

FINAL REPORT

TITLE PAGE

Title: **Do Safety Warnings Change Prescribing among the US Dialysis Population?**

Principal Investigator and Team Members: M Thamer, PI, and other team members (some funded through this project, others not): Y Zhang, D Lai, O Kshirsagar, D Cotter

Organization: Medical Technology and Practice Patterns Institute (MTPPI)

Inclusive Dates of Project: 06/01/2012 – 05/31/2013

Federal Project Officer: Denise Burgess

Acknowledgment of Agency Support: Supported by AHRQ

Grant Award Number: 5R03HS020572-02

REPORT COMPONENTS

Structured Abstract

Purpose: In March 2007, a Black Box warning was issued by the Food and Drug Administration (FDA) to use the lowest possible erythropoiesis-stimulating agent (ESA) doses for the treatment of anemia associated with renal disease. The goal is to determine if a change in ESA use was observed among US dialysis patients after the warning.

Scope: ESA therapy was examined from September 2004 through August 2009 (30 months before and after the FDA Black Box warning) among adult Medicare hemodialysis patients.

Methods: An interrupted time series model assessed the impact of the warnings.

Results: The FDA Black Box warning did not appear to influence ESA prescribing among the overall dialysis population. However, significant declines in ESA therapy after the FDA warnings were observed for select populations. Patients with a hematocrit $\geq 36\%$ had a declining month-to-month trend before (-164 units/week, $p \leq 0.0001$) and after (-80 units/week, $p = .001$) the warnings and had a large drop in ESA level immediately after the Black Box (-4,744 units/week, $p \leq .0001$). Not-for-profit facilities had a declining month-to-month trend before the warnings (-90 units/week, $p = .009$) and a large drop in ESA dose immediately afterward (-2,487 units/week, $p = 0.015$). In contrast, for-profit facilities did not have a significant change in ESA prescribing.

Conclusions: ESA therapy had been both profitable for providers and controversial regarding benefits for nearly two decades. The extent to which an FDA Black Box warning highlighting important safety concerns influenced use of ESA therapy among nephrologists and dialysis providers was unknown. Our study found no evidence of changes in ESA prescribing for the overall dialysis population resulting from an FDA Black Box warning.

Key words: epoetin; ESA therapy; Black Box warnings; interrupted time series; anemia management; ESRD

Purpose

On March 9, 2007, a public health advisory and Black Box warning was issued by the Food and Drug Administration (FDA) outlining new safety information about erythropoiesis-stimulating agents (ESAs), widely used drugs for the treatment of anemia associated with renal disease. The **goal** of this proposal is to determine if these new recommendations resulted in a change in physician prescribing among all US dialysis patients covered by the Medicare End-Stage Renal Disease (ESRD) program.

This proposal addresses the following innovative research questions:

- Did physicians change their prescribing of ESAs within 2 years after a highly publicized government Public Health Advisory meeting (and Black Box warning that went out to all practicing nephrologists) indicating the safety risks associated with ESA therapy and recommendations to use the lowest dose possible to avoid blood transfusions?
- Did this Public Health Advisory and concomitant Black Box warning result in a decline in the previously high ESA doses observed among dialysis patients?

- Are potential changes in prescribing dependent on patient sociodemographic and clinical characteristics and/or on dialysis facility characteristics?

Scope

End-stage renal disease

End-stage renal failure is defined as a permanent state of renal dysfunction severe enough to require renal replacement therapy (dialysis or kidney transplantation) to sustain life. In 1973, Medicare coverage was extended to all patients with end-stage renal disease (ESRD); currently, most patients are eligible 90 days after initiation of chronic dialysis.¹ The ESRD population is sizeable and poses a significant national healthcare burden. The prevalent dialysis population has increased more than threefold since 1988, and in 2006 it exceeded 350,000 patients. Although comprising less than 1% of the Medicare population, the ESRD population consumes almost 6.4% (\$23 billion dollars) of the \$355 billion in Medicare expenditures in 2006.²

Treatment for anemia

Anemia affects nearly all patients with ESRD and results in reduced quality of life and decreased survival rates.^{3,4,5} In 1987, investigators reported successful use of recombinant human erythropoietin (rHuEPO, epoetin, or EPO, trade name EPOGEN®) in treating the anemia by elevating the hemoglobin of ESRD patients. Based on the 1989 FDA approval, ESA was intended to treat blood transfusion--dependent dialysis patients (representing ~10%-30% of the 1988 ESRD patient pool). Today, ESA treatment is provided to virtually all dialysis patients, costing Medicare in excess of \$20 billion through 2008.⁶ Spending for ESA therapy is now the single largest Medicare drug expenditure and comprises 11% of all Medicare ESRD costs.

Public Health Advisory

Recently completed studies found an increased risk of death, blood clots, strokes, and heart attacks in patients with chronic kidney failure when ESAs were given at higher than recommended doses.^{7,8,9} As a result, on March 9, 2007, the FDA issued a public health advisory outlining new safety information, including revised product labeling about erythropoiesis-stimulating agents (ESAs) for anemia associated with renal disease as well as other conditions. The FDA and the manufacturer of these products agreed on revised product labeling that included updated warnings, a new Black Box warning, and modifications to the dosing instructions. The new Black Box warning advised physicians to monitor red blood cell levels (hemoglobin) and to adjust the ESA dose to maintain the lowest hemoglobin level needed to avoid the need for blood transfusions. According to the FDA, “physicians and patients should carefully weigh the risks of ESAs against transfusion risks.”

Specifically, the Black Box warning included the following important study results: “Patients with chronic kidney failure had an increased number of deaths and of non-fatal heart attacks, strokes, heart failure, and blood clots when ESAs were adjusted to maintain higher red blood cell levels (hemoglobin more than 12 g/dL)”; the language warned physicians who prescribe ESAs to consider the important study results above and to:

- Adjust the dose of ESA to maintain the lowest hemoglobin level necessary to avoid the need for transfusions;

- Monitor patients' hemoglobin levels to ensure they do not exceed 12 g/dL;
- Understand that ESAs are given to decrease the chances of receiving transfusions;
- Consider both the risks of transfusions and those of ESAs when deciding to prescribe an ESA; and
- Understand that ESAs should not be given to treat the symptoms of anemia, including shortness of breath, dizziness, fatigue, low energy, or poor quality of life.

Current ESA prescribing patterns

Currently, the FDA recommends a target hemoglobin of 10-12 g/dL for all patients; however, studies¹⁰ (including our own¹¹) have shown that patients are routinely targeted to the higher end of the FDA-recommended hemoglobin target range and that providers often overshoot the high end of this range. Furthermore, given Medicare's current reimbursement policy, allowing hemoglobin to be as high as 13 g/dL, the overshooting has not been deemed a major problem. The goal of this proposal is to examine whether the Public Health Advisory recommendations and subsequent Black Box warning issued in March 2007 by the FDA advocating the lowest possible ESA use influenced physician prescribing.

Before the FDA Public Health Advisory regarding ESA use issued in March 2007, physicians were prescribing large doses of ESAs to their dialysis patients. ESA dosing has changed dramatically in the past decade and a half. Use of ESAs has evolved from a low-dose treatment to correct severe anemia among patients with chronic kidney failure in the early 1990s to, more recently, the treatment of mild and moderate anemia using very high doses of ESAs. Between 1991 and 2005, the mean ESA dose increased about fourfold in dialysis patients.¹²

Role of reimbursement

The extent to which physicians have changed their prescribing habits as a result of the Black Box warnings is largely unknown. Despite the increasing evidence that ESA therapy has serious side effects and might be associated with decreased survival and increased risk of adverse cardiovascular outcomes,^{13,14,15,16,17,18} ESA therapy has been an important source of profit, particularly for large dialysis chains that are able to buy the drug at discount rates. Although the largest source of dialysis facility income is a predetermined payment (exclusive of injectable drugs) for each dialysis treatment, that rate has changed minimally in the last 20 years, and the real dollar value has actually declined by about 65%.¹⁹ ESA therapy is the second largest source of facility income, comprising approximately 25% of all dialysis facility profits.²⁰ ESA therapy is reimbursed on a fee-for-service basis, so more is paid as more is used, creating a financial incentive for increased utilization of this therapy. The Medicare Payment Advisory Commission (MedPAC) concluded that the profitability of certain separately billable drugs, including epoetin, has "provided incentives for their inefficient use."²¹

Methods

Data sources and study design

We used data from the United States Renal Data System (USRDS) Standard Analytic Files (SAFs) to conduct this study.²² The USRDS data system is a national resource that includes demographic and clinical data on ~97% of all US ESRD patients and their institutional

providers of dialysis treatment. (The USRDS website, <http://www.usrds.org>, "Researcher's Guide to the USRDS Database" describes the variables, data source, collection methods, and validation studies.) The hematocrit reading taken prior to the first administration of ESA therapy during the billing period (usually the beginning of the month) was submitted for payment with the total dose of ESA administered over the exposure period.

Specifically, *September 2004 to February 2007* was chosen as the 30-month base period (prior to the FDA Black Box warning), and *March 2007 to August 2009* was chosen as the 30-month follow-up period. ESA therapy is usually administered during outpatient dialysis via intravenous administration three times a week. In an effort to stabilize a large increase in hematocrit, physicians will periodically prescribe a zero ESA dose for a particular month. We also included these so-called zero dose months in our analysis. To ensure the availability of claims, the study population was restricted to adult ESRD hemodialysis patients with Medicare as a primary payor, as indicated by a variable in the USRDS Payor History File. We excluded those patients with MSP, as they have incomplete ESA data because their primary (usually private) payor is likely to get billed for ESA therapy. Our study period included only one form of ESA (epoetin alfa) for treatment of anemia associated with renal failure.

Age was categorized as follows: 18-44, 45-64, and ≥ 65 years. Race was categorized as White or not White. Duration of dialysis was determined as <12 , $12- <36$, and ≥ 36 months. Diabetes was determined if it was reported to be the primary cause of renal failure and/or if diabetes was listed as a comorbid condition when a patient enrolled in the Medicare ESRD program. Dialysis organizational status was defined by 1) chain membership (based on size and affiliation) and 2) profit status.

Interrupted time series analysis

Trends in anemia treatment before and after the FDA Public Health Advisory were statistically analyzed by categorical methods and interrupted time series models.^{23,24} To determine if there was a differential impact resulting from the FDA Black Box warning, we stratified our analyses by demographic, clinical, and facility characteristics. Trends in ESA treatment patterns across the study period were modeled using a general linear model, with the monthly dose per week as the dependent variable and the month as the independent variable. Monthly prescription rates for each patient were calculated by dividing the total ESA dose by the number of days in each dialysis claim (typically 30) and multiplying by seven to calculate the weekly dose per month. These monthly ESA doses per week were then used to determine an average monthly ESA dose per week for the entire population.

An interrupted time series model using the AUTOREG procedure in SAS was used to evaluate changes in average ESA dosages in the 30 months prior (base) and 30 months subsequent (follow up) to the FDA Black Box warning, as follows²⁵:

$$Y = \text{Beta}0 + \text{Beta}1 * m1 + \text{Beta}2 * m2 + \text{Beta}3 * x1$$

For which **Y** is the average ESA dose per week in each study month; **Beta0** estimates ESA prescribing at the beginning of the study period; **Beta1** estimates change in ESA prescribing in each month before the FDA warnings (*m1* study months in period 1); **Beta2** estimates change in ESA prescribing in each month after the FDA warnings (*m2* study months in period 2); and **Beta3** estimates the change in ESA prescribing level following the FDA warnings (*x1* is an indicator variable [0 for period one and 1 for period two]).

In our model, we took into account *autocorrelations* of the prescribing patterns along the time period. We built our model using a maximum likelihood method with two autocorrelation lags. The first-order autocorrelation coefficient was significantly different from zero for almost all models. Time series sometimes exhibit seasonality or seasonal fluctuations. We tested for *seasonality* using proc spectra in SAS against white noise of the residuals from the models and found that the residuals from our models were consistent with white noise indicating that no extra seasonality modeling was needed.²⁶ In some cases, models need to be corrected for *lagged effects* (i.e., the effect of an intervention might take time to appear). However, in our study, the FDA Black Box warning was immediately reported to all nephrologists through the Dear Doctor letters; therefore, no lag effects were entered into our main model, although possible random lag effects were modeled through serial correlations.

Study limitations

Several study limitations are noteworthy, however. One, when ESRD patients are hospitalized, on average twice a year, information on ESA dosing is not available. Two, the analysis was confined to those individuals with Medicare as the primary payor, so the generalizability to other payers is limited. And three, because of the exploratory nature of our analysis, we did not adjust for the size of the type-I error rate in conducting multiple statistical tests. One way to address the potential threat regarding the validity of an interrupted time series by historical/secular shifts is to compare, in our case, ESA drug doses to drug dosing of other profitable injectable drugs that should not be affected by the FDA warning (e.g., injectable vitamin D or iron). After increasing each year since 1992 (including growth of 11%-19% in 2002-2004) to reach nearly \$2 billion, Medicare ESA costs (a surrogate for use) were stable in 2004-2007 and in 2008 declined to a pre-2004 level of \$1.8 billion. Conversely, use of other intravenous drugs continued to increase in 2008: 12% for IV vitamin D, 4.8% for IV iron, and 13.2% for other injectables.²⁷

Results

Principal Findings

Across the study period, the study population was predominately elderly (49%), White (55%), and male (54%); had a duration of dialysis greater than 3 years (50%); was nondiabetic (56%); received dialysis services from for-profit facilities (81%) and from one of the two largest for-profit chains (27% and 30%, respectively); and had hematocrit values between 30% and 36%, within the FDA recommended range (comprising 46% of the study population), or higher (46%).

Overall, there was a significant 7% decrease in average ESA dose between the base and follow-up 30-month periods for all dialysis patients (19,486 versus 18,191 units/week). Most covariate strata also showed a decline in average dose between the two periods ($p < 0.0001$) except for Chain 3. Notably, Chain 3 (the largest nonprofit chain), which administers ~4.4% of all ESA doses, administered the lowest mean ESA dose *both* in the base and follow-up periods compared with other medium and large dialysis facilities. Overall, nonprofit and hospital-based facilities had the lowest average base and follow-up ESA doses. Hospital-based facilities are anomalous, however, due to their small size, sicker population, and disproportionate use of darbepoetin, a different form of ESA that is longer acting and that was not included in this study.

Younger, non-White, and new patients were most likely to be prescribed a higher ESA dose ($\geq 30,000$ units/week, reflecting the highest ESA dose quartile; $p < 0.0001$). Not unexpectedly, patients with the lowest hematocrit levels were significantly more likely to receive a higher ESA dose ($p < 0.0001$). For-profit facilities in general and the two largest for-profit chains prescribed higher ESA doses ($p < 0.0001$).

Interrupted time series results

A model was performed to determine if the average 7% observed decline in ESA dose was consistent with a change in dosing practice as of the FDA Black Box warning. Model results include a general trend in ESA dose/week for each month in the base period prior to the warnings (*Beta1*); a general trend in ESA dose/week for each month in the follow-up period after the warnings, often referred to as 'sustainability' (*Beta2*); and a post-intervention change (or shift) in ESA dose/week level immediately after the warnings (*Beta3*).

The FDA Black Box warning did not appear to influence ESA prescribing among the overall US dialysis population. Model results show the declining trend in month-to-month ESA dose was not statistically significant either before or after the FDA warnings. The drop in ESA dose level after the warnings was also not significant. Stratification by patient demographics and by clinical and facility characteristics suggests a differential impact in the effect of the FDA Black Box warning on ESA prescribing. Only a few covariates had statistically significant findings linked to the FDA warnings. For example, patients with a hematocrit $\geq 36\%$ had a declining month-to-month trend both before (-164 units/week, $p \leq .0001$) and after (-80 U/wk, $p = .001$) the warnings and had a large drop in ESA levels after the warnings (-4,744 U/wk, $p \leq .0001$). In contrast, patients with a hematocrit $< 30\%$ had a large increase in ESA dose level after the warnings (6,220 U/wk, $p = .013$), consistent with an increasing month-to-month trend before the warnings (224 units/week, $p = .01$). After the warnings, there was no significant decline in trend in ESA prescribing for patients with a hematocrit $< 30\%$. For patients within the FDA-recommended hematocrit range of 30%-36%, the change in ESA level immediately after the warnings was not significant, but there was a decline in month-to-month trend after the warnings (-103 U/wk, $p = 0.014$).

The other area of significant findings and wide variation in response to FDA warnings is dialysis facility organizational status. The ESA prescribing trend in not-for-profit facilities declined month to month before the warnings (-90 units/week, $p = .009$), with a significant drop in ESA dose immediately after the warnings (-2,487 U/wk, $p \leq .015$). In contrast, there was no evidence of change in ESA prescribing linked to the Black Box warning among for-profit facilities overall. Each of the three largest US dialysis chains responded differently to the FDA warnings. Chain 1 patients experienced a declining month-to-month trend before (-90 units/week, $p = .004$) and after (-103 U/wk, $p = .002$) the warnings and had a drop in ESA dose level after the warnings (-2,148 U/wk, $p = .017$). Chain 2 patients experienced no change in ESA prescribing before or after the warnings. Chain 3 patients experienced an increasing month-to-month trend before the warnings (94 U/wk, $p = .041$) and an increase in the ESA dose level after the warnings (3,189 U/wk, $p = .016$), followed by a flat insignificant trend.

Conclusions

Although there was a decline in ESA dose across the 60-month study period, the FDA Black Box warning issued in March 2007 did not appear to influence ESA prescribing for the

overall dialysis population. However, for patients with the highest hematocrit values and for those receiving treatment in certain dialysis facilities, nephrologists and dialysis providers were more likely to heed the FDA Black Box warning.

The FDA Black Box warning issued for ESA therapy included the following important study results: “Patients with chronic kidney failure had an increased number of deaths and of non-fatal heart attacks, strokes, heart failure, and blood clots when ESAs were adjusted to maintain higher red blood cell levels (hemoglobin more than 12 g/dL).” A new patient medication guide accompanied the warnings and posed the following question and answer: ‘*What is the most important information I should know about Epogen?* Using Epogen can lead to death or other serious side effects.’²⁸ Given these warnings, our findings raise questions as to why providers did not lower ESA doses further than what we observed when faced with mounting evidence of risks.^{8,9,29,30,31,32} Prior to the warnings, and during our study, although the FDA recommended a target hematocrit of 30%-36%, studies suggested that providers often overshot the high end of this target range, given Medicare’s reimbursement policy allowance of hematocrit to be as high as 39%.^{33,34} ESA therapy was an important source of profit, particularly for large dialysis chains that were also able to recoup large rebates and receive discounts,³⁵ producing the second largest source of facility income of ~22%.³⁶ For instance, a spike in ESA dose evident in the beginning of 2006, also confirmed by USRDS data,³⁷ appears to be associated with a new lower payment method for ESA therapy that changed from a per-unit rate to a rate of 6% above manufacturers’ average sales price (ASP).³⁸ During our study period, ESA therapy continued to be reimbursed on a fee-for-service basis, creating a financial incentive for increased utilization of this therapy.

Significance

Although USRDS data show a decline in both ESA dose and hematocrit levels following the issuance of the FDA Black Box warning, it remained unclear, until now, whether these results were related to the FDA warnings or, rather, which groups, if any, benefited from the FDA warnings. Patients who had the highest hematocrit values showed the largest shift or decline in ESA dose level after the FDA warning, with a drop of 4,744 U/week, perhaps because providers were concerned about their safety given the publication of CHOIR⁸ and CREATE⁹ findings in mid-November 2006, which showed potential harm and no benefit for ESA therapy, respectively. It is noteworthy, however, that, *on average*, the percentage of patients with a monthly hematocrit reading above 36% declined from 51% to 41% following the FDA warnings. Given the appropriate goals of ESA therapy, two in five patients had hematocrit levels deemed unacceptably high in the 30 months following the FDA Black Box warning. For ESA-resistant patients, those with the highest doses and hematocrit levels <30%, there was a large increase in ESA dose level immediately after the warnings (and no subsequent significant decline in ESA trend)---findings contrary to the FDA Black Box warning. Perhaps providers felt justified not to decrease dose for their resistant patients after the warnings, given the Black Box emphasis on avoiding transfusions, which are sometimes triggered at a hematocrit threshold of ~27%-30% for patients with serious comorbidities.³⁹ High hematocrit levels appear to be of more concern than high ESA doses to nephrologists following the Black Box warnings. Implications of these findings require further investigation.

Variations in treatment practice patterns across more than 4,000 US dialysis facilities are well established and controversial.^{11,40,41,42,43,44,45} In our study, nonprofit facilities overall

had a declining trend before the warnings and a large drop in ESA dose immediately afterward. In contrast, for-profit facilities that overall prescribed *higher* ESA doses in both the periods before and after the FDA warnings compared with nonprofit facilities---on average 19,514 versus 12,185 U/week in the post-warning period---did not change their ESA prescribing related to the FDA warnings. However, not all for-profit facilities responded similarly to the FDA warnings. During our study, two thirds of dialysis patients received treatment in one of two large for-profit dialysis chains. Notably, one chain had significant declines in ESA doses consistent with FDA Black Box warnings, and the other chain did not. Chains are owned by different entities that make individual corporate decisions regarding anemia protocols and anemia management goals among their patients.

Implications

Evidence of adverse events commonly emerges after a drug has been on the market for several years, necessitating the issuance of a Black Box warning.⁴⁶ According to Green et al.,⁴⁷ there are three categories of factors relevant to behavior change among physicians: *predisposing factors* (communicating or disseminating information); *enabling factors* (facilitating the desired change in the practice site); and *reinforcing factors* (by reminders or feedback). The model suggests that interventions that are most successful in changing physician practice are those that use enabling strategies or reinforcing methods in addition to predisposing or disseminating strategies. For example, an FDA Black Box warning on ESA use *for oncology patients* was also released on March 2007 and included a mandate that providers engage in a risk/benefit discussion with the patient and document that this discussion occurred by completing and signing the Patient Acknowledgment Form; this is a more stringent requirement that is absent from dialysis provider ESA prescribing. In contrast to the results presented herein, ESA use for oncology patients plummeted following the Black Box warning.^{48,49}

After nearly three decades of the same ESRD payment system, an enhanced ESRD Prospective Payment System (PPS) was initiated in January 2011, bundling separately billable items (primarily ESA therapy) into the larger dialysis composite rate.⁵⁰ Under PPS, facilities have no financial incentive to use more drugs than are clinically necessary. We anticipate that changes in reimbursement rates will have a greater impact on access and reduce exposure to ESA therapy compared with the impact of the March 2007 FDA Black Box warning. Indeed, early indications suggest that both ESA use⁵¹ and hematocrit levels⁵² have been dramatically reduced since implementation of ESRD PPS.

List of Presentations and Publications

Thamer M. *Do Safety Warnings Change ESA Prescribing among the US Dialysis Population?* Accepted for Poster Presentation at National Kidney Foundation (NKF) Annual Meeting in Washington, DC, May 9-13, 2012.

Thamer M. *Effect of a FDA Black Box Warning on Prescribing for Anemia Management Among ESRD Dialysis Patients.* Presented at the 6th AHRQ Annual Conference, September 9-11, 2012, Bethesda, Maryland.

Thamer M, Zhang Y, Lai D, Kshirsagar O, Cotter D. *Influence of safety warnings on ESA prescribing among dialysis patients using an interrupted time series.* BMC Nephrol. 2013 Aug 9;14:172. doi: 10.1186/1471-2369-14-172.

REFERENCES

1. Eggers PW. Medicare's end-stage renal disease program. *Health Care Financing Rev* 2000;22:55-60.
2. U.S. Renal Data System, USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008.
3. Collins AJ, Li S, St Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%, *J Am Soc Nephrol* 2001;12:2465-2473.
4. Lowrie EG, Huang WH, Lew NL, Liu, Y. The relative contribution of measured variables to death risk among hemodialysis patients, Chapter 13 in *Death on hemodialysis*, edited by Friedman EA, Dordrecht, Kluwer Academic Publishers; 1994. pp 121-141
5. Ma, JZ, Ebben, J, Xia, H, Collins, AJ. Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 1999;10:610-619.
6. Centers for Medicare & Medicaid Services. 2001 Annual Report, End Stage Renal Disease, Clinical Performance Measures, Project. Department of Health and Human Services, Centers for Medicare & Medicaid Services, Center for Beneficiary Choices, Baltimore, Maryland, December 2001, pg 39.
7. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339:584-590.
8. 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;355:2085-2098.
9. 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.
10. Foley RN, Collins AJ. End-stage renal disease in the United States: an update from the United States Renal Data System. *J Am Soc Nephrol*. 2007;18(10):2644-8. Epub 2007 Jul 26.
11. Thamer M, Zhang Y, Kaufman J, Dong F, Cotter D, Hernan MA Dialysis Facility Ownership and Epoetin Dosing in Patients Receiving Hemodialysis *JAMA* 2007;297(15):1667-74.
12. US Renal Data System: USRDS 2006 Annual Data Report, Atlas of End-stage Renal Disease in the United States. 2006 Available at: <http://www.usrds.org/adr.htm>. Accessed December 8, 2006.
13. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998;339:584-590.
14. Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol*. 2005;16:2180-2189.
15. Foley RN, Parfrey PS, Morgan J, et al. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int*. 2000;58:325-335.
16. Laupacis A. A randomized double-blind study of recombinant human erythropoietin in anaemic hemodialysis patients. Canadian Erythropoietin Study Group. *Transplant Proc*. 1991;23:1825-1826.

-
17. Furuland H, Linde T, Ahlmen J, Christensson A, Strombom U, Danielson BG: A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. *Nephrol Dial Transplant* 18:353-361, 2003.
 18. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006 Nov 16;355(20):2085-98
 19. Pub. L. No. 108-173, § 623(a), 117 Stat. 2066, 2315.
 20. DePalma J.R. External quality review will not improve American ESRD healthcare. *Dialysis and Transplant*. 2000;29:694-686.
 21. Medicare Payment Advisory Commission. Report to Congress: Medicare Payment Policy. Washington DC, MedPAC. March 2001.
 22. United States Renal Data System: *2009 Researcher's Guide to the USRDS Database, National Institutes of Health, National Institute of Diabetes and Digestive Diseases*. Bethesda, MD; 2010.
 23. Garey KW, Lai D, Dao-Tran TK, Gentry LO, Hwang LY, Davis BR: Vancomycin compared to cefuroxime for surgical prophylaxis in patients undergoing cardiac surgery: An interrupted time series analysis. *Antimicrobial Agents and Chemotherapy* 2008, 52:446-451.
 24. Gillings D, Makuc D, Siegel E: Analysis of interrupted time series mortality trends: An example to evaluate regionalized perinatal care. *Am J Pub Health* 1981, 71:38-46.
 25. SAS Institute: *SAS user's guide*. Cary, NC; 2010.
 26. Lai D: White noise. *International Encyclopedia of Social Sciences. 2nd edition*. 2008, 9:82-83.
 27. US Renal Data System: USRDS 2010 Annual Data Report, Atlas of End-Stage Renal Disease in the United States [<http://www.usrds.org/adr.htm>]
 28. MEDICATION GUIDE Epogen® (Ee-po-jen) (epoetin alfa) Amgen Manufacturing Limited, a subsidiary of Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799, Revised: 06/2011 ©1989-2011 Amgen Inc. [<http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088591.pdf>]
 29. Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D: Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol* 2005, 16:2180-2189.
 30. Foley RN, Parfrey PS, Morgan J, Barré PE, Campbell P, Cartier P, Coyle D, Fine A, Handa P, Kingma I, Lau CY, Levin A, Mendelssohn D, Muirhead N, Murphy B, Plante RK, Posen G, Wells GA: Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 2000, 58:325-335.
 31. Laupacis A: A randomized double-blind study of recombinant human erythropoietin in anaemic hemodialysis patients. Canadian Erythropoietin Study Group. *Transplant Proc* 1991, 23:1825-1826.
 32. Furuland H, Linde T, Ahlmen J, Christensson A, Strombom U, Danielson BG: A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. *Nephrol Dial Transplant* 2003, 18:353-361.
 33. Foley RN, Collins AJ: End-stage renal disease in the United States: an update from the United States Renal Data System. *J Am Soc Nephrol* 2007, 18:2644-2648.
 34. Thamer M, Zhang Y, Kaufman J, Cotter D, Dong F, Hernán MA: Dialysis facility ownership and epoetin dosing in patients receiving hemodialysis. *JAMA* 2007, 297:1667-1674.

-
35. Goozner M: The making and selling of a star drug. Chicago Tribune; May 24, 1999.
 36. Office of Inspector General: Medicare Reimbursement for Existing End-stage Renal Disease Drugs. Washington, DC: *OIG Publication #OEI-03-04-00120*; 2004.
 37. US Renal Data System, USRDS 2007 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2007 (Figure 5.9).
 38. General Accounting Office. End Stage Renal Disease: Bundling Medicare's Payment for Drugs with Payment for All ESRD Services Would Promote Efficiency and Clinical Flexibility. GAO-07-77; November 2006.
 39. Carless PA, Henry DA, Carson JL, Hebert PP, McClelland B, Ker K: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion (Review). *Cochrane Database Syst Rev* 2010, 10:CD002042.
 40. Fink JC, Blahut SA, Briglia AE, Gardner JF, Light PD: Effect of center- versus patient-specific factors on variations in dialysis adequacy. *J Am Soc Nephrol* 2001, 12:164-169.
 41. Hirth RAM, Turenne N, Wheeler JR, Ma Y, Messana JM: Do resource utilization and clinical measures still vary across dialysis chains after controlling for the local practices of facilities and physicians? *Med Care* 2010, 48:726-732.
 42. Tangri N, Moorthi R, Tighiouhart H, Meyer KB, Miskulin DC: Variation in fistula use across dialysis facilities: is it explained by case-mix? *Clin J Am Soc Nephrol* 2010, 5:307-313.
 43. Garg PP, Frick KD, Diener-West M, Powe NR: Effect of the ownership of dialysis facilities on patients' survival and referral for transplantation. *N Engl J Med* 1999, 341:1653-1660.
 44. Zhang Y, Thamer M, Cotter DJ, Kshirsagar O: Does higher injectable medication use mediate increased mortality? *Health Serv Res* 2013, 48:949-971.
 45. Zhang Y, Thamer M, Cotter D: The effect of dialysis chains on mortality among patients receiving hemodialysis. *Health Serv Res* 2011, 46:747-767.
 46. Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH: Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002, 287:2215-2220.
 47. Green L, Kreuter M, Deeds S, Partridge K: *Health Education Planning: A diagnostic approach*. Palo Alto, CA: Mayfield Press; 1980.
 48. Amgen Media News Release
[http://www.amgen.com/media/media_pr_detail.jsp?year=2007&releaseID=1067247]
 49. Bennett CL, McKoy JM, Henke M, Silver SM, MacDougall IC, Birgegård G, Luminari S, Casadevall N, Schellekens H, Sartor O, Lai SY, Armitage JO: Reassessments of ESAs for cancer treatment in the US and Europe. *Oncology (Williston Park)* 2010, 24:260-268.
 50. General Accounting Office: *End-Stage Renal Disease: Medicare Should Pay a Bundled Rate For All ESRD Items and Services*. GAO-07-1050T; 2007.
 51. EPOGEN® (Epoetin alfa) sales decreased 27 percent to \$476 million in the third quarter of 2011 reflecting a decrease in dose utilization due to implementation of the bundled payment system [http://www.amgen.com/media/media_pr_detail.jsp?year=2011&releaseID=1620695]
 52. DOPPS Practice Monitor [<http://www.nephronline.com/renal-policy/article/dopps-esrd-bundle-monitoring-tool-preliminary-results>]