Greater Epoetin alfa Responsiveness Is Associated With Improved Survival in Hemodialysis Patients

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Background and objectives: Among hemodialysis patients, achieved hemoglobin is associated with Epoetin alfa dose and erythropoietin responsiveness. A prospective erythropoietin responsiveness measure was developed and its association with mortality evaluated.

Design, setting, participants, & measurements: Data from 321 participants were used and randomized to the hematocrit normalization arm of the Normal Hematocrit Cardiac Trial. Subjects were to receive a 50% Epoetin alfa dose increase at randomization. The prospective erythropoietin responsiveness measure was defined as the ratio of weekly hematocrit change (over the 3 wk after randomization) per Epoetin alfa dose increase (1000 IU/wk) corresponding to the mandated 50% dose increase at randomization. The distribution of responsiveness was divided into quartiles. Over a 1-yr follow-up, Cox proportional hazard modeling evaluated associations between this responsiveness measure and mortality.

Results: Erythropoietin responsiveness values ranged from −2.1% to 2.4% per week per 1000 IU. Although subjects were similar across response quartiles, mortality ranged between 14% and 34% among subjects in the highest and lowest response quartiles ($P = 0.0004$), respectively. After adjusting for baseline prognostic indicators, highest *versus* lowest responsiveness was associated with a hazard ratio of 0.41 (95% confidence interval, 0.20 to 0.87).

Conclusion: Lower erythropoietin responsiveness is a strong, independent predictor of mortality risk and should be considered when evaluating associations between clinical outcomes and potential prognostic indicators, such as Epoetin alfa dose and achieved hemoglobin values.

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More than 90% of end-stage renal disease patients require exogenous erythropoietin or transfusion to achieve and maintain target hemoglobin values (1,2) because of decreased endogenous erythropoietin production. The ability to achieve and maintain target hemoglobin levels is complicated by a variety of mediating factors that impact responsiveness to erythropoietin, including comorbidities, inflammation, and malnutrition. These factors are independently associated with poor clinical outcomes (3–9).

The impact of erythropoietin responsiveness on mortality is not well understood. Although higher hemoglobin levels have been associated with reduction in mortality in observational studies (10,11), evidence from randomized clinical trials of hemodialysis patients does not suggest a mortality benefit (12). Paradoxically, in the Normal Hematocrit Cardiac Trial (13), the largest randomized trial conducted to date in hemodialysis patients, survival rates were higher among those achieving higher hematocrit values, but targeting a higher hematocrit was associated with a 1.3-fold increased risk of mortality or nonfatal myocardial infarction (95% confidence interval [CI], 0.9 to 1.9). This suggests that unknown/unmeasured patient characteristics associated with the ability to achieve greater hemoglobin values may confound analyses assessing mortality risks among dialysis patients.

Achieved hemoglobin level is associated with both the Epoetin alfa doses administered and patient responsiveness to erythropoietin. Greater survival among patients with higher hemoglobin values may be partly due to greater erythropoietin responsiveness (14) in addition to a direct result of anemia correction. Likewise, lower survival among those with lower achieved hemoglobin values may be partly the result of lower relative erythropoietin responsiveness. Patients who require higher Epoetin alfa doses to achieve a given hemoglobin level, that is, who are less responsive to erythropoietin, may experience poorer outcomes at any achieved hemoglobin value (15).

In this study, data from the hematocrit normalization arm of the Normal Hematocrit Cardiac Trial (13) were used to develop a prospective measure of erythropoietin responsiveness, which was then evaluated in relation to mortality.

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Materials and Methods

Data Source

The open-label, randomized, multicenter Normal Hematocrit Cardiac Trial (13) was conducted between 1993 and 1996 to evaluate the effect of normalizing hematocrit on mortality and cardiovascular morbidity in hemodialysis patients with preexisting cardiac disease. Briefly, 1233 maintenance hemodialysis patients with congestive heart failure (excluding New York Heart Association class IV) or ischemic heart disease were randomly assigned to one of two groups: a hematocrit normalization group ($n = 618$; to achieve and maintain a hematocrit of 42% ± 3%) or a low-hematocrit group ($n = 615$; to achieve and maintain a hematocrit of 30% ± 3%). All subjects were required to have had hematocrit values consistently between 27% and 33% and stable Epoetin alfa (EPOGEN, Amgen, Thousand Oaks, CA) dosages during the 4 wk before enrollment. The initial total weekly Epoetin alfa dose for subjects randomized to the hematocrit normalization group was to be 50% greater than the (baseline) dose received in the week preceding randomization. Subsequent dose increases of 25% of the baseline dose, beginning at study week 4 and to occur no more frequently than every 2 wk, were allowed if hematocrit values did not increase at least 2 percentage points. Conversely, a 25-IU/kg dose reduction was recommended if the hematocrit increased more than 4 percentage points during any 2-wk period.

Analysis Population

Only data from participants randomized to the hematocrit normalization arm were used in this analysis. Baseline data consisted of subject information collected before the date of randomization into the Normal Hematocrit Cardiac Trial (subject index date). A measure of erythropoietin response could be calculated for 514 of the 618 subjects in the normalization arm. Reasons for the inability to calculate this measure included insufficient Epoetin alfa dose and hematocrit data ($n = 56$), and not having received an initial on-study dose increase (n = 48) or any Epoetin alfa at all during the week before randomization ($n = 32$). Because we wished to evaluate responsiveness to an erythropoietin dose increase that was not indicated for clinical reasons, we further restricted the analysis to subjects that received a uniform dose increase: subjects were excluded if they had an initial post-randomization dose increase <30% ($n = 124$) or >70% ($n = 83$) from baseline. Thus, a total of 321 subjects remained for inclusion in the analysis.

Erythropoietin Response Measure

We developed a prospective measure of erythropoietin responsiveness that evaluated change in hematocrit resulting from a uniform (percentage) Epoetin alfa dose increase. For each subject, erythropoietin response was defined as the ratio of weekly hematocrit change per Epoetin alfa dose increase (1000 IU per week). The denominator of this ratio, the absolute Epoetin alfa dose increase (corresponding to a relative increase of 30% to 70% from baseline), was calculated as the change in weekly Epoetin alfa dose from baseline to the first on-study week. The numerator of the ratio was the change in weekly hematocrit modeled as the slope parameter obtained from a simple linear regression of study week on weekly hematocrit postrandomization. This measure, although derived from the EPO index (15), quantifies the *rate* of hematocrit change in response to a *protocolized* dose increase as opposed to the EPO index, which is the ratio of EPO dose per hemoglobin value at one point in time. Correlations were examined between initial Epoetin alfa dose change and subsequent hematocrit change over the first few study weeks to characterize the temporal effect of the initial Epoetin alfa dose increase. The Epoetin alfa dose increase was associated with a hematocrit rise primarily between weeks 2 and 3 ($r = 0.16$, $P = 0.01$). Based on this observation, and as the next study dose increase occurred at study week 4, only hematocrit values from weeks 1 through 3 were included in the erythropoietin response measure (Figure 1). The distribution of erythropoietin response measures was also categorized into quartiles.

Outcome

The endpoint was all-cause mortality from the index date until the first of date of death, transplantation, loss to follow-up, or 365 d.

Statistical Analysis

Characteristics of subjects who were included *versus* excluded in the analyses, and participants across the four quartiles of erythropoietin response were compared using Mantel-Haenszel χ^2 tests for categorical variables, and two-tailed t test or analysis of variance for continuous variables. The crude association between quartiles of the erythropoietin response distribution and mortality was evaluated using the Cochran-Armitage trend test (16). Pearson correlation coefficients assessed pairwise correlations between erythropoietin response, Epoetin alfa dose increase, change in hematocrit, and baseline Epoetin alfa dose. The association between erythropoietin response and 1-yr mortality was assessed using Cox proportional hazard modeling. Unadjusted models included only the erythropoietin response measure. Case-mix models adjusted for age, gender, race, diabetes mellitus, dialysis vintage (difference in days from the first reported dialysis date to the date of study randomization), and vascular access (arteriovenous fistula, graft, or other [predominantly catheter]). The full models included the previous covariates plus lymphocytes, albumin, transferrin saturation, ferritin, body mass index, Kt/V (as a measure of dialysis adequacy, where K = rate of urea clearance by the dialyser in ml/min, t = duration of the dialysis session, and V = patient's total body water; urea reduction ratio was used in clinics that did not measure Kt/V), and New York

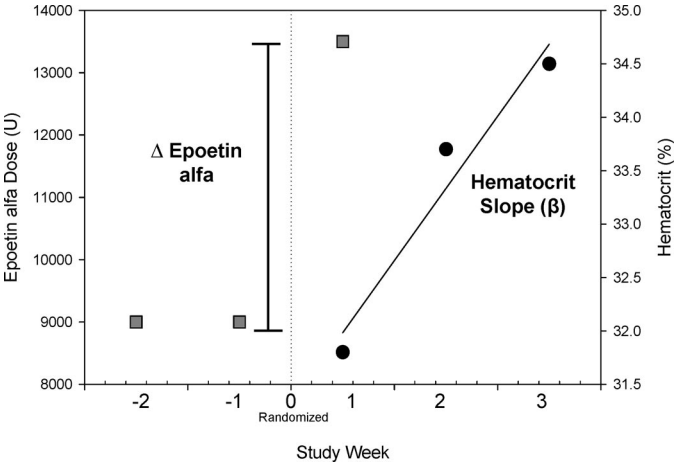

Figure 1. Representative example illustrating the calculation of the erythropoietin response measure. Total weekly Epoetin alfa dose in units (Y) and weekly hematocrit values (●) are shown. The hematocrit slope is calculated as the simple linear regression of hematocrit on study week during weeks 1 through 3. Epoetin alfa increase is the change in dose from the first pre-study week (week −1) to the first on-study week (week 1). In this example, erythropoietin response = hematocrit slope (1.35% per week) per Epoetin alfa increase (13,500 − 9000 IU = 4500 IU) = (0.0003% per week) per IU. Hematocrit values were calculated by multiplying hemoglobin concentrations (g/dl) by 3.

Heart Association class. Missing covariate values (which never exceeded 10% of observations) were imputed as the population mean value. New York Heart Association class information was missing for 8 subjects who were not included in the full model. All analyses were conducted using SAS, version 9.1 (SAS Institute, Cary, NC).

Results

Because our aim was to measure hematocrit response to a protocolized dose increase, only those subjects in the normalization arm who were titrated at the time of randomization according to the trial protocol (dose increase of 50% ± 20%) were included in this analysis. Subjects randomized to the hematocrit normalization group and included in the analysis ($n = 321$) were generally comparable to the excluded subjects ($n = 297$) with respect to mortality risk and baseline demographic, laboratory, and medical history characteristics (Table 1). However, included subjects had a 20.5% higher average baseline Epoetin alfa dose compared with the excluded group ($P = 0.004$), which reflects the 37 subjects in the excluded group who did not receive Epoetin alfa during the week before randomization. The average baseline dose was similar among the excluded and included subjects who received Epoetin alfa (156 and 164 IU/kg per week, respectively).

Overall, the mean value for the erythropoietin response measure was 0.11 (± 0.43) hematocrit percentage points (%) per week over the first 3 study weeks per 1000 IU increase in Epoetin alfa dose: values ranged from a decrease of 2.1% per 1000 IU/wk to an increase of 2.4% per 1000 IU/wk. The calculated erythropoietin response for all subjects, plotted by numerator and denominator of the measure, is shown in Figure 2A. Individuals in the highest erythropoietin response quartile had an expected average hematocrit increase of 0.5% per 1000 IU Epoetin alfa per week compared with a mean decrease of 0.4% per 1000 IU/wk for subjects in the lowest quartile. Greater variability in the erythropoietin response measure and greater levels of responsiveness were seen among subjects with lower baseline Epoetin alfa doses (Figure 2B). Although baseline Epoetin alfa dose was highly correlated with the absolute Epoetin alfa dose increase ($r = 0.99$) and with the modeled hematocrit increase over the first 3 study weeks ($r = 0.20$, $P < 0.001$), baseline Epoetin alfa dose was not correlated with the ratio erythropoietin response measure ($r = 0.01$) (Figure 2B).

Table 1. Comparison of Normal Hematocrit Cardiac Trial participants from the hematocrit normalized group that were included *versus* excluded in the analysis

Variable	Included ($n = 321$)	Excluded ($n = 297$)
Age (yr)	65 ± 12	65 ± 12
>65 yr (%)	54	54
Gender, female (%)	48	52
Diabetes mellitus (%)	54	54
Race/ethnicity (%)		
white	46	44
black	40	42
other	14	14
Time on dialysis (yr)	3.2 ± 3.6	3.4 ± 4.0
Vascular access (%)		
graft	66	67
natural fistula	23	19
other/not specified	12	14
Current hypertension (%)	70	72
Peripheral vascular disease (%)	40	37
Cardiac-related hospitalizations (%)	73	74
Hematocrit (%)	30.4 ± 2.9	30.7 ± 3.1
Epoetin alfa dose (U/kg per wk)[a,b]	164 ± 103	137 ± 127
Albumin (g/L)	37.4 ± 3.7	37.3 ± 3.5
Creatinine (μmol/L)	849 ± 274	875 ± 292
Transferrin saturation (%)	26.2 ± 13.0	27.6 ± 12.8
White blood cell count ($\times 10^9$/L)	7.0 ± 2.2	7.1 ± 2.3
Lymphocytes (% of white blood cell count)	23.2 ± 9.6	22.6 ± 9.0
Mortality (%)	25	22

Categorical data are percentages and continuous measures are mean ± standard deviation (SD).
[a]$P = 0.004$.
[b]Includes 37 participants with a dose of zero for the week before randomization (5 of whom were excluded based on multiple criteria).

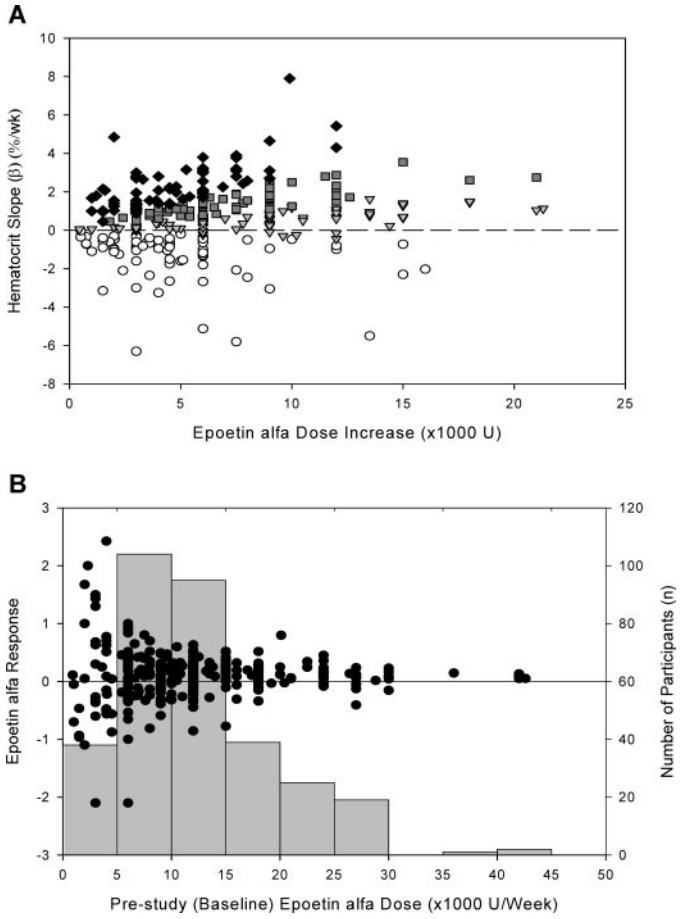

Figure 2. (A) Erythropoietin response for all subjects, plotted by numerator and denominator of the measure. Subjects were characterized by value of the erythropoietin response measure, which was categorized into quartiles (1st (○) 2nd (■) 3rd (▲) and 4th (◆)). For each subject, the quartile of erythropoietin response was plotted by the increase in Epoetin alfa dose at randomization (denominator of the response measure) on the horizontal axis, and hematocrit response (numerator of the response measure, which was the hematocrit slope derived from a simple linear regression of study week on hematocrit) on the vertical axis. (B) Erythropoietin response as a function of prestudy (baseline) Epoetin alfa dose. Erythropoietin response values (●) on the vertical axis are shown plotted against baseline Epoetin alfa dose (×1000 U/wk) on the horizontal axis. A histogram showing the number of subjects at each level of baseline dose is shown in the background.

Subjects across the four response quartiles were compared with respect to a number of demographic, clinical, and laboratory factors (Table 2). No appreciable differences in demographic factors were observed; however, a strong trend was observed between erythropoietin response quartile and 1-yr all-cause mortality, with mortality ranging from 34% to 14% ($P = 0.004$) among subjects in the lowest and highest quartiles of erythropoietin response, respectively. This relationship was not attenuated by adjustment for age, gender, race, diabetes mellitus, vintage, and vascular access (case-mix model) or for lymphocytes, albumin, transferrin saturation, ferritin, body mass index, Kt/V, and New York Heart Association class (full model) (Figure 3A). In the full model, the 1-yr mortality hazard ratios (95% CI) for the second, third, and fourth quartiles of response, as compared with the lowest quartile, were 0.94 (0.54 to 1.74), 0.72 (0.39 to 1.33), and 0.41 (0.20 to 0.87), respectively (Figure 3B). Furthermore, to assess the potential impact of selection bias that might have been introduced by the exclusion of subjects that did not receive the protocol-specified dose increase at randomization, the erythropoietin response measure was calculated for the entire hematocrit normalization arm. A positive association between greater erythropoietin responsiveness and survival was still observed in this larger group ($P < 0.0001$).

In analyses evaluating the relationship between baseline Epoetin alfa dose and mortality, no association was found in models that either included or excluded erythropoietin response (hazard ratio [95% CI]: 1.02 [0.99 to 1.04] and 1.02 [0.91 to 1.05], respectively). Furthermore, this lack of association between Epoetin alfa dose and mortality was consistent across erythropoietin response groups, including those subjects who experienced the least hematocrit response per unit of Epoetin alfa increase (low responders; Figure 4A, B).

Because responsiveness was a major determinant of mortality outcome, average hematocrit values and Epoetin alfa doses among those who survived at least 1 yr were examined across the response quartiles. Participants in the highest responder group were receiving the lowest doses of Epoetin alfa at 1 yr (mean of 17,893 IU/wk *versus* 29,865 IU/wk among subjects in the other response quartiles), although mean hematocrit values were similar (42.8% *versus* 43.0%, respectively).

Discussion

Despite the uniform inclusion criteria for patients enrolled in the Normal Hematocrit Cardiac Trial, large variability in erythropoietin responsiveness to a standardized percentage dose increase was observed after randomization. Lower responsiveness was associated with higher all-cause 1-yr mortality, whereas the most responsive patients had an approximate 60% lower risk of death during this same time period. Importantly, this responsiveness-mortality association was not attenuated after adjustment for various patient characteristics known to influence both Epoetin alfa dose and mortality risk.

Large variation in hemoglobin response to a given Epoetin alfa dose has long been recognized (17–19). In this study, there was a nearly 50-fold range in baseline Epoetin alfa dose (900 to 42,600 IU per week), reflecting the range of patient comorbidities and other characteristics associated with the Epoetin alfa dose needed to achieve and maintain the hematocrit level required for study eligibility (27% to 33%). Furthermore, even though the initial relative Epoetin alfa dose increase was similar for all subjects (30% to 70% above baseline), large variability was observed in subsequent hematocrit change, underscoring the importance of our measure evaluating the rate of hematocrit increase/decrease resulting from an Epoetin alfa dose adjustment that was not motivated by clinical considerations. In contrast, the majority of responsiveness measures used in previous studies have been based on Epoetin alfa dose and hemat-

Table 2. Comparison of participants across the four quartiles of the erythropoietin-response measure distribution.

Variable	Quartile of Erythropoietin Response			
	1 (low)	2	3	4 (high)
Mortality (%)[a]	34	28	25	14
Age (yr)	64 ± 2	64 ± 12	64 ± 12	67 ± 11
<45	6	8	9	4
45–59	26	30	28	18
60–74	48	44	46	53
≥75	20	19	17	26
Gender, female (%)	54	51	56	49
Diabetes mellitus (%)	58	54	54	51
Race, ethnicity (%)				
white	41	51	48	45
black	45	39	36	40
other	14	10	16	15
Time on dialysis (yr)				
<1 yr	31	22	26	30
1-<3	41	33	37	41
3-<5	14	18	21	13
>5	14	28	16	16
Vascular access (%)				
graft	66	62	68	68
natural fistula	20	27	20	24
other/not specified	14	11	12	9
Current hypertension (%)	76	69	62	75
Peripheral vascular disease (%)	40	41	42	37
Cardiac-related hospitalizations (%)	66	83	58	60
New York Heart Disease Association class (%)				
I	26	37	32	30
II	55	44	42	52
III	19	19	26	18
Hematocrit (%)	30.4 ± 3.0	30.4 ± 2.6	30.6 ± 2.9	30.3 ± 3.0
Epoetin alfa dose (U/kg per wk)[b]	132 ± 100	209 ± 119	183 ± 87	133 ± 83
Albumin (g/L)	37.6 ± 3.4	37.9 ± 3.6	36.9 ± 4.2	37.2 ± 3.4
Creatinine (μ mol/L)	822 ± 301	902 ± 283	859 ± 256	822 ± 239
Transferrin saturation (%)	27.5 ± 15.4	26.3 ± 11.7	25.3 ± 13.1	25.4 ± 11.6
White blood cell count ($\times 10^9$/L)	7.0 ± 2.3	6.8 ± 1.7	7.1 ± 2.4	7.0 ± 2.2
Lymphocytes (% of white blood cell count)	22.7 ± 10.3	21.3 ± 7.76	24.7 ± 10.7	24.1 ± 9.1
Erythropoietin-response (% hematocrit/ wk per 1000 IU Epoetin alfa)[b]	−0.38 ± 0.37	0.05 ± 0.05	0.20 ± 0.05	0.56 ± 0.39

Categorical data are percentages and continuous measures are mean ± standard deviation (SD).
[a] $P = 0.03$; P (trend) = 0.004.
[b] $P < 0.0001$.

ocrit values assessed at one point in time, including current Epoetin alfa dose (20), a ratio of Epoetin alfa dose to body weight (21), Epoetin alfa dose within levels of achieved hematocrit (19), current hematocrit (18), and average hematocrit over a specific time period (22).

Previous studies evaluating associations between mortality and exposures, such as Epoetin alfa dose (19,23) or achieved hemoglobin (23), have attempted to adjust for potential confounding by including predictors of erythropoietin response. The vast majority (89%) of subjects included in the current analysis reached at least the lower target hematocrit of 39%, with no difference between response quartiles in the percentage of those who achieved this target (range, 86% to 90%). Erythropoietin response, however, was negatively associated with the Epoetin alfa dose ultimately needed to achieve the high target hemoglobin, suggesting that erythropoietin responsiveness, as defined here, may reflect either unknown or unmeasured innate or other patient characteristics (*e.g.*, C-reactive protein level or other inflammatory markers) associated with mortality risk (24). As the current erythropoietin response mea-

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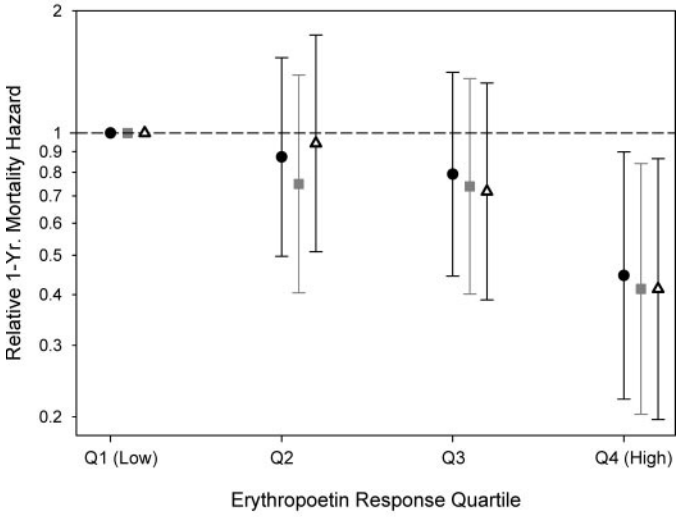

B

Erythropoietin Response Quartile	Unadjusted Model Hazard Ratio (95% CI)	*P*	Case-Mix Model Hazard Ratio (95% CI)	*P*	Full Model Hazard Ratio (95% CI)	*P*
1 (Low)	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
2	0.87 (0.50 to 1.53)	0.43	0.75 (0.40 to 1.39)	0.36	0.94 (0.51 to 1.74)	0.85
3	0.79 (0.44 to 1.41)	0.31	0.73 (0.40 to 1.35)	0.33	0.72 (0.39 to 1.33)	0.29
4 (High)	0.45 (0.22 to 0.90)	0.02	0.42 (0.21 to 0.85)	0.02	0.41 (0.20 to 0.87)	0.02

Figure 3. Association between erythropoietin response quartile, and all-cause 1-yr mortality assessed using a Cox proportional hazard model. (A) Results from models at three levels of adjustment are plotted: unadjusted (●), case-mix (■), and full (Δ). (B) Results are presented in a tabular format. CI, confidence interval

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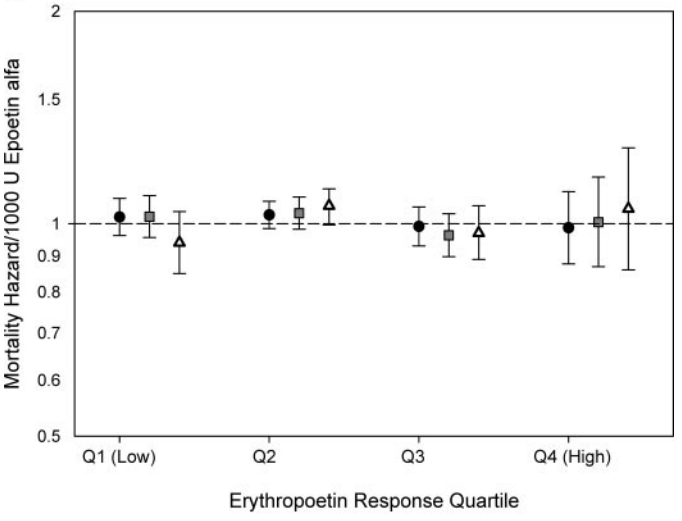

B

Erythropoietin Response Quartile	Unadjusted Model Hazard Ratio (95% CI)	*P*	Case-Mix Model Hazard Ratio (95% CI)	*P*	Full Model Hazard Ratio (95% CI)	*P*
1 (Low)	1.02 (0.96 to 1.09)	0.48	1.02 (0.96 to 1.10)	0.5	0.94 (0.85 to 1.04)	0.25
2	1.03 (0.89 to 1.08)	0.21	1.04 (0.98 to 1.09)	0.2	1.06 (1.00 to 1.12)	0.07
3	0.99 (0.93 to 1.01)	0.78	0.96 (0.90 to 1.03)	0.29	0.97 (0.89 to 1.06)	0.48
4 (High)	0.99 (0.88 to 1.11)	0.82	1.01 (0.87 to 1.16)	0.94	1.05 (0.86 to 1.28)	0.63

Figure 4. Lack of association between baseline Epoetin alfa dose and all-cause 1-yr mortality within each erythropoietin response quartile. A Cox proportional hazard model was used to evaluate the association between baseline Epoetin alfa dose (U) and mortality within quartiles of erythropoietin response. The hazard ratio is the relative hazard per 1000 IU baseline Epoetin alfa dose. (A) Results from models at three levels of adjustment are plotted: unadjusted (●), case-mix (■), and full (Δ). (B) Results are presented in a tabular format. CI, confidence interval

sure remained a strong predictor of mortality after controlling for covariates previously shown to be important, prior observational studies evaluating associations of clinical outcomes with Epoetin alfa dose or hematocrit/hemoglobin value may be confounded by erythropoietin responsiveness (or proxy measures of erythropoietin responsiveness) that remain unaccounted for even after adjusting for conventional covariates. No association was observed between baseline Epoetin alfa dose and 1-yr mortality in the overall subject cohort or within any of the four erythropoietin response quartiles.

This study has limitations. Subjects included in these analyses represented a population of maintenance hemodialysis patients with cardiac disease who had hematocrit values of 30% ± 3% during the month before randomization. The hematocrit target (27% to 33%) and Epoetin alfa dose (approximately 12,000 IU/wk) used to maintain hemodialysis patients is significantly different from the target hematocrit (33% to 36%) and average Epoetin alfa doses (approximately 20,000 IU/wk) used in current clinical practice (25). The erythropoietin response measure used here is based on hematocrit response over a 3-wk time period following the first protocol-mandated Epoetin alfa dose increase. Subsequent dose titrations were based on achieved patient hematocrit levels, which prevent the calculation and application of this measure to subsequent time points in this study, as well as to other observational cohorts reflecting clinical practice where dose is changed in response to achieved hematocrit values. Lastly, our analysis did not evaluate the impact of concomitant iron use on erythropoietin responsiveness because all patients were required to be iron replete (TSAT ≥20%) at study entry and previous iron utilization was not collected.

Conclusion

Erythropoietin response was a strong predictor of mortality risk that was independent of a variety of other risk-associated patient characteristics. These findings reinforce the importance of defining valid measures of erythropoietin responsiveness when evaluating associations of clinical outcomes with factors, such as Epoetin alfa dose or hematocrit/hemoglobin values in clinical trials and observational studies.

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Disclosures

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See related editorial, "Erythropoietin Stimulating Agents and Epoetin Alfa Revisited: What's Really Relevant?" on pages 935–937.