Renal Anemia: Current Controversies and Future Trends in ESA Use

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Antalya May 22nd 2008

Outline

- Update on the target hemoglobin paradox
- Current thoughts on renal anemia management
- Future of ESA therapy in renal anemia

The target hemoglobin paradox

The target hemoglobin paradox

- Registry data show that morbidity and mortality in dialysis patients is lowest at higher hemoglobins

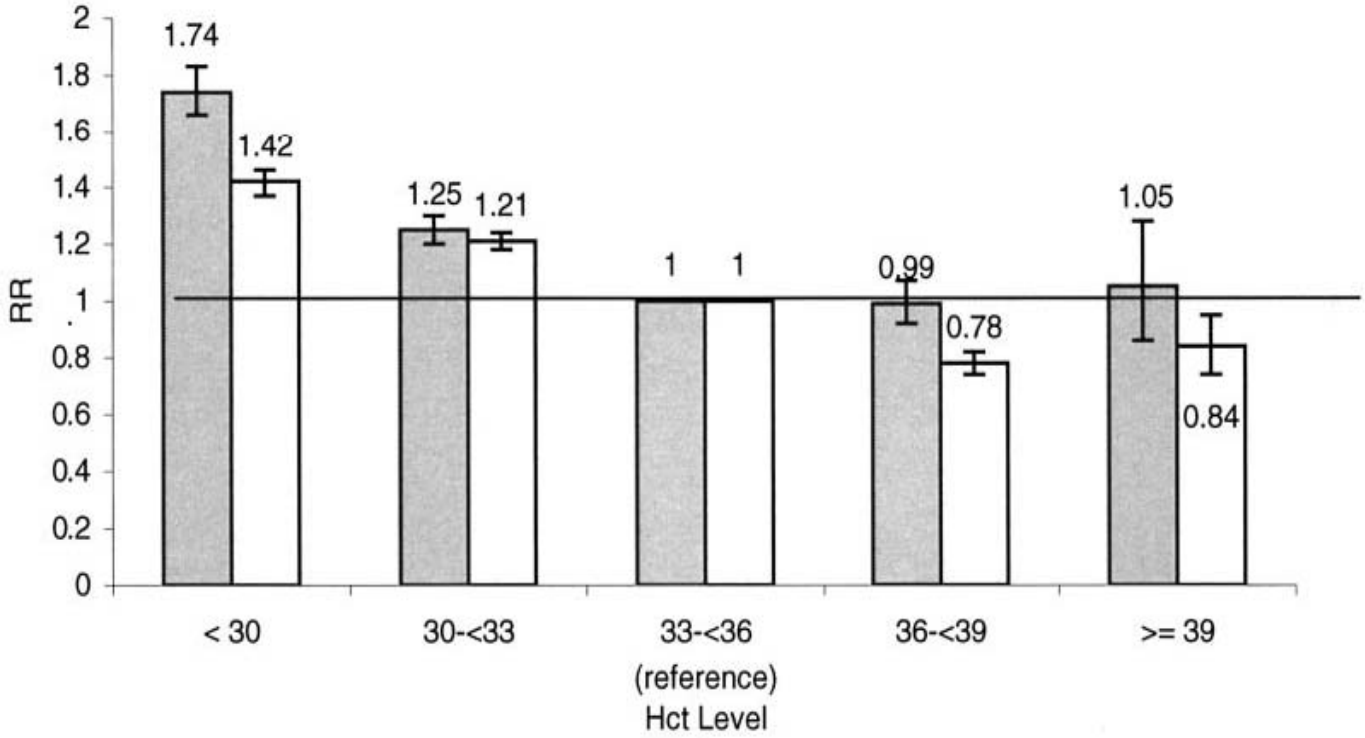


Figure 1. Relative risks (RR) of death (▨) and hospitalization (□) from all causes [with 95% confidence intervals (CI)]. Hct, hematocrit.

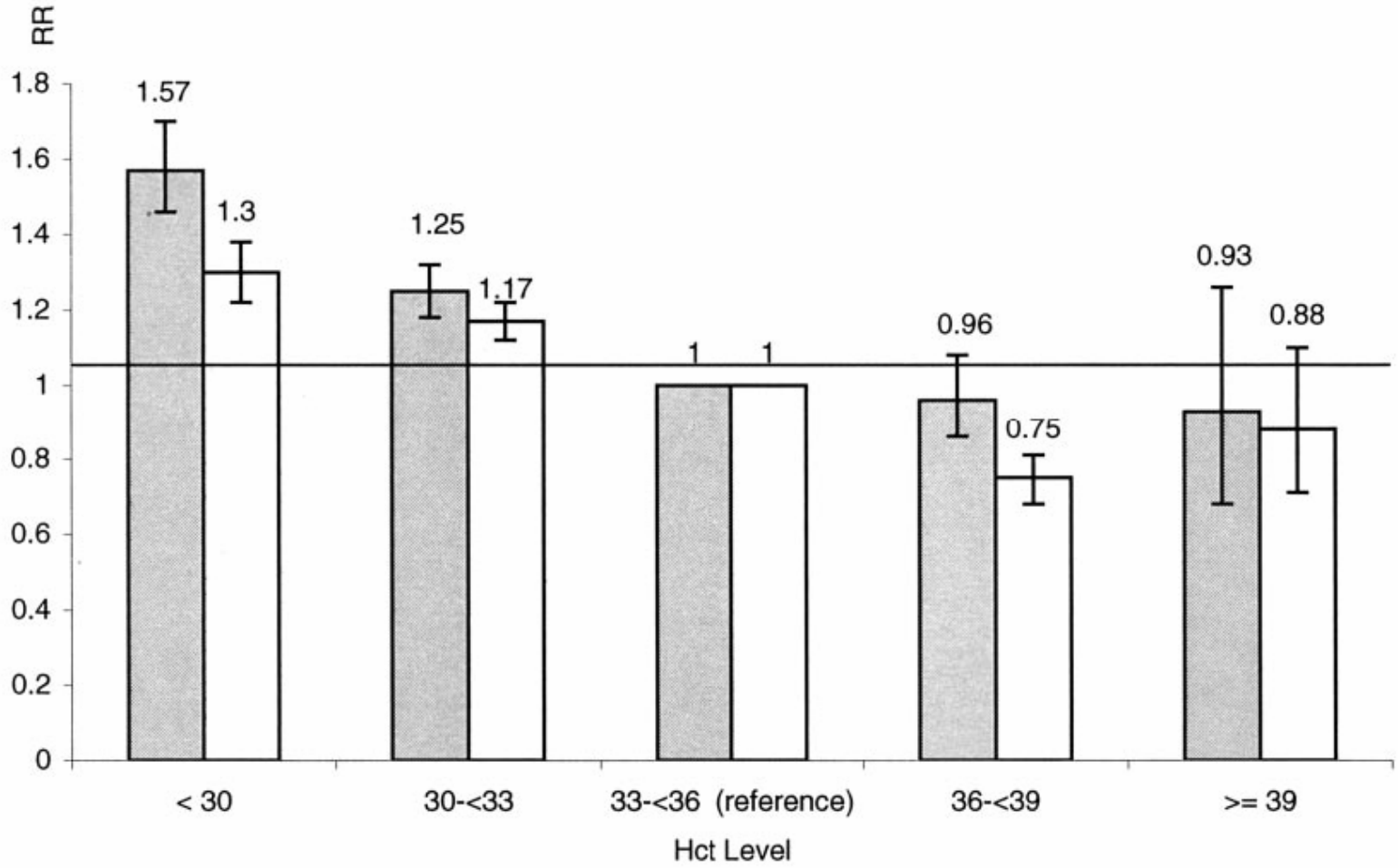


Figure 2. Relative risks (RR) of death (▒) and hospitalization (□) from cardiac causes (with 95% CI). Hct, hematocrit.

The target hemoglobin paradox

- Registry data show that morbidity and mortality in dialysis patients is lowest at higher hemoglobins
- RCTs suggest that attempts to reach higher Hb target are associated with excess morbidity and possibly mortality, specifically for cardiac events

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

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

N Engl J Med 2006;355:2071-84.

CREATE: Design

- 603 patients with stage 3 or 4 CKD
- Open label design
- eGFR 15-35ml/min/1.73m^2
- Baseline Hb 110-125g/l
- Targeted Hb 130-150g/l or 105-115g/l
- Primary endpoint:
  - Composite of 8 CV events

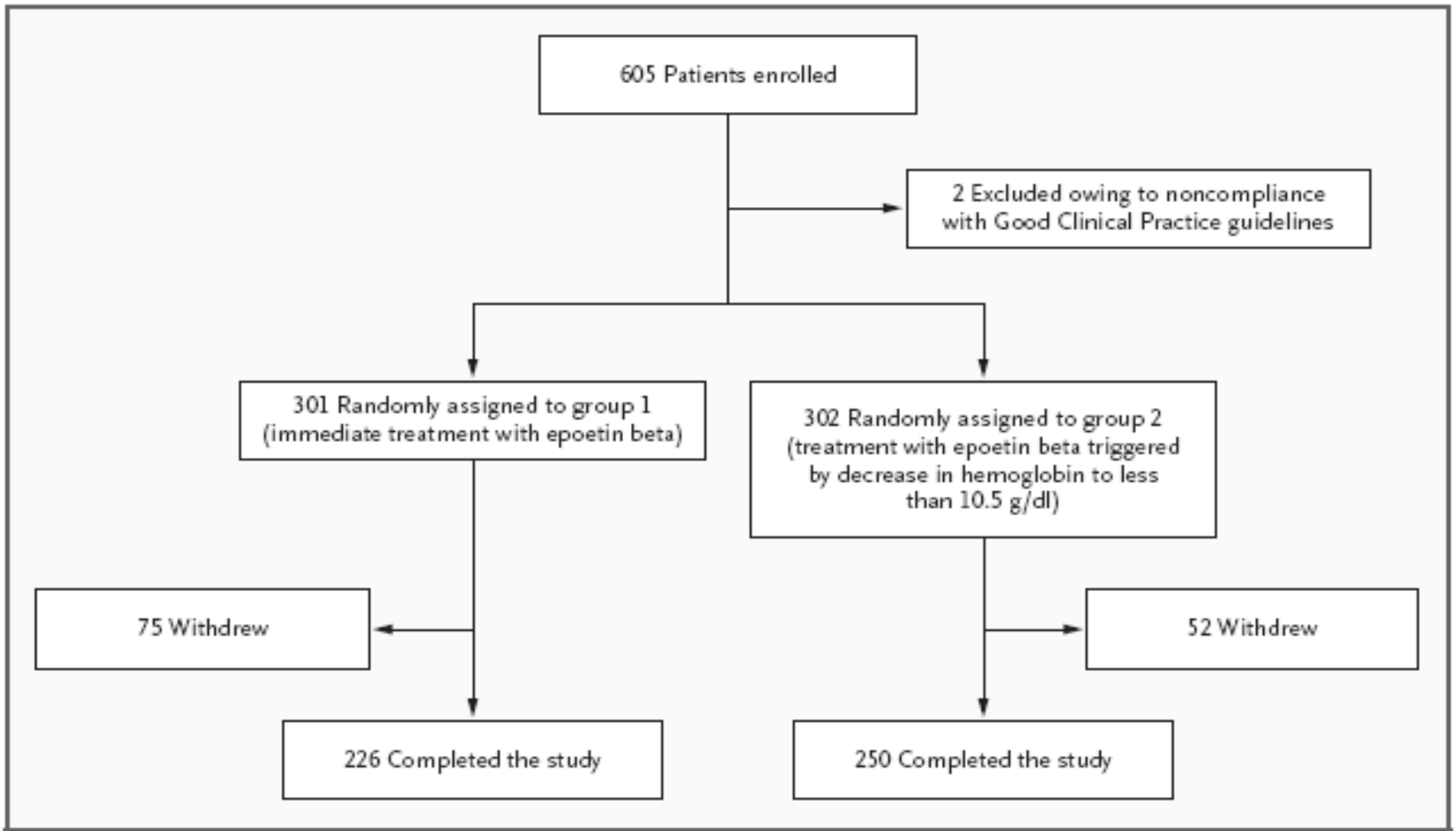


Figure 1. **Enrollment, Randomization, and Study Completion.**

N Engl J Med 2006;355:2071-84.

Table 1. Demographic and Baseline Characteristics.*

Characteristic	Group 1 (N=301)	Group 2 (N=302)	P Value
Weight (kg)	74.7±15.6	71.8±14.2	0.05
Body-mass index	26.6±4.5	26.2±4.8	0.42
Age — yr	59.3±14.6	58.8±13.7	0.36
Male sex — no. (%)	171 (57)	154 (51)	0.16
Estimated GFR — ml/min†	24.9±6.3	24.2±6.0	0.30
Cause of chronic kidney disease — no. of patients (%)			
Glomerulonephritis	62 (21)	71 (24)	0.43
Hypertensive renal disease	69 (23)	57 (19)	0.23
Diabetic nephropathy	61 (20)	63 (21)	0.91
Polycystic kidney disease	37 (12)	39 (13)	0.88
Pyelonephritis	22 (7)	21 (7)	0.92
Interstitial nephritis	22 (7)	16 (5)	0.35
Other	52 (17)	56 (19)	0.74
Unknown	15 (5)	15 (5)	0.94
Diabetes mellitus — no. of patients (%)	80 (27)	77 (25)	0.64
Insulin-dependent	13 (4)	10 (3)	0.58
Dyslipidemia — no. of patients (%)	119 (40)	93 (31)	0.23
Hypertension — no. of patients (%)‡	275 (91)	269 (89)	0.38
Blood pressure — mm Hg			
Systolic	139±17	139±16	0.87
Diastolic	79±10	80±9	0.28
Receipt of at least one antihypertensive agent — no. of patients (%)†	287 (96)	272 (90)	0.16
Angiotensin converting–enzyme inhibitors	152 (51)	142 (47)	0.39
Angiotensin II–receptor blockers	57 (19)	66 (22)	0.41
Beta-blockers	130 (43)	102 (34)	0.02
Calcium-channel blockers	155 (52)	156 (52)	0.97
Alpha-blockers	50 (17)	41 (14)	0.32
Loop diuretics	145 (48)	127 (42)	0.13
Thiazide or other diuretic	27 (9)	28 (9)	0.96

CREATE: Principal results

- Anemia correction did not reduce first CV events (58 vs 47; p=0.2)
- No change in secondary endpoints or in change in eGFR
- RRT more frequent in normalised group 127 vs 111; p=0.03)
- More hypertension and headache in normalisation group

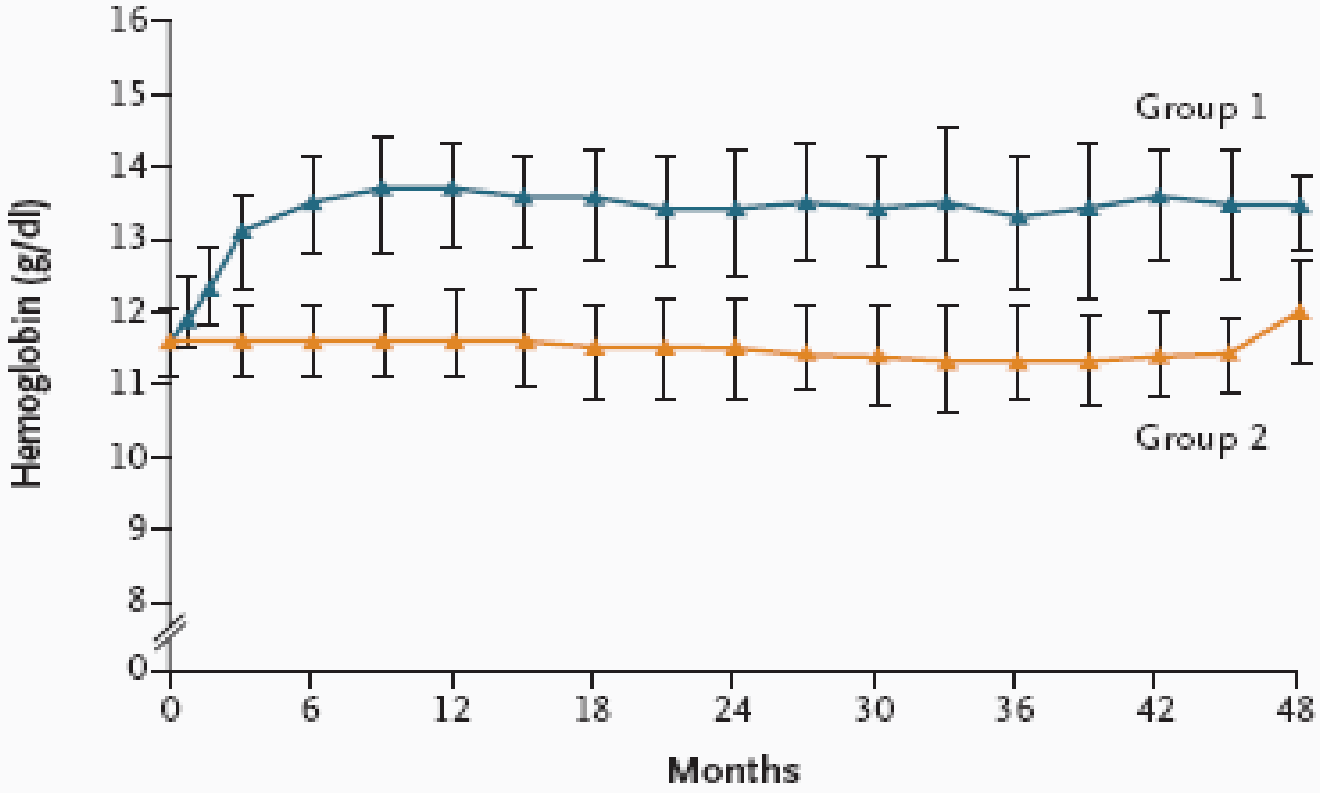


Figure 2. Median Hemoglobin Levels in the Intention-to-Treat Population during the Study.

I bars indicate standard deviations.

Appendix Table. Primary Composite Endpoint: Distribution of First Cardiovascular Events *

	Group 1 (N = 301) N (%)	Group 2 (N = 302) N (%)
Arrhythmia	12 (4)	12 (4)
Acute cardiac failure	7 (2)	12 (4)
Myocardial infarction	8 (3)	7 (2)
Angina pectoris	7 (2)	4 (1)
Cerebrovascular accident	6 (2)	5 (2)
Transient cerebral ischemic attack	5 (2)	1 (<1)
Peripheral vascular disease	8 (3)	4 (1)
Sudden death	4 (1)	0
Total	58 (19)	47 (16)

*** Some patients experienced more than one cardiovascular event, which are all included in this Table, but of which only the first was counted for the primary composite endpoint.**

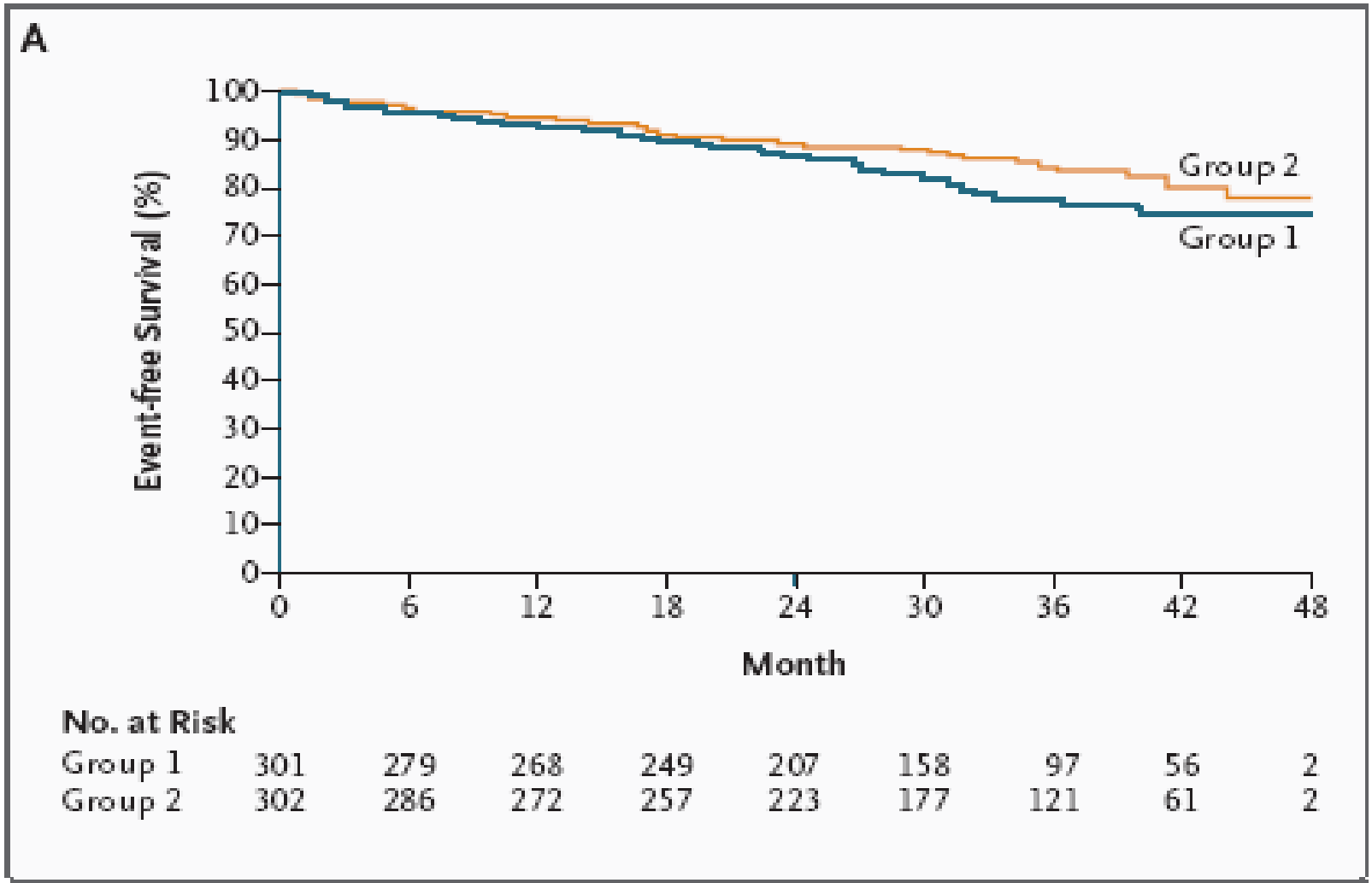


Figure 3. Time to the Primary End Point of a First Cardiovascular Event before (Panel A) and after (Panel B) Censoring of Data on Patients at the Time of Initiation of Dialysis.

Issues with CREATE

- Dropout rate close to 25%
- Neither group reached their intended target Hb
- Event rate much lower than anticipated (105 vs 200 predicted events)
- CV profile of study population
- Dialysis endpoint subjective

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*

N Engl J Med 2006;355:2085-98.

CHOIR: Design

- Open label study of 1432 patients with Stage 2b-4 CKD
- eGFR 15-50ml/min/1.73m^2
- Hb<110g/l at enrolment
- Epoetin alfa s.c.(starting dose 10,000u/wk) given to target Hb of 113 vs 135g/l
- Primary endpoint:
  - Composite of death, MI, HF, stroke

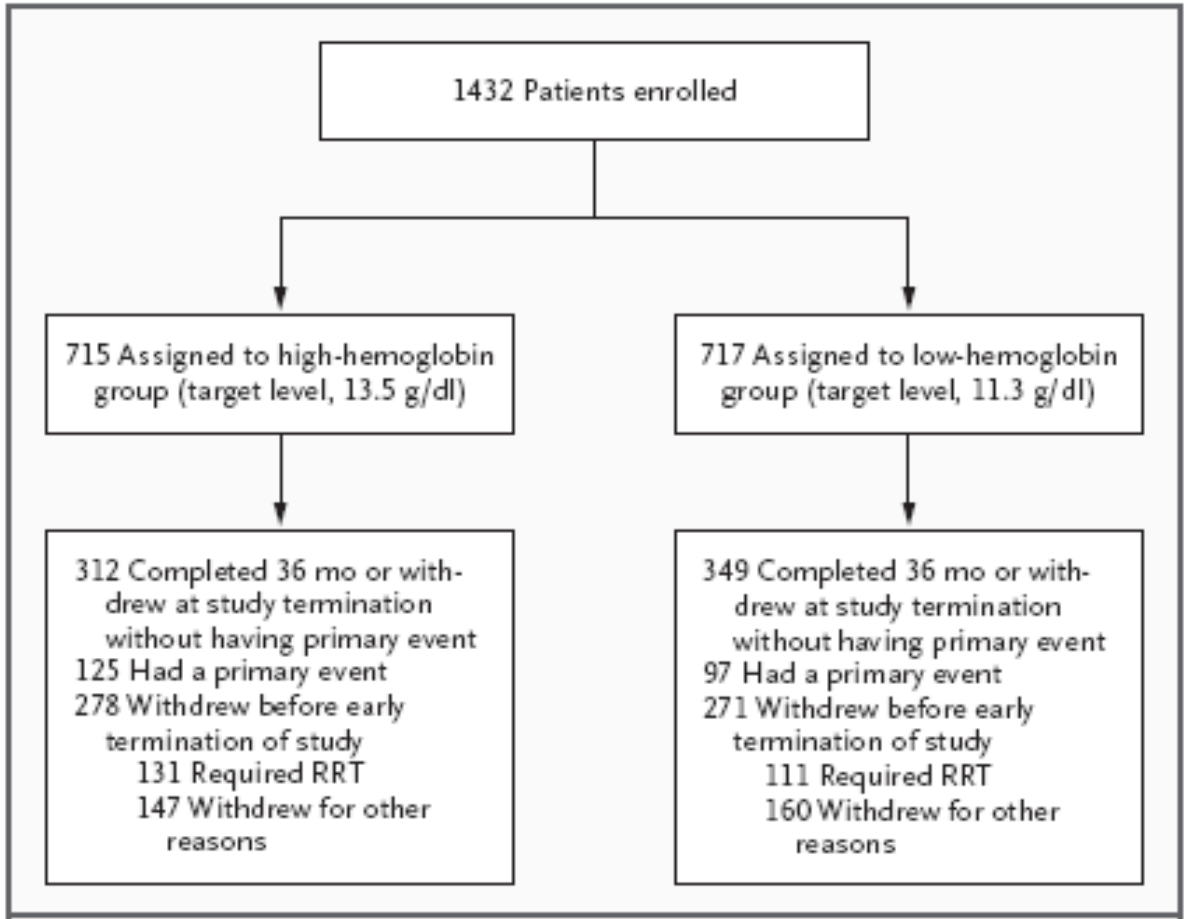


Figure 1. Enrollment and Outcomes.

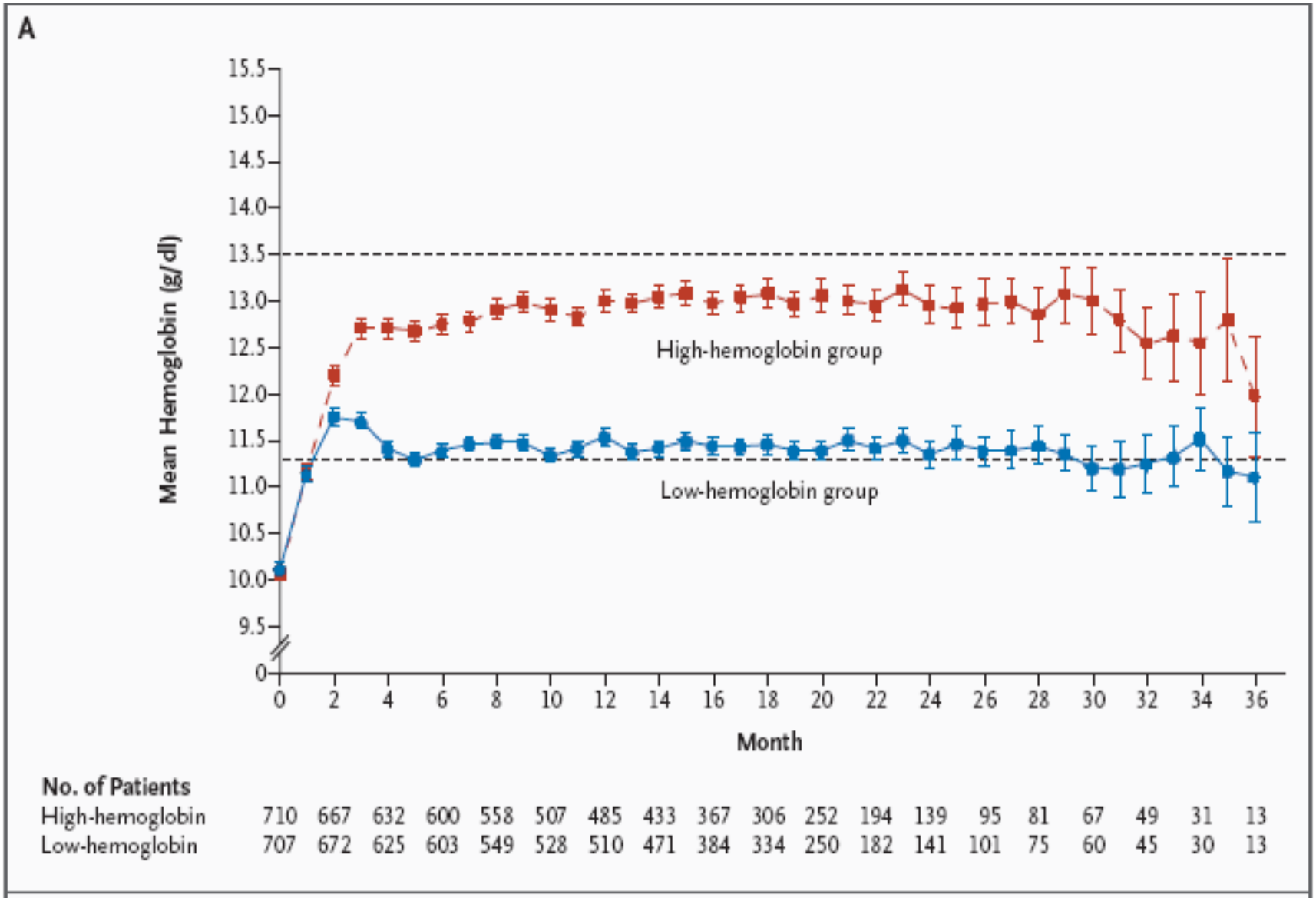
A total of 1432 patients were enrolled; 715 were assigned to the high-hemoglobin group (with a target level of 13.5 g per deciliter), and 717 were assigned to the low-hemoglobin group (with a target level of 11.3 g per deciliter). In addition to the stated reasons for withdrawal from the study, other reasons included a request from a patient, an investigator, or the study sponsor; pregnancy; an adverse event; a protocol violation; or a loss to follow-up. RRT denotes renal replacement therapy.

Table 1. Baseline Characteristics of the Patients.*

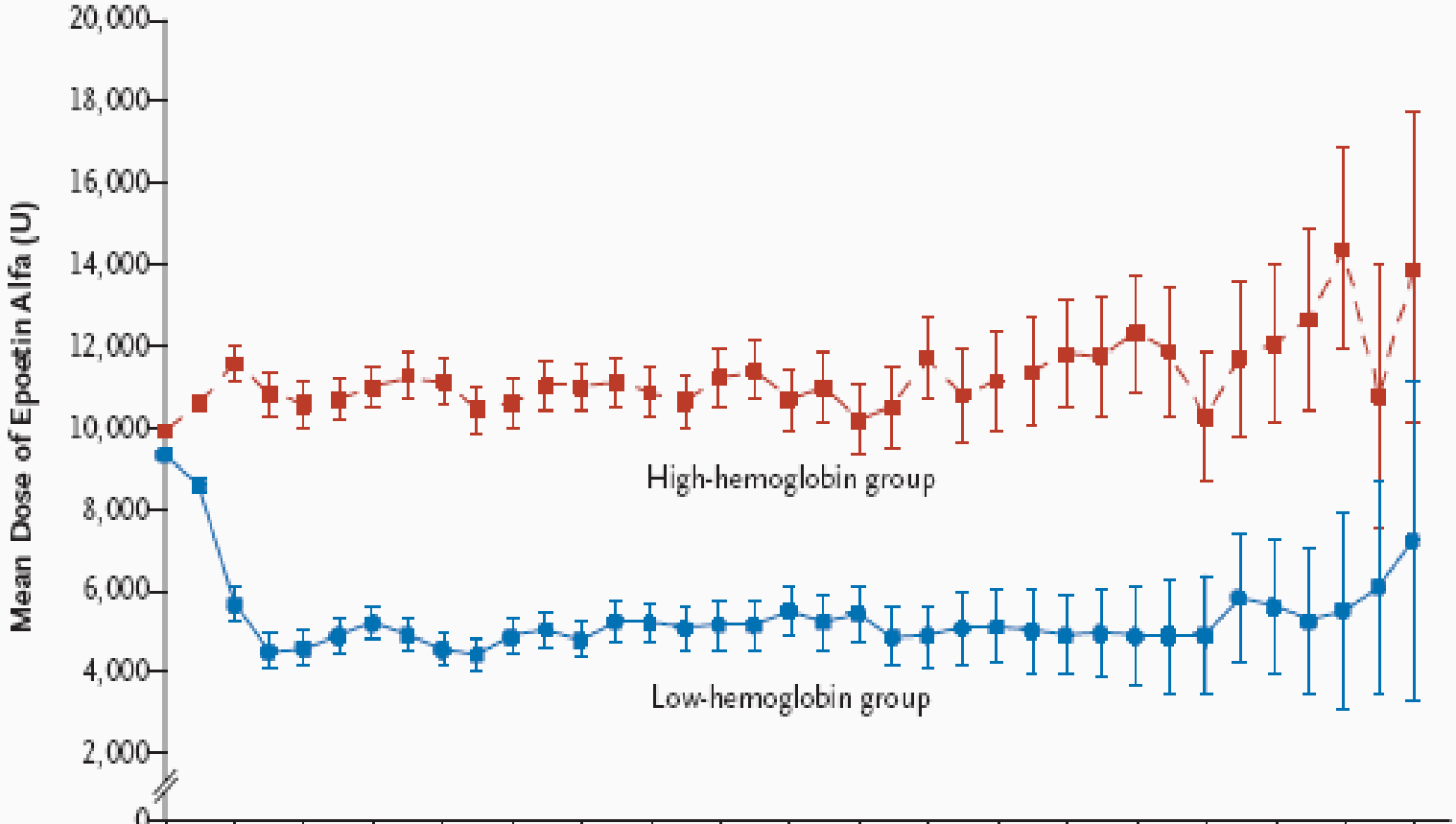
Characteristic	High-Hemoglobin Group (N=715)	Low-Hemoglobin Group (N=717)
Age (yr)	66.0±14.3	66.3±13.5
Female sex (%)	56.2	54.1
Race (%)		
White	62.3	61.1
Black	28.6	29.3
American Indian or Alaskan Native	0.1	0.4
Asian or Pacific Islander	3.4	3.2
Other	5.6	6.0
Hispanic ethnic background (%)	12.5	13.5
History of smoking tobacco (%)	47.5	44.6
Cause of chronic kidney disease (%)		
Diabetes	46.8	50.8
Hypertension	29.9	27.5
Other	23.3	21.6
Cardiovascular history (%)		
Hypertension	95.8	93.2†
Myocardial infarction	16.4	15.0
CABG	17.4	13.5‡
PCI	10.9	11.9
Congestive heart failure	24.4	22.9
Atrial fibrillation	9.4	8.6
Stroke	9.8	10.0
Peripheral vascular disease	16.4	16.4
Myocardial infarction, stroke, CABG, PCI, or amputation of a lower limb	36.3	34.5
Body-mass index	30.4±7.7	30.4±7.5
Blood pressure (mm Hg)		
Systolic	136.7±19.7	135.6±20.0
Diastolic	71.6±11.6	70.9±11.2
Mean arterial	93.3±12.1	92.5±12.0

Table 1. (Continued.)

	High-Hemoglobin Group (N=715)	Low-Hemoglobin Group (N=717)
Hemoglobin (g/dl)	10.1±0.9	10.1±0.9
Hematocrit (%)	31.4±2.9	31.4±2.9
Transferrin saturation (%)	25.2±11.8	24.6 ±10.1
Ferritin (ng/ml)	167.8±157.2	179.2±171.5
Creatinine clearance (ml/min/1.73 m^2)§	36.7±17.0	37.1±17.9
GFR (ml/min)¶	27.0±8.7	27.3±9.1
Albumin (g/dl)	3.7±0.5	3.8±0.5
Ratio of total protein to creatinine in urine	1.6±2.3	1.5±2.3
Medications (%)		
ACE inhibitor only	35.7	37.8
ARB only	29.7	26.8
Combination of ACE inhibitor and ARB	8.3	9.6
Beta-blocker (including labetalol)	46.9	47.7
Platelet aggregation inhibitor (excluding heparin)	42.8	45.0
HMG CoA reductase inhibitor	52.8	52.3
Iron		
Intravenous	2.6	1.6
Oral	26.5	26.7
Unknown route	3.1	1.6


A
Mean Hemoglobin (g/dl)
15.5
15.0
14.5
14.0
13.5
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
0
High-hemoglobin group
Low-hemoglobin group
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
Month
No. of Patients
High-hemoglobin 710 667 632 600 558 507 485 433 367 306 252 194 139 95 81 67 49 31 13
Low-hemoglobin 707 672 625 603 549 528 510 471 384 334 250 182 141 101 75 60 45 30 13

B

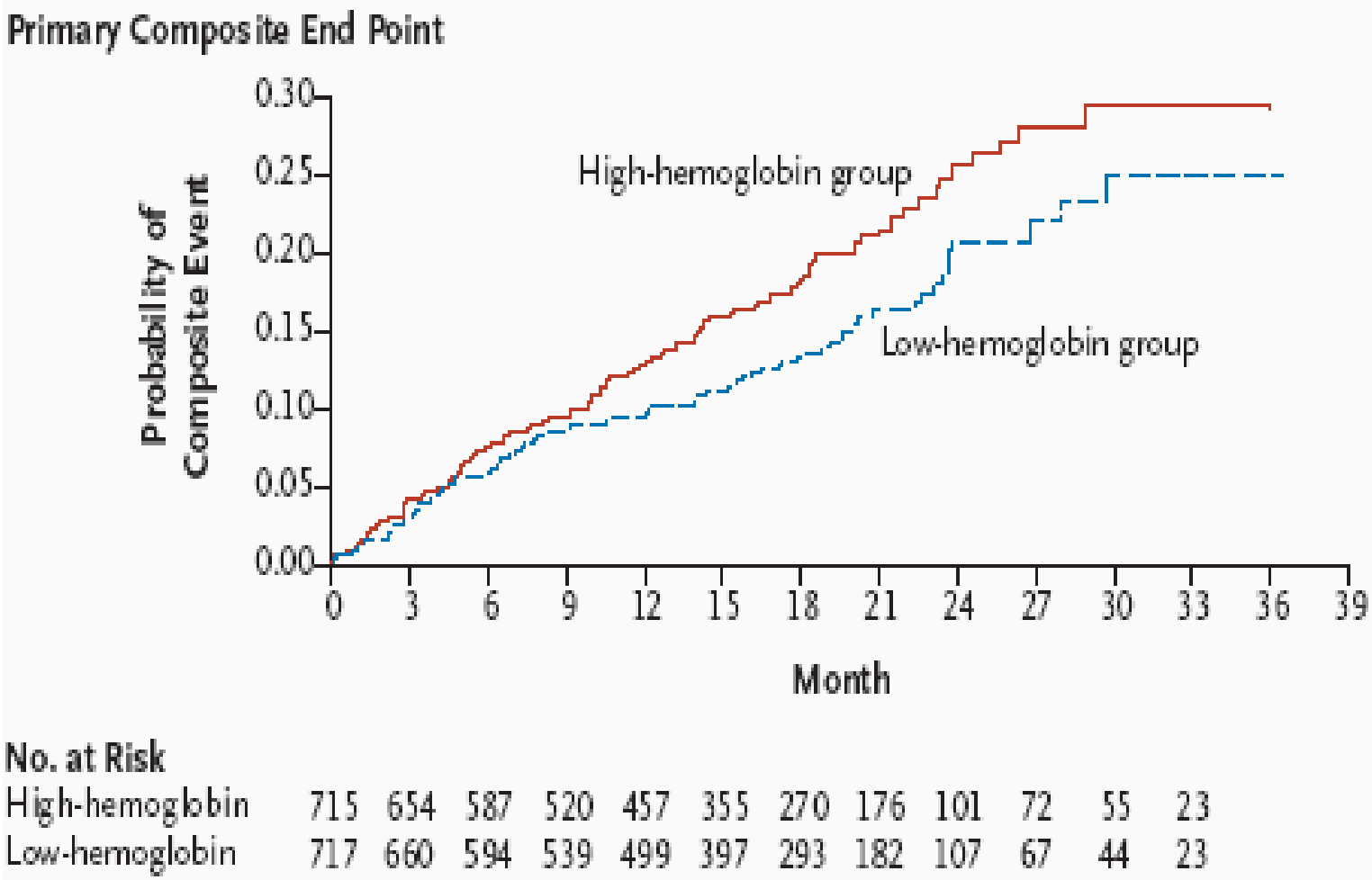


No. of Patients																			
High-hemoglobin	709	693	659	623	578	530	500	452	370	310	258	189	132	97	79	65	52	27	11
Low-hemoglobin	707	691	655	621	577	549	526	479	393	333	262	189	141	95	73	54	43	27	12

CHOIR: Results

- 222 composite endpoints reached
  - 125/715 high Hb (17.5%)
  - 97/717 low Hb (13.5%)
  - HR 1.34 (95% CI 1.03-1.74; p=0.03)

End Point	High-Hemoglobin Group (N=715)	Low-Hemoglobin Group (N=717)	Hazard Ratio (95% CI)	P Value†
	no. of patients (%)			
Clinical results				
Components of the primary end point‡				
Death	52 (7.3)	36 (5.0)	1.48 (0.97–2.27)	0.07
Hospitalization for congestive heart failure (without renal replacement therapy)	64 (9.0)	47 (6.6)	1.41 (0.97–2.05)	0.07
Myocardial infarction	18 (2.5)	20 (2.8)	0.91 (0.48–1.73)	0.78
Stroke	12 (1.7)	12 (1.7)	1.01 (0.45–2.25)	0.98
Renal replacement therapy				
Any renal replacement therapy§	155 (21.7)	134 (18.7)	1.19 (0.94–1.49)	0.15
Hospitalization for renal replacement therapy	99 (13.8)	81 (11.3)	1.25 (0.93–1.68)	0.13
Hospitalization				
Cardiovascular causes	233 (32.6)	197 (27.5)	1.23 (1.01–1.48)	0.03
Any cause	369 (51.6)	334 (46.6)	1.18 (1.02–1.37)	0.03


Primary Composite End Point
Probability of Composite Event
0.30
0.25
0.20
0.15
0.10
0.05
0.00
High-hemoglobin group
Low-hemoglobin group
0 3 6 9 12 15 18 21 24 27 30 33 36 39
Month
No. at Risk
High-hemoglobin 715 654 587 520 457 355 270 176 101 72 55 23
Low-hemoglobin 717 660 594 539 499 397 293 182 107 67 44 23

P=0.07

Problems with CHOIR

- Dropout rate 38.3%!
  - 16.9% for RRT
  - 21.4% dropped out
- Patients censored at start of RRT
- Open label –potential for bias
- Mean Hb difference only 13g/l

Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis

Arintaya Phrommintikul, Steven Joseph Haas, Maros Elsik, Henry Krum

Summary

Background Recombinant human erythropoietin is commonly used for treatment of anaemia. Our aim was to determine whether targeting different haemoglobin concentrations with such treatment is associated with altered all-

Lancet 2007; 369: 381–88

See Comment page 346

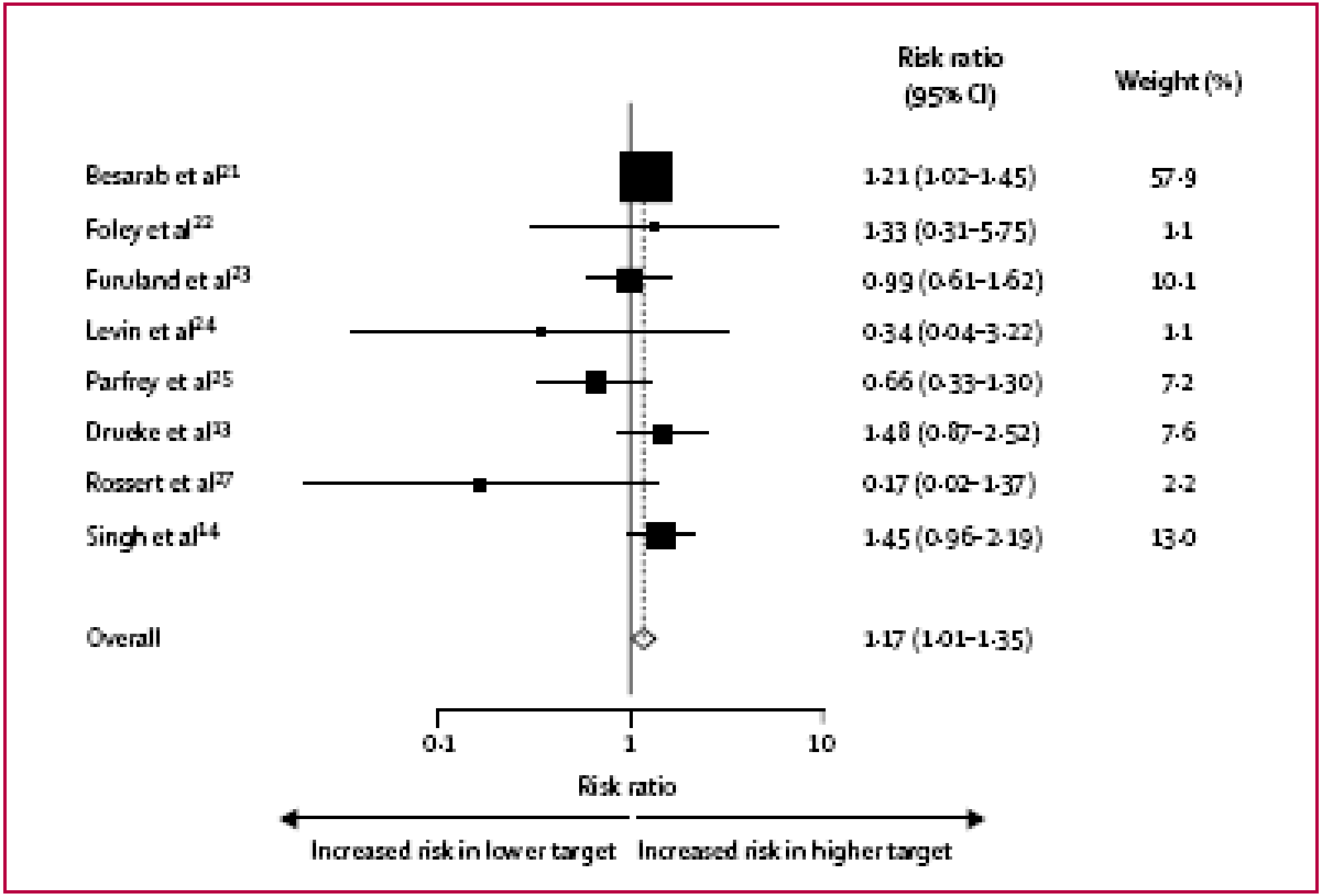


Figure 2: Risk of all-cause mortality in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

The Roger et al trial[26] is not reported because there were no deaths in either group.

Considerations

Physicians and other healthcare professionals should consider the following when using erythropoiesis stimulating agents:

- **For all patients:**
  - Adhere to dosing to maintain the recommended target hemoglobin range of 10 to12 g/dL.
  - Measure hemoglobin twice a week for 2 to 6 weeks after any dosage adjustment to ensure that hemoglobin has stabilized in response to the dose change.
  - Decrease the dose of the ESA if the hemoglobin increase exceeds 1g/dL in any 2 week period.

- **For Chronic Renal Failure (CRF) patients**: Measure hemoglobin twice a week after initiating treatment until hemoglobin has stabilized
- **For cancer patients and zidovudine-treated HIV patients:** Measure hemoglobin once a week after initiating treatment until hemoglobin has stabilized

Report serious adverse events to
FDA's MedWatch reporting system by completing a form on line at
http://www.fda.gov/medwatch/report.htm, by faxing (1-800-FDA-0178),
by mail using the postage-paid address form provided online
(5600 Fishers Lane, Rockville, MD 20852-9787),
or by telephone (1-800-FDA-1088).

Canadian Society of Nephrology Clinical Practice Recommendations for the Management of Anemia Associated with Chronic Kidney Disease

Chair, CSN Anemia Guidelines
Braden Manns

CSN Anemia Work Group Members
Colin White [1]
Francois Madore [2]
Louise Moist [3]
Scott Klarenbach [4]
Brendan Barrett
Rob Foley

Chair, CSN Guidelines Process
Bruce Culleton

Chapter 3: Evidence-based use of Erythropoietic Stimulating Agents

3.1 Target hemoglobin levels

POPULATION: All ND-CKD patients not receiving ESA therapy

Clinical practice recommendation:

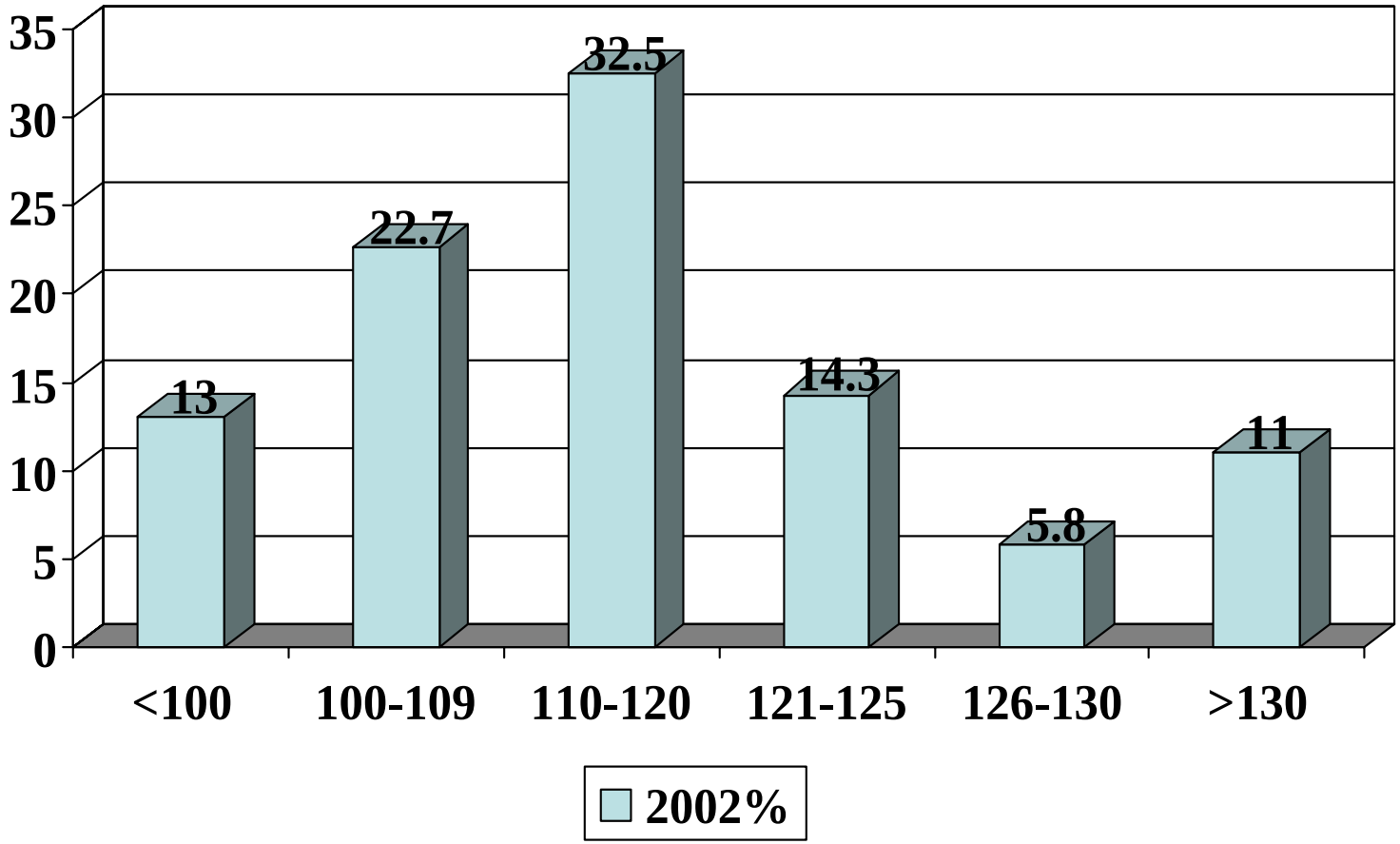
3.1.1. Initiate ESA therapy when iron stores have been corrected, other reversible causes of anemia have been treated, and the hemoglobin is sustained below 100 g/L (OPINION).

POPULATION: All CKD patients receiving ESA therapy

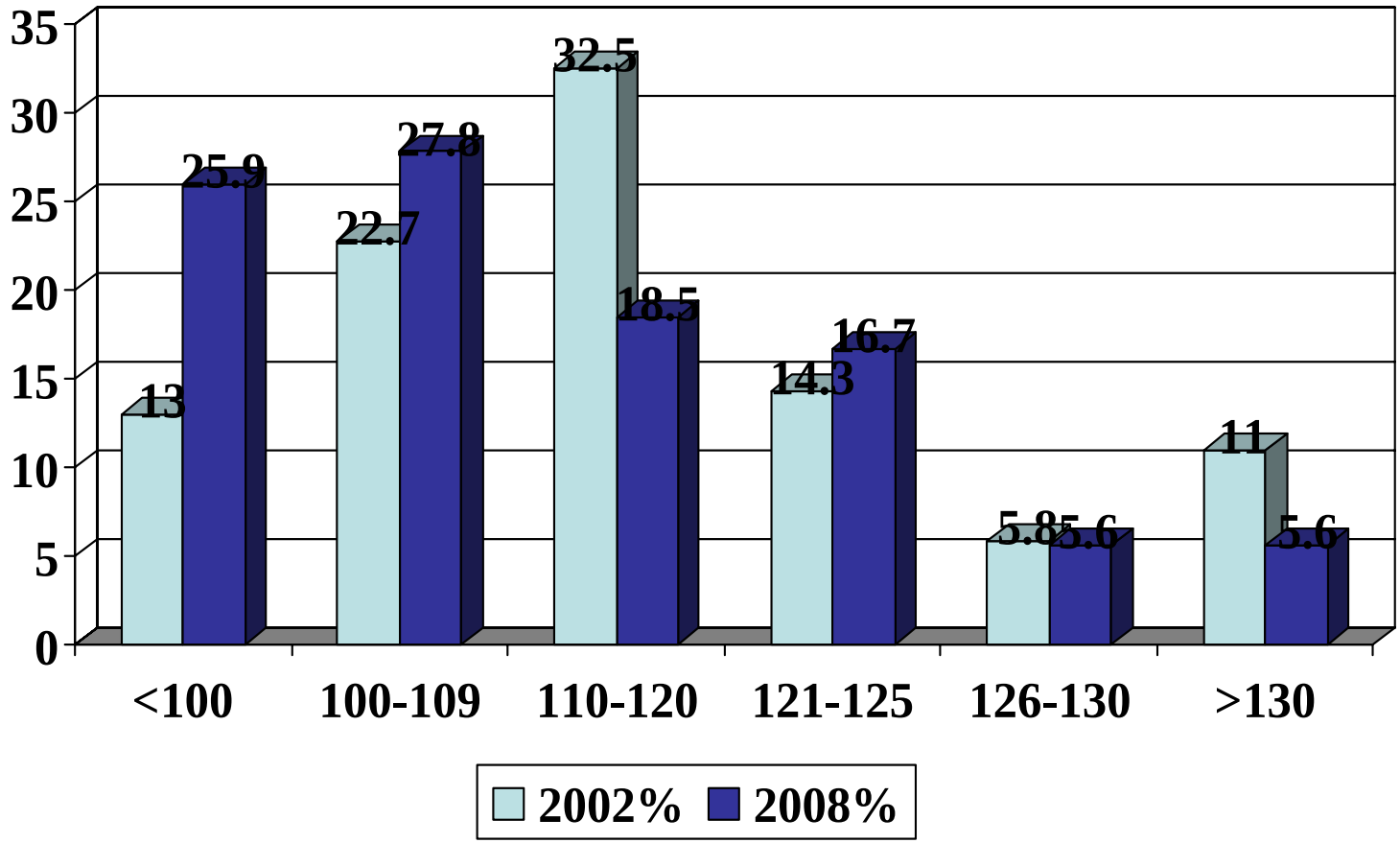
Clinical practice recommendation:

3.1.2. Prescribe ESA therapy to achieve a target hemoglobin of 110 g/L (Grade A for HD-CKD and ND-CKD; Grade B for PD-CKD). An acceptable hemoglobin range is 100 – 120 g/L.

Achieved Hb at LHSC



Achieved Hb at LHSC



Mean Hb 2002 – 118.2g/l; mean Hb 2008 108.7g/l

TREAT Study

- Approx. 4000 patients with CKD (stage 2-4) and type 2 diabetes
- Double-blind, placebo-controlled RCT
- Darbepoetin given s.c.
- Hb target >125g/l
- “Rescue” darbepoetin for Hb <95g/l in placebo group
- Death and CV events

TREAT Study

- Enrolment complete
- Safety analyses to date indicate no need to halt trial
- TREAT should provide a clear answer to the question of target Hb and CV risk

What factors should we use to determine target hemoglobin?

- Relief of anemia-related symptoms?
- Improvement in quality of life?
- Mortality considerations?
- Potential differences for CKD vs dialysis patients?
- Evidence vs clinical judgement?
- Reimbursement considerations?

Thoughts on current management of renal anemia

- We have forgotten what renal anemia looks like

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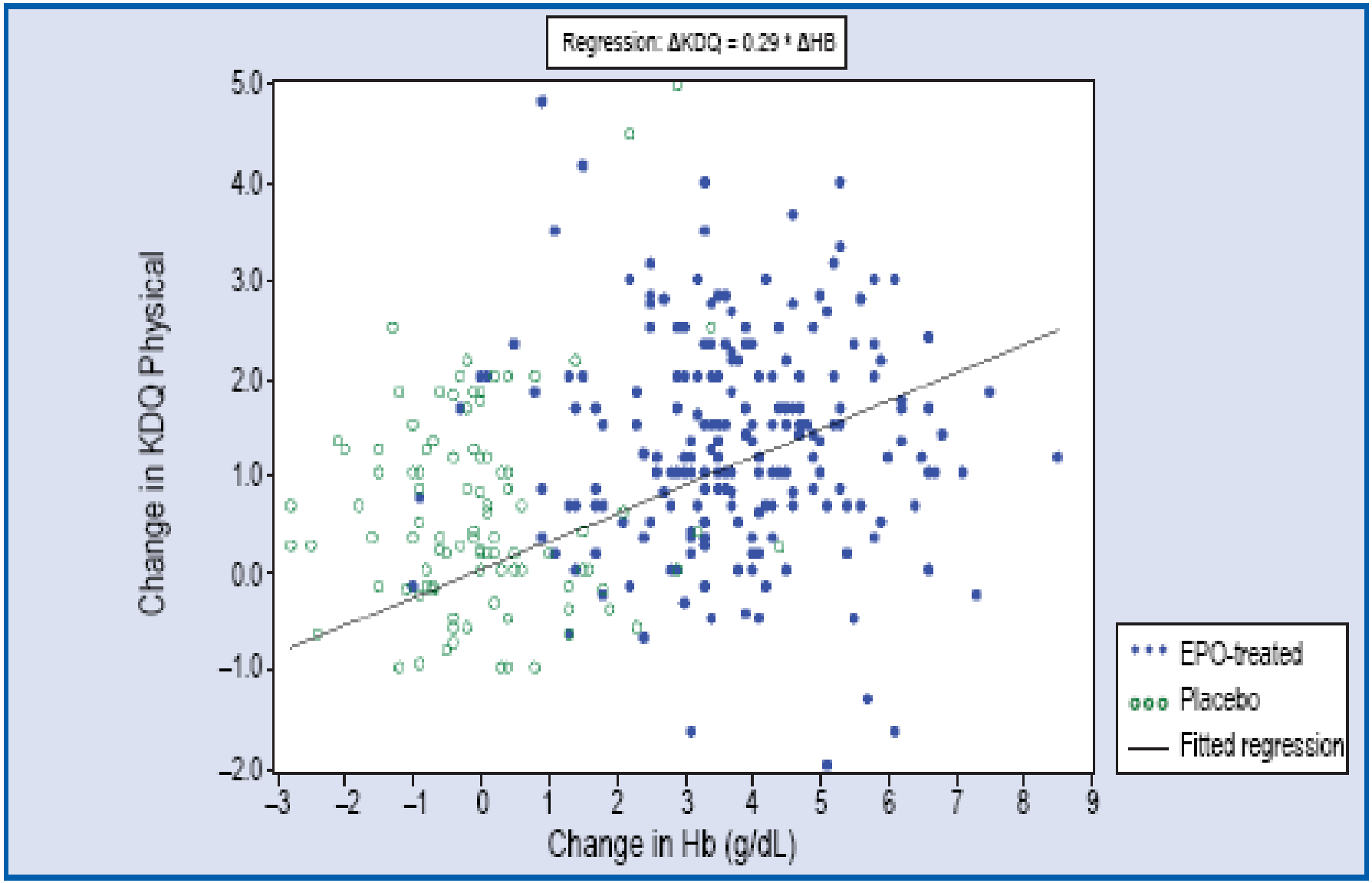
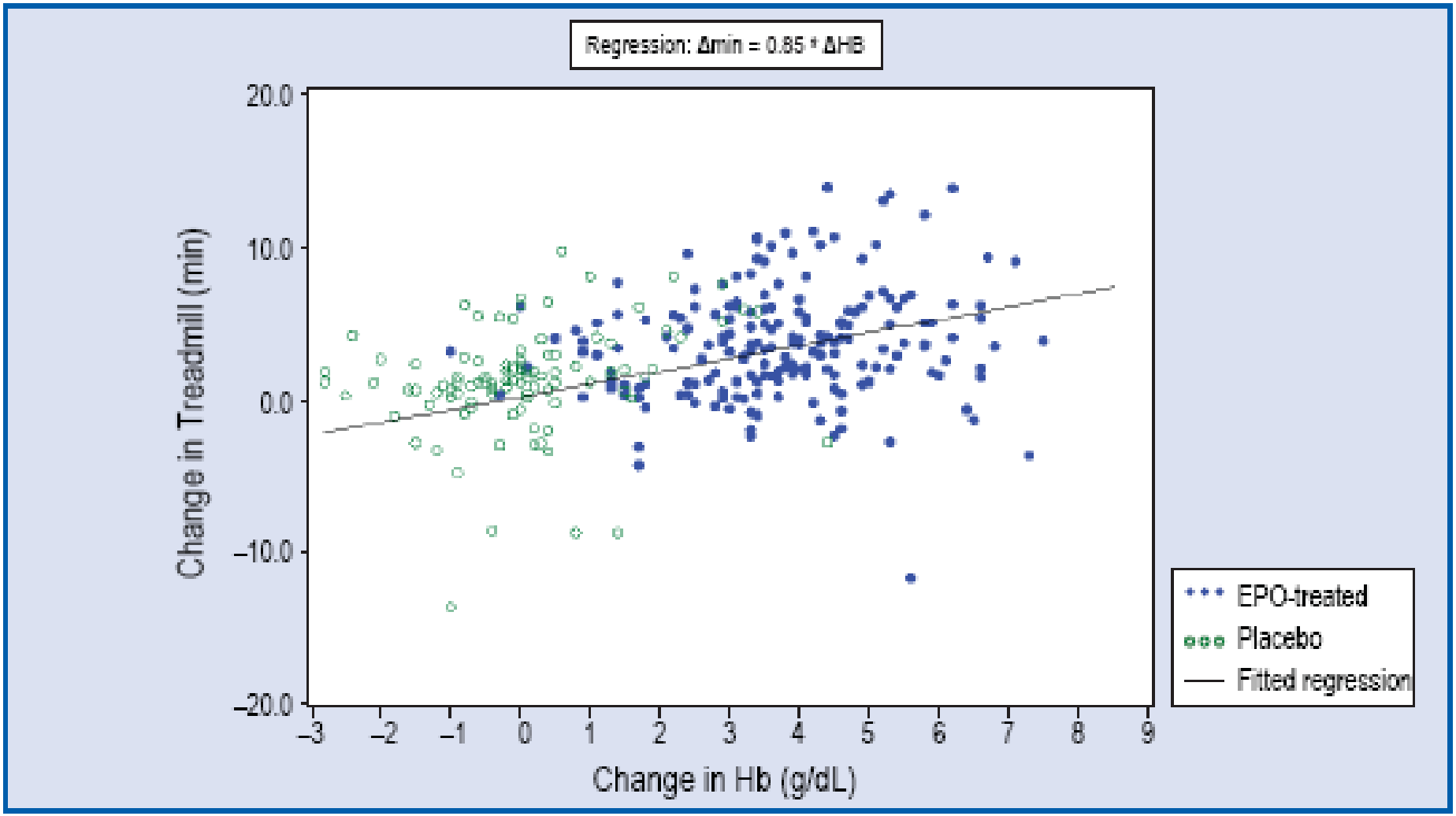
- We have forgotten what renal anemia looks like
- QOL and exercise benefits of ESAs are linearly related to increase in hemoglobin


Regression: ΔKDQ = 0.29 * ΔHB
Change in KDQ Physical
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
-3
-2
-1
0
1
2
3
4
5
6
7
8
9
Change in Hb (g/dL)
EPO-treated
Placebo
Fitted regression

NKF 2008


Regression: Δmin = 0.85 * ΔHB
20.0
10.0
0.0
−10.0
−20.0
Change in Treadmill (min)
−3
−2
−1
0
1
2
3
4
5
6
7
8
9
Change in Hb (g/dL)
EPO-treated
Placebo
Fitted regression

NKF, 2008

Thoughts on current management of renal anemia

- We have forgotten what renal anemia looks like
- QOL and exercise benefits of ESAs are linearly related to increase in hemoglobin
- Because we now initiate ESAs at a higher hemoglobin level the perception of benefit is less

Thoughts on current management of renal anemia

- We have forgotten what renal anemia looks like
- QOL and exercise benefits of ESAa are linearly related to increase in hemoglobin
- Because we now initiate ESAs at a higher hemoglobin level the perception of benefit is less
- We therefore need a new paradigm to drive anemia management

Individualised anemia management

- Understand impact of anemia on individual patients
- Derive strategies to evaluate response to anemia correction with ESAs
  - Use QOL measures and PROs
- Identify non-responders and stop the ESA!!!!
- Consider lower starting Hb

What’s next in ESAs?

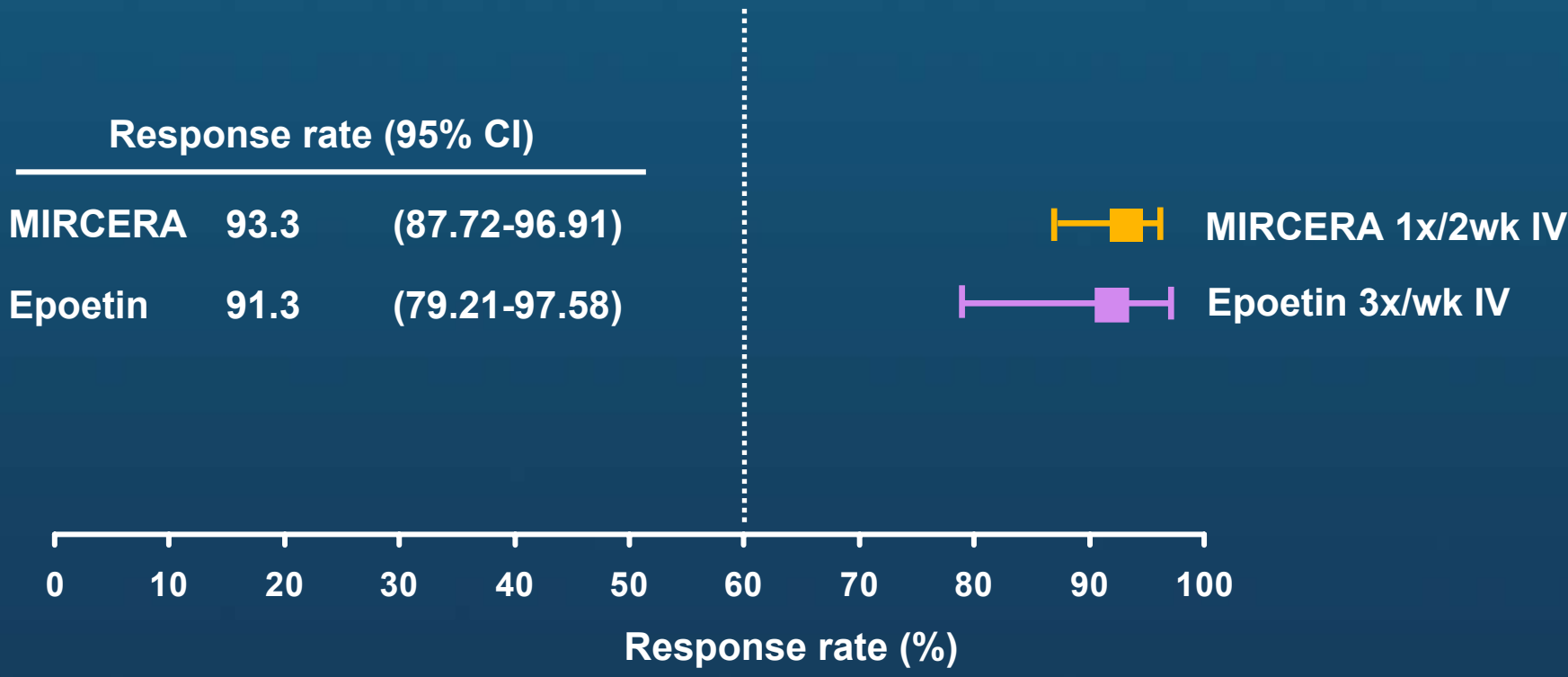
- CERA
- Biosimilars
- Protein-bound ESAs
- Small molecule ESAs
- Other

CERA

- Marketed by Roche as MIRCERA
- Available in Europe, Australia and Far East
- Similar performance to Epoetin alfa or beta and to darbepoetin
- Fewer dose adjustments and less Hb overshoot
- Slower rate of rise in Hb
- Can be used every 2-4 weeks for correction or maintenance

High Response Rate with MIRCERA

Hemoglobin response rate during correction period (ITT population)

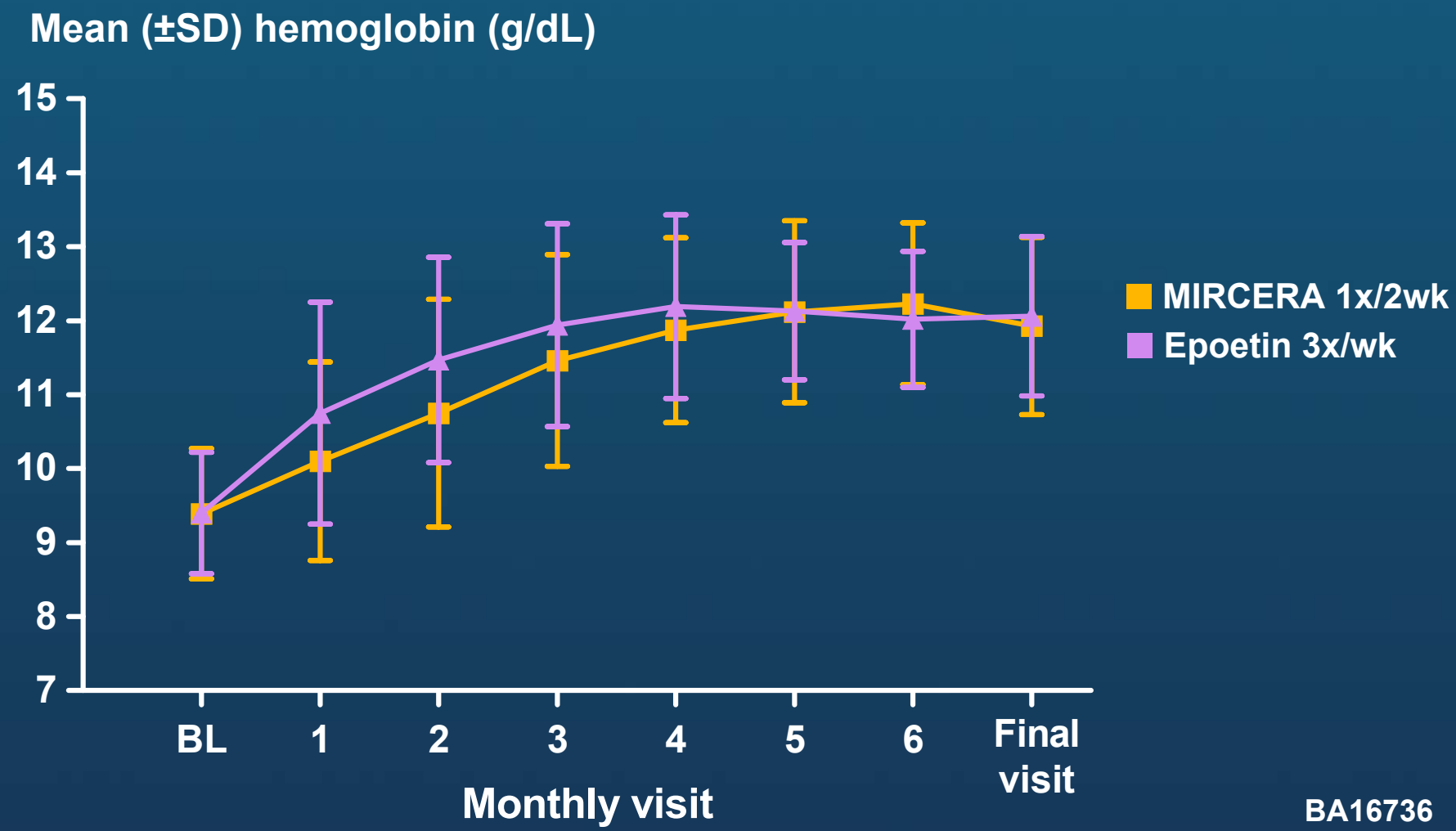


Criteria for response: hemoglobin increase ≥1 g/dL above baseline and hemoglobin ≥11 g/dL during correction period without RBC transfusion

AMICUS (BA16736)

Predictable Hemoglobin Control with MIRCERA

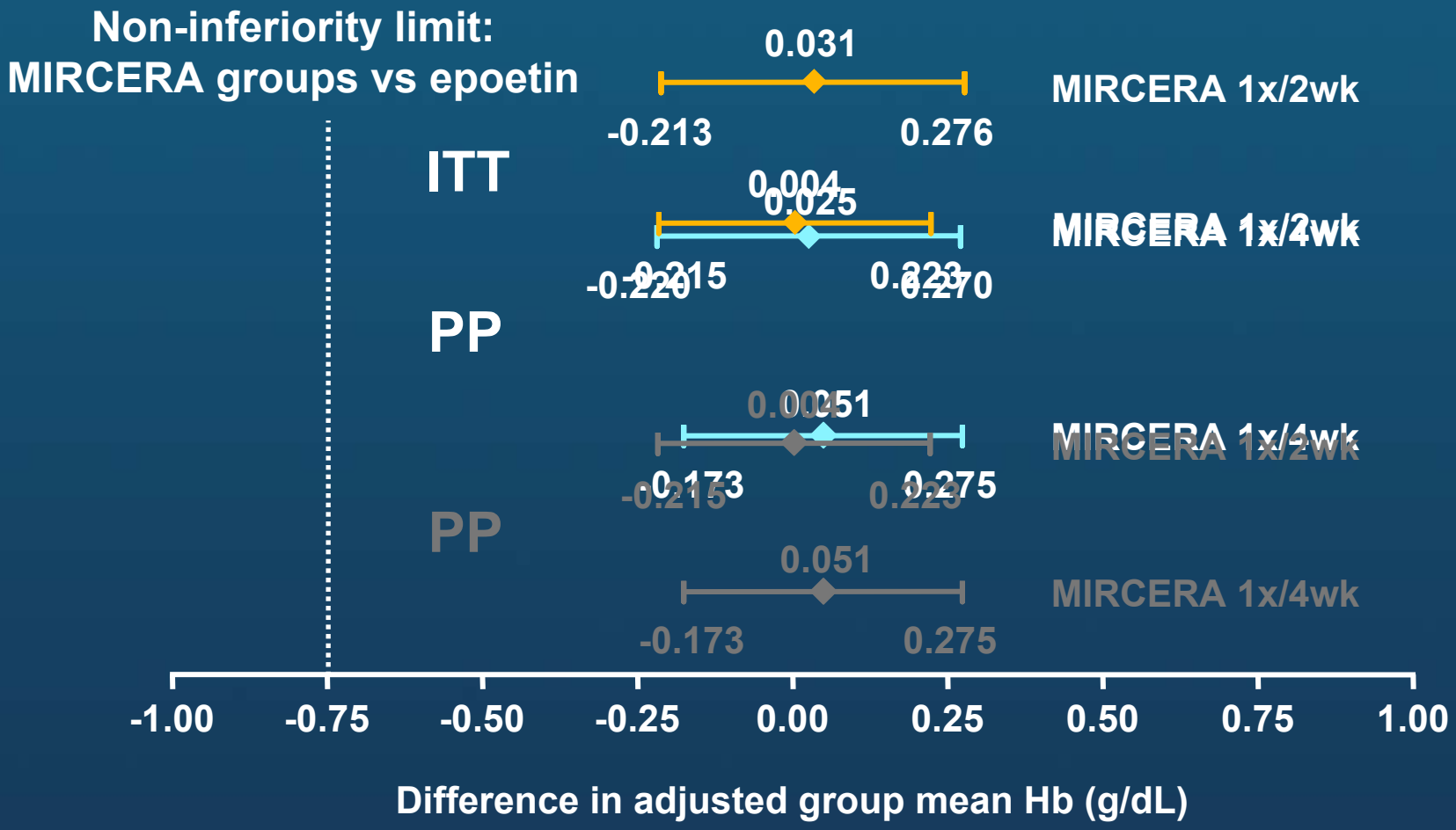
Hemoglobin over time during correction period (ITT population)



BA16736

Primary Efficacy Analysis

Hb change between baseline and evaluation (97.5% CI)



P<0.0001 for all comparisons

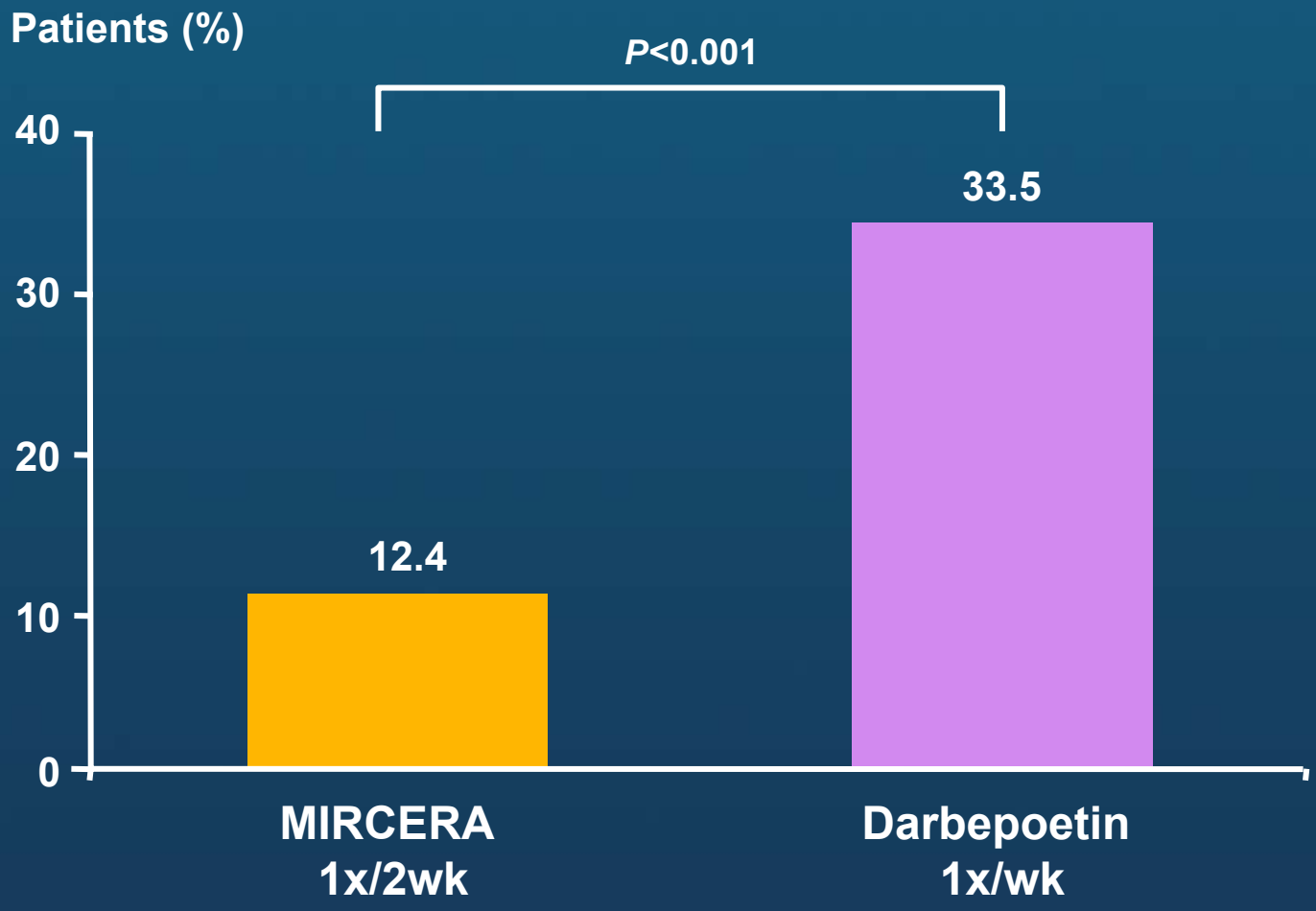
MAXIMA (BA16739)

Roche

Pharmaceuticals

Fewer Overshoots With MIRCERA

Patients with at least one Hb >13 g/dL first 8 weeks of treatment



ARCTOS (BA16738)

Biosimilars

- Generic “copies” of epoetin alpha approved by EMEA
  - Binocrit (Sandoz, Austria)
  - Epoetin alfa Hexal (Hexal, Germany)
  - Abseamed (Germany)
- All manufactured in same plant!
- AA sequence identical to epoetin alfa
- Minor differences in glycosylation
- Single IV comparison study with epoetin alfa available
- Licensed for CKD, HD, PD, adult and pediatric patients, chemotherapy associated anemia, perioperative use in elective orthopedic surgery

Protein-bound ESAs

- Epoetin omega
  - Produced in BHK cells
- Epoetin delta
  - Produced in human fibrosarcoma (HT-1080) cell line
  - EPO gene activated by CMV promoter

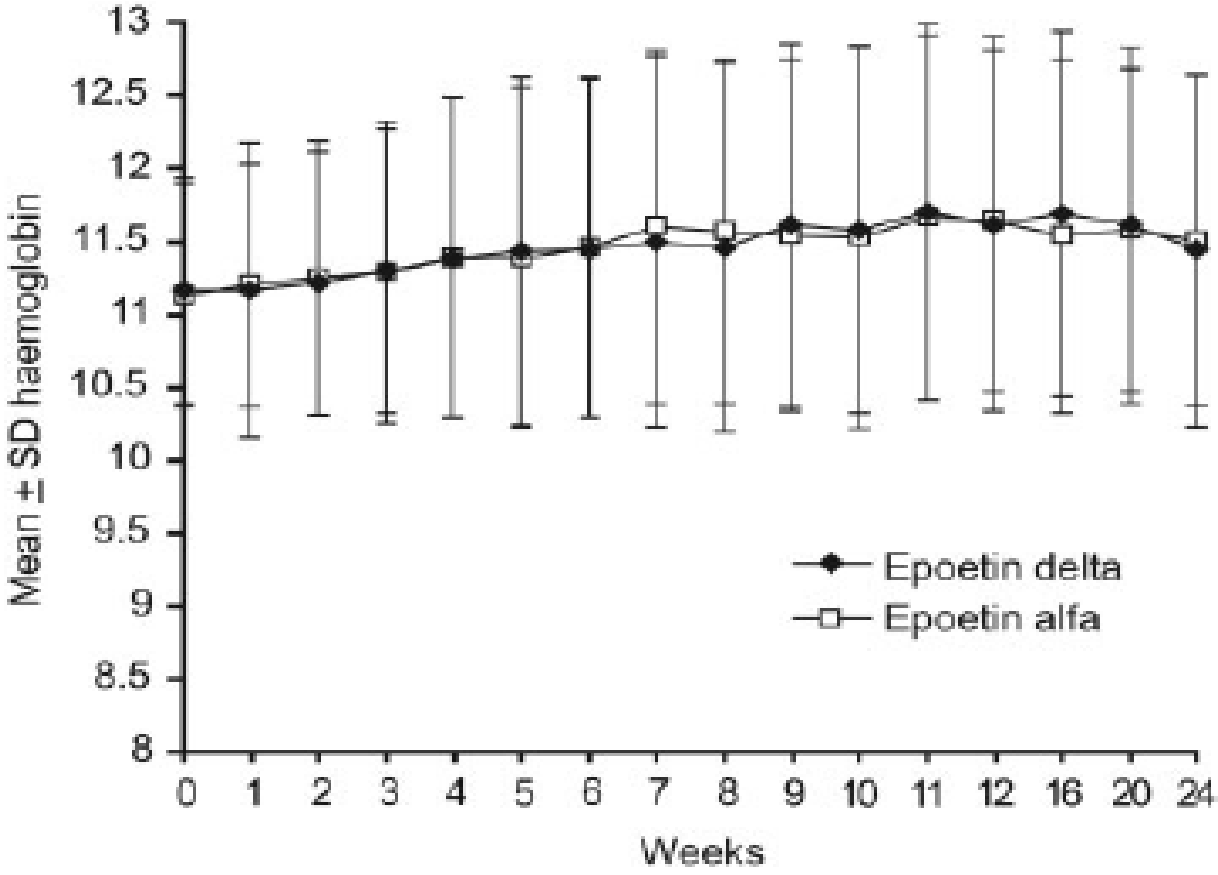
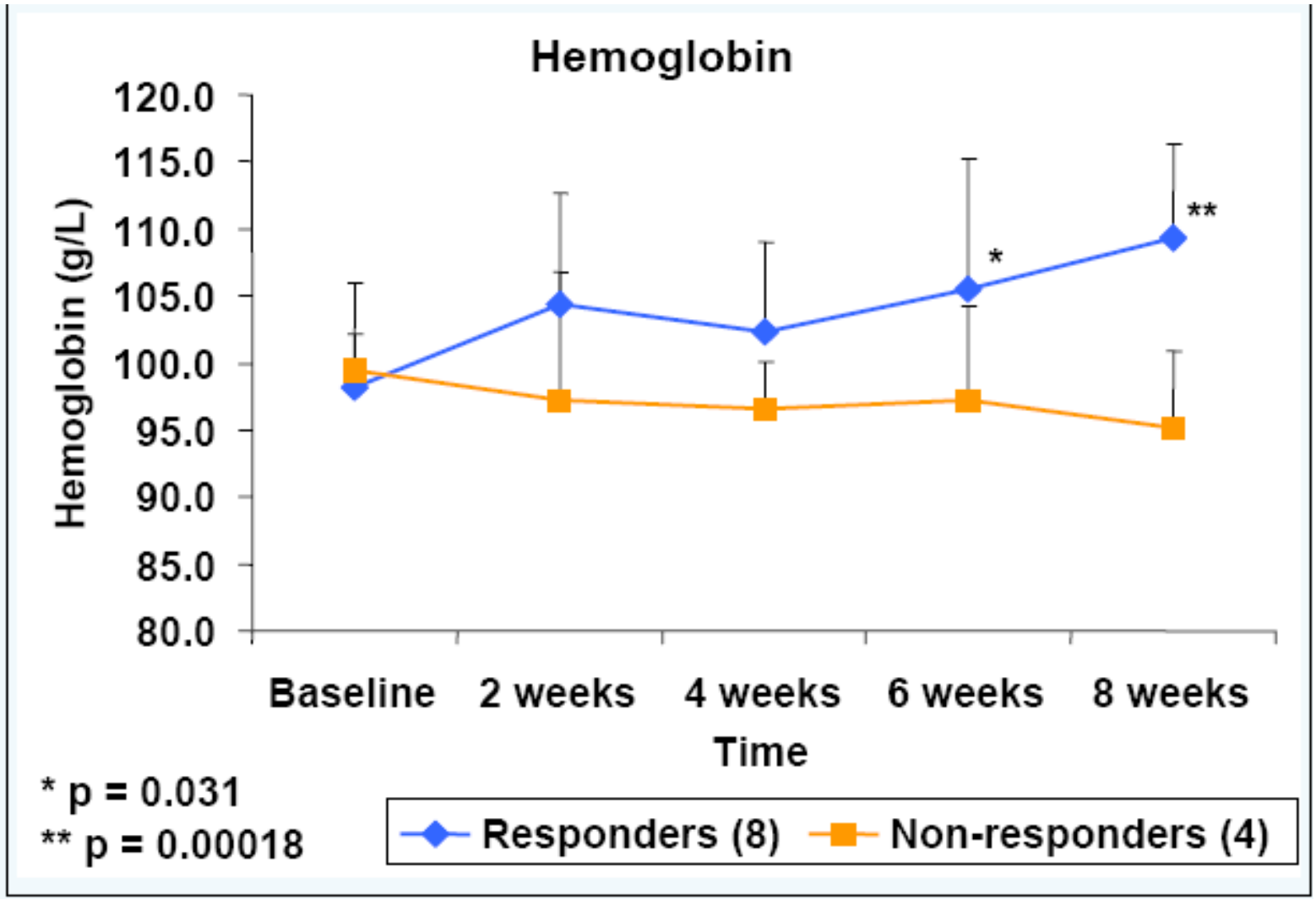


Fig. 1. Mean ± SD haemoglobin in the modified ITT population.

Nephrol Dial Transplant (2007) 22: 3052–3054

Small molecule ESAs

- Peptide vs non-peptide
  - Hematide (Affymatix)
    - Data in rat remnant kidney model
    - Limited clinical data
    - Trials underway
    - Given orally every 2-4 weeks
  - PBI-1042 (Prometic)
    - Limited clinical data in chemotherapy induced anemia
    - Improves anemia in rat remnant kidney model
    - Orally active
    - Clinical trials planned



Impact of a non-peptide orally active agent on hemoglobin in patients with chemotherapy induced anemia

Other

- HIF stabilisers
- GATA inhibition
- Hemopoietic cell phosphatase inhibition
- EPO gene therapy

Summary

- The target hemoglobin paradox is not resolved
- TREAT may clarify or further muddy the debate
- For the present, a move to individualised care seems appropriate
- The interrelationships of anemia and heart failure deserve further investigation
- Newer ESAs offer the promise of longer duration of action, more stable hemoglobin maintenance and the prospect of oral agents to correct anemia