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Recombinant human erythropoietin versus placebo or no treatment for the anaemia of chronic kidney disease in people not requiring dialysis (Review)

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[Intervention Review]

Recombinant human erythropoietin versus placebo or no treatment for the anaemia of chronic kidney disease in people not requiring dialysis

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ABSTRACT

Background

Treatment with recombinant human erythropoietin (rHuEPO) in dialysis patients has been shown to be highly effective in terms of correcting anaemia and improving quality of life. There is debate concerning the benefits of rHuEPO use in predialysis patients which may accelerate the deterioration of kidney function. However the opposing view is that if rHuEPO is as effective in predialysis patients, improving the patient's sense of well-being may result in the onset of dialysis being delayed. This is an update of a review first published in 2001 and last updated in 2005.

Objectives

The objective of this review was to ascertain the effects of rHuEPO treatment in predialysis patients primarily in terms of the timing of the onset of dialysis; but also that predialysis rHuEPO: 1) corrects haemoglobin/haematocrit (markers of anaemia); 2) improves quality of life; and 3) is not associated with an increased incidence of adverse events such as hastening of the onset of dialysis, increased hypertension, clotting of arterio-venous fistulae or seizures.

Search methods

We searched the Cochrane Kidney and Transplant's Specialised Register (up to 29 June 2015) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs comparing the use of rHuEPO with no treatment or placebo in predialysis patients.

Data collection and analysis

Only published data were used. Quality assessment was performed by two assessors independently. Data were abstracted by a single author onto a standard form, a sample of which was checked by another author. Results were expressed as risk ratio (RR) or mean difference (MD) with 95% confidence intervals (CI).

Main results

Nineteen studies (enrolling 993 participants) were included. Due to the age of the included studies (most performed prior to 2000) the risk of bias was judged to be unclear in the majority of the studies for most of the domains. There was an improvement in haemoglobin (MD 1.90 gm/L, 95% CI -2.34 to -1.47) and haematocrit (MD 9.85%, 95% CI 8.35 to 11.34) with treatment and a decrease in the number of

patients requiring blood transfusions (RR 0.32, 95% CI 0.12 to 0.83). The data from studies reporting quality of life or exercise capacity demonstrated an improvement in the treatment group. Most of the measures of progression of kidney disease showed no statistically significant difference. No significant increase in adverse events was identified.

Authors' conclusions

Treatment with rHuEPO in predialysis patients corrects anaemia, avoids the requirement for blood transfusions and also improves quality of life and exercise capacity. We were unable to assess the effects of rHuEPO on progression of kidney disease, delay in the onset of dialysis or adverse events. Based on the current evidence, decisions on the putative benefits in terms of quality of life are worth the extra costs of predialysis rHuEPO need careful evaluation.

PLAIN LANGUAGE SUMMARY

Erythropoietin helps people with kidney failure and symptoms from anaemia who are not yet on dialysis

Anaemia (low red blood cells) is a common complication of kidney failure. Anaemia causes some of the tiredness and problems associated with kidney failure. Manufactured erythropoietin (a hormone that increases red blood cell production) improves this, and is used by people on dialysis (treatment from an artificial kidney machine). This review found it can also reduce anaemia for people with kidney failure who are not yet on dialysis. It is not known if erythropoietin use can delay the need for dialysis.

BACKGROUND

Anaemia is often an associated condition in patients with chronic kidney disease (CKD). There is a direct relationship between the severity of the anaemia and the decline in kidney function (Koch 1991). This anaemia is a source of significant morbidity causing symptoms such as lack of energy, breathlessness, dizziness, angina, poor appetite and decreased exercise tolerance (Canadian EPO Study Group 1990; Lundin 1989). The main cause of this anaemia is a decreased production of erythropoietin, a naturally occurring hormone mainly produced by the kidney (Jensen 1994). Much of the impaired quality of life and morbidity suffered by patients with CKD may be a consequence of this anaemia and it may have a major impact on their sense of well-being as well as impairing their ability to work and affecting their social and sexual lives. In the past, iron and folate were the main treatments for this condition and blood transfusions, with their associated risks of transmission of infection and induction of cytotoxic antibodies, which could jeopardise a future kidney transplant (Ward 1990), were used sparingly. In 1983 the cloning of the human gene for erythropoietin was achieved (Lin 1985), production of recombinant human erythropoietin (rHuEPO) followed and by 1986 the efficacy of rHuEPO treatment in dialysis patients was first demonstrated (Winearls 1986).

Although treatment with rHuEPO in dialysis patients has been shown to be highly effective in terms of correcting anaemia and improving quality of life (Canadian EPO Study Group 1990), there is debate concerning the benefits of rHuEPO use in predialysis patients (patients with CKD anticipated to start renal replacement therapy (RRT) in the near future). Nonetheless there is increasing use of erythropoietin in predialysis patients and professional guidelines are increasingly recommending its use. Anaemia may be a cause of significant morbidity in such patients and substantial numbers of the predialysis population may benefit from treatment with rHuEPO. Its use may enable patients to carry on working longer and, importantly, by improving the patients' sense of well-being could delay the onset of dialysis. In a survey of 20 investigators in rHuEPO clinical trials and 250 randomly selected nephrologists it was estimated that by improving symptoms of anaemia, rHuEPO therapy could delay the initiation of dialysis for an average of 3.7 months (Sheingold 1990). This could have important cost implications which need to be taken into account in an economic evaluation should such a delay exist. The converse opinion, based on results from animal studies, is that rHuEPO may cause or worsen hypertension (Garcia 1985) and potentially cause an accelerated deterioration in kidney function hence bringing forward initiation of dialysis. Based on work with partially nephrectomised rats, Garcia 1985 suggested that anaemia may have a protective effect on the development of progressive kidney failure and could be an adaptive mechanism. One small clinical study suggested a similar detrimental effect of rHuEPO on kidney function (Muirhead 1994). Other adverse effects which have also been attributed to the use of rHuEPO are clotting of the arterio-venous fistula which provides access to the circulation for haemodialysis, elevation of blood pressure and seizures (Koch 1991).

The debate about the effectiveness of treating predialysis patients with rHuEPO combined with the perceived increased cost of using this expensive drug may have led to a reluctance to use rHuEPO in this group of patients.

This review aimed to determine the effects of treating the anaemia of CKD with rHuEPO in predialysis patients. Studies evaluating newer erythropoietic stimulating agents (darbepoetin, CERA) have not been included as they are the subject of other reviews (Palmer 2012; Palmer 2014).

OBJECTIVES

The objective of this review was to ascertain the effects of rHuEPO treatment in predialysis patients primarily in terms of the timing of the onset of dialysis; but also that predialysis rHuEPO:

- corrects haemoglobin/haematocrit (markers of anaemia);
- improves quality of life;
- is not associated with an increased incidence of adverse events such as hastening of the onset of dialysis, increased hypertension, clotting of arterio-venous fistulae or seizures.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCT) or quasi-RCTs (in which concealment of allocation of patients to treatment groups is less secure e.g. alternation where patients are consecutively allocated to different treatments) comparing rHuEPO treatment (experimental group) with either placebo or no rHuEPO (control group) in predialysis patients with renal anaemia were included in this review.

Types of participants

Patients with the anaemia of CKD who have not yet commenced dialysis were included. The definitions of anaemia and CKD used by each individual study were accepted. There were no age exclusions.

Types of interventions

Treatment with rHuEPO irrespective of dose or mode of delivery versus placebo or no rHuEPO were included.

Types of outcome measures

1. Measures of progression of kidney failure: time from start of rHuEPO to start of dialysis; numbers starting RRT in each group; glomerular filtration rate (GFR) at the end of the study; change in GFR; serum creatinine at the end of the study and change in creatinine in each group. Accepted methods for measurement of GFR were inulin clearance, any isotopic measure and formula based estimated GFR (e.g. MDRD and Cockcroft Gault).
2. Measures of correction of anaemia: haemoglobin/haematocrit values; numbers of blood transfusions.
3. Quality of life measures, including changes in exercise capacity.
4. Measures of hypertension: systolic blood pressure; diastolic blood pressure; numbers with an increase or introduction of antihypertensive treatment.
5. Other adverse events: numbers discontinued due to adverse events; access problems for patients commenced on haemodialysis; seizures.
6. Mortality.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register (to 29 June 2015) through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the [Cochrane Kidney and Transplant](#).

See [Appendix 1](#) for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

All electronically-derived citations and abstracts were read by two assessors. All studies, relevant to the use of erythropoietin in kidney failure which might possibly be an RCT or a quasi-RCT, were identified. Assessment and identification was designed to be sensitive and not precise (specific). This was to avoid missing possible RCTs/quasi-RCTs. The full published copies of all identified relevant studies were retrieved.

Data extraction and management

The full published hard copies of studies identified through electronic searching and by our other methods of study ascertainment were assessed for subject relevance, eligibility for inclusion in our review and methodological quality. A standard form, which recorded details of quality of randomisation (particularly security of concealment of randomisation), blinding, description of withdrawals/dropouts and numbers lost to follow-up and whether intention-to-treat analysis was possible on the available data, was used for this quality assessment. If it was unclear from the published study whether it met the methodological inclusion criteria the authors were contacted. These studies remained excluded unless the authors confirmed

that our eligibility criteria had been met. Assessment was undertaken by two assessors independently, one of whom was a clinician (nephrologist). If disagreement could not be resolved by discussion a third assessor made the final decision. The assessors were not blind to author, institution or journal. Where appropriate, studies were translated prior to methodological assessment.

Studies which met the criteria for methodological quality and subject relevance for this review passed to the stage of data abstraction. Data relevant to the pre-stated outcome measures, the characteristics of the study, interventions and participants were abstracted by a single assessor on to a data abstraction form generated for this review. Data relevant to study methodology had already been abstracted onto the quality assessment form. These data were then, where appropriate, entered by a single researcher into Review Manager. No raw data were sought from the authors. Apart from translation by the authors and ascertainment of study methodology all data were obtained from the published paper or abstract.

Assessment of risk of bias in included studies

For the 2016 update all studies were reassessed using the risk of bias assessment tool ([Appendix 2](#)) ([Higgins 2011](#)).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
 - * Participants and personnel (performance bias)
 - * Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

Where appropriate, data were quantitatively combined using meta-analysis to determine the typical effect of the intervention. We calculated a relative risk (RR) for dichotomous data and a mean difference (MD) or a standardised mean difference (SMD) for continuous data. A random effects model was used for analyses of both dichotomous and continuous data. Following the convention of the Cochrane Collaboration, all comparisons were framed in terms of unfavourable events such as adverse symptoms or death. RRs of less than one therefore favour the experimental treatment while RRs greater than one favour the control treatment. Ninety-five per cent confidence intervals (95% CI) were derived for all comparisons.

Assessment of heterogeneity

Evidence of statistical heterogeneity across studies was explored using the Chi-squared test for heterogeneity and the I^2 test ([Higgins 2003](#)).

Data synthesis

Data which could not be combined quantitatively were presented in a narrative form.

Certain outcomes were expressed as negative values so that the estimated effect size would lie on the left side of the line of no effect. These outcomes were;

- GFR: a higher GFR (mL/min) indicates better kidney function.
- Haemoglobin and haematocrit levels: a higher haemoglobin (g/dL) or haematocrit level (%) is considered a beneficial outcome.
- Quality of life measures: a higher quality of life measure is a beneficial outcome.
- Change in exercise capacity: a higher score in change in exercise capacity (watts (W)) is a beneficial outcome.

Subgroup analysis and investigation of heterogeneity

Studies were also examined for methodological and clinical heterogeneity particularly if significant statistical heterogeneity was identified (Thompson 1994).

RESULTS

Description of studies

Results of the search

2001 review

Twelve studies (Abraham 1990; Brown 1995; Clyne 1992; Eschbach 1989; Kleinman 1989; Kuriyama 1997; Lim 1989; Roth 1994; Stone 1988; Teehan 1989; Teehan 1991; Watson 1990) with a total of 232 participants, reported in published papers, one in abstract form (Brown 1995), were included in the review after methodological assessment. Four studies (Abraham 1990; Eschbach 1989; Lim 1989; Stone 1988) formed part of a larger multicentre study (Teehan 1991). If an outcome measure was common to both a small study and the multicentre study, only the results from the multicentre study were included in the meta-analysis (see [Characteristics of included studies](#)); the smaller studies were analyses of individual centres' data.

Ten studies were conducted in the USA, one in Sweden (Clyne 1992), and one in Japan (Kuriyama 1997). The majority of studies had few participants and were of short duration (8 to 12 weeks) not long enough to assess the effects on the progression of kidney disease. Only three studies (Brown 1995; Kuriyama 1997; Roth 1994) were of longer duration between 36 weeks and one year, however Brown 1995 only included 17 participants.

2005 review update

For the 2005 update of the review, three studies (Ganguli 2003; Teplan 2001b; Teplan 2003) were identified for inclusion, and 10 were excluded either because they did not fit the inclusion criteria of the review or it was unclear how patients had been allocated to groups. This brought the total number of included studies to 15. For the update some authors (Mignon 2001; Teplan 2003) were contacted to seek clarification on how patients were allocated to groups and for data which could be included in the review. Teplan confirmed patients were randomised and that Teplan 2001b was a separate sample of participants from Teplan 2003. No response was received for Mignon and this study was excluded as it appeared both groups received erythropoietin. Unfortunately no additional data were received from Ganguli 2003 and Teplan 2001b.

These new studies were conducted in India (Ganguli 2003) and the Czech Republic (Teplan 2001b; Teplan 2003). The number of participants ranged from 36 to 186 and the duration of the studies was six months to three years.

2016 review update

This update found an additional four studies (four reports) (Akizawa 1993; Kim 2006e; Kristal 2008; Wang 2004b). Three studies were only available as abstracts (Akizawa 1993; Kim 2006e; Wang 2004b). Therefore a total of 19 studies have been included in this review (Figure 1).

Figure 1. Study flow diagram.

These new studies were conducted in Japan (Akizawa 1993), Korea (Kim 2006e), Israel (Kristal 2008), and Hong Kong (Wang 2004b). The number of participants ranged from 40 to 107 and the duration of the studies was 12 weeks to 21 months.

Because the benefit of EPO therapy is now established for patients with CKD not yet on dialysis, further updates of this review with the addition of studies comparing EPO with placebo or no

treatment are unnecessary and therefore this review will no longer be updated.

Risk of bias in included studies

The risk of bias was reassessed for 13 studies; for the six studies only reported as a conference abstract (Akizawa 1993; Brown 1995; Ganguli 2003; Kim 2006e; Teplan 2001b; Wang 2004b) the risk of bias was not assessed resulting in blank rows in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

The empty rows relate to abstract-only publications - risk of bias could not be assessed

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abraham 1990	?	?	?	?	+	+	-
Akizawa 1993							
Brown 1995							
Clyne 1992	?	?	-	?	-	-	?
Eschbach 1989	?	?	?	?	+	+	-
Ganguli 2003							
Kim 2006e							
Kleinman 1989	?	?	+	?	?	?	-
Kristal 2008	?	-	-	+	-	-	?
Kuriyama 1997	?	?	-	?	+	?	?
Lim 1989	+	+	+	?	?	?	?
Roth 1994	?	?	-	?	-	?	-
Stone 1988	?	?	+	?	?	?	-
Teehan 1989	?	?	+	?	?	-	?
Teehan 1991	?	?	+	?	?	?	-
Teplan 2001b							
Teplan 2003	?	+	-	+	+	?	?
Wang 2004b							
Watson 1990	+	+	+	?	+	?	-

Allocation

Random sequence generation was at low risk of bias in two studies (Lim 1989; Watson 1990) and unclear in 11 studies

Allocation concealment was at low risk of bias in three studies (Lim 1989; Teplan 2003; Watson 1990), high in Kristal 2008 (patients allocated according to visit to clinic), and unclear in nine studies.

Blinding

Performance bias was assessed as high in five studies; two explicitly stated there was no blinding of patients or health care providers (Clyne 1992; Roth 1994), and three studies randomised the control group to no treatment (Kristal 2008; Kuriyama 1997; Teplan 2003). Six studies were assessed as being at low risk of performance bias (Kleinman 1989; Lim 1989; Stone 1988; Teehan 1989; Teehan 1991; Watson 1990) and performance bias was unclear in two studies (Abraham 1990; Eschbach 1989).

Detection bias was low in two studies (Kristal 2008; Teplan 2003) and unclear in the remaining 11 studies.

Incomplete outcome data

Five studies (Clyne 1992; Kleinman 1989; Kuriyama 1997; Lim 1989; Roth 1994) mentioned the numbers and reasons for withdrawals or dropouts. Attrition bias was low in five studies (Abraham 1990; Eschbach 1989; Kuriyama 1997; Teplan 2003; Watson 1990), high in three studies (Clyne 1992; Kristal 2008; Roth 1994) and unclear in five studies.

Selective reporting

Reporting bias was low in two studies (Abraham 1990; Eschbach 1989), high in three studies (Clyne 1992; Kristal 2008; Teehan 1989), and unclear in eight studies.

Other potential sources of bias

Other potential biases were high (industry funding) in seven studies (Abraham 1990; Eschbach 1989; Kleinman 1989; Roth 1994; Stone 1988; Teehan 1991; Watson 1990) and unclear in six studies.

Effects of interventions

Measures of progression of kidney failure

Number of patients starting renal replacement therapy during study period

Five studies (Brown 1995; Clyne 1992; Kuriyama 1997; Roth 1994; Stone 1988) with a total of 207 patients recorded data on the number of patients starting RRT during the study period. Overall the numbers starting dialysis (Analysis 1.1.1 (5 studies, 207 participants): RR 0.70, 95% CI 0.43 to 1.14; $I^2 = 24\%$) showed no evidence of a difference between the two groups. The confidence interval is sufficiently wide for a clinically and economically important difference to exist. There was no evidence of heterogeneity. The different lengths of study duration should be considered when interpreting these data. The study periods ranged from 8 to 10 weeks for three studies (Brown 1995; Clyne 1992; Stone 1988), 48 weeks for Kuriyama 1997 and Roth 1994, and 36 months for Teplan 2003. In the study by Teplan 2003 there was no mention of anyone progressing to dialysis presumably because their progression of kidney failure was less advanced (serum creatinine 2.79 ± 0.97 mg/dL).

Akizawa 1993 reported that the proportions of patients with deteriorating kidney function did not differ between groups.

Time to commencement of dialysis

Only Roth 1994 reported data on time from start of rHuEPO therapy to onset of dialysis. The time to start of dialysis for patients receiving rHuEPO (43) compared with those not receiving rHuEPO (40) was not statistically significant at conventional levels, Kaplan - Meier survival curves (Log-rank test $P = 0.99$).

GFR at the end of study

Seven studies (Abraham 1990; Clyne 1992; Kristal 2008; Roth 1994; Teplan 2003; Wang 2004b; Watson 1990) compared GFR in a manner that allowed the data to be combined (i.e. reported both means and standard deviations). The overall estimate of effect favoured treatment and while this was statistically significant it was not clinically significant (Analysis 1.2 (7 studies, 283 participants): MD -2.11 mL/min, 95% CI -3.08 to -1.15; participants = 283; studies = 7; $I^2 = 7\%$).

Reduction in GFR

Roth 1994 recorded change in GFR. Of the original 83 participants reduction in GFR was only available for 28 participants at the end of the study. The result was not statistically significant (Analysis 1.3: MD of -0.70 mL/min, 95% CI -3.20 to 1.80).

Serum creatinine at end of study

Eight studies (Abraham 1990; Brown 1995; Clyne 1992; Eschbach 1989; Kristal 2008; Kim 2006e; Teplan 2003; Watson 1990) measured serum creatinine at the end of the study period in a way that could be incorporated into the meta-analysis. There was no statistically significant difference between the groups (Analysis 1.4 (8 studies, 327 participants): MD 27.86 μ mol/L, 95% CI -32.04 to 87.76; participants = 327; studies = 8; $I^2 = 82\%$). There was significant heterogeneity between studies; differences in baseline serum creatinine were not taken into account in this analysis which may have accounted for this.

Change in serum creatinine from baseline

Only Roth 1994 reported change in serum creatinine in a form which could be entered for analysis. Although this showed a significantly greater rise in creatinine at the end of the study with participants receiving rHuEPO (Analysis 1.5 (1 study, 83 participants): MD 114.92 μ mol/L, 95% CI 37.83 to 192.01), other included studies reported data which were not consistent with this finding. Teehan 1991 reported mean change in serum creatinine without standard deviations and found no significant difference between participants treated with rHuEPO and those receiving placebo ($P > 0.05$). Kleinman 1989 recorded the change in kidney function by measuring the change in the slope of the inverse of serum creatinine over time and concluded that there was no statistical difference between those receiving rHuEPO and the controls ($P = 0.83$). Eschbach 1989 reported the inverse of serum creatinine level multiplied by 100 as the measure of change in kidney function. The slopes were determined for each patient and the pre- and post-treatment slopes compared. There was no significant change ($P = 0.78$) in the rate of decline of kidney function after a median of 12 months of rHuEPO therapy. Teehan 1991 measured the inverse of serum creatinine as a function of time for 83 participants in whom serum creatinine values were available for

at least two months before and after the study; the slopes did not increase after initiation of rHuEPO therapy.

Measures of correction of anaemia

Haemoglobin at the end of the study

Four studies (Clyne 1992; Kristal 2008; Teplan 2003; Wang 2004b) reported haemoglobin at the end of the study. rHuEPO significantly increased Hb compared to placebo or no treatment (Analysis 1.6 (4 studies, 237 participants): MD 1.90 g/dL, 95% CI 1.47 to 2.34; $I^2 = 30\%$).

Haematocrit at the end of the study

Seven studies (Abraham 1990; Eschbach 1989; Kuriyama 1997; Lim 1989; Stone 1988; Teehan 1989; Watson 1990) reported haematocrit levels at the end of the study period in a manner that could be combined in a meta-analysis. rHuEPO significantly improved haematocrit compared to placebo or no treatment (Analysis 1.7 (7 studies, 145 participants): MD 9.85%, 95% CI 8.35 to 11.34; $I^2 = 20\%$). Three additional studies measured haematocrit levels results of which could not be used in the meta-analysis. Kleinman 1989 presented data without standard deviations and showed at the end of the study that a haematocrit of 35.8% was achieved for those treated with rHuEPO compared with 28.3% for the placebo group ($P = 0.004$). Roth 1994 noted mean haematocrit (again no standard deviations) were available. He reported, however, that correction of anaemia to at least 36% was achieved in 34/43 participants receiving rHuEPO compared with none in the control group. Teehan 1991 demonstrated that 90% of participants treated with 150 units rHuEPO/kg of body weight, 79% who received 100 units and 57% receiving 50 units responded to therapy (defined as an increase of six percentage points in haematocrit) compared with a response rate of 10% in the placebo group. This response rate of 10% was based on an increase in haematocrit, on a single occasion in three placebo participants.

Change in haemoglobin or haematocrit levels

No study recorded change in haemoglobin or haematocrit in a form that could be used in a meta-analysis and no study recorded data on haemoglobin values one to three months after commencement of RRT.

Number of participants requiring blood transfusions

Three studies (Kleinman 1989; Lim 1989; Roth 1994) reported the number of participants who required blood transfusions. the number requiring blood transfusions in the rHuEPO group was significantly less than those in the placebo or no treatment group (Analysis 1.8 (3 studies, 111 participants): RR 0.32, 95% CI 0.12 to 0.83; $I^2 = 0\%$).

Quality of life measures at the end of the study period

Only Kleinman 1989 recorded data on quality of life in a manner suitable for analysis (reported means and standard deviations). Quality of life was assessed by asking participants to:-

- "Rate your energy level during the past week"
- "Judge your ability to do work during the previous week"
- "Rate your overall quality of life during the past week"

Participants treated with rHuEPO had a better quality of life after 12 weeks. There was evidence of a statistically significant difference between the two groups favouring treatment with rHuEPO (Analysis 1.9: MD 35.00, 95% CI 12.47 to 57.53).

Roth 1994 used a health-related quality of life (HRQL) assessment carried out at 16, 32 and 48 weeks. Scales from the Sickness Impact Profile (SIP) were used. Four scales taken from the Medical Outcomes Study Short Form and other Medical Outcome Study measures, which have demonstrated acceptable validity and reliability, were also included. During the 48 weeks of follow up the control group showed a significant decrease in physical function ($P = 0.03$); those receiving rHuEPO showed significant increases in energy ($P = 0.045$) and physical function ($P = 0.015$). The results from Kleinman 1989 and Roth 1994 could not be combined as different measures were used. Lim 1989 reported that all 11 participants who received rHuEPO experienced an increased sense of well-being, felt more energetic and were more able to perform their work. Ganguli 2003 reported a significant improvement in quality of life and work capacity in those receiving EPO.

Change in exercise capacity

Only data from Clyne 1992 could be entered in the analysis. A standardised exercise test was performed using a bicycle ergometer. Clyne 1992 demonstrated a marginally significant result favouring treatment with rHuEPO (Analysis 1.10: MD 46.00 W, 95% CI 1.27 to 90.73). Participants in Teehan 1991 completed questionnaires before and after the study, rating their energy levels and ability to do work during the previous week. Teehan 1991 concluded that correction of anaemia was associated with significant improvements in participants' energy levels.

Measures of blood pressure control

Blood pressure measurements

Clyne 1992 measured systolic blood pressure at the end of the study. The point-estimate favours treatment, however the result was not statistically significant (Analysis 1.11: MD -11.00 mm Hg, 95% CI -25.95 to 3.95). Abraham 1990 recorded mean arterial blood pressure and showed no evidence of a significant difference between the groups. Kleinman 1989 measured changes in systolic blood pressure but no standard deviations were reported and hence the data could not be used in the analysis; the investigators however reported no evidence of a significant increase in blood pressure for several months after the study although several participants had begun dialysis at that time. An analysis by Teehan 1991 showed no statistically significant difference either in systolic or diastolic blood pressure at the end of the study. He also reported that no medically significant change occurred in any treatment group. Watson 1990 reported that there were no major problems with blood pressure. No study reported change in systolic blood pressure in a form that could be entered for analysis. Roth 1994 however, reported that the change in systolic blood pressure during the study was not significantly different between the group receiving rHuEPO and the control group ($P = 0.67$). Diastolic blood pressure at the end of the study was reported by Clyne 1992 and showed a lower diastolic blood pressure at the end of the study in those receiving rHuEPO but the difference was not significant (Analysis 1.12: MD -5.00, 95% CI -12.39 to 2.39).

Antihypertensive treatment

Seven studies reported data on numbers of participants in whom there was an increase in or introduction of antihypertensive treatment. Data in [Abraham 1990](#), [Lim 1989](#) and [Stone 1988](#) formed a subset of those in the multicentre study of [Teehan 1991](#), and hence only [Teehan 1991](#) data were used in the meta-analysis. Of the four remaining studies ([Clyne 1992](#); [Kleinman 1989](#); [Roth 1994](#); [Teehan 1991](#)) three showed that there was a more frequent need to increase or introduce antihypertensive treatment in participants receiving rHuEPO. The overall estimate of effect was not statistically significant ([Analysis 1.13](#) (4 studies, 232 participants): RR 1.26, 95% CI 0.76 to 2.11; $I^2 = 50\%$), however the CIs were sufficiently wide enough to include a clinically important difference. There was some evidence of heterogeneity between the studies however this was not significantly different ($P = 0.11$). [Eschbach 1989](#) recorded that 11 participants required an increase in or initiation of antihypertensives but the study did not report to which groups the participants belonged. [Clyne 1992](#) reported that in 4/12 participants receiving rHuEPO therapy, rHuEPO treatment was stopped until blood pressure was controlled. It is worth noting that in the earlier studies higher doses of rHuEPO were used than is used in current practice.

Other adverse events

Discontinued treatment due to adverse events

Four studies ([Kleinman 1989](#); [Roth 1994](#); [Teehan 1991](#); [Watson 1990](#)) recorded numbers of participants discontinuing treatment due to adverse events including sepsis, myocardial infarction, nausea and vomiting, and suspicion of acceleration of kidney failure. There was no statistically significant difference between the treatment and control groups ([Analysis 1.14](#) (4 studies, 223 participants): RR 0.86, 95% CI 0.28 to 2.59; $I^2 = 17\%$). [Eschbach 1989](#) and [Roth 1994](#) both reported "no adverse events attributable to rHuEPO therapy".

Access problems for patient commenced on haemodialysis

[Kleinman 1989](#) was the only study to report on venous access (arterio-venous fistula/synthetic graft) problems. Two of seven participants in each group had either an arterio-venous fistula or bovine graft in preparation for haemodialysis and there were no clotting episodes.

Seizures

Three studies reported seizures ([Kleinman 1989](#); [Teehan 1991](#); [Watson 1990](#)). [Teehan 1991](#) and [Watson 1990](#) reported one seizure in each of their studies in the control group and [Kleinman 1989](#) reported there were no seizures during the course of their study ([Analysis 1.15](#) (3 studies, 140 participants): RR 0.22, 95% CI 0.02 to 1.94; $I^2 = 0\%$).

Mortality

Mortality was reported in four studies ([Kleinman 1989](#); [Kuriyama 1997](#); [Roth 1994](#); [Stone 1988](#)). [Kuriyama 1997](#), [Roth 1994](#) and [Stone 1988](#) recorded data on mortality within their studies, however, the wide confidence interval reflects the small number of events (six deaths in total). [Kleinman 1989](#) reported there were no deaths during the course of the study ([Analysis 1.16](#) (4 studies, 182 participants): RR 0.60, 95% CI 0.13 to 2.88; $I^2 = 0\%$).

DISCUSSION

This review has generated no clear evidence that rHuEPO treatment has either a beneficial or adverse effect on the progression of CKD or on the timing of initiation of dialysis. Though a formal meta-analysis, of quality of life and exercise capacity measures were not possible, all the studies reporting these outcomes demonstrated statistically significant differences favouring treatment with rHuEPO. There was no statistically significant result as regards deterioration in blood pressure control or seizure necessitating withdrawal of treatment, however study duration was short and the confidence intervals wide. The combined results from two studies ([Teehan 1991](#); [Watson 1990](#)) provide no evidence that rHuEPO treatment was associated with seizures although the short duration of most of the studies resulted in very few events. The meta-analysis of four studies did not indicate a significant increase in the number of participants in whom antihypertensives were introduced, although as the confidence interval is wide this could not be ruled out. The increase in the use of antihypertensives in some of the studies could have been as a result of the higher doses of rHuEPO used in some of the earlier studies, lower doses are now used. The review also generated convincing evidence that predialysis rHuEPO does correct renal anaemia and reduces blood transfusion requirements.

Left ventricular hypertrophy (LVH) was not one of the predetermined outcomes of this review. Though it may be an independent predictor of mortality in participants with CKD ([Harnett 1995](#); [Levin 1996](#)) it is clearly a surrogate marker. There is no convincing evidence that reversing or delaying the progression of LVH has an impact on mortality, morbidity or quality of life. If such evidence becomes available it would support LVH becoming an outcome measure in future RCTs and systematic reviews in this area.

GFR was statistically significantly higher at the end of the study period in the rHuEPO treated group. This result was driven mainly by [Teplan 2003](#) included in this first update. The difference of 2.5 mL/min may however not be clinically significant. In addition the numbers are still small and the GFR was higher at the beginning of [Teplan 2003](#) in the rHuEPO group and when we calculated the relative risk this difference was statistically significant. This imbalance was not incorporated into the meta-analysis.

It is regrettable that none of the included RCTs continued follow-up beyond commencement of dialysis. It is possible that participants whose haemoglobin/haematocrit has been partially corrected by rHuEPO may have less morbidity, less hospitalisation, less initial rHuEPO requirements and consume less health care resources around the period of dialysis commencement.

A number of characteristics of the included studies make it difficult to demonstrate either clear evidence of benefit or lack of benefit of predialysis rHuEPO. Many of the studies were of short duration not long enough to assess the effects on the progression of kidney disease and included small numbers of randomised participants. Participants were not equally distributed between treatment and placebo groups in 7/15 studies ([Clyne 1992](#); [Eschbach 1989](#); [Kuriyama 1997](#); [Lim 1989](#); [Roth 1994](#); [Stone 1988](#); [Teehan 1991](#)). The way data were reported in many of the studies included in this review (without means or measures of dispersion) made incorporation into a meta-analysis impossible.

and thus the statistical power of combined patient numbers could not always be utilised. [Teplan 2003](#) was one of the largest studies and longest duration of 36 months, and contributed to the statistically significant result in the GFR favouring EPO, although clinical significance is questionable. There was no mention of any of the participants progressing to dialysis, presumably because their kidney failure was less advanced, a follow-up study of these participants to start of dialysis would be interesting.

With the exception of two studies ([Brown 1995](#); [Kuriyama 1997](#)) which included participants with diabetes, the studies generally excluded participants with significant comorbidity. The results of this review may not be generalisable to the present predialysis patient population.

This review also demonstrated the potential pitfall of double-counting randomised participants in systematic reviews when some individual centres in a multi-centre RCT publish their data separately in addition to their inclusion in the full report of the complete RCT. All the reports from multi-centre RCTs should clearly describe the involvement of all centres and highlight any previous or potential future publications derived from the RCT.

In summary there was a marked improvement in measures of anaemia with the treatment and a decrease in the number of participants requiring blood transfusion. Though difficult to summarise, the data from all studies which reported quality of life or exercise capacity demonstrated an improvement in the rHuEPO group. Only one of the measures of progression of kidney disease (GFR) (when a summary statistic was calculated) demonstrated a statistically significant difference but with questionable clinical significance. Hence there is no evidence from this review of the hypothesised delay in requirement for RRT or of a further deterioration in kidney function attributable to rHuEPO treatment. The requirement for antihypertensive treatment appears not to be increased by rHuEPO therapy and there was no other statistically significant increase in adverse events.

The addition of four studies in 2016 did not alter the conclusions of the review.

AUTHORS' CONCLUSIONS

Implications for practice

The benefits of rHuEPO treatment in predialysis participants are that it corrects anaemia and avoids the requirement for blood transfusions. In the long term the critical question as to whether treatment with rHuEPO either speeds or delays the onset of RRT remains unanswered.

Implications for research

A future RCT to look specifically at whether rHuEPO can delay or hasten RRT in patients with chronic kidney failure is required. Nephrology is a low volume specialty and multicentre studies are therefore necessary to recruit sufficient numbers to achieve acceptable statistical power. Further RCTs should be designed to be large enough and of long enough duration to address this question adequately. These studies could also examine the proposition that a patient with a higher haemoglobin is in better health and better able to cope with the commencement of dialysis when it is eventually necessary. Hospitalisation duration for initiation of dialysis, hospitalisation rates and mortality for the first three months of RRT should provide further relatively hard end-points. Considering the demonstrable effectiveness of rHuEPO in improving haemoglobin it may be impossible to blind health care providers effectively in such a study.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abraham 1990

Methods	<ul style="list-style-type: none"> Study design: parallel RCT with short- and long-term phases Duration of study: 8 to 12 weeks until HCT reached goal of 40% for males and 37% for females
Participants	<ul style="list-style-type: none"> Country: USA Setting: single centre

Abraham 1990 (Continued)

- Clinically stable for at least 1 month prior to therapy (BP, physical examination, chemistry profile, electrocardiogram, chest X-ray, diet and medications)
 - * Kidney function: SCr > 3.0 mg/dL
 - * Anaemia: HCT < 36%
- Number: treatment group (4); control group (4)
- Mean age: 47 years
- Sex (M/F): treatment group (2/2); control group (3/1)
- Exclusion criteria: anaemia other than renal anaemia; concomitant therapy with androgen; immunosuppressant or corticosteroid therapy within 2 months; other conditions which might interfere with or complicate EPO therapy including active hepatitis; asthma or severe allergic diathesis; active ischaemic heart disease; SLE; chronic inflammatory diseases; acute rheumatoid arthritis; severe or uncontrolled hypertension (supine diastolic BP > 110 mm Hg); thrombocytopenia (< 100,000/mm³); neutropenia (< 2000/mm³); drug abuse; history of seizures; malignancy; pregnancy

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Type of EPO: erythropoietin alfa • Route of administration: IV or SC • Dose: 50 to 150 units/kg 3 times/week <p>Control group</p> <ul style="list-style-type: none"> • Placebo • Route of administration: IV or SC • Dose: not described <p>Co-interventions (both groups)</p> <ul style="list-style-type: none"> • Iron administered: If serum iron < 50 µg/dL or Fe/TIBC < 20% ferrous sulphate • Folate administered: daily 1 mg <p>Duration of study: 8 to 12 weeks until goal HCT of 40% (males) or 37% (females)</p>
Outcomes	<ul style="list-style-type: none"> • HCT • SCr • Number with an increase or introduction of antihypertensive treatment
Notes	<ul style="list-style-type: none"> • Formed part of multicentre study (Teehan 1991) • Conducted in USA • Funded by Ortho Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear, reported to be randomised however method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear, states "double-blind placebo-controlled..."
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported

Abraham 1990 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the first phase of the study
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	"Financial support and erythropoietin was provided by Ortho Pharmaceutical Corporation, Raritan, N.J., USA"

Akizawa 1993

Methods	<ul style="list-style-type: none"> Study design: unclear Duration of study: 12 weeks
Participants	<ul style="list-style-type: none"> Country: Japan Setting: not reported Participants with CKD not on dialysis <ul style="list-style-type: none"> * Kidney function: SCr 5.7 ± 1.2 mg/dL * Anaemia: not reported Number: 107 (did not specify how many were in each group) Age: not reported Sex (M/F): not reported
Interventions	Treatment group <ul style="list-style-type: none"> Type of EPO: not reported Route of administration: SC Dose: 6000 IU/week for 12 weeks Control group <ul style="list-style-type: none"> Placebo
Outcomes	<ul style="list-style-type: none"> GFR HCT
Notes	<ul style="list-style-type: none"> Abstract only Funding: not reported

Brown 1995

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Duration of study: 1 year
Participants	<ul style="list-style-type: none"> Country: USA Setting: single centre Anaemic diabetic predialysis patients <ul style="list-style-type: none"> * Kidney function: SCr 221 to 442 μmol/L * Anaemia: HCT < 30%

Brown 1995 (Continued)

- Number: treatment group (8); control group (9)
- Age: not reported
- Sex (M/F): not reported
- Exclusion criteria: not mentioned

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Type of EPO: erythropoietin alfa • Route of administration: SC • Dose: 50 U/kg 3 times/week <p>Control group</p> <ul style="list-style-type: none"> • Usual care: not reported <p>Duration of study: 1 year</p>
Outcomes	<ul style="list-style-type: none"> • HCT • SCr
Notes	<ul style="list-style-type: none"> • Abstract only • Funding: not reported

Clyne 1992

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Duration of study: 12 weeks
Participants	<ul style="list-style-type: none"> • Country: Sweden • Setting: Karolinska Hospital and Danderyd Hospitals • CKD patients <ul style="list-style-type: none"> * Kidney function: eGFR < 25 mL/min/1.73 m² * Anaemia: HCT ≤ 28% • Number: treatment group (12); control group (10) • Mean age ± SD (years): treatment group (46 ± 12), control group (53 ± 15) • Sex (M/F): treatment group (6/6), control group (5/3) • Exclusion criteria: RRT; diabetes; angina or prior acute myocardial infarction; platelet count of > 500 x 10⁹/L; epilepsy; treatment with cytotoxic agents; hormone preparations or immunosuppressants; poorly controlled hypertension; and deficiency of folic acid or vitamin B₁₂
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Type of EPO: Epoetin beta • Starting at 300 U/kg/week IV to achieve HCT > 30% for 3 months <p>Control group</p> <ul style="list-style-type: none"> • No treatment for 3 months <p>Iron supplementation</p> <ul style="list-style-type: none"> • Oral or IV <p>Duration of treatment: 12 weeks</p>
Outcomes	<ul style="list-style-type: none"> • Number starting RRT during study period

Clyne 1992 (Continued)

- Change in QoL
- Hb
- GFR
- Systolic BP
- Number with an increase or introduction of antihypertensive treatment

Notes • Funding: unable to determine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open randomised parallel-group study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was 1/12 (8%) in the epoetin beta arm and 2/10 (20%) in the control arm. As this was > 10% overall this was judged to be high risk
Selective reporting (reporting bias)	High risk	Major cardiovascular outcomes were not available
Other bias	Unclear risk	Unable to determine

Eschbach 1989

Methods • Study design: parallel RCT, short-term phase followed by open-label maintenance phase
• Duration of study: April 1987 to August 1988

Participants • Country: USA
• Setting: single centre
• CKD patients
* Kidney function: SCr 353 to 972 µmol/L
* Anaemia: HCT < 30%
• Number: treatment group (11); control group (6)
• Age range: 24 to 72 years
• Sex (M/F): 10/7
• Exclusion criteria: inflammatory disease; immunosuppressive therapy

Interventions Treatment group
• Type of EPO: erythropoietin alfa

Eschbach 1989 (Continued)

- Route of administration: IV and SC
- Dose: 50, 100 or 150 U/kg 3 times/week
- Duration of study
 - * IV: 8 weeks or until target HCT reached
 - * SC: 12 weeks or until target HCT reached

Control group

- Placebo, IV or SC 3 times/week

Outcomes	<ul style="list-style-type: none"> • SCr • HCT
Notes	<ul style="list-style-type: none"> • Formed part of multicentre study (Teehan 1991) • Funding: part funded by Ortho Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Patients and physicians blinded were blinded to the identify of the study medication but not the dose
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the short phase study
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	High risk	Portions of this study were funded by research grants from National Institutes of Health and Ortho Pharmaceutical Corporation.

Ganguli 2003

Methods	<ul style="list-style-type: none"> • Study design: parallel 3-arm RCT • Duration of study: 6 months
Participants	<ul style="list-style-type: none"> • Country: India • Setting: single centre • Anaemic non diabetic predialysis patients <ul style="list-style-type: none"> * Kidney function: SCr 3.42 ± 0.27 mg * Anaemia: Hb 7.83 ± 24 g/dL

Ganguli 2003 (Continued)

- Number: treatment group 1 (12); treatment group 2 (12); control group (12)
- Age range: 18 to 75 years
- Sex (M/F): treatment group 1 (6/6); treatment group 2 (6/6); control group (6/6)
- Exclusion criteria: diabetics

Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Type of EPO: not reported • Route of administration: SC • Dose: 100 U/kg 2 divided doses a week <p>Treatment group 2</p> <ul style="list-style-type: none"> • Nandrolone 200 mg IM <p>Control group</p> <ul style="list-style-type: none"> • Placebo, route and dose not reported <p>Duration of study: 6 months</p>
Outcomes	<ul style="list-style-type: none"> • Anthropometric measurements • Haematological parameters • Serum albumin • SCr • Treadmill tests • Work capacity • QoL • Progression of kidney disease
Notes	<ul style="list-style-type: none"> • Abstracts only • Treatment group 2 not included in the meta-analyses • Study could not be included in the meta-analyses • Funding: not reported

Kim 2006e

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Duration of study: said to continue for 21 months
Participants	<ul style="list-style-type: none"> • Country: Korea • Setting: multicentre • Patients with CKD not on dialysis <ul style="list-style-type: none"> * Kidney function: SCr 1.5 to 4 mg/dL * Anaemia: Hb < 10 g/dL • Number: treatment group (60); control group (43) • Age: not reported (reported no statistical difference between the 2 groups) • Sex: not reported (reported no statistical difference between the 2 groups) • Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • EPO (no dose provided) SC for 3 months of stabilisation to Hb 10 g/L <p>Control group</p>

Kim 2006e (Continued)

- Placebo SC injections for 3 months

Study said to continue for further 21 months but unclear whether all patients received EPO after 3 months

Outcomes	<ul style="list-style-type: none"> • Composite of doubling of SCr • Initiation of dialysis • Death
Notes	<ul style="list-style-type: none"> • Abstract only • Funding: not reported

Kleinman 1989

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Duration of study: 12 weeks or until reaching a HCT 38% to 40%
Participants	<ul style="list-style-type: none"> • Country: USA • Setting: single centre • Inclusion criteria: stable laboratory parameters; adequate serum folate and B₁₂ levels and iron stores, as reflected by serum iron; total iron binding capacity and ferritin; ensured that anaemia was not caused by a vitamin or elemental iron deficiency; no evidence of chronic gastrointestinal blood loss <ul style="list-style-type: none"> * Kidney function: SCr 265 to 972 µmol/L * Anaemia: HCT < 30% • Number: treatment group (7); control group (7) • Age range: 38 to 73 years • Sex M/F: treatment group (5/2); control group (4/3) • Exclusion criteria: marked obesity or inanition; active hepatitis or hepatic disease; asthma; severe atopic illness; significant cardiovascular, pulmonary, malignant, or haematologic diseases; severe or uncontrolled hypertensive disease; neurological disease or history of seizure activity; presence of gross haematuria, sickle cell anaemia, untreated ischaemic heart disease of 3 months duration or presence of clinically significant gastrointestinal disease; systemic diseases such as lupus erythematosus, rheumatoid arthritis or other inflammatory diseases or infectious states that might interfere with the effects of EPO; thrombocytopenia or leukopenia; alcohol or drug abuse; acute illness within 7 days of initiation of the screening period; androgen therapy for chronic anaemia corticosteroid and other immunosuppressive medications were discontinued 2 and 1 months respectively before study entry
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Type of EPO: erythropoietin alfa • Dose: 100 U/kg 3 times/week • Route of administration: SC <p>Control group</p> <ul style="list-style-type: none"> • Placebo: • Route of administration: SC • Dose: 3 times/week <p>Iron administered</p> <ul style="list-style-type: none"> • All received oral iron <p>Duration of study: 12 weeks or until HCT of 38% or 40%</p>

Kleinman 1989 (Continued)

Outcomes	<ul style="list-style-type: none"> • Change in quality of life measures • Discontinued due to adverse events • Increase or introduction of antihypertensive treatment • Need for blood transfusions
Notes	<ul style="list-style-type: none"> • Funding: EPO prepared by recombinant DNA technology (Amgen Corporation) • "After the 12-week control period, the seven placebo patients received r-HuEPO subcutaneously at a dose of 150 U/kg until the target hematocrit of 38% to 40% was reached. The difference in dosages between the two groups was determined by the Ortho Pharmaceutical Corporation before the study"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 patient withdrew from EPO group
Selective reporting (reporting bias)	Unclear risk	Unable to determine
Other bias	High risk	Ortho Pharmaceutical Corporation was an author on the paper

Kristal 2008

Methods	<ul style="list-style-type: none"> • Study design: quasi-RCT • Duration of study: 20 weeks; 2000 to 2001
Participants	<ul style="list-style-type: none"> • Country: Israel • Setting: unclear • Patients with CKD stages 4-5 not on dialysis or EPO <ul style="list-style-type: none"> * Kidney function: not reported * Anaemia: Hb 8.1 to 11 g/dL • Number: treatment group (20); control group (20) • Mean age $\pm$ SEM (years): treatment group (70.2 $\pm$ 2.0); control group (67.2 $\pm$ 2.7) • Sex (M/F): treatment group (4/16); control group (6/14) • Exclusion criteria: not reported
Interventions	Treatment group

Kristal 2008 (Continued)

- Type of EPO: Eprex
- Dose: 6000 IU/week
- Route of administration: SC

Control group

- No treatment

All patients received oral maintenance iron supplementation, calcium bicarbonate, statins, beta-blockers, and calcium channel blockers

Outcomes	<ul style="list-style-type: none"> • SCr • Calculated GFR • Hb
Notes	<ul style="list-style-type: none"> • Primary outcomes of study related to non-erythropoietic actions of EPO • Funding: "This work was partially supported by a grant from by the R.W. Johnson Pharmaceutical Research Institute, a division of Ortho-McNeil Pharmaceutical, Inc."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	High risk	Patients allocated in order according to visit to clinic (information from authors)
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding; open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Relevant outcomes were laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	12/40 (30%) did not complete study (3/20 in treatment group and 9/20 in control group)
Selective reporting (reporting bias)	High risk	No report of adverse effects
Other bias	Unclear risk	Unable to determine

Kuriyama 1997

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Duration of study: commenced 1 January 1993
Participants	<ul style="list-style-type: none"> • Country: Japan • Setting: single centre

Kuriyama 1997 (Continued)

- Predialysis patients aged 30 and 75 years
 - * Kidney function: SCr 2 to 4 mg/dL
 - * Anaemia: HCT < 30%
- Number: treatment group (43; control group (31)
- Mean age $\pm$ SD (years): treatment group (63.8 ± 10.6); control group (59.2 ± 13.4)
- Sex (males): treatment group (55%); control group (52%)
- Exclusion criteria: iron deficiency anaemia; transfusion dependency; presence of any other systemic disease; any inflammatory condition or infection that might interfere with the effect of EPO

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Type of EPO: not reported • Dose: 6,000 IU once a week varied to achieve target HCT of 33% to 35% • Route of administration: IV <p>Control group</p> <ul style="list-style-type: none"> • No treatment <p>Iron: at the investigators discretion Duration of study: 36 weeks</p>
Outcomes	<ul style="list-style-type: none"> • Patients whose creatinine doubled regarded as having reached kidney death • Inability to attend regularly and death from non-kidney disease • Number commencing dialysis • HCT
Notes	<ul style="list-style-type: none"> • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group received no treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Unclear risk	Unable to determine
Other bias	Unclear risk	Unable to determine

Lim 1989

Methods	<ul style="list-style-type: none"> Study design: 4-arm parallel RCT Duration of study: 8 weeks
Participants	<ul style="list-style-type: none"> Country: USA Setting: single centre Adults with renal insufficiency <ul style="list-style-type: none"> * Kidney function: SCr $548.08 \pm 70.72 \mu\text{mol/L}$ * Anaemia: HCT $27\% \pm 1\%$ Number: treatment group (11); control group (3) Age range: 30 to 70 years Sex M/F: 10/4 Exclusion criteria: active lupus; malignancy; haemolysis; bleeding; clinically unstable; taking steroid or immunosuppressive medication
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Type of EPO: not reported Dose: 50, 100 and 150 U/kg 3 times/week Route of administration: IV <p>Control group</p> <ul style="list-style-type: none"> Placebo Route of administration: IV <p>Iron administered: ferrous sulphate 300 mg orally 3 x day Folate administered: folic acid 1 mg orally daily Duration of study: 8 weeks</p>
Outcomes	<ul style="list-style-type: none"> Change in quality of life measures Number discontinued due to adverse events Number with an increase or introduction of antihypertensive treatment Number who need blood transfusions Number experiencing seizures Exercise tolerance HCT levels
Notes	<ul style="list-style-type: none"> Formed part of multicentre study (Teehan 1991)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Third party
Allocation concealment (selection bias)	Low risk	Adequate, third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind

Lim 1989 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to determine
Selective reporting (reporting bias)	Unclear risk	Unable to determine
Other bias	Unclear risk	Unable to determine

Roth 1994

Methods	<ul style="list-style-type: none"> Study design: parallel RCT duration of study: 48 weeks
Participants	<ul style="list-style-type: none"> Country: USA Setting: 11 centres CKD patients aged 18 to 75 years; mean arterial pressure controllable below 114 mm Hg; not currently receiving HD treatment <ul style="list-style-type: none"> * Kidney function: SCr 265.2 to 707.2 $\mu\text{mol/L}$ * Anaemia: HCT < 30% Number: treatment group (43); control group (40) Mean age $\pm$ SE (years): treatment group (56.5 ± 11.4); control group (58.4 ± 13.2) Sex (females): treatment group (65%); control group (70%) Exclusion criteria: proteinuria > 5g/d; iron deficiency anaemia; transfusion dependency; presence of any other systemic disease, inflammatory condition, infection that might interfere with effects of EPO
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Type of EPO: not reported Dose: 50 U/kg 3 times/week which could be increased 75 U/kg/week on a monthly basis to a maximum of 450 U/kg/week Route of administration: SC; could self-administer after 1st month <p>Control group</p> <ul style="list-style-type: none"> No treatment <p>Iron administered: investigators discretion Folate administered: no Duration of study: 48 weeks</p>
Outcomes	<ul style="list-style-type: none"> Number of starting RRT during study period Number discontinued due to adverse events GFR Decrease in GFR Increase in SCr level Number with an increase or introduction of antihypertensive treatment Number who need blood transfusions Mortality

Roth 1994 (Continued)

Notes

- Funding: "Supported by a grant from the R. W. Johnson Pharmaceutical Research Institute and Ortho Biotech Inc. Raritan. NJ."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Nor reported
Incomplete outcome data (attrition bias) All outcomes	High risk	23/43 in the EPO group and 25/40 in the control group did not complete the study
Selective reporting (reporting bias)	Unclear risk	Unable to determine
Other bias	High risk	Funded by Ortho Biotech

Stone 1988

Methods

- Study design: parallel 4-arm RCT
- Duration of study: 8 weeks

Participants

- Country: USA
- Setting: multicentre
- Patients with chronic renal insufficiency
 - * Kidney function: CrCl 0.17 to 0.51 mL/s (10 to 30 mL/min)
 - * Anaemia: PCV < 41% males; 35% females
- Number: treatment group (9); control group (3)
- Mean age (range): 62 years (45 to 73 years)
- Sex M/F: 11/1
- Exclusion criteria: severe allergic disorders; asthma; active hepatitis; history of seizures; malignancy; uncontrolled hypertension; ischaemic heart disease; neutropenia; iron deficiency; haemolytic anaemia; thrombocytopenia

Interventions

Treatment group

- Type of EPO: erythropoietin alfa
- Dose: 50, 100 or 150 U/kg 3 times/week
- Route of administration: IV
- Administered by: 1st and last dose in hospital all others in outpatient clinic

Stone 1988 (Continued)

Control group

- Placebo 3 times/week
- Route of administration: IV
- Administered by: 1st and last dose in hospital all others in outpatient clinic

Iron administered: ferrous sulphate 300 mg 3 times/day

Folate administered: 1 mg daily

Duration of study: 8 weeks

Outcomes	<ul style="list-style-type: none"> • Number progressing to dialysis • Number with increase or introduction of antihypertensives • Mortality
Notes	<ul style="list-style-type: none"> • Formed part of multicentre study (Teehan 1991) • Funded in part by a grant from Ortho Pharmaceutical Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind, placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to determine
Selective reporting (reporting bias)	Unclear risk	Unable to determine
Other bias	High risk	Funded by Ortho Pharmaceutical

Teehan 1989

Methods	<ul style="list-style-type: none"> • Study duration: parallel RCT • Study duration: 3 months
Participants	<ul style="list-style-type: none"> • Country: USA • Setting: single centre

Teehan 1989 (Continued)

- Predialysis CKD patients
 - * Kidney function: mean SCr 5.1 ± 2.4 mg/dL
 - * Anaemia: mean HCT $25.2\% \pm 3.5\%$
- Number: treatment group (6); control group (6)
- Age: not reported
- Sex M/F: 6/6
- Exclusion criteria: patients with gastrointestinal bleeding; acute or chronic infection; sickle-cell anaemia; collagen vascular disease; known seizure disorder; drug or alcohol abuse; recent myocardial infarction; pregnancy; deficiencies of iron folic acid, or vitamin B₁₂

Interventions	Treatment group <ul style="list-style-type: none"> • Type of EPO: not reported • Dose: 100 U/kg 3 times/week • Route of administration: SC Control group <ul style="list-style-type: none"> • Placebo 3 times/week SC
Outcomes	<ul style="list-style-type: none"> • Haematology
Notes	<ul style="list-style-type: none"> • It was assumed that this study included a different set of patients from the multicentre study (Teehan 1991) since the methods were different i.e. different dosing regimen, different route of administration, different outcome measures and different study duration • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	High risk	Data for cardiovascular outcomes not available
Other bias	Unclear risk	Unable to determine

Teehan 1991

Methods	<ul style="list-style-type: none"> Study design: parallel 4-arm study Duration of study: 8 weeks
Participants	<ul style="list-style-type: none"> Country: USA Setting: multicentre (15 centres) Anaemic predialysis patients <ul style="list-style-type: none"> * Kidney function: SCr 260 to 880 µmol/L * Anaemia: HCT < 38% male; < 32% women Number: treatment group (88); control group (29) Mean age (range): 57.1 years (24 to 79 years) Sex M/F: 71/46 Exclusion criteria: significant clinical conditions affecting the hepatic; cardiovascular hematologic (other than anaemia); neurologic; or pulmonary systems
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Type of EPO: not reported Dose: 50, 100 or 150 u/kg 3 times/week Route of administration: IV <p>Control group</p> <ul style="list-style-type: none"> Placebo, 3 times/week IV <p>Folate administered: yes</p> <p>Duration of study: 8 weeks or until HCT reached 40% for men or 37% for women</p>
Outcomes	<ul style="list-style-type: none"> Number discontinued due to adverse events Number with an increase or introduction of antihypertensive treatment Number experiencing seizures HCT
Notes	<ul style="list-style-type: none"> Multicentre study including patients from Abraham 1990; Eschbach 1989; Lim 1989; Stone 1988 Funded in part by a grant from Ortho Pharmaceutical Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	106/117 completed the study

Teehan 1991 (Continued)

All outcomes

Selective reporting (reporting bias)	Unclear risk	Unable to determine
Other bias	High risk	Part funded by Ortho Pharmaceuticals

Teplan 2001b

Methods	<ul style="list-style-type: none"> Study design: parallel 3-arm RCT Duration of study: 3 years
Participants	<ul style="list-style-type: none"> Country: Czech Republic Setting: single centre Predialysis CKD patients with good compliance to diet <ul style="list-style-type: none"> * Kidney function: 22 to 36 mL/min/1.73m² * Anaemia: Hb < 11.5 g/dL, HCT < 32% Number: treatment group 1 (35); treatment group 2 (38), control group (32) Age range: 26 to 78 years Sex M/F: 50/55 Exclusion criteria: not reported
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> EPO + low protein diet + keto acids Type of EPO: not reported Dose: 40 U/kg/week Route of administration: unclear <p>Treatment group 2</p> <ul style="list-style-type: none"> EPO + low protein diet Type of EPO: not reported Dose: 40 U/kg/week Route of administration: unclear <p>Control group</p> <ul style="list-style-type: none"> Low protein diet <p>Duration of study: 3 years</p>
Outcomes	<ul style="list-style-type: none"> GFR (CrCl and inulin clearance) Serum branched chain amino acids Albumin Transferrin BMI HDL cholesterol Proteinuria Serum triglycerides Serum fractional leucine excretion
Notes	<ul style="list-style-type: none"> Abstract only Funding: not reported

Teplan 2003

Methods	<ul style="list-style-type: none"> Study design: parallel 3-arm RCT Duration of study: 36 months
Participants	<ul style="list-style-type: none"> Country: Czech Republic Setting: multicentre study Patients with good compliance to diet preceding entry to study <ul style="list-style-type: none"> * Kidney function: CrCl (29.4 ± 8.2 mL/min); SCr (2.79 ± 0.97 mg/dL) * Anaemia: Hb < 10.5 g/dL Number: treatment group 1 (63); treatment group 2 (61); control group (62) Mean age $\pm$ SD: 52 ± 8 years Sex M/F: treatment group 1 (31/32); treatment group 2 (29/32); control group (30/32) Exclusion criteria: diabetic kidney disease; polycystic kidney disease
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> EPO + low protein diet + keto acids EPO: epoetin alfa and epoetin beta <ul style="list-style-type: none"> * Dose: 40 U/kg twice a week * Route of administration: SC Keto acids: 100 mg/kg/d <p>Treatment group 2</p> <ul style="list-style-type: none"> EPO + low protein diet <p>Control group</p> <ul style="list-style-type: none"> Low protein diet: 0.6 g protein/kg/d <p>Duration of study: 36 months</p>
Outcomes	<ul style="list-style-type: none"> CrCl Inulin clearance SCr Serum urea Serum leucine Serum albumin Proteinuria Serum cholesterol Serum LDL cholesterol Serum triglyceride Serum HDL cholesterol Hb BP
Notes	<ul style="list-style-type: none"> Author confirmed sealed envelopes were used for allocation concealment Funding: "Supported by grant no. 305/01/0578 from the Grant Agency of the Czech Republic."

Risk of bias

Bias	Authors' judgement	Support for judgement
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Teplan 2003 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Adequate; sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Unclear risk	Only biochemical parameters reported
Other bias	Unclear risk	Unable to determine

Wang 2004b

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Duration of study: 48 weeks
Participants	<ul style="list-style-type: none"> Country: Hong Kong Setting: single centre Patients with CKD not on dialysis <ul style="list-style-type: none"> * Kidney function: SCr 150 to 750 µmol/L * Anaemia: Hb < 11 g/dL Number: treatment group (32); control group (34) Age: not reported Sex (M/F): not reported Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> EPO 4000 IU weekly SC. Dose titrated to achieve and maintain Hb 12 to 14 g/dL <p>Control group</p> <ul style="list-style-type: none"> No treatment
Outcomes	<ul style="list-style-type: none"> GFR Hb
Notes	<ul style="list-style-type: none"> Abstract only Other outcomes were surrogate markers for vascular function Funding: not reported

Watson 1990

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Duration of study: 12 weeks
Participants	<ul style="list-style-type: none"> Country: USA Setting: single centre Patients with pre-existing CKD <ul style="list-style-type: none"> * Kidney function: not reported * Anaemia: not reported Number: treatment group (5); control group (6) Age range: 43 to 79 years Sex M/F: 6/5 Exclusion criteria:
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Type of EPO: not reported Route of administration: SC Dose: 100 U/kg 3 times/week <p>Control group</p> <ul style="list-style-type: none"> Placebo <p>Duration of study: 12 weeks or until target HCT of 38% is achieved</p>
Outcomes	<ul style="list-style-type: none"> HCT Number discontinued due to adverse events GFR SCr Number experiencing seizures
Notes	<ul style="list-style-type: none"> Funding: "supported in part by Orth Pharmaceuticals Inc. and by grants DK 32008 and CRC 5-M01R-R00722 from the National Institutes of Health"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Performed by a third party
Allocation concealment (selection bias)	Low risk	Performed by a third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated double blind; placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	All patients accounted for

Watson 1990 (Continued)

All outcomes

Selective reporting (reporting bias)	Unclear risk	Unable to determine
Other bias	High risk	Funded by Ortho Pharmaceuticals

BP - blood pressure; CKD - chronic kidney disease; CrCl - creatinine clearance; EPO - erythropoietin; GFR - glomerular filtration rate; Hb - haemoglobin; HCT - haematocrit; HDL - high-density lipoprotein; IV - intravenous; LDL - low-density lipoprotein; M/F - male/female; PCV - packed cell volume; QoL - quality of life; RCT - randomised control trial; RRT - renal replacement therapy; SC - subcutaneous; SCr - serum creatinine; SD - standard deviation; SE - standard error

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brown 1988	All patients received EPO
CREATE Study 2001	Comparing the same ESA derivative in different treatment arms
EPOCARES Study 2010	Ineligible population
Frenken 1989	All patients received EPO
Frenken 1992	All patients received EPO
Furukawa 1992	All patients received EPO
Jabs 1994	Not randomised
Koene 1990	All patients received EPO
Macdougall 2007	Compares early with late commencement of EPO
Marcas 2003	All patients received EPO
Meloni 2003	Unclear how patients allocated to groups. Written to authors for clarification
Mignon 2001	All patients received EPO
Muirhead 1992	Haemodialysis patients
N0287023177	All patients received EPO
Palazzuoli 2007	Ineligible population. Cardiac failure patients
Pratt 2006	Compares EPO delta with EPO alpha
Schwartz 1989	Data only from EPO treated patients
Singh 1999	Randomised study. Not all participants were predialysis some had commenced dialysis
Teehan 1990	Unclear if randomised. Wrote to authors all patients received EPO
Yamazaki 1993	All patients received EPO

Study	Reason for exclusion
Zheng 1992	All patients received EPO

EPO - erythropoietin

DATA AND ANALYSES

Comparison 1. rHuEPO versus placebo or no rHuEPO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number starting RRT	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Starting RRT during the study period	5	207	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.43, 1.14]
1.2 Starting RRT in the follow-up to the study	1	8	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.50, 17.95]
2 GFR	7	283	Mean Difference (IV, Random, 95% CI)	-2.11 [-3.08, -1.15]
3 Reduction in GFR	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Serum creatinine	8	327	Mean Difference (IV, Random, 95% CI)	27.86 [-32.04, 87.76]
5 Increase in serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Haemoglobin	4	237	Mean Difference (IV, Random, 95% CI)	-1.90 [-2.34, -1.47]
7 Haematocrit	7	145	Mean Difference (IV, Random, 95% CI)	-9.85 [-11.34, -8.35]
8 Number of patients transfused	3	111	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.12, 0.83]
9 Quality of life measures	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Change in exercise capacity	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11 Systolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Diastolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Number with an increase or introduction of antihypertensive treatment	4	232	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.76, 2.11]
14 Number discontinued due to adverse events	4	223	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.28, 2.59]
15 Seizures	3	140	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.02, 1.94]
16 Mortality	4	182	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.13, 2.88]

Analysis 1.1. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 1 Number starting RRT.

Analysis 1.2. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 2 GFR.

Analysis 1.3. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 3 Reduction in GFR.

Analysis 1.4. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 4 Serum creatinine.

Analysis 1.5. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 5 Increase in serum creatinine.

Analysis 1.6. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 6 Haemoglobin.

Analysis 1.7. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 7 Haematocrit.

Analysis 1.8. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 8 Number of patients transfused.

Analysis 1.9. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 9 Quality of life measures.

Study or subgroup	rHuEPO		Placebo/no treatment		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Kleinman 1989	7	-68 (22)	7	-33 (21)		-35[-57.53,-12.47]
					Favours rHuEPO	Favours no treatment

Analysis 1.10. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 10 Change in exercise capacity.

Study or subgroup	rHuEPO		Placebo/no treatment		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Clyne 1992	12	-147 (57)	10	-101 (50)		-46[-90.73,-1.27]
					Favours rHuEPO	Favours no treatment

Analysis 1.11. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 11 Systolic blood pressure.

Study or subgroup	rHuEPO		Placebo/no treatment		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Clyne 1992	12	140 (19)	8	151 (15)		-11[-25.93,3.95]
					Favours rHuEPO	Favours no treatment

Analysis 1.12. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 12 Diastolic blood pressure.

Study or subgroup	rHuEPO		Placebo/no treatment		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Clyne 1992	12	85 (7)	8	90 (9)		-5[-12.39,2.39]
					Favours rHuEPO	Favours no treatment

Analysis 1.13. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 13 Number with an increase or introduction of antihypertensive treatment.

Study or subgroup	rHuEPO		Placebo/no treatment	Risk Ratio		Weight	Risk Ratio
	n/N	n/N		M-H, Random, 95% CI	M-H, Random, 95% CI		
Clyne 1992	8/12	3/8			1.78[0.67,4.74]	17.8%	
Kleinman 1989	4/7	6/7			0.67[0.33,1.35]	25.79%	
Roth 1994	26/43	13/40			1.86[1.12,3.09]	33.96%	
Teehan 1991	20/86	6/29			1.12[0.5,2.53]	22.44%	
Total (95% CI)	148	84			1.26[0.76,2.11]	100%	
Total events: 58 (rHuEPO), 28 (Placebo/no treatment)							
Heterogeneity: Tau ² =0.13; Chi ² =5.98, df=3(P=0.11); I ² =49.83%							
Test for overall effect: Z=0.9(P=0.37)							
				Favours rHuEPO		Favours no treatment	

Analysis 1.14. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 14 Number discontinued due to adverse events.

Analysis 1.15. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 15 Seizures.

Analysis 1.16. Comparison 1 rHuEPO versus placebo or no rHuEPO, Outcome 16 Mortality.

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
MEDLINE	<ol style="list-style-type: none"> 1. Renal Insufficiency/ 2. exp Renal Insufficiency, Chronic/ 3. Kidney Diseases/ 4. (chronic kidney or chronic renal).tw. 5. (CKF or CKD or CRF or CRD).tw. 6. (pre-dialy\$ or predialy\$).tw. 7. exp Uremia/ 8. ur\$emi\$.tw. 9. or/1-8 10.exp Anemia/ 11.(anemia or anaemia).tw. 12.or/10-11 13.exp Erythropoietin/ 14.(EPO or darbepoetin\$ or epoetin or erythropoietin).tw. 15.or/13-14 16.and/9,12,15
EMBASE	<ol style="list-style-type: none"> 1. Kidney Disease/ 2. Chronic Kidney Disease/ 3. Kidney Failure/ 4. Chronic Kidney Failure/ 5. Kidney dysfunction/ 6. (chronic kidney or chronic renal).tw. 7. (CKF or CKD or CRF or CRD).tw. 8. (pre-dialy\$ or predialy\$).tw. 9. or/1-8 10.exp anemia/ 11.(anemia or anaemia).tw. 12.or/10-11 13.exp recombinant erythropoietin/ 14.(EPO or darbepoetin\$ or epoetin or erythropoietin).tw. 15.or/13-14 16.and/9,12,15

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to	<i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).

(Continued)

inadequate generation of a randomised sequence

High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.

Unclear: Insufficient information about the sequence generation process to permit judgement.

Allocation concealment

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment

Low risk of bias: Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).

High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear: Randomisation stated but no information on method used is available.

Blinding of participants and personnel

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

Low risk of bias: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Unclear: Insufficient information to permit judgement

Blinding of outcome assessment

Detection bias due to knowledge of the allocated interventions by outcome assessors.

Low risk of bias: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Unclear: Insufficient information to permit judgement

Incomplete outcome data

Attrition bias due to amount, nature or handling of incomplete outcome data.

Low risk of bias: No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.

High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

(Continued)

Unclear: Insufficient information to permit judgement

Selective reporting

Reporting bias due to selective outcome reporting

Low risk of bias: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear: Insufficient information to permit judgement

Other bias

Bias due to problems not covered elsewhere in the table

Low risk of bias: The study appears to be free of other sources of bias.

High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
24 March 2016	Review declared as stable	As of January 2016 this Cochrane Review is no longer being updated. The clinical efficacy of rHuEPO compared with placebo or no treatment is now clinically well established.

HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 4, 2001

Date	Event	Description
29 June 2015	New search has been performed	Studies awaiting classification have been resolved
29 June 2015	New citation required but conclusions have not changed	Four new studies included with no change to the conclusions
27 February 2014	Review declared as stable	As of March 2014 this Cochrane Review is no longer being updated. The clinical efficacy of recombinant human erythropoietin (rHuEPO) is now clinically well established
23 December 2013	Amended	Search strategies revised and updated

Date	Event	Description
14 October 2008	Amended	Converted to new review format
25 May 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

- 2001 and 2005 review: JC and MC undertook, independently, the quality assessment of the studies. Data extraction was performed by JC and a sample was double-checked by SP. Extensive literature searching was performed by SW. JC entered the data and wrote the text of the review. MC and AG gave statistical and methodological advice. AM, CD, KR and IK provided a clinical perspective. CD and LV provided a health economics perspective. All reviewers commented on the review.
- 2016 review: EH assessed the four studies and updated the review

DECLARATIONS OF INTEREST

None known.

NOTES

As of January 2016 this Cochrane Review is no longer being updated. The clinical efficacy of rHuEPO compared with placebo or no treatment is now clinically well established.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia [blood] [*drug therapy] [etiology]; Disease Progression; Erythropoietin [adverse effects] [*therapeutic use]; Hematocrit; Kidney Failure, Chronic [*complications]; Quality of Life; Randomized Controlled Trials as Topic; Recombinant Proteins [adverse effects] [therapeutic use]

MeSH check words

Humans