Erythropoiesis-Stimulating Agents (ESA) for Preventing the Progression of Chronic Kidney Disease: A Meta-Analysis of 19 Studies

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Key Words

Chronic kidney disease · Anemia ·
Erythropoiesis-stimulating agents · ESA ·
CKD-progression · Meta-analysis · Systematic review

Abstract

Background: The effect of anemia correction on kidney function in chronic kidney disease (CKD) patients remains unclear. As 19–40% of patients with CKD receive an erythropoiesis-stimulating agent (ESA), this is a potentially important consideration. **Summary:** We conducted a systematic review and meta-analysis of randomized trials to January 1, 2014 in adult patients with CKD stages 1 to 4. Selection criteria for studies: randomized controlled trials of at least 2 months duration. Patients were allocated to ESA versus placebo, no treatment, or different ESA doses with the purpose of achieving a higher versus a lower hemoglobin target. The analyzed outcomes were the need for renal replacement therapy, doubling of serum creatinine, change in GFR (ml/min), mortality and withdrawal of treatment due to adverse events. A total of 19 trials (n = 8,129 participants with CKD stage 1–4) were reviewed. There was no difference in the risk of end-stage kidney disease (RR, 0.97 [CI 0.83–1.20], 17 trials, 8,104 participants), change in GFR (Mean Difference [MD] –0.45 [–2.21, 1.31], 9 trials, 1,848 participants) or with-

drawal of treatment due to adverse events (RR, 1.18 [CI 0.77–1.81], 10 trials, n = 1,958 participants) for patients at higher hemoglobin (Hb) targets. Furthermore, no statistically significant differences in mortality (Risk Ratio [RR] 1.10 [CI 0.90–1.35], 16 trials, n = 8,082 participants) were observed. **Key Messages:** There is no evidence that ESA treatment affects renal function in patients with CKD. Use of these agents should not therefore be influenced by considerations about influencing CKD progression.

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Introduction

Chronic kidney disease (CKD) is a worldwide health burden, affecting about 10–15% of the Western adult population [1]. It is associated with premature death, cardiovascular disease, infection and cancer; it also consumes many valuable healthcare resources [2–5]. Prevention of CKD progression therefore is pivotal. Control of blood pressure (BP) by blockade of the renin-angiotensin-aldosterone system (RAAS) is the cornerstone of current CKD preventive treatment, delaying both cardiovascular and renal disease progression [6, 7]. Alternative nephroprotective therapies have yet uncertain values (statins, pentoxifyllin, bicarbonate) [8]. Despite the

currently available therapy, CKD patients remain at a highly increased risk for progression toward end-stage renal disease and concomitant cardiovascular complications [9].

The effect of anemia correction on kidney function and progressive GFR loss is an under-researched topic. In this regard, the available literature is contradictory, with some researchers suggesting that correction of anemia with ESAs is beneficial for preventing further renal functional decline, while others suggest potential detrimental effects [10, 11].

Recently, comprehensive meta-analysis focusing on the impact of anemia treatment on mortality and cardiovascular impacts of anemia treatment was published [12]. They did not, however, focus on or report conclusive information on the impact of anemia treatment on renal function over time. Since some recent studies [13–15] have suggested that anemia treatment has a beneficial impact on renal function, we decided to perform a systematic analysis of the existing literature in order to establish if different degrees of anemia correction (low or high Hb targets) by ESAs may have different impact on renal function trajectories in CKD patients.

Methods

The systematic review and meta-analysis was performed according to a previously published protocol (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014007162).

We searched MEDLINE (January 1966 to 1st of January 2014) and the Cochrane Controlled Clinical Trials Register Database (through Issue 1 of 12, January 2014); we also hand searched reference lists of textbooks, articles, and scientific proceedings for relevant articles (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000366025).

We included all RCTs and quasi-RCTs with a study period of at least 2 months duration and assessed the effects of different hemoglobin (Hb) targets in pre-dialysis patients with anemia of CKD on the prevention of the progression of CKD. The first period of randomized crossover studies was also considered for inclusion. There was no language restriction. The higher Hb target could be achieved by EPO (α or β) or darbepoetin; the lower target could be achieved by lower doses of the same drugs or by a placebo or no treatment or blood transfusion.

Studies enrolling any patient with CKD stages 1–4 (as defined by the Kidney-Disease Outcomes and Quality Initiative [K-DOQI] guidelines: stage 1 = GFR ≥ 90 ml/min/1.73 m²; stage 2 = GFR 60–89 ml/min/1.73 m²; stage 3 = GFR 30–59 ml/min/1.73 m²; stage 4 = GFR 15–29 ml/min/1.73 m²; stage 5 = GFR < 15 ml/min/1.73 m² not requiring dialysis) were included. We excluded studies enrolling patients with CKD stage 5 (GFR < 15 ml/min/1.73 m²) and who were receiving hemodialysis or other forms of dialysis including peritoneal dialysis. We also included studies on kidney transplanted patients if participants had residual GFR > 15 ml/min/1.73 m².

Data on the effects of ESAs on the following outcome measures were analyzed:

- (1) Primary outcome:
  - (a) Need for renal replacement therapy (RRT);
- (2) Secondary outcomes:
  - (b) Doubling of serum creatinine;
  - (c) A composite outcome – death or need for RRT (whichever came first) – since numerous authors [16] argue that the main outcome for CKD is in fact death [17, 18], and only ‘CKD survivors’ reach dialysis – in order to verify the previous result.
  - (d) Renal function measured as end-of-treatment GFR (ml/min or ml/min/1.73 m²) and serum creatinine value at the end of the study (mg/dl or μ mol/l); change in GFR (ml/min);
  - (e) End-of-treatment BP – systolic BP and diastolic BP (mm Hg);
  - (f) Adverse events – (cardiovascular events, myocardial infarction and stroke, or any other serious adverse events as defined by the authors of the included studies);
  - (g) End-of-treatment urinary albumin/protein excretion (24 h proteinuria or 24 h albuminuria in g/dl);
  - (h) All-cause or cardiovascular-mortality (online suppl. fig. 5).

Data extraction was carried out independently by the reviewers, using standard data extraction forms. It was planned that studies reported in non-English language journals would be translated before assessment. It was also planned that where more than one publication of one trial existed, reports would be grouped and the most recent or complete dataset would be used. Disagreements between reviewers were resolved in consultation with AC.

The quality of included studies was assessed independently by (IN) and (DG) without blinding to authorship or journal according to recommendations from the Cochrane Collaboration [19]. The quality items assessed were selection bias (random sequence generation, allocation concealment), performance bias (blinding of patients and investigators), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other forms of bias (significant different group comparisons, funding sources, early termination of a trial). We considered the RCT to be at a high risk of selective outcome reporting when investigators did not report data for all-cause mortality, need for renal replacement therapy, doubling of serum creatinine and adverse events or patient symptoms.

For dichotomous outcomes (all-cause mortality, number of patients starting RRT), the results were expressed as relative risks (RR) with 95% confidence intervals (CI). Data were pooled using a random-effects model, but the fixed-effects model was also analyzed to ensure robustness of the model chosen and susceptibility to outliers. Where continuous scales of measurement were used to assess the effects of treatment (serum creatinine value at the end of the study, GFR, BP), the mean differences and its 95% CI were used.

Heterogeneity was analyzed with a chi-squared test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test [20, 21]. An I² value of $> 50\%$ indicates statistically large heterogeneity among the included studies. If substantial statistical heterogeneity were noted (I² $> 50\%$), we planned to explore individual study characteristics and those of subgroups of the main body of evidence. Plausible reasons for variations in treatment effect (heterogeneity) were explored using subgroup analysis specifically for the length of follow-up, and type of ESA used and number of participants. All analyses were performed using Revman 5.1 (©2011, The Cochrane Collaboration, UK).

Fig. 1. Flowchart showing the number of citations retrieved by individual searches and number of trials included in the systematic review.

Results

Search Results

The combined search of MEDLINE, CENTRAL databases, and hand search by experts identified 5,257 citations, of which 3,808 were excluded (non-RCTs or studies evaluating other interventions not relevant to this review). Full-text assessment of 319 potentially relevant articles resulted in the identification of 19 eligible trials enrolling a total of 8,129 patients [10, 11, 13–15, 22–35] (fig. 1).

Characteristics of the Included Studies

Baseline studies characteristics are presented in table 1. The population sample sizes varied between 88 and 4,038 patients [10, 35]. Study duration ranged from twelve weeks [22–24], to 3.3 years [30]. The mean of the Glomerular filtration rate at the trial outsets spanned from 16 to 51 ml/min 1.73 m². Baseline albuminuria/proteinuria ranged from 0.5 to 3.1 g/day. Only two studies did not include patients with diabetes mellitus [10, 24]. One study included only renal transplant recipients [15].

Table 1. Characteristics of the populations and interventions in the included trials

No	Study	Baseline kidney disease	Baseline renal function, ml/min/1.73 m ² (mean ± SD)	Baseline Hb level, g/l (mean ± SD)	Use of ACE inhibitor or ARB	No. of patients	Intervention	Co-intervention in treatment arm (n), type of ESA, notes	Study duration, months	Study end points
1	Kleinman 1989 [22]	Diabetic nephropathy: 57%	Creatinine values from 3 to 11 mg/dl	HCT (%) Arm 1 (placebo): 28.2 Arm 2 (ESA): 28.1	Not reported	Arm 1: n = 7 Arm 2: n = 7	Arm 1: placebo subcutaneously, thrice weekly at no less than 48-h intervals, for 12 weeks or until a target hematocrit of 38–40% was attained Arm 2: receive 100 U/kg of r-HuEPO, thrice weekly at no less than 48-h intervals, for 12 weeks or until a target hematocrit of 38–40% was attained	Iron therapy was available for all patients	3 months	Renal function outcomes, adverse effects, quality of life
2	Watson 1990 [23]	Diabetic nephropathy: 9%	Cr-DTPA clearance: Arm 1: 12.4±3.5 Arm 2: 13.02±4.4	Not reported	Not reported	Arm 1 (no ESA): n = 6 Arm 2 (ESA): n = 5	Arm 1: Aiming Ht level of 38% with placebo injection Arm 2: Aiming Ht level of 38% with rHuEPO (100 units/kg body weight, subcutaneous injection three times per week for 12 weeks)	All patients required iron supplementation	3 months	Renal function outcomes, serum potassium levels, adverse events and blood pressure control
3	Clyne 1992 [24]	Diabetes mellitus: exclusion criterion	Insulin creatinine clearance: Arm 1 (no ESA): 8.0±3.0 Arm 2 (ESA): 10.0±4.0	Arm 1: 93±8 Arm 2: 86±8	Not reported	Arm 1: n = 12 Arm 2: n = 10	Arm 1: No ESA injection, standard care; Arm 2: Aiming HCT level of >30% with EPO intravenously injection once a week	Iron therapy was available for all patients is the ferritin levels were within the normal range	3 months	Number of patients starting RRT during study period, change in quality of life, Glomerular filtration rate at end of study; Serum creatinine level at end of study; blood pressure at end of study; Number of patients with new antihypertensive treatment
4	Revicki 1995 [25]	Diabetic nephropathy: not reported	Creatinine clearance: Arm 1 (no ESA): 10.0±4.1 Arm 2 (ESA): 10.2±4.1	HCT (%) Arm 1: 26.8±3.6 Arm 2: 26.8±4.5	Not reported	Arm 1: n = 40 Arm 2: n = 43	Arm 1: no ESA treatment Arm 2: ESA 50 U/kg/week × 3 to achieve and maintain HCT >35%	All patients received oral iron supplements not to exceed 200 mg elemental iron per day if their serum iron decreased below 50 µg/dl or the iron/total iron-binding capacity decrease <20%	12 months	Quality of life, All-cause mortality, cardiovascular mortality, Adverse events

Table 1. (continued)

No	Study	Baseline kidney disease	Baseline renal function, ml/min/1.73 m ² (mean ± SD)	Baseline Hb level, g/l (mean ± SD)	Use of ACE inhibitor or ARB	No. of patients	Intervention	Co-intervention in treatment arm (n), type of ESA, notes	Study duration, months	Study end points
5	Kuriyama 1997 [26]	Diabetes mellitus: Arm 1 (no ESA): 58% Arm 2 (ESA): 55%	Creatinine clearance: Arm 1: 17.1±7.2 Arm 2: 19.1±7.2	HCT (%) Arm 1: 27.9±1.8 Arm 2: 27±2.3	Arm 1: 68.0% Arm 2: 59.0%	Arm 1: n = 31 Arm 2: n = 42	Arm 1: Aiming HCT level of 38% with placebo injection Arm 2: Aiming HCT level of 38% with EPO intravenously injection once a week for 36 weeks, when HCT level reached 38% doses were adjusted to maintain it at a level of 33–35%	Iron therapy was under the responsibility of each investigator	9 months	Doubling of serum creatinine, mortality rates, adverse events, need for dialysis, proteinuria level, diabetes control
6	Furuland 2003 [27]	Diabetic nephropathy (type 2): 24–15%	24-h urine collection, iohexol clearance or Cr-EDTA clearance: Arm 1: 16±9 Arm 2: 17±6	Arm 1: 106±10 Arm 2: 109±7	Not reported	Arm 1: n = 36 Arm 2: n = 36	Arm 1: Aiming Hb level 135–150 g/l in females and 145–160 g/l in males Arm 2: Aiming Hb level 90–120 g/l	IV iron to keep transferrin saturation >20% and serum ferritin between 400–800 mg/dl; Epoetin alfa administered subcutaneously; In the low Hb group, the target level was obtained with or without ESA treatment	12 months weeks to 19 months	Quality of life, all-cause mortality, cardiovascular/non cardiovascular mortality, renal function, hospitalization, serious adverse events, thromboembolic events, blood pressure control
7	Gouva 2004 [10]	Diabetes mellitus was an exclusion criterion	Cockcroft–Gault equation: Arm 1: 25.7±9.1 Arm 2: 22.3±6.0	Arm 1 (means ± SD): 101.0±5 Arm 2 (means ± SD): 101.0±6	Not reported	Arm 1: n = 45 Arm 2: n = 43	Arm 1: Aiming Hb level range of ≥130 g/l Arm 2: start erythropoietin only when Hb level range <90 g/l	Subcutaneous EPO alpha (Eprex, Janssen-Cilag)	Protocol: until all patients had completed 2 years of follow-up. Because of EPO alpha withdrawal, patients were followed for a median of 22.5 months (interquartile range 16 to 24 months)	The primary end point was a composite of doubling of creatinine, renal replacement, or death; hospitalizations, hypertension, severe anemia, allergic local or systemic reactions

Table 1. (continued)

No	Study	Baseline kidney disease	Baseline renal function, ml/min/1.73 m ² (mean ± SD)	Baseline Hb level, g/l (mean ± SD)	Use of ACE inhibitor or ARB	No. of patients	Intervention	Co-intervention in treatment arm (n), type of ESA, notes	Study duration, months	Study end points
8	Roger 2004 [28]	Diabetes mellitus: Arm 1: 24% Arm 2: 33%	Cockcroft–Gault equation: Arm 1: 26±11 Arm 2: 25±11	Arm 1: (means ± SD): 112±9 Arm 2: (means ± SD): 112±8	Arm 1: 74.0% Arm 2: 74.0%	Arm 1: n = 75 Arm 2: n = 80	Arm 1: Aiming Hb level range between 120 and 130 g/l Arm 2: start erythropoietin only when Hb level range <90 g/l, aiming for a Hb level between 90 and g/l	Subcutaneous epoetin alpha	24 months	Changes in LVMi in 2 years, renal function, cardiac performance, and quality of life, renal deterioration was assessed on the basis of the time to the onset of renal replacement therapy, the calculated creatinine clearance, and nuclear estimations of GFR
9	Levin 2005 [29]	Diabetes mellitus: Arm 1: 41% Arm 2: 35.1%	Cockcroft–Gault equation: Arm 1: 37.4±13.6 Arm 2: 35.1±13.0 MDRD Arm 1: 29.7±11.1 MDRD Arm 2: 27.8±9.3	Arm 1: 117.6±7.6 Arm 2: 117.3±8.0	Arm 1: 37.2% Arm 2: 29.7%	Arm 1: n = 78 Arm 2: n = 74	Arm 1: Aiming Hb level range between 120 and 140 g/l Arm 2: start erythropoietin only when Hb level range <90 g/l	Subcutaneous epoetin alpha; iron supplementation as necessary	24 months	Changes in LVMi, renal function, functional cardiac status, QoL from baseline to 24 months
10	CHOIR 2006 [31]	Diabetic nephropathy: 46.8–50.8%	MDRD Arm 1: 36.7±17.0 MDRD Arm 2: 37.1±17.9	Arm 1: 101.0±9.0 Arm 2: 101.0±9.0	Arm 1: 73.7% Arm 2: 74.2%	Arm 1: n = 715 Arm 2: n = 717	Arm 1: Aiming Hb level 135 g/l Arm 2: Aiming Hb level 113 g/l	Both groups of patients initially received epoetin alpha subcutaneously weekly; Iron Arm 1: % = 31.2 Arm 2: % = 29.9	16 months	Time to the composite of death, myocardial infarction, hospitalization for congestive heart failure, or stroke; time to RRT, hospitalization by any cause, quality of life
11	ECAP 2006 [30]	Diabetic nephropathy: 26–27%	MDRD Arm 1: 30.3±10.5 MDRD Arm 2: 28.3±8.9	Arm 1: 115.0±10.0 Arm 2: 116.0±9.0	Arm 1: 91.0% Arm 2: 87.0%	Arm 1: n = 192 Arm 2: n = 193	Arm 1: Aiming Hb level range (130–150 g/l) Arm 2: Aiming Hb level range (110–120 g/l)	Epoetin (Eprex) therapy was administered subcutaneously once per week. Because of labeling changes for Eprex, this study was terminated prematurely	7.4 months for group 1 and 8.3 months for group 2	Rate of GFR decline (by measuring plasma iohexol clearance), need for renal replacement therapy, hospitalizations, cardiovascular and thrombotic adverse events, deaths, quality of life, nutritional status, blood pressure control

Table 1. (continued)

No	Study	Baseline kidney disease	Baseline renal function, ml/min/1.73 m ² (mean ± SD)	Baseline Hb level, g/l (mean ± SD)	Use of ACE inhibitor or ARB	No. of patients	Intervention	Co-intervention in treatment arm (n), type of ESA, notes	Study duration, months	Study end points
12	CREATE 2006 [11]	Diabetes mellitus: Arm 1: 27% Arm 2: 25%	Cockcroft–Gault equation: Arm 1: 24.9±6.3 Arm 2: 24.2±6.0	Arm 1 (means ± SD): 116.0±6.0 Arm 2 (means ± SD): 116±6.0	Arm 1: 70.0% Arm 2: 69.0%	Arm 1: n = 301 Arm 2: n = 302	Arm 1: Aiming Hb level range of 130–150 g/l Arm 2: Aiming Hb level range 105–115 g/l	Subcutaneous erythropoietin-epoetin beta; Iron supplementation (intravenous or oral) was recommended at the discretion of the investigators	Mean follow-up duration of 36 months (1,044 days for arm 1 and 1,092 days for arm 2)	Time to the first cardiovascular event, death from any cause; congestive heart failure; hospitalization for any cause; changes in left ventricular mass index, left ventricular volume, and left ventricular fractional shortening; time to initiation of renal replacement therapy; changes in nutritional status, quality of life, need for dialysis, decrease in the estimated GFR
13	Macdougall 2007 [32]	Diabetic nephropathy: 22.0–23.4%	Cockcroft–Gault equation: Arm 1: 25.75±12.23 Arm 2: 23.26±10.15	Arm 1: 108.9±6.0 Arm 2: 107.6±6.6	Not reported	Arm 1: n = 65 Arm 2: n = 132	Arm 1: Aiming Hb level 11.0±1.0 g/dl Arm 2: Aiming Hb level 11.0±1.0 g/dl; Patients in group 1 started epoetin at an early stage and those in group 2 were monitored every 2 months until their Hb concentration had fallen to a trigger level of <9.0 g/dl	left ventricular mass (LVM), progression of renal failure, exercise tolerance, epoetin-a doses, number of patients who withdrew because of starting dialysis or death	24.1±10.8 months for group 1 and 21.1±10.8 months for group 2	
14	ACORD 2007 [33]	Diabetes mellitus type 1 or 2: 100%	Cockcroft–Gault equation (median (IQR)): Arm 1: 51 (39–67) Arm 2: 46 (35–55)	Arm 1 (median (IQR)): 11.9 (11.3–12.2) Arm 2 (median (IQR)): 11.7 (11.3–12.0)	Not reported	Arm 1: n = 88 Arm 2: n = 82	Arm 1: Aiming Hb level range of 130–150 g/l Arm 2: Aiming Hb level range 105–115 g/l	subcutaneous erythropoietin-epoetin beta;	15 months of follow-up	Primary end point was change in left ventricular mass index (LVMI). Secondary end points included echocardiographic variables, renal function, quality of life, and safety

Table 1. (continued)

No	Study	Baseline kidney disease	Baseline renal function, ml/min/1.73 m ² (mean ± SD)	Baseline Hb level, g/l (mean ± SD)	Use of ACE inhibitor or ARB	No. of patients	Intervention	Co-intervention in treatment arm (n), type of ESA, notes	Study duration, months	Study end points
15	Cianciaruso 2008 [34]	Diabetes mellitus: Arm 1: 23.9% Arm 2: 12.2%	Cockcroft–Gault equation: Arm 1: 28.5±15.6 Arm 2: 29.4±14.0 MDRD Arm 1: 26.2±17.4 MDRD Arm 2: 26.7±14.0	Arm 1: 116.0±7.0 Arm 2: 117.0±8.0	Arm 1: 78.2% Arm 2: 73.4%	Arm 1: n = 46 Arm 2: n = 49	Arm 1: Aiming Hb level range between 120 and 140 g/l Arm 2: start erythropoietin only when Hb level range <90 g/l	subcutaneous epoetin alpha	24 months-intended; 12-month analysis carried out	Changes in LVMI, renal function, functional cardiac status, QoL from baseline to 24 months
16	TREAT 2009 [35]	Type 2 diabetes 100%	MDRD Arm 1: median 34 MDRD Arm 2: median 33	Arm 1: median 105.0 Arm 2: median 104.0	Arm 1: 79.7% Arm 2: 80.0%	Arm 1: n = 2,012 Arm 2: n = 2,026	Arm 1: Aiming Hb level range of ~130 g/l Arm 2: start erythropoietin only when Hb level range <90 g/l	'Patients in the placebo group were assigned To receive darbepoetin alfa as a rescue agent if the Hb level fell below 9.0 g per deciliter, with a return to placebo once the hemoglobin level was 9.0 g per deciliter or higher'	Median follow-up duration of 29.1 months	Death from any cause, cardiovascular events, time to the composite outcome of death or end-stage renal disease, quality of life
17	NEPHRODIA2 2011 [14]	Diabetic nephropathy (type 2): 50–62.8%	Cockcroft and Gault Arm 1: 37.0±9.1 Cockcroft and Gault Arm 2: 36.6±9.4 MDRD Arm 1: 29.6±12.8 MDRD Arm 2: 31.8±14.3	Arm 1: 114.7±8.10 Arm 2: 114.2±10.6	Arm 1: 97.7% Arm 2: 89.1%	Arm 1: n = 43 Arm 2: n = 46	Arm 1: Aiming Hb level range (110–129 g/l) Arm 2: Aiming Hb level range (130–149 g/l)	Iron and ESA therapy modality was under the responsibility of each investigator (type of iron and ESA was free). ESA therapy was not started unless serum ferritin was <200 g/l	24 months	Change from baseline in eGFR at 24 months; mean daily iron use and mean weekly ESA use, QOL, critical events (e.g., death from all causes, myocardial infarction, stroke)
18	Akizawa 2011 [37]	Diabetes mellitus: Arm 1: 21.1% Arm 2: 22.5%	MDRD Arm 1: 19.04±6.96 MDRD Arm 2: 18.57±6.32	Arm 1: 91.5±7.9 Arm 2: 91.8±8.6	Arm 1: 82.6% Arm 2: 83.8%	Arm 1: n = 161 Arm 2: n = 160	Arm 1: Aiming Hb level range between 110 and 130 g/l Arm 2: Aiming Hb level range 90–110 g/l	High Hb group (11.0–13.0 g/dl) received darbepoetin alfa (DA) and the low Hb group (9.0–11.0 g/dl) received recombinant human erythropoietin (rHuEPO)	The study lasted 12 months for both groups	The number of patients with and the occurrence rate of adverse events, changes in LVMI, functional cardiac status, QoL from baseline to week 12

Table 1. (continued)

No	Study	Baseline kidney disease	Baseline renal function, ml/min/1.73 m ² (mean ± SD)	Baseline Hb level, g/l (mean ± SD)	Use of ACE inhibitor or ARB	No. of patients	Intervention	Co-intervention in treatment arm (n), type of ESA, notes	Study duration, months	Study end points
19	CAPRIT 2012 [15]	On patients with post-transplant anemia only; no data about the incidence of diabetes mellitus	Cockcroft-Gault equation: Arm 1: 38.9±10.6 Arm 2: 37.8±11.0 MDRD Arm 1: 34.4±10.0 MDRD Arm 2: 33.7±10.8	Arm 1 (means ± SD): 104.0±9 Arm 2 (means ± SD): 106.0±7	Arm 1: 69.8% Arm 2: 71.0%	Arm 1: n = 63 Arm 2: n = 62	Arm 1: Aiming Hb level range of 130–150 g/l Arm 2: Aiming Hb level range 105–115 g/l	Subcutaneous erythropoietin-epoetin beta	24 months	eGFR at the end of study, the variation in eCrcl, doubling of serum creatinine, proteinuria, number of patients who progressed to ESRD, time to return to dialysis, graft survival, occurrence of acute graft rejection, patient survival, QoL

Four studies reported the decline in renal function or progression of renal disease as the primary endpoint [10, 14, 15, 26]. Only one study reported early termination due to safety issues [30].

Baseline Hb levels varied from 9.0 [10, 27] to 12.9 g/dl [14]. In trials performed earlier (between 1990 and 2005), there was a trend toward a higher Hb target level (in the intervention group the upper Hb level limit was 15.0 g/dl [11, 27, 30, 33]). After 2006, the anemia guideline committee of the KDOQI raised the suggested Hb cut-offs to 11.0 g/dl for the lower limit (evidence-based recommendation) and 13.0 g/dl for the upper limit (clinical practice recommendation) [36]. Following these guideline modifications, the more recent trials referred to a lower limit for the high Hb target (13 g/dl [35], 13.5 g/dl [13]), with two notable exceptions: 14.9 g/dl [14] and 15 g/dl [15].

The treatment comparisons in the identified trials were: (a) ESA versus placebo or no treatment or, (b) different doses of ESA therapy as needed to achieve two (higher vs. lower) hemoglobin target levels. Doses of ESA used in the trials were not available in one third of the study reports (table 2).

As for the type of ESA, Erythropoietin alpha was used in eight trials [10, 27–32, 34], erythropoietin beta in three [11, 15, 33] and darbepoetin alpha in two studies [35, 37]. In old studies, the type of ESA was not specified [14, 22–24, 26].

In the control arm, different treatment strategies were used. Treatment comparisons included different types of ESA versus placebo or no treatment unless Hb levels decreased below a specified value [10, 11, 22–24, 26, 28–30, 32–35], or different doses of ESA [14, 15, 31, 37].

Trial Quality

Trial quality was sub-optimal on overall. Allocation concealment was adequate in three of 19 trials (16%) [29, 32, 34] and unclear in the remaining 10 out of 19 trials (85%). A consistent high risk of bias concerning the blinding of participants and personnel was found for the majority of included studies, with exception of one, in which the investigators stated the ‘double-blinded’ design of the trial, but without providing any additional information [23] and two studies with low risk of bias [22, 35]. Only three of the 19 trials (16%) were analyzed on an intention-to-treat basis [11, 35, 37]. The dropout rate ranged from 0 to 15% and did not differ between the treatment and control groups (fig. 2).

Table 2. Baseline, target and achieved hemoglobin concentrations for the included studies

Study	Baseline Hgb concentration, g/dl	Target Hgb concentration, g/dl		Achieved Hgb concentration, g/dl	
		high/active group	low/no treatment	high/active group	low/no treatment
Kleinman et al., 1989 [22]	HCT of 28.2%	HCT of 38–40%	HCT of 38–40%	HCT of 35.8%	HCT of 28.3%
Watson et al., 1990 [23]	HCT of 28±2%	HCT of 38%	No target	HCT of 35±2%	HCT of 26±2%
Clyne et al., 1992 [24]	8.6±0.8	HCT of >30%	No target	11.7±1.1	9.4±1.0
Revicki et al., 1995 [25]	HCT of 26.8±3.6%	HCT of 35%	No target	Not reported	8.9±1.2
Kuriyama et al., 1997 [26]	HCT of 27.9±1.8%	HCT of 33–35%	HCT <30%	11.83±1.33	8.43±0.63
Furuland et al., 2003 [27]	10.6±1	13.0–15.0	9.0–12.0	14.3±1.1	11.3±1.3
Gouva et al., 2004 [10]	9.0–11.6	≥13.0	Unless Hb <9.0	≥12.5	≥12.5
Roger et al., 2004 [28]	11.0–13.0 to 10.0–12.0	12.0–13.0	Unless Hb <9.0 at 2 consecutive clinic visits or Hb <8.0 at any visit	12.2±0.7	11.0±1.0
Levin et al., 2005 [29]	11.0–13.5	12.0–14.0±0.5 but not >14	Unless Hb <9	Not reported	11.4±1.2
CHOIR 2006 [31]	<11.0	13.5	11.3	Not reported	Not reported
ECAP 2006 [30]	Men: <13.0 Women: <12.5	13.0–15.0	11.0–12.0	16.2	16.1
CREATE 2006 [11]	11.0–12.5	13.0–15.0	10.5–11.5	Not reported	Not reported
Macdougall et al., 2007 [32]	11.0±0.5	11.0±1	Unless Hb <9.0 – for maintaining Hb level at 11.0±1	Not reported	Not reported
ACORD 2007 [33]	Not reported	13.0–15.0	10.5–11.5	13.0–15.0	>10.5–11.5
Cianciaruso et al., 2008 [34]	11.6±0.7	12.0–14.0±0.5	Unless Hb <9.0	Not reported at the end of the study	Not reported at the end of the study
TREAT 2009 [36]	<11.0	>13.0	Unless Hb ≤9.0	12.5 (IR, 12.0–12.8)	10.6 (IR, 9.9–11.3)
NEPHRODIAB2 2011 [14]	10.0–12.9	13.0–14.9	11.0–12.9	<12.0	>13.0
Akizawa et al., 2011 [37]	<10.0	11.0–13.0	9.0–11.0	Not reported (achieved target range)	Not reported
CAPRIT 2012 [15]	10.5±0.8	13.0–15.0	10.5–11.5	13.1±1.7	11.4±1.0

Fig. 2. Risk of bias graph available according to recommendations from the cochrane collaboration.

Quantitative Analysis

Number of Patients Starting RRT during the Study Period

With regard to the number of patients that required the initiation of RRT during the study, there were no data that would favor either of the two groups (low versus high Hb target) (17 trials, 8,104 participants, RR 0.97; 95% CI 0.83–1.15). The heterogeneity for this outcome was moderate: ($\chi^2 = 28.59$, $I^2 = 44\%$) (fig. 3, table 3).

For the composite outcome all-cause mortality or RRT, there was no statistically significant difference between the high Hb and the low Hb arm (17 trials, 8,104 participants, RR = 0.95; 95% CI 0.81–1.12); heterogeneity was again moderate ($\chi^2 = 38.23$, $I^2 = 58\%$) (fig. 3).

Reduction in GFR at the End of the Study. Doubling of Serum Creatinine

Nine studies reported changes in GFR, and did not reveal a significant difference between the two groups (9 trials, 1,828 participants, Mean Difference (MD) -0.45 ; 95% CI -2.21 – 1.31 ml/min), although for this outcome measure, the heterogeneity was important ($\chi^2 = 302.4$; $I^2 = 97\%$) (fig. 4, table 3).

Doubling of serum creatinine was reported only by three small studies ($n = 286$ participants) [10, 15, 26]. There was a statistically significant difference indicating a 47% reduction in the risk of doubling of the serum creatinine when aiming at higher Hb values (fig. 3, table 3).

Serum Creatinine or GFR Value at the End of the Study

There was no difference between the high and the low Hb target in serum creatinine values or GFR (ml/min) at the end of the study. This analysis included four studies for the creatinine outcome and 8 studies for the GFR outcome (fig. 4); an important heterogeneity was found for both outcomes ($\chi^2 = 15.29$; $I^2 = 80\%$ and $\chi^2 = 29.90$; $I^2 = 77\%$).

Proteinuria at the End of the Study and Changes in Proteinuria from Baseline

Proteinuria was reported only by three studies [14, 30, 33]. One study [33] reported that there was no change in urine protein, a more recent study [14] reported no statistically significant difference between baseline proteinuria and end-of-treatment proteinuria and the oldest one [30] reported the worsening of proteinuria in a dichotomous format with more events in the low Hb group (10 events vs. 4 events, $n = 195$ participants per arm).

Blood Pressure at the End of the Study. Changes in BP

Targeting for a higher Hb level was not associated with higher systolic or diastolic BP levels (5 studies; 934 participants; MD = 1.83; 95% CI -0.79 – 4.45 mm Hg). Heterogeneity across these 5 studies was moderate ($\chi^2 = 9.33$; $I^2 = 57\%$). However, the CREATE study [11] mostly contributes (32%) to the overall weight of this analysis (fig. 4).

Adverse Effects

The number of participants who discontinued the treatment due to adverse events was reported by ten studies as 1,958 participants, and these studies did not reveal any statistically significant difference between the two comparison groups (fig. 3, table 3). Also, there was no difference for the number of patients experiencing at least one adverse event, including one serious event during the intervention period (RR = 1.01, 95% CI 1.00–1.03, 8 studies, 7,108 participants). Heterogeneity was low for both the analyses ($I^2 = 0\%$).

However, there was an 18% higher risk of having at least one serious adverse event during the intervention period for higher as compared to lower Hb targets (6 studies, 6,268 participants, RR 1.18, 95% CI 1.01–1.07).

Finally, the risk of having at least one hospitalization during the intervention period was 11% higher in the higher-Hb target (3 studies, 1,910 participants, RR = 1.11, 95% CI 1.00–1.23; $I^2 = 0\%$) (fig. 3).

Investigation for Sources of Heterogeneity

Heterogeneity in the effects of lower or higher Hb targets on renal function at the end of treatment (end of study GFR and change in GFR from baseline) was explored through sub-group analyses based on the type of ESA used (erythropoietin alpha, erythropoietin beta, darbopoetin alpha or undefined ESA), number of participants (less or more than 100) and study duration (less or more than 12 weeks) (online suppl. fig. 1). Causes of heterogeneity were not explored for the serum creatinine outcome since few studies looked at this endpoint. The analysis showed that the type of treatment, number of participants and length of follow-up did not change the effects of anemia corrections at different Hb targets on renal function. In addition, a subgroup sensitivity analysis, with or without data available from the TREAT 2009 trial [35] (fig. 3) and with or without data available from the CAPRIT trial [15] (transplanted patients), was performed for all dichotomous and continuous outcomes that included this study in the analysis (online suppl. fig. 2).

Fig. 3. Effect of high Hb target versus low Hb target on dichotomous outcomes: 1.2.1 number of patients starting RRT during study period. 1.2.2 number of patients starting RRT during study period_TREAT trial excluded. 1.2.3 number of patients starting RRT and all-cause mortality: composite outcome. 1.2.4 doubling of serum creatinine. 1.2.5 number discontinued due to adverse events.

Fig. 3. Effect of high Hb target versus low Hb target on dichotomous outcomes: 1.2.6 number of patients with at least one adverse event during the intervention period. 1.2.7 number of patients with at least one hospitalization during the intervention period.

Table 3. Summary of findings

Outcome	Trials reporting more than one event/total number of trials included in the outcome	Number of patients included in the outcome	Relative effect	95% CI	Median treatment duration, months	Quality of evidence*
Number of patients starting RRT during study period	17/17	8,104	0.97	(0.83, 1.15)	18.41	Moderate
Doubling of serum creatinine	3/3	286	0.53	(0.31, 0.89)	18.5	Very low
Number discontinued due to adverse events	9/10	1,958	1.18	(0.77, 1.81)	15.25	Low
Reduction in GFR at the end of the study, ml/min	9/9	1,828	-0.45	(-2.21, 1.31)	21.67	Very low

* Definition of quality of evidence: High quality = additional research is very unlikely to change our confidence in the estimates of effect; Moderate quality = additional research is likely to have an important impact on our confidence in the estimate of effect; Low quality = additional research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality = any estimate of the effect is very uncertain.

and 3) showing roughly the same effect. For the TREAT [35] subgroup sensitivity analysis, the analysis performed without the inclusion of this trial did not reveal significant effects estimates differences (with TREAT, effect estimates: 0.97 (0.83, 1.15) and without TREAT: 0.94 (0.77, 1.16)) (fig. 3). As new data regarding a higher prevalence of resistance to ESA treatment in US-CKD patients compared to non-US patients has been recently hypothesized [38], a geographical-subgroup sensitivity analysis was conducted for the adverse events outcome including a comparison of relative effect and heterogeneity with studies comprising US participants versus studies with only

non-US participants. There were no significant effect estimates or heterogeneity differences found (online suppl. fig. 4).

Discussion

Key Findings

Our analysis included 19 studies, enrolling 8,129 participants with CKD stages 1–4. There was no difference in risks for end-stage kidney disease, reduction in GFR, serum creatinine or GFR (ml/min) values, or in protein-

Fig. 4. Effect of high Hb target versus low Hb target on continuous outcomes: 1.3.1 reduction in GFR at the end of the study (ml/min). 1.3.2 GFR at end of study (ml/min). 1.3.3 diastolic blood pressure at end of the study (mm Hg).

uria, at the end of the study periods when aiming at higher hemoglobin (Hb) targets. Furthermore, no statistically significant differences in a composite outcome need for RRT plus mortality (Risk Ratio [RR] 0.95 [CI 0.81–1.12], 17 trials, $n = 8,104$ patients) were observed. Withdrawal of treatment due to adverse events was similar, as well as the general control of BP, between high and low Hb targets cohorts of patients.

Some important shortcomings in the manner of reporting outcomes deserve mentioning. Only four studies out of 19 had renal endpoints as primary outcomes; the remaining studies only described these events as secondary outcomes. The studies did not generally feature or recruit from ‘rapidly-progressing’ CKD cohorts. The

overall quality of the investigational and trial design approaches used to address this key end-point was suboptimal. Finally, data on proteinuria were reported only by three studies.

Two rather different studies included in our meta-analysis seemed to show protective outcomes for the deployment of ESAs in CKD. These were the studies by Gouva et al. (2004) [10] and the more recent CAPRIT study from 2012 [15].

The Gouva study was one of the smallest ones ($n = 88$) of the 19 included in the meta-analysis, and was focused on non-diabetic patients with a wide range of serum creatinine concentrations (2–6 mg/dl) and mild-to-moderate anemia (Hb 9–11 g/dl), from 14 clinical centers in

Greece. It was non-blinded, the intervention being early versus later use of ESA. To be eligible for inclusion, patients also had to have stopped all ACEI and/or ARBs for 2 months, and to have controlled BP on non-ACE/ARB therapy. These stringent, unusual, selection criteria make it very challenging to extrapolate the findings of this study, since a large proportion of current CKD patients are on ACE/ARB-based drug therapy for BP control and proteinuria reduction. During follow-up, 13 (3 deaths) versus 23 (4 deaths) patients reached the end point of doubling of creatinine, renal replacement, or death, in the early versus deferred treatment arms, respectively. Thus, the difference between the two arms was largely caused by the initiation of renal replacement (a notoriously subjective, symptom-led, judgment).

The CAPRIT study [15] was a two-year, open-label trial involving 125 post-renal transplant patients. Beside the well-known multifactorial pathogenesis of post-renal transplant anemia (including the presence of immunosuppressive therapy and the altered inflammatory environment), the most notable anemia risk factor still remains and that is the loss of renal allograft function [39]. This is consistent with the loss of endogenous EPO production in CKD patients. The findings of the CAPRIT trial suggested improved allograft survival among patients treated to a higher Hb level.

Indeed, in the CAPRIT, the patient admixture and comorbidity were highly different from those seen in other anemia studies: <5% of subjects having primary diabetes, and only around 15% subjects with prior cardiovascular history. Adverse event rates were very low compared to CREATE [11], CHOIR [31] and TREAT [35] studies. Additionally, there was little or no information on iron status, or on its therapeutic usage. The ESA dose used, 4,000–6,000 IU Epoetin weekly, was about half to a third seen in the other trials.

Most importantly, there was neither presumption nor demonstration of declining renal function at study entry; no renal biopsy information was obtained to differentiate the immunologically driven loss of GFR from many other potential causes, and no direct measurements of GFR were undertaken. Patient entry back onto dialysis was inevitably partly subjective, and symptom-based, and so with higher Hb values was intrinsically less likely to happen.

Comparison to Other Studies

It was our intention to assess the evidence culled from publications until 2014 date range. The first comparison should be done with two early systematic reviews [40, 41],

published in 2004, although the evidence was quite limited, 4 trials including 77 patients in one meta-analysis and 5 trials with 207 patients in the second. Nevertheless, both meta-analyses showed no difference between Hb groups regarding the renal progression outcome.

The most meaningful comparison should probably be made with a 2010 meta-analysis by Palmer et al. [12] that evaluated the effects of ESA in CKD patients. Our work has in addition three subsequent published studies included. Most importantly, our main aim was to focus on assessing different renal outcomes, which were not the main output focus of the Palmer paper, whose principal objective was a cardiovascular event/mortality analysis.

Strengths and Limitations

Our review has a number of strengths and limitations. Strengths include a systematic search of medical databases, data extraction and analysis, and trial quality assessment by two independent reviewers. We also carefully analyzed the most important potential renal end-points including loss of renal function, and dialysis initiation. This has not been done before. Another strength of our review was a detailed examination of trials quality and heterogeneity. The major limitation is the lack of long-term studies analyzing the efficacy of ESA on mortality, progression of CKD, and entry onto dialysis. Another limitation is the populations included in the 19 studies, and how many of them were truly demonstrating progressive loss of GFR prior to enrollment. The majority of the included studies enrolled a relatively small number of patients; they were powered to observe differences in surrogate end-points rather than patient-focused outcomes, and used nonoptimal measures of renal function change over time. Also, in our aim to study ESA role in CKD progression, our search found limited data for all proposed outcomes. The absence of data for some relevant outcomes (e.g., doubling of serum creatinine) might represent an open pathway for future research. In addition, the preponderance of high risk of bias regarding the lack of blinding could be considered a possible limitation.

Implications for Practice

In CKD patients with anemia, the current KDIGO [42] and ERBP guidelines [43] suggest that a careful exploration of the risk-benefit relationship between Hb, ESAs, and outcomes, should be undertaken for all patients. In some cases, it is expected that clinically relevant benefits of using ESAs to raise Hb will be seen, but not in all cases, while there are definite risks associated

with active therapy. However, in the quest for ‘nephro-protection’ to prevent progressive loss of renal function and the eventual need for dialysis, adjusting the patient’s Hb concentration using ESAs does not seem, from our evidence, to have a compelling logic to support it.

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