

# 腎性貧血

輔英科大附設醫院 腎臟內科

羅章翰 醫師



輔英科技大學附設醫院  
Fooyin University Hospital



# 個人簡歷

- ◆ 輔英科大附設醫院腎臟內科醫師
- ◆ 整合醫學專科醫師
- ◆ 中華民國部定內科專科醫師
- ◆ 中華民國腎臟內科專科醫師
- ◆ 屏東地區糖尿病共照網醫師
- ◆ PGY 訓練教師及導師
- ◆ 教育部審定講師
- ◆ 臺灣腎臟醫學會會員
- ◆ 美國腎臟醫學會會員



10:12



ChatGPT 3.5 >



CL

You

何謂腎性貧血？



ChatGPT

腎性貧血是一種由於腎臟功能異常而導致的貧血狀態。當腎臟無法有效產生足夠的促使紅血球生成的激素（稱為促紅血球生成素），可能導致貧血，因為紅血球的生成需要這種激素的刺激。腎性貧血通常與慢性腎臟病有關。

10:13



ChatGPT 3.5 >



CL

You

腎性貧血該如何治療？



ChatGPT

腎性貧血的治療通常包括使用人工合成的紅細胞生成素 (EPO) 以刺激紅細胞的產生。此外，必要時可能會進行鐵補充和其他治療，以處理與腎功能不足相關的問題。最好的治療方案應由您的醫生根據您的具體情況制定。

10:13



ChatGPT 3.5 >



CL

You

洗腎患者如果貧血該怎麼辦？



ChatGPT

洗腎患者如果貧血，應該諮詢醫生建議，可能需要進行血液檢查以確定原因。治療選項可能包括鐵補充劑、EPO 注射或其他醫療措施，具體取決於貧血的嚴重程度和原因。



10:43

4G

=

ChatGPT 3.5 >



CL

You

腎性貧血有什麼新的領域嗎？



ChatGPT

截至我知識截止日期（2022年1月），腎性貧血的研究仍在進行中。新的領域可能包括基因療法、幹細胞治療以及更精準的診斷方法。建議查閱最新的醫學文獻或諮詢專業醫生以獲取最新的資訊。

2:53

4G



登入



Copilot

當然，我可以



您

請問目前臺灣紅血球生成素的種類？



Copilot

目前在台灣上市的紅血球生成素（EPO）有幾種不同的劑型，包括：

1. **epoetin alfa**（商業名稱：Eprex®）
2. **epoetin beta**（商業名稱：Recormon®）
3. **darbepoetin alfa**（商業名稱：NESP®）
4. **methoxy PEG epoetin beta**（商業名稱：Mircera®）

這些紅血球生成素之間的主要差異在於分子結構上的糖鏈數和鍵結位置的不同。由於結構上的差異，這些藥品的半衰期也有所不同 [1](#) [2](#)。



全民愛健康  
腎臟病篇8

# 認識腎性貧血



健談

圖文創作：健談 havemary.com

專家諮詢：新光醫院腎臟科  
張瑞廷醫師

腎臟病患因腎臟功能受損，連帶影響造血功能而出現腎性貧血問題



紅血球生成素(EPO)

健談 havemary.com

腎性貧血的症狀包括容易感到疲倦、精神不濟、易喘、食慾減退等



欲改善腎性貧血問題，可依醫囑注射紅血球生成素EPO藥物或口服鐵劑來改善



腎臟病患的飲食限制較多，若想額外服用營養品或保健食品者，最好先諮詢醫師的建議



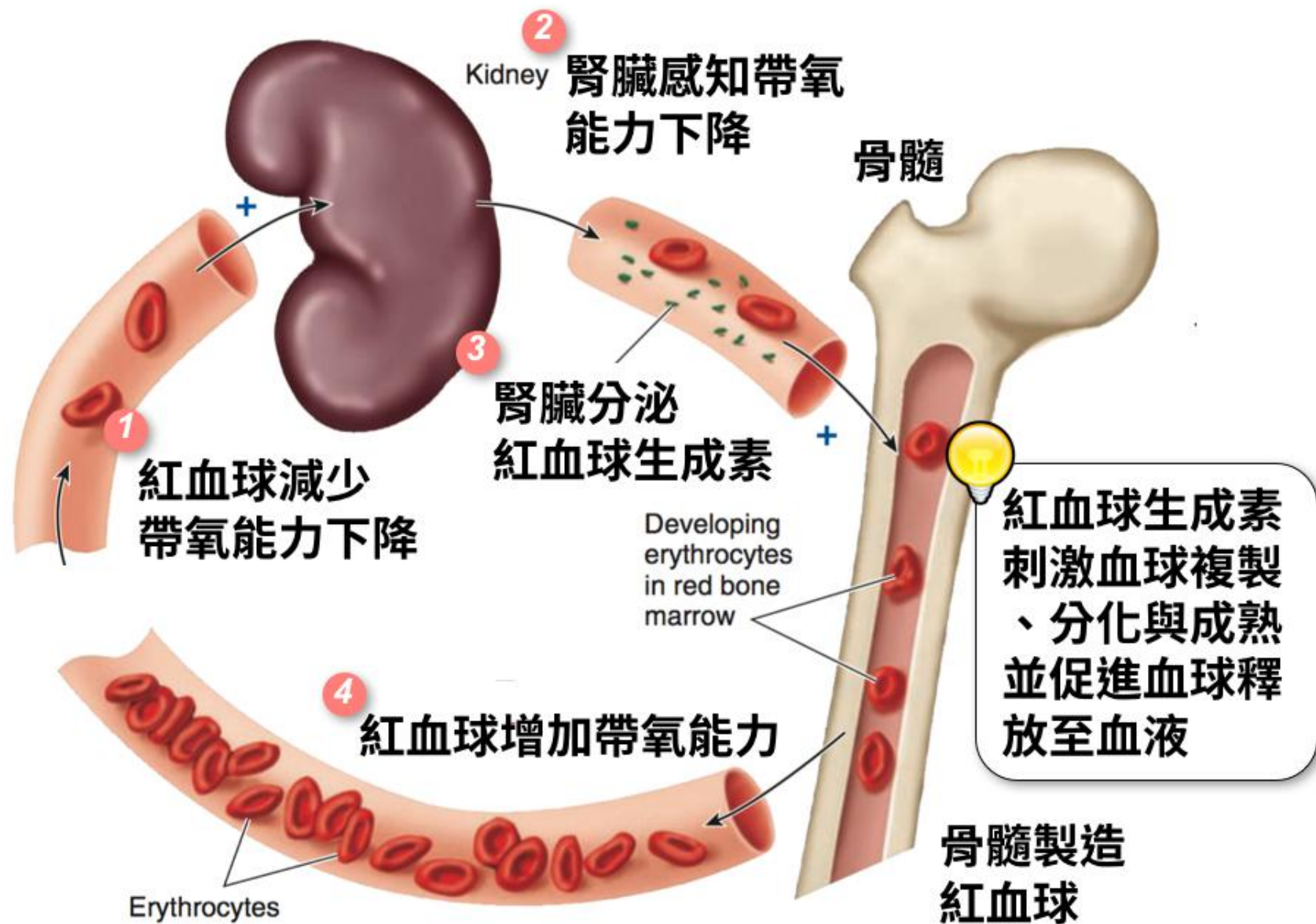
腎性貧血相關問題，建議諮詢「腎臟科」

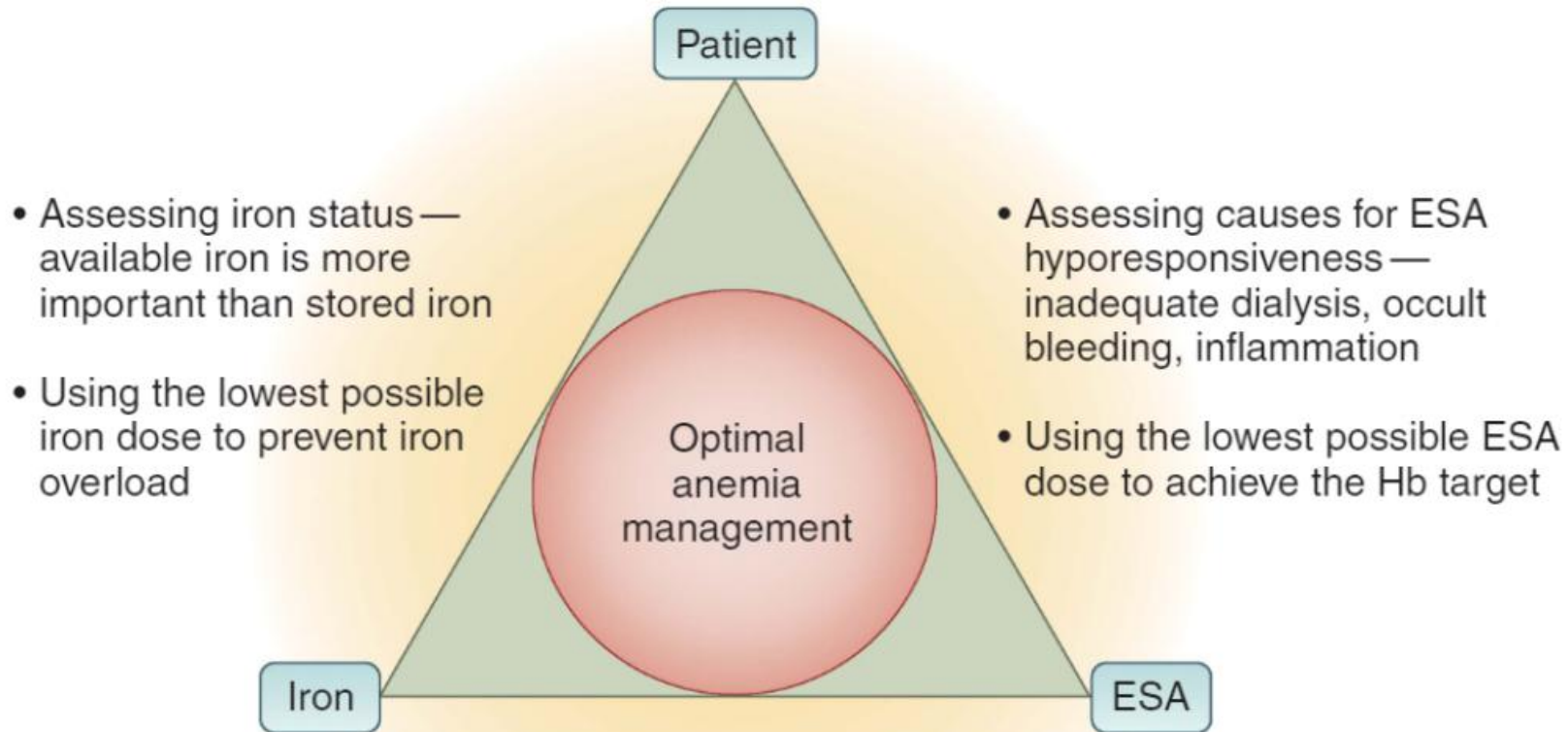
更多資訊請上 健談 havemary.com



# 報告用大圖 紅血球生成素的功用

The New England  
Journal of Stupid





- Individualized anemia management to reduce Hb variability
- Using IV iron during ESA therapy to prevent iron deficiency-induced reactive thrombocytosis
- Balancing potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm

POCKET  
NOTEBOOK

# POCKET NEPHROLOGY

Woojin Ahn  
Jai Radhakrishnan

 COLUMBIA | COLUMBIA UNIVERSITY  
IRVING MEDICAL CENTER

 Wolters Kluwer

## Anemia Background

↓ EPO production by the kidney; normocytic normochromic [Hb] <13.0 in males and <12.0 in females.  
↑ prevalence w/ CKD progression: 1% eGFR 60, 9% eGFR 30, 33–67% eGFR 15 (*Arch IM* 2002;162:1401)  
✓ RBC indices, retic count, iron, TIBC, ferritin, WBC w/ diff, platelets, and B<sub>12</sub> and folate if MCV >100  
If **anemia** + off ESA, monitor every 3 mo

## Anemia – Iron

Iron deficiency + if TSat ≤20% or ferritin ≤100 ng/mL  
Iron may ↑ Hb if TSat ≤30% and ferritin ≤500 ng/mL  
Oral iron: 65-mg elemental iron QD or QOD (1–3 mo trial)  
IV iron (iron dextran, ferric carboxymaltose, sodium ferric gluconate complex, ferumoxytol, iron sucrose, ferric pyrophosphate citrate) if severe deficiency or no ↑ Hb w/ oral iron

## Anemia – ESA

Address correctable causes of **anemia** prior to ESA  
Treating **anemia** to near-normal Hb in pre-dialysis CKD with darbepoetin ↑ stroke (TREAT *NEJM* 2009;361:2019)  
Consider ESAs if Hb <10 to prevent blood transfusion

Goal Hb 10–11.5  
Don't use if malignancy, severe HTN, recent stroke



# Anemia (↓Hb and Hct)

MCV, RDW, Retic

MCV ↓

MCV (N)

MVC ↑

Retic ↓ or (N)  
RDW (N)

Retic, RDW ↑

Retic ↓ or (N),  
RDW (N)

Retic, RDW ↑

Retic ↓ or (N),  
RDW (N)

Retic, RDW ↑

- Iron deficiency anemia (↑RDW)
- Thalassemia trait
- Lead poisoning
- Chronic disease
- Sideroblastic anemia

- Thalassemia syndromes (SB thalassemia, Hb H disease)
- Hb C disorders
- Hb E disorders

- **Chronic disease**
- Transient erythroblastopenia of childhood
- Acute inflammation
- Acute hemorrhage
- Malignancy

- Immune hemolysis
- RBC membrane disorder (HS, He)
- RBC enzyme defects (G6PD, PK deficiency)
- Microangiopathic hemolysis (HUS, TTP, DIC)
- Sickle cell anemia

- Folate deficiency
- B12 deficiency
- Bone marrow failure (aplastic anemia, Fanconi anemia, DBA)
- Myelodysplastic syndrome
- Hypothyroidism
- Drug-induced (anti-convulsants)

- Active hemolysis with brisk reticulocytosis

Review of smear

Further diagnostic test

- Iron studies
- Hb electrophoresis
- Lead level

Review of smear

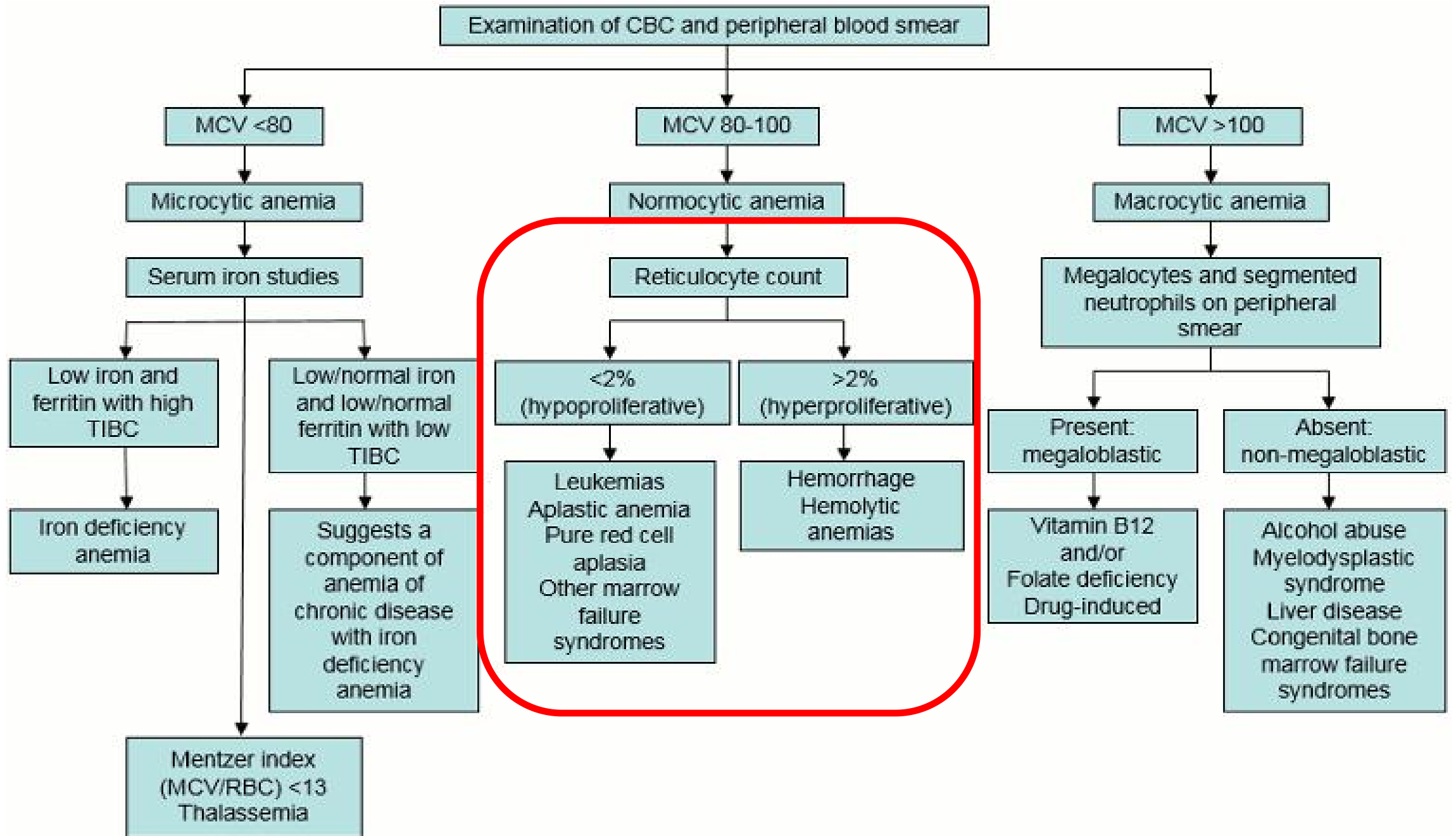
Further diagnostic test

- Other diseases (infection, renal, liver, metabolic)
- Coombs test
- Osmotic fragility
- Enzyme assays (G6PD, PK)
- Hb electrophoresis

Review of smear

Further diagnostic test

- Folate, B-12 level
- Thyroid function test
- Bone marrow aspirate and biopsy
- Evaluate hemolysis



1



EPO 製造不足

2



紅血球壽命短

3



鐵質運用不佳

4



B12或葉酸缺乏

5



慢性發炎狀態



腎病患者貧血原因

6



溶血或血流失

7



急性感染疾病

8



副甲狀腺亢進

9



慢性鋁中毒

10



血液相關疾病



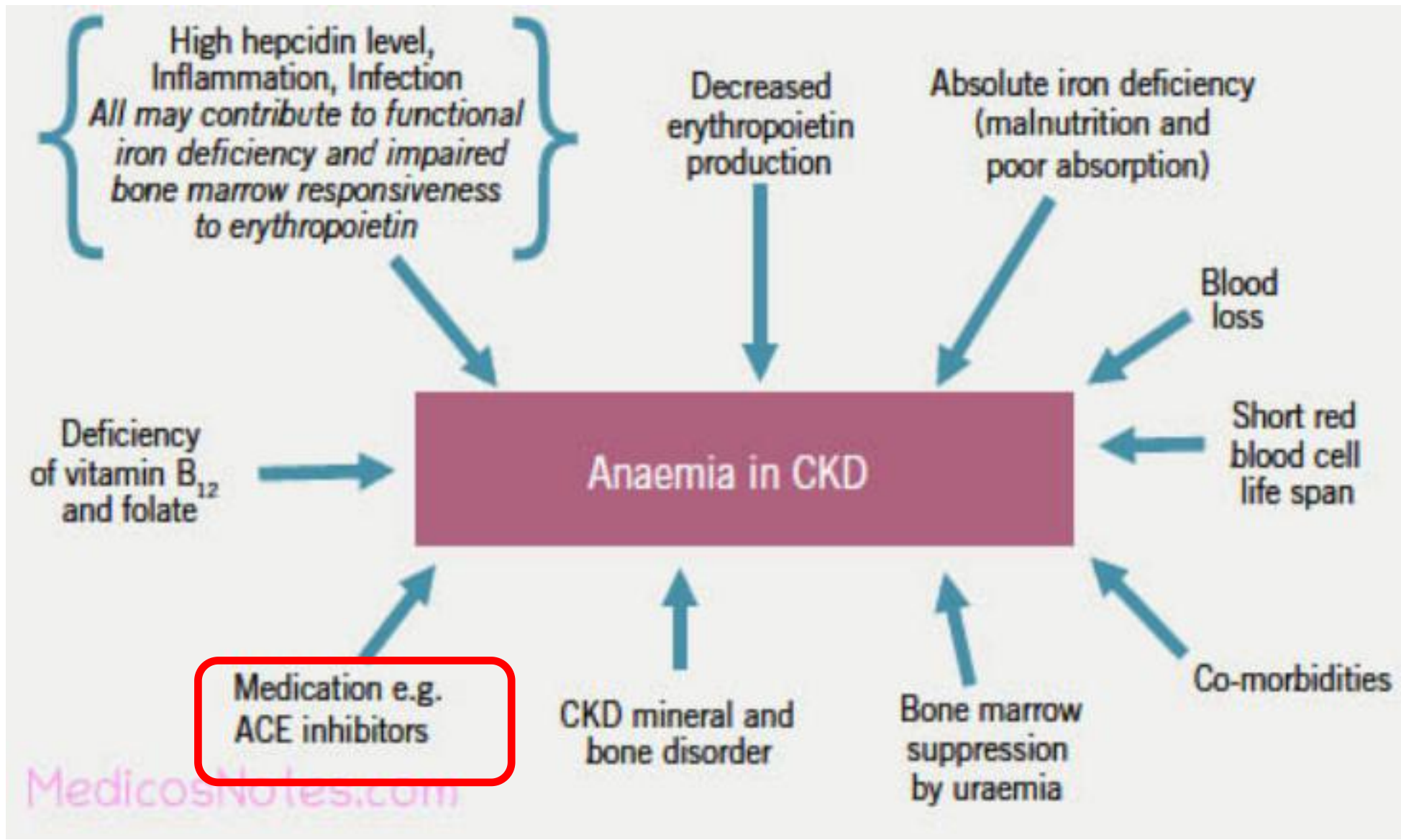
# 透析病患貧血原因

- 與透析相關之因素

1. Blood loss ↑
2. Hemolysis ↑
3. Hyperparathyroidism
4. Inflammation ↑
5. EPO dose ↓
6. Kt/V ↓
7. PRCA

- 與病患相關之因素

1. Iron-deficiency
2. Hyperphosphatemia
3. GI bleeding ↑
4. Infection ↑
5. Folate, vitamin B12 ↓
6. ACEi/ARB ↑
7. Malignancy
8. Hypoalbuminemia



## TABLE 2. Possible Anemia-Inducing Mechanisms of Angiotensin-Converting Enzyme Antagonists and Angiotensin I Antagonists\*

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Renal

Decrease in the synthesis of endogenous EPO

Bone marrow

Decrease in the response to EPO

Inhibition of the growth of erythroid precursors

Change in the response to treatment with rHuEPO

Decrease in IGF-1 levels

Inhibition of the catabolism of N-acetyl-seryl-aspartyl-proline, a peptide that reduces the proliferation of precursors of the red cell series

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\*EPO indicates erythropoietin; IGF-1, insulin-like growth factor 1; rHuEPO, recombinant human erythropoietin.



**Table 1: Mechanisms of anemia in CKD**

<b>Mechanism</b>	<b>Outcome</b>
Renal Impairment	Decreased erythropoietin production
Uremia	Bone marrow suppression Decreased RBC life span
Nutritional deficiency	Deficiency of Vitamin B <sub>12</sub> , folate or Iron
Secondary Hyperparathyroidism	Fibrosis of bone marrow Failure of erythropoiesis
Chronic Inflammation Increased inflammatory cytokines Increased hepcidin	Abnormal iron homeostasis and erythroid progenitor proliferation
Aluminium Toxicity	
Hypothyroidism	Reduced GFR Increased peripheral vascular resistance

# Definition of ESA Resistance

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- No single accepted definition of ESA resistance
- KDOQI: hyporesponse to ESAs and iron therapy<sup>[a]</sup>
  - A significant increase in the ESA dose requirement to maintain a certain Hb level or a significant decrease in Hb level at a constant ESA dose
  - A failure to increase the Hb level >11 g/dL despite an ESA dose equivalent to epoetin > 500 IU/kg/wk
- European best practice guidelines for managing anemia: resistance to ESAs should be suspected when a patient either<sup>[b]</sup>:
  - Fails to attain the target Hb concentration while receiving >300 IU/kg/wk (~20,000 IU/wk) epoetin or 1.5 mg/kg darbepoetin alfa (~100 mg/wk)
  - Has a continued need for such high dosages to maintain the target

a. KDOQI. *Am J Kidney Dis.* 2006;47(suppl 3):S1-S146.

b. Locatelli F, et al. *Nephrol Dial Transplant.* 2004;19(suppl 2):ii1-ii47.

## TABLE 3. Common Causes of Resistance to Erythropoietin\*

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### Blood loss

Iron deficiency: absolute and relative

Chronic renal disease: also provokes endogenous EPO deficiency

Acute and chronic inflammation

Antagonist agents: ACE inhibitors, nonsteroidal antiinflammatory drugs

Malnutrition and deficiency of factors, such as vitamin B<sub>12</sub>, folic acid

Bone marrow depression

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\*ACE indicates angiotensin-converting enzyme; EPO, erythropoietin.





# Etiology of ESA resistance



Risk factor	Mechanism of ESA resistance	Therapeutic intervention
Uremic toxins	↓EPO synthesis / ↓erythroid response	Longer effective dialysis
Oxidative stress	Downregulation of HIF	Vit E and Vit C
Inflammation	Cytokines: IL-1, IL-6, TNF- $\alpha$	Avoid sepsis and malnutrition
Iron deficiency	Hemoglobin synthesis	Replenish iron/ ↓blood loss
Hyperparathyroidism / Vit D deficiency	Vitamin D synergism (erythropoiesis)	Low P diet/ 1,25 (OH) <sub>2</sub> vit D
Aluminum toxicity	Aluminum bone disease	Avoid aluminum intake
Hemolysis	HbSS/G6PDD/AIHA	Treat underlying disease
Drug: angiotensin-modulating agents	↓Erythroid ANG II receptors/ ↑ endogenous EPO inhibitor, AcSDKP	↓Dose of ACEI/ARB

## detecting ESA resistance

- target Hb levels not being reached despite appropriate treatment
- continuing need for high doses to maintain Hb

## other possible causes

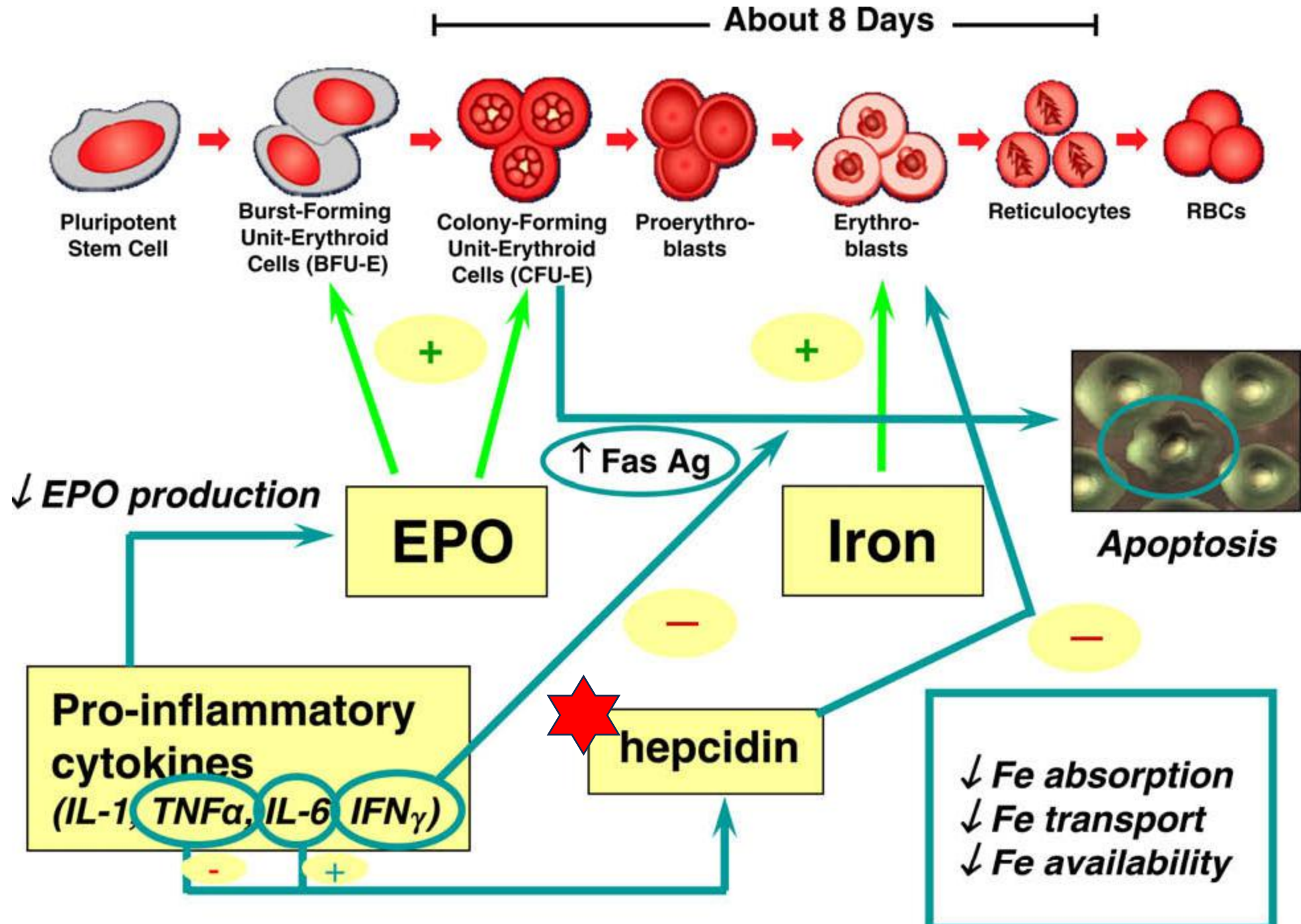
- exclude other causes of anaemia
- check medicine concordance
- algorithm for poor response to ESAs

# ESA resistance

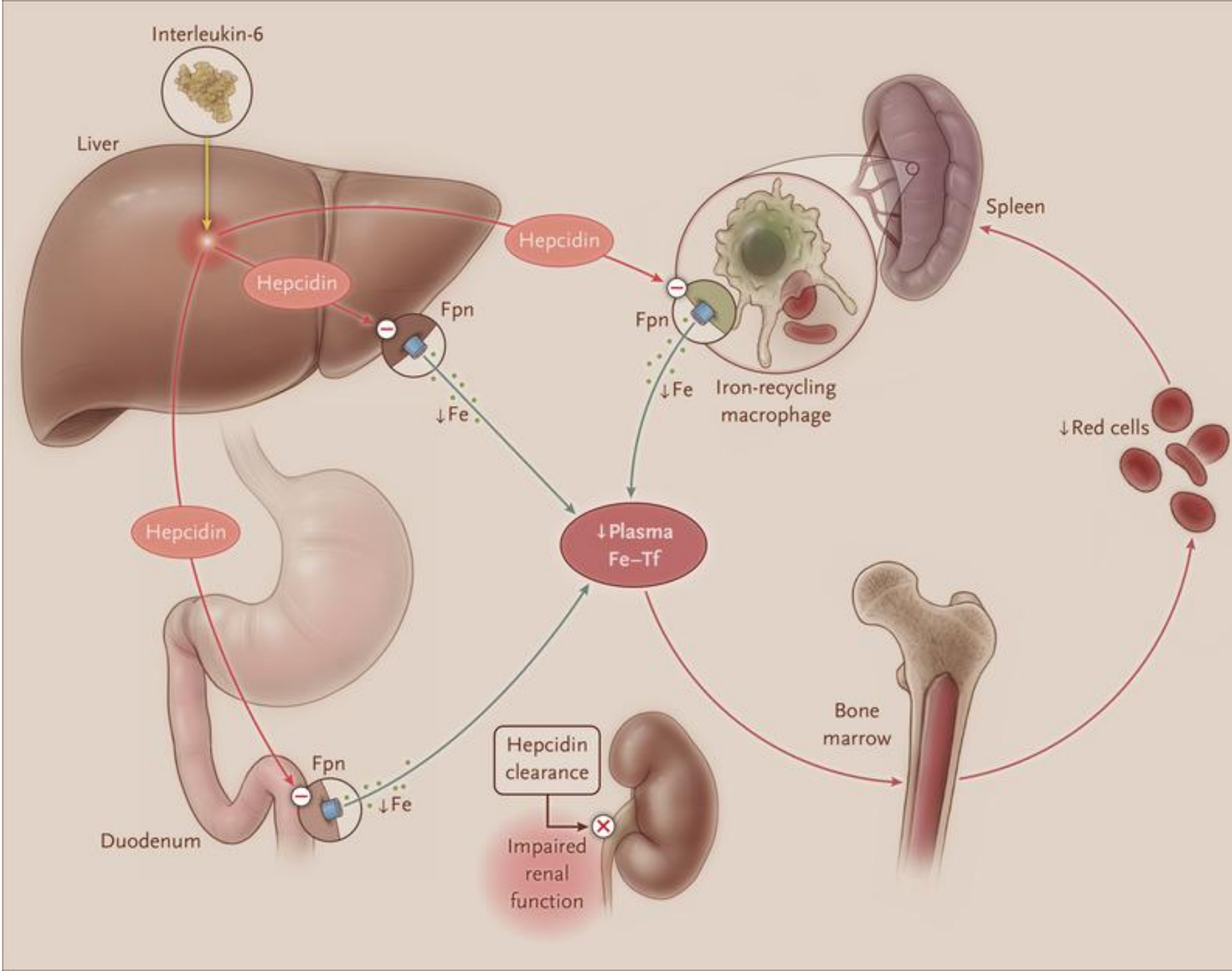
## ESA resistance

- aluminium toxicity – desferrioxamine test when aluminium toxicity suspected

- pure red cell aplasia (PRCA) – ESA-induced PRCA managed in accordance with best practice







# 缺氧誘發因子 HIF 作用



# 上升



壓制 運鐵素  
鐵的吸收運用下降



鐵調素  
Hepcidin

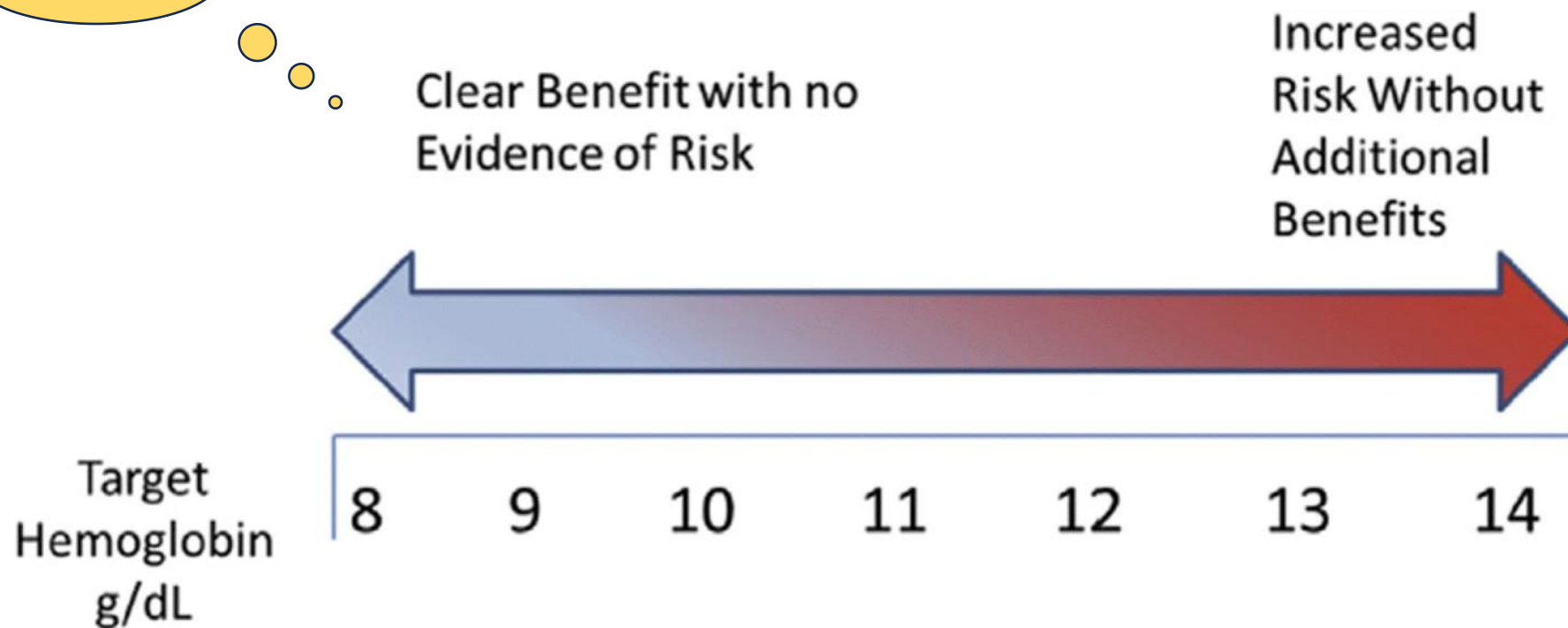
# 下降



運鐵素 增加  
鐵的吸收運用增加



血色素範圍到底  
要多少才好？



## Table 2: Target hemoglobin and iron indices

	Target hemoglobin	Target ferritin	Target transferrin saturation
Chronic kidney disease	> 10 g/dL	> 100 ng/dL	> 20%
End-stage renal disease	10–11.5 g/dL	200–1,200 ng/dL	30%–50%

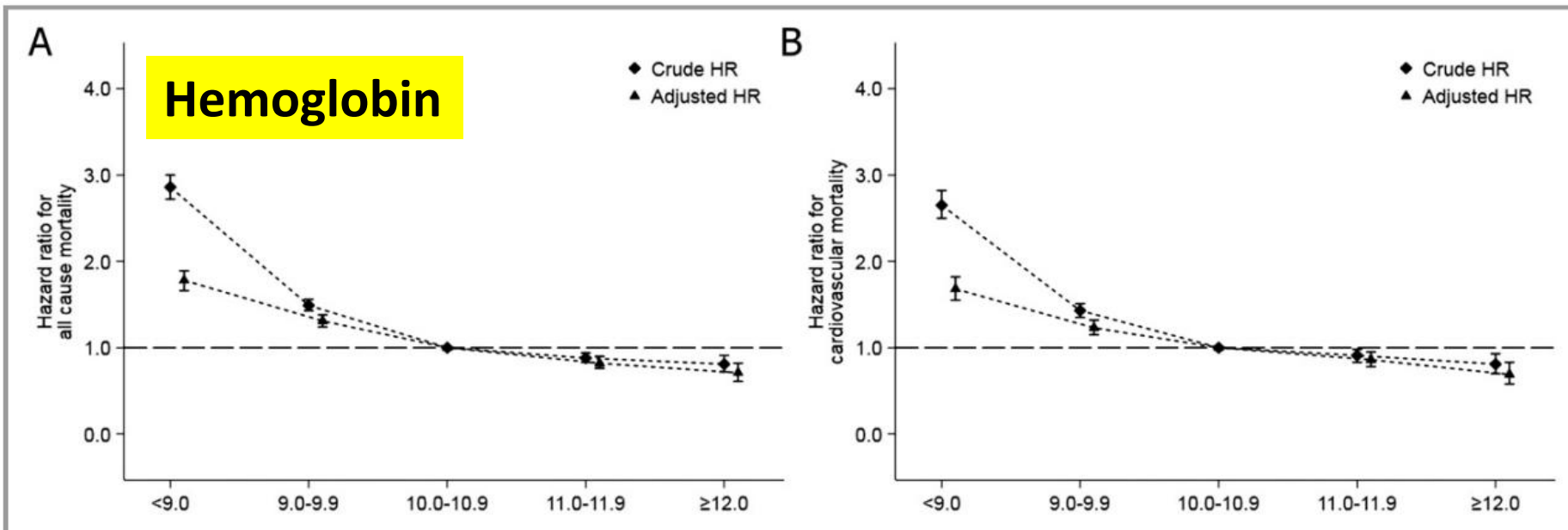
Based on information in KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl* 2012; 2:279–335.

## Association of Anemia and Iron Parameters With Mortality Among Patients Undergoing Prevalent Hemodialysis in Taiwan: The AIM-HD Study

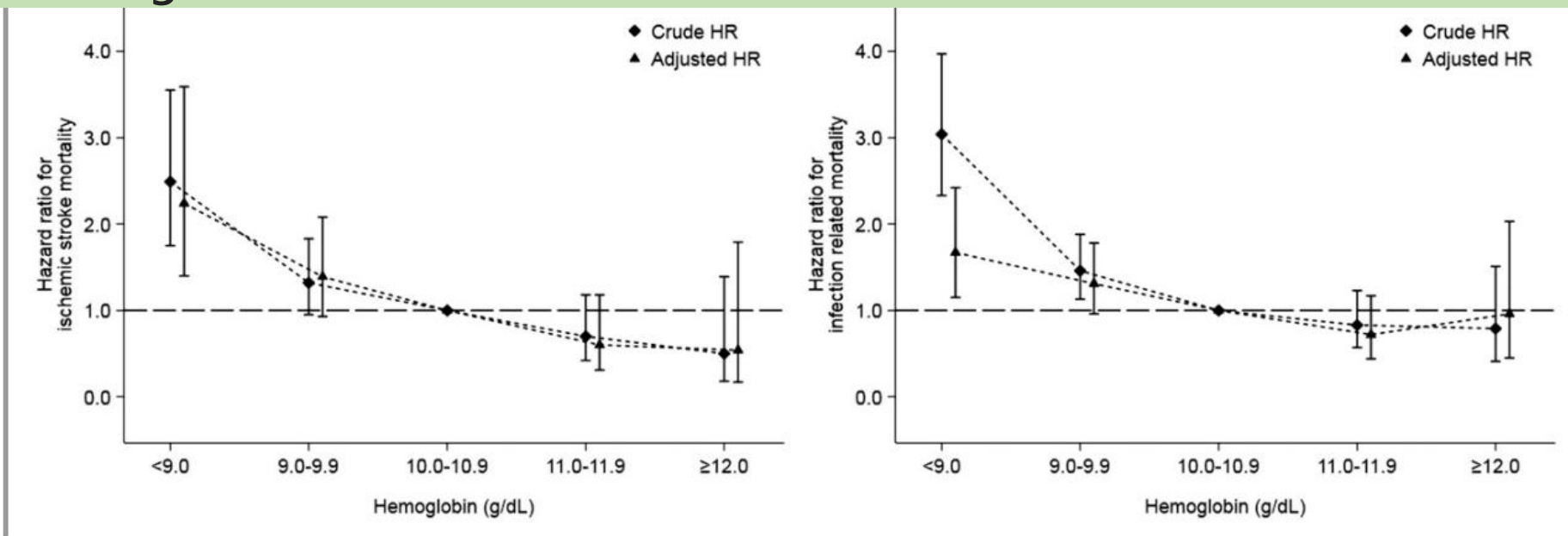
Ko-Lin Kuo, MD, PhD; Szu-Chun Hung, MD; Wei-Cheng Tseng, MD; Ming-Tsun Tsai, MD; Jia-Sin Liu, MS; Ming-Huang Lin, MS; Chih-Cheng Hsu, MD, DrPH; Der-Cherng Tarng, MD, PhD; on behalf of the Taiwan Society of Nephrology Renal Registry Data System\*

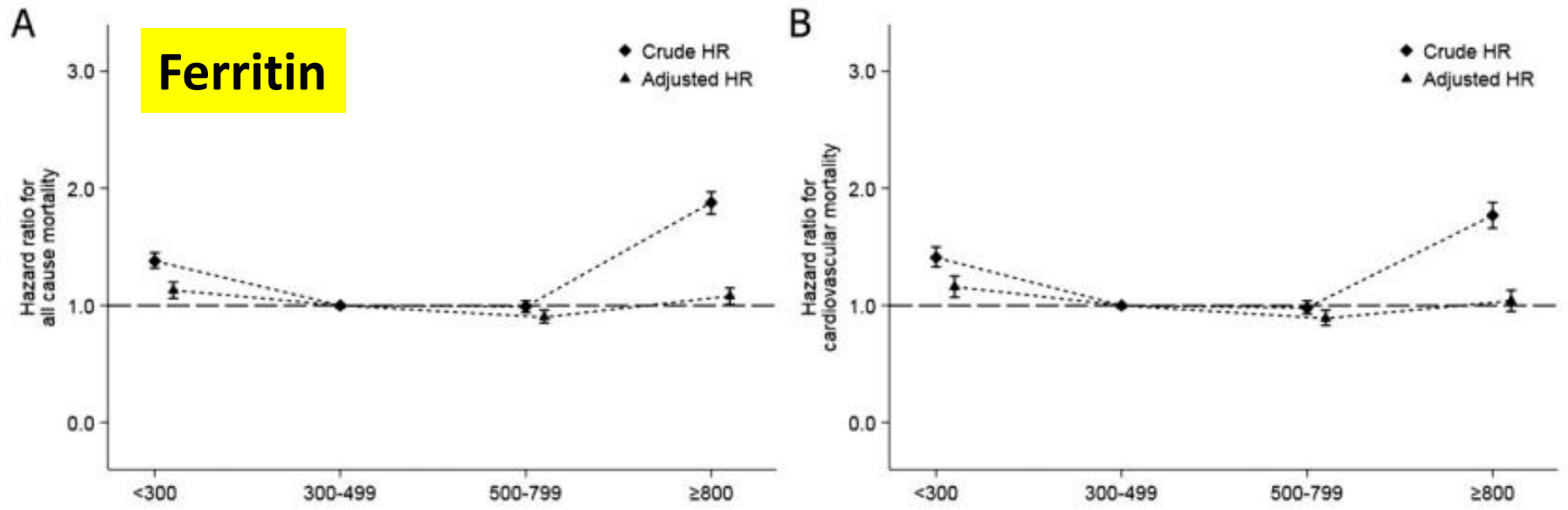
- 2001-2008 健保資料庫，42230 patients，age > 20 & HD > 1 year
- AIM-HD (Association of Anemia, Iron parameters, and Mortality among the prevalent Hemodialysis patients) Study in Taiwan
- 探討anemia與iron parameters 對於全死亡率、心血管死亡率、缺血性腦中風、感染相關死亡率之關係



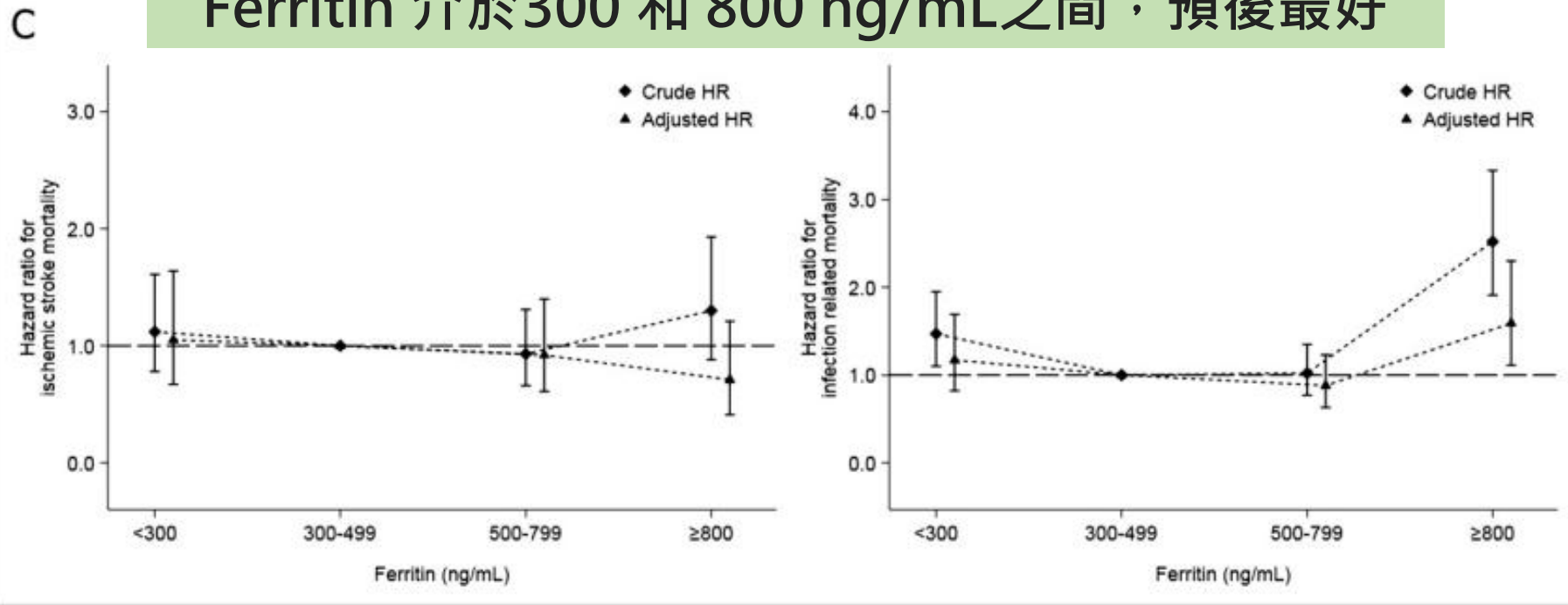


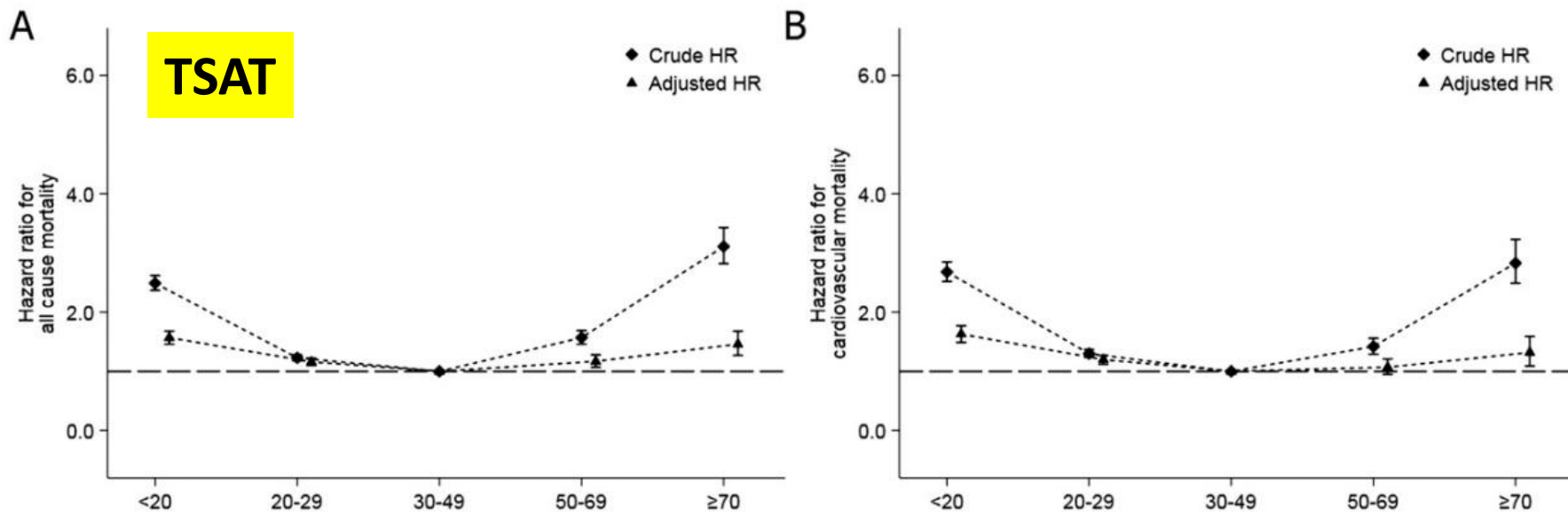
Hb < 10 g/L，總死亡率、心血管死亡率、腦梗塞死亡率、感染相關死亡率皆上升



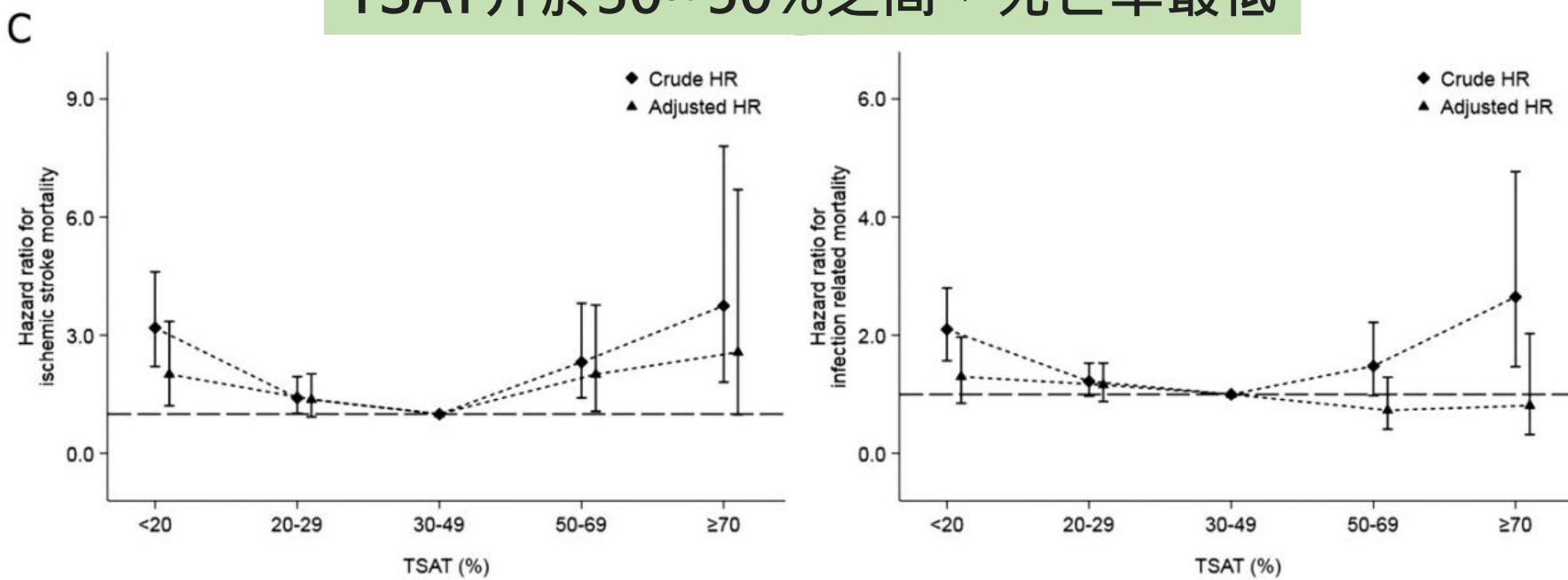


Ferritin 介於300 和 800 ng/mL之間，預後最好





TSAT介於30~50%之間，死亡率最低





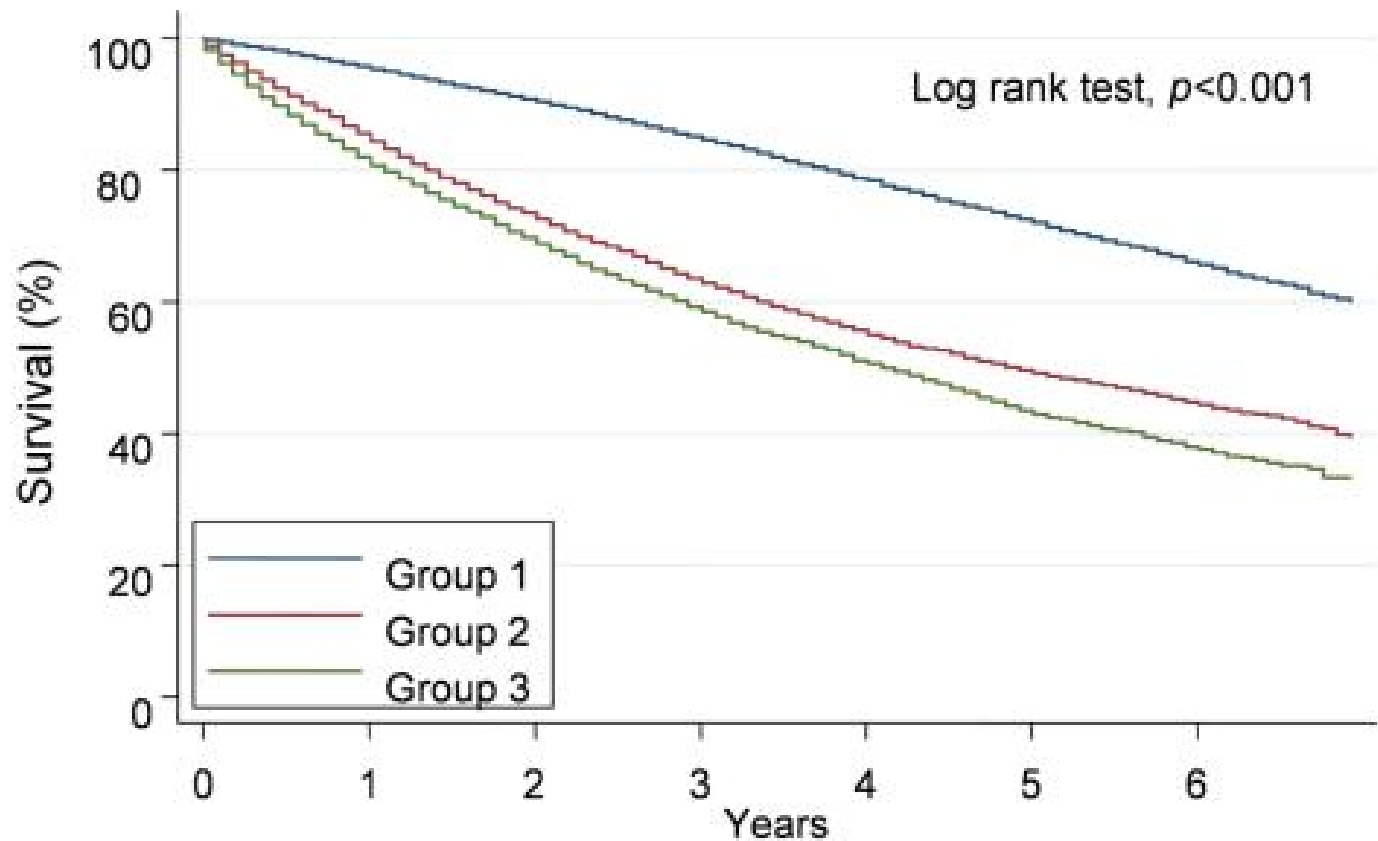
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Hb < 10 g/L，總死亡率、心血管死亡率、腦梗塞死亡率、感染相關死亡率皆上升

Ferritin 介於 300 和 800 ng/mL 之間，預後最好

TSAT 則發現 30~50% 之間，死亡率最低



**Ferritin <800 & TSAT <50%, Fe (+)  
存活率最高**

Ferritin <800 & TSAT <50%, Fe (-)

Ferritin >800 or TSAT >50%

Number at risk

Group 1	20038	16319	12496	8692	5661	3308	1474
Group 2	13005	9704	7155	5151	3594	2250	1093
Group 3	9187	6651	4844	3321	2180	1235	538

Group 1: ferritin < 800 ng/mL and TSAT < 50 % with iron supplementation,

Group 2: ferritin < 800 ng/mL and TSAT < 50 % without iron supplementation,

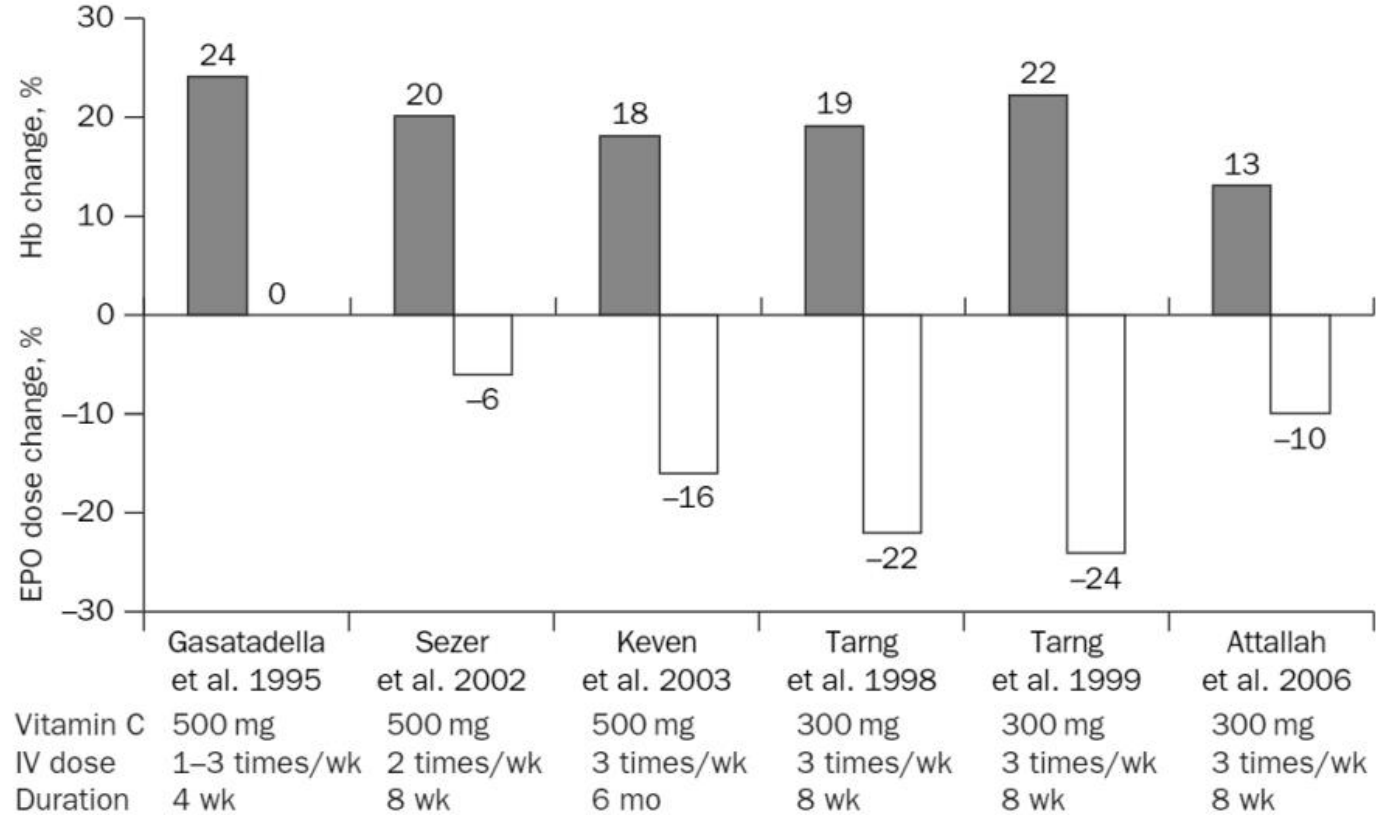
Group 3: ferritin  $\geq$  800 ng/mL or TSAT  $\geq$  50 %.

**Table 1** Haemoglobin and iron targets in different clinical practice guidelines of anaemia management

	Taiwan 1996	DOQI 2000	European 2004	K/DOQI 2006	K/DOQI 2007 revised	KDIGO 2012
Hb (g/dL)	10~11	11~12	11~12	>11 (<13)		11.5
TSAT (%)	>30 (30~50)	≥20 (<50)	>20 (30~40)	>20	>20	>30
Ferritin (μg/L)	>300 (300~500)	≥100 (<800)	≥100 (200~500)	>100 (<500)	>100	>500
Hypochromic RBC (%)			<10 (<2.5)			
CHr (pg/cell)			>29 (~35)	>29	>29	

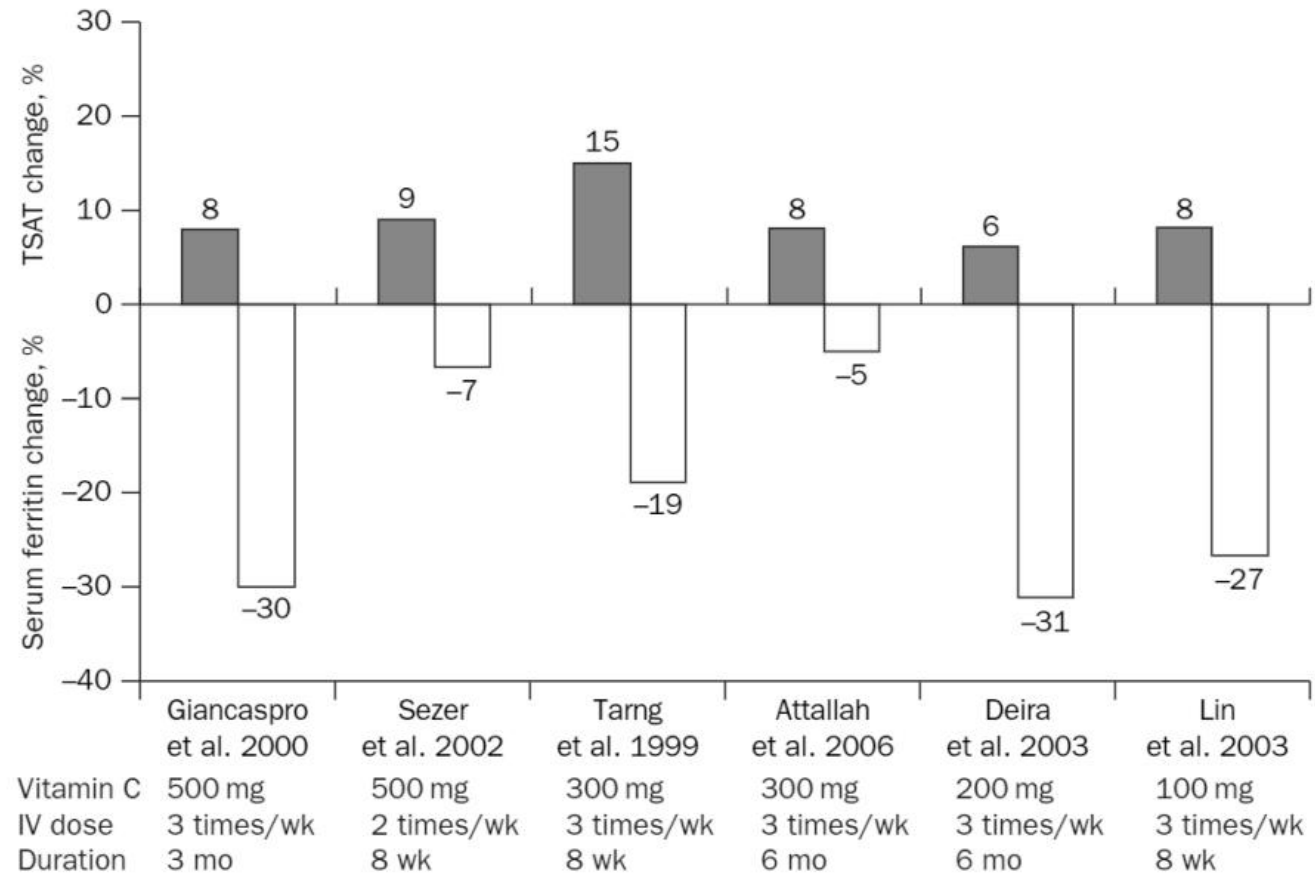
CHr, reticulocyte hemoglobin content; DOQI, Disease Outcomes Quality Initiative; Hb, haemoglobin; K/DOQI, Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease Improving Global Outcomes; RBC, red blood cell; TSAT, transferrin saturation.





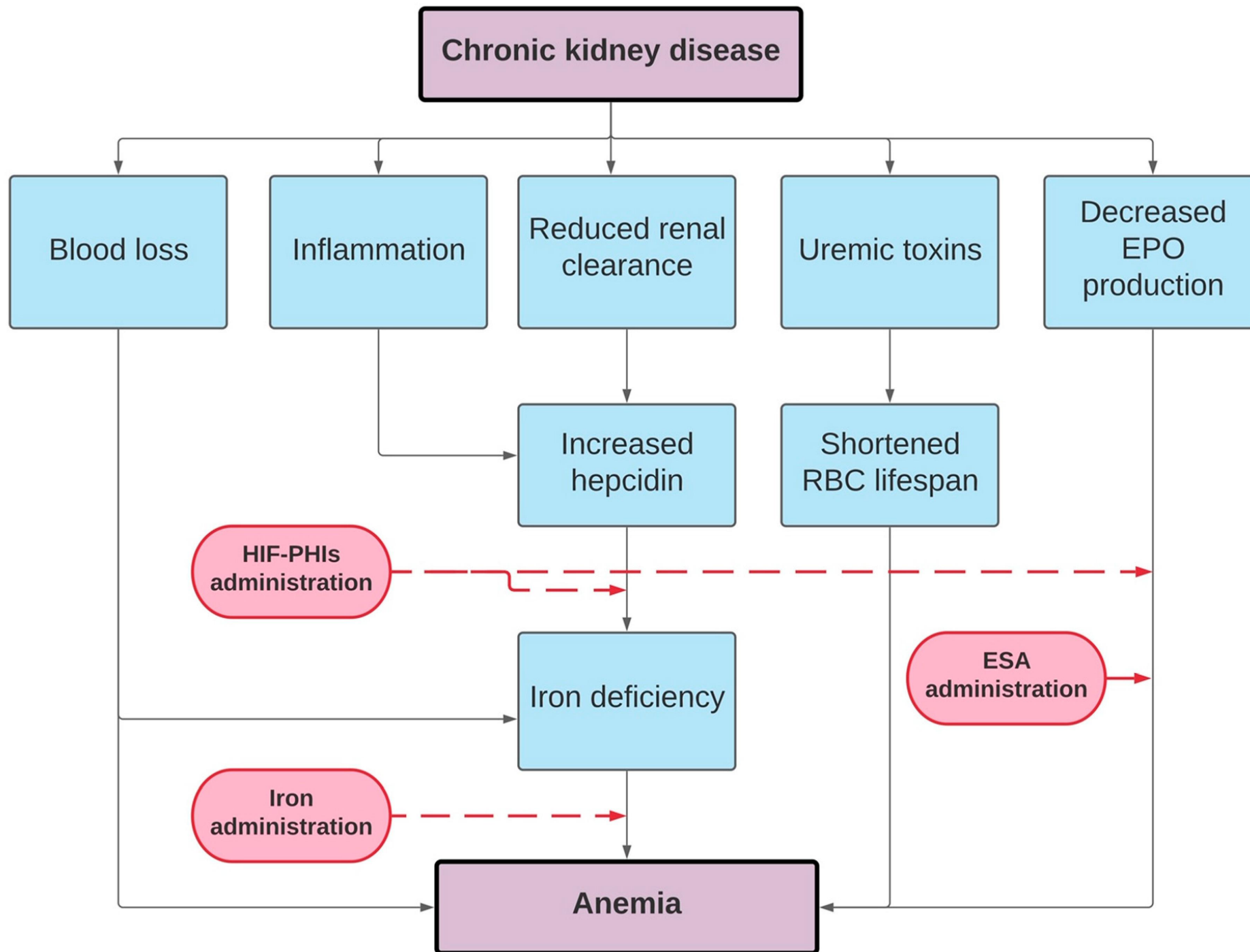
**Figure 1.** Intravenous vitamin C effects on hemoglobin (Hb) response (gray bars) and epoetin (EPO) dose (white bars) in patients receiving hemodialysis.

適度使用vitamin C，可增加Hgb，減少EPO dose



**Figure 2.** Intravenous vitamin C effects on transferrin saturation (TSAT) changes (gray bars) and serum ferritin changes (white bars) in patients receiving hemodialysis.

適度使用vitamin C，可增加TSAT，減少ferritin

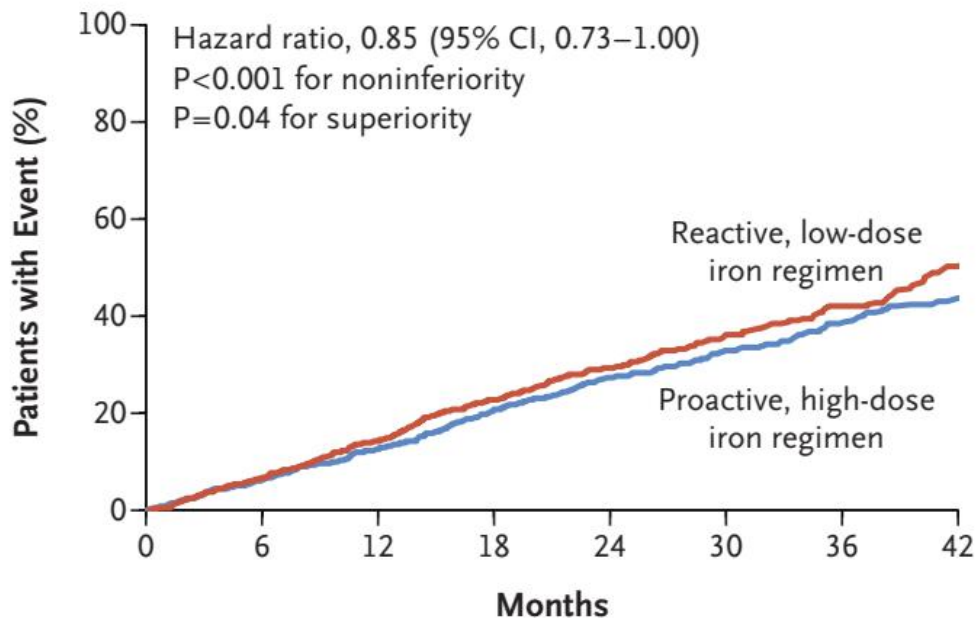






## Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

### A Primary Efficacy End Point



#### No. at Risk

Reactive, low-dose iron regimen	1048	732	496	183
Proactive, high-dose iron regimen	1093	799	548	194

**主動靜脈輸注鐵劑** ( iron sucrose 400 mg/month 直到 ferritin 700  $\mu\text{g/L}$  或 TSAT > 40% ) 與 **被動輸注** ( 當 ferritin < 200  $\mu\text{g/L}$  或 TSAT < 20% 時才用 iron sucrose 0-400 mg/month ) 比較

- **能降低主要終點** ( 急性心肌梗塞、心衰竭住院率、死亡率 )
- **降低次要終點** ( EPO 的用量 )
- **不影響感染率**

# ESA for renal anemia treatment



Iron deficiency



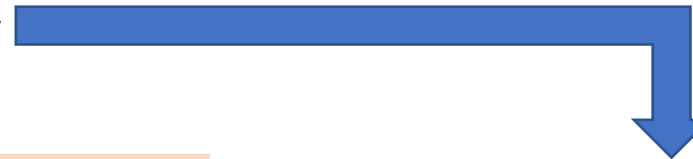
Ferritin < 300 ng/ml  
And /or  
Transferrin saturation < 30%



Parenteral iron supplementation



To maintain  
**Ferritin 300-500 ng/ml**  
**And TSAT 30-50%**  
**Hb 10-11 g/dL**



Ferritin > 800 ng/ml  
TAST < 20%  
→ **Functional iron deficiency**

Response  
No



Look for other possible causes



Response  
Yes



Check iron status every 3 months

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

**Table 2 | Evidence for clinical benefits of iron administration**

	Patients with CKD not on dialysis	Patients on dialysis
Reduction of congestive heart failure	Limited <sup>60,61</sup>	Yes <sup>62</sup>
Reduced occurrence of myocardial infarction	Limited <sup>63</sup>	Yes <sup>62</sup>
Improved quality of life	Not studied	Limited <sup>64</sup>
Reduced occurrence of fatigue	Not studied	Limited <sup>64</sup>
Improved cognitive function	Not studied	Limited <sup>64</sup>
ESA dose reduction	Yes <sup>65</sup>	Yes <sup>65</sup>
Reduced blood transfusions	Not studied	Yes <sup>62</sup>

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agents; RCT, randomized controlled trial.

Limited: data from retrospective, observational studies. Yes: supported by RCT data.

*Kidney International* (2021) **99**, 1280–1295; <https://doi.org/10.1016/j.kint.2021.03.020>

**Table 3 | Evidence for increased risk of clinical harm with iron administration**

	Patients with CKD not on dialysis	Patients on dialysis
Infections	Limited <sup>78,79</sup>	No <sup>80,81</sup>
Cardiovascular events	Limited <sup>78,79,82</sup>	No <sup>62</sup>
Diabetes	Limited <sup>83</sup>	Limited <sup>83</sup>
CKD progression	Limited <sup>78,79</sup>	Not applicable
Anaphylaxis	Minimal <sup>84</sup>	Minimal <sup>84</sup>

CKD, chronic kidney disease; i.v., intravenous; RCT, randomized controlled trial.

No: supported by RCT data. Limited: data from retrospective, observational trials only. Minimal: overall minimal risk for contemporary i.v. iron formulations.



Medication	Molecular Weight (Da)	Maximum Daily Dose	Iron Concentration (mg/ml)	Test-Dose Required	Black Box Warning
Iron dextran	265,000	100 mg	50	Yes	Yes
Low mol wt iron dextran	165,000 low mol wt iron dextran	100 mg	50	Yes	Yes
Sodium ferric gluconate complex in sucrose injection	289,000–444,000	125 mg	12.5	No	No
Iron sucrose injection, United States Pharmacopeial	34,000–60,000	200 mg in CKD (100 mg if on hemodialysis, 300–400 mg if on peritoneal dialysis)	20	No	No
Ferumoxytol	750,000	510 mg	30	No	Yes
Iron isomaltoside' FCM injection	150,000	20 mg/kg	100	No	No
	150,000	750 mg if weight >50 kg (15 mg/kg if weight <50 kg)	50	No	No



**Table 6 | I.v. iron formulations for treating anemia in CKD**

Preparation (brand name <sup>a)</sup> <sup>b</sup>	Concentration of elemental iron (mg/ml)	Max. single dose	Max. weekly dose	Min. infusion time for max. dose	Min. injection time for max. dose
Iron sucrose (Venofer); Iron sucrose similars (FerMed)	20	200 mg	500 mg	30 min (EMA) 15 min (FDA)	10 min (EMA) 2–5 min (FDA)
Sodium ferric gluconate (Ferrlecit)	12.5	125 mg	Not stated	60 min (FDA)	10 min (FDA)
LMW iron dextran (Cosmofer [Europe]; INFeD [USA])	50	20 mg/kg	Not stated	15 min, then 100 mg/15 min (EMA) Total infusion: 4–6 h	Approx. 20 min (EMA) >60 min (FDA)
Ferric carboxymaltose (Ferinject [Europe]; Injectafer [USA])	50	1000 mg (EMA) 750 mg (FDA)	1000 mg (EMA) 750 mg (FDA)	15 min	15 min (EMA) 7.5 min (FDA)
Iron isomaltoside/ferric derisomaltose (Monofer [Europe], Monoferric [USA])	100	20 mg/kg (EMA) 1000 mg (FDA)	20 mg/kg (EMA) Not stated (FDA)	More than 15 min (≤1000 mg) (EMC) 30 min or more (>1000 mg) (EMC) 20 min for ≤1000 mg (FDA)	250 mg/min (max. 500 mg) (EMA)
Ferumoxytol (Rienso [Europe] <sup>c</sup> , Feraheme [USA])	30	510 mg	1020 mg	15 min (EMA)	15 min (FDA)



# HIF stabilizer (HIF-PHI)

## Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitors in the Treatment of Anemia of Chronic Kidney Disease

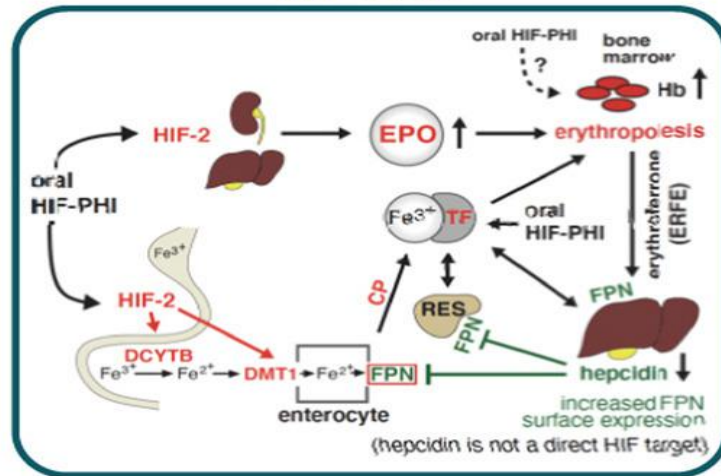
Orally administered HIF-PHIs



Global and regional phase 3 clinical trials address



Clinical effects of HIF-PHIs



<b>NDD-CKD</b>	<b>DD-CKD</b>
<b>HIF-PHIs vs PBO</b>	
<b>HIF-PHIs vs ESAs</b>	
<ul style="list-style-type: none"> <li>• Correction or maintenance of Hb</li> <li>• Iron parameters (ferritin, TIBC, transferrin, hepcidin)</li> <li>• IV iron use</li> <li>• Need for blood transfusions</li> <li>• Serum cholesterol</li> <li>• Safety</li> </ul>	

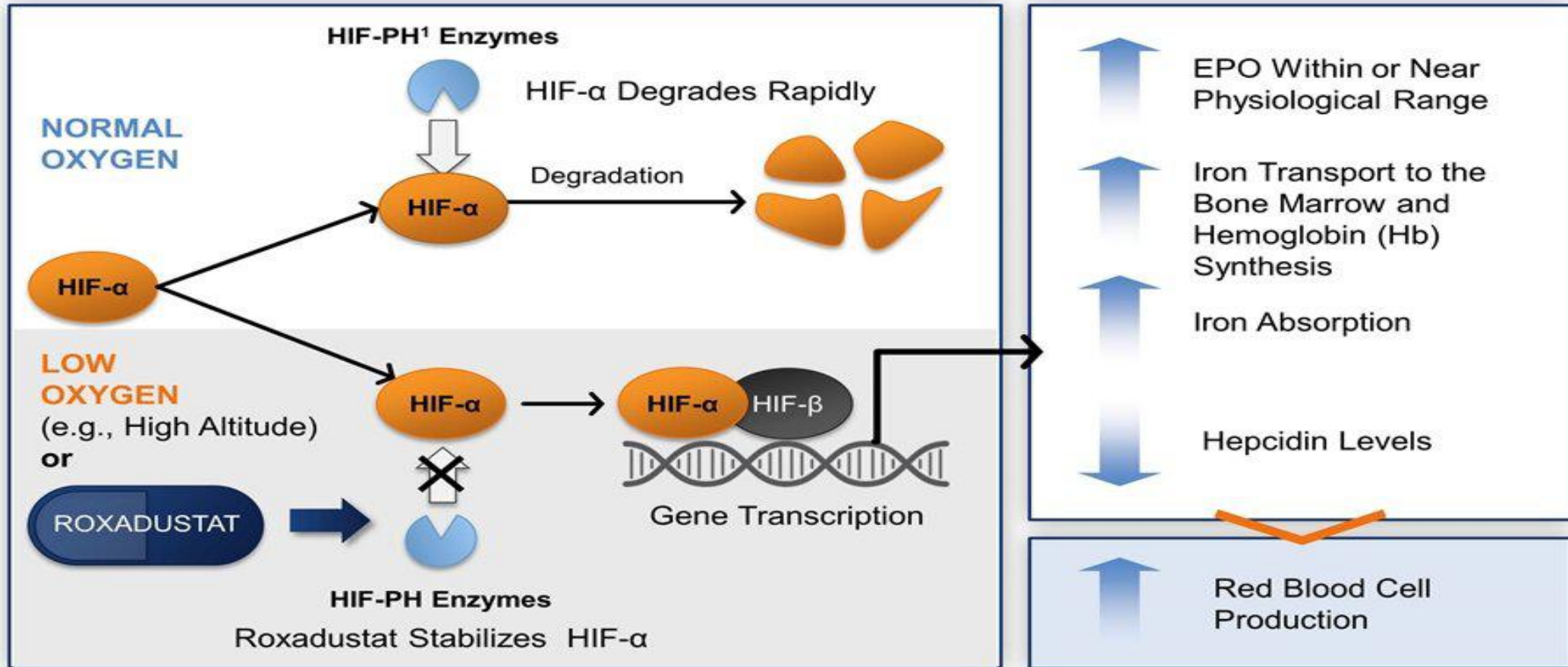
- Stimulation of endogenous EPO
- Promotes iron mobilization and utilization
- Efficacy in CKD patients with ↑ CRP
- Impact on cardiovascular safety (MACE)?
- Delay of renal disease progression?
- Other safety considerations

- CONCLUSIONS:**
- HIF-PHIs demonstrate efficacy in the treatment of anemia of CKD
  - Preliminary data suggest that HIF-PHIs have effects beyond erythropoiesis and iron metabolism impacting cardiovascular safety
  - Long-term safety needs to be established in extended trials and post-marketing analysis

CKD, chronic kidney disease; DCYTb, duodenal cytochrome B; DMT1, divalent metal transporter 1; DD, dialysis-dependent; CP, ceruloplasmin; CRP, C-reactive protein; EPO, erythropoietin; ESA, erythropoietin-stimulating agent; FPN, ferroportin; Hb, hemoglobin; HIF, hypoxia-inducible factor; HIF-PHI, hypoxia-inducible factor-prolyl hydroxylase inhibitor; NDD, non-dialysis-dependent; RES, reticulocyte endothelial system; TF, transferrin; TIBC, total iron binding capacity

# Roxadustat Activates a Natural Pathway to Increase Red Blood Cell Production

FIBROGEN



<sup>1</sup>HIF-PH - hypoxia-inducible factor prolyl hydroxylase



# Molidustat for Japanese Patients with Renal Anemia Receiving Dialysis



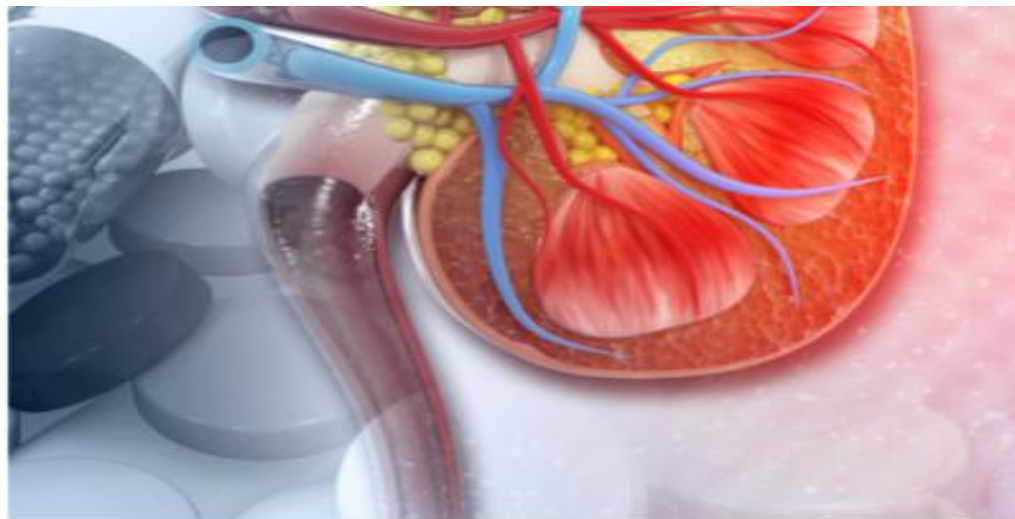
Methods and Cohort	Intervention	Results				
<ul style="list-style-type: none"> <li>Double-blinded phase 3 trial</li> <li>53 centers in Japan</li> <li>229 adults</li> <li>End-stage kidney disease on hemodialysis</li> <li>Previously treated with erythropoiesis-stimulating agents (ESAs)</li> <li>Baseline hemoglobin (Hb) = 10.8 g/dL</li> </ul>	<ul style="list-style-type: none"> <li>molidustat</li> <li>n = 153</li> </ul>	<p>52 weeks</p>	<p>Mean Hb at 33-36 wks (g/dL)</p> <p>10.63 [10.42-10.84]</p>	<p>Change in mean Hb level from baseline</p> <p>-0.14 [-0.37 to 0.09]</p>	<p>Use of rescue treatment due to lack of efficacy</p> <p>11.1% 17 of 153</p>	<p>Incidence of treatment-emergent adverse events</p> <p>95.4%</p>
	<ul style="list-style-type: none"> <li>darbepoetin</li> <li>n = 76</li> </ul>		<p>10.77 [10.59-10.95]</p>	<p>-0.07 [-0.30 to 0.16]</p>	<p>1.3% 1 of 76</p>	<p>94.7%</p>

Generic Name	Investigational Name	Sponsor	Half-Life, h	Dosing Frequency	Investigational Status
Roxadustat	FG-4592	FibroGen, Astellas, & AstraZeneca	12-13	3×/wk	Phase 3
Vadadustat	AKB-6548	Akebia	4.5	Daily	Phase 3
Daprodustat	GSK-1278863	GlaxoSmithKline	4	Daily	Phase 2 (US) Phase 3 (Japan)
Molidustat	BAY 85-3934	Bayer	NA	Daily	Phase 2

**Table 1. Select HIF-PHIs and approval status**

HIF-PHI Product	Half-Life	Phase 3 Trials' Status	US Approval Status	Approved for Use in
Roxadustat 商:EVRENZO	14.7–19.4 h	All completed	Submitted for approval; FDA response required 3/20/21	Japan, China
Vadadustat	1.9–3.6 h	All completed	Anticipated FDA new drug submission early 2021	Japan
Daprodustat	0.9–2.3 h	Completed, except CKD-non-dialysis study (tentative closure April 2021)	Anticipated FDA new drug submission 2021	Japan





NEWS IN BRIEF | 09 February 2023

## FDA approves first hypoxia-inducible factor prolyl hydroxylase inhibitor

By [Asher Mullard](#)



The US FDA has approved [GSK's daprodustat](#) for anaemia caused by chronic kidney disease in adults on dialysis, overcoming safety concerns for this class. Daprodustat is the first hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor to secure FDA approval, and provides a

慢性腎病導致貧血治療突破，GSK 口服 Jesduvroq 獲美國 FDA 核准

大大大

BY KATHY HUANG ON 2023 年 2 月 2 日

產業動態

2 月 1 日，美國食品藥物管理局（FDA）宣布核准 [Jesduvroq \(daprodustat\)](#)，用於慢性腎病 (chronic kidney disease, CKD) 且曾接受 4 個月以上腎透析而導致貧血的成年病人。Jesduvroq 口服藥由 GSK (GlaxoSmithKline, 葛蘭素史克) 藥廠所研發。

Jesduvroq 於 2020 年已獲得日本厚生勞動省 (JMHLW) 核准用於罹患腎臟病貧血病人，其於歐盟 EMA 的上市申請也在審核中，預計今年上半年能得知結果。

# HIF stabilizer (HIF-PHI)

## HIF生血素潛在風險



腫瘤生長



囊泡生長



發炎反應

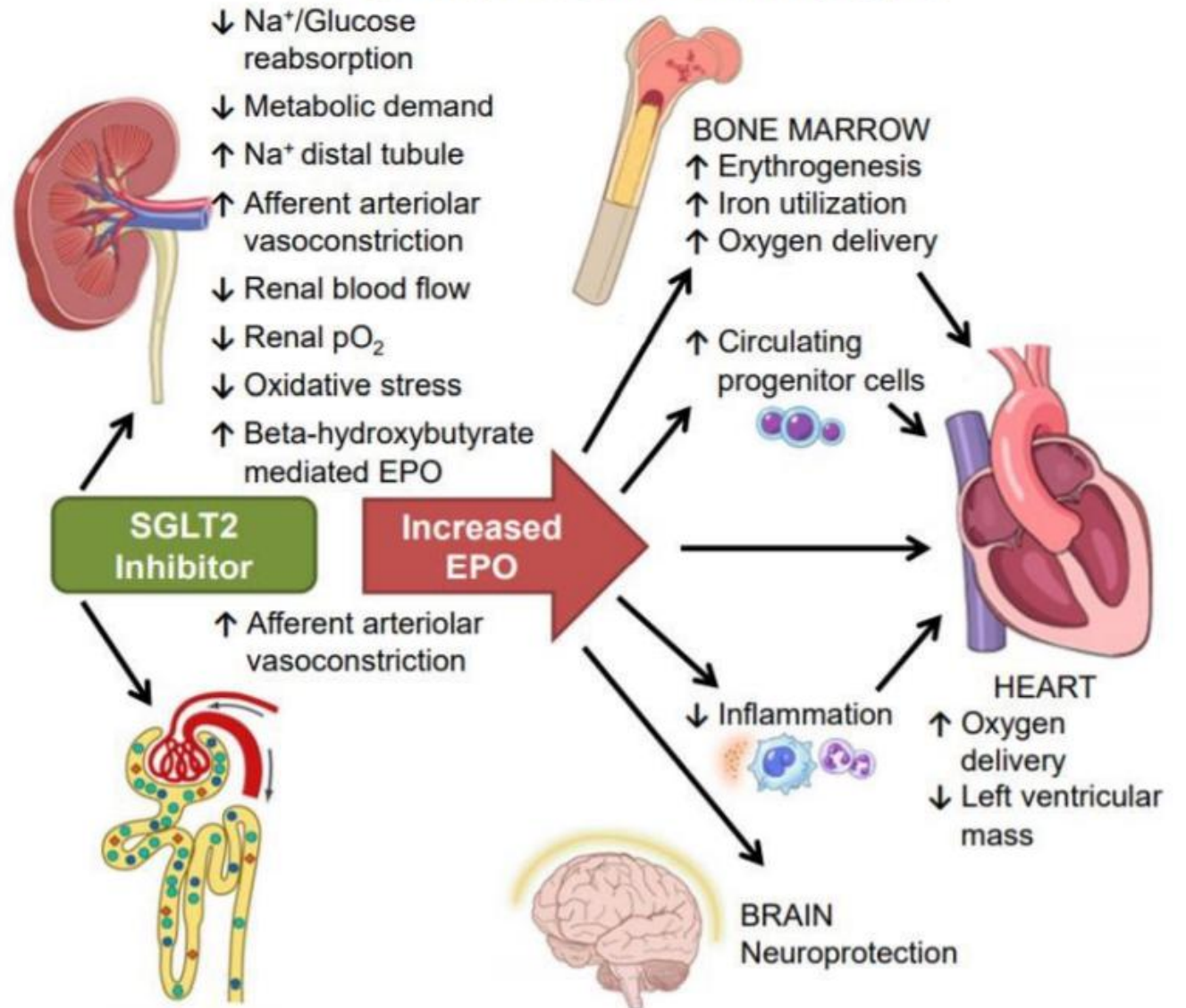


腎纖維化



A diabetes drug  
for anemia??

### c) Proposed Renal Mechanisms for Increased EPO with SGLT2 Inhibitors



# Take home message

## Key Points: Anemia of Chronic Kidney Disease

### Causes and Effects

- **↓ EPO production**
- **↑ hepcidin**
  - Due to ↓ renal clearance and ↑ IL-6
  - Leads to:
    - iron sequestration in macrophages
    - iron-restricted erythropoiesis, resistance to EPO
- **True iron deficiency**
  - Due to increased blood loss and hepcidin-mediated decrease in intestinal iron absorption)
- **Suppression of erythropoiesis by inflammatory cytokines** (important in acute inflammation)
- **Shortened erythrocyte lifespan**
  - Due to inflammation and uremia

### Treatments and Modulators

- **Exogenous EPO/Erythropoietin Stimulating Agents (ESAs)**
  - Causes pulsatile erythropoiesis and transient high demand for iron
  - High doses ↓ hepcidin but at the cost of side effects
- **Iron**
  - Overcomes hepcidin-induced blockade of iron release from macrophages
  - Decreases resistance to EPO
- **HIF-PHD Inhibitors**
  - Increases uptake of iron
  - Increases endogenous EPO release, leads to:
    - Inhibition of downstream effects of hepcidin

Thank you  
for  
listening!





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誰說牛肉最補血？

每100g含量



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豬血

Fe 28.0 mg



西施舌

Fe 25.7 mg



鴨血

Fe 15.6 mg



九孔

Fe 11.4 mg



豬肝

Fe 10.2 mg



文蛤

Fe 8.2 mg



小魚干

Fe 6.8 mg



章魚

Fe 6.1 mg



牡蠣

Fe 5.2 mg



雞心

Fe 4.4 mg



豬舌

Fe 3.0 mg



牛腱

Fe 3.0 mg



牛腩

Fe 2.3 mg



雞胗

Fe 2.2 mg



鵝肉

Fe 1.9 mg



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每100g



生紫菜

Fe 56.2 mg



髮菜

Fe 40.7 mg



熟海苔

Fe 37.9 mg



紅莧菜

Fe 11.8 mg



山芹菜

Fe 7.8 mg



龍葵

Fe 6.7 mg



紅鳳菜

Fe 6.0 mg



水蓮

Fe 3.7 mg



空心菜

Fe 3.1 mg



菠菜

Fe 2.9 mg



地瓜葉

Fe 2.5 mg



小松菜

Fe 2.5 mg



蔥

Fe 2.2 mg



青江菜

Fe 1.7 mg



茼蒿

Fe 1.5 mg



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