I PER-CORSI IN NEFROLOGIA E DIALISI

19 ottobre 2023
NH Hotel Pontevecchio
Lecco

LE COMPLICANZE DEL TRATTAMENTO SOSTITUTIVO

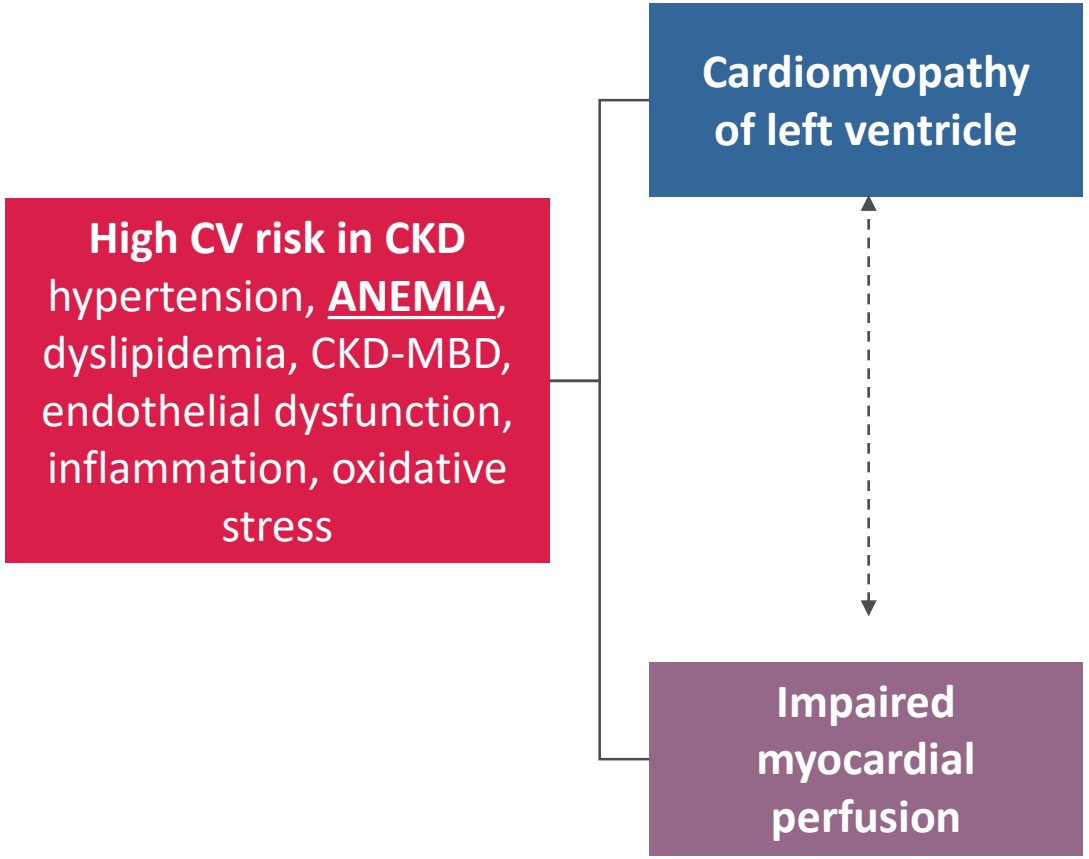
Supplementazione di ferro ev in emodialisi, EPO ed HIF: quale futuro per il trattamento dell'anemia nei pazienti in dialisi?

Luca De Nicola, MD-PhD
Nephrology and Dialysis Unit

Università
degli Studi
della Campania
Luigi Vanvitelli

Why optimal treatment of anemia in dialysis ?

When treating anemia in dialysis don’t forget why doing it !



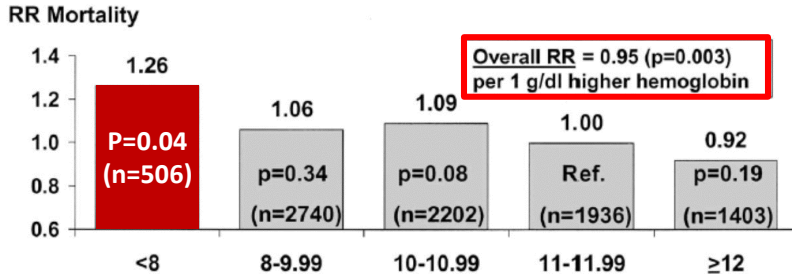
Rigatto C, et al. Nat Clin Pract Nephrol 2006;2:514–526

American Journal of Kidney Diseases, Vol 44, No 1 (July), 2004:

Anemia Management and Outcomes From 12 Countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Ronald L. Pisoni, PhD, Jennifer L. Bragg-Gresham, MS, Eric W. Young, MD, Tadao Akizawa, MD, PhD, Yasushi Asano, MD, PhD, Francesco Locatelli, MD, Juergen Bommer, MD, Jose Miguel Cruz, MD, Peter G. Kerr, MD, David C. Mendelssohn, MD,, Philip J. Held, PhD, and Friedrich K. Port, MD, MS

N= 11,041
HD maintenance patients
Endpoint: all-cause death
(DOPPS I)

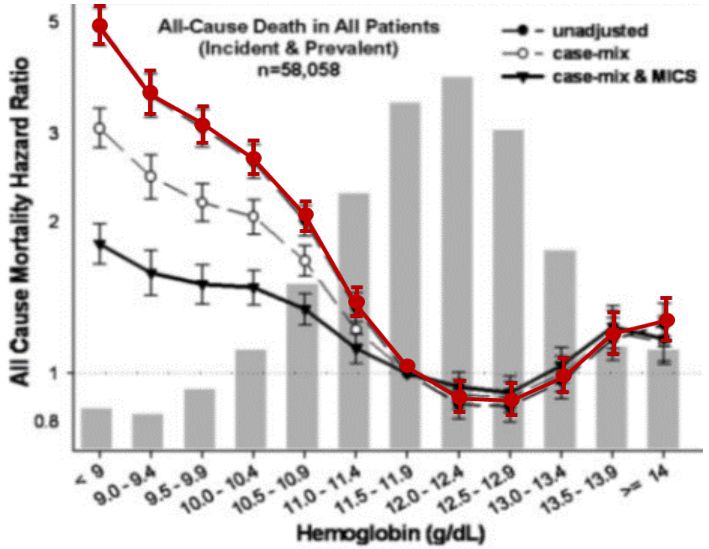


J Am Soc Nephrol 17: 1181–1191, 2006.

Associations between Changes in Hemoglobin and Administered Erythropoiesis-Stimulating Agent and Survival in Hemodialysis Patients

Deborah L. Regidor,*† Joel D. Kopple,*†‡ Csaba P. Kovesdy,§ Ryan D. Kilpatrick,*† Charles J. McAllister,‖ Jason Aronovitz,‖ Sander Greenland,† and Kamyar Kalantar-Zadeh*‡

N= 58,058
HD maintenance patients
Endpoint: all-cause death
FU: 24 months

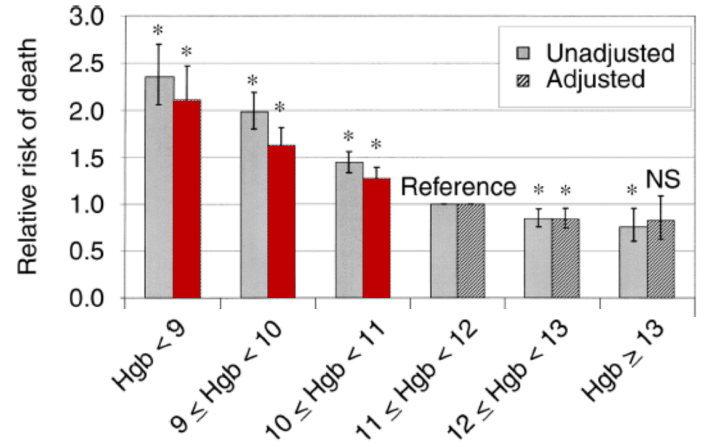


Kidney International, Vol. 63 (2003),

The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients

NORMA OFSTHUN, JOHN LABRECQUE, EDUARDO LACSON, MARCIA KEEN, and J. MICHAEL LAZARUS

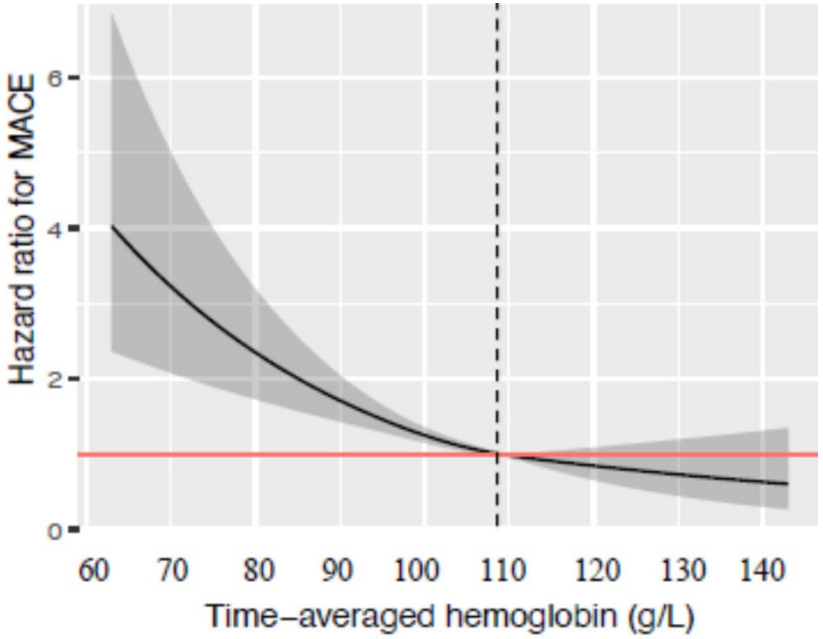
N= 44,550
HD maintenance patients
Endpoint: all-cause death
FU: 6 months

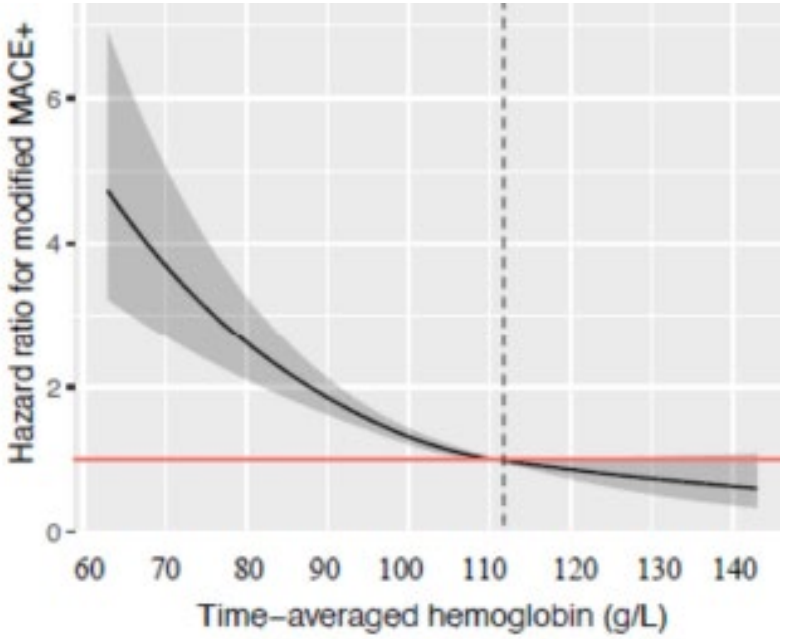


Goal Hb ≥11 g/dL

Cut-off values of hemoglobin and clinical outcomes in incident PD: the Peritoneal Dialysis Telemedicine-assisted Platform (PDTAP) study

- 2,591 PD patients enrolled 6/2016-4/2019, and followed till 12/2020
- Primary outcomes: all-cause mortality, major adverse cardiovascular events (MACE) and modified MACE +
- MACE: MI, unstable angina, stroke, and CV death.
- MACE +: MACE + heart failure and all-cause mortality





Independent value of time-averaged Hb <11 in predicting MACE and MACE+ in PD population

Goal Hb ≥11 g/dL

Xu et al., NDT 17 July 2023

Low hemoglobin at hemodialysis initiation: an international study of anemia management and mortality in the early dialysis period *Clinical Kidney Journal*, 2020

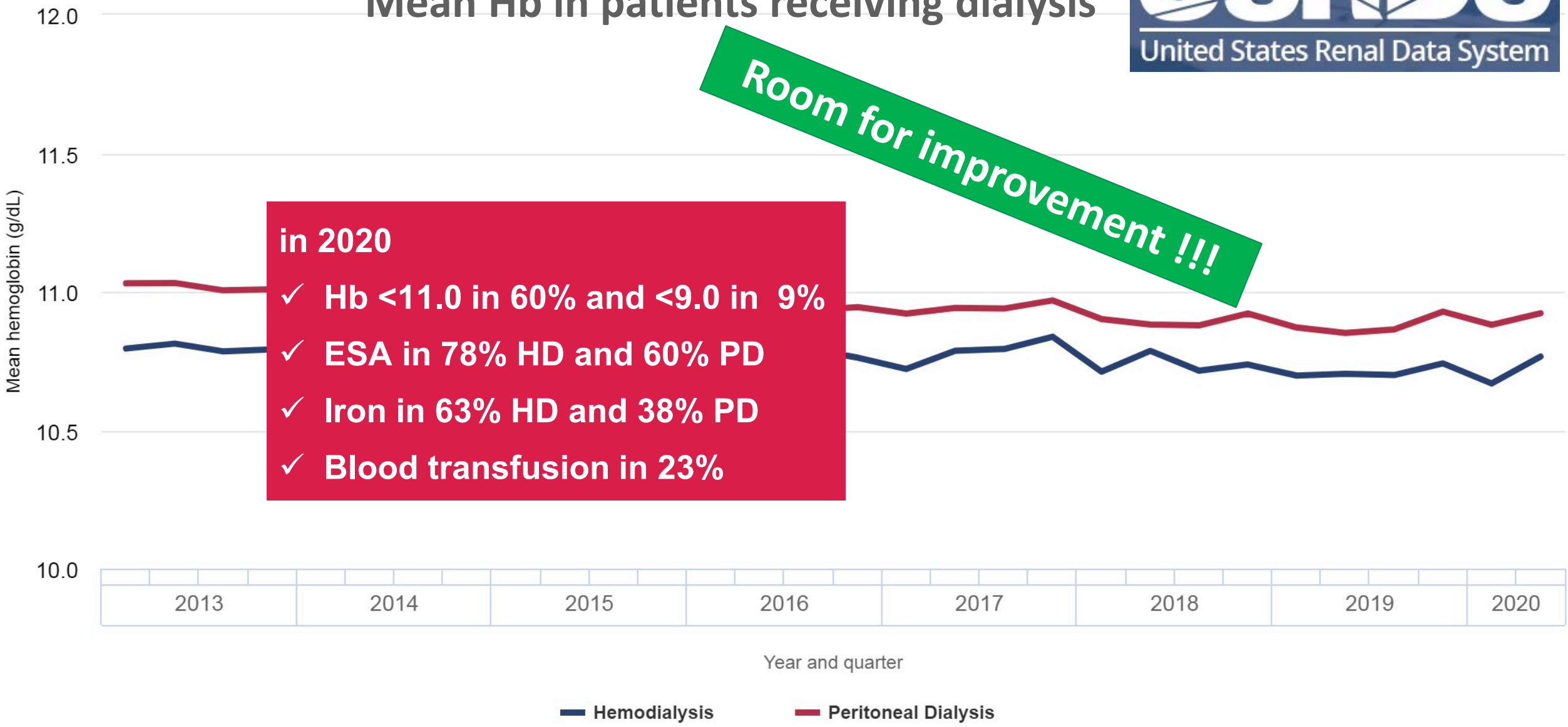
- 4604 incident HD patients from 21 countries
- Phases 4–5 (2009–2015)

Hb at Month 1 after starting HD

Exposure	N (%)	
Hgb (g/dL) in Month 1 after HD start, categories		
<8.0	283 (6)	
8.0–8.9	822 (18)	**79%**
9.0–9.9	1260 (28)	**Hb <11**
10.0–10.9	1209 (27)	
≥11.0	897 (20)	

Anemia in dialysis
after 30 years of ESA ?

Mean Hb in patients receiving dialysis



United States Renal Data System

Room for improvement !!!

in 2020

- ✓ **Hb <11.0 in 60% and <9.0 in 9%**
- ✓ **ESA in 78% HD and 60% PD**
- ✓ **Iron in 63% HD and 38% PD**
- ✓ **Blood transfusion in 23%**

Data Source: 2022 United States Renal Data System Annual Data Report

Clinical Kidney Journal

Management of anaemia in French dialysis patients: results from a large epidemiological retrospective study

Methods

Retrospective observational study

January–December 2016

1632 DD CKD patients
→ **1286 had anaemia**

Outcomes:
- Demographics
- Anaemia status
- CKD-related anaemia treatments and outcomes

Results

Mean age: 70.4 years

57.2% male

Follow-up 2 years

Patients with anaemia of DD CKD (at index date)

Hb levels	Iron deficiency
10–11 g/dL, 29.9%	Functional 21.3%
11–12 g/dL, 36.2%	Absolute 11.7%

Most common treatments (65.1%)

IV iron + ESA

Erythropoietin-stimulating agents

Hb target 10–13 g/dL
achieved by 347/364 (95.3%) patients

Response maintained for 113 days (median)

Room for improvement !!!

Conclusion: Despite use of ESA and IV iron, duration within the Hb target range was short, suggesting that anaemia management can be further improved.

Dubel et al., Clin Kidney J 2022

Current guidelines are restrictive on Hb goal because based on the "ONE-SIZE-FITS-ALL" approach

Secondary analyses of the key RCTs for current guidelines reveal *individual response to ESA (Hb by dose) is important as the Hb goal !!!*

Study	Setting	N	Analysis	Endpoint	Results
TREAT	DM-CKD	1872	**Poor initial response** (based on ESA response to the first two doses)	**Composite** (CV death, MI, stroke, HF)	**Risk increased by 31%** (HR 1.31, 1.09–1.59)

It is critical to identify and treat ESA hyporesponsive patients because they are unlikely to benefit from any increase in ESA dose while being at **greater risk of adverse CV events if ESA dose is uptitrated**

Provatopoulou ST 2011; De Nicola L Drugs 2014; Mimura I *Nephron* 2015.

Kilpatrick RD, et al. *Clin J Am Soc Nephrol* 2008; Szczech LA, et al. *Kidney Int* 2008; Solomon SD, et al. *N Engl J Med* 2010

ESA resistance in HD patients

- DOPPS III (2005-2008)
- 12 countries, 300 facilities
- >7500 patients on HD ≥6 mo

Hb and ESA dose in DOPPS study

	Hemoglobin (g/l)	ESA dose (U/week)	ESA >35,000 U/week (%)
ANZ[d]	119 (109–130)	12,500 (8000–20,000)	3.8%
Belgium	120 (112–127)	12,000 (6750–18,000)	3.1%
Canada	118 (109–125)	13,200 (8000–20,000)	11.3%
France	118 (108–126)	9900 (6000–16,500)	5.6%
Germany	118 (108–126)	7200 (4000–12,000)	1.8%
Italy	115 (106–124)	12,000 (6600–21,900)	6.5%
Japan	104 (96–112)	4500 (3000–9000)	0.0%
Spain	120 (111–129)	10,500 (6000–18,000)	4.0%
Sweden	119 (110–128)	14,775 (9000–26,250)	12.7%
UK[d]	117 (105–127)	10,000 (6600–19,800)	6.6%
US[d]	120 (112–128)	14,000 (6725–28,500)	18.1%

MacFarlane, Kidney Int 2010

ESA resistance and mortality in HD and PD patients

Methods: NECOSAD is a Dutch multi-center prospective cohort study of incident dialysis patients who started dialysis between January 1997 and January 2007. ESA resistance was defined as hemoglobin level < 11 g/dL with an above median ESA dose (i.e. 8,000 units/week in HD and 4,000 units/week in PD patients). Unadjusted and adjusted Cox regression analysis for all-cause 5-year mortality was performed for HD and PD patients separately.

				mortality	
				ted HR[1]	Adjusted HR[2]
· HD patients					
≤8,000	≥11	380	1	1	1
≤8,000	<11	264	1.29 (1.01-1.65)	1.33 (1.04-1.70)	1.18 (0.91-1.52)
>8,000	≥11	158	1.35 (1.01-1.80)	1.52 (1.13-2.04)	1.28 (0.94-1.73)
>8,000	<11	211	1.72 (1.34-2.20)	1.91 (1.48-2.47)	1.37 (1.04-1.80)
· PD patients					
≤4,000	≥11	204	1	1	1
≤4,000	<11	91	1.59 (0.96-2.63)	1.94 (1.15-3.27)	1.56 (0.91-2.68)
>4,000	≥11	113	2.55 (1.66-3.92)	1.89 (1.20-2.97)	1.56 (0.96-2.51)
>4,000	<11	53	2.34 (1.34-4.10)	3.18 (1.74-5.79)	2.41 (1.27-4.57)

Values are shown as hazard ratios (95% CI).

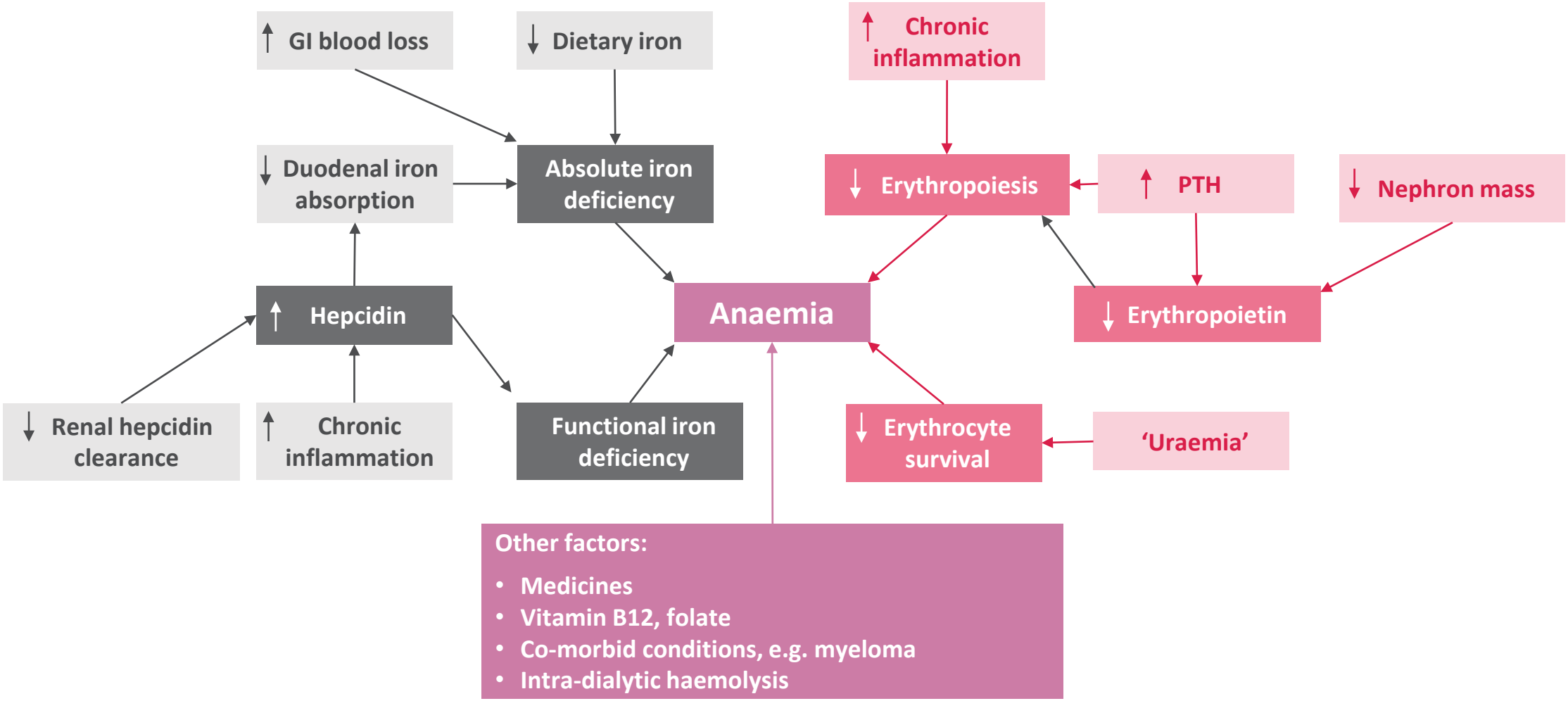
Categories are defined by a combination of ESA dose (below or from median) and Hb level (≥11 and <11 g/dL). The category with the high ESA dose and Hb <11 corresponds to ESA resistant patients and the category with the low ESA dose and Hb ≥11 corresponds to good ESA responders.

[1] Adjusted for age, sex, weight, primary kidney disease, diabetes mellitus, malignancy, cardiovascular disease.

[2] Additional adjusted for weekly Kt/V urea, rGFR, nutritional status, albumin, ferritin, PTH and CRP.

Suttorp et al. BMC Nephrology 2013

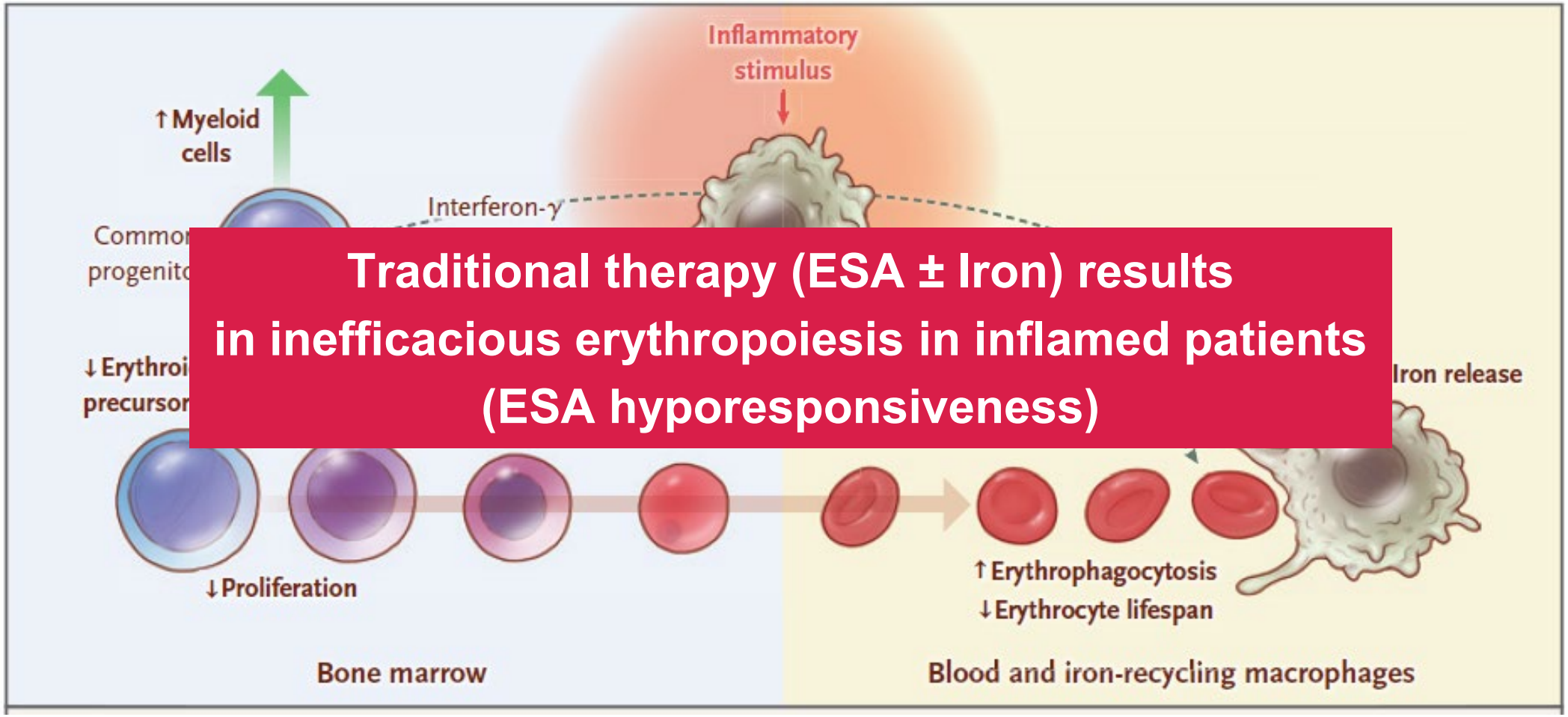
Resistance ?...CKD-related anemia is a multifactorial disease



Geddes, Nephrol Dial Transplant 2019

CKD-related anemia is a multifactorial disease

…and CKD-inflammation is part of the game



Traditional therapy (ESA ± Iron) results in inefficacious erythropoiesis in inflamed patients (ESA hyporesponsiveness)

Ganz, NEJM 2019

Multifactorial approach to CKD-anemia is a MAIN THERAPEUTIC GOAL

1) Dx/Treat all causes of anemia
2) Iron supplementation
3) ESA prescription
   - ***HIF stabilizer as "multifactorial option"***

Weir MR; Am J Nephrol 2021;52:450–466

IRON

KDIGO executive conclusions

Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference

At present, only PIVOTAL has been of sufficient sample size and duration to allow statistically valid conclusions regarding the effects of iron administration on hard clinical outcomes in HDCKD patients.

Kidney International (2021)

IRON

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

Iain C. Macdougall, M.D., Claire White, B.Sc., Stefan D. Anker, M.D., Sunil Bhandari, Ph.D., F.R.C.P., Kenneth Farrington, M.D., Philip A. Kalra, M.D., John J.V. McMurray, M.D., Heather Murray, M.Sc., Charles R.V. Tomson, D.M., David C. Wheeler, M.D., Christopher G. Winearls, D.Phil., F.R.C.P., and Ian Ford, Ph.D., for the PIVOTAL Investigators and Committees*

RCT in 2141 HD patients receiving either high-dose iv iron sucrose, administered proactively or low-dose iron sucrose, administered reactively. The primary end point was the composite of nonfatal MI, nonfatal stroke, hospitalization for HF, or death. The median follow-up was 2.1 years

Randomization

Proactive IV iron administration: 400 mg monthly *(200 x 2 HD)*
- *No iron if ferritin >700 µg/L*
- *No iron if TSAT ≥40%:*

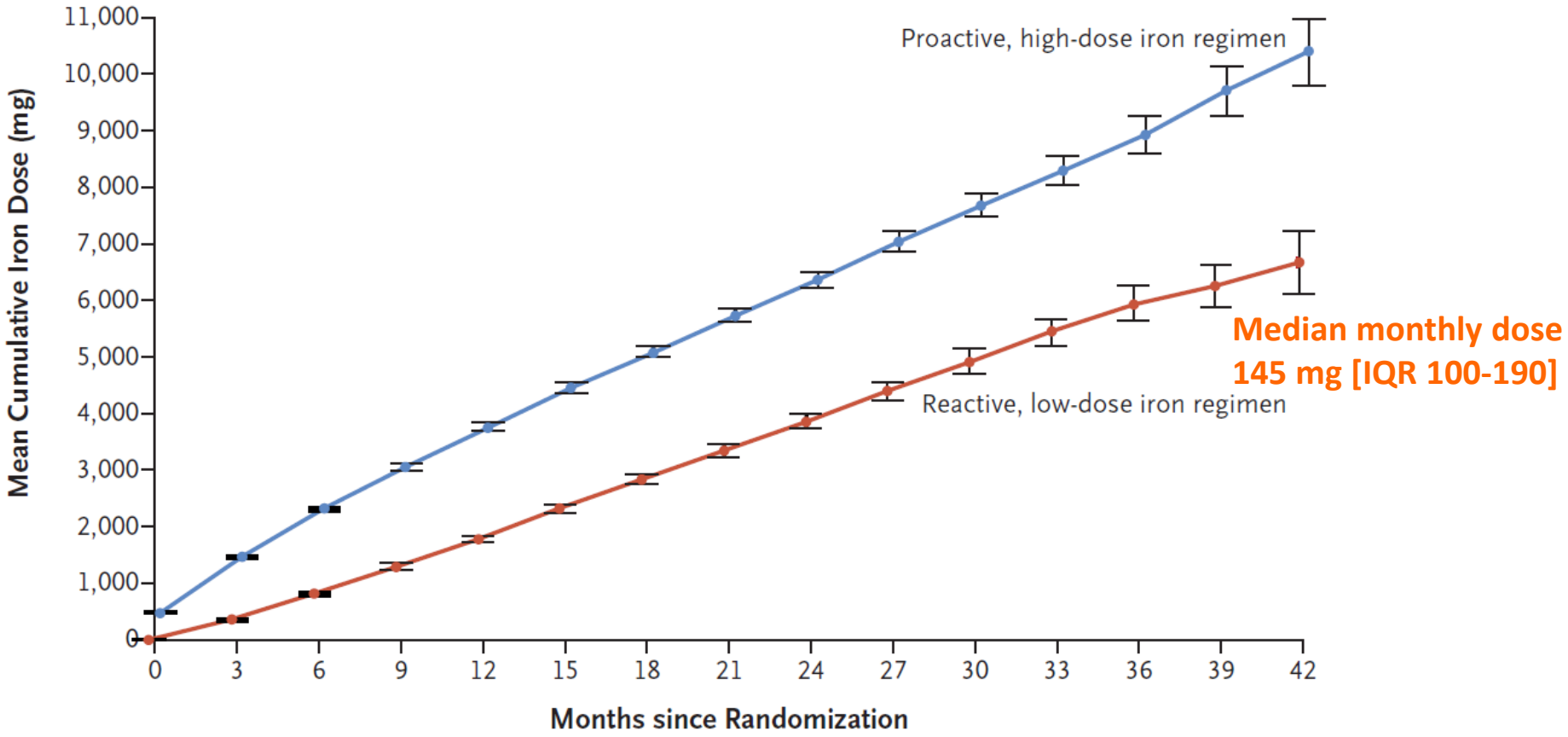
Reactive IV iron administration: 100-400 mg monthly
- *If ferritin <100 µg/L and TSAT <40%: 400 mg monthly (200 x 2 HD)*
- *If ferritin 100-200 µg/L and TSAT <40%: 200 mg monthly*
- *If ferritin 201-700 µg/L and TSAT ≤20%: 100 mg monthly*
- *If ferritin >200 µg/L and TSAT >20%: no iron*
- *If ferritin >700 µg/L and/or TSAT ≥40%: no iron*

NEJM 2019;380:447-458

IRON

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

Median monthly dose
264 mg [IQR 200-336]



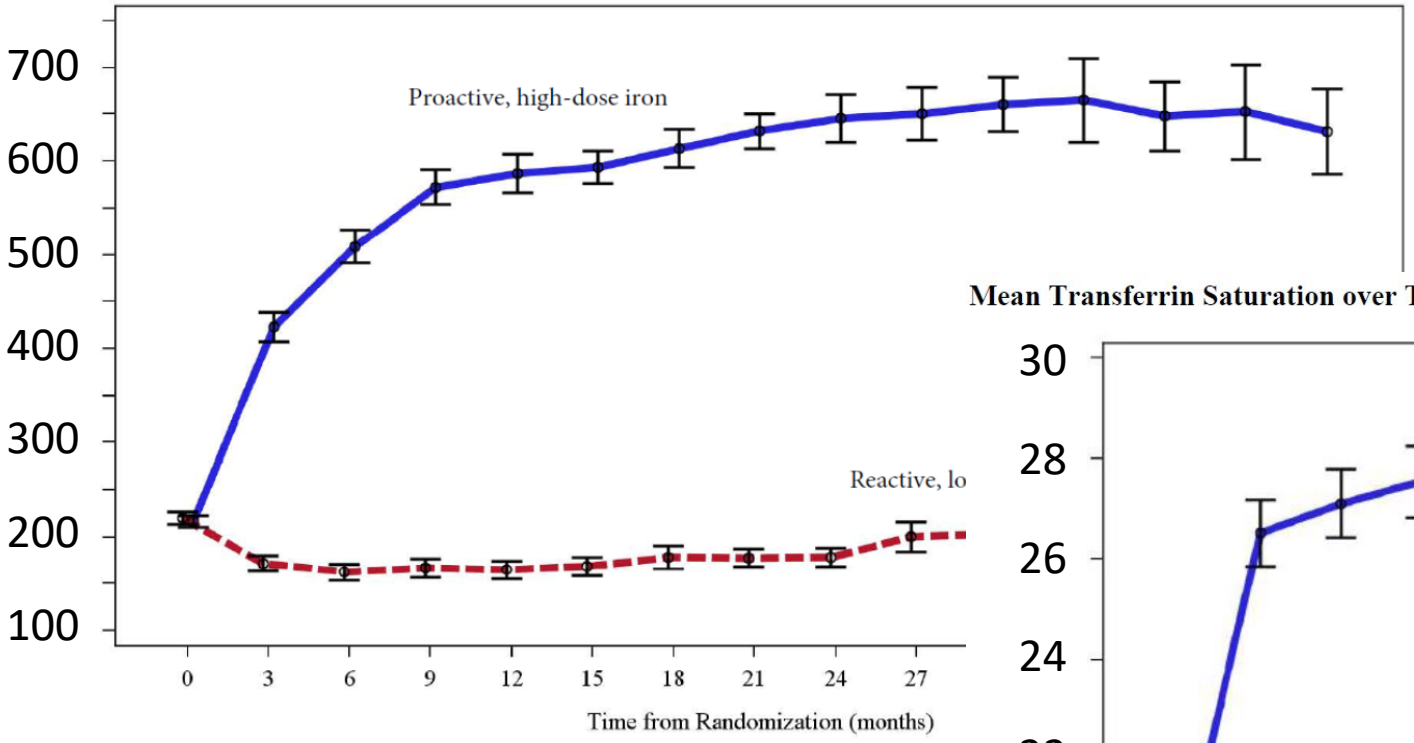
Median monthly dose
145 mg [IQR 100-190]

PIVOTAL, NEJM 2019

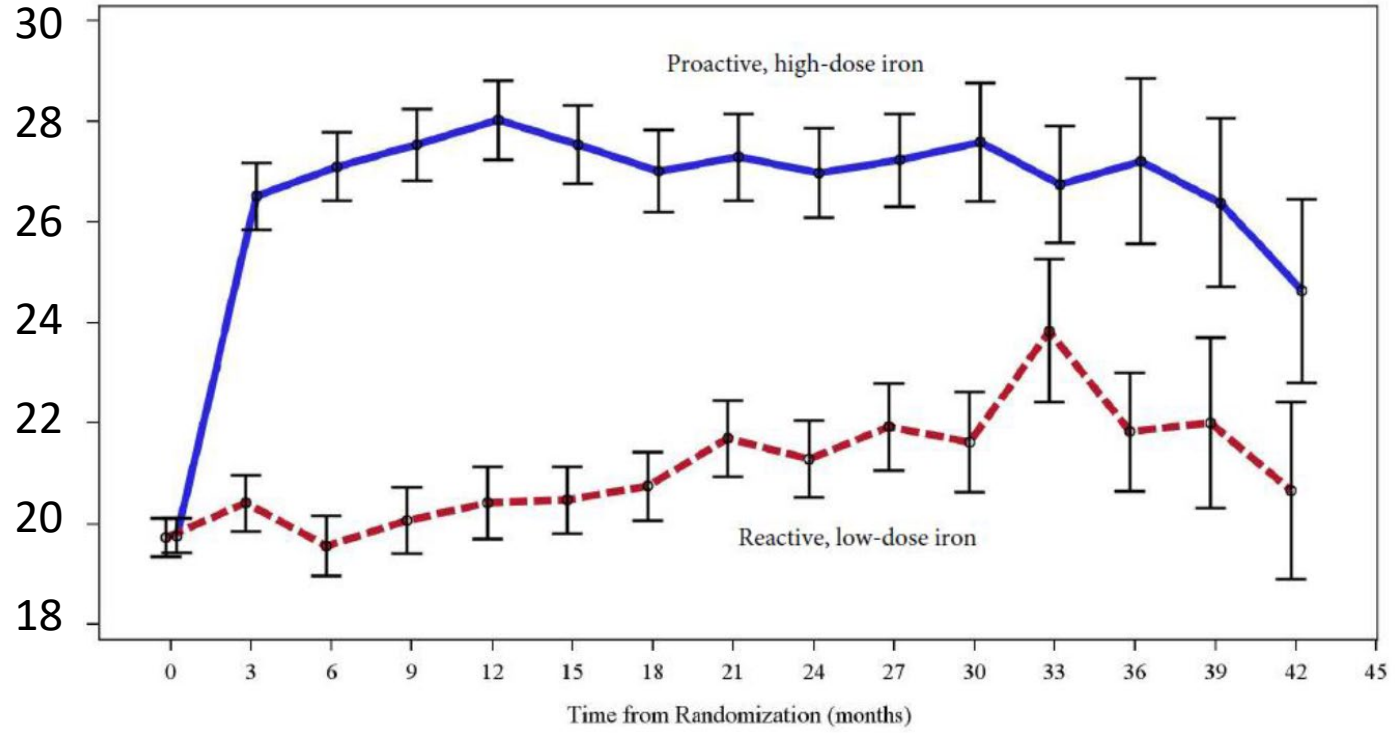
Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

IRON

Mean Serum Ferritin Concentration over Time.



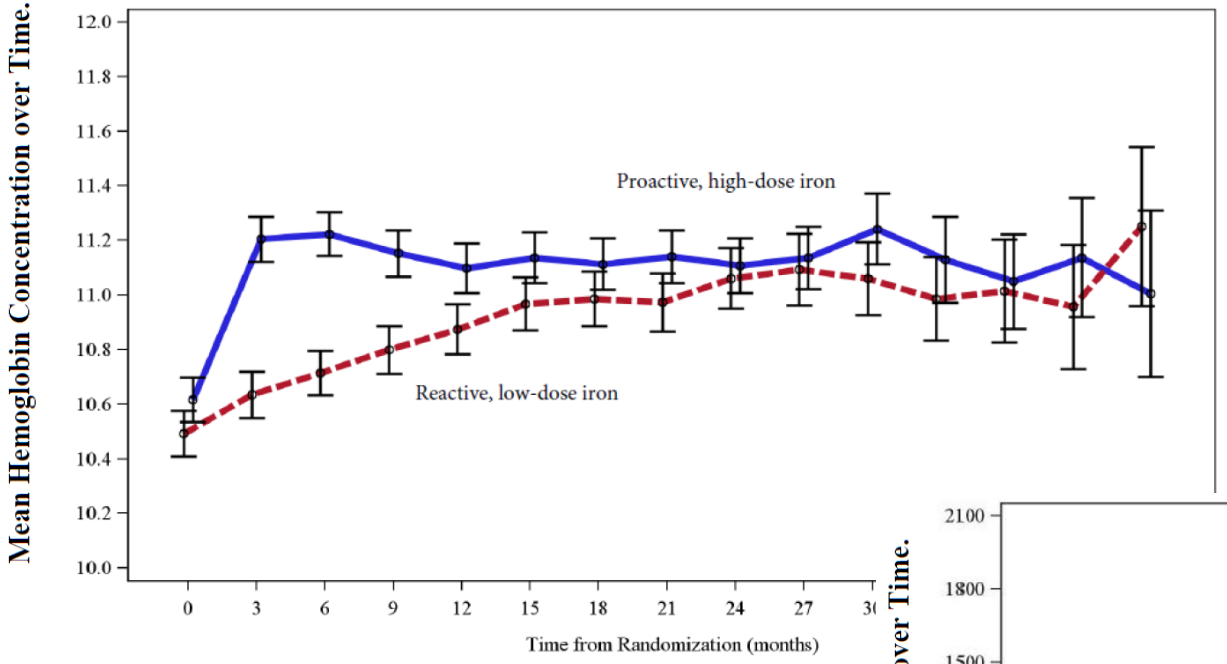
Mean Transferrin Saturation over Time.

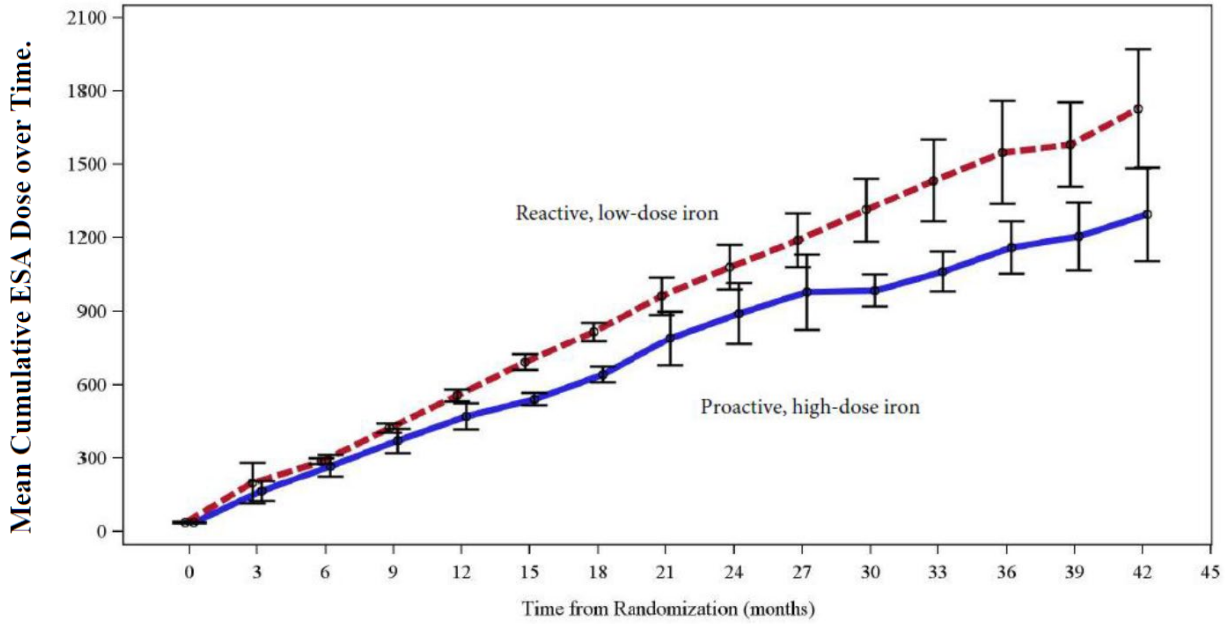


PIVOTAL, NEJM 2019

IRON

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis





Proactive group
↓ ESA dose by 19%

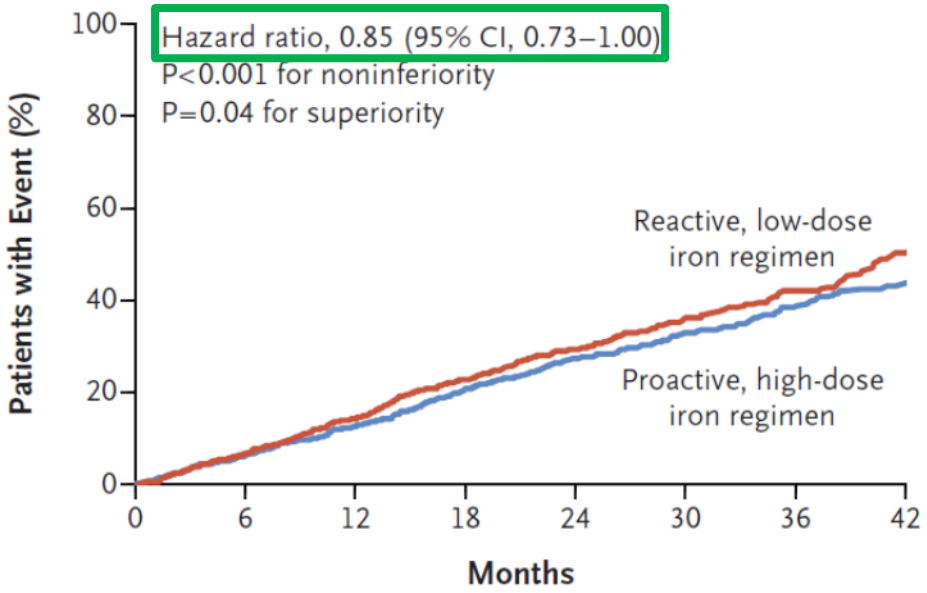
PIVOTAL, NEJM 2019

IRON

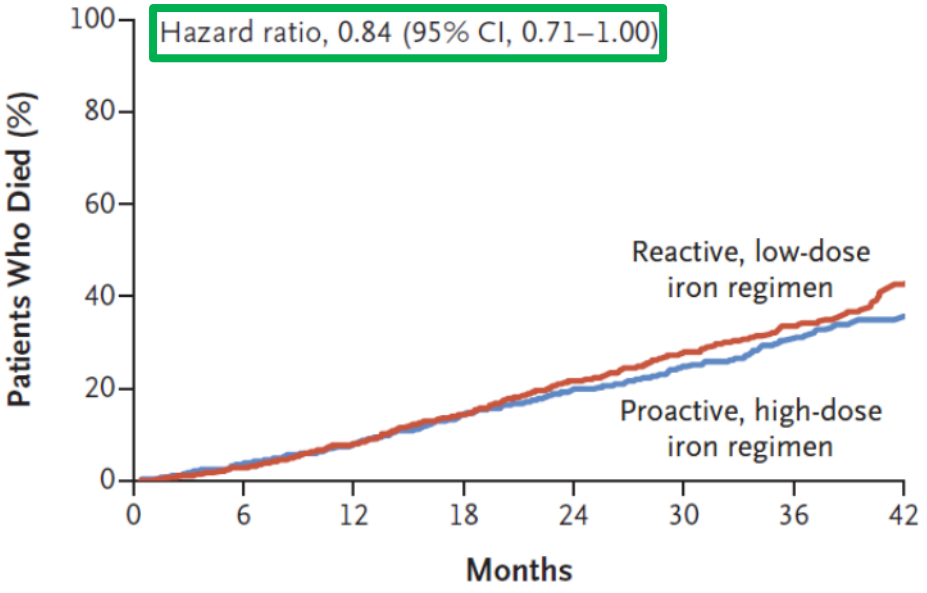
Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

Primary Efficacy End Point

(Death, MI, stroke, and hospitalization for HF)



Death from Any Cause



PIVOTAL, NEJM 2019

IRON

Heart Failure Hospitalization in Adults Receiving Hemodialysis and the Effect of Intravenous Iron Therapy

JACC: HEART FAILURE
JULY 2021:518-27

CONCLUSIONS Compared with a lower-dose regimen, high-dose intravenous iron decreased the occurrence of first and recurrent heart failure events in patients undergoing hemodialysis, with large relative and absolute risk reductions.

High-dose intravenous iron reduces myocardial infarction in patients on haemodialysis

ESC European Society of Cardiology

Cardiovascular Research (2023) **119**
https://doi.org/10.1093/cvr/cvab317

High dose v low dose intravenous iron

31%

myocardial infarction

(HR 0.69, 95% CI 0.52-0.93, p=0.01)

Death after non-fatal MI

1 year mortality - 40%

2 year mortality - 60%

PIVOTAL Investigators and Committees

IRON

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

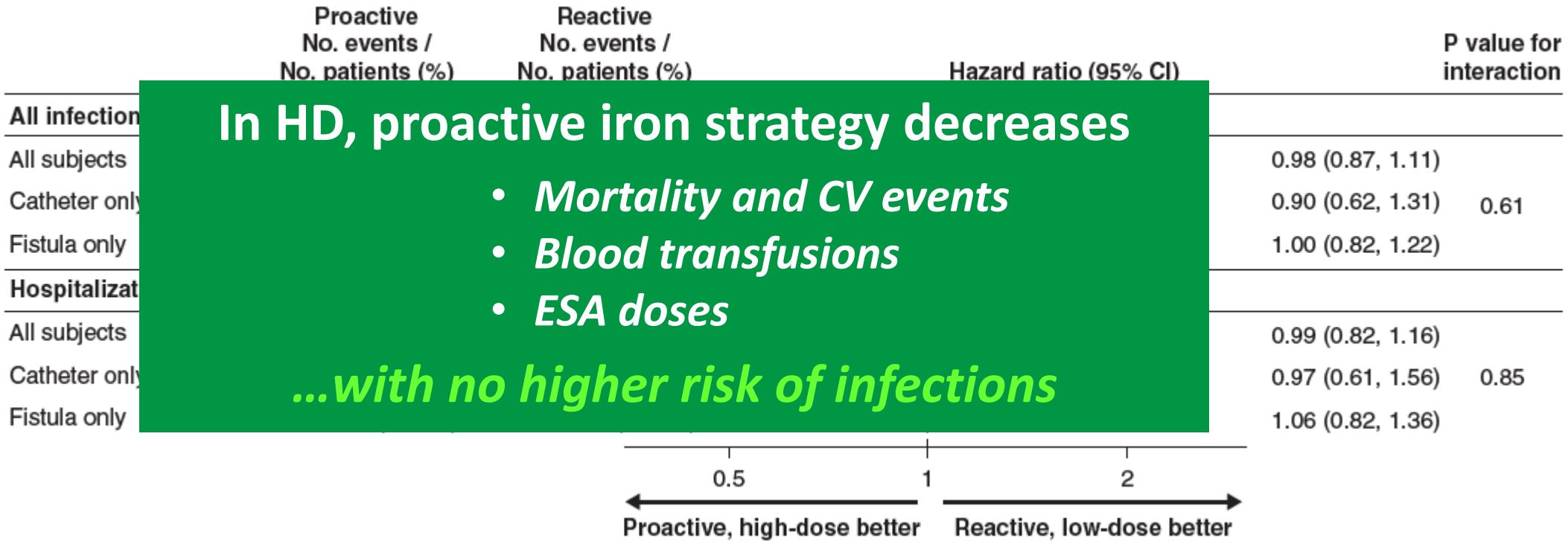
Table 2. Primary and Secondary End Points.*

	Proactive, High-Dose Iron Regimen (N=1093)	Reactive, Low-Dose Iron Regimen (N=1048)	Estimated Treatment Effect (95% CI)
Secondary efficacy end points			
Median monthly dose of erythropoiesis-stimulating agent (IQR) — IU¶	29,757 (18,673 to 48,833)	38,805 (24,377 to 60,620)	−7539 (−9485 to −5582)
Blood transfusion			
Any transfusion — no. (%)	198 (18.1)	226 (21.6)	0.79 (0.65 to 0.95)
Total no. of units transfused	967	1122	NA‖
No. of units transfused per yr	0.43±2.23	0.72±4.26	—
Secondary safety end points			
Vascular access thrombosis — no. (%)	262 (24.0)	218 (20.8)	1.15 (0.96 to 1.38)
Hospitalization for any cause — no. (%)	651 (59.6)	616 (58.8)	1.01 (0.90 to 1.12)
Hospitalization for infection — no. (%)	323 (29.6)	307 (29.3)	0.99 (0.82 to 1.16)

PIVOTAL, NEJM 2019

Intravenous Iron Dosing and Infection Risk in Patients on Hemodialysis: A Prespecified Secondary Analysis of the PIVOTAL Trial

IRON



In HD, proactive iron strategy decreases

- ***Mortality and CV events***
- ***Blood transfusions***
- ***ESA doses***

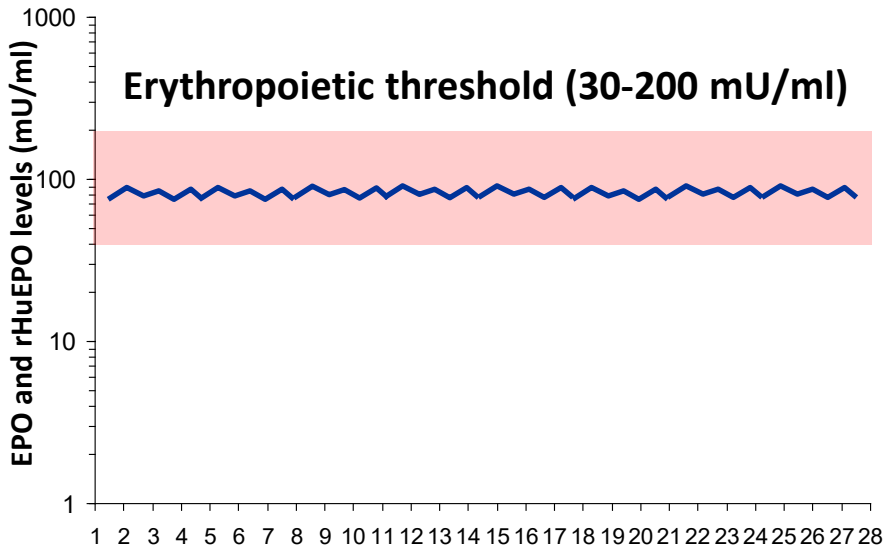
…with no higher risk of infections

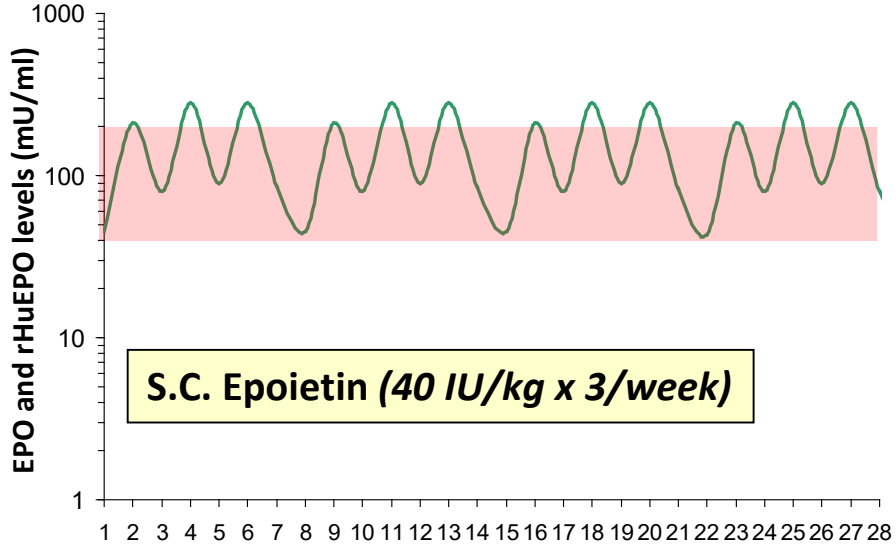
Macdougall, JASN 2020

All ESAs are effective if used properly…

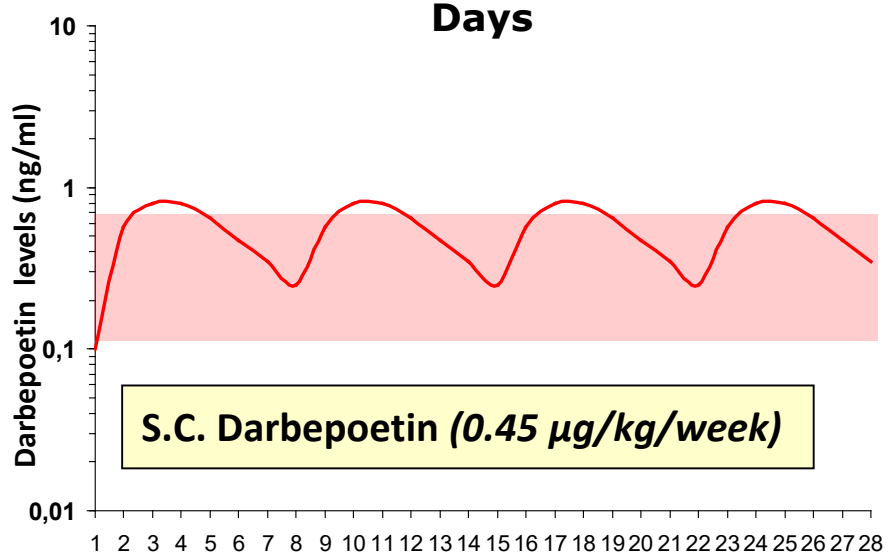
…allowing serum epo levels within the erythropoiesis threshold

ESA

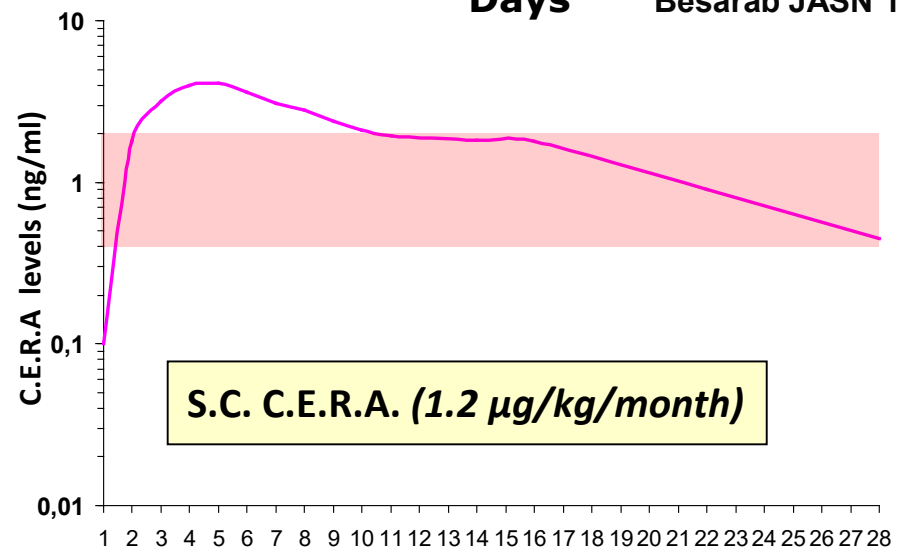




Besarab JASN 1992



Macdougall JASN 1999



Macdougall CJASN 2006

ESA

Clinical Pharmacology and Economics of Recombinant Human Erythropoietin in End-Stage Renal Disease: The Case for Subcutaneous Administration[1]

Anatole Besarab,[2] Kristen K. Flaharty, Allan J. Erslev, Jacqueline B. McCrea, Peter H. Vlasses, Fani Medina, Jaime Caro, and Edward Morris

(J. Am. Soc. Nephrol. 1992; 2:1405–1416)

N=16 patients treated with same weekly dose of Epoetin (120 IU/kg s.c.) but at different dosing intervals

The 3 Key Questions on HIFs

HIFs

1. **Which**…mechanism of action ?

2. **Who**…should be treated ?

3. **Where**…differences versus ESA ?

Which…mechanism of action ?

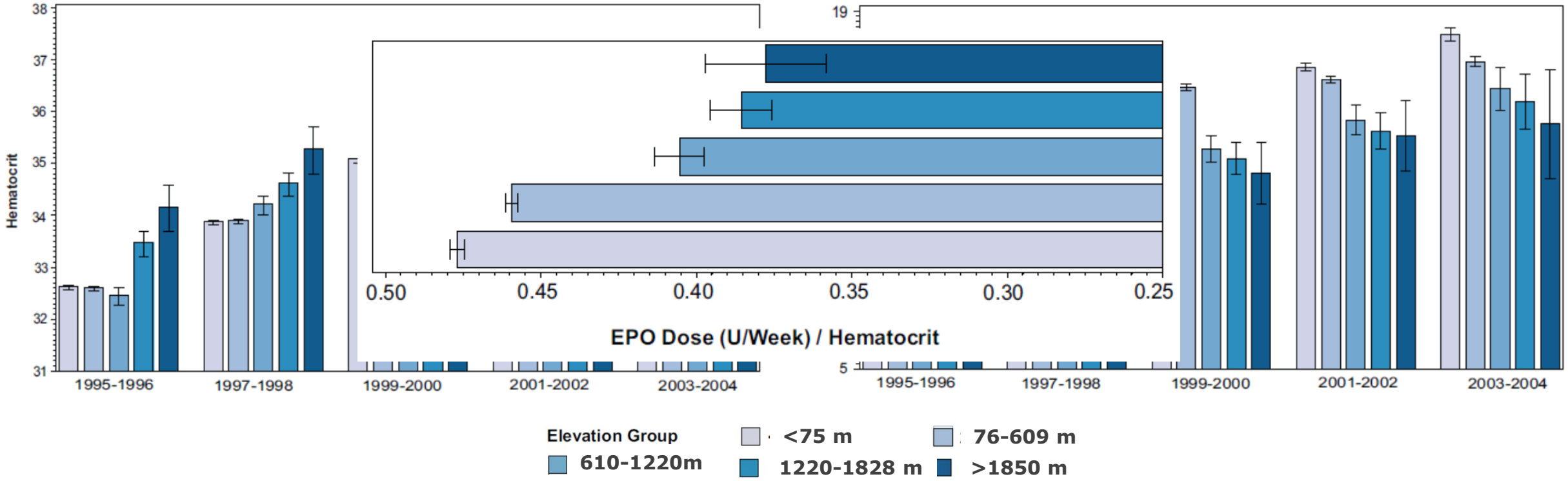
HIFs

The Effect of Altitude on Dosing and Response to Erythropoietin in ESRD

M. Alan Brookhart,* Sebastian Schneeweiss,* Jerry Avorn,* Brian D. Bradbury,‡
Kenneth J. Rothman,*§ Michael Fischer,* Jyotsna Mehta,* and Wolfgang C. Winkelmayer*†

J Am Soc Nephrol 19: 1389–1395, 2008.

Retrospective cohort study in 341,737 incident HD patients stratified by elevation data from the U.S. Geological Survey to evaluate whether altitude at which a patient lives may affect the dose-response relationship of EPO.



Which…mechanism of action ?

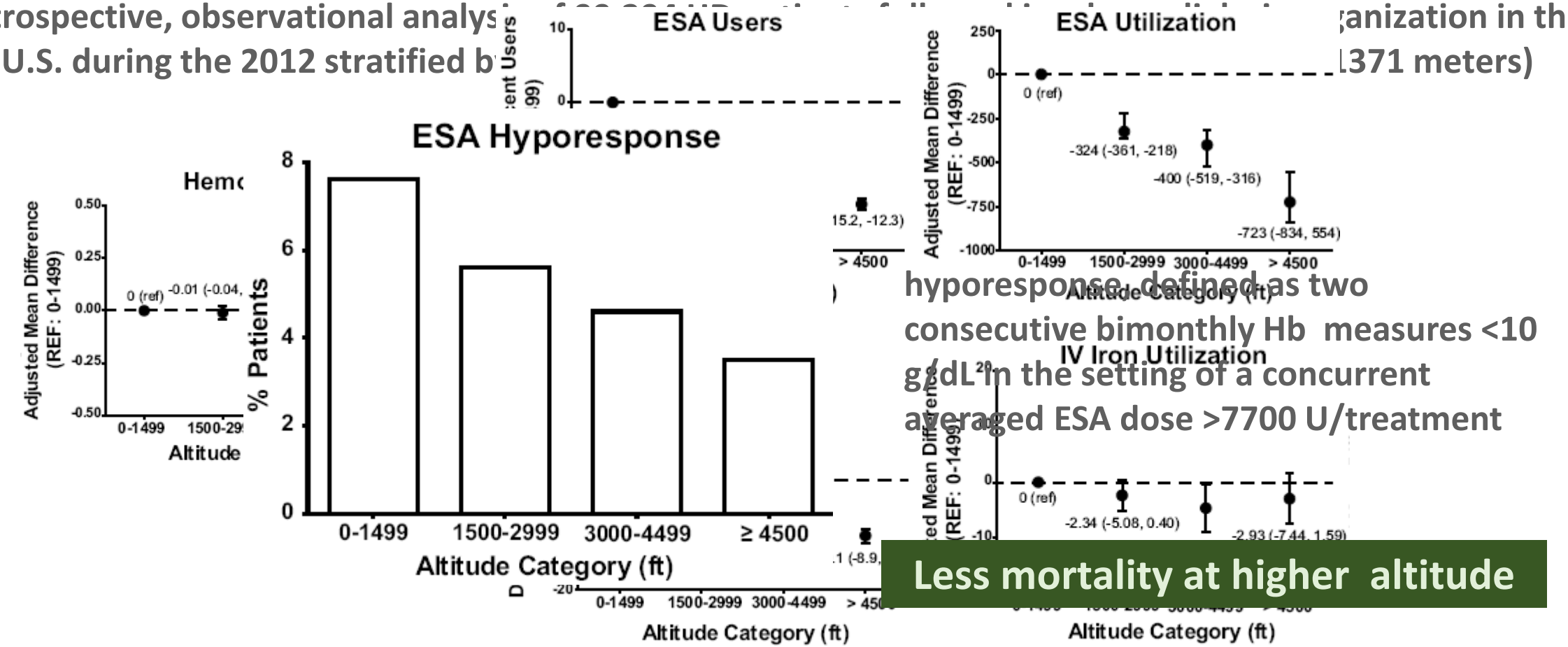
HIFs

The effect of altitude on erythropoiesis-stimulating agent dose, hemoglobin level, and mortality in hemodialysis patients

Scott Sibbel[1] · Bradley J. Maroni[2] · Steven M. Brunelli[1]

J Nephrol (2017) 30:821–829

Retrospective, observational analys… …ganization in the U.S. during the 2012 stratified b… …1371 meters)



hyporesponse, defined as two consecutive bimonthly Hb measures <10 g/dL in the setting of a concurrent averaged ESA dose >7700 U/treatment

Less mortality at higher altitude

Which…mechanism of action ?

HIFs

At altitude, the hypoxic stimulus to endogenous erythropoietin production…

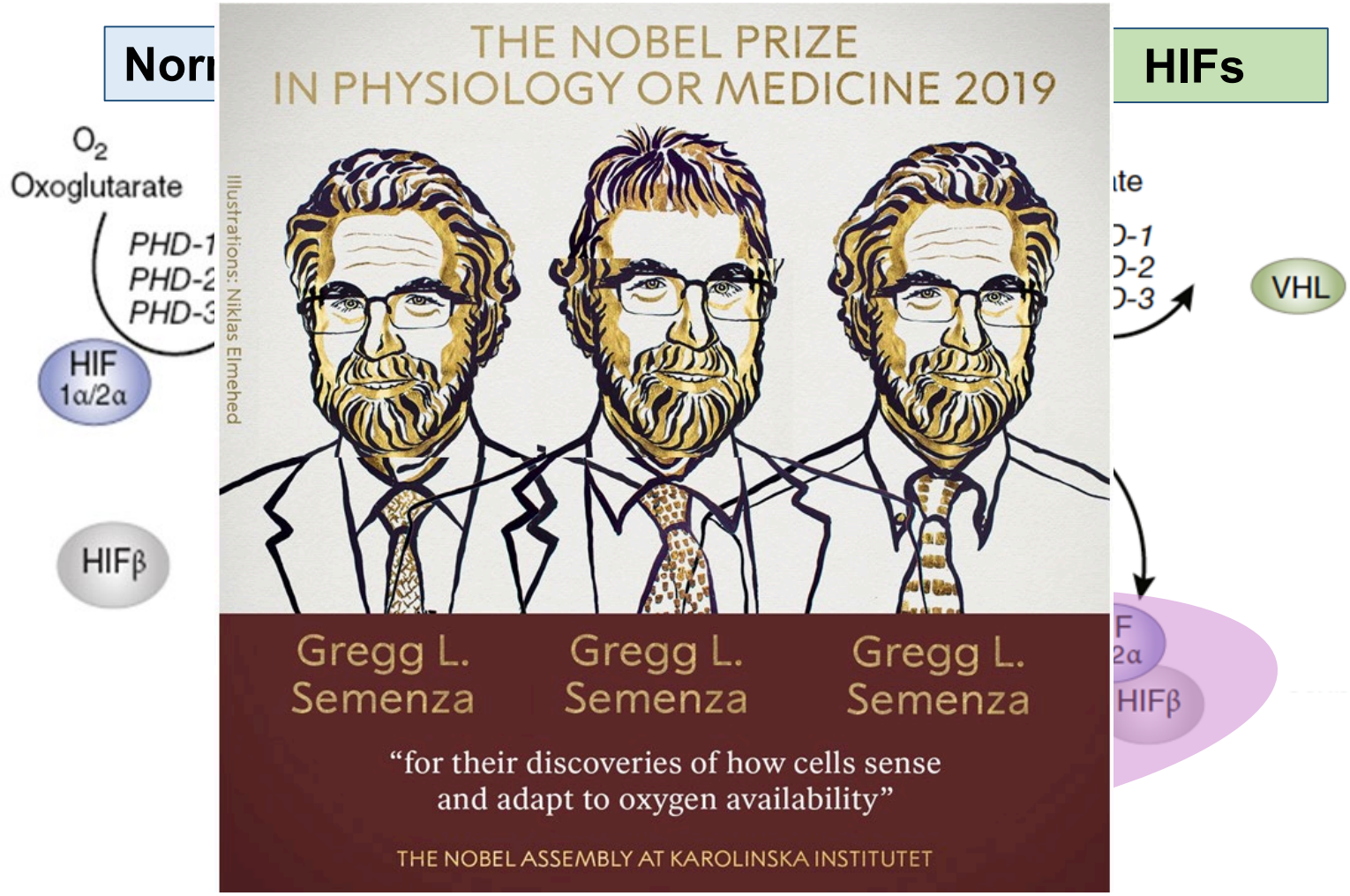
…persists in hemodialyzed patients !!!

Which…mechanism of action ?

HIFs

The noblesse of kidney physiology

Kidney International (2019) · Kai-Uwe Eckardt



Which…mechanism of action ?

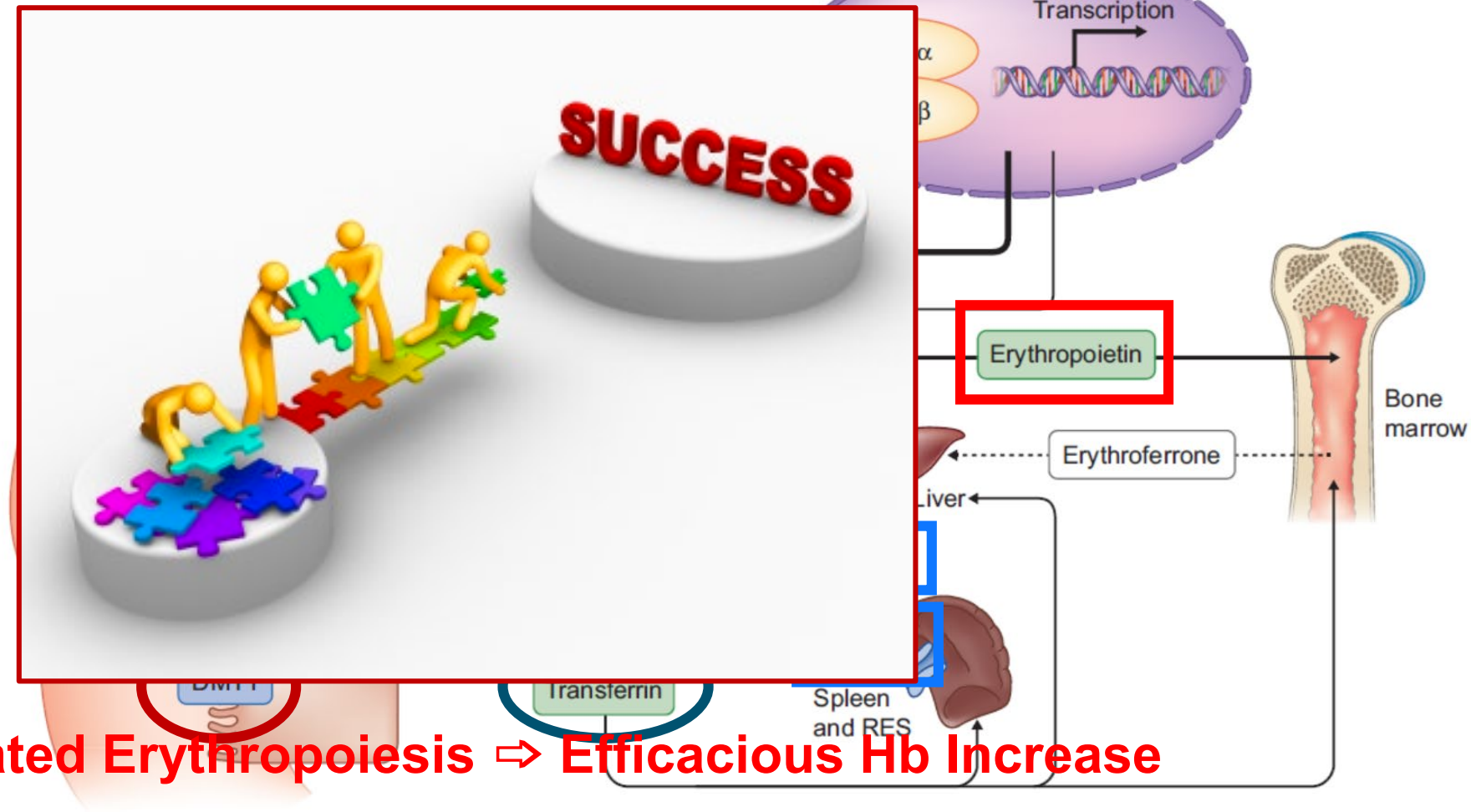
HIFs

⇧ endogenous erythropoetin synthesis

⇧ intestinal iron absorption

⇧ iron mobilization by ↓ hepcidin-mediated ferroportin expression

⇧ iron delivery by up-regulating transferrin



Coordinated Erythropoiesis ⇨ Efficacious Hb Increase

Locatelli, Del Vecchio, De Nicola, Minutolo. NDT 2020

Who…should be treated ?

HIFS

Anemic patients
with non-dialysis or dialysis CKD

32 phase-3 RCTs including 29,241 participants

26 in 24,387 patients (59% in dialysis)
had ESA as control arm

Most RCTs had Hb target 10-11 (US) and 10-12 (non-US)
according to ESA trials and subsequent guidelines !!!

Who…should be treated ?

HIFs

EFFICACY: mean difference in Hb change from baseline and Hb target achievement

Effic
hydr
dise
con

Hb change from baseline: HIF-PHIs vs ESA

Table 2. Moderator analyses of change in Hb levels from baseline and Hb target achievement between HIF-PHI and ESA comparator.

	Hb change, g/dL [OR (95% CI)]	P	Target achievement [OR (95% CI)]	P
ESA comparator		<.001		.003
Long-acting ESA	−0.01 (−0.09 to 0.07)		0.91 (0.76 to 1.10)	
Short-acting ESA	0.21 (0.12 to 0.29)		1.38 (1.13 to 1.68)	
CKD stage		.144		.634
Non-dialysis	0.03 (−0.04 to 0.10)		1.08 (0.83 to 1.42)	
Dialysis	0.12 (0.02 to 0.22)		1.00 (0.80 to 1.24)	
HIF-PHI		.290		.005
Roxadustat	0.18 (0.06 to 0.30)		1.17 (0.88 to 1.55)	
Molidustat	−0.07 (−0.39 to 0.25)		0.88 (0.34 to 2.29)	
Daprodustat	0.06 (−0.04 to 0.15)		1.30 (0.63 to 2.67)	
Desidustat	0.13 (−0.04 to 0.30)		1.59 (1.21 to 2.08)	
Enarodustat	NA		0.71 (0.30 to 1.69)	
Vadadustat	0.00 (−0.15 to 0.16)		0.85 (0.72 to 1.00)	
Previous ESA therapy		.594		.154
Naïve	0.12 (0.02 to 0.23)		1.36 (1.00 to 1.86)	
ESA	0.07 (−0.03 to 0.18)		0.98 (0.80 to 1.19)	
Mixed	0.19 (−0.03 to 0.40)		0.83 (0.46 to 1.49)	

Favour ESA Favour HIF-PHI

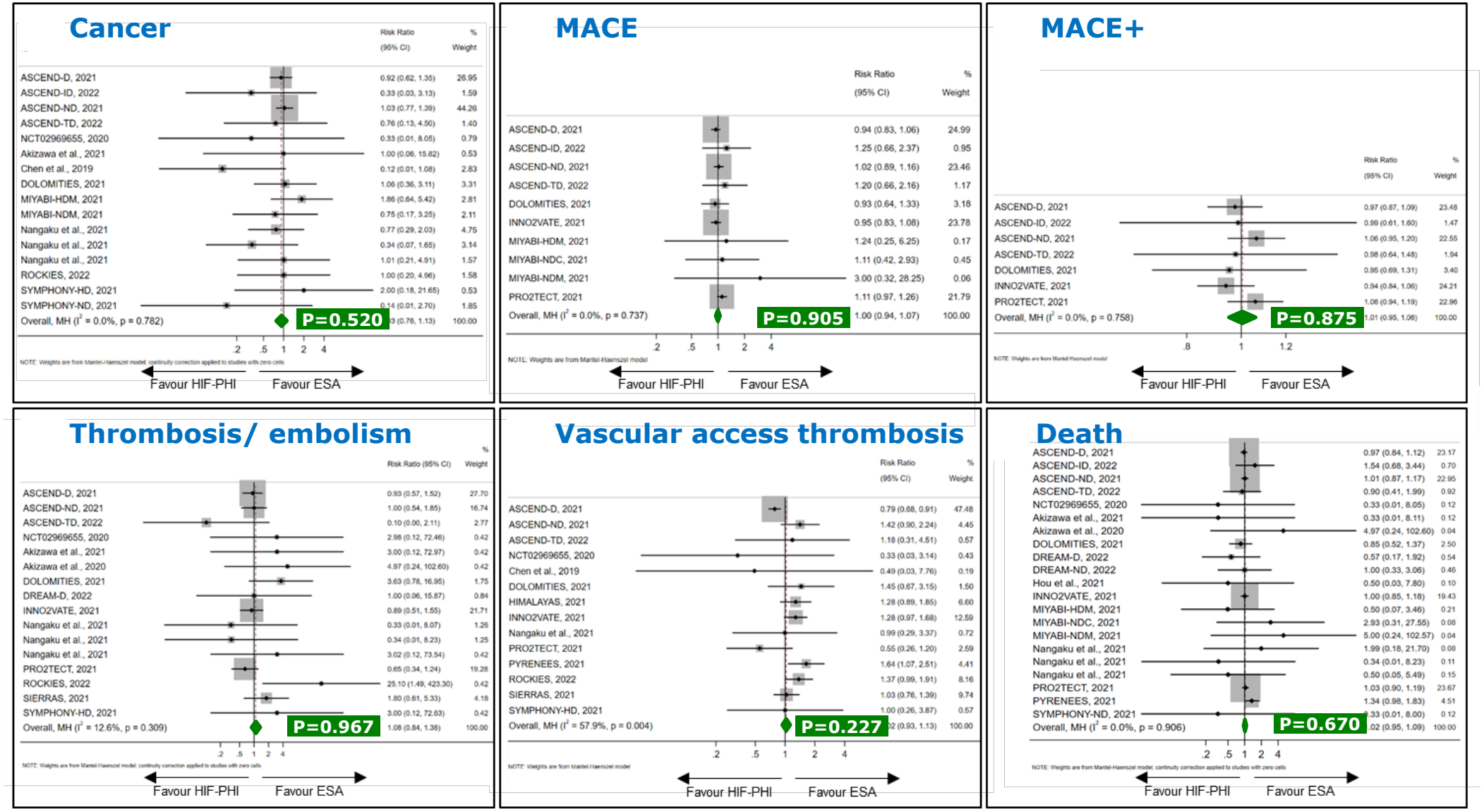
Favour ESA Favour HIF-PHI

Minutolo…De Nicola, Clin Kidney J 2023

Who…should be treated ?

HIFs

SAFETY: rate ratio for main hard endpoints between HIF stabilizers and ESA comparator



Minutolo...De Nicola,. Clin Kidney J 2023

Who…should be treated ?

HIFs

Cardiac and Kidney Adverse Effects of HIF Prolyl-Hydroxylase Inhibitors for Anemia in Patients With CKD Not Receiving Dialysis

Setting & Participants

- Systematic review and meta-analysis
- Patients with anemia and CKD not receiving maintenance dialysis
- 23 RCTs with 15,144 participants
- HIF-PHIs vs placebo/ESAs

Results

OUTCOMES	RR (95% CI) HIF-PHIs Vs Placebo	RR (95% CI) HIF-PHIs Vs ESA	GRADE HIF-PHIs Vs Placebo	GRADE HIF-PHIs Vs ESA
Cardiac Disorders	**1.02** (0.89-1.16)	**1.06** (0.98-1.14)	⊕⊕⊕◯ Moderate	⊕⊕◯◯ Low
Kidney-Related AEs	**1.09** (0.98-1.20)	**1.00** (0.94-1.06)	⊕⊕⊕◯ Moderate	⊕⊕◯◯ Low
Hypertension	**1.35** (1.14-1.60)	**0.89** (0.81-0.98)	⊕⊕⊕⊕ High	⊕⊕⊕◯ Moderate
Hyperkalemia	**1.25** (1.03-1.51)	**0.92** (0.81-1.04)	⊕⊕⊕⊕ High	⊕⊕◯◯ Low
ESKD or Dialysis	**1.05** (0.93-1.19)	**0.99** (0.91-1.08)	⊕⊕⊕◯ Moderate	⊕⊕◯◯ Low

CONCLUSION: The occurrence of cardiac or kidney-related adverse events in the HIF-PHI groups were not different compared with placebo or ESA groups.

Qiyan Zheng, Yahui Wang, Huisheng Yang, et al
@AJKDonline | DOI: 10.1053/j.ajkd.2022.09.014

AJKD AMERICAN JOURNAL OF KIDNEY DISEASES

Where…differences versus ESA ?

HIFs

Besides and beyond the oral formulation and no need of cold chain…

The CHANGE in the treatment of CKD-anemia

from Pharmacological

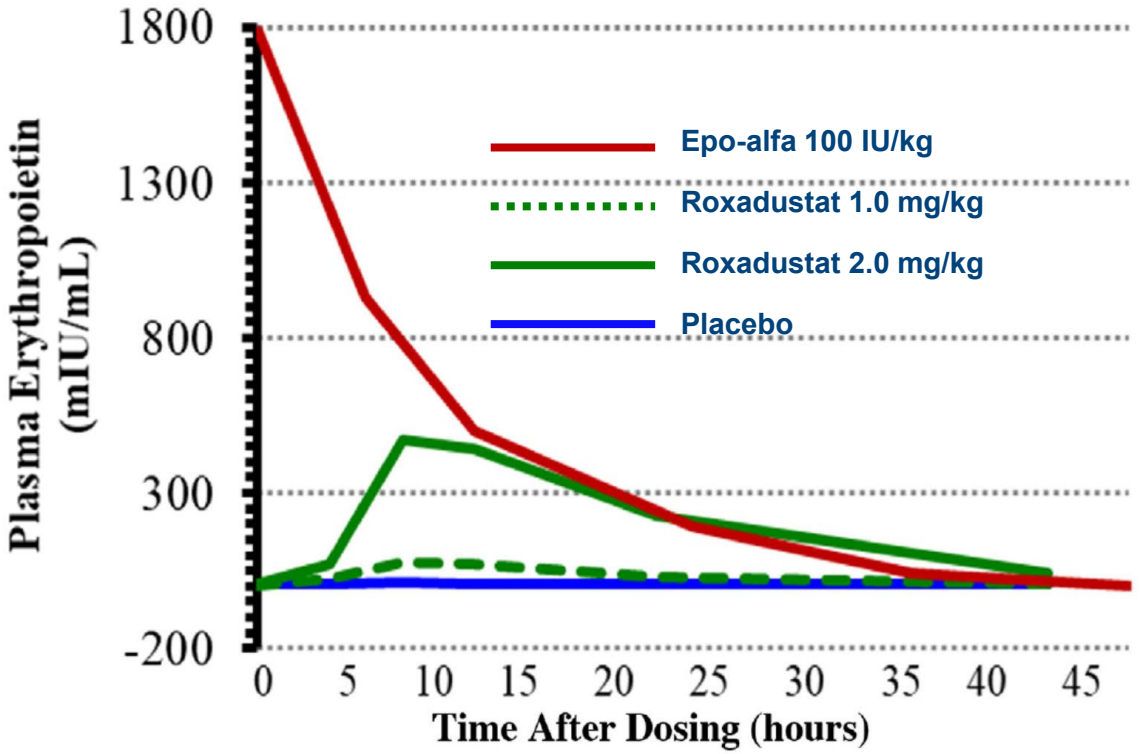
-substitutive single therapy-

to Physiological

-restoration of full endogenous mechanisms-

Intervention

No peaks of plasma EPO levels that remain within physiologic range

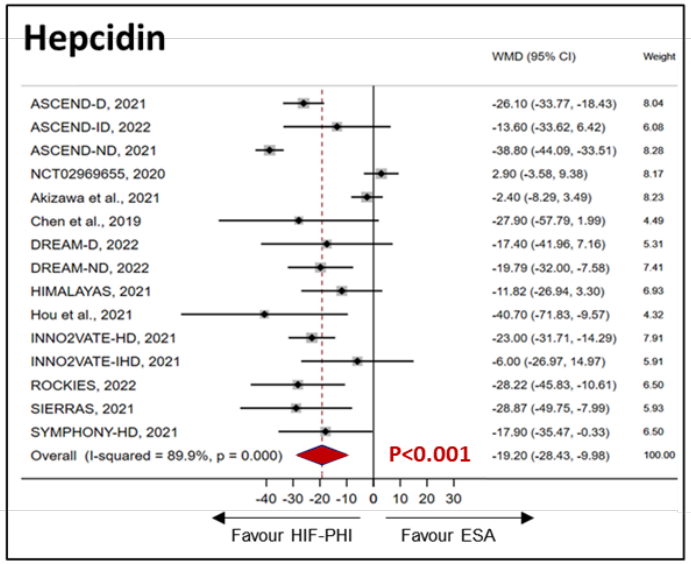


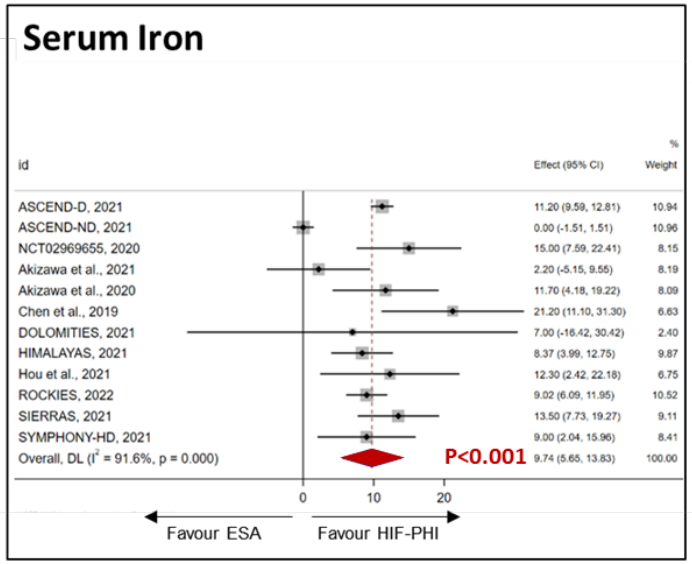
Provenzano, J Clin Pharm 2020

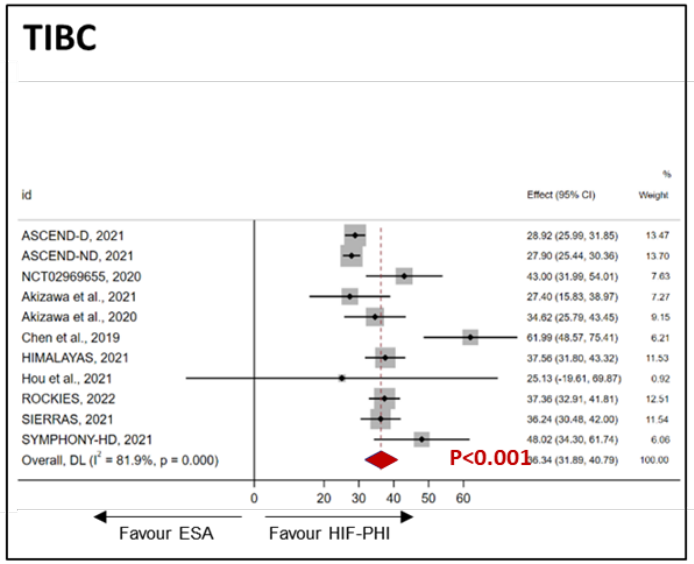
Where…differences versus ESA ?

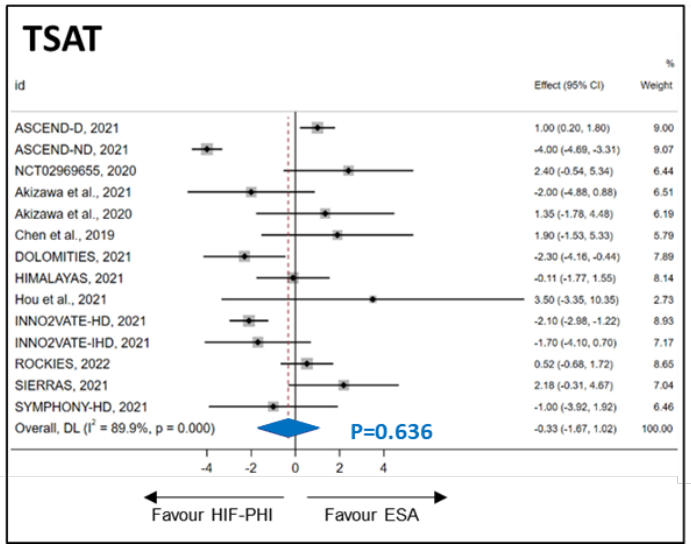
HIFs

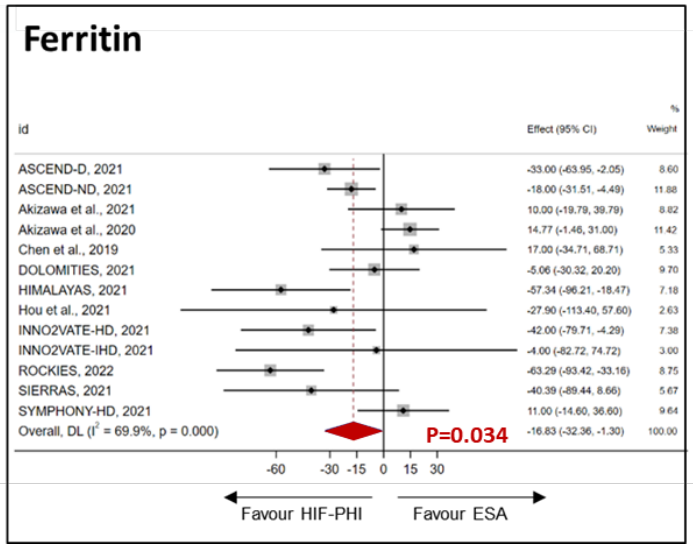
Iron parameters and IV iron dose: differences in the changes from baseline between HIF-PHIs and ESAs

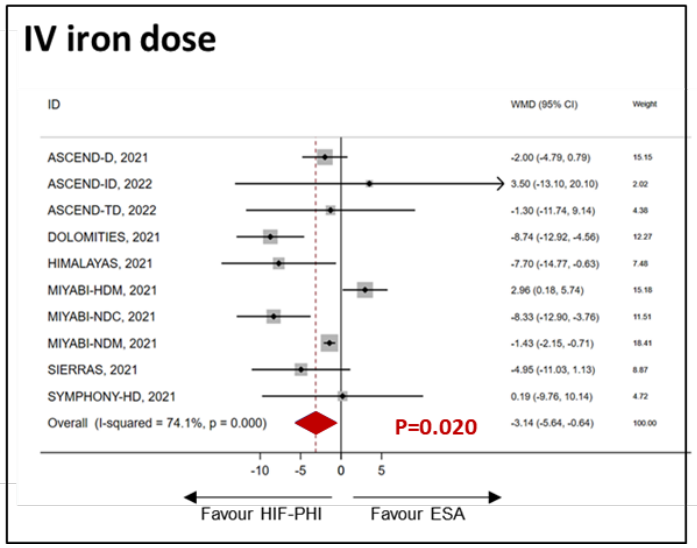












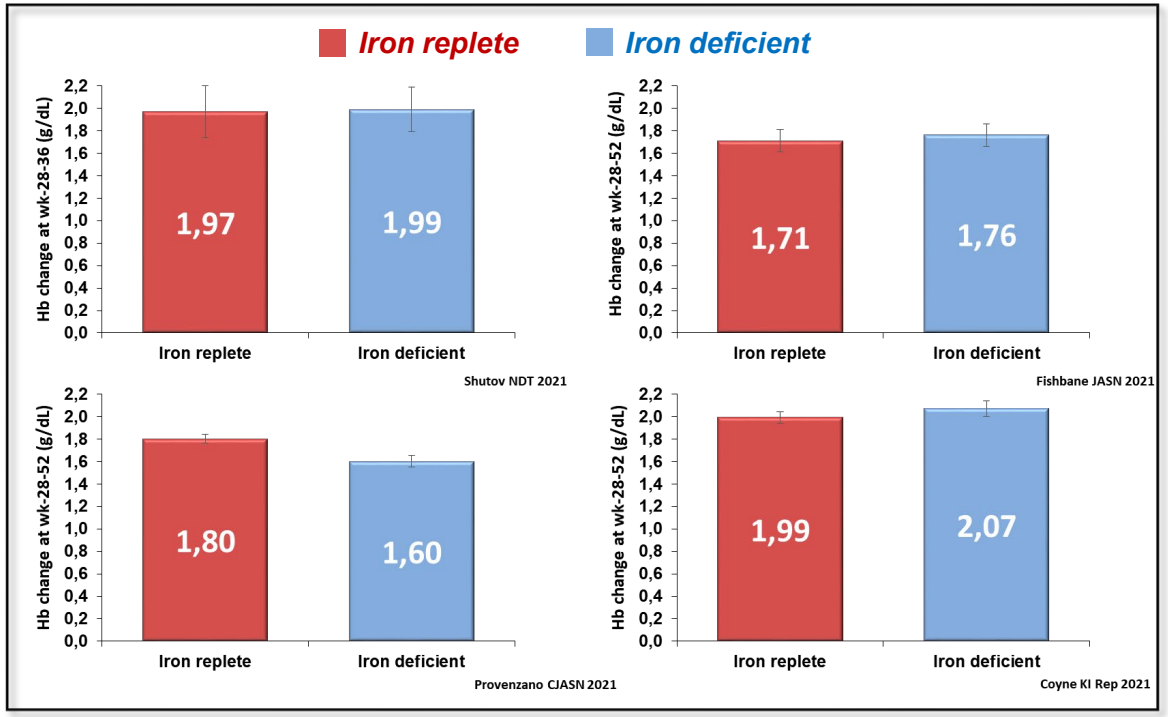
Minutolo…De Nicola, Clin Kidney J 2023

Where…differences versus ESA ?

HIFs

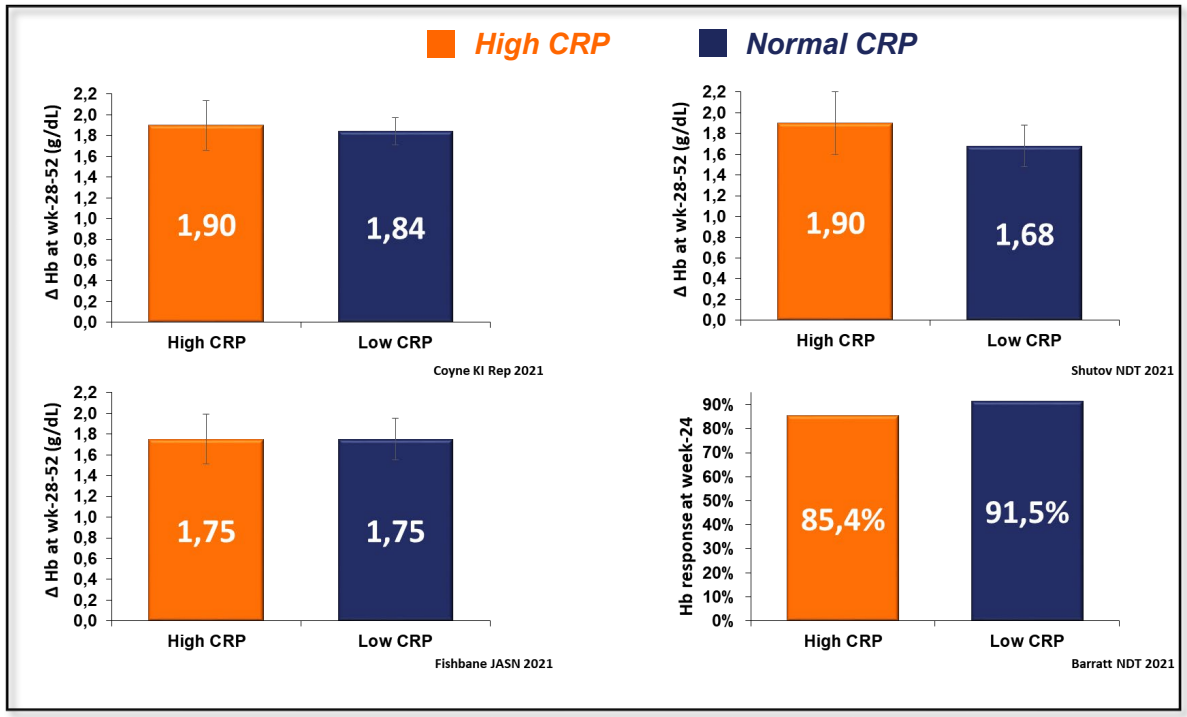
IRON DEFICIENCY
(Ferritin <100 ng/ml or TSAT <20%)

Hb response to roxadustat is independent from iron status in ND-CKD



INFLAMMATION
(CRP above the upper normal limit)

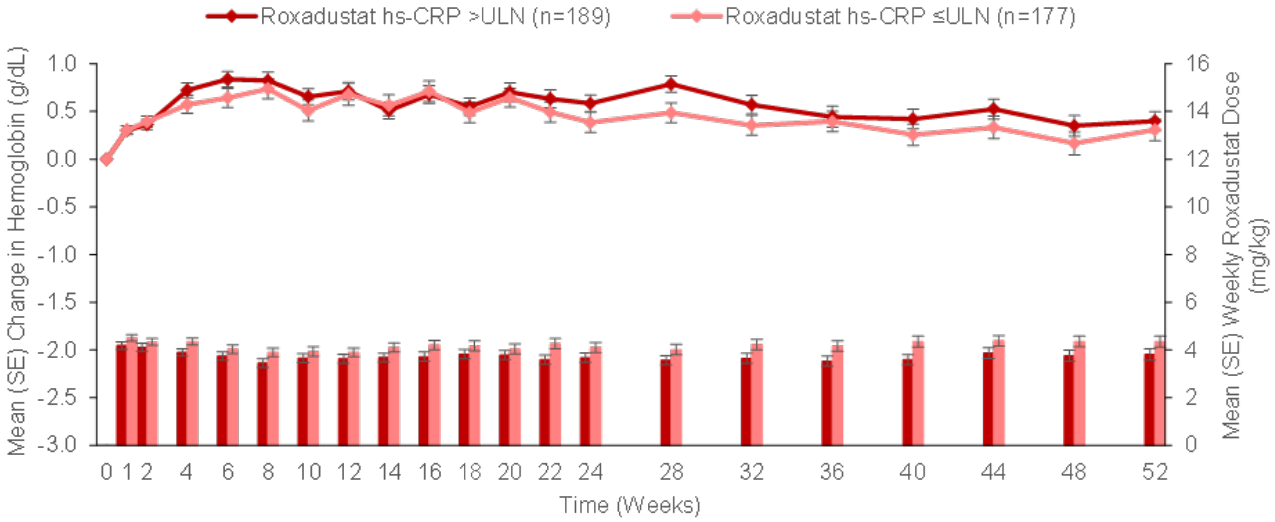
Hb response to roxadustat is independent from CRP levels in ND-CKD

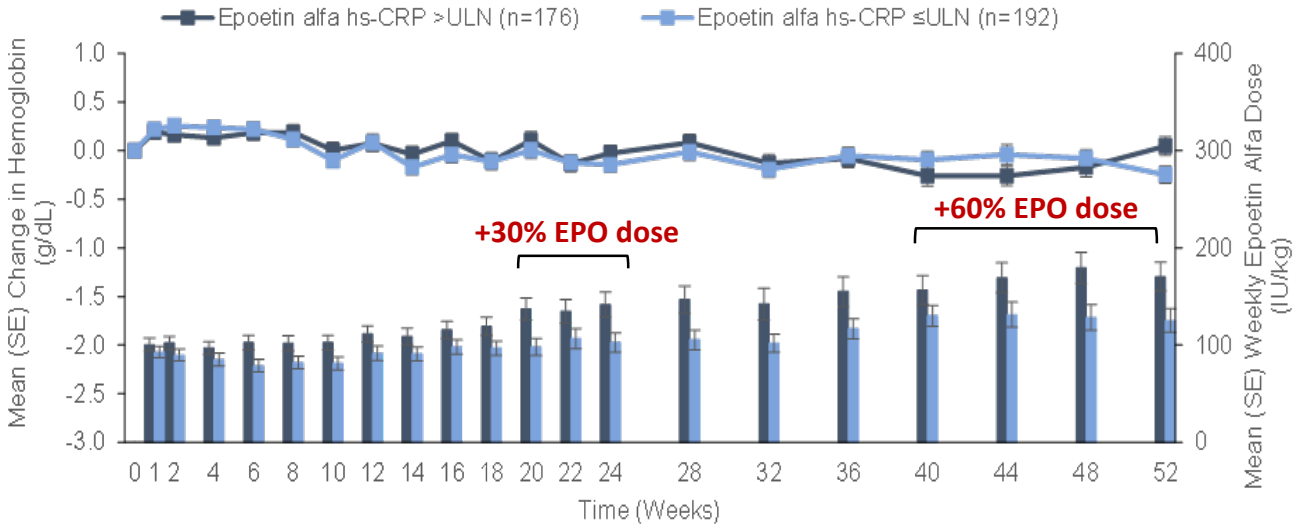


Where…differences versus ESA ?

HIFs

Hb response and roxadustat or Epoetin-α dose in 741 HD patients stratified by CRP levels



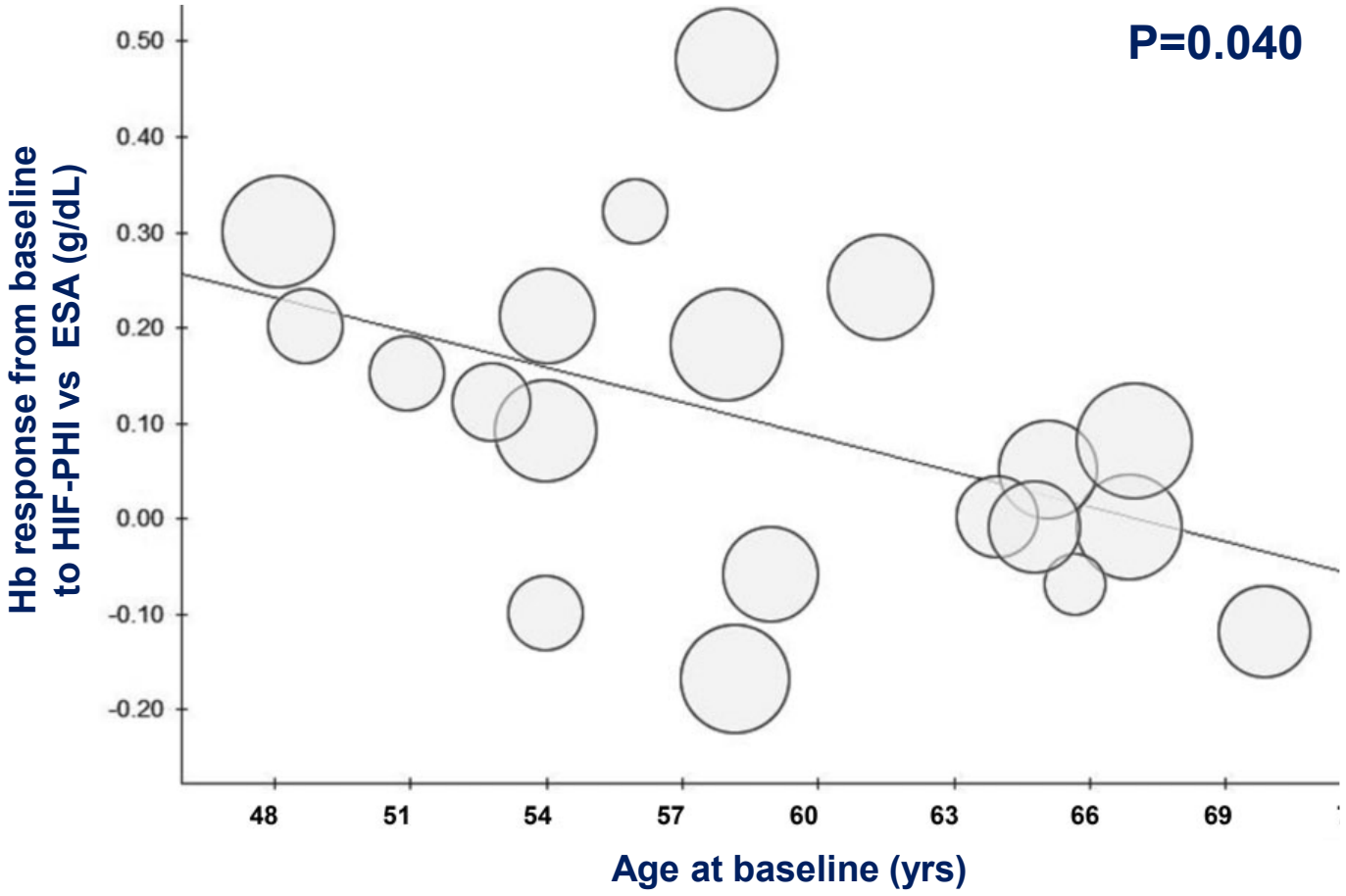


Charytan et al (SIERRAS), KI rep 2021

Where…differences versus ESA ?

HIFs

Efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in patients with chronic kidney disease: meta-analysis of phase 3 randomized controlled trials



At meta-regression

Greater Hb response to HIF-PHI vs ESA in younger patients

younger more inflamed than older ?

Minutolo...De Nicola,. Clin Kidney J 2023

HIF stabilizer as a more physiological approach to CKD-anemia

- **Hb goal achievement and safety similar to ESA**
- **At variance with ESA:**
  - Oral tablets stored at ambient temperature
  - Quasi-physiological mechanism harmonizing endogenous erythropoietin production with higher iron availability
  - Erythropoietic response less dependent on iron supplementation and inflammation

The Future ?

"physiological normalization" of Hb levels

Anemia in Dialysis

Key messages

After 30 yrs of ESA, anemia correction still remains far to be optimal due to the multifactorial pathogenesis that contrasts with the "one-size-fits-all" design of RCTs (*and derived guidelines !*)

Iron is an essential component of anti-anemic therapy with the large PIVOTAL trial definitely proving effectiveness of proactive therapy (*do not wait and see !*)

Major barrier to anemia correction is clinical and subclinical inflammation (*where ESA or iron are not effective !*)

HIFs are a major step toward optimal management due to the "physiological" mechanism…however, its full expression -complete anemia correction- could not be tested in the RCTs because the Hb target was mandated by the results of ESA trials and dependent guidelines (*scientific paradox !*)