

Antalya May 20, 2010



**12° National Congress of Turkish Society of
Hypertension and Renal Disease**

**Anemia treatment in dialysis patients and
related problem**

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A Manzoni Hospital, Lecco, Italy

Anemia and CKD: is it a battle of the past?



HOT
topic of the day

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la Repubblica

13 luglio 2003

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EL PAIS

CORRIERE DELLA SERA

Le Monde

SUPPLEMENT
ECONOMIE
108 000 chômeurs
de moins :
où sont-ils passés ?

The New York Times

WEDNESDAY, OCTOBER 6, 1999

THE REVIEW

*Inspired by the Traditions of Africa
But Ruled by a Contemporary Spirit*

welcome.
Some good work in this field has been done by
the African Odyssey series at the John F.
Kennedy Center for the Performing Arts in
Washington and Dance Africa and 651 Arts,
both associated with the Brooklyn Academy of



- Near half of ESRD patients die because of cardiovascular disease
- Their life-expectancy is markedly decreased compared to subjects with the same age and gender in the general population

- **Is anaemia a risk factor for cardiovascular disease and patient outcome in renal disease?**
- **Is treatment of anaemia really able to reduce the cardiovascular burden of renal patients?**
- **When should the treatment be started and which target should be aimed for?**
- **Is treatment of anaemia in line with current clinical practice guidelines?**

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Cardiovascular Risk Factors in CKD

Traditional Risk Factors

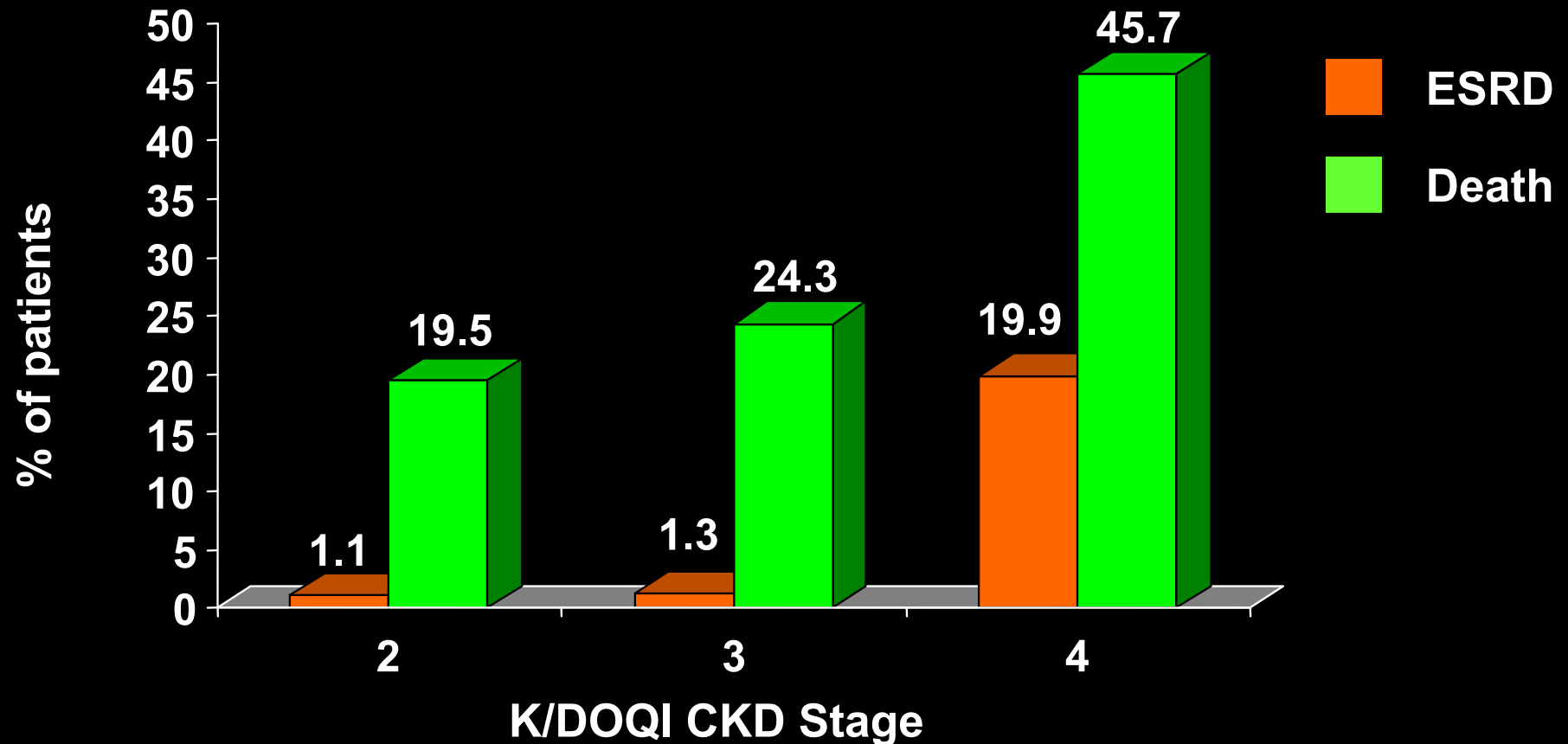
Older age
Male sex
Hypertension
Higher LDL cholesterol
Low HDL cholesterol
Diabetes
Smoking
Physical inactivity
Menopause
Family history of CVD
Left ventricular hypertrophy

Nontraditional Risk Factors

Albuminuria/proteinuria
Homocysteine
Lipoprotein(a) and apolipoprotein(a) isoforms
Lipoprotein remnants
Anemia
Abnormal calcium-phosphate metabolism
Extracellular fluid overload
Oxidative stress
Inflammation
Malnutrition
Altered nitric oxide/endothelin balance

Death is far more common than ESRD in CKD patients

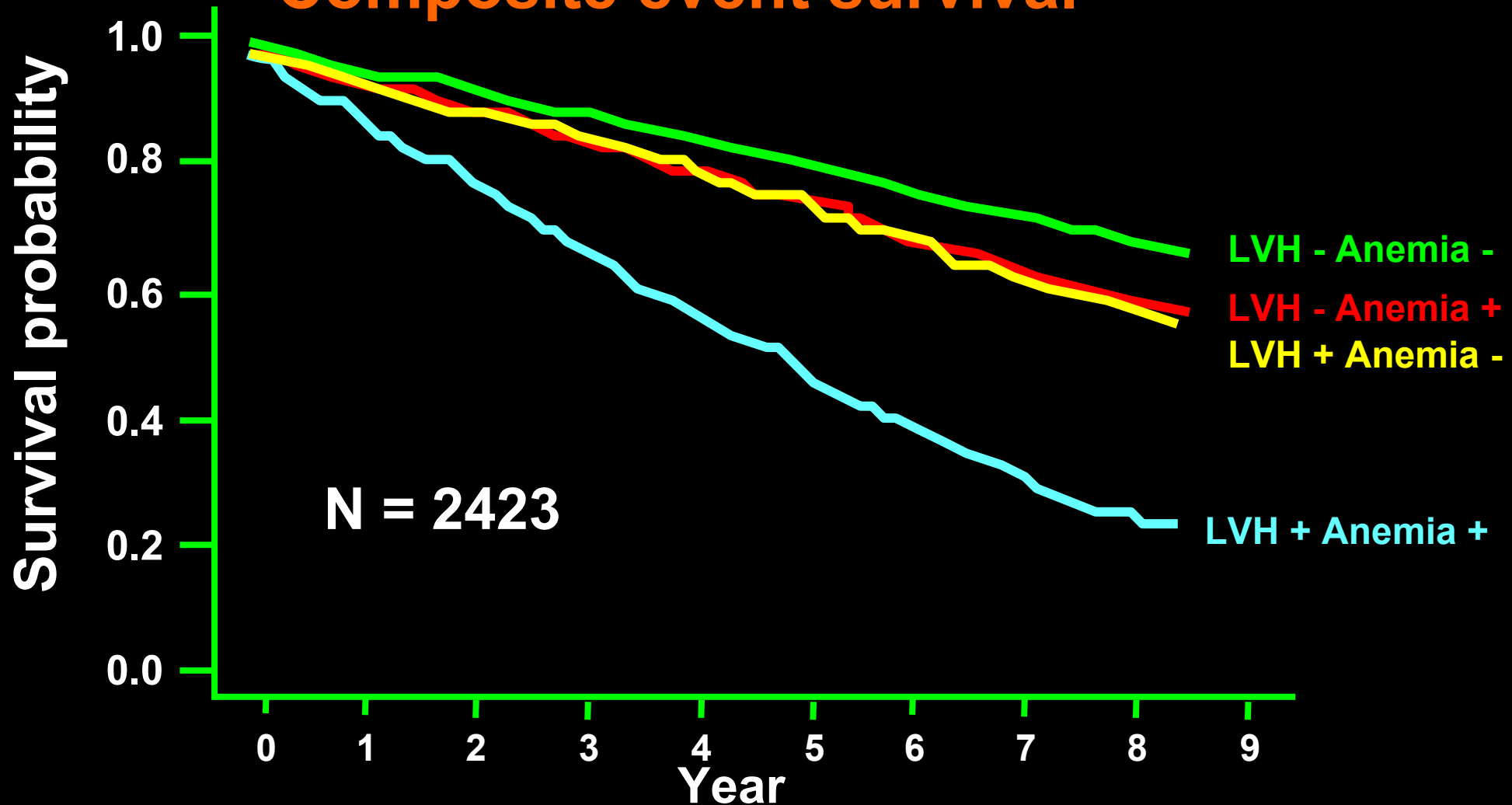
27998 CKD patients followed up for up to 66 months



Keith DS et al. Arch Intern Med 2004; 164: 659-663

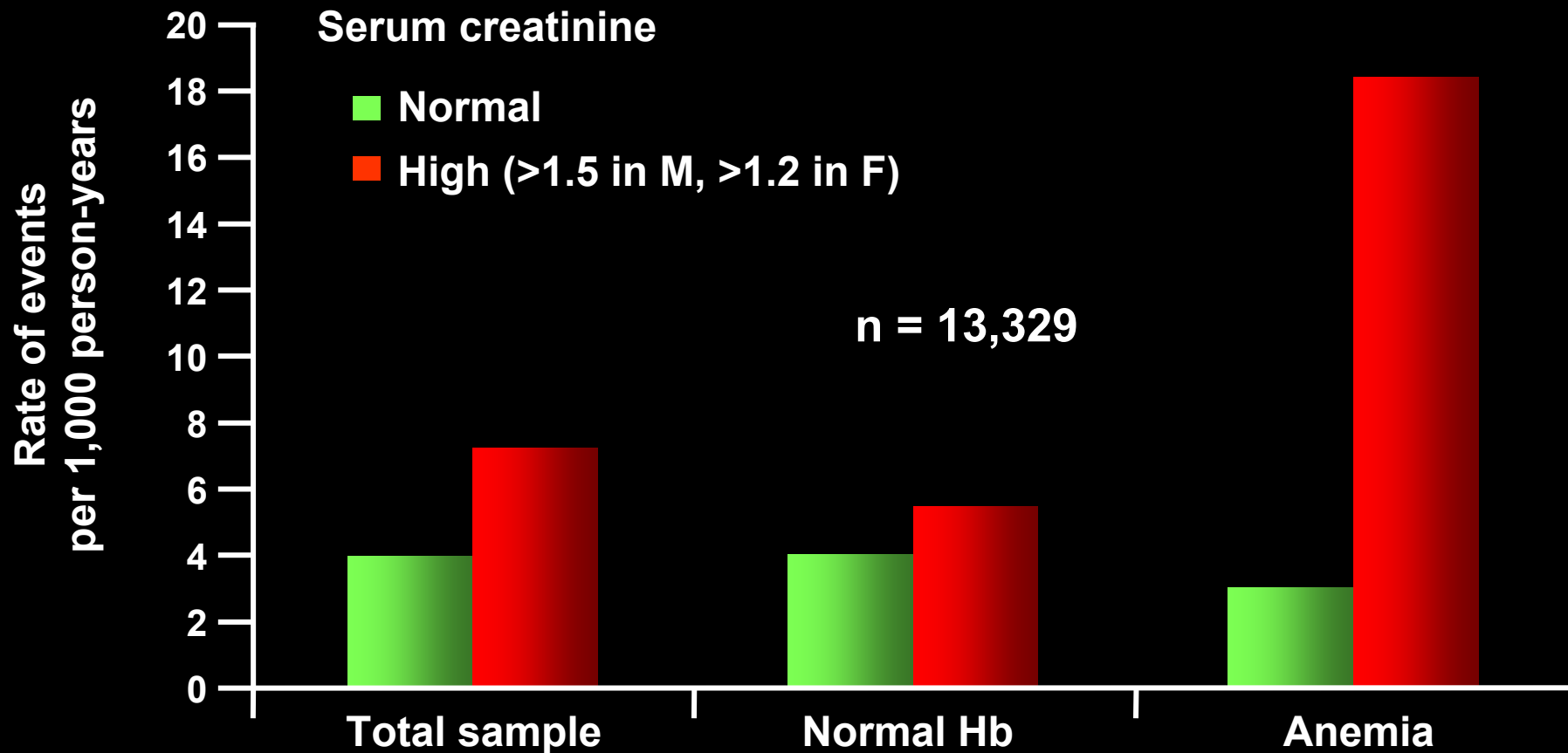
Effects of anemia and LVH on cardiovascular disease in CKD patients

Composite event survival



Anemia increases risk of coronary heart disease (CHD) in patients with CKD

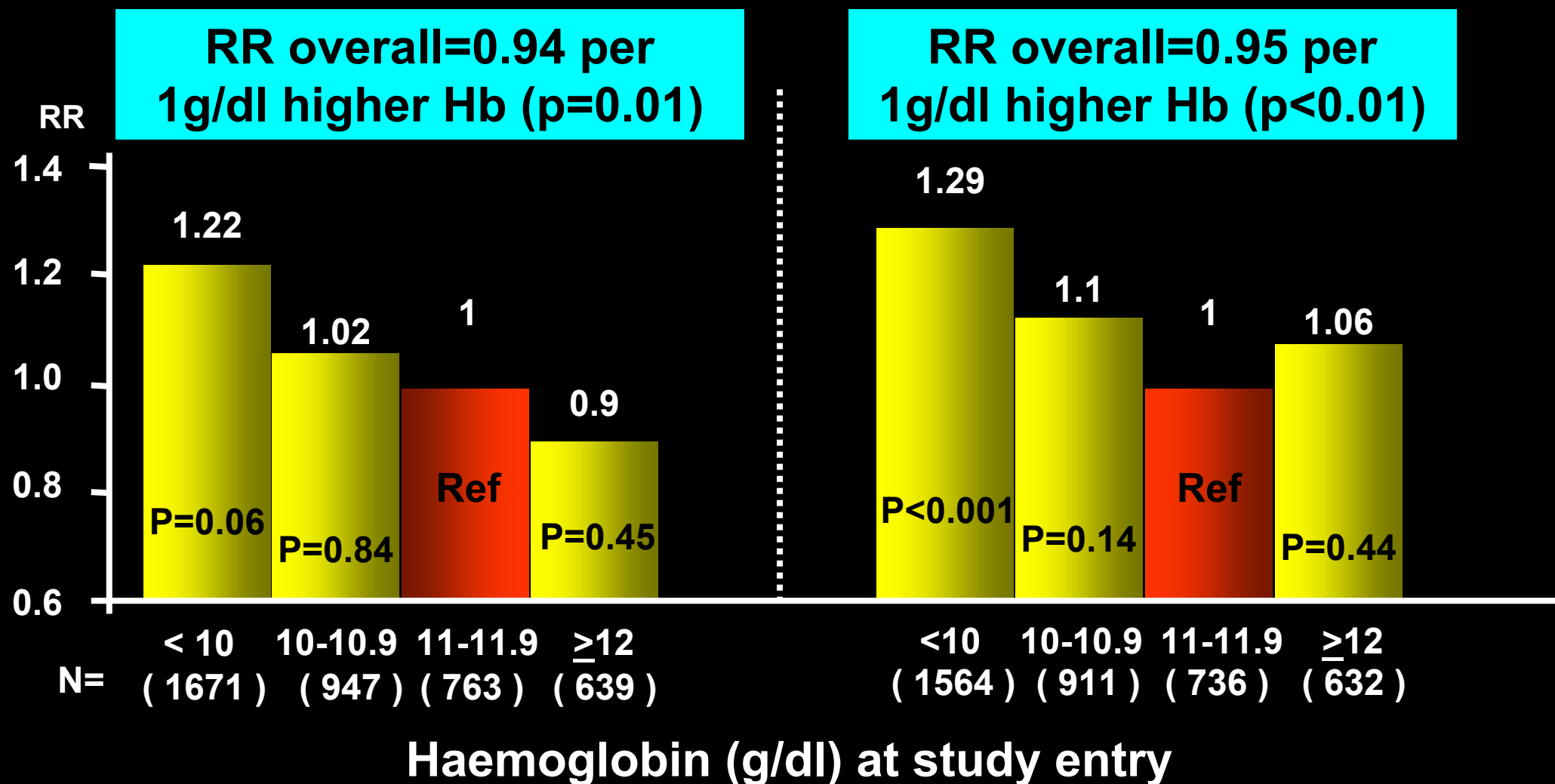
Atherosclerosis Risk In Communities (ARIC) study



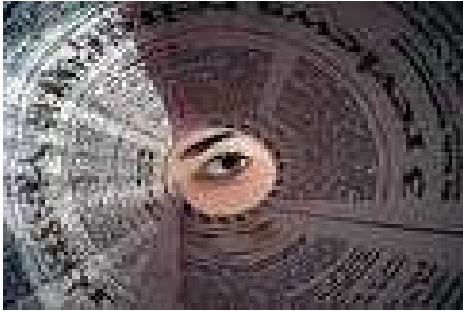
Mortality and hospitalisation risks and anemia

Relative Risk of Death

Relative Risk of Hospitalisation



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**There is a clear relationship
between anaemia and outcome**

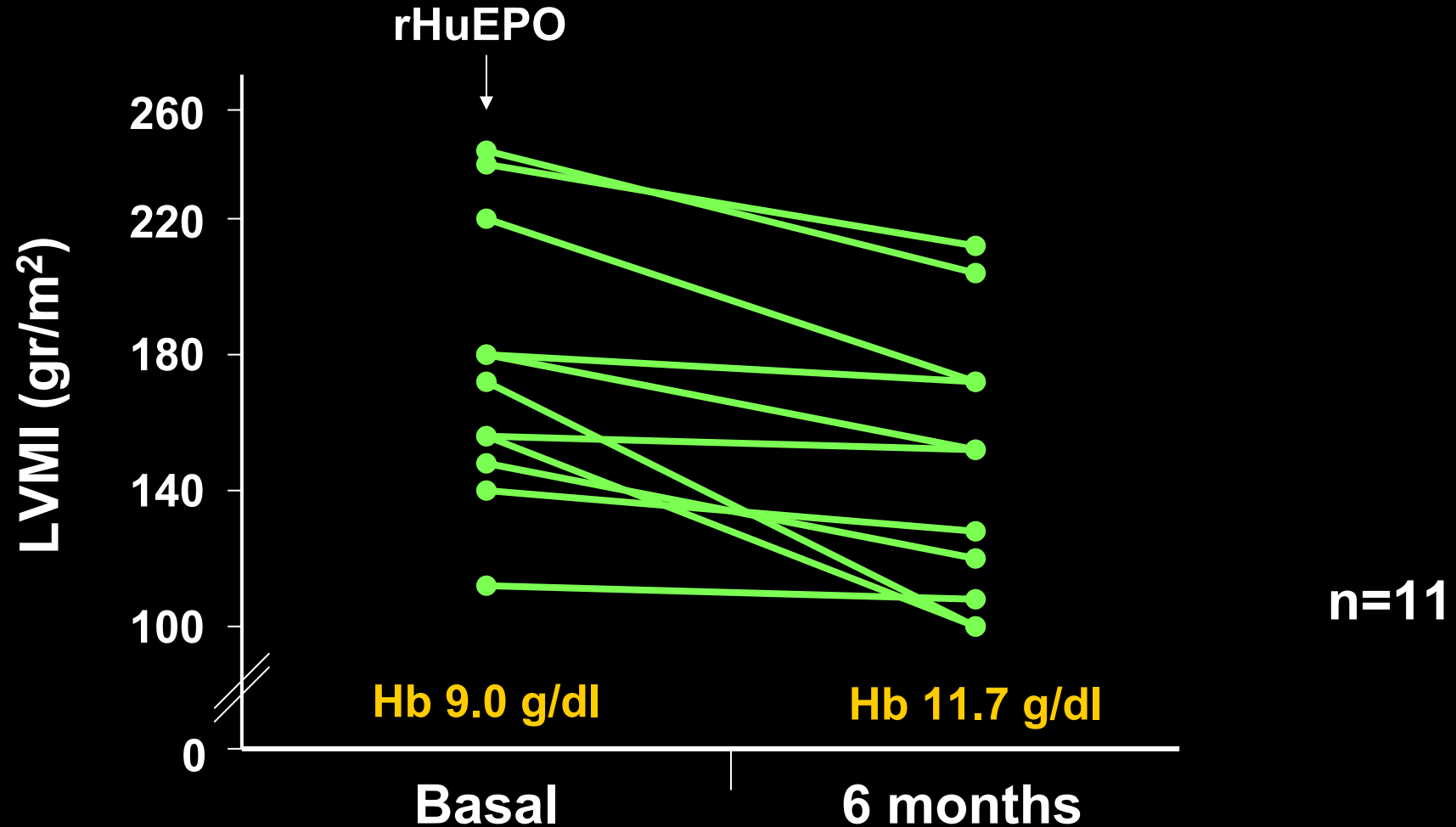




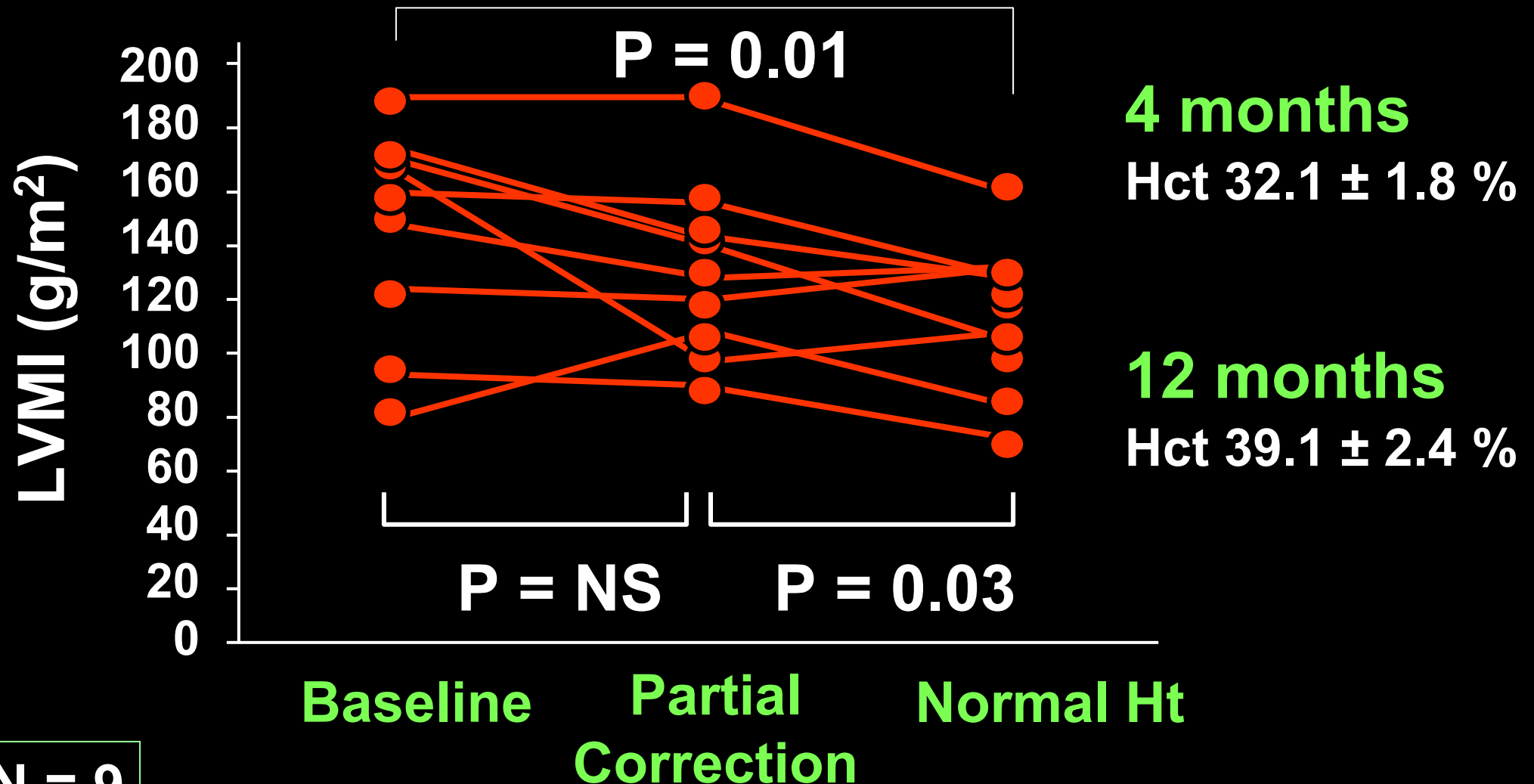
HOWEVER

**Interventional trials of
complete anaemia correction
did not give the expected results**

LVH reduction after anemia correction in CKD pre-dialysis patients



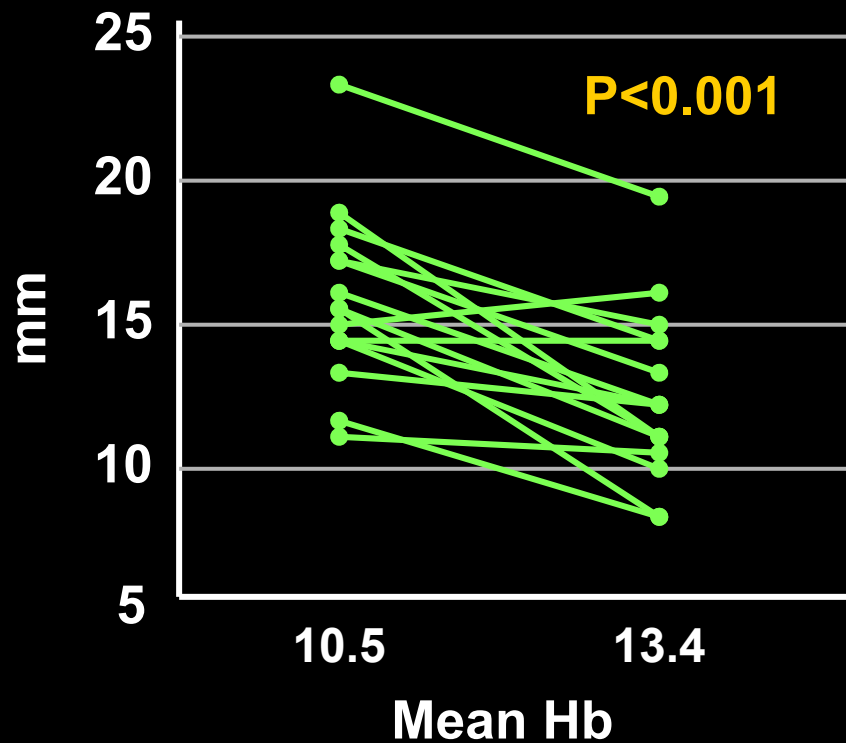
LVH reduction after anemia correction in CKD pre-dialysis patients



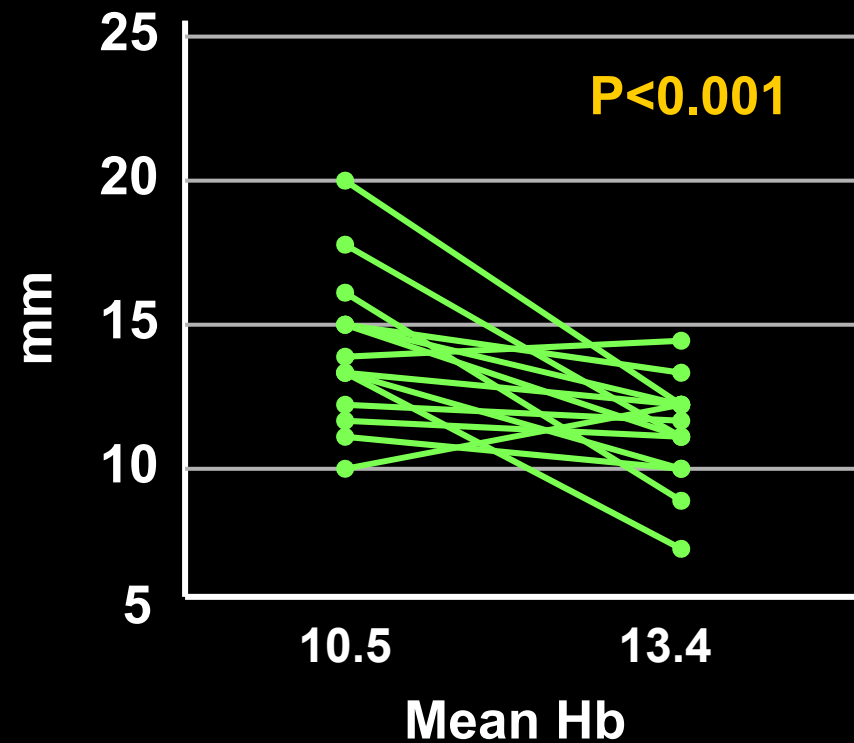
N = 9

Effects of anemia correction on left ventricular wall thickness

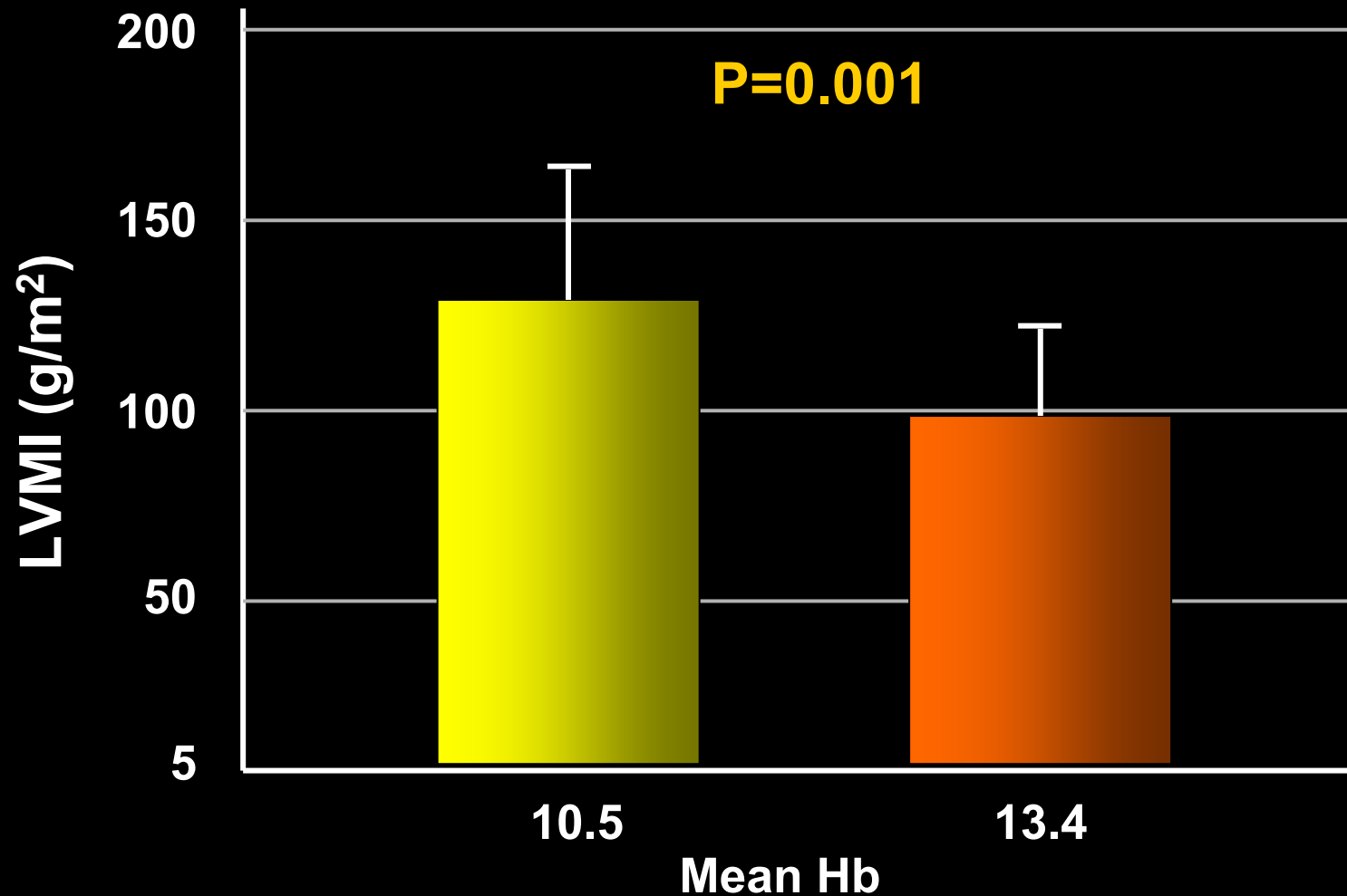
Septal



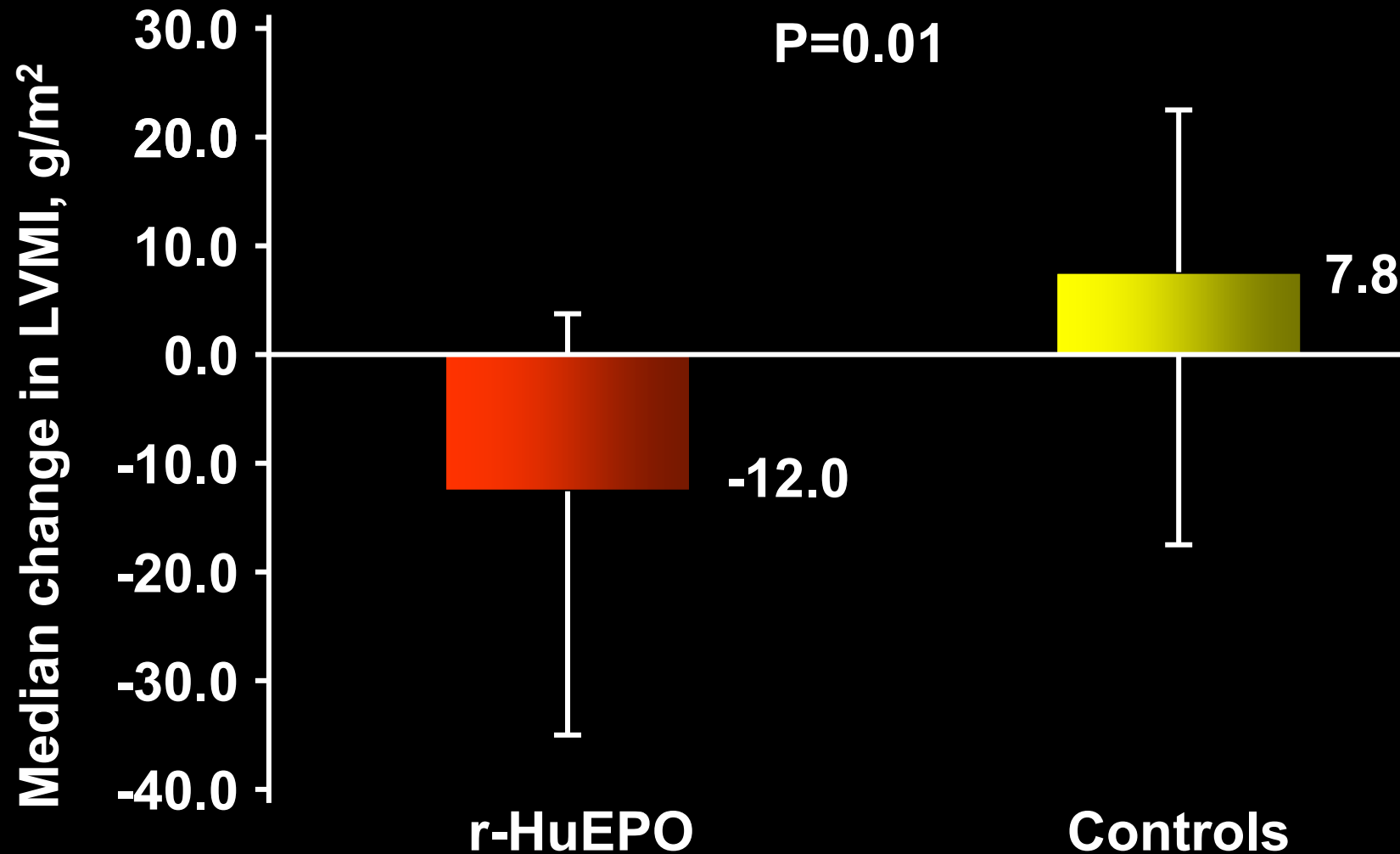
Posterior wall



Effects of anemia correction on left ventricular mass index



Effect of rHuEPO on LVH in adults with severe CKD and Hb < 10 g / dl



Results of the intervention study

Non-diabetic patients ($n = 95$)

| | Before | After | <i>P</i> |
|------------------------|--------------|--------------|----------|
| Haemoglobin (g/dL) | 10.5 ± 1.0 | 12.9 ± 1.2 | < 0.05 |
| EPO dose (IU/kg/week) | | 65.3 ± 45.0 | |
| LVEF (%) | 35.0 ± 15.5 | 37.6 ± 11.7 | < 0.05 |
| NYHA (1-4) | 3.91 ± 0.24 | 2.55 ± 0.48 | < 0.05 |
| Systolic BP (mmHg) | 135.3 ± 26.1 | 132.7 ± 26.9 | n.s. |
| Diastolic BP (mmHg) | 74.0 ± 11.3 | 74.4 ± 11.6 | n.s. |
| Serum creatinine (mg%) | 2.37 ± 1.14 | 2.38 ± 1.60 | n.s. |
| Δ GFR (ml/min/month) | -1.12 ± 1.30 | +0.21 ± 1.30 | < 0.05 |

Results of the intervention study

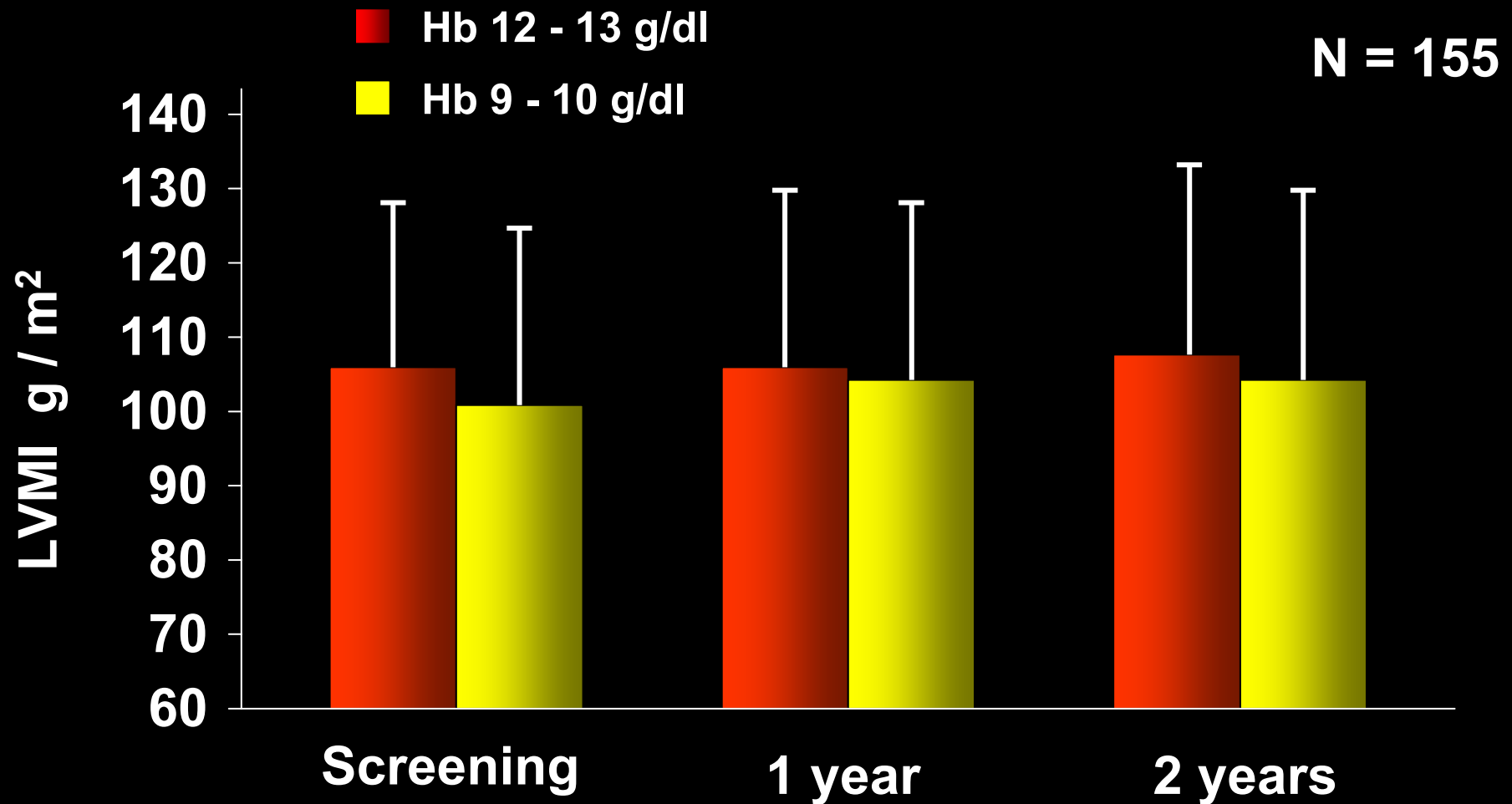
Diabetic patients ($n = 84$)

| | Before | After | <i>P</i> |
|------------------------|--------------|--------------|----------|
| Haemoglobin (g/dL) | 10.4 ± 1.1 | 13.1 ± 1.3 | < 0.05 |
| EPO dose (IU/kg/week) | | 68.3 ± 36.1 | |
| LVEF (%) | 34.8 ± 13.5 | 39.8 ± 8.0 | < 0.05 |
| NYHA (1-4) | 3.89 ± 0.24 | 2.53 ± 0.42 | < 0.05 |
| Systolic BP (mmHg) | 134.8 ± 27.2 | 132.2 ± 20.8 | n.s. |
| Diastolic BP (mmHg) | 77.5 ± 11.1 | 74.2 ± 10.7 | n.s. |
| Serum creatinine (mg%) | 2.14 ± 0.80 | 2.21 ± 0.95 | n.s. |
| Δ GFR (ml/min/month) | -1.18 ± 1.49 | +0.13 ± 1.54 | < 0.05 |

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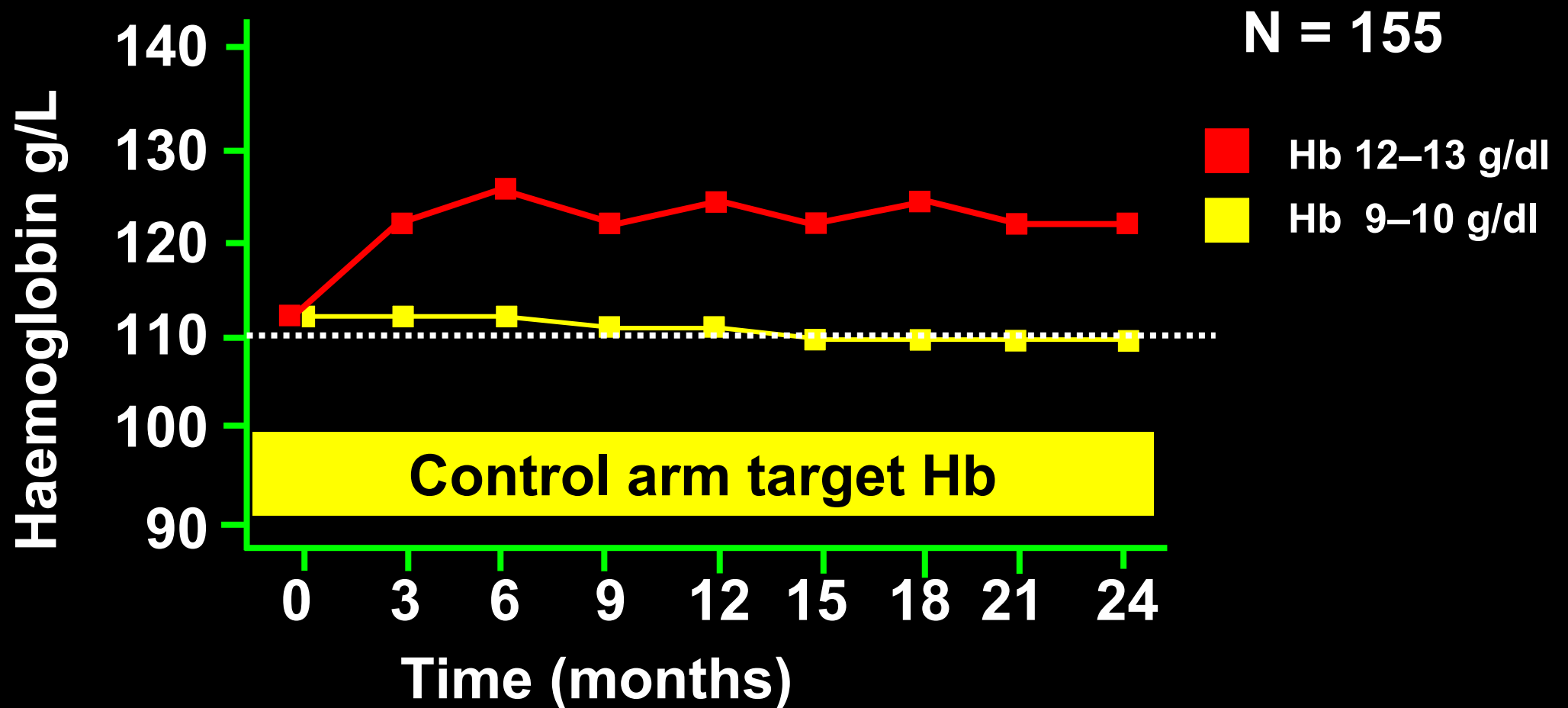
Effects of early and late anemia correction

Left ventricular mass index



Effects of early and late anemia correction

Haemoglobin

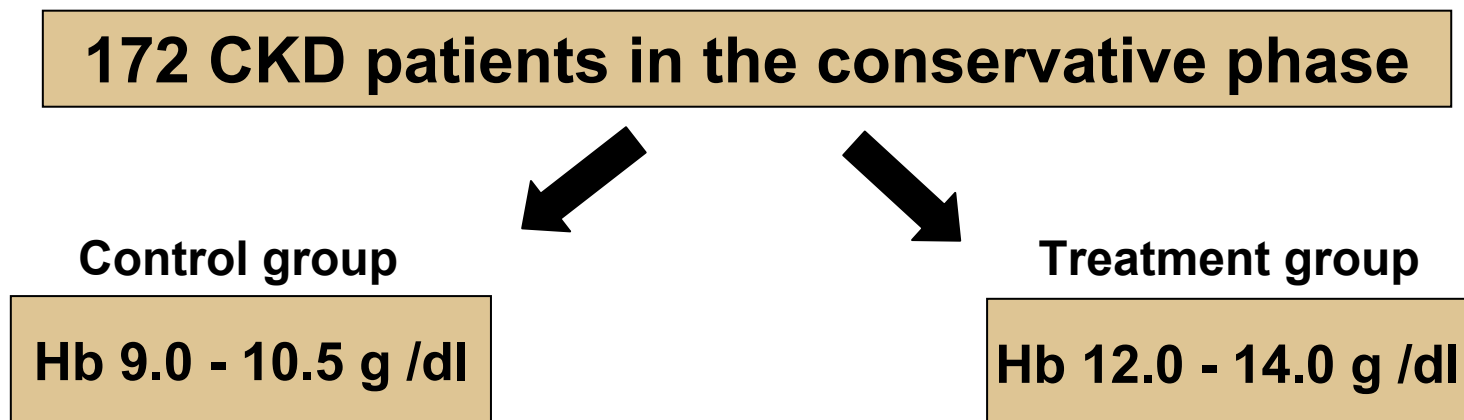




Volume 46, Issue 5, Pages 799-811 (November 2005)

Canadian Randomized Trial of Hemoglobin Maintenance to Prevent or Delay Left Ventricular Mass Growth in Patients With CKD

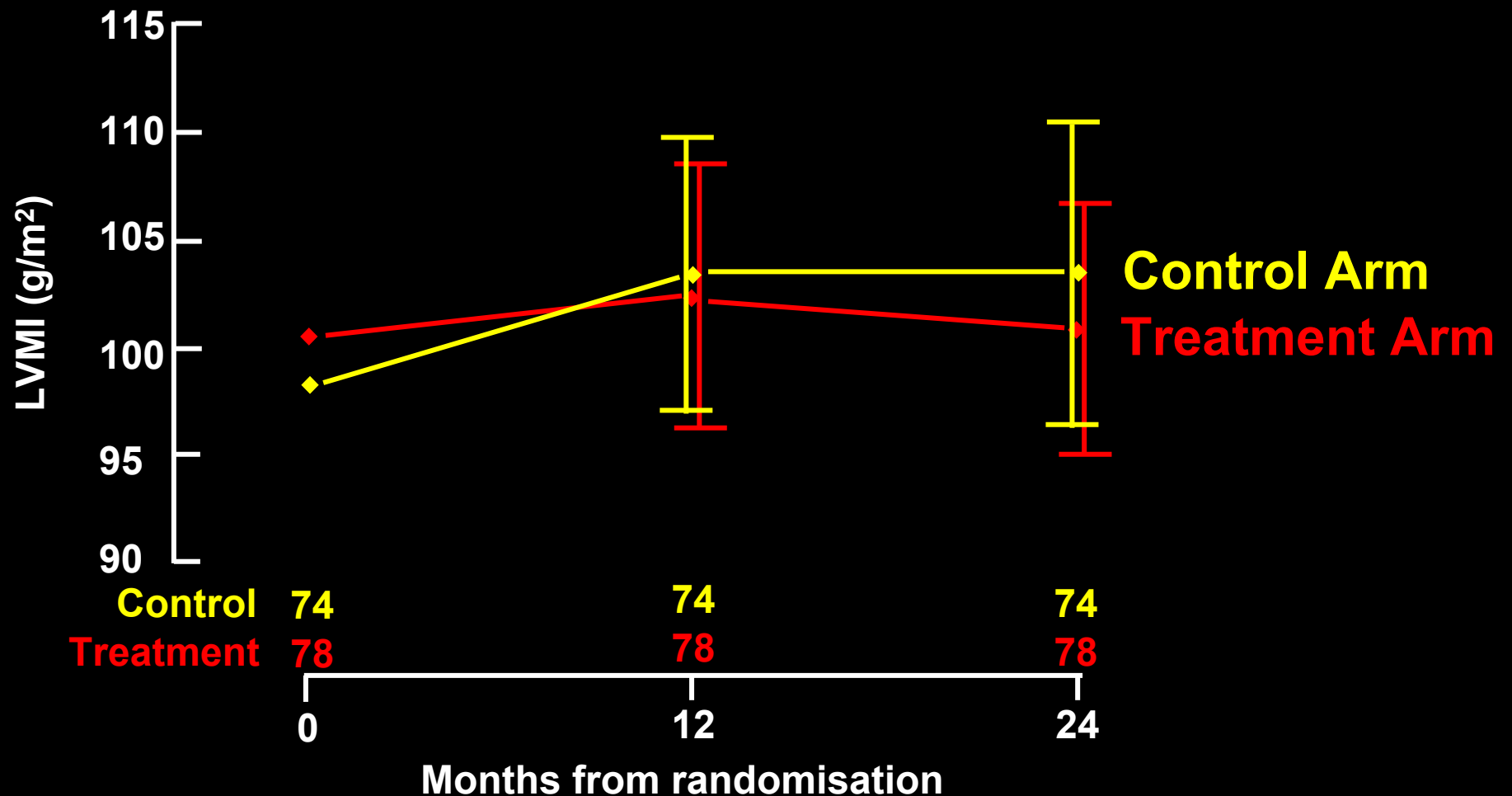
[Adeera Levin, MD](#), [Ognjenka Djurdjev, MSc](#), [Christopher Thompson, MD](#), [Brendan Barrett, MD](#), [Jean Ethier, MD](#), [Euan Carlisle, MD](#), [Paul Barre, MD](#), [Peter Wagner, MD](#), [Norman Muirhead, MD](#), [Sheldon Tobe, MD](#), [Paul Tam, MD](#), [Jose Arturo Wadgyman, MD](#), [Joanne Kappel, MD](#), [David Holland, MD](#), [Vincent Pichette, MD](#), [Ahmed Shoker, MD](#), [George Soltys, MD](#), [Mauro Verrelli, MD \(FRCOC\)](#), [Joel Singer, PhD](#)



Primary end-point
LV growth at 24 months

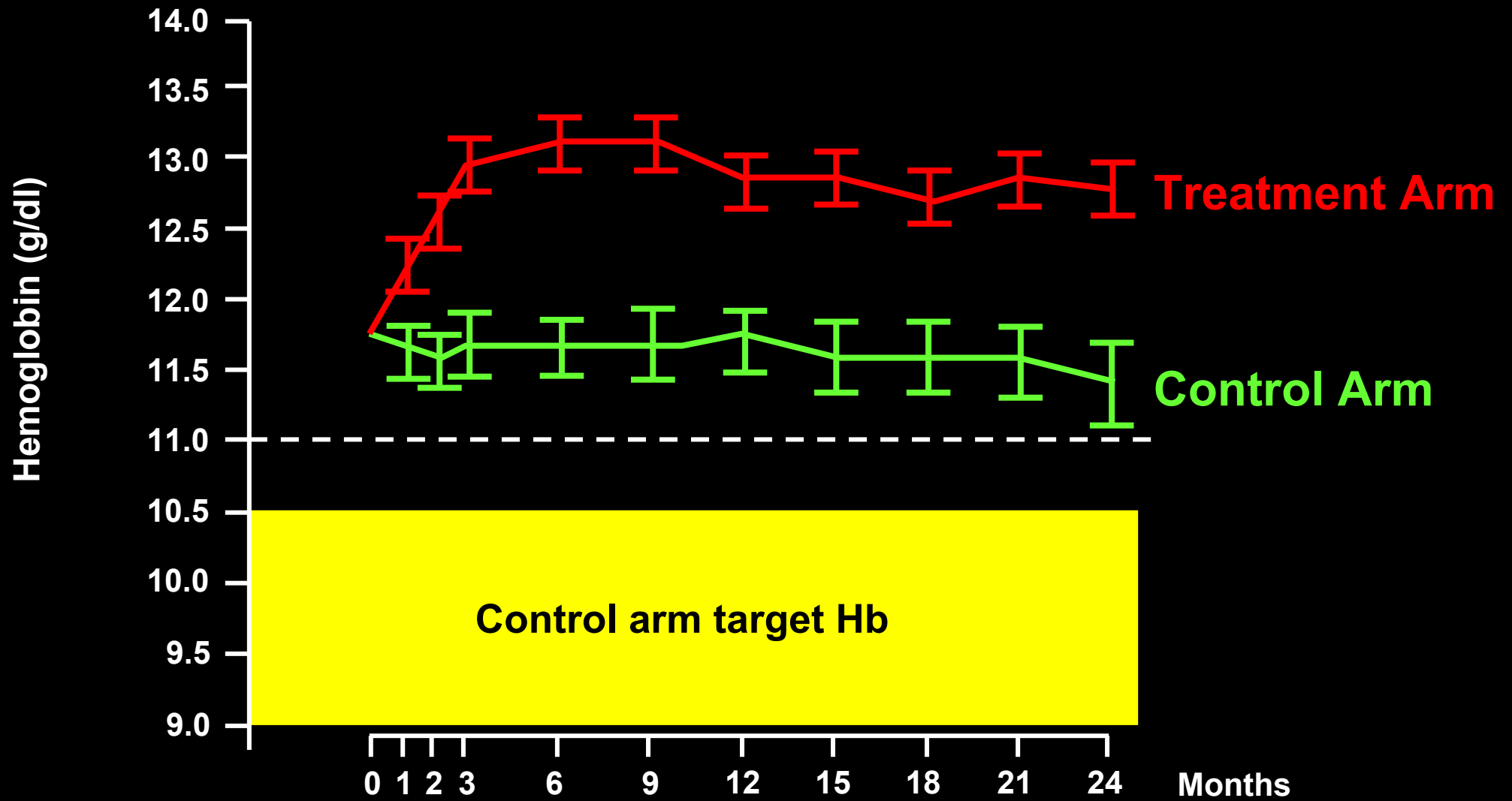
Canadian randomized trial of hemoglobin maintenance to prevent or delay LV mass growth

Left ventricular mass index during follow up

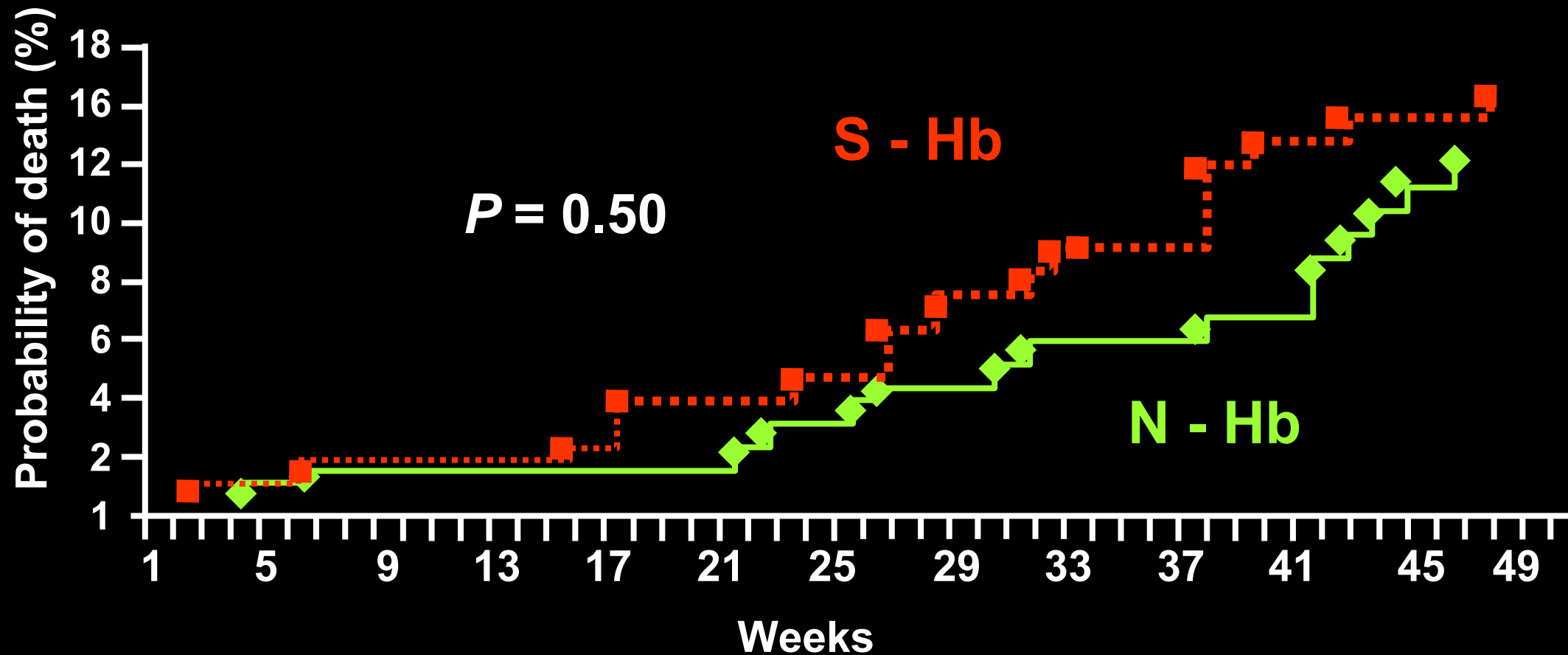


Levin A et al Am J Kidney Dis 2005; 46: 799-811

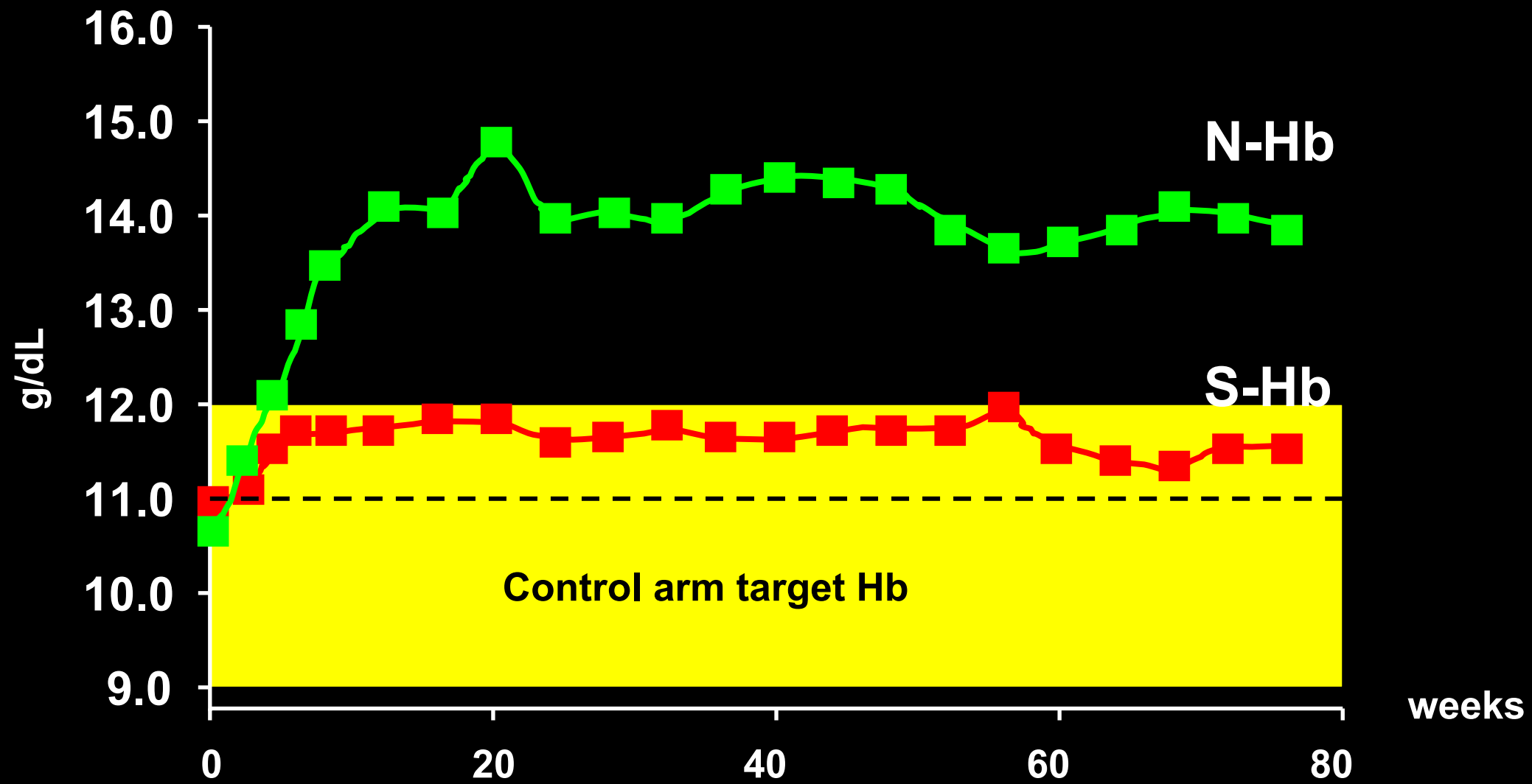
Canadian randomized trial of hemoglobin maintenance to prevent or delay LV mass growth



Probability of death for HD patients until week 48 in the N-Hb and S-Hb groups



Mean Hb concentration in pre-dialysis patients during the study



CREATE: open-label, randomised, multicentre trial

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

NOVEMBER 16, 2006

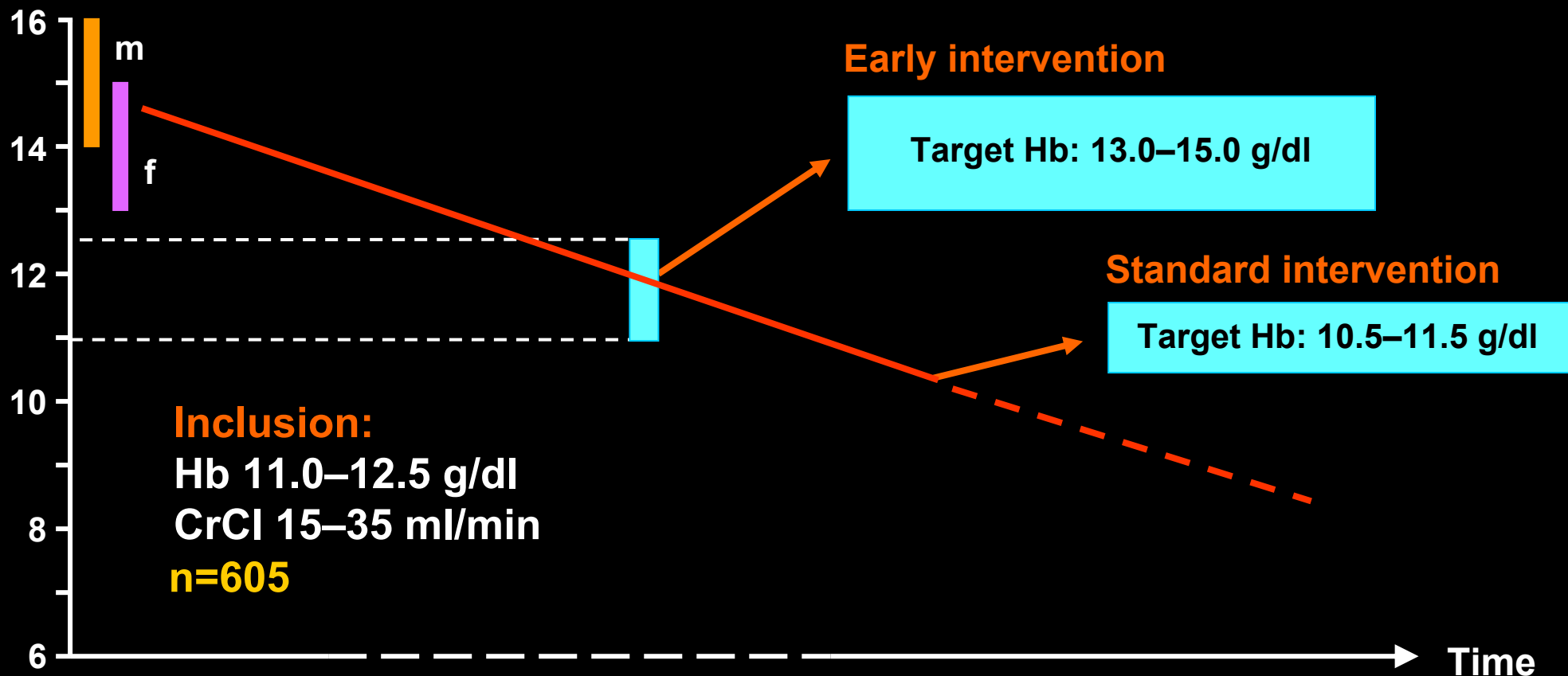
VOL. 355 NO. 20

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*

CREATE: open-label, randomised, multicentre trial

Hb (g/dl)

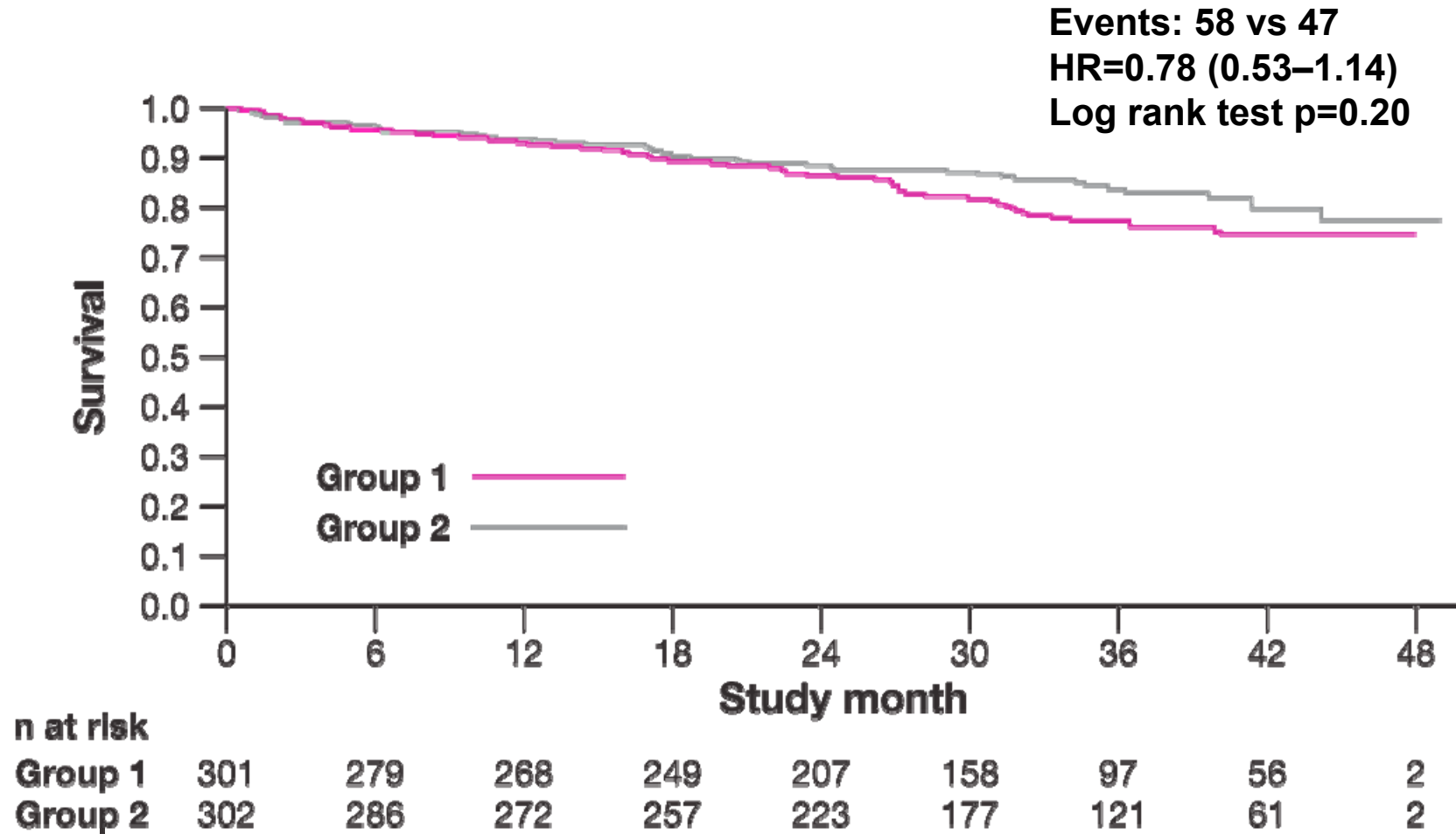


Starting dose in both groups is 2000 IU NeoRecormon® SC, self-administered with Reco-Pen®

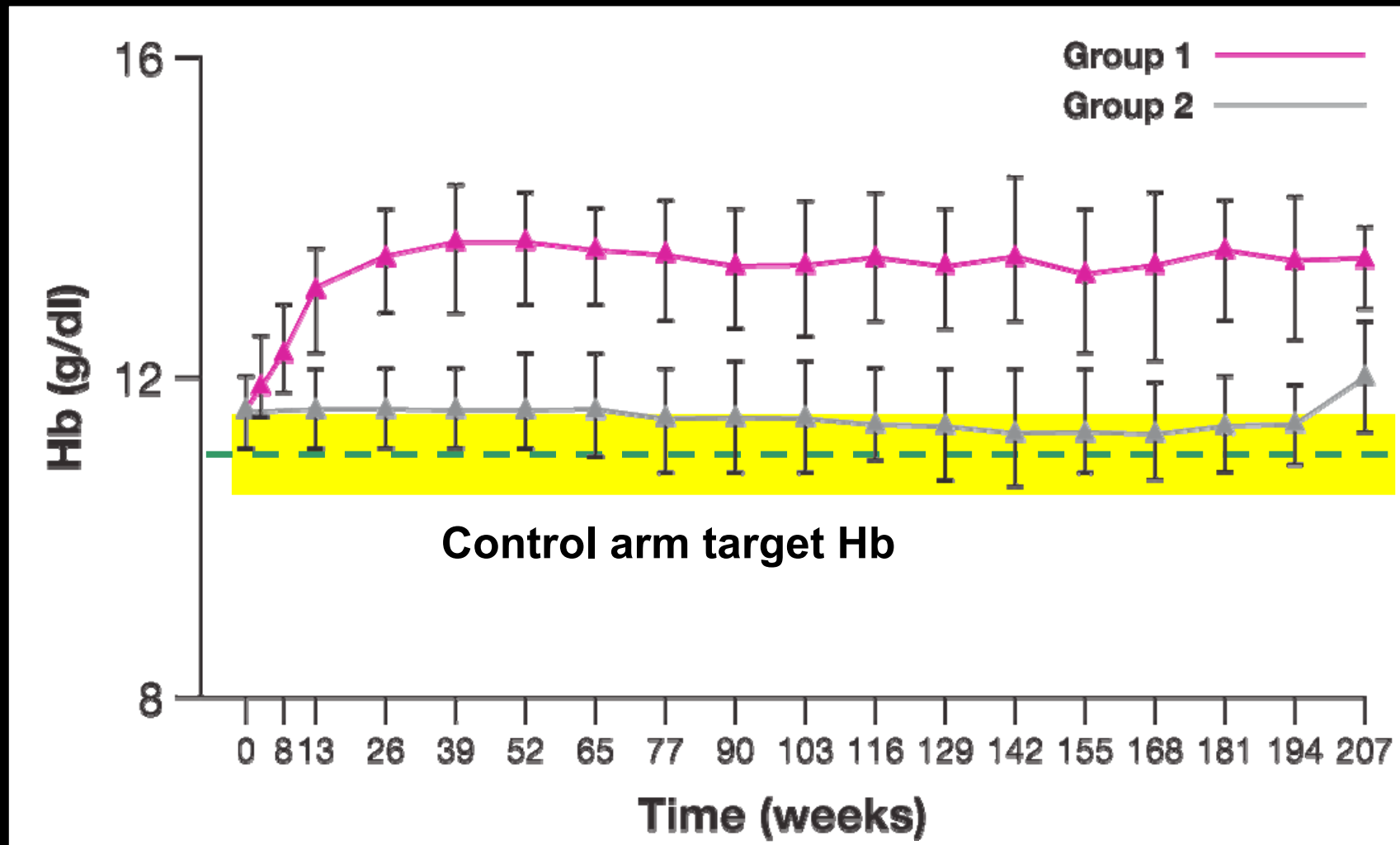
Drueke T, Locatelli F et al. N Engl J Med 2006; 355; n°20, 2071-84

CREATE Study

Time to first CV event

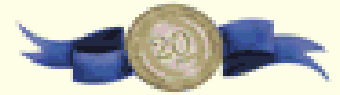


Hemoglobin levels over time



CLINICAL RESEARCH

JASN



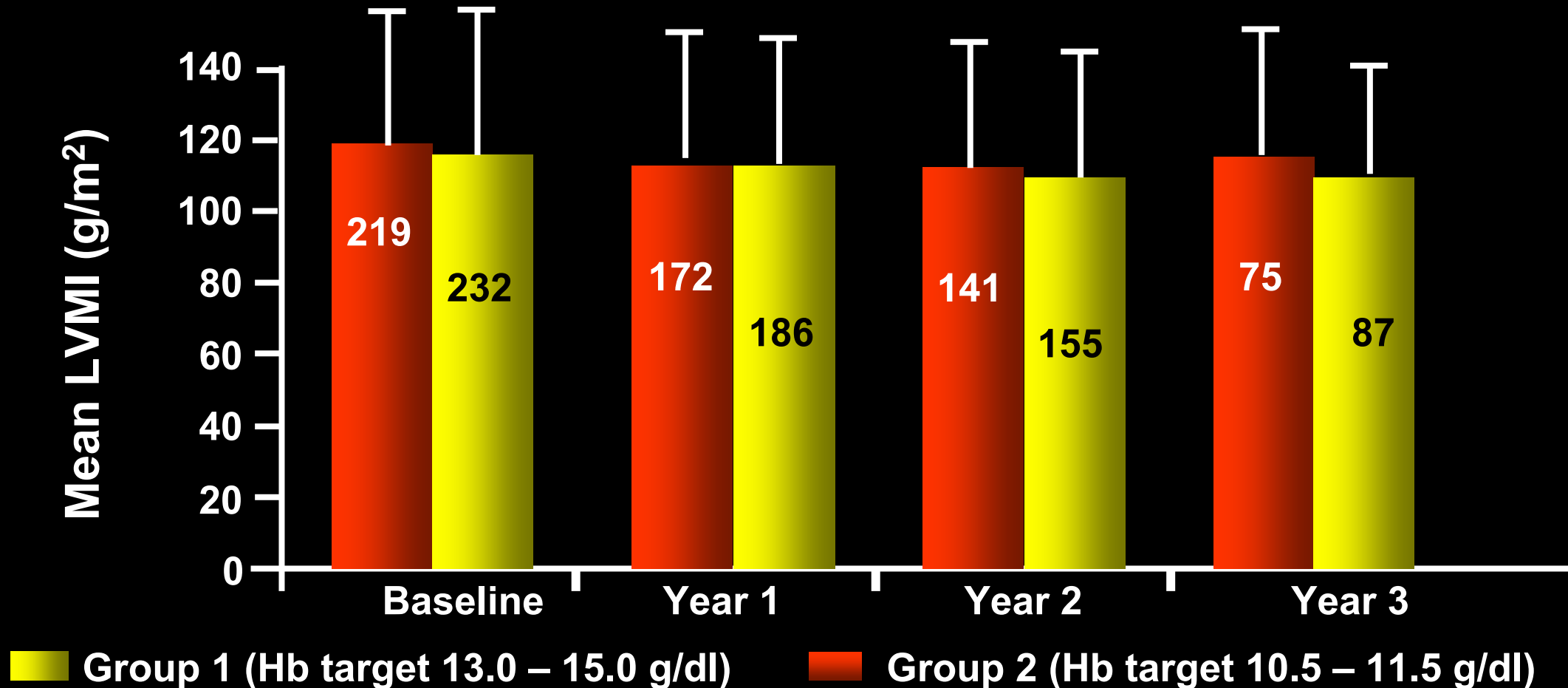
Journal of the American Society of Nephrology

Left Ventricular Geometry Predicts Cardiovascular Outcomes Associated with Anemia Correction in CKD

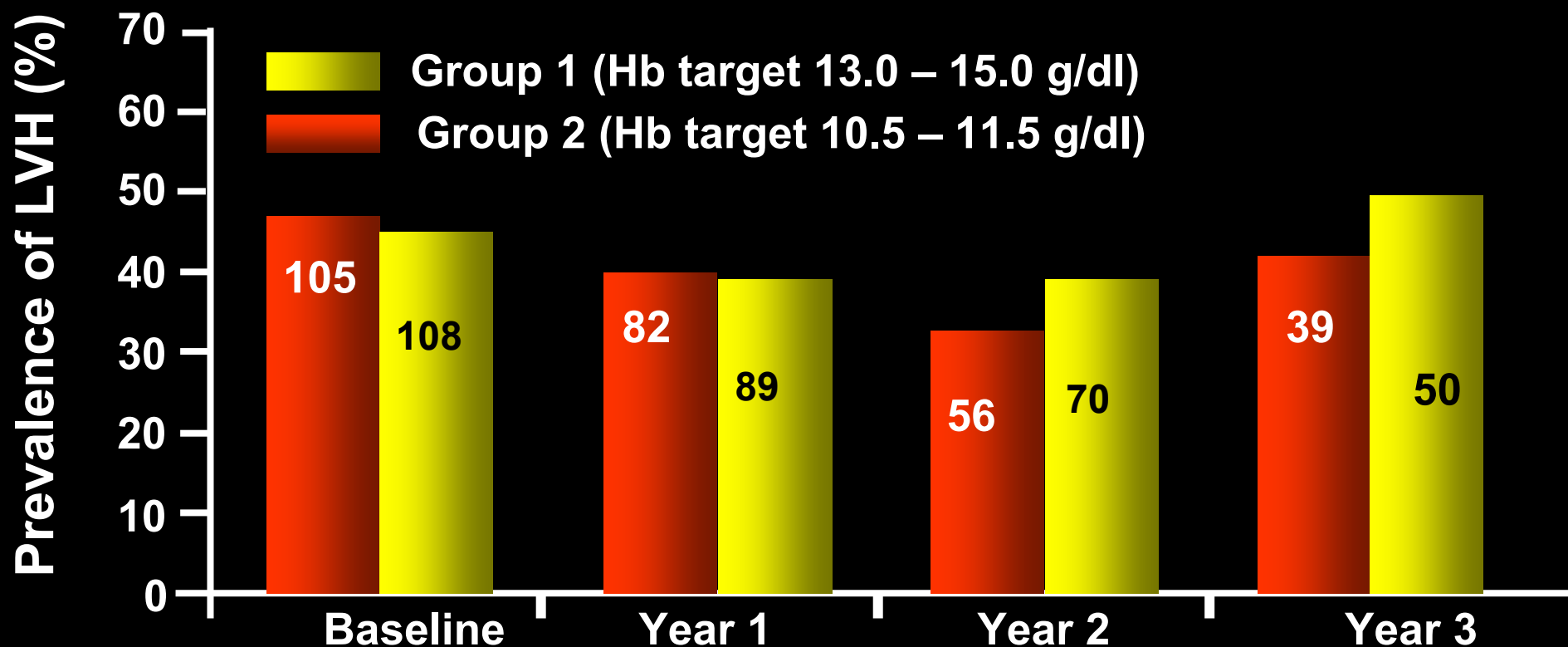
Kai-Uwe Eckardt,^{*} Armin Scherhag,^{†‡} Iain C. Macdougall,[§] Dimitrios Tsakiris,^{||} Naomi Clyne,[¶] Francesco Locatelli,^{**} Michael F. Zaug,[†] Hans U. Burger,[†] and Tilman B. Drueke^{††}

J Am Soc Nephrol 20: 2651 – 2660, 2009

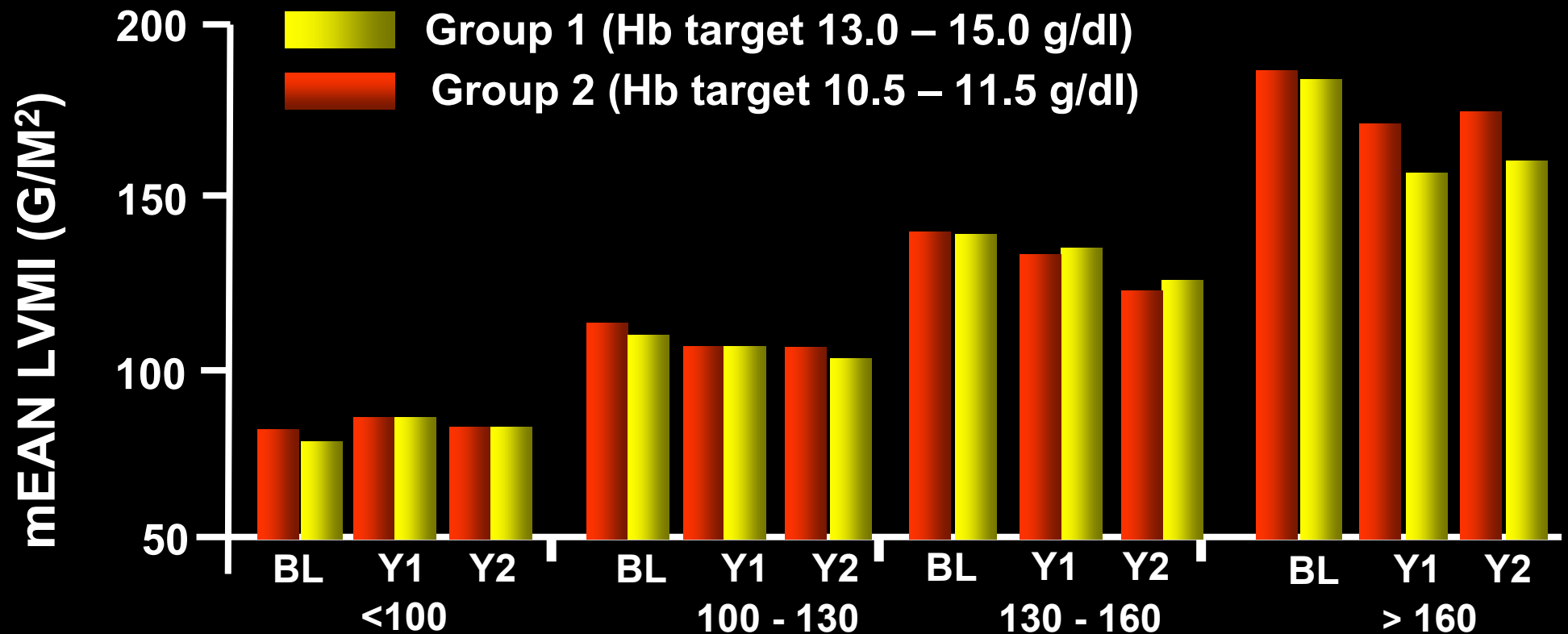
Mean LVMI from Years 1 to 3 in group 1 (full Hb correction) and group 2 partial Hb correction



Prevalence of LVH from Years 1 to 3 in group 1 (full Hb correction) and group 2 partial Hb correction



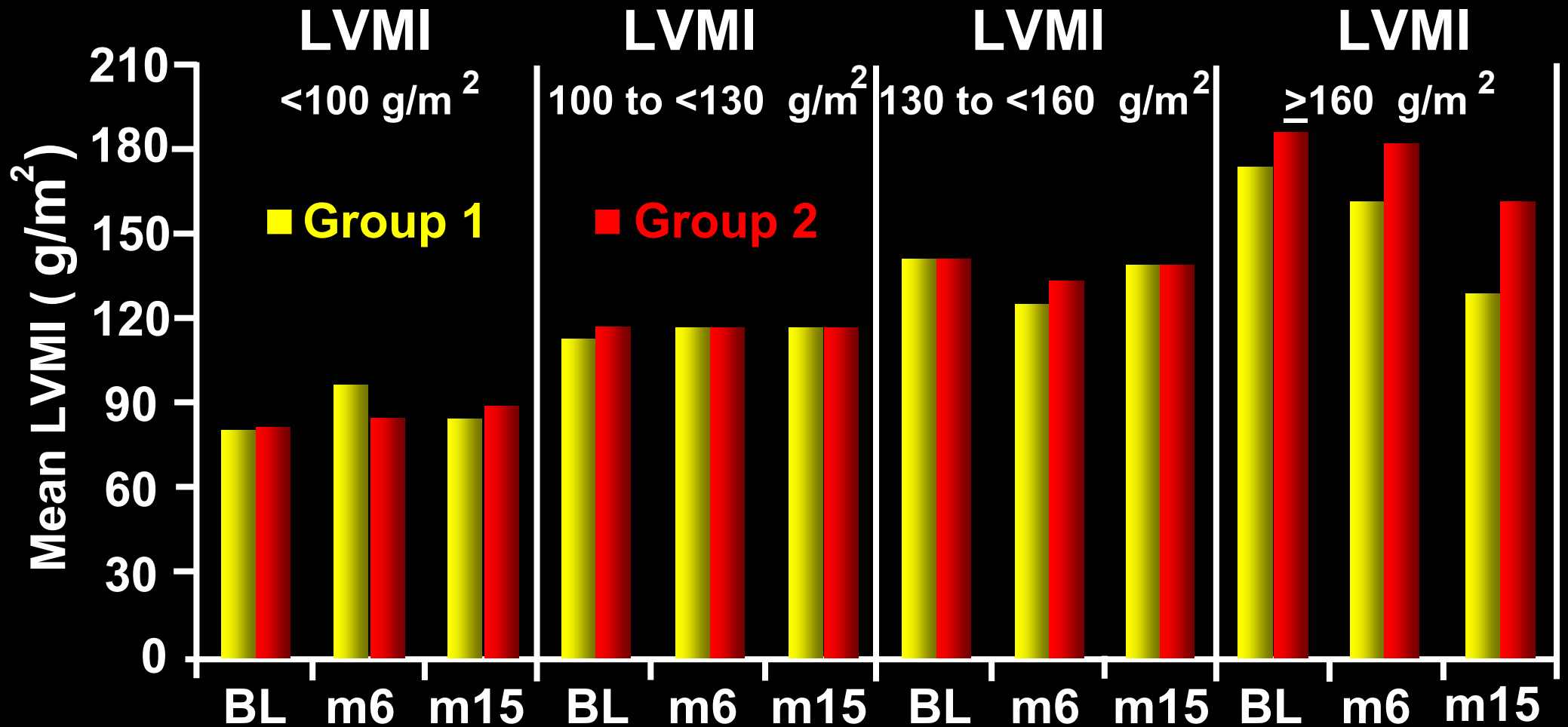
Mean Level LVMI over time in patients stratified according to baseline LVM range BL, Baseline; Y1 year 1 Y2 Year 2 *P <0.05 **P < 0.01 versus baseline



LVMI (MEAN + SD) over time by degree of LVH at baseline

Group 1: target: 13 – 15 g/dl

Group 2: target: 10.5 – 11.5 g/dl



CHOIR Study: an open label randomised study

The primary end-point: the time to the composite of death, myocardial infarction (MI), hospitalisation for congestive heart failure (CHF) or stroke

N: 1432 CKD pts

Group 1 target: Hb 13.5 g/dl

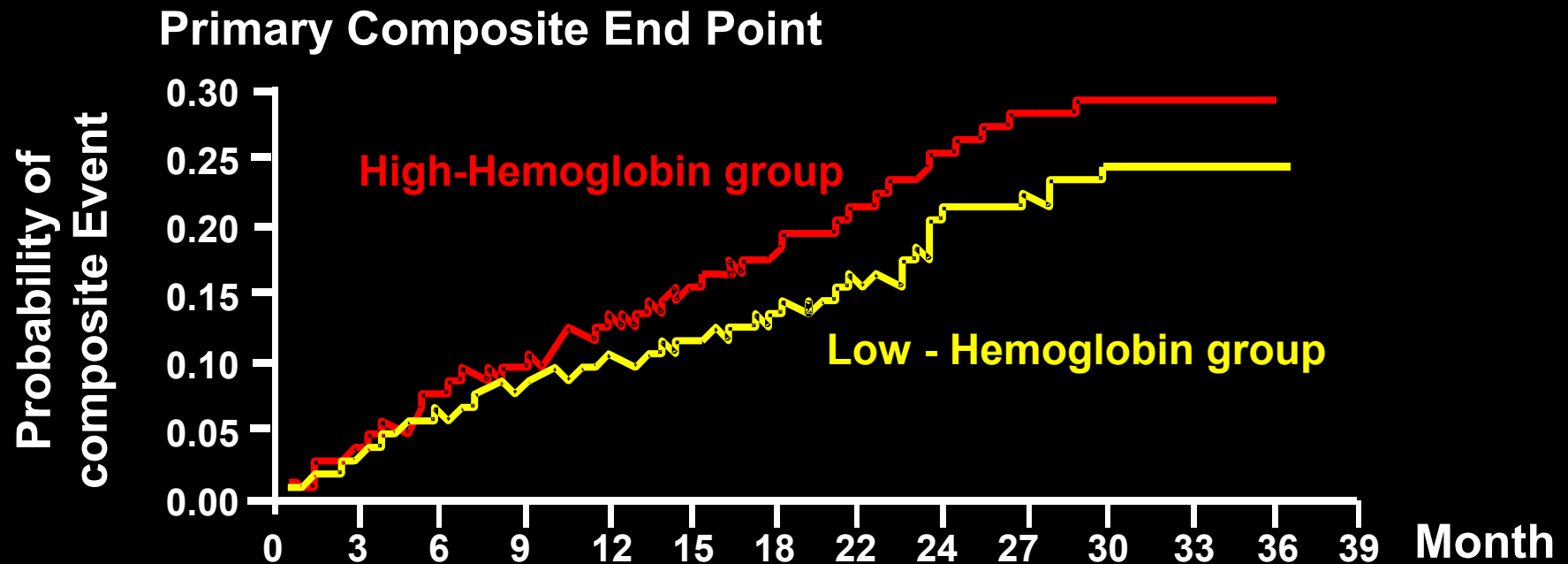
Group 2 target: Hb 11.3 g/dl

125 vs 97 events

HR 1.34;

95%confidence interval: 1.03 to 1.74

P=0.03



| | | | | | | | | | | | | |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|
| High-Hemoglobin | 715 | 654 | 537 | 520 | 457 | 355 | 270 | 176 | 101 | 72 | 55 | 23 |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|

| | | | | | | | | | | | | |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|
| Low -Hemoglobin | 717 | 660 | 524 | 530 | 499 | 327 | 293 | 182 | 107 | 57 | 44 | 23 |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|

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

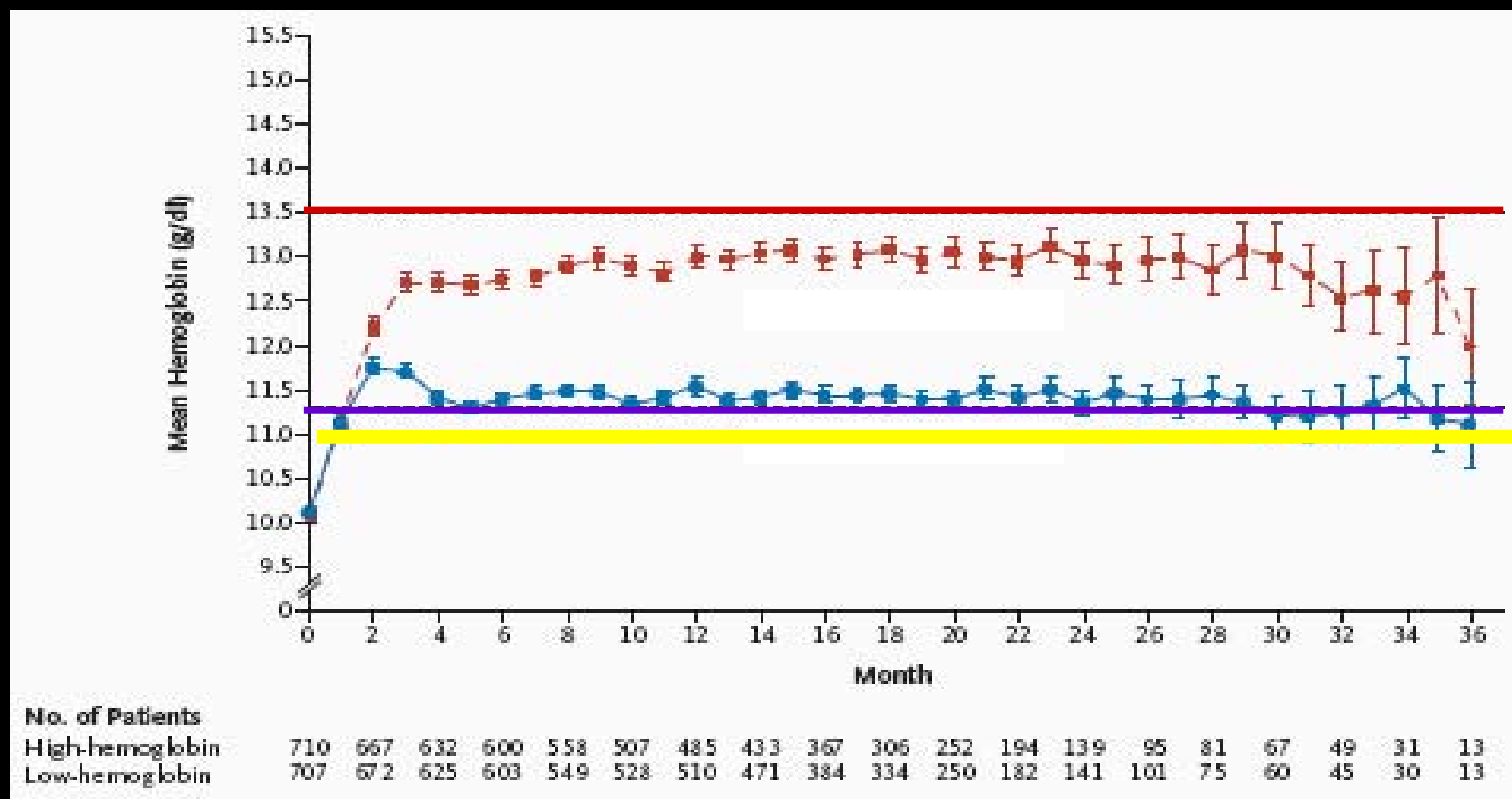
CHOIR Study: an open label randomised study

Median study duration: 16 months

N: 1432 CKD pts

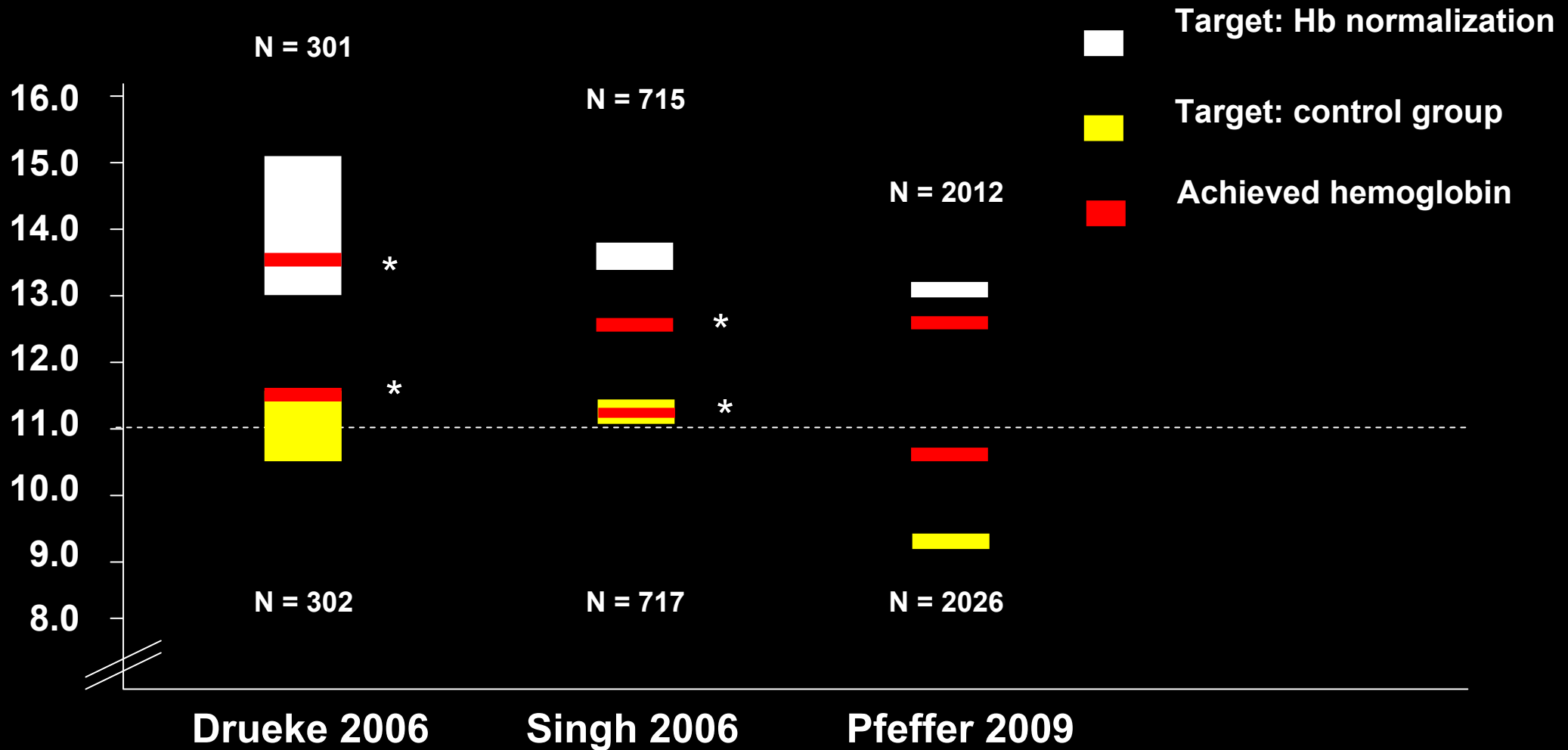
Group 1 target: Hb 13.5 g/dl

Group 2 target: Hb 11.3 g/dl



Target and achieved Hb levels in randomised clinical trials

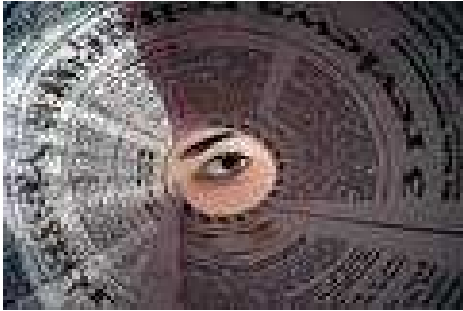
CKD (stage 3-4) patients



Estimated from the graph;

modified from Locatelli F et al. J Am Soc Nephrol 2006, 17; suppl3,s262-s266

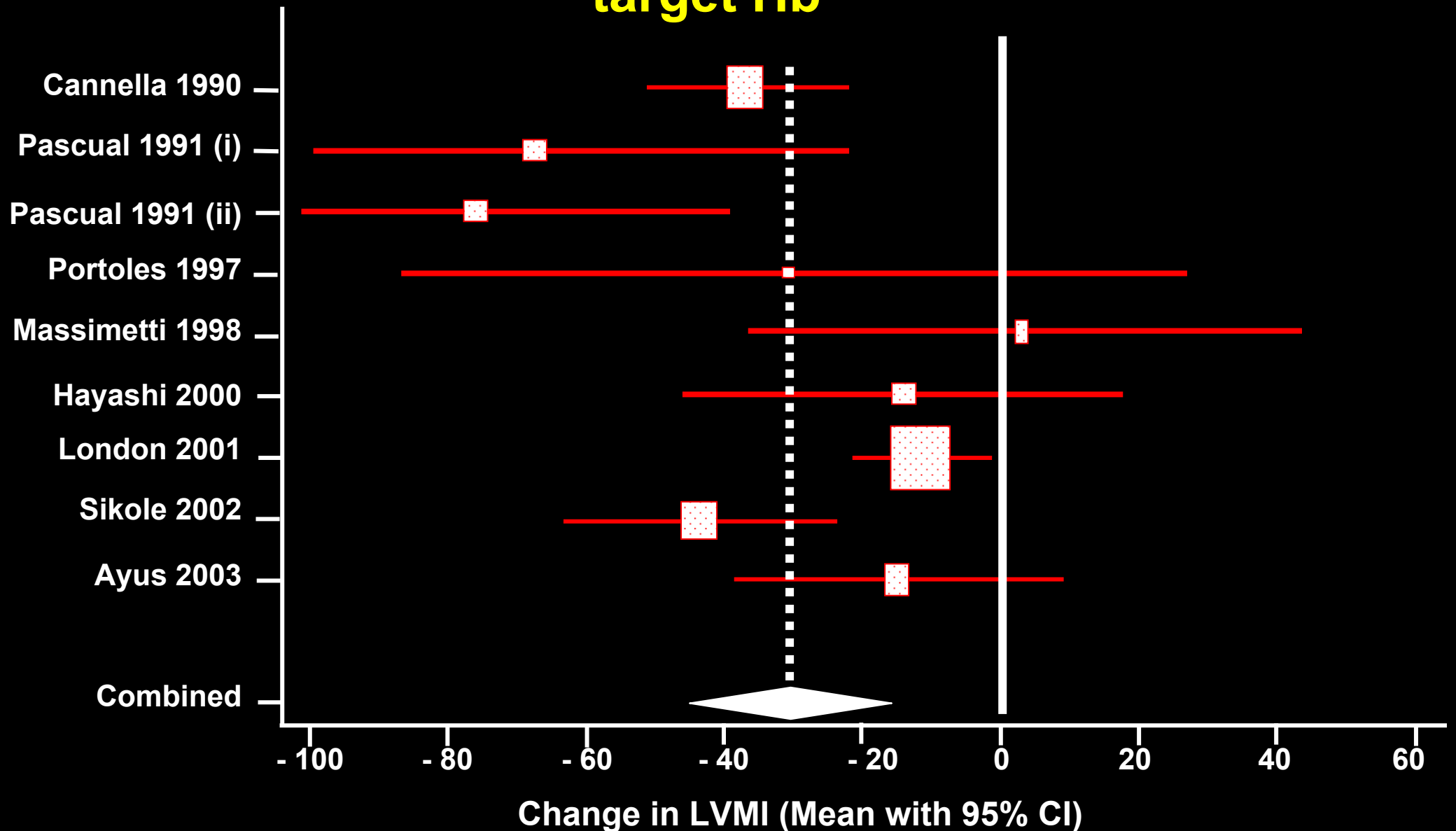
PRO



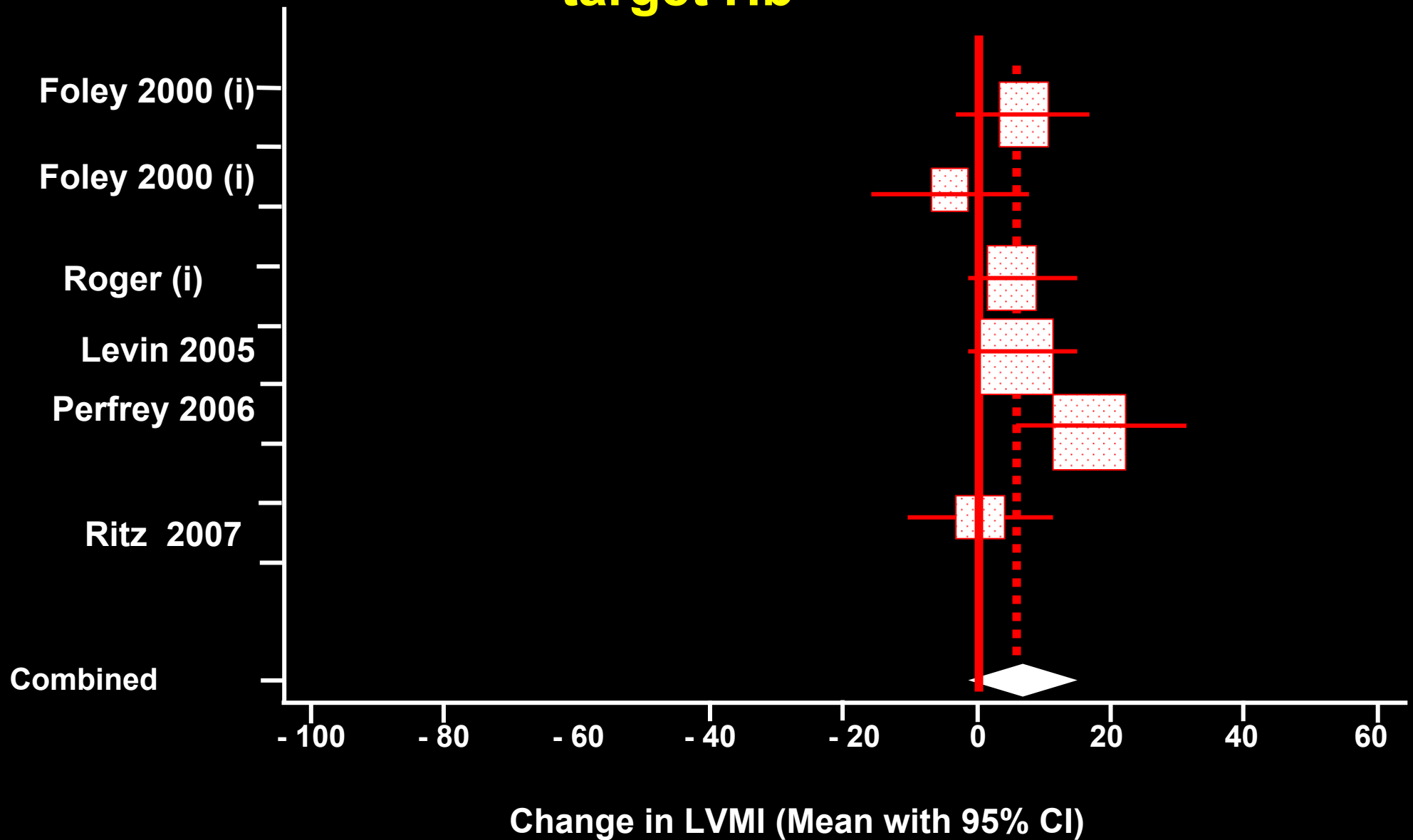
**Partial anemia correction
improve outcome**



Study cohorts with severe anemia at baseline and lower target Hb

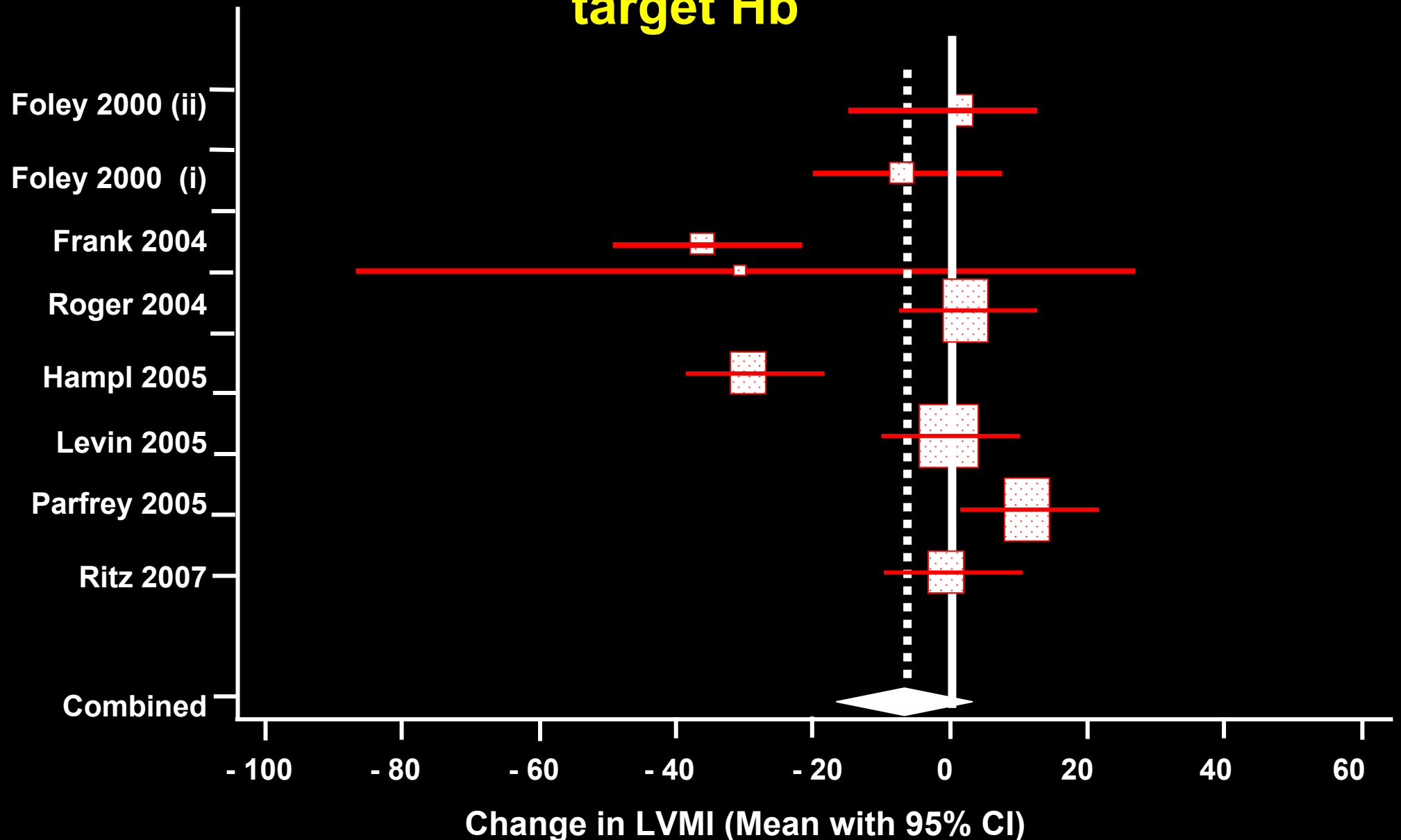


Study cohorts with moderate anemia at baseline and lower target Hb



Parfrey P et al. Clin J Am Soc Nephrol 2009, 4: 755-762

Study cohorts with moderate anemia at baseline and higher target Hb



Parfrey P et al. Clin J Am Soc Nephrol 2009, 4: 755-762

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Nephrology Dialysis Transplantation



ISSN 0931 - 0509

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Volume 19 (May 2004) · Supplement 2

Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure

Produced by

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Bernard Canaud (France)

Fernando Carrera (Portugal)

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Alison Macleod (UK)

Ardziej Wiecek (Poland)

Stewart Cameron, *Chairman Emeritus* (UK)

Guidelines – specific guidelines requiring attention

- 1.1 Which patients should be evaluated and when?**
- 2.1 What is target Hb should we aim for?**
- 2.2 What target Fe should we aim for?**
- 3.1 How should we treat renal anaemia with erythropoietic protein?**
- 4.2 Antibody-mediated pure red cell aplasia (PRCA)**

European Best Practice Guidelines

Recommendation

Exact target Hb concentrations > 11 g / dl should be defined for individual patients, taking gender, age ethnicity and activity into account

- In HD patients, Hb concentrations above 14 g / dl are not desirable due to the risk of post-dialysis haemoconcentration**

Locatelli et al. Nephrol Dial Transpl 2004; 19, suppl 2

European Best Practice Guidelines

Recommendation

The optimal target Hb concentration may vary in patients with co-morbidity or “non-standard” causes of renal failure

- Hb > 11 -12 g / dl are not recommended for patients with severe cardiovascular disease (class II of NYHA classification) unless continuing severe symptoms dictate otherwise
- Until data become available, patients with diabetes should be maintained at a Hb of 11 -12 g / dl
- Patients with chronic hypoxaemic pulmonary disease
- Patients with sickle cell disease (homozygotes) -> Hb of 7-9 g/dl

Kidney Disease: Improving Global Outcome(KDIGO)

Position statement on anemia

The current evidence, based on mortality data, for hemoglobin target levels intentionally aimed with ESA treatment in CKD patients treated indicates that levels of 9.5–11.5 g/dl are associated with better outcomes compared with >13 g/dl

New evidences about Hb target will be available only after the completion of the TREAT study

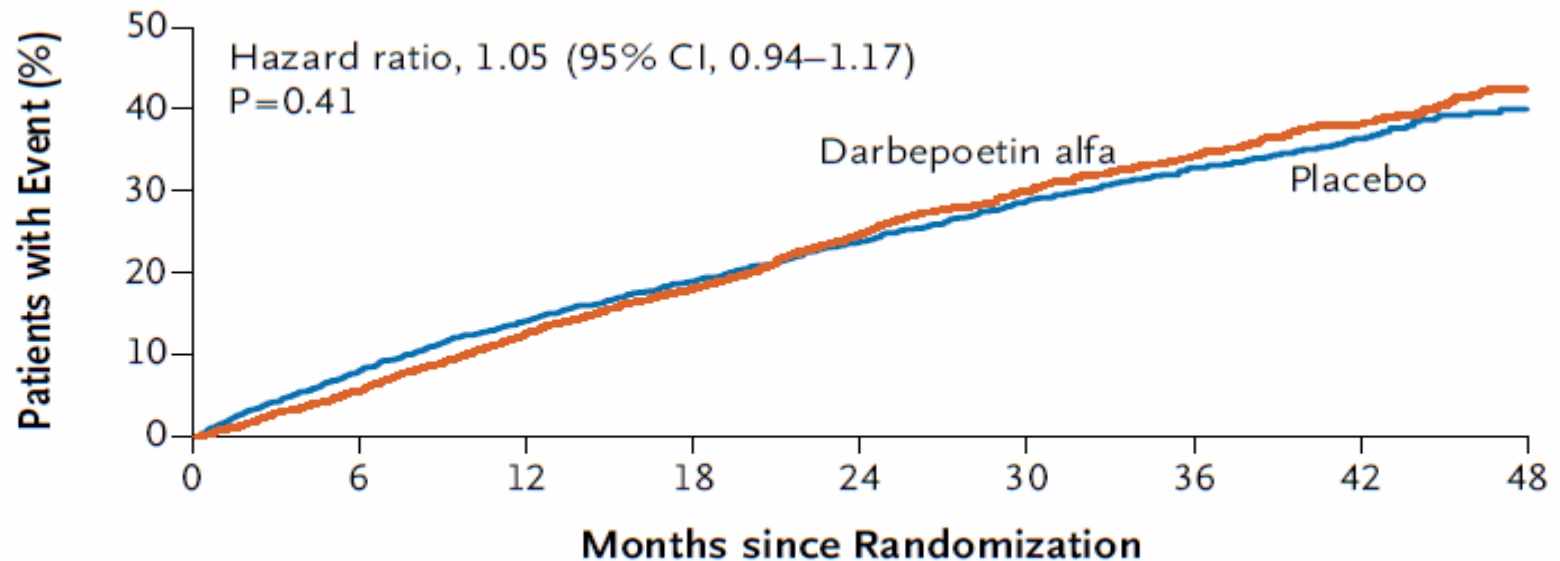
The NEW ENGLAND
JOURNAL *of* MEDICINE

A Trial of Darbepoetin Alfa in Type 2 Diabetes
and Chronic Kidney Disease

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D.,
Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D.,
Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D.,
John J.V. McMurray, M.D., Patrick Parfrey, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D.,
Ajay K. Singh, M.D., Scott D. Solomon, M.D., and Robert Toto, M.D., for the TREAT Investigators*

TREAT STUDY

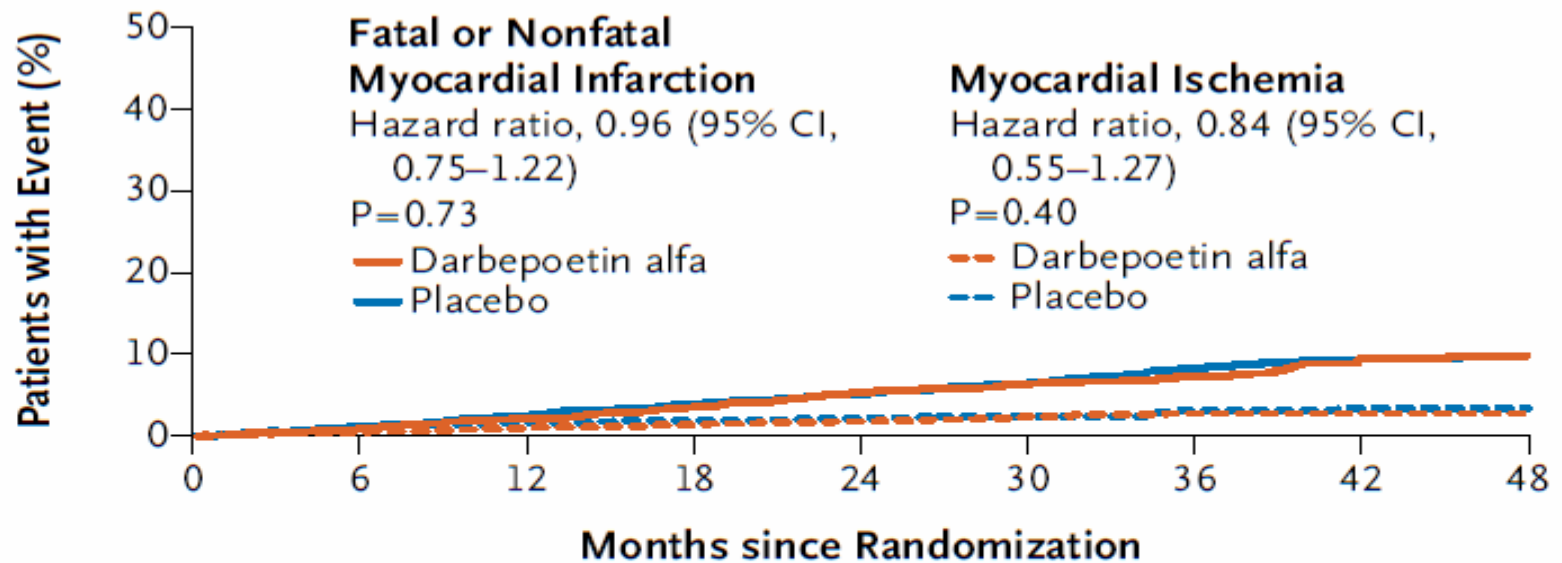
Cardiovascular Composite End Point



No. at Risk

| | | | | | | | | | |
|------------------|------|------|------|------|------|-----|-----|-----|-----|
| Darbepoetin alfa | 2012 | 1882 | 1717 | 1515 | 1180 | 817 | 551 | 318 | 130 |
| Placebo | 2026 | 1836 | 1687 | 1487 | 1178 | 834 | 529 | 319 | 122 |

Fatal or Non-fatal Myocardial Infarction and Myocardial Ischemia



No. at Risk

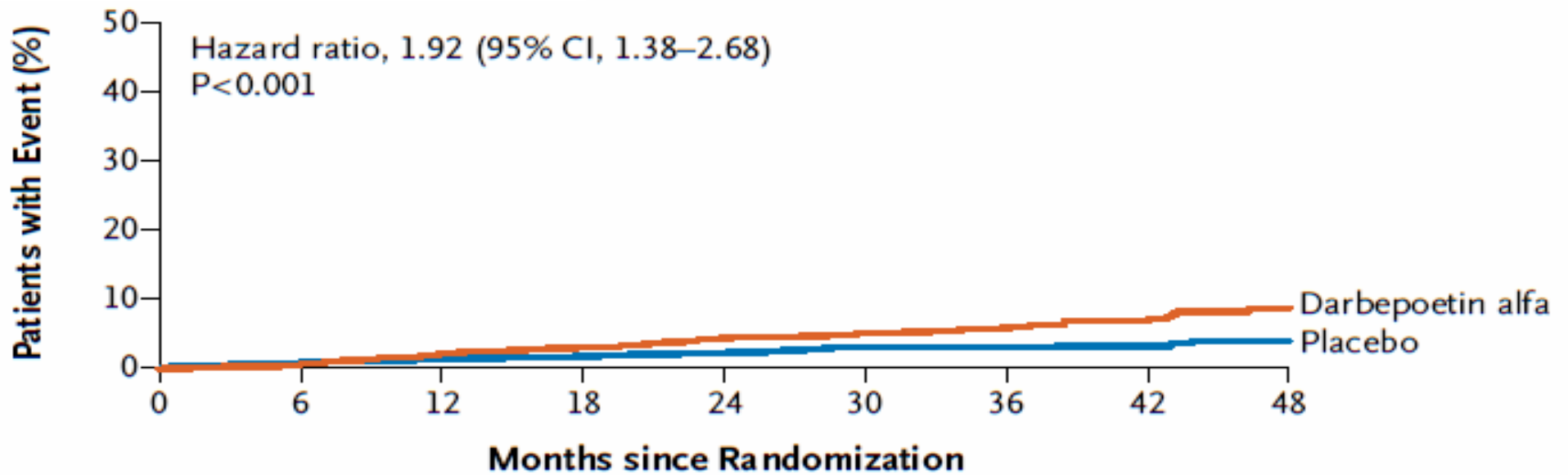
Fatal or Nonfatal Myocardial Infarction

| | | | | | | | | | |
|------------------|------|------|------|------|------|-----|-----|-----|-----|
| 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 |

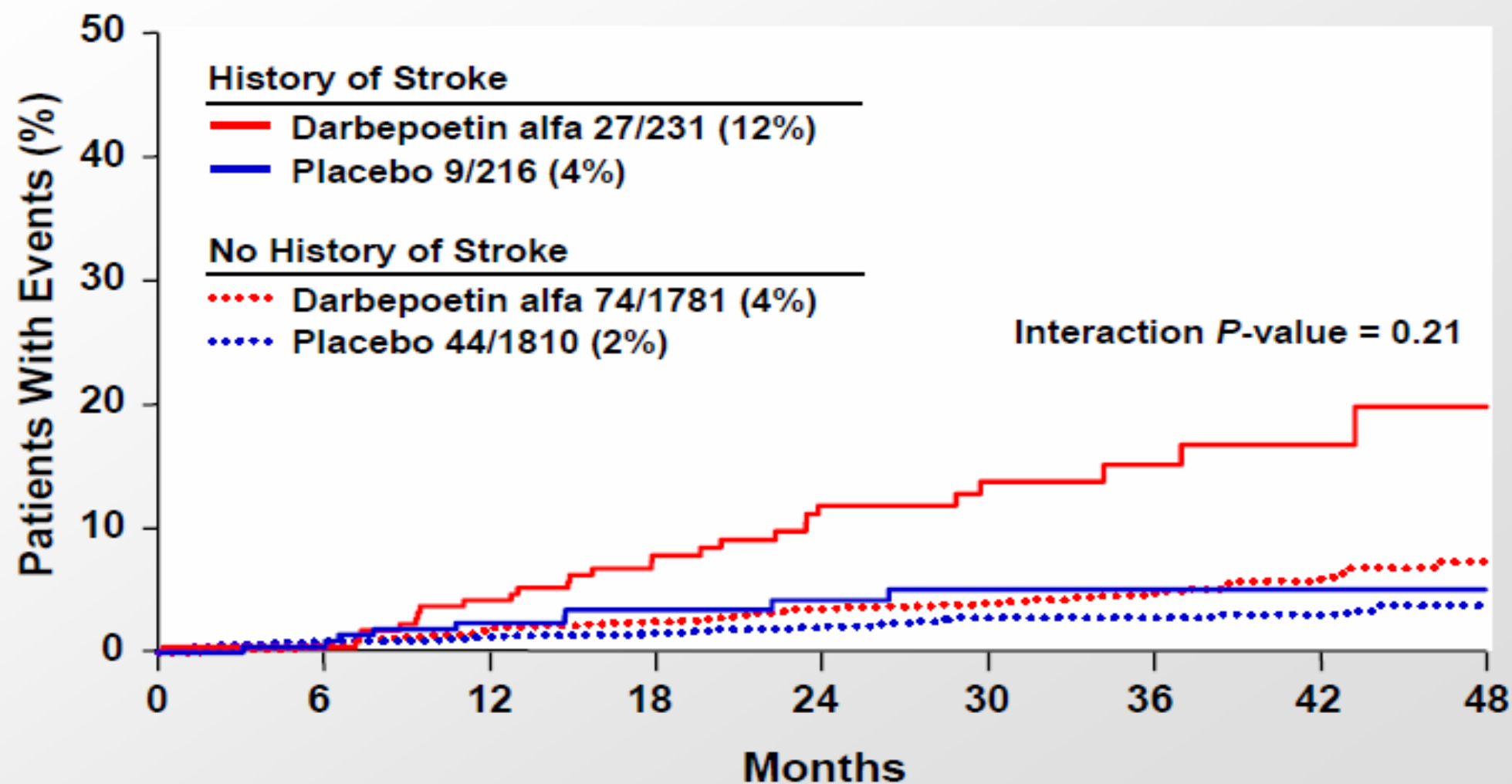
Fatal or non-fatal Stroke



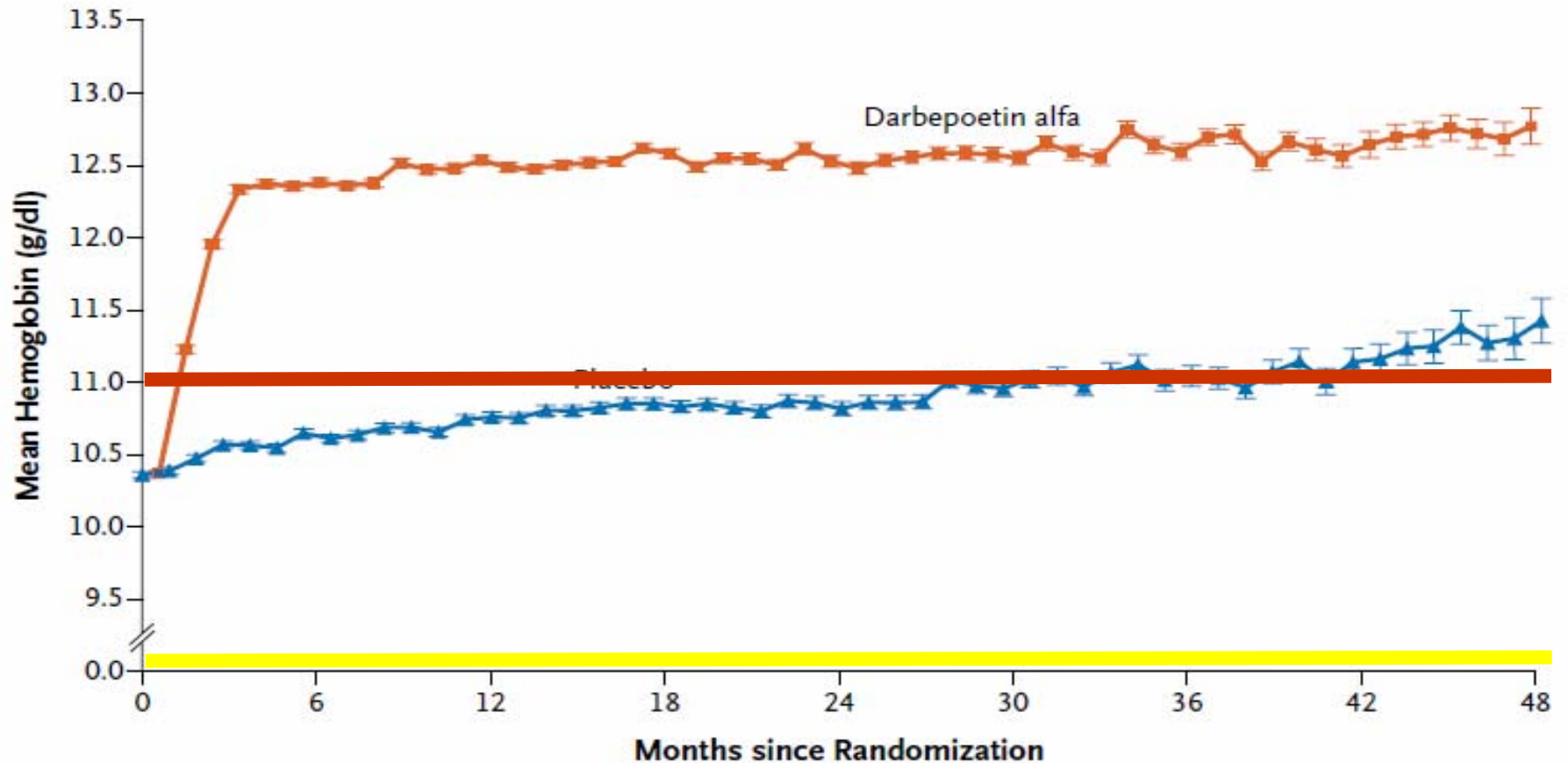
No. at Risk

| | | | | | | | | | |
|------------------|------|------|------|------|------|-----|-----|-----|-----|
| Darbepoetin alfa | 2012 | 1923 | 1787 | 1581 | 1247 | 863 | 590 | 341 | 141 |
| Placebo | 2026 | 1914 | 1783 | 1575 | 1262 | 886 | 561 | 338 | 132 |

Fatal and Nonfatal Stroke and History of Stroke (Post-hoc analysis)



TREAT study: mean hemoglobin levels through 48 months



No. of Patients

| | | | | | | | | | |
|------------------|------|------|------|------|-----|-----|-----|-----|----|
| Darbepoetin alfa | 2004 | 1768 | 1503 | 1300 | 946 | 635 | 404 | 253 | 97 |
| Placebo | 2019 | 1742 | 1460 | 1221 | 887 | 620 | 356 | 216 | 79 |

Anaemia management in patients with chronic kidney disease: a position statement by the Anaemia Working Group of European Renal Best Practice (ERBP)

Francesco Locatelli, Adrian Covic, Kai-Uwe Eckardt, Andrzej Wiecek, and Raymond Vanholder;
On behalf of the ERA-EDTA ERBP Advisory Board

In the opinion of the ERBP Work Group, it appears reasonable to maintain the lower limit of the target, although the actual evidence for choosing this value is also very limited. On the basis of new evidence, Hb values of 11-12 g/dl should be generally sought in the CKD population without intentionally exceeding 13 g/dl.

CORRESPONDENCE



Darbepoetin Alfa and Chronic Kidney Disease

TO THE EDITOR: The TREAT study showed a neutral effect in aiming at a hemoglobin level of 12 g per deciliter as compared with a target value

Should we stop treating our patients?

patients with chronic kidney disease and type 2 diabetes. The group with high levels of hemoglobin had more strokes and deaths related to cancer and mild improvement in quality of life. Should we stop treating our patients?

Darbepoetin Alfa and Chronic Kidney Disease

Nearly half these patients received darbepoetin alfa (the mean dose was not reported); this cannot be considered true “placebo”

Given that the mean achieved hemoglobin level in the control group (10.6g per deciliter)... there is no evidence that we should stop treating anemia

The position of ERBP

Quality of life

- **The available quality of life data vary in quality and are often inconclusive**
- **More reliable methods of assessing patient-related outcomes and functional status are now available**
- **There is room for new studies testing the effect of anaemia correction on more robust measures of the quality of life**

TREAT Versus Treatment:

A Patient's View of a Scientific Interpretation

**Alexander Prisant
Boynton Beach, FL**

American Journal of Kidney Diseases, Vol 55, No 3 (March), 2010

TREAT Versus Treatment:

A Patient's View of a Scientific Interpretation

***Treat the patient as an individual, or treat
in line with
the latest empirical study***

Prisant A. American Journal of Kidney Diseases, Vol 55, No 3 (March), 2010

TREAT Versus Treatment:

A Patient's View of a Scientific Interpretation

“I feel that it is relevant to consider studies like TREAT from the patient's view, particularly in conditions like anemia which can impact patients' well-being independent of “hard” outcomes such as incident-free longevity”

Prisant A. American Journal of Kidney Diseases, Vol 55, No 3 (March), 2010

TREAT Versus Treatment:

A Patient's View of a Scientific Interpretation

“I am symptom free and feel great, despite a persistently low ejection fraction and a GFR that hovers in a range where many patients are considered for dialysis”

Prisant A. American Journal of Kidney Diseases, Vol 55, No 3 (March), 2010

TREAT Versus Treatment:

A Patient's View of a Scientific Interpretation

“Quality-of-life should be considered along with more classic “hard clinical end-points” such as those studied in TREAT, to inform physician and policymaking guidelines and facilitate informed patient consent.”

Prisant A. American Journal of Kidney Diseases, Vol 55, No 3 (March), 2010



The Anaemia Working Group of European Renal Best Practice (ERBP)

European Renal Best Practice

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



F.Locatelli et al.

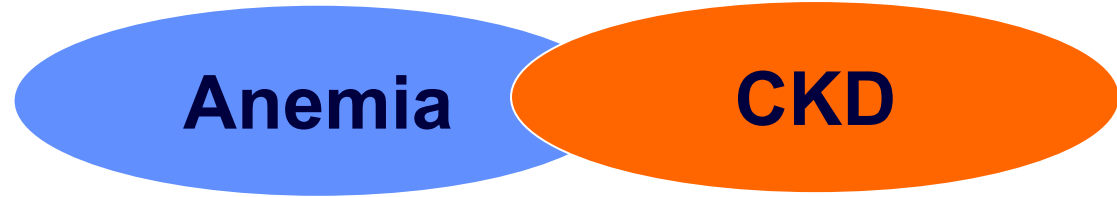
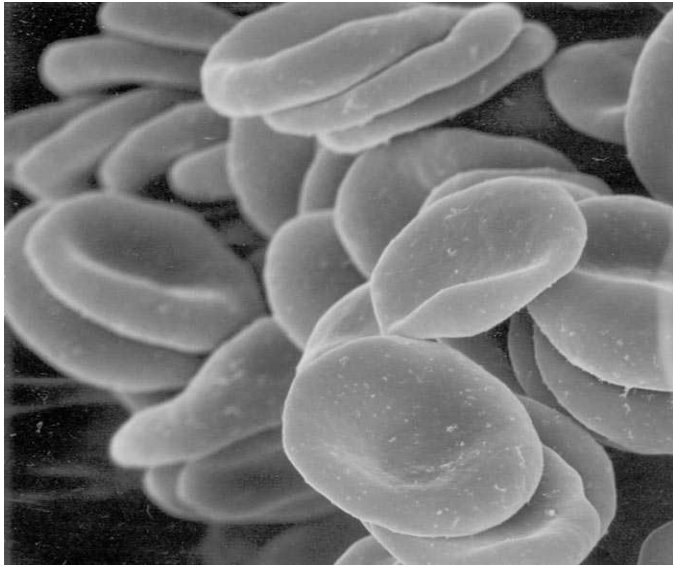
Conclusions

- **CKD-related anemia is an independent risk factor for adverse CV outcomes and for death from CV disease**
- **Anemia correction may lead to at least partial regression of LVH**
- **Starting correction of anaemia very early or achieving a complete Hb normalization seems to provide any further CV and survival benefit and even harm**

Anemia: why can it be improved by dialysis?



Anemia and chronic kidney disease



- ✿ **Relative EPO deficiency**
- ✿ **Iron deficiency**
- ✿ **Occult blood loss**
- ✿ **Impairment of RBC survival**

Inflammation
↑ oxidative stress
uremic toxins



Premature changes in
RBC membrane and
cytoskeleton

Anemia and dialysis procedure

HDF



- **Water quality and distribution system**
- **Dialysate**
- **Extracorporeal circuit**
- **Dialysis dose and frequency**
- **Membranes and convective treatments**
- **Online treatments**



Dialysis adequacy

THE INTENSITY OF HEMODIALYSIS AND THE RESPONSE TO ERYTHROPOIETIN IN PATIENTS WITH END-STAGE RENAL DISEASE

ONYEKACHI IFUDU, M.B., B.S., JOSEPH FELDMAN, DR.P.H., AND ELI A. FRIEDMAN, M.D.

Design Prospective non randomized

Aim To compare increased dose of dialysis
(URR from 60.7 to 72.0%) with high-flux polysulphone vs.
conventional dialysis with modified cellulose acetate

Patients 135 pts ⇒ observation
20 vs. 20 followed up for 6 weeks

Outcome Haematocrit level

OdL1

Administrator 23/03/2004

Background Anemia (characterized by a hematocrit of 30 percent or lower) persists in 40 to 60 percent of patients treated for end-stage renal disease with maintenance hemodialysis, despite concomitant erythropoietin (epoetin) therapy. We tested the hypothesis that inadequate dialysis is a key reason for the insufficient response to erythropoietin in patients with end-stage renal disease who are receiving hemodialysis.

Methods we prospectively studied 135 randomly selected patients undergoing hemodialysis who had been receiving intravenous erythropoietin for at least four months. The adequacy of dialysis was assessed by measuring the percent reduction in the blood urea nitrogen concentration and the serum albumin concentration. The hematocrit was measured weekly for four weeks, transferrin saturation was measured, and coexisting illnesses were documented. To determine the effect of an increased level of dialysis on the hematocrit, the thrice-weekly schedule of dialysis was increased to raise the mean urea-reduction value from 60.7 to 72.0 percent for six weeks in 20 consecutive patients whose base-line urea-reduction value was less than 65 percent. The change in the hematocrit in these patients was compared with that observed in the next 20 patients who had an equivalent base-line urea-reduction value but whose level of dialysis was not altered.

Results The mean (\pm SD) hematocrit of the entire group was 29.2 ± 4 percent, and the mean thrice-weekly dose of erythropoietin was 59 ± 29 U per kilogram of body weight. The mean serum albumin concentration was 3.8 ± 0.4 g per deciliter, the mean urea-reduction value was 62 ± 4.8 percent, and the mean transferrin saturation was 20 ± 9 percent. Multiple regression analysis revealed direct correlations between the hematocrit and the serum albumin concentration ($P = 0.009$) and between the hematocrit and the urea-reduction value ($P = 0.012$) after adjustment for other factors. A logistic-regression analysis indicated that an 11 percent increase in the urea-reduction value doubled the odds that a patient would have a hematocrit above 30 percent. After six weeks of increased intensity of dialysis in 20 patients with base-line urea-reduction values of less than 65 percent, the mean (\pm SE) hematocrit rose from 28.4 ± 0.78 percent to 32.3 ± 0.71 percent ($P = 0.002$); there was no significant change in a control group of 20 patients with equivalent base-line urea-reduction values in whom the dialysis level was not altered (28.2 ± 0.84 percent to 26.3 ± 0.85 percent; $P = 0.175$).

Conclusions In patients with end-stage renal disease, inadequate hemodialysis is associated with a suboptimal response to erythropoietin therapy. Increasing the intensity of dialysis in patients with anemia who are receiving inadequate dialysis results in a significant increase in the hematocrit.

Effect of an Increased Level of Dialysis on the HCT

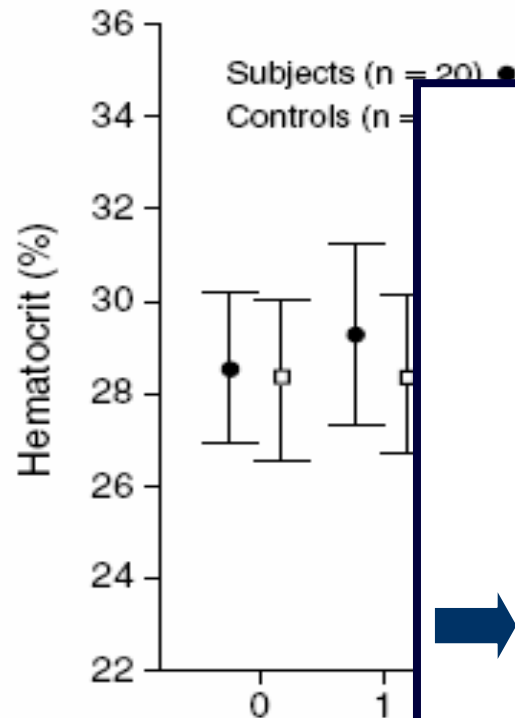
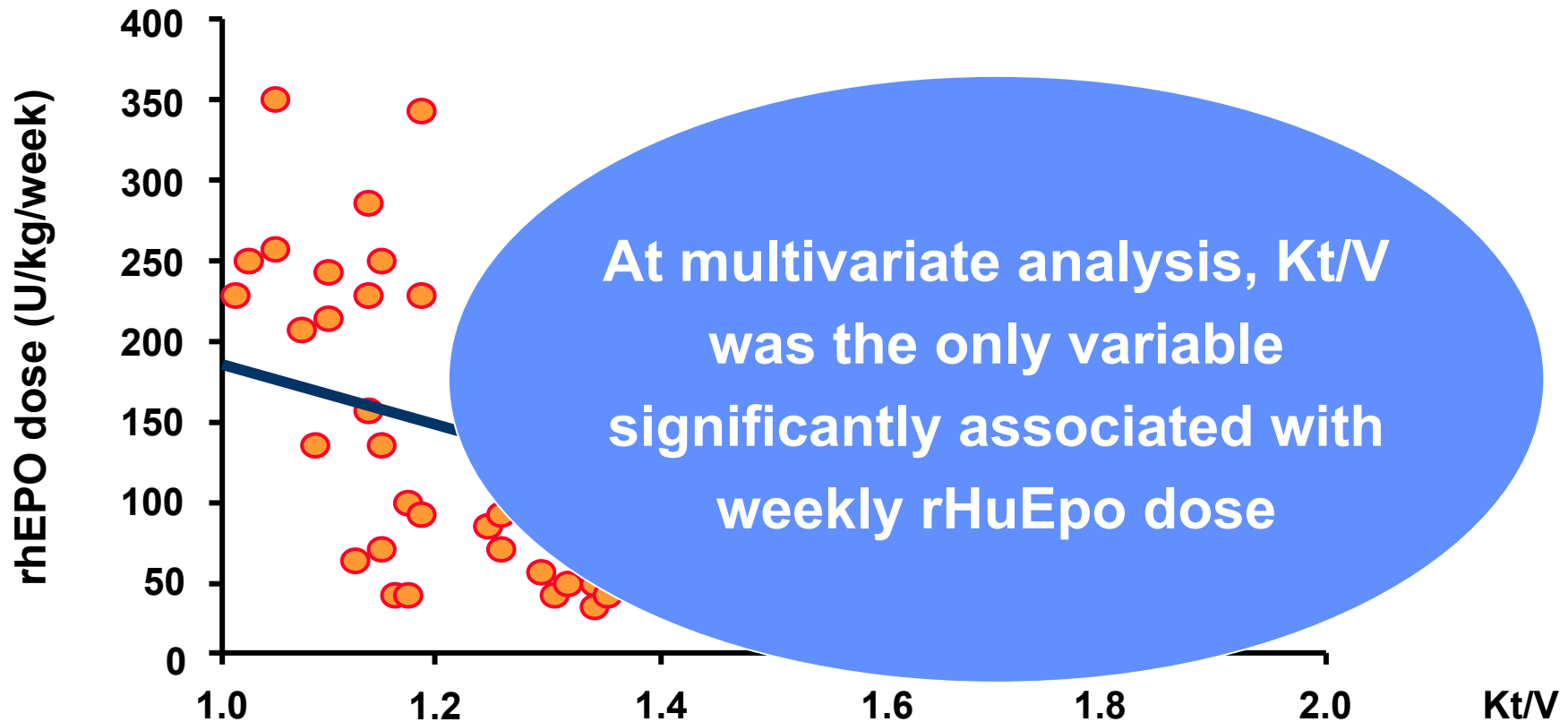


Table 4. Results of Multiple Logistic-Regression Analysis with a Hematocrit above 30 Percent as the Outcome Variable.

| VARIABLE* | ODDS RATIO | 95% CONFIDENCE INTERVAL | P VALUE |
|--|------------|-------------------------|---------|
| Serum albumin concentration | 5.895 | 1.68–20.72 | 0.006 |
| Percent reduction in blood urea nitrogen | 1.065 | 1.01–1.12 | 0.011 |
| Dose of erythropoietin | 0.971 | 0.94–1.00 | 0.053 |

Dialysis adequacy and erythropoietin dose



A2

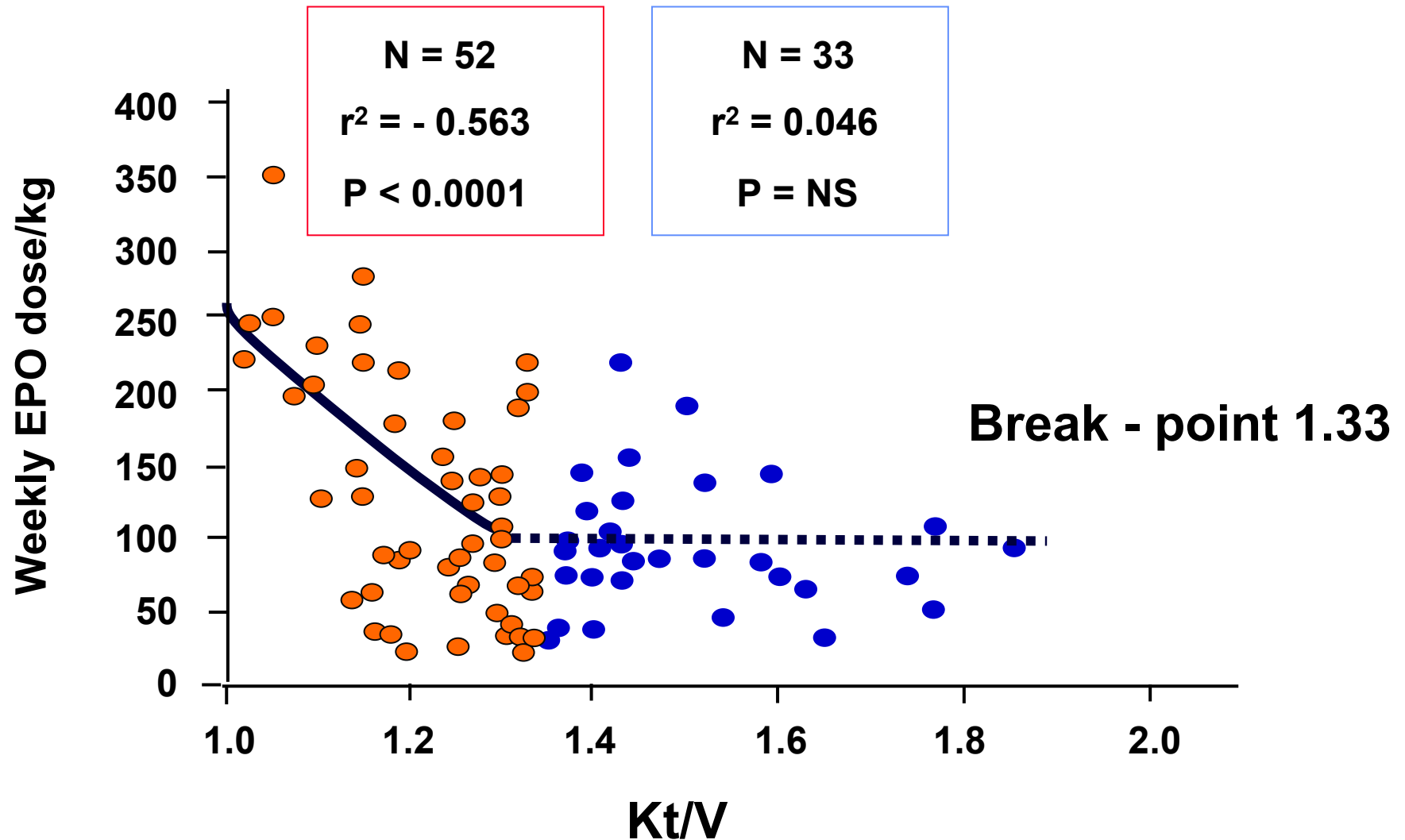
Background. The effect of the adequacy of dialysis on the response to recombinant human erythropoietin (rHuEpo) therapy is still incompletely understood because of many confounding factors such as iron deficiency, biocompatibility of dialysis membranes, and dialysis modality that can interfere.

Methods. We investigated the relationship between Kt/V and the weekly dose of rHuEpo in 68 stable haemodialysis (HD) patients (age 65 ± 15 years) treated with bicarbonate HD and unsubstituted cellulose membranes for 6–343 months (median 67 months). Inclusion criteria were HD for at least 6 months, subcutaneous rHuEpo for at least 4 months, transferrin saturation (TSAT) 20%, serum ferritin 100 ng/ml, and haematocrit (Hct) level targeted to 35% for at least 3 months. Exclusion criteria included HBsAg and HIV positivity, need for blood transfusions or evidence of blood loss in the 3 months before the study, and acute or chronic infections. Hct and haemoglobin (Hb) levels were evaluated weekly for 4 weeks; TSAT, serum ferritin, Kt/V, PCRn, serum albumin (sAlb), and weekly dose of rHuEpo were evaluated at the end of observation. No change in dialysis or therapy prescription was made during the study.

Results. The results for the whole group of patients were: Hct $35 \pm 1.2\%$, Hb 12.1 ± 0.6 g/dl, TSAT $29 \pm 10\%$, serum ferritin 204 ± 98 ng/ml, sAlb 4.1 ± 0.3 g/dl, Kt/V 1.33 ± 0.19 , PCRn 1.11 ± 0.28 g/kg/day, weekly dose of rHuEpo 123 ± 76 U/kg. Hct did not correlate with Kt/V, whereas rHuEpo dose and Kt/V were inversely correlated ($r = -0.49$; $P < 0.0001$). Multiple regression analysis with rHuEpo as dependent variable confirmed Kt/V as the only significant variable ($P < 0.002$). Division of the patients into two groups according to Kt/V (group A, Kt/V 1.2; group B, Kt/V 1.4), showed no differences in Hct levels between the two groups, while weekly rHuEpo dose was significantly lower in group B than in group A (group B, 86 ± 33 U/kg; group A, 183 ± 95 U/kg, $P < 0.0001$).

Conclusions. In iron-replete HD patients treated with rHuEpo in the maintenance phase, Kt/V exerts a significant sparing effect on rHuEpo requirement independent of the use of biocompatible synthetic membranes. By optimizing rHuEpo responsiveness, an adequate dialysis treatment can contribute to the reduction of the costs of rHuEpo therapy.

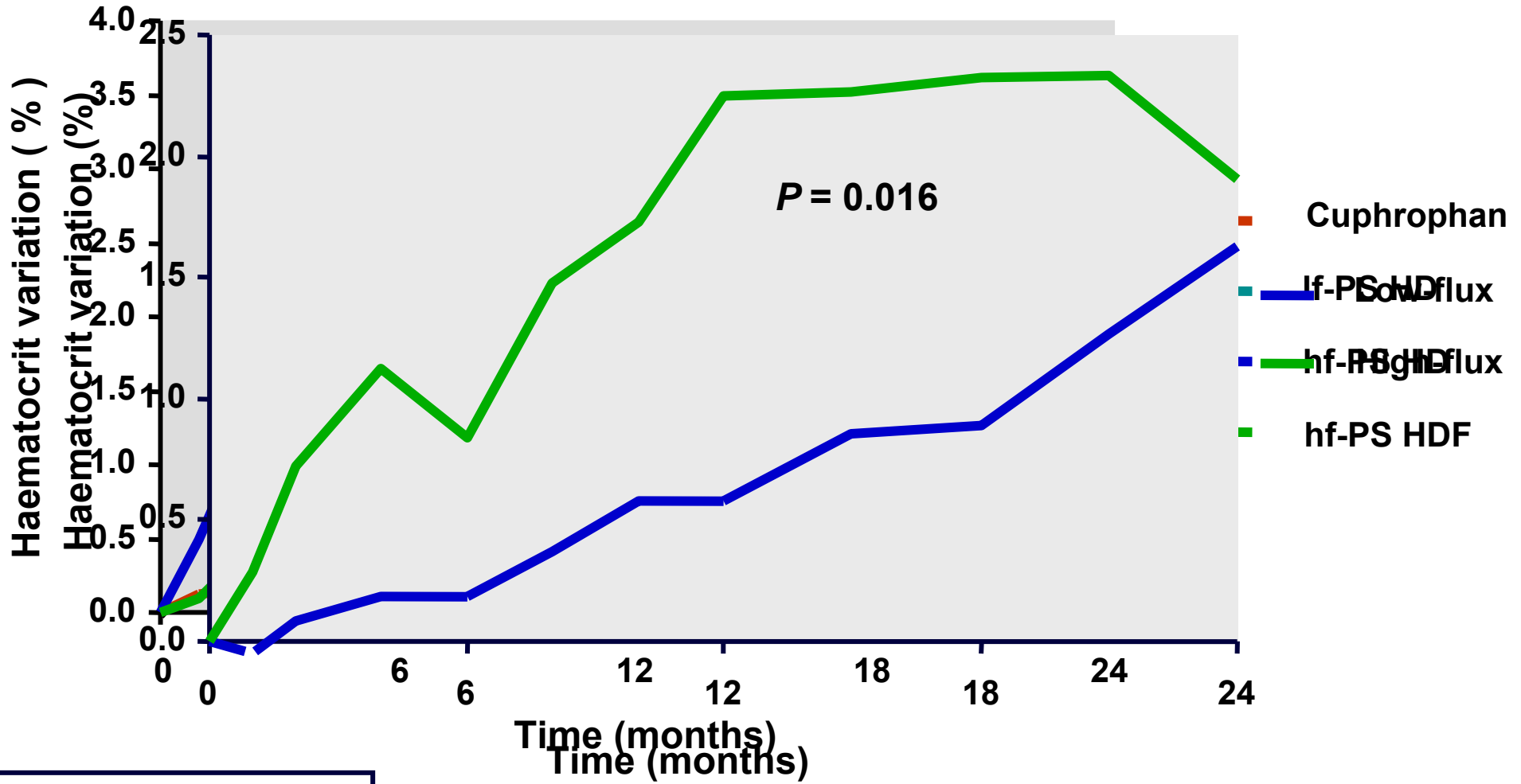
Dialysis adequacy and erythropoietin dose





Treatment modality

Anaemia and treatments



N = 380
Follow-up 24 months

A3

There is increasing evidence that the biochemical and cellular phenomena induced by blood/ membrane/dialysate interactions contribute to dialysis-related intradialytic and long-term complications. However, there is a lack of large, prospective, randomized trials comparing biocompatible and bioincompatible membranes, and convective and diffusive treatment modalities. The primary aim of this prospective, randomized trial was to evaluate whether the use of polysulfone membrane with bicarbonate dialysate offers any advantage (in terms of treatment tolerance, nutritional parameters and pre-treatment beta-microglobulin levels) over a traditional membrane (Cuprophan). A secondary aim was to assess whether the use of more sophisticated methods consisting of a biocompatible synthetic membrane with different hydraulic permeability at different ultrafiltration rate (high-flux hemodialysis and hemodiafiltration) offers any further advantages. Seventy-one Centers were involved and stratified according to the availability of only the first two or all four of the following techniques: Cuprophan hemodialysis (Cu-HD), low-flux polysulfone hemodialysis (LfPS-HD), high-flux polysulfone high-flux hemodialysis (HfPS-HD), and high-flux polysulfone hemodiafiltration (HfPS-HDF). The 380 eligible patients were randomized to one of the two or four treatments (132 to Cu-HD, 147 to LfPS-HD, 51 to HfPS-HD and 50 to HfPS-HDF). The follow-up was 24 months. No statistical difference was observed in the algebraic sum of the end points between bicarbonate dialysis with Cuprophan or with low-flux polysulfone, or among the four dialysis methods under evaluation. There was a significant decrease in pre-dialysis plasma beta 2-microglobulin levels in high-flux dialysis of 9.04 +/- 10.46 mg/liter (23%) and in hemodiafiltration of 6.35 +/- 12.28 mg/liter (16%), both using high-flux polysulfone membrane in comparison with Cuprophan and low-flux polysulfone membranes (P = 0.032). The significant decrease in pre-dialysis plasma beta 2-microglobulin levels could have a clinical impact when one considers that beta 2-microglobulin accumulation and amyloidosis are important long-term dialysis-related complications.

*Original Article***Effect of high-flux dialysis on the anaemia of haemodialysis patients**

Francesco Locatelli¹, Simeone Andrulli¹, Franco Pecchini², Luciano Pedrini³, Silvano Agliata⁴, Leonardo Lucchi⁵, Marco Farina⁶, Vincenzo La Milia¹, Claudio Grassi⁷, Marcello Borghi⁸, Bruno Redaelli⁹, Ferruccio Conte¹⁰, Gaudenzio Ratto¹¹, Gianfranca Cabiddu¹², Carlo Grossi¹³ and Roberto Modenese¹⁴

- **Parallel - group design**
- **12 - week follow-up**
- **84 patients centrally randomized**
- **Two haemodialysis treatments:**

**Cellulose membrane****BK-F PMMA membrane**

A4

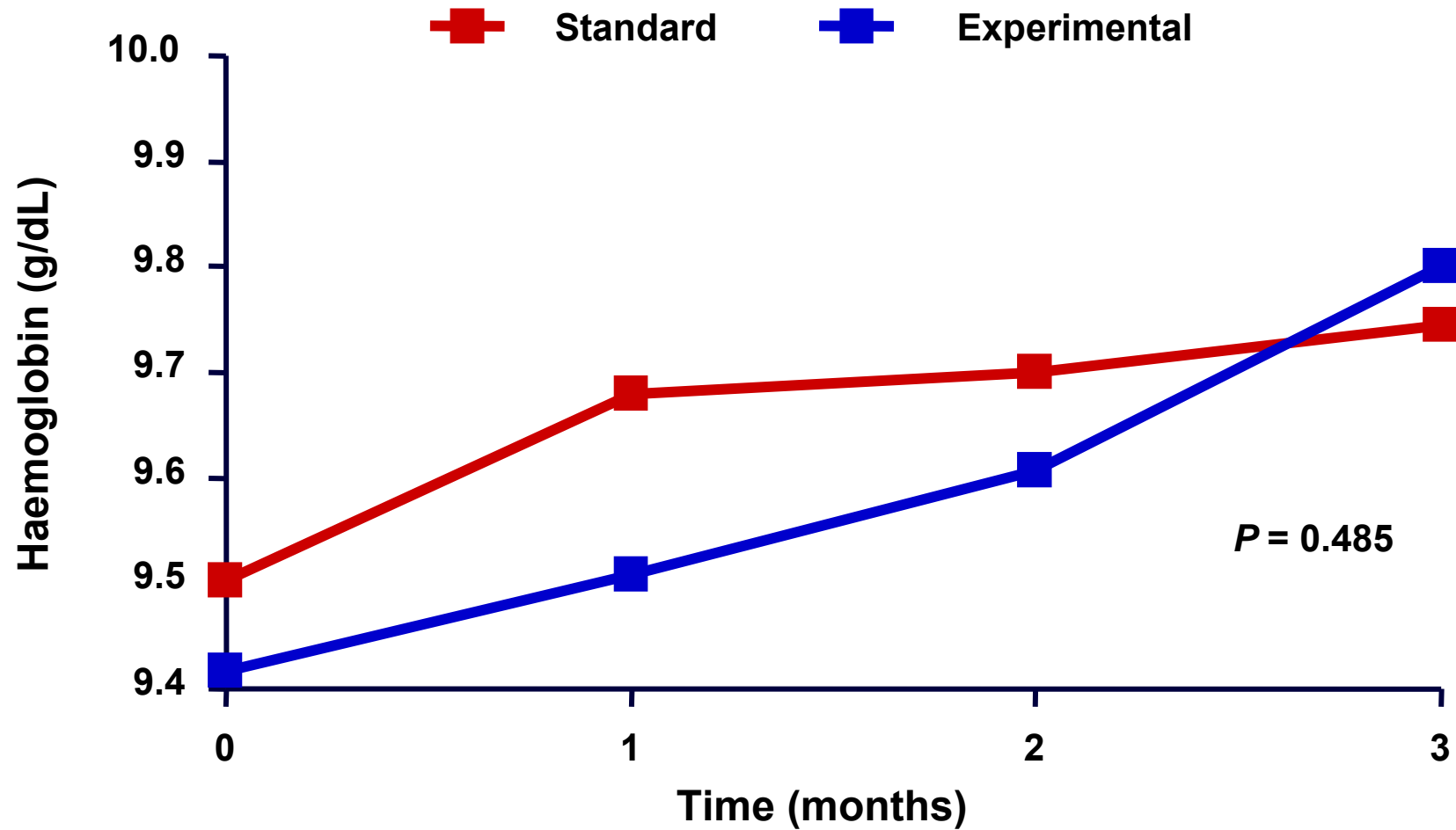
Background. Anaemia is one of the major clinical characteristics of patients with chronic renal failure, and has a considerable effect on morbidity and mortality. Adequate dialysis is of paramount importance in correcting anaemia by removing small and medium-sized molecules, which may inhibit erythropoiesis. However, high-molecular-weight inhibitors cleared only by means of highly porous membranes have also been found in uraemic serum and it has been claimed from uncontrolled studies that high-flux dialysis could improve anaemia in haemodialysis patients.

Methods. We therefore planned this multicentre randomized controlled trial with the aim of testing whether the use of a large-pore biocompatible membrane for a fixed 12-week follow-up improves anaemia in haemodialysis patients in comparison with the use of a conventional cellulose membrane. Eighty-four (5.3%) of a total of 1576 adult haemodialysed patients attending 13 Dialysis Units fulfilled the entry criteria and were randomly assigned to the experimental treatment (42 patients) or conventional treatment (42 patients).

Results. Haemoglobin levels increased non-significantly from 9.5 ± 0.8 to 9.8 ± 1.3 g/dl ($dP=0.069$) in the population as a whole, with no significant difference between the two groups ($P=0.485$). Erythropoietin therapy was given to 32/39 patients (82%) in the conventional group, and 26/35 (74%) in the experimental group ($P=0.783$) with subcutaneous administration to 26/32 patients in conventional and to 23/26 patients in experimental group, $P=0.495$. Dialysis dose (Kt/V) remained constant in both groups (from 1.30 ± 0.17 to 1.33 ± 0.20 in the conventional group and from 1.28 ± 0.26 to 1.26 ± 0.21 in the experimental group, $P=0.242$). Median pre- and post-dialysis β_2 -microglobulin levels remained constant in the conventional group (31.9 and 34.1 mg/dl at baseline) and decreased in the experimental group (pre-dialysis values from 31.1 to 24.7 mg/dl, $P=0.004$ and post-dialysis values from 24.8 to 20.8 mg/dl, $P=0.002$). Median erythropoietin doses were not different at baseline (70 IU/kg/week in conventional treatment and 90 IU/kg/week in experimental treatment, $P=0.628$) and remained constant during follow-up (from 70 to 69 IU/kg/week in the conventional group and from 90 to 91 IU/kg/week in the experimental group, $P=0.410$). Median erythropoietin plasma levels were in the normal range and remained constant (from 12.1 to 12.9 mU/ml in the conventional group and from 13.2 to 14.0 mU/ml in the experimental group, $P=0.550$).

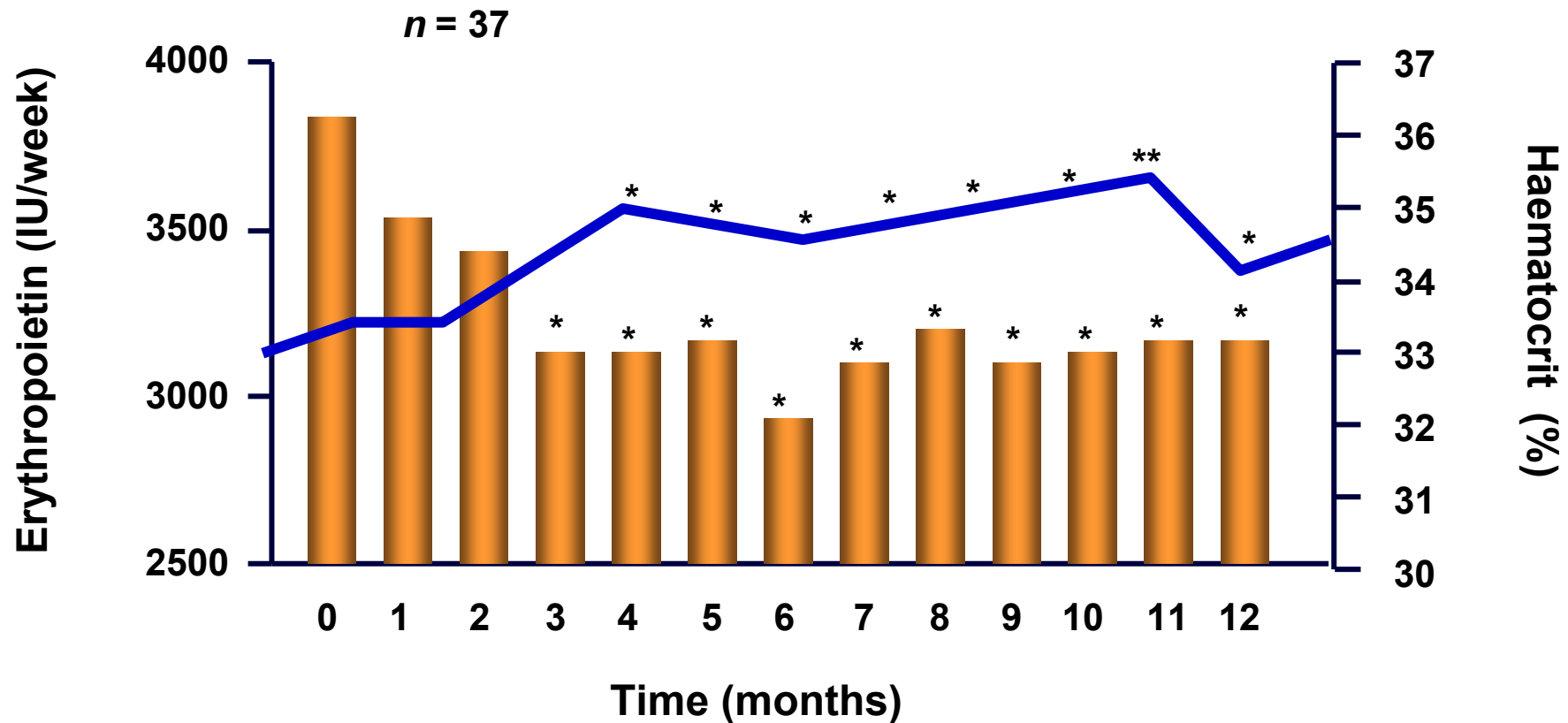
Conclusions. This study showed no difference in haemoglobin level increase between patients treated for 3 months with a high-flux biocompatible membrane in comparison with those treated with a standard membrane. When patients are highly selected, adequately dialysed, and have no iron or vitamin depletion, the effect of a high-flux membrane is much less than might be expected from the results of uncontrolled studies.

Haemoglobin



Change from conventional to online haemodiafiltration

Kt/V $1.35 \pm 0.21 \Rightarrow 1.56 \pm 0.29$; $p < 0.01$



* $P < 0.05$

** $P < 0.001$

Maduell F *et al.* Nephrol Dial Transplant 1999; 14: 1202 – 7

Online haemodiafiltration vs. low-flux haemodialysis

Design: Prospective randomized

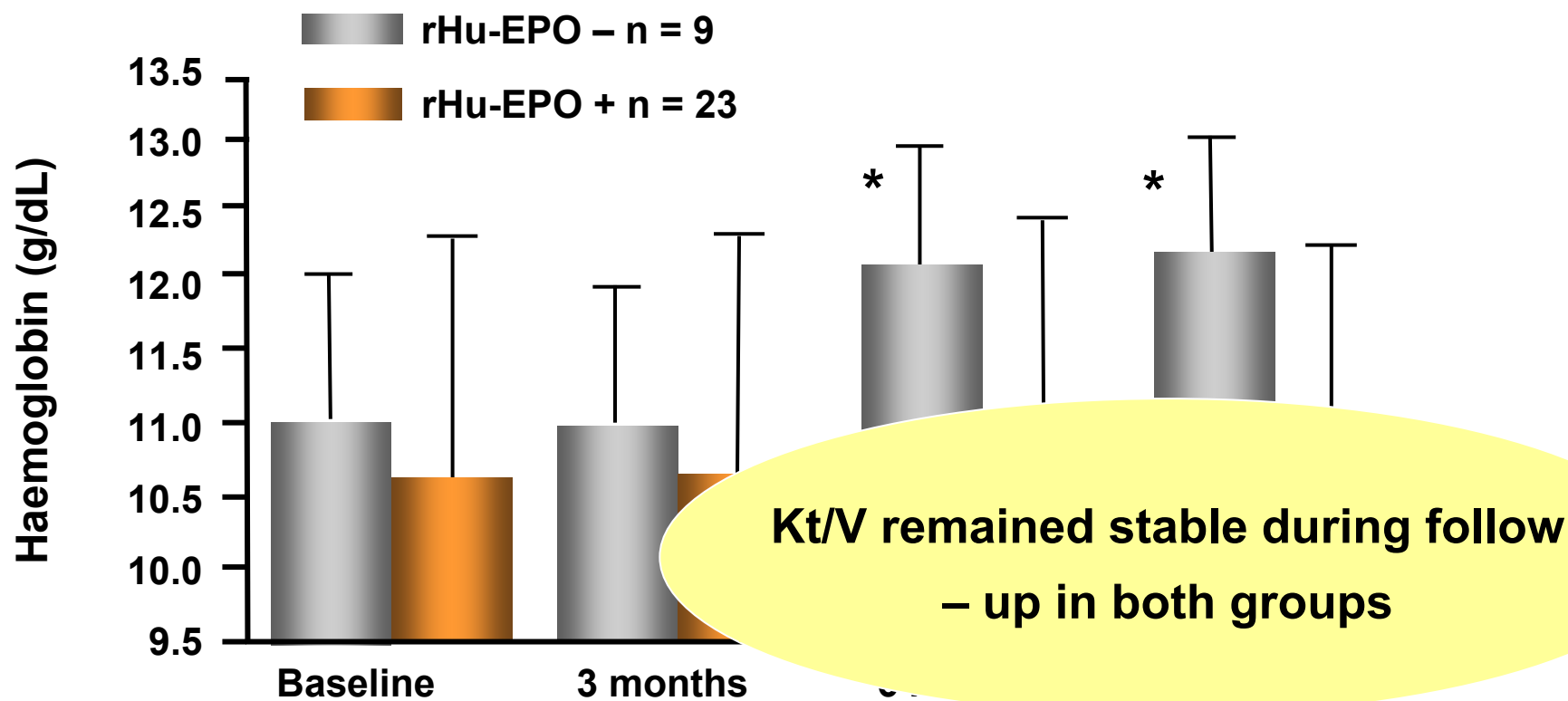
Patients: 44 followed up for 24 months

Results: Morbidity, mortality, blood pressure, intradialytic hypotension, haematocrit and erythropoietin dose did not differ between the two groups

A5

BACKGROUND: Current methods of renal replacement therapy lead only to an insignificant removal of larger, potentially toxic, substances, which are excreted by healthy kidneys. On-line preparation of substitute from dialysate and the use of high-flux membranes allow substantial convective removal of such substances. A modified on-line haemodiafiltration method with the use of a large membrane surface and a high convective part was chosen to test whether the elimination of larger substances, such as low-molecular-mass proteins, has a clinical impact. **METHODS:** In a prospective, controlled study over 24 months, 44 unselected chronic dialysis patients were randomized to undergo either low-flux haemodialysis (HD; n = 21) or haemodiafiltration (HDF; n = 23). To eliminate confounding factors, low-molecular efficacy was matched (Kt/V 1.8), and the same membrane material (polysulfone), ultrapure dialysate and the same treatment duration (4.5 h) were applied to each group. **RESULTS:** Morbidity, mortality, blood pressure, dialysis-associated hypotensive episodes, haematocrit and erythropoietin dose did not differ between the groups. The same was true for body weight and, accordingly, bioimpedance values, clinical hydration score, skinfold thickness, plasma albumin, prealbumin and transferrin. beta2-Microglobulin in the plasma did not change in the HD group and varied between 32 and 43 mg/l throughout the 2 years. In HDF, beta2 microglobulin decreased from similar values to 18 mg/l predialysis (P<0.01) in the first 6 months of HDF treatment and then remained constant during the remaining 18 months. **CONCLUSION:** In the absence of any clinical marker of uraemic toxicity the removal of larger molecules over the time-span of 2 years during HDF had no clinical implication compared with extremely (and for routine practice unrealistically) well-dialysed patients with low-flux HD. In the absence of any side-effects of on-line HDF and supposing that plasma beta2-microglobulin is a marker of morbidity, on-line HDF ensures an excellent dialysis quality which apparently takes time to translate into measurable clinical sequelae.

Haemoglobin values during the first 9 months of on-line treatment



* P < 0.05 vs. baseline

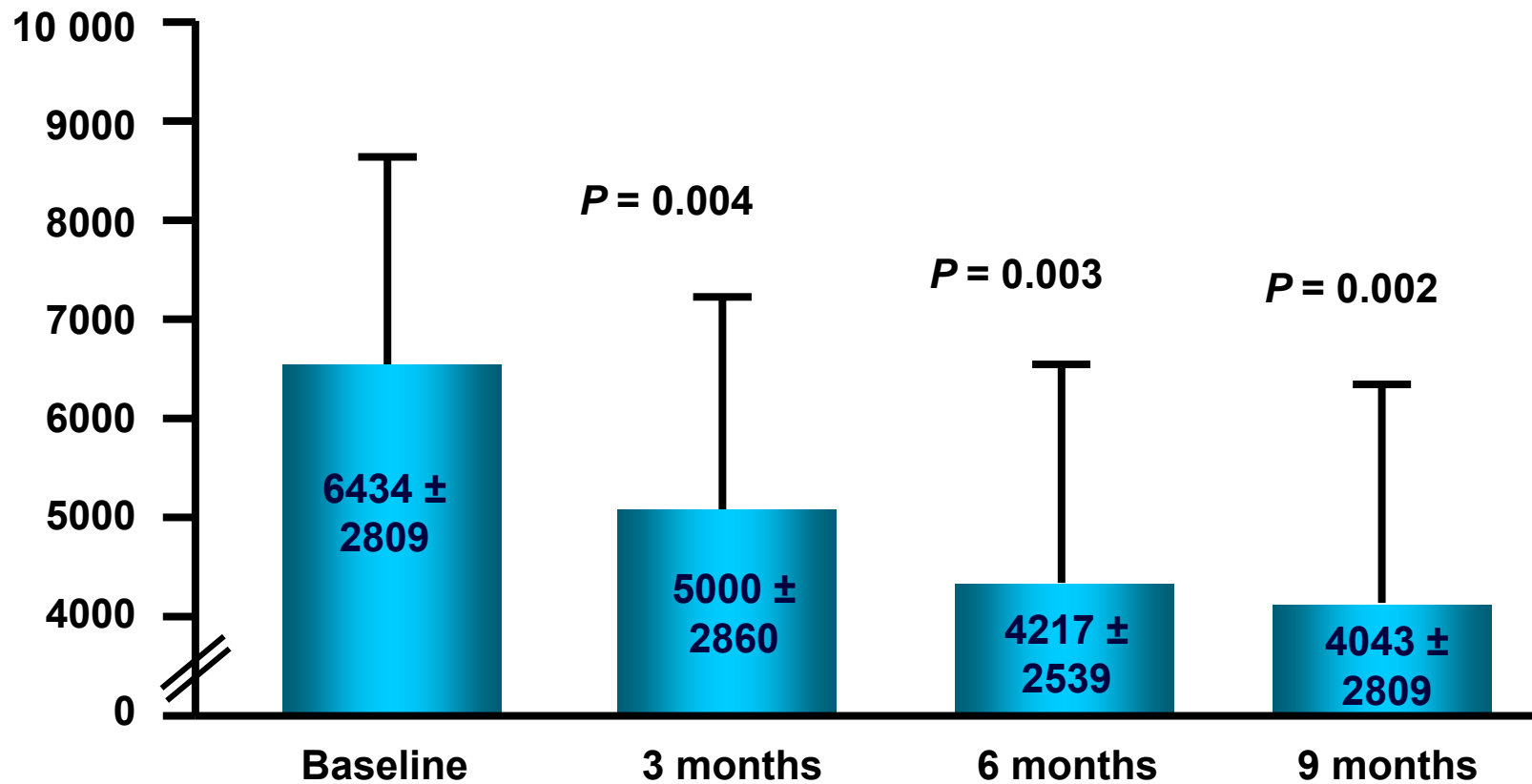
A6

BACKGROUND: Hemodiafiltration (HDF) is associated with a lower incidence of neuropathy, carpal tunnel syndrome, joint pain, and partial correction of anemia. HDF with on-line-prepared substitution fluid (OL HDF), as compared with conventional hemodialysis, increases the treatment tolerance and, as compared with standard HDF, avoids storage problems and allows a higher substitution volume at low cost. **METHODS:** Thirty-two hemodialysis patients treated by OL HDF for at least 9 months were studied. Hemoglobin, hematocrit, iron metabolism, serum albumin, dialysis dose and dry body weight were determined under a settled condition with regular hemodialysis 3 months before the transfer to OL HDF. The same parameters were analyzed 3, 6 and 9 months after the beginning of the new treatment modality. **RESULTS:** During OL HDF, hemoglobin values significantly increased in patients without addition of recombinant human erythropoietin (rHuEPO): baseline vs. 6 months 11 +/- 1.7 vs. 12 +/- 1.8 g/dl ($p < 0.01$); baseline vs. 9 months 11 +/- 1.7 vs. 12 +/- 1.6 g/dl ($p < 0.05$). In patients on a maintenance dose of rhuEPO, this could be significantly reduced, while the target hemoglobin levels were maintained (10.6 +/- 0.9 g/dl): baseline 99.8 +/- 50.4 U/kg/week, 3rd month 76.2 +/- 43 U/kg/week, 6th month 64.3 +/- 37 U/kg/week, and 9th month 59.4 +/- 38.6 U/kg/week ($p = 0.007$, $p = 0.0006$, and $p = 0.0007$, respectively, vs. baseline). Iron metabolism, dialysis dose, dry body weight and serum albumin levels did not significantly change during the follow-up period. Further, a stability of the rHuEPO supplementation was observed in 14 patients followed up for 24 months. **CONCLUSIONS:** OL HDF influences anemia and rHuEPO dose. It allows considerable anemia correction in patients without rHuEPO treatment, while it significantly reduces rHuEPO doses in those on rHuEPO treatment as compared with standard hemodialysis. The rHuEPO costs are consequently reduced. Copyright 2002 S. Karger AG, Basel

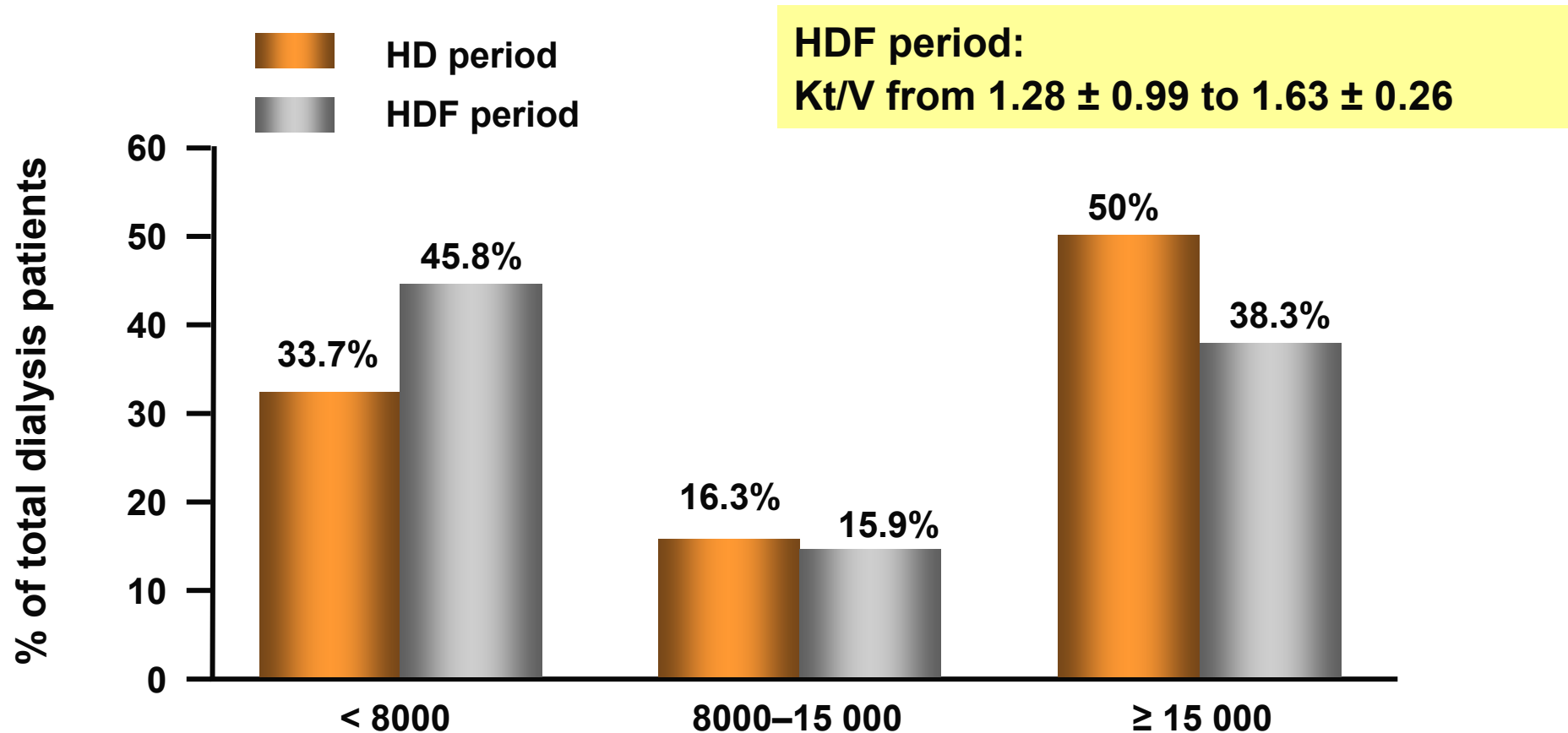
Administrator; 23.03.2004

rHu-EPO supplementation at the start of online HDF and after 3, 6 and 9 months

rHu-EPO-treated patients only



Distribution of total EPO dose/month among patients during the HD and online HDF periods



N = 92

Mean HDF period 19 ± 8.2 months

Lin CL *et al. Blood Purif* 2002;20:349–56

A7

BACKGROUND: Recent investigation has shown that on-line hemodiafiltration (HDF) can reduce the amount of recombinant human erythropoietin (rhEPO) deemed necessary to reach the target hematocrit. The aim of this study was to analyze the potential effect of on-line HDF on rhEPO resistance in relation to iron utilization and anemia-related parameters, when compared to conventional hemodialysis (HD).

METHODS: Ninety-two chronic uremic patients were treated with conventional HD and then shifted to on-line HDF. Measurements of various erythropoiesis-related parameters were collected during HD and on-line HDF periods for statistical analysis for erythropoietin resistance.

RESULTS: Patients treated with on-line HDF switching from conventional HD significantly contributed to the reduction of EPO dose to reach a higher mean hematocrit level (31.8 +/- 4.4% vs. 29.5 +/- 3.9%, $p < 0.001$) and a reduction of the serum ferritin level (322.5 +/- 268.4 vs. 544.9 +/- 642.4, $p < 0.001$). The median EPO/Hct ratio was greater in the HD period (504.6 +/- 310.1) than in the on-line HDF period (307.6 +/- 334.4) ($p < 0.001$). These results indicated a reduced EPO resistance and improved iron utilization by on-line HDF. By multiple regression analysis, the significant predictors of EPO resistance are ferritin, transferrin, albumin, and TACurea (Time average concentration of urea) in HD treatment. In on-line HDF modality, in addition to ferritin and albumin, the duration of on-line HDF is a negative predictor in EPO resistance.

CONCLUSION: When on-line HDF is recommended to chronic dialysis patients, long-term use of this technique provides an efficient means of achieving the goal of an elevated hemoglobin by reducing EPO resistance, improved iron utilization and may further improve the quality of life.

Administrator; 23.03.2004

Long-Term Outcomes in Online HDF and High-Flux HD: A Comparative Analysis

- **858 incident patients during an 18-yr period**
- **Outcome comparison in those who were treated with HDF (>50% sessions) and those with high-flux HD**

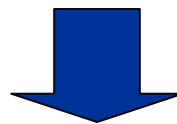
Despite a significant lower HR for death (0.66), no benefits were found of HDF over high-flux HD with respect to anemia management

On-line HDF versus HD: a cross-over study

70 patients
CKD stage 5D

3 months with low-flux HD using cuprophane

Randomized, open, crossover



Group A

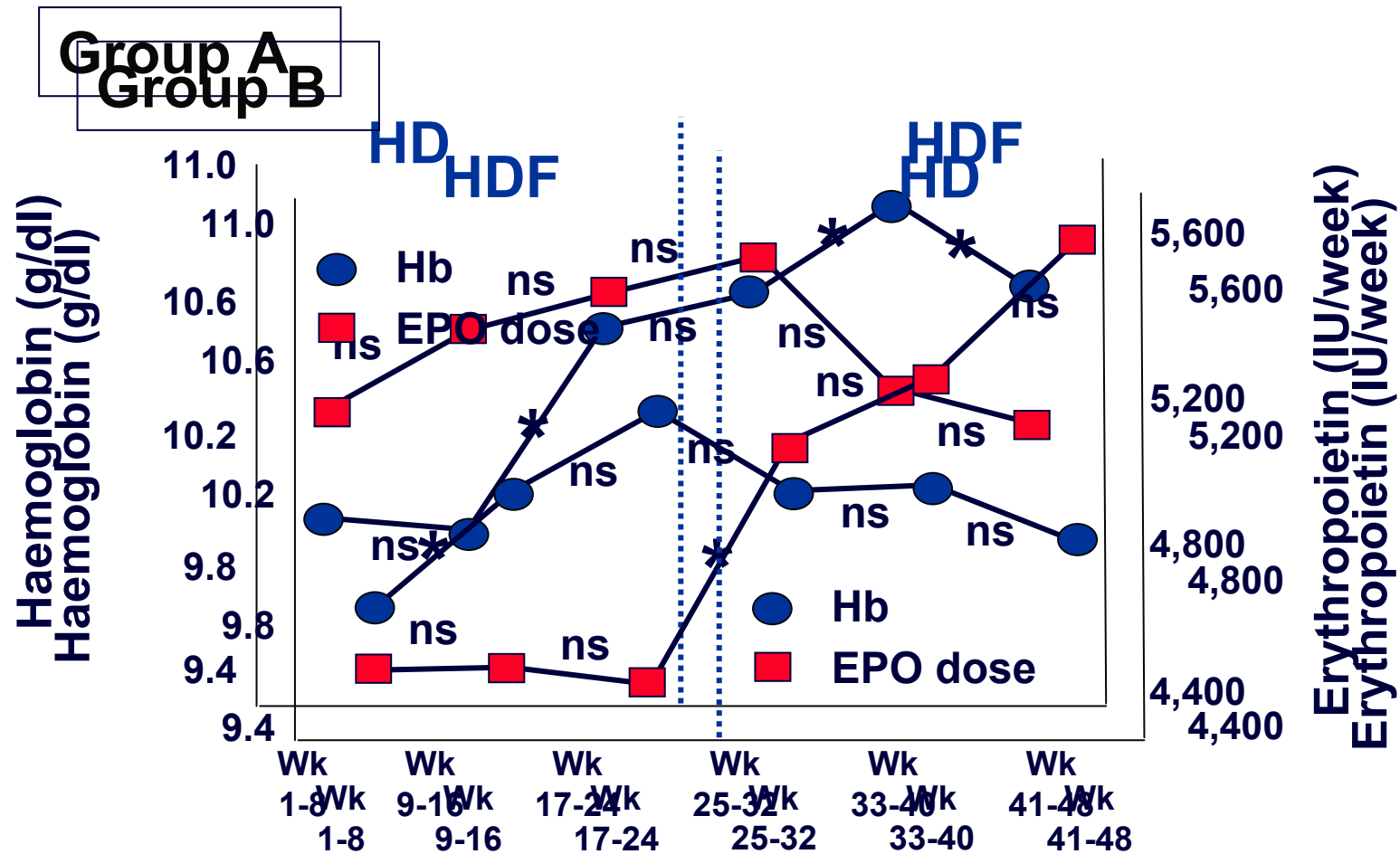
HD
low-flux polysulfone

Group B

HDF
high-flux polysulfone

Switch to the other treatment modality after 24 weeks

On-line HDF versus HD: stable haematocrit with less erythropoietin





Ultrapure dialysate

Pyrogen-free dialysate and response to EPO

- ④ **Design** Prospective, randomized study
- ④ **Aim** To compare the effect of two dialysis fluids on rhEPO response
- ④ **Patients** 15 on conventional HD, 15 switched to online-produced ultrapure dialysate
- ④ **Follow-up** 12 months

The ultrapure dialysate significantly decreased the rhEPO dosage

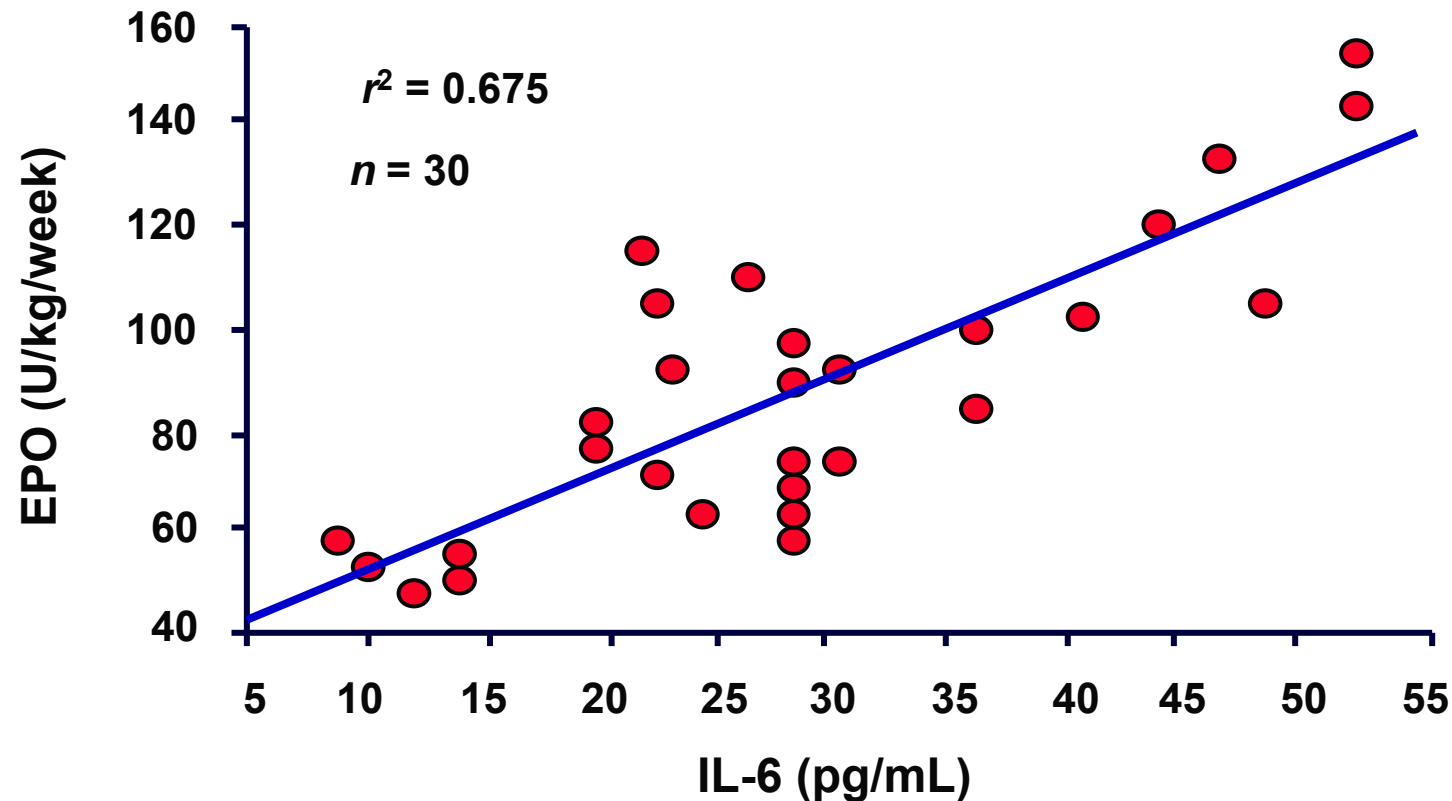
A8

BACKGROUND: Chronic inflammatory disorders or infections represent a major cause of hyporesponsiveness to recombinant human erythropoietin (rHuEpo). To test the hypothesis that dialysate-related cytokine induction alters the response to rHuEpo, we conducted a prospective study with matched pairs of chronic haemodialysis patients. We compared the effect of two dialysis fluids, differing in their microbiological quality, on the rHuEpo therapy. **METHODS:** Thirty male patients with end-stage renal disease maintained on regular haemodialysis were assigned either to a group treated with conventional (potentially microbiologically contaminated) dialysate (group I) or to a group treated with online-produced ultrapure dialysate (group II). Randomization was stratified according to the maintenance dose of rHuEpo necessary to maintain a target haemoglobin level of 10-10.5 g/dl. Patients were followed for 12 months. Kt/V was calculated by the formula of Daugirdas. Haemoglobin levels were measured weekly and serum ferritin concentrations were determined at 6-week intervals. C-reactive protein (CRP) and interleukin-6 (IL-6) was measured by an ELISA at the start of the study and after 3, 6 and 12 months. **RESULTS:** In group I, continuous use of bicarbonate dialysate did not change the rHuEpo dosage given to achieve the target haemoglobin level and was associated with elevated surrogate markers (CRP, IL-6) of cytokine-induced inflammation. The switch from conventional to online-produced ultrapure dialysate in group II resulted in a lower bacterial contamination with a significant decrease of CRP and IL-6 blood levels. It was accompanied by a significant and sustained reduction of the rHuEpo dosage, which was required to correct the anaemia. Using multiple regression analysis, IL-6 levels are shown to have a strong predictive value for rHuEpo dosage in both groups. **CONCLUSIONS:** Our data demonstrate that dialysate-related factors such as low bacterial contamination can induce the activation of monocytes, resulting in elevated serum levels of IL-6. Dialysate-related cytokine induction might diminish erythropoiesis. The use of pyrogen free ultrapure dialysate resulted in a better response to rHuEpo. Not only would it save money, but it would also help to maintain an optimal haemoglobin level without further increase in rHuEpo dosage.

Administrator; 23.03.2004

Pyrogen-free dialysate and response to EPO

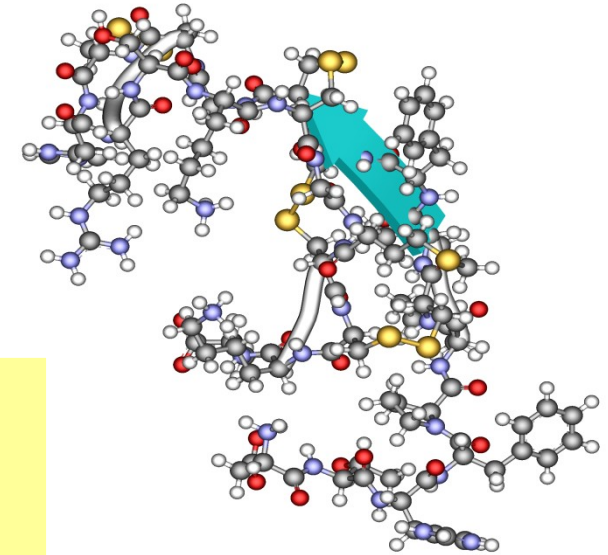
Conventional HD vs. Online - produced ultrapure dialysate





Hepcidin removal

Hepcidin



☀ Antibacterial protein produced in the liver

☀ 84-aa pre-prohepcidin



☀ hepcidin-25: biologically active form

☀ Key regulator of systemic iron homeostasis:

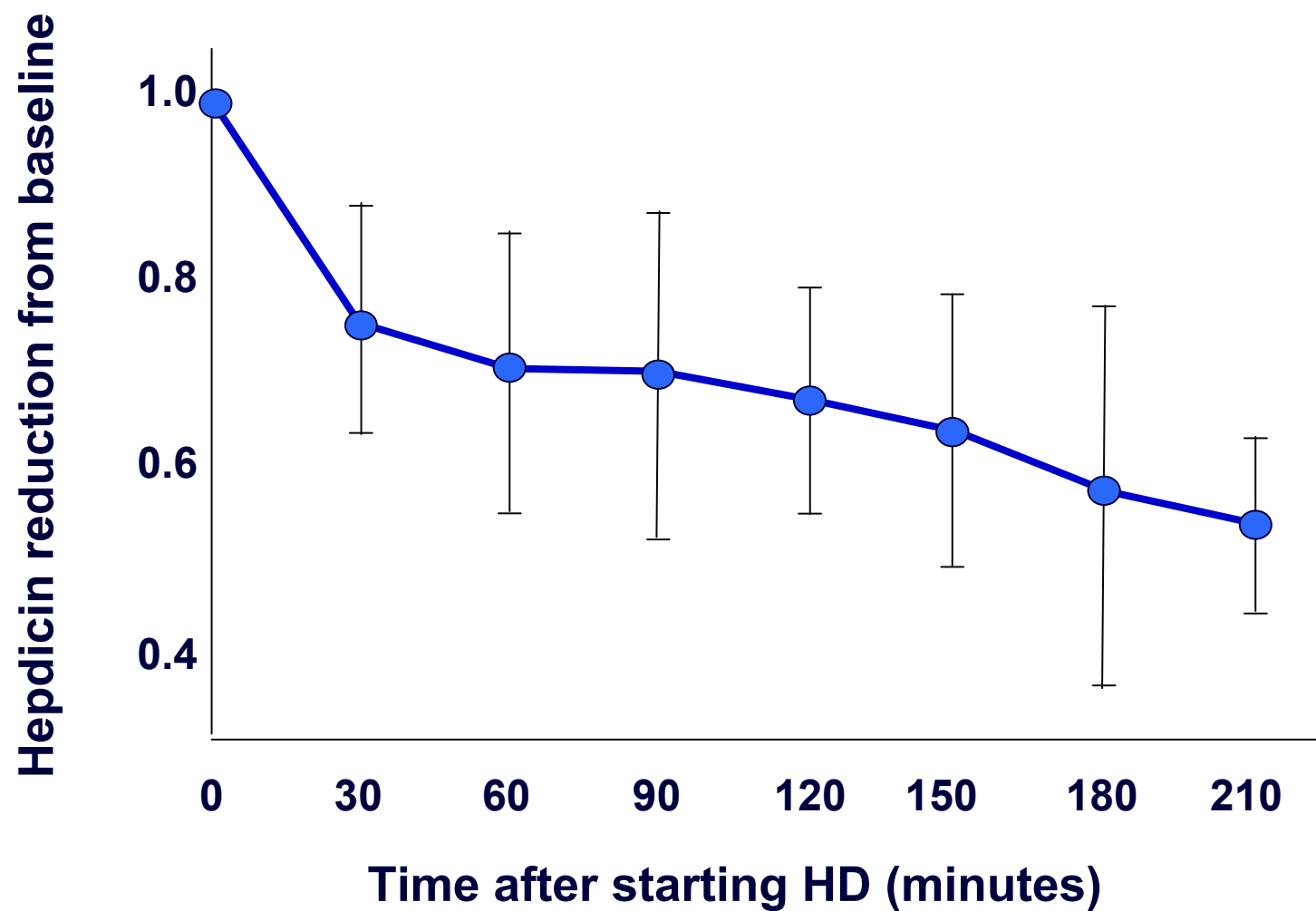
▶ Internalization and degradation of the iron exporter ferroportin



▶ Inhibition of the release of iron by macrophages

▶ Decrease of iron uptake in the gut

Hepcidin reduction from baseline during HD



Zaritsky J et al. Clin Am J Soc Nephrol 2010; Mar 18. [Epub ahead of print]

Serum hepcidin concentration in chronic haemodialysis patients: associations and effects of dialysis, iron and erythropoietin therapy

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Hepcidin and pro-hepcidin values before and after dialysis

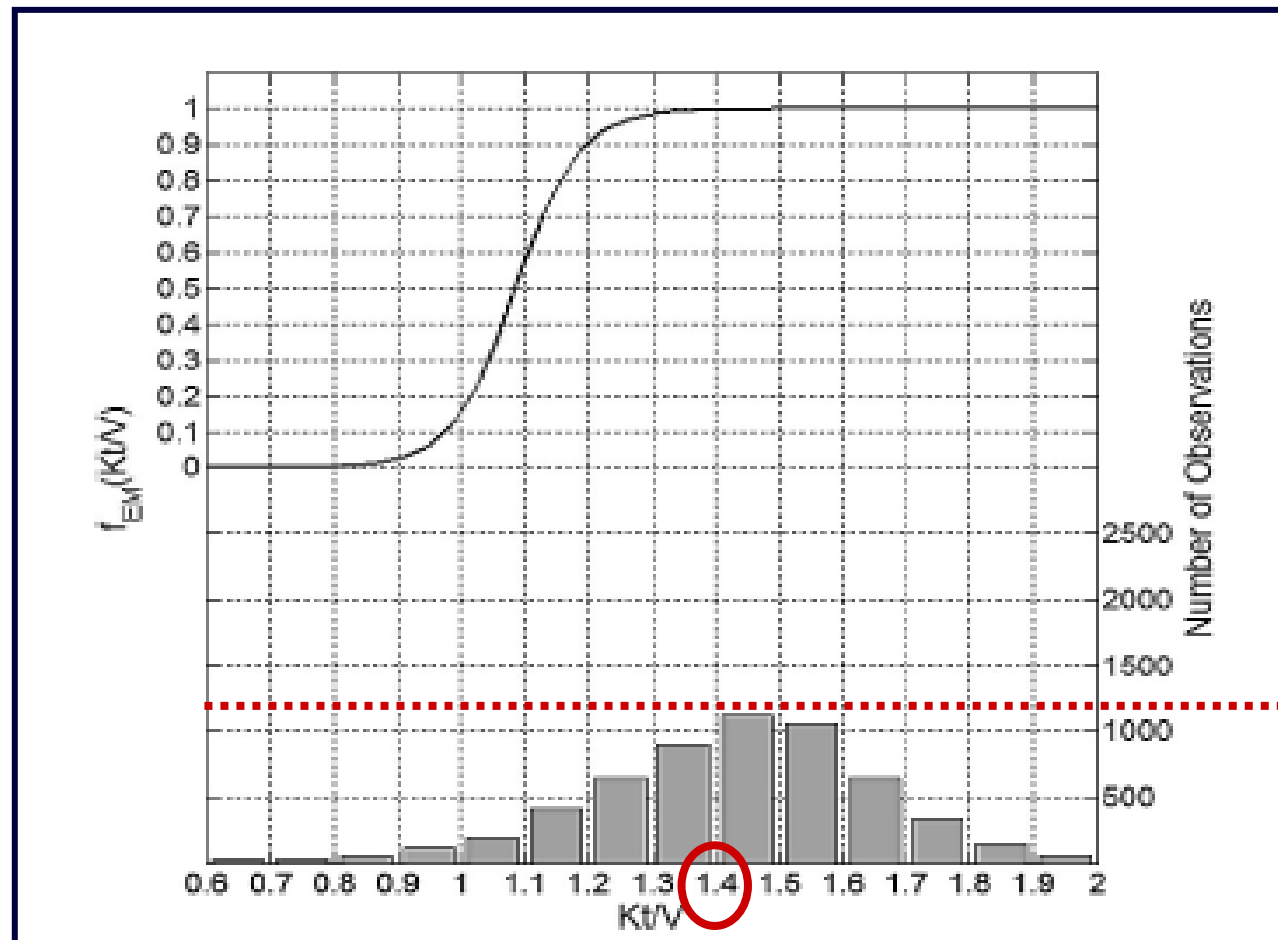
| | High flux n = 6 | Low flux n = 14 |
|--------------------------------|------------------------|------------------------|
| Hepcidin before HD (fmol/l) | 17 ± 3.9 | 16 ± 2.9 |
| Hepcidin after HD (fmol/l) | 8.4 ± 1.2* | 12.7 ± 2.5† |
| Pro-hepcidin before HD (ng/ml) | 216 ± 13 | 208 ± 13 |
| Pro-hepcidin after HD (ng/ml) | 201 ± 18 | 198 ± 13 |

Conclusions

- ▣ **In an era of uncertainty about ESA use, means of reducing ESA doses are of importance**
- ▣ **On-line HDF may improve anemia by increasing dialysis adequacy and removing uremic toxins, and reducing inflammation**
- ▣ **Large, well-designed, randomised trials investigating this hypothesis are lacking**

Iron, Inflammation, Dialysis Adequacy, Nutritional Status, and Hyperparathyroidism Modify Erythropoietic Response

Plot of the mean effect modification by Kt/V and the histogram of data distribution



Retrospective data from 209 HD patients receiving Epoetin alfa