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Association of higher erythropoiesis stimulating agent dose and mortality in children on dialysis

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Abstract

Background—Higher doses of erythropoiesis-stimulating agents (ESA) have been associated with an increased risk of adverse outcomes in adults with chronic kidney disease (CKD) and end-stage kidney disease (ESRD), but to our knowledge no trials have been performed in children. We examined the association between ESA dose and all-cause mortality in a prevalent pediatric dialysis population.

Methods—Retrospective cohort study utilizing national data on all prevalent dialysis patients aged <18 years from the Centers for Medicare and Medicaid Services' 2005 ESRD Clinical Performance Measures (CPM) project, linked to 18-month mortality records from the United States Renal Data System. Multivariate Cox proportional hazards regression was performed to determine the risk of mortality by mean weekly ESA dose.

Results—Eight-hundred and twenty-nine children were included in the analysis; 7 % died during follow-up. A higher proportion of patients receiving ESA doses in the highest category (erythropoietin ≥350 units/kg/week or darbepoetin ≥1.5 units/kg/week) died (50 % vs 28 %, p=0.002), and also demonstrated a trend toward lower hemoglobin (11.0 vs 11.4 g/dL, p=0.05). In multivariate analysis, patients receiving the highest dose of ESA demonstrated an increased risk of mortality (hazard ratio 3.37; p value <0.01).

Conclusion—Higher ESA dose is independently associated with mortality in children on chronic dialysis.

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Disclaimer The findings and conclusions in this article are those of the authors and do not necessarily represent the official policy or interpretation of the Centers for Medicare and Medicaid Services, the United States Renal Data System (USRDS), or the US government.

Keywords

Hemoglobin; Anemia; Death; Epogen; Darbepoetin alfa

Introduction

Treatment with recombinant human erythropoietin has transformed the management of anemia related to chronic kidney disease (CKD) in children, and erythropoiesis-stimulating agents (ESA) are now a core component of their care, both on dialysis and in pre-dialysis CKD. Observational studies have demonstrated that anemia in patients with end-stage kidney disease (ESRD) is associated with poor survival [1–3], and the treatment of anemia with ESA has been associated with improved health-related quality of life [4–6]. However, although ESA use has clearly decreased the need for red blood cell transfusions in patients with CKD and ESRD, clinical trials conducted in adults over the past few years have raised concerns about the efficacy and safety of using escalating ESA doses to normalize hemoglobin (Hgb) levels. In the CREATE trial, adults with CKD received epoetin beta to target higher (13–15 g/dL) or lower (11.5–12.5 g/dL) Hgb values, and the study found no difference in the risk of a first cardiovascular event between treatment groups [4]. In contrast, the CHOIR study, also performed in adults with CKD and anemia, found that treatment with epoetin alfa to target Hgb 13.5 g/dL vs 11.3 g/dL was associated with an increased risk of the composite primary outcome of death, myocardial infarction, stroke or hospitalization for congestive heart failure [7]. In 2007, as a result, CHOIR and other studies, including the Normal Hematocrit Trial [8], the National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) updated its goal Hgb target recommendation for adults and children on ESA therapy to 11–12 g/dL rather than ≥13 g/dL, and added a guideline suggesting that Hgb levels >13 g/dL should not be targeted [9]. Subsequently, the TREAT trial, in which over 4,000 adults with diabetes and CKD were treated with darbepoetin alfa to achieve Hgb 13 g/dL vs placebo with darbepoetin alfa rescue therapy for Hgb <9 g/dL, identified an increased risk of stroke in the intervention group, providing additional evidence that ESA treatment to normalize Hgb in CKD leads to adverse events [10].

In 2011 the US Food and Drug Administration changed ESA product labeling to recommend that the Hgb target range of 10–12 g/dL should be replaced by the practice of using the lowest possible ESA dose to prevent red cell transfusions, and that ESA dosing should be reduced or interrupted for Hgb levels exceeding 11 g/dL [11]. Most recently, the Kidney Disease: Improving Global Outcomes (KDIGO) workgroup published a comprehensive and evidence-based Clinical Practice Guideline for Anemia In Chronic Kidney Disease in August 2012 that suggests that Hgb concentration in children with CKD receiving ESA therapy should be maintained within the range 11–12 g/dL, while acknowledging that selection of the specific Hgb level at which to initiate ESA treatment in individual patients should include consideration of the relative benefits of therapy vs the harm that may be caused by therapy [12]. While it is acknowledged that high ESA doses rather than higher Hgb values per se may be more closely associated with adverse events, no randomized controlled trials examining the effects of ESA administration on clinical outcomes in

children with CKD or those on dialysis have been performed. One recent observational study conducted in the voluntary registry of the International Pediatric Peritoneal Dialysis Network (IPPN) found that patient survival was inversely associated with ESA dose, the first time any such association has been observed in children on peritoneal dialysis (PD) [2]. However, the current application of the KDIGO Hgb target recommendations to children is still extrapolated from adult trials rather than based on pediatric-specific evidence, which may not be appropriate given differences in both the causes of CKD and the association of comorbidities with outcomes in children compared with adults.

The Centers for Medicare and Medicaid Services (CMS) Clinical Performance Measures Project (CPM) collect data, including the ESA dose administered, on all children receiving dialysis (hemodialysis [HD] or PD) in the USA. Our objective for this study was to examine the association between ESA dose and all-cause mortality in a prevalent pediatric dialysis population, independent of achievement of the KDIGO recommended Hgb target level of 11 g/dL.

Materials and methods

For this retrospective cohort study, national data on prevalent dialysis patients aged <18 years who had not undergone transplantation during the follow-up period, and who had complete data available for analysis, were obtained from the CMS 2005 ESRD CPM project. Data for HD patients were collected October through December 2004, and for PD patients October 2004 through March 2005. This information was then linked with mortality records from the United States Renal Data System (USRDS) through 30 June 2006 by unique USRDS identification numbers. Complete details of the methods of the ESRD CPM [13] and USRDS [14] collections have been reported elsewhere. Patients were included in the study if they remained on dialysis throughout the follow-up period or were on dialysis at the time of death, and had at least one hemoglobin value and one albumin value recorded during the study period. Additionally, patients had to be clearly identified (yes vs no) as having been prescribed recombinant human erythropoietin (EPO) or darbepoetin alfa (DARBO) during at least one of the months during the collection periods, with a prescribed dose recorded.

Clinical and demographic variables of interest were obtained from the CPM dataset and compared by mortality group. The covariates examined included age as a continuous variable, sex, race (white, black or other), cause of ESRD (focal segmental glomerulosclerosis [FSGS], urological disease, systemic lupus erythematosis [SLE], or other based on ICD-9 codes for primary diagnosis), and dialysis modality (PD, HD with arteriovenous [AV] fistula/graft, or HD with catheter). Mean hemoglobin level (from up to three available levels) was calculated for each subject and then dichotomized as ≥vs <11 g/dL, in accordance with the KDIGO recommendation for the lower limit of goal Hgb in ESA-treated children [12]. Mean serum albumin levels were calculated for each subject (with the associated laboratory method, Bromocresol Green [BCG] or Bromocresol Purple [BCP], as these two methods have been shown to yield systematically different results), and then transformed into a dichotomous variable representing target albumin (target ≥3.5 g/dL for BCG; ≥3.2 g/dL for BCP). This albumin target was selected based upon prior studies that

found albumin levels at this threshold to be associated with decreased morbidity and mortality [15]. Time on dialysis was measured in years. Mean Kt/V was calculated for HD patients using the Daugirdas formula: Kt/V = −In (R−0.008 * t) + (4−3.5 *R) *UF/W. For PD patients, total Kt/V was calculated as the sum of renal Kt/V (when data available) and dialysis Kt/V. Total body water was calculated using the sex-specific formulas developed by Morgenstern et al. specifically for children on peritoneal dialysis [16]. Renal Kt/V was calculated for patients who had urine samples available as: (renal urea clearance × 1,440 min/day × 7)/(1,000 ml × V). Renal urea clearance was then calculated as: (volume of 24 h urine in ml × urine urea)/(1,440 min/day × serum BUN). We then calculated weekly dialysis Kt/V as (24 h dialysis urea/serum urea) × (24 h drain volume of PD fluid/1,000) × 7/V). For patients in whom urine was not reported or who no longer made urine, the dialysis Kt/V was used. As defined by the KDOQI guidelines, individuals maintained on HD were determined to have met the target when mean Kt/V was ≥1.2, and individuals maintained on PD were determined to have met targets when total Kt/V ≥1.8 [17, 18].

The ESA dose (EPO or DARBO) was collected by the CPM. Up to three separate values were available per patient; if more than one dose value was available, a mean was utilized. For HD patients, the mean weekly EPO dose (units/kg/week) was calculated as the weekly EPO dose divided by the post-dialysis weight for that week. For PD patients, the monthly EPO dose was first divided by four to generate an estimated weekly EPO dose, then divided by the patient's weight. Mean weekly EPO dose was categorized as follows: no EPO, 0 to <100 units/kg/week, 100 to <200 units/kg/week, 200 to <350 units/kg/week, and ≥350 units/kg/week. Mean weekly DARBO dose (units/kg/week) was calculated from the monthly DARBO dose for the collection period divided by 4. The weekly dose was then divided by the weight reported for that collection period to generate units/kg/week. DARBO dose was categorized as follows: no DARBO, 0 to <0.49 units/kg/week, 0.49 to <1 units/kg/week, 1 to <1.5 units/kg/week, and ≥1.5 units/kg/week. Finally, five ESA dose categories were created: no ESA, EPO 0 to <100 units/kg/week or DARBO 0 to <0.49 units/kg/week, EPO 100 to <200 units/kg/week or DARBO 0.49 to <1 units/kg/week, EPO 200 to <350 units/kg/week or DARBO 1 to <1.5 units/kg/week, and EPO>350 units/kg/week or DARBO≥1.5 units/kg/week.

All data management and analyses were conducted using Stata 11.0 software (StataCorp, College Station, TX, USA). Summary statistics were generated for each variable. Associations of clinical data with patient characteristics were tested using Chi-squared, hierarchical analysis of variance and two-tailed Student's *t* tests. A *p* value of less than 0.05 was considered significant. Multivariate Cox proportional hazards analysis was used to determine the association of ESA dosing with mortality, adjusting for other demographic and clinical characteristics of interest, as described above. Serum ferritin values were not available for all subjects in the cohort, but were included in a sensitivity Cox model both continuously and categorically as < or ≥500 ng/mL.

Results

Of the 1,453 eligible patients included in the CPM data collection, 602 were transplanted during the follow-up period and thus eliminated from the study group. Thirty-one additional

patients were eliminated owing to missing or incomplete data, one of whom died during the follow-up period. This left a total of 820 patients included in the analysis, 60 of whom (7 %) died during the observation period. Of the patients who did not survive, 31 (52 %) had cardiac etiology listed as their primary cause of death. Infection was the cause of death for 12 patients (20 %). Eight patients died of either vascular (13 %) or gastrointestinal (13 %) complications respectively, and in 1 patient the cause of death was unknown (1 %).

Demographic characteristics of the study subjects by survival status are presented in Table 1. The mean age was younger among the deceased subjects (10.5 vs 12.9 years, $p<0.001$). There were no differences in sex or race distribution. Mean Hgb was slightly higher among the surviving patients, but this difference did not reach statistical significance (11.4 vs 11.0 g/dL, $p=0.05$). The mean serum albumin of patients in the deceased group was also lower than in the survivors (3.5 vs 3.7 g/dL, $p=0.01$). Among the deceased subjects a significantly higher proportion was undergoing HD via a catheter (45 % vs 25 %) and fewer via an AV fistula or graft (8 % vs 24 %; $p=0.001$). ESAs were prescribed to the vast majority of patients in both groups (95%of survivors and 93 % of non-survivors, $p=0.59$). Eighty-six percent of patients prescribed an ESA had at least two doses available for analysis. However, mean weekly EPO and DARBO doses were significantly lower in the survivors than in the non-survivors (EPO: 290 vs 502 units/kg/week, $p<0.001$; DARBO: 0.59 vs 2.6 units/kg/week, $p<0.001$). Furthermore, among the deceased patients a significantly higher proportion were prescribed ESA doses in the highest category (50 % vs 28 %, $p=0.002$).

Clinical and demographic characteristics by ESA dose category are presented in Table 2. No significant differences in sex, race, or age distribution were noted between groups. In terms of dialysis modality, a significantly higher proportion of those in the lower ESA dose categories were maintained on PD, while a higher proportion of patients undergoing HD via catheter received ESA doses in the highest category ($p<0.001$). A significantly higher proportion of patients in the highest ESA dose category died during the observation period ($p=0.002$). There were no significant differences between groups in mean Kt/V or dialysis vintage. Mean Hgb was lowest among those in the highest ESA category at 10.9 g/dL ($p<0.001$). Mean serum albumin was higher among those in the two lowest ESA dose categories than among those in the higher categories, or those not prescribed an ESA ($p<0.001$).

Results of the multivariate Cox analysis are shown in Table 3. Subjects receiving the highest doses of ESA (category 4) had >3 times higher hazard of death than those in the reference group (EPO 100 to <200 units/kg/week or DARBO 0.49 to <1 units/kg/week; HR 3.37, 95 % CI 1.37–8.26, $p= 0.01$). HD patients dialyzed via catheter had a higher likelihood of death than patients undergoing peritoneal dialysis (HR 2.14, 95 % CI 1.19–3.86, $p=0.01$), while those dialyzed via an arteriovenous graft or fistula were at no increased risk of death compared with those on PD (HR 0.47, 95%CI 0.17–1.27, $p=0.14$). Younger age (HR 0.91, 95%CI 0.86–0.96, $p= 0.001$), urological disease (HR 0.42, 95 % CI 0.21–0.81, $p= 0.01$), and meeting Kt/V targets (HR 0.63, 95%CI 0.32–1.23, $p=0.01$) were all associated with decreased risk of mortality.

Only 743 out of 820 patients had at least one serum ferritin value recorded during the study period. However, in a sensitivity analysis including ferritin in the model as a continuous variable, the HR for death in the highest ESA dose category was 3.89, 95 % CI 1.31–11.55 p=0.014, and with ferritin included as a categorical variable (< vs ≥500 ng/mL) the HR was 2.98, 95 % CI 1.19–7.42, p=0.019.

Discussion

This study is the first to demonstrate that among a prevalent population of children maintained on chronic dialysis (HD and PD), higher administered doses of ESA are associated with a risk of death more than three times that seen in patients receiving lower doses. The observed association between receiving ESA doses in the highest quintile and an increased risk of death over 12–18 months of follow-up was independent of other factors that may contribute to the risk of mortality in children on dialysis, including the underlying cause of ESRD, dialysis modality and access type, and achievement of the recommended minimum Hgb target level on ESA therapy of 11 g/dL. Furthermore, although mortality is a less common outcome in children than in adults on chronic dialysis, with death occurring during the follow-up period in 7 % of this pediatric cohort, we still observed a significant increase in mortality risk in those receiving the highest ESA doses.

Most clinical pediatric nephrologists have likely observed that there is a wide range of ESA dose requirements among children on chronic dialysis. Results from the CHOIR and TREAT trials have notably demonstrated that escalation of ESA dose with the aim of achieving higher Hgb levels in adult patients with CKD leads to adverse outcomes [7, 10]. The study populations for both of these trials consisted of adults with not only CKD, but also a high prevalence of long-standing diabetes and hypertension, both independent and significant risk factors for cardiovascular disease. Additionally, primary outcomes for both trials were composites (including death, myocardial infarction or stroke in CHOIR, death or cardiovascular event including stroke in TREAT) [7, 10]. Other observational studies in adults have shown that ESA dose requirement is a predictor of mortality in adults on HD, independent of hematocrit level [19]. An advantage of examining the association between ESA dose and mortality in a pediatric dialysis cohort is that the prevalence of advanced cardiovascular disease in these patients is comparatively low, and thus we are able to characterize the association without the significantly increased risk conferred to older adults. Clarifying these associations in children is crucial, especially given that the children require higher absolute ESA doses to maintain goal Hgb levels than adults [20]. Although no such similar trials have been conducted in children, Borzych-Duzalka et al. recently showed that in a voluntary international pediatric PD registry, risk of death was independently associated with the use of high ESA doses, to our knowledge the first time any such association has been observed in children on PD [2]. The results of our analysis in a prevalent population of US children on chronic dialysis are consistent both with this recently published pediatric observational data and with the trend toward increasing adverse events in adults treated with ESA to target higher Hgb levels seen in multiple adult trials.

Data from adult trials have informed the current KDIGO clinical practice recommendation that ESA initiation be considered when Hgb levels fall below 10 g/dL in children on

dialysis, with goal Hgb level in ESA-treated children maintained within the range 11–12 g/dL [12]. However, the KDIGO guideline also explicitly acknowledges the absence of pediatric-specific randomized controlled trial data regarding hard outcomes, and recognizes that there may be biologically plausible reasons to advocate for the normalization of Hgb in children on dialysis, including optimization of quality of life, growth and development, and cardiovascular function [12, 21, 22]. The guideline cautions that direct extrapolation of results from adult trials to pediatric patients is inappropriate, and advocates an individualized approach in which the selection of the Hgb concentration at which to begin ESA therapy should be the result of consideration of the benefits vs risks of treatment in individual patients for both adults and children [12]. Although diabetic adults with CKD in the TREAT trial demonstrated an increased risk of stroke with darbepoetin alfa treatment to target Hgb of 13 g/dL, they also demonstrated improvement in patient-reported fatigue and were less likely to require blood transfusion than those receiving placebo, both outcomes that can indicate improved quality of life [10]. It is unclear whether, in the absence of the cardiovascular co-morbidities so prevalent in the adult CKD population, children with CKD derive relatively more benefit from maintaining consistently higher Hgb levels. There has been inconsistency between observational studies—in both adults and children—demonstrating an association between higher Hgb levels (achieved through ESA use) and decreased risks of morbidity and mortality, and trials demonstrating an increased risk of adverse outcomes in patients receiving ESAs to target high Hgb [22, 23]. Even among children with pre-dialysis CKD, Staples et al. demonstrated that anemia was associated with a 55 % increased risk of hospitalization compared with children without anemia [24]. Borzych-Duzalka et al.'s recently conducted observational study in the IPPN registry, however, demonstrated that patient survival was inversely associated with ESA dose independently of Hgb level [2], supporting the concern that Hgb level and ESA dose are risk factors reflecting two distinct mechanisms of disease that exert different effects on clinical outcomes.

A much debated question has been whether it is higher ESA doses in particular that increase mortality risk via a Hgb-independent mechanism, or the higher Hgb levels that result from the higher doses administered. In this analysis, we found that those children receiving the highest ESA doses actually had lower mean Hgb levels, and this has been observed in other pediatric and adult studies as well [2, 19]. Indeed, data in adults do indicate that patients treated with higher ESA doses are at an increased risk of adverse events independent of Hgb level, the proposed mechanisms for which include increased hypertension and increased thrombotic risk. In a very large international observational study in adults on hemodialysis, Goodkin et al. demonstrated that a naturally occurring higher Hgb concentration (>12 g/dL) was not associated with an increased risk of mortality, suggesting that Hgb level specifically might not be the key factor in the causal pathway [25]. More recently, Koulouridis et al. conducted a metaregression analysis in 31 randomized controlled trials (12,956 patients) of ESA use in adults with CKD and found that higher ESA dose was associated with an increased risk of all-cause mortality, independently of either target or mean achieved Hgb level, suggesting that absolute ESA dose in particular may be in the causal pathway [26].

An alternate possibility is that, rather than conferring increased mortality risk, higher ESA doses may instead reflect a more severe disease state in which higher ESA doses are

required to effect an increase in Hgb. Chief among the causes of ESA hypo-responsiveness is inflammation, resulting in increased production of the iron-regulatory protein hepcidin. Hepcidin mediates iron-restricted erythropoiesis by causing iron to be trapped intracellularly, such that stored iron is not made available for erythropoiesis [27–29]. Inflammation has been identified as a risk factor for ESA hypo-responsiveness in children on dialysis [30].We cannot exclude the possibility that high ESA doses could be a marker of increased mortality risk rather than the cause in this population; we did not have access to data such as C-reactive protein, interleukin-6 levels, or other inflammatory markers that could be used to characterize other factors that may be related to both ESA hypo-responsiveness and mortality. In a sensitivity analysis including ferritin, an admittedly limited marker of inflammation, a significantly increased risk of mortality in the highest ESA dose category was still observed, suggesting that the increased risk conferred by ESA dose might be independent of inflammatory factors that are reflected by elevated serum ferritin. Although low serum albumin can be associated with inflammation and has been linked to increased mortality risk in adolescents on dialysis [15], low albumin was not significantly associated with mortality risk in our final Cox model; this suggests that serum albumin might not be the most appropriate or specific marker of the type of inflammation that is associated with ESA hypo-responsiveness.

This analysis is further limited by its observational nature, and thus cannot be used to infer causality. Although the final Cox model was adjusted for multiple variables likely to be related to mortality risk, the presence of unmeasured confounding cannot be ruled out. We did not have access to parathyroid hormone level data to assess for hyperparathyroidism as a potential contributor to ESA hypo-responsiveness. Additionally, we did not have access to a measure of adherence to ESA therapy in PD patients specifically. The limitations of analysis of registry data also deserve to be mentioned, including issues of data accuracy and completeness, and concern about whether data collected for a relatively short, defined period in a prevalent population accurately reflect the long-term variability in the status or anemia management of subjects. However, to our knowledge, ours is the first such analysis performed in a national prevalent dialysis cohort, both HD and PD, and our results are consistent with those observed in both adult trials and in other pediatric observational studies.

In conclusion, we have demonstrated that higher administered doses of ESA are associated with a significantly increased risk of death in children on chronic dialysis, independent of the achievement of a minimum Hgb target level of 11 g/dL and other factors likely to be associated with the risk of mortality. However, further study is needed before these results can be extrapolated to clinical care. Only a well-designed clinical trial will be able to clarify whether ESA dose is truly part of the causal pathway for mortality in children on dialysis, and if ESA dose is also associated with cardiovascular morbidity in these patients. A clinical trial would also help to establish whether ESA resistance, rather than the dose administered, is the critical factor, and could suggest that children who demonstrate persistently low Hgb values despite high ESA doses should be considered for other adjunctive anemia therapies beyond ESA escalation, including intravenous iron or anti-inflammatory interventions to bypass iron-sequestration. A key question, however, is whether, in the face of adult trial data and observational pediatric data including those presented here, such a trial could be safely

and ethically conducted in children on dialysis. While the use of ESA has critically enhanced the care of children with ESRD, it is also a costly intervention with adverse associations demonstrated, and we in the pediatric nephrology community must strive to use it to optimize benefit while minimizing risk. At the very least, the creation of an ESA safety data registry could help to answer some of these important questions and guide the treatment of anemia in our patients. In the meantime, our findings would seem to support the ongoing practice of an individualized approach to ESA management in which the underlying causes of apparent ESA hypo-responsiveness are strongly considered and addressed.

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Table 1

Baseline clinical characteristics in 829 children on dialysis by mortality status

	Living (*n*=769) mean (SD) or *n* (%)	**Deceased (*n*=60) mean (SD) or *n*(%)**	***p* value**
Age (years)	12.9 (4.8)	10.5 (6.0)	<0.001*
Male	413 (54)	32 (53)	0.96**
Race			0.76**
White	447 (58)	32 (53)	
Black	237 (31)	21 (35)	
Other	85 (11)	7 (12)	
Hemoglobin (g/dL)	11.4 (1.6)	11.0 (1.9)	0.05*
Albumin (g/dL)	3.7 (0.6)	3.5 (0.6)	0.01*
ESA prescribed	729 (95)	55 (92)	0.59*
ESA dose category[a]			0.002**
No ESA	40 (5)	5 (8)	
1	150 (19)	7 (12)	
2	181 (24)	6 (10)	
3	183 (24)	12 (20)	
4	215 (28)	30 (50)	
Mean EPO dose *N*=726 (units/kg/week)	290 (296)	502 (643)	<0.001*
Mean DARBO dose *N*=66 (units/kg/week)	0.59 (0.74)	2.6 (3.5)	<0.001*
Cause of ESRD			0.15**
FSGS	117 (15)	6 (10)	
Urological	232 (30)	13 (22)	
SLE	38 (5)	2 (3)	
Other	382 (50)	39 (65)	
Dialysis modality			0.001**
PD	394 (51)	28 (47)	
HD: AV fistula/graft	184 (24)	5 (8)	
HD: catheter	191 (25)	27 (45)	
Kt/V	1.9 (1.0)	2.0 (1.2)	0.72*
Time on dialysis (years)	3.5 (3.9)	3.0 (3.4)	0.37*

*Student's *t* test;

**Chi-squared analysis

a

ESA U/kg/week	Category 1	Category 2	Category 3	Category 4
Erythropoietin	0 to <100	100 to <200	200 to <350	≥350

Darbepoetin	0 to <0.49	0.49 to <1.0	1.0 to <1.5	≥1.5

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Table 2

Baseline clinical characteristics in 820 children on dialysis by ESA dose quartile

	No ESA (*N*=45) *n* (%) or mean (SD)	**Category 1 (*N*=157) *n* (%) or mean (SD)**	**Category 2 (*N*=187) *n* (%) or mean (SD)**	**Category 3 (*N*=195) *n* (%) or mean (SD)**	**Category 4 (*N*=245) *n* (%) or mean (SD)**	***p* value**
Male	29 (64)	88 (56)	107 (57)	102 (25)	119 (49)	0.19[b]
Race						
White	23 (51)	93 (59)	114 (61)	108 (55)	141 (58)	0.54[b]
Black	16(36)	44(28)	59(32)	59(30)	80 (32)	
Other	6 (13)	20 (13)	14 (7)	28 (14)	24 (10)	
Age (years)	13.1 (5.5)	13.2 (4.8)	12.8 (4.8)	12.8 (4.7)	12.4 (5.1)	0.56[a]
Cause of ESRD						
Urological	6 (13)	54 (35)	54 (29)	59 (30)	72 (29)	0.01[b]
FSGS	7 (16)	30 (19)	25 (13)	24 (13)	37 (15)	
SLE	3 (7)	2 (1)	3 (2)	16 (8)	16 (7)	
Other	29 (64)	71 (45)	105 (56)	96 (49)	120 (49)	
Dialysis modality						
PD	22 (49)	121 (77)	104 (56)	94 (48)	81 (33)	<0.001
HD with AVF/AVG	7 (16)	24 (15)	43 (23)	46 (24)	69 (28)	
HD with catheter	16 (35)	12 (8)	40 (21)	55 (28)	95 (39)	
Deceased	5 (11)	7 (4)	6 (3)	12 (6)	30 (12)	0.002[b]
Kt/V	1.5 (0.4)	2.0 (0.8)	1.9 (0.6)	2.0 (1.4)	1.9 (0.9)	0.17[a]
Time on dialysis (years)	2.5 (2.9)	3.1 (3.4)	3.3 (3.9)	3.6 (4.3)	3.9 (4.1)	0.09[a]
Hemoglobin (g/dL)	11.6 (2.0)	11.74 (1.2)	11.8 (1.5)	11.4 (1.6)	10.9 (1.7)	<0.001[a]
Albumin (g/dL)	3.6 (0.7)	3.8 (0.6)	3.8 (0.6)	3.7 (0.6)	3.6 (0.6)	<0.001[a]

[*] Student's *t* test;

[**] Chi-squared analysis

ESA U/kg/week	Category 1	Category 2	Category 3	Category 4
Erythropoietin	0 to <100	100 to <200	200 to <350	≥350

Darbepoetin	0 to <0.49	0.49 to <1.0	1.0 to <1.5	≥1.5

Table 3

Cox proportional hazard regression for mortality risk by ESA category (*n*=820)

	Hazard ratio	95 % confidence Interval	*p* value
ESA category (U/kg/week)[a]			
1. No ESA	2.71	0.81–9.00	0.39
2. EPO: 0 to <100/DARBO: 0 to <0.49	1.62	0.54–4.90	0.10
3. EPO: 200 to <350/DARBO 1 to <1.5	1.81	0.67–4.87	0.24
4. EPO ≥350/DARBO ≥1.5	3.37	1.37–8.26	0.01
Race			
Black vs white	1.36	0.77–2.41	0.29
Other vs white	0.98	0.42–2.28	0.97
Diagnosis			
Urological vs other	0.42	0.21–0.81	0.01
SLE vs other	0.43	0.97–1.90	0.27
FSGS vs other	0.57	0.23–1.38	0.21
Hemoglobin≥11 g/dL (yes vs no)	0.79	0.47–1.33	0.37
Albumin≥3.5 g/dL BCG/3.2 g/dL BCP (yes vs no)	0.66	0.38–1.14	0.13
Dialysis modality			
HD AVG/AVF vs PD	0.47	0.17–1.27	0.14
HD with catheter vs PD	2.14	1.19–3.86	0.01
Age (per 1 year increase)	0.91	0.86–0.96	0.001
Male vs female	1.3	0.76–2.23	0.34
Kt/V ≥1.2 (HD)/1.8 (PD) vs <1.2/1.8	0.63	0.32–1.23	0.01
Time on dialysis ≥1 year vs <1 year	1.26	0.73–2.19	0.40

[a]ESA dose category EPO 100 to <200/DARBO 0.49 to 1.0 U/kg/week reference