

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

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### ABSTRACT

**Background** In patients with end-stage renal disease, anemia develops as a result of erythropoietin deficiency, and recombinant human erythropoietin (epoetin) is prescribed to correct the anemia partially. We examined the risks and benefits of normalizing the hematocrit in patients with cardiac disease who were undergoing hemodialysis.

**Methods** We studied 1233 patients with clinical evidence of congestive heart failure or ischemic heart disease who were undergoing hemodialysis: 618 patients were assigned to receive increasing doses of epoetin to achieve and maintain a hematocrit of 42 percent, and 615 were assigned to receive doses of epoetin sufficient to maintain a hematocrit of 30 percent throughout the study. The median duration of treatment was 14 months. The primary end point was the length of time to death or a first nonfatal myocardial infarction.

**Results** After 29 months, there were 183 deaths and 19 first nonfatal myocardial infarctions among the patients in the normal-hematocrit group and 150 deaths and 14 nonfatal myocardial infarctions among those in the low-hematocrit group (risk ratio for the normal-hematocrit group as compared with the low-hematocrit group, 1.3; 95 percent confidence interval, 0.9 to 1.9). Although the difference in event-free survival between the two groups did not reach the prespecified statistical stopping boundary, the study was halted. The causes of death in the two groups were similar. The mortality rates decreased with increasing hematocrit values in both groups. The patients in the normal-hematocrit group had a decline in the adequacy of dialysis and received intravenous iron dextran more often than those in the low-hematocrit group.

**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.)

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**A**DVANCED kidney failure usually leads to anemia, primarily as a result of deficient renal erythropoietin production. Most patients undergoing hemodialysis are treated with recombinant human erythropoietin (epoetin) to stimulate erythropoiesis and correct the anemia partially. In a random sample of 940 patients at 188 U.S. hemodialysis centers obtained before the initi-

ation of this study, we found that 69 percent of the patients had hematocrits of 27 to 33 percent, 15 percent had values below 27 percent, and 16 percent had values above 33 percent (unpublished data). Yet the normal ranges for hematocrit values are 37 to 48 percent for women and 42 to 52 percent for men,<sup>1</sup> prompting the question of whether increasing the doses of epoetin would benefit patients who are undergoing hemodialysis. Cerebral oxygen delivery among patients with ischemic cerebrovascular disease, for example, is maximal when the hematocrit is 40 to 45 percent.<sup>2</sup>

Cardiac disease is the most common cause of death among patients who are regularly receiving dialysis.<sup>3</sup> Among these patients, partial correction of anemia reduces exercise-induced cardiac ischemia<sup>4,5</sup> and ameliorates the left ventricular hypertrophy<sup>4,6-9</sup> that predisposes patients to death and cardiac-related morbidity.<sup>10-12</sup> In two pilot studies of patients who were receiving hemodialysis who maintained a normal hematocrit value<sup>13</sup> (and unpublished data), there were no increases in blood pressure, thrombosis of the vascular access site, seizures, or cardiovascular events, and normal hematocrit values were associated with an improved quality of life, shorter hospitalizations, and increased exercise performance. The present trial was designed to examine the benefits and risks of a normal hematocrit in a large group of patients with cardiac disease who were undergoing hemodialysis.

### METHODS

#### Study Subjects

In this randomized, prospective, open-label trial, we studied 1233 patients with congestive heart failure or ischemic heart disease who were undergoing hemodialysis at 51 centers (see the Appendix). The institutional review boards at all centers approved the protocol, and all the patients gave written, informed consent. All the patients had end-stage renal disease and were undergoing long-term hemodialysis, and they had hematocrit values of 27 to 33 percent while receiving epoetin during the four weeks before enrollment. Ninety percent of the patients received epoetin intrave-

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nously, and 88 percent received it three times per week. According to the protocol, all patients had to have documented congestive heart failure (defined as the need for hospitalization or nonroutine ultrafiltration for congestive heart failure in the preceding two years) or ischemic heart disease (defined as angina pectoris requiring medication in the preceding two years, coronary artery disease documented by cardiac catheterization, or prior myocardial infarction) and a serum transferrin saturation of 20 percent or higher. Exclusion criteria included a diastolic blood pressure of 100 mm Hg or more; a life expectancy of less than six months; severe cardiac disability (New York Heart Association class IV); myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary-artery bypass grafting in the three months before the study began; pericardial disease; cardiac valvular disease likely to require surgery; cardiac amyloidosis; and androgen therapy.

### Study Protocol

The patients were randomly assigned to one of two groups. One was a normal-hematocrit group, in which the patients received increasing doses of epoetin alfa (Epogen, Amgen, Thousand Oaks, Calif.) to achieve and maintain hematocrit values of 42 percent ( $\pm 3$  percentage points). The other was a low-hematocrit group, in which the patients received doses of epoetin sufficient to maintain the hematocrit at 30 percent ( $\pm 3$  percentage points). The planned duration of the study was three years after the enrollment of the last patient. The epoetin was administered intravenously or subcutaneously, according to the route of administration at base line, and at the same frequency per week as before the study. In the normal-hematocrit group, the dose was increased by a factor of 1.5 on study entry. Subsequently, doses were increased by 25 percent of the base-line dose if the hematocrit had not increased by at least 2 percentage points during the preceding two weeks. If the hematocrit increased by more than 4 percentage points in a two-week period, the dose was reduced by 25 U per kilogram of body weight. Iron status (as determined by the serum transferrin saturation and serum ferritin concentration) was reevaluated in patients who had no responses to increases in the dose of epoetin. In the low-hematocrit group, the dose was adjusted by 10 to 25 U per kilogram at two-week intervals, when needed, to maintain a hematocrit of 30 percent. To avoid spuriously elevated hematocrit values that result from swelling of red cells during transport to the central laboratory, we calculated the hematocrit values (in percentage points) by multiplying the hemoglobin concentrations (in grams per deciliter) by 3, and all hematocrit values after randomization are expressed in this way.

### Evaluations

All adverse events, hospitalizations, coronary-artery bypass graft or percutaneous transluminal coronary angioplasty procedures, thromboses at vascular access sites or any change or procedure involving a vascular access site, transfusions, and deaths were recorded. Serial records were kept of the patients' hemodialysis regimens; blood pressure; hematologic, chemical, and coagulation profiles; serum transferrin saturation; and concomitant drug therapy. We also recorded  $Kt/V$ , a unitless measure of the adequacy of hemodialysis therapy, where  $K$  is the rate of urea clearance by the artificial kidney,  $t$  is the duration of each hemodialysis session,  $V$  is the volume of distribution of urea within the patient, and 1.20 is considered to be the minimal recommended value, although the measurement technique varied among the centers and was estimated from the urea reduction ratio for the small number of patients treated at centers that did not calculate  $Kt/V$ . Blood specimens for laboratory analyses were drawn just before hemodialysis. Quality of life was assessed at base line and every six months thereafter with the 36-item Medical Outcomes Study Short-Form Health Survey,<sup>14</sup> which evaluates eight health-related aspects: physical function, social function, physical role, emotional role, mental health, energy, pain, and general health perceptions. Each portion of the test is scored on a scale that ranges from 0 (severe limitation) to 100 (no limitation).

The primary end point was the length of time to death or a first nonfatal myocardial infarction. A myocardial infarction was considered to be fatal if death occurred within 24 hours after the infarction; the event was then counted as a death in tabulating the primary end point. Three criteria were required for the diagnosis of myocardial infarction: clinical suspicion of acute myocardial infarction, a peak serum creatine kinase concentration that was more than 1.5 times the upper limit of the normal range, and a high fraction of creatine kinase MB. Secondary end points were congestive heart failure requiring hospitalization, angina pectoris requiring hospitalization, coronary-artery bypass grafting, percutaneous transluminal coronary angioplasty, hospitalization for all causes, change in cardiovascular drugs, red-cell transfusion, and changes in the quality-of-life scores.

### Statistical Analysis

We estimated that 1000 patients were required to provide the study with a power of 90 percent to detect a 20 percent difference in primary event-free survival after three years at an overall  $\alpha$  level of 0.05 for two-sided tests, for a risk ratio of 1.3 with the log-rank test used to compare Kaplan-Meier curves. We used a Lan-DeMets procedure for group-sequential testing with an O'Brien-Fleming boundary.<sup>15</sup> The trial was stopped at the third interim analysis. We report the risk ratio, with 95 percent confidence intervals adjusted for the previous interim analyses, using the method of repeated confidence intervals.<sup>16</sup> Analyses were conducted on an intention-to-treat basis (data on patients who discontinued the study regimen, switched to peritoneal dialysis, underwent kidney transplantation, or died before receiving study medication were included). We compared the adjusted event-free times to death or myocardial infarction using Cox proportional-hazards regression analysis with 11 prespecified covariates.<sup>17</sup> We also assessed mortality using one prospectively defined subgroup analysis that excluded patients in the normal-hematocrit group who did not attain the target hematocrit value. Cumulative incidences were calculated for other secondary end points.

## RESULTS

A total of 1233 patients were enrolled between October 27, 1993, and March 31, 1996; 618 were assigned to the normal-hematocrit group, and 615 to the low-hematocrit group. The study period ranged from 4 days to 30 months (median, 14 months). Concern about safety at the third interim analysis prompted the independent data monitoring committee to recommend that the study be stopped. The interim results of the study did not reach the prespecified stopping boundary corresponding to an overall 5 percent level of significance, complicating the reporting and interpretation of P values.

The base-line characteristics of the two groups, including the mean hematocrit values and mean epoetin doses, were similar (Table 1). By six months the mean hematocrit in the normal-hematocrit group had increased to the target range. To maintain their hematocrit values in the target range these patients required approximately three times as much epoetin as before the study (Fig. 1). Although the mean hematocrit values were stable in the low-hematocrit group throughout the study and in the normal-hematocrit group after six months, the values varied considerably in individual patients, often in association with intercurrent illnesses.

The probability of the primary end point (death

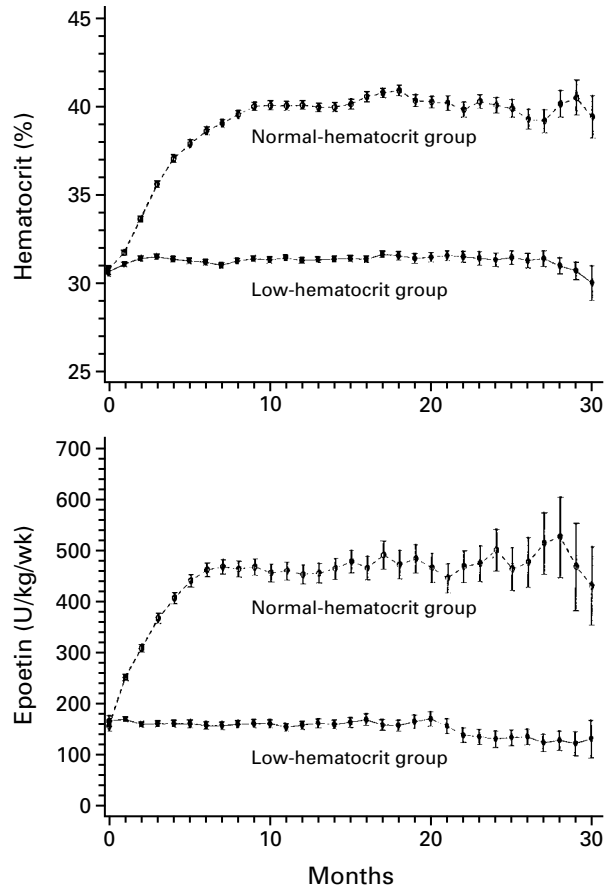
**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\***

CHARACTERISTIC	NORMAL-HEMATOCRIT GROUP (N=618)	LOW-HEMATOCRIT GROUP (N=615)
Age (yr)	65±12	64±12
Female sex (%)	50	52
Race or ethnic group (%)		
White	45	42
Black	41	44
Hispanic	8	9
Other	6	5
Duration of dialysis (yr)	3.2±3.6	3.1±3.3
Cause of renal failure (%)		
Diabetes mellitus	42	46
Hypertension	28	27
Glomerulonephritis	7	8
Other	23	19
Type of vascular access (%)		
Graft	66	67
Natural fistula	23	23
Catheter	10	10
Not specified	2	0
Hypertension (%)	71	69
Diabetes mellitus (%)	54	58
Peripheral vascular disease (%)	39	38
Cardiac-related hospitalization (%)		
Angina pectoris	32	28†
Congestive heart failure	44	47
Myocardial infarction	25	23
Coronary-artery bypass graft	20	19
Percutaneous transluminal coronary angioplasty	10	9
New York Heart Association class (%)		
I	29	31
II	51	52
III	19	15
Hematocrit (%)	30.5±3.0	30.5±2.9
Epoetin dose (U/kg/wk)	146±103	153±119

\*Plus-minus values are means ±SD. Because of rounding, not all percentages total 100.

†P=0.04.

or a first nonfatal myocardial infarction) is shown in Figure 2. After 29 months, there were 183 deaths and 19 first nonfatal myocardial infarctions among the patients in the normal-hematocrit group and 150 deaths and 14 nonfatal myocardial infarctions among the patients in the low-hematocrit group (risk ratio for the normal-hematocrit group as compared with the low-hematocrit group, 1.3; 95 percent confidence interval, 0.9 to 1.9). Increasing age, the presence of peripheral vascular disease, New York Heart Association class III cardiac disability, and the absence of hypertension at base line were significant risk factors for death or a first nonfatal myocardial infarction for both groups combined, whereas sex, race, the type of vascular access, Kt/V, and the presence of congestive heart failure, ischemic heart disease, and diabetes mellitus were not. These 11 prespecified base-line characteristics do not explain the differences in outcomes in the two groups, because adjustment for these factors did not change the risk ratio for the normal-hematocrit group as



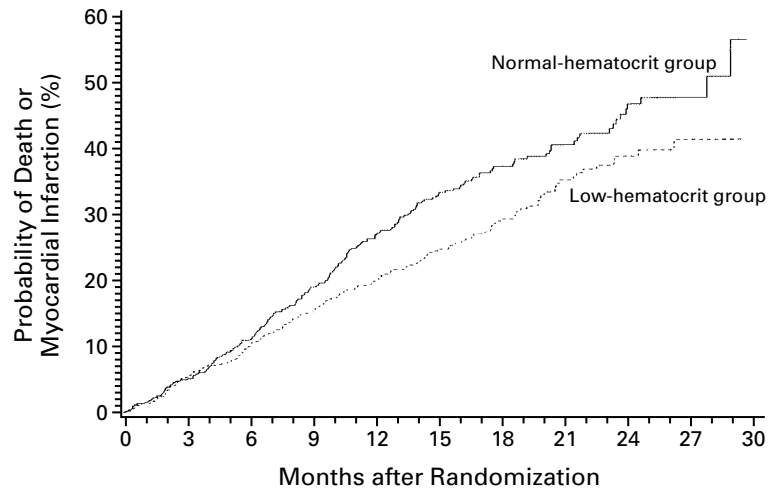
**Figure 1. Mean Monthly Hematocrit Values and Epoetin Doses during the Study in the Normal-Hematocrit and Low-Hematocrit Groups.**

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.

compared with the low-hematocrit group (risk ratio 1.3; 95 percent confidence interval, 0.9 to 1.8). There were no significant differences in outcomes between study centers.

The one-year and two-year mortality rates were 7 percentage points higher in the normal-hematocrit group than in the low-hematocrit group. Thirty-two patients in the normal-hematocrit group died between 16 and 318 days after prematurely stopping study therapy. In many of these patients the hematocrit fell considerably before they died, but the deaths were counted in the normal-hematocrit group according to the intention-to-treat analysis. The causes of death, as ascribed by the investigators, were similar in the two groups, the majority (67 percent) being cardiovascular in nature (Table 2).

There were no significant differences between the groups in the rates of hospitalization for all causes, nonfatal myocardial infarction, angina pectoris requir-



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.

ing hospitalization, congestive heart failure requiring hospitalization, coronary-artery bypass grafting, or percutaneous transluminal coronary angioplasty (Table 3). During the study, 129 patients in the normal-hematocrit group (21 percent) received red-cell transfusions, as compared with 192 patients in the low-hematocrit group (31 percent) ( $P < 0.001$ ). Events such as gastrointestinal bleeding and surgical blood loss prompted many of these transfusions. There were no significant differences in the use of six categories of cardiovascular drugs (angiotensin-converting–enzyme inhibitors, antiarrhythmic drugs,  $\beta$ -adrenergic antagonists, calcium-channel blockers, digoxin or digitoxin, and nitrates) between the two groups at base line, 6 months, or 12 months.

The physical-function score on the quality-of-life questionnaire at 12 months increased by 0.6 point for each percentage-point increase in the hematocrit ( $P = 0.03$ ). For example, an increase in the hematocrit from 30 percent to 42 percent was associated with a clinically meaningful increase of 7.2 points in the score on the physical-function scale. There were no significant changes in the scores on the other seven scales.

There were no significant differences in blood pressure between the two groups during the study, the mean values being approximately 150 mm Hg for systolic blood pressure and 78 mm Hg for diastolic blood pressure. 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 natu-

ral fistulae clotted more often in the normal-hematocrit group. There were no differences between groups in the incidence of cerebrovascular accidents, transient ischemic attacks, peripheral gangrene, intestinal ischemia, or seizures. There were no significant differences between the groups in routine serum chemical values, nonerythroid hematologic values, or coagulation test results at base line. At six months, there were significant differences for several assays, but none were of clinically meaningful magnitude. The mean ( $\pm$ SD) serum ferritin concentration was lower in the normal-hematocrit group than in the low-hematocrit group at base line ( $334 \pm 313$  vs.  $403 \pm 436$  ng per milliliter,  $P = 0.002$ ) and during the study ( $391 \pm 424$  vs.  $503 \pm 442$  ng per milliliter at 12 months,  $P = 0.005$ ). Serum transferrin saturation did not differ significantly between the groups at base line (normal-hematocrit group,  $26.8 \pm 12.9$  percent; low-hematocrit group,  $26.3 \pm 12.0$  percent) or during treatment. The adequacy of hemodialysis, as gauged by the Kt/V, was similar at base line, with values of  $1.38 \pm 0.35$  for both groups, but diverged by one year: Kt/V decreased to  $1.35 \pm 0.36$  in the normal-hematocrit group and increased to  $1.44 \pm 0.36$  in the low-hematocrit group ( $P < 0.001$  for the comparison between groups). Thirty-two percent of the patients in the normal-hematocrit group had a Kt/V value below 1.20 at six months, as compared with 22 percent of the patients in the low-hematocrit group.

The mortality rate in each group at various hematocrit values, calculated as the average of all values for each patient until death, loss to follow-up, or

**TABLE 2. CAUSES OF DEATH.\***

CAUSE OF DEATH	NORMAL- HEMATOCRIT GROUP (N=195)	LOW- HEMATOCRIT GROUP (N=160)
	no. (%)	
<b>Cardiovascular causes</b>	125 (64)	112 (70)
Cardiac arrest	30 (15)	24 (15)
Acute myocardial infarction	22 (11)	28 (18)
Arrhythmia	19 (10)	14 (9)
Unwitnessed death	18 (9)	9 (6)
Cerebrovascular accident	14 (7)	9 (6)
Coronary artery disease	6 (3)	7 (4)
Cardiomyopathy	5 (3)	6 (4)
Ischemic bowel	3 (2)	2 (1)
Congestive heart failure	2 (1)	2 (1)
Valvular heart disease	1 (1)	3 (2)
Cardiogenic shock	1 (1)	0
Other	4 (2)	8 (5)
<b>Noncardiovascular causes</b>	70 (36)	48 (30)
Sepsis or infection	32 (16)	22 (14)
Voluntary withdrawal from dialysis	11 (6)	7 (4)
Cancer	4 (2)	3 (2)
Hemorrhage	4 (2)	2 (1)
Encephalopathy	3 (2)	2 (1)
Hyperkalemia	3 (2)	2 (1)
Hepatic failure	0	3 (2)
Other	13 (7)	7 (4)

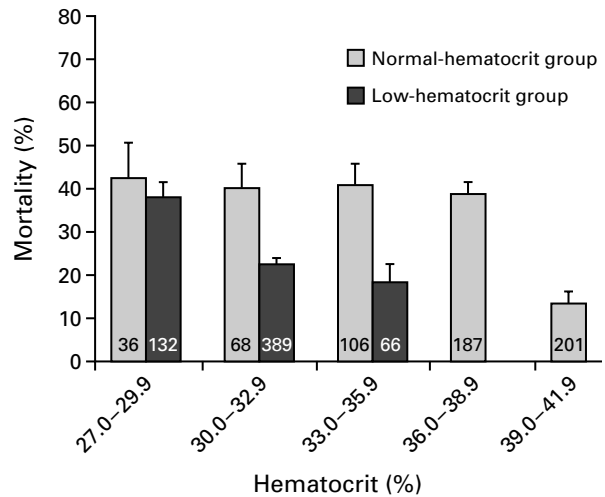
\*Because of rounding, percentages do not total 100.

**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

\*The P values were calculated with Fisher's exact test.

March 31, 1996, decreased at higher hematocrit values, but the mortality rate in the normal-hematocrit group was higher than that in the low-hematocrit group for any given range of hematocrit values (Fig. 3). When the average hematocrit replaced group assignment in the Cox regression analysis of the pre-



**Figure 3.** Mean ( $\pm$ SE) Mortality Rate as a Function of the Average Hematocrit Value in the Normal-Hematocrit and Low-Hematocrit Groups.

The number of patients in each group is shown in the bars. Only hematocrit values for which there were at least 20 patients per group are shown.

specified covariates described earlier, the risk ratio was 0.7 (95 percent confidence interval, 0.6 to 0.8;  $P<0.001$ ), indicating a 30 percent decrease in the risk of death or myocardial infarction per 10-point increase in hematocrit, for all patients. The mortality rates in the two groups also declined at higher hematocrit values when the values for only the last four weeks before death or censoring (at loss to follow-up or on March 31, 1996) were averaged. Mortality was also compared between the 443 patients in the normal-hematocrit group who had hematocrits of 39 percent (the lower boundary of the target range) or higher for four consecutive weeks and all patients in the low-hematocrit group, according to a prespecified subgroup analysis. The mortality rate in the low-hematocrit group exceeded that in the normal-hematocrit subgroup, but not significantly. A higher epoetin dose was not associated with increased mortality. The rate of thrombosis of the vascular access sites did not increase in either group at higher hematocrit values or at higher epoetin doses.

Intravenous iron dextran was administered to 526 patients in the normal-hematocrit group and 464 patients in the low-hematocrit group ( $P<0.001$ ). Among the patients in the normal-hematocrit group who were studied for at least six months, logistic-regression analysis yielded an odds ratio of mortality of 2.4 ( $P<0.001$ ) for patients who received intravenous iron dextran during the six months before death or censoring, as compared with those who did not. During the six months before death or censoring, the patients in the normal-hematocrit group

who survived received an average of  $152 \pm 150$  mg of iron dextran per four-week period and those who died received an average of  $214 \pm 190$  mg per four-week period ( $P < 0.001$ ); among the patients in the low-hematocrit group the respective values were  $119 \pm 133$  and  $145 \pm 179$  mg ( $P = 0.36$ ). Bleeding episodes were not more frequent in the normal-hematocrit group than in the low-hematocrit group; in other words, it is unlikely that the increased use of intravenous iron was a marker of hemorrhaging in patients in the normal-hematocrit group.

## DISCUSSION

Many earlier studies of patients who were undergoing dialysis have demonstrated the benefits of increasing hematocrit values from below 30 percent to 30 to 38 percent. The benefits include a decrease in the need for transfusion<sup>18</sup> and an improvement in the quality of life and cognitive function,<sup>19-21</sup> cardiac function and dimensions,<sup>4-9</sup> exercise capacity,<sup>22,23</sup> and immune function.<sup>24,25</sup> Furthermore, in retrospective studies, the mortality rate among patients with hematocrits below 30 percent was higher than that among patients with hematocrits of 30 to 35 percent, and the risk for the smaller number of patients with hematocrits above 35 percent was not significantly different from the risk associated with hematocrits of 30 to 35 percent.<sup>26,27</sup> Earlier studies also suggested that up to 35 percent of patients had increases in blood pressure after the partial correction of anemia,<sup>18</sup> whereas the risk of thrombosis of vascular access sites has remained controversial.<sup>18,28-30</sup> In several small studies, normalization of hematocrit was associated with improvements in cognitive function,<sup>31</sup> quality of life,<sup>13</sup> exercise capacity,<sup>13,32</sup> and sleep.<sup>33</sup> Thus, the results of the present study were unexpected.

Our 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. However, our results may not be applicable to all patients who are undergoing dialysis, because we studied patients receiving hemodialysis who had cardiac disease, who were older, and who had more coexisting diseases (e.g., diabetes mellitus and hypertension as a cause of renal failure) than the general U.S. population of patients who are undergoing dialysis.<sup>34</sup>

What could explain the higher mortality rate in the normal-hematocrit group? The higher hematocrit values themselves do not appear to account for the disparate outcomes. In both groups, higher hematocrit values were associated with lower mortality, notwithstanding the differences between groups. The patients in the normal-hematocrit group received higher doses of epoetin, but a higher dose was not

associated with increased mortality (data not shown). The causes of death were similar in the two groups, and the patients were closely matched with respect to demographic and laboratory characteristics and coexisting diseases. The differences in mortality were not associated with differences in serum chemical values, serum ferritin concentrations, coagulation profiles, blood pressure, or treatment with antihemostatic medications (aspirin, dipyridamole, warfarin, or daily heparin).

There may be no single, unifying explanation for the results, and multiple factors related to the study intervention may have had a cumulative effect. Two factors that differed between the groups during the study were the Kt/V values and the receipt of intravenous iron dextran. Higher Kt/V values are thought to correlate with more adequate dialysis and improved patient survival. The patients in the normal-hematocrit group had decreases in Kt/V values during the first year, whereas the values increased among the patients in the low-hematocrit group. More patients in the normal-hematocrit group received intravenous iron dextran therapy, and in greater quantities, and this treatment was associated with an increased risk of death among the patients in this group. Preliminary studies of patients undergoing coronary-artery bypass grafting suggest that iron may catalyze the generation of oxygen-derived free radicals, damaging the myocardium (Ambrus CM: personal communication), and higher iron stores may be associated with detrimental coronary outcomes in men.<sup>35,36</sup> In addition, iron may predispose patients who are undergoing hemodialysis to infection<sup>37,38</sup> and increase the risk of death due to infection<sup>39</sup> (there were 10 more deaths related to infection in the normal-hematocrit group than in the low-hematocrit group). The post hoc nature of these observations limits their validity, however.

Other, unrecognized mechanisms associated with the attempt to achieve and maintain a hematocrit of 42 percent could increase the likelihood of death. Two additional prospective trials assessing the effects of a normal hematocrit are under way in Canada and Scandinavia and may shed further light on these issues. At present, however, the use of epoetin therapy to achieve a target hematocrit value of 42 percent among patients with clinically evident congestive heart failure or ischemic heart disease who are receiving hemodialysis is not recommended.

Supported by Amgen. Drs. Schwab and Nissenson have served as consultants to Amgen.

*We are indebted to the patients who participated in this trial, to the study coordinators who worked diligently to conduct a rigorous study, to Ms. Mary Holleron for skillful preparation of the manuscript, to Chao Wang, Ph.D., for select statistical analyses, and to Leslie Lescale-Matys, Ph.D., for participating in the steering committee with the authors.*

## APPENDIX

The following principal investigators participated in the study: M. Allon, Birmingham, Ala.; G. Appel, New York; R. Benz, Wynnewood, Pa.; J. Berns, Philadelphia; K. Bleifer, Van Nuys, Calif.; J. Bower, Jackson, Miss.; W. Cleveland, Atlanta; I. Cruz, Washington, D.C.; D. Domoto, St. Louis; S. Fishbane, Mineola, N.Y.; D. Gentile, Orange, Calif.; L. Glowacki, Dallas; J. Goldman, Philadelphia; J. Hertel, Augusta, Ga.; D. Hoffman, Miami; H. Karp, Somers Point, N.J.; C. Kaupke, Orange, Calif.; K. Kleinman, Tarzana, Calif.; S. Korbet, Chicago; A. Lauer, Brockton, Mass.; V. Lim, Iowa City, Iowa; J. Lindberg, New Orleans; M. Linsey, Pasadena, Calif.; J. MacLaurin, Columbus, Ohio; T. Marbury, Orlando, Fla.; S. Mischel, Hammond, Ind.; D. Molony, Houston; J. Navarro, Tampa, Fla.; E. Paganini, Cleveland; D. Price, Boston; R. Raja, Philadelphia; J. Reiter, Missoula, Mont.; J. Rimmer, Burlington, Vt.; P. Schoenfeld, San Francisco; W. Smith, New Orleans; D. Spiegel, Denver; M. Stegman, Memphis, Tenn.; K. Stenzel, New York; J. Sugihara, Honolulu; G. Ting, Mountain View, Calif.; N. Vaziri, Orange, Calif.; M. Walczyk, Portland, Oreg.; D. Van Wyck, Tucson, Ariz.; S. Wen, Madison, Wis.; B. Wilkes, Manhasset, N.Y.; M. Weiner, Lancaster, Pa.; and B. Wood, Kansas City, Mo. **Data monitoring committee:** P. Parfrey (chairman), St. John's, Newf., Canada; W. Bennett, Portland, Oreg.; T. Fleming, Seattle; D. Levy, Framingham, Mass.; N. Muirhead, London, Ont., Canada; M. Pfeffer, Boston; C. Winearls, Oxford, England.

## REFERENCES

- Case Records of the Massachusetts General Hospital: normal reference laboratory values. *N Engl J Med* 1992;327:718-24.
- Kusunoki M, Kimura K, Nakamura M, Isaka Y, Yoneda S, Abe H. Effects of hematocrit variations on cerebral blood flow and oxygen transport in ischemic cerebrovascular disease. *J Cereb Blood Flow Metab* 1981;1:413-7.
- Rostand SG, Rutsky EA. Cardiac disease in dialysis patients. In: Nissenson AR, Fine RN, Gentile DE, eds. *Clinical dialysis*. 2nd ed. Norwalk, Conn.: Appleton & Lange, 1990:409-46.
- Macdougall IC, Lewis NP, Saunders MJ, et al. Long-term cardiorespiratory effects of amelioration of renal anaemia by erythropoietin. *Lancet* 1990;335:489-93. [Erratum, *Lancet* 1990;335:614.]
- Wizemann V, Kaufmann J, Kramer W. Effect of erythropoietin on ischemia tolerance in anemic hemodialysis patients with confirmed coronary artery disease. *Nephron* 1992;62:161-5.
- Cannella G, La Canna G, Sandrini M, et al. Reversal of left ventricular hypertrophy following recombinant human erythropoietin treatment of anaemic dialysed uraemic patients. *Nephrol Dial Transplant* 1991;6:31-7.
- Pascual J, Teruel JL, Moya JL, Liano F, Jimenez-Mena M, Ortuno J. Regression of left ventricular hypertrophy after partial correction of anemia with erythropoietin in patients on hemodialysis: a prospective study. *Clin Nephrol* 1991;35:280-7.
- Goldberg N, Lundin AP, Delano B, Friedman EA, Stein RA. Changes in left ventricular size, wall thickness, and function in anemic patients treated with recombinant human erythropoietin. *Am Heart J* 1992;124:424-7.
- Zehnder C, Zuber M, Sulzer M, et al. Influence of long-term amelioration of anemia and blood pressure control on left ventricular hypertrophy in hemodialyzed patients. *Nephron* 1992;61:21-5.
- Silberberg JS, Barre PE, Prichard SS, Sniderman AD. Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int* 1989;36:286-90.
- Parfrey PS, Griffiths SM, Harnett JD, et al. Outcome of congestive heart failure, dilated cardiomyopathy, hypertrophic hyperkinetic disease, and ischemic heart disease in dialysis patients. *Am J Nephrol* 1990;10:213-21.
- Parfrey PS, Harnett JD, Barre PE. The natural history of myocardial disease in dialysis patients. *J Am Soc Nephrol* 1991;2:2-12.
- Eschbach JW, Glenny R, Robertson T, et al. Normalizing the hematocrit (HCT) in hemodialysis patients (HDP) with EPO improves quality of life (Q/L) and is safe. *J Am Soc Nephrol* 1993;4:425. abstract.
- McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36). II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;31:247-63.
- Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659-63.
- Jennison C, Turnbull BW. Statistical approaches in interim monitoring of medical trials: a review and commentary. *Stat Sci* 1990;5:299-317.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease: results of a phase III multicenter clinical trial. *Ann Intern Med* 1989;111:992-1000.
- Evans RW, Rader B, Manninen DL, Cooperative Multicenter EPO Clinical Trial Group. The quality of life of hemodialysis recipients treated with recombinant human erythropoietin. *JAMA* 1990;263:825-30.
- Beusterien KM, Nissenson AR, Port FK, Kelly M, Steinwald B, Ware JE Jr. The effects of recombinant human erythropoietin on functional health and well-being in chronic dialysis patients. *J Am Soc Nephrol* 1996;7:763-73.
- Marsh JT, Brown WS, Wolcott D, et al. rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. *Kidney Int* 1991;39:155-63.
- Lundin AP, Akerman MJ, Chesler RM, et al. Exercise in hemodialysis patients after treatment with recombinant human erythropoietin. *Nephron* 1991;58:315-9.
- Braumann KM, Nonnast-Daniel B, Böning D, Böcker A, Frei U. Improved physical performance after treatment of renal anemia with recombinant human erythropoietin. *Nephron* 1991;58:129-34.
- Veys N, Vanholder R, Ringoir S. Correction of deficient phagocytosis during erythropoietin treatment in maintenance hemodialysis patients. *Am J Kidney Dis* 1992;19:358-63.
- Sennesael JJ, Van der Niepen P, Verbeelen DL. Treatment with recombinant human erythropoietin increases antibody titers after hepatitis B vaccination in dialysis patients. *Kidney Int* 1991;40:121-8.
- Collins A, Ma J, Umen A. Hematocrit as a time-dependent risk factor. *J Am Soc Nephrol* 1994;5:439. abstract.
- Lowrie EG, Ling J, Lew NL. The anemia of ESRD and related thoughts about iron and EPO therapy. Waltham, Mass.: National Medical Care, August 10, 1995 (memorandum).
- Canadian Erythropoietin Study Group. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. *BMJ* 1990;300:573-8.
- Eschbach JW. Erythropoietin is not a cause of access thrombosis. *Semin Dial* 1993;6:180-4.
- Muirhead N. Erythropoietin is a cause of access thrombosis. *Semin Dial* 1993;6:184-8.
- Nissenson AR, Pickett JL, Theberge DC, Brown WS, Schweitzer SV. Brain function is better in hemodialysis (HD) patients (PTS) when hematocrit is normalized with erythropoietin (rHuEPO). *J Am Soc Nephrol* 1996;7:1459. abstract.
- Bárány P, Svendenhag J, Katzarski K, et al. Physiological effects of correcting anemia in hemodialysis patients (HD pts) to a normal HB. *J Am Soc Nephrol* 1996;7:1472. abstract.
- Benz RL, Pressman MR, Hovick ET, Peterson DD. Relationship between anemia of chronic renal failure (ACRF) and sleep, sleep disorders and daytime alertness: benefits of normalizing hematocrit (the Sleepo Trial). *J Am Soc Nephrol* 1996;7:1473. abstract.
- Renal Data System. USRDS 1996 annual data report. Bethesda, Md.: National Institute of Diabetes and Digestive and Kidney Diseases, April 1996:23.
- Salonen JT, Nyyssonen K, Korpela H, Tuomilehto J, Seppanen R, Salonen R. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. *Circulation* 1992;86:803-11.
- Sullivan JL. Iron and the sex difference in heart disease risk. *Lancet* 1981;1:1293-4.
- Tielemans CL, Lenclud CM, Wens R, Collart FE, Dratwa M. Critical role of iron overload in the increased susceptibility of haemodialysis patients to bacterial infections: beneficial effects of desferrioxamine. *Nephrol Dial Transplant* 1989;4:883-7.
- Hoehn B, Kessler M, Hestlin D, Mayeux D. Risk factors for bacterial infections in chronic haemodialysis adult patients: a multicentre prospective survey. *Nephrol Dial Transplant* 1995;10:377-81.
- Collins A, Ebben J, Ma J. Frequent IV iron dosing is associated with higher infectious deaths. *J Am Soc Nephrol* 1997;8:190A. abstract.