Therapeutic Apheresis and Dialysis

Therapeutic Apheresis and Dialysis 15(5):431–440
doi: 10.1111/j.1744-9987.2011.00931.x

Positive Outcomes of High Hemoglobin Target in Patients With Chronic Kidney Disease Not on Dialysis: A Randomized Controlled Study

Tadao Akizawa,[1] Fumitake Gejyo,[9] Shinichi Nishi,[11] Yasuhiko Iino,[2] Yuzou Watanabe,[12] Masashi Suzuki,[10] Akira Saito,[13] Takashi Akiba,[3] Hideki Hirakata,[14] Shunichi Fukuhara,[15] Satoshi Morita,[16] Michiaki Hiroe,[4] Yoshiyuki Hada,[5] Makoto Suzuki,[6] Makoto Akaishi,[7] Manabu Iwasaki,[8] Yoshiharu Tsubakihara,[17] and the KRN321 STUDY Group*

[1]Showa University School of Medicine, [2]Nippon Medical School Hospital, [3]Tokyo Women's Medical University Hospital, [4]International Medical Center of Japan, [5]Sakakibara Memorial Clinic, [6]Toho University Ohashi Medical Center, [7]Kitasato University Kitasato Institute Hospital, and [8]Seikei University, Tokyo, [9]Niigata University Medical and Dental Hospital, and [10]Shinrakuen Hospital, Niigata, [11]Kobe University Graduate School of Medicine, Kobe, [12]Kasugai Municipal Hospital, Kasugai, [13]International University of Health and Welfare Atami Hospital, Atami, [14]Japanese Red Cross Fukuoka Hospital, Fukuoka, [15]Kyoto University Graduate School of Medicine, Kyoto, [16]Yokohama City University General Medical Center, Yokohama, and [17]Osaka General Medical Center, Osaka, Japan

Abstract: Correcting anemia in patients with chronic kidney disease (CKD) to higher hemoglobin (Hb) levels may be associated with increased risk. No optimal target for Hb has been established. This controlled study examined 321 patients with CKD who were not on dialysis, had a Hb level of <10 g/dL, and a serum creatinine of 2.0 to 6.0 mg/dL. They were randomized into two target Hb groups: 161 to high Hb (11.0–13.0 g/dL) to receive darbepoetin alfa and low Hb to 160 (9.0–11.0 g/dL) to receive recombinant erythropoietin. The study lasted 48 weeks. Of 154 and 153 patients with adverse events, cardiovascular adverse events developed in 42 and 51 patients in the high and low Hb groups, respectively, with no significant difference in the incidence. All quality of life scores improved in the high Hb group and vitality improved significantly more with high Hb ($P = 0.025$). The left ventricular mass index (LVMI) remained stable in the low Hb group, but there was a significant decrease in LVMI in the high group ($P < 0.001$). There were no safety concerns with targeting a higher Hb level during the 48 weeks of this study. Patients with a higher Hb target had comparatively better outcomes with respect to quality of life and LVMI. **Key Words:** Anemia, Cardiac function, Chronic kidney disease, Darbepoetin alfa, Erythropoietin, Quality of life.

Anemia is common among patients with chronic kidney disease (CKD). Erythropoiesis stimulating agent (ESA) is considered to be extremely effective in correcting anemia, and treatment guidelines have been established for hemoglobin (Hb) targets in several countries in reference to previous clinical trials (1–8).

In Japan the target for corrected Hb in patients with CKD who are not on dialysis is approximately 10 g/dL, which is lower than guidelines in other countries (9,10). Although there are several reports that considered higher Hb (targeted to 12 g/dL or more), and no major safety concerns have been expressed with Hb levels below 14 g/dL (7,8,11), no optimal Hb target has been defined. Consequently, we conducted this clinical study to evaluate the efficacy and safety of a high Hb target in patients with CKD who are not on dialysis.

Received November 2010; revised February 2011.
Address correspondence and reprint requests to Professor Tadao Akizawa, Division of Nephrology, Department of Medicine, Showa University School of Medicine, 1–5-8 Hatanodai, Shinagawa-ku, Tokyo, 142–8666, Japan. Email: akizawa@med.showa-u.ac.jp
*Members and their affiliations are listed in Appendix I.

The results of two large, randomized, controlled studies of the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) (1) and the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) (2) were reported during this trial. In the CHOIR study a higher Hb (13.5 g/dL) target group had an increased risk for adverse outcomes (death, myocardial infarction, hospitalization for congestive heart failure, and stroke) than a lower Hb (11.3 g/dL) group. Furthermore, a meta-analysis of these trials reported a significantly increased risk of death and uncontrolled blood pressure in the high Hb group (12 g/dL≤) (12). As a result, the 2007 National Kidney Foundation's "Kidney Disease Outcomes Quality Initiative" anemia guidelines recommended that target Hb should not exceed 13.0 g/dL (13).

In this trial we compared the safety of high (11.0 to 13.0 g/dL) and low Hb targets (9.0 to 11.0 g/dL). Secondary endpoints were the clinical significance of a high Hb target based on quality of life (QOL) and left ventricular mass index (LVMI).

PATIENTS AND METHODS

Study subjects

We conducted this randomized, multicenter, open-label, parallel-group study according to the Declaration of Helsinki. Protocols were approved by the Institutional Review Board at each of the 79 medical institutions that participated. All patients gave written, informed consent. The study lasted from November 2005 to April 2007.

We enrolled 322 CKD patients not receiving dialysis. The patients had to be at least 20 years old and have a Hb level <10.0 g/dL. CKD was defined by a serum creatinine level equal to or between 2–6 mg/dL. Key exclusion criteria included uncontrolled hypertension, congestive heart failure (above class III on the New York Heart Association classification), malignancy, blood disease or active bleeding, and critical allergy.

Intervention

Eligible patients were assigned to either of two groups by a computer according to a minimization method: a high Hb group (11.0–13.0 g/dL) to receive darbepoetin alfa (DA) or a low Hb group (9.0–11.0 g/dL) to receive recombinant human erythropoietin (rHuEPO). Modulators for randomization were Hb level (<9.0 or ≥9.0 g/dL), serum creatinine level (<4.0 mg/dL or ≥4.0 mg/dL), whether they had diabetes, and medical institution. The study lasted 48 weeks for both groups.

Iron supplements were administered to maintain transferrin saturation >20% or serum ferritin >100 ng/mL. Management targets for blood pressure were systolic <130 mm Hg and diastolic <80 mm Hg.

Safety

The number of patients with and the occurrence rate of adverse events were summarized to assess safety. An adverse event was defined as any unfavorable or unexpected diagnosis, symptom or disease (including abnormal changes in laboratory test values) that occurred after administration of the study drug began. Causal relationships were not considered.

Quality of life

Quality of life was assessed at baseline and at week 12 using short-form health survey (SF-36) version 2 acute form which was validated in advance (14) and the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale.

Left ventricular mass index

The left ventricular mass index was calculated from two-dimensional, echo-guided, M-mode echocardiograms that were obtained at baseline and week 32. Three independent cardiologists evaluated the echocardiograms from patients that were measurable and assessable at both baseline and week 32 without knowing the clinical profiles of patients, including their Hb level. LVMI corrected for body surface areas was calculated using the Devereux formula: $0.8 \times (1.04 \times [(LVDd + IVST + PWT)^3 - LVDd^3]) + 0.6$, where LVDd is the left ventricular end-diastolic diameter; IVST is the interventricular septal thickness; and PWT is the left ventricular posterior wall thickness (15).

Statistical analysis

The ICH E1 guideline states that 100 patients are needed to evaluate the safety of a new drug in a one-year clinical trial. From the safety results of past clinical trials we estimated that 150 patients were required for each group. This number was estimated to be sufficient to detect 95% of adverse events at a 2% rate of occurrence. The population size also minimized the standard error of the estimated mean Hb relative to amounts calculated from past clinical trials. Furthermore, this number had a statistical power of 80–90% to detect a significant level of two-sided probability at 0.05 in comparing LVMI and QOL between the two groups. To evaluate patient characteristics or baseline standard values between the two groups, categorical variables were compared

TABLE 1. *Reasons for withdrawal from the study*

Number of patients (%)	High Hb group $N = 161$	Low Hb group $N = 160$
Complete	118 (73.3)	111 (69.4)
Withdrawal	43 (26.7)	49 (30.6)
Reason for withdrawal		
Patient was unsuitable according to inclusion or exclusion criteria after the start of the study	3 (1.9)	1 (0.6)
Patient asked to withdraw from the study	5 (3.1)	4 (2.5)
Occurrence of an adverse event	7 (4.3)	7 (4.4)
Start of renal replacement therapy	20 (12.4)	23 (14.4)
More than eight weeks of continuous discontinuation of study drug	2 (1.2)	3 (1.9)
Treatment resulted in a higher hemoglobin (Hb) level than that allowed for in the continuation criteria: High Hb Group, Hb ≥ 14 g/dL; Low Hb Group; Hb ≥ 12 g/dL	1 (0.6)	2 (1.3)
Maximum dose failed to improve anemia or maintain the Hb target	3 (1.9)	5 (3.1)
Severe bleeding from surgery or red blood cell transfusion	2 (1.2)	3 (1.9)
Determination by the investigator	0 (0.0)	1 (0.6)

by the χ^2-test and continuous variables with Student's *t*-test. For safety assessments, we summarized the incidence of adverse events descriptively and calculated the odds ratios of the high Hb group divided by those of the low Hb group. To evaluate efficacy we used the Student's *t*-test to compare QOL and LVMI between the two groups. Changes from baseline for LVMI were compared by analysis of covariance. The statistical significance level for efficacy was $P < 0.05$ (two-sided). All analyses were performed with SAS software version 8.2 (SAS Institute, Cary, NC, USA).

RESULTS

Patients and baseline characteristics

A total of 322 CKD patients not on dialysis were enrolled. One withdrew from the study before receiving treatment, so 161 patients were randomized to the high Hb group and 160 to a low Hb. After administration of one of DA or rHuEPO began, 43 high Hb and 49 low Hb patients withdrew. The reasons for withdrawal and the number of patients who withdrew were similar in the two groups; the primary reason was initiation of renal replacement therapy to treat end-stage renal disease (Table 1). In the high and low Hb groups, respectively, 118 and 111 patients completed the study (Fig. 1). Demographic and baseline characteristics were similar between the two groups, including Hb, serum creatinine, and estimated GFR (Table 2).

Anemia correction and maintenance

The mean ± SD Hb level in the high Hb group was 9.15 ± 0.79 g/dL at baseline. By week 10, the mean Hb had achieved the target level and was maintained within the target range until the study ended. The Hb in the low Hb group was 9.18 ± 0.86 g/dL at baseline and maintained within the target range throughout the study (Fig. 2a). For the high Hb group, the mean ± SD dose at the start of administration was 30.0 ± 0.0 μg/week and was maintained at around 30 μg/week thereafter. For the low Hb group, the starting dose was 4321.9 ± 1431.2 IU/week and the maintenance dose was around 4000 IU/week.

Blood pressure

Changes in the mean systolic and diastolic blood pressures in the two groups were similar (Fig. 2b).

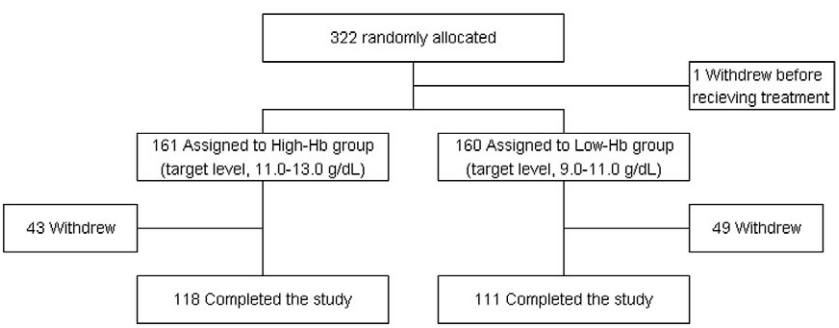

FIG. 1. Enrollment and outcomes. A total of 322 CKD patients were enrolled in this study. One withdrew before receiving treatment so that 161 patients were assigned to the high hemoglobin (Hb) group and 160 to the low Hb group; 43 and 49 patients withdrew from the high and low Hb groups, respectively, with 118 and 111 completing the study. The major reason for withdrawal was initiation of renal replacement therapy.

TABLE 2. *Baseline characteristics of the patients*

Characteristic	High Hb group ($N = 161$)	Low Hb group ($N = 160$)	*P* value
Age (years)	65.2 ± 11.8	64.1 ± 11.7	0.422
Female sex	81 (50.3)	89 (55.6)	0.340
Cause of chronic kidney disease			
Glomerulonephritis	70 (43.5)	69 (43.1)	0.949
Diabetic nephropathy	34 (21.1)	36 (22.5)	0.764
Pyelonephritis	0 (0.0)	1 (0.6)	0.315
Polycystic kidney disease	7 (4.3)	7 (4.4)	0.990
Nephrosclerosis	28 (17.4)	28 (17.5)	0.979
Other	22 (13.7)	19 (11.9)	0.631
Cardiovascular history			
Cerebrovascular accident	30 (18.6)	20 (12.5)	0.129
Congestive heart failure	10 (6.2)	14 (8.8)	0.387
Peripheral vascular disease	10 (6.2)	6 (3.8)	0.311
Myocardial infraction	9 (5.6)	5 (3.1)	0.279
Atrial fibrillation	7 (4.3)	4 (2.5)	0.362
Coronary artery bypass graft	1 (0.6)	1 (0.6)	0.996
Weight (kg)	56.71 ± 11.23	56.62 ± 11.06	0.941
Height (cm)	157.78 ± 9.45	157.45 ± 8.27	0.741
Blood pressure (mm Hg)			
Systolic	132.7 ± 16.5	136.0 ± 18.2	0.084
Diastolic	72.1 ± 10.6	73.6 ± 11.3	0.215
Hemoglobin (g/dL)	9.15 ± 0.79	9.18 ± 0.86	0.732
Transferrin saturation (%)	31.46 ± 12.32	29.98 ± 12.39	0.281
Ferritin (ng/mL)	124.46 ± 126.48	130.23 ± 256.02	0.797
Creatinine (mg/dL)	3.540 ± 1.058	3.570 ± 1.078	0.797
Creatinine clearance (mL/min)	19.04 ± 6.96	18.57 ± 6.32	0.525
Estimated GFR (mL/min/1.73 m^2)	12.55 ± 4.68	12.34 ± 4.59	0.676
Use of anti-hypertensive drugs	135 (83.9)	134 (83.8)	1.000
ACEi only	11 (6.8)	8 (5.0)	0.486
ARB only	89 (55.3)	95 (59.4)	0.458
Combination of ACEi and ARB	33 (20.5)	31 (19.4)	0.801
History of ESA use (treated)	91 (56.5)	95 (59.0)	0.651

Values are listed as No. of patients (%) or mean ± SD, unless otherwise indicated. GFR was estimated according to the MDRD formula. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESA, erythropoiesis stimulating agent; GFR, glomerular filtration rate.

There was no difference in the use of anti-hypertensive agents, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers throughout the study.

Safety

Adverse events occurred in 154 patients (95.7%, 95% confidence interval (CI): 91.2 to 98.2%) in the high Hb group and 153 patients (95.6%, 95% CI: 91.2 to 98.2%) in the low Hb group. The odds ratios (95% CI) between the two groups for all adverse events with an occurrence rate >5% are illustrated in Figure 3. All the adverse events were notorious for ESA and there was no significant difference between the groups in any components. During the study period, one patient in the high Hb group died of an alveolar hemorrhage resulting from progression of underlying ANCA-related glomerulonephritis, so a causal relationship between death and the study medication was ruled out.

We particularly examined the occurrence of cardiovascular events (defined in Table 3). Cardiovascular events occurred in 42 high Hb patients (26.1%, 95% CI: 19.5 to 33.6%) and 51 low Hb patients (31.9%, 95% CI; 25.3 to 40.3%) (difference not significant). The major event was hypertension or increased blood pressure.

The numbers of patients who left the study because of beginning renal replacement therapy (renal survival) was 21 for the high Hb group and 26 for the low Hb group. The mean change ± SD of the estimated GFR from baseline to the end of the study was –2.3 ± 3.18 mL/min/1.73 m^2 in the high Hb group and –2.4 ± 3.06 mL/min/1.73 m^2 in the low Hb group. GFR was estimated according to the Modification of Diet in Renal Disease (MDRD) formula.

Adverse events related to cancer occurred in two patients in each group who did not have a history of malignancy at baseline, but a causal relationship between these events and the study medication was

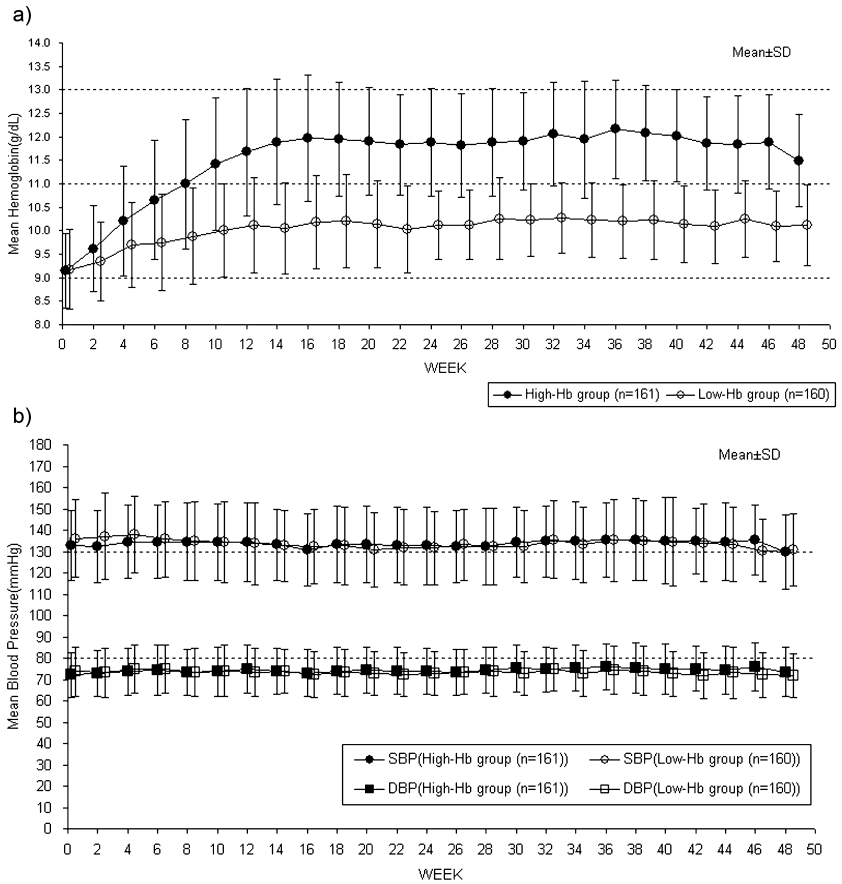

FIG. 2. Transition of hemoglobin (Hb) level and blood pressure. (a) Transition of the mean Hb level. The high and low Hb groups were targeted to achieve Hb levels of 11.0–13.0 g/dL and 9.0–11.0 g/dL, respectively. (b) Transition of the mean blood pressure. DBP, diastolic blood pressure; SBP, systolic blood pressure.

excluded. No patients died from cancer during this study.

Quality of life

Twelve patients withdrew from the study before the second QOL evaluation (week 12) so that 309 (157 for the high Hb group and 152 for the low Hb group) were objects of this assessment. At baseline the mean ± SD Hb values were not significantly different between the high Hb and low Hb groups, but became significant at week 12 (11.75 ± 1.28 g/dL and 10.44 ± 0.99 g/dL, respectively; $P < 0.001$).

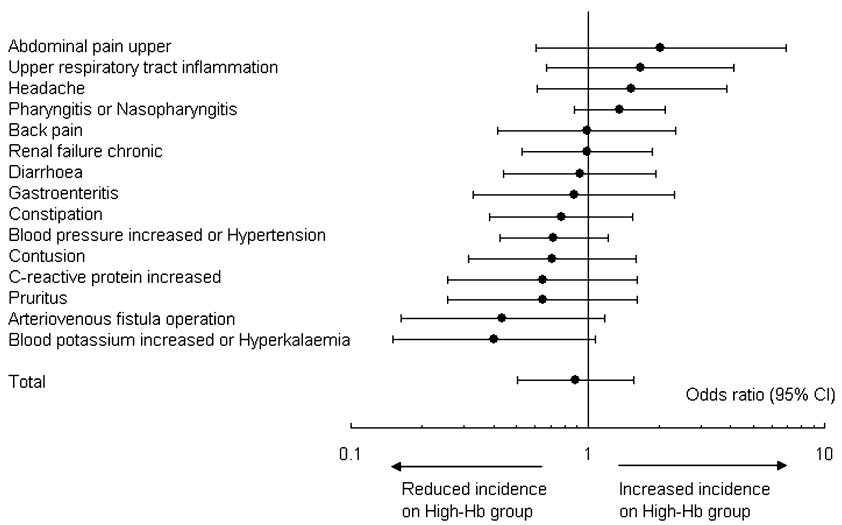

FIG. 3. Odds ratio of adverse events with occurrence rates above 5% (High hemoglobin [Hb]/Low Hb). Adverse events data are presented as the proportion of patients who experienced an event one or more times, and comparisons between treatment groups were made by calculating the odds ratio (95% CI) for these proportions.

TABLE 3. *Cardiovascular events considered as adverse*

Preferred term (MedDRA/J Version 8.1)	High Hb group ($N = 161$)	Low Hb group ($N = 160$)
Hypertension	17 (10.6)	11 (6.9)
Blood pressure increased	15 (9.3)	30 (18.8)
Chest pain	3 (1.9)	—
Palpitations	3 (1.9)	—
Cardiomegaly	2 (1.2)	4 (2.5)
Chest discomfort	2 (1.2)	—
Myocardial ischemia	2 (1.2)	—
Lacunar infarction	1 (0.6)	2 (1.3)
Atrial fibrillation	1 (0.6)	1 (0.6)
Blood pressure decreased	1 (0.6)	1 (0.6)
Tachycardia	1 (0.6)	1 (0.6)
Angina pectoris	1 (0.6)	—
Cardiac failure	—	2 (1.3)
Cardiac failure, congestive	—	2 (1.3)
Cerebral ischemia	—	2 (1.3)
Bradycardia	—	1 (0.6)
Cardiac failure, chronic	—	1 (0.6)
Heart rate increased	—	1 (0.6)
Mitral valve incompetence	—	1 (0.6)
Procedural hypertension	—	1 (0.6)

Data are presented as no. of patients (%).

In the high Hb group, the QOL scores improved in all eight domains of the SF-36 and FACIT fatigue score (Fig. 4). Improvements were especially significant in vitality scores ($P = 0.025$), where the difference in mean change between the two groups was 4.8 (95% CI: 0.6 to 8.9).

Left ventricular mass index

Once patients who had cardiac disorders or echocardiograms that were difficult to read were excluded, 111 patients in the high Hb and 95 in the low Hb groups remained for cardiographic examination.

At baseline, the mean ± SD Hb was similar between the high and low Hb groups. At week 32, the Hb levels were 11.98 ± 1.17 g/dL and 10.12 ± 0.97 g/dL, respectively, and the difference between the groups was statistically significant ($P < 0.001$).

In the low Hb group, the LVMI at baseline was 126 ± 35.1 g/m^2 and the change was –0.1 g/m^2 (95% CI: –4.0 to +3.8 g/m^2); however, LVMI decreased significantly ($P < 0.001$) from baseline (128 ± 37.2 g/m^2) in the high Hb group (–7.8 g/m^2; 95% CI: –12.1 to –3.6 g/m^2). The difference in mean LVMI changes between the two groups was –7.70 g/m^2 (95% CI: –13.5 to –1.9 g/m^2) and statistically significant at $P = 0.009$ (Fig. 5a).

We performed an exploratory analysis of the associations between the Hb level and regression of LVMI by dividing the patients, regardless of treatment group, into five classes based on their Hb level at the second echocardiographic examination: Hb < 10 g/dL, 10 g/dL ≤ Hb < 11 g/dL, 11 g/dL ≤ Hb < 12 g/dL, 12 g/dL ≤ Hb < 13 g/dL, and 13 g/dL ≤ Hb. The elevation of Hb was strongly associated with reduced LVMI at the second examination ($P < 0.001$) (Fig. 5b).

DISCUSSION

In this study, two Hb targets (high and low) were evaluated for their effect on endpoints such as safety, LVMI and QOL. We observed no significant difference in adverse events or renal survival between the two groups. Furthermore, QOL was improved and LVMI decreased in the high Hb group compared to the low Hb group.

There have been other reports of improved QOL (3,16) and LVMI (11,17) among CKD patients when Hb was raised to 12.0 g/dL or more. In our previous dose-response study of DA (18), we observed improved QOL and LVMI when the Hb level was raised to 12.0–13.0 g/dL. We confirmed the reproducibility of these results in our present study.

However, in the CHOIR study correcting anemia to a Hb level of 13.5 g/dL increased the rate of occurrence of composite events compared with 11.3 g/dL (1). In our study there were no significant differences in adverse events between the two groups. Patient background and the dose of ESA required to maintain the target Hb value should be considered in explaining the difference in cardiovascular risk between this study and CHOIR.

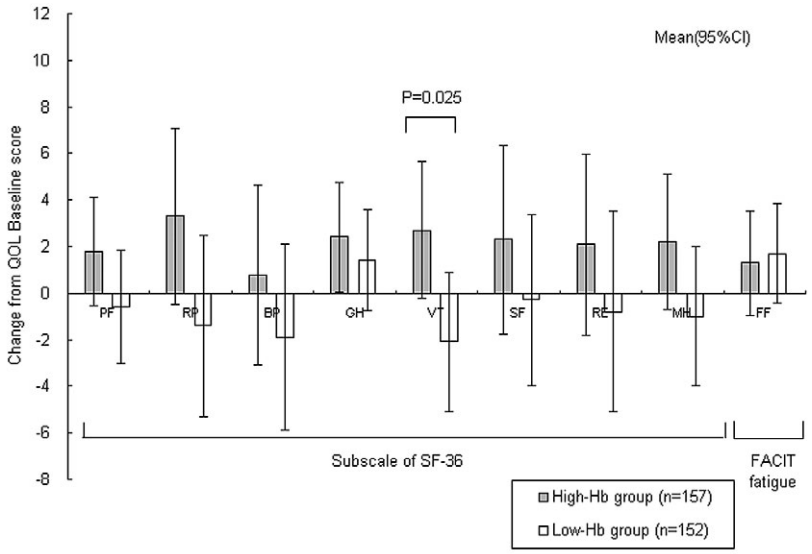

FIG. 4. Change in the quality of life (QOL) score from baseline and a comparison between the groups. PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health; FACIT, Functional Assessment of Chronic Illness Therapy; FF, FACIT fatigue.

QOL Baseline score

SF-36 Subscale	High-Hb group (n=161)	Low-Hb group (n=160)
PF	73.3±22.4	76.1±19.0
RP	77.2±26.7	80.9±22.8
BP	79.4±23.7	78.2±23.0
GH	47.7±17.9	46.1±17.9
VT	63.4±21.7	65.0±20.4
SF	82.7±23.7	87.2±20.6
RE	81.3±25.0	83.0±23.6
MH	73.2±20.0	75.2±18.3
FF	75.5±16.8	75.5±15.7

In the CHOIR study, approximately 35% of patients had had a myocardial infarction, stroke, coronary artery bypass graft, percutaneous coronary intervention, or amputation of a lower limb; in this study, these patients comprised approximately 18% of the study population. In addition, patients in a large, ongoing epidemiologic study for CKD patients not on dialysis in Japan (19) had characteristics similar to ours. We suggest that the baseline risk for cardiovascular events in CKD patients not on dialysis differs markedly between the US and Japanese populations.

It was ascertained in a post hoc analysis of the CHOIR and the Normal Hematocrit Trials (20), in which poor outcomes of the higher Hb target were reported, that failing to achieve the target Hb level resulting from hypo-responsiveness to ESA was related to more frequent adverse events (21). Furthermore, a secondary analysis of the CHOIR trial (22) suggested that a high dose of ESA in patients who had lesser Hb amounts than the target Hb value may be a risk factor for poor outcomes.

The CREATE study reported no scientific evidence for an association of full correction of anemia with adverse outcomes (2). The CREATE investigators stated that, although the target Hb level was similar to that of the CHOIR trial, the first and final doses of ESA were less than half those in the CHOIR trial. Similarly to the CREATE study, we did not require a high dose of ESA to maintain the targeted level of Hb, and the number of patients in the high Hb group who required the maximum dose (90 μg/week) was only 18 (11.2%).

In our study, there was no relation between any two of mean dosage, mean Hb level or the rate of occurrence of cardiovascular adverse events (data not shown). This may have been because our patients were at low cardiovascular risk and few patients were hypo-responsive to ESA.

The results of the large clinical trial for patients with type 2 diabetes and chronic kidney disease, the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), were released recently (23). In the TREAT study, patients were assigned randomly to the DA (target Hb: 13 g/dL) and placebo groups (target Hb: 9.0 g/dL). Primary endpoints were the composite outcomes of death or a cardiovascular event, and death or end-stage renal disease. As a

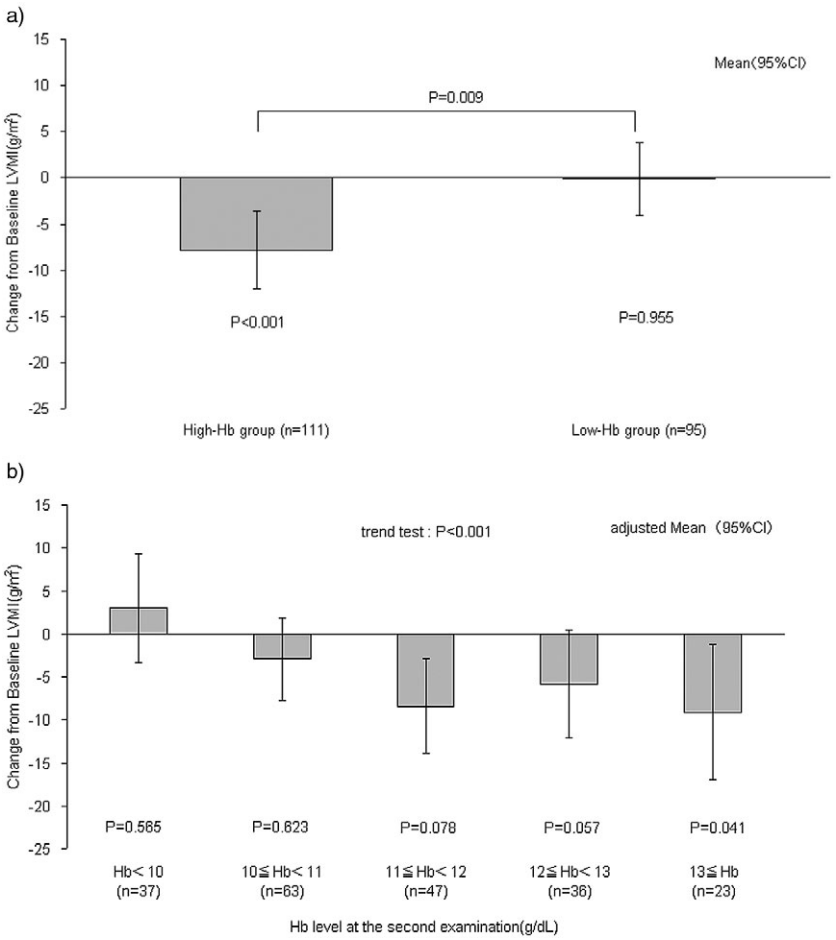

FIG. 5. Change of left ventricular mass index (LVMI). (a) Change of LVMI from baseline to week 32 and comparison between the high and low hemoglobin (Hb) groups. The *P*-value described below the bar indicates the the difference in LVMI between baseline and week 32. (b) Change of LVMI divided into five classes according to Hb level. Change of LVMI from baseline to week 32, and the comparison between the two groups when divided into five classes by the Hb level at week 32 (Hb < 10 g/dL, 10 g/dL ≤ Hb < 11 g/dL, 11 g/dL ≤ Hb < 12 g/dL, 12 g/dL ≤ Hb < 13 g/dL, and Hb ≥ 13 g/dL).

result there was no significant difference regarding the primary endpoint; however, fatal and nonfatal stroke were more frequent in the DA group. In our study, only one patient from the high Hb group and three from the low Hb group experienced a stroke. Furthermore, when we calculated the rate of stroke for those with complications of diabetes, both groups had only one patient each.

In the TREAT study, deaths attributed to cancer were significantly higher in the DA group among those who had a history of malignant conditions. In this study, however, no increase in cancer deaths nor onset of cancer were observed in the high Hb group. Because every trial has had different baseline patient characteristics, study design and target Hb level, it is difficult to compare the safety and required dose of ESA. From the results of recent, large, randomized, clinical trials (1,4,7,8), fully correcting Hb levels in all patients, including those with cardiovascular complications, may be unfavorable. However, from the results of our study, targeting a higher Hb level (11.0–13.0 g/dL) in patients without severe cardiovascular disease and uncontrollable hypertension seemed appropriate.

Although this study was a randomized trial, there were several limitations. Most importantly, this trial was openly labeled and there may have been some biases. To particularly minimize the bias for LVMI, three cardiologists who were independent of this study reviewed the echocardiograms while blinded to treatment and patient information.

The second limitation was the use of different products in the two treatment arms (DA for the high Hb group and rHuEPO for low Hb). This was due to the fact that rHuEPO is the only drug therapy approved for CKD patients not on dialysis with a target Hb level of 10.0 g/dL in Japan. So we had to demonstrate the usefulness of DA in this indication as a new drug with its target Hb level of 11.0–13.0 g/dL to receive approval. However, DA has approximately the same pharmacological effects as rHuEPO (24) and the minor difference in the pharmacological effects of DA from rHuEPO is negligible in this clinical trial. The results of safety, as well as

improved LVMI and QOL, can be ascribed solely to the Hb level.

Although these limitations should be considered, the results of this study suggested that maintaining a high target Hb (11.0–13.0 g/dL) was not associated with increased risk (especially cardiovascular events), but did improve QOL and reduce LVMI.

CONCLUSIONS

We conducted a randomized, open trial to study the safety and availability of maintaining a higher Hb target in Japanese CKD patients not on dialysis. No significant differences in adverse outcomes were found between the high and low Hb groups, but improvement in QOL and LVMI were significantly different. Our results suggested that a higher Hb level is more beneficial than a lower Hb target and that 11.0 to 13.0 g/dL is the appropriate Hb for CKD patients not on dialysis.

Acknowledgments: This Randomized Controlled Study was sponsored by Kyowa Hakko Kirin Co., Ltd (Tokyo, Japan). Registration of Clinical Trials: The Cochrane Renal Group registry: autoid 121, crg_id CRG030600049. The authors participated in this study as advisers and received consultation fees from Kyowa Hakko Kirin Co., Ltd.

REFERENCES

1. Singh AK, Szczech L, Tang KL et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085–98.
2. Drüeke TB, Locatelli F, Clyne N et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;355:2071–84.
3. Rossert J, Levin A, Roger SD et al. Effect of early correction of anemia on the progression of CKD. *Am J Kidney Dis* 2006; 47:738–50.
4. Ritz E, Laville M, Bilous RW et al. Anemia Correction in Diabetes Study Investigators. Target level for hemoglobin correction in patients with diabetes and CKD: primary results of the Anemia Correction in Diabetes (ACORD) Study. *Am J Kidney Dis* 2007;49:194–207.
5. Kuriyama S, Tomonari H, Yoshida H, Hashimoto T, Kawaguchi Y, Sakai O. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. *Nephron* 1997;77:176–85.
6. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. *Kidney Int* 2004;66:753–60.
7. Roger SD, McMahon LP, Clarkson A et al. Effects of early and late intervention with epoetin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): results of a randomized clinical trial. *J Am Soc Nephrol* 2004;15:148–56.
8. Furuland H, Linde T, Ahlmén J, Christensson A, Strömbom U, Danielson BG. A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. *Nephrol Dial Transplant* 2003;18:353–61.
9. National Kidney Foundation. K/DOQI clinical practice guidelines for anemia of chronic kidney disease, 2000. *Am J Kidney Dis* 2001;37(Suppl 1):S182–238.
10. Locatelli F, Aljama P, Bárány P et al. Revised European best practice guidelines for the management of anemia in patients with chronic renal failure. *Nephrol Dial Transplant* 2004; 19(Suppl 2):ii1–47.
11. Hayashi T, Suzuki A, Shoji T et al. Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. *Am J Kidney Dis* 2000;35:250–6.
12. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. *Lancet* 2007;369:381–8.
13. KDOQI. KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. *Am J Kidney Dis* 2007;50:471–530.
14. Hasegawa T, Suzukamo Y, Akizawa T. Validation of the Japanese SF-36 v2 acute form in patients with chronic kidney disease. *Nippon Jinzo Gakkai Shi* 2008;50:42–50.
15. Devereux RB, Alonso DR, Lutas EM et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;57:450–8.
16. Macdougall IC, Walker R, Provenzano R et al. C.E.R.A. corrects anemia in patients with chronic kidney disease not on dialysis: results of a randomized clinical trial. *Clin J Am Soc Nephrol* 2008;3:337–47.
17. Pappas KD, Gouva CD, Katopodis KP et al. Correction of anemia with erythropoietin in chronic kidney disease (stage 3 or 4): effects on cardiac performance. *Cardiovasc Drugs Ther* 2008;22:37–44.
18. Hirakata H, Tsubakihara Y, Gejyo F et al. Maintaining high hemoglobin levels improved the left ventricular mass index and quality of life scores in pre-dialysis Japanese chronic kidney disease patients. *Clin Exp Nephrol* 2010;14:28–35.
19. Suzuki M, Saito A, Gejyo F. Baseline characteristics and anemia treatment in newly-introduced hemodialysis patients. *J Jpn Soc Dial Ther* 2008;41:251–4.
20. Besarab A, Bolton WK, Browne JK et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339:584–90.
21. Kilpatrick RD, Critchlow CW, Fishbane S et al. Greater epoetin alfa responsiveness is associated with improved survival in hemodialysis patients. *Clin J Am Soc Nephrol* 2008;3: 1077–83.
22. Szczech LA, Barnhart HX, Inrig JK et al. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney Int* 2008;74:791–8.
23. Pfeffer MA, Burdmann EA, Chen CY et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;361:2019–32.
24. Macdougall IC, Gray SJ, Elston O et al. Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. *J Am Soc Nephrol* 1999;10: 2392–5.

APPENDIX I

We would like to express our deepest appreciation to the following members and investigators for their participation in this study.

Medical Advisor—Yusuke Tsukamoto (Shuwa General Hospital); **Clinical Pharmacology Advisor—**Eiji Uchida (Showa University School of Medicine); **Investigators—**Atsushi Wada (Asahikawa Red Cross

Hospital), Izumi Yamaji (Teine Keijinkai Clinic), Tetsuo Sakurai (Sapporo City General Hospital), Noritomo Itami (Nikko Memorial Hospital), Jun Soma (Iwate Prefectural Central Hospital), Yoshio Taguma (Sendai Shakaihoken Hospital), Masahiko Ogihara (Ogihara Clinic), Takashi Shigematsu, Hiroshi Hayakawa, and Masato Ikeda (Jikei University School of Medicine Aoto Hospital), Noriaki Shimada (Koto Hospital), Matsuhiko Suenaga (Tokyo Metropolitan Bokutoh Hospital), Satoshi Hijiya (Miyanomae Clinic), Sei Sasaki (Tokyo Medical and Dental University Hospital Faculty of Medicine), Yasuhiko Tomino (Juntendo University Hospital), Yasuhiko Iino (Nippon Medical University Hospital), Tatsuo Hosoya (Jikei University School of Medicine), Kouzou Kitazawa (Showa University Hospital), Tomoko Gomi (Kanto Medical Center NTT EC), Kosaku Nitta (Tokyo Women's Medical University), Toshiyuki Nakao (Tokyo Medical University), Ken-ichi Oguchi (Ikegami General Hospital, Medical Corporation of Showakai), Ryoichi Ando (Japan Red Cross Musashino Hospital), Takahiro Mochizuki (Kameda Clinic), Yoshiyuki Toya (Yokohama City University Graduate School of Medicine), Eriko Kinugasa (Showa University Northern Yokohama Hospital), Akira Saito (Tokai University), Koju Kamata (Kitasato Institute Hospital), Yuichiro Hukudome (Yokosuka Kyosai Hospital), Sohji Nagase and Kunihiro Yamagata (Tsukuba University Hospital), Yoshitaka Maeda (Toride Kyodo General Hospital), Hironobu Kawai (Saiseikai Maebashi Hospital), Yoshihisa Nojima (Gunma University Hospital), Shinichi Nishi (Niigata University Medical and Dental Hospital), Masashi Suzuki (Shinrakuen Hospital), Shin-ichi Tokunaga and Tadashi Ideura (Nagano Red Cross Hospital), Yukio Yuzawa (Nagoya University Graduate School of Medicine), Kunio Morozumi (Nagoya Daini Red Cross Hospital), Chikao Yamazaki (Masuko Memorial Hospital), Hiroshi Ogawa (Shinseikai Dai-ichi Hospital), Tomohiko Naruse (Kasugai Municipal Hospital), Hirokazu Imai (Aichi Medical University School of Medicine), Satoshi Sugiyama (Fujita Health University Hospital), Daijo Inaguma and Kei Kurata (Tosei General Hospital), Satoshi Suzuki (Kainan Hospital Aichi Prefectural Welfare Federation of Agricultural Cooperatives), Hiroshige Ohashi (Gifu Prefectural General Medical Center), Shinsuke Nomura (Mie University Hospital), Atsushi Fukatsu (Kyoto University Hospital), Akira Wada (National Hospital Organization Osaka National Hospital), Tatsuya Shoji (Osaka General Medical Center), Tamotsu Minakata and Masahiko Miyamoto (Osaka Red Cross Hospital), Hirofumi Hasegawa (Kinki University Hospital), Atsushi Yamauchi (Osaka Rosai Hospital), Masayuki Tsuchihashi (Hoshigaoka Koseinenkin Hospital), Terumasa Hayashi (Izumisano Municipal Hospital, Rinku General Medical Center), Hiroyuki Iida (Toyama Prefectural Central Hospital), Hisao Mutoh (Kanazawa Social Insurance Hospital), Shigeo Yamamoto (Kansai Rosai Hospital), Takeshi Nakanishi (The Hospital of Hyogo College of Medicine), Masato Kasahara and Akihiro Yoshimoto (Institute of Biomedical Research and Innovation Hospital), Yoshihiko Saito (Nara Medical University Hospital), Haruhisa Otani (Wakayama Kidney Disease Clinic), Hirofumi Makino (Okayama University Hospital), Masafumi Taki (Shigei Medical Research Hospital), Noriaki Yorioka (Hiroshima University Hospital), Shigeaki Hayashida (Tokuyama Central Hospital), Yasuhiko Oyabu (Yamaguchi-ken Saiseikai Shimonoseki General Hospital), Jun Minakuchi (Kawashima Hospital), Akira Numata (Takamatsu Red Cross Hospital), Atsumi Harada (Matsuyama Red Cross Hospital), Kenji Yuasa (Kochi Takasu Hospital), Akiyo Shiro-zu (Kokura Daiichi Hospital), Kazuhiko Tsuruya (Kyushu University Hospital), Hideki Hirakata (Kyushu University Hospital and Fukuoka Red Cross Hospital), Harumitsu Kumagai and Kiyoshi Ikeda (Fukuoka Red Cross Hospital), Kei Hori (Munakata Medical Association Hospital), Seiya Okuda (Kurume University School of Medicine), Harumichi Higashi (St. Mary's Hospital), Masanobu Miyazaki, Katsushige Abe and Akira Furusu (Nagasaki University Hospital), Kimio Tomita (Kumamoto University Hospital), Shuichi Hisanaga (Koga General Hospital), Toru Ikeda (Ikeda Hospital), and Yoshiki Shiohira (Yuaikai Tomishiro Central Hospital).