25 years of treating anaemia in CKD patients

Fernando Carrera M.D.

ERA-EDTA Distinguished Fellow

Detrimental effects of anaemia in CKD patients

- ↓ Exercise tolerance
- ↓ Work capacity
- ↓ Skeletal muscle oxidative capacity
- ↓ Coagulation
- ↓ Cognitive function
- ↓ Sexual function
- ↓ Appetite
- ↓ Nutrition
- ↓ Quality of life

- ↑ Depression
- ↑ Sleep/wake pattern
- ↑ Cardiac output
- ↑ Angina pectoris
- ↑ Left ventricular hypertrophy
- ↑ Cardiac failure
- ↑ Myopathy
- ↑ Morbidity and mortality
- ↑ Progression of renal failure

CKD = chronic kidney disease

Anaemia management milestones

1977 Human erythropoietin (EPO) isolated from 2,500L of urine

1983

1986 **pproved fo**

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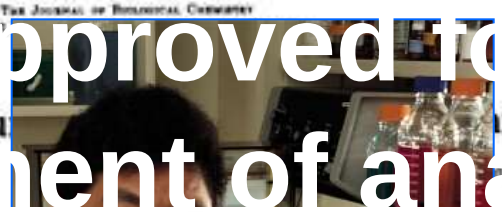
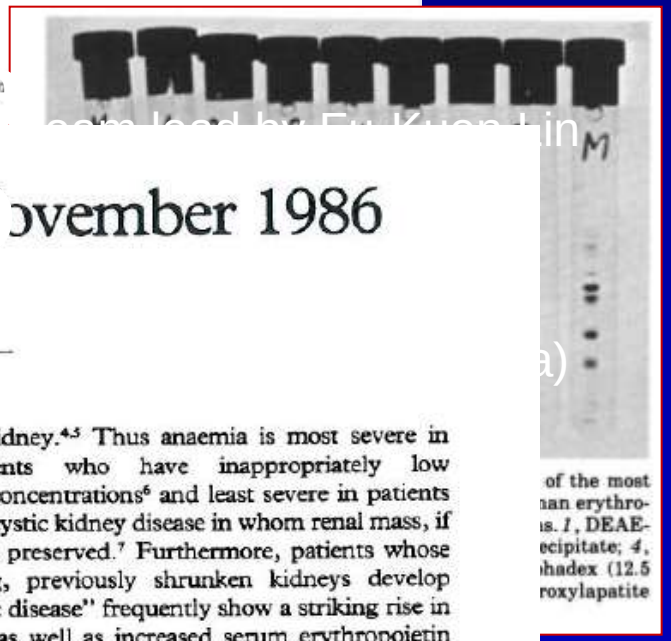
1989



Pu ropoietin*



The Lancet Saturday 22 November 1986

EFFECT OF HUMAN ERYTHROPOIETIN DERIVED FROM RECOMBINANT DNA ON THE ANAEMIA OF PATIENTS MAINTAINED BY IC HAEMODIALYSIS

EARLS[1] DESMOND O. OLIVER[2]
RD[3] CECIL REID[3]
NING[4] P. MARY COTES[3]

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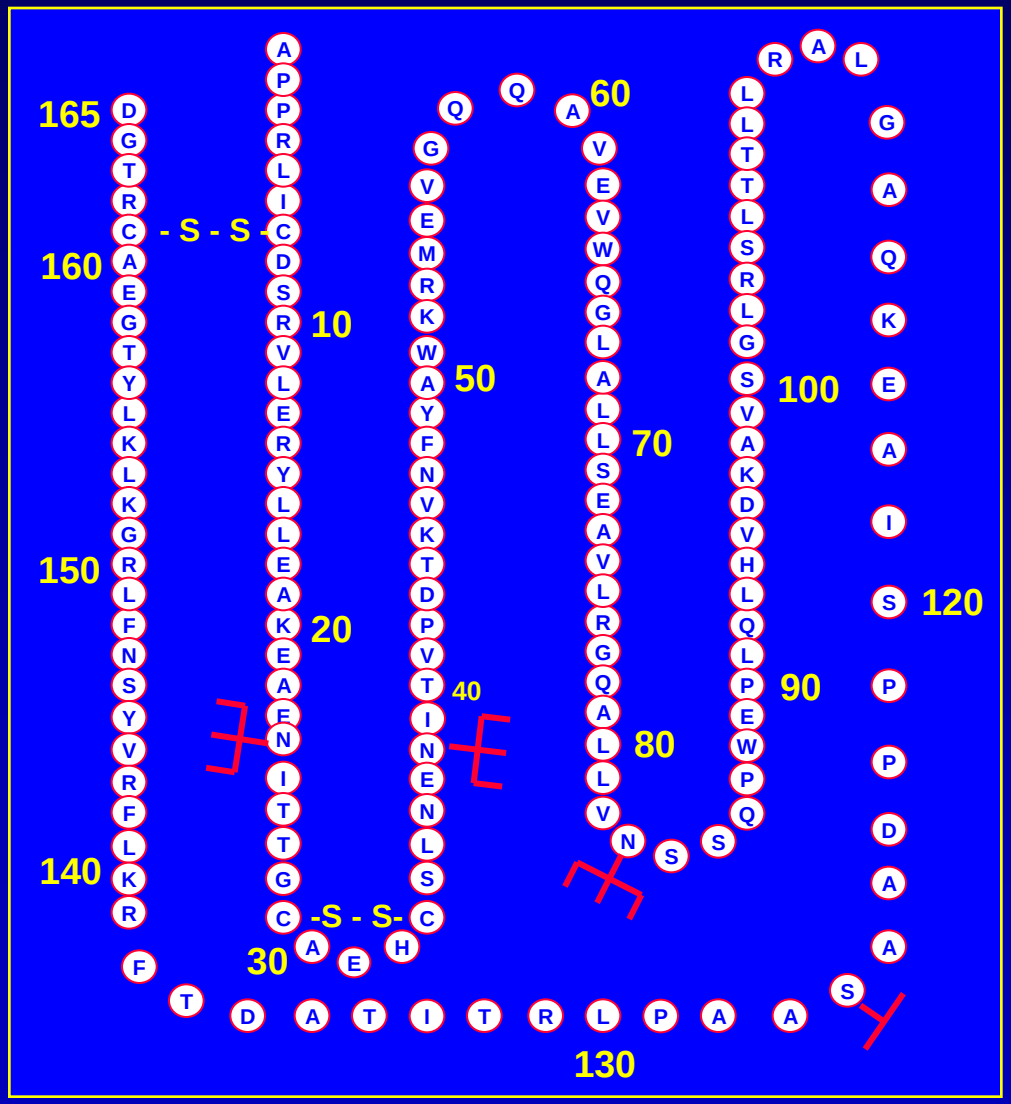
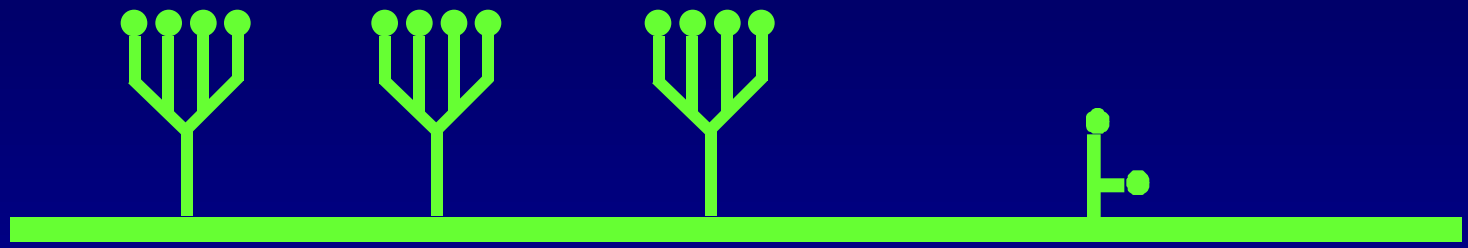
solely by the kidney.[4,5] Thus anaemia is most severe in anephric patients who have inappropriately low erythropoietin concentrations[6] and least severe in patients with adult polycystic kidney disease in whom renal mass, if not function, is preserved.[7] Furthermore, patients whose non-functioning, previously shrunken kidneys develop "acquired cystic disease" frequently show a striking rise in haemoglobin[8,9] as well as increased serum erythropoietin concentrations[10] despite an unchanged uraemic state. Lately, Eschbach and colleagues[11] have shown that daily infusions of erythropoietin-rich plasma can completely

Amino Acid Sequence of Human EPO



Structure of rHuEPO



- Three N-linked and one O-linked carbohydrate chains
- 30,400 daltons
- 40% carbohydrate
- Up to 14 sialic acid residues:
  - naturally occurring EPO — up to 14 sialic acid residues
  - rHuEPO (CHO cells) — 4–14 sialic acid residues
  - commercial rHuEPO — 9–14 sialic acid residues

Management Principles for Anaemia in CRF

- More than 10 years experience with rHuEPO
- Organised and summarized in EBPG

European Best Practice Guidelines

Nephrol Dial Transplant 1999;14(suppl 5):1-50


F. CARRERA
Prof. Fernando Valderrabano
Congress President
J.S. CAMERON

European Best Practice Guidelines

- **Epoetin can be administered either sc or iv in patients on HD but the sc route will usually lead to lower doses of epoetin being required.**

  (Evidence level A)

- **Randomized studies show a median reduction in dosage of 21%.**

- **Hb > 11 g/dL *(upper limit not defined)***

***Nephrol Dial Transplant* 1999;14(suppl 5):1-50**

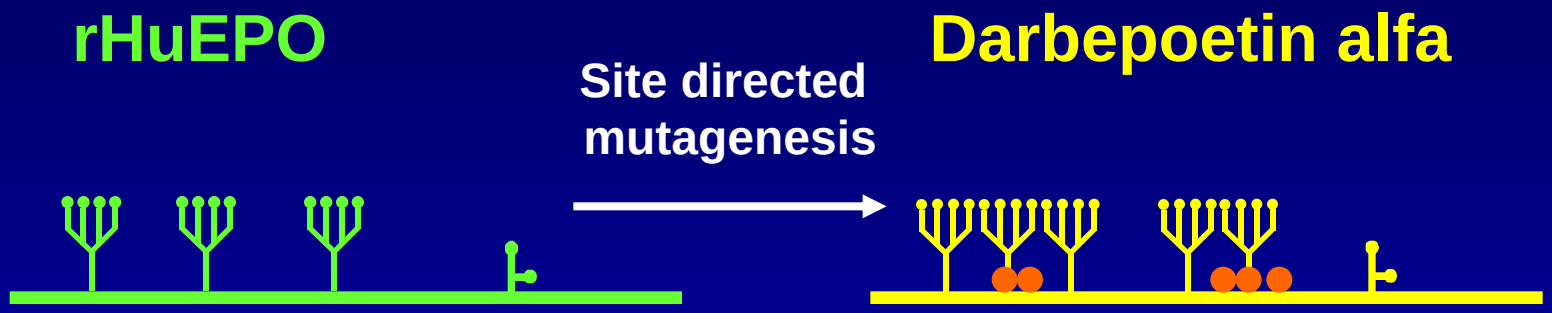
Pharmacological developments in ESAs

2001 Aranesp® (darbepoetin alfa)

2007 Mircera® (C.E.R.A., mPEG-epoetin bet)

2012 Hematide™ (peginesatide)

Comparison of rHuEPO and darbepoetin alfa



- Three N-linked carbohydrate chains
- Up to 14 sialic acid residues
- 30,400 daltons
- 40% carbohydrate

- Five N-linked carbohydrate chains
- Up to 22 sialic acid residues (eight additional residues)
- 37,100 daltons
- 51% carbohydrate

rHuEPO = recombinant human erythropoietin

Macdougall I. Semin Nephrol 2000;20:375–81

Darbepoetin alfa Usage Guidelines

***Nephrol Dial Transplant* 2001;16(suppl 3):22-28**

Nephrol Dial Transplant (2001) 16 [Suppl 3]: 22–28

Nephrology
Dialysis
Transplantation

Practical guidelines for the use of NESP in treating renal anaemia

The NESP Usage Guidelines Group: Pedro Aljama, Jürgen Bommer, Bernard Canaud, Fernando Carrera, Kai-Uwe Eckardt, Walter H. Hörl, Raymond T. Krediet, Francesco Locatelli, Iain C. Macdougall and Björn Wikström

Keywords: anaemia; chronic kidney disease; chronic renal failure; chronic renal insufficiency; darbepoetin alfa; end-stage renal disease; erythropoietin; NESP; pre-dialysis

Introduction

The introduction of novel erythropoiesis stimulating protein (NESP; also known as darbepoetin alfa) re

These differences are similar to those found with rHuEPO [6,7]. A licence application has been submitted for the use of NESP in adult and paediatric chronic renal failure (CRF) patients aged 11 years and above. Pending the availability of safety/efficacy data in the younger paediatric patient population, recommendations on the use of NESP will refer to the use in patients aged 11 years and above.

This document uses the convention 'chronic renal insufficiency' (CRI) to describe patients with CRF who do not yet require dialysis.

Throu ument, doses

Darbepoetin alfa Usage Guidelines

Nephrol Dial Transplant **2001;16(suppl 3):22-28**

Initial Darbepoetin alfa Administration

- **Pre-dialysis and PD**
  - **The recommended starting dose of darbepoetin alfa is 0.45 mcg/kg once weekly by the SC route**
- **HD**
  - **The recommended starting dose of darbepoetin alfa is 0.45 mcg/kg once weekly by either the IV or SC route**

***Nephrol Dial Transplant* 2001;16(suppl 3):22-28**

Nephrol Dial Transplant (2006) 21: 2846–2850
doi:10.1093/ndt/gfl387
Advance Access publication 5 August 2006

NDT
Nephrology Dialysis Transplantation

Original Article

The efficacy of intravenous darbepoetin alfa administered once every 2 weeks in chronic kidney disease patients on haemodialysis

Fernando Carrera, Lino Oliveira, Pedro Maia, Teresa Mendes and Candido Ferreira

Dialysis Unit, Eurodial, Leiria, Portugal

Abstract

Background. It is becoming increasingly more common to administer intravenous (i.v.) darbepoetin alfa to haemodialysis (HD) patients at less frequent dosing intervals in routine clinical practice. This study investigated extending the dosing interval for i.v. darbepoetin alfa treatment from once a week (QW) to once every 2 weeks (Q2W) at the same dose in order to maintain target haemoglobin (Hb) concentrations (11–13 g/dl).

Methods. Stable HD patients in routine clinical

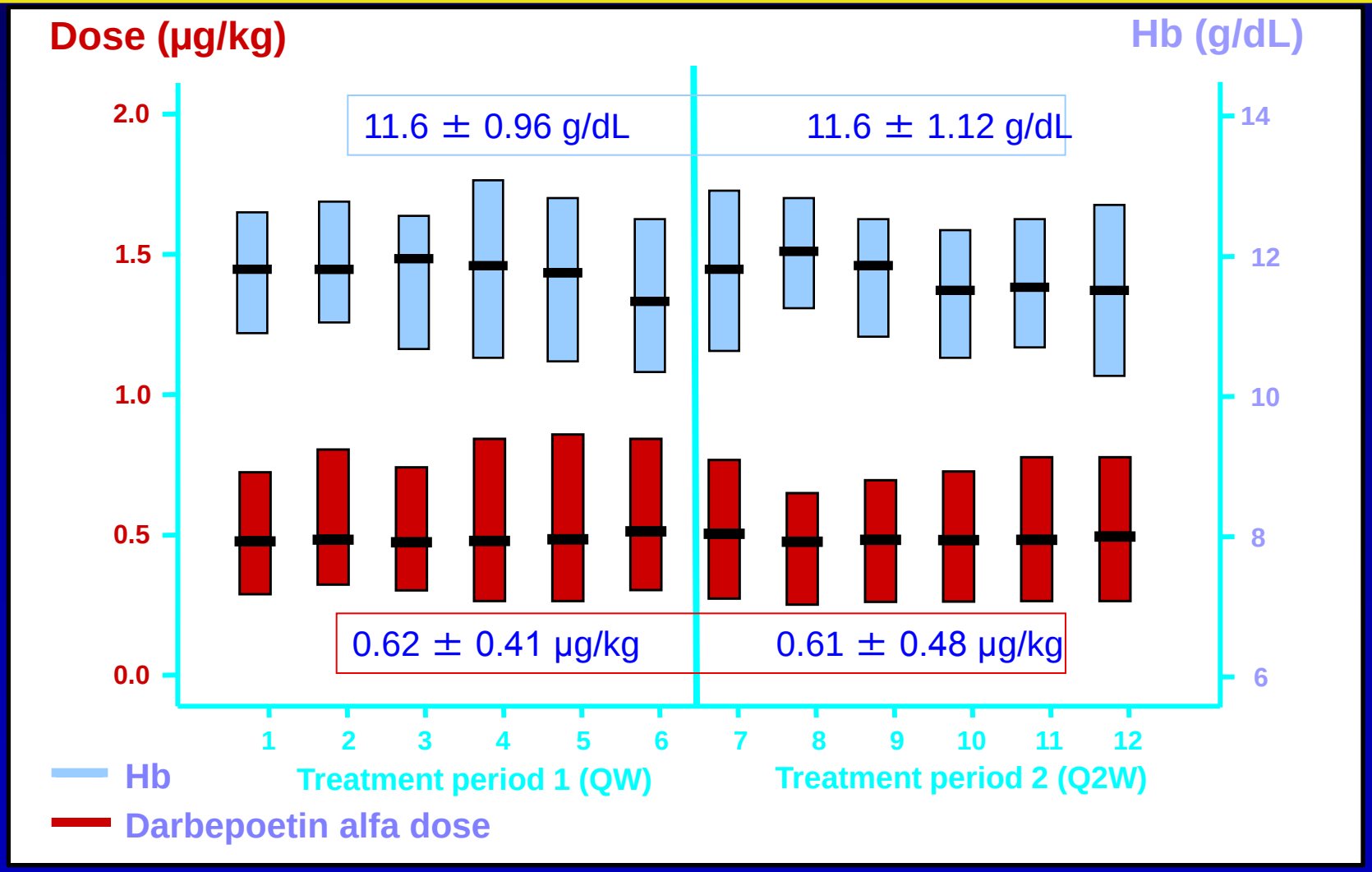
Keywords: darbepoetin alfa; frequency of administration; haemodialysis (HD); intravenous dosing; once every 2 weeks dosing (Q2W); renal anaemia

Introduction

The treatment of renal anaemia using erythropoiesis stimulating agents (ESAs) [darbepoetin alfa and recombinant human erythropoietin (rHuEPO) alfa or

Hb values and darbepoetin alfa dose remained stable throughout the study*

HD Q2W



Carrera F *et al. Nephrol Dial Transplant* 2006;21:2846–2850

*Values expressed as mean values ± SD


Best Practice Guidelines
Anaemia
Chair: F. Locatelli, Lecco, Italy
F. Carrera, Lisbon, Portugal
Guidelines in European Nephrology: from the beginning to 2004
J.S. Cameron, London, United Kingdom
Kidney Disease: Improving Global Outcomes
G. Eknoyan, Houston, USA

Treatment of renal anaemia: frequency of ESA administration

- Epoetin alfa and epoetin beta are commonly given two or three times a week, or even daily (Evidence level A)

- Evidence from randomized trials shows that darbepoetin alfa administered once weekly or once every two weeks can effectively treat anaemia in CKD patients on dialysis (Evidence level A)

NDT Plus (2009) 2 [Suppl 1]: i9–i17
doi: 10.1093/ndtplus/sfn175

NDT PLUS
Nephrology Dialysis Transplantation

Use of darbepoetin alfa in the treatment of anaemia of chronic kidney disease: clinical and pharmacoeconomic considerations

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[1]Dialysis Unit, Eurodial, Euromedic, Leiria, Portugal and [2]University Hospital of Lausanne, Lausanne, Switzerland

Abstract

The introduction of erythropoiesis-stimulating agents (ESAs) into everyday clinical practice has greatly improved the care of patients with chronic kidney disease. ESAs have reduced the need for blood transfusions, improved survival, decreased cardiovascular complications and enhanced patient quality of life. The longer acting ESA, darbepoetin alfa (Aranesp®), which can be administered less frequently than traditional ESAs, provides further benefits to both patients and healthcare professionals relative to the epoetins. Clinical studies have shown that darbepoetin alfa administered once every 2 weeks or once every month allows enhanced convenience and cost savings with no compromise in efficacy, while maintaining patients within target haemoglobin ra

recently published secondary analysis of the CHOIR study [15] suggests that high doses of epoetin alfa, rather than high Hb targets, were the culprit for the increased risk of poor outcomes. The ongoing randomized Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT) is anticipated to add further clarity to this issue [16,17].

Thus, anaemia management is rapidly evolving, as new trial designs and an increasing number of treatment options continue to advance the understanding of Hb control in patients with CKD. Clearly, maintaining patients within target Hb ranges is more important than ever, and the ability of ESAs to contribute to Hb control will be under new scrutiny. Darbepoetin alfa, the first ESA to offer extended dosing intervals over the erythropoietin molecules, epoetins a and beta layed an important le in en ing

Dose savings on switching from epoetin alfa or epoetin beta BIW or TIW to darbepoetin alfa QW or Q2W

Study	Number patients	Study design	Treatment + evaluation	Hb target (g/dL)	Outcome
Tolman 2005	217	EB TIW → DA QW vs EB TIW → EB QW Single centre, open label	9 months	11-12	Change in mean dose on conversion to DA: −20% Change in mean dose on conversion to EB QW: +24%
Molina 2004	112	rHuEPO s.c. → rHuEPO i.v. vs rHuEPO s.c. → DA QW s.c. or i.v.	24 weeks	11-13	DA group: 25% decrease in REI by week 24 rHuEPO group: 39% increase in REI by week 24
Hörl 2002	250	rHuEPO BIW/TIW → DA QW	24 weeks	10-13	Change in mean dose on conversion to DA: −13.3%
Nissenson 2002	507	rHuEPO TIW → DA QW vs continued rHuEPO TIW Multicentre, double-blind	28 weeks	9-13	Change in mean (SD) dose on conversion to DA: Decrease from 63.18 (49.27) to 54.18 (47.56) µg/week Change in mean (SD) dose with continued rHuEPO: increase from 12 706 (10 349) to 13 639 (12 805) U/week
Bock 2008	132	rHuEPO BIW/TIW or QW → DA QW or Q2W, Multicentre, open-label	24 weeks	Within ±1 of baseline levels (10.8-13)	Change in mean DA dose: −25%
Locatelli 2003	343	rHuEPO BIW/TIW or QW → DA QW or Q2W, Multicentre, open label	24 weeks	10-13	Change in mean DA dose: i.v. group: 25.2 to 21.5 µg/week s.c. group: 20.8 to 22.7 µg/week
Brunkhorst 2004	1502	rHuEPO BIW/TIW or QW → DA QW or Q2W, Multicentre, open label	24 weeks	10-13	Change in mean dose on conversion to DA: i.v. group: decrease from 23.23 to 19.92 µg/ week s.c. group: decrease from 22.95 to 21.61 µg/ week
Kessler 2006	1008	rHuEPO BIW/TIW or QW → DA QW or Q2W, Multicentre	24 weeks	10-13	Change in median dose on conversion to DA: i.v. group: decrease from 27.3 to 22.3 µg/week s.c. group: increase from 22.9 to 23.3 µg/week
Martinez Castelao 2003	826	rHuEPO BIW/TIW or QW → DA QW or Q2W, Multicentre	24 weeks	10-13	Change in mean dose on conversion to DA: i.v. group: −19.7% s.c. group: −4.7%

Carrera et al., *NDT Plus* (2009) 2 [Suppl 1]: i9–i17

NDT Plus Advance Access published August 4, 2009

NDT Plus (2009) 1 of 7
doi: 10.1093/ndtplus/sfp097

In-Depth Clinical Review

A meta-analysis of the relative doses of erythropoiesis-stimulating agents in patients undergoing dialysis

Xavier Bonafont[1], Andreas Bock[2], Dave Carter[3], Reinhard Brunkhorst[4], Fernando Carrera[5], Michael Iskedjian[6], Bart Molemans[3], Bastian Dehmel[7] and Sean Robbins[7]

[1]Department of Pharmacy, University Hospital Germans Trias i Pujol, Badalona, Spain, [2]Chefarzt Nephrologie, Kantonsspital, Aarau, Aarau, Switzerland, [3]Department of Statistics, Amgen Ltd, Uxbridge, UK, [4]Klinikum Hannover-Oststadt, Hannover, Germany, [5]Eurodial, Dialysis Unit, Leiria, Portugal, [6]Pharm*Ideas*, Research & Consulting Inc, Oakville, Ontario, Canada and [7]Amgen Europe GmbH, Zug, Switzerland

Correspondence and offprint requests to: Xavier Bonafont; E-mail: xbonafont.germanstrias@gencat.cat

Abstract

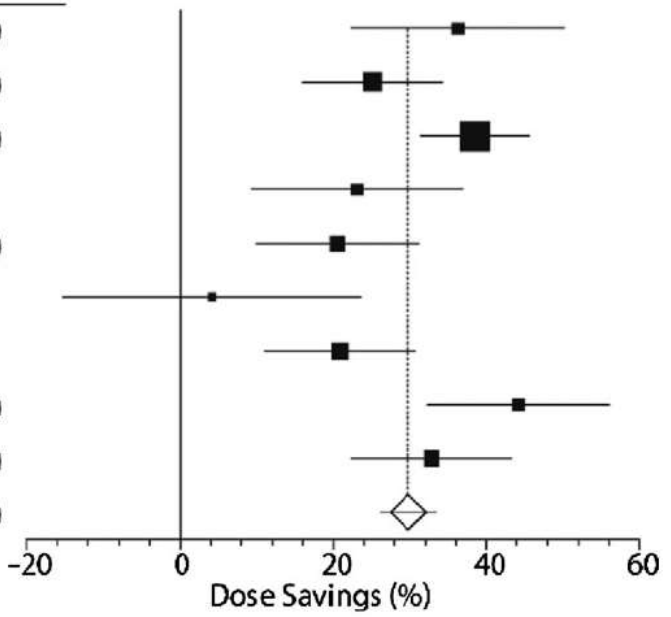
Background. Erythropoiesis-stimulating agents (ESAs) such as epoetin alfa and beta, and darbepoetin alfa have improved the management of anaemia secondary to chronic kidney disease. Numerous studies have reported a dose reduction when patients receiving dialysis were converted from epoetin to darbepoetin alfa using the starting dose conversion of 200:1 as indicated on the prescribing label by the European Medicines Agency. The objective of this

Introduction

Anaemia is a common consequence of chronic kidney disease (CKD) because of the inability of the kidney to produce enough erythropoietin to stimulate the production of red blood cells [1]. This deficiency results in lower haemoglobin (Hb) levels and oxygen availability [2]. Several studies have demonstrated that erythropoiesis (and subsequent increased Hb levels) can be stimulated ad-

Meta-analysis: ca. 30% dose savings could be achieved when HD patients were converted from epoetin to darbepoetin alfa

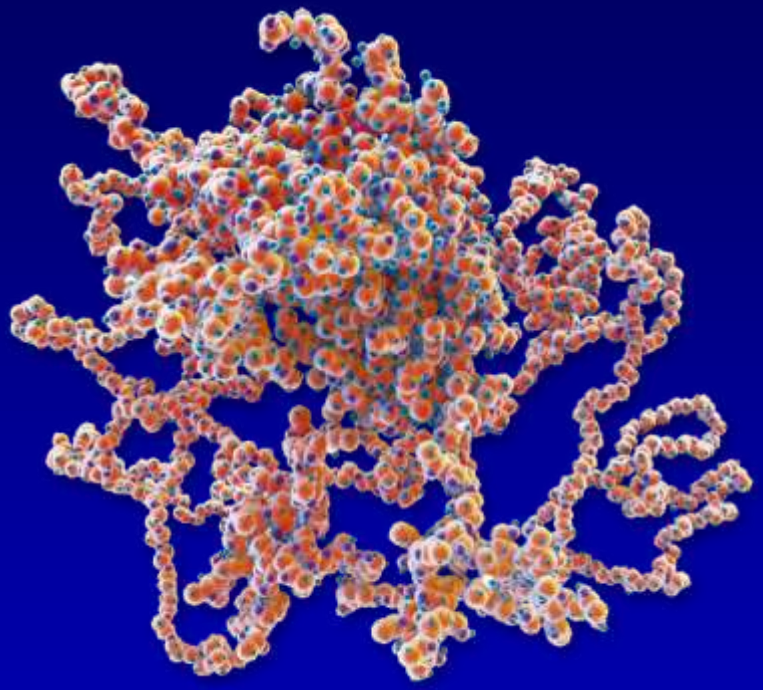
Study	Study Design	Dose savings % (95% CI)
Ardevol et al.[22]	Switch	36.31 (22.45, 50.16)
Bock et al.[14]	Switch	25.10 (15.99, 34.22)
Icardi et al.[25]	Switch	38.50 (31.45, 45.55)
Molina et al.[15]	Switch	23.18 (9.48, 36.88)
Nissenson et al.[16]	RCT	20.55 (10.02, 31.09)
Remón et al.[26]	Switch	4.24 (-15.18, 23.67)
Roger et al.[19]	Switch	20.93 (11.09, 30.78)
Shaheen et al.[27]	Switch	44.19 (32.30, 56.08)
Tolman et al.[17]	RCT	32.87 (22.49, 43.25)
Overall - Pooled		29.85 (26.34, 33.37)



% = percentage; 95% CI = 95% confidence interval; RCT = randomized controlled trial; Switch = Switch-over study

Bonafont X *et al*. NDT Plus 2009;2:347-53

mPEG-epoetin beta
A continuous EPO receptor activator



Molecular weight ~60,000Da

The image represents an artist's view of a possible structure for mPEG-epoetin beta

- **mPEG-epoetin beta is the first continuous EPO receptor activator for treatment of anaemia**
  - **chemically synthesised**
  - **integration of amide bonds between amino groups on N-terminus or lysine residues and methoxy-polyethylene glycol-butanoic acid**

Macdougall I, et al. Annual Renal Week (ASN) 2003, Philadelphia, PA, USA

MIRCERA Pharmacological Properties
Summary

- Different interaction with the erythropoietin receptor compared with epoetin beta
  - lower binding affinity to erythropoietin receptor
  - slower association at the receptor
  - slightly faster dissociation at the receptor
  - slower consumption
  - higher potency *in vivo*
- The same long half-life (~130 h) following IV and SC administration
- Pharmacologic properties might allow extended administration intervals and provide stable erythropoietic response

MIRCERA has a Long Half-Life

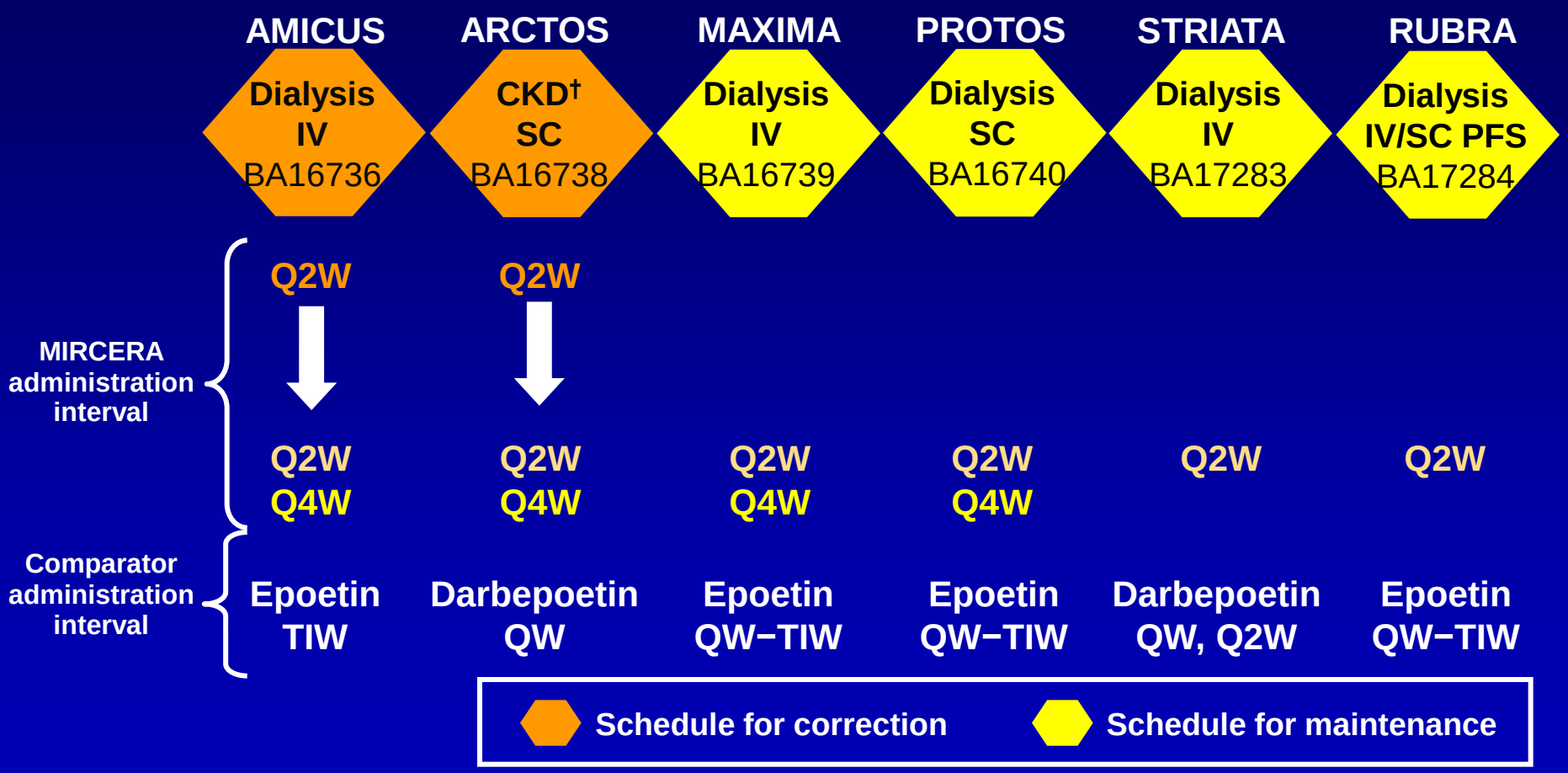
Approximately 130 h following IV and SC administration

Agent	Population	Mean (± SD) half-life (h)	
		IV	SC
Epoetin alfa	Healthy volunteers[1]	6.8 ± 0.6	19.4 ± 2.5
Epoetin beta	Healthy volunteers[1]	8.8 ± 0.5	24.2 ± 2.6
Darbepoetin alfa	Peritoneal dialysis patients[2]	25.3 ± 2.2	48.8 ± 5.2
	Pre-dialysis patients[3]	-	69.6 (29.8)†
MIRCERA	Healthy volunteers[4]	133 ± 9.8	137 ± 21.9
	Peritoneal dialysis patients[4,5]	134 ± 19	139 ± 20

†Mean (SD)

1. Halstenson et al. *Clin Pharmacol Ther*. 1991:50:702-712
2. Macdougall et al. *J Am Soc Nephrol*. 1999;10:2392-2395
3. Padhi et al. *Clin Pharmacokinet*. 2006;45:503-510
4. Macdougall et al. *Am J Kidney Dis*. 2006;47:A41
5. Macdougall et al. *J Am Soc Nephrol*. 2005; 16:759A

Phase III Programme: Study Overview

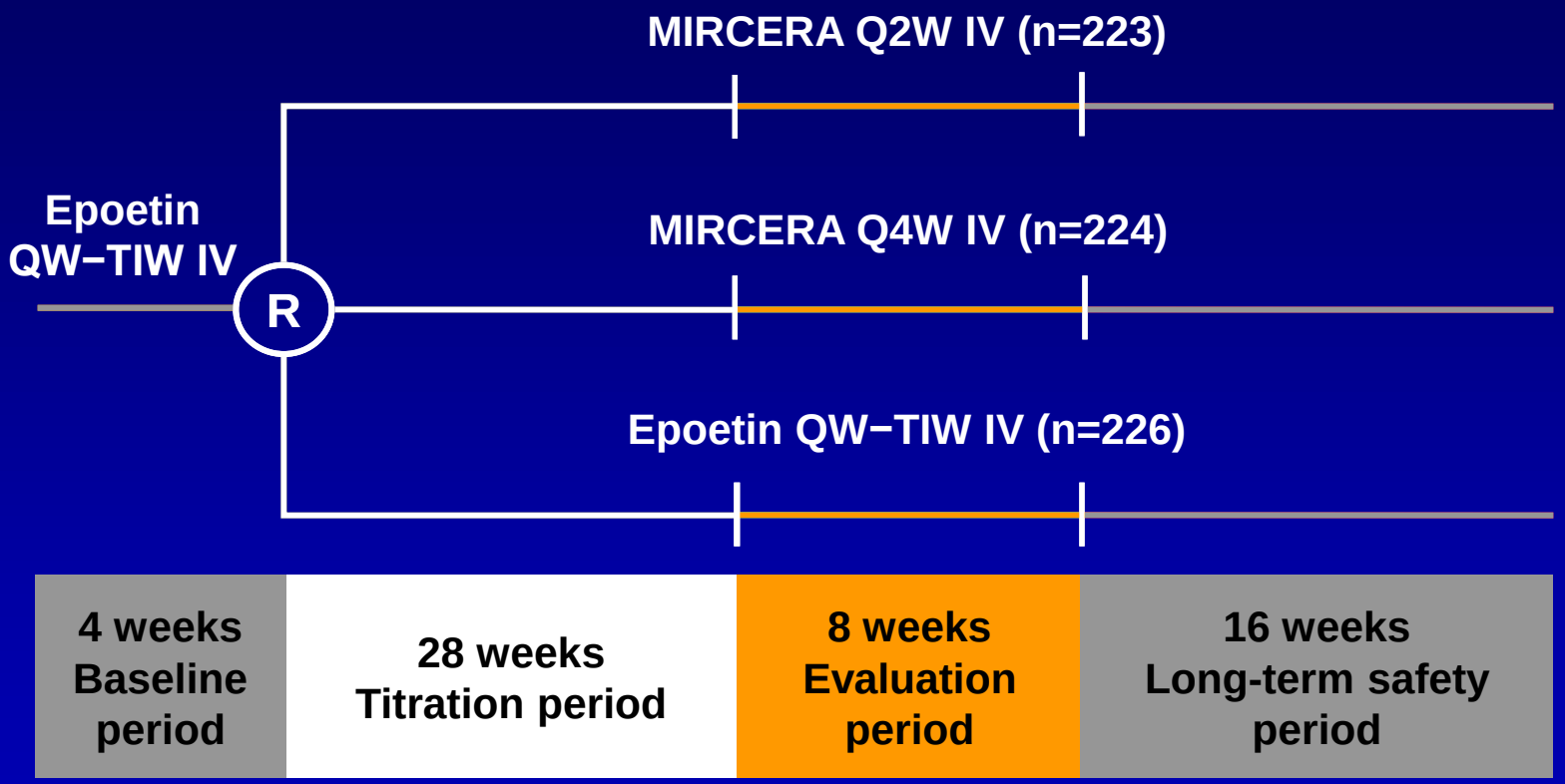


†Chronic kidney disease (CKD) patients not on dialysis

PFS, pre-filled syringe

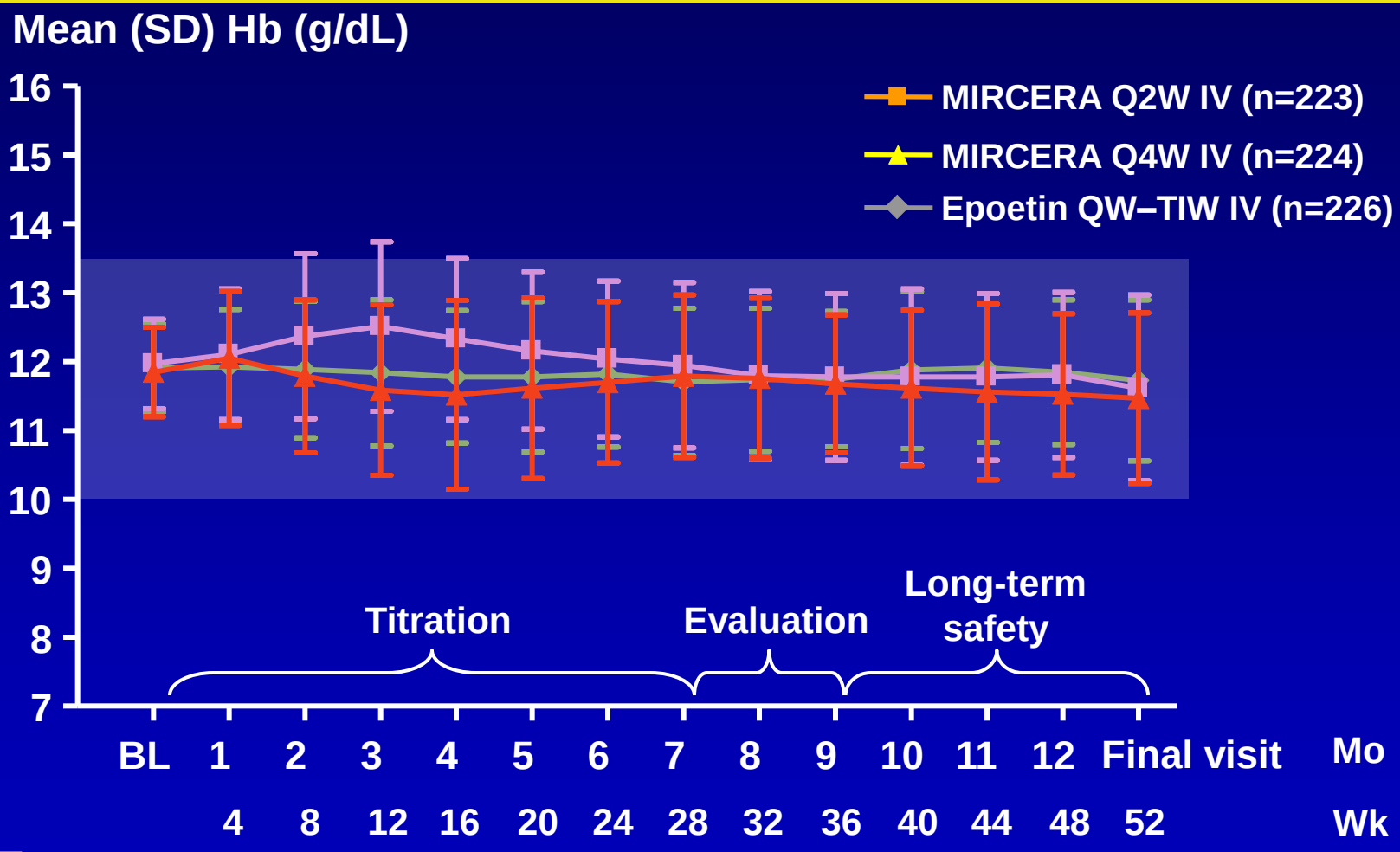
MAXIMA: Study Design

IV conversion from epoetin in patients with CKD on dialysis



Levin et al. *Lancet* 2007;370:1415-1421

Hb Stability Maintained Over 1 Year with Once-Monthly MIRCERA IV



ITT populations

Levin et al. *Lancet*. 2007;370:1415-1421

Once-Monthly IV MIRCERA Maintains Stable Hb Levels After Direct Conversion from Epoetin QW–TIW

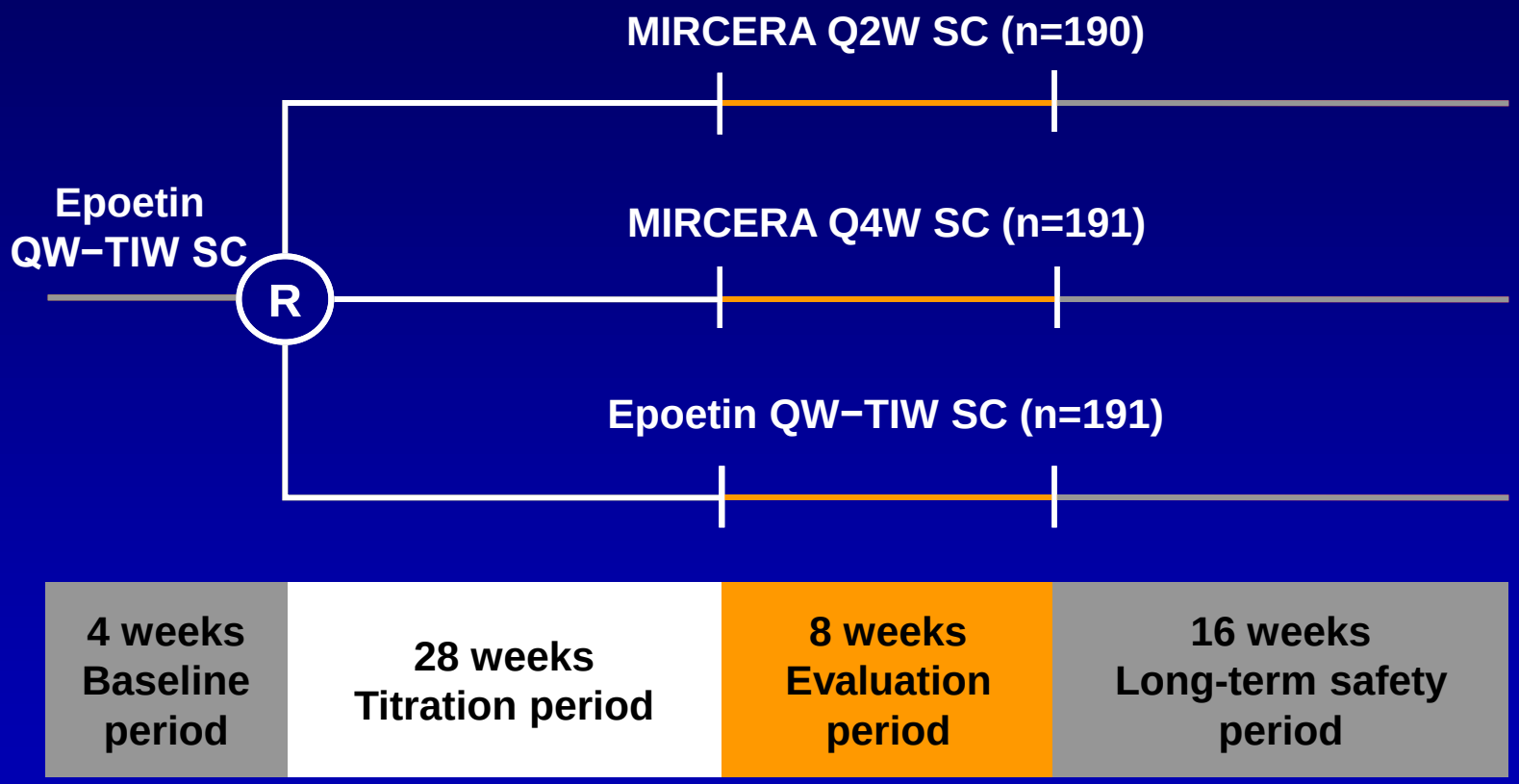
	MIRCERA Q2W IV (n=188)	MIRCERA Q4W IV (n=172)	Epoetin QW–TIW IV (n=180)
Mean (SD) Hb, g/dL†			
Baseline (wk −4 to 0)	12.0 (0.6)	11.8 (0.6)	12.0 (0.6)
Evaluation period (wk 29 to 36)	11.9 (1.1)	11.9 (1.0)	11.9 (0.9)
Long-term safety period (wk 37 to 52)	11.8 (1.0)	11.6 (1.0)	11.8 (1.0)
Patients requiring transfusion, %	9.5	7.3	7.6

†PP populations; results comparable in ITT population

Levin et al. *Lancet*. 2007;370:1415-1421

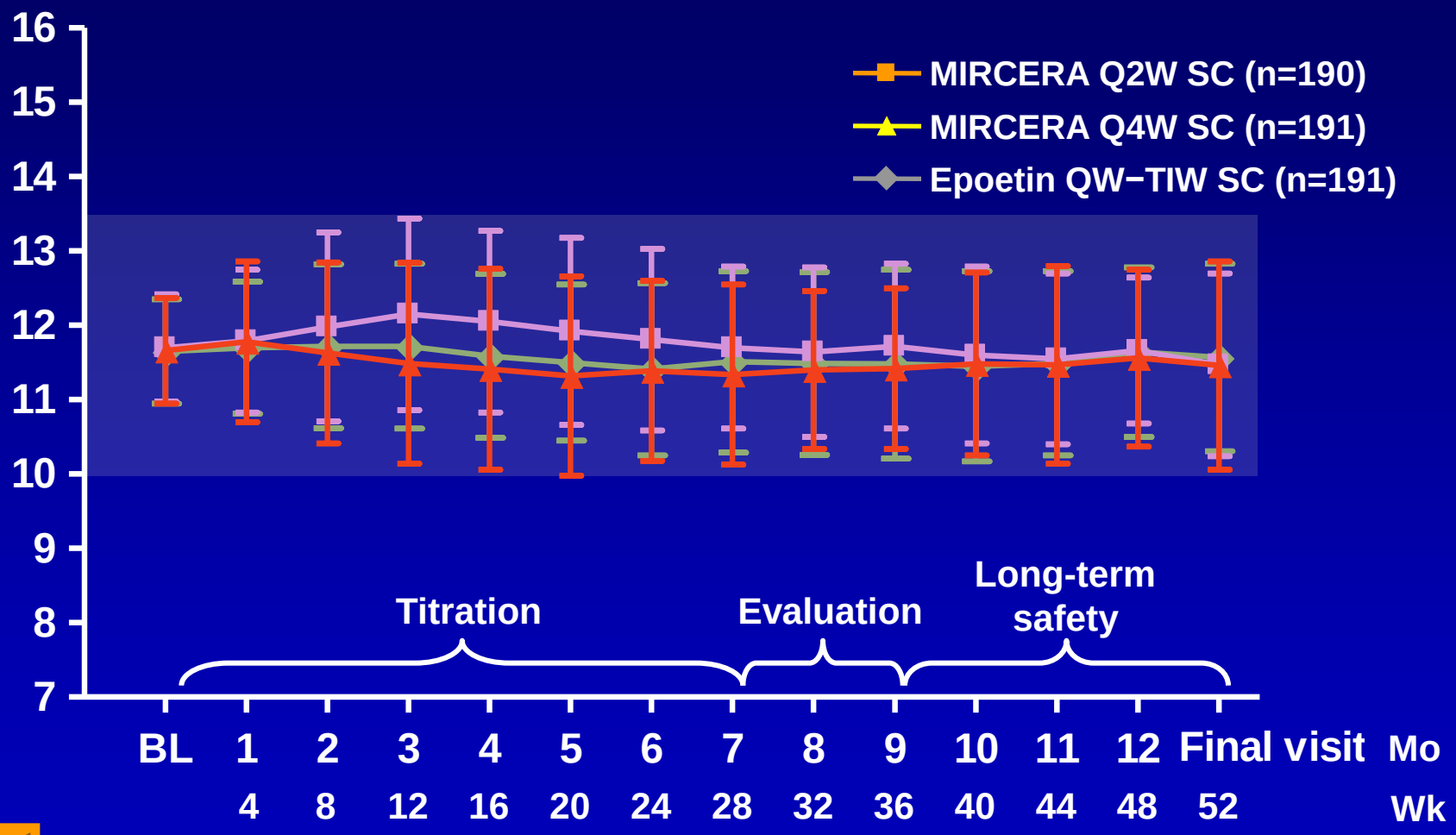
PROTOS: Study Design

SC conversion in patients with CKD on dialysis



Sulowicz et al. *Clin J Am Soc Nephrol.* 2007;2:637-646

Hb Stability Maintained Over 1 Year with Once-Monthly MIRCERA SC



ITT populations

Sulowicz et al. *Clin J Am Soc Nephrol.* 2007;2:637-646

Once-Monthly SC MIRCERA Maintains Stable Hb Levels After Direct Conversion from Epoetin QW–TIW

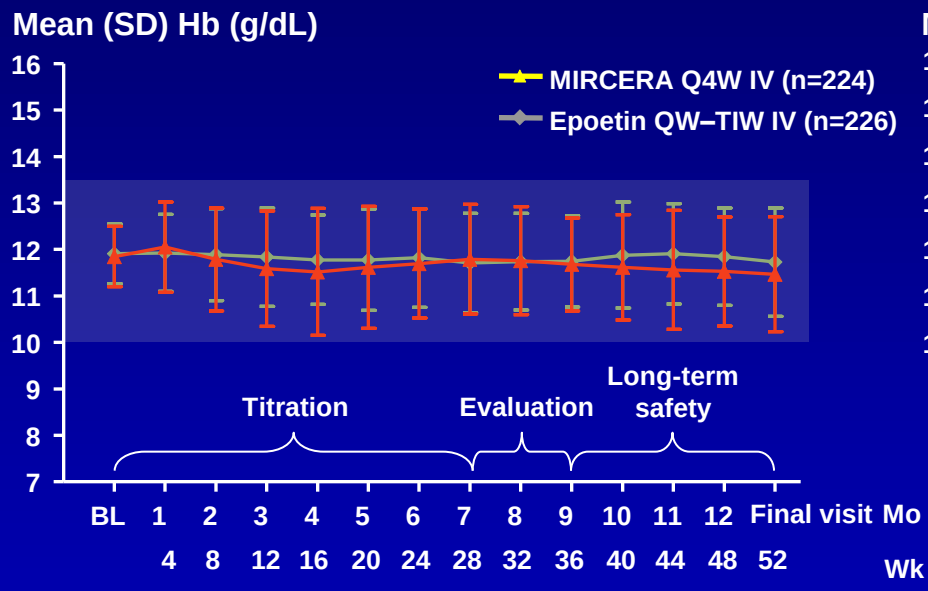
	MIRCERA Q2W SC (n=154)	MIRCERA Q4W SC (n=153)	Epoetin QW–TIW SC (n=167)
Mean (SD) Hb, g/dL†			
Baseline (wk −4 to 0)	11.7 (0.7)	11.6 (0.7)	11.6 (0.7)
Evaluation period (wk 29 to 36)	11.7 (1.0)	11.5 (1.0)	11.5 (1.1)
Long-term safety period (wk 37 to 52)	11.6 (1.0)	11.5 (1.0)	11.6 (1.1)
Patients requiring transfusion, %	6.3	10.5	9.9

†PP populations; results comparable in ITT population

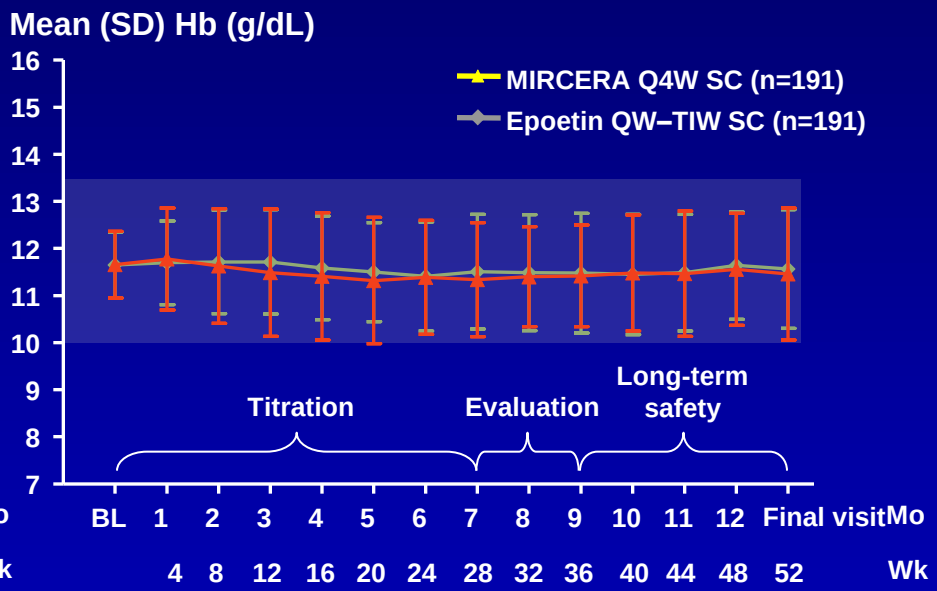
Sulowicz et al. EDTA 2006;
Sulowicz et al. *Clin J Am Soc Nephrol.* 2007;2:637-646

Maintenance: Once-Monthly MIRCERA IV and SC Provides Stable and Sustained Hb Control

PROTOS and MAXIMA studies: patients included were stable on epoetin alfa or beta at baseline



MAXIMA



PROTOS

ITT populations

Levin et al. *Lancet* 2007;370:1415-1421;
Sulowicz et al. *Clin J Am Soc Nephrol* 2007;2:637-646

WCN May 25, 2009

Anemia Management Forum Asia, 2011

M558] C.E.R.A. *VS*. DARBEPOETIN ALFA AS MAINTENANCE THERAPY FOR ANAEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD): THE PATRONUS STUDY

12 BEST ABSTRACTS

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Nephrol Dial Transplant (2010) 1 of 9
doi: 10.1093/ndt/gfq305

Original Article

NDT
Nephrology Dialysis Transplantation

Maintenance treatment of renal anaemia in haemodialysis patients with methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa administered monthly: a randomized comparative trial

Fernando Carrera[1], Charmaine E. Lok[2], Angel de Francisco[3], Francesco Locatelli[4], Johannes F.E. Mann[5], Bernard Canaud[6], Peter G. Kerr[7], Iain C. Macdougall[8], Anatole Besarab[9], Giuseppe Villa[10], Isabelle Kazes[11], Bruno Van Vlem[12], Shivinder Jolly[13], Ulrich Beyer[14], Frank C. Dougherty[14] and on behalf of the PATRONUS Investigators

[1]Eurodial, Dialysis Unit, Leiria, Portugal, [2]Toronto General Hospital, Toronto, Canada, [3]Hospital Universitario Valdecilla, Santander, Spain, [4]Ospedale Alessandro Manzoni, Lecco, Italy, [5]University of Erlangen Medical Center and KfH Kidney Center, Munchen, Germany, [6]Lapeyronie University Hospital, CHU Montpellier, Montpellier, France, [7]Nephrology Monash Medical Centre, Clayton, Australia, [8]King's College Hospital, London, UK, [9]Henry Ford Health System, Detroit, USA, [10]Nephrology and Dialysis Dept., S. Maugeri Foundation IRCCS, Pavia, Italy, [11]Centre Hospitalier Universitaire de Reims, Reims, France, [12]Renal Unit OLV, Aalst, Belgium, [13]Clinical Research Solutions Inc., Kitchener, Canada and [14]F. Hoffmann-La Roche, Basel, Switzerland

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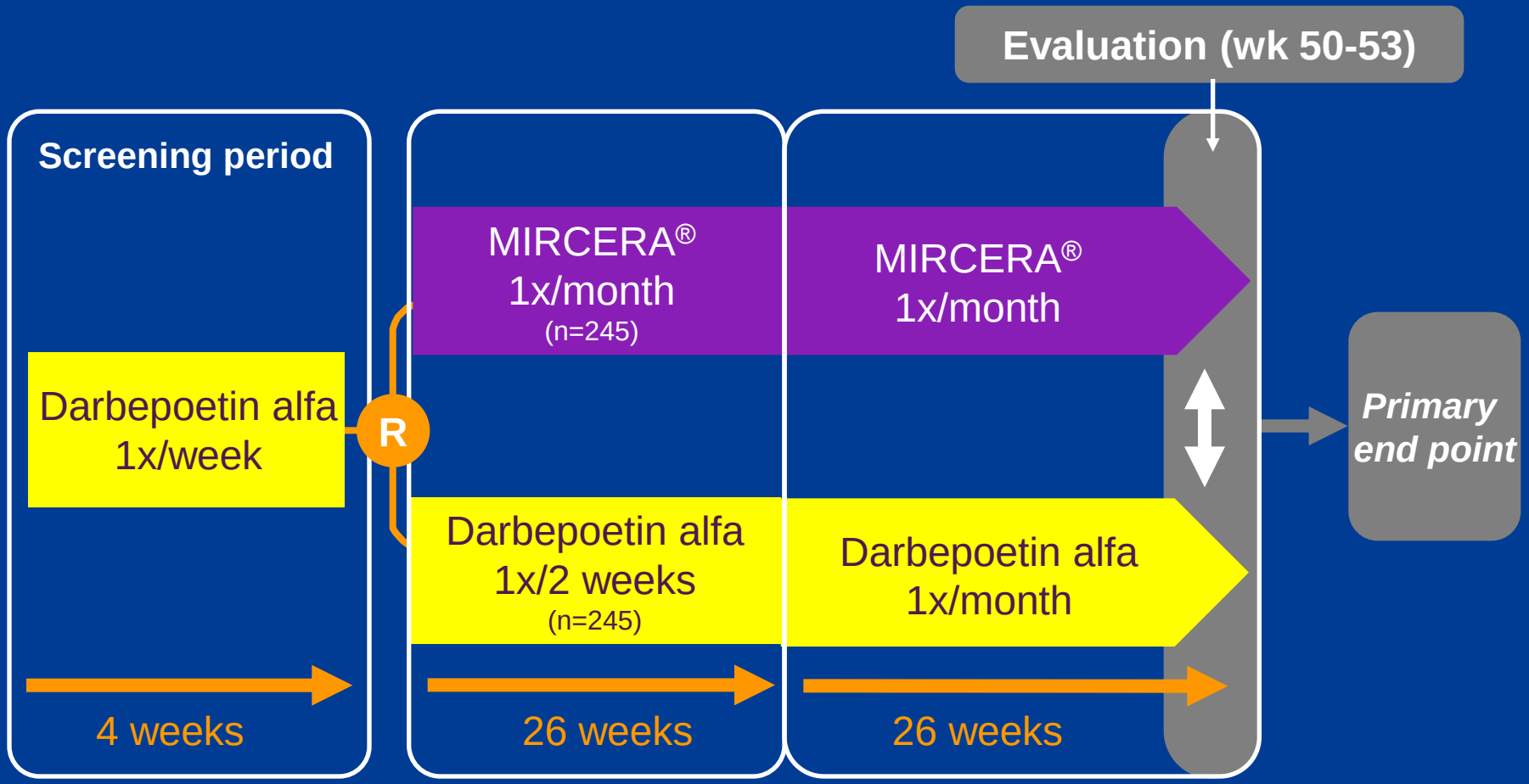
PATRONUS compared once-monthly MIRCERA® and darbepoetin alfa maintenance treatment

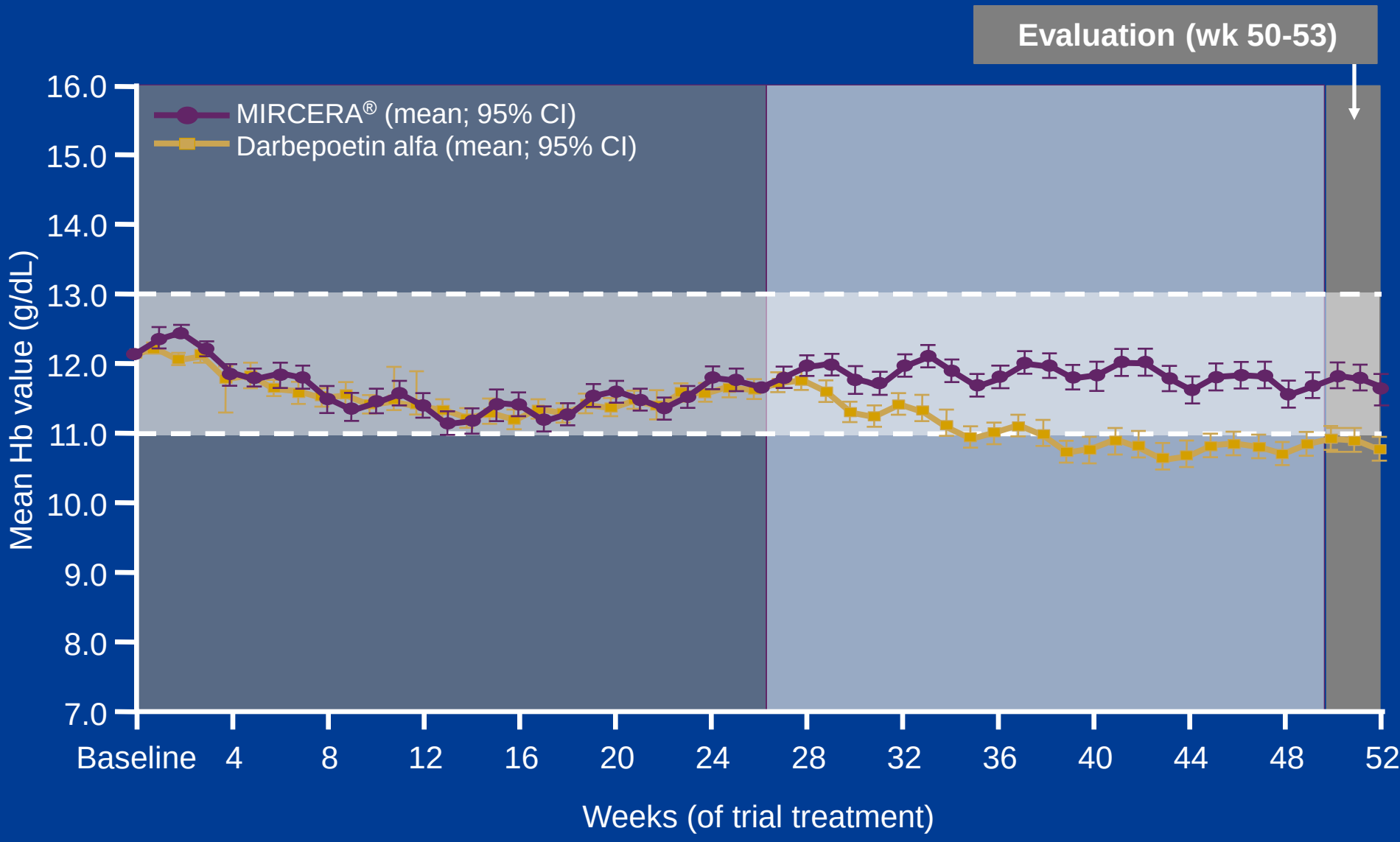
Anemia Management Forum Asia, 2011



R, randomisation

Only once-monthly MIRCERA® maintained Hb levels during the second 26-week treatment period

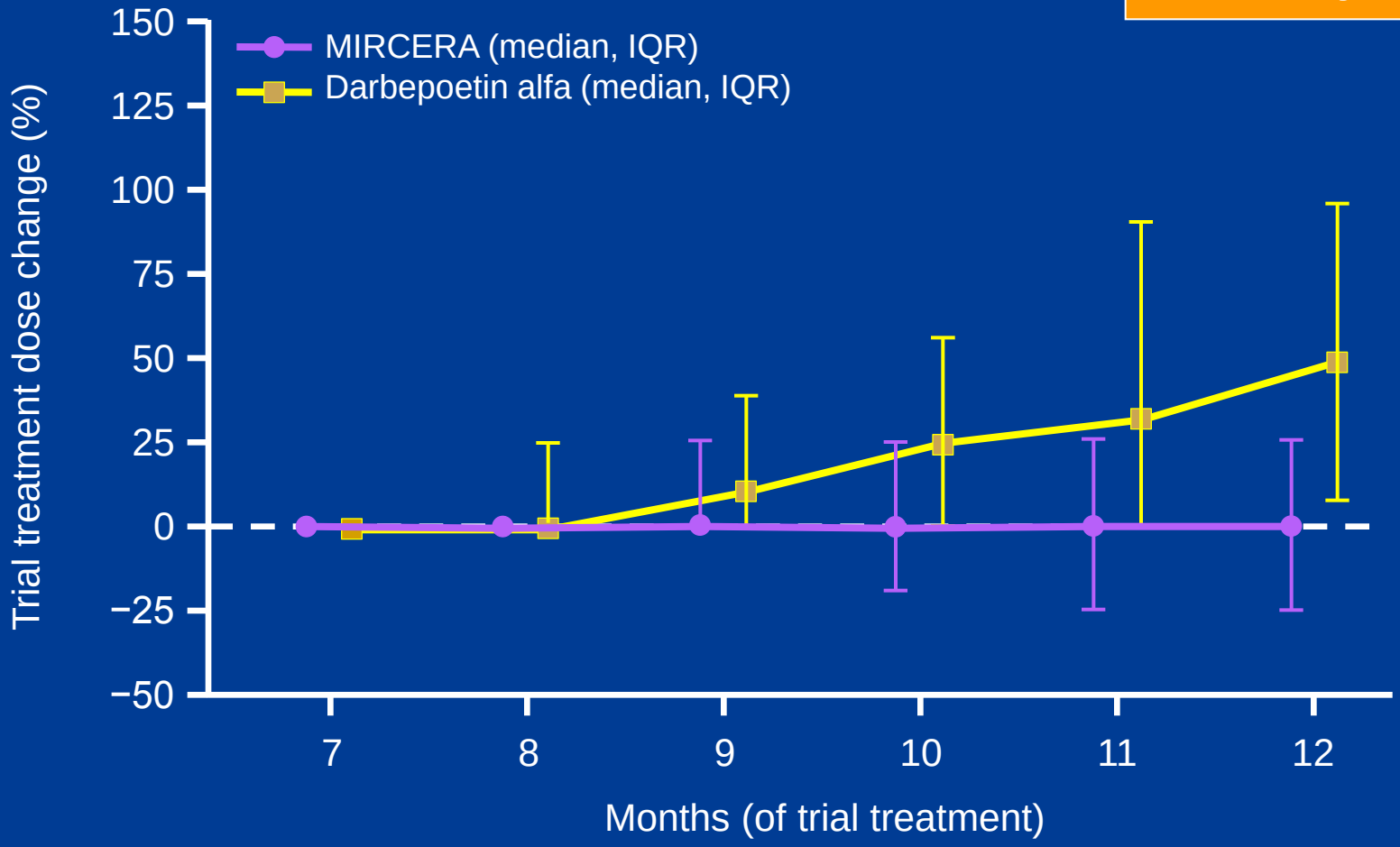
Anemia Management Forum Asia, 2011



MIRCERA® dose was unchanged during the second 26-week treatment period

Anemia Management Forum Asia, 2011

Secondary end point



Darbepoetin alfa dose increased by >35% during the second 26-week treatment period

Anemia Management Forum Asia, 2011

Secondary end point

Median (IQR) treatment dose, μg/month	MIRCERA® n=211	Darbepoetin alfa n=219
Week 27	**200** (120-313)	**150** (80-280)
Months 11 and 12	**196** (120-351)	**225** (106-400)

0%

+35%

- **The median MIRCERA® dose was virtually unchanged during the second 26-week treatment period whereas darbepoetin alfa substantially increased by 35%**

Conclusions

MIRCERA® was shown to be superior to darbepoetin alfa as once-monthly treatment:

- **Significantly more patients responded with MIRCERA® compared with darbepoetin alfa**
- **MIRCERA® maintained Hb levels within a tight target range during the second 26-week treatment period**
- **Mean Hb levels for patients receiving darbepoetin alfa fell to below the lower target (11 g/dL) over the same 26-week period, despite substantial dose increases**

This is the first large, randomised, prospective head-to-head study that has shown one ESA to offer superior efficacy compared with another

Carrera F. *Nephrol Dial Transplant 2010;25:4009-4017*

Variations in ESA half life

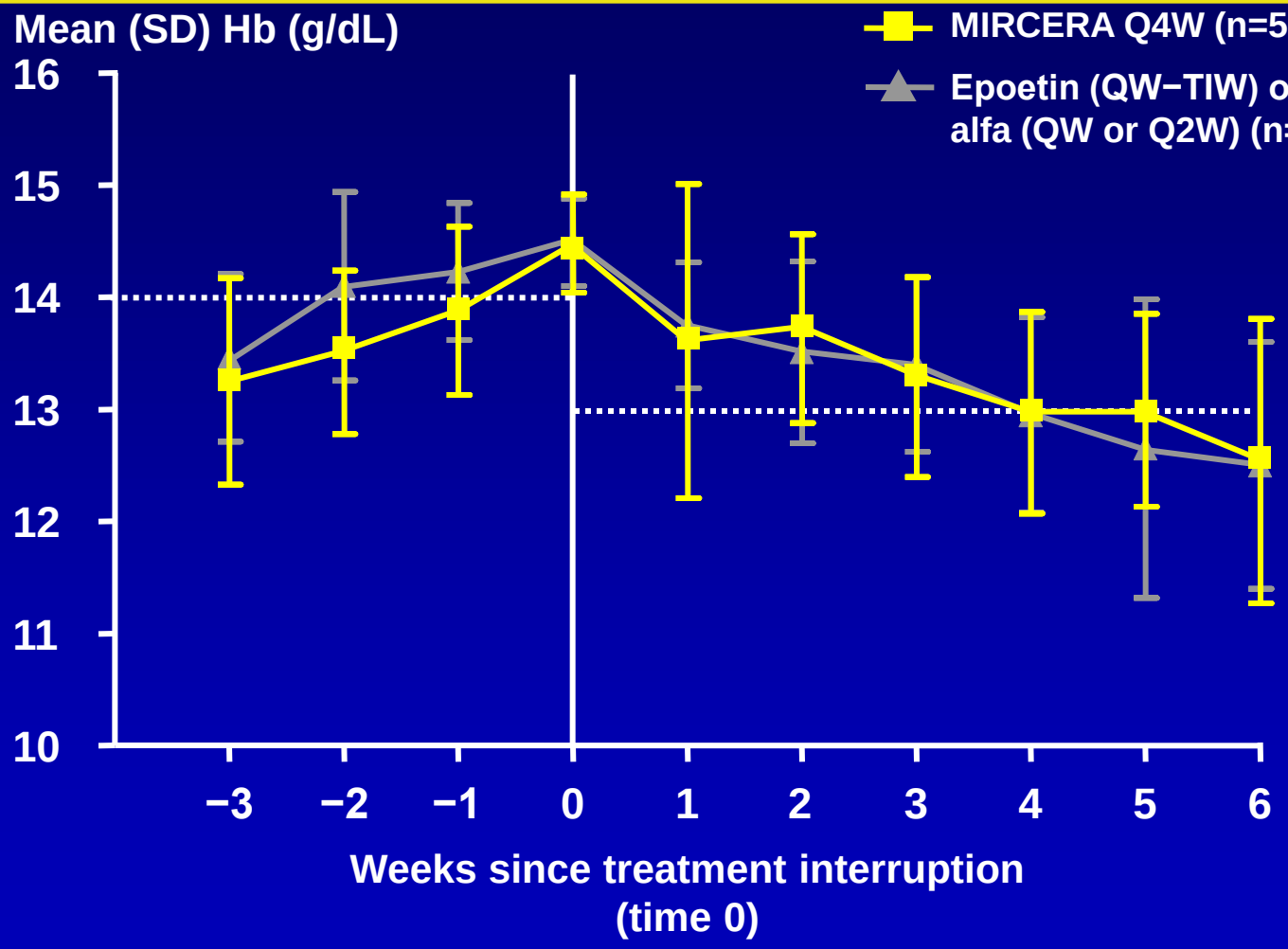
Agent	Population	Mean (±SE) half life (h)	
		i.v.	s.c.
Epoetin alfa	Healthy volunteers[1]	6.8±0.6	19.4±2.5
Epoetin beta	Healthy volunteers[1]	8.8±0.5	24.2±2.6
Darbepoetin alfa	PD patients[2]	25.3±2.2	48.8±5.2
	Pre-dialysis patients[3]	–	69.6 (29.8)†
mPEG epoetin beta	Healthy volunteers[4]	133±9.8	137±21.9
	PD patients[4,5]	134±19	139±20

†Mean (SD)

s.c. = subcutaneous; SE = standard error
SD = standard deviation

1. Halstenson CE, et al. Clin Pharmacol Ther 1991:50:702–12
2. Macdougall IC, et al. J Am Soc Nephrol 1999;10:2392–5
3. Padhi D, et al. Clin Pharmacokinet 2006;45:503–10
4. Macdougall IC, et al. Am J Kidney Dis 2006;47:A41
5. Macdougall IC, et al. J Am Soc Nephrol 2005;16:759A

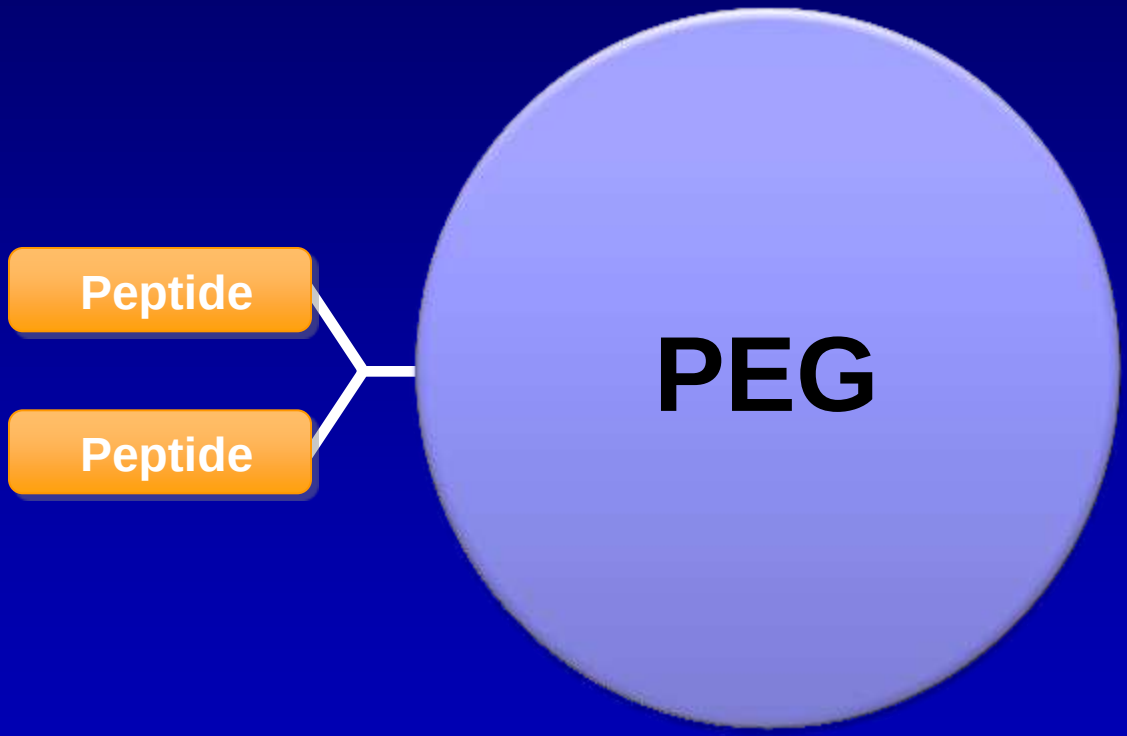
Rate of Hb Decline After Dose Interruption is not Affected by MIRCERA Half-Life



Safety populations

Heifets & Dougherty. WCN 2007

Peginesatide structure: polyethylene glycol (PEG) and peptide



Peginesatide: a novel investigational ESA

- The amino acid sequence of peginesatide is unrelated to that of EPO
- In phase II studies, monthly dosing increased and maintained Hb within target
- Peginesatide does not appear to generate antibodies to endogenous EPO
- Preliminary results to date support the treatment of anaemia with peginesatide in PRCA patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N Engl J Med 2009; 361:1848–55

A Peptide-Based Erythropoietin-Receptor Agonist for Pure Red-Cell Aplasia

Iain C. Macdougall, M.D., Jerome Rossert, M.D., Nicole Casadevall, M.D., Richard B. Stead, M.D., Anne-Marie Duliege, M.D., Marc Froissart, M.D., and Kai-Uwe Eckardt, M.D.

ABSTRACT

BACKGROUND

We investigated whether a novel, synthetic, peptide-based erythropoietin-receptor agonist (Hematide, Affymax) can stimulate erythropoiesis in patients with anemia that is caused by antierythropoietin antibodies.

METHODS

In this open-label, single-group trial, we enrolled patients with chronic kidney disease who had pure red-cell aplasia or hypoplasia due to antierythropoietin antibodies and treated them with a synthetic peptide-based agonist of an erythropoietin receptor. The agonist was administered by subcutaneous injection at an initial dose

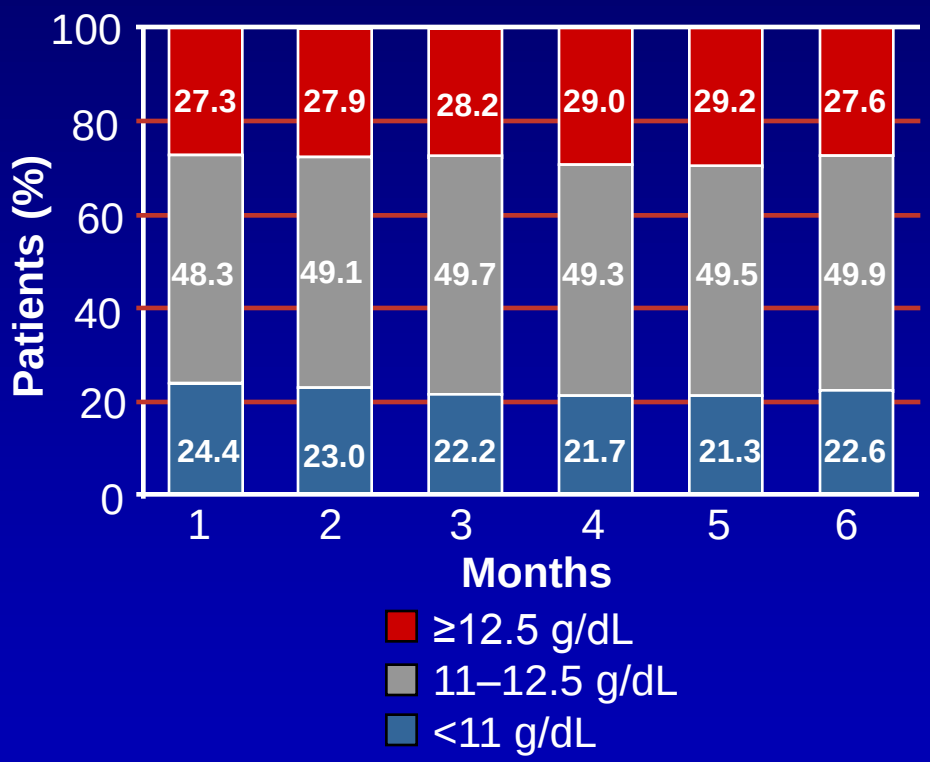
From the Department of Renal Medicine, King's College Hospital, London (I.C.M.); the Departments of Nephrology, (J.R.) and Physiology (M.F.), Georges Pompidou European Hospital, Assistance Publique–Hôpitaux de Paris; Paris-Descartes University (J.R., M.F.); and the Department of Hematology, Hôpital Saint Antoine, Assistance Publique–Hôpitaux de Paris and Pierre et Marie Curie University (N.C.) — all in Paris; INSERM U 790, Villejuif, France (N.C.); BioPharma Consulting Ser-

Mean Hb levels are not the whole story

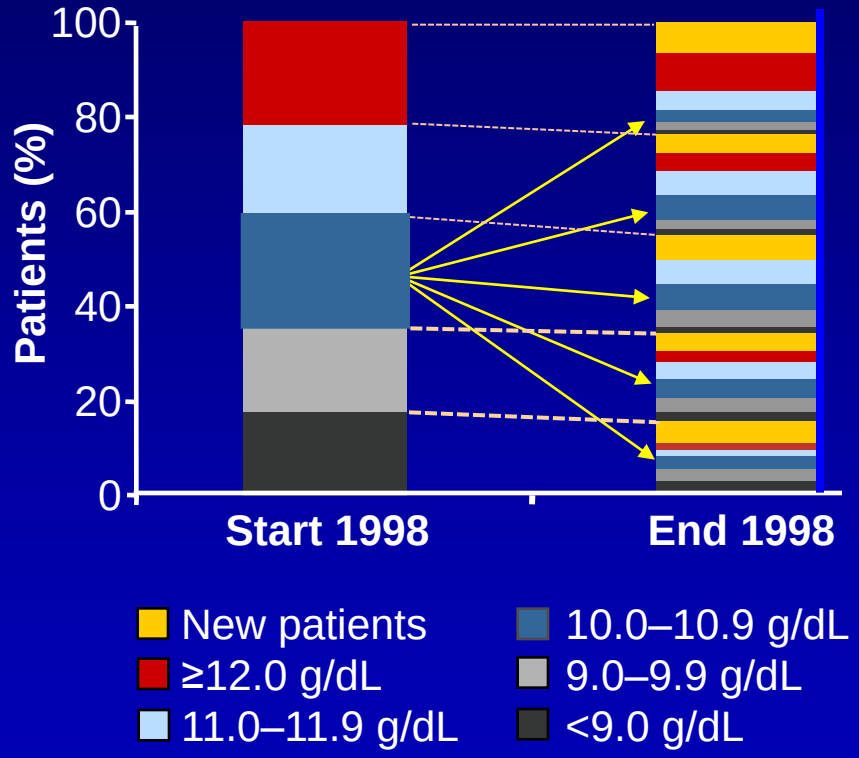
Hb cycling and variability

In a population-based view Hb appears stable, but in individual patients Hb varies considerably with time

Distribution of monthly Hb levels for the overall study population



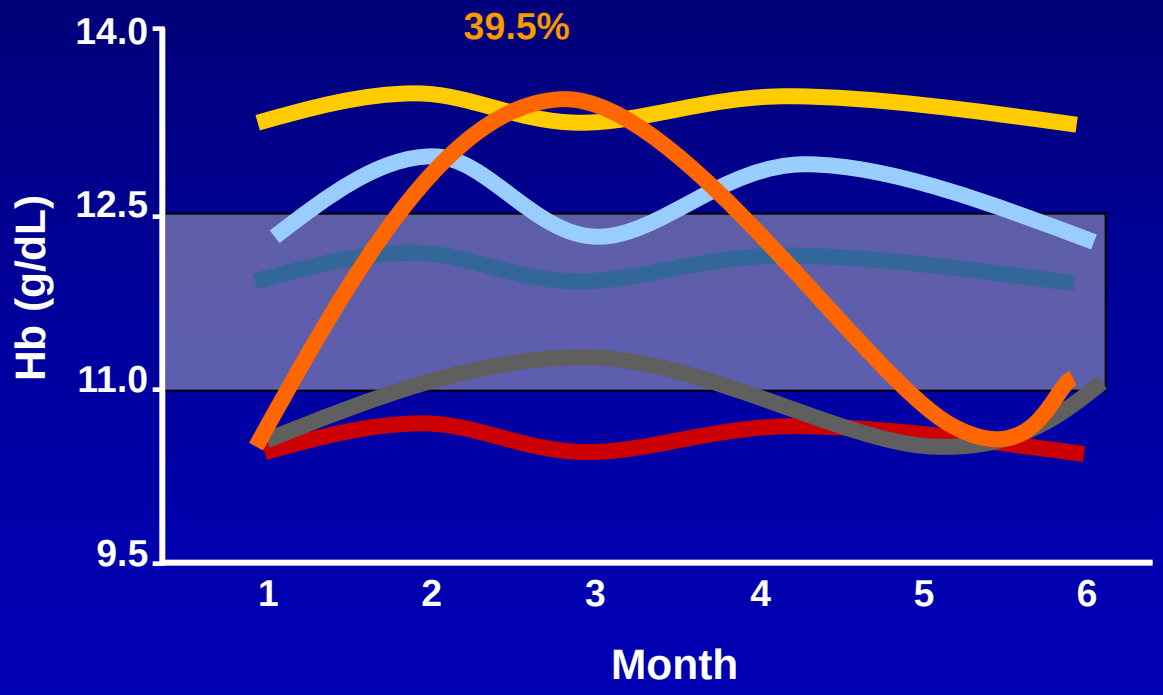
Hb fluctuations in a cohort of UK dialysis patients



UK Renal Registry Report 1999, www.renalreg.com/reports

More than 90% of patients experience Hb fluctuations

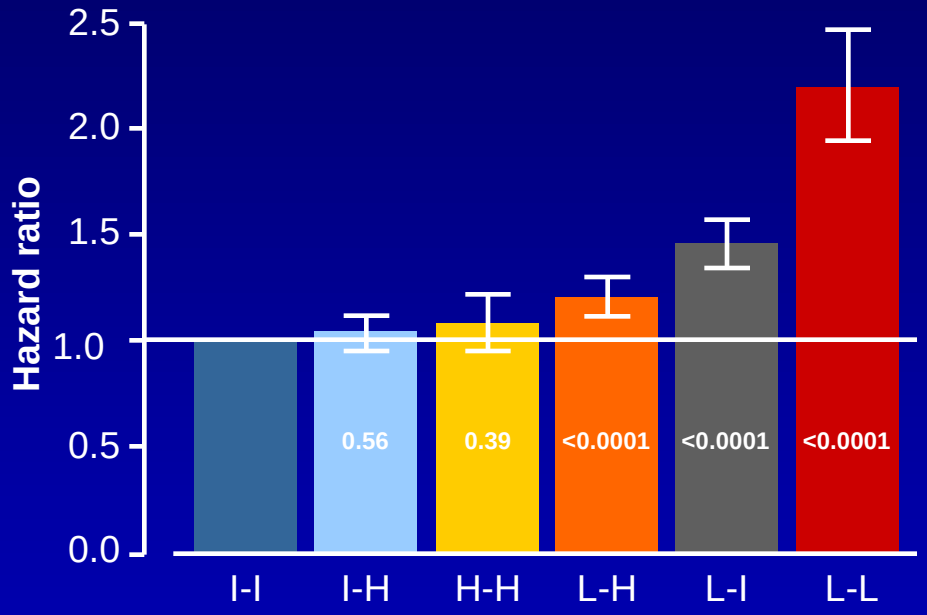
Nearly 40% of patients crossed two Hb boundaries within 6 months (n=152’846)

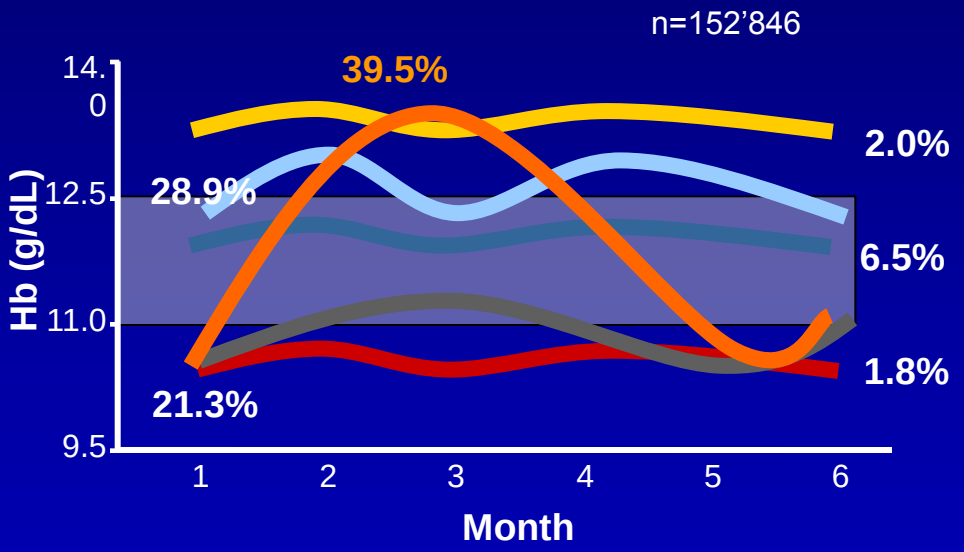


2.0%	High Hb
28.9%	Low amplitude high Hb
6.5%	Target Hb
39.5%	High amplitude fluctuations
21.3%	Low amplitude low Hb
1.8%	Low Hb

Ebben J et al. *Clin J Am Soc Nephrol* 2006;1:1205–1210

Hb values below the target range, rather than Hb variability itself may be the primary driver of increased risk of death

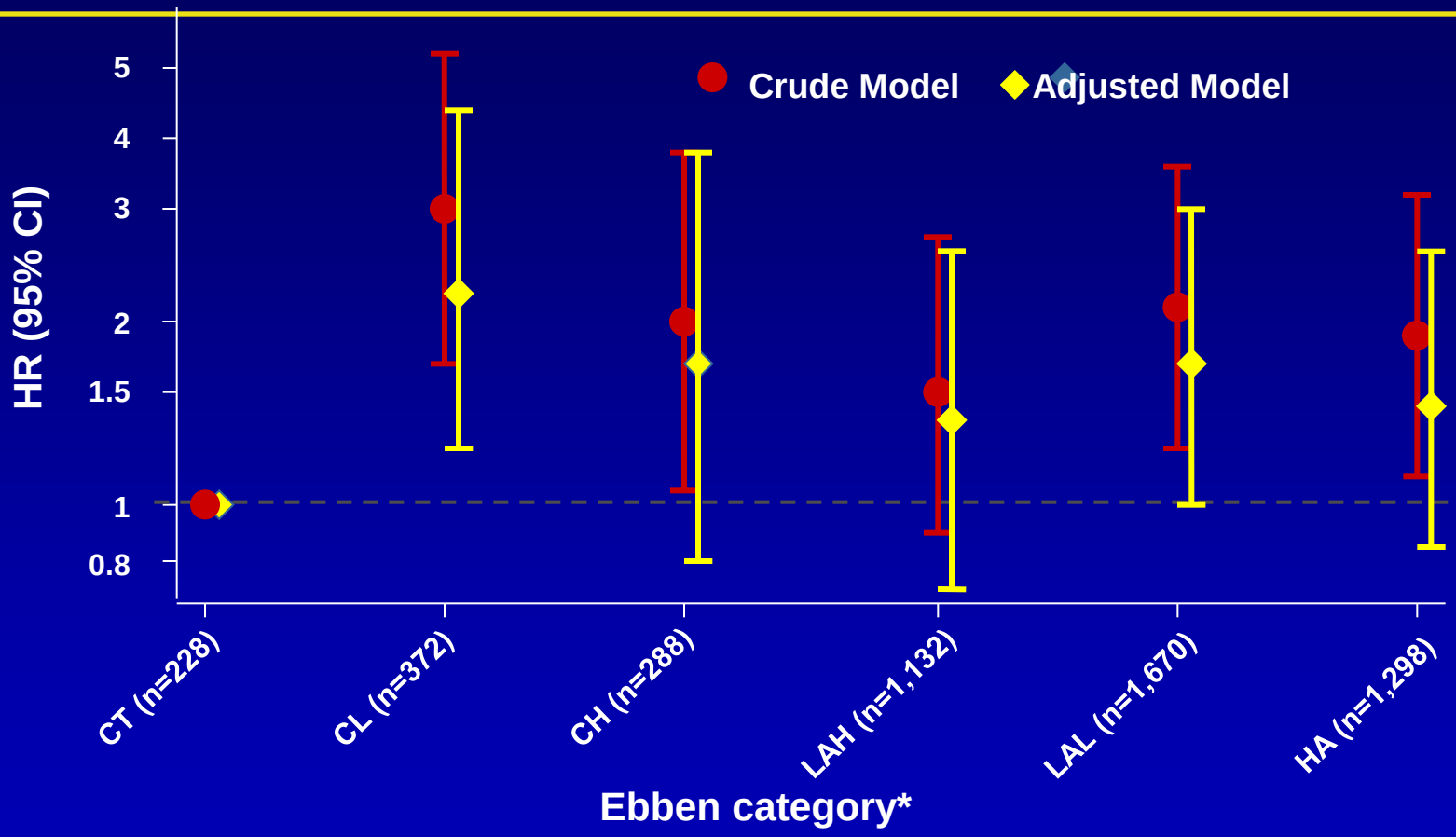




I-I, intermediate-intermediate; I-H, intermediate-high; H-H, high-high; L-H, low-high; L-I, low-intermediate; L-L, low-low

Gilbertson DT et al. *Clin J Am Soc Nephrol* 2008;3:133–138
Ebben J et al. *Clin J Am Soc Nephrol* 2006;1:1205–1210

Patients with consistently low (CL) levels of Hb had over twice the risk of death compared to patients consistently on target (CT) – ARO Study



CL, consistently low (<11 g/dl)

CT, consistently on target (11–12.5 g/dl)

CH, consistently high (>12.5 g/dl)

LAH, low-amplitude fluctuation / high Hb levels (>11 g/dl)

LAL, low-amplitude fluctuation / low Hb levels (<12.5 g/dl)

HA, high-amplitude fluctuation (≤11 g/dl to ≥12.5 g/dl)

K.U. Eckardt, *et al*. WCN 2009. Abstract M557

*Ebben J *et al. Clin J Am Soc Nephrol* 2006;1:1205–1210

Hb variability patterns and mortality

- There is a significant association between Hb variability patterns and increased mortality risk
- Key factors include
  - the overall direction of Hb values during that period
  - the timing of Hb values <11g/dL during a specific time period
  - **the longer the amount of time with Hb <11g/dL, the greater the risk of death**

Gilbertson ET, et al. Clin J Am Soc Nephrol 2008;3:133–8

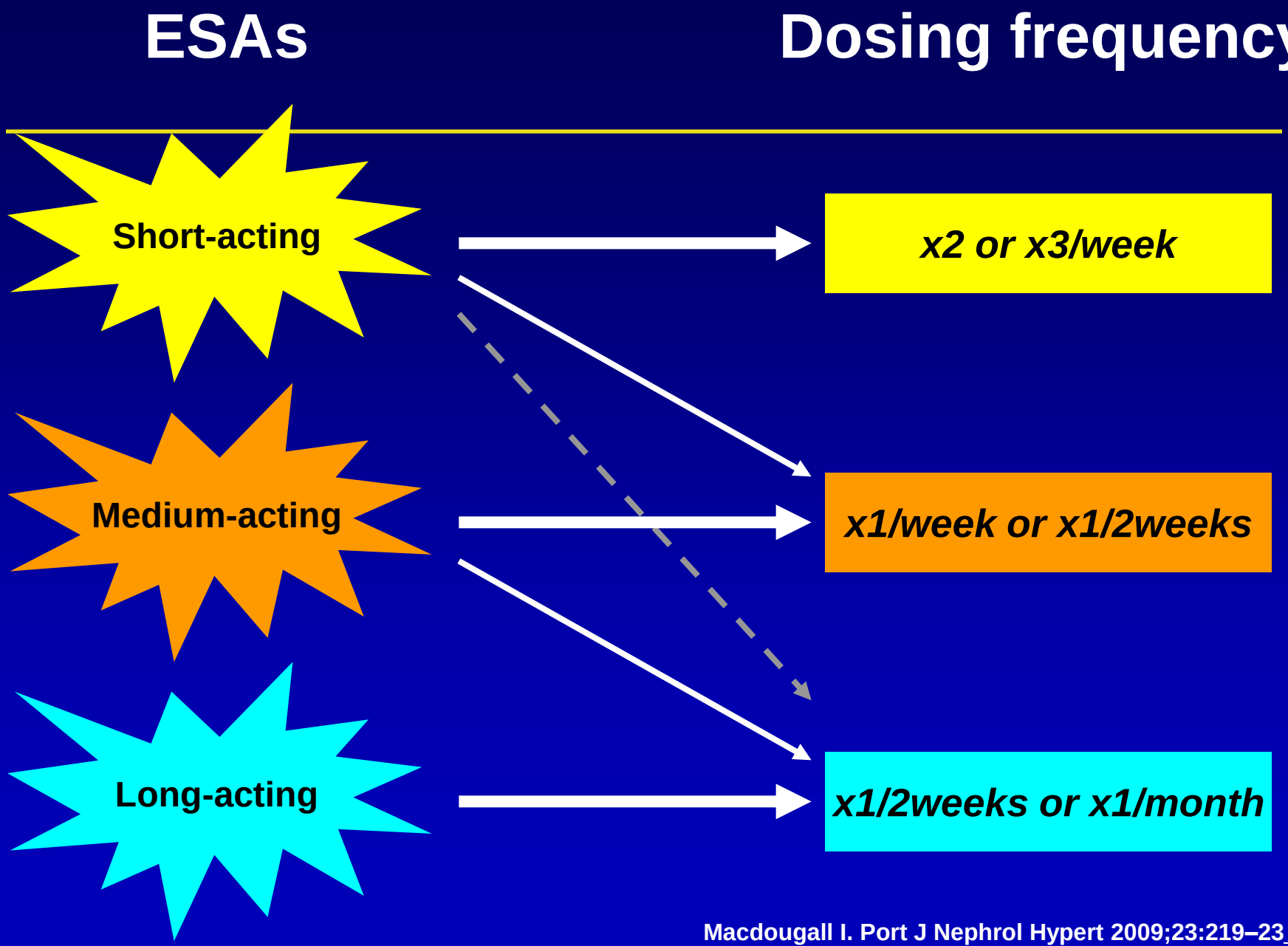
Factors Impacting on Hb Variability

Optimal ESA usage may improve stability

Patient-related factors	Intercurrent events	Practice pattern-related
• Vascular access modality	• Hospitalisation	• **Anaemia management**
• RBC survival	• Infection	• **ESA dose changes**
• Secondary hyperparathyroidism	• Inflammation	• Narrow target Hb range
• Cancer	• Bleeding / haemolysis	• Iron management
• Haematology disorders	• Nutritional deficiencies	• Dialysis adequacy
• Diabetes	• PRCA	• Water purity
	• Medications	• Payment restrictions
	• Interdialytic weight gain	

Limited capacity for physician influence

Fishbane & Berns. *Kidney Int*. 2005;68:1337-1343;
Gilbertson et al. *Nephrol Dial Transplant*. 2006;21(Suppl 4):iv169

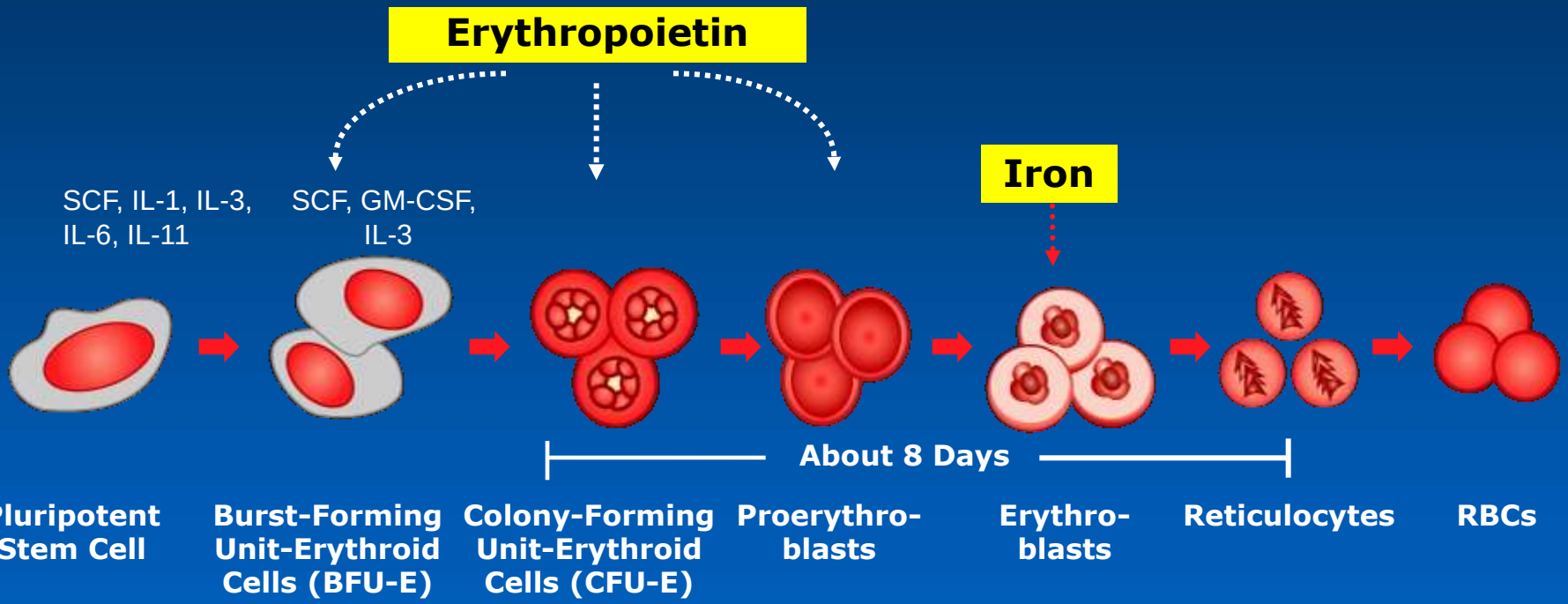


Macdougall I. Port J Nephrol Hypert 2009;23:219–23

Anaemia of CKD: It is not just EPO!

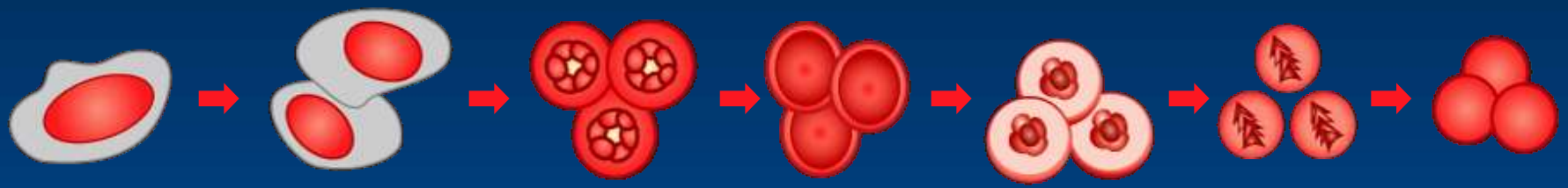
What About the Iron?

Erythropoiesis in CKD



Papayannopoulou T, et al. In: Hoffman R, et al., ed. *Hematology: Basic Principles and Practice*. 4th ed. 2005;267-288.

Erythropoiesis in CKD



+

+

↑ Fas Ag

Apoptosis

↓EPO production

EPO

Iron

–

–

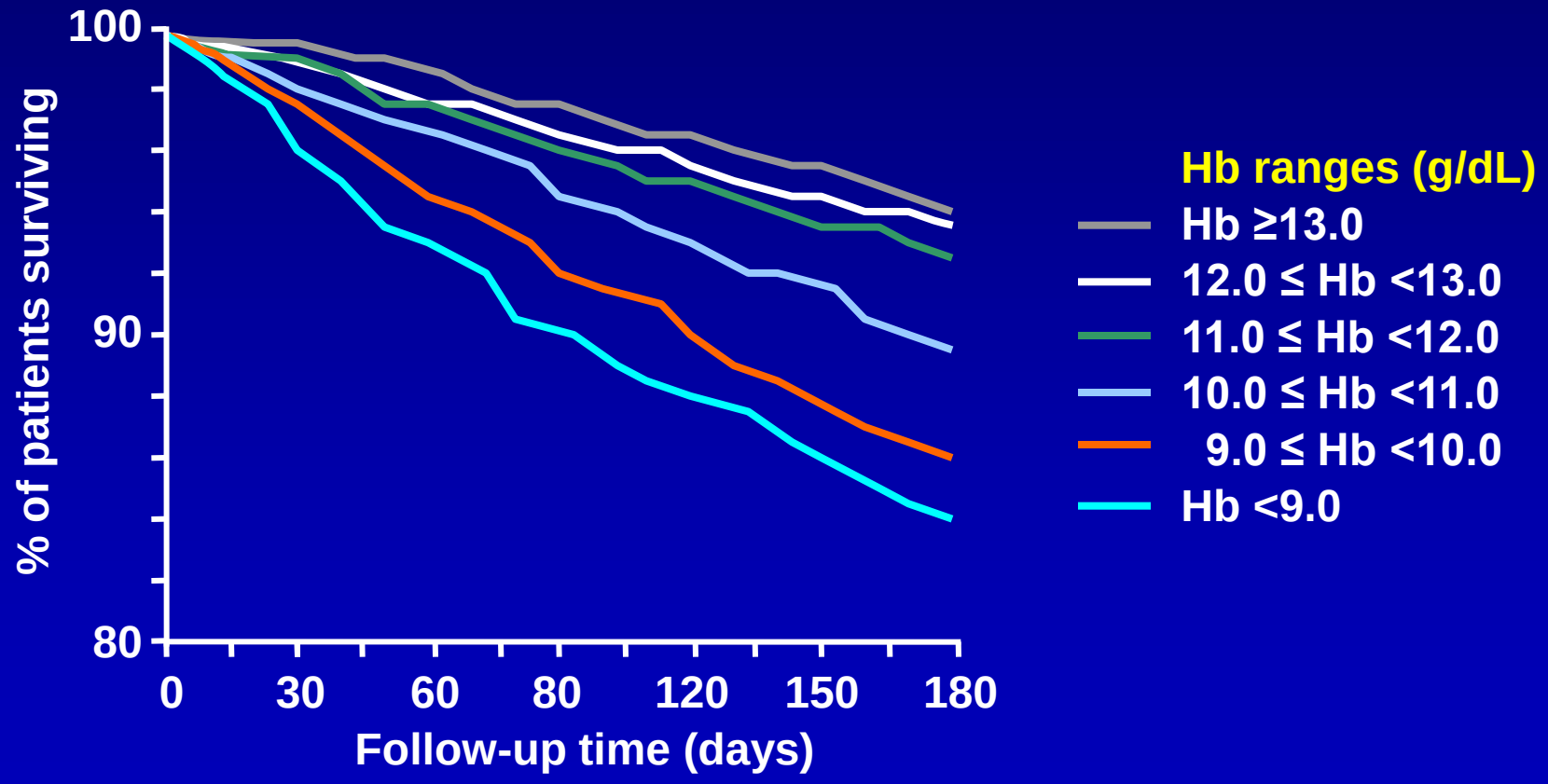
Pro-inflammatory cytokines
(IL-1, TNFα, IL-6, IFNγ)

hepcidin

↓Fe absorption
↓Fe transport
↓Fe availability
(EPO-R, Tf, TfR, Ferriportin, DMT-1)

Decreased survival with Hb values <11g/dL in HD patients

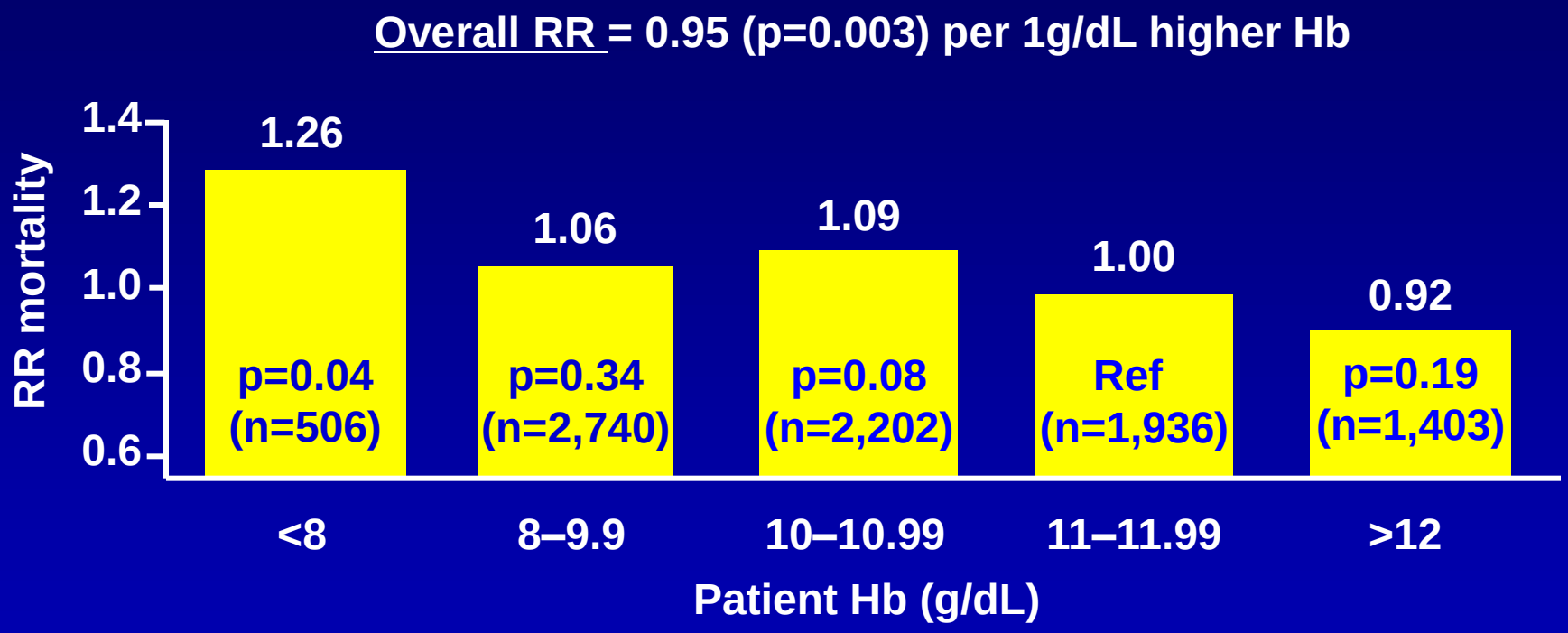
Retrospective longitudinal study in 44,550 HD patients (Fresenius Medical Care)



Hb = haemoglobin
HD = haemodialysis

Ofsthun N, et al. Kidney Int 2003;63:1908–14

DOPPS I: increased relative risk (RR) of mortality with Hb values <11g/dL (1996–2001)

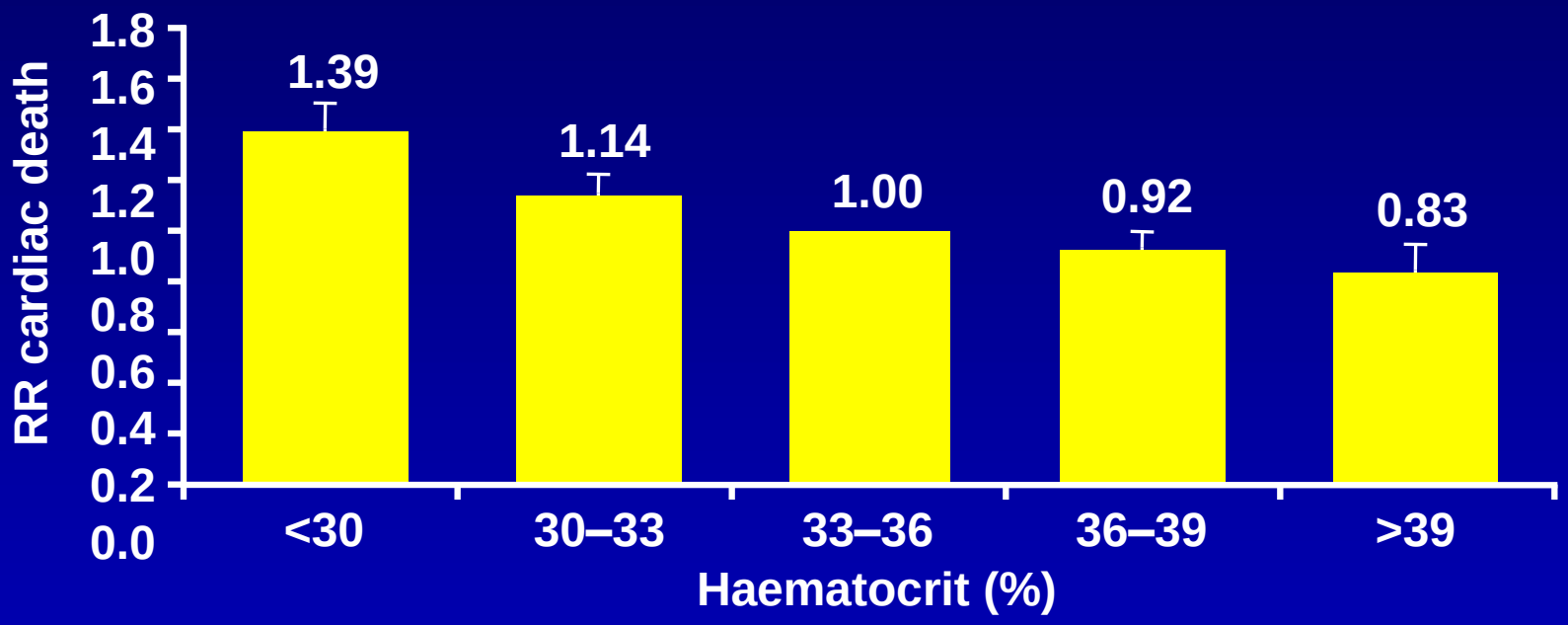


- Furthermore, RR of death = 0.90 for every 1g/dL higher mean Hb concentration at treatment facility level (p=0.02)

DOPPS = Dialysis Outcomes and Practice Patterns Study

Pisoni RL, et al. Am J Kid Dis 2004;44:94–111

ESRD – USRDS: higher haematocrit is associated with lower risk of cardiac death

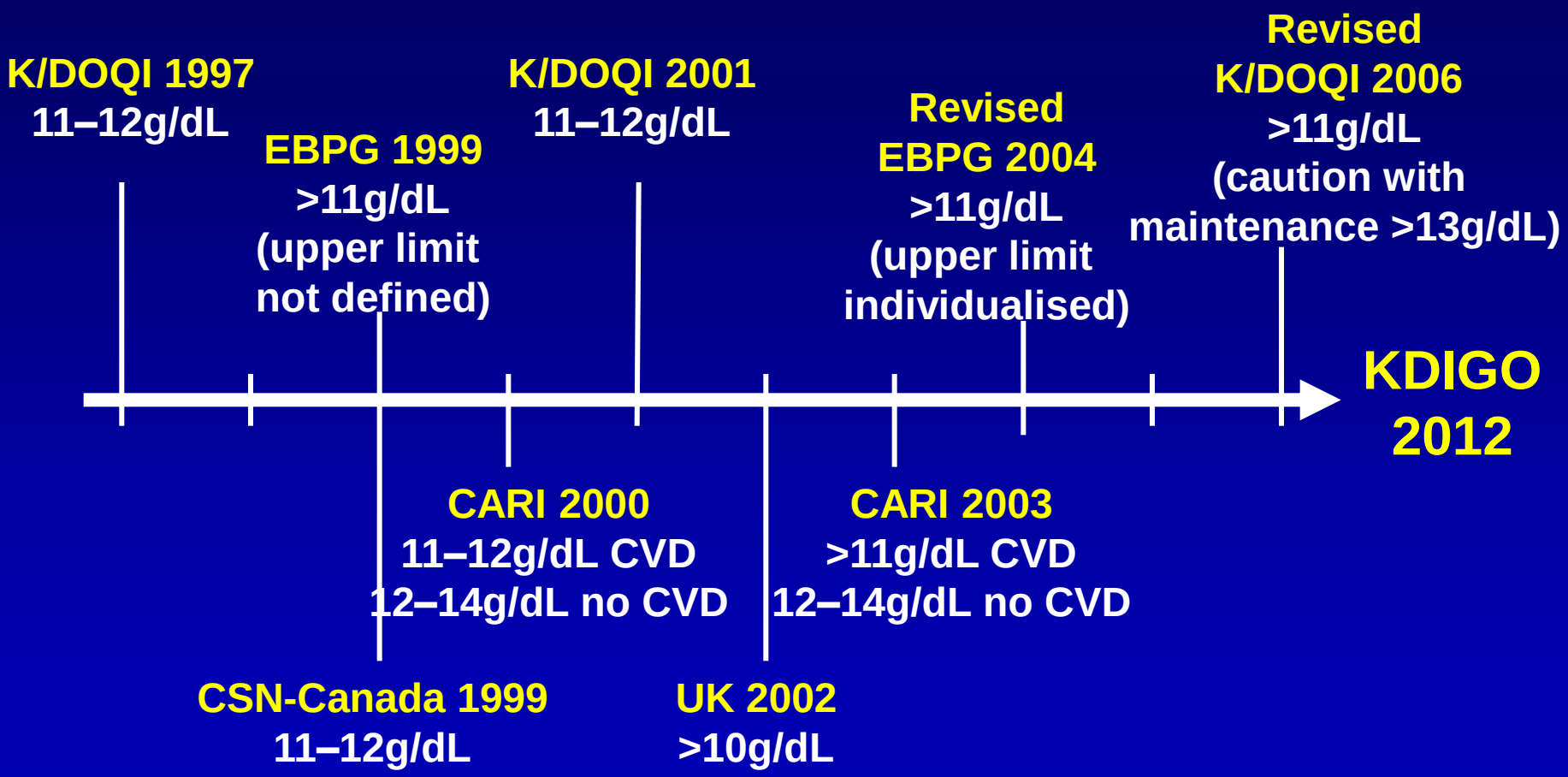


- 50,579 incident HD patients in the USA Jan 98–Dec 99
- Follow-up 2.5 years (hospitalisation) and 3.0 years (mortality)

ESRD = end-stage renal disease
USRDS = US Renal Data System

Li S, Collins AJ. Kidney Int 2004;65:626–33

Target Hb in anaemia management guidelines



DOQI = Dialysis Outcomes Quality Initiative
CSN = Canadian Society of Nephrology
CARI = Caring for Australians with Renal Impairment
CVD = cardiovascular disease; KDIGO = Kidney Disease Improving Global Outcomes

Kidney International, Vol. 61, Supplement 80 (2002), pp. S39–S43

What should the optimal target hemoglobin be?[1]

Juan M. López Gómez and Fernando Carrera

Department of Nephrology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; and Department of Nephrology, Hospital SAMS, Lisbon, Portugal

What should the optimal target hemoglobin be? Partial correction of anemia in patients with chronic kidney disease (CKD) improves anemia-related symptoms. However, controversy remains as to whether total correction of anemia provides benefits over and above those afforded by partial correction. There is some evidence showing that normalization of hemoglobin (Hb) concentrations may improve the cardiac hyperdynamic state in CKD patients and reduce the diameter of the left ventricle. Further studies have shown that normalization of Hb improves cognitive function and physical capacities as mea-

worsens as renal function declines, such that when creatinine clearance is below 25 mL/min, the prevalence of anemia is approximately 87% [1]. These findings suggest that patients with CKD may be anemic for a long time during the progression of the disease. If this is the case, then patients are exposed to an important risk factor that could influence clinical outcomes.

As oxygen supply to the tissues decreases due to ane-

EDITORIAL

Port J Nephrol Hypert 2007; 21(3): 181-183

Haemoglobin targets in CKD patients: the state of play

Fernando Carrera

Eurodial, Euromedic, Dialysis Unit. Leiria, Portugal

Received for publication: 25/06/2007
Accepted: 29/06/2007

This editorial overviews the current state of play in anaemia correction but bucks medical tradition by

with decreased hospitalisations and morbidity, coupled with better quality of life, in dialysis patients.

Clinical Nephrology, Vol. 69 – No. 1/2008 (8-9)

Hemoglobin targets: the jury is still out

F. Carrera[1] and I.C. Macdougall[2]

[1]Dialysis Unit, Eurodial, Euromedic, Leiria, Portugal and [2]Department of Renal Medicine, King's College Hospital, London, UK

Much has been made recently of the results of the CREATE [Drüeke et al. 2006] and CHOIR [Singh et al. 2006] studies which, together with the findings of a meta-analysis of nine randomized, controlled clinical trials [Phrommintikul et al. 2007] have indicated

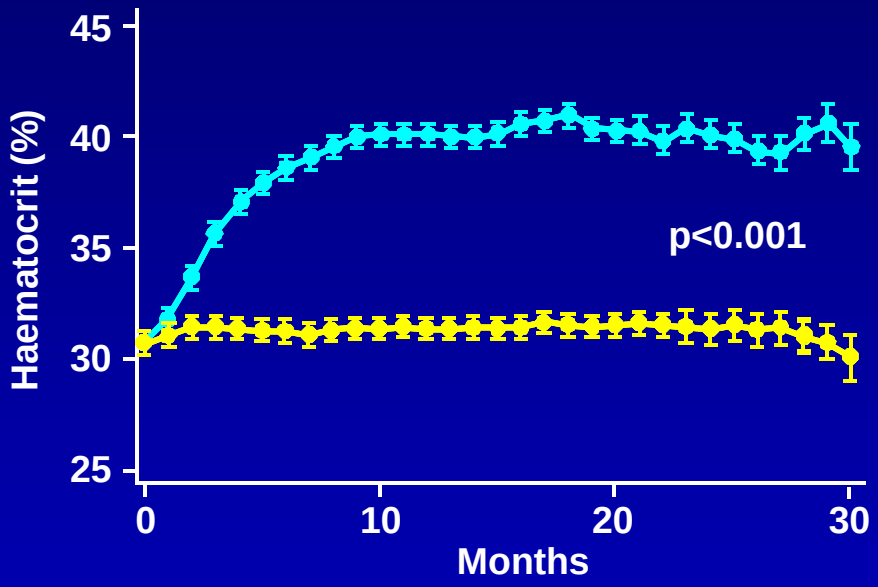
study's conduct, and the high withdrawal rate – 38% of patients did not complete the trial and no reasons for discontinuation were cited for over half of them. Moreover, the analysis did not include all randomized patients, ex-

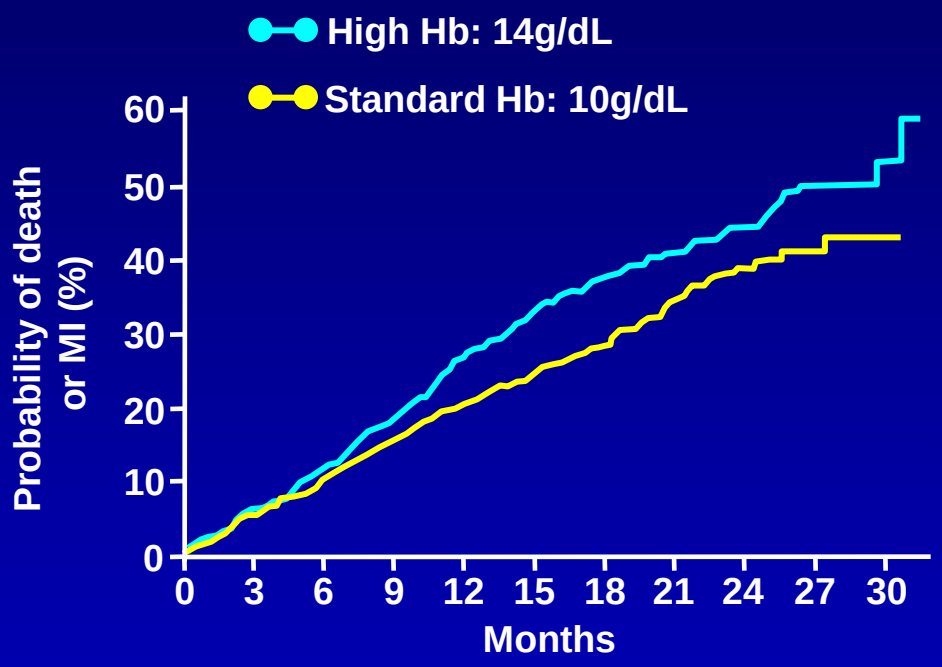
The impact of anaemia correction on mortality and cardiovascular (CV) morbidity

Did we aim too high?

NHS: In HD patients with CHF or ischaemic heart disease, administration of epoetin to raise their haematocrit to 42% was not recommended

Primary endpoint: time to death or non-fatal MI
Risk ratio*:1.3 (95% CI, 0.9–1.9)





- Normal haematocrit group (43%): 183 deaths, 19 non-fatal MIs (n=618)
- Low haematocrit group (30%): 150 deaths, 14 non-fatal MIs (n=615)

*New analysis by FDA p=0.01, 95% CI: 1.06–1.56
NHS = Normal Hematocrit Study; CHF = congestive heart failure
MI = myocardial infarction; FDA = Food and Drug Administration

Besarab A, et al. N Engl J Med 1998;339:584–90
Coyne DW. Semin Dial 2008;21(3):212–6

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*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

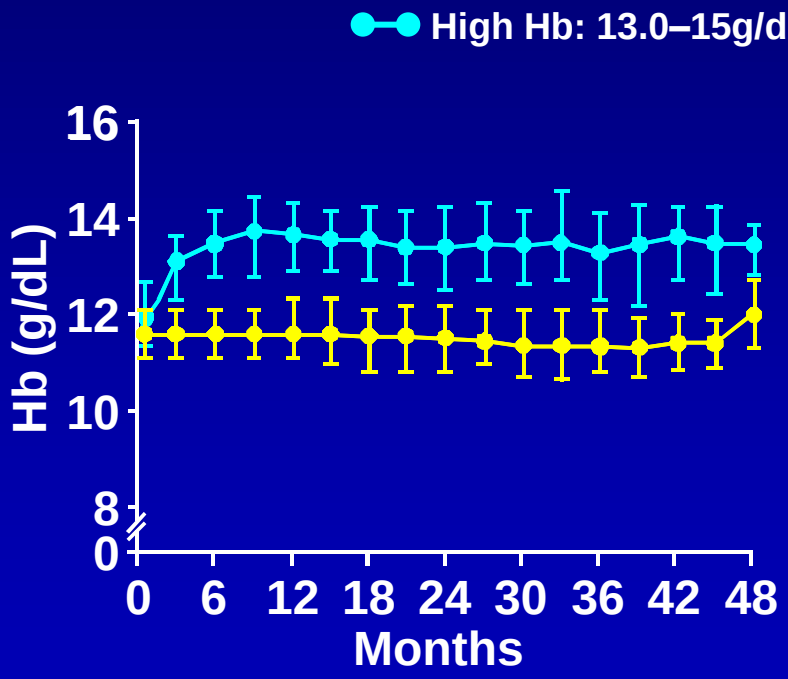
Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

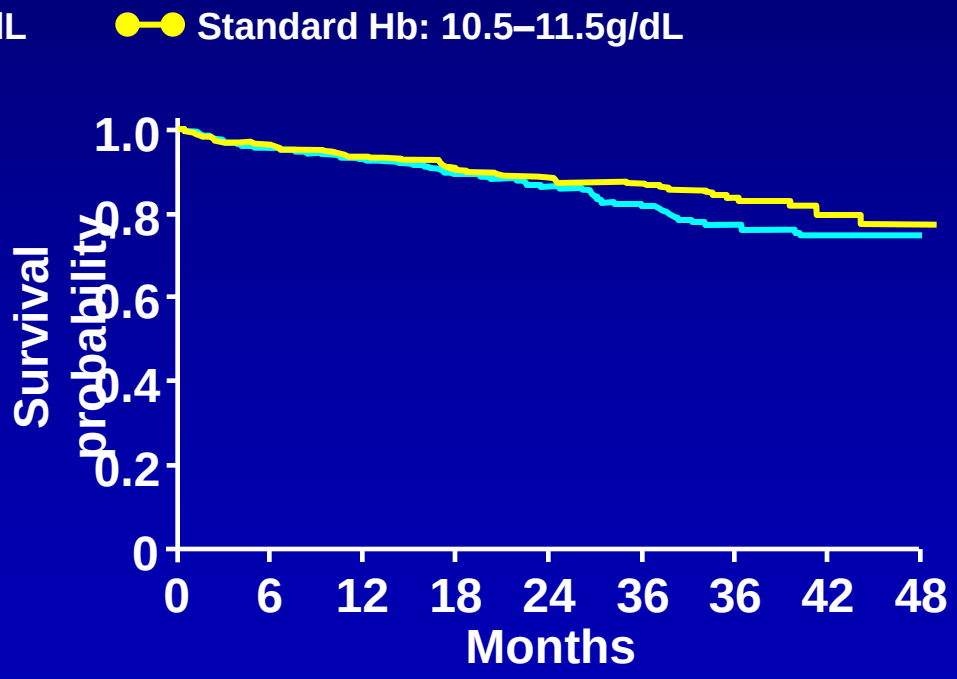
Ajay K. Singh, M.B., B.S., Lynda Szczech, M.D., Kezhen L. Tang, Ph.D., Huiman Barnhart, Ph.D., Shelly Sapp, M.S., Marsha Wolfson, M.D., and Donal Reddan, M.B., B.S., for the CHOIR Investigators*

CREATE: early and complete correction of anaemia did not reduce the risk of CV events

Primary endpoint: time to first CV event
HR: 0.78; 95% CI, 0.53–1.14; p=0.20

58 events (high Hb, n=301) versus 47 events (low Hb, n=302)



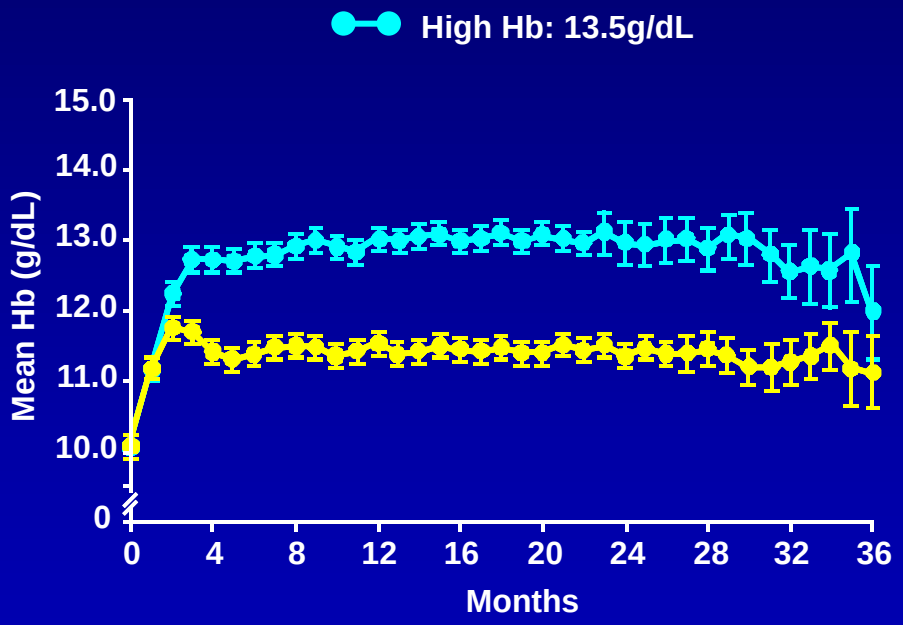


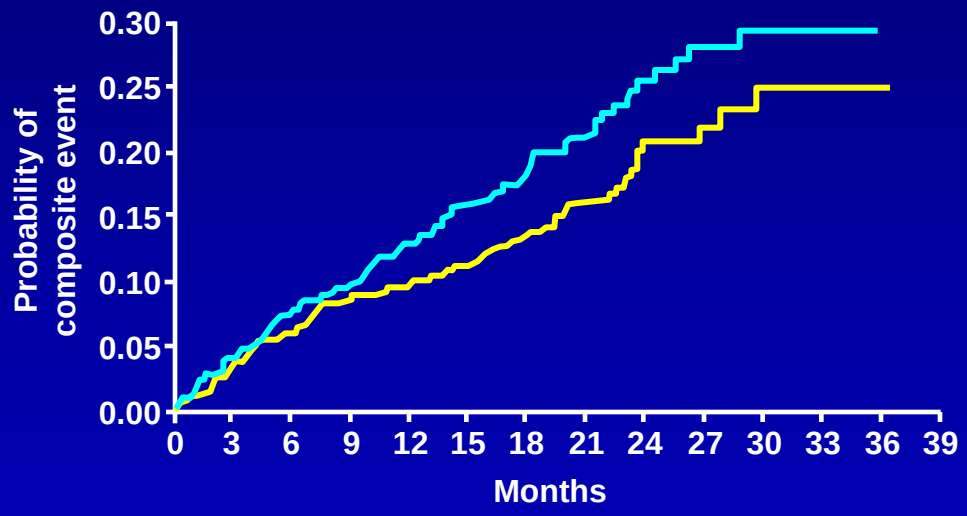
CREATE = Cardiovascular Risk reduction in Early Anaemia Treatment with Epoetin beta

Drüeke TB, et al. N Engl J Med 2006;355:2071–84

CHOIR: The use of a high target Hb level was associated with increased CV risk

Primary endpoint: time to death or CV event
HR: 1.34; 95% CI, 1.03–1.74; p=0.03





- **125 events (high Hb, n=715) versus 97 events (low Hb, n=717)**

CHOIR = Correction of Hemoglobin and Outcomes in Renal Insufficiency

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

2007 March
FDA boxed warning

WARNINGS: Erythropoiesis-Stimulating Agents

Use the lowest dose of [Aranesp®/EPOGEN®/PROCRIT®] that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion (see DOSAGE AND ADMINISTRATION).

[Aranesp®/EPOGEN®/PROCRIT®] and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

Cancer Patients: Use of ESAs

- **shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin of greater than 12 g/dL;**
- **shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL;**
- **increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population.**

(See WARNINGS: Increased Mortality and/or Tumor Progression)

Patients receiving ESAs pre-operatively for reduction of allogeneic red blood cell transfusions: A higher incidence of deep venous thrombosis was documented in patients receiving Epoetin alfa who were not receiving prophylactic anticoagulation. Antithrombotic prophylaxis should be strongly considered when EPOGEN®/PROCRIT® is used to reduce allogeneic red blood cell transfusions. Aranesp® is not approved for this indication (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

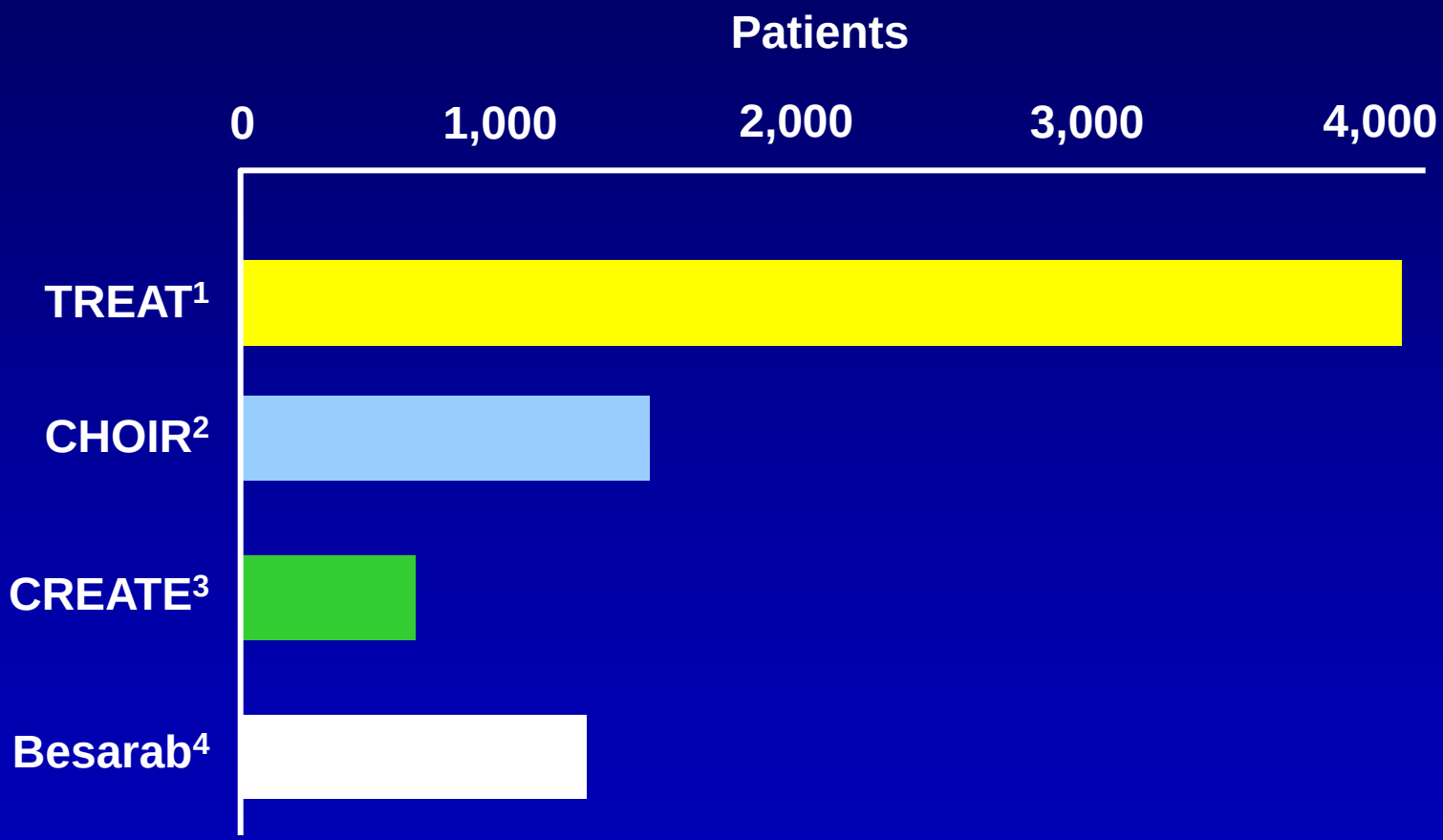
2008 February European Medicines Agency (EMA): ESA label update

- The EMA had initiated a review of the safety of ESAs because data from recent off-label clinical trials, targeting Hb levels higher than those in approved labelling, showed unexplained excess mortality in patients with anaemia associated with cancer and an increase in the risk of mortality and CV morbidity in treatment of anaemia in patients with CKD
- The Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of these products continue to outweigh their risks in the approved indications, but recommended the following changes to the product information:

PRODUCT USAGE:

- Changes to the 'Indication' section, saying that epoetins should be used in the treatment of anaemia only if associated with symptoms
- Changes to the 'Posology' section, stipulating a uniform target haemoglobin range for all epoetins of 10g/dL to 12g/dL

TREAT is the largest anaemia trial in CKD



TREAT = Trial to Reduce Cardiovascular Events with Aranesp Therapy

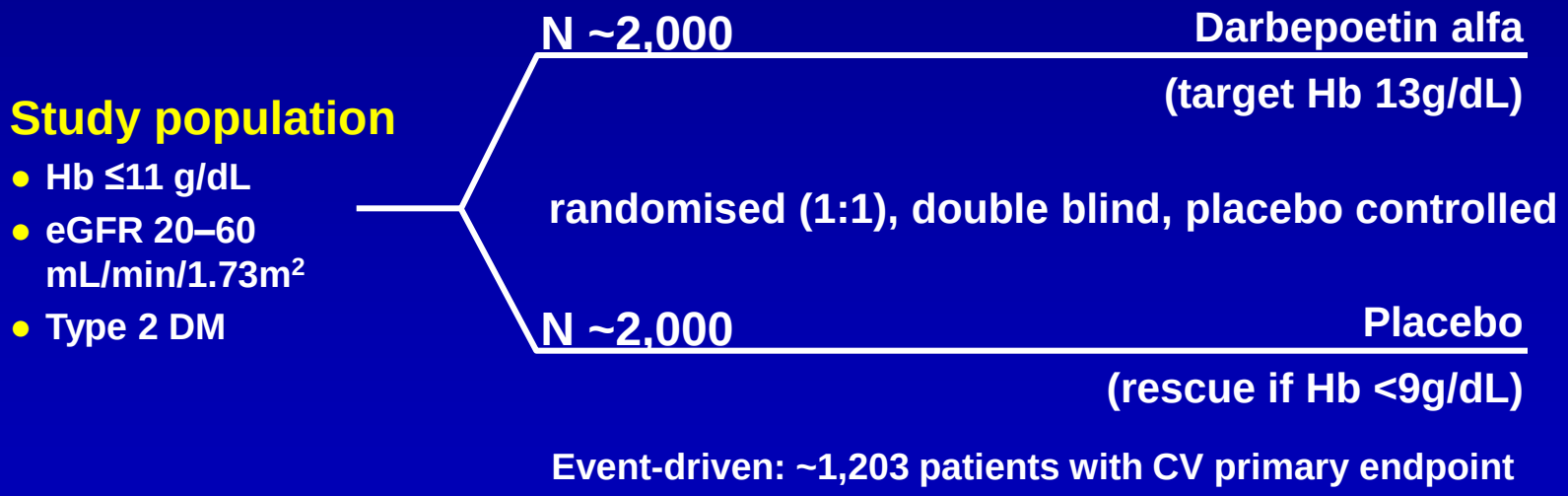
1. Mix TC, et al. Am Heart J 2005;149:408–13
2. Drüeke TB, et al. N Engl J Med 2006;355:2071–84
3. Singh AK, et al. N Engl J Med 2006;355:2085–98
4. Besarab A, et al. N Engl J Med 1998;339:584–90

TREAT: trial to reduce cardiovascular events with darbepoetin alfa therapy

Hypotheses:

Treatment of patients with darbepoetin alfa in subjects with CKD and type 2 diabetes mellitus (DM) decreases mortality and CV morbidity

Treatment of anaemia with darbepoetin alfa in patients with CKD and type 2 DM will delay the progression to ESRD



eGFR = estimated glomerular filtration rate

Pfeffer M, et al. Am J Kidney Dis 2009;54:59–69

Composite and component endpoints

Endpoint	Darbepoetin alfa (n=2,012) n (%)	Placebo (n=2,026) n (%)	HR (95% CI)	p value†
Primary endpoints				
Cardiovascular composite 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
MI §	124 (6.2)	129 (6.4)	0.96 (0.75–1.22)	0.73
Stroke §	101 (5.0)	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 ischaemia	41 (2.0)	49 (2.4)	0.84 (0.55–1.27)	0.40
Renal composite endpoint (ESRD or death)	652 (32.4)	628 (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 CV causes	259 (12.9)	250 (12.3)	1.05 (0.88–1.25)	0.61
Cardiac revascularisation	84 (4.2)	117 (5.8)	0.71 (0.54–0.94)	0.02

†p values have not been adjusted for multiple comparisons

§ This category includes both fatal and non-fatal events

Pfeffer MA, et al. N Engl J Med 2009;361:2019–32

Author's conclusions

- The use of darbepoetin alfa in patients with diabetes, CKD, and moderate anaemia who were not undergoing dialysis **did not reduce the risk of either of the two primary composite outcomes (either death or a CV 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 J Med 2009;361:2019–32

Nephrol Dial Transplant (2010) 25: 2846–2850
doi: 10.1093/ndt/gfq336
Advance Access publication 29 June 2010

Editorial Reviews

NDT
Nephrology Dialysis Transplantation

Target haemoglobin to aim for with erythropoiesis-stimulating agents: a position statement by ERBP following publication of the Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) Study

Francesco Locatelli[1], Pedro Aljama[2], Bernard Canaud[3], Adrian Covic[4], Angel De Francisco[5], Iain C. Macdougall[6], Andrzej Wiecek[7], Raymond Vanholder[8] and On behalf of the Anaemia Working Group of European Renal Best Practice (ERBP)

(i) Iron administration is an important factor for the successful treatment with any kind of ESA, in order to use the lowest dose for reaching and maintaining the desired Hb target.

(ii) ESA treatment should not be started in patients who are iron-deficient.

(iii) Iron replacement should be used first in any CKD patient who is proven or likely to be iron-deficient, and only once the iron stores are replete should ESA therapy be initiated.

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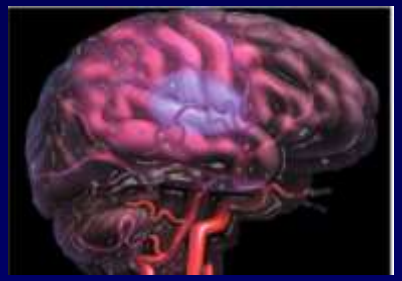

In CKD patients, ESA treatment should be considered when Hb levels are consistently (i.e. measured twice at least 2 weeks apart) below 11 g/dL (possibly < 10 g/dL in patients with type 2 diabetes and with a history of strokes), and all other causes of anaemia have been excluded; the threshold for treatment should be decided according to patient characteristics and symptoms, and the desired Hb target

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The use of high ESA dose in patients who are hyporesponsive to treatment should be carefully evaluated; increased cardiovascular risk should be weighed against the possible benefits of anaemia correction. It seems wise to avoid progressively increasing the ESA dose in those patients who do not respond to treatment as expected or in whom it is obvious that worsening of anaemia is linked to non-renal factors

ESA treatment should be started at a low dose, in order to avoid overshooting to high Hb levels; dose adjustments should be made smoothly in the following months in order to avoid too rapid increases in Hb levels (Hb increases of >2 g/dL per month should be avoided if possible).

After 20 years …

- *"It is time to establish, through randomised trials, the optimal Hb target, dosing algorithm, and monitoring approach for patients with anaemia from CKD"* [1]
- **Normal Hematocrit Study[2], CHOIR[3] and TREAT[4] suggest that Hb>13.0g/dL are harmful**
- **The FDA anticipates a public advisory committee meeting in 2010 to re-evaluate the use of ESAs in the treatment of anaemia due to CKD[1]**

1. Unger EF, et al. New Engl J Med 2010;362:189–192
2. Besarab A, et al. New Engl J Med 2006;355:584–90
3. Singh AK, et al. New Engl J Med 2006:355:2085–98
4. Pfeffer MA, et al. New Engl J Med 2009;361:2019–32

FDA news release June 2011

- For patients with the anaemia of chronic kidney disease NOT on dialysis

  • Consider starting ESA treatment only when the haemoglobin level is less than 10 g/dL and when certain other considerations apply

  • If the haemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of ESA

FDA news release June 2011

- For patients with the anaemia of chronic kidney disease ON dialysis

  • Initiate ESA treatment when the haemoglobin level is less than 10 g/dL

  • If the haemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of ESA

KIDNEY DISEASE GLOBAL OUTCOMES

K/DIGO March 2012
ESA therapy

- CKD ND with Hb ≥ 10.0 g/dL - no ESA therapy
- CKD ND with Hb ≤ 10.0 g/dL – to be individualised

- CKD 5D ESA therapy to avoid Hb < 9.0 g /dL

In general, ESAs should not be used to maintain Hb > 11.5 g/dL

In paediatric patients 11.0 to 12.0 g/dL