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ORIGINAL ARTICLE

Erythropoietic Response and Outcomes in Kidney Disease and Type 2 Diabetes

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ABSTRACT

BACKGROUND

Non–placebo-controlled trials of erythropoiesis-stimulating agents (ESAs) comparing lower and higher hemoglobin targets in patients with chronic kidney disease indicate that targeting of a lower hemoglobin range may avoid ESA-associated risks. However, target-based strategies are confounded by each patient's individual hematopoietic response.

METHODS

We assessed the relationship among the initial hemoglobin response to darbepoetin alfa after two weight-based doses, the hemoglobin level achieved after 4 weeks, the subsequent darbepoetin alfa dose, and outcomes in 1872 patients with chronic kidney disease and type 2 diabetes mellitus who were not receiving dialysis. We defined a poor initial response to darbepoetin alfa (which occurred in 471 patients) as the lowest quartile of percent change in hemoglobin level (<2%) after the first two standardized doses of the drug.

RESULTS

Patients who had a poor initial response to darbepoetin alfa had a lower average hemoglobin level at 12 weeks and during follow-up than did patients with a better hemoglobin response (a change in hemoglobin level ranging from 2 to 15% or more) (P<0.001 for both comparisons), despite receiving higher doses of darbepoetin alfa (median dose, 232 μg vs. 167 μg; P<0.001). Patients with a poor response, as compared with those with a better response, had higher rates of the composite cardiovascular end point (adjusted hazard ratio, 1.31; 95% confidence interval [CI], 1.09 to 1.59) or death (adjusted hazard ratio, 1.41; 95% CI, 1.12 to 1.78).

CONCLUSIONS

A poor initial hematopoietic response to darbepoetin alfa was associated with an increased subsequent risk of death or cardiovascular events as doses were escalated to meet target hemoglobin levels. Although the mechanism of this differential effect is not known, these findings raise concern about current target-based strategies for treating anemia in patients with chronic kidney disease. (Funded by Amgen; ClinicalTrials.gov number, NCT00093015.)

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Erythropoiesis-stimulating agents (ESAs) have been credited with a reduced need for red-cell transfusion and improved quality of life for patients with end-stage kidney disease who have severe anemia.[1] In patients with chronic kidney disease who do not require dialysis and have moderate anemia, the use of ESAs remains substantial, despite little evidence of benefit and increased concern that these agents may confer harm.[2-4] Trials comparing lower and higher hemoglobin targets have been interpreted to suggest that targeting of a lower hemoglobin range would be a safer approach in these patients,[2,5,6] leading to recommendations for continued use of ESAs in patients with chronic kidney disease who are not undergoing dialysis, but at lower hemoglobin targets.[7,8]

Although anemia has been associated with increased rates of death and complications in patients with chronic kidney disease who are undergoing dialysis and in those not undergoing dialysis,[9,10] a reduced hematopoietic response to ESAs has also been associated with an increased risk of an adverse outcome.[11-15] In patients undergoing dialysis, the risk of death has been shown to be inversely associated with a good hematopoietic response to ESAs.[16] Unfortunately, such data have been confounded by the fact that patients with a poor response to ESAs received increased doses of the drugs by virtue of target dosing.

In the recently reported Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT),[17] we assessed the effect of darbepoetin alfa (Aranesp, Amgen) in patients with anemia, diabetes, and chronic kidney disease who were not undergoing dialysis. We found no reduction in the risk of cardiovascular or renal events or death in patients who were receiving darbepoetin alfa, as compared with those receiving placebo, but we found nearly a doubling in the risk of stroke. We used data from TREAT to assess the relationship between responsiveness to ESAs, achieved hemoglobin levels, and outcomes in patients with chronic kidney disease and type 2 diabetes.

METHODS

STUDY DESIGN AND PATIENTS

TREAT was a randomized, double-blind, placebo-controlled trial conducted at 623 sites in 24 countries from August 25, 2004, to March 28, 2009. Patients who were included in the trial had type 2 diabetes and chronic kidney disease (defined as an estimated glomerular filtration rate [GFR] of 20 to 60 ml per minute per 1.73 m^2 of body-surface area) and anemia (defined as a hemoglobin level of ≤11.0 g per deciliter) and were not undergoing dialysis. The inclusion and exclusion criteria and overall results have been reported previously.[17,18] The institutional review board or ethics committee at each site approved the protocol, which is available with the full text of this article at NEJM.org. The study was conducted in accordance with the protocol as amended. All patients provided written informed consent.

Patients were randomly assigned to receive either subcutaneous darbepoetin alfa or placebo. The initial dose of darbepoetin alfa was 0.75 μg per kilogram of body weight and was repeated after 2 weeks if hemoglobin values did not exceed 14 g per deciliter. A point-of-care device was used to monitor hemoglobin levels, and after 1 month, a computer algorithm was used to assign subsequent doses to achieve and maintain the hemoglobin level at approximately 13.0 g per deciliter in the treatment group, with assigned treatment every 2 weeks until the hemoglobin target was reached and then subsequent monthly administration. Patients in the placebo group received a placebo injection unless the hemoglobin level fell below 9.0 g per deciliter, in which case they received rescue therapy with darbepoetin alfa until the hemoglobin level reached 9.0 g per deciliter.[18] Details about the algorithm for the determination of dose are available in the Supplementary Appendix at NEJM.org.

For this analysis, we divided patients in the treatment group into quartiles on the basis of the percent change in hemoglobin level after the first 4 weeks of therapy (after the initial two weight-based doses of darbepoetin alfa). Among the 4038 patients who underwent randomization (2012 in the darbepoetin alfa group and 2026 in the placebo group), we excluded from this analysis patients who did not receive the first two doses of a study drug during this period (60 in the darbepoetin alfa group and 63 in the placebo group), those who had a primary event (12 and 25, respectively), and those in whom a change in hemoglobin level at the end of week 4 was not known (68 and 49, respectively). This left 1872 patients in the darbepoetin alfa group and 1889 in the

placebo group who received the first two doses of a study drug, had no clinical events, and had hemoglobin measured at the end of week 4.

DEFINITION OF POOR RESPONSE

Patients in the lowest quartile of change in hemoglobin level (<2%) in the darbepoetin alfa group after the first month were operationally considered to have had a poor initial response, as compared with those in the upper three quartiles of change in hemoglobin level (2 to 15% or more). In each quartile, we assessed the mean hemoglobin level at 12 weeks (early phase) and the mean dose of darbepoetin alfa that patients received just before week 12, as well as the mean hemoglobin level in the late phase (after 12 weeks) and the mean dose of darbepoetin alfa received after 12 weeks.

OUTCOME MEASURES

The end points for the present analysis were adjudicated by an independent clinical end-points committee whose members were unaware of study-group assignment, dose of darbepoetin alfa, and hemoglobin or hematocrit values. These end points included death from any cause, the composite cardiovascular end point of death from any cause or cardiovascular events (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia), and fatal or nonfatal stroke. We also compared differences from baseline through 25 weeks between patients with a poor response and those with a better response, using the primary patient-reported outcome, the score on the Functional Assessment of Cancer Therapy (FACT)–Fatigue scale[17] (on a scale ranging from 0 to 52, with a higher score indicating less fatigue).

STUDY OVERSIGHT

The study was designed by the academic steering committee in conjunction with the sponsor, Amgen. The sponsor was not involved in the initial analyses of the data but subsequently verified the results. The first draft of the manuscript was written by the lead academic author and edited by all the coauthors, who vouch for the completeness and accuracy of the data and the analyses. The decision to submit the manuscript for publication was made by the academic authors.

STATISTICAL ANALYSIS

We assessed between-group comparisons of the response quartiles for baseline characteristics, using Kruskal–Wallis rank tests for continuous variables and chi-square tests for categorical variables. We assessed between-group differences in hemoglobin levels with t-tests and compared received doses of darbepoetin alfa, which were not normally distributed, with Wilcoxon rank-sum tests. Event rates for all end points were determined for each quartile of hemoglobin response and in the placebo group for comparison. We used a prospective cohort design within the darbepoetin alfa group to compare risk in patients who had a poor initial hemoglobin response with the remainder of the patients in the group in a Cox proportional-hazards model, with adjustment for 12 baseline covariates, including age, sex, race, history of cardiovascular disease, urinary protein-to-creatinine ratio, baseline estimated GFR, baseline albumin level, history of cardiac arrhythmia, glycated hemoglobin level, baseline hemoglobin level, a history of diabetic neuropathy, and C-reactive protein (CRP) level. We determined whether baseline covariates could account for a poor response by assessing the predictive value of 92 baseline covariates and assessed the incremental value of the direct measurement of hemoglobin response in predicting outcome.

Values are presented as means (±SD) unless otherwise noted. A two-sided significance level of 0.05 was used for all analyses, and P values for differences in baseline characteristics were not adjusted for multiplicity.

RESULTS

PATIENTS

The percent change in hemoglobin level in response to the first two weight-based doses of darbepoetin alfa was normally distributed. Patients in the lowest quartile of hemoglobin responsiveness to the initial weight-based two doses of darbepoetin alfa had a median reduction in hemoglobin level of 0.2 g per deciliter (interquartile range, −0.7 to 0.0) and were considered to have had a poor initial response (Table 1). Patients with a poor initial response were more likely to be women, to have a history of cardiovascular disease, to be treated with aldosterone antagonists, and to have a marginally lower serum potassium level and a marginally higher CRP level than patients with a better initial response. Ferritin and transferrin saturation levels were lower among patients with a poor initial response. In these patients, smoking was less common, and the body-mass in-

dex was slightly higher, than in patients with a better initial response. Other important determinants of outcome were similar among the quartiles (Table 1, and Table 1 in the Supplementary Appendix).

HEMOGLOBIN AT 12 WEEKS

Among treated patients, the dose of darbepoetin alfa that was received during weeks 5 to 12 of therapy was inversely related to the increase in the hemoglobin level during the first 4 weeks (P<0.001) (Fig. 1A). After two opportunities for a potential dose increase, the mean achieved hemoglobin level at 12 weeks was still lower among patients with a poor initial response (P<0.001) (Fig. 1A). Similarly, the average monthly dose of darbepoetin alfa after 12 weeks and throughout the remainder of the trial was substantially higher among patients with a poor initial response (median dose, 232 μg; interquartile range, 126 to 390) than among those with a better initial response (167 μg; interquartile range, 95 to 310; P<0.001). The average hemoglobin level after 12 weeks remained marginally lower among patients with a poor initial response than among those with a better initial response (12.2±0.9 vs. 12.4±0.7, P<0.001). There was no significant between-group difference in the use of intravenous iron at baseline, the percent of patients receiving intravenous iron during the first 12 weeks of therapy or over the course of the trial, the time to the use of intravenous iron, or the amount of intravenous iron received. The percentage of patients receiving red-cell transfusion did not differ between the two groups.

ESA RESPONSIVENESS AND OUTCOMES

Patients with a poor initial response had higher rates of the cardiovascular composite end point and death from any cause than patients with a better initial response. In a multivariable model adjusting for 12 baseline covariates associated with outcome, patients with a poor initial response were more likely to have a cardiovascular composite event (hazard ratio, 1.31; 95% confidence interval [CI], 1.09 to 1.59) and more likely to die (hazard ratio, 1.41; 95% CI, 1.12 to 1.78) during the course of the study than patients with a better initial response. Patients with a poor initial response had the slowest rate of hemoglobin increase during this period, and the overall rate of hemoglobin increase during the first 12 weeks was inversely related to adverse outcomes. For comparison, event rates for the cardiovascular composite outcome and death from any cause were also higher among patients with a poor initial response than among patients in the placebo group, but event rates among patients with a better response were similar to those in the placebo group (Table 2 and Fig. 2). In contrast, event rates for stroke were similar in the two response groups but higher in both groups than in the placebo group[17] (Table 2 and Fig. 2). There was no significant difference in the change in the FACT–Fatigue score at 25 weeks between patients with a poor response and those with a better response (4.2±10.8 vs. 4.3±10.6, P=0.86).

The ability to predict a poor initial response from a model incorporating 92 baseline characteristics was relatively limited. The direct measure of a poor initial response provided incremental value over baseline covariates in predicting outcome, with improvement in the prediction model for the cardiovascular composite outcome of 7% (95% CI, 2 to 11) and improvement in the prediction model for death of 7% (95% CI, 2 to 12).

DISCUSSION

A poor hemoglobin response to the initial two weight-based doses of darbepoetin alfa during the first 4 weeks of therapy was associated with subsequently increased rates of adverse cardiovascular events and death from any cause. Thereafter, patients with a poor initial response according to the protocol received higher doses of darbepoetin alfa throughout the trial and had lower hemoglobin values than patients with a better initial response. Patients with a poor initial response had higher subsequent rates of adverse outcomes than those with a better initial response and those in the placebo group.

These data extend previous observations regarding the prognostic value of a poor initial response to ESAs in a number of ways.[11-15] First, our definition of a poor initial response was based on a fixed weight-based ESA dose in patients who were not receiving ESA therapy at the time of randomization, whereas in previous studies, including the Normal Hematocrit Study,[5,19] responsiveness was assessed on the basis of a dose that had been determined by a patient's previous response to the drug. The adoption of a fixed weight-based ESA dose for an operational definition of response avoids confounding by previous response, in which ESA doses were progres-

Table 1. Baseline Characteristics of the Patients, According to the Quartile of Initial Hemoglobin Response in the First Month.*

Variable	Poor Response		Better Response		P Value†
	Quartile 1 (N=471)	Quartile 2 (N=467)	Quartile 3 (N=467)	Quartile 4 (N=467)	
Change in hemoglobin (first month)					
Percent change	<2	2 to <8	8 to <15	≥15	
Median — g/dl (interquartile range)	–0.2 (–0.7 to 0.0)	0.5 (0.4 to 0.7)	1.2 (1.0 to 1.4)	2.0 (1.7 to 2.6)	
Demographic characteristics					
Age — yr					
Mean	67.4±11.1	67.8±10.5	66.7±10.2	66.8±10.7	0.36
Median	68	68	67	68	
Interquartile range	60 to 75	61 to 75	59 to 75	59 to 74	
Female sex — no. (%)	294 (62.4)	286 (61.2)	261 (55.9)	251 (53.7)	0.02
Race — no. (%)‡					
White	300 (63.7)	307 (65.7)	287 (61.5)	299 (64.0)	
Black	105 (22.3)	100 (21.4)	95 (20.3)	85 (18.2)	0.16
Other	66 (14.0)	60 (12.8)	85 (18.2)	83 (17.8)	
Clinical characteristics					
Body-mass index§	32.17±8.14	32.38±7.78	31.54±7.00	30.79±7.03	0.02
Current smoker — no. (%)	14 (3.0)	20 (4.3)	29 (6.2)	37 (7.9)	0.004
Medical history					
Cardiovascular disease — no. (%)	326 (69.2)	288 (61.7)	295 (63.2)	287 (61.5)	0.04
Stroke — no. (%)	61 (13.0)	48 (10.3)	63 (13.5)	45 (9.6)	0.17
Myocardial infarction — no. (%)	92 (19.5)	87 (18.6)	86 (18.4)	78 (16.7)	0.73
Heart failure — no. (%)	165 (35.0)	147 (31.5)	139 (29.8)	139 (29.8)	0.26
Diabetic neuropathy — no. (%)	224 (47.6)	233 (49.9)	244 (52.2)	223 (47.8)	0.44
Abnormal electrocardiogram — no. (%)	311 (66.0)	303 (64.9)	312 (66.8)	277 (59.3)	0.07
Ventricular tachycardia or fibrillation, implantable converter–defibrillator, or pacemaker — no. (%)	33 (7.0)	29 (6.2)	34 (7.3)	20 (4.3)	0.22
Laboratory data					
Blood pressure (mm Hg)					
Systolic	135.4±19.1	135.0±17.6	136.6±19.7	137.6±18.9	0.07
Diastolic	72.3±11.4	71.8±11.1	72.1±11.1	73.3±10.6	0.16
Urinary protein-to-creatinine ratio¶					0.18
Median	0.4	0.3	0.4	0.4	
Interquartile range	0.1 to 2.1	0.1 to 1.8	0.1 to 1.8	0.1 to 1.9	
Estimated glomerular filtration rate — ml/min/1.73 m^2	35.0±11.5	35.6±11.9	36.3±11.9	35.6±11.3	0.47
Hemoglobin (central laboratory) — g/dl	10.50±0.92	10.44±0.92	10.36±0.93	10.20±1.08	<0.001
Albumin — g/dl	3.95±0.45	4.00±0.43	3.94±0.44	3.95±0.43	0.21
Total cholesterol — mg/dl	180.5±57.0	175.5±50.4	176.6±53.5	174.0±47.6	0.68
Ferritin — μg/liter					0.01
Median	120	116	133	152	
Interquartile range	61 to 258	63 to 231	72 to 260	72 to 271	
Transferrin saturation — %	23.3±10.0	24.3±10.7	24.6±8.3	25.6±10.3	<0.001

Table 1. (Continued.)

Variable	Poor Response		Better Response		P Value†
	Quartile 1 (N=471)	Quartile 2 (N=467)	Quartile 3 (N=467)	Quartile 4 (N=467)	
Potassium — mmol/liter	4.62±0.65	4.73±0.60	4.69±0.62	4.78±0.64	<0.001
Platelets — 1.0×10^{-3}/mm³	247.4±85.6	251.8±79.5	247.4±79.7	246.1±75.6	0.48
Reticulocytes — %	1.87±0.82	1.89±0.81	1.90±1.02	1.79±0.81	0.23
C-reactive protein — mg/dl‖					<0.001
Median	3.2	3.2	3.0	3.0	
Interquartile range	3.0 to 7.8	3.0 to 7.2	3.0 to 5.9	3.0 to 5.2	
Blood urea nitrogen — mg/dl	42.62±18.85	42.19±16.48	41.21±15.94	42.16±16.86	0.91
Medications					
Iron — no. (%)	205 (43.5)	184 (39.4)	211 (45.2)	225 (48.2)	0.05
Aldosterone-receptor blocker — no. (%)	40 (8.5)	22 (4.7)	22 (4.7)	20 (4.3)	0.02
Statin — no. (%)	259 (55.0)	292 (62.5)	286 (61.2)	277 (59.3)	0.10
Insulin — no. (%)	237 (50.3)	233 (49.9)	234 (50.1)	212 (45.4)	0.37

* Plus–minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for potassium to milligrams per deciliter, divide by 0.2558. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357.
† P values are for the comparison among all four quartile groups.
‡ Race was self-reported.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ The urinary protein-to-creatinine ratio was measured in grams of protein to grams of creatinine.
‖ All values for C-reactive protein that could not be detected on a standard assay were reported as 3.0 mg per deciliter, which was the lower limit of the assay.

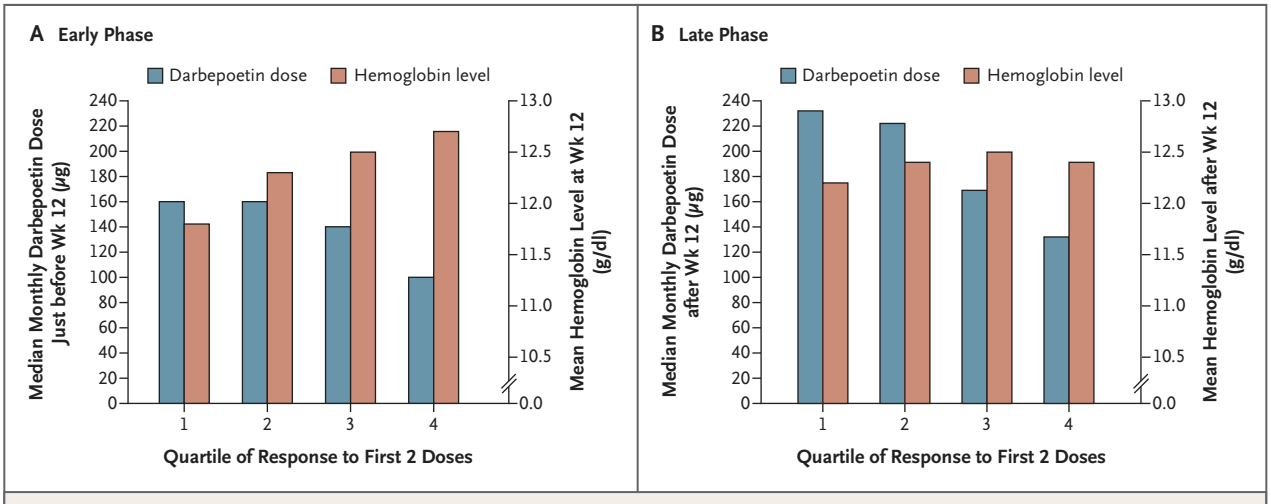


Figure 1. Association between Hemoglobin Level and Dose of Darbepoetin Alfa, According to the Level of Response to the First Two Doses.
Panel A shows the mean hemoglobin level at week 12 and the median monthly dose of darbepoetin alfa received before week 12, according to quartile of change in hemoglobin level (response) after the first two weight-based doses. Panel B shows the mean hemoglobin level after week 12 and the median monthly darbepoetin alfa dose during the trial after week 12, according to quartile of response after the first two weight-based doses.

Table 2. Rate of End Points and Adjusted Hazard Ratios.*

	Placebo (N=1889)	Poor Response (N=471)	Better Response (N=1401)	Adjusted Hazard Ratio (95% CI)†
	rate per 100 patient-yr (95% CI)			
Cardiovascular composite	12.3 (11.3–13.4)	16.3 (14.0–18.9)	12.4 (11.2–13.6)	1.31 (1.09–1.59)
Death from any cause	7.5 (6.8–8.3)	9.9 (8.3–11.9)	7.5 (6.7–8.5)	1.41 (1.12–1.78)
Stroke	1.0 (0.8–1.4)	2.3 (1.6–3.4)	2.0 (1.6–2.6)	1.26 (0.78–2.02)

* Event rates are shown for patients who survived the first 5 weeks without an event. CI denotes confidence interval.
† Hazard ratios are for patients with a poor initial response as compared with those with a better initial response. Hazard ratios have been adjusted for 12 baseline covariates, including age, sex, race, history of cardiovascular disease, urinary protein-to-creatinine ratio, baseline estimated glomerular filtration rate, baseline albumin level, history of cardiac arrhythmia, glycated hemoglobin level, baseline hemoglobin level, history of diabetic neuropathy, and baseline C-reactive protein level.

sively increased to reach a target hemoglobin level. Second, most of the data on ESA responsiveness have emerged from dialysis populations. Our study extends these observations to patients with chronic kidney disease who are not undergoing dialysis. Finally, this study has long-term follow-up, an important consideration for a treatment that is used indefinitely once it is started and includes adjudicated end points other than death. Our operational definition of a poor initial response was supported by the normally distributed change in hemoglobin during the early period and by a sensitivity analysis that showed a threshold effect from 20 to 30%. This simple definition did not require a priori assumptions about a cutoff point for responsiveness.

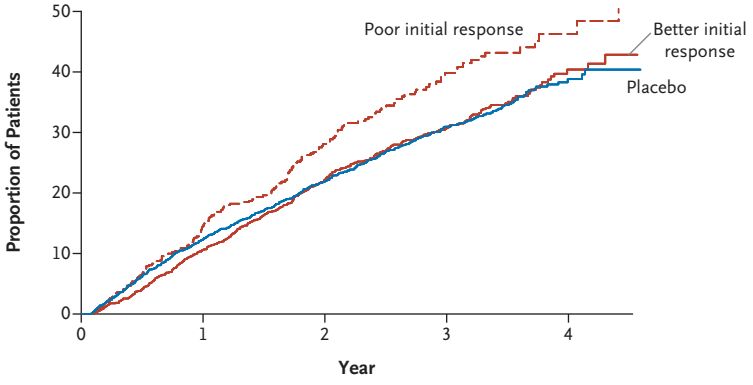
A number of factors may have contributed to the extent of the hematopoietic response to ESAs. Absolute or functional iron deficiency may be related to blood loss, decreased iron absorption, or impaired release of stored iron.[20] We observed lower transferrin saturation and ferritin levels in patients who had a poor initial response than in those with a better initial response, with substantial overlap between the groups and no significant between-group differences in the proportion of patients receiving intravenous iron and the amount of intravenous iron received. Resistance to ESA therapy can occur in patients with malnutrition, folate or vitamin B_{12} deficiency, secondary hyperparathyroidism, hemolysis, hemoglobinopathies, or primary bone marrow disorders (e.g., pure red-cell aplasia) or in response to certain drugs.[21] The weak association between a poor initial response and the C-reactive protein level suggests that inflammatory factors may contribute to a poor initial response. We did not observe differences in baseline platelet levels among patients with a poor initial response, as has been seen in patients undergoing dialysis.[22] Additional analyses will be needed to determine the specific mechanisms of hyporesponsiveness in the patients in our study.

It is likely that a poor initial response to ESA treatment in this population represents a marker for severity of illness. Nevertheless, our ability to predict a poor initial response from baseline characteristics was limited, suggesting that the available baseline measures may not completely reflect factors that contribute to a poor initial response. The measure of hemoglobin responsiveness provided incremental value in predicting outcome beyond standard baseline measures, suggesting that this simple measure itself may have clinical value.

The target-based approach of our study mimics the target-based strategies that have been clinically used to treat anemia in patients with chronic kidney disease who have a reduced initial response, with higher doses of darbepoetin alfa used to attain the target hemoglobin level. Although the patients with the poorest initial response received the highest average doses of darbepoetin alfa and had the highest event rates, it is not possible with the existing data to determine whether this increased risk was due to

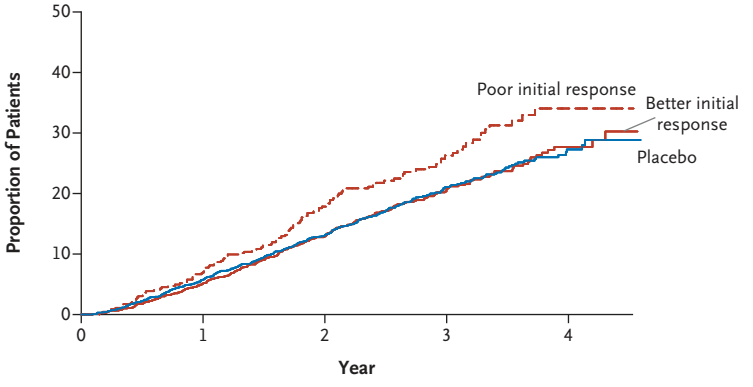
Figure 2 (facing page). Rates of Primary End Points.
Shown are the rates of the study's primary end points among patients with a poor initial response to darbepoetin alfa, those with a better initial response, and those in the original placebo group for the cardiovascular composite outcome (Panel A), death from any cause (Panel B), and fatal or nonfatal stroke (Panel C).

A **Death, Myocardial Infarction, Stroke, Heart Failure, or Hospitalization for Myocardial Ischemia**



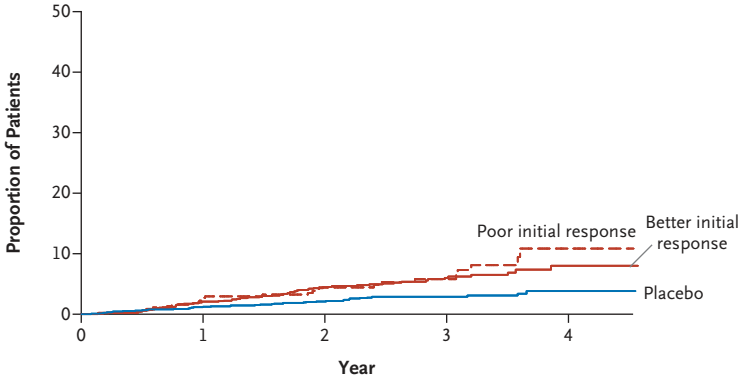
No. at Risk					
Poor initial response	471	394	272	125	30
Better initial response	1401	1234	854	408	94
Placebo	1889	1611	1138	514	117

B **Death from Any Cause**



No. at Risk					
Poor initial response	471	428	312	158	38
Better initial response	1401	1307	952	469	119
Placebo	1889	1732	1274	607	149

C **Fatal or Nonfatal Stroke**



No. at Risk					
Poor initial response	471	415	299	142	30
Better initial response	1401	1271	887	423	104
Placebo	1889	1687	1197	537	125

the increased dose. On the basis of these data, the potential use of an ESA test dose might be a reasonable strategy in a future clinical trial. Of note, a higher rate of increase in the hemoglobin level was not associated with greater risk, a concern that had been raised previously.[2,3] Indeed, patients with the greatest increase in hemoglobin level during the initial month of therapy had the lowest risk of clinical events.

Previous randomized trials of ESAs that tested various hemoglobin targets have suggested that higher targets (>13.5 g per deciliter) were associated with higher rates of cardiovascular events and, by inference, that lower targets were safer,[2,5] which led to the adoption of treatment guidelines for anemia that recommended a hemoglobin target of less than 13 g per deciliter.[7,8] We found that the extent of responsiveness to darbepoetin alfa varied widely, despite a single hemoglobin target in the treatment group; a lack of responsiveness, and not the achieved hemoglobin level, was associated with the highest risk. Since most of the high-risk patients with a poor initial response had hemoglobin levels that were within the range of current target guidelines (<12.5 g per deciliter), these data raise the question of whether lower hemoglobin targets alone could mitigate any potential risk associated with ESAs.

A limitation of our study is the inability to determine whether therapy with darbepoetin alfa conferred greater risk in patients with a poor initial response or conversely whether patients with the best response derived greater benefit from the drug. We could not directly compare risk between patients with a poor initial response in the treatment group and equivalent patients in the placebo group, since we could not determine which patients in the placebo group would have had a poor initial response. We also could not determine whether the increased risk observed among patients with a poor initial response was due to intrinsic factors reflecting severity of illness, subject to unidentified confounders, to the increased dose of darbepoetin alfa received, or a combination of these factors. We also cannot rule out a differential relationship between the ESA dose and outcome in different patient populations or at different ends of the hemoglobin spectrum, as has been suggested in the Medicare dialysis population.[24] Since we studied patients with both chronic kidney disease and diabetes who were not undergoing dialysis, we need to be cautious in generalizing our findings to other populations.

In summary, we observed that patients with chronic kidney disease, diabetes, and anemia who were not undergoing dialysis and who had a poor initial response to the initial two doses of darbepoetin alfa were at greatest risk for cardiovascular adverse events and death among all patients receiving therapy. Hemoglobin levels in these highest-risk patients fell within currently recommended targets. We cannot determine whether a poor initial response to an ESA places patients at increased risk for these adverse outcomes or whether the risk was augmented by the higher doses of darbepoetin alfa they received. However, these findings raise the question of whether the degree of hematopoietic responsiveness to ESA treatment, and not just the target hemoglobin level, should be taken into account in ESA therapy.

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