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

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ABSTRACT

BACKGROUND

Whether correction of anemia in patients with stage 3 or 4 chronic kidney disease improves cardiovascular outcomes is not established.

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 m² 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.

RESULTS

During the 3-year study, complete correction of anemia did not affect the likelihood of a first cardiovascular event (58 events in group 1 vs. 47 events in group 2; hazard ratio, 0.78; 95% confidence interval, 0.53 to 1.14; P=0.20). Left ventricular mass index remained stable in both groups. The mean estimated GFR was 24.9 ml per minute in group 1 and 24.2 ml per minute in group 2 at baseline and decreased by 3.6 and 3.1 ml per minute per year, respectively (P=0.40). Dialysis was required in more patients in group 1 than in group 2 (127 vs. 111, P=0.03). General health and physical function improved significantly (P=0.003 and P<0.001, respectively, in group 1, as compared with group 2). There was no significant difference in the combined incidence of adverse events between the two groups, but hypertensive episodes and headaches were more prevalent in group 1.

CONCLUSIONS

In patients with chronic kidney disease, early complete correction of anemia does not reduce the risk of cardiovascular events. (ClinicalTrials.gov number, NCT00321919.)

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ANEMIA IS A COMMON COMPLICATION OF chronic kidney disease. However, the optimal target hemoglobin levels for patients with various stages of chronic kidney disease are unclear. Anemia is strongly predictive of complications and death from cardiovascular causes in patients with chronic kidney disease.[1] Observational data indicate that correction of anemia is associated with improved outcomes.[1-8] However, the normalization of hemoglobin in prospective trials involving patients receiving hemodialysis did not improve left ventricular indexes or decrease the risk of death.[9-11]

Among patients with chronic kidney disease, the effect of correction of anemia may differ between those who require dialysis and those who do not. The latter group generally has less advanced cardiovascular disease and no risk of dialysis-related increases in hemoglobin or vascular access thrombosis. Several observational and small interventional studies of patients with chronic kidney disease who were not receiving dialysis reported an inverse relation between hemoglobin levels and cardiovascular outcomes.[12-14] However, two recent randomized studies did not confirm that left ventricular mass decreased in response to complete correction of anemia.[15,16]

In the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial, we tested the hypothesis that complete correction of anemia in patients with stage 3 or 4 chronic kidney disease improves cardiovascular outcomes as compared with partial correction of anemia.

METHODS

The trial was designed, implemented, and overseen by the steering committee together with representatives of the sponsor, F. Hoffmann–La Roche. The sponsor was responsible for monitoring the centers and the data collection and for checking the quality of the data. The sponsor also conducted all statistical analyses and holds the data. The members of the steering committee had access to all the study data, which they analyzed in close collaboration with the sponsor. The initial manuscript was prepared by Drs. Drüeke and Scherhag and underwent several revisions with contributions from all coauthors. An independent data and safety monitoring board (see the Appendix) reviewed the data regularly. All cardiovascular end points were reviewed and adjudicated by an end-point committee (see the Appendix) whose members were unaware of the group assignments of the patients.

STUDY POPULATION

Eligible patients were enrolled at 94 centers in 22 countries. The study began in July 2000 and ended in November 2004, 2 years after enrollment of the last patient. Patients older than 18 years were eligible for inclusion if they had mild-to-moderate chronic anemia (hemoglobin level, 11.0 to 12.5 g per deciliter) related to their chronic kidney disease, an estimated glomerular filtration rate (GFR) of 15.0 to 35.0 ml per minute per 1.73 m² of body-surface area (calculated with the use of the Cockcroft–Gault formula), and a blood pressure of 170/95 mm Hg or less. The use of antihypertensive treatment to achieve the target blood pressure was encouraged. Major exclusion criteria were an anticipated need for renal replacement therapy within 6 months, advanced cardiovascular disease (as defined by a diagnosis of clinically significant valvular disease, congestive heart failure, myocardial infarction, unstable angina, or stroke within the preceding 3 months), nonrenal causes of anemia, receipt of blood transfusions within the preceding 3 months, a serum ferritin level of less than 50 ng per milliliter, a C-reactive protein level exceeding 15 mg per liter, and previous treatment with erythropoietin.

All patients provided written informed consent. The study protocol was approved by local ethics committees. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

STUDY PROTOCOL

This was an open-label, randomized, two-group study with a parallel-group design. The primary objective was to investigate the effect on complications from cardiovascular causes of early treatment with subcutaneous erythropoietin (epoetin beta [NeoRecormon, F. Hoffmann–La Roche]) to normalize hemoglobin values (target level, 13.0 to 15.0 g per deciliter; group 1), as compared with treatment to partially correct anemia (target level, 10.5 to 11.5 g per deciliter; group 2). Secondary study objectives included the investigation of the effects of these treatments on the left ventricular

mass index, the progression of chronic kidney disease, and the quality of life. The study design and other details of the study protocol have been published elsewhere.[17]

Patients were randomly assigned (at a 1:1 ratio) to receive either immediate treatment with epoetin beta in order to reach a target hemoglobin level of 13.0 to 15.0 g per deciliter (group 1) or treatment with epoetin beta only after the hemoglobin level had decreased to less than 10.5 g per deciliter (group 2). Patients in group 2 were to maintain a hemoglobin level of 10.5 to 11.5 g per deciliter. The starting dose of epoetin beta was 2000 IU, and the treatment was administered subcutaneously once weekly with the use of an automatic pen device (Reco-Pen). Dose adjustments to achieve the target hemoglobin level were permitted. The dose was reviewed every 4 weeks; if the hemoglobin level had increased by less than 0.5 g per deciliter, the dose was increased by 25 to 50%, and if the level had increased by more than 1.0 g per deciliter, the dose was reduced by 25 to 50%. Iron supplementation (intravenous or oral) was recommended at the discretion of the investigators, who were encouraged to follow current clinical practice guidelines. Routine clinical visits were scheduled every 2 weeks during the hemoglobin correc-

tion phase (lasting 3 months) and every 3 months thereafter. Study end points and adverse events were continuously monitored. Follow-up of clinical events continued until the end of the study for all patients, including those undergoing dialysis.

STUDY END POINTS

The primary efficacy end point was the time to a first cardiovascular event, including sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalization for 24 hours or more or prolongation of hospitalization, complication of peripheral vascular disease (amputation or necrosis), or cardiac arrhythmia resulting in hospitalization for 24 hours or more.

Secondary efficacy end points included death from any cause; death from cardiovascular causes; congestive heart failure (according to New York Heart Association [NYHA] class); the need for cardiovascular intervention; hospitalization for any cause; hospitalization for cardiovascular reasons for 24 hours or more or prolongation of hospitalization; changes in left ventricular mass index, left ventricular volume, and left ventricular fractional shortening; time to initiation of renal replacement therapy; changes in nutritional status, as reflect-
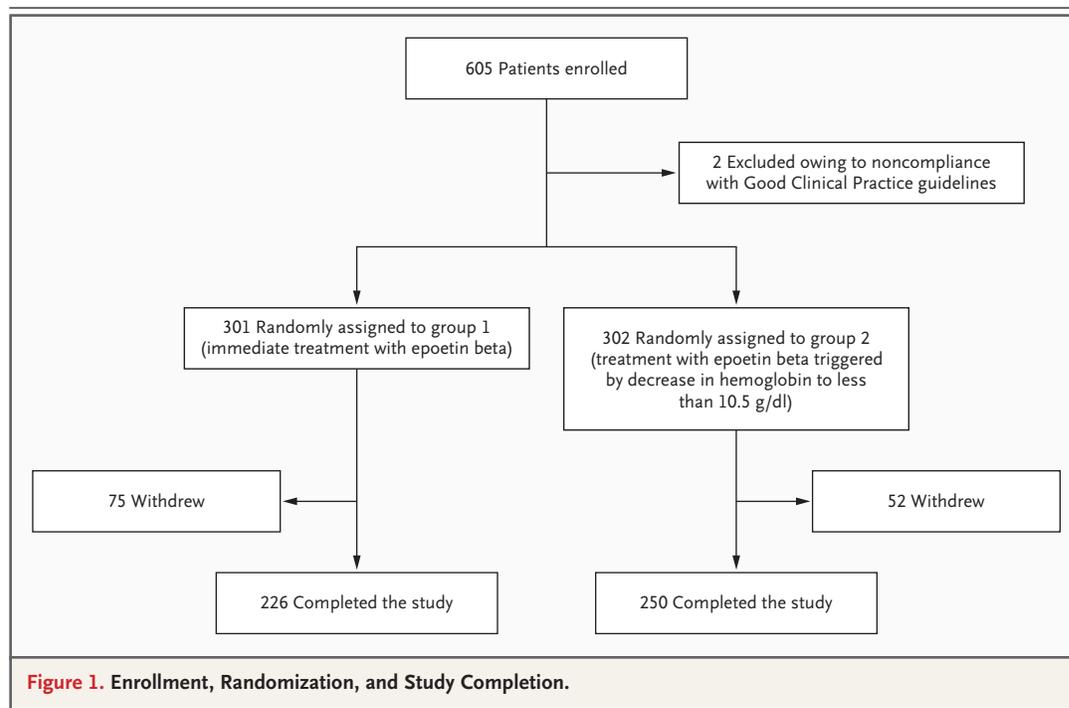

Figure 1. Enrollment, Randomization, and Study Completion.

605 Patients enrolled

2 Excluded owing to noncompliance with Good Clinical Practice guidelines

301 Randomly assigned to group 1 (immediate treatment with epoetin beta)

302 Randomly assigned to group 2 (treatment with epoetin beta triggered by decrease in hemoglobin to less than 10.5 g/dl)

75 Withdrew

52 Withdrew

226 Completed the study

250 Completed the study

Table 1. Demographic and Baseline Characteristics.*

Characteristic	Group 1 (N = 301)	Group 2 (N = 302)	P Value
Weight (kg)	74.7±15.6	71.8±14.2	0.05
Body-mass index	26.6±4.5	26.2±4.8	0.42
Age — yr	59.3±14.6	58.8±13.7	0.36
Male sex — no. (%)	171 (57)	154 (51)	0.16
Estimated GFR — ml/min†	24.9±6.3	24.2±6.0	0.30
Cause of chronic kidney disease — no. of patients (%)			
Glomerulonephritis	62 (21)	71 (24)	0.43
Hypertensive renal disease	69 (23)	57 (19)	0.23
Diabetic nephropathy	61 (20)	63 (21)	0.91
Polycystic kidney disease	37 (12)	39 (13)	0.88
Pyelonephritis	22 (7)	21 (7)	0.92
Interstitial nephritis	22 (7)	16 (5)	0.35
Other	52 (17)	56 (19)	0.74
Unknown	15 (5)	15 (5)	0.94
Diabetes mellitus — no. of patients (%)	80 (27)	77 (25)	0.64
Insulin-dependent	13 (4)	10 (3)	0.58
Dyslipidemia — no. of patients (%)	119 (40)	93 (31)	0.23
Hypertension — no. of patients (%)‡	275 (91)	269 (89)	0.38
Blood pressure — mm Hg			
Systolic	139±17	139±16	0.87
Diastolic	79±10	80±9	0.28
Receipt of at least one antihypertensive agent — no. of patients (%)†	287 (96)	272 (90)	0.16
Angiotensin converting–enzyme inhibitors	152 (51)	142 (47)	0.39
Angiotensin II–receptor blockers	57 (19)	66 (22)	0.41
Beta-blockers	130 (43)	102 (34)	0.02
Calcium-channel blockers	155 (52)	156 (52)	0.97
Alpha-blockers	50 (17)	41 (14)	0.32
Loop diuretics	145 (48)	127 (42)	0.13
Thiazide or other diuretic	27 (9)	28 (9)	0.96

ed by the body-mass index (the weight in kilograms divided by the square of the height in meters), serum albumin level, and C-reactive protein level; changes in the quality of life, according to the score for the 36-item Medical Outcomes Study Short-Form Health Survey (SF-36), on which scores for each subscale range from 0 to 100, with higher scores indicating better health[18]; changes in hemoglobin levels; changes in the weekly epoetin dose; the need for dialysis; the need for transfusion; and decrease in the estimated GFR, which was estimated with the use of the Cockcroft–Gault equation and the simplified Modification of Diet in Renal Disease IV study equation (see the glossary in the Supplementary Appendix, available with the full text of this article at www.nejm.org).

ECHOCARDIOGRAPHIC ASSESSMENT

Standard echocardiography was performed according to the guidelines of the American Society of Echocardiography[19,20] at baseline and then annually or at the initiation of dialysis. The results were interpreted in an independent echocardiographic

Table 1. (Continued.)

Characteristic	Group 1 (N = 301)	Group 2 (N = 302)	P Value
Preexisting cardiovascular disease — no. of patients (%)§	280 (93)	278 (92.1)	0.71
Chronic heart failure	93 (33)	87 (31)	0.61
Previous myocardial infarction	3 (1)	4 (1)	0.85
Cerebrovascular disease	10 (4)	6 (2)	0.37
Coronary artery disease	9 (3)	10 (4)	0.91
Peripheral vascular disease	6 (2)	5 (2)	0.88
NYHA class — no. of patients (%)			
0	167 (55)	149 (49)	0.14
I	37 (12)	43 (14)	0.52
II	53 (18)	44 (15)	0.34
Echocardiographic variables			
Left ventricular volume — ml			
Mean	67.7±19.2	65.1±19.2	0.17
Median	64.0	62.7	
Left ventricular mass index — g/m^2			
Mean	120.3±35.0	118.0±34.3	0.44
Median	116.0	113.0	
Hemoglobin — g/dl	11.6±0.6	11.6±0.6	0.89
Serum ferritin — ng/ml			
Mean	174.4±148.3	189.4±157.7	0.56
Median	131.1	128.3	
Transferrin saturation — %			
Mean	25.6	38.1	0.59
Median	23.9	25.1	

* Plus–minus values are means ±SD.
† The percentages are the number of patients divided by the total number of patients receiving at least one dose of epoetin beta (300 in group 1 and 302 in group 2).
‡ Hypertension was defined as systolic blood pressure of more than 160 mm Hg.
§ For the subcategories, the percentages are the number of patients divided by the total number of patients with preexisting cardiovascular disease, excluding hypertension.

core laboratory by staff members who were unaware of the patient's target hemoglobin range. Left ventricular hypertrophy was defined as a left ventricular mass index greater than 100 g per square meter of body-surface area in women and greater than 130 g per square meter in men.

STATISTICAL ANALYSIS

We calculated that 600 patients would need to be enrolled for the study to have a statistical power of 80% to detect a significant difference in the primary end point between the two groups, given an annual incidence of the primary end point of 15% among patients in group 2[21] and a significance level of 5% with the use of a two-sided log-rank test. Randomization was performed centrally with the use of a dynamic randomization method including a random element of 30% and stratification according to study site, previous cardiovascular risk, and estimated GFR. With a recruitment period of 2 years and a follow-up period of another 2 years, we calculated that 200 events would have to occur in order to show, with a statistical power of 80%, a reduction in the hazard ratio for a first cardiovascular event by one third. The study followed a sequential design, with interim analyses adjusted for multiplicity with the use of an O'Brien–Fleming spending function. The study was sched-

uled to end, at the latest, 2 years after the final patient had undergone randomization or after 200 events had occurred.

All analyses followed the intention-to-treat principle. The primary end point — the time to the first cardiovascular event — was adjusted for the presence or absence of underlying cardiovascular disease at baseline and analyzed with the use of the log-rank test. A Cox proportional-hazards model was used to estimate the relative risk (hazard ratio) and the corresponding 95% confidence interval (CI). The times to events were expressed as Kaplan–Meier curves. A similar method was used to analyze secondary end points, time to death from cardiovascular causes, time to death from any cause, and time to dialysis. Analysis of covariance was used for secondary efficacy end points that were continuous variables, with baseline value and treatment as covariates. Data are reported as means ±SD, unless otherwise indicated.

RESULTS

PATIENTS AND BASELINE CHARACTERISTICS

We enrolled 605 patients, but 2 were excluded from the analysis because they were from a center that was closed owing to failure to adhere to Good Clinical Practice guidelines (Fig. 1). The intention-to-treat population therefore included 603 patients (301 patients in group 1 and 302 patients in group 2); of these, 476 (79%) completed the study. The mean duration of observation for the primary end point was approximately 3 years (1044 days for group 1 and 1092 days for group 2, P=0.42).

Except for a small difference in the sex ratio, the baseline characteristics of the patients were similar in the two groups (Table 1). Seventy-five patients (25%) withdrew prematurely from group 1, and 52 (17%) from group 2 (P=0.02). The major reasons for withdrawal were death (21 patients in group 1 and 17 in group 2; P=0.60), adverse events (17 and 10 patients, respectively; P=0.20), and withdrawal of consent or lack of cooperation (23 and 14 patients, respectively; P=0.15).

TREATMENT OF ANEMIA

At baseline, the mean hemoglobin level was 11.6± 0.6 g per deciliter in both groups. In group 1, 98% of patients received at least one dose of epoetin beta. In group 2, 32% of patients had received epoetin beta at year 1, 52% at year 2, and 76% at the

end of the study. Overall, an average of 67% of patients in group 2 received epoetin beta at any time during the study. The difference in the median hemoglobin level between the two groups was 1.9 g per deciliter at year 1, 1.7 g per deciliter at year 2, and 1.5 g per deciliter at the end of the study (Fig. 2). The median weekly epoetin dose was 5000 IU (range, 3000 to 8000) in group 1 and 2000 IU (range, 1000 to 3000) in group 2. In group 1, 62% of patients received at least one dose of oral iron, as did 60% of those in group 2; 52% of patients in group 1 and 42% of those in group 2 received at least one dose of intravenous iron. Twenty-six patients in group 1 received a blood transfusion, as did 33 patients in group 2.

CONTROL OF BLOOD PRESSURE

Normalization of the hemoglobin level was not associated with a long-term increase in mean blood pressure in group 1 (at baseline, systolic blood pressure was 139±17 mm Hg and diastolic blood pressure was 79±10 mm Hg; at the end of the study, systolic blood pressure was 136± 21 mm Hg and diastolic blood pressure was 79±11 mm Hg). The mean blood pressure values in group 1 did not differ significantly from those in group 2 (group 2: at baseline, systolic blood pressure was 139±16 mm Hg and diastolic blood pressure was 80±9 mm Hg; at the end of the study, systolic blood pressure was 135±19 mm Hg and diastolic blood pressure was 77±12 mm Hg). However, hypertension (defined as a systolic blood pressure of more than 160 mm Hg) was reported as an adverse event in more patients in group 1 than in group 2 (Table 2). Despite a higher rate of beta-blocker use in group 1, there was no significant difference between groups in the numbers of patients prescribed at least one antihypertensive agent at baseline (Table 1). During the study, the number of prescriptions for angiotensin II–receptor blockers, beta-blockers, and calcium-channel blockers increased by approximately 10% and prescriptions for alpha-blockers increased by approximately 15%, with no significant differences between the two groups.

CARDIOVASCULAR EVENTS AND DEATH

At the end of the study, 105 patients had had a first cardiovascular event, 58 in group 1 and 47 in group 2 (the distribution in each group is shown in the table in the Supplementary Appendix). There was no significant difference in the likelihood of a first

cardiovascular event (primary end point) between group 1 and group 2 (hazard ratio, 0.78; 95% CI, 0.53 to 1.14; adjusted P=0.20) (Fig. 3A). Censoring data on patients at the time of initiation of dialysis did not significantly affect the hazard ratio (1.04; 95% CI, 0.66 to 1.65) (Fig. 3B). There were no significant differences between the two groups in the frequency and incidence of death from any cause (31 deaths [10%] in group 1 and 21 deaths [7%] in group 2; hazard ratio, 0.66; 95% CI, 0.38 to 1.15; adjusted P=0.14), incidence of death from cardiovascular causes (4% and 3%, respectively; hazard ratio, 0.74; 95% CI, 0.33 to 1.70; adjusted P=0.48), mean time to worsening of NYHA class (P=0.97), percentage of patients undergoing cardiovascular intervention (7% and 6%, respectively), incidence of hospital admission (61% and 59%, respectively), or mean duration of hospitalization for cardiovascular reasons (33.0 and 28.2 days, respectively).

FINDINGS ON ECHOCARDIOGRAPHY

Echocardiographic assessments were available for 451 patients at baseline. There were no significant least-square mean changes in left ventricular mass index between baseline (120.3±35.0 and 118.0± 34.3 g per square meter in groups 1 and 2, respectively) and year 1 (a change of −4.6 and −3.3 g per square meter, respectively) and year 2 (a change of −6.4 and −7.8 g per square meter, respectively); the changes between groups at year 1 and year 2 also did not differ significantly (year 1, P=0.59; year 2, P=0.65).

QUALITY OF LIFE

At year 1, the quality of life (measured with the use of the SF-36) was significantly better in group 1 than in group 2 with regard to general health (P=0.003), mental health (P<0.001), physical function (P<0.001), physical role (P=0.01), social function (P=0.006), and vitality (P<0.001) (Fig. 4A). At year 2, the significant difference between groups was maintained for general health (P=0.008) and vitality (P=0.01).

RENAL FUNCTION

At baseline, the mean estimated GFR was 24.9± 6.3 ml per minute for group 1 and 24.2±6.0 ml per minute for group 2. At year 1, the mean estimated GFR had decreased by 3.6±6.7 ml per minute in group 1 and by 3.1±5.3 ml per minute in group 2 (P=0.40) (Fig. 4B). At the end of the study, the

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

I bars indicate standard deviations.
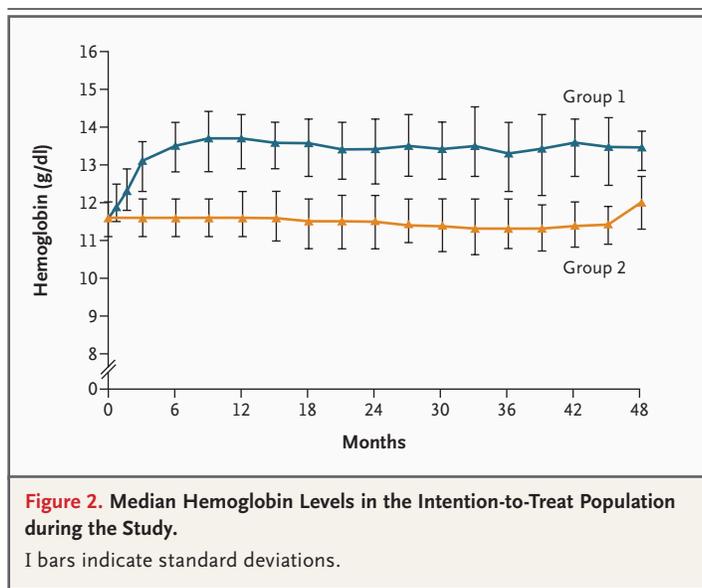
mean estimated GFR was 18.1±11.5 ml per minute in group 1 and 19.2±19.0 ml per minute in group 2 (P=0.36). In total, 127 patients in group 1 and 111 patients in group 2 started dialysis (Fig. 4C). On average, there was no significant difference between the two groups in the last available estimated GFR value before the initiation of dialysis (group 1, 10.9±3.4 ml per minute; group 2, 12.1±4.2 ml per minute). A difference in the time to initiation of dialysis became apparent at 18 months, after which the time to dialysis was shorter in group 1 than in group 2 (P=0.03). The decrease in estimated GFR over time did not differ significantly according to the length of time patients remained in the study (less than 1 year, 1 to 2 years, and more than 2 years) in either group (data not shown). Using the Modification of Diet in Renal Disease IV study equation to calculate the mean estimated GFR did not change the results significantly (at baseline, 20.2±6.6 ml per minute in group 1 and 20.4±7.1 ml per minute in group 2; at year 1, 17.6±10.0 and 17.8±8.1 ml per minute, respectively; and at year 2, 17.8±16.6 and 18.2± 28.8 ml per minute, respectively; all comparisons were not significant).

ADVERSE EVENTS

Adverse events, most of which were mild or moderate, occurred in 93% of patients in group 1 and 90% of patients in group 2 (Table 2). Overall, there were no major differences in adverse events between the two groups. There were more vascular

Table 2. Summary of the Most Frequent Adverse Events and Other Relevant Adverse Events.*

Adverse Event	Group 1 (N = 300)	Group 2 (N = 302)	P Value
	no. of patients (%)		
Most frequent adverse events	279 (93)	273 (90)	0.28
Cardiac disorders	73 (24)	70 (23)	0.78
Acute cardiac failure	13 (4)	23 (8)	0.11
Arrhythmia	18 (6)	16 (5)	0.78
Myocardial infarction	14 (5)	15 (5)	0.94
Angina pectoris	16 (5)	7 (2)	0.07
Progression of chronic kidney disease	166 (55)	163 (54)	0.77
Vascular disorders	135 (45)	89 (29)	<0.001
Hypertension†	89 (30)	59 (20)	0.005
Hypotension	14 (5)	17 (6)	0.66
Peripheral vascular disorder	17 (6)	8 (3)	0.08
Nervous system disorders	77 (26)	53 (18)	0.02
Headache	31 (10)	16 (5)	0.03
Dizziness	19 (6)	14 (5)	0.41
Infections	168 (56)	165 (55)	0.77
Urinary tract infection	28 (9)	35 (12)	0.40
Nasopharyngitis	24 (8)	23 (8)	0.92
Upper respiratory tract infection	17 (6)	28 (9)	0.11
Influenza	26 (9)	12 (4)	0.02
Pneumonia	15 (5)	14 (5)	0.91
Bronchitis	26 (9)	22 (7)	0.58
Gastrointestinal disorders	119 (40)	104 (34)	0.20
Diarrhea	26 (9)	25 (8)	0.92
Constipation	24 (8)	19 (6)	0.46
Nausea	16 (5)	14 (5)	0.76
Vomiting	15 (5)	15 (5)	0.94

disorders in group 1 (P<0.001), mainly because of a greater incidence of hypertension (P=0.005), and more headaches (P=0.03). Arteriovenous fistula thrombosis occurred in 12 of the 127 patients who underwent dialysis in group 1 and in 8 of the 111 patients who underwent dialysis in group 2 (130 and 108 patient-years spent receiving dialysis, respectively).

DISCUSSION

Our findings indicate that as compared with partial correction, early and complete correction of anemia to hemoglobin levels between 13.0 and 15.0 g per deciliter has no beneficial effect on the time to a first cardiovascular event in patients with chronic kidney disease of stage 3 or 4 and mild-to-moderate anemia from renal causes. There were no significant differences between the two groups in the frequency of death from cardiovascular causes or the time to death from cardiovascular causes or any cause.

The lack of a beneficial effect of the normalization of hemoglobin levels on cardiovascular outcomes thus appears to be consistent and independent of whether patients have sufficient residual renal function or require dialysis.[9-11] Although we found no evidence of adverse cardiovascular effects of the normalization of hemoglobin levels, the hazard ratios for the primary end point, death from any cause, and death from cardiovascular causes consistently (although not significantly) fa-

Table 2. (Continued.)

Adverse Event	Group 1 (N=300)	Group 2 (N=302)	P Value
	no. of patients (%)		
Metabolic and nutritional disorders	111 (37)	106 (35)	0.66
Hyperkalemia	30 (10)	31 (10)	0.97
Hypercholesterolemia‡	25 (8)	22 (7)	0.69
Gout	15 (5)	16 (5)	0.94
Hypoglycemia	16 (5)	5 (2)	0.02
Musculoskeletal and connective-tissue disorders	87 (29)	98 (32)	0.38
Back pain	25 (8)	32 (11)	0.38
Arthralgia	21 (7)	19 (6)	0.79
Pain in arms, legs, hands, or feet	18 (6)	16 (5)	0.77
Muscle cramp	9 (3)	16 (5)	0.19
General disorders	86 (29)	77 (25)	0.41
Asthenia	17 (6)	17 (6)	0.95
Peripheral edema	22 (7)	12 (4)	0.09
Fatigue	14 (5)	18 (6)	0.54
Skin and subcutaneous-tissue disorders	61 (20)	47 (16)	0.14
Pruritus	27 (9)	18 (6)	0.18
Respiratory, thoracic, or mediastinal disorders	50 (17)	47 (16)	0.75
Cough	20 (7)	16 (5)	0.53
Psychiatric disorders	35 (12)	38 (13)	0.78
Insomnia	12 (4)	23 (8)	0.07
Blood and lymphatic disorders	12 (4)	24 (8)	0.05
Referral for unplanned investigations	45 (15)	30 (10)	0.07
Increased blood pressure	21 (7)	13 (4)	0.18
Other relevant adverse events			
Cerebrovascular accident	8 (3)	5 (2)	0.48
Transient ischemic attack	5 (2)	2 (<1)	0.34
Arteriovenous fistula			
Thrombosis	12 (4)	8 (3)	0.42
Complication	8 (3)	3 (1)	0.17

* Data are for the total number of patients receiving at least one dose of epoetin beta. Data were lacking for some patients. The most frequent adverse events were those with an incidence of 5% or more.
† Hypertension was defined as systolic blood pressure of more than 160 mm Hg.
‡ Hypercholesterolemia was defined as a serum cholesterol level of more than 200 mg per deciliter (5.17 mmol per liter).

vored the group with the lower hemoglobin target range, which is similar to trends in previous studies.[9,11] The imbalance favoring the lower target range disappeared when data on patients receiving dialysis were censored (Fig. 3B).

Subgroup analysis indicated that there were fewer cardiovascular events in group 1 than in group 2 (34 vs. 39 events) before the initiation of dialysis. In contrast, among patients undergoing dialysis, those in group 1 had more cardiovascular events than those in group 2 (24 vs. 8 events). This difference might be related to the intermittent increase in hemoconcentration after dialysis.

Several large analyses have shown an inverse relation between hemoglobin levels and adverse outcomes and have also identified anemia as an
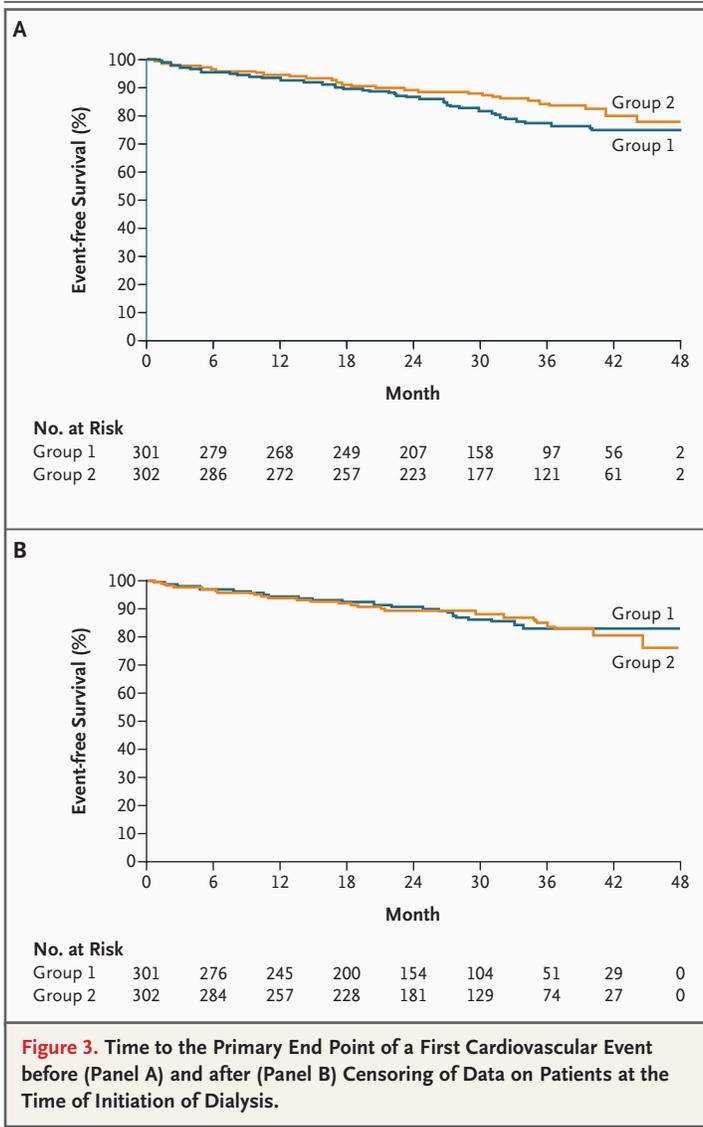
A

No. at Risk									
Group 1	301	279	268	249	207	158	97	56	2
Group 2	302	286	272	257	223	177	121	61	2

B

No. at Risk									
Group 1	301	276	245	200	154	104	51	29	0
Group 2	302	284	257	228	181	129	74	27	0

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.

Figure 4 (facing page). Changes from Baseline to Year 1 in SF-36 Quality-of-Life Scores (Panel A) and Mean Changes in Estimated GFR (Panel B), and the Time to Dialysis (Panel C) during the Study.

In Panel A, values are expressed as least-square means. Positive changes indicate improvement in, and negative changes worsening of, the quality of life. There were no significant differences in the mean changes in GFR, estimated by means of the Cockcroft–Gault formula, between the two groups (Panel B). Six patients (two in group 1 and four in group 2) for whom complete information for the estimation of GFR was lacking were excluded from the analysis. There was a significant difference in time to dialysis between the two groups, favoring group 2 (P=0.03) (Panel C). Data were missing for some patients. I bars indicate standard deviations.

with stage 3 or 4 chronic kidney disease in response to correction of anemia, with a target hemoglobin level of 13.5 g per deciliter, as compared with the standard target of 11.3 g per deciliter. However, among our patients with chronic kidney disease, we found no significant difference in the risk of cardiovascular outcomes between those who underwent partial and those who underwent complete correction of anemia. To explain the observed differences in risk between the study by Singh et al. and our study, potential differences in the study populations and design should be considered. Moreover, in the study by Singh et al., the low end of the target hemoglobin range for complete correction of anemia was lower than that in our study, and the initial and final doses of epoetin were more than twice those used in our study to achieve similar hemoglobin levels, indicating a more severe profile of cardiovascular risk, with an annual event rate nearly thrice that in our study. Singh et al. censored data on patients after they started renal replacement therapy. In our study, when the analysis was limited to patients with chronic kidney disease who did not need renal replacement therapy, there was no difference at all between the two groups in the time to the first cardiovascular event (Fig. 3B).

A major limitation of our study was that the rate of cardiovascular events was considerably lower than anticipated: 6% per year, as compared with 15% per year in the study by Levin et al.[21] At the end of the study, only half the predicted number of cardiovascular events (105 actual events vs. 200 expected) had occurred, and almost half the patients were receiving dialysis. However, the lack of benefit from complete hemoglobin correction appears to be driven not by the lower-than-expect-

independent risk factor for left ventricular growth and morbidity and mortality from cardiovascular causes.[21,22] The lack of benefit from the normalization of hemoglobin levels in our study suggests that although the degree of anemia is a strong indicator of poor prognosis, complete correction of anemia does not improve outcomes. It also suggests that factors causing the anemia, not the anemia itself, have adverse consequences. Alternatively, with increasing hemoglobin values, possible adverse effects such as vascular events might come into play, counterbalancing the potential benefits.[9,23] In this issue of the *Journal*, Singh et al.[24] report an increased risk of complications and death from cardiovascular causes among patients
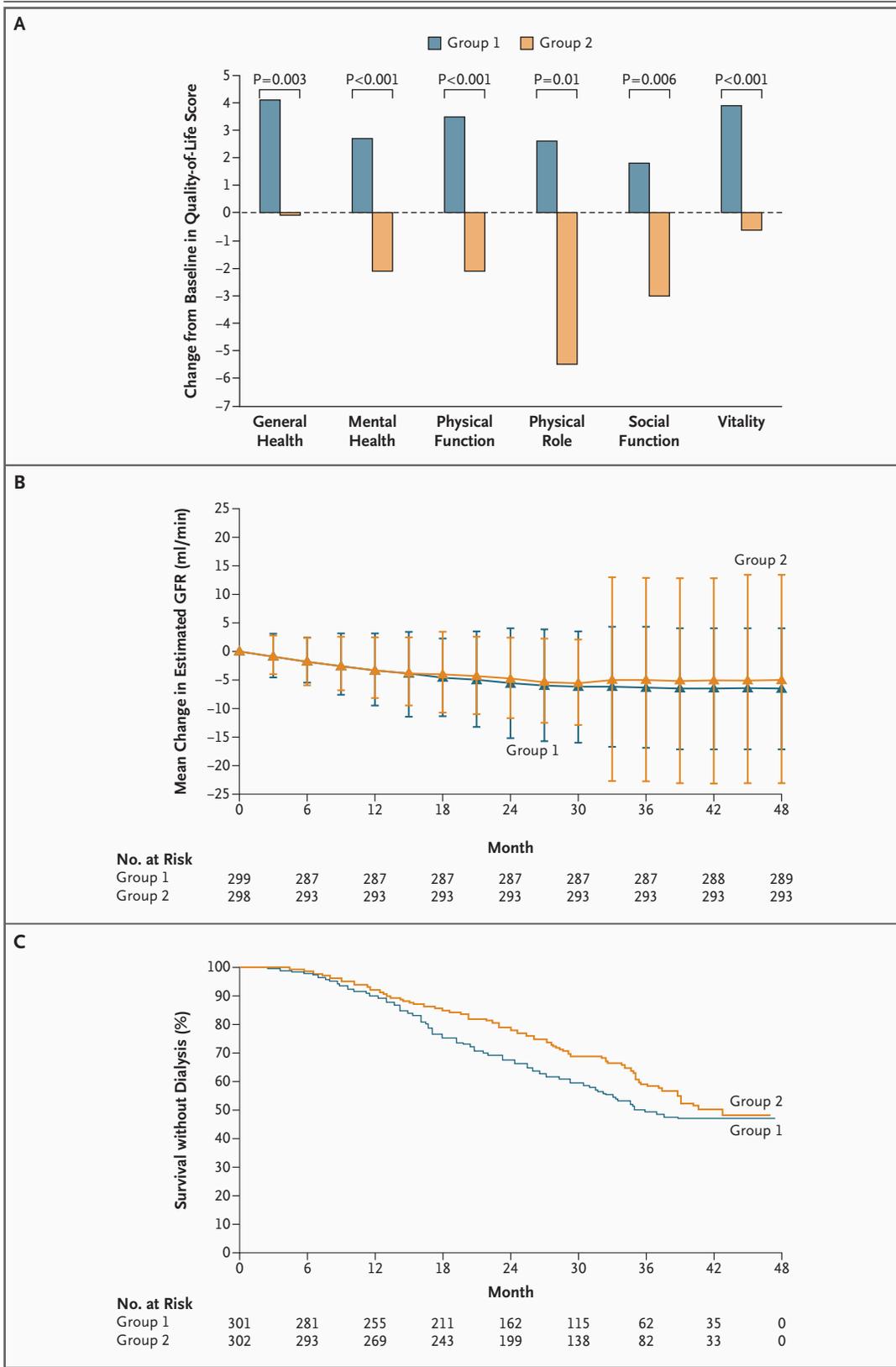
ed number of events but by the lack of an effect. A possible explanation for the lower overall incidence of cardiovascular events is that the nephrologists progressively increased their awareness of and protection against the heavy burden of cardiovascular disease, together with the usually better prognosis of patients enrolled in randomized controlled trials than of patients not enrolled. For example, nearly 70% of patients at the beginning of the trial were receiving agents that block the renin–angiotensin system, and approximately 40% were receiving beta-blockers (Table 1).

Renal end points were secondary, and we did not comprehensively assess renal function (such as by directly measuring GFR rather than estimating GFR, or measuring proteinuria). Moreover, there were no firm criteria in the protocol for the initiation of dialysis. Although the two groups did not differ significantly in the mean decrease in estimated GFR (despite an absolute difference of approximately 0.5 ml per minute per year), the observed difference in the time to dialysis was significant (P=0.03). However, given the lack of standardized rules for the initiation of analysis, these data should be interpreted with caution. As for cardiovascular outcomes, observational studies have recently reported an inverse relation between the hemoglobin level and the decrease in GFR in patients with renal disease.[25-27] Previous, smaller interventional trials found either no effect of high target ranges of hemoglobin levels on the decrease in GFR[15,28-30] or even an attenuation.[31] Experimental evidence suggests that epoetin may exert renoprotective effects independent of its erythropoietic capacity.[32,33]

In line with previous studies,[11,34,35] our study showed significant benefits of higher hemoglobin targets on the quality of life. These benefits were particularly evident with regard to physical function, vitality, and mental health, which generally deteriorate as chronic kidney disease progresses.[36] The capacity for physical exercise also diminishes progressively, and anemia has been shown to be a clinically significant cause of this decline.[37]

In conclusion, we found that in patients with chronic kidney disease of stage 3 or 4 and mild-to-moderate anemia, the normalization of hemoglobin levels to 13.0 to 15.0 g per deciliter did not reduce cardiovascular events as compared with the use of a lower target range (10.5 to 11.5 g per deciliter). Thus, the CREATE study adds direct evidence to confirm the current best practice guidelines, which recommend partial correction of anemia and not routine normalization of hemoglobin levels.[7,38]

APPENDIX

The following committee members and investigators participated in the CREATE study (the numbers of enrolled patients are given in parentheses): **Steering Committee** — *Necker Hospital, Paris* — T.B. Drüeke (chair); *Ospedale A. Manzoni, Lecco, Italy* — F. Locatelli (vice chair); *Södertälje Hospital, Södertälje, Sweden* — N. Clyne; *University of Erlangen–Nürnberg, Erlangen, Germany* — K.-U. Eckardt; *King's College Hospital, London* — I.C. Macdougall; *General Hospital of Veria, Veria, Greece* — D. Tsakiris; **End Point Committee** — *University of Rotterdam, Thoraxcenter, Rotterdam, the Netherlands* — J. Roelandt; *Klinik im Park, Zurich, Switzerland* — W. Kiowski; *Necker Hospital, Paris* — P. Jungers; **Data and Safety Monitoring Board** — *University of Minnesota, Minneapolis* — R.N. Foley (chair); *University Hospital Basel, Switzerland* — M. Pfisterer; *University of British Columbia, St. Paul's Hospital, Vancouver, Canada* — A. Levin; *Nottingham Clinical Research Group, Nottingham, United Kingdom* — A. Skene; **Investigators** — **Austria** — *Landeskrankenhaus St. Poelten* (3) — P. Balcke; *Allgemeines Öffentliches Krankenhaus, Linz* (3) — G. Biesenbach; **Belgium** — *Hôpital Erasme, Brussels* (5) — C. Tielemans; *Universitair Ziekenhuis Antwerp, Edegem* (5) — G. Verpooten; *Academisch Ziekenhuis Vrije Universiteit Brussel, Brussels* (3) — J. Sennesael; **China** — *Queen Mary Hospital, Hong Kong* (10) — T. Chan; **Czech Republic** — *Faculty Hospital, Ostrava* (18) — I. Valkovsky; *Fakultativn Nemocnice, Brno* (13) — M. Hertlova; *Hospital Havirov, Havirov* (3) — S. Schwarzova; *Faculty Hospital, Olomouc* (1) — Z. Kosatikova; **Denmark** — *Herlev Amtssygehus, Herlev* (10) — S. Strandgaard; *Roskilde Amtssygehuset, Roskilde* (9) — K. Rasmussen; *Fredericia Sygehus, Fredericia* (8) — G. Steffensen; *Holbaek Centralsygehus, Holbaek* (1) — K. Soelling; **Finland** — *Keski-Suomen Keskussairaala, Jyväskylä* (16) — A. Koistinen; *Tampere University Hospital, Tampere* (4) — J. Mustonen; **France** — *Centre Hospitalier La Beauchée, Saint Brieuc* (13) — P. Simon; *Centre Hospitalier de Boulogne, Boulogne* (10) — P. Bataille; *Groupe Hospitalier Sud, Amiens* (8) — G.

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