

Erythropoietin Therapy, Hemoglobin Targets, and Quality of Life in Healthy Hemodialysis Patients: A Randomized Trial

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Background and objectives: The effects of different hemoglobin targets when using erythropoiesis-stimulating agents on quality of life are somewhat controversial, and predictors of change in quality of life in endstage renal disease have not been well characterized.

Design, setting, participants, & measurements: Five hundred ninety-six incident hemodialysis patients without symptomatic cardiac disease were randomly assigned to hemoglobin targets of 9.5 to 11.5 g/dl or 13.5 to 14.5 g/dl for 96 weeks, using epoetin_alfa as primary therapy. Patients and attending physicians were masked to treatment assignment. Quality of life, a secondary outcome, was prospectively recorded using the Kidney Disease Quality of Life (KDQoL) questionnaire at weeks 0, 24, 36, 48, 60, 72, 84, and 96, with prespecified outcomes being fatigue and quality of social interaction.

Results: The mean age and prior duration of dialysis therapy of the study population were 50.8 and 0.8 yr. Mortality was low, reflecting the relatively healthy group enrolled. Of 20 domains within the KDQoL only the prespecified domain of fatigue showed significant change over time between the two groups. Improvement in fatigue scores in the high-target group ranged from 3.2 to 7.9 over time ($P = 0.007$) compared with change in the low-target group. Higher body mass index and lower erythropoietin dose at baseline were independent predictors of improvement in multiple KDQoL domains.

Conclusions: In relatively healthy hemodialysis patients, normal hemoglobin targets may have beneficial effects on fatigue. Improvement in multiple domains of quality of life is associated with higher body mass index and lower erythropoietin requirements.

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Anemia is highly prevalent in end-stage renal disease patients, and inadequate renal erythropoietin production is a contributing cause (1,2). Although erythropoiesis-stimulating agents have been used to treat anemia in patients with chronic kidney disease (CKD) for almost two decades, optimal hemoglobin targets remain unclear, and concerns remain about the safety of normal hemoglobin levels as a target for erythropoietin therapy. In this regard, the United States Food and Drug Administration recently issued an alert to healthcare professionals about revisions to the product label for erythropoiesis-stimulating agents in patients with chronic kidney disease (3). Notable features of this label change were the recommended hemoglobin target range of 10 to 12 g/dl and the removal of all quality of life claims, with the exception of improved exercise tolerance and functional ability.

In practice, hemoglobin levels have sometimes been maintained at levels higher than 12.0 g/dl because individual patients perceive better quality of life at higher hemoglobin levels. However, randomized trials of higher hemoglobin targets have shown heterogeneous quality of life effects. Improvements

were observed in prevalent hemodialysis patients with preexisting cardiac disease (4), in Scandinavian predialysis and dialysis patients (5), and in nondialysis patients enrolled in CREATE (6), but no improvement was observed in patients enrolled in CHOIR who had less severe CKD than those in CREATE (7). In addition, the validity of quality of life findings in most of these trials is uncertain because treatment assignments were not concealed from study subjects.

We enrolled 596 incident hemodialysis patients without symptomatic cardiac disease in a randomized, controlled trial that compared a normal hemoglobin target to partial correction of anemia, with epoetin-alfa as the erythropoiesis-stimulating agent. Cardiac structure constituted the primary study outcome, and no difference was observed between the two groups (8). Clinically relevant secondary outcomes included quality of life, with prespecified outcomes being Energy/Fatigue scores and Quality of Social Interaction scores on the Kidney Disease Quality of Life (KDQoL) questionnaire and Vitality scores on the Short Form 36 (SF36) questionnaire. We have not previously reported the results from this trial of serial measurements using the KDQoL questionnaire. In this article, we examine the hypothesis that normal hemoglobin targets improve quality of life in comparatively “healthy” incident hemodialysis patients, and we also report the independent predictors of changes in the various quality of life domains assessed by the KDQoL.

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Materials and Methods

Design

The design, methods and sample size assumptions of the study have been reported previously (8).

Patients were randomly assigned to one of the following hemoglobin targets: 9.5 to 11.5 g/dl (“low target”) and 13.5 to 14.5 g/dl (“high target”). Patients were masked to treatment assignment. Local investigators and the dialysis unit were also masked to treatment assignment. However, attending physicians had access to local clinic hemoglobin levels. The central coordinating centers provided treatment recommendations on erythropoietin dose, intravenous iron dose, and antihypertensive therapy for each patient (see below), but the local investigator was responsible for ordering treatment changes. Mean hemoglobin levels at the end of the initial 24-wk titration phase were 13.3 and 10.9 g/dl, respectively. During the maintenance phase, from weeks 24 to 96, corresponding mean hemoglobin levels were 13.1 and 10.8 g/dl.

Study Population

Inclusion criteria were as follows: age \geq 18 yr, inception of maintenance hemodialysis within the previous 3 to 18 mo, predialysis hemoglobin between 8 and 12 g/dl, left ventricular volume index $<$ 100 ml/m², and predialysis diastolic BP $<$ 100 mmHg. Exclusion criteria were as follows: clinical evidence or history of symptomatic cardiac failure or ischemic heart disease; daily prednisone dose \geq 10 mg; medical conditions likely to reduce epoetin responsiveness, including uncorrected iron deficiency; concurrent malignancy; blood transfusion in the preceding month; therapy with cytotoxic agents; seizure in the preceding year; hypersensitivity to intravenous iron; and current pregnancy or breastfeeding.

Description of Study Procedures

Laboratory tests were measured centrally by Quest Diagnostics (Van Nuys, CA and Heston, UK). Hemoglobin was measured weekly for 24 wk and biweekly thereafter. With the high target, the treatment goal was increments of 0.5 to 1.0 g/dl every 2 wk, until achieving stability between 13.5 and 14.5 g/dl. Other treatment goals included predialysis diastolic BP between 70 and 90 mmHg; urea reduction ratio $>$ 67% and transferrin saturation \geq 20%.

After random treatment assignment, patients assigned to the low target remained on their prestudy epoetin dose. Patients with the higher target received a 25% dose escalation, or an initial dose of 150 units per kilogram per week if naive to epoetin. In both groups, when hemoglobin levels deviated from target, epoetin doses were changed by 25% of the previous dose or 25 units per kilogram. For each patient, a standardized form was faxed weekly from the study sites to the coordinating center, showing hemoglobin, epoetin dose, BP, and transferrin saturation levels. In response, treatment recommendations were faxed weekly from the coordinating center to the study sites. Initially, the choice of subcutaneous or intravenous epoetin alfa administration was discretionary; concerns about pure red cell aplasia (9) led to a study amendment on August 22, 2002, limiting administration to the intravenous route. The last patient completed the study in May 2003.

Quality of life was assessed using the KDQoL questionnaire (10), with prespecified outcomes being Energy/Fatigue scores, and Quality of Social Interaction Scores. In the original article, we reported the changes in the other prespecified outcome: Vitality scores measured using the SF36 questionnaire (8). Assessments using KDQoL were made at weeks 0, 24, 36, 48, 60, 72, 84, and 96. There was no difference in the clinical or demographic characteristics or in treatment assignment of those who had only one KDQ assessment ($n = 112$) and those

who had serial assessments ($n = 484$). At each assessment, $>$ 90% of patients remaining in the study completed the questionnaire. In a recent article, we have reported differences in transfusion rates between high and low target groups (11).

Sample Size Estimate

The sample size needed to detect a 15% difference between treatment groups in the primary outcome (left ventricular cavity volume index) 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% (8). With an expected dropout rate of 40%, primarily as a result of transplantation, 277 patients were required for each treatment group.

Analysis

Repeated measures ANOVA with mixed modeling was used to estimate time-integrated quality of life effects, over time, while simultaneously examining quality of life at each individual study assessment. Change from baseline in the high-target group compared with change from baseline in low-target group was calculated for each KDQoL domain. To identify factors predictive of changes in quality of life by domain the high- and low-target groups were combined. Repeated measures ANOVA with mixed modeling was used to estimate changes in quality of life over time. Multivariate models included target hemoglobin group, baseline hemoglobin, baseline epoetin dose, baseline transferrin saturation, age, sex, race, time on dialysis, body mass index, primary cause of renal disease, European or Canadian patients, type of vascular access and baseline serum albumin. Details of the reported model are included in Table 3. SAS, version 9.1 (SAS Institute Inc., Cary, NC) was used for data analysis.

Results

Five hundred ninety-six incident hemodialysis patients were enrolled in 95 treatment centers in 10 countries between February 2000 and June 2001. Table 1 compares baseline characteristics by random hemoglobin target assignment (8). Baseline characteristics were similar except for the older age of high-target subjects (52.2 *versus* 49.4 yr). As dictated by the study design, initial on-study epoetin doses were greater in high-target subjects (7009 *versus* 6183 IU per week). Also, as dictated by the study design, only patients without symptomatic heart failure or ischemic heart disease were enrolled. Eighteen percent of participants were diabetic, and median serum albumin level was 4 mg/dl. The relatively healthy group of hemodialysis patients studied was reflected in the relatively low mortality rate: 4.7 (95% confidence interval [CI] 3.0 to 7.3) per 100 patient years in the low-target group and 3.1 (1.8 to 5.4) in the high-target group, ($P = 0.25$).

The proportions of study subjects with ≥ 1 , ≥ 2 , ≥ 3 , ≥ 4 , ≥ 5 , and ≥ 6 , and 7 quality of life assessments were 93.5%, 81.2%, 73.0%, 64.0%, 58.1%, 47.2% and 29.3%, respectively. Table 2 shows the effect of the high hemoglobin target on KDQoL scores. Beneficial changes were seen in at least one of the seven assessments that followed randomization for nine scales. When all study assessments were considered, the high hemoglobin target had an overall, time-integrated effect on energy/fatigue and no effect on the other 19 dimensions assessed (Table 2). The improvement in Energy/Fatigue scores in the high-target group ranged from 3.2 to 7.9 over time ($P = 0.007$) compared

Table 1. Baseline characteristics of patients enrolled in this randomized trial compared by target hemoglobin level

Characteristic	Target 9.5 to 11.5 g/dl	Target 13.5 to 14.5 g/dl	P
<i>n</i>	300	296	
Hemoglobin (g/dl)	11.0 (10.8 to 11.1)	11.0 (10.9 to 11.2)	0.54
Epoetin dose (IU per week)	6183 (5698 to 6667)	7009 (6528 to 7490)	0.02
Transferrin saturation (%)	36.8 (34.9 to 38.8)	35.8 (33.8, 37.7)	0.44
Age	49.4 (47.7 to 51.2)	52.2 (50.4 to 53.9)	0.03
Female sex (%)	39.7	39.5	0.97
Race			0.24
white	87.7	91.2	
black	5.7	4.4	
Asian	4.3	1.7	
other	2.3	2.7	
Dialysis duration (months)	10.2 (9.6 to 10.8)	10.0 (9.4 to 10.5)	0.58
Body mass index (kg/m ²)	26.3 (25.7 to 26.9)	26.5 (25.9 to 27.1)	0.78
Country (%)			
Austria	3.0	4.1	
Belgium	3.3	4.7	
Canada	32.0	27.7	
France	3.0	2.7	
Germany	11.0	12.5	
Greece	2.3	1.4	
Hungary	10.7	12.2	
Poland	22.3	22.6	
Spain	3.0	3.0	
United Kingdom	9.3	9.1	
Primary cause of renal disease			0.54
glomerulonephritis	29.0	28.4	
diabetes	16.7	18.9	
hypertension	9.3	6.8	
polycystic kidney disease	7.7	10.5	
Other/unknown	37.3	35.5	
Dialysis access (%)			0.21
fistula	82.7	85.8	
graft	5.0	6.1	
catheter	12.3	8.11	
Serum albumin (mg/dl)	4.0 (3.9 to 4.0)	4.0 (3.9 to 4.0)	0.88

Data are reported either as percent or as means (95% confidence intervals). The chi-squared test and analysis of variance were used for between-target comparisons.

with the changes in the low-target group. There was little difference in the changes of Quality of Social Interaction scores (Table 2)

The independent predictors of changes in quality of life for each domain were identified by combining both high- and low-target groups (Table 3). Among the covariates analyzed, no associations were identified for quality of social interaction, cognitive function, effects of kidney disease, dialysis staff encouragement, and patient satisfaction.

Older age was an independent predictor of deterioration in physical function only. Female sex was an independent predictor of increasing burden of kidney disease only. Nonwhite race was a strong predictor of not working.

Diabetes as a cause of renal disease had an independent and

negative impact on sexual function and physical functioning, but was associated with improvement in scores for burden of kidney disease and emotional well being.

Higher body mass index (> 25.5) was independently predictive of improvement in scores for burden of kidney disease, symptoms/problems, sleep, physical functioning, role limitations-physical, general health, emotional well being, role limitations-emotional, social functioning, and energy/fatigue (Table 3).

High baseline erythropoietin dose (>6000 IU/wk) was a significant predictor of deterioration in scores for symptoms/problems, overall health, pain, and energy/fatigue independent of other risk factors, including target hemoglobin (Table 3).

Table 2. Effect of target hemoglobin on quality of life scores

	Baseline Values		Change from Baseline in High Target (vs. Change from Baseline in Low Target)							<i>P</i> ¹
	Target Hemoglobin g/dl		Week							
	10.5 - 11.5	13.5 - 14.5	24	36	48	60	72	84	96	
Burden of kidney disease	47.1 (2.0)	44.8 (2.0)	2.4 (2.0)	1.0 (2.0)	3.7 (2.0)	2.2 (2.1)	4.9* (2.2)	1.6 (2.2)	2.1 (2.2)	0.34
Quality of social interaction	66.6 (2.2)	62.8 (2.3)	0.6 (1.7)	2.9 (1.7)	0.9 (1.7)	1.4 (1.8)	0.8 (1.8)	1.9 (1.9)	1.1 (1.9)	0.76
Cognitive function	69.9 (2.3)	63.3 (2.4)	2.9 (1.7)	3.8* (1.7)	2.2 (1.7)	4.7** (1.8)	2.5 (2.5)	2.4 (1.9)	4.3* (1.9)	0.20
Symptoms/problems	80.3 (1.0)	80.0 (1.1)	0.5 (1.2)	-0.5 (1.3)	0.1 (1.3)	-0.3 (1.3)	-0.1 (1.30)	1.3 (1.4)	0.2 (1.4)	0.91
Effects of kidney disease	64.6 (1.5)	65.2 (1.5)	-0.2 (1.5)	1.2 (1.5)	-0.7 (1.6)	-0.1 (1.6)	1.7 (1.6)	1.1 (1.7)	0.5 (1.7)	0.77
Sexual function	69.3 (2.6)	62.3 (2.7)	2.6 (2.9)	4.5 (3.0)	5.6 (3.0)	4.4 (3.1)	6.5* (3.2)	3.1 (3.3)	5.6 (3.3)	0.54
Sleep	67.9 (1.4)	64.7 (1.4)	-0.5 (1.7)	1.0 (1.7)	-1.0 (1.7)	-0.9 (1.8)	-0.3 (1.8)	-1.7 (1.9)	-2.0 (1.8)	0.72
Social support	75.2 (1.7)	74.0 (1.8)	0.6 (2.7)	1.1 (2.7)	2.3 (2.7)	0.4 (2.8)	0.2 (2.9)	1.7 (2.9)	-1.6 (2.9)	0.92
Work status	40.3 (3.0)	34.4 (3.1)	1.4 (2.9)	-0.6 (3.0)	4.2 (3.0)	4.0 (3.1)	1.6 (3.2)	1.0 (3.2)	5.2 (3.2)	0.39
Dialysis staff encouragement	82.6 (1.5)	79.7 (1.5)	3.0 (2.0)	-0.3 (2.0)	0.4 (2.0)	2.9 (2.1)	1.4 (2.1)	2.7 (2.2)	1.1 (2.2)	0.49
Patient satisfaction rating	75.9 (1.5)	77.3 (1.6)	-0.8 (1.9)	-0.2 (1.9)	0.4 (2.0)	-2.6 (2.0)	0.5 (2.1)	0.1 (2.1)	-1.2 (2.1)	0.76
Overall health rating	62.0 (1.4)	62.0 (1.5)	0.3 (1.9)	1.5 (1.9)	1.7 (1.9)	0.1 (2.0)	2.5 (2.0)	1.6 (2.1)	0.5 (2.1)	0.76
Physical functioning	67.1 (1.8)	62.5 (1.9)	3.1 (2.0)	4.6* (2.0)	3.5 (2.0)	4.0 (2.1)	4.4* (2.1)	5.1* (2.2)	2.4 (2.2)	0.32
Role limitations -physical	48.4 (3.1)	47.7 (3.2)	3.6 (4.4)	1.2 (4.4)	3.7 (4.4)	5.8 (4.5)	5.6 (4.7)	9.7* (4.8)	-1.3 (4.8)	0.33
Pain	72.0 (2.0)	70.7 (2.0)	-2.5 (2.6)	1.4 (2.6)	-0.9 (2.7)	-2.2 (2.7)	3.5 (2.8)	0.6 (2.9)	-0.7 (2.9)	0.34
General health	49.4 (1.6)	48.6 (1.6)	1.3 (1.7)	1.6 (1.7)	3.2 (1.7)	1.2 (1.8)	4.0* (1.8)	1.2 (1.9)	0.6 (1.9)	0.35
Emotional well-being	74.0 (1.4)	67.8 (1.6)	1.7 (1.8)	2.2 (1.8)	3.9* (1.8)	2.1 (1.8)	4.5* (1.9)	2.7 (1.9)	0.7 (1.9)	0.21
Role limitations -emotional	68.4 (3.0)	69.1 (3.0)	-3.8 (4.4)	-2.1 (4.4)	-1.7 (4.4)	0.4 (4.5)	0.6 (4.7)	1.3 (4.8)	-0.8 (4.8)	0.95
Social function	74.5 (1.7)	71.4 (1.9)	2.0 (2.4)	1.2 (2.5)	3.1 (2.5)	5.8* (2.5)	4.8 (2.6)	1.1 (2.7)	1.3 (2.7)	0.25
Energy/fatigue	57.9 (1.5)	53.9 (1.7)	6.2** (1.9)	5.7** (1.9)	3.8* (1.9)	5.4** (2.0)	7.9*** (2.1)	5.4* (2.1)	3.2 (2.1)	0.0066

Repeated measures analysis of variance with mixed modeling was used to estimate changes in quality of life over time. Positive values represent improvements in quality of life. Parameter estimates are presented with standard errors in parentheses.

P* < 0.05, *P* < 0.01, ****P* < 0.001, ¶*P* < 0.0001 for the effect of target hemoglobin at week 24, 36, 48, 72, or 96.

Table 3. Multivariate analysis of changes in quality of life: Baseline associations

	Change from Baseline							P ¹
	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	
Burden of kidney disease								
female sex	1.4 (2.0)	1.4 (2.1)	-0.4 (2.1)	5.2* (2.1)	-2.2 (2.2)	0.7 (2.3)	-0.6 (2.3)	0.02
body mass index > 25.5 kg/m ²	-1.0 (2.0)	-0.8 (2.0)	1.1 (2.0)	0.9 (2.1)	3.7 (2.1)	4.6* (2.2)	4.3 (2.2)	0.02
diabetic renal disease	1.1 (2.7)	7.5† (2.7)	7.8† (2.7)	6.7* (2.8)	8.4† (2.9)	5.7* (2.9)	6.6* (2.9)	0.01
Europe	-2.4 (2.1)	-1.0 (2.1)	3.1 (2.1)	1.8 (2.2)	1.8 (2.3)	3.6 (2.3)	3.8 (2.3)	0.03
Symptoms/problems								
epoetin dose > 6000 IU per week	-1.0 (1.3)	1.6 (1.3)	1.6 (1.3)	-1.3 (1.3)	-2.9* (1.4)	-0.4 (1.4)	-3.0* (1.4)	0.0004
body mass index >25.5 kg/m ²	-0.1 (1.2)	-1.2 (1.3)	0.7 (1.3)	0.5 (1.3)	2.3 (1.3)	2.6 (1.4)	2.8* (1.4)	0.01
Sexual function								
diabetic renal disease	-2.0 (4.0)	-2.1 (4.0)	-8.3* (4.1)	-9.4* (4.2)	-6.9 (4.3)	-14.6§ (4.3)	-10.0* (4.4)	0.008
Sleep								
body mass index >25.5 kg/m ²	2.2 (1.7)	-1.7 (1.7)	0.2 (1.7)	-1.1 (1.8)	1.3 (1.8)	2.5 (1.8)	3.4 (1.8)	0.024
Work status								
nonwhite race	-8.2 (4.3)	-6.2 (4.3)	-1.6 (4.4)	-17.9¶ (4.6)	-10.6* (4.6)	-6.2 (4.9)	-3.8 (4.7)	0.003
Overall health rating								
epoetin dose > 6000 IU per week	1.9 (1.9)	2.6 (1.9)	-0.2 (2.0)	-1.4 (2.0)	-3.7 (2.1)	-0.8 (2.1)	-1.4 (2.1)	0.04
Physical functioning								
age > 50.5 yr	-0.5 (2.0)	-2.7 (2.0)	-1.3 (2.0)	-4.2* (2.0)	-5.2* (2.1)	-7.0† (2.2)	-6.8† (2.2)	0.002
body mass index > 25.5 kg/m ²	-0.6 (2.0)	0.9 (2.0)	2.6 (2.0)	2.0 (2.0)	2.1 (2.1)	5.1* (2.2)	7.4§ (2.2)	0.002
diabetic renal disease	0.0 (2.6)	0.4 (2.6)	-2.6 (2.7)	-2.7 (2.7)	2.3 (2.8)	-9.0§ (2.9)	-7.9§ (2.8)	<0.0001
Role limitations-physical								
body mass index > 25.5 kg/m ²	-2.4 (4.4)	-2.6 (4.4)	6.9 (4.4)	6.1 (4.5)	5.0 (4.7)	8.2 (4.8)	8.8 (4.8)	0.028
Pain								
epoetin dose > 6000 IU per week	-3.4 (2.7)	0.9 (2.7)	3.0 (2.7)	-1.0 (2.8)	-5.2 (2.9)	-1.1 (3.0)	-4.9 (2.9)	0.027
transferrin saturation ≤ 32.0%	-0.2 (2.6)	-3.2 (2.6)	-2.1 (2.7)	5.1 (2.7)	3.1 (2.8)	1.5 (2.9)	1.8 (2.9)	0.03
General health								
body mass index > 25.5 kg/m ²	0.2 (1.7)	2.2 (1.7)	2.6 (1.7)	0.9 (1.8)	3.5 (1.8)	5.3** (1.9)	6.1** (1.9)	0.0039
Emotional well-being								
dialysis duration > 9.0 months	-3.9* (1.8)	0.4 (1.8)	-2.9 (1.8)	-2.7 (1.8)	0.6 (1.9)	-2.7 (1.9)	-2.3 (1.9)	0.04
body mass index > 25.5 kg/m ²	-2.1 (1.8)	-3.7* (1.8)	0.1 (1.8)	-1.3 (1.8)	0.2 (1.9)	2.2 (1.9)	2.6 (1.9)	0.007
diabetic renal disease	3.9 (2.4)	7.1** (2.4)	5.6* (2.4)	5.1* (2.4)	6.9** (2.5)	1.7 (2.6)	4.1 (2.6)	0.04

Table 3. Multivariate analysis of changes in quality of life: Baseline associations (continued)

	Change from Baseline							P ¹
	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	
Role limitations-emotional								
body mass index >25.5 kg/m ²	-4.5 (4.4)	-2.9 (4.4)	4.1 (4.4)	6.5 (4.5)	4.6 (4.7)	13.3* (4.8)	12.1* (4.8)	0.0002
Social function								
body mass index >25.5 kg/m ²	0.1 (2.4)	-1.1 (2.5)	0.4 (2.5)	1.0 (2.5)	1.6 (2.6)	8.0** (2.7)	6.1* (2.7)	0.004
Energy/fatigue								
target hemoglobin 13.5 to 14.5 g/dl	6.2* (1.9)	5.7** (1.9)	3.8 (1.9)	5.3** (2.0)	7.8*** (2.1)	5.4* (2.1)	3.1 (2.1)	0.007
epoetin > 6000 IU per week	1.4 (1.9)	2.2 (2.0)	4.3* (2.0)	-0.4 (2.0)	-0.9 (2.1)	1.7 (2.2)	-2.3 (2.1)	0.028
body mass index > 25.5 kg/m ²	-1.9 (1.9)	-0.8 (1.9)	0.7 (1.9)	0.6 (2.0)	0.3 (2.1)	3.3 (2.1)	6.3*** (2.1)	0.002

Repeated measures analysis of variance with mixed modeling was used to estimate changes in quality of life over time. Increasing values represent better quality of life. Parameter estimates are presented with standard errors in parentheses. Adjustment was made for target hemoglobin, hemoglobin, epoetin dose, transferrin saturation, age, sex, race, dialysis duration, body mass index, primary cause of renal disease, European or Canadian patient, vascular access for dialysis and serum albumin. The following reference groups were used: target hemoglobin 10.5 to 11.5 g/dl, hemoglobin > 11.1 g/dl, epoetin dose \leq 6000 units per week, transferrin saturation > 32.0%, age \leq 51.5 up years, male sex, white race, dialysis duration \leq 9.0 months, body mass index \leq 25.5 kg/m², renal disease not due to diabetes, Canada, fistula or graft for dialysis access, serum albumin > 4.0 g/dl. No associations were identified for quality of social interaction, cognitive function, effects of kidney disease, dialysis staff encouragement, and patient satisfaction.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, ¶ $P < 0.0001$ for week 24, 36, 48, 72 or 96.

Discussion

Randomized controlled trials comparing a normal hemoglobin target to partial corrections of anemia with epoetin have varied in the stage of CKD disease of patients enrolled, primary outcomes assessed, statistical power to compare major clinical outcomes, and research methodology. Nonetheless, signals have emerged to suggest that higher hemoglobin targets may be harmful. Clinical events related to higher hemoglobin targets in some trials have included higher vascular access thrombosis (4), higher BP or greater requirements for antihypertensives (7,8,12), cardiovascular events (4,7), earlier need for renal replacement therapy (6), and higher mortality (4,7). Adverse events for the current study were reported in the original paper, and a significantly higher number of cerebrovascular events occurred in the high hemoglobin group ($n = 12$) compared with the low hemoglobin group ($n = 4$) (8). These adverse outcomes have not been seen uniformly across studies, and several outcomes have had marginal statistical significance and wide confidence intervals for effect estimates. However higher vascular access thrombosis and hypertension have been observed in the early studies comparing no treatment of anemia with partial correction using erythropoietin (13).

Controversy exists concerning target hemoglobin levels for erythropoiesis-stimulating agent therapy in CKD. The European Medicines Agency stipulated a uniform target hemoglobin range for all patients with CKD of 10 to 12 g/dl, with a warning not to exceed a concentration of 12 g/dl (14). It noted that trials with high target hemoglobin concentrations “have

not shown significant benefits attributable to the administration of epoetins to increase hemoglobin concentrations beyond the level necessary to control symptoms of anemia and to avoid blood transfusion.” However, the current study of “healthy” patients starting hemodialysis, with a sample size similar to CREATE (6), clearly demonstrates that higher hemoglobin targets reduce the need for blood transfusions (11) and produce an improvement in symptoms of fatigue. The latter is consistent with the significant improvements in vitality scores, measured by the SF36, reported in an earlier paper (8).

Although only one of 20 domains in the KDQoL and one in the SF36 showed significant improvements, these occurred in two of the three prespecified quality of life outcomes identified before starting the trial, on the basis of previous studies and biologic plausibility. Energy/fatigue scores were significantly higher in the high hemoglobin group compared with the low hemoglobin group, and the differences were of clinical significance (10,13). We compared our results to those obtained from one of the initial erythropoietin randomized controlled trials (RCTs) reported in 1990 (13). Change in baseline fatigue score at 6 mo in the group whose hemoglobin level increased from 69 to 102 g/d ($n = 32$) versus that of controls ($n = 34$) was 8, whereas in the current study the comparable change in the group whose hemoglobin level increased from 11.0 to 13.3 versus the control group was 6. Of interest, the baseline fatigue seen in the 1990 study in the intervention group was 41, and in our study it was 54, reflecting the healthier patients enrolled in the current study.

It is likely that the cost of the higher hemoglobin needed to obtain this quality of life benefit will be high (15). The improvement in quality of life observed is consistent with results in hemodialysis patients with overt cardiovascular disease (4), in Scandinavian predialysis and dialysis patients (5), and in non-dialysis-dependent CKD patients enrolled in CREATE, but is divergent from the CHOIR trial, in subjects with non-dialysis-dependent CKD (7). It should be noted however, the improvement in quality of life observed in the Besarab *et al.* study (4) was for improved Physical Function score in relation to achieved hematocrit.

Meta-analysis of reported RCTs conclude that normalization of hemoglobin with erythropoietin is harmful (16). We await the results of TREAT, a global RCT of 4000 predialysis diabetic patients with chronic kidney disease, planned to stop after the occurrence of 1800 cardiovascular events, to provide further evidence on the potential benefit and safety of hemoglobin targets above those currently recommended (<12 g/dl) (17). Quality adjusted costs of higher targets are extremely expensive (15). Although current international guidelines for erythropoietin therapy are justified (3,14) nonetheless, in a patient centered paradigm of care, individuals who need to avoid blood transfusions, or those at low risk of adverse outcomes who value improved energy and vitality, should not be disadvantaged by strict adherence to guidelines.

Some of the limitations of this study are worth considering. Attending physicians were masked as to assigned target hemoglobin group, but they had access to local clinic results for patient care, making it possible to unmask the assigned group. Unmasking patients to treatment assignment could influence their perceptions of quality of life. However, patients were masked, a design feature that tends to lessen the possibility that patient-related biases could explain the findings. By design, we studied hemodialysis patients without overt cardiac disease, and the generalizability of our findings to other populations with chronic kidney disease is not certain. Our results are applicable to approximately 50% of the dialysis population (18). The high dropout rate was anticipated because patients such as those in our study are usually referred for and then wait for renal transplantation. This was taken into account in the sample size estimate.

Combining both the intervention and control groups from whom serial measurements of quality of life were obtained provided a valuable resource to examine changes in quality of life in an incident cohort of hemodialysis patients. Multivariate modeling suggested that higher body mass index and lower erythropoietin dose at baseline were independent predictors of better quality of life across several domains. These predictions were independent of age, sex, diabetes mellitus, and serum albumin, and were identified in a group without symptomatic cardiac disease. Further investigation of the role of inflammation and cardiac biomarkers on quality of life is underway in this cohort, particularly because it is possible that both lower body mass index and higher erythropoietin requirements are markers for subclinical inflammation or even subclinical cardiac disease.

We conclude that in incident, relatively healthy, hemodialy-

sis patients without symptomatic cardiac disease, normal hemoglobin targets improve energy scores. Higher body mass index and lower erythropoietin dose at baseline were independent predictors of change in several domains of quality of life.

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