ΑΝΤΙΜΕΤΩΠΙΣΗ ΑΣΘΕΝΟΥΣ ΜΕ ΔΙΑΒΗΤΙΚΗ ΝΕΦΡΟΠΑΘΕΙΑ ΤΕΛΙΚΟΥ ΣΤΑΔΙΟΥ

Η διαχείριση της αναιμίας

Στέλιος Παναγούτσος

Πανεπιστημιακή Νεφρολογική Κλινική ΔΠΘ

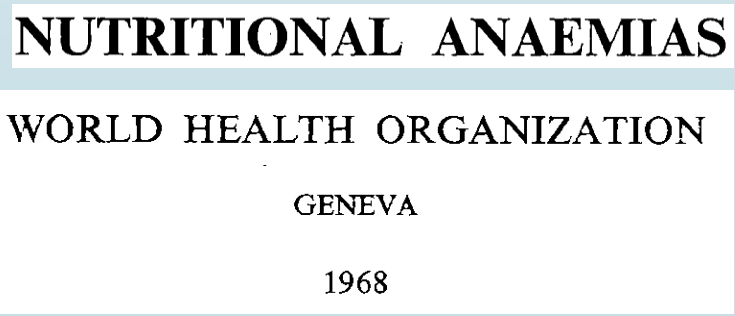
Δήλωση σύγκρουσης συμφερόντων

- Τα τελευταία 2 χρόνια έχω λάβει τιμητικές αμοιβές από:
  - Honoraria: ASTELLAS; ASTRA ZENECA; BOEHRINGER; GLAXO; BAYER
  - Advisory or Leadership Role: GLAXO; ASTRA ZENECA

Αναιμία
Ορισμός

- According to the World Health Organization (WHO), anemia is defined as **hemoglobin (Hb) levels:**

- For adults:
- Men and postmenopausal women **Hb < 130 g/L**
- Premenopausal women **Hb < 120 g/L**



Αναιμία
Ορισμός

Diagnosis of anemia

1.2.1: Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females. (*Not Graded*)

1.2.2: Diagnose anemia in children with CKD if Hb concentration is <11.0 g/dl (<110 g/l) in children 0.5–5 years, <11.5 g/dl (115 g/l) in children 5–12 years, and <12.0 g/dl (120 g/l) in children 12–15 years. (*Not Graded*)

Kidney International Supplements (2012) 2, 283–287

Αναιμία
Ορισμός

Guideline 1.2 - evaluation of anaemia - Haemoglobin level

We recommend that all patients with chronic anaemia associated with chronic kidney disease should be investigated for the cause and possible treatment, irrespective of the grade of kidney disease or requirement for renal replacement therapy if:

- their haemoglobin (Hb) levels are less than 110 g/L (less than 105 g/L if younger than 2 years) or
- they develop symptoms attributable to anaemia

BMC Nephrology (2017) 18:345

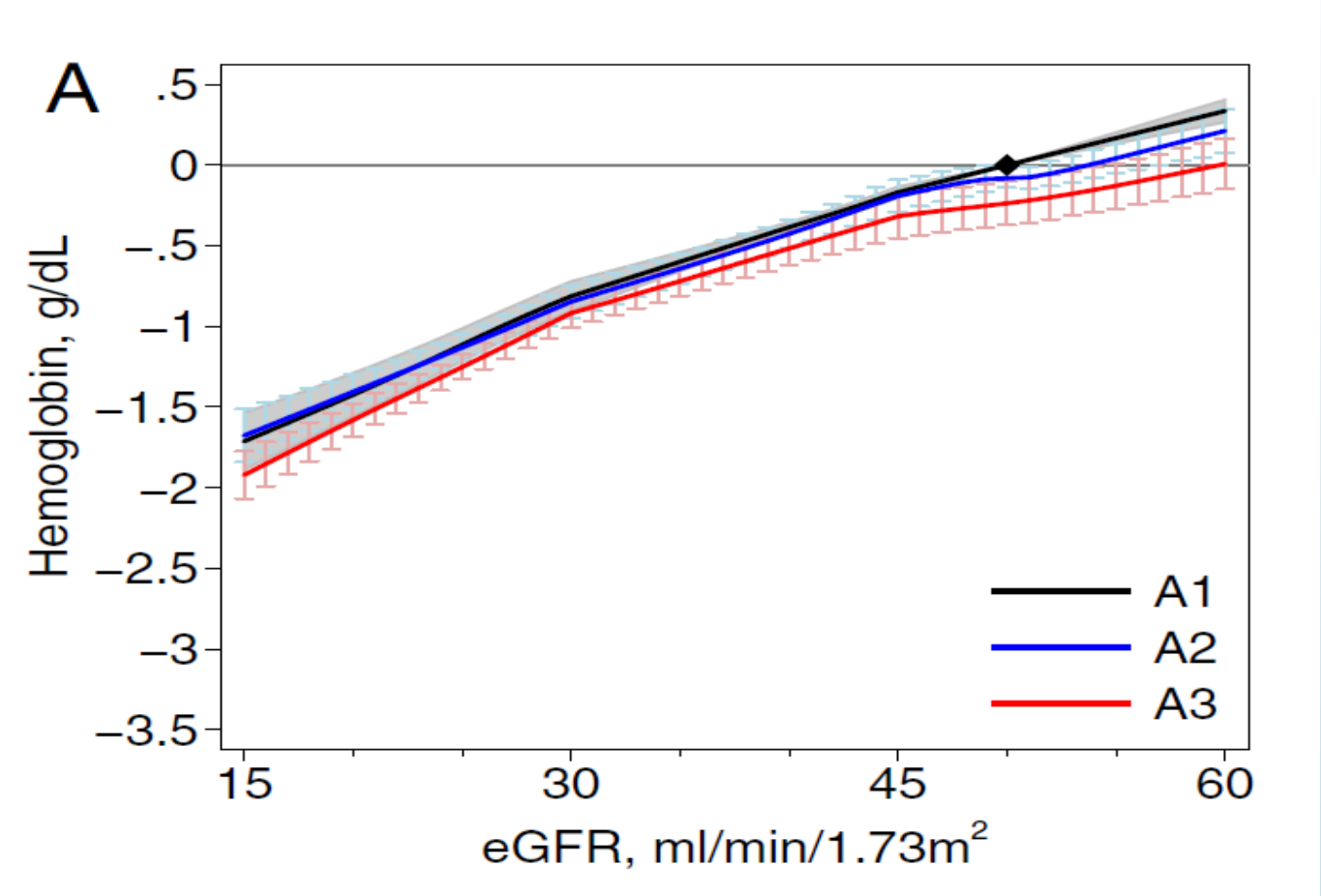
Αναιμία
Επιπολασμός σε CKD

Table 3. Prevalence of anemia. **USA - NHANES**

	N	Weighted percentage	95% CI	Projected number in US
With CKD	410	15.4	13.1–18.2	4.8×10^6
Stage 1	57	8.4	5.5–12.4	0.6×10^6
Stage 2	68	12.2	9.2–16.0	0.9×10^6
Stage 3	231	17.4	13.7–21.8	2.7×10^6
Stage 4	37	50.3	37.2–63.4	0.5×10^6
Stage 5	17	53.4	34.1–71.7	0.2×10^6
Without CKD	729	6.3	5.3–7.4	11×10^6

PLoS ONE 9(1): e84943.

Αναιμία
Επιπολασμός σε CKD



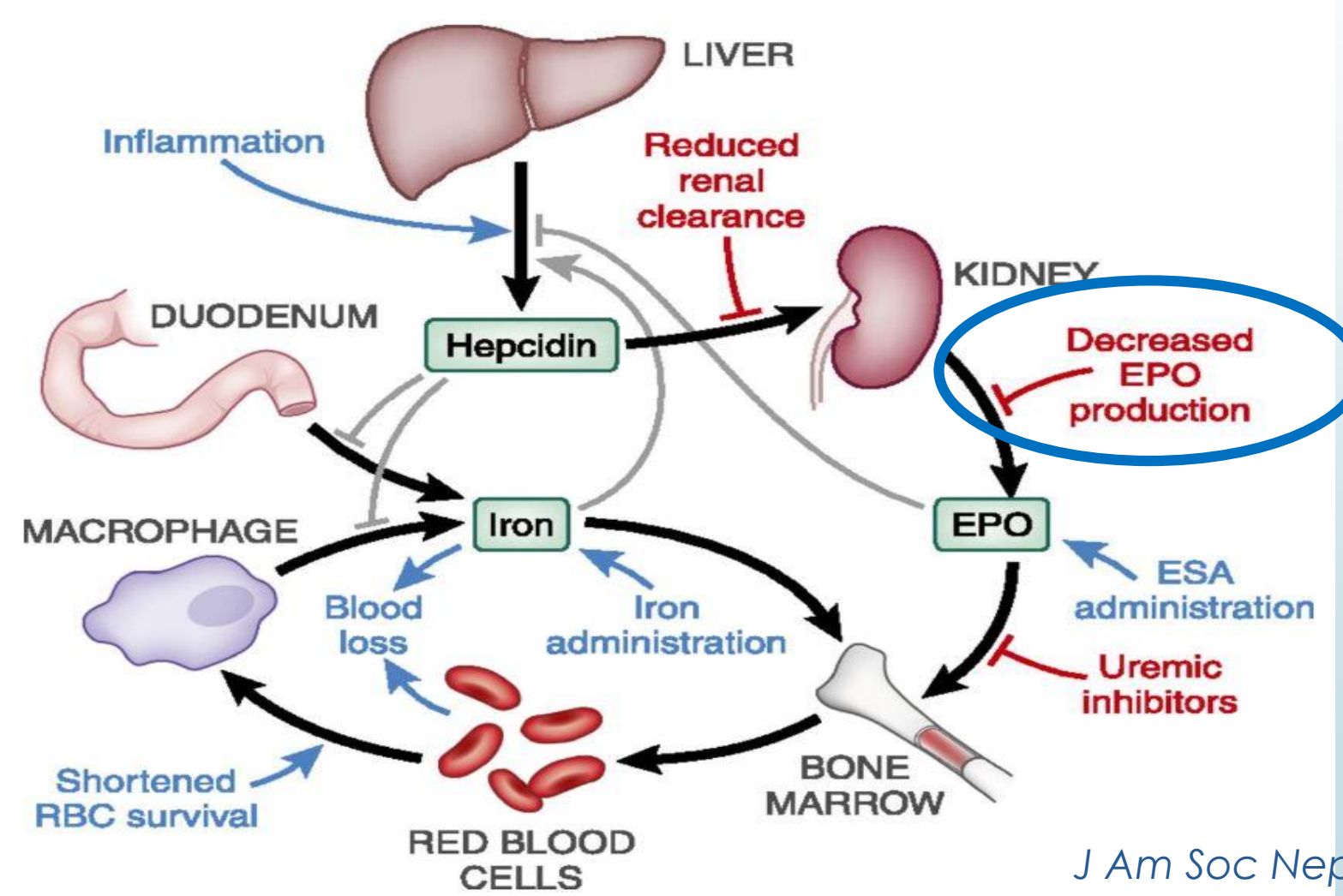
Am J Kidney Dis. 2019; 73(2): 206–217

Αναιμία
Αιτίες σε CKD

- *Ανεπάρκεια παραγωγής Ερυθροποιητίνης*
- *Βράχυνση της ζωής των ερυθρών αιμοσφαιρίων*
- *Ανεπάρκεια Σιδήρου*
- *Λοίμωξη - Φλεγμονή*

- *Αναστολείς της Ερυθροποίησης*
- *Δευτεροπαθής Υπερπαραθυρεοειδισμός*
- *Αιμορραγία*
- *Τοξικότητα από Αργίλιο*

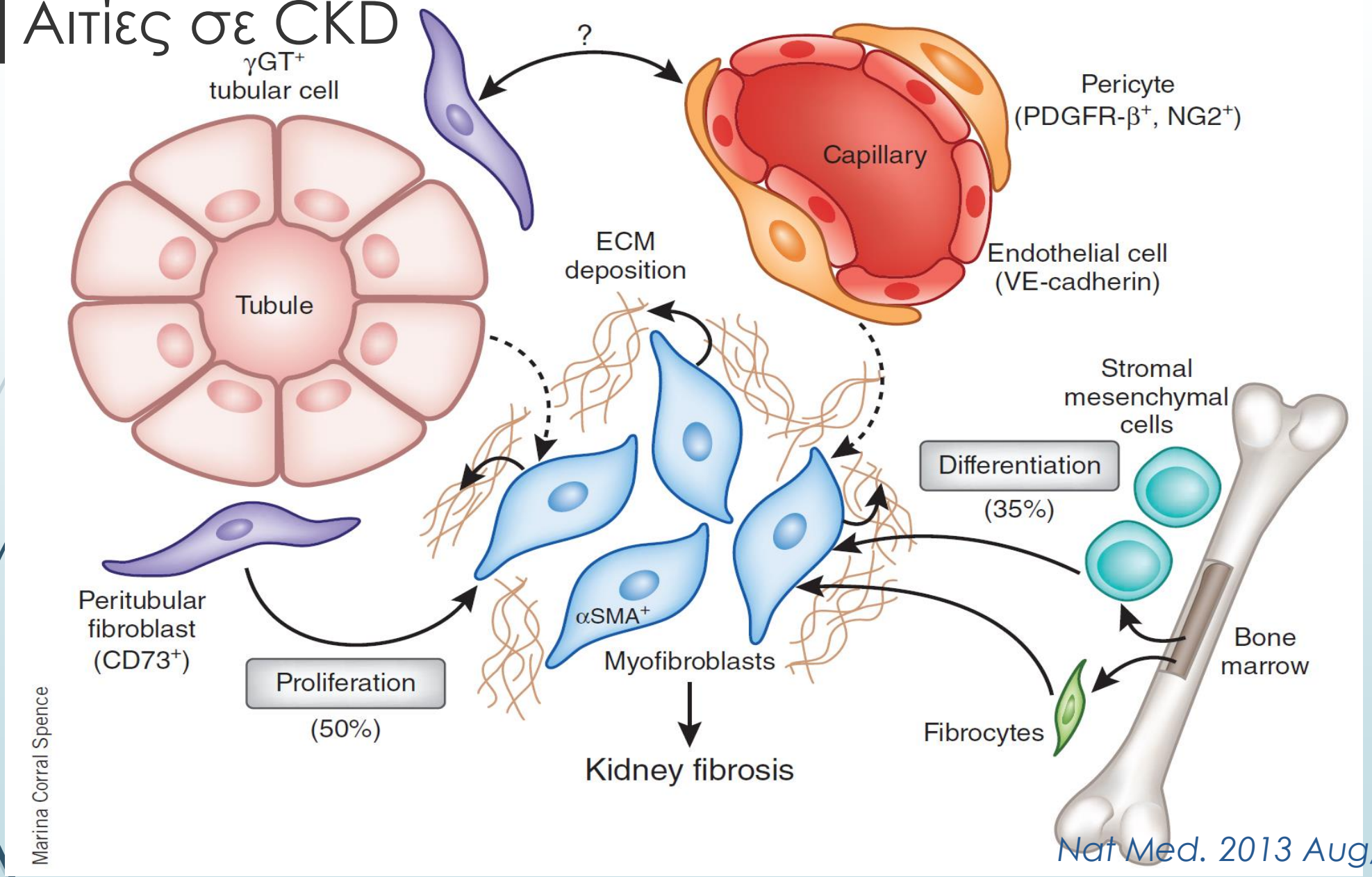
Αναιμία
Αιτίες σε CKD



J Am Soc Nephrol 23: 1631–1634, 2012

Αναιμία

Αιτίες σε CKD



Nat Med. 2013 Aug;19(8):964-6

Αναιμία
Επιπολασμός σε DKD

No Diabetes

	Anemia		
eGFR	A1	A2	A3
>90			
75-89			
60-74	14.9% (11.8, 18.6)	23.1% (18.7, 28.2)	23.4% (18.9, 28.5)
45-59	22.1% (17.7, 26.9)	24.9% (20.2, 30.2)	29.1% (23.9, 34.9)
30-44	39.2% (33.0, 45.7)	36.9% (30.8, 43.2)	40.8% (34.4, 47.3)
15-29	60.6% (54.0, 66.7)	60.7% (54.1, 66.8)	64.2% (57.7, 70.0)

Diabetes

	Anemia		
eGFR	A1	A2	A3
>90			
75-89			
60-74	23.7% (19.2, 28.8)	27.9% (22.7, 33.5)	33.9% (28.1, 40.1)
45-59	32.1% (26.4, 38.1)	34.8% (28.9, 41.0)	40.1% (33.8, 46.6)
30-44	47.2% (40.5, 53.8)	48.3% (41.6, 54.9)	53.3% (46.5, 59.8)
15-29	66.1% (59.8, 71.8)	66.5% (60.2, 72.1)	74.5% (69.0, 79.2)

Am J Kidney Dis. 2019; 73(2): 206–217

Αναιμία
Επιπολασμός σε DKD

Association between anemia and primary etiology of CKD.

Underlying disease	Overall	eGFR, mL/min/1.73 m^2				
		Stage 1, eGFR ≥90	Stage 2, 90 > eGFR ≥ 60	Stage 3, 60 > eGFR ≥ 30	Stage 4, 30 > eGFR ≥ 15	Stage 5, eGFR <15
Chronic glomerulonephritis, n (%)	599 (46.1)	102 (22.4)	78 (29.3)	110 (51.9)	115 (79.5)	194 (87.7)
Hypertensive renal damage, n (%)	180 (56.6)	6 (21.4)	9 (22.2)	36 (36.6)	53 (76.5)	76 (93.6)
Diabetic nephropathy,* n (%)	206 (68.0)	10 (25.0)	22 (51.2)	39 (58.7)	56 (83.8)	79 (91.4)

Medicine (2016) 95:24(e3872)

Αναιμία
Αιτίες σε CKD

- *Ανεπάρκεια παραγωγής Ερυθροποιητίνης*
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- *Αιμορραγία*
- *Τοξικότητα από Αργίλιο*

Αναιμία
Αιτίες σε DKD

- *Ανεπάρκεια παραγωγής Ερυθροποιητίνης*
  - *Η παρουσία μικροαγγειοπάθειας οδηγεί σε σωληναριοδιάμεση βλάβη*
  - *Η χρόνια υπογλυκαιμία ευνοεί την αποδόμηση του παράγοντα που επάγεται από την υποξία (HIF)*
  - *Η συστηματική φλεγμονή ευνοεί τη διάμεση ίνωση*

Pathophysiology 2023, 30, 327–345

Αναιμία
Αιτίες σε DKD

Model Histopathological variables		Standardized coefficient	95% CI	*P*
Glomerular class I (reference)	(n = 11)			
Glomerular class IIA	(n = 34)	−0.06	−1.50–1.02	0.71
Glomerular class IIB	(n = 28)	−0.10	−1.90–1.09	0.59
Glomerular class III	(n = 20)	−0.34	−3.10– −0.06	0.042
Glomerular class IV	(n = 8)	−0.14	−2.85–1.01	0.35
IFTA score 0 (reference)	(n = 13)			
IFTA score 1	(n = 38)	−0.18	−1.95–0.62	0.31
IFTA score 2	(n = 35)	−0.31	−2.80–0.46	0.16
IFTA score 3	(n = 15)	−0.46	−4.28– −0.35	0.022
Interstitial inflammation score 0 (reference)	(n = 20)			
Interstitial inflammation score 1	(n = 76)	0.02	−1.10–1.28	0.88
Interstitial inflammation score 2	(n = 5)	−0.11	−2.82–0.93	0.32
Arteriolar hyalinosis score 0 (reference)	(n = 12)			
Arteriolar hyalinosis score 1	(n = 12)	−0.16	−2.13–0.39	0.17
Arteriolar hyalinosis score 2	(n = 77)	−0.20	−2.20–0.50	0.21
Arteriosclerosis score 0 (reference)	(n = 10)			
Arteriosclerosis score 1	(n = 54)	−0.02	−1.23–1.06	0.88
Arteriosclerosis score 2	(n = 37)	0.07	−1.02–1.52	0.70
Exudative lesions [yes (n = 45)/no (n = 56)]		0.13	−0.25–1.20	0.20

IFTA, interstitial fibrosis and tubular atrophy.

Diabet. Med. 32, 546–555 (2015)

Αναιμία
Αιτίες σε DKD

- *Ανεπάρκεια Σιδήρου*
  - *Η χρόνια φλεγμονή οδηγεί σε αύξηση της Εψιδίνης*
  - *Η χρόνια υπογλυκαιμία προκαλεί μεταβολές στην ικανότητα μεταφοράς του σιδήρου*

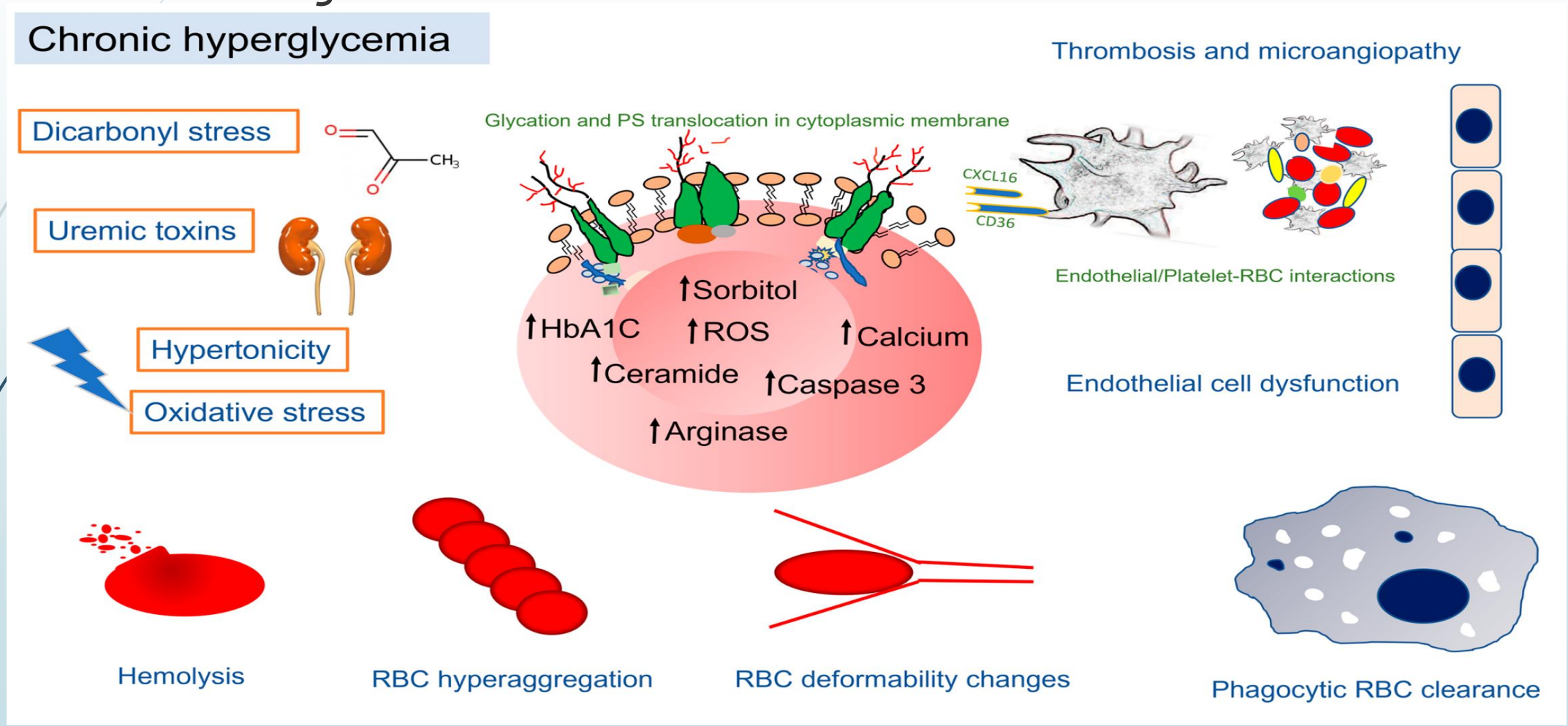
Pathophysiology 2023, 30, 327–345

Αναιμία
Αιτίες σε DKD

- *Βράχυνση της ζωής των ερυθρών αιμοσφαιρίων*
  - *Υπερωσμωτικότητα στον εξωκυττάριο χώρο*
  - *Οξειδωτικό stress*
  - *Χρόνια υπεργλυκαιμία*

Pathophysiology 2023, 30, 327–345

Αναιμία
Αιτίες σε DKD



Pathophysiology 2023, 30, 327–345

Αναιμία
Αιτίες σε DKD

- *Αναστολείς της Ερυθροποίησης*
- *Μειωμένη ερυθροποίηση στο μυελό*
  - *Μικροαγγειοπάθεια*
  - *Χρόνια φλεγμονή*
  - *Παρουσία AGEs*

Αναιμία
Αιτίες σε DKD

- *Λήψη αναστολέων του άξονα PAA (ACEIs και ARBs)*

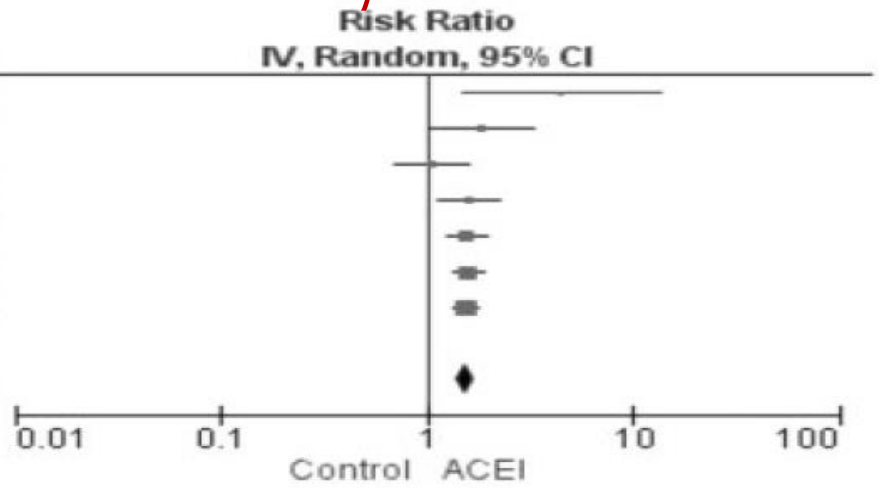
Αναιμία

Αιτίες σε DKD

Λήψη RAS αναστολέων (ACEIs και ARBs)

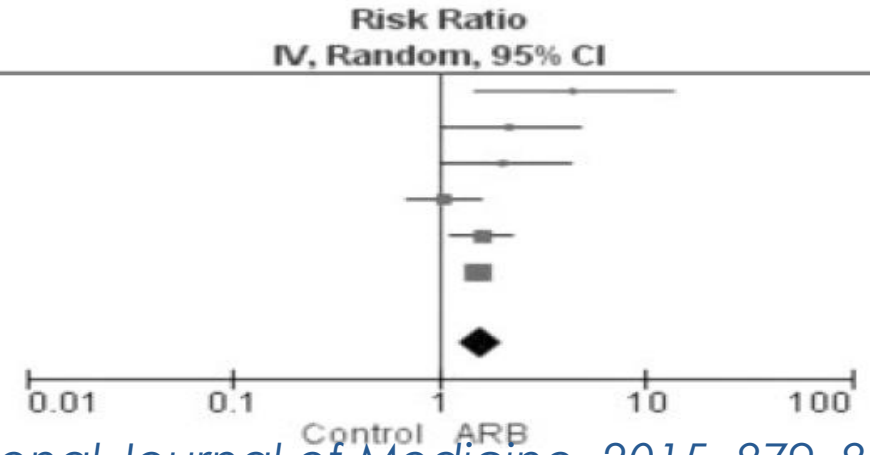
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Guerrero-Riscos et el.	1.495149	0.565481	0.9%	4.46 [1.47, 13.51]
Winkelmayer et al.	0.620576	0.298403	3.3%	1.86 [1.04, 3.34]
Chhabra et al.	0.058269	0.212477	6.3%	1.06 [0.70, 1.61]
Muñoz et al.	0.482426	0.175712	8.9%	1.62 [1.15, 2.29]
Ishani et al.	0.444686	0.108778	19.8%	1.56 [1.26, 1.93]
Leshem-Rubinow et el.	0.463734	0.086378	27.7%	1.59 [1.34, 1.88]
Vanrenterghem et al.	0.438255	0.075285	33.1%	1.55 [1.34, 1.80]
Total (95% CI)			**100.0%**	**1.56 [1.40, 1.73]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.21$, $df = 6$ ($P = 0.30$); $I^2 = 17\%$
Test for overall effect: $Z = 8.01$ ($P < 0.00001$)



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Guerrero-Riscos et el.	1.495149	0.565481	3.8%	4.46 [1.47, 13.51]
Leshem-Rubinow et el.	0.792993	0.39815	7.1%	2.21 [1.01, 4.82]
Winkelmayer et al.	0.727549	0.37096	8.0%	2.07 [1.00, 4.28]
Chhabra et al.	0.058269	0.212477	18.3%	1.06 [0.70, 1.61]
Muñoz et al.	0.482426	0.175712	22.7%	1.62 [1.15, 2.29]
Vanrenterghem et al.	0.438255	0.075285	40.1%	1.55 [1.34, 1.80]
Total (95% CI)			**100.0%**	**1.60 [1.27, 2.00]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.15$, $df = 5$ ($P = 0.15$); $I^2 = 39\%$
Test for overall effect: $Z = 4.07$ ($P < 0.0001$)

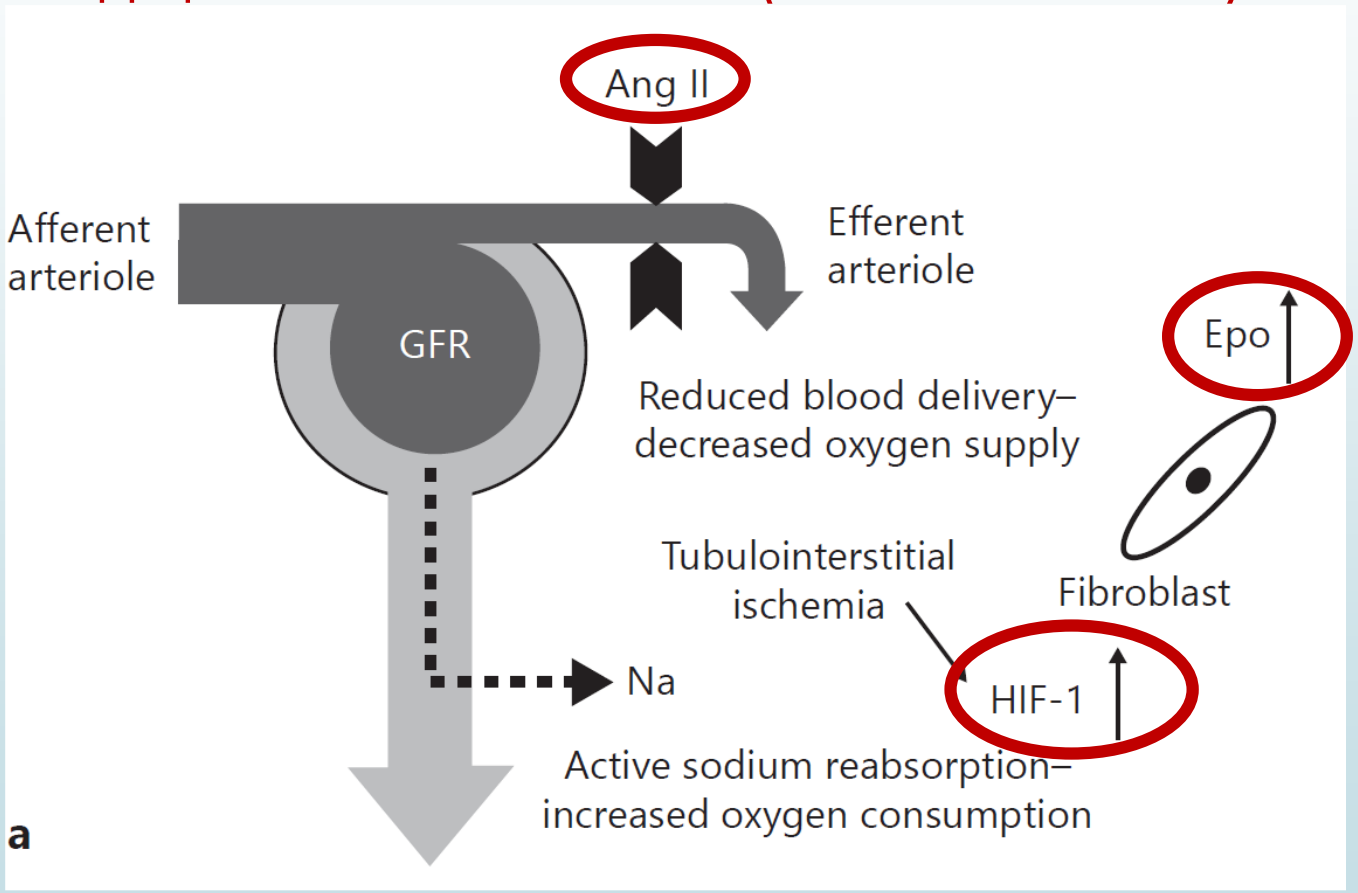


QJM: An International Journal of Medicine, 2015, 879–884

Αναιμία

Αιτίες σε DKD

Λήψη RAS αναστολέων (ACEIs και ARBs)



Am J Nephrol 2020;51:349–356

Αναιμία

Αντιμετώπιση

- Χορήγηση ανασυνδυασμένης Ερυθροποιητίνης
- Χορήγηση Σιδήρου

- Νέοι Ερυθροποιητικοί παράγοντες

Αναιμία

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- Νέοι Ερυθροποιητικοί παράγοντες

EPO Ιστορικό

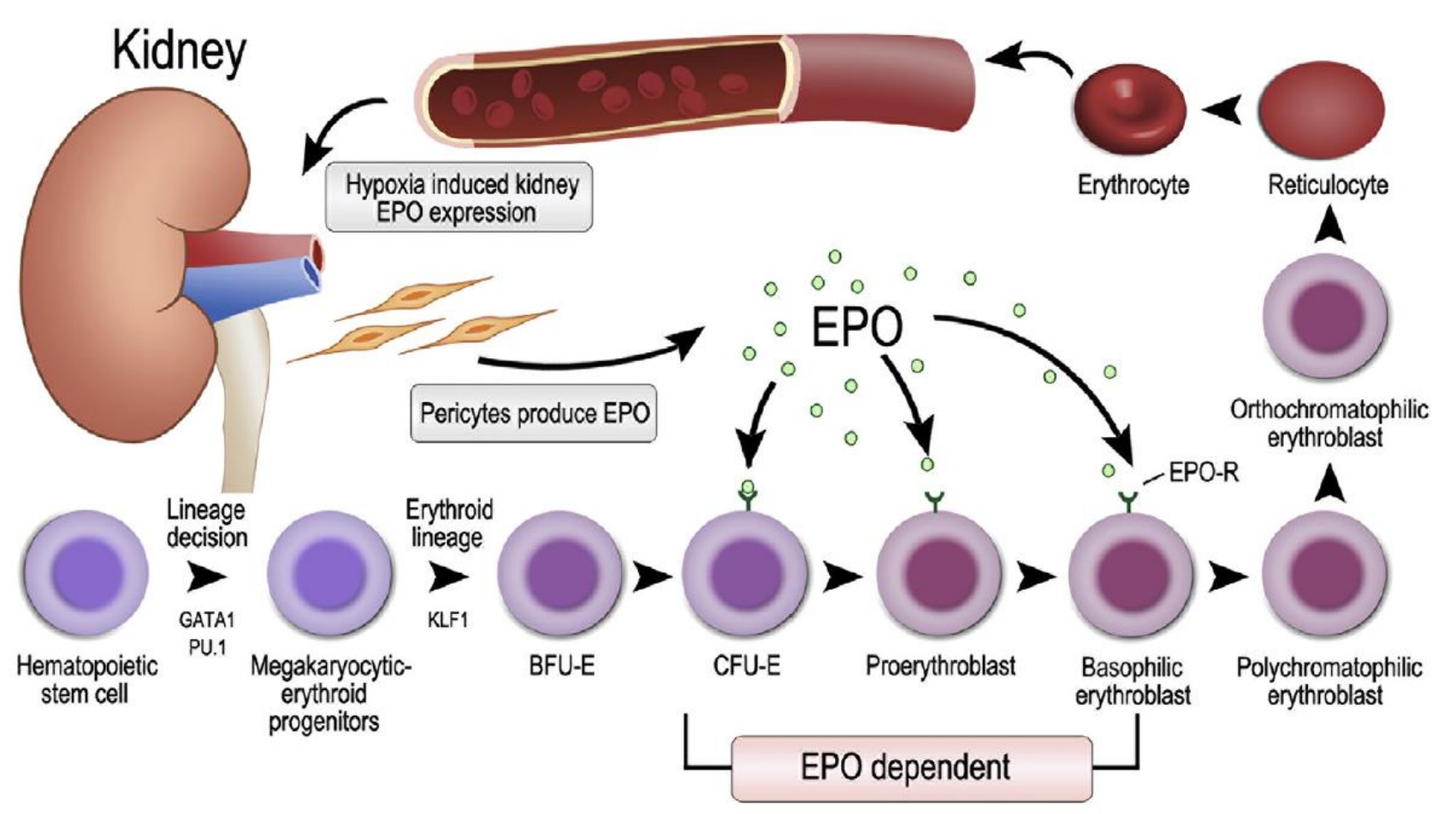
Contributors	Contributions	Comment
Bert (1882) Viault (1890) Miescher (1890)	Observation of increased RBC count at high altitude	A direct relationship of hypoxia to RBC count was proposed
Carnot and Deflandre (1906)	Experiment on injected blood from anaemic rabbits to donor rabbits causing a 20%–40% increased RBC in blood	Suggested a humoral factor "haemopoietine" to control RBC production
Muller (1912) Sandor (1932) Krumdieck (1943)	Experiment on injected blood from hypoxic rabbits to donor rabbits causing an increased RBC in blood	A direct relationship of hypoxia to RBC count demonstrated
Bonsdorff and Jalavisto (1948)	Experiment on injected blood from hypoxic animals to untreated animals causing a raised RBC production	"Erythropoietin" was introduced to support the presence and the transferability of the humoral factor
Reissmann (1950) Ruhenstroth-Bauer (1950)	Increased RBC production on parabiotic animals when hypoxia and anaemia was introduced in one of them	A direct evidence of the presence of EPO to cause an increase in RBC in hypoxia/anaemia
Erslev (1953)	Repeated infusing plasma from severely anaemic rabbits to donor rabbits causing increased packed cell volume/reticulocyte count	Predicted the therapeutic potential of EPO if purified
Hodgson and Toha (1954)	EPO activity isolated in urine and plasma of anaemic rabbits	First to demonstrate EPO activity in urine
Stohlman *et al* (1954) Schmid and Gilbersten (1955)	Observations of RBC hyperplasia in bone marrow in patients with patent ductus arteriosus	Suggested hypoxia of lower part of body and increased erythropoiesis
Jacobson *et al* (1957)	No increase in RBC in nephrectomised animals	First to support EPO production of renal origin
Kuratowsha *et al* (1961) Fisher and Birdwell (1961)	Detection of EPO activity in isolated perfused kidney	Confirmed kidney as a source of EPO production
Fischer *et al* (1965) Frenkel *et al* (1968)	Localisation of EPO production to renal glomeruli	Suggested the regional secretion of EPO in kidney
Katz *et al* (1968) Fried (1972)	Detection of EPO activity in liver	Confirmed liver as another source of EPO production
Essers *et al* (1974)	Suggested liver being insufficient to replace kidney for EPO production	Supported kidney as the main source of EPO production
Miyake *et al* (1977)	Purification of EPO from urine in patients with aplastic anaemia	First to isolate and characterise EPO
Anagnostone *et al* (1977) Van Stone and Max (1979) Eschbach *et al* (1984)	EPO on animals with anaemia of renal failure	Demonstrated the effectiveness of EPO to correct anaemia
Jacobs *et al* (1985) Lin *et al* (1985)	Cloning of EPO gene via "reverse genetics"	Paved the way for industrial manufacturing of recombinant EPO Allowed sufficient quantity of EPO for clinical use

Postgrad Med J 2003; 79:367–376

Ερυθροποιητίνη
ιστορικό

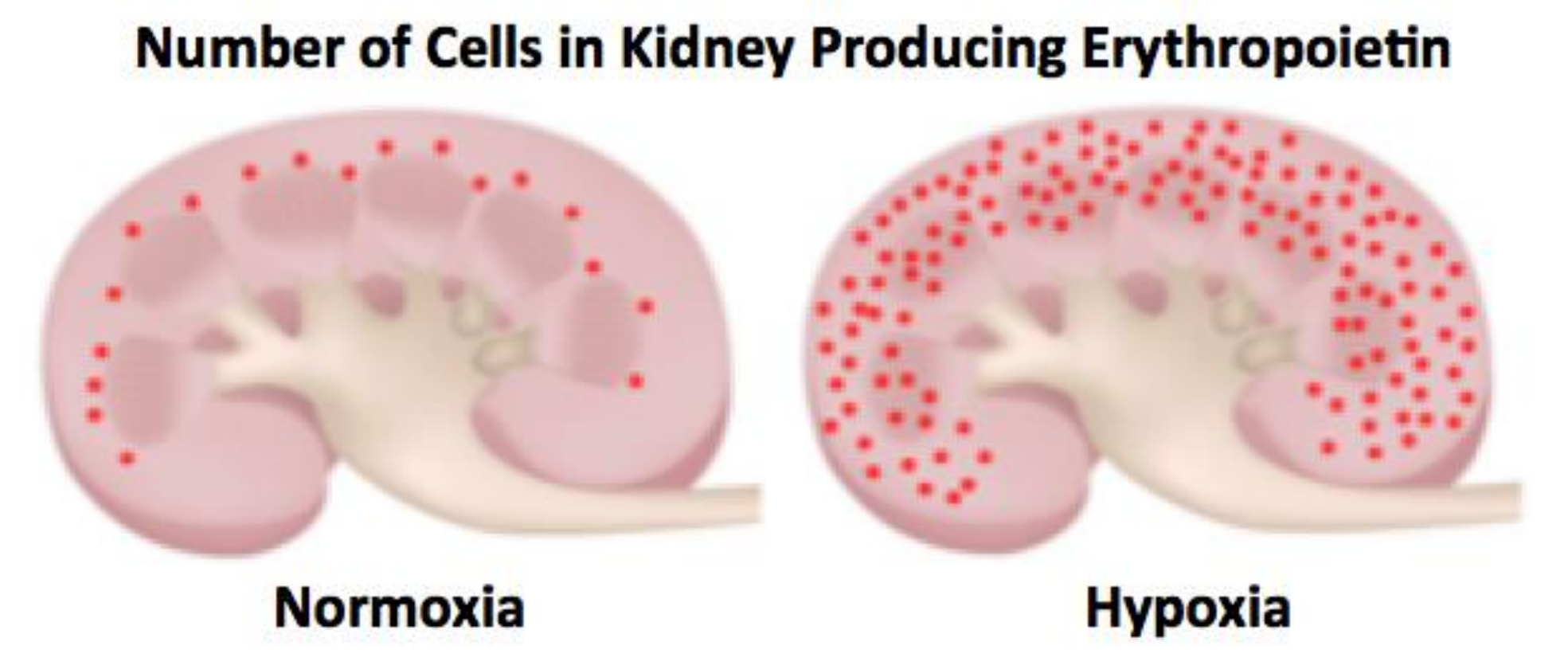
- 1906, οι Carnot και Deflandre υπέθεσαν ότι στον ορό αναιμικών ασθενών υπάρχει "Αιμοποιητίνη" και η οποία διεγείρει το μυελό των οστών για ερυθροποίηση
- 1953, ο Erslev επιβεβαιώνει την ύπαρξη ενός "παράγοντα διεγερτικού της ερυθροποίησης" και τον ονομάζει Ερυθροποιητίνη
- 1957, ο Jacobson ήταν ο πρώτος, που διαπίστωσε ότι οι νεφροί είναι επιφορτισμένοι με τη ρύθμιση της παραγωγής ερυθρών αιμοσφαιρίων, αφού παράγουν Ερυθροποιητίνη

Ερυθροποιητίνη
δράση



Journal of the Formosan Medical Association (2018) 117, 955-963

Ερυθροποιητίνη
δράση



http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/otherendo/epo.html

Ερυθροποιητίνη
ιστορικό

- 1977, οι Miyake και συν. απομόνωσαν καθαρή μορφή ανθρώπινης Ερυθροποιητίνης στα ούρα
- 1985, οι Lin και συν. και οι Jacobs και συν. κατόρθωσαν να απομονώσουν και να κλωνοποιήσουν το γονίδιο για την ανθρώπινη Ερυθροποιητίνη
- Εισαγωγή του ανασυνδυασμένου γονιδίου της EPO σε κύτταρα ωοθηκών κινέζικου hamster, τα οποία καλλιεργούμενα παρήγαγαν την ορμόνη
- 1989 Άδεια κυκλοφορίας FDA

Ερυθροποιητίνη
εφαρμογή

The Lancet · Saturday 22 November 1986

EFFECT OF HUMAN ERYTHROPOIETIN DERIVED FROM RECOMBINANT DNA ON THE ANAEMIA OF PATIENTS MAINTAINED BY CHRONIC HAEMODIALYSIS

CHRISTOPHER G. WINEARLS[1] DESMOND O. OLIVER[2]
MARTIN J. PIPPARD[3] CECIL REID[3]
MICHAEL R. DOWNING[4] P. MARY COTES[3]

Department of Medicine, Royal Postgraduate Medical School, London W12 0HS;[1] Renal Unit, Churchill Hospital, Oxford,[2] Section of Haematology, Clinical Research Centre, Harrow, Middlesex, UK;[3] and Amgen, Thousand Oaks, California, USA[4]

solely by the kidney.[4,5] Thus anaemia is most severe in anephric patients who have inappropriately low erythropoietin concentrations[6] and least severe in patients with adult polycystic kidney disease in whom renal mass, if not function, is preserved.[7] Furthermore, patients whose non-functioning, previously shrunken kidneys develop "acquired cystic disease" frequently show a striking rise in haemoglobin[8,9] as well as increased serum erythropoietin concentrations[10] despite an unchanged uraemic state. Lately, Eschbach and colleagues[11] have shown that daily infusions of erythropoietin-rich plasma can completely reverse anaemia in uraemic sheep. However, the routine

Ερυθροποιητίνη
εφαρμογή

CORRECTION OF THE ANEMIA OF END-STAGE RENAL DISEASE WITH RECOMBINANT HUMAN ERYTHROPOIETIN

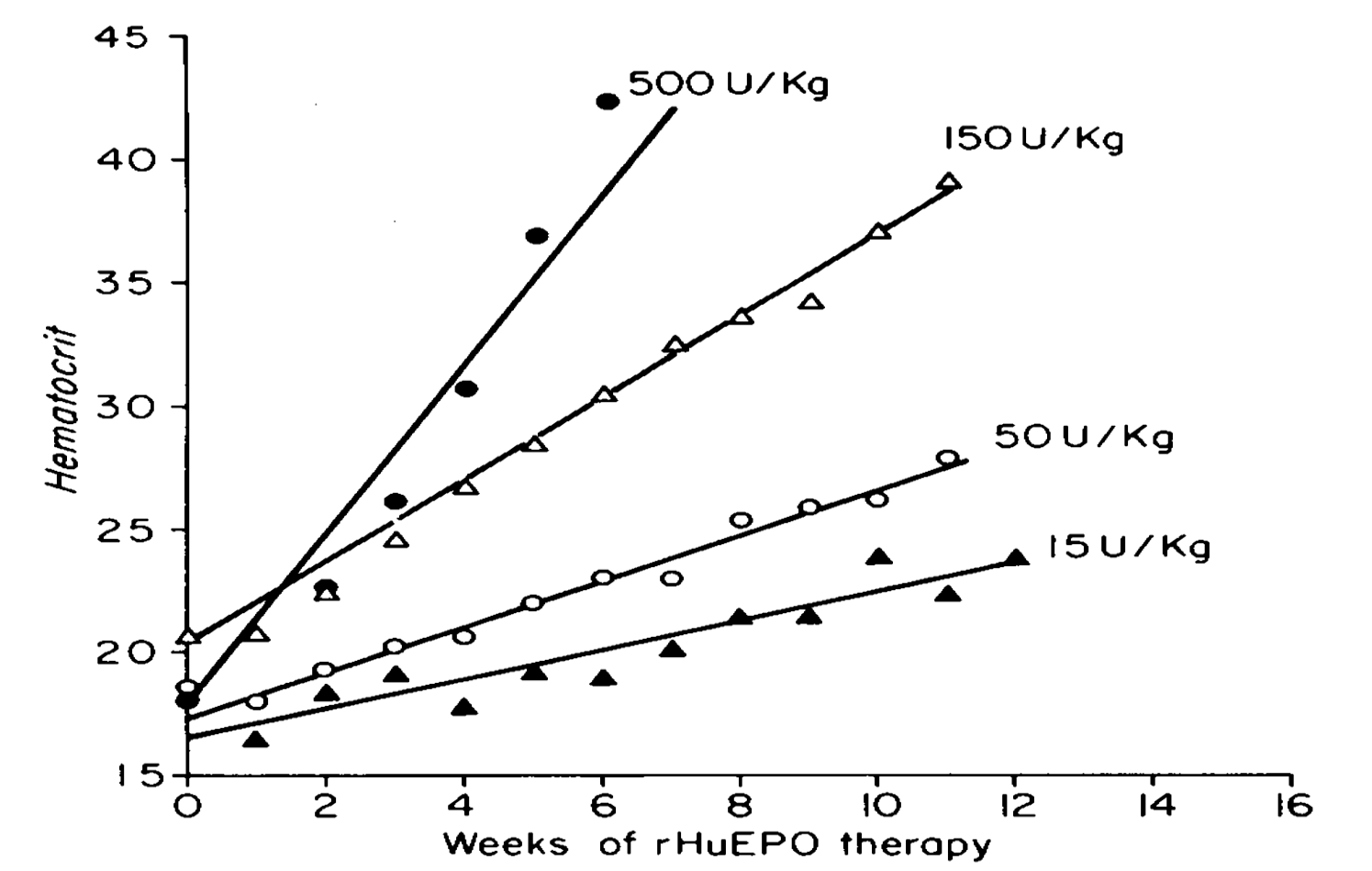
Results of a Combined Phase I and II Clinical Trial*

JOSEPH W. ESCHBACH, M.D., JOAN C. EGRIE, PH.D., MICHAEL R. DOWNING, PH.D., JEFFREY K. BROWNE, PH.D., AND JOHN W. ADAMSON, M.D.

Drs. John Adamson and Joseph Eschbach have helped develop a hormone injection **that makes life safer and more pleasant for kidney dialysis patients.**

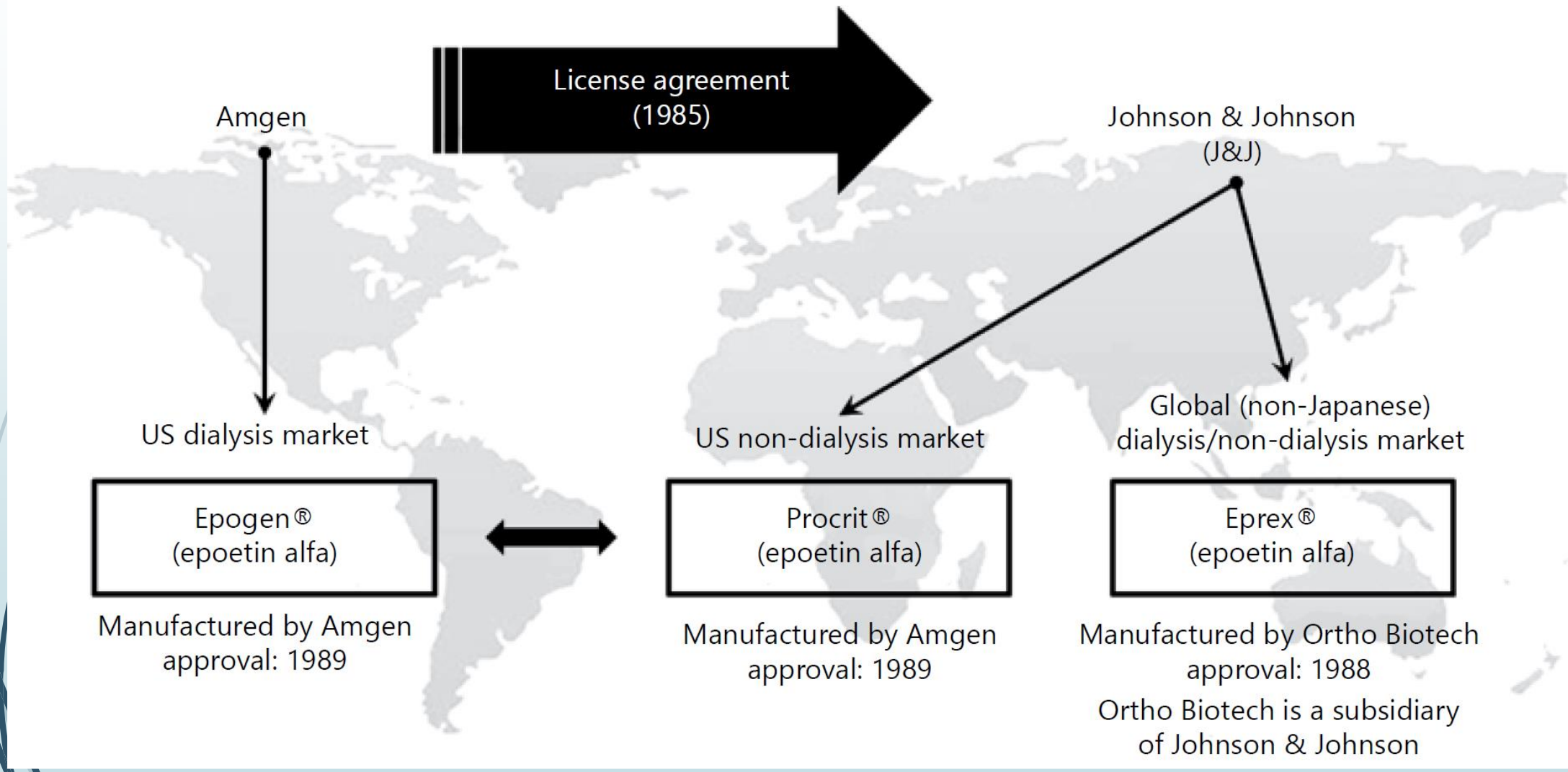
N Engl J Med 1987;316:73-78

Ερυθροποιητίνη
εφαρμογή



N Engl J Med 1987;316:73-78

Ερυθροποιητίνη
σκευάσματα



Am J Nephrol 2017;45:235–247

Ερυθροποιητίνη σκευάσματα

INN	Trade name	License holder	Approval	Manufacturing process	Licensed in		
					European Union	United States	Other regions
First generation							
Epoetin alfa	Epogen®	Amgen	1989	Recombinant DNA technology (in CHO cells)		✓	
	Eprex®	Ortho Biotech	1988		✓	✓	✓
	Procrit®	Amgen	1989			✓	
Epoetin beta	Recormon®	Boehringer Mannheim	1990	Recombinant DNA technology (in CHO cells)	✓		
Epoetin omega	Epomax® Hemax®	Elanex/Baxter	1990	Recombinant DNA technology (in hamster kidney cells)			✓
Second generation							
Epoetin beta	NeoRecormon®	Roche	1997	Recombinant DNA technology (in CHO cells)	✓		✓
Darbepoetin alfa	Aranesp®	Amgen	2001	Recombinant DNA technology (in CHO cells)	✓	✓	
Third generation							
Epoetin delta	Dynepo®	Transkaryotic therapies/Shire	2002	Gene activation technology (in HT-1080 cells)	✓	✓	
Methoxy polyethylene glycol epoetin beta	Mircera®	Roche	2007	Recombinant DNA technology (in CHO cells)	✓	✓	
Epoetin alfa (biosimilar)	Binocrit®	Sandoz	2007	Recombinant DNA technology (in CHO cells)	✓		
	Abseamed®	Medice					
	Epoetin Alfa Hexal®	Hexal AG					
Epoetin zeta (biosimilar)	Retacrit™	Hospira, a Pfizer company	2007	Recombinant DNA technology (in CHO cells)	✓		
	Silapo™	Stada					✓
Epoetin theta	Biopoin®	Teva	2009	Recombinant DNA technology (in CHO cells)	✓		
	Eporatio®	RatioPharm					

INN, international nonproprietary name; NCE, new chemical entity; NME, new molecular entity.

Am J Nephrol 2017;45:235–247

Ερυθροποιητίνη
σκευάσματα

	Half-Life, h	
	Intravenous Administration	Subcutaneous Administration
Epoetin alfa	6.8	19.4
Darbepoetin alfa	25.3	48.8
Methoxy polyethylene glycol-epoetin beta	130	133

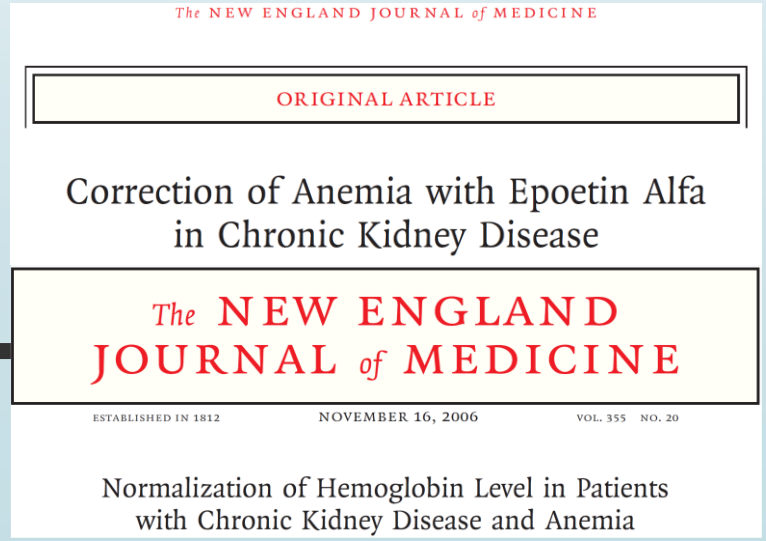
Am J Kidney Dis. 71(3): 423-435.

Ερυθροποιητίνη
Αποτελεσματικότητα

- Μείωση των μεταγγίσεων
- Βελτίωση συμπτωμάτων όπως αδυναμία, καταβολή κλπ
- Βελτίωση της υπερτροφίας της αριστεράς κοιλίας
- Βελτίωση της καρδιαγγειακής θνητότητας
- Βελτίωση της ποιότητας ζωής

Ερυθροποιητίνη
Κλινικές οδηγίες Θεραπευτικός στόχος

- DOQI 1997: Ht 33%-36% (Hb 11-12 g/dl)
- KDOQI 2000: Hb 11-12 g/dl (Ht 33%-36%)
- EBPG 2000: Hb > 11 g/dl (…NO UPPER LIMIT)
- EBPG 2004: Hb > 11 g/dl (UPPER LIMIT: 14 g/dl)
- KDOQI 2006: Hb > 11 g/dl (UPPER LIMIT: …13 g/dl?)
- KDOQI 2007: Hb > 11 g/dl (UPPER LIMIT: 13 g/dl)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

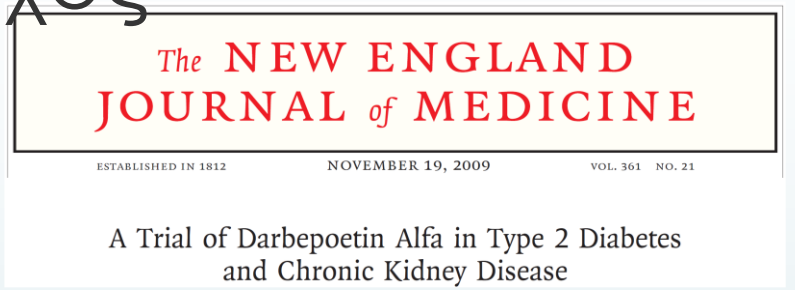
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2006 VOL. 355 NO. 20

Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia

Ερυθροποιητίνη
Κλινικές οδηγίες Θεραπευτικός στόχος

- KDIGO 2008: Hb 9.5 – 11.5 g/dl
- ERBP 2009: Hb 11 – 12 g/dl (UPPER LIMIT: 13 g/dl)
- ERBP 2010: Hb 11 – 12 g/dl (UPPER LIMIT: 13 g/dl) **Diabetic: Hb 10-12 g/dl**
- KDIGO 2012:
  - CKD ND: Hb 10 - 11.5 g/dl (UPPER LIMIT: 13 g/dl)
  - CKD D: Hb 9 - 11.5 g/dl (UPPER LIMIT: 13 g/dl)
- ERBP 2013: Hb 10 – 12 g/dl (UPPER LIMIT: 13 g/dl)
- KDOQI 2013: Hb 9 - 11 g/dl
- NICE 2020: Hb 10 – 12 g/dl



Ερυθροποιητίνη Ασφάλεια

The New England Journal of Medicine

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

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

N Engl J Med 1998;339:584-90

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

Ajay K. Singh, M.B., B.S., Lynda Szczech, M.D., Kezhen L. Tang, Ph.D., Huiman Barnhart, Ph.D., Shelly Sapp, M.S., Marsha Wolfson, M.D., and Donal Reddan, M.B., B.S., for the CHOIR Investigators*

N Engl J Med 2006;355:2085-98

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2006 VOL. 355 NO. 20

Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia

Tilman B. Drüeke, M.D., Francesco Locatelli, M.D., Naomi Clyne, M.D., Kai-Uwe Eckardt, M.D., Iain C. Macdougall, M.D., Dimitrios Tsakiris, M.D., Hans-Ulrich Burger, Ph.D., and Armin Scherhag, M.D., for the CREATE Investigators*

N Engl J Med 2006;355:2071-84

The NEW ENGLAND JOURNAL of MEDICINE

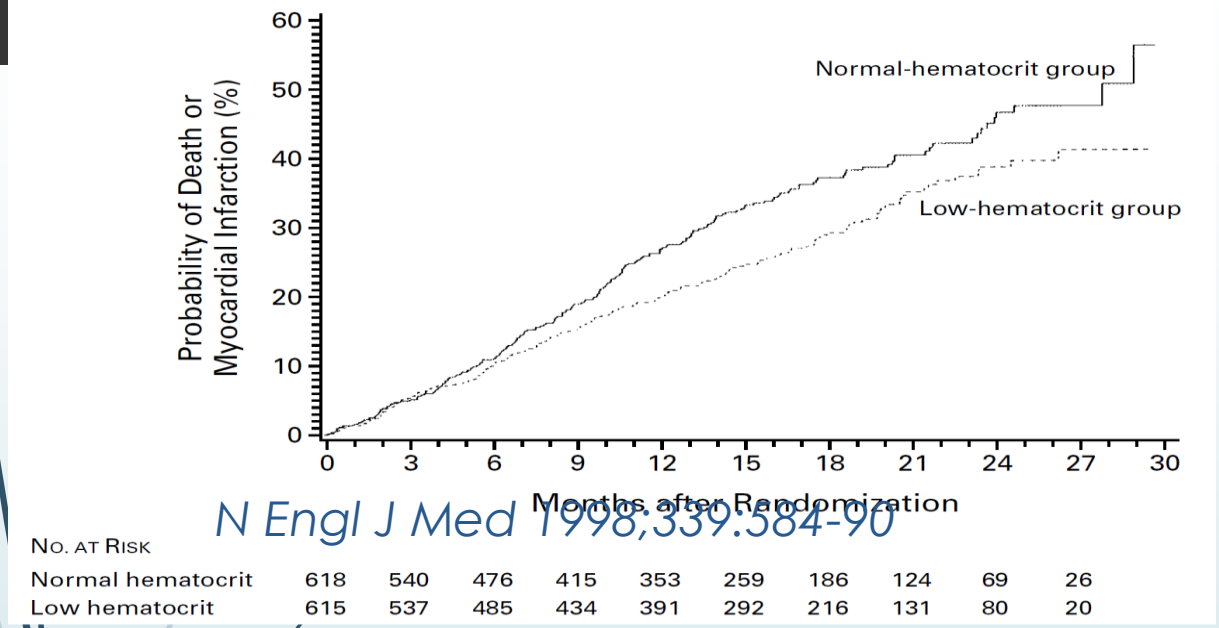
ESTABLISHED IN 1812 NOVEMBER 19, 2009 VOL. 361 NO. 21

A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D., Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D., Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D., John J.V. McMurray, M.D., Patrick Parfrey, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D., Ajay K. Singh, M.D., Scott D. Solomon, M.D., and Robert Toto, M.D., for the TREAT Investigators*

N Engl J Med 2009;361:2019-32

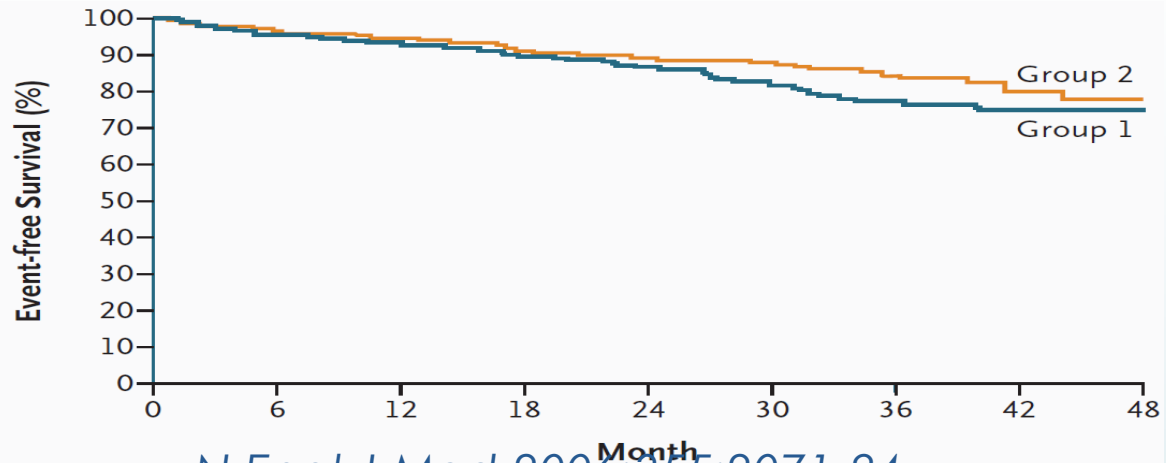
Ερυθροποιητίνη Ασφάλεια



No. at Risk

Normal hematocrit	618	540	476	415	353	259	186	124	69	26
Low hematocrit	615	537	485	434	391	292	216	131	80	20

N Engl J Med 1998;339:584-90

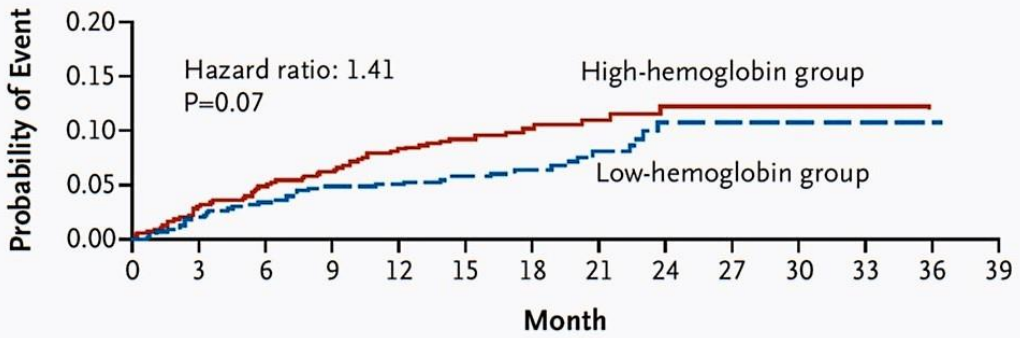


No. at Risk

Group 1	301	279	268	249	207	158	97	56	2
Group 2	302	286	272	257	223	177	121	61	2

N Engl J Med 2006;355:2071-84

Hospitalization for CHF (without RRT)

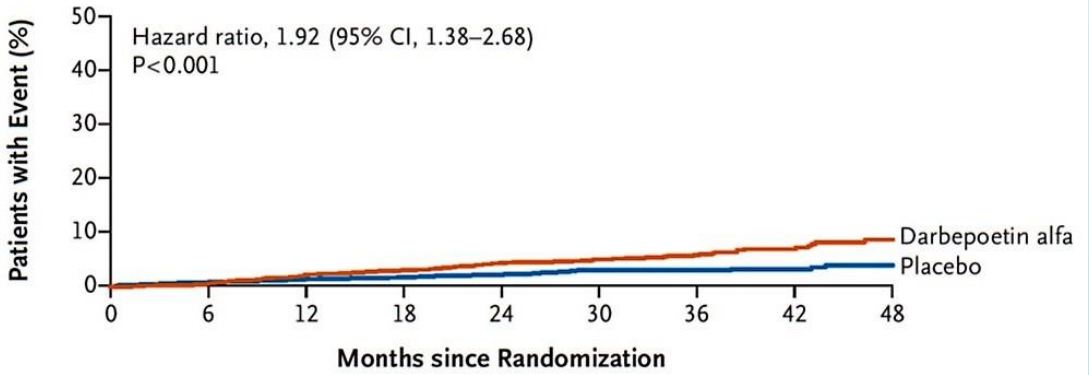


No. at Risk

High-hemoglobin	715	656	591	523	461	359	273	179	102	73	56	23
Low-hemoglobin	717	663	596	544	504	402	299	187	111	70	45	24

N Engl J Med 2006;355:2085-98

Fatal or Nonfatal Stroke



No. at Risk

Darbepoetin alfa	2012	1923	1787	1581	1247	863	590	341	141
Placebo	2026	1914	1783	1575	1262	886	561	338	132

N Engl J Med 2009;361:2019-32

Ερυθροποιητίνη
Ασφάλεια

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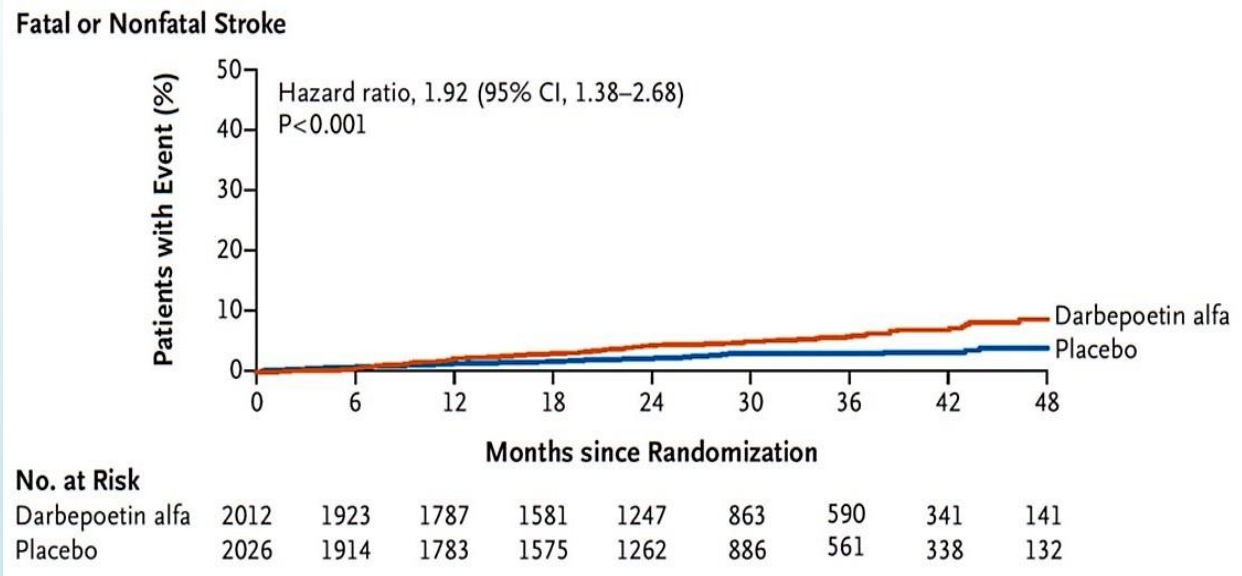


N Engl J Med 2009;361:2019-32

Ερυθροποιητίνη
Ασφάλεια

2009: A Requiem for rHuEPOs—But Should We Nail Down the Coffin in 2010?

David Goldsmith
Renal Department, Guy's Hospital, King's Health Partners, London, United Kingdom

ANEMIA

To TREAT or not to TREAT—that is the question

Andrzej Wiecek

NATURE REVIEWS Nephrology, 6, may 2010, 255

Clin J Am Soc Nephrol 5: 929–935, 2010

Ερυθροποιητίνη
Ασφάλεια

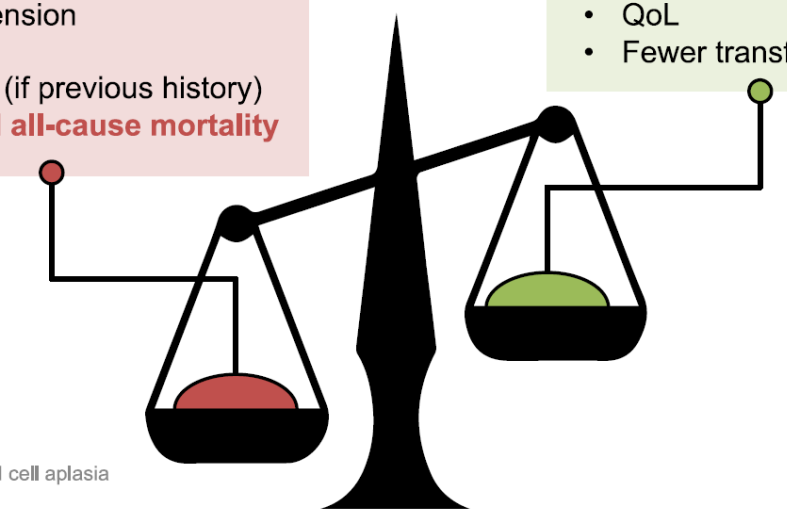
Complete anemia correction with ESAs

Risks

- Blood viscosity
- Platelets, adhesiveness
- Thromboembolic events
- Hypertension
- PRCA
- Cancer (if previous history)
- **CV and all-cause mortality**

Benefits

- Tissue oxygenation
- Physical performance
- Mental performance
- QoL
- Fewer transfusions



PRCA, pure red cell aplasia

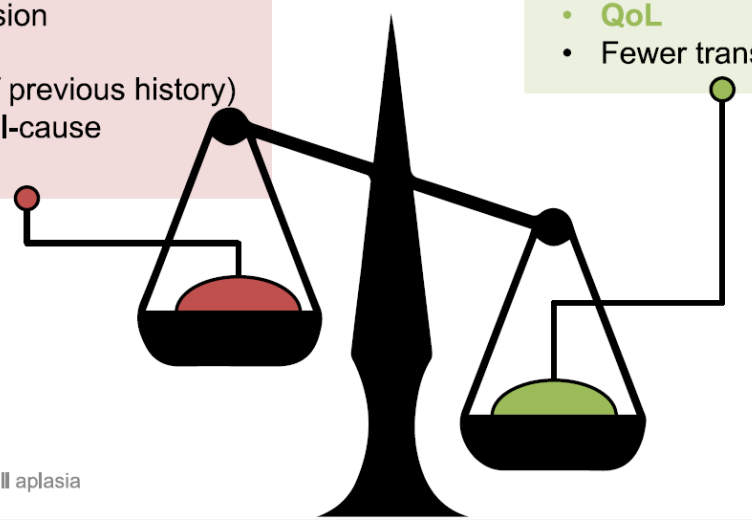
Partial anemia correction with ESAs

Risks

- Blood viscosity
- Platelets, adhesiveness
- Thromboembolic events
- Hypertension
- PRCA
- Cancer (if previous history)
- CV and all-cause mortality

Benefits

- Tissue oxygenation
- **Physical performance**
- **Mental performance**
- **QoL**
- Fewer transfusions



PRCA, pure red cell aplasia

Drüeke Renal Replacement Therapy (2018) 4:46

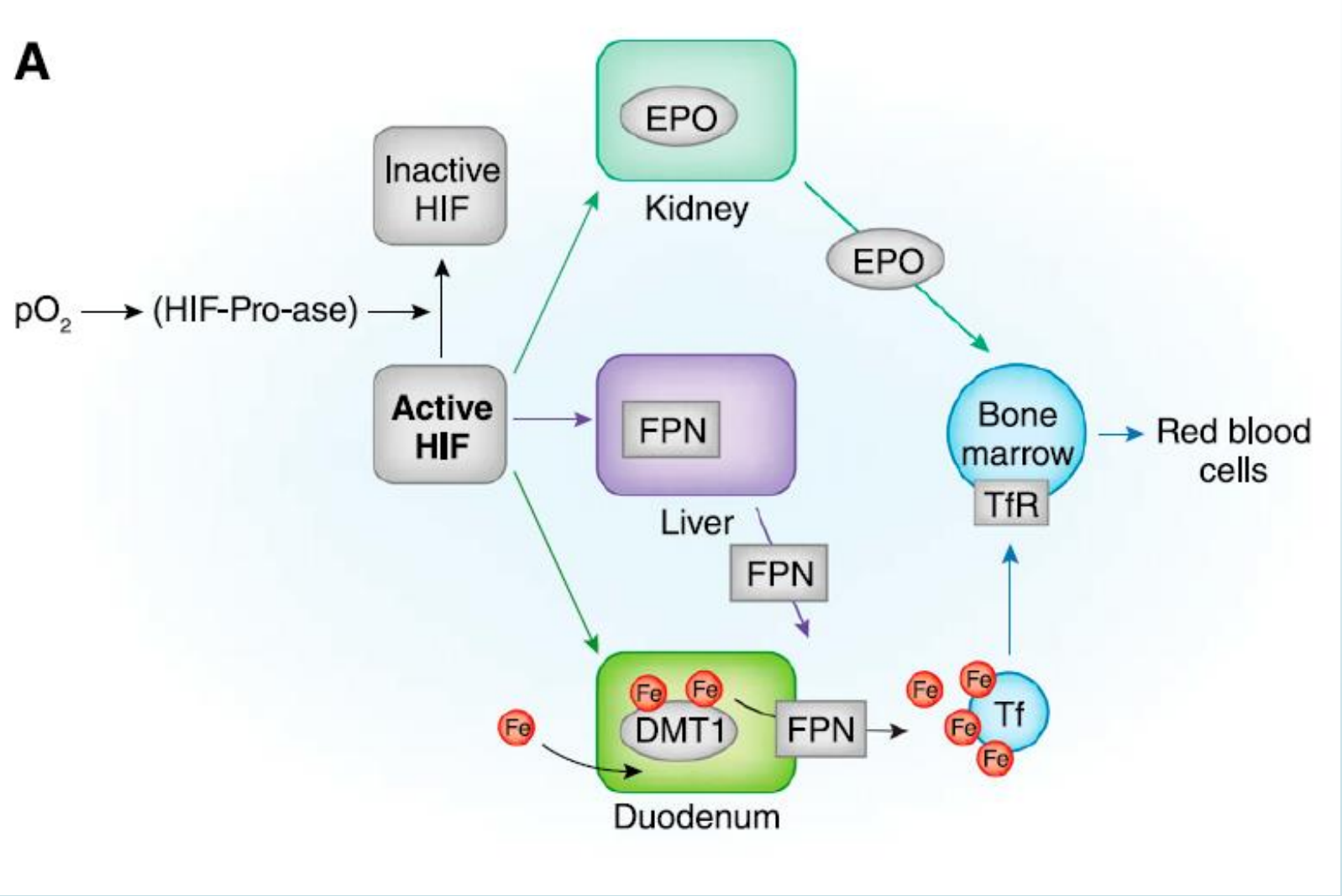
Αναιμία

Αντιμετώπιση

- Χορήγηση ανασυνδυασμένης Ερυθροποιητίνης
- Χορήγηση Σιδήρου

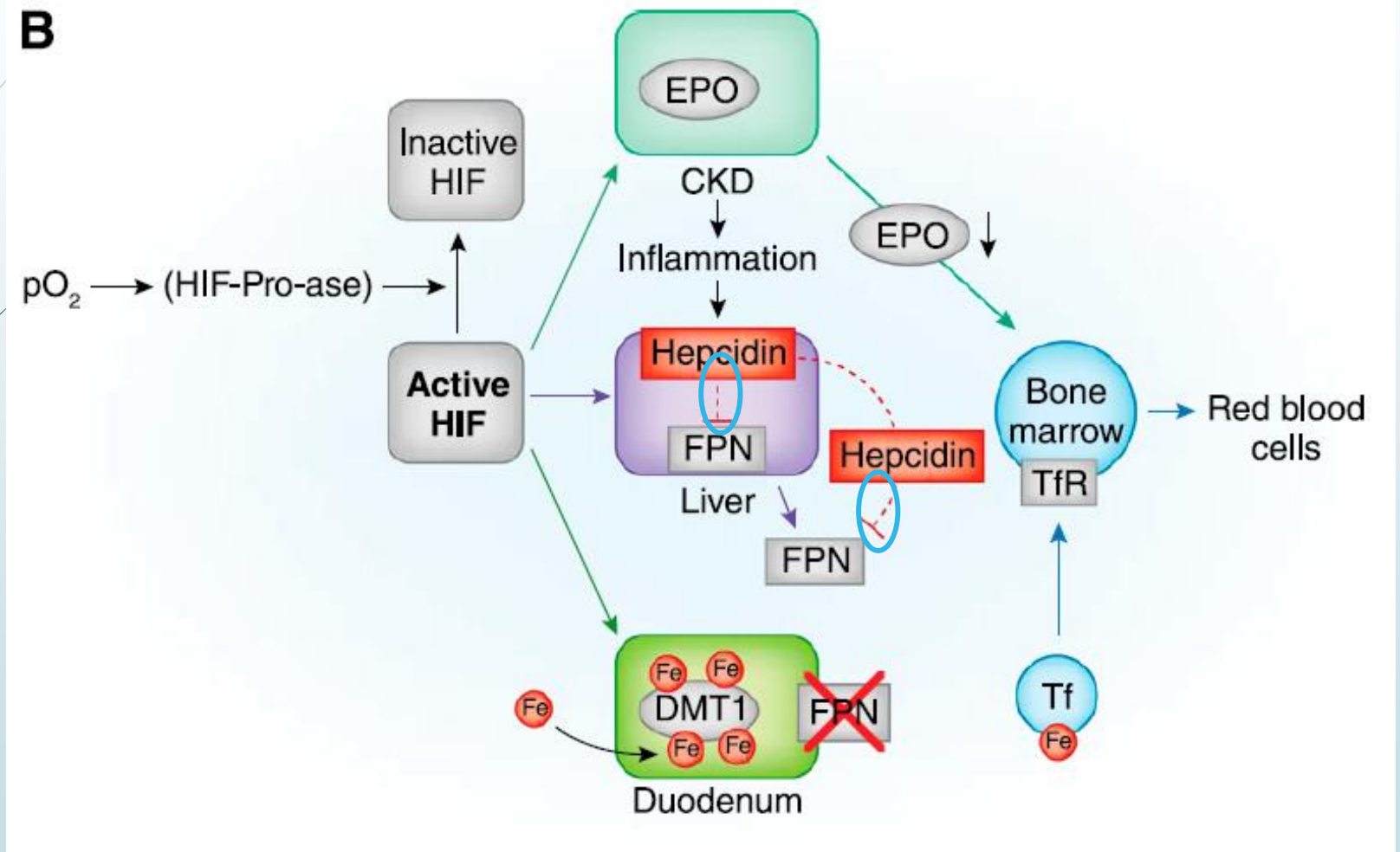
- Νέοι Ερυθροποιητικοί παράγοντες

Χρόνια Νεφρική Νόσος και σίδηρος



Clin J Am Soc Nephrol 11: 1269–1280, 2016

Χρόνια Νεφρική Νόσος και σίδηρος



Clin J Am Soc Nephrol 11: 1269–1280, 2016

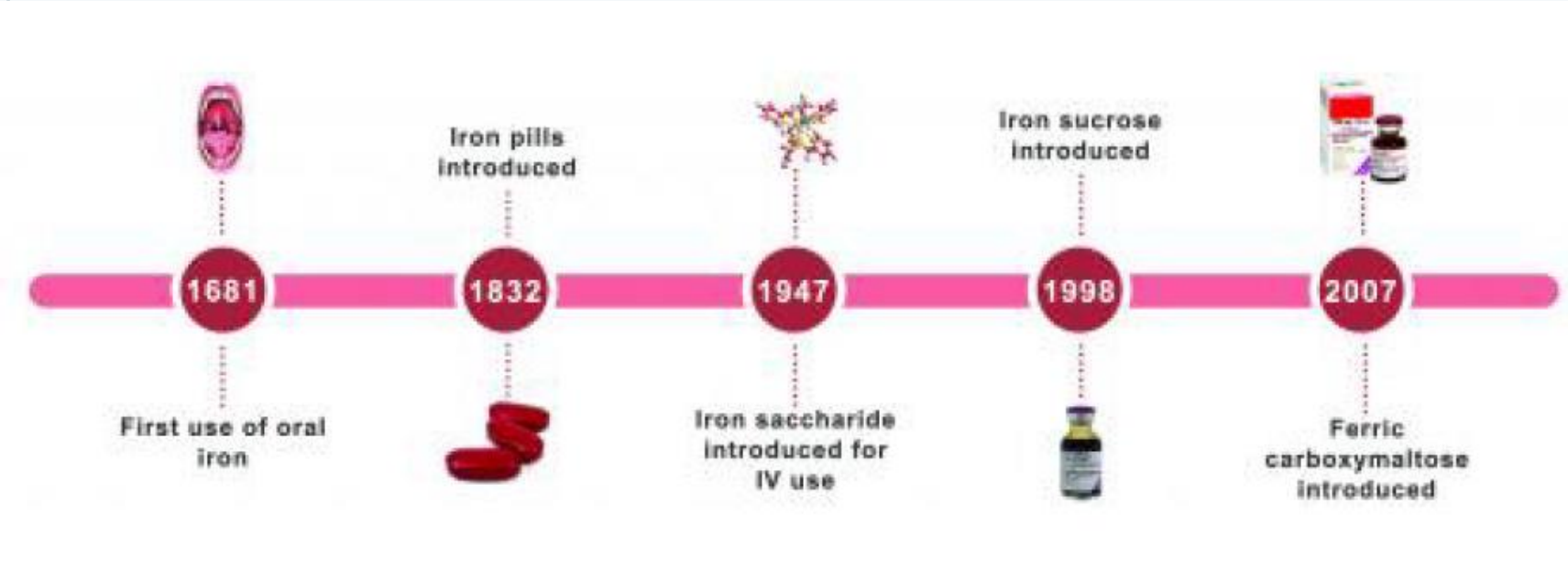
Χρόνια Νεφρική Νόσος και σίδηρος

- Απόλυτη ανεπάρκεια σιδήρου
  - Μειωμένη απορρόφηση
  - Αυξημένες απώλειες
- Λειτουργική ανεπάρκεια σιδήρου
  - Μειωμένη ικανότητα μεταφοράς σιδήρου
  - Αυξημένη ερυθροποίηση λόγω χορήγησης ESA

Χρόνια Νεφρική Νόσος και σίδηρος
Διάγνωση

- Χρώση σιδήρου σε επίχρισμα μυελού
- Φερριτίνη ορού (Ferritin)
- Κορεσμός Τρανσφερίνης (TSAT)
- Ποσοστό υπόχρωμων ερυθροκυττάρων (%HRC)
- Αιμοσφαιρίνη δικτυοερυθροκυττάρων (CHr)

Χορήγηση σιδήρου
Σκευάσματα



The Pharmaceutical Journal 5 MAR 2014

Χορήγηση σιδήρου
Σκευάσματα

Iron product generic name (brand name)	Year of U.S. FDA approval	Molecular weight in kilodaltons (kDa)	Maximum approved single dose, administration time	Common off-label maximal dose and administration time	Test dose?
Iron dextran, low molecular weight (INFeD)	1991	165	100 mg over >30 s	1000 mg or more i.v. over 4 h	Yes, 25 mg; monitor 15–30 min
Iron dextran, high molecular weight (Dexferrum)	1996	265	100 mg over >30 s	1000 mg or more i.v. over 4 h	Yes, 25 mg; monitor 15–30 min
Sodium ferric gluconate complex (Ferrlecit, Nulecit)	1999	289–444	125 mg i.v. push over 10 min	250 mg i.v. over 15 min	No
Iron sucrose (Venofer)	2000	34–60	200 mg i.v. over 2–5 min[a]	300 mg i.v. over 1 h	No
Newer iron products					
Ferumoxytol (Feraheme)	2009	750 kDa	510 mg i.v., <1 min	Same dose as 15 min infusion	No
Ferric carboxymaltose (Injectafer in USA; Ferinject in Europe)	2013	150	750 mg slow push or infusion over 15 min	None	No
Iron isomaltoside (Monofer in Europe; not approved in USA)	Europe only, 2009, not submitted for U.S. approval	150	20 mg/kg over 30–60 min	None	No

Curr Opin Nephrol Hypertens 2014, 23:186–191

Χορήγηση σιδήρου
Σκευάσματα

Table 2. Oral iron supplementation therapies in patients with nondialysis-dependent CKD

Therapy	Chemical Formula	Therapy Duration	Efficacy Measures[a]			Adverse Events		Studies in Nondialysis CKD
			Hb	Fer	TSAT	Frequency, %[b]	Most Common Adverse Events[c]	
Ferrous sulfate	$FeSO_4$	8 wk	X	X	X	68.1	Stool discoloration, URI, diarrhea, traumatic injury, fall, constipation, dyspnea, chest pain, dizziness, UTI, hyperkalemia, hypertension	Agarwal *et al.* (57)
Ferrous sulfate	$FeSO_4$	52 wk	X	X	X	81.7	Diarrhea, constipation, hypertension, peripheral edema, dyspepsia, UTI, nasopharyngitis	Macdougall *et al.* (58)
Ferrous sulfate	$FeSO_4$	56 d	X	—	X	59.2	Constipation	Qunibi *et al.* (59)
Ferrous sulfate	$FeSO_4$	12 mo	—	—	—	NR	NR	McMahon *et al.* (87)
Ferrous sulfate	$FeSO_4$	6 wk	—	X	X	20[d]	Constipation, stool discoloration, nausea, diarrhea	Agarwal *et al.* (88)
Ferrous sulfate	$FeSO_4$	29 d	X	—	—	NR	NR	Charytan *et al.* (89)
Ferrous sulfate	$FeSO_4$	56 d	X	X	X	19	Constipation, diarrhea, nausea, vomiting	Van Wyck *et al.* (90)
Ferrous sulfate	$FeSO_4$	3 mo	X	—	—	NR	NR	Aggarwal *et al.* (91)
Ferrous sulfate	$FeSO_4$	5.2 mo	X	X	NR	NR	NR	Stoves *et al.* (92)
Ferrous fumarate	$C_4H_2FeO_4$	21 d	X	X	X	52	Constipation, diarrhea	Spinowitz *et al.* (93)
Ferric citrate	$FeC_3H_5O(COO)_3$	12 wk	X	X	X	68.3	Diarrhea, constipation, abdominal discomfort, abdominal distension[e]	Yokoyama *et al.* (94)
Ferric citrate	$FeC_3H_5O(COO)_3$	12 wk	X	X	X	69.3	Stool discoloration, diarrhea, constipation, nausea, vomiting, URI	Block *et al.* (74)
Heme iron		6 mo	X	X	X	NR	Constipation, abdominal cramps, muscle cramps, bloating, diarrhea, nausea	Nagaraju *et al.* (80)
Liposomal iron	$Fe_4(P_2O_7)_3$	3 mo	X	—	—	3.1[d]	—	Pisani *et al.* (81)

Clin J Am Soc Nephrol 11: 1269–1280, 2016

Τοξικότητα σιδήρου

The NEW ENGLAND JOURNAL of MEDICINE

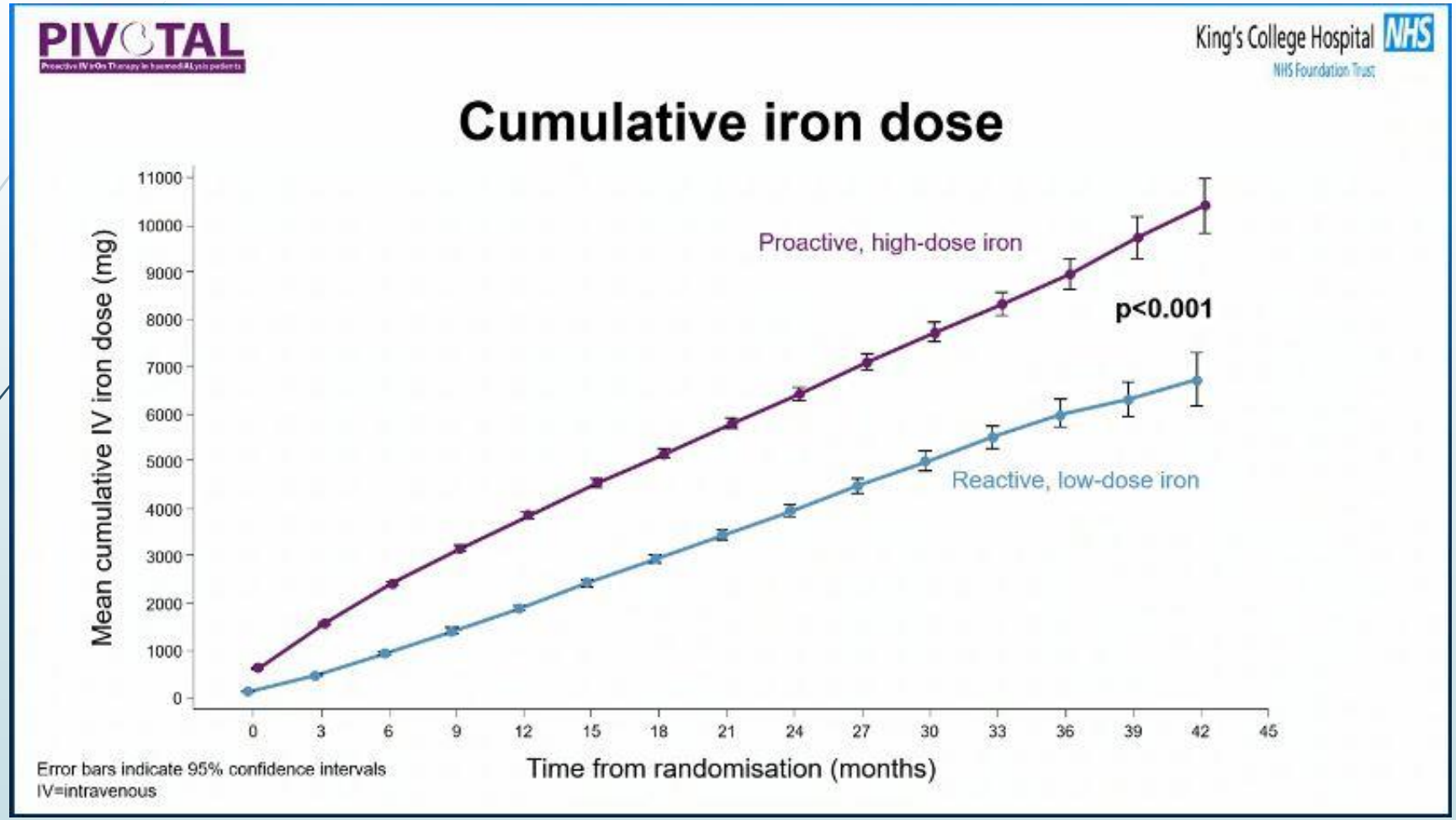
ORIGINAL ARTICLE

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*

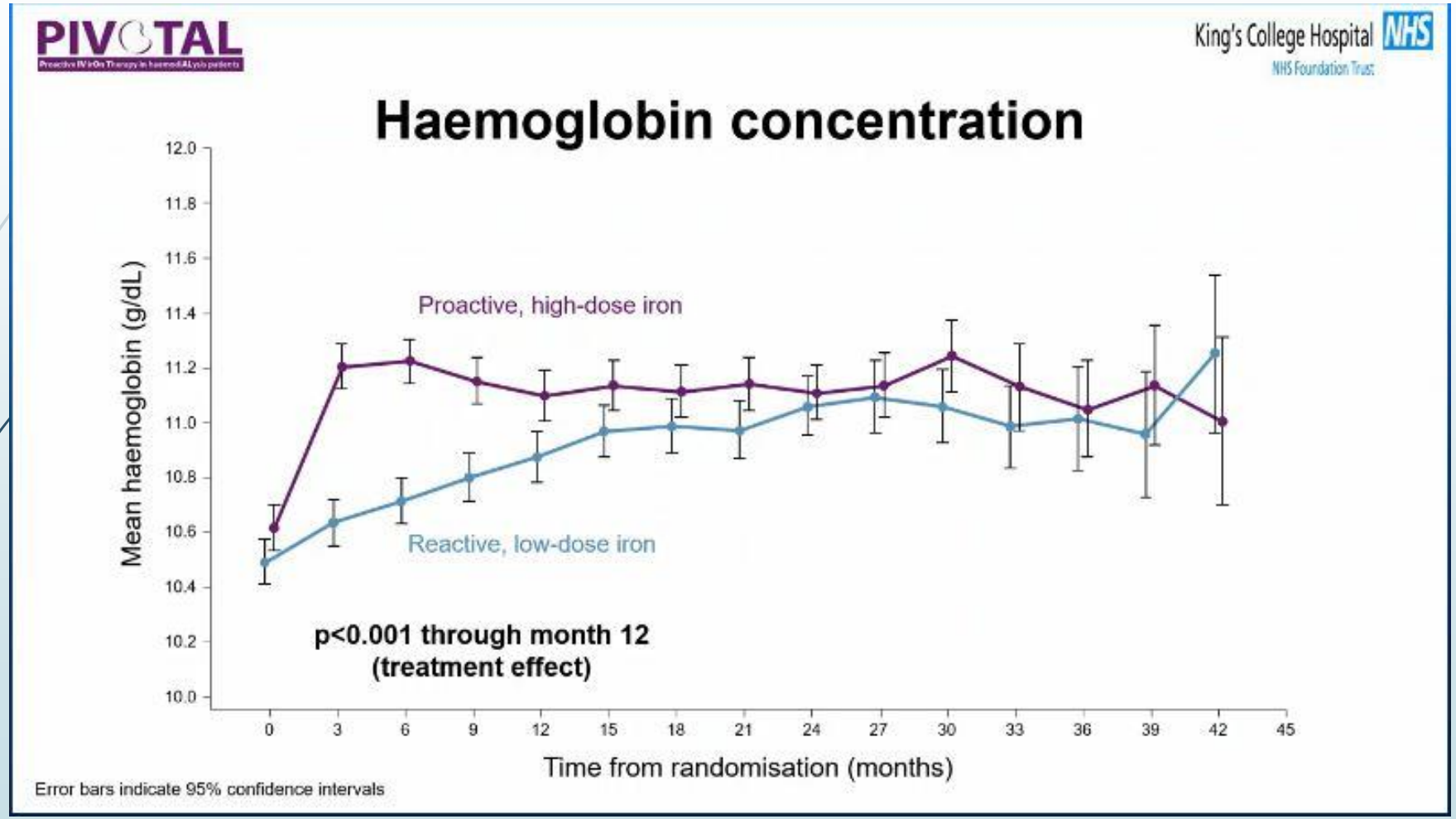
N Engl J Med 2019;380:447-58

Τοξικότητα σιδήρου



N Engl J Med 2019;380:447-58

Τοξικότητα σιδήρου



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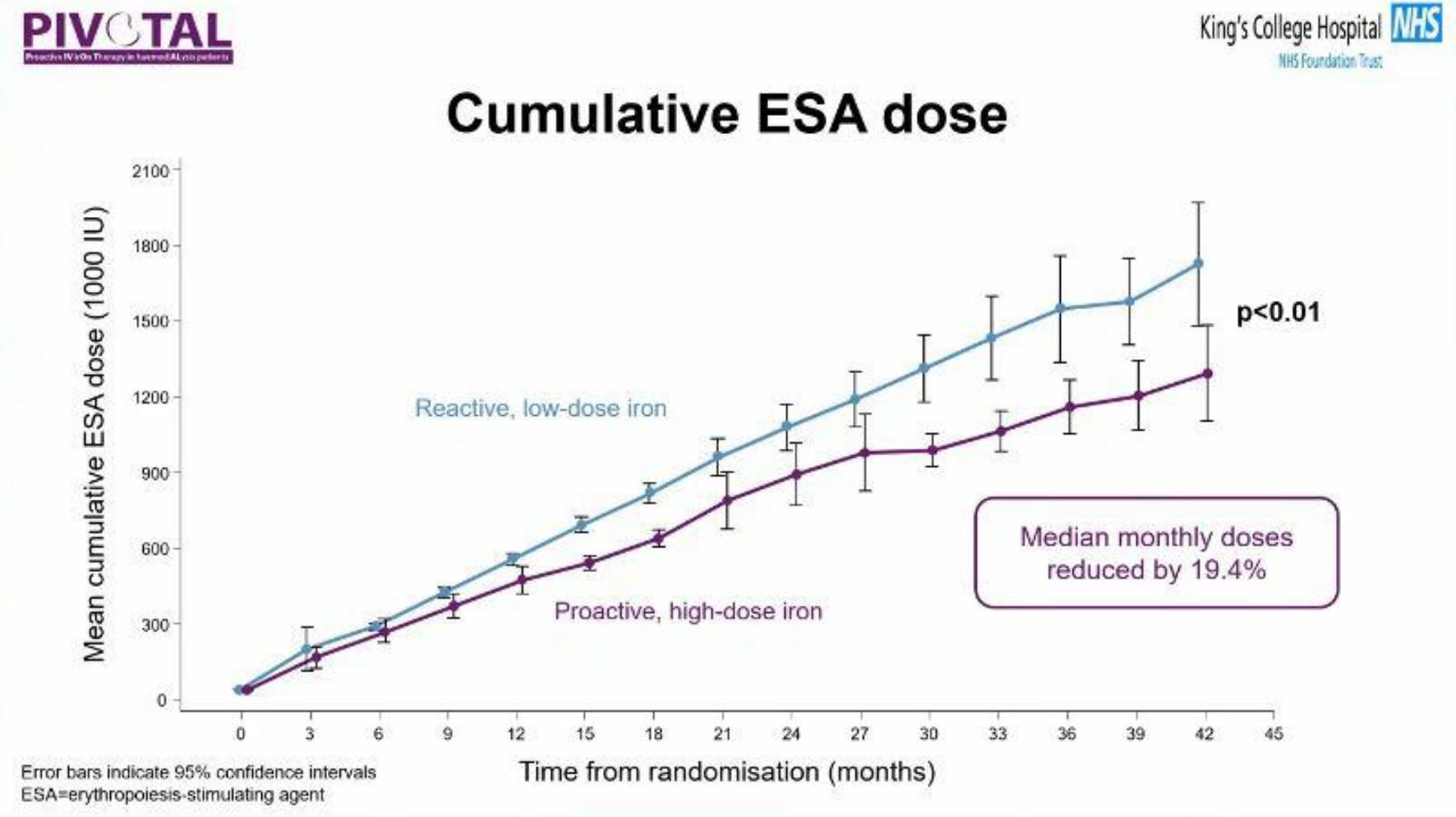
Τοξικότητα σιδήρου



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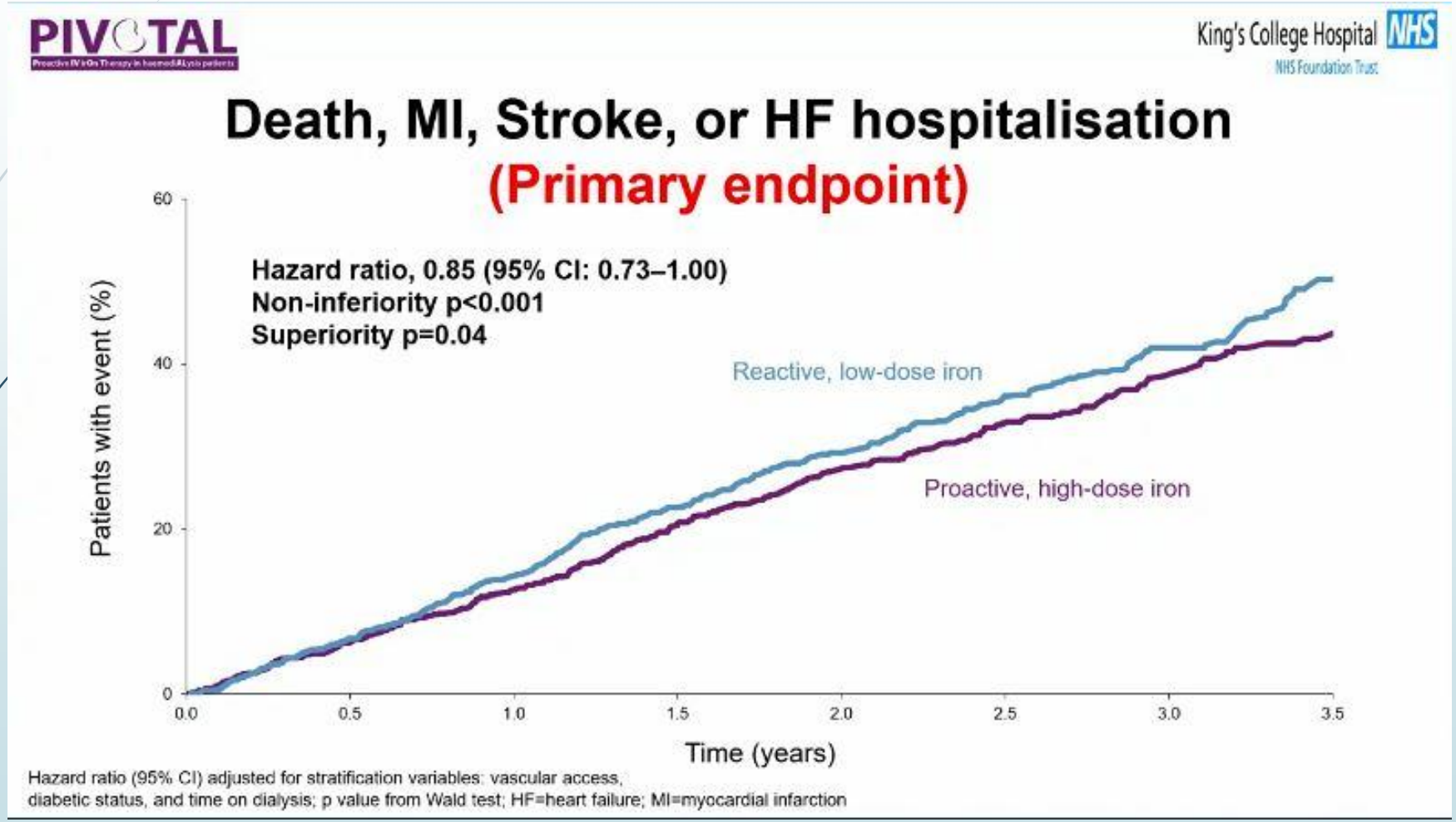
Τοξικότητα σιδήρου



N Engl J Med 2019;380:447-58

Τοξικότητα σιδήρου

PIVOTAL

King's College Hospital NHS
NHS Foundation Trust

Cardiovascular events

Outcome	Proactive, high-dose IV iron (N=1093) n (%)	Reactive, low-dose IV iron (N=1048) n (%)	Hazard ratio (95% CI)	p value
Fatal or nonfatal MI, fatal or nonfatal stroke, or hospitalisation for HF	149 (13.6)	168 (16.0)	0.80 (0.64–1.00)	**0.049**
Fatal or nonfatal MI	78 (7.1)	102 (9.7)	0.69 (0.52–0.93)	**0.015**
Fatal or nonfatal stroke	34 (3.1)	35 (3.3)	0.90 (0.56–1.44)	0.663
Hospitalisation for HF	51 (4.7)	70 (6.7)	0.66 (0.46–0.94)	**0.023**

Hazard ratio (95% CI) adjusted for stratification variables: vascular access, diabetic status, and time on dialysis; p value from Wald test
CI=confidence interval; HF=heart failure; IV=intravenous; MI=myocardial infarction

N Engl J Med 2019;380:447-58

Αναιμία

Αντιμετώπιση

- Χορήγηση ανασυνδυασμένης Ερυθροποιητίνης
- Χορήγηση Σιδήρου

- Νέοι Ερυθροποιητικοί παράγοντες

Νέοι ερυθροποιητικοί παράγοντες

- 1. Πεγκυνεσατίδη (Peginesatide)
- 2. Σταθεροποιητές HIF (HIF stabilizers)
- 3. Ρυθμιστές Εψιδίνης (Hepcidin modulation)
- 4. Αναστολείς GATA-2 (GATA-2 Inhibitors)
- 5. Γονιδιακή θεραπεία (EPO gene therapy)

Νέοι ερυθροποιητικοί παράγοντες

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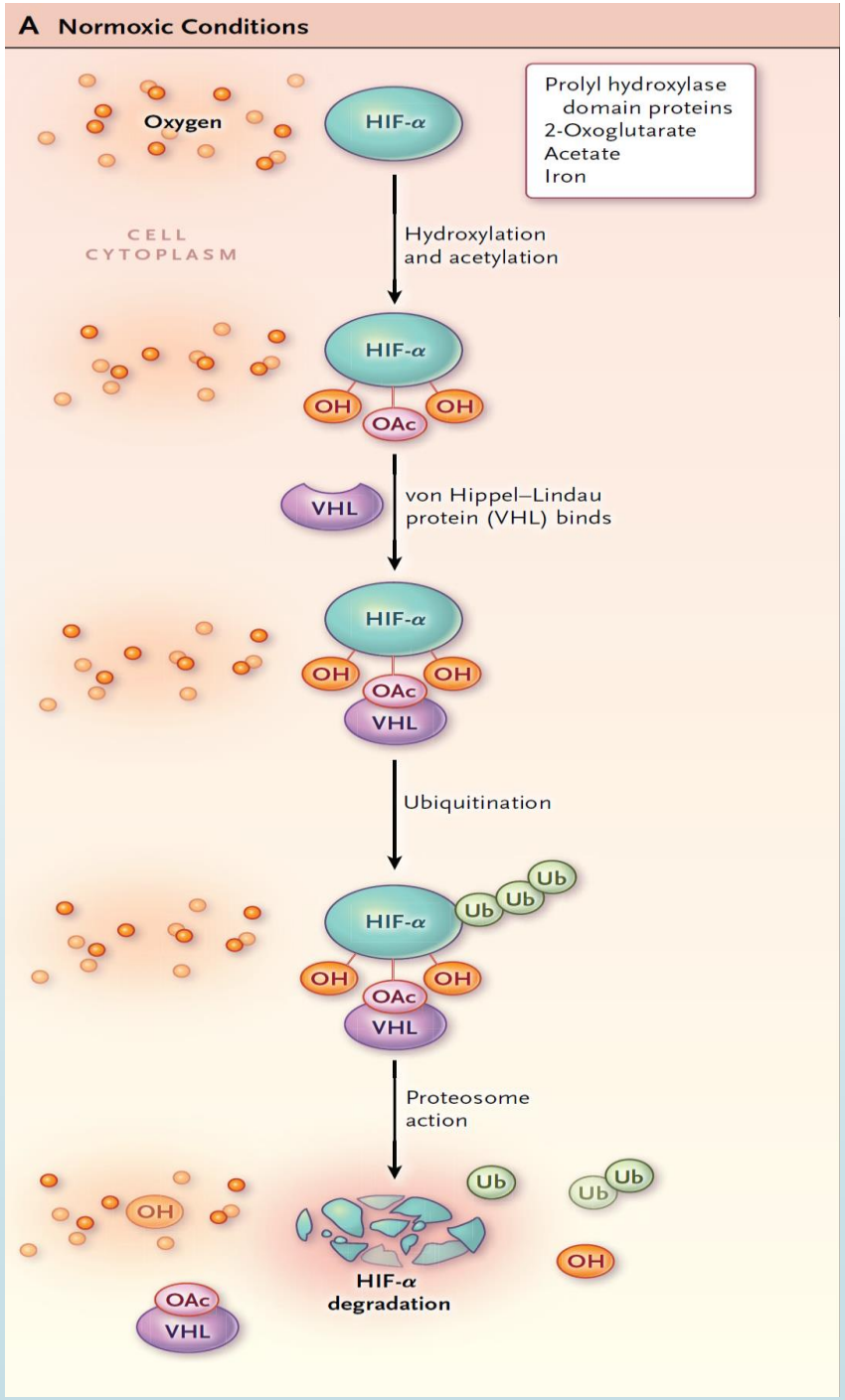
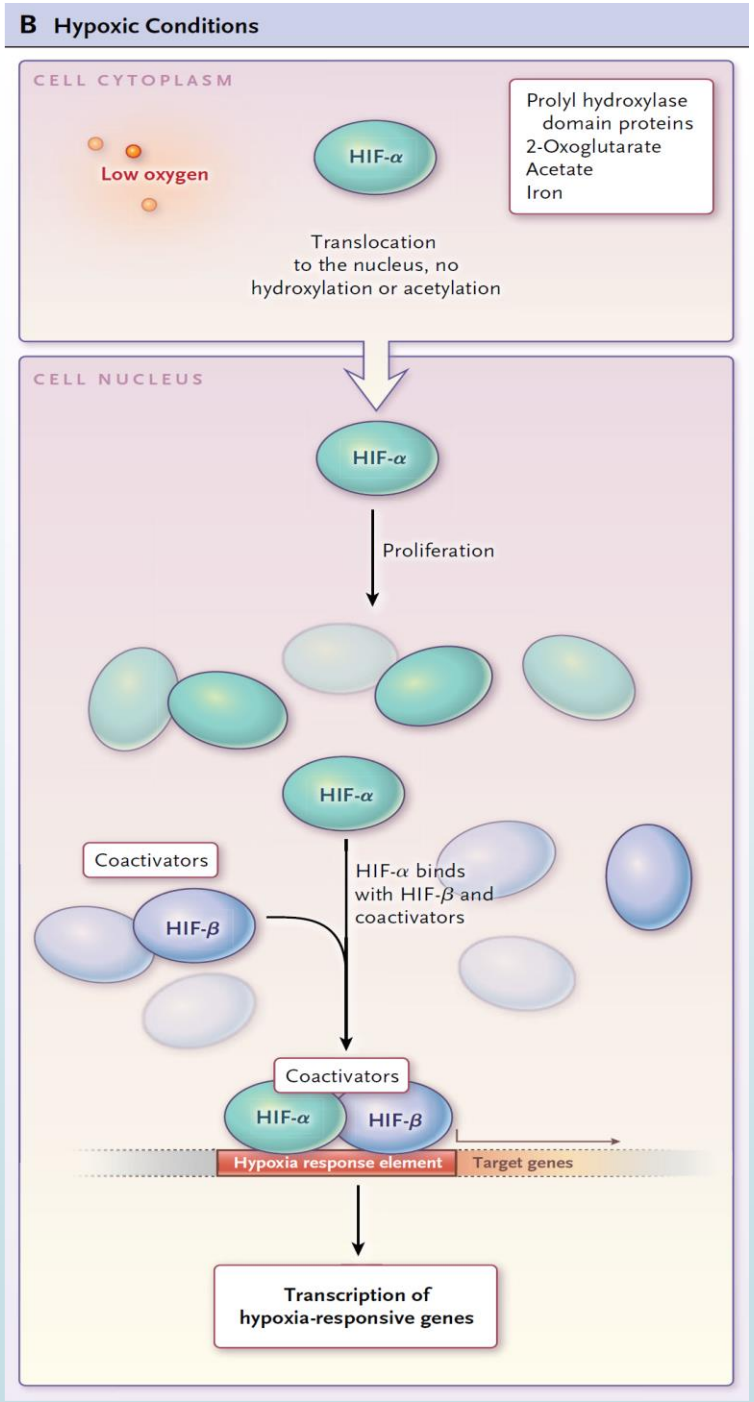
- 2. Σταθεροποιητές HIF (HIF stabilizers) – Αναστολείς Προπυλ-υδροξυλάσης (HIF-PHIs)
- 3. Ρυθμιστές Εψιδίνης (Hepcidin modulation)
- 4. Αναστολείς GATA-2 (GATA-2 Inhibitors)
- 5. Γονιδιακή θεραπεία (EPO gene therapy)

Hypoxia-Inducible Factor - HIF
Παράγοντας επαγόμενος από την υποξία

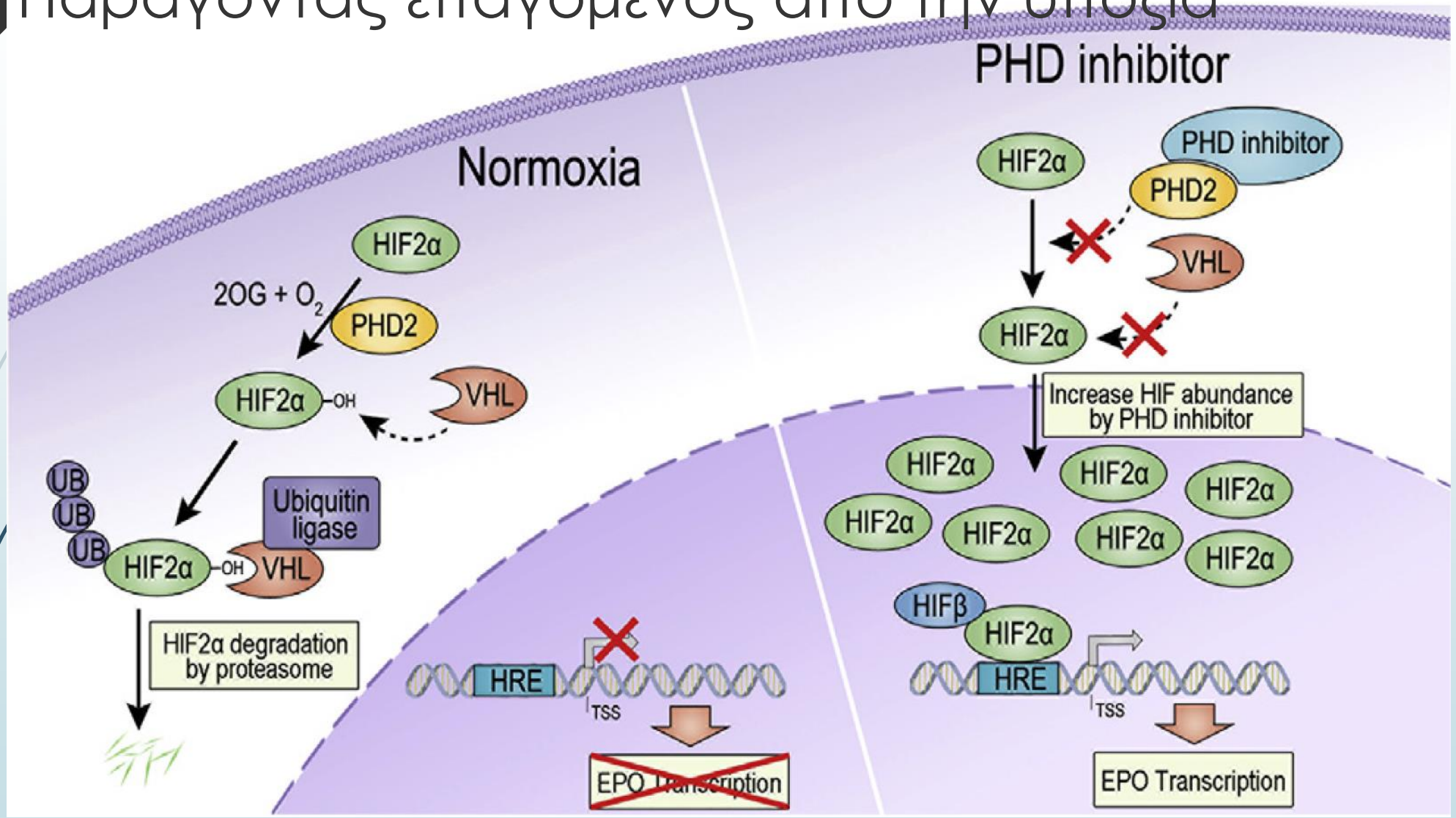
N Engl J Med 2017;376:1965-71





Hypoxia-Inducible Factor - HIF

Παράγοντας επαγόμενος από την υποξία



Journal of the Formosan Medical Association (2018) 117, 955-963

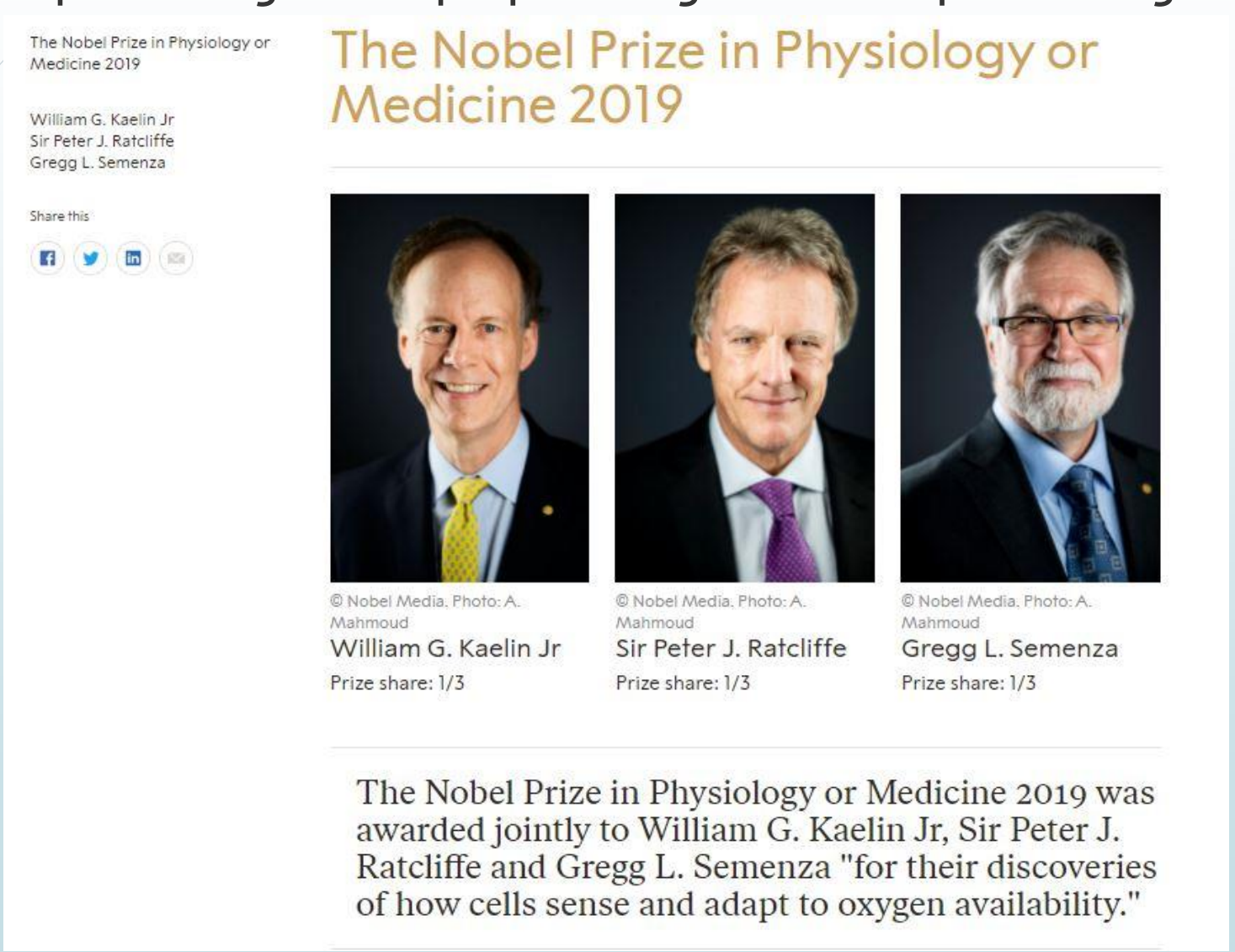
Hypoxia-Inducible Factor - HIF

Παράγοντας επαγόμενος από την υποξία

The Nobel Prize in Physiology or Medicine 2019

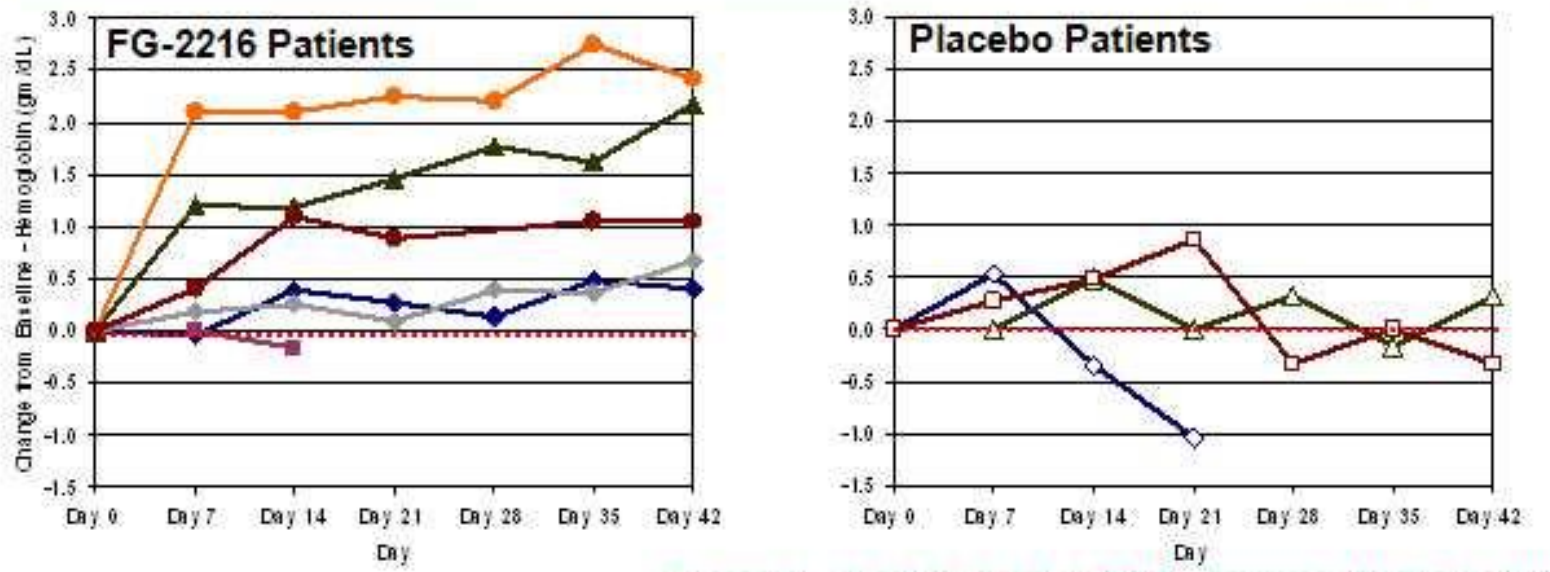
William G. Kaelin Jr
Sir Peter J. Ratcliffe
Gregg L. Semenza

Share this



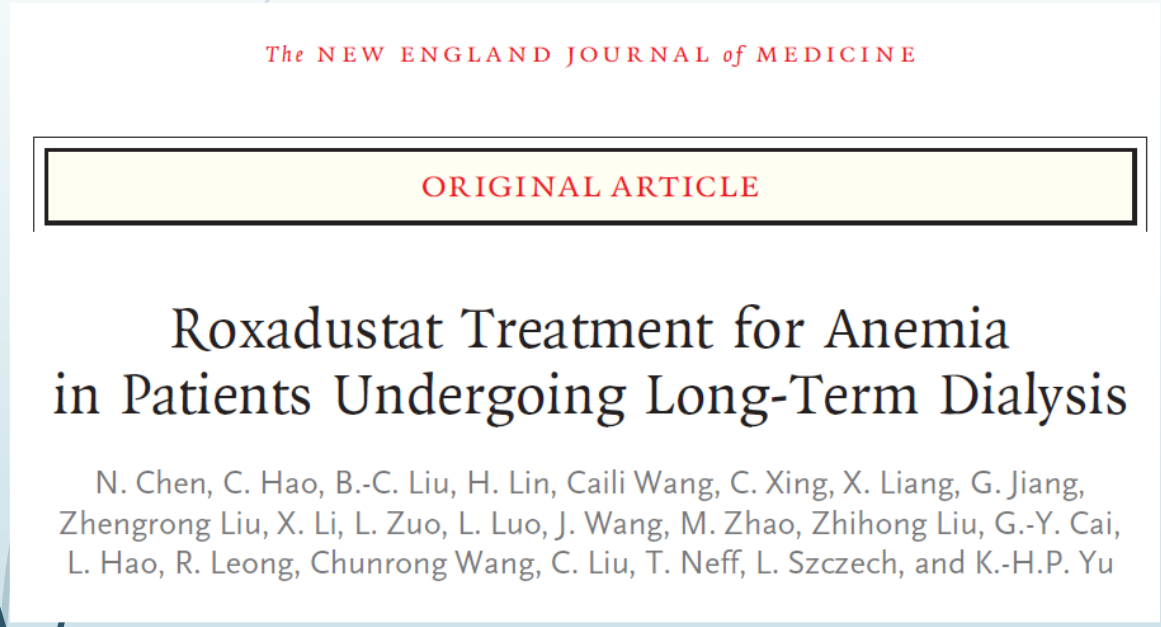
HIF-αναστολείς προπυλ-υδροξυλάσης

- Orally-active inhibitors of HIF prolyl hydroxylase have been synthesized (FG-2216; FG-4592 - FibroGen)
- They cause an increase in EPO levels, even in CKD patients



Wiecek A. et al. XLII ERA-EDTA Congress, Istanbul 2005.

HIF-αναστολείς προπυλ-υδροξυλάσης



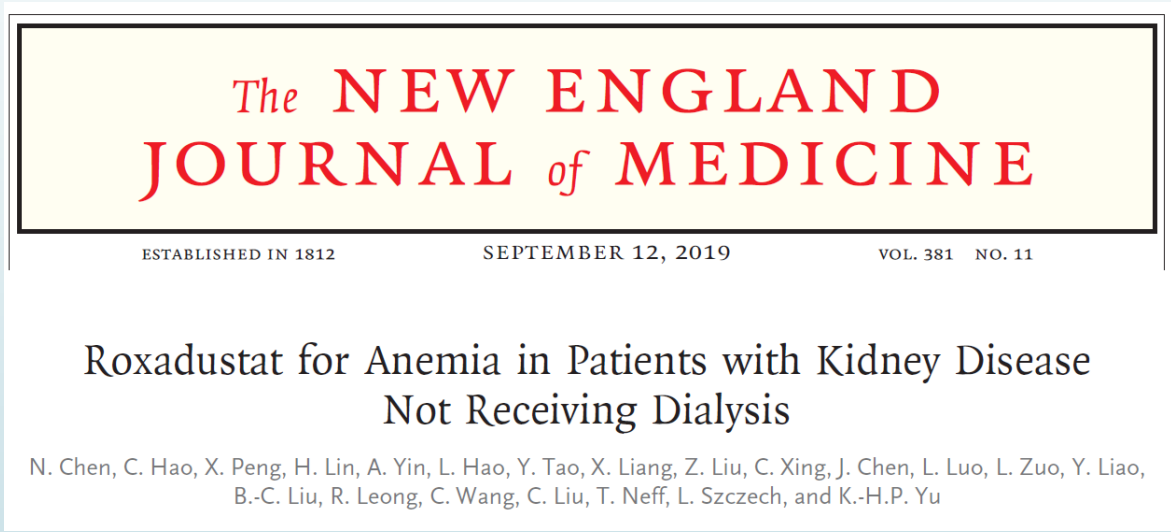
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis

N. Chen, C. Hao, B.-C. Liu, H. Lin, Caili Wang, C. Xing, X. Liang, G. Jiang, Zhengrong Liu, X. Li, L. Zuo, L. Luo, J. Wang, M. Zhao, Zhihong Liu, G.-Y. Cai, L. Hao, R. Leong, Chunrong Wang, C. Liu, T. Neff, L. Szczech, and K.-H.P. Yu

N Engl J Med 2019;381:1011-22



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 12, 2019 VOL. 381 NO. 11

Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis

N. Chen, C. Hao, X. Peng, H. Lin, A. Yin, L. Hao, Y. Tao, X. Liang, Z. Liu, C. Xing, J. Chen, L. Luo, L. Zuo, Y. Liao, B.-C. Liu, R. Leong, C. Wang, C. Liu, T. Neff, L. Szczech, and K.-H.P. Yu

N Engl J Med 2019;381:1001-10

HIF-1 και αναστολείς προπυλ-υδροξυλάσης

PHARMACEUTICAL TECHNOLOGY

All Sections | News | Analysis | Sectors | Themes | Insights | Companies | Events

NEWS | August 12, 2021 | updated 22 Nov 2021 7:15am

FDA declines to approve FibroGen's roxadustat for anaemia of CKD

The agency issued a complete response letter seeking an additional trial on the drug's safety in both NDD and DD-CKD patients.

HIF-αναστολείς προπυλ-υδροξυλάσης

Roxadustat approved in China for the treatment of anaemia in chronic kidney disease patients on dialysis

PUBLISHED
18 December 2018

18 December 2018 09:00 GMT

China is the first country to approve roxadustat

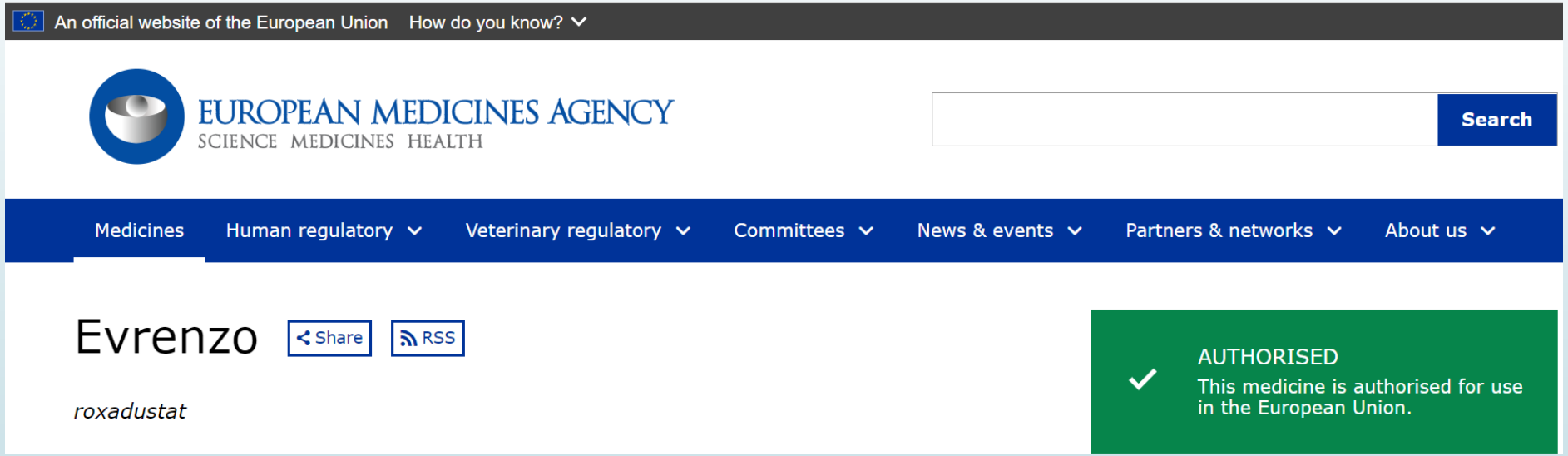
Press Release

View printer-friendly version

« Back

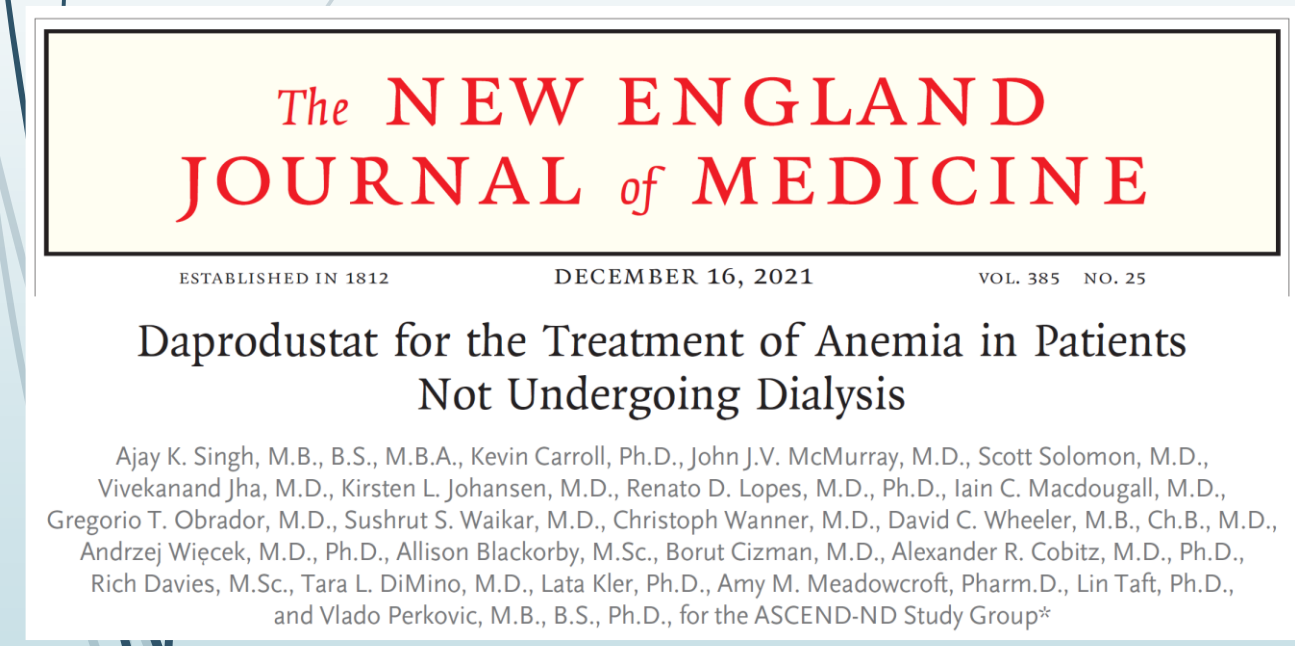
Roxadustat Approved in Japan for the Treatment of Anemia Associated with Chronic Kidney Disease in Dialysis Patients

HIF-1 και αναστολείς προπυλ-υδροξυλάσης



AUG 2021

HIF-αναστολείς προπυλ-υδροξυλάσης



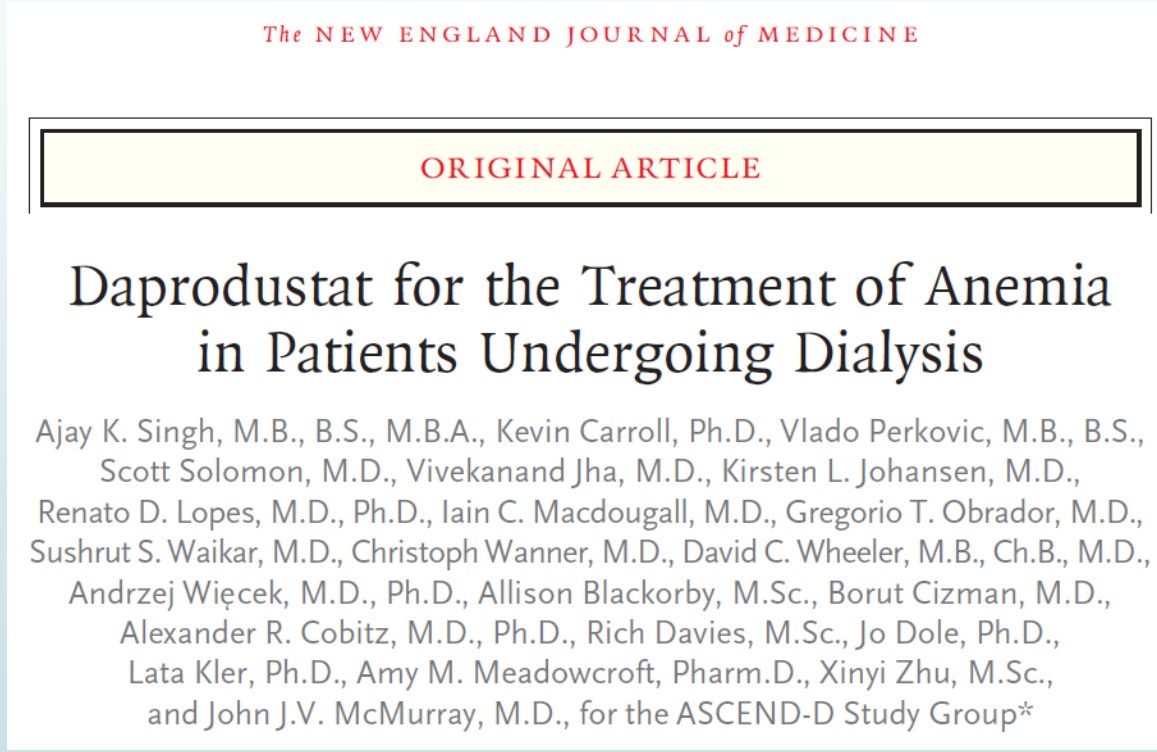
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 16, 2021 VOL. 385 NO. 25

Daprodustat for the Treatment of Anemia in Patients Not Undergoing Dialysis

Ajay K. Singh, M.B., B.S., M.B.A., Kevin Carroll, Ph.D., John J.V. McMurray, M.D., Scott Solomon, M.D., Vivekanand Jha, M.D., Kirsten L. Johansen, M.D., Renato D. Lopes, M.D., Ph.D., Iain C. Macdougall, M.D., Gregorio T. Obrador, M.D., Sushrut S. Waikar, M.D., Christoph Wanner, M.D., David C. Wheeler, M.B., Ch.B., M.D., Andrzej Więcek, M.D., Ph.D., Allison Blackorby, M.Sc., Borut Cizman, M.D., Alexander R. Cobitz, M.D., Ph.D., Rich Davies, M.Sc., Tara L. DiMino, M.D., Lata Kler, Ph.D., Amy M. Meadowcroft, Pharm.D., Lin Taft, Ph.D., and Vlado Perkovic, M.B., B.S., Ph.D., for the ASCEND-ND Study Group*

N Engl J Med 2021;385:2313-24



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis

Ajay K. Singh, M.B., B.S., M.B.A., Kevin Carroll, Ph.D., Vlado Perkovic, M.B., B.S., Scott Solomon, M.D., Vivekanand Jha, M.D., Kirsten L. Johansen, M.D., Renato D. Lopes, M.D., Ph.D., Iain C. Macdougall, M.D., Gregorio T. Obrador, M.D., Sushrut S. Waikar, M.D., Christoph Wanner, M.D., David C. Wheeler, M.B., Ch.B., M.D., Andrzej Więcek, M.D., Ph.D., Allison Blackorby, M.Sc., Borut Cizman, M.D., Alexander R. Cobitz, M.D., Ph.D., Rich Davies, M.Sc., Jo Dole, Ph.D., Lata Kler, Ph.D., Amy M. Meadowcroft, Pharm.D., Xinyi Zhu, M.Sc., and John J.V. McMurray, M.D., for the ASCEND-D Study Group*

N Engl J Med 2021;385:2325-35


An official website of the United States government Here's how you know
FDA U.S. FOOD & DRUG ADMINISTRATION
Home / News & Events / FDA Newsroom / Press Announcements / FDA Approves First Oral Treatment for Anemia Caused by Chronic Kidney Disease for Adults on Dialysis
FDA NEWS RELEASE
FDA Approves First Oral Treatment for Anemia Caused by Chronic Kidney Disease for Adults on Dialysis

FEB 2023

Jesduvroq: Withdrawal of the marketing authorisation application

Share

Based on the review of the data and the company's response to the Agency's questions, at the time of the withdrawal, the Agency had recommended granting a marketing authorisation for Jesduvroq to treat the symptoms of anaemia caused by chronic kidney disease in adult patients who are on dialysis.

The Agency did not recommend authorising Jesduvroq for patients who are not on dialysis as there were insufficient data to establish its safety in these patients.

JUL 2023

HIF 1 -αναστολείς προπυλ-υδροξυλάσης

Journal of Clinical Pharmacy and Therapeutics

ORIGINAL ARTICLE | Full Access

Long-term efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in anaemia of chronic kidney disease: A meta-analysis including 13,146 patients

Huanhuan Chen MS, Qingfeng Cheng MD, Jiuxiang Wang MS, Xiaofang Zhao MS, Shenyin Zhu PhD

First published: 21 February 2021 | https://doi.org/10.1111/jcpt.13385

Results and discussion: A total of 30 studies comprising 13,146 patients were included. The HIF-PHD inhibitors used included roxadustat, daprodustat, vadadustat, molidustat, desidustat and enarodustat. HIF-PHD inhibitors significantly increased haemoglobin levels in comparison with placebo [weighted mean difference (WMD)

J Clin Pharm Ther. 2021;00:1–11.

HIF 1 -αναστολείς προπυλ-υδροξυλάσης

Clinical Benefits	Potential disadvantages and safety concerns
• Correction and/or maintenance of hgb is associated with lower plasma EPO levels compared to ESA • Lowering of hepcidin levels and beneficial effects on iron metabolism • Potential anti-inflammatory effects • Potential benefits in ESA-resistance patients • Potential protection from ischemic events • Potential blood pressure lowering effects	• Potential pro-tumorigenic effects • Neuroendocrine tumor development • Pulmonary hypertension • Pro-angiogenic effects negatively impacting retinal diseases or cancer development • Thromboembolic complications • CKD progression (the role o HIF in renal fibrogenesis is controversial, cell-type and context-dependent) • Renal and liver cyst progression in PKD • Effects in autoimmune disease are not clear • Effects on underlying infectious processes is unclear • Adverse metabolic effects such as hyperglycemia and hyperuricemia • Adverse effects on blood pressure • Hyperkalemia (reported phase II studies) • Adverse effects in patients with chronic hepatitis

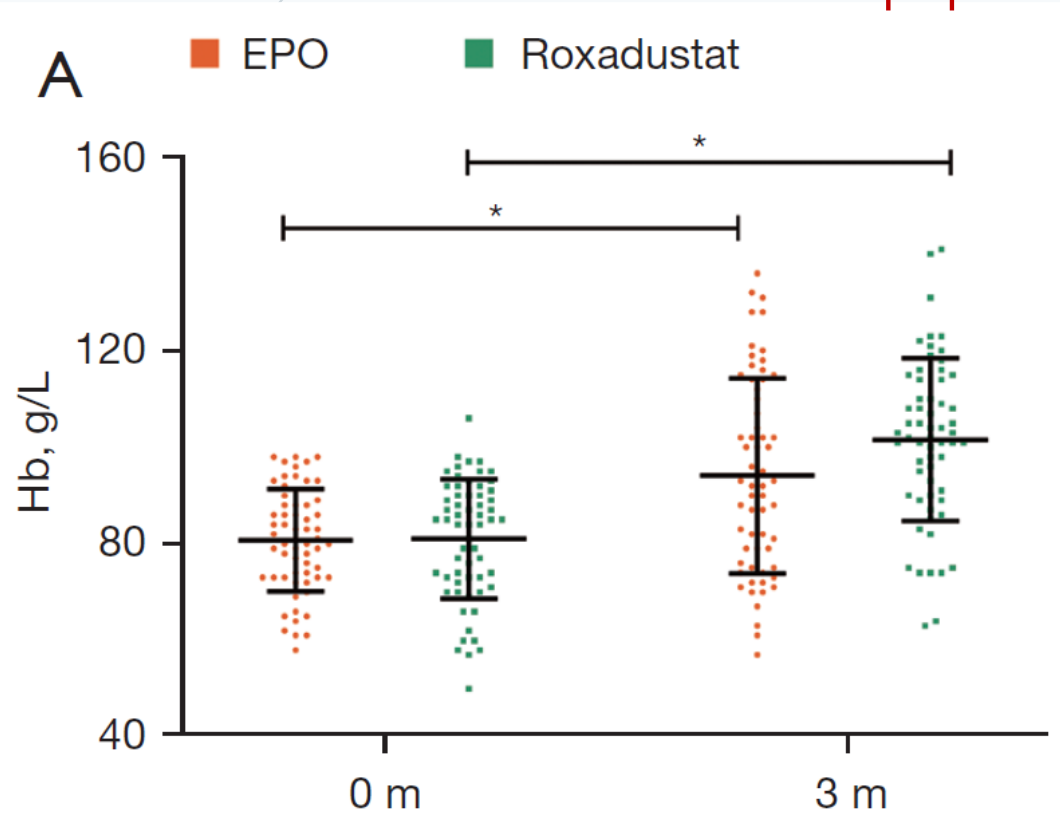
Adv Chronic Kidney Dis. 2019 Jul;26(4):253-266

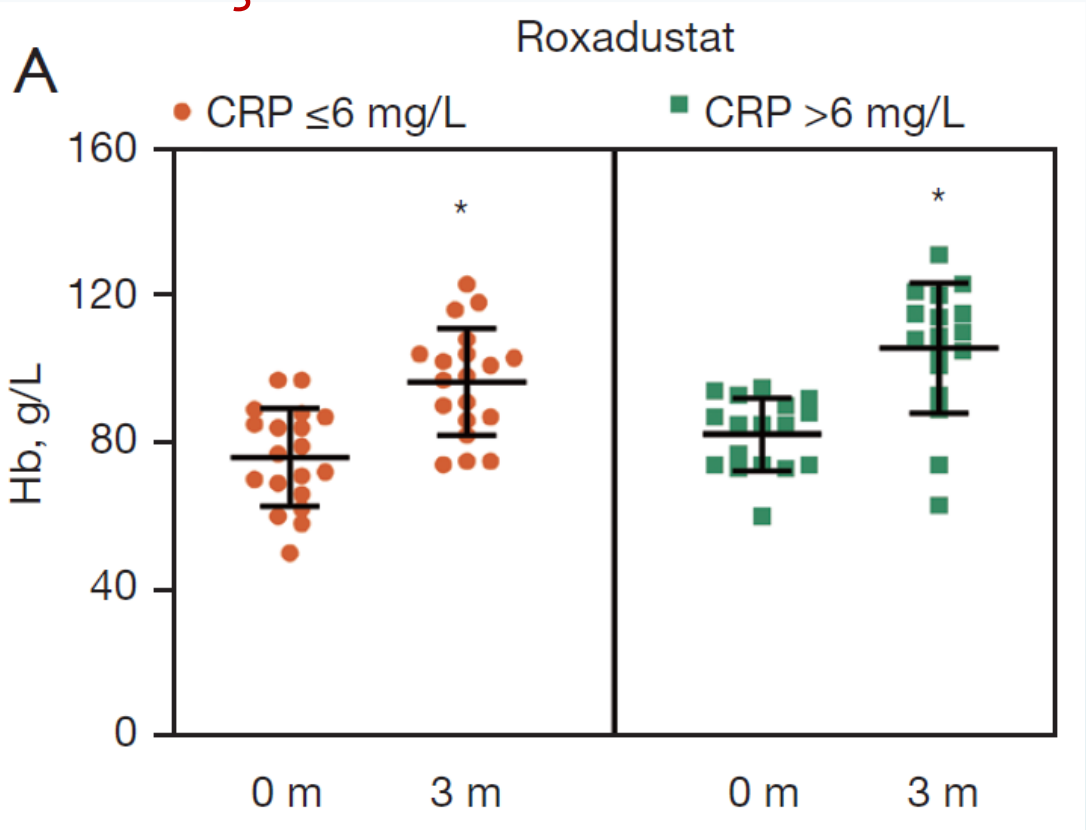
HIF-1 και αναστολείς προπυλ-υδροξυλάσης

- Πλεονεκτήματα
  - Χορήγηση από το στόμα
  - Μείωση της παραγωγής της Εψιδίνης
  - Απλός τρόπος αποθήκευσης
- Μειονεκτήματα
  - Ενεργοποίηση άλλων γονιδίων ευαίσθητων στην υποξία

HIF-1 και αναστολείς προπυλ-υδροξυλάσης

Διαβητικοί Ασθενείς

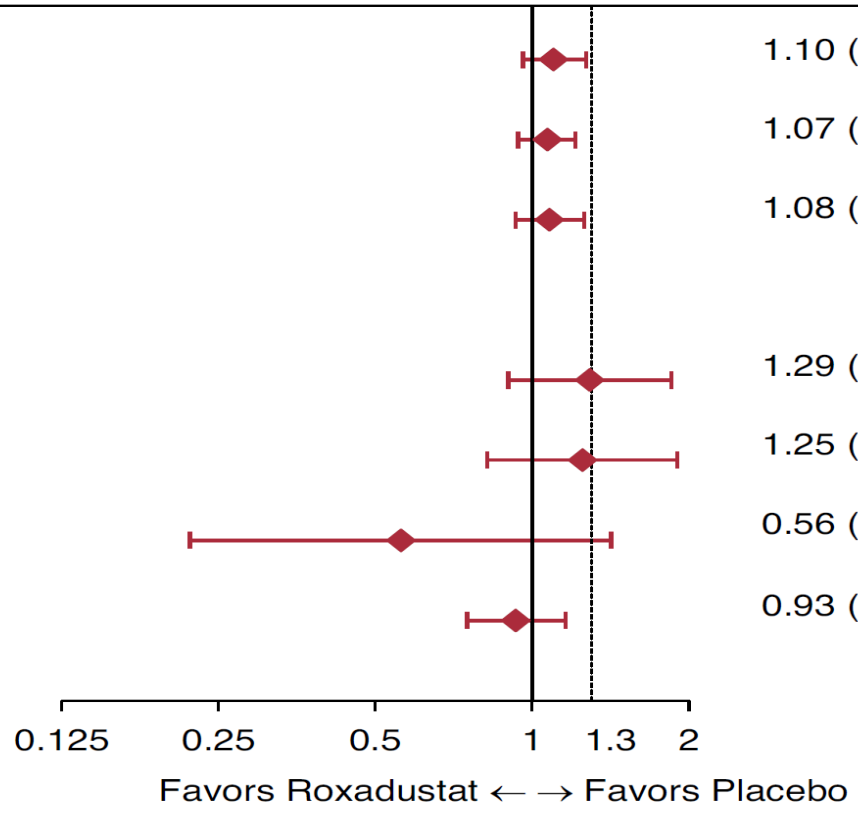




Ann Transl Med 2022;10(22):1224

HIF-αναστολείς προπυλ-υδροξυλάσης Καρδιαγγειακός κίνδυνος Roxadustat (ALPS – ANDES – OLYMPUS)

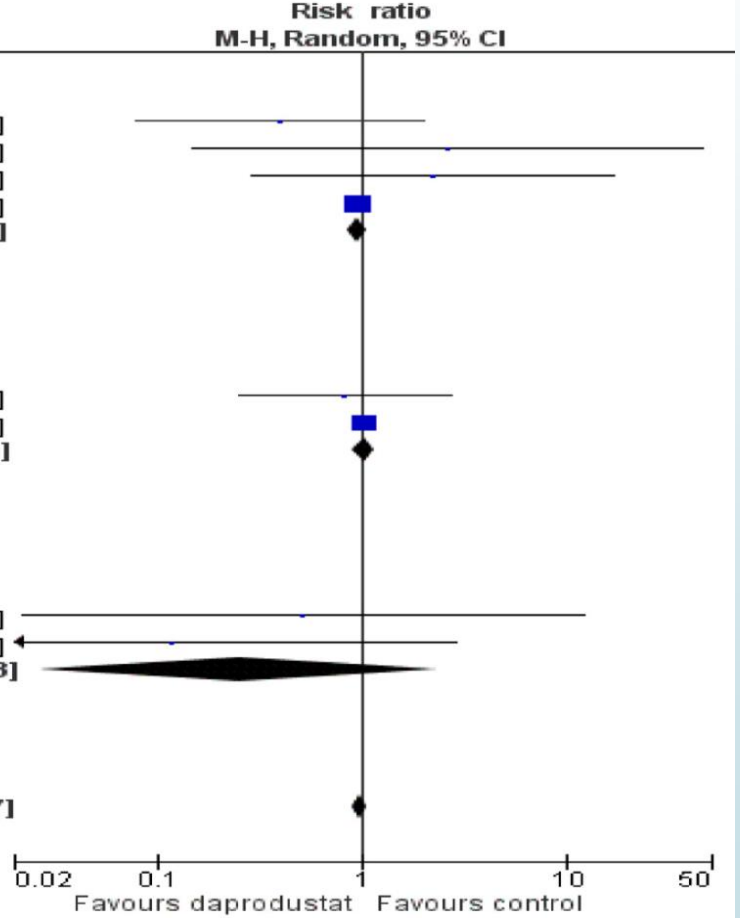
Patients w/ event, n (Follow-up–adjusted incidence rate†)	Roxadustat N=2386	Placebo N=1884	HR (95% CI)
MACE	480 (10.6)	350 (10.3)	1.10 (0.96, 1.27)
MACE+	578 (13.2)	432 (13.2)	1.07 (0.94, 1.21)
All-Cause Mortality	400 (8.3)	301 (8.1)	1.08 (0.93, 1.26)
Myocardial Infarction	86 (1.9)	52 (1.5)	1.29 (0.90, 1.85)
Stroke	56 (1.2)	36 (1.1)	1.25 (0.82, 1.90)
Unstable Angina (H)	15 (0.3)	12 (0.4)	0.56 (0.22, 1.42)
Congestive Heart Failure (H)	175 (3.9)	151 (4.6)	0.93 (0.75, 1.16)



CJASN 16: 1190–1200, 2021

Σταθεροποιητές HIF – ND D patients Daprodustat Καρδιαγγειακός κίνδυνος

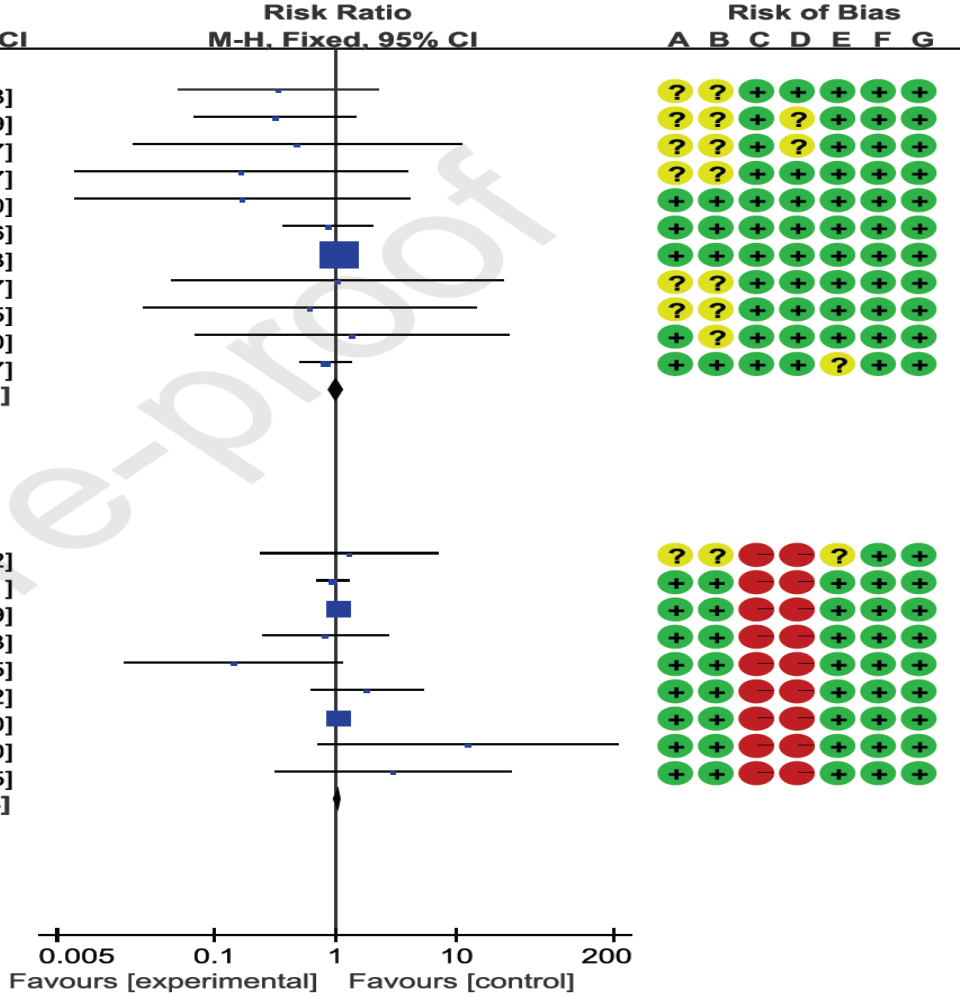
Study or Subgroup	Daprodustat Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI
1.1.1 Dialysis						
Akizawa 2017	0	78	0	19		Not estimable
Akizawa 2020	2	136	5	135	0.3%	0.40 [0.08 to 2.01]
Bailey 2019	5	84	0	19	0.1%	2.59 [0.15 to 44.91]
Meadowcroft 2019	10	177	1	39	0.2%	2.20 [0.29 to 16.71]
Singh 2021 A	374	1478	394	1477	52.1%	0.95 [0.84 to 1.07]
Subtotal (95% CI)		**1953**		**1689**	**52.7%**	**0.95 [0.84 to 1.07]**
Total events	391		400			
Heterogeneity: Tau² = 0.00; χ^2 = 2.25, df = 3 (p = 0.52); I^2 = 0%						
Test for overall effect: Z = 0.85 (p = 0.39)						
1.1.2 Non-dialysis						
Holdstock 2019	7	170	4	80	0.5%	0.82 [0.25 to 2.73]
Singh 2021 B	378	1937	371	1935	46.6%	1.02 [0.89 to 1.16]
Subtotal (95% CI)		**2107**		**2015**	**47.2%**	**1.02 [0.89 to 1.15]**
Total events	385		375			
Heterogeneity: Tau² = 0.00; χ^2 = 0.12, df = 1 (p = 0.73); I^2 = 0%						
Test for overall effect: Z = 0.23 (p = 0.82)						
1.1.3 Dialysis + Non-dialysis						
Brigandi 2016	1	92	0	15	0.1%	0.52 [0.02 to 12.12]
Holdstock 2016	0	112	1	39	0.1%	0.12 [0.00 to 2.84]
Subtotal (95% CI)		**204**		**54**	**0.2%**	**0.25 [0.03 to 2.33]**
Total events	1		1			
Heterogeneity: Tau² = 0.00; χ^2 = 0.42, df = 1 (p = 0.52); I^2 = 0%						
Test for overall effect: Z = 1.22 (p = 0.22)						
Total (95% CI)		**4264**		**3758**	**100.0%**	**0.98 [0.90 to 1.07]**
Total events	777		776			
Heterogeneity: Tau² = 0.00; χ^2 = 4.80, df = 7 (p = 0.68); I^2 = 0%						
Test for overall effect: Z = 0.51 (p = 0.61)						
Test for subgroup differences: χ^2 = 2.01, df = 2 (p = 0.37), I^2 = 0.7%						



Am J Cardiol 2022;170:166–167

HIF-αναστολείς προπυλ-υδροξυλάσης Καρδιαγγειακός κίνδυνος

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 HIF-PHIs VS placebo						
Akizawa2019(1)	2	80	2	27	0.9%	0.34 [0.05, 2.28]
Besarab2015	3	88	3	28	1.3%	0.32 [0.07, 1.49]
Brigandi2016	1	61	0	9	0.2%	0.48 [0.02, 11.07]
Chen2017	0	61	1	30	0.6%	0.17 [0.01, 3.97]
Chen2019	0	101	1	51	0.6%	0.17 [0.01, 4.10]
Coyne2021	14	611	8	305	3.1%	0.87 [0.37, 2.06]
Fishbane2021	316	1384	293	1377	84.1%	1.07 [0.93, 1.23]
holdstock2016	1	54	0	18	0.2%	1.04 [0.04, 24.37]
Macdougall2018 (a)	1	101	0	20	0.2%	0.62 [0.03, 14.65]
Martin2017	2	72	0	19	0.2%	1.37 [0.07, 27.40]
Shutov2021	37	391	23	203	8.7%	0.84 [0.51, 1.37]
Subtotal (95% CI)		**3004**		**2087**	**100.0%**	**1.02 [0.89, 1.16]**
Total events	377		331			
Heterogeneity: Chi² = 7.57, df = 10 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.27 (P = 0.79)						
1.1.2 HIF-PHIs VS ESA						
Akizawa2021	4	201	2	131	0.3%	1.30 [0.24, 7.02]
Barratt2021	63	323	60	293	6.8%	0.95 [0.69, 1.31]
Chertow2021	451	1741	424	1731	45.9%	1.06 [0.94, 1.19]
Holdstock 2019	7	170	4	80	0.6%	0.82 [0.25, 2.73]
Nangaku2021(1)	1	149	7	150	0.8%	0.14 [0.02, 1.15]
Nangaku2021(2)	9	151	5	153	0.5%	1.82 [0.63, 5.32]
Singh2021	444	1937	417	1935	45.0%	1.06 [0.95, 1.20]
Yamamoto2021(1)	6	82	0	79	0.1%	12.53 [0.72, 218.80]
Yamamoto2021(2)	3	82	1	82	0.1%	3.00 [0.32, 28.25]
Subtotal (95% CI)		**4836**		**4634**	**100.0%**	**1.06 [0.98, 1.14]**
Total events	988		920			
Heterogeneity: Chi² = 8.88, df = 8 (P = 0.35); I² = 10%						
Test for overall effect: Z = 1.40 (P = 0.16)						



Am J Kidney Dis. 2022 14;S0272-6(22)

Αναιμία

Αντιμετώπιση

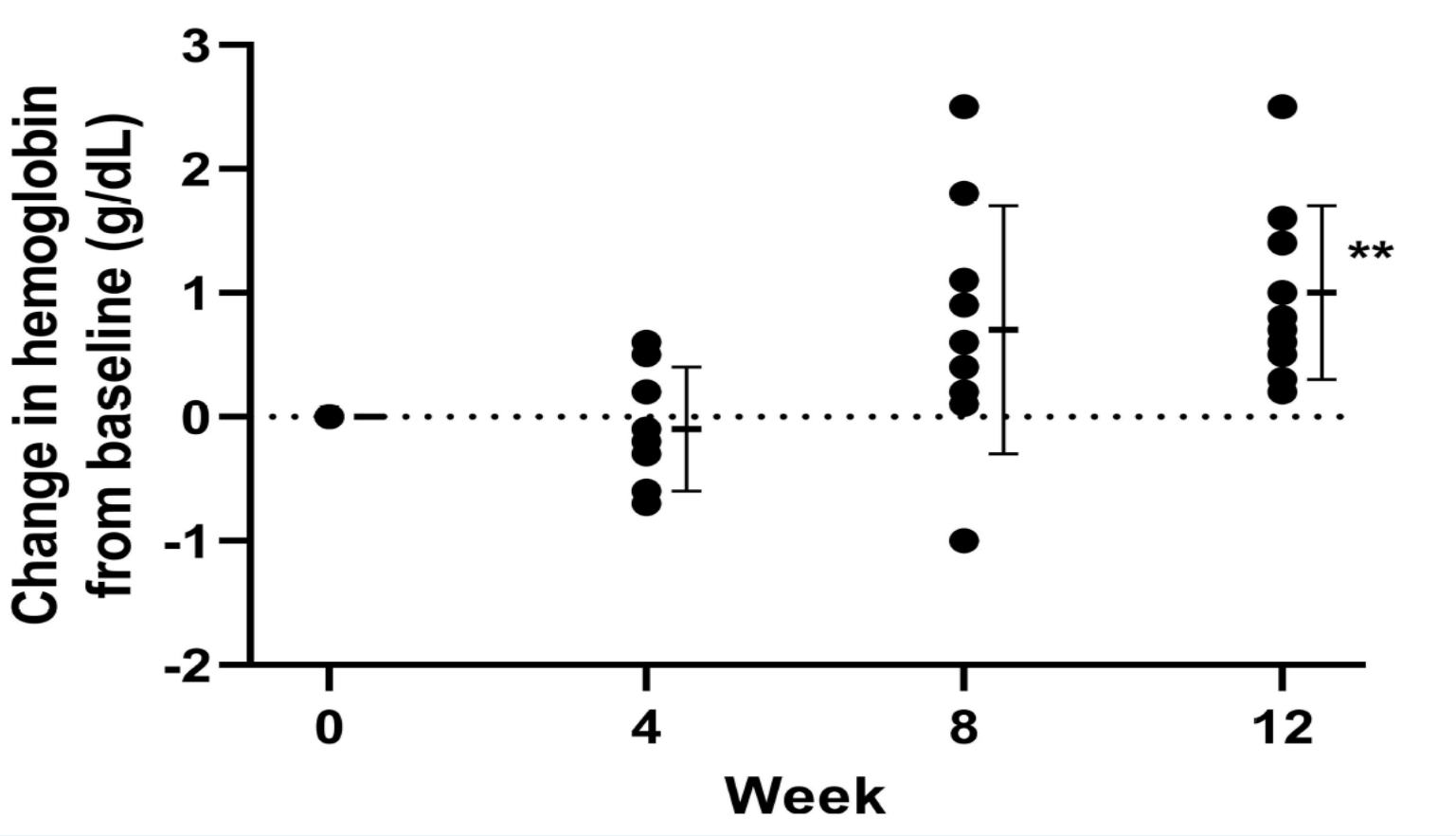
- Χορήγηση ανασυνδυασμένης Ερυθροποιητίνης
- Χορήγηση Σιδήρου

- Νέοι Ερυθροποιητικοί παράγοντες

- SGLT2 inhibitors

Αναιμία
Αντιμετώπιση

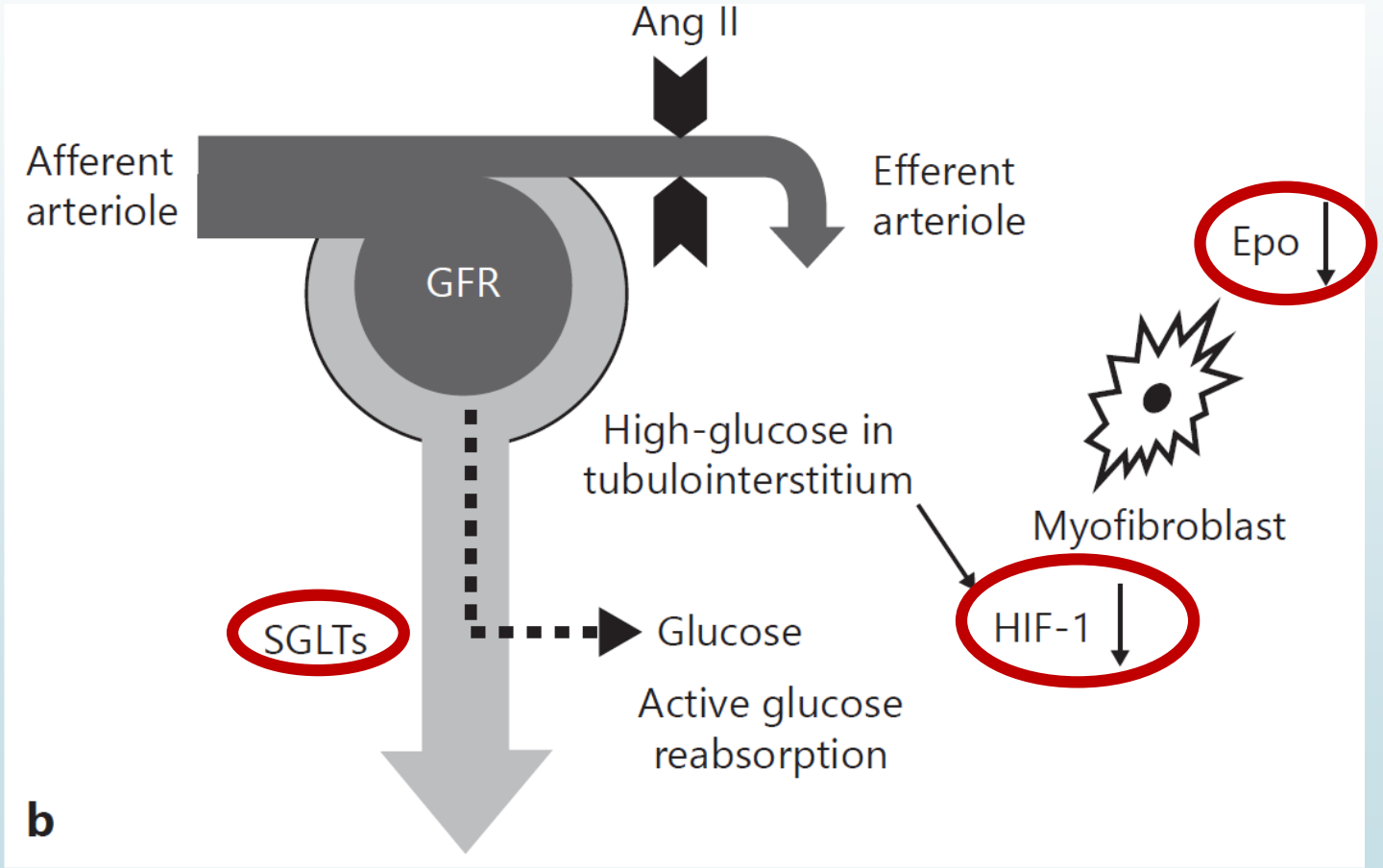
SGLT2 Αναστολείς



Diabetes, Metabolic Syndrome and Obesity 2023:16

Αναιμία
Αντιμετώπιση

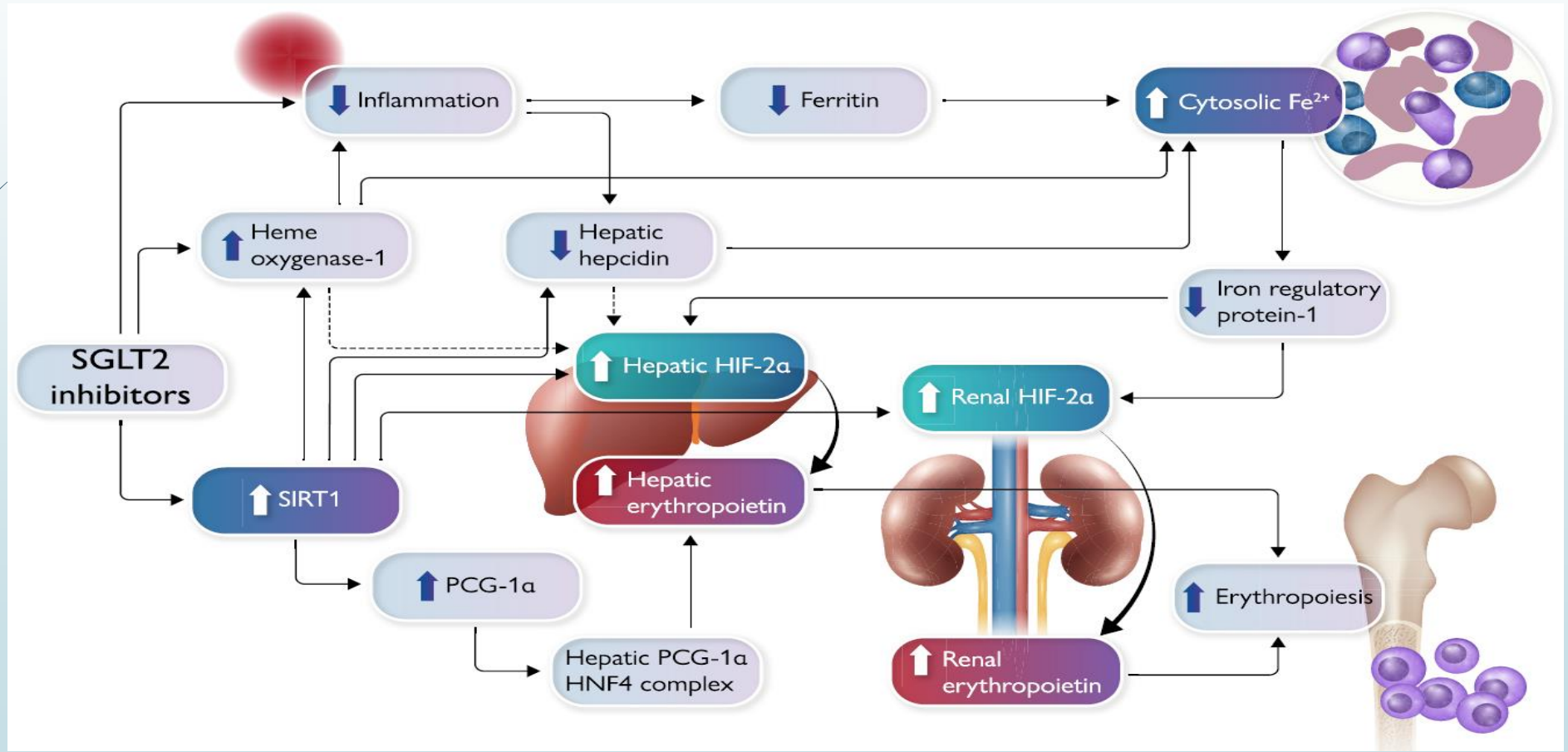
SGLT2 Αναστολείς



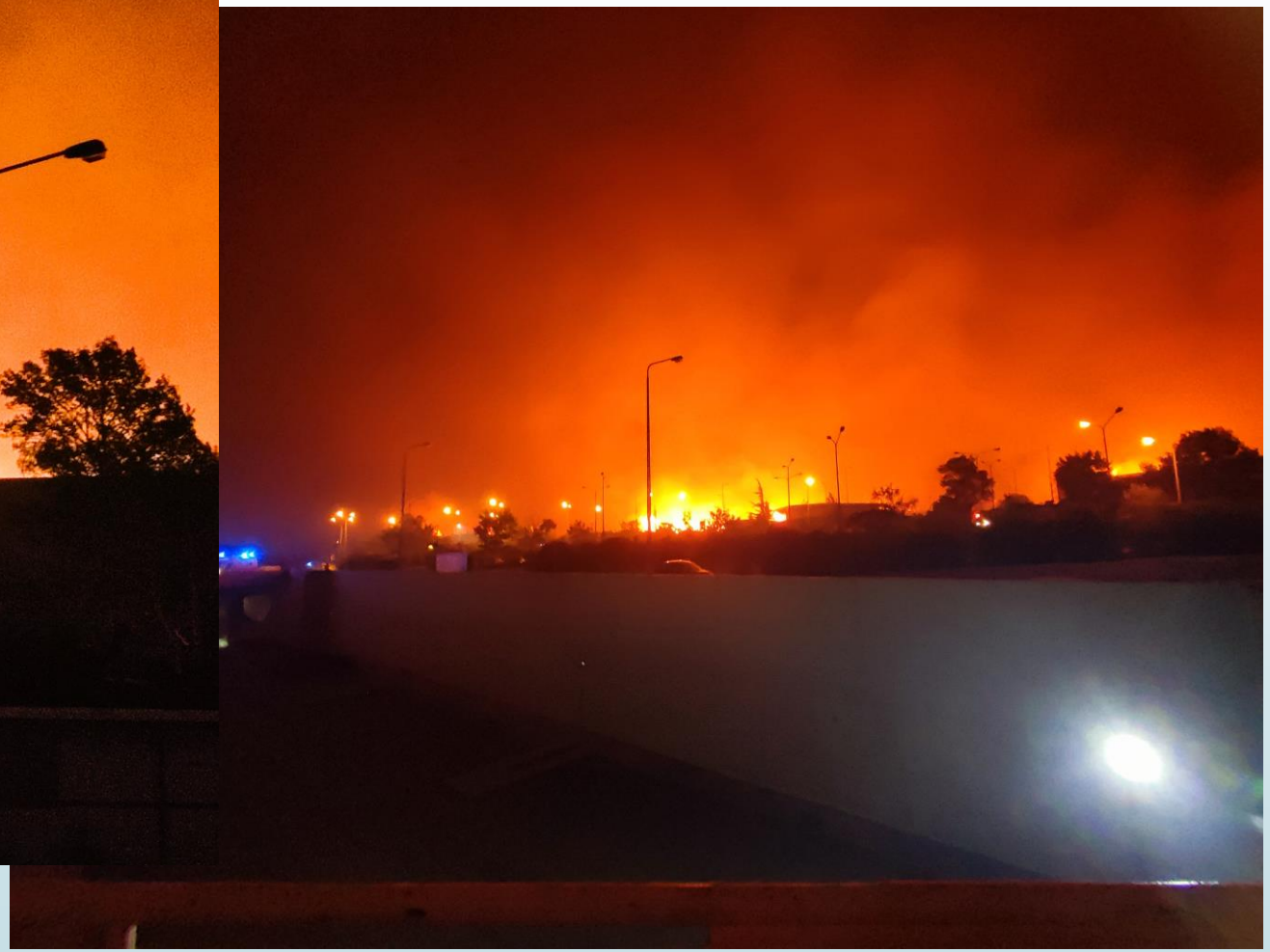
Am J Nephrol 2020;51:349–356

Αναιμία
Αντιμετώπιση

SGLT2 Αναστολείς



European Heart Journal (2023) 00, 1–9



Ευχαριστώ