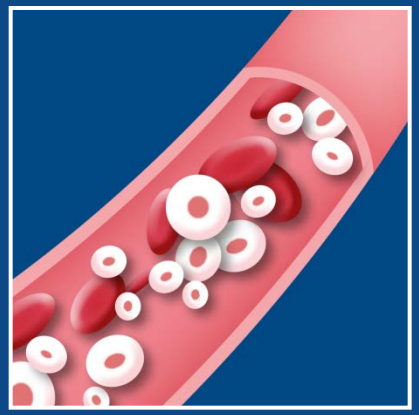
# Nephro Update Europe 2017

## 6-7 October, Vienna

# Renal Anemia



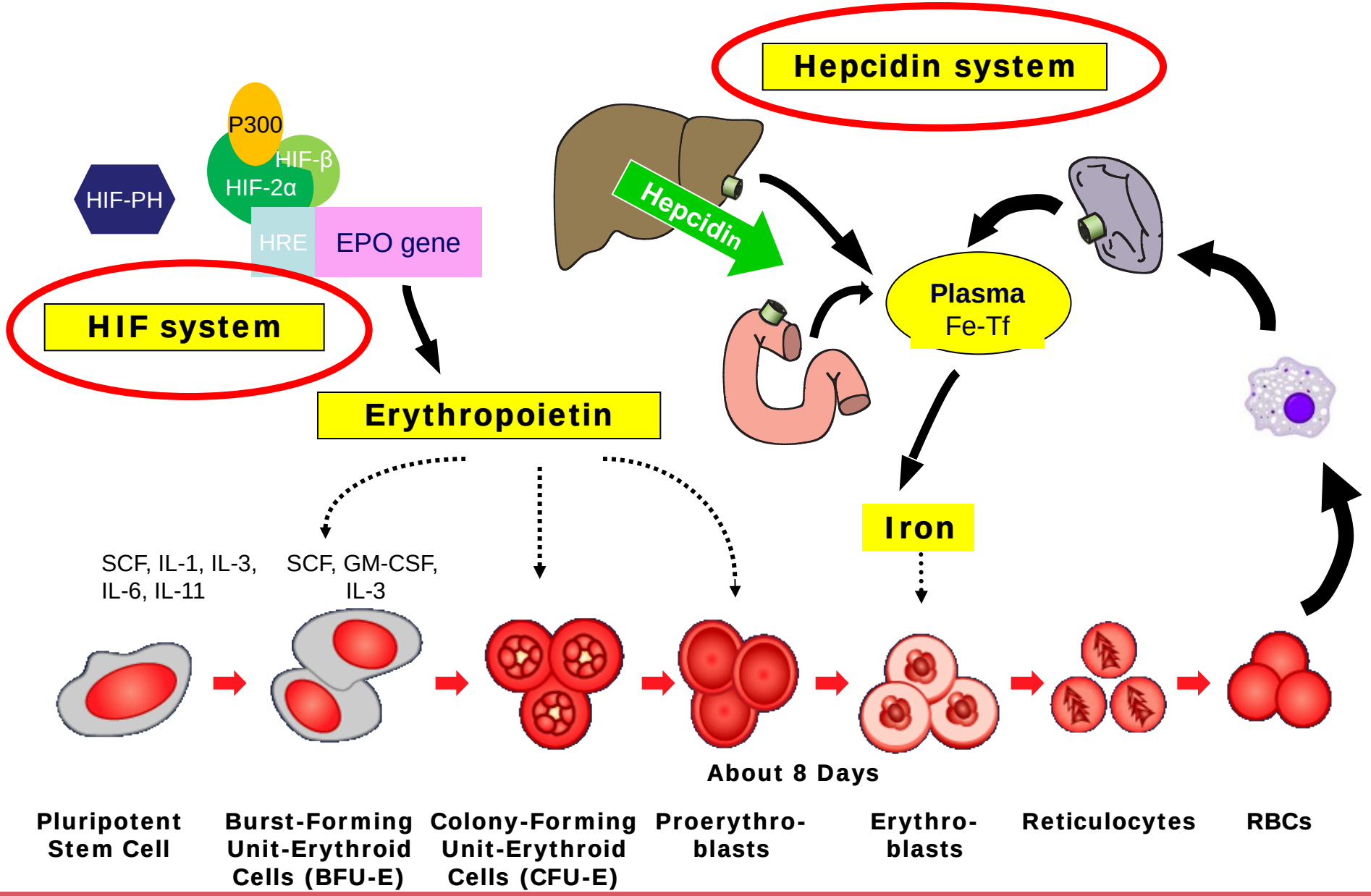
Iain Macdougall, UK

# Subtopics

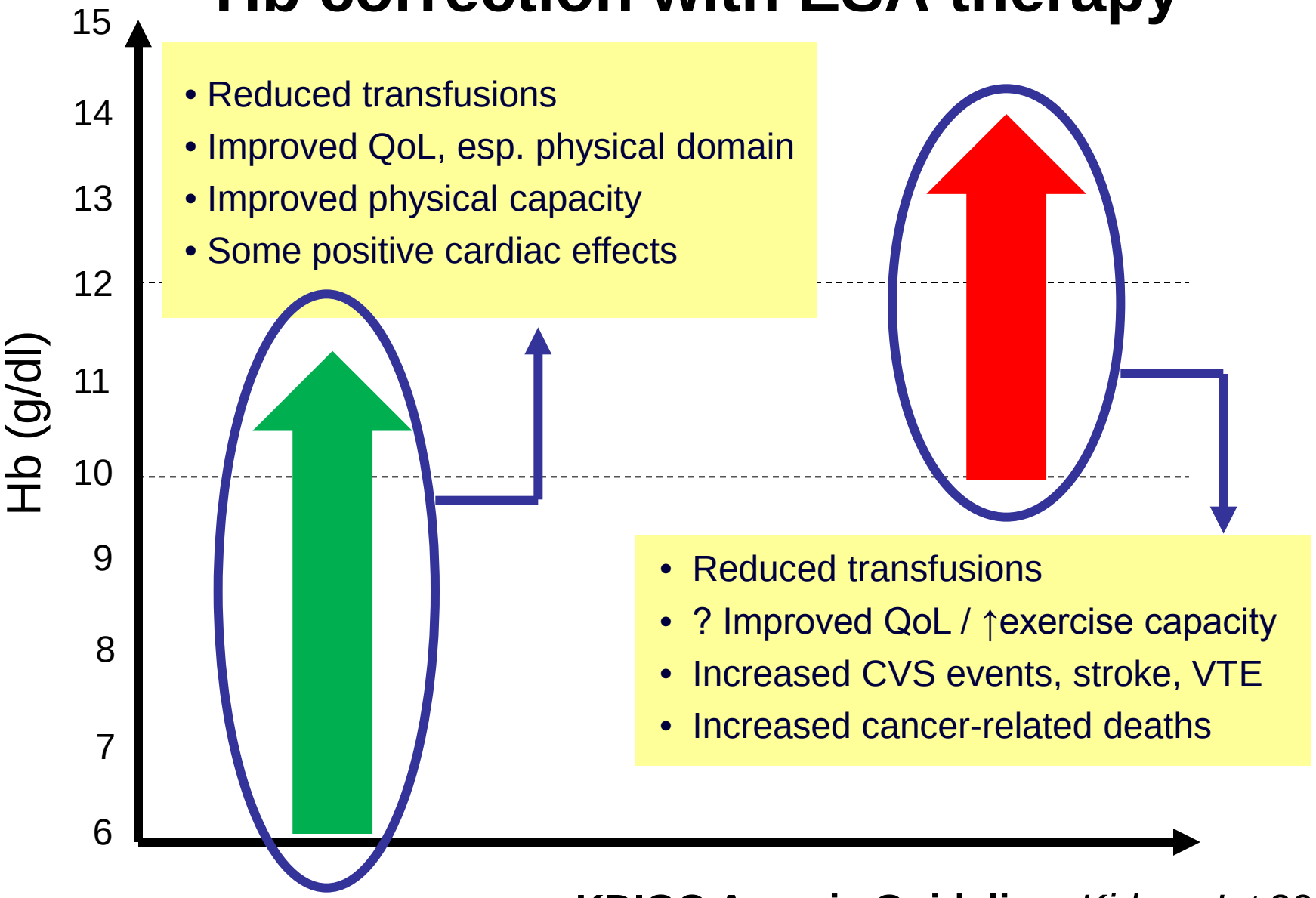
- ESA and iron therapy – standard-of-care
- Iron management (oral *vs* IV) in ND-CKD
- IV iron in HD
- HIF stabilisers
- Newer iron management strategies

# ESA and iron therapy – standard-of-care

# Regulation of erythropoiesis

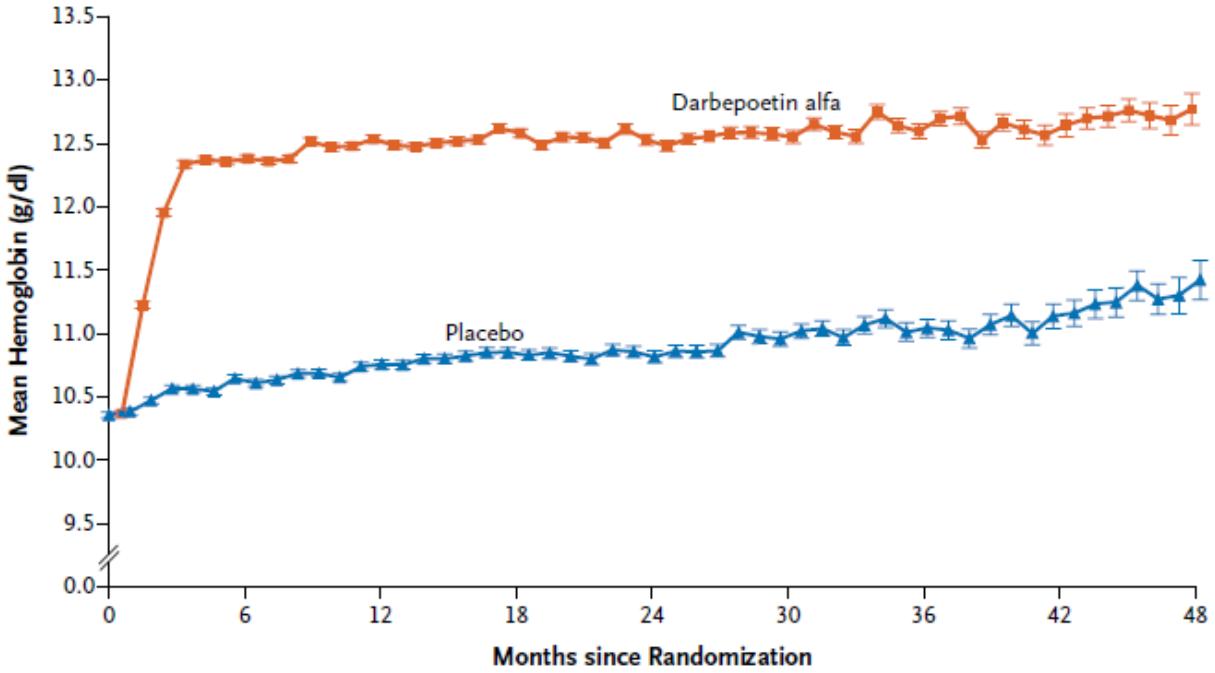


# Hb correction with ESA therapy




**KDIGO Anemia Guideline,** *Kidney Int* 2012.

# TREAT study: Haemoglobin



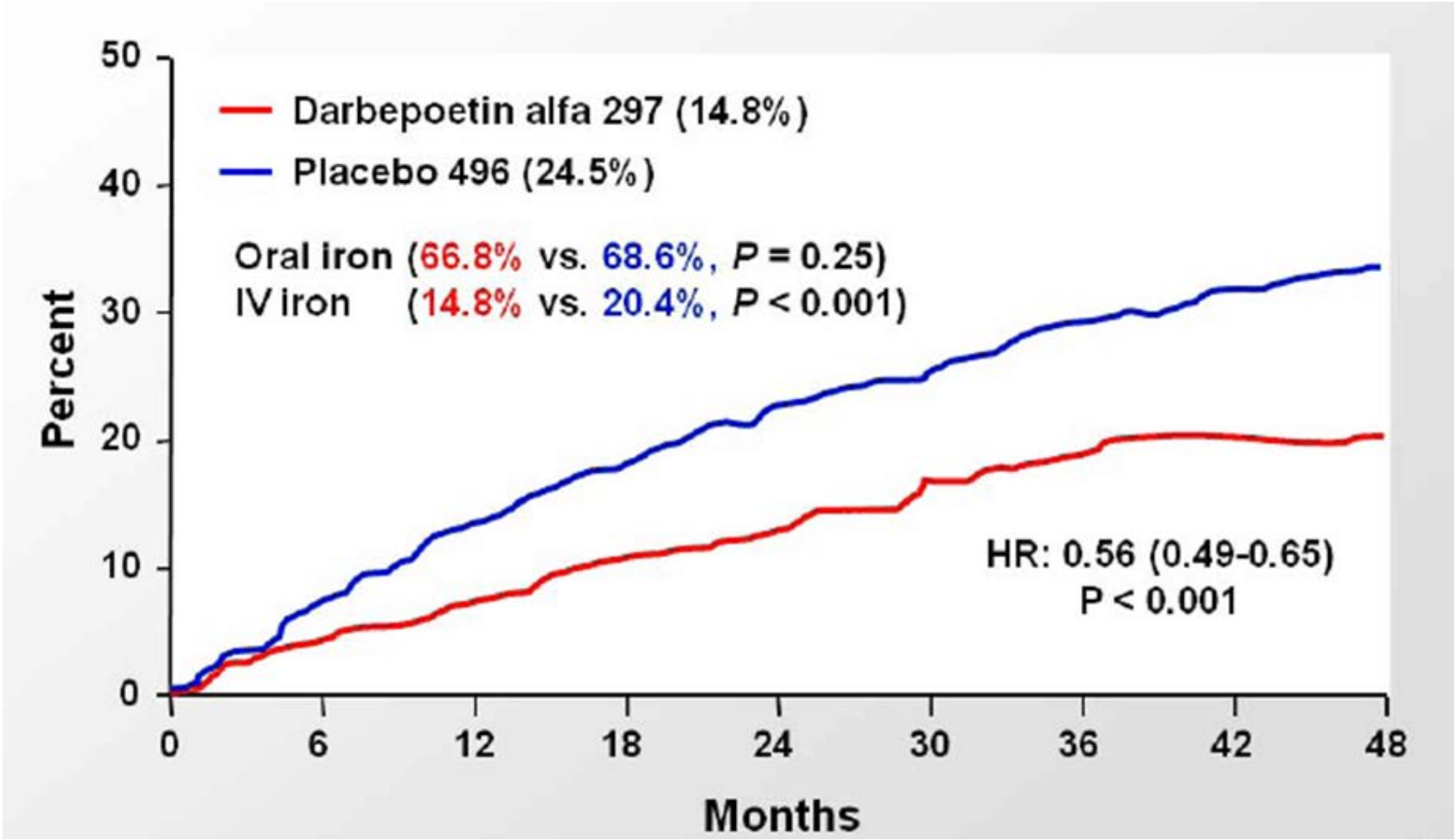

| No. of Patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Darbepoetin alfa | 2004 | 1768 | 1503 | 1300 | 946 | 635 | 404 | 253 | 97 |
| Placebo | 2019 | 1742 | 1460 | 1221 | 887 | 620 | 356 | 216 | 79 |

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

I bars represent standard errors.

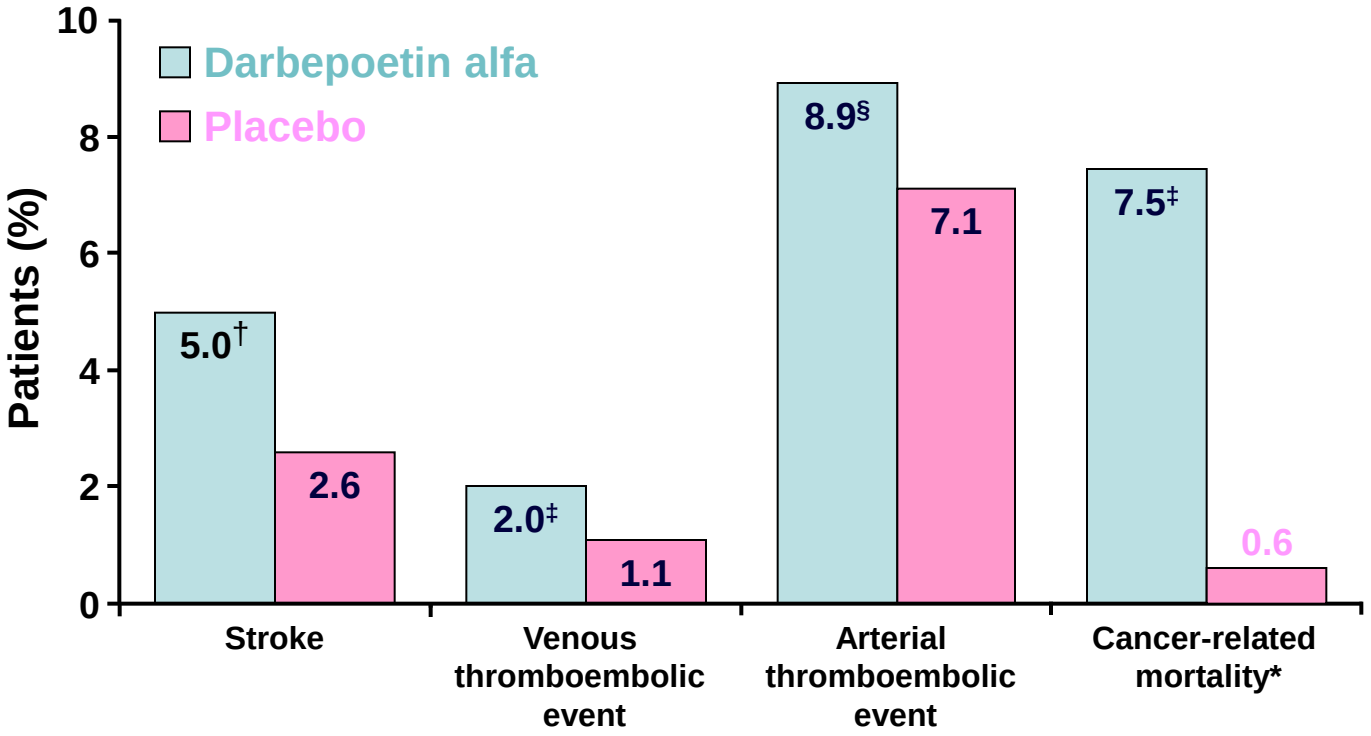
**Pfeffer MA *et al.*** *N Engl J Med* 2009; 361: 2019-32.

# TREAT study: Blood transfusions




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

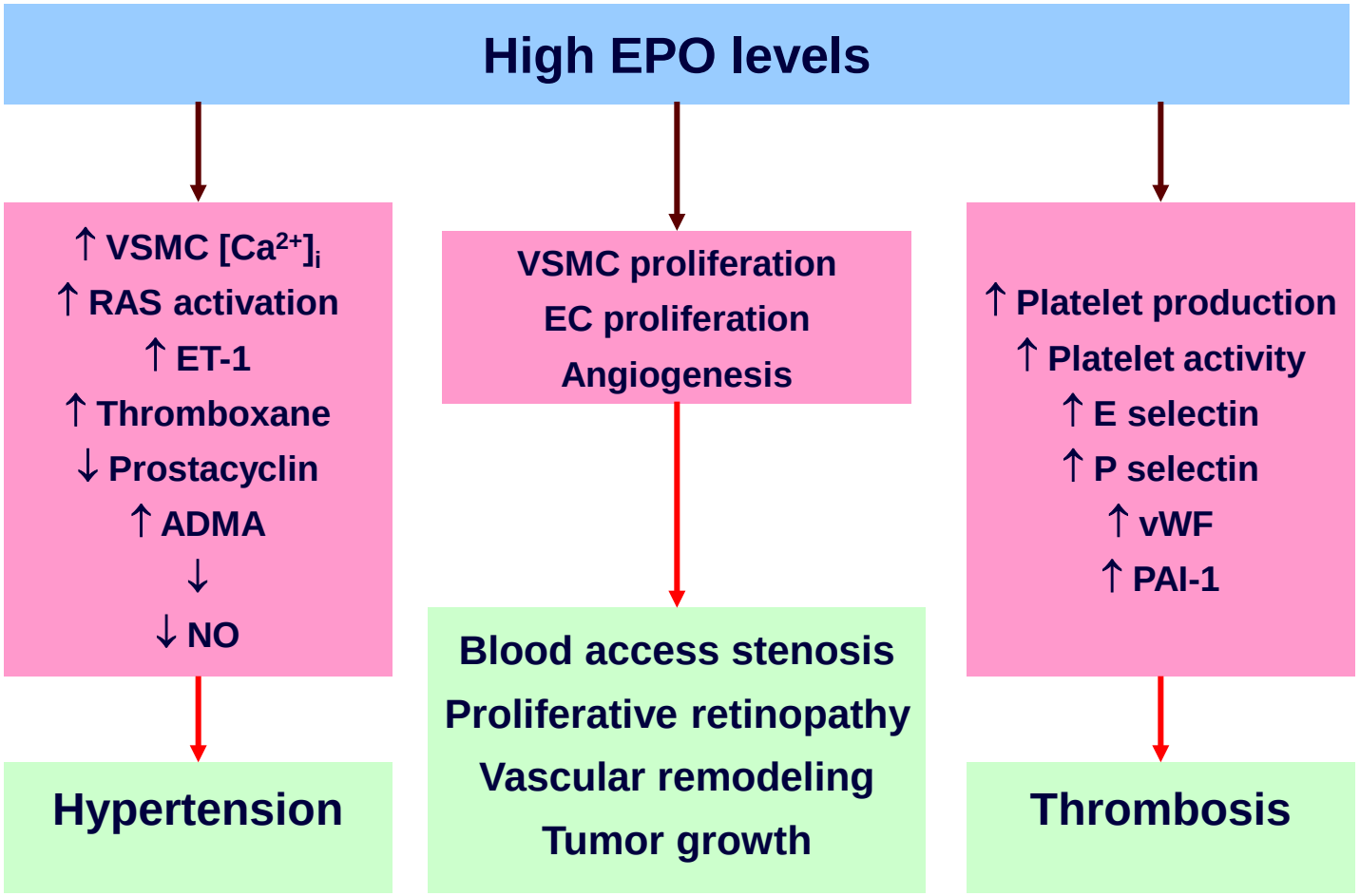
# TREAT study: Safety issues




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

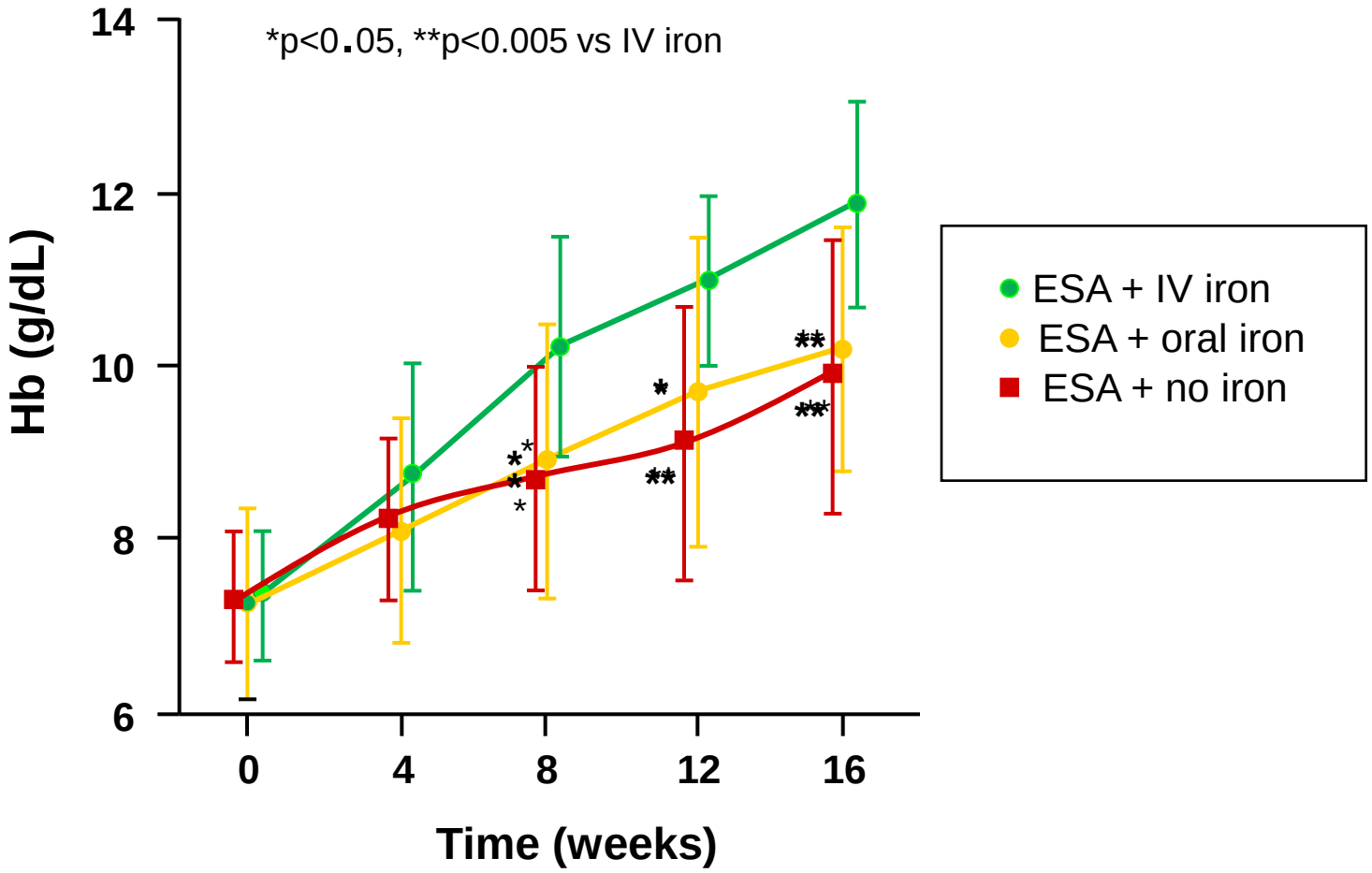
**Pfeffer MA *et al.*** *N Engl J Med* 2009; 361: 2019-32.

# 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.

# 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

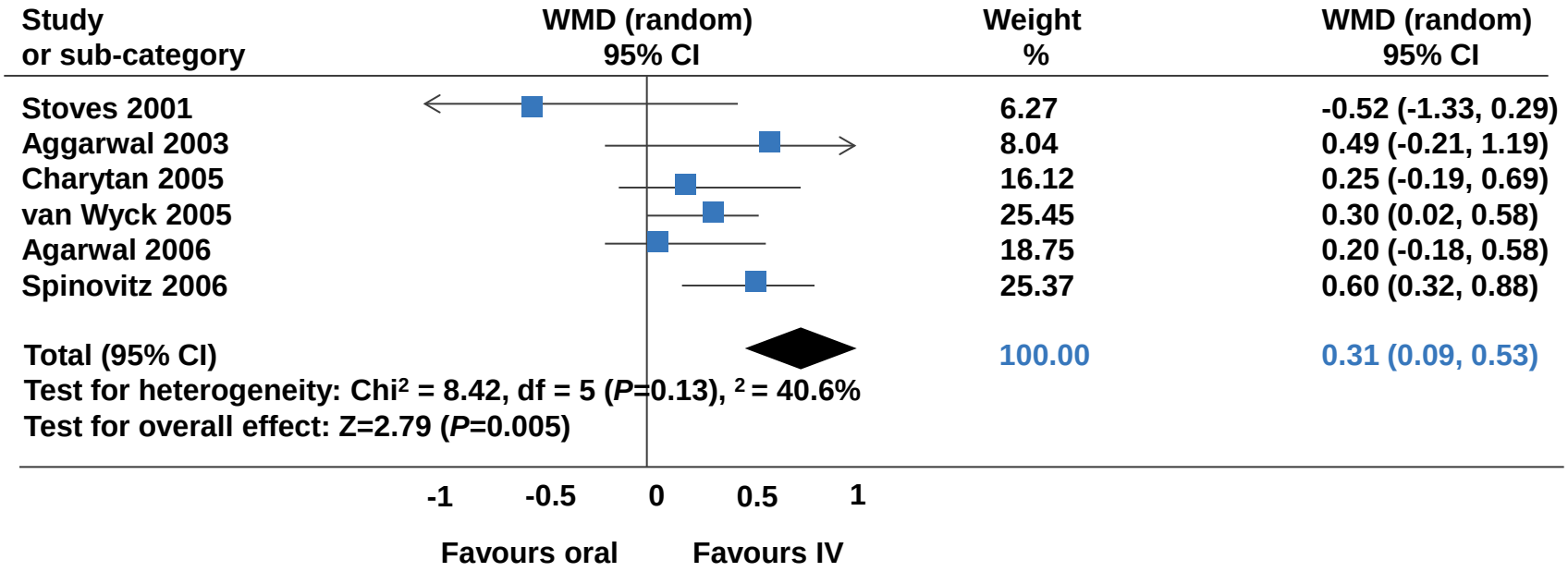
- ESA therapy and IV iron are the mainstay of anaemia management in CKD
  - -- both have unquestionable efficacy
  - -- both have safety concerns

- The relative balance between the two remains obscure

# Iron management (oral vs IV) in ND-CKD

# 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

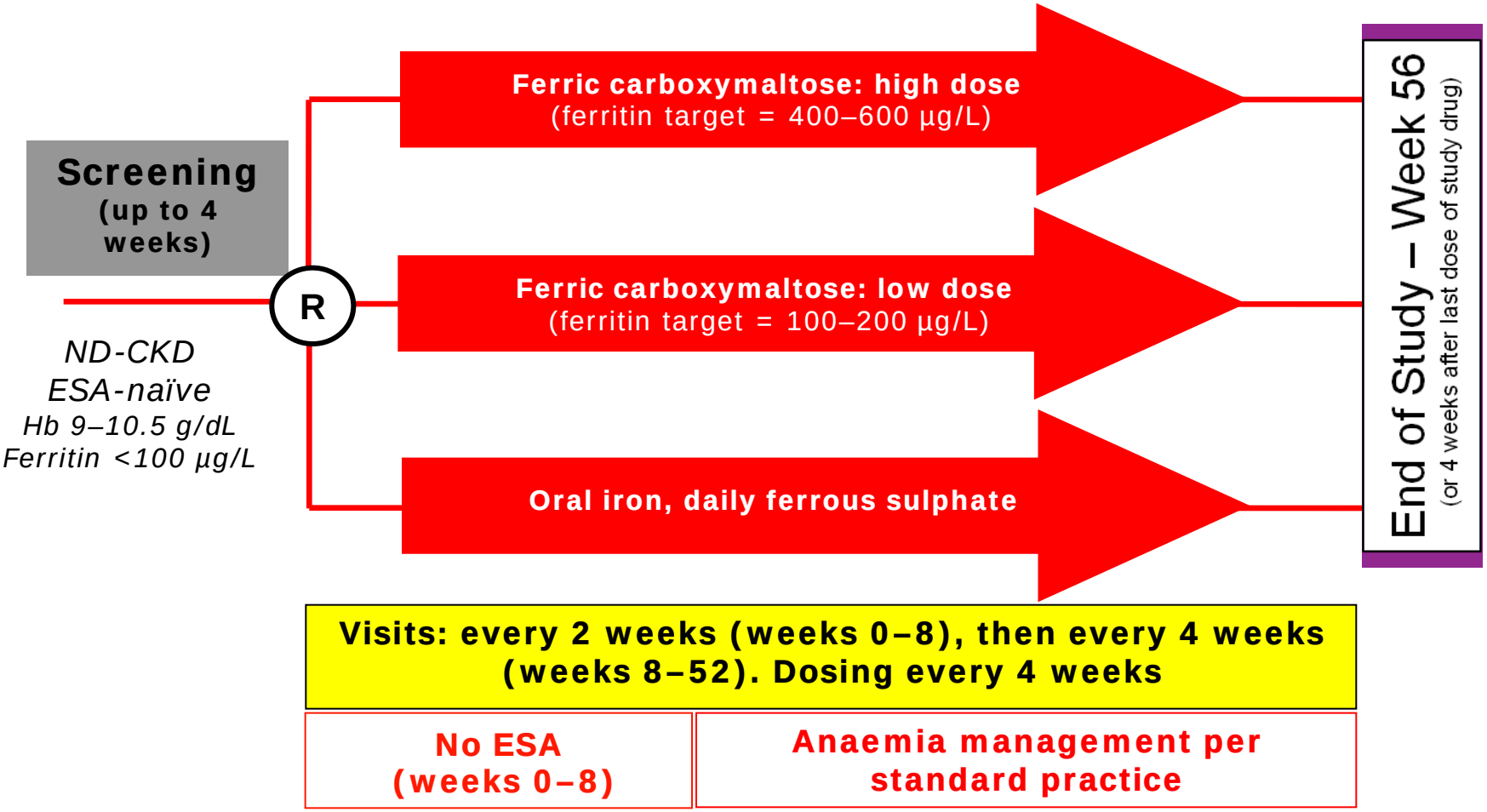



- Most studies had short duration of follow-up
- More randomized trials are required

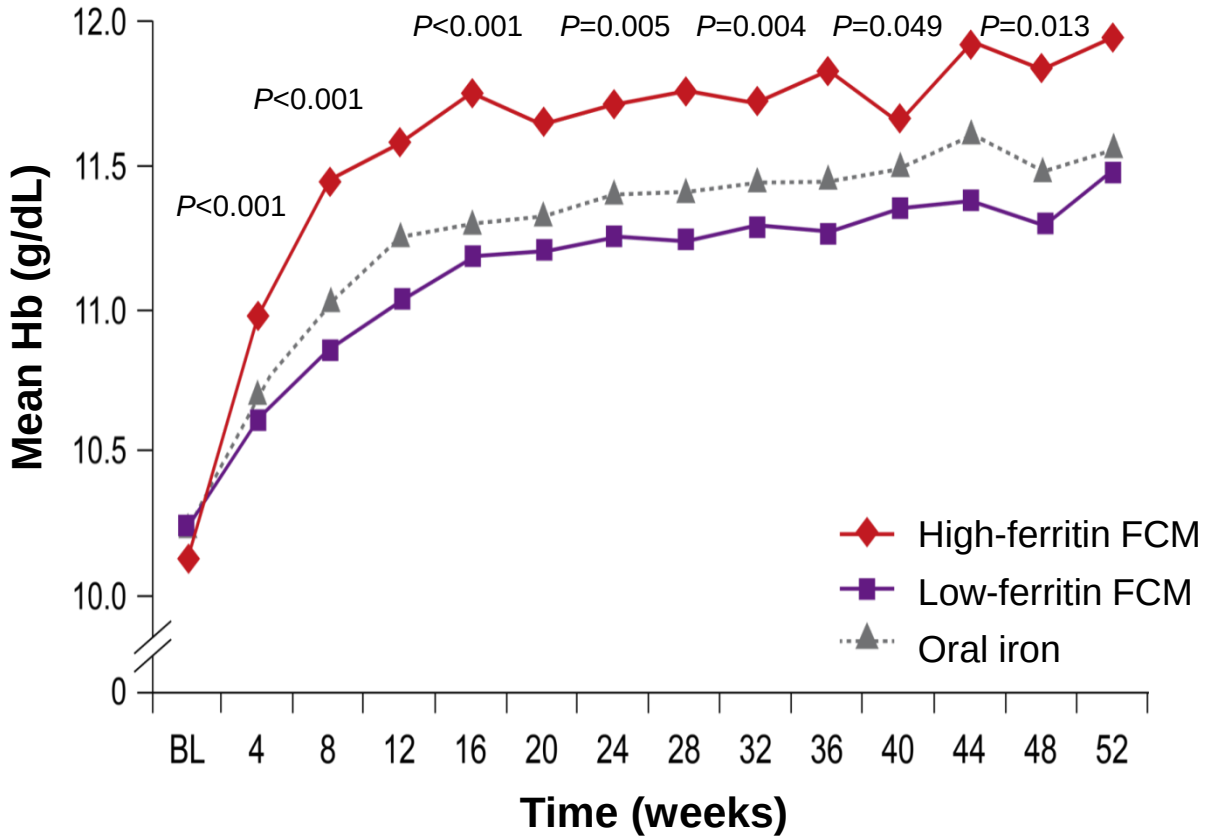
**Rozen-Zvi *et al.*** *Am J Kidney Dis* 2008;52:897–906.

# The FIND-CKD trial

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

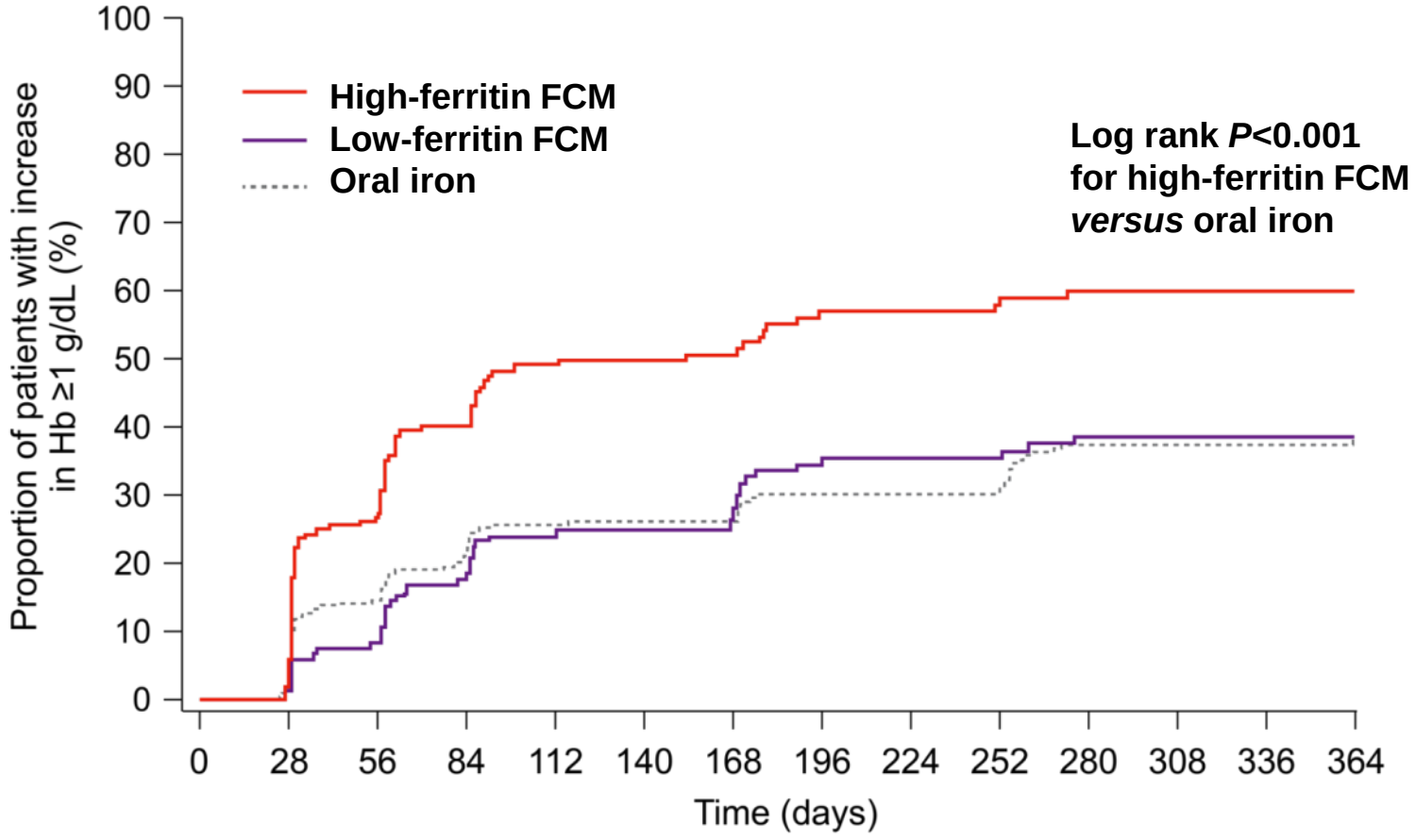


# FIND-CKD – haemoglobin




**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 trial -- safety

| | High-ferritin ferric carboxymaltose (n=154) | Low-ferritin ferric carboxymaltose (n=150) | Oral iron (n=312) |
|---|---|---|---|
| Any serious adverse event*, % | 25.3 | 24 | 18.9 |
| **Cardiac disorders, %** | 6.5 | 4.7 | 4.5 |
| Acute myocardial infarction | 1.3 | 0 | 1.3 |
| Cardiac failure | 0.6 | 0 | 1.0 |
| **Infections, %** | **3.9** | **3.3** | **3.8** |
| **Pneumonia** | **0** | **0.7** | **1.3** |
| Injury, poisoning & procedural complications, % | 2.6 | 2.0 | 2.6 |

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

# The FIND-CKD study– renal function

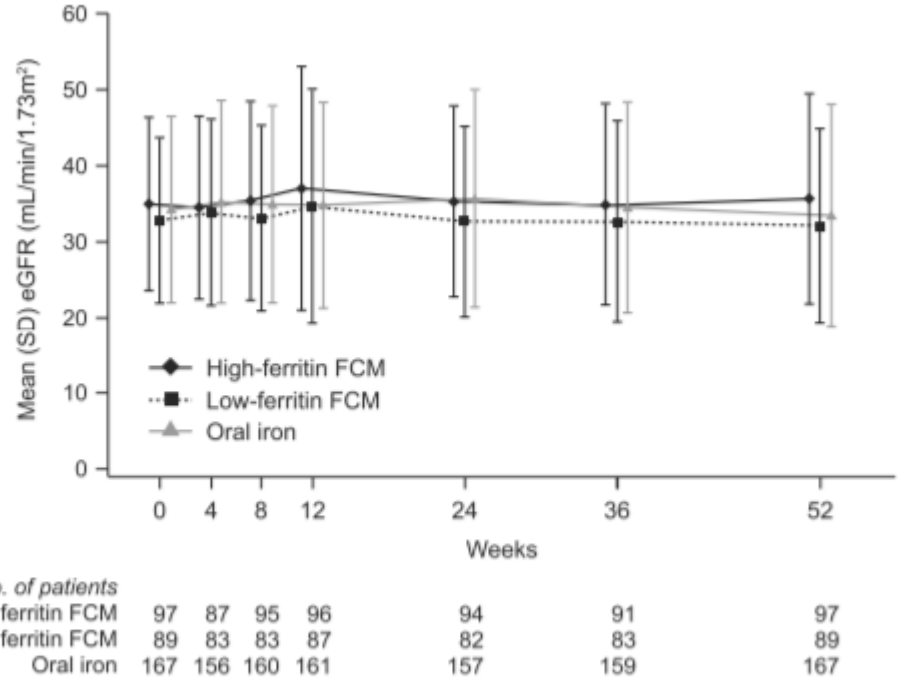



**Fig. 1** Estimated GFR to month 12 according to treatment group in patients with eGFR values at baseline and month 12. Values are shown as mean (SD). FCM, ferric carboxymaltose; eGFR, estimated GFR

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

# FIND-CKD – renal function

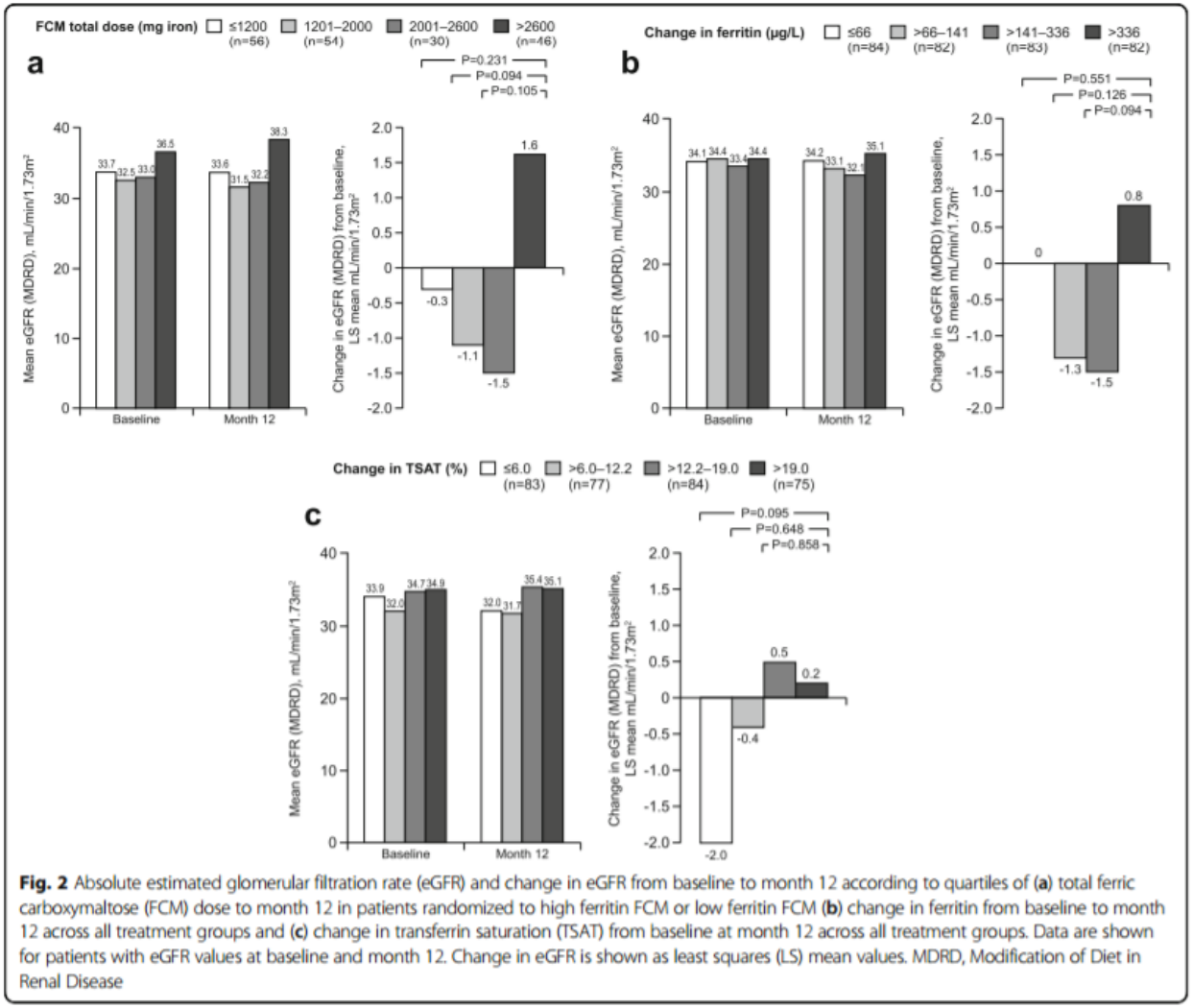


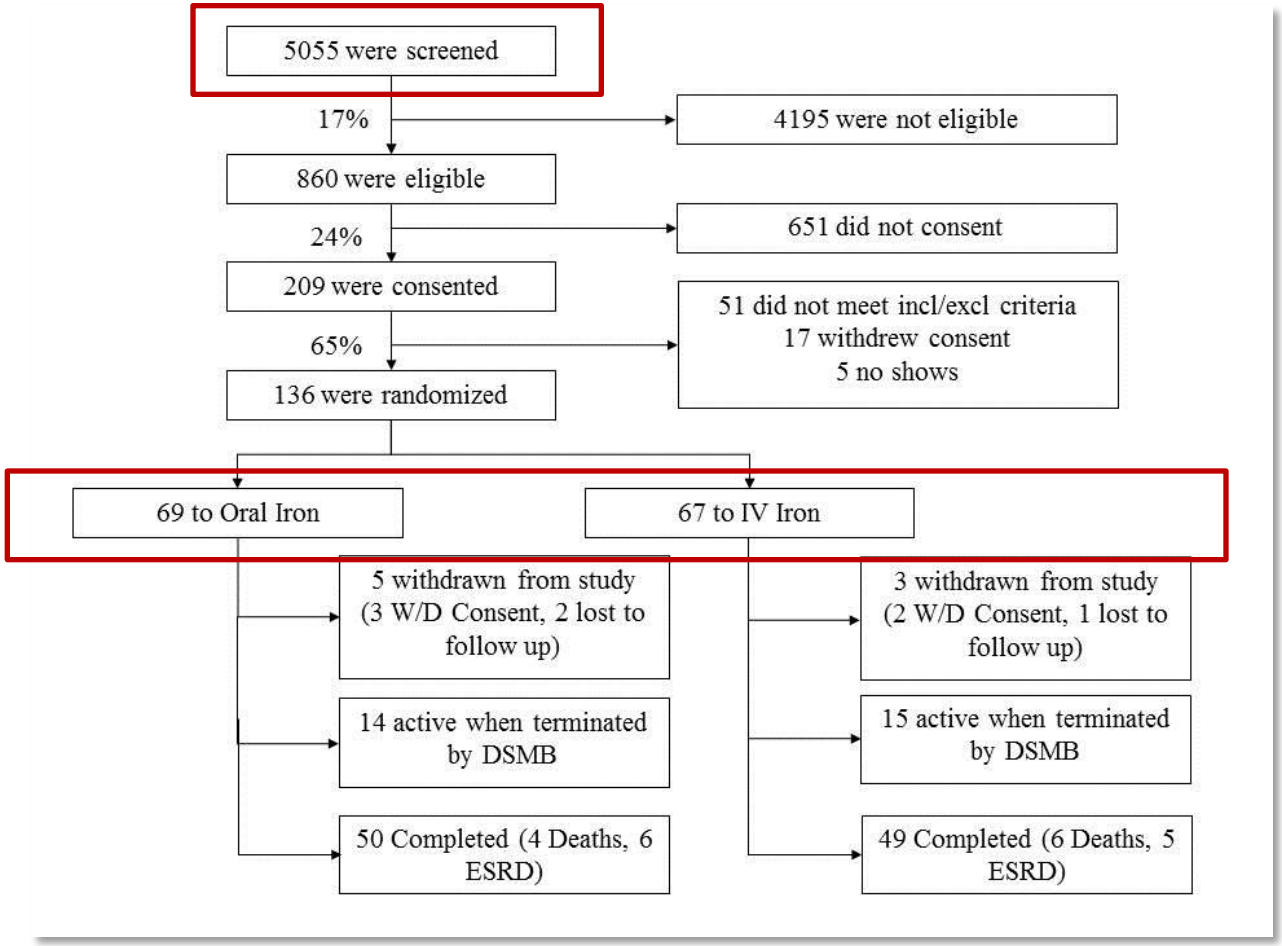

**Fig. 2** Absolute estimated glomerular filtration rate (eGFR) and change in eGFR from baseline to month 12 according to quartiles of (**a**) total ferric carboxymaltose (FCM) dose to month 12 in patients randomized to high ferritin FCM or low ferritin FCM (**b**) change in ferritin from baseline to month 12 across all treatment groups and (**c**) change in transferrin saturation (TSAT) from baseline at month 12 across all treatment groups. Data are shown for patients with eGFR values at baseline and month 12. Change in eGFR is shown as least squares (LS) mean values. MDRD, Modification of Diet in Renal Disease

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

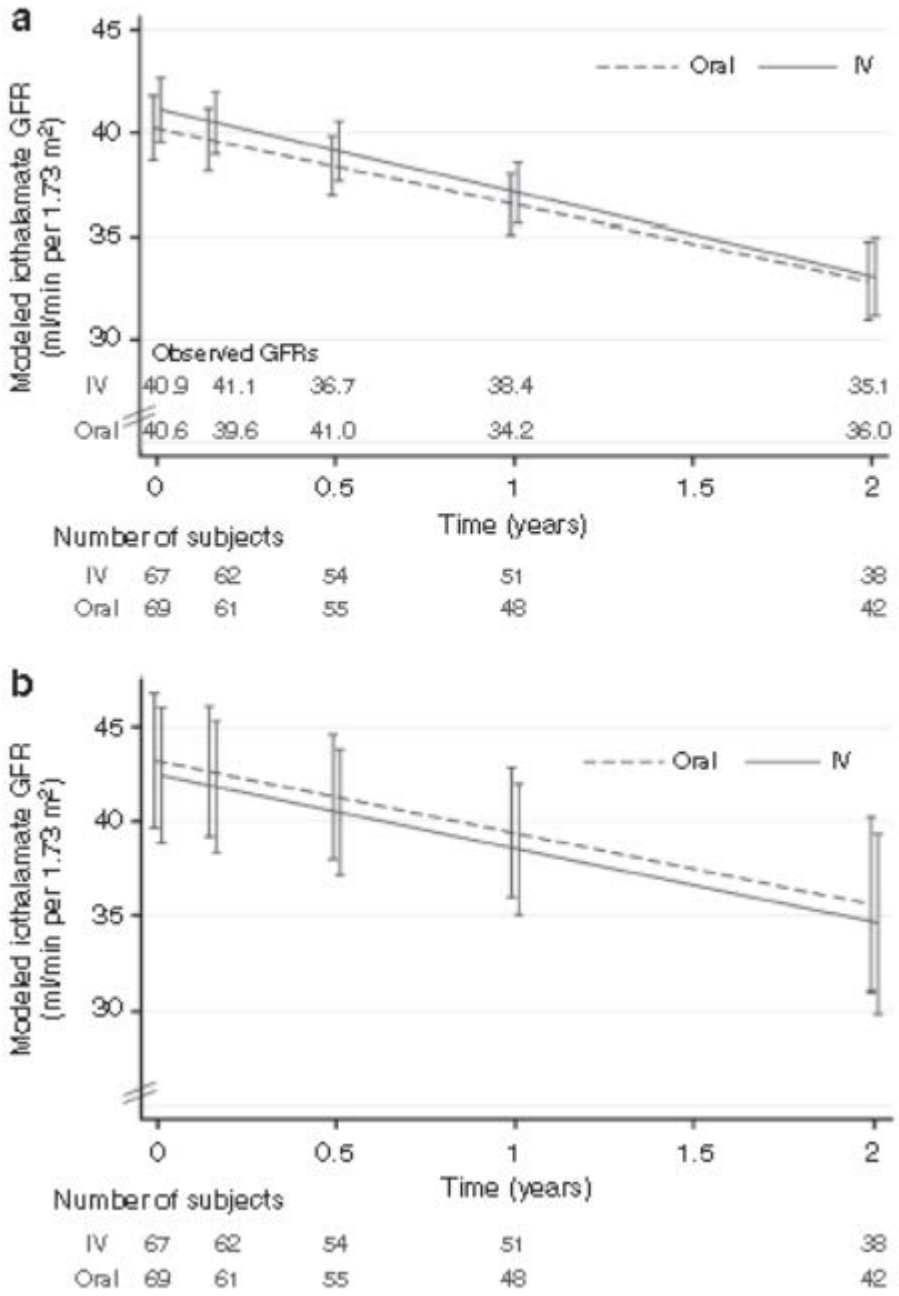
# REVOKE:

## *Disposition of the study participants*

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



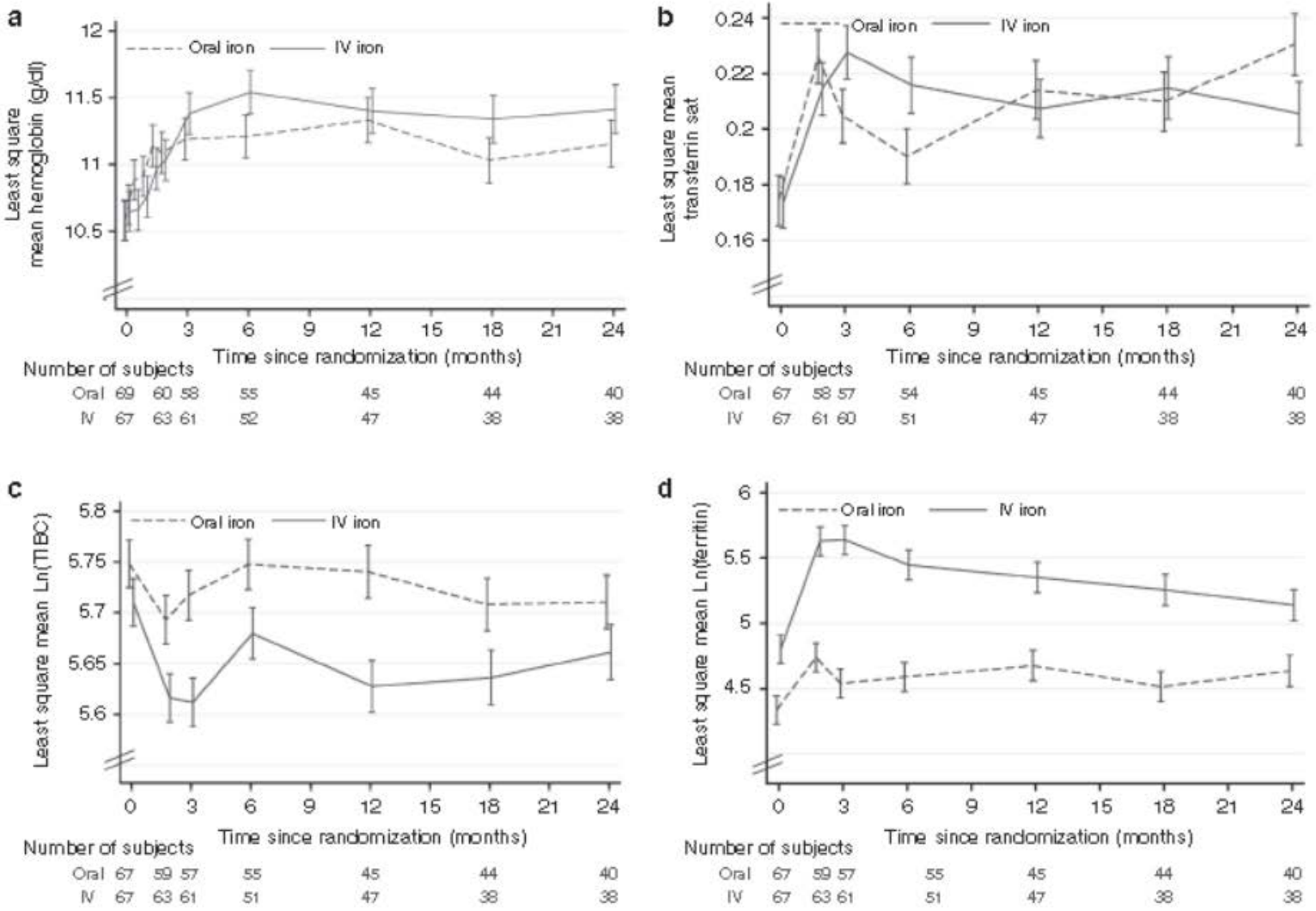

- **The trial early terminated on the recommendation of the DSMB based on an increase in the SAE rate in IV iron treatment group compared to oral iron group and little difference in mGFR between treatment groups**
- **Median follow up of all participants was 24.0 months (11.0–24.3) → No difference between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




# REVOKE study: Renal function (measured GFR)

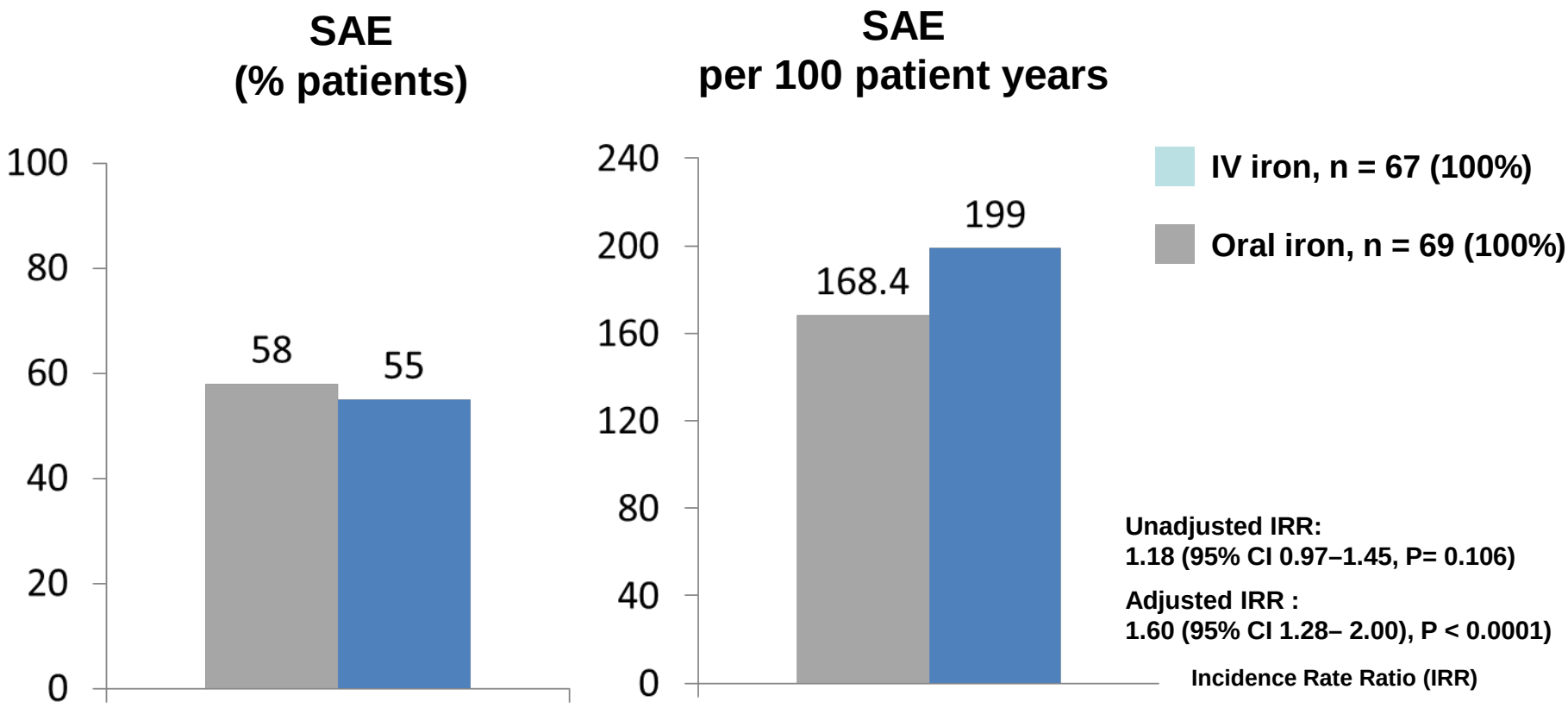
**Agarwal R *et al.***
*Kidney Int* 2015; 88: 905-914.

# REVOKE study: Hb and iron status




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

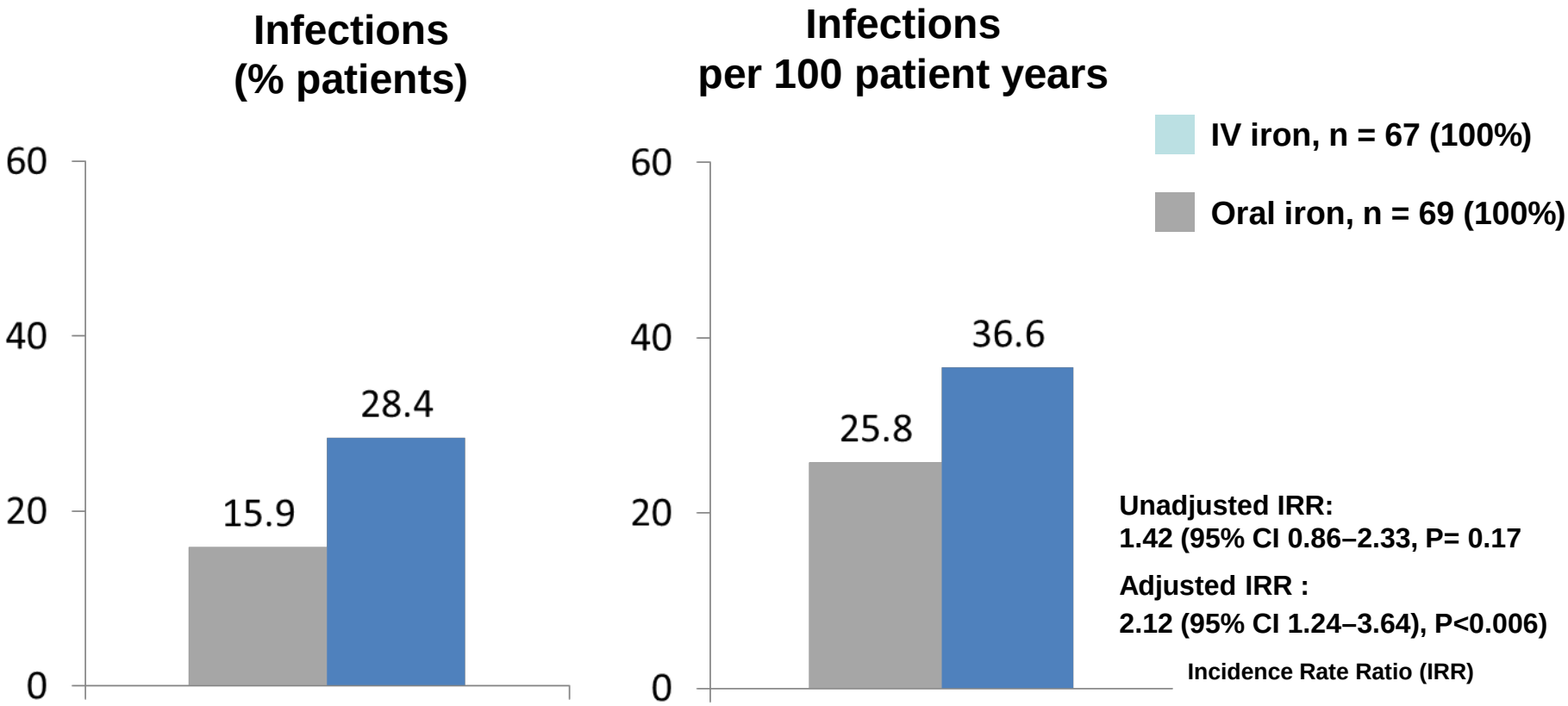
# REVOKE: *Overall serious adverse events*




- **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.

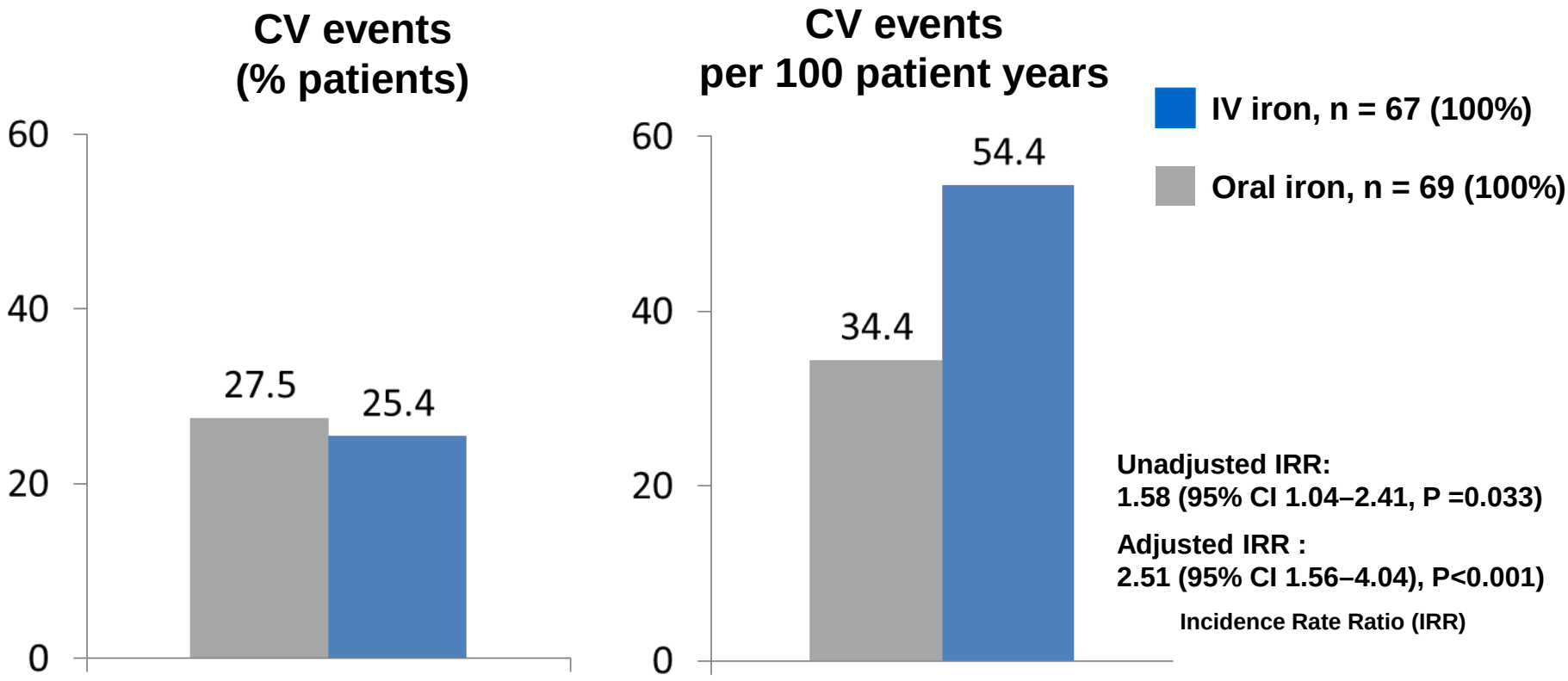
# REVOKE: *Infection-related SAEs*




- **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*

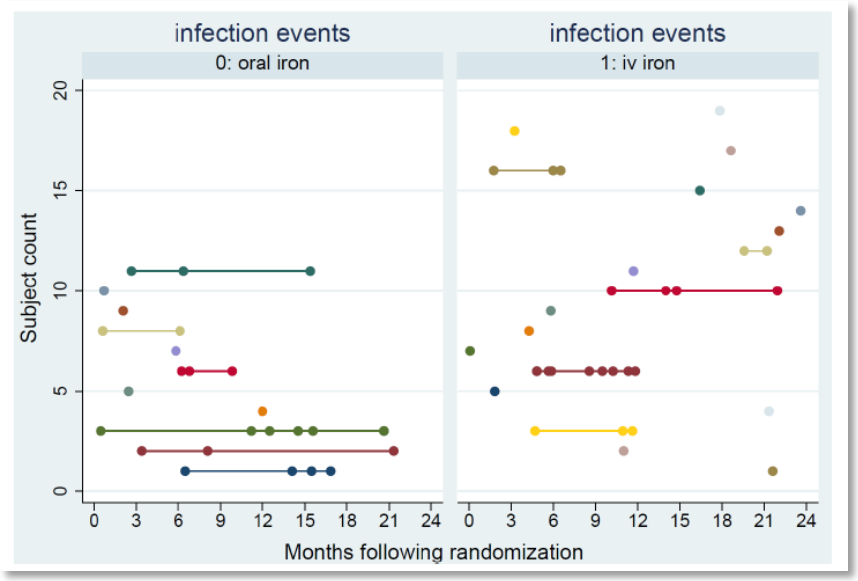


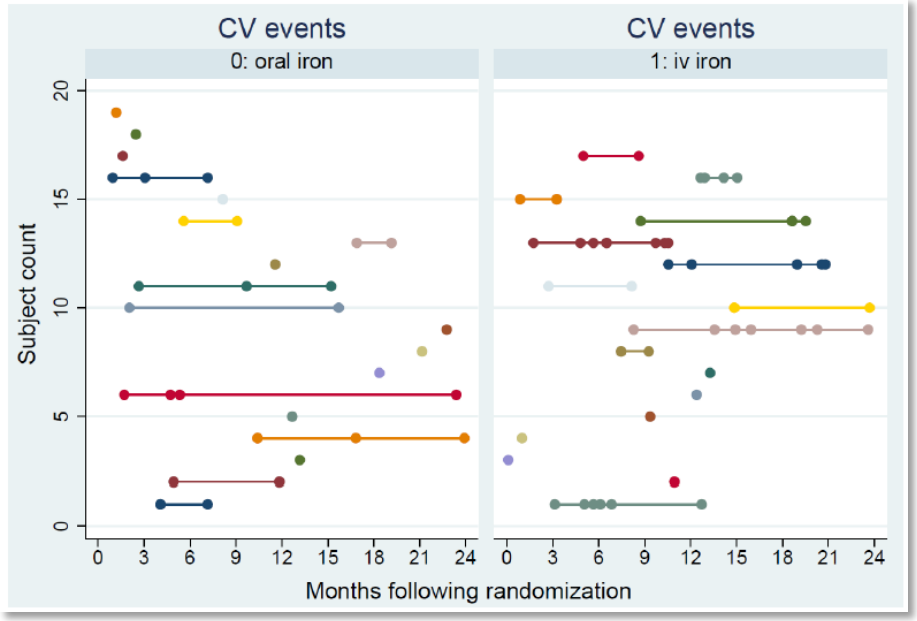

- **The incidence of hospitalized heart failure was increased approximately twofold in the IV iron group**

**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

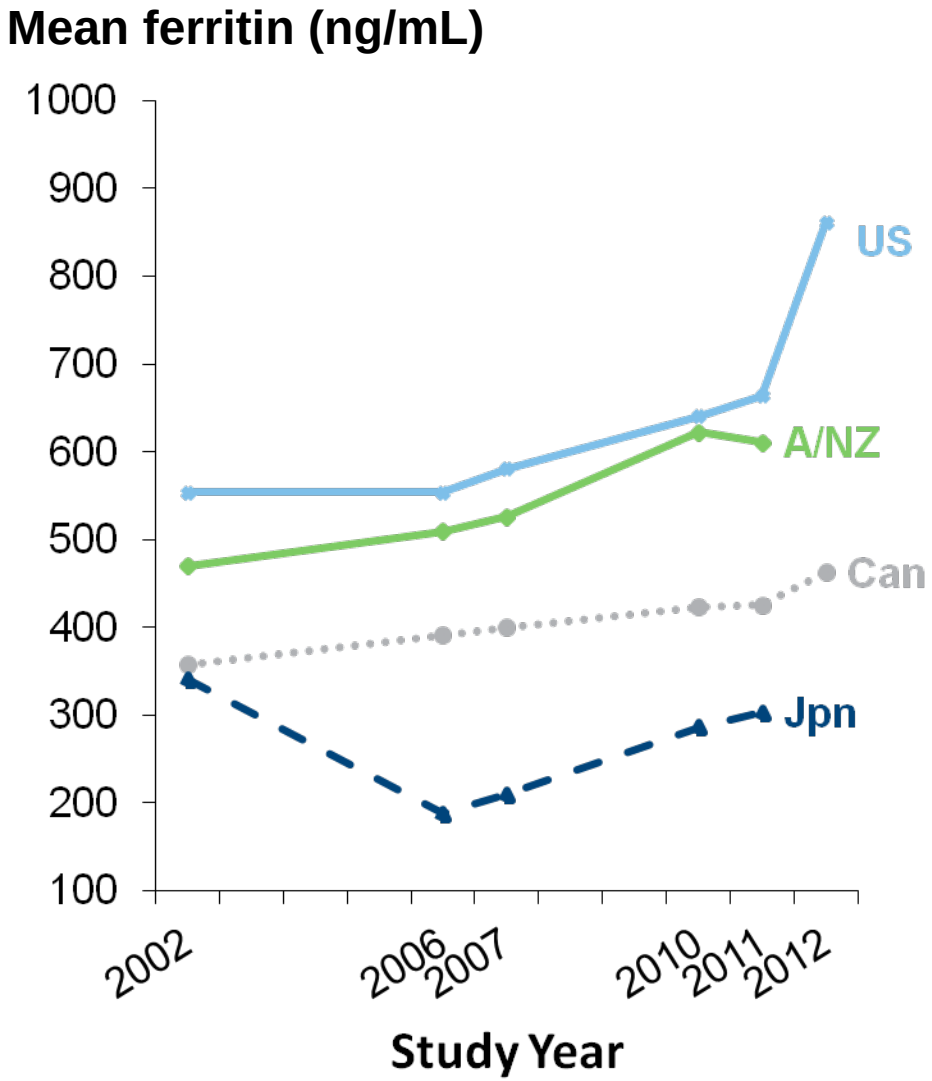
# Take-Home Message

- 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

# Ferritin and IV iron use in DOPPS

**Bailie GR et al.** *Nephrol Dial Transplant* 2013; 28: 2570-9.



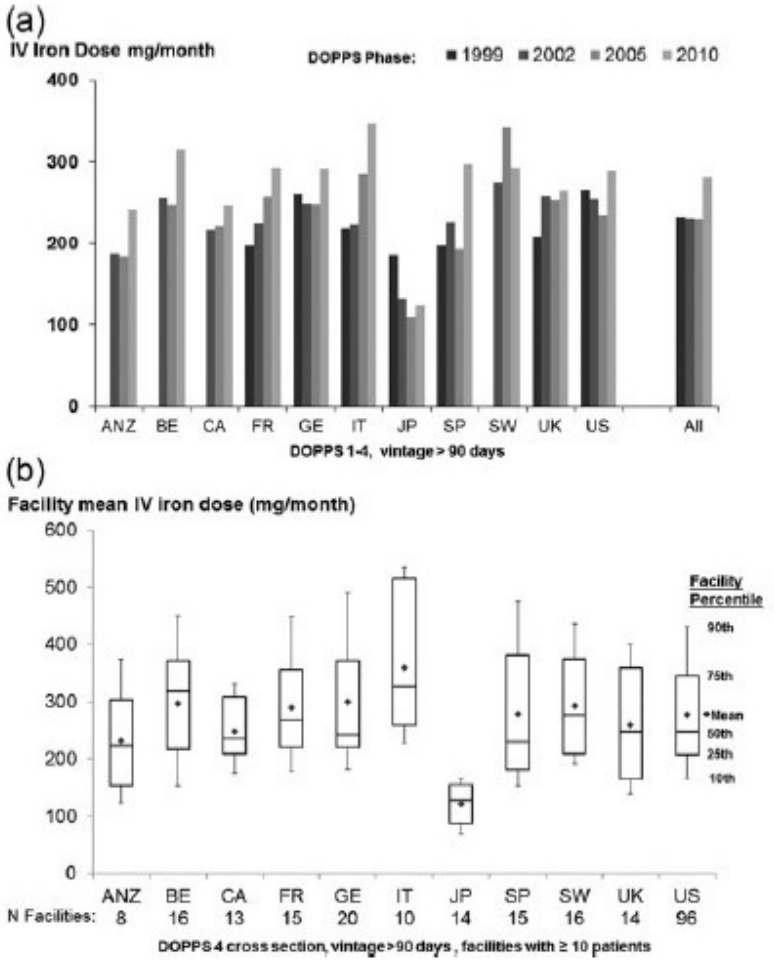
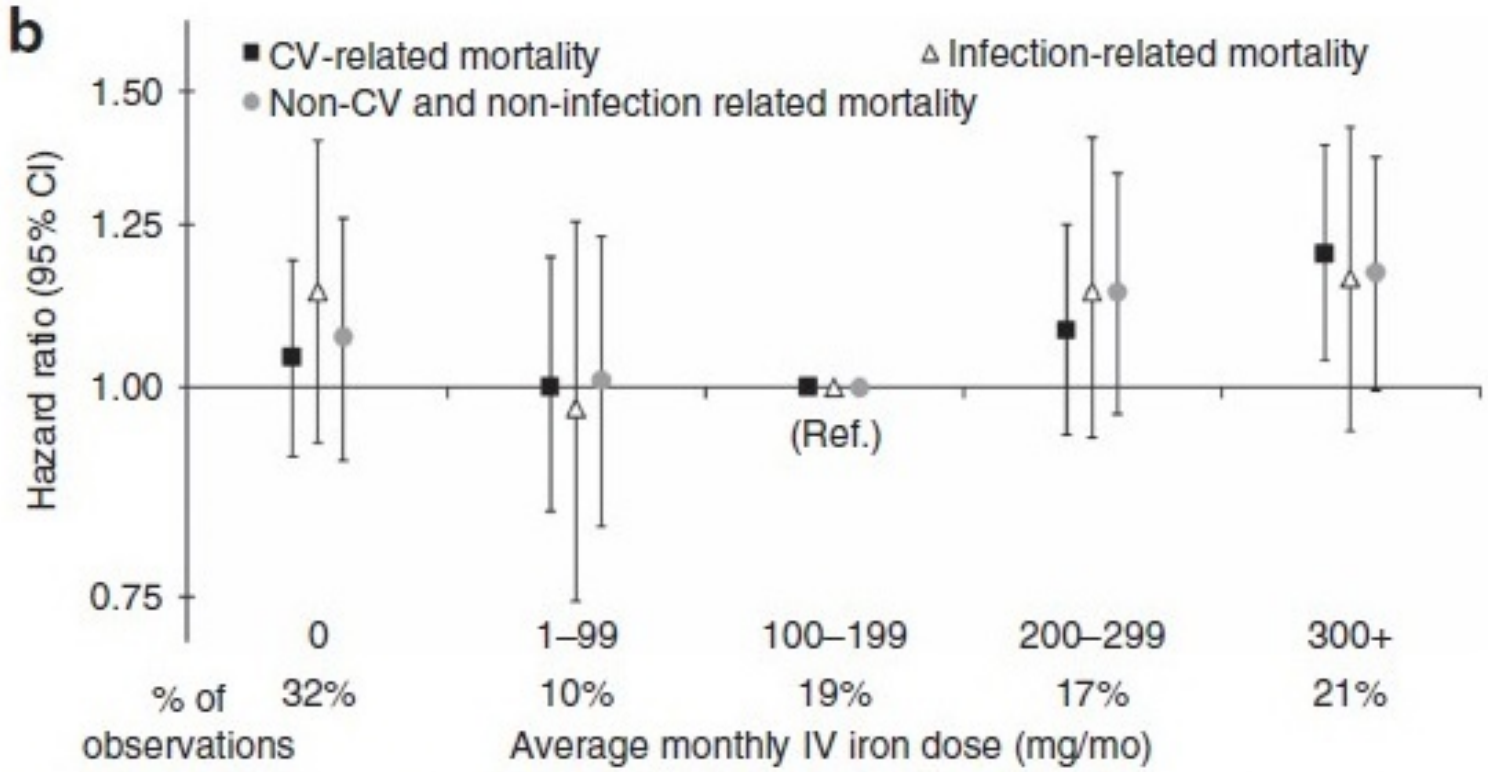




FIGURE 2: (a). Mean IV iron dose (4-month dose, expressed as mg/month) among patients receiving IV iron, by country and study phase. (b). Distribution of within-facility mean IV iron dose, by country in Phase 4 (2010).

# Association of IV iron and mortality *DOPPS*




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

# Association of IV iron and mortality

**Table 3. Association of intravenous iron dose with time to all-cause, cardiovascular, and infection-related death**

| Doses (mg) | *n* (patient-mo) | Percent | All-Cause Mortality | | Cardiovascular Mortality | | Infection-Related Mortality[a] | |
|---|---|---|---|---|---|---|---|---|
| | | | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value[b] |
| **One-month iron exposure** | | | | | | | | |
| None | 90,178 | 34.32 | 0.98 (0.79 to 1.22) | 0.01 | 1.11 (0.84 to 1.48) | 0.66 | 0.92 (0.54 to 1.57) | 0.43 |
| >0–150 | 53,302 | 20.16 | Reference | | Reference | | Reference | |
| >150–350 | 63,327 | 23.96 | 0.78 (0.64 to 0.95) | | 1.08 (0.80 to 1.44) | | 0.77 (0.47 to 1.26) | |
| >350 | 56,993 | 21.56 | 0.79 (0.62 to 0.99) | | 0.95 (0.70 to 1.29) | | 1.26 (0.75 to 2.12) | |
| **Three-month iron exposure** | | | | | | | | |
| None | 45,247 | 19.17 | 1.19 (0.90 to 1.57) | 0.41 | 1.06 (0.72 to 1.54) | 0.49 | 0.86 (0.38 to 1.96) | 0.24 |
| >0–450 | 60,407 | 25.59 | Reference | | Reference | | Reference | |
| >450–1050 | 81,396 | 34.48 | 0.99 (0.81 to 1.20) | | 0.87 (0.67 to 1.14) | | 0.99 (0.56 to 1.74) | |
| >1050 | 49,038 | 20.77 | 1.09 (0.84 to 1.42) | | 1.02 (0.74 to 1.41) | | 1.69 (0.87 to 3.28) | |
| **Six-month iron exposure** | | | | | | | | |
| None | 18,555 | 9.19 | 1.24 (0.92 to 1.69) | 0.31 | 1.46 (0.98 to 2.16) | 0.28 | 0.75 (0.29 to 1.95) | 0.48 |
| >0–900 | 62,845 | 31.14 | Reference | | Reference | | Reference | |
| >900–2100 | 95,058 | 47.10 | 0.98 (0.80 to 1.21) | | 1.15 (0.85 to 1.56) | | 0.98 (0.53 to 1.81) | |
| >2100 | 25,375 | 12.57 | 1.12 (0.81 to 1.57) | | 1.17 (0.76 to 1.79) | | 1.59 (0.73 to 3.46) | |

The weighting on cumulative iron doses received was on the basis of iron history, age, sex, race, ethnicity, baseline comorbidity at 90 days, baseline body mass index, cause of ESRD, year of starting dialysis, baseline iron doses, hemoglobinopathies, saturation of transferrin (TSat)/ferritin categories, hemoglobin categories, weekly erythropoietin (EPO) doses categories, change in EPO, interaction of TSat/ferritin categories and hemoglobin categories, albumin, creatinine, predialysis systolic BP, body weight, change in weight, vascular access type, noninfection-related hospitalization, and infection. Demographics and baseline comorbidity were included in the outcome models. HR, hazard ratio; 95% CI, 95% confidence interval.

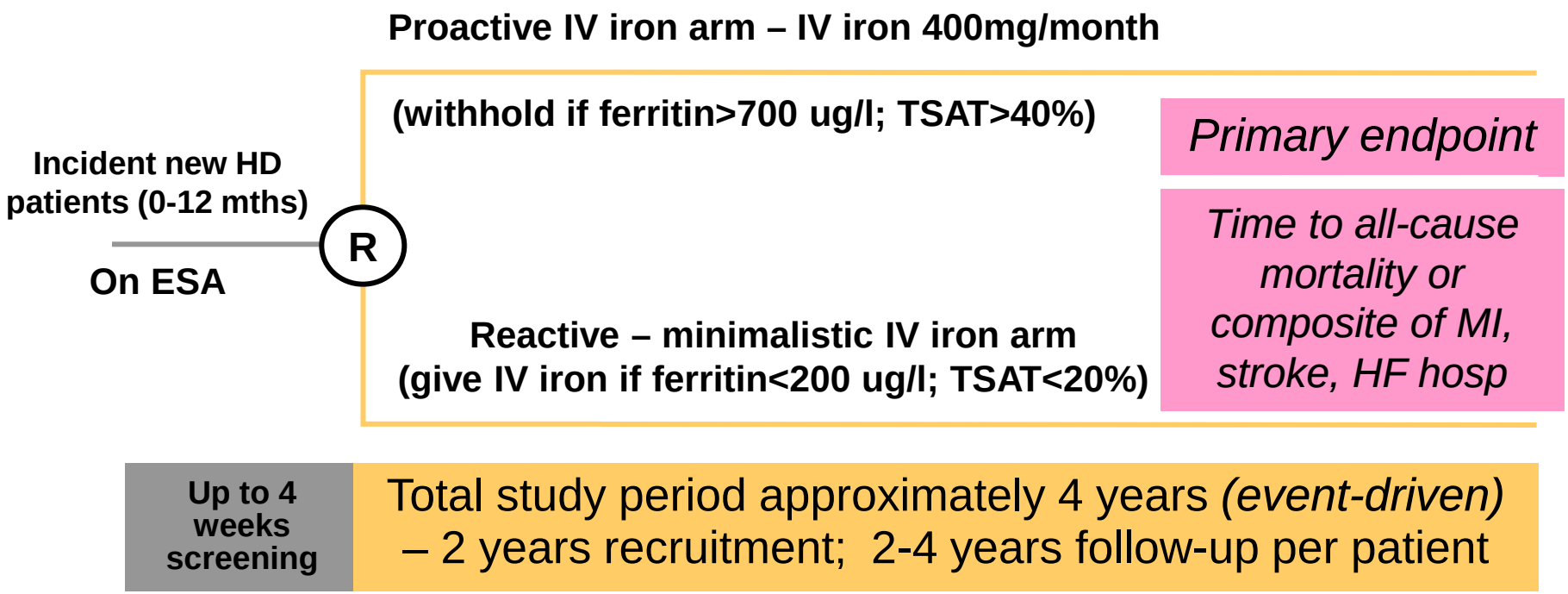
[a]Models were adjusted for all covariates included in all-cause and cardiovascular morality models, except recent infection.

[b]Global tests of iron exposure.

**Miskulin D *et al.*** *Clin J Am Soc Nephrol* 2014; 9: 1930-9.

# PIVOTAL
# (Proactive IV Iron Therapy in haemodialysis patients)

## Study design




**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: 2080 patients**

EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002267-25/GB.. Accessed Sept 26, 2017.

# PIVOTAL
# (Proactive IV Iron Therapy in haemodialysis 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

EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002267-25/GB.. Accessed Sept 26, 2017.

# 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**

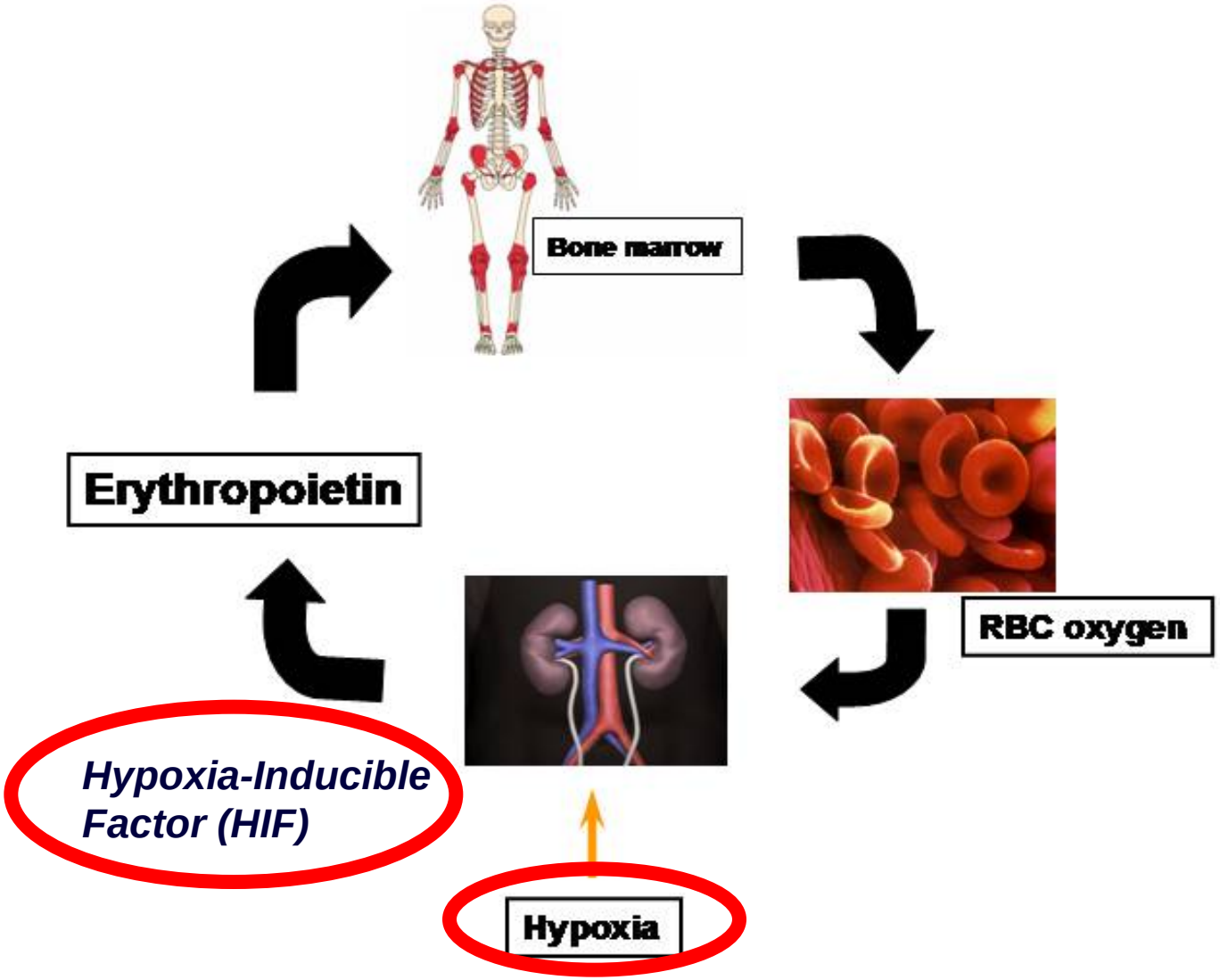

EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002267-25/GB.. Accessed Sept 26, 2017.

# Take-Home Message

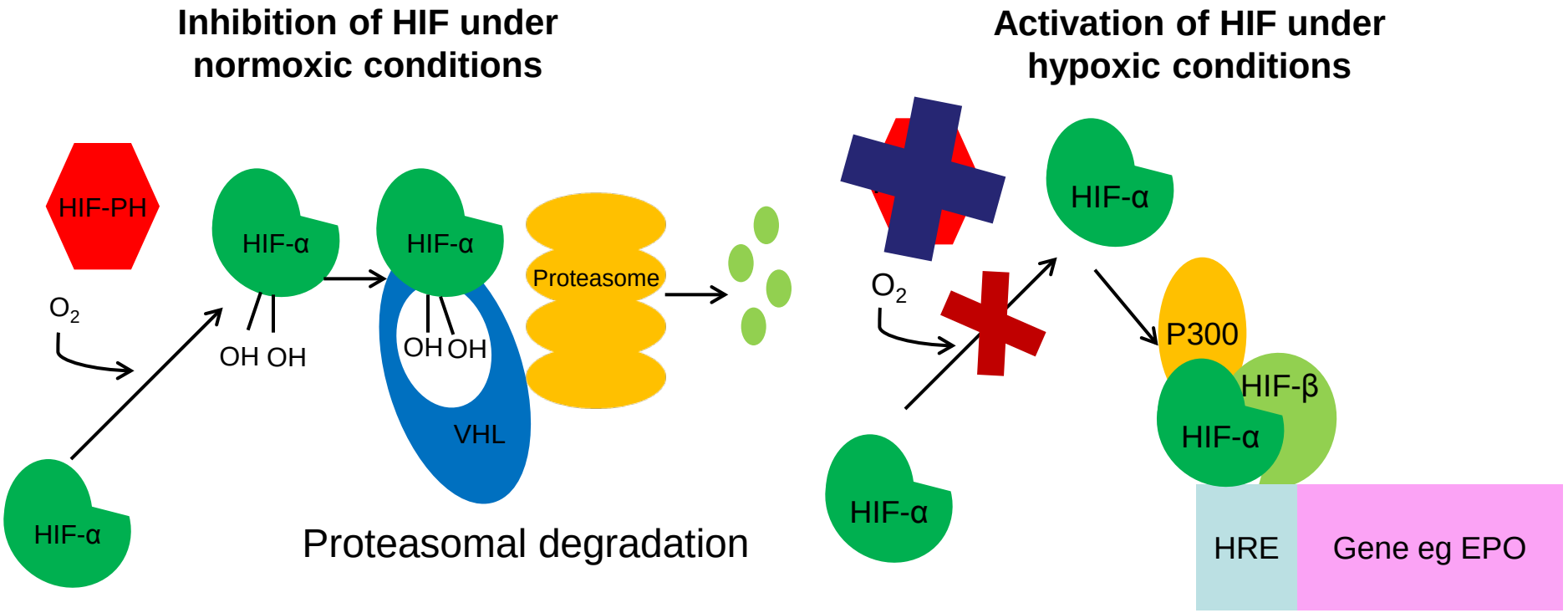
- We do not know the optimum amount of IV iron to administer to HD patients
- PIVOTAL should correct this deficit in the evidence-base

# HIF stabilisers

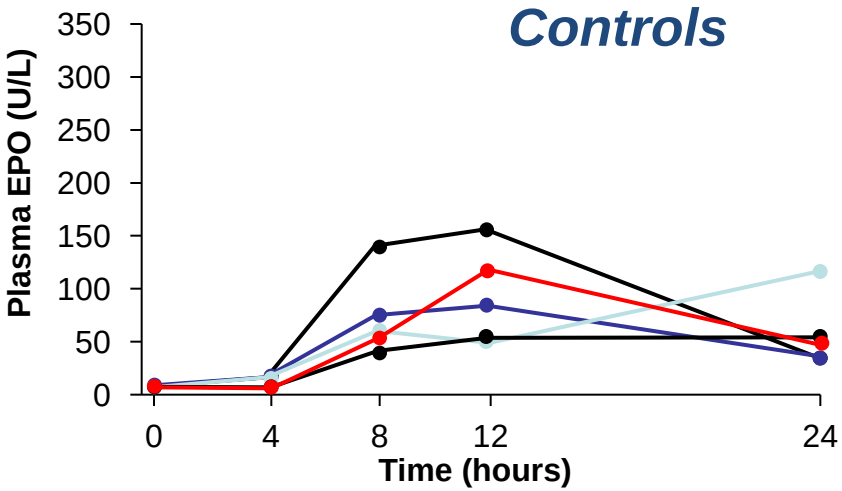
# Regulation of erythropoietin

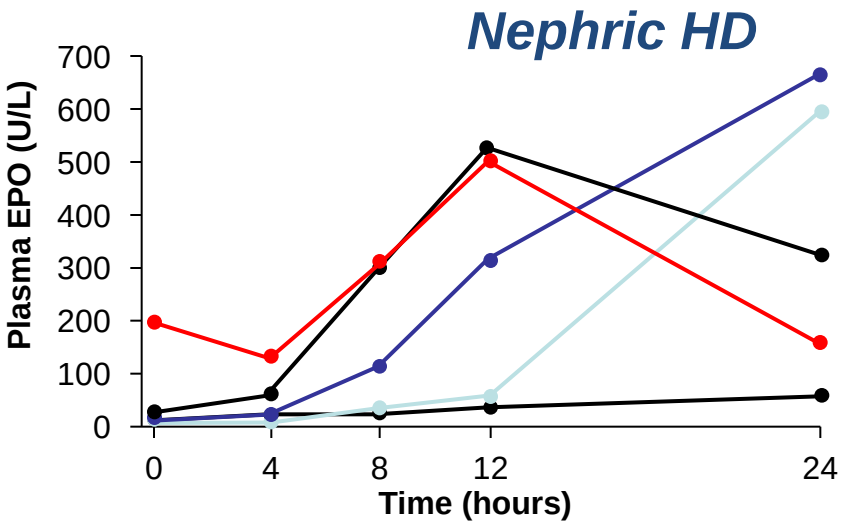


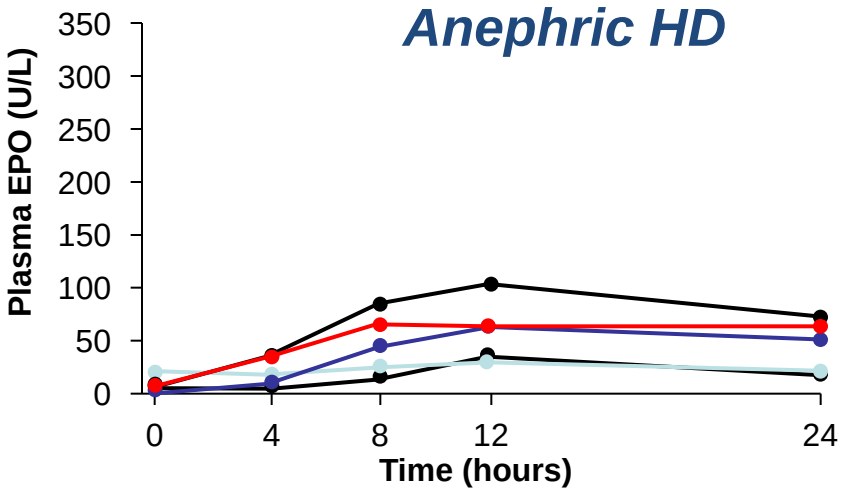
# Regulation of HIF activity



# Increase in plasma EPO after HIF stabilisation



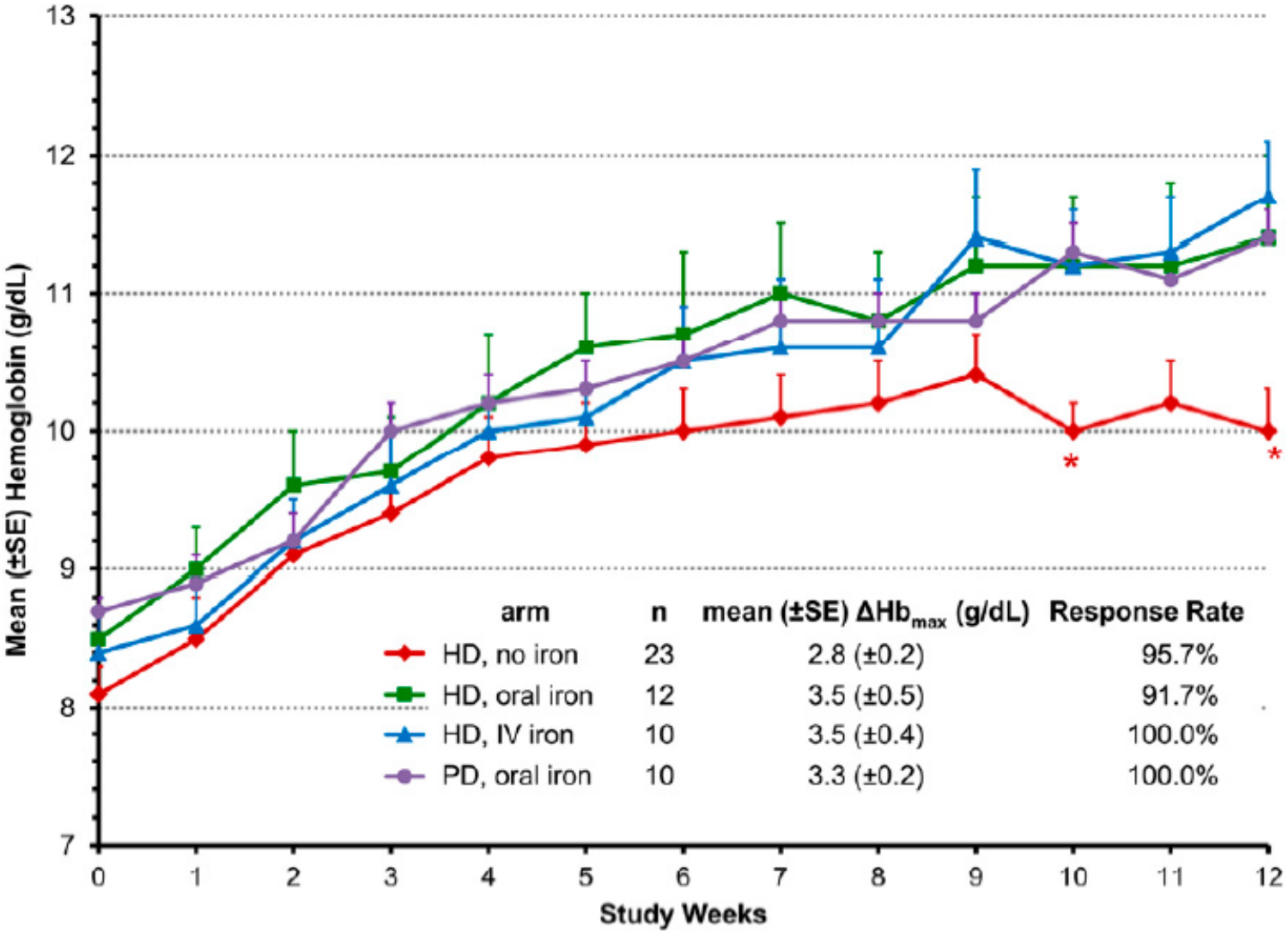




**Bernhardt WM *et al.*** *J Am Soc Nephrol* 2010; 21: 2151–6.

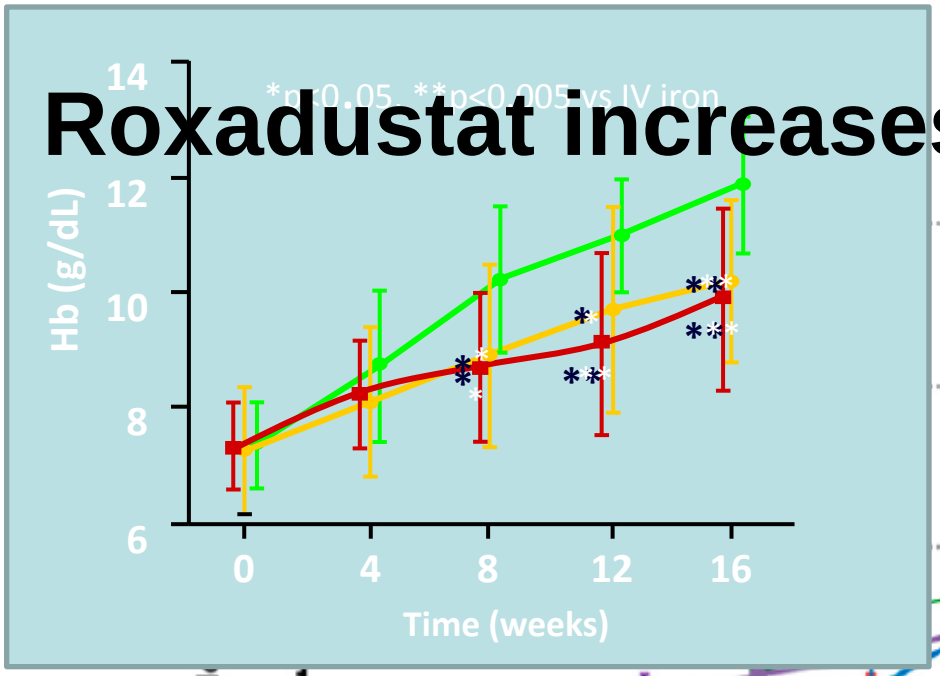
# HIF PHIs in development

| Company | Molecule | Drug name | Phase of development |
|---|---|---|---|
| FibroGen<br>Astellas<br>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 |




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

# Roxadustat increases haemoglobin levels

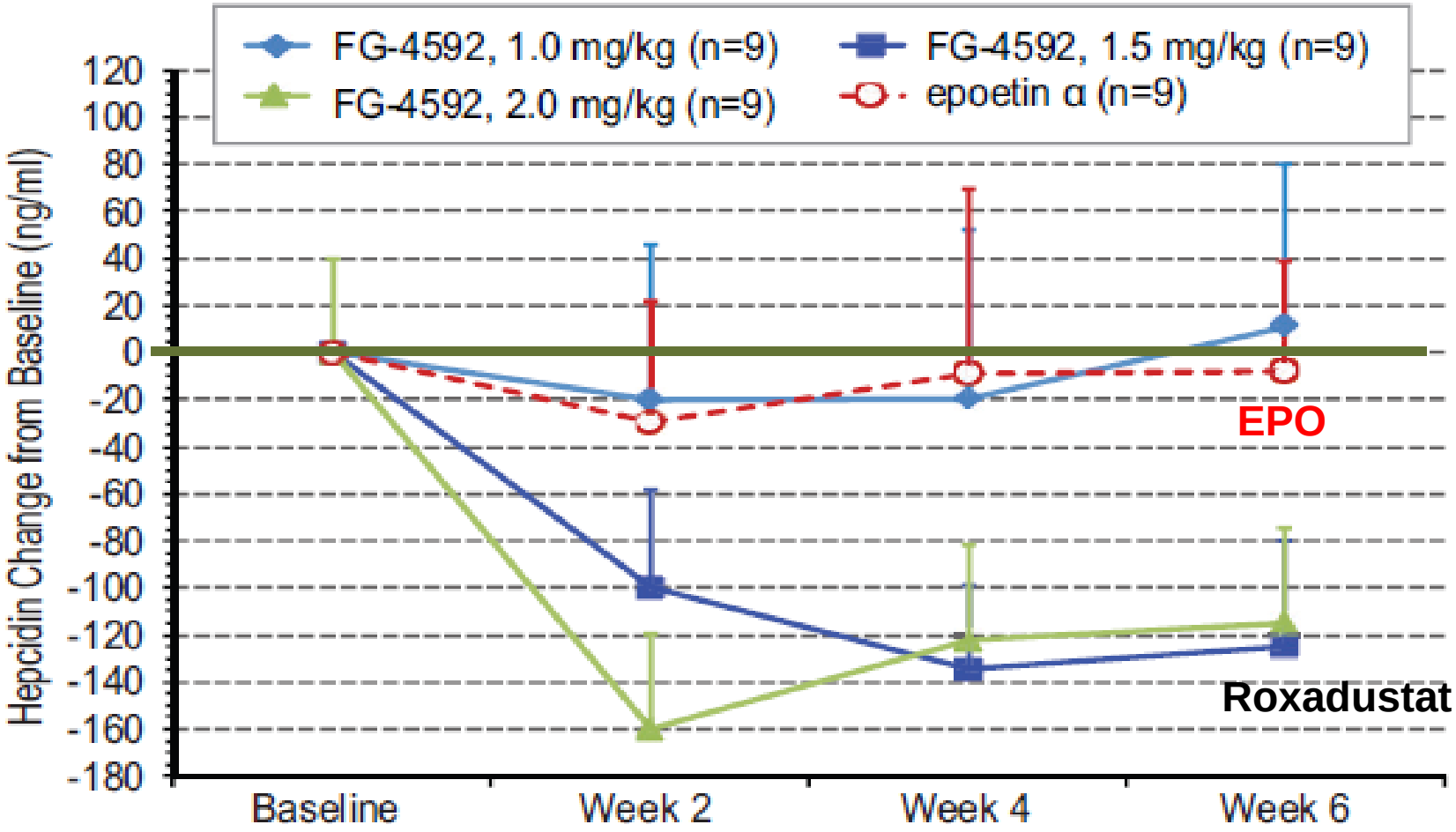






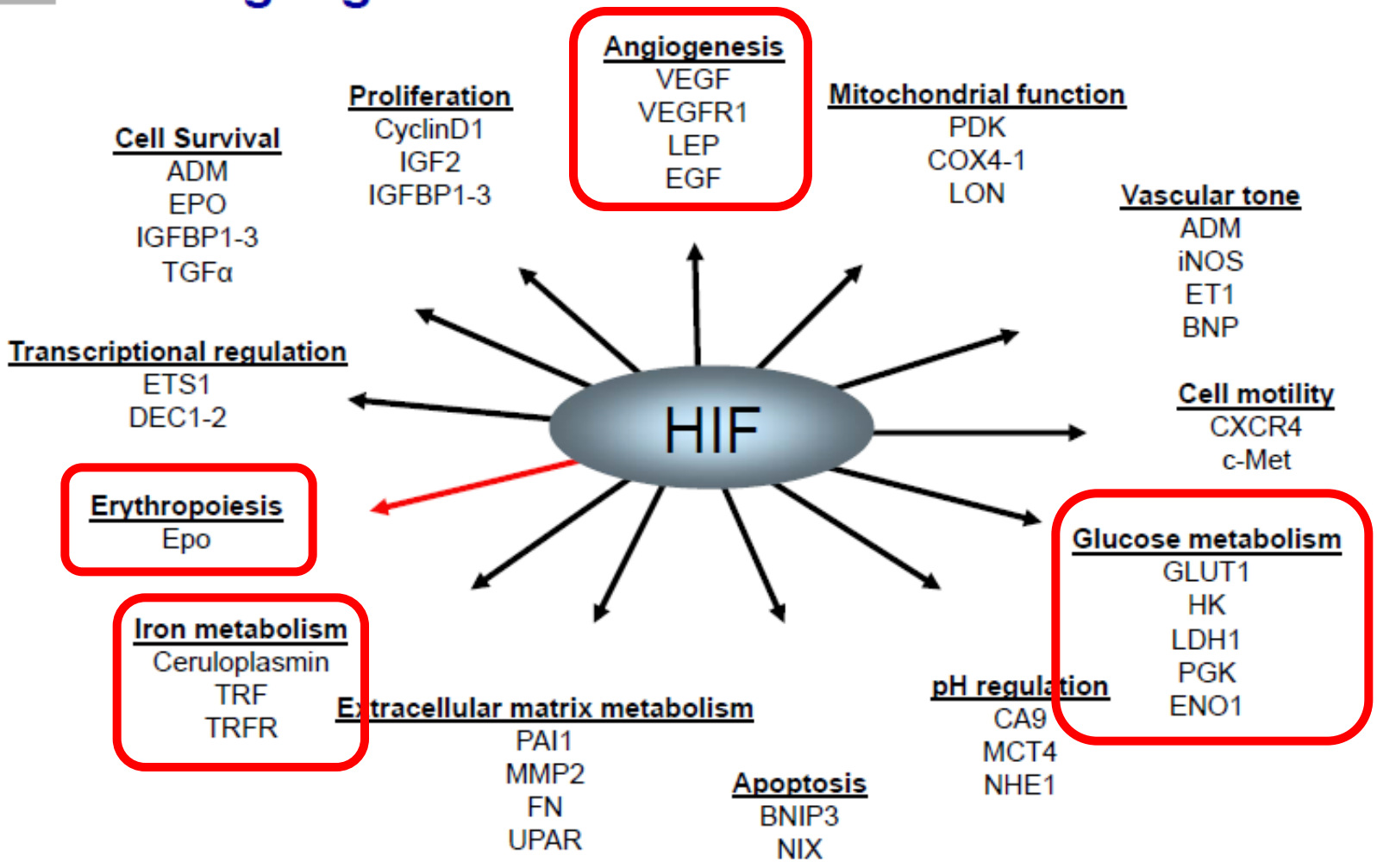
**Besarab A *et al.*** *J Am Soc Nephrol* 2016; 27: 1225-33.

# Roxadustat lowers hepcidin levels




Provenzano R *et al*. ASN 2012 Abstract.

# HIF target genes




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

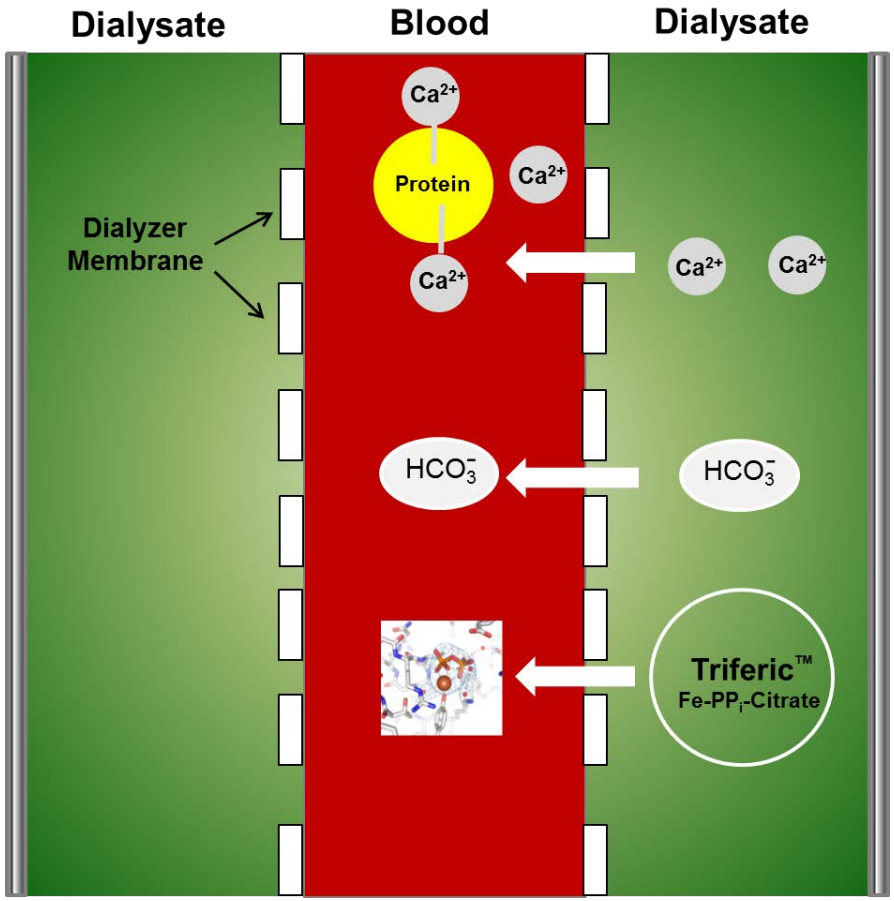
# Newer iron management strategies

# Iron management: new strategies

- **Intra-dialytic ferric pyrophosphate citrate (FPC)**
- **Ferric citrate**
- **Hepcidin modulators**
- **HIF stabilisers (PHI‘s)**

# 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

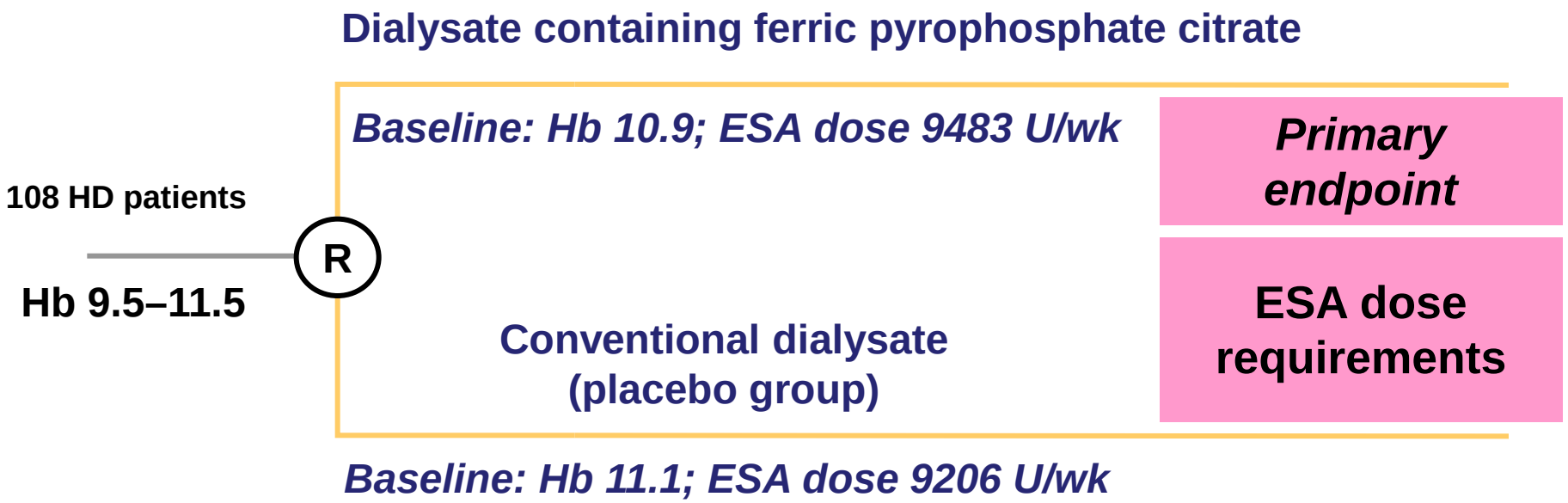



**Gupta A *et al.*** *Kidney Int* 2015; 88:1187-94.

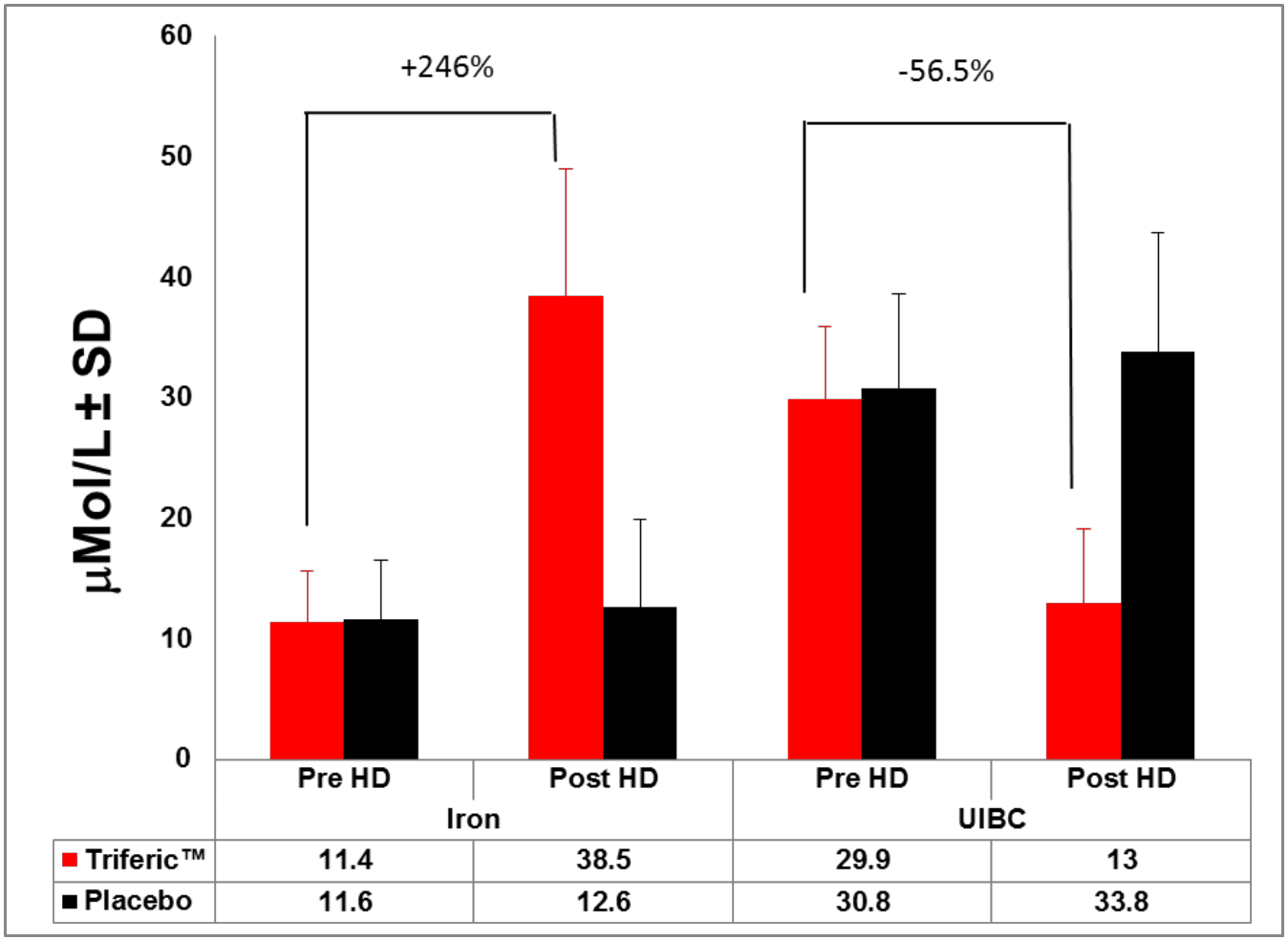
# PRIME study

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

- **Prospective, randomised, placebo-controlled, double-blind trial**
- **Study duration = 9 months**



# 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 |

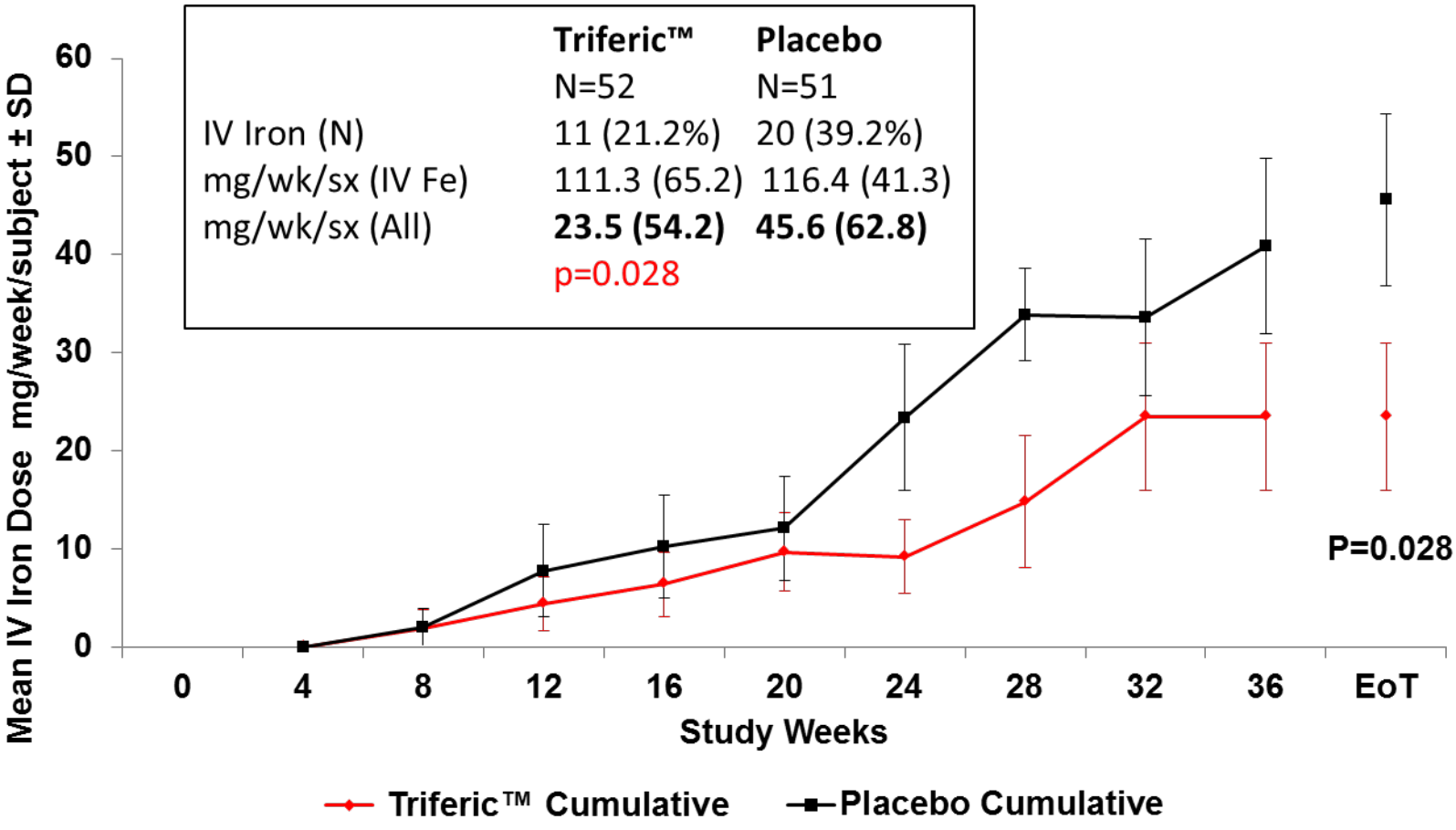
**Gupta A *et al*.** *Kidney Int* 2015; 88:1187-94.

# 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%

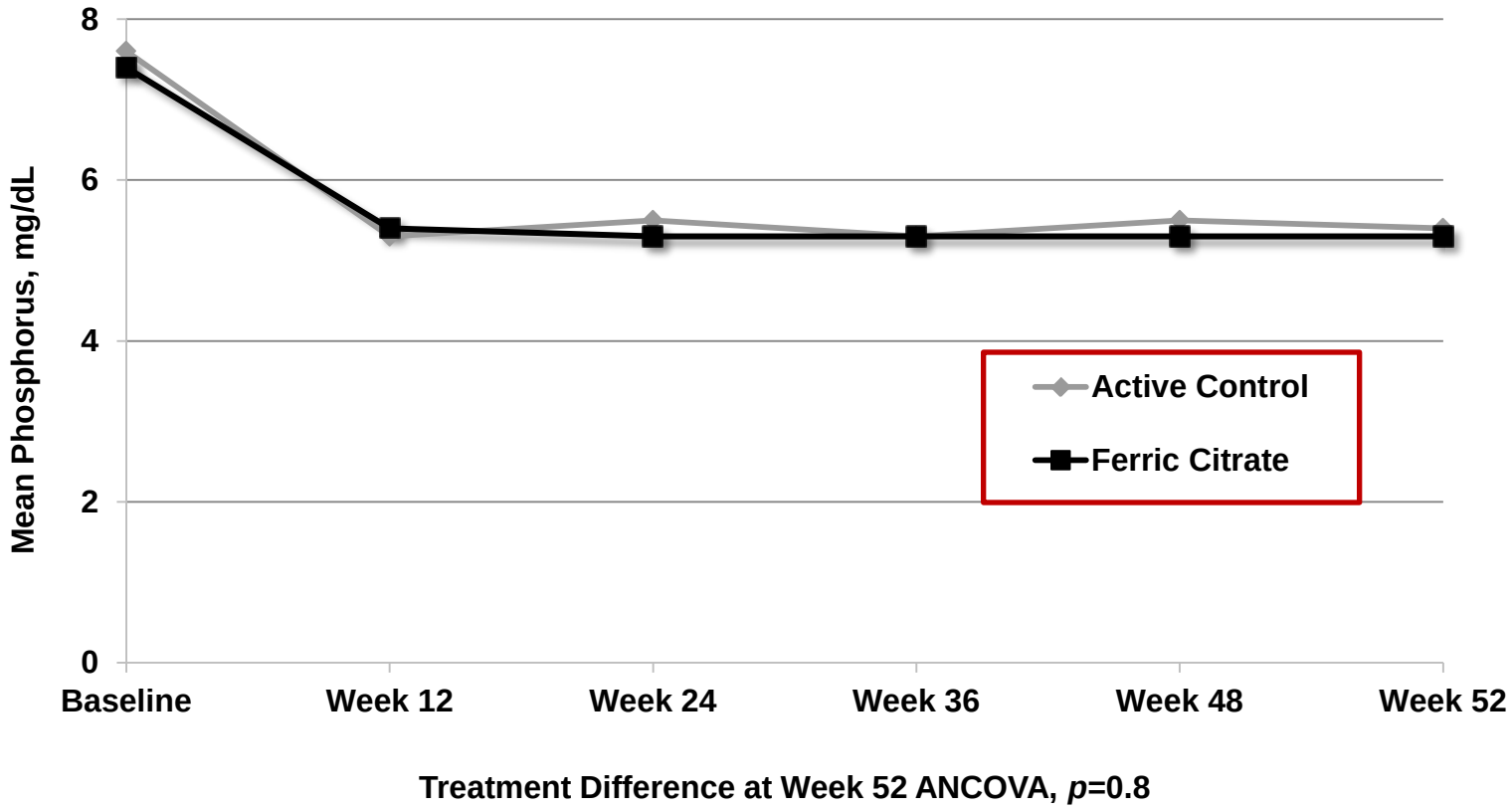



**Gupta A *et al.*** *Kidney Int* 2015; 88:1187-94.

# Iron management: new strategies

- Intra-dialytic ferric pyrophosphate citrate (FPC)
- Ferric citrate
- Hepcidin modulators
- HIF stabilisers (PHI‘s)

# Serum phosphate control over 52 weeks




**Treatment Difference at Week 52 ANCOVA, *p*=0.8**

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

# Effect of phosphate-binders on ferritin

| Mean Ferritin (ng/mL) | Active Control (n=135) | Ferric Citrate (n=252) |
|---|---|---|
| Baseline (Day 0) | 609 | 593 |
| Week 12 | 649 | 751 |
| Week 24 | 652 | 846 |
| Week 36 | 631 | 862 |
| Week 48 | 619 | 881 |
| Week 52 | 624 | 898 |
| Change from Baseline at Week 52<br>*% Change from Baseline* | 15<br>*2.5%* | 305<br>*51.4%* |
| Least Squares Mean Difference at Week 52<br>P-value | | 285<br><0.0001 |

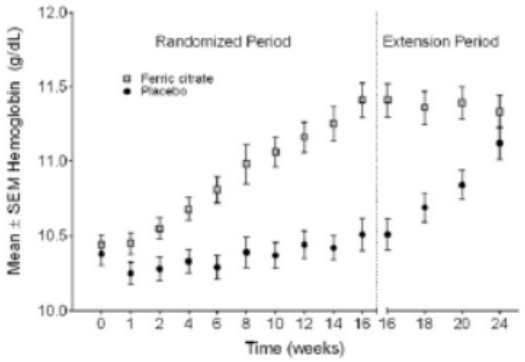
**Lewis JB *et al.*** *J Am Soc Nephrol* 2015; 26: 493-503.

# Effect of phosphate-binders on TSAT

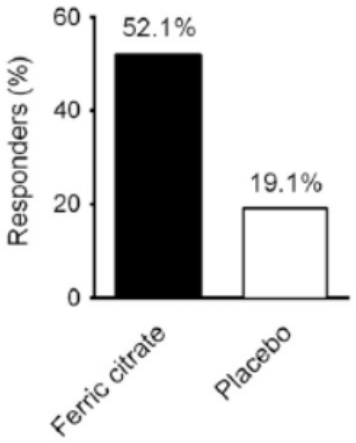
| Mean TSAT (%) | Active Control (n=135) | Ferric Citrate (n=252) |
|---|---|---|
| Baseline (Day 0) | 31 | 31 |
| Week 12 | 31 | 40 |
| Week 24 | 31 | 40 |
| Week 36 | 31 | 40 |
| Week 48 | 29 | 41 |
| Week 52 | 30 | 39 |
| Change from Baseline at Week 52<br>*% Change from Baseline* | -1<br>*-3.2%* | 8<br>*25.8%* |
| Least Squares Mean Difference at Week 52<br>P-value | | 9<br><0.0001 |

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

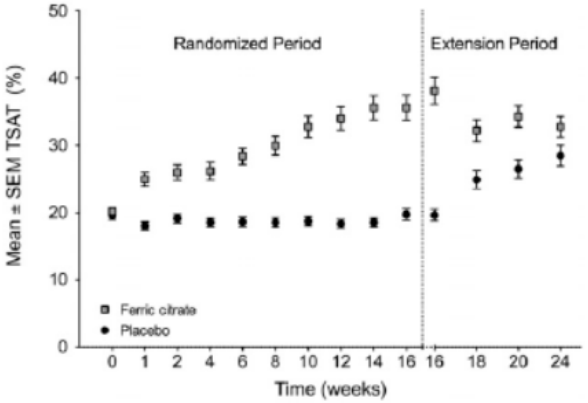
**A Hemoglobin**



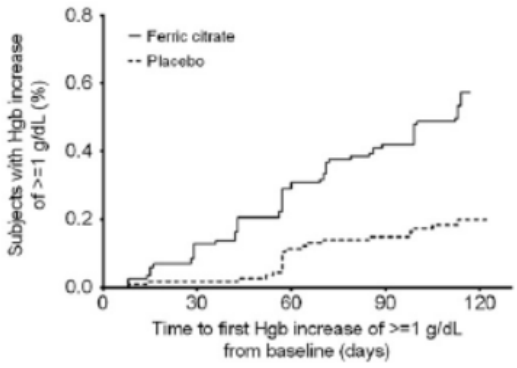

**B Percent responders achieving ≥ 1g/dL Rise in Hemoglobin**



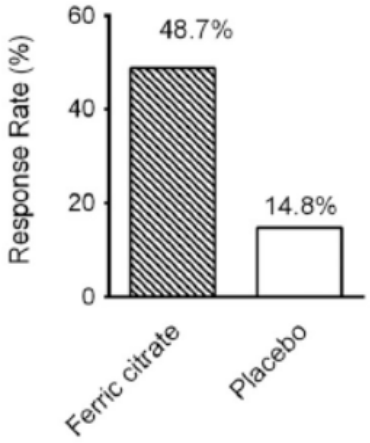

**A Transferrin Saturation**



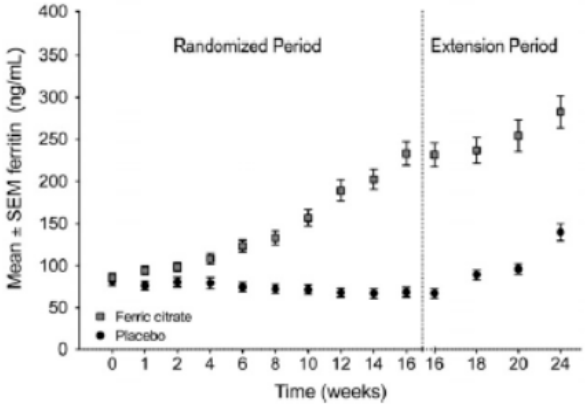

**C Time to first response of ≥ 1g/dL Hemoglobin rise**




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




**B Serum Ferritin**

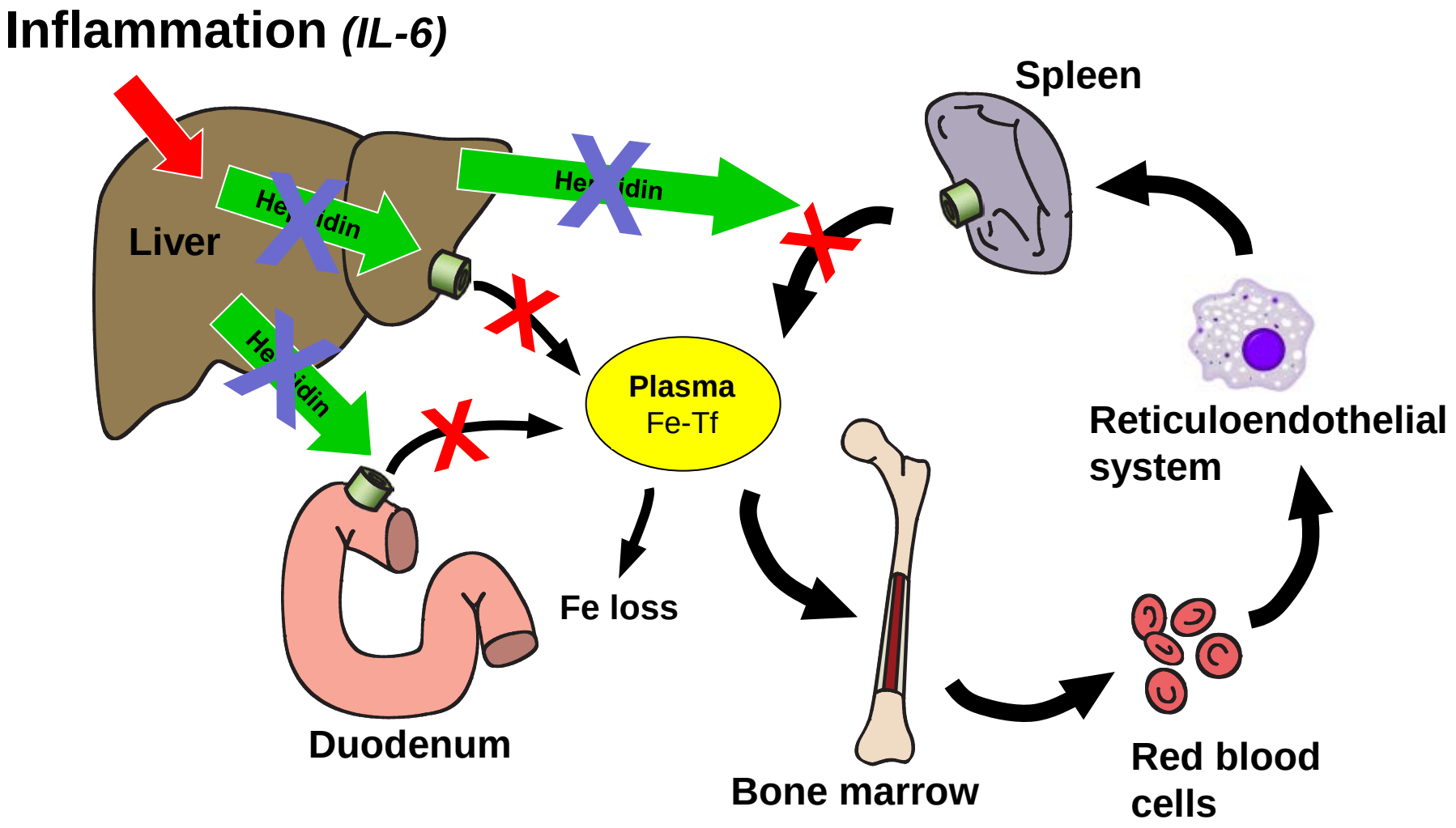



**Fishbane *et al.*** *J Am Soc Nephrol* 2017; 28: 1851-1858.

# Iron management: new strategies

- Intra-dialytic ferric pyrophosphate citrate (FPC)
- Ferric citrate
- Hepcidin modulators
- HIF stabilisers (PHI‘s)

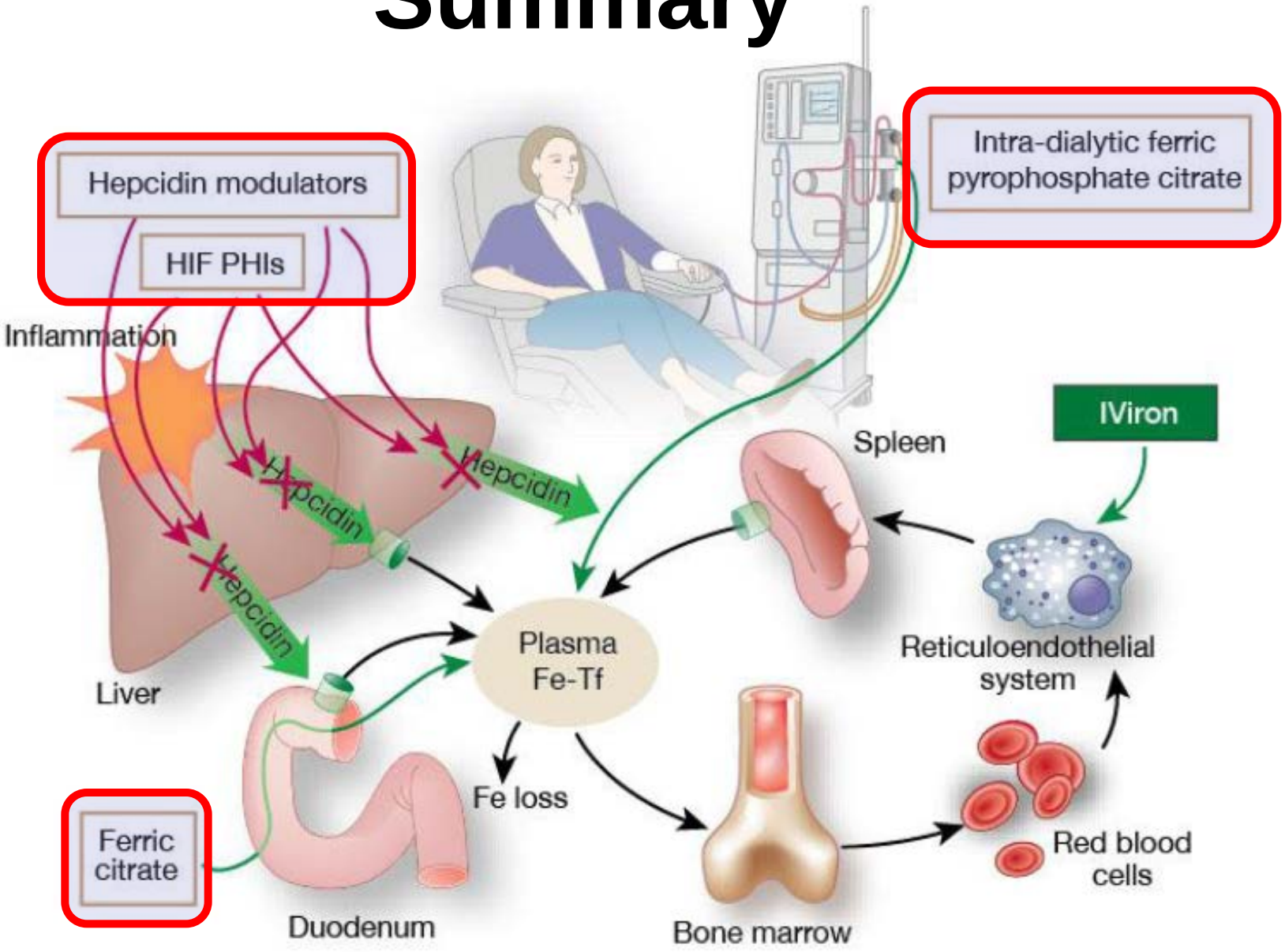
# Regulation of iron supply to bone marrow



# Strategies for modulating hepcidin

- Anti-hepcidin antibodies
- Short interference RNA and anti-sense oligonucleotides
- Hepcidin-binding proteins
- Hepcidin-binding spiegelmeyers
- Hepcidin production inhibitors
- BMP6-HJV-SMAD pathway inhibitors
- IL-6 inhibitors
- Vitamin D
- Ferroportin agonists / stabilisers

# Summary






**Macdougall IC.** Kidney Int 2015; 88: 946-949.

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16. Besarab A *et al. J Am Soc Nephrol* 2016; 27:1225-33.
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18. Schofield & Ratcliffe P. *Nat Rev Mol Cell Biol* 2004.
19. Gupta A *et al. Kidney Int* 2015; 88:1187-94.
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.
22. Macdougall IC. Kidney Int 2015; 88: 946-949.


.

# 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