Double-Blind Comparison of Full and Partial Anemia Correction in Incident Hemodialysis Patients without Symptomatic Heart Disease

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It is unclear whether physiologic hemoglobin targets lead to cardiac benefit in incident hemodialysis patients without symptomatic heart disease and left ventricular dilation. In this randomized, double-blind study, lower (9.5 to 11.5 g/dl) and higher (13.5 to 14.5 g/dl) hemoglobin targets were generated with epoetin α over 24 wk and maintained for an additional 72 wk. Major eligibility criteria included recent hemodialysis initiation and absence of symptomatic cardiac disease and left ventricular dilation. The primary outcome measure was left ventricular volume index (LVVI). The study enrolled 596 patients. Mean age, duration of dialysis therapy, baseline predialysis hemoglobin, and LVVI were 50.8 yr, 0.8 yr, 11.0 g/dl, and 69 ml/m^2, respectively; 18% had diabetic nephropathy. Mean hemoglobin levels in the higher and lower target groups were 13.3 and 10.9 g/dl, respectively, at 24 wk. Percentage changes in LVVI between baseline and last value were similar (7.6% in the higher and 8.3% in the lower target group) as were the changes in left ventricular mass index (16.8 *versus* 14.2%). For the secondary outcomes, the only between-group difference was an improved SF-36 Vitality score in the higher *versus* the lower target group (1.21 *versus* −2.31; $P = 0.036$). Overall adverse event rates were similar in both target groups; higher ($P < 0.05$) rates of skeletal pain, surgery, and dizziness were seen in the lower target group, and headache and cerebrovascular events were seen in the higher target group. Normalization of hemoglobin in incident hemodialysis patients does not have a beneficial effect on cardiac structure, compared with partial correction.

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Left ventricular hypertrophy (LVH) is present in nearly 80% of dialysis patients (1). Morphologically, left ventricular dilation and concentric hypertrophy are approximately equally represented, and both conditions are associated with higher rates of cardiovascular events (1–7). In dialysis patients, anemia is associated with LVH, left ventricular dilation, congestive heart failure, hospitalization, and mortality (8–11). Controlled studies with quality of life (QOL) and left ventricular mass as end points support partial correction of hemoglobin in dialysis patients (12–14). These findings underpin guidelines from the United States, Europe, and Canada, which suggest hemoglobin levels between 11 and 12 g/dl in dialysis patients (15–17). The potential risks and benefits of higher hemoglobin targets in dialysis patients have generated considerable discussion. Evaluation of studies reported to date (18–21), with the benefit of hindsight, led to concerns in one or more of the following areas: Late intervention, small sample size, short follow-up, and nonblinded participants. The current study was conducted to compare the impact of higher *versus* lower hemoglobin targets on left ventricular size in incident hemodialysis patients without symptomatic cardiac disease. Secondary outcomes included left ventricular mass index (LVMI), 6-min walking test, QOL, and the occurrence of adverse events.

Materials and Methods

Among incident hemodialysis patients without symptomatic cardiac disease and left ventricular dilation, we compared the effects of higher (13.5 to 14.5 g/dl) and lower (9.5 to 11.5 g/dl) hemoglobin targets maintained with epoetin α on (*1*) left ventricular volume index (LVVI), the primary outcome; (2) LVMI; (*3*) the incidence of *de novo* congestive heart failure; (*4*) QOL, as revealed by vitality, fatigue, and quality of social interaction scores; and (*5*) 6-min walking test performance.

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P.S.P. and R.N.F. contributed equally to this work.

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Study Population

Adult (≥18 yr of age) hemodialysis patients were selected using the following inclusion criteria: (*1*) Predialysis hemoglobin between 8 and 12 g/dl; (*2*) hemodialysis started in the preceding 3 to 18 mo (this relatively broad definition for early intervention was chosen to facilitate enrollment); (*3*) LVVI <100 ml/m^2 on screening echocardiography, with normal being <90 ml/m^2; and (*4*) predialysis diastolic BP <100 mmHg. The exclusion criteria were (*1*) symptomatic ischemic heart disease or heart failure; (*2*) angiographic critical coronary artery disease; (*3*) current treatment ≥10 mg of prednisone daily for a failed renal transplant; (*4*) surgery for pericardial or valvular disease within the last 2 yr; (*5*) medical conditions that are likely to reduce the response to epoetin α, including uncorrected iron deficiency; (*6*) concurrent malignancy; (*7*) blood transfusion within the preceding month; (*8*) therapy with cytotoxic agents; (*9*) seizure within the previous year; (*10*) hypersensitivity to intravenous iron; and (*11*) current pregnancy or breastfeeding.

Design

A randomized, double-blind design was used with patients and outcome assessors but not treating physicians, who were blinded to assigned hemoglobin target. The study was divided into a 24-wk titration phase, which was used to achieve hemoglobin targets, and a 72-wk maintenance period.

Local independent ethics committees or institutional review boards approved the study protocol form before study initiation. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients gave informed consent before study enrollment.

Study Procedures

The study was centrally monitored from St. John's, Canada (P.S.P.), for Canadian patients and Manchester, England (R.N.F.), for European patients. Thirty percent of patients enrolled were from Canada, and 70% were from Europe. Screening echocardiograms were sent to a central site (Cardialysis B.V., Rotterdam, The Netherlands) to determine whether LVVI was <100 ml/m^2. Randomization was performed at the two coordinating centers with an interactive voice randomization telephone system, using permuted blocks, stratified by gender and concurrent epoetin use.

Laboratory tests were measured by Quest Diagnostics (Van Nuys, CA, and Heston, UK). Baseline evaluations included medical history, vital signs, height and weight, blood chemistry, M-mode echocardiography, electrocardiography, Kidney Disease Quality of Life (KDQOL) (22), Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale (23), and a 6-min walking test (24). As part of the sponsor's effort to investigate the occurrence of pure red-cell aplasia in patients who received epoetin α, the protocol was amended after 36 mo to mandate measurement of anti-erythropoietin antibodies and serum erythropoietin.

The following treatment targets were used: (*1*) Predialysis hemoglobin levels of 9.5 to 11.5 g/dl throughout in the lower target group and, in the higher target group, increments of 0.5 to 1.0 g/dl biweekly, until achieving stability between 13.5 and 14.5 g/dl (measured weekly for 24

Table 1. Baseline characteristics for the lower and higher target groups[a]

	Total (n = 596; Mean ± SD or %)	Lower (9.5 to 11.5 g/dl; n = 300; Mean ± SD or %)	Higher (13.5 to 14.5 g/dl; n = 296; Mean ± SD or %)
Age (yr)	50.8 ± 15.4	49.4 ± 15.2	52.2 ± 15.6
Duration of dialysis (mo)	10.1 ± 5.0	10.2 ± 5.1	10.0 ± 4.9
Weight (kg)	75 ± 16	74 ± 17	75 ± 16
Height (m)	1.68 ± 0.10	1.68 ± 0.10	1.68 ± 0.09
Hemoglobin (g/dl)	11.0 ± 1.2	11.0 ± 1.2	11.0 ± 1.2
Transferrin saturation (%)	36.2 ± 17.2	36.8 ± 17.8	35.7 ± 16.7
Urea reduction ratio (%)	65.9 ± 10.7	66.0 ± 11.3	65.7 ± 10.1
Serum albumin (g/dl)	3.9 ± 0.3	4.0 ± 0.3	3.9 ± 0.3
Male	60	60	60
Previous epoetin use	92	91	93
Race			
white	89	88	91
black	5	6	4
Primary cause of renal failure			
glomerulonephritis	29	29	28
diabetic nephropathy	18	17	19
polycystic kidney disease	9	8	10
hypertension	8	9	7
unknown	10	10	9
other	27	27	27
Dialysis access			
fistula	84	83	86
graft	6	5	6
catheter	10	12	8

[a] $P > 0.05$ for all comparisons between lower and higher target groups, except age ($P = 0.02$).

wk, then biweekly); (2) predialysis diastolic BP between 70 and 90 mmHg (measured weekly for 24 wk, then every 4 wk); (3) urea reduction ratio >67% (measured every 4 wk for 24 wk, then every 12 wk); and (4) transferrin saturation ≥20% (measured biweekly for 24 wk, then every 4 wk).

Between February 2000 and June 2001, 596 patients were enrolled in 95 treatment centers in 10 European countries and Canada. For each patient, a form was faxed weekly to the coordinating center displaying hemoglobin, epoetin α regimen, BP, and transferrin saturation levels. Treatment recommendations were faxed back, weekly. Initially, epoetin α could be administered subcutaneously or intravenously. A study amendment, effective August 22, 2002, limited administration to the intravenous route. The last patient completed the study in May 2003.

A predefined algorithm was used for epoetin α therapy. Epoetin-naïve patients in the higher target group were assigned a dose of 150 IU/kg per wk. For hemoglobin levels that deviated from target, epoetin doses were changed by 25% of the previous dose or 25 IU/kg.

Outcome Measures

Echocardiograms were performed at 24, 48, and 96 wk after study start. Standard echocardiographic recordings were performed within 1 kg of dry weight, usually within 24 h after the midweek dialysis. Dry weight was the optimal postdialysis weight for BP control without symptoms of blood volume contraction. American Society of Echocardiography criteria (25) were used, and echocardiograms were read by an independent central reader, Cardialysis. Left ventricular volume, in milliliters, was calculated as 0.001047 (left ventricular end-diastolic diameter mm)^3 (26). Left ventricular mass, in grams, was calculated as 0.00083 × [(end-diastolic diameter mm + interventricular septum thickness mm + posterior wall thickness mm)^3 − (end-diastolic diameter mm)^3 + 0.6] (27). LVVI and LVMI were calculated as left ventricular volume/M^2 body surface area and left ventricular mass/M^2 body surface area, respectively (28).

The 6-min walking test was performed at 24, 48, and 96 wk after study start, and QOL scales were recorded at 24, 36, 48, 60, 72, 84, and 96 wk. The FACIT fatigue scale and two subscales from the KDQOL, the SF-36 Vitality and KDQOL Quality of Social Interaction, were chosen for analysis before initiating the study, with higher values representing better QOL. The 6-min walking test measured the distance walked in 6 min, change in heart rate from pre- to postexercise, and perceived exertion (24). *De novo* heart failure was defined as dyspnea at rest with two of the following: Increased jugular venous pressure, bilateral basal crackles, radiographic pulmonary hypertension, and radiographic interstitial edema. Safety evaluations included adverse events as defined by the investigator, vital signs, and laboratory measures.

Statistical Analyses

Data from Canadian Normalization of Hemoglobin trial were used to guide sample size estimation (19). The sample size needed to detect a 15% difference between treatment groups was calculated as 166 per treatment group, given a two-tailed significance of 0.05, a power of 0.90, and an SD of the percentage change in left ventricular cavity volume index of 42%. With an expected dropout rate of 40%, primarily as a result of transplantation, 277 patients were required for each treatment group.

The intention-to-treat philosophy was used. Analysis of covariance (adjusted for age, epoetin use at randomization, and baseline LVH) was used to adjust the effect of hemoglobin target on percentage change in LVVI and LVMI. *De novo* heart failure rates were compared using time-to-event analyses. QOL outcomes were compared in patients with at least one QOL score, using piecewise linear regression, where QOL growth curves were allowed to change slopes at week 24, *i.e.*, one slope was used from weeks 0 to 24, and another slope was used from week 24 and beyond. The main QOL analysis assumed that missing QOL data were missing at random; however, a sensitivity analysis, which did not assume that data were missing at random, yielded similar findings. The primary QOL assessment was mean follow-up minus baseline QOL score, with *P* values adjusted for multiple comparisons using the Hochberg procedure (29).

The proportions with at least one treatment-emergent adverse event were compared by treatment assignment; because the number of component conditions was very large, any adverse event that occurred in >10% of patients is reported here, as are vascular events, access loss events, cardiac events, and death when the occurrence rates exceeded 2%. Parametric, two-sided statistical tests were used throughout, with a type I error of 0.05, using SAS Version 6.12.

Role of the Funding Source

The study sponsor, Johnson & Johnson Pharmaceutical Research and Development, LLC, identified the participating centers, monitored the data collection, and entered the data in a central database.

Results

Patients

Baseline characteristics of the 596 patients enrolled are shown in Table 1 and were similar in the two randomly assigned treatment groups, apart from age, which was greater in the higher target group. As anticipated, 324 (54%) patients remained in the study for 96 wk, 160 (54%) in the higher and 164 (55%) in the lower target groups. The reasons for study exit—renal transplantation (n = 133, 67 in the higher and 66 in the lower target group), adverse events (n = 76, 39 and 37), patient choice (n = 28, 9 and 19), loss to follow-up (n = 2, 1 and 1), and other (n = 36, 21 and 15)—were similar in the two target

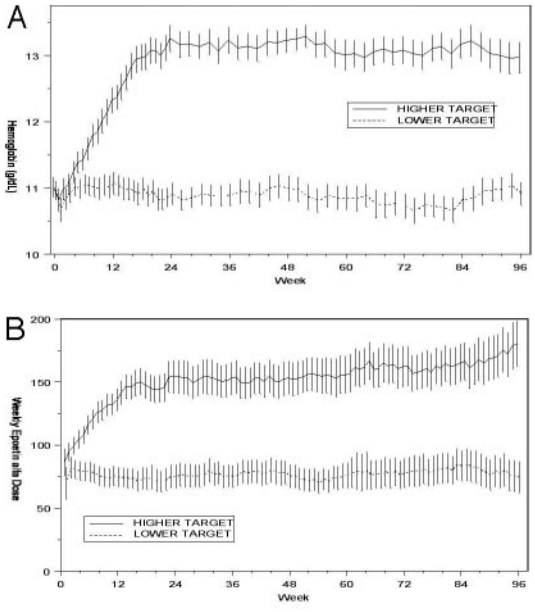

Figure 1. Hemoglobin levels (top) and epoetin α doses (bottom), presented as means ± 2 SE in the higher and lower target groups.

Table 2. Clinical indicators for the lower and higher target groups

	Lower (9.5 to 11.5 g/dl)		Higher (13.5 to 14.5 g/dl)	
	N	Mean ± SD or *n* (%)	*N*	Mean ± SD or *n* (%)
Transferrin saturation (%)				
baseline	294	36.8 ± 17.5	293	35.7 ± 16.72
last value	294	34.2 ± 16.53	293	34.6 ± 14.91
Systolic BP (mmHg)				
baseline[a]	300	140 ± 20	295	144 ± 21.65
last value	299	139 ± 22	295	141 ± 22.14
Diastolic BP (mmHg)				
baseline	298	80 ± 12	295	81 ± 11.48
last value	299	79 ± 14	295	80 ± 12.57
No. of antihypertensive drugs				
baseline	300	1.8 ± 1.4	296	2.0 ± 1.5
last value[a]	300	1.7 ± 1.5	296	2.0 ± 1.7
Urea reduction ratio (%)				
baseline	281	66 ± 11	281	66 ± 10.10
last value[a]	292	68 ± 10	285	66 ± 10.87
Serum albumin (g/dl)				
baseline	296	4.0 ± 0.3	290	3.9 ± 0.29
last value	279	4.0 ± 0.4	279	3.9 ± 0.35
No. with transferrin saturation <20%				
baseline	294	40 (14)	293	35 (12)
last value	294	42 (14)	293	33 (11)
No. receiving intravenous iron				
baseline	300	129 (43)	296	139 (47)
last value[a]	300	75 (25)	296	110 (37)
No. receiving antihypertensives				
baseline	300	242 (81)	296	244 (82)
last value	300	222 (74)	296	226 (76)

[a]The following comparisons were statistically significant: Baseline systolic BP ($P = 0.019$), last value for number of antihypertensive drugs ($P = 0.020$), last value for urea reduction ratio ($P = 0.044$), and last value for number receiving intravenous iron ($P = 0.001$).

groups. The mean times in the study were similar for both target groups: 73.4 ± 31.1 wk for the higher compared with 74.0 ± 31.8 for the lower target group. In total, 339 patients had echocardiograms performed after 72 wk of follow-up.

Figure 1 shows hemoglobin levels and epoetin α doses in the two target groups. Toward the end of the titration phase, at 24 wk, the mean hemoglobin levels in the higher and lower target groups were 13.3 ± 1.5 and 10.9 ± 1.2 g/dl, respectively. During the maintenance phase, from weeks 24 to 96, mean hemoglobin levels were 13.1 ± 0.9 g/dl in the higher and 10.8 ± 0.7 g/dl in the lower target group. Predialysis hemoglobin levels, averaged for the whole study, including both the titration and the maintenance phases, were 12.6 ± 1.0 g/dl in the higher and 10.9 ± 0.7 g/dl in the lower target group, whereas the corresponding postdialysis levels were 13.5 ± 1.2 and 11.8 ± 1.1 g/dl, respectively. The proportionate increase in post- to predialysis hemoglobin, which reflects interdialytic weight gain, were similar in both groups (7 *versus* 8%).

Table 2 summarizes clinical indicators at the beginning and at the end of the study. The last observed values were similar in the two target groups except for a higher proportion receiving intravenous iron, number of antihypertensive drugs, and lower urea reduction ratios in the higher target group (all $P < 0.05$). There was no difference in the change in number of antihypertensive drugs from baseline to last value, comparing the two groups.

Table 3 shows the major cardiac outcomes of the study, compared by assigned hemoglobin target. LVVI did not change significantly over time in the overall study population, and changes in LVVI were similar in both target groups. Although LVMI increased over time in the overall study population ($P < 0.001$), the changes observed were unaffected by target hemoglobin assignment. These conclusions were unchanged when only those who had echocardiogram performed after week 80 were included in the analysis. Rates of *de novo* heart failure were similar in both target groups, as were the changes in 6-min walking distance.

Table 4 shows the QOL outcomes, by assigned hemoglobin.

Table 3. Changes in LVVI, LVMI, 6-min walking test, and incidence of heart failure for the lower and higher target groups[a]

	Lower (9.5 to 11.5 g/dl)	Higher (13.5 to 14.5 g/dl)	Between Group	
			Effect[b]	*P*
LVVI (ml/m^2; *n* [mean ± SD])				
baseline	300 (68.6 ± 21.1)	296 (68.8 ± 20.9)		
week 24	254 (70.6 ± 21.7)	255 (69.4 ± 22.4)		
week 48	222 (70.4 ± 25.5)	223 (67.5 ± 23.4)		
week 96	169 (68.5 ± 25.2)	170 (66.7 ± 26.1)		
last value	256 (69.0 ± 25.2)	264 (68.4 ± 25.7)		
% change from baseline[c] (*n* [Est ± SE])	256 (8.3 ± 4.7)	264 (7.6 ± 4.7)	−0.7	0.8726
LVMI (g/m^2; *n* [mean± SD])				
baseline	300 (111.9 ± 33.2)	296 (116.6 ± 35.5)		
week 24	254 (121.3 ± 37.2)	255 (121.7 ± 40.1)		
week 48	222 (122.8 ± 42.5)	223 (124.2 ± 38.9)		
week 96	169 (128.2 (40.3)	166 (128.4 ± 43.2)		
last value	256 (126.3 ± 40.9)	260 (126.8 ± 42.4)		
% change from baseline[c] (*n* [Est± SE])	256 (16.8 ± 3.5)	260 (14.2 ± 3.5)	−2.6	0.4353
Six-min walking test (m; *N* [mean± SD])				
baseline	277 (399 ± 136)	284 (385 ± 136)		
week 24	233 (416 ± 133)	242 (407 ± 141)		
week 48	200 (416 ± 138)	203 (416 ± 142)		
week 96	143 (415 ± 144)	142 (412 ± 142)		
last value	242 (416 ± 141)	254 (410 ± 144)		
change from baseline[d] (*n* [Est± SE])	237 (26 ± 9)	249 (32 ± 9)	6.6	0.4462
Congestive heart failure (*N*; *n* [%])	300 (12 [4%])	296 (11 [4%])		0.8687[e]

[a]LVVI, left ventricular volume index; LVMI, left ventricular mass index.
[b]Estimated treatment difference (higher target group minus lower target group).
[c]Compared with analysis of covariance, adjusted for baseline left ventricular hypertrophy, gender, and epoetin α usage at randomization.
[d]Compared with analysis of covariance, adjusted for baseline gender and epoetin α usage at randomization.
[e]Log-rank statistic from the time-to-event analysis.

SF-36 Vitality scores improved more in the higher than in the lower target group ($P = 0.036$), and differences between target groups, adjusted for multiple comparisons, were significant at weeks 24, 36, 48, 60, and 72 (Figure 2). No significance between-group differences were seen in the time course of FACIT Fatigue scores and the KDQOL Quality of Social Interaction scores.

Thirty-three patients, 20 in the lower and 13 in the higher target group, died during the study ($P = 0.28$). Table 5 shows rates of treatment-emergent adverse events, vascular events, access loss events, cardiac events, and death. The proportions with at least one treatment-emergent adverse event were similar in both target groups; more patients in the lower target group experienced skeletal pain ($P = 0.009$), surgery ($P = 0.013$), and dizziness ($P = 0.001$), whereas more patients in the higher target group experienced headache ($P = 0.030$) and cerebrovascular events ($P = 0.045$).

Discussion

We studied patients who had recently started hemodialysis therapy without overt cardiac disease. The fraction of incident dialysis patients in the Canadian echocardiographic cohort study (1), with manifestations similar to the inclusion criteria of the current study (no symptomatic heart failure or ischemic heart disease and LVVI < 100 ml/m^2) was 43%. Hemoglobin targets higher than the current guidelines had no effect on cardiac dimensions, the incidence of congestive heart failure, or performance on a 6-min walking test. QOL (in terms of vitality) was improved. Adverse event rates were comparable in both groups, except for skeletal pain, surgery, and dizziness being significantly higher in the lower target group and headaches and cerebrovascular events being higher in the higher target group.

Several observational studies have shown associations between anemia and adverse outcomes in dialysis patients (8–11). Both uncontrolled (30,31) and controlled (14) studies have shown that partial correction of anemia leads to partial regression of LVH in dialysis patients, in addition to improving QOL and physical performance (12,13). Three controlled studies of normalization of hemoglobin with erythropoietin in hemodialysis populations have been reported to date. The United States Normal Hematocrit Trial differed from our study in several

Table 4. Quality-of-life outcomes for the lower and higher target groups[a]

	Lower (9.5 to 11.5 g/dl)		Higher (13.5 to 14.5 g/dl)		Between Group		
	N	Est ± SE	*N*	Est ± SE	Est ± SE	P^b	P^c
FACIT-Fatigue[d]							
week 24	291	69.7 ± 1.0	291	70.9 ± 1.0	1.3 ± 1.2	0.28	0.56
week 36	291	68.9 ± 1.0	291	70.5 ± 1.0	1.6 ± 1.1	0.16	0.32
week 48	291	68.1 ± 1.0	291	70.0 ± 1.0	1.9 ± 1.2	1.00	0.20
week 60	291	67.3 ± 1.0	291	69.5 ± 0.1	2.3 ± 1.3	0.08	0.16
week 72	291	66.4 ± 1.2	291	69.1 ± 1.2	2.6 ± 1.5	0.08	0.15
week 84	291	65.6 ± 1.3	291	68.6 ± 1.3	3.0 ± 1.7	0.08	0.16
week 96	291	64.8 ± 1.4	291	68.1 ± 1.5	3.3 ± 1.9	0.09	0.17
mean follow-up minus baseline	291	−3.21 ± 1.0	291	−1.0 ± 1.0	2.3 ± 1.3	0.08	0.16
SF-36 Vitality[d]							
week 24	282	55.1 ± 1.1	282	59.2 ± 1.1	4.1 ± 1.4	0.002	0.007
week 36	282	54.6 ± 1.1	282	58.5 ± 1.1	3.9 ± 1.3	0.003	0.008
week 48	282	54.2 ± 1.1	282	57.9 ± 1.1	3.7 ± 1.3	0.005	0.014
week 60	282	53.7 ± 1.1	282	57.2 ± 1.1	3.5 ± 1.4	0.011	0.035
week 72	282	53.3 ± 1.2	282	56.6 ± 1.2	3.3 ± 1.6	0.032	0.096
week 84	282	52.8 ± 1.3	282	56.0 ± 1.4	3.1 ± 1.8	0.073	0.220
week 96	282	52.4 ± 1.5	282	55.3 ± 1.5	2.9 ± 2.0	0.147	0.275
mean follow-up minus baseline	282	−2.31 ± 1.08	282	1.21 ± 1.08	3.5 ± 1.4	0.012	0.036
KDQOL quality of social interaction[d]							
week 24	282	67.6 ± 1.4	282	68.2 ± 1.4	0.5 ± 1.3	0.68	0.68
week 36	282	67.4 ± 1.3	282	68.0 ± 1.3	0.6 ± 1.2	0.62	0.62
week 48	282	67.1 ± 1.3	282	67.8 ± 1.3	0.7 ± 1.2	0.58	0.56
week 60	282	66.9 ± 1.3	282	67.7 ± 1.3	0.8 ± 1.3	0.56	0.58
week 72	282	66.7 ± 1.4	282	67.5 ± 1.4	0.8 ± 1.4	0.56	0.56
week 84	282	66.4 ± 1.4	282	67.3 ± 1.5	0.9 ± 1.6	0.56	0.56
week 96	282	66.2 ± 1.5	282	67.1 ± 1.6	1.0 ± 1.7	0.57	0.58
mean follow-up minus baseline	282	0.03 ± 1.0	282	0.8 ± 1.0	0.8 ± 1.30	0.56	0.56

[a]FACIT, Functional Assessment of Chronic Illness Therapy; KDQOL, Kidney Disease Quality of Life.
[b]Unadjusted *P* value.
[c]The *P* value is adjusted for multiple comparisons across the three primary QOL scales using the Hochberg procedure.
[d]Results from piecewise linear regression, where one slope was used from weeks 0 to 24 and another slope was used from week 24 and beyond. This analysis assumed that missing QOL data were missing at random and unstructured covariance.

respects, including the requirement of pre-existing symptomatic cardiac disease, a higher proportion of patients with diabetes, patients on dialysis therapy an average of 3 yr or more, the predominance of synthetic grafts for vascular access, and the administration of substantially larger epoetin α doses in both target groups. Primary outcome rates (death or first nonfatal myocardial infarction) were higher in the higher target groups, although this was not statistically significant. Although rates of access loss were significantly higher in the normalized group, QOL was better (18). The study was stopped early because of significantly higher rates of vascular access thrombosis and loss, together with 30% higher mortality in the high hematocrit group. The Canadian Normalization of Hemoglobin trial included patients with asymptomatic LVH or LV dilation. The higher hemoglobin target failed to induce regression of pre-existing LVH or dilation. Secondary outcome analysis suggested that higher hemoglobin levels could prevent *de novo* left ventricular dilation; in addition, QOL was improved without

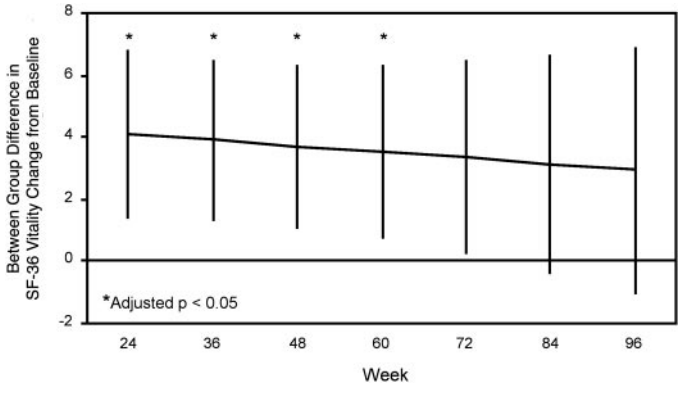

Figure 2. Mean of change in SF-36 Vitality scores from baseline in the lower and higher target groups, presented ± 2 SE. *$P < 0.05$.

Table 5. Treatment-emergent adverse events that occurred in ≥10% of patients; vascular, access loss, and cardiac events that occurred in ≥2% of patients; and death in lower and higher target groups[a]

	Lower (9.5 to 11.5 g/dl; $n = 300$)	Higher (13.5 to 14.5 g/dl; $n = 296$)
Treatment emergent AE in ≥10% of patients		
any AE	281 (94%)	284 (96%)
cardiovascular		
hypertension	110 (37)	120 (41)
hypotension	105 (35)	85 (29)
platelet, bleeding, and clotting		
arteriovenous fistula thrombosis	23 (8)	30 (10)
hematoma	36 (12)	45 (15)
vascular (extracardiac) disorders		
arteriovenous fistula loss	26 (9)	30 (10)
gastrointestinal		
vomiting	52 (17)	54 (18)
diarrhea	53 (18)	50 (17)
nausea	53 (18)	47 (16)
abdominal pain	46 (15)	45 (15)
respiratory		
upper respiratory tract infection	69 (23)	72 (24)
dyspnea	42 (14)	35 (12)
cough	36 (12)	35 (12)
pharyngitis	31 (10)	29 (10)
musculoskeletal		
myalgia	85 (28)	81 (27)
skeletal pain[b]	64 (21)	39 (13)
arthralgia	43 (14)	36 (12)
nervous system		
headache[b]	64 (21)	86 (29)
dizziness[b]	40 (13)	16 (5)
skin		
skin disorder	39 (13)	41 (14)
pruritus	33 (11)	23 (8)
other		
infection	32 (11)	34 (11)
urinary tract infection	27 (9)	29 (10)
hyperparathyroidism	30 (10)	19 (6)
pain	47 (16)	41 (14)
back pain	40 (13)	35 (12)
fever	42 (14)	30 (10)
influenza-like symptoms	37 (12)	30 (10)
device complications	27 (9)	42 (14)
surgery[b]	39 (13)	20 (7)
Vascular, access loss, and cardiac events in ≥2% of patients		
vascular		
arteriovenous fistula thrombosis	36 (12)	45 (15)
Non–site-specific embolism thrombosis	12 (4)	14 (5)
permanent catheter thrombosis	9 (3)	8 (3)
cerebrovascular disorder[b]	4 (1)	12 (4)
peripheral ischemia	7 (2)	8 (3)
angina pectoris	8 (3)	9 (3)
myocardial infarction	4 (1)	7 (2)
chest pain	7 (2)	4 (1)
access loss		
permanent catheter loss	6 (2)	7 (2)
arteriovenous fistula loss	27 (9)	30 (10)
arteriovenous graft loss	9 (3)	9 (3)
cardiac		
angina pectoris	8 (3)	9 (3)
myocardial infarction	4 (1)	7 (2)
chest pain	7 (2)	4 (1)
tachycardia	15 (5)	22 (7)
palpitations	9 (3)	6 (2)
atrial fibrillation	7 (2)	6 (2)
bradycardia	5 (2)	7 (2)
pulmonary edema	16 (5)	9 (3)
cardiac failure	6 (2)	2 (1)
pulmonary edema or heart failure	19 (61)	11 (4)
death	20 (7)	13 (4)

[a]AE, adverse events.

[b]$P > 0.05$ for all comparisons except headache ($P = 0.030$), skeletal pain ($P = 0.009$), surgery ($P = 0.013$), dizziness ($P = 0.001$), and cerebrovascular disorders ($P = 0.045$).

compromising vascular access (arteriovenous fistulas, predominantly) (19). Another study used a double-blind crossover design to compare hemoglobin targets of 10 and 14 g/dl, each applied for 6 wk; the higher target led to reduced cardiac output and improved QOL (21).

Two trials of higher hemoglobin targets, not restricted to hemodialysis patients, have been reported. A Scandinavian study with target hemoglobin levels of 9.0 to 12.0 or 13.5 to 16.0 g/dl included dialysis and nondialysis patients with chronic kidney disease. QOL improved with the higher target, whereas thrombovascular event rates, including those involving vascular access, were similar (20). An Australian study compared strategies of early or delayed anemia therapy targets in patients with chronic kidney disease. Eligible patients had hemoglobin levels of 11.0 to 12.0 g/dl (women) or 11.0 to 13.0 g/dl (men). One group received epoetin α immediately, to maintain hemoglobin between 12.0 and 13.0 g/L. In the other group, hemoglobin was allowed to decline below 9.0 g/dl; epoetin α then was used to maintain levels between 9.0 and 10.0 g/dl. The mean hemoglobin levels achieved, in practice, were 12.1 and 10.8 g/dl, respectively. In this 2-yr study, changes in LVMI were similar in both target groups (32). Thus, the available literature suggests, as in our study, that enhanced QOL is the only consistent benefit conferred by normalizing hemoglobin in patients with chronic kidney disease.

Assessment of different adverse event rates should take account of the fact that multiple comparisons were made. The observation that a higher number of cerebrovascular events occurred in the higher ($n = 12$) compared with the lower ($n = 4$) target group requires further study. Previous trials in chronic kidney disease did not report a higher incidence of stroke in the higher target group (18–21), but concern has been expressed regarding thrombotic events during erythropoietin therapy in oncology studies (33). The higher cerebrovascular event rate was not supported by a higher death rate in the higher target ($n = 13$) compared with the lower ($n = 20$) target group, and other cardiovascular events rates were similar. The BP levels were similar in both groups. Although a higher number of antihypertensive agents were prescribed in the higher group (compared with the lower group) at study end, the change in number of antihypertensive agents from baseline was similar in both groups.

Certain limitations in our study need to be considered. (*1*) The study was not powered to examine major cardiovascular events and death. This being said, our study used a randomized, double-blind design; a reasonable duration of follow-up; and sequential measurements in an incident cohort that started hemodialysis. (*2*) The positive findings of our study—that higher hemoglobin levels increase vitality—were generated from secondary outcome analyses. The changes observed were probably clinically important (34). (*3*) Our study, by design, selected hemodialysis patients without symptomatic cardiac disease and severe left ventricular dilation, and its findings can be truly generalized only to such patients (approximately 40 to 50% of incident dialysis patients). As a result of the inclusion criteria, the average age of the patients studied (51 yr) was younger than the median age of incident patients in Canada in 2000 (65 yr), and the proportion with diabetes (18%) was lower (44%) (35). This is reflected in the low mortality rate during the study (5.5%). (*4*) Despite central monitoring with real-time treatment recommendations, we approached but failed to reach intended hemoglobin targets in the higher target group. However, the separation by target group was approximately 2.3 g/dl throughout the maintenance phase of the study and was compatible with the sample size assumption that a 15% difference in LVVI changes would be associated with a 2-g/dl difference in hemoglobin levels (19). Therefore, it seems unlikely that the failure to achieve hemoglobin targets could fully account for the similarity seen in the primary outcome comparisons. (*5*) Although we observed no difference in cardiovascular, access, and malignancy rates, the actual event rates were low, and an untreated placebo group was not used. Thus, small or moderate differences in event rates cannot be excluded. (*6*) The high dropout rate was anticipated because patients such as those in our study are usually referred and then wait for renal transplantation. No differences in the primary outcome were observed whether analyzed by changes from baseline to last value or by analysis of serial measurements.

Despite its limitations, we believe that this randomized, controlled trial, in enrolling a large number of incidence hemodialysis patients, in achieving a clinically important difference in hemoglobin levels, and in serial follow-up of several clinically important outcomes over 2 yr, provides important information regarding the question of normalizing hemoglobin in dialysis patients. It suggests that normalization of hemoglobin in patients who start hemodialysis, although improving vitality, has no effect on left ventricular size when compared with patients who are maintained with hemoglobin levels between 9.5 and 11.5 g/dl.

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