

Anemia therapy in patients with chronic kidney disease: Role of epoetin zeta

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Renal Anemia

- A severe complication of chronic kidney disease (CKD)
- Seen in more than 80% of CKD patients
- Inadequate production of erythropoietin by damaged kidneys
- Correction by erythropoiesis stimulating agents (ESAs)
- Adjuvant therapy (e.g. intravenous iron) for optimal ESA response

Treatment of renal anemia with erythropoiesis stimulating agents

- Epoetin alfa
- Epoetin beta
- Darbepoetin alfa
- C.E.R.A.
- Biosimilars
- Hematide

Epoetin Zeta

- **New recombinant human erythropoietin**
- **Identical to epoetin alfa in its amino acid sequence**
- **Comparable in its carbohydrate composition**
- **Classified as biosimilar to epoetin alfa**

Comparison of the galenics between epoetin zeta, epoetin beta, and epoetin alfa

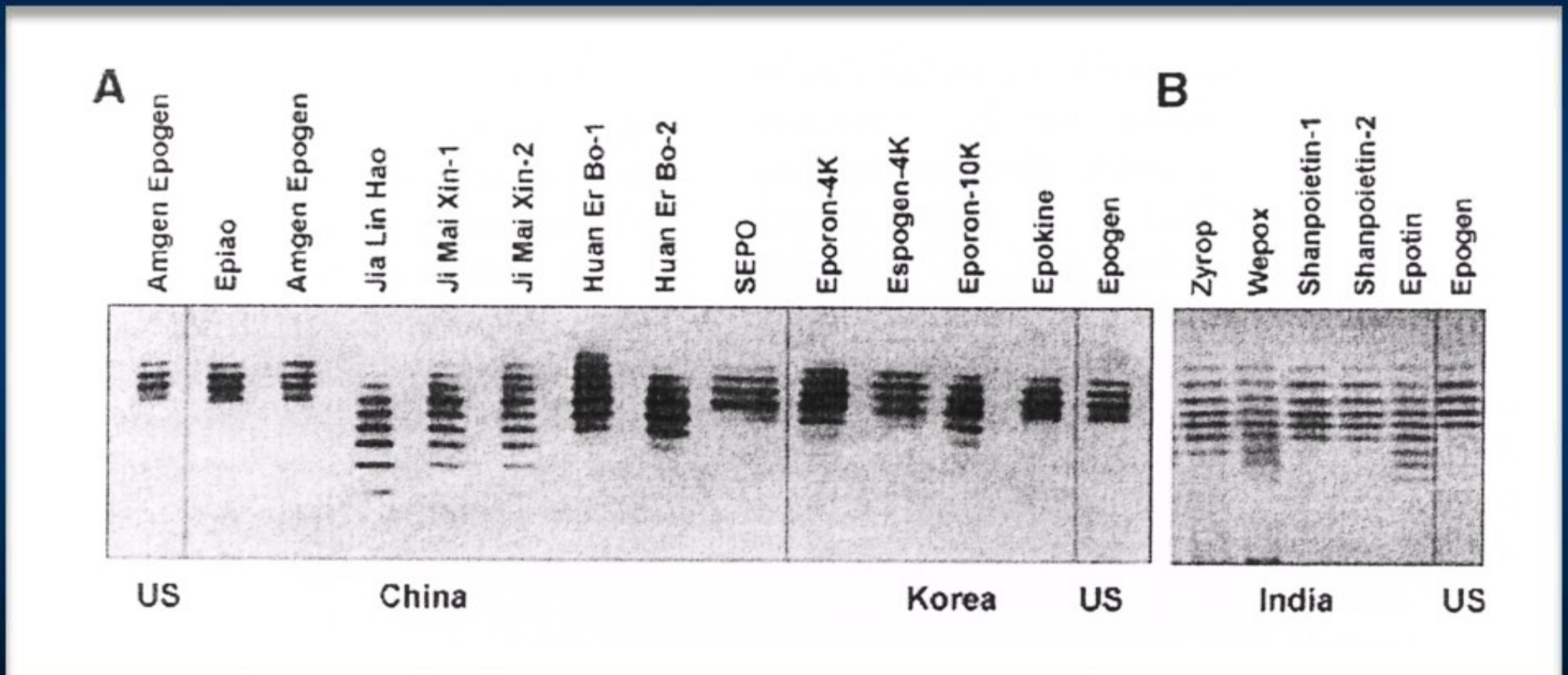
Epoetin zeta	Epoetin beta	Epoetin alfa
Polysorbate 20	Polysorbate 20	Polysorbate 80
Sodiumdihydrogenphosphate	Sodiumdihydrogenphosphate	Sodiumdihydrogenphosphate
Sodiummonohydrogenphosphate	Sodiummonohydrogenphosphate	Sodiummonohydrogenphosphate
Calciumchloride	Calciumchloride	
Glycine	Glycine	Glycine
Leucine	Leucine	
Isoleucine	Isoleucine	
Threonine	Threonine	
Glutamineacid	Glutamineacid	
Phenylalanine	Phenylalanine	
Sodiumchloride	Sodiumchloride	Sodiumchloride
	Urea	
Water for injection	Water for injection	Water for injection

Biosimilars

- Biological products
- Closely related (similar) to the reference product
- Not necessarily identical
- Therapeutic equivalence to the reference product
 - Efficacy
 - Safety
 - Tolerability
- Erythropoietin-specific biosimilar guidelines by the European Medicines Agency (EMA)

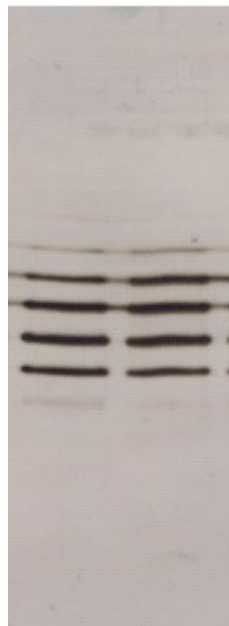
Iso-electro-focus gel with western blots for isoform detection: (A) samples from China (lanes 2-9) and Korea (lanes 10-13) and (B) samples from India (lanes 1-5)

Park SS et al, J Pharm Sci 98:1688-1699, 2009



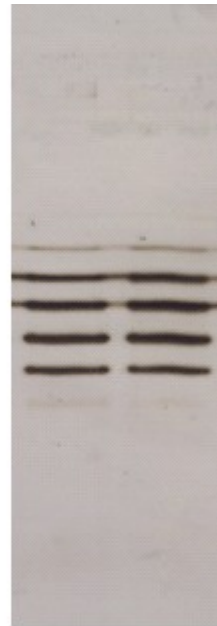
Results of quality by design approach: Binocrit® equivalence demonstrated with physicochemical analysis

Gel A



1 2

Gel B



3 4

1 Binocrit®
2 Eprex®
3 Binocrit®
4 Eprex®

- Physicochemical analysis techniques allow high resolution comparison of new and existing versions of medicines
- Gel electrophoresis technique is a useful starting point for comparison
- Other more modern techniques allow comparison at the atomic level

Anti-EPO antibody-mediated pure red cell anemia (PRCA)

- Progressive, severe, transfusion-dependent anemia (with sudden onset)
- Decline of hemoglobin levels by 1 g/dl per day
- Low reticulocyte counts
- Decreased number of bone marrow erythroid precursors
- ESA- and iron-resistant anemia
- Detection of neutralizing anti-erythropoietin antibodies against exogenous and endogenous erythropoietin

Potential risk factors for immunogenicity of erythropoiesis stimulating agents (1)

- Subcutaneous injection
- Interruption of cooling
- Protein degradation (during production and/or storage)
- Protein modification (e.g. oxidation of Met-54 or Trp-64)
- Protein denaturation (alterations of protein structure)
- Formation of dimeres and aggregates
- „Microparticles“

Potential risk factors for immunogenicity of erythropoiesis stimulating agents (2)

- Organic softeners
- Silicon oil
- Metal ions (tungsten)
- Polysorbate micelles
- Host cell proteins (HCP)
- Specific interactions between the product (epoetin) and the patients (HLA system)

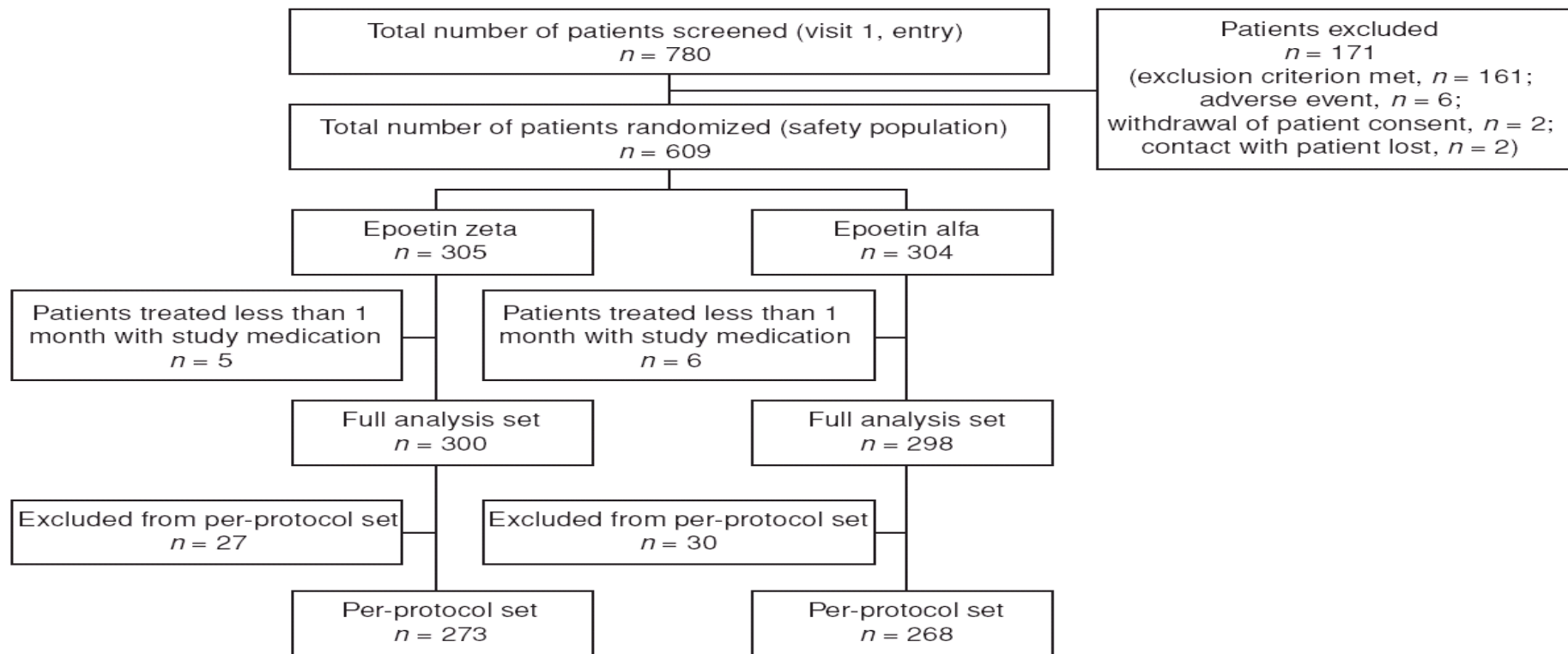
Anemia therapy in patients with chronic kidney disease: Role of epoetin zeta

Four important studies for the efficacy, safety and tolerability

- Comparison of the therapeutic effects of epoetin zeta and epoetin alfa in the correction of renal anemia
(Krivoshiev S et al, Curr Med Res Opin 24: 1407-1415, 2008)
- Long-term safety and tolerability of epoetin zeta, administered intravenously, for maintenance treatment of renal anemia
(Baldamus C, Adv Ther 25: 1215-1228, 2008)
- Comparison of the therapeutic effects of epoetin zeta to epoetin alfa in the maintenance phase of renal anemia treatment
(Wizemann V et al, Curr Med Res Opin 24: 625-637, 2008)
- Therapeutic equivalence of epoetin zeta and alfa, administered subcutaneously, for maintenance treatment of renal anemia
(Krivoshiev S et al, Adv Ther 27: 105-117, 2010)

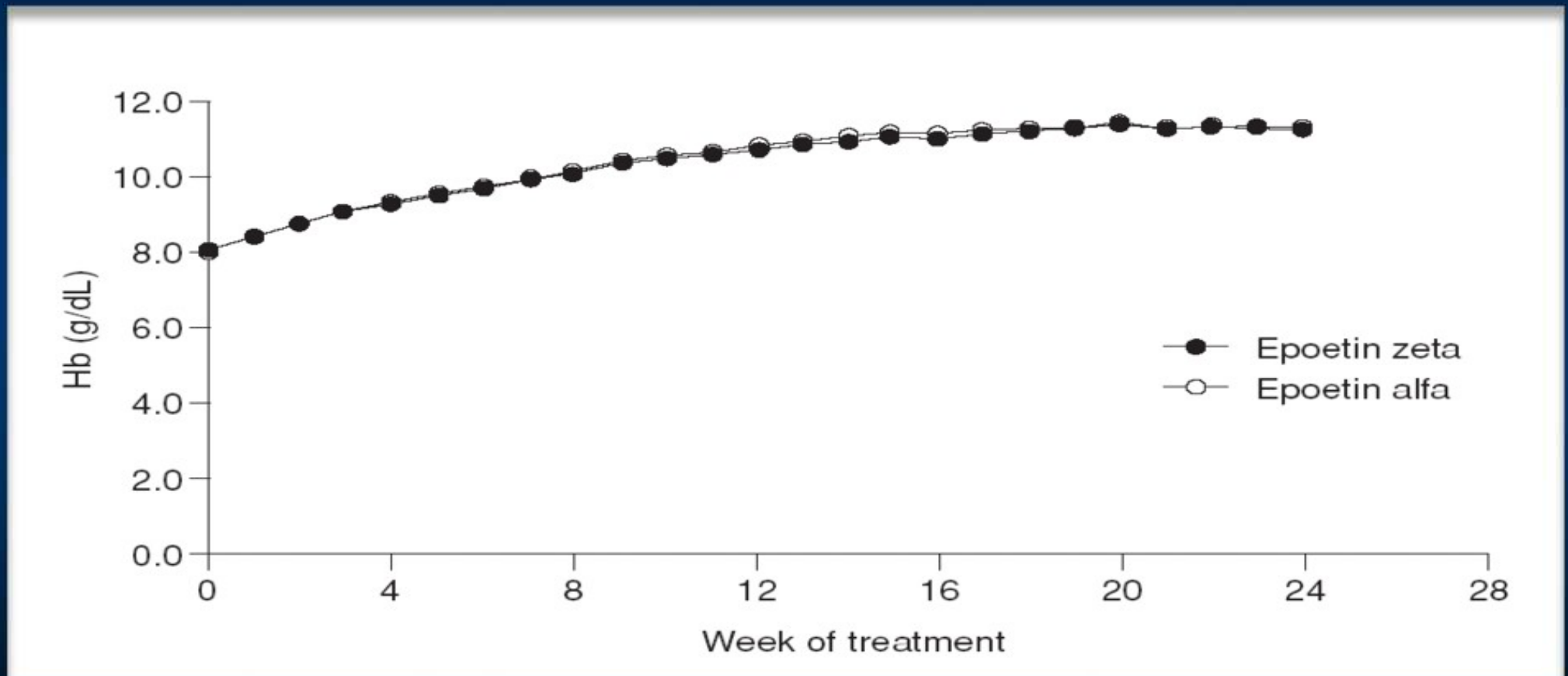
Baseline demographic and clinical data of the safety population (n = 609)

Krivoshiev S et al, Curr Med Res Opin 24: 1407-1415, 2008



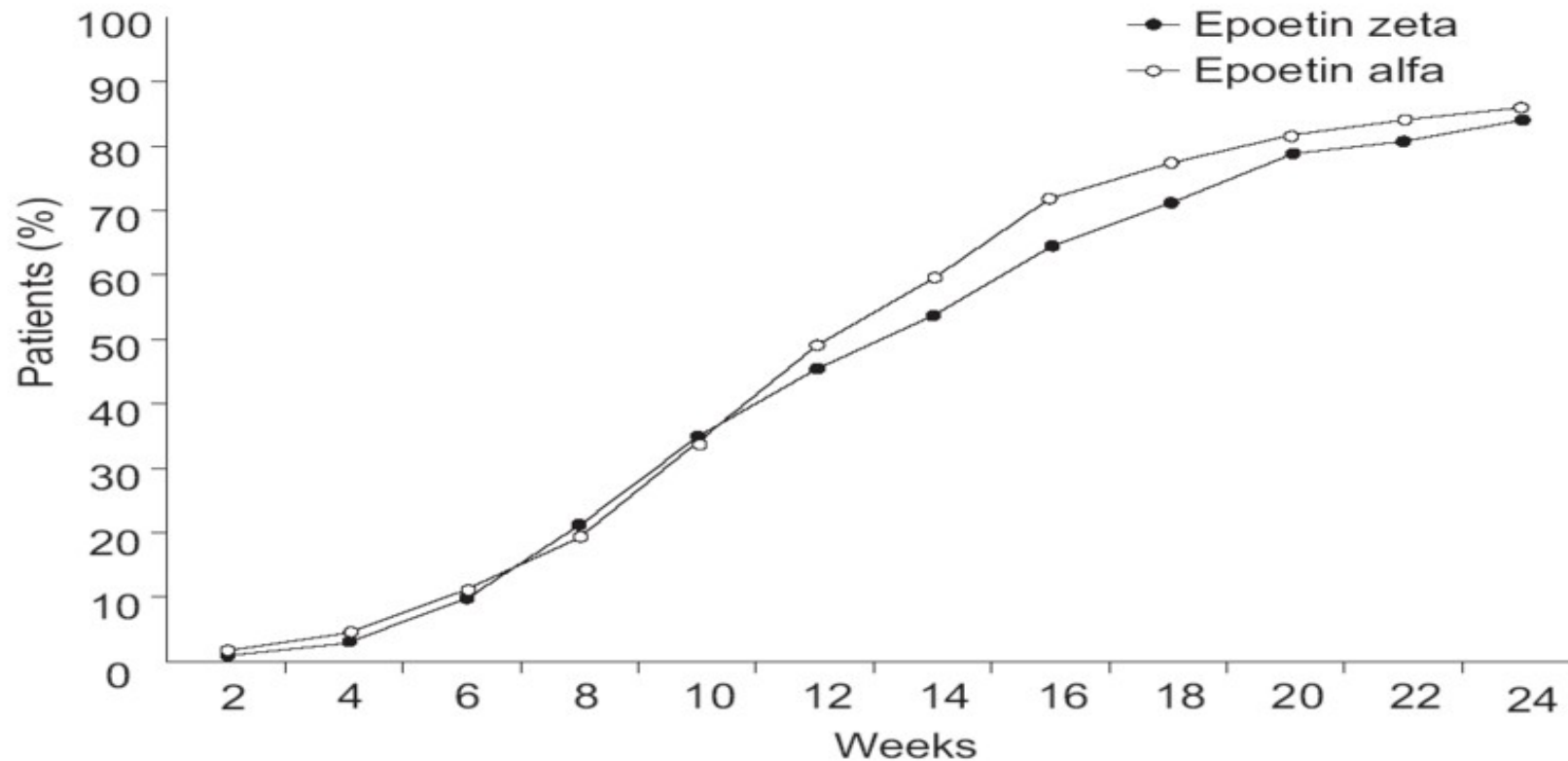
Comparison of the therapeutic effects of epoetin zeta and epoetin alfa in the correction of renal anemia

Krivoshiev S et al, Curr Med Res Opin 24: 1407-1415, 2008



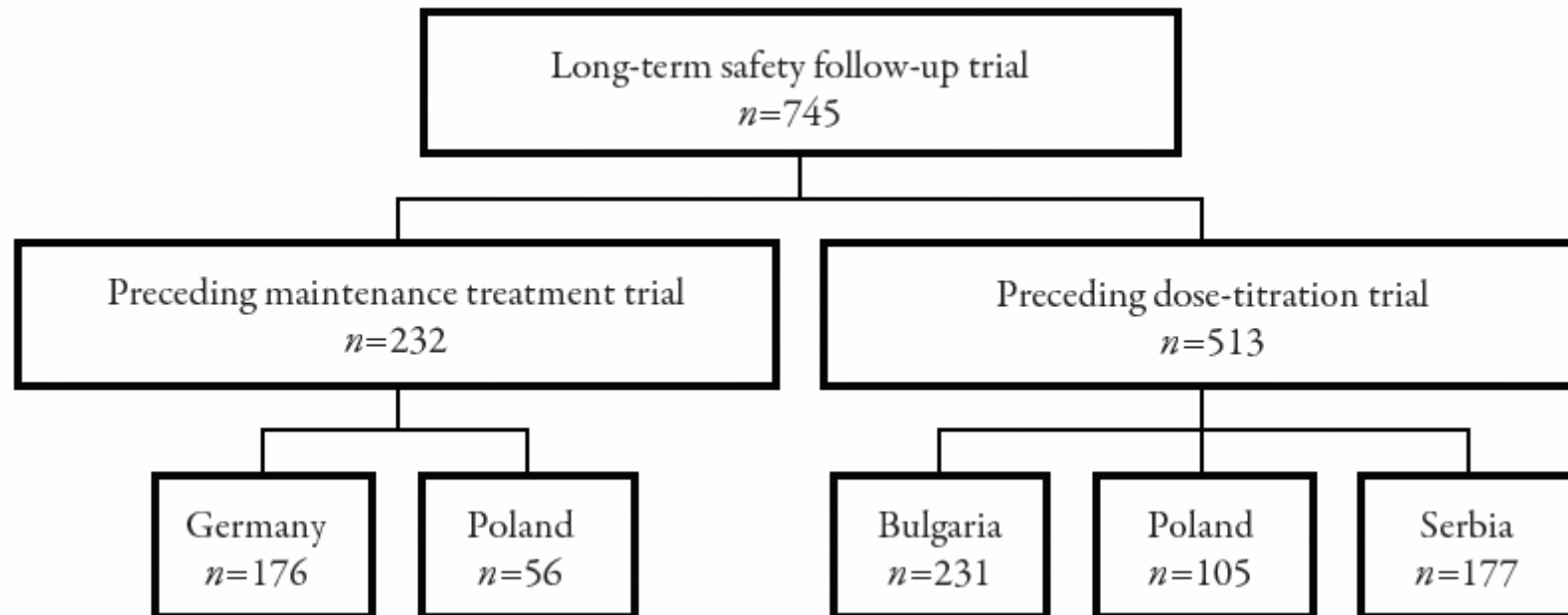
Proportion of patients with (cumulative) treatment success

Krivoshiev S et al, Curr Med Res Opin 24: 1407-1415, 2008



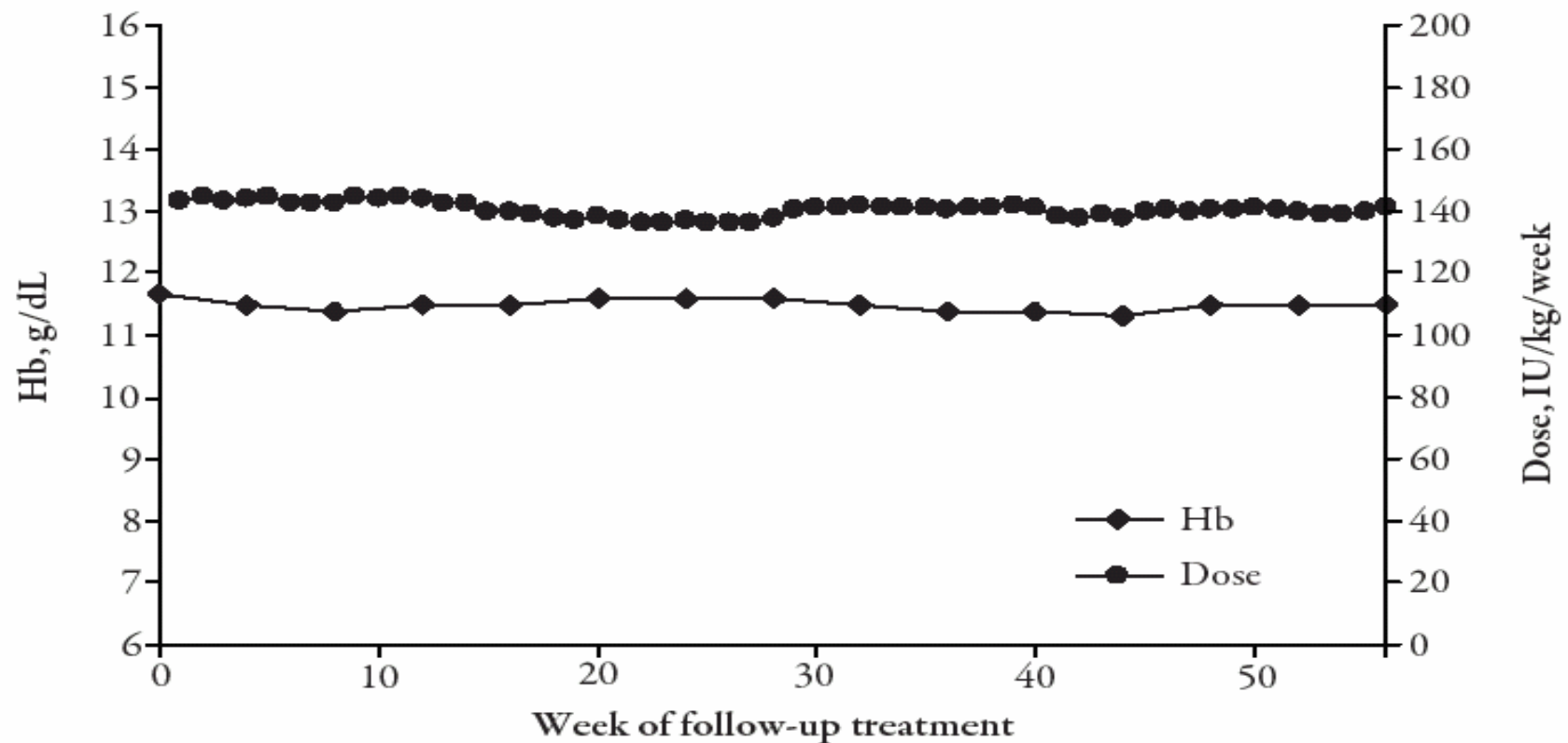
Long-term safety and tolerability of epoetin zeta, administered intravenously, for maintenance treatment of renal anemia (1)

Baldamus C et al, Adv Ther 25: 1215-1228, 2008



Long-term safety and tolerability of epoetin zeta, administered intravenously, for maintenance treatment of renal anemia (2)

Baldamus C et al, Adv Ther 25: 1215-1228, 2008

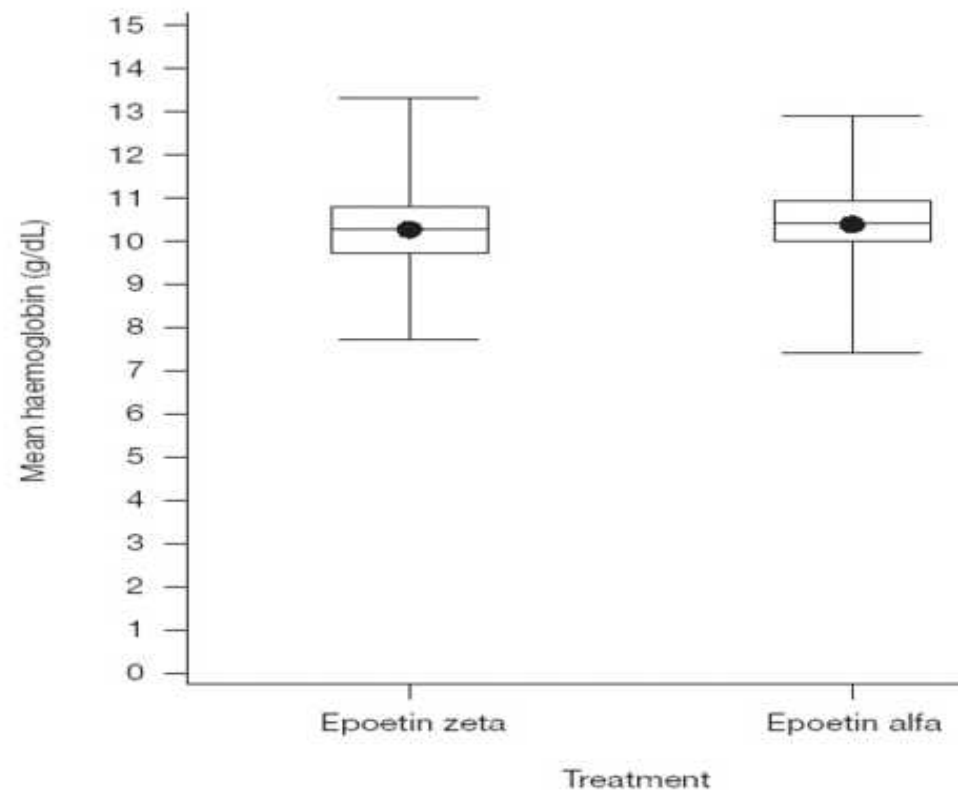


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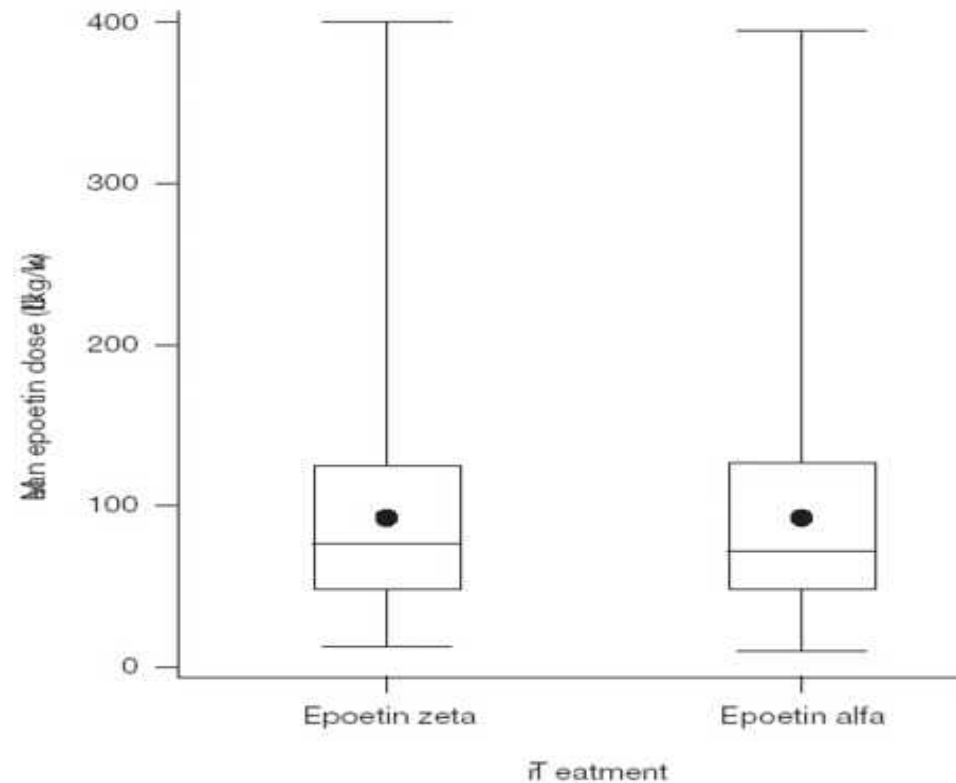
Comparison of the therapeutic effects of epoetin zeta to epoetin alfa in the maintenance phase of renal anemia treatment (1)

Wizemann V et al, Curr Med Res Opin 24: 625-637, 2008



Comparison of the therapeutic effects of epoetin zeta to epoetin alfa in the maintenance phase of renal anemia treatment (2)

Wizemann V et al, Curr Med Res Opin 24: 625-637, 2008

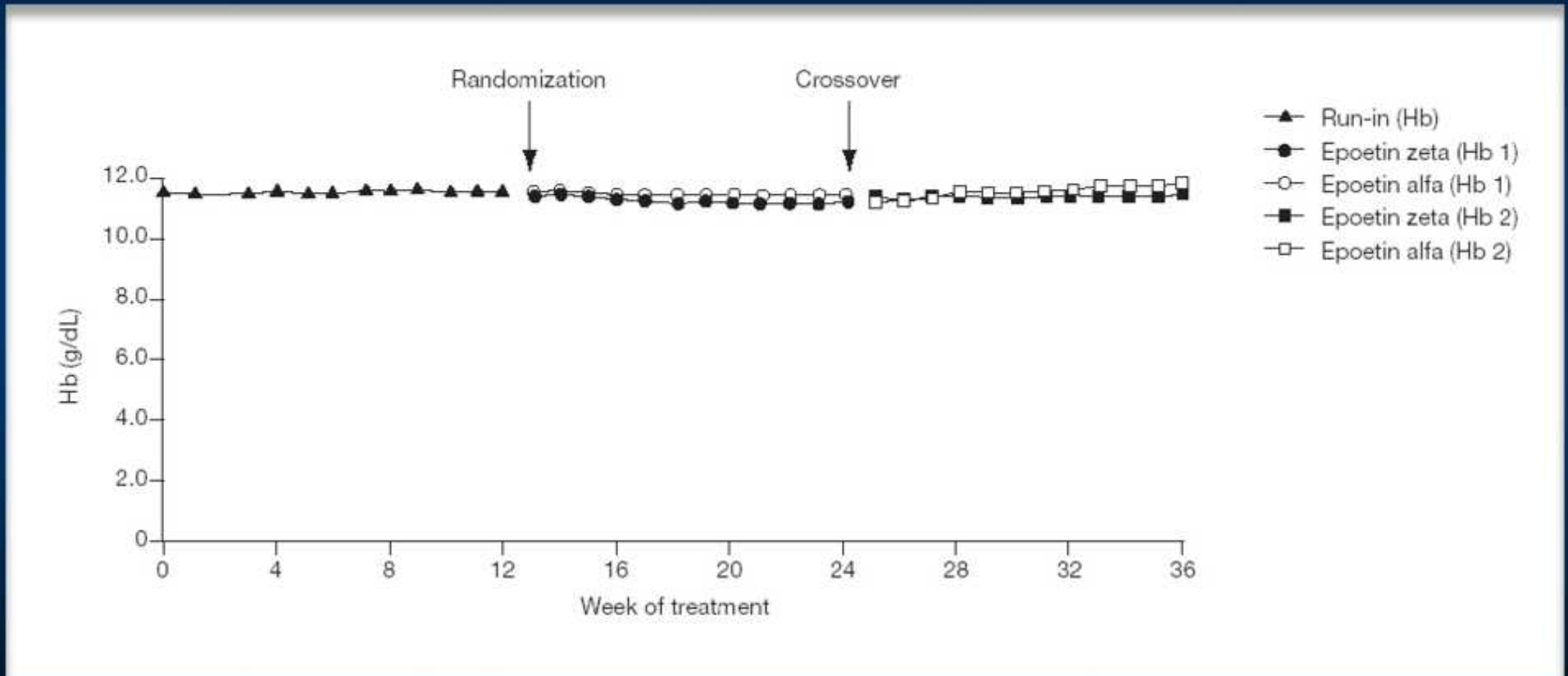


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Comparison of the therapeutic effects of epoetin zeta to epoetin alfa in the maintenance phase of renal anemia treatment (3)

Wizemann V et al, Curr Med Res Opin 24: 625-637, 2008

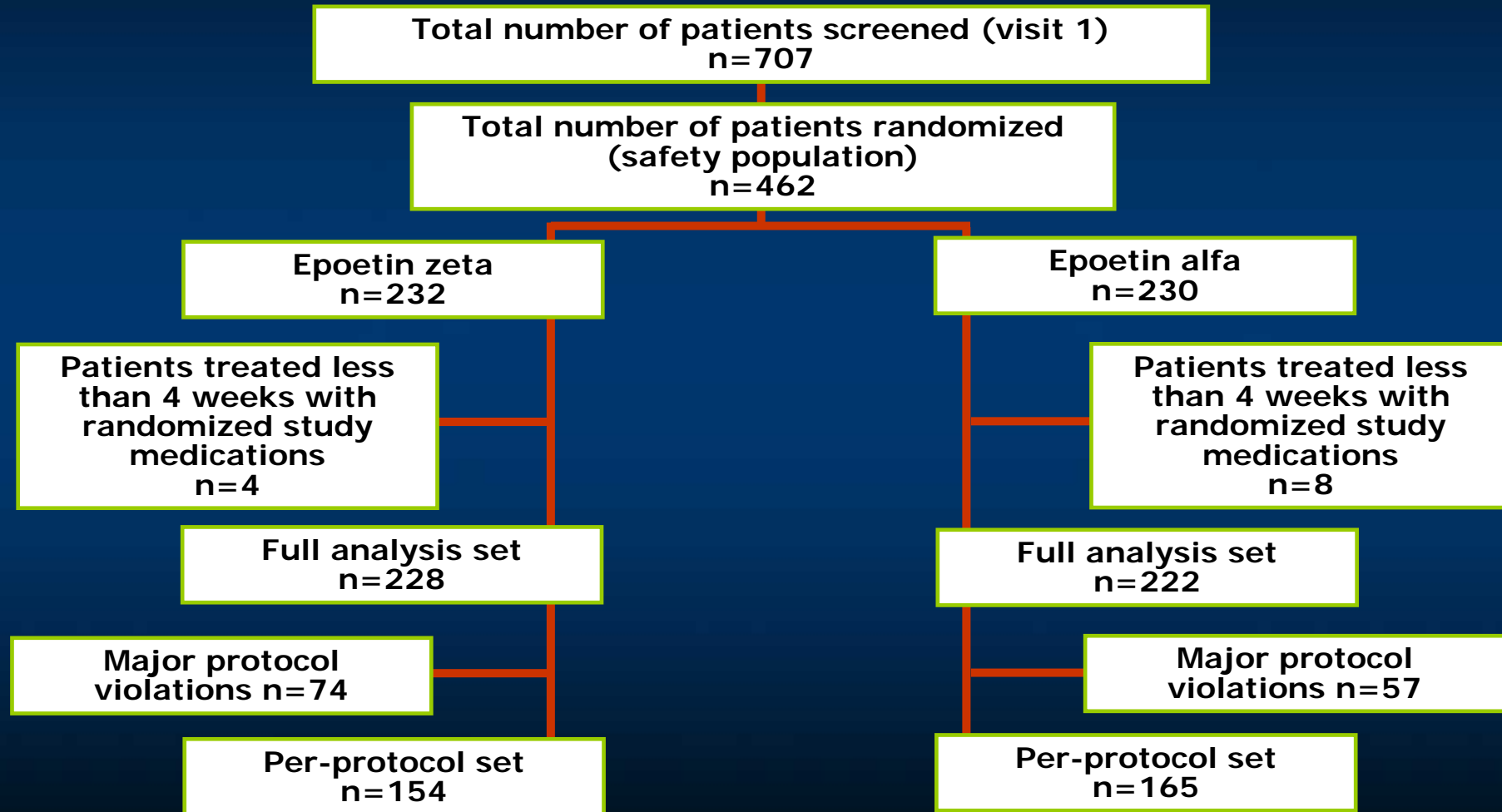


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Disposition of hemodialysis patients for the SC epoetin zeta study

Krivoshiev S et al, Adv Ther 27: 105-117, 2010



Baseline demographic and clinical characteristics, safety population (n=462) (1)

Krivoshiev S et al, Adv Ther 27: 105-117, 2010

Characteristic	Epoetin zeta (n=232)	Epoetin alfa (n=230)
Female, n (%)	94 (40.5)	96 (41.7)
Male, n (%)	138 (59.5)	134 (58.3)
Age, years (mean \pm SD)	55.6 \pm 12.47	55.2 \pm 12.58
Height, cm (mean \pm SD)	167.9 \pm 8.77	167.0 \pm 9.50
Weight, kg (mean \pm SD)	70.5 \pm 15.11	70.8 \pm 15.84
Time since end-stage renal failure, months (median)	37.0	36.5
Diagnosis leading to renal failure, n=%:		
Diabetic nephropathy	31 (13.4)	25 (10.9)
Hypertensive nephropathy	36 (15.5)	34 (14.8)
Glomerulonephritis	73 (31.5)	69 (30.0)
Other	92 (39.7)	102 (44.3)

Baseline demographic and clinical characteristics, safety population (n=462) (2)

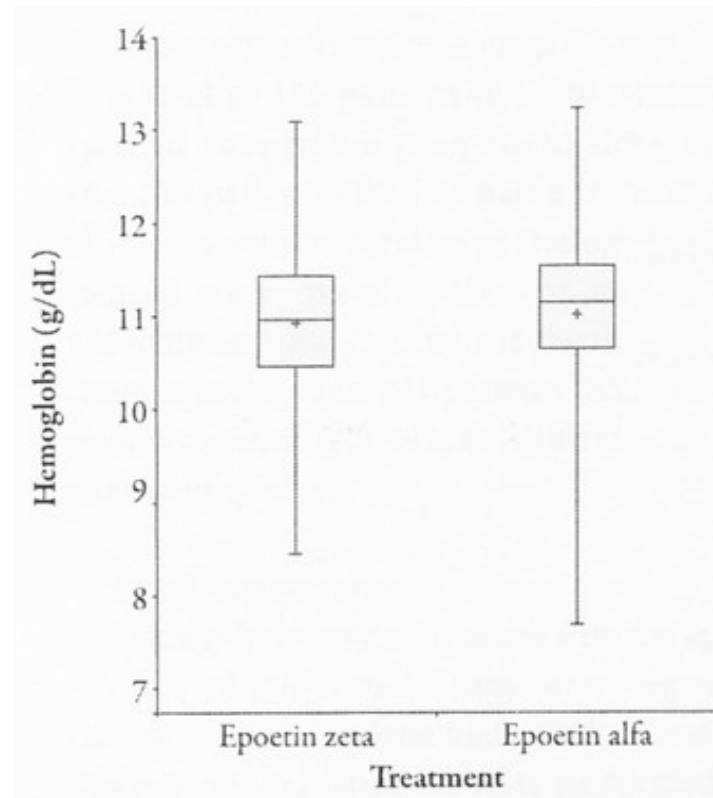
Krivoshiev S et al, Adv Ther 27: 105-117, 2010

Characteristic	Epoetin zeta (n=232)	Epoetin alfa (n=230)
Hb, g/dL (mean \pm SD*)	10.56 \pm 1.35	10.40 \pm 1.43
Hematocrit, % (mean \pm SD*)	31.9 \pm 4.4	31.3 \pm 4.1
Heart rate, beats/min(mean \pm SD)	76.2 \pm 9.59	74.7 \pm 8.48
Blood pressure, systolic, mmHg(mean \pm SD)	135.6 \pm 17.81	136.7 \pm 16.99
Blood pressure, diastolic, mmHg (mean \pm SD)	78.5 \pm 10.30	79.5 \pm 9.59

* Values for the per-protocoll set

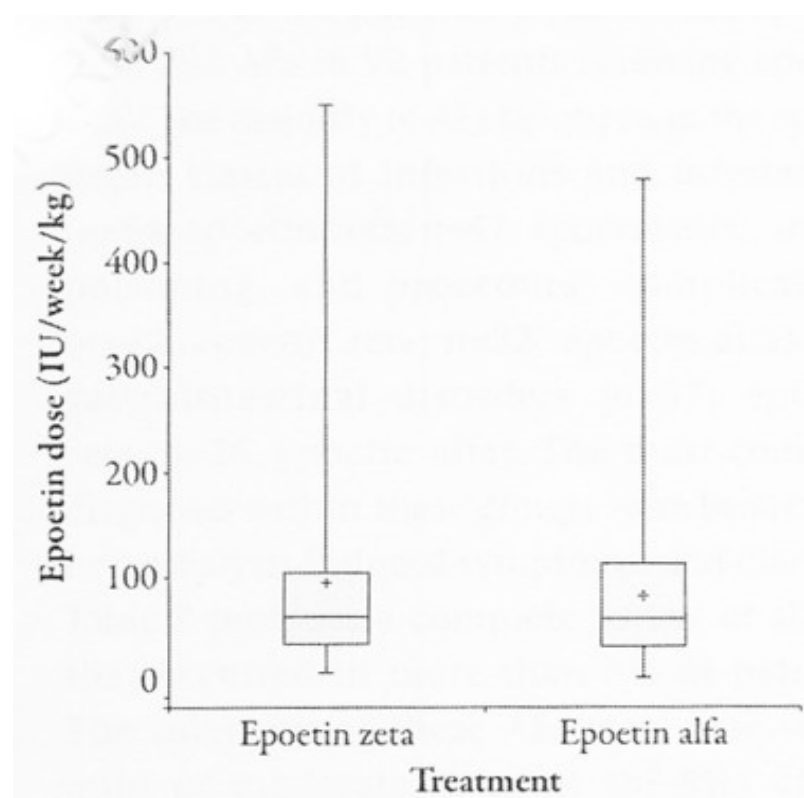
Mean Hb level during the last 4 weeks of treatment with epoetin zeta versus epoetin alfa in hemodialysis patients

Krivoshiev S et al, Adv Ther 27: 105-117, 2010



Mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment with epoetin zeta versus epoetin alfa

Krivoshiev S et al, Adv Ther 27: 105-117, 2010



Selected major serious adverse events, safety population (n=462)

Krivoshiev S et al, Adv Ther 27: 105-117, 2010

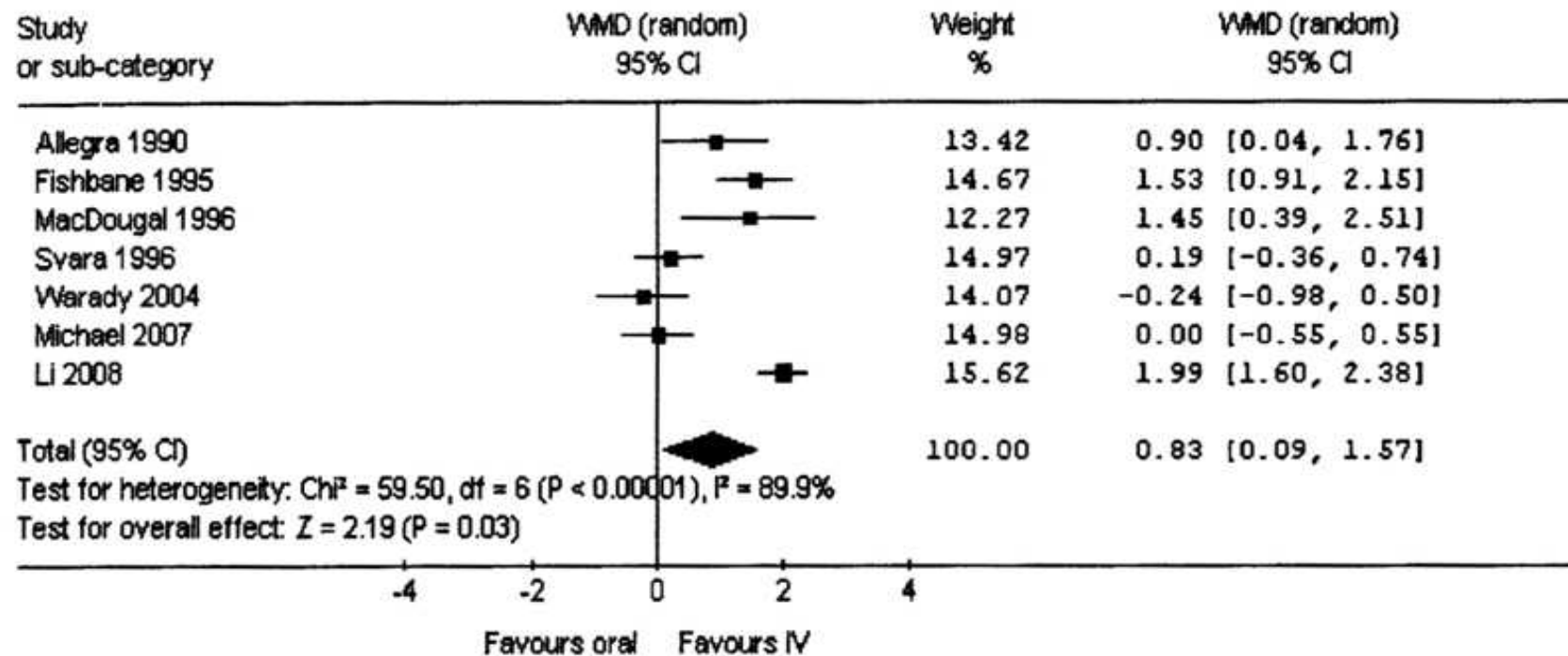
Serious adverse events	Epoetin zeta (n=232)	Epoetin alfa (n=230)
Hypertension/hypertensive crisis, %	3.3	5.9
Thrombotic vascular events, %	4.4	2.0
Hemorrhagic/ischemic stroke, %	4.4	3.9
Myocardial infarction, %	2.2	3.9

Possible reasons for ESA hyporesponse in patients with chronic kidney disease

- **Traditional risk factors**
 - Iron-, vitamin-, folic acid deficiency
 - Infect/Inflammation
 - Malignom
 - Hematologic disease
- **Non-traditional risk factors**
 - Secondary hyperparathyroidism
 - Hypervolemia/congestive heart failure
 - Dialysis catheters/synthetic grafts
 - Non-sterile dialysate
 - Failed kidney graft
 - Uremic toxins/underdialysis

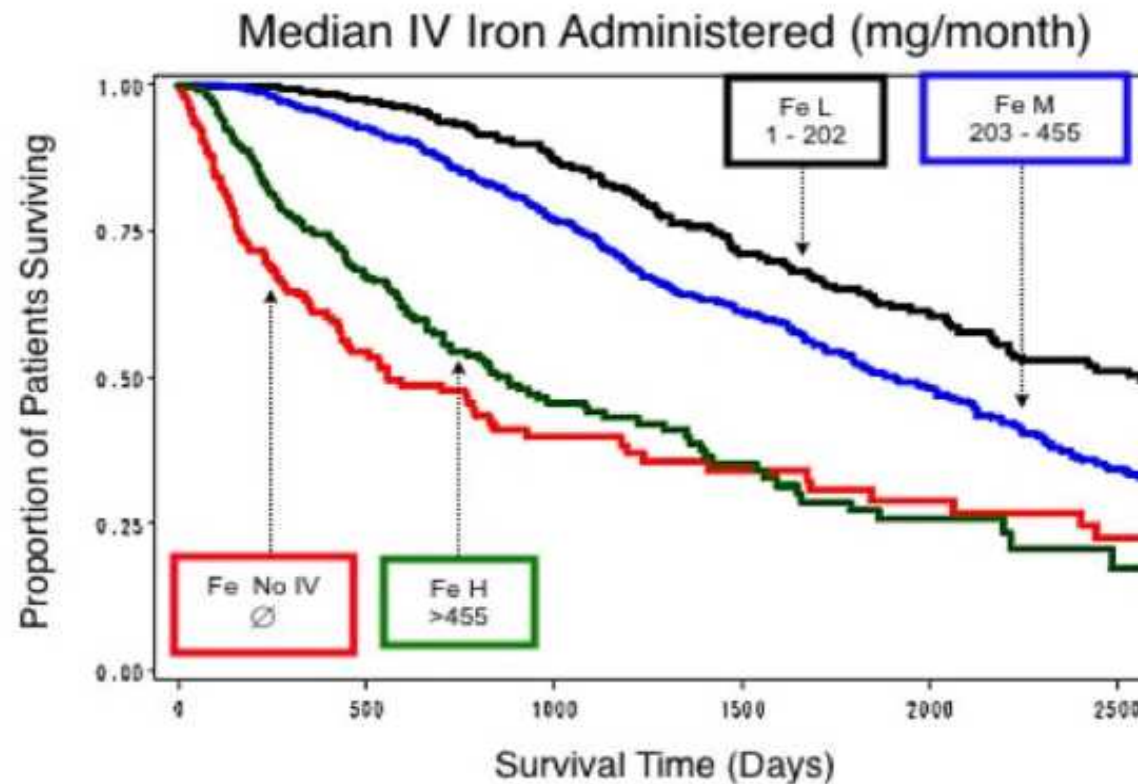
Hemoglobin (Hb) level or change from baseline for trials comparing intravenous (IV) iron versus oral iron in dialysis patients

Rozen-Zvi B et al, Am J Kidney Dis 52: 897-906, 2008



Estimated proportion of 1774 hemodialysis patients from New York surviving by levels of IV iron administration

Pollak VE et al, BMC Nephrol 10: 6, 2009

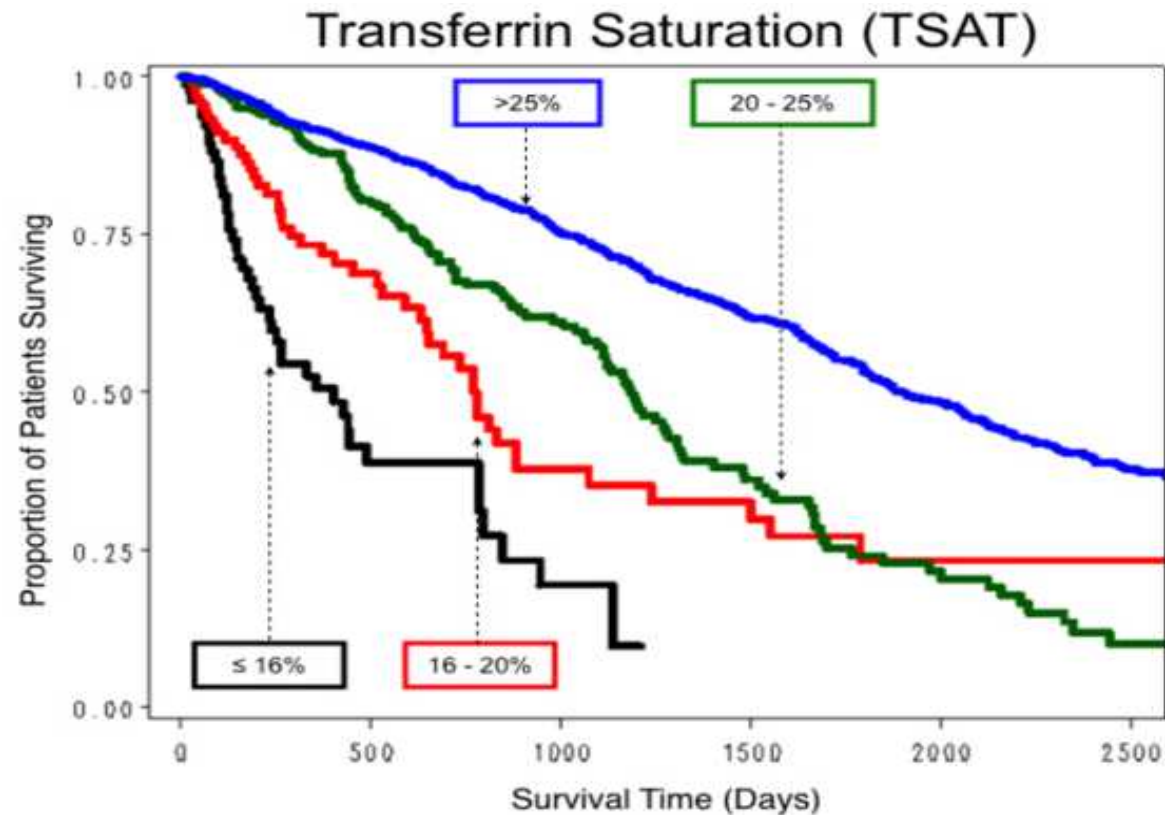


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Estimated proportion of 1774 hemodialysis patients from New York surviving by four levels of TSAT

Pollak VE et al, BMC Nephrol 10: 6, 2009

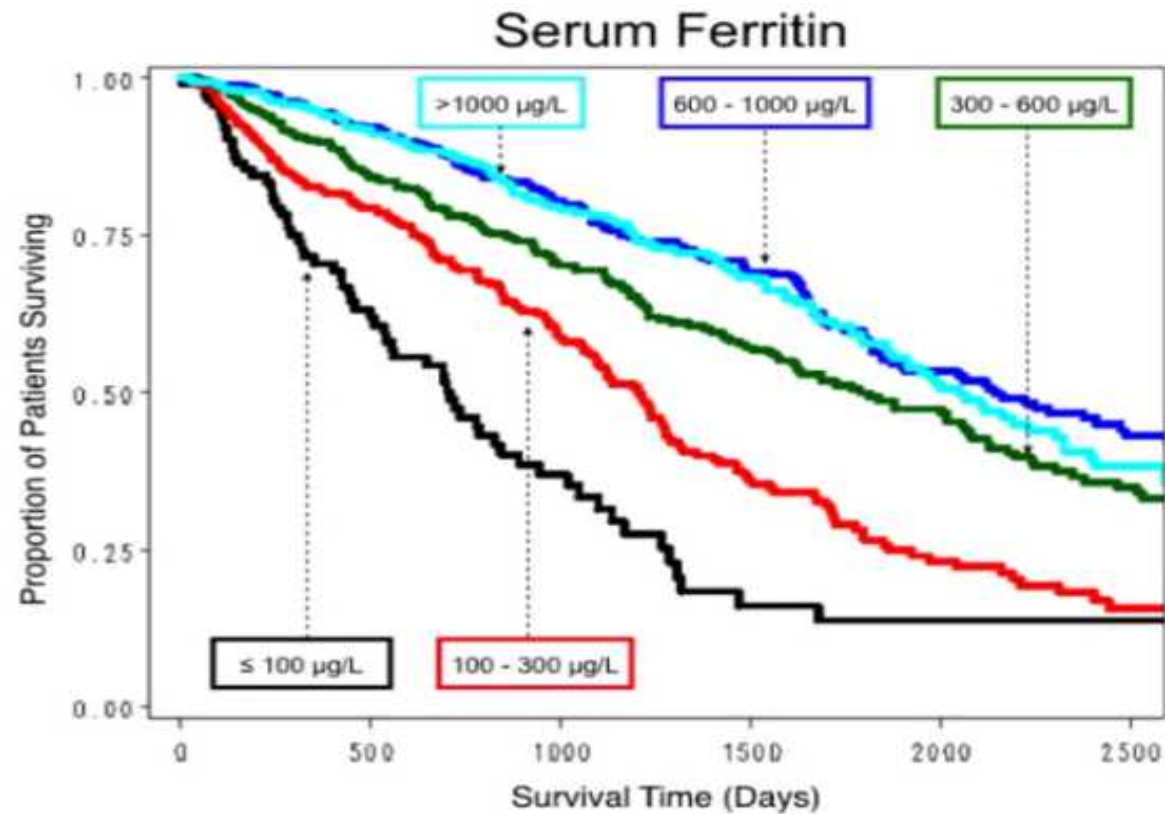


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Estimated proportion of 1774 hemodialysis patients from New York surviving by five levels of serum ferritin

Pollak VE et al, BMC Nephrol 10: 6, 2009

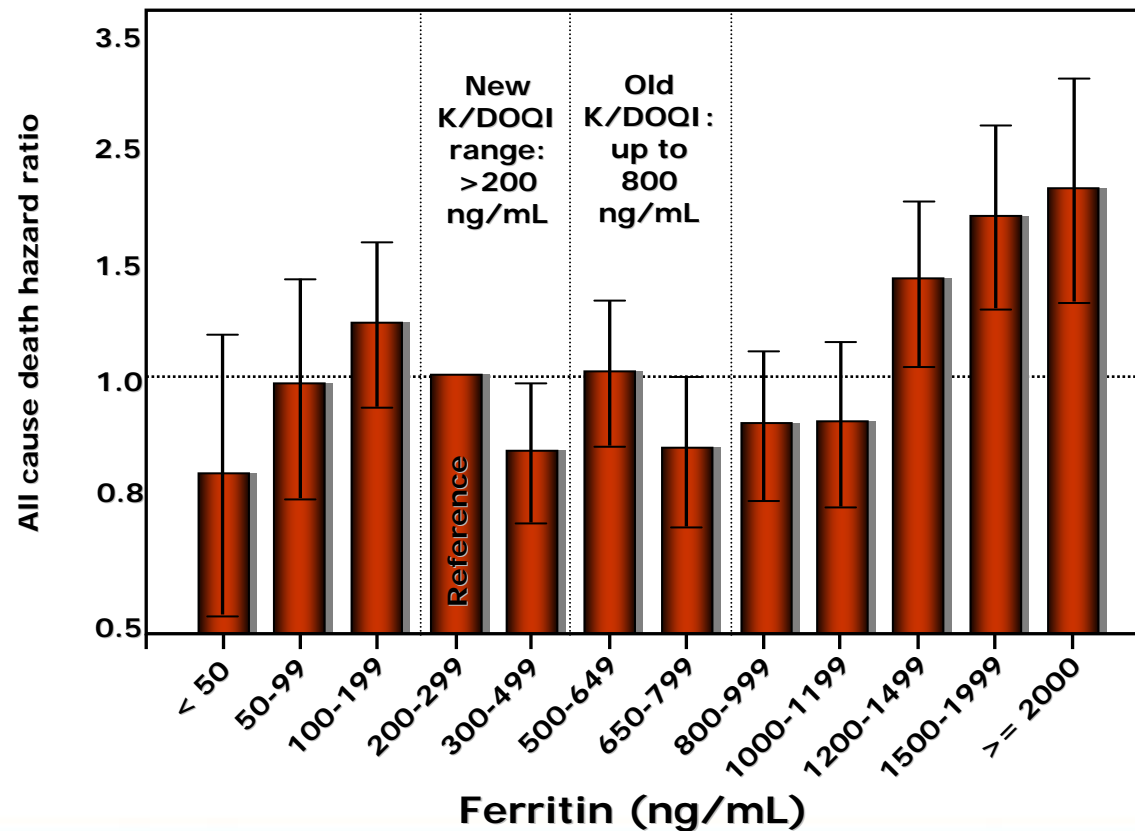


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Multivariate adjusted association between serum ferritin and all-cause mortality: Quarterly serum ferritin and 2-year survival in 58.058 MHD patients

Kalantar-Zadeh K et al, Clin J Am Soc Nephrol 1: S9-S18, 2006

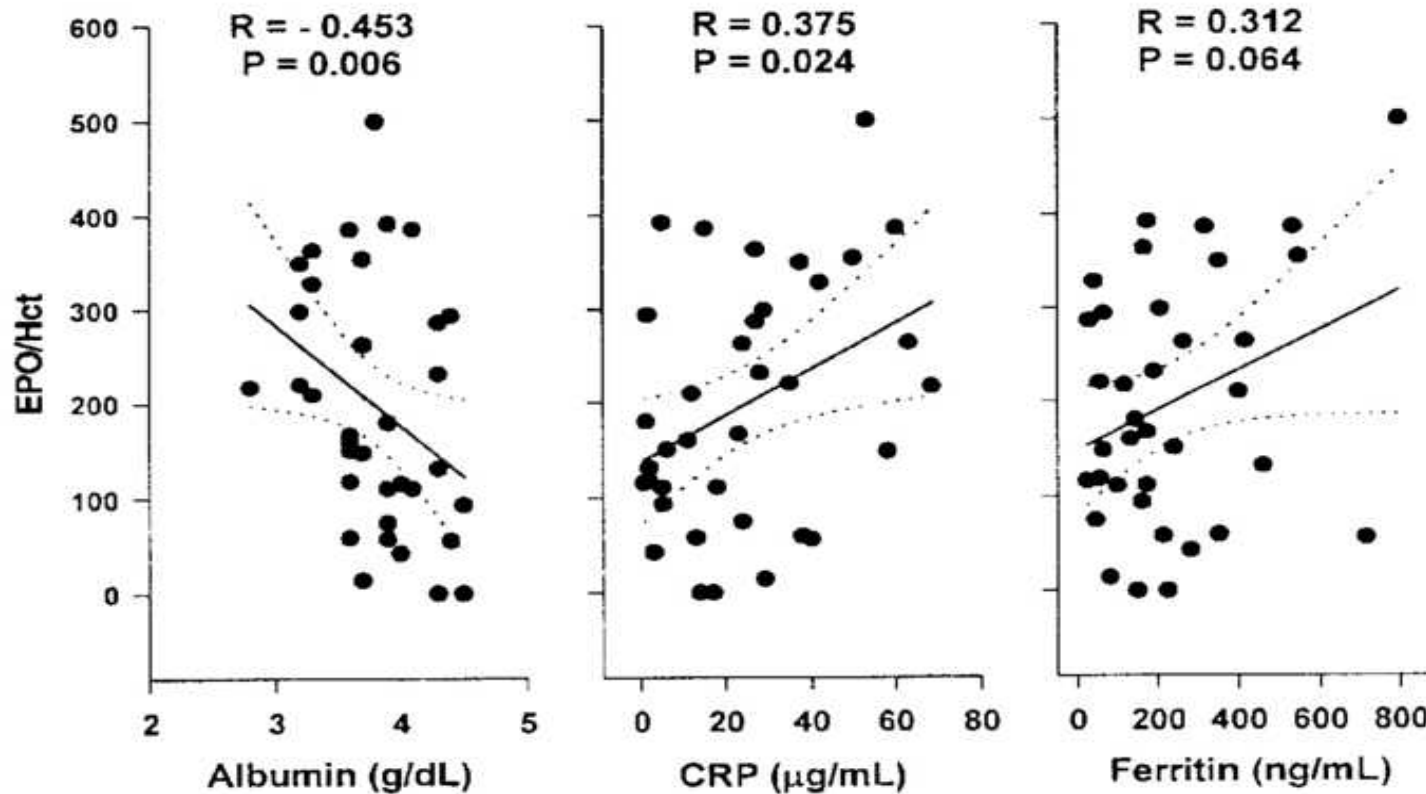


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Relationship between EPO/Hct and albumin, CRP, and ferritin levels in PD patients

Gunnell J et al, Am J Kidney Dis 33: 63-72, 1999

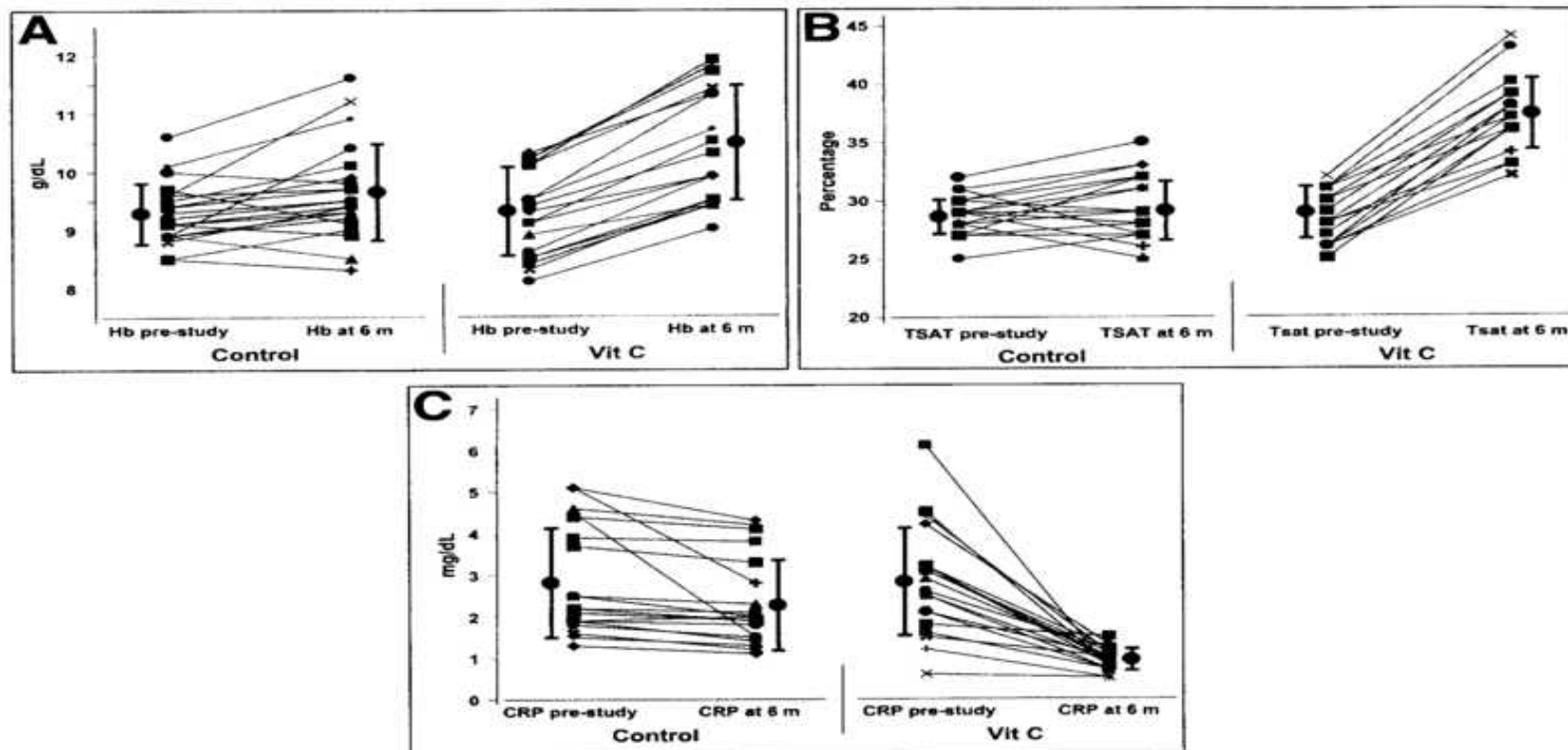


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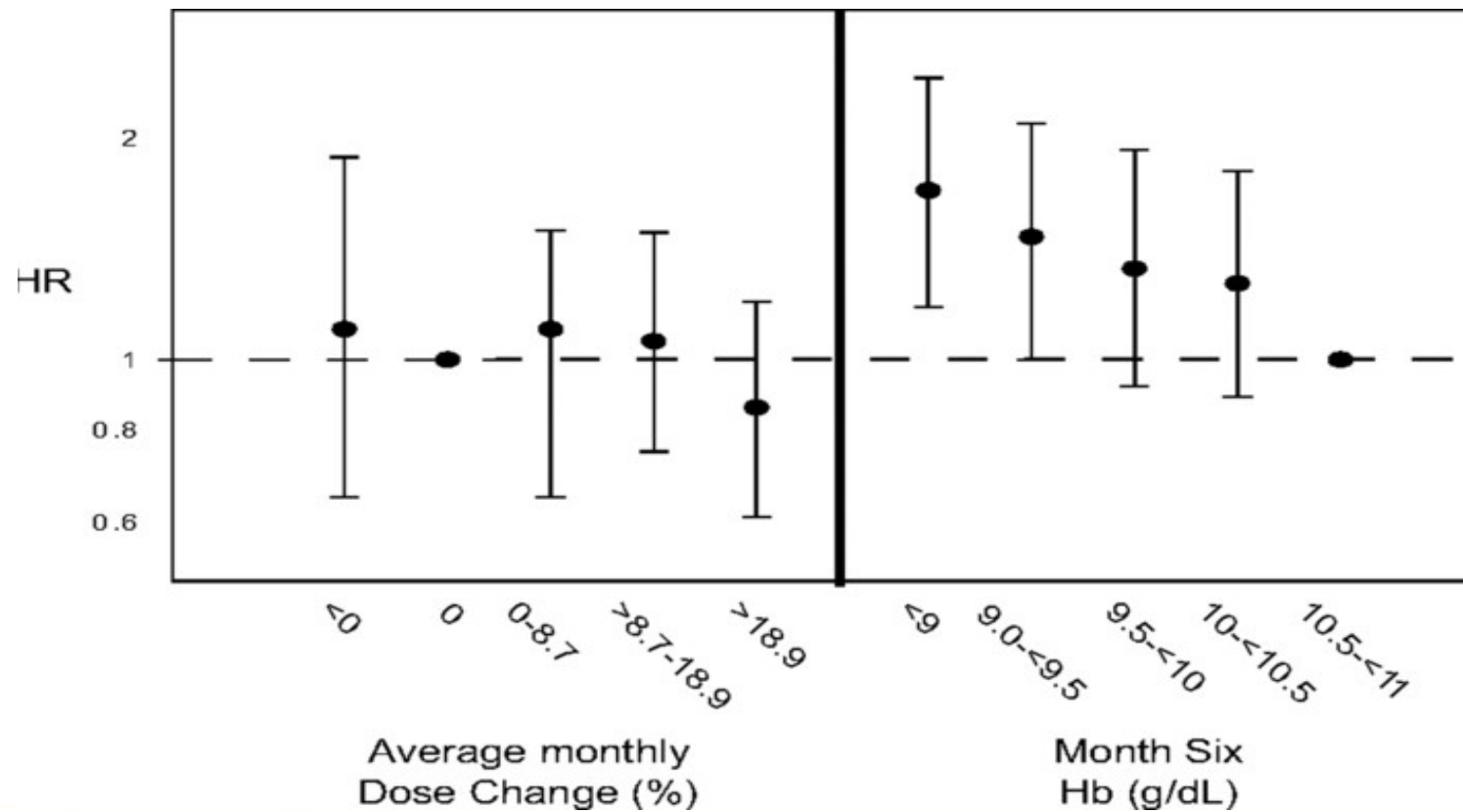
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Changes in individual data in both groups for (A) Hb levels, (B) TSATs, and (C) CRP levels

Attallah N et al, Am J Kidney Dis 47: 644-654, 2006



Association between (1) the mean monthly percentage change in EPO dose and the risk of death and (2) the month-6 achieved Hb level and the risk of death



Adjusted hazard ratios and 95% confidence intervals from multivariable Cox regression including an interaction of ESA use and hemoglobin level

Heinze G et al, Br Med J 339: b4018, 2009

Hemoglobin level	Adjusted hazard ratio (95% confidence interval)		
	(A) ESA non-users	(B) ESA users	(C) ESA users vs. non-users
9.5 g/dl	3.5 (2.0 to 6.0)	8.0 (3.1 to 20.6)	1.4 (0.9 to 1.9)
11 g/dl	2.5 (1.5 to 4.0)	4.7 (2.1 to 10.5)	1.1 (0.7 to 1.7)
12.5 g/dl	1 (reference)	1 (reference)	0.6 (0.2 to 1.5)
14 g/dl	0.7 (0.4 to 1.5)	2.8 (1.0 to 7.9)	2.2 (0.8 to 6.0)
15.5 g/dl	0.7 (0.3 to 1.6)	4.7 (1.4 to 16.2)	3.8 (1.3 to 10.9)

Potential advantages with the use of epoetin zeta for the treatment of renal anemia

- Biosimilar which can safely be administered subcutaneously in CKD patients
- Biosimilar without any case of pure red cell aplasia (so far)
- Biosimilar with therapeutic equivalence to the reference product
- Biosimilar with long-term efficacy, safety and tolerability data
- Biosimilar which probably reduces costs for anemia therapy

Anemia therapy in patients with chronic kidney disease: Role of epoetin zeta

Summary (1)

- Renal anemia a frequent and severe complication in CKD patients
- Correction of renal anemia (target hemoglobin levels 10-12 g/dl) by ESAs and adjuvant therapies (e.g. iron)
- Biosimilar epoetin zeta a novel ESA for anemia therapy

Anemia therapy in patients with chronic kidney disease: Role of epoetin zeta

Summary (2)

- Long-term safety, tolerability and efficacy data
 - Therapeutically equivalent to epoetin alfa in the correction of low hemoglobin concentration (by the IV route of administration)
 - Effective regarding its ability to maintain stabilized hemoglobin levels within the target range (by the IV route of administration)
 - Therapeutically equivalent to the reference product in respect to efficacy, safety and tolerability (even if administered subcutaneously)

End