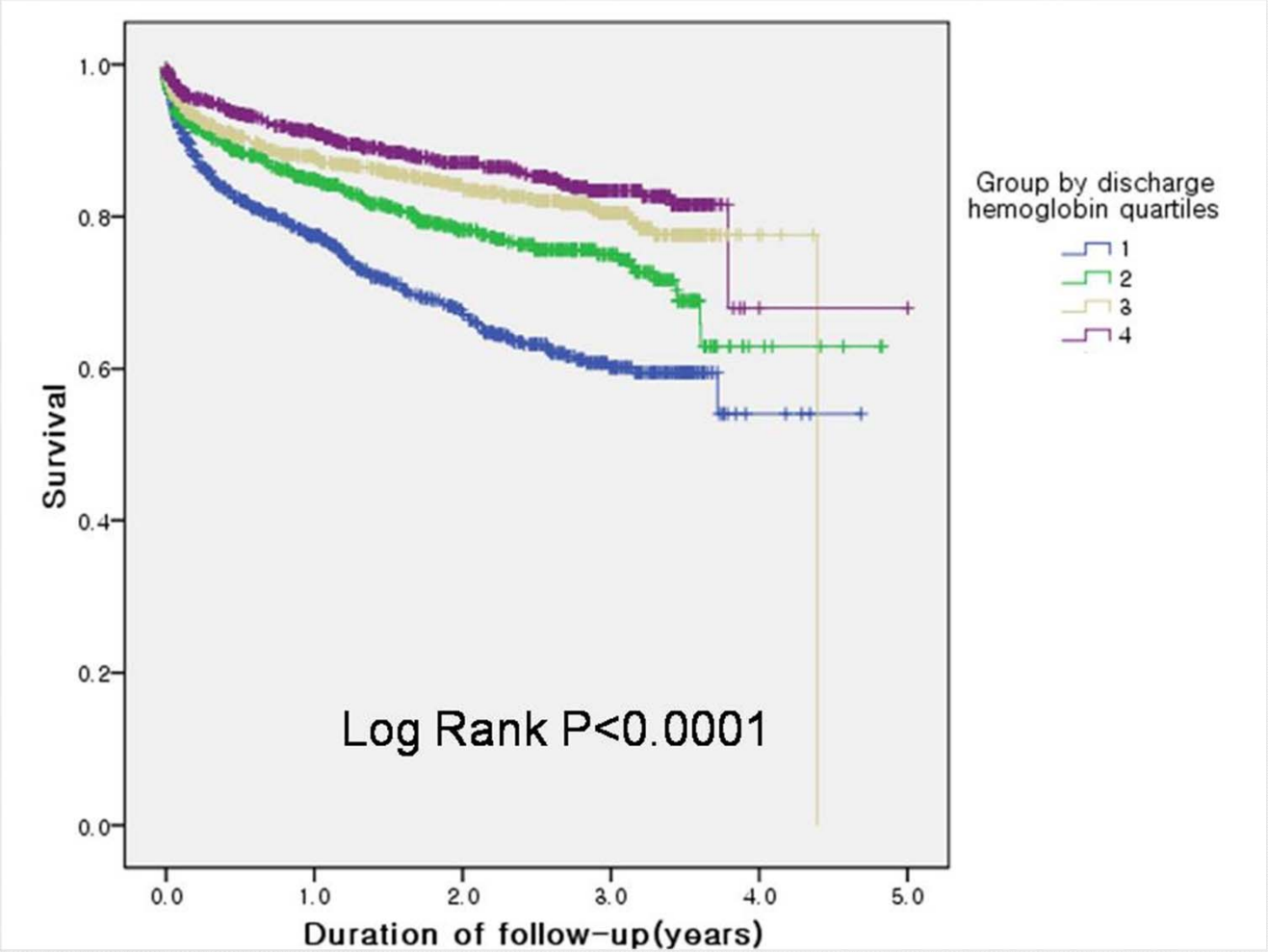
		Anemia (n=1543)	Non-Anemic (n= 1638)
Demograhpic	Age, yrs	71.7±12.4	64.7±14.9
	Male	454 (34.5)	1146(60.8)
	Height , cm	156.8±9.4	162.2±9.7
	Weight, Kg	55.24±11.4	62.55±13.7
	BMI, kg/m^2	0.225±0.04	0.238±004
Medical Hx	Hypertension	690 (52.4)	796 (42.3)
	Diabetes	503 (38.2)	472 (25.1)
	COPD	49 (3.7)	55 (2.9)
	IHD	229 (17.4)	226 (12)
	PCI Hx	132 (10.7)	129 (7.5)
	CABG Hx	40 (3.2)	36 (2.1)
	PVD	24 (1.8)	28 (1.5)
	CKD	232 (17.6)	63 (3.3)
	Stroke Hx	148 (11.2)	151 (8)
	NYHA I	100 (7.6)	183 (9.7)
	NYHA II	152 (11.6)	267 (14.2)
	NYHA III	562 (42.7)	814 (43.2)
	NYHA IV	290 (22)	326 (17.3)
P/E	SBP, mmHg	130.94±30.3	130.22±30.1
	DBP, mmHg	75.9±17.0	79.4±18.6
	HR, bpm	89.8±24.1	92.3±26.2
Cause	Ischemic HD	548 (43)	646 (35)
	VHD	187 (14.7)	220 (11.9)
	Myocarditis	5 (0.4)	17 (0.9)
	HCMP	24 (1.8)	49 (2.6)
	Pregnancy-induced	8 (0.6)	3 (0.2)
	Idiopathic CMP	94 (7.1)	121 (6.4)
	Systolic HF	1307 (77.6)	793 (68.4)
	Diastolic HF	366 (31.6)	377 (22.4)
Laboratory data	Hemoglobin ,g/dl	10.2±1.37	14.1±1.46
	LVEF, %	42.6±16.1	37.5±16.4
	Sodium , mmol/L	137.5±5.4	138.5±5.0
	Potassium, mmol/L	4.38±0.87	4.21±0.67
	NT-proBNP, pg/ml	12045±11616	6126±7583

Anemia in KorHF registry

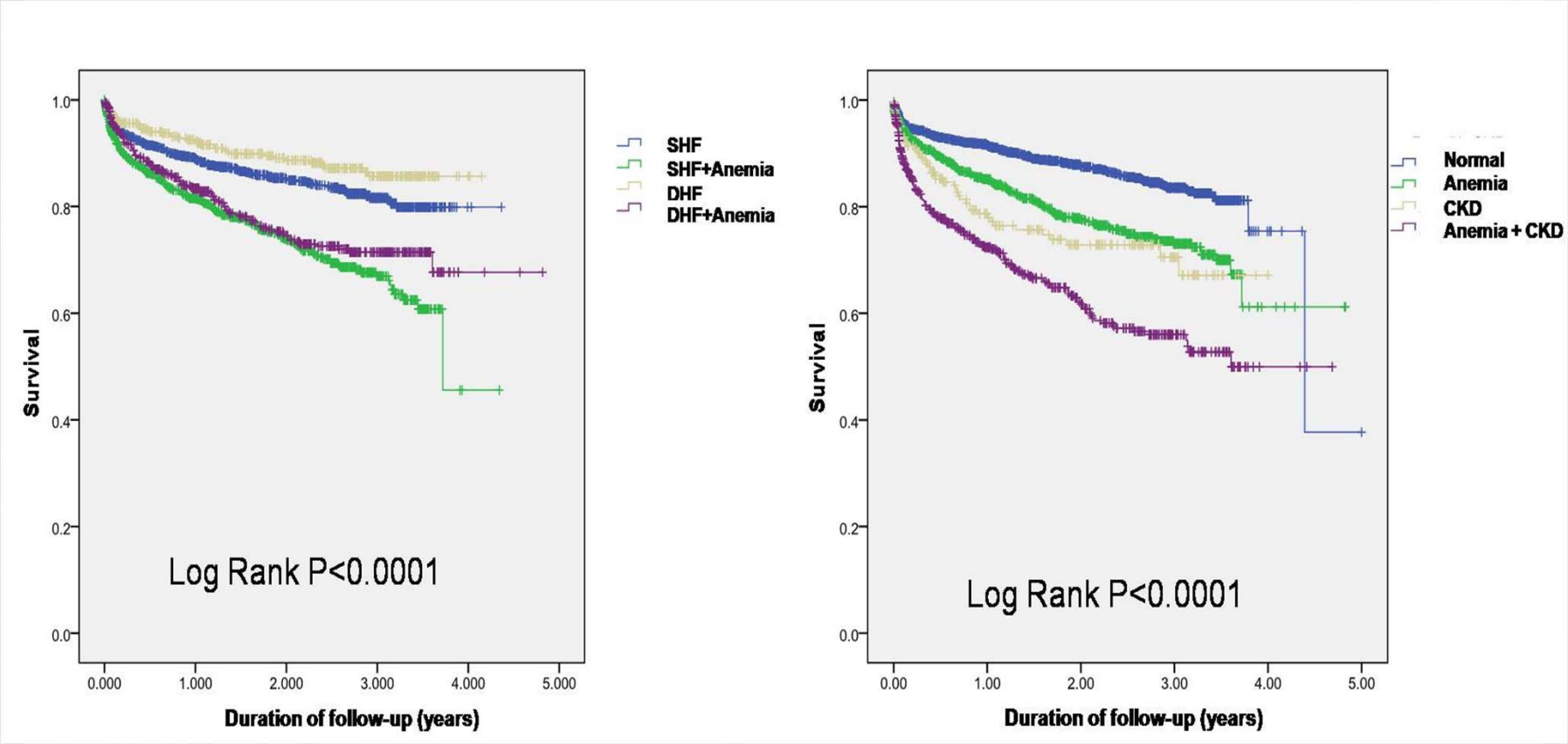
Multivariate analysis

Variables	H.R.	95% C.I.		P
Age	1.015	1.007	1.024	.000
Weight	.966	.956	.976	.000
Sex	1.178	.929	1.492	.176
DM	.622	.489	.792	.000
CKD	.311	.176	.550	.000
SBP	1.008	1.003	1.013	.003
T-Cholesterol	.991	.988	.993	.000
EF>50%	.743	.588	.939	.013

Anemia in KorHF registry



Anemia in KorHF registry



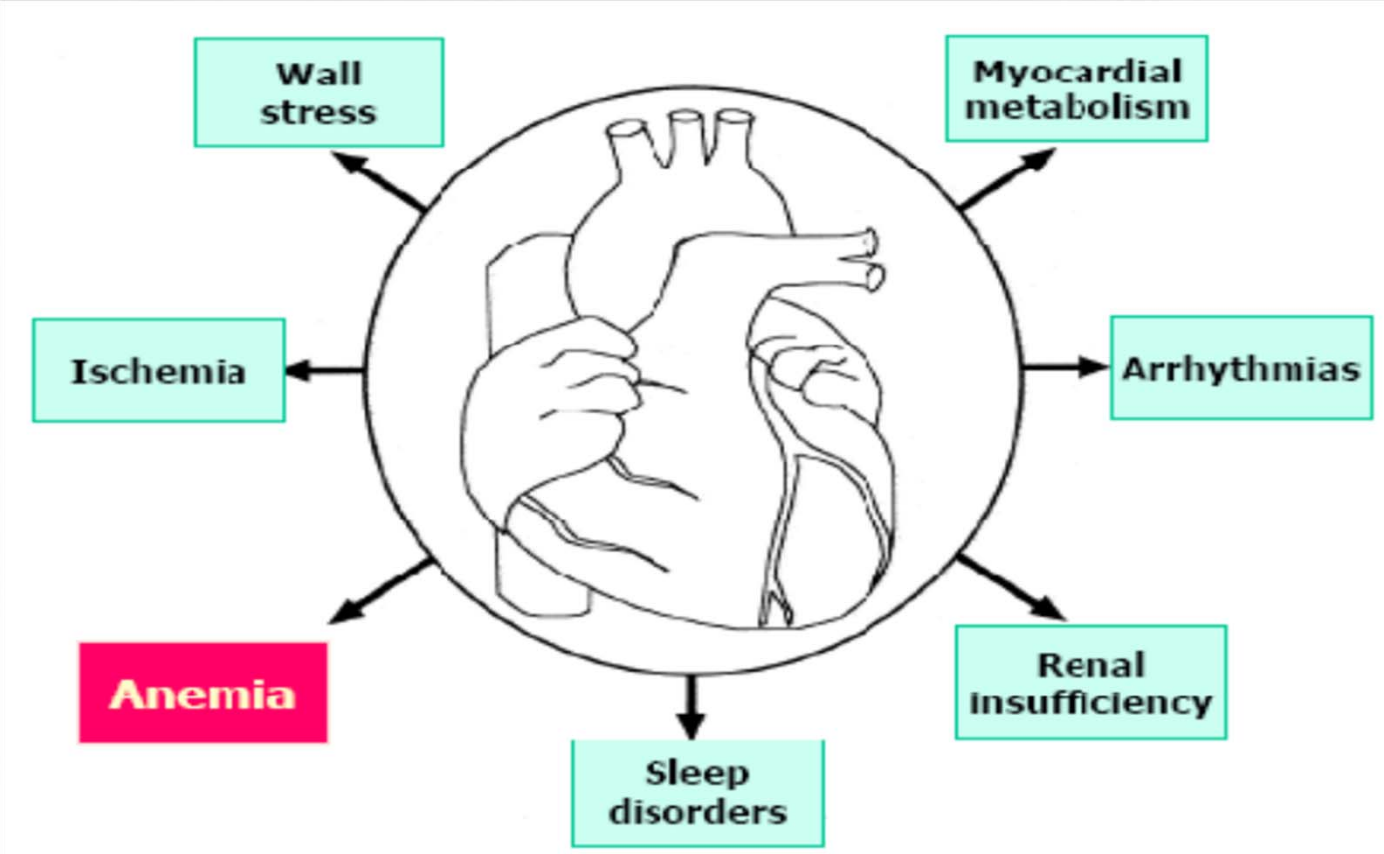
Rationale for Anemia Correction

Potential Benefits of Treating Anemia in CVD

1. Improved oxygen delivery
2. Improved exercise tolerance
3. Attenuate adverse remodeling
4. Improved QoL
5. Antiapoptotic?
6. Decrease in hosp./death?

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

New therapeutic target?



When To Treat?

1. Hemoglobin level ≤12.0g/dl
2. with repeated episode of ADHF
3. and already receiving maximally therapy

Treatment options

1. Blood transfusion:

- short term effect
- increase the intravascular volume,
- can cause infections,
- costly.

Treatment options

2. rHuEPO:

- Increases hemoglobin level
- Increases peak oxygen consumption max
- Improves functional class
- Decreases ventricular remodeling

Treatment options

2. rHuEPO:

Disadvantage Increases

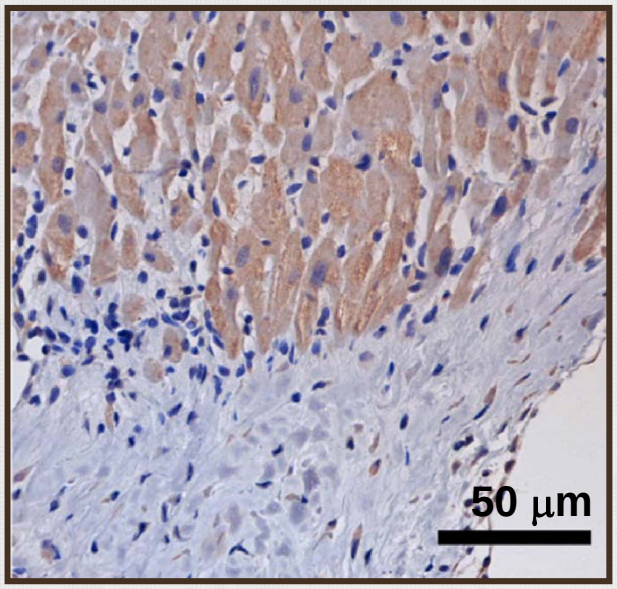
- Increases hypertension
- Increases thrombosis
- Increases endothelin activation
- Expensive

★***Darbepoietin alfa***

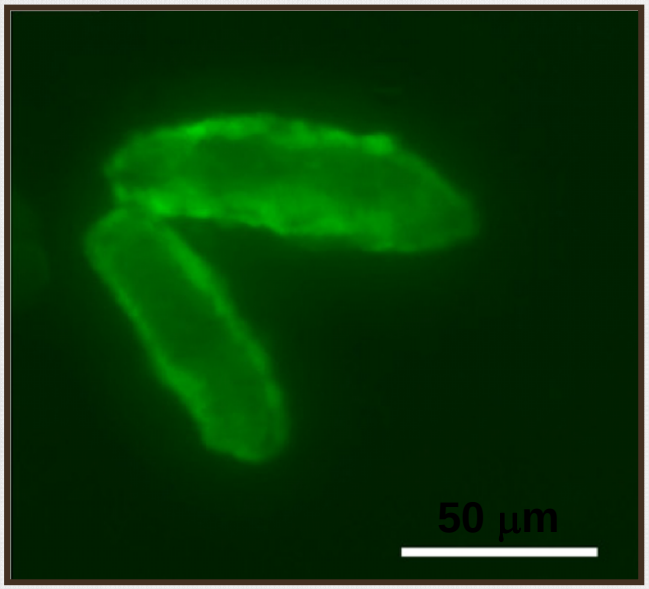
N-linked supersialylated analog,

T1/2 48h, Since 2001

Erythropoietin Receptors are Present on *Adult* Cardiac Myocytes



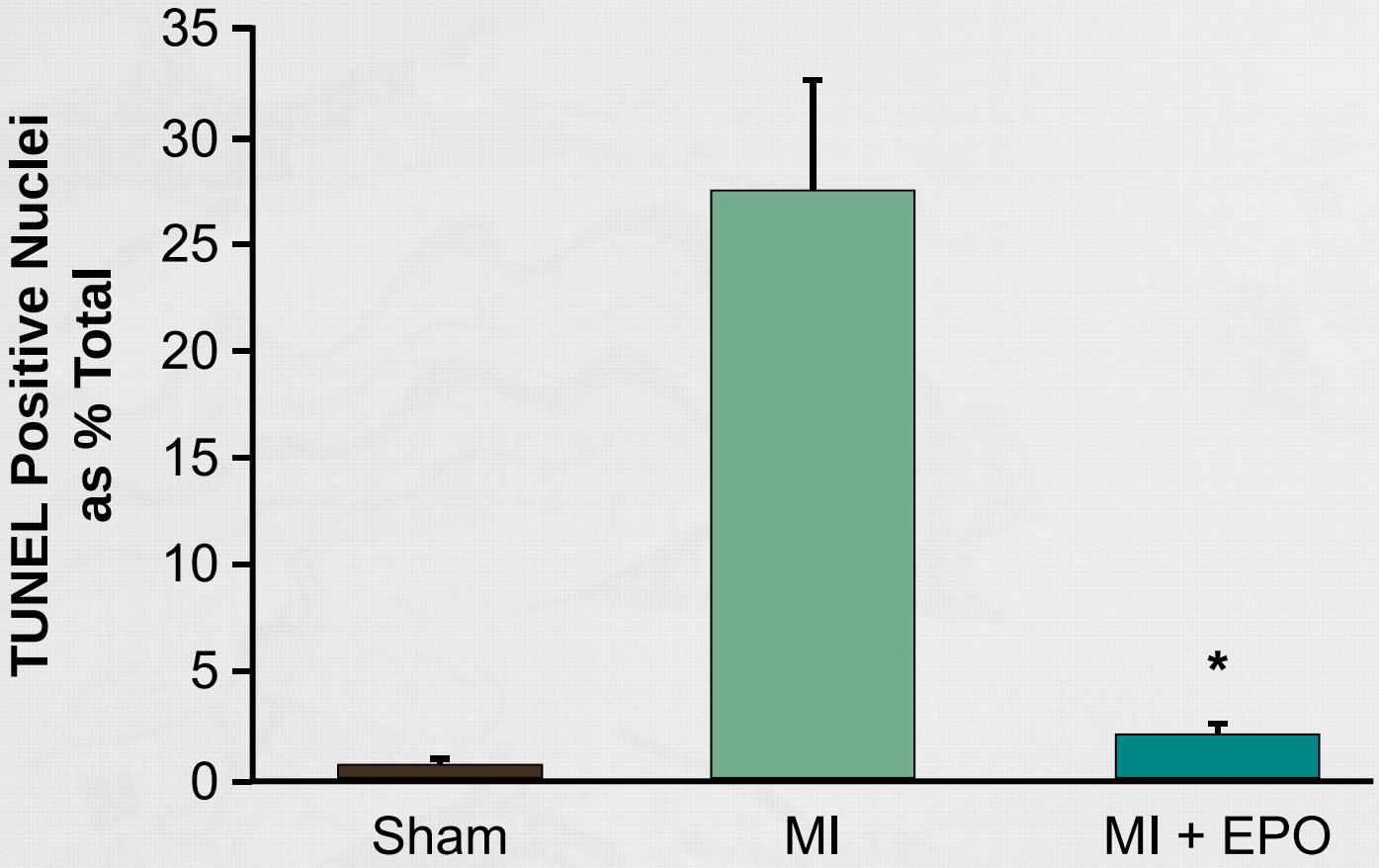
EPOR protein in adult rat heart sections using immuno-histochemistry



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

Wright et al. 2004. FASEB.

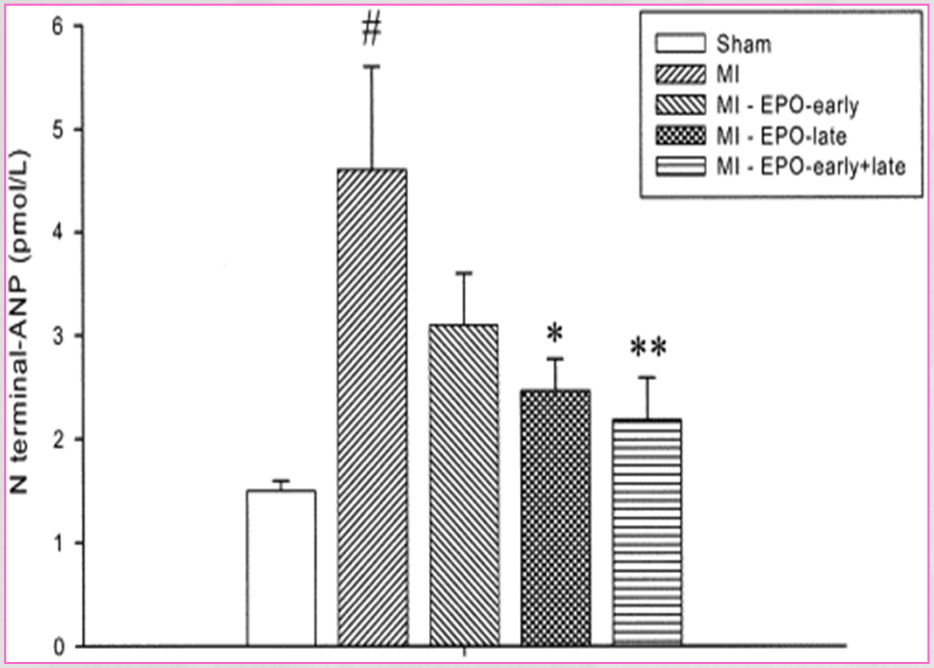
EPO Administered at time of LAD Ligation Reduces Myocyte Apoptosis



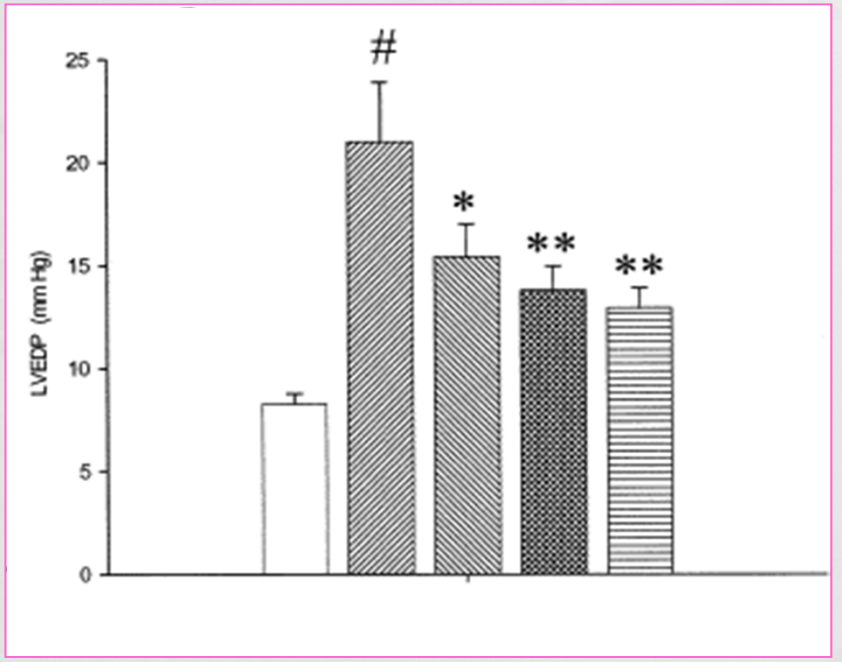
Tramontano et al. *Biochem Biophys Res Commun*. 2003;308:990-994.

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

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

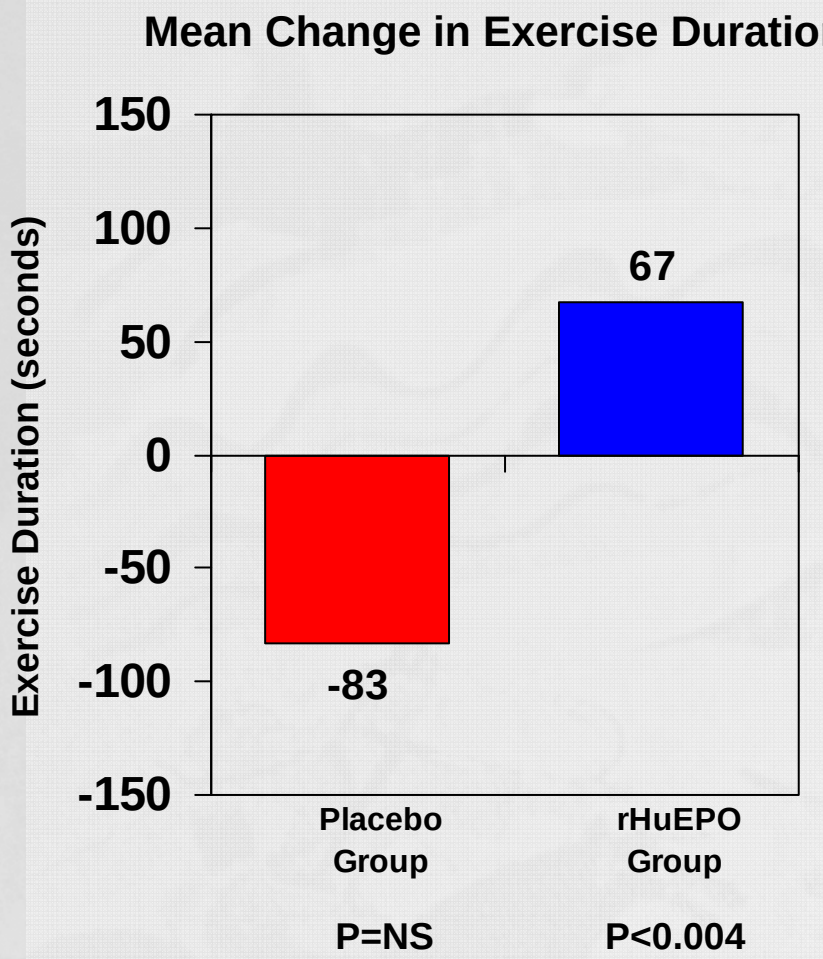
126 Anemic Patients With Resistant CHF

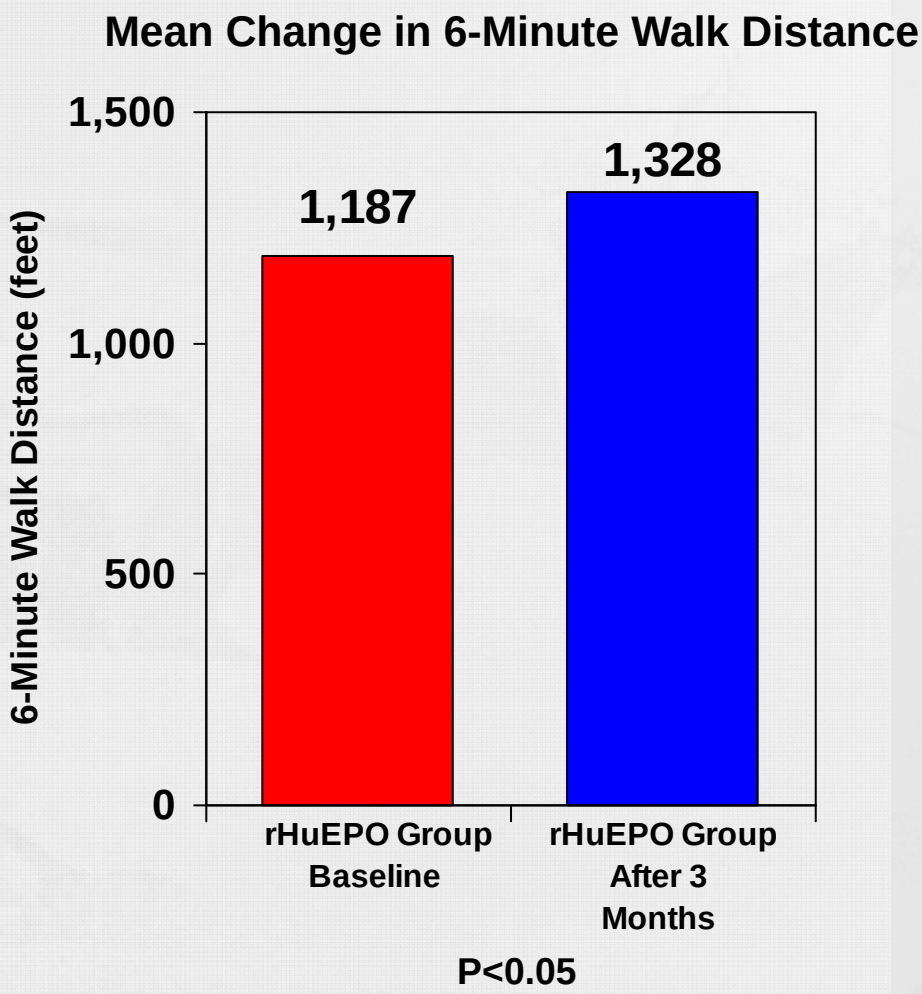
	Before	After
Hemoglobin (g/dL)*	10.3	13.1*
Serum creatinine (mg/dL)	2.4	2.3
GFR (mL/min/month)*	-0.95	0.27*
NYHA class (0–4)*	3.8	2.7*
Fatigue/SOB index (0–10)*	8.9	2.7*
Hospitalizations*	3.7	0.2*
Systolic BP (mmHg)	132	131
Diastolic BP (mmHg)	75	76

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...

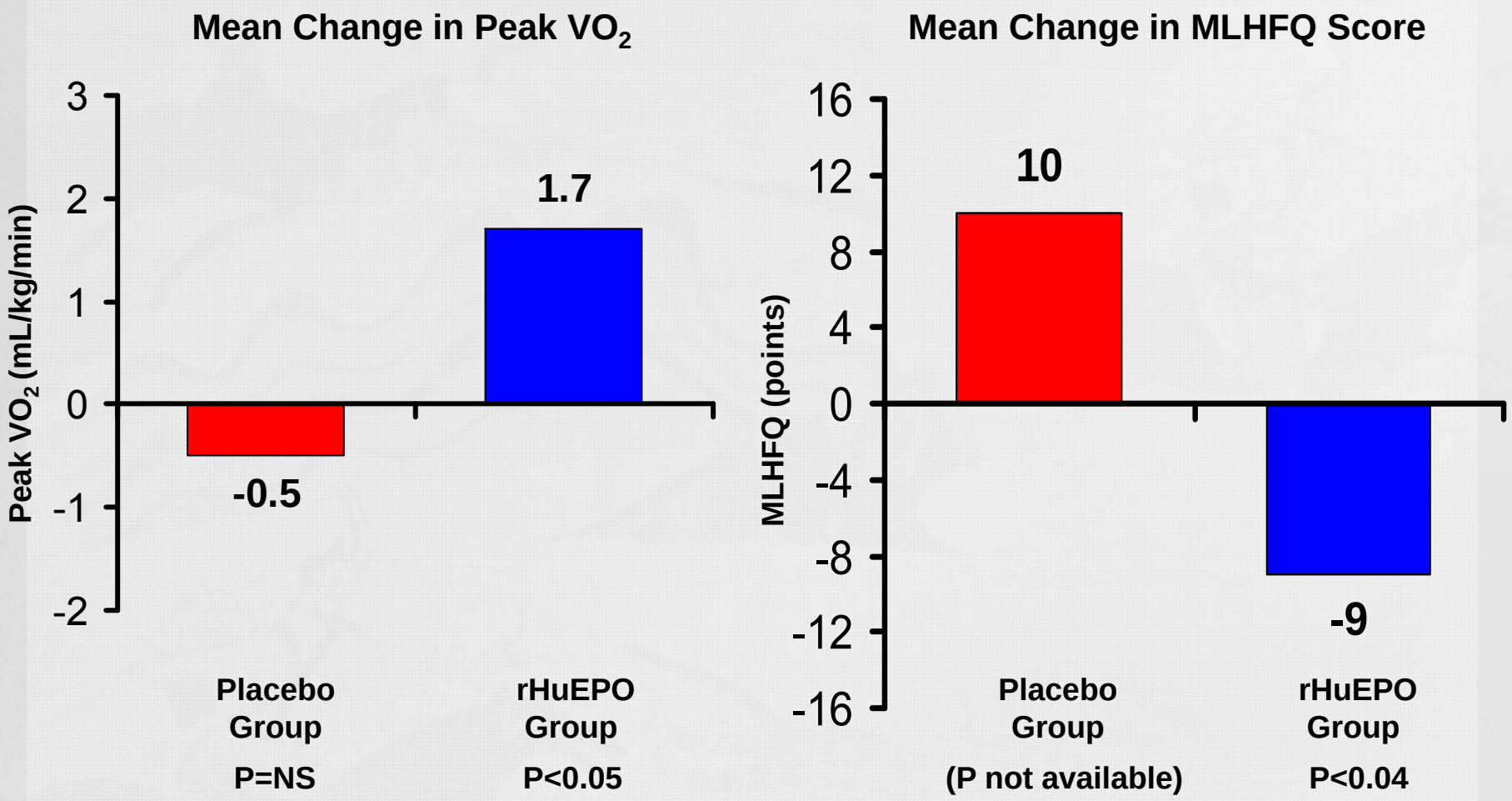




Randomized, placebo-controlled, single-blinded study; N=23 (n=8 for placebo group, n=15 for EPO group)

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.

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The effect of intravenous administration of erythropoietin on the infarct size in primary percutaneous coronary intervention

Jung-Won Suh [a,1], Woo-Young Chung [b,1], Yong-Seok Kim [c], Kwang-Il Kim [b], Eun-Ju Jeon [d], Young-Seok Cho [b], Tae-Jin Youn [b], In-Ho Chae [b], Cheol-Ho Kim [b], Dong-Ju Choi [b,*]

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Table 1
Inclusion and exclusion criteria.

Inclusion criteria
Age >18 years
The onset of chest pain <12 h
ST-elevation >0.1 mV in two contiguous leads
Occlusion of proximal to mid left anterior descending artery
Thrombolysis in Myocardial Infarction (TIMI) flow grade 0
Exclusion criteria
Cardiac arrest, ventricular fibrillation or cardiogenic shock at admission
Previous myocardial infarction, stent thrombosis
Uncontrolled hypertension or angina within 48 h
Occlusion of left main, left circumflex or right coronary artery
Evidence of coronary collaterals to the region at risk on initial coronary angiography
History of hypercoagulable disorder, thromboembolic events, venous thrombosis
History of stroke, transient ischemic attack (TIA) or seizures
Hypersensitivity to EPO, patients with contraindication to MRI
Pregnant woman, Woman in child bearing age without using contraception

(rhEPO, 50 U/kg)
before PCI

Table 2
Clinical characteristics of patients.

	EPO group ($n=29$)	Control group ($n=28$)	p-value
Age	59.3 ± 13.7	59.3 ± 8.8	0.99
Sex (M/F)	23/6	20/8	0.55
Body mass index	24.5 ± 2.7	24.2 ± 2.6	0.72
Hypertension, %	51.7	42.9	0.60
Dyslipidemia, %	17.2	28.6	0.36
Diabetes, %	27.6	21.4	0.76
Current smoker, %	51.7	35.7	0.48
History of coronary artery disease, %	34.5	25.0	0.57
Ischemia time (min)	336 ± 163	341 ± 291	0.94
Hemoglobin, g/dL	14.9 ± 1.9	14.9 ± 1.3	0.92
Platelet, /μL	261.0 ± 59.3	264.5 ± 64.8	0.84
NT-proBNP, pg/mL	233.9 ± 298.9	301.5 ± 404.7	0.50

NT-proBNP, amino-terminal fragment of pro-brain natriuretic peptide (NT-proBNP).

Table 5
Clinical outcomes of two groups.

	EPO group ($n=29$)	Control group ($n=28$)	p-value
One month			
Death	0	0	
Myocardial infarction	1	0	
Ischemic stroke	0	0	
Composite outcomes	1	0	1.0
Six months			
Death	0	1	
Myocardial infarction	0	0	
Ischemic stroke	1	0	
Composite outcomes	1	1	1.0

Table 6
Results of MRI analysis of two groups.

	EPO group ($n=25$)	Control group ($n=25$)	p-value
Ejection fraction, %	51.5 ± 52.4	52.4 ± 14.1	0.81
End-systolic volume, mL	67.3 ± 30.3	64.0 ± 32.9	0.71
End-diastolic volume, mL	134.2 ± 32.6	127.3 ± 35.6	0.48
Total infarct volume, cm^3	52.4 ± 23.6	54.8 ± 28.6	0.74
Infarct size, % of LV	34.4 ± 11.7	37.0 ± 13.8	0.50

LV, left ventricle.

Table 5
Clinical outcomes of two groups.

	EPO group ($n=29$)	Control group ($n=28$)	p-value
One month			
Death	0	0	
Composite outcomes	1	1	1.0

Conclusions: Intravenous administration of erythropoietin was safe and was not associated with thrombotic or hypertensive side effects. However, it did not reduce the infarct size when assessed by MRI and cardiac enzyme. Further studies about the dose or routes of administration of EPO are needed (ClinicalTrials.gov Identifier NCT00882466).

Table 6
Results of MRI analysis of two groups.

	EPO group ($n=25$)	Control group ($n=25$)	p-value
Ejection fraction, %	51.5 ± 52.4	52.4 ± 14.1	0.81
End-systolic volume, mL	67.3 ± 30.3	64.0 ± 32.9	0.71
End-diastolic volume, mL	134.2 ± 32.6	127.3 ± 35.6	0.48
Total infarct volume, cm^3	52.4 ± 23.6	54.8 ± 28.6	0.74
Infarct size, % of LV	34.4 ± 11.7	37.0 ± 13.8	0.50

LV, left ventricle.

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

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

Potential Benefits and Risks of Treating Anemia with EPO in HF

Potential Benefits

1. Improved oxygen delivery
2. Improved exercise tolerance
3. Attenuate adverse remodeling
4. Improved QoL
5. Antiapoptotic?
6. Decrease in hosp./death?

Potential Risks

1. Increased thrombosis
2. Platelet activation
3. Hypertension
4. Endothelial activation

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

Conclusions

1. Anemia is a VERY COMMON co-morbidity in HF patient (upto 50%).
2. Cause of anemia in heart failure is most likely multifactorial.
3. It represent a novel therapeutic target.

However!

4. No guidelines or large clinical trial available regarding managing anemia in heart failure patient.
5. The ideal target hemoglobin level for patients with heart failure is not yet known.
6. The issue of ACE inhibitor associated anemia remains controversial and needs more study.


열린 마음, 나누는 사랑
경청해 주셔서 감사합니다.
The lower,
the worse!
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SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL