

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 6, 2007

VOL. 357 NO. 10

Efficacy and Safety of Epoetin Alfa in Critically Ill Patients

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ABSTRACT

BACKGROUND

Anemia, which is common in the critically ill, is often treated with red-cell transfusions, which are associated with poor clinical outcomes. We hypothesized that therapy with recombinant human erythropoietin (epoetin alfa) might reduce the need for red-cell transfusions.

METHODS

In this prospective, randomized, placebo-controlled trial, we enrolled 1460 medical, surgical, or trauma patients between 48 and 96 hours after admission to the intensive care unit. Epoetin alfa (40,000 U) or placebo was administered weekly, for a maximum of 3 weeks; patients were followed for 140 days. The primary end point was the percentage of patients who received a red-cell transfusion. Secondary end points were the number of red-cell units transfused, mortality, and the change in hemoglobin concentration from baseline.

RESULTS

As compared with the use of placebo, epoetin alfa therapy did not result in a decrease in either the number of patients who received a red-cell transfusion (relative risk for the epoetin alfa group vs. the placebo group, 0.95; 95% confidence interval [CI], 0.85 to 1.06) or the mean (\pm SD) number of red-cell units transfused (4.5 ± 4.6 units in the epoetin alfa group and 4.3 ± 4.8 units in the placebo group, $P=0.42$). However, the hemoglobin concentration at day 29 increased more in the epoetin alfa group than in the placebo group (1.6 ± 2.0 g per deciliter vs. 1.2 ± 1.8 g per deciliter, $P<0.001$). Mortality tended to be lower at day 29 among patients receiving epoetin alfa (adjusted hazard ratio, 0.79; 95% CI, 0.56 to 1.10); this effect was also seen in pre-specified analyses in those with a diagnosis of trauma (adjusted hazard ratio, 0.37; 95% CI, 0.19 to 0.72). A similar pattern was seen at day 140 (adjusted hazard ratio, 0.86; 95% CI, 0.65 to 1.13), particularly in those with trauma (adjusted hazard ratio, 0.40; 95% CI, 0.23 to 0.69). As compared with placebo, epoetin alfa was associated with a significant increase in the incidence of thrombotic events (hazard ratio, 1.41; 95% CI, 1.06 to 1.86).

CONCLUSIONS

The use of epoetin alfa does not reduce the incidence of red-cell transfusion among critically ill patients, but it may reduce mortality in patients with trauma. Treatment with epoetin alfa is associated with an increase in the incidence of thrombotic events. (ClinicalTrials.gov number, NCT00091910.)

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N Engl J Med 2007;357:965-76.

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ANEMIA IS COMMON IN THE CRITICALLY ill, often resulting in red-cell transfusions.^{1,2} Two observational studies reported that 35 to 45% of patients admitted to intensive care units (ICUs) receive transfusions of almost 5 red-cell units while in the ICU.^{3,4} However, the view that red-cell transfusion is beneficial for critically ill patients has been questioned because of data suggesting that red-cell transfusion may decrease the likelihood of survival in critically ill adults.⁵⁻⁸

Anemia is evident early in the courses of critical illnesses, and hemoglobin concentrations fall throughout stays in the ICU.^{1,4} Impaired production of red cells contributes to the development and persistence of anemia. Although there are multiple reasons for this anemia, it has characteristics similar to the anemia of chronic inflammatory disease.⁹ A feature of anemia of critical illness is a lack of appropriate elevation of circulating erythropoietin concentrations in response to physiological stimuli.^{2,10} Such observations suggest that the administration of recombinant human erythropoietin (epoetin alfa) might raise hemoglobin concentrations in critically ill patients, thereby preventing the need for exposure to allogeneic blood.

We previously conducted two trials of the efficacy of epoetin alfa in reducing the number of red-cell transfusions.^{11,12} Both trials showed that treatment with epoetin alfa decreased the number of red-cell transfusions and increased hemoglobin concentrations. No other clinical benefits were found. We designed the current study to assess the safety and efficacy of a reduced dose of epoetin alfa and to evaluate clinical outcomes and subgroup differences suggested by our previous studies of critically ill patients.

METHODS

GENERAL DESCRIPTION

We conducted this prospective, randomized, double-blind, placebo-controlled trial at 115 medical centers between December 2003 and June 2006. It was approved by the institutional review committee at each participating institution, and written informed consent was obtained from each patient (or his or her surrogate). If a surrogate provided consent, patients were approached for written informed consent when it was medically appropriate. An independent data and safety monitoring board monitored the safety of the study.

The two academic authors who were the principal investigators designed the study in conjunction with the clinical research organization and the sponsor. Patient enrollment and data collection were done at each site and supervised by the clinical research organization, which provided randomization and initial data analysis. The authors analyzed, interpreted, and had full access to the data; were responsible for the manuscript; and verify the completeness and accuracy of the data. An independent statistical consultant reviewed the statistical methods and data analyses. The final manuscript was written by the authors and reviewed by the sponsor.

STUDY POPULATION

All patients who were admitted to medical, surgical, or medical-surgical ICUs in each of the participating institutions and remained in that ICU for 2 days were evaluated for eligibility. Other inclusion criteria were as follows: age of 18 years or older, hemoglobin concentration of less than 12 g per deciliter, and written informed consent. Exclusion criteria were as follows: expected discharge from the ICU within 48 hours after the second day in the ICU; acute ischemic heart disease (myocardial infarction or unstable angina) during the ICU stay; a stay of more than 48 hours' duration in the ICU of a transferring hospital; presence of a left ventricular assist device; history of pulmonary embolus, deep venous thrombosis, ischemic stroke, other arterial or venous thrombotic event (excluding superficial thrombosis), or a chronic hypercoagulable disorder; dialysis for any indication; uncontrolled hypertension (systolic blood pressure of >200 mm Hg or diastolic blood pressure of >110 mm Hg) after adequate antihypertensive therapy; new-onset seizures within the past 3 months or seizures not controlled by medication; third-degree burns on more than 20% of the body-surface area; pregnancy or lactation; diagnosis of acute, clinically significant gastrointestinal bleeding on admission; transfusion at the time of planned enrollment; treatment with epoetin alfa within the past 30 days; inability or unwillingness to receive blood products; participation in another study; and hypersensitivity to epoetin alfa or any of its components.

Randomization was performed between 48 and 96 hours after admission to the ICU (study day 1). Randomization was achieved with the use of computer-generated random numbers and was strat-

ified according to site and three mutually exclusive admission groups (trauma, surgical nontrauma, and medical nontrauma).

STUDY DESIGN

The study drug (epoetin alfa [Procrit, Ortho Biotech], 40,000 U) or an identical-appearing placebo was administered by means of subcutaneous injection on study day 1 and weekly thereafter, for a total of three doses (on days 1, 8, and 15), in patients remaining in the hospital. The study drug was withheld from patients with hemoglobin concentrations of 12 g per deciliter or greater at the time at which the second or third dose would have been given. All patients received liquid iron (150 mg elemental iron per day) by mouth or by nasogastric tube beginning on day 1 or when they could tolerate oral feeding. Parenteral iron was given if the response to the oral iron was inadequate (i.e., transferrin saturation, <20%; and serum ferritin concentration, <100 ng per milliliter).

The need for red-cell transfusion was determined by each patient's treating physician. Red-cell transfusion was targeted to maintain a hemoglobin concentration between 7 g per deciliter and 9 g per deciliter; transfusion was not recommended if the hemoglobin concentration was 9 g per deciliter or more or the hematocrit was 27% or greater, unless there was a specific clinical indication (e.g., active bleeding or ischemia). Transfusion in patients with a hemoglobin concentration of less than 9 g per deciliter or a hematocrit of less than 27% was undertaken at the discretion of the physician. There was no hemoglobin concentration or hematocrit that mandated a red-cell transfusion.

STUDY OUTCOMES

The primary end point was the percentage of patients receiving any red-cell transfusion between days 1 and 29. Secondary end points were the number of red-cell units transfused between days 1 and 42, mortality at day 29 and at day 140, and the change in hemoglobin concentration from baseline to day 29. Reports of all adverse events were collected through day 140.

STATISTICAL ANALYSIS

On the basis of our previous trials,^{11,12} we calculated that 1300 patients would be required for the study to have a statistical power of 80% to detect an absolute difference of 8% in the primary end

point between the epoetin alfa group and the placebo group. According to the results of a blinded review during the current study, the protocol was amended in order to maintain the planned statistical power, and we increased the number of patients by 160, for a total of 1460 patients. All patients were followed for 140 days, unless death occurred earlier. Statistical analyses were based on the intention-to-treat principle and involved all patients who had undergone randomization.

The primary end point, the percentage of patients receiving a red-cell transfusion, was evaluated with the use of the Cochran–Mantel–Haenszel test, stratified according to the admission group (trauma, surgical nontrauma, or medical nontrauma), which was prespecified. Patients who had not yet received a transfusion when they discontinued the study drug or were lost to follow-up were considered not to have received a transfusion during the study period. Another evaluation was performed, which was identical except that patients who discontinued the study drug or were lost to follow-up were considered to have received a transfusion. Relative risks and their 95% confidence intervals were calculated.

The numbers of red-cell units transfused were compared between the epoetin alfa group and the placebo group with the use of the Wilcoxon–Mann–Whitney test. The transfusion rate was expressed as the number of units that were transfused for a given patient divided by the total number of days the patient was alive. The change in hemoglobin concentration from baseline was compared between the two groups with the use of an analysis of covariance, with the effects of baseline hemoglobin value, admission group, and study group included in the model. We imputed missing values using the last-observation-carried-forward method.

Mortality data were analyzed with the use of the stratified Kaplan–Meier method, evaluated at days 29 and 140. The Greenwood formula was used to calculate the corresponding standard error for the survival rate, and the inverse-variance approach was used to standardize the test statistics accounting for the three strata (trauma, medical nontrauma, and surgical nontrauma) (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). We believed that this Kaplan–Meier approach was more appropriate than the log-rank test, because approximately 90% of the patients did not die during the study and,

as a result, there was a large percentage of data censored. A permutation test was done to confirm the robustness of the analysis. Data for time to death were censored at the date of the last assessment if a patient was withdrawn before day 140. Data were censored at day 140 for patients who were alive at the end of the study period.

We evaluated the interaction between the study group (epoetin alfa or placebo) and the admission group (trauma, medical nontrauma, or surgical nontrauma) using a Cox regression model including study group, admission group, and the interaction between the study group and the admission group. A Cox regression analysis was also performed to adjust hazard ratios for mortality, with several covariates: age; sex; admission group; types of coexisting conditions; score on the Acute Physiology and Chronic Health Evaluation II; baseline hemoglobin concentration, iron studies, erythropoietin concentration, and serum creatinine concentration; and Injury Severity Score. The unadjusted hazard ratio was also determined.

We studied the use of mechanical ventilation by analyzing the numbers of ventilator-free days and the duration of mechanical ventilation. Kaplan-Meier estimates were calculated in addition to descriptive statistics. Lengths of stay in the ICU and hospital were analyzed in a similar manner to mechanical ventilation.

Analyses according to the prospectively identified admission group (trauma, surgical nontrauma, and medical nontrauma) were performed similarly to those in the overall population. The final analyses were based on a two-sided significance level of 0.05.

RESULTS

STUDY POPULATION

We enrolled 1460 patients, of whom 733 were randomly assigned to receive epoetin alfa and 727 to receive placebo (Fig. 1). In total, 94.3% of patients completed the study through day 29 (95.2% of patients in the epoetin alfa group and 93.4% of patients in the placebo group), 90.9% through day 42 (93.2% and 88.6%, respectively), and 82.9% through day 140 (84.3% and 81.6%, respectively). Overall, 140 patients (9.5%) discontinued the study drug: 61 patients in the epoetin alfa group (8.3%) and 79 in the placebo group (10.9%). Five of these patients died after discontinuation (three in the epoetin alfa group and two in the placebo group). A total of 109 patients (7.5%) were lost to follow-

up, 55 in the placebo group (7.6%) and 54 in the epoetin alfa group (7.4%).

After the study was completed and the database was locked, we established the status of 26 of the 109 patients who had been lost to follow-up (11 in the epoetin alfa group and 15 in the placebo group). Of these 26, 5 patients had died (3 in the epoetin alfa group and 2 in the placebo group). In our analyses, these 26 patients were considered to be lost to follow-up.

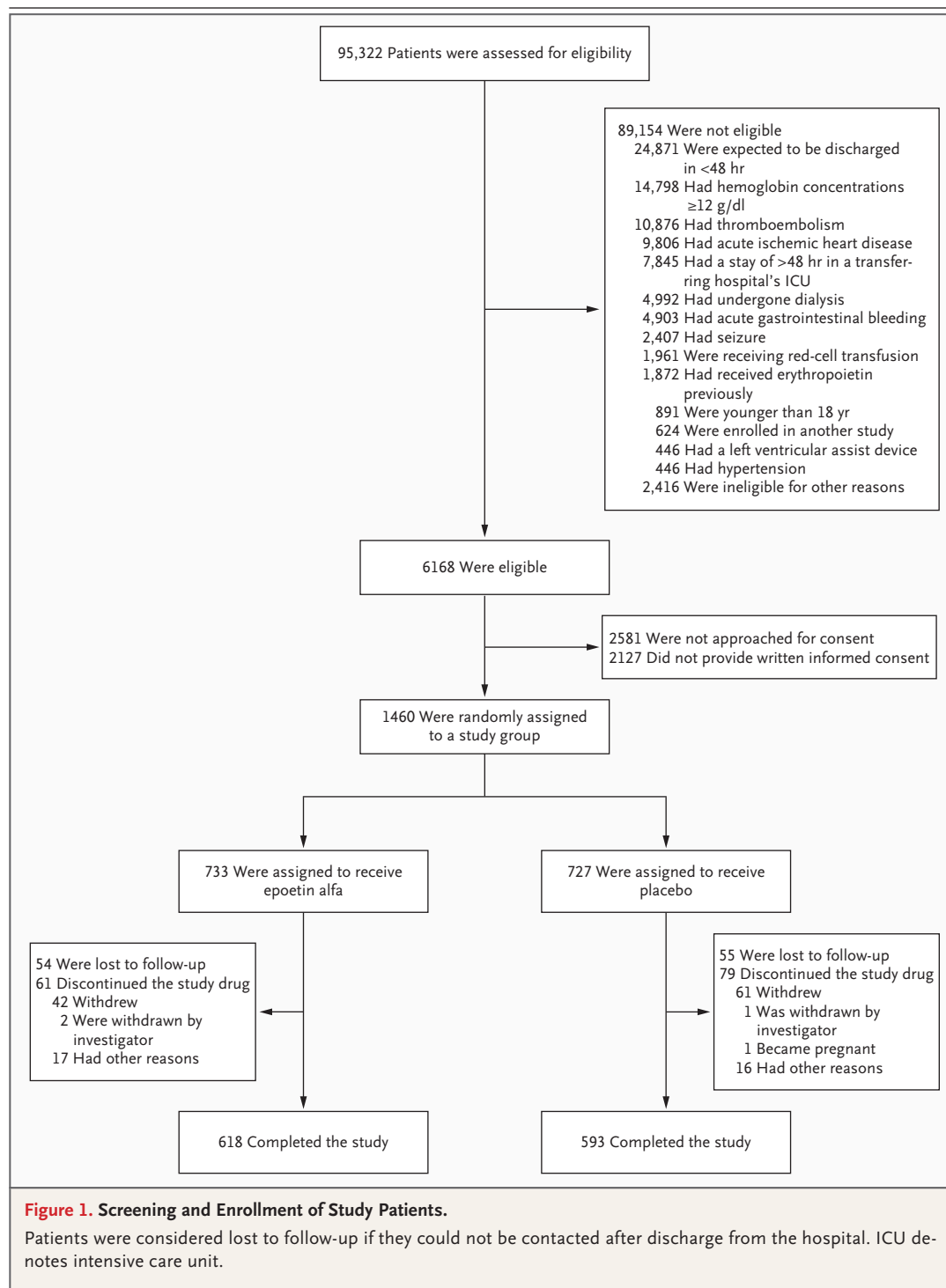
The characteristics of the patients in the two study groups were similar at enrollment (Table 1). However, surgical patients and medical patients were older than trauma patients (mean age [\pm SD], 64 ± 14 years and 60 ± 16 years, respectively, vs. 41 ± 17 years) and more had one or more coexisting conditions (89.1% and 89.3%, respectively, vs. 32.2%). Within each of the three admission groups, patients in the epoetin alfa group and the placebo group had similar baseline characteristics.

Among patients receiving epoetin alfa, 28.2% received one dose during the study, 32.2% received two doses, and 38.9% received three doses. Twelve patients (seven in the placebo group and five in the epoetin alfa group) did not receive study medication.

RED-CELL TRANSFUSION

There was no significant difference between the groups in the percentage of patients who received a red-cell transfusion (46.0% in the epoetin alfa group vs. 48.3% in the placebo group; relative risk, 0.95; 95% confidence interval [CI], 0.85 to 1.06; $P=0.34$) (Table 2). Among patients who received a red-cell transfusion, there was no significant difference between the epoetin alfa group and the placebo group for the trauma patients, for the surgical nontrauma patients, or for the medical nontrauma patients. In the analysis in which patients who discontinued the study drug or were lost to follow-up were considered to have received a transfusion, there were fewer patients receiving a transfusion in the epoetin alfa group than in the placebo group (52.7% vs. 57.1%; relative risk, 0.92; 95% CI, 0.84 to 1.01; $P=0.08$). There was no significant difference between the two study groups in the total number of red-cell units transfused or the transfusion rate (Table 2).

Transfusion practices appeared to be similar in the two study groups. The mean pretransfusion hemoglobin concentration was 8.0 ± 1.0 g per deciliter in the placebo group and 8.2 ± 0.9 g per deciliter in the epoetin alfa group, and the hemoglo-



bin concentrations before the first transfusion and at subsequent transfusions were similar. Only 13.4% of patients received a transfusion when their hemoglobin concentration was above 9.0 g per deciliter. A total of 74.8% of patients in the epoetin alfa group and 77.2% in the placebo group

received red-cell transfusions to maintain a hemoglobin concentration between 7 g per deciliter and 9 g per deciliter. A total of 11.4% of patients in the placebo group and 11.6% in the epoetin alfa group received transfusions for acute bleeding. Before randomization, 56.2% of patients (54.6%

Table 1. Baseline Characteristics.*

Characteristic	Epoetin Alfa (N=733)	Placebo (N=727)
Age — yr	50.0±19.4	50.7±19.6
Sex — no. (%)		
Male	459 (62.6)	463 (63.7)
Female	274 (37.4)	264 (36.3)
APACHE II score	19.9±7.7	20.0±7.5
Injury Severity Score	28.2±12.6	27.8±12.2
Revised Trauma Score	6.29±1.85	6.09±1.95
Trauma Injury Severity Score	75.5±27.9	74.7±28.9
Glasgow Coma Score — no. (%)		
≤8	149 (38)	153 (41)
9–12	25 (6)	33 (9)
≥13	217 (56)	183 (50)
Mechanical ventilation on day 1 — no. (%)	506 (69.0)	501 (68.9)
Admission group — no. (%)		
Trauma	402 (54.8)	391 (53.8)
Surgical, nontrauma	162 (22.1)	168 (23.1)
Medical, nontrauma	169 (23.1)	168 (23.1)
Type of trauma — no. (%)		
Penetrating	52 (13)	58 (15)
Blunt	349 (87)	322 (85)
Specific diagnosis on admission — no. (%)		
Postoperative care	347 (47.3)	321 (44.2)
Trauma	402 (54.8)	391 (53.8)
Neurologic disease	182 (24.8)	182 (25.0)
Cardiovascular disease	121 (16.5)	115 (15.8)
Respiratory disease	315 (43.0)	319 (43.9)
Pneumonia	110 (15.0)	118 (16.2)
ARDS	45 (6.1)	40 (5.5)
Other	242 (33.0)	240 (33.0)
Sepsis	95 (13.0)	93 (12.8)
Primary hematologic disease	3 (0.4)	8 (1.1)
Other nonsurgical disease	59 (8.0)	64 (8.8)

in the placebo group and 57.8% in the epoetin alfa group, $P=0.27$) received 1 or more red-cell units (5.9 ± 7.2 in the placebo group and 6.3 ± 7.3 in the epoetin alfa group, $P=0.43$).

HEMOGLOBIN CONCENTRATION

At day 29, the increase in the hemoglobin concentration from baseline was greater in the epoetin alfa group than in the placebo group (1.6 ± 2.0 g per deciliter vs. 1.2 ± 1.8 g per deciliter, $P<0.001$), as was the absolute hemoglobin concentration

(11.2 ± 1.8 g per deciliter vs. 10.8 ± 1.7 g per deciliter, $P<0.001$). By day 42, the hemoglobin concentrations in the two study groups were not significantly different. The reticulocyte count increased, paralleling the increase in the hemoglobin concentration during the study, peaking at day 22.

MORTALITY

Mortality at day 29 (Fig. 2) was significantly lower in the epoetin alfa group than in the placebo group (8.5% vs. 11.4%, $P=0.02$), according to

Table 1. (Continued.)

Characteristic	Epoetin Alfa (N = 733)	Placebo (N = 727)
Medical history — no. (%)		
≥1 Coexisting condition	429 (58.5)	421 (57.9)
Autoimmune disease	25 (3.4)	36 (5.0)
Cardiac disease	177 (24.1)	166 (22.8)
Myocardial infarction	53 (7.2)	54 (7.4)
Myocardial ischemia	45 (6.1)	43 (5.9)
Chronic pulmonary disease	158 (21.6)	168 (23.1)
Chronic renal disease	38 (5.2)	37 (5.1)
Diabetes mellitus	130 (17.7)	138 (19.0)
Hypercholesterolemia	128 (17.5)	133 (18.3)
Hypertension	307 (41.9)	294 (40.4)
Liver disease	33 (4.5)	43 (5.9)
Solid tumor	59 (8.0)	67 (9.2)
Peripheral vascular disease	38 (5.2)	39 (5.4)
Primary hematologic disease	11 (1.5)	16 (2.2)
Venous insufficiency	11 (1.5)	14 (1.9)
Laboratory value		
Hemoglobin — g/dl	9.6±1.2	9.6±1.1
Reticulocytes — %	2.0±4.0	1.8±1.2
Erythropoietin — mU/ml	71.3±57.9	69.6±69.4
Iron — µg/dl	24.8±27.3	24.3±27.6
Ferritin — ng/ml	510±919	540±1267
Transferrin saturation — %	14.9±15.9	14.7±16.4
Creatinine — mg/dl	1.0±0.6	1.0±0.6

* Plus–minus values are means ±SD. Subcategories of specific diagnosis on admission and medical history are not mutually exclusive. There was a small number of missing values for some variables. The Acute Physiology and Chronic Health Evaluation (APACHE II) score ranges from 0 to 71, with higher scores indicating more severe illness. The Injury Severity Score ranges from 0 to 75, with higher scores indicating more severe injury. The Revised Trauma Score is derived from the score on the Glasgow Coma Scale, the systolic blood pressure, and the respiratory rate, with scores ranging from 0 to 7.84 and higher scores indicating a higher probability of survival. The Glasgow Coma Scale ranges from 3 to 15, with higher scores correlated with less brain injury. Data on the Injury Severity Score, the Revised Trauma Score, the Trauma Injury Severity Score, the Glasgow Coma Scale, and type of injury were collected for trauma patients only. To convert values for iron to micromoles per liter, multiply by 0.1791. To convert values for creatinine to micromoles per liter, multiply by 88.4.

Kaplan–Meier estimates. In the trauma group, mortality was also significantly lower in the epoetin alfa group than in the placebo group (3.5% vs. 6.6%, $P=0.04$). The mortality pattern was similar at day 140, both among all patients (14.2% in the epoetin alfa group vs. 16.8% in the placebo group, $P=0.08$) and among the trauma patients alone (6.0% vs. 9.2%, $P=0.08$). In the Cox model, the hazard ratios for mortality in the overall population tended toward significance; the mortality hazard ratios for the trauma patients were significant at day 29 and day 140 (Table 3).

The interaction between the admission group and study group was not significant ($P=0.16$), confirming that our findings regarding mortality are consistent among the three admission groups.

The trauma patients in the epoetin alfa group and those in the placebo group had similar baseline characteristics, including those related to trauma (Table 1). There was no relationship between the survival outcome with epoetin alfa and the Injury Severity Score, the score on the Glasgow Coma Scale, or the diagnosis on admission.

Table 2. Summary of Data on Red-Cell Transfusion.*

Variable	Epoetin Alfa (N = 733)	Placebo (N = 727)	Relative Risk (95% CI)	P Value
Patients receiving a transfusion — no. (%)	337 (46.0)	351 (48.3)	0.95 (0.85–1.06)	0.34
Admission group — no./total no. (%)				
Trauma	215/402 (53.5)	216/391 (55.2)	0.97 (0.85–1.10)	
Surgical, nontrauma	59/162 (36.4)	74/168 (44.0)	0.83 (0.63–1.08)	
Medical, nontrauma	63/169 (37.3)	61/168 (36.3)	1.03 (0.78–1.36)	
Units transfused per patient				
Mean	4.5±4.6	4.3±4.8		0.42
Median	3.0	3.0		0.69†
Total no. of days alive	10,073	10,879		
Total no. of units transfused	1525	1530		
Transfusion rate‡	0.15±0.09	0.14±0.18		0.36§

* Plus–minus values are means ±SD.

† The P value was calculated with the use of the Wilcoxon–Mann–Whitney test.

‡ Transfusion rate was defined as the total number of units transfused divided by the total number of days alive.

§ The P value was calculated with the use of the t-test.

ADVERSE EVENTS

At least one adverse event occurred in 94.4% of patients in the placebo group and in 94.8% of patients in the epoetin alfa group. Similarly, 43.5% of patients receiving placebo and 44.0% of those receiving epoetin alfa had a serious adverse event (Table 4). There was an increased incidence of thrombotic vascular events among the patients in the epoetin alfa group as compared with those in the placebo group (16.5% vs. 11.5%; hazard ratio, 1.41; 95% CI, 1.06 to 1.86; $P=0.008$). Post hoc analyses showed that the incidence of thrombotic vascular events in the epoetin alfa group as compared with the placebo group was increased among patients who did not receive heparin at baseline (20.3% vs. 12.8%; hazard ratio, 1.58; 95% CI, 1.09 to 2.28; $P=0.008$) but not among those who received heparin at baseline (12.3% vs. 10.2%; hazard ratio, 1.16; 95% CI, 0.75 to 1.80; $P=0.41$). Similar trends in thrombotic vascular events were found among patients in each of the three admission groups. The increase in the incidence of thrombotic vascular events was most apparent among patients who received three doses of epoetin alfa, as compared with those who received three doses of placebo (22.8% vs. 16.1%, $P=0.048$), although the trend was similar (albeit not significant) for those receiving one dose (11.1% vs. 6.5%, $P=0.31$) and for those receiving two doses (13.6% vs. 9.5%, $P=0.19$).

One patient who received a single dose of epoetin alfa tested positive for antibodies to erythropoietin at day 7 and day 140. A follow-up blood specimen collected on day 240 was positive for antibodies to erythropoietin but negative for erythropoietin-neutralizing antibody, which was not tested for on day 7 and day 140. That patient had no adverse outcomes.

LENGTH OF STAY AND USE OF MECHANICAL VENTILATION

There was no significant difference between the epoetin alfa group and the placebo group in the median lengths of stay in the ICU (8 days and 7 days, respectively; $P=0.43$) and in the hospital (15 days in both groups, $P=0.43$).

At day 140, mechanical ventilation had been discontinued for 96.6% of patients receiving epoetin alfa and 98.4% of patients receiving placebo ($P=0.02$). However, the epoetin alfa group and the placebo group had a similar number of ventilator-free days (29.0 ± 15.5 and 28.7 ± 14.9 , respectively; $P=0.72$) and a similar median duration of mechanical ventilation (15 days and 14 days, respectively; $P=0.16$).

DISCUSSION

Two previous trials involving critically ill patients showed that treatment with epoetin alfa reduced

the number of red-cell transfusions and raised the hemoglobin concentration.^{11,12} In the present study, we found no reduction in the incidence of red-cell transfusions in the epoetin alfa group, an unexpected finding. A likely explanation for this lack of reduction is a change in transfusion practice. In the previous trials, the mean pretransfusion hemoglobin concentration was 8.5 g per deciliter, consistent with observational studies at the time.^{3,4} In the present study, the mean pretransfusion hemoglobin concentration was 0.5 g per deciliter lower, at 8.0 g per deciliter.

The percentage of patients in the placebo group who received a transfusion fell from 60% in the previous trials to approximately 50%, similar to the percentage of patients in the epoetin alfa group who received a red-cell transfusion in this study and in the earlier trials.^{11,12} The decrease in the percentage of patients receiving a transfusion was greatest among medical and surgical patients, who had a 20% decrease as compared with those reported in prior trials. Our results suggest that efforts to limit transfusion in the critically ill, made after the publication of the Transfusion Requirements in Critical Care (TRICC) trial,⁵ have affected clinical practice. Our finding that patients who received epoetin alfa therapy had a greater increase in hemoglobin concentration than those who received placebo suggests that epoetin alfa had the expected hematopoietic effect, despite the lack of a reduction in the incidence of transfusion.

The most important finding in the current trial is the reduction in mortality among patients who received epoetin alfa as compared with those who received placebo, which was most apparent in the trauma patients. Our previous trial¹² also showed decreased mortality among trauma patients treated with epoetin alfa as compared with placebo (4.8% vs. 10.4%; odds ratio, 0.43; 95% CI, 0.23 to 0.81). In that trial, the trauma, surgical nontrauma, and medical nontrauma admission groups were not prospectively identified, nor was randomization stratified according to these groups. As a result, patients within these groups who received epoetin alfa were not necessarily similar to those who received placebo, and multivariate analysis suggested that mortality was not affected by study group or admission group.

In the current trial, randomization was stratified according to the admission group identified in the earlier trial. The decreased mortality that we found among trauma patients who received

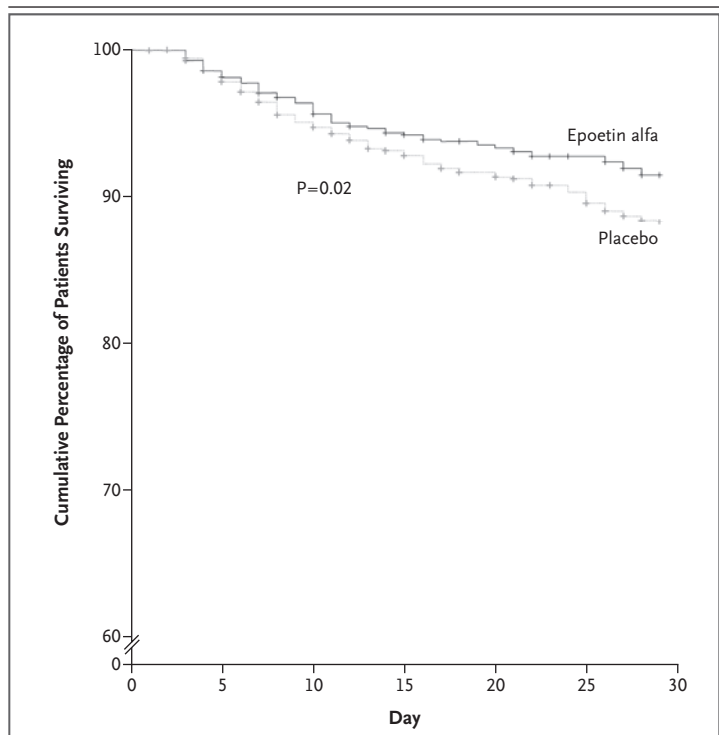


Figure 2. Kaplan–Meier Estimates of Mortality through Day 29 for the 733 Patients Receiving Epoetin Alfa and the 727 Patients Receiving Placebo.

Stratified Kaplan–Meier estimates were calculated with the use of the Greenwood formula for the corresponding standard error for survival rate and with the use of the inverse-variance approach to standardize the test statistics accounting for the three admission groups (trauma, medical, and surgical) (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). The Kaplan–Meier estimates for trauma patients were similar to those shown in the figure, with a P value of 0.04. The number of patients who died was 62 in the epoetin alfa group (8.5%) and 83 in the placebo group (11.4%). Data were censored for 667 patients in the epoetin alfa group (91.0%) and 638 in the placebo group (87.8%).

epoetin alfa in the previous trial was replicated in the present trial: the study groups were similar, and the decreased mortality was confirmed by the adjusted hazard ratio. Taken together, the previous and present trials suggest a decreased mortality with epoetin alfa for trauma patients who are in the ICU for more than 48 hours. In contrast, no significant reduction in mortality was seen among surgical and medical patients receiving epoetin alfa. It is unclear whether this is because the study was underpowered for nontrauma patients or whether in fact only certain subgroups within the medical or surgical populations have a benefit.

Our prestudy hypothesis was that improvement in clinical outcome with the use of epoetin alfa would result from the prevention of adverse effects

Table 3. Mortality at Day 29 and Day 140 in the Intention-to-Treat Population.

Group	Epoetin Alfa	Placebo	Hazard Ratio (95% CI)*	
			Unadjusted	Adjusted
	<i>no./total no. (%)</i>			
Day 29				
All patients	62/733 (8.5)	83/727 (11.4)	0.73 (0.53–1.02)	0.79 (0.56–1.10)
Admission group				
Trauma	14/402 (3.5)	26/391 (6.6)	0.52 (0.27–0.99)	0.37 (0.19–0.72)
Surgical, nontrauma	10/162 (6.2)	14/168 (8.3)	0.73 (0.33–1.65)	0.70 (0.31–1.63)
Medical, nontrauma	38/169 (22.5)	43/168 (25.6)	0.88 (0.57–1.36)	1.04 (0.65–1.67)
Day 140				
All patients	104/733 (14.2)	122/727 (16.8)	0.83 (0.64–1.08)	0.86 (0.65–1.13)
Admission group				
Trauma	24/402 (6.0)	36/391 (9.2)	0.63 (0.38–1.06)	0.40 (0.23–0.69)
Surgical, nontrauma	27/162 (16.7)	27/168 (16.1)	1.02 (0.60–1.74)	0.91 (0.52–1.60)
Medical, nontrauma	53/169 (31.4)	59/168 (35.1)	0.88 (0.60–1.27)	0.99 (0.66–1.49)

* The unadjusted hazard ratio is from a Cox regression with study group as the only covariate. The adjusted hazard ratio is from a Cox regression with study group, age, sex, admission group, Acute Physiology and Chronic Health Evaluation (APACHE II) score, baseline hemoglobin, iron, and serum creatinine concentrations, types of coexisting conditions, and Injury Severity Score (for trauma patients) as covariates.

of transfused red cells. This was clearly not the case. The reduction in mortality was found in the absence of a reduction in the incidence of transfusion. Similarly, the timing of both the decreased mortality and the moderate degree of increase in hemoglobin concentration makes it unlikely that the increase in hemoglobin was responsible for the reduction in mortality. A more likely explanation is nonhematopoietic effects of epoetin alfa.

Erythropoietin has actions other than stimulation of the bone marrow to produce mature erythrocytes. It acts as a cytokine with antiapoptotic activity.^{13–15} In this role, erythropoietin has been shown in preclinical and small clinical studies to protect cells from hypoxemia and ischemia. Multiple tissues express erythropoietin and the erythropoietin receptor in response to stress and also to mediate local stress responses. These nonhematopoietic activities of erythropoietin in the protection of cells suggest a role for erythropoietin in critically ill patients.¹³ Apoptosis is important in the pathogenesis of many critical illnesses, such as sepsis and multiple-organ failure. Similar mechanisms may also be involved in mediating injury in trauma patients. Could the antiapoptotic activity of erythropoietin result in improved outcomes in critically ill patients? Although our current study

does raise this possibility, further preclinical and clinical studies will be necessary to establish the mechanism responsible for the effects of epoetin alfa.

Trials in other populations (patients with cancer and those with chronic renal failure) that aimed to achieve target hemoglobin concentrations above 12 g per deciliter with the use of epoetin alfa have reported an increase in the risk of thrombotic complications and death.^{16–19} Patients with a history of thrombotic events were excluded from the present trial; however, we still observed an increase in the incidence of thrombotic events with epoetin alfa. In contrast to studies of erythropoietin in patients with cancer and those with renal failure, the findings in this trial are notable in two respects: first, the increase in the incidence of thrombotic events occurred with a hemoglobin target below 12 g per deciliter; and second, the duration of therapy was brief (three or fewer doses). A post hoc analysis did not show an increase in the incidence of thrombotic events among patients receiving epoetin alfa who also received heparin (prophylactic or therapeutic). An increase in the incidence of thrombotic events was not noted in our previous trials.^{11,12}

In conclusion, despite the lack of reduction in

the incidence of red-cell transfusion, we found a decrease in mortality among trauma patients who received epoetin alfa, consistent with our previous observations.¹² This may suggest that epoetin alfa has actions distinct from hematopoiesis. On the basis of the available data, we believe that epoetin alfa could benefit trauma patients remaining in an ICU for more than 48 hours and who have hemoglobin concentrations below 12 g per deciliter and no history of thrombotic disease, provided they meet all the other inclusion criteria and do not have any of the exclusion criteria in the study. However, our present data suggest that, without further study, epoetin alfa should not be administered before a patient has been in the ICU for 48 hours, since administration early in the course may alter the risk–benefit ratio. The use of epoetin alfa is not supported for patients admitted to the ICU with a nontraumatic surgical or medical diagnosis, unless they have an approved indication for epoetin alfa.

Further study is needed to explore possible mechanisms that are responsible for the effects of epoetin alfa and to determine whether other critically ill patients might benefit from epoetin alfa therapy. Furthermore, our results increase the concern about thrombotic complications associated with epoetin alfa, and our post hoc analysis suggests that prophylactic heparin could be considered for critically ill patients receiving epoetin alfa.

Supported by Johnson & Johnson Pharmaceutical Research and Development.

Dr. H. Corwin reports receiving consulting and lecture fees from Ortho Biotech and Johnson & Johnson Pharmaceutical

Table 4. Serious Adverse Events.*

Event	Epoetin Alfa (N = 728) <i>no. of patients (%)</i>	Placebo (N = 720) <i>no. of patients (%)</i>	P Value
Any	320 (44.0)	313 (43.5)	0.87
Respiratory-system disorders			
Respiratory insufficiency	20 (2.7)	37 (5.1)	0.02
Dyspnea	12 (1.6)	15 (2.1)	0.57
Resistance-mechanism disorders			
Sepsis	47 (6.5)	50 (6.9)	0.67
Abscess	20 (2.7)	13 (1.8)	0.29
Multiple-organ failure	18 (2.5)	16 (2.2)	0.86
Clinically relevant thrombotic vascular event	120 (16.5)	83 (11.5)	0.008
Pulmonary embolism	16 (2.2)	12 (1.7)	0.57
Deep venous thrombosis	63 (8.7)	42 (5.8)	0.04
Cerebrovascular event	14 (1.9)	16 (2.2)	0.72
Myocardial infarction	15 (2.1)	6 (0.8)	0.08
Cardiac arrest or ventricular fibrillation	15 (2.1)	12 (1.7)	0.69

* The serious adverse events listed are those that occurred in more than 2% of patients in either study group. One patient in the epoetin alfa group who had received one dose had a positive scheduled mammogram at the day-140 visit. Biopsy of the lesion showed ductal carcinoma.

Research and Development; Drs. Fabian and May receiving consulting fees from Ortho Biotech; Dr. Pearl receiving lecture fees from Ortho Biotech; Drs. An, Bowers, Burton, and Klausner being employees of Johnson & Johnson Pharmaceutical Research and Development; and Dr. M. Corwin being an employee of BattelleCRO, which is a paid contractor to Johnson & Johnson Pharmaceutical Research and Development. No other potential conflict of interest relevant to this article was reported.

APPENDIX

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