

ORIGINAL ARTICLE

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

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

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.)

From the Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston (A.K.S.); the Renal Division, Duke University Medical Center (L.S., D.R.), Duke Clinical Research Institute (L.S., S.S.), and the Department of Biostatistics and Bioinformatics, Duke University (H.B.) — all in Durham, NC; Ortho Biotech Clinical Affairs, Bridgewater, NJ (K.L.T., M.W.); and the Department of Medicine, University College Galway, Galway, Ireland (D.R.). Address reprint requests to Dr. Singh at the Renal Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at asingh@partners.org.

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

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ANEMIA IS COMMON AMONG PATIENTS with chronic kidney disease.¹ In such patients, treatment with erythropoietin has been shown to enhance the quality of life.²⁻⁵ 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 cardiovascular causes.⁶⁻⁸ Other evidence has also indicated that cardiovascular complications, such as left ventricular hypertrophy, might be improved through the use of a high hemoglobin level as a target.⁴ However, in a randomized, controlled study comparing a hematocrit target of 42% with that of 30% among patients with heart disease who were undergoing hemodialysis, the former group had higher rates of nonfatal myocardial infarction and death, but not significantly so.⁵

In 2000, a panel of the Kidney Disease Outcomes 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.⁹ A recent update of guidelines regarding anemia in such patients expanded the target range to 11.0 to 13.0 g per deciliter,¹⁰ with the increase in the upper limit of the target range justified on the basis of a potential improvement in the patients' quality of life. In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial, we hypothesized that in patients with chronic kidney disease, the use of recombinant human erythropoietin (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).

METHODS

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 enrollment, 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-surface area, with the use of the Modification of Diet in Renal Disease (MDRD) formula.¹¹ Key exclusion criteria included the presence of uncontrolled hypertension, active gastrointestinal bleeding, an iron-overload state, a history of frequent transfusions in the previous 6 months, refractory iron-deficiency anemia, active cancer, previous therapy 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 hemoglobin 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 hemoglobin 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 weekly; administration was subsequently permitted every other week if the hemoglobin level was stable. (For details about the epoetin alfa regimen, see the Supplementary Appendix, available with the full text of this article at www.nejm.org.) The institutional review board at each center approved the protocol, and all the patients gave written informed consent.

LABORATORY TESTS AND CLINICAL OUTCOMES

A central laboratory (Covance) performed all biochemical and hematologic analyses. We assessed the patients' quality of life using the Linear Analogue Self-Assessment (LASA) (scores range from 0 to 100, with higher scores indicating better function),¹² the Kidney Disease Questionnaire (KDQ) (total scores range from 4 to 35, with higher scores indicating better health),¹³ and the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) (scores for each subscale range from 0 to 100, with higher scores indicating better health).¹⁴ 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

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 end point. 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.^{15–17} 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

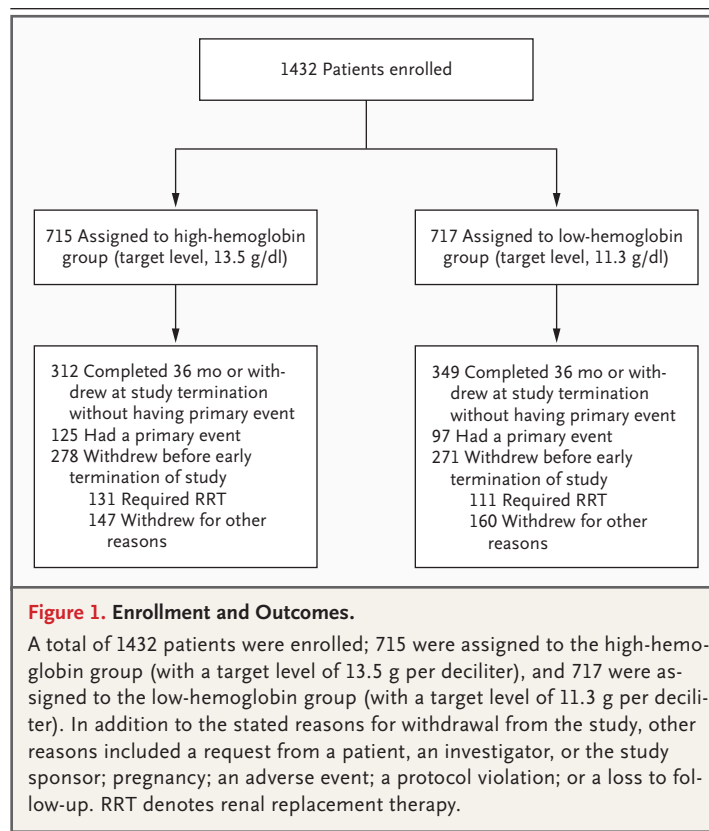


Table 1. Baseline Characteristics of the Patients.*

Characteristic	High-Hemoglobin Group (N=715)	Low-Hemoglobin Group (N=717)
Age (yr)	66.0±14.3	66.3±13.5
Female sex (%)	56.2	54.1
Race (%)		
White	62.3	61.1
Black	28.6	29.3
American Indian or Alaskan Native	0.1	0.4
Asian or Pacific Islander	3.4	3.2
Other	5.6	6.0
Hispanic ethnic background (%)	12.5	13.5
History of smoking tobacco (%)	47.5	44.6
Cause of chronic kidney disease (%)		
Diabetes	46.8	50.8
Hypertension	29.9	27.5
Other	23.3	21.6
Cardiovascular history (%)		
Hypertension	95.8	93.2†
Myocardial infarction	16.4	15.0
CABG	17.4	13.5‡
PCI	10.9	11.9
Congestive heart failure	24.4	22.9
Atrial fibrillation	9.4	8.6
Stroke	9.8	10.0
Peripheral vascular disease	16.4	16.4
Myocardial infarction, stroke, CABG, PCI, or amputation of a lower limb	36.3	34.5
Body-mass index	30.4±7.7	30.4±7.5
Blood pressure (mm Hg)		
Systolic	136.7±19.7	135.6±20.0
Diastolic	71.6±11.6	70.9±11.2
Mean arterial	93.3±12.1	92.5±12.0

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. (Continued.)

	High-Hemoglobin Group (N=715)	Low-Hemoglobin Group (N=717)
Hemoglobin (g/dl)	10.1±0.9	10.1±0.9
Hematocrit (%)	31.4±2.9	31.4±2.9
Transferrin saturation (%)	25.2±11.8	24.6±10.1
Ferritin (ng/ml)	167.8±157.2	179.2±171.5
Creatinine clearance (ml/min/1.73 m ²) [§]	36.7±17.0	37.1±17.9
GFR (ml/min) [¶]	27.0±8.7	27.3±9.1
Albumin (g/dl)	3.7±0.5	3.8±0.5
Ratio of total protein to creatinine in urine	1.6±2.3	1.5±2.3
Medications (%)		
ACE inhibitor only	35.7	37.8
ARB only	29.7	26.8
Combination of ACE inhibitor and ARB	8.3	9.6
Beta-blocker (including labetalol)	46.9	47.7
Platelet aggregation inhibitor (excluding heparin)	42.8	45.0
HMG CoA reductase inhibitor	52.8	52.3
Iron		
Intravenous	2.6	1.6
Oral	26.5	26.7
Unknown route	3.1	1.6

* 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.

hemoglobin group). The reasons for early withdrawal were similar in 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 de-

crease 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

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; $P=0.03$). The per-protocol population excluded 37 patients from the intention-to-treat population who did not meet the criteria required by the protocol and either underwent incorrect randomization, did not receive any dose of study medication, had no measurements of hemoglobin obtained after randomization, or did not meet all criteria for inclusion.

On the basis of data from the intention-to-treat population, but including all events from randomization to study termination or 30 days after the last administration of study medication, the hazard ratio for the primary outcome in the high-hemoglobin group, as compared with the low-hemoglobin group, was 1.30 (95% CI, 1.01 to 1.68; $P=0.04$). 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; $P=0.04$).

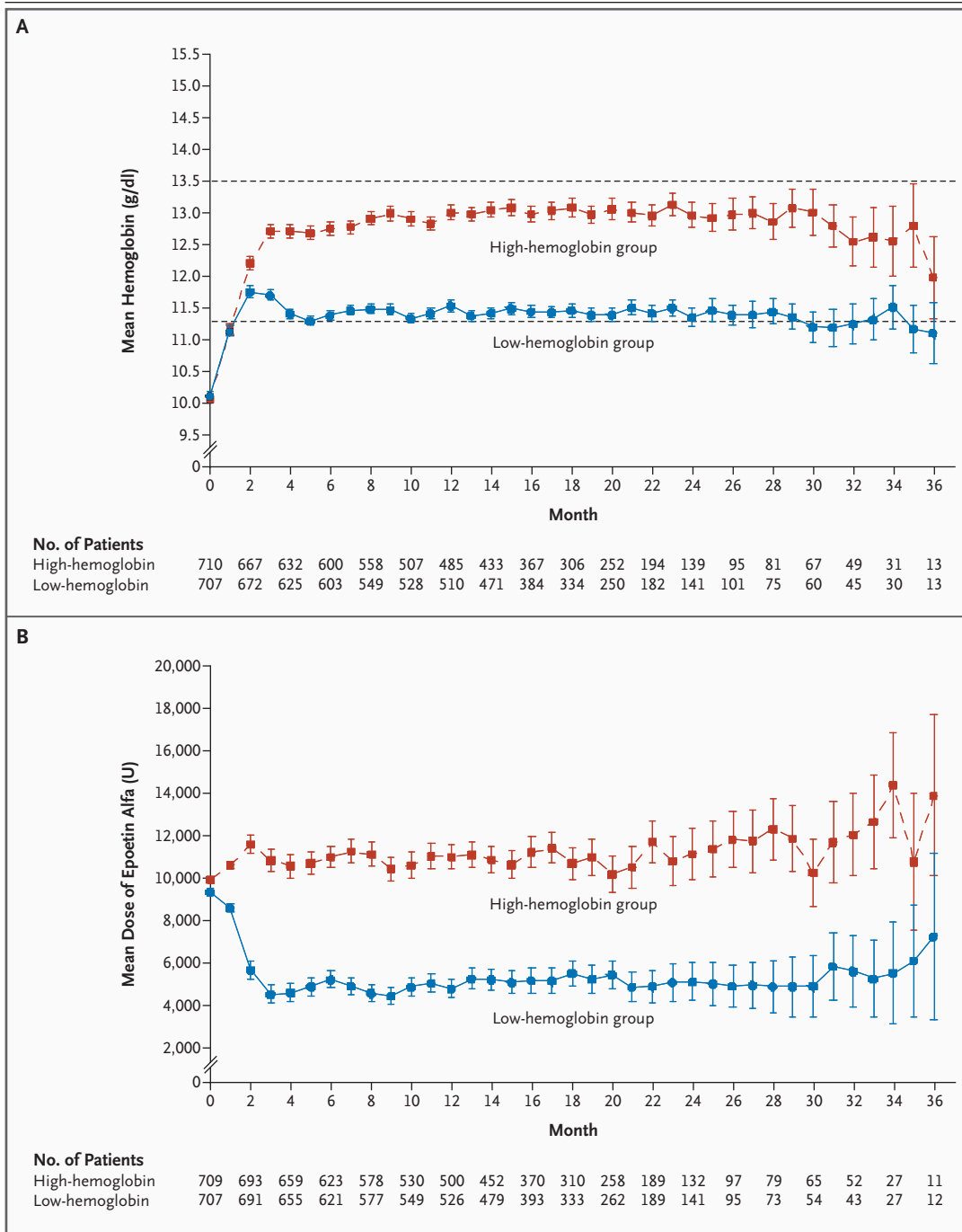
Figure 2 (facing page). Mean Monthly Hemoglobin Levels (Panel A) and Mean Weekly Doses of Epoetin Alfa (Panel B).

In Panel A, a separation in hemoglobin values between the two groups was observed just before the third month. Mean hemoglobin values were close to the target of 11.3 g per deciliter in the low-hemoglobin group but were consistently below the target of 13.5 g per deciliter in the high-hemoglobin group. A total of 93.9% of patients in the low-hemoglobin group and 75.9% of patients in the high-hemoglobin group had at least one hemoglobin value that reached the target. The median time for patients in the high-hemoglobin group to reach the target of 13.5 g per deciliter was 126 days (95% confidence interval [CI], 113 to 139), whereas it took a median of 36 days (95% CI, 29 to 43) for patients in the low-hemoglobin group to reach the target level of 11.3 g per deciliter ($P<0.001$). In Panel B, the mean dose of epoetin alfa for patients in the high-hemoglobin group who reached the target level was 10,694 U per week; for those who did not reach the target, the mean dose was 12,884 U per week ($P<0.001$). The mean dose of epoetin alfa for patients in the low-hemoglobin group who reached the target level was 6057 U per week; for those who did not reach the target level, the mean dose was 11,098 U per week ($P<0.001$). I bars denote 95% CIs.

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.^{5,18} However, as Strippoli et al. have observed,¹⁹ 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

Figure 3 (facing page). Kaplan–Meier Estimates of the Probability of the Primary Composite End Point and Secondary End Points of Individual Components — Hospitalization for Congestive Heart Failure (CHF) without Renal Replacement Therapy (RRT), Myocardial Infarction, Stroke, and Death.

Panel A shows that the largest separation between the two groups in the primary composite end point occurred at 15 months. At that time, the Kaplan–Meier estimate of the difference in cumulative event rates between the two groups reached 4.7 percentage points (15.8% in the high-hemoglobin group vs. 11.1% in the low-hemoglobin group). After 15 months, the difference between the two groups remained constant, with 752 patients (52.5%) remaining in the study (355 in the high-hemoglobin group and 397 in the low-hemoglobin group). There were no significant differences between the two groups in the four individual components of the primary composite end point (Panels B, C, D, and E). However, the hazard ratios for death and hospitalization for CHF had strong trends toward a higher risk in the high-hemoglobin group than in the low-hemoglobin group.

an increase in adverse events or no benefit from the normalization of hemoglobin levels.^{20–26} Furthermore, in several studies, complete correction of anemia, as compared with partial correction, did not improve left ventricular hypertrophy.^{18,20–23} Our results, coupled with the results of other recent interventional trials involving patients with chronic kidney disease,^{27,28} reinforce the differences between observational and clinical trial data, which appear particularly notable in the setting of anemia therapy.²⁹

The Anemia Guideline Committee of the Dialysis Outcomes Quality Initiative has recently updated its guidelines.¹⁰ 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

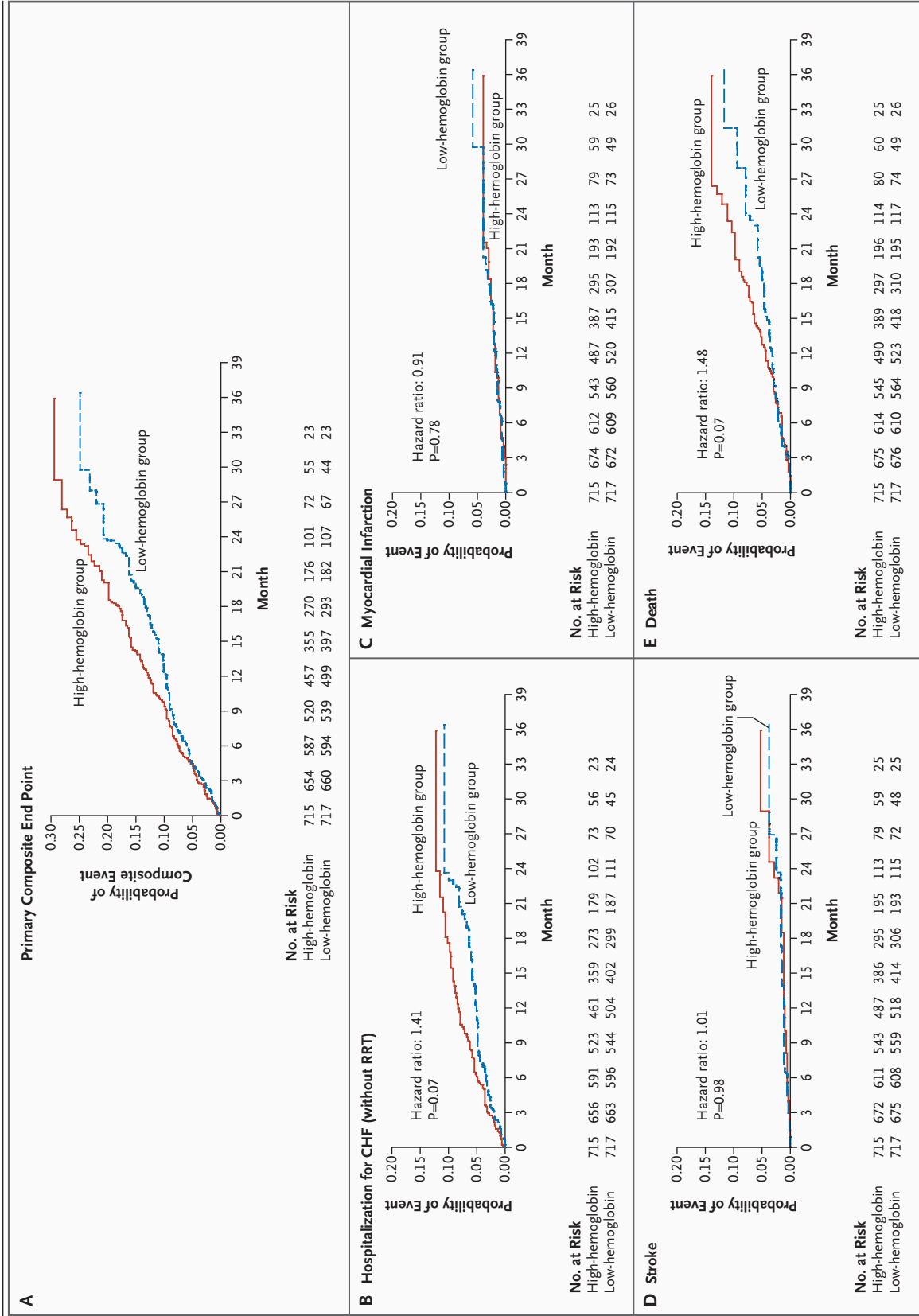


Table 2. Secondary End Points.*

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

* 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 the 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).

** P values for comparisons of change from baseline were between <0.001 and 0.01.

†† 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).

Table 3. Adverse Events.*

Adverse Event	High-Hemoglobin Group (N = 686)	Low-Hemoglobin Group (N = 688)	P Value†
	<i>no. of patients (%)</i>		
Any event	607 (88.5)	589 (85.6)	0.11
Thrombovascular event			
Any event	126 (18.4)	120 (17.4)	0.65
Any clinically relevant event‡	74 (10.8)	82 (11.9)	0.51
Any serious adverse event	376 (54.8)	334 (48.5)	0.02
Any serious adverse event associated with epoetin alfa§	10 (1.5)¶	3 (0.4)‖	0.05
Serious adverse events**			
Congestive heart failure	77 (11.2)	51 (7.4)	0.02
Myocardial infarction	10 (1.5)	19 (2.8)	0.09
Gastrointestinal hemorrhage	18 (2.6)	18 (2.6)	0.99
Chest pain	23 (3.4)	16 (2.3)	0.25
Cellulitis	16 (2.3)	11 (1.6)	0.33
Pneumonia	32 (4.7)	28 (4.1)	0.59
Renal failure	95 (13.8)	73 (10.6)	0.07

* 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.

deciliter, with an increase in risk with no quality-of-life benefit. Furthermore, the number of patients 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.

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. Smaller 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 deciliter reduced the rate of the composite end point

of a doubling of creatinine levels, renal replacement, or death, as compared with deferred initiation 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 studies either demonstrate no apparent benefit or actually may show an increased risk of progression to renal replacement therapy with the targeting 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 replacement therapy, no further data were collected;

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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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. Aronoff; North Shore University Hospital, Great Neck, NY — A. Ashfaq; Worcester Medical Center, Worcester, MA — R. Black; Louisiana State University Medical Center, Shreveport — J. Blondin; Balboa 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; Clinica 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 Center/Associates in Nephrology, Erie, PA — E. Clark, F. Foti; Internal Medicine Specialists, Orlando, FL — J. Cohen; Carolina Kidney Associates, Greensboro, NC — J.A. Coladonato; Renal Hypertension Physicians, Mount Laurel, NJ — M. Conrad;

Southwest Kidney Institute, Tempe, AZ — R. Cooper; University of California, Los Angeles, Medical Center, Sylmar — D. Corry; Cleveland Clinic Foundation, Cleveland — V. Dennis; Advanced Medical Research Institute, Fresno, CA — G. Dhillon; University of Miami Hospital and Clinics, Miami — J. Diego; Virginia Commonwealth University, Richmond — S. DiGiovanni; St. Louis — D.T. Domoto; Research Center of Florida, Miami — F. Dumenigo; Sislen and Associates, Washington, DC — G. Eisner; University of Southern California, Los Angeles — M. El Shahawy; Charles River Medical Associates, Framingham, MA — L. Epstein; California Institute of Renal Research, San Diego — G. Fadda; Kidney Associates, Houston — S. Fadem; Nephrology Associates, Rock Hill, SC — J. Fassler; Winthrop University Hospital, Mineola, NY — S. Fishbane; Talbert Medical Group, Huntington Beach, CA — M. Fredrick; San Antonio Kidney Disease Center, San Antonio, TX — T. Fried; Wake Nephrology Associates, Raleigh, NC — L. Garrett; Western New England Renal and Transplant Associates, Springfield, MA — M. Germain; South Florida Nephrology Associates, Lauderdale Lakes — R. Gerone-mus; Georgetown University Medical Center, Washington, DC — J. Gonin; Renal Medical Group, Visalia, CA — R.J. Haley; Mayo Clinic, Jacksonville, FL — W.E. Haley; Regional Kidney Disease Center, Erie, PA — R.D. Halligan; University of Oklahoma, Health Science Center, Oklahoma City — L. Harag-sim; Bronx Nephrology Hypertension, Bronx, NY — M. Henriquez; Nephrology Associates of Western New York, Amherst — T. Herman; North Shore Diabetes and Endocrine Associates, New Hyde Park, NY — K. Hershon; Miami Kidney Group, Miami — D. Hoffman; University of California, Los Angeles, Medical Center, Los Angeles — E. Jacobson; Indiana University Medical Center, Indianapolis — M. Jaradat; Empire Health Services, Spokane, WA — S. Joshi; University Internal Medicine Associates, Cincinnati — S. Kant; Northwest Louisiana Nephrology, Shreveport — M. Kaskas; George Wash- ington University Medical Center, Washington, DC — P. Kimmel; Medical Group of North County, Vista, CA — S. Kipper; Stanford University Medical Center, Stanford, CA — R. Lafayette; Apex Research of Riverside, Riverside, CA — J. Lee; Southbay Pharma Research, Buena Park, CA — S. Lee; Univer- sity of Arizona Health Sciences Center, Tucson — H.Y. Lien; Discovery Medical Research Group, Ocala, FL — H.R. Locay; Twin Cities Clinical Research, Brooklyn Center, MN — N. Lunde; Bronx Westchester Medical Group, Bronx, NY — R. Lynn; Health Research Association, Los Angeles — H. Madkour; Jefferson Nephrology, Charlottesville, VA — K. McConnell; Foundation Research, St. Petersburg, FL — M. McIvor; Arlington Nephrology, Arlington, TX — B.R. Mehta; University of California, San Diego, Medical Center, San Diego — R. Mehta; Model Clinical Research, Baltimore — J.H. Mersey; Glendale Internal Medicine and Cardiology Medical Group, Glendale, CA — R. Minasian; Hurley Medical Center, Flint, MI — A. Mohammed; University of Chi- cago Hospitals, Chicago — P. Murray; Nephrology Associates of Orangeburg, Orangeburg, SC — M. Nassri; Genesis Clinical Research Corporation, Tampa, FL — J. Navarro; University of California at Los Angeles, Los Angeles — A.R. Nissenson; State University of New York at Stony Brook, Stony Brook — E. Nord; Empire Health Services, Spokane, WA — L.E. Obermiller; Morehouse School of Medicine, Atlanta — C. Obialo; Grand Street Medical Associates, Kingston, NY — P. Pagnozzi; Odyssey Research Services, Bullhead City, AZ — S.M. Parekhezad; InterMedix, Winter Haven, FL — E. Perez; Medical College of Wisconsin, Milwaukee — W. Piering; Nephrology and Endocrine Associates Research, Las Vegas — N. Pokroy; Saint Clair Specialty Physicians, Detroit — R. Provenzano; Columbia University Medical Center, New York — J. Radhakrishnan; Charlotte Nephrology Associates, Port Charlotte, FL — R. Rajaram; InterMedix, Tampa, FL — G. Ramirez, G. Serrano; Nephrology Associates of Central Florida, Orlando — U. Ranjit; Citrus Nephrology, Crystal River, FL — P. Reddy; East Bay Nephrology, San Pablo, CA — D. Ricker; Dallas Nephrology Associates, Dallas — J. Roman-Latorre; Univer- sity of Pennsylvania Health System—Presbyterian Medical Center, Philadelphia — M. Rudnick; State University of New York, Brooklyn — M. Salifu; University of Kentucky Medical Center, Lexington — B.P. Sawaya; West Virginia University, Morgantown — R. Schmidt; Vanderbilt University Medical Center, Nashville — G. Schulman; Drexel University College of Medicine, Philadelphia — A.B. Schwartz; Diabetes and Glandular Disease Research Associ- ates, San Antonio, TX — S.L. Schwartz; Springfield Gardens, NY — D. Scott; Clinical Research Solutions, Knoxville, TN — D.M. Sellers; Brookdale University Hospital and Medical Center, Brooklyn, NY — W. Shapiro; Jefferson Renal Association, Philadelphia — K. Sharma; Rhode Island Hospital, Providence — D. Shemin; Redrock Research Center, Las Vegas — L.K. Shete; Temple University Hospital, Philadelphia — P. Silva; Metabolism Associates, New Haven, CT — D.B. Simon; Brigham and Women's Hospital, Boston — A. Singh; FutureCare Studies, Springfield, MA — J. Slater; Nephrology Associates, Augusta, GA — M. Smith; Fletcher Allen Health Care, Burlington, VT — R. Solomon; Ohio State University Hospitals, Columbus — D. Spe- tie; University of Colorado Hospitals and Health Sciences Center, Denver — D. Spiegel; National Institute of Clinical Research, Los Angeles — M. Spira; Evanston Northwestern Healthcare, Evanston, IL — S.M. Sprague; Methodist Research Institute, Indianapolis — T. Taber; Salem Hospital, Salem, OR — D. Tran; California Kidney Medical Group, Simi Valley — K. Tucker; Emory Clinic, Atlanta — J. Tumlin; Associates in Family Practice Clinical Re- search, Davie, FL — M. Vacker; Associates in Nephrology, Fort Myers, FL — J. Van Sickler; Penn State Milton S. Hershey Medical Center, Hershey — N. Verma; Long Island Jewish Medical Center, New Hyde Park, NY — J.D. Wagner; Baltimore — M. Waseem; Hypertension and Nephrology, Providence, RI — M. Weinberg; West Palm Beach, FL — R. Weiss; Tennessee Cardiovascular Research Institute, Nashville — M. Wigger; Clinical Research Associates of Tidewater, Norfolk, VA — D. Wombolt; Queens Medical Center, Honolulu — E. Wong; Western Nephrology and Metabolic Bone Disease, Lakewood, CO — M. Yanover; Northwest Louisiana Nephrology, Shreveport — R.I. Zabaneh; and Southwest Nephrology, Evergreen Park, IL — D. Zikos; **Clinical Event Adjudication Committee:** DCRI, Duke University School of Medicine, Durham, NC — K.W. Mahaffey (chair), D.T. Laskowitz, L.A. Szczech; University of Texas Southwestern, Dallas — S. Hedayati; Hennepin County Medical Center, Minneapolis — C.A. Herzog; William Beaumont Hospital, Royal Oak, MI — P. McCullough; **Data and Safety Monitoring Board:** Brigham and Women's Hospital, Boston — M. 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