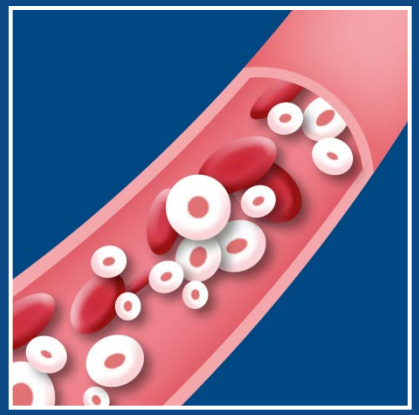
Nephro Update Europe 2018

5-6 October, Budapest

Renal Anemia



Iain Macdougall, UK

Conflicts of Interest

Research Support: Akebia, Astellas, GSK, Vifor Pharma

Lecturing: Akebia, Astellas, FibroGen, Pharmacosmos, Vifor Pharma

Consulting activities: Akebia, AMAG, GSK, Vifor Pharma

Subtopics

- Pathogenesis of Renal anemia
- ESA and iron therapy – standard-of-care
- Iron management (oral *vs* IV) in ND-CKD
- IV iron in HD
- HIF stabilisers
- Newer iron management strategies

Pathogenesis of Renal anemia

Nephrol Dial Transplant (2018) 1–2
doi: 10.1093/ndt/gfy266

Geddes CC *et al.* *Nephrol Dial Transplant 2018:1-2.*

Pathophysiology of renal anaemia

Colin C. Geddes

Glasgow Renal and Transplant Unit, UK

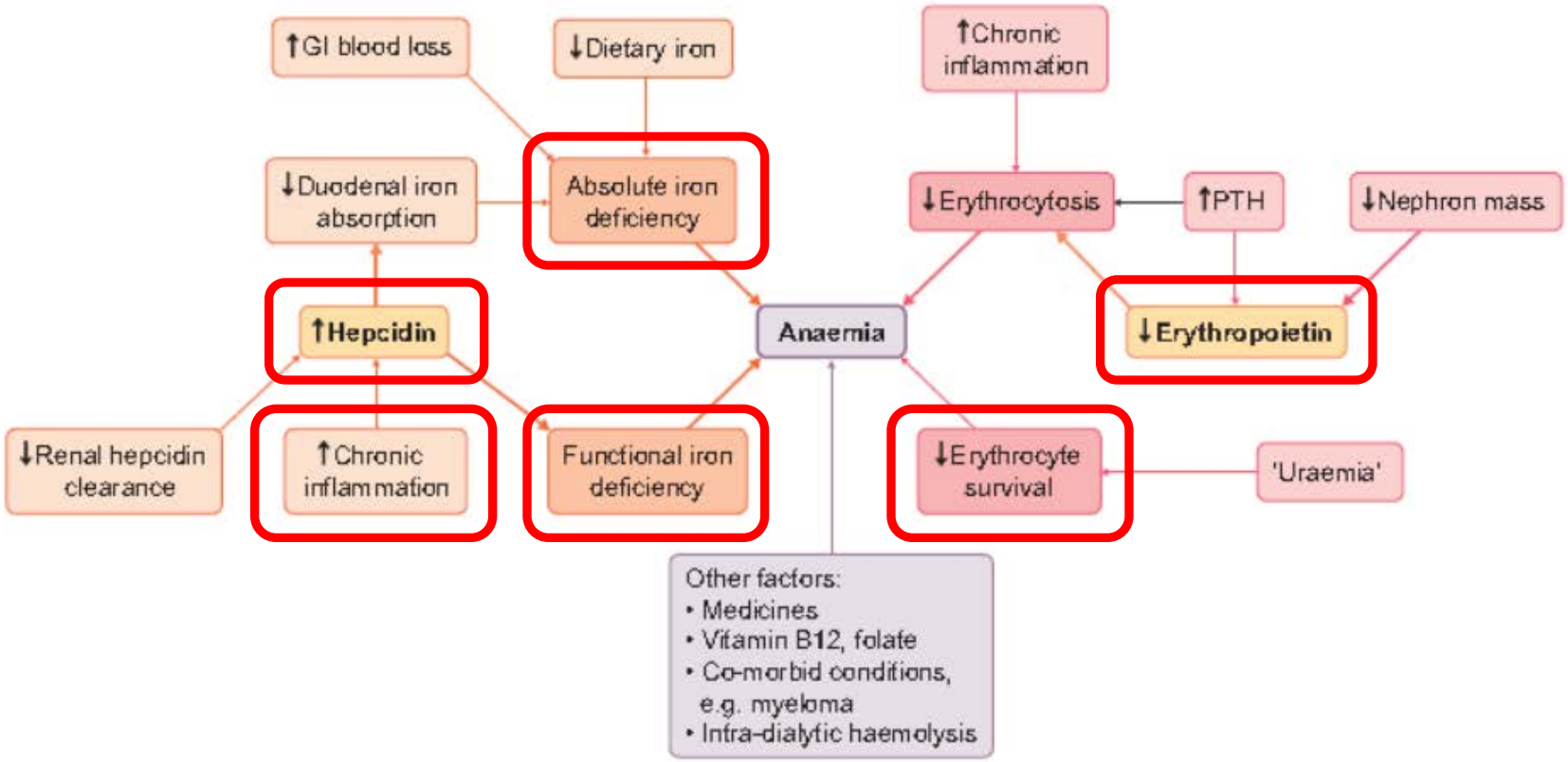


FIGURE 1: Schematic representation of factors involved in the pathophysiology of anaemia in patients with chronic kidney disease. The bold arrows represent the more dominant pathways.

Fibroblast Growth Factor 23 and Anemia in the Chronic Renal Insufficiency Cohort Study

Rupal Mehta, Xuan Cai, Alexander Hodakowski, Jungwha Lee, Mary Leonard, Ana Ricardo, Jing Chen, Lee Hamm, James Sondheimer, Mirela Dobre, Valentin David, Wei Yang, Alan Go, John W. Kusek, Harold Feldman, Myles Wolf, and Tamara Isakova, for the CRIC Study Investigators

Abstract

Background and objectives Anemia is an early complication of CKD that is associated with increased morbidity and mortality. Prior data show associations between abnormal mineral metabolism markers and decreased erythropoiesis. However, few studies have investigated elevated fibroblast growth factor 23 as a risk factor for the development of anemia in patients with CKD.

Design, setting, participants, & measurements We conducted a prospective cohort study of 3869 individuals with mild to severe CKD enrolled in the Chronic Renal Insufficiency Cohort Study between 2003 and 2008 and followed through 2013. We hypothesized that elevated baseline fibroblast growth factor 23 levels are associated with prevalent anemia, decline in hemoglobin over time, and development of incident anemia, defined as serum hemoglobin level <13 g/dl in men, serum hemoglobin level <12 g/dl in women, or use of erythropoietin stimulating agents.

Results In the 1872 of 3869 individuals who had prevalent anemia at baseline, mean age was 58 (11) years old, and mean eGFR was 39 (13) ml/min per 1.73 m^2. Higher levels of fibroblast growth factor 23 were significantly associated with prevalent anemia (odds ratio per 1-SD increase in natural log–transformed fibroblast growth factor 23, 1.39; 95% confidence interval, 1.26 to 1.52), decline in hemoglobin over 4 years, and risk of incident anemia (hazard ratio per 1-SD increase in natural log–transformed fibroblast growth factor 23, 1.13; 95% confidence interval, 1.04 to 1.24; quartile 4 versus quartile 1: hazard ratio, 1.59; 95% confidence interval, 1.19 to 2.11) independent of demographic characteristics, cardiovascular disease risk factors, CKD-specific factors, and other mineral metabolism markers. The results of our prospective analyses remained unchanged after additional adjustment for time-varying eGFR.

Conclusions Elevated fibroblast growth factor 23 is associated with prevalent anemia, change in hemoglobin over time, and development of anemia. Future studies are needed to elucidate the mechanisms for these associations.

Clin J Am Soc Nephrol 12: 1795–1803, 2017. doi: https://doi.org/10.2215/CJN.03950417

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

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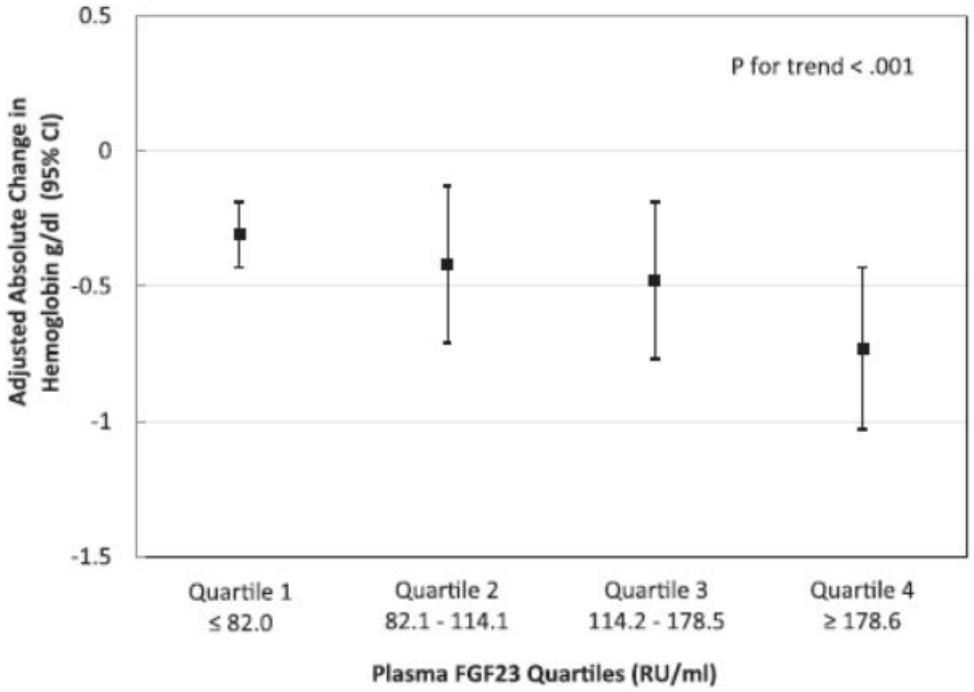
CRIC: prospective cohort study

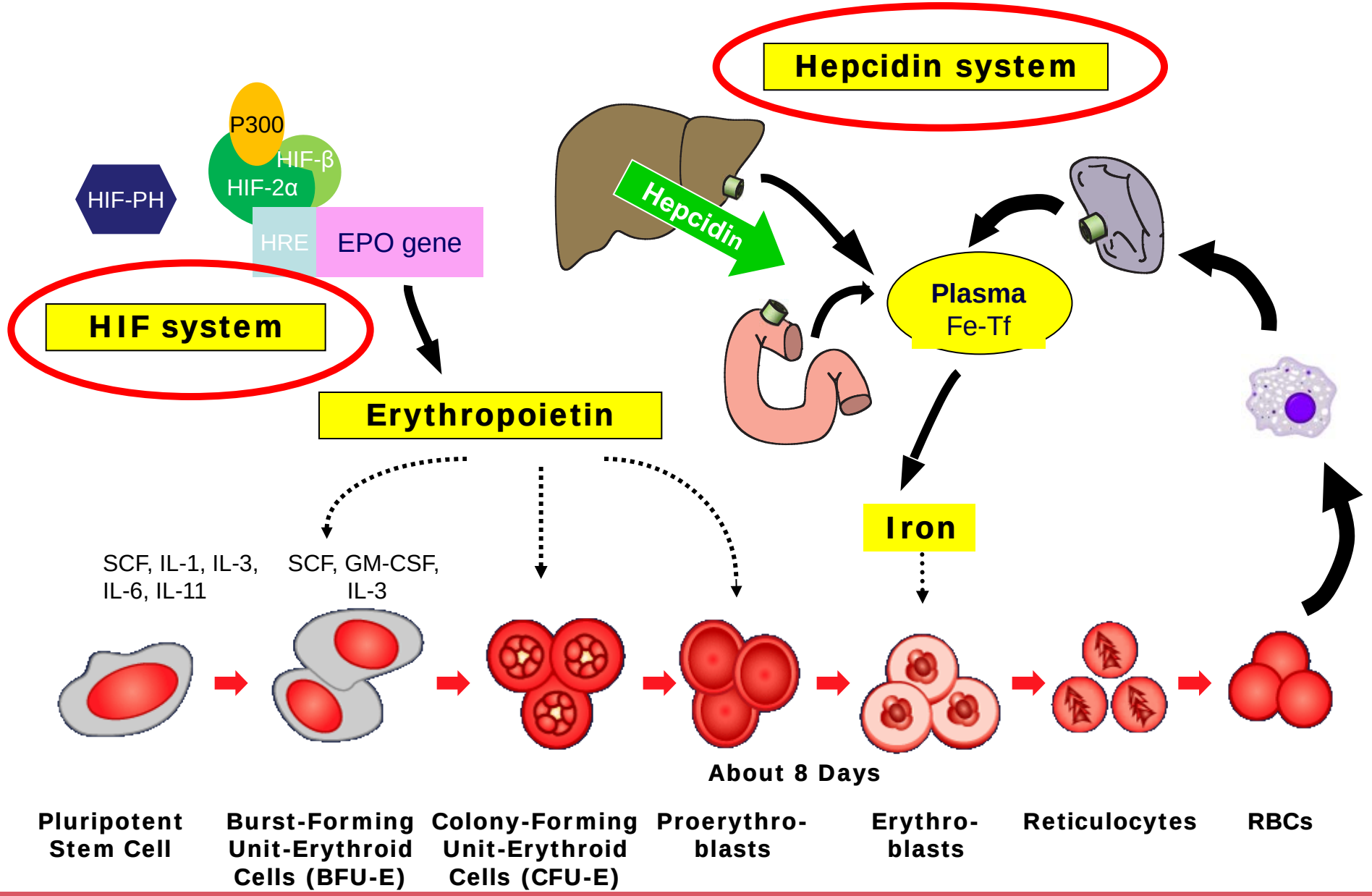
- 3869 individuals 2003-2008 – 1872 had anemia
- ↑ FGF23 associated with: **prevalent** anemia (OR 1.39 (1.26–1.52)
  decline in Hb over 4 years
  incident anemia (HR 1.13 (1.04–1.24)
  (adjusted for time-varying eGFR)



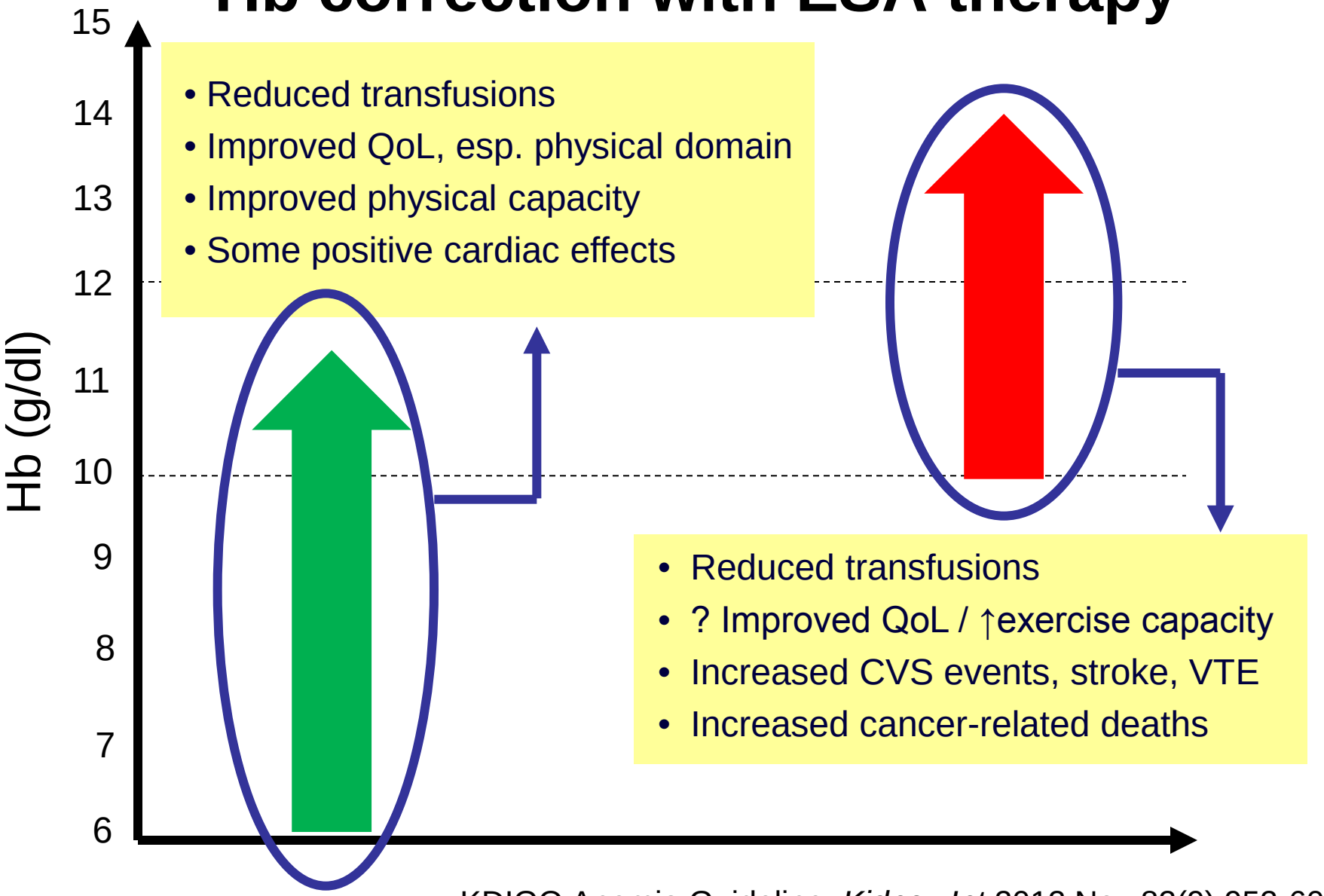
Mehta R et al. *CJASN* 2017; 12: 1795-1803.

ESA and iron therapy – standard-of-care

Regulation of erythropoiesis

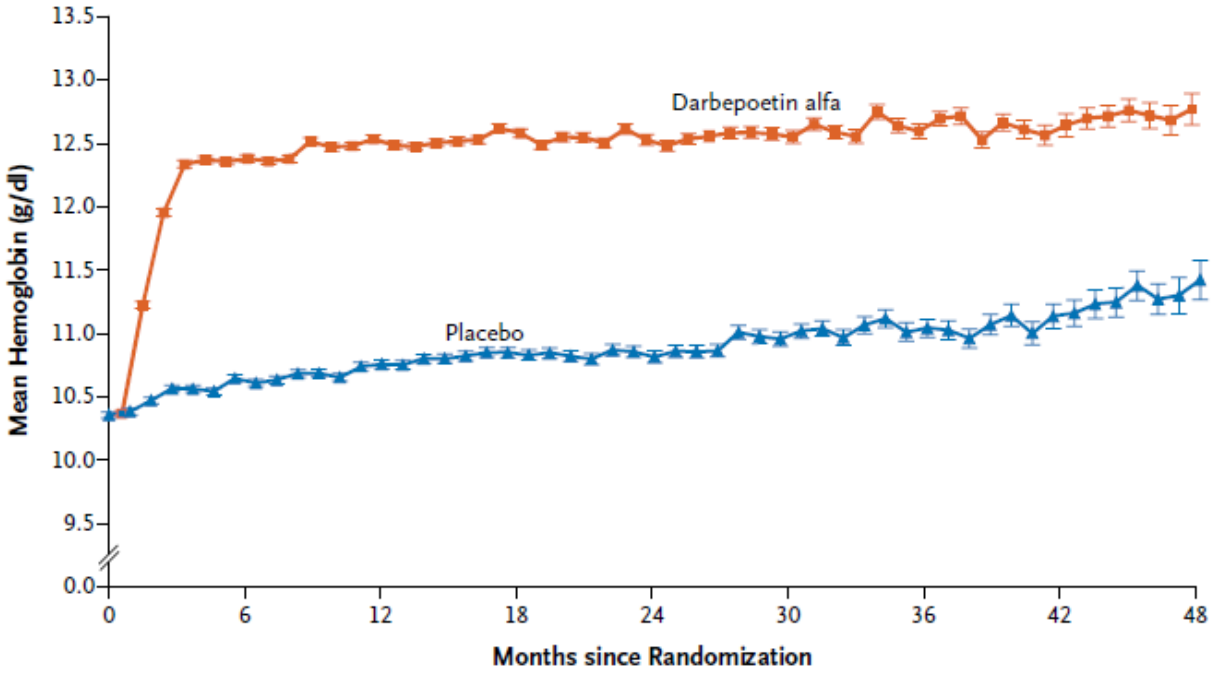


Hb correction with ESA therapy



KDIGO Anemia Guideline, *Kidney Int* 2012 Nov;82(9):952-60.

TREAT study: Haemoglobin



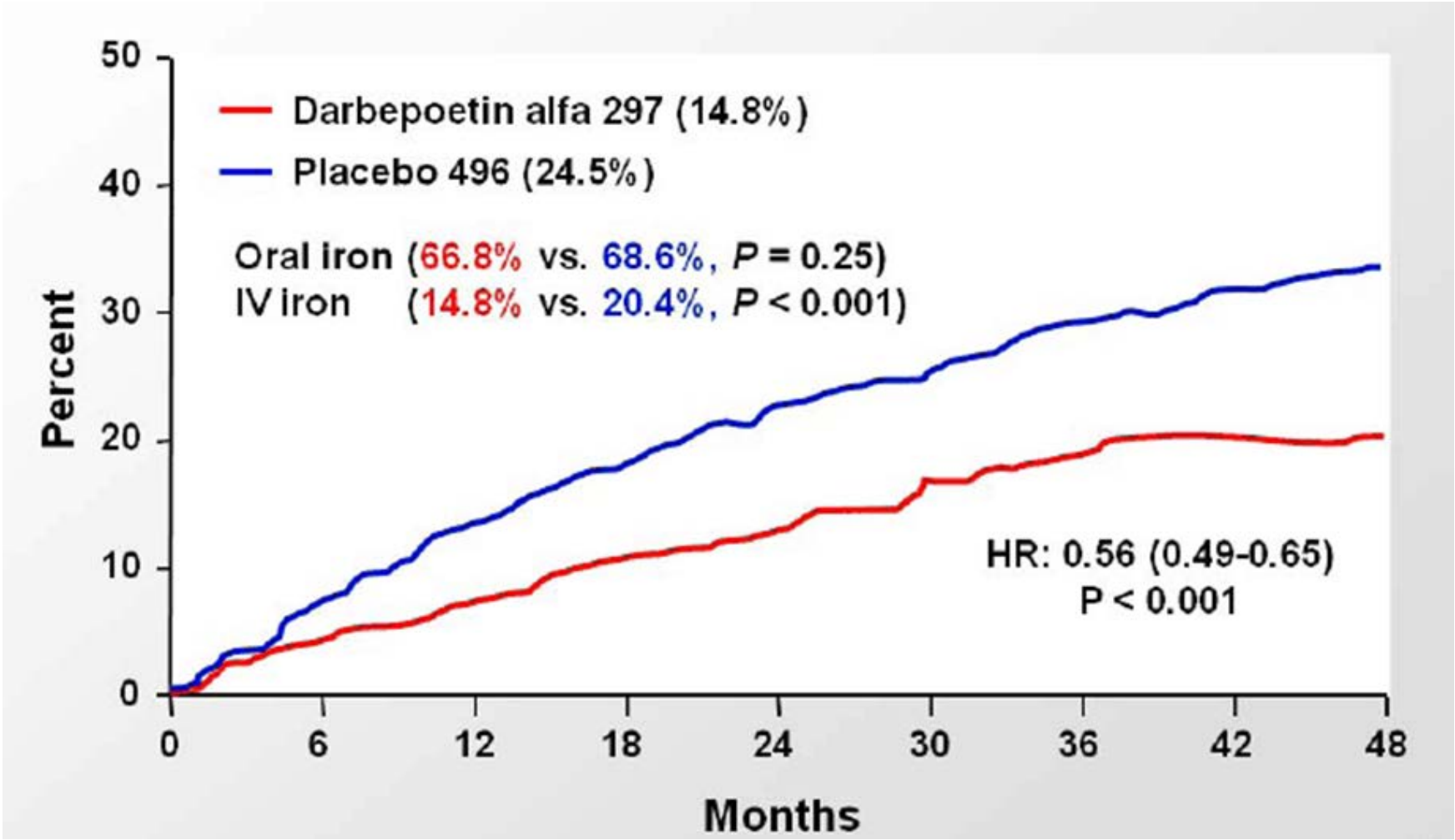
No. of Patients									
Darbepoetin alfa	2004	1768	1503	1300	946	635	404	253	97
Placebo	2019	1742	1460	1221	887	620	356	216	79

Figure 1. Mean Hemoglobin Levels through 48 Months among Patients Who Were Assigned to Receive Darbepoetin Alfa or Placebo.

I bars represent standard errors.

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

TREAT study: Blood transfusions

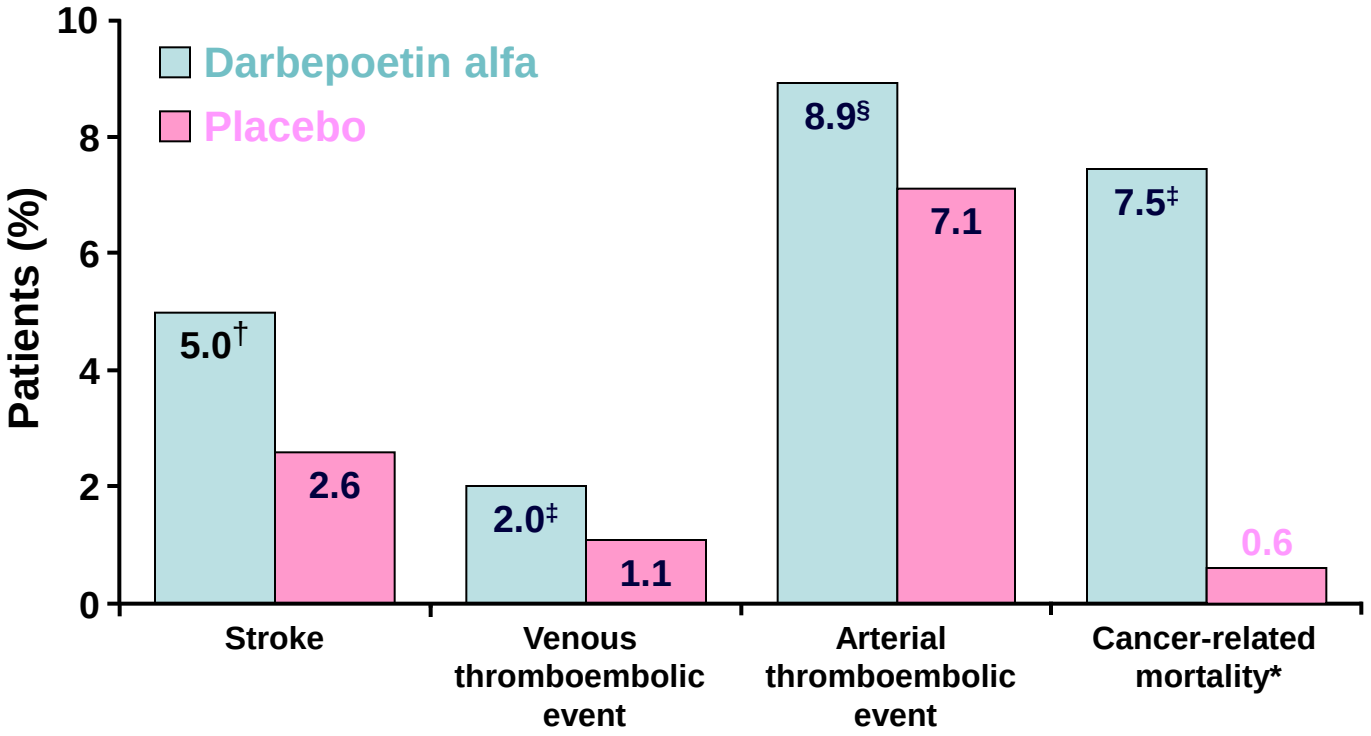


Pfeffer MA *et al.* *N Engl J Med* 2009; 361: 2019-32.

What were the major concerns in the TREAT study?

A. Doubling of all-cause mortality
B. Doubling of heart attack risk
C. Doubling of stroke risk
D. Increase in cancer -related death for all subjects randomised to the active arm?

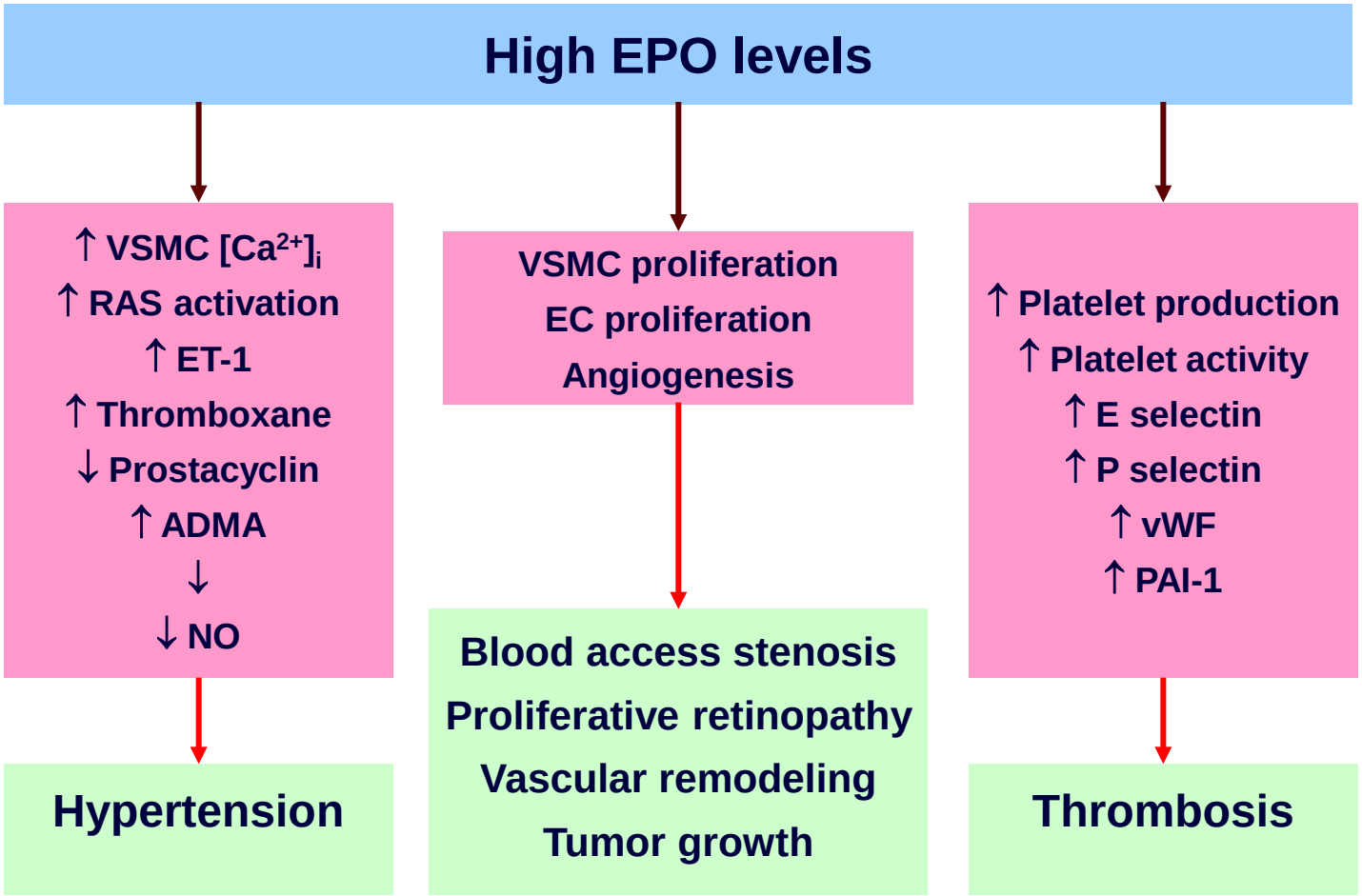
TREAT study: Safety issues



†, p<0.001 versus placebo
‡, p=0.02 versus placebo
§, p=0.04 versus placebo
*Amongst patients with a history of malignancy at baseline

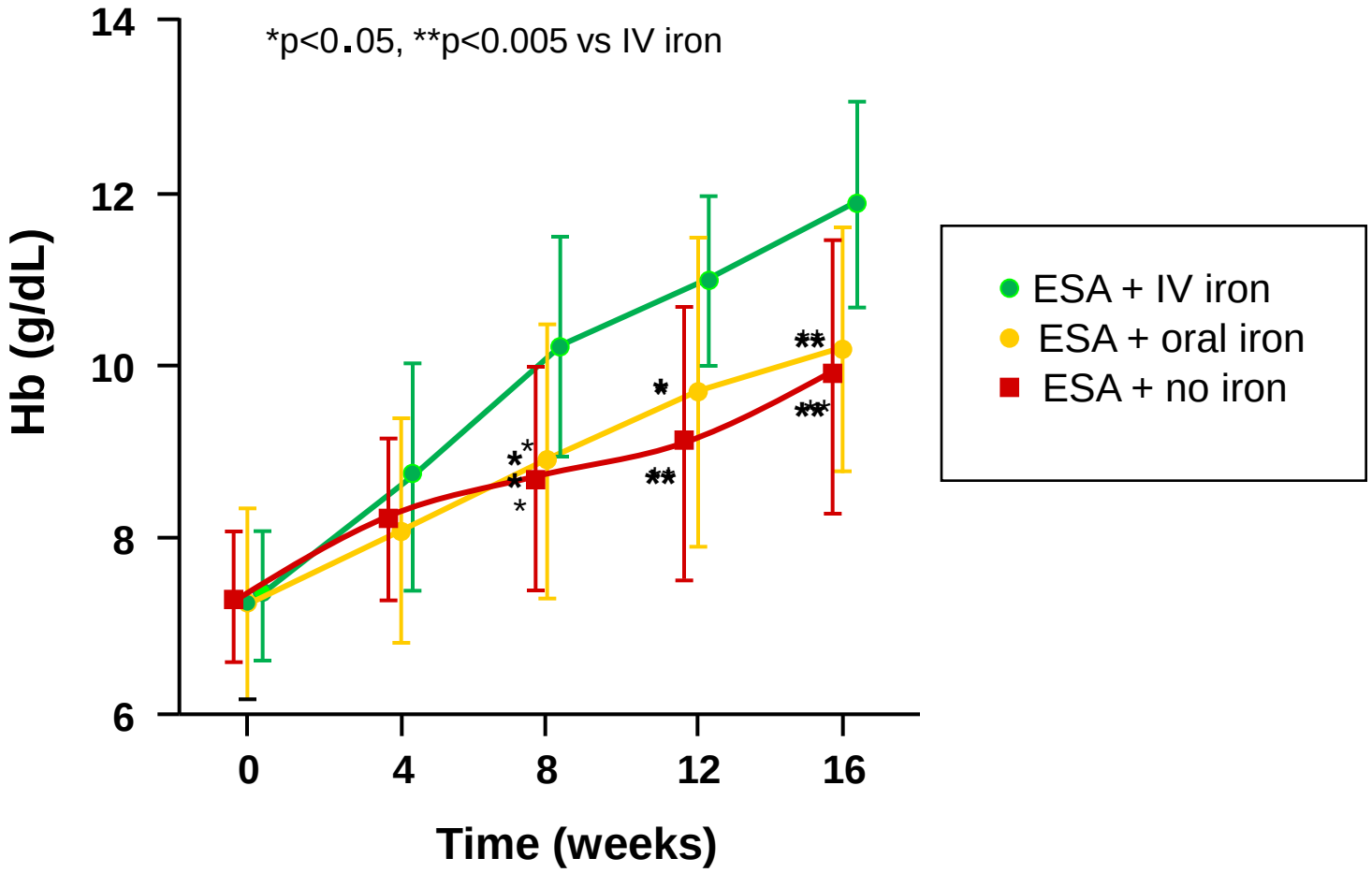
Pfeffer MA *et al.* *N Engl J Med* 2009; 361: 2019-32.

EPO has non-erythropoietic actions



Vaziri ND & Zhou X. *Nephrol Dial Transplant* 2009; 24: 1082–1088.

IV iron enhances the response to ESAs



Macdougall IC *et al.* *Kidney Int* 1996; 50: 1694-1699.

Which of the following are concerns regarding the liberal use of IV iron?

a) Increased oxidative stress
b) Increased atherogenesis
c) Increased risk of renal progression
d) Increased risk of diabetes
e) Increased risk of infection
f) Increased all-cause and CV mortality

A. (a),(b),(e)

B. (b),(c),(e)

C. (a),(b),(c),(e),(f)

D. All of the above

KDIGO Controversies Conference on Iron Management in CKD

Concerns about IV iron

- **Iron Overload**
- **Inflammation & Oxidative Stress (Renal tubular toxicity)**
- **Iron & Infection**
- **Hypersensitivity Reactions to IV Iron**

Macdougall IC *et al.* *Kidney Int* 2016; 89 : 28-39.

Take-Home Messages

- ESA therapy and IV iron are the mainstay of anaemia management in CKD
  - -- both have unquestionable efficacy
  - -- both have safety concerns

- The relative balance between the two remains obscure

Iron management (oral vs IV) in ND-CKD

How would you treat the following CKD patient?

- 37 years woman c/o worsening fatigue
- CKD due to reflux nephropathy
- eGFR 24
- Hb 9.6 g/dl
- Ferritin 15 ug/l
- TSAT 17%

A. Oral iron

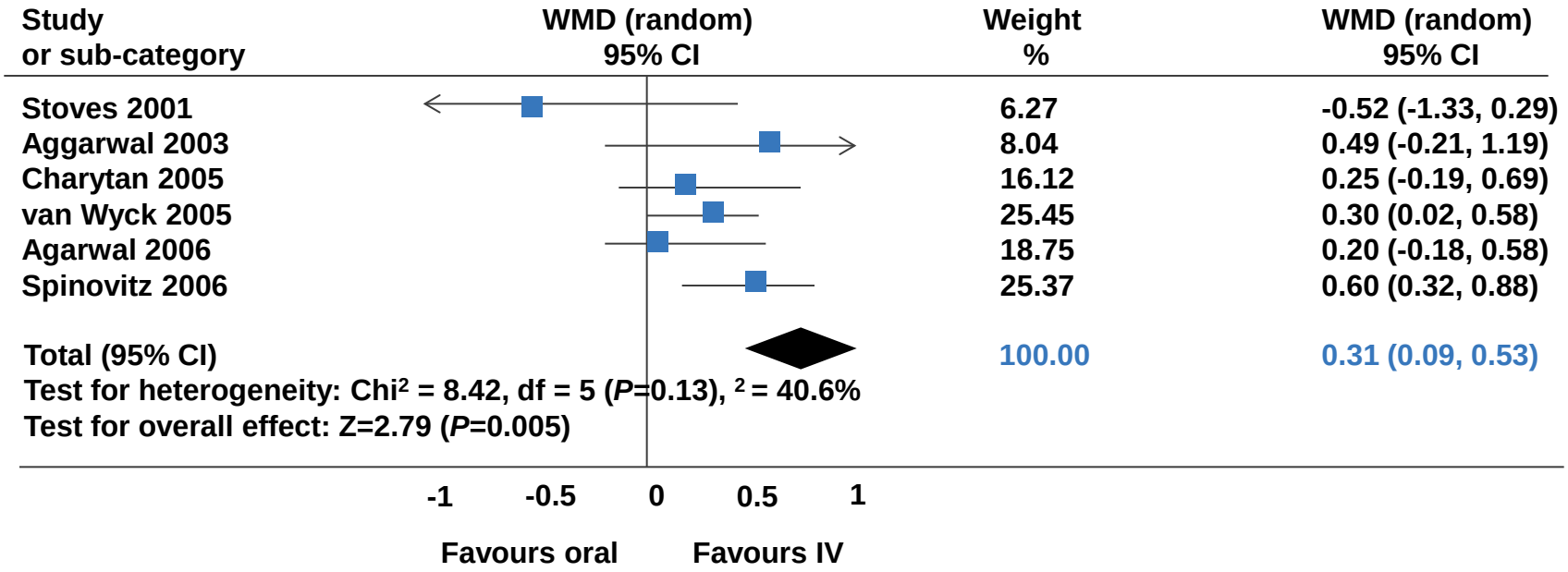
B. IV iron

C. ESA therapy

D. ESA + iron

Meta-analysis showed intravenous iron to be more favourable vs oral iron therapy in patients with ND-CKD

Haemoglobin (Hb) level or change from baseline

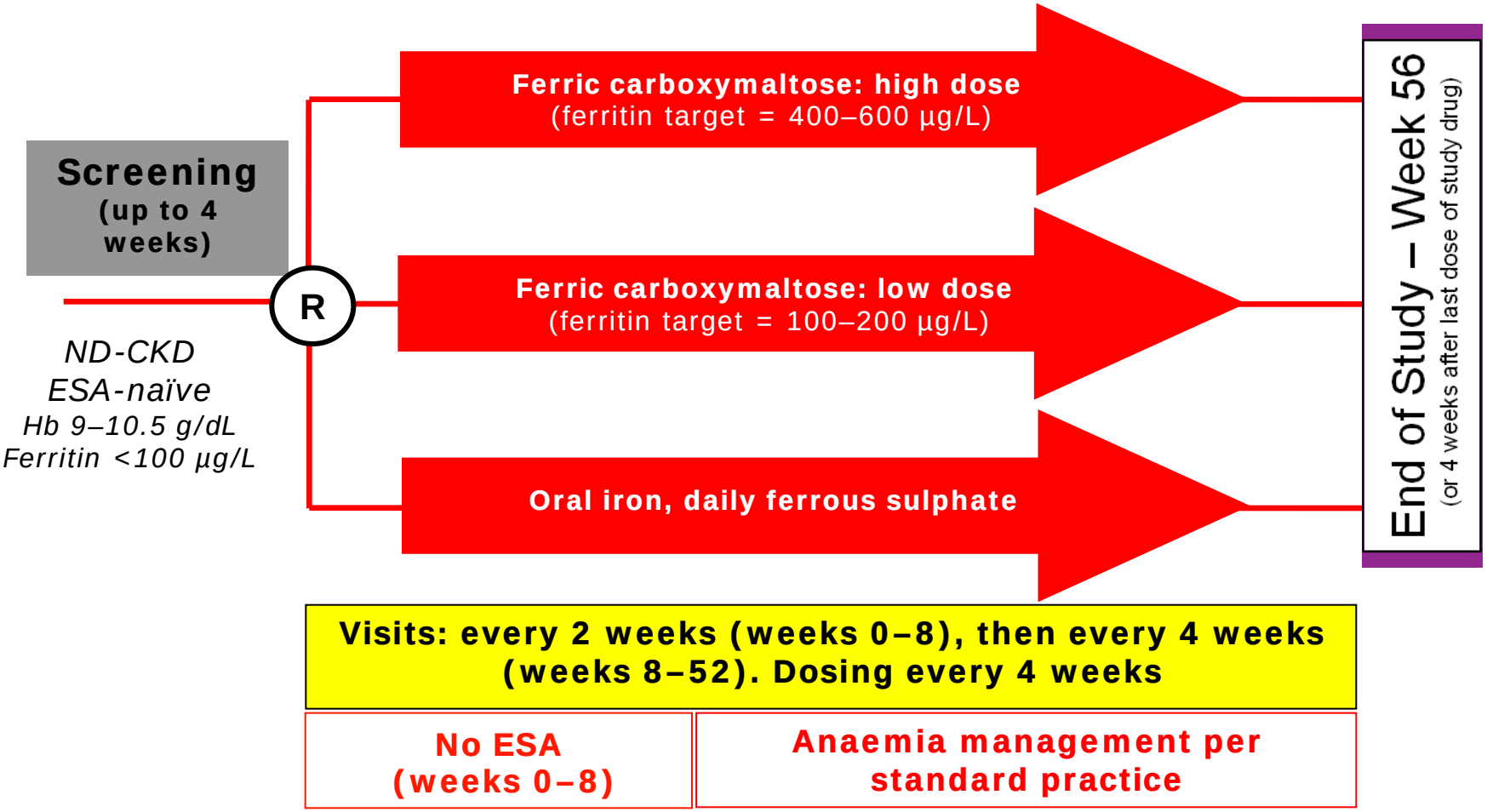


- **Most studies had short duration of follow-up**
- **More randomized trials are required**

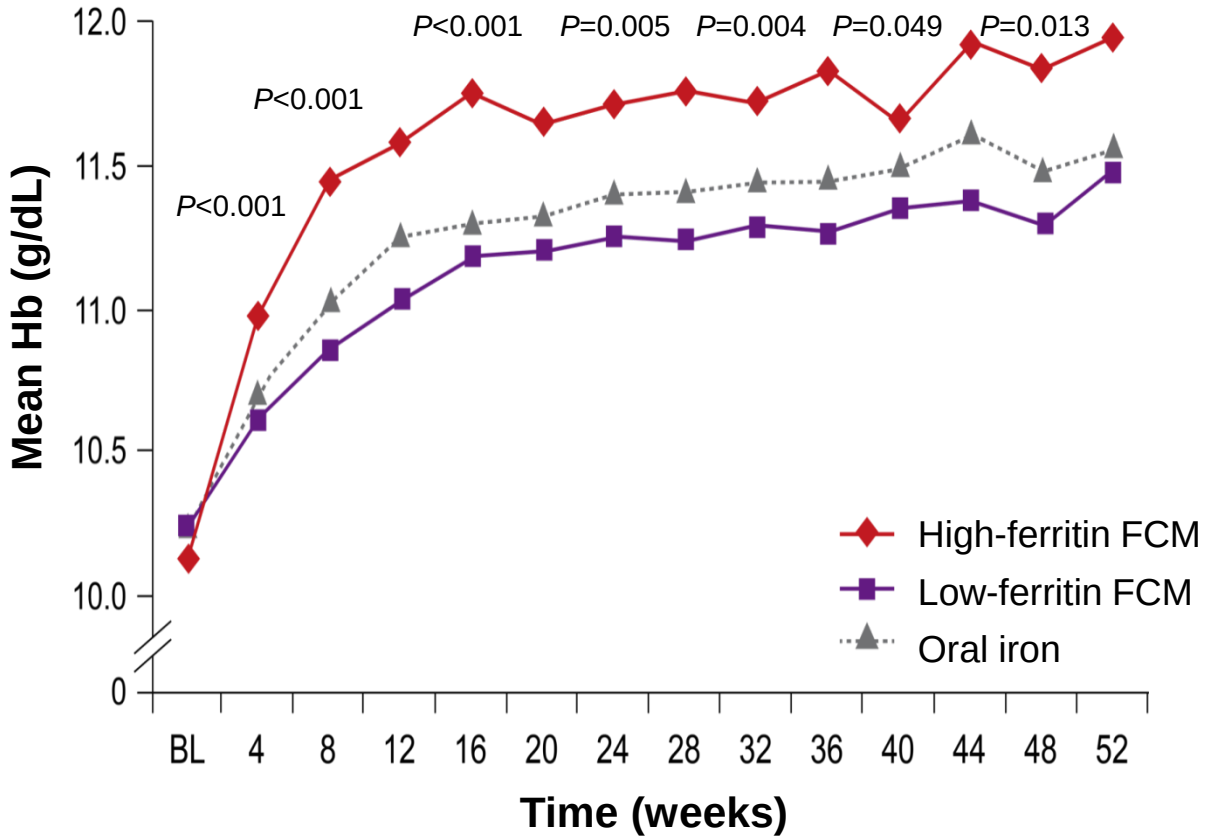
Rozen-Zvi *et al.* *Am J Kidney Dis* 2008;52:897–906.

The FIND-CKD trial

Macdougall IC et al. *Nephrol Dial Transplant* 2014; 29: 2075–2084.

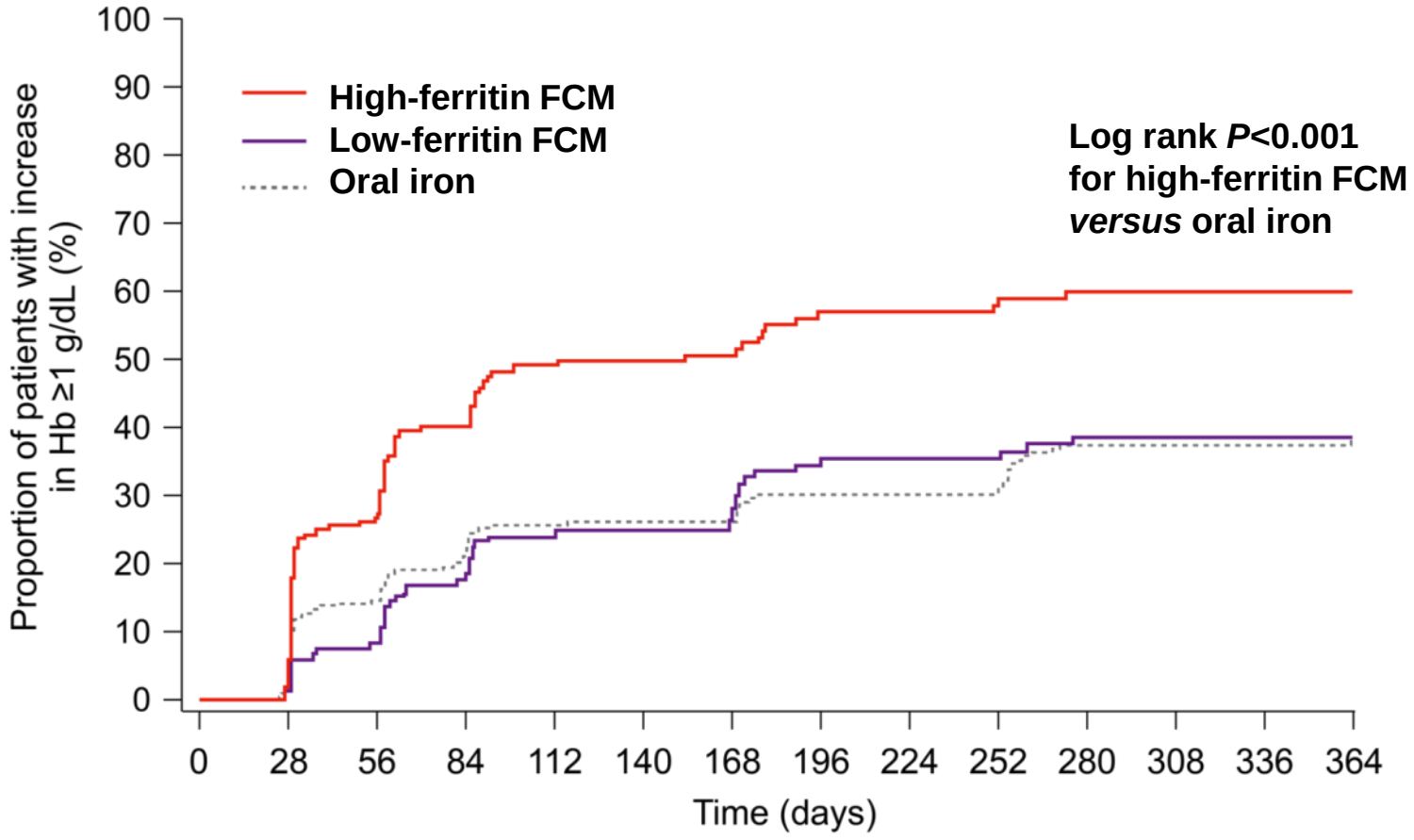


FIND-CKD – haemoglobin



Macdougall IC *et al*. *Nephrol Dial Transplant* 2014; 29: 2075–2084.

FIND-CKD – Hb ≥1 g/dL increase



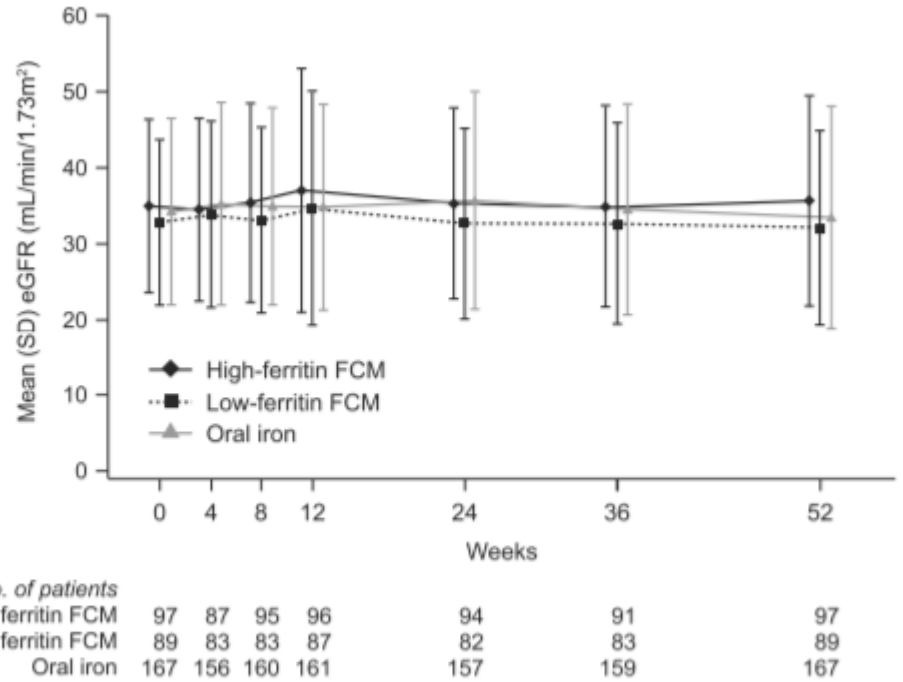
Macdougall IC *et al*. *Nephrol Dial Transplant* 2014; 29: 2075–2084.

The FIND-CKD trial -- safety

	High-ferritin ferric carboxymaltose (n=154)	Low-ferritin ferric carboxymaltose (n=150)	Oral iron (n=312)
Any adverse event, n (%)	126 (81.8)	130 (86.7)	255 (81.7)
Gastrointestinal disorders	32 (20.8)	38 (25.3)	128 (41.0)
Diarrhoea	15 (9.7)	11 (7.3)	45 (14.4)
Constipation	2 (1.3)	5 (3.3)	37 (11.9)
Nausea	9 (5.8)	7 (4.7)	15 (4.8)
Dyspepsia	2 (1.3)	3 (2.0)	17 (5.4)
Infections	**51 (33.1)**	**51 (34.0)**	**95 (30.4)**
Urinary tract infection	18 (11.7)	10 (6.7)	17 (5.4)
Nasopharyngitis	13 (8.4)	10 (6.7)	16 (5.1)
Influenza	4 (2.6)	8 (5.3)	7 (2.2)
General disorders and administration-site conditions	36 (23.4)	35 (23.3)	67 (21.5)
Peripheral oedema	21 (13.6)	21 (14.0)	29 (9.3)

Roger SD *et al*. *Nephrol Dial Transplant* 2017; 32: 1530–1539.

The FIND-CKD study– renal function



No. of patients							
High ferritin FCM	97	87	95	96	94	91	97
Low ferritin FCM	89	83	83	87	82	83	89
Oral iron	167	156	160	161	157	159	167

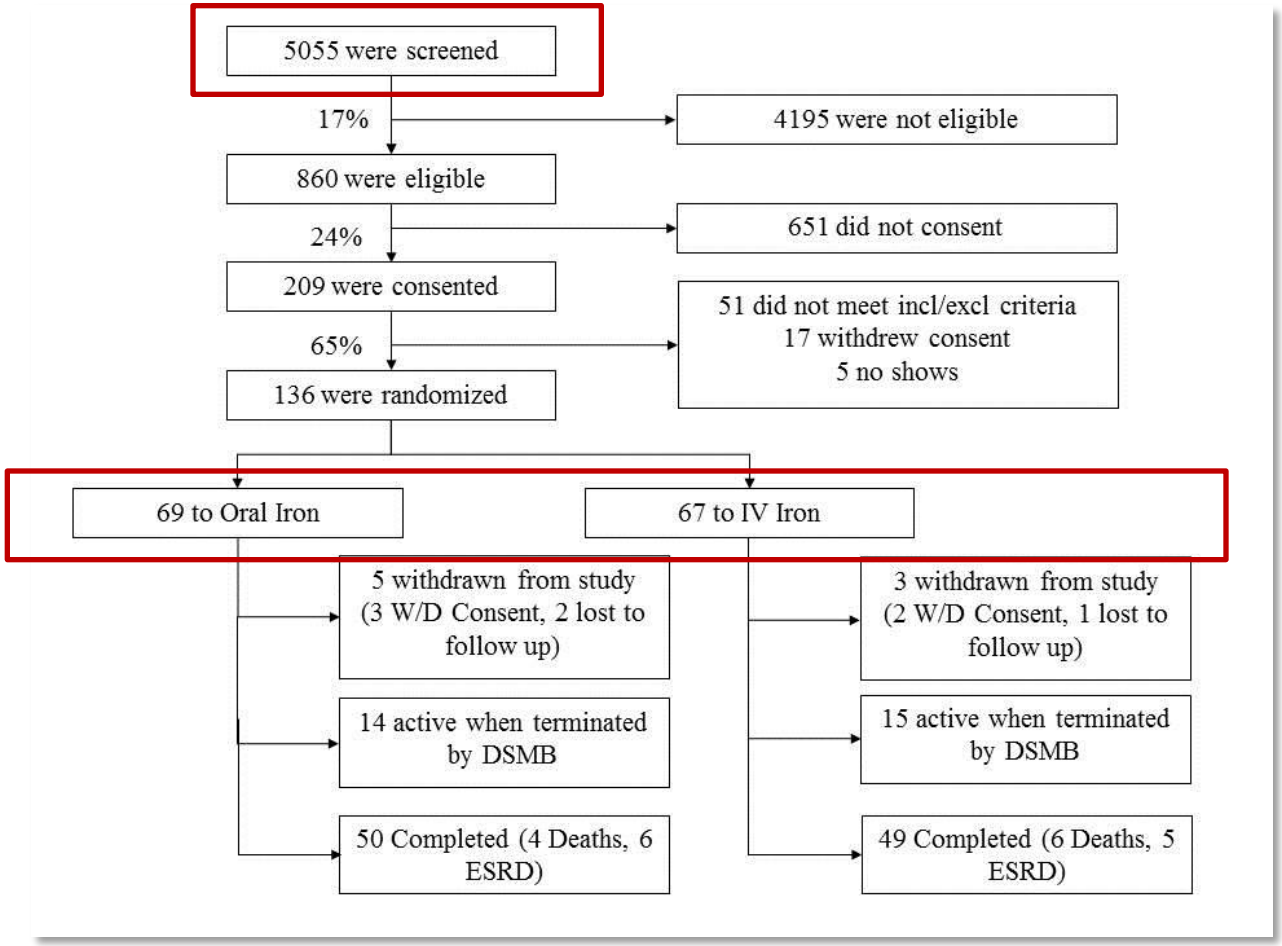
Fig. 1 Estimated GFR to month 12 according to treatment group in patients with eGFR values at baseline and month 12. Values are shown as mean (SD). FCM, ferric carboxymaltose; eGFR, estimated GFR

Macdougall IC *et al.* *BMC Nephrology* 2017; 18: 24.

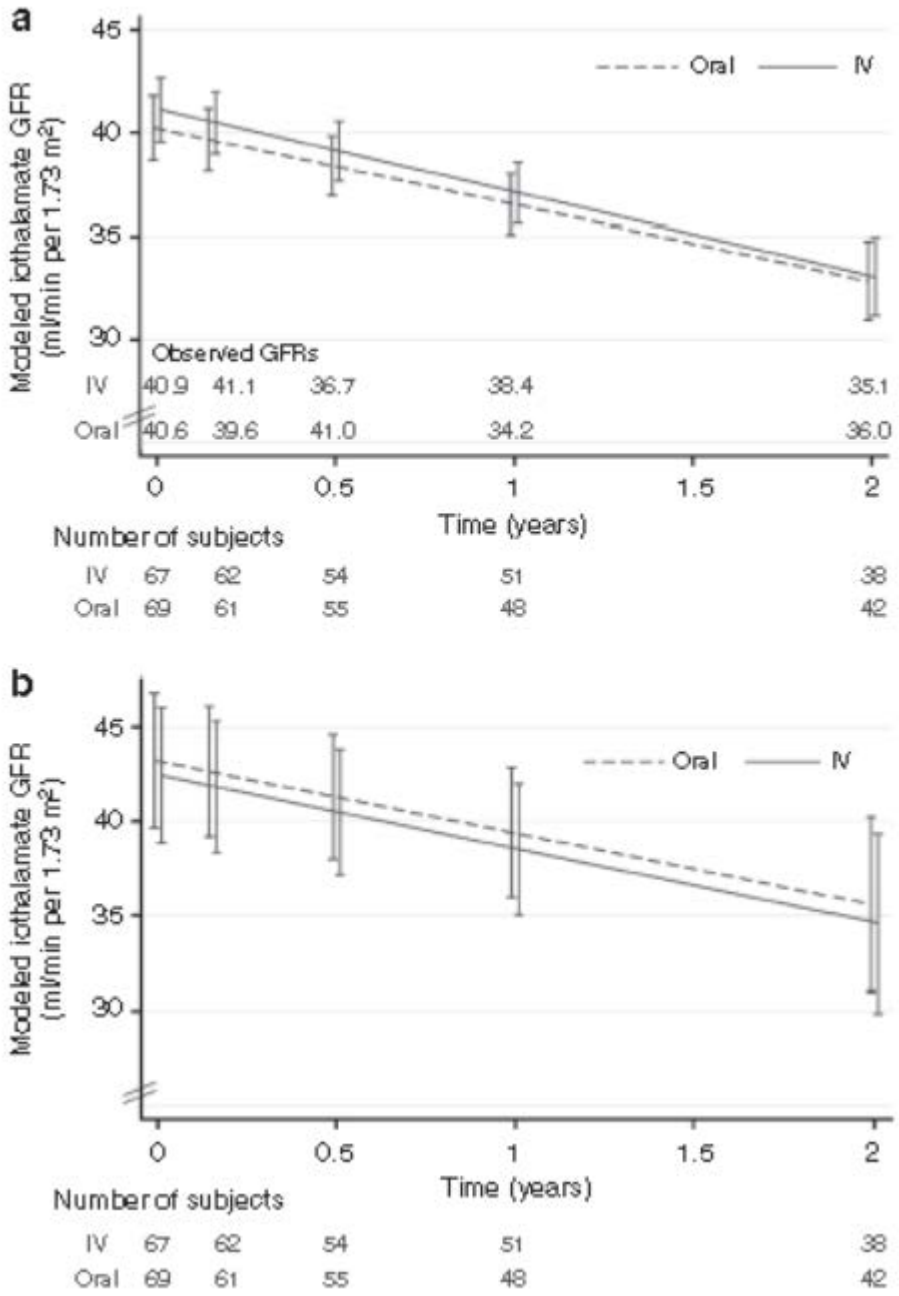
REVOKE:

Disposition of the study participants

Agarwal R *et al.*
Kidney Int 2015; 88: 905-914.



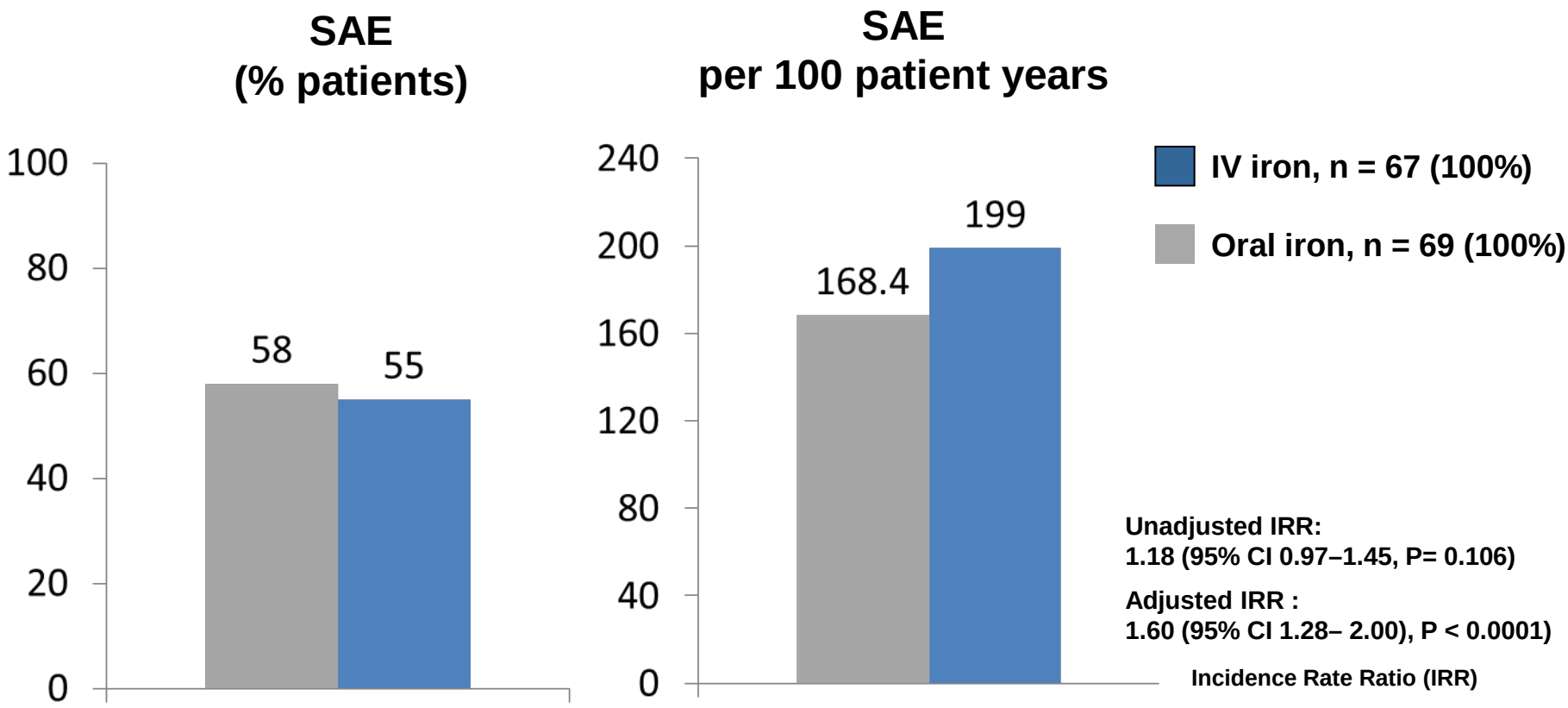
- **The trial early terminated on the recommendation of the DSMB based on an increase in the SAE rate in IV iron treatment group compared to oral iron group and little difference in mGFR between treatment groups**
- **Median follow up of all participants was 24.0 months (11.0–24.3) → No difference between treatment groups**



REVOKE study: Renal function (measured GFR)

Agarwal R *et al.*
Kidney Int 2015; 88: 905-914.

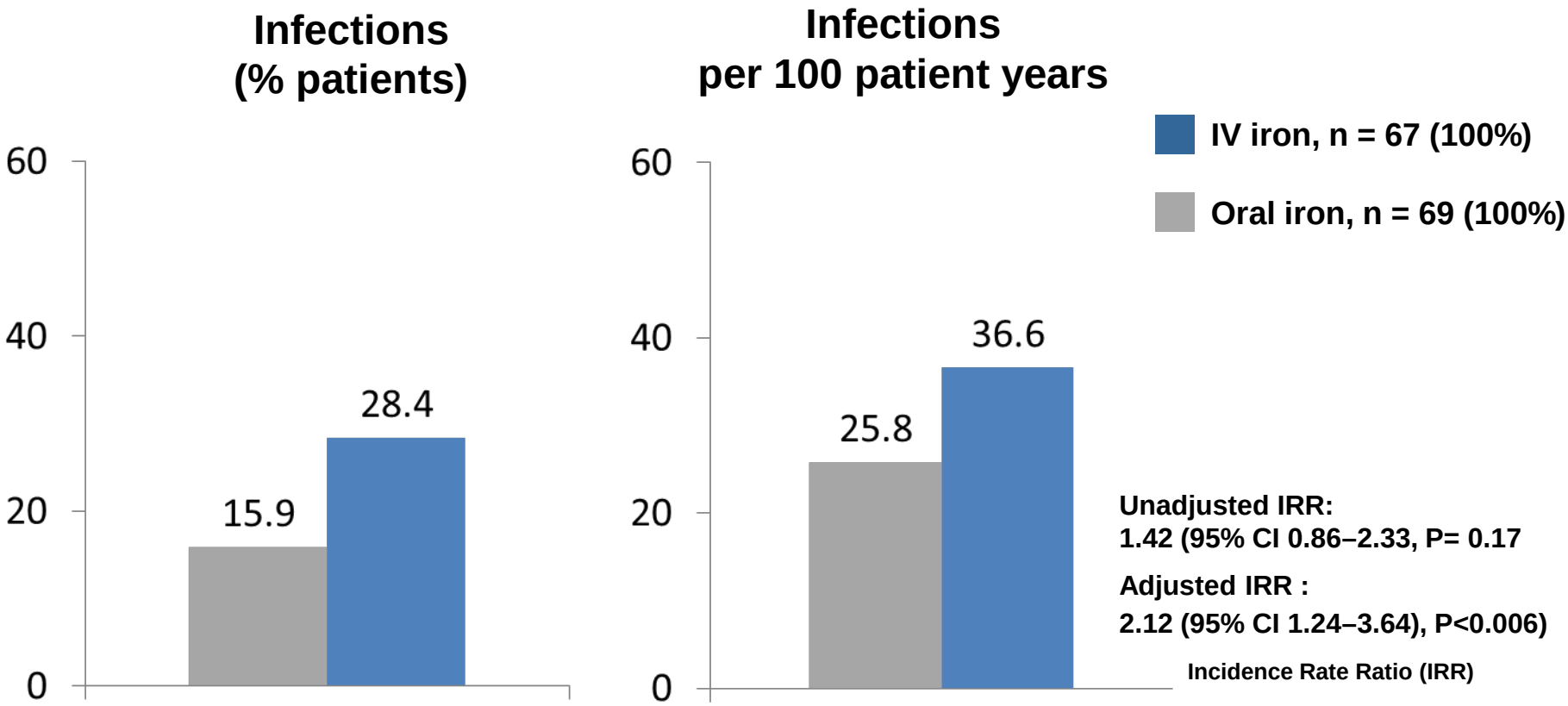
REVOKE: *Overall serious adverse events*



- **A total of 104.5 patient-years (PY) of follow-up in oral iron group and 101 PY of follow up in the IV iron group**

Agarwal R *et al.* *Kidney Int* 2015; 88: 905-914.

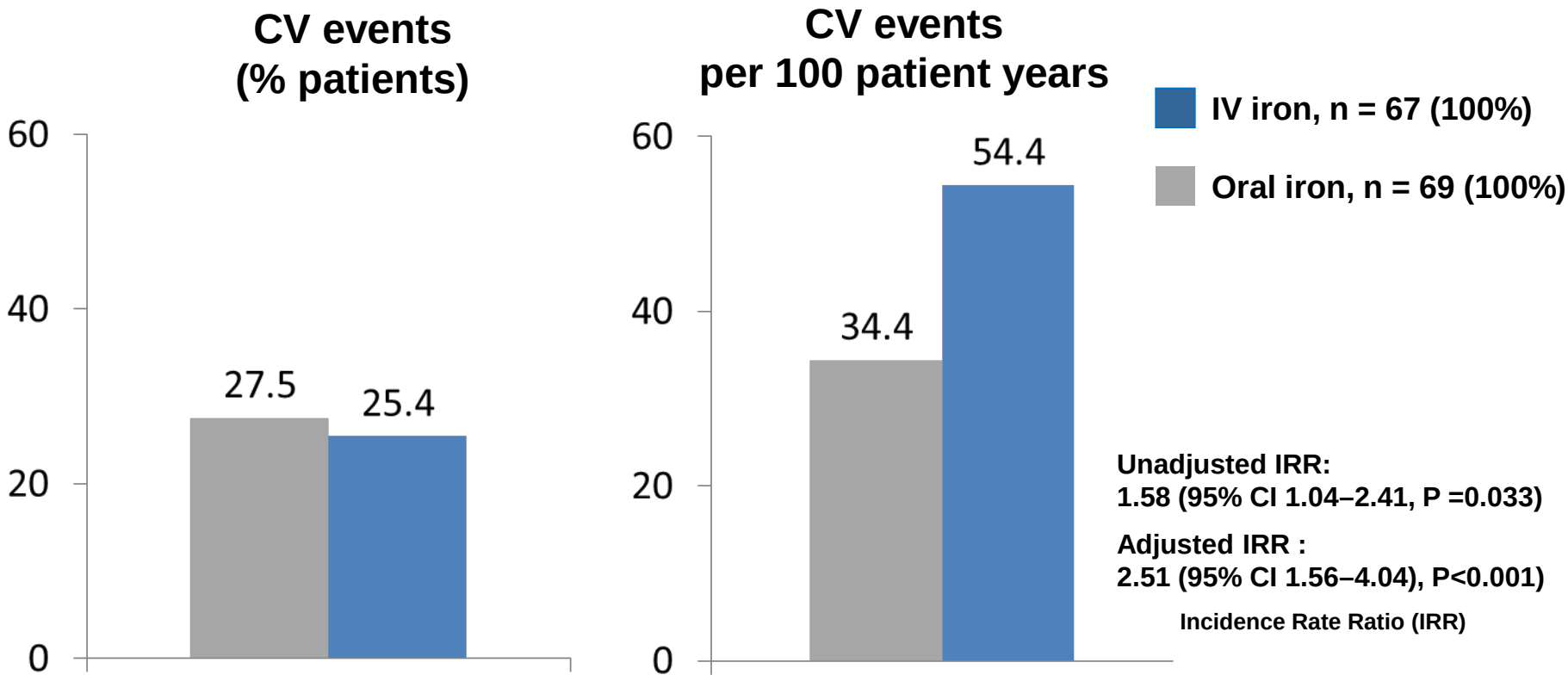
REVOKE: *Infection-related SAEs*



- **The incidence of lung and skin infections were increased between three- and fourfold in the IV iron group**

Agarwal R *et al.* *Kidney Int* 2015; 88: 905-914.

REVOKE: *CV-related SAEs*

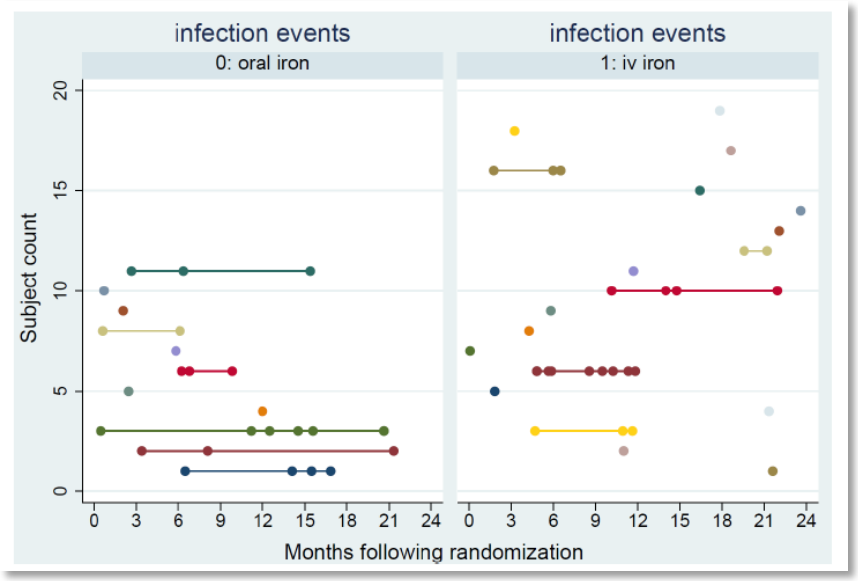


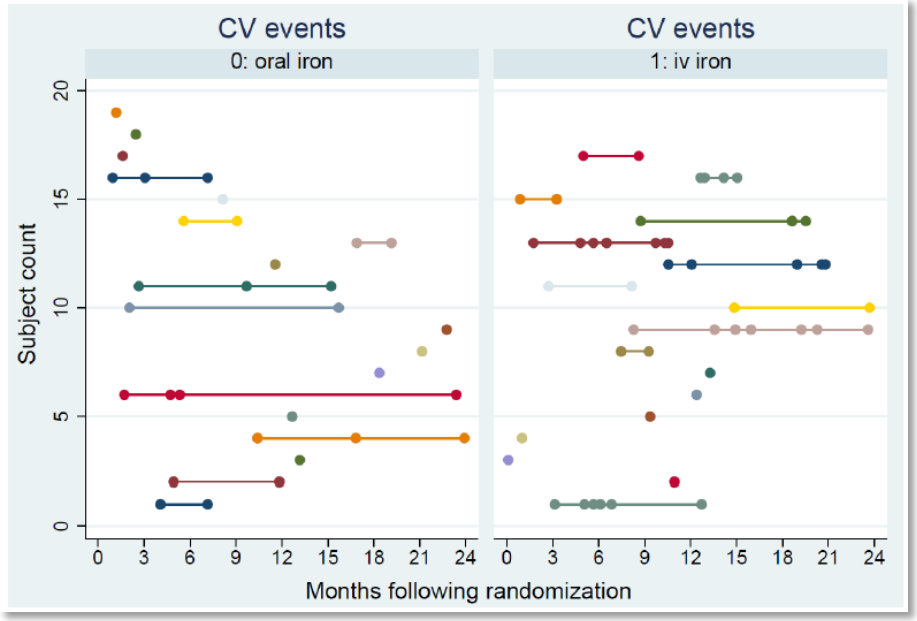
- **The incidence of hospitalized heart failure was increased approximately twofold in the IV iron group**

Agarwal R *et al.* *Kidney Int* 2015; 88: 905-914.

REVOKE:

Onset of Adverse events





- **Intervention period 8 weeks post randomization**
- **Safety period 24 month follow-up post randomization**

Agarwal R *et al.* *Kidney Int* 2015; 88: 905-914.

REVOKE: *Limitations*

- **Single-centre**
- **99 patients completed trial (limited power)**
- **Randomization method: opaque envelopes; 4.6 year difference in age between the two groups *(p=0.02)***
- **Non-independent DSMB; SAEs adjudicated by investigator**
- **Events occurred long after intervention complete**
- **Adjustment questionable**
- **Adjusting the incidence rate ratio (IRR) for SAEs due to infections changed the p value from 0.17 to < 0.006**
- **Repeated events in same patients drove safety signal**
  - **CV events – oral iron: 19 patients; 36 events;**
    – IV iron: 17 patients; 55 events
  - **Overall SAEs – oral iron: 40 patients**
    – IV iron: 37 patients

Agarwal R *et al.* *Kidney Int* 2015; 88: 905-14.
Richard Haynes – personal communication

Take-Home Message

- FIND-CKD and REVOKE have informed the evidence-base of oral iron *versus* IV iron in ND-CKD, but have confused it!

IV iron in HD

Which strategy is best for a HD patient just starting dialysis?

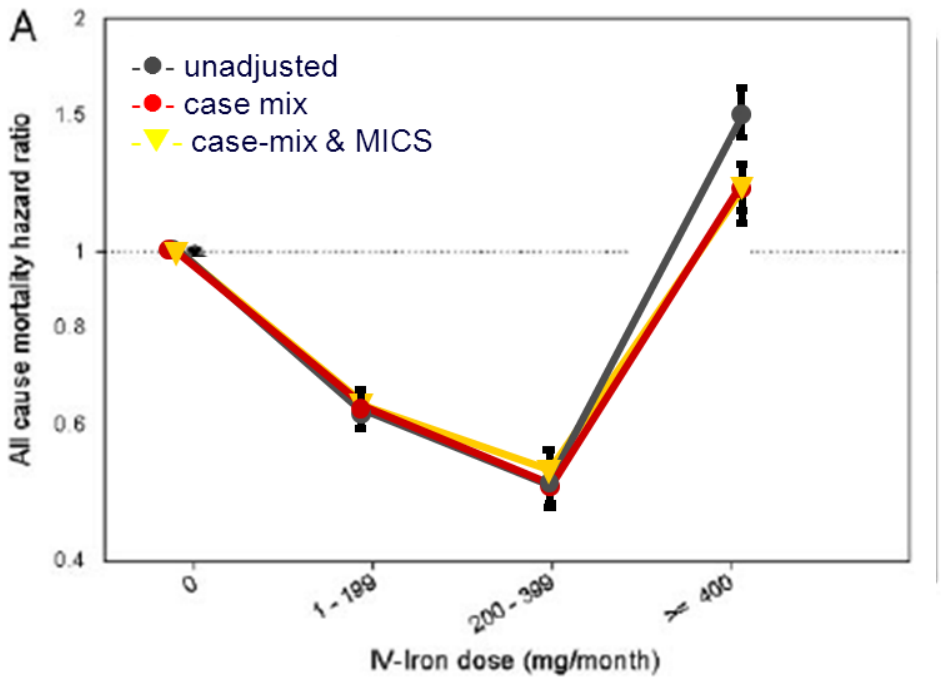
- 58 years man
- ESRD due to hypertension
- On EPO
- Hb 11.1 g/dl
- Ferritin 215 ug/l
- TSAT 24%

A. Give IV iron as required to maintain ferritin >200 and TSAT >20% in line with ERBP guidelines.

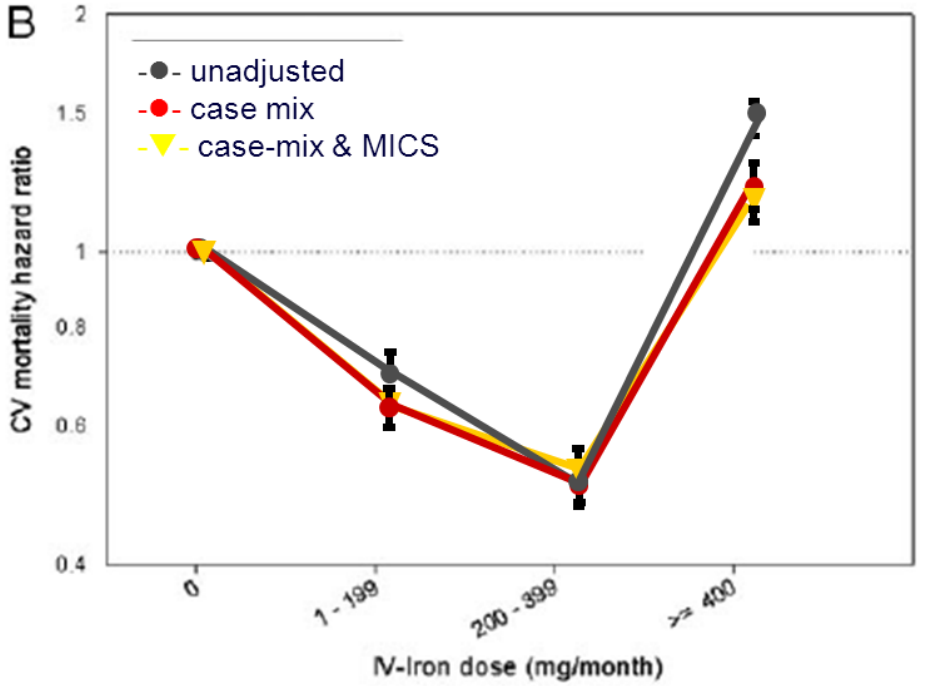
B. Proactively administer 400 mg of IV iron per month, only withholding iron if ferritin >700 ug/l and/or TSAT >40%

Association of IV iron dose with all-cause and CVS-cause mortality

All-cause mortality

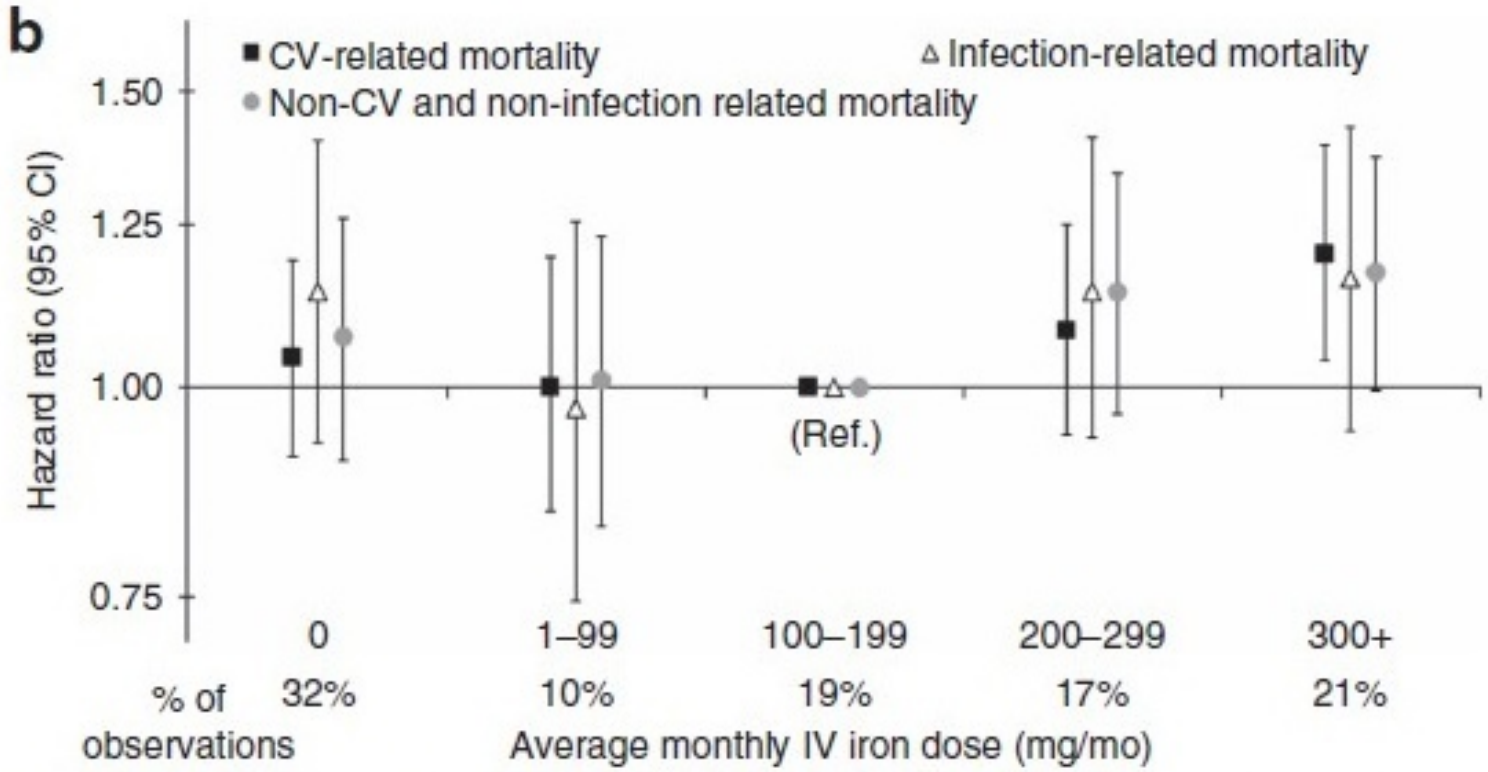


CVS-cause mortality



Kalantar-Zadeh K *et al*. *J Am Soc Nephrol* 2005;16:3070-80.

Association of IV iron and mortality *DOPPS*

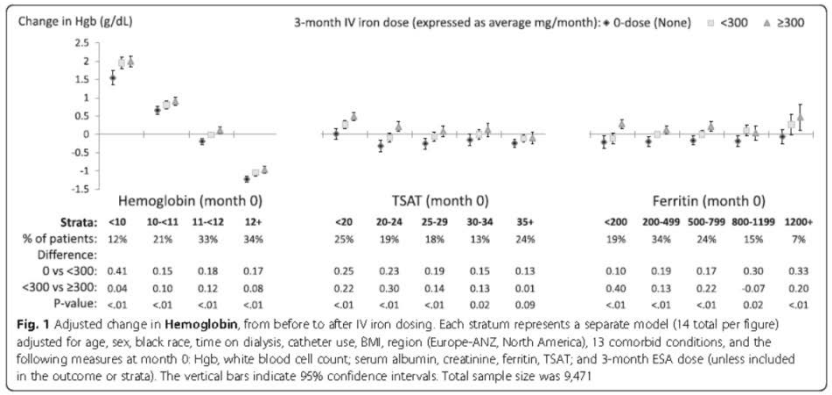


Bailie GR *et al.* *Kidney Int* 2015; 87: 162-8.

RESEARCH ARTICLE Open Access

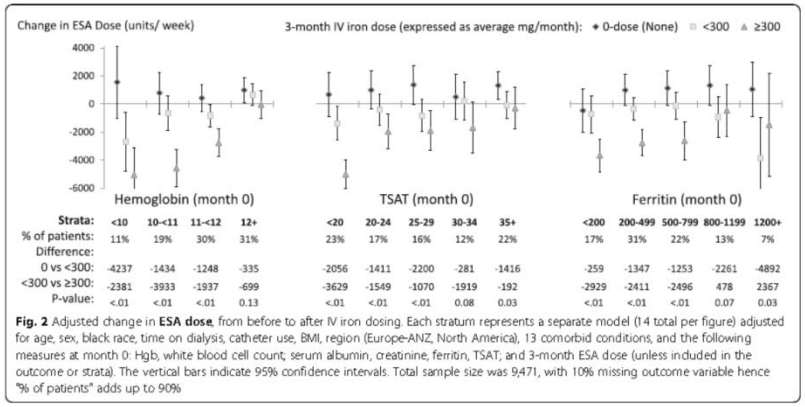
Evaluating the effectiveness of IV iron dosing for anemia management in common clinical practice: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Bruce M. Robinson[1,2*], Maria Larkina[1], Brian Bieber[1], Werner Kleophas[3], Yun Li[1,2], Francesco Locatelli[4], Keith P. McCullough[1], Jackie G. Nolen[5], Friedrich K. Port[1] and Ronald L. Pisoni[1]



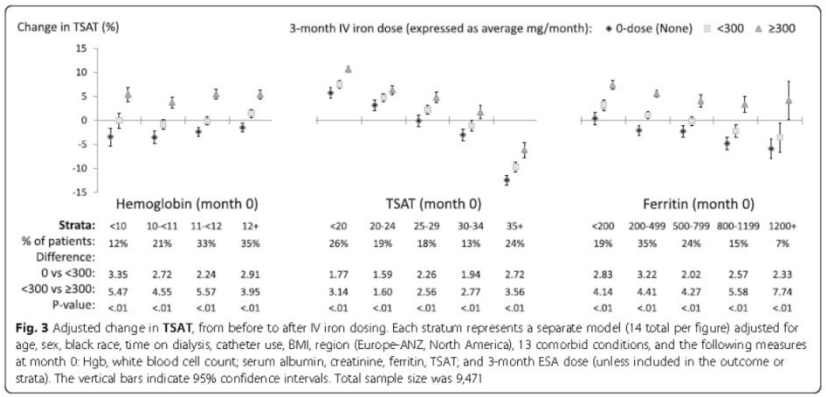
Strata:	<10	10-<11	11-<12	12+	<20	20-24	25-29	30-34	35+	<200	200-499	500-799	800-1199	1200+
% of patients:	12%	21%	33%	34%	25%	19%	18%	13%	24%	19%	34%	24%	15%	7%
Difference:														
0 vs <300:	0.41	0.15	0.18	0.17	0.25	0.23	0.19	0.15	0.13	0.10	0.19	0.17	0.30	0.33
<300 vs ≥300:	0.04	0.10	0.12	0.08	0.22	0.30	0.14	0.13	0.01	0.40	0.13	0.22	-0.07	0.20
P-value:	<.01	<.01	<.01	<.01	<.01	<.01	<.01	0.02	0.09	<.01	<.01	<.01	0.02	<.01

Fig. 1 Adjusted change in **Hemoglobin**, from before to after IV iron dosing. Each stratum represents a separate model (14 total per figure) adjusted for age, sex, black race, time on dialysis, catheter use, BMI, region (Europe-ANZ, North America), 13 comorbid conditions, and the following measures at month 0: Hgb, white blood cell count; serum albumin, creatinine, ferritin, TSAT; and 3-month ESA dose (unless included in the outcome or strata). The vertical bars indicate 95% confidence intervals. Total sample size was 9,471



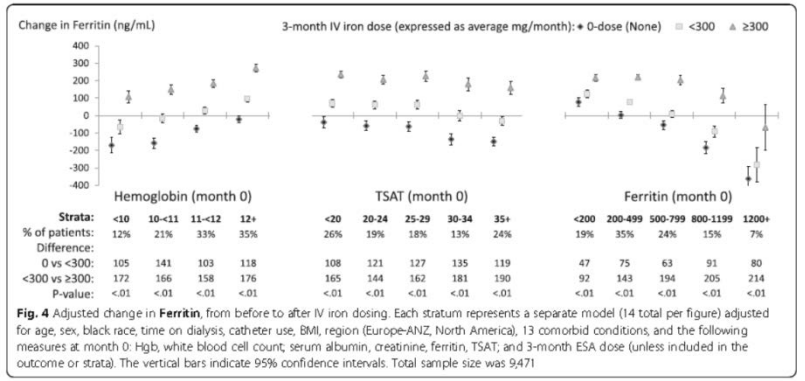
Strata:	<10	10-<11	11-<12	12+	<20	20-24	25-29	30-34	35+	<200	200-499	500-799	800-1199	1200+
% of patients:	11%	19%	30%	31%	23%	17%	16%	12%	22%	17%	31%	22%	13%	7%
Difference:														
0 vs <300:	-4237	-1434	-1248	-335	-2056	-1411	-2200	-281	-1416	-259	-1347	-1253	-2261	-4892
<300 vs ≥300:	-2381	-3933	-1937	-699	-3629	-1549	-1070	-1919	-192	-2929	-2411	-2496	478	2367
P-value:	<.01	<.01	<.01	0.13	<.01	<.01	<.01	0.08	0.03	<.01	<.01	<.01	0.07	0.03

Fig. 2 Adjusted change in **ESA dose**, from before to after IV iron dosing. Each stratum represents a separate model (14 total per figure) adjusted for age, sex, black race, time on dialysis, catheter use, BMI, region (Europe-ANZ, North America), 13 comorbid conditions, and the following measures at month 0: Hgb, white blood cell count; serum albumin, creatinine, ferritin, TSAT; and 3-month ESA dose (unless included in the outcome or strata). The vertical bars indicate 95% confidence intervals. Total sample size was 9,471, with 10% missing outcome variable hence "% of patients" adds up to 90%



Strata:	<10	10-<11	11-<12	12+	<20	20-24	25-29	30-34	35+	<200	200-499	500-799	800-1199	1200+
% of patients:	12%	21%	33%	35%	26%	19%	18%	13%	24%	19%	35%	24%	15%	7%
Difference:														
0 vs <300:	3.35	2.72	2.24	2.91	1.77	1.59	2.26	1.94	2.72	2.83	3.22	2.02	2.57	2.33
<300 vs ≥300:	5.47	4.55	5.57	3.95	3.14	1.60	2.56	2.77	3.56	4.14	4.41	4.27	5.58	7.74
P-value:	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01

Fig. 3 Adjusted change in **TSAT**, from before to after IV iron dosing. Each stratum represents a separate model (14 total per figure) adjusted for age, sex, black race, time on dialysis, catheter use, BMI, region (Europe-ANZ, North America), 13 comorbid conditions, and the following measures at month 0: Hgb, white blood cell count; serum albumin, creatinine, ferritin, TSAT; and 3-month ESA dose (unless included in the outcome or strata). The vertical bars indicate 95% confidence intervals. Total sample size was 9,471



Strata:	<10	10-<11	11-<12	12+	<20	20-24	25-29	30-34	35+	<200	200-499	500-799	800-1199	1200+
% of patients:	12%	21%	33%	35%	26%	19%	18%	13%	24%	19%	35%	24%	15%	7%
Difference:														
0 vs <300:	105	141	103	118	108	121	127	135	119	47	75	63	91	80
<300 vs ≥300:	172	166	158	176	165	144	162	181	190	92	143	194	205	214
P-value:	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01

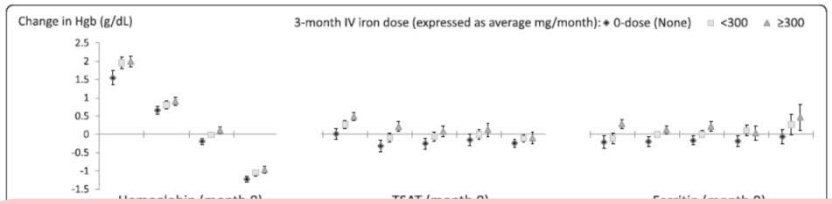
Fig. 4 Adjusted change in **Ferritin**, from before to after IV iron dosing. Each stratum represents a separate model (14 total per figure) adjusted for age, sex, black race, time on dialysis, catheter use, BMI, region (Europe-ANZ, North America), 13 comorbid conditions, and the following measures at month 0: Hgb, white blood cell count; serum albumin, creatinine, ferritin, TSAT; and 3-month ESA dose (unless included in the outcome or strata). The vertical bars indicate 95% confidence intervals. Total sample size was 9,471

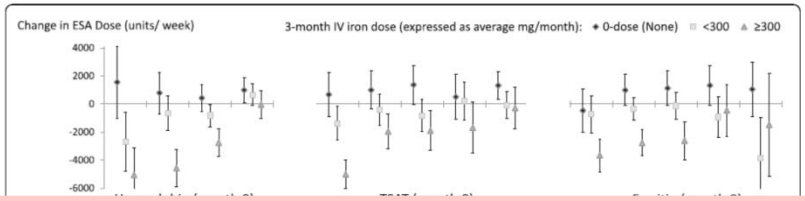
Robinson et al. BMC Nephrol. 2017 Nov 9;18(1):330

RESEARCH ARTICLE Open Access

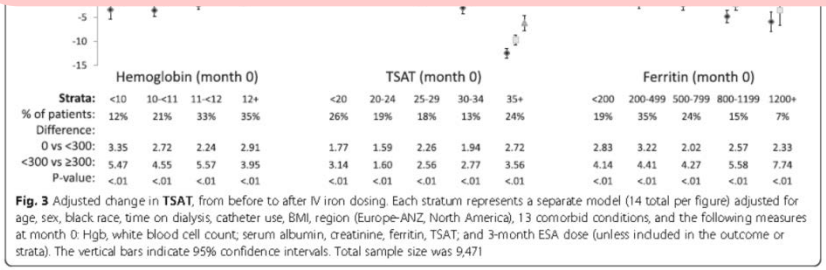
Evaluating the effectiveness of IV iron dosing for anemia management in common clinical practice: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Bruce M. Robinson[1,2*], Maria Larkina[1], Brian Bieber[1], Werner Kleophas[3], Yun Li[1,2], Francesco Locatelli[4], Keith P. McCullough[1], Jackie G. Nolen[5], Friedrich K. Port[1] and Ronald L. Pisoni[1]



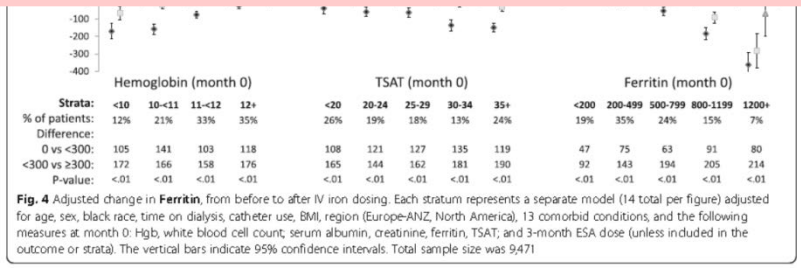


Conclusions: Though residual confounding cannot be ruled out in this observational study, findings suggest that IV iron dosing <300 mg/month, as commonly seen with maintenance dosing of 100-200 mg/month, may be a more effective approach to support Hgb than the higher IV iron doses (300-400 mg/month) often given in many European and North American hemodialysis clinics. Alongside studies supporting the safety of IV iron in 100-200 mg/month dose range, these findings help guide the rational dosing of IV iron in anemia management protocols for everyday hemodialysis practice.



Strata:	<10	10-<11	11-<12	12+	<20	20-24	25-29	30-34	35+	<200	200-499	500-799	800-1199	1200+
% of patients:	12%	21%	33%	35%	26%	19%	18%	13%	24%	19%	35%	24%	15%	7%
Difference:														
0 vs <300:	3.35	2.72	2.24	2.91	1.77	1.59	2.26	1.94	2.72	2.83	3.22	2.02	2.57	2.33
<300 vs ≥300:	5.47	4.55	5.57	3.95	3.14	1.60	2.56	2.77	3.56	4.14	4.41	4.27	5.58	7.74
P-value:	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01

Fig. 3 Adjusted change in **TSAT**, from before to after IV iron dosing. Each stratum represents a separate model (14 total per figure) adjusted for age, sex, black race, time on dialysis, catheter use, BMI, region (Europe-ANZ, North America), 13 comorbid conditions, and the following measures at month 0: Hgb, white blood cell count, serum albumin, creatinine, ferritin, TSAT, and 3-month ESA dose (unless included in the outcome or strata). The vertical bars indicate 95% confidence intervals. Total sample size was 9,471



Strata:	<10	10-<11	11-<12	12+	<20	20-24	25-29	30-34	35+	<200	200-499	500-799	800-1199	1200+
% of patients:	12%	21%	33%	35%	26%	19%	18%	13%	24%	19%	35%	24%	15%	7%
Difference:														
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P-value:	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01

Fig. 4 Adjusted change in **Ferritin**, from before to after IV iron dosing. Each stratum represents a separate model (14 total per figure) adjusted for age, sex, black race, time on dialysis, catheter use, BMI, region (Europe-ANZ, North America), 13 comorbid conditions, and the following measures at month 0: Hgb, white blood cell count, serum albumin, creatinine, ferritin, TSAT, and 3-month ESA dose (unless included in the outcome or strata). The vertical bars indicate 95% confidence intervals. Total sample size was 9,471

Robinson et al. BMC Nephrol. 2017 Nov 9;18(1):330

PIVOTAL

***P*roactive *IV* Ir*O*n *T*herapy in Haemodi*AL*ysis Patients**

Study design

Proactive IV iron arm – IV iron 400mg/month

(withhold if ferritin>700 ug/l; TSAT>40%)

Incident new HD patients (0-12 mths)

On ESA

R

Reactive – minimalistic IV iron arm
(give IV iron if ferritin<200 ug/l; TSAT<20%)

Primary endpoint

Time to all-cause mortality or composite of MI, stroke, HF hosp

Up to 4 weeks screening

Total study period approximately 4 years *(event-driven)*
– 2 years recruitment; 2-4 years follow-up per patient

Sample size: 2141 patients

Courtesy: I. Macdougall

PIVOTAL

***P*roactive *IV* Ir*O*n *T*herapy in Haemodi*AL*ysis Patients**

Primary endpoint

- Time to all-cause death or a composite of non-fatal cardiovascular events (MI, stroke, and HF hospitalisation)
  -- adjudicated by a blinded Endpoint Adjudication Committee

Secondary endpoints

- Incidence of all-cause death and a composite of myocardial infarction, stroke, and hospitalisation for heart failure as recurrent events.
- Time to (and incidence of) all-cause death
- Time to (and incidence of) composite cardiovascular event
- Time to (and incidence of) myocardial infarction
- Time to (and incidence of) stroke
- Time to (and incidence of) hospitalisation for heart failure
- ESA dose requirements
- Transfusion requirements
- EQ-5D QOL and KDQOL
- Vascular access thrombosis
- All-cause hospitalisation
- Infections; hospitalisation for infection

Courtesy: I. Macdougall

PIVOTAL

Proactive IV IrOn Therapy in HaemodiALysis Patients

NETWORK OF SITES

England
Queen Elizabeth Hospital, Birmingham; Heartlands Hospital, Birmingham; Royal Free, London, King's College Hospital, London; Guy's & St Thomas', London; St Helier, Surrey; St George's, London; Royal Liverpool Hospital, University Hospital Aintree; Sheffield Teaching Hospital; Lister Hospital, Stevenage; Salford Royal Hospital, Manchester; Manchester Royal Hospital; Queen Alexandra Hospital, Portsmouth; Kent & Canterbury Hospital, Leicester General Hospital, Hull Royal Infirmary; Freeman Hospital, Newcastle; Churchill Hospital, Oxford; University Hospital of North Staffordshire, Stoke-on-Trent; Southmead Hospital, Bristol; Royal Cornwall Hospital; Nottingham City Hospital; Norfolk & Norwich Hospital; New Cross Hospital, Wolverhampton; Royal London Hospital; Wirral University Teaching Hospital; Royal Shrewsbury Hospital, Royal Devon & Exeter Hospital, Royal Preston Hospital, St James' Hospital, Leeds; Hammersmith Hospital, London; Royal Sussex Hospital, Brighton; Bradford Teaching Hospital; Coventry University Hospital; Southend University Hospital; Gloucestershire Royal Hospital; Derriford Hospital, Plymouth; Royal Berkshire, Reading

Wales
Morriston Hospital, Swansea; University Hospital, Cardiff

Scotland
Western Infirmary, Glasgow; Victoria Hospital, Kirkcaldy; Ninewells Hospital, Dundee; Royal Edinburgh Hospital

N. Ireland
Belfast City Hospital, Antrim Area Hospital;
Daisy Hill Hospital, Newry; Altnagelvin Hospital, Derry

Courtesy: I. Macdougall

PIVOTAL

Proactive IV IrOn Therapy in HaemodiALysis Patients

-- Where are we now?

- Study closed June 2018
- 2141 patients randomised
- Longest patient follow-up – 55 months
- Median follow-up – 27 months
- 676 primary endpoints
- No. of deaths – 515
- Total no. of hospitalisations – 1267
- No. of hospitalisations for infections – 630
- No. of infections – 985

Courtesy: I. Macdougall

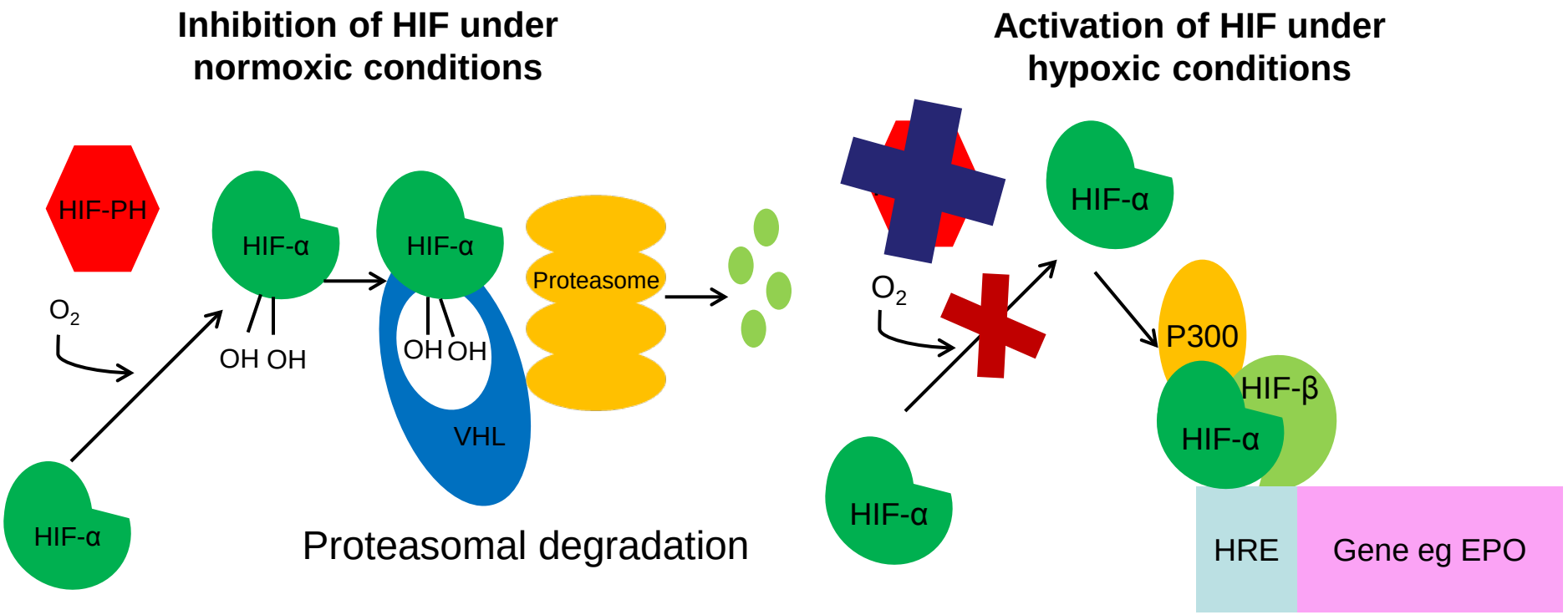
Take-Home Message

- We do not know the optimum amount of IV iron to administer to HD patients

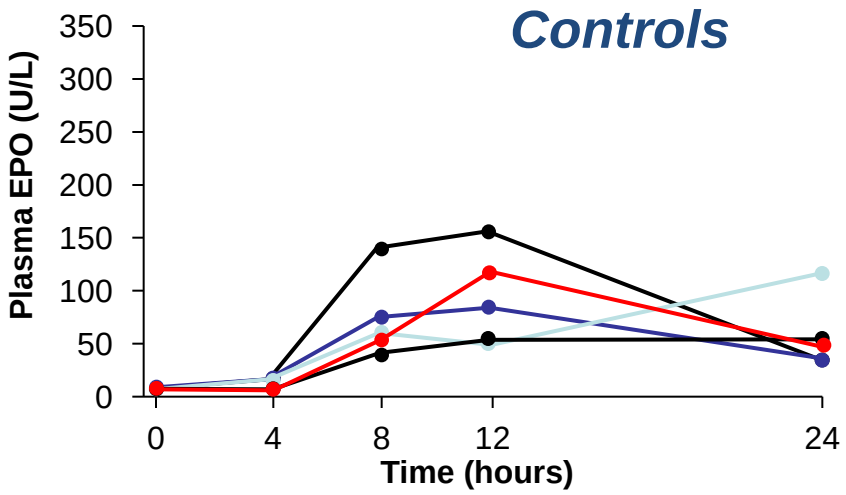
- ***PIVOTAL*** should correct this deficit in the evidence-base

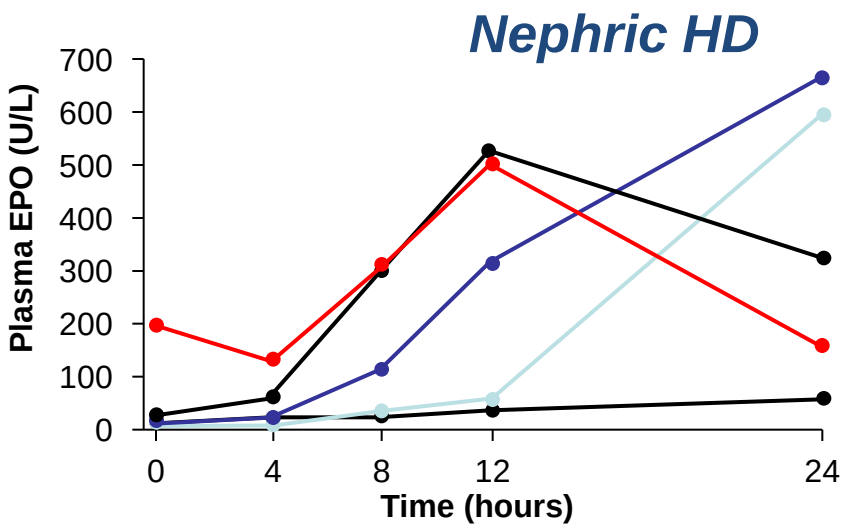
HIF stabilisers

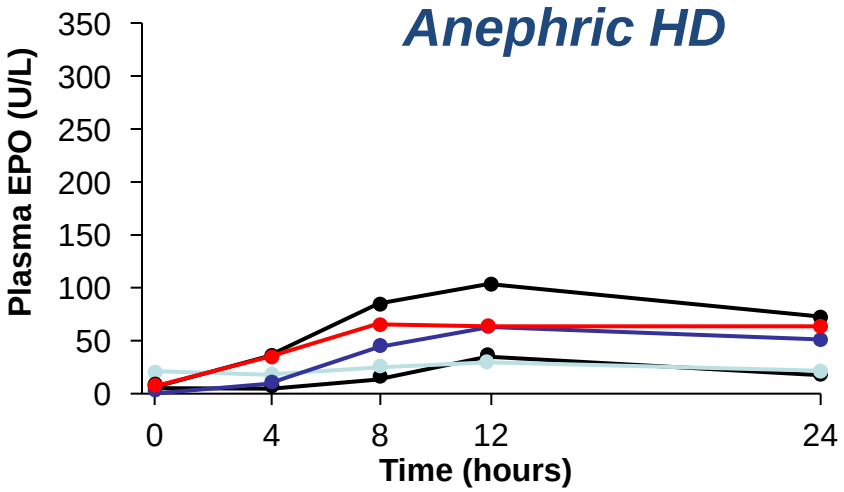
Regulation of HIF activity



Increase in plasma EPO after HIF stabilisation





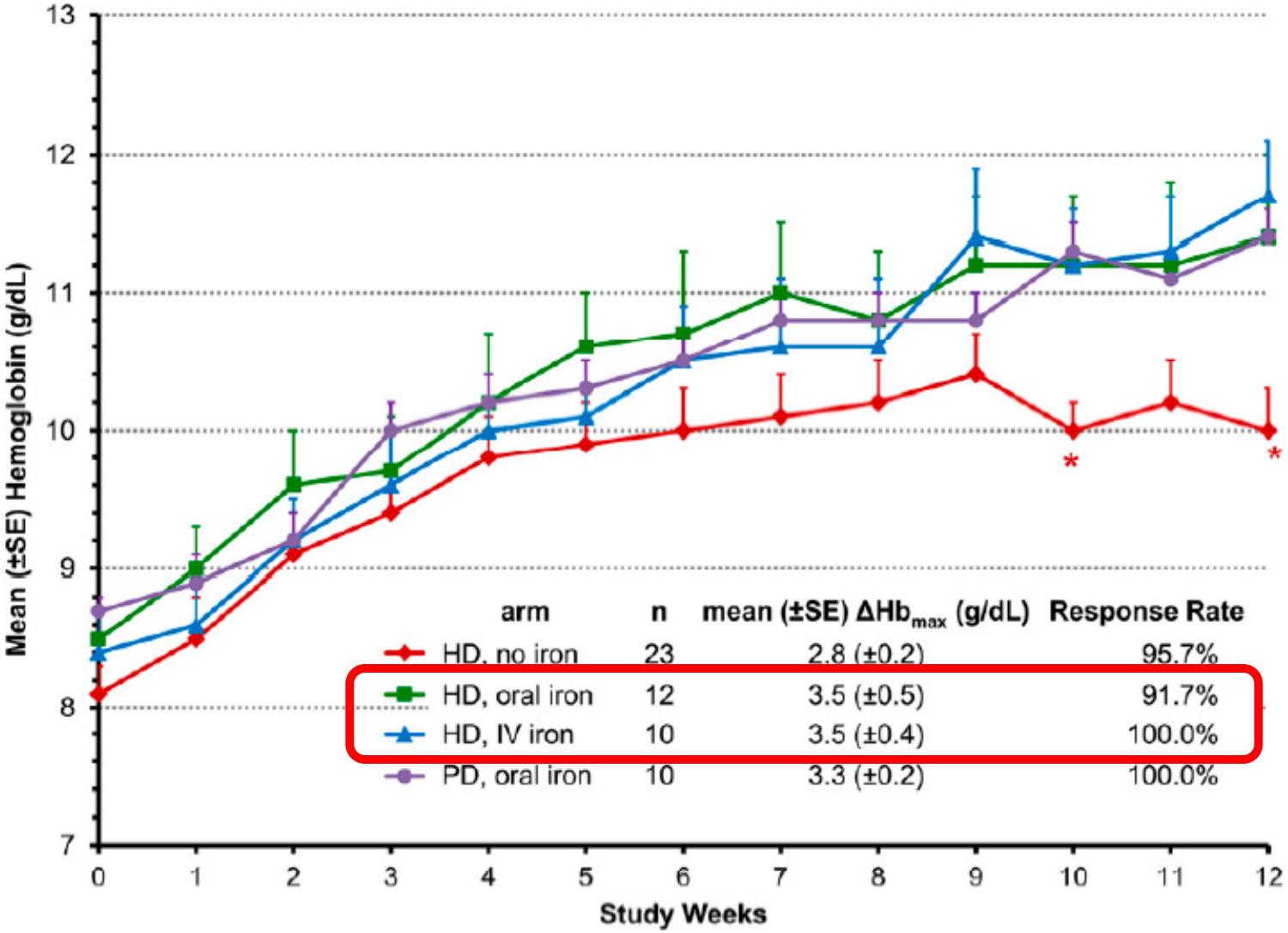


Bernhardt WM *et al.* *J Am Soc Nephrol* 2010; 21: 2151–6.

HIF PHIs in development

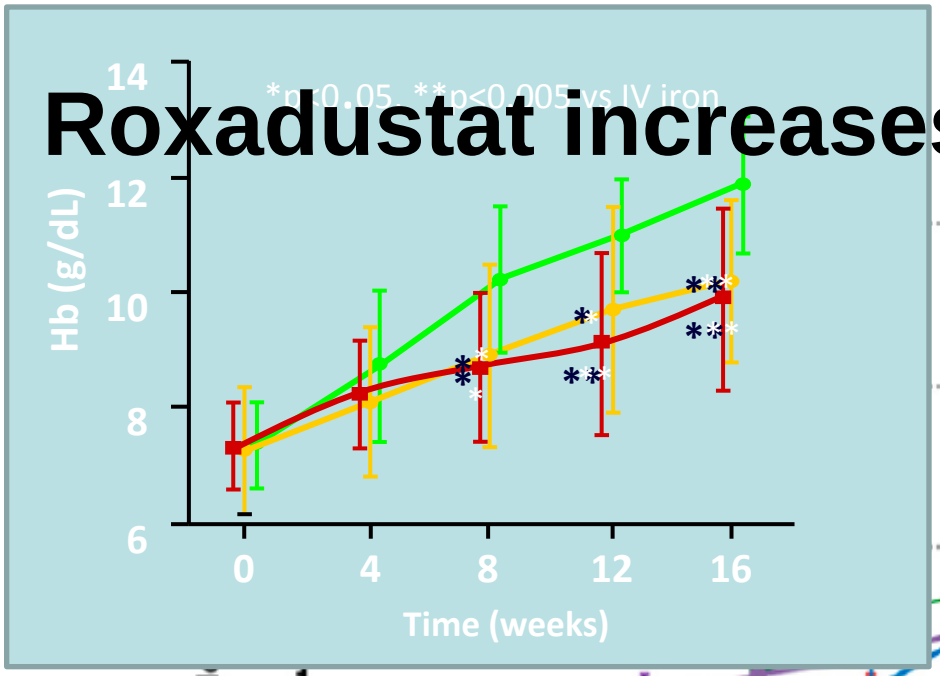
Company	Molecule	Drug name	Phase of development
FibroGen Astellas Astra Zeneca	FG-4592	Roxadustat	Phase 3
GSK	GSK 1278863	Daprodustat	Phase 3
Akebia	AKB-6548	Vadadustat	Phase 3
Bayer	BAY 85-3934	Molidustat	Phase 2/3
Japan Tobacco Inc	JTZ-951		Phase 1

Roxadustat increases haemoglobin levels



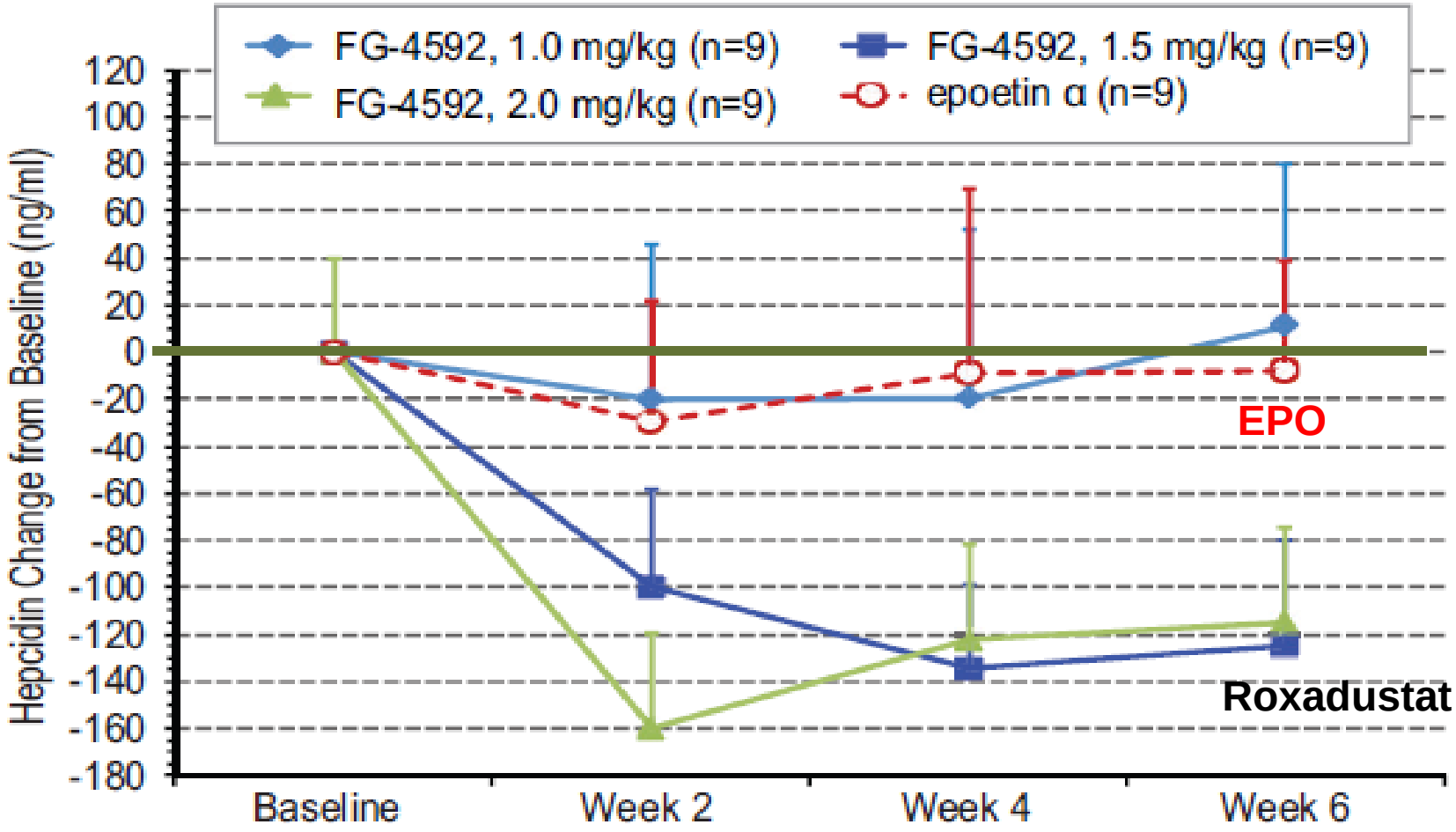
Besarab A *et al.* *J Am Soc Nephrol* 2016; 27: 1225-33.

Roxadustat increases haemoglobin levels



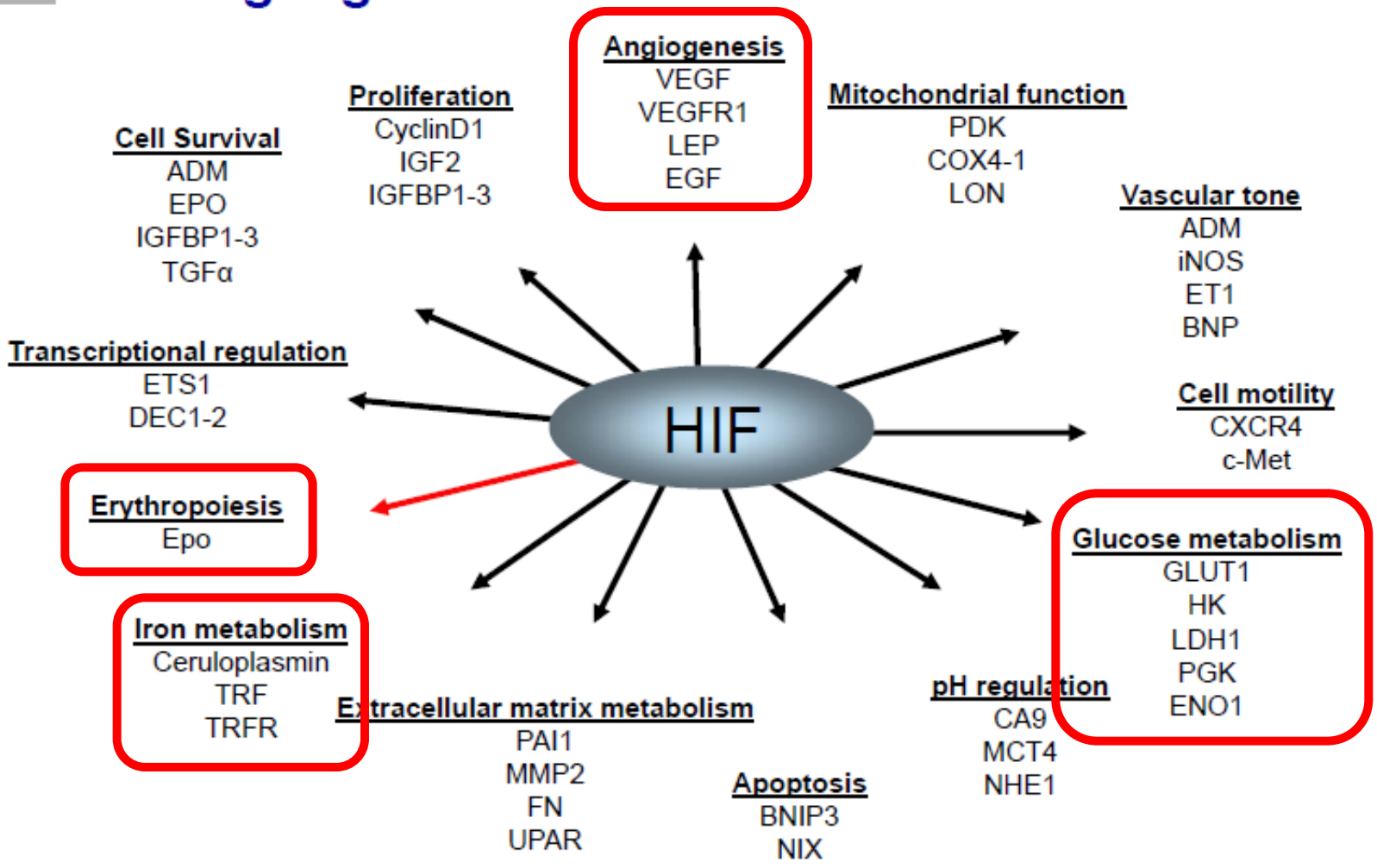
Besarab A *et al.* *J Am Soc Nephrol* 2016; 27: 1225-33.

Roxadustat lowers hepcidin levels



Provenzano R *et al*. ASN 2012 Abstract.

HIF target genes



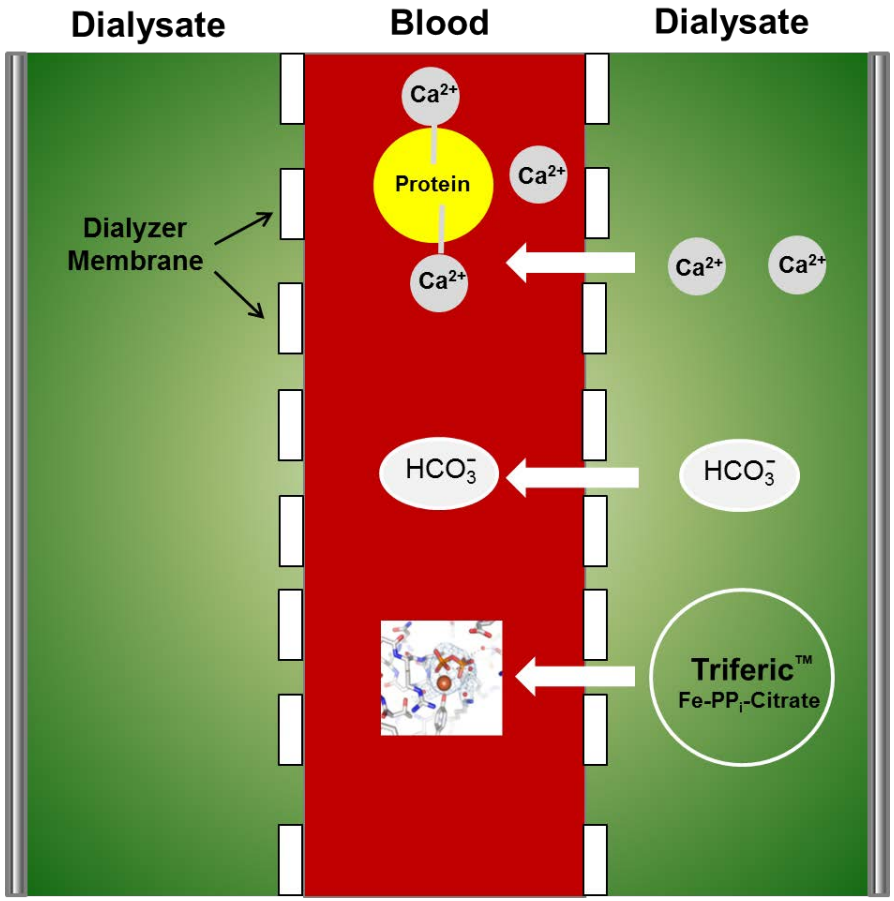
Adapted from Schofield & Ratcliffe, *Nat Rev Mol Cell Biol 2004*

Schofield et al. Nat Rev Mol Cell Biol. 2004 May;5(5):343-54

Newer iron management strategies

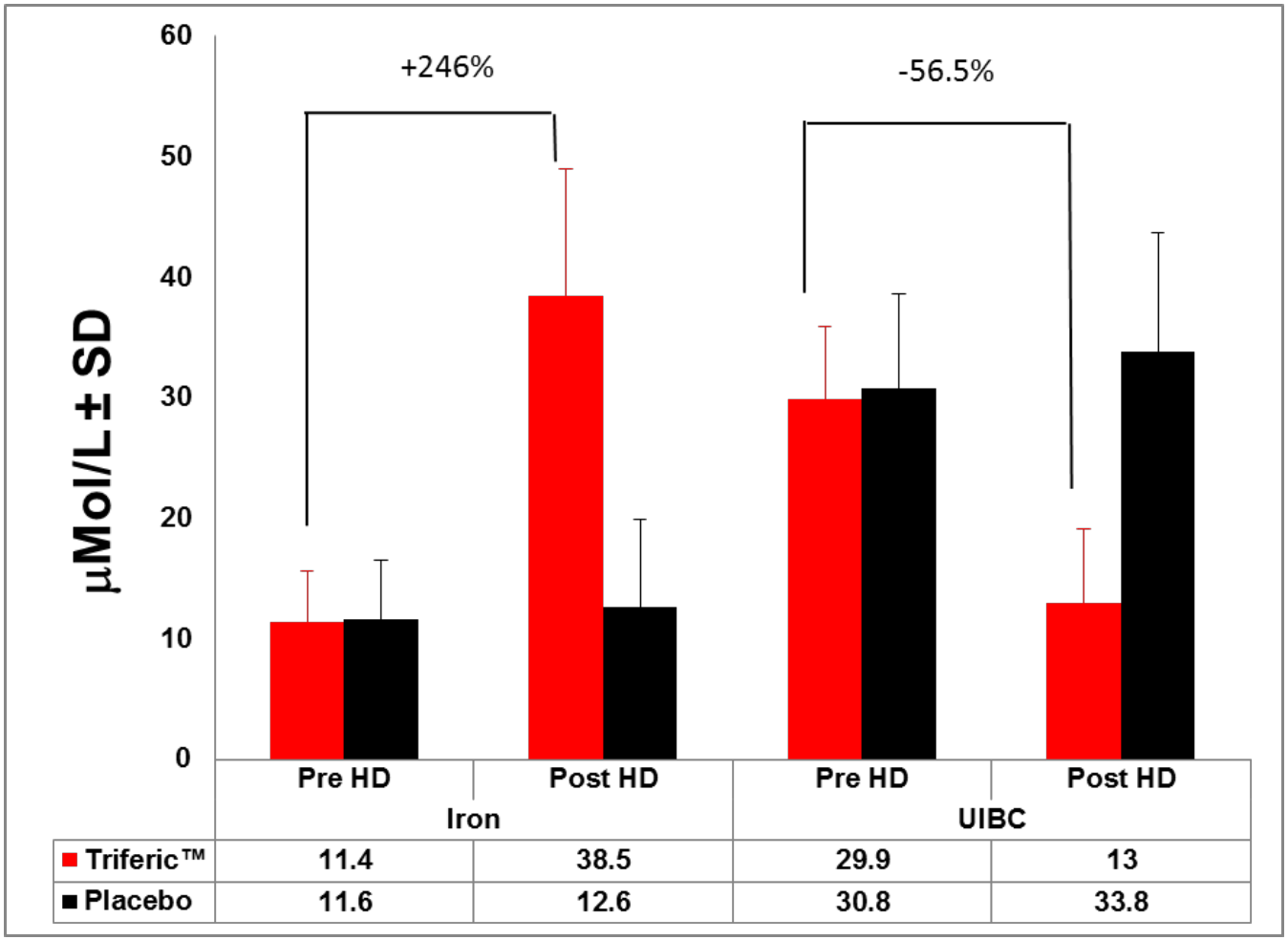
Iron delivered via dialysate

- Soluble and non-colloidal iron salt, not conjugated with a sugar moiety
- Iron- citrate- pyrophosphate
- MW ~1000 Da, similar to vitamin B_{12}
- Added to bicarbonate concentrate
- Crosses the dialyzer during the haemodialysis treatment and binds immediately to apotransferrin, largely bypassing the RE system



Gupta A *et al.* *Kidney Int* 2015; 88:1187-94.

Iron parameters during a single HD



	Iron		UIBC	
	Pre HD	Post HD	Pre HD	Post HD
Triferic™	11.4	38.5	29.9	13
Placebo	11.6	12.6	30.8	33.8

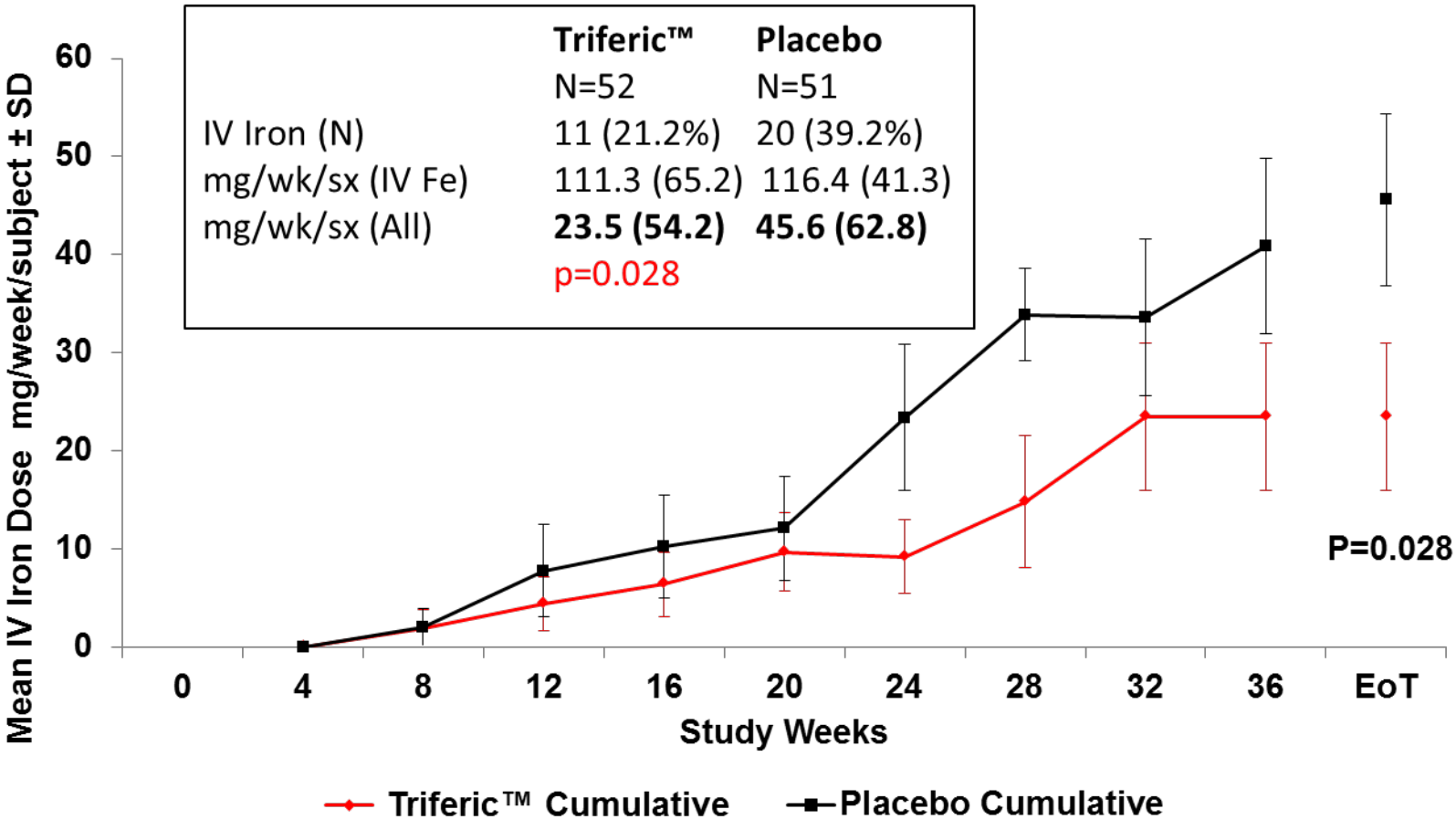
Gupta A *et al*. *Kidney Int* 2015; 88:1187-94.

35% ESA dose reduction vs. placebo

	Triferic N=52		Placebo N=51	
	U/wk (SD)	% Change from Baseline	U/wk (SD)	% Change from Baseline
Hgb g/dL Baseline	11.0		11.1	
Hgb g/dL EoT	10.4	-5.1	10.5	-5.8
Prescribed ESA Dose U/wk (SD) Baseline	9483 (5414)		9206 (5500)	
Prescribed ESA Dose U/wk (SD) EoT	9871 (7523)	7.3 (67.66)	12,628 (13,967)	37.3 (106.9)
LS mean (SE) % Change from Baseline	4.9 (12.1)		39.8 (12.2)	
95% CI LS mean	-19.1, 28.8		15.7, 64.0	
LS mean difference from Placebo	**-35.0 (17.20)**			
95% CI LS mean difference	**-69.1, -0.8**			
P-value	**0.045**			

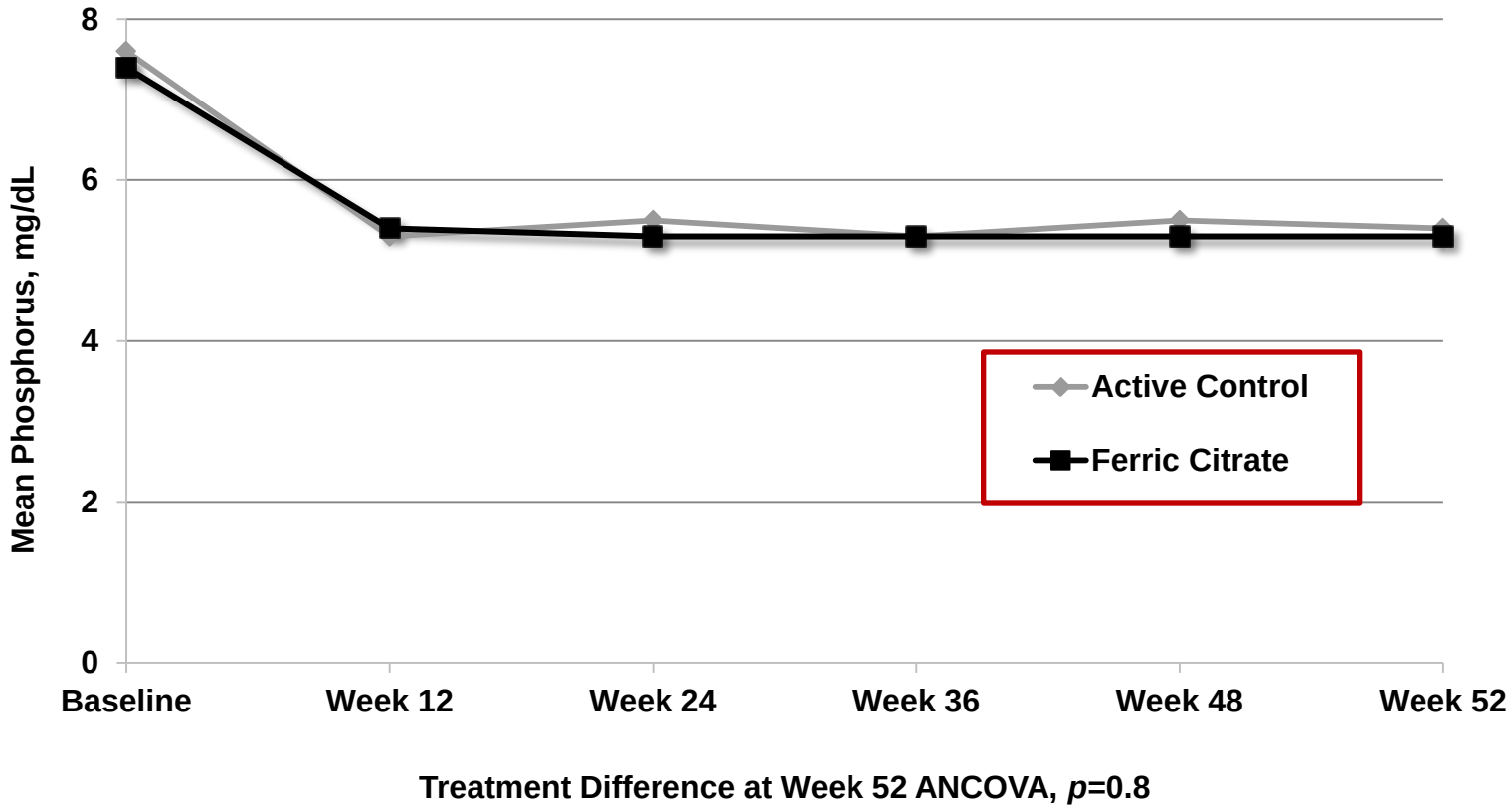
Gupta A *et al.* *Kidney Int* 2015; 88:1187-94.

Triferic reduces IV iron requirements by 48%



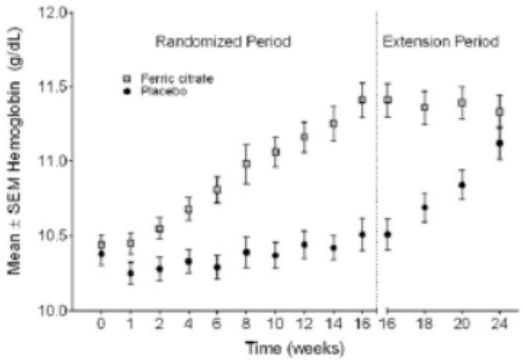
Gupta A *et al.* *Kidney Int* 2015; 88:1187-94.

Ferric citrate – effect on serum phosphate

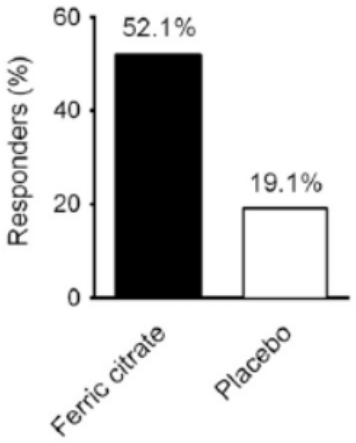


Lewis JB *et al.* *J Am Soc Nephrol* 2015; 26: 493-503.

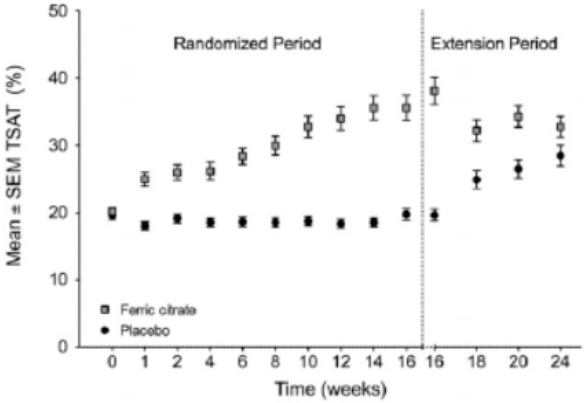
A Hemoglobin



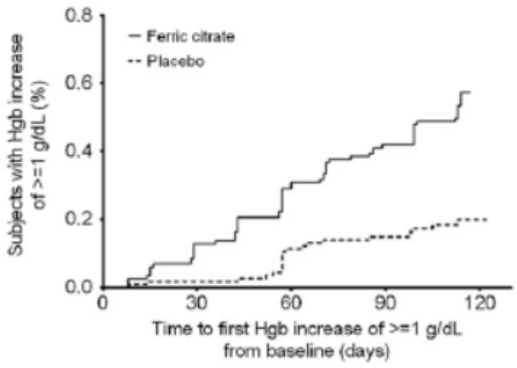
B Percent responders achieving ≥ 1g/dL Rise in Hemoglobin



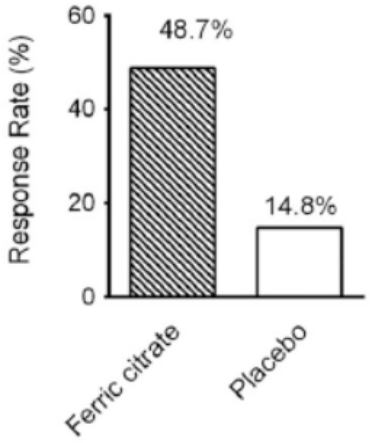
A Transferrin Saturation



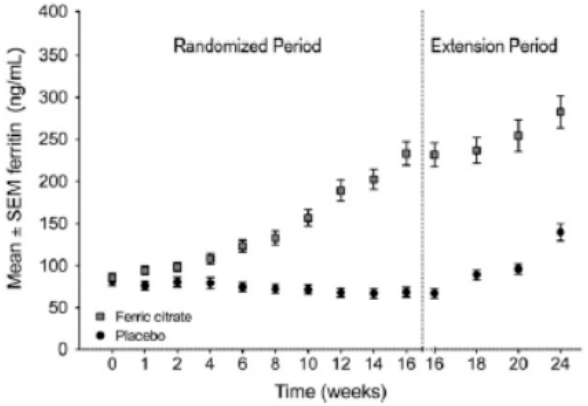
C Time to first response of ≥ 1g/dL Hemoglobin rise



D Sustained effect of >0.75 g/dL over any 4 week period



B Serum Ferritin



Fishbane *et al.* *J Am Soc Nephrol* 2017; 28: 1851-1858.

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20. Lewis JB *et al. J Am Soc Nephrol* 2015; 26 :493-503.
21. Fishbane *et al. J Am Soc Nephrol* 2017; 28: 1851-1858.

List of Abbreviations

- CVS – cardiovascular system
- DOPPS – Dialysis and Practice Patterns Survey
- EPO – erythropoietin
- ESA – erythropoiesis-stimulating agent
- FCM – ferric carboxymaltose
- HIF – hypoxia-inducible factor
- IRR – Incidence Rate Ratio
- ND-CKD – non-dialysis chronic kidney disease
- PHI – prolyl hydroxylase inhibitor
- QoL – quality-of-life
- SAEs – serious adverse events
- TSAT – transferrin saturation
- VTE – venous thromboembolism