1. Hopkinson NS, Kemp SV, Toma TP, et al. Atelectasis and survival after bronchoscopic lung volume reduction for COPD. Eur Respir J 2010 October 14 (Epub ahead of print).
2. Martinez FJ, Han MK, Andrei A, Wise R, Murray S. Longitudinal change in the BODE index predicts mortality in severe emphysema. Am J Respir Crit Care Med 2008;178:491-9.
3. Naunheim KS, Wood DE, Krasna MJ, et al. Predictors of operative mortality and cardiopulmonary morbidity in the National Emphysema Treatment Trial. J Thorac Cardiovasc Surg 2006; 131:43-53.

Erythropoietin in Kidney Disease and Type 2 Diabetes

TO THE EDITOR: In a secondary analysis of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), Solomon et al. (Sept. 16 issue)[1] report that the quartile of patients who had the lowest hematopoietic response to darbepoetin alfa had the highest risk of death or cardiovascular events. These data suggest that a subgroup of patients can be identified who will have a poor outcome after receiving erythropoiesis-stimulating agents (ESAs). However, it remains to be clarified whether these patients represent a subgroup with an intrinsically poor prognosis or a subgroup with a poor prognosis because of extrinsic causes (i.e., receipt of an increased ESA dose). Therefore, it would be of interest to know whether patients with a poor hematopoietic response had an increased rate of occult bleeding or occult tumors. It is also somewhat surprising that the group of patients with a poor hematopoietic response did not receive more intravenous iron, despite their reduced transferrin saturation and ferritin levels. Was this lack of adaptation of iron-replacement therapy mandated by the protocol? And did the protocol specify the subgroup analysis of quartiles of hematopoietic response to two doses of darbepoetin?

Peter Schnuelle, M.D.
Urs Benck, M.D.
Bernhard K. Krämer, M.D.
Mannheim University Hospital
Mannheim, Germany
bernhard.kraemer@umm.de

No potential conflict of interest relevant to this letter was reported.

1. Solomon SD, Uno H, Lewis EF, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med 2010;363:1146-55.

TO THE EDITOR: The secondary analysis of TREAT showed that patients who had a poor initial response to darbepoetin alfa were at greater risk for the primary composite end point than those having a better initial response. We understand that it is difficult to ascertain whether this increased risk was due to preexisting characteristics of the patients, to an increased dose of darbepoetin alfa, or to a combination of both factors. However, the between-group difference in the median dose of darbepoetin alfa was not impressive (only 65 μg), and there was substantial overlap in doses between the two groups. Conversely, patients with a poor initial response to darbepoetin alfa had increased levels of C-reactive protein and an increased rate of cardiovascular disease at baseline. These findings suggest that the presence of coexisting illnesses in the patients may have been more important than the dose of darbepoetin alfa with respect to outcome. We agree that the target hemoglobin level should not be considered alone. Thus, in line with the last position statement of the European Renal Best Practice Anaemia Working Group,[1] practitioners should consider which dose of erythropoietin is needed to achieve the target hemoglobin level.

Francesco Locatelli, M.D.
Lucia Del Vecchio, M.D.
Donatella Casartelli, M.D.
Ospedale Alessandro Manzoni
Lecco, Italy
f.locatelli@ospedale.lecco.it

Dr. Locatelli reports serving on advisory boards for Abbott, Affimax, Amgen, Genzyme, Merck, Roche, Shire, Takeda, and GlaxoSmithKline and being a member of a safety committee for Sandoz. No other potential conflict of interest relevant to this letter was reported.

1. Locatelli F, Aljama P, Canaud B, et al. Target haemoglobin to aim for with erythropoiesis-stimulating agents: a position statement by ERBP following publication of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study. Nephrol Dial Transplant 2010;25:2846-50.

TO THE EDITOR: Solomon et al. report that patients with chronic kidney disease and type 2 diabetes who had a poor hematopoietic response to darbepoetin alfa had an increased risk of death and cardiovascular events. Patients in their study had anemia (defined as a hemoglobin level of <11.0 g per deciliter) and low ferritin levels. The limited response to ESAs may be due to the presence of functional iron deficiency. In our studies

involving patients with heart failure,[1,2] we defined functional iron deficiency as a serum ferritin level of less than 100 μg per liter or ranging from 100 to 299 μg per liter with a transferrin saturation of less than 20%. In the original report on TREAT,[3] more than 30% of patients had heart failure at baseline, and that number increased during follow-up. Hence, we would anticipate that there would be a high number of patients with functional iron deficiency. The prevalence and incidence of iron deficiency were not reported in the study by Solomon et al. or in the previous TREAT report.[3] The presence of iron deficiency could be an explanation for the failure of darbepoetin alfa in this select subgroup of patients. Such patients might benefit from concurrent iron-replacement therapy to optimize the response to erythropoietin. These issues should be addressed in this and future clinical trials involving patients with anemia who have chronic illnesses.

Thomas Thum, M.D., Ph.D.
Hannover Medical School
Hannover, Germany
thum.thomas@mh-hannover.de

Kamyar Kalantar-Zadeh, M.D.
Harbor–UCLA Medical Center
Torrance, CA

Stefan D. Anker, M.D., Ph.D.
Charité Campus Virchow-Klinikum
Berlin, Germany

Dr. Kalantar-Zadeh reports receiving honoraria from Amgen, Fresenius, and Watson, which manufacture or distribute ESAs or iron products; and Dr. Anker, receiving consulting fees from Amgen, Vifor Pharma, and Teva, research grants from Vifor Pharma, and lecture fees from Amgen and Vifor Pharma. No other potential conflict of interest relevant to this letter was reported.

1. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009;361:2436-48.
2. Thum T, Anker SD. Nutritional iron deficiency in patients with chronic illnesses. Lancet 2007;370:1906.
3. Pfeffer MA, Burdmann EA, Chen C-Y, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361:2019-32.

TO THE EDITOR: In TREAT, patients with a poor response to erythropoietin had an increased risk of cardiovascular outcomes. Hyperglycemia is central to the pathobiology of diabetes, and its importance in complications of type 2 diabetes has been established. In the United Kingdom Prospective Diabetes Study (UKPDS),[1] for every 1% reduction in the glycated hemoglobin level, there were reductions of 21% in the risk of a diabetes-related event, of 25% in the risk of death related to vascular disease, of 14% in the risk of myocardial infarction, and of 12% in the risk of stroke. In the original TREAT, there was a statistically significant between-group difference in the glycated hemoglobin level (7.0% in the darbepoetin group vs. 6.9% in the placebo group, P=0.02). Although the mean glycated hemoglobin levels reflected good glycemic control overall, half the patients were above the clinical target of 7.0%. Due consideration of the effects of glycemic control is not provided either in the report by Solomon et al. or in the original analysis of TREAT. Testing for an interaction between glycemic control and outcome is warranted.

Sandra Donnelly, M.D.C.M.
University of Toronto
Toronto, ON, Canada
sandra.donnelly@utoronto.ca

Dr. Donnelly reports having served on an advisory board for Amgen Canada. No other potential conflict of interest relevant to this letter was reported.

1. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.

THE AUTHORS REPLY: We agree that we cannot determine whether the increased risk of cardiovascular adverse events in patients with the poorest hemoglobin response to the initial doses of darbepoetin alfa was due to intrinsic disease, the increased doses that these patients eventually received, or both. Glycemic control was an unlikely contributor, since the mean (±SD) glycated hemoglobin level at baseline was similar in the two response groups (7.4±1.7% vs. 7.3±1.5%, P=0.12), with no significant interaction between the glycated hemoglobin level, the erythropoietic response, and outcome.

The benefit of additional iron repletion in these patients remains unknown. Patients in the poor-response group had reduced ferritin levels and transferrin saturations at baseline, as compared with the better-response group, and the percentage of patients with a ferritin level of less than 100 μg per liter was higher in the poor-response group (43.0% vs. 38.2%, P=0.06). There was no significant difference between the poor-response group and the better-response group in the percentage of patients receiving intravenous iron (15.7% vs. 14.7%, P=0.60), oral iron (67.3% vs. 67.4%, P=0.98), or transfusions (15.1% vs. 14.3%, P=0.67) and no significant difference in the rate of either serious gastrointestinal bleeding (1.5% vs. 2.0%, P=0.48) or incident cancer (7.4% vs. 7.0%, P=0.51).

The target hemoglobin range recommended by the Anaemia Working Group of the European Renal Best Practice is 11 to 12 g per deciliter.[1] However, we found a near doubling in the rate of stroke among patients receiving darbepoetin alfa, as compared with those receiving placebo, an increase that could not be predicted from either the initial hemoglobin response or the hemoglobin level during therapy before the stroke.[2]

Scott D. Solomon, M.D.
Brigham and Women's Hospital
Boston, MA
ssolomon@rics.bwh.harvard.edu

Kai-Uwe Eckardt, M.D.
University of Erlangen–Nuremberg
Erlangen, Germany

Marc A. Pfeffer, M.D., Ph.D.
Brigham and Women's Hospital
Boston, MA

Since publication of their article, the authors report no further potential conflict of interest.

1. Locatelli F, Aljama P, Canaud B, et al. Target haemoglobin to aim for with erythropoiesis-stimulating agents: a position statement by ERBP following publication of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study. Nephrol Dial Transplant 2010;25:2846-50.
2. Skali H, Parving HH, Parfrey PS, et al. Stroke in patients with diabetes and CKD treated with darbepoetin alfa: the TREAT experience. J Am Soc Nephrol 2010;21:390A. abstract.

Permethrin Treatment of Head Lice with Knockdown Resistance–like Gene

TO THE EDITOR: Chosidow and colleagues (March 11, 2010, issue)[1] justify their study of oral ivermectin for the treatment of pediculosis capitis by the increasing resistance of head lice to pyrethroids because of amino acid substitutions (Thr929Ile and Leu932Phe) in the alpha subunit of the voltage-gated sodium channel. These substitutions are considered to reduce or delay the insecticidal effects of permethrin and dichlorodiphenyltrichloroethane (DDT).[2] The DNA sequence bearing the two mutations is called the knockdown resistance (kdr)–like gene, which has been detected in up to 95% of head lice examined in Europe.[3,4] However, the gene has not been studied in relation to treatment outcomes in prospective studies.

We asked pediatricians from all over Germany to send us head lice and received 146 samples, including some of nits only. Using our polymerase-chain-reaction assay targeting the gene encoding the alpha subunit,[5] we obtained a product for sequencing from 100 of the samples (68%). The kdr-like gene was found in 93 of the 100 samples; the remaining 7 samples showed the wild-type sequence (Table 1).

Table 1. Studies of the kdr-like Gene in Head Lice and Treatment Response to Permethrin or Pyrethrin.

Study Characteristics	Positive for kdr-like Gene*	Cure Achieved†	
	no./total no. tested (%)	*no./total no. treated (%)*	*compound used*
Epidemiologic study involving 146 head-louse samples collected from all over Germany	93/100 (93)		
Observational treatment study involving intention-to-treat analysis of data from 150 children (1–15 yr of age, 71% female) enrolled at 12 pediatric private practices across Germany‡	112/120 (93)	104/112 (93)	0.5% Permethrin
Head louse–prevalence study of 1518 children (3–12 yr of age, 49% female) in primary or nursery school in Kiel	44/44 (100)		
Randomized, controlled 3-group study of treatment involving intention-to-treat analysis of data from 87 persons (3–19 yr of age, 83% female) enrolled in Kiel and vicinity	40/41 (98)	20/27 (74)	0.3% Pyrethrin

* Positivity for the kdr-like gene was determined for the subgroup of children who had head lice yielding a polymerase-chain-reaction product for sequencing.
† Cure was defined as absence of living lice (adults or larvae) 16 to 20 days after treatment.
‡ The observational study was conducted by Burow et al.[5]