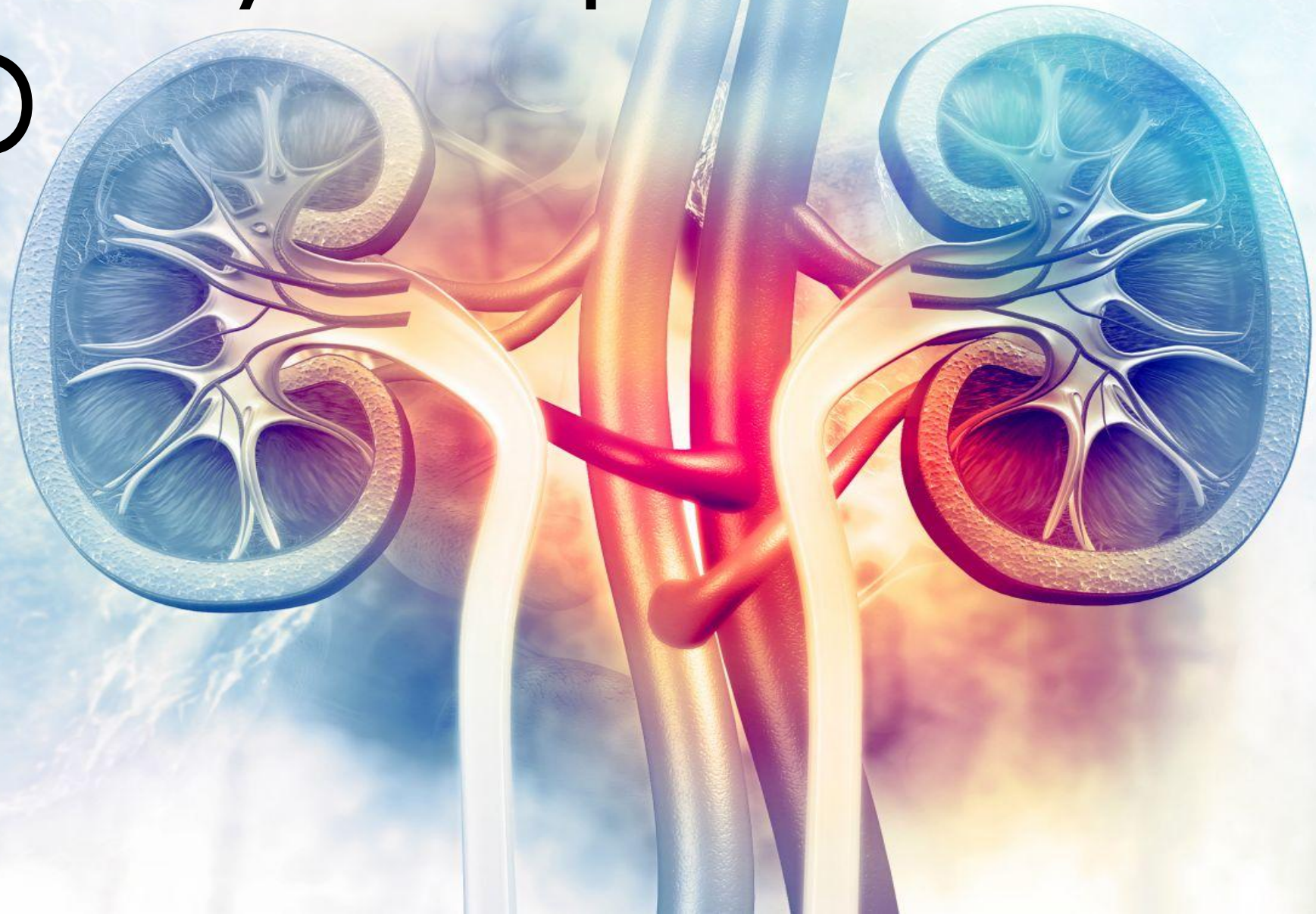
# Role of Erythropoietin in CKD



# Chronic Kidney Disease

**Criteria for CKD**

1) Kidney damage for > 3 mo( structural or functional abnormality of the kidney) with or without decreased GFR manifested by 1 or more of following features

- Abnormality in composition of blood or urine
- Abnormality in imaging test
- Abnormality in kidney biopsy

2) GFR < 60 ml / min / 1.73 m2 for >3 mo,with or without other signs of kidney damage

Chapter 1: Definition and classification of CKD. Kidney Int Suppl (2011). 2013;3(1):19–62.

# Stages of CKD

| Stage | Description | GFR ml/min/1.73 m2 |
|---|---|---|
| 1 | Kidney damage with normal or increased GFR | > 90 |
| 2 | Kidney damage with mild decrease in GFR | 60 -89 |
| 3 | Moderate decrease in GFR | 30-59 |
| 4 | Severe decrease in GFR | 15-29 |
| 5 | Kidney failure | < 15 |
| 5D | Kidney failure , dialysis dependent | < 15 0n dialysis |

Chapter 1: Definition and classification of CKD. Kidney Int Suppl (2011). 2013;3(1):19–62.

# Complication's in CKD

a) Edema
b) Hypertention
c) Hematuria
d) Protinuria
e) Failure to thrive (short stature)
f) **Anemia**
g) Elevation in BUN
h) Hyperkalemia
i) Hypocalcemia
j) Hyperphosphatemia
k) Hypo and hypernatreia
l) Renal osteodystrophy

Chapter 1: Definition and classification of CKD. Kidney Int Suppl (2011). 2013;3(1):19–62.

# Anemia in CKD

# Historical background

- **Richard Bright (1836):** First observed that anemia was a complication of renal failure.
- **Robert Christison:** Further described renal anemia.
- **Miyake (1977):** Purified and identified erythropoietin.
- **Eschbach (Dec 2, 1985):** First human use of EPO

# Anemia in CKD Definition

*It is defined as a low level of hemoglobin (Hb), <12 g/dL in females and <13 g/dL in males among CKD patients*

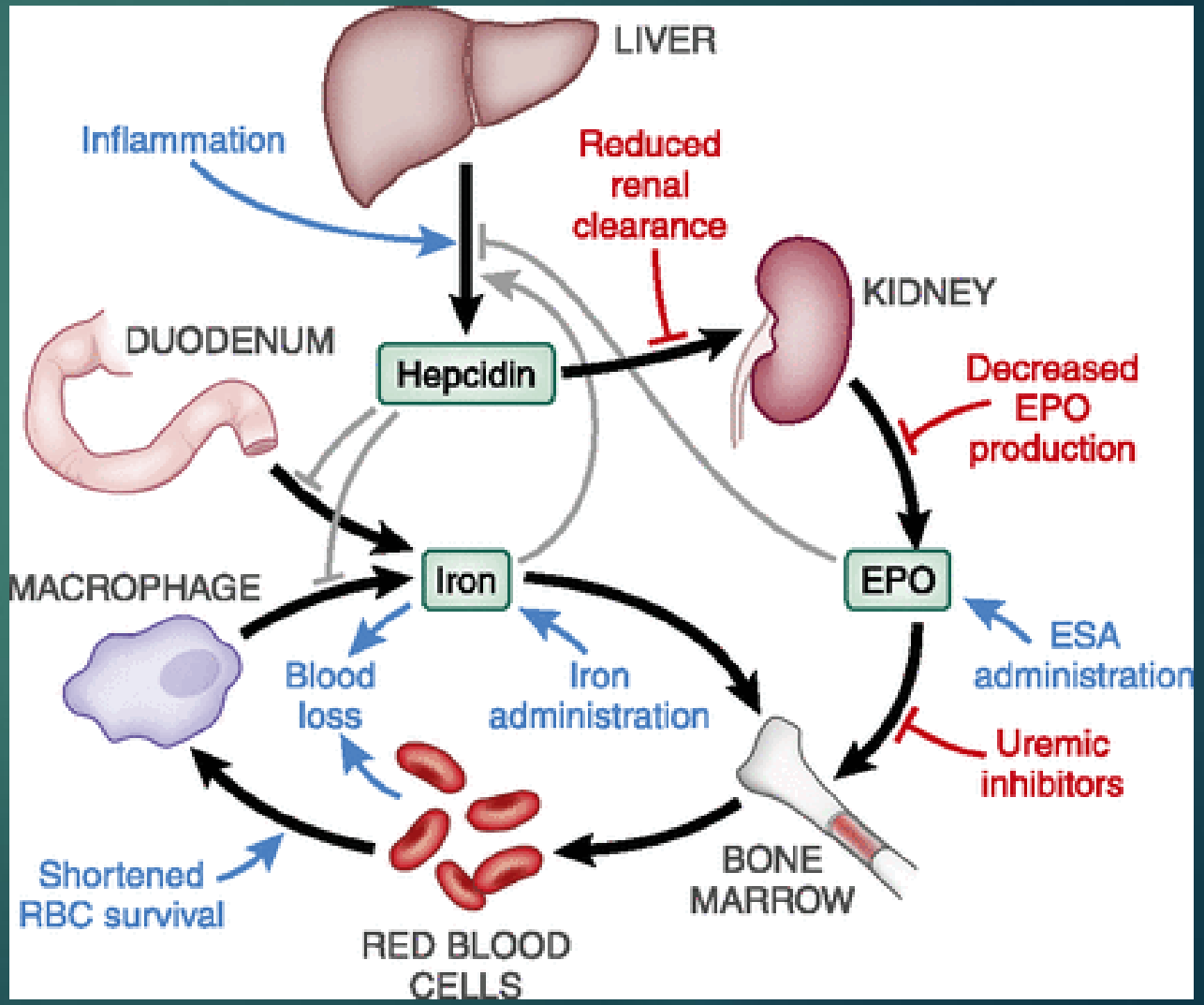
Renal Association Clinical Practice Guideline on Anaemia of Chronic Kidney Disease.BMC Nephrol. 2017;18(1):345

# Anemia in CKD

- The prevalence of anemia ranges from about 1% in stage 2 of CKD to almost 100% in end stage renal disease (ESRD) patients[1].
- In India Anemia affects 60-80% of patients with renal impairment and common in both pre-dialysis and on dialysis[2]
- Inadequate production of Erythropoietin
- Contributory factors-
  - Iron deficiency
  - Folic acid deficiency
  - Vit B12 deficiency

1.Kaze FF, et al. Afr Health Sci. 2015;15:253–260.
2. Mudiyammanavara RN et al. Ind J Bas App Med Res 2015; 4(2):414-419

# Mechanism of Anemia in CKD




Babitt JL, et al. JASN October 2012, 23 (10) 1631-1634

# Guidelines for frequency of testing of anemia

1. **For CKD patients without anemia**
    - at least annually in patients with CKD 3
    - at least twice per year in patients with CKD 4-5 ND
    - at least every 3 months in patients with CKD 5HD and CKD 5PD

Renal Association Clinical Practice Guideline on Anaemia of Chronic Kidney Disease.BMC Nephrol. 2017;18(1):345

# Guidelines for frequency of testing of anemia

**2. For CKD patients with anemia not being treated with an ESA**

- Measure Hb concentration when clinically indicated
- At least every 3 months in patients with CKD 3-5ND and CKD 5PD
- At least monthly in patients with CKD 5HD

Renal Association Clinical Practice Guideline on Anaemia of Chronic Kidney Disease.BMC Nephrol. 2017;18(1):345

# Investigation for CKD with anemia

- Complete blood count (CBC)
- Hb concentration, red cell indices
- TLC and DLC
- Platelet count
- Absolute reticulocyte count
- Serum ferritin level
- Serum transferrin saturation (TSAT)
- Serum vitamin B12 and folate levels

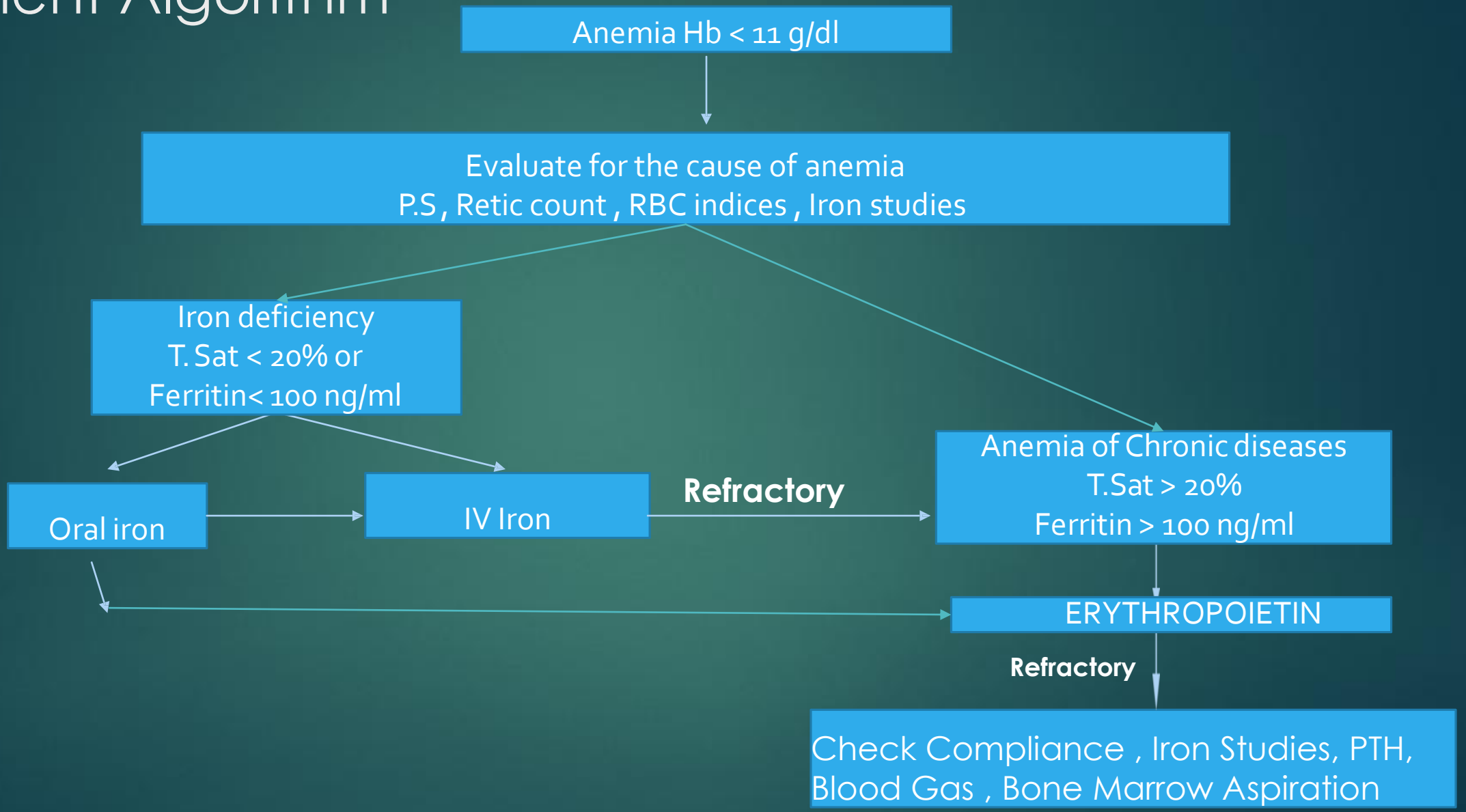
Renal Association Clinical Practice Guideline on Anaemia of Chronic Kidney Disease.BMC Nephrol. 2017;18(1):345

# Management

- **Address all correctable causes of anemia** (including iron deficiency and inflammatory states) prior to initiation of ESA therapy
- In ESA therapy, it is **recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm** in individual patients (e.g., stroke, vascular access loss, hypertension).

Renal Association Clinical Practice Guideline on Anaemia of Chronic Kidney Disease.BMC Nephrol. 2017;18(1):345

# Treatment Algorithm

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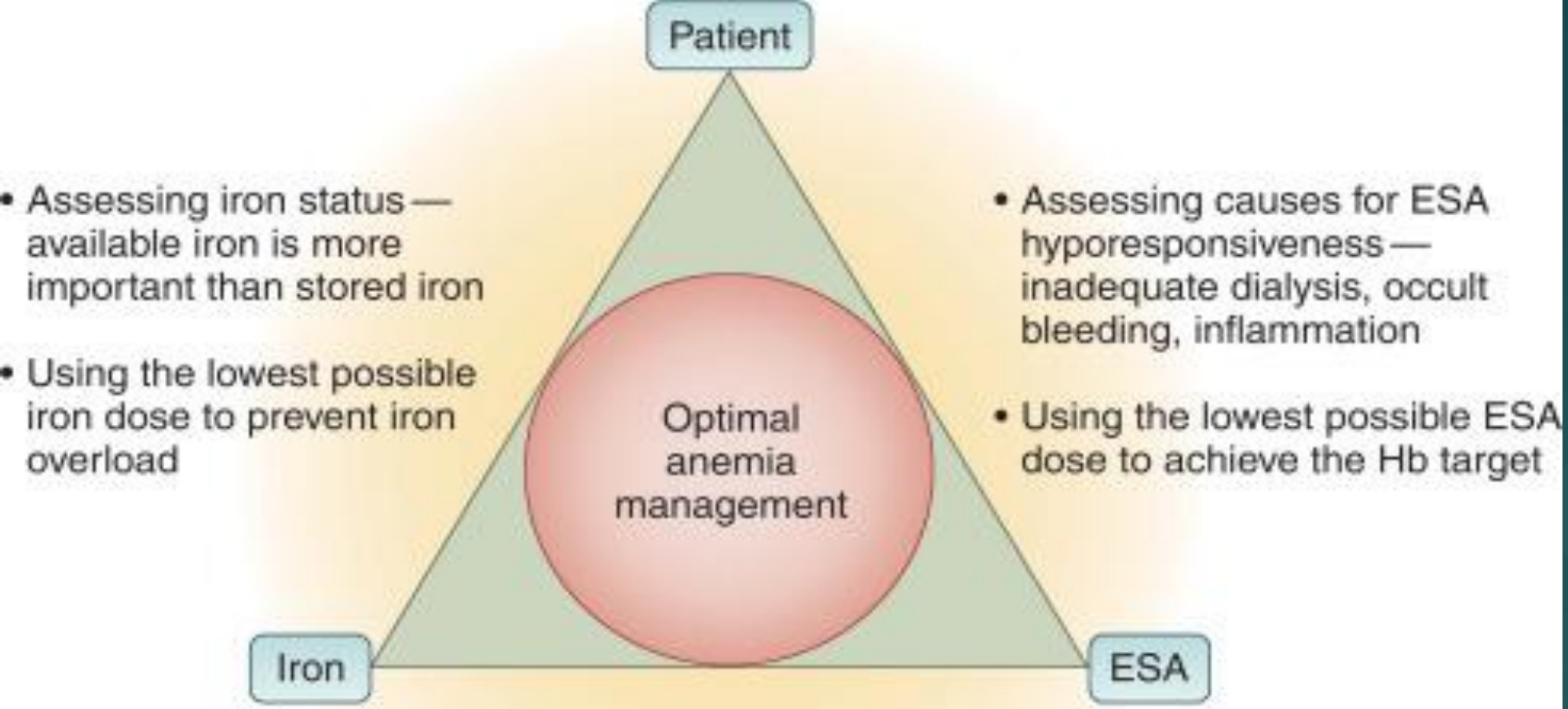



- Individualized anemia management to reduce Hb variability
- Using IV iron during ESA therapy to prevent iron deficiency-induced reactive thrombocytosis
- Balancing potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm

Hung SC, et al. Kidney International 2014; 86: 676–678

# Management

- Oral iron supplementation
  - Dose 2- 6 mg/kg/day on empty stomach
- Vit B12 supplementation
- Folic acid supplementation

Hörl WH. *Pediatr Nephrol*. 2007;22(4):480–489

# Management

**Indication of IV iron**

1. Blood loss
2. Can not tolerate oral iron
3. Patient on hemodialysis
4. Patient on peritoneal dialysis not responding to oral iron

Chapter 2: Use of iron to treat anemia in CKD. *Kidney Int Suppl (2011)*. 2012;2(4):292–298.

# Management

**IV iron supplementation**

- Iron sucrose or iron dextran
- Dose 1-2 mg/kg once per week
- Target:
  - Transferrin saturation 20-50 %
  - Serum ferritin >100 ng /ml

Hörl WH. *Pediatr Nephrol*. 2007;22(4):480–489

# Management

## Role of erythropoietin

- The **objective of initial ESA therapy** is a rate of increase in Hb concentrations of 1.0 to 2.0 g/dl per month.
- Route of administration
    1. Subcutaneous
    2. Intravenous

    Dose –

    Initial dose – 30 to 300 units/kg

    Maintenance dose – 60 to 600 units/kg

Chapter 3: Use of ESAs and other agents to treat anemia in CKD. Kidney Int Suppl (2011). 2012;2(4):299–310

# KDIGO Guideline Recommendations for Initiation and Maintenance of ESAs

- Address all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy.
- For adult CKD ND patients with Hb concentration ≥ 10.0 g/dl (≥100 g/l), we suggest that ESA therapy not be initiated.
- For adult CKD ND patients with Hb concentration< 10.0 g/dl (<100g/L) decision whether to initiate ESA therapy be based on:
  - The rate of fall of Hb concentration,
  - Prior response to iron therapy,
  - The risk of needing a transfusion,
  - The risks related to ESA therapy and
  - The presence of symptoms attributable to anemia.
- For adult CKD 5D patients, ESA therapy be used when the hemoglobin is between 9.0–10.0 g/dl (90–100 g/l).

Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney inter., Suppl. 2012;2:279–335.

# ESA MAINTENANCE THERAPY

- In general, ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD.

- In all pediatric CKD patients receiving ESA therapy, the selected Hb concentration be in the range of 11.0 to 12.0 g/dl (110 to 120 g/l).

Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney inter., Suppl. 2012;2:279–335.

# Novel EPO stimulating proteins (NESPs)

**Darbepoetin alfa –**

- New generation
- Long acting protein
- Have 2-3 fold increased half life
- Allows one weekly or alternate weekly administration
- Same safety profile similar to EPO

Macdougall IC. Clin J Am Soc Nephrol 2008;3: 200 –207

# Novel EPO stimulating proteins (NESPs)

**Mircera-**

- Continuous erythropoietin receptor activators
- Have different receptor binding activity
- This allows continuous erythropoiesis
- Also has extended half life
- This allows one monthly dosing
- This agent still being investigated for use in children

Macdougall IC. Clin J Am Soc Nephrol 2008;3: 200 –207

## ESA administration

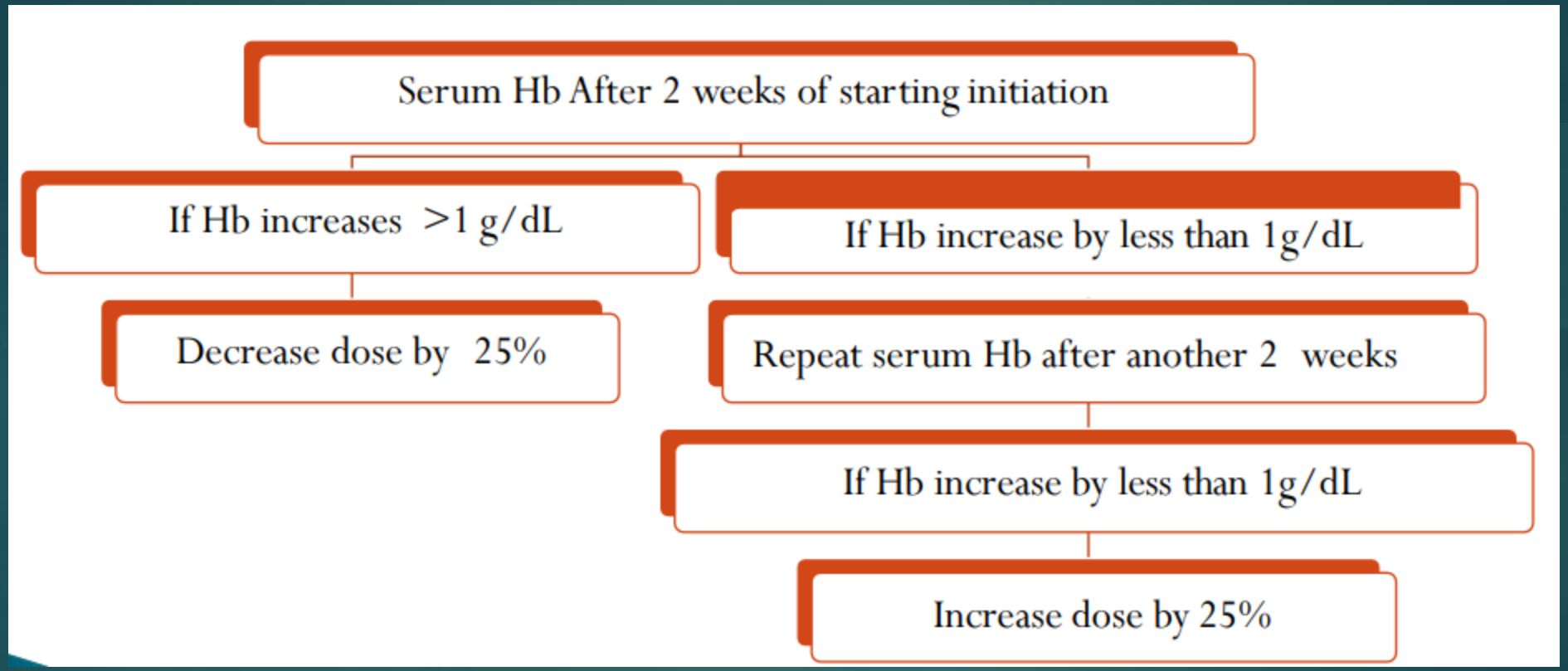
- For CKD 5HD patients – either intravenous or subcutaneous administration of ESA.
- For CKD ND and CKD 5PD – subcutaneous administration of ESA.

**Frequency of administration**:

It is suggested that the frequency of ESA administration based on CKD stage, treatment setting, efficacy considerations, patient tolerance and preference, and type of ESA

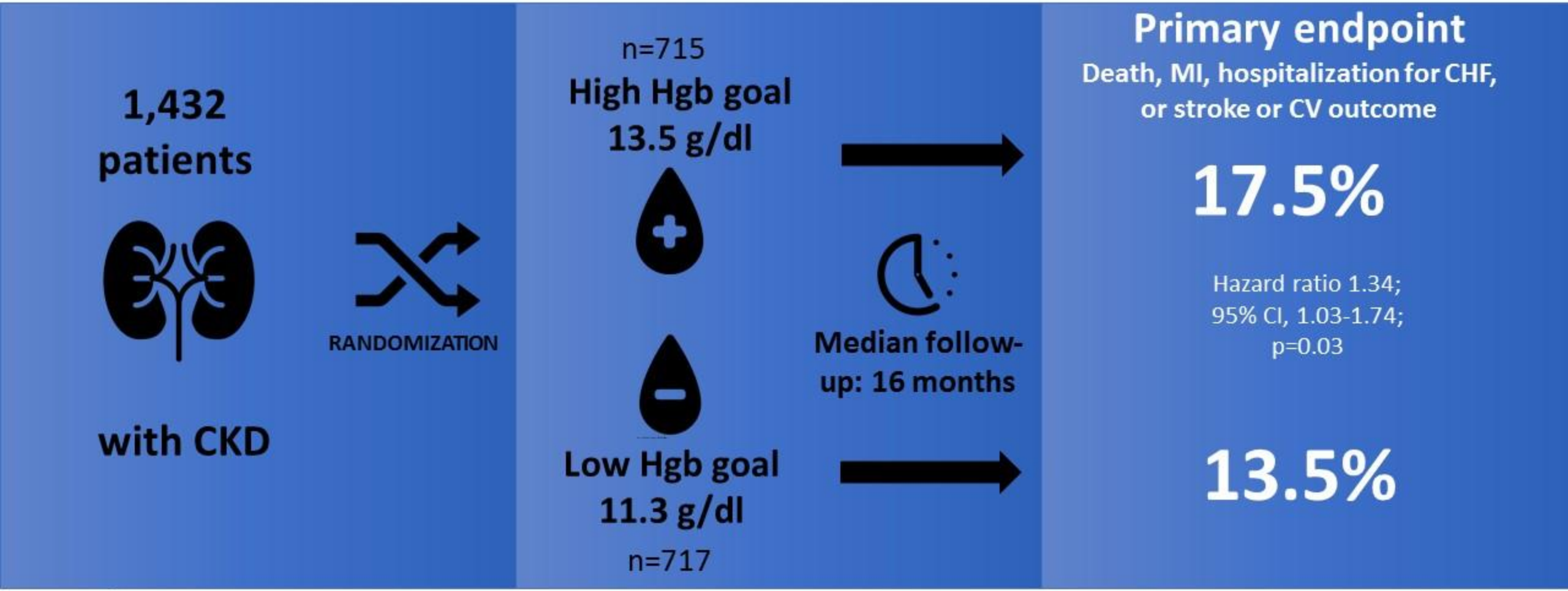
Chapter 2: Use of iron to treat anemia in CKD. *Kidney Int Suppl (2011)*. 2012;2(4):292–298.

# Titration of ESA




International brand prescribing information

# CHOIR Trial. Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease




Singh AK, et al. N Engl J Med, Vol. 355, No. 20. November 16, 2006

# Types of erythropoietin-stimulating agents and mortality among patients undergoing hemodialysis

## METHODS

A nation-wide cohort study in Japan

Patients undergoing HD
n=194,698

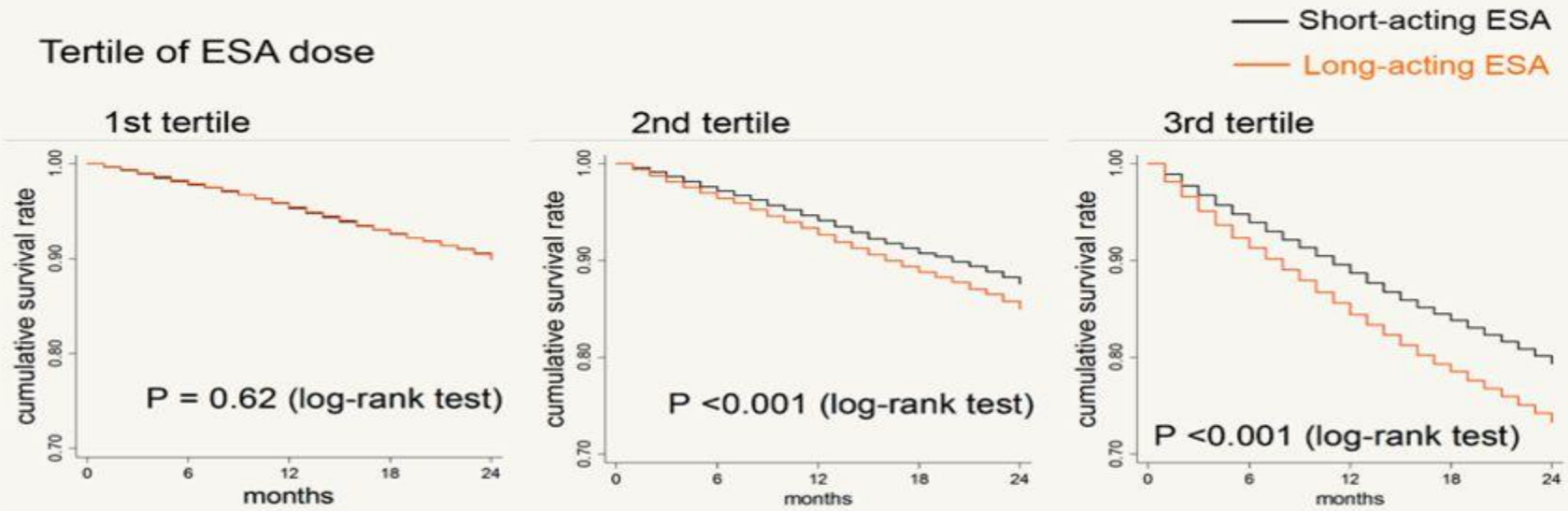
- 2-year follow-up
- 31,557 deaths occurred

| | |
|---|---|
| **Short-acting ESA** | **n=70,631 (36.3%)** |
| epoetin-alfa/beta | n=50,809 (26.1%) |
| epoetin-kappa | n=19,822 (10.2%) |
| **Long-acting ESA** | **n=124,067 (63.7%)** |
| darbepoetin-alfa | n=97,391 (50.0%) |
| epoetin beta pegol | n=26,676 (13.7%) |

ESA: erythropoietin-stimulating agents

## OUTCOME: All-cause mortality

Tertile of ESA dose




Multivariable Cox model for all-cause mortality

| | adjusted HR | 95% CI | P-value |
|---|---|---|---|
| Short-acting ESA | 1.00 | - | - |
| Long-acting ESA | 1.13 | 1.10–1.17 | <0.001 |

## CONCLUSION

Long-acting ESA use might be associated with a higher rate of death than short-acting ESA use among patients undergoing hemodialysis.

doi: 10.1681/ASN.2018101007

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

# Benefits of anemia treatment in CKD

| Secondary Effects of Anemia Correction on the Cardiovascular System |
|---|
| Reduction in high cardiac output |
| Reduced stroke volume |
| Reduced heart rate |
| Increase in peripheral vascular resistance |
| Reduction in anginal episodes |
| Reduction in myocardial ischemia |
| Regression of left ventricular hypertrophy |
| Stabilization of left ventricular dilation |
| Increase in whole blood viscosity |

Secondary effects of anemia correction on the cardiovascular system.

| Other Secondary Effects of Anemia Correction |
|---|
| Reduced blood transfusions |
| Increased quality of life |
| Increased exercise capacity |
| Improved cognitive function |
| Improved sleep patterns |
| Improved immune function |
| Improved muscle function |
| Improved depression |
| Improved nutrition |
| Improved platelet function |
| (Hypertension) |
| (Vascular access thrombosis) |

Other secondary effects of anemia correction.

Silverberg DS, et al.Int J Mol Sci. 2015;16(6):14056–14074.

# Side effects of Erythropoietin

- High blood pressure.
- Stroke
- Swelling.
- Fever.
- Dizziness.
- Nausea.
- Pain at the site of the injection.
- ROP

International brand prescribing information

# EVALUATION FOR PURE RED CELL APLASIA (PRCA)

- Investigate for possible antibody-mediated PRCA when a patient receiving ESA therapy for more than 8 weeks develops the following
- Sudden rapid decrease in Hb concentration at the rate of 0.5 to 1.0 g/dl per week OR requirement of transfusions at the rate of approximately 1 to 2 per week, AND
  - Normal platelet and white cell counts, AND
  - Absolute reticulocyte count less than 10,000/ml
- It is recommend that ESA therapy be stopped in patients who develop antibody-mediated PRCA
- Peginesatide should be used to treat antibody-mediated PRCA

# Role of Adjuvants

- **L-Carnitine**: There is insufficient evidence to recommend the use of Lcarnitine in the management of anemia in patients with CKD.
- **Vitamin C**: In the opinion of the Work Group, there is insufficient evidence to recommend the use of vitamin C (ascorbate) in the management of anemia in patients with CKD.
- **Androgens**: Androgens should not be used as an adjuvant to ESA treatment in anemic patients with CKD.

American Journal of Kidney Diseases(Suppl 3) 2006; 47(5): pp S71-S78

Thank you