XIX CONGRESSO PAULISTA DE NEFROLOGIA
INOVAÇÃO SUSTENTÁVEL
4-7 OUT 2017

CKD-RELATED ANEMIA

CONCLUSION FROM KDIGO CONTROVERSIES CONFERENCE

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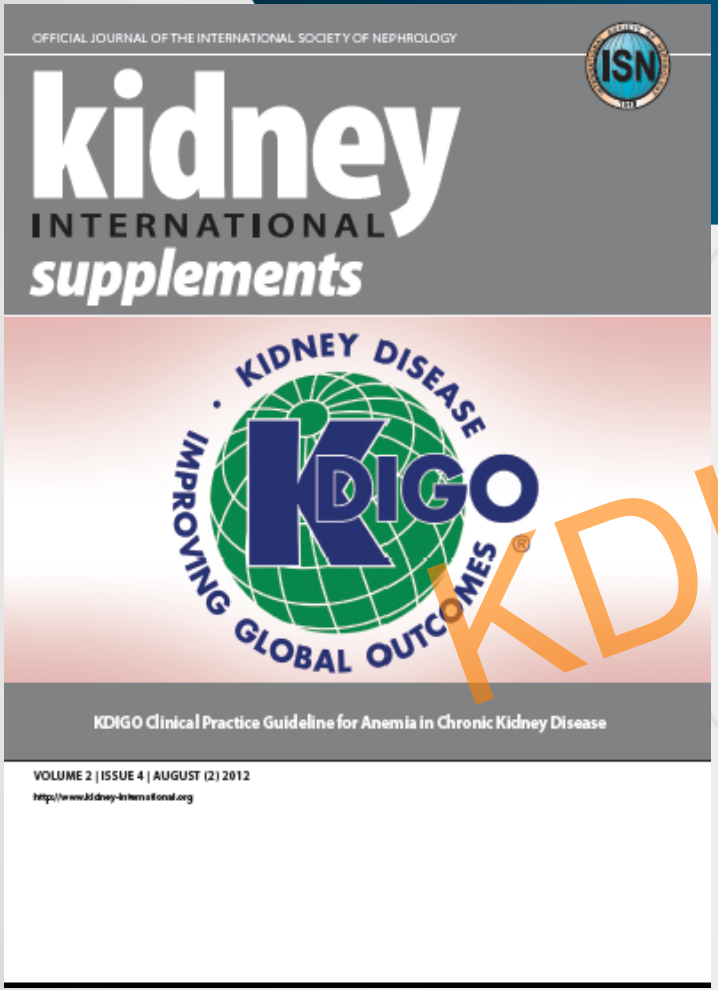
Clinical Practice Guidelines on the Treatment of CKD-related Anemia

1989	Introduction of EPO for clinical use
1997	KDOQI Guidelines on CKD-related anemia
2006	UPDATE → KDOQI Guidelines on CKD-related anemia
2007	UPDATE → KDOQI Guidelines on Hb target level
2010	REVISION → KDIGO Guidelines on CKD-related anemia
2012	PUBLICATION → KDIGO Guidelines on CKD-related anemia
2014	KDIGO Controversies Conference on the use of iron
2016	PUBLICATION → Article of the CC on the use of iron

KDIGO



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Kidney International Supplements (2012) 2, 281; doi:10.1038/kisup.2012.39

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KDIGO Controversies Conference

Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

Iain C. Macdougall[1], Andreas J. Bircher[2], Kai-Uwe Eckardt[3], Gregorio T. Obrador[4], Carol A. Pollock[5,6], Peter Stenvinkel[7], Dorine W. Swinkels[8], Christoph Wanner[9], Günter Weiss[10], and Glenn M. Chertow[11]; for Conference Participants[12]

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OPEN
Kidney International (2016) **89,** 28–39

- Iron overload
- Oxidative stress
- Infections
- Anaphylactoid reactions

2012 KDIGO Guidelines Anemia in CKD

- ✓ **Identification, diagnosis and evaluation of the cause**
- Role of iron to treat CKD-related anemia
- Role of ESAs and other drugs to treat CKD-related anemia
- Role of blood transfusions to treat CKD-related anemia

Evaluation of Anemia
FREQUENCY

PATIENTS WITHOUT ANEMIA When it is clinically advised and	
CKD 3	At least annually
CKD 4 and CKD 5ND	At least once every 6 months
CKD 5HD and CKD 5PD	At least once every 3 months

PATIENTS WITH ANEMIA & WITHOUT TREATMENT WITH ESA When it is clinically advised and	
CKD 3-5ND and CKD 5PD	At least once every 3 months
CKD 5HD	At least once a month

ANEMIA: Definition in Previous Guidelines

WHO 2001	• Hb <13 g/dL → Men • Hb <12 g/dL → Women
KDOQI 2001	• Hb <12.0 g/dL → Adult men and postmenopausal women • Hb <11 g/dL → Premenopausal and prepuberal women
EBPG 2004	• Hb <13.0 g/dL → Adult men • Hb <12 g/dL → Men >70 years old • Hb <11.5 g/dL → Adult women

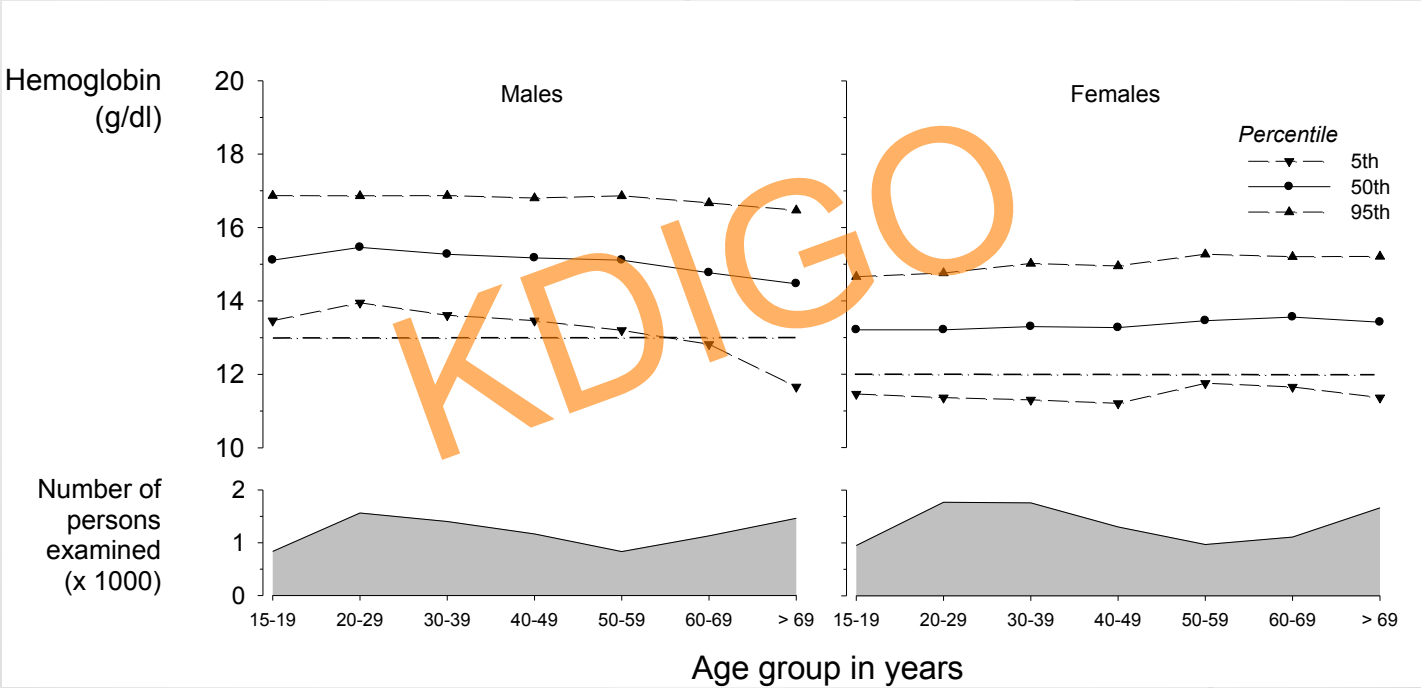
ANEMIA: Definition in 2006 KDOQI Guidelines

1.1.3 Diagnosis of anemia:

In the opinion of the Work Group, diagnosis of anemia should be made and further evaluation should be undertaken at the following Hb concentrations:

- <13.5 g/dL in adult males.
- <12.0 g/dL in adult females.

NHANES III (1988-1994) Distribution of Hb Levels



Vital Health Stat 11 (247), 2005
MMWR 47:1-36, 1998

ANEMIA: Definition in 2012 KDIGO Guidelines

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*)

ANEMIA: Definition - WHO 2008

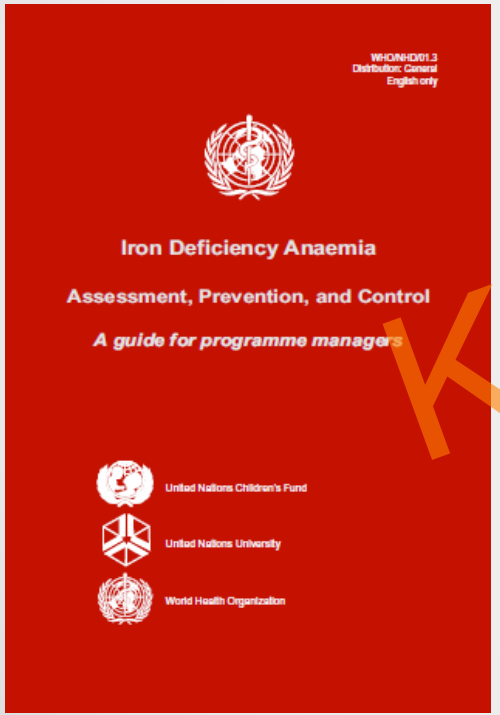
Table 2.1 ***Haemoglobin thresholds used to define anaemia***

Age or gender group	Haemoglobin threshold (g/l)
Children (0.50–4.99 yrs)	110
Children (5.00–11.99 yrs)	115
Children (12.00–14.99 yrs)	120
Non-pregnant women (≥15.00 yrs)	120
Pregnant women	110
Men (≥15.00 yrs)	130

Source: adapted from reference (2)

Iron deficiency anaemia: assessment, prevention, and control. A guide for programme managers. Geneva, World Health Organization, 2001 (WHO/NHD/01.3).

ANEMIA: Definition - WHO 2001



Age or gender group	Haemoglobin g/l
Children 6 months to 59 months	110
Children 5–11 years	115
Children 12–14 years	120
Non-pregnant women (above 15 years of age)	120
Pregnant women	110
Men (above 15 years of age)	130

ANEMIA: Definition

REPORT OF A WHO SCIENTIFIC GROUP

3. CRITERIA FOR THE DIAGNOSIS OF ANAEMIA

In detecting and evaluating an anaemia problem in a community, reference standards are necessary, even though they may be somewhat arbitrary. The report [2] of the 1958 WHO Study Group recommended haemoglobin values below which anaemia could be considered to exist. These figures were chosen arbitrarily and it is still not possible to define normality precisely.[3] However, more recent data [4] indicate that the values given previously should be modified. It is recommended that, in future studies, anaemia should be considered to exist in those whose haemoglobin levels are lower than the figures given below (the values given are in g/100 ml of venous blood of persons residing at sea level):

children aged 6 months to 6 years:	11
children aged 6–14 years:	12
adult males:	13
adult females, nonpregnant:	12
adult females, pregnant:	11

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1959, No. 182, p. 4.

[4] Natvig, K. (1966) *Acta med. scand.*, **180**, 613; Tibblin, G., unpublished observations; Kilpatrick, G. S. & Hardisty, R. M. (1961) *Brit. med. J.*, **1**, 778; De Leeuw, N. K. M., Lowenstein, L. & Hsiek, Y. S. (1966) *Medicine (Baltimore)*, **45**, 291; Sturgeon, P. (1959) *Brit. J. Haemat.*, **5**, 31.

ANEMIA: Definition Challenges

- WHO's anemia definition is **questionable**; it could be included as a research recommendation in the guidelines
- Ideally a **Hb distribution** should be obtained to define appropriate cut-off levels for each population
- It is necessary to correct the Hb level according to **altitude, smoking, and race**

Impact of Altitude on Hb Concentration

Altitude (meters)	Hb (g/dL) increase
<1000	0
1000	+ 0.2
1500	+ 0.5
2000	+ 0.8
2500	+ 1.3
3000	+ 1.9
3500	+ 2.7
4000	+ 3.5
4500	+ 4.5

WHO, 2001

Impact of Smoking on Hb Concentration

Smoker Status	Hb (g/dL) increase
Non smokers	0
Smokers (all)	**+ 0.3**
• *½-1 package/day*	**+ 0.3**
• *1–2 package/ day*	**+ 0.5**
• *>2 package/ day*	**+ 0.7**

Am J Kidney Dis 41:S1-S135, 2005

Impact of Race on Hb Concentration

- Hb concetration levels **vary** among individuals of **different races**
- **African-American individuals** have Hb levels that are **0.5-0.9 g/dl lower** than those of non African-American individuals
- Since the cause of the difference in Hb levels among races is unknown and could reflect different degrees of comorbidity, the guideline **did not include specific cut-off levels** for defining anemia among different races

Evaluation of the Causes of Anemia

1.3: In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia (*Not Graded*):

- **Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count**
- **Absolute reticulocyte count**
- **Serum ferritin level**
- **Serum transferrin saturation (TSAT)**
- **Serum vitamin B_{12} and folate levels**

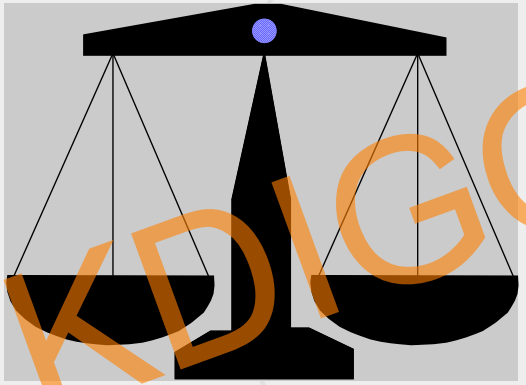
Additional tests

Other tests, in addition to those indicated above, may be appropriate in individual patients and in certain specific clinical settings. For instance measurement of high sensitivity C-reactive protein (CRP) may be indicated if occult inflammation is a concern. In certain countries and/or in patients of specific nationalities or ethnicities, testing for hemoglobinopathies, parasites, and other conditions may be appropriate.

2012 KDIGO Guidelines Anemia in CKD

- ✓ **Identification, diagnosis and evaluation of the cause**
- ✓ **Role of iron to treat CKD-related anemia**
- Role of ESAs and other drugs to treat CKD-related anemia
- Role of blood transfusions to treat CKD-related anemia

Treatment with Iron
BENEFITS VS RISKS



Benefits

Avoid or minimize

- Transfusions
- ESAs
- Symptoms

Risks

- Anaphylactoid and other acute reactions
- Unknown long-term risks

KDIGO Guidelines 2012

Treatment with Iron
OBJECTIVES AND INDICATIONS

No Iron or ESA

IV Iron (or oral iron x 1-3 months if CKD-ND)

↑ Hb without initiating ESA, and

TSAT ≤30% and ferritin ≤500 ng/ml (***2C***)

ESA

IV Iron (or oral iron x 1-3 months if CKD-ND)

↑ Hb or ↓ dose of ESA, and

TSAT ≤30% y ferritin ≤500 ng/ml (***2C***)

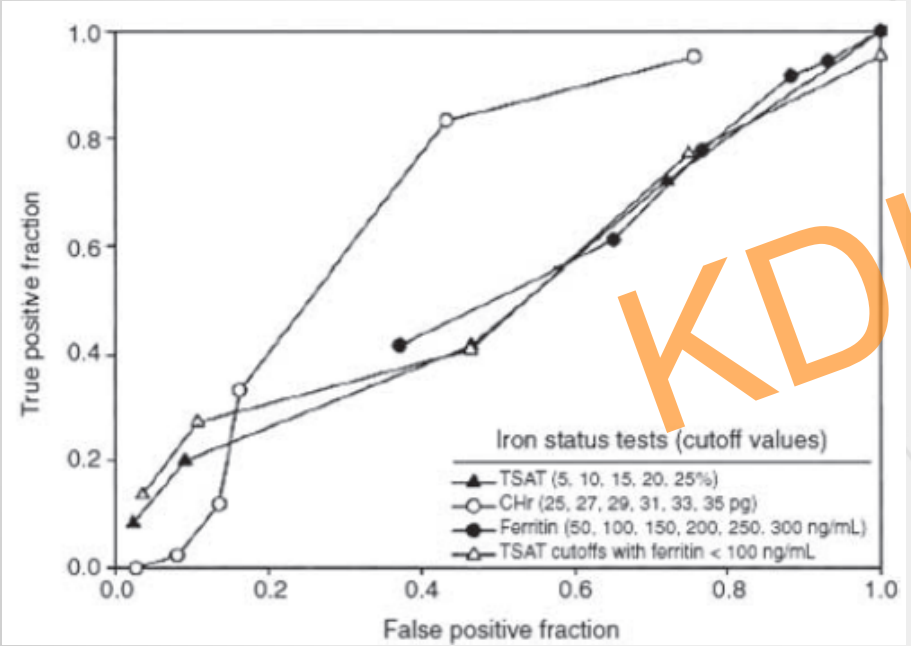
KDIGO Guidelines 2012

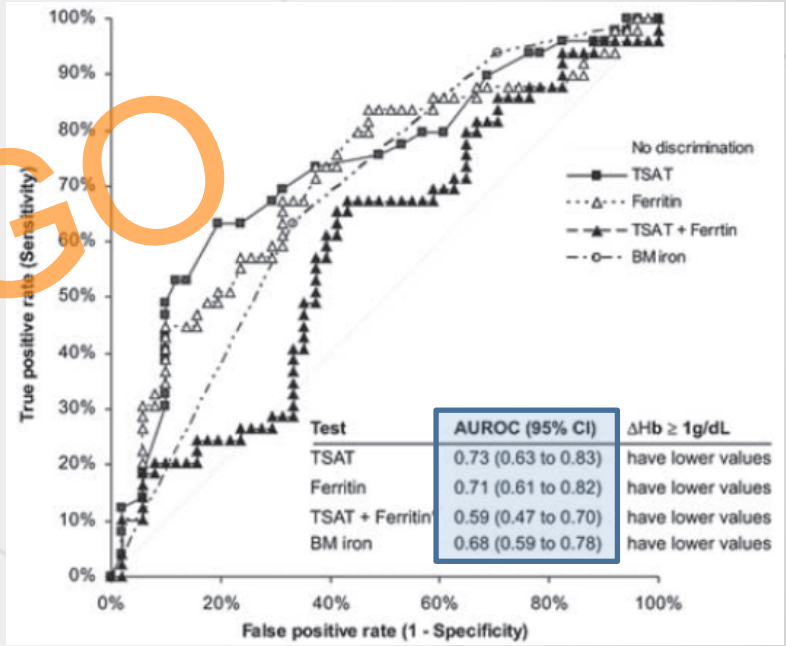
Treatment with Iron
OBJECTIVES AND INDICATIONS

Initiating Treatment	
TSAT	≤20%
Serum Ferritin	≤100 ng/ml in CKD-ND and CKD-5PD ≤200 ng/ml in CKD-5HD Do not exceed 500 ng/ml

KDOQI Guidelines 2006

Sensitivity and Specificity of TSAT and Serum Ferritin





Treatment with Iron
OBJECTIVES AND INDICATIONS

TSAT ≤ 30%

- A level of TSAT < 30% usually indicates iron deficiency
- Patients with anemia and TSAT > 20% tend to respond to treatment with iron either by increasing the Hb level or by decreasing the ESA dose
- With other levels of TSAT, the sensitivity and specificity are limited to predict iron deficiency or Hb increase after treatment with iron

KDIGO Guidelines 2012

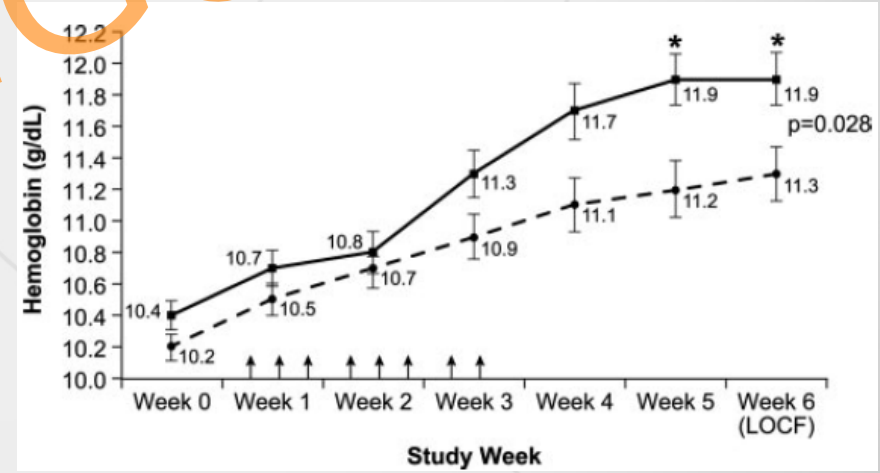
Treatment with Iron
OBJECTIVES AND INDICATIONS

Ferric Gluconate Is Highly Efficacious in Anemic Hemodialysis Patients with High Serum Ferritin and Low Transferrin Saturation: Results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study

Daniel W. Coyne,* Toros Kapoian,† Wadi Suki,† Ajay K. Singh,§ John E. Moran,‖ Naomi V. Dahl,¶ and Adel R. Rizkala;¶ the DRIVE Study Group

J Am Soc Nephrol 18: 975–984, 2007

- **134 HD patients** with Hb ≤11 g/dl, ferritin of 500-1200 ng/ml, and TSAT ≤25%
- **Randomized** to receive 125 mg of IV ferric gluconate for 8 consecutive sessions VS no iron
- Baseline **Epo** dose was ↑ 25% in both groups
- Follow-up to **6 weeks**



Treatment with Iron
OBJECTIVES AND INDICATIONS

Serum Ferritin ≤ 500 ng/dl

- Although most patients with serum ferritin > 100 ng/dl have normal iron stores in the bone marrow, they **tend to respond** to treatment with iron by increasing the Hb concentration or decreasing the ESA dose

- There is not enough evidence to determine the benefits and the risks of administering additional iron to patients with serum ferritin > 500 ng/dl

KDOQI 2006 and other sources recommend NOT to administer iron to patients with serum ferritin levels between 500-800 ng/dl, because the increase in Hb level and the decrease in ESA dose is limited and potential adverse effects

KDIGO Guidelines 2012

Treatment with Iron
OBJECTIVES AND INDICATIONS

- It does not define the **lower limit** of TSAT and of ferritin due to insufficient evidence
- It defines the **upper limit** of TSAT and ferritin
- It emphasizes the importance of **individualizing** treatment

KDIGO Guidelines 2012

European Renal Best Practice (ERBP) Recommendations for Iron Treatment

Without ESA or Fe	With ESA	Comments
• If there is absolut iron deficiency, or • If ↑ Hb level without recurring to ESA is desired, and - TSAT **<25%,** and - Ferritin **<200** ng/ml (CKD ND) or **<300** ng/ml (CKD 5D) • Do not intentionally exceed ferritin **>500** ng/ml or TSAT **>30%**	• If ↑ in Hb level or ↓ in ESA dose is desired, and - TSAT **<30%,** and - Ferritin **<300** ng/ml (even higher levels in patients in HD with a weak response to ESAs or unfavorable risk/benefit with ESAs) • Do not intentionally exceed ferritin **>500** ng/ml or TSAT **>30%**	It defines the lower limit of TSAT and ferritin to start iron treatment based more on pragmatic criteria than on evidence It defines the upper limit of TSAT and ferritin **Risk of minimizing the importance of individualizing treatment with iron**

Treatment with Iron
ROUTE OF ADMINISTRATION

- In patients with **CKD-ND**, select the **route of administration based on**
  - Severity of iron deficiency
  - IV access availability
  - Previous response to oral or IV iron
  - Treatment compliance
  - Costs

KDIGO Guidelines 2012

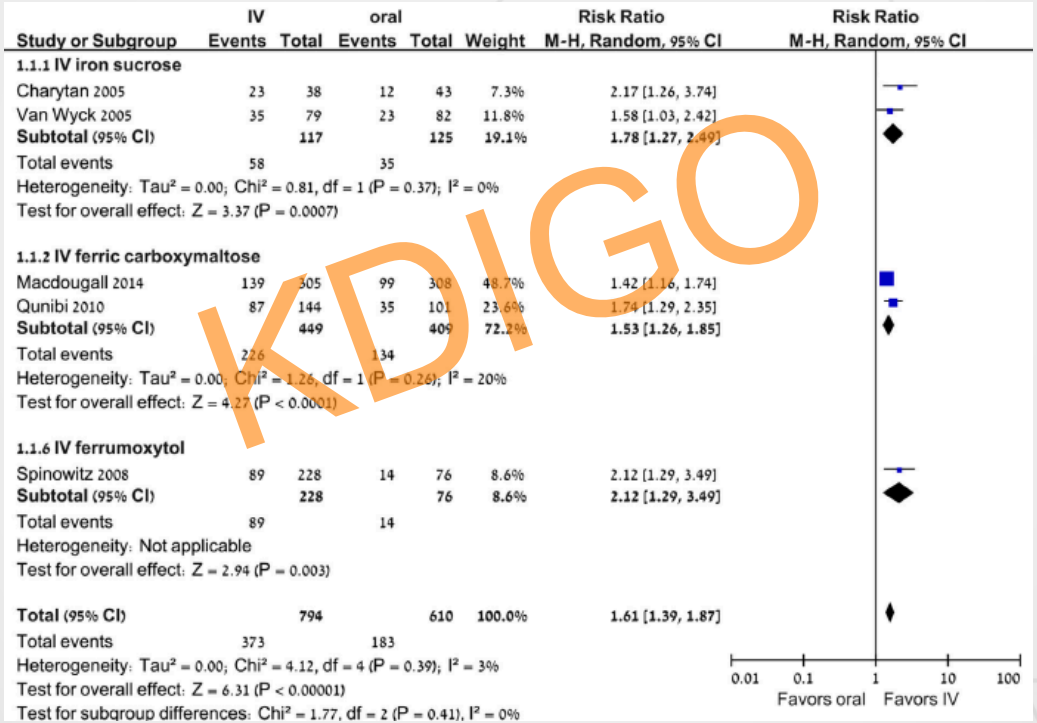
Treatment with Iron
ROUTE OF ADMINISTRATION

	Evidence
CKD ND	**No clear evidence** of the benefits of IV vs PO iron (Hb ↑ 0.31 g/dl with IV versus PO iron)
CKD 5HD	**IV iron** is more effective than PO iron and it is easier to administer
CKD 5PD	**Limited evidence** that IV iron is more effective than PO iron (KDOQI CPG 2006 favored PO iron as initial treatment)

KDIGO Guidelines 2012

Intravenous Versus Oral Iron Supplementation for the Treatment of Anemia in CKD: An Updated Systematic Review and Meta-analysis

Am J Kidney Dis 68:677-690, 2016



Treatment with Iron
DOSAGE

- **Initial Dose**
  - Administered as a single dose or as repeat lower doses that add up to 1 gram

- **Maintenance Dose**
  - Periodic doses when needed
  - Low doses at regular intervals

KDIGO Controversies Conference

Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

Iain C. Macdougall[1], Andreas J. Bircher[2], Kai-Uwe Eckardt[3], Gregorio T. Obrador[4], Carol A. Pollock[5,6], Peter Stenvinkel[7], Dorine W. Swinkels[8], Christoph Wanner[9], Günter Weiss[10], and Glenn M. Chertow[11]; for Conference Participants[12]

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OPEN
Kidney International (2016) **89**, 28–39

- Iron overload
- Oxidative stress
- Infections
- Anaphylactoid reactions

Iron Overload

- An elevated level of **total body iron** could be associated with a greater risk of organ damage over time
- Little is known about the **circumstances** in which the excess of iron causes damage to the organs where it accumulates and the consequences of the overload
- In patients with **CKD**, organ dysfunction caused by iron overload is **rare**; however, it could take **longer** to accumulate for being clinically relevant

Oxidative Stress I

- Administration of IV iron to patients with CKD
  - **Oxidative damage** to DNA and peripheral blood lymphocytes
  - Protein oxidation and lipids peroxidation
  - Celular apoptosis, endothelial dysfunction, and monocyte adhesion

- Current **methods** to measure oxidative stress and assess risk or prognosis are inconsistent

Oxidative Stress II

- Evidence that the administration of iron promotes **atherosclerosis** and vascular remodeling is also inconsistent

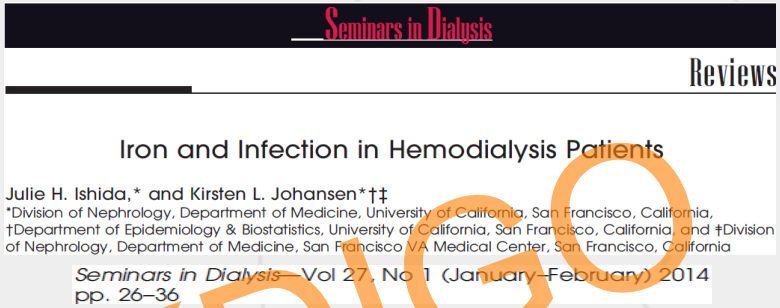
- The effect of **antioxidants** in patients with CKD is unclear

Infections
BASIC SCIENCE EVIDENCE

- **Iron** is important for
  - Proliferation and pathogenicity of mutliple organisms
  - Regualtion of the immune response (i.e., modulates cell proliferation and diferentiation, cytokine production, and other actions of the immune system against infections)

- Homeostatic imbalance of iron can affect not only the **risk** but also the **consequences** of infections

Infections
CLINICAL EVIDENCE



Seminars in Dialysis

Reviews

Iron and Infection in Hemodialysis Patients

Julie H. Ishida,* and Kirsten L. Johansen*†‡
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Seminars in Dialysis—Vol 27, No 1 (January–February) 2014
pp. 26–36

Clinical evidence is **insufficient** to determine if the administration of iron is associated with an increased risk of infection

- Most of the evidence derives from observational studies in HD patients
- Few controlled clinical trials with few patients and short follow-up
- Very limited evidence in predialysis and PD patients
- Several meta-analysis and systematic reviews have been inconclusive

Infection Risk with Bolus versus Maintenance Iron Supplementation in Hemodialysis Patients

J Am Soc Nephrol 24: 1151–1158, 2013

Table 2. HRs and RDs for high versus low dose and bolus versus maintenance dosing comparisons

Parameter Estimate (95% CI)	High Versus Low Dose			Bolus Versus Maintenance Dosing		
	Hospitalized for Infection	Infection-Related Death	Infection-Related Hospitalization or Death	Hospitalized for Infection	Infection-Related Death	Infection-Related Hospitalization or Death
Unadjusted HR	1.37 (1.33 to 1.40)	1.43 (1.32 to 1.55)	1.37 (1.34 to 1.40)	1.51 (1.47 to 1.56)	1.63 (1.48 to 1.78)	1.52 (1.48 to 1.56)
Adjusted HR	1.05 (1.02 to 1.07)	1.08 (0.99 to 1.19)	1.05 (1.02 to 1.08)	1.08 (1.05 to 1.11)	1.11 (1.00 to 1.23)	1.08 (1.05 to 1.11)
Adjusted RD/1000 person-yr	12.1 (5.7 to 18.8)	1.2 (−0.74 to 2.8)	13.0 (6.2 to 19.5)	24.8 (15.8 to 33.1)	2.0 (−0.36 to 4.1)	26.1 (17.6 to 35.0)

Table 3. HRs and RDs for high versus low and bolus versus maintenance dosing comparisons using expanded definitions of infection

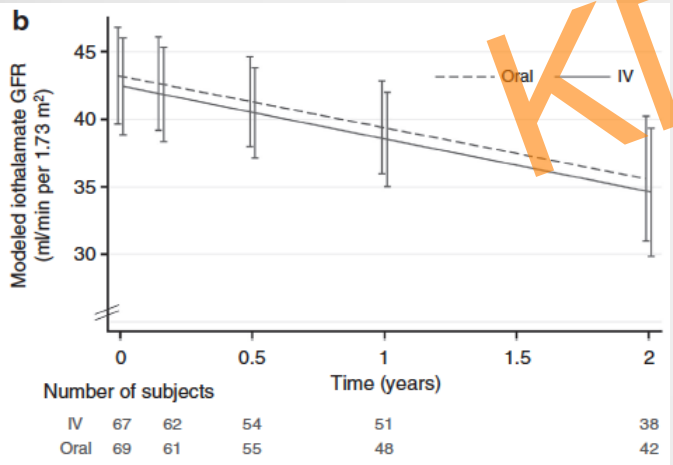
Parameter Estimate (95% CI)	Hospitalized for Infection of Any Organ System		Use of IV Antibiotics		Hospitalized for Infection or Use of IV Antibiotics	
	High Versus Low	Bolus Versus Maintenance	High Versus Low	Bolus Versus Maintenance	High Versus Low	Bolus Versus Maintenance
Unadjusted HR	1.32 (1.30 to 1.35)	1.44 (1.41 to 1.47)	1.24 (1.22 to 1.27)	1.34 (1.32 to 1.37)	1.27 (1.25 to 1.28)	1.37 (1.35 to 1.39)
Adjusted HR	1.03 (1.01 to 1.06)	1.05 (1.03 to 1.08)	1.02 (1.00 to 1.03)	1.05 (1.03 to 1.07)	1.02 (1.00 to 1.03)	1.05 (1.03 to 1.07)
Adjusted RD/1000 person-yr	13.9 (4.8 to 24.2)	27.7 (17.5 to 38.0)	12.3 (2.7 to 22.9)	39.8 (27.4 to 53.0)	18.3 (5.4 to 31.9)	56.9 (38.3 to 72.5)

A randomized trial of intravenous and oral iron in chronic kidney disease

Rajiv Agarwal[1], John W. Kusek[2] and Maria K. Pappas[1]

Kidney International advance online publication, 17 June 2015

- 136 patients with CKD 3-4 and iron deficiency anemia
- Randomized to receive IV iron sucrose or PO iron
- Objective: assess differences in GFR



Serious Adverse Events	Adjusted Incidence Rate
Global	1.60 (1.28 – 2.00)
Cardiovascular	2.51 (1.56 – 4.04)
Infections	**2.12 (1.24 – 3.64)**

Infections
CLINICAL EVIDENCE

FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia

Nephrol Dial Transplant (2014) 0: 1–10

Event	High-ferritin FCM ($n = 154$)	Low-ferritin FCM ($n = 150$)	FCM total ($n = 304$)	Oral iron ($n = 312$)
Any adverse event, *n* (%)	126 (81.8)	129 (86.0)	255 (83.9)	255 (81.7)
Gastrointestinal disorders	32 (20.8)	38 (25.3)	70 (23.0)	128 (41.0)
Diarrhoea	15 (9.7)	11 (7.3)	26 (8.6)	45 (14.4)
Constipation	2 (1.3)	5 (3.3)	7 (2.3)	37 (11.9)
Nausea	9 (5.8)	7 (4.7)	16 (5.3)	15 (4.8)
Dyspepsia	2 (1.3)	3 (2.0)	5 (1.6)	17 (5.4)
Infections	51 (33.1)	51 (34.0)	102 (33.6)	95 (30.4)
Urinary tract infection	18 (11.7)	10 (6.7)	28 (9.2)	17 (5.4)
Nasopharyngitis	13 (8.4)	10 (6.7)	23 (7.6)	16 (5.1)
Influenza	4 (2.6)	8 (5.3)	12 (3.9)	7 (2.2)

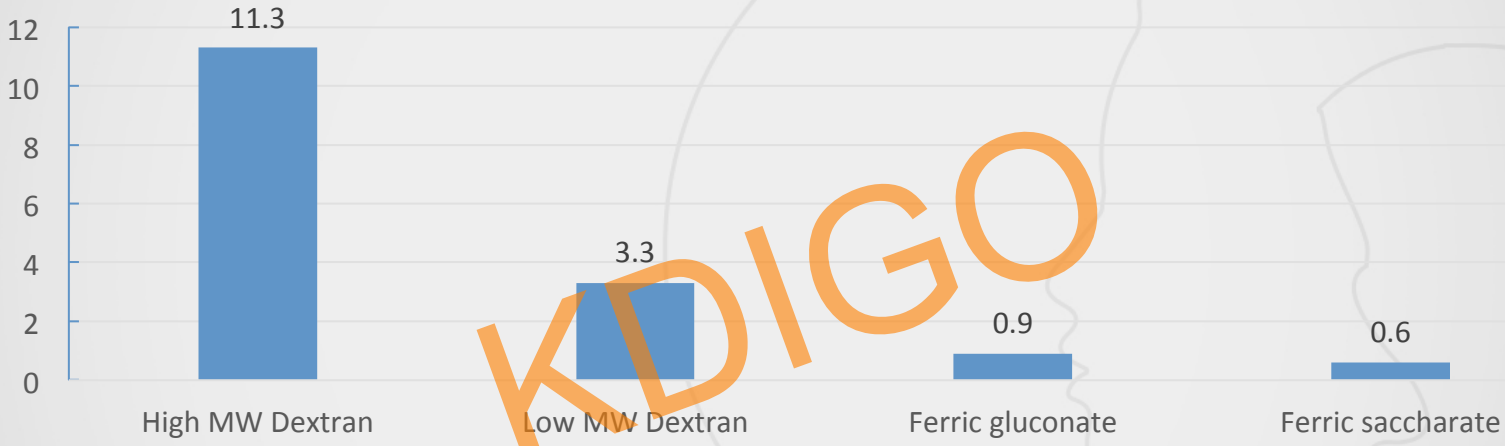
Infections

- There are significant methodological differences between the two studes (REVOKE and FIND-CKD), so they are not fully comparable

- There is an urgent need for a **controlled clinical trial** to assess the safety of the treatment with IV iron in patients with CKD

- KDIGO's recommendation to avoid use of IV iron in the presence of systemic bacterial infections is reasonable (**Not Graded**)

Anaphylactoid Reactions FREQUENCY



- If high MW iron dextran is excluded, the frequency of anaphylactoid reactions is **< 1:200,000 administrations**
- The FDA recommends to slow the infusion of **Ferumoxytol** due to severe anaphylactoid reactions

KDIGO Recommendation

- If the initial dose of IV iron is dextran (**1B**) or not dextran (**2C**), we recommend/suggest
  - To monitor the patient for **60 minutes** after the infusion
  - Have **cardiopulmonary resuscitation equipment** at hand (including drugs) and trained personnel to potentially treat serious adverse events

KDIGO Guidelines 2012

2012 KDIGO Guidelines Anemia in CKD

- ✓ **Identification, diagnosis and evaluation of the cause**
- ✓ **Role of iron to treat CKD-related anemia**
- ✓ **Role of ESAs and other drugs to treat CKD-related anemia**
- Role of blood transfusions to treat CKD-related anemia

KDIGO Recommendations Regarding ESA Use

Recommendations
3.1 Identify any **treatable cause** of anemia (e.g. iron deficiency, CKD-related) before starting treatment with ESAs (**Not Graded**)
3.2 For the decision to initiate and maintain treatment with ESAs, it is recommended to **balance the benefits** (reduction of the risks associated with transfusions and symptoms related to anemia) **and the risks** (CVA, HTN, loss of vascular acces, malignancy) (**1B**)
3.3 It is recommended **not to use ESAs or only with extreme caution** in patients with: • Active malignancy (specially if cure is anticipated) (**1B**) • History of CVA (**1B**) • History of malignancy (**2C**)

Benefits of ESA
TREAT STUDY

Transfusions	
Absolute risk of transfusions	15% in the high Hb group 25% in the placebo group

Quality of Life	
TREAT Study	Compared with placebo, the treatment with darbepoetin in the high Hb group resulted in a **modest but consistent improvement** in fatigue and global quality of life, but not in energy and functional capacity
2 recent systematic reviews	Both suggest the that the highest improvement in quality of life is with Hb levels between **10-12 g/dl**

Risks of ESA I TREAT STUDY

Cerebrovascular Accident	
Relative risk of CVA	1.92 (95% CI, 1.38 – 2.68)
Absolute risk of CVA	5% in the high Hb group 2.6% in the placebo group
Absolute risk in patients with history of CVA	12% in the high Hb group 4% in the placebo group
Absolute risk of CVA attributable to a high level of Hb/darbepoeitin	8% in patients with history of CVA 1% in patients without history of CVA

Venous Thrombosis	
Absolute risk of VT	2% in the high Hb group 1.1% in the placebo group

Risks of ESA II
TREAT STUDY

Malignant Neoplasm	
In patients with **history** of malignant neoplasm at the beggining of the study	Mortality of 7.4% in the high Hb group Mortality of 0.6% in the placebo group

Recommendations for Starting Treatment with ESA

CKD ND	CKD 5D
Do not initiate when Hb is ≥ 10 g/dl (**2D**) When Hb < 10 g/dl, it is suggested to individualize the decision to start depending on (**2C**) • Rate of ↓ of the Hb level • Response to previous Rx with iron • Risk of requiring transfusion • Risks associated with ESA use • Symptoms of anemia	Start when Hb is between 9-10 g/dl to prevent it falling to < 9 g/dl (**2B**)

Recommendations for Maintaining Treatment with ESAs

CKD ND and 5D

In general it is suggested not to use ESAs to maintain Hb > 11.5 g/dl (**2C**)

Individualize treatment because some patients can have a better quality of life with Hb > 11.5 g/dl if they are willing to accept the risks (**Not Graded**)

Do not intentionally maintain Hb > 13 g/dl (**1A**)

Reasons for the Lower Limit of the Hb Target

- In the TREAT study, patients randomized to placebo had a mean Hb level of **10.6 g/dl** despite that they did not receive or only received small doses of darbepoietin if the Hb was < 9 g/dl

- There is no evidence to support that all patients with Hb levels between **9-10 g/dl** should receive treatment with ESAs - INDIVIDUALIZE

- In patients with CKD 5HD, Hb tends to drop faster and reach levels of 8 g/dl; risk of transfusion is significantly reduced if Hb does not fall to **< 9 g/dl**

Canadian Erythropoietin Study Group

- 118 patients with CKD 5HD
- Epo was administered if Hb < 9 g/dl to ↑ to 9.5 – 11 g/dl (Group I) or > 11 g/dl (Group II) versus placebo

	Placebo	Group I	Group II
Transfusions	58%	2.5%	2.6%
QOL		Improved compared to placebo	Improvement was similar to Group I

NDT 7:811-16, 1992

Reasons for the Upper Limit of the Hb Target

- It is based upon the interpretation that the maximum Hb level reached in the control group of the recent ECCs was < **11.5 g/dl**
- There is no enough evidence regarding the potential benefit of increasing the Hb level between **11.5-13 g/dl**
  - CREATE showed benefits in quality of life but CHOIR didn't
- A Hb level **> 13 g/dl** is associated with a higher risk of complications

Reasons for the Upper Limit of the Hb Target

	Besarab (98)	Parfrey (05)	CREATE (06)	CHOIR (06)	TREAT (09)
Patients	1233 HD with CVD	596 HD w/o CVD	603 CKD 3-4	1423 CKD 3-4	4038 CKD 3-4
Achieved Hb (g/dl)	12.7-13.3 10.0	13.3 10.9	13.4 11.6	12.7 11.4	12.5 10.6
Mortality	↑ IAM	↑ CVA	ND	↑ CV events	ND
QOL	↑ physical domain	↑ vitality score	↑↑↑	~	↑
Transfusions	?	?	26 vs 33	?	↓

2012 KDIGO Guidelines Anemia in CKD

- ✓ Identification, diagnosis and evaluation of the cause
- ✓ Role of iron to treat CKD-related anemia
- ✓ Role of ESAs and other drugs to treat CKD-related anemia
- ✓ Role of blood transfusions to treat CKD-related anemia

Role of Blood Transfusions to Treat Anemia

4.1.1: When managing chronic anemia, we recommend avoiding, when possible, red cell transfusions to minimize the general risks related to their use. (*1B*)

4.1.2: In patients eligible for organ transplantation, we specifically recommend avoiding, when possible, red cell transfusions to minimize the risk of allosensitization. (*1C*)

Risk of Transfusions
IMMUNOLOGICAL MECHANISMS

Table 5 | Estimated risk associated with blood transfusions per unit transfused

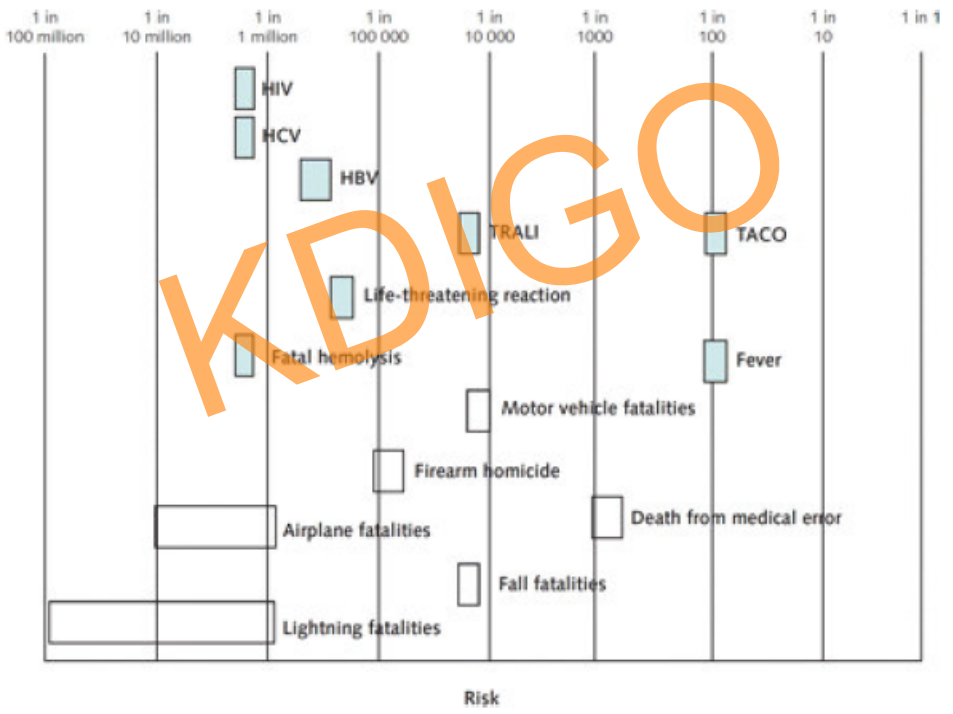
Adverse event	Estimated risk*
Immunological	
Fever/allergic reactions	1 in 100–200[a,b]
Hemolytic reaction	1 in 6000[b]
Transfusion-related acute lung injury (TRALI)	1 in 12,350[a]
Anaphylaxis	1 in 50,000[b]
Fatal hemolysis	1 in 1,250,000[a]
Graft versus host disease (GVHD)	Rare
Other	
Mistransfusion	1 in 14,000–19,000[c]

*United States data.
[a]Data from Carson JL *et al.*[212]
[b]Data from Klein.[213]
[c]Data from Klein HG *et al.*[214]

Clinical Guidelines

Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB

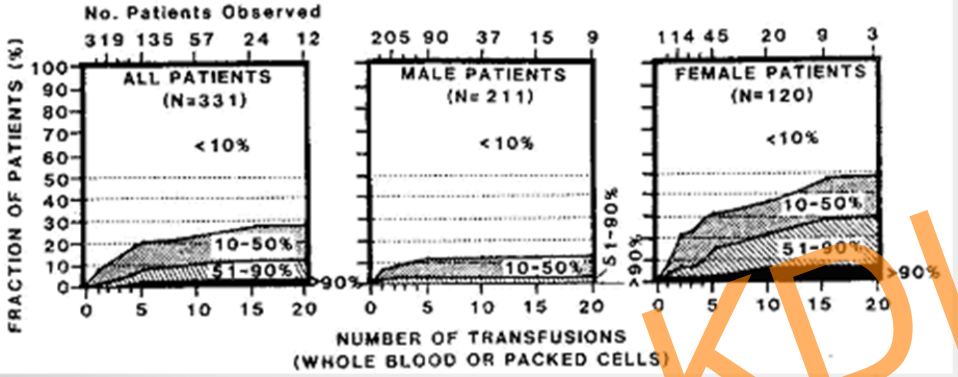
First published March 26, 2012 on annals.org.

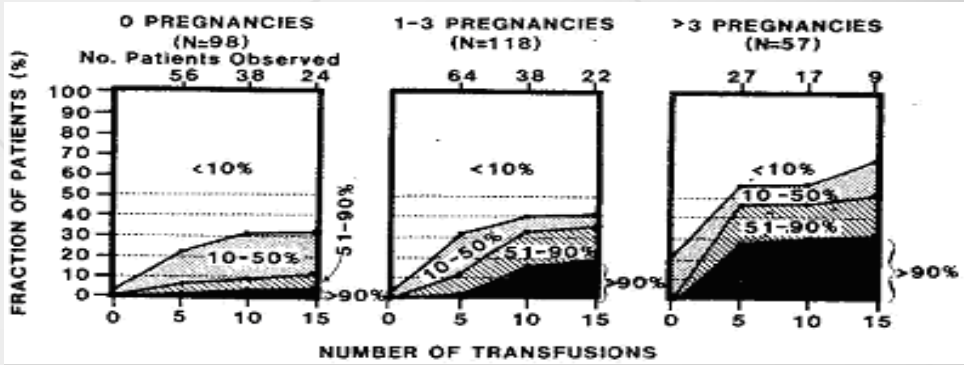


LYMPHOCYTOXIC ANTIBODY RESPONSES TO TRANSFUSIONS IN POTENTIAL KIDNEY TRANSPLANT RECIPIENTS[1]

GERHARD OPELZ,[2] BEVERLY GRAVER, M. RAY MICKEY, AND PAUL I. TERASAKI

Department of Surgery, UCLA School of Medicine, University of California, Los Angeles, California 90024





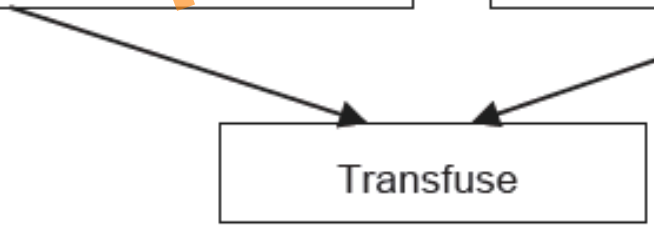
KDIGO Recommendations I

Acute clinical situations

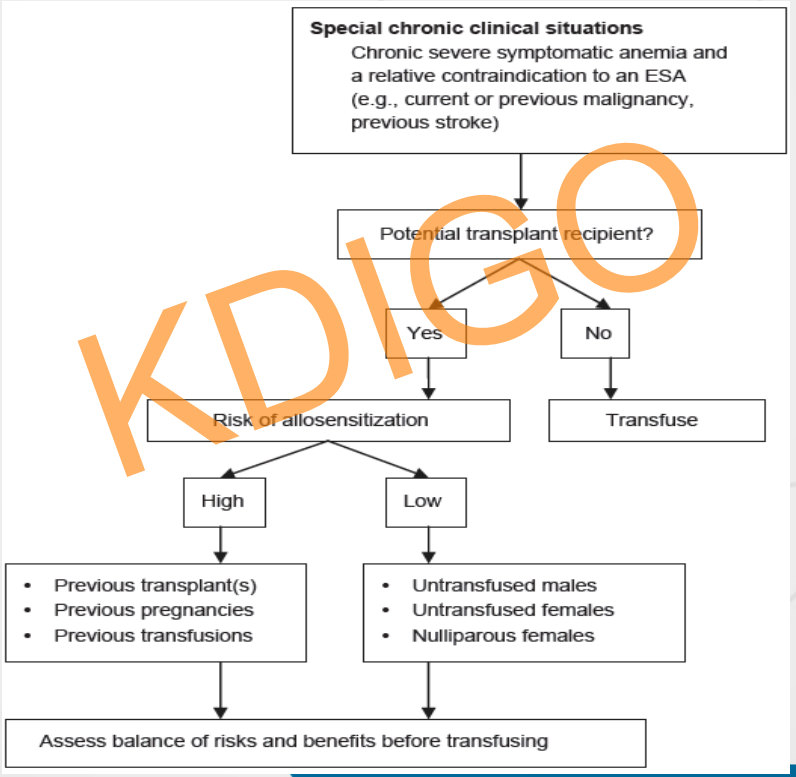
- Acute severe hemorrhage
- Unstable coronary artery disease
- When rapid preoperative Hb correction is required

Chronic clinical situations

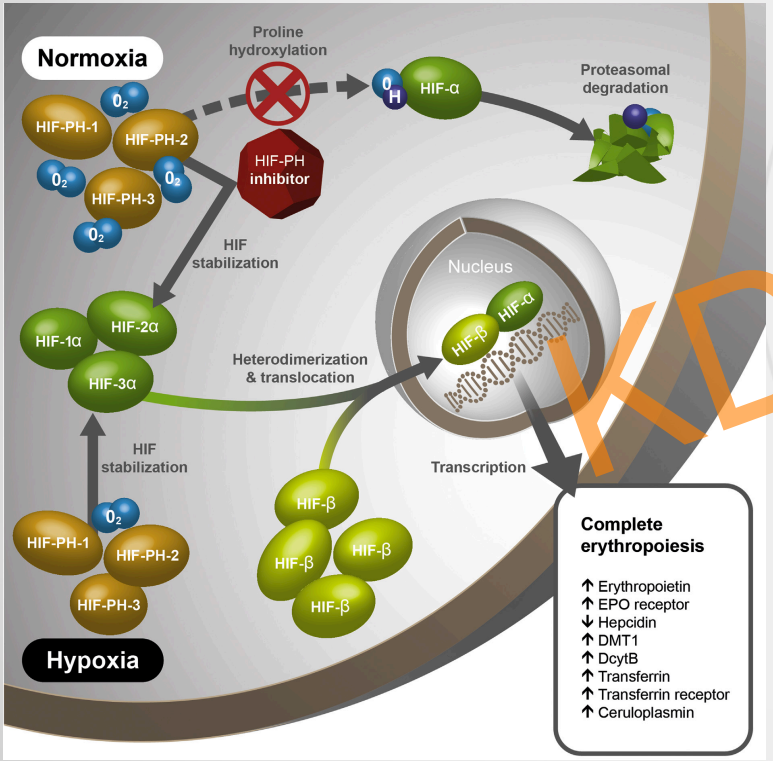
- Chronic anemia and ESAs are ineffective (hemoglobinopathies, bone marrow failure, ESA resistance)

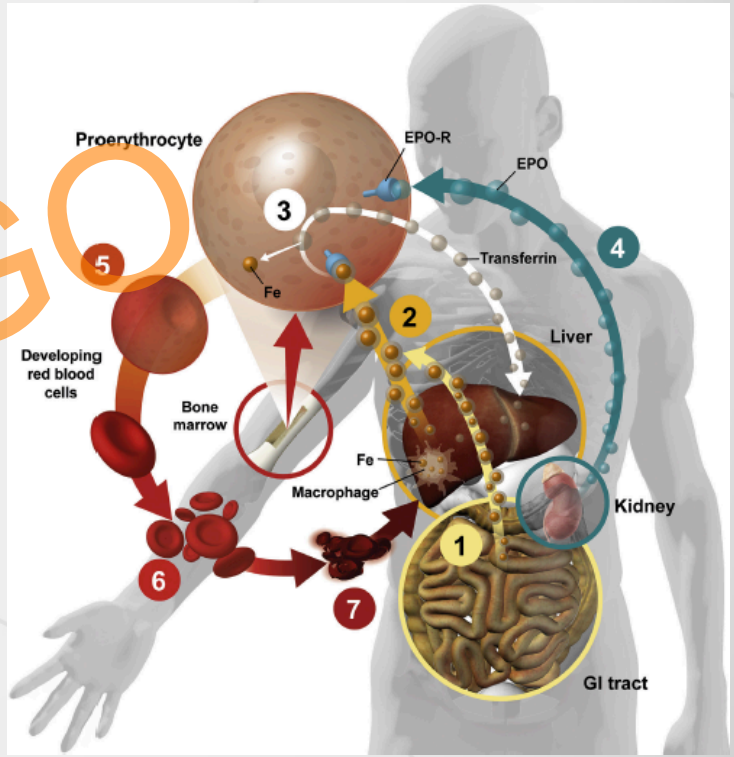


KDIGO Recommendations II



New Therapies
HIF STABILIZERS





New Therapies
HIF-PH inhibitors under Development

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

Am J Kidney Dis 69:815-26, 2017

Potential Advantages of HIF Stabilizers

- Consistent although not continuous and more physiological doses of endogenous Epo
- Increased availability of iron for erythropoiesis
- Oral administration

Unanswered Questions

- Effect on cardiovascular health
- Impact of normalizing Hb with these agents
- Risks associated with activation of VEGF (progressive retinopathy, tumor growth…)

Conclusions

- KDIGO guideline recommendations for the management of anemia of CKD are based on current limited evidence
- There are gaps of knowledge that require further investigation
- Current treatment of anemia of CKD is not optimal
- New therapies such as HIF stabilizers are promising