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Dose of Erythropoiesis-Stimulating Agents and Adverse Outcomes in CKD: A Metaregression Analysis

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Abstract

Background—Targeting higher hemoglobin with erythropoiesis-stimulating agents (ESAs) to treat anemia of chronic kidney disease (CKD) is associated with increased cardiovascular risk.

Study Design—Meta-regression analysis examining the association of ESA dose with adverse outcomes, independent of target or achieved hemoglobin.

Setting and Population—Patients with anemia of CKD, irrespective of dialysis status.

Selection Criteria for Studies—We searched MEDLINE (inception to August 2010) and bibliographies of published meta-analyses and selected randomized controlled trials assessing the efficacy of ESAs for treatment of anemia in adults with CKD, with minimum 3-month duration. Two authors independently screened citations and extracted relevant data. Individual study arms were treated as cohorts and constituted the unit of analysis.

Predictors—ESA dose standardized to a weekly epoetin alfa equivalent, and hemoglobin levels.

Outcomes—All-cause and cardiovascular mortality, cardiovascular events, kidney disease progression or transfusion requirement.

Results—31 trials (12,956 patients) met criteria. All-cause mortality was associated with higher (per epoetin-alfa–equivalent 10,000-U/wk increment) first-3-month mean ESA dose (incidence rate ratio [IRR], 1.42; 95% CI, 1.10–1.83) and higher total-study-period mean ESA dose (IRR, 1.09; 95% CI, 1.02–1.18). First-3-month ESA dose remained significant after adjusting for first-3-

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month mean hemoglobin (IRR, 1.48; 95% CI, 1.02- 2.14), as did total-study-period mean ESA dose adjusting for target hemoglobin (IRR, 2 1.41; 95% CI, 1.08–1.82). Parameter estimates between ESA dose and cardiovascular mortality were similar in magnitude and direction but not statistically significant. Higher total-study-period mean ESA dose was also associated with increased rate of hypertension, stroke, and thrombotic events including dialysis vascular access-related thrombotic events.

Limitations—use of study-level aggregated data; use of epoetin alfa–equivalent doses; lack of adjustment for confounders.

Conclusions—In patients with CKD, higher ESA dose might be associated with all-cause mortality and cardiovascular complications independent of hemoglobin.

Keywords

erythropoietin; ESA; epoetin; darbepoetin; anemia; CKD; dose; mortality; cardiovascular morbidity; meta-regression

The lack of endogenous erythropoietin production in patients with chronic kidney disease (CKD) results in the development of anemia, which is associated with impaired quality of life [1,2], and increased morbidity and mortality [3–5]. The gold standard for managing anemia of CKD is the use of erythropoiesis-stimulating agents (ESAs). Targeting higher hemoglobin levels with ESAs has, however, been associated with an increased risk of cardiovascular disease–related morbidity and mortality [6–8]. It is not well established whether the ESA dose itself has an effect on adverse clinical outcomes. Understanding the potential role of the ESA dose, versus the target or achieved hemoglobin level, is of crucial importance as there is no universal consensus on the exact ESA dosage algorithm that should be adopted while minimizing patient exposure to these potential health risks. If such an association exists, high doses of ESAs could result in increased morbidity even at low hemoglobin levels.

Several previously published systematic reviews have established a clear association between target hemoglobin level and adverse outcomes in patients with CKD [2,6,7,9–15], resulting in a change to the ESA label regarding target hemoglobin. However, these analyses did not address whether there is a dose-response gradient of ESAs and potential harm. To examine this question, we performed a systematic review with metaregression of randomized controlled trials (RCTs) of ESAs in patients with CKD to evaluate whether the potential harm associated with their use for the treatment of anemia follows a dose-response gradient, adjusting for the target or achieved hemoglobin level.

METHODS

Data Sources and Selection

We searched MEDLINE for all published RCTs that examined the use of ESAs in CKD (inception-August 2010) and for published systematic reviews (inception-June 2010) (search strategies shown in Item S1, available as online supplementary material). The searches were limited to human studies with no language restrictions. Two authors (MA and IK) screened titles and abstracts to identify potentially relevant articles. We selected parallel-arm RCTs reporting efficacy (i.e., change in hemoglobin level) of ESAs with a minimum 12-week treatment duration that documented doses of ESA, levels of baseline and achieved hemoglobin, and at least one endpoint of interest (as defined below). We included only studies of epoetin alfa, epoetin beta, or darbepoetin alfa. Reports of ESA trials in clinical settings other than anemia of CKD (e.g., cancer or heart failure) were excluded.

Data Extraction and Quality Assessment

Data were independently extracted in duplicate from full-text articles by two authors (MA and IK). Where indicated, the G3 data graph analyzer (version 1.5.3) was used to extract data from graphs [16]. Disagreements were resolved through consensus and arbitration by a third author (BLJ). Corresponding authors of four trials were contacted for data clarification.

Data extracted from full-text articles included country of origin, year of publication, study sponsor, study design, sample size in each arm, CKD stage and dialysis status, sex, mean age, mean weight, comorbidities, target hemoglobin in each arm, ESA type (epoetin alfa, epoetin beta, or darbepoetin alfa), prior ESA use, route of ESA administration (subcutaneous *vs.* intravenous) and trial duration. Due to inconsistent reporting, total and average follow-up times were used interchangeably. For each study 5 arm, according to a pre-specified analysis plan, we extracted the mean ESA dose and mean hemoglobin level at enrollment, during the first 3 months (in an attempt to capture rapid correction of anemia), and throughout the total follow-up period.

In studies reporting only hematocrit values, hemoglobin values were calculated by dividing the hematocrit by 3 [17]. We converted the darbepoetin alfa dose to an equivalent epoetin alfa dose using a dose conversion ratio of 331 units of epoetin alfa per 1 μg of darbepoetin alfa [18,19]. The doses of epoetin alfa and beta were considered equivalent. If reported in units/kg/wk, the recombinant erythropoietin dose was converted to units/week by using the mean weight of the participants in each study arm. If not reported, a weighted average weight was calculated using data from the National Health and Nutrition Examination Survey (NHANES) [20,21] for patients with CKD who were not on dialysis, and the 2008 annual data report from the United States Renal Data System (USRDS) for dialysis patients [22]. The weighted average used in these calculations took into consideration the year of publication, mean age, and sex ratio in each study arm.

Our two primary outcomes of interest were all-cause mortality and cardiovascular mortality as defined by the authors. Secondary outcomes included cardiovascular events, acute myocardial infarction, de novo or worsening angina, heart failure, arrhythmias, stroke, de novo or worsening hypertension as defined by the authors, thrombotic events (e.g., deep venous thrombosis, peripheral arterial thrombotic events, and dialysis vascular access thrombosis), any serious adverse event (SAE) as defined in the individual trials, progression to kidney failure (end-stage renal disease), need for blood transfusions, and change in glomerular filtration rate (GFR).

The estimated GFR, measured GFR, and creatinine clearance were assumed to be 6 equivalent. When reported in ml/min, the GFR was transformed to ml/min/1.73 m^2 by calculating the mean body surface area of the participants in each arm according to the Mosteller method [23], using the provided mean height and weight. If not reported, we used a weighted mean body surface area based on the NHANES database [20,21]. Median values were converted to estimates of means if the study arm included more than 25 participants [24].

All categorical outcomes were expressed as incidence rates (events per personyears of follow-up). The continuous outcome (GFR) was expressed as an annual slope (change from baseline over the length of follow-up in years).

We assessed study methodological quality in terms of randomization adequacy, blinding, and attrition rates using the Jadad scale [25].

Data Synthesis and Analysis

Using individual study arms (cohorts) as the unit of analysis, we performed metaregressions to separately explore the association of the first-3-month and total-studyperiod mean recombinant erythropoietin dose (in units/week) with the outcomes of interest. For the two primary outcomes (all-cause and cardiovascular mortality), we performed three sets of analyses. The first set of analyses used the first-3-month and total-study-period mean recombinant erythropoietin dose (in units/week) as the sole predictor. The second set added the target hemoglobin level to the model. The third set adjusted either for the first-3-month or total-study period achieved hemoglobin level (corresponding to the mean ESA dose time frame).

Models were deemed fit only if there were at least four degrees of freedom more than the number of predictors in each model. We did not report analyses where the 7 covariance matrix of the resulting coefficients indicated presence of collinearity among predictors. For the secondary outcomes, we performed only the first two sets of metaregressions due to a lack of sufficient observations; however, we performed additional analyses adjusting for the mortality rate (per 1000 person-years) in the control group of each trial in an attempt to control for heterogeneity of comorbidities in the study populations.

All analyses of binary outcomes were fit using generalized linear random-effects Poisson regressions with a fixed slope and random intercept, accounting for the clustering of cohorts (or trial arms) by study, and the person-years of exposure as the offset. The respective exposure for the Poisson is in terms of person time; the weighting of each study arm (cohort) is thus naturally accounted for through the Poisson distribution. When exponentiated, the coefficient expresses a change in the incidence rate of an event per unit change in the predictor. We report these results as incidence rate ratios (IRRs) with accompanying 95% confidence intervals (CI). For the annualized change in GFR, we fit random-effects variance-weighted meta-regressions [26]. The GFR analysis is reported as an estimate of the annual change in GFR (in ml/min/1.73m^2) per unit of change in the predictor.

In sensitivity analyses of all-cause mortality models with statistically significant predictors, we arbitrarily removed two cohorts with the highest mortality rate to evaluate the robustness of the results. In addition, we conducted subgroup analyses for the primary outcome stratified according to dialysis status, baseline hemoglobin level ($<$ *vs.* $\geq$ 10.5 g/dL, representing the median value), and ESA type (epoetin *vs.* darbepoetin). All analyses were performed in Stata SE version 11 (Stata Corp, College Station, TX) and 8 Meta-Analyst [27] version 3 (Tufts Medical Center, Boston, MA). All p-values were two tailed and considered to be statistically significant at the 0.05 level.

RESULTS

Search Yield

A total of 4493 potentially relevant citations were identified and screened (Figure 1). We retrieved full-text articles of 133 citations for evaluation, of which 26 satisfied the selection criteria. In addition, 92 potentially relevant systematic reviews were identified and screened, 10 of which were evaluated in full-text; 172 potentially relevant citations were identified from the references of these systematic reviews, of which 23 satisfied the selection criteria. After removal of duplicate reports, 31 unique trials with 72 study arms (cohorts) were included [8,28–57]. All eligible studies were in English.

Study Characteristics

Table 1 summarizes the trial characteristics. Published over 20 years, there were 8 placebo-controlled trials and 23 active comparator trials, of which 25 were industry sponsored, 5 provided no sponsorship disclosures, and 1 was funded by a non-industry source. The 31 trials enrolled a total of 12,956 participants. Sample sizes ranged from 42 to 4038 patients. The percentages of men ranged from 35% to 99%, and mean ages from 51 to 71 years. Fifteen trials were restricted to dialysis patients. Mean baseline GFRs (reported in 16 trials) ranged from 9.2 to 45.1 ml/min/1.73 m^2. Mean weights ranged from 64.0 to 85.4 kg. Two trials included only patients with diabetes.

The anemia parameters for each trial arm, including the mean hemoglobin and recombinant erythropoietin dose (or dose equivalent) throughout the study period are summarized in Table 1. Epoetin was used in 58 cohorts (43 used alfa, 9 used beta, and 6 9 did not specify); 6 used darbepoetin alfa, and 8 included placebo. Follow-up durations ranged from 3 to 36 months.

The randomization procedure was described in 14 RCTs [8,34,42–50,52,54,55]. All but two trials documented blinding, but the procedure was described in only 8, of which 6 were "double blinded." The blinding procedure was well-documented in only four studies [8,28,34,43]. All-cause mortality was ascertained in all trials throughout the follow-up period. The ascertainment of cardiovascular mortality was more heterogeneous since it relied upon arbitrary definitions of composite outcomes. Similarly, secondary outcome definitions, such as hypertension and any serious adverse event, varied widely across studies. Two trials did not report the mean ESA dose but instead described a protocoldriven algorithm of the ESA dosing regimen [30,34]. The attrition rates over the full duration of follow-up, reported in 29 trials, ranged from 0% to 80%. Six trials reported drop-out rates of less than 10% [29,31,35,49,56,57] and 7 trials of more than 40% [33,37,38,41,43,46,48]. Two trials did not report their drop-out rates [39,53]. Among the 29 trials that provided sufficient documentation, the intention-to-treat principle was followed in 21 [8,28–31,33–37,41–43,45_ 49,52,53,55].

ESA Dose and All-Cause Mortality

In the unadjusted analysis (Table 2, full models provided in Table S1), higher first- 3-month mean ESA dose (per epoetin alfa–equivalent 10,000-U/wk increment) was associated with a higher rate of all-cause mortality (IRR, 1.42; 95% CI, 1.10–1.83).This association persisted after adjustment for the first-3-month achieved mean hemoglobin level (IRR, 1.48; 95% CI, 1.02–2.14). After adjustment for the target hemoglobin level, the association strengthened in magnitude but lost statistical significance (IRR, 1.71; 95% 10 CI, 0.90–3.24).

A similar association (Figure 2) was observed in the unadjusted analysis for the association of the total-study-period mean ESA dose and all-cause mortality (IRR, 1.09; 95% CI, 1.02–1.18). This association persisted after adjustment for the trials' target hemoglobin level (IRR, 1.41; 95% CI, 1.08–1.82); after adjustment for the total-studyperiod mean hemoglobin level, the parameter estimate remained similar but lost statistical significance (IRR, 1.27; 95% CI, 0.97–1.65).. Of note, the target hemoglobin level was associated with a lower rate of all-cause mortality after adjustment for the total-studyperiod mean ESA dose (IRR, 0.91; 95% CI, 0.82–1.00).

In sensitivity analyses after removing the 2 cohorts with the highest all-cause mortality rates, only the total-study-period mean ESA dose, adjusted for target hemoglobin, remained significantly associated with all-cause mortality (IRR, 1.54; 95% CI, 1.02–2.30). Subgroup analyses are shown in Figure 3. In studies of dialysis patients, higher ESA dose was associated with higher mortality in the unadjusted (IRR, 1.12; 95% CI, 1.01–1.24) as well as the adjusted (IRR, 2.21; 95% CI, 1.30–3.75) analyses for target hemoglobin and achieved

mean hemoglobin (IRR, 1.64; 95% CI, 1.03–2.59). In studies that used epoetin, the association of ESA dose with mortality persisted in the unadjusted and adjusted analyses.

ESA Dose and Cardiovascular Mortality

The relationship between mean ESA dose and cardiovascular mortality was in the same direction as with overall mortality, albeit not statistically significant (Table 2, Table S1). In unadjusted analyses, IRRs of the first-3-month and total-study-period mean ESA dose (per epoetin alfa–equivalent 10,000-U/wk increment) were 1.31 (95% CI, 0.92–1.86) 11 and 1.07 (95% CI, 0.97–1.17), respectively. Adjusted analyses were limited due to the insufficient number of observations or collinearity between the predictor variables.

ESA Dose and Other Adverse Outcomes

In the unadjusted analyses (Figure 4A), the total-study-period mean ESA dose was associated with a higher rate of stroke (IRR, 1.60; 95% CI, 1.25–2.04), de novo or worsening hypertension (IRR, 1.13; 95% CI, 1.03–1.24), thrombotic events (IRR, 1.25; 95% CI, 1.08–1.44), and dialysis vascular access thrombosis (IRR, 1.17; 95% CI, 1.07–1.29), and with a lower rate of transfusion requirement (IRR, 0.73; 95% CI, 0.68–0.79). Similar associations were observed for the first-3-month mean ESA dose in the unadjusted analyses (data not shown) with the exception of a lower rate of stroke (IRR, 0.43; 95% CI, 0.19–0.93).

After adjustment for target hemoglobin (Figure 4B), the association of the totalstudy- period mean ESA dose strengthened only with the outcome of thrombotic events (IRR, 2.37; 95% CI, 1.32–4.27) while a lower rate for any serious adverse event was observed (IRR, 0.61; 95% CI, 0.40–0.92). After adjustment for mortality rate in the control group of each trial (Figure 4C), the results were strikingly similar to the unadjusted analyses, suggesting that the effects of these two predictors are completely orthogonal.

We found no association between the total-study-period mean ESA dose and the annual GFR change (in ml/min/1.73m^2 per epoetin alfa–equivalent 10,000-U/wk increment) either in the unadjusted analysis (−0.50; 95% CI, −15.93 to 14.93) or after adjustment for target hemoglobin (−0.42; 95% CI, −22.24 to 21.40).

DISCUSSION

In the present meta-regression analysis, we identify an association between the first-3-month and total-study-period mean ESA dose and all-cause mortality, both in unadjusted models and models adjusting for target hemoglobin. When restricting the analyses to dialysis patients or those treated with epoetin, the association persisted in both the unadjusted and adjusted analyses. Although not significant, a similar relationship was observed for cardiovascular mortality. We also observed an association between total-study- period mean ESA dose and several secondary endpoints including development of hypertension, stroke, and thrombotic events. These findings favor the recent US Food and Drug Administration's relabeling on ESAs, recommending a more conservative dosing regimen for the treatment of patients with CKD [58].

In a post hoc analysis of the CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) trial, a higher epoetin alfa dose was associated with increased risk for the composite endpoint of mortality, myocardial infarction, stroke, or heart failurerelated hospitalization, independently of randomization to a higher hemoglobin target [59]. Another post hoc analysis, of TREAT (Trial to Reduce Cardiovascular Events with Aranesp [darbepoetin alfa] Therapy), demonstrated that escalation of the darbepoetin alfa dose in "poor responders", attempting to reach the target hemoglobin level, was associated with an

increased risk of death or cardiovascular events [60]. Treatment-byindication bias might account for this association as the need for a higher ESA dose might be a proxy for comorbidities and inflammation thereby contributing to ESA hyporesponsiveness. More specifically, patients with ESA hypo-responsiveness were more likely to be older, have more comorbidities, and lower GFR levels, driving the association of higher ESA dose with higher mortality. In our analysis, the adjustment for 13 achieved hemoglobin partially controls for ESA hypo-responsiveness. Furthermore, the use of randomized trials minimized comorbidity imbalances among patients assigned to higher vs. lower target hemoglobin levels. Nevertheless, presence of ecological fallacy, especially in light of the heterogeneous dispersion depicted in Figure 2, cannot be ruled out and treatment-by-indication bias towards higher ESA doses among patients with ESA hypo-responsiveness might have influenced our results.

The risk of poorly controlled hypertension in ESA-treated patients targeted to higher target hemoglobin levels has previously been shown [6,61–64] and a drug effect has been theorized [8,45,47]. Our unadjusted analysis demonstrated an association between ESA dose and hypertension; the analysis that was adjusted for the mortality rate in the control group confirmed this finding, but the target hemoglobin-adjusted analysis did not. The similar association between ESA dose and increased risk of stroke in our analyses supports the findings of TREAT[8], and raises concerns about the use of these agents, particularly in patients with poorly controlled hypertension or in those with a prior history of stroke.

We found strong associations between ESA dose and increased risk of thrombotic events, which had previously been observed in some [8,36,41] but not all trials [45,46].

The unexpected finding of a protective effect of the higher total-study-period mean ESA dose on the incidence of any serious adverse event, after adjustment for target hemoglobin level, is of unclear significance. Significant heterogeneity in the definition of this clinical endpoint raises concerns about its content validity. Similarly, the protective effect of a higher first-3-month mean ESA dose against stroke is of unclear significance as the total-study-period mean ESA dose was not protective. Alternatively, a potential 14 ESA neuroprotective effect might be short-term lived [65].

To our knowledge, there are no published trials explicitly designed to answer the potential harm of ESA dose. A recent retrospective cohort study found that, at higher hematocrit levels, an increased risk of death was associated with greater ESA and iron use [66]. Prior systematic reviews on this topic either did not explore the potential effect of ESA dose on mortality or other adverse outcomes [2,6,9–15] or reported that the data were insufficient for this analysis [7].

We observed a non-significant trend between a higher target hemoglobin level and a lower adjusted IRR for all-cause and cardiovascular mortality. This counterintuitive observation might be due to collinearity between predictors, whereby the hemoglobin level may be an intermediate factor between the ESA dose and mortality or a determinant of ESA dose. Adjusting for an intermediate factor typically results in estimates that are biased towards the null [67]. This protective effect could hold true but the possibility of collinearity does not allow such inference, especially in light of several large RCTs demonstrating an association between higher target hemoglobin and adverse outcomes [8,36,40,42,43,45,47]. The presence of this counterintuitive protective effect suggests that collinearity, ecological fallacy, or treatment-by-indication bias, were not addressed adequately, a problem that is impossible to unwind in the setting of meta-regression without access to patient-level data.

To our knowledge, this is the first meta-regression analysis that formally explores the association of the ESA dose, adjusted for target and achieved hemoglobin level, with several

clinically important endpoints in patients with CKD. The inclusion of RCTs, which typically mandate pre-defined outcome assessment and have more complete follow 15 up compared to cohort studies, helped minimize ascertainment bias. We also dissected the differential effect of ESA dose over the first 3 months of therapy vs. the total-study period. If not spurious, our findings are consistent with the notion that rapid correction of anemia with ESAs might be an independent predictor of adverse outcomes [59], a factor commonly overlooked by clinicians that might deserve more attention.

Our major limitation is the use of study-level aggregated data, which are susceptible to ecological fallacy. In addition, numerous assumptions and transformations were required to harmonize results from individual trials and bring them into the same unit and scale, possibly introducing additional biases. Similarly, we were unable to effectively differentiate between mean follow-up time and total duration of individual trials, inserting bias into the ascertainment of our outcomes. We used epoetin alfa– equivalent dose, which is an oversimplification, as ESAs likely have different properties. Finally, we could not adequately control for potential confounding effects of other factors, and heterogeneity among the selected trials.

Our analysis raises concerns as to whether the ESA dose is an independent predictor of mortality and other adverse cardiovascular events in patients with CKD. Our results call for the design of trials that examine the effect of the ESA dose rather than target hemoglobin on cardiovascular endpoints. Such trials, using an absolute dosing protocol rather than a titration protocol, would hopefully advance the field and help revise current anemia treatment guidelines in CKD by incorporating not only the target hemoglobin but also the optimal ESA dose.

In conclusion, after adjusting for target or mean achieved hemoglobin, higher ESA dose for the treatment of anemia in patients with CKD might be associated with a higher 16 mortality risk. Lack of adjustment for comorbidities and inflammatory markers as well as inadequate control for treatment-by-indication bias and ecological fallacy in the setting of meta-regression precludes definitive conclusions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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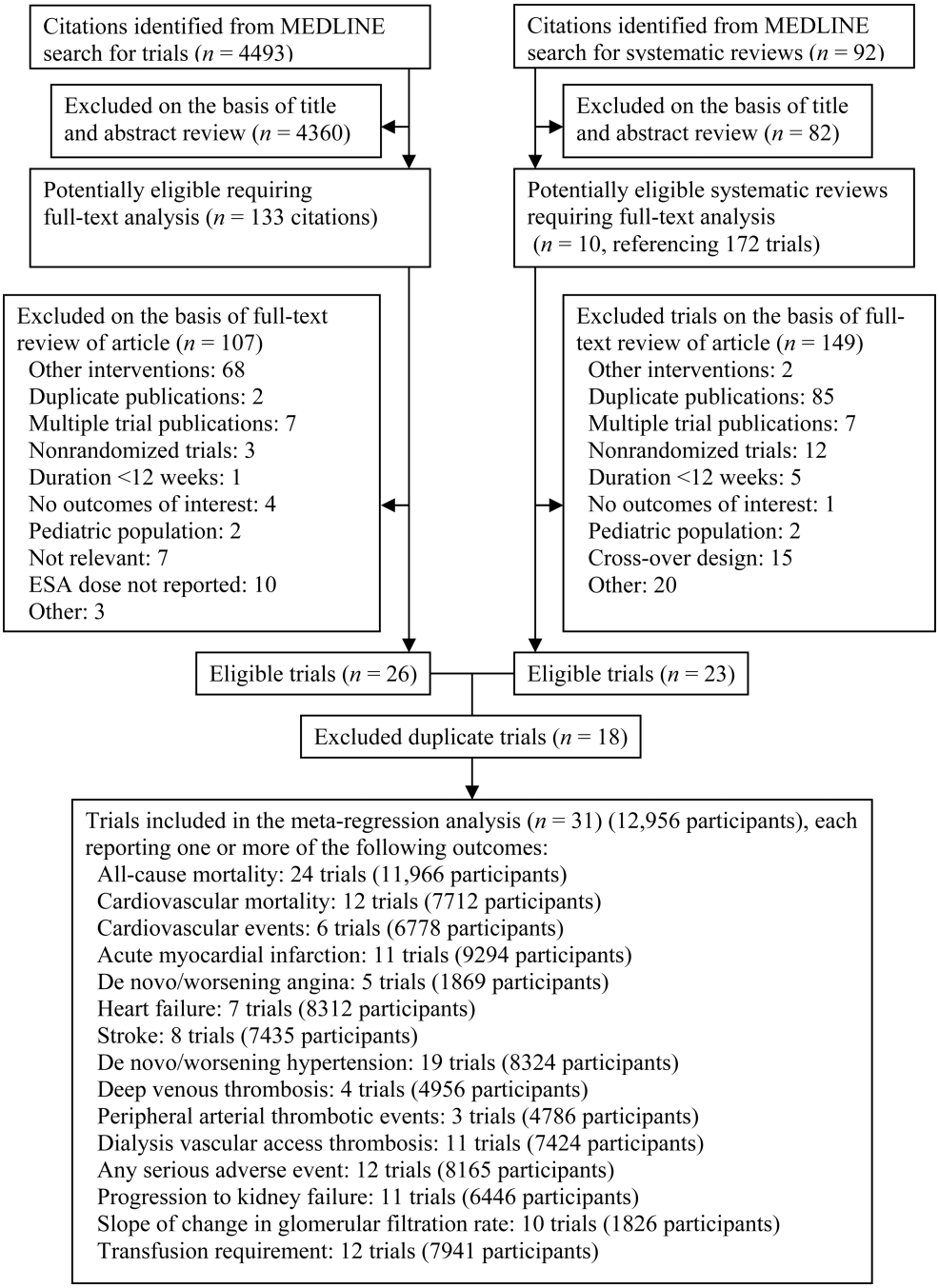

Figure 1.
Literature search and selection. ESA denotes erythropoiesis-stimulating agent.

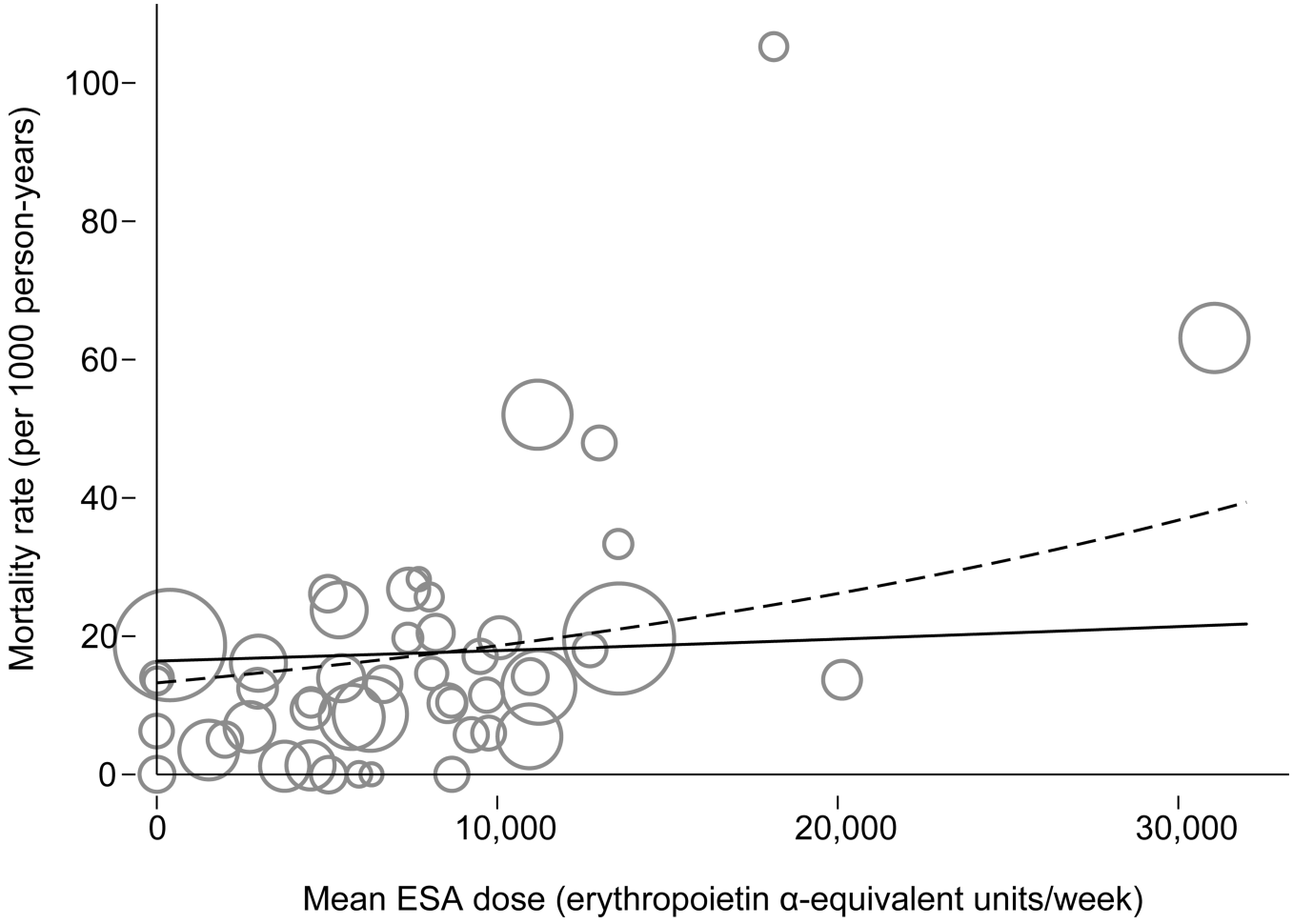

Figure 2.

Association of the total-study-period mean weekly ESA dose with all-cause mortality. *Continuous* line, unadjusted analysis (IRR 1.09; 95% CI 1.02, 1.18; P = 0.02); *Dashed* line, target hemoglobin-adjusted (fixed at 11 gm/dL) analysis (IRR, 1.41; 95% CI, 1.08–1.82; P = 0.01). Each circle represents a study arm. The radius of a circle corresponds to a study arm's weight in the metaregression. Here, "erythropoietin α" refers to epoetin alfa.

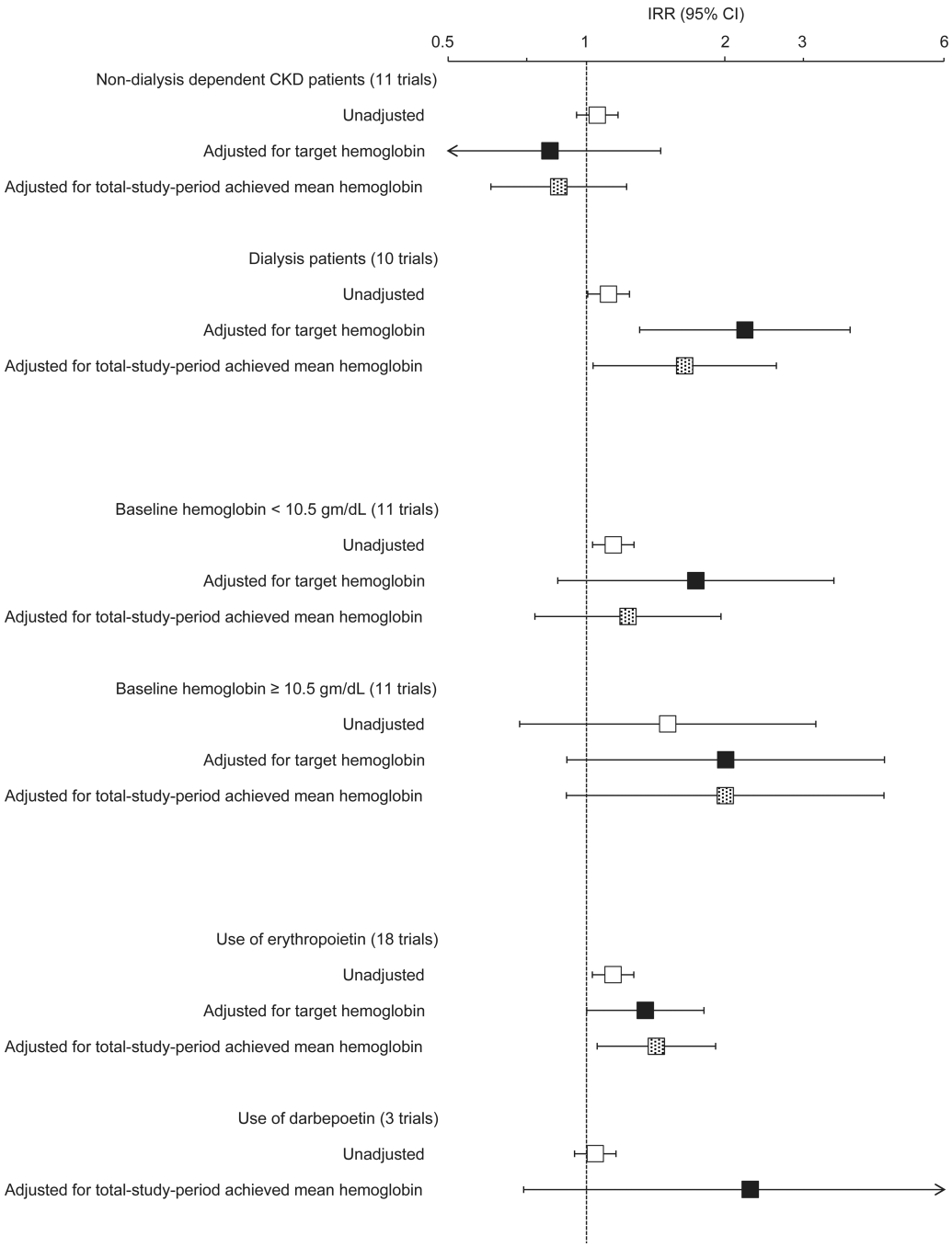

Figure 3.

Subgroup meta-regression analyses examining the association of total-study-period ESA dose (per epoetin alfa–equivalent 10,000-U/wk increment) with all-cause mortality. The incidence rate ratio (IRR) and 95% confidence interval (CI) is displayed on a logarithmic scale. Here, “erythropoietin” refers to epoetin (alfa or beta); “darbepoetin” refers to darbepoetin alfa.

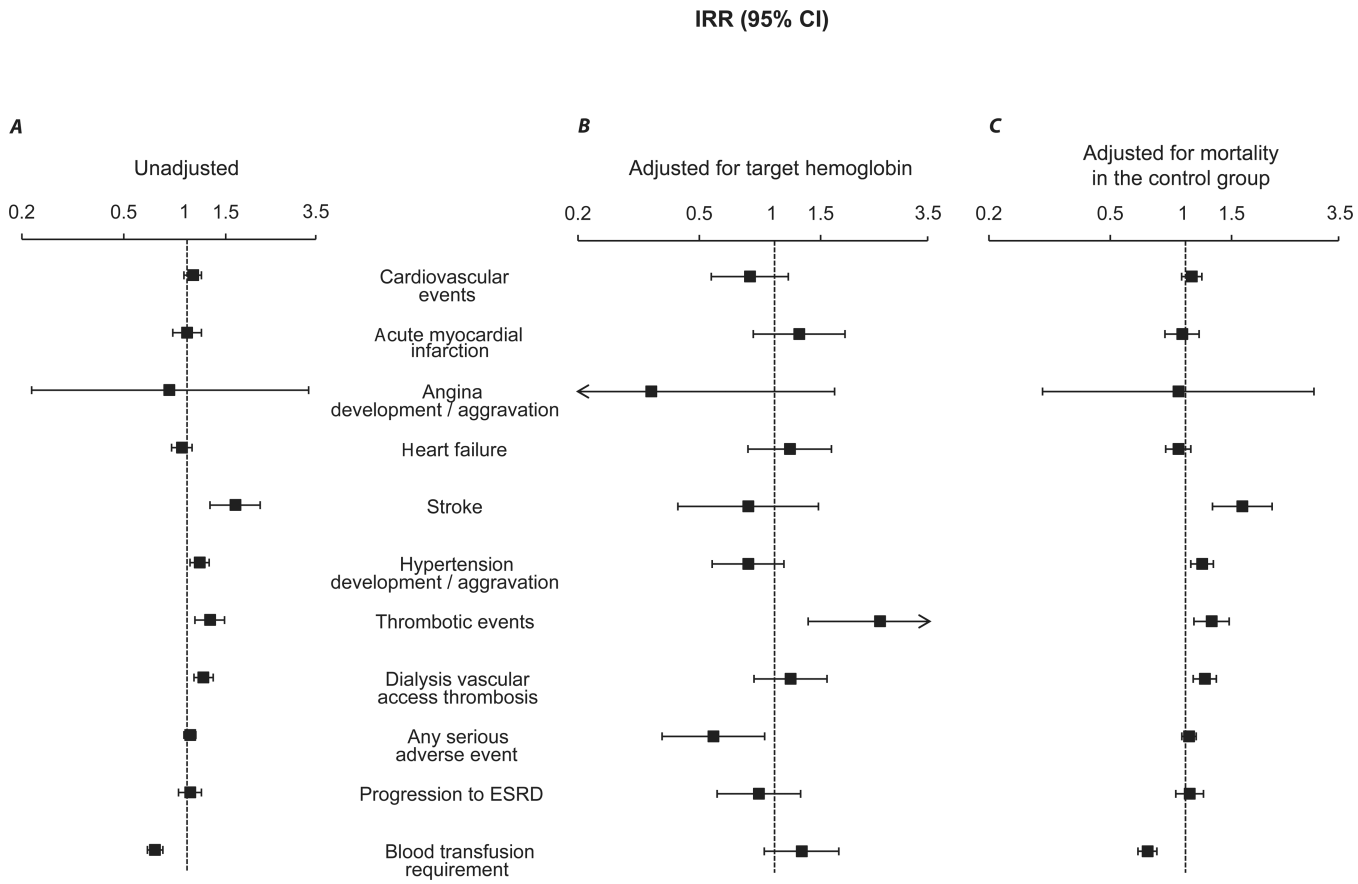

Figure 4.

Meta-regression analyses examining the association of total-study-period ESA dose (per epoetin alfa–equivalent 10,000 U/wk increment) with the secondary outcomes [4A, unadjusted; 4B, adjusted for target hemoglobin; and 4C, adjusted for mortality rate (expressed per 1000 person-years) in the control group]. The incidence rate ratio (IRR) and 95% confidence interval (CI) is displayed on a logarithmic scale. ESRD denotes end-stage renal disease.

Table 1

Characteristics of trials included in the meta-regression analysis.

Study	Industry funded	CKD Stage	No. Pt	age[a] (y)	Men (%)	Wt[a] (kg)	GFR[b]	DM (%)	F/U (wk)	ESA type	Hb (g/dL)					ESA dose (U/wk)				Fe use
											Target	Baseline[a]	1st 3mo[a]	Total-study-period[a]	End-of-study[a]	Starting[a]	1st 3 mo[a]	Total-study-period[a]	End-of-study[a]	
Canadian EPO Study Group [28] (1990)	NR	5-HD	118	45	59	74.9*	-	NR	26	Placebo	NR	7.1	7.1	7.2	7.4	0	NR	NR	0	Y
										Epo	10.3	6.9	9	9.7	10.2	21,686¶	NR	NR	14,746¶	Y
										Epo	10.3	7.1	9.5	10.6	11.7	23,302¶	NR	NR	15,845¶	Y
Abraham [29] (1991)	Y	5-HD	151	52	23	70.4*	-	NR	12	Epo-β	NR	7.1	7.1	9	10.9	25,613¶	NR	NR	NR	Y
										Placebo	NR	7	7	7.3	7.5	0	NR	NR	NR	Y
										Epo-β	NR	7.2	7.2	8	8.8	5,468¶	NR	NR	NR	Y
										Epo-β	NR	7	7	9	11	21,870¶	NR	NR	NR	Y
										Epo-β	NR	6.9	6.9	9.3	11.6	43,740¶	NR	NR	NR	Y
Bahlmann [30] (1991)	NR	5-HD	129	57	38	64	-	20	26	Epo	10.8	7.7	9.2	9.5	10.4	16,152	NR	8,076	8,076	NR
										Placebo	NR	7.7	7.7	7.7	8	0	0	0	0	NR
Clyne [31] (1992)	N	4, 5-NDD	20	46	55	79*	9.2	0	13	Epo-β	NR	8.6	NR	NR	11.7	23,505¶	NR	NR	18,409¶	Y
										Placebo	NR	9.3	NR	NR	9.4	0	0	0	0	Y
Muirhead [32] (1992)	Y	5-HD	128	58	55	66	-	NR	24	Epo	11.5	8	NR	11.8	10.9	9,870	NR	13,548	9,679	NR
										Epo	11.5	7.7	NR	11.5	11.2	9,915	NR	18,118	12,156	NR
Roth [33] (1994)	Y	4, 5-NDD	83	57	33	78.1*	9.2	NR	48	Epo	11.7	8.9	10.7	10.8	10.9	8,298¶	8,792¶	8,657¶	9,106¶	Y
										Placebo	NR	8.9	8.9	8.9	9	0	0	0	0	Y
Nissenson [34] (1995)	Y	5-PD	152	48	39	71.2	-	26	12	Epo-α	11.7	7.9	10	10	11.2	12,000	8,000	8,000	NR	Y
										Placebo	NR	7.9	8	8	8	0	0	0	NR	Y
Virot [35] (1996)	NR	5-HD	49	63	55	70.6*	-	NR	17	Epo-α	9.5	9.6	9.7	9.7	9.9	7,424¶	7,696¶	7,691¶	7,844¶	NR
										Epo-α	9.5	9.9	9.6	9.6	9.7	6,864¶	6,392¶	6,303¶	5,883¶	NR
Besarab [36] (1998)	Y	5-HD	1233	65	49	70.9*	-	56	60	Epo-α	14	10.2	11	13	13.2	11,777¶	19,298¶	31,067¶	30,239¶	Y
										Epo-α	10	10.2	10.4	10.4	10	11,349¶	11,801¶	11,179¶	9,704¶	Y

Study	Industry funded	CKD Stage	No. Pt	age[a] (y)	Men (%)	Wt[a] (kg)	GFR[b]	DM (%)	F/U (wk)	ESA type	Hb (g/dL)					ESA dose (U/wk)				Fe use
											Target	Baseline[a]	1st 3mo[a]	Total-study-period[a]	End-of-study[a]	Starting[a]	1st 3 mo[a]	Total-study-period[a]	End-of-study[a]	
Kaufman [37] (1998)	Y	5-HD	208	60	99	76.1	-	NR	46	Epo-α	10.5	10.5	NR	10.4	NR	NR	NR	7,397	NR	Y
									48	Epo-α	10.5	10.6	NR	10.3	NR	NR	NR	10,068	NR	Y
Berns [38] (1999)	Y	5-HD	28	61	33	73.3	-	54	52	Epo-α	14	10.2	11	12.4	14	13,200	21,700	31,300	32,200	NR
										Epo-α	10	10.2	10.3	10.5	10.1	10,900	11,700	9,120	6,400	NR
Conlon [39] (2000	NR	5-HD	31	55	55	NR	-	NR	28	Epo-α	14	9.7	10.5	12.3	13.6	14,400	NR	NR	43,200	Y
										Epo-α	10	9.7	9.7	9.9	10	10,095	NR	NR	18,300	Y
Foley [40] (2000	Y	5-HD	146	62	62	68	-	NR	48	Epo-α	13.5	10.2	11.2	12.3	12.8	8,110	15,397	20,122	21,190	Y
										Epo-α	10	10.1	10.4	10.4	10.6	9,265	9,509	8,536	6,459	Y
Furuland [41] (2003)	Y	4, 5-NDD, 5-HD/PD[§]	416	63	65	73	16.5	19	48	Epo-α	15.1	10.9	12	13.3	13.4	6,862	NR	NR	15,133	Y
										Epo-α	10.8	11	11.2	11.4	11.3	6,986	NR	NR	8,052	Y
Levin [42] (2005)	Y	2, 3, 4	172	57	62	78	26.3	34	104	Epo-α	13	11.8	12.4	12.7	12.7	2,000	NR	NR	3,146	Y
										Epo-α	9.8	11.7	11.7	11.7	11.4	0	NR	NR	3,552	Y
Parfrey [43] (2005)	Y	5-HD	596	51	60	74.4	-	NR	96	Epo-α	14	11	11.6	12.9	13	7,185	8,981	10,955	13,077	NR
										Epo-α	10.5	11	11	10.9	10.9	5,910	5,682	5,728	5,634	NR
Provenzano [44](2005)	Y	4, 5-NDD	519	69	51	84.2	21.1	NR	16	Epo-α	12	11.8	12.4	12.4	12.2	10,000	NR	9,235	NR	Y
										Epo-α	12	11.8	12.1	12.1	11.9	10,000	NR	9,681	NR	Y
										Epo-α	12	11.9	11.8	11.7	11.2	10,000	NR	9,489	NR	Y
										Epo-α	12	11.9	11.9	11.7	11.4	10000	NR	9,748	NR	Y
Drüeke [45] (2006)	Y	3, 4	603	59	54	73.2	22.8	26	52	Epo-β	14	11.6	12.2	13.2	13.5	2,000	2,646	5,350	5,833	Y
									54	Epo-β	11	11.6	11.6	11.5	12	2,000	2,077	2,983	3,310	Y
Rossert [46] (2006)	Y	3, 4	390	58	60	58.3[*]	29.3	35	47	Epo-α	14	11.5	12.5	13.3	13.5	5,333[¶]	NR	4,514	NR	Y
									54	Epo-α	11.5	11.6	11.8	11.9	11.9	5,333[¶]	NR	2,730	NR	Y
Singh [47] (2006)	Y	3, 4	1432	66	45	30.4[≠]	36.9	NR	69	Epo-α	13.5	10.1	11.5	12.7	12	9,896	10,743	11,215	13,869	Y
										Epo-α	11.3	10.1	11.2	11.4	11.1	9,357	7,052	6,276	7,248	Y
Macdougall [48] (2007	Y	2, 3, 4, 5-NDD	197	55	62	78	21.7	22	154	Epo-α	11	10.9	NR	11.5	11	2,000	NR	3,761	3,219	Y
										Epo-α	9	10.8	NR	10.9	10.5	0	NR	1,531	1,837	Y

Study	Industry funded	CKD Stage	No. Pt	age[a] (y)	Men (%)	Wt[a] (kg)	GFR[b]	DM (%)	F/U (wk)	ESA type	Hb (g/dL)					ESA dose (U/wk)				Fe use
											Target	Baseline[a]	1st 3mo[a]	Total-study-period[a]	End-of-study[a]	Starting[a]	1st 3 mo[a]	Total-study-period[a]	End-of-study[a]	
Ritz [49] (2007	Y	1, 2, 3	170	58	51	72.9	45.1	100	64	Epo-β	14	11.9	12.7	13.3	13.6	2,000	NR	3,500	NR	Y
										Epo-β	11	11.7	11.8	11.9	12.2	2,000	NR	NR	NR	Y
Bommer [50] (2008)	Y	5-HD	114	62	46	71.3	-	NR	48	Darb[†]	11.5	11.6	NR	11.9	11.6	10,480	NR	10,976	10,282	Y
										Darb[†]	11.5	12	NR	11.9	11.7	8,529	NR	8,199	8,893	Y
Chen [51] (2008)	NR	4, 5-NDD	42	64	36	81.8[*]	10.4	24	24	Epo-α	10.5	8.5	NR	NR	10.6	7,414[¶]	NR	2,350	NR	Y
										Darb[†]	10.5	8.2	NR	NR	10.7	7,321[¶]	NR	3,759	NR	Y
Spinowitz [54] (2008)	Y	2, 3, 4	259	67	41	30.6[≠]	30.2	NR	16	Epo-α	11.5	10.3	11.2	11.3	11.5	10,000	NR	5,943	NR	Y
										Epo-α	11.5	10.4	11.1	11.2	11.4	10,000	NR	7,376	NR	Y
										Epo-α	11.5	10.1	10.8	10.9	11.2	5,000	NR	4,522	NR	Y
										Epo-α	11.5	10.2	11	11.1	11.4	10,000	NR	8,660	NR	Y
Cianciaruso [52] (2008)	Y	2, 3, 4	95	58	62	69.5	26.2	18	52	Epo-α	13	11.6	11.8	12.2	12.3	2,000	NR	2,000	NR	Y
										Placebo	9.8	11.7	11.6	11.5	11.3	0	0	0	NR	Y
Locatelli [53] (2008)	Y	5-HD	287	66	58	66.4	-	NR	28	Epo-α	12	11.6	11.5	11.5	11.3	6,210	6,516	6,344	6,239	NR
										Epo-α	12	11.6	11.1	11	10.8	6,791	7,445	8,069	8,936	NR
Pfeffer [8] (2009)	Y	3, 4	4038	68	43	82.8[*]	33.5	100	125	Darb[†]	13	10.5	11.5	12.5	12.8	20,473	NR	13,577	NR	Y
										Placebo	9	10.4	10.5	10.9	11.4	0	NR	386[//]	NR	Y
Pergola [56] (2009)	Y	3, 4	369	70	35	76[*]	30	NR	22	Epo-α	11.5	9.6	11	11.3	11.3	11,393	NR	5,039	NR	Y
										Epo-α	11.5	9.7	10.8	11.1	11.3	10,000	NR	5,035	NR	Y
										Epo-α	11.5	9.8	10.9	11	11.1	10,000	NR	6,662	NR	Y
Chazot [55] (2009)	Y	5-HD	154	63	46	84.9[*]	-	NR	26	Darb[†]	10	11.6	11.7	11.7	11.7	12,624	12,905	12,718	12,344	NR
										Darb[†]	10	11.5	11.7	11.8	12	12,905	13,045	12,998	12,905	NR
Pergola [57] (2010)	Y	3, 4	428	71	38	85.4	28.1	NR	36	Epo-α	11.5	11	11.1	11	11	5,503	NR	2,967	NR	Y
										Epo-α	11.5	11.1	11.2	11.1	11.1	6,348	NR	4,529	NR	Y
										Epo-α	11.5	11.2	11.3	11.1	11.1	5,991	NR	5,423	NR	Y

1st, first; CKD, chronic kidney disease; DM, diabetes mellitus; Fe, iron; F/U, follow-up; GFR, glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis; D, dialysis; NDD, non—dialysis-dependent; NR, not reported; EPO, (recombinant) erythropoietin; Epo, epoetin (alfa or beta not specified in individual study); Epo-α, epoetin alfa; Epo-β , epoetin beta; Darb, Darbopoietin; ESA, erthropoietin-stimulating agent; Hb, hemoglobin; Pt, patient; Wt, weight

[*] Weighted average derived from NHANES (for the NDD-CKD subjects) or USRDS (for those receiving dialysis) according to age, sex and year of report.

[†] The ESA dose was converted to an equivalent epoetin alfa dose.

[‡] The value represents the mean body mass index (kg/m^2).

[§] 72 in 4,5-NDD group; 293 in 5-HD group; 46 in 5-PD group.

[‖] This was a placebo arm where the protocol necessitated rescue ESA therapy for Hb < 9 gm/dL. Over the course of this trial, 46% of patients in this placebo arm received at least one dose of darbepoetin alfa as rescue therapy.

[¶] Denotes conversion of ESA dose from U/kg/wk to U/wk by using the mean weight of the participants in each study arm.

a) mean

b) in mL/min/1.73 m2.

Table 2

Metaregression analyses of the association of ESA dose with all-cause and cardiovascular mortality.

Outcome / predictor	No. patients	No. trials	IRR (95% CI)	P
All-cause mortality				
First-3-month mean ESA dose				
Unadjusted	4565	11	1.42 (1.10–1.83)	0.007
Adjusted for target Hb	4385	10	1.71 (0.90–3.24)	0.1
Adjusted for first-3-month achieved mean Hb	4565	11	1.48 (1.02–2.14)	0.04
Total-study-period mean ESA dose				
Unadjusted	11,285	21	1.09 (1.02–1.18)	0.02
Adjusted for target Hb	11,105	21	1.41 (1.08–1.82)	0.01
Adjusted for total-study-period achieved mean Hb	11,285	21	1.27 (0.97–1.65)	0.08
Cardiovascular mortality				
First-3-month mean ESA dose				
Unadjusted	2085	6	1.31 (0.92–1.86)	0.1
Adjusted for target Hb	1979	5	Not performed *	-
Adjusted for first-3-month achieved mean Hb	2085	6	Not performed *	-
Total-study-period mean ESA dose				
Unadjusted	7148	10	1.07 (0.97–1.17)	0.2
Adjusted for target Hb	7042	10	Not performed †	-
Adjusted for total-study-period achieved mean Hb	7148	10	1.38 (0.93–2.03)	0.1

ESA dose is per epoetin alfa--equivalent 10,000-U/wk increment. IRR, incidence rate ratio; CI, confidence interval; Hb, hemoglobin; ESA, erythropoiesis-stimulating agent.

* The analysis was not performed due to insufficient observations.

† The analysis was not performed due to collinearity.