Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

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*Investigators in the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial are listed in the Appendix.

ABSTRACT

BACKGROUND

Anemia, a common complication of chronic kidney disease, usually develops as a consequence of erythropoietin deficiency. Recombinant human erythropoietin (epoetin alfa) is indicated for the correction of anemia associated with this condition. However, the optimal level of hemoglobin correction is not defined.

METHODS

In this open-label trial, we studied 1432 patients with chronic kidney disease, 715 of whom were randomly assigned to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 13.5 g per deciliter and 717 of whom were assigned to receive a dose targeted to achieve a level of 11.3 g per deciliter. The median study duration was 16 months. The primary end point was a composite of death, myocardial infarction, hospitalization for congestive heart failure (without renal replacement therapy), and stroke.

RESULTS

A total of 222 composite events occurred: 125 events in the high-hemoglobin group, as compared with 97 events in the low-hemoglobin group (hazard ratio, 1.34; 95% confidence interval, 1.03 to 1.74; P=0.03). There were 65 deaths (29.3%), 101 hospitalizations for congestive heart failure (45.5%), 25 myocardial infarctions (11.3%), and 23 strokes (10.4%). Seven patients (3.2%) were hospitalized for congestive heart failure and myocardial infarction combined, and one patient (0.5%) died after having a stroke. Improvements in the quality of life were similar in the two groups. More patients in the high-hemoglobin group had at least one serious adverse event.

CONCLUSIONS

The use of a target hemoglobin level of 13.5 g per deciliter (as compared with 11.3 g per deciliter) was associated with increased risk and no incremental improvement in the quality of life. (ClinicalTrials.gov number, NCT00211120.)
A

EMIA IS COMMON AMONG PATIENTS
with chronic kidney disease. In such pa-
tients, treatment with erythropoietin has
been shown to enhance the quality of life. However, evidence suggesting that the correction of
anemia improves cardiovascular outcomes has
largely been derived from observational studies and
small interventional trials associating a high level of
hemoglobin (>12.0 g per deciliter) with a lower
rate of complications and death from cardiovascu-
ar causes. Other evidence has also indicated that
cardiovascular complications, such as left ventric-
ular hypertrophy, might be improved through the
use of a high hemoglobin level as a target. How-
ever, in a randomized, controlled study compar-
ing a hematocrit target of 42% with that of 30%
among patients with heart disease who were un-
dergoing hemodialysis, the former group had
higher rates of nonfatal myocardial infarction and
death, but not significantly so.

In 2000, a panel of the Kidney Disease Out-
comes Quality Initiative of the National Kidney
Foundation recommended that the target level of
hemoglobin should be 11.0 to 12.0 g per deciliter
in patients with chronic kidney disease, whether
or not they were receiving dialysis. A recent up-
date of guidelines regarding anemia in such pa-
tients expanded the target range to 11.0 to 13.0 g
per deciliter, with the increase in the upper limit
of the target range justified on the basis of a po-
tential improvement in the patients’ quality of life.

In the Correction of Hemoglobin and Outcomes
in Renal Insufficiency (CHOIR) trial, we hypoth-
esized that in patients with chronic kidney dis-
ease, the use of recombinant human erythropoi-
etin (epoetin alfa) to achieve a high hemoglobin
level (13.5 g per deciliter) would decrease the risk of complications from cardiovascular causes
and death, as compared with a lower hemoglobin
level (11.3 g per deciliter).

MET
HODS

STUDY SUBJECTS
We conducted an open-label, randomized trial to
study the risks and benefits of the correction of
anemia in patients with chronic kidney disease
who were not receiving dialysis. We enrolled 1432
patients at 130 sites in the United States. At en-
rollment, patients had to be at least 18 years of age,
have a hemoglobin level of less than 11.0 g per
deciliter, and have chronic kidney disease, defined
by an estimated glomerular filtration rate (GFR) of
15 to 50 ml per minute per 1.73 m² of body-surf
face area, with the use of the Modification of Diet
in Renal Disease (MDRD) formula. Key exclusion
criteria included the presence of uncontrolled
hypertension, active gastrointestinal bleeding, an
iron-overload state, a history of frequent transfu-
sions in the previous 6 months, refractory iron-
deficiency anemia, active cancer, previous thera-
py with epoetin alfa, or angina pectoris that was
unstable or present at rest.

INTERVENTION
Patients were assigned by computer-generated
permuted-block randomization to one of two groups:

- A high-hemoglobin group (with an initial hemo-
globin target of 13.0 to 13.5 g per deciliter) or
- A low-hemoglobin group (with an initial target of
10.5 to 11.0 g per deciliter).

A protocol amendment on February 25, 2003, changed the original hemo-
globin targets to 13.5 g per deciliter and 11.3 g per
deciliter, respectively. At the time of the protocol
amendment, 347 of the 1432 patients (24.2%) had
been enrolled, and only 132 of the total of 1939
patient-years had accrued. Both groups of patients
initially received epoetin alfa subcutaneously week-
ly; administration was subsequently permitted ev-
ery other week if the hemoglobin level was stable.

LABORATORY TESTS AND CLINICAL OUTCOMES
A central laboratory (Covance) performed all bio-
chemical and hematologic analyses. We assessed
the patients’ quality of life using the Linear Ana-
logue Self-Assessment (LASA) (scores range from
0 to 100, with higher scores indicating better func-
tion), the Kidney Disease Questionnaire (KDQ)
total scores range from 4 to 35, with higher scores
indicating better health), and the Medical Out-
comes Study 36-item Short-Form Health Survey
(SF-36) (scores for each subscale range from 0 to
100, with higher scores indicating better health).

Investigator-reported events were independently
adjudicated by the clinical committee reviewing
end points at the Duke Clinical Research Institute
(DCRI), whose members were unaware of patients’
study-group assignments. The primary end point

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Correction of Anemia and Chronic Kidney Disease

was the time to the composite of death, myocardial infarction, hospitalization for congestive heart failure (excluding renal replacement therapy), or stroke. Myocardial infarction was defined on the basis of any two of the following: chest pain that lasted for 15 minutes, abnormal cardiac enzyme levels, or new findings on electrocardiography suggestive of myocardial infarction. Hospitalization for congestive heart failure was defined as an unplanned presentation requiring admission, during which the patient received intravenous therapy with inotropes, diuretics, or vasodilators. If hospitalization involved renal replacement therapy, the event was not included in the primary composite endpoint. Stroke was defined as a new neurologic deficit of sudden onset that was not reversible within 24 hours and that was not due to a readily identifiable nonvascular cause (e.g., a brain tumor or trauma). Other secondary outcomes included the time to renal replacement therapy, hospitalization for either a cardiovascular cause or any cause, and quality of life.

STATISTICAL ANALYSIS

We calculated that 1352 patients would need to be enrolled for the study to have a statistical power of 80% to detect a 25% reduction in the composite event rate in the high-hemoglobin group over a period of 3 years, assuming a 30% event rate in the low-hemoglobin group, the occurrence of at least 295 composite events overall during the 3-year period, a 30% rate of early withdrawal for reasons other than the occurrence of the primary end point, and a type I error of 0.05. Four interim analyses were planned in which efficacy guidelines used the O’Brien–Fleming alpha-spending boundary, guidelines for futility in which the likelihood that the study would be mistakenly stopped because of a nonsignificant difference between groups was 2% or less, and a conditional power calculation. An independent data and safety monitoring board reviewed the study.

We used the Kaplan–Meier method to analyze the time to the first event for events that occurred during the study period. We used the log-rank test to compare the times to the first event between the two groups. Data on patients who did not have an event were censored at the time of study termination (either completion or early withdrawal). Repeated-measures analysis of variance was used to evaluate hemoglobin levels over time. Hemoglobin levels obtained within 28 days after a transfu-

sion were excluded. All patients who received at least one dose of study medication were included in the safety analysis. Serious adverse events were defined as life-threatening, resulting in death, hospitalization, or substantial disability, or leading to a congenital anomaly or birth defect. The principal investigators (Drs. Singh and Reddan) developed the protocol and all amendments in collaboration with the DCRI and the industry sponsor. The DCRI acquired and queried all data. The database was developed and locked at DCRI, and a copy was provided to the sponsor. The investigators had full access to the data. DCRI performed all the primary analyses, and the sponsor performed all secondary analyses, the results of which were verified by the DCRI. All analyses were performed with the use of SAS software, version 8.2 or higher.

RESULTS

EARLY TERMINATION OF THE STUDY

The data and safety monitoring board recommended that the study be terminated in May 2005 at the time of the second interim analysis, even though

Figure 1. Enrollment and Outcomes.

A total of 1432 patients were enrolled; 715 were assigned to the high-hemoglobin group (with a target level of 13.5 g per deciliter), and 717 were assigned to the low-hemoglobin group (with a target level of 11.3 g per deciliter). In addition to the stated reasons for withdrawal from the study, other reasons included a request from a patient, an investigator, or the study sponsor; pregnancy; an adverse event; a protocol violation; or a loss to follow-up. RRT denotes renal replacement therapy.
neither the efficacy nor the futility boundaries had been crossed, because the conditional power for demonstrating a benefit for the high-hemoglobin group by the scheduled end of the study was less than 5% for all plausible values of the true effect for the remaining data. Other factors that the board considered included an examination of differences between the treatment groups in adverse events, biochemical data, and quality-of-life data.

On the basis of the intention-to-treat principle, data from all 1432 patients were included in the final analysis (Fig. 1), and the nominal P value at final analysis is reported. Both the mean and the median duration of follow-up of all patients were 16 months; 661 patients (46.2%) completed 36 months of study or withdrew at study termination without having had a composite event. A total of 549 patients (38.3%) withdrew before termination of the study without having had a composite event. Among these patients, 242 (16.9%) withdrew because they began renal replacement therapy, and 307 patients (21.4% [147 from the high-hemoglobin group and 160 from the low-hemoglobin group]) withdrew for other reasons. However, the low-hemoglobin group had more patient-years of follow-up (980, as compared with 959 in the high-

### Table 1. Baseline Characteristics of the Patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High-Hemoglobin Group (N=715)</th>
<th>Low-Hemoglobin Group (N=717)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66.0±14.3</td>
<td>66.3±13.5</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>56.2</td>
<td>54.1</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62.3</td>
<td>61.1</td>
</tr>
<tr>
<td>Black</td>
<td>28.6</td>
<td>29.3</td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>3.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Other</td>
<td>5.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Hispanic ethnic background (%)</td>
<td>12.5</td>
<td>13.5</td>
</tr>
<tr>
<td>History of smoking tobacco (%)</td>
<td>47.5</td>
<td>44.6</td>
</tr>
<tr>
<td>Cause of chronic kidney disease (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>46.8</td>
<td>50.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29.9</td>
<td>27.5</td>
</tr>
<tr>
<td>Other</td>
<td>23.3</td>
<td>21.6</td>
</tr>
<tr>
<td>Cardiovascular history (%)</td>
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<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>95.8</td>
<td>93.2‡</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16.4</td>
<td>15.0</td>
</tr>
<tr>
<td>CABG</td>
<td>17.4</td>
<td>13.5‡</td>
</tr>
<tr>
<td>PCI</td>
<td>10.9</td>
<td>11.9</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>24.4</td>
<td>22.9</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9.4</td>
<td>8.6</td>
</tr>
<tr>
<td>Stroke</td>
<td>9.8</td>
<td>10.0</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>16.4</td>
<td>16.4</td>
</tr>
<tr>
<td>Myocardial infarction, stroke, CABG, PCI, or amputation of a lower limb</td>
<td>36.3</td>
<td>34.5</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>30.4±7.7</td>
<td>30.4±7.5</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>136.7±19.7</td>
<td>135.6±20.0</td>
</tr>
<tr>
<td>Diastolic</td>
<td>71.6±11.6</td>
<td>70.9±11.2</td>
</tr>
<tr>
<td>Mean arterial</td>
<td>93.3±12.1</td>
<td>92.5±12.0</td>
</tr>
</tbody>
</table>
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In the high-hemoglobin group. The reasons for early withdrawal were similar in both the two groups (data not shown).

CHARACTERISTICS OF THE PATIENTS

The demographic and baseline characteristics of the two groups were similar (Table 1), except for a higher rate of a self-reported history of hypertension (P = 0.03) and coronary-artery bypass grafting in the high-hemoglobin group (P = 0.05). During the course of the study, the overall use of iron in both the high-hemoglobin group and the low-hemoglobin group was similar (52.0% and 48.3%, respectively; P = 0.18). The mean (±SD) systolic blood pressure decreased modestly from baseline to the end of study, with a decrease of 2.3±22.8 mm Hg in the high-hemoglobin group and a decrease of 2.6±21.9 mm Hg in the low-hemoglobin group. The difference was not statistically significant between the two groups (P = 0.27). The mean diastolic blood pressure increased by 0.2±12.9 mm Hg in the high-hemoglobin group and decreased by 0.7±12.4 mm Hg in the low-hemoglobin group by the end of the study, as compared with baseline (P = 0.02).

The hemoglobin levels over time are shown in Figure 2A. The mean change in the hemoglobin level from baseline to the final measurement was 2.5 g per deciliter for the high-hemoglobin group and 1.2 g per deciliter for the low-hemoglobin group, a mean difference of 1.3 g per deciliter (P < 0.001). The mean weekly doses of epoetin alfa are shown in Figure 2B. The mean dose of epoetin alfa that was required to maintain the target

Table 1. (Continued.)

<table>
<thead>
<tr>
<th></th>
<th>High-Hemoglobin Group (N = 715)</th>
<th>Low-Hemoglobin Group (N = 717)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.1±0.9</td>
<td>10.1±0.9</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>31.4±2.9</td>
<td>31.4±2.9</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>25.2±11.8</td>
<td>24.6±10.1</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>167.8±157.2</td>
<td>179.2±171.5</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m2)§</td>
<td>36.7±17.0</td>
<td>37.1±17.9</td>
</tr>
<tr>
<td>GFR (ml/min)¶</td>
<td>27.0±8.7</td>
<td>27.3±9.1</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.7±0.5</td>
<td>3.8±0.5</td>
</tr>
<tr>
<td>Ratio of total protein to creatinine in urine</td>
<td>1.6±2.3</td>
<td>1.5±2.3</td>
</tr>
<tr>
<td>Medications (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor only</td>
<td>35.7</td>
<td>37.8</td>
</tr>
<tr>
<td>ARB only</td>
<td>29.7</td>
<td>26.8</td>
</tr>
<tr>
<td>Combination of ACE inhibitor and ARB</td>
<td>8.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Beta-blocker (including labetalol)</td>
<td>46.9</td>
<td>47.7</td>
</tr>
<tr>
<td>Platelet aggregation inhibitor (excluding heparin)</td>
<td>42.8</td>
<td>45.0</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitor</td>
<td>52.8</td>
<td>52.3</td>
</tr>
<tr>
<td>Iron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>2.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Oral</td>
<td>26.5</td>
<td>26.7</td>
</tr>
<tr>
<td>Unknown route</td>
<td>3.1</td>
<td>1.6</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. Race and ethnic group were assigned by the investigators. Cardiovascular history was reported either by the patient or by chart review. CABG denotes coronary-artery bypass grafting, PCI percutaneous coronary intervention, ACE angiotensin-converting enzyme, ARB angiotensin II–receptor blocker, and HMG CoA 3-hydroxy-3-methylglutaryl coenzyme A.
† P = 0.03 for the comparison with the high-hemoglobin group.
‡ P = 0.05 for the comparison with the high-hemoglobin group.
§ The rate was calculated with the use of the Cockcroft–Gault formula.
¶ The GFR was calculated according to the MDRD formula.
level in the high-hemoglobin group was nearly twice that required in the low-hemoglobin group (11,215 U and 6276 U per week, respectively).

**PRIMARY OUTCOMES**
In the primary analysis of the composite events, a patient was counted only once (e.g., if a myocardial infarction occurred before a stroke, then only the time from randomization to the myocardial infarction was included in the composite event for the patient). A total of 222 composite events (death, myocardial infarction, hospitalization for congestive heart failure without renal replacement therapy, or stroke) occurred: 125 among the 715 patients in the high-hemoglobin group, as compared with 97 among the 717 patients in the low-hemoglobin group (17.5% vs. 13.5%; hazard ratio, 1.34; 95% confidence interval [CI], 1.03 to 1.74; P = 0.03) (Fig. 3A). Of the 222 composite events, there were 65 deaths (29.3%), 101 hospitalizations for congestive heart failure without renal replacement therapy (45.5%), 25 myocardial infarctions (11.3%), and 23 strokes (10.4%). Notably, seven patients (3.2%) were hospitalized for congestive heart failure and had a myocardial infarction on the same day, and one patient (0.5%) died after having a stroke on the same day. Death and hospitalization for congestive heart failure accounted for 74.8% of the composite events. Sensitivity analyses yielded similar results. A per-protocol analysis of primary outcome data for 1395 patients showed a hazard ratio of 1.34 (95% CI, 1.03 to 1.75; P = 0.03) (Table 2). To account for possible bias from early withdrawal due to renal replacement therapy, the time from randomization to study termination or 30 days after the last administration of study medication, the hazard ratio was also 1.30 (95% CI, 1.01 to 1.66; P = 0.04). When the analysis included all events from randomization to 90 days after study termination, the hazard ratio was also 1.30 (95% CI, 1.01 to 1.66; P = 0.04). The four individual components of the primary event (death, myocardial infarction, hospitalization for congestive heart failure without renal replacement therapy, or stroke) occurred: 125 among the 715 patients in the high-hemoglobin group, as compared with 97 among the 717 patients in the low-hemoglobin group (17.5% vs. 13.5%; hazard ratio, 1.34; 95% confidence interval [CI], 1.03 to 1.75; P = 0.03) (Fig. 3A). Of the 222 composite events, there were 65 deaths (29.3%), 101 hospitalizations for congestive heart failure without renal replacement therapy (45.5%), 25 myocardial infarctions (11.3%), and 23 strokes (10.4%). Notably, seven patients (3.2%) were hospitalized for congestive heart failure and had a myocardial infarction on the same day, and one patient (0.5%) died after having a stroke on the same day. Death and hospitalization for congestive heart failure accounted for 74.8% of the composite events. Sensitivity analyses yielded similar results. A per-protocol analysis of primary outcome data for 1395 patients showed a hazard ratio of 1.34 (95% CI, 1.03 to 1.75; P = 0.03) (Table 2). To account for possible bias from early withdrawal due to renal replacement therapy, the time from randomization to study termination or 30 days after the last administration of study medication, the hazard ratio was also 1.30 (95% CI, 1.01 to 1.66; P = 0.04). When the analysis included all events from randomization to 90 days after study termination, the hazard ratio was also 1.30 (95% CI, 1.01 to 1.66; P = 0.04). When the analysis included all events from randomization to 90 days after study termination, the hazard ratio was also 1.30 (95% CI, 1.01 to 1.66; P = 0.04).

**SECONDARY OUTCOMES**
The four individual components of the primary end point, which were each evaluated independently, are shown in Figures 3B, 3C, 3D, and 3E and Table 2. As secondary outcomes, components of the primary end point (composite events) were analyzed separately (i.e., if a patient had more than one type of event, each event was counted the first time it occurred; therefore, a patient could be included in more than one event category). The four individual components of the primary event did not differ significantly between the two groups. However, the hazard ratio for death and hospitalization for congestive heart failure had a strong trend toward a higher risk in the high-hemoglobin group, unlike the trends for myocardial infarction and stroke. The role of renal replacement therapy was explored because, according to the protocol, the participation of patients in the study was terminated when renal replacement therapy was initiated. There was no significant difference in the percentage of patients who required renal replacement therapy between the two groups (P = 0.15) (Table 2). To account for possible bias from early withdrawal due to renal replacement therapy, the time to composite events or renal replacement therapy
was examined; the difference between the two groups persisted (hazard ratio, 1.28; 95% CI, 1.07 to 1.54; P=0.007). Results similar to those in the primary analysis were observed when hospitalization for congestive heart failure with renal replacement therapy was included in the composite end point (hazard ratio for the high-hemoglobin group vs. the low-hemoglobin group, 1.37; P=0.02). In addition, the results comparing all hospitalizations for congestive heart failure (including those involving renal replacement therapy) in the two groups were similar to the results of hospitalization for congestive heart failure in the primary end point (hazard ratio, 1.44; P=0.04).
The patients’ quality of life (as assessed by LASA, KDQ, and SF-36 scores) showed similar levels of improvement from baseline values in both groups, except for the score for the emotional role subscale of the SF-36, which was significantly higher in the low-hemoglobin group (Table 2).

Of the patients who reported adverse events, a total of 376 of 686 patients (54.8%) in the high-hemoglobin group and 334 of 688 patients (48.5%) in the low-hemoglobin group had at least one serious adverse event between the time of randomization and the end of the study (P = 0.02) (Table 3). The types of serious adverse events were similar in the two groups, with the exception of congestive heart failure, which occurred more frequently in the high-hemoglobin group (11.2% vs. 7.4%, P = 0.02). The types of serious adverse events that occurred after the end of study were also similar in the two groups (data not shown).

**Discussion**

We observed an increased risk of the primary composite end point in the high-hemoglobin group, as compared with the low-hemoglobin group. Death and hospitalization for congestive heart failure accounted for 74.8% of the composite events. On the basis of findings of three validated instruments (LASA, KDQ, and SF-36), the overall quality of life improved when anemia was treated with epoetin alfa, but aiming for a target value of 13.5 g of hemoglobin per deciliter provided no additional quality-of-life benefit. Since our study showed no apparent additional benefit in quality of life, and since the cost of epoetin alfa treatment increases with higher doses, we believe that the use of a high target hemoglobin level provides no cost benefit for either patients or payers in this population, even before considering risk.

Several studies have demonstrated that the correction of anemia in patients with chronic kidney disease improves the quality of life and exercise tolerance while reducing the need for transfusion. However, as Strippoli et al. have observed, there remains much uncertainty about the validity of various assessments of the quality of life in published studies.

Data on the effects of the correction of anemia on cardiovascular outcomes and survival have been both discordant and controversial. Recent large, controlled studies involving patients with pre–end-stage or end-stage renal disease have shown either an increase in adverse events or no benefit from the normalization of hemoglobin levels. Furthermore, in several studies, complete correction of anemia, as compared with partial correction, did not improve left ventricular hypertrophy. Our results, coupled with the results of other recent interventional trials involving patients with chronic kidney disease, reinforce the differences between observational and clinical trial data, which appear particularly notable in the setting of anemia therapy.

The Anemia Guideline Committee of the Dialysis Outcomes Quality Initiative has recently updated its guidelines. The lower limit of the hemoglobin level was set at 11.0 g per deciliter as an “evidence-based recommendation,” whereas the upper limit was set at 13.0 g per deciliter as a “clinical practice recommendation.” The committee concluded that there was insufficient evidence to recommend the routine maintenance of a hemoglobin level of 13.0 g per deciliter or higher in patients being treated with erythropoiesis-stimulating agents. There was also concern that the narrow range of 11 to 12 g per deciliter could not be achieved because of hemoglobin cycling. The panel emphasized that the use of a high target hemoglobin level may be associated with an increased risk. In the high-hemoglobin group in our study, we used a level of 13.5 g per deciliter as a target but achieved a mean level of just 12.6 g per
Primary Composite End Point

Myocardial Infarction
Hazard ratio: 1.41  \( P = 0.07 \)

Death
Hazard ratio: 1.01  \( P = 0.98 \)

Hospitalization for CHF (without RRT)
Hazard ratio: 1.41  \( P = 0.07 \)

Stroke
Hazard ratio: 1.01  \( P = 0.98 \)

Death
Hazard ratio: 1.48  \( P = 0.07 \)

A

No. at Risk
High-hemoglobin  Low-hemoglobin
25 612 612 587 520 457 355 270 176 101 72 55 23
717 660 594 539 491 397 291 182 107 67 44 23

B

No. at Risk
High-hemoglobin  Low-hemoglobin
23 564 591 523 461 359 273 179 102 73 56 23
717 663 596 544 504 402 299 187 111 70 45 24

C

No. at Risk
High-hemoglobin  Low-hemoglobin
715 674 612 543 487 387 295 193 115 79 59 25
717 672 609 560 520 415 307 192 115 73 49 26

D

No. at Risk
High-hemoglobin  Low-hemoglobin
715 675 611 543 487 386 295 195 113 79 59 25
717 675 610 564 523 418 310 195 117 74 49 26
**Table 2. Secondary End Points.**

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

* Plus–minus values are means ±SD. Hazard ratios are for the comparison of the high-hemoglobin group with the low-hemoglobin group. P values were calculated by the log-rank test.

† Components of the primary end point were analyzed separately. For example, if a patient had more than one type of event, each event was counted the first time it occurred. Therefore, a patient could be included in more than one category of events. In the primary analysis of the composite events, a patient was counted only once (e.g., if a myocardial infarction occurred before a stroke, then only the time from randomization to the myocardial infarction was included in the composite event for the patient).

‡ A total of 47 patients (24 in the high-hemoglobin group and 23 in the low-hemoglobin group) had a composite event.

¶ P values were calculated by analysis of covariance with the baseline score as a covariate.

∥ P values for comparisons of change from baseline were between <0.001 and 0.02 for all scales except for three subscales on the SF-36: pain (P=0.63), social function (P=0.23), and emotional role (P=0.81).

** Quality of life was measured with the LASA (scores range from 0 to 100, with higher scores indicating better function), the KDQ (total scores range from 4 to 35, with higher scores indicating better health), and the SF-36 (for each subscale, scores range from 0 to 100, with higher scores indicating better health).
Correction of Anemia and Chronic Kidney Disease

Patients in the high-hemoglobin group had a higher (but not significantly higher) rate of both progression to renal replacement therapy and hospitalization for renal replacement therapy. Small-er interventional studies have suggested the contrary. In a recent randomized, controlled study involving 88 patients, Gouva et al. reported that the early initiation of epoetin alfa treatment in patients with chronic kidney disease in an effort to achieve a hemoglobin level of 13.0 g per deci-liter reduced the rate of the composite end point of a doubling of creatinine levels, renal replace-ment, or death, as compared with deferred ini-tiation of treatment (\( P = 0.008 \) by the log-rank test).\(^{30} \) However, elsewhere in this issue of the Journal, the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) investigators report that more patients assigned to complete correction of anemia than to partial correction progressed to dialysis at the end of the study (\( P = 0.03 \)).\(^{24} \) Thus, it appears that larger stud-ies either demonstrate no apparent benefit or actually may show an increased risk of progres-sion to renal replacement therapy with the target-ing of a high hemoglobin value. Clearly, additional studies will be required to address this issue.

Our study has several potential limitations. Since we prespecified the censoring of data on patients at the time of the initiation of renal replace-ment therapy, no further data were collected; deciliter, with an increase in risk with no quality-of-life benefit. Furthermore, the number of pa-tients who had at least one serious adverse event was higher in the high-hemoglobin group than in the low-hemoglobin group. Thus, our study does not provide support for the expanded target range recently advocated by the National Kidney Foundation.

### Table 3. Adverse Events.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>High-Hemoglobin Group (N = 686)</th>
<th>Low-Hemoglobin Group (N = 688)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>607 (88.5)</td>
<td>589 (85.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Thrombovascular event</td>
<td>Any event</td>
<td>126 (18.4)</td>
<td>120 (17.4)</td>
</tr>
<tr>
<td>Any clinically relevant event;‡</td>
<td>74 (10.8)</td>
<td>82 (11.9)</td>
<td>0.51</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>376 (54.8)</td>
<td>334 (48.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Any serious adverse event associated with epoetin alfa§</td>
<td>10 (1.5)¶</td>
<td>3 (0.4)∥</td>
<td>0.05</td>
</tr>
<tr>
<td>Serious adverse events**</td>
<td>Congestive heart failure</td>
<td>77 (11.2)</td>
<td>51 (7.4)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10 (1.5)</td>
<td>19 (2.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>18 (2.6)</td>
<td>18 (2.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Chest pain</td>
<td>23 (3.4)</td>
<td>16 (2.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>16 (2.3)</td>
<td>11 (1.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>32 (4.7)</td>
<td>28 (4.1)</td>
<td>0.59</td>
</tr>
<tr>
<td>Renal failure</td>
<td>95 (13.8)</td>
<td>73 (10.6)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

- The analysis includes 1374 patients in the two study groups who received at least one dose of epoetin alfa and for whom data were collected regarding adverse events.
- † P values were calculated by the chi-square test.
- ‡ The thrombovascular events that were considered to be clinically relevant included myocardial infarction, stroke, angina pectoris, transient ischemic attack, deep-vein thrombosis, pulmonary embolism, and retinal-vein occlusion.
- § The event was deemed by the investigators to be related to drug administration.
- ¶ These events included two cases of deep-vein thrombosis and one case each of pulmonary embolism, retinal-vein occlusion, transient ischemic attack, deep-vein thrombosis and pulmonary embolism, priapism, rash, allergic dermatitis, and unstable angina.
- ∥ These events included one case each of hypertension, pulmonary embolism, and stroke.
- ** Serious adverse events that occurred in at least 2% of patients in either study group are listed.
there is a possibility of bias if the rates of renal replacement therapy differed between the two groups. Our analysis showed that there was no significant difference between the two groups with respect to the time to renal replacement therapy (P=0.15). Furthermore, when renal replacement therapy was treated as an event and added to the composite outcome, the difference between the two groups was similar to that obtained in the primary analysis. A potential limitation of the reporting of the components of the primary end point is the issue of death as a competing risk. It could be argued that the results with respect to myocardial infarction and stroke should be interpreted with caution; however, our primary results remain unchanged. We also censored data from the time-to-event analysis for a large number of patients because they required renal replacement therapy (16.9%) or withdrew from the study (21.4%) (Fig. 1). This factor would be a limitation if the censoring that occurred was not random in nature; however, such confounding is unlikely because the numbers of patients whose data were censored or who withdrew for other reasons did not differ significantly between the two groups. The differential withdrawal rate could also have generated bias. The low-hemoglobin group did have a higher number of early withdrawals for other reasons than did the high-hemoglobin group. However, the low-hemoglobin group had more patient-years of follow-up (980, as compared with 959 in the high-hemoglobin group). Furthermore, the two groups had similar demographic characteristics at baseline.

Another potential limitation is the lack of a double-blind design; this could have biased the assessment of some end points, such as congestive heart failure and the quality of life, which have an element of subjectivity. To address this issue, we used a tighter definition of congestive heart failure (i.e., without renal replacement therapy). In addition, the adjudication process by the committee reviewing clinical end points should have attenuated the possibility of bias because committee members were unaware of patients’ study-group assignments.

In conclusion, our study showed that the use of a target hemoglobin level of 13.5 g per deciliter (as compared with a level of 11.3 g per deciliter) is associated with an increased risk among patients with anemia caused by chronic kidney disease. Furthermore, no incremental improvement in the quality of life was observed. Hence, we recommend the use of a target hemoglobin level of 11.0 to 12.0 g per deciliter rather than a level of 11.0 to 13.0 g per deciliter to correct anemia in patients with chronic kidney disease, because of increased risk, a likely increased cost, and no quality-of-life benefit. This study did not provide a mechanistic explanation for the poorer outcome with the use of a high target hemoglobin level. More studies will be required to explore the role of the level of hemoglobin and the dose of epoetin alfa to understand these findings more completely.

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Dr. Singh reports receiving consulting fees from Ortho Biotech Clinical Affairs, Amgen, Roche, Merck (Germany), Abbott, Watson, and Horizon Blue Cross Blue Shield and lecture fees from Ortho Biotech Clinical Affairs, Roche, Amgen, Abbott, Watson, Scios, Pfizer, and Genzyme; serving on advisory boards for Ortho Biotech Clinical Affairs, Roche, Acologix, Watson, Advanced Magnetics, and Amgen; and receiving grant support from Ortho Biotech Clinical Affairs, Dialysis Clinic, Roche, Baxter, Johnson & Johnson, Amgen, Watson, and Aspresa. Dr. Szczepk reports receiving consulting fees from Ortho Biotech Clinical Affairs, Nabi Pharmaceuticals, Gilead, Kura, Acologix, and Roche; lecture fees from Nabi Biopharmaceuticals, GlaxoSmithKline, Genzyme, Abbott, Amgen, and Ortho Biotech; and grant support from Ortho Biotech Clinical Affairs. Dr. Barnhart reports receiving consulting fees and grant support from Ortho Biotech Clinical Affairs. Drs. Tang and Wolfson report being employees of Ortho Biotech Clinical Affairs. Dr. Reddan reports receiving consulting fees from Ortho Biotech Clinical Affairs and Shire Pharmaceuticals; lecture fees from Amgen, Novartis, Pfizer, AstraZeneca, and General Electric; and grant support from Ortho Biotech Clinical Affairs. Drs. Novartis, Novartis, AstraZeneca, and General Electric; and grant support from Ortho Biotech Clinical Affairs, Amgen, and Novartis. No other potential conflict of interest relevant to this article was reported.

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APPENDIX

The following investigators participated in the CHOIR trial: Study Chairs: A.K. Singh and D. Reddan. Investigators: University of Tennessee, Memphis — S. Acchiardo; Outcomes Research International, Hudson, FL — M.K. Acharya; University of Southern California, Los Angeles — M. Akmal; Research Institute of Dallas, Dallas — S. Arozenoff; North Shore University Hospital, Great Neck, NY — A. Ashfaq; Worcester Medical Center, Worcester, MA — R. Black; Louisiana State University Medical Center, Shreveport — J. Blondin; Bellłożyo Nephrology Medical Group, La Jolla, CA — M. Boiskin; University of Virginia Health System, Charlottesville — W.K. Bolton; South Dakota Health Research Foundation, Sioux Falls — L. Burris; Clínica Las Americas, San Juan, Puerto Rico — J.L. Cangiano; Emory Hypertension Research Center, Decatur, GA — A. Chapman; New York Hospital Medical Center of Queens, Flushing — C. Charytan; Regional Kidney Disease Centers/Associates in Nephrology, Erie, PA — E. Clark, F. Foti; Internal Medicine Specialists, Orlando, FL — I. Cohen; Carolina Kidney Associates, Greensboro, NC — J.A. Coladonato; Renal Hypertension Physicians, Mount Laurel, NJ — M. Conrad;