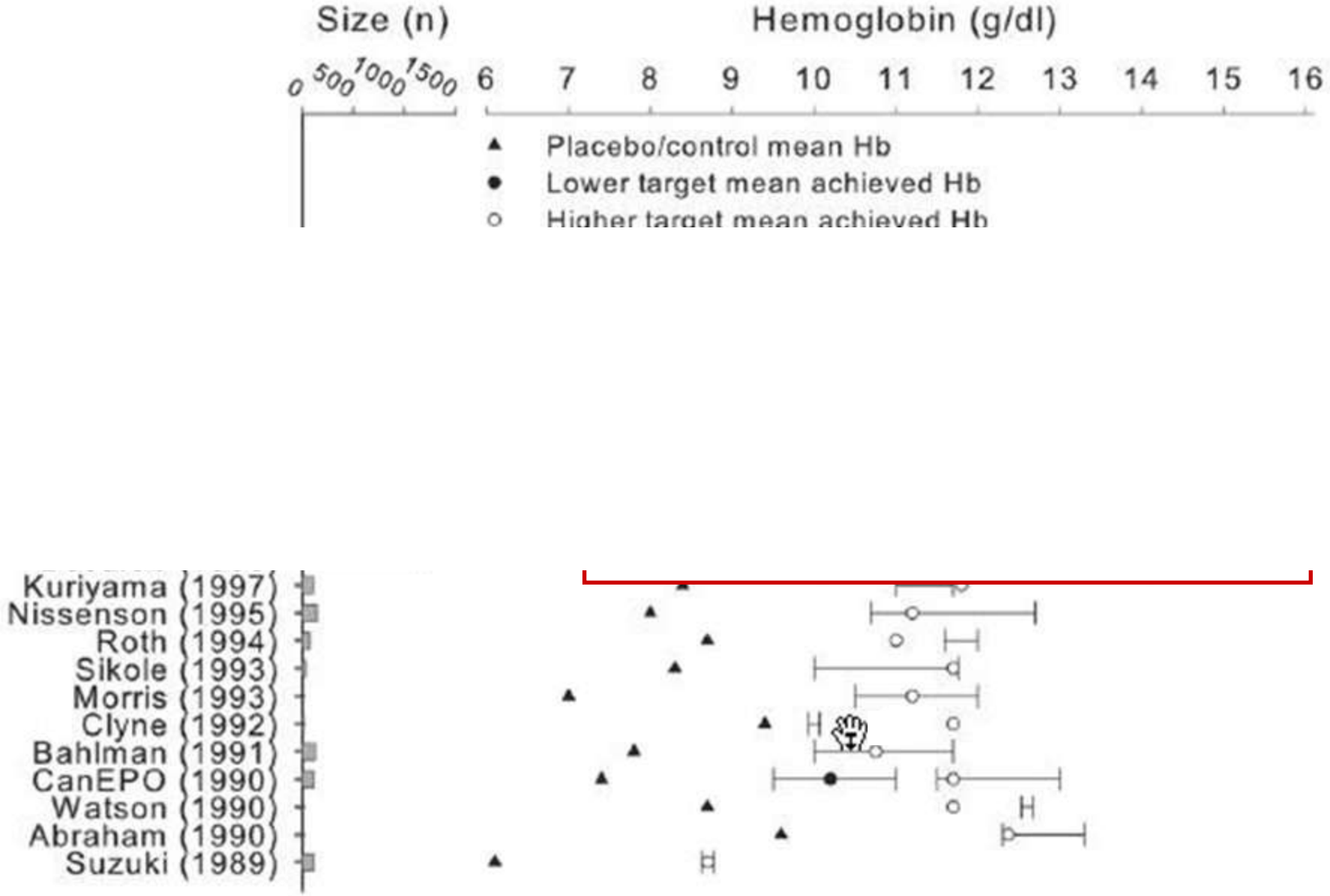
Where are we now in managing anaemia in patients with ND-CKD ?

XLVII ERA-EDTA / II DGfN Congress
Munich, Germany, 26 June 2010


Size (n)
0
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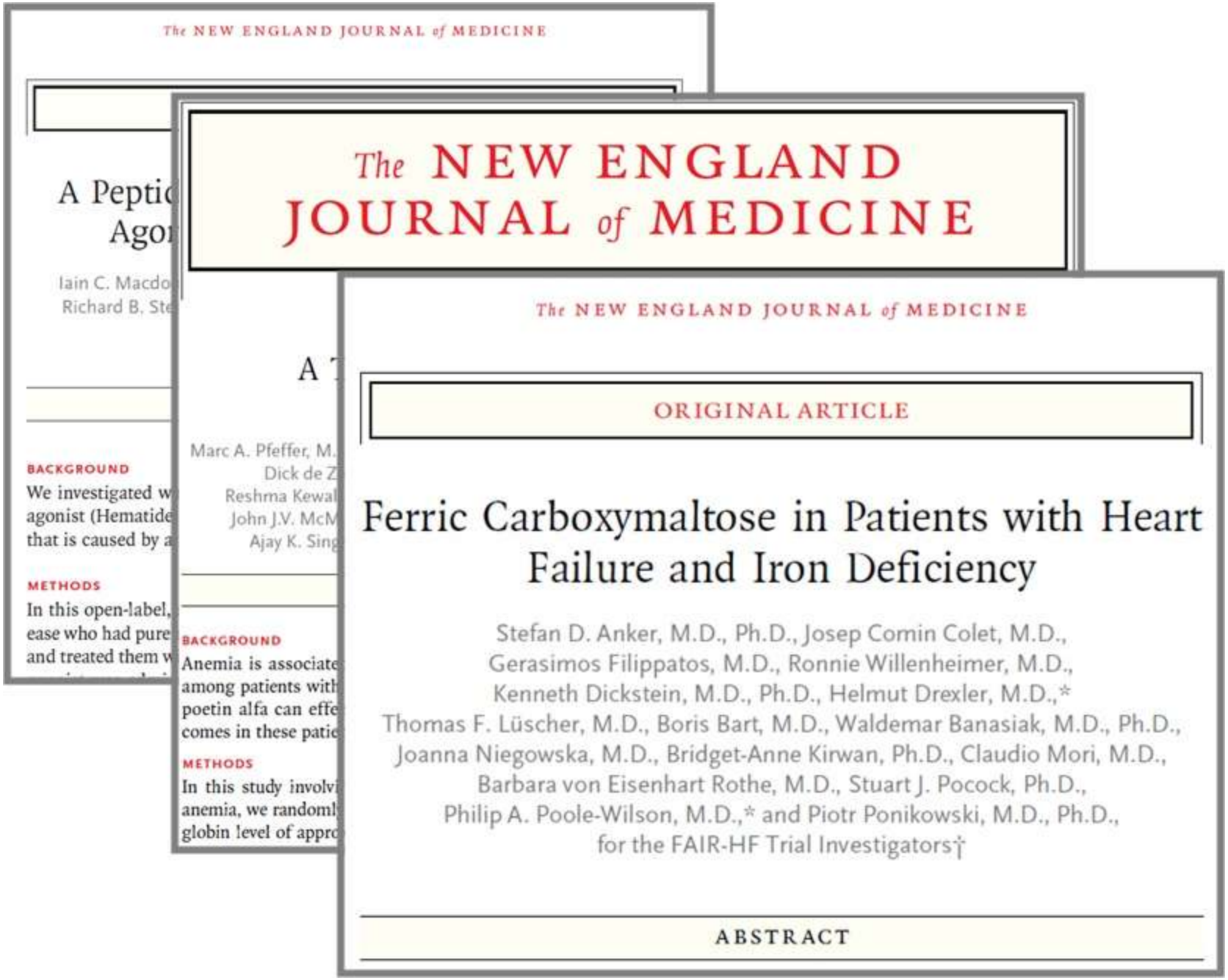
Hemoglobin (g/dl)
6
7
8
9
10
11
12
13
14
15
16
Placebo/control mean Hb
Lower target mean achieved Hb
Higher target mean achieved Hb
Kuriyama (1997)
Nissenson (1995)
Roth (1994)
Sikole (1993)
Morris (1993)
Clyne (1992)
Bahlman (1991)
CanEPO (1990)
Watson (1990)
Abraham (1990)
Suzuki (1989)


The NEW ENGLAND JOURNAL of MEDICINE
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BACKGROUND
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The NEW ENGLAND JOURNAL of MEDICINE
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Marc A. Pfeffer, M.
Dick de Z
Reshma Kewal
John J.V. McM
Ajay K. Sing
BACKGROUND
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The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency
Stefan D. Anker, M.D., Ph.D., Josep Comin Colet, M.D.,
Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D.,
Kenneth Dickstein, M.D., Ph.D., Helmut Drexler, M.D.,*
Thomas F. Lüscher, M.D., Boris Bart, M.D., Waldemar Banasiak, M.D., Ph.D.,
Joanna Niegowska, M.D., Bridget-Anne Kirwan, Ph.D., Claudio Mori, M.D.,
Barbara von Eisenhart Rothe, M.D., Stuart J. Pocock, Ph.D.,
Philip A. Poole-Wilson, M.D.,* and Piotr Ponikowski, M.D., Ph.D.,
for the FAIR-HF Trial Investigators†
ABSTRACT

Erscheinungsort: Wien; Verlagspostamt: A-8600 Bruck/Mur

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NEPHRO-NEWS

Forum für Nephrologie und Hypertensiologie

REPRINT

KONSENSUSPAPIER

Eisen-Management bei Patienten mit chronischer Niereninsuffizienz

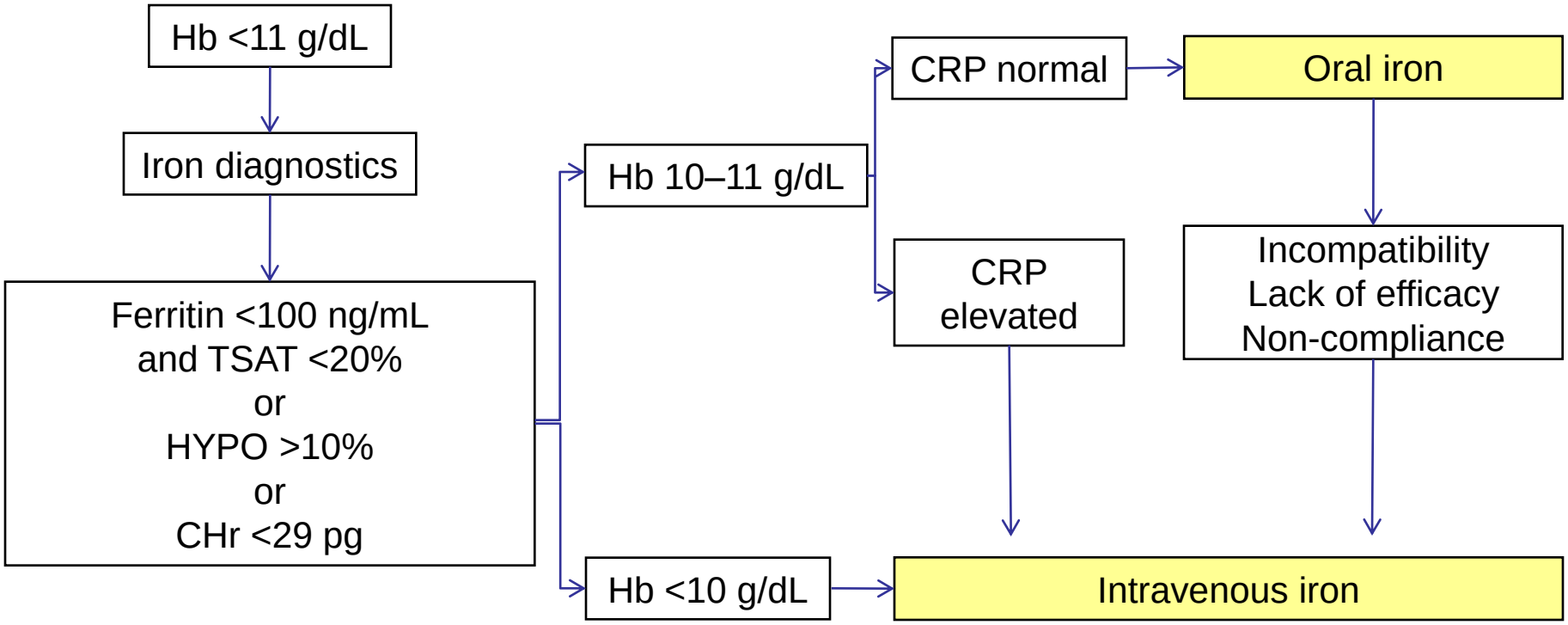
Bei etwa 11% der erwachsenen amerikanischen Bevölkerung besteht eine chronische Nierenerkrankung, definiert als vermehrte Eiweißausscheidung mit dem Urin und/oder als Reduktion der glomerulären Filtrationsrate (GFR). Entsprechende repräsentative Zahlen fehlen für den deutschsprachigen Raum. Chronische Nierenerkrankungen lassen in den USA weiter zunimmt, zumindest partiell bedingt durch die höhere Prävalenz von Diabetes und arterieller Hypertonie *(Coresh J, JAMA 298:2038-2047, 2007)*, vermutlich auch im deutschsprachigen Raum.

PRÄVALENZ UND URSACHEN DER RENALEN ANÄMIE

Transferrinsättigung [TSAT] <20%), Vitamin- und Folsäuremangel, Blutverluste, Inflammation, Infektionen, Malignome oder Medikamente, die die Erythropoiese negativ beeinflussen können, von Bedeutung.

RISIKOFAKTOR EISENMANGEL

Iron management in predialysis (CKD stage 3–4)



Calculation of iron requirement using Ganzoni's formula:
Total iron deficit (mg) = [target Hb – actual Hb (g/dL)] x body weight (kg) x 2.4 + 500 mg (depot iron)

Modified from Schaefer RM *et al*. *NephroNews* 8/2009

Disclosures

- Prof. Wanner has received consultancy fees and speaker's honoraria from Vifor Pharma Ltd and a research grant from Amgen

Disclosures

- Dr Macdougall has received consultancy fees and speaker's honoraria from Vifor Pharma Ltd and consultancy fees, speaker's honoraria and research grants from Affymax, Amgen, Ortho Biotech, Roche and Shire Pharmaceuticals

Programme

Iron and anaemia management in ND-CKD: where are we going?

Co-chairs: Christoph Wanner (Würzburg, Germany) and Iain Macdougall (London, UK)

Introduction

Anaemia management in ND-CKD: where are we?

Bernard Canaud (Montpellier, France)

Iron metabolism: where is the science taking us?

Iain Macdougall (London, UK)

Optimizing anaemia management: which is the right path?

Simon Roger (Gosford, Australia)

Discussion

Iron and anaemia management in ND-CKD: where are we going?

XLVII ERA-EDTA Congress

Munich, Germany
26 June 2010

Anaemia management in non-dialysis CKD: where are we?

Bernard Canaud, MD, PhD

Nephrology, Dialysis and Intensive Care Unit,

Lapeyronie University Hospital, Montpellier, France

Disclosures

- Professor Canaud has received speaker's honoraria and/or research grants from Amgen, Baxter, Fresenius Medical Care and Roche

Roadmap of presentation

- Anaemia is a frequent and severe comorbid complication that starts early in chronic kidney disease (CKD)
- Anaemia is not correlated with circulating erythropoietin (EPO) but is aggravated by iron deficiency
- Optimal haemoglobin (Hb) and iron indices targets are still under debate in CKD
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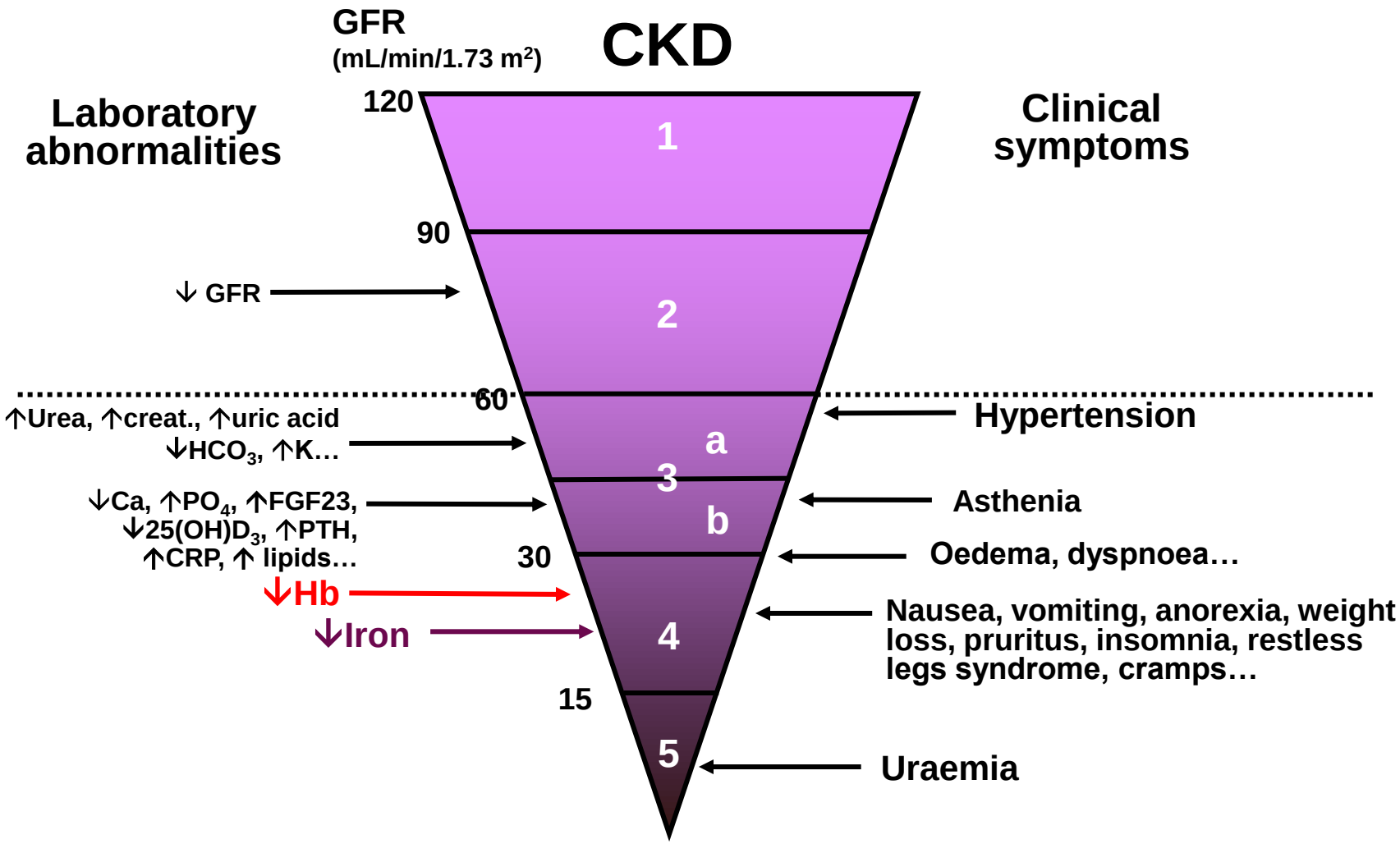
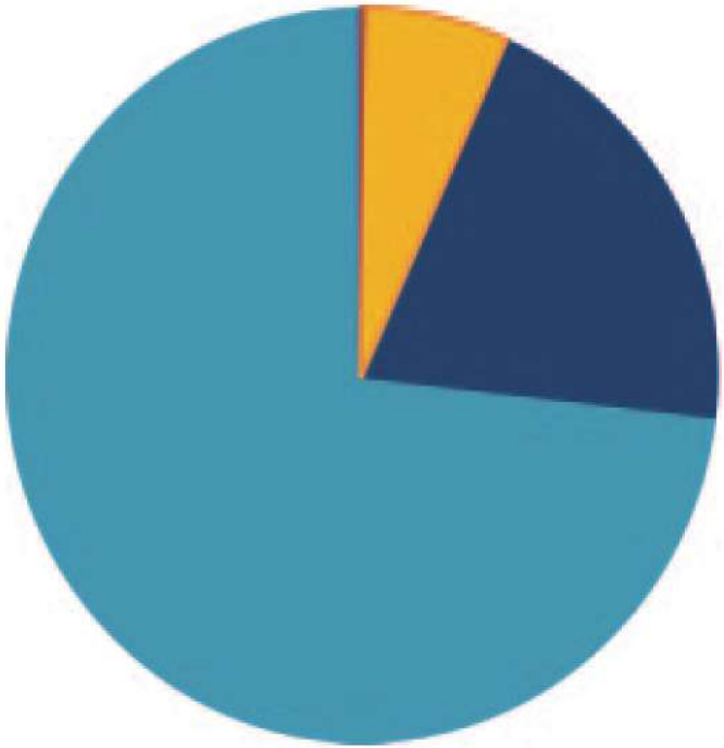
Natural history of CKD



Creat., creatinine; CRP, C-reactive protein; FGF, fibroblast growth factor; GFR, glomerular filtration rate; PTH, parathyroid hormone

Prevalence of CKD in the US general population



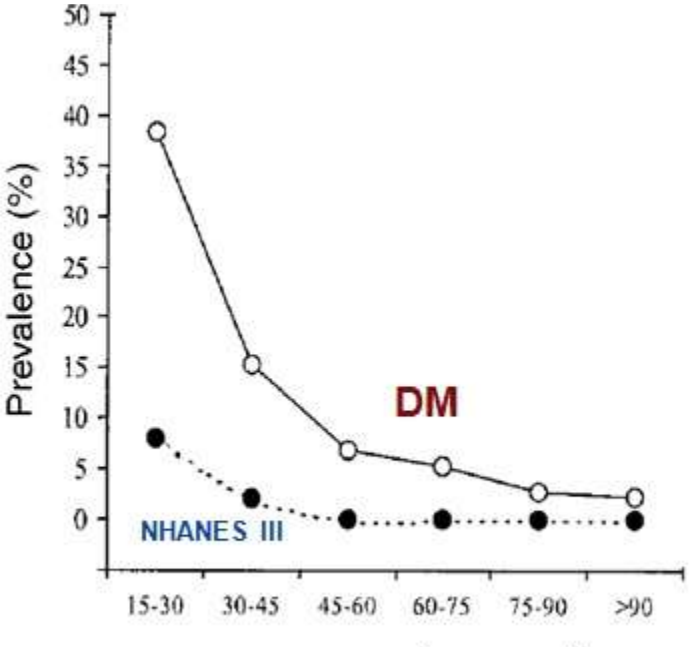
NHANES III 1988–1994
NHANES 2-yr datasets from 1999-2004
n=62437

NHANES, National Health and Nutritional Examination Survey

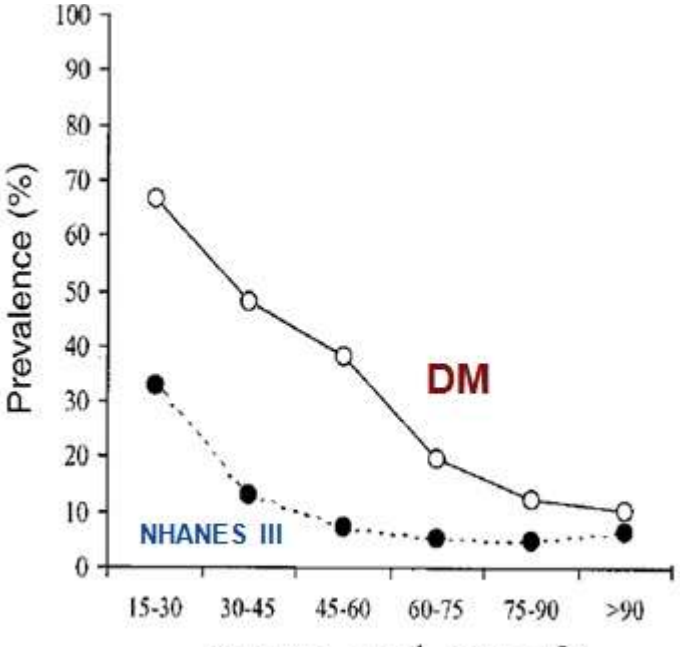
Fishbane S *et al*. *Clin J Am Soc Nephrol* 2009;4:57–61

Anaemia starts earlier in patients with diabetes

Males



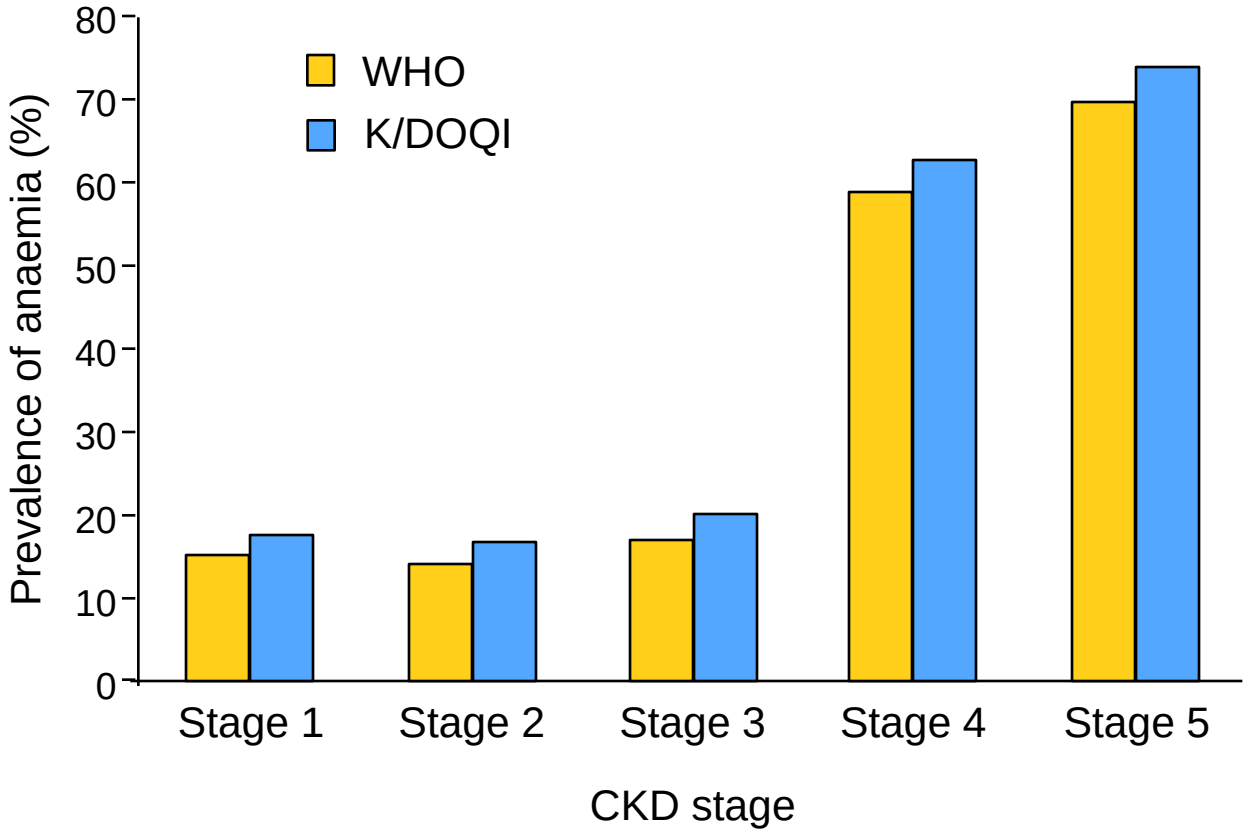
Females



NHANES, National Health and Nutrition Examination Survey
DM, diabetes mellitus; MDRD, Modification of Diet in Renal Disease

Thomas MC *et al*. *Diabetes Care* 2003;26:1164–9

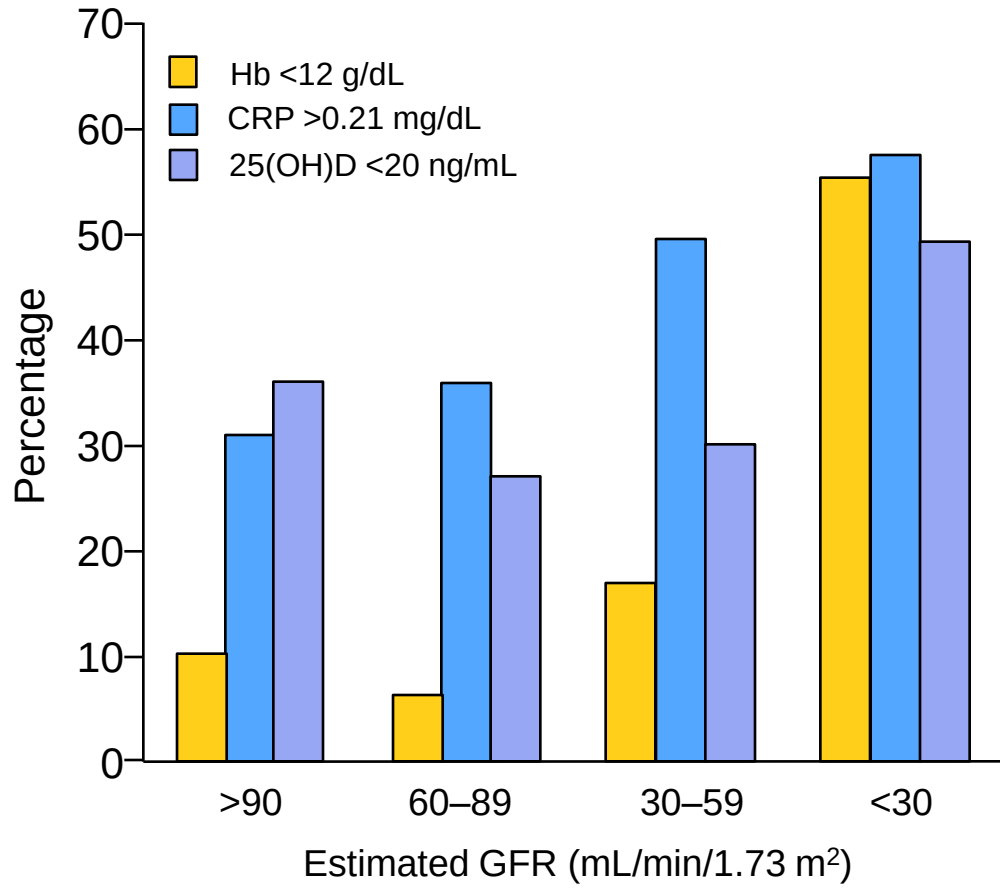
Prevalence of anaemia in CKD increases sharply after stage 4 (GFR <30 mL/min/1.73 m^2) in KEEP study



KEEP, Kidney Early Evaluation Program.
K/DOQI, Kidney Disease Outcomes Quality Initiative;
WHO, World Health Organization

McFarlane SI *et al*. *Am J Kidney Dis* 2008;51(Suppl 2):S46–55

Prevalence of 25(OH)D_3 deficiency, inflammation and anaemia is associated with CKD progression

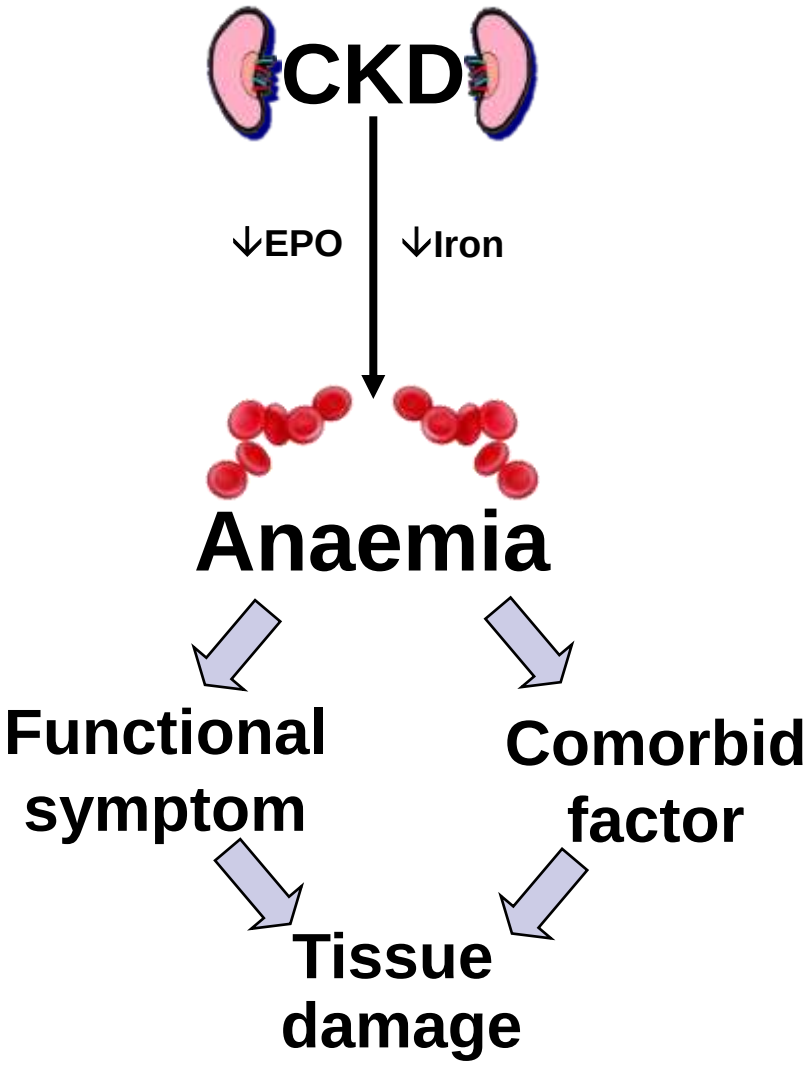


NHANES III 1988–1994

NHANES, National Health and Nutritional Examination Survey

Kendrick J *et al*. *Am J Nephrol* 2009;30:64–72

Anaemia amplifies CKD disease complications



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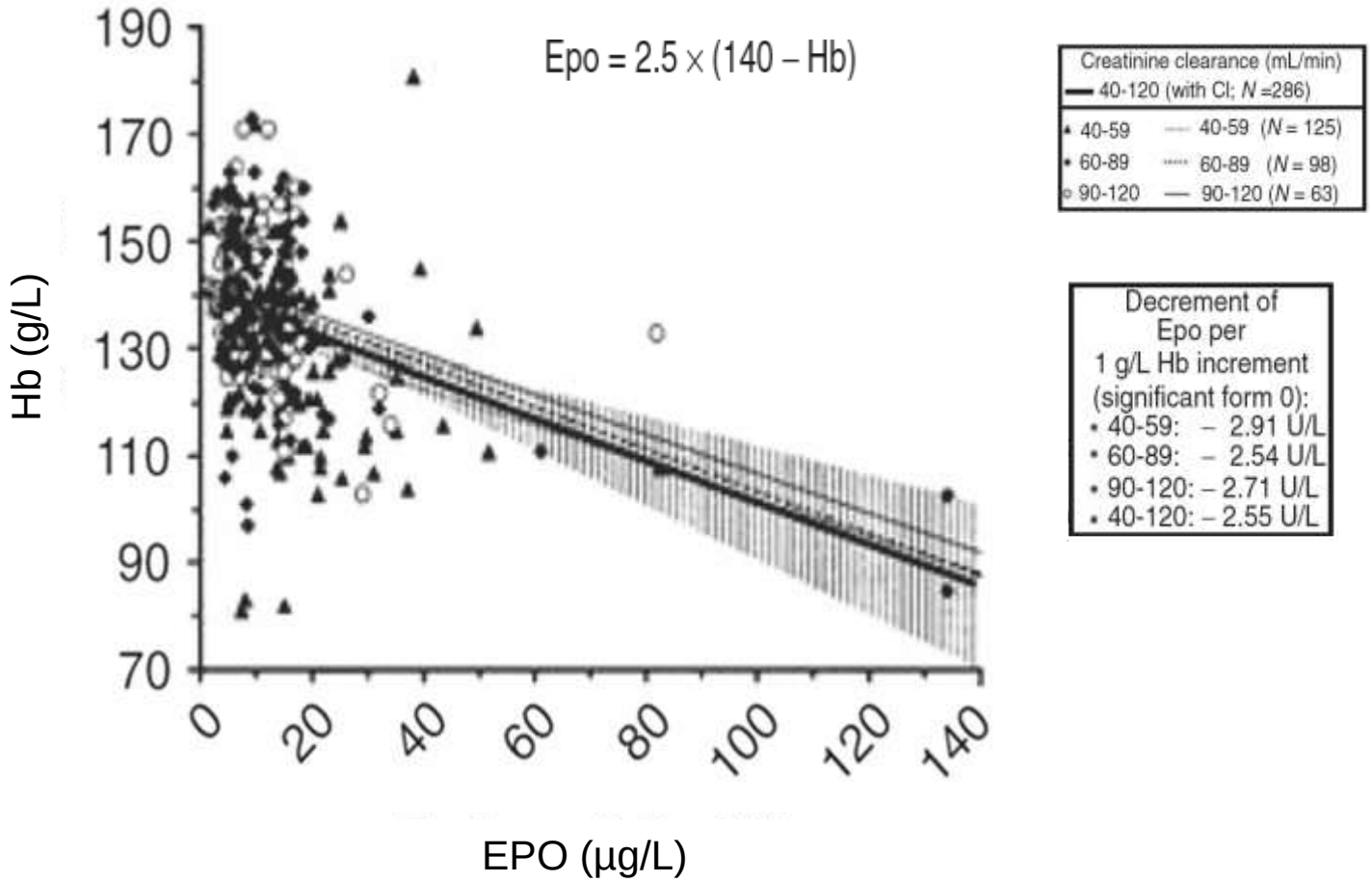
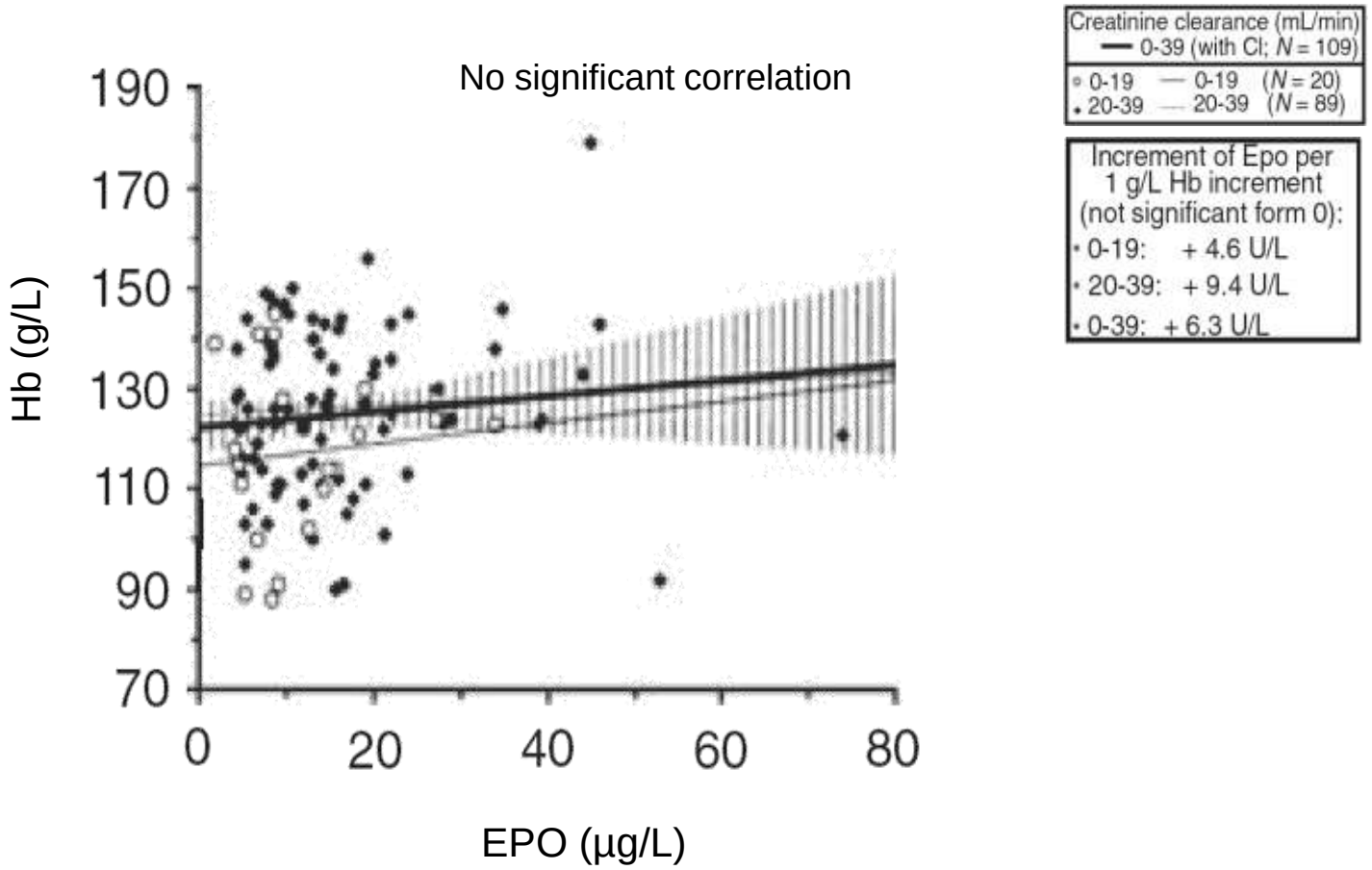
Hb concentrations are not linearly correlated to EPO levels in patients with CKD stages 1–3



Swiss cohort
1490 patients with CKD

Fehr T *et al*. *Kidney Int* 2004;66:1206–11

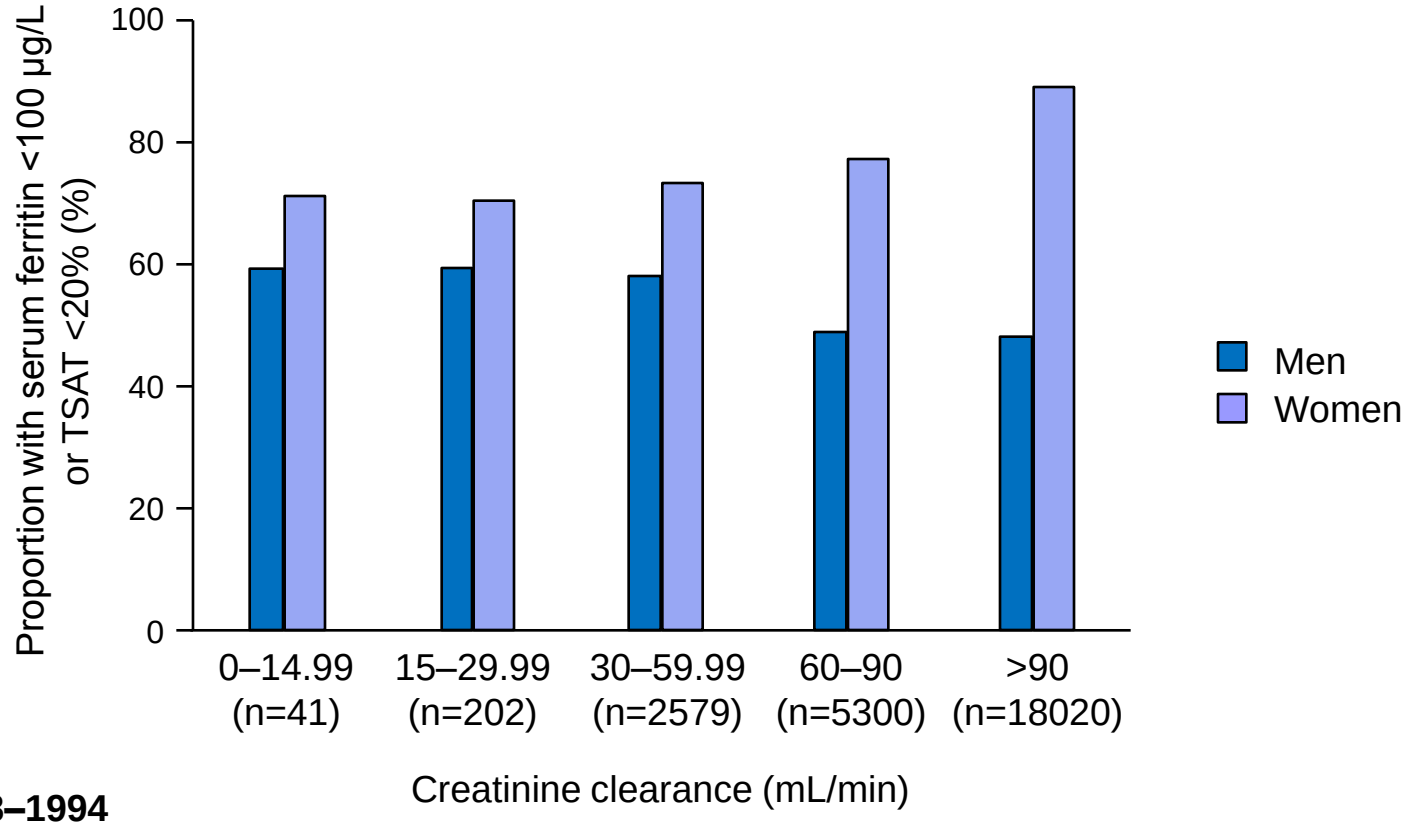
Hb concentrations are not linearly correlated to EPO levels in patients with CKD stages 4–5



Swiss cohort
1490 patients with CKD

Fehr T *et al*. *Kidney Int* 2004;66:1206–11

Prevalence of absolute iron deficiency increases with CKD progression



NHANES III 1988–1994
NHANES 2-yr datasets from 1999-2004
n=62437
Iron deficiency: Men: 57.8–58.8%; Women: 69.9–72.8%

NHANES, National Health and Nutritional Examination Survey. TSAT, transferrin saturation

Fishbane S *et al*. *Clin J Am Soc Nephrol* 2009;4:57–61

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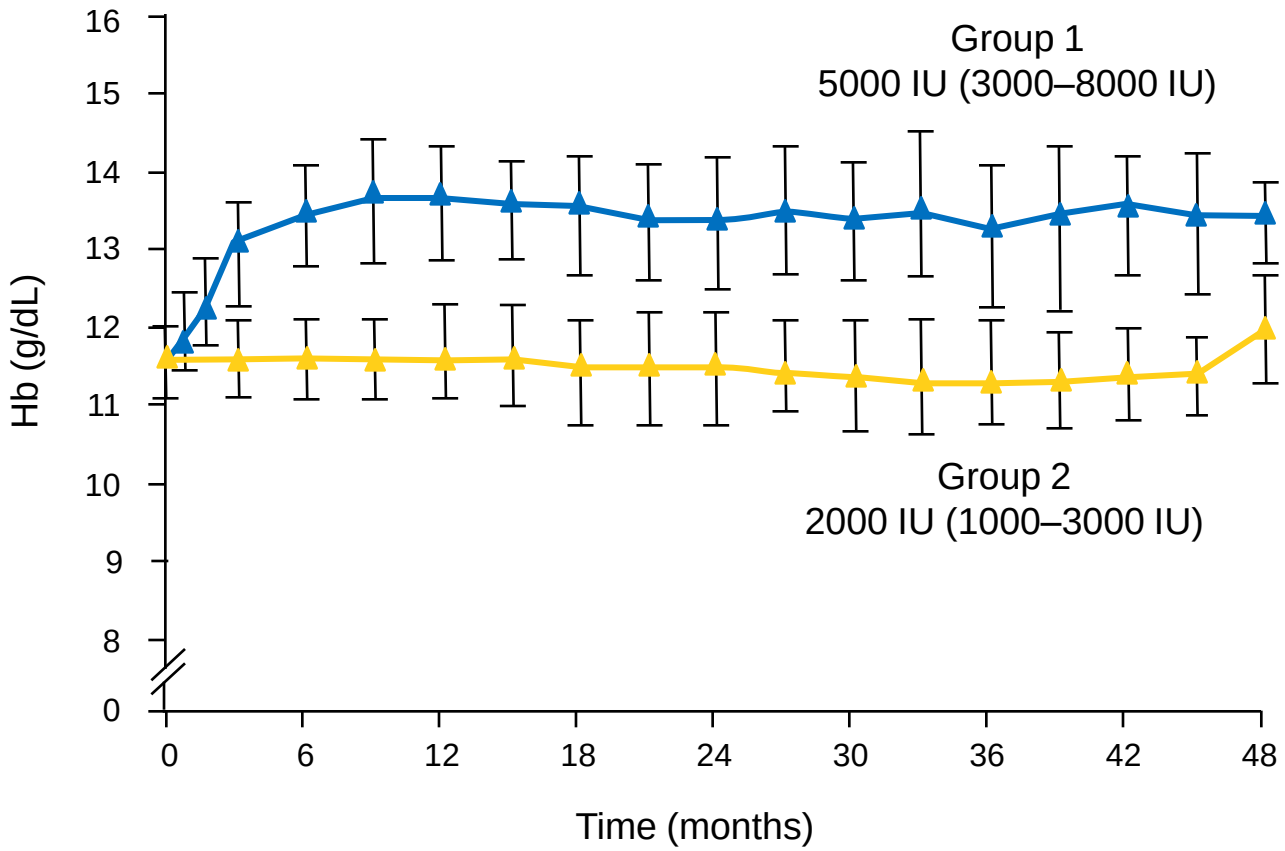
Toward universal recommendations: EBPG 2004–2007, ERBP 2009…

Hb target recommendations have changed over the past few years

EBPG 2004		≥11.0 g/dL (Ht >33%) with personal adaptation >12 g/dL not recommended with diabetes or heart failure >14 g/dL 'undesirable' in HD
ERBP 2009		≤11.0 and <13 g/dL (not intentionally >13 g/dL)
NKF-K/DOQI	2001	11–12 g/dL
	2006	≤11.0 and >13 g/dL not recommended
NKF-K/DOQI 2007		≤11.0 and <13 g/dL
NKF-K/DOQI 2009		≤10.5 and <12 g/dL

EBPG, European Best Practice Guidelines; ERBP, European Renal Best Practice; HD, haemodialysis; Ht, haematocrit; NKF, National Kidney Federation

Normalization of Hb may be easily achieved in non-dialysis CKD management with ESA and iron



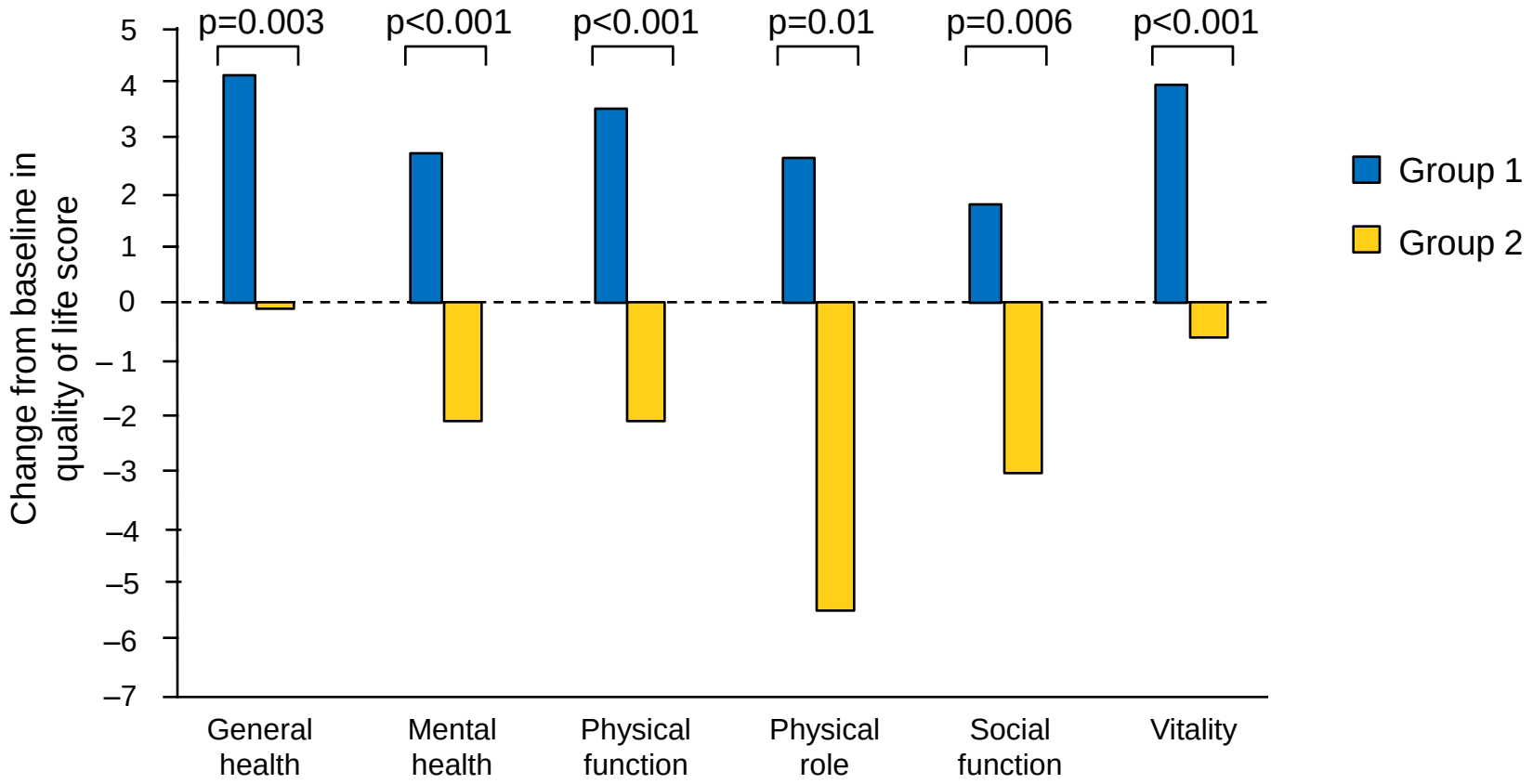
CREATE study

Randomized controlled trial (RCT), CKD3–5, 1/1 ESA conv/norm

ESA, erythropoiesis-stimulating agent

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

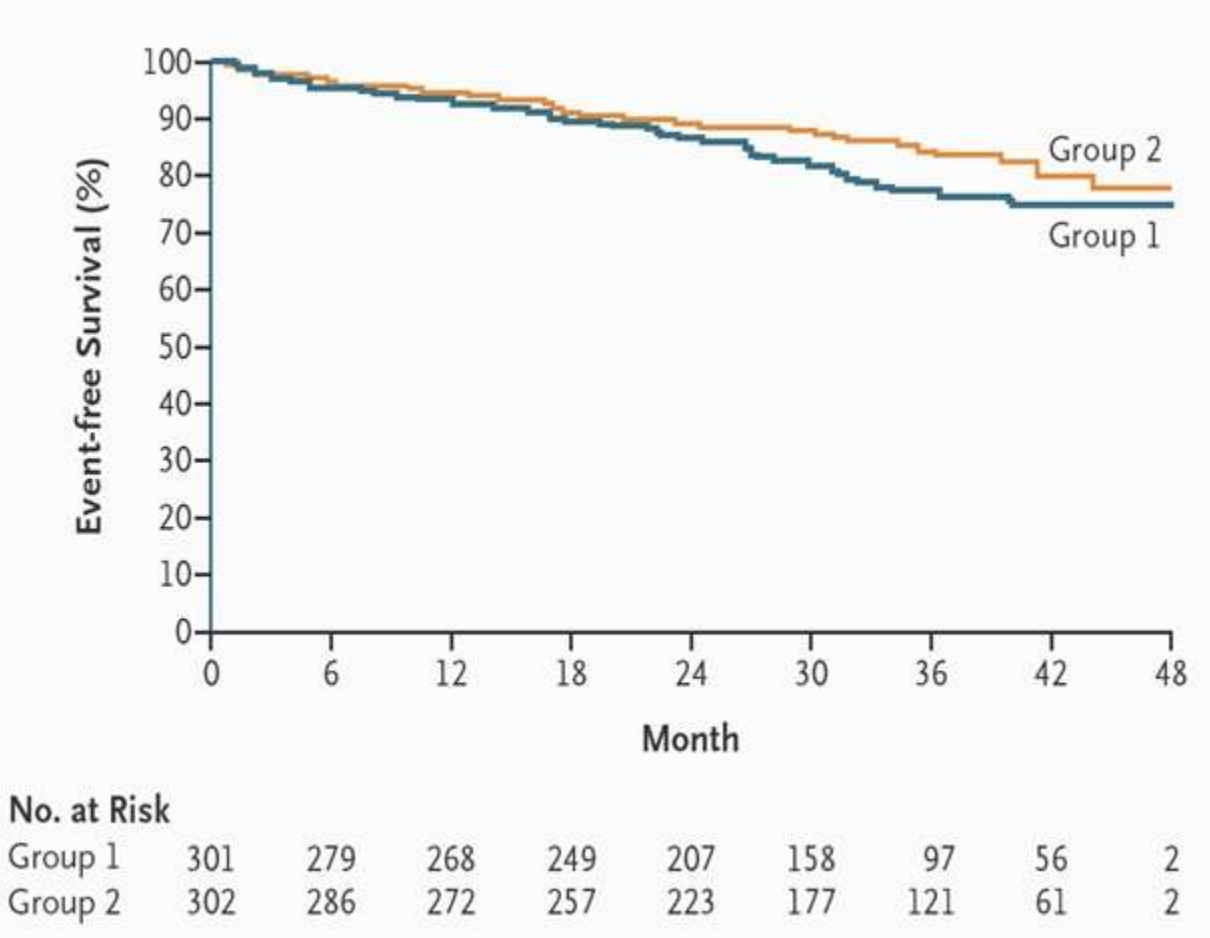
Normalization of anaemia in CKD has a positive impact on quality of life (all components)



CREATE study RCT, CKD3–5, 1/1 ESA conv/norm

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

But, normalization of anaemia in CKD has no significant impact on survival and CV events

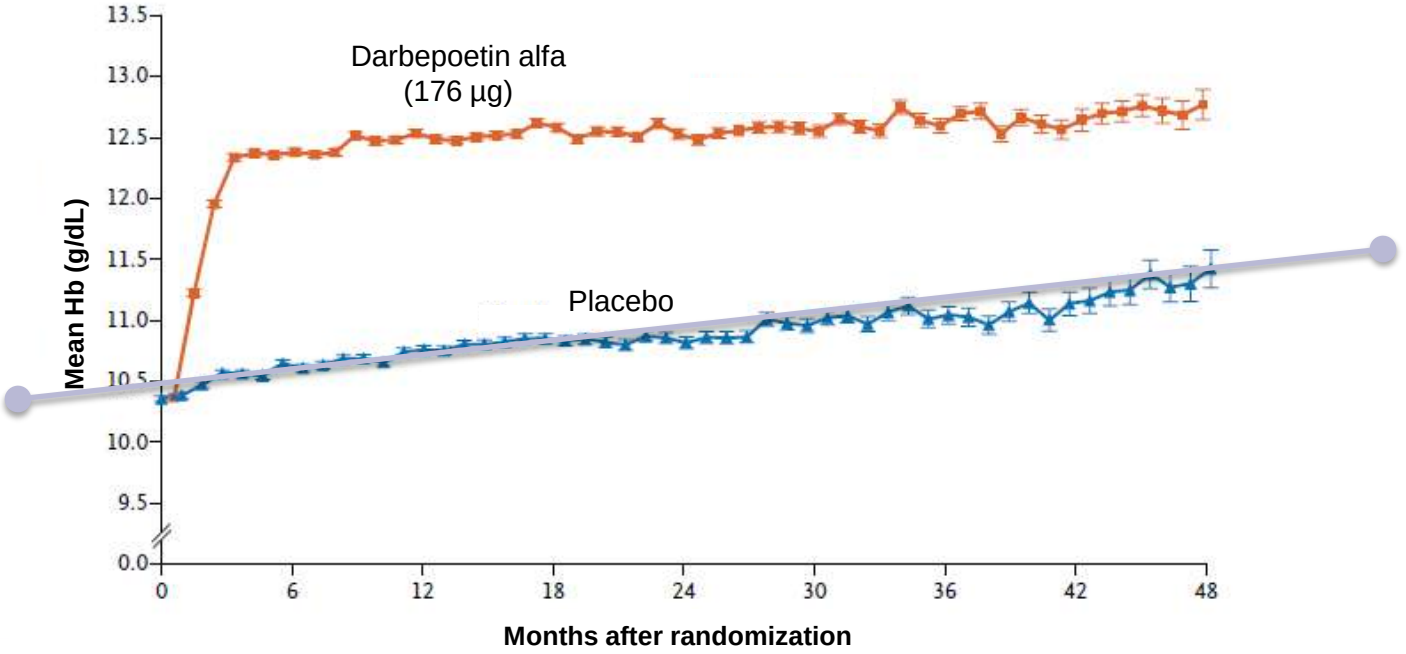


CREATE study RCT, CKD3–5, 1/1 ESA conv/norm

CV, cardiovascular

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

TREAT Study: Hb response to ESA



No. of patients

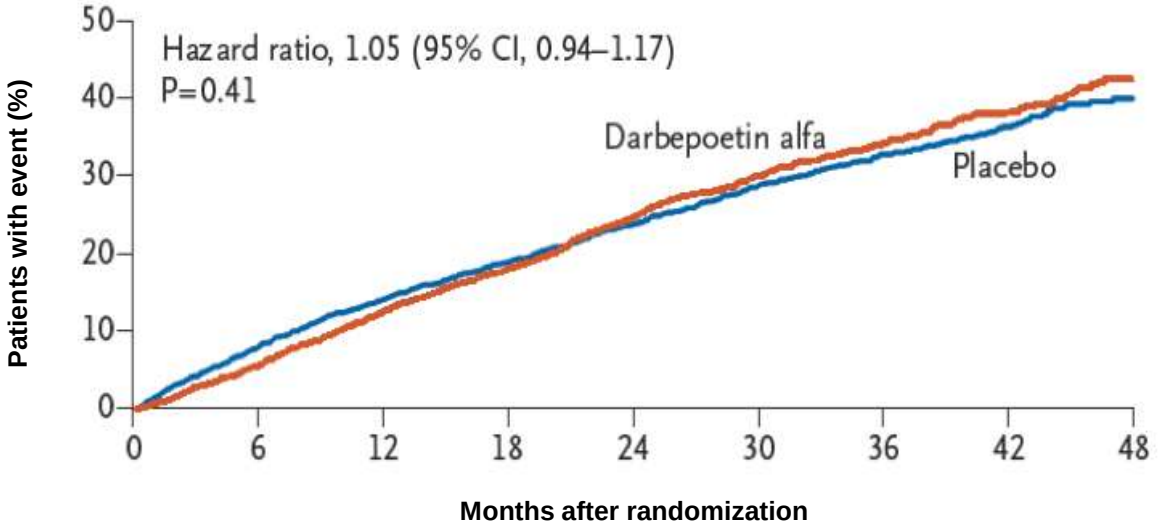
Darbepoetin alfa	2004	1768	1503	1300	946	635	404	253	97
Placebo	2019	1742	1460	1221	887	620	356	216	79

TREAT study

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

Complete correction of anaemia does not improve CV mortality in patients with CKD and diabetes

CV composite endpoint

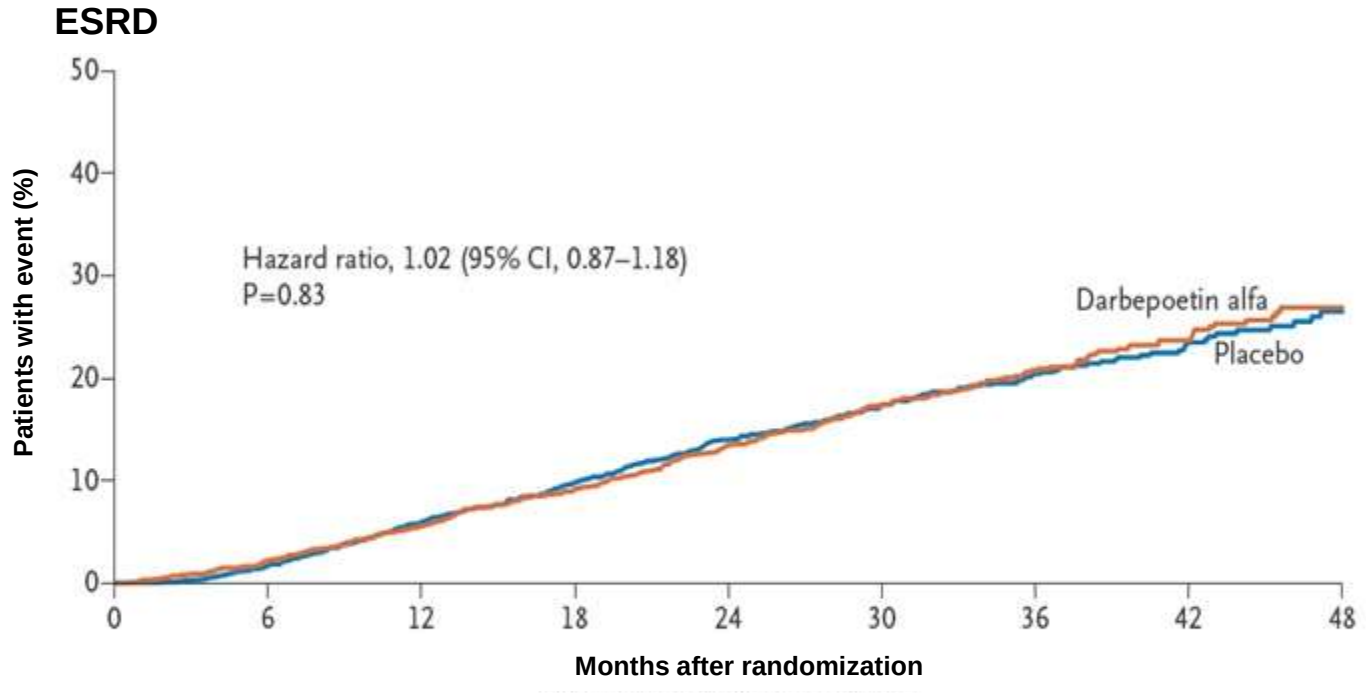


No. at risk

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

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

Complete correction of anaemia does not delay ESRD in patients with CKD and diabetes



No. at risk

Darbepoetin alfa	2012	1908	1755	1527	1187	802	535	296	129
Placebo	2026	1907	1729	1491	1162	811	513	292	115

ESRD, end-stage renal disease

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

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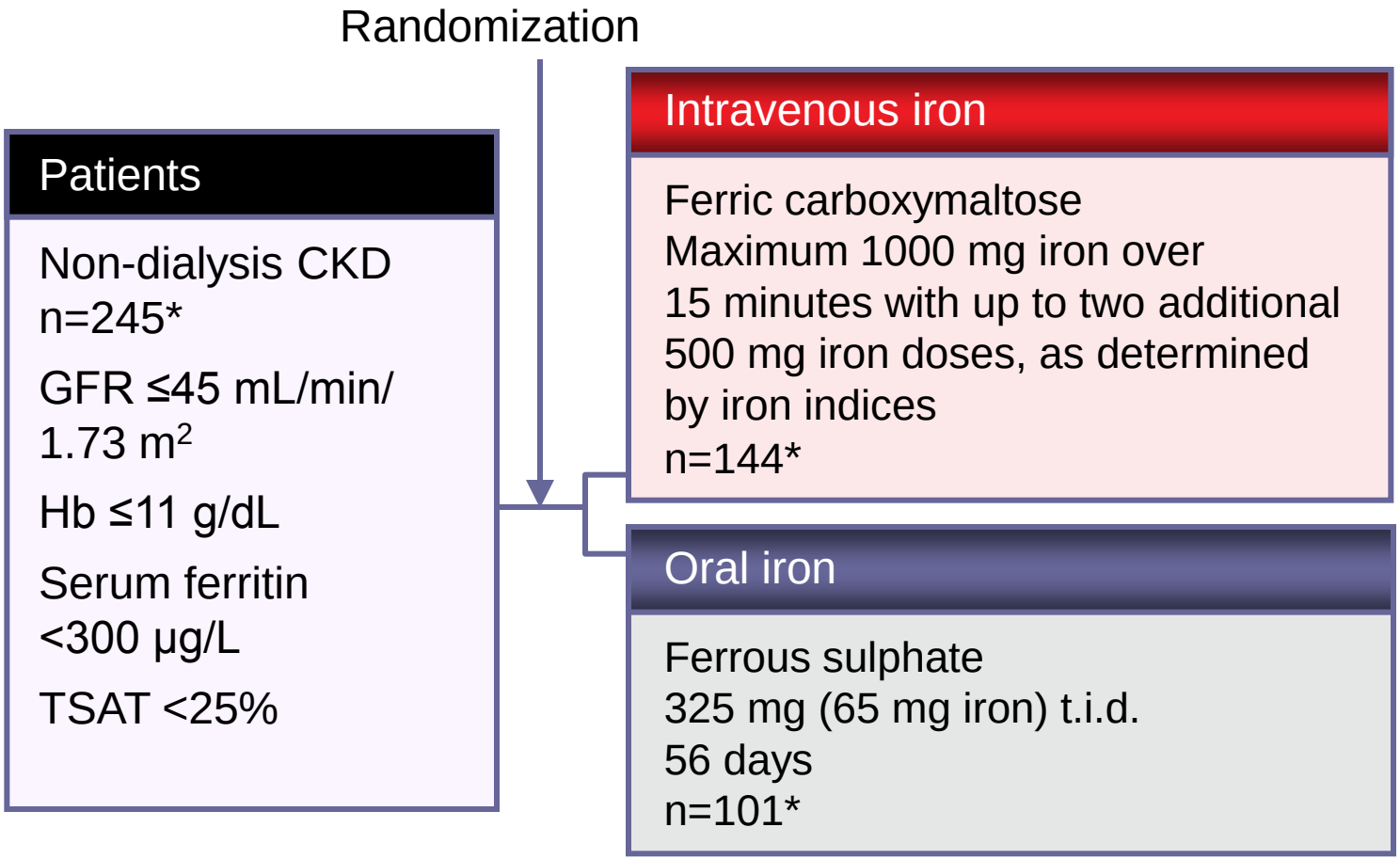
Efficacy of i.v. ferric carboxymaltose vs oral iron in patients non-dialysis CKD and diabetes

Randomized, multicentre, open-label study

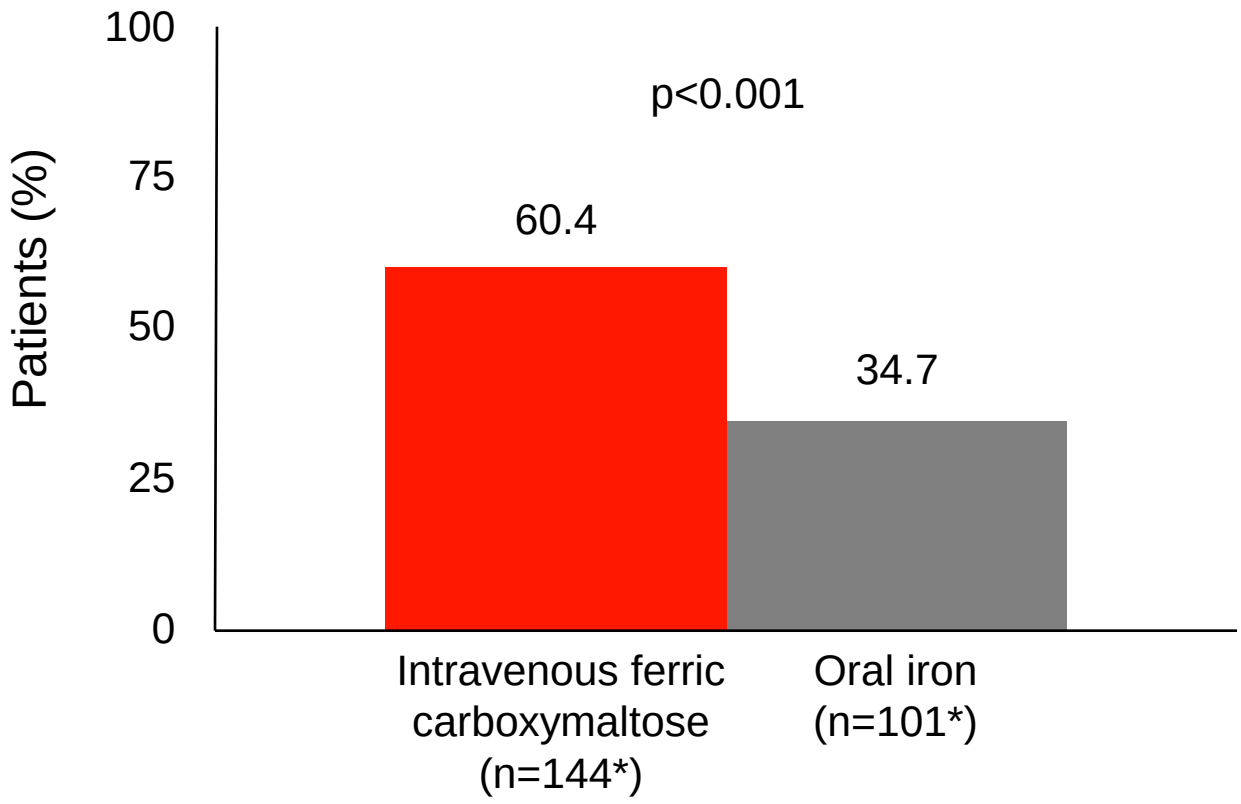


* Modified intent-to-treat population

Benjamin J. World Congress of Nephrology 2009, Abstract M574

Efficacy is greater with of i.v. ferric carboxymaltose vs oral iron

- Patients achieving Hb increase ≥1 g/dL at any time during the study (%); 56 days duration



* Modified intent-to-treat population

Benjamin J. World Congress of Nephrology 2009, Abstract M574

Efficacy and tolerability profile of i.v. ferric carboxymaltose vs oral iron

	Intravenous ferric carboxymaltose (n=147)*	Oral iron (n=103)*
Hb increase >1g/dL	60.4%	34.7%
Mean change to highest Hb	1.3 g/dL	0.8 g/dL
Mean increase in Hb by day 42	1.0 g/dL	0.5 g/dL
Incidence of adverse events	2.7%	26.2%
Serious adverse events or hypotensive episodes	0	0

* Safety population

Benjamin J. World Congress of Nephrology 2009, Abstract M574

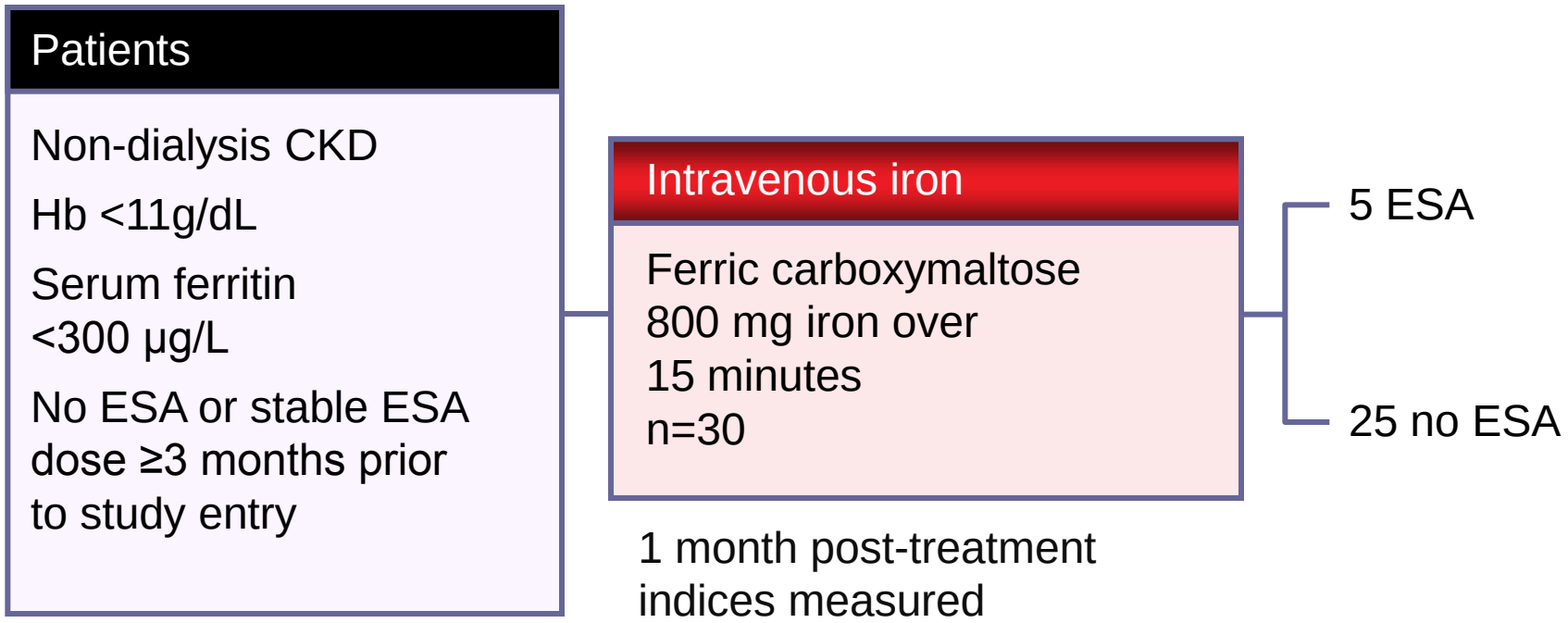
Overview of results: Benjamin *et al*., 2009

- I.V. ferric carboxymaltose showed significantly greater efficacy compared with oral iron in patients with non-dialysis CKD with anaemia and low iron indices
  - A significantly greater proportion of patients achieved an Hb increase >1 g/dL (60.4% vs 34.7%, $p<0.001$)
- There was a markedly lower incidence of adverse events with i.v. ferric carboxymaltose vs oral iron (2.7% vs 26.2%)
  - No serious adverse events or hypotensive episodes occurred

Benjamin J. World Congress of Nephrology 2009, Abstract M574

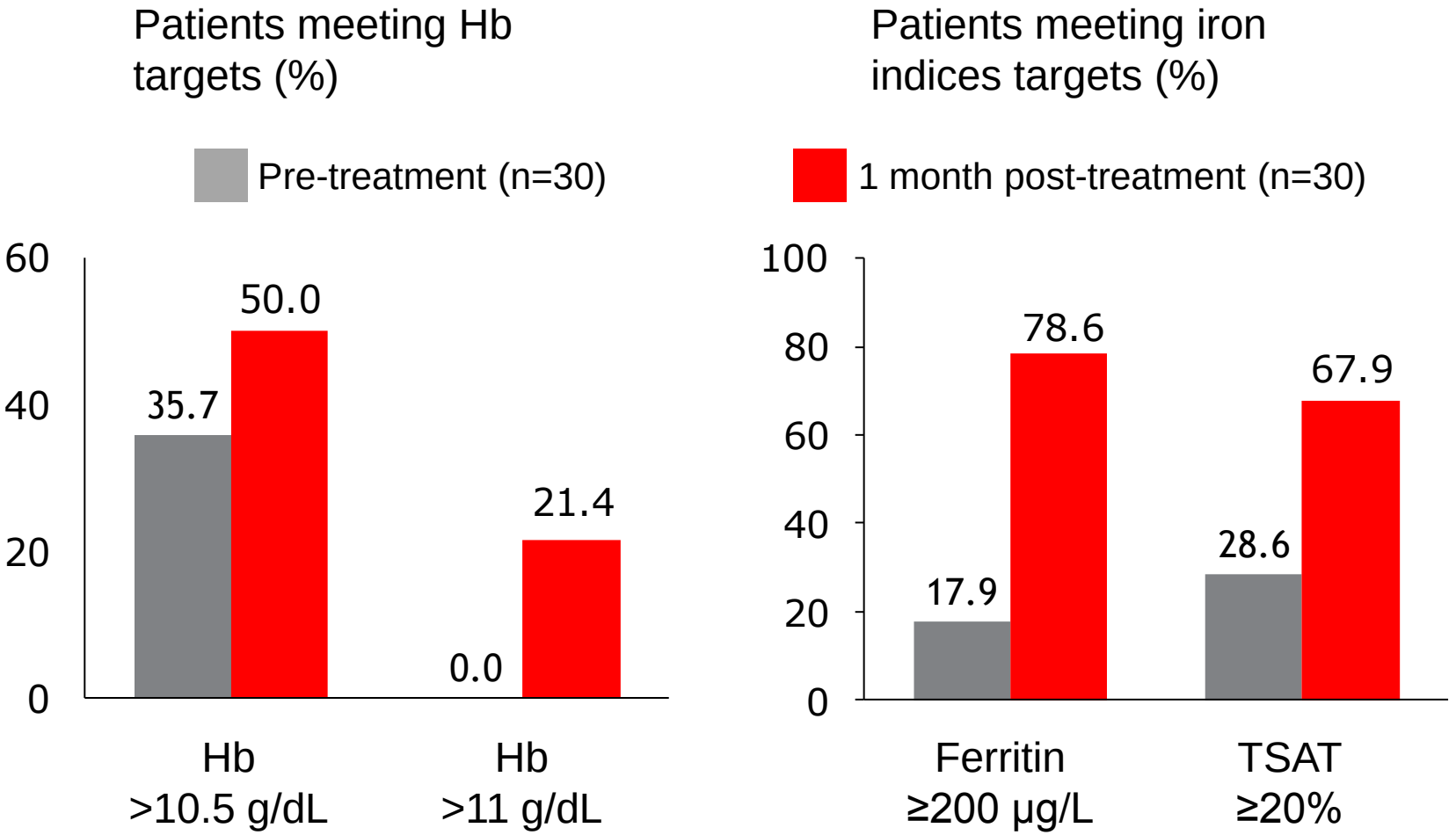
Single-dose i.v. iron in non-dialysis CKD

Single-arm, single-centre study



Tagboto S *et al. J Ren Care* 2009;35:18–23

Single-dose i.v. iron is effective in patients with non-dialysis CKD



Tagboto S *et al. J Ren Care* 2009;35:18–23

Overview of results: Tagboto *et al*., 2009

- One month after a single 15-minute infusion of 800 mg iron as ferric carboxymaltose (25/30 patients did not receive ESA):
  - Hb levels increased in 80% of patients, did not change in 3% and fell slightly in 17%
  - The mean Hb level increased by 0.73 g/dL (0.53 g/dL after 2 weeks)
  - Only two patients reported minor side-effects (metallic taste in the mouth and discomfort at the infusion site)
- Authors' conclusion: *"Intravenous ferric carboxymaltose administration in predialysis patients rapidly improves Hb levels in the majority of patients after 2 weeks with a further small increase at 1 month"*

Tagboto S *et al. J Ren Care* 2009;35:18–23

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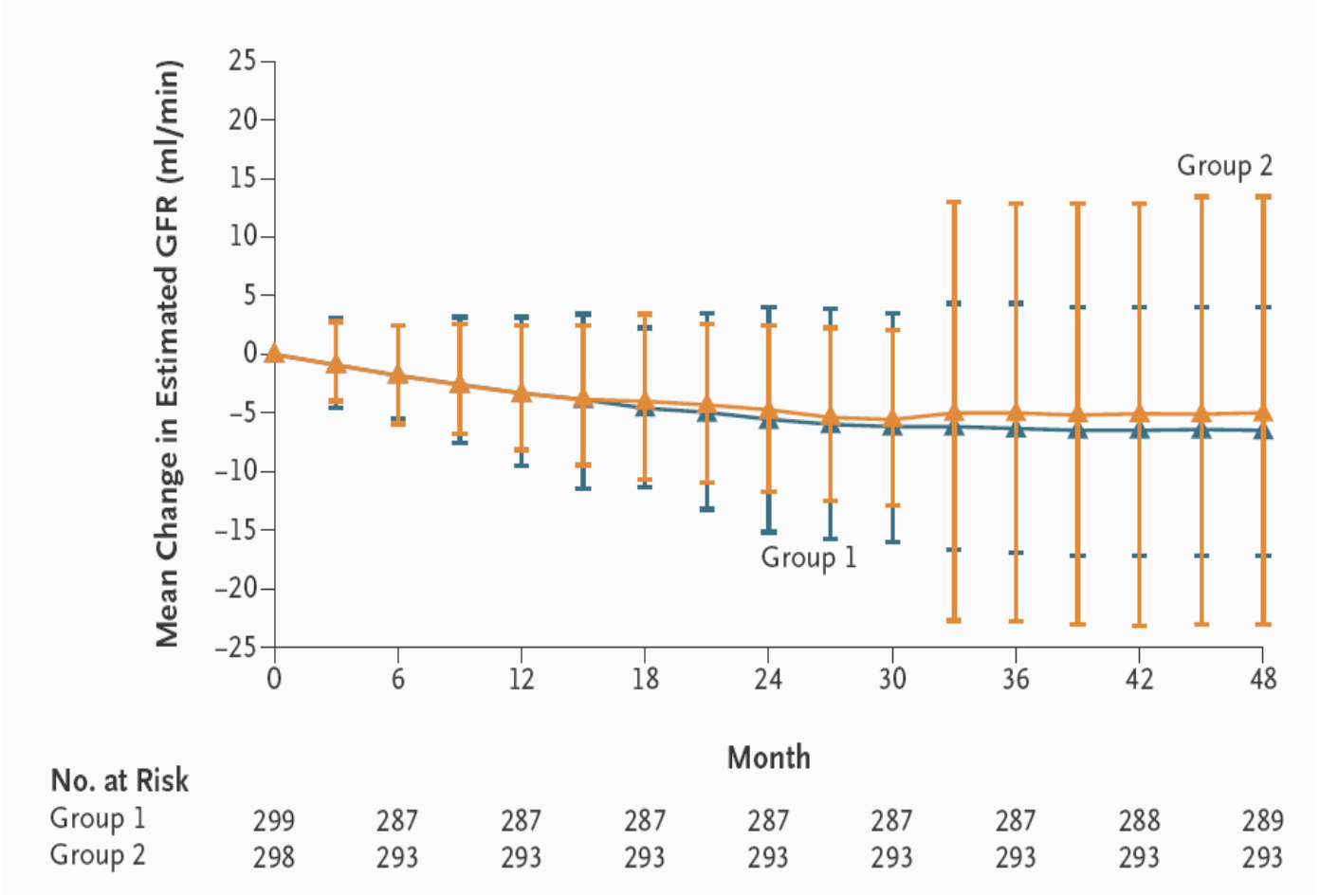
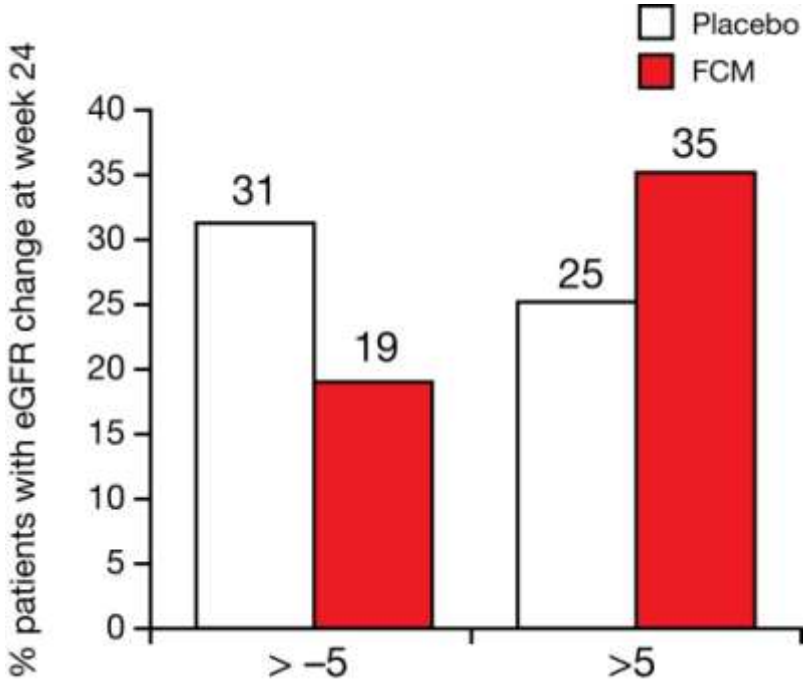
Anaemia correction with epoetin beta does not precipitate CKD progression



CREATE study RCT, CKD3–5, 1/1 ESA conv/norm

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

Impact of i.v. FCM on renal function
Categorized by change in mL/min/1.73 m^2 at week 24

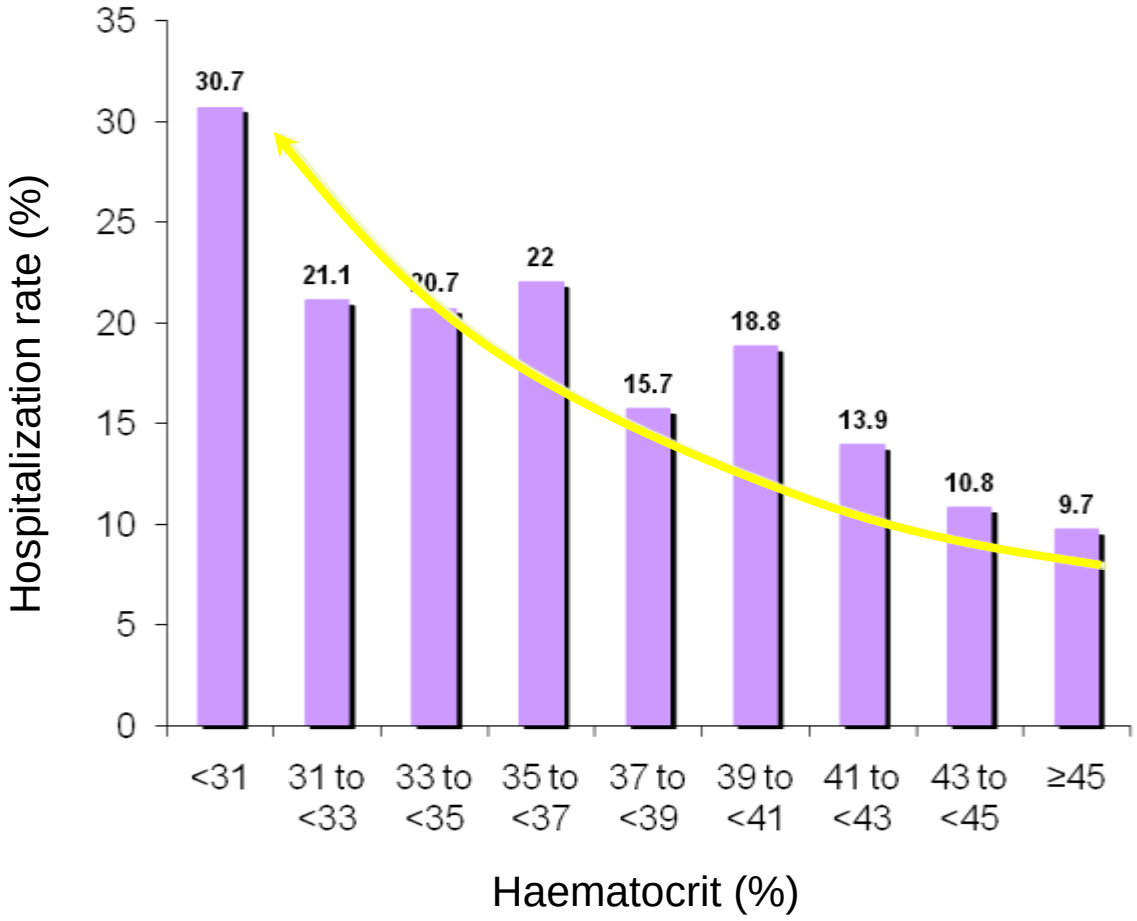


Change in eGFR from baseline (mL/min/1.73 m^2)

- 35% of FCM patients experienced >5 mL/min/1.73 m^2 change vs 25% for placebo

Ponikowski P *et al.* HFA Congress 2010; Abstract 114 & LBT Oral Presentation

Anaemia increases the risk of hospitalization in paediatric patients with CKD

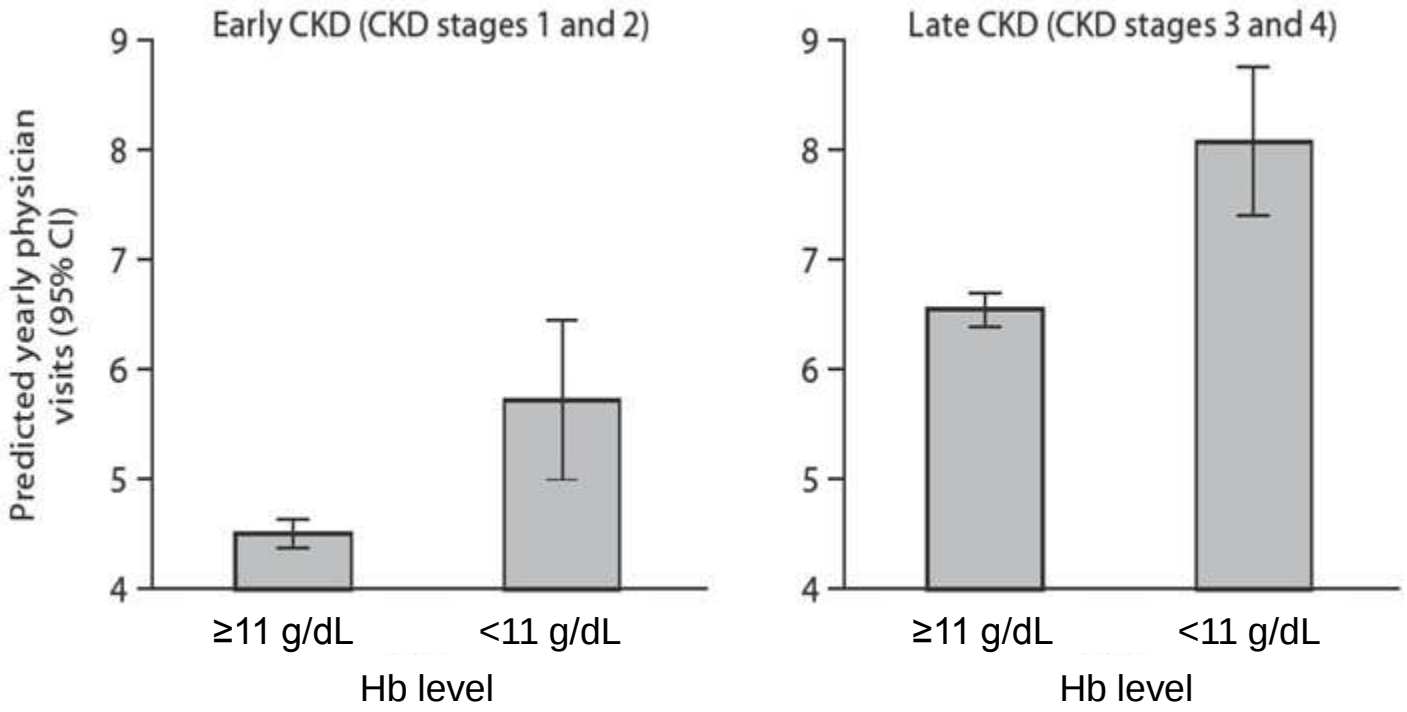


n=2779 paediatric patients with CKD
Prospective database registry

Staples AO *et al*. *Clin J Am Soc Nephrol* 2009;4:48–56

Anaemia increases consumption of health care resources (physician visits) in patients with CKD

Yearly physician visits



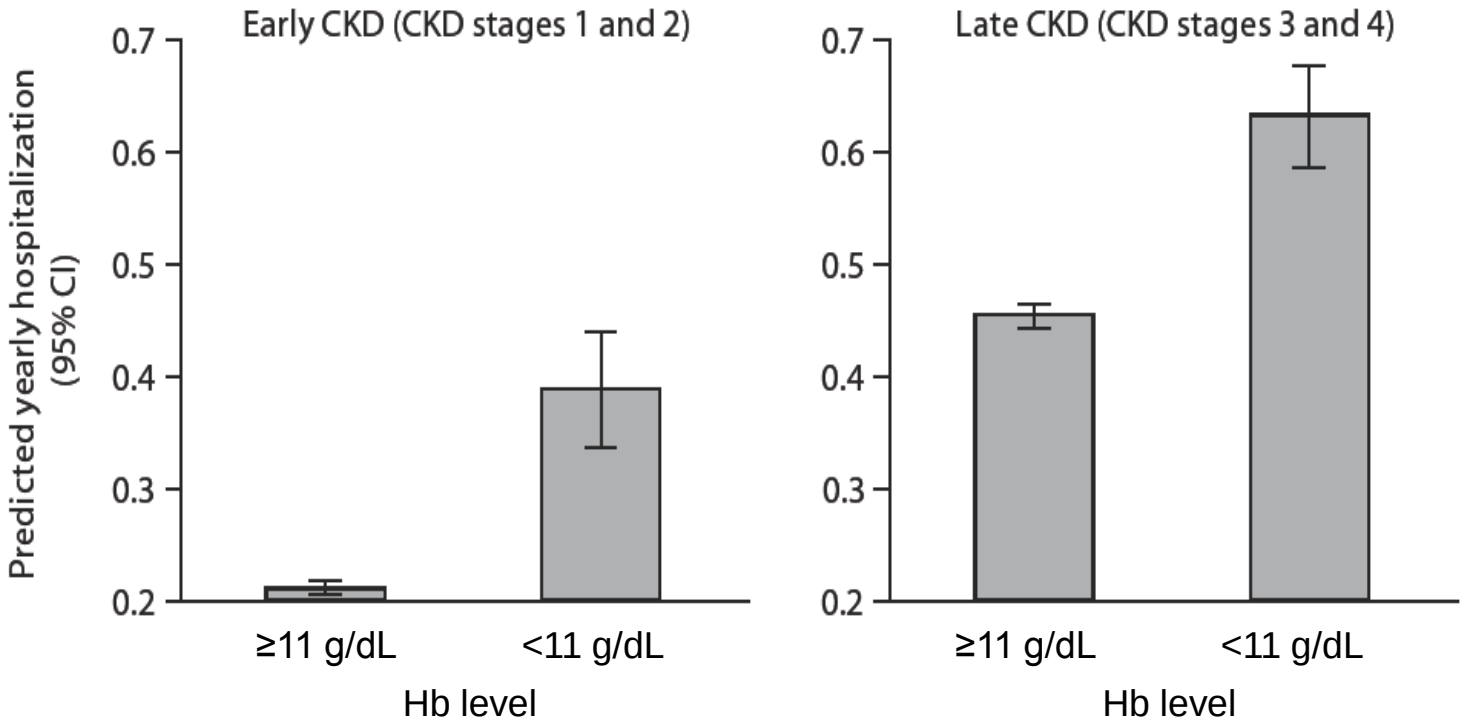
NHANES III 1988–1994

NHANES, National Health and Nutritional Examination Survey

Alexander M *et al*. *Am J Nephrol* 2009;29:473–82

Anaemia increases consumption of health care resources (hospitalization) in patients with CKD

Yearly hospitalization



NHANES III 1988–1994

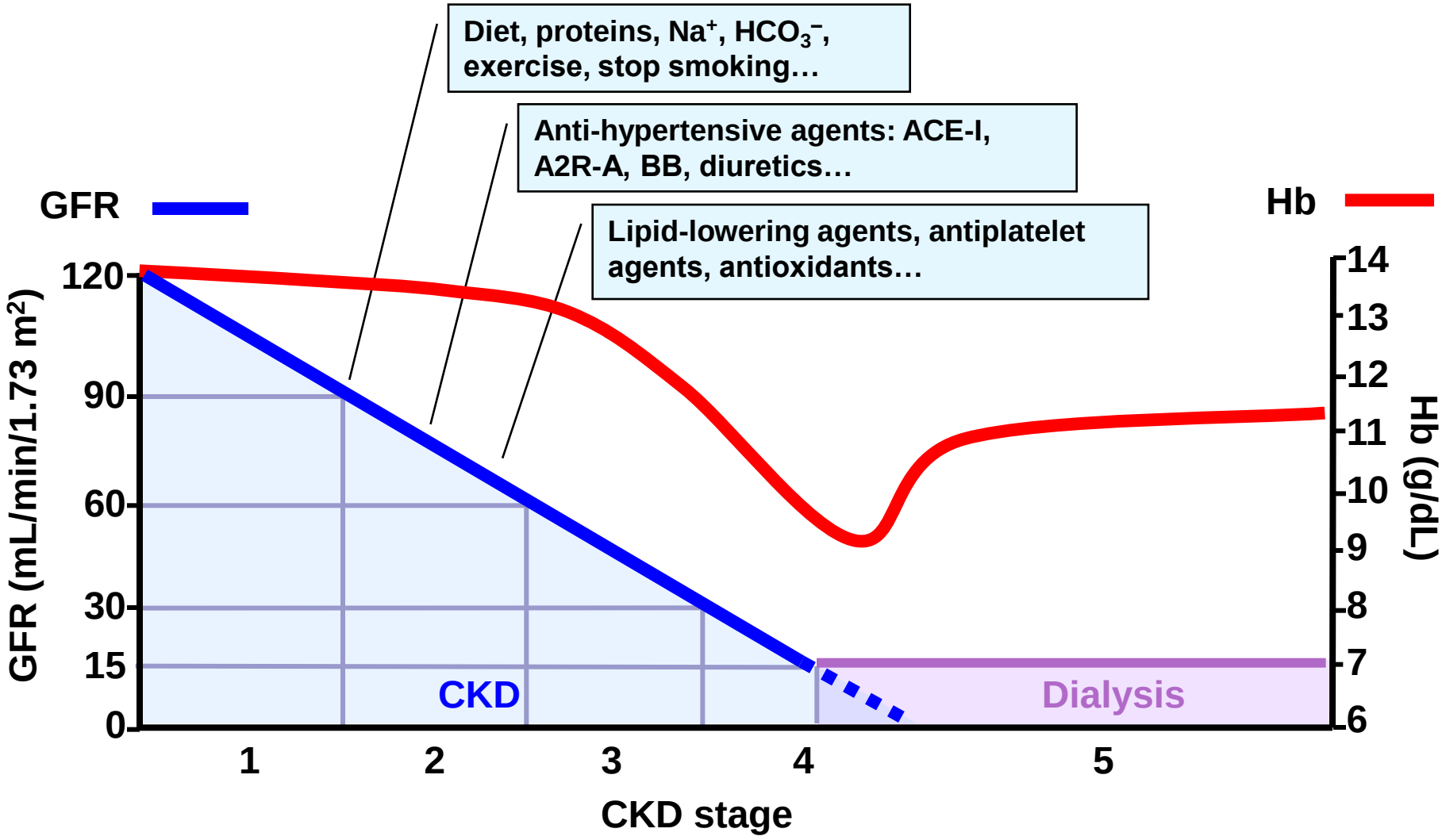
NHANES, National Health and Nutritional Examination Survey

Alexander M *et al. Am J Nephrol* 2009;29:473–82

Roadmap of presentation

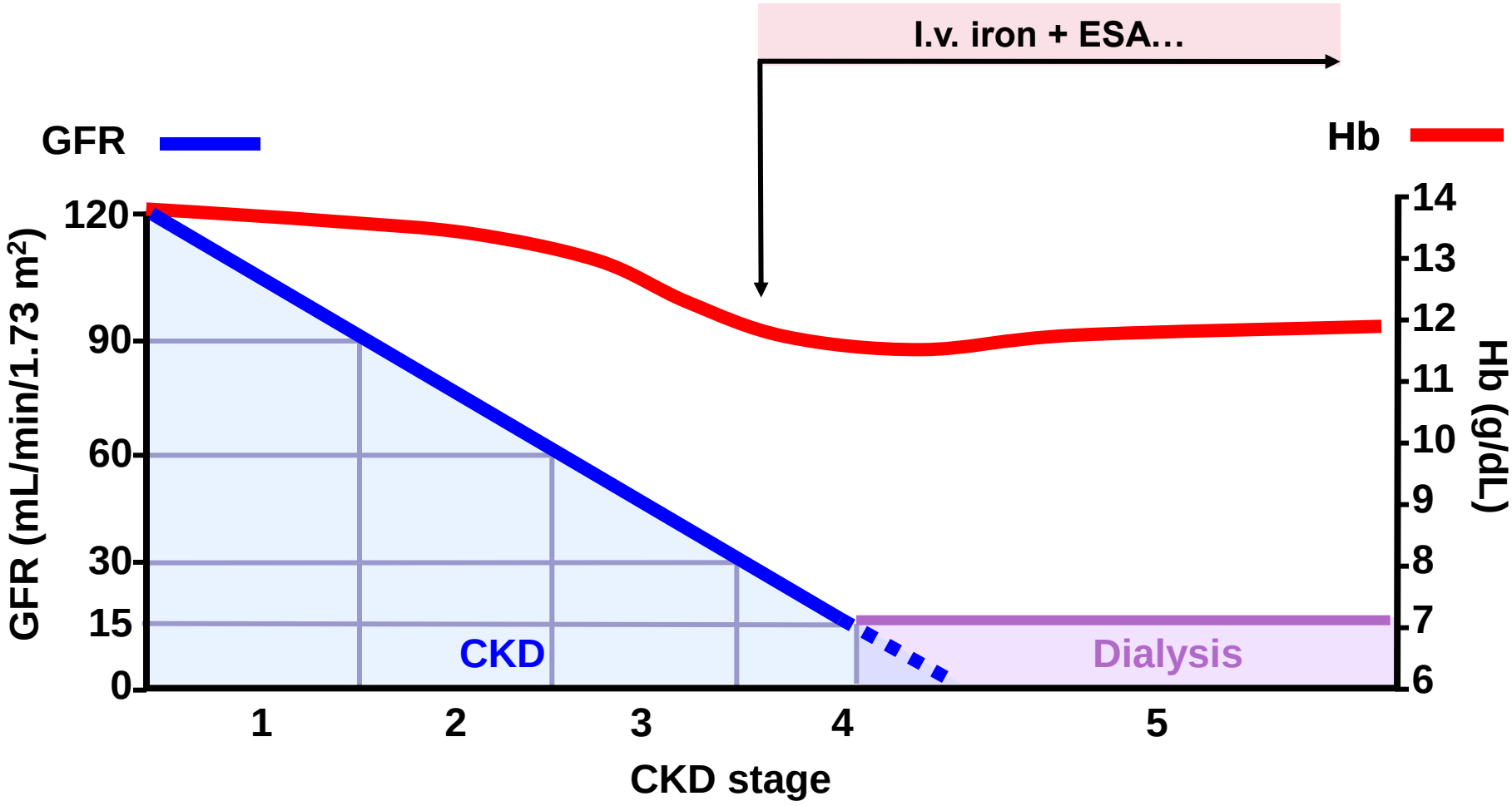
- Anaemia is a frequent and severe comorbid complication that starts early in chronic kidney disease (CKD)
- Anaemia is not correlated with circulating erythropoietin (EPO) but is aggravated by iron deficiency
- Optimal haemoglobin (Hb) and iron indices targets are still under debate in CKD
- Intravenous (i.v.) iron is effective and well-tolerated in patients with non-dialysis CKD
- Correction of anaemia and iron deficiency is a part of renal protective action and decreased morbidity in patients with CKD
- Early correction of anaemia is appropriate in patients with non-dialysis CKD

Management of patients with non-dialysis CKD usually consists of nephroprotection



ACE-I, angiotensin converting enzyme inhibitor; A2RA , angiotensin 2 receptor antagonist; BB, beta-blocker

Today, optimal care of patients with non-dialysis CKD should correct anaemia and iron deficiency

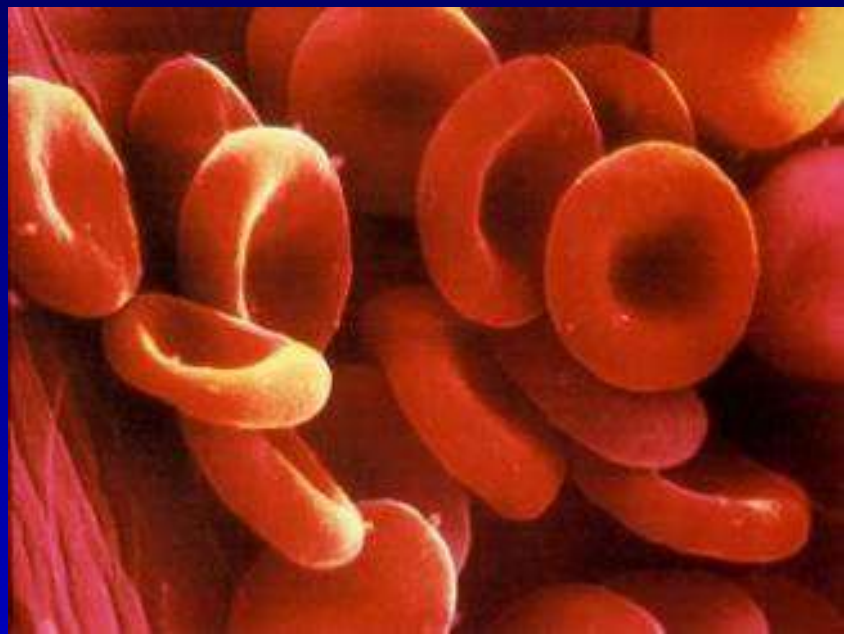


Iron metabolism: where is the science taking us?

Dr Iain C. Macdougall, MD

King's College Hospital, London

UK



Disclosures

- Dr Macdougall has received consultancy fees and speaker's honoraria from Vifor Pharma Ltd and consultancy fees, speaker's honoraria and research grants from Affymax, Amgen, Ortho Biotech, and Roche

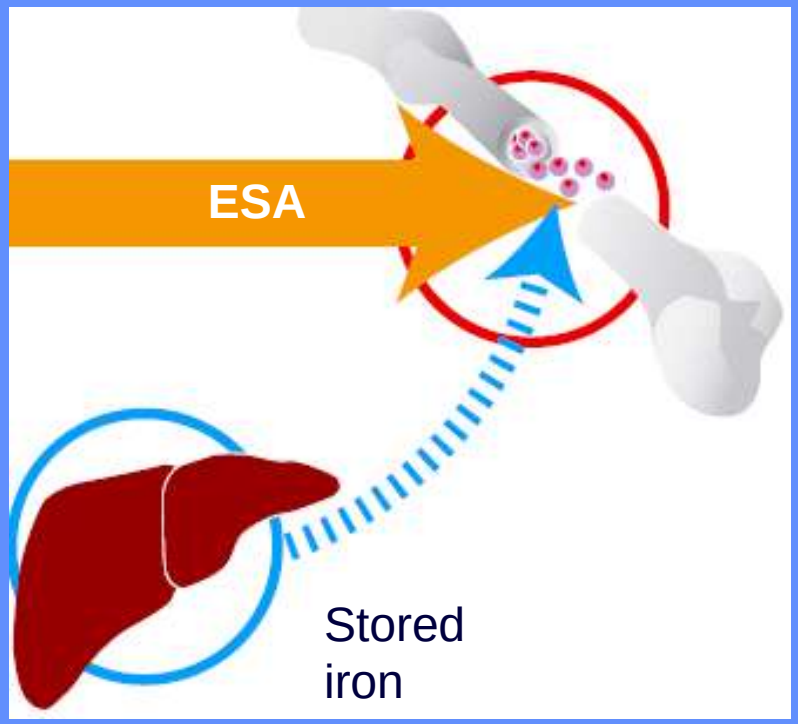
Questions regarding iron metabolism in chronic kidney disease (CKD)

- Why are patients with CKD prone to developing iron deficiency?
- How can we best detect iron deficiency?
- How can we best treat iron deficiency?

Why are patients with CKD prone to developing iron deficiency?

REDUCED IN

- Poor appetite
- Poor gastroin
  (GI) absorpti
- Concurrent m
  (e.g. omepra
- Food interac

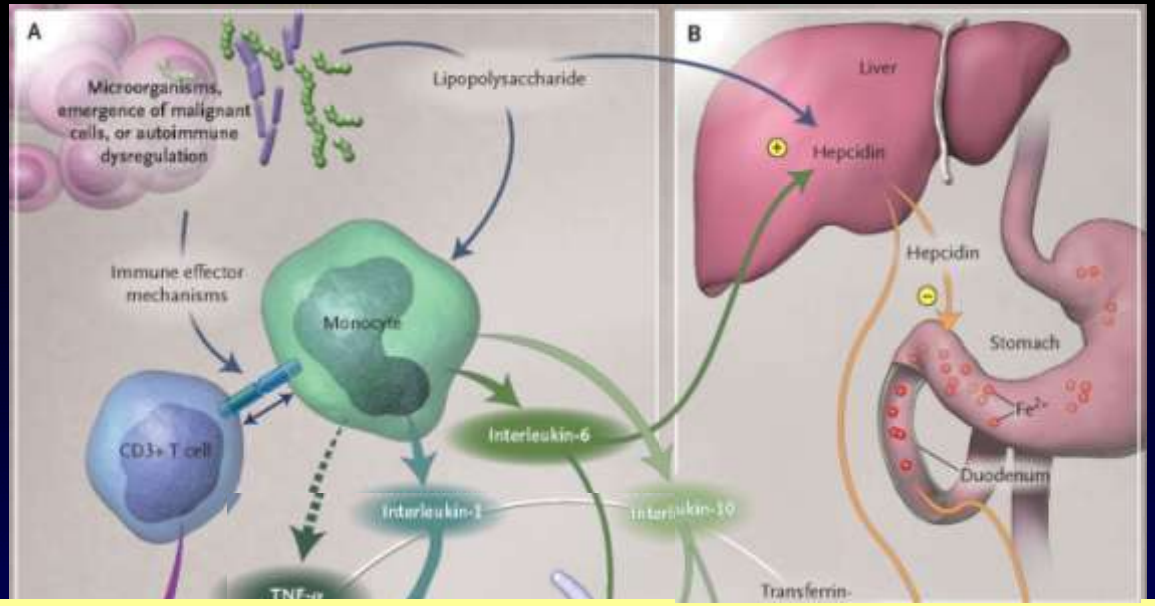


Increased iron needs during ESA therapy

EASED LOSSES

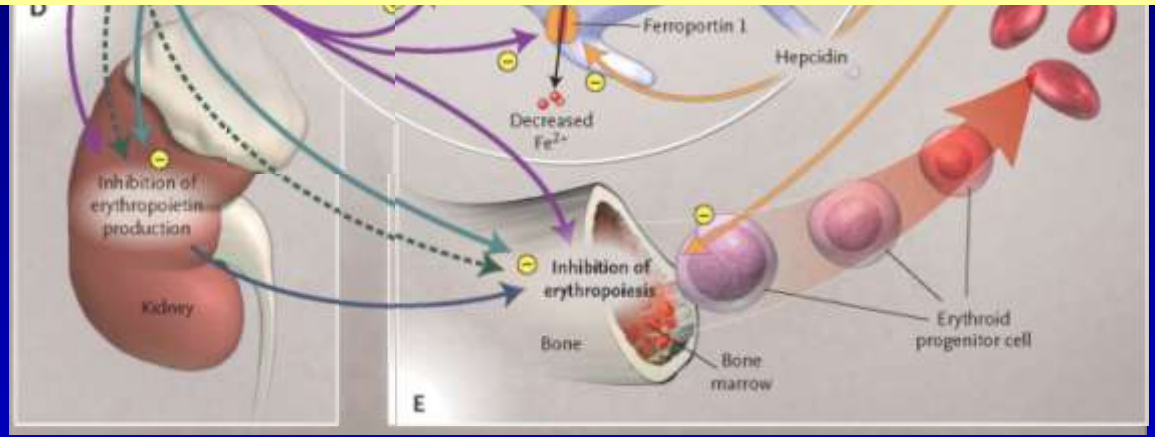
- Occult GI losses
- Peptic ulceration
- Blood sampling
- Dialyser losses
- Concurrent medication (e.g. aspirin)
- Heparin on dialysis

ESA, erythropoiesis-stimulating agent



Why are patients with CKD prone to developing iron deficiency?

Where is the science taking us?

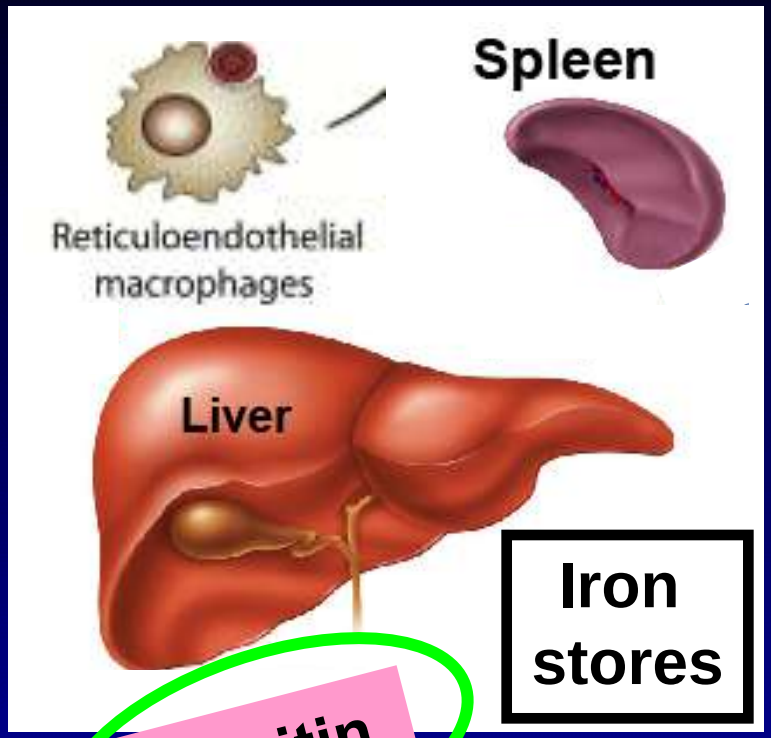


Weiss G, Goodnough LT.
N Engl J Med 2005;352:1011–23

Questions regarding iron metabolism in CKD

- Why are patients with CKD prone to developing iron deficiency?
- **How can we best <u>detect</u> iron deficiency?**
- How can we best treat iron deficiency?

Iron metabolism



Serum TfR

PLASMA

Serum iron/TIBC
TSAT

Marrow stainable iron

% Hypochromic RBC

RBC ZPP

CHr

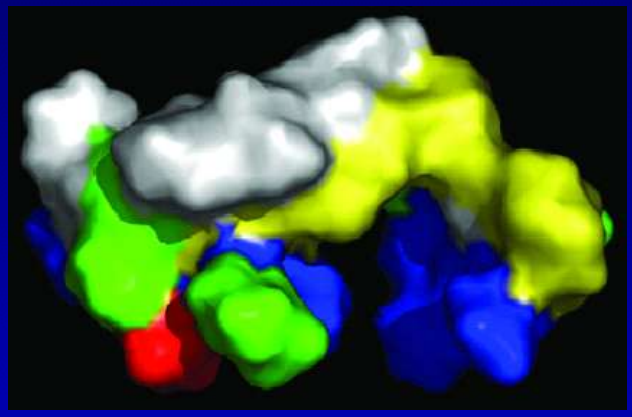
CHr, reticulocyte haemoglobin; RBC, red blood cell; TfR, transferrin receptor; TIBC, total iron-binding capacity; TSAT, transferrin saturation; ZPP, zinc protoporphyrin

Monitoring iron status

How best to detect iron deficiency?

Where is the science taking us?

Measure levels of hepcidin?



Questions regarding iron metabolism in CKD

- Why are patients with CKD prone to developing iron deficiency?
- How can we best detect iron deficiency?
- **How can we best <u>treat</u> iron deficiency?**

Iron therapy

- Oral

- Intravenous (i.v.)

Oral iron

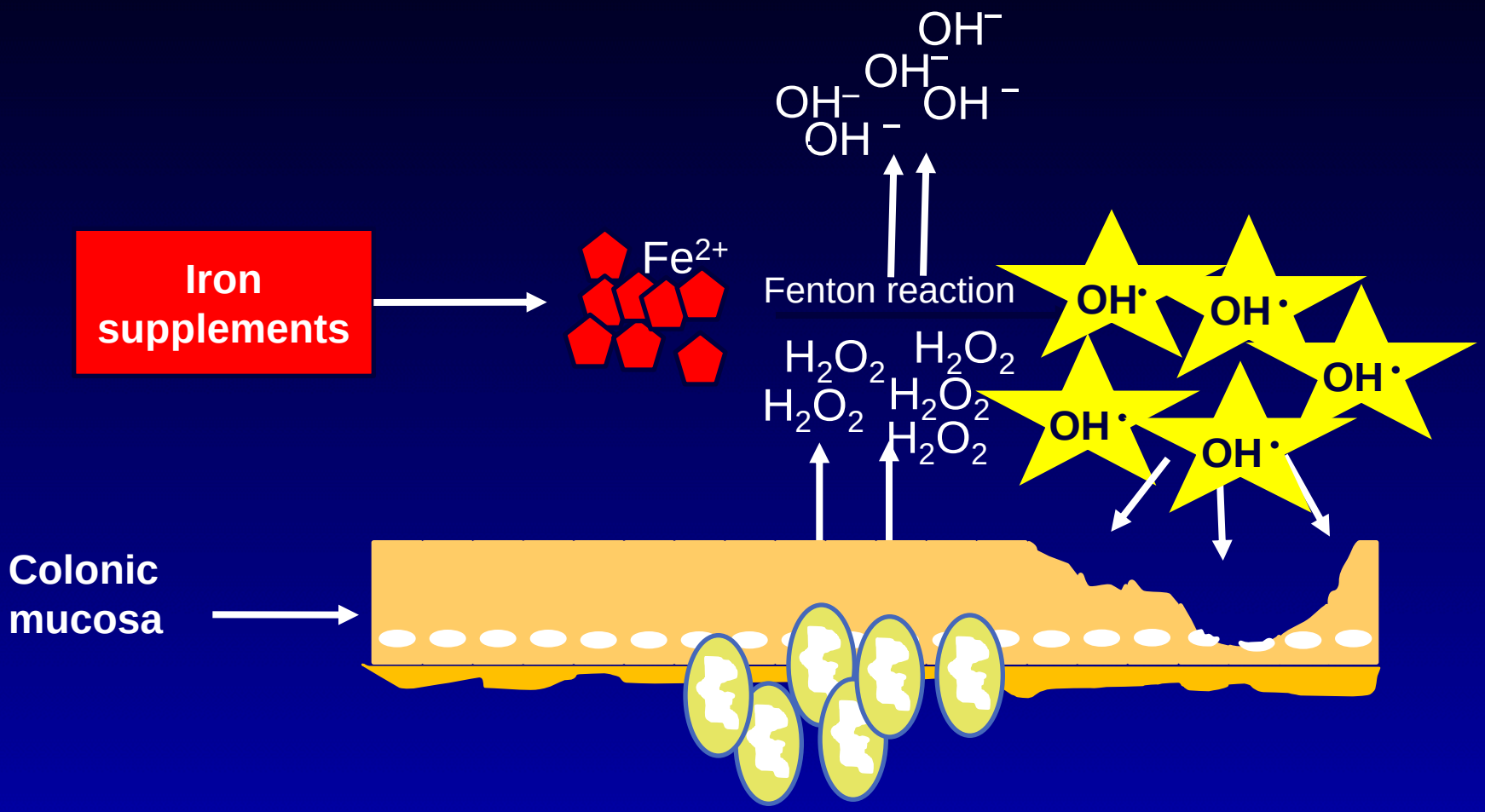
- **Simple**
- **Cheap**
  (a few pence/cents per week)

GI side-effects

- Healthy, pregnant patients (100 mg Fe/day)[1]: dyspepsia 10%, constipation 5%, diarrhoea 3%
- CKD stage 3–4 (325 mg $FeSO_4$ t.i.d.)[2]: constipation 35%, nausea 13%, vomiting 8%, diarrhoea 6%

1. Sharma *et al*. *Am J Clin Nutr* 2004;79:116–22
2. Charytan *et al*. *Nephron Clin Pract* 2005;100:c55–62

Oral iron and oxidative stress



Gasche C *et al*. UNI-MED Verlag, 2008

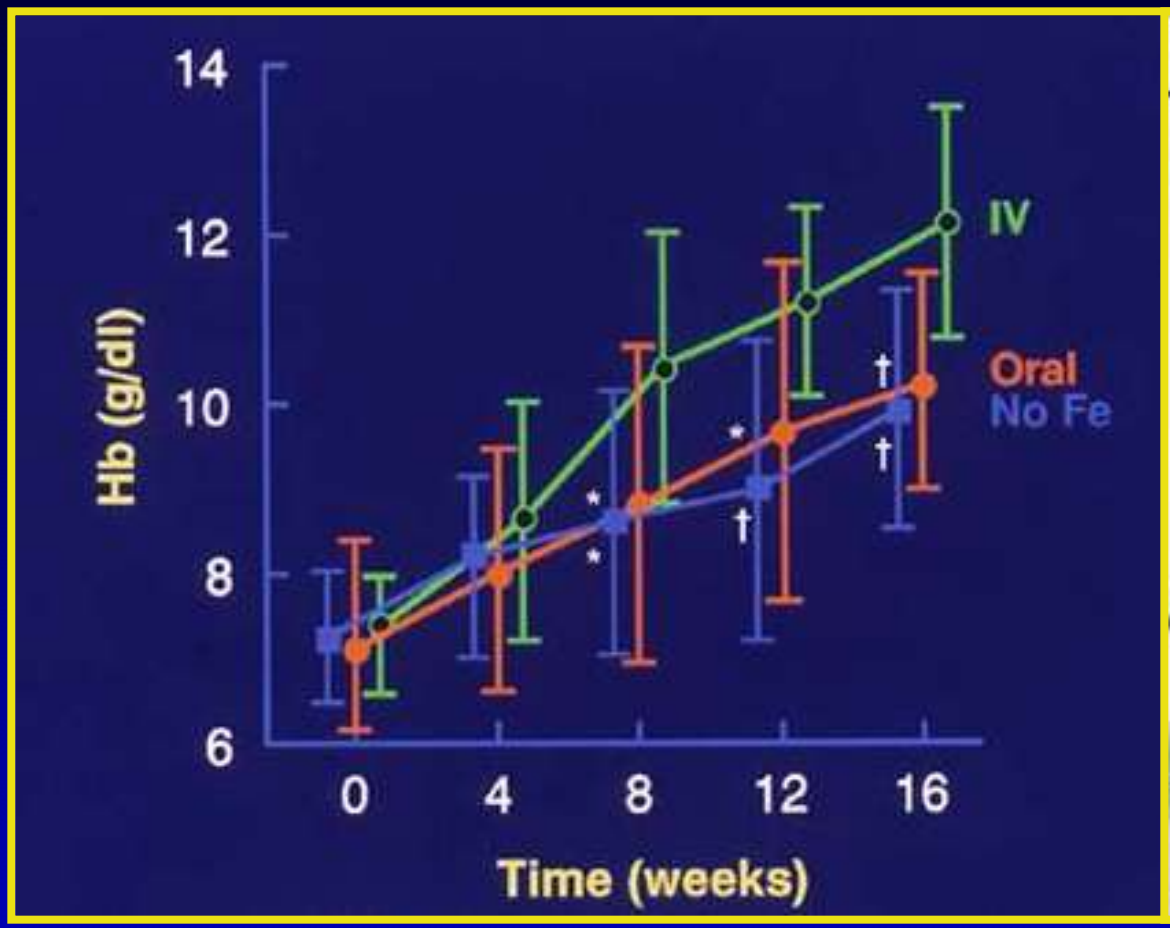
Iron therapy

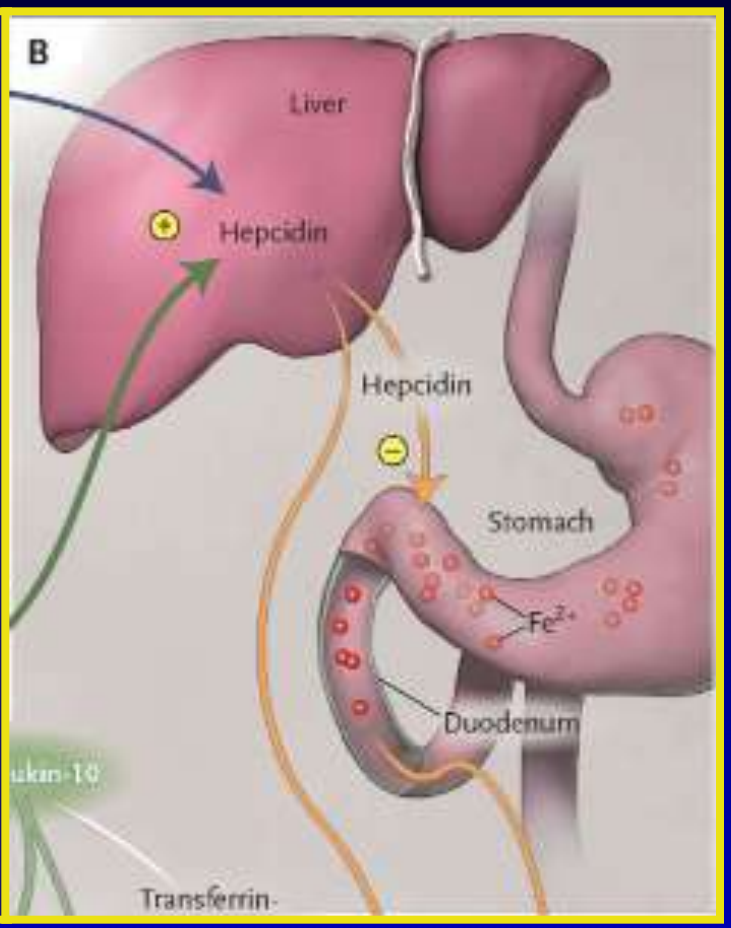
- Oral

- Intravenous

Absorption of iron is poor in CKD

Haemoglobin (Hb) response to i.v., oral and no Fe supplementation





*p<0.05 vs i.v.; †p<0.005 vs i.v.

Macdougall IC *et al. Kidney Int* 1996;50:1694–9.

Intravenous iron compounds

	High MW Iron Dextran	Low MW Iron Dextran	Iron Gluconate	Iron Sucrose	Ferric Carboxy-maltose[a]
Trade names[b] (US, Europe)	Dexferrum	Infed, Cosmofer	Ferrlecit	Venofer	Injectafer, Ferinject
Manufacturer	Luitpold Pharmaceuticals	Pharmacosmos	Sanofi-Aventis	Vifor Int.	Vifor Int.
Chemical properties[c]					
MW [kD]	265	165	< 50	30–100	> 100
Complex stability	High	High	Low	Moderate	High
Acute toxicity	Low	Low	High	Medium	Low

MW, molecular weight.
[a]According to Kulnigg S *et al*, *Gastroenterology* 2007;132(Suppl 1):A501, Seid MH *et al*, *Blood* 2006;108:8B.
[b]Prescribing information of marketed products.
[c]According to Crichton RR *et al*, Bremen: UNI-MED; 2005.

Gasche C *et al, Inflamm Bowel Dis. 2007;* 13 (12).

Benefits of i.v. iron in patients with CKD

- Intravenous iron can improve anaemia in patients with CKD, even in the absence of ESA therapy
- Intravenous iron can significantly enhance the response to ESA therapy, even in iron-replete patients

Macdougall IC. *Curr Med Res Opinion* 2010;26(2):473-482.

Tolerability of i.v. iron?

Short-term

Anaphylactic reactions (iron dextran only; dextran antibodies)

‘Free iron’ reactions (all i.v. iron preparations)

Long-term

Increased susceptibility to infection

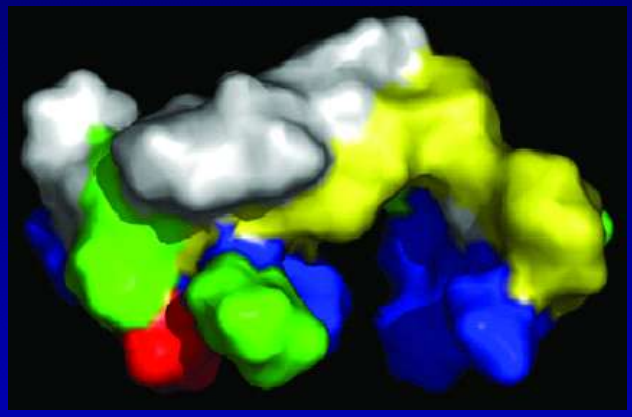
Increased oxidative stress

Iron overload

Questions regarding iron metabolism in CKD

How best to treat iron deficiency?
Where is the science taking us?

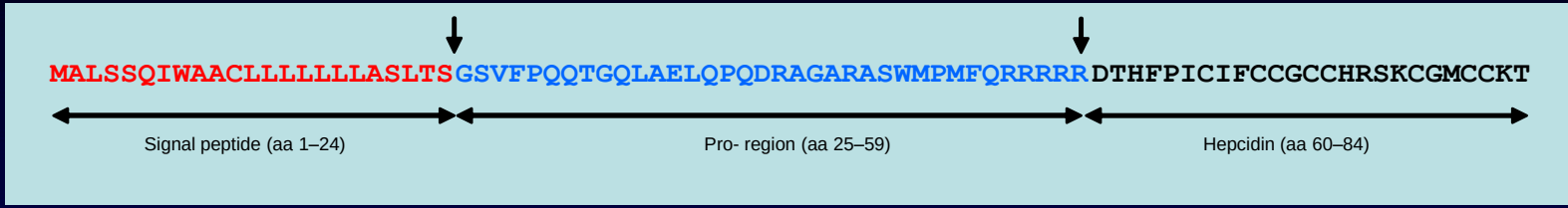
Hepcidin as a target for CKD anaemia management



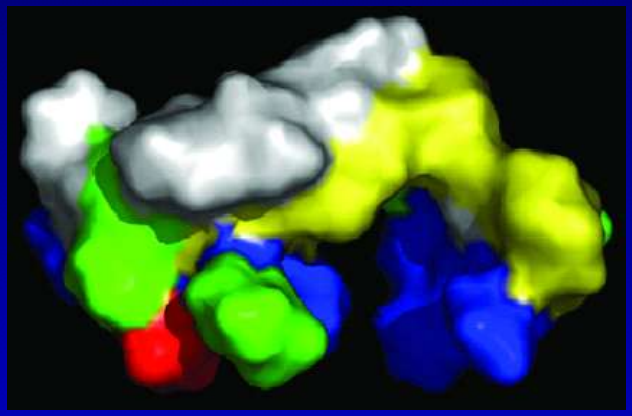
Hepcidin

- What is it?
- What does it do?
- How can we measure it?
- Implications for the nephrologist

What is hepcidin?



- Hepatic antimicrobial peptide
- Found incidentally by a French medical student
- *HAMP* gene
  - Pre-hormone: 84 amino acids
  - Active peptide: 25 amino acids
- Excreted by the kidney



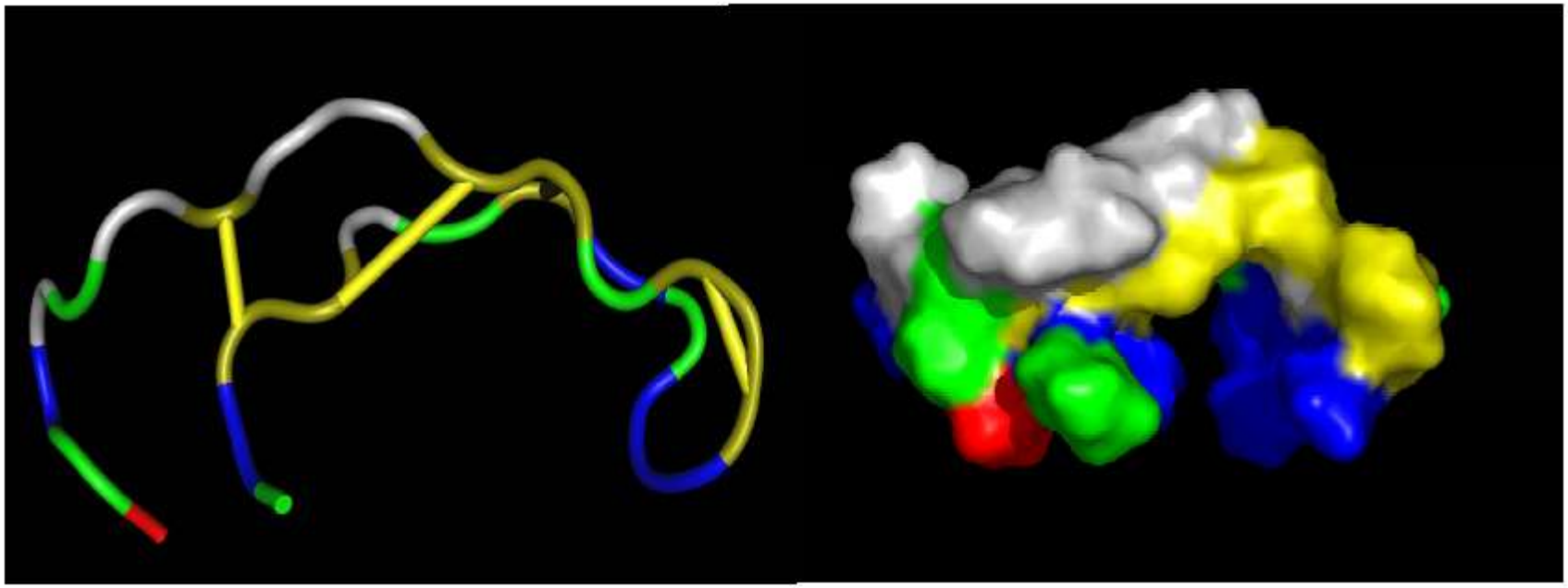
Hepcidin

- What is it?
- What does it do?
- How can we measure it?
- Implications for the nephrologist

Hepcidin is the iron-regulatory hormone

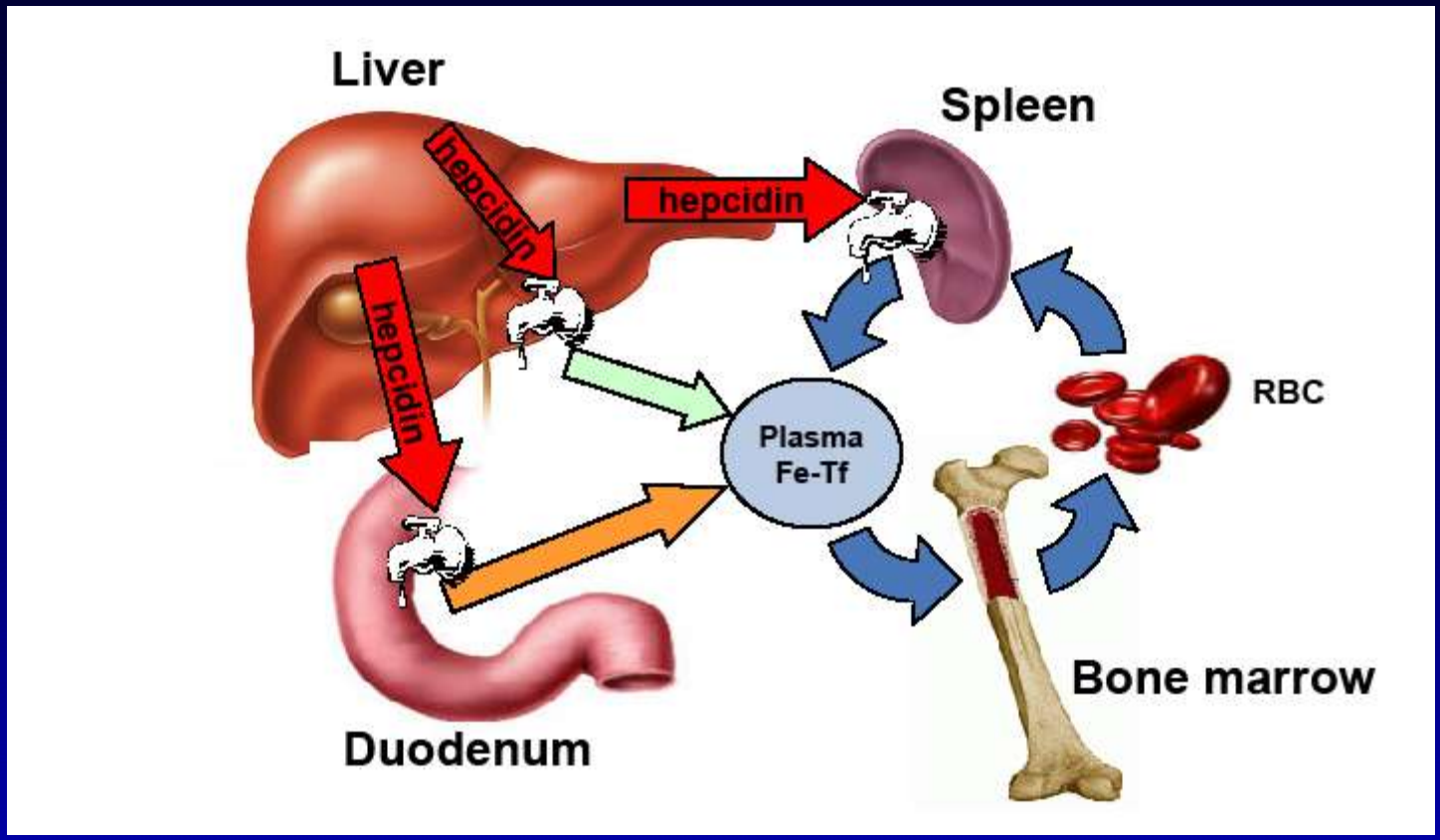
Park et al.: JBC 276: 7806-7810, 2001

Hunter et al.: JBC 277:37597-603, 2002



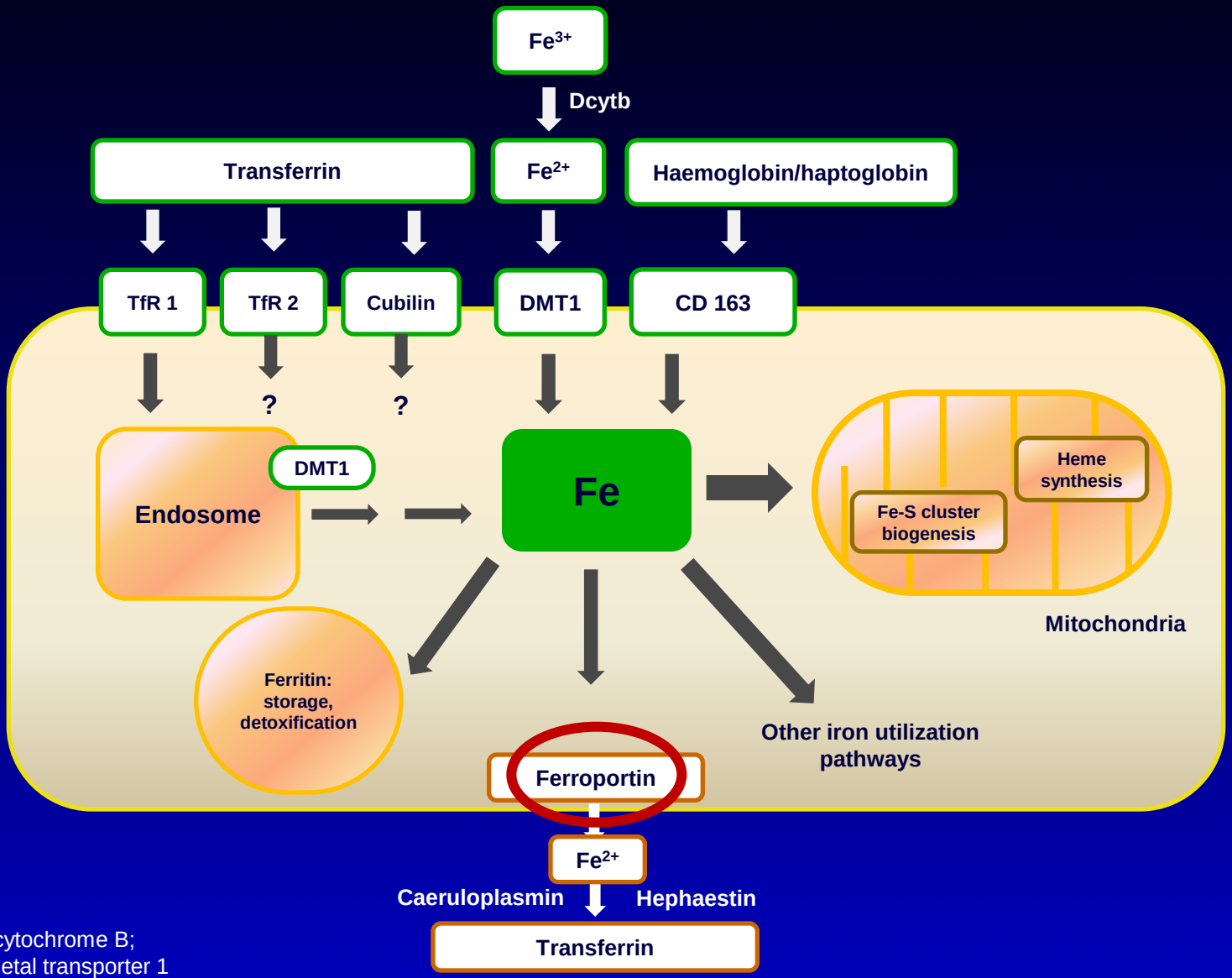
Ganz T, Nemeth E. *Am J Physiol Gastrointest Liver Physiol* 2006;290:G199–203.

Hepcidin regulates iron flow into plasma

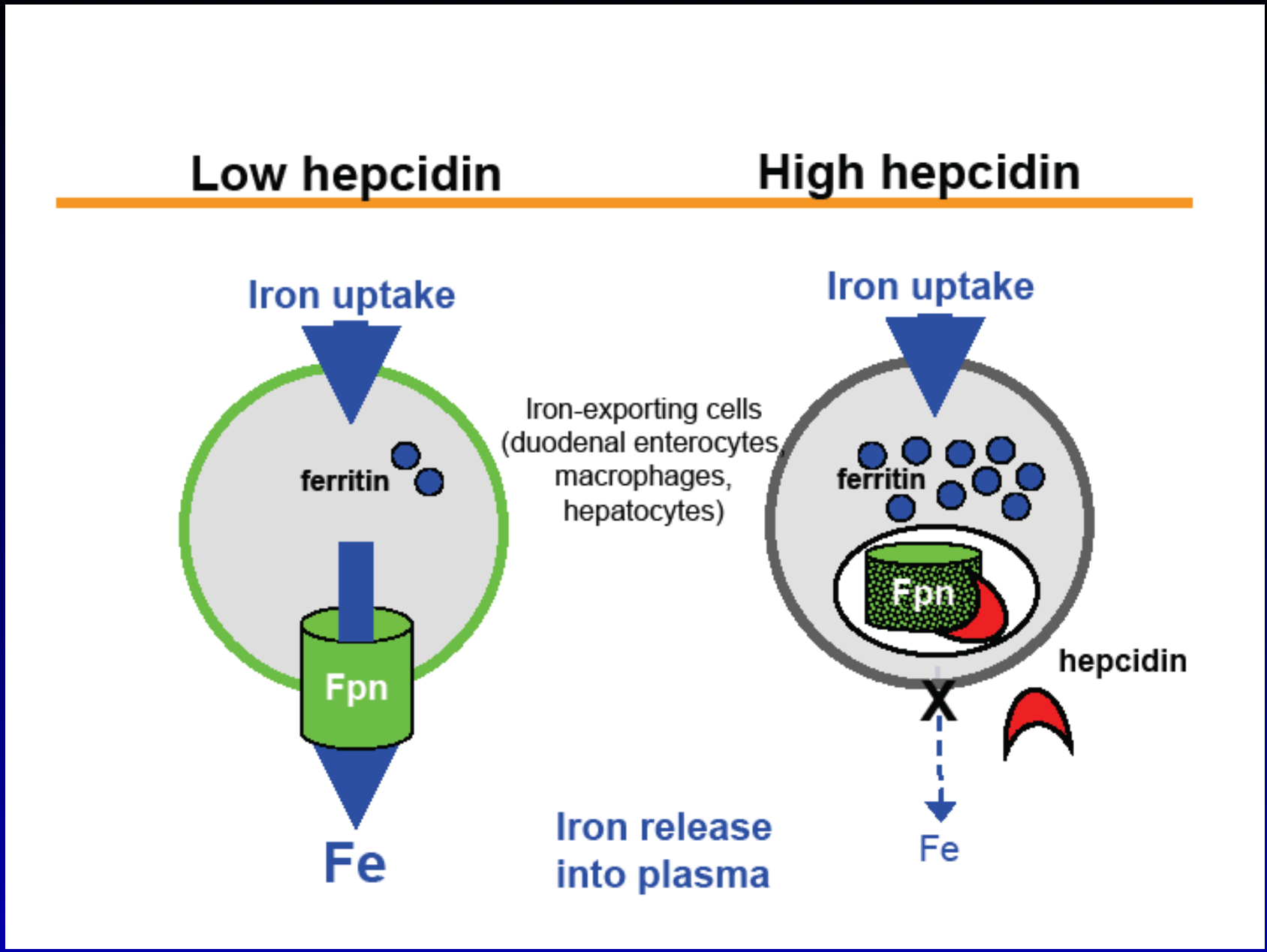


Ganz T, Nemeth E. *Am J Physiol Gastrointest Liver Physiol* 2006;290:G199–203.

Iron transport



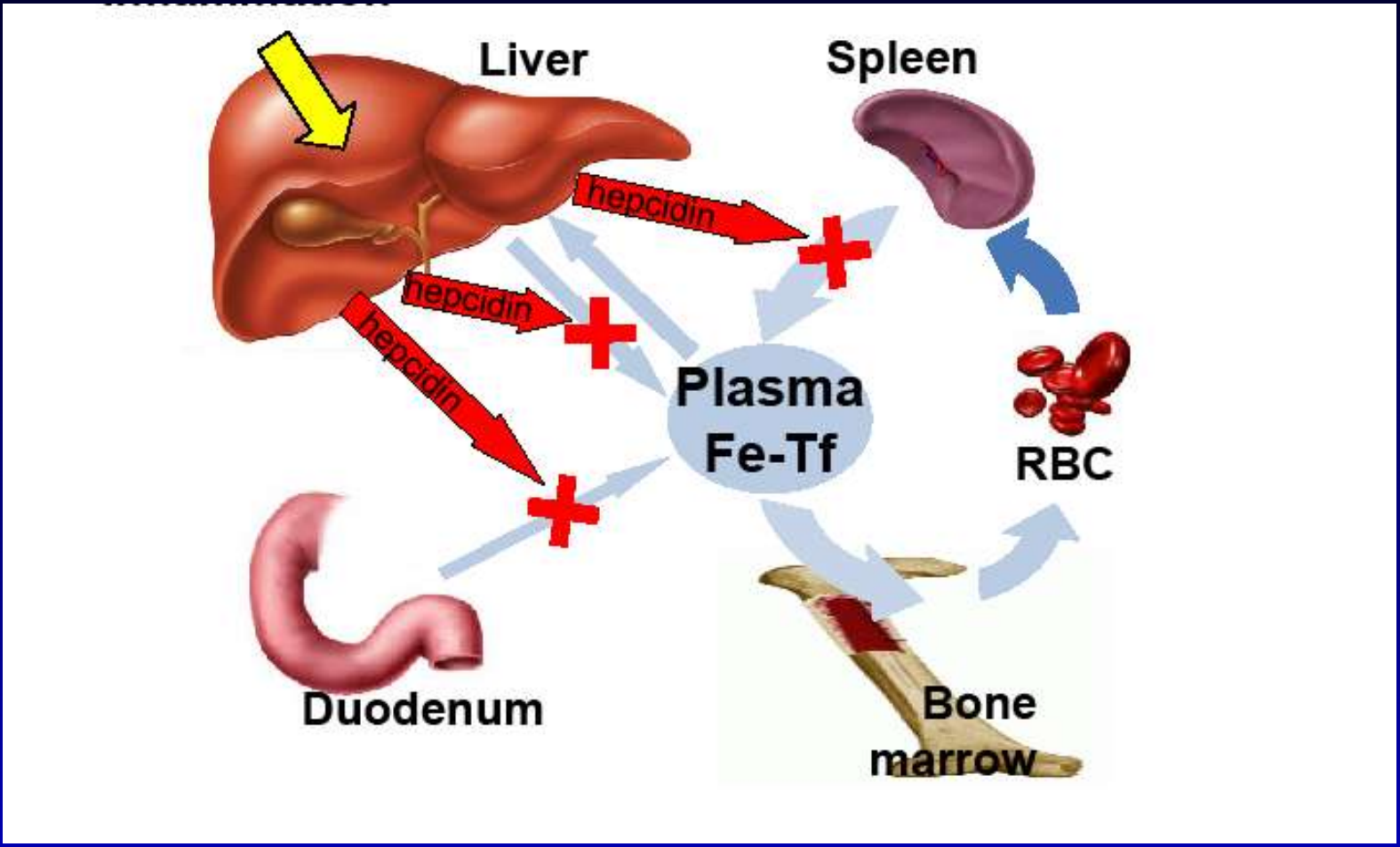
Dcytb, duodenal cytochrome B;
DMT1, divalent metal transporter 1



Fpn, ferroportin

Ganz T, Nemeth E. *Am J Physiol Gastrointest Liver Physiol* 2006;290:G199–203.

Regulation of hepcidin by inflammation



Hepcidin

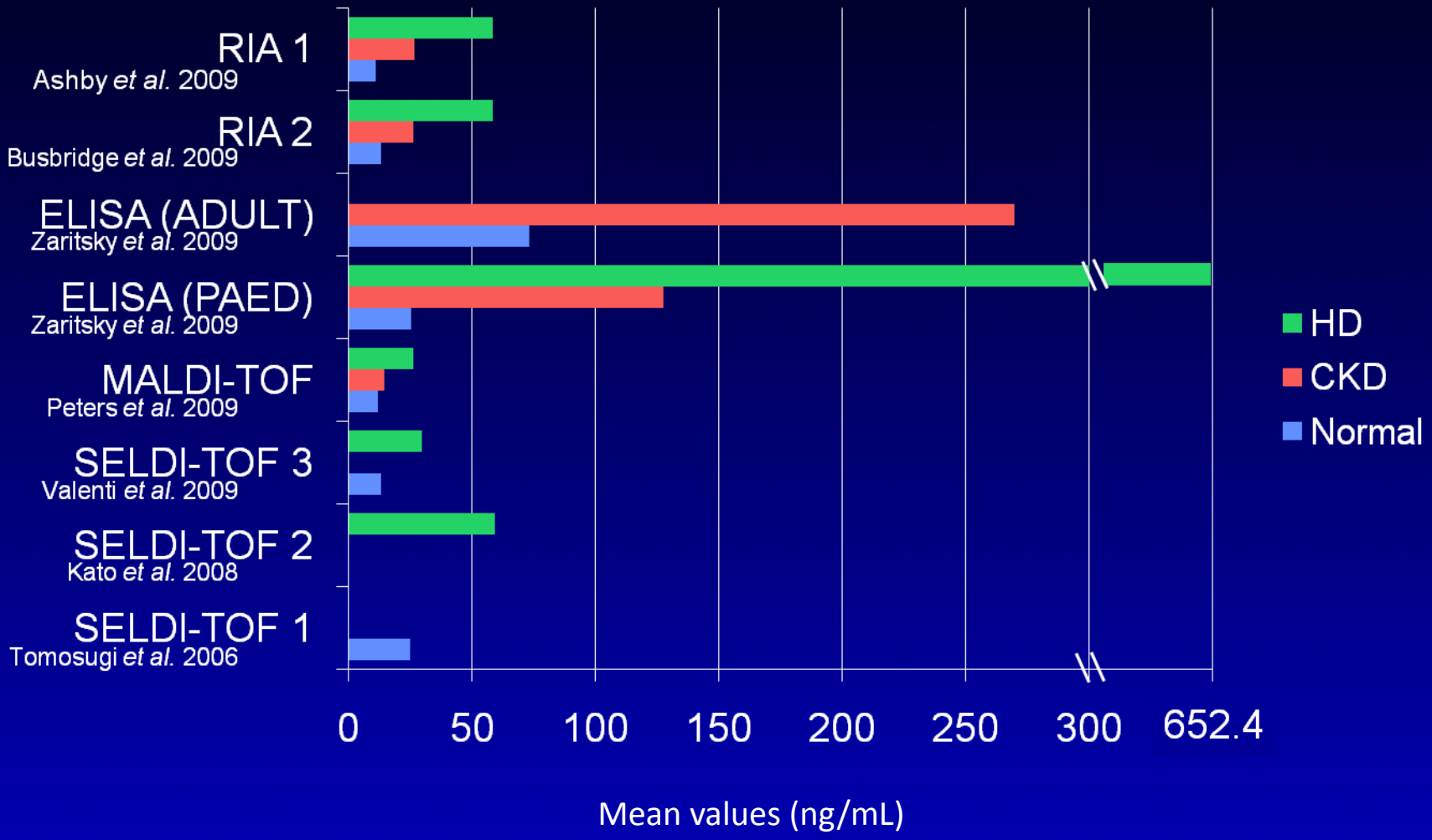
- What is it?
- What does it do?
- How can we measure it?
- Implications for the nephrologist

Measurement of hepcidin

- Radioimmunoassay (RIA)
- Enzyme-linked immunosorbent assay (ELISA)
- Ligand-binding assay
- Mass spectrometry (MS)
  - Surface-enhanced laser desorption (SELDI)/ matrix-assisted laser desorption ionization (MALDI)
  - Liquid chromatography tandem MS

Macdougall IC *et al*. *Clin J Am Soc Nephrol* 2010: in press

Blood hepcidin assays used to measure levels in CKD patients



HD, haemodialysis; TOF, time of flight

Macdougall IC *et al*. *Clin J Am Soc Nephrol* 2010: in press

Hepcidin

- What is it?
- What does it do?
- How can we measure it?
- Implications for the nephrologist

Hepcidin – implications for the nephrologist

- Hepcidin is the reason patients with CKD (particularly those undergoing HD) do not absorb oral iron from the GI tract
- It is the pivotal mediator of functional iron deficiency in inflammatory states
- It may be a key factor in the pathogenesis of erythropoietin resistance in infectious and inflammatory states
- Once assays are optimized, measurement of hepcidin may replace measurement of ferritin, iron, TIBC and hypochromic red cells

Hepcidin – implications for the nephrologist

- Hepcidin may be a potential target for future anaemia therapies

Antihepcidin antibody treatment modulates iron metabolism and is effective in a mouse model of inflammation-induced anemia

Barbra J. Sasu,[1] Keegan S. Cooke,[1] Tara L. Arvedson,[1] Cherylene Plewa,[2] Aaron R. Ellison,[2] Jackie Sheng,[2] Aaron Winters,[2] Todd Juan,[2] Hongyan Li,[3] C. Glenn Begley,[1] and Graham Molineux[1]

Departments of [1]Hematology/Oncology, [2]Protein Sciences, and [3]Pharmacokinetics and Drug Metabolism, Amgen Inc, Thousand Oaks, CA

Iron maldistribution has been implicated in multiple diseases, including the anemia of inflammation (AI), atherosclerosis, diabetes, and neurodegenerative disorders. Iron metabolism is controlled by hepcidin, a 25-amino acid peptide. Hepcidin is induced by inflammation, causes iron to be sequestered, and thus, potentially contributes to AI. Human hepcidin (hHepc) overexpression in mice caused an iron-deficient phenotype, including stunted growth, hair loss, and iron-deficient erythropoiesis. It also caused resistance to supraphysiologic levels of erythropoiesis-stimulating agent, supporting the hypothesis that hepcidin may influence response to treatment in AI. To explore the role of hepcidin in inflammatory anemia, a mouse AI model was developed with heat-killed *Brucella abortus* treatment. Suppression of hepcidin mRNA was a successful anemia treatment in this model. High-affinity antibodies specific for hHepc were generated, and hHepc knock-in mice were produced to enable antibody testing. Antibody treatment neutralized hHepc in vitro and in vivo and facilitated anemia treatment in hHepc knock-in mice with AI. These data indicate that antihepcidin antibodies may be an effective treatment for patients with inflammatory anemia. The ability to manipulate iron metabolism in vivo may also allow investigation of the role of iron in a number of other pathologic conditions.
(*Blood*. 2010;115(17):3616-3624)

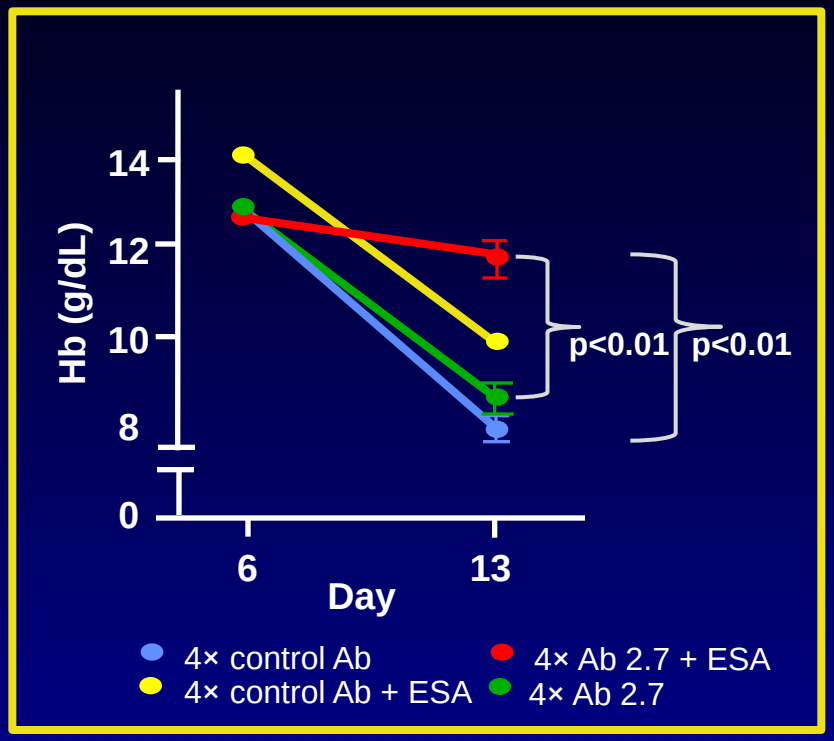
MAb against hepcidin was effective in a mouse model of inflammation-induced anaemia

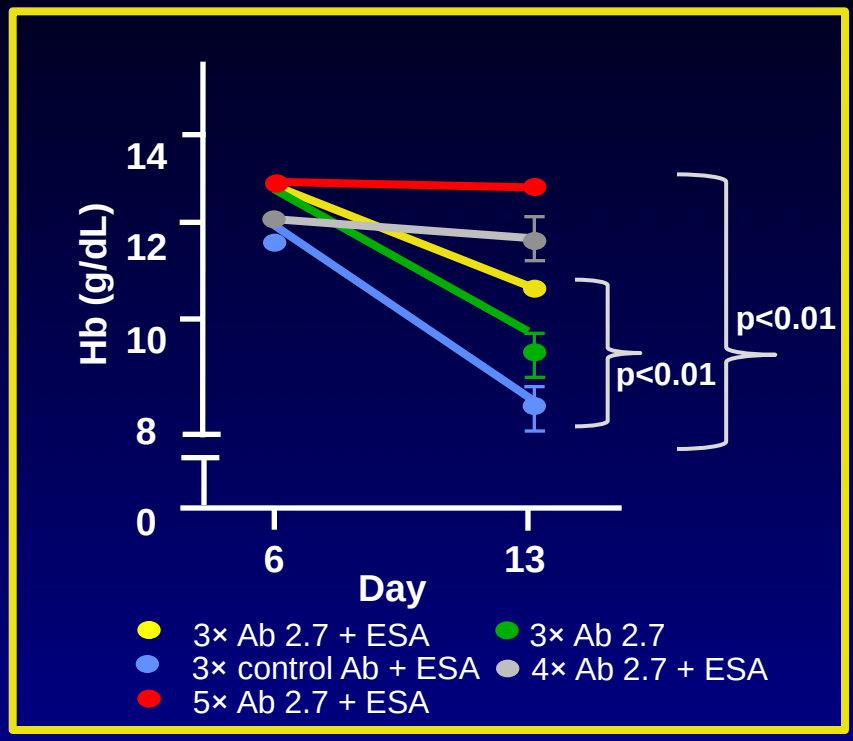
- Suppression of hepcidin mRNA improved anaemia in a mouse model of inflammation
- High-affinity Ab treatment neutralized hHepc and increased haemoglobin levels in hHepc knock-out mice
- Anti-hepcidin Abs may be an effective treatment for inflammatory anaemia
- Manipulation of iron metabolism *in vivo* may allow investigation of the role of iron in other conditions

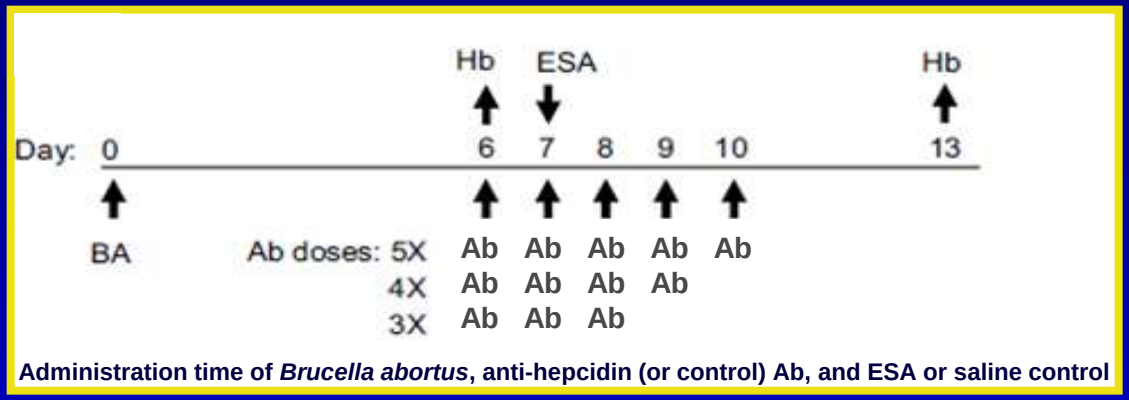
Ab, antibody; hHepc, human hepcidin; MAb, monoclonal antibody

Sasu BJ *et al*. *Blood* 2010;115:3616–24

MAb against hepcidin was effective in combination therapy for anaemia of inflammation







Administration time of *Brucella abortus*, anti-hepcidin (or control) Ab, and ESA or saline control

Ab 2.7 restored response to ESA treatment in hHepc knock-in anaemia of inflammation mice

Sasu BJ *et al*. *Blood* 2010;115:3616–24

Conclusions

- Patients with CKD are at an increased risk of developing iron deficiency
- Several diagnostic markers are available to monitor iron status – all have limitations
- Intravenous iron is beneficial in patients with non-dialysis CKD, even in the absence of ESA therapy
  - *Newer formulations may overcome the limitations of older i.v. preparations*
- Hepcidin is a key regulator of iron availability
  - *It is a potential future therapeutic target for managing anaemia in CKD*

Optimizing anaemia management: which is the right path?

Dr Simon D. Roger, MD, FRACP
Gosford Hospital
Australia

Disclosures

- Dr Roger has served on advisory boards/ speaker bureaux for Amgen, Hoffman-La Roche, Janssen-Cilag, Sandoz and Vifor Pharma Ltd
- In addition, he has undertaken clinical trials in anaemia/iron management for Takeda and the above companies

What is wrong with anaemia management in 2010?

- Is it the wrong target haemoglobin (Hb)?
- Is it the wrong target Hb for the wrong patient?
- Is it too much erythropoiesis-stimulating agent (ESA)?
- Is it underlying illness, compounded by high ESA dosages?
- Should iron be the starting point in anaemia management?
- Should there be a target Hb when considering iron repletion in patients with non-dialysis chronic kidney disease (ND-CKD)?

Is it the wrong target Hb for the wrong patient?

- Young vs elderly

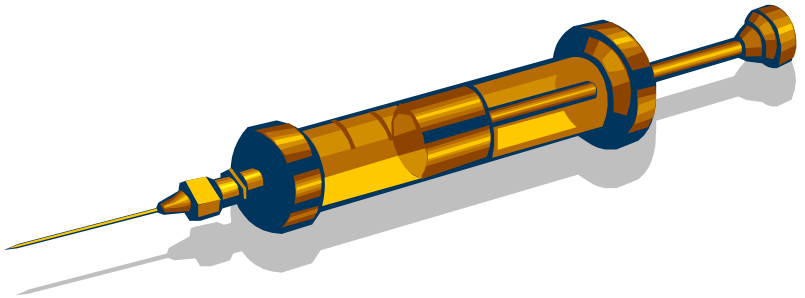
STiMULATE

Is it the wrong target Hb for the wrong patient?

- Young vs elderly
- ‘Better’ cardiac function vs heart failure

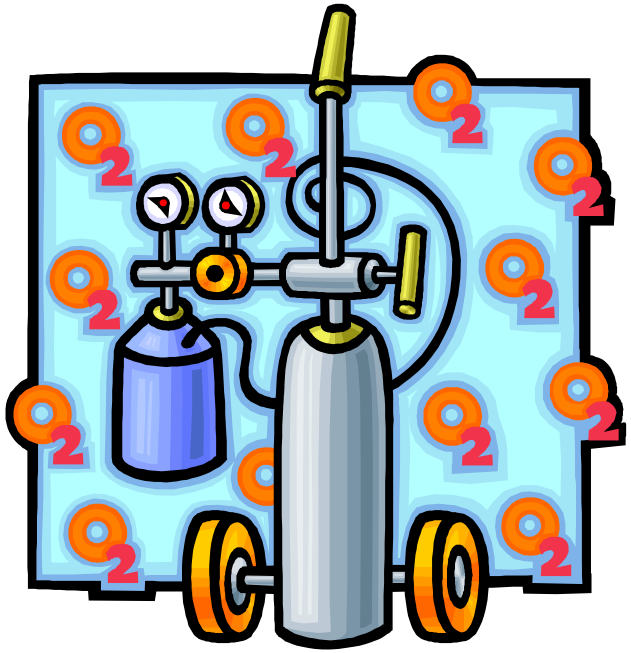
Is it the wrong target Hb for the wrong patient?

- Young vs elderly
- ‘Better’ cardiac function vs heart failure
- ‘Normals’ vs diabetics



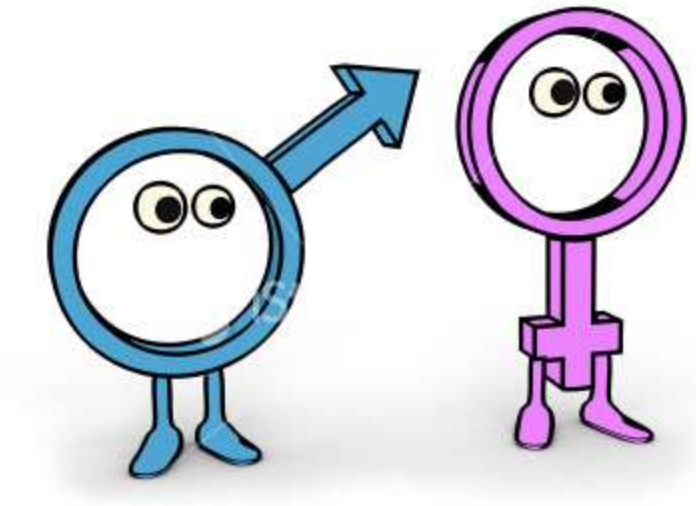
Is it the wrong target Hb for the wrong patient?

- Young vs elderly
- ‘Better’ cardiac function vs heart failure
- ‘Normals’ vs diabetics
- ‘Normals’ vs chronic obstructive airway disease



Is it the wrong target Hb for the wrong patient?

- Young vs elderly
- ‘Better’ cardiac function vs heart failure
- ‘Normals’ vs diabetics
- ‘Normals’ vs chronic obstructive airway disease
- Patients with chronic inflammation vs others
- Males vs females



Is it the wrong target Hb for the wrong patient?

- Young vs elderly
- ‘Better’ cardiac function vs heart failure
- ‘Normals’ vs diabetics
- ‘Normals’ vs chronic obstructive airway disease
- Patients with chronic inflammation vs others
- Males vs females

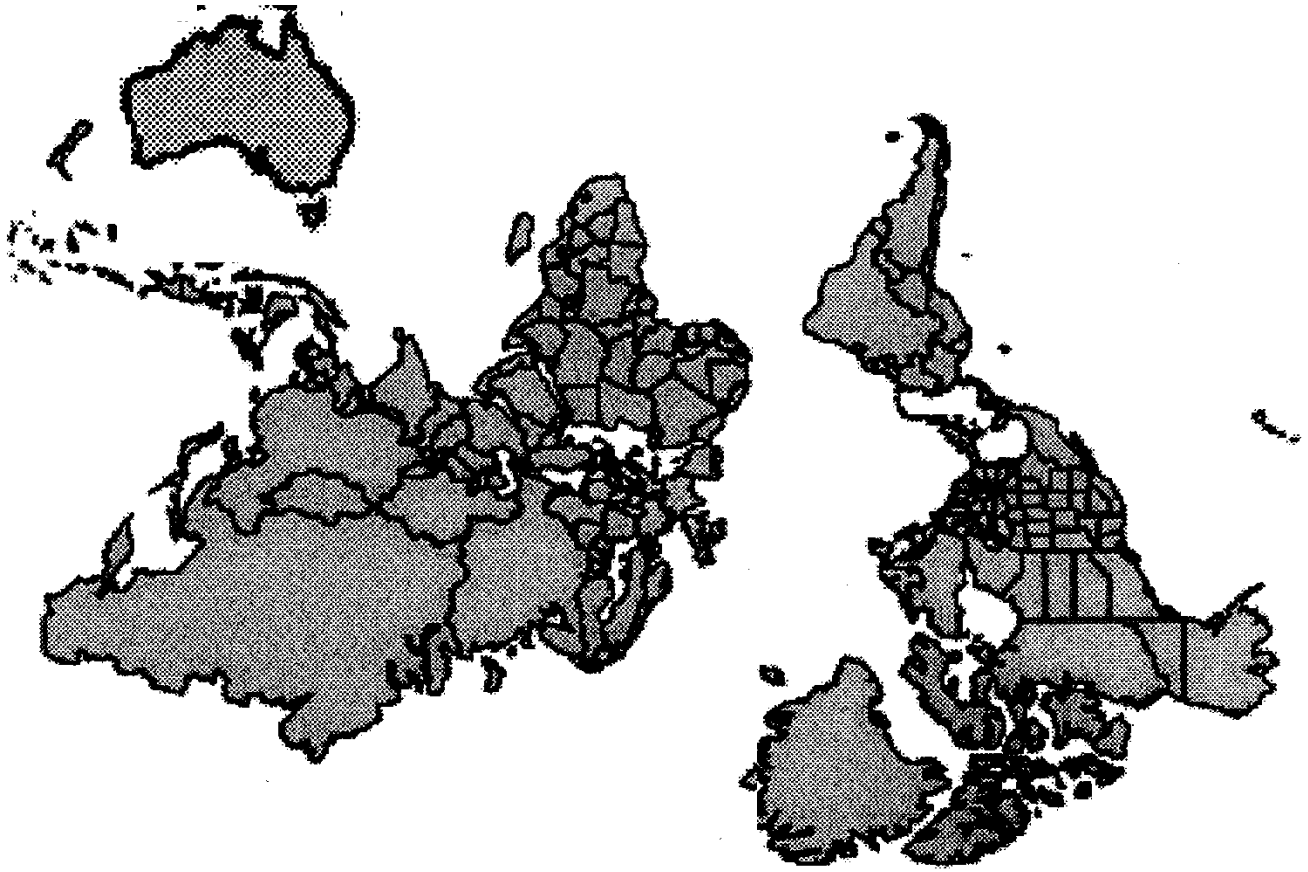
…patients in whom higher Hb concentrations are achieved may be healthier and therefore more responsive to ESAs…

What is the wrong target Hb?

…The recently published landmark study the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) has turned the world of anaemia management upside down…

Singh AK. *J Am Soc Nephrol* 2010;21:2–6

The world…



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*

ABSTRACT

BACKGROUND

Anemia is associated with an increased risk of cardiovascular and renal events among patients with type 2 diabetes and chronic kidney disease. Although darbepoetin alfa can effectively increase hemoglobin levels, its effect on clinical outcomes in these patients has not been adequately tested.

METHODS

In this study involving 4038 patients with diabetes, chronic kidney disease, and anemia, we randomly assigned 2012 patients to darbepoetin alfa to achieve a hemoglobin level of approximately 13 g per deciliter and 2026 patients to placebo, with

The affiliations of the authors are listed in the Appendix. Address reprint requests to Dr. Pfeffer at the Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at mpfeffer@rics.bwh.harvard.edu.

*The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) committees and teams are listed in the Appendix, and investigators and individual

The NEW ENGLAND JOURNAL of MEDICINE

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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*

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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*

The New England Journal of Medicine

THE EFFECTS OF NORMAL AS COMPARED WITH LOW HEMATOCRIT VALUES IN PATIENTS WITH CARDIAC DISEASE WHO ARE RECEIVING HEMODIALYSIS AND EPOETIN

ANATOLE BESARAB, M.D., W. KLINE BOLTON, M.D., JEFFREY K. BROWNE, PH.D., JOAN C. EGRIE, PH.D., ALLEN R. NISSENSON, M.D., DOUGLAS M. OKAMOTO, PH.D., STEVE J. SCHWAB, M.D., AND DAVID A. GOODKIN, M.D.

Is it too much ESA?

…vs placebo

- ESA did not reduce the risk of cardiovascular composite endpoints
- It increased the risk of fatal and non-fatal stroke and thromboembolism
- An increase in cancer incidence was observed in patients with a prior history of malignancies

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

Is it underlying illness, compounded by high ESA dosages?

- Should ESAs be avoided?[1,2]
- Is it a question of (median) dose?
  - CHOIR[3] 10925 units/week epoetin alfa
  - TREAT[4] 8800 units (equiv.)/week darbepoetin alfa*
  - CREATE[5] 5000 units/week epoetin beta

*176 µg/month, converted at 200 units/µg

1. Roger SD. *N Engl J Med* 2007;356:958;
2. Singh AK. *J Am Soc Nephrol* 2010;21:2–6;
3. Singh AK *et al*. *N Engl J Med* 2006;355:2085–98;
4. Pfeffer MA *et al*. *N Engl J Med* 2009;361:2019–32;
5. Drueke TB *et al. N Engl J Med* 2006;355:2071–84.

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…or is it the ESA?

- Methoxy polyethylene glycol-epoetin beta (Mircera)?
- Peginesatide (Hematide)?
- Hypoxia-inducible factor inhibitors?

*176 µg/month, converted at 200 units/µg

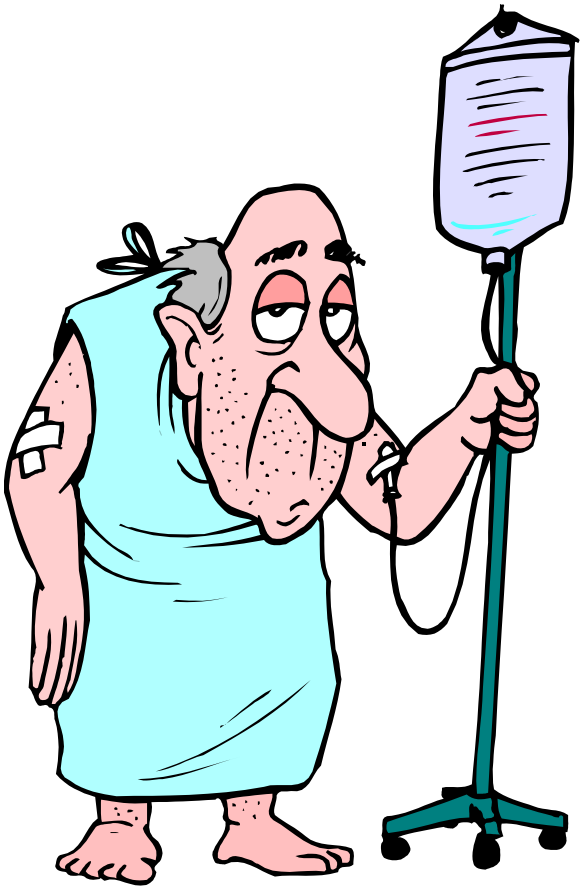
1. Roger SD. *N Engl J Med* 2007;356:958;
2. Singh AK. *J Am Soc Nephrol* 2010;21:2–6;
3. Singh AK *et al*. *N Engl J Med* 2006;355:2085–98;
4. Pfeffer MA *et al*. *N Engl J Med* 2009;361:2019–32;
5. Drueke TB *et al. N Engl J Med* 2006;355:2071–84.

Is it underlying diabetes that skews the results?

- TREAT[1]: all patients had diabetes
- CHOIR[2]: 50% of patients had diabetes
- CREATE[3]: 25% of patients had diabetes

1. Pfeffer MA *et al*. *N Engl J Med* 2009;361:2019–32;
2. Singh AK *et al*. *N Engl J Med* 2006;355:2085–98;
3. Drüeke TB *et al*. *N Engl J Med* 2006;355:2071–84

What about blood transfusions?



- Is reduction in transfusions the aim of ESAs?
- Cancer patients?
- Patients on the transplant waiting list?

What about quality of life (QoL)? (I)

- Evaluated multiple patient-reported:
  - Outcomes
  - QoL indices
- Overall QoL effects were small and inconsistent:
  - Normal Haematocrit Study[1]:
    - Significant improvement on the physical-functioning scale of the short-form 36 (SF-36)
    - No significant effects on any of the other seven scales of the SF-36

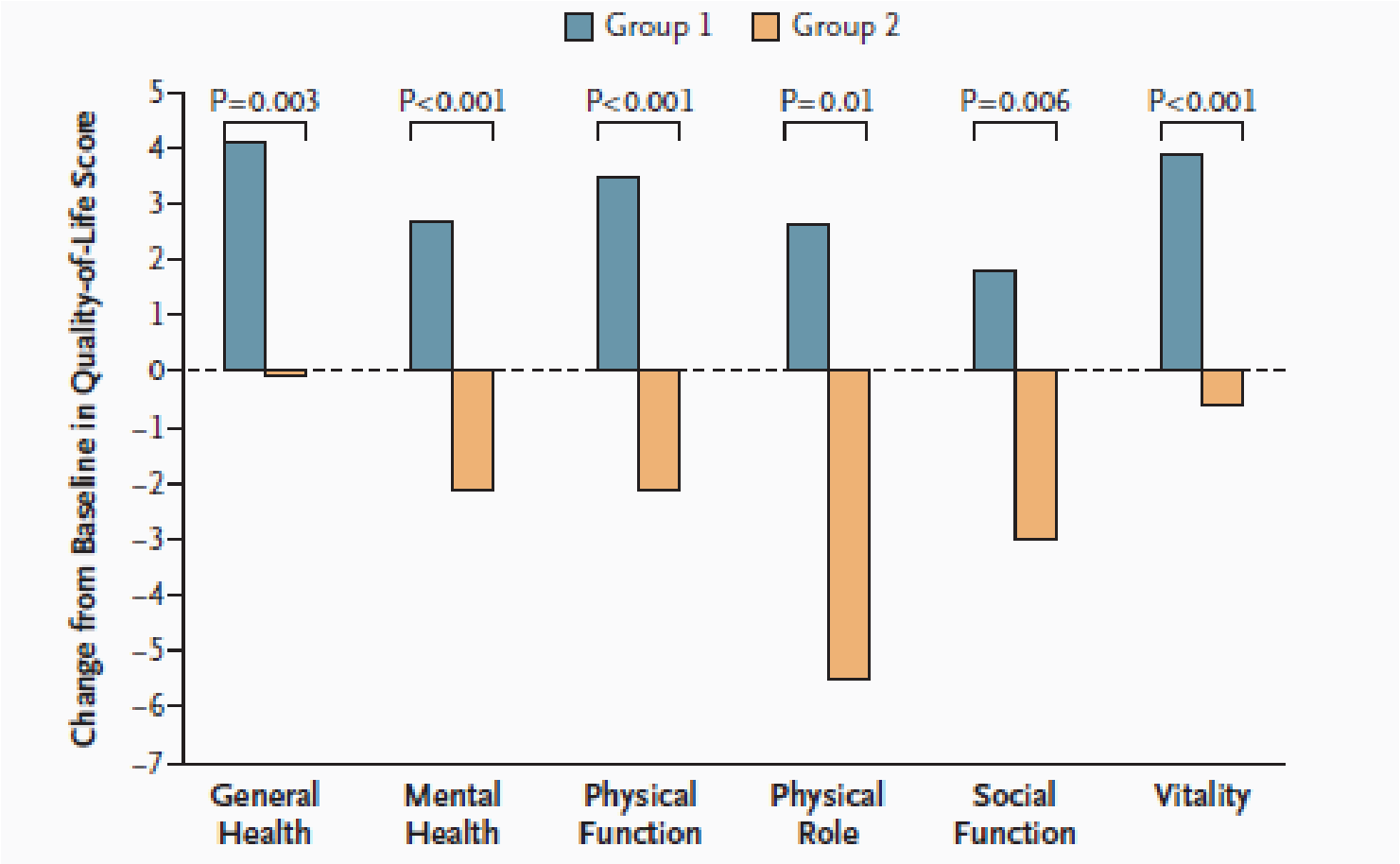
1. Besarab A et al. N Engl J Med 1998;339(9):584–90.

What about QoL? (II)

- CHOIR[1]:
  - Did not show significant improvement on any scale of the SF-36 in the high vs low Hb group
- TREAT[2]:
  - Showed a significant effect on the Functional Assessment of Cancer Therapy–Fatigue instrument
  - No effect on QoL assessments based on the SF-36

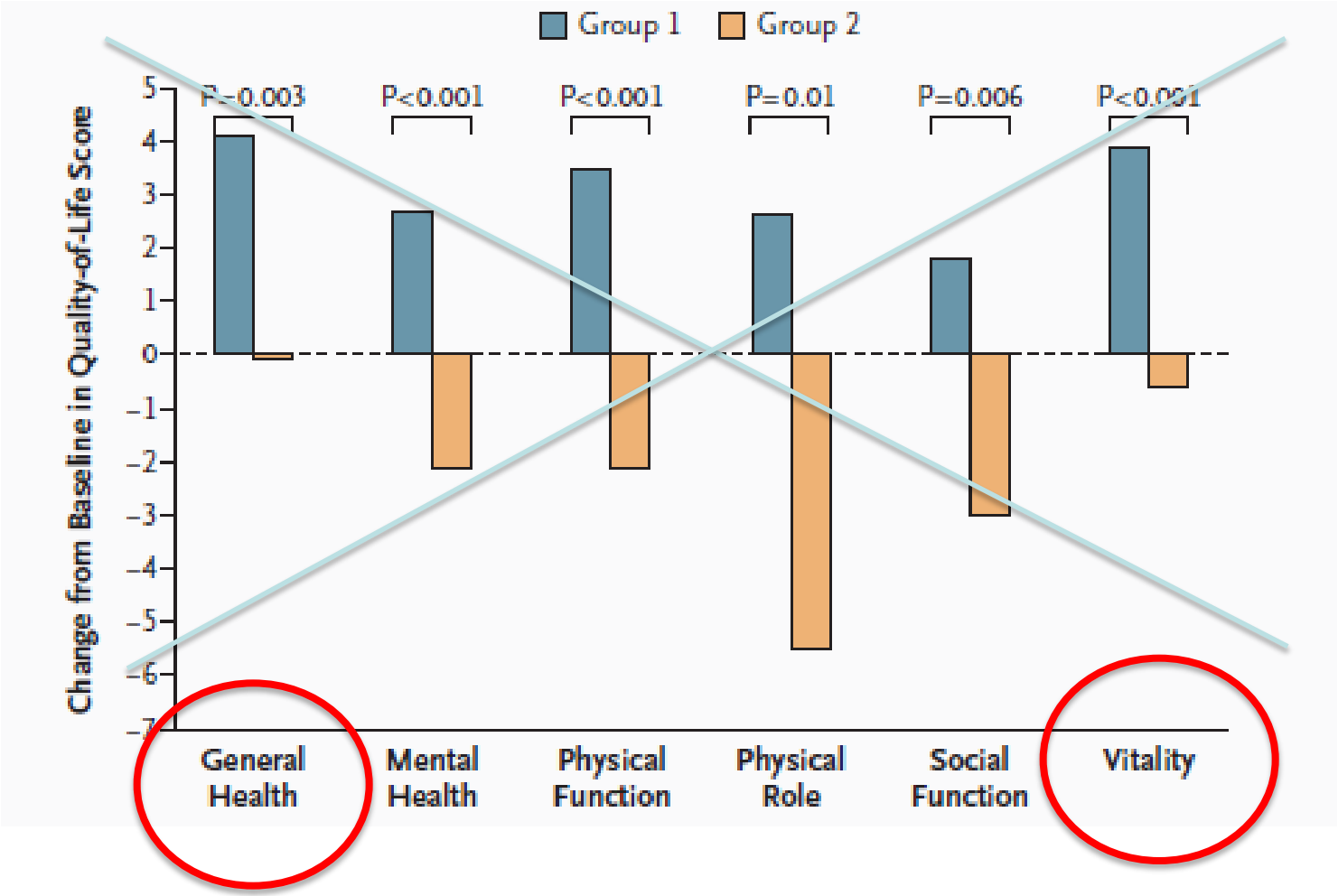
1. Singh AK *et al*. *N Engl J Med* 2006;355:2085–98;
2. Pfeffer MA *et al*. *N Engl J Med* 2009;361:2019–32

CREATE: QoL (SF-36) 12 months



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

CREATE: QoL (SF-36) 24 months



Drueke TB *et al*. *N Engl J Med* 2006;355:2071–84

What does the FDA think?

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Perspective

Erythropoiesis-Stimulating Agents — Time for a Reevaluation

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

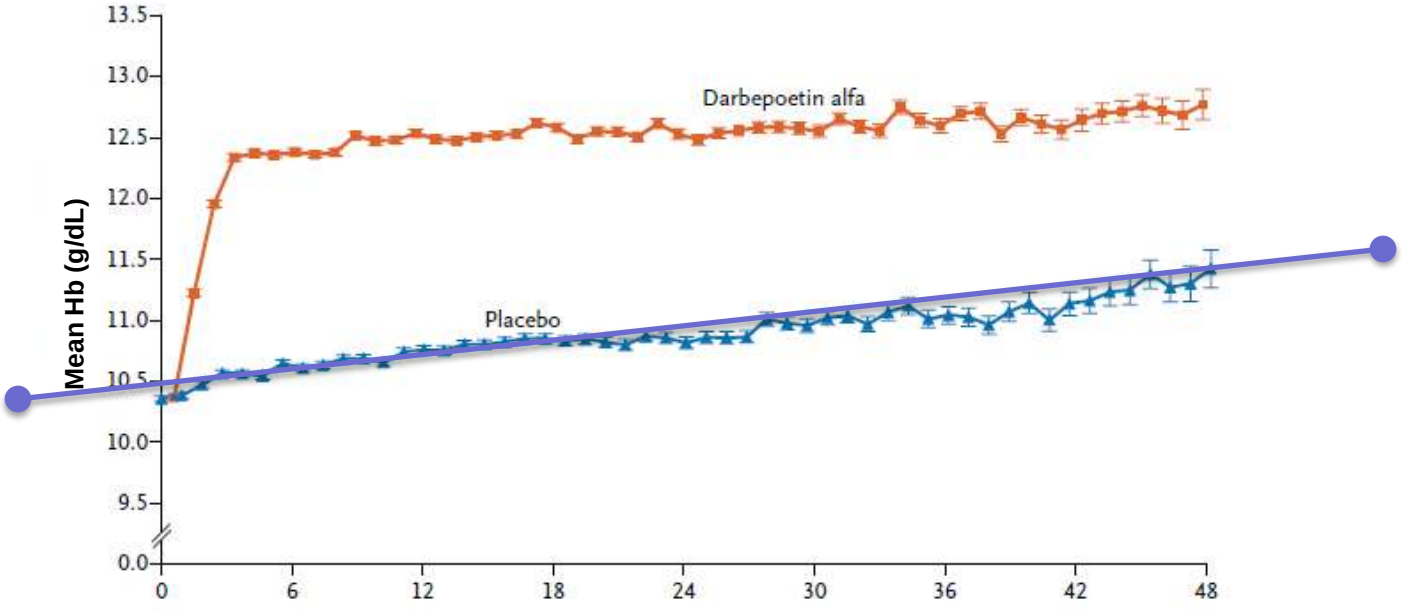
“Epoetin alfa was approved in 1989 by the Food and Drug Administration (FDA) for the treatment of anemia associated with chronic kidney disease ‘to elevate or maintain the red blood cell level…and to decrease the need for transfusions.’”

Unger EF *et al*. *N Engl J Med* 2010;362:189–92

What is wrong with anaemia management in 2010?

- Is it the wrong target Hb?
- Is it the wrong target Hb for the wrong patient?
- Is it too much ESA?
- Is it underlying illness, compounded by high ESA dosages?
- **Should iron be the starting point in anaemia management?**
- Should there be a target Hb when considering iron repletion in patients with ND-CKD?

TREAT Study: Hb response to ESA



No. of patients

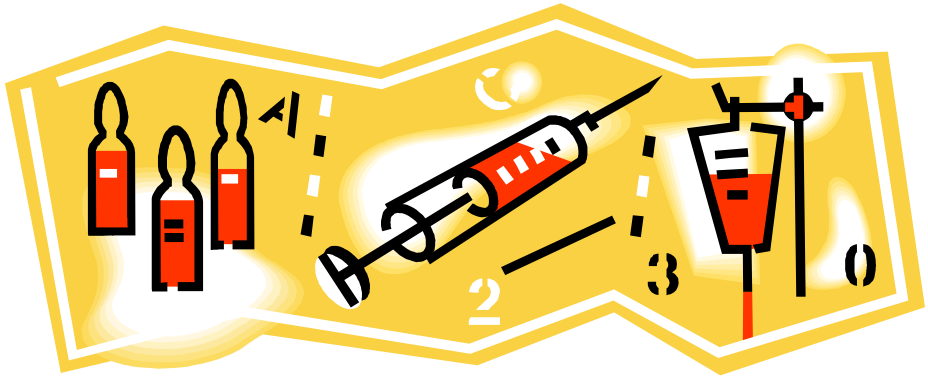
Darbepoetin alfa	2004	1768	1503	1300	946	635	404	253	97
Placebo	2019	1742	1460	1221	887	620	356	216	79

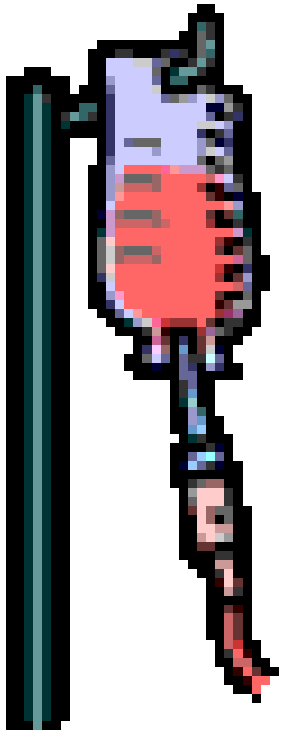
Mean (standard error) Hb levels through 48 months among patients who were assigned to receive darbepoetin alfa or placebo.

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

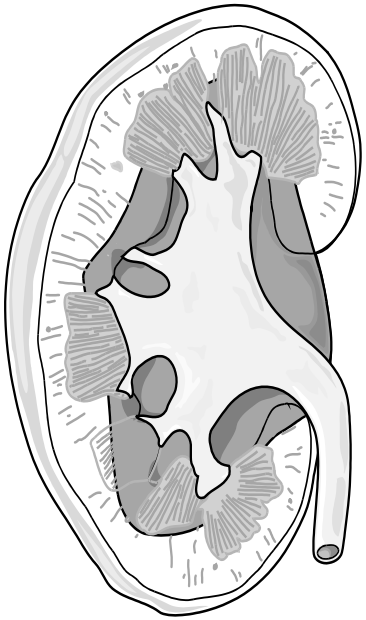
TREAT – interventions

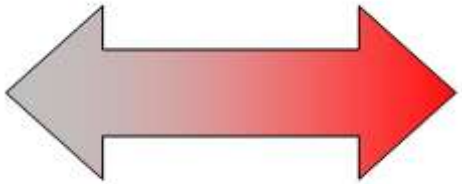
- Iron repletion was frequent throughout the study:
  - 66.8% in the darbepoetin alfa group vs 68.6% in the placebo group received oral iron (P=0.25)
  - More patients in the placebo group received i.v. iron (20.4% vs 14.8% in the darbepoetin alfa group; P<0.001)
- Red-blood-cell transfusion was more frequent in the placebo group (24.5% vs 14.8% in the darbepoetin alfa group; P<0.001)





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





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ORIGINAL ARTICLE

Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

Stefan D. Anker, M.D., Ph.D., Josep Comin Colet, M.D., Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D., Kenneth Dickstein, M.D., Ph.D., Helmut Drexler, M.D.,* Thomas F. Lüscher, M.D., Boris Bart, M.D., Waldemar Banasiak, M.D., Ph.D., Joanna Niegowska, M.D., Bridget-Anne Kirwan, Ph.D., Claudio Mori, M.D., Barbara von Eisenhart Rothe, M.D., Stuart J. Pocock, Ph.D., Philip A. Poole-Wilson, M.D.,* and Piotr Ponikowski, M.D., Ph.D., for the FAIR-HF Trial Investigators†

ABSTRACT

BACKGROUND

Iron deficiency may impair aerobic performance. This study aimed to determine whether treatment with intravenous iron (ferric carboxymaltose) would improve

Anker SD *et al*. *N Engl J Med* 2009;361:2436–48

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ORIGINAL ARTICLE

Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

- 459 patients
- Chronic heart failure NYHA II or III
- Left ventricular ejection fraction (LVEF) of 40–45%
- Iron deficiency: ferritin level
  - <100 µg/L or
  - between 100 and 299 µg/L if TSAT <20%
- Hb level of 9.5–13.5 g/dL
- 200 mg of intravenous (i.v.) iron (FCM)/week to achieve iron repletion or saline (placebo) and maintance of 200mg iron every 4 weeks

FCM, ferric carboxymaltose; NYHA, New York Heart Association ; TSAT, transferrin saturation

Anker SD *et al*. *N Engl J Med* 2009;361:2436–48

FAIR-HF: baseline demographics

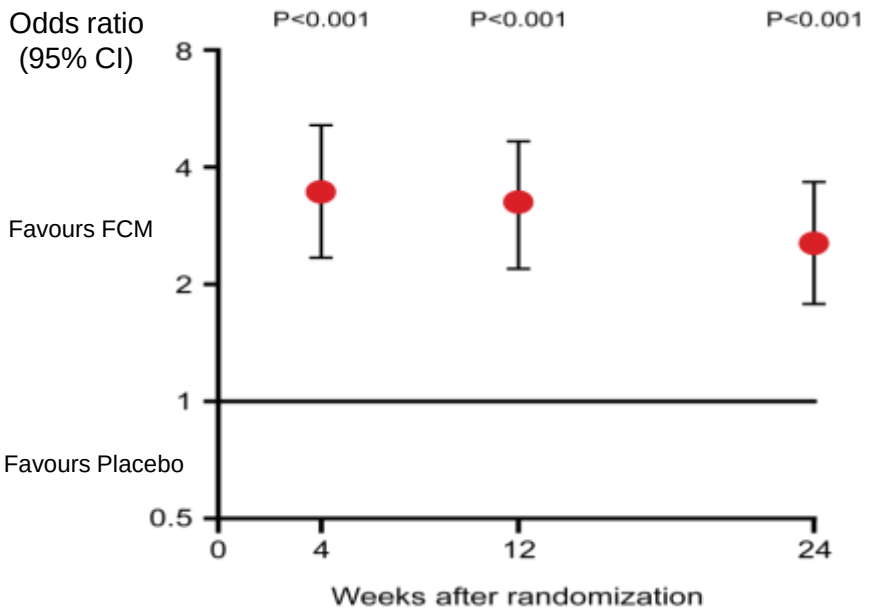
Baseline demographic and clinical characteristics of the study population in the intent-to-treat population, according to study group		
Laboratory measurements*	**FCM**	**Placebo**
Hb (g/dL)	11.9 (1.3)	11.9 (1.4)
Mean corpuscular volume (μm^3)	92 (8.1)	92 (6.7)
Serum ferritin (µg/L)	53 (55)	60 (67)
Transferrin saturation (%)	17.7 (12.6)	16.7 (8.4)
C-reactive protein (mg/L)	7.5 (5.3)	9.1 (5.5)
Sodium (mmol/L)	141 (3)	141 (3)
Potassium (mmol/L)	4.65 (0.61)	4.58 (0.52)
Alanine aminotransferase (U/L)	20.5 (12.3)	18.8 (8.1)
Aspartate aminotransferase (U/L)	23.1 (10.4)	22.4 (7.2)
Creatinine (mg/dL)	1.2 (0.6)	1.2 (0.6)
Estimated glomerular filtration rate (mL/min/1.73 m^2)	64 (21)	65 (25)

* Mean (SD)

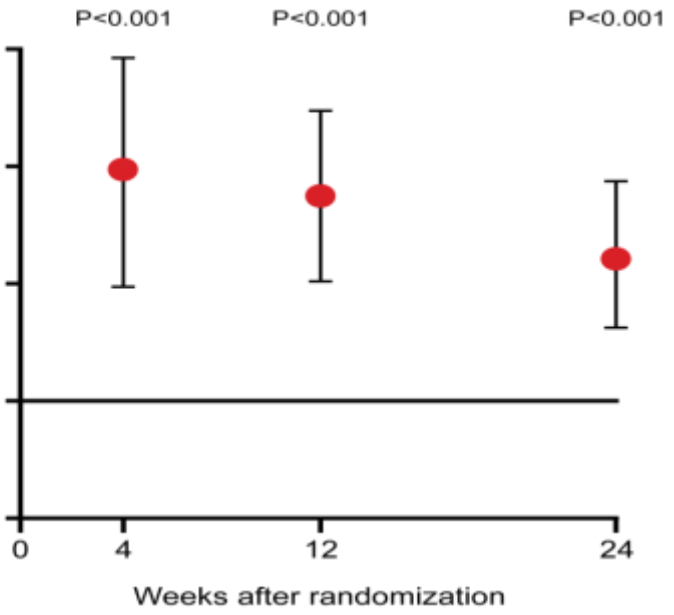
Anker SD *et al*. *N Engl J Med* 2009;361:2436–48

FAIR-HF: improved symptoms and functional status

Patient Global Assessment Score



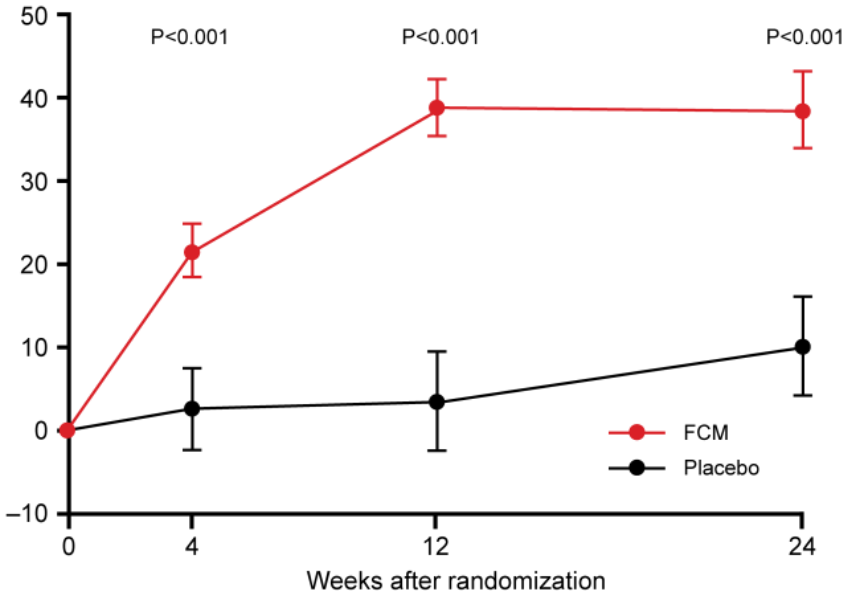
NYHA Functional Class



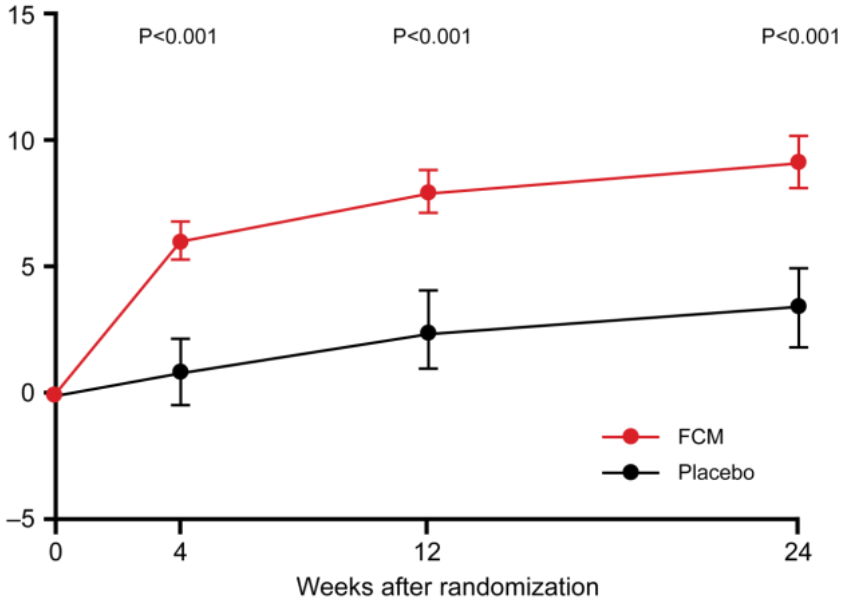
Anker SD *et al*. *N Engl J Med* 2009;361:2436–48

FAIR-HF: improved exercise capacity and QoL

Change (m) **6-minute walk test**



Change in score **EQ-5D VAS**

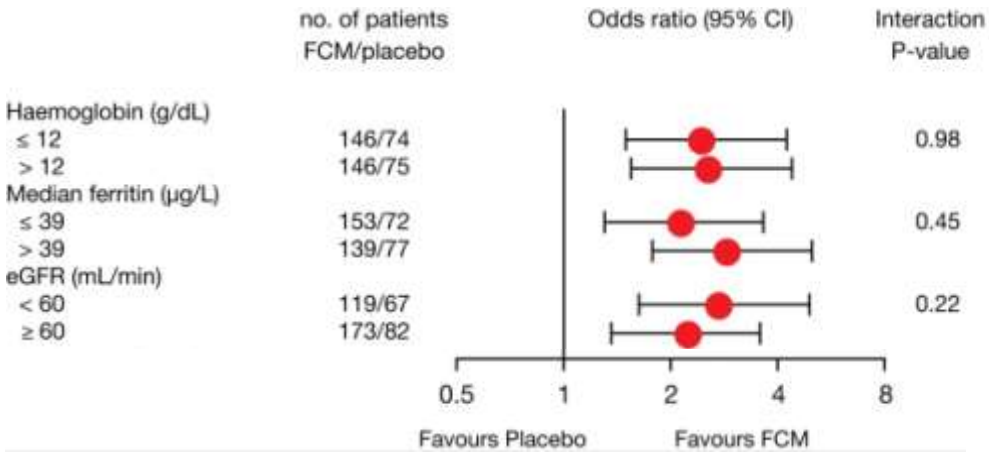


EQ-5D, European Quality of Life – 5 Dimensions; VAS, visual analogue scale

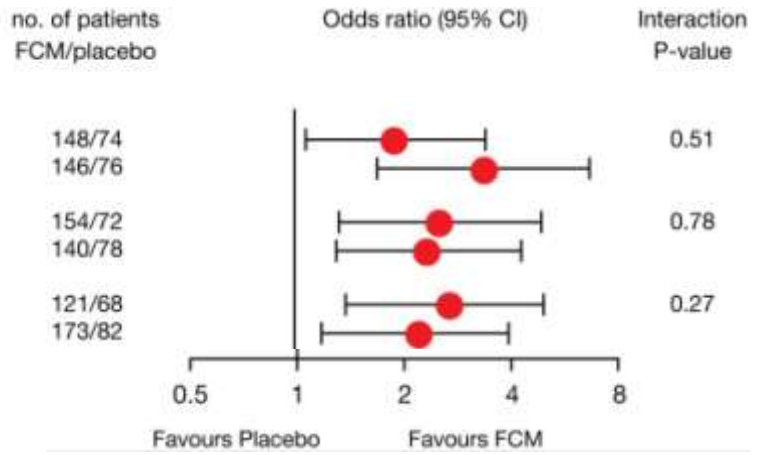
Anker SD *et al*. *N Engl J Med* 2009;361:2436–48

FAIR-HF: analyses for Hb, ferritin and eGFR

Self-reported Patient Global Assessment Score



NYHA Functional Class



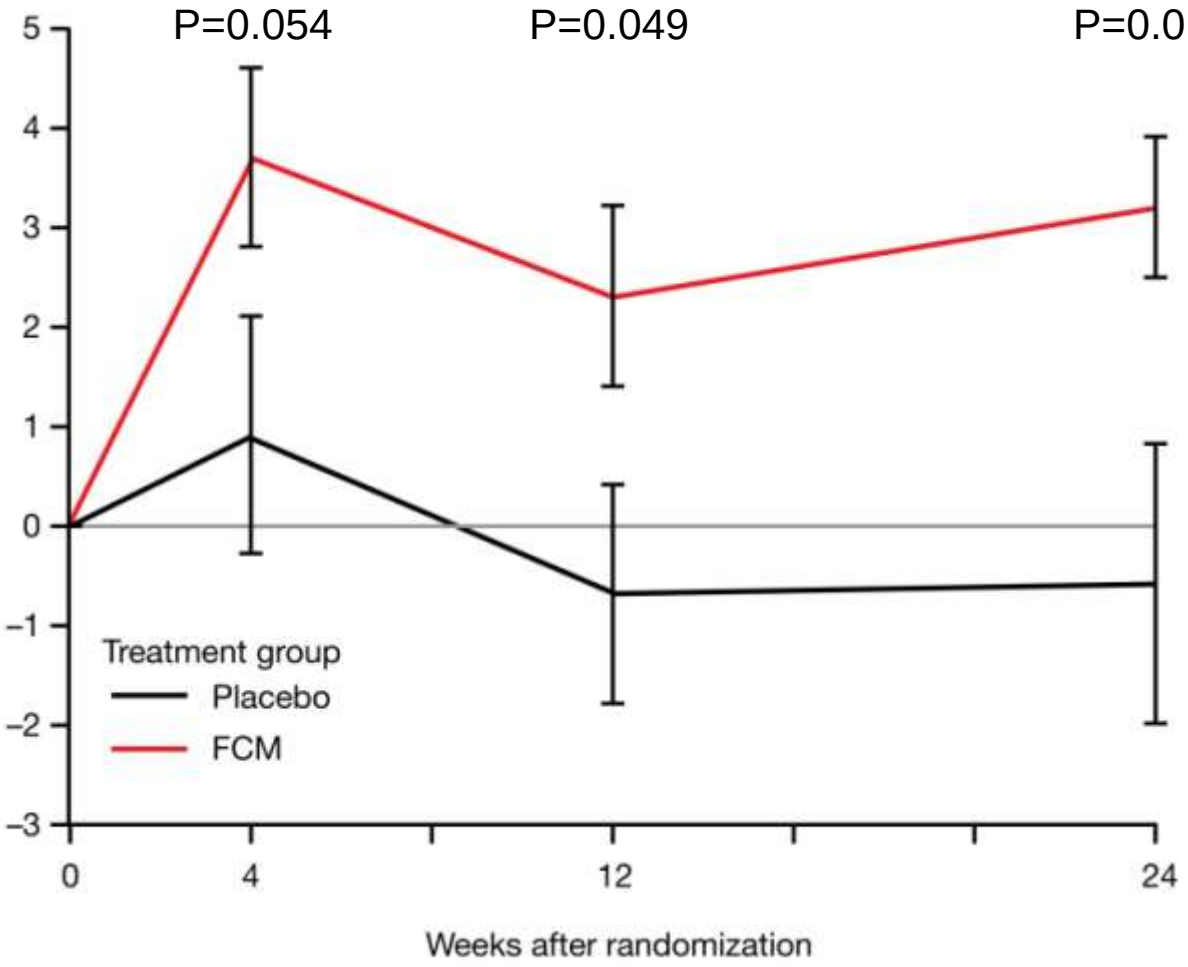
In the anaemic sub-population, a significant rise in Hb of almost 1 g/dL was observed over the 6-month treatment period

eGFR, estimated glomerular filtration rate

Anker SD *et al*. *N Engl J Med* 2009;361:2436–48

Impact of i.v. FCM on renal function

Change in eGFR ($mL/min/1.73m^2$)*



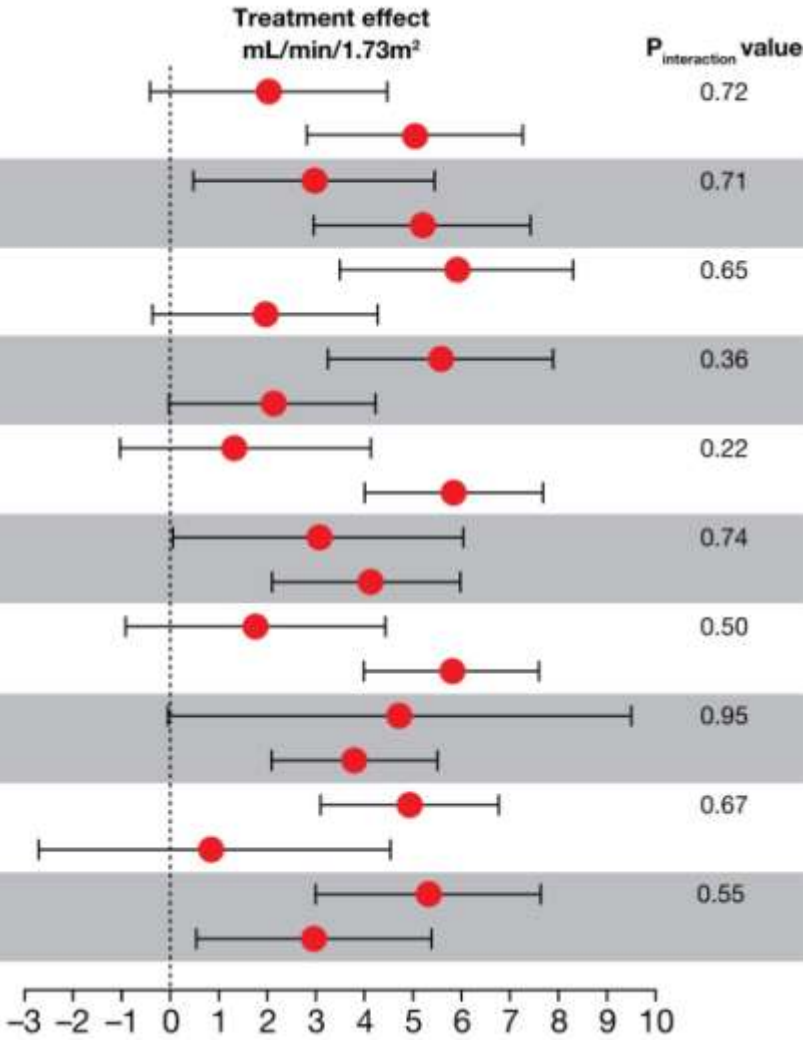
Treatment effect ($mL/min/1.73\ m^2$)*:	**2.8 ± 1.5**	**3.0 ± 1.5**	**4.0 ± 1.7**

* Least square mean ± SE

Ponikowski P *et al.* HFA Congress 2010; Abstract 114 & LBT Oral Presentation

Treatment effect on renal function in predefined subgroups

Endpoint (Week 24)	FCM	Placebo	$P_{interaction}$ value
eGFR <60 mL/min/1.73 m²	8.19 ± 1.42	6.13 ± 2.00	0.72
eGFR ≥60 mL/min/1.73 m²	−0.24 ± 1.23	−5.31 ± 1.87	
Hb ≤12 g/dL	4.11 ± 1.42	1.10 ± 2.04	0.71
Hb >12 g/dL	2.76 ± 1.22	−2.46 ± 1.86	
Ferritin ≤39 µg/L	4.35 ± 1.30	−1.58 ± 2.02	0.65
Ferritin >39 µg/L	2.32 ± 1.34	0.36 ± 1.88	
Age ≤69.7 years	3.22 ± 1.42	−2.64 ± 2.15	0.36
Age >69.7 years	3.61 ± 1.21	1.45 ± 1.75	
Male	3.29 ± 1.54	2.02 ± 2.40	0.22
Female	3.46 ± 1.09	−2.41 ± 1.52	
NYHA Class II	1.31 ± 1.63	−1.80 ± 2.45	0.74
NYHA Class III	3.88 ± 1.09	−0.20 ± 1.60	
LVEF ≤33%	4.21 ± 1.41	2.45 ± 2.31	0.50
LVEF >33%	2.44 ± 1.11	−3.40 ± 1.46	
Non-ischaemic HF	5.40 ± 2.73	0.64 ± 3.89	0.95
Ischaemic HF	2.97 ± 0.95	−0.86 ± 1.42	
Non diabetic	3.30 ± 1.07	−1.63 ± 1.50	0.67
Diabetic	3.77 ± 1.88	2.88 ± 3.19	
BMI ≤27.37kg/m²	3.66 ± 1.25	−1.67 ± 1.90	0.55
BMI >27.37kg/m²	3.08 ± 1.39	0.12 ± 1.98	



BMI, body mass index; HF, heart failure

Ponikowski P *et al.* HFA Congress 2010; Abstract 114 & LBT Oral Presentation

FAIR-HF: QoL subanalysis

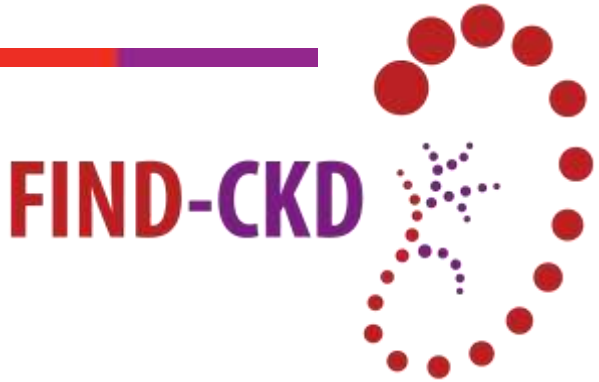
- FCM improved HRQoL in patients
  - *with and without* ***anaemia*** (p-values for interaction: 0.93 [VAS] and 0.66 [KCCQ overall score])
  - *with and without* ***chronic kidney disease*** (42% had eGFR <60 mL/min/1.73 m^2; p-values for interaction: 0.36 [VAS] and 0.24 [KCCQ overall score])
- "Intravenous FCM significantly improved QoL during 24 weeks of therapy. The positive effects were seen after 4 weeks of treatment and were independent of anaemia status and the presence of CKD."

Comin-Colet J. XLVII ERA-EDTA 2010; Abstract 451242.

FIND-CKD STUDY

Intravenous iron in the ND-CKD population:

Hypothesis



That the use of i.v. iron in patients with ND-CKD with iron-deficiency anaemia will provide effective Hb correction to postpone the use of ESA therapy

Macdougall IC. *J Ren Care* 2009;35(Suppl 2):8–13.
www.clinicaltrial.gov; NCT00994318

Rationale for FIND-CKD Study

- Guidelines for the management of iron deficiency in CKD
- Available studies examining the management of iron deficiency in pre-dialysis CKD

CARI
Caring for Australasians with Renal Impairment

Iron in patients with CKD and anaemia

Uncontrolled studies

Study	Iron agents	N	Follow-up	% on ESA	Conclusions
Silverberg DS *et al.* *Am J Kidney Dis* 1996;27:234–8	Intravenous iron sucrose (previously failed on oral iron)	33	6 months	0	22/33 patients treated with i.v. iron had an Hb response 0.4–3.6 g/dL
Mircescu G *et al.* *Nephrol Dial Transplant* 2006;21:120–4	Intravenous iron sucrose	60	12 months	0	55% of patients reached Hb >11 g/dL after 12 months' i.v. iron
Silverberg DS *et al.* *Clin Nephrol* 2001;55:212–9	Intravenous iron sucrose	90	12 months	50%	Intravenous iron augmented low-dose ESA in patients with ND-CKD
Tagboto S *et al.* *J Ren Care* 2009;35:18–23	Intravenous FCM	30	1 month	20%	Hb levels increased in 80% of patients

Macdougall IC. *J Ren Care* 2009;35(Suppl 2):8–13.

Iron in patients with CKD and anaemia

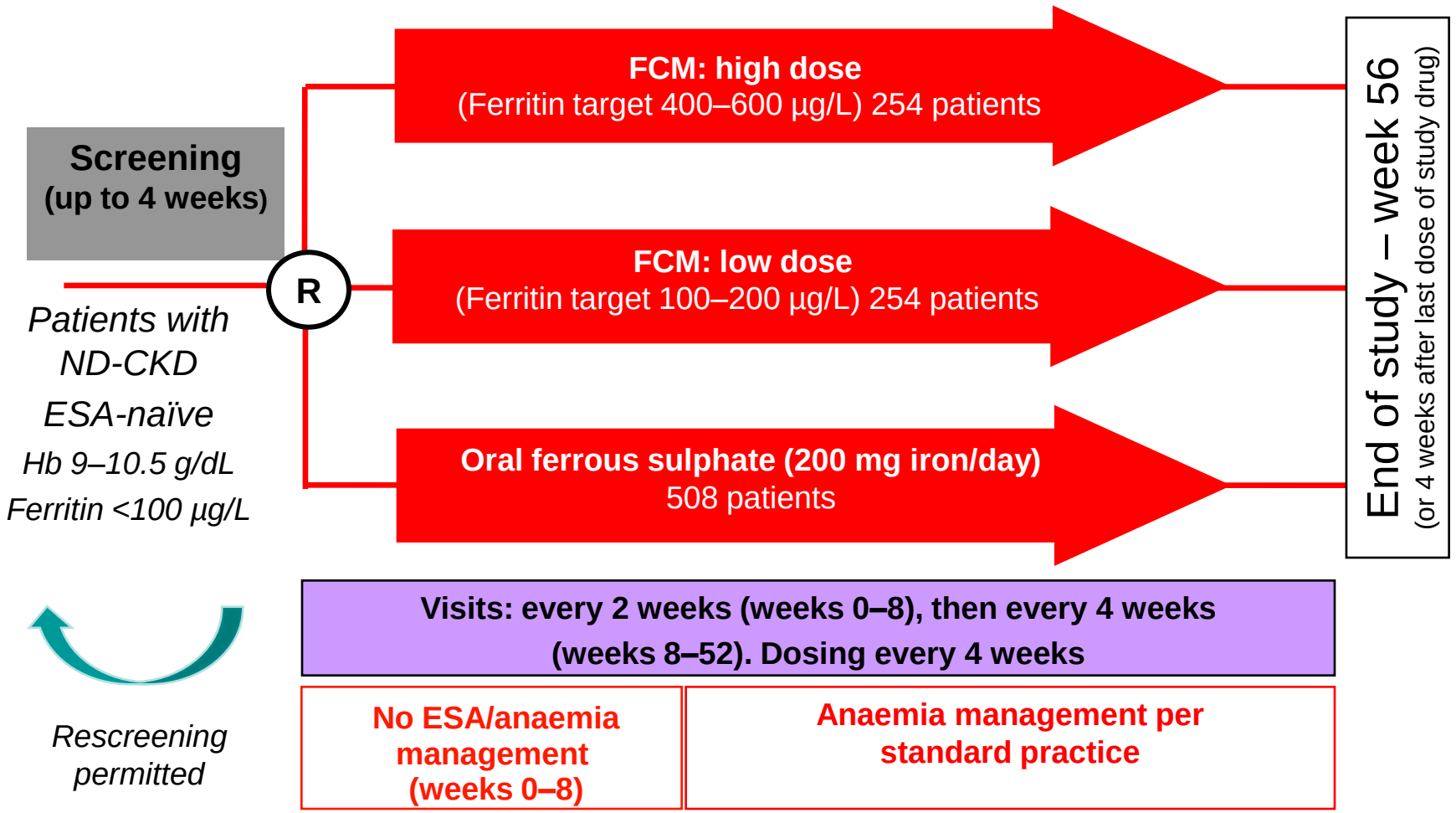
Randomized controlled trials (RCTs)

Study	Iron agents	N	Follow-up	% on ESAs	Conclusions
Van Wyck DB *et al.* *Kidney Int* 2005;68:2846–56	Intravenous iron sucrose vs oral ferrous sulphate	95 vs 93	8 weeks	38–41%	Intravenous iron superior to oral iron; no difference in AEs
Charytan C *et al.* *Nephron Clin Pract* 2005;100:c55–62	Intravenous iron sucrose vs oral ferrous sulphate	48 vs 48	6 weeks	100%	Intravenous iron superior to oral iron; no difference in AEs
Agarwal R *et al.* *Am J Nephrol* 2006;26:445–54	Intravenous sodium ferric gluconate vs oral ferrous sulphate	36 vs 39	6 weeks	0	Faster repletion of iron stores with i.v. iron; ↑ QoL
Aggarwal HK *et al.* *J Assoc Physic India* 2003;51:170–4	Intravenous iron dextran vs oral ferrous sulphate	20 vs 20	3 months	100%	Intravenous iron superior to oral iron; no difference in AEs
Stoves J *et al.* *Nephrol Dial Transplant* 2001;16:967–74	Intravenous iron sucrose vs oral ferrous sulphate	22 vs 23	6 months	100%	No difference between i.v. iron and oral iron
Spinowitz BS *et al.* *J Am Soc Nephrol* 2009;19:1599–605	Intravenous ferumoxytol vs oral iron	228 vs 76	5 weeks	36–43%	Intravenous iron superior to oral iron; fewer AEs
Qunibi W *et al.* ERA-EDTA Congress 2008;Abs MO018	Intravenous FCM vs oral ferrous sulphate	147 vs 103	8 weeks	23–25%	Intravenous iron superior to oral iron; fewer AEs

AE, adverse event

Macdougall IC. *J Ren Care* 2009;35(Suppl 2):8–13.

FIND-CKD: defining the role of iron in CKD



Macdougall IC. *J Ren Care* 2009;35(Suppl 2):8–13.
www.clinicaltrial.gov; NCT00994318

FIND-CKD: study objectives

- Primary objectives:
  - Evaluate the long-term efficacy of FCM or oral iron to delay and/or reduce ESA use and/or other anaemia management options in patients with ND-CKD and iron-deficiency anaemia
- Secondary objectives:
  - Evaluate the ESA requirements, long-term safety and tolerability of iron therapy
  - Assess the health resource and economic burden of the treatment of anaemia in patients with ND-CKD

Macdougall IC. *J Ren Care* 2009;35(Suppl 2):8–13.
www.clinicaltrial.gov; NCT00994318

What is wrong with anaemia management in 2010?

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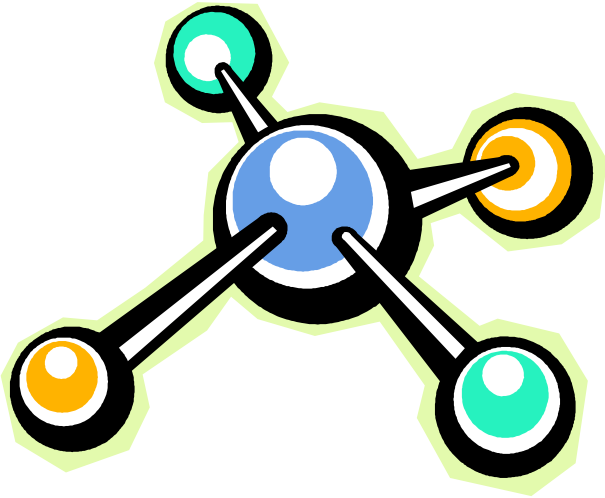

Fe Iron

Atomic Number: 26

Atomic Mass: 55.85

Iron and anaemia management in ND-CKD: where are we going?

XLVII ERA-EDTA Congress

Munich, Germany
26 June 2010