Changes in ESA dosing and Hb levels in US CKD-NOD patients between 2005 and 2009

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Abstract

Background. Recent clinical trials in cancer patients treated with erythropoiesis-stimulating agents (ESAs) and in CKD patients treated to haemoglobin (Hb) targets above the labeled range of 10–12 g/dL with ESAs raised safety concerns regarding ESA therapy. Subsequently, product labeling was revised including addition of a black-box warning and removal of many quality of life claims not supported by current standards, and there were changes in reimbursement and anaemia guidelines. The extent to

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which these events influenced ESA dosing and Hb levels in patients with chronic kidney disease not on dialysis (CKD-NOD) is not known.

Methods. We used data collected in a series of cross-sectional surveys between March 2005 and July 2009. Patients with CKD-NOD were selected from a random sample of free-standing US nephrology clinics. Information on demographics, insurance information, laboratory data and ESA use was abstracted from medical records by site investigators. We evaluated ESA treatment (use and dosing) and Hb levels over time and used multivariate linear regression to assess changes in ESA doses and Hb levels over time adjusting for case-mix differences.

Results. Between 2005 and 2009, 15,836 CKD-NOD patients were sampled. During this period, ESA use declined from 60 to 46%, and the mean dose declined from 176 to 136 mcg/month; the largest decline in use and in dose occurred beginning in 2007. Simultaneously, the mean (standard deviation) Hb level in ESA-treated patients declined from 11.5 (1.4) to 10.6 (1.2) g/dL, though the decline was most pronounced starting in 2007. As the mean Hb declined, the percent of treated patients with an Hb >12 g/dL dropped from 27 to 12%, and the mean dose in this sub-population declined from 173 to 111 mcg/month.

Conclusion. The emergence of safety concerns and the subsequent changes in product labeling, reimbursement and clinical practice guidelines all appear to have influenced physician dosing practices resulting in less frequent use of ESAs, lower ESA doses and lower achieved Hb levels in CKD-NOD patients.

Keywords: anaemia; chronic kidney disease; haemoglobin; non-dialysis; trends

Introduction

Chronic kidney disease (CKD) affects an estimated 26.3 (13.1%) million adults in the USA [1]. Anaemia is a frequent complication of CKD and is primarily due to declining erythropoietin production [2,3]. Non-experimental studies have shown that patients with CKD who have anaemia are at elevated risk of cardiovascular hospitalizations [4] and all-cause mortality [5–7] and have greater health-care utilization compared with CKD patients with no anaemia [8]. Clinical studies have shown that treating CKD patients with erythropoiesis-stimulating agents (ESAs) is effective in correcting and maintaining haemoglobin (Hb) levels within clinical target ranges [9] and is effective in reducing the need for red blood cell transfusions [10], but when used to treat to Hb levels above the Food & Drug Administration (FDA)-approved target range (10–12 g/dL) has documented risks for mortality and arterial and venous thromboembolic events [11–15].

In late 2006, the results of two large randomized clinical trials of CKD patients not on dialysis (CKD-NOD) with anaemia who were treated with ESAs and iron to Hb targets higher than the approved range were published [13,14]. The Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease (CHOIR) study [13] was stopped early because the probability of demonstrating benefit in the high Hb group was <5%, resulting from an excess of the composite endpoint (death or cardiovascular hospitalization) in patients targeted to Hb levels of 13.5 g/dL compared to patients targeted to 11.3 g/dL. The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE) study [14] found a slightly elevated (though not statistically significant) occurrence of cardiovascular events for patients targeted between 13.0 and 15.0 g/dL compared to a lower target of 10.5 to 11.5 g/dL. These findings raised concerns about attempting to normalize Hb levels with ESAs in CKD-NOD and potential ESA dose toxicity. These findings were generally consistent with the results from the Normal Hematocrit Cardiac Trial [16], which was conducted in haemodialysis patients with pre-existing heart failure or ischaemic heart disease. During this same period, results from a meta-analysis of 57 studies in cancer patients that were treated with ESAs compared to placebo showed an excess of thromboembolic events in the ESA treatment arms [17]. Subsequently, additional meta-analyses conducted by the same group (including information from additional studies) and by another group of investigators provided more evidence of risk for thromboembolic events and suggested potential mortality risks when treating cancer patients with ESAs [18–22]. In March of 2007, the FDA issued a black-box warning on ESAs and modified the label to ‘use the lowest dose to avoid the need for red blood cell transfusion’. Later that year, the FDA convened separate advisory committee meetings to examine the risk:benefit profile of ESAs in both cancer (May 2007) and CKD (September 2007). Subsequent to the September meeting, the ESA label was then revised to ‘treat to a target of 10–12 g/dL to avoid the need for red blood cell transfusions’ and many of the quality of life claims were determined to not be adequately supported given current standards and were removed (November 2007 [11,12]).

In addition to these publications and regulatory actions, there were various other events that occurred during and after this period, including public health advisory communications to physicians, numerous publications discussing the safety of anaemia management with ESAs, revisions to clinical practice guidelines and changes in reimbursement for ESAs. The extent to which these events influenced physician prescribing behaviour when treating anaemia in CKD-NOD patients has not been well described. The purpose of this study is to examine trends in ESA dosing and achieved Hb levels among CKD-NOD patients receiving care in US nephrology clinics during the period spanning 2005–2009, which covers the periods preceding, concurrent with and subsequent to these major events.

Materials and methods

Data source

This study uses data collected from a random sample of CKD patients receiving outpatient care in free-standing US nephrology clinics between January 2002 and July 2009. Random samples of nephrology clinics and patients within those clinics were selected quarterly (waves) for participation in a cross-sectional survey. At each wave, a pool of eligible nephrology clinics was identified from a list maintained by the American Medical Association. Clinics were required to be a dedicated nephrology clinic and had to treat an average of 10 or more CKD-NOD patients.
From the pool of eligible facilities, trained telephone interviewers using a computer-assisted telephone interview script contacted randomly selected nephrology clinics to determine eligibility and seek participation in the study. This process continued until ~350 facilities were identified. Facilities participating in one wave were not eligible for selection in the next wave, but were eligible for subsequent waves.

**Patient selection**

Selected facilities were mailed an instruction package which included a computer-generated random 5-digit number or a set of three letters (e.g. CAM) to be used for initiating the selection of patients. The chronologically most recent patient record with a diagnosis of CKD whose medical record number or first three letters of his/her last name corresponded to the number or letters provided was designated as the index patient. Working backwards, every 10th record was evaluated for a CKD diagnosis. This process continued until six records were identified.

**Data abstraction**

Site investigators abstracted patient information from the medical record as of the survey date. The information abstracted included demographic characteristics, insurance information, the most recently collected laboratory data and information on ESA dosing. The data were then transcribed into a computerized database using double entry. Discrepancies between the two entry processes were evaluated and resolved by a third party. Sites were queried to resolve out of range or inconsistent responses and missing values. The study population for this analysis was limited to those patients identified between January 2005 and July 2009. All patient information obtained for this analysis was de-identified in accordance with the standards set by the Health Insurance Portability and Accountability Act Privacy Rule.

**Measurements (definition of exposure, outcome and other study variables)**

**Exposure and outcome**

Information on ESA treatment was collected during each wave. Site investigators assessed whether patients were currently receiving, had previously received or never received ESA treatment. For this study, we excluded previously treated patients from our analysis of Hb levels and ESA doses over time because previous ESA use could not be well defined (i.e. the time between the most recent ESA administration and the date of data collection could be months or years). Consequently, the impact of previous treatment on current Hb levels could not be determined and would make interpreting current Hb levels in this context difficult.

Information on ESA dosing was also available; however, because of the different formulations for epoetin alfa [international units (IU)] and darbepoetin alfa [micrograms (mcg); epoetin alfa doses (in units per week) were converted to darbepoetin alfa doses (in mcg/week), using the sliding scale conversion table in the darbepoetin alfa (Aranesp) package insert [12]. For example, an EPO dose of 1 to 2499 IU was converted to 6.25 mcg and 0-99 000 IU to 200 mcg. Darbepoetin alfa dose was then multiplied by four to arrive at a monthly dose (mcg/month).

The most recently recorded Hb/hematocrit (Hct) measurement as of the date of data abstraction was assessed. For patients 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 as both continuous and categorical (<10, 10-12, >12 g/dL) variables.

**Other measurements**

Demographic characteristics included age, gender, race (white, black, other) and body mass index (BMI; kg/m²; <20, 20-<25, 25-<35, ≥35), and primary insurance provider [Medicare, Medicaid, private (HMO, PPO, self-pay) and other]. The most recent serum creatinine (mg/dL) value as of the date of data abstraction was evaluated. We used the abbreviated Modification of Diet in Renal Disease (MDRD) equation [23,24] to calculate the estimated glomerular filtration rate (eGFR). We categorized patients into CKD stages (1 to 5) using the National Kidney Foundation classification system [23]: ≥90 mL/min/1.73 m² (stage 1), 60-89 mL/min/1.73 m² (stage 2), 30-59 mL/min/1.73 m² (stage 3), 15-29 mL/min/1.73 m² (stage 4) and <15 mL/min/1.73 m² (stage 5).

Albumin levels were not collected, and therefore, we were unable to estimate the albumin-to-creatinine ratio, which is necessary for assessing micro- and macro-albuminuria and for classifying patients into CKD stages 1 and 2. Consequently, we may have misclassified patients without CKD as having either CKD stage 1 or 2. For the purpose of our analyses and to improve the precision of our estimates, we combined patients in stages 1 and 2, and separately, stages 4 and 5.

**Timeline of events**

Between January 2005 and September 2009, there were a number of events that occurred relating to anaemia management with ESAs that may have impacted physician treatment patterns. These included the following:

1. Publication of results from randomized clinical trials in CKD patients [13,14] that identified risks when targeting patients to Hb levels above the labeled target range of 10–12 g/dL;
2. Publication of two meta-analyses examining the effects of treatment with ESAs to higher versus lower Hb targets in CKD patients [25,26];
3. Publication of results from clinical trials in cancer patients identifying thromboembolic and mortality risks when treating with ESAs [27,28] and the publication of meta-analyses showing elevated risks for thromboembolic events [17–19] and mortality [18–22] when compared to treatment with ESAs to placebo in patients with cancer.
4. Convening of separate FDA drug advisory committee meetings (Oncology Drug Advisory Committee and Cardio-renal Drug Advisory Committee and Drug Safety and Risk Management) to evaluate the risk/benefit profile of anaemia management with ESAs in cancer and kidney disease patients, respectively;
5. Revisions to the ESA labels that first removed the target range of 10–12 g/dL and replaced it with ‘use the lowest dose to avoid the need for red blood cell transfusions’ and added a black-box warning highlighting the risks identified when targeting Hb levels of 13.5 and 14 g/dL; subsequently, the Hb range of 10–12 g/dL was reinstated; however, many of the quality of life (QoL) claims were identified as not being adequately supported given current standards and were removed, and in the cancer setting, a ‘not indicated’ statement was added for patients receiving chemotherapy when the anticipated outcome is cure;
6. FDA and ESA manufacturer communications to healthcare professionals regarding changes to the ESA label and the insertion of a black-box warning;
7. Revisions to the anaemia management guidelines issued by the Kidney Disease Outcomes Quality Initiative (KDOQI) [26], the American Society for Clinical Oncology/American Society for Hematology (ASCO/ASH) [29] and the National Comprehensive Cancer Network (NCCN) [30];
8. Implementation of a national coverage determination in the cancer setting by the Centers for Medicare and Medicaid Services (CMS) restricting reimbursement for ESA treatment to an Hb level <10 g/dL; and
9. Revisions to the erythropoietin monitoring policy in dialysis patients reducing payment by 50% if Hb levels remained >13 g/dL for three consecutive months.

Figure 1 provides a timeline of these events.

**Statistical analysis**

We present descriptive statistics for continuous variables [mean, standard deviation (SD)] and categorical variables [count (%)] for sampling wave and year. For comparisons across years, all patients sampled within a given year were grouped together. We characterized patients by treatment group in each year and then used Mantel–Haenszel chi-square analysis for categorical variables and analysis of variance for continuous variables to compare patient characteristics within treatment groups across years. We estimated mean (SD) Hb levels and ESA doses in each sampling wave over the study period. Mean achieved Hb levels were estimated separately for treated and non-treated patients. We also examined mean Hb levels and ESA doses stratified by patient characteristics. Lastly, we evaluated mean ESA doses over the study period within categories of current Hb level (<10, 10–12, >12 g/dL).

We then used multiple variable linear regression to examine trends in achieved Hb levels and ESA doses over the study period. These ana-
yses were conducted with and without adjustment for differences in case-mix over time. Separate analyses were conducted for each outcome; in both, the independent variable was calendar time (sampling wave) and the dependent variable was either ESA dose or Hb level. The case-mix variables adjusted for in these models included age, sex, race, BMI, eGFR and primary payer. All analyses were conducted using SAS v 9.1 (Cary, NC).

Results

Between 2005 and 2009, there were 18 distinct waves of facility and patient sampling (assessed approximately quarterly). The number of nephrology facilities identified per wave ranged from an average of 2911 facilities in 2007 to 4569 in 2009 (Table 1). The sampling fraction was adjusted to target ~350 facilities per wave. A total of 15 836 non-dialysis CKD patients were sampled over the study period: 3424 in 2005, 3647 in 2006, 2441 in 2007, 3830 in 2008 and 2494 through July 2009. The mean age [67.5 years (SD 14.7)] and distribution of other demographic characteristics (51% female, 65% white) remained constant over the study period. The percentage of patients who were currently receiving an ESA decreased from 60% in 2005 to 46% in 2009, with the largest drop occurring between 2007 and 2008. During the same period, mean (SD) eGFR of patients receiving care in a nephrology clinic increased from 29.9 (17.8) to 35.2 (21.0) mL/min/1.73 m².

Over the study period, there were no major changes in the gender or race distribution of patients in either the treated or non-treated groups (Table 2). Mean age changed slightly in the ESA-treated group from 69.2 to 70.2 years, as did the mean eGFR, from 25.1 to 26.8 mL/min/1.73 m². Among non-treated subjects, the mean eGFR increased from 38.4 to 43.6 mL/min/1.73 m². In 2005, treated subjects were more likely to be older than non-treated subjects [mean age: 69.2 (13.8) vs 64.4 (15.0) years], female (54 vs 46%) and covered by Medicare (68 vs 54%); these differences remained relatively consistent over the study period. In 2005, the mean eGFR among treated patients was 13 mL/min/1.73 m² lower than among non-treated patients (25.1 vs 38.4 mL/min/1.73 m²). By 2009, the difference in eGFR increased by nearly 17 mL/min/1.73 m², from 26.8 to 43.6 mL/min/1.73 m². Among treated patients, the proportion with Hb <10 g/dL increased from 14 to 25%, the proportion of patients with Hb 10–12 g/dL increased from 59 to 63% and the proportion with Hb >12 g/dL decreased from 27 to 12% (P < 0.0001). Among the non-treated group, the proportions of patients in each Hb category were consistent over the study period.

Figure 2 shows the Hb mean and SD by sampling wave over the study period for treated and non-treated patients. Among non-treated patients, Hb remained relatively stable throughout the study period, ~12.6 (1.7) g/dL. Among treated patients, mean (SD) Hb levels were relatively stable from the beginning of 2005 [11.5 g/dL (1.4)] to the end of 2006 [11.4 g/dL (1.3)] but then began to decline by the middle of 2007 [11.1 g/dL (1.2)] and continued to drop throughout 2008 [10.9 g/dL (1.2)] and 2009 [10.6 g/dL (1.2)] (P-value for trend <0.0001).

The decline in Hb levels over the study period was paralleled by a decline in ESA dose; from early 2005 to mid-2009, mean monthly ESA dose dropped from 172 to 136 mcg/month, a 21% decline (P-value for trend <0.0001) (Figure 3). Between 2005 and 2006, ESA dose remained relatively stable: 159 mcg/month (SD 147) at the end of 2006. Beginning in 2007, the ESA dose began to decline substantially and by the end of the year was at 140 mcg/month (SD 92). The dose continued to drop through the end of 2008 [132 mcg/month (SD 93)] and leveled off by the middle of 2009 [136 mcg/month (SD...
Changes in ESA dosing and Hb levels in US CKD-NOD patients between 2005 and 2009

### Table 1. Facility sampling and patient case-mix by year (2005–2009)

<table>
<thead>
<tr>
<th>Year</th>
<th>Facilities identified per wave</th>
<th>Sampling fraction</th>
<th>Age (years)</th>
<th>Insured type</th>
<th>Race</th>
<th>Facilities identified per wave</th>
<th>Sampling fraction</th>
<th>Age (years)</th>
<th>Insured type</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>4149 (632)</td>
<td>8.7</td>
<td>67.4 (14.5)</td>
<td>White</td>
<td>64.6</td>
<td>4149 (632)</td>
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<td>67.4 (14.5)</td>
<td>White</td>
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<td>2006</td>
<td>4496 (456)</td>
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<td>67.3 (14.8)</td>
<td>Black</td>
<td>23.9</td>
<td>4496 (456)</td>
<td>8.2</td>
<td>67.3 (14.8)</td>
<td>Black</td>
<td>23.9</td>
</tr>
<tr>
<td>2007</td>
<td>2911 (476)</td>
<td>12.0</td>
<td>67.4 (14.9)</td>
<td>Other</td>
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<td>12.0</td>
<td>67.4 (14.9)</td>
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<td>67.8 (14.8)</td>
<td>Medicare</td>
<td>5.9</td>
<td>4378 (108)</td>
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<td>2009</td>
<td>4569 (228)</td>
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<td>Medicaid</td>
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<td>4569 (228)</td>
<td>7.6</td>
<td>67.5 (15.3)</td>
<td>Medicaid</td>
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</tbody>
</table>

ESA = erythropoiesis-stimulating agents, GFR = glomerular filtration rate.

*Based on MDRD, mL/min/1.73 m².

The changes in mean ESA dose and achieved Hb levels over the study period did not change substantively after adjustment for differences in patient case-mix (data not shown). In addition, similar changes in achieved Hb levels and ESA doses were observed when the analyses were stratified by demographic characteristics (age, sex, race and CKD stage) (data not shown).

### Discussion

We studied 15 836 CKD-NOD patients receiving care in US nephrology clinics between January 2005 and July 2009. This period covers the two modifications to the epoetin alfa and darbepoetin alfa product labeling (March 2007 and November 2007), which included addition of a black-box warning and removal of many of the QoL claims that were not adequately supported given current standards. In addition, during this period, there were changes to ESA payment policy, various public health advisory communications to healthcare providers, numerous publications discussing the risks of targeting Hb levels above the approved range in CKD patients and the risks relating to treatment in cancer patients, and revisions to clinical practice recommendations regarding anaemia management. During this period, we observed substantive declines in the percentage of patients receiving an ESA, the mean ESA dose and the mean achieved Hb level among ESA-treated patients. These changes were most marked in 2007 and 2008. Among treated patients, there was a 20% decline in the mean ESA dose overall, and a >35% decline in doses among patients with Hb levels > 12 g/dL.

We observed a significant decline in the proportion of patients with an Hb >12 g/dL and an increase in the proportion with an Hb within the 10–12 g/dL range. The most notable change in Hb levels occurred early in 2007 following the publication of the CHOIR and CREATE studies [13,14], the first label change and the addition of the black-box warning, and this decline continued through the end of 2007. These observed changes in Hb levels were consistent across age, sex, race and other patient subgroups. In contrast, Hb levels remained relatively constant at ~12.6 g/dL among non-treated patients. Interestingly, during this same period, we observed an increase in the mean eGFR among patients receiving care in nephrology clinics despite little change in the patient case-mix, suggesting that patients with CKD-NOD were being referred to nephrologists earlier in their disease course.

The safety concerns raised by the publication of the CHOIR and CREATE studies [13,14], in addition to the safety concerns linked to ESA treatment in the cancer setting [17,18], resulted in a number of regulatory and reimbursement actions regarding anaemia management with ESAs. A black-box warning was included on the FDA-approved ESA label, public health advisory communications to physicians were issued regarding the black-box warning, and restrictions on reimbursement for ESA treatment in cancer patients were implemented (i.e. no reimbursement for ESA treatment when the Hb exceeds 10 g/dL). During this same period, there were a number of publications discussing the risks related to ESA treatment (e.g. potential off-target effects) and targeting Hb levels above the approved range both in kidney disease [23,24,31–33] and cancer patients [17–22,27,28]. In addition, clinical practice guidelines were also revised. KDOQI revised its anaemia management guidelines and recommended targeting an Hb of 11–12 g/dL [26], ASCO/ASH recommended targeting an Hb of 12–13 g/dL [29] and NCCN guidelines removed references to...
<table>
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<th></th>
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<td><strong>Hb (g/dL)</strong></td>
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<td>29 (58%)</td>
<td>31 (47%)</td>
<td>28 (49%)</td>
</tr>
</tbody>
</table>

BMI = body mass index, ESA = erythropoiesis-stimulating agents, GFR = glomerular filtration rate, Hb = haemoglobin.

^a Test for differences in patient characteristics over time among treated patients.

^b Test for differences in patient characteristics over time among non-treated patients.

^c Results were missing for ~26% of study population.

^d Based on MDRD, mL/min/1.73 m^2.
Hb levels when considering ESA treatment as well as drawing attention to revisions to product labeling [30].

The findings from this study suggest that physicians responded to these events and changed their prescribing behavior: ~25% fewer patients were receiving ESA therapy by the middle of 2009, and among those treated, there was a marked decline in ESA doses and achieved Hb levels. These changes may reflect physicians’ apprehension to treat anaemic patients with ESAs, a general reluctance to use greater ESA doses or concerns about treating to higher Hb levels. The downward shift observed in these nephrology clinics also suggests that nephrologists, in response to the emerging safety information, instituted new, lower Hb targets into their anaemia management protocols in order to lower ESA dosing and minimize potential Hb excursions into the ranges where harm was observed in the CKD trials. Although we could not evaluate this explicitly (information on facility targets was not available), our findings provide some support for this explanation. First, the decline in ESA doses was most pronounced for patients with Hb levels above 12 g/dL, and second, the proportion of patients with Hb levels above 12 g/dL dropped by more than 50% (27 to 12%).

Previous studies have examined the impact of major regulatory or reimbursement actions on anaemia therapy. Decreases in population mean Hb levels observed among dialysis patients subsequent to the Hematocrit Measurement Audit (HMA) policy instituted by the CMS in 1997 [34] are similar to those observed in this study. Subsequent to FDA approval and CMS coverage of epoetin alfa in 1989, Hb levels in the population with end-stage renal disease increased steadily [34]. The percentage of ESA claims with Hb levels >12 g/dL increased from <5% in 1990 to ~10% in 1996. In 1997, the HMA policy was initiated, which aimed to reduce the number of ESA claims for Hb >12% (Hct >36%). This policy evaluated a rolling 3-month average Hb, with denial of payment for patients with Hb >12.2 g/dL (Hct >36.5%). After initiation of the policy in September 1997, the percentage of patients with Hb >12.2 g/dL decreased. Elimination of the program in 1998 was accompanied by a steady increase in Hb, until 2000, when levels stabilized between 11.3 and 11.5 g/dL (Hct between 34 and 34.5%) [35,36]. To our knowledge, this is the first study to investigate changes in anaemia management in the US CKD-NOD patient population following the emergence of safety concerns from clinical trials examining anaemia management with ESAs and the ensuing revisions to ESA labeling and reimbursement.

In the US, information on dialysis patient care, including anaemia management, is captured and reported on in the United States Renal Data Systems annual data report [37]. Since monthly Hb levels are included in reimbursement claims submitted to CMS for ESAs, Hb monitoring
is possible and routinely done. In the non-dialysis setting, no surveillance system exists to enable monitoring of patient care including the management of anaemia. Unlike dialysis patients for whom dialysis services and medical care are covered by Medicare, CKD-NOD patients may be insured by any number of providers in addition to Medicare (e.g. private insurance, Medicaid, HMOs). Thus, there is no central repository for information on patient care. In addition, an important limitation of the available databases that could be used to monitor CKD-NOD patient care is that laboratory data (e.g. Hb levels) are not routinely collected. For this study, we used data obtained as part of a series of randomly selected samples of CKD patients receiving care in US nephrology clinics between 2005 and 2009. Both laboratory data (serum creatinine and Hb) and ESA treatment were assessed as of the time of data collection, which provided the opportunity to assess kidney function and to evaluate changes in ESA doses and achieved Hb levels over time. Hb levels in non-treated patients, in particular, are often under-represented or not available in most databases since these patients tend to be less sick and require less intensive clinical management. In this study, the non-treated patients represent an important comparison population to evaluate the impact of changes in physician management of anaemia with ESAs. As anticipated, the mean and SD of the Hb level remained largely unchanged for those not receiving ESA therapy.

This study should be evaluated in light of the following limitations. First, over the study period, ~8–12% of facilities participated in each wave. If these facilities differed meaningfully from those not participating with respect to patient case-mix or anaemia management practices, the results presented herein may not be generalizable. Secondly, the results from our unadjusted and case-mix adjusted analyses were not meaningfully different, suggesting that the changes in Hb levels among treated patients and the changes in ESA doses were not driven by changes in patient case-mix. However, we did not have access to information on comorbidities, recent hospitalization events or other concomitant medications, in particular, iron therapy, which studies in dialysis patients have shown to influence achieved Hb levels and ESA doses [38–40]. Consequently, there may be some residual bias in our estimates. Lastly, these data were obtained from multiple cross-sectional assessments over the study period rather than from a longitudinal analysis of a cohort of CKD-NOD patients. The cross-sectional design offers the opportunity to assess trends over time using independent patient populations but does not allow for the evaluation of treatment patterns within a cohort of individuals (i.e. changes within individuals over time).

**Conclusion**

This study suggests that physicians have responded to the safety concerns regarding ESA treatment raised by recent studies in the CKD and cancer settings as well as changes in product labeling, reimbursement and clinical practice guidelines and have changed their treatment practices. There has been a marked decline in the number of CKD-NOD patients receiving ESA therapy, as well as a lowering of ESA doses, and consequently, achieved Hb levels. There are now fewer patients with Hb levels above 12 g/dL and there are more patients within the target range of 10–12 g/dL. Continued surveillance of anaemia management with ESAs and other interventions, including iron and transfusions, in the CKD-NOD population is important for ensuring patient safety and better understanding of current anaemia management practices.

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**References**

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