CRD summary
This review assessed the effects of erythropoiesis-stimulating agents on anaemia in patients with chronic kidney disease and concluded that higher haemoglobin target levels increased risks of stroke, hypertension and vascular access thrombosis. Risk of death, serious cardiovascular events and end-stage renal disease may also be increased, but further research was needed. The authors’ recommendations for further research seem appropriate.

Authors’ objectives
To assess the effects of erythropoiesis-stimulating agents on anaemia in patients with chronic kidney disease.

Searching
MEDLINE and EMBASE were searched up to November 2009. Cochrane Renal Group trial register and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to March 2010 for articles in any language. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared erythropoiesis-stimulating agents (erythropoietin-alpha or beta, darbepoetin or a continuous erythropoietin receptor activator) at any dose and route of administration versus placebo, no treatment or dose comparison studies of erythropoiesis-stimulating agents were eligible for inclusion. Eligible trials assessed treatment of anaemia in patients with any stage of chronic kidney disease. Trials were required to target a higher versus lower haemoglobin concentration and have a duration of at least three months.

Included trials were published between 1989 and 2009. The stage of chronic kidney disease ranged between 2 and 5. Where reported, most trials included patients with a mean age range of 43 to 68 years; one trial included patients with mean ages of six and eight years. Inclusion criteria varied across the trials; some trials recruited only patients with established cardiovascular disease and others included only patients with diabetes mellitus. Baseline haemoglobin levels were similar between trial treatment arms. The proportion of males in each treatment arm ranged from 30% to 100%. Patients received pre-dialysis treatment, haemodialysis or peritoneal dialysis. Some trials administered oral or intravenous iron as a co-intervention. Primary outcomes were all-cause mortality, serious cardiovascular events, stroke, hypertension, vascular access thrombosis and end-stage kidney disease that required renal replacement therapy. Other outcomes included requirement of blood transfusion and iron supplementation and patient quality of life.

Two reviewers independently screened studies for inclusion. Disagreements were resolved through discussion with an arbitrator.

Assessment of study quality
Two reviewers assessed the quality of included studies using criteria published by the Cochrane Collaboration (allocation concealment, blinding, attrition rates and intention-to-treat analyses). The proportion of studies (%) categorised as yes (low risk for bias), no (high risk for bias) or unclear/unavailable were calculated for each criterion. Disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted data on clinical outcomes to calculate relative risks (RRs) for dichotomous data and mean differences for continuous data (quality of life), and their 95% confidence intervals (CIs). Discrepancies were resolved by discussion with an arbitrator.

Where studies had very low event rates in one or both study arms, the standard continuity correction of 0.05 was used.
Methods of synthesis
A random-effects model was used to combine relative risks and their 95% CIs. Statistical heterogeneity was assessed using the $X^2$ test and $I^2$ statistic. Cumulative meta-analyses were conducted using a random-effects model to identify how evidence has changed over time.

Subgroup analyses and meta-regression were conducted to explore the effects of population characteristics, trial design, intervention duration and individual quality criteria on all-cause mortality, hypertension and fatal and non-fatal stroke.

Results of the review
Twenty-seven RCTs (n=10,452, range 11 to 4,038) were included in the review. Follow-up ranged from three to 48 months. Trial quality was reported to be suboptimal; none of the trials reported on allocation concealment, 17 did not conduct intention to treat analyses and attrition rates ranged from 0 to 32%.

A higher haemoglobin target statistically significantly increased the risk for stroke (RR 1.51, 95% CI 1.03 to 2.21; six RCTs), hypertension (RR 1.67, 95% CI 1.31 to 2.12; 12 RCTs) and vascular access thrombosis (RR 1.33, 95% CI 1.16 to 1.53; eight RCTs) compared with a lower haemoglobin target. Patients assigned to a higher haemoglobin target were statistically significantly more likely to require intravenous iron therapy than patients assigned to a lower haemoglobin target (RR 1.57, 95% CI 1.13 to 2.02; six RCTs), but were statistically significantly less likely to require a blood transfusion (RR 0.61, 95% CI 0.49 to 0.77; eight RCTs).

There was evidence of statistical heterogeneity for hypertension ($I^2=63\%$) and iron therapy (p<0.001). Further exploration indicated that there was a statistically significantly lower risk of worsening hypertension with a higher haemoglobin target in longer trials, trials with greater sample sizes and trials where outcome assessment was not blinded. Subgroup analyses were reported.

There were no statistically significant differences between haemoglobin target level groups for the risk of all-cause mortality (18 RCTs), fatal and non-fatal myocardial infarction, serious cardiovascular events (seven RCTs) and end-stage kidney disease (10 RCTs).

Authors’ conclusions
Higher haemoglobin target levels in patients with chronic kidney disease increased risk of stroke, hypertension and vascular access thrombosis and may have increased risk of death, serious cardiovascular events and end-stage renal disease. Further research was needed.

CRD commentary
The review question was clear and supported by appropriate inclusion criteria for patients, intervention, control and study design. Inclusion criteria for outcomes were not clearly defined. The literature search was adequate. There were no restrictions on language. Publication bias was not formally assessed. The authors assessed validity of included studies using appropriate criteria. But, the authors reported quality to be suboptimal, which could affect reliability of the subsequent conclusions. The authors undertook each stage of the process in duplicate, which reduced potential for reviewer error and bias. There appeared to be variability among studies in terms of participant characteristics and methodology. However, the authors attempted to investigate heterogeneity and the effects of certain variables on the outcomes. Details on erythropoiesis-stimulating agents and controls were very limited. The authors’ conclusions appear to reflect the more recent evidence and their recommendation for further research seems appropriate and would strengthen these findings.

Implications of the review for practice and research
Practice: The authors stated that there was more than 20 years of evidence for harm when targeting higher haemoglobin values in chronic kidney disease. This evidence should be incorporated in guidelines and used in clinical practice.

Research: The authors stated that a meta-analysis of individual patient data and trials on fixed erythropoiesis-
stimulating agents doses were needed to identify the mechanisms for harm with erythropoiesis-stimulating agent therapy.

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