Anemia Management: Reducing Blood Transfusion Rates

December 2021

ESRD NW 10&12/ Telligen QIN/QIO

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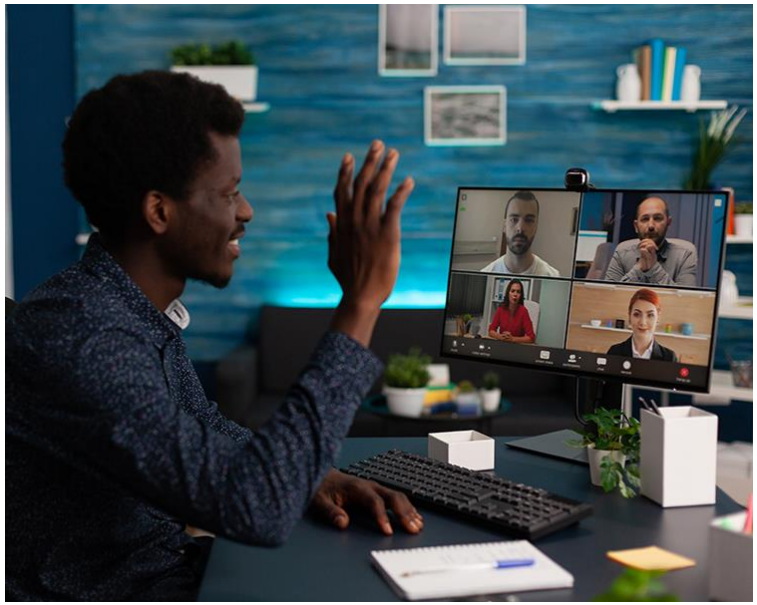
Housekeeping

- Q & A at the end of presentation
  - Raise hand feature
  - Question Box
- Polling questions distributed throughout presentation



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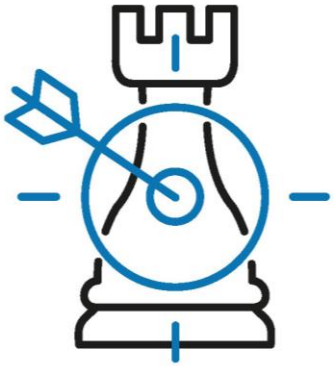
Objectives

- Discuss the management of anemia in ESRD patients who reside and receive dialysis in the nursing home setting
- Identify issues surrounding anemia management in ESRD patients who reside and receive dialysis in the nursing home setting
- Discuss laboratory findings in anemia management with this patient population
- Discuss treatment recommendations and contraindications
- Discuss benefits vs. risk of blood transfusion



ESRD Network Program Overview

The End Stage Renal Disease Network Organization Program (ESRD Network Program) is a national quality improvement program funded by the Centers for Medicare & Medicaid Services (CMS), a federal agency of the U.S. Department of Health and Human Services.

Following passage of the 1972 Amendments to the Social Security Act, in response to the need for effective coordination of ESRD care, hospitals and other health care facilities were organized into networks to enhance the delivery of services to people with ESRD.

In 1978, Public Law 95-292 modified the Social Security Act to allow for the coordination of dialysis and transplant services by linking dialysis facilities, transplant centers, hospitals, patients, physicians, nurses, social workers, and dietitians into Network Coordinating Councils, one for each of 32 administrative areas.

In 1988, CMS consolidated the 32 jurisdictions into 18 geographic areas and awarded contracts to 18 ESRD Network Organizations, now commonly known as ESRD Networks. The ESRD Networks, under the terms of their contracts with CMS, are responsible for: supporting use of the most appropriate treatment modalities to maximize quality of care and quality of life; encouraging treatment providers to support patients' vocational rehabilitation and employment; collecting, validating, and analyzing patient registry data; identifying providers that do not contribute to the achievement of Network goals; and conducting onsite reviews of ESRD providers as necessary.

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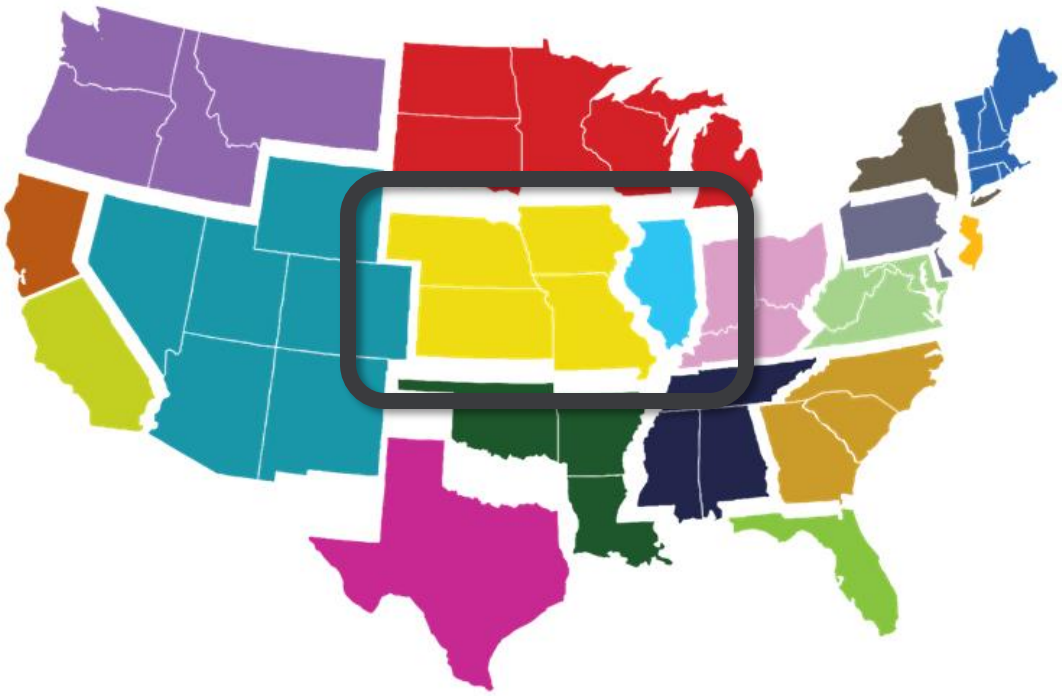

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Telligen Quality Innovation Network – Quality Improvement Organization (QIN-QIO)

Telligen QIN-QIO brings together Medicare providers, beneficiaries, and communities together in data-driven initiatives that increase patient safety, improve clinical quality, better coordinate post-discharge care, and make communities healthier. Learn more and join us in partnership at Telligen QIN-QIO.

Telligen QIN-QIO is funded by CMS to deliver quality improvement services at no cost to you or your organization. We partner with and leverage local, regional and national expertise with our:

- training, service, and data infrastructure
- education and support through quality improvement learning and action sessions
- peer-to-peer learning through our monthly coalition calls and resource sharing platforms
- technical assistance programs reflecting evidence-based practices

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Guest Speaker

Dr. J. Kevin Tucker is Vice-President for Education at Mass General Brigham and Assistant Professor of Medicine at Harvard Medical School. He is also co-director of Harvard Medical School's Masters in Clinical Service Operations program. His clinical appointment is at Brigham and Women's Hospital, where he focuses on the management of chronic kidney disease patients, hemodialysis patients, and peritoneal dialysis patients.

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Disclosures

Nothing to disclose.

Case Presentation 1

The patient is an 81-year-old man who resides in a skilled nursing facility. He has ESRD and has been on hemodialysis (HD) three times weekly for five years.

Past Medical History

- Diabetes mellitus type 2
- Hypertension
- Coronary artery disease
  - status post coronary artery bypass graft surgery (CABG)
- Peripheral arterial disease
  - status post bilateral below-the-knee amputations
    - Never has been able to use prostheses
- Hyperparathyroidism

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Medications

- Carvedilol 25 mg twice daily
- Amlodipine 5 mg daily
- Clopidogrel 75 mg daily
- Sevelamer carbonate 1600 mg po with meals
- Cinacalcet 60 mg po daily
- Methoxy polyethylene glycol-epoetin beta 200 ug every two weeks

Social History

- The patient is a widower with no children.
- He is a retired teacher.
- He has a 50-pack per year cigarette smoking history.
- He has lived in a skilled nursing facility since shortly after starting dialysis.
- He is dependent for most of his activities of daily living (ADLs).
- He spends most of the day in bed, but occasionally an aide will put him in a wheelchair and take him to the solarium.

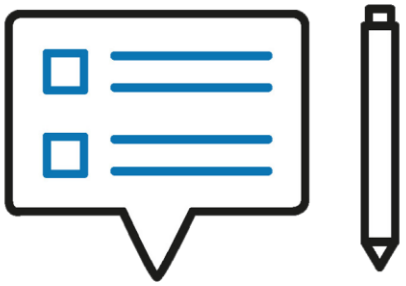
Anemia labs

Hemoglobin	T-sat	Ferritin
7.5* g/dL	31%	2060 ug/L

*The hemoglobin with the prior month's labs was 7.9 g/dL.

Poll Question #1

Should this patient be referred for a blood transfusion?



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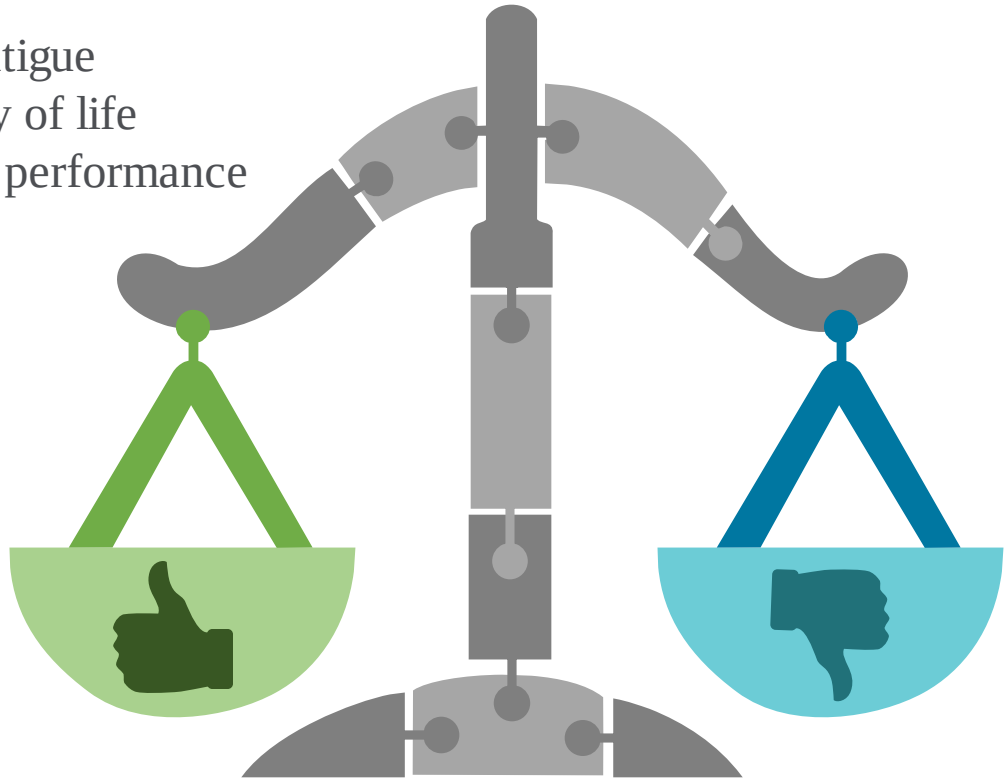
Balancing Rewards and Risks of Transfusion

Rewards

- Improving fatigue
- Better quality of life
- Better QOL/HRQOL performance



Risks

- Transfusion reactions
- Alloimmunization
- Volume overload
- Iron overload
- Infections
- Costs to the healthcare system
- Depletion of a limited resource

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Medicine is Full of Uncertainty and Shades of Gray

There is no absolute number to indicate when to transfuse.	The decision to transfuse requires careful balance of a number of considerations that are subtle and sometimes difficult to manage given the way in which dialysis care is practiced.
	• Symptoms • Fatigue among the most difficult symptoms to diagnose • Patient goals/values • Quality of life • Likelihood that transfusion will improve symptoms and quality of life • Risks of high-dose ESAs • Risks of transfusions • Hassle factor associated with transfusions

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Case Presentation 2

A 72-year-old man with ESRD on hemodialysis (HD), diabetes mellitus type 2, and peripheral arterial disease is admitted with a diabetic foot ulcer. He has a hemoglobin of 7.8 g/dL on admission. He has had no evidence of gastrointestinal (GI) bleeding.

Case 2 Past Medical History

- ESRD
- Diabetes mellitus type 2
- Hypertension
- Colon cancer status post partial colectomy 5 years prior; no metastatic disease
- Transient ischemic attack (TIA)

Case 2 Outpatient Medications

- Amlodipine 10 mg daily
- ASA 81 mg daily
- Calcitriol 0.25 ug 3x/weekly
- Labetalol 300 mg bid
- Lisinopril 10 mg daily
- Pravastatin 40 mg daily
- Renal multivitamin daily
- Iron gluconate 125 mg weekly

Anemia Labs

Hemoglobin	T-sat	Ferritin
7.8 g/dL	33%	1352 ug/L

Polling Question #2

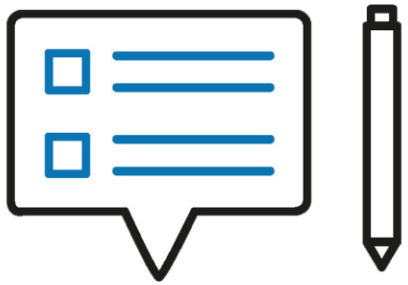
What would you do next in managing this patient's anemia?

A) Do nothing. The patient is asymptomatic.

B) Add an erythropoiesis-stimulating agent (ESA).

C) Transfuse to a hemoglobin of 10-11 g/dL.

D) Refer to hematology for an anemia evaluation.



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Case 2 Explanation

The patient's hemoglobin will continue to decline such that he will ultimately need transfusion. He has not been on an ESA because of the remote history of colon cancer. The risks of repeated transfusion are greater than the risk of an ESA in this setting.

Kidney Disease: Improving Global Outcomes (KDIGO) Recommendations

In initiating and maintaining ESA therapy, we 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). (1B)

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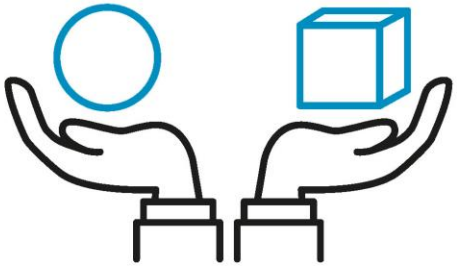
Special Considerations with ESAs in Dialysis

- Cancer
- Stroke
- Vascular access thrombosis



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Trials Indicating Adverse Outcomes with ESA's in Cancer

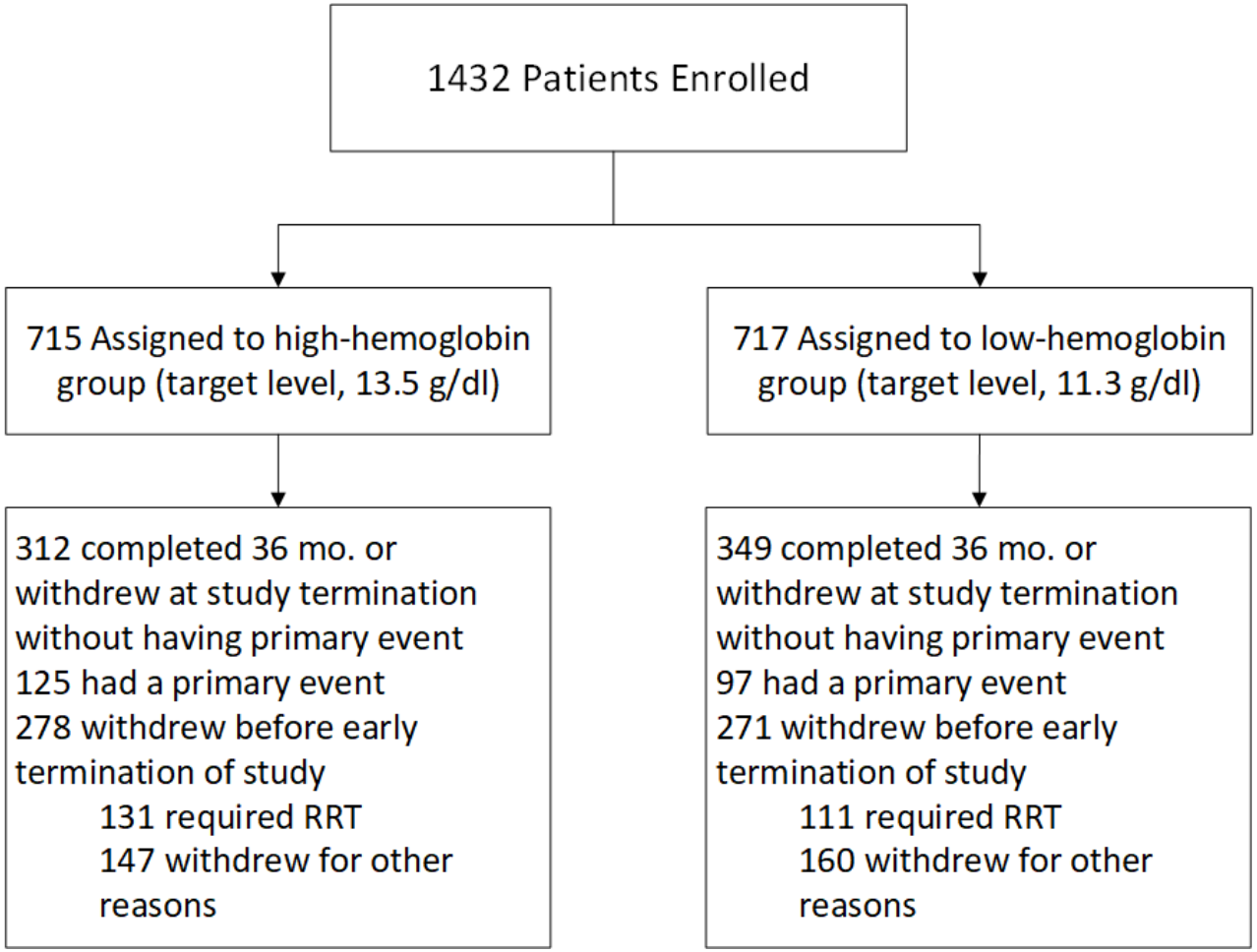
Source	Cancer Type	Concomitant Therapy	# of Patients Randomized	ESA Treatment	Hemoglobin Stopping Value g/dL	Adverse Outcome
Henke et al. 2003	Head and neck	Radiotherapy	351	Epoetin beta (300 IU/kg 3x/week)	$\geq$ 14 (women) $\geq$ 15 (men)	Locoregional progression
Hedenus et al. 2003	Lympho-proliferative cancers	Chemotherapy	349	Darbepoetin alfa (2.25 ug/kg/week)	$\geq$ 14 (women) $\geq$ 15 (men)	Shortened overall survival
Leyland-Jones et al. 2005	Metastatic breast cancer	Chemotherapy	939	Epoetin alfa (40000 U/wk)	> 14	Overall survival vs placebo
Overgaard et al. 2007	Locally advanced head and neck	Radiotherapy	522	Darbepoetin alfa (150 ug/week)	> 15.5	Increased risk in local-regional failure
PREPARE	Breast cancer	Chemotherapy	733	Darbepoetin alfa (4.5 ug/kg/2 wk)	$\geq$ 13	Shortened overall survival

Bennett CL *et al* JAMA 2008; 299: 914-924

What is the evidence for an increased risk of cardiovascular events?

- Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)
- Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)

The CHOIR Study



Singh AK et *al.* N Engl J Med 2006; 355: 2085-2098

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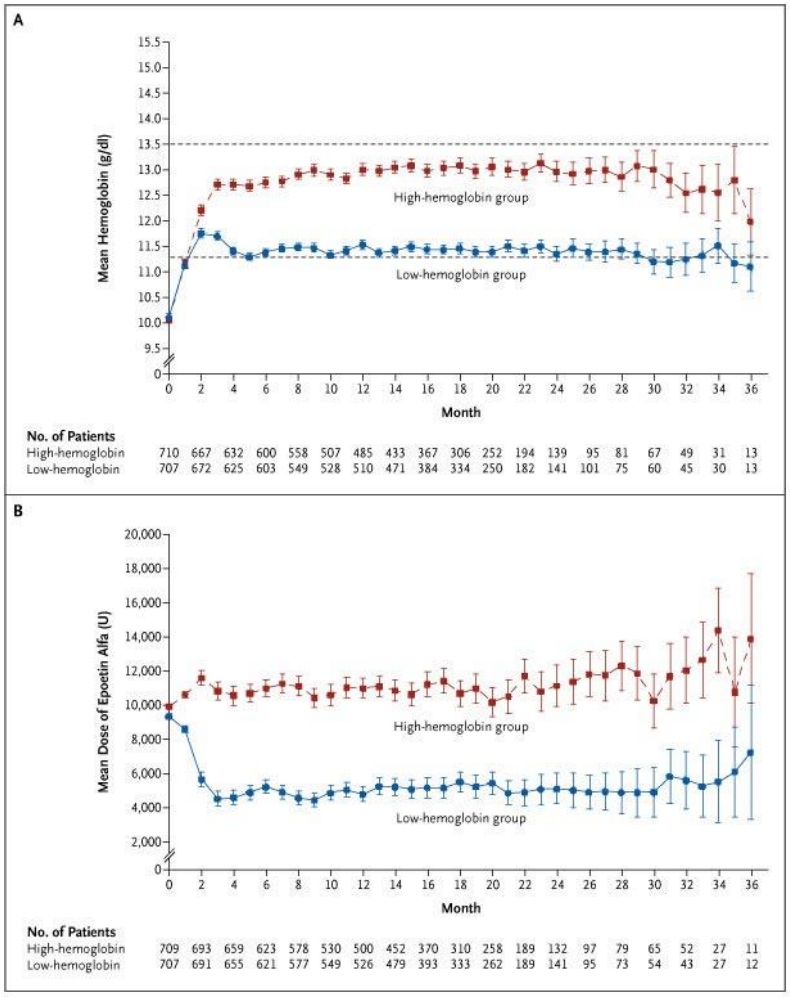
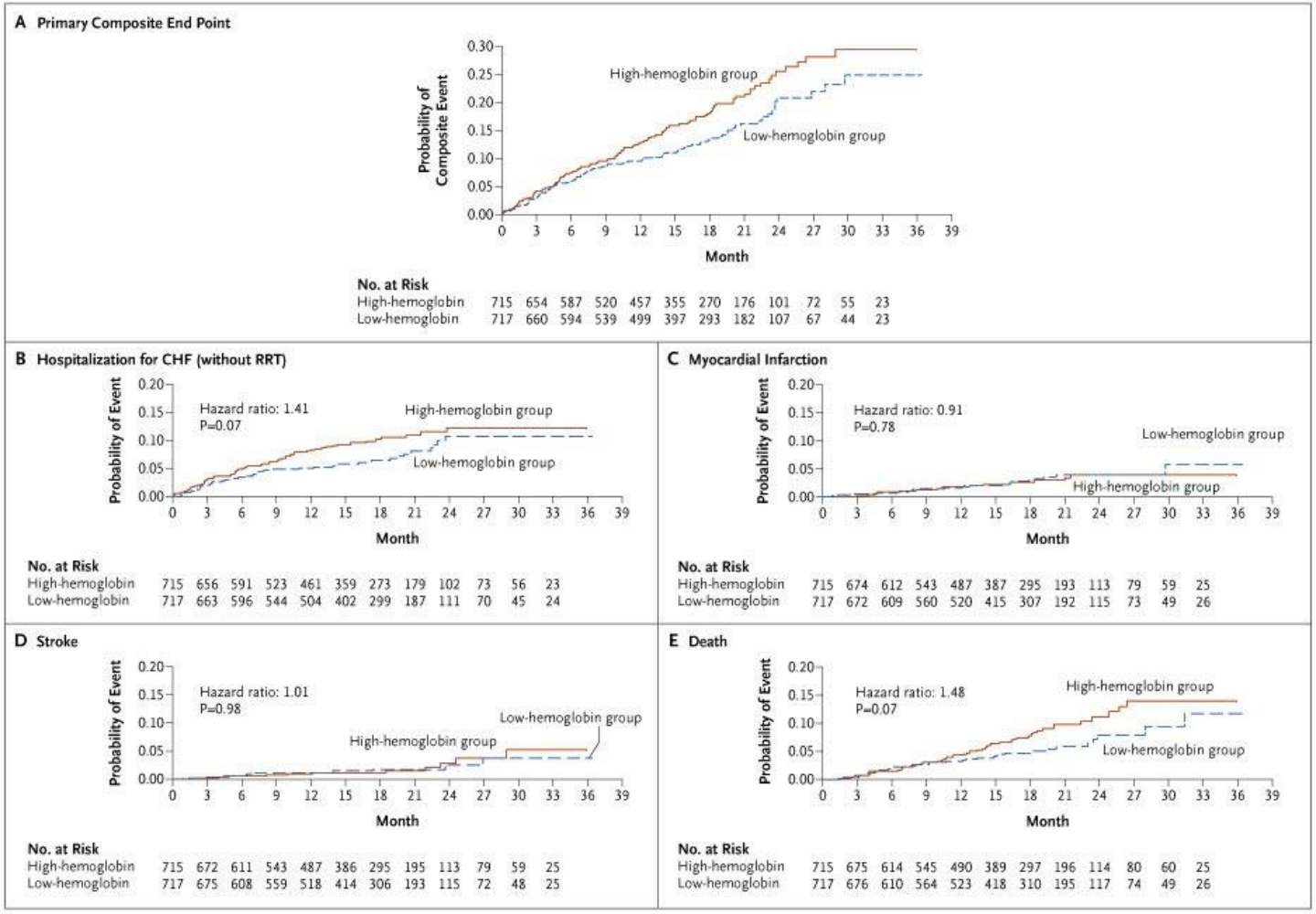
Mean Monthly Hemoglobin Levels (Panel A) and Mean Weekly Doses of Epoetin Alfa (Panel B)



Singh AK *et al.* N Engl J Med 2006; 355: 2085-2098

Probabilities of the Primary and Secondary End Points

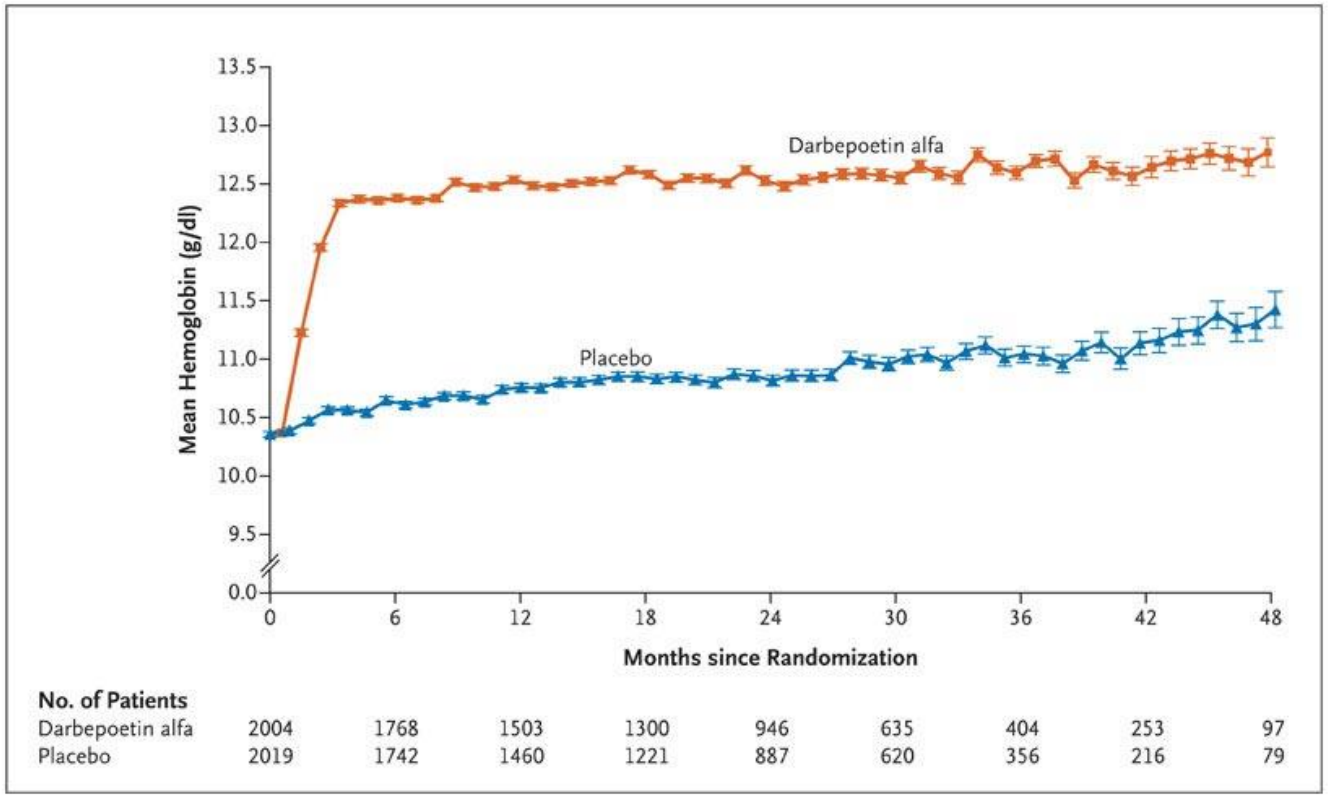


Singh AK *et al.* N Engl J Med 2006; 355: 2085-2098

TREAT Study

- Randomized study involving 4038 subjects with diabetes, anemia, and Chronic Kidney Disease (CKD)
- 2012 subjects randomized to receive darbepoetin to achieve a hemoglobin of 13 g/dL
- 2026 randomized to placebo with rescue darbepoetin given when hemoglobin less than 9 g/dL
- Primary outcomes: death or a Cardiovascular (CV)event and death or ESRD

Mean Hemoglobin Levels through 48 Months among Patients Who Were Assigned to Receive Darbepoetin Alfa or Placebo



Pfeffer *M et al.* N Engl J Med 2009; 361: 2019-2032

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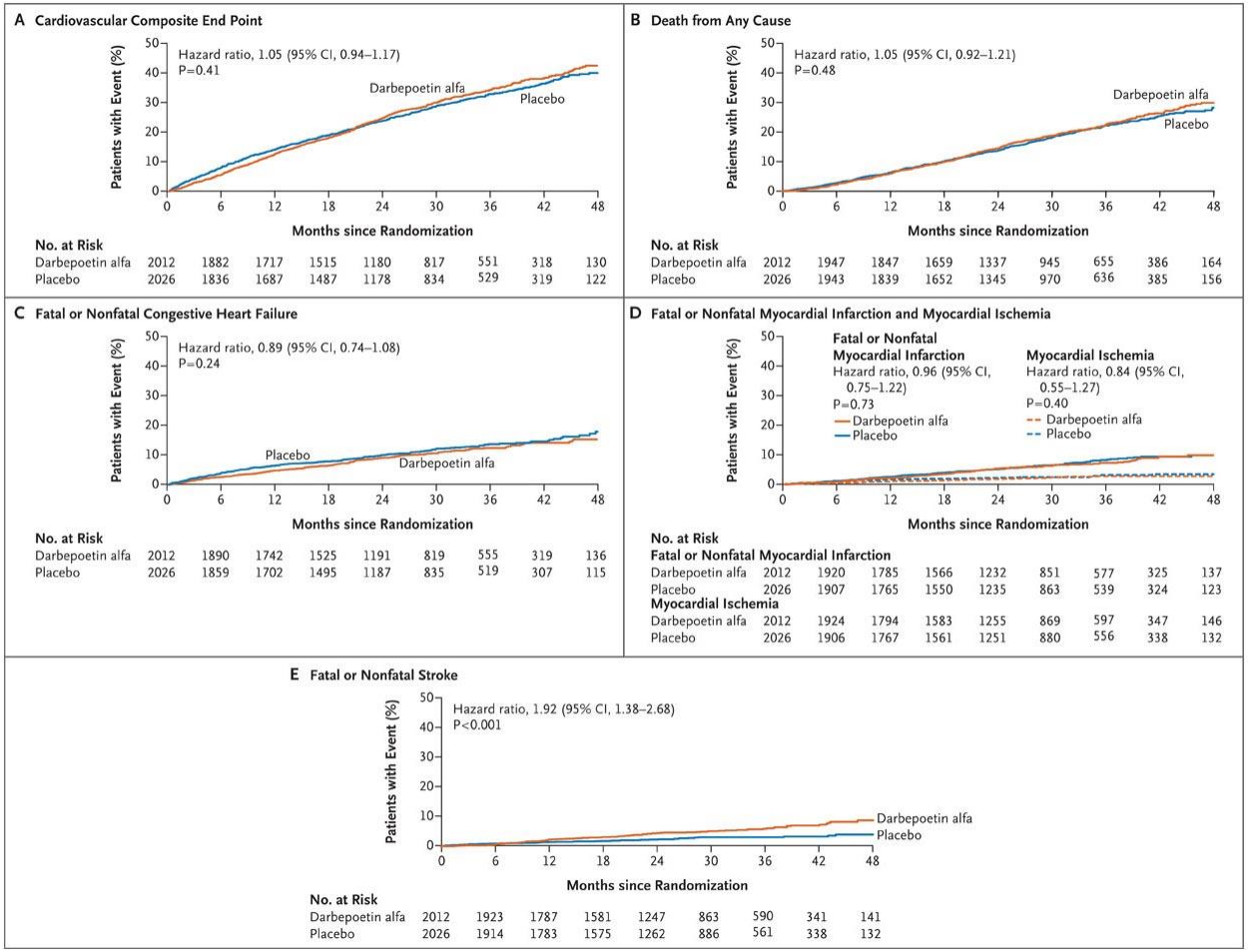
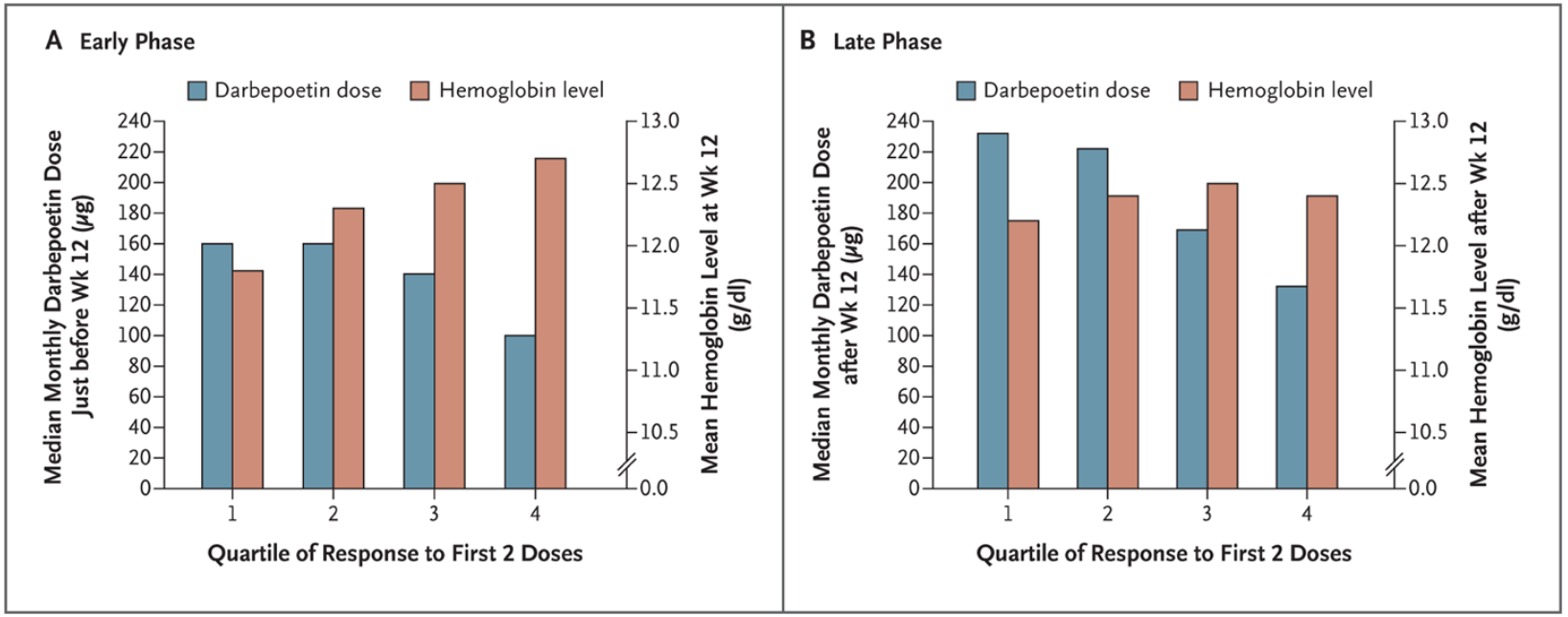
Kaplan-Meier Estimates of the Probability of the Primary and Secondary End Points: Note Panel E



Pfeffer M *et al.* N Engl J Med 2009; 361: 2019-2032

Association between Hemoglobin Level and Dose of Darbepoetin Alfa, According to the Level of Response to the First Two Doses



Solomon SD et al. N Engl J Med 2010; 363: 1146-1155

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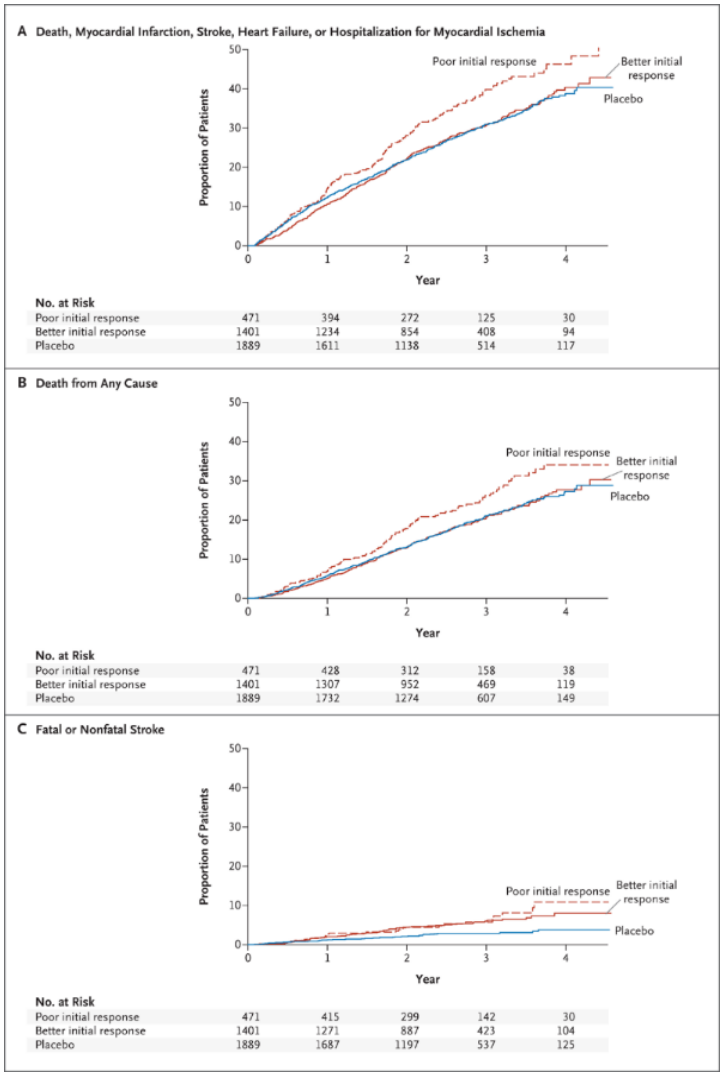
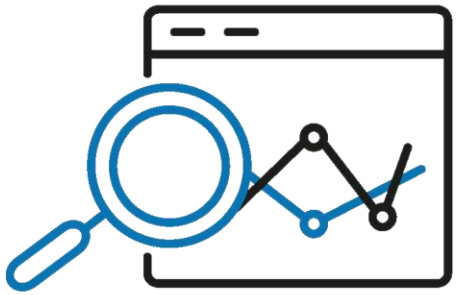
Rates of Primary End Points



Solomon SD et al. N Engl J Med 2010; 363: 1146-1155

Is a higher hemoglobin better in dialysis patients?



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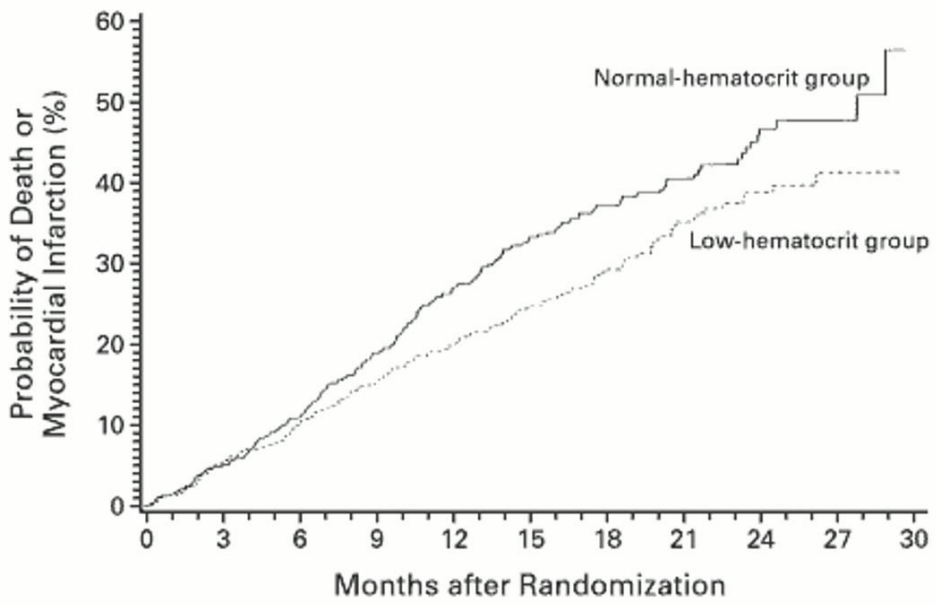
Probability of Death or a First Non-fatal Myocardial Infarction in the Normal-Hematocrit and Low-Hematocrit Groups



No. at Risk

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

Besarab A et al. N Engl J Med 1998; 339: 584-590

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Are ESAs Associated with Vascular Access Thrombosis?

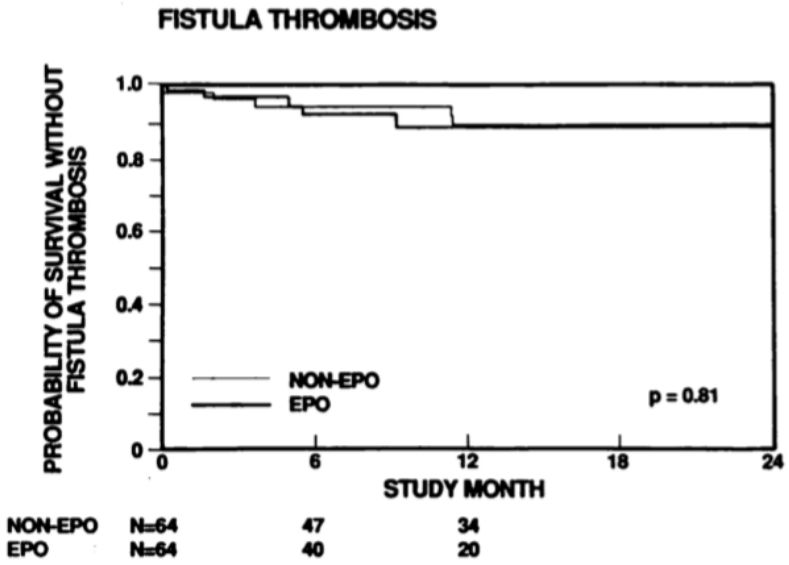

Figure 1. Effect of EPO treatment on the probability of fistula thrombosis.

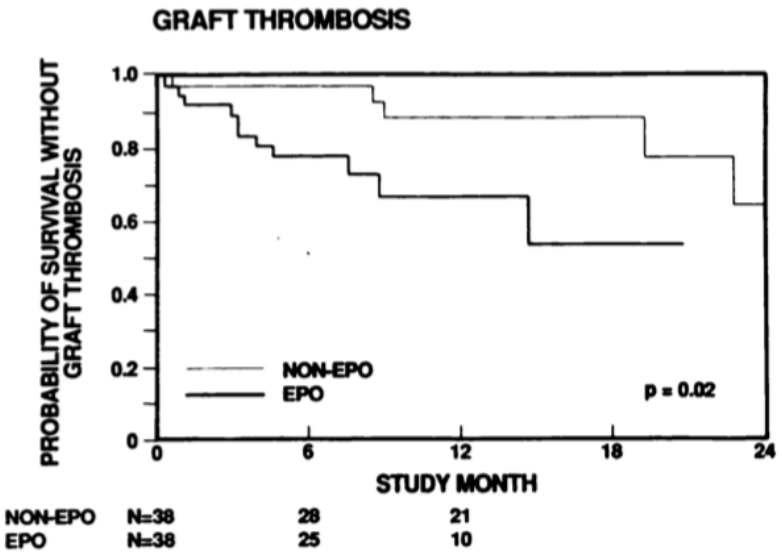

Figure 2. Effect of EPO treatment on the probability of graft thrombosis.

Churchill *et al* J Am Soc Nephrol 1994; 4: 1809-1813

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Use IV Iron Appropriately

Variable	Lab Parameters for ESRD
Iron deficiency unconditional	T-sat $\leq$ 20% and/or serum ferritin $\leq$ 200 ug/L
Iron deficiency conditional	T-sat $\leq$ 30% and/or serum ferritin $\leq$ 500 ug/L

Adapted from Gutierrez OM 2021; Kidney Int Rep 6: 2261-2269

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What About Patients with a High Ferritin?

Dialysis Patients' Response to Intravenous [IV] Iron With Elevated Ferritin (DRIVE) Trial

- Randomized patients with anemia who were receiving hemodialysis
- Ferritins between 500 and 1200 ug/L
- T-sat < 25%
- 1 gram of ferric gluconate or no iron for six weeks
- Those receiving iron had a higher increase in iron parameters and hemoglobin without any adverse events.

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What about Patients with a High Ferritin?

PIVOTAL Trial

- 2141 patients randomized to iron sucrose in a proactive approach or a reactive approach
- Proactive: 400 mg monthly unless the ferritin was > 700 ug/L or T-sat > 40%
- Reactive: Iron given only when T-sat < 20% or ferritin < 200 ug/L
- After 2.1 years of follow-up:
  - Subjects randomized to proactive approach had higher serum ferritin and T-sat
  - More rapid increase in hemoglobin among those receiving iron proactively
  - Lower doses of ESAs among those receiving iron proactively
  - Lower risk of composite outcome of nonfatal Myocardial Infarction (MI), nonfatal stroke, hospitalization for heart failure, death among those receiving iron proactively

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Case 2 Outcome

- Using a patient-centered approach, risks and benefits were discussed.
- Based upon that discussion, a low, fixed dose of darbepoetin was started.
- Patient had a good response, with his hemoglobin rising to 10-11 g/dL.

Case Presentation 3

A 71-year-old woman with ESRD on HD three times weekly presents to interventional nephrology for a vascular access procedure. Following the procedure, she is prescribed apixaban 2.5 mg bid for seven days. Five days later she reported to the dialysis charge nurse that she had been having bright red blood per rectum. Immediately, following dialysis, she went to the bathroom and passed blood with clots and had a syncopal event.

Per nursing notes: "Patient did not have complete Level of consciousness (LOC). Patient placed in a chair and in Trendelenburg position and her arm was recannulated. Approx 400cc saline given with good effect. Patient did have a small amount of vomiting and was diaphoretic. 911 was called, and patient was transported to the emergency room (ER). Dr. Tucker notified."

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Case Presentation 3

Past Medical History

- ESRD
- Human immunodeficiency virus (HIV)
- Coronary artery disease status post failed kidney transplant
  - Post-transplant lymphoproliferative disorder (PTLD)
- Lung cancer

Medications

- Apixaban 2.5 mg bid
- ASA 81 mg daily
- Rosuvastatin 5 mg daily
- Calcium acetate 1334 po three times a day with meals
- Isosorbide mononitrate 30 mg daily
- Metoprolol succinate 50 mg daily
- Ritonavir 100 mg daily
- Lamivudine 100 mg daily
- Dolutegravir 50 mg daily
- Darunavir 800 mg daily
- Renal vitamin daily
- Methoxy polyethylene glycol-epoetin beta 50 ug every two weeks

Case Presentation 3: Anemia labs

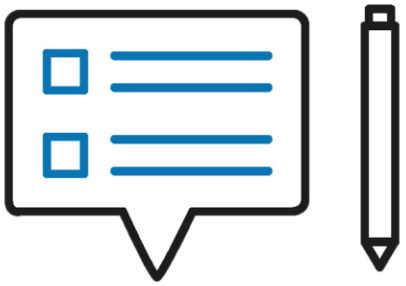
Date	Hgb	Ferritin	% Sat	MCV	WBC	Plt	URR	Alb	Dry Wgt
7/20/2021	8.2	1021	30	114	5.6	215		3.9	70
8/17/2021	8.9	848	19	109	6.2	206		3.9	70

Case 3 Presentation: Hospital Course

The patient was admitted to the hospital and required intensive care unit (ICU) transfer because of ongoing GI bleeding, although she remained hemodynamically stable. Her initial hemoglobin on presentation to the hospital was 6.9 g/dL.

Poll Question #3

Should this patient be TRANSFUSED in the hospital?



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Case 3 Presentation Outcome

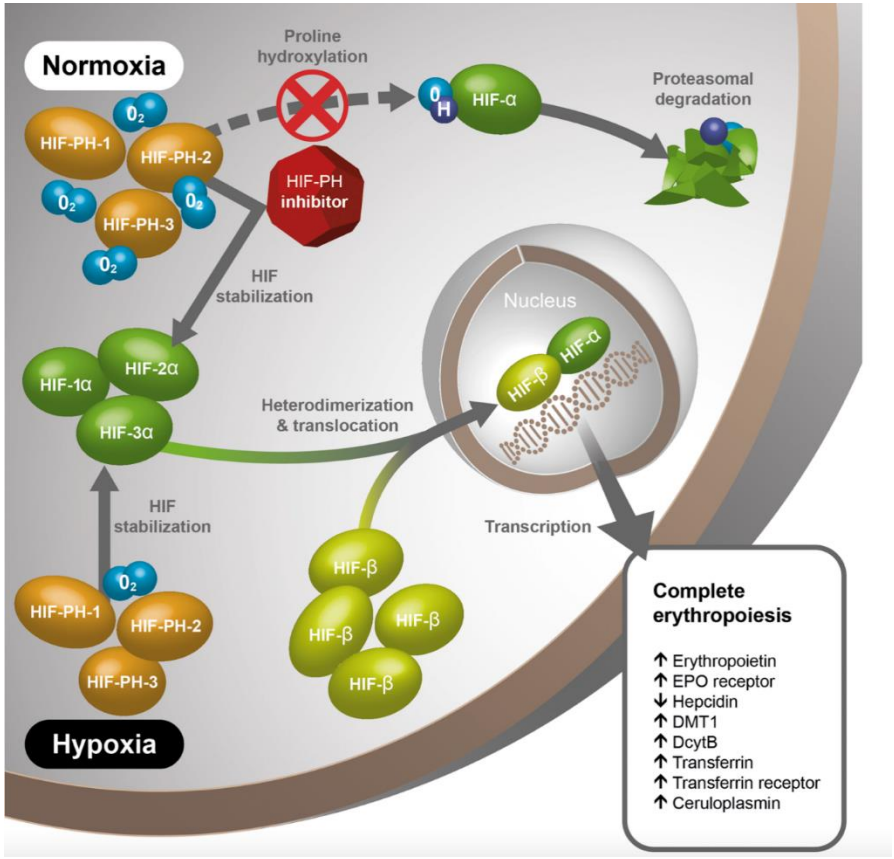
Note that the patient's baseline hemoglobin was in the 8s. In a patient-centered approach, she had been on a fixed low dose of an ESA because of lung cancer. She was transfused to a hemoglobin of ~ 8 g/dL. Her bleeding stopped with discontinuation of anticoagulation.

New Drugs to Treat Anemia of Chronic Kidney Disease

Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors

- Stabilize the HIF complex
- Stimulate endogenous EPO production
- Orally administered

Biochemistry of HIF-PH



Gupta N and Wish JB. Am J Kidney Dis 2017; 69: 815-826

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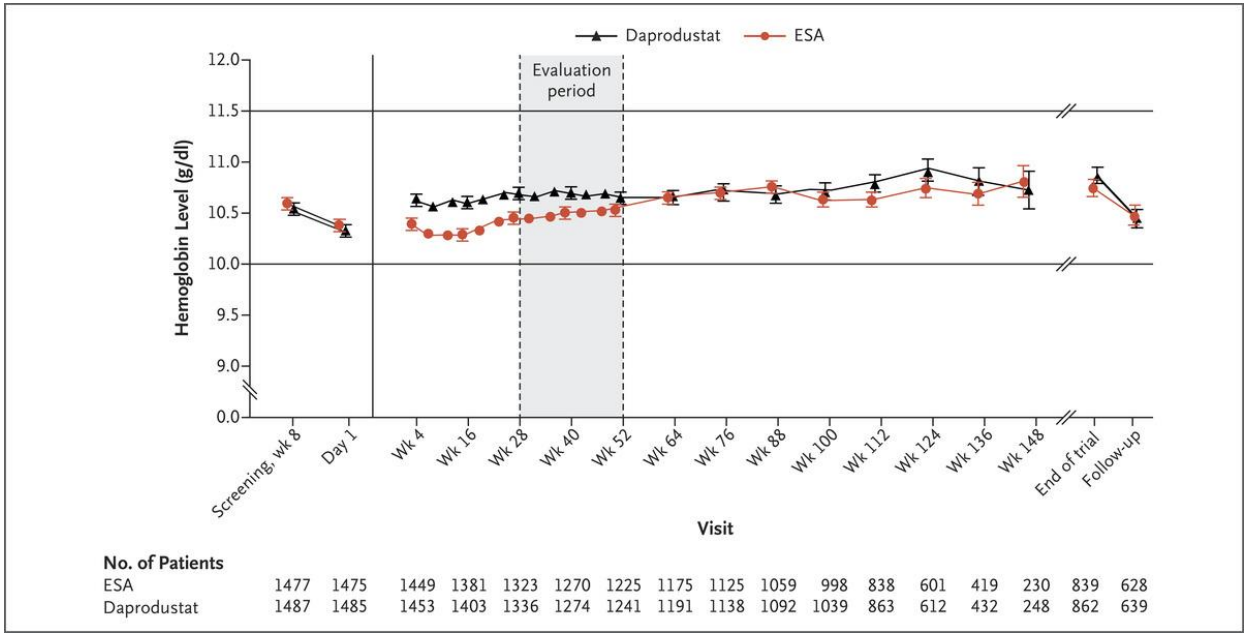
HIF-PH Inhibitors under Development

Drug	Dosing Frequency
Roxadustat	3x/week
Vadadustat	Daily
Daprodustat	Daily
Molidustat	Daily

Daprodustat Non-inferior to ESA with Respect to Hemoglobin



AK Singh et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2113379

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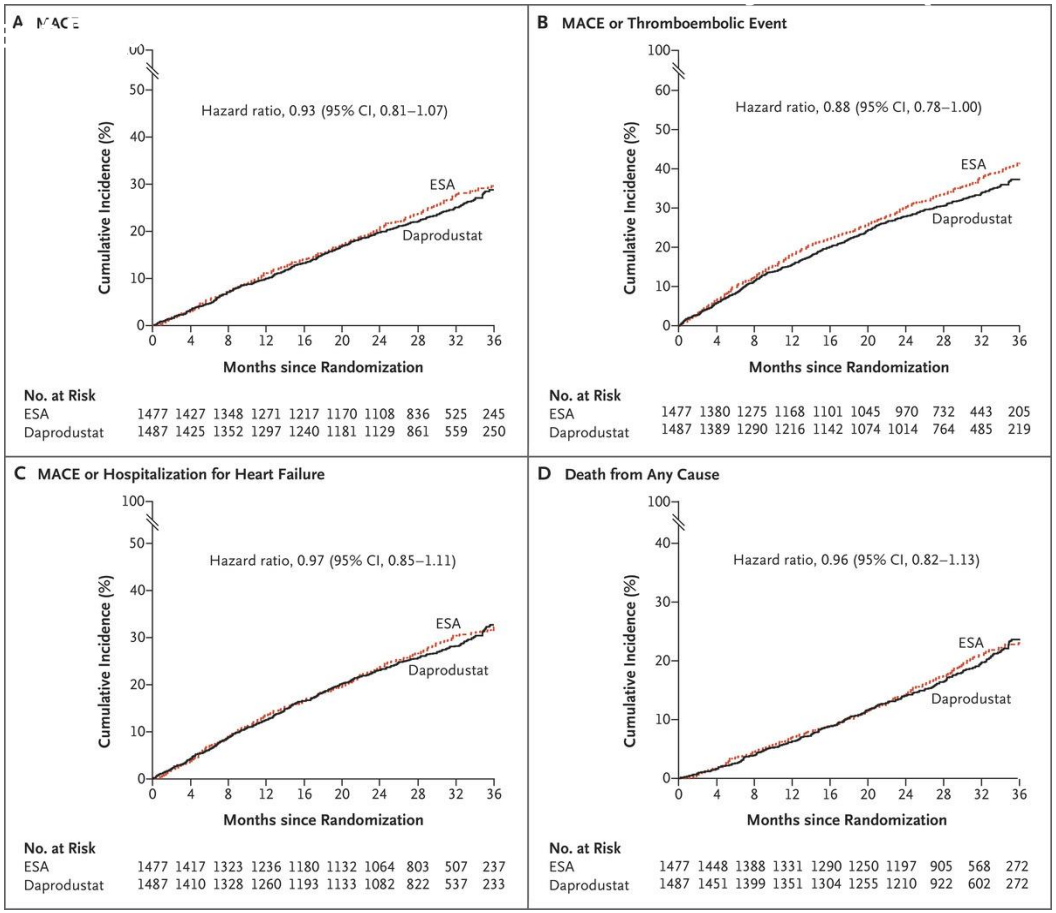
Daprodustat Non-inferior to ESA with Respect to MACE



AK Singh et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2113379

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Summary and Conclusions

The decision to transfuse an anemic dialysis patient often falls into the gray zone of decision-making and requires clinical judgement and consideration of patient factors into each decision.

There is no single correct number or target to indicate when to transfuse.

The benefits of transfusion must be weighed against all of the potential risks.

Judicious use of ESA and IV iron should minimize the need for transfusion.

New therapies for anemia of CKD are on the horizon.

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Q&A

Thank you! Connect with us…

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