Uptake of evidence by physicians: De-adoption of erythropoiesis-stimulating agents after TREAT trial showed they are ineffective and unsafe

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Abstract

Variation in de-adoption of ineffective or unsafe treatments is not well-understood. We examined de-adoption of erythropoiesis-stimulating agents (ESA) in anemia treatment among patients with chronic kidney diseases (CKD) following new clinical evidence of harm and ineffectiveness (the TREAT trial) and the FDA’s revision of its safety warning. We used an interrupted time series approach to estimate changes in use of epoetin alfa (EPO) and darbepoetin alfa (DPO) in the commercial and Medicare Advantage (MA) and Medicare fee-for-service (FFS) populations. We also examined how changes in both trends and levels of use were associated with physicians’ characteristics. Study cohort included patients with CKD stages 3 to 5 during 2007-2015. Use of DPO and EPO declined over the study period. There were no consistent changes in DPO trend across insurance groups, but the level of DPO use decreased right after the FDA revision in all groups. The decline in EPO use trend was faster after the TREAT trial for all groups. Nephrologists were largely more responsive to evidence than primary care physicians. Differences by physician’s gender, and age were not consistent across insurance populations and types of ESA.

Background

There is a growing interest in understanding physicians’ decisions to discontinue use of (“de-adopt”) treatments in light of new clinical evidence suggesting that a previously-approved treatment is ineffective or unsafe. While existing studies mostly focus on measuring the rate of de-adoption or reductions in prescribing, there is less evidence regarding variation in de-adoption. Of particular interest are the impact of physician attributes and patient insurance type. Previous research on physicians’ adoption of new treatments based on clinical evidence suggests that physicians’ decisions are influenced by various factors such as physicians’ specialization and experience as well as patients’ health insurance. However, the de-adoption process is not simply a mirror reflection of the adoption process and, hence, may not be influenced by the same factors or in similar manners.

In this study, we examined the de-adoption of erythropoiesis-stimulating agents (ESA) in the treatment of anemia among patients with chronic kidney disease (CKD) and subsequent changes in prescribing. Anemia is common among CKD patients, and ESA treatment is used to stimulate bone marrow to produce red blood cells, preventing the need for blood transfusion. EPO treatment is typically triggered when a patient’s level of hemoglobin concentration (measured in gram per deciliter, or g/dL) is too low, and the treatment is used until the hemoglobin concentration reaches a “safe” range for patients. The target range has changed over time as recent clinical studies have highlighted the potential danger of setting the target hemoglobin level too high. The main types of ESA in the U.S. are epoetin alfa (EPO) and darbepoetin alfa (DPO), which mainly differ in how frequently the drug is administered to patients. DPO is a newer, synthetic form of naturally-occurring erythropoietin that has a longer duration of action, requiring less frequent administration; EPO is usually administered three times a week while DPO is administered once a week up to once every a month.

The first study to show evidence of unsafety and ineffectiveness of ESA use was the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) published in October 2009. The trial found that targeting a hemoglobin level of 13 g/dL using DPO did not reduce mortality, cardiovascular, or renal events, but resulted in a higher risk of stroke, compared to using DPO when the hemoglobin level fell below 9 g/dL. Following this publication, the Food and Drug Administration (FDA) revised its original black-box warnings in June 2011, recommending to only start ESA treatment when the hemoglobin level falls below 10 g/dL, with the lowest dose necessary to avoid blood transfusion.

Several studies have used administrative claims data to examine changes in overall ESA prescribing following the TREAT trial publication and the FDA revision of the original warnings. Thamer et al. compared ESA prescribing among Medicare patients with CKD stages 3 and 4 before and after the TREAT trial publication and found that prescribing rates dropped significantly; trend analysis suggested that ESA prescribing had been declining before the publication, but the decline accelerated following the event. Similarly, Park et al. found that ESA prescribing among patients in the Truven MarketScan database with CKD stages 3 to 5 dropped significantly following the trial and the FDA revision. Finally, Sarpatwari et al. evaluated changes in initiation of ESA among patients with cancer after a Risk Evaluation and Mitigaton (REMS) program was implemented and did not find significant changes in trends. However, neither study examined physician patterns of de-adoption, nor whether these patterns differed by insurance type. If certain types of physicians or certain pharmacy plans were associated with lower rates of de-adoption, the information could guide efforts to reduce the use unproven treatments. Moreover, neither study separated the impact of the evidence on the use of EPO and DPO.

Therefore, we examined ESA de-adoption among advanced CKD stages 3–5 patients - those who are more likely to have anemia relative to patients with early stages of the disease. First, we examined de-adoption of EPO separately from that of DPO; while the TREAT trial was about DPO treatment, the FDA revision applied to both EPO and DPO, and it is plausible that the impact of the TREAT evidence differed between the two. Second, we examined which physician characteristics were associated with de-adoption, examining changes in prescribing in both levels and trends in response to both the trial and the FDA revision. And third, we examined de-adoption in multiple insurance...
populations, namely commercially insured, Medicare Advantage (MA), and Medicare Fee-for-Service (FFS) beneficiaries, and assessed whether physician attributes had different associations across these payers.

**Methods**

**Data source**

We used administrative claims data from two sources. The first source was the 2007–2015 commercial and MA administrative claims from the OptumLabs® Data Warehouse (OLDW), a comprehensive, longitudinal, real-world data asset with de-identified claims and clinical information. The second source was a 20% random sample of Medicare Fee for Service (FFS) beneficiaries from 2007–2013. We combined the administrative data with information about physicians from Doximity®. Doximity is a data resource that allowed us to observe key physician characteristics. This database includes information from a wide range of sources, such as the National Provider Identifier Registry and state medical boards, and has been validated and used in previous literature.

**Study population**

We identified three separate cohorts of patients who had at least one claim for CKD diagnosis (based on ICD 9-CM and ICD 10-CM diagnosis codes) anytime between 1/2007 and 12/2015; all were identified using medical claims in either commercial, MA or FFS data sources. We restricted the cohorts to those who had continuous medical and prescription drug coverage for the 12 months before the index diagnosis claim for CKD. In any given month, we flagged a patient to have CKD if they had at least one inpatient claim or two outpatient claims spaced more than 30 days apart with CKD diagnosis in the past 6 months. Our final analytical samples consisted of the patient-months identified to have CKD stages 3–5 without dialysis treatment. Supplemental Digital Content, Sect. 1 provides details on the ICD 9-CM and ICD 10-CM diagnosis codes and CPT codes used to identify the study sample.

**Physician Assignment**

To analyze changes in ESA use by physician characteristics, we attributed each patient-month observation to the physician responsible for making decisions concerning the ESA treatment following a 2-step procedure. In the first step, we isolated medical claims for all evaluation and management (E&M) visits for each patient-month observation and divided claims into four categories based on the specialty of the associated physician: (1) nephrology, (2) internist, (3) hematology and oncology, and (4) all others. Drawing from the literature, we ranked these categories based on relevance to anemia treatment for patients with CKD with (1) being the most relevant and (4) being the least relevant specialty. For example, even if an internist has more E&M claims than a nephrologist in a given month, the nephrologist is attributed to the patient-month. Within each specialty category, the physician with the most E&M visits was attributed to the patient-month (ties were assigned randomly); and we carried forward that attribution, month after month, until an interruption in patient-months at risk or a change in physician with the most visits. Once each patient-month observation was attributed to a physician, we used the National Physician Identification (NPI) to merge in physician characteristics from the Doximity™ database.

**Measures**

The two outcome variables were dichotomous indicators for DPO and EPO use in a given patient-month observation (unit of analysis). The indicators were constructed by identifying ESA administration in outpatient claims (CPT codes "J0881" (Darbepoetin Alfa) and "J0885" (Epoetin Alfa)) or in pharmacy claims.

Patient covariates included sex, age, CKD stage, and Elixhauser comorbidity index. Physician characteristics included sex, specialty, and age (< 50, 50 or older), and physician specialty (primary care physicians (PCPs), nephrologists, and non-nephrology specialists, including internists, hematologists, and oncologists).

**Statistical Analysis**

We summarized DPO and EPO use, patient and physician characteristics, reporting mean (SD) or n (%) according the characteristic. Then, to assess patterns of de-adoption we estimated a series of mixed effects models. First, we examined changes in ESA use among CKD patients after new evidence of unsafety and ineffectiveness from the TREAT trial publication (10/2009) and the FDA revision (6/2011), using standard interrupted time series (ITS) models. We considered three time-periods based on these events:

- Baseline period (pre-TREAT): 1/2007 (start) to 6/2009
- Period 1 (post-TREAT/pre-FDA): 2/2010 to 2/2011
- Period 2 (post-TREAT/post-FDA): 10/2011 to 12/2015 (end)
We excluded the three-month periods before and after each event to avoid capturing any anticipatory or short term effects. We estimated changes in the level and the trend in use of DPO and EPO use in period 1 relative to the baseline, as well as in period 2 relative to period 1. All models adjusted for patient and physician characteristics and included calendar month dummy variables to account for seasonality. Standard errors were clustered at the patient level. Models were estimated separately for commercially insured, MA, and Medicare FFS cohorts. These models let us assess whether there were differences in de-adoption by payer; though data use agreements precluded combining these cohorts for formal testing, we report the effect magnitudes and P-values for each. Then, to assess whether de-adoption (changes in levels or trends) differed by physician characteristics, we estimated a second set of models which included interactions of the levels and trends with physician characteristics one at a time (for example nephrologist or not). Details of the model specifications are provided in Supplemental Digital Content, Sect. 2.

All analyses were performed with SAS, Version 9.4 (Copyright © 2002–2012 SAS Institute Inc.) and Stata 14.2 (StataCorp, College Station, TX). The study was deemed exempt from review by the University of Minnesota Institutional Review Board because the data were de-identified.

**Results**

Our study included 501,287 patient-month observations for the commercially insured, 1,206,050 for MA, and 17,405,319 for Medicare FFS. Unadjusted rates of DPO use were 5.3%, 3.2% and 2.6% for each insurance group respectively, while corresponding unadjusted rates of EPO use were 7.2%, 5.3% and 3.1% (Table 1). For the commercially insured, the mean (SD) age was 61.7 (13.1) and the mean Elixhauser comorbidity index was 6.1 (3.0). For MA and Medicare FFS samples, the mean ages were 75.2 (8.0) and 76.5 (10.1), and the mean comorbidity index was 7.2 (3.1) and 14.1 (10.1), respectively. CKD stage 3 was the most prevalent in all three samples (75.3–76.0%). The majority of the observations for the commercially insured and MA patients were attributed to nephrologists (63.2% and 46.1%, respectively), while only 22.9% of the Medicare FFS observations were attributed nephrologists.

| Table 1 | Patients with Chronic Kidney Disease (CKD) stages 3–5 |
|---------|-----------------------------------------------|
|         | Commercial | Medicare Advantage | Medicare FFS |
|         | (N = 501,287) | (N = 1,206,050) | (N = 17,405,319) |
| **ESA use** |         |                  |              |
| EPO use (%) | 7.2   | 5.3   | 3.1   |
| DPO use (%) | 5.3   | 3.2   | 2.6   |
| **Patient characteristics** |         |                  |              |
| Female (%) | 42.9  | 53.1  | 51.8  |
| Mean Age (SD) | 61.7 (13.1) | 75.2 (8.0) | 76.5 (10.1) |
| Mean Elixhauser score (SD) | 6.1 (3.0) | 7.2 (3.1) | 14.1 (10.2) |
| CKD stage 3 (%) | 75.3  | 76.0  | 76.0  |
| CKD stage 4 (%) | 21.5  | 21.8  | 20.1  |
| CKD stage 5 (%) | 3.2   | 2.2   | 3.9   |
| **Physician characteristics** |         |                  |              |
| Female (%) | 19.3  | 19.8  | 17.4  |
| Completed residency under 20 years ago (%) | 55.0  | 53.7  | -    |
| Under 50 years old (%) | 47.2  | 45.6  | 39.8  |
| Nephrologist (%) | 63.2  | 46.1  | 22.9  |
| Internist (%) | 11.2  | 22.2  | 2.6   |
| Hematologist (%) | 2.5   | 2.2   | 4.5   |
| Other specialties | 25.5  | 32.2  | 46.6  |
For all three cohorts, unadjusted rates of EPO and DPO use were declining before the TREAT trial and over the entire study period (Fig. 1). For example, among the commercially insured, EPO use was 16% and DPO use was 12% in January 2007, while corresponding rates were 10% and 8% in September 2009, just before the TREAT trial.

### Changes in levels and trends of use over time by insurance cohort

#### DPO (Table 2, Panel A)

|                  | Commercial | Medicare Advantage | Medicare FFS |
|------------------|------------|---------------------|--------------|
|                  | Baseline trend | Changes from previous period | Baseline trend | Changes from previous period | Baseline trend | Changes from previous period |
|                  | Period 1 | Period 2 | Period 1 | Period 2 | Period 1 | Period 2 | Period 1 | Period 2 |
| **Panel A: DPO use** |          |          |          |          |          |          |          |          |
| Trends           | -0.13    | 0.10     | -0.13    | 0.02     | 0.08     | -0.13    | 0.07     | 0.03     |
|                  | (-0.17, -0.09) | (0.02, 0.17) | (-0.2, -0.09) | (-0.05, 0.09) | (0.03, 0.13) | (-0.13, -0.11) | (0.05, 0.08) | (0.01, 0.004) |
| Levels           | -0.85    | -1.33    | -0.245   | -0.66    | 0.61     | -0.60    |
|                  | (-1.74, -0.03) | (-2.2, -0.05) | (-1.11, 0.62) | (-1.28, -0.03) | (0.45, 0.77) | (-0.77, -0.48) |
|                  | [0.061]  | [0.003]  | [0.581]  | [0.040]  | [< 0.001] | [< 0.001] |

#### Panel B: EPO use

|                  | Commercial | Medicare Advantage | Medicare FFS |
|------------------|------------|---------------------|--------------|
|                  | Baseline trend | Changes from previous period | Baseline trend | Changes from previous period | Baseline trend | Changes from previous period |
|                  | Period 1 | Period 2 | Period 1 | Period 2 | Period 1 | Period 2 | Period 1 | Period 2 |
| Trends           | -0.07    | -0.18    | 0.19     | -0.003   | -0.17    | 0.11     | -0.07    | -0.03    | 0.10     |
|                  | (-0.1, -0.03) | (-0.27, -0.09) | (0.11, 0.26) | (-0.05, -0.09) | (-0.24, -0.09) | (0.05, 0.17) | (-0.08, -0.07) | (-0.05, -0.02) | (0.08, 0.11) |
| Levels           | -0.62    | 0.61     | -0.80    | -0.87    | 0.32     | -0.18    |
|                  | (-1.63, 0.39) | (-3.6, 1.58) | (-1.78, 0.18) | (-1.65, -0.09) | (0.15, 0.49) | (-0.3, -0.01) |
|                  | [0.228]  | [0.215]  | [0.110]  | [0.028]  | [< 0.001] | [0.034]  |

**Notes:** Estimates are reported for baseline trends and changes of trends and levels of DPO and EPO use, compared to previous periods. Baseline refers to the period between Jan-2007 to June-2009; period 1 (post-TREAT/pre-FDA) is between Feb-2010 and Feb-2011; period 2 (post-TREAT/post-FDA) is between Oct-2011 and Dec-2015. All estimates were multiplied with 100 to represent percentage point changes. All samples consist of patients with CKD stage 3 to 5. All models control for patients’ sex and age and physicians’ specialty, age, sex, and experience (see text for details). Standard errors are clustered at the patient level; 95% confidence interval is reported in parentheses, and p-value is reported in brackets.

Prior to the TREAT trial, DPO use declined by an average of 0.13 percentage points per month in each insurance group (all P-values < 0.001). Following the trial publication, commercially insured and MA did not have a change in levels of use, but Medicare FFS had an increase in levels of use (P-value < 0.01). Commercially insured and Medicare FFS patients had an increase in trend of use (less negative trend), while MA did not. After the FDA revised its black box warning, there was an immediate decline in the levels of DPO use in all 3 groups (all P-values < 0.05). Commercially insured patients experienced no changes in trends while MA and FFS patients experienced increases in trends (both P-values < 0.005).

#### EPO (Table 2, Panel B)
Before the TREAT trial publication, EPO use was decreasing for commercial and Medicare FFS patients (both, P < 0.001), but was flat for MA patients. After the publication, there was no change in levels for commercially insured and MA but an increase in level for Medicare FFS (P < 0.001). EPO trends decreased further for all three cohorts (all P-values < 0.001). Following the FDA revision, MA and FFS patients experienced a decrease in levels (both P-values < 0.05), and all patient groups experienced an increase in trends (all P < 0.005).

Changes in trends and levels of use over time by physician characteristics

DPO (Table 3)
### Table 3
Changes in DPO use levels and trends by physician characteristics

|                  | Commercial | Medicare Advantage | Medicare FFS |
|------------------|------------|--------------------|--------------|
|                  | Change from baseline to Period 1 | Change from Period 1 to 2 | Change from baseline to Period 1 | Change from Period 1 to 2 | Change from baseline to Period 1 | Change from Period 1 to 2 |
| Trends           | (1)        | (3)                | (5)         | (7)         | (9)         | (11)       |
| Levels           | (2)        | (4)                | (6)         | (8)         | (10)        | (12)       |
| Panel A: PCPs versus Nephrologists |
| PCPs             | 0.01       | -0.95              | 0.07        | 1.05        | -0.03       | -0.30      |
|                  | (-0.16, 0.17) | (-3.32, 1.41) | (-0.07, 0.21) | (-0.64, 2.74) | (-0.13, 0.07) | (-1.53, 0.93) |
|                  | (0.01)     | [0.934]            | [0.429]     | [0.322]     | [0.222]     | [0.572]    |
|                  | [0.001]    | [< 0.001]          | [0.01]      | [< 0.001]   | [< 0.001]   | [< 0.001]  |
| Nephrologists    | 0.13       | 0.11               | -0.03       | -0.91       | 0.10        | 0.32       |
|                  | (0.05, 0.21) | (-0.81, 1.02) | (-0.10, 0.05) | (-1.89, 0.07) | (0.01, 0.19) | (-0.76, 1.41) |
|                  | (0.01)     | [0.002]            | [0.821]     | [0.464]     | [0.070]     | [0.028]    |
|                  | [0.001]    | [< 0.001]          | [< 0.001]   | [< 0.001]   | [< 0.001]   | [< 0.008]  |
| Diff. P-value    | 0.189      | 0.407              | 0.220       | 0.050       | 0.057       | 0.442      |
|                  | [0.001]    | [< 0.001]          | [< 0.001]   | [< 0.001]   | [< 0.001]   | [< 0.001]  |
| Panel B: Male versus Female |
| Male             | 0.14       | -0.75              | -0.06       | -1.70       | 0.06        | -0.15      |
|                  | (0.06, 0.23) | (-1.73, 0.24) | (-0.13, 0.02) | (-2.69, -0.72) | (-0.02, 0.13) | (-1.1, 0.80) |
|                  | (0.01)     | [0.001]            | [0.137]     | [0.142]     | [0.001]     | [0.156]    |
|                  | [0.001]    | [< 0.001]          | [< 0.001]   | [< 0.001]   | [< 0.001]   | [< 0.001]  |
| Female           | -0.09      | -1.44              | 0.11        | 0.22        | -0.15       | -0.78      |
|                  | (-0.24, 0.06) | (-3.32, 0.44) | (-0.02, 0.24) | (-1.51, 1.96) | (-0.31, 0.01) | (-2.77, 1.22) |
|                  | (0.01)     | [0.249]            | [0.133]     | [0.102]     | [0.800]     | [0.060]    |
|                  | [0.001]    | [< 0.001]          | [< 0.001]   | [< 0.001]   | [< 0.001]   | [< 0.001]  |
| Diff. P-value    | 0.007      | 0.512              | 0.030       | 0.057       | 0.573       | 0.032      |
|                  | [0.001]    | [< 0.001]          | [< 0.001]   | [< 0.001]   | [0.025]     | [< 0.001]  |
| Panel C: Under versus Over 50 years old |
| Above 50         | 0.06       | -0.99              | -0.01       | -1.09       | 0.01        | -1.22      |
|                  | (-0.04, 0.16) | (-2.16, 0.19) | (-0.1, 0.08) | (-2.3, 0.15) | (-0.07, 0.10) | (-2.33, -0.10) |
|                  | (0.06)     | [0.237]            | [0.101]     | [0.778]     | [0.081]     | [0.765]    |
|                  | [0.001]    | [< 0.001]          | [< 0.001]   | [0.025]     | [< 0.001]   | [< 0.001]  |
| Under 50         | 0.15       | -0.58              | -0.05       | -1.61       | 0.04        | 1.29       |
|                  | (0.04, 0.26) | (-1.88, 0.72) | (-0.14, 0.05) | (-2.88, -0.34) | (-0.05, 0.21) | (-0.05, 2.63) |
|                  | (0.05)     | [0.006]            | [0.379]     | [0.348]     | [0.013]     | [0.516]    |
|                  | [0.002]    | [< 0.001]          | [< 0.001]   | [< 0.001]   | [< 0.001]   | [< 0.001]  |

Note: Estimates are reported for changes of trends and levels of DPO use (compared to previous periods) by physician's characteristics as well as P-value for differences across physician characteristics. Baseline refers to the period between Jan-2007 to June-2009; period 1 (post-TREAT/pre-FDA) is between Feb-2010 and Feb-2011; period 2 (post-TREAT/post-FDA) is between Oct-2011 and Dec-2015. All estimates were multiplied with 100 to represent percentage point changes. All samples consist of patients with CKD stage 3 to 5. All models control for patients’ sex and age and physicians’ specialty, age, sex, and experience (see text for details). Standard errors are clustered at the patient level; 95% confidence interval is reported in parentheses, and P-value is reported in brackets.
In Medicare FFS, levels in DPO use increased immediately following the trial publication, and decreased following the FDA revision (all P-values < 0.05) both for nephrologists and PCPs. There were no immediate level changes in commercially insured and MA for either the nephrologists or PCPs.

Monthly DPO trends increased after TREAT publication for nephrologists in all three insurance cohorts, but increased for PCPs only in the Medicare FFS cohort (all P-values < 0.05); however there was no significant difference in trends between these two specialty groups in any cohort. After FDA revision, monthly trends increased more for nephrologists in the FFS group, but all other trends were stable.

Levels of DPO use increased immediately following the trial publication similarly for male and female physicians, but only in Medicare FFS (P-values < 0.01). Following the FDA revision, levels of use decreased for male physicians across all insurance groups (P-values < 0.01); and decreased for female physicians only in Medicare FFS (P-value < 0.001).

Trends in DPO among male physicians increased (became less negative) in commercial and Medicare FFS groups after the trial publication (P-value < 0.01) and remained stable in MA group. Among female physicians, trend increased only in Medicare FFS (P-value < 0.001).

Changes in trends after the FDA revision was also largely statistically insignificant except for increases in MA among female physicians, and in Medicare FFS among male physicians (P-values < 0.01).

There was a decrease in DPO levels following trial publication and the FDA revision for physicians aged 50 and older, but only in commercially insured (P-values < 0.05). In Medicare FFS, levels increased similarly in both age groups following the trial publication, but decreased following the FDA revision (all P-values < 0.001).

There were no changes in DPO trends by physician age across the three insurance groups. Only in Medicare FFS, we observed that physicians aged 50 and older had a larger increase in DPO trend after the trial publication (P-value of difference = 0.037). However, this relationship was reversed after the FDA revision with the older physicians having a smaller increase in trend compared with the younger physicians.

**EPO (Table 4)**
## Changes in EPO use levels and trends by physician characteristics

|                  | Commercial | Medicare Advantage | Medicare FFS |
|------------------|------------|--------------------|--------------|
|                  | Change from baseline to Period 1 | Change from Period 1 to 2 | Change from baseline to Period 1 | Change from Period 1 to 2 | Change from baseline to Period 1 | Change from Period 1 to 2 |
| **Trends**       | (1)        | (2)                | (3)          | (4)          | (5)          | (6)          |
| **Levels**       | (7)        | (8)                | (9)          | (10)         | (11)         | (12)         |
| Panel A: PCPs versus Nephrologists |
| PCPs             |-0.19       | -1.26              | 0.07         | 0.37         | -0.09        | -0.56        | 0.03          | -0.09         | -0.04         | 0.25          | 0.09          | -0.25         |
|                  | (-0.22)    | (-3.86, 1.33)      | (-0.1, 0.25) | (-1.96, 2.70) | (-0.21, 0.03) | (-2.07, 0.95) | (-0.07, 0.13) | (-1.35, 1.17) | (-0.06, 0.01) | (-0.03, 0.54) | (0.07, 0.11)  | (-0.51, 0.02) |
|                  | [0.906]    | [0.340]            | [0.399]      | [0.755]      | [0.157]      | [0.467]      | [0.517]      | [0.887]      | [0.005]       | [0.078]      | [< 0.001]     | [0.070]       |
| Nephrologist     |-0.19       | 0.14               | 0.23         | 0.54         | -0.20        | -1.14        | 0.18          | -0.72        | -0.05         | 0.16          | 0.13          | -0.37         |
|                  | (-0.29)    | (-0.97, 1.25)      | (0.14, 0.32) | (-0.56, 1.65) | (-0.30, -0.10) | (-2.46, 0.17) | (0.10, 0.26)  | (-1.75, 0.31) | (-0.08, -0.02) | (-0.17, 0.49) | (0.10, 0.15)  | (-0.71, -0.04) |
|                  | [< 0.001]  | [0.808]            | [< 0.001]    | [0.337]      | [< 0.001]    | [0.088]      | [< 0.001]    | [0.169]      | [< 0.003]     | [0.342]      | [< 0.001]     | [0.030]       |
| Diff. P-value    | 0.085      | 0.323              | 0.101        | 0.896        | 0.145        | 0.565        | 0.024         | 0.447        | 0.601         | 0.661         | 0.020         | 0.548         |
| Panel B: Male versus Female |
| Male             |-0.16       | -0.47              | 0.17         | 0.52         | -0.21        | -1.15        | 0.12          | -0.88        | -0.03         | 0.35          | 0.09          | -0.18         |
|                  | (-0.26)    | (-1.56, 0.62)      | (0.08, 0.26) | (-0.56, 1.60) | (-0.3, -0.12) | (-2.23, -0.06) | (0.05, 0.19)  | (-1.75, -0.01) | (-0.05, -0.01) | (-0.17, 0.54) | (0.07, 0.10)  | (-0.36, -0.01) |
|                  | [0.001]    | [0.400]            | [< 0.001]    | [0.349]      | [< 0.001]    | [0.038]      | [0.001]      | [0.048]      | [< 0.001]     | [< 0.001]     | [< 0.001]     | [0.041]       |
| Female           |-0.24       | -1.27              | 0.26         | 1.01         | 0.03         | 0.97         | 0.06          | -0.85        | -0.05         | 0.16          | 0.12          | -0.13         |
|                  | (-0.43)    | (-3.65, 1.11)      | (0.09, 0.43) | (-1.2, 3.2)  | (-0.15, 0.21) | (-1.23, 3.17) | (-0.08, 0.2)  | (-2.6, 0.91)  | (-0.08, -0.01) | (-0.22, 0.55) | (0.09, 0.15)  | (-0.5, 0.23)  |
|                  | [0.016]    | [0.296]            | [0.002]      | [0.368]      | [0.741]      | [0.390]      | [0.388]      | [0.344]      | [0.005]       | [0.409]      | [< 0.001]     | [0.474]       |
| Diff. P-value    | 0.480      | 0.543              | 0.324        | 0.691        | 0.017        | 0.088        | 0.432         | 0.974        | 0.326         | 0.373         | 0.091         | 0.810         |
| Panel C: Under versus Over 50 years old |
| Above 50         |-0.17       | -0.92              | 0.16         | 0.48         | -0.20        | 0.02         | 0.16          | -0.53        | -0.03         | 0.29          | 0.08          | -0.25         |
|                  | (-0.29)    | (-2.23, 0.38)      | (0.05, 0.27) | (-0.89, 1.85) | (-0.3, -0.09) | (-1.26, 1.3)  | (0.07, 0.24)  | (-1.56, 0.50) | (-0.05, -0.01) | (-0.08, 0.50) | (0.07, 0.10)  | (-0.45, -0.04) |
|                  | [0.004]    | [0.166]            | [0.004]      | [0.495]      | [< 0.001]    | [0.979]      | [< 0.001]    | [0.317]      | [0.005]       | [0.007]      | [< 0.001]     | [0.016]       |
| Under 50         |-0.18       | -0.17              | 0.21         | 0.81         | -0.13        | -2.02        | 0.05          | -1.34        | -0.04         | 0.37          | 0.11          | -0.06         |
|                  | (-0.30)    | (-1.68, 1.33)      | (0.1, 0.32)  | (-0.53, 2.15) | (-0.25, -0.02) | (-3.48, -0.55) | (-0.05, 0.14) | (-2.52, -0.16) | (-0.07, -0.02) | (-0.11, 0.63) | (0.09, 0.13)  | (-0.3, 0.18)  |
|                  | [0.005]    | [0.821]            | [< 0.001]    | [0.236]      | [0.025]      | [0.007]      | [0.328]      | [0.026]      | [< 0.001]     | [0.005]      | [< 0.001]     | [0.844]       |

**Note:** Estimates are reported for changes of trends and levels of EPO use (compared to previous periods) by physician’s characteristics as well as P-value for differences across physician characteristics. Baseline refers to the period between Jan-2007 to June-2009; period 1 (post-TREAT/pre-FDA) is between Feb-2010 and Feb-2011; period 2 (post-TREAT/post-FDA) is between Oct-2011 and Dec-2015. All models control for patients’ sex and age and physicians’ specialty, age, sex, and experience (see text for details). Standard errors are clustered at the patient level; 95% confidence interval is reported in parentheses, and P-value is reported in brackets.
Discussion

In this examination of ESA use in three insurance cohorts, we found that DPO and EPO use were both already declining prior to the TREAT trial publication, and they continued to decrease following the TREAT trial and the FDA black box warning revision. While this was consistent with prior research, we also found differences in how the trends and levels changed: by treatment, by insurance group and by physician characteristics. Consistent with expectations, the decline in EPO use became steeper after the TREAT trial across all three insurance groups, but surprisingly, the decline in DPO use slowed (the trend was less negative) after the TREAT trial in commercially insured and Medicare FFS groups, and was unaffected in MA group. Moreover, after the FDA revision, the trends in DPO use increased again in the MA and Medicare FFS, though not in the commercial group, while the trend in EPO use increased in all three groups.

Notably, although the DPO trend increased after both the TREAT trial and the FDA revision, DPO use overall dropped after the FDA revision in all three insurance groups; this suggests both that the subsequent weaker decline (relative to the trend prior to the FDA revision) may reflect in part lower overall use, and also that the FDA revision is viewed as a stronger evidence relative to the TREAT trial publication associated with a decrease in use. We observed the similar immediate decline for EPO use after the FDA revision as well.

Differences in de-adoption across insurance cohorts were minor and with no consistent relationship between insurance group and changes in levels or trends. That we found fewer changes in levels and trends in the commercial cohort may reflect the smaller sample size, especially compared with the FFS group (with 34 x as many patients), but even that cohort had more than half a million patients. More likely these differences reflect differences in providers who treat more or fewer commercial, FFS or MA patients.

With regards to providers, we found that both the less negative trend in DPO use as well as the steeper decline in EPO use after the TREAT trial were generally driven by nephrologists to a greater extent. We also observed some differences in responses to the trial and the warning revision by physician’s gender and age, but the differences were not consistent for DPO and EPO and for different insurance populations. These results suggest that physician specialty have a dominant role in prescribing decision, and that specializations with higher use of

Table 1: Differences in levels and trends of ESA use.

|                      | Commercial | Medicare Advantage | Medicare FFS |
|----------------------|------------|--------------------|--------------|
| Diff. P-value        | 0.967      | 0.451              | 0.517        |
|                      | 0.732      | 0.422              | 0.037        |
|                      | 0.081      | 0.309              | 0.231        |
|                      | 0.614      | 0.025              | 0.211        |

Note: Estimates are reported for changes of trends and levels of EPO use (compared to previous periods) by physician's characteristics as well as P-value for differences across physician characteristics. Baseline refers to the period between Jan-2007 to June-2009; period 1 (post-TREAT/pre-FDA) is between Feb-2010 and Feb-2011; period 2 (post-TREAT/post-FDA) is between Oct-2011 and Dec-2015. All estimates were multiplied with 100 to represent percentage point changes. All samples consist of patients with CKD stage 3 to 5. All models control for patients’ sex and age and physicians’ specialty, age, sex, and experience (see text for details). Standard errors are clustered at the patient level; 95% confidence interval is reported in parentheses, and P-value is reported in brackets.

There were no EPO level changes after the TREAT trial for either the nephrologists or PCPs; the level decreased after the FDA revision for nephrologists, but only in Medicare FFS (P-value = 0.03). After the TREAT trial, EPO monthly use trend decreased for nephrologists in all insurance groups (P-values < 0.01). In contrast, for PCPs, decrease in trend was observed only in Medicare FFS (P-value < 0.01). Following the FDA revision, trends increased among nephrologists in all three insurance groups (P-values < 0.001). Among PCPs, increase was observed only in Medicare FFS (P < 0.001).

Among female physicians, there were no changes in EPO levels across insurance groups after the TREAT trial or the FDA revision. However, among male physicians, levels decreased in MA and increased in Medicare FFS after the trial publication (P-values < 0.05), and decreased in both insurance groups after the FDA revision (P-values < 0.05).

The change in trends after TREAT trial was significantly different between male and female physicians only in MA. While the trend declined for male physicians (P-value < 0.001), it remained stable for female physicians (P-value = 0.741), a relative difference significant at P-value = 0.017. There were no significant differences in the change of trends following the FDA revision.

Among physicians aged 50 and older, there were no changes in EPO levels across the board except in Medicare FFS; an increase after the TREAT trial (P-value = 0.007) and a decrease following the FDA revision (P-value = 0.016). Among the younger group of physicians, levels declined in MA and increased in Medicare FFS after the TREAT trial (P-values < 0.01), and declined in MA following the FDA revision (P-value = 0.005).

Older and younger physicians had similar changes in trends after the TREAT trial, and after FDA revision with no significant differences in relative change in trends except for Medicare FFS where physicians aged 50 and older had slightly lower increase in trend after the FDA revision relative to younger physicians (P-values < 0.001, a difference significant at P = 0.025).
treatment were more responsive to new evidence of unsafety and ineffectiveness. This is likely because the patient populations attributed to specialists for a given condition, in this case nephrologists, may be more severe in unobserved ways.

Our findings are broadly consistent with prior research on de-adoption of treatments, which has found variation across providers in how rapidly treatments fall out of use in the wake of new evidence. Borne et al.\textsuperscript{34} found that variation across institutions increased with increasing de-adoption of defibrillation following evidence of risk, indicating that providers de-adopted at different rates; they attribute this to different institutional practices. Bekelis et al.\textsuperscript{4} found that more experienced physicians reduced their use of carotid revascularization more quickly than other physicians, while higher volume physicians reduced their use more slowly. More generally, van Dulmen et al.\textsuperscript{35} identified 263 barriers to de-adoption of treatments, of which the majority were physician factors. Thus, there are large variety of factors that may systematically influence the de-adoption of EPO and DPO, which suggests the need for systematic efforts to promote de-adoption.\textsuperscript{36}

There are several limitations this study. Our patient populations were identified using diagnosis codes and medication use in administrative claims. Moreover, our analyses could not account for many unobserved factors of ESA use such as treatment cost, patient preference, and ESA treatment appropriateness. The FDA warning indicated that ESA treatment can be considered if the hemoglobin level was less than 10 g/dL, the rate of hemoglobin declined, and reducing the risk of alloimmunization and/or red blood cell transfusion was the goal. These unobserved conditions would influence physician decisions whether to prescribe ESA treatment for patients.

In summary, we found that the use of DPO and EPO started decreasing before new evidence on their ineffectiveness and unsafety, and continued to decrease over the study period. However, the impact of the TREAT trial and of the FDA revision was limited and inconsistent, with a trend that decelerated for DPO for some payers. Our findings indicate that de-adoption of ineffective and unsafe treatments varies across insurance type and across physician specialty and characteristics. It is important to take these variations into account when designing practice guidance to promote efficient de-adoption.

**Declarations**

**Abbreviations**

ESA: Erythropoiesis-stimulating agents

CKD: Chronic kidney Disease

EPO: Epoetin alfa

DPO: Darbepoetin alfa

TREAT: Trial to Reduce Cardiovascular Events with Aranesp Therapy

FDA: Food and Drug Administration

MA: Medicare Advantage

FFS: Fee-for-Service

OLDW: OptumLabs® Data Warehouse

E&M: Evaluation and management

NPI: National Physician Identification

PCP: Primary care physicians

SD: Standard deviation

ITS: Interrupted Time Series

**Declarations**

**Ethics approval and consent to participate:** Not applicable

**Consent for publication:** Not applicable
**Availability of data and material**: We are using proprietary data accessed from OptumLabs approved a Detailed Research Application (DRA) and administrative Medicare files from CMS that are approved under a Data Use Agreement (DUA) purchased from CMS for this project. As such we are not authorized to share any data, but we are happy to suggest researchers interested the appropriate steps to acquire data on their own for their specific DUA.

**Competing interests**

In the past 36 months, Alexander Everhart has worked as a graduate research fellow at Medtronic plc. Nihar Desai reports grants and personal fees from Amgen, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Cytokinetics, personal fees from Novartis, grants and personal fees from Relypsa, and personal fees from SC Pharmaceuticals. Jeph Herrin reports grants from the Agency for Healthcare Research and Quality. Anupam Jena reports grants from the National Institutes of Health, personal fees from Pfizer, personal fees from Hill Rom Services, Inc, personal fees from Bristol Myers Squibb, personal fees from Novartis Pharmaceuticals, personal fees from Vertex Pharmaceuticals, personal fees from Precision Health Economics, personal fees from Amgen, personal fees from Eli Lilly, personal fees from Analysis Group, personal fees from Sanofi Aventis, personal fees from Celgene, personal fees from Tesaro, personal fees from AstraZeneca, and personal fees from Biogen. Joseph Ross reports grants from the Food and Drug Administration, grants from Medtronic plc, grants from Johnson & Johnson, grants from the Centers for Medicare and Medicaid Services, grants from Blue Cross-Blue Shield Association, grants from the Agency for Healthcare Research and Quality, grants from Laura and John Arnold Foundation, grants from the National Institutes of Health - National Heart Lung, and Blood Institute, grants from the Laura and John Arnold Foundation, and grants from the Medical Devices Innovation Consortium. Dr. Shah has received research support through Mayo Clinic from the Food and Drug Administration, the Centers of Medicare and Medicaid Services, Agency for Healthcare Research and Quality, National Science Foundation, and PCORI. Dr. Karaca Mandic reports grants from the Agency for Healthcare Research and Quality, grants from the National Institutes of Health - National Heart, Lung, and Blood Institute, grants from the American Cancer Society, personal fees from Tactile Medical, Precision Health Economics and Sempre Health for work unrelated to this project.

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**Authors’ contributions**: PKM designed the study and acquired the data; KV and JZ analyzed the data; KV made the tables and figures; KV, PKM, AE, JZ drafted and revised the paper; all authors approved the final version of the manuscript.

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**Figures**

![Figure 1](https://example.com/Section1.png)

**Figure 1**

Unadjusted rates of ESA use by insurance, 2007-2015 period, CKD stages 3-5

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- Section1.png
- Section2.png