

Nononcologic Use of Human Recombinant Erythropoietin Therapy in Hospitalized Patients

Michael A. Fischer, MD, MS; Charles A. Morris, MD, MPH; Wolfgang C. Winkelmayr, MD, ScD; Jerry Avorn, MD

Background: Human recombinant erythropoietin (rHuEPO) is widely used to stimulate red blood cell production in patients with anemia due to cancer, renal disease, and other medical conditions, but concern has grown about its overuse and potential for harm. Little is known about the nature of rHuEPO use in hospitalized patients who receive rHuEPO therapy for nononcologic indications.

Methods: We reviewed the drug utilization data from a large academic medical center for all patients admitted during 3 years to identify all patients without cancer who received at least 1 dose of rHuEPO, including their age and sex; diagnoses; hematocrit and hemoglobin and iron levels; and use of supplemental iron. We also compared the rates of laboratory testing and iron supplementation in patients with and without chronic kidney disease (CKD).

Results: A total of 1360 distinct patients with 3094 hospitalizations received at least 1 dose of rHuEPO. In 2959 admissions for which hematocrit was determined within 14 days before rHuEPO use, mean values were less than 33% in 1792 (61%) and greater than 36% in 553 (19%).

Patients with CKD were more likely than patients without CKD to receive rHuEPO with hematocrit greater than 36% (22% vs 8%; $P < .001$). Monitoring of iron status was more common in patients with CKD than in those without CKD (64% vs 45%; $P < .001$). Almost one fourth (23%) of rHuEPO recipients in whom iron levels were measured had absolute iron deficiency (serum ferritin concentration < 100 ng/mL). In patients with CKD, only about half (54%) had adequate iron stores at the time of rHuEPO administration; this rate was even lower in patients without CKD (33%; $P < .001$). Only 66% of patients with documented iron deficiency who were receiving rHuEPO also received concomitant iron supplementation; this rate did not differ between patients with or without CKD.

Conclusions: There is significant variability in the degree of anemia, completeness of iron measurement, and use of iron supplementation in hospitalized patients without cancer who are prescribed rHuEPO. Our results identify potential targets for quality improvement in patients both with and without CKD.

Arch Intern Med. 2007;167:840-846

HUMAN RECOMBINANT erythropoietin (rHuEPO) is the most widely used biotechnology product, with important applications in a variety of clinical situations including treatment of anemia of chronic kidney disease (CKD),^{1,2} chemotherapy-associated anemia,^{3,4} and anemia related to zidovudine therapy in patients infected with human immunodeficiency virus,⁵ and preoperative administration to reduce allogeneic blood transfusions.⁶ While rHuEPO is of enormous clinical importance, concern has emerged about its possible role in increasing thrombotic events and mortality if used excessively, especially if hematocrit becomes excessively high.⁷⁻¹² Its use also has considerable economic importance. Medicare is the single largest payer of rHuEPO claims and spends more than \$1 billion on rHuEPO

therapy annually for patients with CKD alone.¹³ More recently, rHuEPO therapy has been studied in anemic patients with congestive heart failure^{14,15}; and its use has been studied in intensive care units.¹⁶

Erythropoietin requires adequate iron stores for effective hematopoiesis. As many as 60% of patients with CKD who receive rHuEPO are unable to increase hemoglobin levels despite dose escalation, frequently because of absolute iron deficiency (serum ferritin concentration < 100 ng/mL)^{17,18} or functional iron deficiency (iron saturation $< 20\%$ with normal or elevated serum ferritin levels) in which iron stores are insufficient to support accelerated hematopoiesis.^{19,20}

While rHuEPO is commonly used, little is known about prescribing patterns. The European Survey on Anemia Management found that in 41% of patients receiving renal replacement therapy, iron sta-

Author Affiliations: Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass.

tus was not monitored according to recommendations and that only one fifth of patients undergoing hemodialysis received any supplemental iron during a 6-month period.²¹ Target hematocrit values for patients receiving rHuEPO are defined only for those with CKD; exceeding these values may be associated with increased costs²² and mortality.^{7,8,12,23} Patterns of rHuEPO use in patients without CKD are not well described.

We designed the current analysis of all inpatient recipients of rHuEPO at a large academic medical center to define patterns of use in relation to underlying diagnoses, hematocrit values, and iron level management. We also studied differences between patients with and without CKD, hypothesizing that those with CKD would be more likely to receive rHuEPO with hematocrit values in the indicated range and appropriate monitoring and supplementation of iron.

METHODS

PATIENT SELECTION

We identified all patients admitted to an academic tertiary care medical center between April 1, 2000, and March 31, 2003, who had received at least 1 dose of rHuEPO (epoetin alfa; Epogen, Amgen Inc, Thousand Oaks, Calif, or Procrit, Ortho Biotech Products, Bridgewater, NJ). We collected data on patient age, sex, and race; comorbid conditions; and medication use. All unique patient identifiers were removed before analysis to protect patient privacy. Institutional review board approval was obtained for all aspects of this research.

Patients with a primary diagnosis of malignancy were excluded from analysis. The primary unit of analysis was the admission, and, accordingly, individual patients could contribute more than 1 admission to the data, provided each admission was associated with at least 1 dose of rHuEPO. If a patient received multiple doses of rHuEPO during an admission, the date of the first dose was used as the administration date. All routes of administration were included. Patients with primary or secondary ICD-9 (*International Classification of Diseases, Ninth Revision*) codes for end-stage renal disease or a CPT-4 (*Current Procedural Terminology, Fourth Revision*) code for renal replacement therapy for any admission were considered to have these diagnoses for all admissions included in the analysis. Patients with primary or secondary ICD-9 codes for chronic renal disease were considered to have CKD for all admissions included in the analysis. **Table 1** lists the codes used to define these conditions.

LABORATORY TESTS

For every hospital admission, we defined the mean, maximum, minimum, and most recent hematocrit values in the 14 days before the first administration of rHuEPO therapy. To assess iron stores, we recorded the maximum, minimum, mean, and most recent values for serum iron, total iron binding capacity, and ferritin in the 90 days before the administration of rHuEPO therapy. Transferrin saturation (T_{SAT}) was calculated from the highest serum iron value divided by the lowest iron binding capacity in the 90 days before drug administration. We divided iron status into 3 categories: absolute iron deficiency (serum ferritin concentration of <100 ng/mL), indeterminate iron stores (T_{SAT} <20% and serum ferritin concentration of >100 ng/mL), and adequate or replete iron stores (T_{SAT} >20% and serum ferritin concentration of >100 ng/mL). For patients with CKD, we defined

Table 1. Diagnosis Codes Used to Define Chronic Renal Disease

Disease and Code
End-stage renal disease/renal replacement therapy
CPT codes
90918-90999
ICD-9 codes
585, Chronic renal failure
V45.1, Postsurgical renal dialysis status
V56.0, Encounter for extracorporeal dialysis
V56.1, Encounter for fitting and adjustment of dialysis (extracorporeal or peritoneal) catheter
996.73, Other complications due to renal dialysis device, implant, and graft
Chronic renal failure
Codes as for end-stage renal disease/renal replacement therapy, above
CPT codes
90918-90999
ICD-9 codes
285.21, Anemia in end-stage renal disease
403.91, Hypertensive renal disease, unspecified, with renal failure
581.81, Nephrotic syndrome in diseases classified elsewhere
581.9, Nephrotic syndrome with unspecified pathological lesion in kidney
582.4, Chronic glomerulonephritis with lesion of rapidly progressive glomerulonephritis
582.81, Chronic glomerulonephritis in diseases classified elsewhere
581.89, Chronic glomerulonephritis with other specified pathological lesion in kidney
582.9, Chronic glomerulonephritis with unspecified pathological lesion in kidney
583.1, Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranous glomerulonephritis
583.2, Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranoproliferative glomerulonephritis
583.4, Nephritis and nephropathy, not specified as acute or chronic, with lesion of rapidly progressive glomerulonephritis
583.81, Nephritis and nephropathy, not specified as acute or chronic, in diseases classified elsewhere
583.89, Nephritis and nephropathy, not specified as acute or chronic, with other specified pathological lesion in kidney
583.9, Nephritis and nephropathy, not specified as acute or chronic, with unspecified pathological lesion in kidney
586, Renal failure, unspecified
587, Renal sclerosis, unspecified

Abbreviations: CPT, *Current Procedural Terminology*; ICD-9, *International Classification of Diseases, Revision 9*.

indeterminate iron stores as functional iron deficiency. For patients without CKD, this category is consistent with anemia of chronic disease.²⁴ While not all patients received outpatient care at the same facility, we assumed that patients with results documented for commonly performed outpatient laboratory tests received local ambulatory care. To study this, we obtained results for 13 additional laboratory tests (the levels of serum creatinine, rHuEPO, glycosolated hemoglobin, potassium, vitamin B₁₂, folic acid, serum urea nitrogen, thyrotropin, and alanine aminotransferase; prostate-specific antigen concentration; platelet and white blood cell counts; and mean corpuscular volume) from the 90 days before the admission. All laboratory test results used for this analysis were available to the rHuEPO prescriber at the time of the initial drug order through the hospital electronic laboratory reporting system.

Table 2. Characteristics of Patients and Admissions With More Than 1 rHuEPO Administration

Characteristic	Value†
Total admissions	3094
Principle diagnosis of chronic kidney disease*	2443 (79)
Total unique patients	1360
Age, y	
Mean ± SD	64 ± 16.6
<30	54 (4)
30-39	105 (8)
40-49	179 (13)
50-59	243 (18)
60-69	271 (20)
70-79	335 (25)
≥80	173 (13)
Male sex	685 (50)
Race	
White	864 (63)
Black	286 (21)
Hispanic	71 (5)
Asian	19 (1)
Other or not recorded	120 (9)
Comorbidities	
Chronic kidney disease*	866 (64)
Hypertensive renal disease	667 (49)
Coronary artery disease	565 (42)
Congestive heart failure	576 (42)
Diabetes mellitus	528 (39)
Essential hypertension	397 (29)
Atrial fibrillation or flutter	309 (23)
Chronic obstructive pulmonary disease	138 (10)

Abbreviation: rHuEPO, human recombinant erythropoietin.

*See Table 1 for definitions.

†Data are given as number (percentage) unless otherwise indicated.

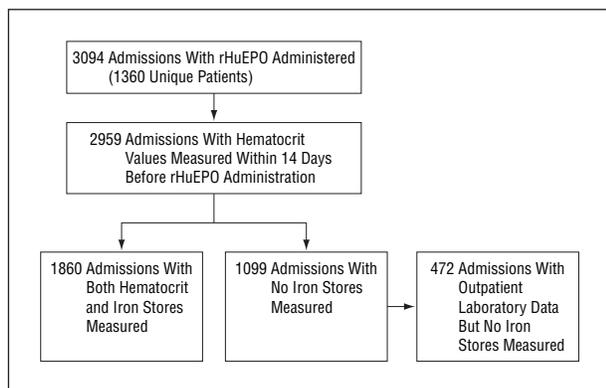


Figure 1. Availability of laboratory data for the 3094 admissions included in the study. Of these admissions, hematocrit readings were available for 2959. Of these 2959 admissions, iron studies were available for 1860. Among the 1099 admissions without iron studies, 472 had other common outpatient laboratory tests performed during the study period, suggesting that laboratory monitoring was occurring but iron levels were not being checked. rHuEPO indicates human recombinant erythropoietin.

IRON SUPPLEMENTATION

We identified all other medications used by patients given rHuEPO during the hospitalization and all forms of iron supplementation. Both oral and intravenous preparations were included. Use of any dosage was considered evidence of iron supplementation.

Table 3. Mean and Lowest Hematocrit in 14 Days Before the Administration of rHuEPO Therapy in Admissions With Hematocrit Results Available*

Hematocrit	Patients With CKD (n = 2314)	Patients Without CKD (n = 645)	Total (N = 2959)
Mean level, %			
<30	664 (29)	306 (47)	970 (33)
30-33	630 (27)	192 (30)	822 (28)
33-36	519 (22)	95 (15)	614 (21)
36-40	382 (17)	37 (6)	419 (14)
>40	119 (5)	15 (2)	134 (5)
<33†	1294 (56)	498 (77)	1792 (61)
>36†	501 (22)	52 (8)	553 (19)
Lowest level, %			
<30	1324 (57)	500 (78)	1824 (62)
30-33	422 (18)	78 (12)	500 (17)
33-36	348 (15)	39 (6)	387 (13)
36-40	177 (8)	17 (3)	194 (7)
>40	43 (2)	11 (2)	54 (2)
<33†	1746 (75)	578 (89)	2324 (79)
>36†	220 (10)	28 (4)	248 (8)

Abbreviations: CKD, chronic kidney disease; rHuEPO, human recombinant erythropoietin.

*Data are given as number (percentage).

† $P < .001$ for difference between patients with and without CKD.

STATISTICAL ANALYSIS

Patterns of rHuEPO use were summarized as a function of hematocrit, presence and value of iron studies, and use of iron supplementation. Rates of iron monitoring and replacement and levels of iron and hematocrit were compared between patients with and without CKD using the Fisher exact test. All analyses were conducted using SAS for Windows software (SAS release 8.2; SAS Institute Inc, Cary, NC).

RESULTS

We identified 3094 admissions during which eligible patients received at least 1 dose of rHuEPO; 2443 admissions (79%) were primarily because of CKD (**Table 2**). These 3094 admissions involved 1360 unique patients. Their mean ± SD age was 64 ± 16.6 years; 50% were male, and 63% were white. The largest group of patients (866 [64%]) had CKD, and 454 (52%) of these patients underwent dialysis during at least 1 admission. Among patients admitted primarily because of CKD, the mean serum creatinine level was 6.7 mg/dL (592 μmol/L) compared with 2.1 mg/dL (186 μmol/L) in those admitted because of other causes. Hypertension, cardiac disease, and diabetes mellitus were common comorbidities.

HEMATOCRIT AND HEMOGLOBIN LEVEL

Figure 1 shows the availability of laboratory test results. The distribution of mean hematocrit values in recipients of rHuEPO therapy is given in **Table 3**. For 2959 admissions, the hematocrit was available in the 14 days before the administration of rHuEPO. The mean hematocrit was less than 33% in 1792 patients (61%), greater than 36% in 553 (19%), and greater than 40% in 134 (5%).

In comparisons of patients with or without CKD, 56% of those with CKD had a hematocrit less than 33% while receiving rHuEPO therapy compared with 77% of those without CKD ($P < .001$). In 22% of patients with CKD, the hematocrit was greater than 36% while receiving rHuEPO therapy compared with only 8% of those without CKD ($P < .001$). Hematocrit exceeded 40% in 5% of patients with CKD and in 2% of patients without CKD.

To avoid misclassification of patients with clinically significant anemia whose mean hematocrit might be spuriously elevated by an outlier result, we recalculated this distribution as a function of the lowest rather than the mean hematocrit value (Table 3). By these criteria, 248 rHuEPO courses (8%) were administered in patients whose lowest hematocrit was greater than 36% in the 14 days before drug administration. Similar to the results for mean hematocrit (Table 2), patients with CKD received rHuEPO despite hematocrit values greater than 36% about 2.5 times more frequently than patients without CKD (10% vs 4%; $P < .001$).

IRON STATUS

Serum ferritin concentrations or T_{SAT} results were available for 1860 admissions in the 90 days before rHuEPO administration (Table 4). These tests were more common in patients with than without CKD (64% vs 45%; $P < .001$). Of the 1234 admissions in which T_{SAT} or serum ferritin was not measured in the 90 days preceding rHuEPO use, 472 (38%) had other outpatient laboratory tests obtained in that same period. Among the 1860 patients with iron studies, nearly one fourth (435 [23%]) of rHuEPO orders were written for patients who had absolute iron deficiency. In admissions for patients with CKD who had iron studies, 721 (46%) had either absolute or functional iron deficiency at the time of rHuEPO use. Among 290 patients without CKD with iron tests, 111 (38%) had absolute iron deficiency, 82 (28%) had indeterminate iron stores (consistent with the anemia of chronic disease), and 97 (33%) had adequate iron stores.

Figure 2A shows the distribution of mean hematocrit and iron status for all admissions with rHuEPO therapy. We examined patterns of rHuEPO administration separately for patients with CKD (Figure 2B) and without CKD (Figure 2C). The largest single group of rHuEPO recipients were anemic with adequate iron stores. However, substantial numbers of patients, both with and without CKD, had relatively normal hematocrits, inadequate iron stores, or both. As shown in Figure 2C, many patients without CKD with anemia had significant iron deficiency at the time of rHuEPO administration.

IRON SUPPLEMENTATION

Only half of rHuEPO administrations (1497/3094 [48%]) were accompanied by iron supplementation (Table 5); this rate differed slightly between patients with and without CKD (47% vs 53%; $P = .01$). No iron studies were available for analysis in 513 patients who received iron supplementation. Even in patients with demonstrated iron deficiency, only two thirds received iron supplementation. The rate of iron supplementation in patients at all

Table 4. Iron Saturation in rHuEPO Recipients by Presence or Absence of CKD*

Iron Status	Patients With CKD (n = 2443)	Patients Without CKD (n = 651)	Total (N = 3094)
Total admissions			
Iron studies not available	873 (36)	361 (55)	1234 (40)
Iron studies available	1570 (64)	290 (45)	1860 (60)
Admissions with iron studies			
Absolute iron deficiency†	324 (21)	111 (38)	435 (23)
Indeterminate iron stores‡	397 (25)	82 (28)	479 (26)
Adequate iron stores§	849 (54)	97 (33)	946 (51)

Abbreviations: CKD, chronic kidney disease; rHuEPO, human recombinant erythropoietin.

*Data are given as number (percentage). $P < .001$, unless otherwise indicated, for difference between patients with and without CKD.

†Serum ferritin concentration of less than 100 ng/mL.

‡Serum ferritin concentration of greater than 100 ng/mL and iron saturation of less than 20%. $P = .28$ value not significant.

§Serum ferritin concentration greater than 100 ng/mL and iron saturation of greater than 20%.

of the defined levels of iron saturation was similar regardless of CKD status.

COMMENT

To our knowledge, this is the first study documenting rHuEPO prescribing patterns in inpatients with and without CKD. Although more than half of the recipients receiving rHuEPO therapy had hematocrit values less than 33%, almost one fifth had recent mean hematocrit values greater than 36% before rHuEPO use, and 134 patients received the drug despite mean hematocrit values exceeding 40%. Patients with CKD were more likely to receive rHuEPO despite relatively high hematocrits; patients without CKD were likely to have more significant anemia. Laboratory testing of iron status was not consistently performed, and iron deficiency was often not appropriately treated. Iron saturation less than 20% or a serum ferritin concentration greater than 100 μ g/L suggests functional iron deficiency in patients with CKD, in which iron administration might permit rHuEPO cessation or dose reduction. Almost half (46%) of the recipients with CKD who received rHuEPO therapy had either absolute or functional iron deficiency, and only 63% of these received iron supplementation. Iron supplementation rates increased with decreasing iron stores. Even so, one third of all patients with absolute iron deficiency did not receive iron therapy. In patients without CKD, absolute iron deficiency was present even more often, although rates of iron supplementation were the same at each level of iron deficiency.

These findings in patients with CKD are consistent with previously published data on patterns of rHuEPO use in other settings. The European Survey on Anemia Management reported that 15% to 22% of patients undergoing hemodialysis and 41% to 45% of those undergoing peritoneal dialysis had absolute iron deficiency (defined as a serum ferritin concentration of < 100 μ g/L).²¹ In patients with iron deficiency, only 19% to 34% re-

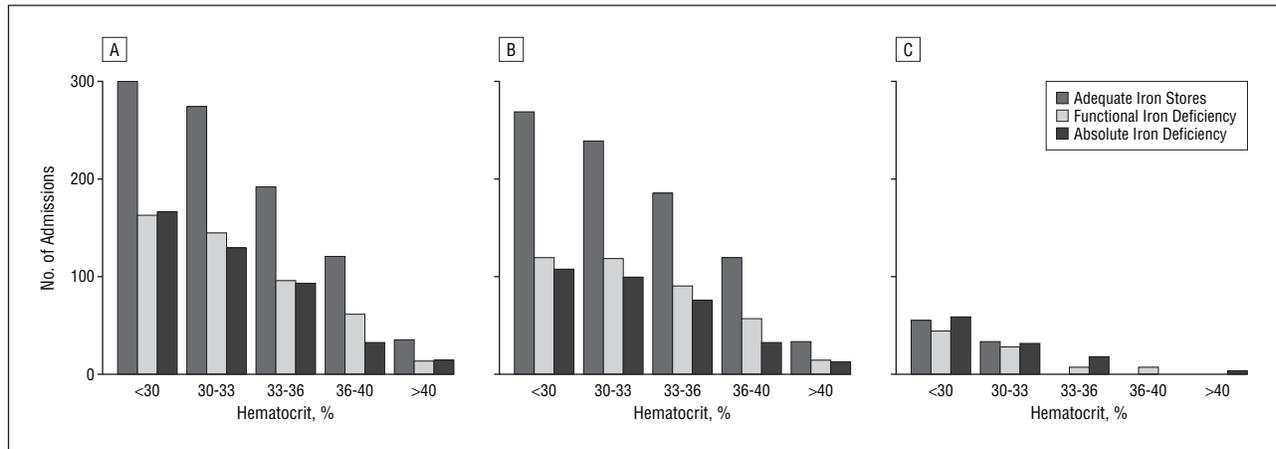


Figure 2. Distribution of mean hematocrit levels and iron stores in admissions for study patients treated with human recombinant erythropoietin (rHuEPO). The bars show the number of admissions with adequate iron stores, functional iron deficiency, and absolute iron deficiency at each hematocrit level. For example, the left-most bar in each cluster of 3 shows the number of admissions with that hematocrit level and adequate iron stores at the time of rHuEPO prescribing. Moving rightward, the middle bar in each cluster shows the number of admissions with that hematocrit level and functional iron deficiency at the time of rHuEPO prescribing, while the right-most bar shows the number of admissions with absolute iron deficiency. A, Overall study population results. B, Admissions with chronic kidney disease. C, Admissions without chronic kidney disease.

Table 5. Rates of Iron Supplementation in Hospitalized Patients Receiving rHuEPO*

Iron Status	Patients With CKD† (n = 2443)	Patients Without CKD (n = 651)	Total (N = 3094)
Admissions with iron supplementation	1154 (47)	343 (53)	1497 (48)
Iron studies available	835 (72)‡	168 (49)‡	984 (66)
Iron supplement given/iron stores checked	835/1570 (53)§	168/290 (58)§	1003/1860 (54)§
Iron supplement given/iron deficiency	211/324 (65)§	74/111 (67)§	285/435 (66)§
Iron supplement given/indeterminate iron stores	245/397 (62)§	52/82 (63)§	297/479 (62)§
Iron supplement given/adequate iron stores	379/849 (45)§	42/97 (43)§	421/946 (45)§

Abbreviations: CKD, chronic kidney disease; rHuEPO, human recombinant erythropoietin.

*Data are given as number (percentage) unless otherwise indicated.

†See Table 1 for definitions.

‡ $P < .001$ for comparison between patients with and without CKD; P value not significant for all other comparisons shown.

§The numerator indicates the number of patients given iron supplementation; the denominator, the number of patients with iron stores at a given level; and parenthetical values, percentages.

ceived iron supplementation. Similar rates of iron supplementation in iron-deficient patients undergoing dialysis have been reported in the United States.²⁵ Patients without CKD composed a smaller fraction of recipients of rHuEPO therapy in our study; iron deficiency with inconsistent use of iron supplementation was a common problem in this population as well.

There are several potential explanations for our findings. Physicians prescribing rHuEPO may have been unaware of recommended target hematocrit. The Food and Drug Administration has set the target hematocrit for patients with CKD receiving rHuEPO therapy at 30% to 33%, and the National Kidney Foundation Dialysis Outcomes Quality Initiative recommends 30% to 36%.¹⁸ Continuing treatment when a patient's hematocrit exceeds the target level may impose risk: in a study of patients with end-stage renal disease and cardiac disease, rHuEPO administration with a goal hematocrit of 42% was associated with a trend toward increased mortality.²³ These findings are of particular concern in light of the early termination of the CHIOR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) trial because of increased mortality in pa-

tients given rHuEPO with the goal of elevating the hematocrit above previously targeted levels.^{7,8,12}

Physicians caring for hospitalized patients may be reluctant to stop long-term outpatient therapies, but there may be circumstances when changes in therapy are warranted. We found higher rates of significant anemia in patients without CKD. Erythropoietin is heavily marketed to both patients and physicians, and our findings in the population without CKD may reflect rHuEPO prescribing for patients with anemic states without a specific indication for the drug (eg, anemia of chronic disease) or for conditions that may be more appropriately treated with other medications (eg, iron deficiency).

This analysis is subject to limitations that may affect its conclusions. Therapy with rHuEPO results in increased iron consumption, and it is possible that the iron deficiency in some recipients of rHuEPO was a result of prolonged rHuEPO therapy. However, iron deficiency was most common in patients with low hematocrits, which suggests that effective hematopoiesis was not the cause of iron loss. Our assessment of iron deficiency states was based only on iron saturation

and serum ferritin concentrations. A serum ferritin concentration of less than 100 µg/L to define absolute iron deficiency is consistent with European and US guidelines.^{18,21} An iron saturation level less than 20% with a serum ferritin concentration greater than 100 µg/L in patients with CKD suggests functional iron deficiency, and according to National Kidney Foundation Dialysis Outcomes Quality Initiative guidelines warrants a trial of iron repletion before initiation of rHuEPO therapy.¹⁸ Alternatively, these values may reflect the anemia of chronic disease that would not be expected to respond to iron supplementation. If anything, patients having an acute-phase reaction may have elevated serum ferritin concentrations, which would lead to underestimation of the prevalence of iron deficiency.

Hematocrit readings for a 14-day period that includes an acute-care hospitalization may significantly differ from average values for longer periods, inasmuch as dehydration, volume resuscitation, acute blood loss, dialysis, and transfusions may introduce variability in hematocrit measurements. Hemoglobin levels may reflect actual counts more reliably in these settings; however, our analysis did not differ substantially when calculated with hemoglobin values. Diagnoses recorded in the hospital computer system may not be completely accurate, so the true distribution of comorbidities may differ from those we recorded. Some of the admissions that we recorded as non-CKD may have included patients with milder forms of renal disease that were not recognized at the time; this is reflected in the modestly elevated mean creatinine level in these patients. We did not collect data on the indication for rHuEPO therapy or rHuEPO dosage, and could not differentiate long-term from newly initiated therapy. However, practice recommendations including aggressive iron replacement are relevant regardless of the duration of therapy or indication. Our data on iron supplementation in patients with end-stage renal disease undergoing dialysis may have failed to capture previous intravenous iron supplementation administered at outside dialysis facilities.

This work suggests multiple potential targets for improving the care of patients receiving rHuEPO therapy. As reflected by the limitations of our study, our data cannot provide definitive support for the following recommendations, but additional studies may further clarify the optimal approaches. Patients should have recent iron studies, and iron supplementation should be instituted before and in combination with rHuEPO therapy. Such measures will enable a more rapid hematopoietic response to rHuEPO and, potentially, a reduction in rHuEPO dosage or elimination of rHuEPO therapy entirely, which could have clinical and economic benefit. Uncomplicated iron deficiency anemia, particularly in patients older than 50 years, warrants a thorough evaluation for potential etiologies and iron supplementation rather than rHuEPO therapy. Iron saturation less than 20% in the setting of a normal or an elevated serum ferritin concentration, particularly in patients with CKD, indicates functional iron deficiency that may be responsive to iron supplementation; in patients without CKD, this suggests anemia of chronic disease best treated by addressing the underlying medical condition associated with the

disruption of iron mobilization. Current trials are under way to further explore the benefit of higher target hematocrit,²⁶ but until such data are available, there is no evidence to support the administration of rHuEPO to patients with hematocrits greater than 40%, and emerging data suggest risk.^{7,8,12}

These findings point to potentially important targets for improved prescribing of rHuEPO in the inpatient setting for patients both with or without CKD. Replication of these analyses at other hospitals and in outpatient settings could provide important insights into how widespread these problems are. Follow-up studies measuring the effect of ongoing educational programs and guideline use will provide useful information for quality improvement efforts in other hospitals and health plans.

Accepted for Publication: December 26, 2006.

Correspondence: Michael A. Fischer, MD, MS, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, 1620 Tremont St, Suite 3030, Boston, MA 02120 (mfischer@partners.org).

Author Contributions: Drs Fischer and Morris had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Fischer, Morris, Winkelmayr, and Avorn. *Acquisition of data:* Morris and Avorn. *Analysis and interpretation of data:* Fischer, Morris, Winkelmayr, and Avorn. *Drafting of the manuscript:* Fischer and Morris. *Critical revision of the manuscript for important intellectual content:* Fischer, Morris, Winkelmayr, and Avorn. *Statistical analysis:* Fischer, Morris, and Winkelmayr. *Obtained funding:* Avorn. *Administrative, technical, and material support:* Fischer and Avorn. *Study supervision:* Avorn.

Financial Disclosure: Drs Winkelmayr and Avorn performed research funded by an unrestricted research grant to Brigham and Women's Hospital from Research Triangle Institute, which in turn receives funding from Amgen Inc.

Previous Presentation: This study was presented at the 22nd International Conference on Pharmacoepidemiology and Therapeutic Risk Management; August 25, 2006; Lisbon, Portugal.

Acknowledgment: We thank Raisa Levin, MSc, and Claire Canning, MA, of the Brigham and Women's Hospital Division of Pharmacoepidemiology and Pharmacoeconomics for assistance with computer programming.

REFERENCES

1. Winearls CG, Oliver DO, Pippard MJ, Reid C, Downing MR, Cotes PM. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet*. 1986;2:1175-1178.
2. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin: results of a combined phase I and II clinical trial. *N Engl J Med*. 1987;316:73-78.
3. Littlewood TJ, Bajetta E, Nortier JW, Vercaemmen E, Rapoport B; Epoetin Alfa Study Group. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 2001;19:2865-2874.

4. Rizzo JD, Lichter AE, Woolf SH, et al; American Society of Hematology. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *Blood*. 2002;100:2303-2320.
5. Henry DH, Beall GN, Benson CA, et al. Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy: overview of four clinical trials. *Ann Intern Med*. 1992;117:739-748.
6. Faris PM, Ritter MA, Abels RI; American Erythropoietin Study Group. The effects of recombinant human erythropoietin on perioperative transfusion requirements in patients having a major orthopaedic operation. *J Bone Joint Surg Am*. 1996;78:62-72.
7. Singh AK, Szczech L, Tang KL, et al; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006;355:2085-2098.
8. Cassels C. CHOIR silenced as findings show increased risk of CVD outcomes/death. <http://www.medscape.com/viewarticle/539039>. Accessed October 6, 2006.
9. Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet*. 2003;362:1255-1260.
10. Leyland-Jones B. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol*. 2003;4:459-460.
11. Pollack A. Drug company halts trials of Procrit. *New York Times*. November 27, 2003.
12. Rowland C. As kidney drug doses rise, so do warnings. *Boston Globe*. September 14, 2006; §A1.
13. Kimmel PL, Greer JW, Milam RA, Thamer M. Trends in erythropoietin therapy in the U.S. dialysis population: 1995-1998. *Semin Nephrol*. 2000;20:335-344.
14. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation*. 2003;107:294-299.
15. Silverberg DS, Wexler D, Blum M, et al. The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. *Nephrol Dial Transplant*. 2003;18:141-146.
16. Corwin HL, Gettinger A, Pearl RG, et al; EPO Critical Care Trial Group. Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. *JAMA*. 2002;288:2827-2835.
17. Sunder-Plassman G, Horl W. Iron therapy during erythropoietin treatment in haemodialysis patients. *Kidney Forum*. 2000;2:23-25.
18. National Kidney Foundation. K/DOQI clinical practice guidelines for anemia of chronic kidney disease, 2000. *Am J Kidney Dis*. 2001;37(suppl 1):S182-S238.
19. Goodnough L. The role of iron in erythropoiesis in the absence and presence of erythropoietin therapy. *Nephrol Dial Transplant*. 2002;17:14-18.
20. Kaltwasser JP, Gottschalk R. Erythropoietin and iron. *Kidney Int Suppl*. 1999;55: S49-S56.
21. Macdougall IC, Horl WH, Jacobs C, et al. European best practice guidelines 6-8: assessing and optimizing iron stores. *Nephrol Dial Transplant*. 2000;15: 20-32.
22. Tonelli M, Winkelmayer W, Jindal K, Owen W, Manns B. The cost-effectiveness of maintaining higher hemoglobin targets with erythropoietin in hemodialysis patients. *Kidney Int*. 2003;64:295-304.
23. Besarab A, Bolton W, Browne J, 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*. 1998;339:584-590.
24. Weiss G. Iron and anemia of chronic disease. *Kidney Int Suppl*. 1999;55:S12-S17.
25. US Renal Data System. *USRDS 1996 Annual Data Report*. Bethesda, Md: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 1996.
26. Eckardt KU; Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta (CREATE) Trial. The CREATE Trial: building the evidence. *Nephrol Dial Transplant*. 2001;16(suppl 2):16-18.