Erythropoiesis-Stimulating Agents : Old Friends with New Faces

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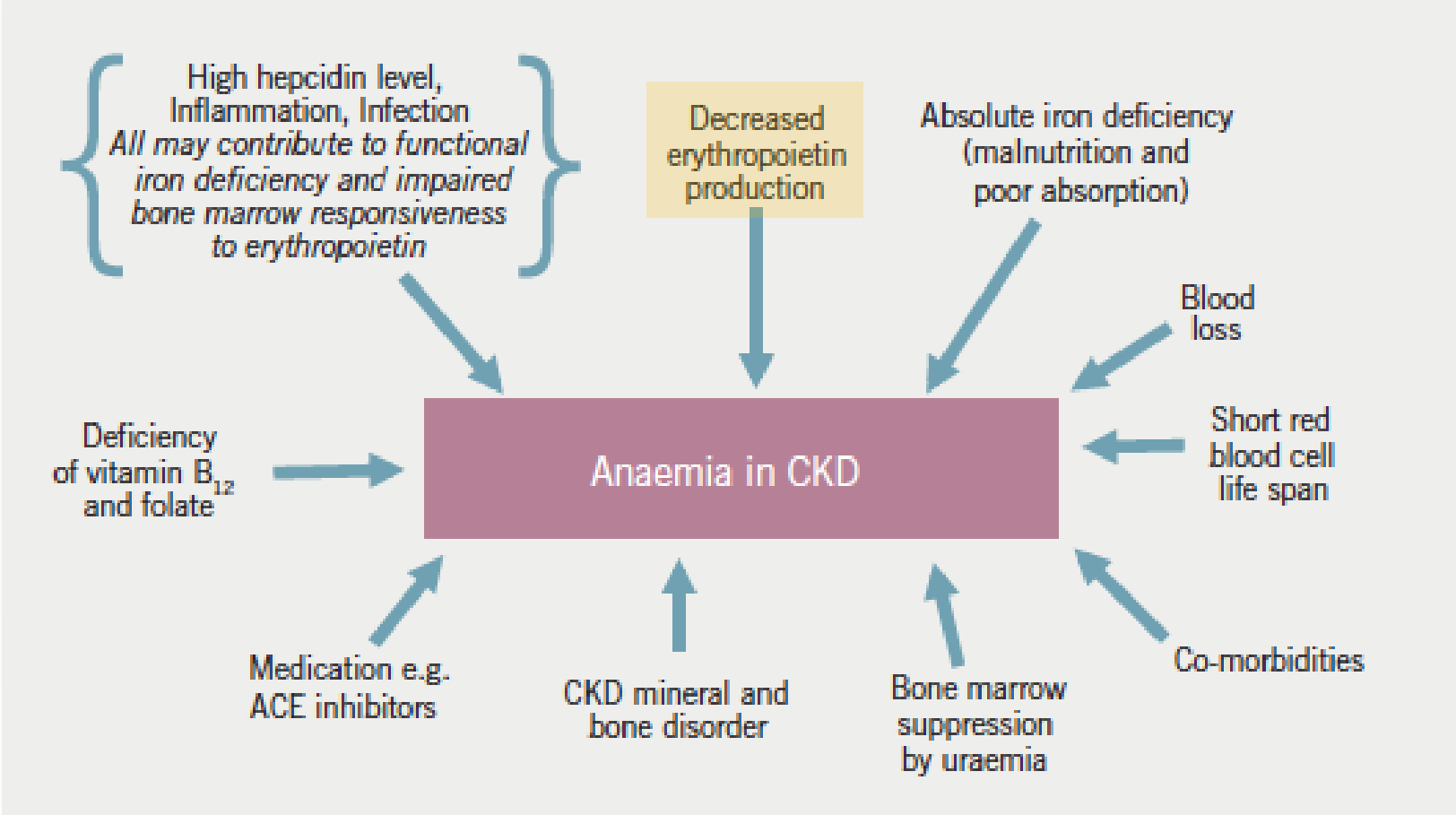
Introduction

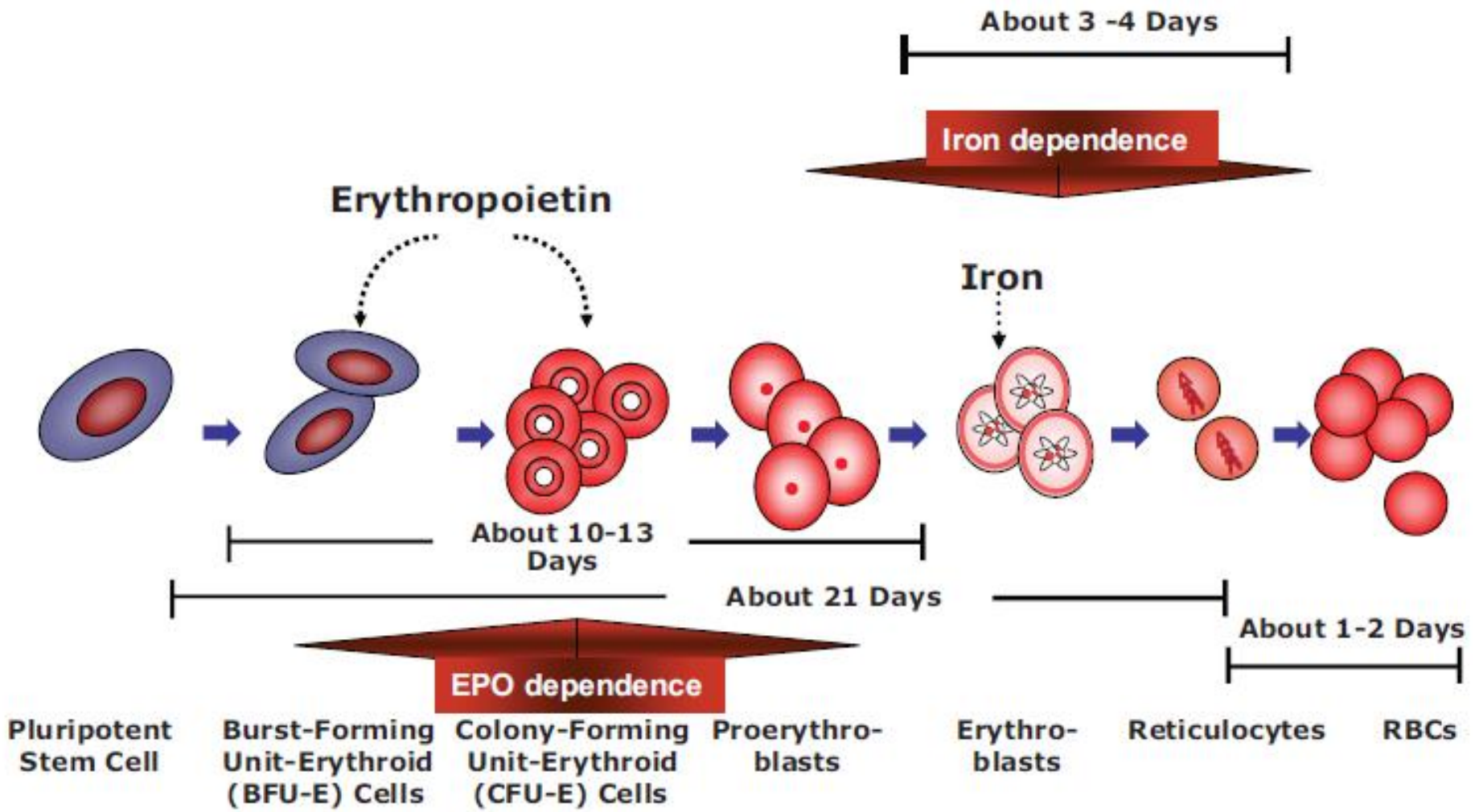
Etiology of anemia in CKD



J A Med Dir Assoc 2006, 7:S7-S12

Erythropoiesis

- Erythropoietin (EPO) and iron are both important in erythropoiesis.



The Oncologist 2009;14(suppl 1):22–33

Erythropoietin (EPO)

- Hematopoietic cytokine that is produced in kidney peritubular fibroblast
- Promote RBC production in bone marrow

- EPO deficiency
  - Delays the maturation of RBCs from progenitor cells into normoblasts and reticulocytes
  - Decreases survival of these immature RBC

- Erythropoiesis stimulating agent (ESA)/Recombinant human EPO (rhEPO)

Milestones in the use of ESA in CKD

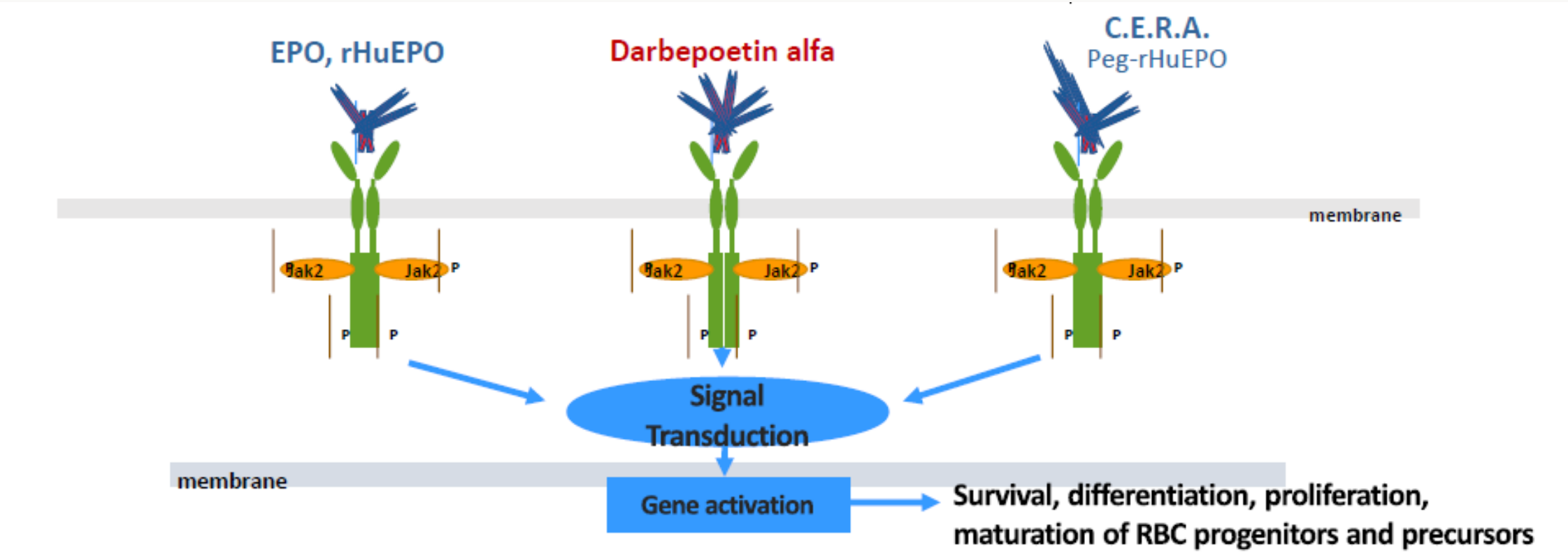
1836	Bright described anemia as a complication of renal failure[51]
1957	Jacobson et al established that the kidney produces EPO[52]
1977	Miyake et al purified human EPO from the urine of patients with aplastic anemia[7]
1983	Lin et al cloned and expressed the human EPO gene[8]
1986	Winearls et al reported the first use of rHuEPO for anemia in patients on chronic hemodialysis[14]
1987	Eschbach et al reported the correction of anemia of end-stage renal disease with rHuEPO. Results of a combined phase I and II clinical trial[1]
1989	FDA approval of the first rHuEPO for the treatment of renal anemia
1996	PRCA reported[9]
1998	Normal Hematocrit Trial[15]
2001	FDA approval of Aranesp (darbepoetin α)
2006	KDOQI guideline for anemia in CKD[53]
2006	CREATE and CHOIR studies[16,17]
2007	FDA approval of MIRCERA
2007	DRIVE study[34]
2009	TREAT study[18]
2011	FDA modifies dosing recommendations for ESAs
2012	KDIGO Clinical Practice Guideline for Anemia in CKD[21]
2012	CAPRIT study[22]
2013	EMERALD and PEARL studies[12,13]

Journal of the Formosan Medical Association (2014) 113, 3e10

Types of ESA and administration methods

ESAs may differ from one another:

- Biophysical characteristics (ex. Molecular weight)
- EPO receptor binding affinity
- Pharmacokinetic properties (ex. serum half-life, clearance)



Transfus Med Hemother. 2013; 40(5): 302–30

Types of ESA

Agent	Active Compound	Manufacturing Process	Year Licensed
Epoetin alfa/beta (Epogen, Eprex, Erypo, NeoRecormon)	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene–transfected CHO cells	1989 (Epogen, in US); 1990 (Eprex/ Erypo/NeoRecormon, in Europe)
Epoetin delta (Dynepo)	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene–transfected human cells	2006 (outside of US); product withdrawn by Shire in 2009
"Biosimilar" epoetins (Binocrit, Hexal, Retacrit, Silapo, Eporatio)	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene–transfected CHO cells	2009 onward
Nonapproved or locally approved "copy" epoetins	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene-transfected human cells	Available in many countries outside of US and Europe, eg, India, China, Thailand, Argentina, Brazil
Darbepoetin alfa (Aranesp)	Hyperglycosylated recombinant human EPO analogue	Recombinant DNA technology; mutated EPO cDNA–transfected CHO cells	2001 (both US and Europe)
C.E.R.A. (Mircera)	Pegylated recombinant human EPO analogue		2009 (outside of US only)

Abbreviations: EPO, erythropoietin; cDNA, complementary DNA; C.E.R.A., continuous erythropoietin receptor activator; CHO, Chinese hamster ovary; US, United States.

Macdougall, Am J Kidney Dis. 2012;59(3):444-51

Epoetin-alfa, epoetin-beta

- Epoetin-alfa, epoetin-beta, which differ in glycosylation
  - Epokine® , Eposis® , Epotin®

- Relatively shorter half-life: 4-13hrs (IV), 27hrs (SC)

- Administered up to 3 times weekly in hemodialysis patients
- Non-dialysis CKD: epoetin-alfa is usually administered once weekly or once every other week.

Darbepoetin-alfa

- Darbepoetin-alfa
  - Nesp®, Aranesp®
  - Two additional N-linked carbohydrate chains attached to the protein backbone => improved stability
- 3 times longer half-line than epoetin
  - Once a week epoetin -> once every 2 weeks darbepoetin-alfa
  - Half-life: 25hrs(IV) ~ 48hrs(SC)
- Monthly administration of darbepoetin has also shown effectiveness in nondialysis CKD patients.
- Typically, darbepoetin-alfa can hence be given once weekly in patients on dialysis while the dosing may be reduced to up to once every 4 weeks in patients not yet on dialysis.

Diabetes Spectr 2008;21:12-9

Methoxy polyethylene glycol epoetin beta

- Methoxy polyethylene glycol epoetin beta
  CERA (continuous erythropoiesis receptor activator)
  - Mircera®

- Modified from EPO by inserting a large pegylation chain to make it longer acting
- Significantly longer elimination half-life *in vivo*
  - Half-life: 134hrs(IV) ~ 139hrs(SC)
  - Every 2 weeks or once every month

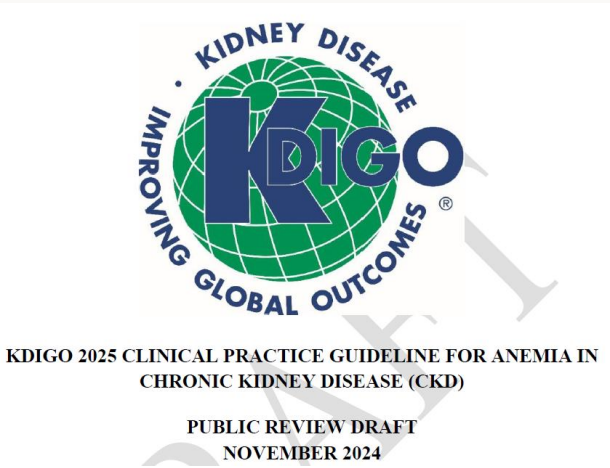
KDIGO 2025 draft

: Clinical practice guideline for anemia in CKD

Use of ESAs to treat anemia in CKD

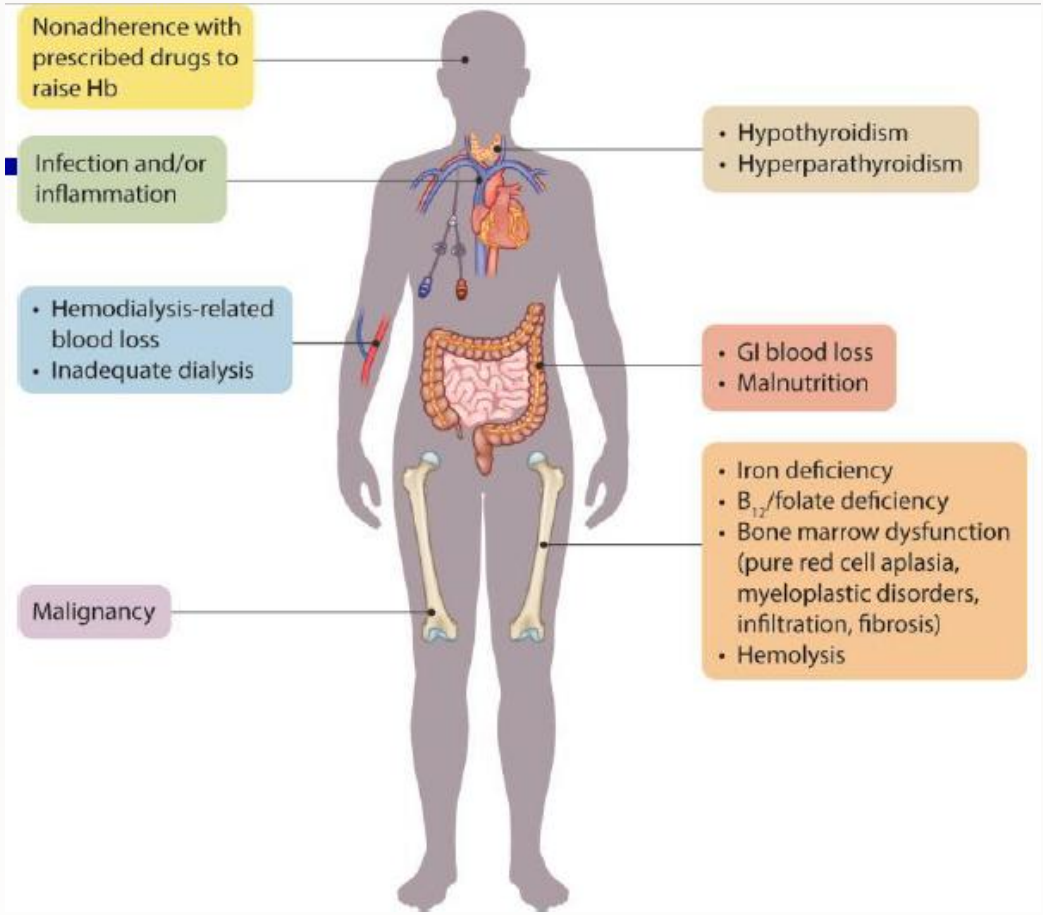
3.1. Treatment initiation

- Practice Point 3.1.1: In people with anemia and CKD (whether treated with dialysis or not), the decision to **use erythropoietin- stimulating agents (ESAs)** or hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) to raise the hemoglobin (Hb) should be made **together with patients** and consider each **individual's symptoms,** potential for **harm from red blood cell (RBC) transfusions**, and potential risk of **adverse events (e.g. stroke, cardiovascular event, cancer).**



2025 KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease Draft

Practice Point 3.1.2.: In people with anemia and CKD, **address all correctable causes of anemia** prior to **initiation of treatment with an ESA** or a HIF-PHI.



Potentially reversible causes of anemia in CKD in addition to decreased EPO production

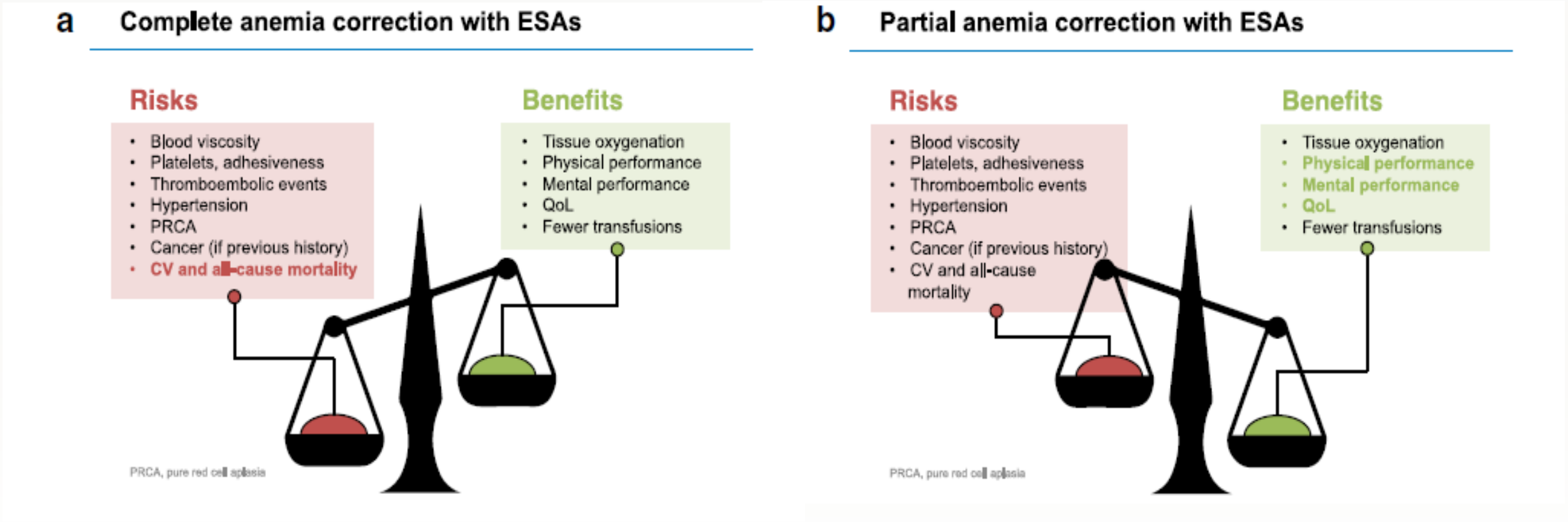
Recommendation 3.1.1: In people with anemia and CKD in whom correctable causes of anemia have been addressed, we suggest using an ESA rather than a HIF-PHI as first-line therapy for treatment of anemia (*2D*).

3.2. ESA initiation

Recommendation 3.2.1: In people with anemia and CKD G5D treated with hemodialysis (HD) or peritoneal dialysis (PD), we suggest initiation of ESA therapy when the Hb concentration is ≤9.0–10.0 g/dl (90–100 g/l) (2D). (2012 KDIGO: 2B)

This recommendation places **a relatively high value on the risk of RBC transfusions and poor functional status associated with Hb concentrations <9.0 g/dl (90 g/l) in people with CKD G5D**.
People who are **at higher risk for adverse events from ESA** treatment, such as those with a recent stroke or recurrent HD access thrombosis, may be more likely to **prefer ESA initiation when Hb is closer to 9.0 g/dl** (90 g/l), thus delaying or potentially avoiding ESA treatment.
People with **lower cardiovascular risk and symptoms or reduced exercise capacity attributable to anemia**, and people who **especially prefer to avoid RBC transfusions (e.g., those being considered for kidney transplantation**) may be more likely to **prefer ESA initiation when Hb is closer to 10.0 g/dl** (100 g/l).

Potential risks and benefits with full versus partial anemia correction in patients with CKD in response to treatment with ESA



Renal Replacement Therapy volume 4, Article number: 46 (2018)

3.3. ESA maintenance therapy

Recommendation 3.3.1: In adults with anemia and CKD treated with an ESA, we recommend targeting a Hb level below 11.5 g/dl (115 g/l) (1D). (2012 KDIGO: 2C)

This recommendation places a high value on **avoiding the critically important risk of stroke and thromboembolic events** and the **important risk of high blood pressure** reported when ESAs are used to target or achieve Hb levels of 11.5 g/dl or greater in RCTs.

Maintaining a Hb higher than 11.5 g/dl (115 g/l) with ESA therapy **does not improve survival** in people with anemia and CKD G5D or CKD not receiving dialysis and may **result in adverse cardiovascular outcomes such as stroke**. The potential for further **improvement in QoL** when Hb levels are maintained above 11.5 g/dl (115 g/l) is **uncertain** and, in some trials, was not considered clinically significant.
This recommendation attempts to balance the benefits of ESA treatment to maintain a higher Hb target against its harms.

3.4.1. ESA dosing

- Practice Point 3.4.1.1: In people with anemia and CKD treated with ESA, **the initial dose of ESA should be** determined by the **Hb concentration of the person, their body weight**, and **clinical circumstances**.

- Practice Point 3.4.1.2: In people with anemia and CKD treated with ESA, **avoid adjusting the dose of ESA more frequently than once every 4 weeks.** The exception is when Hb increases by **more than 1.0 g/dl** (10 g/l) in 2–4 weeks after initiation of therapy, at which time the dose **should be reduced by 25%–50%.**

- Practice Point 3.4.1.3: In people with anemia and CKD treated with ESA, **administer ESAs with the lowest dose possible** which **achieves and maintain treatment goals**.

ESA dosing: CKD not receiving dialysis

ESA agent	Initial dose	Dose adjustment
Epoetin alfa and beta	4,000 or 10,000 units weekly or every 2 weeks	Increase or decrease dose and/or dosing frequency as needed (generally **not given more than once per week**)
Darbepoetin	40-100 µg every 2–4 weeks	Increase or decrease dose and/or dosing frequency as needed (generally **not given more than once per week**)
Methyl polyethylene glycol-epoetin beta	50-120 µg every two weeks or 120–200 µg every month	Increase or decrease dose and/or dosing frequency as needed (generally **not given more than once every 2 weeks**)

ESA dosing: CKD G5D

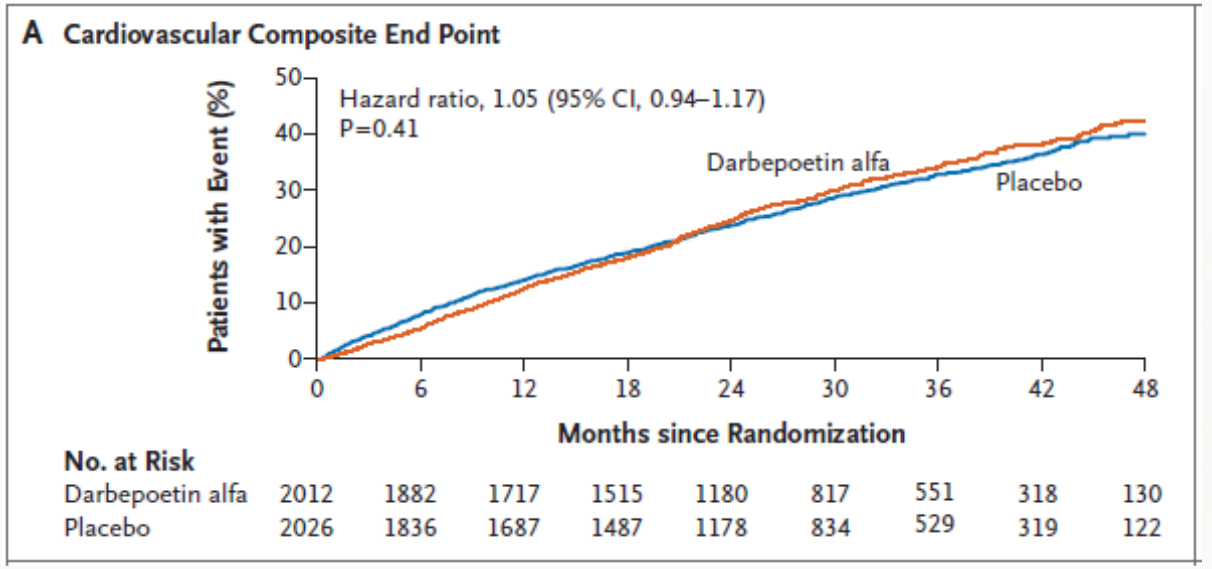
ESA agent	Initial dose	Dose adjustment
Epoetin alfa and beta	50-100 units/kg, 3 times weekly (may round to convenient dose in units)	Increase by 25 units/kg/dose if Hb rise is <1.0 g/dl (<10 g/l) after 4 weeks. Reduce by 10–25 units/dose if Hb rise is >2 g/dl (20 g/l) in 4 weeks
Darbepoetin	0.45 µg/kg weekly or 0.75 µg/kg every 2 weeks (may round to convenient dose: 25, 40, 60, 100, 150, or 200 µg) (300 µg and 500 mcg also available)	Increase by 25% if Hb rise is <1.0 g/dl (<10 g/l) after 4 weeks. Decrease dose by 25% if Hb rise is >2 g/dl (20 g/l) in 4 weeks
Methyl polyethylene glycol-epoetin beta	0.6 µg/kg every 2 weeks (may round to convenient dose)	Increase by 30-50 µg/dose if Hb rise is <1.0 g/dl (<10 g/l) in 4 weeks. Reduce by 30–50 µg/dose if Hb rise is >2 g/dl (20 g/l) in 4 weeks

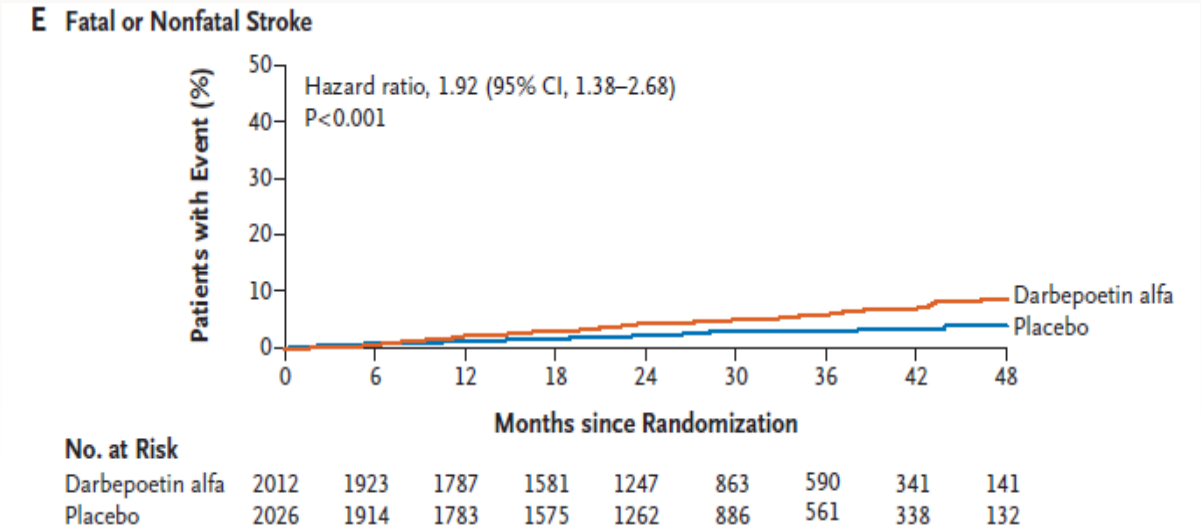
Conversion dosing between ESAs

Epoetin alfa and beta (IV or SC) (IU/week)	**Darbepoetin (IV or SC)** (mcg/week)	**CERA (IV or SC)** (mcg/month)
<8000	<40	120
8000-16000	40-80	200
>16000	>80	360

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

- 4038 patients with diabetes, CKD
- RCT
  - Darbepoietin alfa
    : Hb ~13 g/dL
  - Placebo: Hb < 9g/dL

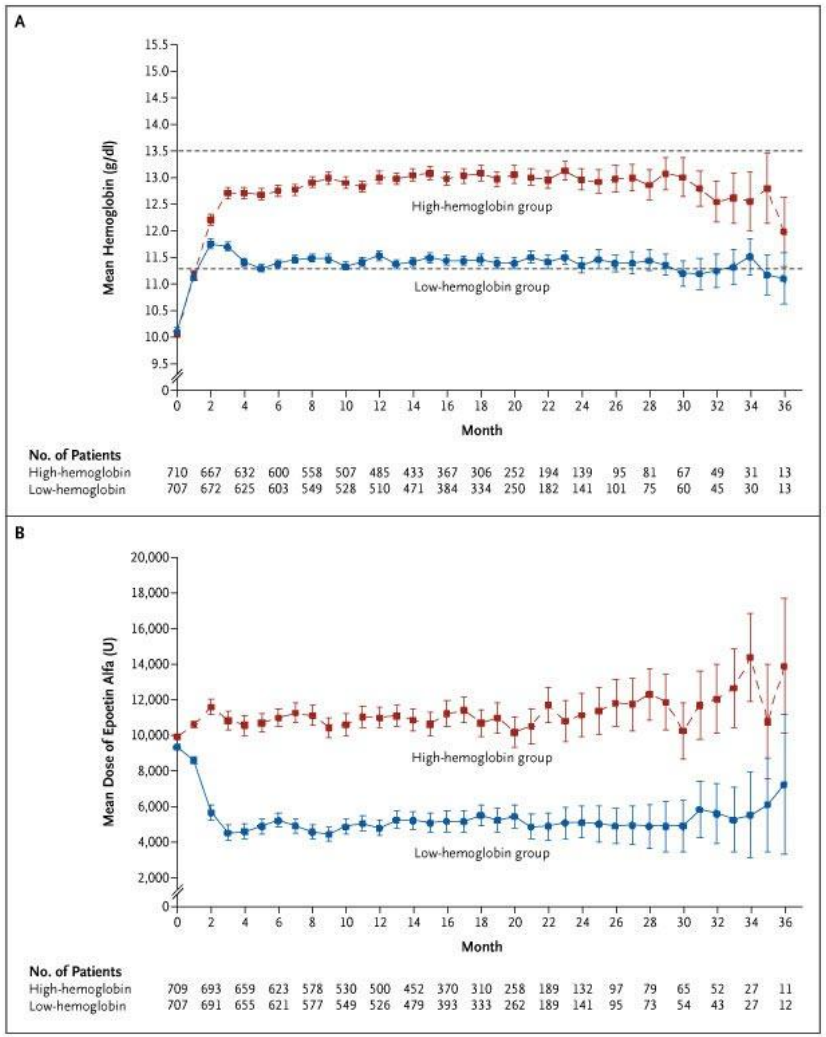


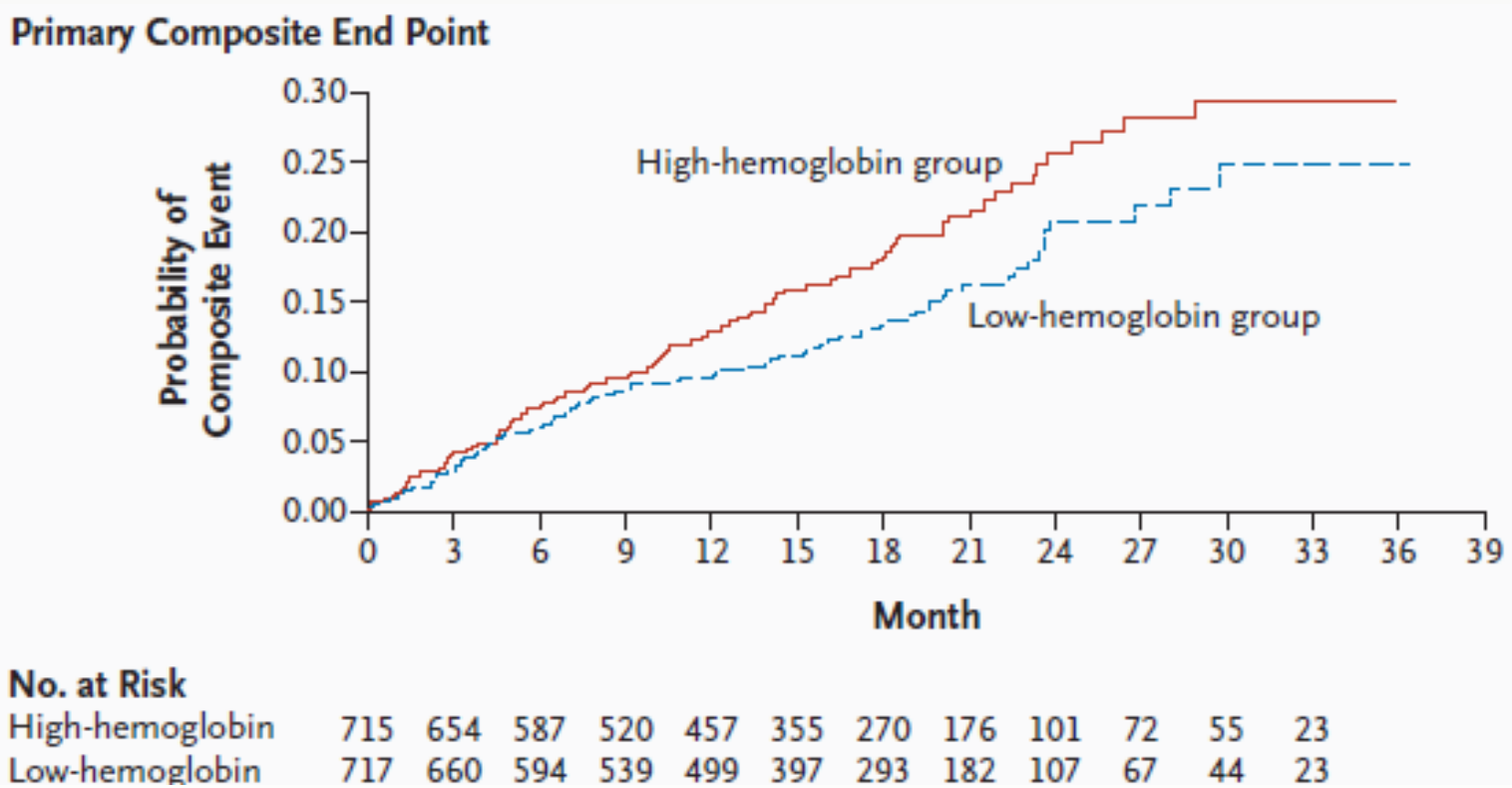


N Engl J Med 2009;361:2019-2032

CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) **Trial**

- 1432 patients with CKD
- 1:1 Randomly assigned to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 13.5 g/dL vs 11.3 g/dL





The use of a target hemoglobin level of 13.5 g per deciliter (as compared with 11.3 g per deciliter) was associated with increased risk and no incremental improvement in the quality of life.

N Engl J Med. 2006 Nov 16;355(20):2085-98

3.4.2. ESA route of administration

- Practice Point 3.4.2.1: In adults and children with anemia and CKD G5HD treated with ESA, choose the **ESA administration route (i.v. vs. subcutaneous)** based on patient preferences, local practices, and costs.

  Higher doses of epoetin are required when administered via i.v. as compared with s.c., which in turn will increase costs. However, people with CKD G5HD may prefer an i.v. route to reduce injection pain.

- Practice Point 3.4.2.2: In adults and children with anemia and **CKD not receiving dialysis**, **CKD G5PD, or kidney transplant recipients** receiving ESA therapy, administer ESA by the **subcutaneous route.**

3.4.3. Frequency of administration and monitoring of ESAs

- Practice Point 3.4.3.1: In people with CKD G5 or CKD not receiving dialysis, **individualize the frequency of administration of ESA** based on **patient preferences and type of ESA** administered.

Patient preferences and local practice patterns often determine the choice of ESA and the frequency of ESA administration.

- Practice Point 3.4.3.2: In people with anemia and CKD, following the initiation of ESA therapy or change in dose, **monitor Hb every 2–4 weeks** and adjust the dose accordingly **to avoid a rapid rise of >1.0 g/dl** (10 g/l) during that interval.

This practice point emphasizes the need to detect rapid rises in Hb to prevent overshooting Hb targets where RCT data indicate an increased risk of adverse events such as hypertension and cardiovascular events.

- Practice Point 3.4.3.3: In people with anemia and CKD, and during the **maintenance phase** of ESA therapy, monitor Hb level **at least once every 3 months**.

ESA therapy to avoid overshooting the Hb beyond target, as well as being able to identify ESA hyporesponsiveness.

3.4.3. Frequency of administration and monitoring of ESAs

- Practice Point 3.4.3.4: In people with anemia and CKD treated with ESA, it is reasonable to **suspend ESA during hospitalization for acute stroke, vascular access thrombosis, or thromboembolic events**. **Individualize consideration for ESA reinitiation** based on **patient characteristics, Hb level, and preferences regarding risks and benefits of ESA** treatment.

- Practice Point 3.4.3.5: In people with CKD, anemia, and **active cancer or a history of cancer**, use **shared decision-making regarding continuation or discontinuation of ESA** therapy based on **patient preferences and anticipated outcomes**, especially when treatment is aimed at cure.

Studies in people with cancer have shown that using ESAs to treat anemia of some cancers **may lead to increased cancer progression and death.**
The content of the clinical practice guideline by the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) on the use of ESAs in adults with cancer and anemia is cited.

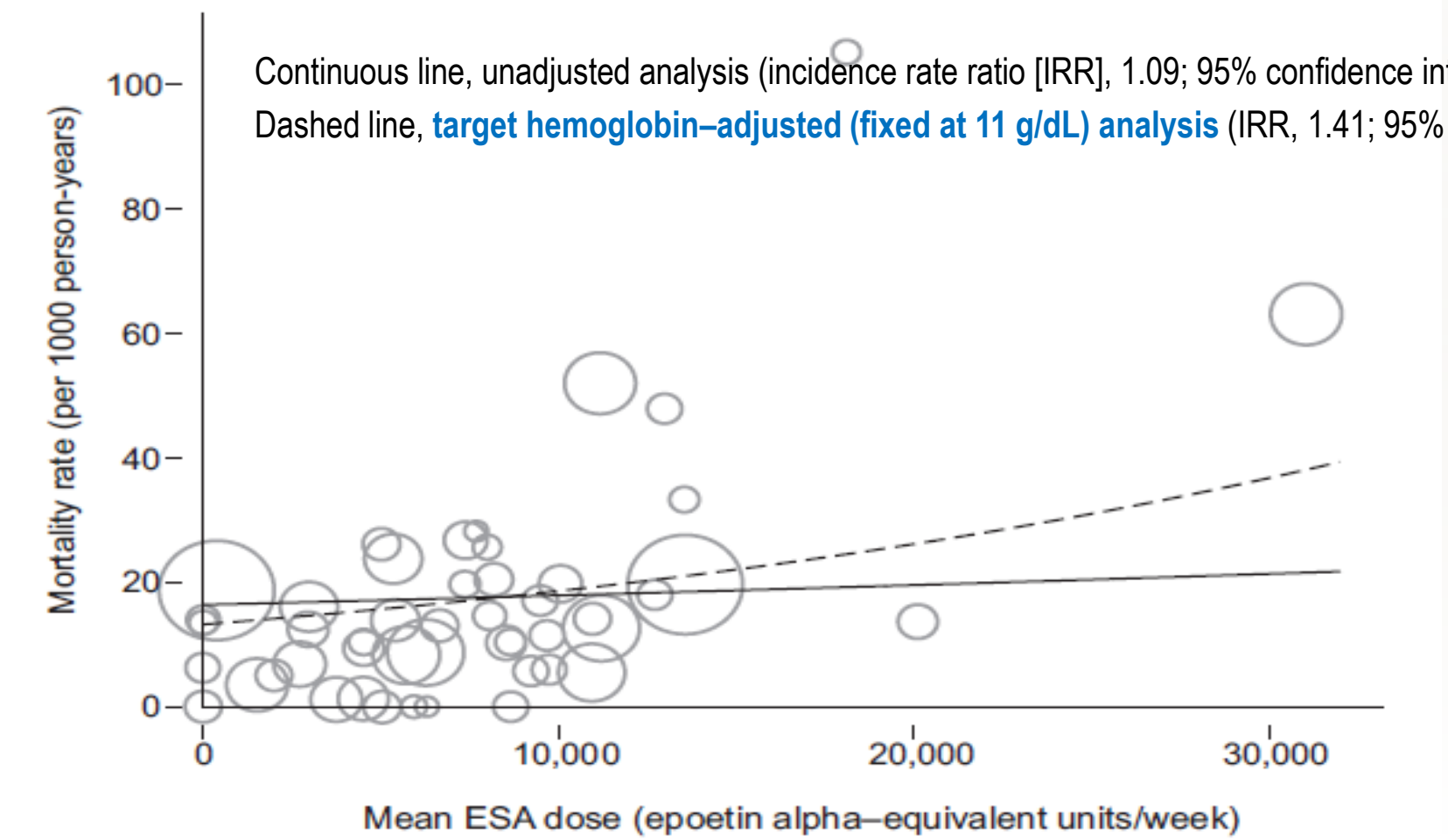
Considerations in ESA treatment

[Potential Complications of ESAs in CKD]

- Increased thrombotic risk
- Worsening hypertension
- Increased stroke risk
- Increased progression of malignancy

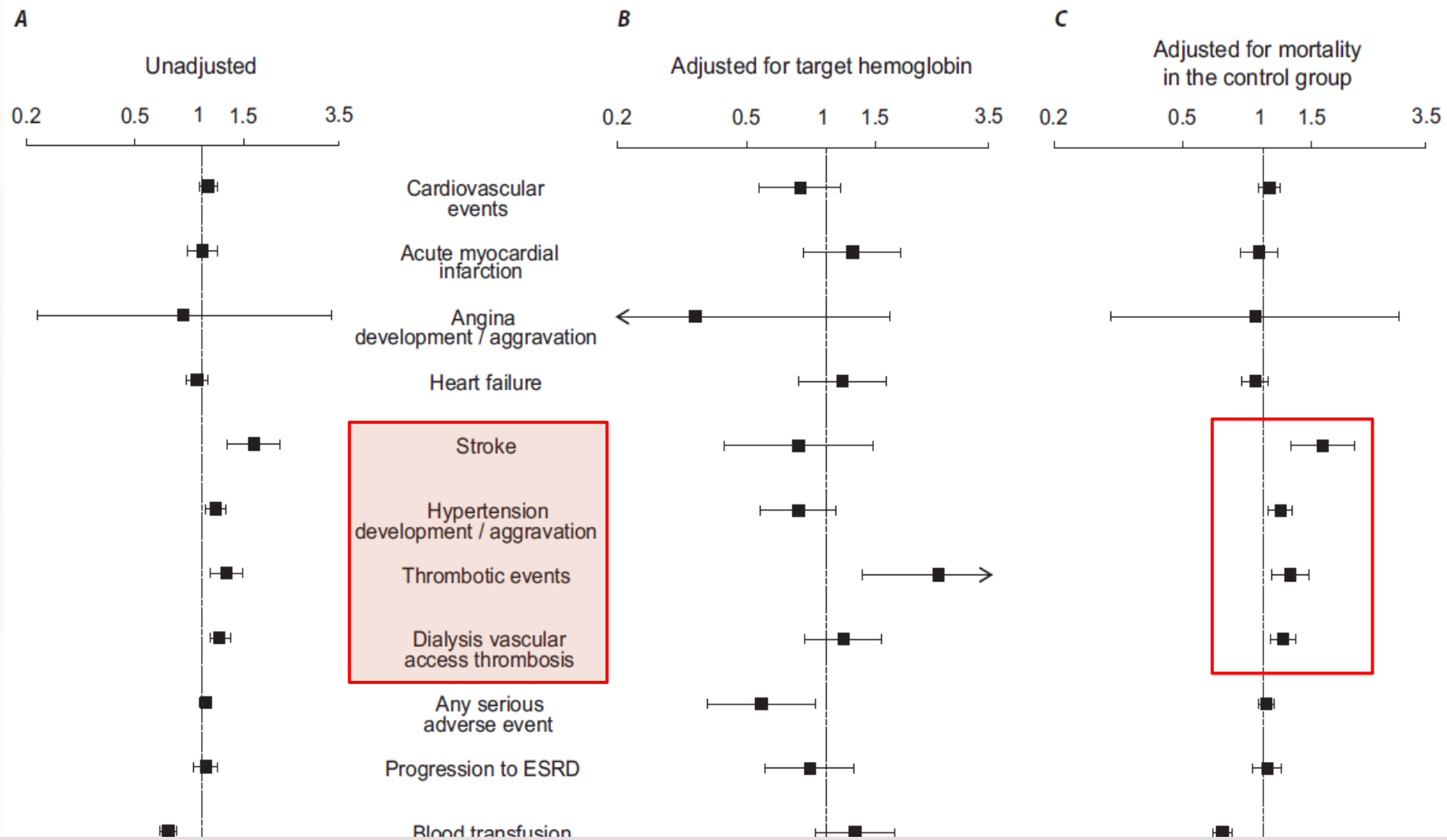
Dose of ESA and adverse outcomes in CKD: a meta-regression analysis

- 31 trials



Koulouridis et al. Am J Kidney Dis 61:44-56, 2013

Meta-regression analyses examining the association of total-study-period ESA dose with the **secondary outcomes**

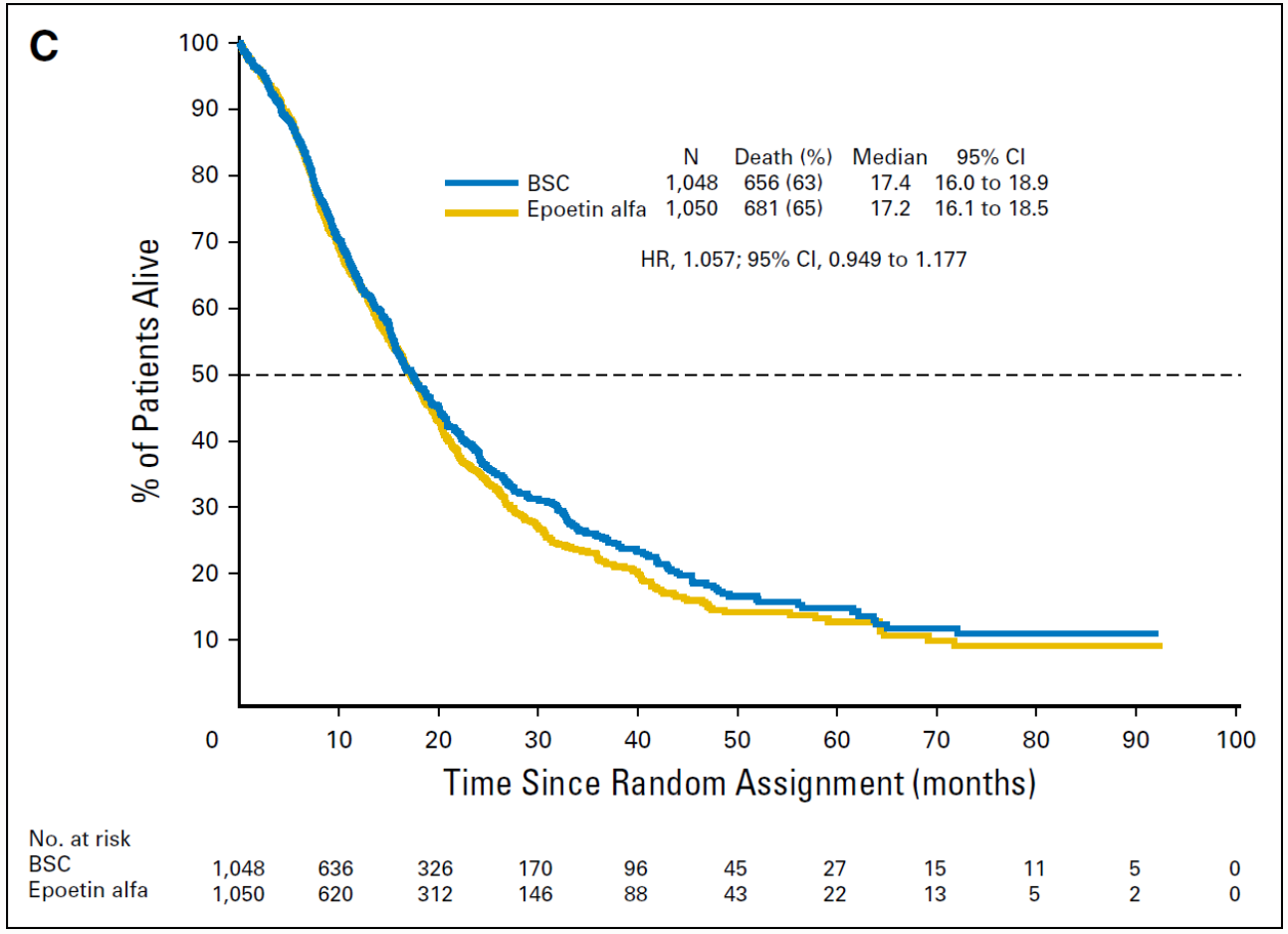


In patients with CKD, higher ESA dose might be associated with all-cause mortality and cardiovascular complications independent of hemoglobin level.

Koulouridis et al. Am J Kidney Dis 61:44-56, 2013

A Randomized, Open-Label, Multicenter, Phase III Study of Epoetin Alfa Versus Best Standard of Care in Anemic Patients With Metastatic Breast Cancer Receiving Standard Chemotherapy

- Metastatic breast cancer patients



The primary end point, progression-free survival based on investigator-determined progressive disease **did not meet noninferiority criteria.**

Overall, this study did not achieve noninferiority objective in ruling out a 15% increased risk in progressive disease /death.

RBC transfusion should be the preferred approach for the management of anemia in this population.

J Clin Oncol 2016; 34: 1197-1207

Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update

Recommendation 1.1. Depending on clinical circumstances, ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin (HgB) has declined to <10 g/dL. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances.

Recommendation 1.2. ESAs should not be offered to patients with chemotherapy-associated anemia whose cancer treatment is curative in intent.

Recommendation 2.1. ESAs should not be offered to most patients with nonchemotherapy-associated anemia.

Recommendation 2.2. ESAs may be **offered to patients with lower risk myelodysplastic syndromes** and a serum erythropoietin level ≤500 IU/L.

Recommendation 3. In patients with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia, clinicians should observe the hematologic response to cancer treatment before considering an ESA.

Recommendation 5. The Expert Panel considers epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa to be equivalent with respect to effectiveness and safety.

Recommendation 8. HgB may be increased to the lowest concentration needed to avoid or reduce the need for RBC transfusions, which may vary by patient and condition.

Recommendation 9. ESAs should be **discontinued in patients who do not respond within 6 to 8 weeks**. Patients who do not respond to ESA treatment should be reevaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia.

*American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH)

J Clin Oncol 2019; 37: 1336-1351

Summary

- ESAs remain an essential therapy for correcting anemia in patients with CKD.
- Multiple ESA formulations and administration routes allow individualized treatment based on patient needs.
  - Epoetin alpha, beta, darbepoetin, CERA : different half-life
- The KDIGO 2025 draft guideline emphasizes careful initiation, Hb targets, and minimizing ESA dose to reduce risks.
  - Initiation of ESA therapy when the Hb concentration is ≤9.0–10.0 g/dl,
  - Recommend targeting a Hb level below 11.5 g/dl.
- ESA therapy may be associated with an increased risk of stroke, thrombotic events, and potential cancer progression.
- Optimal ESA use requires balancing efficacy with safety through ongoing monitoring and shared decision-making.


Thank you for listening