Karolinska Institutet

Anemia Update

Peter Bárány
Department of Renal Medicine/ Karolinska University Hospital and Division of Renal Medicine
Department of Clinical Science, Intervention and Technology
Karolinska Institutet, Stockholm, Sweden

Anemia Update

- Target Hb – TREAT study
- Functional iron deficiency - Hepcidin
- Biosimilar epoetins

Anemia is Associated with Poor Survival of Patients with CKD

- Dynamic, retrospective cohort study among 8761 patients with CKD at Kaiser Permanente Northwest
- Assessment of outcomes
  - Death
  - Cardiovascular (CV) hospitalization
  - End-stage renal disease (ESRD)

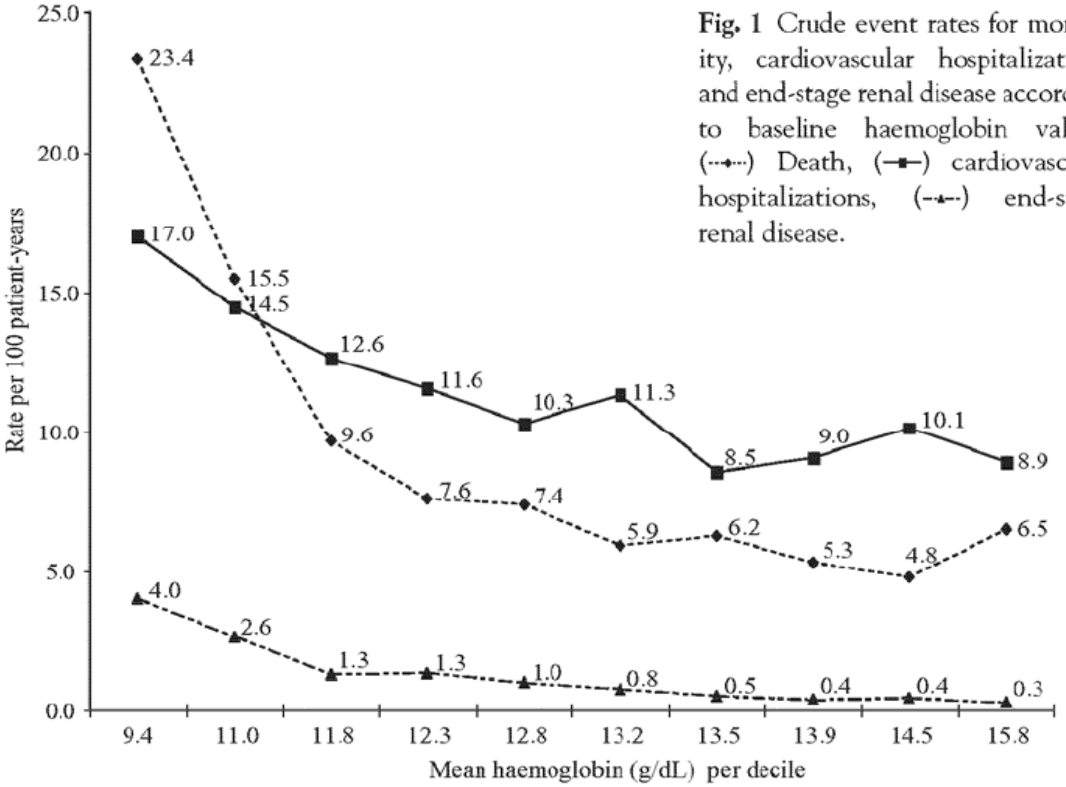
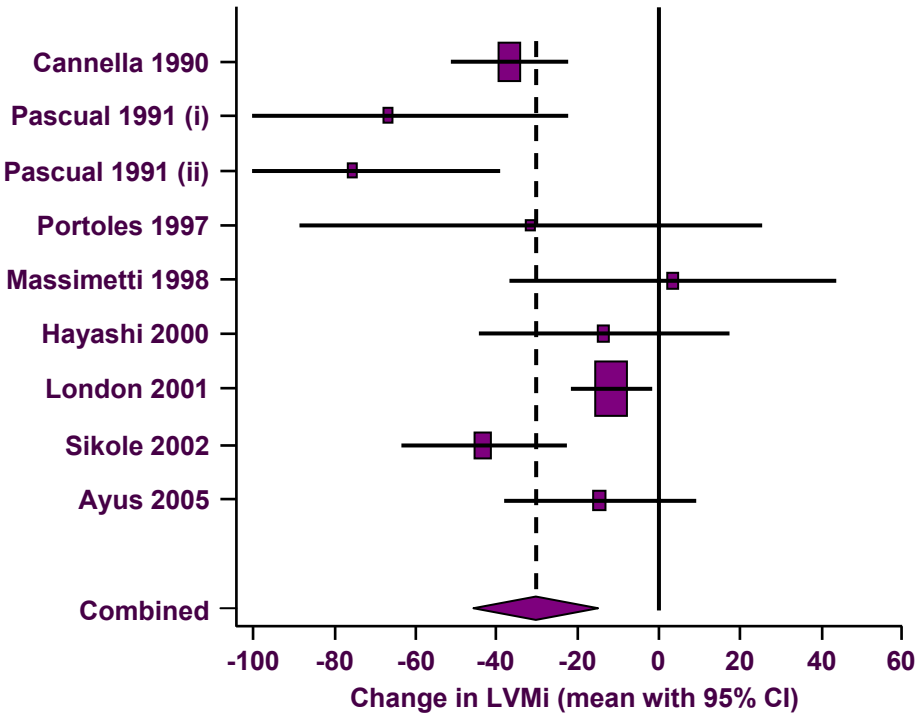


Fig. 1 Crude event rates for mortality, cardiovascular hospitalizations and end-stage renal disease according to baseline haemoglobin values. (--◆--) Death, (—■—) cardiovascular hospitalizations, (--▲--) end-stage renal disease.

1. Fishbane S. *Heart Fail Clin* 2008;4:401–410; 2. Thorp ML et al. *Nephrology* 2009;14:240–246; 3. Kovesdy CP et al. *Kidney Int* 2006;69:560–564; 4. Hörl WH et al. *Nephrol Dial Transplant* 2007;22(suppl 3):iii20–iii26; 5. Locatelli et al. *Nephrol Dial Transplant* 2004;19(suppl 2):ii2–ii5; 6. Gouva C et al. *Kidney Int* 2004;66:753–760

Patients with Severe Anemia have a Substantial Improvement in Cardiac Function When Targeted to an Hb ≤ 12 g/dL

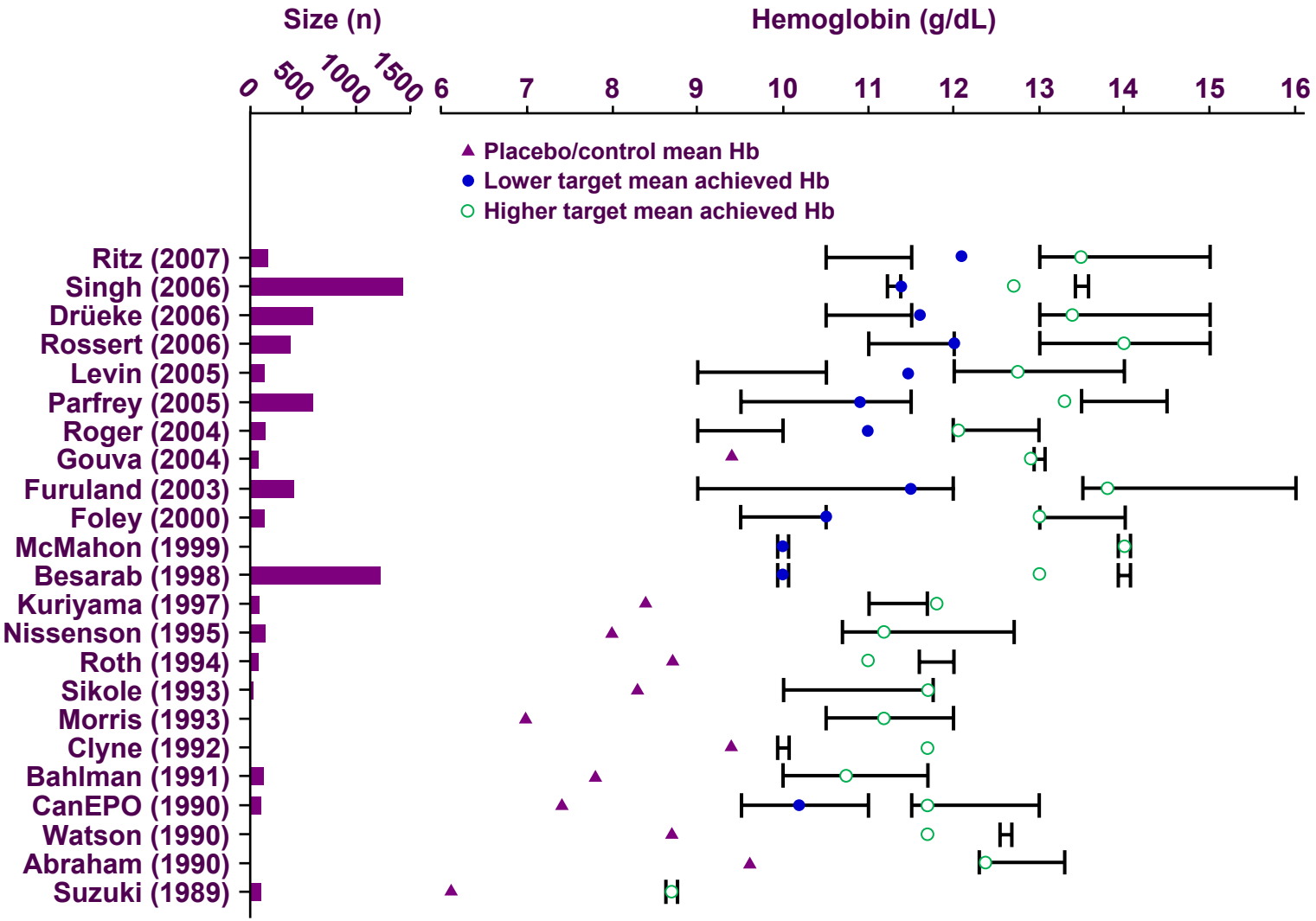
- Systematic review of studies relating ESA therapy and cardiac outcomes
  - January 1990–February 2007
  - 15 unique studies
  - 1731 CKD and ESRD patients
  - Anemia at baseline defined as;
    - Severe: Hb <10 g/dL
    - Moderate: Hb ≥10 g/dL <12 g/dL
  - Target Hb
    - Low: Hb ≤12 g/dl or ≤Hct 36%
    - High: Hb >12 g/dl or >Hct 36%



Patients with severe anemia had a substantial improvement in LVMi when assigned to a target Hb 12 g/dl

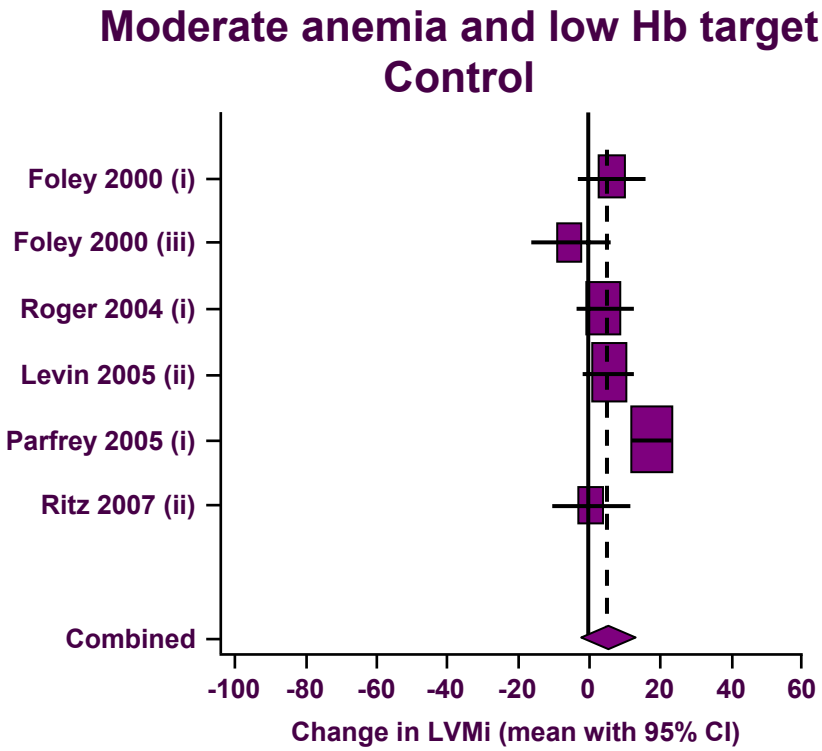
Parfrey PS et al. *Clin J Am Soc Nephrol* 2009;4:755–762

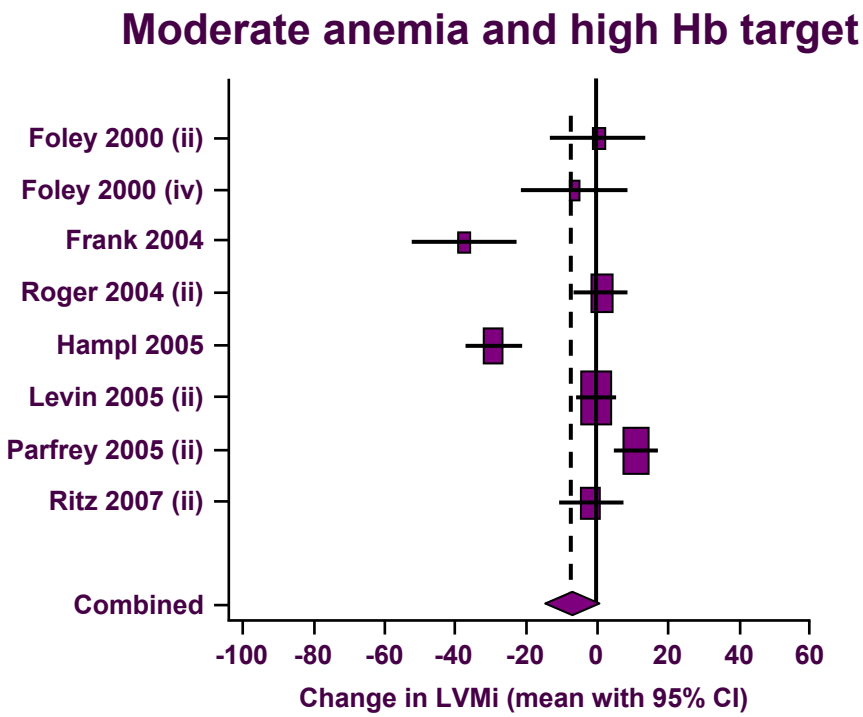
Studies Comparing Different Target Hb in Chronic Kidney Disease Patients with Anemia



KDOQI™. *Am J Kidney Dis* 2007;50:471–530

Correction of Moderate Anemia Has No Effect on LVMi

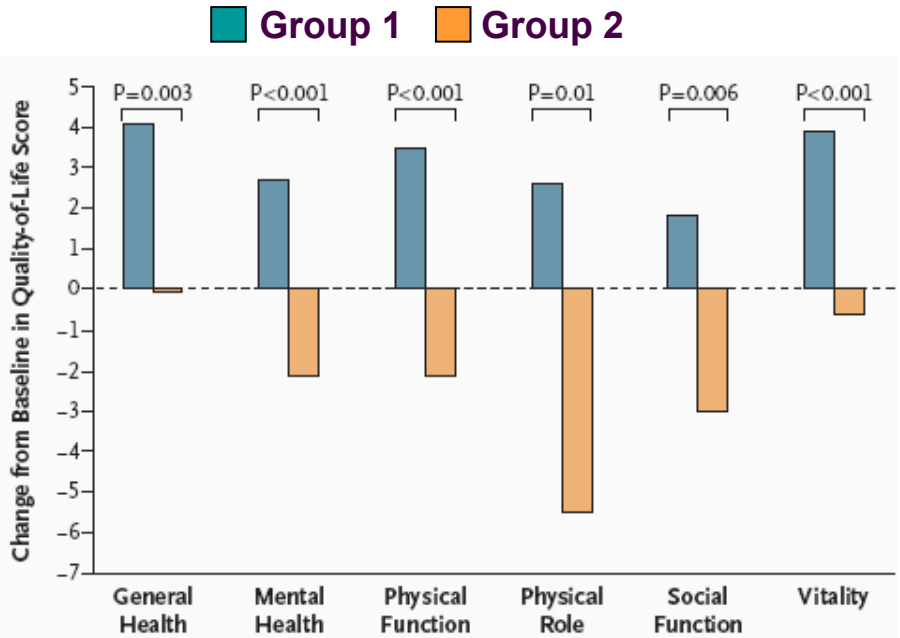




Patients with moderate anemia had no improvement in LVMi, irrespective of target Hb

Parfrey PS et al. *Clin J Am Soc Nephrol* 2009;4:755–762

Higher Hb Targets are Associated with Improvements in QoL Parameters



- CV risk reduction by early anemia treatment with epoetin beta (CREATE) study
  - 603 patients with CKD and anemia treated with ESA
  - Randomized to Hb target of:
    - 13–15 g/dL (group 1)
    - 10.5–11.5 g/dL (group 2)

Higher Hb targets in pre-dialysis CKD patients are associated with significant improvements in quality of life (QoL) parameters

1. Drüeke TB et al. *N Engl J Med* 2006;355:2071–2084; 2. Levin A. *Nephrol Dial Transplant* 2007;22:309–312

Four Large Trials Have Examined the Efficacy and Safety of ESAs to Achieve High or Low Hb Targets

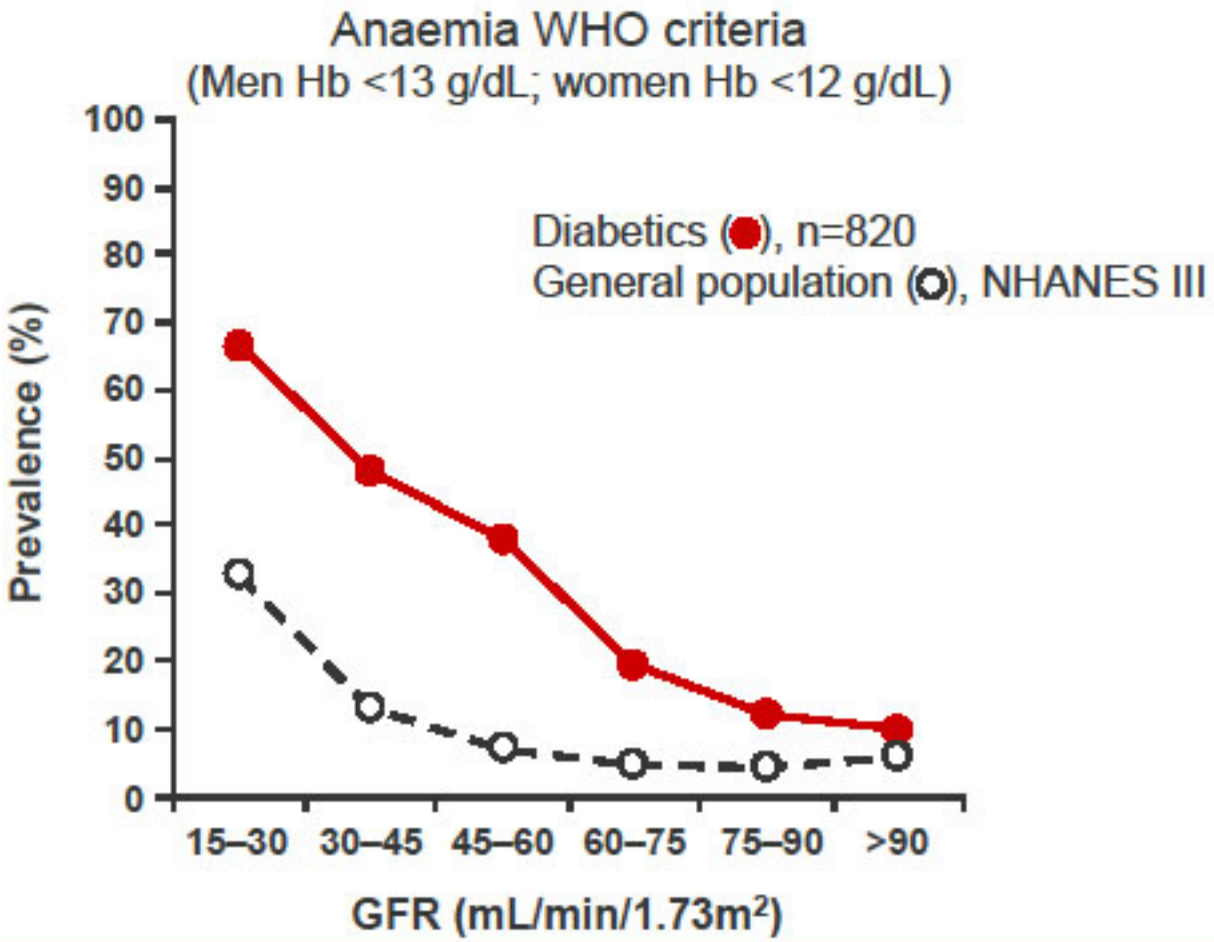
	Normal HCT	CHOIR	CREATE	TREAT
Region	USA	USA	Europe	Americas, Europe, Australia
N	1233	1432	603	4044
Patients	CKD5D with cardiac disease	CKD 3–4	CKD 3–4	CKD 3–4 with Type 2 DM
eGFR, ml/min/1.73 m^2	HD pts.	15-50	15-35	20-60
Target/achieved Hb, g/dL				
Low	Hct 30±3 %	11.3	10.5–11.5	Placebo/ESA at 9.0
High	Hct 42±3 %	13.5/12.6	13.0–15.0	13.0
Follow-up, months	30	16	35	48
Primary outcome	Death, MI	Death, MI, stroke, CHF	CV events	Death, CV events
HR (95 % CI)	1.3 (0.9-1.9)	1.34 (1.03-1.74)	0.78 (0.53-1.14)	1.05 (0.94-1.17)
ESA dose/week	≈150 IU/kg ≈475 IU/kg	≈5000 IU ≈11000 IU	≈2000 IU ≈5000 IU	≈0 ≈44 µg

TREAT

Trial to Reduce Cardiovascular Events With Aranesp® (Darbepoetin alfa) Therapy

Pfeffer MA, et al. Am J Kidney Dis. 2009;54:59-69.
Pfeffer MA, et al. N Engl Med. 2009;361:2019-2032.

Prevalence of anaemia is higher in diabetic patients versus normal population

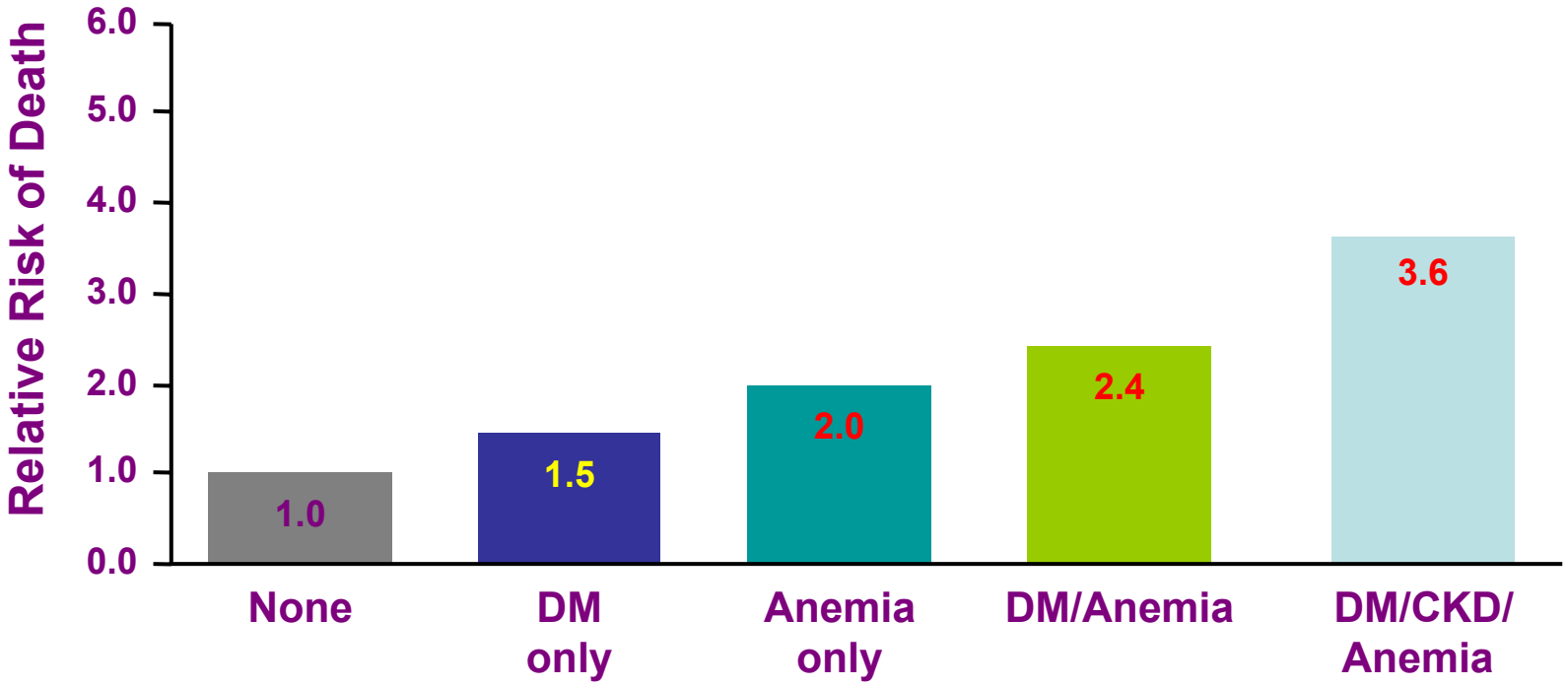


WHO, World Health Organization;
NHANES, National Health and Nutrition Examination Survey

Thomas MC et al. *Diabetes Care* 2003;26:1164–1169

TREAT Rationale

CKD, Diabetes and Anemia are Additive CV Risk Factors



Relative risk of death before end-stage renal disease over a 2-year follow-up in patients on Medicare with CHF, CKD, diabetes, and/or anemia

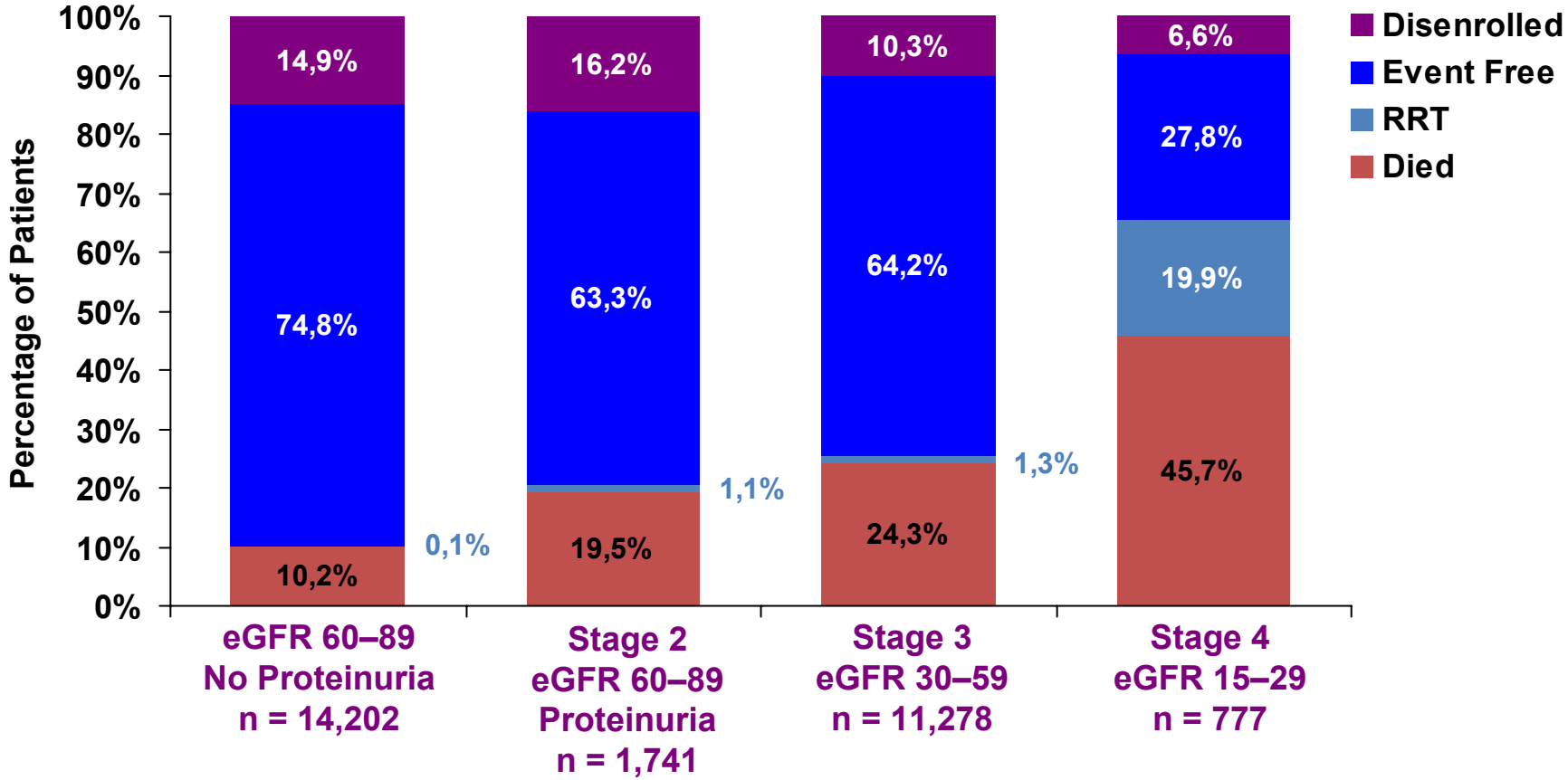
CHF = Congestive heart failure.
CKD = Chronic kidney disease.

Modified from Collins, AJ. *Adv Stud Med.* 2003;3(3C):S194-S197.

TREAT Rationale

CKD Patients Are More Likely to Die Than Progress to Renal Replacement Therapy

5-Year Follow-Up



CKD = chronic kidney disease; ESRD = end stage renal disease;
RRT = renal replacement therapy; eGFR = glomerular filtration rate mL/min/1.73 m^2

Keith D, et al. *Arch Int Med*. 2004;164:659-663.

TREAT: Trial to Reduce Cardiovascular Events With Aranesp® (Darbepoetin alfa) Therapy

Hypotheses:

Treatment of anemia with Aranesp® in subjects with chronic kidney disease (CKD) and type 2 diabetes mellitus decreases mortality and cardiovascular (CV) morbidity

Treatment of anemia with Aranesp® in subjects with CKD and type 2 diabetes mellitus will delay the progression to ESRD

Study Population

- Hb ≤ 11 g/dL
- eGFR 20-60 mL/min/1.73 m^2
- Type 2 DM

Design –
randomized (1:1), double blind, placebo-controlled

N ~ 2000 — Aranesp® (Target Hb 13 g/dL)

N ~ 2000 — Placebo (rescue if Hb < 9 g/dL)

Event-driven: :~1,203 patients with cardiovascular primary endpoint

Primary Endpoints

- **CV Endpoint:** Time to the first confirmed composite event, comprising all-cause mortality and CV events including myocardial ischemia, CHF, MI and CVA

- **Renal Endpoint:** Time to ESRD (end-stage renal disease) or all-cause mortality

Key Inclusion Criteria

- ≥ 18 years of age
- Clinical history of CKD (eGFR ≥ 20 mL/min/1.73 m^2 and ≤ 60 mL/min/1.73 m^2 during screening)
- Clinical history of Type 2 diabetes mellitus
- Hemoglobin ≤ 11 g/dL
- Transferrin saturation ≥ 15%*

*** Originally one TSAT level ≥ 15% was required during the screening period. This was changed in Amendment 2 to require that the mean of two TSAT levels during the screening period be ≥ 15%.**

Patients Enrolled and Time on Study
n = 4038

U.S.A.	2,339 (57.8%)	Australia	58
Poland	213	Latvia	51
Brazil	190	U.K.	49
Canada	176	Romania	47
Mexico	150	Bulgaria	28
Germany	135	Portugal	17
Russia	117	Estonia	16
Czech Republic	96	Chile	14
Italy	87	Slovenia	12
Argentina	84	France	11
Hungary	70	Denmark	10
Slovakia	65	Austria	3

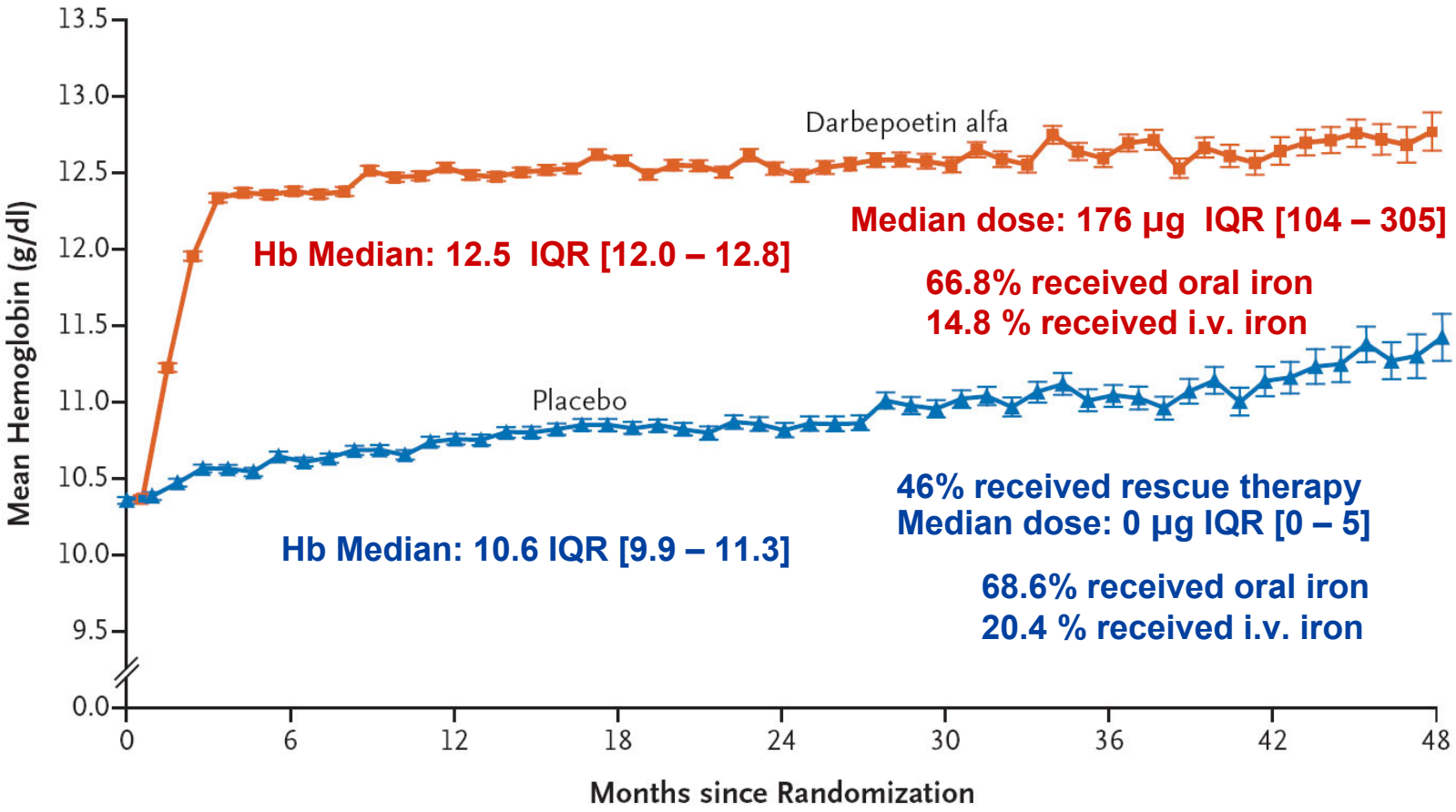
Median Follow-up: 29.1 months (9941 patient-years)

Baseline Characteristics

Variable %	Darbepoetin alfa N = 2012	Placebo N = 2026	*P*-value
Age (years)	68	68	0.22
Women	58.5	56.0	0.10
Known duration of DM (years)	15.3	15.5	0.94
CVD history	64.0	66.9	0.05
CAD	43.2	45.5	0.16
Heart failure	31.5	35.2	0.01
Myocardial infarction	18.4	18.3	0.95
Stroke	11.5	10.7	0.41
PAD	21.2	20.8	0.73
Systolic BP mmHg	136	135	0.25
Diastolic BP mmHg	71	70	0.55
eGFR mL/min/1.73 m^2	34	33	0.03
Hemoglobin A1c %	7.0	6.9	0.02
Baseline Hb g/dL	10.5	10.4	0.15
Transferrin saturation %	23	23	0.80

Modified from Pfeffer MA, et al. *N Engl J Med* 2009;361:2019-2032

Mean Hemoglobin Levels



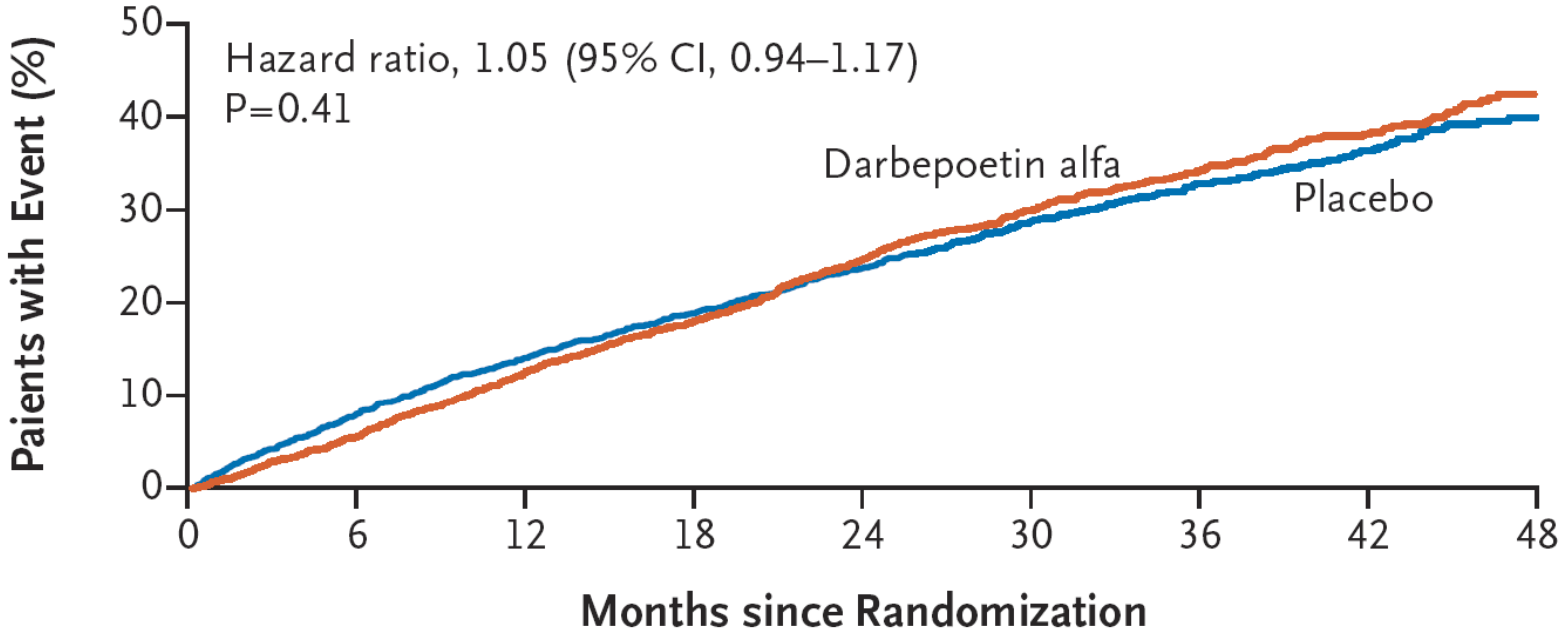
No. of Patients									
Darbepoetin alfa	2004	1768	1503	1300	946	635	404	253	97
Placebo	2019	1742	1460	1221	887	620	356	216	79

Pfeffer MA, et al. N Engl Med. 2009;361:2019-2032.

Composite and Component Endpoints

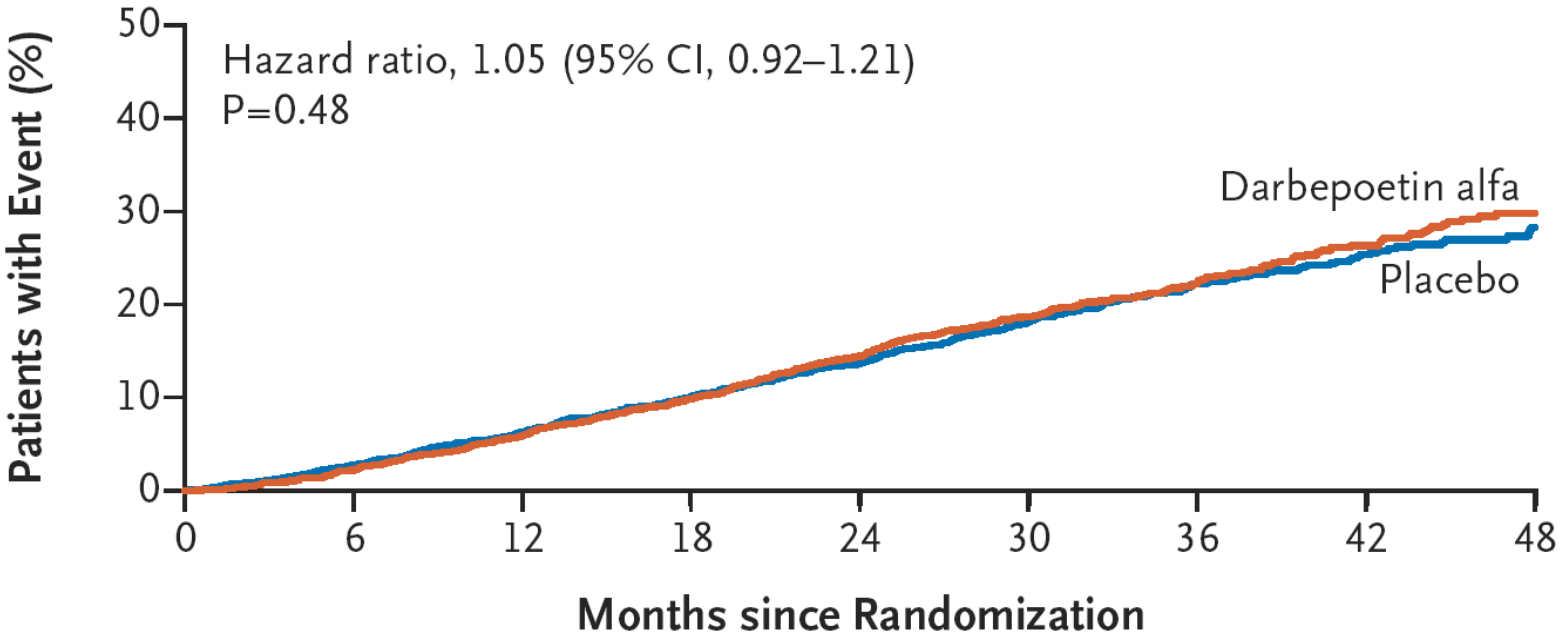
	Darbepoetin alfa (n = 2,012)	Placebo (n = 2.026)	Hazard Ratio (95% CI)	P Value
End points	Number (%)	Number (%)		
Primary composite cardiovascular endpoint	632 (31.4)	602 (29.7)	1.05 (0.94–1.17)	0.41
Death from any cause	412 (20.5)	395 (19.5)	1.05 (0.92–1.21)	0.48
Myocardial infarction	124 (6.2)	129 (6.4)	0.96 (0.75–1.22)	0.73
Stroke	101 (5)	53 (2.6)	1.92 (1.38–2.68)	< 0.001
Heart failure	205 (10.2)	229 (11.3)	0.89 (0.74–1.08)	0.24
Myocardial ischemia	41 (2)	49 (2.4)	0.84 (0.55–1.27)	0.40
Primary composite renal endpoint (ESRD or death)	652 (32.4)	618 (30.5)	1.06 (0.95–1.19)	0.29
ESRD	338 (16.8)	330 (16.3)	1.02 (0.87–1.18)	0.83
Additional adjudicated endpoints				
Death from cardiovascular causes	259 (12.9)	250 (12.3)	1.05 (0.88–1.25)	0.61
Cardiac revascularization	84 (4.2)	117 (5.8)	0.71 (0.54–0.94)	0.02

Cardiovascular Composite End Point



No. at Risk									
Darbepoetin alfa	2012	1882	1717	1515	1180	817	551	318	130
Placebo	2026	1836	1687	1487	1178	834	529	319	122

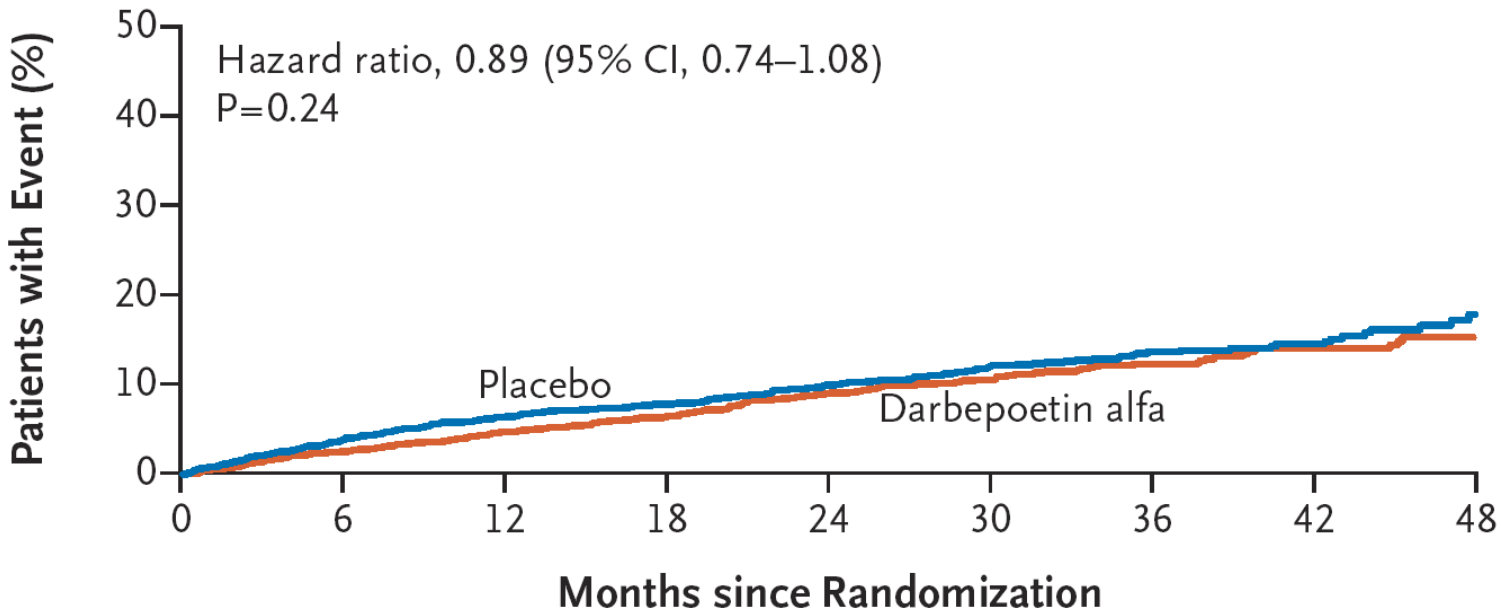
Death from Any Cause



No. at Risk

Darbepoetin alfa	2012	1947	1847	1659	1337	945	655	386	164
Placebo	2026	1943	1839	1652	1345	970	636	385	156

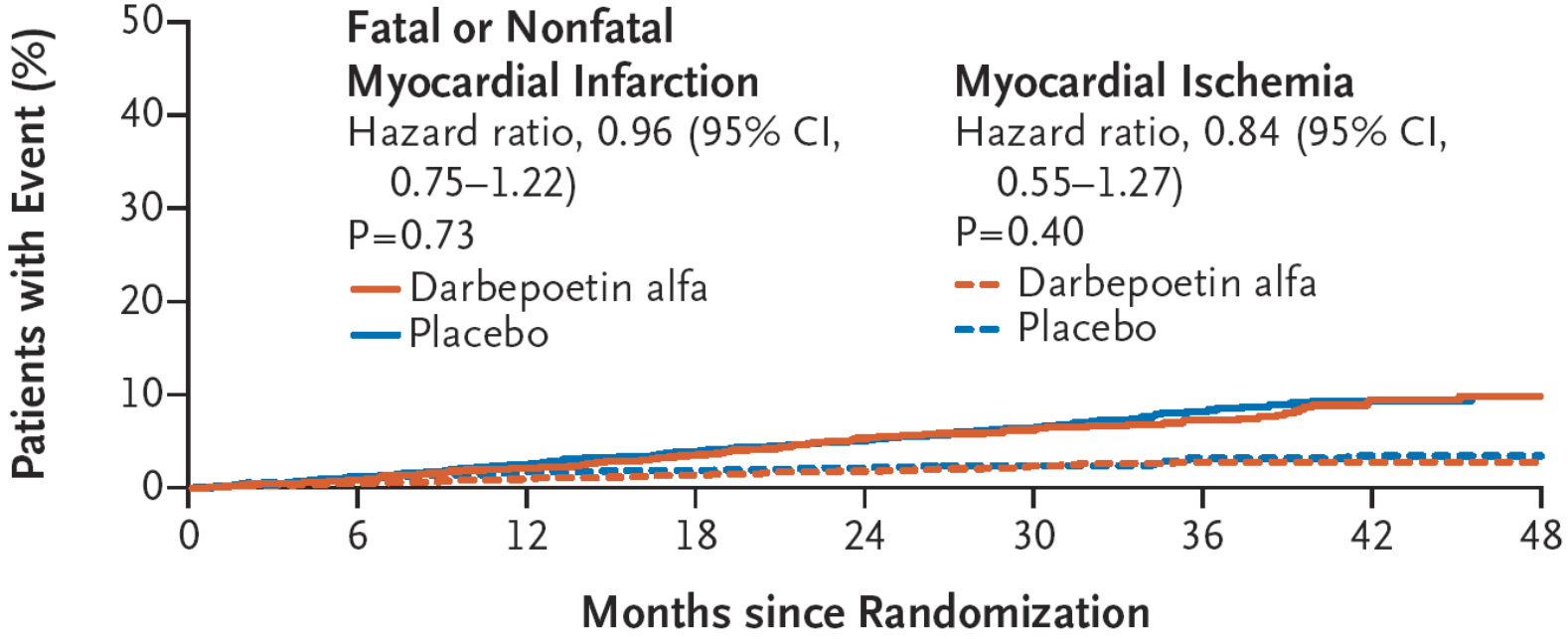
Fatal or Nonfatal Congestive Heart Failure



No. at Risk

Darbepoetin alfa	2012	1890	1742	1525	1191	819	555	319	136
Placebo	2026	1859	1702	1495	1187	835	519	307	115

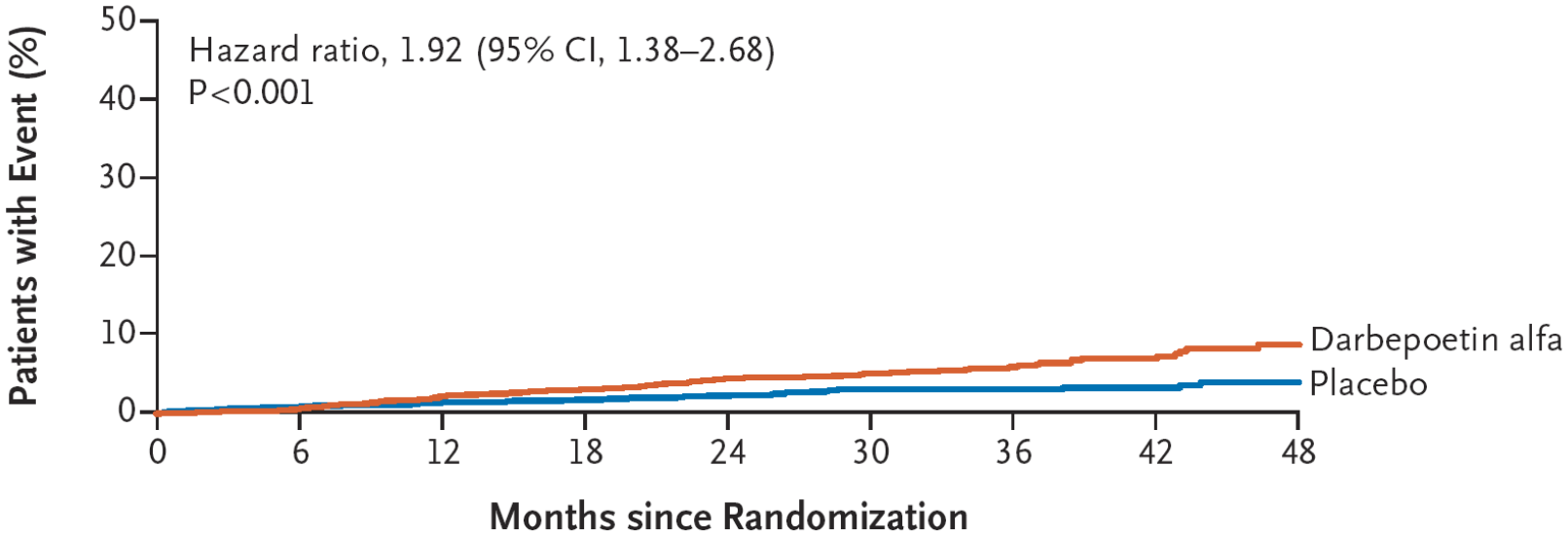
Fatal or Nonfatal Myocardial Infarction and Myocardial Ischemia



No. at Risk

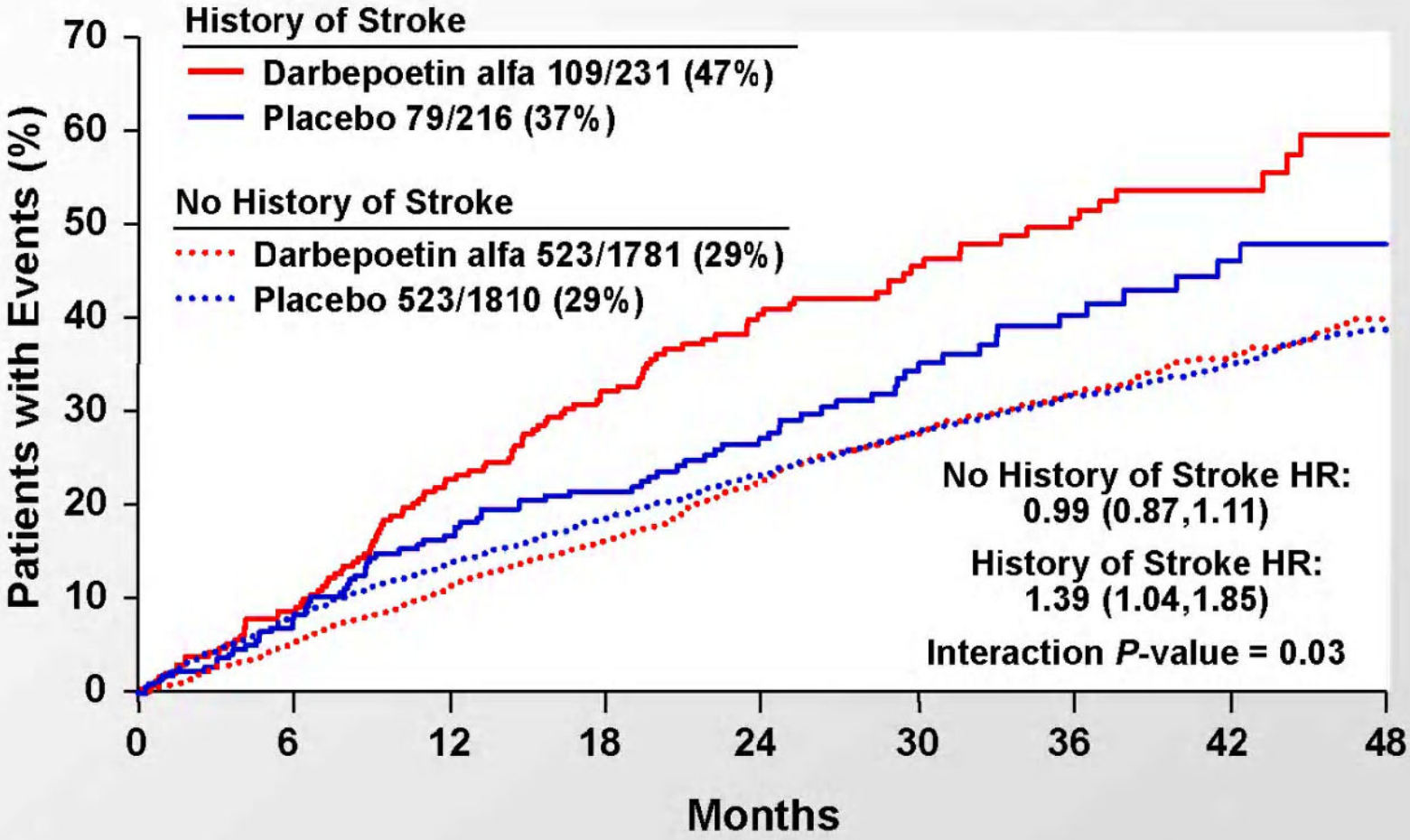
Fatal or Nonfatal Myocardial Infarction									
Darbepoetin alfa	2012	1920	1785	1566	1232	851	577	325	137
Placebo	2026	1907	1765	1550	1235	863	539	324	123
Myocardial Ischemia									
Darbepoetin alfa	2012	1924	1794	1583	1255	869	597	347	146
Placebo	2026	1906	1767	1561	1251	880	556	338	132

Fatal or Nonfatal Stroke

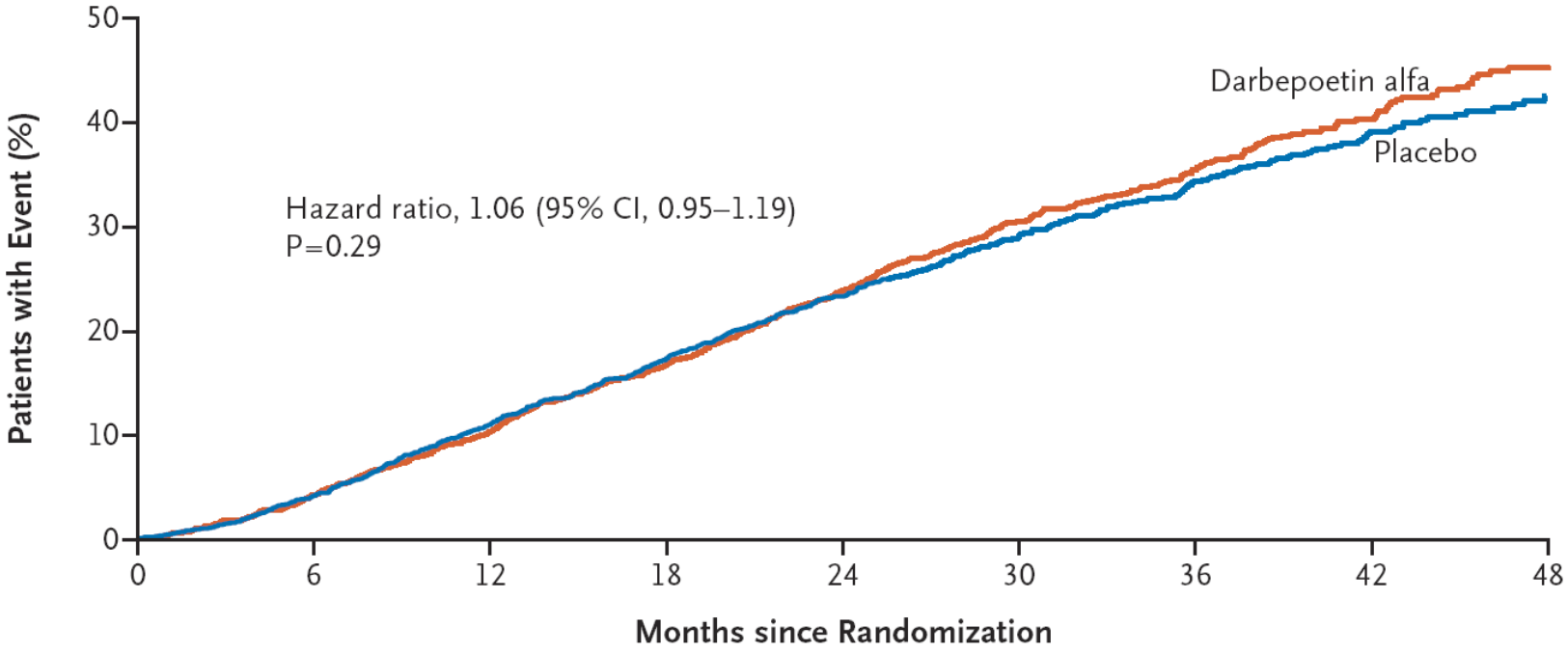


No. at Risk									
Darbepoetin alfa	2012	1923	1787	1581	1247	863	590	341	141
Placebo	2026	1914	1783	1575	1262	886	561	338	132

CV Composite by History of Stroke

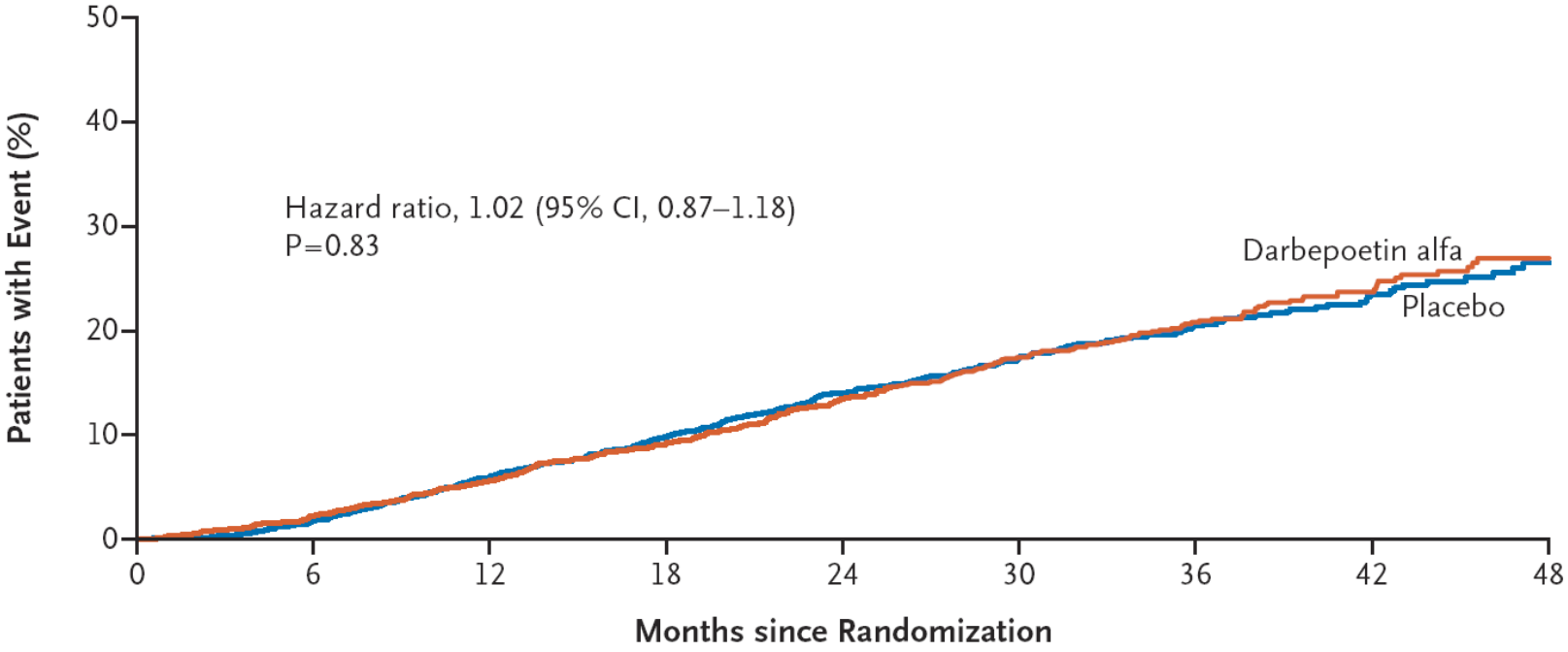


Renal Composite (ESRD or Death)



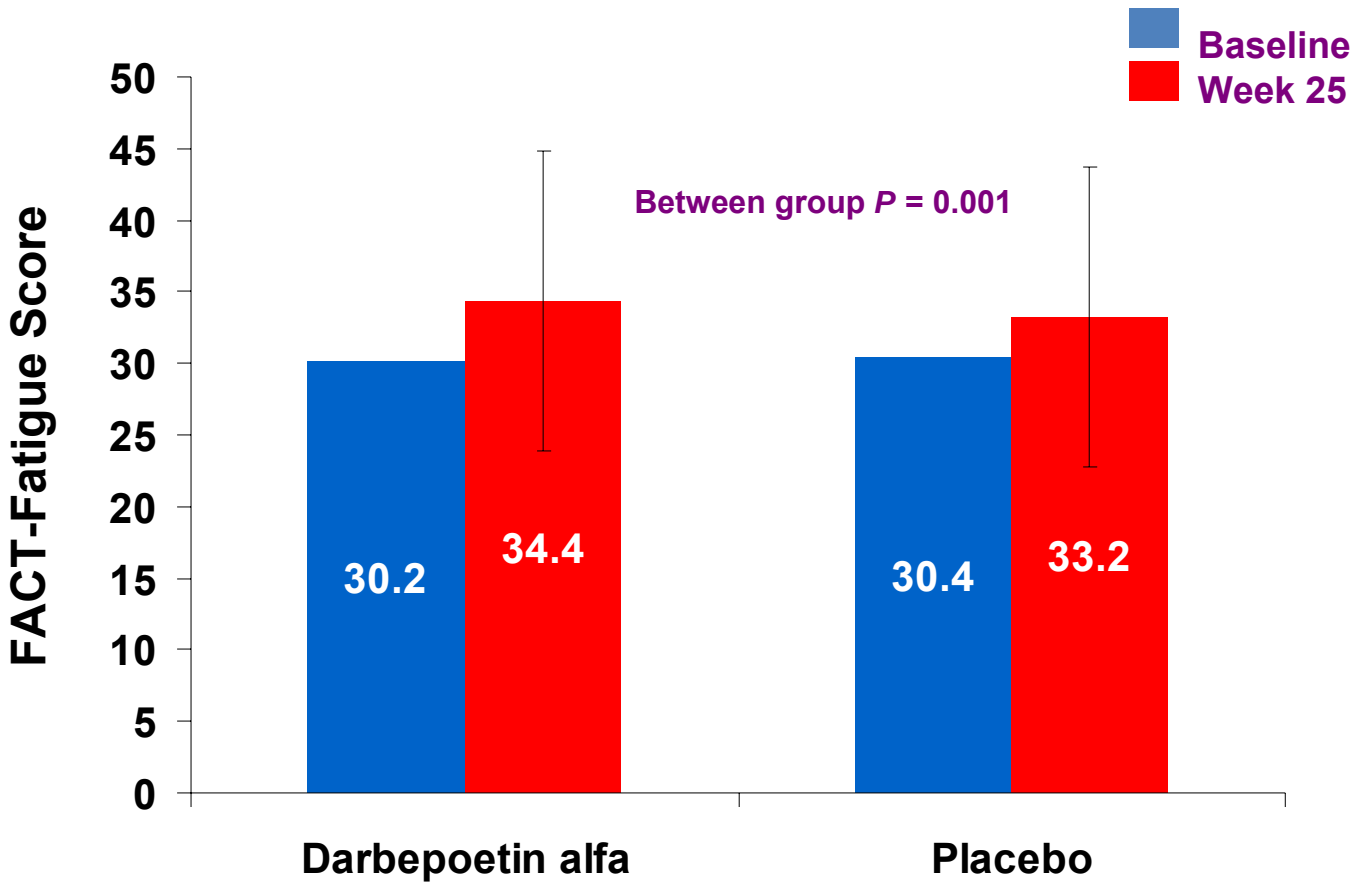
No. at Risk									
Darbepoetin alfa	2012	1910	1762	1544	1207	820	552	309	134
Placebo	2026	1915	1748	1519	1193	842	540	312	123

End-stage renal disease (ESRD)



No. at Risk									
Darbepoetin alfa	2012	1908	1755	1527	1187	802	535	296	129
Placebo	2026	1907	1729	1491	1162	811	513	292	115

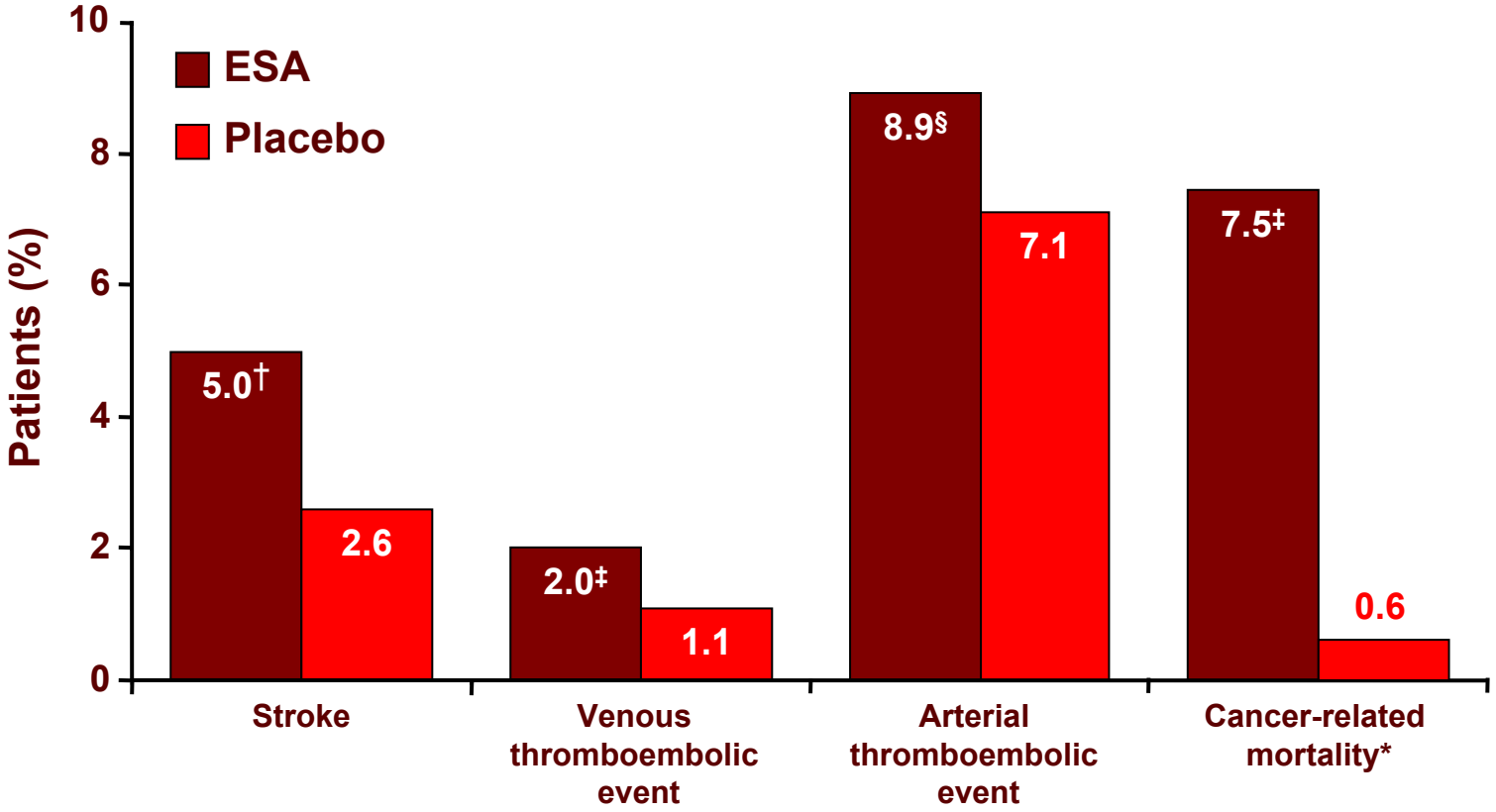
Change in the FACT-Fatigue Score From Baseline to Week 25



Other reported outcomes

- Red-cell transfusions:
  - 297 patients in the darbepoetin alfa group (14.8%)
  - 496 patients in the placebo group (24.5%)
  - hazard ratio = 0.56; 95% confidence interval [CI], 0.49 to 0.65; $P<0.001$

Safety Concerns in the TREAT Study



†, p<0.001 versus placebo
‡, p=0.02 versus placebo
§, p=0.04 versus placebo
*Amongst patients with a history of malignancy at baseline

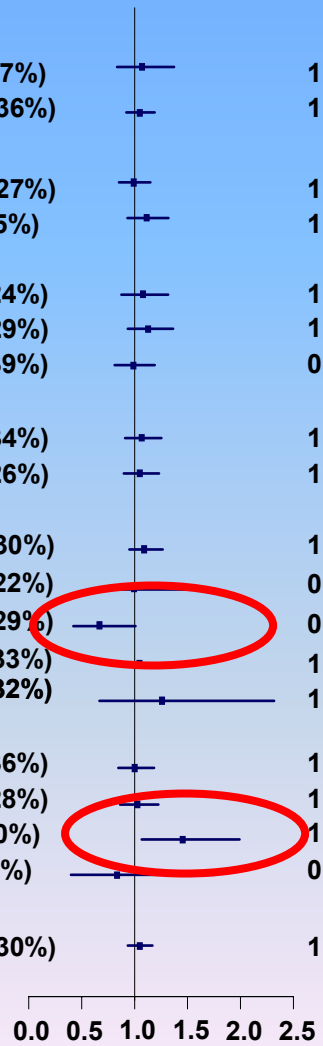
Pfeffer MA et al. *N Engl J Med* 2009;361:2019–2032

Post-Hoc Analysis of Patients With a Prior History of Cancer

	Darbepoetin alfa	Placebo	P-value
Overall			
Cancer-related AE	139/2012 6.9%	130/2026 6.4%	0.53
Deaths attributed to cancer	39/2012 1.9%	25/2026 1.2%	0.08
Subgroup analysis **Number of patients with history of malignancy at baseline (n = 348)**			
All cause mortality	60/188 31.9%	37/160 23.1%	0.13
Deaths attributed to cancer	14/188 7.4%	1/160 0.6%	0.002

Pre-defined subgroup analysis
Cardiovascular composite endpoint

Subgroup	Darbepoetin alfa	Placebo	Hazard Ratio (95% CI)
History of CVD			
No	138/725 (19%)	117/671 (17%)	1.08 (0.84,1.38)
Yes	494/1287 (38%)	485/1355 (36%)	1.06 (0.93,1.20)
Baseline Proteinuria (g/g creatinine)			
< 1	371/1324 (28%)	355/1315 (27%)	1.00 (0.86,1.16)
≥ 1	260/686 (38%)	247/711 (35%)	1.12 (0.94,1.33)
Age (years)			
< 65	196/777 (25%)	174/737 (24%)	1.08 (0.88,1.32)
65 - 74	228/706 (32%)	212/731 (29%)	1.13 (0.94,1.36)
≥ 75	208/529 (39%)	216/558 (39%)	0.99 (0.81,1.19)
Gender			
Male	305/834 (37%)	306/892 (34%)	1.07 (0.91,1.25)
Female	327/1178 (28%)	296/1134 (26%)	1.05 (0.90,1.23)
Region			
North America	416/1259 (33%)	380/1256 (30%)	1.10 (0.96,1.26)
Latin America	48/229 (21%)	47/209 (22%)	0.99 (0.66,1.48)
W Europe/AUS	36/172 (21%)	57/198 (29%)	0.66 (0.43,1.01)
E Europe	109/297 (37%)	98/301 (33%)	1.04 (0.79,1.37)
Russia	23/55 (42%)	20/62 (32%)	1.26 (0.69,2.31)
eGFR (mL/min/1.73m2)			
< 30	266/740 (36%)	286/801 (36%)	1.00 (0.85,1.18)
30 ≤ 44	258/881 (29%)	229/824 (28%)	1.03 (0.86,1.23)
45 ≤ 59	92/334 (28%)	68/347 (20%)	1.46 (1.06,1.99)
> 60	16/56 (29%)	18/52 (35%)	0.84 (0.40,1.75)
Overall	632/2012 (31%)	602/2026 (30%)	1.05 (0.94,1.17)



Adapted from: Supplementary Appendix to Pfeffer MA *et al.* *N Engl J Med* 2009;361. DOI: 10.1056/NEJMoa0907845

Author's conclusions

CONCLUSIONS

The use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who were not undergoing dialysis did not reduce the risk of either of the two primary composite outcomes (either death or a cardiovascular event or death or a renal event) and was associated with an increased risk of stroke. For many persons involved in clinical decision making, this risk will outweigh the potential benefits. (ClinicalTrials.gov number, NCT00093015.)

Pfeffer MA, et al. N Engl Med. 2009;361:2019-2032.

FDA comment

The NEW ENGLAND JOURNAL of MEDICINE

Interpretation of these findings is not straightforward.

Erythropoiesis-Stimulating Agents — Time for a Reevaluation

Ellis F. Unger, M.D., Aliza M. Thompson, M.D., Melanie J. Blank, M.D., and Robert Temple, M.D.

Epoetin alfa was approved in 1989 by the Food and Drug Administration (FDA) for the treatment of anemia associated with chronic kidney disease "to elevate or maintain the red blood cell level . . . and to decrease the need for transfusions." Although epoetin alfa and darbepoetin alfa, a related

ESAs to raise hemoglobin concentrations to higher targets improves clinical outcomes. Unfortunately

therapy were enrolled and randomly assigned either to receive increasing doses of epoetin alfa to reach and maintain a "normal" hematocrit value of 42±3% or to continue epoetin alfa therapy to maintain a hematocrit value of 30±3%. The trial was halted after an interim analysis because of an

Unger EF et al. *N Engl J Med* 2010;362:189–192

Anemia Update

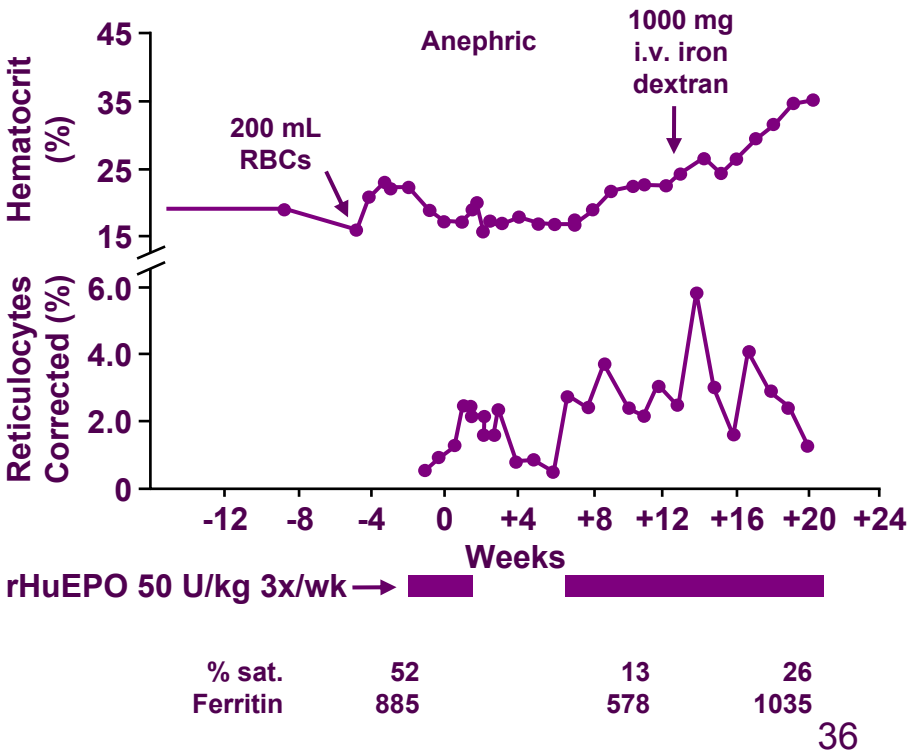
- Target Hb – TREAT study
- Functional iron deficiency - Hepcidin

Functional Iron Deficiency Was Described Early in Epoetin-treated CKD5D Patients

- Combined Phase I and II trial data for recombinant human erythropoietin (rHuEPO) in 25 HD patients with anemia
- rHuEPO administration induced a fall in TSAT and serum iron levels

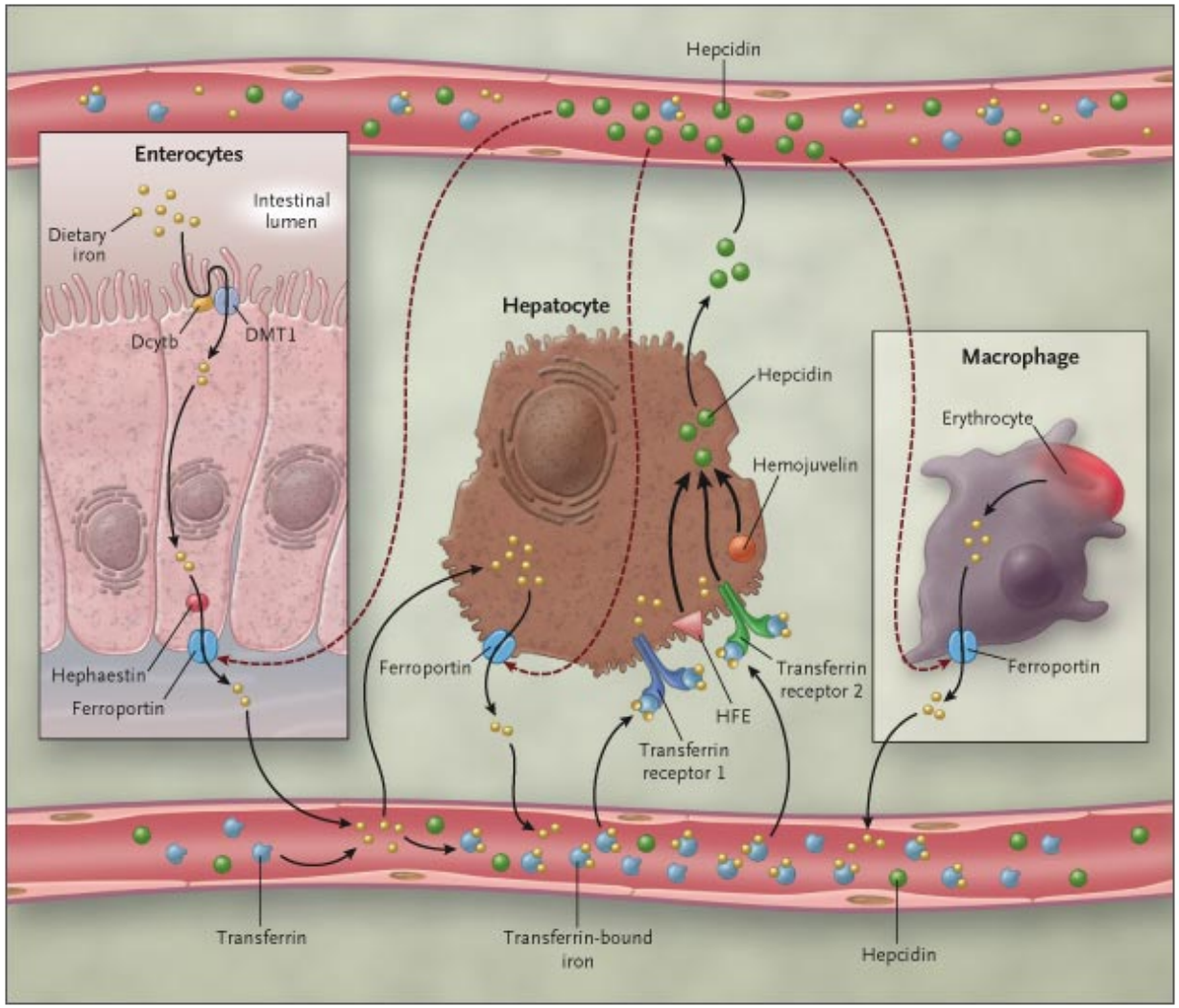
Dr. Joseph Eschbach
1933–2007

'One of the clinical features seen with this form of treatment was a state of functional iron deficiency'



Eschbach JW et al. *N Engl J Med* 1987;316:73–78

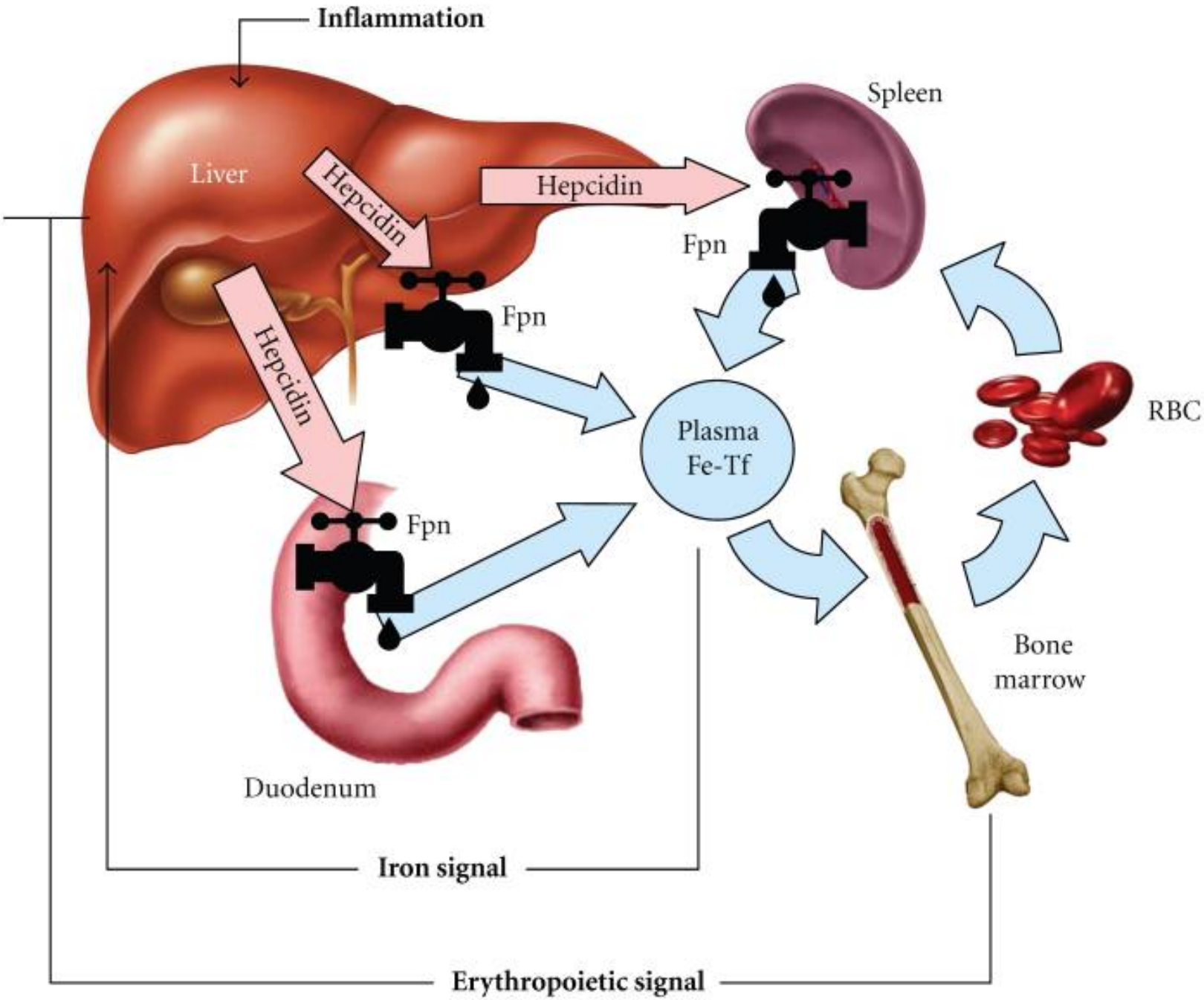
Iron Release From the Duodenum, Liver and Macrophages is Regulated by Hepcidin



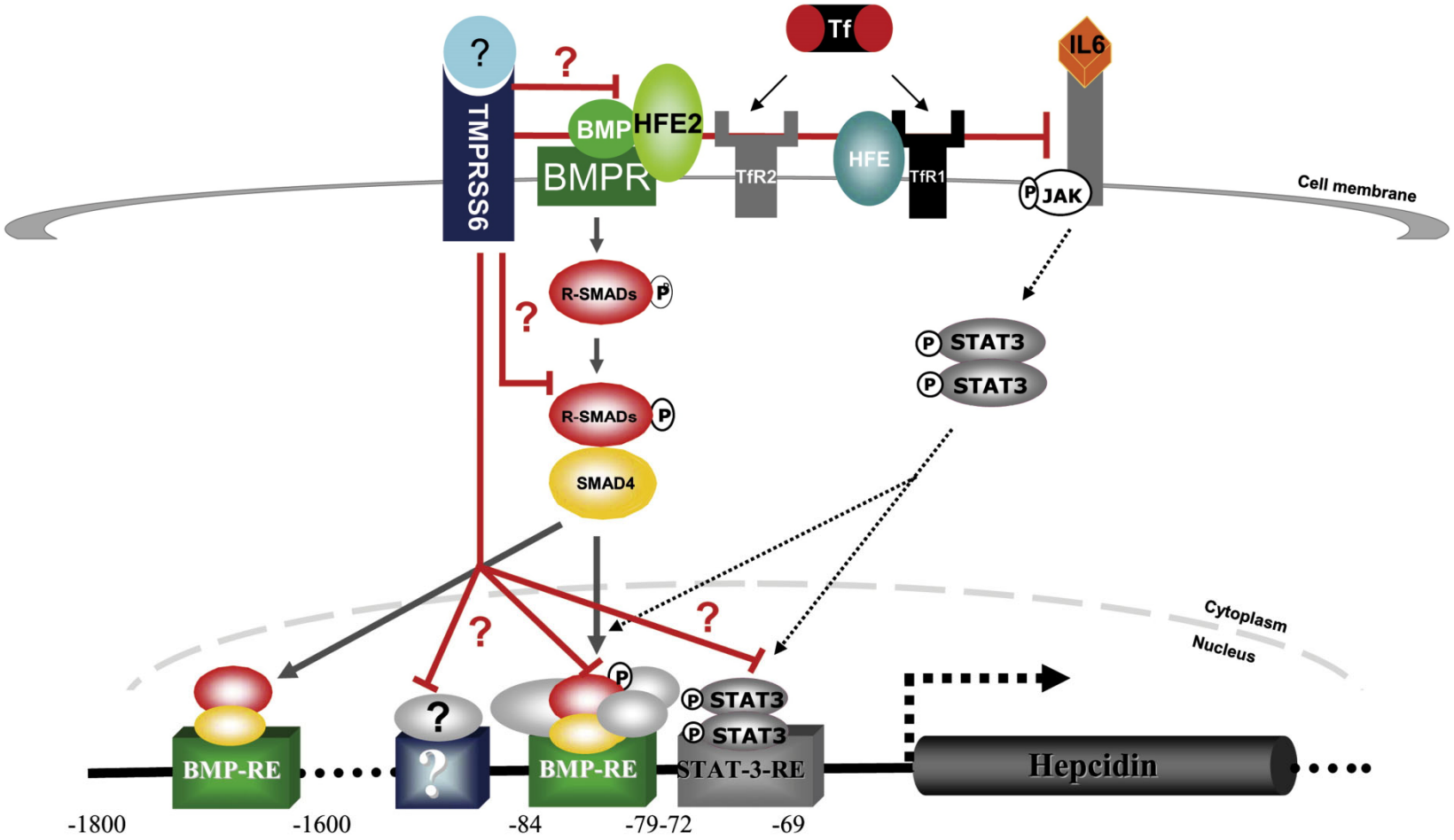
Interplay of Key Proteins in Iron Homeostasis.

1. **Iron is transported into the cell by divalent metal transporter 1 (DMT1),**
2. **Ferroportin mediates iron release into the circulation.**
3. **Hepcidin down-regulates the ferroportin-mediated release of iron from enterocytes, macrophages, and hepatocytes (dashed red lines).**

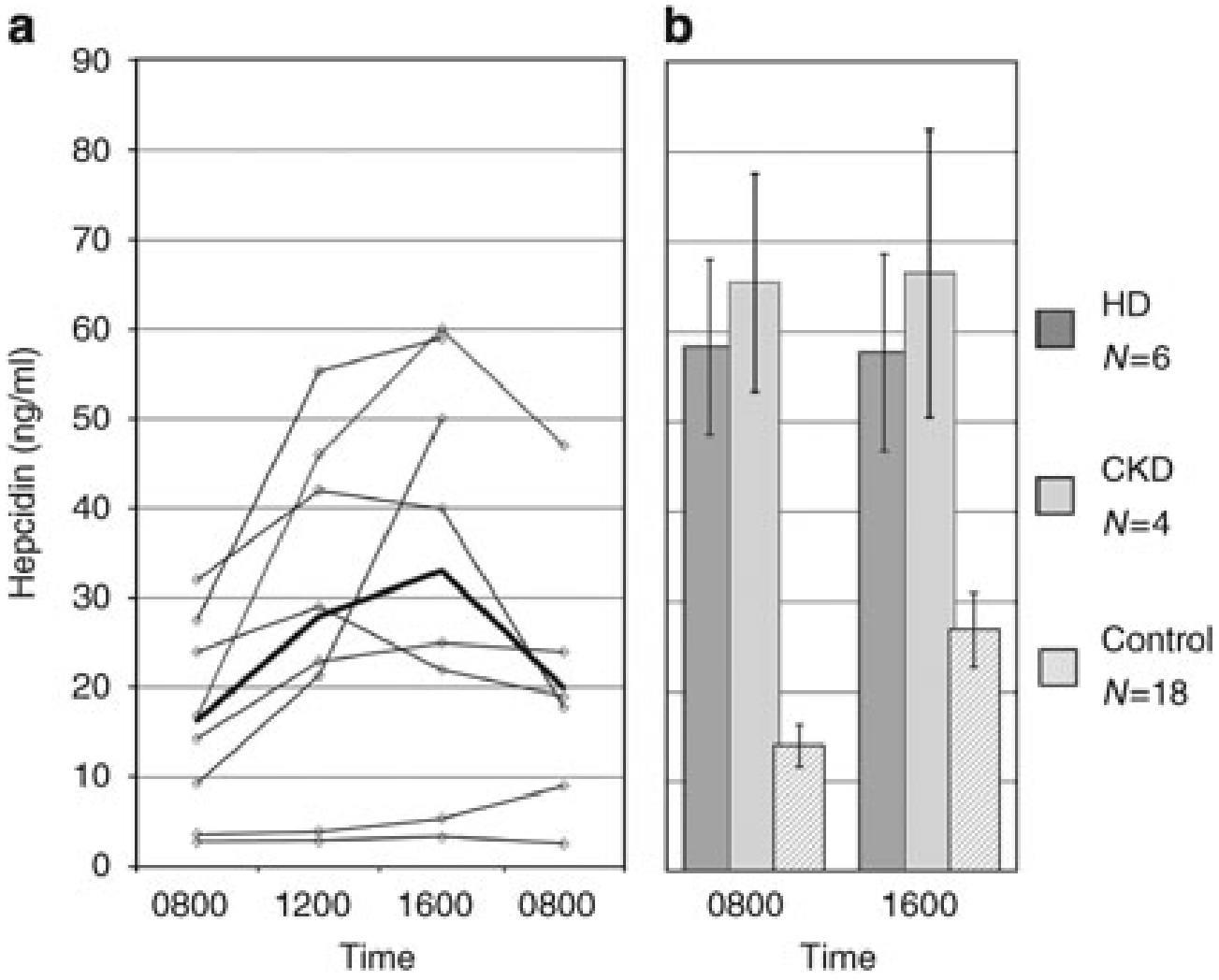
Fleming RE et al. *N Engl J Med* 2005;352:1741–1744


Inflammation
Liver
Hepcidin
Hepcidin
Hepcidin
Spleen
Fpn
Fpn
Fpn
Plasma
Fe-Tf
RBC
Bone
marrow
Duodenum
Iron signal
Erythropoietic signal

Hepcidin is Regulated at the Gene Level by Iron Levels and Inflammation

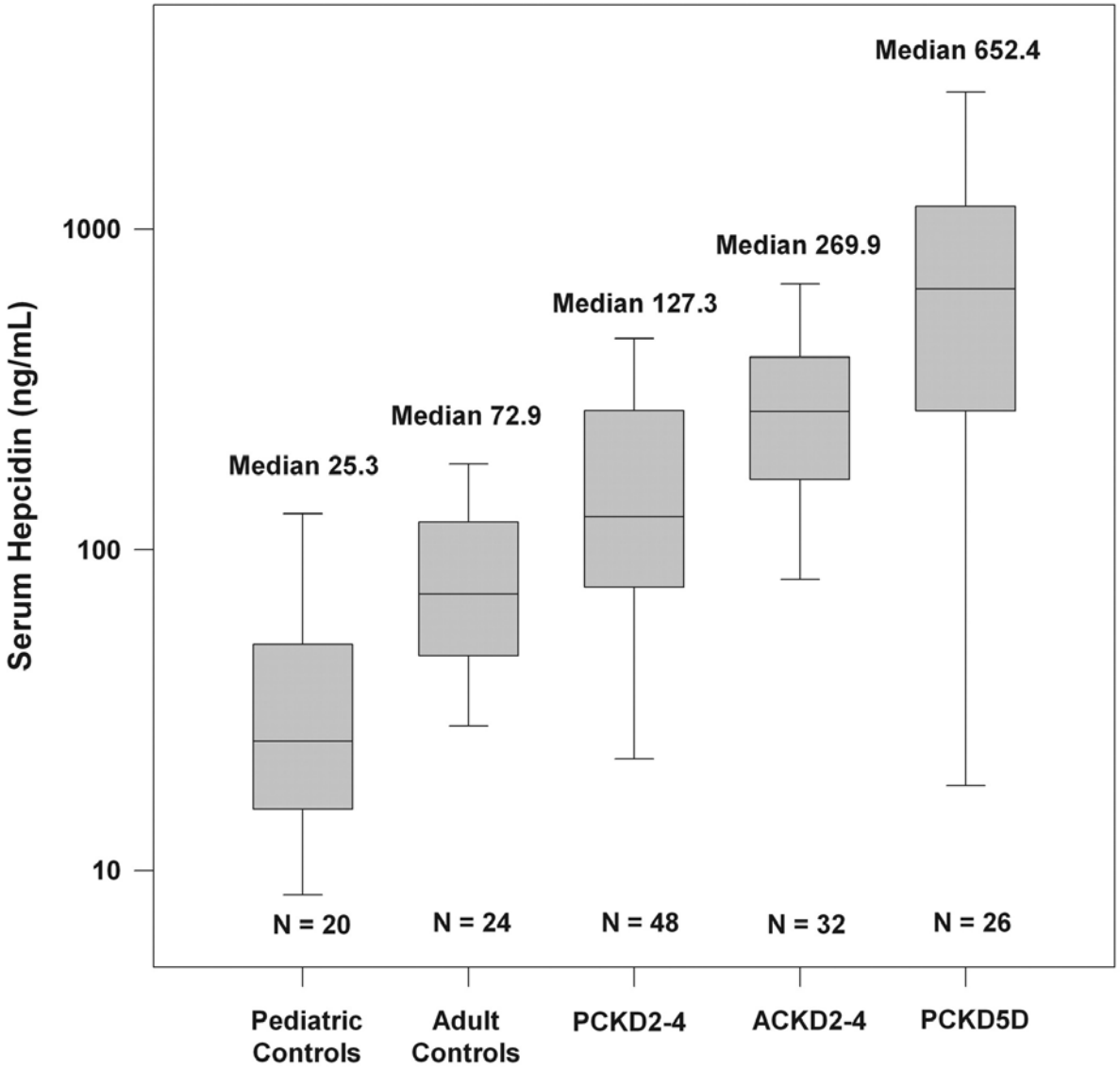


Muckenthaler MU. *Cell Metab* 2008;8:1–3



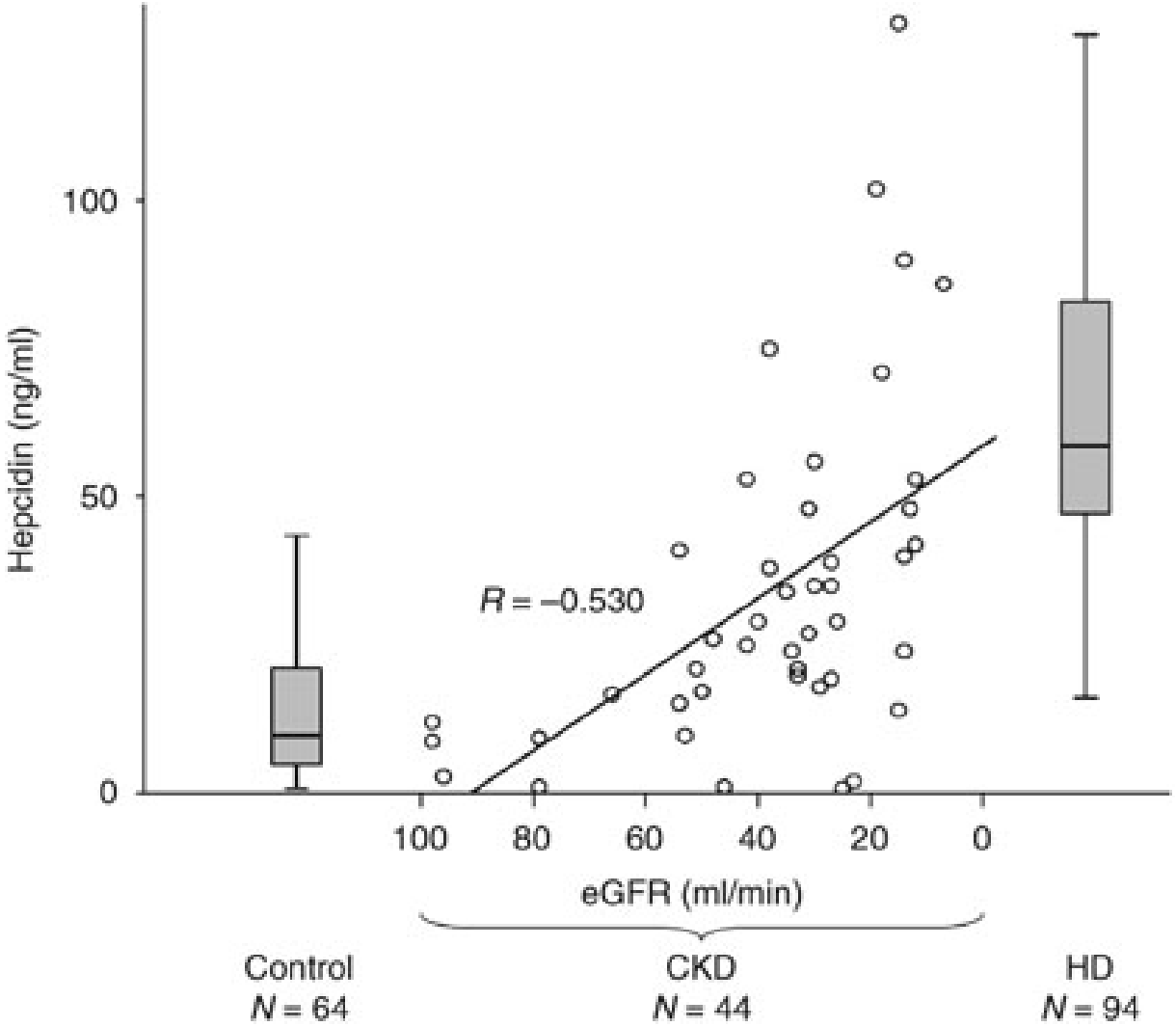
Ashby et al. *Kidney International*. 2009;75(9):976–981.

Serum hepcidin across chronic kidney disease (CKD) stages



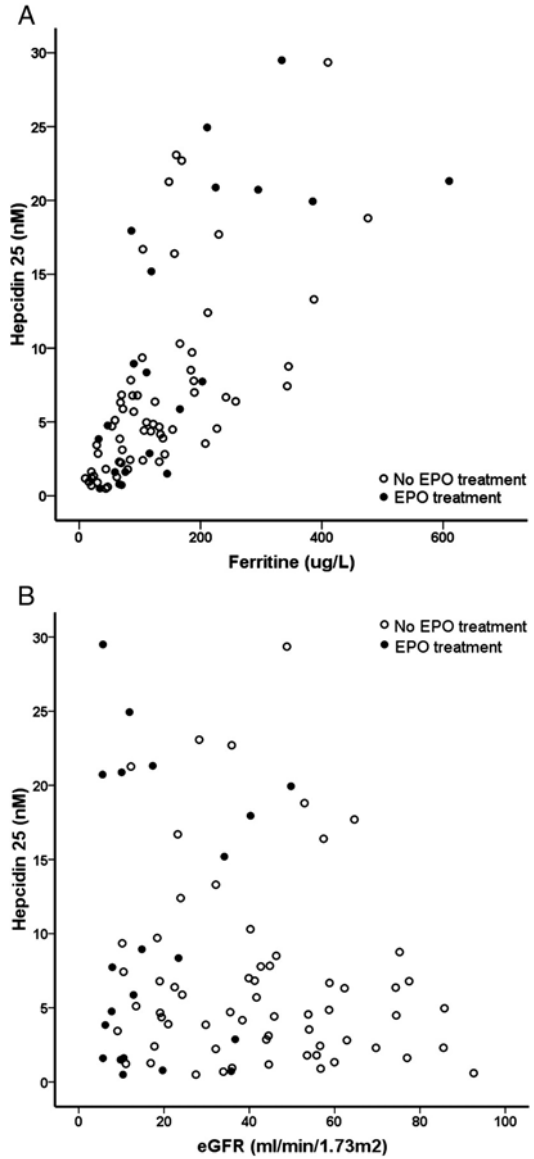
Zaritsky, J. et al. Clin J Am Soc Nephrol 2009;4:1051-1056

CJASN

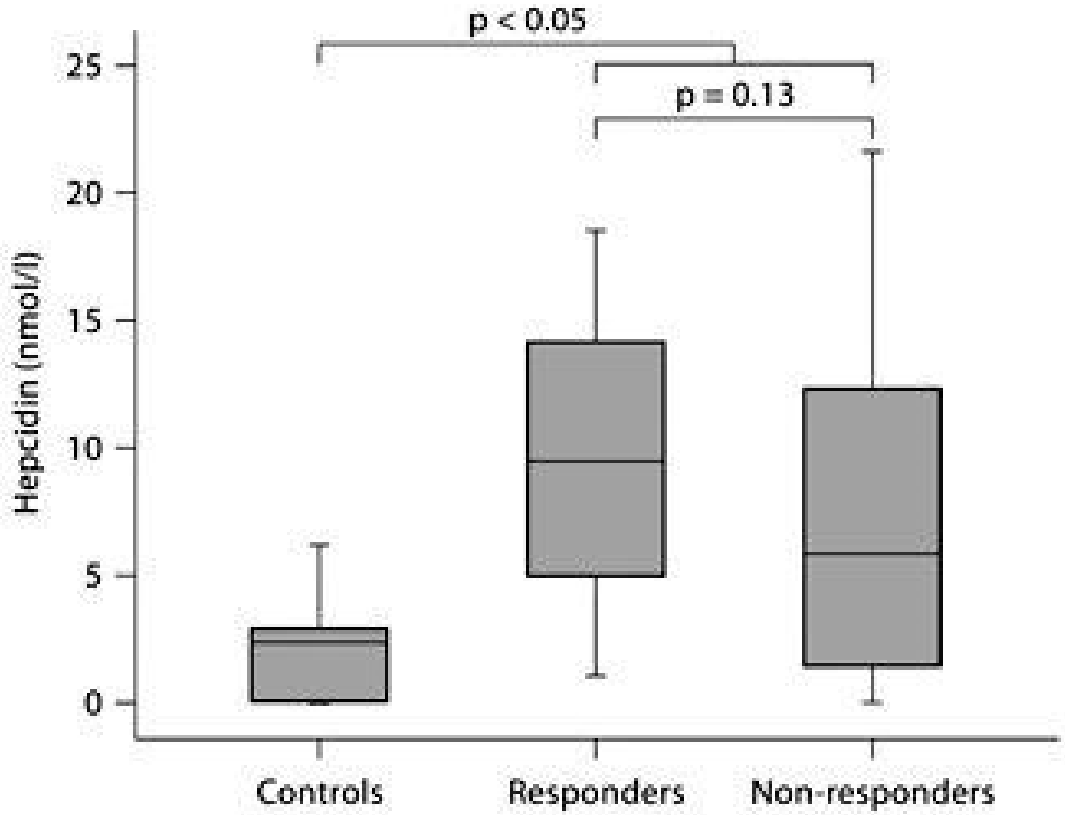


Ashby et al. *Kidney International*. 2009;75(9):976–981.

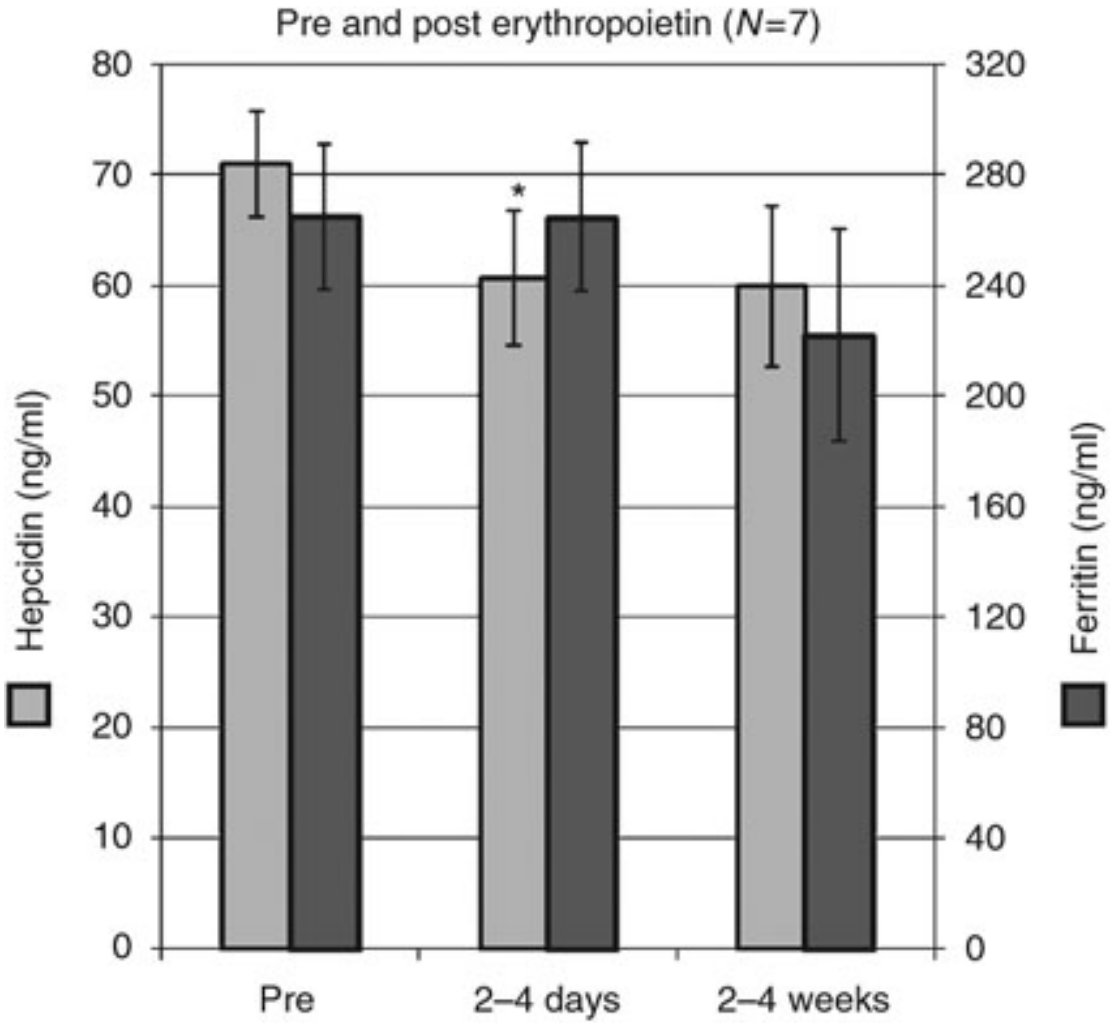
Relationship between serum hepcidin-25, serum ferritin and eGFR in patients with chronic kidney disease not requiring dialysis



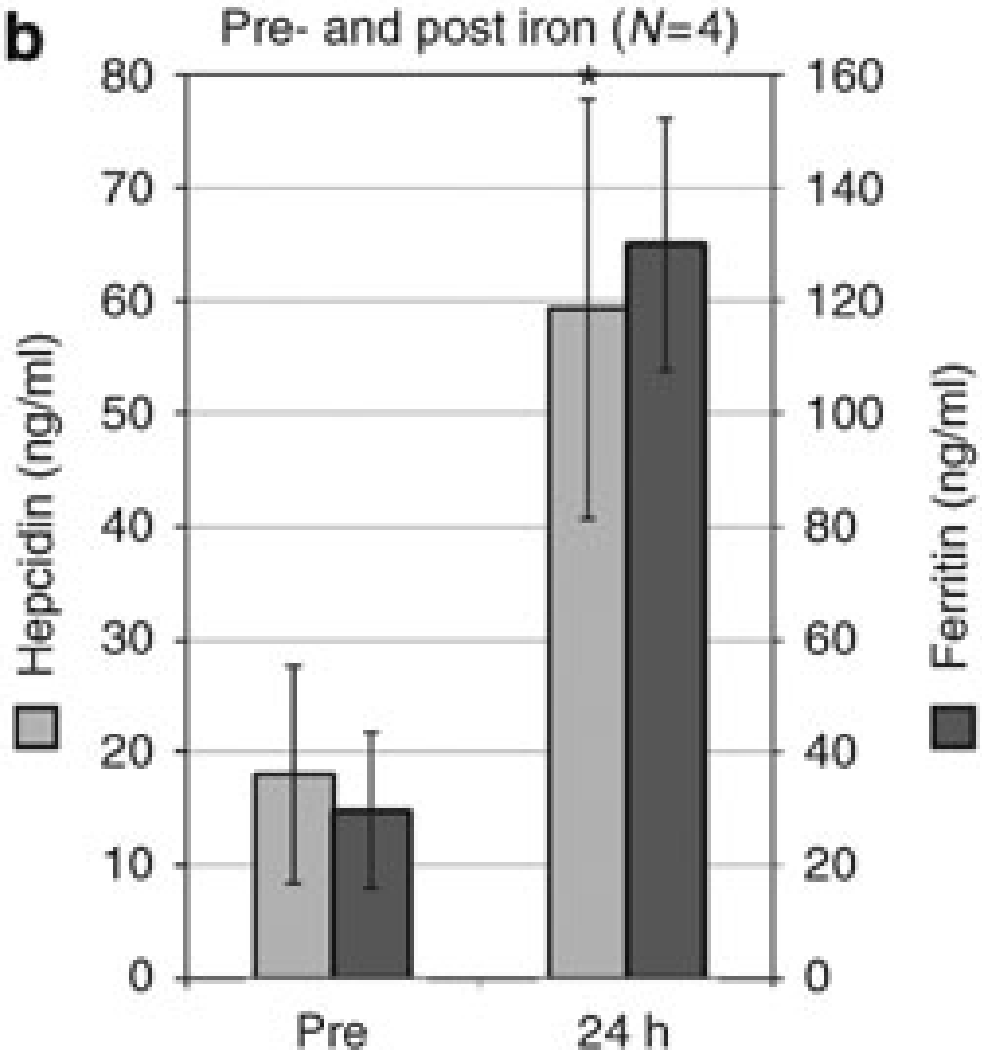
Peters, H. P.E. et al. Nephrol. Dial. Transplant. 2009 0:gfp546v1-546



Costa et al. Acta Haematol 2009;122:226–229



Ashby et al. *Kidney International*. 2009;75(9):976–981.



Ashby et al. *Kidney International*. 2009;75(9):976–981.

Anemia Update

- Target Hb – TREAT study
- Functional iron deficiency - Hepcidin
- Biosimilar epoetins

What is a biosimilar medicine?

- A biosimilar medicine is a medicine
  - →which is similar to a biological medicine that has already been authorised (the ‘biological reference medicine’). The active substance of a biosimilar medicine is similar to the one of the biological reference medicine.
  - →The name, appearance and packaging of a biosimilar medicine differ to those of the biological reference medicine.

What is the difference between biotech medicines and chemical medicines?

- Biotech medicines are made from living cells
  → Chemical medicines are made from chemical processes

- Biotech medicines are complex in structure
  → Chemical medicines have a simple and well-defined structure

- Because of the way they are expressed by living cells, biotech medicines contain a mixture of related molecules and are difficult to characterise
  → Chemical medicines, on the other hand, are easy to characterise

There are more than 150 biotechnology medicines on the market

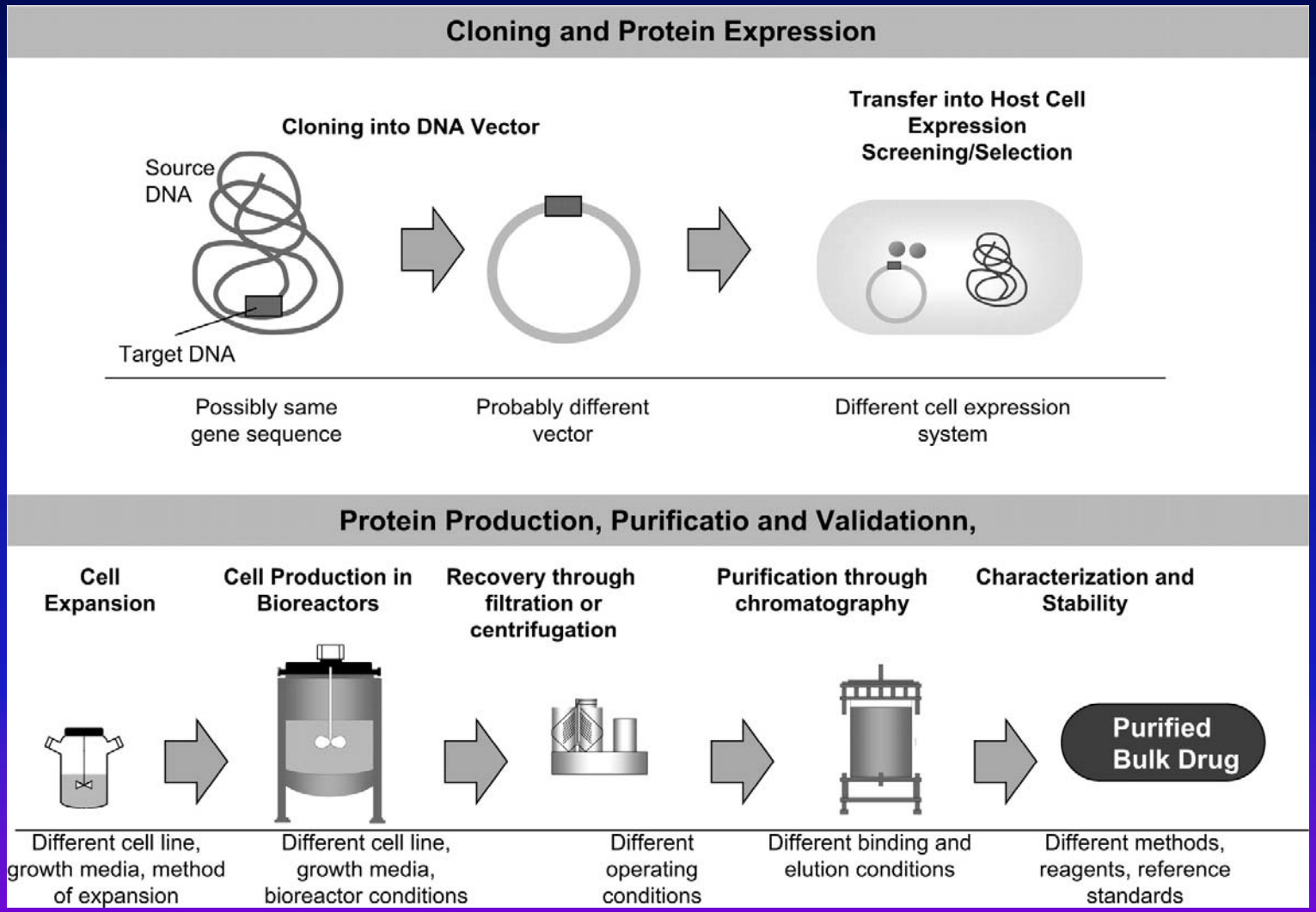
More than 325 million patients worldwide use biotech medicines

50% of medicines in clinical development are biotech medicines

Overview of EMEA Guidelines

TOPIC	TITLE	APPLICATION
Overarching	Guideline on Similar Biological Medicinal Products	General: Applies to all Biosimilars
Quality	Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues	
Nonclinical & Clinical	Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical & Clinical Issues	
Annexes Nonclinical & Clinical	Recombinant Human Erythropoietin; Recombinant Human G-CSF; Recombinant Human Insulin; Recombinant Human Growth Hormone	Specific: Product data requirements

Recombinant protein production: sources of variation between manufacturers



Mellstedt, H et al. Ann Oncol 2007

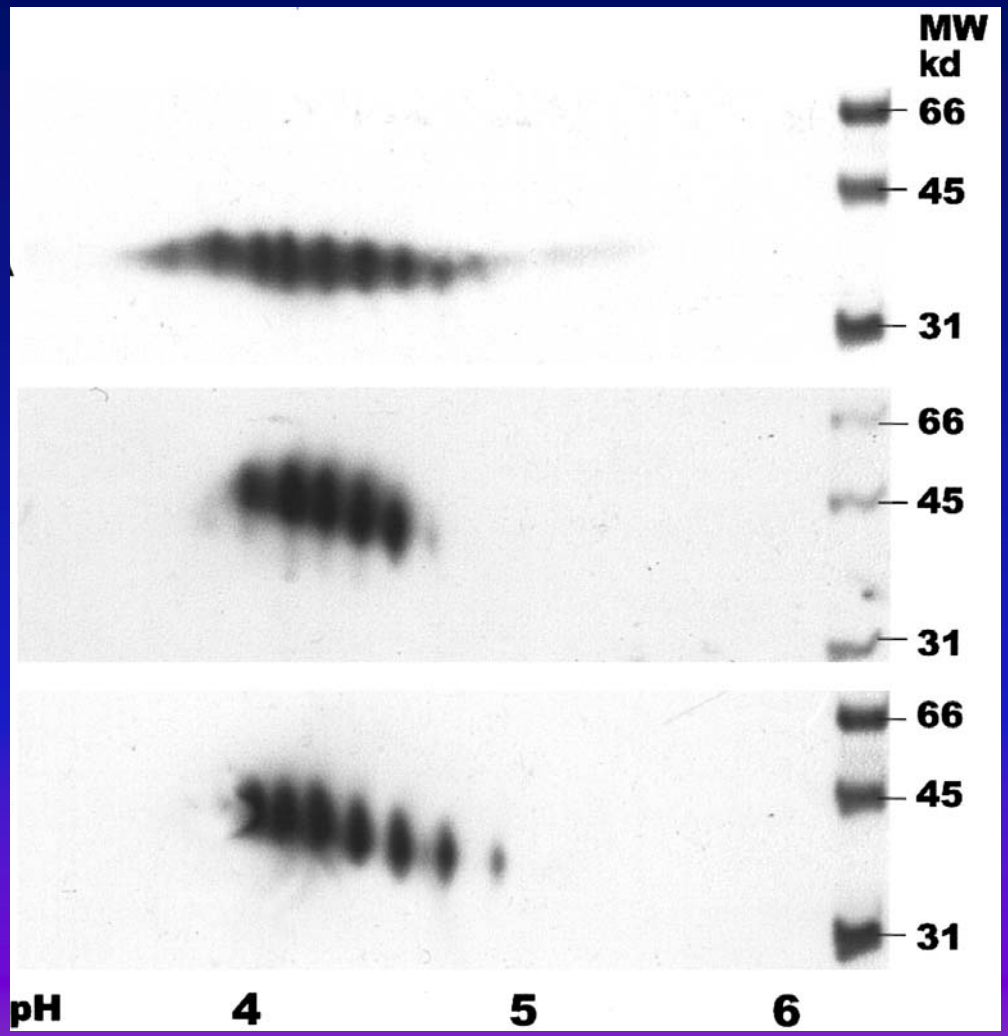
Annals of Oncology

Epoetins are not the same

Human Erythropoietin

Epoetin -α

Epoetin -β



Skibeli, V. et al. Blood 2001;98:3626-3634

Biosimilar epoetins approved by EMEA

- Epoetin alfa (Abseamed®, Binocrit®, Epoetin alfa Hexal®)
- Epoetin zeta (Retacrit®, Silapo®)
- Epoetin theta (Eporatio® and Biopoin®),

Summary – (1)

- Biosimilars are a new class of medicinal product
  - →Not generics in the small-molecule sense
- EMEA have established a good standard for approval
  - →Outstanding questions can be addressed post-approval

Summary – (2)

- There are still outstanding topics relating to their introduction into clinical practice
  - →Pharmacovigilance
  - →Application of automatic substitution rules
  - →Labelling (Summary of Product Characteristics)
  - →Naming (International Non-proprietary Names)

Summary of my talk

- The TREAT study, which is the largest RCT in nephrology, do not show any benefit of early treatment with ESA's.
- EMEA. FDA and international guidelines for treatment of anemia in CKD patients have pointed out the risk of harm with high targets (i.e. normal Hb levels)
- Hepcidin emerges as a key factor in iron metabolism. Because of the complexity of its regulation it is too early to suggest determination of plasma hepcidin levels as a marker of functional iron deficiency in clinical practice.
- The introduction of biosimilars needs special attention to safety issues