RESEARCH

Clinical and Economic Outcomes in Medicare Beneficiaries with Stage 3 or Stage 4 Chronic Kidney Disease and Anemia: The Role of Intravenous Iron Therapy

Tyler G. Knight, MS; Kellie Ryan, MPH; Caroline P. Schaefer, MBA; Lynell D'Sylva, BSN, RN; and Emily D. Durden, PhD

ABSTRACT

BACKGROUND: Anemia in patients with chronic kidney disease (CKD) is associated with increased morbidity and mortality, decreased quality of life, and substantial health care costs. Iron therapy is recommended, usually in combination with an erythropoiesis-stimulating agent (ESA), in many CKD patients with anemia and low iron levels to raise hemoglobin levels to a range of 10 to 12 grams per deciliter; iron deficiency is defined by a ferritin score less than 100 micrograms (mcg) per liter and transferrin saturation (TSAT) less than 20%.

OBJECTIVE: To examine the use of intravenous (IV) iron and its associated economic and clinical outcomes in Medicare beneficiaries with stage 3 or stage 4 CKD and anemia.

METHODS: This was a retrospective cohort analysis using 2006 and 2007 Medicare 5% Standard Analytic Files (SAF). Use of therapy with IV iron and/or ESAs was identified among patients diagnosed with CKD and anemia. The study index quarter was the first quarter in 2006 during which the patient had primary or secondary diagnoses of both CKD and anemia. Based on the receipt of IV iron or ESA treatment in the index quarter, patients were classified into 1 of 4 treatment groups: IV iron and ESA; IV iron without ESA; ESA without IV iron; neither IV iron nor ESA. Therapy with oral iron was not measurable with this database. Clinical and economic outcomes, including the progression to advanced CKD stages, development of anemia, mortality, hospitalization, and net Medicare reimbursement (i.e., not including patient or supplemental plan contribution) for all-cause health care services, were examined for 1 year following the index quarter. Between-group differences were tested using Pearson chi-square for categorical variables and the Kruskal-Wallis nonparametric test for reimbursement. Multivariate logistic regression models were estimated to assess the associations of mortality, inpatient hospitalization, skilled nursing facility (SNF) admission, and hospice care with treatment regimen, controlling for patient demographic and clinical characteristics.

RESULTS: Of the 4,310 study patients with both CKD and anemia, 2,913 (67.6%) received neither IV iron nor ESA; 984 (22.8%) received ESA without IV iron; 277 (6.4%) received IV iron and ESA; and 136 (3.2%) received IV iron without ESA in the index quarter. Logistic regression analyses showed that patients receiving neither IV iron nor ESA (reference group) were at increased risk of death compared with patients receiving both IV iron and ESA (OR = 0.62, 95% CI = 0.42-0.90). Additionally, patients receiving neither IV iron nor ESA were more likely to be hospitalized compared with patients receiving both IV iron and ESA (OR = 0.66, 95% CI = 0.50-0.87), IV iron without ESA (OR = 0.55, 95% CI = 0.38-0.79), and ESA without IV iron (OR = 0.73, 95% CI = 0.62-0.87). Further, patients not receiving IV iron or ESA were more likely to be admitted to an SNF than patients receiving both IV iron and ESA (OR = 0.44, 95% CI = 0.32-0.61), IV iron without ESA (OR = 0.57, 95% CI = 0.36-0.88), and ESA without IV iron (OR = 0.56, 95% CI = 0.47-0.67). Patients receiving neither IV iron nor ESA in the index quarter had the highest mean [SD] total Medicare reimbursement per patient in the subsequent year ($42,353 [$52,887]) compared with patients receiving IV iron without ESA ($28,654 [$32,068]), IV iron and ESA ($34,152 [$30,506]), or ESA without IV iron ($38,172 [$35,591], $P = 0.001$).

CONCLUSIONS: Use rates of IV iron and ESA in a sample of Medicare enrollees with CKD and anemia in 2006 suggest that anemia management therapies may be underutilized; however, oral iron therapy use was not measurable with the study database, and therapies initiated after the index quarter were not measured. Patients not treated with IV iron or ESA had significantly higher rates of hospitalization and SNF admission than patients treated with either IV iron or ESA. Further, mortality was significantly higher in patients receiving neither IV iron nor ESA than in patients who received IV iron and ESA. Additionally, total all-cause health care costs were higher among patients receiving neither IV iron nor ESA treatment compared with patients treated with IV iron and/or ESA.

J Manag Care Pharm. 2010;16(8):605-15

What is already known about this subject

- Anemia is a common occurrence in patients with chronic kidney disease (CKD), with reported prevalence rates of 9%-64% depending on CKD stage and definition of anemia and is associated with increased morbidity and mortality. In a sample of patients with incident CKD, Thorp et al. (2009) found that patients with severe anemia (hemoglobin less than 10.5 grams per deciliter) had higher odds of mortality (hazard ratio [HR] = 5.27, 95% CI = 4.37-6.35), cardiovascular hospitalizations (HR = 2.18, 95% CI = 1.76-2.70), and end-stage renal disease (HR = 5.46, 95% CI = 3.38-8.82) compared with patients without anemia.
- Clinical guidelines from the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK, 2008) recommend the use of iron supplements (oral or intravenous [IV]) in CKD patients with anemia (defined as hematocrit less than 33% in women of childbearing age or less than 37% in men and postmenopausal women) in whom therapy with an erythropoiesis-stimulating agent (ESA) does not raise the hematocrit above the threshold levels because iron levels are too low. Iron deficiency is defined in the NIDDK guidelines as a ferritin score less than 100 micrograms (mcg) per liter and a transferrin saturation (TSAT) score less than 20%.
- While previous research has demonstrated the effectiveness of IV iron therapy in correcting anemia in some patients with CKD, the clinical and economic outcomes associated with IV iron therapy compared with other treatments including ESA in routine clinical practice are unknown.

What this study adds

- In a sample of Medicare beneficiaries with both CKD and anemia in at least 1 quarter in 2006 (index quarter), a lower percentage of patients were treated with IV iron (9.6%) than an ESA (29.3%).
- Compared with patients receiving neither IV iron nor ESA in the index quarter, patients receiving both IV iron and ESA were at lower risk of death in the subsequent year (OR = 0.62, 95% CI = 0.42-0.90); and patients receiving ESA and/or IV iron were at lower risk of hospitalization (patients receiving both IV iron and ESA OR = 0.66, 95% CI = 0.50-0.87; IV iron without ESA OR = 0.55, 95% CI = 0.38-0.79; and ESA without IV iron OR = 0.73, 95% CI = 0.62-0.87) and admission to a skilled nursing facility (patients receiving both IV iron and ESA: OR = 0.44, 95% CI = 0.32-0.61; IV iron without ESA: OR = 0.57, 95% CI = 0.36-0.88; and ESA without IV iron: OR = 0.56, 95% CI = 0.47-0.67).
- In the year subsequent to the index quarter, anemic CKD patients receiving neither IV iron nor ESA in the index quarter incurred significantly higher all-cause health care costs with mean (SD) annual Medicare reimbursements per patient totaling $42,353 ($52,887) per patient compared with patients receiving IV iron and ESA ($34,152 [$30,506]), IV iron without ESA ($28,654 [$32,068]), and ESA without IV iron ($38,172 [$35,591], $P = 0.001$).

An estimated 26 million adults in the United States have chronic kidney disease (CKD).[1] Patients with CKD have a high burden of morbidity and mortality. In its early stages (stages 1 and 2), CKD is often asymptomatic, but affected individuals are at risk of progressing to later stages.[2] As kidney function declines (stages 3 and 4), patients may begin to experience fatigue, pruritus, constipation, anorexia, pain, sleep disturbance, dyspnea, nausea, restless legs, and depression.[3] Despite treatment, CKD may progress to end-stage renal disease (ESRD) or complete kidney failure, requiring the use of renal replacement therapy.[2]

Anemia is a common occurrence in CKD patients and is associated with increased morbidity and mortality.[4] In a sample of patients with incident CKD, Thorp et al. (2009) found that patients with severe anemia (hemoglobin [Hb] less than 10.5 grams per deciliter [gm per dL]) had higher odds of mortality (hazard ratio [HR] = 5.27, 95% confidence interval [CI] = 4.37-6.35), cardiovascular hospitalizations (HR = 2.18, 95% CI = 1.76-2.70), and end-stage renal disease (HR = 5.46, 95% CI = 3.38-8.82) compared with patients without anemia.[4] Anemia is defined by a decrease in hematocrit or Hb. It develops as kidney function deteriorates primarily due to the decreased production of erythropoietin (EPO) and impairs the body's ability to provide an adequate oxygen supply to organs.[3,5] Impaired oxygen delivery can adversely affect organ function, particularly cardiac function.[2,6,7] Anemia has been shown to have a negative impact on quality of life and gives rise to symptoms such as lethargy, decreased cognition, and reduced mental acuity.[8] Additionally, anemia in CKD patients is associated with substantial health care costs,[9] possibly because it serves as a marker for disease severity.[10]

Anemia treatment in patients with CKD to Hb or hematocrit targets that have varied among different studies has been associated with improvements in quality of life, sexual function, muscle strength, endurance, reduced risk of hospitalization, and improved cardiovascular outcomes.[11-16] The correction of anemia in patients with congestive heart failure also has been associated with improved outcomes, including improved cardiac function, a reduction in the number of hospitalizations, and slowed progression of both heart and renal failure.[17]

Anemia in patients with CKD is treated with erythropoiesis-stimulating agents (ESAs), intravenous (IV) or oral iron, and less commonly, blood transfusions. Recommendations for clinical practice promulgated by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI, 2006) vary according to patient hemodialysis status, the underlying cause of anemia, and other factors.[18] For patients undergoing hemodialysis, ESAs are the mainstay of treatment.[18] For patients not undergoing hemodialysis, clinical practice guidelines suggest that iron agents may be used as primary treatment or as adjuvant therapy for patients treated with ESAs.[18,19] For those patients with decreased EPO production and iron deficiency, a combination of ESAs and iron may be used; iron deficiency reduces the effectiveness of ESAs to stimulate the production of red blood cells, thereby interfering with their ability to raise a patient's Hb level.[20] Clinical guidelines from the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK, 2008) recommend the use of oral or IV iron supplements in CKD patients with anemia (defined as hematocrit less than 33% in women of childbearing age or less than 37% in men and postmenopausal women) in whom therapy with an ESA does not raise the hematocrit above the threshold levels because iron levels are too low.[19] Iron deficiency is defined in the NIDDK guidelines as a ferritin score less than 100 micrograms (mcg) per liter and a transferrin saturation (TSAT) score less than 20%.[19] In their investigation of 47 non-dialyzed patients with CKD and Hb less than 12 gm per dL, Gotloib et al. (2006) observed that replenishing iron stores significantly increased mean (standard deviation [SD]) Hb levels from 10.16 (1.32) gm per dL to 11.96 (1.52) gm per dL.[21]

According to NKF-KDOQI (2006) guidelines, IV iron is strongly recommended over oral iron for iron deficient CKD patients who are hemodialysis-dependent. For patients who are nondialyzed (ND-CKD) or peritoneal dialysis-dependent, the guidelines do not indicate a preference for oral or IV iron.[18] The effective use of oral iron therapy may be limited in patients with CKD due to insufficient intestinal absorption and gastrointestinal complaints that may reduce patient compliance with treatment.[22] Three of the four published randomized controlled trials that examined the efficacy of treatment with IV and oral iron in anemic, ND-CKD patients indicated that IV iron was more efficacious than oral iron,[23,24,25] whereas a fourth showed no added benefit from IV iron.[26] Taken together, these studies

suggest that IV iron may modestly improve efficacy compared with oral iron for patients with ND-CKD. However, IV iron is also associated with adverse effects including hypotension, flushing, and the potential risk of hypersensitivity reactions including anaphylaxis.[27,28,29] The product label for iron dextran injection includes a black box warning specifying that it should be used "only in patients in whom clinical and laboratory investigations have established an iron deficient state not amenable to oral iron therapy" and that prior to administration at a therapeutic dose, a test dose should be administered.[27] Iron sucrose and sodium ferric gluconate complex do not have the black box warning and do not require a test dose.[28,29]

Although the treatment of anemia in patients with CKD has predominantly been focused on ESAs, the results of several recent randomized, placebo-controlled studies have raised new safety concerns with these therapies when used to achieve Hb targets higher than 10-12 gm per dL[30,31,32] leading to a reevaluation of their use. In the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study, for example, rates on the primary end point outcome (a composite of all-cause death, stroke, or cardiovascular events) did not significantly differ for ND-CKD patients treated with placebo versus darbepoetin alfa dosed to a target Hb of 13 gm per dL, and the risk of stroke was nearly twice as high for the patients treated with darbepoetin alpha.[30] Further, there is a discrepancy between the NKF-KDOQI guidelines, which suggest ESA treatment to target Hb levels to 11-12 gm per dL (Hb range recommendations, updated 2007),[18] and the ESA product labels, which indicate that Hb levels should be targeted to 10-12 gm per dL.[33,34] Given the more recent safety concerns associated with ESA use, we may expect the practice of targeting higher Hb levels with ESAs to decline.

Despite the importance placed on treating anemia in patients with CKD, many receive inadequate treatment, as evidenced by the low Hb levels often seen in individuals with CKD.[35,36] Among patients with ND-CKD, Voormolen et al. (2010) found that 48% had Hb of 11 gm per dL or less at the start of care,[37] and McClellan et al. (2004) found that rates of anemia defined as Hb 10 gm per dL or less and 12 gm per dL or less were 8.9% and 47.7%, respectively.[36] In a study of patients treated for CKD in nephrology clinics, Kammerer et al. (2002) found that 26.3% had Hb below 10 gm per dL, 46.7% had Hb below 11 gm per dL, and 63.9% had Hb below 12 gm per dL.[38] The purpose of this study was to examine the use of IV iron and its associated economic and clinical outcomes among Medicare beneficiaries with stage 3 or stage 4 CKD and anemia.

Methods

Study Design and Data Sources

In this retrospective study, clinical outcomes, mortality, and medical resource use for patients with stages 3 or 4 CKD and anemia were examined among Medicare beneficiaries in the United States in years 2006 and 2007 using the Medicare 5% Standard Analytic Files (SAF).[39] For these patients, data from 2005 were used to identify pre-existing comorbidities including diabetes, hypertension, bone disease, malnutrition, liver cirrhosis, and heart disease in the year prior to CKD diagnosis. The Medicare 5% SAF contain final action claim-level data, which can be linked across multiple years and settings of care, and represent all claims for 5% of Medicare beneficiaries in a given year. Medicare beneficiaries remain in the SAF until they no longer receive Medicare benefits or expire. The SAF data include separate files for hospital inpatient, hospital outpatient, physician/supplier Part B, skilled nursing facility (SNF), home health, hospice, durable medical equipment (DME) claims, and a demographic file that indicates age, gender, date of death (if applicable), and eligibility information. Each beneficiary is assigned an encrypted identifier by the Centers for Medicare & Medicaid Services (CMS) that protects the identity of the patient but allows for researchers to track a patient from one year to the next or across different practice settings. To further protect patient confidentiality, the SAF data do not provide actual dates of service; rather, quarters of service are provided in the claims data. Institutional Review Board (IRB) review or determination was not sought as no patient-identifying information was used in the analysis.

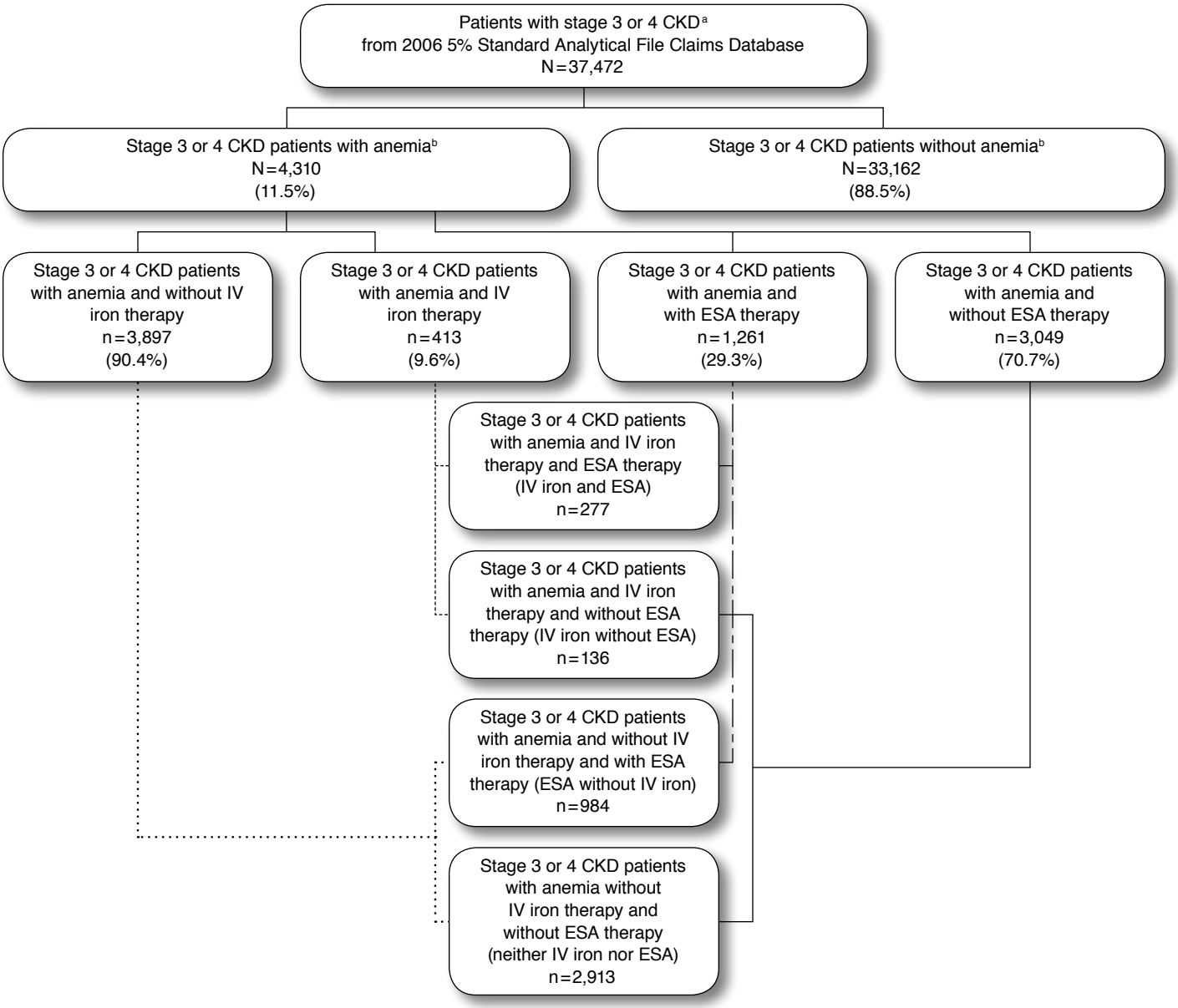
As an initial step, all claims with a primary or secondary *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis code for stage 3 (585.3) or stage 4 (585.4) CKD were selected from the 2006 SAF claims data. Claims data from 2006 were used to identify an index stage 3 or 4 diagnosis because 2006 was the first year that CKD stage could be determined from the ICD-9-CM diagnosis code. If the first identification of stage 3 CKD diagnosis occurred in the same quarter as a stage 4 CKD diagnosis, then the patient was classified as a stage 4 CKD patient. If the first identification of a stage 3 or 4 CKD diagnosis occurred in the same quarter as a stage 5 CKD or end-stage renal disease (ESRD) diagnosis, the patient was excluded from the analysis because those patients had greater disease severity than the intended patient population.

Using this method, the index quarter identified the initial quarter of CKD diagnosis in 2006. Because data for 2005 were not examined for CKD diagnosis, the first diagnosis in 2006 was not necessarily the first diagnosis of CKD for the patient (i.e., the CKD might or might not have been newly diagnosed). Four quarters of data were then extracted after the index quarter to investigate clinical outcomes, medical resource use, and mortality. Only patients with continuous eligibility in all 5 quarters or with continuous eligibility through their quarter of death were included in the analysis.

Study Sample

The sample of patients with stages 3 or 4 CKD was divided into 10 subgroups based on combinations of the following characteristics: with and without anemia, with and without IV iron therapy, with and without ESA treatment, and specific combinations of IV iron therapy and ESA treatment (Figure

FIGURE 1 *Study Population and Subgroups*



[a]*Patients with CKD were identified from 2006 5% Standard Analytic File data by primary or secondary ICD-9-CM diagnosis code for stage 3 or stage 4 CKD (Table 1) during 2006. The first quarter in 2006 in which a CKD diagnosis appeared was designated as the index quarter.*

[b]*Anemia was defined by primary or secondary ICD-9-CM diagnosis code for anemia (Table 1) in the index quarter. Receipt of ESA and/or IV iron therapy was identified based on the index quarter only.*

CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; IV = intravenous.

1). Patients with anemia were defined as having a claim with at least 1 primary or secondary ICD-9-CM diagnosis code for anemia in the index quarter (Table 1). Treatments were identified and classified based on the index quarter using Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes (Table 2). IV iron therapy was defined by the receipt of iron sucrose, iron dextran, or iron gluconate. ESA therapy was defined by the receipt of Aranesp (darbepoetin alfa), Procrit (epoetin alfa), or Epogen (epoetin alfa). IV iron and ESA treatments initiated after the index

TABLE 1 ICD-9-CM Diagnosis Codes

Comorbidity	ICD-9-CM Diagnosis Codes
Chronic kidney disease	
Stage 3	585.3
Stage 4	585.4
Stage 5	585.5
End-stage renal disease	585.6
Anemia	280.X, 285.21
Hypertension	403.00, 403.10, 403.90, 404.00, 404.01, 404.30, 404.31, 404.90, 404.91
Diabetes	250.XX, 337.1X, 790.29
Bone disease	588.81, 275.8X, 275.9X
Malnutrition	263.X
Liver cirrhosis	571.5X
Heart disease	401.00 to 405.99, 414.01, 425.1X, 410.XX, 412, 428.XX, 411.1X, 413.XX, 427.0X, 272.XX, 490.00 to 492.99, 494.XX, 496

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

quarter were not measured. Oral iron use was not assessed because prescription claims data were not available in this database.

Construction of Outcome and Treatment Variables

Outcomes were investigated in the index quarter and the subsequent 4 quarters. Clinical outcomes, including the progression to advanced CKD stages, development of anemia, and development of coronary disease, were identified using appropriate ICD-9-CM codes (Table 1) in the 4 quarters following the index quarter. Disease progression was defined as having a claim in any of the 4 follow-up quarters with a primary or secondary diagnosis of a more advanced stage of CKD compared with the index quarter (e.g., at least 1 claim for stage 4 CKD in a patient classified in the index quarter as having stage 3 CKD). Patients who progressed to ESRD were not censored and were followed in the same way as all other study patients.

Specific treatments of iron sucrose, iron dextran, iron gluconate, darbepoetin alfa and epoetin alfa, blood transfusion, and dialysis were identified by appropriate CPT, HCPCS, and ICD-9-CM procedure codes (Table 2). Medical resource use was identified using inpatient, hospital outpatient, physician office, SNF, hospice, home health, DME, and emergency room claims. Total length of stay (LOS) per patient for the 4-quarter period following index quarter in the inpatient, SNF, and hospice settings was collected. Total net Medicare reimbursement (not including patient or supplemental plan contribution) was collected for each of these settings and reported in 2007 U.S. dollars (USD). Dollar amounts from years prior to 2007 were converted to 2007 USD using the medical care component of the Consumer Price Index.[40] The Medicare reimbursement amounts for each treatment were collected and converted to 2007 USD.

TABLE 2 Anemia Treatment Codes

Treatment	CPT Code	HCPCS Code	ICD-9-CM Procedure Code
Iron sucrose		J1756	
Iron dextran		J1751, J1752	
Iron gluconate		J2916	
Darbepoetin alfa		J0881, J0882	
Epoetin alfa		J0885	
Blood transfusion	36430		99.04
Dialysis	90947, 90945, 90999, 90925, 90935, 90937		

CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Statistical Analysis

Analyses were performed for patients with a diagnosis of stage 3 or stage 4 CKD and for subgroups (Figure 1). Descriptive statistics were calculated on demographic characteristics at baseline and on clinical characteristics in the year prior to the index quarter. Clinical characteristics included number of comorbid conditions (diabetes, hypertension, bone disease, malnutrition, liver cirrhosis, and heart disease) and proportion of patients with each pre-identified comorbidity. Additional data analyzed in the 4 follow-up quarters included clinical outcomes and Medicare reimbursed amounts in total and for all 7 settings of care.

Comparisons were made among 4 key subgroups of patients with anemia, defined based on treatment in the index quarter: IV iron and ESA, IV iron without ESA, ESA without IV iron, and neither IV iron nor ESA treatment. Pearson chi-square tests were used to compare the demographic characteristics, mortality, inpatient hospitalization, admission to either SNF or hospice, and the proportion of patients progressing to advanced CKD stages. Given the large sample size and the expected normal distributions of age and LOS, Student's t-tests were used to compare those outcomes. However, Kruskal-Wallis nonparametric tests were used to compare Medicare reimbursement because distributions of cost data are typically skewed.

Multivariate logistic regression analyses on the outcomes of mortality, hospitalization, and admission to SNF or hospice, were performed while adjusting for covariates, including demographics, treatment group, and comorbidities (diabetes, hypertension, heart disease, bone disease, malnutrition, and liver cirrhosis) measured in the year prior to the index quarter. The regression analyses were performed by specifying the occurrence of each outcome event (mortality, occurrence of hospitalization, admission to SNF, and receipt of hospice care) as the dependent variable and forcing demographic characteristics (age, gender, Medicare eligibility category, and race) and treatment group (reference group of IV iron and ESA, IV iron without ESA, ESA without IV iron, and neither IV iron

nor ESA) variables in the model. The remaining covariates were introduced into the model in a forward stepwise fashion (*P* value for entry = 0.10) using Wald chi-square goodness-of-fit tests.

Statistical significance was evaluated at the 0.05 level. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC).

Results

Of 37,472 patients with stage 3 or stage 4 CKD in the SAF database, 4,310 (11.5%) also had an anemia diagnosis in the index quarter (Figure 1). Of these patients, 413 (9.6%) received IV iron treatment in the index quarter, and 1,261 (29.3%) received ESA treatment in the index quarter. The majority of sample patients receiving IV iron also received ESA treatment (277 [67.1%] of 413 IV iron users, 6.4% of the sample overall), and 136 patients (3.2% of the sample) received IV iron without ESAs. Less than one-quarter of patients receiving ESA treatment also received IV iron (277 [22.0%] of 1,261 ESA users).

Comparisons Among 4 Key Treatment Subgroups

Across the 4 patient groups, age was statistically different, with the group of patients treated with IV iron and not ESAs a mean of 3.5 to 4.0 years younger than the other groups ($P < 0.001$; Table 3). There was no significant difference in gender among the groups ($P = 0.502$). Most patients (78.5%-85.3%) in each treatment group were white with slightly higher percentages of white patients in the IV iron and ESA and IV iron without ESA groups (85% in each, $P = 0.011$).

During the index quarter, a larger proportion of patients in the IV iron and ESA group had stage 4 CKD (49.8%) compared with the other groups (39.0% IV iron without ESA, 44.4% ESA without IV iron, 32.1% neither IV iron nor ESA, $P < 0.001$). Approximately 7% of all sample patients received dialysis in the year following the index quarter, and dialysis was most commonly used in the ESA without IV iron group (9.5%) followed by the group with neither IV iron nor ESA (6.1%), IV iron and ESA (< 5.0%), and IV iron without ESA (< 5.0%, $P = 0.002$).

Progression to advanced CKD stages was more common among patients receiving either IV iron or ESAs (progression rates of 27.2%-31.0%) compared with those not receiving either treatment (progression rate of 22.6%; Table 4). For patients treated with IV iron and/or an ESA (n = 1,397), there was no significant difference among treatment groups in the proportions advancing to later CKD disease stages ($P = 0.655$; not shown in table).

The mortality analysis showed that 20.5% of the subgroup receiving neither IV iron nor ESA died in the year following the index quarter, compared with mortality rates of 18.1% for ESA without IV iron, 11.0% for IV iron without ESA, and 12.6% for IV iron and ESA ($P < 0.001$). For the 1,397 patients receiving IV iron and/or ESA, the difference in mortality rates among the 3 treatment groups was statistically significant ($P = 0.020$; not shown in table). A composite measure of progression to later CKD stages or death was calculated; however, the proportion of patients progressing to later CKD stages or dying was not significantly different among the 4 patient groups ($P = 0.062$).

Compared with the other treatment groups, patients receiving neither IV iron nor ESA were more likely to be hospitalized (64.0%-71.7% vs. 78.0%, respectively, $P < 0.001$) or admitted to SNF (17.7%-22.6% vs. 34.1%, respectively, $P < 0.001$; Table 4). As a result, these patients had longer mean total LOS for all settings of care (35.3 days for patients with neither IV iron nor ESA vs. 18.7 to 21.9 days for other subgroups, $P < 0.001$). Driven primarily by inpatient hospital utilization, patients receiving neither IV iron nor ESA had the highest mean [SD] total medical costs per patient in the year following diagnosis ($42,353 [$52,887]) compared with patients receiving IV iron without ESA ($28,654 [$32,068]), IV iron and ESA ($34,152 [$30,506]), or ESA without IV iron ($38,172 [$35,591], $P = 0.001$).

Multivariate logistic regressions showed that patients receiving neither IV iron nor ESA (reference group) were at increased risk for the outcome of death compared with the group of patients receiving both IV iron and ESA (odds ratio [OR] = 0.62, 95% CI = 0.42-0.90; Table 5). Additionally, patients receiving neither IV iron nor ESA were more likely to be hospitalized compared with patients receiving both IV iron and ESA (OR = 0.66, 95% CI = 0.50-0.87), IV iron without ESA (OR = 0.55, 95% CI = 0.38-0.79), and ESA without IV iron (OR = 0.73, 95% CI = 0.62-0.87). Further, patients not receiving IV iron or ESA were more likely to be admitted to an SNF than patients receiving both IV iron and ESA (OR = 0.44, 95% CI = 0.32-0.61), IV iron without ESA (OR = 0.57, 95% CI = 0.36-0.88), and ESA without IV iron (OR = 0.56, 95% CI = 0.47-0.67). There was no statistical difference between the groups for the proportion of patients receiving hospice care. Among the subgroup of 1,397 patients treated with ESA and/or IV iron, odds of mortality for those receiving ESA without IV iron were 54% higher compared with patients receiving IV iron and ESA (OR = 1.535, 95% CI = 1.025-2.296; data not shown). No other outcomes had significant results among the subgroup of patients treated with ESA and/or IV iron.

Each additional year of age was associated with increased odds of death (OR = 1.07; 95% CI = 1.06-1.08), inpatient hospitalization (OR = 1.03, 95% CI = 1.02-1.04), SNF admission (OR = 1.07, 95% CI = 1.06-1.08), and hospice care (OR = 1.08; 95% CI = 1.06-1.10; data not shown). Patients who were Asian, Hispanic, or a race other than white or black were less likely to die (OR = 0.59, 95% CI = 0.38-0.92), be hospitalized (OR = 0.70, 95% CI = 0.50-0.97), be admitted to an SNF (OR = 0.47, 95% CI = 0.32-0.69), or receive hospice care (OR = 0.35, 95% CI = 0.17-0.73; data not shown). Of the 6 pre-existing comorbidities that were investigated, malnutrition and liver cirrhosis were significant predictors in all 4 outcomes. History of diabetes was predictive of death, inpatient hospitalization, and SNF admission. Conversely, history of bone disease was inversely associated with death, inpatient hospitalization, and SNF admission, with ORs all less than 1.00 for these outcomes. History of

TABLE 3 Demographic and Clinical Characteristics of Study Sample

Characteristic	IV Iron[a]			Treatment Group[a]				
	Yes	No	*P* Value[b]	IV Iron and ESA	IV Iron Without ESA	ESA Without IV Iron	Neither IV Iron nor ESA	*P* Value[b]
Age			0.030					<0.001
N	413	3,897		277	136	984	2,913	
Mean [SD]	75.00 [9.84]	76.14 [10.19]		76.19 [9.18]	72.59 [10.71]	76.55 [9.25]	76.00 [10.49]	
Median (range)	76 (23-94)	77 (24-98)		77 (31-94)	73 (23-93)	77 (28-98)	77 (24-98)	
Gender, n (%)			0.504					0.502
Male	179 (43.3)	1,756 (45.1)		119 (43.0)	60 (44.1)	425 (43.2)	1,331 (45.7)	
Female	234 (56.7)	2,141 (54.9)		158 (57.0)	76 (55.9)	559 (56.8)	1,582 (54.3)	
Race, n (%)			0.025					0.011
Unknown	0 (0.0)	NR		0 (0.0)	0 (0.0)	0 (0.0)	NR	
White	352 (85.2)	3,090 (79.3)		236 (85.2)	116 (85.3)	803 (81.6)	2,287 (78.5)	
Black	48 (11.6)	620 (15.9)		33 (11.9)	15 (11.0)	128 (13.0)	492 (16.9)	
Other	13 (3.1)	180 (4.6)		NR	NR	53 (5.4)	127 (4.4)	
Medicare eligibility category, n (%)			0.068					<0.001
Aged without ESRD	373 (90.3)	3,489 (89.5)		256 (92.4)	117 (86.0)	891 (90.5)	2,598 (89.2)	
Aged with ESRD	NR	92 (2.4)		NR	NR	37 (3.8)	55 (1.9)	
Disabled without ESRD	31 (7.5)	288 (7.4)		14 (5.1)	17 (12.5)	49 (5.0)	239 (8.2)	
Disabled with ESRD	0 (0.0)	25 (0.6)		0 (0.0)	0 (0.0)	NR	NR	
ESRD only	NR	NR		NR	NR	NR	NR	
Baseline CKD stage in index quarter, n (%)			<0.001					<0.001
Stage 3	222 (53.8)	2,526 (64.8)		139 (50.2)	83 (61.0)	547 (55.6)	1,979 (67.9)	
Stage 4	191 (46.2)	1,371 (35.2)		138 (49.8)	53 (39.0)	437 (44.4)	934 (32.1)	
Received dialysis within 1 year of index quarter, n (%)	22 (5.3)	271 (7.0)	0.212	NR	NR	93 (9.5)	178 (6.1)	0.002
Comorbidities in the year prior to index quarter								
Diabetes, n (%)	255 (61.7)	2,515 (64.5)	0.260	167 (60.3)	88 (64.7)	647 (65.8)	1,868 (64.1)	0.409
Hypertension, n (%)	55 (13.3)	575 (14.8)	0.432	35 (12.6)	20 (14.7)	138 (14.0)	437 (15.0)	0.684
Bone disease, n (%)	46 (11.1)	228 (5.9)	<0.001	NR	NR	84 (8.5)	144 (4.9)	<0.001
Malnutrition, n (%)	16 (3.9)	278 (7.1)	0.013	NR	NR	43 (4.4)	235 (8.1)	<0.001
Liver cirrhosis, n (%)	13 (3.2)	94 (2.4)	0.361	NR	NR	25 (2.5)	69 (2.4)	0.520
Heart disease, n (%)	409 (99.0)	3,877 (99.5)	0.237	275 (99.3)	134 (98.5)	978 (99.4)	2,899 (99.5)	0.468

[a]*Treatment classifications were based on the index quarter only. Index quarter was the first quarter in 2006 during which patient had primary or secondary diagnoses of CKD and anemia. Treatments during the 1-year follow-up after the index quarter were not measured.*

[b]*Pearson chi-square test for categorical variables and Student's t-test for continuous variables.*

CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; ESRD = end-stage renal disease; IV = intravenous; NR = not reportable (i.e., not disclosed to protect patient confidentiality, per guidelines promulgated by the Centers for Medicare & Medicaid Services); SD = standard deviation.

hypertension was a significant predictor of hospitalization and hospice care.

Discussion

In a sample of Medicare beneficiaries with stage 3 or stage 4 CKD and anemia, 29.3% received ESA therapy and 9.6% received IV iron during a study index quarter within which the patient received diagnoses of both CKD and anemia for the first time in 2006. Although anemia treatment may not be indicated for all patients, greater utilization of these treatments may be expected; however, oral iron therapy was not measurable in the present study database.

Within this sample of Medicare beneficiaries, stage 3 and stage 4 CKD patients with anemia who were treated with ESA and/or IV iron during the index quarter experienced more favorable outcomes in the subsequent year than those patients receiving neither ESA nor IV iron therapy. In the unadjusted bivariate results, the study cohorts who received IV iron, ESA, or both demonstrated lower mortality than those receiving neither IV iron nor ESA. After adjusting for demographics and pre-index comorbidities, those treated with both IV iron and ESA still had a significantly lower risk of death in the year

TABLE 4 Comparison of Study Endpoints Among 4 Key Treatment Groups[a]

Endpoint	IV Iron and ESA (n = 277)	IV Iron Without ESA (n = 136)	ESA Without IV Iron (n = 984)	Neither IV Iron nor ESA (n = 2,913)	*P* Value[b]
Progression to stage 4, n (%)	39 (14.1)	20 (14.7)	137 (13.9)	336 (11.5)	<0.001
Progression to stage 5, n (%)	35 (12.6)	12 (8.8)	107 (10.9)	166 (5.7)	<0.001
Progression to ESRD, n (%)	28 (10.1)	14 (10.3)	162 (16.5)	318 (10.9)	<0.001
Progression to advanced CKD stage, n (%)	83 (30.0)	37 (27.2)	305 (31.0)	658 (22.6)	<0.001
Mortality, n (%)	35 (12.6)	15 (11.0)	178 (18.1)	598 (20.5)	<0.001
Disease progression or death (composite measure), n (%)	107 (38.6)	49 (36.0)	432 (43.9)	1,152 (39.5)	0.062
Inpatient hospitalization, n (%)	188 (67.9)	87 (64.0)	706 (71.7)	2,271 (78.0)	<0.001
Inpatient LOS					<0.001
Mean [SD]	8.70 [12.53]	9.23 [14.84]	11.11 [16.05]	16.19 [22.42]	
Median (range)	4.00 (0.0-90.0)	3.00 (0.0-72.0)	5.00 (0.0-140.0)	8.00 (0.0-264.0)	
Inpatient payment ($)					<0.001
Mean [SD]	14,813 [20,668]	14,721 [23,147]	18,279 [25,804]	25,753 [41,945]	
Median (range)	7,410 (0-150,059)	5,477 (0-120,296)	9,060 (0-279,480)	13,081 (0-1,044,275)	
SNF, n (%)	49 (17.7)	26 (19.1)	222 (22.6)	993 (34.1)	<0.001
SNF LOS					<0.001
Mean [SD]	5.71 [17.29]	6.99 [25.38]	7.60 [21.47]	14.12 [30.01]	
Median (range)	0.00 (0.0-101.0)	0.00 (0.0-187.0)	0.00 (0.0-200.0)	0.00 (0.0-232.0)	
SNF payment ($)					<0.001
Mean [SD]	2,106 [6,124]	2,263 [7,675]	2,764 [7,516]	4,539 [9,425]	
Median (range)	0 (0-44,638)	0 (0-56,332)	0 (0-61,885)	0 (0-101,660)	
Hospice, n (%)	23 (8.3)	NR	86 (8.7)	305 (10.5)	0.228
Hospice LOS					0.212
Mean [SD]	5.35 [27.56]	2.43 [12.20]	3.14 [19.98]	4.95 [28.75]	
Median (range)	0.00 (0.0-262.0)	0.00 (0.0-107.0)	0.00 (0.0-303.0)	0.00 (0.0-422.0)	
Hospice payment ($)					0.179
Mean [SD]	918 [4,711]	399 [1,896]	538 [3,140]	794 [4,181]	
Median (range)	0 (0-46,684)	0 (0-15,238)	0 (0-52,733)	0 (0-68,508)	
Total LOS					<0.001
Mean [SD]	19.77 [38.58]	18.65 [37.21]	21.86 [36.67]	35.26 [53.43]	
Median (range)	5.00 (0.0-298.0)	3.00 (0.0-245.0)	7.00 (0.0-303.0)	12.00 (0.0-477.0)	
Total payment ($)					0.001
Mean [SD]	34,152 [30,506]	28,654 [32,068]	38,172 [35,591]	42,353 [52,887]	
Median (range)	25,120 (0-203,354)	15,299 (118-156,204)	27,121 (0-287,861)	27,384 (0-1,069,101)	

[a] *Treatment classifications were based on the index quarter only. Index quarter was the first quarter in 2006 during which patient had primary or secondary diagnoses of CKD and anemia. Treatments during the 1-year follow-up after the index quarter were not measured.*

[b] *Pearson chi-square test for categorical variables, Student's t-test for nonpayment continuous variables, and Kruskal-Wallis nonparametric test for payment variables.*

CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; ESRD = end-stage renal disease; IV = intravenous; LOS = length of stay; NR = not reportable (i.e., not disclosed to protect patient confidentiality per guidelines promulgated by the Centers for Medicare & Medicaid Services); SD = standard deviation; SNF = skilled nursing facility.

following index than did patients not treated with IV iron or ESA. Among the cohorts treated with IV iron and/or ESA, the unadjusted results showed that those receiving IV iron without ESA had the lowest mortality, followed by those receiving IV iron and ESA, and those receiving ESA without IV iron. However, the adjusted results failed to show significant differences between those receiving IV iron without ESA and the other 2 treatment groups. Patients receiving neither IV iron nor ESA were also more likely to be hospitalized and admitted to an SNF during follow-up than patients treated with ESA and/or IV iron. Interestingly, although patients treated with either IV iron and/or ESA demonstrated lower mortality and lower rates of hospitalization, those treated with either IV iron and/or ESA had higher rates of progression to advanced stages of CKD. Finally, study patients who received neither ESA nor IV iron therapy incurred the highest mean all-cause Medicare reimbursements of all groups examined. Among the treated cohorts, those receiving IV iron without ESA had the lowest mean Medicare reimbursements, followed by those receiving IV iron and ESA and those receiving ESA without IV iron.

Current approaches to the treatment of anemia in patients with CKD emphasize the use of ESA. In our study, almost 30%

TABLE 5 *Multivariate Logistic Regression for Outcomes of Mortality, Hospitalization, Admission to SNF, and Hospice Treatment as a Function of Demographic and Baseline Clinical Characteristics*[a]

Outcome	Adjusted Odds Ratio (95% Confidence Interval)						C-Statistic
	IV Iron and ESA[b]		IV Iron Without ESA[b]		ESA Without IV Iron[b]		
Mortality[c]	0.615	(0.422-0.897)	0.590	(0.338-1.031)	0.909	(0.749-1.104)	0.697
Hospitalization[d]	0.661	(0.502-0.871)	0.548	(0.378-0.793)	0.733	(0.619-0.868)	0.647
Admission to SNF[e]	0.438	(0.315-0.607)	0.566	(0.362-0.883)	0.558	(0.468-0.666)	0.701
Hospice treatment[f]	0.842	(0.536-1.322)	0.855	(0.438-1.668)	0.856	(0.661-1.108)	0.705

[a]*Baseline clinical characteristics include history (1 year prior to index quarter) of diabetes, hypertension, heart disease, bone disease, malnutrition, and liver cirrhosis.*

[b]*Treatment classifications were based on the index quarter only. Index quarter was the first quarter in 2006 during which patient had primary or secondary diagnoses of CKD and anemia. Treatments during the 1-year follow-up after the index quarter were not measured. Reference group is neither IV Iron nor ESA.*

[c]*One-year history of diabetes (OR = 1.224, 95% CI = 1.032-1.452), bone disease (OR = 0.676, 95% CI = 0.462-0.989), malnutrition (OR = 3.879, 95% CI = 3.006-5.005), and liver cirrhosis (OR = 2.656, 95% CI = 1.719-4.104) were included in the forward selection for the outcome of mortality.*

[d]*One-year history of diabetes (OR = 1.501, 95% CI = 1.292-1.743), hypertension (OR = 1.572, 95% CI = 1.261-1.959), bone disease (OR = 0.478, 95% CI = 0.367-0.621), malnutrition (OR = 3.528, 95% CI = 2.300-5.410), and liver cirrhosis (OR = 3.310, 95% CI = 1.704-6.428) were included in the forward selection for the outcome of hospitalization.*

[e]*One-year history of diabetes (OR = 1.580, 95% CI = 1.358-1.838), bone disease (OR = 0.544, 95% CI = 0.391-0.758), malnutrition (OR = 2.768, 95% CI = 2.147, 3.567), and liver cirrhosis (OR = 1.615, 95% CI = 1.055-2.474) were included in the forward selection for the outcome SNF admission.*

[f]*One-year history of hypertension (OR=1.415, 95% CI=1.080-1.854), malnutrition (OR=2.190, 95% CI=1.593-3.010), and liver cirrhosis (OR=3.054, 95% CI=1.839, 5.073) were included in the forward selection for the outcome of hospice treatment.*

CI = confidence interval; CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; IV = intravenous; OR = odds ratio; SNF = skilled nursing facility.

of patients received ESA while approximately 10% received IV iron, and less than one-third of patients with anemia and CKD in the study sample received one of these treatments in the index quarter. ESA therapy is recommended by the NKF-KDOQI to target Hb levels between 11.0 to 12.0 gm per dL (Hb range recommendations, updated 2007),[18] which differs from the labeled indication of targeting Hb levels between 10.0 to 12.0 gm per dL.[33,34] Moreover, recent clinical trial results showing increased mortality and cardiovascular morbidity of patients treated with ESA to Hb targets above those required to avoid erythrocyte transfusions have raised serious safety concerns with these therapies, and the future use of ESA seems unlikely to target Hb levels higher than 10.0 to 12.0 gm per dL (see Unger et al. [2010] for a review).[41] Additionally, particular attention to a patient's iron level should continue to be made as ESA treatment will not be effective if the patient's iron level is too low.[19]

Limitations

First, the retrospective nature of this analysis does not allow for the attribution of causality between treatments and outcomes. Retrospective database studies can, however, indicate associations worthy of further investigation using additional research designs. Second, because exact dates of service are not reported in the Medicare database, dates of service were considered in this analysis in terms of quarters. As such, it was not always possible to determine which event occurred first when 2 or more events (e.g., treatment and a hospitalization) occurred within the same quarter.

Third, because of the lack of outpatient pharmacy data in the Medicare database, the use of oral iron was not evaluated. Additionally, because pharmacy data were not available, we were unable to capture all medication costs (including oral iron). Given that only 7% of patients in our study received dialysis during the 1-year period following the index diagnosis, and that treatment guidelines suggest no preferred route of iron administration in CKD patients not receiving dialysis, it is reasonable to assume that a certain proportion of patients in each study cohort may have received oral iron. Other oral medications such as those used to treat worsening hypertension are also missed due to the lack of pharmacy data in our analysis.

Fourth, the assignment of treatment group was made based on the treatment received in the index quarter only. Therefore, for example, it is possible that some patients who did not receive either IV iron or ESA in the index quarter may have received one or both of the treatments in a subsequent quarter but still were labeled as "neither IV iron nor ESA." Similarly, a patient assigned to either IV iron without ESA or ESA without IV iron may have received the alternate treatment during the 1-year follow-up.

Fifth, an inherent limitation of administrative claims analyses is the reliance on the accuracy of coding in the claims. Anemia is unlikely to be the primary diagnosis on a medical claim for a CKD patient, and as the patient may have more serious comorbidities, anemia may not be recorded as a secondary diagnosis. Thus, it is possible that an anemia diagnosis may have been missed on a claim form in the initial quarter of CKD diagnosis for some patients. As a result, some CKD patients with anemia may have been misclassified and thus not included in this analysis. The possibility that an anemia diagnosis may be required to receive reimbursement for the administration of ESA or IV iron treatment suggests that few anemia patients were missed in the sampling process. However, if anemia diagnoses were recorded to ensure

reimbursement for the administration of IV iron or ESA treatment, the sample may be biased to include patients receiving IV iron or ESA treatment.

Sixth, the anemia diagnosis was based on the index quarter only. Although expanding the patient sample to include patients developing anemia during the 4 quarters subsequent to CKD diagnosis might have captured those missed patients, this approach would have also flagged any persons developing anemia late in the analysis period where the chances for mortality, hospitalization, and other adverse outcomes can be reduced due to a shorter observation period. By confining the anemia diagnosis to the initial quarter of CKD diagnosis, we maintained a consistent follow-up period to identify outcomes for all patient cohorts. Additionally, we noted that exposure to treatment was associated with greater progression of kidney disease and the lack of exposure to treatment was associated with greater risk of death which might be due to some form of informative censoring.

Seventh, physicians may not have treated with IV iron or ESA if the patient's illness was advanced or if the patient had comorbidities that prevented treatment. Thus, it is possible that the patients grouped into the "neither IV iron nor ESA" group simply were in poorer health compared with the other 3 groups. Contrary to this hypothesis, patients in the "neither IV iron nor ESA" group were more likely to be at stage 3 and less likely to be at stage 4 during the index quarter, compared with patients treated with IV iron and/or ESA. Additionally, most baseline comorbidity rates were similar among treatment groups. However, it is possible that unmeasured confounding factors influenced physicians' treatment decisions. The lack of detail on the claim form makes it impossible to assess this possibility fully, and further study on this subject is warranted. Finally, because we examined a Medicare population in this analysis, our results may not be generalizable to other patient populations. However, based on data from the National Health and Nutrition Examination Survey from 1999-2004 indicating that approximately 89% of all stage 3 CKD patients and 81% of stage 4/5 CKD patients are aged 60 years or older, we are confident that we have captured a large proportion of the relevant population.[42]

Conclusions

In this analysis of anemic stages 3 and 4 CKD patients, 29.3% received ESA therapy and 9.6% received IV iron during a study index quarter within which the patient received diagnoses of both CKD and anemia for the first time in 2006. Patients not treated with IV iron or ESA had significantly higher rates of hospitalization and SNF admission than patients treated with IV iron and/or ESA. Further, mortality was significantly higher in patients receiving neither IV iron nor ESA than in patients who received both IV iron and ESA. Additionally, mean total all-cause Medicare reimbursements were higher among patients receiving neither IV iron nor ESA treatment compared with patients treated with IV iron and/or ESA. Although it was not possible to assess the use of oral iron in the present study, the findings suggest that IV iron may be underutilized among patients with CKD and anemia.

Authors

TYLER G. KNIGHT, MS, is Senior Scientist; KELLIE RYAN, MPH, is Senior Associate; CAROLINE P. SCHAEFER, MBA, is Vice President; and EMILY D. DURDEN, PhD, is Senior Scientist, Covance Market Access Services, Inc., Gaithersburg, Maryland. LYNELL D'SYLVA, BSN, RN, is National Clinical Communications Manager, American Regent, Inc., Shirley, New York.

AUTHOR CORRESPONDENCE: Tyler G. Knight, MS, Covance Market Access Services, Inc., 9801 Washingtonian Blvd., 9th Fl., Gaithersburg, MD 20878. Tel: 240.632.3000; Fax: 240.632.3001. Email: tyler.knight@covance.com.

DISCLOSURES

This work was funded by American Regent, Inc., which manufactures iron dextran injection and iron sucrose injection. Knight, Ryan, Schaefer, and Durden are employed by a contract research organization, Covance Market Access Services, Inc., which was contracted by American Regent, Inc., to design the study, perform the analysis, and draft the manuscript. D'Sylva is an employee of American Regent.

Concept and design were done primarily by Knight and Ryan, with the assistance of D'Sylva. Data collection was performed by Knight with the assistance of Ryan. Data interpretation was performed primarily by Knight, Schaefer, and Ryan. Knight wrote the manuscript, with the assistance of Ryan, and revised the manuscript, with the assistance of D'Sylva and Durden.

ACKNOWLEDGEMENTS

The authors acknowledge contributions to study design and manuscript revisions that were made by American Regent employees Walter Tozzi, RPh, MS, MBA, Senior Director of Marketing and Professional Services, and Janice McCarron, AS, Assistant Marketing Manager, and by Lynda Szczech, MD, MSCE, Associate Professor of Medicine, Duke University Medical Center. William Fridrich, RPh, MBA, Manager of Professional Services, and Vasiliki Diamantis, PharmD, Clinical Pharmacist, employees of American Regent, contributed to manuscript revisions.

REFERENCES

1. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17):2038-47. Available at: http://jama.ama-assn.org/cgi/content/full/298/17/2038. Accessed September 17, 2010.

2. Murtagh FE, Addington-Hall J, Higginson IJ. The prevalence of symptoms in end-stage renal disease: a systematic review. *Adv Chronic Kidney Dis*. 2007;14(1):82-99.

3. Weiner DE. Causes and consequences of chronic kidney disease: implications for managed health care. *J Manag Care Pharm*. 2007:13(3 Suppl):S1-S9. Available at: http://www.amcp.org/data/jmcp/Supplement.pdf.

4. Thorp ML, Johnson ES, Yang X, Petrik AF, Platt R, Smith DH. Effect of anaemia on mortality, cardiovascular hospitalizations, and end-stage renal disease among patients with chronic kidney disease. *Nephrology (Carlton)*. 2009;14(2):240-46.

5. Erslev AJ. Erythropoietin. *N Eng J Med*. 1991;324(19):1339-44.

6. Valderrabáno F. Quality of life benefits of early anaemia treatment. *Nephrol Dial Transplant*. 2000;15(Suppl 3):S23-S28. Available at: http://ndt.oxfordjournals.org/cgi/reprint/15/suppl_3/23?view=long&pmid=11032354. Accessed September 17, 2010.

7. Al-Khoury S, Afzali B, Shah N, et al. Diabetes, kidney disease and anaemia: time to tackle a troublesome triad? *Int J Clin Pract.* 2007;61(2):281-89.

8. Dowling TC. Prevalence, etiology, and consequences of anemia and clinical and economic benefits of anemia correction in patients with chronic kidney disease: an overview. *Am J Health Syst Pharm.* 2007;64(13 Suppl 8):S3-S7.

9. Lefebvre P, Duh MS, Buteau S, Bookhart B, Mody SH. Medical costs of untreated anemia in elderly patients with predialysis chronic kidney disease. *J Am Soc Nephrol.* 2006;17(12):3497-502. Available at: http://jasn.asnjournals.org/cgi/reprint/17/12/3497. Accessed September 17, 2010.

10. Nissenson AR, Wade S, Goodnough T, Knight K, Dubois RW. Economic burden of anemia in an insured population. *J Manag Care Pharm.* 2005;11(7):565-74. Available at: http://www.amcp.org/data/jmcp/Original%20Research_565_574.pdf.

11. Jones M, Ibels L, Schenkel B, Zagari M. Impact of epoetin alfa on clinical end points in patients with chronic renal failure: a meta-analysis. *Kidney Int.* 2004;65(3):757-67.

12. Marsh JT, Brown WS, Wolcott D, et al. rHuEPO treatment improves brain and cognitive function of anemia dialysis patients. *Kidney Int.* 1991;39(1):155-63.

13. Beusterien KM, Nissenson AR, Port FK, Kelly M, Steinwald B, Ware JE Jr. The effects of recombinant human erythropoietin on functional health and well-being in chronic dialysis patients. *J Am Soc Nephrol.* 1996;7(5):763-73. Available at: http://jasn.asnjournals.org/cgi/reprint/7/5/763. Accessed September 17, 2010.

14. Guthrie M, Cardenas D, Eschbach JW, Haley NR, Robertson HT, Evans RW. Effects of erythropoietin on strength and functional status of patients on hemodialysis. *Clin Nephrol.* 1993;39(2):97-102.

15. Xia H, Ebben J, Ma JZ, Collins AJ. Hematocrit levels and hospitalization risks in hemodialysis patients. *J Am Soc Nephrol.* 1999;10(6):1309-16. Available at: http://jasn.asnjournals.org/cgi/reprint/10/6/1309. Accessed September 17, 2010.

16. Ma JZ, Ebben J, Xia H, Collins AJ. Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol.* 1999;10(3):610-19. Available at: http://jasn.asnjournals.org/cgi/reprint/10/3/610. Accessed September 17, 2010.

17. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function, functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol.* 2000;35(7):1737-44. Available at: http://content.onlinejacc.org/cgi/reprint/35/7/1737.pdf. Accessed September 17, 2010.

18. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis.* 2006;47(5 suppl 3):S11-S146. Available at: http://www.kidney.org/professionals/kdoqi/guidelines_ANEMIA/index.htm. Accessed September 17, 2010.

19. U.S. Department of Health and Human Services, National Institute of Diabetes and Digestive and Kidney Diseases. Anemia in kidney disease and dialysis. October 2008. Available at: http://kidney.niddk.nih.gov/kudiseases/pubs/pdf/anemia.pdf. Accessed September 17, 2010.

20. Eschbach JW. Iron therapy and the anemia of ESRD: historical perspective. *Semin Dial.* 1999;12(4):212-18.

21. Gotloib L, Silverberg D, Fudin R, Shostak A. Iron deficiency is a common cause of anemia in chronic kidney disease and can often be corrected with intravenous iron. *J Nephrol.* 2006;19(2):161-67.

22. Hörl WH. Clinical aspects of iron use in the anemia of kidney disease. *J Am Soc Nephrol.* 2007;18(2):382-93. Available at: http://jasn.asnjournals.org/cgi/reprint/18/2/382. Accessed September 17, 2010.

23. Agarwal R, Rizkala AR, Bastani B, Kaskas MO, Leehey DJ, Besarab A. A randomized controlled trial of oral versus intravenous iron in chronic kidney disease. *Am J Nephrol.* 2006;26(5):445-54.

24. Van Wyck DB, Roppolo M, Martinez CO, Mazey RM, McMurray S; for the United States Iron Sucrose (Venofer) Clinical Trials Group. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int.* 2005;68(6):2846-56. Available at: http://www.nature.com/ki/journal/v68/n6/pdf/4495631a.pdf. Accessed September 17, 2010.

25. Charytan C, Qunibi W, Bailie GR; Venofer Clinical Studies Group: Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. *Nephron Clin Pract.* 2005;100(3):c55-c62.

26. Stoves J, Inglis H, Newstead CG. A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. *Nephrol Dial Transplant.* 2001;16(5):967-74. Available at: http://ndt.oxfordjournals.org/cgi/reprint/16/5/967. Accessed September 17, 2010.

27. Dexferrum (iron dextran injection). American Regent. August 2008. Available at: http://www.americanregent.com/documents/Product16PrescribingInformation.pdf. Accessed September 17, 2010.

28. Venofer (iron sucrose injection). American Regent. Available at: http://www.venofer.com/pdfs/Venofer%20IN2340%20Rev%2010-08.pdf. Accessed September 17, 2010.

29. Ferrlecit (sodium ferric gluconate complex in sucrose injection). sanofi-aventis. January 2010. Available at: http://products.sanofi-aventis.us/ferrlecit/ferrlecit.html. Accessed September 17, 2010.

30. Pfeffer MA, Burdmann EA, Chen CY, et al.; TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med.* 2009;361(21):2019-32. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa0907845. Accessed September 17, 2010.

31. 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(20):2085-98. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa065485. Accessed September 17, 2010.

32. Drüeke TB, Locatelli F, Clyne N, et al.; CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med.* 2006;355(20):2071-84. Available at: http://content.nejm.org/cgi/reprint/355/20/2071.pdf. Accessed September 17, 2010.

33. Aranesp. Amgen. May 2010. Available at: http://pi.amgen.com/united_states/aranesp/ckd/aranesp_pi_hcp_english.pdf. Accessed September 17, 2010.

34. Epogen. Amgen. February 2010. Available at: http://pi.amgen.com/united_states/epogen/epogen_pi_hcp_english.pdf. Accessed September 17, 2010.

35. Besarab A. Resolving the paradigm crisis in intravenous iron and erythropoietin management. *Kidney Int Suppl.* 2006;(101):S13-S18.

36. McClellan W, Aronoff SL, Bolton WK, et al. The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin.* 2004;20(9):1501-10.

37. Voormolen N, Grootendorst DC, Urlings TA, et al. Prevalence of anemia and its impact on mortality and hospitalization rate in predialysis patients. *Nephron Clin Pract.* 2010;115(2):c133-41.

38. Kammerer J, Ratican M, Elzein H, Mapes D. Anemia in CKD: prevalence, diagnosis, and treatment. Case study of the anemic patient. *Nephrol Nurs J.* 2002;29(4):371-74.

39. US Department of Health and Human Services. Centers for Medicare & Medicaid Services. Standard Analytic Files. Available at: https://www.cms.gov/IdentifiableDataFiles/02_StandardAnalyticalFiles.asp. Accessed September 17, 2010.

40. U.S. Department of Labor. Bureau of Labor Statistics. Measuring price change for medical care in the CPI. April 12, 2010. Available at: http://www.bls.gov/cpi/cpifact4.htm. Accessed September 17, 2010.

41. Unger EF, Thompson AM, Blank MJ, Temple R. Erythropoiesis-stimulating agents—time for a reevaluation. *N Engl J Med.* 2010;362(3):189-92. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMp0912328. Accessed September 17, 2010.

42. Center for Disease Control and Prevention. Prevalence of chronic kidney disease and associated risk factors—United States, 1999-2004. *MMWR Morb Mortal Wkly Rep.* 2007;56(8):161-65. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5608a2.htm. Accessed September 17, 2010.