How to Treat Anemia in Difficult to Manage ESKD Patients

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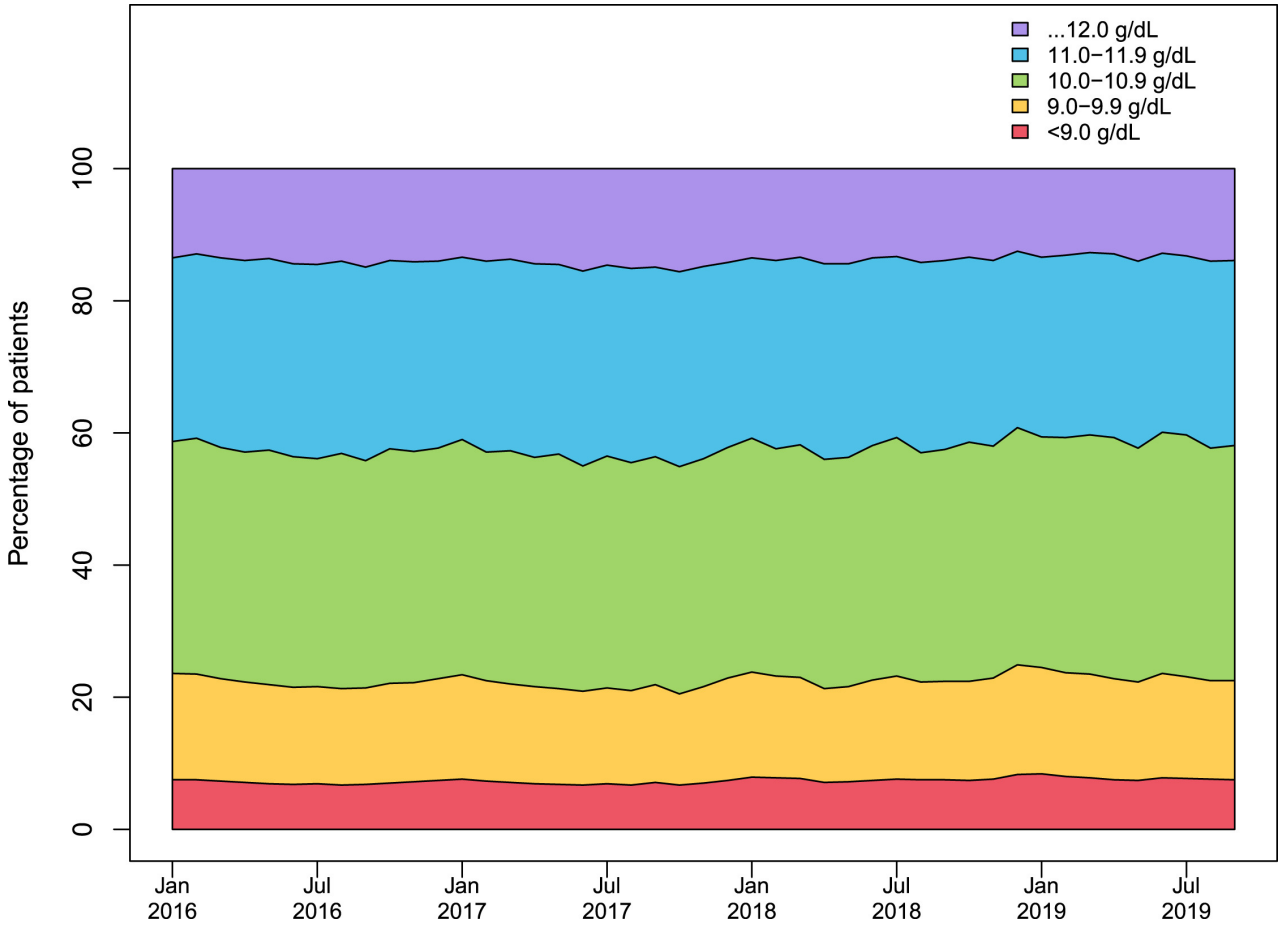
Disclosures

- Board of Directors, Ohio Renal Care Group
- Board of Directors, Kidney Foundation of Ohio

Overview

- Types of challenges in the management of anemia in ESKD
  - Patients that are hypo-responsive to anemia management
  - Avoiding blood transfusions
  - Special populations
    - Sickle cell disease
    - Patients with or prior history of cancer

Overview



USRDS
Little variability in Hgb measurements 2016-2019

~40% of patients with Hgb of 10-11 g/dL

~55% of patients with Hgb of 10-12 g/dL

~ 40% of patients with Hgb ≥ 11 g/dL

~ 20% of patients with Hgb ≤ 10 g/dL

Kidney Int Rep 2023; 8:2616-2624

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ESA Hyporesponsiveness

- Variable definition in the literature
  1. High ESA dose with different thresholds
  2. Hemoglobin below a certain threshold for certain duration of time
  3. High Erythropoietin Resistance Index (ESA dose/hgb/weight)
     a. Sometimes Hct used instead of Hgb
     b. Sometimes weight is not used
     c. Sometimes Hgb reported as g/dL or g/L
  4. Combination 1&2 or 2&3
- KDIGO
  - Initial: No increase in Hgb from baseline after 1 month with ESA therapy
  - Subsequent: Two increases of previously stable ESA dose of up to 50% to keep hemoglobin in target range.

www.kdigo.org

ESA Hyporesponsiveness

- Causes
  - Iron deficiency
  - Inflammation
  - Inadequate dialysis
  - Severe hyperparathyroidism
  - Nutritional deficiencies
  - Occult bleeding
  - Primary bone marrow process

ESA Hyporesponsiveness

Table 1. Point Prevalence of ESA Hyporesponsiveness According to Each of 5 Candidate Definitions

	ESA Hyporesponsiveness Definition				
	1. Two Most Recent Hb Measurements, Separated by 14+ d, Both <10 g/dL	2. Two Most Recent Hb Measurements, Separated by 14+ d, Both <9.5 g/dL	3. ESA Dose >7,700 U/Treatment[a]	4. Meets Criteria for Definitions 1 and 3	5. Meets Criteria for Definitions 2 and 3
Q1 2012 (N = 98,972)	29,287 (29.6)	14,431 (14.6)	25,107 (25.4)	12,361 (12.5)	7,590 (7.7)
Q2 2012 (N = 101,808)	28,195 (27.7)	13,681 (13.4)	24,956 (24.5)	11,975 (11.8)	7,324 (7.2)
Q3 2012 (N = 103,058)	27,199 (26.4)	13,217 (12.8)	24,608 (23.9)	11,483 (11.1)	7,109 (6.9)
Q4 2012 (N = 103,549)	25,884 (25.0)	12,425 (12.0)	23,340 (22.5)	10,537 (10.2)	6,433 (6.2)
Q1 2013 (N = 103,899)	28,306 (27.2)	13,724 (13.2)	23,959 (23.1)	11,530 (11.1)	7,138 (6.9)
Q2 2013 (N = 105,271)	27,475 (26.1)	13,134 (12.5)	23,542 (22.4)	11,117 (10.6)	6,895 (6.6)
Q3 2013 (N = 106,998)	29,239 (27.3)	14,139 (13.2)	23,900 (23.4)	11,690 (10.9)	7,267 (6.8)
Q4 2013 (N = 104,742)	23,465 (22.4)	11,265 (10.8)	23,290 (22.2)	9519 (9.0)	5,901 (5.6)

Note: Values are given as number (percentage).

Abbreviations: ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; Q, quarter.

[a]At the large dialysis organization, ESA treatment is provided almost exclusively in the form of 3-times-weekly epoetin alfa. In rare cases in which patients are treated with other agents (eg, darbepoetin alfa) or other dosing frequencies are used, doses were converted as described in Methods.

Am J Kidney Dis 2016; 68:763-771

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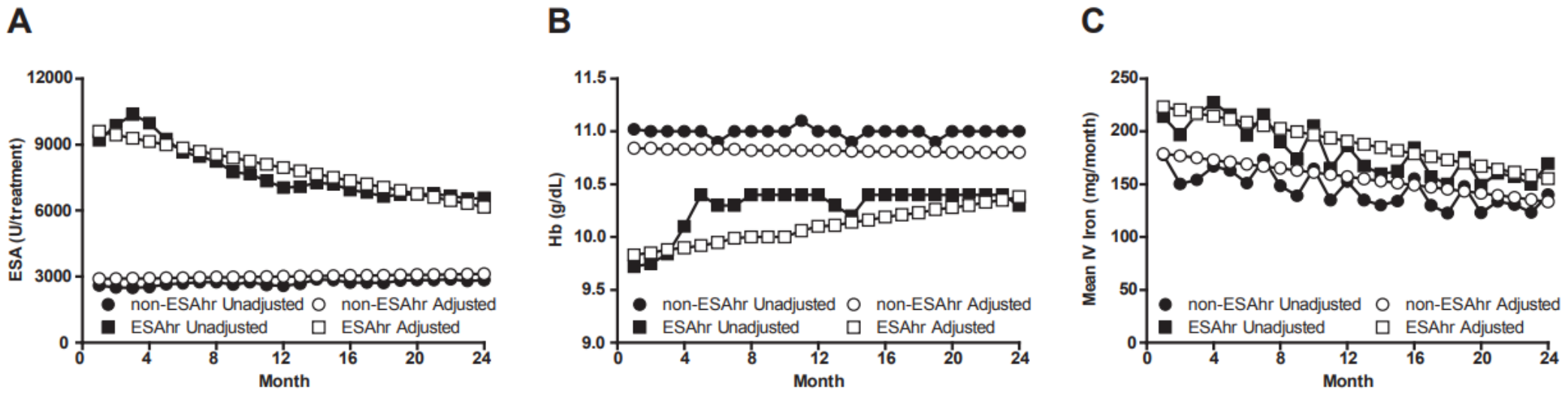
ESA Hyporesponsiveness



Over time, there was a decrease in ESA and iv iron dose and an increase in Hgb in the Hyporesponsive Group

Am J Kidney Dis 2016; 68:763-771

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ESA Hyporesponsiveness

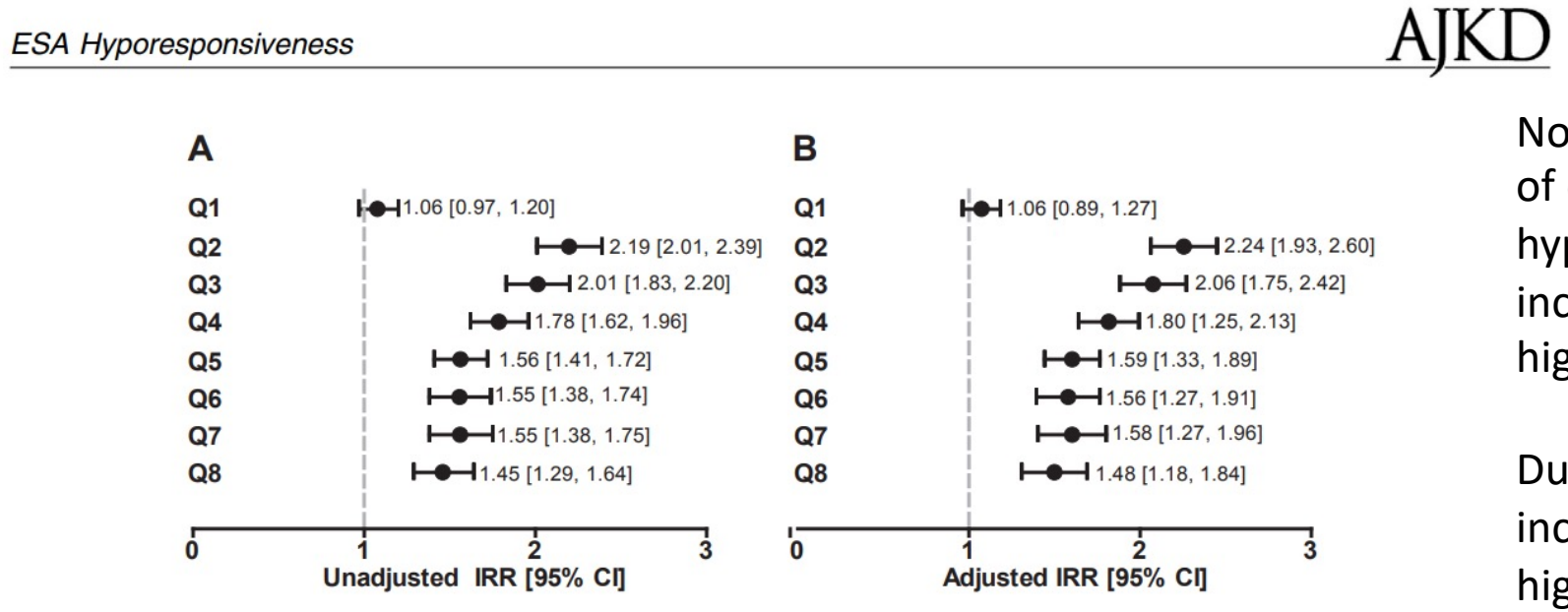

Figure 3. Quarterly mortality incidence rate ratios (IRRs) during follow-up for patients with versus without erythropoiesis-stimulating agent hyporesponsiveness at baseline. Shown are the (A) unadjusted and (B) adjusted IRRs with 95% confidence intervals (CIs). Mortality rates, estimated using general estimating equation Poisson models with exchangeable correlation structure, were adjusted for differences at baseline in age, sex, cause of end-stage renal disease, dialysis vintage, vascular access, cancer, cerebrovascular disease, heart failure, chronic obstructive pulmonary disease, coronary artery disease, gastrointestinal bleeding, human immunodeficiency virus/AIDS, peripheral vascular disease, intravenous (IV) antibiotic use, dry weight, serum ferritin level, saturated transferrin, parathyroid hormone level, albumin level, IV vitamin D use, and Charlson Comorbidity Index score. The interaction between exposure and quarter was significant, $P < 0.001$. In determining all IRRs, ESA non-hyporesponsiveness rates served as the referent.

Am J Kidney Dis 2016; 68:763-771

No difference incidence of death (hypo vs non-hypo) in Q1, but incidence was 2+ times higher in Q2-Q3.

During Q4-Q8, death incidence was 1.5 times higher.

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Risk Factors for ESA Hyporesponsiveness

Table 2. Summary of OR and *p* values from final logistic regression model for predictors of baseline ESA hyporesponder status – using the primary definition of ESA hyporesponsiveness

Parameter Level	OR (95% CI)[1]	Parameter *p* value	Level *p* value
Region		<0.0001	
Region: EMEA versus NAm	0.32 (0.23–0.44)		<0.0001
Region: LA versus NAm	1.81 (1.30–2.51)		0.0004
Region: APAC versus NAm	0.99 (0.68–1.42)		0.9375
Baseline post dialysis BMI, per kg/m^2: lower to higher	0.93 (0.91–0.95)	<0.0001	
Baseline TSAT (per %): lower to higher	0.98 (0.97–0.99)	<0.0001	
Age (per year): younger to older	0.98 (0.97–0.98)	<0.0001	
Baseline albumin, per g/dL: lower to higher	0.41 (0.30–0.56)	<0.0001	
Baseline IV iron dose, per 50 mg/month: lower to higher	1.05 (1.02–1.08)	0.0004	
Sex: female versus male	1.38 (1.08–1.76)	0.0101	
History of heart failure: no versus yes	0.74 (0.56–0.98)	0.0349	
Time since dialysis initiation at screening		0.0770	
Time since dialysis initiation at screening: <2 years versus ≥5 years	0.71 (0.52–0.97)		0.0311
Time since dialysis initiation at screening: 2-<5 years versus ≥5 years	0.95 (0.72–1.26)		0.7120
Smoking status: current versus not current	0.76 (0.47–1.21)	0.2468	
Aspirin use at randomization: no versus yes	0.81 (0.62–1.06)	0.1206	
ACEi/ARB use at randomization: no versus yes	0.86 (0.67–1.09)	0.2143	

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; APAC, Asia Pacific; BMI, body mass index; CI, confidence interval; EMEA, Europe, Middle East, Africa; ESA, erythropoiesis-stimulating agent; IV, intravenous; LA, Latin America; NAm, North America; OR, odds ratio; TSAT, transferrin saturation. [1]The odds ratios describe the direction of the relationship between the variable and hyporesponsive status, given the other variables in the final model are held constant.

ESA hyporesponsiveness associated with

- Lower BMI
- Lower tsat (%)
- Younger age
- Lower serum albumin
- Higher iv iron dose
- Female gender
- Shorter dialysis vintage

Am J Nephrol 2023;54:1–13

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ESA Hyporesponsiveness and Iron Deficiency

Anemia parameter	Normal ERI		High ERI	
	Persistently low Hb: no	Persistently low Hb: yes	Persistently low Hb: no	Persistent low Hb: ye
1-month intervals				
Patient-mo (%)	68.7%	15.1%	8.1%	8.1%
Medications				
ESA dose (IU/mo)	18,000	26,000	94,000	99,000
IV iron dose (mg/mo)	50	50	100	100
Biochemistry				
Hemoglobin (g/dl)	11.0	9.5	10.7	9.1
Ferritin (ng/ml)	922	948	880	893
Transferrin saturation (%)	30.5	30.3	26.5	25.8
ERI (IU/wk/kg/g/dl)	4.6	8.3	27.2	32.4

Anemia parameter	Normal ERI		High ERI	
	Persistently low Hb: no	Persistently low Hb: yes	Persistently low Hb: no	Persistently low Hb: yes
3-month intervals				
Patient-months (%)	82.1%	3.1%	11.1%	3.7%
Medications				
ESA dose (IU/mo)	21,667	33,333	85,467	102,500
IV iron dose (mg/mo)	67	67	100	100
Biochemistry				
Hemoglobin (g/dl)	10.8	9.1	10.2	8.7
Ferritin (ng/ml)	929	911	873	856
Transferrin saturation (%)	30.7	28.2	25.7	23.6
ERI (IU/week/kg/g/dl)	5.9	10.7	26.6	34.3

Anemia parameter	Normal ERI		High ERI	
	Persistently low Hb: no	Persistently low Hb: yes	Persistently low Hb: no	Persistently low Hb: yes
6-month intervals				
Patient-months (%)	85.4%	0.6%	12.3%	1.7%
Medications				
ESA dose (IU/mo)	23,433	38,667	83,633	109,533
IV iron dose (mg/mo)	73	100	100	100
Biochemistry				
Hemoglobin (g/dl)	10.7	8.8	10.1	8.5
Ferritin (ng/ml)	930	803	860	822
Transferrin saturation (%)	30.7	25.0	25.2	22.3
ERI (IU/week/kg/g/dl)	6.4	12.2	26.5	37.0

In any month, 23% of patients have persistently low Hgb levels (Normal ERI > High ERI)

However, less than 7% of 3-month intervals had persistently low Hgb levels (Normal ERI ≈ High ERI)

Less than 3% of 6-month intervals had persistently low Hgb levels (Normal ERI < High ERI)

Median tsat and ferritin were 22% and 822 ng/ml in High/low Hgb category but received similar iv iron dose

Kidney Int Rep 2023; 8:2616-2624

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ESA Hyporesponsiveness and Iron Utilization

Laboratorial Parameters	Population (n=21)	LIC	
	Median [IQR]	Normal (n=9)	Increased (n=12)
Hb (g/dl)	9.8 [8.5-11.4]	12.1 [10.5-13.5]*	8.8 [8.3-9.8]
Ferritin (ng/ml)	494 [136-851]	110 [88-262]*	717 [253-1240]
TSAT (%) n=16	19.9 [13.3-26.0]	13.6 [10.0-26.8]*	23.2 [19.8-38.1]
iPTH (pg/ml) n=20	224 [115-480]	352 [248-531]	208 [123-303]
Albumin (g/dl)	3.3 [3.1-3.7]	3.5 [3.3-3.8]	3.3 [2.7-3.6]
C-reactive protein (mg/dl), n=20	1.7 [0.7-9.4]	1.2 [0.7-2.8]	1.2 [0.1-13.7]
WBC ($x10^9$/L)	9.5 [7.4-15.4]	10.6 [7.7-15.1]	10.7 [7.7-16.5]
Anaemia Therapy			
IV Iron 6 months (mg)	800 [300-1250]	800 [450-1250]	700 [125-1475]
IV Iron 12 months (mg)	1500 [650-2175]	1300 [450-1920]	1600 [875-2737]
EPO (IU/week)	5000 [3000-9000]	2000 [1050-6500]	6000 [4000-13500]
ERI	9.6 [4.2-16.6]	3.3 [1.7-11.7]	14.9 [6.6-21.9]*

Autopsy study showing lower Hgb levels in patients with increased liver content.

ERI levels higher with increased liver iron content despite similar iv iron administration

eBioMedicine 2022;77: 103921

Inflammation and Hyporesponsiveness

- Causes of inflammation
  - Chronic infections
    - Make sure to check the feet and teeth!
  - HD catheters and old AV grafts
  - Failed kidney transplant
  - Malnutrition

Inflammation and Hyporesponsiveness

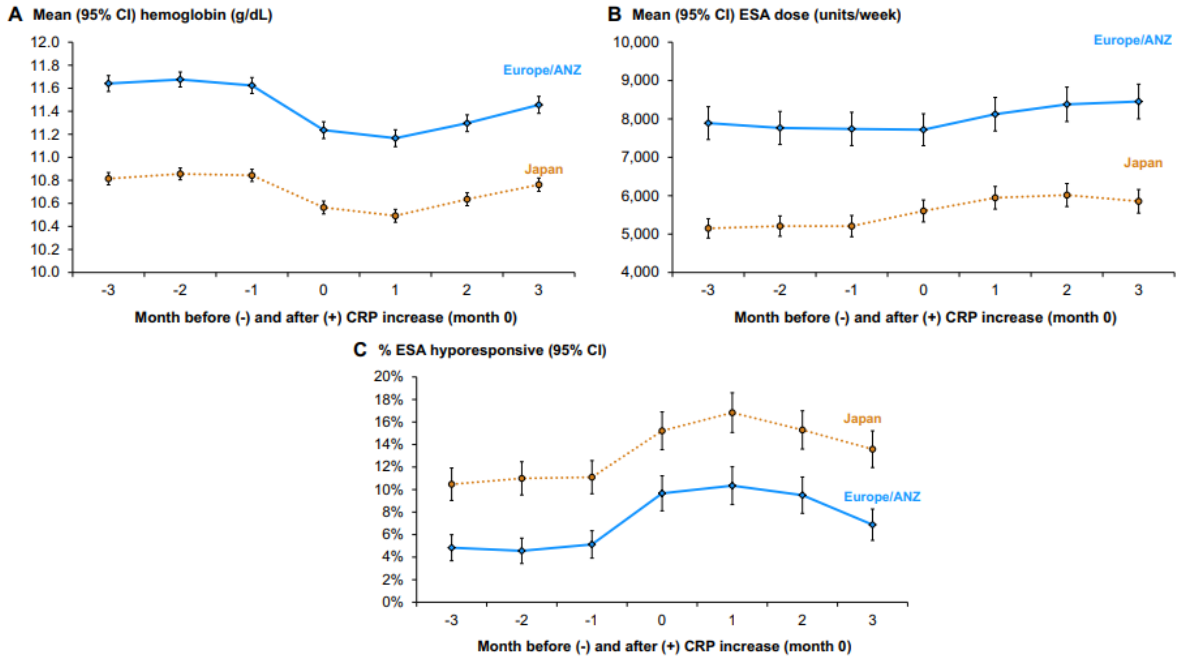


Figure 4. (A) Mean monthly hemoglobin level, (B) mean monthly erythropoiesis-stimulating agent (ESA) dose, and (C) percent ESA hyporesponsive in the 3 months before and after a C-reactive protein (CRP) level increase from ≤5 to >10 mg/L, by region. Mean hemoglobin level and ESA dose were calculated as the average across all patients at each time point. Months during which ESA was not prescribed are considered 0 U/wk. ESA hyporesponsive defined as hemoglobin level <10 g/dL and ESA dose > 6,000 (Japan) or >8,000 (Europe/ANZ) U/wk. Abbreviations: ANZ, Australia/New Zealand; CI, confidence interval.

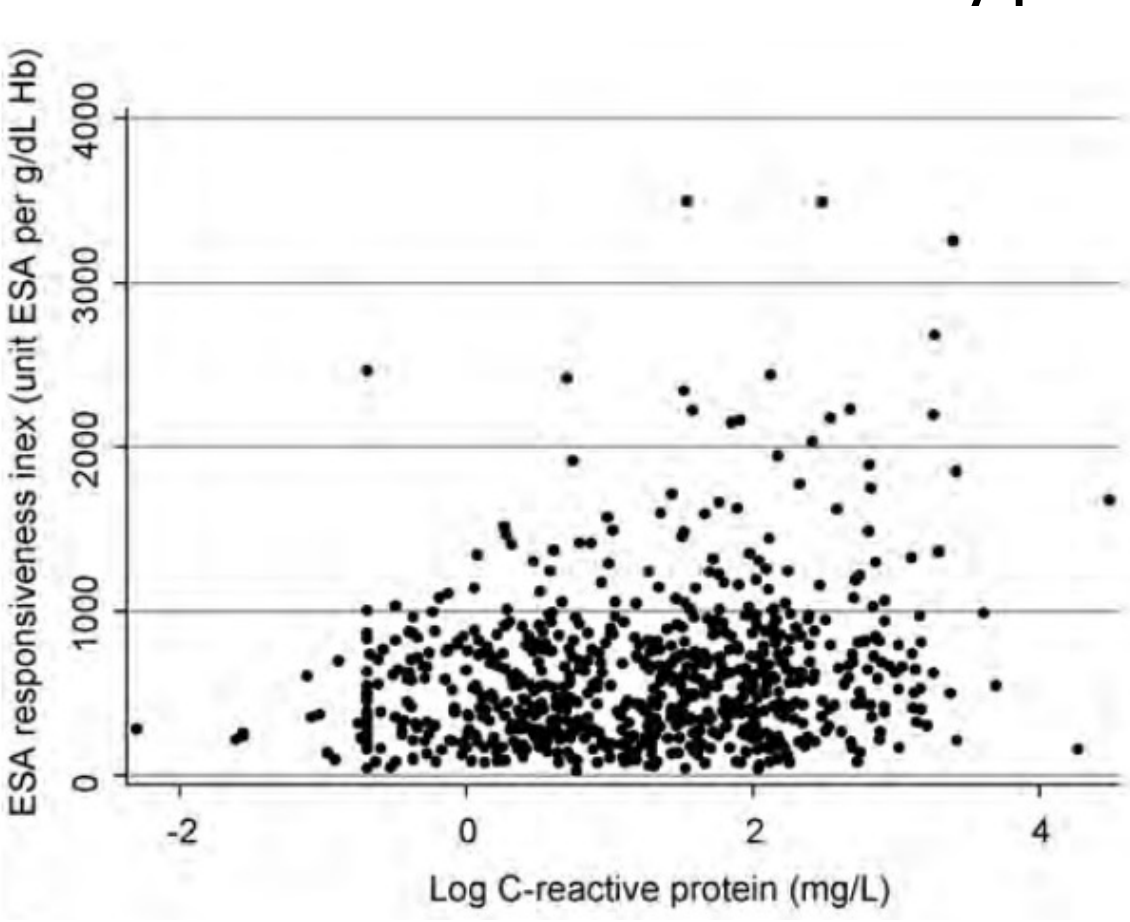
Kidney Med 2020; 2:286-296

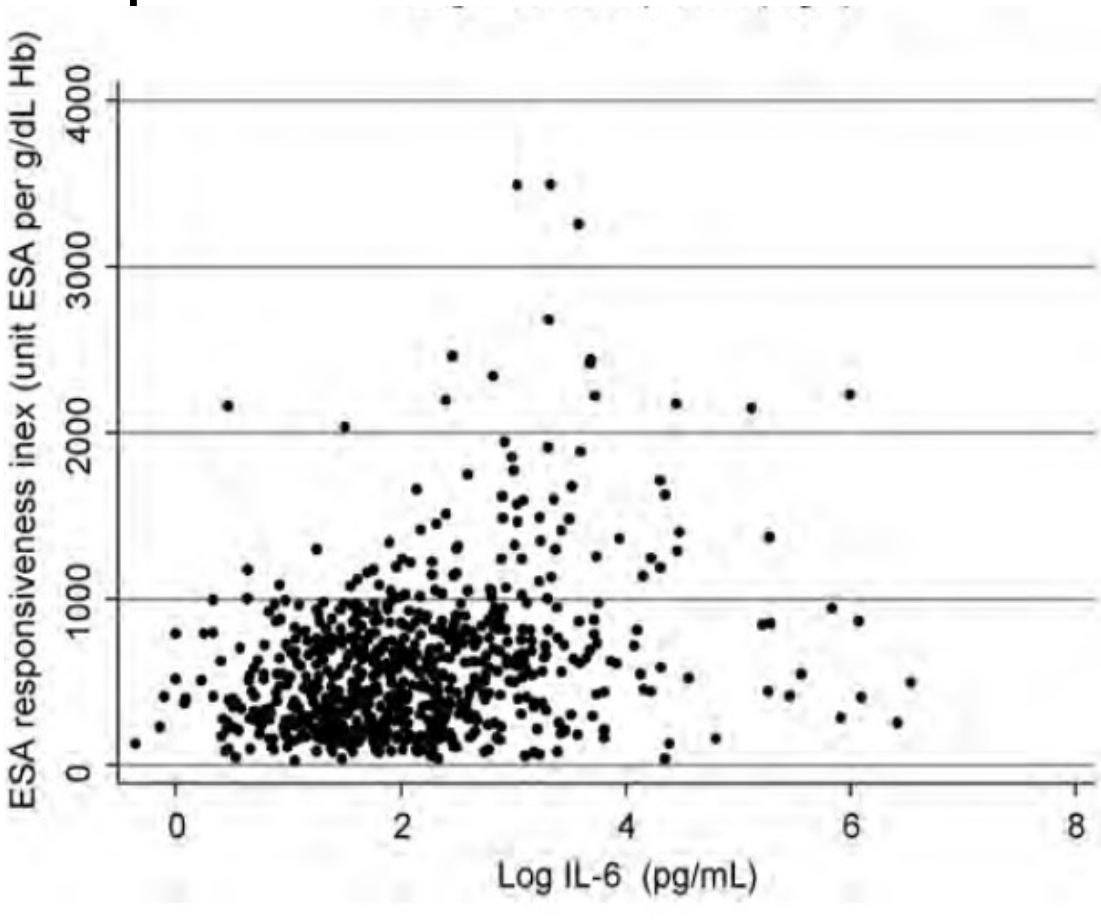
<u>DOPPS</u>

Rise in CRP associated with transient drop in Hgb accompanied by an increase in ESA dose.

Hgb drop in Japan (~0.2 g/dL) was less than drop in Eur/ANZ (~0.5 g/dL) perhaps due earlier increase in ESA dose in Japan. Japan also had greater relative increase in ESA dose (10.8% vs 5.2%)

Inflammation and Hyporesponsiveness





Nephrol Dial Transplant 2013; 28: 1936–1945

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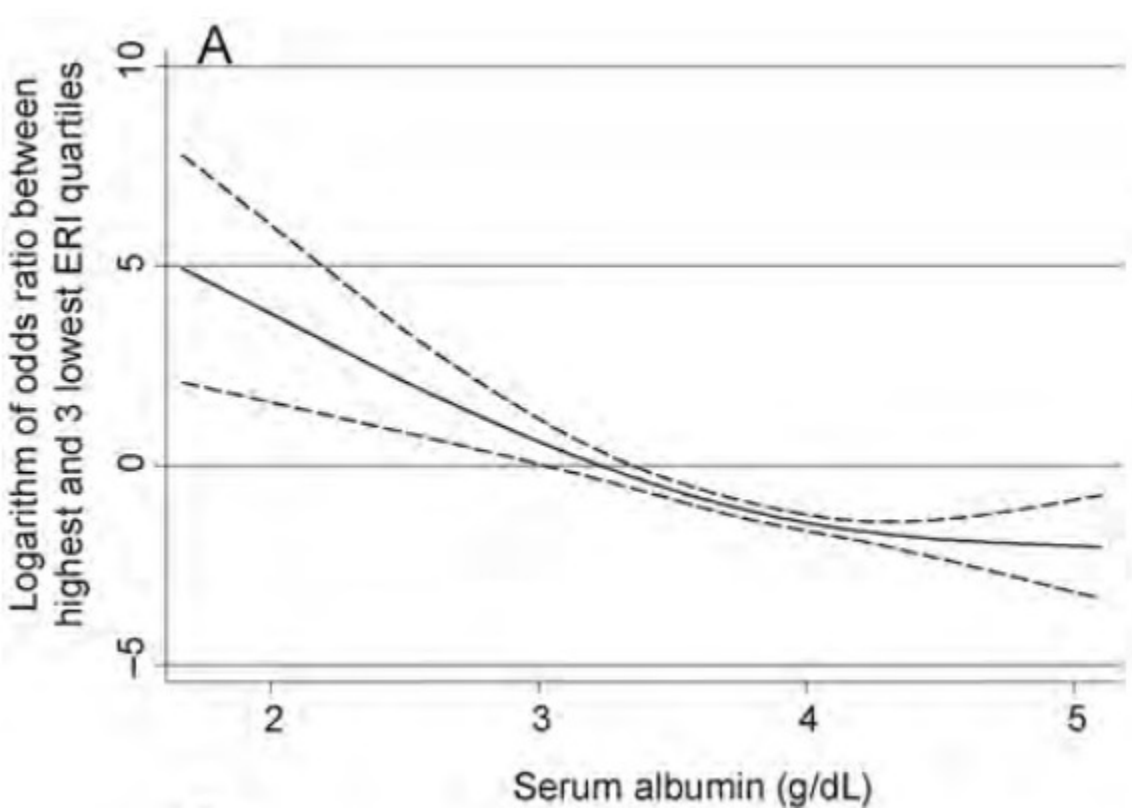
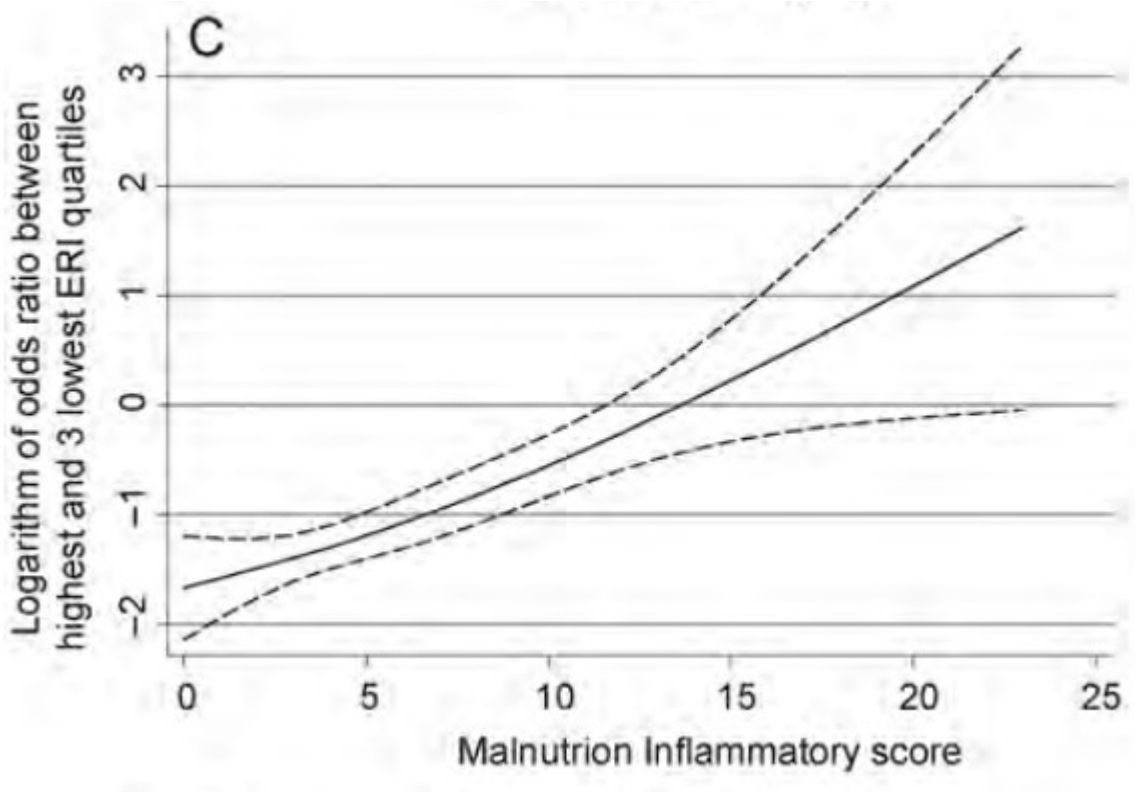




Nephrol Dial Transplant 2013; 28: 1936–1945

Failed Kidney Transplant

Table 1. Baseline demographic, clinical, and laboratory data of group A and group B[a]

	Group A	Group B
N	43	121
Age (yr)	48.6 ± 14.6[b]	62.9 ± 13.8
Gender (% male)	55.8	63.2
Cause of chronic renal failure	GN (32.5%), DN (14%), CIN (11.6%), APCD (20.9%)	GN (22.6%), DN (19.5%), CIN (20.3%), APCD (16.5%)
Hb (g/dl)	10.4 ± 1.9[b]	12.7 ± 1.4
rHu-EPO dose (U/wk)	8862 ± 3924[b]	6380 ± 3706
ERI (U/kg per wk per g/dl)	16.1 ± 9.0[b]	8.3 ± 5.5
Ferritin (μg/L)	469 ± 382[NS]	412 ± 320
TSI (%)	26.7 ± 10.7[NS]	34.5 ± 15
Albumin (g/dl)	3.2 ± 0.6[b]	3.8 ± 0.4
Prealbumin (mg/dl)	25.3 ± 12.1[b]	32.3 ± 7.8
Cholesterol (mg/dl)	181.3 ± 42.7[NS]	191.4 ± 39.5
CRP (mg/dl)	4.1 ± 4.7[b]	1.3 ± 1.9
iPTH (pg/ml)	258.3 ± 271.3[c]	386 ± 400

[a] Data from group A were obtained within 1 wk before transplant nephrectomy. Data are mean ± SD. GN, glomerulonephritis; DN, diabetic nephropathy; CIN, chronic interstitial nephropathy; APCD, adult polycystic disease; Hb, hemoglobin; ERI, erythropoietin resistance index; TSI, transferring saturation index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; iPTH, intact parathyroid hormone; NS, no significance.

Significance between groups A and B at baseline: [b] $P < 0.001$;

[c] $P < 0.05$.

J Am Soc Nephrol 2004; 15:2494-2501

Failed Kidney Transplant

Group A1 – Failed Kidney Transplant Patients With Symptoms and Recommendations for Transplant Nephrectomy

Table 2. Baseline demographic, clinical, and laboratory data of group A1 and group A2[a]

	Group A1 Transplant Nephrectomy Done	Group A2 Transplant Nephrectomy not Done
N	29	14
Age (yr)	43.8 ± 13.0[b]	59.6 ± 12.3
Gender (% male)	58.7	50
Hb (g/dl)	9.8 ± 1.8[b]	11.6 ± 1.5
rHu-EPO dose (U/wk)	8448 ± 2599[NS]	9954 ± 6270
ERI (U/kg per wk per g/dl)	16.5 ± 7.9[NS]	15.1 ± 11.8
Ferritin (μg/L)	594 ± 400[c]	272 ± 259
TSI (%)	23.5 ± 8.0[NS]	30.5 ± 12.4
Albumin (g/dl)	3.1 ± 0.7[NS]	3.4 ± 0.4
Prealbumin (mg/dl)	26.0 ± 13.5[NS]	24.3 ± 10.6
CRP (mg/dl)	6.6 ± 5.2[c]	3.1 ± 4.2
Fibrinogen (mg/dl)	535.3 ± 218.6[NS]	502.3 ± 196.6
ESR (mm/h)	88.4 ± 40.4[c]	48.1 ± 28.7
iPTH (pg/ml)	234.9 ± 250.2[NS]	285 ± 302.9

[a] Data are mean ± SD. ESR, erythrocyte sedimentation rate.

Significance between group A1 and group A2 patients at baseline: [b] $P < 0.01$; [c] $P < 0.05$.

J Am Soc Nephrol 2004; 15:2494-2501

Failed Kidney Transplant – Transplant Nephrectomy

Table 3. Baseline and follow-up laboratory data of group A1[a]

	Baseline	+3 Months	+6 Months
Hb (g/dl)	9.8 ± 1.8	12.2 ± 2.0[b]	12.7 ± 1.1[b]
rHu-EPO dose (U/wk)	8448 ± 2599	7655 ± 2525[NS]	6925 ± 3173[NS]
ERI (U/kg per wk per g/dl)	16.5 ± 7.9	12.4 ± 5.9[b]	9.9 ± 5.5[b]
Ferritin (μg/L)	594.3 ± 400.7	365.2 ± 343.1[NS]	356.7 ± 268.6[e]
TSI (%)	23.5 ± 8.0	39.5 ± 19.8[c]	37.9 ± 14.3[b]
Albumin (g/dl)	3.1 ± 0.7	3.8 ± 0.6[b]	3.9 ± 0.6[b]
Prealbumin (mg/dl)	26.0 ± 13.5	29.6 ± 8.2[NS]	30.8 ± 8.6[d]
CRP (mg/dl)	6.6 ± 5.2	1.3 ± 1.0[d]	0.9 ± 0.5[d]
Fibrinogen (mg/dl)	535.3 ± 218.6	354.8 ± 65.5[NS]	400.2 ± 107.9[b]
ESR (mm first h)	88.4 ± 40.4	35.9 ± 22.8[d]	29.2 ± 14.4[d]
iPTH (pg/ml)	234.9 ± 250.2	379.4 ± 504.0[NS]	526.4 ± 630.3[NS]

[a] Follow-up data were obtained at 3 and 6 mo after transplant nephrectomy. Data are mean ± SD.
Significance with respect to baseline: [b] $P < 0.001$;
[c] $P < 0.005$;
[d] $P < 0.01$;
[e] $P < 0.05$.

J Am Soc Nephrol 2004; 15:2494-2501

Failed Kidney Transplant – Transplant Nephrectomy

Table 5. Comparison of hematologic and biochemical data between group A1 and group A2 at 6 mo of follow-up[a]

	Group A1 Transplant Nephrectomy Done	Group A2 Transplant Nephrectomy not Done
N	29	14
Hb (g/dl)	12.7 ± 1.1[c]	10.9 ± 1.4[c]
rHu-EPO dose (U/wk)	6925 ± 3173[c]	12714 ± 8693[c]
ERI (U/kg per wk per g/dl)	9.9 ± 5.5[c]	20.2 ± 12.3[c]
Ferritin (µg/L)	356.7 ± 268.6[NS]	235 ± 119[NS]
TSI (%)	37.9 ± 14.3[NS]	38.7 ± 18.1[NS]
Albumin (g/dl)	3.9 ± 0.6[b]	3.3 ± 0.4[b]
Prealbumin (mg/dl)	30.8 ± 8.6[c]	27.6 ± 7.9[c]
CRP (mg/dl)	0.9 ± 0.5[b]	3.6 ± 6.0[b]

[a] Data are mean ± SD.

Significance between group A1 and group A2: [b] $P < 0.001$;

[c] $P < 0.005$.

J Am Soc Nephrol 2004; 15:2494-2501

Anti-Inflammatory Agents and Hyporesponsiveness - Statins

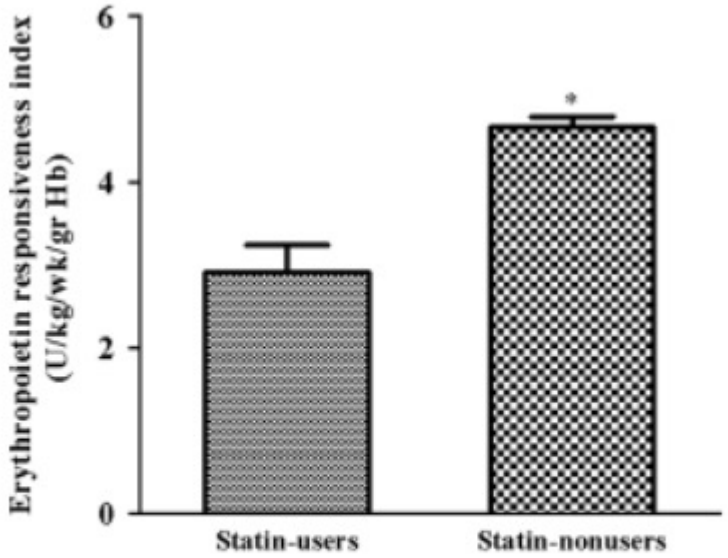


Figure 2 Erythropoietin responsiveness index of statin users and statin nonusers during follow-up. (*P<0.0001).

Hemodial Int 2011; 15:366-373

Table 2.

a Association between statin prescription and subsequent ESA hyporesponsiveness by increasing levels of adjustment

Outcome	Statin Rx	Number of patients	Number of events, *n* (%)	OR (95% CI)			
				model 1[b]	model 2[c]	model 3[d]	model 4[e]
Hgb <10 g/dL	+	585	66 (11.3)	0.88 (0.67–1.13)	0.86 (0.65–1.14)	0.85 (0.64–1.13)	0.87 (0.66–1.15)
ESA dose[a] >6,000 units/week	–	3,017	394 (13.1)				

ESA, erythropoiesis-stimulating agent; Hgb, hemoglobin.
[a] Mircera doses were converted to darbepoetin doses using a 1.2:1 ratio, and darbepoetin doses were converted to epoetin doses using a 250:1 ratio.
[b] Model 1: adjusted for DOPPS phase and accounting for facility clustering.
[c] Model 2: adjusted for model 1+ age, gender, vintage, 11 summary comorbidities and post dialysis weight.
[d] Model 3: adjusted for model 2+ Kt/V, treatment time, hospitalization in past 3 months.
[e] Model 4: adjusted for model 3+ CRP, albumin, TSAT, ferritin.

Am J Nephrol 2017; 46:11-17

Anti-inflammatory Agents And Hyporesponsiveness - Pentoxyfylline

Table 2. Primary and Secondary Outcomes at 4 Months by Treatment Group

Outcome	Control (n = 27)	Pentoxifylline (n = 26)	Difference[a] (95% CI)	*P*
ERI (IU/kg/wk/g/L)[b]	2.60	2.21	−0.39 (−0.89 to 0.10)	0.1
Hemoglobin (g/L)	103.2	110.9	7.6 (1.7 to 13.5)	0.01
ESA dose (IU/kg/wk)[b]	261.2	240.4	−20.8 (−67.2 to 25.7)	0.4
Serum ferritin (μg/L)	543	471	−72 (−215 to 72)	0.3
Serum transferrin saturation (%)	24.5	25.7	1.2 (−3.9 to 6.2)	0.7

Note: Outcomes adjusted for baseline values.

Abbreviations: CI, confidence interval; ERI, erythropoiesis-stimulating agent resistance index; ESA, erythropoiesis-stimulating agent.

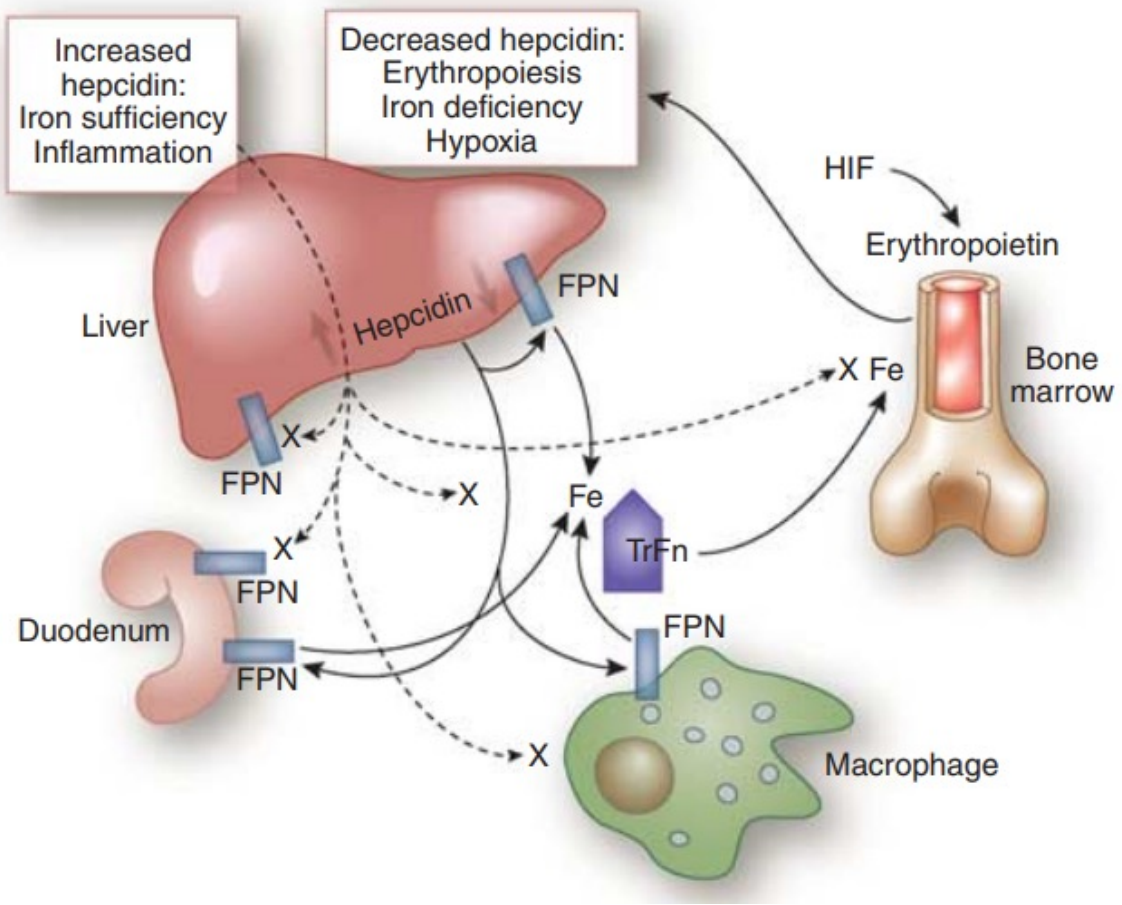
[a]Difference = pentoxifylline − control.

[b]Patients on darbepoetin therapy were converted to an erythropoietin-equivalent dose using a conversion factor of 200:1.

Mild improvement in Hgb with pentoxifylline but entry criteria initially included those with Hgb ≤ 11 g/dL and later ≤ 12 g/dL.

Am J Kidney Dis. 2015;65(1):49-57

Hepcidin and Inflammation



Hepcidin induces the degradation of ferroportin resulting lower iron levels in the blood and increased storage of iron

- Low transferrin saturation
- High ferritin

Inducers of hepcidin

- Inflammation (eg IL-6)
- Iron sufficiency

Inhibitors of hepcidin

- Iron deficiency
- Erythropoiesis
- Hypoxia

Kidney Int 2011; 80: 240-244

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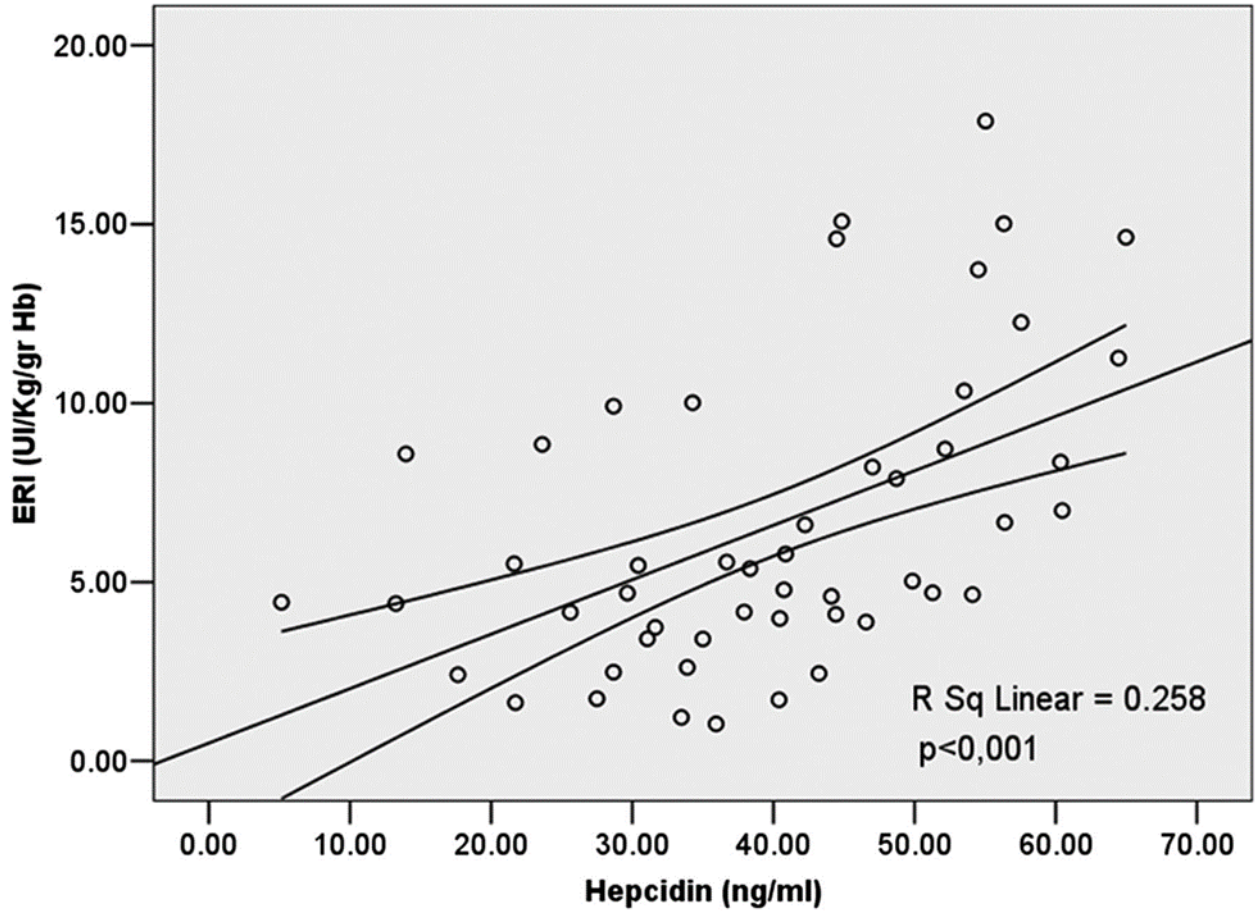
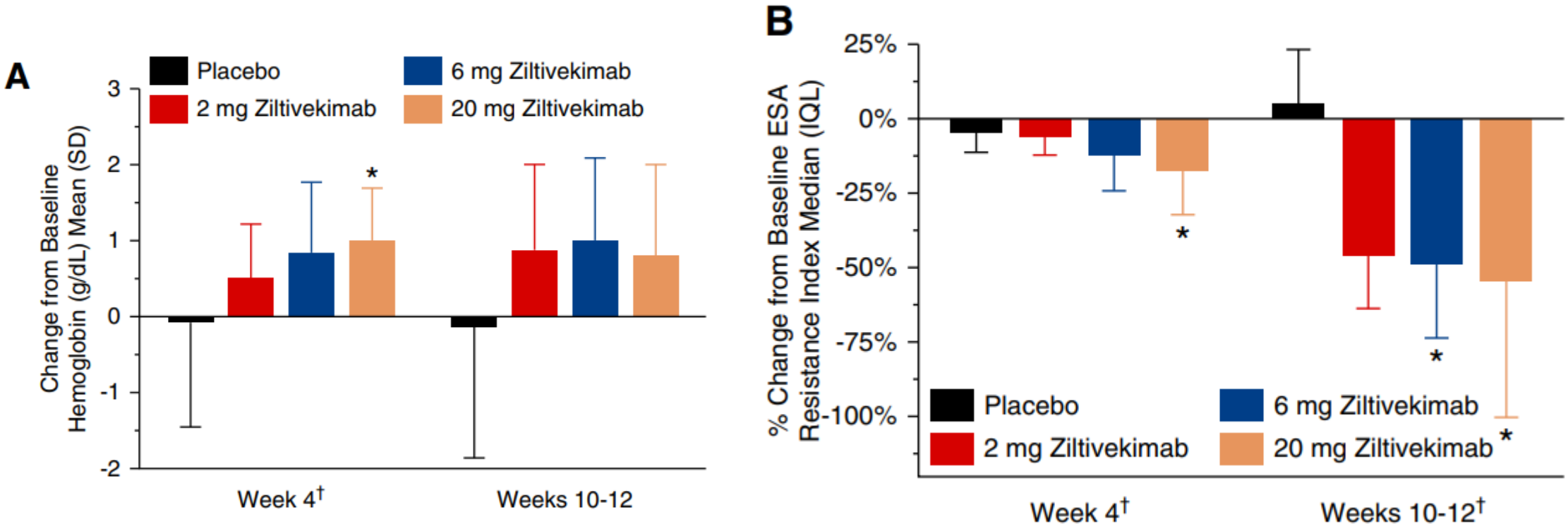
Hepcidin and Hyporesponsiveness



Nephrol Dial Transplant 2015; 30: 682-689

Ziltivekimab (monoclonal antibody against IL-6 ligand)



ESKD patients included in trial had elevated IL-6 levels and genetic susceptibility to enhanced IL-6 mediated hepcidin expression

J Am Soc Nephrol 2021; 32: 211-222

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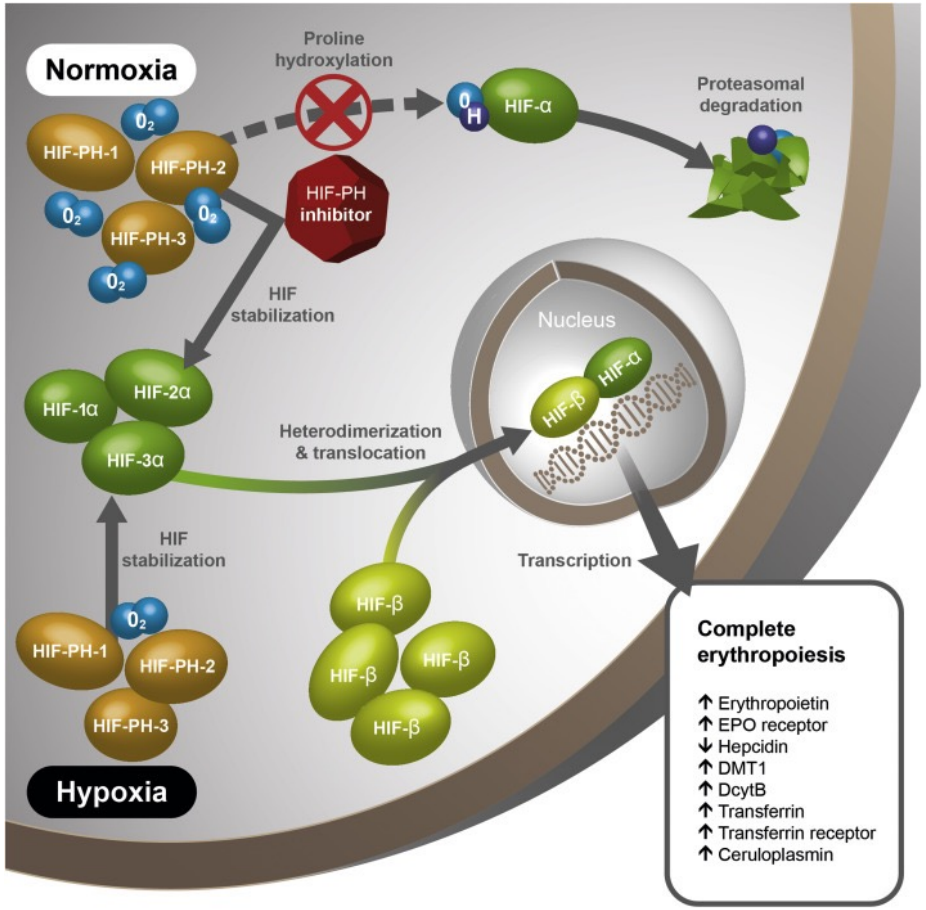
Hypoxia Inducible Factor



In states of normoxia (ie no hypoxia), HIF-α is hydroxylated and degraded.

Hydroxylated enzymes require oxygen and in states of hypoxemia, HIF-α is NOT degraded and forms heterodimer with HIF-β and translocates to the nucleus resulting in

- Increased EPO
- Decreased hepcidin
- Increased iron absorption (DMT1 and CytB)

HIF-PH inhibitors prevent hydroxylation and degradation of HIF-α

Am J Kidney Disease 2017; 69:815-826

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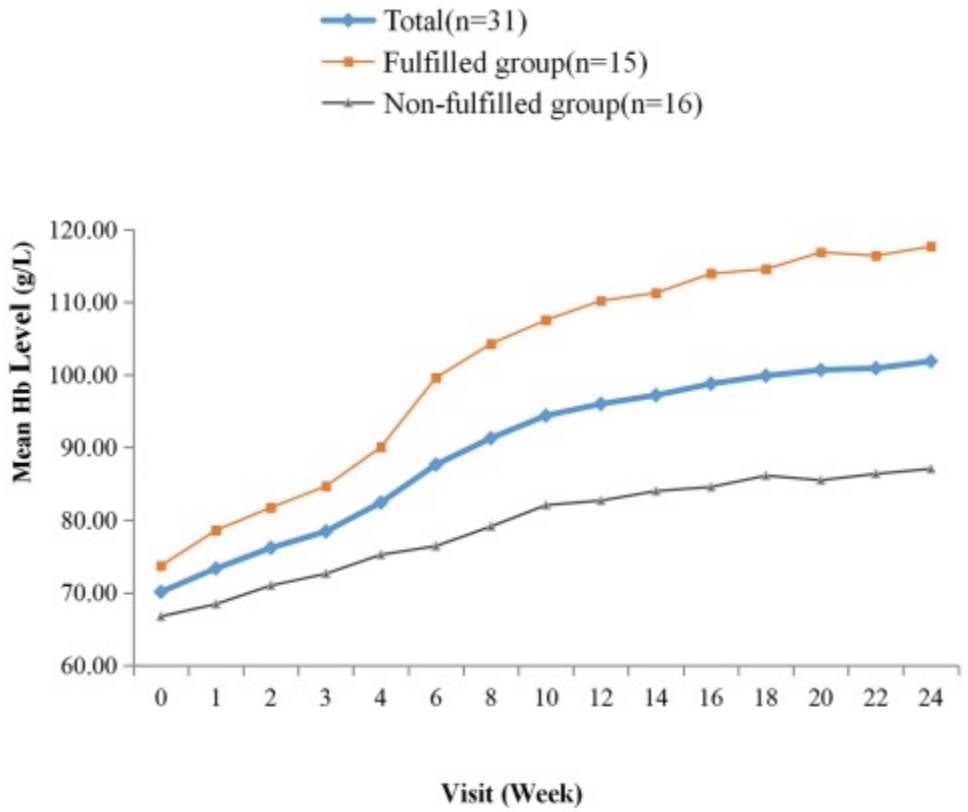
HIF-PH inhibitor in ESA Hyporesponsiveness

Fig. 2 The mean Hb level curves of the patients



Fulfilled = Achieved Hgb target of 10-12 g/dL (100-120 g/L)

Non-fulfilled = Did not reach target

Intern Emerg Med 2021; 16: 2193-2199

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HIF-PH inhibitor in ESA Hyporesponsiveness

Table 4 Baseline characteristics of fulfilled group and non-fulfilled group

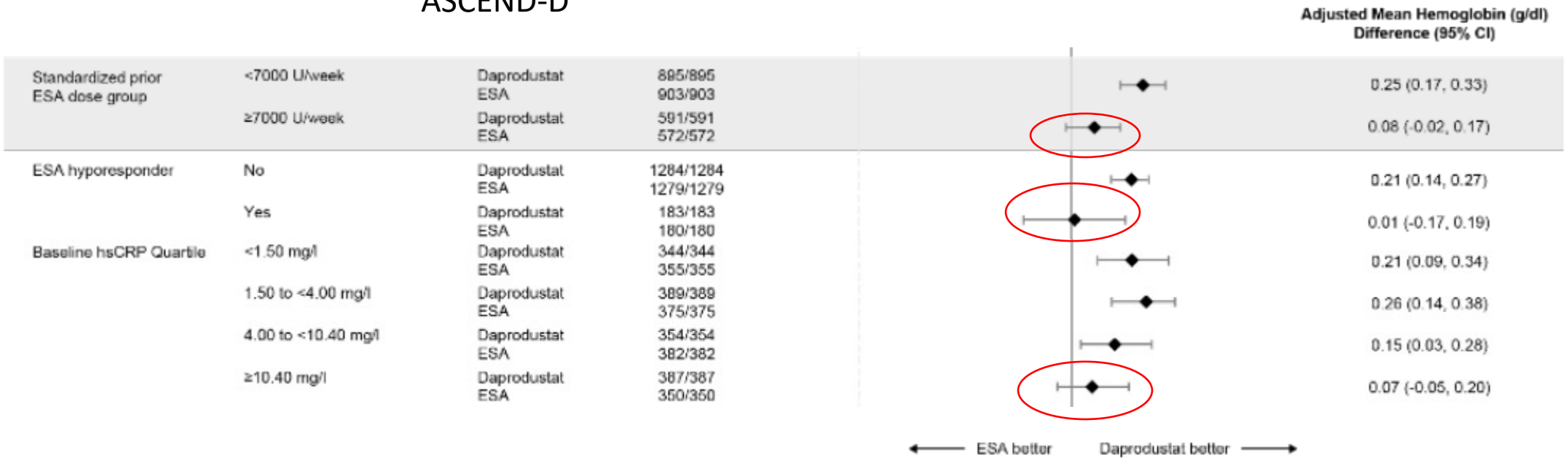
Parameter	Fulfilled ($n=15$)	Non-fulfilled ($n=16$)	Z/t value	P value
Age (years)	54.69 ± 15.92	55.93 ± 16.25	− 0.216	0.831
BMI (kg/m^2)	22.34 ± 4.75	20.86 ± 3.90	0.945	0.352
Duration of dialysis (months)	13.00 (6.25, 55.75)	24.00 (6.00, 73.00)	− 0.718	0.473
HsCRP (mg/L)	1.48 (0.50, 3.28)	13.70 (3.64, 35.52)	− 3.273	**0.001**
IL-6 (pg/ml)	9.76 (4.94, 12.08)	17.43 (12.10, 31.63)	− 3.044	**0.002**
PCT (ng/ml)	0.71 (0.13, 1.24)	0.92 (0.37, 3.28)	− 1.404	0.160
Albumin (g/L)	37.36 ± 2.43	31.34 ± 3.30	5.811	**< 0.001**
Cholesterol (mmol/L)	3.88 ± 0.85	3.41 ± 0.74	1.628	0.114
Triglyceride (mmol/L)	1.69 ± 0.74	1.55 ± 0.58	0.606	0.550
RRF (ml/min/1.73mm^2)	8.19 ± 1.99	4.63 ± 1.83	5.175	**< 0.001**
Iron (μmol/L)	20.06 (17.13, 25.03)	16.64 (14.20, 18.26)	2.589	**0.010**
Transferrin (g/L)	2.29 ± 0.63	1.80 ± 0.59	2.256	**0.032**
TIBC (μmol/L)	53.30 (49.35, 59.30)	43.60 (42.00, 50.73)	2.510	**0.012**
TSAT (%)	39.77 ± 1.90	34.27 ± 7.63	1.637	0.112
SF (ng/ml)	62.30 (28.68, 99.21)	368.37 (200.47, 630.17)	− 4.428	**< 0.001**
EPO (mIU/ml)	45.30 (13.75, 78.83)	46.50 (21.30, 124.65)	− 0.791	0.429

Test results outside the normal range are shown in bold

Intern Emerg Med 2021; 16: 2193-2199

HIF-PH inhibitor vs ESA

ASCEND-D



Similar change in Hgb levels with HIF-PH inh vs ESA among

- Those with higher baseline ESA dose
- Those labeled as ESA hyporesponder
- Those in the highest hsCRP quartile

New Engl J Med 2021; 385: 2325-2335

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HIF-PH inhibitor vs ESA

Baseline responsiveness to ESA led to different patterns of anemia management for Dapro vs ESA, with evidence of lower IV iron utilization with Dapro in those who were ESA hyporesponsive at baseline.

	Hyporesponsive at baseline		Not hyporesponsive at baseline	
	Daprodustat	ESA	Daprodustat	ESA
Number, n/N (%)	183/1487 (12)	180/1477 (12)	1285/1487 (86)	1279/1477 (87)
Baseline Hb, g/dL	9.89	9.99	10.40	10.44
Median dose of study drug, wk 48				
Daprodustat, mg	10.0	-	6.0	-
Epoetin alfa, U	-	15000	-	6000
Darbepoetin, µg	-	200	-	150
RBC transfusions, units/100 PY	97.6	78.9	31.9	41.7
No. requiring rescue leading to discontinuation, n/N (%)	14/183 (7.7)	5/180 (2.8)	39/1284 (3.0)	48/1279 (3.8)
Change in Hb from baseline to wks 28–52				
No. with baseline and evaluation period Hb*	183	180	1284	1279
Adjusted mean change from baseline (SE)†	0.11 (0.065)	0.11 (0.068)	0.31 (0.024)	0.11 (0.024)
Adjusted mean treatment difference (two-sided CI)†	0.01 (-0.17, 0.19)		0.21 (0.14, 0.27)	
p-value‡	0.04			
On-treatment average monthly IV iron dose during day 1 to wk 52				
No. on randomized treatment n/N (%)	183/183 (100)	178/180 (99)	1279/1284 (>99)	1276/1279 (>99)
Adjusted mean IV iron dose, mg (SE)§	111.4 (9.59)	143.1 (9.72)	88.1 (3.59)	95.0 (3.60)
Adjusted mean treatment difference (two-sided 95% CI)§	-31.7 (-58.2, -5.2)		6.9 (-16.8, 3.1)	
p-value‡	0.09			

*Includes both observed and imputed values; †Based on an analysis of covariance model with terms for treatment, baseline hemoglobin, dialysis type, region, subgroup and treatment by subgroup interaction; ‡Interaction test for heterogeneity of treatment effect across subgroups; §Based on an analysis of covariance model with terms for treatment group, baseline IV iron dose, dialysis type, region, subgroup and treatment by subgroup interaction. P-values are interaction values.
CI, confidence interval; Dapro, daprodustat; ESA, Erythropoiesis-stimulating agents; Hb, hemoglobin; IV, intravenous; PY, patient-years; RBC, red blood cell; SE, standard error; wk, week.

Figure. Summary of Dapro and ESA hyporesponsiveness and anemia management in the ASCEND-D Trial

TH-PO686; ASN Renal Week 2022

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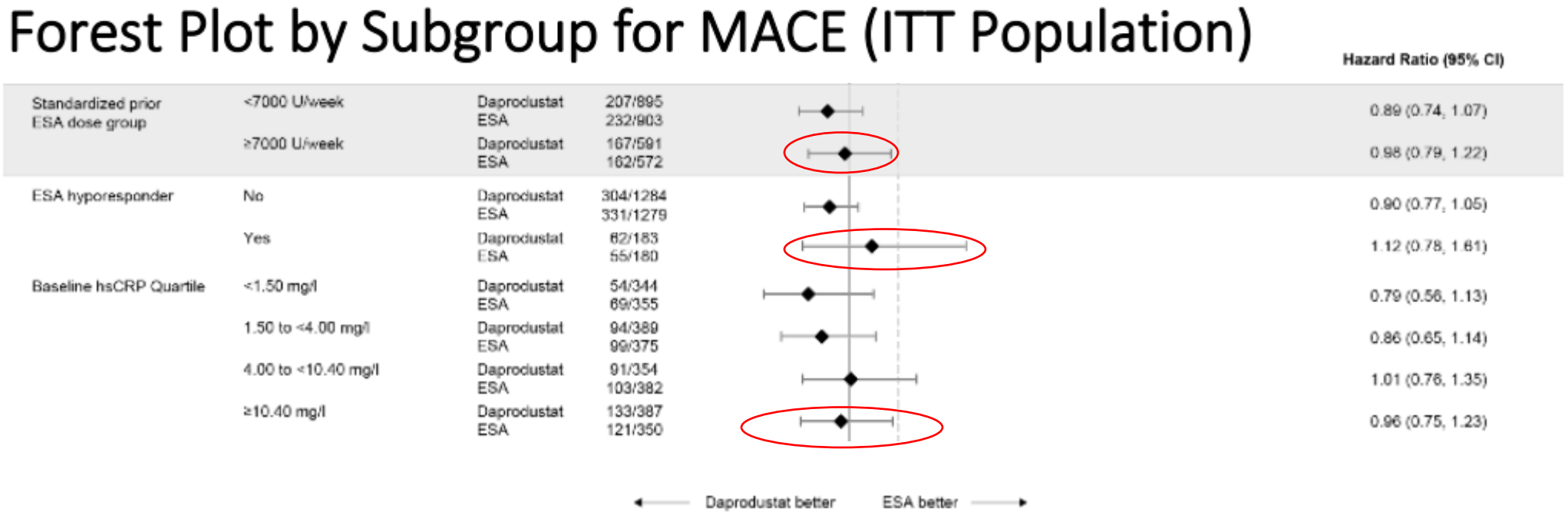
HIF-PH inhibitor vs ESA

ASCEND-D Trial



Cardiovascular events were not increased with ESA among

- Those with higher baseline ESA dose
- Those labeled as ESA hyporesponder
- Those in the highest hsCRP quartile

New Engl J Med 2021; 385: 2325-2335

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Dialysis Adequacy and Hyporesponsiveness

Table S6. The unadjusted and adjusted odds ratios with 95% confidence interval for anemia (hemoglobin level <10 g/dL) and hypoalbuminemia (serum albumin <3.5 g/dL). The group with stdKt/V and SAstdKt/V of 2.00-2.19 were used as reference group.

Categories	Odds ratios (95% confidence interval)							
	Anemia				Hypoalbuminemia			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	stdKt/V	SAstdKt/V	stdKt/V	SAstdKt/V	stdKt/V	SAstdKt/V	stdKt/V	SAstdKt/V
<2.00	**1.78** (1.71-1.86)	**1.95** (1.87-2.04)	**1.63** (1.56-1.71)	**1.70** (1.61-1.79)	**1.24** (1.19-1.29)	**1.20** (1.15-1.26)	**1.33** (1.27-1.38)	**1.23** (1.18-1.29)
2.00-2.19	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
2.20-2.39	**0.52** (0.51-0.54)	**0.63** (0.62-0.65)	**0.66** (0.64-0.68)	**0.79** (0.77-0.81)	**0.59** (0.58-0.60)	**0.62** (0.60-0.63)	**0.58** (0.56-0.59)	**0.62** (0.60-0.63)
2.40-2.59	**0.42** (0.41-0.43)	**0.50** (0.49-0.52)	**0.60** (0.58-0.61)	**0.67** (0.65-0.69)	**0.49** (0.48-0.50)	**0.45** (0.44-0.46)	**0.45** (0.44-0.46)	**0.45** (0.44-0.46)
≥2.60	**0.44** (0.42-0.45)	**0.39** (0.38-0.40)	**0.63** (0.61-0.66)	**0.55** (0.53-0.56)	**0.50** (0.48-0.51)	**0.27** (0.27-0.28)	**0.42** (0.41-0.43)	**0.29** (0.28-0.30)

SAstdKt/V, surface area normalized-standard Kt/V; stdKt/V, standard Kt/V

Adjusted variables for anemia: age, gender, race, Hispanic ethnicity, comorbidities, serum albumin, and dialysis vintage
Adjusted variables for hypoalbuminemia: age, gender, race, Hispanic ethnicity, comorbidities, and dialysis vintage

All P-value <0.001

Hemodial Int 2020; 24: 495-505

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Dialysis Adequacy and Hyporesponsiveness

Table 3. Adjusted Missed Hemodialysis Treatment Rates During Follow-up for Patients With and Without ESA Hyporesponse at Baseline

	Adjusted Quarterly Rate (95% CI)[a]		
Quarter Postbaseline	ESA Hyporesponsiveness	ESA Non-Hyporesponsiveness	Incidence Rate Difference (95% CI)
1	4.75 (4.64-4.85)	2.29 (2.27-2.32)	2.46 (2.32-2.52)
2	4.46 (4.35-4.58)	2.46 (2.43-2.49)	1.98 (1.86-2.07)
3	4.39 (4.28-4.51)	2.64 (2.61-2.68)	1.74 (1.65-1.83)
4	6.32 (6.20-6.44)	4.79 (4.76-4.83)	1.53 (1.41-1.65)
5	4.75 (4.63-4.88)	3.19 (3.16-3.23)	1.56 (1.47-1.74)
6	4.22 (4.10-4.34)	2.75 (2.71-2.78)	1.47 (1.41-1.65)
7	4.40 (4.27-4.53)	2.88 (2.84-2.91)	1.53 (1.44-1.71)
8	7.42 (7.28-7.57)	5.96 (5.92-6.01)	1.47 (1.35-1.68)

Missed treatments more common among hyporesponders

Am J Kidney Dis 2016; 68:763-771

Dialysis Adequacy and Hyporesponsiveness

TABLE 2 Changes in clinical parameters before and after 6 months of combined therapy.

Variables	At start of combined therapy	After 6 months	p^*
Body weight (kg)	69.2 ± 12.0	65.8 ± 10.3	<0.01
Systolic BP (mmHg)	146 ± 19	152 ± 16	0.13
Diastolic BP (mmHg)	77 ± 13	83 ± 11	0.04
Urine volume (mL/day)	100 (33–300)	30 (0–150)	<0.01
Hb (g/dL)	9.0 ± 1.6	11.2 ± 1.5	<0.01
TP (g/dL)	5.9 ± 0.5	6.2 ± 0.6	<0.01
Alb (g/dL)	3.0 ± 0.5	3.3 ± 0.4	<0.01
UN (mg/dL)	59.1 ± 11.4	55.7 ± 16.6	0.19
Cr (mg/dL)	14.1 ± 2.7	13.0 ± 2.6	<0.01
β2 microglobulin (mg/L)	30.4 (26.3–35.1)	31.1 (25.7–35.6)	0.65
ESA dose (unit/week/kg)	9000 (6000–12 000)	6000 (3000–12 000)	0.04
ERI [unit/week/kg/(g/dL)]	11.8 (8.0–20.4)	7.8 (3.9–18.6)	0.047
Amount of PD solution (mL/day)	8000 (6600–8000)	8000 (7300–8000)	0.91
D/P Cr	0.70 ± 0.10	0.65 ± 0.10	0.01

Abbreviations: Alb, serum albumin; BP, blood pressure; Cr, creatinine; D/P Cr, dialysate-to-plasma ratio of creatinine; ERI, erythropoietin-stimulating agents resistance index; ESA, erythropoietin-stimulating agents; Hb, hemoglobin; PD, peritoneal dialysis; TP, total protein; UN, blood urea nitrogen.

Adding extra HD session to 5-6 PD treatments per week (mostly due to inadequate dialysis and/or volume overload) resulted in higher Hgb levels and lower ERI/ESA dose

But possible they could have also improved on their own.

Ther Apher Dial.2023;27:735–741

Hyperparathyroidism

Table 2. Hematologic Values in 18 Patients Undergoing Hemodialysis Who Received Long-Term Erythropoietin Therapy.*

Variable	Good Response (N = 11)	Poor Response (N = 7)
Hematocrit (%)†		
Initial	21.4±1.9	19.6±1.5
Final	33.7±1.8	33.3±3.2
Increment	12.3±3.2	14.6±2.6
Blood transfusions (no./patient)‡	4±3	5±3
Serum ferritin (ng/ml)	450±161	491±194
Transferrin saturation (%)	26±5	32±12
Total dose of parenteral iron (mg)	3500±1830	3429±2524

*Plus–minus values are means ±SD. None of the differences between groups were significant.

†The initial and final hematocrits were those recorded before erythropoietin therapy and at the time of bone biopsy, respectively.

‡Blood transfusions were given before erythropoietin therapy began.

Table 3. Serum Biochemical Values in 18 Patients Undergoing Hemodialysis Who Received Long-Term Erythropoietin Therapy.*

Variable	Good Response (N = 11)	Poor Response (N = 7)
Calcium (mg/dl)	9.9±0.9 (8.5–11.4)	10.0±0.6 (9.4–11.2)
Phosphate (mg/dl)	6.4±3.5 (3.3–10.9)	7.2±2.7 (3.2–10.4)
25-Hydroxyvitamin D (ng/ml)	37±15 (16–60)	35±10 (23–53)
1,25-Dihydroxyvitamin D (pg/ml)	8±3 (5–14)	9±7 (5–27)
Aluminum (μg/dl)	24±12 (5–40)	13±10 (3–31)
Alkaline phosphatase (U/liter)	130±132 (52–517)	296±220† (75–563)
Parathyroid hormone (pg/ml)	266±322 (23–985)	800±648‡ (42–1653)

*Plus–minus values are means ±SD. Data in parentheses are ranges. To convert values for calcium to millimoles per liter, multiply by 0.249; for phosphate, multiply by 0.323. To convert values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496. To convert values for 1,25-dihydroxyvitamin D to picomoles per liter, multiply by 2.368; for parathyroid hormone, multiply by 0.105. To convert values for alkaline phosphatase to microkatals per liter, multiply by 0.017.

†P = 0.06 for the comparison with the good-response group.

Table 4. Bone Histomorphometric Findings in 18 Patients Undergoing Hemodialysis Who Received Long-Term Erythropoietin Therapy.*

Variable	Good Response (N = 11)	Poor Response (N = 7)
Osteoid volume (%)	9.2±4.1 (1.1–15.8)	14.4±8.4 (3.8–28.1)
Osteoid surface (%)	56±19 (12–79)	63±18 (32–86)
Osteoid thickness (μm)	10.6±2.4 (5.9–13.9)	14.8±5.5 (7.4–24.7)
Bone aluminum (% of osteoid surface)	10.4±11.8 (0–29)	12.8±29.8 (0–80)
Osteoclast surface (% of nonosteoid surface)	3.1±2.6 (0.2–7.2)	8.7±7.8† (0.2–25.1)
Marrow fibrosis (%)	1.1±1.1 (0–3.1)	15.6±16.4‡ (0.2–39.9)
Eroded surface (%)	5.0±2.6 (1.7–9.5)	10.2±5.2‡ (3.7–16.6)

*Plus–minus values are means ±SD. Data in parentheses are ranges.

†P = 0.04 for the comparison with the good-response group.

‡P = 0.009 for the comparison with the good-response group.

New Engl J Med 1993; 328: 1715-175

Hyperparathyroidism

Table 5. Correlation between the Dose of Erythropoietin and Serum Parathyroid Hormone and Bone Histomorphometric Values in 18 Patients Undergoing Hemodialysis Who Received Long-Term Erythropoietin Therapy, According to Univariate Analysis.

VARIABLE	r	P VALUE
Serum parathyroid hormone	0.42	0.084
Osteoid volume	0.60	0.008
Osteoid thickness	0.60	0.008
Osteoclast surface	0.60	0.009
Eroded surface	0.59	0.011
Marrow fibrosis	0.47	0.048
Stainable marrow iron	0.75	0.002

New Engl J Med 1993; 328: 1715-175

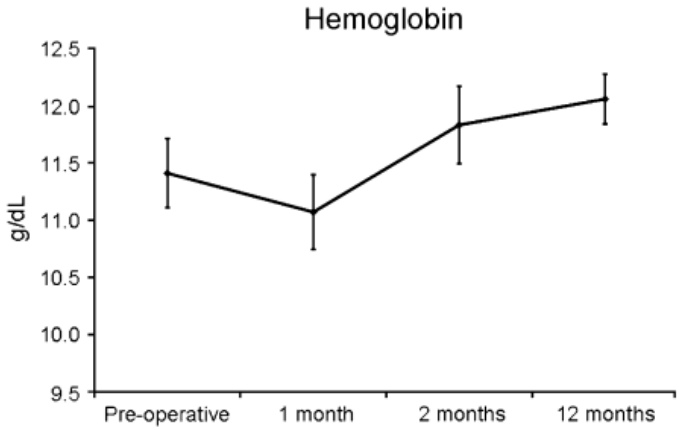

Fig 1. Mean Hg level from pre-operative value through postoperative period.

Fig 2. Mean Hct level from pre-operative value through postoperative period.

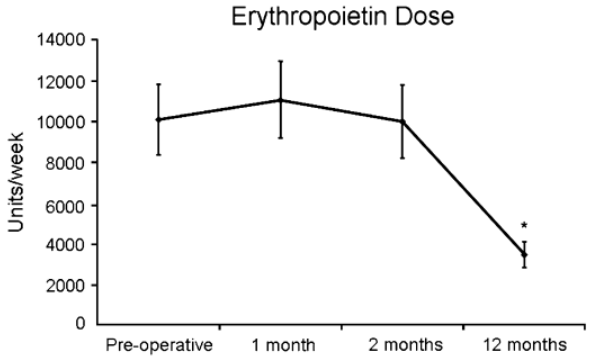

Fig 3. Mean erythropoietin level from the pre-operative value through postoperative period.*$P < .05$ comparing to pre-operative level.

Parathyroidectomy

Surgery 2008; 144: 915-919

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Other causes of hyporesponsiveness

- Assess for GI bleeding
  - Stool cards
  - Check for reticulocytosis
- Nutritional deficiencies
  - Vitamin B12
  - Folate
- Bone marrow failure
  - Myelodysplastic syndrome
  - Pure Red Cell Aplasia
    - Parvovirus
    - Anti-EPO antibody

Blood Transfusions

- Risks
  - Allosensitization
  - Transfusion Associated Circulatory Overload (TACO)
  - Transfusion Related Acute Lung Injury (TRALI)
  - Iron overload
  - Infection (very rare)

Allosensitization

- Causes
  - Prior transplant
  - Pregnancy
  - Blood transfusion
  - Inflammatory events
- Exact risk of transfusion and allosensitization is difficult to determine
  - Prior transplants -> “inflammation” - > “hyporesponsives” -> transfusion
  - Non-transplant inflammatory events -> “hyporesponsiveness”-> transfusion

Allosensitization

- Allosensitization can result in
  - Decreased access to transplant
  - Increased risk of rejection and graft failure
- Calculated PRA (cPRA) estimates the percentage of donors that recipient would be incompatible with
  - Replaced PRA in 2009
  - Incorporates the frequency of donor antigen
  - Very simple interpretation: If a recipient has one antibody to an antigen that is present in 50% of the population, then cPRA is 50%
  - The probability of finding a suitable donor is $1-(cPRA)^n$ **

** n=number of donors.

** Reference: Clin J Am Soc Nephrol 2016; 11:684-693

Allosensitization with Blood Transfusion

UNOS Data 1997-2014

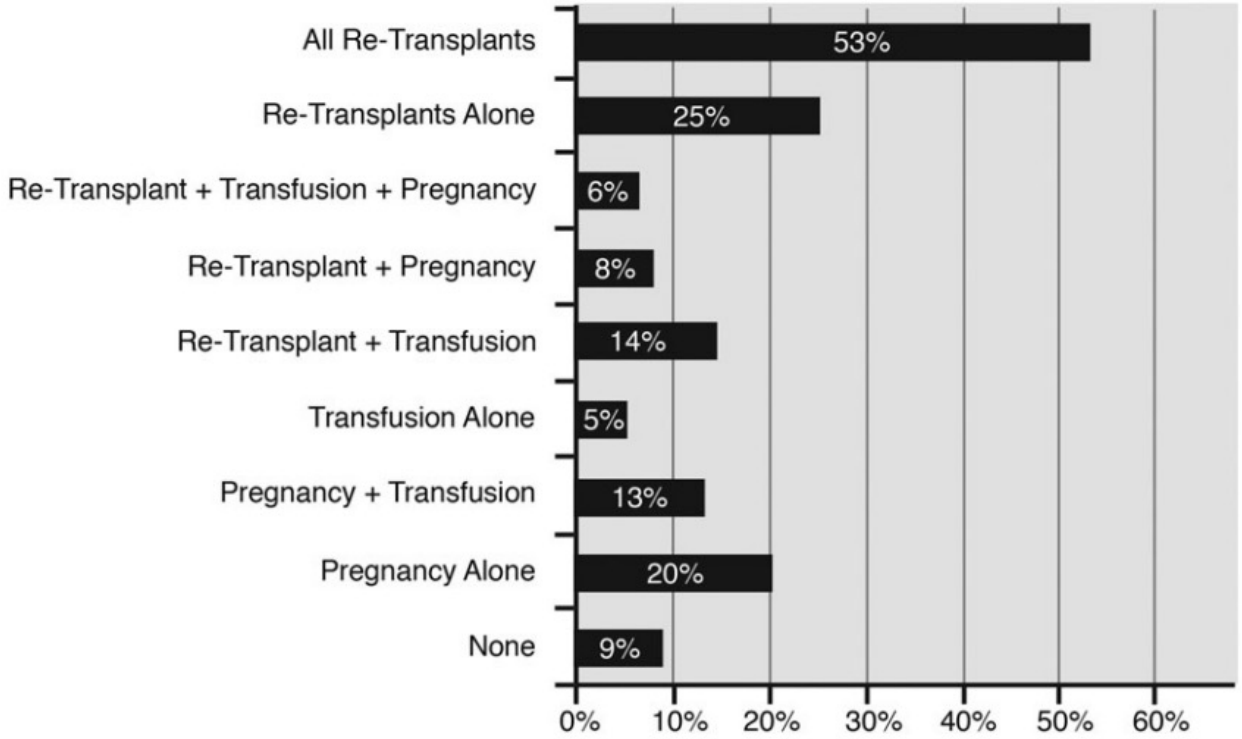


FIGURE 3: Cause of sensitization for PRA/cPRA ≥98%. PRA, panel reactive antibody; cPRA, calculated panel reactive antibody.

Approximately 75% of highly sensitized patients were due to prior transplant or pregnancy.

Only 5% of highly sensitized patients had prior transfusion as the only sensitizing event.

They did not report how many of the transfused were highly sensitized.

Nephrol Dial Transplant 2016; 31: 1746–1753

Allosensitization with Blood Transfusion

Primary Transplants

Figure S7: Change in calculated panel reactive antibody (CPRA) levels for patients in transfused and matched non-transfused groups according to baseline level of sensitization (CPRA=0 [panel a], CPRA > 0 [panel b]).a) b)

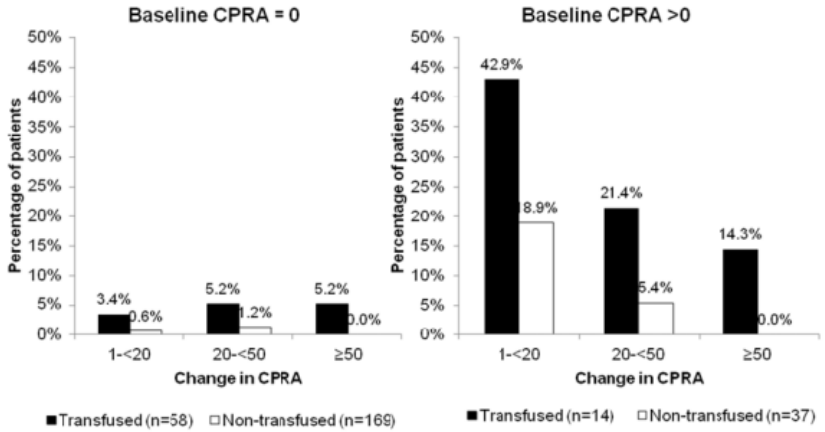
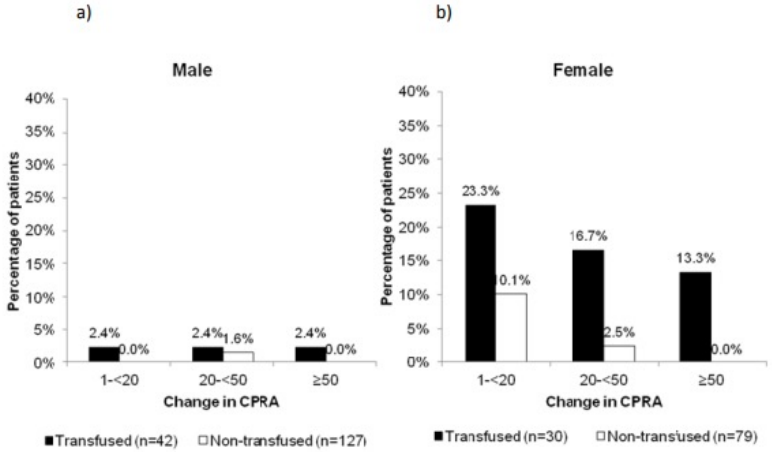


Figure S6. Change in calculated panel reactive antibody (CPRA) levels for patients in transfused and matched non-transfused groups within gender (panels a, b), race (panels c, d), and age (panels e, f, g, h) sub-groups.



Increase in cPRA > 90% was seen in 4.7% of patients transfused

Transplantation 2014; 97: 525-533

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Kidney Allocation System

In 2014, Kidney Allocation System established to give priority to highly sensitized(cPRA 98-100%) for deceased donor kidney transplants

TABLE 4 Cumulative incidence of deceased donor kidney transplantation pre-KAS and post-KAS

	Pre-KAS (%)			Post-KAS (%)		
cPRA	1-y	2-y	3-y	1-y	2-y	3-y
0–79%	$_{12.3}12.5_{12.7}$	$_{22.0}22.2_{22.5}$	$_{31.8}32.1_{32.5}$	$_{13.8}14.0_{14.2}$	$_{22.1}22.3_{22.6}$	$_{30.4}30.7_{31.1}$
80–89%	$_{26.3}28.1_{30.0}$	$_{37.4}39.6_{41.7}$	$_{42.1}44.4_{46.7}$	$_{17.7}19.3_{20.9}$	$_{28.5}30.4_{32.4}$	$_{35.9}38.1_{40.4}$
90–97%	$_{17.6}18.8_{20.1}$	$_{27.5}29.0_{30.6}$	$_{33.9}35.7_{37.4}$	$_{20.4}21.7_{23.0}$	$_{32.2}33.8_{35.4}$	$_{39.6}41.4_{43.2}$
98%	$_{9.1}10.8_{12.7}$	$_{17.5}19.9_{22.4}$	$_{22.9}25.7_{28.6}$	$_{17.2}19.4_{21.8}$	$_{29.4}32.2_{35.0}$	$_{36.0}39.1_{42.2}$
99%	$_{6.4}7.5_{8.7}$	$_{13.6}15.2_{16.9}$	$_{18.4}20.3_{22.3}$	$_{24.3}26.2_{28.1}$	$_{35.8}38.0_{40.2}$	$_{42.4}44.8_{47.2}$
99.5–99.9%	$_{3.2}3.9_{4.8}$	$_{6.9}8.0_{9.2}$	$_{10.6}12.1_{13.6}$	$_{31.0}32.9_{34.8}$	$_{40.9}43.0_{45.1}$	$_{46.2}48.4_{50.5}$
99.9%+	$_{1.0}1.4_{1.9}$	$_{2.4}3.0_{3.8}$	$_{3.5}4.2_{5.1}$	$_{8.5}9.4_{10.4}$	$_{14.6}15.9_{17.1}$	$_{19.7}20.2_{21.6}$

Cumulative incidence and 95% confidence interval of DDKT calculated using a competing risk framework, accounting for waitlist mortality or removal from waitlist due to deteriorating medical status. cPRA, calculated panel-reactive antibody; KAS, kidney allocation system.

Am J Transplant 2019; 19: 1129-1138

Kidney Allocation System

- Patients transplanted with 100% cPRA
  - 93.6% patient survival at 3 years
  - 93.7% death censored graft survival at 3 years
  - 29% with delayed graft function (DGF)
  - 11.2% acute rejection
  - Length of stay (5 days)
  - As compared to 0% cPRA patients
    - Similar patient and graft survival
    - Similar rate of DGF
    - 61% higher risk of acute rejection

Transplantation 2020; 104: 1456-1461

Blood Transfusions

- Non-sensitized patients are not likely to become highly sensitized unless they are transfused repeatedly or have an additional sensitizing event
  - However, there isn't a way to predict who will become highly sensitized or whether such events will occur.
  - Even a 5% chance may be considered too high
- Although KAS has improved access to kidney transplantation for highly sensitized patients, access to transplant is still low for the most highly sensitized patients

Blood Transfusions - KDIGO

- Recommend avoiding blood transfusions (1B)
- Recommend avoiding blood transfusions in transplant candidates (1C)
- Benefits of blood transfusion may exceed risk when
  - There is ESA failure
  - When ESAs are contraindicated
- Decision to transfuse should not be based on an arbitrary hemoglobin value, but on symptoms related to anemia

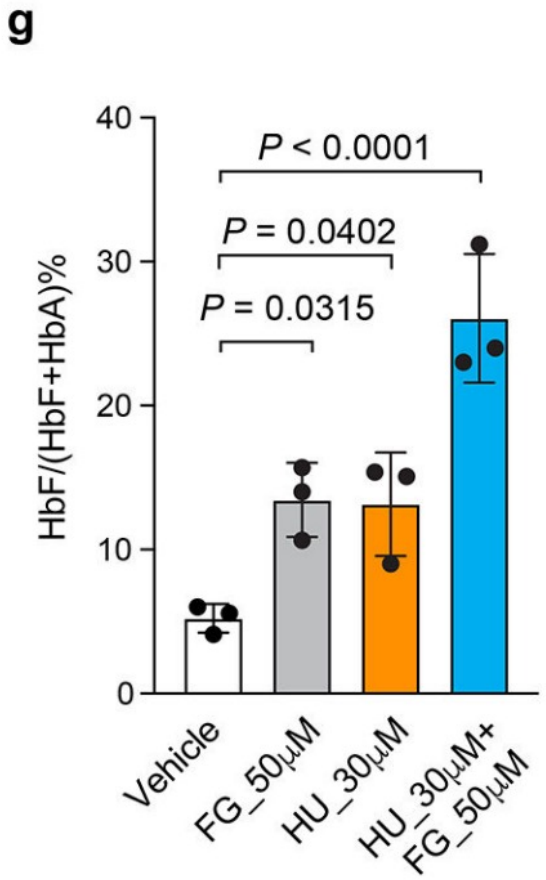
www.kdigo.org

Sickle Cell Disease

- Higher Hgb levels or rapid rise in Hgb levels may precipitate sickle cell crisis
  - Increasing % Hemoglobin F may reduce the risk of sickle cell crises
- Frequent transfusions may lead to iron overload
  - Possible need for iron chelation therapy
- Inflammation induced by sickling may lead to hyporesponsiveness
- Exact hemoglobin target unclear
  - < 10 g/dL
  - 8-9 g/dL[1]
  - I had a patient that we ran 6-8 g/dL

1 Semin Dial 2016; 29:62-70

Sickle Cell Disease



Treatment of red blood cell precursors with FG4592 (HIF-PH inhibitor) and hydroxyurea (HU) increased % fetal hemoglobin to similar levels and had synergistic effect.

** Sickle Cell Disease patients were excluded from HIF-PH inhibitor ESKD trials, so the safety and benefit in this population has not been examined. Therefore, use in this population can't be recommended until further study.

Nature 2022; 610: 783-790

Patients with Cancer

- ESAs in patients with cancer may increase the risk of
  - Cancer progression
  - Thromboembolic disease (including stroke)
  - Death
- No randomized trials specifically in ESKD patients (likely due to adverse events documented in non-ESKD/CKD patients)
- In largely non-ESKD/CKD cancer studies, pooled analyses suggests increased mortality limited to patients with baseline Hgb > 12[1,2]
  - No overall effect on tumor progression
  - Increased thrombotic risk regardless of baseline Hgb

1 Cochrane Database Syst Rev 2012; 12:CD003407
2 Br J Cancer 2010; 102: 301-315

Patients with Cancer

ASCO/ASH, ESMO 2010[39,40]
- ESAs for chemotherapy-induced anemia when Hb < 10 g/dL
- ESAs during active therapy and to be stopped by 1 mo postcompletion
- Aim for lower target Hb
- No recommendations for those with underlying CKD and cancer

KDIGO Anemia Guidelines 2012[48]
- Incorporation of FDA warning
- ESA use with caution if active malignancy or history of malignancy
- If Hb > 10 g/dL, ESA not needed
- If Hb < 10 g/dL, ESA use to avoid Hb < 9 g/dL

FDA 2007, 2017[41,56]
- Cautious use of ESAs for those with history of cancer or current malignancy
- Use of ESA if chemotherapy-induced anemia undergoing active treatment
- Do not continue ESAs beyond 1 mo posttreatment
- Suggested avoidance if anticipated cure
- ESA REMS program
  - ◇ Initiated in 2010 so patients with cancer and chemotherapy-induced anemia understood ESA risks
  - ◇ In 2017, FDA ended the program after determining providers were prescribing ESAs appropriately

Am J Kidney Dis 2019; 74: 667-674

Patients with Cancer

- HIF-PH Inhibitor
  - ASCEND-D trial excluded patients with history of cancer within 2 years of randomization or receiving therapy for cancer[1]
  - Roughly 5% had history of cancer at baseline[1]
  - No difference in cancer related adverse events in ASCEND-D (ESA vs HIF-PH inhibitor)[2]
    - ➢ No placebo arm
- Based on the above information, there is no clear benefit of HIF-PH vs ESA vs placebo in cancer patients

1 New Engl J Med 2021; 385: 2325-2335
2 Nephrol Dial Transplant 2023; 38: 1890-1897

Conclusions

- Anemia management in ESKD patients is complicated
- For hyporesponsive patient, addressing cause of hyporesponsiveness is key
  - Iron deficiency
  - Inflammation
  - Hyperparathyroidism
  - Inadequate dialysis
  - Nutritional deficiencies
  - Occult bleeding
  - Bone marrow failure

Conclusions

- Hyporesponsiveness is usually transient
  - How aggressive should we be in patients with Hgb levels below the “target range” but still tolerable for the patient?
  - Do “hyporesponsive algorithms” work?
- HIF-PH inhibitors do not seem to have clear advantage over ESAs in the following areas but still requires further study
  - Hyporesponsive patients
  - Patients with sickle cell disease
  - Patients with cancer