

Altijd je (beste) vriend?

EPO for ORPADT



W Lemahieu, UZGasthuisberg, Leuven – St John's, Brussels

28 november 2008, Affligem







KADIE

1755

1971

EPO: altijd je vriend?

- EPO, je beste vriend!
 - geschiedenis
 - (patho)fysiologie
- Of toch niet...
 - verontrustende data!
 - (patho)fysiologie
- Quo vadis

EPO: je beste vriend – the story

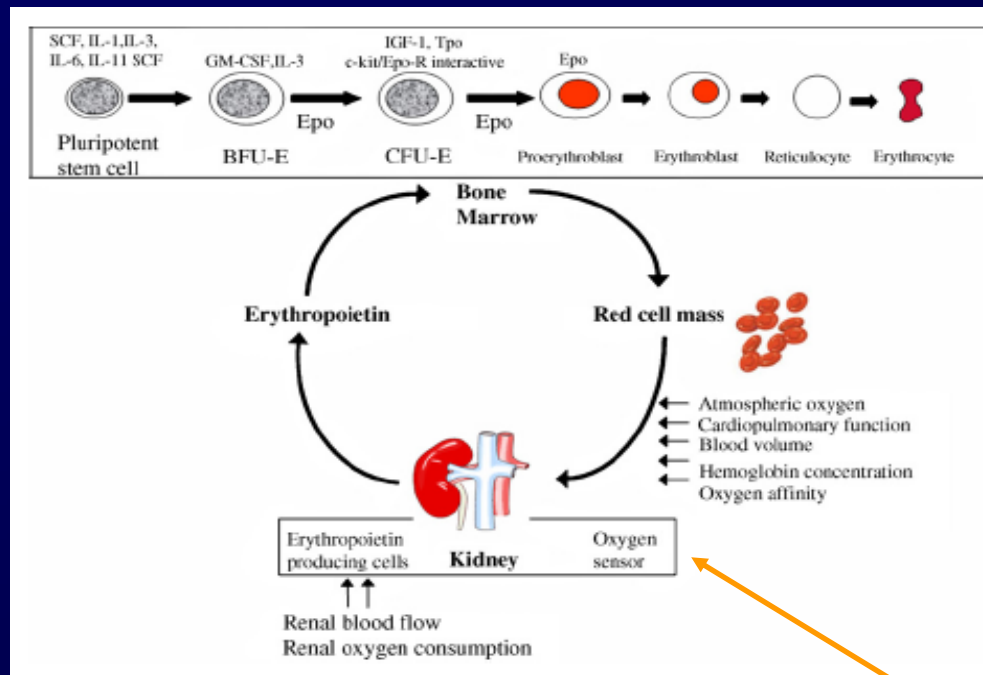
- 1906: Carnot & Deflandre
 - serum bloedend konijn → factor X!
 - factor X → superkonijn!
- 1957: Jacobson (1988: Lacombe et al)
 - factor X = EPO en komt uit de nier (meer bepaald peritubulair)!
- 1985: Miyake - Jacobs / Lin
 - clonen humaan EPO gen
 - copy//paste in chinese hamster cell: EPO à gogo
- 1989: FDA keurt rHuEPO goed
 - fantastische trials – the sky is the limit

EPO: hoe werkt je beste vriend?

- 1959: Reissmann et al
 - serum ratten op 'hoogte' stage → '?' → EPO!
- 1993: Wang et al
 - '?' = H(ypoxia)I(nducible)F(actor)
 - HIF ~ O_2 / VHL/Kobalt/...
- 1985 tot ?: Velen
 - EPO → receptor → Ja(nus)K(inase) 2
 - JaK2 → S(ignal)T(ransducing)A(ctivating)T(ranscriptor)5
 - STAT5 (en nog andere) → stop apoptose preRBC
 - Uiteindelijk: Hematocriet stijging

PS: ook extra hematopoëtische effecten EPO
(oa: bescherming 'reperfusion-injury' hersencellen na CVA!)

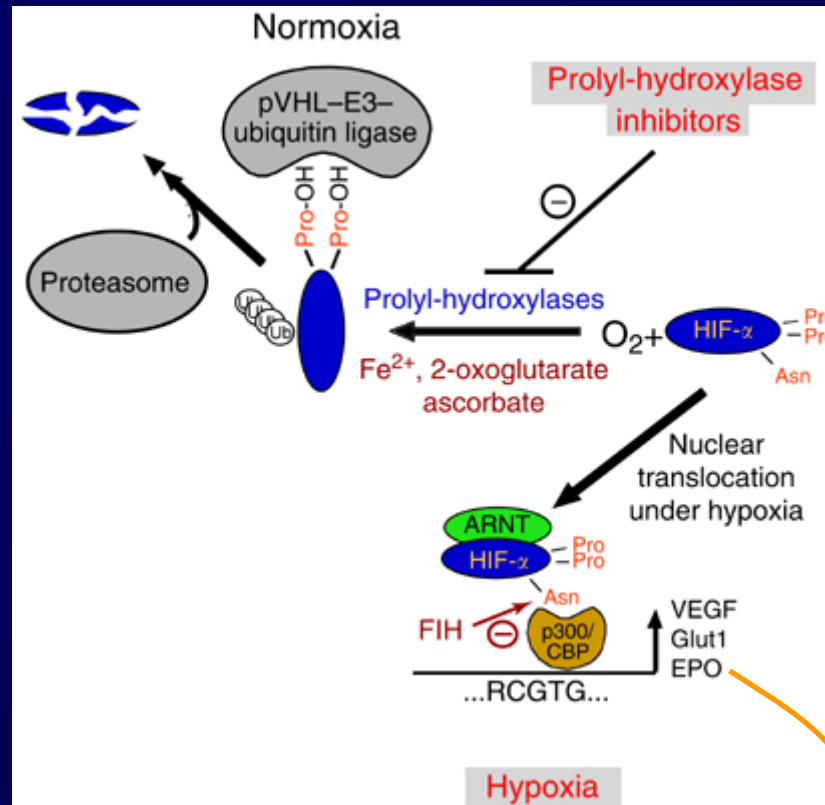
EPO: hoe werkt je beste vriend?



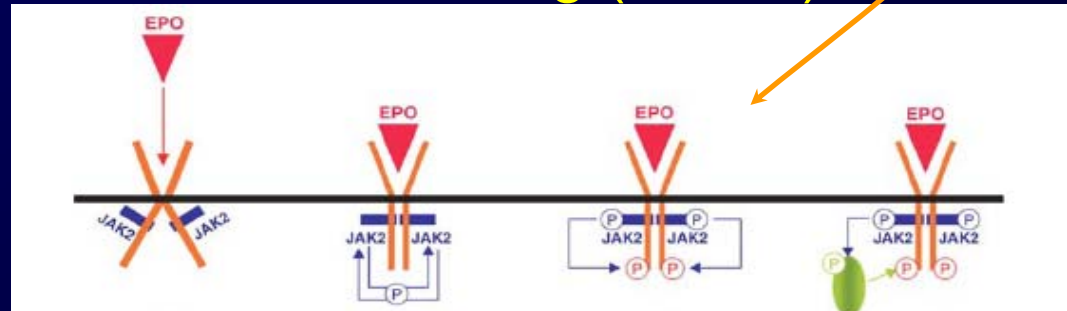
Hodges, crit rev hematol/oncol 2007, 64:139

HIF

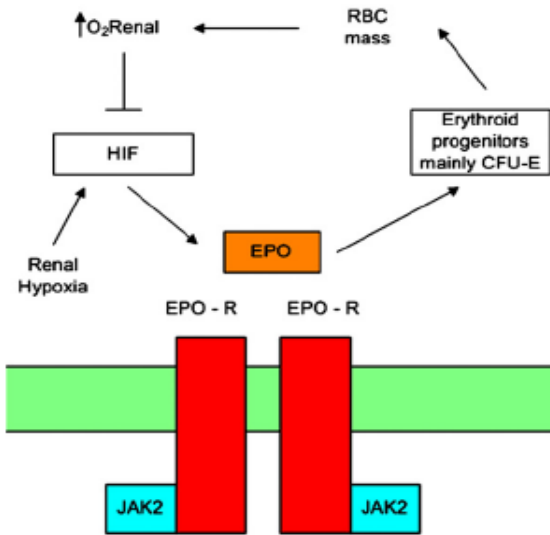
nier



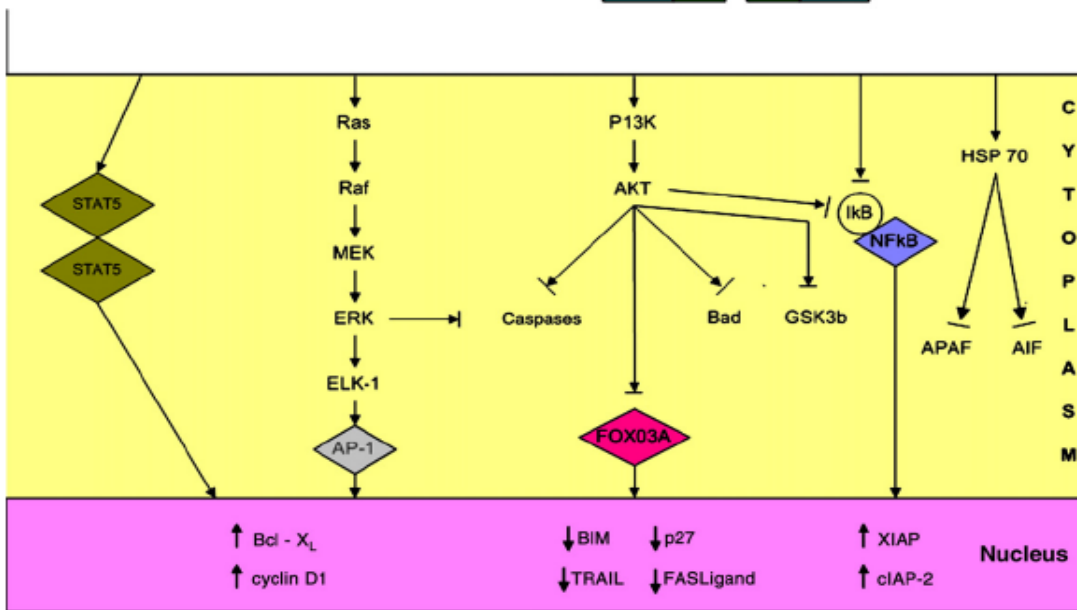
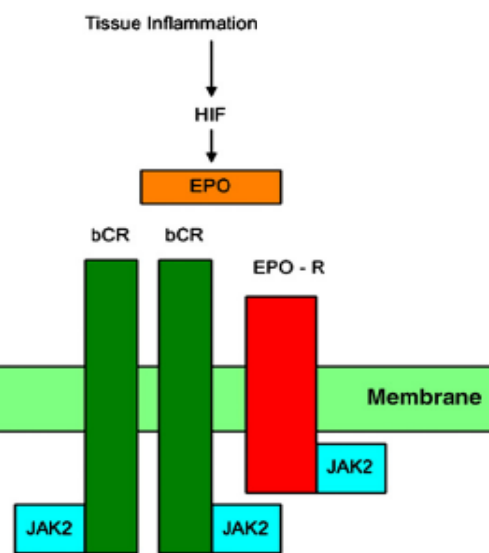
beenmarg (elders)



ERYTHROPOIESIS (Hormonal Mode)



TISSUE PROTECTION (Autocrine / Paracrine Mode)



ERYTHROPOIESIS

TISSUE PROTECTION

EPO: wie zijn je beste vrienden?

'native' EPO

- 165 aminozuren met enkele suikers (glycosylatie) erop: 30.4 kDa
- $T_{1/2} = 2-10$ h
- [norm] = 10-20 mU/ml → tot 100-1000 x hoger bij anemie

Vs

rHuEPO & 'N(ew)E(poreceptor)S(timulating)P(rotein)'s & CERA's

Alpha – epoetine & Beta – epoetine

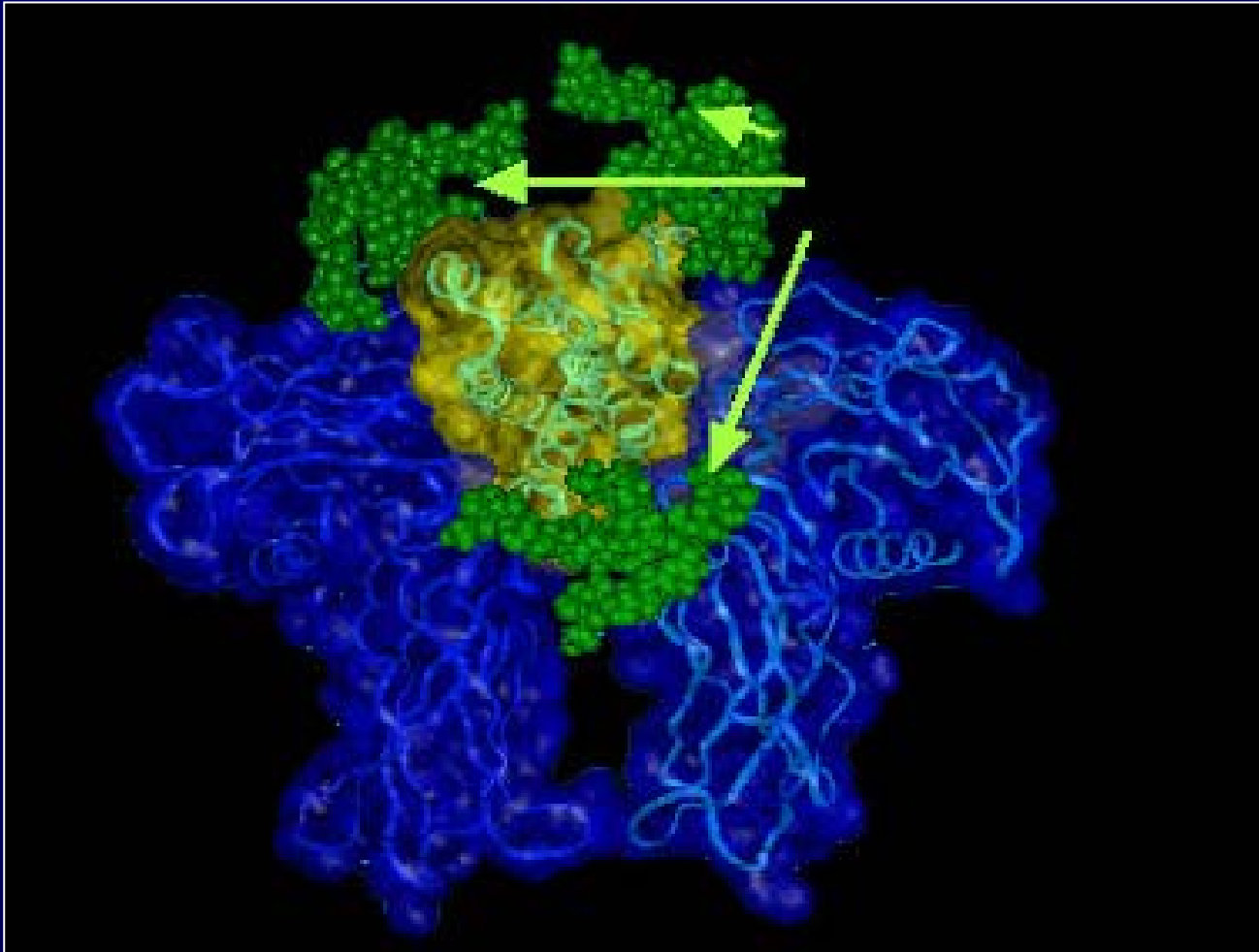
- 165 zelfde aminozuren met licht verschillende glycosylatie
- $T_{1/2} = 2-10$ h na iv – 24 h na sc

Darbepoetine (aka 'WESP')

- 165 aminozuren, 5 extra suikers – 37.1 kDa
- $T_{1/2} = 24$ h na iv – 48 h na sc

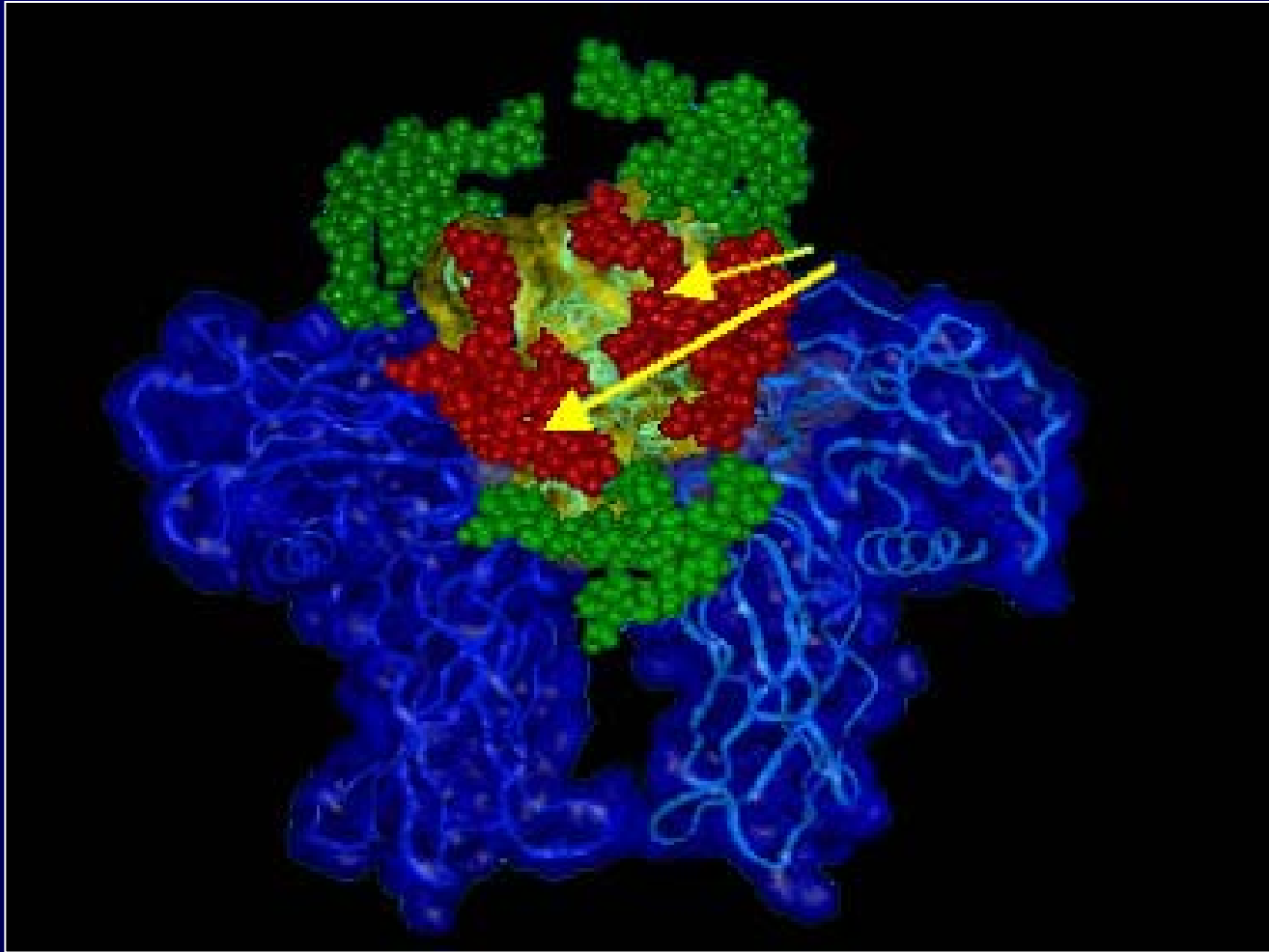
Mircera

- Beta-epoetine met extra PEGstaart – 60 kDa
- $T_{1/2} = \underline{130}$ h na iv & sc



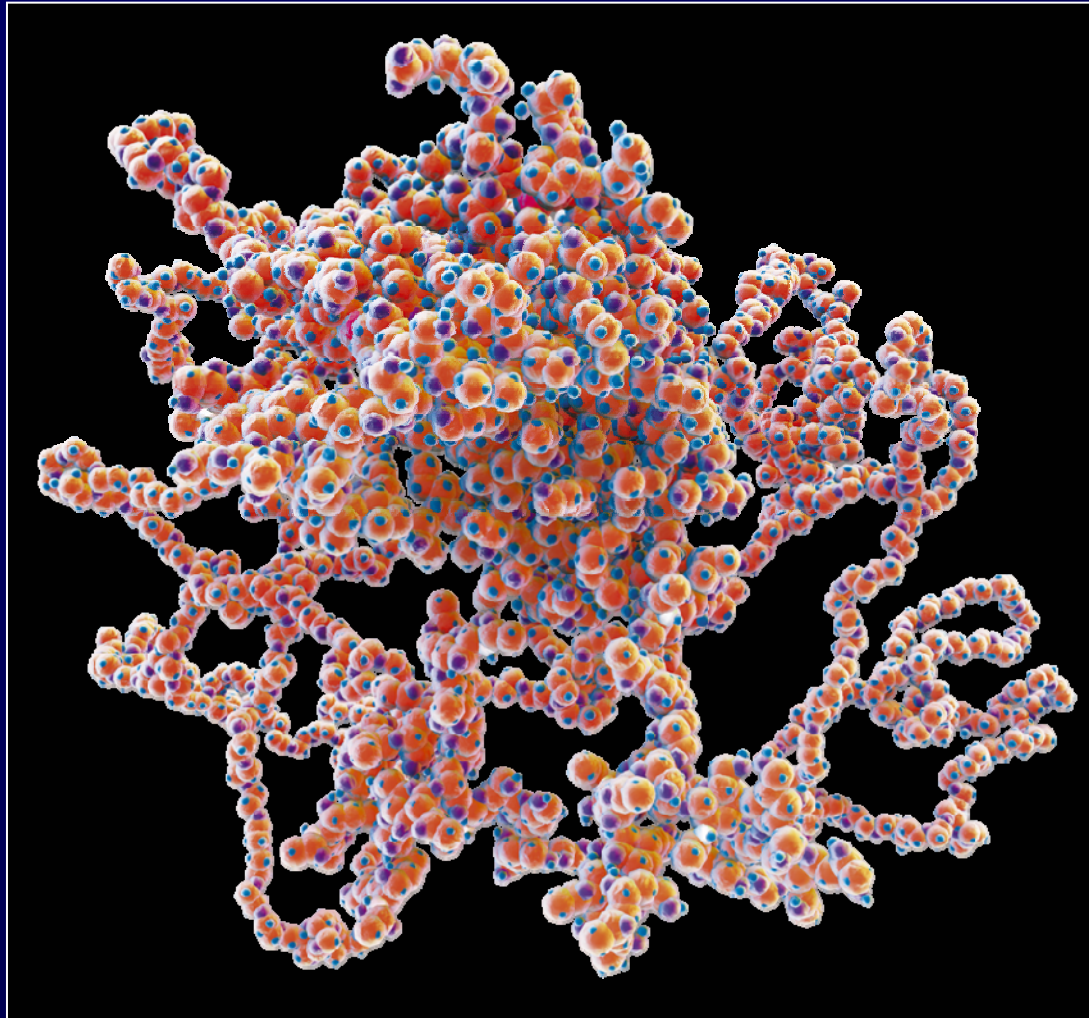
rHuEPO

met dank aan prof Vanrenterghem & Amgen



NESP

met dank aan prof Vanrenterghem & Amgen



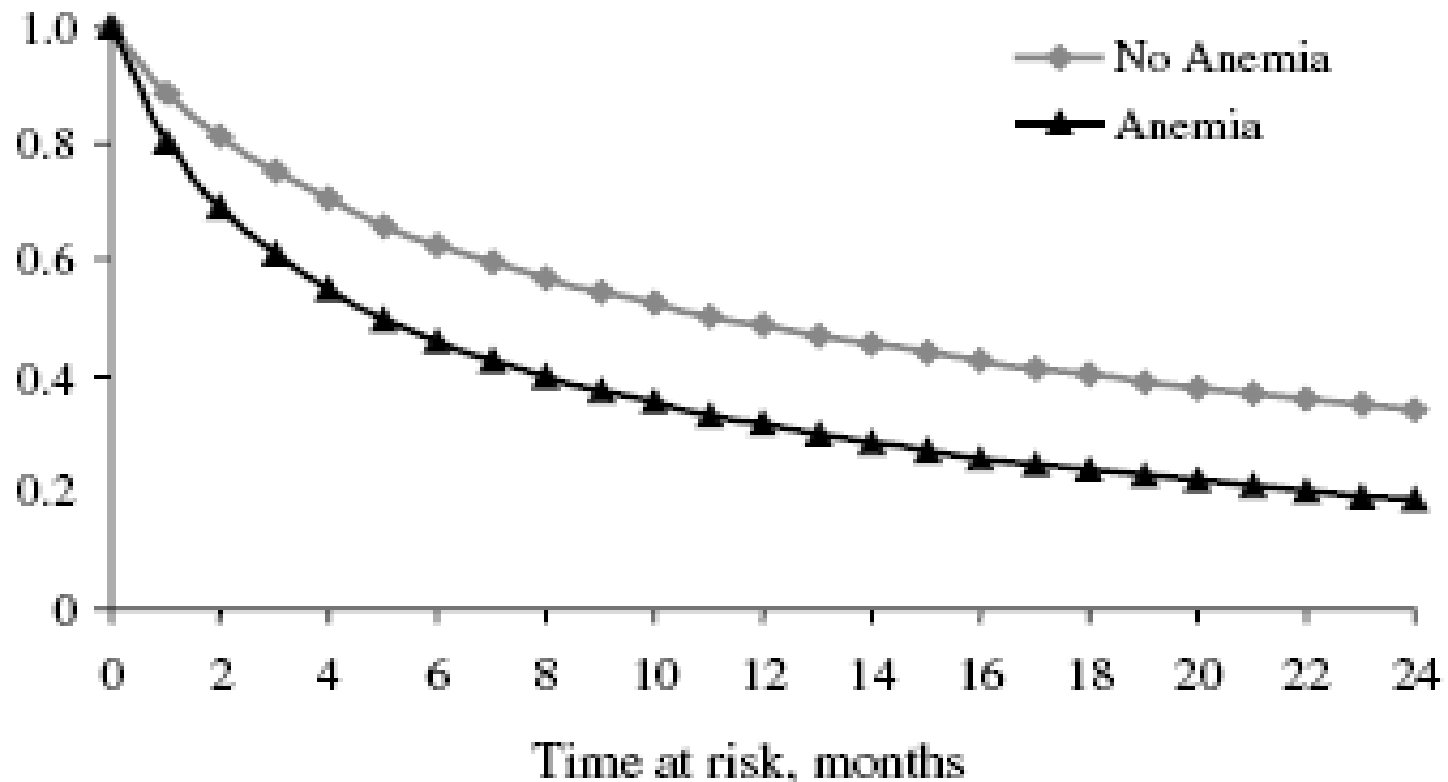
CERA

met dank aan dr Warrinier & Roche

EPO: waarom je beste vriend?

- Anemie = slecht = de vijand
 - Observationele data
 - Pathofysiologische modellen: vb linker ventrikel hypertrofie
- De vijand van de vijand = de vriend
 - Eerste epo trials: prima!
 - Ook cardiologen en oncologen doen mee!

Anemie: meer kans op hospitalisatie/overlijden/dialysenood



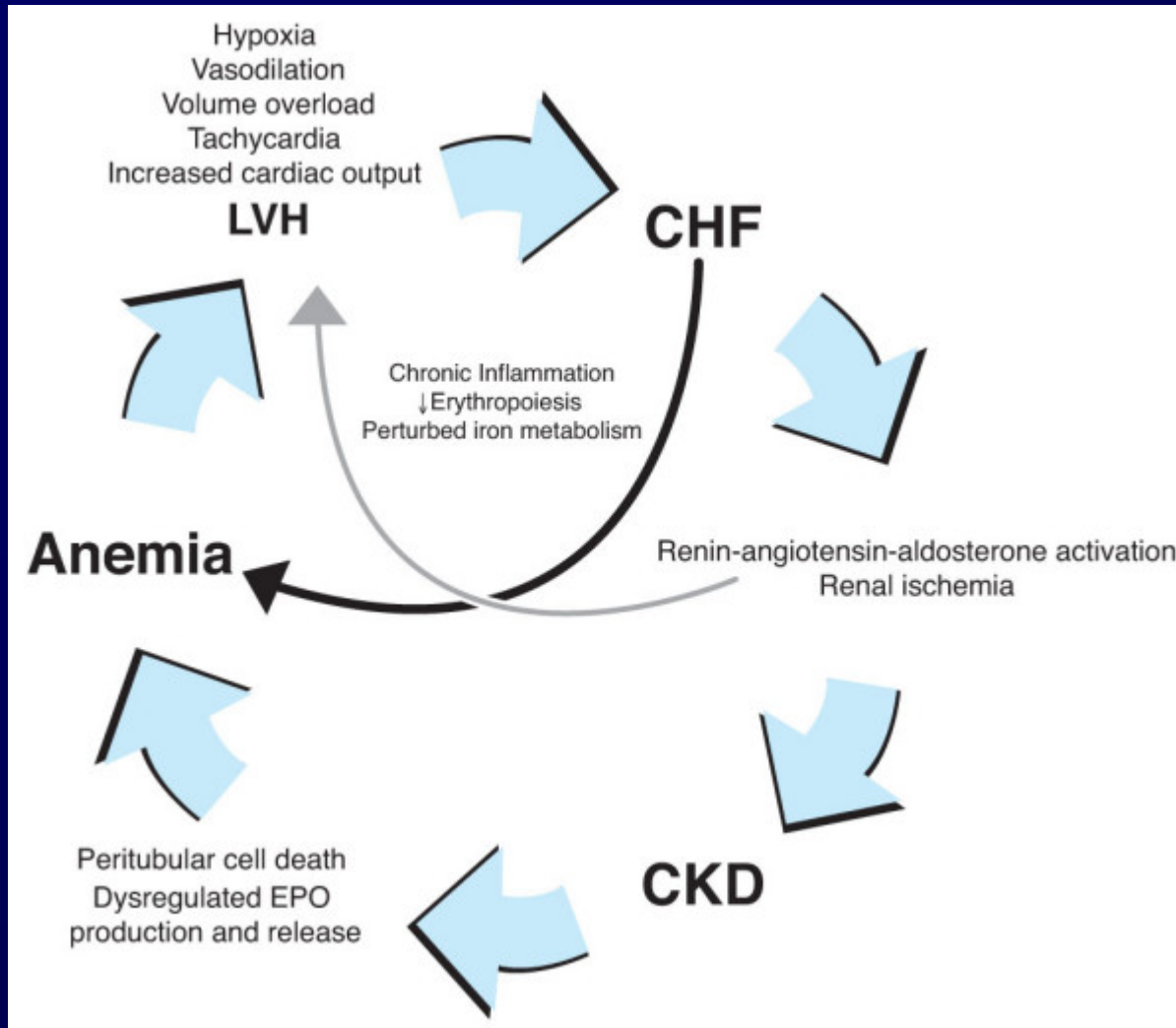
Number at risk:

No anemia	13130	10241	8437	7158
Anemia	9294	6436	4773	3797

Li, foley, collins, int urol nephrol 2005

Gelijkaardige boodschappen in JASN 1999 door Xia, Ebben, Ma et al

Anemie – hartfalen – nierinsufficiëntie: vicieuze cirkel



Sedert de 90ies reeds talloze malen onder talloze vormen in talloze journals

Anemie: we kunnen er iets aan doen ... en het werkt!

• EPO → minder transfusies, betere levenskwaliteit

- Eschbach, NEJM 1987 (25 pt HD) - Can EPO study 1991 (118 pt HD) - etc
- Lim, Ann Int Med 1989 (14 pt pre-dialyse) - Roth, AJKD 1994 (83 pt pre-dialyse) - etc

• EPO → minder linker ventrikel hypertrofie, ↑ fysieke capaciteit

- Mayer, KI 1988 – Wizeman, Nephron 1993 - etc
- MacDougall, Lancet 1990 - Canella, Clin Nephrol 1990 – etc

• EPO → minder snelle nierfunctie achteruitgang

- Kuriyama, Nephron 1997
- Gouva, KI 2004

EPO: meer is beter?

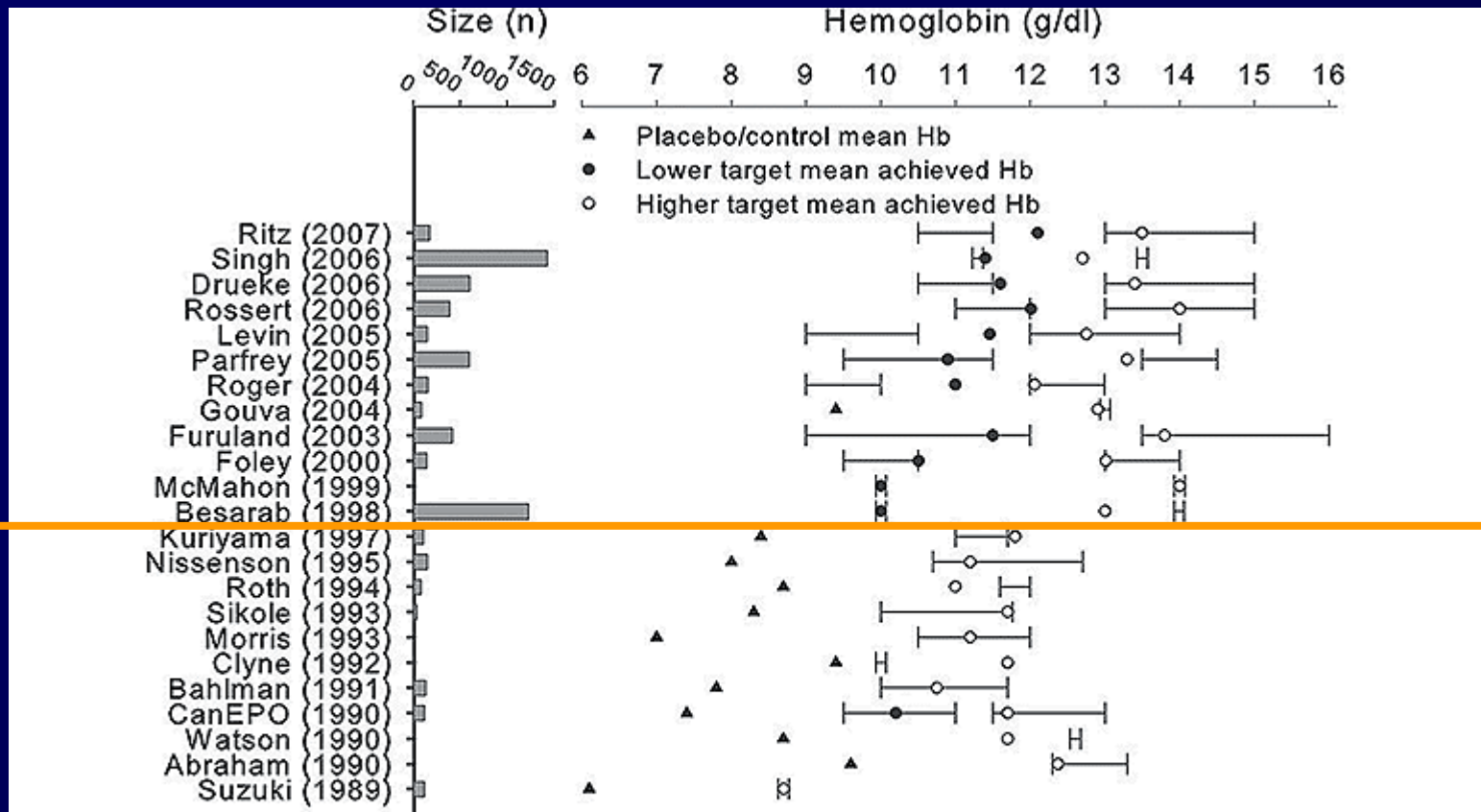


Figure 1. Randomized controlled trials comparing lower with higher hemoglobin (Hb) target levels. Data are represented as target Hb (whiskers), achieved mean Hb for patients assigned to lower (closed circles) or upper (open circles) Hb targets, and placebo or untreated control (filled triangles). Study size (N) is indicated by the bars on the left. In several large trials published since 1998, achieved mean Hb levels were not within the intended target.

EPO: je beste vriend?

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 - Eerste epo trials: prima!
 - Ook de cardiologen en de oncologen doen mee!
- Nefrologen zijn zeurpieten
 - EPO → Hct → viscositeit → CVA, dialyzer/access clot?
 - EPO → Plaatjes activatie → CVA, etc
 - EPO → hypertensie → CVA

Dispuut 'target' Hct nefro vs hemato

NKF K/DOQI GUIDELINES 2000

GUIDELINES FOR ANEMIA OF CHRONIC KIDNEY DISEASE

II. Target Hemoglobin/Hematocrit

BACKGROUND

...The initial patient experience with Epoetin came in a Phase I-II clinical trial in hemodialysis patients with the anemia of CKD. The target maintenance Hct for these patients was 35% to 40%, ie, at the lower range of normal. When investigators met to design the Phase III multicenter clinical trial, hematologists argued that the target Hct should be a normal Hct, while nephrologists proposed a lower level. A compromise target Hct of 35% was used in the trial. The final Hct levels for the more than 300 patients treated with Epoetin in the Phase III trial ranged from 33% to 38%. The results of this study, together with those of the Phase I-II clinical trial, were submitted to the FDA. The FDA approved Epoetin therapy in June, 1989, but the target Hct range recommended by the FDA was only 30% to 33%, for reasons that have never been clear. The FDA recommendation is probably responsible for the previously held belief that a target Hct of 30% to 33% is medically appropriate....

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...Review of the literature which involved predialysis and dialysis patients within and outside the United States showed that, compared to higher Hgb/Hct values, Hgb/Hct values $11 \text{ g/dL}/<33\%$ are associated with increased morbidity and mortality. In addition, a number of recent United States and non-United States **studies reported in abstracts indicate that patients with CKD function better at Hct levels that are near normal or normal and that improvement is continuous as the Hgb/Hct increases above $10 \text{ g/dL}/30\%$ to normal levels.** The only exception to this has been a study sponsored by Amgen that involved more than 1,200 hemodialysis patients with documented heart disease. This study was discontinued when it appeared that those patients randomized to a target Hct in the normal range ($42\% \pm 3\%$) were experiencing a greater incidence (30%, with a confidence interval of 0.9 to 1.9) of non-fatal myocardial infarctions or death than did the control group randomized to a target Hct of $30\% \pm 3\%$. The difference was not statistically significant at the time the study was terminated, however. Additional studies are needed to clarify the relationship between Hgb/Hct and outcomes in CKD patients, particularly those with heart disease....

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EPO: je *valse* vriend

- 1998: A Bessarab, NEJM
- 2002: PRCA
- 2006: black box warning
 - thrombo-embolische fenomenen
 - EPO: cancer – enhancer?
- 200X: ?

EPO: meer is beter?

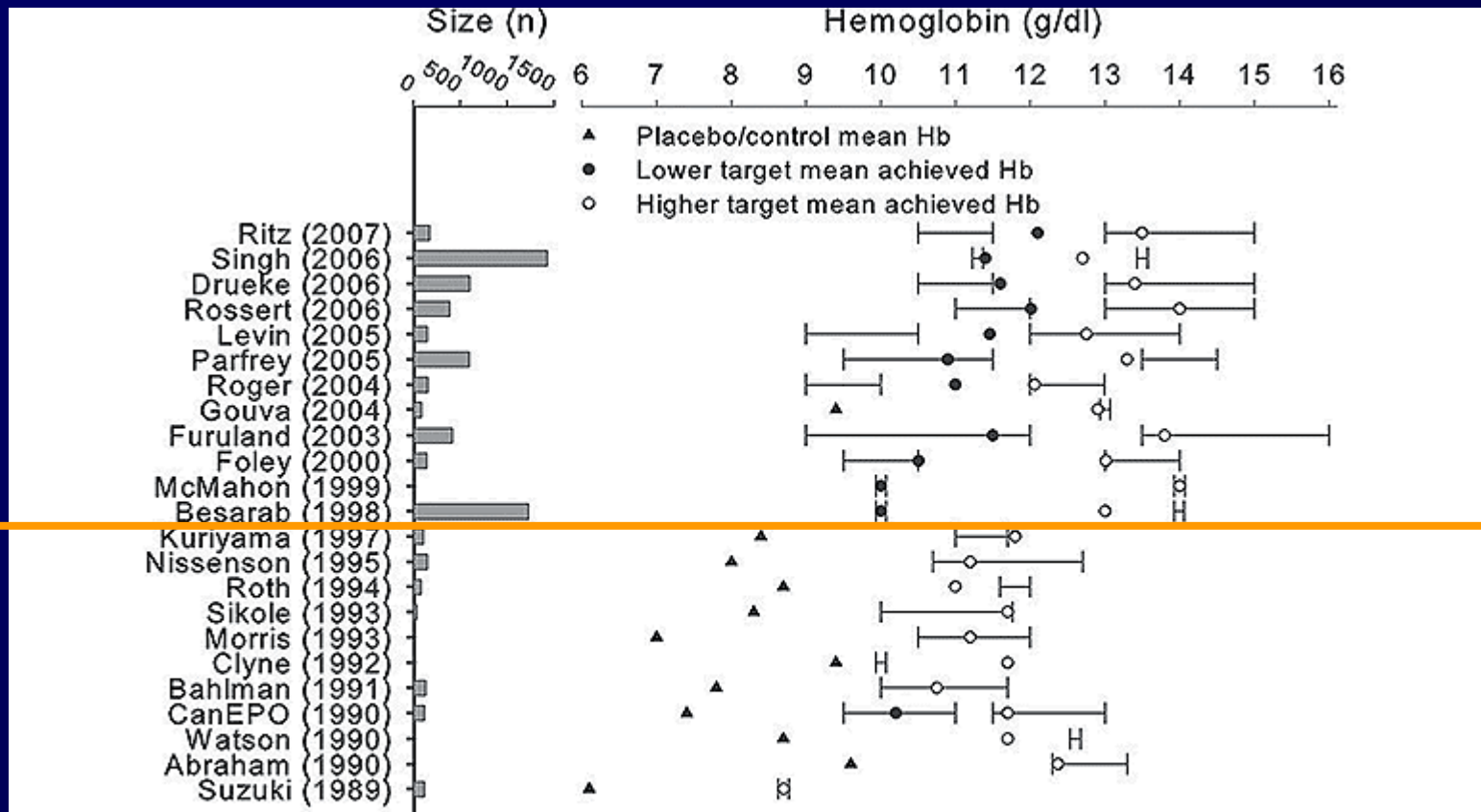
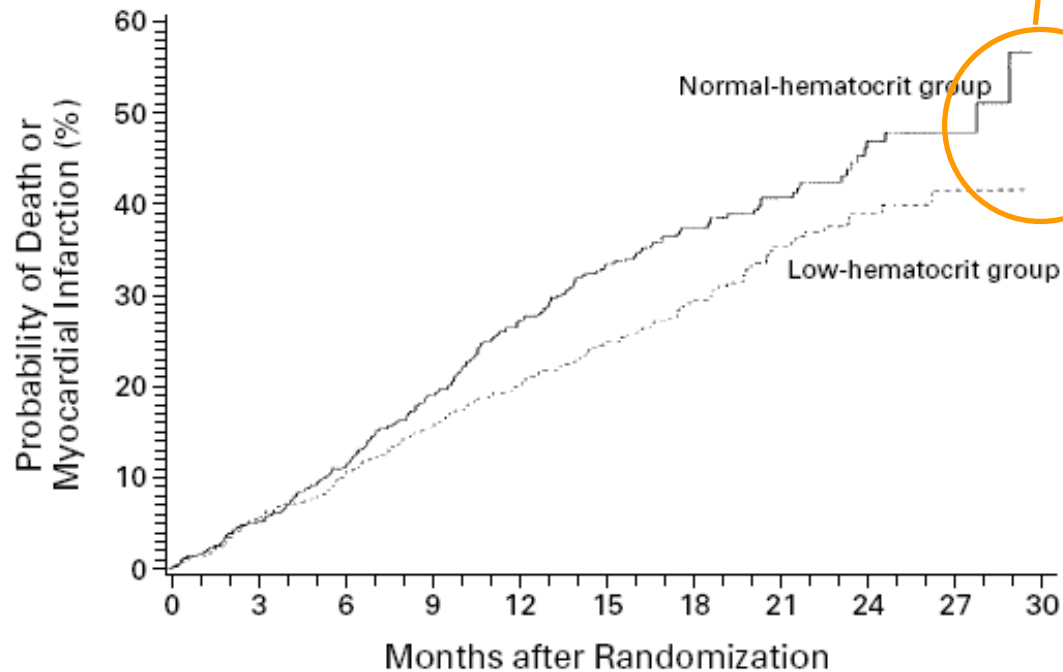


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EPO: meer is beter?

NS, tevens kt/v ↓ en ↑ Fe in 'high' group



No. AT RISK		0	3	6	9	12	15	18	21	24	27	30
Hct 42	Normal hematocrit	618	540	476	415	353	259	186	124	69	26	
Hct 30	Low hematocrit	615	537	485	434	391	292	216	131	80	20	

Figure 2. Kaplan–Meier Estimates of the Probability of Death or a First Nonfatal Myocardial Infarction in the Normal-Hematocrit and Low-Hematocrit Groups.

Hoe minder anemie (en dus hoe [\$meer \$]EPO) – hoe beter?

❖ **nog meer** EPO → nog betere levenskwaliteit? ????

Niet in America: Can EPO, 1991 – CHOIR, NEJM 2006

Wel in Europa: CREATE, NEJM 2006 – ACORD, AJKD 2007

❖ **nog meer** EPO → nog minder linker ventrikel hypertrofie etc?

Nee!

Besarab, NEJM, 1998 – Foley, KI, 2000

Parfrey, JASN, 2005 – Druecke, NEJM, 2006

❖ **nog meer** EPO → nog minder snelle nierfunctie achteruitgang?

Nee

Levin, AJKD, 2005 – Rossert, AJKD, 2006

Roger, JASN, 2004 – Druecke/Singh, NEJM, 2006 – Ritz, AJKD, 2007

NKF K/DOQI GUIDELINES 2007

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In the statement **the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL**, the 2 specific values 11.0 g/dL and 12.0 g/dL define inclusively either a single Hb target range (11.0 to 12.0 g/dL) or a range of possible single-point Hb targets between 11.0 and 12.0 g/dL; entail unavoidable subjectivity in selecting Hb cutoff values; explicitly exclude reference to *achieved* Hb levels; and together reflect the efforts of the Work Group **to balance the potential quality-of life benefits and avoidance of transfusion gained by ESA therapy against the potential harm suffered by patients with Hb targets greater than 13 g/dL.**

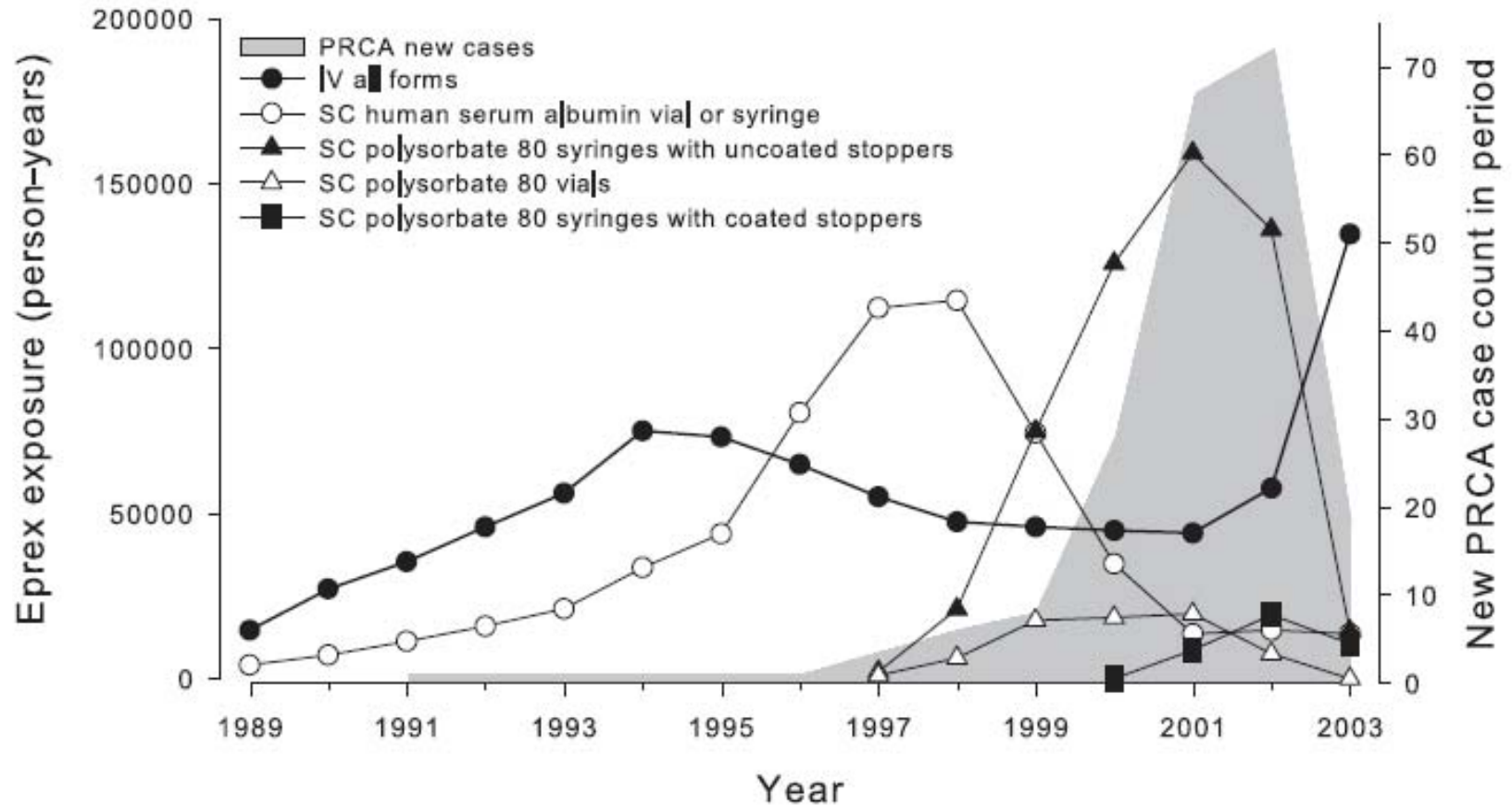
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PRCA: EPO → anemie

- auto-immuniteit, al gekend voor EPO
- 2002: eerste publicaties van reeks gevallen na sc EPO
- mechanisme:
 - interactie verpakking/solvent-eiwit → 'vaccinatie'
 - vooral bij eprex sc: tijdelijk verbod is nu van de baan!
- cave: ook bij andere 'merken' sporadisch geval
- in perspectief te plaatsen:
 - tot op heden alleen bij sc
 - 'piek'frequentie: 4.3/10000 pt jaren – 'background': $\leq 0.5/10000$

PRCA in perspectief



http://www.kidney.org/Professionals/kdoqi/guidelines_anemia/images/figures/fig17.jpg

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and oncologists/cardiologists

Anemie & mortaliteit/morbiditeit: geen nefrologisch monopolie!



EPO: geen nefrologisch monopolie!
(wat denken ze wel!)



Top \$\$ St John's hospital: de 500 µg 'WESP'
(iedereen 'lance')

E(v)(m)idence Based?

Fresher!
Cleaner!

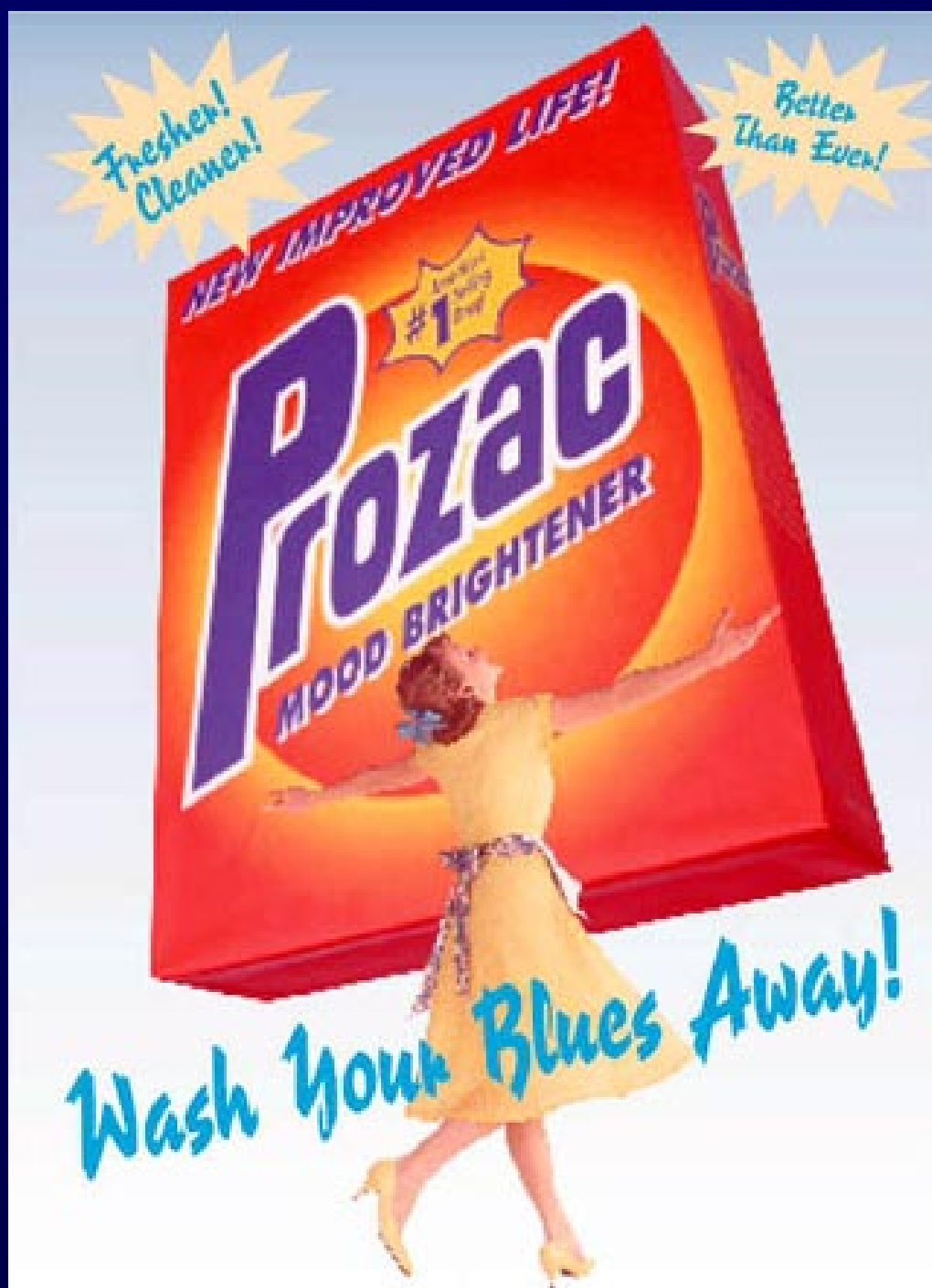
Better
Than Ever!

NEW IMPROVED LIFE!

#1

Prozac
MOOD BRIGHTENER

Wash Your Blues Away!



EPO in onco: van beste vriend naar...

• anemie = de vijand

Meta analyse van mortaliteit uit 60 onco studies – Caro, Cancer, 2001

• EPO = de vijand van de vijand = de vriend

EPO: minder anemie + meer tumor radio/chemo-sensitiviteit

1993: FDA – approval

2006: 11.9 billion \$ omzet in oncology

• de ontnuchtering!

Hencke, Lancet, 2003 & Leyland-Jones, J Clin Oncol, 2005:

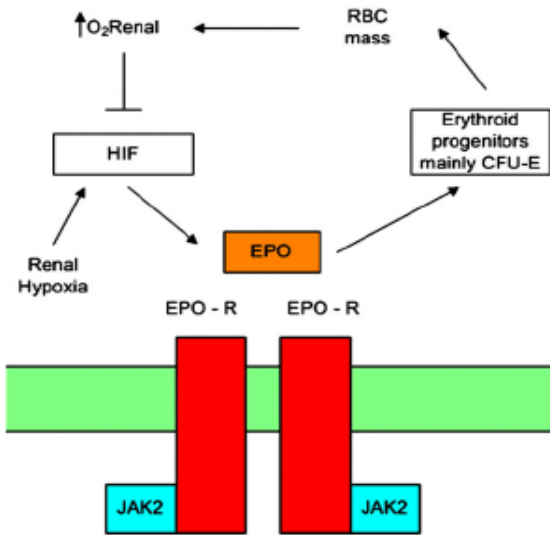
meer thrombo-embolie en borst/NKO kanker progressie!

Blau, Stem Cells, 2007:

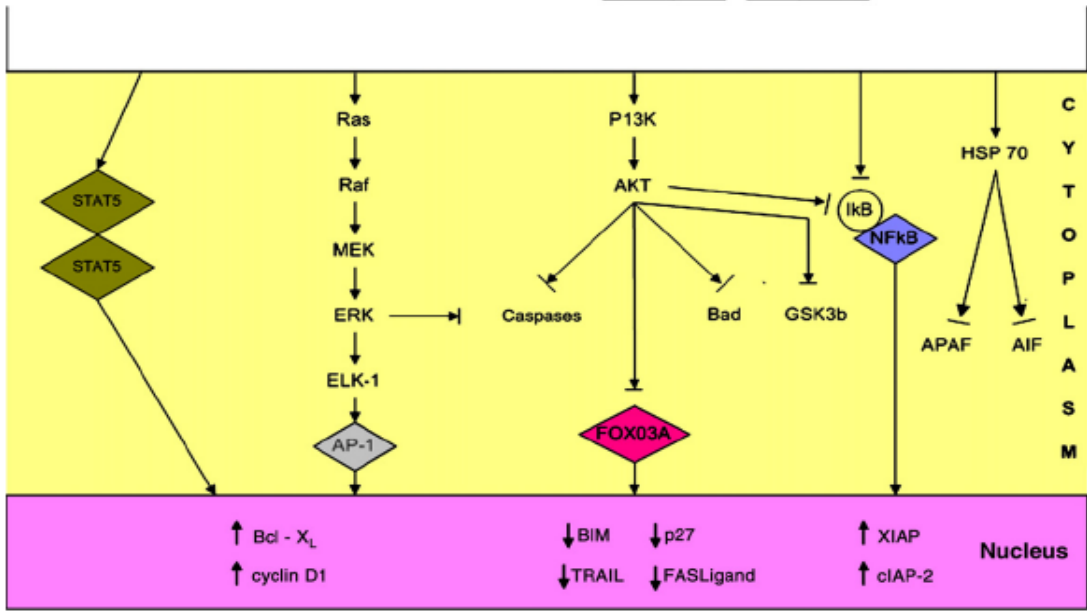
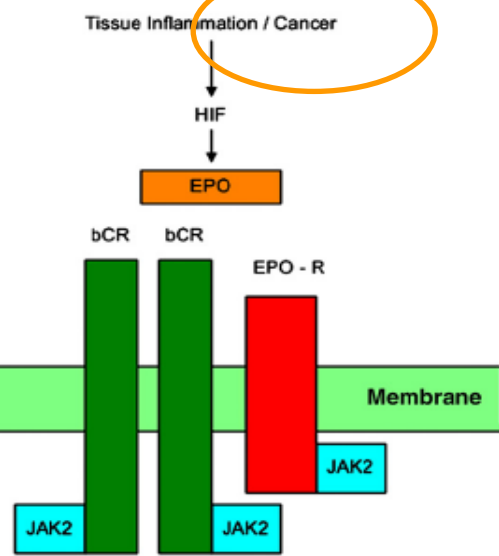
FOUR NEW TRIALS DEMONSTRATE AN
ADVERSE EFFECT OF ERYTHROPOIETIN
ON CANCER SURVIVAL

Why?

ERYTHROPOIESIS (Hormonal Mode)



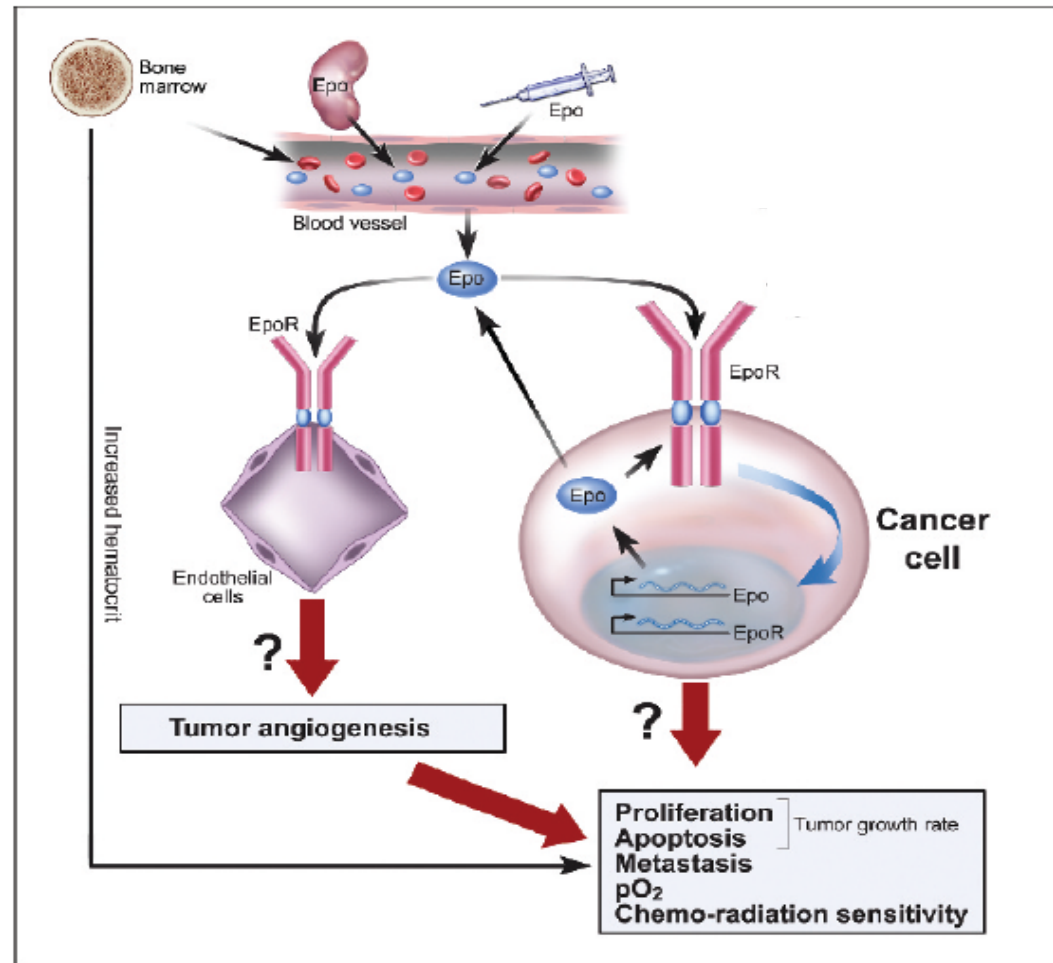
TISSUE PROTECTION (Autocrine / Paracrine Mode)



ERYTHROPOIESIS

TISSUE PROTECTION

Fig. 1. Potential effects and mechanisms of Epo-EpoR signaling in tumors. Cancer cells and tumor endothelium express EpoR, illustrated here as a homodimer, analogous to the functional EpoR in erythroid cells. The exact structure of the cell surface receptor complex that mediates the effects of Epo in nonhematopoietic tissues and cancer cells has not been defined. In this hypothetical model, EpoR activation may be stimulated by Epo from the systemic circulation (renal or exogenous source). In addition, coexpression of Epo and EpoR in tumor cells and the expression of EpoR in vascular endothelial cells may result in the generation of an autocrine-paracrine Epo-EpoR activation loop, constituting a potential therapeutic target in tumors where Epo-EpoR signaling may be involved in tumor angiogenesis and progression. The direct, *in vivo* effects of Epo-EpoR signaling on cellular proliferation, tumor oxygenation, apoptosis, tumor angiogenesis, metastasis, and sensitivity to chemoradiation therapy remain to be characterized.



Konstantinopoulos, *biochimica biophysica acta* 2007, 1776: 1

Hardee, *clin cancer res*, 2006, 12: 332

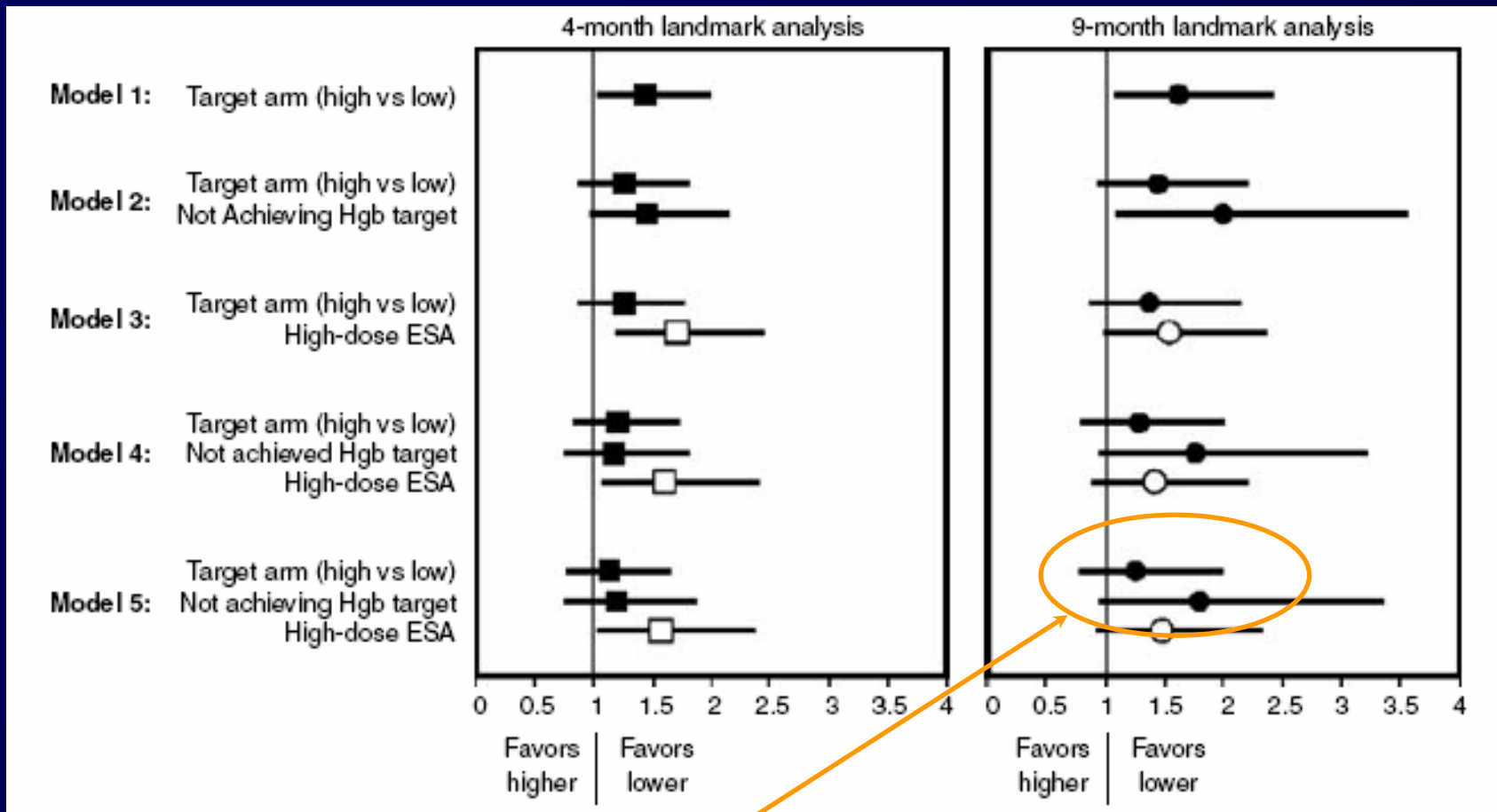
EPO: je *valse* vriend?

• thrombose: is het wel EPO?

• of is het: X → inflammatie/thrombose
→ EPO resistente anemie
→ superdoses EPO

EPO: je *valse* vriend?

Re-analyse van CHOIR (Singh, NEJM, 2006)



Fe/PTH/CRP/X...

Szczech, KI, 2008

EPO: quo vadis?

❁ EPO: je dure vriend!

- equivalent van 1 jaar 8000 E /wk:
 - Eprex-Neorecormon: $87.4 \times 52 =$ 4545 €
 - Aranesp: $x26 = 213.7 \times 26$ 5556 €
 - Mircera: $x13 = 624 \times 13$ 8112 €
- R/ 'merck' EPO?
- R/ terug sc ipv iv? (immers: tot 25% dosis reductie)
maar: 1. vrijwel alleen bij eprex bestudeerd
2. tegenstrijdigheden (in studie+tussen studies)
3. 'spook' van prca

(kaufman, NEJM, 1998, KDOQI 2007)

❁ Pipeline: EPO-pilletjes?

EPO: wat is het nu?

- EPO: nog altijd één van de grootste stappen voorwaarts voor de 'nierpatient' ...

😊 **VRIEND** 😊

- ... maar mirakels bestaan niet en 'trop is teveel'!



Hartelijk dank voor uw aandacht, evt begrip en medeleven!

The EPO pages

- KDOQI anaemia update

http://www.kidney.org/professionals/kdoqi/guidelines_anemia/cpr21.htm

- Review EPO fysiologie

Konstantinopoulos, *biochimica biophysica acta* 2007, 1776: 1

Foley RN, *heart fail rev* 2008, 13: 405

Hardee, *clin cancer res*, 2006, 12: 332

- Kritisch benaderen anemie-comorbiditeit relatie

Zarychanski R, *CMAJ*, 2008, 179: 333

Vaziri ND, *NDT*, 2008, 4: 436

- EPO-onco, de 'ontnuchtering'

Blau C, *Stem Cells*, 2007, 25: 2094

Bennet C, *JAMA*, 2008, 299: 914