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CEPD continuing education and professional development

Anemia of Chronic Kidney Disease

To Treat or Not to Treat and How

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Conflict of Interest Declaration

I have no financial or personal relationships to disclose

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Learning Objectives

- Identify and discuss diagnosis, pathogenesis and evaluation of anemia in CKD
- Examine the use of erythropoiesis-stimulating agents (ESAs) to treat anemia in CKD and new target levels
- Explore the use of iron to treat anemia in CKD and new target levels

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Diagnosis of anemia

Diagnose anemia in adults with CKD when the Hb concentration is <130 g/l in males and <120 g/l in females.

Investigation of anemia

In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia :

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

Kidney International Supplements (2012) 2, 283–287

The association between kidney disease and anemia was first described in 1836 [Bright 1836].

Renal anemia is typically normochromic and normocytic, and regularly develops when the Glomerular Filtration Rate (GFR) falls below 30 ml/min regardless of the etiology of the underlying kidney disease.

Anemia of CKD is a complex disorder in which many factors play a role.

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Pathogenic Factors of Renal Anemia

Shortened red cell life span

-Extracorpuscular factors (uremic plasma)
-Corpuscular factors (reduced osmotic deformability and reduced oxidant resistance)

Blood loss

-Hemodialysis
-Diagnostic blood sampling
-Occult gastrointestinal blood loss

Inhibition of erythropoesis

-EPO deficiency
-Chronic inflammation
-Iron deficiency (absolute or functional)
-Hyperparathyroidism
-Aluminium intoxication

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Absolute or relative Erythropoietin (Epo) deficiency is the main cause of renal anemia.

Epo is a glycoprotein that acts as an essential growth and survival factor on late erythroid progenitor cells in the bone marrow via a specific receptor.

Epo is produced mainly in the kidney (some by the liver) by the peritubular fibroblasts.

Main stimulus for Epo production is reduced oxygen delivery to tissues, (all the components necessary for the detection of hypoxia and production of Epo are equipped within the kidney).

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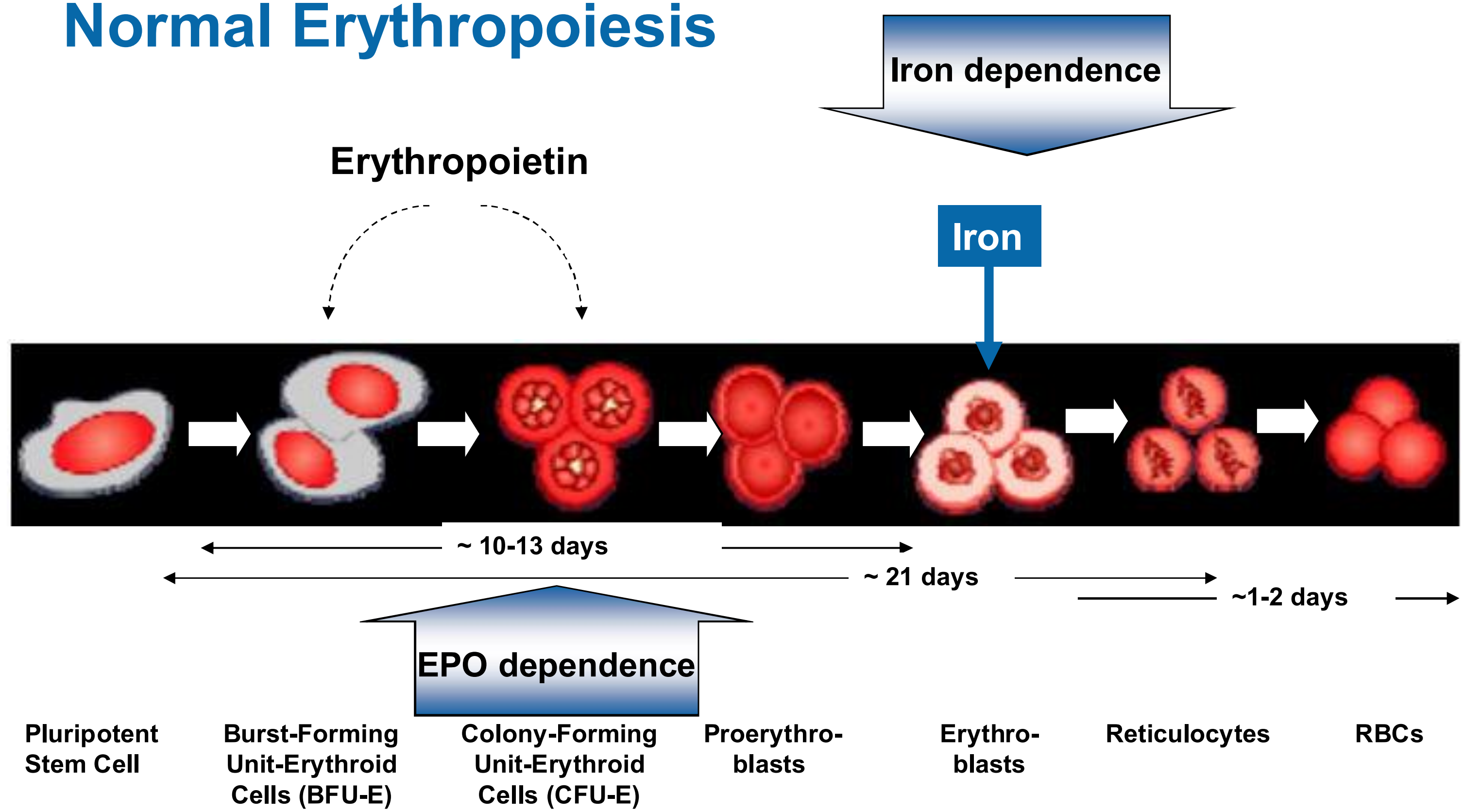
Normal Erythropoiesis



Hillman RS, et al. *Red Cell Manual*, 7th ed. Philadelphia, PA: F.A. Davis Company; 1996:chap 1. Papayannopoulou T, et al. In: Hoffman R, et al. eds. *Hematology: Basic Principles and Practice*, 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005:chap 20. Brock. *Iron Metabolism in Health and Disease*. W.B. Saunders Co; 1994

Possible causes of Epo deficiency in renal anemia

- Destruction of a subpopulation of renal fibroblasts that normally produces EPO
- Transformation of EPO-producing fibroblasts into matrix producing fibroblasts
- Absence of paracrine signals from closely adjacent tubular epithelia
- Local inhibition of EPO production by inflammatory cytokines
- Effect of renin-angiotensin blockers (ACE inh/ARB)

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IRON METABOLISM

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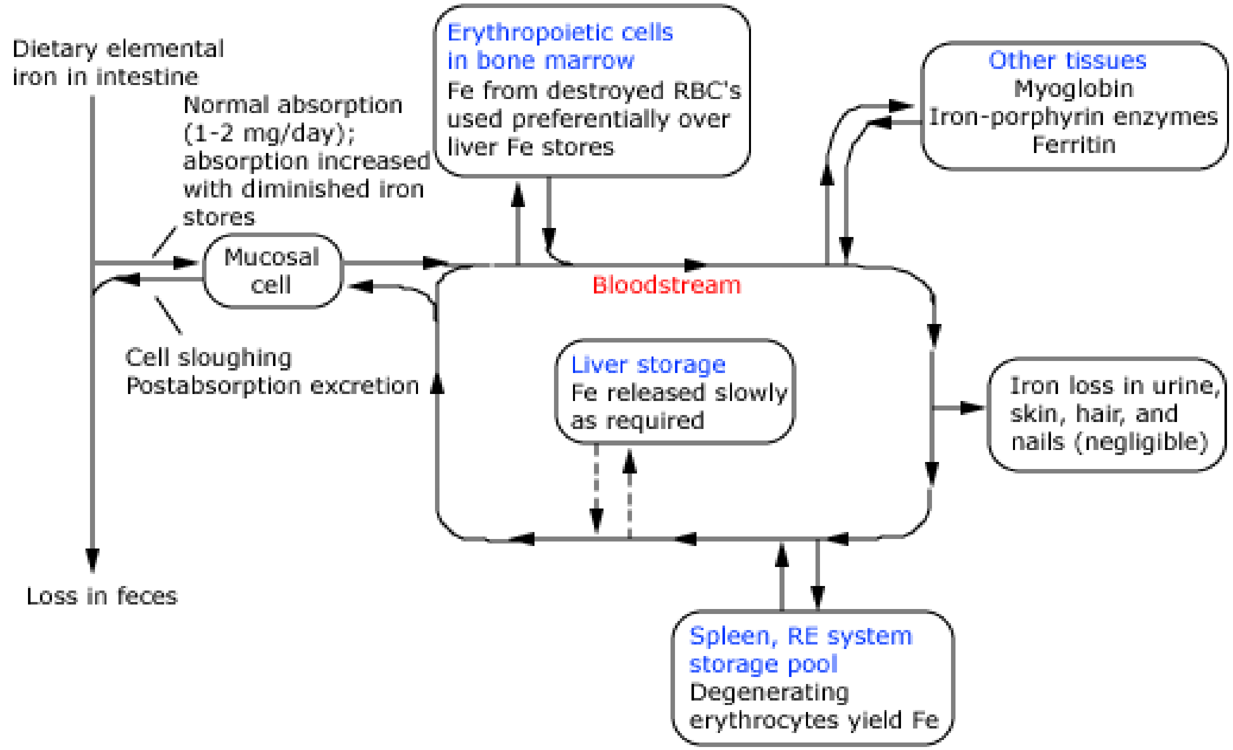
Iron homeostasis



Schematic representation of the pathways involved in iron homeostasis. The amount of iron passing from mucosal cells into the body is determined by the rate of erythropoiesis and the state of body iron stores.

Adapted from Scientific American Medicine, Scientific American, New York, 1995.

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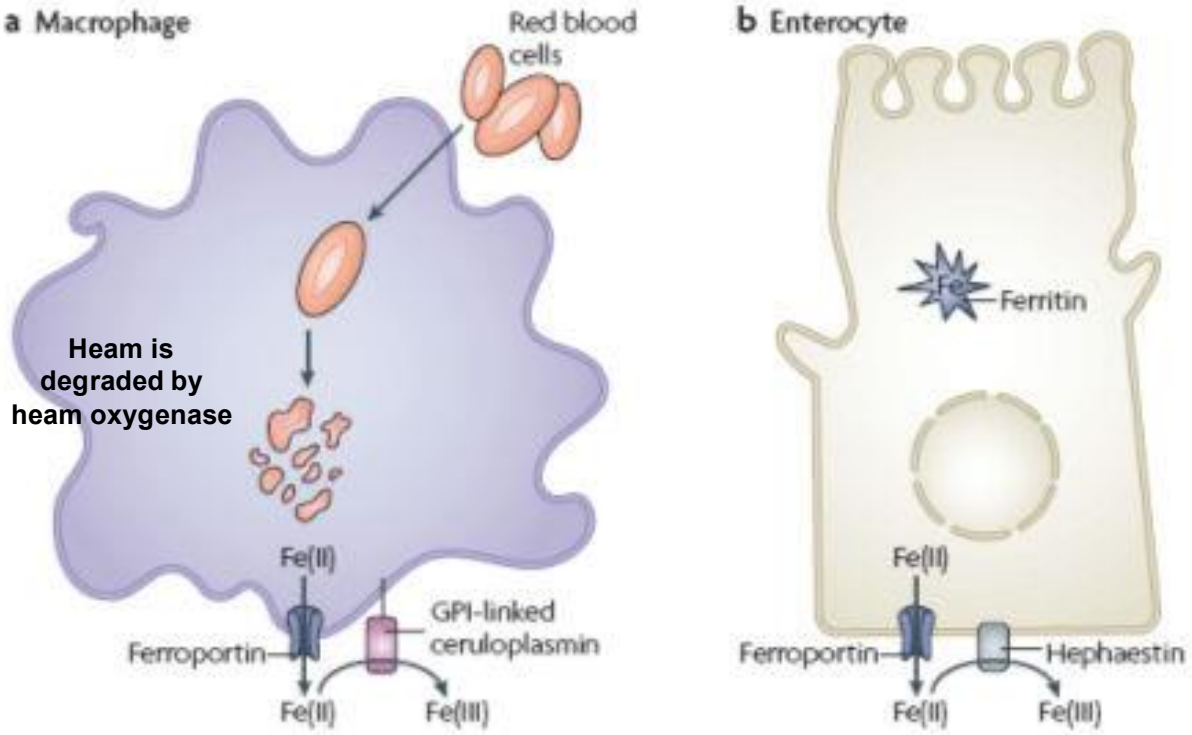
IRON METABOLISM

- There is NO mechanism for iron excretion => iron is regulated at the levels of:
  - Intestinal absorption
  - Macrophage release
- Principal regulator = Hepcidin
- Hepcidin is a peptide produced mainly by the liver but also by the WBCs
- Hepcidin inhibits Ferroportin

Ferroportin Mediated Transport



- Combined action of membrane iron transporter and an iron oxidase

Nature Reviews 9;72-81.2008

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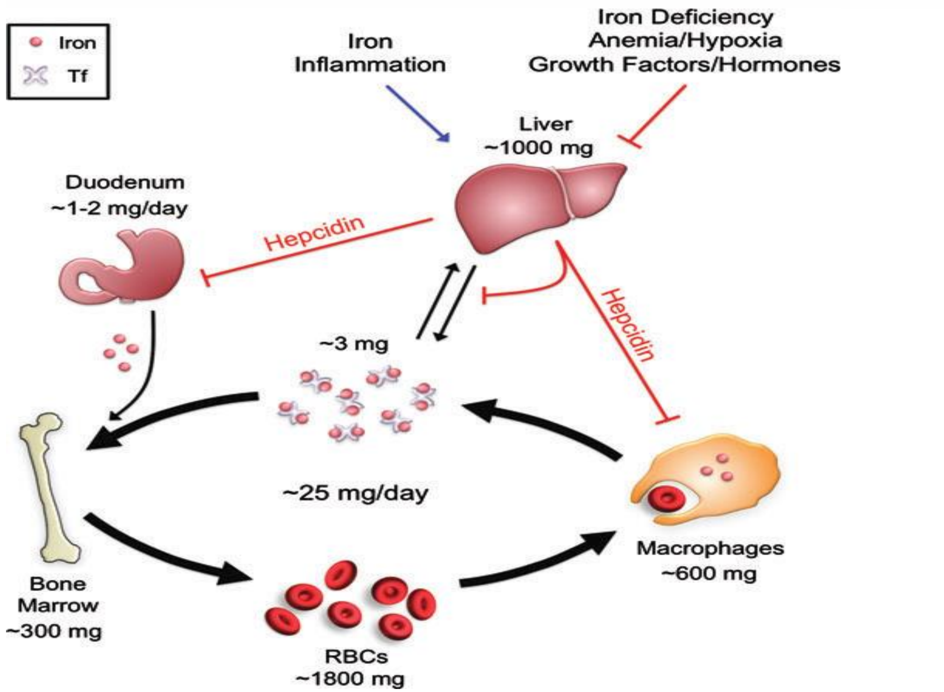

FIGURE 1: Systemic iron regulation. Iron is absorbed by the duodenum where it is released into the circulation via the iron exporter ferroportin to be loaded onto transferrin (Tf). The majority of iron is utilized by red blood cells (RBCs) for the synthesis of the hemoglobin, requiring ~25 mg of iron per day. The daily requirements for intestinal iron uptake are only 1–2 mg per day due to efficient recycling of iron from RBCs. Iron recycling is performed primarily by reticuloendothelial macrophages which phagocytize senescent RBCs and then export iron via ferroportin back into the circulating pool of Tf-bound iron. Excess iron is also stored within hepatocytes. Hepcidin regulates systemic iron balance by inducing ferroportin degradation to inhibit iron absorption from the duodenum and iron release from macrophage and hepatocyte stores. Hepcidin production in the liver is stimulated by iron and inflammation to limit iron availability, while hepcidin production is inhibited by iron deficiency, anemia and hypoxia to increase iron availability. Several other growth factors and steroid hormones have recently been demonstrated to suppress hepcidin expression in the liver, including EGF, HGF, testosterone and estrogen.

Nephrol Dial Transplant (2014) 29: 263–273

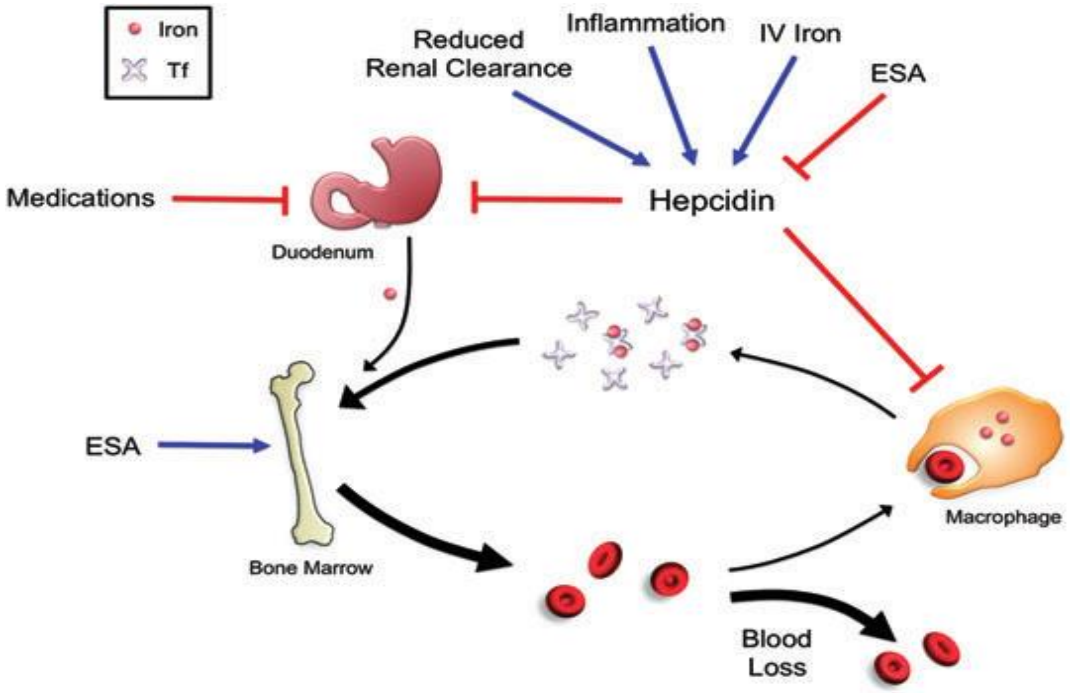

FIGURE 4: Disordered iron balance in CKD. Chronic inflammation and reduced renal clearance in patients with CKD lead to increased levels of hepcidin, which reduces duodenal iron uptake and iron release from cellular iron stores. Intestinal iron uptake is also inhibited by medications such as phosphate binders and antacids. ESAs stimulate increased iron usage for erythropoiesis, while blood loss due to frequent phlebotomy, blood trapping in the dialysis apparatus and gastrointestinal bleeding further deplete the circulating iron pool. Iron administration stimulates hepcidin expression, which can paradoxically worsen the iron restriction, while ESAs have an inhibitory effect on hepcidin expression.

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The New England Journal of Medicine

THE EFFECTS OF NORMAL AS COMPARED WITH LOW HEMATOCRIT VALUES IN PATIENTS WITH CARDIAC DISEASE WHO ARE RECEIVING HEMODIALYSIS AND EPOETIN

Anatole Besarab, M.D., W. Kline Bolton, M.D., Jeffrey K. Browne, Ph.D., Joan C. Egrie, Ph.D., Allen R. Nissenson, M.D., Douglas M. Okamoto, Ph.D., Steve J. Schwab, M.D., and David A. Goodkin, M.D.

A total of 1233 patients were enrolled ; 618 were assigned to the normal-hematocrit group, and 615 to the low-hematocrit group.

The primary end point was the length of time to death or a first nonfatal myocardial infarction.

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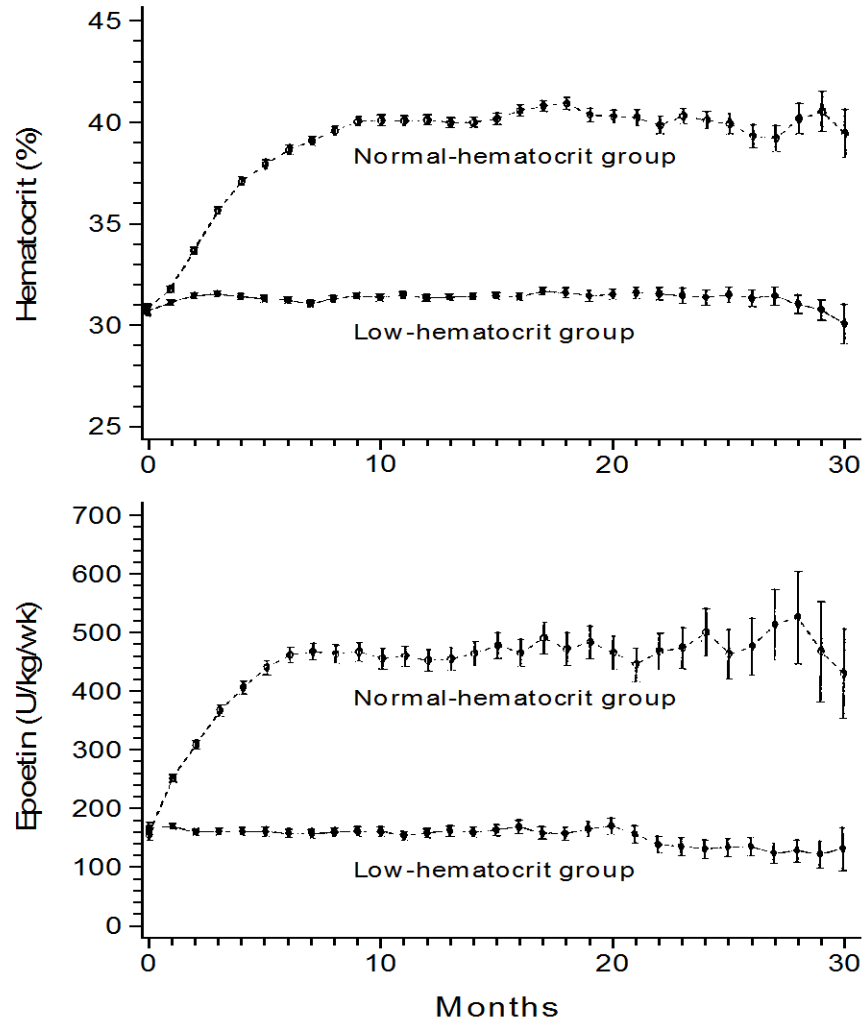

Figure 1. Mean Monthly Hematocrit Values and Epoetin Doses during the Study in the Normal-Hematocrit and Low-Hematocrit Groups.

Both the mean hematocrit values and the mean doses were significantly different between the two groups from one month onward ($P < 0.001$). I bars indicate 95 percent confidence intervals of the mean.

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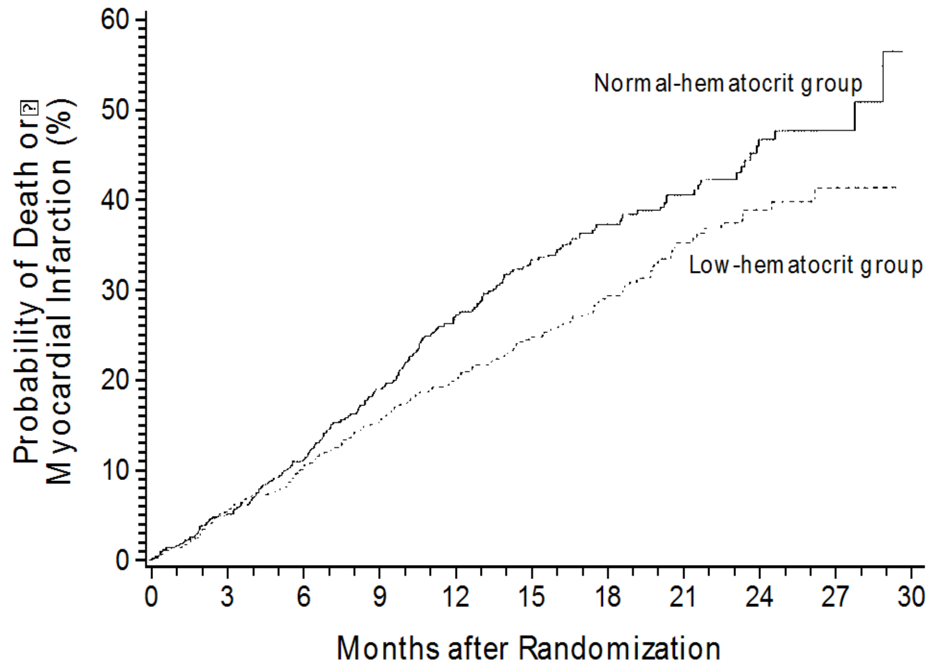
NORMAL VS. LOW HEMATOCRIT IN PATIENTS WITH CARDIAC DISEASE RECEIVING HEMODIALYSIS AND EPOETIN



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

Figure 2. Kaplan–Meier Estimates of the Probability of Death or a First Nonfatal Myocardial Infarction in the Normal-Hematocrit and Low-Hematocrit Groups.

Risk ratio, 1.3; 95 percent confidence interval, 0.9 to 1.9

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The study was halted when differences in mortality between the groups were recognized as sufficient to make it very unlikely that continuation of the study would reveal a benefit for the normal hematocrit group and the results were nearing the statistical boundary of a higher mortality rate in the normal-hematocrit group .

TABLE 3. INCIDENCE OF SEVEN SECONDARY END POINTS.

END POINT	NORMAL-HEMATOCRIT GROUP (N=618)	LOW-HEMATOCRIT GROUP (N=615)	P VALUE*
	no. (%)		
Red-cell transfusion	129 (21)	192 (31)	<0.001
Hospitalization for all causes	445 (72)	425 (69)	0.29
Congestive heart failure requiring hospitalization	80 (13)	90 (15)	0.41
Angina pectoris requiring hospitalization	78 (13)	76 (12)	0.93
Coronary-artery bypass grafting	20 (3)	21 (3)	0.88
Nonfatal myocardial infarction	19 (3)	14 (2)	0.48
Percutaneous transluminal coronary angioplasty	17 (3)	15 (2)	0.86

Conclusions In patients with clinically evident congestive heart failure or ischemic heart disease who are receiving hemodialysis, administration of epoetin to raise their hematocrit to 42 percent is not recommended. (N Engl J Med 1998;339:584-90.)

The incidence of thrombosis of the vascular access sites was higher in the normal hematocrit group than in the low-hematocrit group (243 patients, or 39 percent, vs. 176 patients, or 29 percent; P=0.001).

Both synthetic grafts and natural fistulas clotted more often in the normal hematocrit group.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

Ajay K. Singh, M.B., B.S., Lynda Szczech, M.D., Kezhen L. Tang, Ph.D., Huiman Barnhart, Ph.D., Shelly Sapp, M.S., Marsha Wolfson, M.D., and Donal Reddan, M.B., B.S., for the CHOIR Investigators*

Methods

In this open-label trial, we studied 1432 patients with chronic kidney disease, 715 of whom were randomly assigned to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 13.5 g per deciliter and 717 of whom were assigned to receive a dose targeted to achieve a level of 11.3 g per deciliter

The primary end point was a composite of death, myocardial infarction, hospitalization for congestive heart failure (without renal replacement therapy), and stroke.

The study was terminated early.

N ENGL J MED 355;20 WWW.NEJM.ORG NOVEMBER 16, 2006

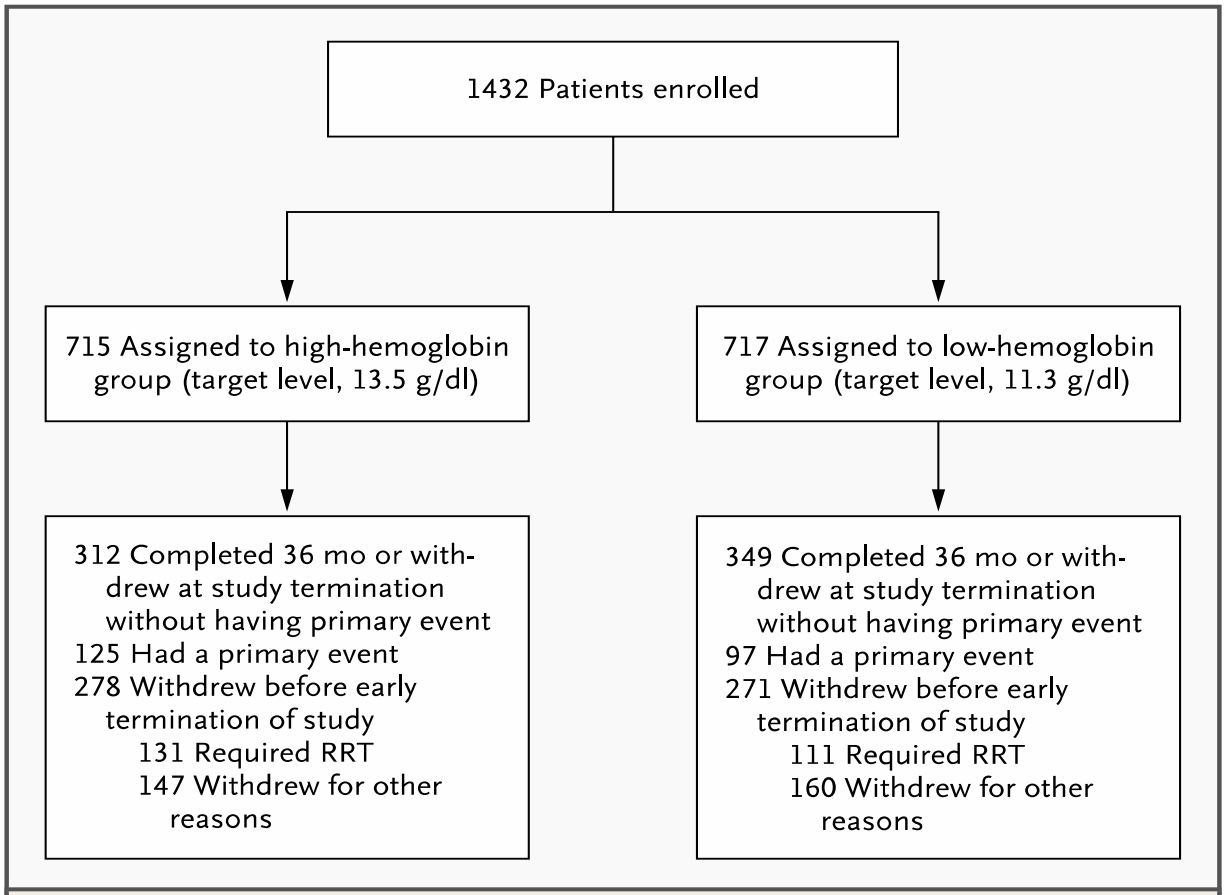

Figure 1. Enrollment and Outcomes.

A total of 1432 patients were enrolled; 715 were assigned to the high-hemoglobin group (with a target level of 13.5 g per deciliter), and 717 were assigned to the low-hemoglobin group (with a target level of 11.3 g per deciliter). In addition to the stated reasons for withdrawal from the study, other reasons included a request from a patient, an investigator, or the study sponsor; pregnancy; an adverse event; a protocol violation; or a loss to follow-up. RRT denotes renal replacement therapy.

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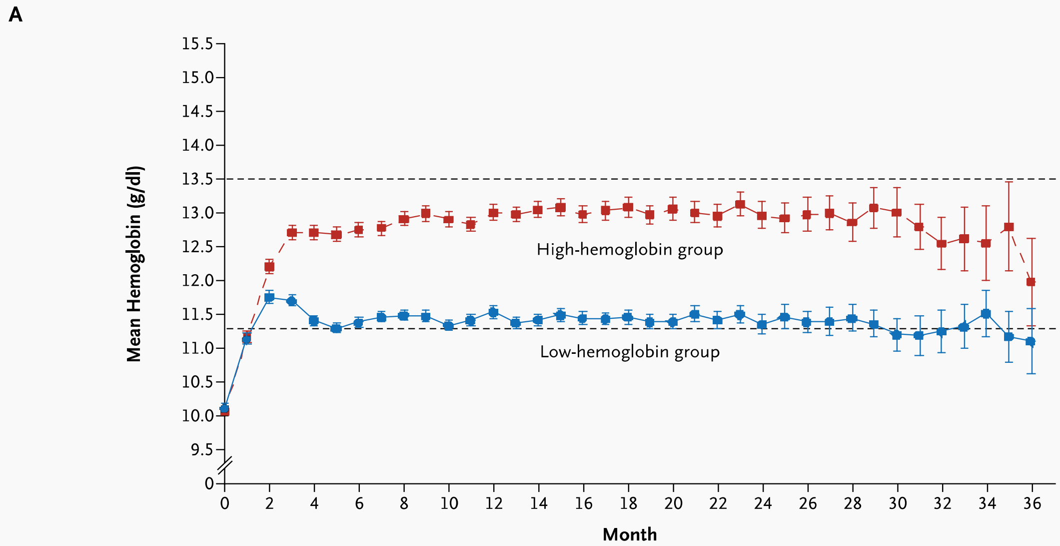
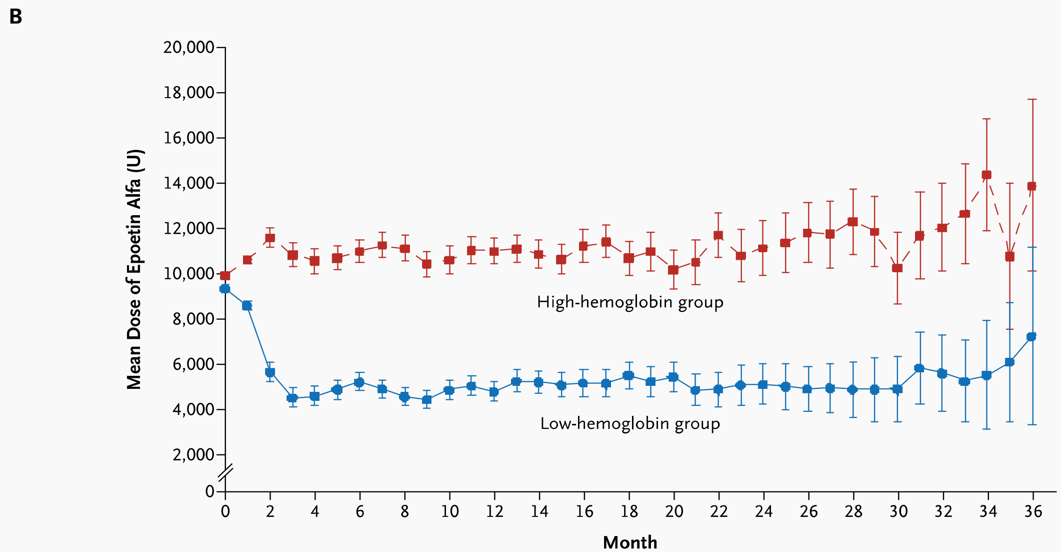


No. of Patients

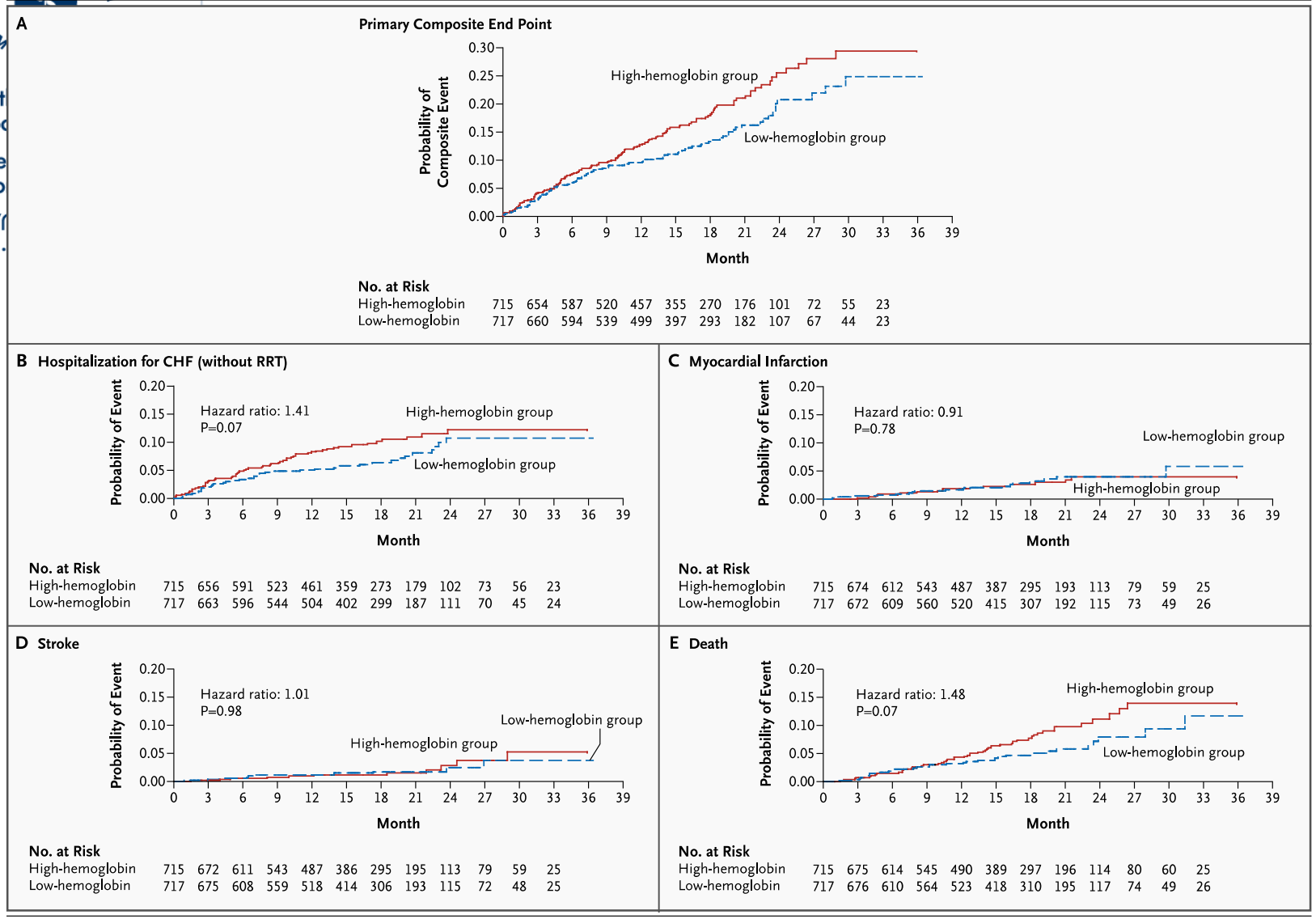
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
High-hemoglobin	710	667	632	600	558	507	485	433	367	306	252	194	139	95	81	67	49	31	13
Low-hemoglobin	707	672	625	603	549	528	510	471	384	334	250	182	141	101	75	60	45	30	13



No. of Patients

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
High-hemoglobin	709	693	659	623	578	530	500	452	370	310	258	189	132	97	79	65	52	27	11
Low-hemoglobin	707	691	655	621	577	549	526	479	393	333	262	189	141	95	73	54	43	27	12

hazard ratio, 1.34; 95% confidence interval, 1.03 to 1.74; P=0.03



N ENGL J MED 355;20 WWW.NEJM.ORG NOVEMBER 16, 2006

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Table 2. Secondary End Points.*

End Point	High-Hemoglobin Group (N=715)	Low-Hemoglobin Group (N=717)	Hazard Ratio (95% CI)	P Value†
	no. of patients (%)			
Clinical results				
Components of the primary end point‡				
Death	52 (7.3)	36 (5.0)	1.48 (0.97–2.27)	0.07
Hospitalization for congestive heart failure (without renal replacement therapy)	64 (9.0)	47 (6.6)	1.41 (0.97–2.05)	0.07
Myocardial infarction	18 (2.5)	20 (2.8)	0.91 (0.48–1.73)	0.78
Stroke	12 (1.7)	12 (1.7)	1.01 (0.45–2.25)	0.98
Renal replacement therapy				
Any renal replacement therapy§	155 (21.7)	134 (18.7)	1.19 (0.94–1.49)	0.15
Hospitalization for renal replacement therapy	99 (13.8)	81 (11.3)	1.25 (0.93–1.68)	0.13
Hospitalization				
Cardiovascular causes	233 (32.6)	197 (27.5)	1.23 (1.01–1.48)	0.03
Any cause	369 (51.6)	334 (46.6)	1.18 (1.02–1.37)	0.03
	High-Hemoglobin Group		**Low-Hemoglobin Group**	**P Value¶**
	Baseline	Change from Baseline‖	Baseline	Change from Baseline**	
Quality of life††					
LASA score					
Energy	38.1±23.7	16.6±28.6	38.2±23.1	15.5±28.6	0.67
Activity	40.8±25.9	15.0±39.9	42.5±25.8	13.3±29.8	0.98
Overall quality of life	46.3±26.2	11.2±29.7	46.1±25.4	11.9±28.1	0.46
KDQ total score	20.3±5.8	1.6±5.6	20.6±6.0	1.1±5.6	0.26
SF-36 score					
Physical function	41.9±28.2	3.2±24.0	42.4±27.3	2.1±23.3	0.49
Physical role	31.9±38.9	6.4±40.7	32.5±39.2	7.5±43.2	0.32
Pain	57.8±28.5	0.4±28.1	58.0±27.1	2.4±26.7	0.15
General health	41.3±20.1	3.0±19.2	42.6±20.1	1.8±17.8	0.87
Vitality	35.2±22.6	10.0±23.8	36.6±22.4	8.2±20.6	0.58
Social function	63.7±29.5	1.3±33.1	63.7±29.0	3.5±28.7	0.16
Emotional role	57.2±43.6	0.8±48.3	57.4±43.3	5.9±48.1	0.01
Mental health	69.6±19.5	1.7±18.5	70.2±20.1	2.4±18.2	0.31

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CONCLUSIONS

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.

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2006 VOL. 355 NO. 20

Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia

Tilman B. Drüeke, M.D., Francesco Locatelli, M.D., Naomi Clyne, M.D., Kai-Uwe Eckardt, M.D., Iain C. Macdougall, M.D., Dimitrios Tsakiris, M.D., Hans-Ulrich Burger, Ph.D., and Armin Scherhag, M.D., for the CREATE Investigators*

METHODS

We randomly assigned 603 patients with an estimated glomerular filtration rate (GFR) of 15.0 to 35.0 ml per minute per 1.73 m^2 of body-surface area and mild-to-moderate anemia (hemoglobin level, 11.0 to 12.5 g per deciliter) to a target hemoglobin value in the normal range (13.0 to 15.0 g per deciliter, group 1) or the subnormal range (10.5 to 11.5 g per deciliter, group 2). Subcutaneous erythropoietin (epoetin beta) was initiated at randomization (group 1) or only after the hemoglobin level fell below 10.5 g per deciliter (group 2). The primary end point was a composite of eight cardiovascular events; secondary end points included left ventricular mass index, quality-of-life scores, and the progression of chronic kidney disease.

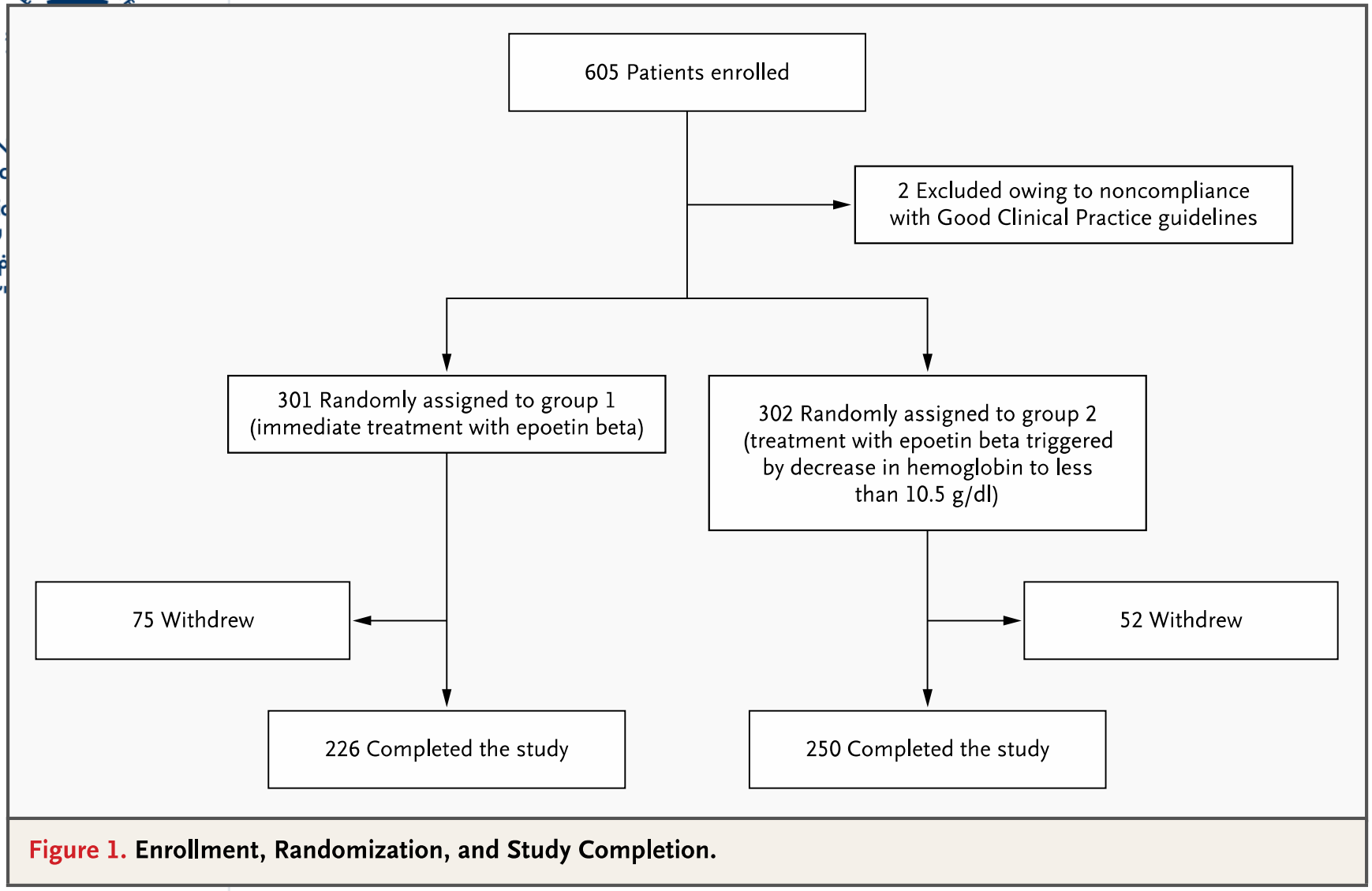

Figure 1. **Enrollment, Randomization, and Study Completion.**

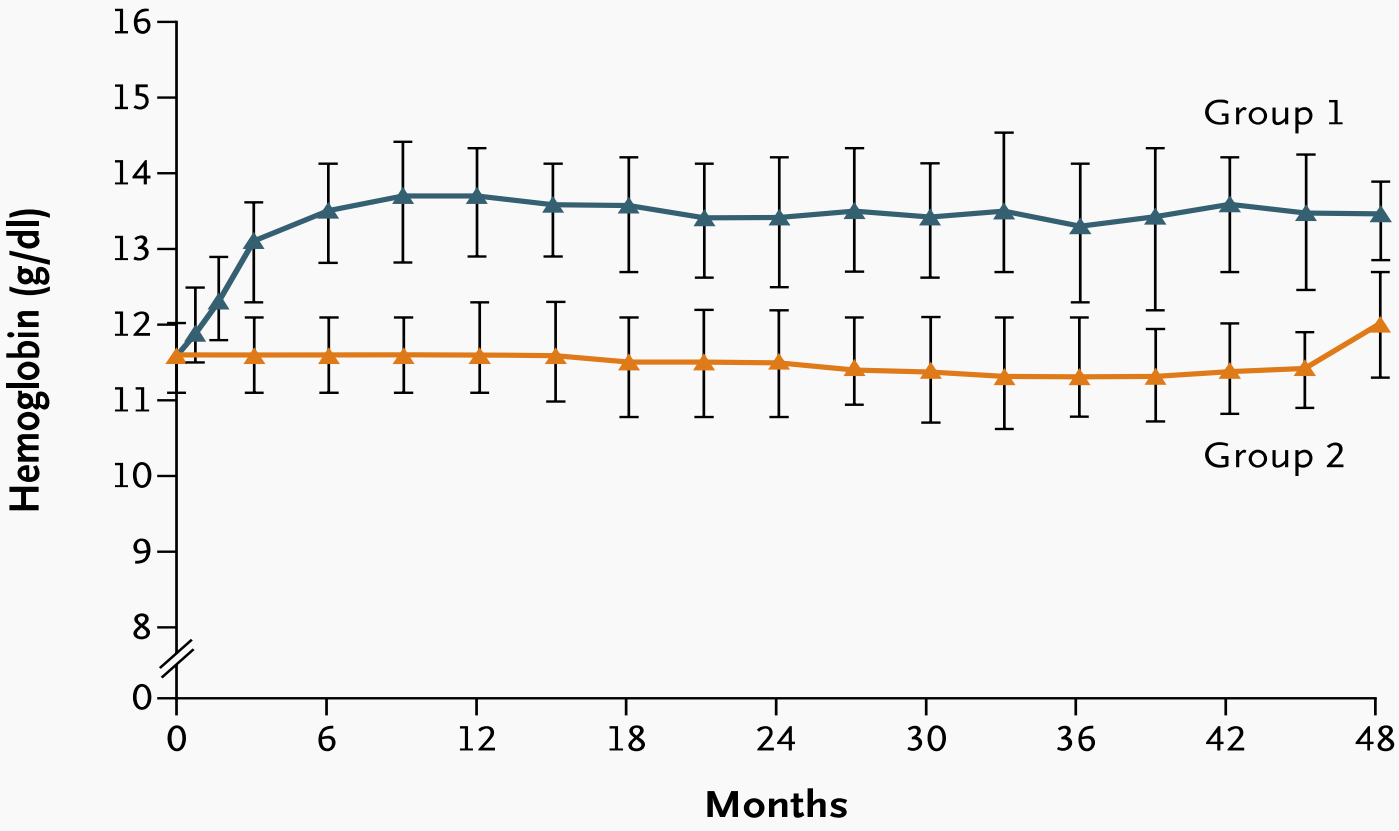

Figure 2. Median Hemoglobin Levels in the Intention-to-Treat Population during the Study.

I bars indicate standard deviations.

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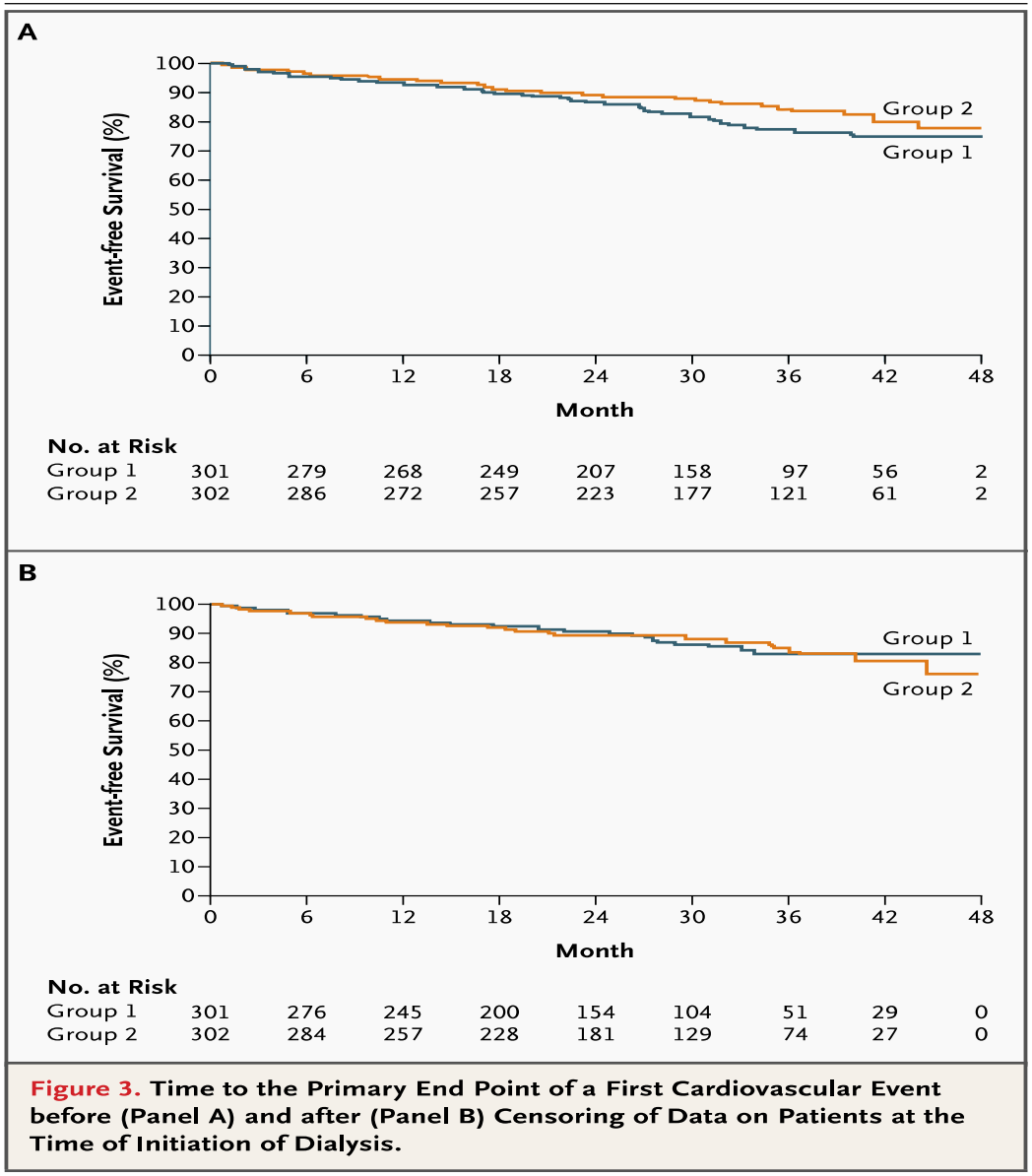

Figure 3. **Time to the Primary End Point of a First Cardiovascular Event before (Panel A) and after (Panel B) Censoring of Data on Patients at the Time of Initiation of Dialysis.**

hazard ratio, 0.78; 95% confidence interval, 0.53 to 1.14; P=0.20

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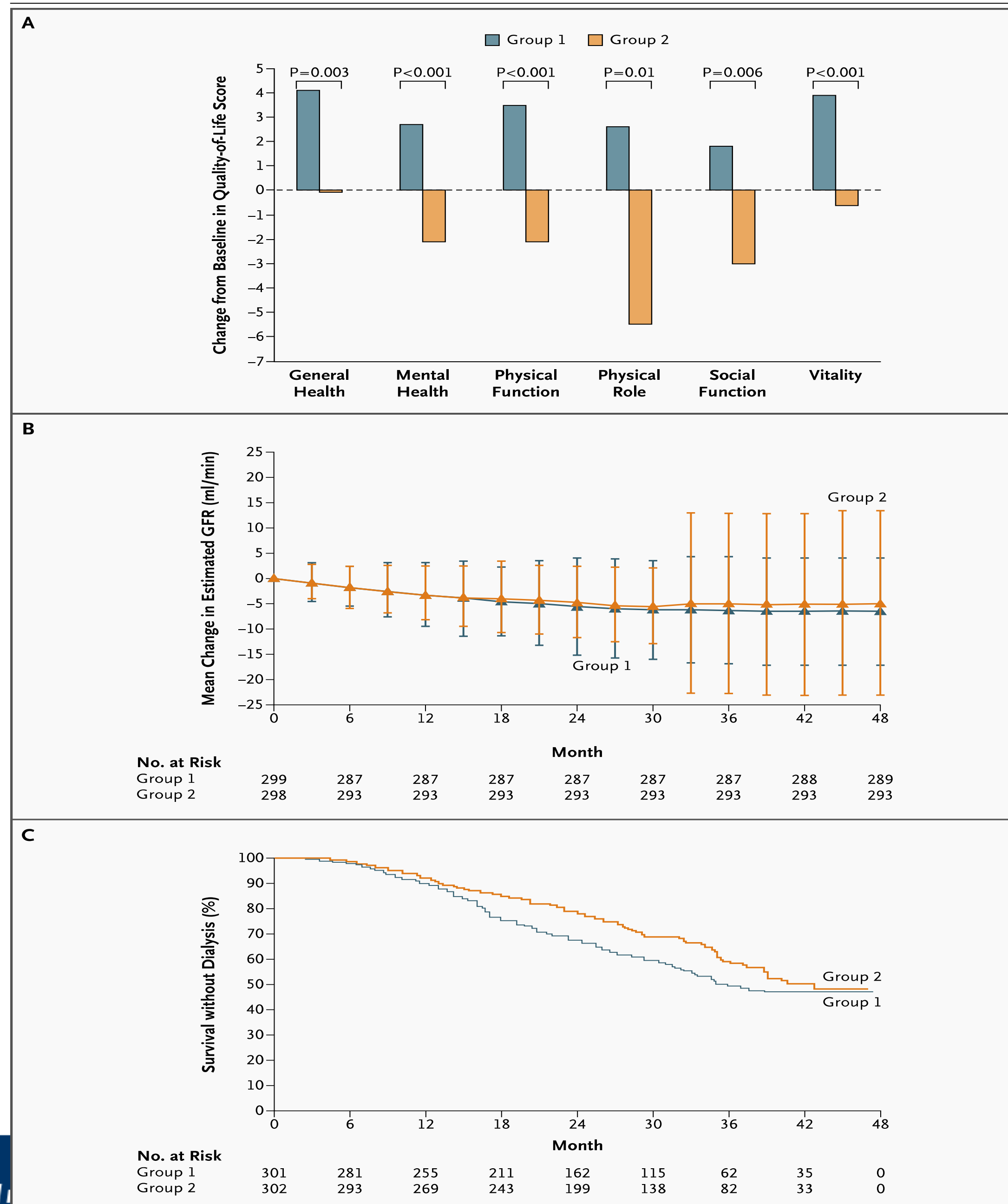

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CONCLUSIONS

In patients with chronic kidney disease, early complete correction of anemia does not reduce the risk of cardiovascular events.

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The NEW ENGLAND JOURNAL of MEDICINE

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

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D., Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D., Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D., John J.V. McMurray, M.D., Patrick Parfrey, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D., Ajay K. Singh, M.D., Scott D. Solomon, M.D., and Robert Toto, M.D., for the TREAT Investigators*

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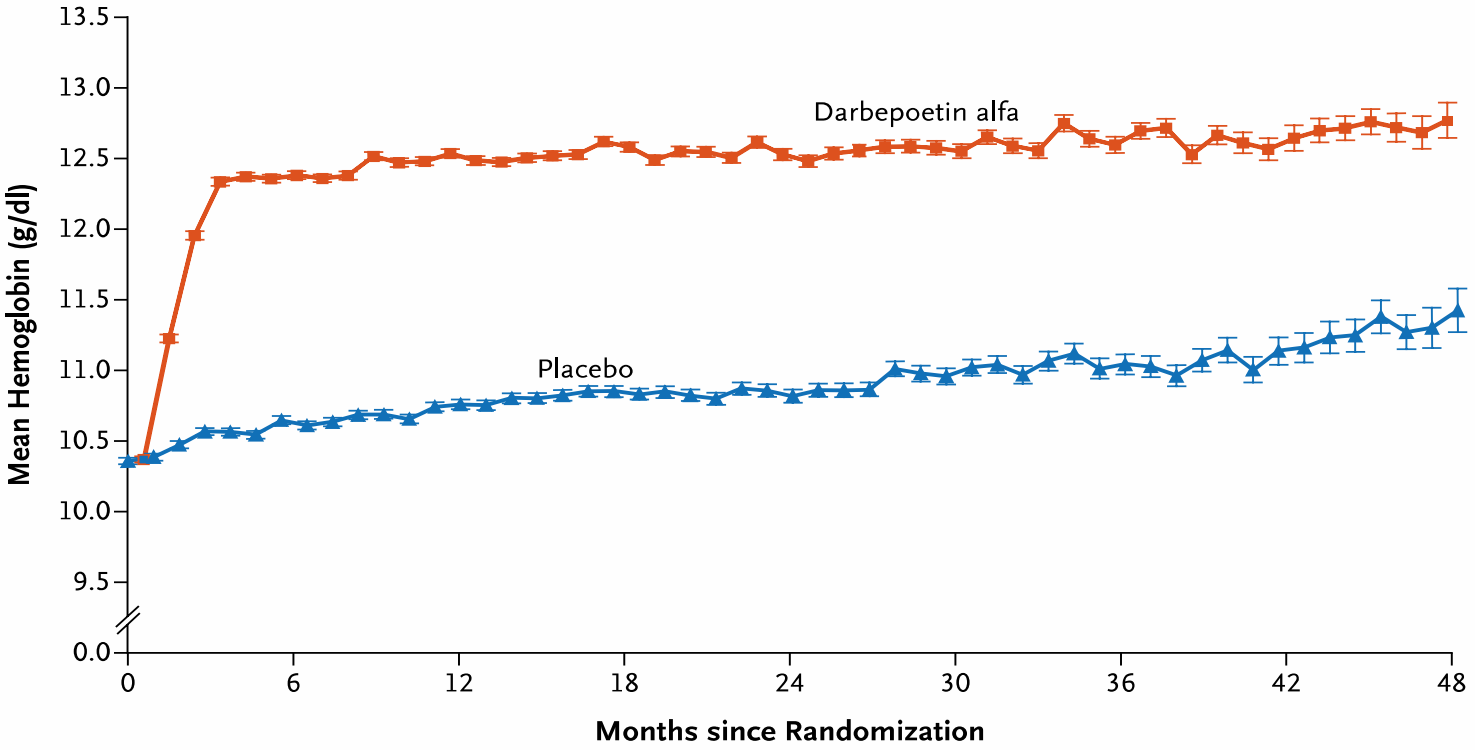
METHODS

In this study involving 4038 patients with diabetes, chronic kidney disease, and anemia, we randomly assigned 2012 patients to darbepoetin alfa to achieve a hemoglobin level of approximately 13 g per deciliter and 2026 patients to placebo, with rescue darbepoetin alfa when the hemoglobin level was less than 9.0 g per deciliter. The primary end points were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease.



No. of Patients									
Darbepoetin alfa	2004	1768	1503	1300	946	635	404	253	97
Placebo	2019	1742	1460	1221	887	620	356	216	79

Figure 1. Mean Hemoglobin Levels through 48 Months among Patients Who Were Assigned to Receive Darbepoetin Alfa or Placebo.

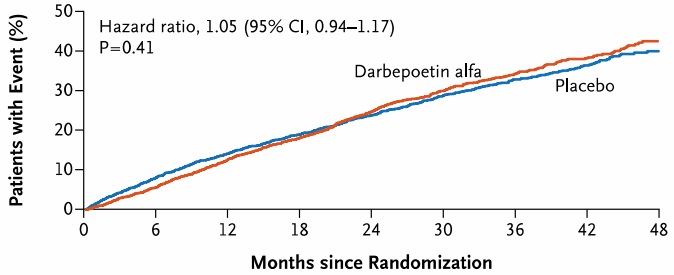
I bars represent standard errors.

Table 2. Composite and Component End Points.*

End Point	Darbepoetin Alfa (N=2012)	Placebo (N=2026)	Hazard Ratio (95% CI)	P Value†
	number (percent)			
Primary end points				
Cardiovascular composite end point‡	632 (31.4)	602 (29.7)	1.05 (0.94–1.17)	0.41
Death from any cause	412 (20.5)	395 (19.5)	1.05 (0.92–1.21)	0.48
Myocardial infarction§	124 (6.2)	129 (6.4)	0.96 (0.75–1.22)	0.73
Stroke§	101 (5.0)	53 (2.6)	1.92 (1.38–2.68)	<0.001
Heart failure§	205 (10.2)	229 (11.3)	0.89 (0.74–1.08)	0.24
Myocardial ischemia	41 (2.0)	49 (2.4)	0.84 (0.55–1.27)	0.40
Renal composite end point (ESRD or death)	652 (32.4)	618 (30.5)	1.06 (0.95–1.19)	0.29
ESRD	338 (16.8)	330 (16.3)	1.02 (0.87–1.18)	0.83
Additional adjudicated end points				
Death from cardiovascular causes	259 (12.9)	250 (12.3)	1.05 (0.88–1.25)	0.61
Cardiac revascularization	84 (4.2)	117 (5.8)	0.71 (0.54–0.94)	0.02

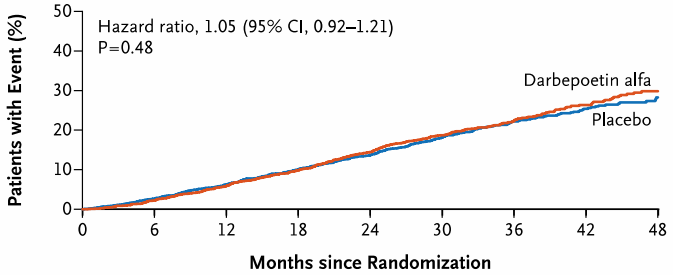
* ESRD denotes end-stage renal disease.
† P values have not been adjusted for multiple comparisons.
‡ A patient may have had multiple cardiovascular events of different types. The cardiovascular composite end point reflects only the first occurrence of any of the components.
§ This category includes both fatal and nonfatal events.

A Cardiovascular Composite End Point



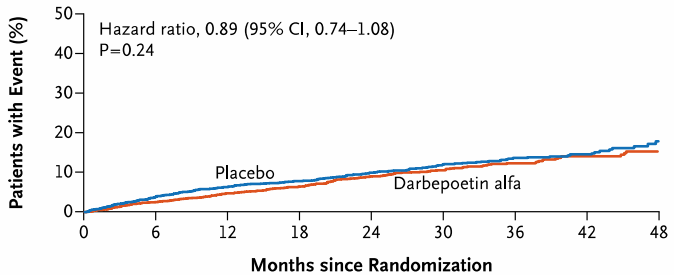
No. at Risk									
Darbepoetin alfa	2012	1882	1717	1515	1180	817	551	318	130
Placebo	2026	1836	1687	1487	1178	834	529	319	122

B Death from Any Cause



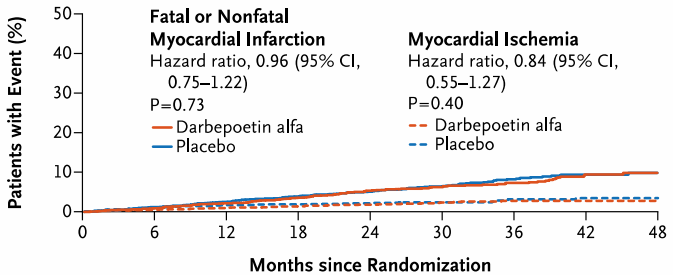
No. at Risk									
Darbepoetin alfa	2012	1947	1847	1659	1337	945	655	386	164
Placebo	2026	1943	1839	1652	1345	970	636	385	156

C Fatal or Nonfatal Congestive Heart Failure



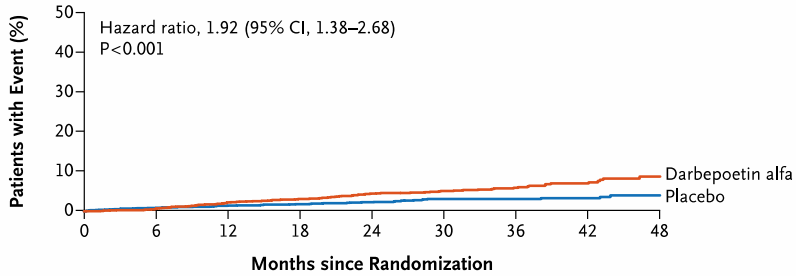
No. at Risk									
Darbepoetin alfa	2012	1890	1742	1525	1191	819	555	319	136
Placebo	2026	1859	1702	1495	1187	835	519	307	115

D Fatal or Nonfatal Myocardial Infarction and Myocardial Ischemia



No. at Risk									
Fatal or Nonfatal Myocardial Infarction									
Darbepoetin alfa	2012	1920	1785	1566	1232	851	577	325	137
Placebo	2026	1907	1765	1550	1235	863	539	324	123
Myocardial Ischemia									
Darbepoetin alfa	2012	1924	1794	1583	1255	869	597	347	146
Placebo	2026	1906	1767	1561	1251	880	556	338	132

E Fatal or Nonfatal Stroke



No. at Risk									
Darbepoetin alfa	2012	1923	1787	1581	1247	863	590	341	141
Placebo	2026	1914	1783	1575	1262	886	561	338	132

CONCLUSIONS

The use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who were not undergoing dialysis did not reduce the risk of either of the two primary composite outcomes (either death or a cardiovascular event or death or a renal event) and was associated with an increased risk of stroke. For many persons involved in clinical decision making, this risk will outweigh the potential benefits. (ClinicalTrials.gov number, NCT00093015.)

N ENGL J MED 361;21 NEJM.ORG NOVEMBER 19, 2009

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Among patients with a history of a malignant condition at baseline, there were 60 deaths from any cause in the 188 patients assigned to darbepoetin alfa and 37 deaths in the 160 patients assigned to placebo (P = 0.13).

In this subgroup, 14 of the 188 patients assigned to darbepoetin alfa died from cancer, as compared with 1 of the 160 patients assigned to placebo (P=0.002).

Venous thromboembolic events were reported in 41 patients in the darbepoetin alfa group (2.0%), as compared with 23 patients in the placebo group (1.1%) (P = 0.02). Arterial thrombo-embolic events (some of which were adjudicated as cardiovascular events) were also reported more frequently in the darbepoetin alfa group (in 178 patients [8.9%] vs. 144 patients [7.1%], P = 0.04).

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KDIGO Clinical Practice Guideline

for Anemia in Chronic Kidney Disease

Northern Ontario School of Medicine
École de médecine du Nord de l'Ontario

ESA INITIATION

For adult CKD, not yet on dialysis, with Hb concentration ≥100 g/l, we suggest that ESA therapy not be initiated. (2D)

For adult dialysis patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 90 g/l by starting ESA therapy when the hemoglobin is between 90–100 g/l. (2B)

Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 100 g/l. (Not Graded)

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)

We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(1B), a history of stroke (1B), or a history of malignancy (2C).

Kidney International Supplements (2012) 2, 283–287

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ESA MAINTENANCE THERAPY

In general, we suggest that ESAs not be used to maintain Hb concentration above 115g/l in adult patients with CKD. (2C)

Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 115 g/l and will be prepared to accept the risks. (Not Graded)

In all adult patients, we recommend that ESAs not be used to intentionally increase the Hb concentration above 130 g/l. (1A)

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Learning Objectives

- Identify and discuss diagnosis, pathogenesis and evaluation of anemia in CKD
- Examine the use of erythropoiesis-stimulating agents (ESAs) to treat anemia in CKD and new target levels
- ***Explore the use of iron to treat anemia in CKD and new target levels***

Use of iron to treat anemia in CKD

The two most widely available tests for assessing iron status are the Tsat and serum ferritin level.

A very low serum ferritin (<30 ng/ml) is indicative of iron deficiency.

TSAT and serum ferritin level have only limited sensitivity and specificity in patients with CKD for prediction of bone marrow iron stores and erythropoietic response to iron supplementation.

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KDIGO Clinical Practice Guideline

for Anemia in Chronic Kidney Disease

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Use of iron to treat anemia in CKD

For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD, non dialysis patients alternatively a 1–3 months trial of oral iron therapy) if (2C):

an increase in Hb concentration without starting ESA treatment is desired and TSAT is ≤30% and ferritin is ≤500 ng/ml

For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD, non dialysis patients alternatively a 1–3 months trial of oral iron therapy) if (2C):

an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤30% and ferritin is ≤500 ng/ml

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Use of iron to treat anemia in CKD

Correction of iron deficiency with oral or intravenous iron supplementation can reduce the severity of anemia in patients with CKD.

Untreated iron deficiency is an important cause of hyporesponsiveness to ESA treatment.

Iron supplementation is widely used in CKD patients to treat iron deficiency, prevent its development in ESA- treated patients, raise Hb levels in the presence or absence of ESA treatment, and reduce ESA doses in patients receiving ESA treatment.

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Take Home messages

There is no convincing evidence that the active increase of Hb towards concentrations in the normal range leads to demonstrable benefit in adult patients with CKD.

Latest KDIGO guideline suggests not to exceed in general a Hb limit of 115 g/l.

Always treat iron deficiency and other causes for anemia first.

Iron deficiency causes bone marrow hyporesponsiveness to erythropoetic agents.

The cut off for ferritin to diagnose iron deficiency is higher in CKD patients. Don't forget that ferritin is an acute phase reactant and can be high despite iron deficiency.

Kidney International Supplements (2012) 2, 283–287

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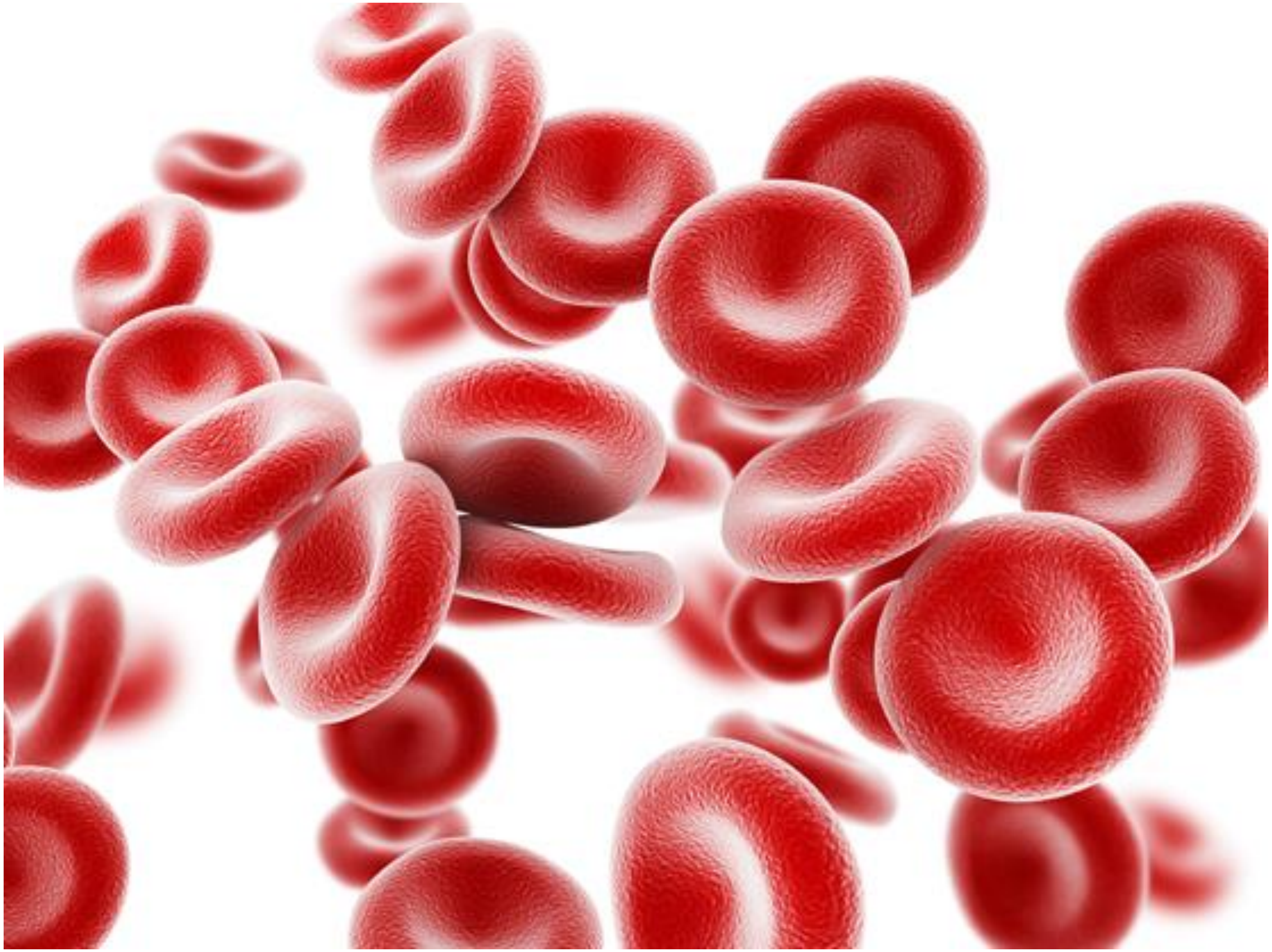

QUESTIONS ?

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Reference Keys

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1**, **Level 2**, or **Not Graded**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

	Implications		
Grade*	Patients	Clinicians	Policy
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.