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Erythropoietin treatment and the risk of hip fractures in hemodialysis patients

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ABSTRACT

Erythropoietin (EPO) is the primary regulator of bone marrow erythropoiesis. Mouse models have provided evidence that EPO also promotes bone remodeling and that EPO-stimulated erythropoiesis is accompanied by bone loss independent of increased red blood cell production. EPO has been used clinically for three decades to treat anemia in end-stage renal disease, and notably, although the incidence of hip fractures decreased in the United States generally after 1990, it rose among hemodialysis patients coincident with the introduction and subsequent dose escalation of EPO treatment. Given this clinical paradox and findings from studies in mice that elevated EPO affects bone health, we examined EPO treatment as a risk factor for fractures in hemodialysis patients. Relationships between EPO treatment and hip fractures were analyzed using United States Renal Data System (USRDS) datasets from 1997 to 2013 and Consolidated Renal Operations in a Web-enabled Network (CROWNWeb) datasets for 2013. Fracture risks for patients treated with <50 units of EPO/kg/week were compared to those receiving higher doses by multivariable Cox regression. Hip fracture rates for 747,832 patients in USRDS datasets (1997–2013) increased from 12.0 per 1000 patient years in 1997 to 18.9 in 2004, then decreased to 13.1 by 2013. Concomitantly, average EPO doses increased from 11,900 units/week in 1997 to 18,300 in 2004, then decreased to 8,800 by 2013. During this time, adjusted hazard ratios for hip fractures with EPO doses of 50–149, 150–299, and ≥ 300 units/kg/week compared to <50 units/kg/week were 1.08 (95% confidence interval [CI], 1.01–1.15), 1.22 (95% CI, 1.14–1.31), and 1.41 (95% CI, 1.31–1.52), respectively. Multivariable analyses of 128,941 patients in CROWNWeb datasets (2013) replicated these findings. This study implicates EPO treatment as an independent risk factor for hip fractures in hemodialysis patients and supports the conclusion that EPO treatment may have contributed to changing trends in fracture incidence for these patients during recent decades. Published 2021. This article is a U.S. Government work and is in the public domain in the USA. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

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Introduction

Erythropoietin (EPO), a hypoxia regulated hormone produced in the kidneys, is required for red blood cell production, and its erythropoietic effects are mediated by EPO binding to its receptor on erythroid progenitor cells in the bone marrow.[1,2] At one time, EPO's actions were believed to be entirely limited to regulating erythropoiesis. However, it is now recognized that EPO receptors (EPOR) are expressed by non-erythroid cells in a variety of tissues, including fat, vascular endothelium, brain, and bone. Moreover, animal models have demonstrated EPO responses in non-erythroid tissues that protect the brain, cardiovascular system, and skeletal muscle from ischemic injury and that inhibit diet-induced obesity.[3–8] In bone marrow, EPOR expression has been detected in stromal cells, adipocytes, bone remodeling osteoblasts, and osteoclasts, in addition to erythroid precursor cells, and EPO signaling has been found to influence the balance between osteogenesis and adipogenesis in bone marrow.[5] EPO also exerts context dependent effects on bone health. In fracture models, EPO has been shown to accelerate

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bone healing and increase bone formation in mice,[9–11] to promote new bone formation for alveolar bone regeneration in rats,[12] and to accelerate bone healing and generate new bone formation during mandibular distraction osteogenesis in rabbits.[13,14] In contrast, in transgenic mice expressing high levels of EPO and in mice treated with exogenous EPO, stimulated erythropoiesis is accompanied by trabecular bone loss.[5,15,16] Moreover, bone loss associated with elevated EPO has been found to be independent of EPO-stimulated erythropoiesis and to require EPOR expression in osteoblasts and B-cells.[5,17,18]

Following approval by the US Food and Drug Administration (FDA) in 1989, EPO has been used widely for management of anemia associated with chronic kidney disease (CKD) and end-stage renal disease (ESRD),[19–22] conditions in which bone fragility and fractures are important complications.[23] Paradoxically, although the incidence of hip fractures has declined progressively in the general US population after 1990 until recently,[24,25] fracture incidence among ESRD patients on hemodialysis rose after 1990. The incidence of hip fractures increased substantially between 1996 and 2007 in ESRD patients, particularly among older individuals,[26] doubling overall from 1992 to 2004, but then declined after 2007.[27,28] These divergent trends in fracture incidence among hemodialysis patients, both over time and compared with the general population, have been unexplained, although changes in clinical management, including the variable use of cinacalcet and bisphosphonates, have been suggested as contributing factors.[26–28] Having previously studied changes in the use of EPO in the United States to treat anemia in hemodialysis patients over time,[29] we were aware that changes in average EPO doses used to treat these patients during recent decades exhibited a pattern of increases and decreases similar to changes in hip fracture incidence among these patients.

Following the introduction of EPO for the treatment of anemia associated with renal failure in 1989, use of blood transfusions in ESRD patients declined from 16% of patients per quarter in 1989 to 3%–4% by 1995.[30] Subsequently, average doses of EPO used to treat ESRD patients increased progressively from 1995 to 2005, based on an apparent inverse relationship between hemoglobin levels and mortality[31,32] and also on quality of care recommendations that favored anemia treatment. With these escalations of EPO dosing to achieve higher hemoglobin targets, use of blood transfusions declined further to <1% by 2005.[33] However, beginning in 2006, several randomized clinical trials of EPO treatment in renal failure patients reported that excess cardiovascular morbidity and mortality was associated with aggressive EPO treatment aimed at normalizing hemoglobin values,[34,35] validating findings of an earlier study reported in 1998.[36] As a result, the FDA issued a "Black Box" warning regarding the use of EPO to achieve hemoglobin levels over 12 g/dl, and concerns about the safety of EPO treatment, particularly when used in high doses, together with changes in Medicare/Medicaid reimbursement policies, led to a downward trend in EPO doses used to treat CKD and ESRD patients after 2007.[37–39]

Given the observation that changes in average EPO doses used to treat hemodialysis patients appeared to coincide with changes in fracture rates for these patients, together with findings from animal studies demonstrating that endogenous EPO levels are important for bone homeostasis and that elevated EPO results in bone loss,[5,15,16] we examined the possibility that dose intensity of EPO treatment in hemodialysis patients might be an independent determinant of hip fracture risk in ESRD. To this end, we conducted a retrospective cohort study of patients on hemodialysis from 1997 to 2013 using United States Renal Data System (USRDS) (www.usrds.org) datasets, combined with Centers for Medicare & Medicaid services (CMS) claims data, using multivariable Cox regression analysis.

Methods

Datasets

Two datasets were created from USRDS standard analysis files for ESRD patients. The first included core, history, and claims data from 1997 to 2013. Core data included patient gender, ethnicity, age at onset of dialysis, time since first dialysis, causes of ESRD, height, weight, and dates of kidney transplant or death. Treatment and payer history data provided information on type of dialysis and Medicare coverage. Monthly Medicare claims data recorded type of provider, units of EPO administered, hemoglobin levels, and the occurrence of fractures and comorbidities. The second dataset added information from Medicare Part D and the Consolidated Renal Operations in a Web-enabled Network (CROWNWeb) statistical analysis file.

Separate yearly analyses were conducted for 1997 to 2013. The baseline period for analysis was defined as October–December of the previous year and the follow-up period as January–December of a given year. Years 1997–1999 were excluded from multivariable analyses because height and/or weight measurements needed to calculate body mass index (BMI; kg/m^2) were missing for most patients during these years. More detailed analyses were subsequently conducted for 2013 using CROWNWeb and Medicare Part D data that included a wide spectrum of laboratory and clinical management variables (e.g., medications) unavailable for earlier years.

Inclusion and exclusion criteria

Inclusion in yearly analyses required that a patient be in the Annual Data Report cohort and also aged >18 years at onset of ESRD and on January 1 of the specified year, to have initiated dialysis at least 1 year but no more than 10 years prior to the specified year, to have not undergone kidney transplant, to have received "in center" hemodialysis with Medicare as primary payer during the specified year and for the prior 6 months, and to have claims data available. Patients were excluded from analyses if information on gender, race, cause of ESRD, treatment network, weight and height for calculating BMI, hemoglobin values, and EPO dose was unavailable (Supplementary Table S1). Inclusion of patients in CROWNWeb data analyses required that both CROWNWeb and claims data for October–December 2012 and for all of 2013 were available and included a wide array of demographic, laboratory, and clinical management variables, outlined in Supplementary Figure S1.

Hip fractures and comorbidities

For each analysis year patients were determined to have had a hip fracture if this diagnosis was a primary reason for a hospitalization (International Classification of Diseases, Ninth Revision [ICD-9] codes of 733.14 and 820.X). The incidence of vertebral fractures (ICD-9 codes of 733.13, 805.X, 806.X) resulting in hospitalization and the combined incidence of hip fractures and/or vertebral fractures, defined previously as "central fractures",[28] were also determined. We also assessed the incidence of these fractures based on the coding of fractures without restriction to the primary diagnosis. The number of days from January 1 to the date of the first fracture during a given year was used for time to event data. Hospitalization claims data from July to December

of the previous year were also searched for ICD-9 codes indicating comorbidities (not necessarily the primary reasons for hospitalization) used previously to determine an ESRD co-morbidity score,[40] including atherosclerotic heart disease, congestive heart failure, dysrhythmias, peripheral vascular disease, other cardiac disease, cerebrovascular accident or transient ischemic attack, chronic obstructive pulmonary disease, cancer, liver disease, gastrointestinal bleeding, and diabetes. These comorbidities were coded 0 if absent and 1 for each of these conditions if present, then summed to create a score from 0 to 11.

Medications

For CROWNWeb analyses, Part D medications were coded using the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System. All medications used from October through December 2012 by at least 1% of patients registered in 2013 were coded. If a drug class had been reported previously to be associated with fractures, then all medications of that drug class were assigned the same code.

Statistical methods

SAS software was used for analyses (version 9.4; SAS Institute Inc., Cary, NC, USA). Continuous variables were grouped into categories as used previously.[41] Patients were censored from analyses following death, kidney transplant, or discontinuation of Medicare as primary payer. Fracture rates were calculated as number of patients with fractures per 1000 patient follow-up years. SAS Proc GENMOD with a Poisson link was used to estimate fracture rates and 95% confidence intervals (CIs), which were not adjusted for multiple comparisons. Mean yearly EPO doses were estimated for each year from 1997 to 2013 by calculating mean patient-month estimates and included data for each month that the patient was in the "at risk" dataset, using the same months for both fracture rate and mean EPO dose. A 3-month moving average EPO dose was calculated for use in multivariable analyses of fracture rates. For each month from January to December of a given year, average EPO doses represented the means of EPO doses recorded during the prior 3 months and were categorized as: <50, 50 to <150, 150 to <300, or ≥300 units per kg per week, as done previously,[29] and used as a time-dependent variable when estimating fracture rates for EPO dose groups and in multivariable Cox regression analyses. Our rationale for using a 3-month moving average instead of a longer-term EPO dose average was informed by animal studies, which indicated that bone loss associated with exogenous EPO treatment did not require prolonged exposure but occurred within weeks. Therefore, fracture risk was assessed in relationship to the dose intensity of EPO exposure close to the time of the exposure.

Patients were included in primary analyses of yearly claims data only for the first year that they met eligibility criteria. An initial univariable Cox regression (SAS Proc PHREG), stratified by year, was performed, followed by a multivariable regression including the three strongest predictors of fracture risk: age, White race, and BMI. A second multivariable regression was then performed with backward selection of statistically significant variables ($p < .05$). An analysis of claims data was also conducted independently by year. Predictive variables for this analysis (i.e., variables with p values <.05 in the prior analysis) included age, gender, race, ethnicity, BMI, diabetes as cause of ESRD, and comorbidity score (0, 1–2, 3+). A multiple imputation analysis was also performed to assess whether excluding patients from analysis because of missing BMI and hemoglobin values (SAS Procs MI and MIANALYZE) may have affected results. Analysis of CROWNWeb data followed a similar format: univariable regression, followed by multivariable regression adjusted for age, White race, and BMI, followed by multivariable regression with backward selection including all variables that were significantly associated with fractures ($p < .05$) after adjusting for age, White race, and BMI.

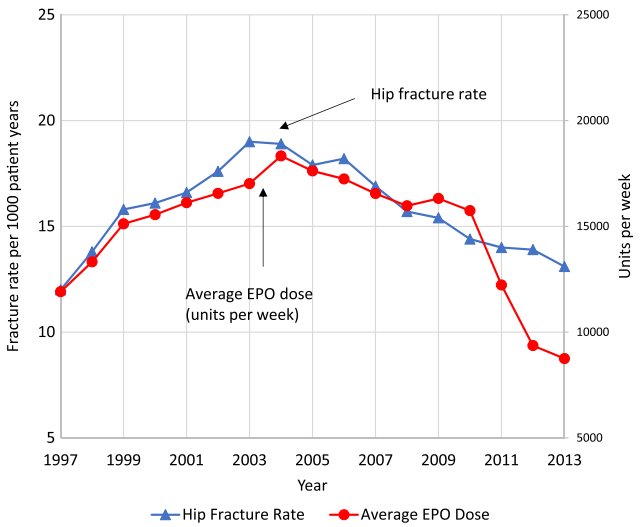

Fig. 1. Hip fracture rate and mean EPO dose per week during 1997–2013. For each year, fracture rates (triangles, blue line) were calculated as the number of patients with a fracture during the year divided by the total number of days of follow-up during that year, expressed as fractures per 1000 patient years. Yearly mean EPO doses (circles, red line) were calculated by averaging the monthly EPO doses (units per week) from claims data for each month that these data were available. Abbreviation: EPO, erythropoietin.

Results

Hip fracture rates and average EPO doses

Analysis of claims data from 1997 to 2013 for 747,832 individual hemodialysis patients revealed that hip fracture rates exhibited a pattern of increases and decreases analogous to that of average weekly EPO doses used to treat anemia in these patients over time (Fig. 1). Hip fracture rates increased from 12.0 per 1000 patient years in 1997 to 18.9 in 2004 and then declined to 13.1 in 2013. Changes in the rates of "central fractures"[28] (i.e., hip and/or vertebral fractures leading to hospitalization) increased and declined similarly over time (Supplementary Figure S2). Coincident with these changes in fracture rates, average EPO doses increased from 11,900 units per week in 1997 to 18,300 in 2004 and declined to 8800 by 2013 (Fig. 1 and Supplementary Figure S2).

Multivariable analyses were then used to evaluate relationships between EPO dose and fracture rates in greater detail. These analyses were restricted to claims data from 2000 to 2013 because BMI measurements, an important predictor of fracture incidence, were unavailable for most patients before 2000. Restricting analysis to the first eligible year for each patient

yielded 580,442 evaluable patients (Table 1). To analyze relationships between average EPO doses and fracture risks, fracture rates for patients treated with EPO doses of 50 to <150, 150 to <300, and ≥300 units per kg per week were compared to those of patients treated with EPO doses <50 units per kg per week. After adjustment for other variables, hazard ratios for occurrence of hip fractures for these three EPO dose groups were 1.08 (95% CI, 1.01–1.15), 1.22 (95% CI, 1.14–1.31), and 1.41 (95% CI, 1.31–1.52), respectively (Table 1). Hazard ratios for these EPO dose groups for hip fractures and/or vertebral fractures leading to hospitalization ("central fractures"[28]), and also for vertebral fractures alone, were very similar (Supplementary Tables S2 and S3). Other variables predictive of increased hip fracture risk included age ≥65 years, female gender, White race, non-Hispanic ethnicity, BMI <25, diabetes as the cause of ESRD, duration of dialysis less than 2 years, and an elevated comorbidity score (Table 1). Conversely, a BMI ≥30 was predictive of decreased fracture risk. Hemoglobin values <10 were associated with increased fracture risks after adjusting for age, race, and BMI (Supplementary Table S4), but not after adjusting for all co-variables included in Table 1.

An analysis of claims data by year (Supplementary Table S5) found changes in average EPO doses/kg/week and fracture rates that were similar to those shown in Fig. 1. When Cox regressions were calculated for each year (based on sample sizes ranging from 70,256 in 2000 to 175,150 in 2013), hazard ratios for hip fractures with EPO doses of ≥300 compared to <50 units/kg/week were significantly greater than 1 for all years except 2000, the year with the smallest sample size (Supplementary Table S6). Also, adjusted hazard ratios for the various EPO dose groups were very similar to those shown in Table 1 when imputed BMI data was used to include patients in the analyses who had been excluded because of missing BMI values (Supplementary Table S7) and when we included all hip and/or vertebral fractures coded during hospitalization regardless of the reason for hospitalization (Supplementary Table S8).

CROWNWeb data

Only about half of 261,515 patients on hemodialysis on January 1, 2013 had complete Medicare claims and part D data recorded in CROWNWeb needed for inclusion in multivariable analyses of hip fracture risk during 2013 based on all potential demographic, disease severity, and management variables available in the CROWNWeb dataset (Supplementary Figure S1). The hip fracture rate for the 128,941 patients included in this analysis was 11.8 per 1000 patient years (95% CI, 11.1–12.4) (Table 2), which was lower than the rate of 13.1 (95% CI, 12.6–13.7) for all 175,150 patients recorded in 2013 claims data (Supplementary Table S5). However, hazard ratios for hip fractures for the various EPO dose groups, determined by multivariable analysis adjusted for all clinical co-variables recorded in the 2013 CROWNWeb dataset were very similar (1.17–1.45, depending on EPO dose, Table 2) to those based on analyses of claims data from 2000 to 2013 (Table 1) and 2013 alone (Supplementary Table S6) adjusted for fewer co-variables. Various medications, other than EPO (i.e., proton pump inhibitors, anti-arrhythmics, cardiac stimulants, and anti-depressants), were also identified as risk factors for fractures (Table 3). Conversely, our study found cinacalcet, phosphate binder, and vitamin D treatment (Tables 2 and 3) to be associated with reduced fracture risks.

Because parathyroid hormone (PTH) measurements were recorded for only a limited number of patients in the 2013 CROWNWeb dataset (and for none in subsequent years because of concerns about their accuracy and consistency), PTH could not be included as a co-variable. However, neither high nor low serum calcium or phosphate levels were associated with fracture risks after adjustment for all other co-variables (Supplementary Table S9).

Discussion

The present study demonstrates a temporal association between median weekly doses of EPO and the risk of hip fractures in ESRD patients on hemodialysis. Specifically, as EPO dosing increased substantially in ESRD patients from 1997 to 2005, fracture rates also rose concomitantly, and as EPO dosing decreased in subsequent years, so also did fracture rates. These changing trends in fracture incidence among ESRD patients over time contrast with the progressively downward trend in fracture incidence observed in the general US population after 1990 until recent years.[24–26] Although a coincidence of changes in the use of EPO over time with changes in hip fracture incidence does not prove causality, it suggested a relationship, and to explore this possibility, EPO treatment and fracture incidence were analyzed in detail using United States Renal Data System (USRDS) datasets from 1997 to 2013 and Consolidated Renal Operations in a Web-enabled Network (CROWNWeb) datasets for 2013. Fracture incidence among patients treated with low EPO doses (<50 units of EPO/kg/week) was compared to that of patients receiving higher doses by multivariable Cox regression analysis, adjusted for numerous demographic, clinical, and management co-variables. Although hip fractures were not frequent (12–19 per 1000 patient years), the very large numbers of ESRD patients for whom data were available lent substantial statistical strength to these analyses, which identified EPO dose intensity as a significant independent risk factor for hip fractures not only when patient histories from the entire, multiyear USRDS dataset were analyzed, but also when analyzed year by year. Moreover, fracture risks associated with EPO doses greater than 150 units/kg/week were found to be comparable to those associated with clinical variables previously recognized as independent risk factors for fractures in ESRD patients (e.g., female gender and low BMI[42]).

Although exogenous EPO treatment has not been reported previously to be associated with fracture risk in renal failure patients or any other patient group, a recent epidemiologic study[43] found high endogenous levels of EPO to be associated with increased fracture risks in elderly Swedish men with normal renal function. Both this finding and the findings of our present study are consistent with the results of animal studies, which have shown bone loss to be induced by elevated EPO levels, whether they occur endogenously in transgenic mice or following exogenous administration of EPO. Animal studies have also found bone loss induced by excess EPO to be independent of EPO's erythropoietic effects,[5,17] and consistent with this finding, increased fracture risks associated with dose-intensive EPO treatment in ESRD patients was found to be independent of hemoglobin values.

Overall, results of our present study indicate that EPO treatment of hemodialysis patients and, in particular, changes in the average doses of EPO used for this treatment over time may have contributed to the changing trends in hip fracture incidence observed among ESRD patients during the past three decades. However, interpretation of our study's findings must necessarily be qualified given its retrospective design, because although a wide range of clinical variables and measures of disease severity were included in multivariable analyses, particularly those based on CROWNWeb data, there may be important co-variables that

TABLE 1. Predictors of 1-year hip fracture rates 2000–2013 (claims data)

Parameter	%	Rate per 1000 patient years (95% CI)	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
All (N = 580,442)[d]	100	16.7 (16.4–17.1)			
Age (years)[e]					
<65	48	6.5 (6.1–6.8)	Reference	Reference	Reference
65 to <75	27	17.7 (17.0–18.4)	**2.75 (2.58–2.93)**	**2.52 (2.36–2.68)**	**2.36 (2.21–2.52)**
75+	25	36.9 (35.8–38.0)	**5.72 (5.41–6.06)**	**4.62 (4.36–4.89)**	**4.36 (4.10–4.63)**
Gender					
Female	46	19.0 (18.5–19.6)	**1.29 (1.23–1.34)**	**1.33 (1.27–1.39)**	**1.28 (1.23–1.34)**
Male	54	14.8 (14.3–15.2)	Reference	Reference	Reference
Race					
Non-White	41	7.9 (7.6–8.3)	Reference	Reference	Reference
White	59	23.2 (22.6–23.7)	**2.93 (2.78–3.09)**	**2.26 (2.14–2.38)**	**2.52 (2.38–2.66)**
Hispanic					
No	85	17.6 (17.3–18.0)	**1.52 (1.42–1.63)**	**1.56 (1.45–1.67)**	**1.63 (1.51–1.75)**
Yes	15	11.6 (10.8–12.4)	Reference	Reference	Reference
BMI (kg/m^2)[f]					
<25	40	21.1 (20.4–21.7)	**1.25 (1.19–1.31)**	**1.26 (1.20–1.33)**	**1.26 (1.20–1.32)**
25 to <30	29	16.8 (16.2–17.5)	Reference	Reference	Reference
30+	31	11.1 (10.6–11.7)	**0.66 (0.62–0.70)**	**0.78 (0.73–0.83)**	**0.73 (0.69–0.78)**
Diabetes as cause of ESRD					
No	51	17.0 (16.5–17.5)	Reference	Reference	Reference
Yes	49	16.4 (15.9–16.9)	0.97 (0.93–1.01)	**1.22 (1.17–1.27)**	**1.20 (1.15–1.26)**
Duration of dialysis (years)					
<2	77	18.4 (18.0–18.8)	**1.66 (1.56–1.76)**	**1.09 (1.02–1.16)**	**1.06 (1.00–1.13)**
2 to <5	20	11.1 (10.5–11.8)	Reference	Reference	Reference
5 to 10	2	11.1 (9.4–13.2)	1.00 (0.84–1.20)	0.89 (0.74–1.06)	0.91 (0.76–1.09)
Gastrointestinal bleeding[g]					
No	97	16.5 (16.1–16.8)	Reference	Reference	Reference
Yes	3	26.6 (24.0–29.6)	**1.62 (1.45–1.80)**	**1.64 (1.48–1.83)**	**1.15 (1.03–1.29)**
Liver disease[g]					
No	99	16.6 (16.3–17.0)	Reference	Reference	Reference
Yes	1	26.7 (22.4–31.9)	**1.60 (1.34–1.92)**	**2.10 (1.75–2.38)**	**1.55 (1.29–1.85)**
Comorbidity score[h]					
0	62	13.7 (13.3–14.1)	Reference	Reference	Reference
1 to 2	20	18.2 (17.4–19.1)	**1.33 (1.26–1.41)**	**1.48 (1.40–1.56)**	**1.40 (1.33–1.48)**
3+	18	27.2 (26.0–28.3)	**1.99 (1.89–2.09)**	**1.81 (1.72–1.90)**	**1.63 (1.54–1.71)**
EPO during dialysis (units/kg/week)[i]					
0 to <50	15	13.3 (12.6–14.0)	Reference	Reference	Reference
50 to <150	34	15.4 (14.8–16.0)	**1.13 (1.05–1.20)**	**1.11 (1.04–1.18)**	**1.08 (1.01–1.15)**
150 to <300	33	17.8 (17.1–18.6)	**1.29 (1.20–1.38)**	**1.32 (1.23–1.41)**	**1.22 (1.14–1.31)**
300+	17	20.7 (19.8–21.6)	**1.48 (1.38–1.59)**	**1.63 (1.52–1.74)**	**1.41 (1.31–1.52)**

Abbreviations: BMI, body mass index; CI, confidence interval; EPO, erythropoietin; ESRD, end-stage renal disease; Hgb, hemoglobin; HR, hazard ratio.

[a]Univariable Cox regression HRs stratified by year. Bold HRs have CIs that do not overlap 1.

[b]Multivariable Cox regression HRs, stratified by year, adjusting for age group, White race, BMI group. Bold HRs have CIs that do not overlap 1.

[c]Multivariable Cox regression HRs, stratified by year, that were significant after backward selection ($p < .05$). Bold HRs have CIs that do not overlap 1. Variables that were removed during backward selection are shown in Supplementary Table S4. These include Hgb, and hospitalizations for atherosclerotic heart disease, congestive heart failure, dysrhythmias, peripheral heart disease, other cardiac disease, cerebrovascular accident or transient ischemic attack, chronic obstructive pulmonary disease, cancer, and diabetes.

[d]Patients not missing demographic data are included during the first (index) year that they met the following eligibility criteria: in center hemodialysis, had Medicare coverage, and had claims data for hemodialysis including data on Hgb and EPO dose during the 3 months before the start of the index year.

[e]As of January1 of the index year.

[f]Height and weight come from the medical evidence form.

[g]Mentioned in hospitalization claims data during the previous 6 months.

[h]Number of comorbidities mentioned in hospitalization claims data during the previous 6 months. Comorbidities were chosen because they had been included in a published comorbidity score.[20] These included atherosclerotic heart disease, congestive heart failure, dysrhythmias, peripheral vascular disease, other cardiac disease, cerebrovascular accident or transient ischemic attack, chronic obstructive pulmonary disease, cancer, liver disease, gastrointestinal bleeding, and diabetes.

[i]From claims data, 3-month moving average of doses from October of the previous year through November of the index year.

TABLE 2. Demographic, laboratory, and management variables and 1-year hip fracture rates during 2013 (CROWNWeb)

Parameter	%	Rate per 1000 patient years (95% CI)	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
All (N = 128,941)[d]	100	11.8 (11.1–12.4)			
Age (years)[e]					
<65	56	5.3 (4.7–4.8)	Reference	Reference	Reference
65 to <75	25	14.7 (13.3–16.2)	**2.80 (2.43–3.23)**	**2.58 (2.24–2.98)**	**2.33 (2.02–2.70)**
75+	19	28.3 (16.1–30.7)	**5.39 (4.72–6.15)**	**4.34 (3.79–4.96)**	**3.73 (3.25–4.28)**
Race					
Non-White	47	6.6 (6.0–7.3)	Reference	Reference	Reference
White	53	16.5 (15.5–17.5)	**2.50 (2.21–2.81)**	**2.14 (1.89–2.41)**	**2.17 (1.91–2.47)**
Hispanic					
No	81	12.0 (11.4–12.8)	**1.15 (1.00–1.32)**	**1.47 (1.27–1.71)**	**1.41 (1.21–1.63)**
Yes	19	10.5 (9.2–12.0)	Reference	Reference	Reference
BMI (kg/m^2)[f]					
<25	37	16.9 (15.7–18.2)	**1.43 (1.27–1.62)**	**1.45 (1.28–1.64)**	**1.37 (1.21–1.56)**
25 to <30	29	11.8 (10.7–13.0)	Reference	Reference	Reference
30+	34	6.3 (5.6–7.2)	**0.54 (0.46–0.63)**	**0.63 (0.54–0.74)**	**0.61 (0.52–0.72)**
Albumin (mg/dL)[f]					
<3.8	30	17.9 (16.5–19.4)	**2.55 (2.21–2.94)**	**2.02 (1.75–2.33)**	**1.66 (1.43–1.92)**
3.8 to <4.1	35	11.7 (10.7–12.8)	**1.67 (1.44–1.93)**	**1.47 (1.27–1.70)**	**1.36 (1.18–1.58)**
4.1+	34	7.0 (6.2–7.9)	Reference	Reference	Reference
Vitamin D during dialysis[g]					
No	22	15.6 (14.1–17.2)	Reference	Reference	Reference
Yes	78	10.7 (10.1–11.4)	**0.69 (0.61–0.77)**	**0.80 (0.71–0.90)**	**0.84 (0.74–0.95)**
EPO during dialysis (units/kg/week)[h]					
0 to <50	31	10.1 (9.2–10.9)	Reference	Reference	Reference
50 to <150	35	12.2 (11.1–13.5)	**1.22 (1.07–1.38)**	1.11 (0.97–1.26)	**1.17 (1.03–1.34)**
150 to <300	24	13.0 (11.4–14.9)	**1.29 (1.11–1.51)**	**1.22 (1.04–1.43)**	**1.21 (1.03–1.42)**
300+	10	16.3 (14.0–18.9)	**1.62 (1.36–1.92)**	**1.58 (1.33–1.89)**	**1.45 (1.21–1.73)**

Abbreviations: BMI, body mass index; CI, confidence interval; CROWNWeb, Consolidated Renal Operations in a Web-enabled Network; EPO, erythropoietin; ESRD, end-stage renal disease; Hgb, hemoglobin; HR, hazard ratio.

[a]Univariable Cox regression HRs, stratified by year. Bold HRs have CIs that do not overlap 1.

[b]Multivariable Cox regression HRs, stratified by year, adjusting for age group, White race, BMI group. Bold HRs have CIs that do not overlap 1.

[c]Multivariable Cox regression HRs, stratified by year, that were significant after backward selection ($p < .05$). Bold HRs have CIs that do not overlap 1. Variables that were not significant in univariable regression or were removed during backward selection are shown in Supplementary Table S9. These include gender, years since start of dialysis, diabetes as a cause of ESRD, inability to ambulate, inability to transfer, working at start of ESRD, geographical location (north vs. south), type of provider, intravenous iron during dialysis, type of vascular access, Hgb, corrected calcium, and phosphorus.

[d]Patients not missing demographic data are included if they met the following eligibility criteria: in center hemodialysis, had Medicare coverage and Medicare Part D, and Hgb and EPO dose data during October to December of 2012.

[e]As of January 1, 2013.

[f]Median of values obtained during October to December 2012.

[g]At any time during October to December 2012.

[h]Three-month moving average of doses during October 2012 through November 2013.

were not included. For example, experimental models have suggested that EPO may induce bone loss by increasing fibroblast growth factor 23 (FGF23) levels,[44,45] known to be elevated in renal failure patients.[46] However, measurements of FGF23, like those of PTH, bone-specific alkaline phosphatase, and vitamin D, were not available for analysis as co-variables. FGF23, an osteocyte derived hormone, has been shown to regulate phosphate and vitamin D_3 metabolism in the kidneys.[47] Study of patients with tumors expressing a mutant, gain-of-function form of HIF2A (*EPAS1*) found that elevated blood levels of EPO in these patients correlated with circulating levels of C-terminal FGF23 (inactive form); however, levels of intact FGF23 (active form) and blood phosphate in these individuals were normal.[48] Other studies have reported that EPO treatment in humans induces elevated blood levels of C-terminal FGF23 but not of intact FGF23.[49,50] Hence, a possible role for FGF23 in mediating the apparent effects of high-dose EPO treatment on fracture risk in ESRD patients remains unclear. Nonetheless, although potentially important co-variables may have been missing from our retrospective analyses, it is notable that essentially all key demographic, disease-related, and management variables, recognized previously to be risk factors for fractures in ESRD patients (e.g., age, female gender, White race, low albumin, low BMI[42]) were also found in our study to be significant independent risk factors for fractures, as was high-dose EPO treatment, lending support to the identification of EPO treatment as a previously unrecognized dose-related risk factor for fractures in ESRD patients. Our findings also reproduced results of previous studies that found certain medications used in the management of these patients to increase fracture risk (i.e., proton pump inhibitors [PPIs] and antidepressants[51,52] and others to reduce fracture risk (i.e., cinacalcet and vitamin D[42,53]).

TABLE 3. Hospitalizations during the previous 6 months and medications during the previous 6 months and 1-year hip fracture rates during 2013 (CROWNWeb)

Parameter	%	Rate per 1000 patient years	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
All (N = 128,941)[d]	100	11.8 (11.1–12.4)			
Cardiac disease[e]					
No	97	11.5 (10.9–12.2)	Reference	Reference	Reference
Yes	3	19.6 (15.3–25.1)	**1.70 (1.32–2.19)**	**1.56 (1.21–2.01)**	**1.31 (1.02–1.69)**
Diabetes[e]					
No	77	10.8 (10.1–11.5)	Reference	Reference	Reference
Yes	23	15.4 (13.9–17.1)	**1.43 (1.27–1.61)**	**1.55 (1.38–1.75)**	**1.33 (1.18–1.51)**
Proton pump inhibitors (A02BC)[f]					
No	67	10.6 (9.9–11.4)	Reference	Reference	Reference
Yes	33	14.1 (13.0–15.4)	**1.33 (1.19–1.48)**	**1.26 (1.13–1.40)**	**1.15 (1.03–1.28)**
Antiarrhythmics (C01B)[f]					
No	96	11.4 (10.8–12.0)	Reference	Reference	Reference
Yes	4	23.0 (18.6–28.4)	**2.02 (1.62–2.51)**	**1.46 (1.17–1.82)**	**1.29 (1.04–1.61)**
Cardiac stimulants (C01C)[f]					
No	96	11.5 (10.9–12.1)	Reference	Reference	Reference
Yes	4	18.9 (15.0–23.7)	**1.64 (1.30–2.07)**	**1.39 (1.10–1.76)**	**1.27 (1.00–1.61)**
Cinacalcet (H05BX01)[f]					
No	75	13.6 (12.9–14.4)	Reference	Reference	Reference
Yes	25	6.3 (5.5–7.3)	**0.47 (0.40–0.54)**	**0.64 (0.55–0.75)**	**0.68 (0.58–0.79)**
Antidepressants (N06A)[f]					
No	76	10.3 (9.6–11.0)	Reference	Reference	Reference
Yes	24	16.8 (15.3–18.4)	**1.63 (1.45–1.83)**	**1.50 (1.34–1.69)**	**1.34 (1.19–1.50)**
Phosphate binders (V03AE)[f]					
No	36	14.6 (13.4–15.8)	Reference	Reference	Reference
Yes	64	**10.2 (9.5–10.9)**	**0.70 (0.63–0.78)**	**0.82 (0.74–0.91)**	**0.84 (0.76–0.94)**

Abbreviations: ATC, Anatomical Therapeutic Chemical; BMI, body mass index; CI, confidence interval; CROWNWeb, Consolidated Renal Operations in a Web-enabled Network; HR, hazard ratio.

[a]Univariable Cox regression HRs stratified by year. Bold HRs have CIs that do not overlap 1.

[b]Multivariable Cox regression HRs, stratified by year, adjusting for age group, White race, BMI group. Bold HRs have CIs that do not overlap 1.

[c]Multivariable Cox regression HRs, stratified by year, that were significant after backward selection ($p < .05$). Bold HRs have CIs that do not overlap 1. Variables that were not significant in univariable regression or were removed during backward selection are shown in Supplementary Table S9. These include hospitalizations for atherosclerotic heart disease, congestive heart failure, dysrhythmias, peripheral heart disease, cerebrovascular accident or transient ischemic attack, chronic obstructive pulmonary disease, number of types of hospitalizations. Medications not related to fracture risk in multivariable regression include drugs used in diabetes, antithrombotic agents, cardiac glycosides, cardiac vasodilators, antihypertensives, diuretics, beta blocking agents, calcium channel blockers, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, lipid modifying agents, benign prostatic hypertrophy alpha-adrenoreceptor agonists, thyroid hormones, systemic antibiotics, direct acting antivirals for human immunodeficiency virus or hepatitis B, muscle relaxants, bisphosphonates, opioids, anti-Parkinson drugs, and psycholeptics.

[d]Patients not missing demographic data are included if they met the following eligibility criteria: in center hemodialysis, had Medicare coverage and Medicare Part D, and Hgb and EPO dose data during October to December of 2012.

[e]Hospitalizations during the previous 6 months.

[f]Letters in parentheses are ATC drug codes.

The present study does not provide insights into possible mechanisms by which EPO treatment may affect fracture risk, and in this regard it is unfortunate that FGF23 levels, PTH values, vitamin D and bone-specific alkaline phosphatase levels, and bone density measurements were not available in the USRDS data sets upon which the study is based. However, our findings suggest that future studies, which follow these parameters prospectively in renal failure patients after the initiation of EPO treatment, could be worthwhile.

With the progressive decline in average EPO doses used to treat ESRD patients after 2004–2005 (Fig. 1), hip fracture rates declined by 2013 to levels observed earlier in 1997. However, it is uncertain whether continued reductions in EPO dosing might contribute to further reductions in fracture rates. Data shown in Fig. 1 suggest that this would not be the case, for although hip fracture incidence declined by 2013 from the peak levels of 2004–2007 to those of 1997, average EPO doses had declined by 2013 to levels below those used in 1997. Nonetheless, findings of the present study provide further justification for minimizing the doses of EPO used to treat patients with renal failure and for avoiding high doses, using EPO to ameliorate rather than to correct anemia. There is no question that patients with renal failure can benefit from EPO treatment with decreased exposure to blood transfusions and improvements in activity tolerance and a sense of well-being. However, as with all medications, a full understanding of potential drug-associated risks favors the likelihood that a positive risk–benefit balance can be achieved with EPO treatment.

Disclosures

The authors declare no conflicts of interest.

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Data availability statement

The data that support the findings of this study are available from the USRDS (www .usrds. org, see "for researchers"). Restrictions apply to the availability of these data, which were used under license for this study.

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