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Erythropoiesis-Stimulating Agent Use Among Non-Dialysis-Dependent CKD Patients Before and After the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) Using a Large US Health Plan Database

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Abstract

Background—In a landmark study, the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) examined use of erythropoiesis-stimulating agent (ESA) therapy to treat anemia among chronic kidney disease (CKD) patients and found no benefit compared to placebo.

Study Design—A retrospective observational design was used to determine the impact of TREAT on clinical practice.

Setting & Participants—A large US health plan database with over 1.2 million claims for patients with non-dialysis-dependent CKD stages 3 and 4.

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Factor—ESA prescribing two years before and after publication of TREAT.

Outcomes—Rate of ESA prescribing for ESA-naïve and -prevalent cohorts.

Measurements—1) monthly ESA prescribing in the two years before and after publication of TREAT (ordinary least squares regression); 2) adjusted likelihood of prescribing ESA after TREAT (clustered logistic regression); and 3) probability of receiving ESA therapy based on anemia status (chi-square test).

Results—For patients with CKD stage 3, the proportion prescribed ESA therapy declined from 17% pre-TREAT to 11% post-TREAT (a 38% decline), and for those with CKD stage 4, from 34% to 27% (a 22% decline). Prescribing of ESA therapy was declining even before TREAT, but the decline accelerated in the post-TREAT period (stage 3: change of slope, -0.08 [$P < 0.001$]; stage 4: change of slope, -0.16 [$P < 0.001$]). ESA prescribing declined after TREAT regardless of anemia status; among patients with hemoglobin < 10 g/dL, only 25% of CKD stage 3 and 33% of stage 4 patients were prescribed ESAs two years after TREAT, a notable 50% decline. After adjusting for all covariates, the probability of prescribing ESAs was 35% lower during a two year period after vs. before publication of TREAT (OR, 0.65; 95% CI, 0.63-0.67).

Limitations—The cumulative effect of adverse safety concerns in the period before TREAT also influenced physician prescribing of ESA therapy and could not be separated from the influence of TREAT.

Conclusions—TREAT appears to be a watershed study that was followed by a marked decline in ESA prescribing for CKD patients.

Keywords

erythropoietin-stimulating agent (ESA); epoetin (EPO); darbepoetin; predialysis chronic kidney disease (CKD); TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy); hemoglobin; anemia; prescribing patterns; Choose Wisely campaign; Thomson Reuters; MarketScan

Erythropoiesis-stimulating agents (ESAs), such as epoetin alfa (erythropoietin [EPO]), were first approved by the US Food and Drug Administration (FDA) in June 1989 to treat the anemia associated with kidney disease. However, not until October 2009 was the first placebo controlled ESA trial in CKD patients with hard outcomes published. The Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) examined the effect of correcting the anemia of chronic kidney disease (CKD) with darbepoetin in patients with diabetes mellitus.¹ It found that treatment with darbepoetin was not beneficial in reducing mortality or in attenuating cardiovascular or renal events, but resulted in a twofold higher rate of stroke and thromboembolic complications and a higher rate of cancer deaths among patients with a history of cancer, suggesting that the placebo arm (rescue when hemoglobin is below 9 g/dL) should be considered as the preferred management strategy for non-dialysis-dependent CKD patients, although this strategy may require higher levels of blood transfusions.^{2,3} After publication of the TREAT results, the FDA revised its ESA labeling and clinical guidelines⁴ in June 2011 and, in the widely publicized Choose Wisely campaign⁵ (disseminated in April 2012), use of the lowest ESA dose to reduce the need for blood transfusions was recommended. To determine the impact of the TREAT results, we

undertook a study using a large US health plan claims database to describe ESA prescribing before and after publication of TREAT.

Methods

Data Source

This analysis was based on retrospective administrative data from the Thomson Reuters MarketScan Commercial Claims and Encounters Database and Medicare Supplemental Database, which represent the healthcare experiences of over 20 million individuals annually who obtain healthcare insurance from large private employers or from government-funded Medicare healthcare insurance plans. Health care in the MarketScan database is provided under a variety of fee-for-service, fully capitated, and partially capitated health plans (including preferred provider organizations, point of service plans, indemnity plans and health maintenance organizations) and is one of the largest collections of patient data in the United States. The elderly are also well represented through the inclusion of groups covered by Medicare. Enrollment records provide health plan enrollees' demographics including age, gender, region of residence, and health insurance plan characteristics. MarketScan databases also provide detailed cost, use, and outcomes data for healthcare services performed in both inpatient and outpatient settings. The inpatient and outpatient medical claims are linked to outpatient prescription drug claims and person-level enrollment data through the use of unique encrypted beneficiary identifiers. MarketScan databases have been used in a number of diverse health research studies. MarketScan research databases meet or exceed requirements of the US Health Insurance Portability and Accountability Act (HIPPA) of 1996. Detailed data description can be found at marketscan.truvenhealth.com/marketscanportal/.

Study Sample

We used the most recent MarketScan data, 2007 through 2011, to identify CKD stages 3 and 4 claims for this study. CKD diagnosis claims were the unit of analysis and were identified as follows. All CKD stage 3 (ICD-9 diagnosis code 585.3) and 4 (ICD-9 diagnosis code 585.4) claims identified from November 2007 through October 2011 (two years before and after TREAT study published in October 2009) were eligible for inclusion. All claims were required to have at least 6 months of previous enrollment coverage for purposes of baseline information, and 3 months post enrollment coverage to examine prescription of ESA therapy. To insure confirmation of a definitive CKD diagnosis (rather than a rule-out diagnosis), we also required that each identified claim had at least one CKD diagnosis code within the previous 6 months. In our analysis of ESA therapy by anemia status, we used laboratory results for hemoglobin (Hb) or hematocrit (Hct) values from a sample of the MarketScan data (5% of all claims). All laboratory results had at least one CKD stage 3 or 4 code in the previous 6 months and we allowed for 3 months after a laboratory test to ascertain any ESA prescribing. For a laboratory result with missing Hb values but for whom Hct data were available, Hct levels were converted to Hb levels by dividing by 3. Hb levels were assessed in two categories: indicating anemia (< 10 g/dL) or non-anemia (≥ 10 g/dL).

ESA Administration

We defined ESA therapy by the receipt of darbepoetin alfa or epoetin alfa. For each eligible CKD claim, we extracted ESA claims data (medical encounters and pharmacy) in the three months following a CKD diagnosis by using Healthcare Common Procedure Coding System (HCPCS) codes for the outpatient setting and National Drug Code (NDC) numbers for outpatient pharmacy claims (see Item S1, available as online supplementary material, for complete list of HCPCS and NDC codes). We restricted our analysis to the outpatient setting because ESA therapy is usually administered during a patient's outpatient visit via subcutaneous injection and cannot be determined in the inpatient setting as it is usually bundled with other inpatient treatments.

The study CKD claims were disaggregated by ESA prevalent and ESA-naïve claims as follows. ESA-naïve CKD claims were those without any evidence of ESA use in the prior 6 months, and ESA-prevalent CKD claims were those with evidence of ESA prescribing in the prior 6 months. We conducted analyses of both ESA-prevalent and -naïve claims for each calendar month in the 2-year pre- and post-TREAT period. Recipient of a red blood cell transfusion in either the inpatient or outpatient setting was identified using Clinical Procedural Terminology (CPT) 4 code, HCPCS code, or ICD-9-CM procedure codes (Item S1).

Statistical Analysis

Patient characteristics were measured during the 6-month period prior to each study claim and compared by two-year pre and post TREAT study periods separately for CKD stages 3 and 4 diagnosis. Data on patient demographics included sex (male, female), age (<65, 65 yrs), insurance status (commercial, Medicare), region of residence (Northeast, North Central, South, and West), Charlson Comorbidity Index⁶ (0, 1-3, and >3), and involvement of a nephrologist (one or more visits in the previous 6 months). Presence of comorbid conditions, based on ICD-9 codes in claims data, including diabetes, ischemic heart disease, congestive heart failure, cancer and hypertension, was also examined. Receipt of ESA therapy in the 3 months after each study claim was analyzed by pre and post-TREAT period and by CKD stage using chi-square tests.

For each month, we determined if a study claim was associated with ESA use and/or a blood transfusion as follows. To assess the monthly rate of usage of ESA and blood transfusion in the 2 years before and after TREAT, availability of 1 or more days' supply of ESA (or receipt of 1 or more blood units) within a given month were considered ESA or blood transfusion users in that month (entered in the numerator). A trend evaluation was performed by using ordinary linear regression analysis and the slopes in each of the two periods (pre- versus post-TREAT) by CKD stage for all CKD claims, ESA prevalent CKD claims, and ESA-naïve CKD claims separately using ordinary least-squares regression. The ESA prescribing based on anemia status during pre- and post-TREAT periods was analyzed and compared by chi-square tests. A clustered logistic regression model using the GEE methodology (to account for repeated measurement from the same patient) was used to identify the predictors of ESA use adjusting for variables influencing ESA prescribing. These variables included age, sex, insurance status, region of residence, Charlson

Comorbidity Index, involvement of nephrologist, presence of comorbid conditions, and CKD stage. An indicator for the post-TREAT period was also included. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, N.C.) with a two-sided α of 0.05 for statistical significance.

Results

We identified a total of 350,955 CKD stage 3 and 193,377 CKD stage 4 claims in the two years before publication of TREAT and 450,330 CKD stage 3 and 230,519 CKD stage 4 claims in the two years after publication of TREAT that met the study selection criteria. The number of claims for individual patients in the two-year study period pre- and post-TREAT was similar (means of 3.3 and 4.5 claims for patients with CKD stage 3 and stage 4, respectively). Baseline patient characteristics were relatively unchanged in the two years before and after TREAT publication with some exceptions (Table 1). Compared to pre-TREAT cohorts, patients in the post-TREAT period tended to be somewhat younger and were more likely to have seen a nephrologist in the previous six months.

Compared to the two-year period before TREAT, there was a significant decrease in ESA prescribing in the two-year period after TREAT for both CKD cohorts (stages 3 and 4) and for all covariate strata (Table 2; $P < 0.001$). For CKD stage 3, the proportion prescribed ESA therapy declined from 17% pre-TREAT to 11% post-TREAT (a 38% decline) and for CKD stage 4, from 34% to 27% (a 22% decline; $P < 0.001$).

Monthly ESA prescribing in the two years before and after publication of TREAT trial are shown in Figure 1 separately for CKD stages 3 and 4. The rate of prescribing ESA therapy was changing among both CKD stages 3 and 4 before publication of TREAT. The slope shown in Figure 1 represents the rate of change in ESA prescribing between the pre- and post-TREAT periods. While the likelihood of prescribing ESA therapy overall was declining in the pre-TREAT period, the decline accelerated in the post-TREAT period (change in slope for CKD stage 3 and 4, respectively, of -0.08 [$P < 0.001$] and -0.16 [$P < 0.001$]).

We analyzed separately the likelihood of prescribing ESA therapy among ESA-prevalent CKD claims (among those currently receiving ESA therapy), and ESA-naïve CKD claims (those without evidence of ESA therapy in the previous six months) and in both cases, there was a significant decline in ESA prescribing in the post-TREAT period. Among ESA prevalent patients, ESA is more likely to be continued to be prescribed during the pre-TREAT period, but is less likely to be continued to be prescribed in the post-TREAT period (change in slope for CKD stage 3 and 4, respectively of -0.37 [$P < 0.001$] and -0.08 [$P < 0.001$]). In contrast, among ESA naïve patients, the likelihood of prescribing ESA therapy was decreasing in the pre-TREAT period, and continued to decline, albeit less so post-TREAT (change in slope for CKD stage 3 and 4, respectively, of $+0.03$ [$P < 0.001$] and $+0.09$ [$P < 0.002$]). Notably, the proportion of CKD claims that were ESA naïve increased among both CKD stage-3 and stage-4 cohorts in the two years post-TREAT, suggesting that fewer patients were prescribed ESA therapy after TREAT. Although ESA prescribing declined in the two year period after TREAT, use of blood transfusions remained stable throughout the study period ($P = 0.3$ and $P = 0.7$ for change in slope for CKD stages 3 and 4,

respectively). Specifically, the proportion of the CKD cohort receiving blood transfusions across the four year study period was 1.6% and 2.8% for CKD stages 3 and 4, respectively.

Laboratory data from MarketScan was available for 5% of all CKD stage-3 and stage-4 claims used in this study. We examined the likelihood of prescribing ESA therapy within 3 months after a hemoglobin laboratory result. A dramatic decline in ESA prescribing for anemic patients post-TREAT is shown (57% were prescribed ESA therapy pre-TREAT compared with 25% two years post-TREAT for patients with CKD stage 3, and 66% compared with 33% for patients with CKD stage 4 ; $P<0.001$) (Figure 2). Furthermore, in the two years after TREAT, few patients with hemoglobin ≥ 10 g/dL were prescribed ESA therapy (7% and 16% of patients with CKD stages 3 and 4 patients, respectively, compared to double that number before TREAT; $P<0.001$).

Adjusting for all covariates, including CKD stage, the probability of prescribing ESA therapy among non-dialysis-dependent CKD patients was 35% less in the two-year post-TREAT vs. pre-TREAT period (adjusted odds ratio [OR], 0.65; 95% confidence interval [CI], 0.63-0.67) (Figure 3). The following ORs are adjusted for all characteristics in Table 1. Characteristics associated with increased likelihood of ESA prescribing included CKD stage 4 (vs. stage 3: OR, 2.59; 95% CI, 2.52-2.67), female sex (OR, 1.51; 95% CI, 1.46-1.57), aged 65 years or older (vs. <65 years: OR, 1.24; 95% CI, 1.07-1.44), cancer as a comorbid condition (OR, 1.42; 95% CI, 1.35-1.49), higher Charlson Comorbidity Index (3 vs. 0: OR, 1.32; 95% CI, 1.26-1.40), and diabetes as a comorbid condition (OR, 1.16; 95% CI, 1.12-1.20). Involvement of a nephrologist was associated with an 18% less likelihood of being prescribed ESA therapy (OR, 0.82; 95% CI, 0.80-0.85).

We conducted numerous secondary and sensitivity analyses to ensure the robustness and validity of our findings. In a secondary analysis among the smaller cohort of CKD patients with hemoglobin measurements, we repeated the analysis in Figure 3 and found that *after adjusting for hemoglobin*, as expected, differences in ESA prescribing are attenuated based on gender, age, cancer, and CKD stage; however, the decreased likelihood of prescribing after TREAT remains significant. Furthermore, given that 87% of all claims used in our analyses are outpatient office visits (the remaining 13% were hospital visits), we conducted a sensitivity analysis using only outpatient office visits and report that the results are similar to the results reported above using all health care encounters. Given that autocorrelation can occur if multiple claims for the same patient are included in the trend analyses, we conducted a sensitivity analysis (using AUTOREG procedure in SAS) to evaluate the extent to which *autocorrelation* existed during the study period. The resultant Durbin Watson statistics were 1.35 (CKD stage 3: $P=0.04$) and 1.75 (CKD stage 4: $P=0.1$) suggesting autocorrelation correction is not a primary concern. We also checked for second- to twelfth-order autocorrelation and all were nonsignificant.

Discussion

To our knowledge, this is the first study to document anemia management practice patterns before and after a watershed study.⁷⁻⁹ The TREAT authors concluded that the risk of using ESA in CKD patients with moderate anemia who were not receiving dialysis “will outweigh

the potential benefits.” Our study suggests that publication of TREAT was followed by a marked decline in use of ESAs. In contrast, the use of blood transfusions did not change significantly before and after TREAT. The current study extends the only previously documented use of ESAs among non-dialysis-dependent CKD patients, which showed a steady decline between 2005 and 2009, prior to the publication of TREAT.¹⁰ Before TREAT, safety concerns regarding ESA therapy among the CKD population were raised by the CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) and CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta) studies published in November 2006,^{11,12} resulting in a number of regulatory and reimbursement measures to restrict ESA use including an FDA black box warning issued in March 2007. The decline in ESA prescribing in our study in the two years prior to the October 2009 publication of TREAT likely resulted from those factors and accelerated after publication of TREAT. Among the ESA prevalent population, a marked decline in ESA use can be seen after June 2011. At that time, safety concerns and TREAT findings prompted the FDA to remove the erstwhile hematocrit target range of 30%-36% and advise physicians to “reduce or interrupt the dose” of epoetin if hematocrit exceeds 33%.

Previous publications have shown that changes in physicians' practice after the publication of clinical trial findings are limited.^{13,14,15,16,17} Heuristic models indicate that 3 categories of factors are relevant concerning changes in physician behavior: *predisposing factors*, communicating or disseminating information; *enabling factors*, facilitating the desired change in the practice site; and *reinforcing factors*, by reminders or feedback.¹⁸ They suggest that interventions that use enabling strategies or reinforcing methods in addition to predisposing or disseminating strategies are most successful. Most likely, TREAT created a tipping point in terms of physician caution with ESA prescribing given the confluence of the earlier randomized trials suggesting harm with ESA therapy and accompanying changes in regulatory and clinical guidelines.

Our finding that cancer patients were 42% more likely to receive ESA therapy compared to noncancer patients both before and after TREAT was troubling, although it is well documented that cancer patients have more severe anemia.^{19,20} The risk of *extra* harm was highlighted in TREAT since CKD patients with a history of cancer taking ESA had a statistically significant increased risk of cancer-related death compared to those not receiving therapy.¹ In our study, we found that in the two year period after TREAT, 17% of stage 3 and 30% of stage 4 CKD patients with a history of cancer received ESA therapy—above the population averages of 11% and 27%, respectively—despite stringent restrictions on ESA use among cancer patients.²¹ These findings regarding cancer also help explain the result that seeing a nephrologist was associated with a decreased likelihood of being prescribed ESA therapy; studies have shown that oncologists and hematologists are more likely than any physician specialist to prescribe ESAs in the outpatient setting.^{22,23} Another explanation for the high use of ESA in cancer patients is the use of CKD diagnoses by oncologists to justify use of ESA. When the Centers for Medicare & Medicaid Services changed the reimbursement for ESA in cancer patients in 2007, oncologists had a marked increase in prescribing ESA under the CKD diagnoses, and marked decrease in using their previously acceptable cancer diagnoses.

A number of study limitations are noteworthy. Foremost, this is a retrospective, observational study with the limitations of such a study design; notably that all conclusions observed are associational and not causal. Second, the cumulative effect of adverse safety concerns in the period before TREAT also clearly influenced physician prescribing of ESA therapy. This study did not attempt to separately measure the effects of each event. Third, as with any source of data, claims data have limitations stemming from the nature of administrative claims for payment purposes, as well as convenience samples as opposed to random samples of the population. However, we used one of the largest US collections of patient data, which includes nearly 20 million individuals annually, 77 large employers, and more than 100 health plans. Fourth, while we used a CKD claim as the basis for analysis, and to the extent that a patient would be prescribed ESA therapy without an accompanying CKD claim in the prior 6 months, ESA prescribing is conservative. However, any such bias would be expected to be randomly distributed throughout the study period. Fifth, although we were limited to a 5% sample of all CKD claims with laboratory data, ~10% and 20% of all laboratory tests indicated anemia for patients with CKD stages 3 and 4, respectively, across the study period (small table in Figure 2), suggesting the data was stable over time. Lastly, since this study was based on administrative data, actual ESA utilization (in contrast to prescription) cannot be definitely ascertained.

Several clinical trials have raised important safety concerns regarding ESA therapy among the CKD population. The most recent study, TREAT, appears to have accelerated the previous decline in physician prescribing of ESAs among patients with CKD stages 3 and 4. Physicians were 35% less likely to prescribe ESA therapy in the two years after publication of TREAT compared to before. In conclusion, TREAT appears to be a watershed study that influenced FDA guidelines and physician prescribing for ESA therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Prescribing of ESA therapy by month in a two year period before and after publication of TREAT in October 2009 in CKD stage (A) 3 and (B) 4 patients. ESA naïve CKD claims are those without any ESA therapy in prior 6 months. ESA prevalent claims CKD are those with evidence of ESA therapy use in prior 6 months. ESA total CKD claims are all ESA prevalent and naïve claims. Triangles, squares and diamonds represent actual values, solid lines represent predicted values based on a linear regression model.

Number of Laboratory Tests

Anemia Status	CKD Stage 3				CKD Stage 4			
	Year 1	Year 2	Year 3	Year 4	Year 1	Year 2	Year 3	Year 4
Hgb < 10	313	1,003	1,226	1,469	394	993	1,243	1,352
Hgb ≥ 10	3,166	8,189	9,800	12,611	1,822	4,188	4,728	5,440

Figure 2.

Prescribing of ESA therapy in CKD stage (A) 3 and (B) 4 patients within three months of a laboratory value in the two years pre and post TREAT publication. Data are restricted to the study population with available laboratory data and are presented by anemia status: hgb < 10 g/dL indicates anemia; and hgb ≥ 10 g/dL indicates nonanemia.

Figure 3.
 Probability of prescribing ESA therapy from November 1, 2007 through October 2011
 based on pre vs. post TREAT period, by patient sociodemographic and clinical predictors.
 All variables in Table 1 are included in the model; only selected predictors are shown.

Table 1

Characteristics of Non-dialysis-dependent MarketScan Study Cohort, by CKD Stage.

Characteristic	CKD Stage 3		CKD Stage 4	
	Pre-TREAT*	Post-TREAT**	Pre-TREAT*	Post-TREAT**
Total no. of CKD claims	350,955	450,330	193,377	230,519
Average claims/patient	3.2 ± 3.4	3.3 ± 3.3	4.4 ± 4.8	4.5 ± 4.8
Age category				
< 65 y	42.8	45.1	40.1	41.6
65 y	57.2	54.9	59.9	58.4
Sex				
Male	56.2	56.4	54.2	55.9
Female	43.8	43.6	45.9	44.1
Insurance type				
Commercial	41.7	44.0	38.8	40.4
Medicare	58.3	56.0	61.3	59.6
Region of residence ^				
Northeast	13.8	16.0	14.6	18.2
North Central	32.2	28.4	35.4	31.4
South	38.8	36.4	35.0	32.5
West	14.3	17.6	13.8	16.1
Charlson Comorbidity Index score				
0	23.2	22.9	19.8	19.2
1-3	49.3	48.2	50.2	48.5
> 3	27.5	29.0	30.0	32.3
Comorbid condition				
Diabetes	45.2	43.8	48.1	47.6
Ischemic heart disease	29.0	26.4	31.5	29.7
Congestive heart failure	20.8	19.7	28.4	28.4
Cancer	13.4	13.4	13.1	12.9
Hypertension	57.0	55.3	59.6	58.3
Involvement of nephrologist	59.5	64.4	61.8	66.6

Note: Analysis based on total patient CKD claims. Unless otherwise indicated, values for categorical variables are given as percentage of cohort; values for continuous variables, as mean ± standard deviation. All p-values are significant (< 0.001) and compare the pre-TREAT vs. post-TREAT period difference in overall patient characteristics.

CKD, chronic kidney disease; TREAT, Trial to Reduce Cardiovascular Events With Aranesp Therapy.

^ Region has ~2% missing values.

* Nov 2007 through Oct 2009.

** Nov 2009 through Oct 2011.

Table 2
Prescribing of ESA Therapy based on Patient Characteristics

Characteristic	CKD Stage 3		CKD Stage 4	
	Pre-TREAT*	Post-TREAT**	Pre-TREAT*	Post-TREAT**
Total no. of CKD claims	350,955	450,330	193,377	230,519
All	17.1	10.6	34.3	26.6
Age category				
< 65 y	12.7	7.6	29.6	22.9
65 y	20.7	14.0	36.0	28.1
Sex				
Male	14.3	9.4	30.3	23.3
Female	21.0	13.4	37.1	29.3
Insurance type				
Commercial	12.5	7.6	29.6	22.8
Medicare	20.6	13.9	35.9	28.1
Region of residence				
Northeast	20.8	13.6	37.4	29.3
North Central	18.3	10.8	33.9	25.7
South	16.1	11.2	32.1	25.7
West	14.6	9.6	32.1	23.4
Charlson Comorbidity Index score				
0	11.3	7.1	29.3	22.1
1-3	17.1	10.6	34.3	26.6
> 3	22.5	15.2	34.8	27.2
Comorbid condition				
Diabetes	15.5	10.2	31.4	24.7
Ischemic heart disease	18.6	13.1	32.5	26.1
Congestive heart failure	20.4	14.3	32.1	26.1
Cancer	25.9	17.4	39.1	29.6
Hypertension	16.4	10.9	33.1	25.9
Involvement of nephrologist	15.1	9.7	32.6	25.5

Note: Unless otherwise indicated, values for are given as percentage *prescribed ESA therapy*. Prescribing of ESA therapy is observed within three months of a CKD claim. All p-values are significant (< 0.001) and compare the pre-TREAT versus post-TREAT period difference in receipt of ESA therapy for each patient characteristic strata.

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; TREAT, Trial to Reduce Cardiovascular Events With Aranesp Therapy.

* Nov 2007 through Oct 2009.

** Nov 2009 through Oct 2011.