Kidney International, Vol. 65 (2004), pp. 626–633

Association of hematocrit value with cardiovascular morbidity and mortality in incident hemodialysis patients

SUYING LI and ALLAN J. COLLINS

Nephrology Analytical Services, Minneapolis Medical Research Foundation, and University of Minnesota, Minneapolis, Minnesota

Association of hematocrit value with cardiovascular morbidity and mortality in incident hemodialysis patients.

Background. Associations between hematocrit values and clinical outcome have been studied with conflicting results in cardiac patients, end-stage renal disease (ESRD) patients, and ESRD patients with cardiac disease. We studied dialysis patients to determine the relationship between hematocrit value and cardiac risk under current Dialysis Outcomes Quality Initiative (DOQI) practices.

Methods. Medicare data were used to study 50,579 incident hemodialysis patients selected from January 1, 1998, to December 31, 1999, who received hemodialysis for 9 months after the onset of ESRD. Patients were divided into groups on the basis of the hematocrit value: ≤30%, >30% to ≤33%, >33% to ≤36%, >36% to ≤39%, and >39%. For hospitalization, the follow-up extended to $2^1/_2$ years; for mortality, 3 years.

Results. Compared to patients with hematocrit values of >33% to ≤36%, patients with values of >36% to ≤39% and those with values of >39% had risk ratios for hospitalization due to cardiac disease of 0.92 (95% CI 0.88 to 0.97) and 0.79 (95% CI 0.72 to 0.87), respectively, and risk ratios for death due to cardiac disease of 0.92 (95% CI 0.87 to 0.98) and 0.83 (95% CI 0.74 to 0.93), respectively, in the follow-up period.

Conclusion. The significant associations we report do not establish a causal relationship between higher hematocrit values and lower risks of cardiac morbidity and mortality. A randomized clinical trial in low-risk patients is needed to establish causality.

Cardiovascular disease is the major cause of death in patients with end-stage renal disease (ESRD). In patients who were ≥67 years old and progressed to ESRD in 1997, 63% had atherosclerotic heart disease, 66% had congestive heart failure (CHF), 50% had peripheral vascular disease, 37% had cerebrovascular accidents or transient ischemic attacks, and 70% had other cardiac diseases [1]. For 1997 to 1999 prevalent ESRD patients, the unadjusted death rate was 179.3 per 1000 patient-years at risk, while the death rate due to cardiac disease was 86.9 per 1000 patient-years at risk [1].

Several investigators have reported that anemia is associated with heart failure and left ventricular dysfunction and that the correction of anemia in longitudinal studies was associated with reduced complication rates for patients with these diseases [2–4]. Associations between hematocrit values and cardiac risk, morbidity, and mortality have been studied with conflicting results in cardiac patients, ESRD patients, and ESRD patients with cardiac disease [5–17].

Randomized clinical trials have shown the effects of normalizing the hematocrit value in ESRD patients who are receiving hemodialysis and have CHF and ischemic heart disease. Besarab et al [15] found that patients randomized to the higher hematocrit group (hematocrit value of 42%) had a nearly statistically significant increased risk of death, compared to the lower hematocrit group (hematocrit value of 30%). Others have shown that correction of anemia or maintenance of a normal hematocrit value in ESRD patients is not associated with worse outcomes such as increased blood pressure [16–18].

Our previous studies found an association between higher hematocrit values (30% to <33% or 33% to <36%) and lower risks of hospitalization and death in the follow-up period [19–22]. Our studies also found better outcomes in terms of morbidity and mortality for patients who maintained or increased hematocrit values to 30% to 33% in a 1-year follow-up period [23] [abstract; Collins AJ, et al, *J Am Soc Nephrol* 9:A1043, 1998; abstract; Collins AJ, et al, *J Am Soc Nephrol* 9:A1044, 1998]. However, little information is available to resolve issues in this area under current guidelines for therapy such as the National Kidney Foundation's Dialysis Outcomes Quality Initiative (NKF DOQI). Therefore, we studied a large sample of Medicare hemodialysis patients to determine the relationship between specific cardiac risk and hematocrit value under current DOQI practices. Specifically, we assessed the association between elevated

Key words: anemia, cardiovascular diseases, Dialysis Outcomes Quality Initiative, ESRD, hematocrit, hemodialysis, kidney failure, chronic, morbidity, mortality.

Received for publication January 29, 2003
and in revised form May 19, 2003, August 6, 2003, and September 2, 2003
Accepted for publication September 16, 2003

hematocrit values (>36% to ≤39% and >39%) and morbidity and mortality due to cardiovascular disease, including CHF, ischemic heart disease, cerebrovascular disease, and other cardiac diseases in a large incident hemodialysis population.

METHODS

Study design and patient population

We retrospectively studied Medicare incident hemodialysis patients selected from January 1, 1998, to December 31, 1999, who survived and consistently received hemodialysis for 9 months after the onset of ESRD. The likelihood of first hospitalization and death due to cardiac events was assessed during the follow-up periods. We tested the hypothesis that higher hematocrit values in the entry period would correlate with lower morbidity and mortality in the follow-up period.

As in our previous studies [19–22], we gathered data on urea reduction ratio (URR) ranges, which are reported on dialysis claims forms (a Medicare reporting requirement) and also adjusted for patients' demographic characteristics, clinical characteristics at ESRD onset, comorbid conditions, and disease severity indicators.

For hospitalization, the follow-up period extended up to 2 $^1/_2$ years from the end of the entry period, with patients being censored upon a modality change, transplant, loss-to-follow-up, death, first admission to hospital, or by December 31, 2000. For mortality, the follow-up period extended up to 3 years from the end of the entry period, with patients being censored upon a modality change, transplant, loss-to-follow-up, death, or by June 30, 2001. We defined the entry period to be 4 to 9 months after the first ESRD dialysis service date, plus 90 days. The 90-day delay was necessary because many patients younger than 65 years of age did not become eligible for Medicare until 90 days after their first dialysis; therefore, the database might not have been complete during that time.

Patients were excluded from the study if they died, changed modality to peritoneal dialysis, or had a transplant during the 9 months after their first ESRD dialysis. When combining patients' demographic data and baseline clinical factors, patients with incomplete data (such as missing birth date, gender, or race, or missing or invalid values for creatinine level at onset of ESRD) were excluded. Patients with fewer than four recombinant human erythropoietin (rHuEPO) claims during the 6-month entry period were excluded (38.6% of patients did not have rHuEPO claims during the entry period) to ensure that study patients were representative of patients receiving maintenance therapy for anemia. The average number of rHuEPO claims during the entry period was 5.53 (standard deviation, 0.74).

Data sources

Demographic and baseline clinical characteristics at onset of ESRD, including data on age, gender, race, primary renal diagnosis, and creatinine level, were obtained from the Identification and Medical Evidence portions of the Renal Beneficiary Utilization System (REBUS) of the Centers for Medicare & Medicaid Services (CMS). Comorbid conditions were characterized using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and Physicians' Current Procedural Terminology (CPT) codes, as previously described [20], from all Medicare Part A and Part B claims during the 6-month study entry period. Data on disease severity indicators, such as number of blood transfusions, vascular access procedures, and hospital days during the entry period, were extracted from Part A and Part B Medicare claims files [20]. Hematocrit data were obtained from Medicare rHuEPO claims files derived from the outpatient Standard Analytical Files, as previously described [22]. The URR data for each patient were obtained from the G-modifier attached to CPT code 90999 with revenue codes 821 or 825. The baseline URR value for each patient was the median of the three previous entry period values [1].

Data on causes of hospitalization were obtained from the CMS Institutional Inpatient Standard Analytical Files and classified as ischemic heart disease, cerebrovascular disease, circulatory system disease, CHF, fluid overload, cardiomyopathy, or other cardiac disease on the basis of the principal ICD-9-CM code for each admission. Data on specific cardiac causes of death (ischemic heart disease, cerebrovascular disease, circulatory system disease, CHF, fluid overload, cardiomyopathy, or other cardiovascular diseases) were obtained through use of specific ICD-9-CM codes. Data on all-cause deaths were obtained from the REBUS Identification and Death Notification Files.

Statistical analyses

To examine the association between hematocrit value and first hospitalization due to cardiac disease, separate Cox regression analyses stratified on the basis of diabetic status were performed for all-cardiac disease, ischemic heart disease, cerebrovascular disease, circulatory system disease, CHF, fluid overload, cardiomyopathy, and other cardiac diseases. Time to cardiac event was the dependent variable. To examine the association of hematocrit value with mortality due to cardiovascular disease, a Cox regression analysis stratified on the basis of diabetic status was conducted. To compare patient baseline characteristics among the hematocrit groups, the χ^2 test was used for the analysis of categorical variables such as gender, race, and primary diabetic status, and the Kruskal-Wallis test was used for the analysis of continuous variables such as

age, hospital days, and baseline glomerular filtration rate (GFR).

To assess the pattern of unadjusted first hospitalization rates due to cardiac diseases, the association between hematocrit value and hospitalization was examined and adjusted for baseline demographic factors (i.e., age, gender, race, and primary renal diagnosis), comorbid conditions, disease severity, GFR, and range of URR. The relative risks and 95% CI for specific hematocrit groups were compared to those of patients with hematocrit values of >33% to ≤36%.

The explanatory predictors were age (<20, 20 to 44, 45 to 64, 65 to 74, and >74 years), race (white, black, and other), gender, primary diagnosis (diabetes vs. nondiabetes), comorbid conditions, disease severity, baseline values of predicted GFR, URR, and hematocrit values. Comorbid conditions were atherosclerotic heart disease, CHF, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, other cardiac diseases, cancer, chronic obstructive pulmonary disease, gastrointestinal disease with bleeding, liver disease, and gallbladder disease. For the entry period, disease severity measures were total inpatient days, with or without blood transfusions, and with or without vascular access procedures. The Levey formula [24–26], which takes four variables (creatinine value, age, gender, and race) into consideration, was used to calculate the predicted GFR. Patients were divided into five groups on the basis of the URR value: <60%, 60% to <65%, 65% to <70%, 70% to <75%, and ≥75%. Patients also were divided into five groups on the basis of the hematocrit value: ≤30%, >30% to ≤33%, >33% to ≤36%, >36% to ≤39%, and >39%. Monthly hematocrit values less than 10% or greater than 50% were not included when the mean hematocrit value was calculated.

RESULTS

Patient characteristics

A total of 50,579 incident hemodialysis patients survived 9 months after their initial dialysis, continued receiving hemodialysis treatment, and had at least four rHuEPO claims during the entry period. Of these, 26,207 and 24,372 patients were selected from the 1998 and 1999 cohorts, respectively. Baseline patient characteristics are summarized in Table 1. As shown in Table 2, when patients were grouped according to hematocrit value, there were significant differences ($P < 0.0001$) in patient characteristics between the >33% to ≤36% group and the other groups. Also, patients in the groups with higher hematocrit values (>36% to ≤39% and >39%) were older and had fewer hospital days and number of vascular access procedures during the entry period. There were relatively more male and white patients in these groups as well.

Table 1. Baseline characteristics of 50,579 patients at study entry

Variable *unit*	
Mean age *years*	65.4 ± 14.3
Male gender %	50.6
Race %	
White	61.0
Black	33.0
Diabetes as primary cause of ESRD %	48.1
Mean GFR at ESRD onset *mL/min*	8.6 ± 3.9
Mean hospital stay *days*	6.1 ± 11.8
Patients with URR ≥ 70 %	54.3
Mean hematocrit value %	34.1 ± 3.0

Abbreviations are: ESRD, end-stage renal disease; GFR, glomerular filtration rate; URR, urea reduction ratio.

Unadjusted hospitalization rates due to cardiac diseases

Unadjusted hospitalization rates (expressed as the number of the first hospitalizations per 1000 treatment-years) due to cardiac diseases for nondiabetic, diabetic, and all patients are provided in Table 3. First hospitalization rates due to CHF, fluid overload, cardiomyopathy, ischemic heart disease, cerebrovascular disease, circulatory system disease, and other cardiovascular disease decreased as hematocrit values increased, indicating that hospitalization rates were higher in patients with hematocrit values of ≤36%, compared to patients with hematocrit values of >36% to ≤39%.

Adjusted relative risk of hospitalization due to cardiac diseases

The pattern of unadjusted first hospitalization rates due to cardiac diseases may reflect differences between groups in baseline characteristics or the presence of comorbid conditions; therefore, additional analyses were conducted after adjustment of demographic factors. Table 4 presents the relative risks of hospitalization due to cardiac disease according to controlled variables. All the relative risks and 95% CI for specific hematocrit groups were compared to those of the >33% to ≤36% hematocrit group.

Using follow-up data, we compared patients with hematocrit values of >36% to ≤39% and those with values of >39% to patients with hematocrit values of >33% to ≤36%. On the basis of hospitalization rate due to any cardiac cause, patients with hematocrit values of >36% to ≤39% and those with values of >39% had risk ratios of 0.92 (95% CI 0.88 to 0.97) and 0.79 (95% CI 0.72 to 0.87), respectively (Fig. 1). On the basis of first hospitalization due to CHF, fluid overload, or cardiomyopathy, patients with hematocrit values of >36% to ≤39% and those with values of >39% had risk ratios of 0.85 (95% CI 0.77 to 0.95) and 0.80 (95% CI 0.65 to 0.97), respectively (Fig. 2). On the basis of first hospitalization due to ischemic heart disease, cerebrovascular

Table 2. Baseline patient characteristics according to hematocrit value

Variable *unit*	Hematocrit value %					*P*
	≤30	>30 to ≤33	>33 to ≤36	>36 to ≤39	>39	
Patients *number*	4308	11,558	22,192	10,265	2256	
Mean age *years*	61.3 ± 15.5	64.6 ± 14.4	66.1 ± 13.9	66.2 ± 14.1	66.1 ± 14.2	<0.0001[a]
Male %	48.3	48.0	50.8	53.1	54.8	<0.0001[b]
Race %						
White	51.6	59.9	63.1	62.1	59.2	<0.0001[b]
Black	44.2	34.8	30.7	31.1	34.1	<0.0001[b]
Diabetes as primary cause of ESRD %	45.4	50.6	48.4	46.4	46.3	<0.0001[b]
Mean GFR at ESRD onset *mL/min*	8.4 ± 4.0	8.6 ± 3.9	8.6 ± 3.9	8.7 ± 4.0	8.6 ± 4.1	<0.0001[a]
Mean hospital stay *days*	13.0 ± 17.6	8.6 ± 13.8	4.9 ± 9.9	3.7 ± 8.7	4.0 ± 9.7	<0.0001[a]
Mean NVP	3.9 ± 5.8	3.4 ± 5.6	2.6 ± 8.3	2.3 ± 4.5	2.4 ± 5.3	<0.0001[a]
Mean hematocrit %	28.0 ± 2.0	31.8 ± 0.8	34.5 ± 0.8	37.2 ± 0.8	40.6 ± 1.5	<0.0001[a]

Abbreviations are: ESRD, end-stage renal disease; GFR, glomerular filtration rate; NVP, number of vascular access procedures.
[a]Kruskal-Wallis test; [b] χ^2 test.

Table 3. Unadjusted hospitalization rates[a] due to cardiac diseases according to hematocrit value

	Hematocrit value %				
	≤30	>30 to ≤33	>33 to ≤36	>36 to ≤39	>39
Nondiabetic patients					
All cardiac	521	401	344	297	251
CHF[b]	182	107	88	72	63
Ischemic[c]	175	168	148	132	117
Other[d]	165	125	108	93	72
Diabetic patients					
All cardiac	507	463	379	340	301
CHF[b]	162	134	93	73	73
Ischemic[c]	242	238	213	191	165
Other[d]	103	91	72	75	62
All patients					
All cardiac	515	430	360[e]	316[e]	273[e]
CHF[b]	173	120	90	73	67
Ischemic[c]	204	201	177	158	137
Other[d]	138	109	92	86	68

CHF is congestive heart failure.
[a]Expressed as number of first hospitalizations per 1000 treatment-years; [b]CHF, fluid overload, and cardiomyopathy; [c]Ischemic heart disease, cerebrovascular disease, and circulatory system disease; [d]All other cardiovascular disease; [e]Sum is result after rounding.

disease, or circulatory system disease, patients with hematocrit values of >36% to ≤39% and those with values of >39% had risk ratios of 0.94 (95% CI 0.88 to 1.01) and 0.81 (95% CI 0.70 to 0.93), respectively (Fig. 2). For first hospitalization due to all other cardiac causes, patients with hematocrit values of >36% to ≤39% and those with values of >39% had risk ratios of 0.95 (95% CI 0.87 to 1.05) and 0.76 (95% CI 0.62 to 0.92), respectively (Fig. 2).

Adjusted relative risk of hospitalization for patients with cardiac comorbid conditions

To determine the association between hospitalization and hematocrit values for hemodialysis patients with cardiac diseases, we investigated a subgroup ($N = 45{,}166$) of patients with one or more of the following comorbid conditions: atherosclerotic heart disease, CHF, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, and other cardiac diseases. We found a pattern similar to that of the relationship between hospitalization and hematocrit value in all selected hemodialysis patients; patients with higher hematocrit values had fewer hospitalizations. Compared to patients with hematocrit values of >33% to ≤36% on the basis of first hospitalization due to any cardiac cause, patients with hematocrit values of >36% to ≤39% and those with values of >39% had risk ratios of 0.93 (95% CI 0.89 to 0.98) and 0.79 (95% CI 0.71 to 0.87), respectively, in the follow-up period (Fig. 3).

Adjusted relative risk of death due to cardiac diseases and all-cause death

Table 4 presents the relative risks of death due to cardiac disease according to controlled variables. The adjusted relative risks of death due to any cardiac cause are shown in Figure 4. As previously indicated, the possible duration of follow-up for mortality extended to 3 years. Higher hematocrit values were associated with lower likelihood of death in the follow-up period. Compared to patients with hematocrit values of >33% to ≤36%, patients with hematocrit values of >36% to ≤39% and those with values of >39% had risk ratios of 0.92 (95% CI 0.87 to 0.98) and 0.83 (95% CI 0.74 to 0.93), respectively, in the follow-up period.

As shown in Figure 5, the same pattern was observed for all-cause deaths (i.e., deaths from cardiac disease, infection, and other causes). Compared to patients with hematocrit values of >33% to ≤36%, patients with hematocrit values of >36% to ≤39% and those with values of >39% had risk ratios of 0.92 (95% CI 0.88 to 0.96) and 0.86 (95% CI 0.80 to 0.93), respectively, in the follow-up period.

Table 4. Relative risks of cardiac hospitalization and cardiac death according to controlled variables

Variable	Hospitalization due to cardiac disease			Death due to cardiac disease		
	RR	Lower limit	Upper limit	RR	Lower limit	Upper limit
Age <20 years	1.59	1.07	2.37	0.43	0.11	1.72
Age 20–44 years (reference)	1.00			1.00		
Age 45–64 years	1.00	0.93	1.08	1.58	1.40	1.77
Age 65–74 years	0.88	0.81	0.95	1.95	1.73	2.19
Age >74 years	0.91	0.84	0.99	2.87	2.55	3.24
Female gender (reference)	1.00			1.00		
Male gender	0.95	0.91	0.99	1.05	1.00	1.10
White race (reference)	1.00			1.00		
Black race	0.93	0.89	0.97	0.72	0.69	0.76
Other race	0.78	0.72	0.85	0.93	0.85	1.02
ASHD	1.39	1.33	1.46	1.23	1.16	1.29
CHF	1.23	1.17	1.29	1.45	1.36	1.54
Other cardiac disease	1.13	1.08	1.19	1.23	1.15	1.31
Peripheral vascular disease	1.09	1.04	1.13	1.10	1.04	1.15
CVA/TIA	1.12	1.07	1.16	1.08	1.03	1.12
Cancer	0.96	0.92	1.01	0.97	0.93	1.02
Gallbladder disease	0.92	0.87	0.99	0.98	0.92	1.05
COPD	1.13	1.09	1.18	1.20	1.15	1.26
Gastrointestinal disease with bleeding	1.04	0.99	1.08	1.08	1.03	1.13
Liver disease	1.00	0.96	1.04	0.99	0.95	1.04
No hospitalization (reference)	1.00			1.00		
Hospitalized 1–10 days	1.44	1.38	1.51	1.19	1.13	1.25
Hospitalized 11–20 days	1.80	1.69	1.93	1.58	1.48	1.70
Hospitalized >20 days	1.85	1.72	1.99	1.78	1.65	1.91
No blood transfusion (reference)	1.00			1.00		
Blood transfusion	0.97	0.89	1.06	1.10	1.01	1.20
No vascular access (reference)	1.00			1.00		
Vascular access	0.90	0.87	0.94	0.94	0.90	0.98
GFR (continuous variable)	1.01	1.00	1.01	1.04	1.03	1.04
URR <60%	1.08	1.01	1.15	1.11	1.03	1.19
URR 60% to <65%	1.01	0.94	1.08	1.03	0.96	1.11
URR 65% to <70% (reference)	1.00			1.00		
URR 70% to <75%	0.99	0.94	1.05	0.94	0.88	0.99
URR ≥75%	0.96	0.91	1.01	0.93	0.88	0.99

Abbreviations are: ASHD, arteriosclerotic heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; GFR, glomerular filtration rate; RR, relative risk; URR, urea reduction ratio.

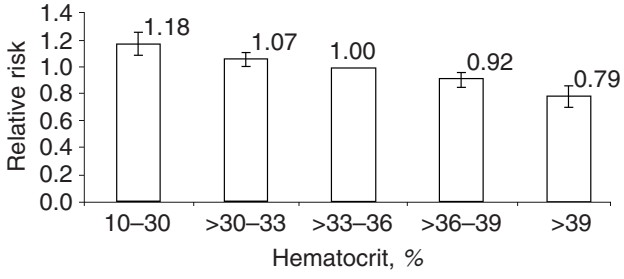

Fig. 1. Adjusted relative risk of first hospitalization due to any cardiac cause, according to hematocrit value. Data are expressed as relative risk and 95% CI.

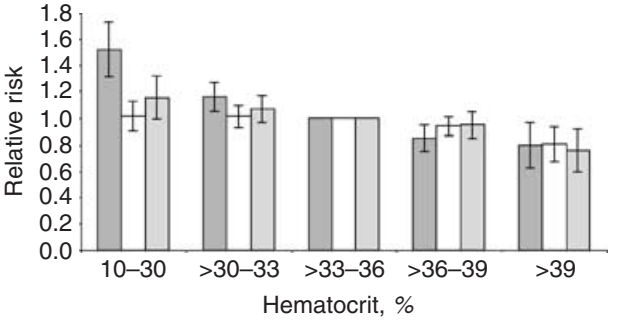

Fig. 2. Adjusted relative risk of first hospitalization due to particular cardiac causes, according to hematocrit value. Data are expressed as relative risk and 95% CI. Symbols are: (■) patients with congestive heart failure, fluid overload, or cardiomyopathy; (□) patients with ischemic heart disease, cerebrovascular disease, or circulatory system disease; (▯) patients with other cardiac diseases.

Adjusted relative risks of hospitalization and death for patients without preexisting cardiac disease

Results for patients without preexisting cardiac disease showed that patients with hematocrit values of >36% to ≤39% had lower adjusted risks of hospitalization and death during the follow-up period, as compared to patients with hematocrit values of >33% to ≤36%. Their relative risks were 0.69 ($P = 0.0002$), 0.69 ($P = 0.0137$), 0.78 ($P < 0.0001$), 0.74 ($P = 0.0005$), 0.71 ($P = 0.026$), 0.68 ($P = 0.045$), and 0.79 ($P = 0.07$) for all-cause death; any cardiac death; all-cause hospitalization; any cardiac hospitalization; hospitalization due to ischemic heart disease and cerebrovascular disease; hospitalization due to CHF,

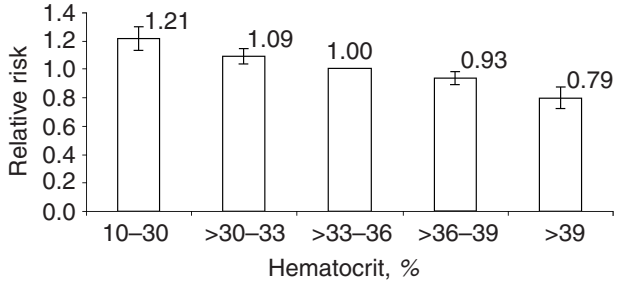

Fig. 3. Adjusted relative risk of first hospitalization due to any cardiac cause for patients with cardiac comorbid conditions, according to hematocrit value. Data are expressed as relative risk and 95% CI.

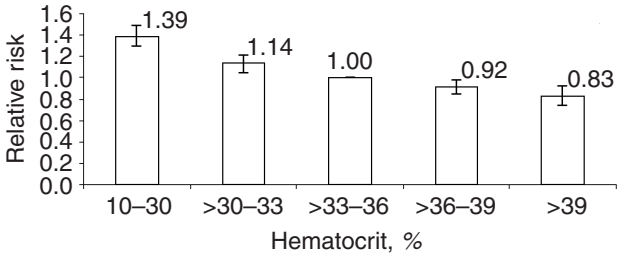

Fig. 4. Adjusted relative risk of death due to any cardiac cause, according to hematocrit value. Data are expressed as relative risk and 95% CI.

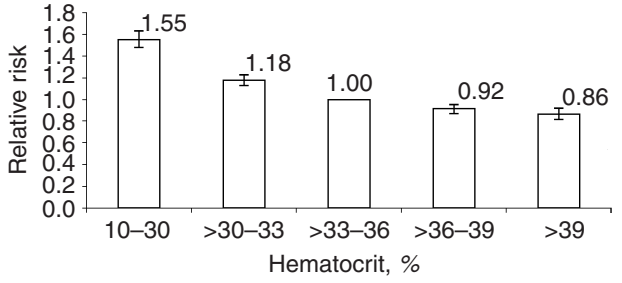

Fig. 5. Adjusted relative risks of death due to any cause, according to hematocrit value. Data are expressed as relative risk and 95% CI.

fluid overload, and cardiomyopathy; and hospitalization due to other cardiac disease, respectively.

We also performed analyses using a 3-month entry period after 90 days of ESRD, with follow-up periods of 1, 2, and 3 months. We obtained similar results (data not shown).

In addition, we analyzed on the basis of broader enrollment criteria, increasing the sample size from 50,579 patients with four or more rHuEPO claims to 52,026 patients with three or more rHuEPO claims, and to 52,473 patients with two or more rHuEPO claims. Again, we obtained similar results (data not shown).

DISCUSSION

In this study of incident hemodialysis patients, we found that patients with hematocrit values in the 6-month entry period of >36% to ≤39% and >39% were at significantly lower risk of hospitalization and death (cardiac and all-cause) in follow-up periods of $2^1/_2$ years and 3 years, respectively. These findings are consistent with and build on the findings of a previous study by our group, in which we found hematocrit values of >36% to ≤39% to be associated with positive effects on morbidity and mortality [22]. We also found that results were similar for both patients with and those without preexisting cardiac disease, that is, higher hematocrit values were associated with reduced morbidity and mortality in the follow-up period. We hypothesize that patients without established cardiac disease may receive a significant benefit from anemia correction, compared to patients with established cardiac disease.

Previous investigations of hematocrit values and associated outcomes in nondialysis populations have yielded contradictory results. In patients with cardiac disease, studies have linked a high hematocrit value (≥33%) to myocardial infarction [5], a reduction in the cardiac index [6], and coronary heart disease [7]. Other studies of patients with cardiac disease have linked a low hematocrit value to an increased mortality due to coronary artery disease [8], an increased prevalence of traditional cardiovascular risk factors [9], and poor clinical course after acute myocardial infarction [10].

Similarly, studies of hematocrit values in ESRD patients have produced conflicting findings. Anemia has been linked to CHF and left ventricular hypertrophy [11], its partial correction seems to have improved cardiac performance and induced regression of left ventricular hypertrophy in 11 patients, and full correction (to a hematocrit value of 40%) was found more effective than partial correction in nine predialysis patients with chronic renal failure who were receiving rHuEPO therapy [13]. A prospective study of hemodialysis patients with no cardiovascular disease suggested that normalization of hematocrit values improved quality of life and decreased morbidity [14]. Some randomized clinical studies in hemodialysis patients with cardiac disease found that normalization of the hematocrit value did not cause increased blood pressure or change the level of silent ischemia; morbidity and mortality outcomes were unclear [16–18]. A clinical trial in hemodialysis patients without symptomatic heart disease found no difference in left ventricular mass index between patients whose hematocrit value had been normalized and those whose anemia had been only partially corrected [27].

We believe our results to be important for several reasons. Because the study was conducted in a nationwide sample of patients, its findings do not reflect local practices. Previous studies have analyzed data from smaller numbers of patients. We analyzed data from a very large number of patients; this allowed us to analyze, for example, patients with hematocrit values of >39% as an

independent group. Earlier studies analyzed data from an earlier time, when there was less consistency in care. Because of the relative newness of our data (data from January 1, 1998, through December 31, 1999), our findings reflect care given under NKF DOQI guidelines. Our finding of a greater number of patients with hematocrit values of >39% may reflect more active care being given in the current era to correct anemia in ESRD patients. Finally, by including GFR and URR data in our analyses, we ensured that our findings reflect a greater complexity of disease than that previously studied. Our results are consistent with those of Silverberg et al [28], who studied patients with CHF to determine the prevalence and severity of anemia and the effects of its correction on cardiac function, renal function, and hospitalization. The investigators found successful treatment of anemia to be associated with a significant improvement in cardiac function and renal function and as well as a marked decrease in the need for diuretics and hospitalization in patients not on dialysis. Our results are also consistent with findings in two studies of patients with chronic anemia, which showed the beneficial effect of blood transfusion on ejection fraction and cardiac function in nondialysis patients [29, 30]. Such results are supported by a study in rats, in which a direct relationship was found between anemia and cardiac disease, especially cardiomegaly [31].

Explanations can be offered regarding the observed relationship between lower hematocrit values and poor clinical outcome. The association in hemodialysis patients of inflammation with lower hematocrit values and higher morbidity and mortality [32, 33] may help explain our finding of an association between hematocrit value and outcome. Lower hematocrit values and poor outcomes may also be secondary to dilution in high weight gainers. Due to data limitations, we could not test these associations.

However, when evaluating clinical outcomes, one should be cautious with regard to patients with hematocrit values of >39%. It may be argued that patients with hematocrit values of >39% were healthier compared to patients with lower hematocrit values. In our study, compared to patients with hematocrit values of ≤33%, those with hematocrit values of >39% were older (mean age 66.1 vs. 63.7 years), used less rHuEPO in the entry period (mean doses/month 49,726 vs. 78,362), and were less likely to have preexisting cardiac disease (86.8% vs. 91.2%). We also investigated whether polycystic kidney disease was present to a greater extent in patients with higher hematocrit values. Diabetes, hypertension, glomerulonephritis, and cystic kidney disease accounted for 48.7%, 28.9%, 7.5%, and 1.4%, respectively, of patients with hematocrit values of ≤36%, and for 46.4%, 31.2%, 7.9%, and 2.3%, respectively, of patients with hematocrit values of >36%.

In the United States, achieving higher hematocrit values has been associated with large expenditures for rHuEPO, approaching $1.5 billion per year [34]. Compared to patients with higher hematocrit values, patients with lower hematocrit values use more than twice the amount of rHuEPO [22], which appears to be driving the high cost. rHuEPO resistance in the United States appears to be secondary to dialysis catheter utilization [35] as well as increased comorbidity and severity of disease, as shown in our study (Table 2). These findings suggest that if higher hematocrit values are of any benefit, more cost-effective use of rHuEPO is needed. A detailed investigation of factors associated with lower hematocrit values and higher rHuEPO doses was beyond the scope of this study but should be undertaken. Prospective clinical trials should be undertaken to investigate the associations found in our study. If such trials confirm the associations we found, it is likely that target hematocrit values will be raised and possible that cost of rHuEPO therapy will increase. However, total cost of care should also be considered.

The chief limitation of our work is that, being an observational study, it can establish an association but not a causal relationship between higher hematocrit values and lower risks of cardiovascular morbidity and mortality. Also, the national data do not include values for pre- and postdialysis weight (allowing calculation of the interdialytic weight gain) and cannot allow determination of the relationships of inflammatory markers to hematocrit values and outcomes in hemodialysis patients. Other limitations include possible selection bias (only patients with more than four rHuEPO/hematocrit claims were included). In addition, hospitalization and mortality are just two of many important measures of outcome and quality of life in ESRD patients. Studies of long-term outcomes and quality of life based on a large ESRD population are needed.

CONCLUSION

We found higher hematocrit values to be associated with lower hospitalization and mortality (cardiac and all-cause) in incident hemodialysis patients, even in those with cardiac disease. These findings are based on 1998 to 1999 data and therefore reflect current clinical practice under NKF DOQI guidelines. For the 2- to 3-year period following initiation of hemodialysis, there appears to be diminished risk of hospitalization and death for patients whose hematocrit values are maintained in the >36% to ≤39% range during the entry period. The significant associations we report do not establish a causal relationship between higher hematocrit values and lower risks of cardiac morbidity and mortality. A randomized clinical trial in low-risk patients is needed to establish causality.

ACKNOWLEDGMENTS

This research was supported in part by the Minneapolis Medical Research Foundation, Minneapolis, Minnesota, and by an unrestricted research grant from Amgen, Inc., Thousand Oaks, California.

The authors thank the Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration) for providing the Medicare data for this study. Within Nephrology Analytical Services, data-handling and processing support was provided by Shu-Cheng Chen, C. Daniel Sheets, Roger Johnson, and Fred Dalleska; regulatory and manuscript-preparation assistance was provided by Dana Knopic, Beth Forrest, and James Kaufmann.

Reprint requests to Allan J. Collins, M.D., F.A.C.P., Nephrology Analytical Services, Minneapolis Medical Research Foundation, 914 South 8th St., Suite D-206, Minneapolis, MN 55404.
E-mail: acollins@nephrology.org

REFERENCES

1. United States Renal Data System: *USRDS 2001 Annual Data Report*, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, 2001, pp 148, 464
2. Levin A, Singer J, Thompson CR, Ross H, *et al*: Prevalent left ventricular hypertrophy in the predialysis population: Identifying opportunities for intervention. *Am J Kidney Dis* 27:347–354, 1996
3. Levin A, Thompson CR, Ethier J, *et al*: Left ventricular mass index increase in early renal disease: Impact of decline in hemoglobin. *Am J Kidney Dis* 34:125–134, 1999
4. Foley RN, Parfrey PS, Harnett JD, *et al*: The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. *Am J Kidney Dis* 28:53–61, 1996
5. Spiess BD, Ley C, Body SC, *et al*: Hematocrit value on intensive care unit entry influence the frequency of Q-wave myocardial infarction after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 116:460–467, 1998
6. Peverill RE, Harper RW, Smolich JJ: Inverse relation of haematocrit to cardiac index in mitral stenosis and atrial fibrillation. *Int J Cardiol* 71:149–155, 1999
7. Danesh J, Collins R, Reto R, *et al*: Haematocrit, viscosity, erythrocyte sedimentation rate: Meta-analyses of prospective studies of coronary heart disease. *Eur Heart J* 21: 515–520, 2000
8. Brown DW, Giles WH, Croft JB: Hematocrit and the risk of coronary heart disease mortality. *Am Heart J* 142:657–663, 2001
9. Al-Ahmad A, Rand WM, Manjunath G, *et al*: Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 38:955–962, 2001
10. Wu WC, Rathore SS, Wang Y, *et al*: Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 345:1230–1236, 2001
11. Harnett JD, Kent GM, Foley RN, *et al*: Cardiac function and hematocrit level. *Am J Kidney Dis* 25(4 Suppl 1):S3–S7, 1995
12. Massimetti C, Pontillo D, Feriozzi S, *et al*: Impact of recombinant human erythropoietin treatment on left ventricular hypertrophy and cardiac function in dialysis patients. *Blood Purif* 16:317–324, 1998
13. Hayashi T, Suzuki A, Shoji T, *et al*: Cardiovascular effect of normalizing the hematocrit level during erythropoeitin therapy in predialysis patients with chronic renal failure. *Am J Kidney Dis* 35:250–256, 2000
14. Moreno F, Sanz-Guajardo D, Lopez-Gomez JM, *et al*: Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. Spanish Cooperative Renal Patients Quality of Life Study Group of the Spanish Society of Nephrology. *J Am Soc Nephrol* 11:335–342, 2000
15. 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* 339:584–590, 1998
16. Berns JS, Rudnick MR, Cohen RM, *et al*: Effects of normal hematocrit on ambulatory blood pressure in epoetin-treated hemodialysis patients with cardiac disease. *Kidney Int* 56:253–260, 1999
17. Conlon PJ, Kovalik E, Schumm D, *et al*: Normalization of hematocrit in hemodialysis patients does not affect silent ischemia. *Ren Fail* 22:205–211, 2000
18. Conlon PJ, Kovalik E, Schumm D, *et al*: Normalization of hematocrit in hemodialysis patients does not increase blood pressure. *Ren Fail* 22:435–444, 2000
19. Xia H, Ebben J, Ma J, *et al*: Hematocrit levels and hospitalization risks in hemodialysis patients. *J Am Soc Nephrol* 10:1309–1316, 1999
20. Ma J, Ebben J, Xia H, *et al*: Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 10:610–619, 1999
21. Collins AJ, Li S, Ebben J, *et al*: Hematocrit levels and associated Medicare expenditures. *Am J Kidney Dis* 36:282–293, 2000
22. Collins AJ, Li S, St. Peter W, *et al*: Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol* 12:2465–2473, 2001
23. Collins AJ, Ma JZ, Xia A, *et al*: Trends in anemia treatment with erythropoeitin usage and patient outcomes. *Am J Kidney Dis* 32 (6 Suppl 4):S133–S141, 1998
24. Levey AS, Bosch JP, Lewis JB, *et al*: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130:461–470, 1999
25. Fink JC, Blahut SA, Weir MR: Optimal strategies for modeling the reciprocal of creatinine versus time in renal transplant recipients and patients with native chronic renal disease. *Am J Kidney Dis* 39:753–761, 2002
26. Fink JC, Burdick RA, Kurth SJ, *et al*: Significance of serum creatinine values in new end-stage renal disease patients. *Am J Kidney Dis* 34:694–701, 1999
27. Foley RN, Parfrey PS, Morgan J, *et al*: Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 58:1325–1335, 2000
28. Silverberg DS, Wexler D, Blum M, *et al*: The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 35:1737–1744, 2000
29. Ho CH: The effect of transfusion on cardiac function in patients with chronic anemia. *Transfusion* 37:1066–1069, 1997
30. Ho CH: The changes of cardiac ejection fraction up to 72 h after transfusion in patients with chronic anaemia. *Transfus Med* 11:189–192, 2001
31. Rakusan K, Cicutti N, Kolar F: Effect of anemia on cardiac function, microvascular structure, and capillary hematocrit in rat hearts. *Am J Physiol Heart Circ Physiol* 280:H1407–H1414, 2001
32. Kalantar-Zadeh K, Kopple JD, Block G, *et al*: A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *Am J Kidney Dis* 38:1251–1263, 2001
33. Yeun JY, Levine RA, Mantadilok V, *et al*: C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 35:469–476, 2000
34. United States Renal Data System: *USRDS 2002 Annual Data Report*, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, 2002, pp 82–87, 200, 529
35. United States Renal Data System: *USRDS 2002 Annual Data Report*, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, 2002, pp 88–89