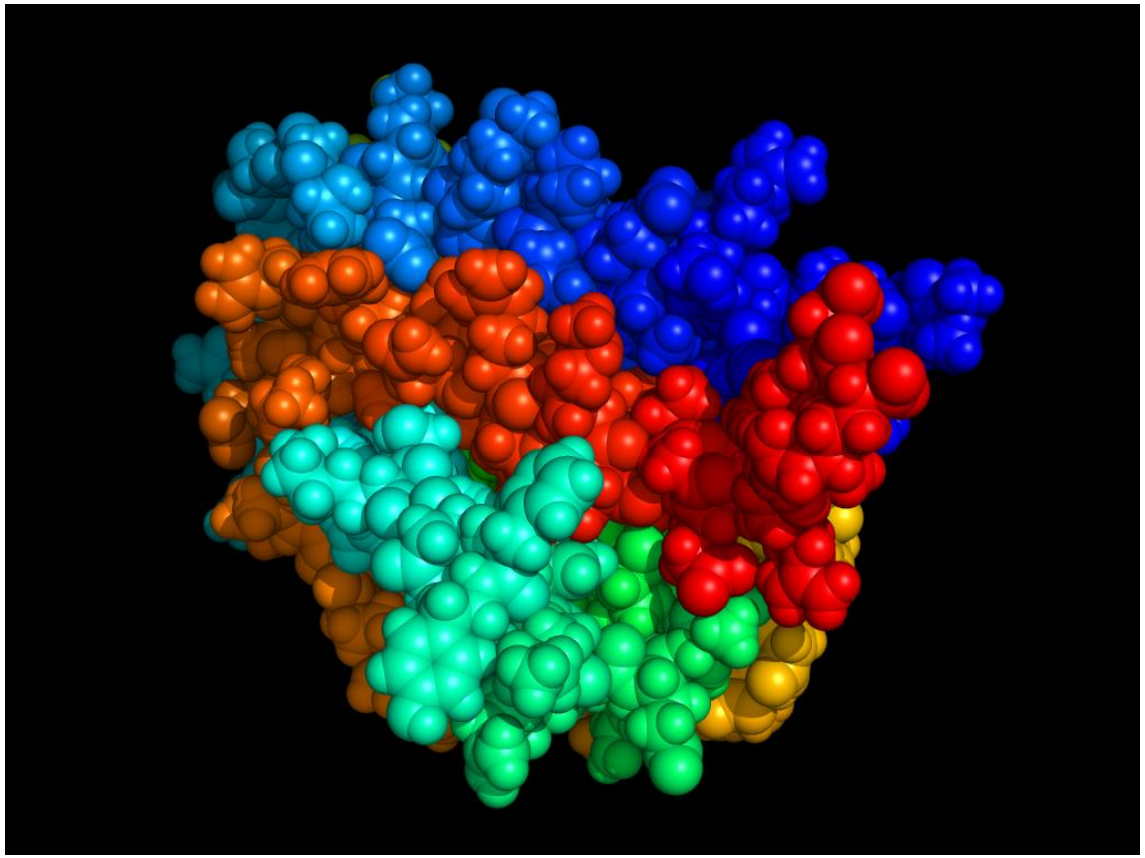
Vantaggi e limiti dell'uso delle eritropoietine

Barbara Scappini

Ai sensi dell'arti 3.3 sul conflitto di interessi, la sottoscritta dichiara di non aver intrattenuto negli ultimi 2 anni rapporti con soggetti portatori di interessi commerciali in campo sanitario



L'eritropoietina (EPO) rappresenta il più importante fattore di crescita della **eritropoiesi**

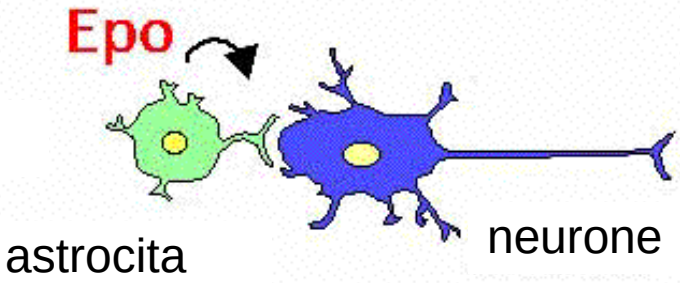
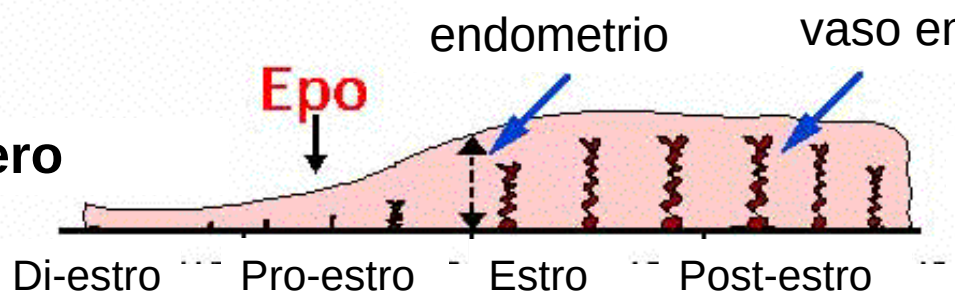
Eritropoietina umana

- L'eritropoietina è una proteina composta da 193 aminoacidi (ma i primi 27 sono scissi durante la secrezione)
- Viene prodotta principalmente dalle cellule interstiziali peritubulari del rene, sotto il controllo di un gene situato sul cromosoma 7
- Dopo la secrezione l'eritropoietina, a livello del tessuto emopoietico , si lega ad un recettore (EPO-R) localizzato sulla superficie dei progenitori eritroidi e viene internalizzata
- In presenza di anemia o ipossiemia la sintesi di EPO cresce rapidamente di più di 100 volte e conseguentemente aumenta la sopravvivenza, proliferazione e maturazione delle cellule progenitrici midollari anche attraverso l'inibizione dell'apoptosi

Storia dell'eritropoietina

- 1905 Carnot e Deflandre ipotizzarono che un fattore umorale, che chiamarono emopoietina, regolava la produzione dei globuli rossi
- 1936 Hjort dimostrò e confermò l'esistenza di questo fattore
- 1950 Reissmann dimostrò che l'espressione genica del fattore era regolata dalla pressione d'ossigeno
- 1977 Miyake riuscì a purificare l'eritropoietina umana
- 1985 Lin e Jacobs clonarono il gene dell'eritropoietina e svilupparono una linea cellulare transfettata (cellule CHO) capace di produrre eritropoietina ricombinante umana
- 1989 clonazione del recettore dell'EPO
- 2000 sintesi della darbepoetina
- 2004 CERA

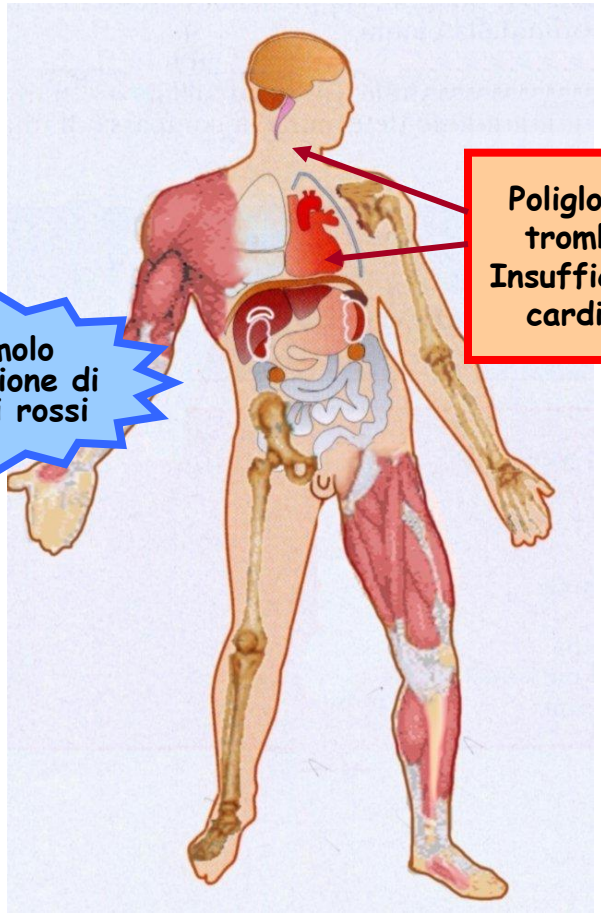
Funzioni fisiologiche dell'eritropoietina (Epo)

Organo		Funzione	Induzione da
Rene		**Eritropoiesi**	**Ipossia**
Cervello		**Sopravvivenza neuronale**	**Ipossia**
Utero		**Angiogenesi**	**Estradiolo (E2)**

Eritropoietina (EPO)

EFFETTI

- Stimolo della produzione dei globuli rossi
- Aumento della capacità di trasporto dell'ossigeno



EFFETTI INDESIDERATI

- Poliglobulia
- Aumento della viscosità del sangue
- Infarto del miocardio
- Trombosi
- Ictus
- Embolia polmonare
- Convulsioni

Erythropoesis stimulating agents

***Erythropoiesis-stimulating agent**, commonly abbreviated **ESA**, an agent similar to the cytokine (erythropoetin) that stimulates red blood cell production (erythropoeisis).*

ESAs, structurally and biologically, are similar to naturally occurring protein erythropoietin.

rHuEPOs

TYPE OF SYNTETIC ERYTHROPOIETIN	MOLECULARE STRUCTURE	HALF - LIFE
EPOETIN α	▪ aa sequence identical to endogenous Epo. ▪ Different composition and arrangements of the sugar moieties.	**7 – 8 h**
EPOETIN β	▪ Higher MW than Epoetin α ▪ Lower number of sialylated glycan residues	**4 – 12 h**
DARBEPOETIN α	▪ 2 N- lynked glycosylation sites, above and beyond the 3 normally present in endogenous Epo	**24 h**
EPOETIN δ	▪ Human- type glycosylation profile (engineered in human fibrosarcoma cell line HT - 1080)	**9 – 13 h**
C.E.R.A. (Continuous Erythropoietin Receptor Activator)	▪ Integration of amide bonds between amino group ▪ Integration of MPGBA	**135 h**

Bunn H.F., Blood, 2007; Deicher R. et al., Drugs, 2004; Osterborg, bjh, 2007; Llop E. et al., Analytical Biochemistry, 2008

EPO biosimilari (EPOETIN alpha, zeta, teta)

- **Per medicinale biosimilare si intende un medicinale sviluppato in modo da risultare simile a un medicinale biologico che è già stato autorizzato (il così detto "medicinale di riferimento")**
- **Il principio attivo di un biosimilare e quello del suo medicinale di riferimento sono di fatto la stessa sostanza biologica, tuttavia possano essere presenti differenze minori dovute alla loro natura complessa e alle tecniche di produzione.**
- **Come il medicinale di riferimento, il biosimilare presenta un certo grado di variabilità naturale. Un biosimilare viene approvato quando è stato dimostrato che tale variabilità naturale ed eventuali differenze rispetto al medicinale di riferimento non influiscono sulla sicurezza o sull'efficacia."**
- **Un biosimilare e il suo prodotto di riferimento, essendo ottenuti mediante modalità differenti, non sono identici, ma essenzialmente simili in termini di qualità, sicurezza ed efficacia.**

CONDIZIONI CLINICHE ASSOCIATE A LIVELLI INADEGUATI DI EPO

- Anemia della IRC
- Malattia neoplastica (indipendentemente dal trattamento)
- In corso di chemioterapia (cisplatino, …..)
- Trapianto allogenico di midollo osseo
- Sindromi mielodisplastiche
- Malattie infiammatorie e autoimmuni croniche
- Anemia del prematuro
- Anemia in corso di AIDS
- Nei gravi stati di malnutrizione

Indicazioni ESA

trattamento dell'anemia (Hb < 11 g/dL) associata ad insufficienza renale cronica in bambini e in adulti sia in trattamento dialitico sia in trattamento conservativo.
quando Hb > 12 g/dL il trattamento deve essere interrotto

trattamento dell'anemia (Hb < 10 g/dL ma non < 8 g/dL) nei pazienti oncologici che ricevono chemioterapia antiblastica.
in caso di Hb < 8 g/dL è è indicata l'emotrasfusione

trattamento dell'anemia (Hb < 10 g/dL o riduzione dell'emoglobina = 2 g/dL durante un qualsiasi periodo di 4 settimane di trattamento) nei pazienti trapiantati di fegato o con diagnosi clinica o istologica di cirrosi, che ricevono ribavirina in combinazione con interferone standard o peghilato e che presentano risposta virologica alla terapia

in pazienti HIV pluritrattati con anemia (Hb < 8,5 g/dL) nei quali l'uso di farmaci anemizzanti è l'unica alternativa terapeutica.

Trattamento per incrementare la quantità di sangue autologo nell'ambito di programmi di predonazione

PRINCIPALI CAUSE DELLA ANEMIA NELLA IRC

Tossine uremiche (riducono la resistenza globulare)
Ridotta emivita degli eritrociti (70-80 gg vs.120)
Possibile carenza di:
-ferro
-Vitamina B12
-Acido folico
Piastrinopatia (facilita emorragie)
Carenza RELATIVA di eritropoietina

Cardiovascular Risk Factors in CKD

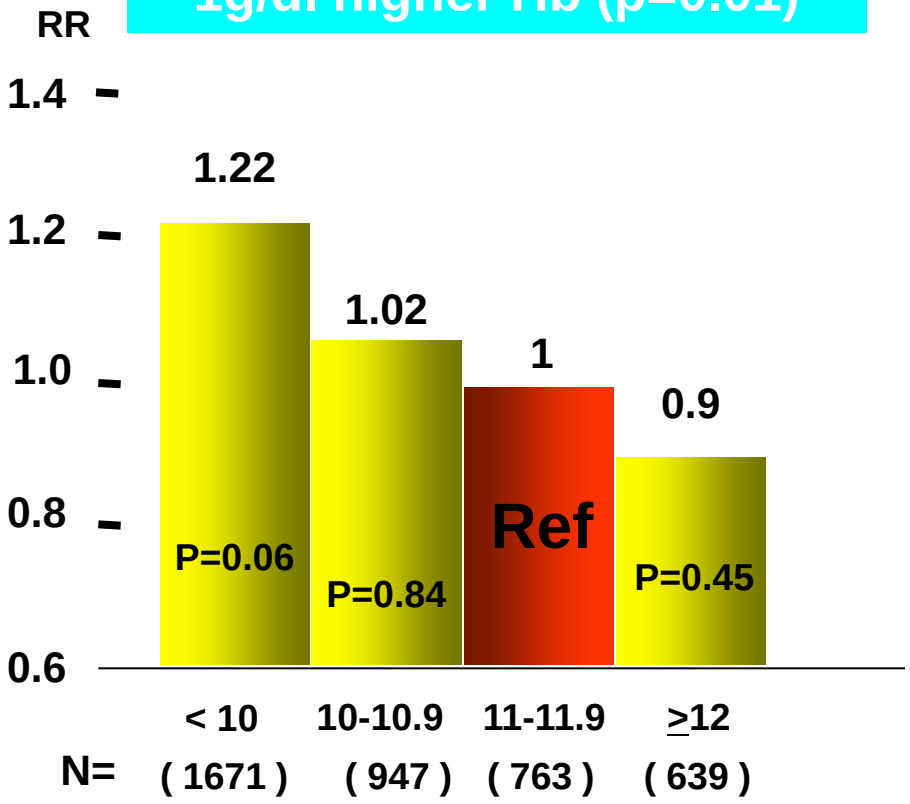
Traditional Risk Factors	Nontraditional Risk Factors
Older age	Albuminuria/proteinuria
Male sex	Homocysteine
Hypertension	Lipoprotein(a) and apolipoprotein(a) isoforms
Higher LDL cholesterol	Lipoprotein remnants
Low HDL cholesterol	**Anemia**
Diabetes	Abnormal calcium-phosphate metabolism
Smoking	Extracellular fluid overload
Physical inactivity	Oxidative stress
Menopause	Inflammation
Family history of CVD	Malnutrition
Left ventricular hypertrophy	Altered nitric oxide/endothelin balance

Sarnak M et al. Circulation 2003; 108: 2154-2169

Mortality and hospitalisation risks and anemia

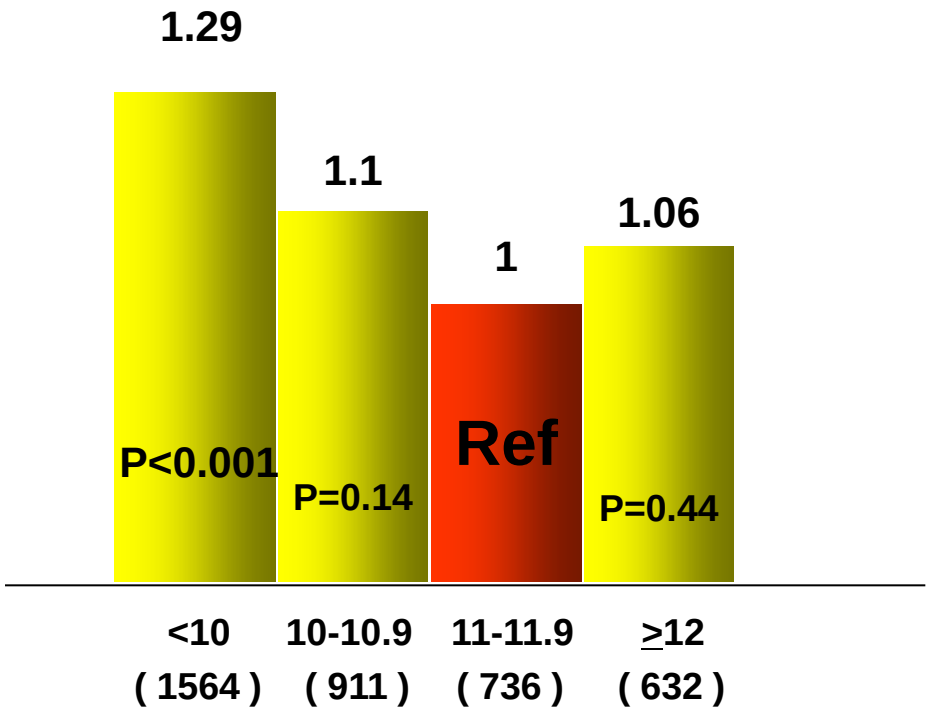
Relative Risk of Death

RR overall=0.94 per 1g/dl higher Hb (p=0.01)



Relative Risk of Hospitalisation

RR overall=0.95 per 1g/dl higher Hb (p<0.01)



Haemoglobin (g/dl) at study entry

CREATE: open-label, randomised, multicentre trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2006 VOL. 355 NO. 20

Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia

Tilman B. Drüeke, M.D., Francesco Locatelli, M.D., Naomi Clyne, M.D., Kai-Uwe Eckardt, M.D., Iain C. Macdougall, M.D., Dimitrios Tsakiris, M.D., Hans-Ulrich Burger, Ph.D., and Armin Scherhag, M.D., for the CREATE Investigators*

N Engl J Med 2006; 355:2071-84

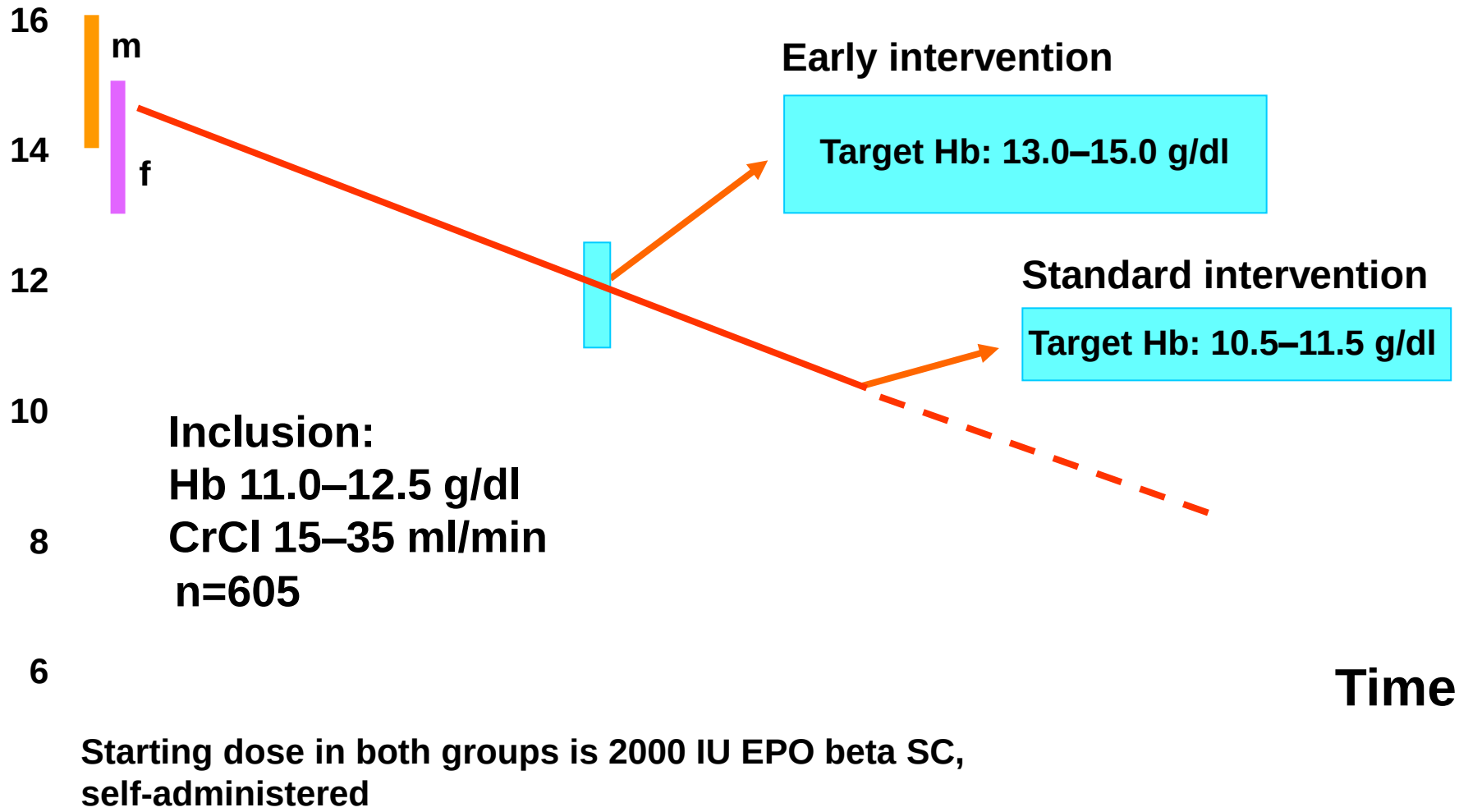
The CREATE Study

Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta

- 603 patients, 3 year follow up
- Patient characteristics
  - Mean GFR 25 ml/min (range 15 to 35) calculated by the Cockcroft-Gault and MDRD equations
  - Baseline Hgb had to be 11 to 12.5 g/dl
- Groups were targeted for Hgb 13.5 g/dl vs. Hgb 11.5 g/dl
- Echocardiography was performed at baseline and then annually or at initiation of hemodialysis

NEJM 355: 2071-2084, 2006

CREATE: open-label, randomised, multicentre trial



Starting dose in both groups is 2000 IU EPO beta SC, self-administered

END POINT PRIMARIO

- Tempo di comparsa evento cardiovascolare
- Morte improvvisa
- Infarto del miocardio
- Scompenso cardiaco acuto
- TIA
- Ictus
- Complicanza di arteriopatia periferica
- Angor precordiale
- Aritmia cardiaca

END POINT SECONDARIO

- Morte per ogni causa

CREATE study: results

Cardiovascular Events

- A total of 105 patients had cardiovascular events
- No significant difference (hazard ratio 0.78; 95% CI; P=0.20)
- Censoring data by start of dialytic therapy did not change the hazard ratio

- Group 1 (High Hgb)
  - 58 events
  - 10% deaths
  - 4% deaths from cardiac cause
  - 7% cardiovascular intervention
  - 61% hospital admission
  - 33 days duration of hospital stay

- Group 2 (Low Hgb)
  - 47 events
  - 21 deaths (7%)
  - 3% deaths from cardiac cause
  - 6% cardiovascular intervention
  - 59% hospital admission
  - 28.3 days duration of hospital stay

CREATE study: results
Control of Blood Pressure

- Control of blood pressure
  - Mean blood pressures did not differ between groups
  - Incidence of hypertension was higher in the high Hgb group (P=0.005)
  - Higher use of beta blockers in group 1 (high Hgb)
  - In all groups the number of antihypertensive drugs increased over the time of the study

Conclusioni Studio CREATE

Sebbene il grado dell'anemia sia un forte fattore predittivo di cattiva prognosi, la sua completa correzione non determina un miglioramento degli eventi sfavorevoli.

Lo Studio raccomanda quindi la opportunità di perseguire una correzione parziale dell'anemia nell'uremico cronico.

CHOIR: open-label, randomised, multicentre trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

Ajay K. Singh, M.B., B.S., Lynda Szczech, M.D., Kezhen L. Tang, Ph.D., Huiman Barnhart, Ph.D., Shelly Sapp, M.S., Marsha Wolfson, M.D., and Donal Reddan, M.B., B.S., for the CHOIR Investigators*

Singh AK et al. N Engl J Med 2006; 355:2085- 98

The CHOIR Study
Correction of Hemoglobin and Outcomes in Renal Insufficiency

- Hypothesis – stable high Hgb level will decrease the risk of cardiovascular outcomes when compared to a lower Hgb level
- Open label, randomized trial
- 130 centers in the United States
- 1432 patients with CKD
  - 715 randomized to target Hgb of 13.5 g/dl
  - 717 randomized to target Hgb of 11.3 g/dl
- Eligibility
  - Age>18 years old
  - eGFR of 15 to 50 ml/min

NEJM 355: 2085-2098, 2006

CHOIR Study Design

- Open label, Epoetin alfa
- Patients
  - no Epoetin alfa in past 3 months
  - not on dialysis
  - hemoglobin < 11 g/dL
- 1:1 randomization to hemoglobin 11.3 or 13.5 g/dL
- Primary endpoint: composite of mortality, CHF hospitalization, non-fatal stroke, non-fatal MI

CHOIR Study Results

- **Randomization:**

  715 to hemoglobin of 13.5 g/dL

  717 to hemoglobin of 11.3 g/dL

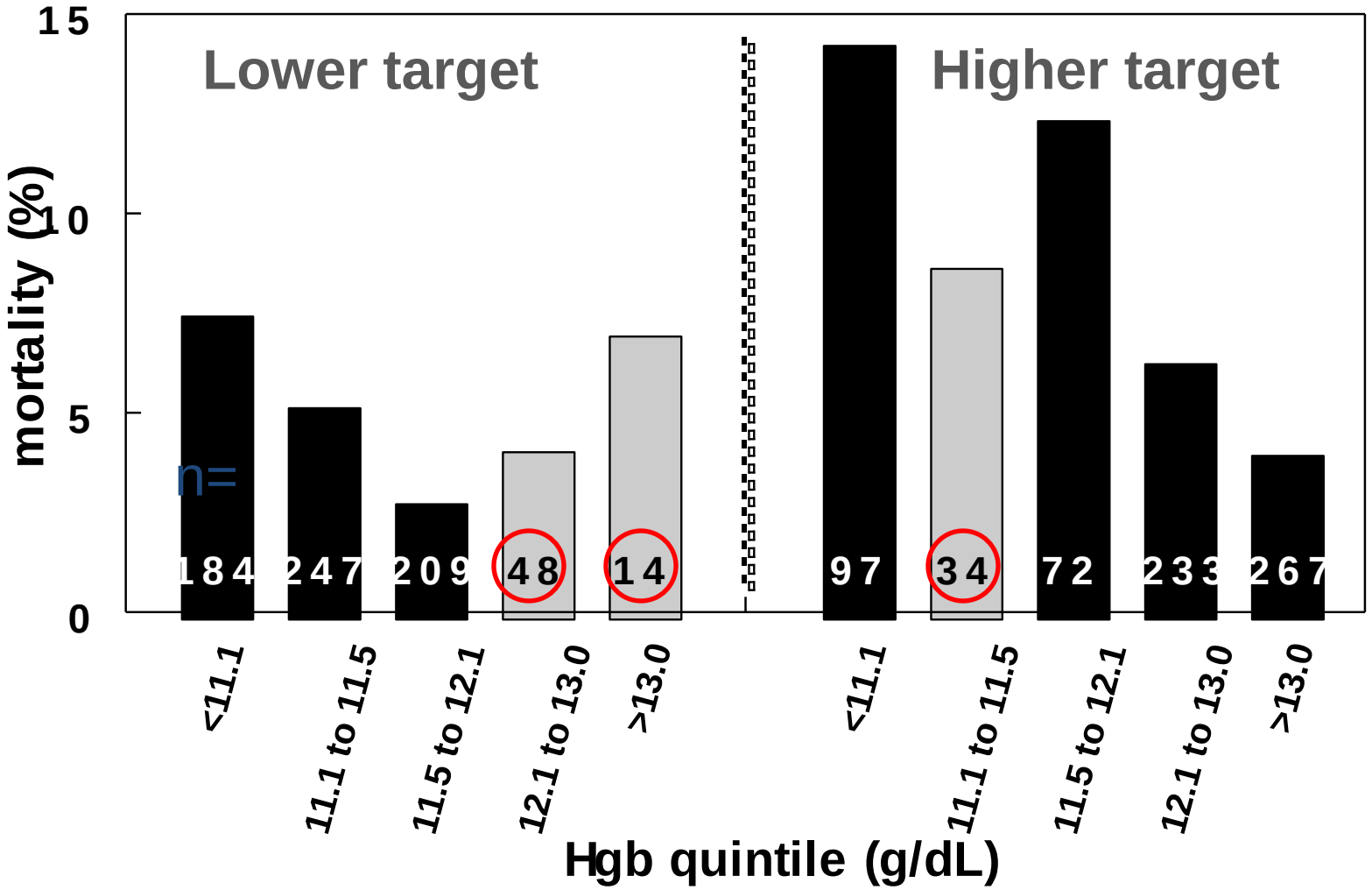
- **Terminated early**

"The DSMB recommended that the study be terminated in May 2005 at the time of the second interim analysis…because the conditional power for demonstrating a benefit for the high-hemoglobin group was less than 5% for all plausible values of the true effect for the remaining data." NEJM, 2006

DSMB = Data and Safety Monitoring Board

CHOIR Study Results

- **Negative Association Between Mean Hemoglobin (throughout study) and Mortality:**



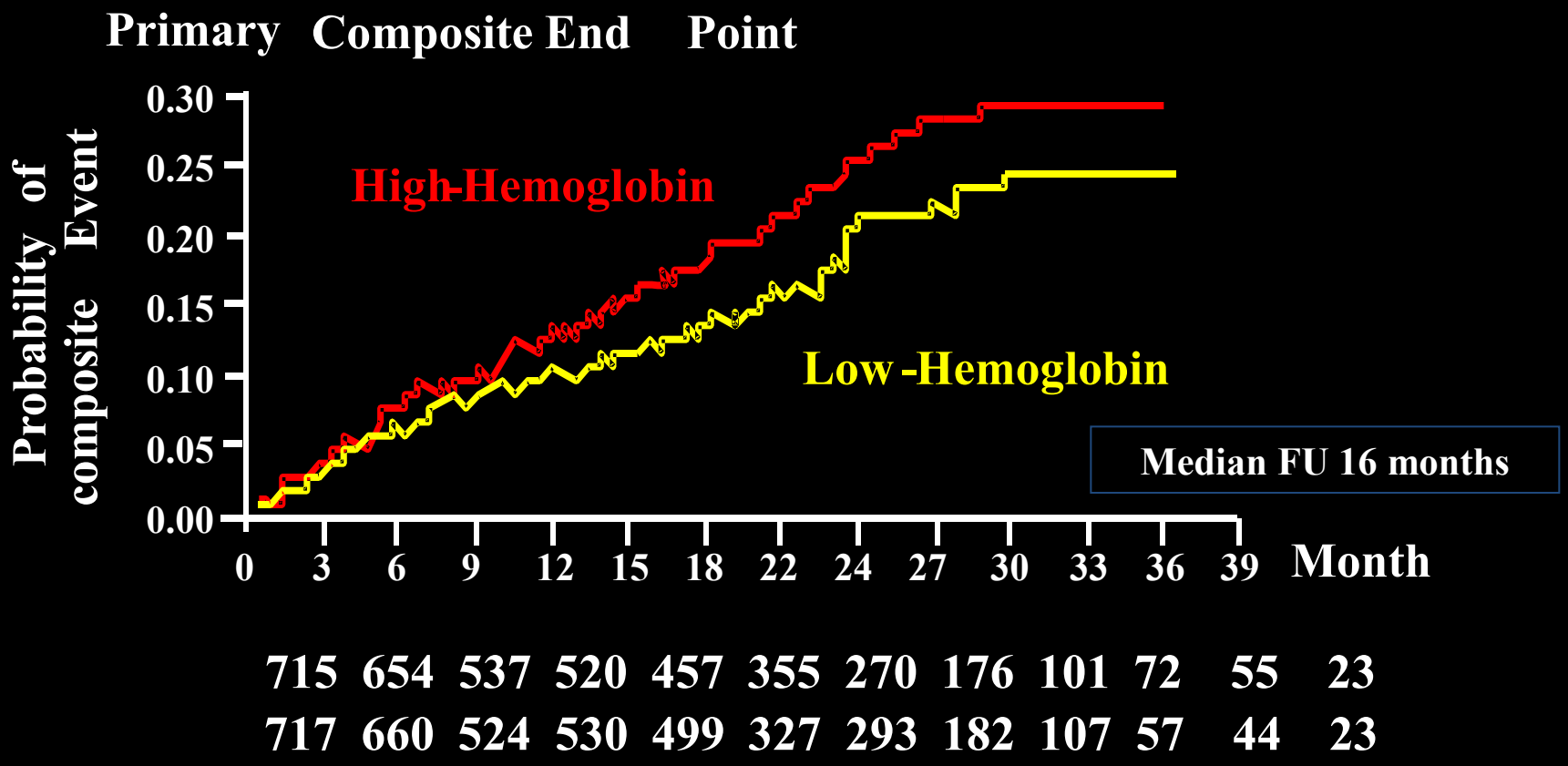
FDA exploratory analysis

CHOIRStudy : an open label randomised study

The primary end -point: the time to the composite of death, myocardial infarction hospitalisation for congestive heart failure or stroke

N: 1432 CKD pts
Group1 target: Hb 13.5 g/dl
Group 2 target: Hb 11.3 g/dl

125vs97 events HR 1.34;
95% confidence interval: 1.03 to 1.74
P=0.03



Singh AK et al. N Engl J Med 2006; 355:2085-98

CONCLUSIONI STUDIO CHOIR

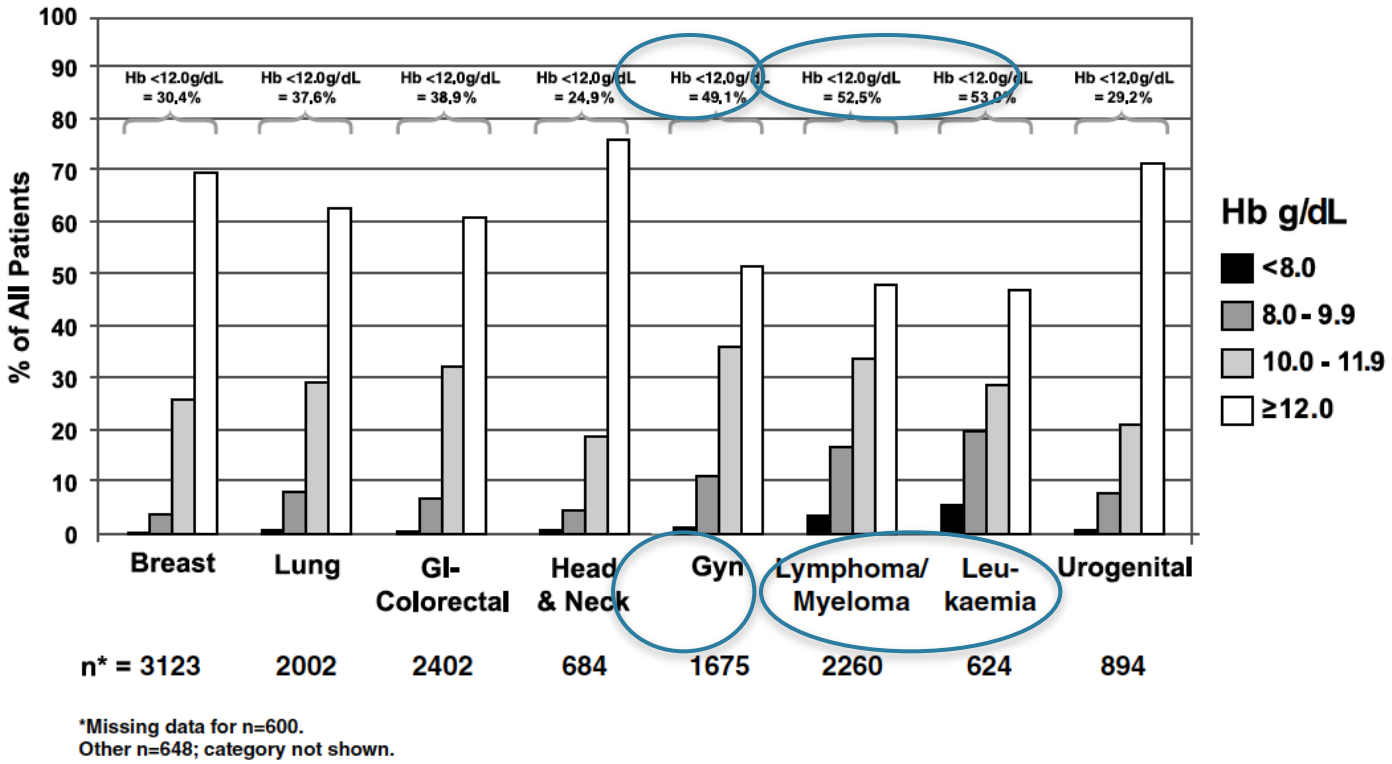
- ✓ L'uso del target di Hb a valori di 13,5 g/dl, confrontato a valori di 11,3 g/dl, è associato ad un aumentato rischio di eventi cardiovascolari (morte, infarto del miocardio, ospedalizzazione e scompenso cardiaco)
- ✓ Non si è assistito ad un miglioramento della qualità di vita

Anemia in cancer patients: the ECAS study

european cancer anaemia survey
ECAS

Prospective study
15.367 pts
748 cancer centres, 24 countries

Hgb <12.0 g/dl=49.1%



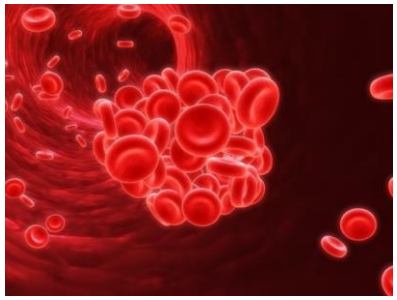
*Missing data for n=600.
Other n=648; category not shown.

Ludwig et al. Eur.J.Cancer 2004

Causes and Effects of Cancer – related Anemia

Causes

- **Disease – related factors[1]**
- **Folate, Vit B12, Iron deficiency[1]**
- **Anemia of chronic disease[1]**
- **Chemotherapy[1]**



Effects

- **Decrease in QOL[2,3,4]**
- **Increase in transfusion rates[5]**
- **Probable decrease in survival[6,7,8]**

1- Grotto, Med Oncol, 2008; 2- Gabrilove, JCO 2001; 3- Littlewood, JCO 2001; 4- Cella D. Ann Oncol, 2003; 5-Benoist S., Surgery, 2001; 6- Caro, Cancer 2001; 7- Waters, JCO 2002; 8- Fuso L. Gynecol Oncol 2005

Benefits and Risks of RBC Transfusions

Quick enhancement of HB level:
1 U of RBC (circa 300 cc) → 1/g/dL icrease in 1 hour

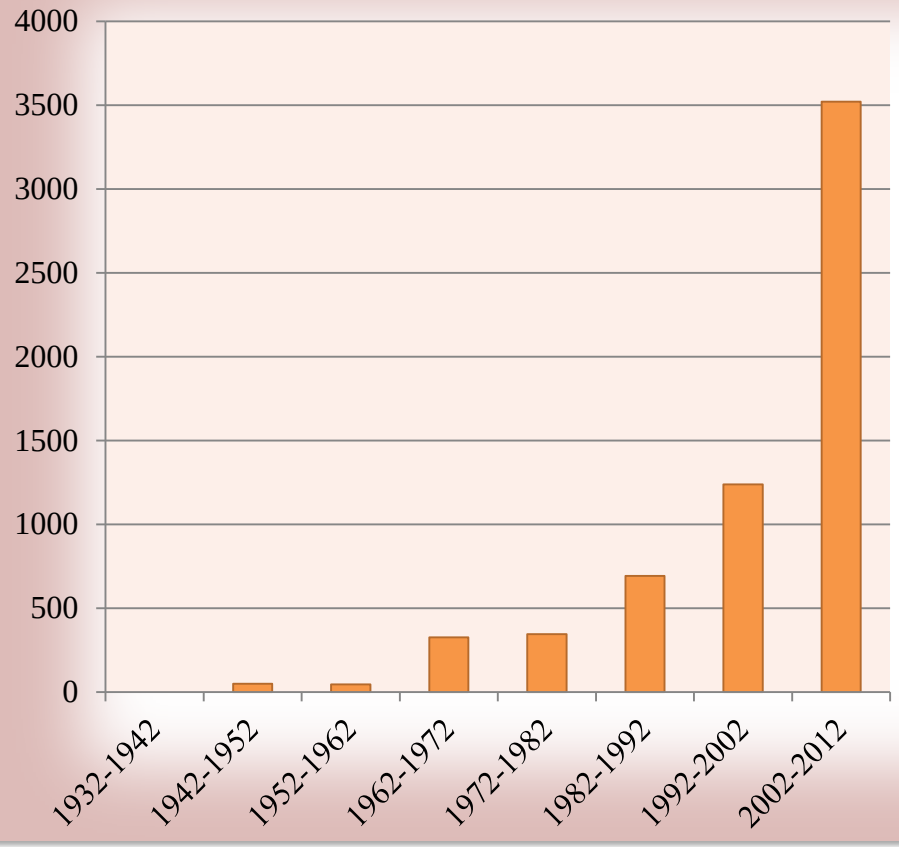
- **Graft-versus-host disease**
- **Transfusion Related Acute Lung Injury (TRALI)**
- **Non emolitic fever related Reactions**
- **Acute Emolisis**
- **Allergy**
- **Anafilaxis**

- **More peri-operative infections**
- **Infectious (HIV, HBV, HCV, HTLV West Nile, Bacteria)**
- **More relapses**
- **Worst prognosis**

Upile, T, et al. Clinical Advances in Hematology & Oncology, 2009

Use of ESAs in cancer patients

N° of publications about the use of ESAs in cancer patients



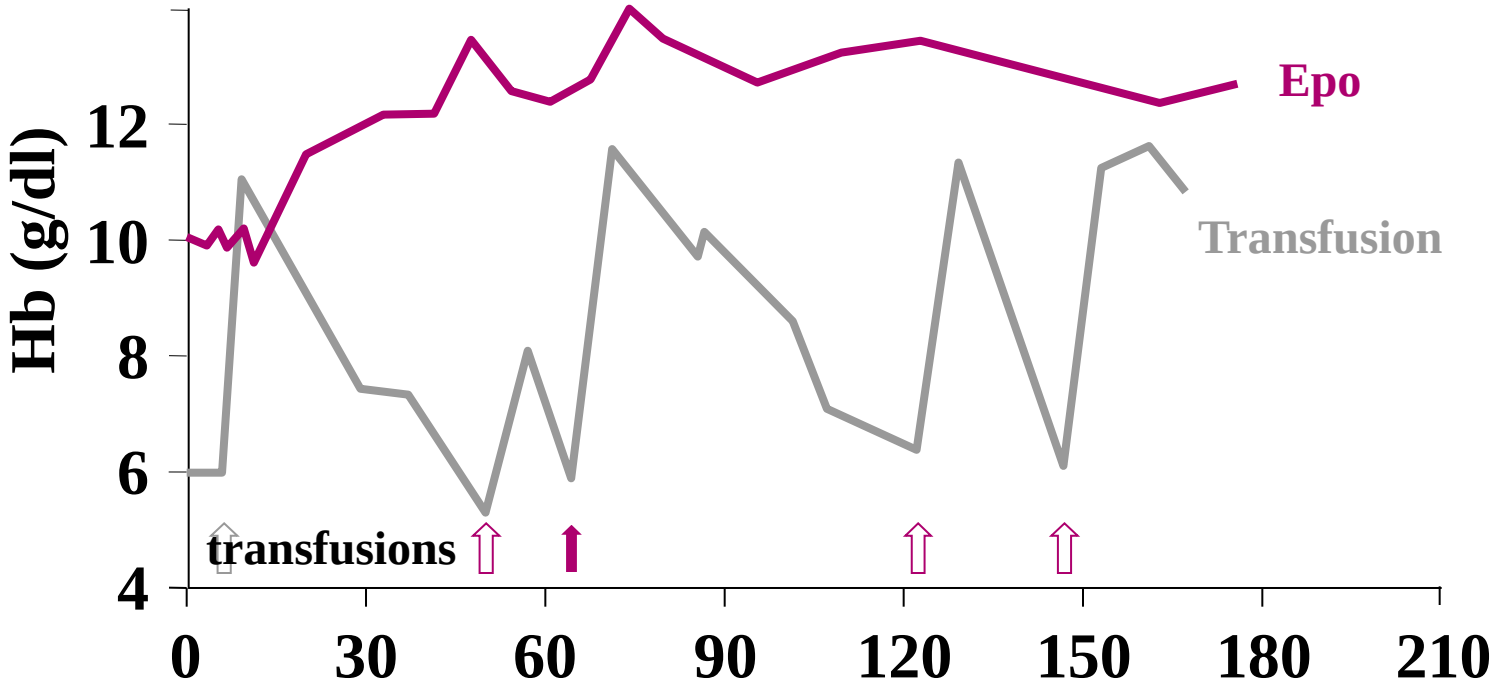
BLOOD TRASFUSION RATE:

ESAs significantly reduced the RR of RBC transfusions (RR 0.64; 95% CI 0.60 to 0.68, 42 trials, n = 6,510).

Bohlius J et al. Cochrane Database Syst Rev, 2006

Pubmed

Use of ESAs in cancer patients



Österborg. Med Oncol 1998; 15 (Suppl 1): S47–9
Ludwig et al. N Engl J Med 1990; 322: 1693–9

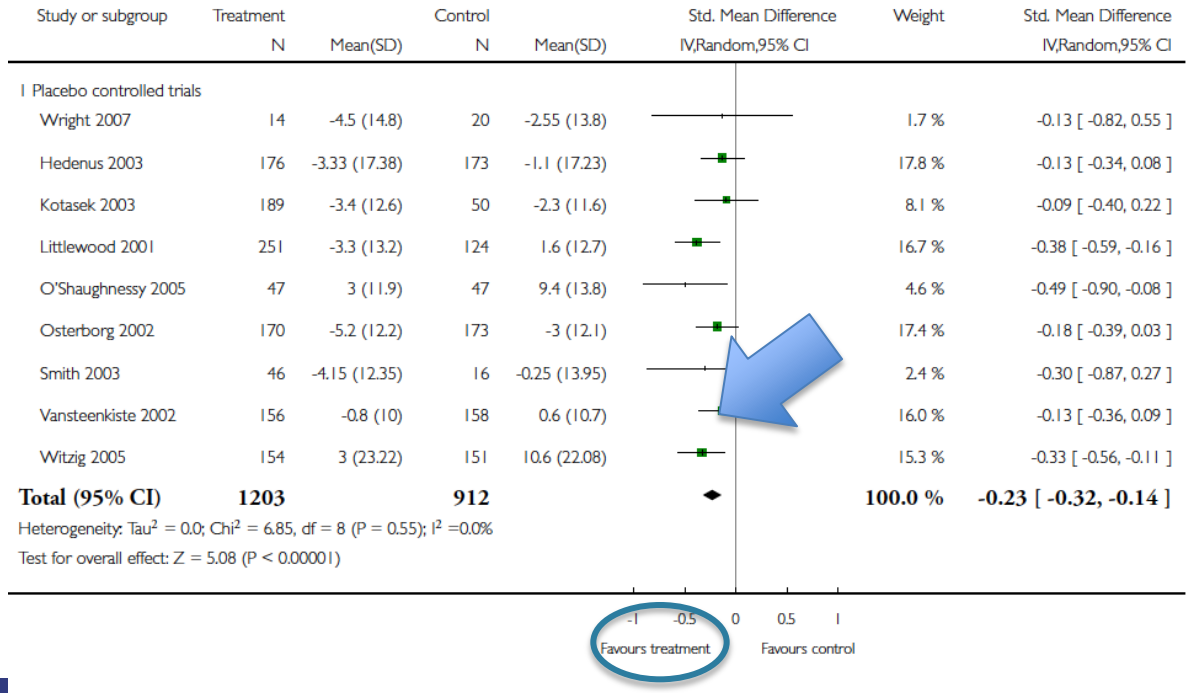
Drug therapy for the management of cancer related fatigue (Review)

Minton O, Stone P, Richardson A, Sharpe M, Hotopf M

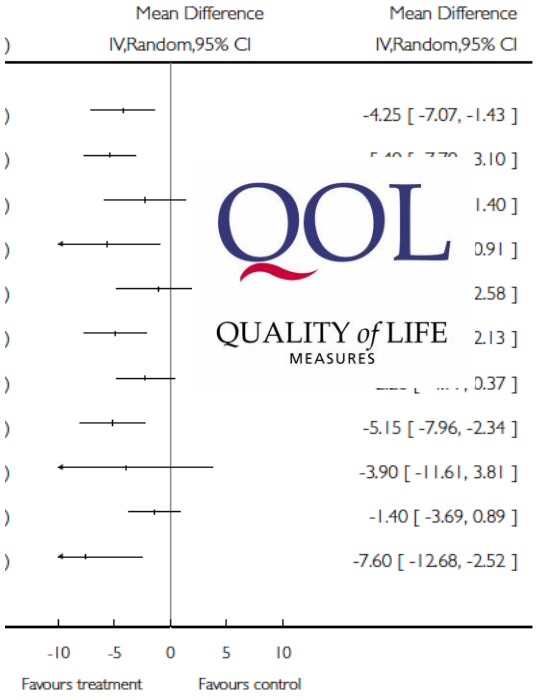
THE COCHRANE COLLABORATION®

ESAs: improvement in CRF.

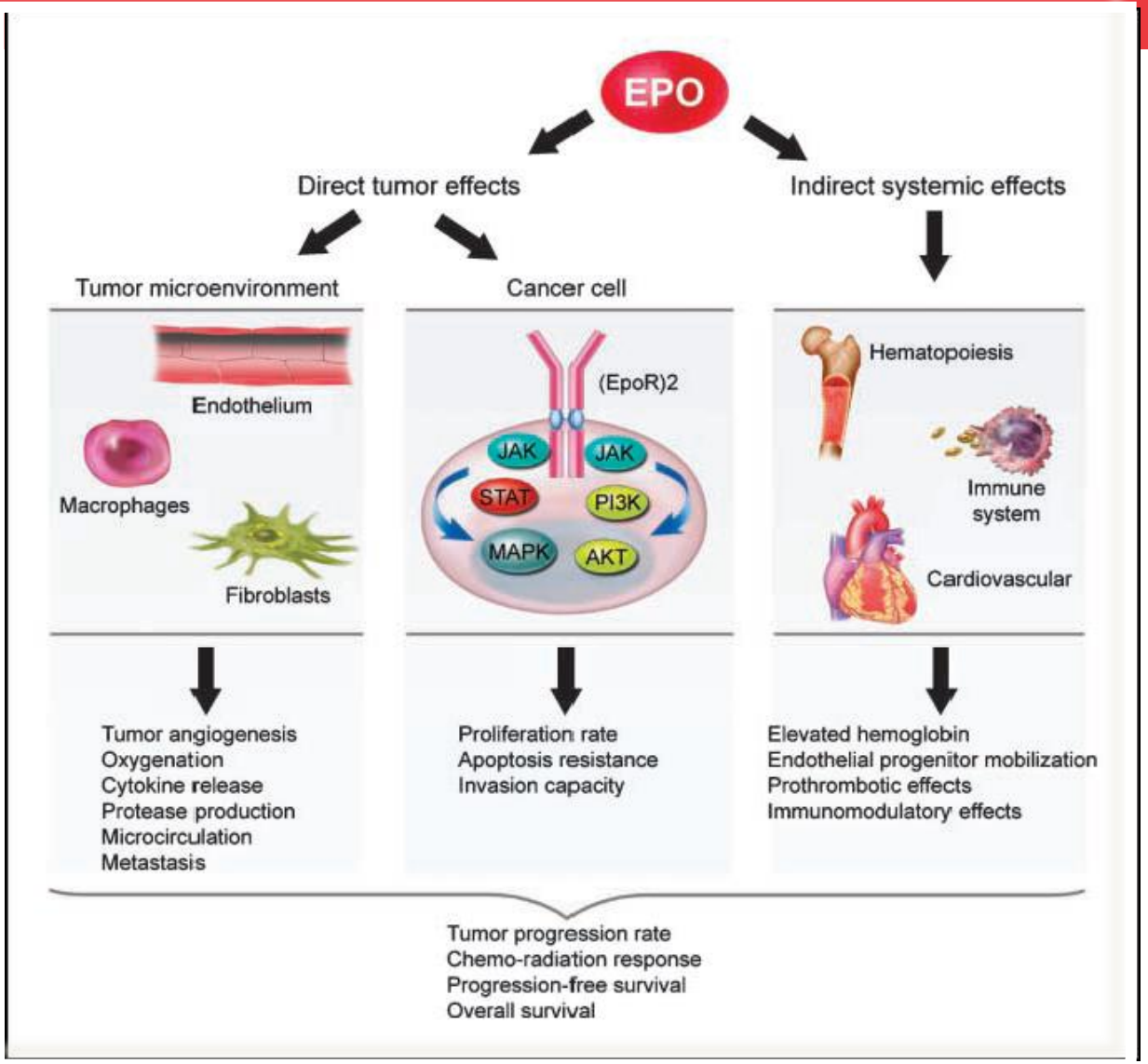
Haemopoetic growth factors versus no intervention.



Studies with FACT F.



"Is it all over for erythropoietin?"

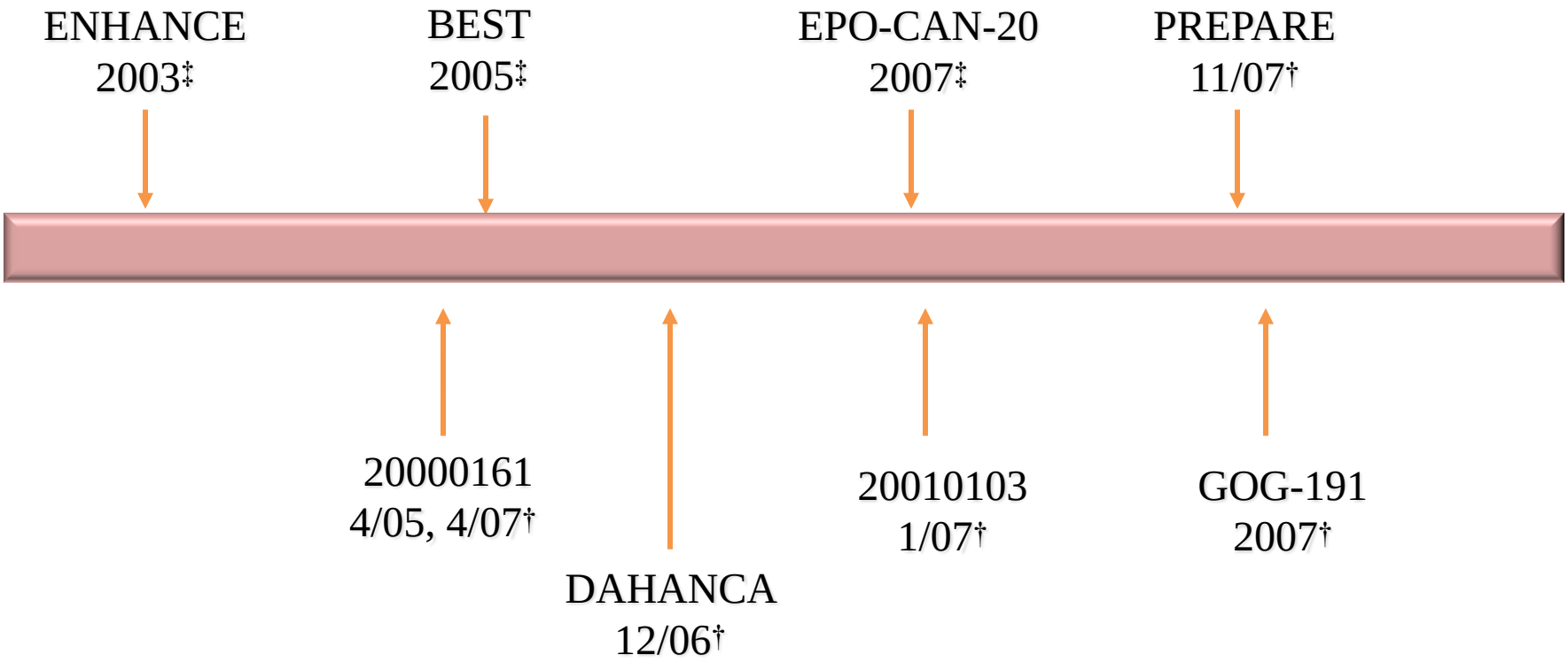


- **The role of *erythropoietin receptors* on the tumour cell surface**
- **Risk of *Thromboembolic events***

Burton A., Lancet Oncology, 2007; Murat O. Arcasoy, Clin Cancer Res, 2008

ESAs and prognosis

Survival, Tumor Progression, TVE*



**8 trials selected by FDA for label inclusion out of 57 total, ‡ publication date, † = date data reported to FDA*

HR for mortality significantly higher for patients with cancer who were treated with **ESA vs the control (placebo)** group (HR, 1.10; 95% CI, 1.01-1.20;***P*=.03**)

Bennett CL et al, JAMA, 2008

Erythropoietin or Darbepoetin for patients with cancer - meta-analysis based on individual patient data (Review)

Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, Zwahlen M, Clarke MJ, Weingart O, Kluge S, Piper M, Napoli M, Rades D, Steensma D, Djulbegovic B, Fey MF, Ray-Coquard I, Moebus V, Thomas G, Untch M, Schumacher M, Egger M, Engert A

- ***ESA treatment in cancer patients increased on study mortality and worsened overall survival.***
- ***For patients undergoing chemotherapy the increase was less pronounced, but an adverse effect could not be excluded.***

53 trials

cHR for on study mortality for OS:

1.17 (95% CI 1.06-1.30)

1.10 (95% CI 0.98-1.24) and 1.04; 95% CI 0.97-1.11) in pts receiving CT.

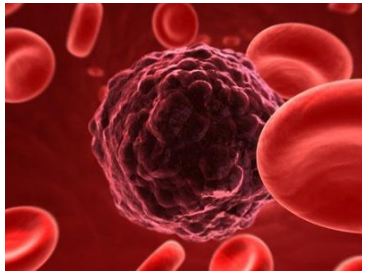
THE COCHRANE COLLABORATION®

Bohlius J et al., Cochrane Database Syst Rev, 2010

Erythropoietin or darbepoetin for patients with cancer (Review)

91 trials
20102 patients

Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, Hyde C, Engert A, Bohlius J



- ESAs increase **mortality** HR1.17 (CI 1.06 to 1.29)
- ESAs decrease **overall survival** HR 1.05 (CI 1.00 to 1.11)
- ESAs Increase Risk ratio for **thromboembolic complications** RR 1.52(CI 1.34 to 1.74)
-
- ESAs may also increase risk for **hypertension** RR 1.30 (CI 1.08 to 1.56) and **thrombocytopenia/haemorrhage** RR 1.21 (CI 1.04 to 1.42)
- Insufficient evidence to support an effect of ESA **on tumour response**

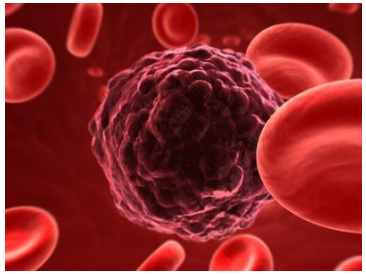
Erythropoietin or darbepoetin for patients with cancer (Review)

91 trials
20102 patients

Tonia T, M… O, Hyde C, Engert A,

BIAS

- **Tumors etherogeneity**
- **Hb <8 g/dl ~ 6%**
  Hb 8-9.9 g/dL ~ 30%
  Hb 10-11.9 g/dL ~ 40%
  Hb 12-14g/dL ~ 22%
  Hb > 14 g/dl ~ 6%
- **65% studies only CT (10 % no RT no CT)**
- **Doses and times of administration outlabel**



- ESAs incr…
- ESAs decre… 1)
- ESAs Increa… **ns** RR 1.52(CI 1.34 to 1.74)
- ESAs may also… 1.08 to 1.56) and **thrombocytope…**
- Insufficient evide… **on tumour response**

Guideline Recommendations for Anaemia Management in Patients with Cancer

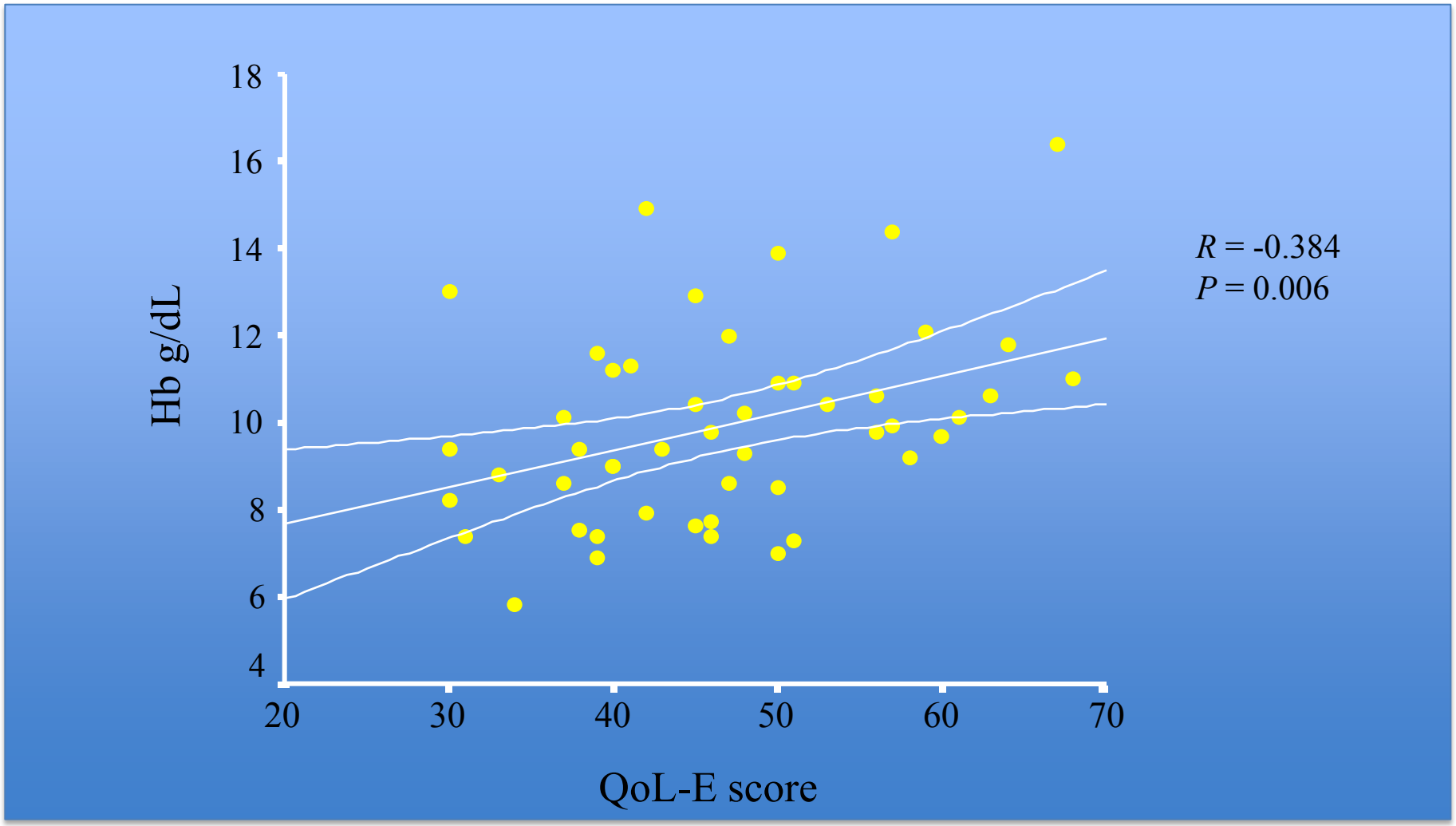
ASCO/ASH

- Initiate epoetin in patients with Hb ≤10 g/dl (or Hb >10 to <12 g/dl depending on clinical circumstances)
- EPO alpha SC 150 IU/kg once weekly (or darbopoietin 2.25 mcg/kg SC weekly; double dose in absence of response (Hb increase <1 g/dl) after 8-6 weeks
- If Hb exceeds 12 g/dL, withhold dose until Hb approaches a level where transfusions may be required; restart dose at 25% below previous dose
- ESAs should be used cautiously with chemotherapy, or in clinical states, associated with elevated risk for thromboembolic complications. The Committee also cautions against ESA use for patients with cancer who are not receiving chemotherapy, since recent trials report increased thromboembolic risks and decreased survival under these circumstances.

Anemia is present in 2/3 of MDS patients :

Improving erythropoiesis eliminating fatigue and symptoms is the main therapeutical target for the majority of MDS patients

MDS: Higher hemoglobin levels correlate with improved QoL



RBC transfusions

30% of MDS patients should require intervention for their anemia (chronic RBC transfusion or pharmacotherapy)

Problems associated with RBC transfusions:

- **Iron overload**
- **Fluctuating Hb levels**
- **Hemoglobin levels usually maintained <10 g/dL**
- **Intolerance reactions, Alloimmunization, Infections**
- **Shortage of blood**

1. Lawrence. *Clin Lab Sci* 2004;17:178–86
2. Balducci, *Cancer* 2006;106(10):2087–94
3. Gardin & Fenaux *Rev Clin Exp Hematol* 2004;8:E3
4. NCCN Guidelines for MDS. Source: www.nccn.org

Trials of erythropoietin alone in MDS

Study	Number of patients	Results	Comments
Hellstrom-Lindberg 1995	205 from 17 trials	16% overall response	Higher response if : a) Serum EPO<200 U/L b) Non-RARS c) Non Transfusion dependent
Rodriguez et al 1994	115 from 10 studies	23.5%	Higher response for RAEB No relation to EPO level
Terpos et al 2002	281	45% at 26 weeks (18% at 12 weeks)	Prolonged therapy increased response
Italian Cooperative	87	14/38 vs 4/37 responders	Low risk MDS pts only (double blind)
Rose et al 1995	116	28%	Serum EPO<100 predicted response (54% of RA with low EPO responded

EPO dose and schedule

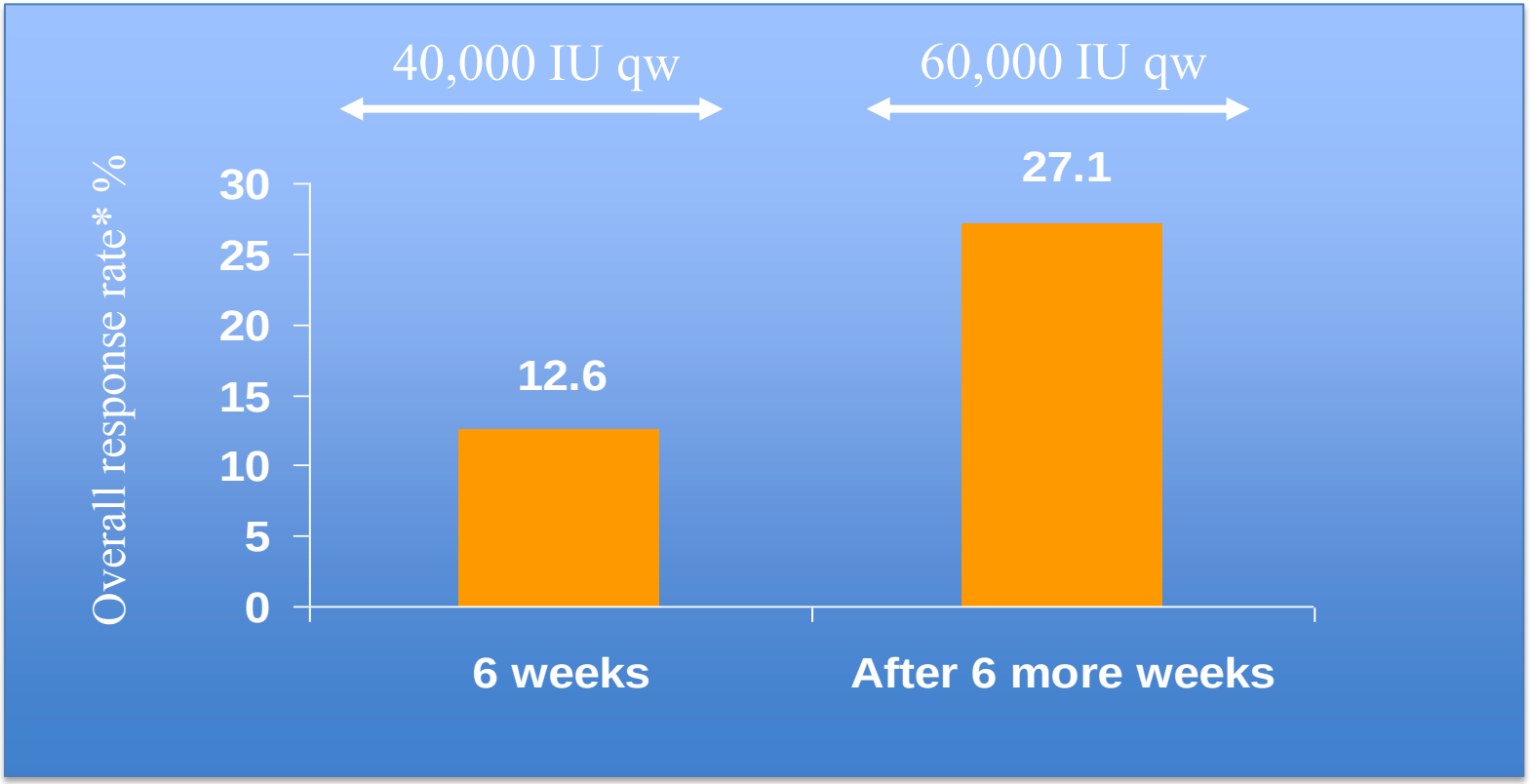
Usual therapy in chemotherapy-related anemia

epoetin 150 IU/kg tiw or 40,000 IU qw

IS MORE BETTER IN MDS?

Gabrilove *et al. J Clin Oncol* 2001;19:2875–82
Straus *et al*. *Cancer* 2006;107:1909–17
Gisselbrecht *et al. Haematologica* 2006;91:294 (Abs. 0799)
Stasi *et al*. *Ann Oncol* 2004;15:1684–90
Spiriti *et al*. *Ann Hematol* 2005;84:167–76

Epoetin alfa dosing in MDS: 40,000 IU qw escalating to 60,000 IU qw



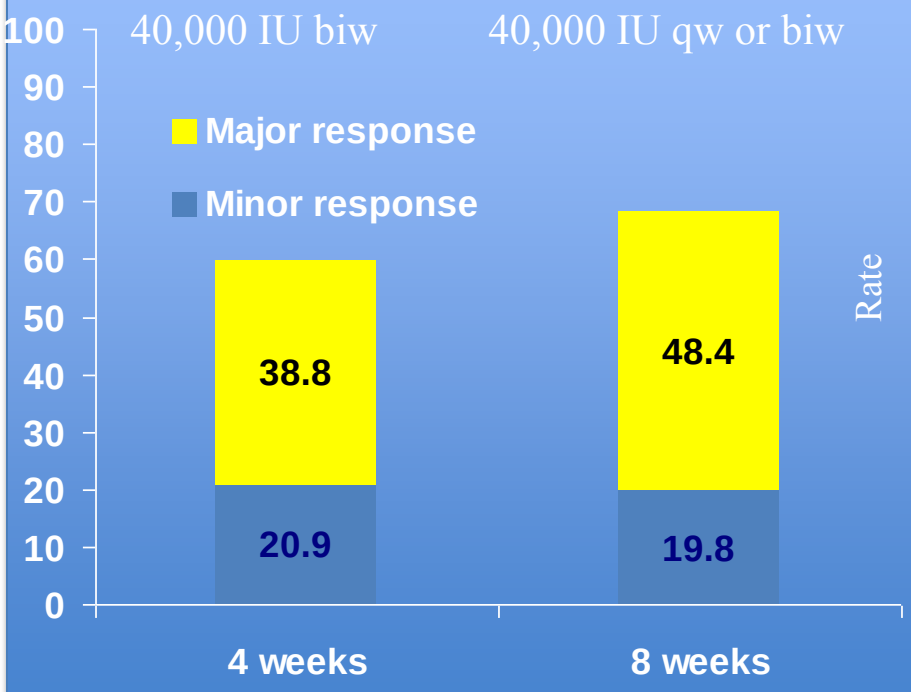
Changes to epoetin alfa dose and schedule may improve outcome in patients with MDS unresponsive to conventional approaches

Stasi *et al. Ann Oncol* 2004;15:1684–90

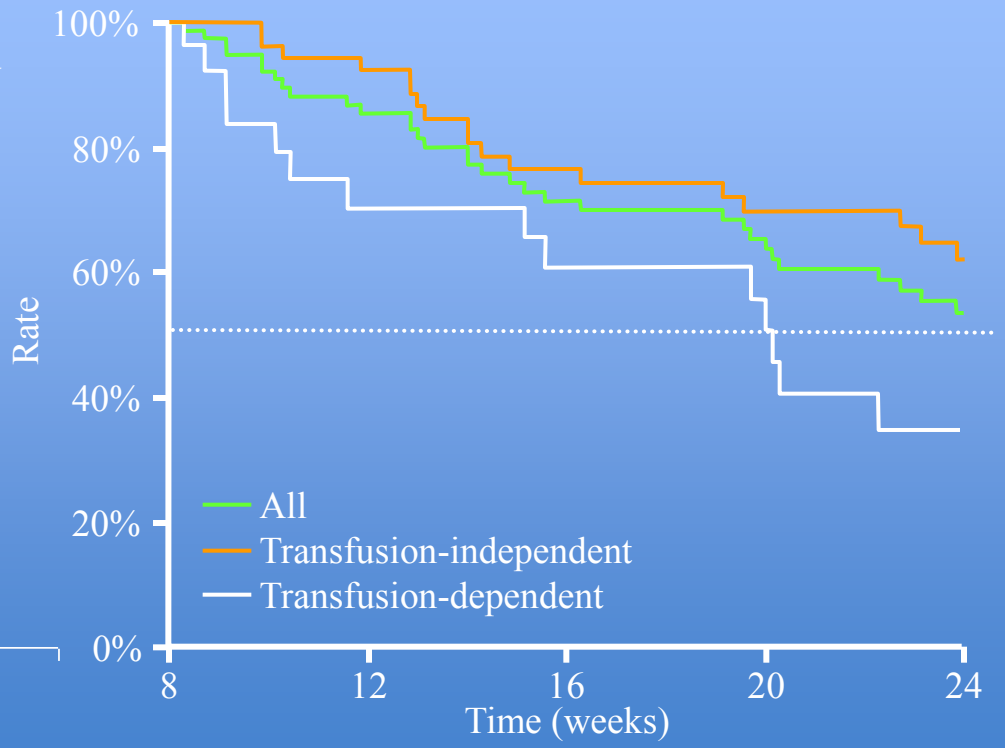
*IWG erythroid response criteria

Erythroid response: ORR 68% (Transfusion independent 74%, Transfusion dependent 59%)

Responders by week and dose

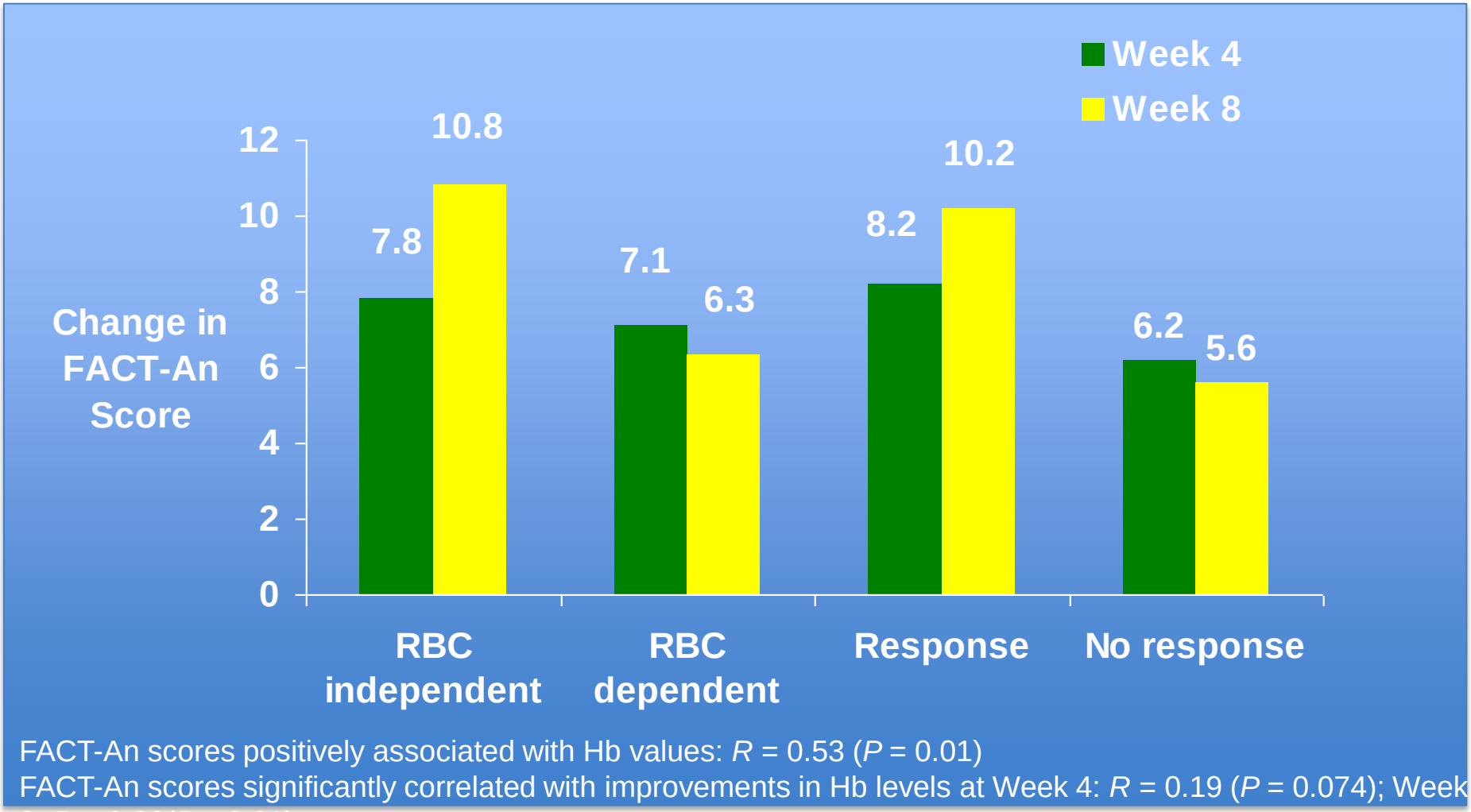


Response duration



Major response = 100% reduction in transfusion in the last 4 weeks
Minor response = >50% and <100% reduction in transfusion in the last 4 weeks

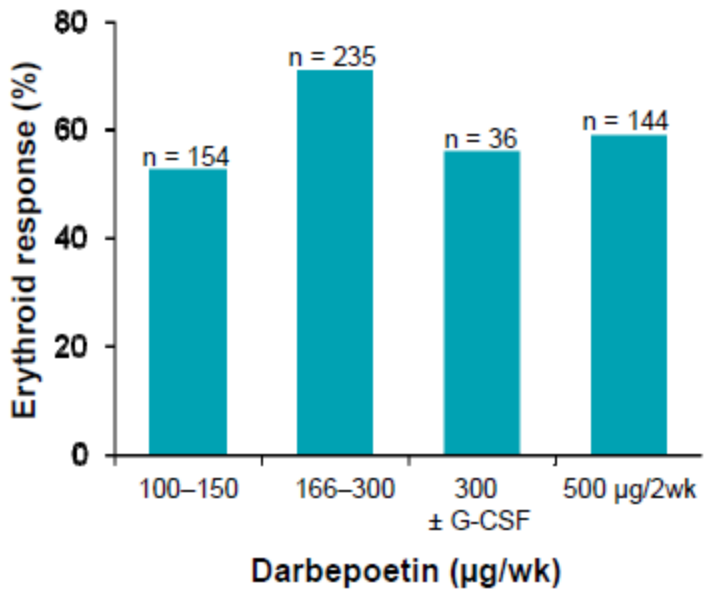
Increases in Hb correlate with QOL improvements

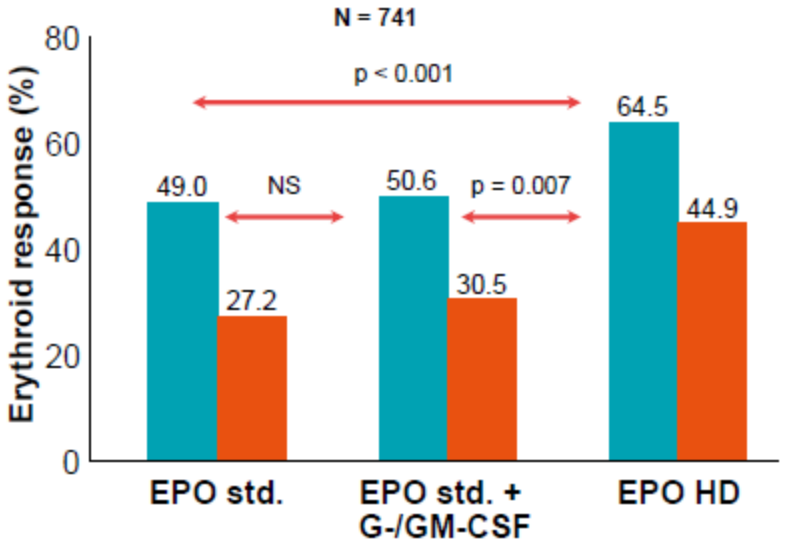


FACT-An scores positively associated with Hb values: $R = 0.53$ ($P = 0.01$)
FACT-An scores significantly correlated with improvements in Hb levels at Week 4: $R = 0.19$ ($P = 0.074$); Week

Spiriti *et al. Ann Hematol* 2005;84:167–76

Meta-analysis of erythroid response to ESAs





Higher dosing regimens of both epoetin alfa (weekly dose 60–80 K U) and darbepoetin alfa (weekly dose 150–300 µg) correlate with higher response rate

Modified from Moyo V, et al Ann Hematol. 2008;87:527-36.
Mundle S, et al. Cancer. 2009;115:706-15.
Nilsson-Ehle H, et al. Eur J Haematol. 2011;87:244-52.
Santini V. Oncologist. 2011;16 Suppl 3:35-42.
Santini V. Semin Hematol. 2012;49:295-303.

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; HD, high dose; NS, not significant; std., standard dose.

Erythropoiesis-stimulating agents are not associated with increased risk of thrombosis in patients with myelodysplastic syndromes

Sheila Weiss Smith,[1,2,3] Masayo Sato,[1,2] Steven D. Gore,[4] Maria R. Baer,[3,5] Xuehua Ke,[2] Diane McNally,[6] and Amy Davidoff[2,3]

5673 MDS patients (WHO classification by disease-code)

212 thrombosis events

Erythropoiesis-stimulating agents are not associated with increased risk of thrombosis in patients with myelodysplastic syndromes

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Variable	Hazard period N	Hazard period %	Control period N	Control period %	*P* value
ESA use (yes)	95	44.8	88	41.5	0.4925
Epoetin alfa					
No use: 0	141	66.5	147	69.3	
Low use: 1-5 weeks	33	15.6	30	14.2	0.8224
High use: +6 weeks	38	17.9	35	16.5	
Darbepoetin alfa					
No use: 0	182	85.9	187	88.2	
Low use: 1-3 weeks	15	7.1	14	6.6	0.6985
High use: +4 weeks	15	7.1	11	5.2	
G-CSF use (yes)	20	9.4	16	7.6	0.4859
RBC (yes)	82	38.7	46	21.7	0.0001
Platelet transfusion (yes)	23	10.9	<11**	<5.2**	0.0101
Chemotherapy (yes)	25	11.8	25	11.8	1.0000
Catheter placement (yes)	30	14.2	<11**	<5.2**	<0.0001
Hospitalization (yes)	166	78.3	51	24.1	<0.0001

**Variables were measured weekly. ** Cell contents are suppressed because they contained fewer than 11 patients and/or incidence <5.2%.*

Sheila Weiss Smith et al. Haematologica 2012;97:15-20

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Published by the Ferrata Storti Foundation

Predictive variables for ESA response in MDS

Predictive variables for ESA response in MDS

Biological
- Endogenous EPO levels < 500 U/L
- Marrow blast < 10%
- IPSS Low/Int-1
- Diagnosis of refractory anaemia
- Normal karyotype

Clinical
- Transfusion independence
- Short duration of disease

Santini V. Oncologist. 2011;16 Suppl 3:35-42.

Selection of patients improves outcome of EPO therapy

15% response → >70% response

UNSELECTED MDS PATIENTS

All WHO/FAB subtypes

MDS PATIENTS SELECTED FOR:

Recent diagnosis

Transfusion independence

EPO <200 U/L (<500 U/L)

Normal cytogenetics – non-5q-

Refractory anemia (?)

Extend period of therapy to 24 weeks

Add G-CSF

ESA

- **Benefits**

Reduction in blood transfusions
Improve cardiac and renal functions
Reduce hospitalization
Reduce mortality rate (small studies)
Improvement in patient's quality of life

- **Disadvantages**

Cardiovascular events
Hypertension
Thromboembolism
Cancer progression
No benefit in CKD progression
Expensive

The ideal ESA

- Effective
- Safe
- Flexible administration route
- Less frequent administration schedule
- Cheap