Trends in Anemia Management among US Hemodialysis Patients

JOSEPH A. COLADONATO,* DIANE L. FRANKENFIELD, † DONAL N. REDDAN,* PRESTON S. KLASSEN,* LYNDA A. SZCZECH,* CURTIS A. JOHNSON,‡ and WILLIAM F. OWEN JR.,* for CMS ESRD Clinical Performance Measures Workgroup

*Duke Institute of Renal Outcomes Research and Health Policy, Duke University Medical Center, Durham, North Carolina; † Office of Clinical Quality and Standards, Centers for Medicare and Medicaid Services, Baltimore, Maryland; ‡ University of Wisconsin School of Pharmacy, Madison, Wisconsin.

Abstract. This study was undertaken to describe the relationship between hematocrit (Hct) and changes in the prescribed dose of erythropoietin (EPO) as well as selected patient and process care measures across annual national samples of hemodialysis patients from 1994 to 1998. This study uses the cohorts identified in the ESRD Core Indicators Project, random samples of 6181, 6241, 6364, 6634, and 7660 patients, stratified by ESRD Networks drawn for each year from 1994 to 1998. Patient demographic and clinical information was collected from October to December for each year. Surrogates of iron stores and patterns of iron and EPO administration were profiled from 1996 to 1998. Multivariable stepwise linear regression analyses were performed to adjust for potential confounding variables and to identify independent variables associated with Hct and EPO dose. Mean Hct and EPO dose increased each year from 31.1 ± 5.2% to 34.1 ± 3.7% and from 58.2 ± 41.8 U/kg to 68.2 ± 55.0 U/kg, respectively (P = 0.0001). Increasing Hct was positively associated with male gender, more years on dialysis, older age, higher urea reduction ratio and transferrin saturation, prescription of intravenous iron, and lower ferritin and EPO dose in multivariable models (all P = 0.0001). Male gender, older age, diabetes, higher Hct, and increasing weight, urea reduction ration, and transferrin saturation were associated with lower EPO doses (all P < 0.01). Conversely, intravenous EPO and iron were associated with higher prescribed EPO doses (all P = 0.0001). Although increasing Hct is associated with decreasing EPO dose at the patient level, the increase in Hct seen across years among the cohorts of hemodialysis patients in the United States has been associated with increasing doses of EPO at the population level.

Anemia is a frequent complication of chronic kidney disease (CKD) and end-stage renal disease (ESRD), especially for patients receiving hemodialysis as renal replacement therapy. Based on Medicare billing data, it is estimated that approximately 95% of Medicare beneficiaries receive recombinant (biosynthetic) human erythropoietin (EPO) as primary treatment for their anemia (1). Since the original availability of EPO for the treatment of anemia in ESRD, the target hematocrit has increased. The initial reimbursed target hematocrit approved by the Food and Drug Administration in August 1989 was 30 to 33% (2); in June 1994, the target was raised to 30 to 36% (3). The increase in the target hematocrit was supported by a structured review of available clinical literature that gave rise to clinical practice guidelines advocating a hematocrit range from 33 to 36% (4). Because absolute or relative iron deficiency, arising from exhaustion of marrow iron stores and/or the inability to deliver adequate iron stores to support normoblast proliferation and maturation (5–10), are common causes of inefficiency in EPO response, concomitant clinical practice guideline statements have been developed for iron administration (4).

To encourage and assist in the achievement of the target hematocrit, quality improvement projects focused at dialysis facilities were established and executed through individual dialysis unit providers and nephrologists. On the basis of the results from several national registries and data sets, the hemoglobin/hematocrit values for hemodialysis patients have increased over the last 8 yr (11–15). For example, data from the Centers for Medicare and Medicaid Services (CMS), formerly the Health Care Financing Administration, National ESRD Core Indicators/Clinical Performance Measures (CPM) Projects reported an increase in mean hematocrit for their nationally representative sample from 32% in 1995 to 34% in 1998 (14). Although improvement in anemia management has been achieved, there have been limited analyses of the relationship between the secular increase in hematocrit and changes in the doses of EPO. Closer examination of this relationship is prudent because: (1) current Medicare expenditures for EPO are approximately $1 billion per year (16); (2) reimbursement for injectable drugs, including EPO, parenteral iron, and
vitamin D preparations are a major revenue source contributing to the profitability of most dialysis facilities in the United States (17); (3) the principal intravenous route of EPO administration in the United States (11,12,18) is atypical on a world-wide basis (19) and associated with less favorable pharmacokinetics (20–23); and (4) the erythropoietic response to EPO is dose-dependent, but the dose-response is variable among ESRD patients (24,25). These background elements prompted us to examine the relationship between the improvement in hematocrit among American ESRD patients and changes in the dose of EPO.

Materials and Methods

Patient Selection and Data Collection

The study design, sampling strategy, and reliability testing of measures used in the National ESRD Core Indicators and CPM Projects are described in detail elsewhere (14,26,27). Briefly, all Medicare-eligible, adult ESRD patients receiving in-center hemodialysis on December 31 of the study year were eligible for inclusion in the sample. A new, random sample of patients, stratified by the ESRD Networks, was drawn separately at the beginning of each calendar year from 1994 to 1998. The sample size was estimated to provide a 95% confidence interval of ± 5% for ESRD Network–specific estimates. Patient demographic and clinical information was collected for the months of October to December for each sample year (1994 to 1998). The demographic and clinical variables used for these analyses included age, gender, race, postdialysis weight, years on dialysis therapy, etiology of ESRD (diabetes mellitus, hypertension, glomerulonephritis, and other/unknown), and ESRD Network in which care was received. For statistical reasons, race was limited to either white or black due to limited numbers categorized as other racial groups. Treatment variables captured included prescribed EPO dose (U/kg predialysis body weight per dose), hematocrit, and urea reduction ratio (URR, which was calculated from first monthly predialysis and postdialysis body weight, and dialysis session length. From 1996 to 1998, additional information was collected on prescribed route of iron administration (intravenous, oral, both, or none/unknown), prescribed route of EPO administration (intravenous or subcutaneous), transferrin saturation (TSAT), and serum ferritin concentration. An EPO Resistance Index (ERI) was calculated by dividing the average prescribed weekly EPO dose by the mean hematocrit for every individual within each year. A low ERI can arise from either a lower weekly dose of EPO and/or a higher achieved hematocrit.

Statistical Analyses

For repeated measures, such as the dose of EPO and the hematocrit, the averages of the values for each patient recorded during the 3-mo abstraction period for each year were used for subsequent analysis. Patients with missing demographic, clinical, or laboratory data were excluded. Demographic, clinical, and laboratory parameters were described at baseline for the patient cohorts stratified by year. Categorical and continuous variables were compared among cohorts using the χ² test and t test, respectively. A two-tailed P < 0.01 was considered significant. Scatter plots were drawn to describe the relationship between hematocrit and EPO dose stratified by year. Average EPO dose and hematocrit were calculated for each year and compared across years using ANOVA.

Linear regression was used to estimate the associations between hematocrit and clinical and demographic variables in both univariate and multivariable analyses. The fully adjusted, multivariable linear regression model was built using both forward and backward stepwise elimination methods. Variables tested for significance included case-mix variables (gender, age, race, years on dialysis, and the presence of diabetes mellitus), mean prescribed EPO dose (U/kg predialysis body weight per dose), clinical variables (postdialysis body weight), and laboratory measurements (transferrin saturation, serum ferritin concentration, and predialysis and postdialysis blood-urea nitrogen values to calculate URR). Interactions between EPO dose and variables, such as prescribed route of EPO administration, prescribed route of iron therapy, TSAT, and serum ferritin concentration, were tested in separate models. Entry and elimination criteria were set at a value of P = 0.01. All P values reported are two-sided, and all confidence intervals reported are 95% intervals. All data analyses were performed using SAS version 8.1 (SAS Institute, Inc., Cary, NC).

Results

Temporal Trends in Hematocrit and EPO Dose

The original sample consisted of 7270, 7310, 7292, 7658, and 8838 patients in 1994, 1995, 1996, 1997, and 1998, respectively. The original sample was reduced to the sample of 6181, 6241, 6364, 6634, and 7660 patients in 1994, 1995, 1996, 1997, and 1998, respectively, who had sufficient data on hematocrit and EPO dose for analysis. The descriptive characteristics of each patient cohort are listed in Table 1. There were no significant differences in characteristics among cohorts across years, except for an increase in the percent of patients with diabetes mellitus as the reported cause of ESRD.

Table 1. Baseline demographic characteristicsa

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1994 (n = 6181)</th>
<th>1995 (n = 6241)</th>
<th>1996 (n = 6364)</th>
<th>1997 (n = 6634)</th>
<th>1998 (n = 7660)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59.7 ± 15.5</td>
<td>60.1 ± 15.3</td>
<td>59.9 ± 15.3</td>
<td>60.5 ± 15.3</td>
<td>60.2 ± 15.1</td>
</tr>
<tr>
<td>White (%)</td>
<td>59.6</td>
<td>58.2</td>
<td>58.4</td>
<td>58.4</td>
<td>57</td>
</tr>
<tr>
<td>Male (%)</td>
<td>51.3</td>
<td>51.9</td>
<td>52.4</td>
<td>53</td>
<td>53.4</td>
</tr>
<tr>
<td>Weightb (kg)</td>
<td>71.3 ± 20.1</td>
<td>72.4 ± 18.9</td>
<td>71.7 ± 18.9</td>
<td>72.0 ± 19.3</td>
<td>72.9 ± 19.6</td>
</tr>
<tr>
<td>Diabetes c (%)</td>
<td>34.4</td>
<td>36.2</td>
<td>38.2</td>
<td>39.2</td>
<td>41.3</td>
</tr>
<tr>
<td>URR (%)</td>
<td>63.9 ± 8.4</td>
<td>65.5 ± 8.0</td>
<td>66.9 ± 7.6</td>
<td>68.0 ± 7.5</td>
<td>68.3 ± 7.8</td>
</tr>
<tr>
<td>Years on dialysis</td>
<td>3.4 ± 3.7</td>
<td>3.4 ± 3.8</td>
<td>3.5 ± 3.8</td>
<td>3.4 ± 3.7</td>
<td>3.3 ± 3.7</td>
</tr>
</tbody>
</table>

a Values given are mean ± SD. Diabetes is the % of patients who have diabetes mellitus as the reported cause of end-stage renal disease (ESRD). URR, urea reduction ratio.

b Significant difference across years: P = 0.001.
patients’ weight, and mean URR (P = 0.001). The mean and median hematocrit, prescribed dose of EPO (not adjusted for the prescribed route of administration), and the percentage of patients prescribed subcutaneous EPO has increased for each successive year as reported in Table 2 (P < 0.001). From 1994 to 1998, the median hematocrit increased from 31 to 34% (P = 0.0001), whereas the median EPO dose (including prescribed subcutaneous and intravenous routes of administration) increased from 49 to 54 U/kg from 1994 to 1998 (P = 0.0001). Information on the route of prescribed EPO administration was not collected in 1994 and 1995. During 1996, 1997, and 1998, a minority of hemodialysis patients were prescribed subcutaneous EPO (7.7%, 11.2%, and 11.7%, respectively). Although there was no significant difference in the mean hematocrit by prescribed route of EPO administration, patients prescribed intravenous EPO received significantly higher doses than those prescribed the subcutaneous route of administration (67.6 U/kg versus 59.9 U/kg, respectively) (P = 0.0001).

Interestingly, the proportion of patients reaching the benchmark hematocrit of ≥33% appears to increase with each successive year. In 1994, 35.6% had a hematocrit ≥33%; 42.3% of the patients in 1995, 56.4% in 1996, 62.0% in 1997, and 72.7% in 1998. In parallel, the increment in hematocrit was also associated with a secular increase in prescribed EPO dose. The percent of patients prescribed an EPO dose ≥58.2 U/kg (mean dose of EPO for referent year 1994) was 35.2% in 1994, 39.6% in 1995, 45.8% in 1996, 42.4% in 1997, and 42% in 1998. To further explore this relationship, the ERI was calculated for patients from 1994 to 1998 as aggregate and with patients stratified by quartiles of hematocrit (Table 3). The ERI increased from 1994 to more contemporary years. When examined by hematocrit quartiles within each year, the ERI was significantly higher in the lowest quartile, suggesting that the increase in EPO dose was disproportionate to the commensurate increment in hematocrit.

The frequency distribution of patients categorized by hematocrit is presented in Figure 1. The increase in the percent of patients in the higher hematocrit category was accompanied by a parallel decrease in the patients with more severe anemia. The mean prescribed EPO dose per hematocrit category for each year is shown in Figure 2. The prescribed EPO dose was inversely associated with the hematocrit level, but it tended to reach a plateau at hematocrit values ≥33%. Patients with a hematocrit <28% were prescribed a significantly higher mean EPO dose over the 5-yr period compared with those with a hematocrit ≥28% (79.6 U/kg versus 62.3 U/kg, respectively) (P = 0.001). This finding was consistent within each year. Moreover, the dose of EPO prescribed for each category of hematocrit has increased over the period of observation, especially for patients whose hematocrit was <33%.

### Relationships Between EPO Dose, Hematocrit, and Iron Stores

Toward examining the relationship between increasing annual EPO requirements even among patients within the same category of hematocrit, surrogate markers of iron stores and patterns of iron administration were profiled. Collection of this information began in 1996, in which 8.3% of the patients had TSAT <20% and serum ferritin concentration <100 ng/ml. This proportion was 5.9% and 8.5% for the years 1997 and 1998, respectively. Figure 3 illustrates the frequency distribution of patients with a TSAT <20% stratified by hematocrit. At lower hematocrit categories, the percentage of patients with TSAT <20% increased significantly (P = 0.0001). Those patients who had a TSAT <20% had significantly higher EPO doses (P = 0.0001) and lower hematocrit values (P = 0.0001) (data not shown). Serum ferritin concentrations were not associated with either hematocrit or EPO dose. Intravenous iron was prescribed to 50.5%, 57.2%, and 59.3% of patients in 1996, 1997, and 1998, respectively. There was no significant difference in the proportion of patients receiving intravenous iron among the different hematocrit categories. Of the subset of patients with a TSAT <20%, only 47.7%, 55.3%, and 58.8% were prescribed intravenous iron in 1996, 1997, and 1998, respectively. When intravenous iron-prescribing patterns were examined as a function of TSAT and serum ferritin concentration, patients with a TSAT <20% and ferritin <100 ng/ml were prescribed parenteral iron less often than patients with TSAT ≥20% and ferritin ≥100 ng/ml (P = 0.001). Moreover, the percent of patients prescribed intravenous iron was inversely proportional to the hematocrit. The patients prescribed intravenous iron were also prescribed significantly higher EPO doses (F value, 11.77; P = 0.0006).

Other variables historically associated with hematocrit and/or EPO level (18, 28, 29) were examined for each year of observation. The mean age of patients with hematocrit values

---

### Table 2. Mean and median hematocrit (Hct) and prescribed EPO dose per year

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Hct (%)</td>
<td>31.1 ± 5.2</td>
<td>31.7 ± 3.7</td>
<td>32.6 ± 3.6</td>
<td>32.9 ± 3.2</td>
<td>34.1 ± 3.7</td>
</tr>
<tr>
<td>Median Hct (%)</td>
<td>31</td>
<td>32</td>
<td>33</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>Mean EPO dose (U/kg)</td>
<td>58.2 ± 41.8</td>
<td>61.8 ± 43.7</td>
<td>67.2 ± 45.8</td>
<td>64.22 ± 46.9</td>
<td>68.2 ± 55.0</td>
</tr>
<tr>
<td>Median EPO dose (%)</td>
<td>49</td>
<td>52</td>
<td>58</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Prescribed iv iron (%)</td>
<td>50.5</td>
<td>57.2</td>
<td>59.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribed iv EPO (%)</td>
<td>92.3</td>
<td>88.8</td>
<td>88.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values given are mean ± SD.*

*Significant difference across years: P < 0.001.*

*Significant difference across years: P < 0.0001.*
<28\% was significantly lower ($P = 0.001$) than those in the other hematocrit categories for each year. Female gender was associated with lower hematocrit levels, but higher prescribed EPO doses ($F$ value, 51.98 [$P = 0.0001$] and $F$ value, 343.25 [$P = 0.0001$], respectively). In contrast, there was no significant difference in EPO dose by race, but black patients were more likely to have a modestly lower mean hematocrit than white patients (32.2\% versus 32.6\%, respectively; $P < 0.001$).
scribed EPO doses \((P = 0.0001)\) (Table 5). Prescription of intravenous iron was associated with higher doses of EPO. Race was not a significant predictor for either hematocrit or EPO dose.

To further explore the relationship between hematocrit and prescribed EPO doses, multivariable analyses were performed using quartiles of hematocrit rather than treating hematocrit as a continuous variable. Quartiles of hematocrit were determined for each sample year, rather than for all the years in aggregate. This approach was chosen because processes of care have been modified over years of observation and to prevent over-representation of patients with lower hematocrit values from earlier years. The associations described above remained unchanged; only the lowest 2 quartiles of hematocrit were significantly associated with increasing doses of EPO \((P = 0.0001)\) (data not shown).

To maximize the cohort years included, the predictors of hematocrit and EPO were reexamined in separate models by using linear regression in a model excluding prescribed routes of iron and EPO administration. Seventy-six percent of the patients (27,540 of 36,066) had adequate data for inclusion. The direction of the significant parameter estimates for predictors of hematocrit were unchanged, and the F values were not substantially different \((P = 0.0001)\) (data not shown). Similarly, in a model with EPO dose as the dependent variable, the direction of the significant parameter estimates were unchanged and the F values were not substantially different \((P = 0.0001)\) (data not shown). However, the years on dialysis were positively associated with EPO dose, although the F value was small \((F value, 8.61; P = 0.003)\) (data not shown). Diabetes mellitus as the cause of ESRD was not found to be significant in the model without iron and EPO administration. Race was not a significant predictor for either hematocrit or EPO dose.

**Discussion**

Because of the association between hematocrit and the morbidity and mortality of ESRD patients (29,30), there have been a series of structured quality improvement programs to increase the hematocrit in hemodialysis patients (4,18). The most recent and comprehensive compilation of these recommendations is the Kidney Dialysis Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation, Inc. The KDOQI Guidelines recommend a minimum hematocrit of 33%, TSAT of \(\geq 20\%\), serum ferritin concentration of \(\geq 100\) ng/dl, and that supplemental iron be administered intravenously (4). Moreover, because of favorable pharmacokinetics and possibly diminished dose and costs (23,31), it has been suggested that EPO be administered subcutaneously, rather than intravenously. The implementation of these recommendations was greatly strengthened by the conversion of the original DOQI anemia clinical practice guideline recommendations into clinical performance measures by CMS (32). As observed in numerous other large data sets, the hematocrit of prevalent hemodialysis patients has risen in the United States, so that the mean hematocrit is now within the recommended range.

**Table 4.** Full linear regression model for predictors of hematocrita

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th>(P)</th>
<th>F value</th>
<th>Type III SSQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin dose (U/kg)</td>
<td>-0.01367</td>
<td>&lt;0.0001</td>
<td>536.64</td>
<td></td>
</tr>
<tr>
<td>URR (%)</td>
<td>5.7295</td>
<td>&lt;0.0001</td>
<td>199.56</td>
<td></td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>0.0206</td>
<td>&lt;0.0001</td>
<td>99.52</td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td>-0.0006</td>
<td>&lt;0.0001</td>
<td>74.87</td>
<td></td>
</tr>
<tr>
<td>Intravenous iron therapy</td>
<td>0.4710</td>
<td>&lt;0.0001</td>
<td>71.06</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.0141</td>
<td>&lt;0.0001</td>
<td>53.30</td>
<td></td>
</tr>
<tr>
<td>Years on hemodialysis</td>
<td>0.0448</td>
<td>&lt;0.0001</td>
<td>31.70</td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.2851</td>
<td>&lt;0.0001</td>
<td>23.23</td>
<td></td>
</tr>
</tbody>
</table>

a Factors entered into the model but found to be insignificant included race, route of EPO administration, cause of ESRD, and weight. TSAT, transferrin saturation.

**Table 5.** Full linear regression model for predictors of EPO dosea

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th>(P)</th>
<th>F value</th>
<th>Type III SSQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>-2.5610</td>
<td>&lt;0.0001</td>
<td>536.64</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-0.6554</td>
<td>&lt;0.0001</td>
<td>927.62</td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>-6.3516</td>
<td>&lt;0.0001</td>
<td>61.72</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>-0.1882</td>
<td>&lt;0.0001</td>
<td>50.80</td>
<td></td>
</tr>
<tr>
<td>TSAT %</td>
<td>-0.1901</td>
<td>&lt;0.0001</td>
<td>45.00</td>
<td></td>
</tr>
<tr>
<td>URR %</td>
<td>-36.9342</td>
<td>&lt;0.0001</td>
<td>43.81</td>
<td></td>
</tr>
<tr>
<td>Intravenous iron therapy</td>
<td>5.0614</td>
<td>&lt;0.0001</td>
<td>43.74</td>
<td></td>
</tr>
<tr>
<td>Intravenous EPO</td>
<td>6.9300</td>
<td>&lt;0.0001</td>
<td>29.61</td>
<td></td>
</tr>
<tr>
<td>Cause of ESRD diabetes</td>
<td>-2.4013</td>
<td>0.003</td>
<td>8.73</td>
<td></td>
</tr>
</tbody>
</table>

a Factors entered into the model but found to be NS included race, ferritin, and duration of dialysis.
This increment has been accomplished by a rightward shift in the frequency distribution of hematocrit values, rather than an increase in hematocrit for a segment of the population. Also, as reported from other data sets, we observed that the overall prescribing of iron and its parenteral administration has increased. Because of the ability of parenteral iron to enhance the erythropoietic response to EPO (33,34), we posited that EPO doses would have stabilized or perhaps decreased over this interval. Lastly, although still a minority practice pattern, the percent of patients prescribed EPO subcutaneously has increased. Because of the favorable pharmacokinetics and dosage reductions achieved in several intervention trials, we posited that this trend would also contribute to stabilization or reduction in EPO doses nationally.

However, the increased hematocrit has occurred in parallel with an increase in EPO dose. The increase in mean EPO dose seems to be driven by the patients with lower Hct values as supported by the EPO Resistance Index and the multivariate analyses by quartiles. An interpretation of these findings is that neither iron nor EPO prescription patterns have been optimized adequately to balance the needed increase in EPO to achieve higher hematocrit values. The inverse relationship between the percent of patients with a TSAT <20% and the hematocrit supports this conjecture. An alternative and not exclusive interpretation is that patients who are relatively EPO-sensitive were the ones who first achieved higher hematocrit values. A greater percentage of the relatively EPO-resistant subpopulation has been provoked to higher hematocrit values each year, resulting in a secular increase in EPO dose, too. In other words, as greater numbers of patients are treated to higher hematocrit values, the heterogeneity of the population’s response to EPO is manifest by higher doses each year. This contention is supported by the demonstration of the inverse relationship between EPO dose and hematocrit. The cause of the heterogeneity on EPO responsiveness is unclear and may be a consequence of other comorbid conditions like overt or covert inflammatory processes (35–37), hyperparathyroidism (38), trace mineral toxicity such as aluminum (39,40), protein-calorie and malnutrition (41), and inadequate hemodialysis (29,42).

The current data set does not permit an examination of all of these relationships. However, the full multivariable analysis illustrates several anticipated and unanticipated hypothesis-generating findings. Because the hematocrit is a clinical end-point that depends on EPO administration as a process of care, a separate analysis was performed of measures associated with EPO dose. Other models evaluating factors predicting EPO dose and hematocrit have included albumin (18,29). We deliberately excluded albumin in our model as low serum albumin has a strong and consistent association with higher EPO doses. Such a notable impact may mask more subtle relationships of interests. Patient-specific variables, such as age, weight, gender, and race (only in the model for hematocrit), were associated with hematocrit and EPO dose. Some of the demographic differences may be reflective of disparities in frequency of drug dosing secondary to patient adherence to their dialysis treatment schedule, because the dialysis unit is the venue where EPO is administered. For example, younger patients miss dialysis more often than older patients (43) and would therefore be prone to miss their EPO doses more frequently. The association of increased years on dialysis (vintage) with higher hematocrit values has been observed by other investigators using different data sets (44,45). This relationship may be a consequence of patient-specific variables, such as better compliance and subsequent fewer missed EPO injections, and/or survival bias giving rise to a patient subgroup with fewer EPO-resistant comorbid conditions. Patient weight is a surprising finding in view of the adjustment for EPO dose by weight and may reflect an interaction between patients’ nutritional state and EPO responsiveness (41). Care processes, such as prescribed EPO dose, the prescribed route of EPO and iron administration, and laboratory surrogates of marrow iron stores, demonstrated associations in the anticipated manner. The finding of reproducibly lower TSAT for those patients with the lowest hematocrit continues to identify a group for whom care processes may be enhanced. Moreover, the availability of non-dextran iron preparations in the United States that have lower occurrence of major side effects should facilitate improving parenteral iron management further (46). Small solute clearance from a single hemodialysis session was quantified by the URR. The current analysis confirms previous reports describing a statistical association between hemodialysis dose, hematocrit, and EPO dose (29,42,47). These relationships may reflect direct or indirect benefits of better solute clearance, such as enhanced removal of putative soluble erythropoietic inhibitors (48,49) and/or improved nutrition and substrate availability for erythropoiesis (41,42). Alternatively, improved anemia correction with increased dialysis doses may be reflective of diligence to other components of patient care that could improve EPO responsiveness, diminish blood losses, and/or enhance erythrocyte survival. For example, patients receiving higher hemodialysis doses may also be more prone to being treated with high-flux, biocompatible dialyzers (50), less likely to use catheters for vascular access (so more reliable blood flow rates, lower thrombosis rates, fewer systemic infections) (51,52), or be aggressively monitored and treated for hyperparathyroidism (38).

The external validity of these findings is high because of the national sampling strategy and the large number of subjects. However, this analysis shares the usual limitations associated with observational analyses, including indication bias that is likely for some elements, such as the administration of parenteral iron and subcutaneous EPO. Similarly, some relationships are likely reflective of care processes that are not within the control of the providers; the inverse relationship between EPO dose and hematocrit may be driven by reimbursement constraints as well as biologic variability. The 3-mo study period may not capture iron use in some patients dosed less frequently or just before the collection period. Nor do the Core Indicators/Clinical Performance Measures data sets collect information on the timing of intravenous iron administration with respect to the measurement of transferrin saturations. Moreover, the absence of administered dosing of iron makes the interpretation of parenteral iron influence more difficult.

On the basis of the findings herein, hematocrit values have increased at the expense of greater EPO doses. Although a minority of the apparently EPO-resistant patients identified were iron deficient, which may attenuate their response to EPO, most patients with higher hematocrit values and pre-
scribed EPO doses were not iron deficient. Population-based differences in EPO dose-response seem to drive the increment in EPO as the achieved hematocrit rises among the hemodialysis population. Using these data, we posit that to achieve still higher hematocrit values, as has been advocated by some (53–56), disproportionately greater EPO dose is likely, unless alternative routes of administration are used (23,31) or different patterns of iron administration are demonstrated to be safe, effective, and can be implemented (33,34). Alternatively, understanding more about how other factors not collected in this data set may influence hematocrit and EPO response, such as markers for inflammation, hyperparathyroidism, trace mineral toxicity, and protein-calorie malnutrition, may offer other interventions to achieve target hematocrit values without a concomitant increase in EPO dose.

Acknowledgments
Dr. Coladonato is partially supported by a National Research Service Award T32 HS0079–03 from the Agency for Healthcare Research and Quality. Dr. Szczes’s work is supported by grant DK02724–01A1 from the National Institutes of Health.

References
2. Health Care Financing Administration: Medicare program: Coverage of epoetin (EPO) used by competent home dialysis patients. 42 CFR Parts 405, 410, 413, and 414. 1-10-1994. BPD-737-F; RIN 0938-AF54 (Generic)
15. Fresenius Medical Care, US 1999 Annual Report-Medical Directors’ Summary. Lexington, MA, Fresenius Medical Care, 1999
27. Health Care Financing Administration: ESRD Core Indicators Project Special Report #A: Results of Validation Study: Comparison of Data Abstracted by ESRD Facility Staff and by ESRD Network Staff. Baltimore, MD, Department of Health and Human Services, Health Care Financing Administration, Office of Clinical Standards and Quality, 1997
28. Health Care Financing Administration: ESRD Core Indicators Project Special Report #A: Results of Validation Study: Comparison of Data Abstracted by ESRD Facility Staff and by ESRD Network Staff. Baltimore, MD, Department of Health and Human Services, Health Care Financing Administration, Office of Clinical Standards and Quality, 1997


