Anemia in Heart Failure

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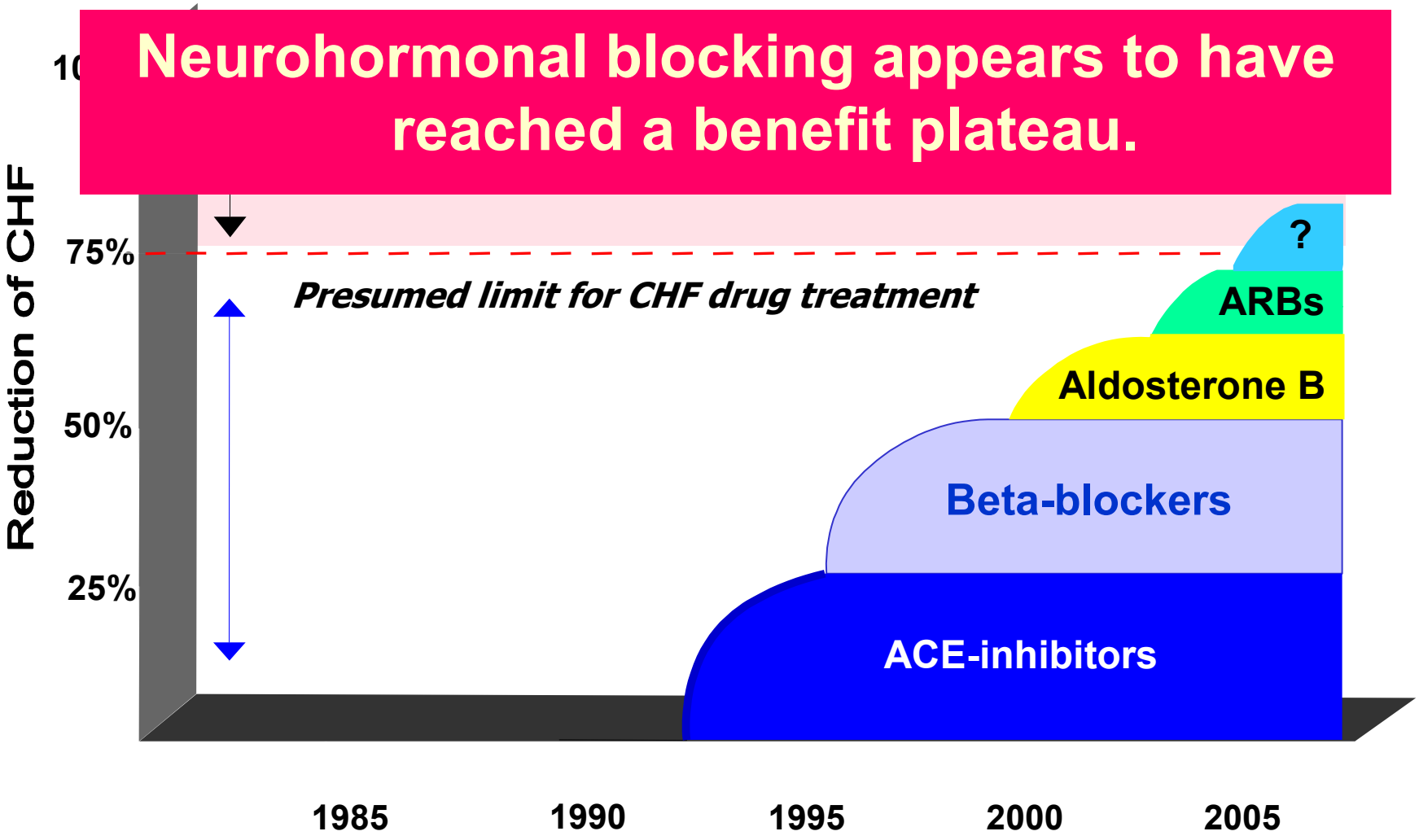
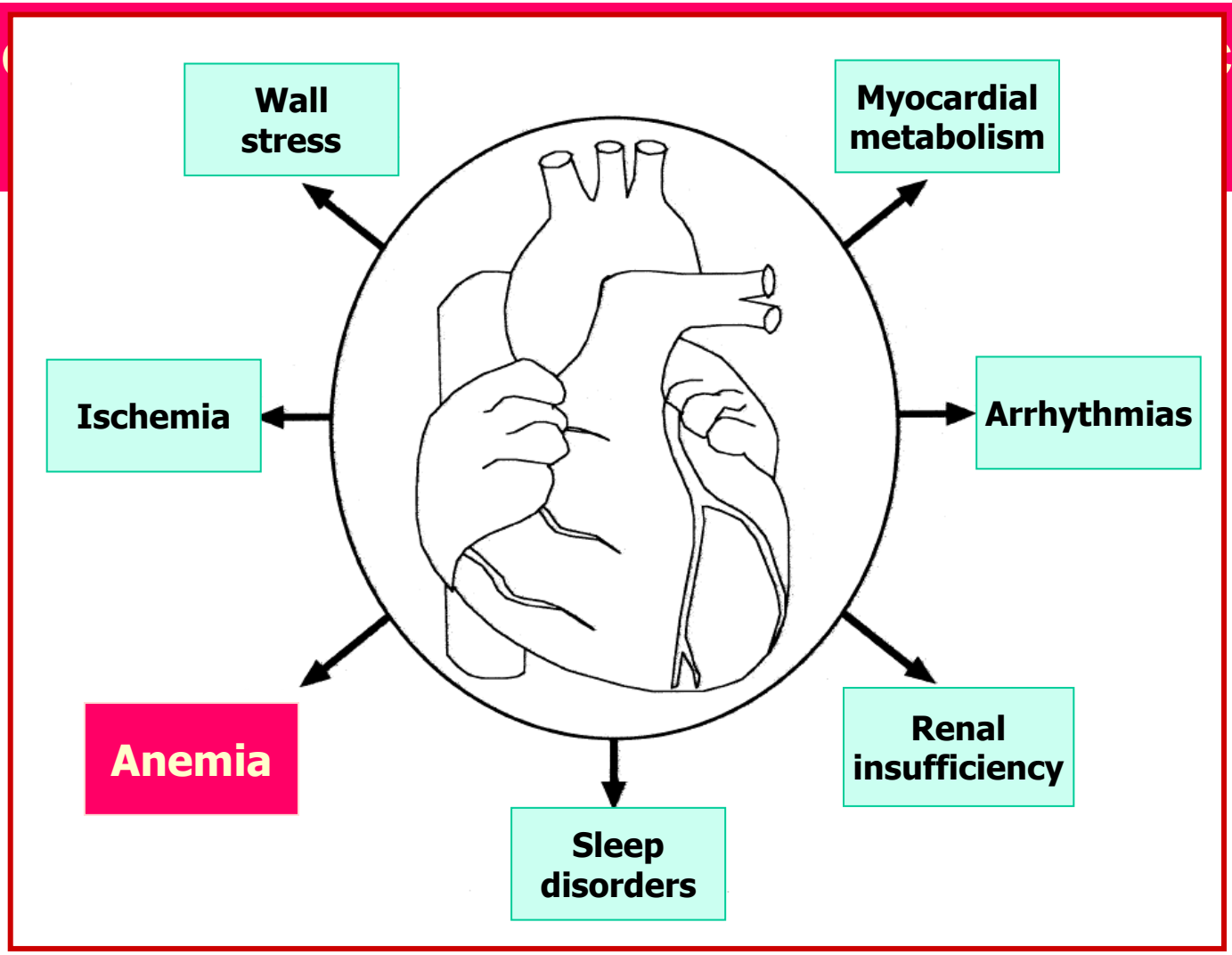
“Ceiling Benefit” of Neurohumoral blocking



Potential Therapeutic Targets



Mehra MR et al. J Am Coll Cardiol 2003;41:606-610

Anemia in General

- Increased tendency for the development of CHF
  - In general population
  - In elderly patients with normal renal function
  - In patients with ischemic heart disease
- Greater risk of end-stage renal disease
  - In anemic CHF patients
- *Anemia ⇒ a novel therapeutic target in CHF.*

Anemia in CKD

- The treatment of anemic patients with renal failure
  - Reduce LV mass, LV volume and improve LVEF
  - If stop treatment, returned to previous levels
- Treatment of anemia in CKD before dialysis
  - A reduction in hospitalization for CHF
- In dialysis patient
  - The higher Hb, the lower the mortality and hospitalization
- Treatment of anemia improves CHF
- *Anemia $\Rightarrow$ a novel therapeutic target in CHF.*

ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult

6.2.6. Patients With Anemia

Anemia is seldom the cause of HF in the absence of underlying cardiac disease. To be the sole cause of high-output HF, anemia must be severe (e.g., hemoglobin levels less than 5 g per deciliter). On the other hand, patients with HF frequently have anemia for a variety of reasons. The severity of anemia may contribute to the increasing severity of HF. Several studies have demonstrated worse outcomes in patients with HF and anemia (659, 660). It is unclear whether anemia is the cause of decreased survival or a result of more severe disease.

Several small studies have suggested benefit from use of erythropoietin and iron for treatment of mild anemia in HF (661-663). There is concern, however, that thromboembolic events may be increased. This therapy is undergoing further investigation.

7. END-OF-LIFE CONSIDERATIONS

RECOMMENDATIONS

Class I

1. **Ongoing patient and family education regarding prognosis for functional capacity and survival is recommended for patients with HF at the end of life.** ***(Level of Evidence: C)***

Definition of anemia

- **WHO criteria**
  - **Men : <13.0 g/dL**
  - **Women : <12.0 g/dL**

- **National Kidney Foundation criteria**
  - **Hb <12 g/dL in men and postmenopausal women**
  - **Hb <11 g/dL in premenopausal women**

Prevalence of anemia in HF

- **Ranges from 4% to 55%**

Study	Population	n	Definition of Anemia	Prevalence
Al-Ahmad et al. (4)	LV dysfunction +/− symptoms, clinical trial	6,563	Hct < 35%	4%
Tanner et al. (7)	Tertiary care HF clinic	193	Hb < 12	15%
Ezekowitz et al. (8)	New HF diagnosis, claims data	12,065	MD defined (ICD9 codes)	17%
Mozaffarian et al. (5)	Severe chronic HF, clinical trial	1,130	Hct < 37.6%	20%
Horwich et al. (9)	Heart transplant referrals single-center	1,061	Hb < 13 men, <12 women	30%
Kosiborod et al. (10)	Medicare patients, claims data	2,281	Hct ≤ 37%	48%
Felker et al. (38)	Acute decompensated HF, clinical trial	949	Hb < 13 men, <12 women	49%
Silverberg et al. (6)	Chronic HF, single-center trial	142	Hb < 12	55%

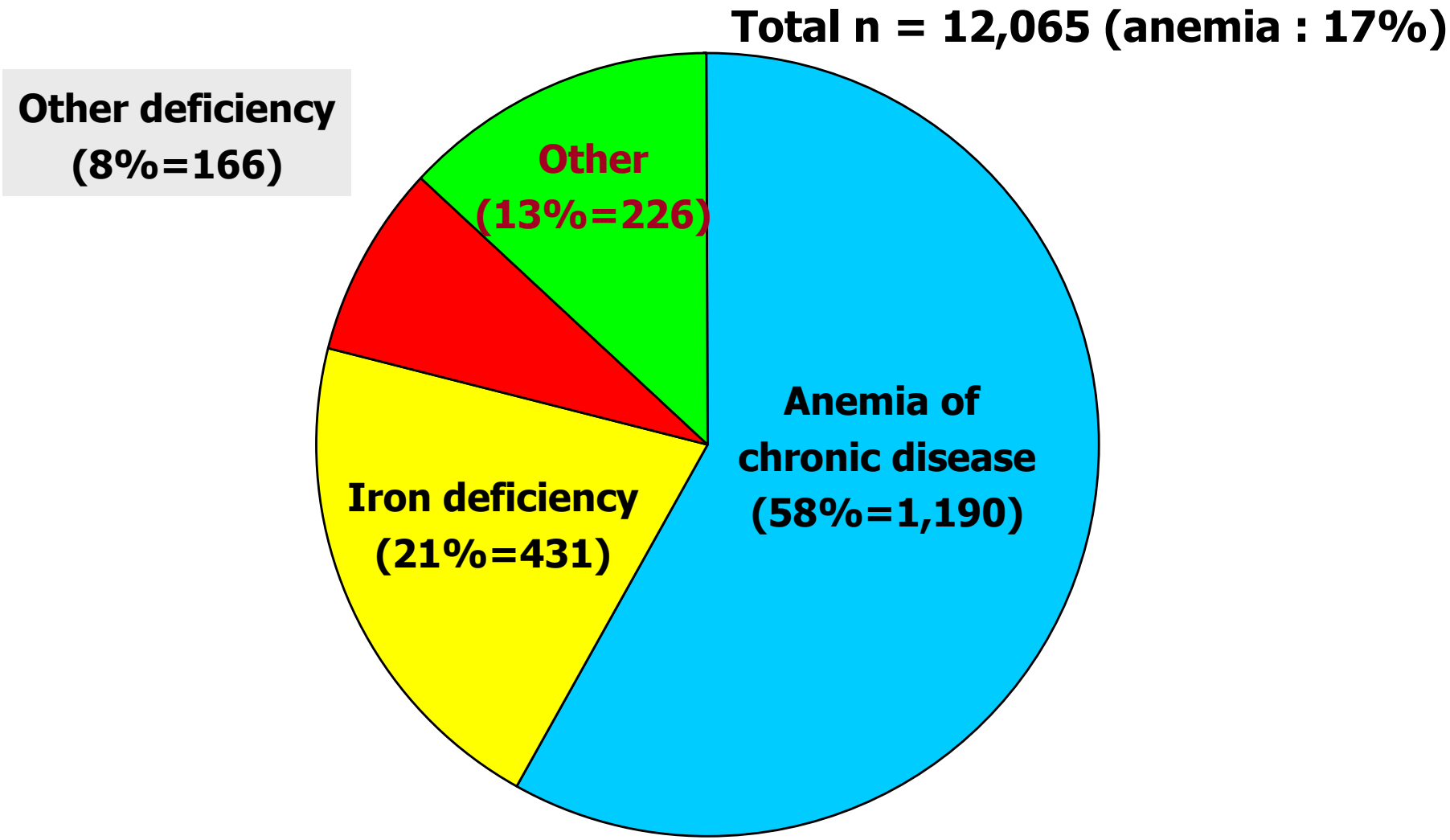
- **Such variance associated with**
  - **Differences in the definition of anemia**
  - **Substantial differences in population studied**
  - **A lack of information about correctable causes of anemia**
- **Study of Anemia in a Heart Failure Population (STAMINA-HFP) registry : 33%.**

Increased Risk of Anemia

1. Increasing age
2. Female gender
3. Chronic kidney disease
   (increased serum Cr or decreased GFR)
4. Decreased body mass index
5. Use of ACE inhibitors
6. Increased jugular venous pressure
7. Lower-extremity edema

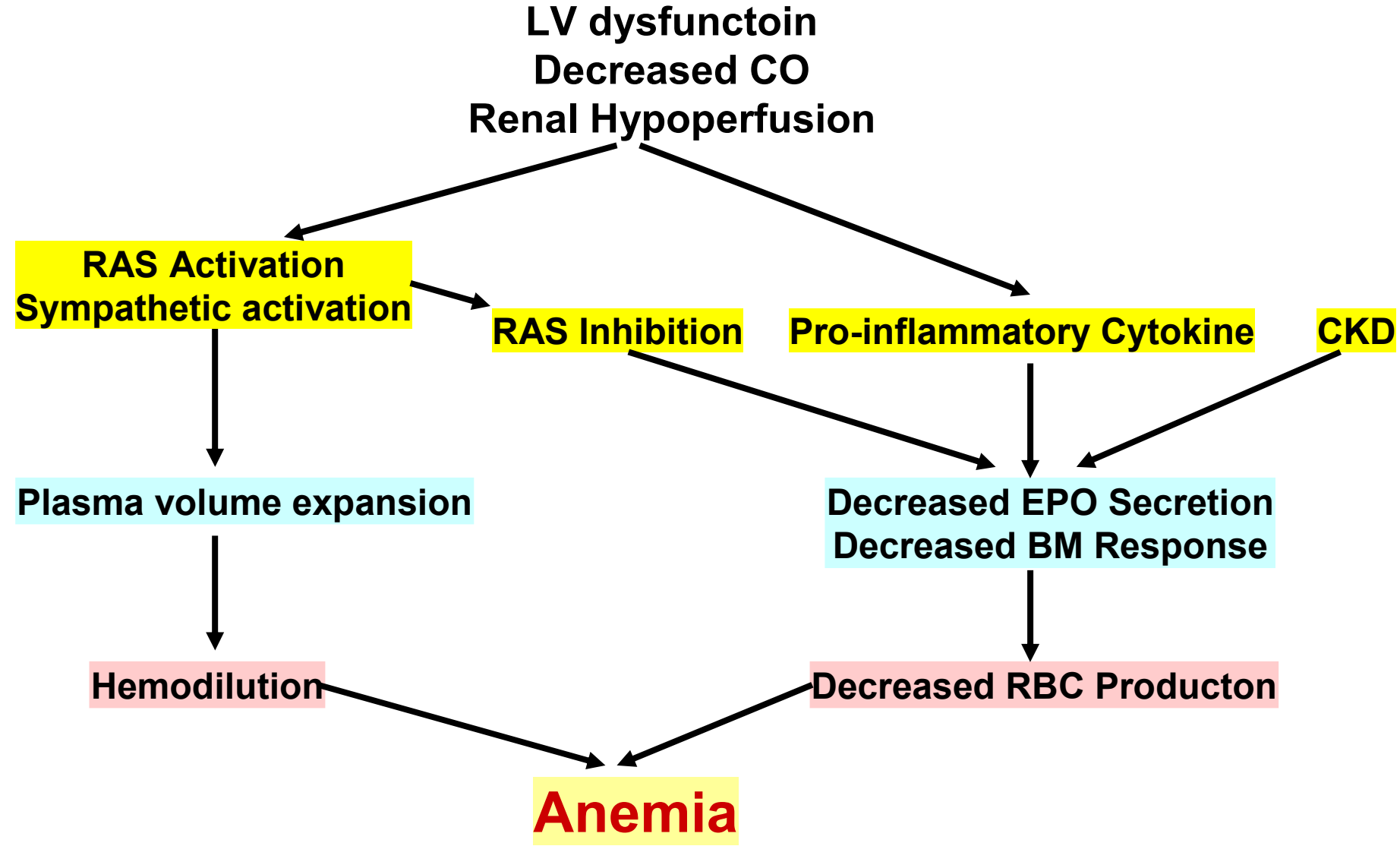
Causes of anemia

Total n = 12,065 (anemia : 17%)



Ezekowitz JA et al. Circulation 2003;107:223-225

Potential Cause of Anemia in CHF



Mechanisms of anemia

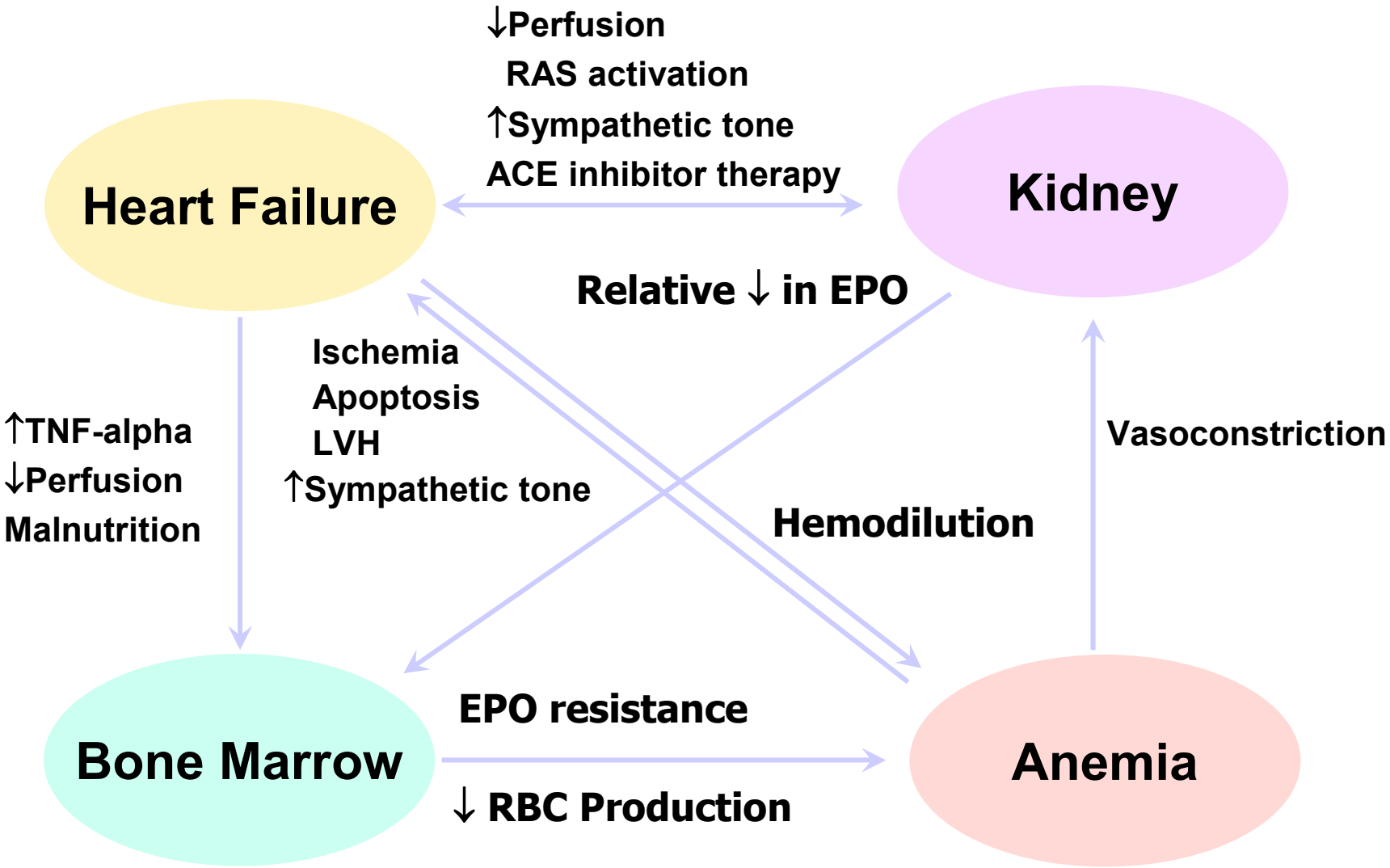
1. **Cytokines – TNF, IL-1, IFN**
   - Reducing EPO production in kidney
   - EPO insensitivity at bone marrow level
   - Inhibiting iron release from RES
   - Bone marrow depression
2. **Renal dysfunction**
   - Cardio-renal-anemia syndrome

Mechanisms of anemia

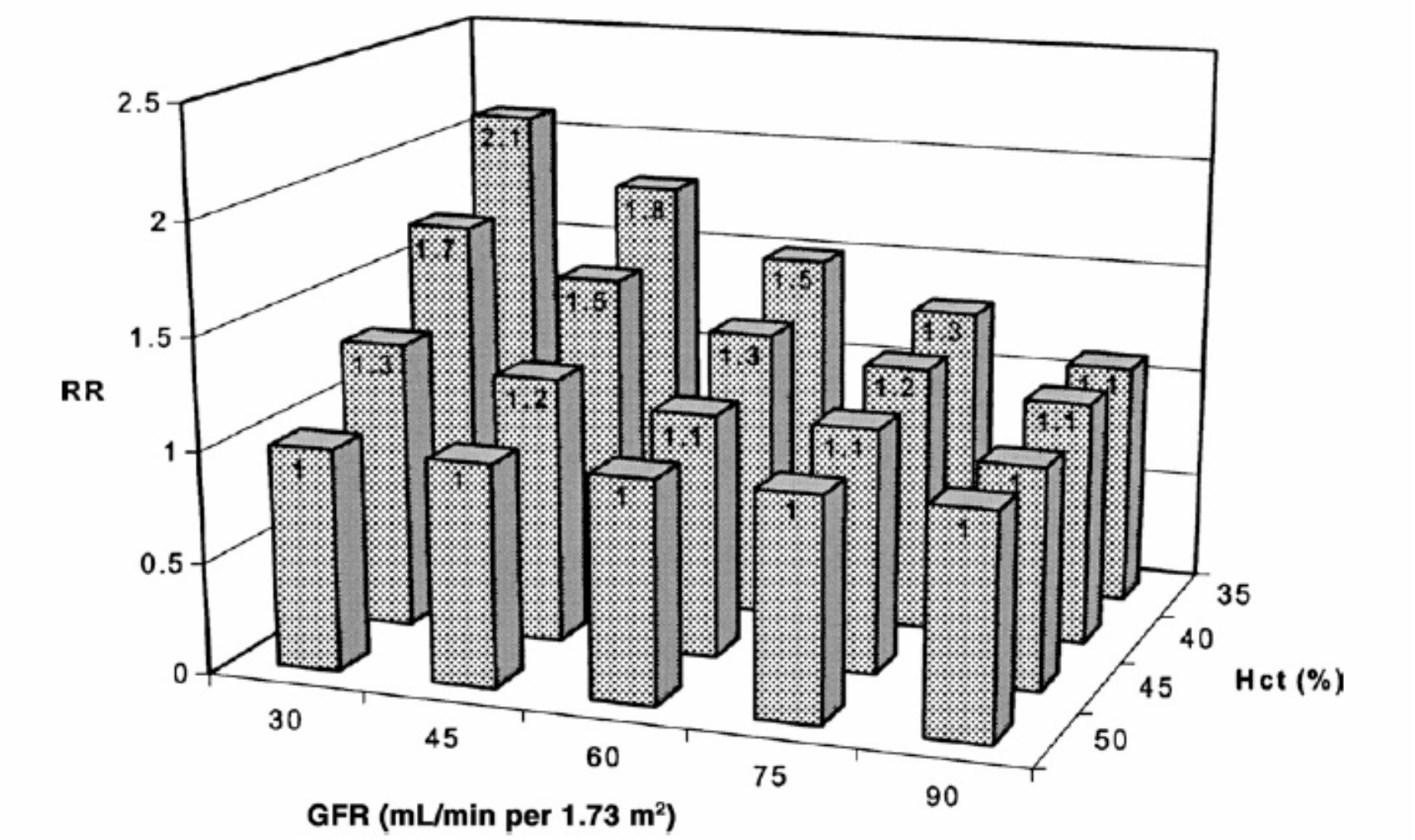
3. Use ACE inhibitor

- Decrease angiotensin II level ; decreased stimulation of the proliferation of erythroid progenitor cells
- Increasing N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) ; hematopoiesis inhibitor
  - almost exclusively hydrolyzed by ACE,
  - partially eliminated in the kidney
- SOLVED trial ; more anemia by 56% in enalapril

Cardio-Renal-Anemia syndrome

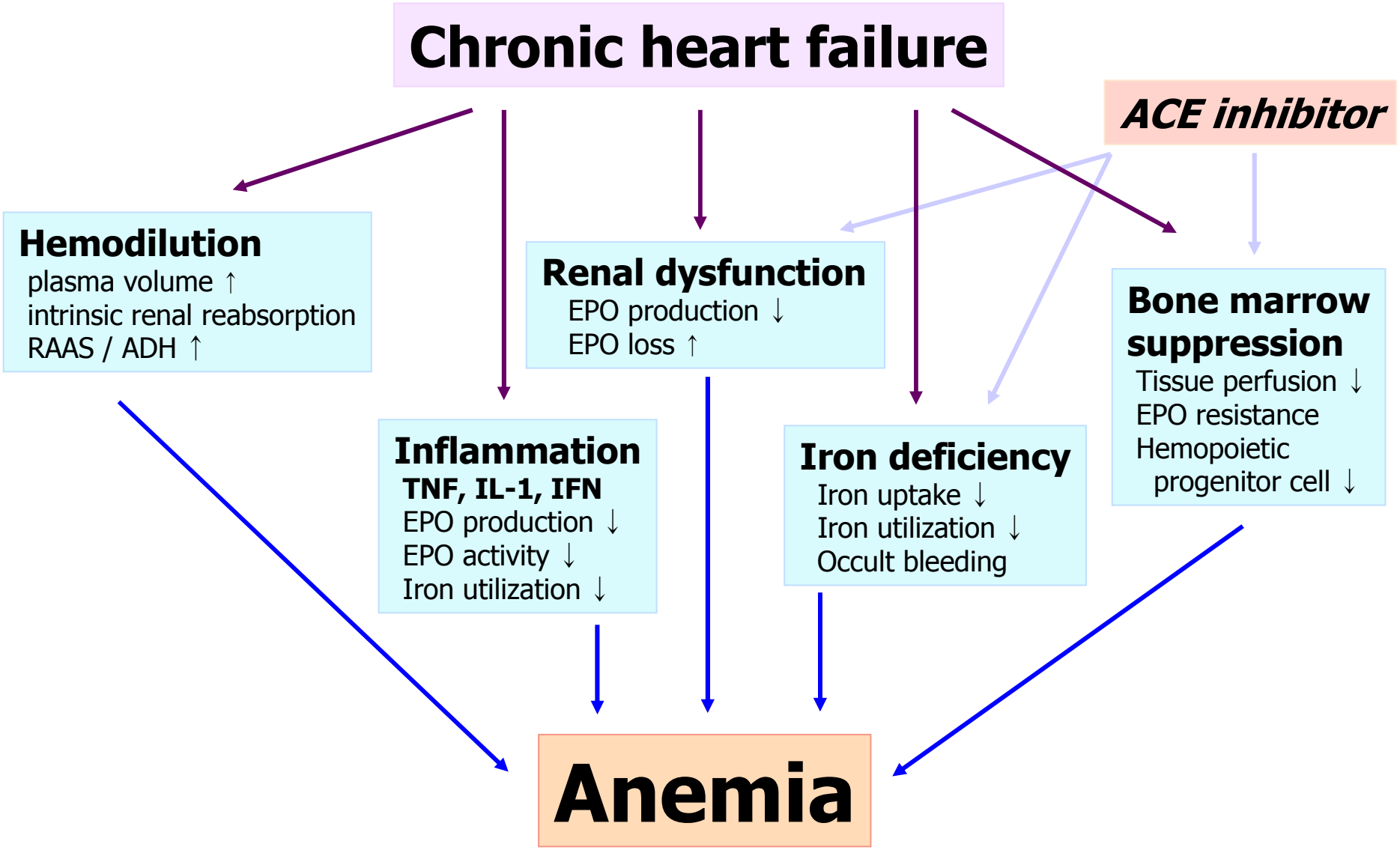


Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction.



Al-Ahmad A, et al. J Am Coll Cardiol 2001;38:955–962.

Mechanisms of anemia

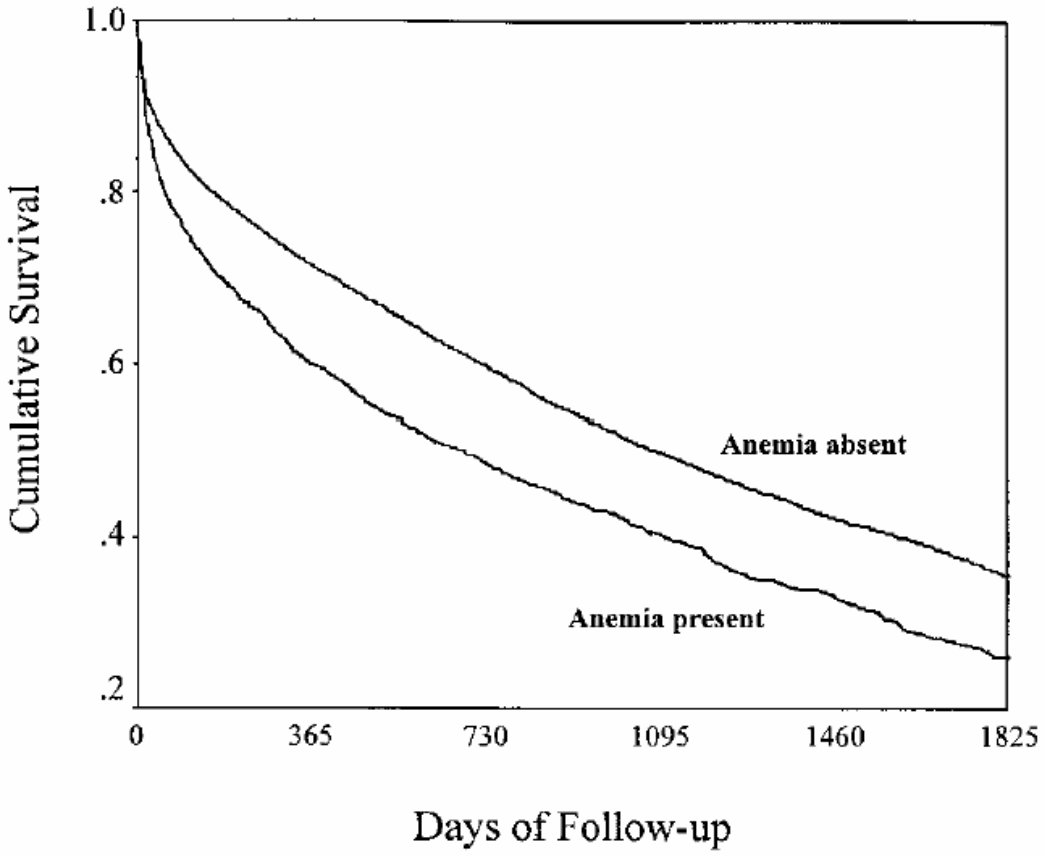


Anemia Is Common in Heart Failure and Is Associated With Poor Outcomes

Insights From a Cohort of 12 065 Patients With New-Onset Heart Failure

Justin A. Ezekowitz, MBBCh; Finlay A. McAlister, MD, MSc; Paul W. Armstrong, MD

Circulation. 2003;107:223-225



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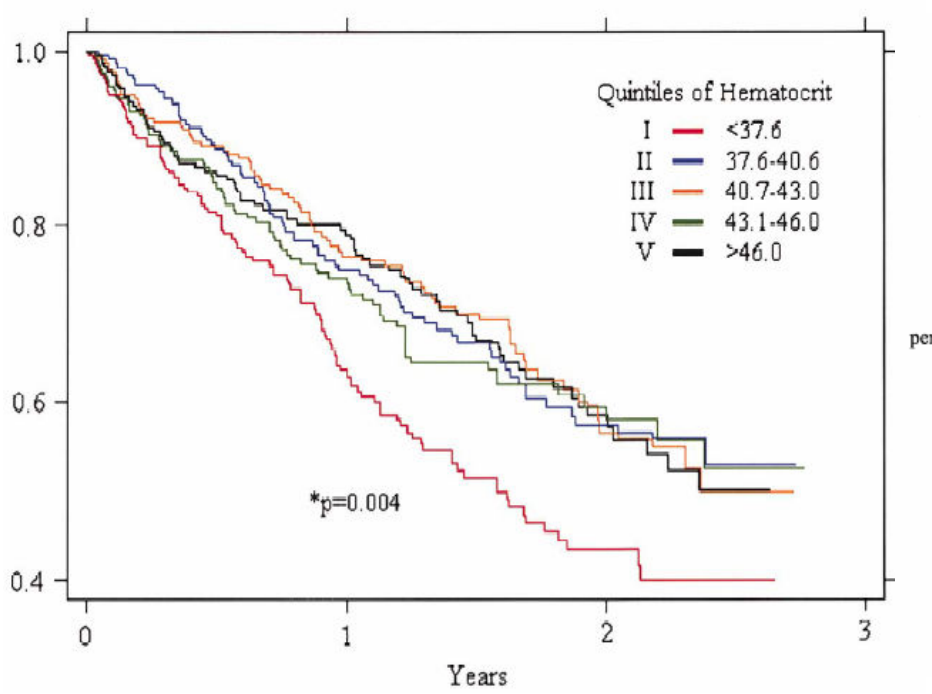
doi:10.1016/S0735-1097(03)00425-X

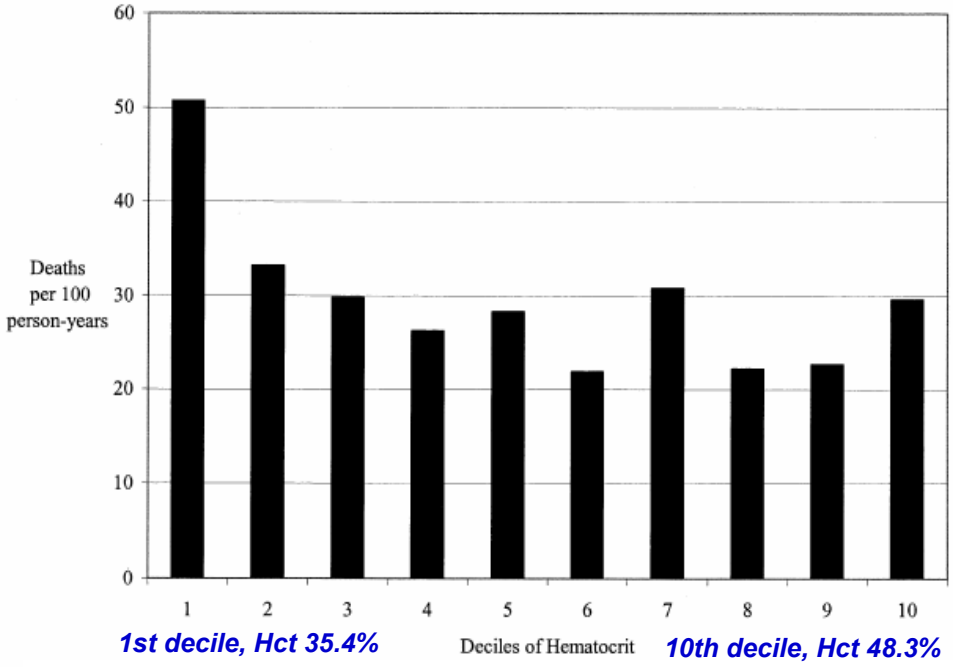
Anemia Predicts Mortality in Severe Heart Failure

The Prospective Randomized Amlodipine Survival Evaluation (PRAISE)

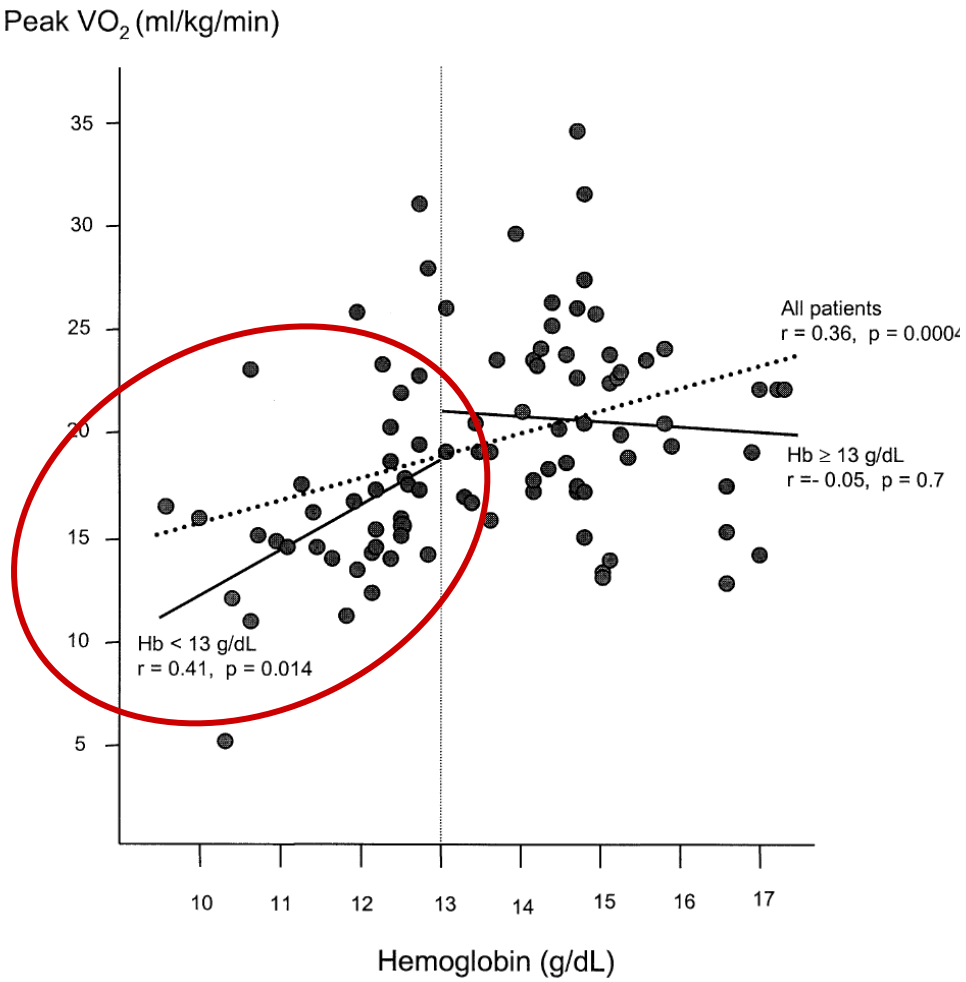
Dariush Mozaffarian, MD, MPH,*† Regina Nye, MPH,‡ Wayne C. Levy, MD†
Seattle, Washington; and New London, Connecticut

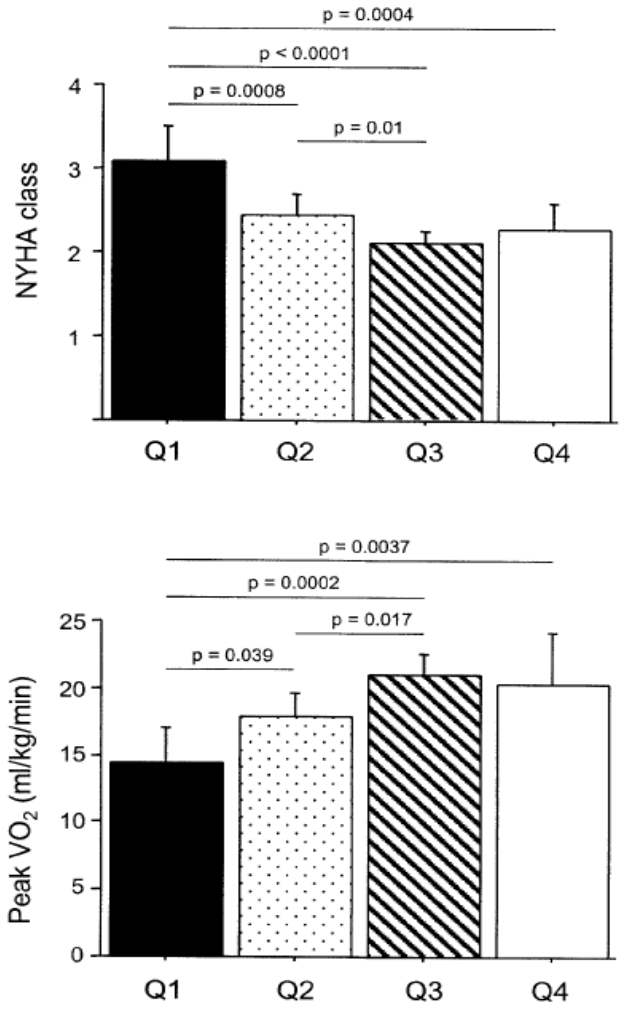
JACC 2003;41:1933-9





Anemia & peak VO_2



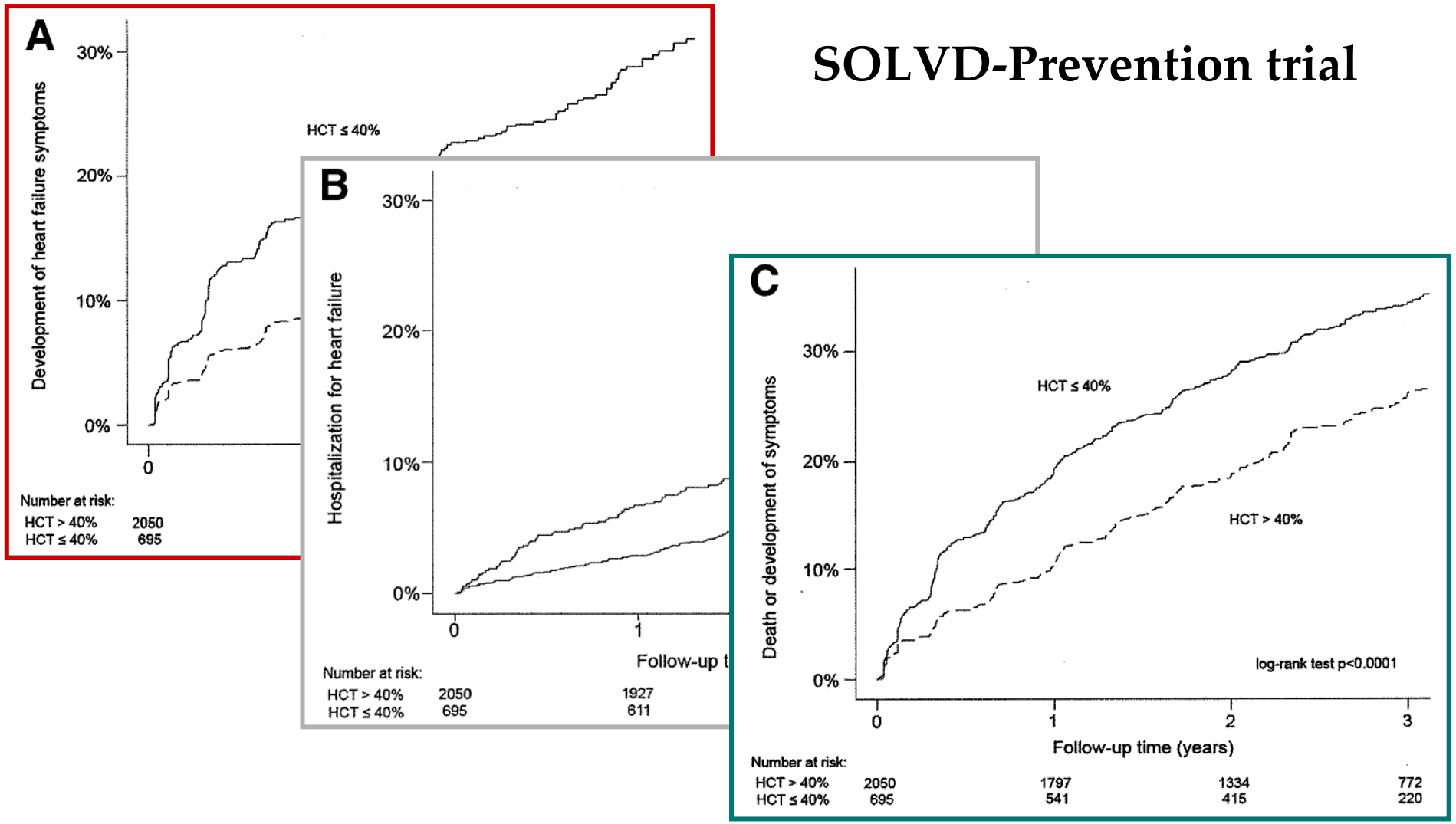


Q1 – Hb 10.0-11.7 g/dL, n=12; Q3 – Hb 13.6-15.3 g/dL, n=37

Q2 – Hb 11.8-13.5 g/dL, n=31; Q4 – Hb 15.4-17.1 g/dL, n=13

Kalra PR et al. Am J Cardiol 2003;91:888-891

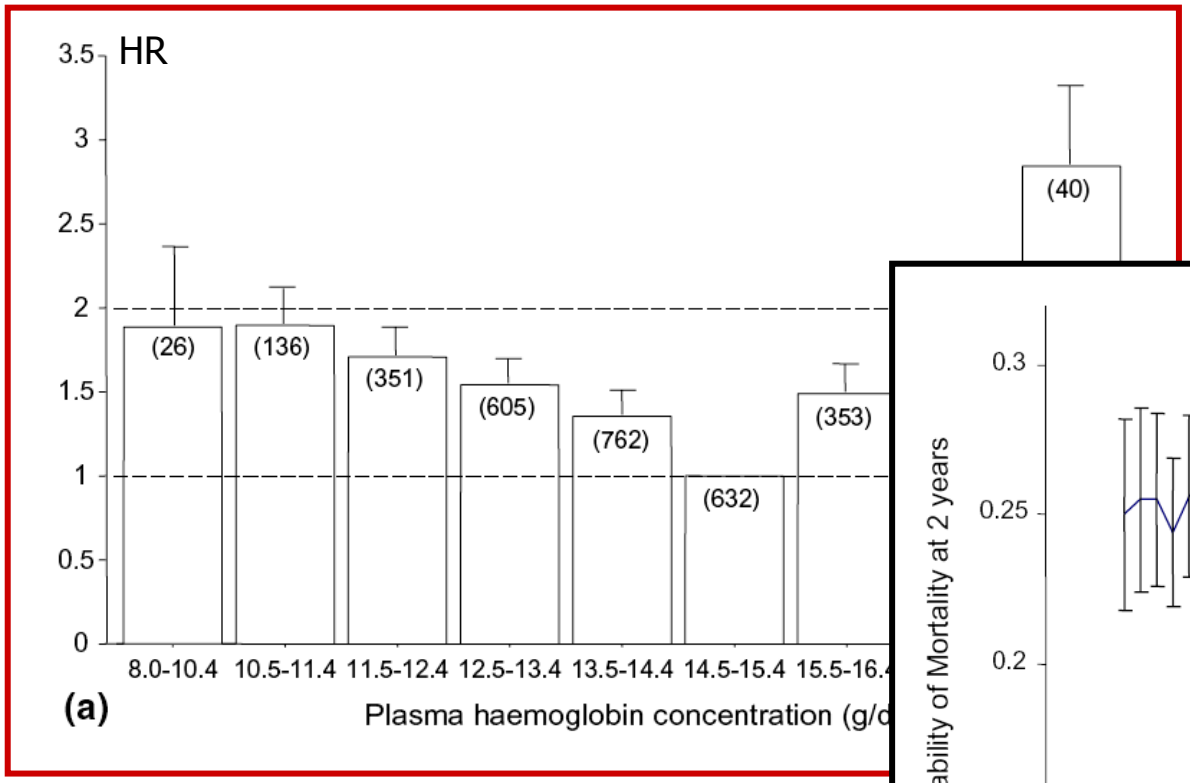
Progression to Symptomatic HF

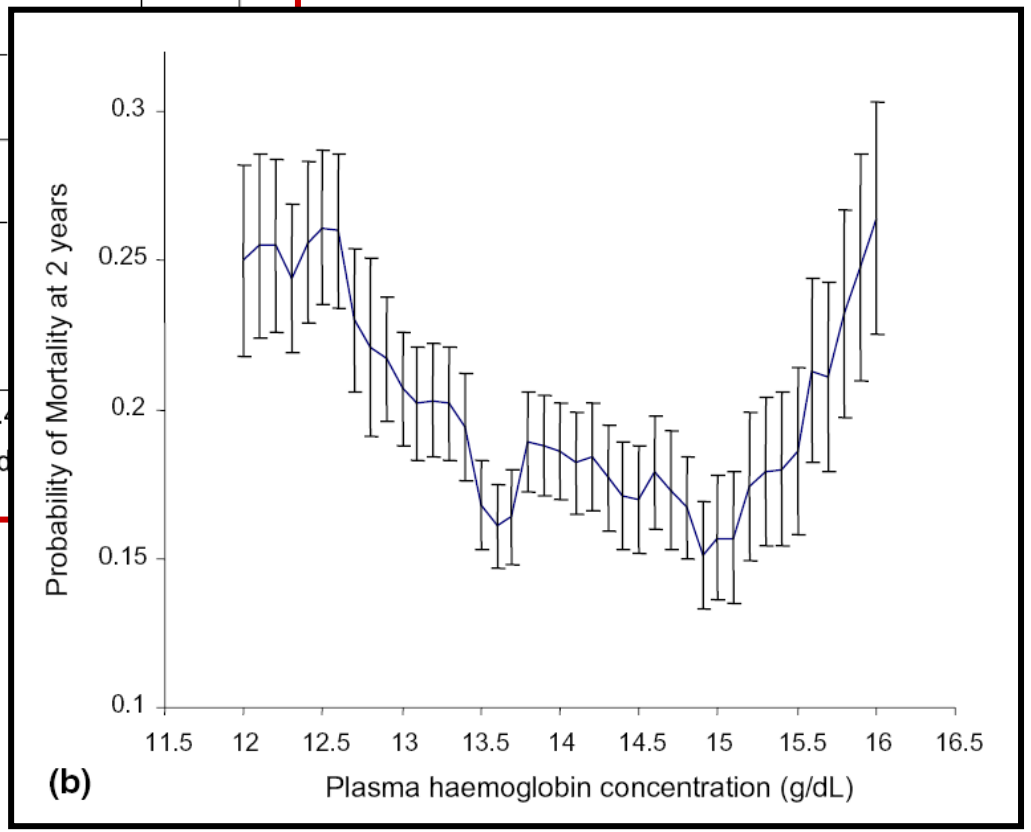


SOLVD-Prevention trial

Das SR et al. Am J Cardiol 2005;96:827-831

ELITE II trial

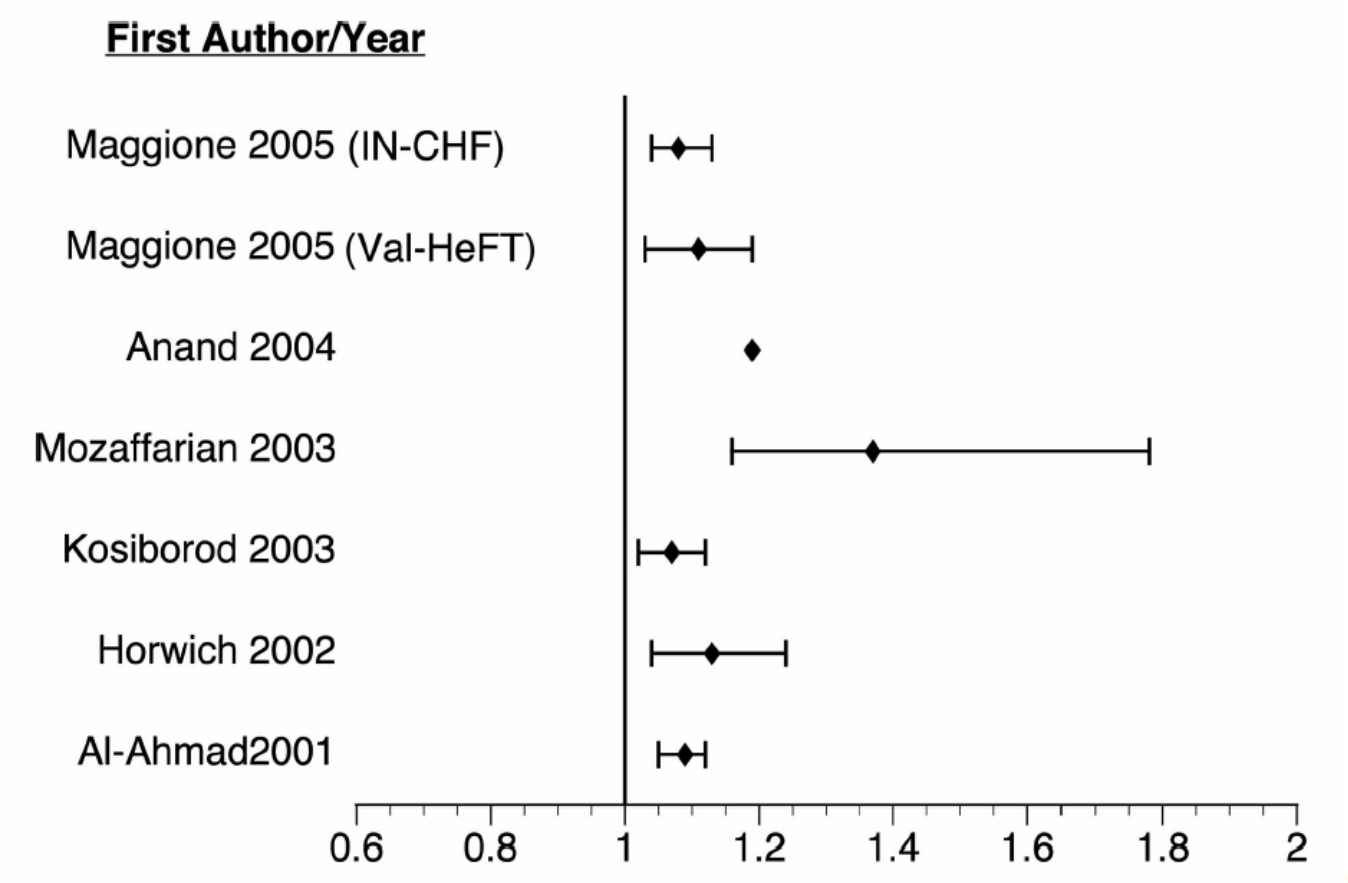




Optimal Hb for survival
Male : 15.0 g/dL
Female : 13.1 g/dL

Sharma R, Eur Heart J 2004;25:1021-1028

Anemia and Clinical Outcome



- Reduced hemoglobin in CHF associated with increased risk of hospitalization and all-cause mortality.

Management of Anemia

- **Anemia ; consistent association with adverse clinical outcome**

  ⇒ ***Potential therapeutic target***

- **Potential treatment**

  1. **RBC transfusion**
  2. **Fe supplementation**
  3. **Erythropoietin**

“Transfusion threshold”

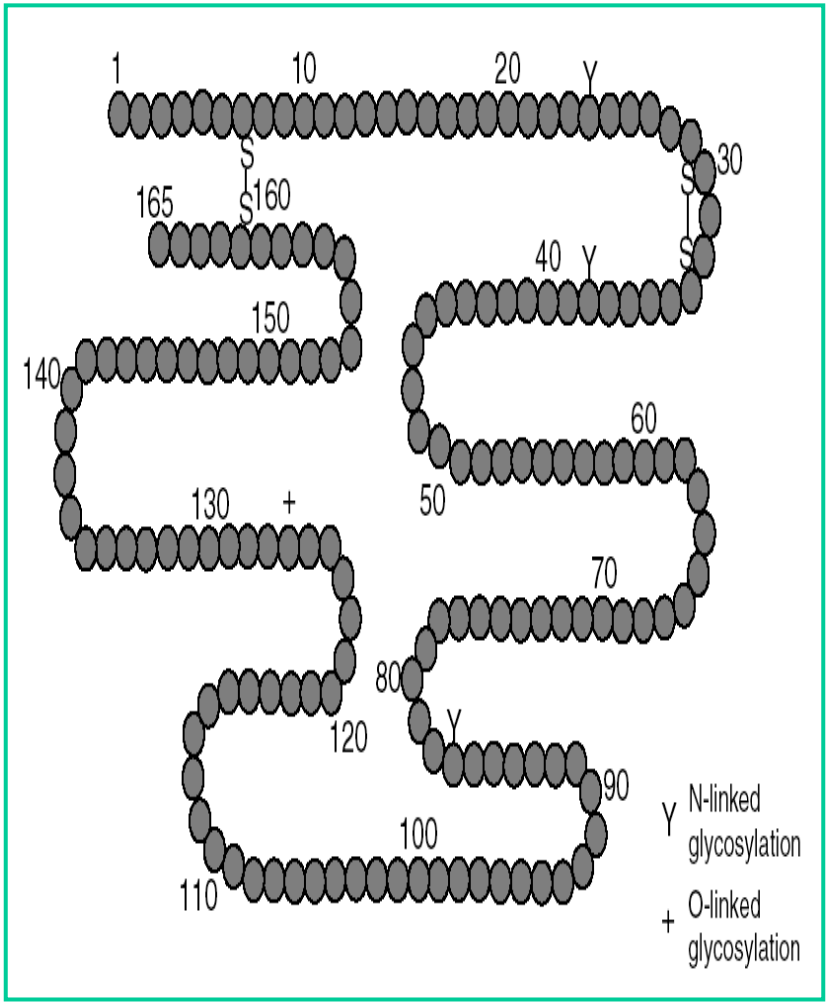
- Hematocrit < 30% in CV disease
  - Based on expert opinion
- The clinical utility in CV disease is controversial.
- Transfusion may be considered as an acute treatment for severe anemia.
- Not appear to be strategy for the long-term management in CHF.

Transfusion

- **Potential Risk**
  - **Infection**
  - **Immunosuppressive effect**
  - **Hemolytic reaction**
  - **Iron overload**
  - **Volume overload**

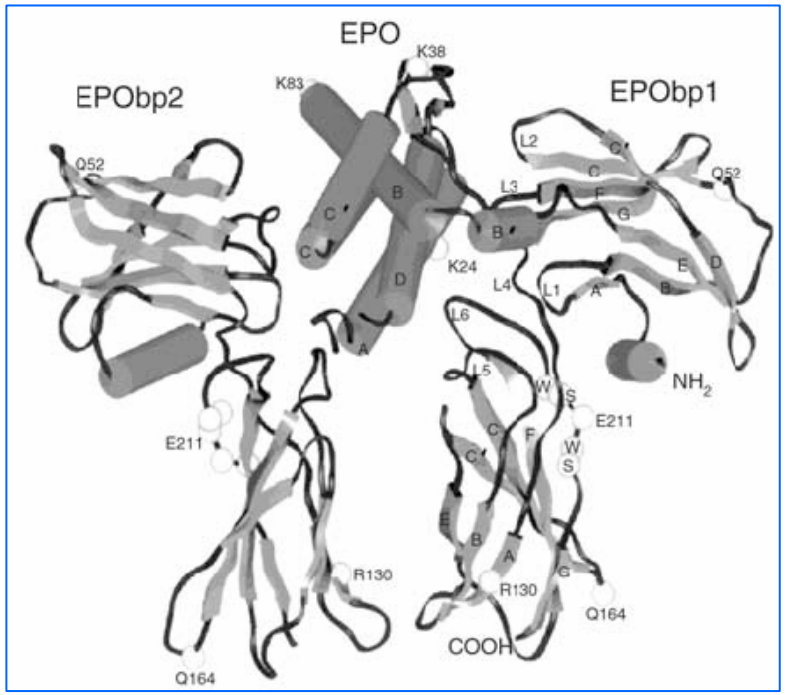
Erythropoietin (EPO)

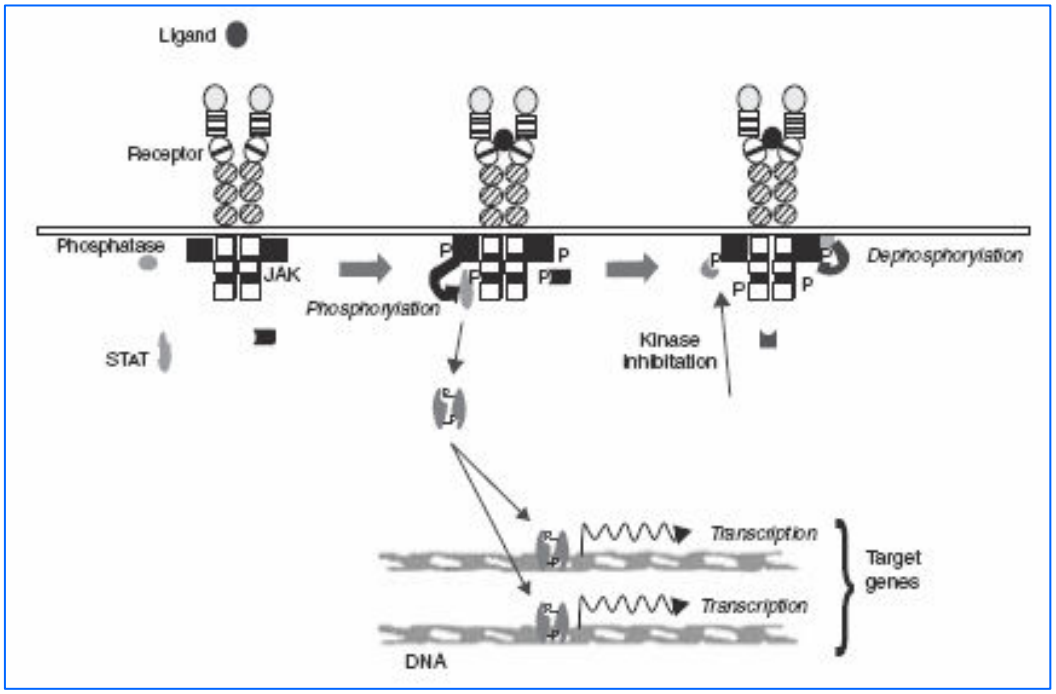
- 30.4-kD glycoprotein
- EPO encodes a protein with 165-amino acid structure.
- Regulator of erythroid progenitor cell
  - Inhibition of apoptosis
  - Increased proliferation
  - Increased differentiation
- Production of EPO
  - regulated by HIF-1 (HIF-1α, 1β, 3α)



Erythropoietin Recepor (EpoR)

Homodimerization to EpoR2





Three available Erythropoietin

1. Epoetin-α and
2. Epoetin-β:
   - rHuEpo , $T_{1/2}$ 6-8h
   - Since 1985
3. Dabepoetin-α:
   - N-linked supersialylated analog, $T_{1/2}$ 48h
   - Since 2001

Effect of EPO in Heart Failure

1. **Severe, resistant CHF with mild anemia with EPO & Iron → ↑ LVEF, ↓ hospitalization**
   (Silverberg et al. JACC 2001)
2. **DM & severe, resistant CHF with mild anemia with EPO → ↑ LVEF, ↓ hospitalization**
   (Silverberg et al. Nephrol Dial Transplat 2003)
3. **Moderate to severe CHF treated with EPO → ↑ exercise duration**
   (Mancini et al. Circulation 2003)

EPO in Heart Failure

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Heart Failure

The Use of Subcutaneous Erythropoietin and Intravenous Iron for the Treatment of the Anemia of Severe, Resistant Congestive Heart Failure Improves Cardiac and Renal Function and Functional Cardiac Class, and Markedly Reduces Hospitalizations

Donald S. Silverberg, MD, Dov Wexler, MD, Miriam Blum, MD, Gad Keren, MD, David Sheps, MD, Eyal Leibovitch, MD, David Brosh, MD, Shlomo Laniado, MD, Doron Schwartz, MD, Tatyana Yachnin, MD, Itzhak Shapira, MD, Dov Gavish, MD, Ron Baruch, MD, Bella Koifman, MD, Carl Kaplan, MD, Shoshana Steinbruch, RN, Adrian Iaina, MD

Tel Aviv, Israel

JACC 2000;35:1737-44

	Initial	15 months F/U	Final
Hematocrit, vol%	30.14 ± 3.12		35.90 ± 4.22*
Hemoglobin, g%	10.16 ± 0.95		12.10 ± 1.21*
Serum ferritin, μg/liter	177.07 ± 113.80		346.73 ± 207.40*
Serum iron, μg%	60.4 ± 19.0		74.8 ± 20.7*
% iron saturation	20.5 ± 6.04		26.14 ± 5.23*
Serum creatinine, mg%	2.59 ± 0.77		2.73 ± 1.55
LVEF, %	27.7 ± 4.8		35.4 ± 7.6*
No. hospitalizations/patient	2.72 ± 1.21		0.22 ±0.65*
Systolic BP, mm Hg	127.1 ± 19.4		128.9 ± 26.4
Diastolic BP, mm Hg	73.9 ± 9.9		74.0 ± 12.7
NYHA (0–4)	3.66 ± 0.47		2.66 ± 0.70*

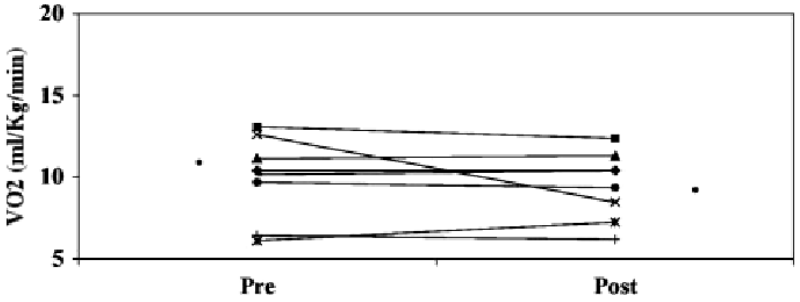
EPO in Heart Failure

Effect of Erythropoietin on Exercise Capacity in Patients With Moderate to Severe Chronic Heart Failure

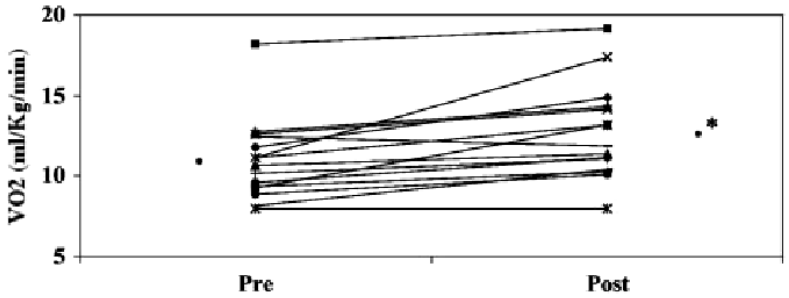
Donna M. Mancini, MD; Stuart D. Katz, MD; Chim C. Lang, MD; John LaManca, PhD; Alhakam Hudaihed, MBBS; Ana-Silvia Androne, MD

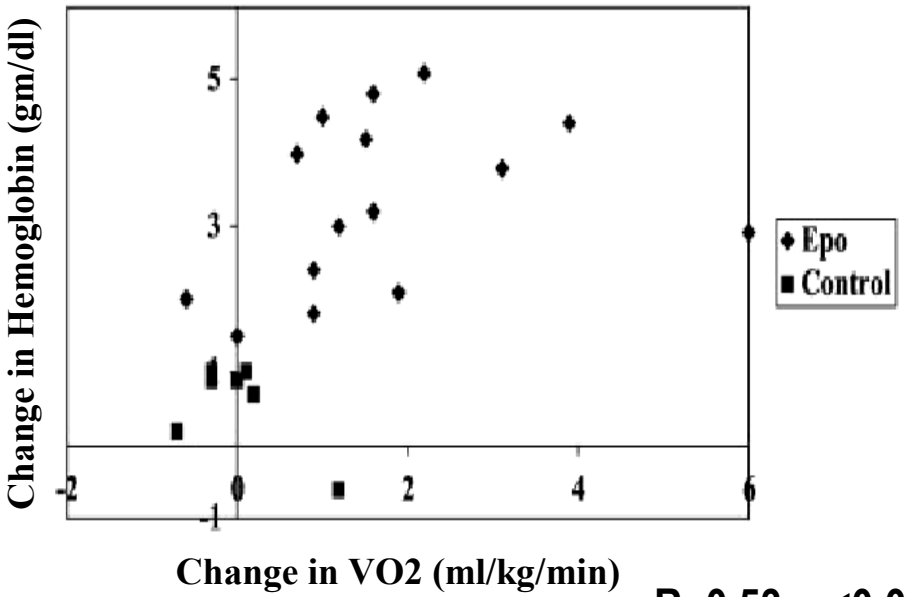
Circulation 2003;107:294-299

Control Group



EPO Group





R=0.53, p<0.02

Advantages of EPO Therapy

1. Increase hemoglobin level
2. Increases peak O2 consumption
3. Improve functional class
4. Decreases ventricular remodeling
5. Improve cardiac and renal functions
6. Reduce diuretic dose
7. Reduce hospitalizations
8. Reduce mortality rate (small study)

Disadvantages of EPO Therapy

1. Increase hypertension
2. Increase thrombosis
3. Increase endothelin activation
4. Expensive

Pleiotropic Effect of EPO

1. Reduce oxidative stress
2. Promote neuronal survival after ischemia
3. Protect against ischemic vascular injury
4. Increasing Circulating EPC & BM stem cell
5. Angiogenesis
6. Mitogenic effect on cardiac myocytes

Carbamylated EPO

1. **Bind to heterodimeric receptor**
   - **EpoR + βcR (common β receptor)**

   (not to classic EPO homodimeric receptor
   - **EpoR + EpoR)**
2. **No erythropoietic effect**
3. **Shows anti-apoptoc and cytoprotective effect**

Erythropoietin reduces myocardial infarction and left ventricular functional decline after coronary artery ligation in rats

Chanil Moon*, Melissa Krawczyk*, Dongchoon Ahn*, Ismayil Ahmet*, Doojin Paik†, Edward G. Lakatta*, and Mark I. Talan*‡

*Laboratory of Cardiovascular Sciences, Gerontology Research Center, National Institute on Aging, Baltimore, MD 21224; and †Department of Anatomy and Cell Biology, Hanyang University, Seoul 133-791, Korea

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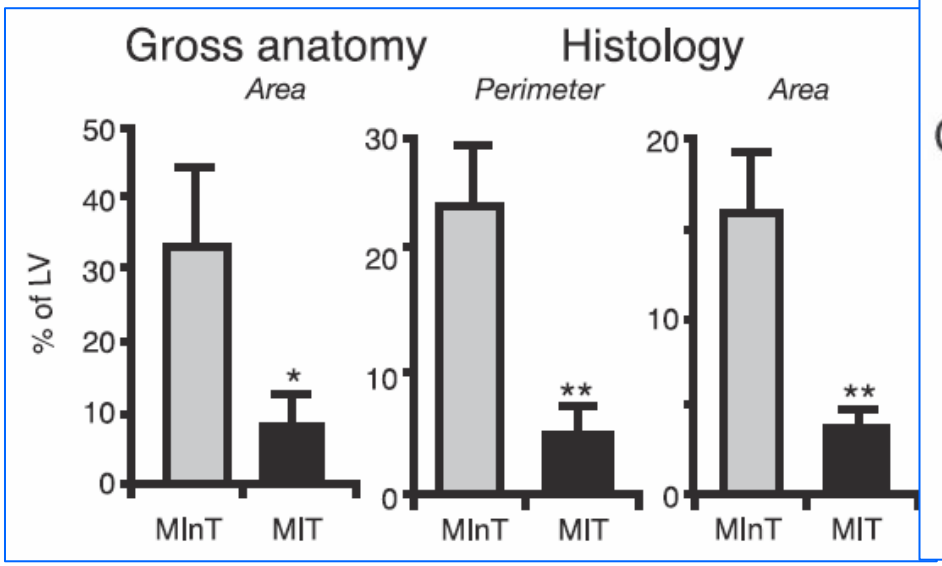
11612–11617 | PNAS | September 30, 2003 | vol. 100 | no. 20



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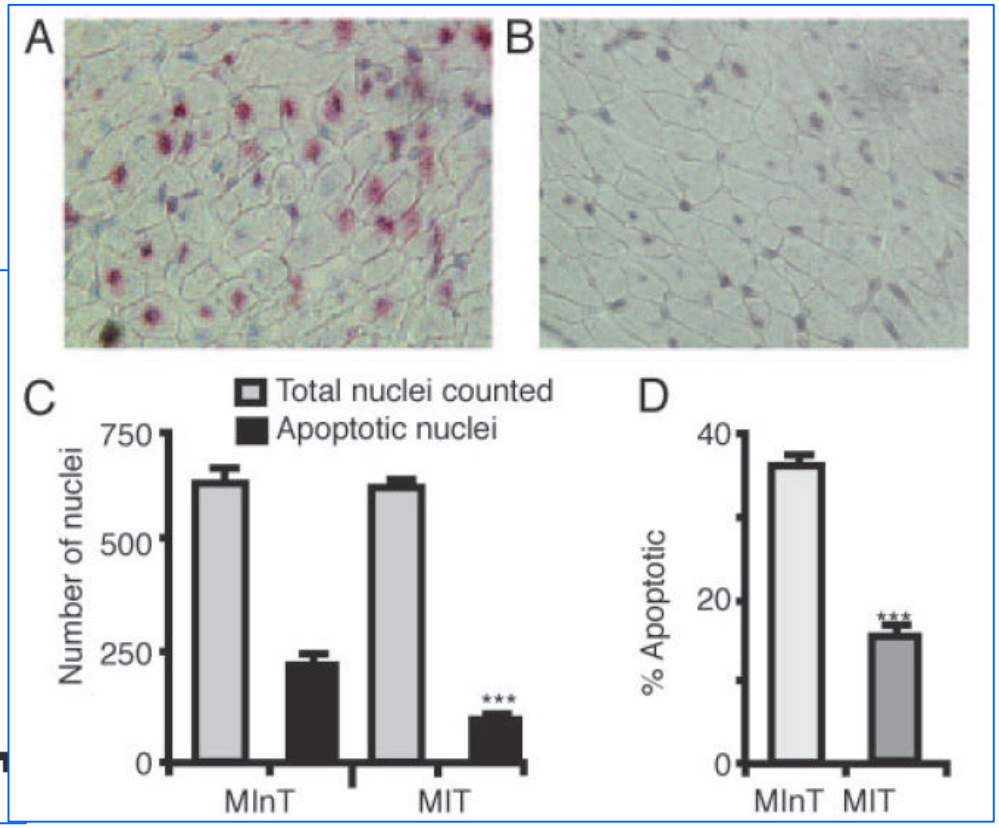


Degree of apoptosis

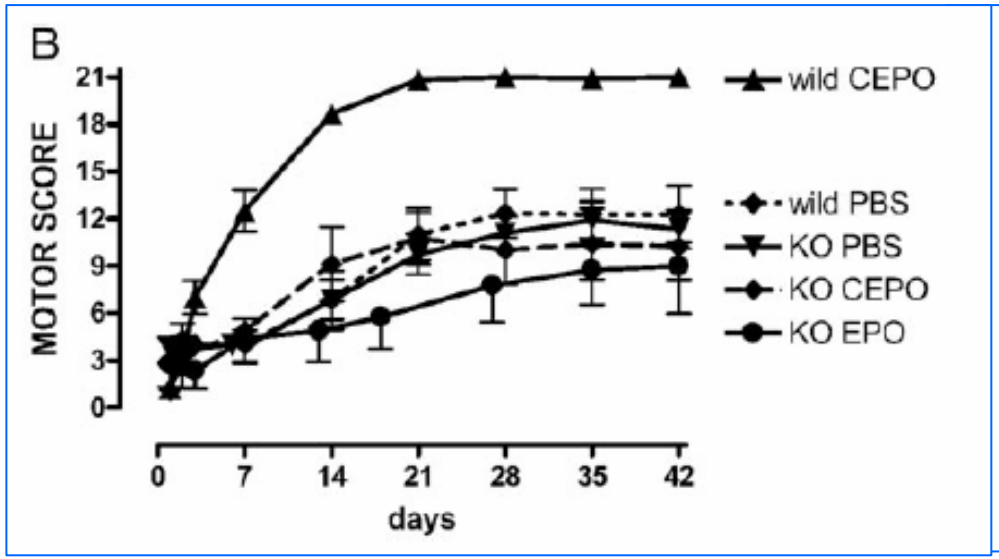
Erythropoietin mediates tissue protection through an erythropoietin and common β-subunit heteroreceptor

Michael Brines*†‡, Giovanni Grasso*§¶, Fabio Fiordaliso¶‖, Alessandra Sfacteria*§, Pietro Ghezzi*†‖, Maddalena Fratelli‖, Roberto Latini‖, Qiao-wen Xie*†, John Smart**, Chiao-ju Su-Rick*†, Eileen Pobre*†, Deborah Diaz*†, Daniel Gomez*†, Carla Hand*†, Thomas Coleman*†, and Anthony Cerami*†

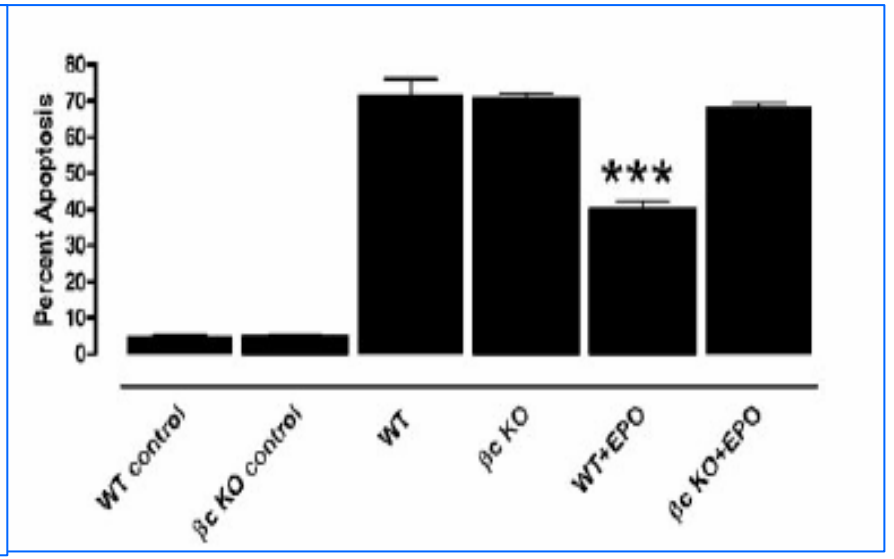
*Kenneth S. Warren Institute and **Warren Pharmaceuticals, Ossining, NY 10563; ‖Mario Negri Pharmacological Research Institute, 20157 Milan, Italy; and §University of Messina, 98122 Messina, Italy

Contributed by Anthony Cerami, September 2, 2004

PNAS | October 12, 2004 | vol. 101 | no. 41 |



Motor recover after cord compression



Myocyte apoptosis

In βcR K-O mouse

Summary

1. Anemia is a frequent co-morbidity in HF
2. Anemia is a independent predictor of morbidity and mortality of the HF.
3. Anemia has emerged as a possible treatment target in HF.
4. But, larger controlled clinical trials are needed for further information and therapy guidelines.

Take Home Massage!

- **Cannot be recommended for general CHF**
  - **No large well-designed study**
  - **No long follow-up study (most less than 1 year)**
  - **No trials about effect on CV mortality or hospitalization**

- **Recommendation based on the available data**
  1. **Hemoglobin level ≤12.0g/dl**
  2. **with repeated episode of ADHF**
  3. **and already receiving maximally therapy**