



Anemia in Patients With Rheumatoid Arthritis (RA)

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National Anemia Action Council

www.anemia.org

NAAC is a 501(c)(3) nonprofit organization

NAAC Mission



The National Anemia Action Council, Inc. (NAAC) is dedicated to raising the awareness of health care professionals and the public regarding the prevalence, symptoms, consequences, and treatment options of anemia.

NAAC is a 501(c)(3) nonprofit organization

NAAC's Online Resources for Medical Professionals



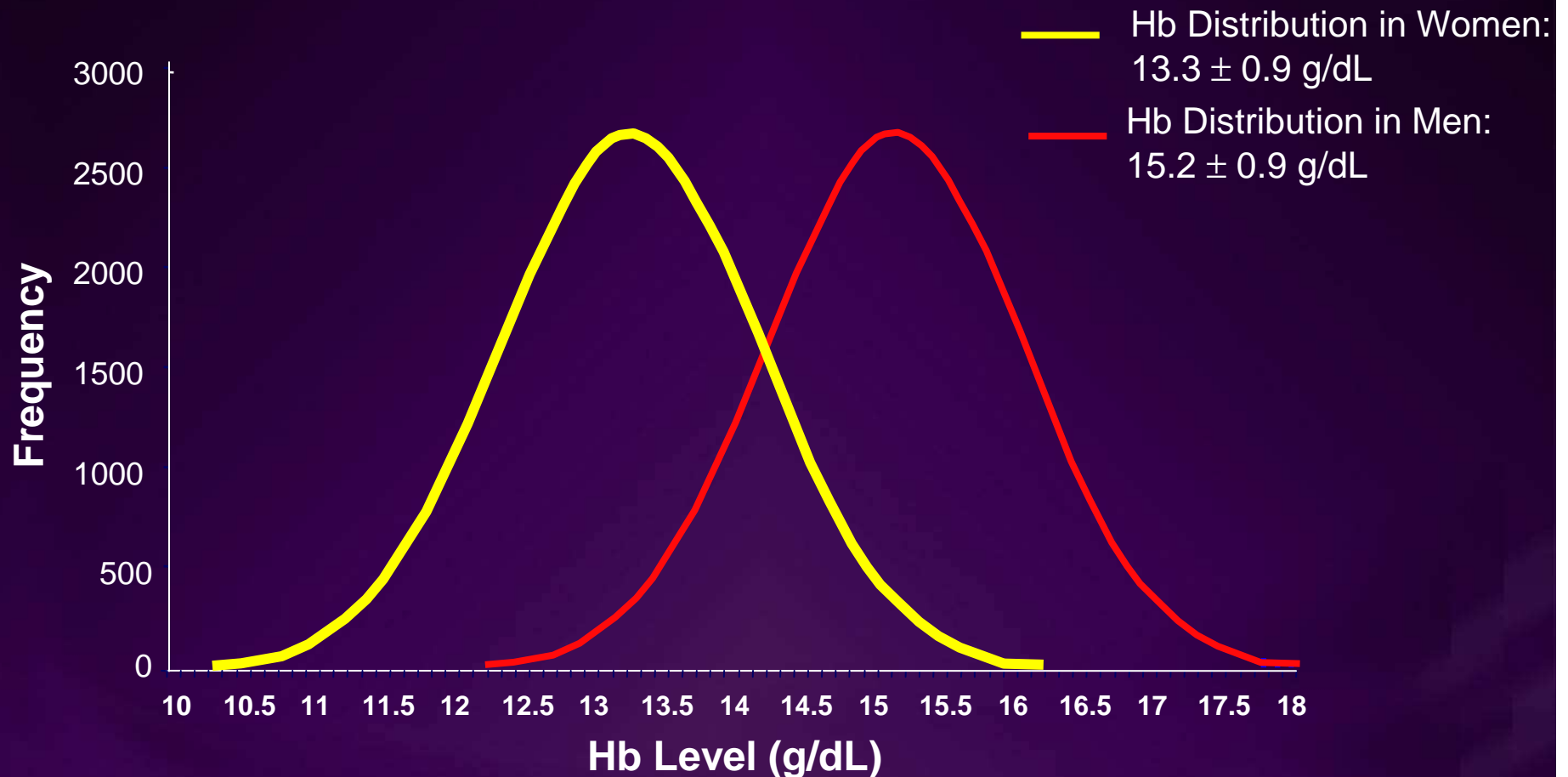
- Research Reviews - Recent clinical trials reviewed
- Ask the Expert - Your anemia questions answered
- Monograph - In-office handbook on anemia
- Feature Articles - Anemia related news and research
- Anemia Alert - Free monthly e-newsletter
- Slide Sets - Educational presentations about anemia
- We have materials for your patients too!

Key Points



- Anemia is the most common extra-articular complication of RA and may be associated with a more progressive course of disease
- The two primary types of anemia in rheumatoid arthritis (RA) patients are anemia of chronic disease (ACD) and iron deficiency anemia (IDA)
- rHuEPO + iron corrects ACD in most patients with RA and may improve RA outcomes and quality of life
- rHuEPO facilitates preoperative autologous blood donation (PAD) in anemic RA patients prior to elective surgery and reduces the need for transfusion

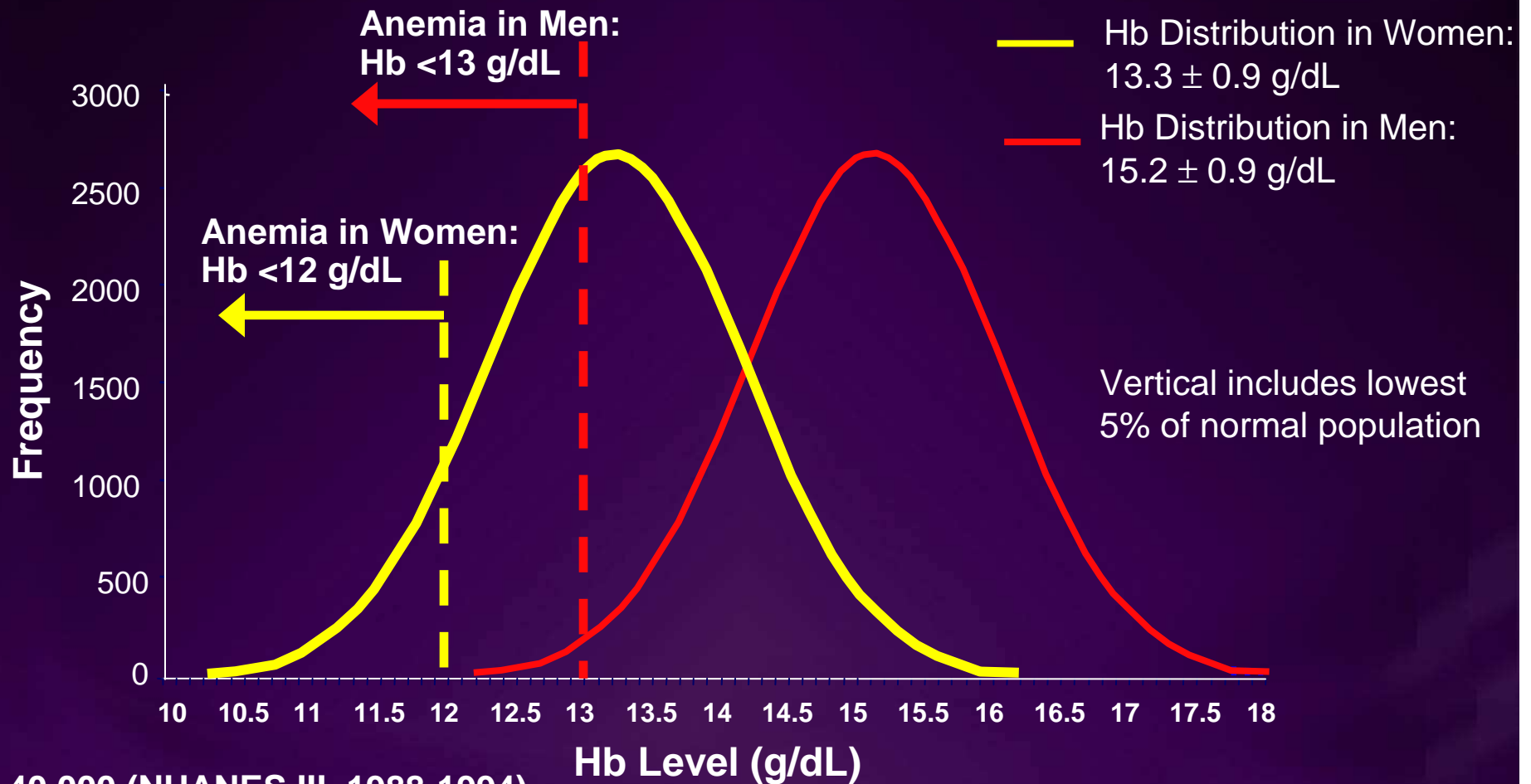
Hemoglobin (Hb) Distribution in the General Population



N = 40,000 (NHANES III, 1988-1994)

Dallman PR, et al. In: *Iron Nutrition in Health and Disease*. London, UK: John Libbey & Co; 1996:65-74.

WHO Definition of Anemia vs. Hb Distribution in General Population



World Health Organization. Geneva, Switzerland; 2001.

Dallman PR, et al. In: *Iron Nutrition in Health and Disease*. London, UK: John Libbey & Co; 1996:65-74.

Laboratory Reference Ranges



Parameter	Male	Female
Hb (g/dL)	14.0 – 17.4	12.3 – 15.3
Hct (%)	41.5 – 50.4	36.0 – 45.0
RBC count ($10^6/\mu\text{L}$)	4.5 – 5.9	4.5 – 5.1
Reticulocyte count (% of RBC count)	0.5 – 2.5	
Mean corpuscular volume (fL)	80 – 96	
Mean corpuscular Hb (MCH) (pg)	27.5 – 33.2	
MCH concentration (g/dL)	33.4 – 35.5	

Hb = hemoglobin; Hct = hematocrit; RBC = red blood cell

Perkins S. In: Lee G, et al, eds. *Wintrobe's Clinical Hematology*. Vol 2. 10th ed. Baltimore, Md: Lippincott, Williams & Wilkins; 1998:2738.

Anemia Signs and Symptoms



Central nervous system

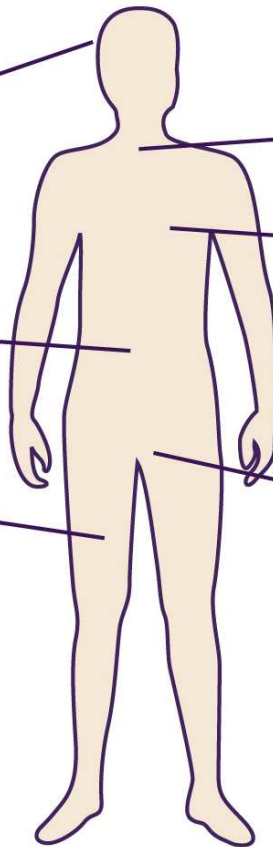
- Fatigue
- Depression
- Impaired cognitive function

Gastrointestinal system

- Anorexia
- Nausea

Vascular system

- Low skin temperature
- Pallor of skin, mucous membranes, and conjunctivae



Immune system

- Impaired T-cell and macrophage function

Cardiorespiratory system

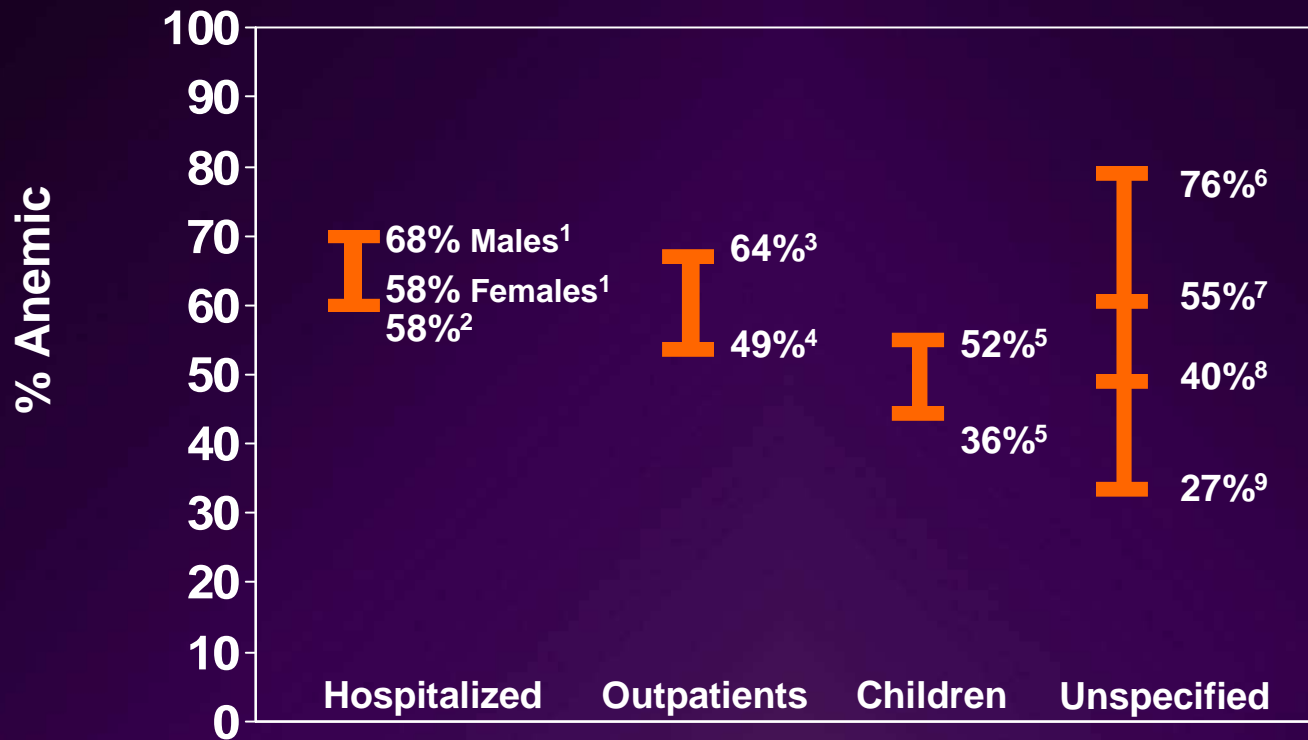
- Exertional dyspnea
- Tachycardia, palpitations
- Cardiac enlargement, hypertrophy
- Increased pulse pressure, systolic ejection murmur
- Risk of cardiac failure

Genital Tract

- Menstrual problems
- Loss of libido

Adapted from Ludwig H, et al. *Semin Oncol.* 2001;28(suppl 8):7-14.

Prevalence of Anemia Varies Among RA Patients Studied



1. Strandberg O. *Acta Med Scand Suppl.* 1966;454:1-153.

2. Miller RK, et al. *Arthritis Rheum.* 1982;25(suppl):S114.

3. Peeters HR, et al. *Ann Rheum Dis.* 1996;55:162-168.

4. Segal R, et al. *Rheumatol Int.* 2004;24:14-19.

5. Seth V, et al. *Indian J Pediatr.* 1996;63:293-300.

6. Baer AN, et al. *Br J Haematol.* 1987;66:559-564.

7. Remacha AF, et al. *J Rheumatol.* 1992;19:1687-1691.

8. Hochberg MC, et al. *Arthritis Rheum.* 1988;31:1318-1321.

9. Baer AN, et al. *Semin Arthritis Rheum.* 1990;19:209-223.

Causes of Anemia Among Patients With RA



- Anemia of chronic disease (ACD)¹⁻⁴
- Iron deficiency anemia (IDA)¹⁻⁴
- Vitamin B₁₂ deficiency^{1-3,5}
- Folic acid deficiency¹⁻⁵

1. Vreugdenhil G, Swaak AJ. *Rheumatol Int.* 1990;9:243-257.
2. Vreugdenhil G, et al. *Ann Rheum Dis.* 1990;49:93-98.
3. Remacha AF, et al. *J Rheumatol.* 1992;19:1687-1691.
4. Bowman SJ. *Scand J Rheumatol.* 2002;31:251-259.
5. Segal R, et al. *Rheumatol Int.* 2004;24:14-19.



Anemia of Chronic Disease (ACD) in RA Patients

Overview of ACD in RA



- Generally mild (10.0-12 g/dL Hb) to moderate (8.0-10.0 g/dL Hb)^{1,2}
- Usually normochromic and normocytic^{1,2}
- Diagnostic criteria:³
 - Decreased serum iron (males: normal 65-175 mcg/dL; females: 50-170 mcg/dL)⁴
 - Decreased transferrin saturation (normal 212-360 mg/dL)⁴ check values
 - Normal or elevated ferritin (normal 20-150 ng/mL male; 10-120 ng/mL female)⁴

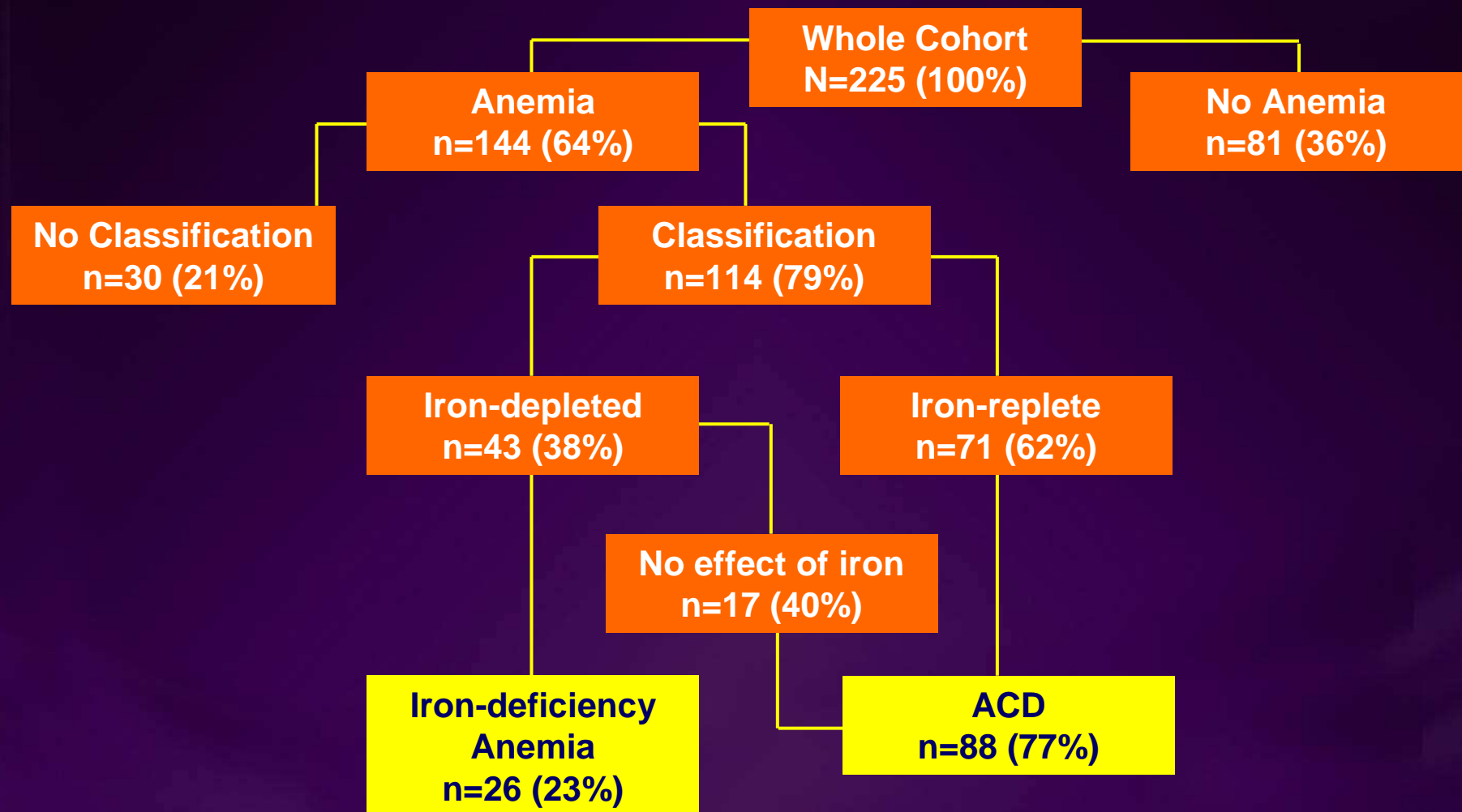
1. Vreugdenhil G, et al. *Rheumatol Int.* 1990;9:243-257.

2. Means RT Jr, et al. *Blood.* 1992;80:1639-1647.

3. Bowman SJ. *Scand J Rheumatol.* 2002;31:251-259.

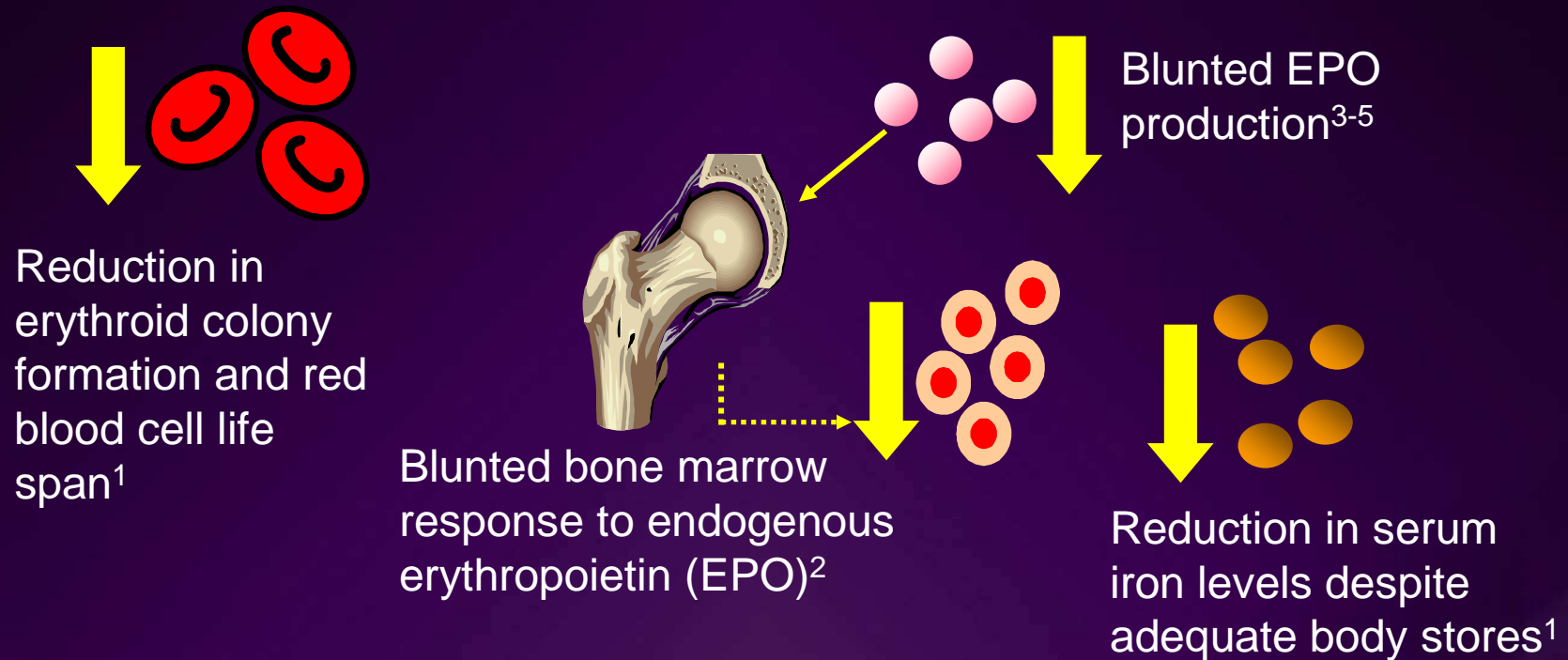
4. Kovacs S, Hess K. *Stedman's Pathology & Laboratory Medicine.* 2002.

ACD Is More Common Than IDA in RA Patients



Peeters H, et al. *Ann Rheum Dis*. 1996;55:162-168.

ACD in RA Is Multifactorial



1. Vreugdenhil G, et al. *Rheumatol Int.* 1990;9:243-257.

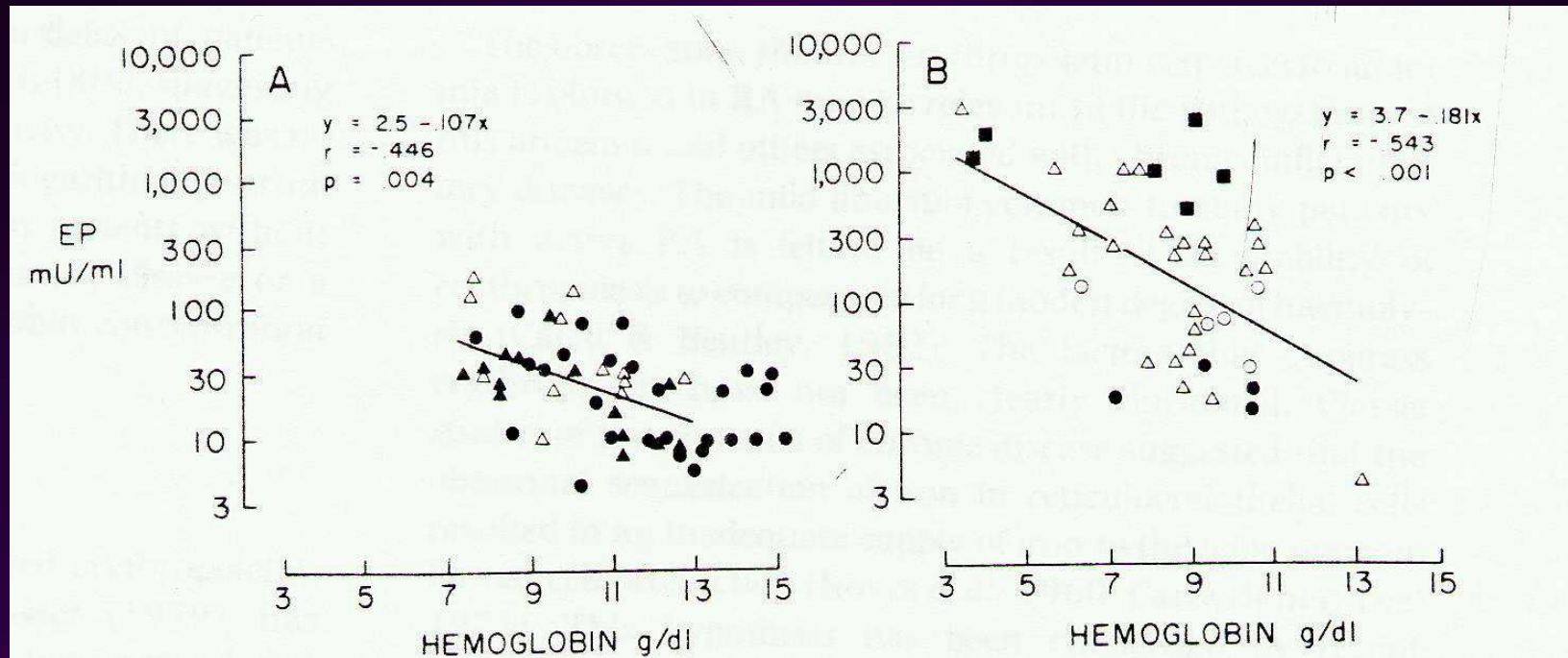
2. Baer AN, et al. *Semin Arthritis Rheum.* 1990;19:209-223.

3. Baer AN, et al. *Br J Haematol.* 1987;66:559-564.

4. Hochberg MC, et al. *Arthritis Rheum.* 1988;31:1318-1321.

5. Boyd HK, et al. *Br J Rheumatol.* 1991;30:255-259.

EPO Production Is Blunted in RA Patients With ACD

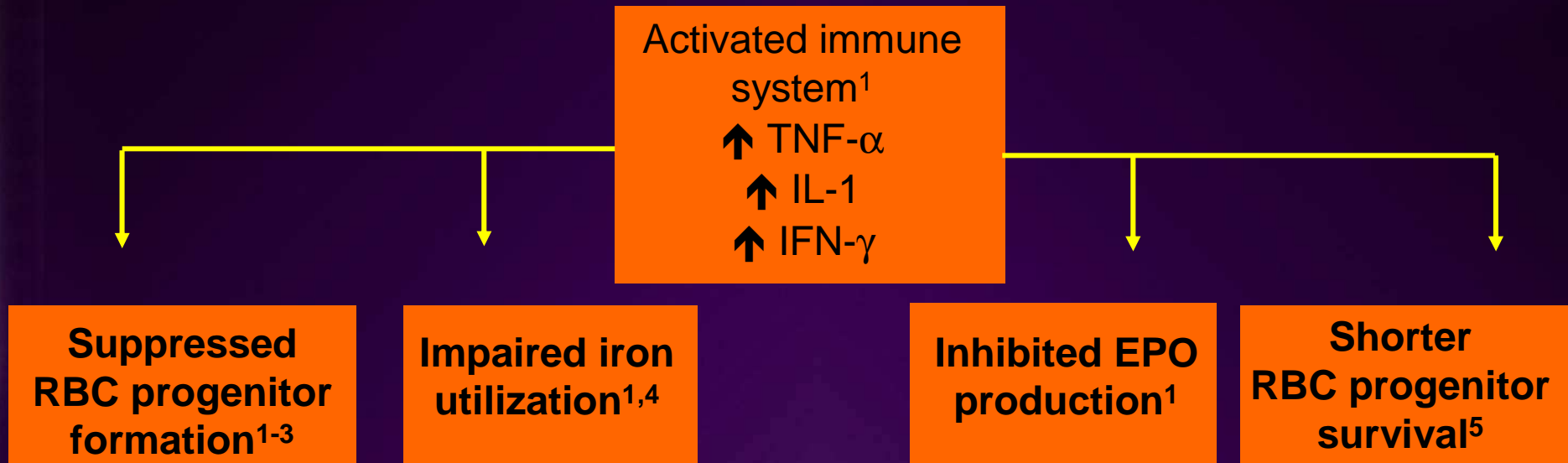


**RA Patients
(n=54)**

**Anemic Patients
Without RA
(n=41)**

Baer AN, et al. *Br J Haematol.* 1987;66:559-564.

Elevated Cytokine Levels Mediate ACD in RA



TNF, tumor necrosis factor; IL, interleukin; IFN, interferon

1. Means RT Jr, et al. *Blood*. 1992;80:1639-1647.

4. Cazzola M, et al. *Blood*. 1996;87:4824-4830.

2. Vreugdenhil G, et al. *Eur J Clin Invest*. 1992;22:488-493.

5. Papadaki HA, et al. *Blood*. 2002;100:474-482.

3. Voulgari PV, et al. *Clin Immunol*. 1999;92:153-160.



Iron Deficiency Anemia (IDA) in RA Patients

Overview of IDA in RA



- Present in ~50% of anemic RA patients¹⁻³
- Coexists with ACD in 30% to 70% of all RA patients⁴
- Most commonly due to GI bleeding secondary to NSAID or corticosteroid therapy³
- Generally hypochromic and microcytic⁵

1. Nielsen OJ, et al. *Ann Rheum Dis*. 1990;49:349-353.

2. Vreugdenhil G, et al. *Ann Rheum Dis*. 1990;49:93-98.

3. Song JS, et al. *Rheumatol Int*. 2001;21:24-29.

4. Vreugdenhil G, et al. *Rheumatol Int*. 1990;9:243-257.

5. Bowman SJ. *Scand J Rheumatol*. 2002;31:251-259.

IDA Can Be Difficult to Diagnose in RA Patients



Serum iron – reflects iron available for Hb

- Subnormal in both IDA and ACD

Transferrin saturation – reflects iron available for Hb

- Subnormal in both IDA and ACD

Serum ferritin – reflects body's iron stores

- Acute phase reactant
- Decreased in IDA
- Normal or increased in ACD, even if IDA also present

Bowman SJ. *Scand J Rheumatol*. 2002;31:251-259.

Tips for Diagnosing IDA in RA Patients



- A trial of iron is not reliable as a test for IDA¹
- Serum transferrin receptor (sTfR)
 - Elevated level strongly suggests IDA^{2,3}
 - Unlike ferritin, not affected by degree of inflammation^{2,3}
- sTfR >2.50 mg/L and serum ferritin <50 µg/L
 - 100% sensitive for IDA⁴
 - 97% specific for IDA⁴

1. Baer AN, et al. *Semin Arthritis Rheum.* 1990;19:209-223.

2. Chijiwa T, et al. *Clin Rheumatol.* 2001;20:307-313.

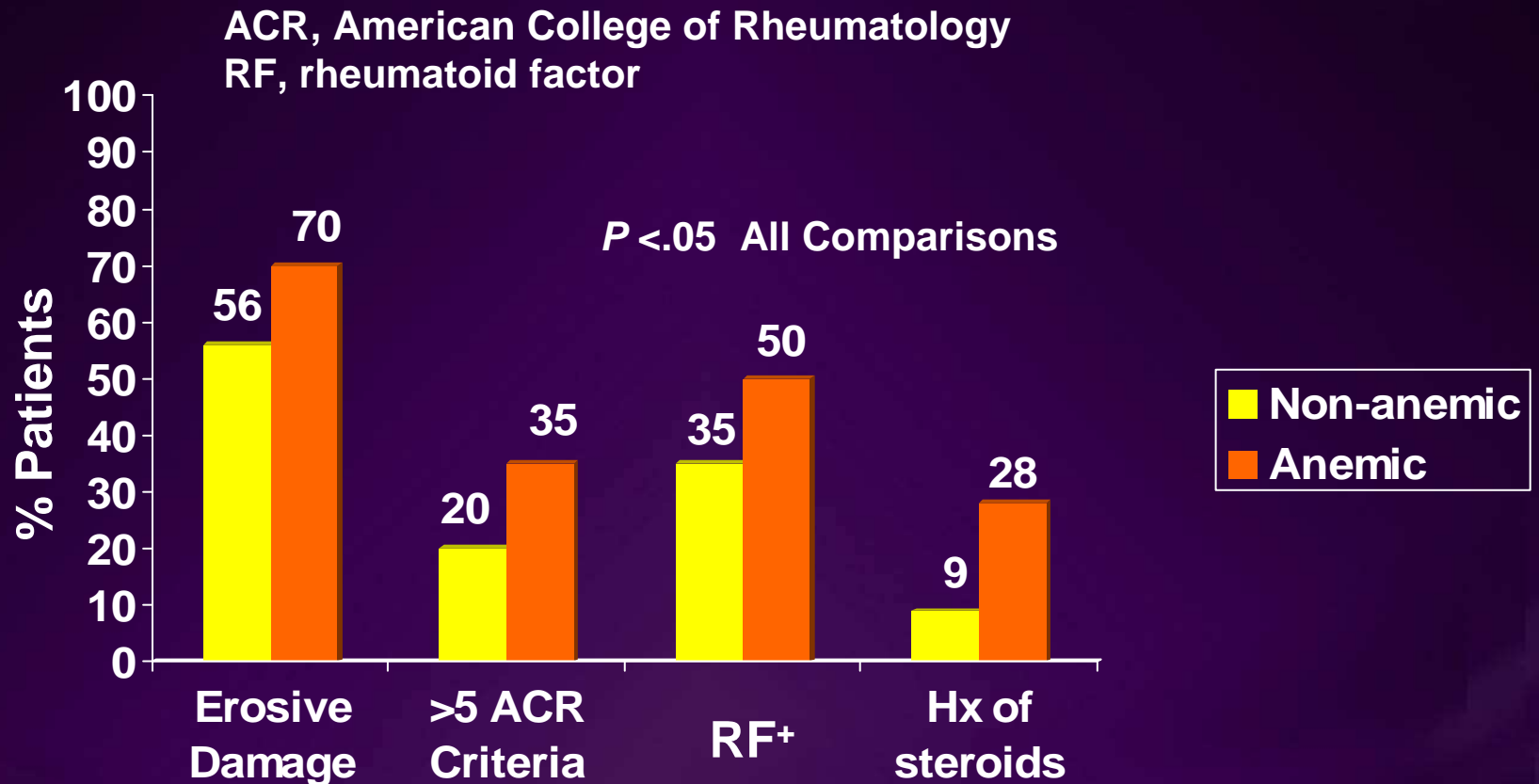
3. Song JS, et al. *Rheumatol Int.* 2001;21:24-29.

4. Bultink IE, et al. *Arthritis Rheum.* 2001;44:979-981.



Clinical Consequences of Anemia in Patients With RA

Anemic RA Patients Have More Active Disease



Peeters H, et al. *Ann Rheum Dis*. 1996;55:162-168.



Treatment of RA-Associated Anemia

Treatment Options for RA-Associated Anemia



- Anti-inflammatory therapy
- Oral or IV iron supplementation
- Allogeneic blood transfusion (ABT)
- Recombinant human erythropoietin (rHuEPO)



Anti-inflammatory Therapy

Anti-inflammatory Therapy Can Correct ACD



- The first principle of treating RA-associated anemia is to reduce inflammation with methotrexate and other disease-modifying antirheumatic drugs¹
- Infliximab significantly increases Hb from baseline, as do other effective drugs and TNF-blocking agents²
- Anakinra increases Hct significantly more than placebo³
- The addition of etanercept and/or methotrexate improved activity level and well-being⁴

1. Chijiwa T, et al. *Clin Rheumatol*. 2001;20:307-313.

2. Davis D, et al. *Br J Rheumatol*. 1997;36:950-956.

3. Kay J, et al. *Ann Rheum Dis*. 2001;60(suppl):152 [abstract].

4. Kietz DA, et al. *J Rheumatol*. 2001;28:360-362.



Allogeneic Blood Transfusion

Current ABT Guidance



“Except when the patient’s symptoms require immediate enhancement of oxygen-carrying capacity, red-cell containing components should not be used to treat anemias that can be corrected with specific medications such as iron, vitamin B₁₂, folic acid or recombinant erythropoietin.”

American Association of Blood Banks, America’s Blood Centers, the American Red Cross; 2000.



Iron Supplementation

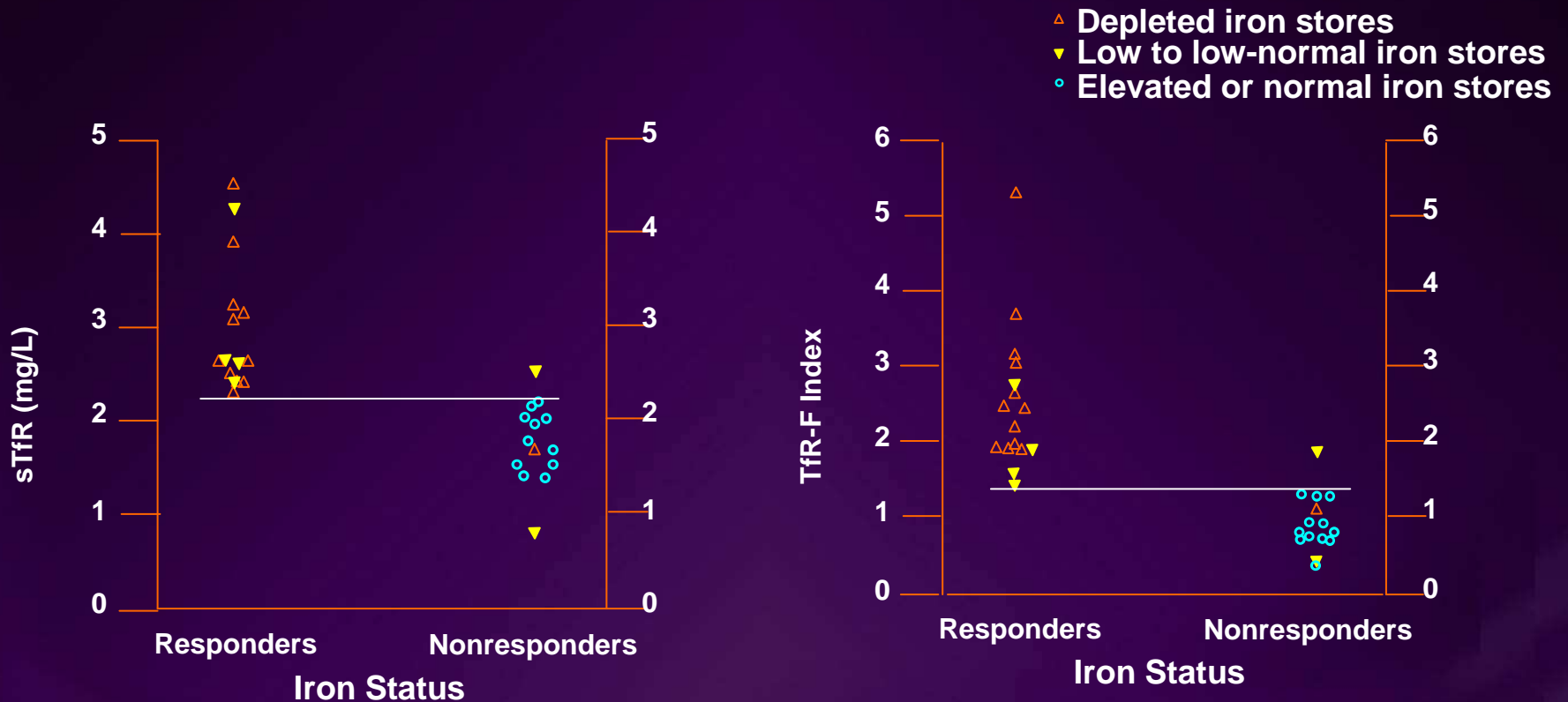
Functional Iron Deficiency Affects Need for Iron



- Some RA patients with anemia have functional iron deficiency (iron-deficiency erythropoiesis in the presence of normal or increased iron stores)
- These patients can benefit from iron supplementation even though they do not have IDA

Suominen P, et al. *Arthritis Rheum.* 2000;43:1016-1020.

sTfR, Ferritin Useful in Detecting Functional Iron Deficiency



Solid horizontal lines represent the optimal cutoff values of each analyte.
 sTfR – serum transferrin receptor

Suominen P, et al *Arthritis Rheum.* 2000;43:1016-1020.

Other Guidelines for Iron Supplementation in RA



- Oral or IV iron is important for RA patients with IDA¹
- Severely anemic patients often have both ACD and IDA and can benefit from IV iron²
- IV iron should be considered for patients with systemic-onset juvenile RA (SoJRA) who are unresponsive to oral iron³

1. National Anemia Action Council. *Anemia: A Hidden Epidemic*. Los Angeles; 2002.

2. Cazzola M, et al. *Blood*. 1997;89:4248-4267.

3. Cazzola M, et al. *Blood*. 1996;87:4824-4830.



rHuEPO

Evidence for the Efficacy of rHuEPO in RA

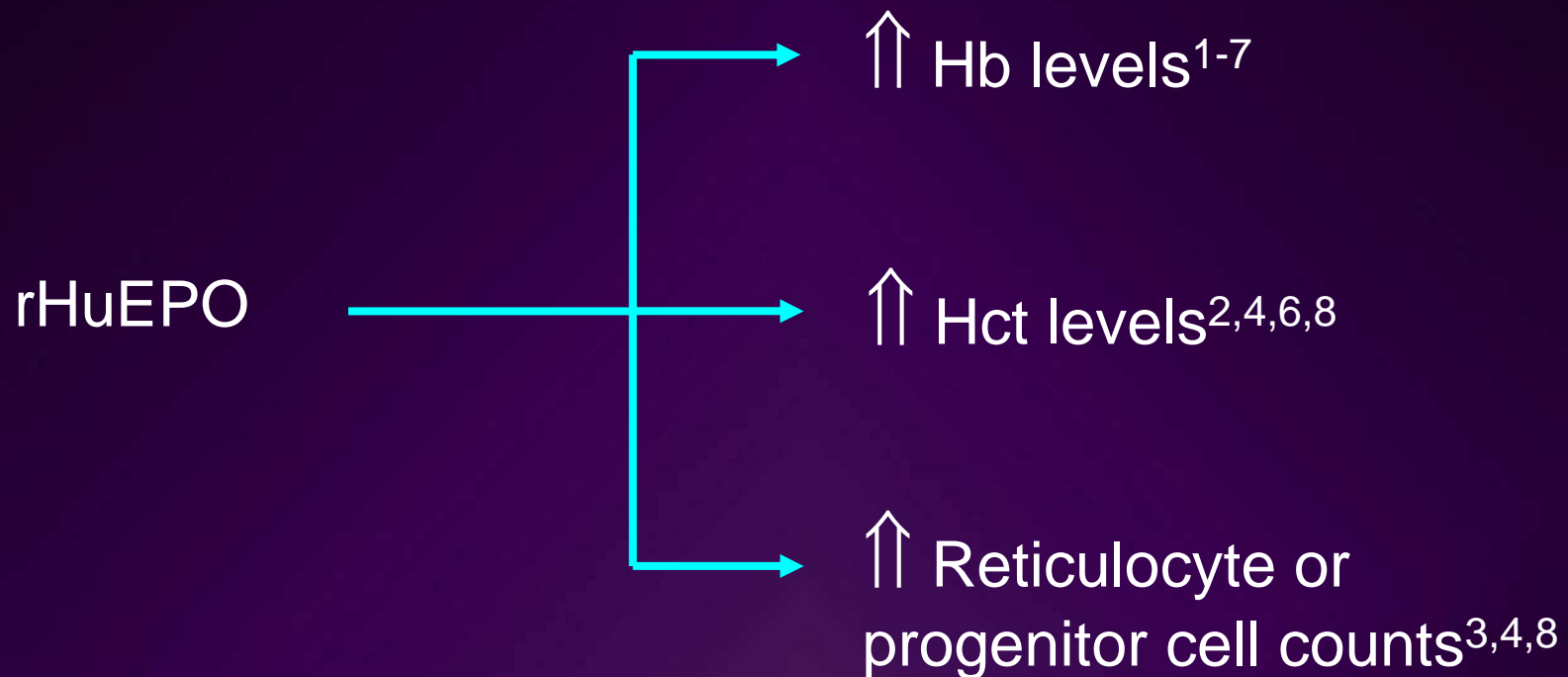


- 6 short-term open-label studies of adults
- A short-term open-label study of children with SoJRA
- 3 shorter-term randomized controlled trials (RCTs) of rHuEPO plus oral iron
- A 52-week RCT of rHuEPO plus oral iron
- A 12-week open-label study of rHuEPO plus IV iron
- 4 studies of rHuEPO, plus oral or IV iron, for preoperative autologous blood donation (PAD)



Early, Short-Term, Open-Label Studies of rHuEPO

rHuEPO Improved Hb/Hct in Open-Label Studies



1. Takashina N, et al. *J Rheumatol*. 1990;17:885-887.

2. Salvarani C, et al. *J Rheumatol*. 1991;18:1168-1171.

3. Gudbjörnsson B, et al. *Ann Rheum Dis*. 1992;51:747-752.

4. Vreugdenhil G, et al. *Ann Hematol*. 1992;65:265-268.

5. Pettersson T, et al. *Scand J Rheumatol*. 1993;22: 188-193.

6. Kato Y, et al. *Intern Med*. 1994;33:193-197.

7. Swaak AJ, et al. *Clin Exp Rheumatol*. 1994;12:577.

8. Means RT Jr, et al. *Arthritis Rheum*. 1989;32:638-642.

rHuEPO Modified Disease Activity in Some Open-Label Studies

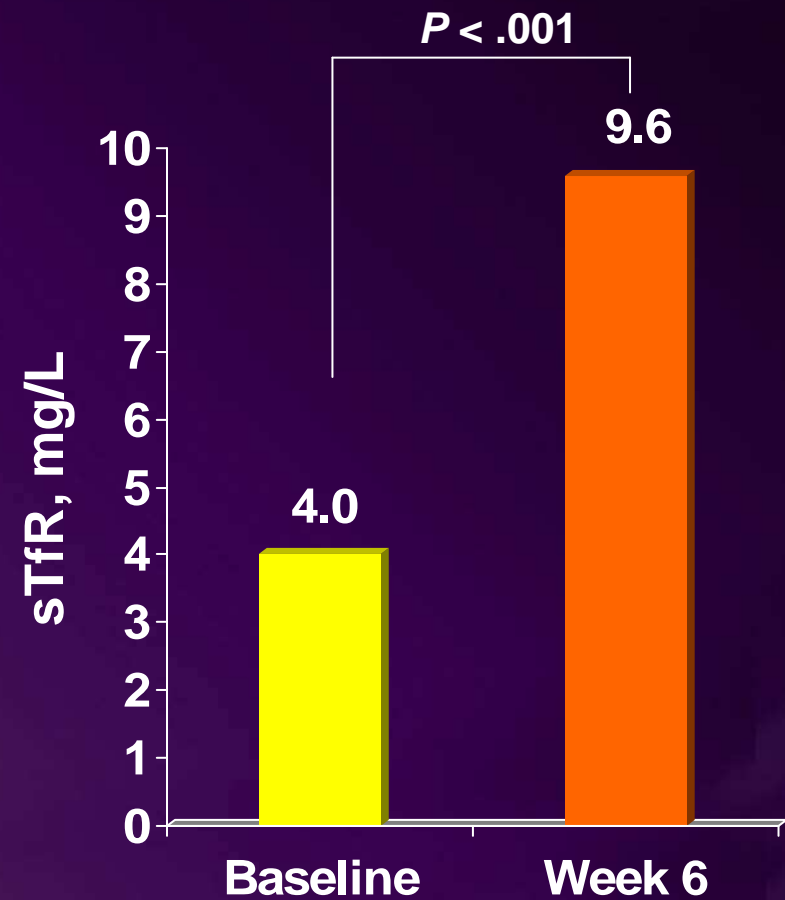
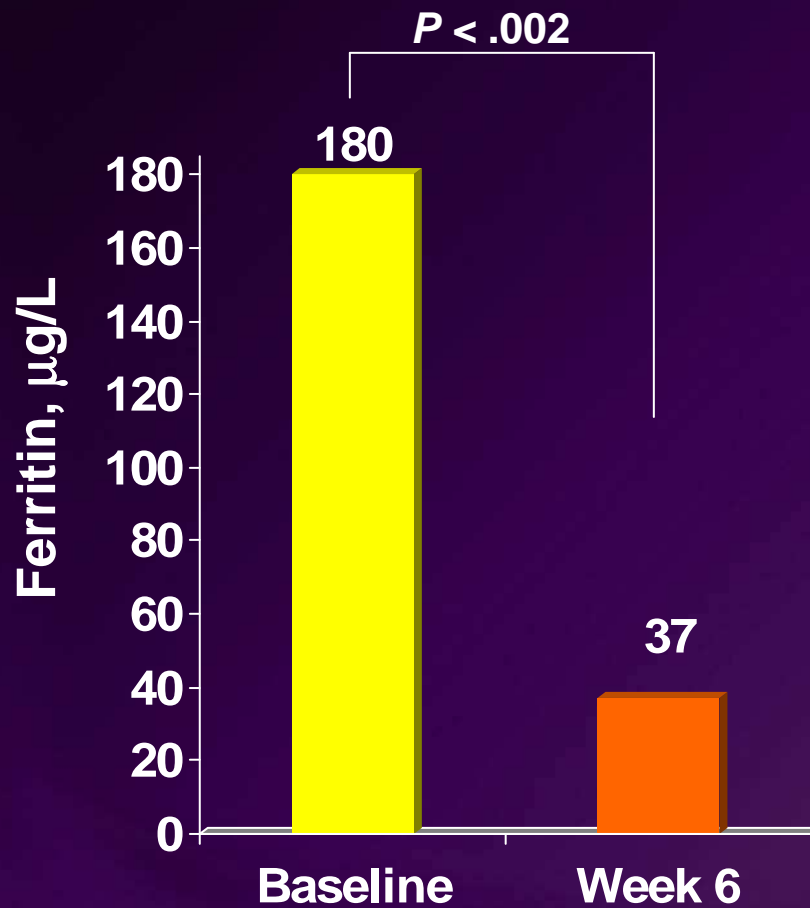


Measure	Significant improvement	No change
CRP	Ref 1	Refs 2, 4
ESR	Ref 4	Refs 2, 3
Functional capacity	---	Ref 4
General condition, VAS	Ref 4	---
Joint pain/tenderness	Ref 1	Refs 2-4
Morning stiffness	---	Ref 4
Need for daily rest	Ref 4	---
Pain, VAS	Ref 1	---

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; VAS, visual analog scale; ---, not measured in other studies

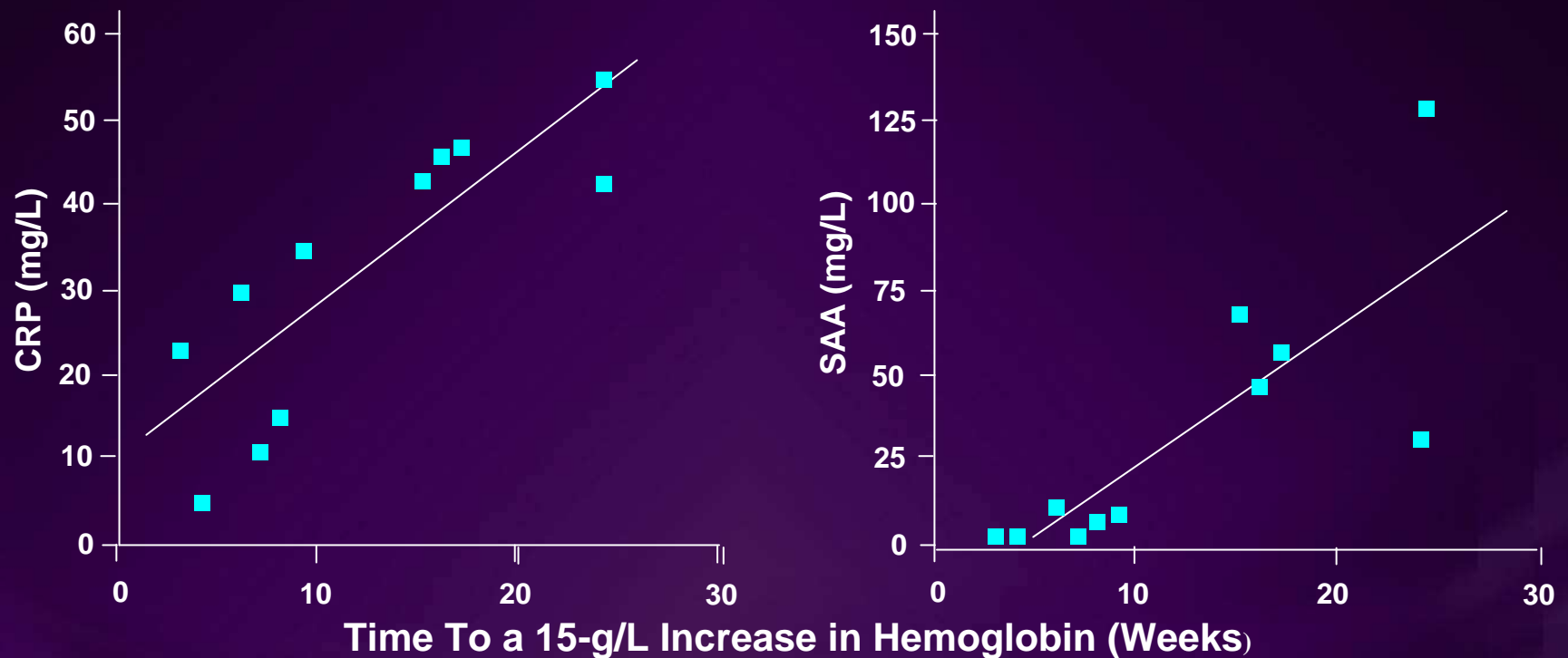
1. Swaak AJ, et al. *Clin Exp Rheumatol*. 1994;12:577 [letter].
2. Pettersson T, et al. *Scand J Rheumatol*. 1993;22:188-193.
3. Salvarani C, et al. *J Rheumatol*. 1991;18:1168-1171.
4. Gudbjörnsson B, et al. *Ann Rheum Dis*. 1992;51:747-752.

rHuEPO May Improve Iron Metabolism in RA



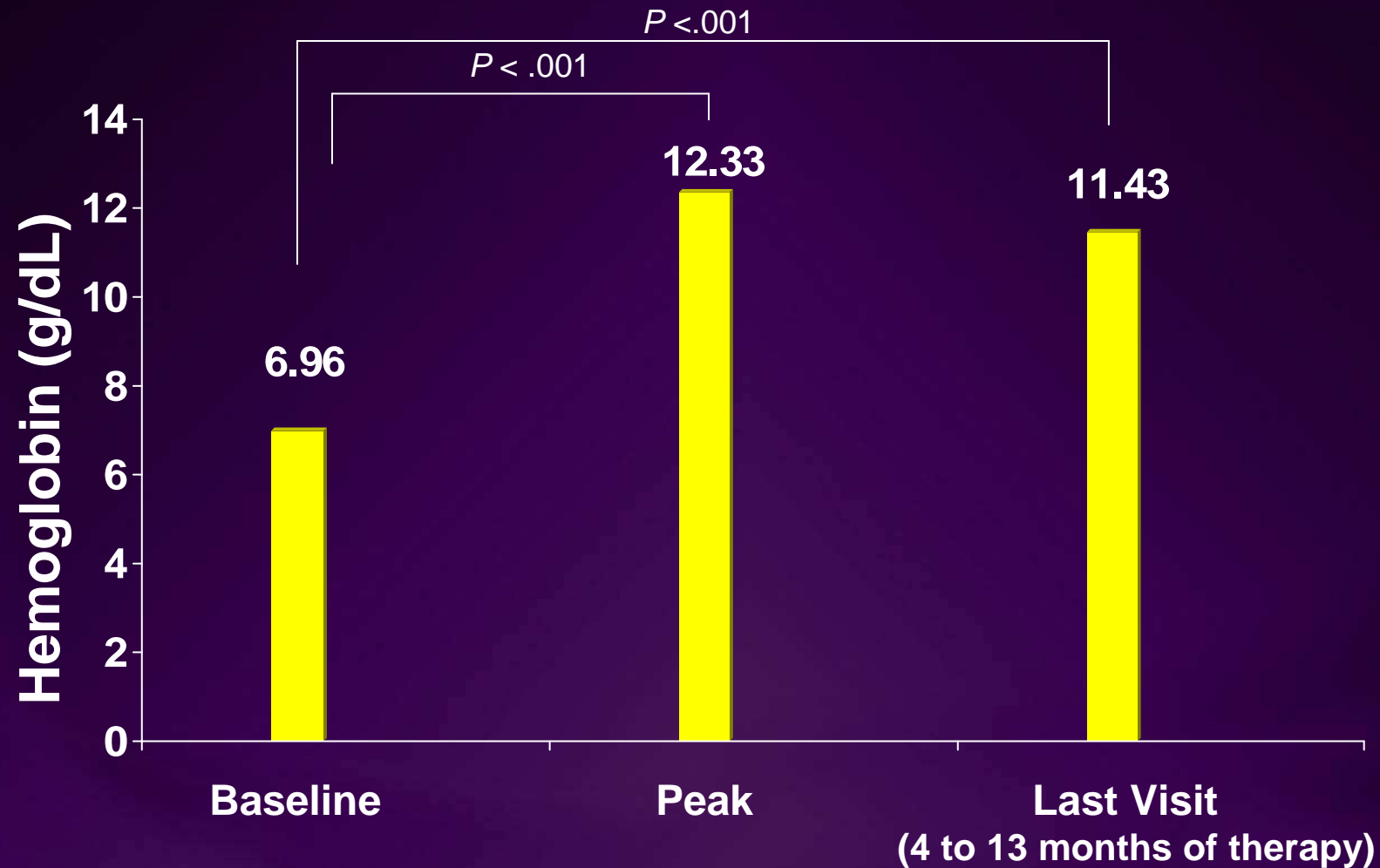
Vreugdenhil G, et al. *Ann Hematol.* 1992;65:265-268.

Response to rHuEPO Is Slowest in Patients With Severe Inflammation



Pettersson T, et al. *Scand J Rheumatol.* 1993;22:188-193.

rHuEPO Treats Anemia in Patients With SoJRA



Fantini F, et al. *Arthritis Rheum.* 1992;35:724-726.



Shorter-Term, Randomized, Controlled Studies of rHuEPO

rHuEPO Improved Hb/Hct in Shorter-Term Studies



Study Group	N (completers)	Duration	Findings
Pincus et al., 1990 (multicenter)	13 rHuEPO 4 placebo	8 weeks	Mean change in Hct: +4 units w/ rHuEPO -1 unit w/ placebo
Murphy et al., 1994	10 rHuEPO 10 placebo	20 weeks	Increase in Hb greater with rHuEPO ($P < .02$ vs placebo)
Nordström et al., 1997 (multicenter)	36 rHuEPO 10 placebo	12 weeks	Increase in Hb greater with rHuEPO ($P < .05$ vs placebo)

Pincus T, et al. *Am J Med.* 1990;89:161-168.

Murphy EA, et al. *BMJ.* 1994;309(6965):1337-1338.

Nordström D, et al. *Rheumatol Int.* 1997;17:67-73.

rHuEPO Modified Disease Activity in Shorter-Term Studies



Measure	Significant improvement	No change
CRP		Refs 1-3
ESR	Refs 1-3	
Energy level on NHP	Refs 1-3	
HAQ		Refs 1-3
Joint pain/tenderness		Refs 1-3
Morning stiffness		Refs 1-3
Pain, VAS	---	Refs 1, 2

NHP, Nottingham Health Profile; HAQ, Stanford Health Assessment Questionnaire; ---, not measured in other study

1. Pincus T, et al. *Am J Med.* 1990;89:161-168.
2. Murphy EA, et al. *BMJ.* 1994;309(6965):1337-1338.
3. Nordström D, et al. *Rheumatol Int.* 1997;17:67-73.



52-Week, Randomized, Controlled Study of rHuEPO in Patients With RA

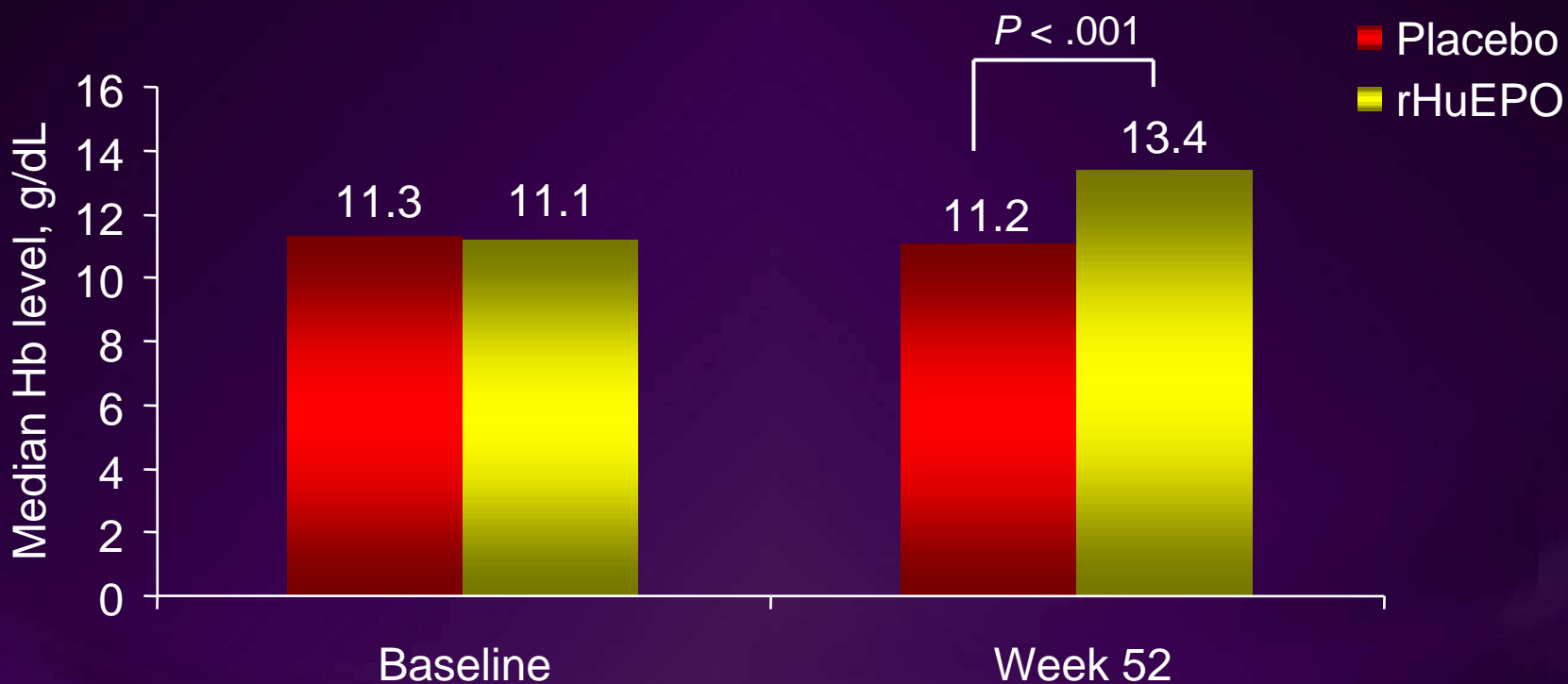
52-Week Randomized, Controlled Study of rHuEPO



- 70 patients with active RA, Hb < 11.7 g/dL, and no evidence of IDA
 - 36 received placebo
 - 34 received 240 U/kg rHuEPO SC 3 times weekly
- Primary endpoints:
 - Hb level
 - Paulus index (a measure of disease activity)
- Secondary endpoints:
 - CRP, ESR, Ritchie articular index, number of swollen joints, duration of morning stiffness, global status

Peeters H, et al. *Ann Rheum Dis*. 1996;55:739-744.

rHuEPO Improved Hb Levels

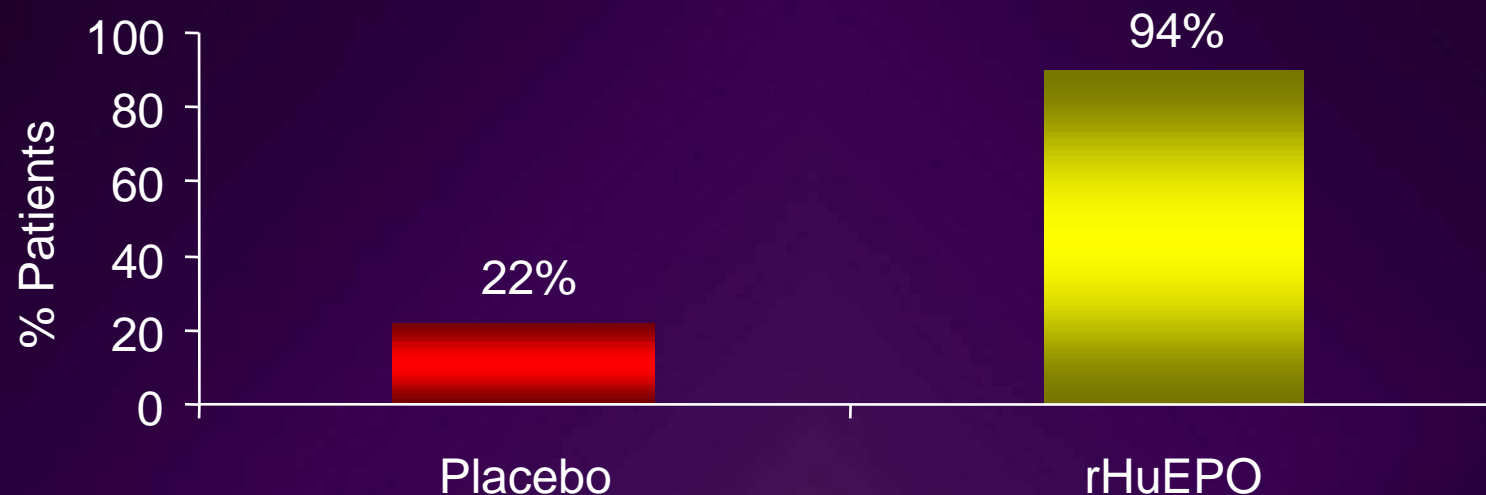


Peeters H, et al. *Ann Rheum Dis.* 1996;55:739-744.

Response to rHuEPO Was High



Patients achieving normal Hb level during the treatment period



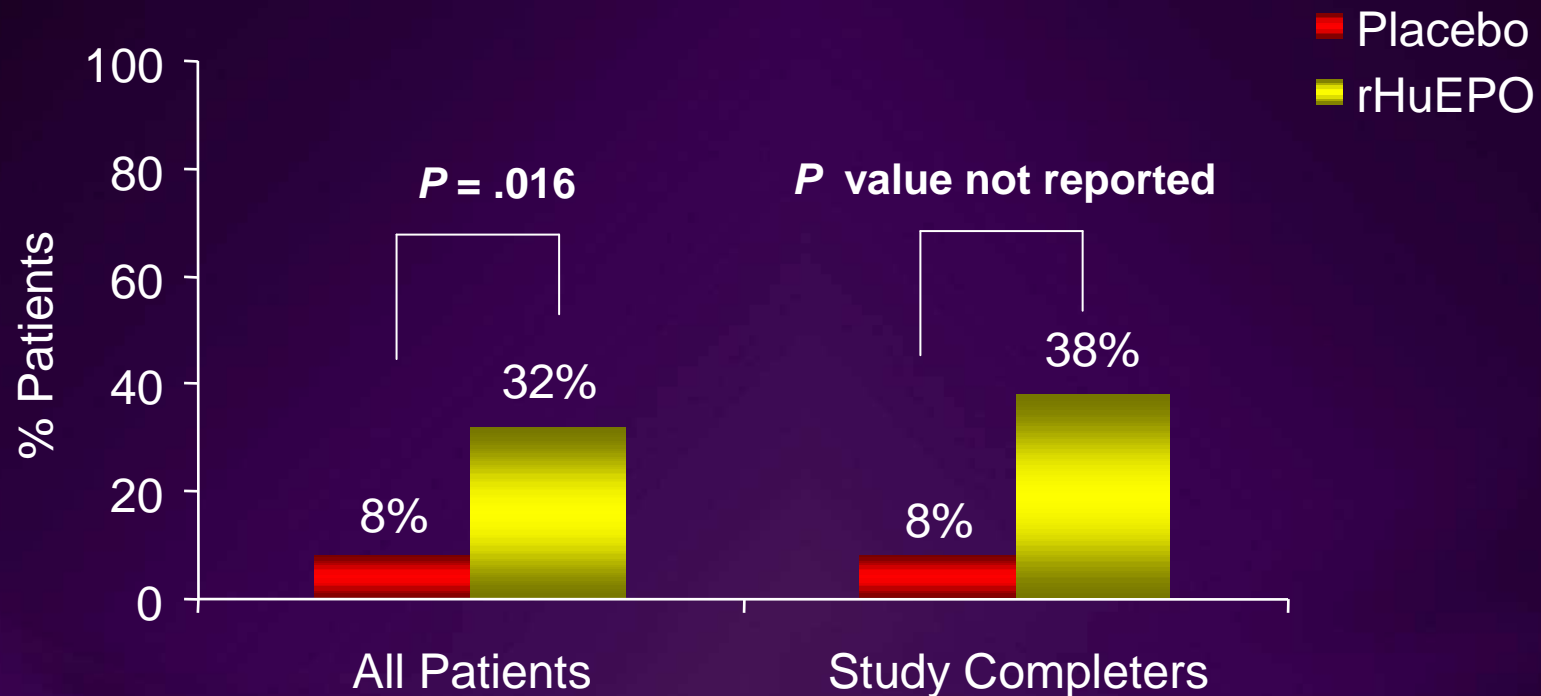
A normal Hb level was defined as >11.7 and >13.6 g/dL for women and men, respectively

Peeters H, et al. *Ann Rheum Dis.* 1996;55:739-744.

rHuEPO Improved Disease Activity According to Primary Endpoint

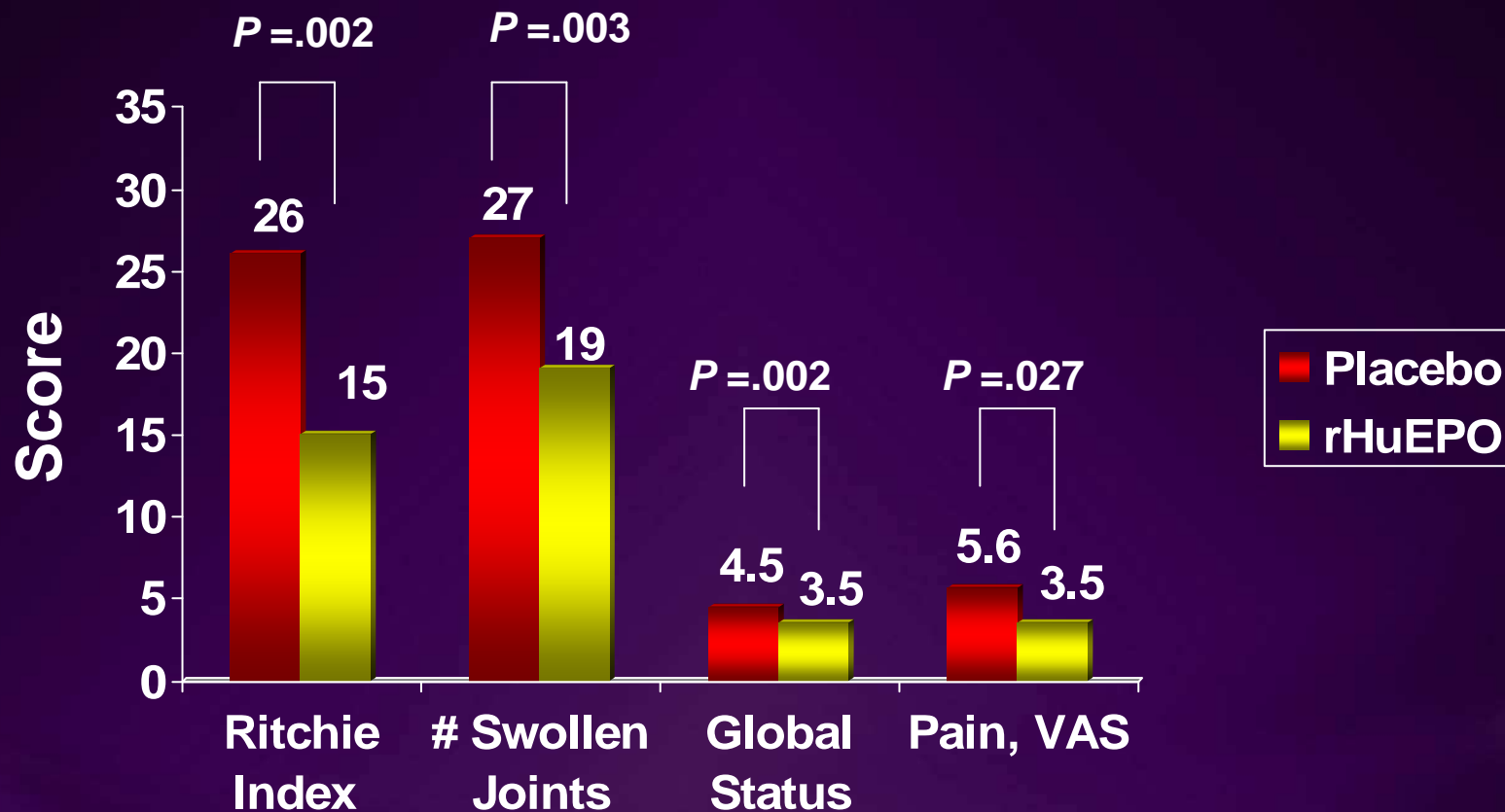


Patients Achieving a 20% Paulus Response



Peeters H, et al. *Ann Rheum Dis*. 1996;55:739-744.

rHuEPO Improved Disease Activity According to Secondary Endpoints

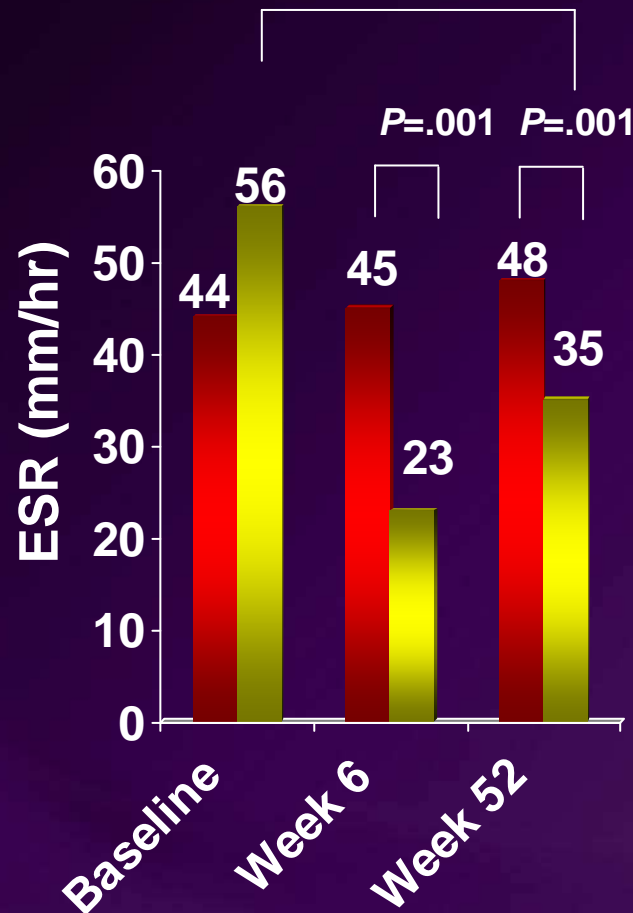


Peeters H, et al. *Ann Rheum Dis.* 1996;55:739-744.

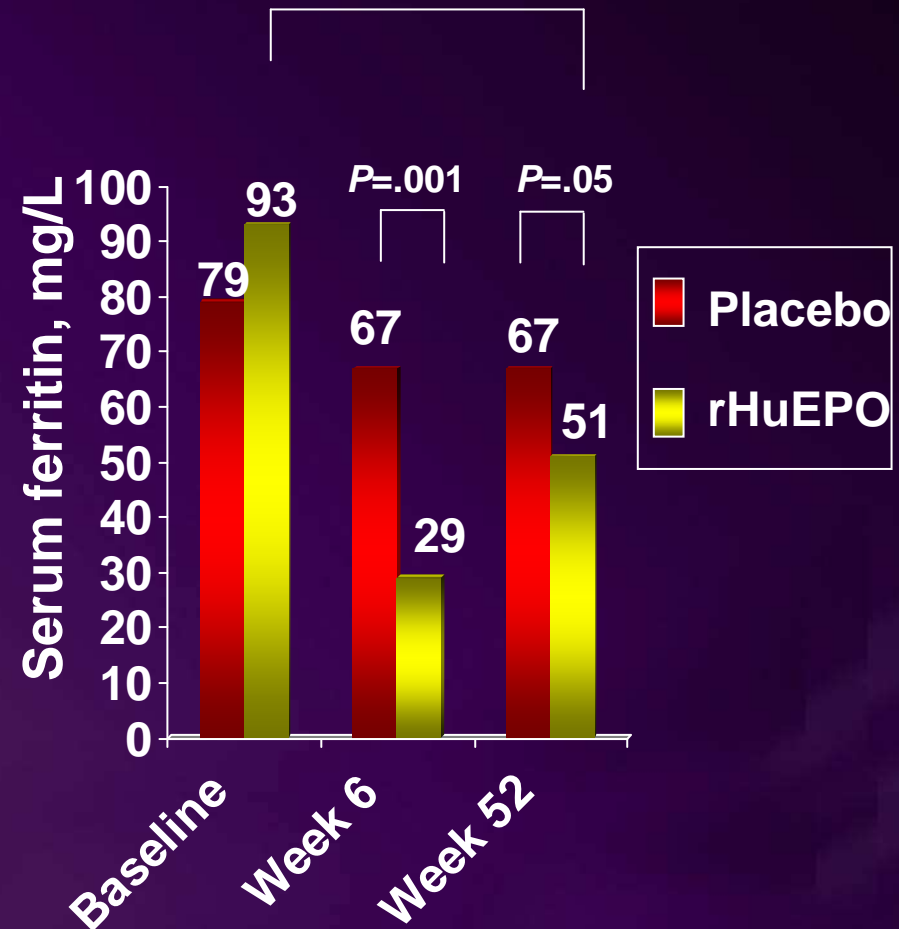
Decreases in Ferritin and ESR Occurred Rapidly



rHuEPO group from baseline $P=.035$

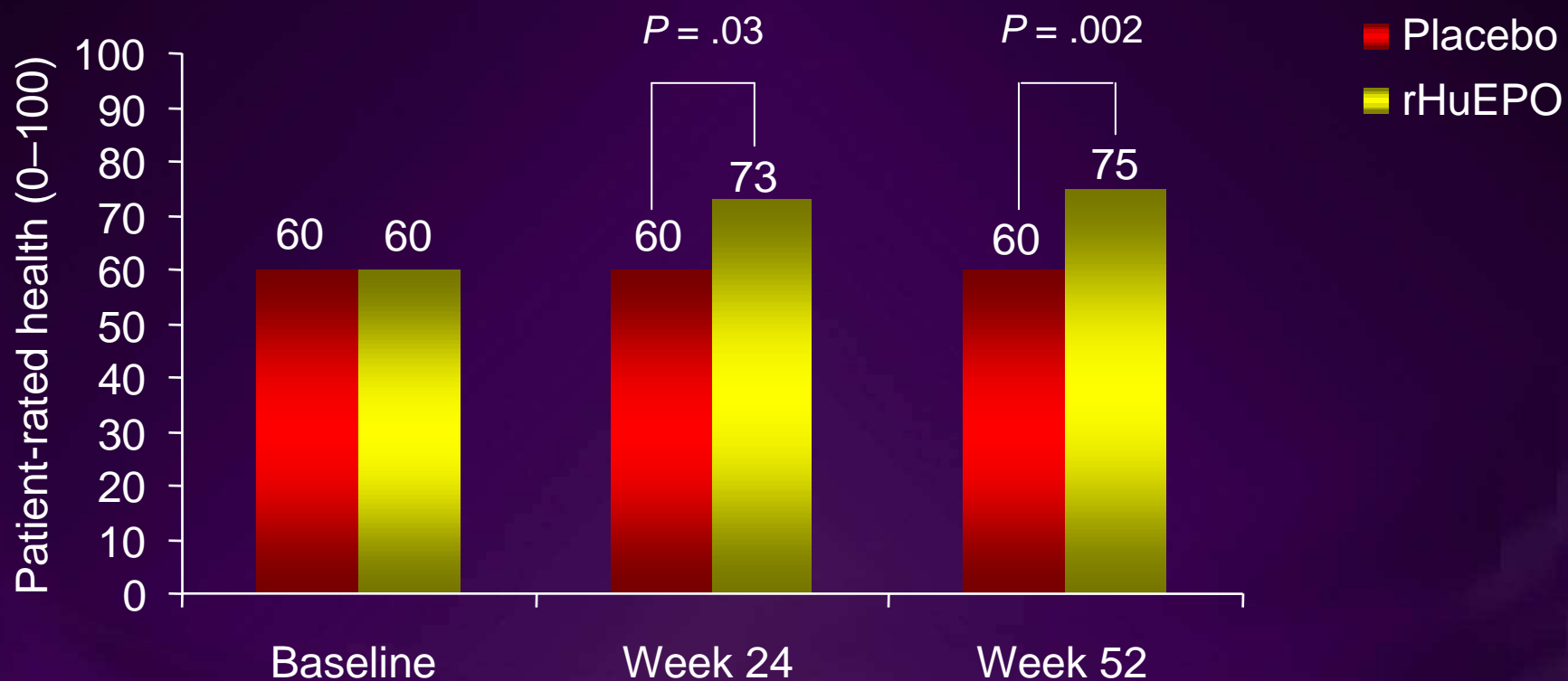


rHuEPO group from baseline $P<.001$



Peeters H, et al. *Ann Rheum Dis.* 1996;55:739-744.

rHuEPO Improved Quality of Life

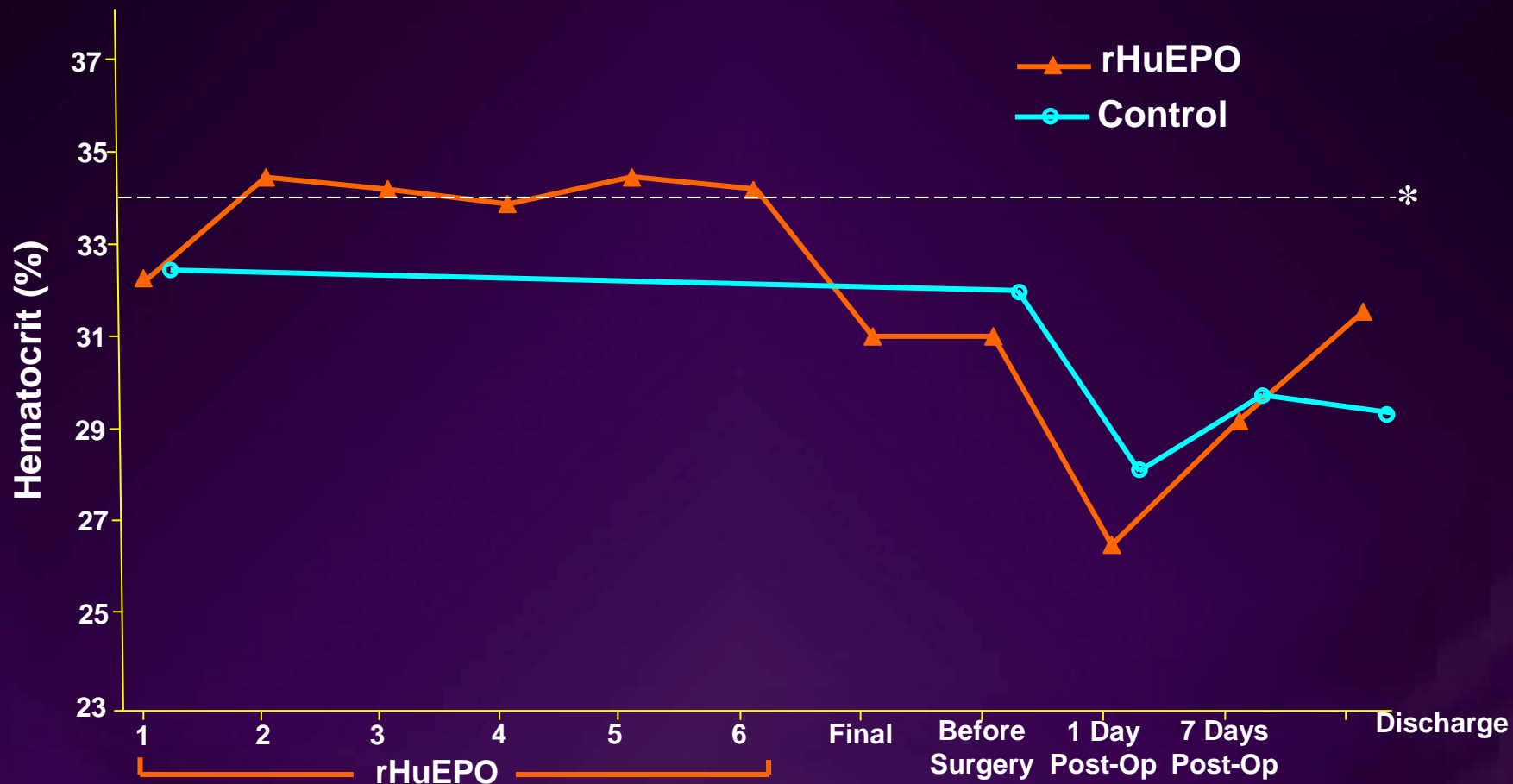


Peeters H, et al. *Rheumatol Int.*1999;18:201-206.



Studies of rHuEPO for Facilitation of PAD

rHuEPO Facilitated PAD in Surgical Patients With RA

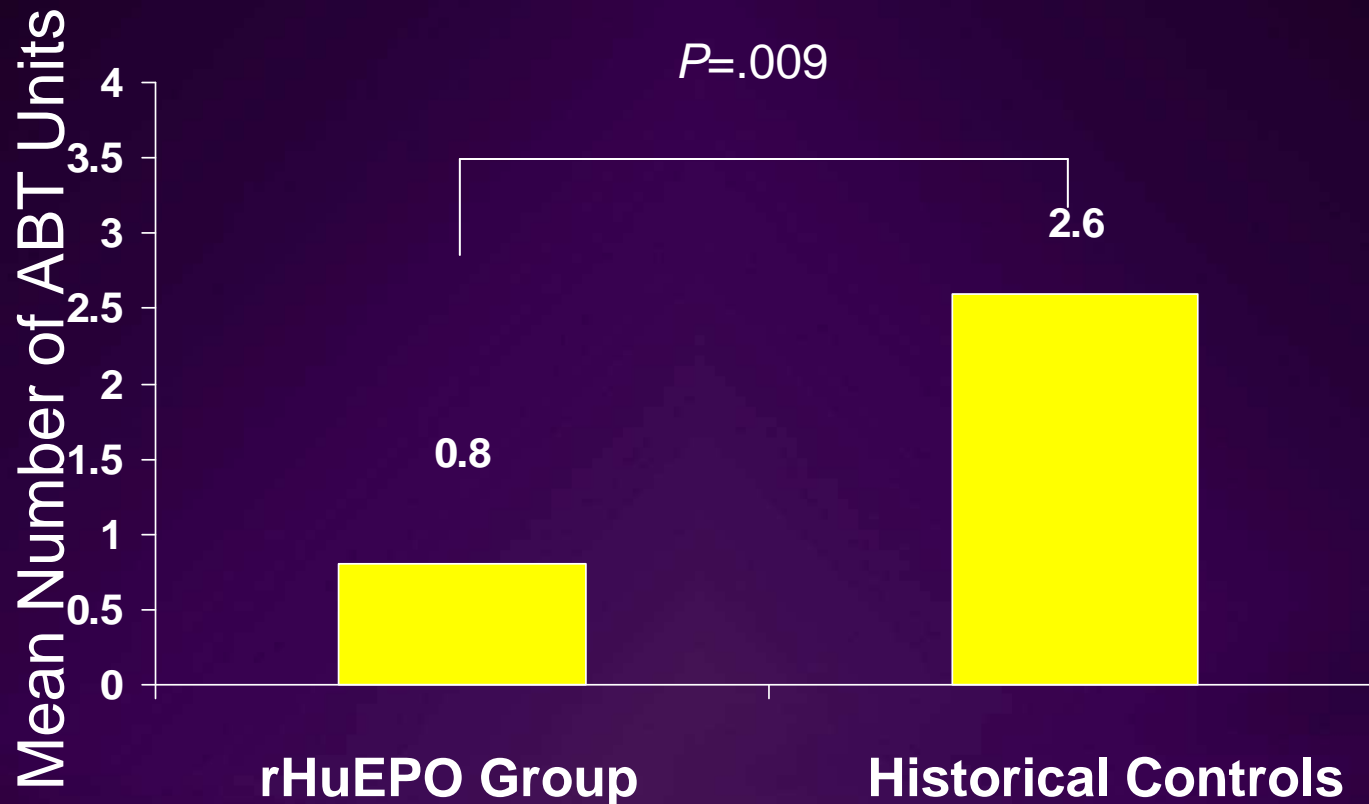


N=11

*Hematocrit of 34% = threshold for PAD.

Mercuriali F, et al. *Transfusion*. 1994;34:501-506.

rHuEPO Reduced Need for ABT in Surgical Patients With RA



Mercuriali F, et al. *Transfusion*. 1994;34:501-506.

Nonresponse to rHuEPO for PAD Can Be Predicted



Risk factors for nonresponse to rHuEPO for PAD:

- Severe anemia (Hb < 8 g/dL)¹
- Greater baseline levels of CRP, ESR^{1,2}
- Greater number of swollen joints, greater duration of morning stiffness, higher Ritchie articular index²
- Greater levels of TNF- α , IL-6²

1. Matsui H, et al. *Clin Exp Rheumatol*. 1999;17:69-74.

2. Tanaka N, et al. *Clin Rheumatol*. 1999;18:293-298.



Open-Label Study of rHuEPO + IV Iron for Treatment of Anemia

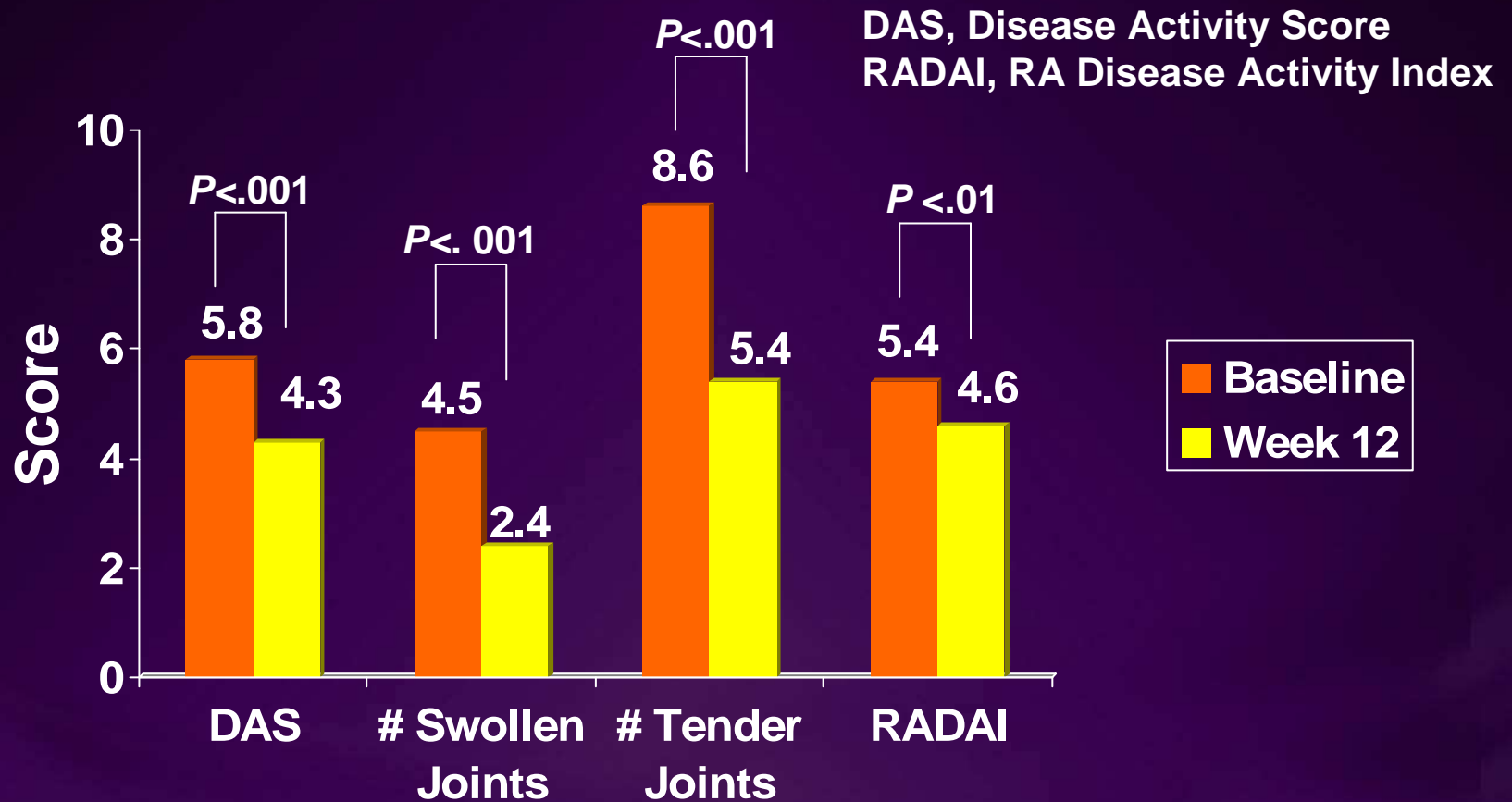
Nonresponse to rHuEPO Can Be Due to Functional Iron Deficiency



- In studies of rHuEPO for treatment of RA-associated anemia, nonresponse has ranged from 6% to 80%
- Kaltwasser et al. hypothesized that at least some cases of nonresponse are due to functional iron deficiency
- In a 12-week open-label study, the response rate was 100% in 28 patients, of whom 23 received IV iron when functional iron deficiency developed during rHuEPO therapy

Kaltwasser JP, et al. *J Rheumatol.* 2001;28:2430-2436.

rHuEPO + IV Iron Had Disease-Modifying Effects



Kaltwasser JP, et al. *J Rheumatol.* 2001;28:2430-2436.

Disease-Modifying Effect of rHuEPO May Be Iron-Independent



- As in some studies of rHuEPO + oral iron,¹⁻⁵ ESR was reduced in the 12-week trial of rHuEPO + IV iron ($P < .001$)⁶
- Yet serum ferritin increased throughout the 12-week trial,⁶ whereas it was reduced in previous studies^{4,5,7}
- Thus, the anti-inflammatory effect of rHuEPO may be due to an increased number of erythrocytes or an iron-independent effect on inflammation⁶

1. Gudbjörnsson B, et al. *Ann Rheum Dis*. 1992;51:747-752.

2. Pincus T, et al. *Am J Med*. 1990;89:161-168.

3. Murphy EA, et al. *BMJ*. 1994;309(6965):1337-1338.

4. Nordström D, et al. *Rheumatol Int*. 1997;17:67-73.

5. Peeters HR, *Ann Rheum Dis*. 1996;55:739-744.

6. Kaltwasser JP, et al. *J Rheumatol*. 2001;28:2430-2436.

7. Vreugdenhil G, et al. *Ann Hematol*. 1992;65:265-268.



rHuEPO Therapy Conclusions

Recommendations Regarding rHuEPO Therapy for RA



Before considering rHuEPO treatment:

- Thoroughly investigate and treat for types of anemia other than ACD¹
- Make every effort to control the inflammation itself¹⁻³

1. Nordström D, et al. *Rheumatol Int.* 1997;17:67-73.

2. Matsui H, et al. *Clin Exp Rheumatol.* 1999;17:69-74.

3. Pettersson T, et al. *Scand J Rheumatol.* 1993;22:188-193.

rHuEPO Is Suitable for Certain Subgroups of Anemic RA Patients



- Those who undergo PAD for elective surgical procedures¹⁻⁴
- Those with severe anemia unresponsive to IV iron^{1,2}
- Those starting second-line treatment who require faster correction of anemia than such drugs would achieve³
- Those with coexisting angina pectoris, heart failure, or respiratory failure⁴
- Those with SoJRA who would otherwise need corticosteroid treatment for severe anemia⁵

1. Pincus T, et al. *Am J Med.* 1990;89:161-168.

2. Cazzola M, et al. *Blood.* 1997;89:4248-4267.

3. Murphy EA, et al. *BMJ.* 1994;309(6965):1337-1338.

4. Nordström D, et al. *Rheumatol Int.* 1997;17:67-73.

5. Fantini F, et al. *Arthritis Rheum.* 1992;35:724-726.

Summary



- Anemia is the most common extra-articular complication of RA and may be associated with a more serious course of disease
- The two primary types of anemia in RA patients are ACD and IDA
- rHuEPO + iron corrects ACD in most patients with RA and may improve RA outcomes and quality of life
- rHuEPO facilitates PAD in anemic RA patients prior to elective surgery and reduces the need for transfusion

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