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Short-acting erythropoiesis-stimulating agents for anaemia in predialysis patients (Review)

Hahn D, Esezobor CI, Elserafy N, Webster AC, Hodson EM

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[Intervention Review]

Short-acting erythropoiesis-stimulating agents for anaemia in predialysis patients

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ABSTRACT

Background

The benefits of erythropoiesis-stimulating agents (ESA) for chronic kidney disease (CKD) patients have been previously demonstrated. However, the efficacy and safety of short-acting epoetins administered at larger doses and reduced frequency as well as of new epoetins and biosimilars remains uncertain.

Objectives

This review aimed to evaluate the benefits and harms of different routes, frequencies and doses of epoetins (epoetin alpha, epoetin beta and other short-acting epoetins) for anaemia in adults and children with CKD not receiving dialysis.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 12 September 2016 through contact with the Information Specialist using search terms relevant to this review. Studies contained in the Specialised Register are identified through search strategies specifically designed for CENTRAL, MEDLINE, and EMBASE; handsearching conference proceedings; and searching the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

We included randomised control trials (RCTs) comparing different frequencies, routes, doses and types of short-acting ESAs in CKD patients.

Data collection and analysis

Two authors independently assessed study eligibility and four authors assessed risk of bias and extracted data. Results were expressed as risk ratio (RR) or risk differences (RD) with 95% confidence intervals (CI) for dichotomous outcomes. For continuous outcomes the mean difference (MD) with 95% confidence intervals (CI) was used. Statistical analyses were performed using the random-effects model.

Main results

We identified 14 RCTs (2616 participants); nine studies were multi-centre and two studies involved children. The risk of bias was high in most studies; only three studies demonstrated adequate random sequence generation and only two studies were at low risk of bias for allocation concealment. Blinding of participants and personnel was at low risk of bias in one study. Blinding of outcome assessment was

judged at low risk in 13 studies as the outcome measures were reported as laboratory results and therefore unlikely to be influenced by blinding. Attrition bias was at low risk of bias in eight studies while selective reporting was at low risk in six included studies.

Four interventions were compared: epoetin alpha or beta at different frequencies using the same total dose (six studies); epoetin alpha at the same frequency and different total doses (two studies); epoetin alpha administered intravenously versus subcutaneous administration (one study); epoetin alpha or beta versus other epoetins or biosimilars (five studies). One study compared both different frequencies of epoetin alpha at the same total dose and at the same frequency using different total doses.

Data from only 7/14 studies could be included in our meta-analyses. There were no significant differences in final haemoglobin (Hb) levels when dosing every two weeks was compared with weekly dosing (4 studies, 785 participants: MD -0.20 g/dL, 95% CI -0.33 to -0.07), when four weekly dosing was compared with two weekly dosing (three studies, 671 participants: MD -0.16 g/dL, 95% CI -0.43 to 0.10) or when different total doses were administered at the same frequency (four weekly administration: one study, 144 participants: MD 0.17 g/dL 95% CI -0.19 to 0.53).

Five studies evaluated different interventions. One study compared epoetin theta with epoetin alpha and found no significant differences in Hb levels (288 participants: MD -0.02 g/dL, 95% CI -0.25 to 0.21). One study found significantly higher pain scores with subcutaneous epoetin alpha compared with epoetin beta. Two studies (165 participants) compared epoetin delta with epoetin alpha, with no results available since the pharmaceutical company withdrew epoetin delta for commercial reasons. The fifth study comparing the biosimilar HX575 with epoetin alpha was stopped after patients receiving HX575 subcutaneously developed anti-epoetin antibodies and no results were available.

Adverse events were poorly reported in all studies and did not differ significantly within comparisons. Mortality was only detailed adequately in four studies and only one study included quality of life data.

Authors' conclusions

Epoetin alpha given at higher doses for extended intervals (two or four weekly) is non-inferior to more frequent dosing intervals in maintaining final Hb levels with no significant differences in adverse effects in non-dialysed CKD patients. However the data are of low methodological quality so that differences in efficacy and safety cannot be excluded. Further large, well designed, RCTs with patient-centred outcomes are required to assess the safety and efficacy of large doses of the shorter acting ESAs, including biosimilars of epoetin alpha, administered less frequently compared with more frequent administration of smaller doses in children and adults with CKD not on dialysis.

PLAIN LANGUAGE SUMMARY

Short-acting erythropoiesis agents in chronic kidney disease patients not requiring dialysis

What is the issue?

Anaemia due to reduced production by the kidneys of erythropoietin (a hormone which increases red cell production) is a major cause of tiredness and other problems experienced by people with chronic kidney disease requiring or not requiring dialysis.

Manufactured erythropoietins (epoetins) improve anaemia and are often prescribed for people with chronic kidney disease. Several different manufactured epoetins are now available.

What did we do?

We searched the Cochrane Kidney and Transplant Specialised Register to 12 September 2016 through contact with the Information Specialist using search terms relevant to this review. We included randomised control trials (RCTs) comparing different frequencies, routes, doses and types of short-acting ESAs in patients with chronic kidney disease.

What did we find?

We examined the evidence from 14 studies with 2616 participants with CKD not receiving dialysis published before 12 September 2016 to determine whether differences in improvement in anaemia and in side effects existed between different short-acting epoetins or between the same epoetins given at different frequencies. We did not find any studies using different frequencies of epoetins in children.

We found that the traditionally shorter acting epoetins given less often (two weekly to every four weeks) resulted in similar correction of anaemia compared with administration every week or every two weeks; there were no differences in side effects between the different comparisons. One study comparing subcutaneous administration of a newly manufactured HX575 epoetin alpha compared with epoetin alpha was discontinued after two patients developed anti-erythropoietin antibodies. However more studies are required as most studies were small and poorly designed, which limits their application to the care of patients.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Epoetin alpha every 2 weeks versus to weekly for anaemia in CKD patients not receiving dialysis

Epoetin alpha every 2 weeks versus to weekly for anaemia in CKD patients not receiving dialysis

Patient or population: anaemia in predialysis patients
Intervention: epoetin alpha every 2 weeks
Comparison: weekly

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with weekly	Risk with Epoetin alpha every 2 weeks				
Change in Hb level	The mean change in Hb level was 0 g/dL	The mean change in Hb level in the intervention group was 0.19 g/dL lower (0.32 g/dL lower to 0.06 g/dL lower)	-	798 (4)	⊕⊕⊖⊖ LOW [1,2]	downgraded for study limitations and indirectness
Number reaching target Hb	Study population		RR 0.96 (0.93 to 0.99)	798 (4)	⊕⊕⊖⊖ LOW [1,2]	downgraded for study limitations and indirectness
	960 per 1000	922 per 1000 (893 to 951)				
	Moderate					
	947 per 1000	910 per 1000 (881 to 938)				
Number of deaths	Study population		RR 0.89 (0.38 to 2.07)	838 (4)	⊕⊕⊖⊖ LOW [1,3]	downgraded for study limitations and imprecision
	28 per 1000	24 per 1000 (10 to 57)				
	Moderate					
	22 per 1000	20 per 1000 (9 to 46)				
Adverse events: RBC transfusions	Study population		RR 1.56 (0.71 to 3.45)	580 (3)	⊕⊕⊖⊖ LOW [3,4]	downgraded for imprecision and study limitations
	33 per 1000	52 per 1000				

		(23 to 114)				
	Moderate					
	37 per 1000	58 per 1000 (26 to 128)				
Adverse events: hypertension	Study population		RR 0.85 (0.55 to 1.32)	838 (4)	⊕⊕⊕⊖ MODERATE [1]	downgraded for study limitations
	100 per 1000	85 per 1000 (55 to 132)				
	Moderate					
	95 per 1000	81 per 1000 (52 to 126)				
Adverse events: thrombovascular events	Study population		RR 1.41 (0.67 to 3.00)	838 (4)	⊕⊕⊖⊖ LOW [1 3]	downgraded for study limitations and imprecision
	28 per 1000	39 per 1000 (18 to 83)				
	Moderate					
	27 per 1000	38 per 1000 (18 to 80)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **Hb:** haemoglobin; **RBC:** red blood cells

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] allocation concealment unclear in 3 of 4 studies
[2] surrogate outcome
[3] few studies with low numbers and wide confidence
[4] allocation concealment unclear in 2 of 3 studies

Summary of findings 2. Epoetin alfa every four weeks versus with every two weeks in CKD patients not receiving dialysis

Epoetin alfa every four weeks versus with every two weeks in CKD patients not receiving dialysis

Patient or population: anaemia in predialysis patients
Intervention: epoetin alpha every 4 weeks
Comparison: every 2 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with every 2 weeks	Risk with Epoetin alpha every 4 weeks				
Change in Hb level	The mean change in Hb level was 0	The mean change in Hb level in the intervention group was 0.15g/dL lower (0.41 g/dL lower to 0.1g/dL more)	-	671 (3)	⊕⊖⊖⊖ VERY LOW [1 2 3]	downgraded for study limitations, heterogeneity and indirectness
Number reaching target Hb	Study population		RR 0.95 (0.84 to 1.07)	687 (3)	⊕⊖⊖⊖ VERY LOW [1 2 3]	downgraded for study limitations, heterogeneity and indirectness
	916 per 1000	870 per 1000 (769 to 980)				
	Moderate					
	895 per 1000	850 per 1000 (752 to 957)				
Number of deaths	Study population		RR 0.95 (0.33 to 2.75)	724 (3)	⊕⊕⊖⊖ LOW [1 4]	downgraded for study limitations, imprecision
	22 per 1000	21 per 1000 (7 to 62)				
	Moderate					
	26 per 1000	25 per 1000 (9 to 72)				
Adverse events: RBC transfusions	Study population		RR 1.26 (0.53 to 2.98)	470 (2)	⊕⊕⊖⊖ LOW [1 4]	downgraded for study limitations, imprecision
	38 per 1000	48 per 1000 (20 to 114)				

	Moderate					
	35 per 1000	44 per 1000 (18 to 103)				
Adverse events: hypertension	Study population		RR 1.02 (0.62 to 1.69)	724 (3)	⊕⊕⊕⊖ MODERATE [1]	downgraded for study limitations
	70 per 1000	72 per 1000 (44 to 119)				
	Moderate					
	62 per 1000	63 per 1000 (38 to 104)				
Adverse events: arteriovenous complications	Study population		RR 1.02 (0.39 to 2.68)	724 (3)	⊕⊕⊖⊖ LOW [1 4]	downgraded for study limitations, imprecision
	26 per 1000	26 per 1000 (10 to 68)				
	Moderate					
	23 per 1000	24 per 1000 (9 to 62)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **Hb:** haemoglobin; **RBC:** red blood cells

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] two of the three studies had unclear allocation concealment
[2] surrogate outcome
[3] unexplained heterogeneity
[4] small numbers with wide confidence intervals

Summary of findings 3. Epoetin theta versus epoetin beta in CKD patients not receiving dialysis

Epoetin theta versus epoetin beta in CKD patients not receiving dialysis

Patient or population: anaemia in predialysis patients
Intervention: epoetin theta
Comparison: epoetin beta

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with epoetin beta	Risk with Epoetin theta				
Final Hb	The mean final Hb was 0 g/dL	The mean final Hb in the intervention group was 0.02 g/dL lower (0.25 g/dL lower to 0.21 g/dL higher)	-	288 (1)	⊕⊕⊕⊖ MODERATE [1]	downgraded for indirectness - surrogate outcomes
Mean weekly epoetin dose	The mean weekly epoetin dose was 0 units/week	The mean weekly epoetin dose in the intervention group was 0.4 units per week higher (5.68 units per week lower 6.48 units/week higher)	-	288 (1)	⊕⊕⊖⊖ LOW [1 2]	downgraded for indirectness - surrogate outcomes and imprecision
Deaths	Study population		RR 2.46 (0.29 to 20.77)	288 (1)	⊕⊕⊖⊖ LOW [2]	downgraded for imprecision
	11 per 1000	26 per 1000 (3 to 219)				
	Moderate					
	11 per 1000	26 per 1000 (3 to 218)				
Adverse events: hypertension	Study population		RR 0.35 (0.11 to 1.08)	288 (1)	⊕⊕⊕⊖ MODERATE [2]	downgraded for imprecision
	74 per 1000	26 per 1000 (8 to 80)				
	Moderate					
	74 per 1000	26 per 1000 (8 to 80)				
Adverse events: RBC transfusions	Study population		RR 1.48 (0.06 to 36.10)	288 (1)	⊕⊕⊖⊖ LOW [2]	downgraded for imprecision
	0 per 1000	0 per 1000				

		(0 to 0)				
Adverse events: discontinuation of therapy	Study population		RR 1.77 (0.68 to 4.63)	288 (1)	⊕⊕⊖⊖ LOW [2]	downgraded for imprecision
	53 per 1000	93 per 1000 (36 to 244)				
	Moderate					
	53 per 1000	93 per 1000 (36 to 244)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **RBC:** red blood cells

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Surrogate outcome, not a patient-centred outcome
[2] Small numbers, wide confidence intervals

BACKGROUND

Description of the condition

Anaemia is defined as haemoglobin (Hb) levels < 12.0 g/dL and 13.0 g/dL in adult females and males respectively based on the World Health Organization's definition of anaemia (KDIGO 2012; WHO 2011). Anaemia is diagnosed in children with chronic kidney disease (CKD) if Hb concentration is < 11.0 g/dL in children aged from six months to five years, < 11.5 g/dL in children aged five to 12 years, and < 12.0 g/dL in children from 12 to 15 years of age according to the Kidney Disease Improving Global Outcomes guidelines (KDIGO 2012). Anaemia is a known complication of CKD (Dmtrieva 2013) which develops as kidney function declines; prevalence increases as glomerular filtration rate (GFR) falls. CKD stage 3 to 5 is a predictor variable of decline in Hb (Dmtrieva 2013).

Anaemia prevalence ranges from 25% to 70% (Hsu 2002; Koch 1991), and most people with CKD stage 5 (GFR < 15 mL/min/1.73 m^2) are anaemic (Astor 2002). Anaemia related to CKD results in significant morbidity, mortality and increased cardiovascular events, with symptoms including lack of energy, breathlessness, dizziness, angina, poor appetite and decreased exercise tolerance (Canadian EPO 1990; Lundin 1989).

The primary cause of anaemia in CKD is decreased production of the naturally-occurring hormone, erythropoietin (EPO) in the kidney. Anaemia may be exacerbated by concurrent iron deficiency anaemia (KDIGO 2012).

Prior to the availability of recombinant human EPO (rHuEPO), anaemia was managed with blood transfusions together with iron and folate supplements. Cloning of the human gene for EPO was achieved in 1983 (Lin 1985) and production of rHuEPO followed. The efficacy of erythropoiesis-stimulating agents (ESA) treatment in dialysis patients was demonstrated in 1986 (Winearls 1986) and several randomised controlled trials (RCTs) have documented a beneficial effect of ESA treatment in correcting the anaemia of CKD in non-dialysis patients (Cody 2005; Stone 1988).

The increase in Hb levels following treatment with ESA leads to improved energy levels (Wolcott 1989), improved cardiac performance and increased ejection fraction (Pappas 2008) with normalisation of cardiac output and reduced left ventricular mass (Cannella 1990). The benefits of early treatment of anaemia with ESA in predialysis patients include increased exercise capacity, improved quality of life, improved cognitive function and a slower decline in kidney function (Ritz 2000; Roth 1994).

Description of the intervention

Administration of an ESA aims to replace endogenous EPO production, raise Hb levels and alleviate signs and symptoms of anaemia. Epoetin alpha has proven efficacy in treating anaemia in people with CKD (Eschbach 1987). Epoetin alpha has a relatively short half-life and typically is administered twice or thrice weekly (Locatelli 2011). More recently new longer acting ESAs, which can be administered less frequently than short-acting ESAs, have been developed allowing administration of ESA every one to four weeks depending on the preparation used and the individual patient response. Darbepoetin was the first ESA with a prolonged half-life to enter the market enabling administration once a week to four weekly (Macdougall 1999). More recently, the use of the continuous EPO receptor activator (CERA), a pegylated epoetin, has extended dosing intervals to one dose every two to four weeks (Macdougall 2005). ESAs have to be administered intravenously or subcutaneously so the benefits of using ESAs in non-dialysis CKD patients, who will generally receive subcutaneous injections in an outpatient setting, must be balanced against the inconvenience and/or discomfort of injections as well as potential harms of ESAs, which include hypertension, vascular access thrombosis and cardiovascular events. A significant concern in ESA therapy is the Hb target to be achieved. The CHOIR study reported a target Hb level of 13.5 g/dL compared with 11.3 g/dL was associated with increased mortality and cardiovascular risk and no considerable improvement in the quality of life. The study could not provide an explanation for poorer outcomes in patients with a higher target Hb (Singh 2006). Recommendations on when to commence ESA therapy are outlined in the KDIGO guidelines (KDIGO 2012). As the patents for epoetin alpha have expired, cheaper biosimilars of epoetin alpha have been developed. These biological products are highly similar though not identical to reference products and undergo a more limited appraisal before receiving marketing approval. As they are not generic versions of the reference products and could have differences particularly in adverse effects, these products should be submitted to rigorous assessment before marketing and to long term monitoring to ensure that adverse effects are recognised and attributed to the responsible biological preparation (Mikhail 2013; Schellekens 2009).

How the intervention might work

The primary cause of anaemia in CKD is the relative insufficiency of EPO which is mainly produced by peritubular fibroblasts in the kidney. EPO is part of a widespread system of hypoxia-inducible gene expression mediated by hypoxia-inducible transcription factors (HIFs).The factors associated with inadequate EPO production in progressive CKD remain unclear, though recent data indicate a deranged oxygen sensing, in addition to loss of EPO production, is involved (Bernhardt 2010). ESAs accelerate erythropoiesis, increase iron utilisation and raise Hb levels with clinical improvement in signs and symptoms of anaemia and avoidance of blood transfusions. ESA therapy aims to increase Hb levels slowly at a rate of 1 to 2 g/dL per month to correct anaemia. After correction of anaemia, dose adjustment may be necessary to maintain a stable Hb level. Anaemia is corrected slowly with ESA to avoid major side effects including hypertension and thrombotic events. ESA requirements are difficult to predict in individual patients, and may be increased in people with associated co-morbidities including cardiovascular disease, diabetes, chronic inflammation and severe secondary hyperparathyroidism. ESA requirements are generally lower in patients not receiving dialysis. A major issue in ESA use relates to the Hb target to be achieved with increased cardiovascular risk noted with higher Hb targets (Drueke 2006; Singh 2006). Recent systematic reviews have suggested that aiming for Hb levels similar to those seen in healthy adults is associated with a significantly higher risk of mortality due to cardiovascular events, such as stroke and hypertension (Palmer 2010). The mechanisms for these treatment-related harms are poorly understood though observational studies suggest treatment related toxicity secondary to impaired Hb responses and incremental erythropoietin dosing (Szczech 2008). KDIGO guidelines (KDIGO 2012) recommend that in general ESAs should not be used to raise Hb levels > 11.5 g/dL.

Why it is important to do this review

In a previous Cochrane systematic review, which included 15 RCTs, rHuEPO (epoetin alpha) significantly increased Hb (two studies) or haematocrit (HCT) levels (five studies) compared with placebo or no treatment and significantly reduced blood transfusion requirements (Cody 2005). Determining the ESA agent to be used should include assessment of the drug's pharmacodynamics, pharmacokinetics, route and frequency of administration, adverse effects, availability and any economic issues (KDIGO 2012). In most high income countries, the use of short-acting ESAs (epoetin alpha, epoetin beta) in patients with CKD has been superseded by longer acting ESAs (darbepoetin, CERA) because of the reduced frequency of administration. In low income countries where newer longer acting ESAs are less likely to be accessible, clinicians may be limited to use short-acting ESAs. The cost of using newer ESAs agents would have to be balanced against the costs and inconvenience of more frequent administration. Since the efficacy and safety of rHuEPO compared with placebo or no treatment has already been demonstrated (Cody 2005), this review aims to evaluate short-acting ESAs (epoetin alpha, epoetin beta, other epoetins or epoetin biosimilars) in patients, both adults and children with CKD not on dialysis (CKD stages 2 to 5) with reference to route of administration (intravenous versus subcutaneous), frequency of administration, different doses and direct comparisons of different epoetins to provide additional information about the value of these agents for institutions where shorter acting ESAs are used.

This review will not evaluate studies comparing short-acting with longer acting ESAs in CKD, different longer acting ESAs in CKD, different routes of administration in dialysis patients or kidney transplant recipients and different Hb targets as these are subject of other Cochrane published or planned systematic reviews (Hahn 2014; Palmer 2012; Palmer 2014a; Palmer 2014b; Strippoli 2006).

OBJECTIVES

This review aimed to evaluate the benefits and harms of different routes, frequencies and doses of epoetins (epoetin alpha, epoetin beta and other short-acting epoetins) for anaemia in adults and children with CKD not receiving dialysis.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at epoetins (short-acting ESAs) for treatment of anaemia in patients with CKD not on dialysis.

Types of participants

Inclusion criteria

Patients of any age (adults and children) with anaemia due to CKD (stages 2 to 5) of any severity, who were not receiving dialysis, were included. The definitions of CKD and anaemia used in individual studies were used in this review.

Exclusion criteria

Patients of any age receiving dialysis treatment. Patients receiving long-acting ESAs or included in studies comparing shorter with longer acting ESAs were excluded. Kidney transplant recipients were also excluded.

Types of interventions

- Short-acting ESAs including epoetins alpha (Eprex®, Procrit®, Epogen®), beta (Recormin®), delta (Dynepo®), epoetin theta (Biopoin®) and biosimilars of epoetin alpha (HX575, EPO- hexal®, Abseamed®), epoetin zeta (Silapo®, Retacrit®, Epoetin Hospira®)
- Short-acting ESAs including epoetins with different routes of administration
- Short-acting ESAs including epoetins used at different frequencies of administration
- Short-acting ESAs including epoetins used at different doses
- Head-to-head comparisons of different short-acting ESAs.

Types of outcome measures

Primary outcomes

1. Death
   - All-cause mortality
   - Mortality due to cardiac disease or cerebrovascular events
2. Measures of correction of anaemia
   - Values of Hb/HCT or change in Hb/HCT at the end of the study
3. Quality of life.

Secondary outcomes

1. Hypertension and blood pressure outcomes
   - Hypertension (number of patients presenting one or more episodes of hypertension)
   - Systolic blood pressure at end of treatment (mm Hg)
   - Diastolic blood pressure at end of treatment (mm Hg).
2. Cardiovascular morbidity
3. Cerebrovascular morbidity
4. Adverse effects
   - Number needing blood transfusion
   - Thrombotic events
   - Number ceasing ESA for adverse effects
   - Number of patients requiring hospitalisations for any cause
   - Number of patients developing antibody-mediated pure red cell aplasia
   - Number of patients developing a malignancy.
5. Kidney function measures (GFR, serum creatinine (SCr), doubling of SCr) as reported by the authors of primary studies
6. Need for iron supplementation.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register up to 12 September 2016 through contact with the Information Specialist 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 were identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of 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 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

The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable; however studies and reviews that might have included relevant data or information on studies were retained initially. Two authors independently assessed the retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by at least two authors using standard data extraction forms. Where there was more than one publication of a study, reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions these data were used. Any discrepancy between published versions was highlighted.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- 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)?
- Were 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

For dichotomous outcomes (e.g. all-cause mortality, adverse events, number needing transfusions) results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (e.g. final Hb/HCT or change in Hb/HCT, blood pressure, SCr), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales had been used.

Unit of analysis issues

We included only data from the first period of treatment in cross-over studies (Higgins 2011). Data expressed in different metrics were analysed using SMD.

Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing corresponding authors) and any relevant information obtained in this manner was included in the review. We aimed to analyse available data in meta-analyses using intention-to-treat (ITT) data. However, where only ITT data were available graphically or were not provided and additional information could not be obtained from the study authors, per-protocol (PP) data was used in analyses.

We imputed a change-from-baseline standard deviation using an imputed correlation coefficient when sufficient data were available.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

The search strategy applied aimed to reduce publication bias caused by lack of publication of studies with negative results. We investigated for publication bias using funnel plots if there were sufficient studies of each comparison (Higgins 2011).

Data synthesis

Data were summarised using the random-effects model but the fixed-effect model was also used to ensure robustness of the model chosen. We qualitatively summarised data where insufficient data were available for meta-analysis. Where there were multiple publications of the same study, all reports were reviewed to ensure that all details of methods and results were included. Qualitative review was conducted for adverse events and quality of life outcomes.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity (participants, interventions and study quality). Heterogeneity among participants could be related to age (adult versus children) or stage of CKD. Heterogeneity in interventions could be related to dose, duration or frequency of rHuEPO treatment or to the route of administration. . Where possible, the risk ratio with 95% CI was calculated for each adverse effect, either compared to no treatment or to another agent.

Sensitivity analysis

Sensitivity analyses tested decisions where inclusion of a study may have altered the results of the meta-analysis. In particular, sensitivity analysis may be used to test decisions where ITT and PP data were included in the same analyses.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We presented the following outcomes in the 'Summary of findings' tables.

- Epoetin alpha every 2 weeks compared to weekly for anaemia in CKD patients not receiving dialysis (Summary of findings for the main comparison)
  - Final or change in Hb level (g/dL)
  - Number reaching target Hb
  - Number of deaths
  - Number with adverse events: red blood cell transfusions, hypertension, thrombovascular events
- Epoetin alfa every four weeks compared with every two weeks in CKD patients not receiving dialysis (Summary of findings 2)
  - Final or change in Hb level (g/dL)
  - Number reaching target Hb
  - Number of deaths
  - Number with adverse events: red blood cell transfusions, hypertension, thrombovascular events
- Epoetin theta versus epoetin beta (Summary of findings 3)
  - Final Hb (g/dL)
  - Mean weekly epoetin dose (U/kg)
  - Number of deaths
  - Number with adverse events: hypertension, red blood cell transfusions, discontinuation of therapy.

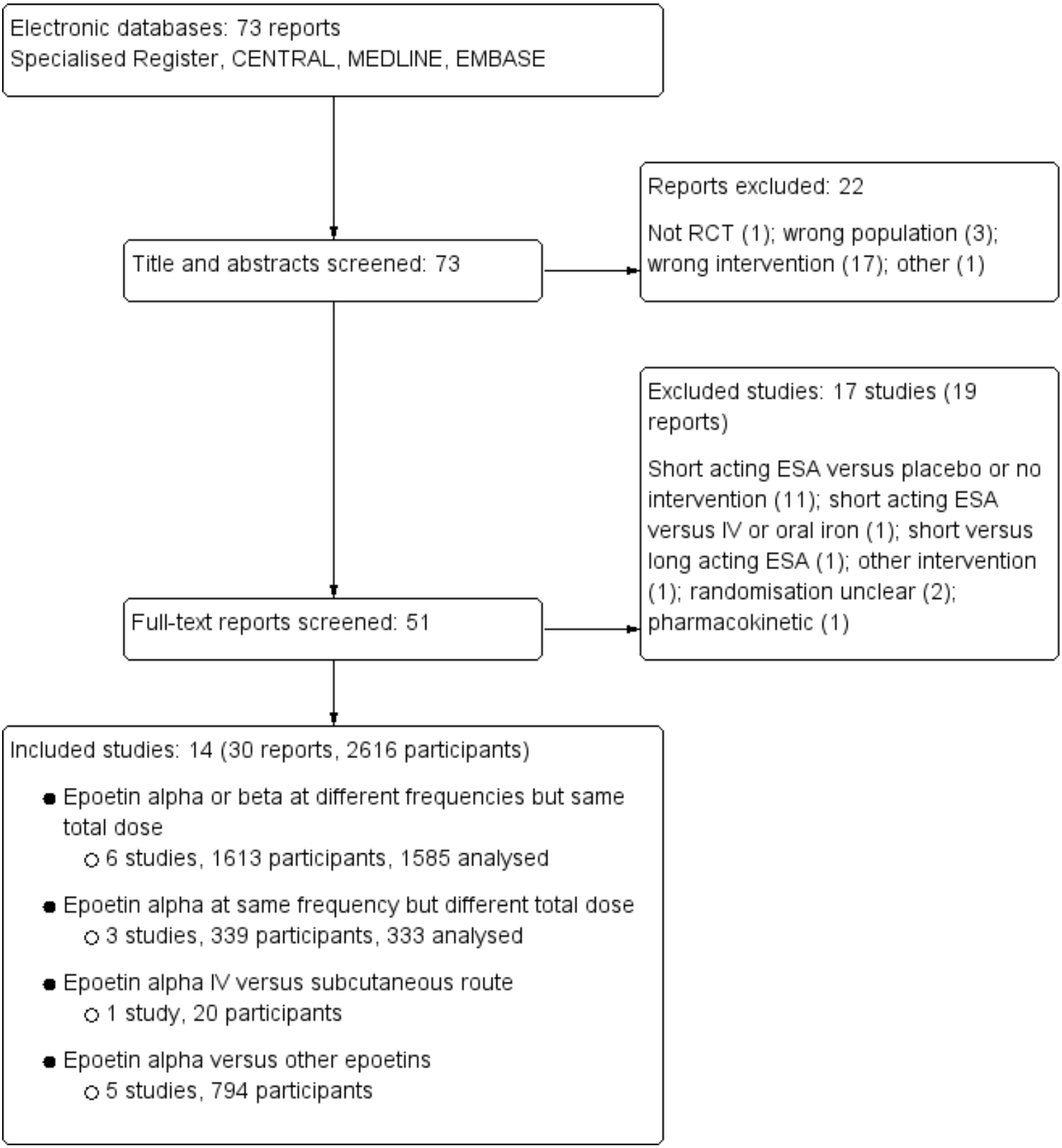
RESULTS

Description of studies

Results of the search

Seventy-three reports were identified from the search to 12 September 2016. After title and abstract screening 22 reports were excluded. Full-text review was carried out the remaining 51 reports. Fourteen studies (30 reports) (Aggarwal 2002; Akiba 1992; Amon 1992; Frenken 1989; Gertz 2012; Haag-Weber 2012; Knebel 2008; Kronborg 1994; Mignon 2000; Pergola 2009; Pergola 2010; PROMPT Study 2005; Sohmiya 1998; Spinowitz 2008) were included and 17 studies (19 reports) (Brown 1988; Clyne 1992; Duliege 2005; Furukawa 1992; Li 2004; Meloni 2003; NCT00240734; NCT00492427; NCT00563355; Patel 2012; Schwartz 1989; Shaheen 1983; Singh 1999; Teehan 1990; Teplan 1995; Yamazaki 1993; Zheng 1992) were excluded. Two recently completed studies (NCT01576341; NCT01693029) will be assessed in a future update of this review (Figure 1).

Figure 1. Study flow diagram.



Included studies

The 14 studies were divided into four treatment comparisons groups (Figure 1).

Epoetin alpha or beta administered at different frequencies using the same total dose

Six studies (Amon 1992; Pergola 2009; Pergola 2010; PROMPT Study 2005; Sohmiya 1998; Spinowitz 2008) (1613 enrolled/1585 evaluated participants) compared epoetin alpha or beta at different frequencies using the same total dose in each group.

- Four studies (Pergola 2009; Pergola 2010; PROMPT Study 2005; Spinowitz 2008) with 840 enrolled (838 analysed) participants compared epoetin alpha administered at 10,000IU per week with 20,000IU given every two weeks.
- Three studies (Pergola 2010; PROMPT Study 2005; Spinowitz 2008) with 724 analysed participants also compared epoetin alpha administered at 20,000 IU every two weeks with 40,000 IU every four weeks.
- Amon 1992 (22 enrolled, 18 evaluated) compared subcutaneous epoetin alpha 50 IU/kg three times a week with 150 IU/kg given once weekly in children.
- Sohmiya 1998 (5 enrolled, 5 evaluated) compared continuous infusion of epoetin beta with weekly subcutaneous injections for four weeks using the same total dose in each group in a cross over study.

Epoetin alpha administered at the same frequency using different total doses

Three studies (Akiba 1992; Frenken 1989; Spinowitz 2008) (339 enrolled/333 analysed participants) compared epoetin alpha at different doses but at the same frequencies.

- Spinowitz 2008 (150 enrolled/144 evaluated) compared 20,000 IU given four weekly with 40 000IU given four weekly
- Akiba 1992 (165 enrolled and evaluated) compared 3000 IU, 6000 IU and 12 000 IU given weekly to three groups
- Frenken 1989 (24 enrolled and evaluated) compared 50 IU/Kg, 100 IU/kg and 150 IU/Kg given three times weekly.

Epoetin alpha intravenous versus subcutaneous administration

- Aggarwal 2002 (20 participants enrolled and evaluated) compared subcutaneous with intravenous administration of epoetin alpha.

Epoetin alpha or beta versus other epoetins or biosimilars of epoetin alpha

Five studies Gertz 2012; Haag-Weber 2012; Knebel 2008;Kronborg 1994; Mignon 2000) (794 participants) were included in this comparison.

- Gertz 2012 (288 enrolled and evaluated) compared weekly subcutaneous epoetin theta with epoetin beta
- Haag-Weber 2012 (337 enrolled) compared a bio-similar HX575 epoetin alpha with epoetin alpha (Eprex). This study was terminated due to the development of neutralising antibodies in two patients receiving subcutaneous HX575. Efficacy could not be assessed because the authors did not provide the number of patients, who contributed data to efficacy endpoints. Limited safety data were available.
- Two studies (Mignon 2000, Knebel 2008) (140 enrolled) compared subcutaneous administration of epoetin delta with epoetin alpha. Both studies were terminated before completion when the pharmaceutical company ceased production of epoetin delta for commercial reasons and no data were available.
- Kronborg 1994 (29 enrolled and evaluated) compared pain scores in participants treated with epoetin alpha or epoetin beta given subcutaneously using a visual analogue scale (VAS) and a verbal descriptive scale (VDS). As the results included a median with inter-quartile ranges the data could not be included in a meta-analysis.

Excluded studies

Seventeen studies were excluded. Eleven studies were ineligible as they compared a short-acting ESA with placebo or no treatment (Brown 1988; Clyne 1992; Meloni 2003; NCT00240734; NCT00563355; Patel 2012; Schwartz 1989; Shaheen 1983; Singh 1999; Teehan 1990; Teplan 1995). NCT00492427 compared short-acting ESA with the long acting ESA, darbepoetin and this study is included in another review (Palmer 2014b). Three studies assessed other interventions, or were pharmacokinetic studies (Duliege 2005; Furukawa 1992; Li 2004). Randomisation was unclear in two studies (Yamazaki 1993; Zheng 1992).

Risk of bias in included studies

The results of the risk of bias assessment are shown in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

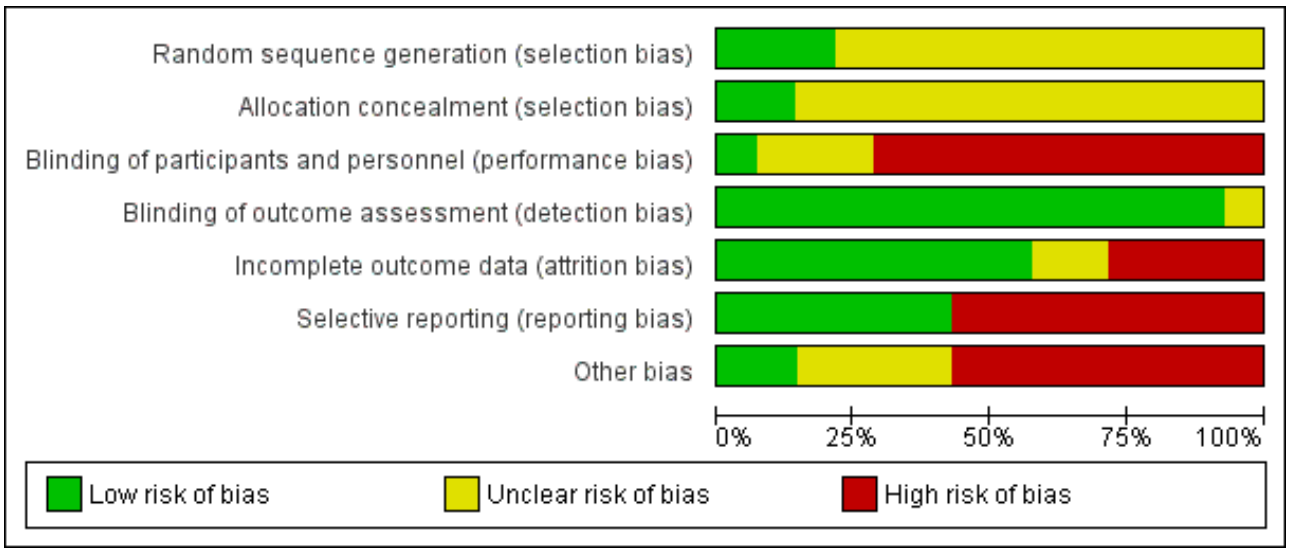


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

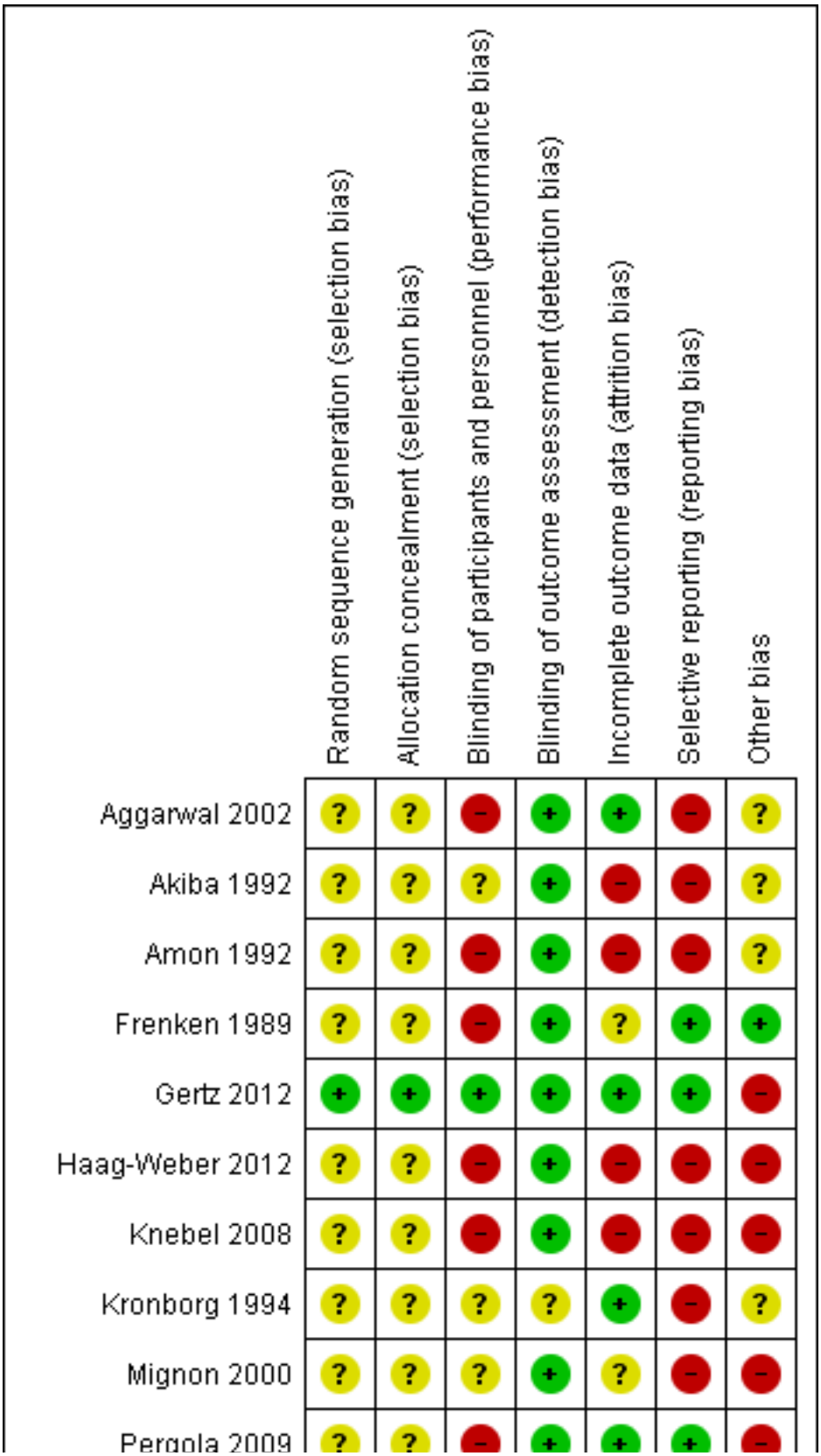
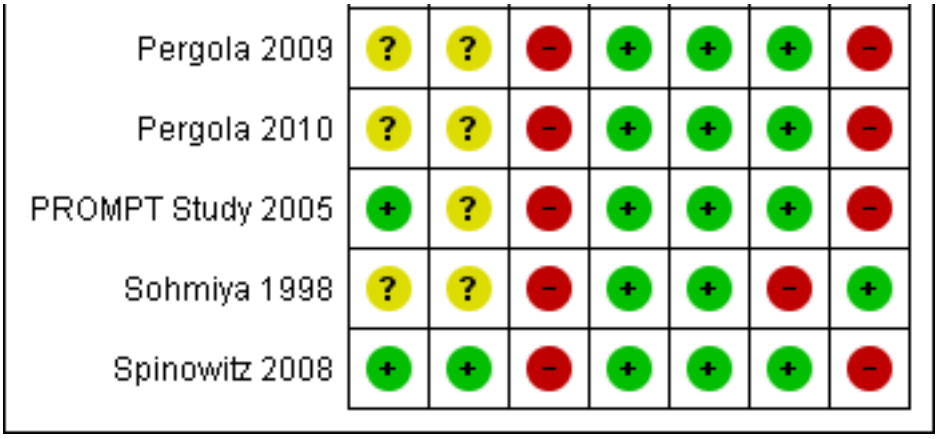


Figure 3. (Continued)



Allocation

Sequence generation was deemed at low risk of bias in three studies (Gertz 2012; PROMPT Study 2005; Spinowitz 2008) and unclear in the remaining eleven studies (Aggarwal 2002; Akiba 1992; Amon 1992; Frenken 1989; Haag-Weber 2012; Knebel 2008; Kronborg 1994; Mignon 2000; Pergola 2009; Pergola 2010; Sohmiya 1998).

Allocation concealment was at low risk of bias in two studies (Gertz 2012; Spinowitz 2008) and unclear in the remaining twelve studies (Aggarwal 2002; Akiba 1992; Amon 1992; Frenken 1989; Haag-Weber 2012; Knebel 2008; Kronborg 1994; Mignon 2000; Pergola 2009; Pergola 2010; PROMPT Study 2005; Sohmiya 1998).

Blinding

Only one study (Gertz 2012) was blinded and considered to be at low risk of bias for performance bias. Ten studies were not blinded and determined as high risk of performance bias (Aggarwal 2002; Amon 1992; Frenken 1989; Haag-Weber 2012; Knebel 2008; Pergola 2009; Pergola 2010; PROMPT Study 2005; Sohmiya 1998; Spinowitz 2008). Blinding was unclear in the remaining three studies (Akiba 1992; Kronborg 1994; Mignon 2000).

As the primary outcomes (final Hb level or change in Hb level) in all studies were based on laboratory assessment, and therefore unlikely to be influenced by blinding, 13 studies were deemed to be at low risk of detection bias. The study by Kronborg 1994 was considered at unclear risk of detection bias; it assessed pain scores and was said to be double-blinded though no information was provided as to how this was performed.

Incomplete outcome data

Eight studies were determined to be at low risk of attrition bias (Aggarwal 2002; Gertz 2012; Kronborg 1994; Pergola 2009; Pergola 2010; PROMPT Study 2005; Sohmiya 1998; Spinowitz 2008). Four studies were at high risk of bias because meta-analyses could not be performed as total patient numbers were not provided (Akiba 1992; Haag-Weber 2012; Knebel 2008) or because more than 10% patients were excluded from analysis (Amon 1992). Attrition bias was deemed unclear in the remaining two studies (Frenken 1989; Mignon 2000).

Selective reporting

Studies that did not provide data on final or change in Hb and on patient-centred outcomes including adverse events such as blood transfusions, vascular access complications or all-cause mortality were considered to be at high risk for selective reporting. Eight studies were considered at high risk of reporting bias (Aggarwal 2002; Akiba 1992; Amon 1992; Haag-Weber 2012; Knebel 2008; Kronborg 1994; Mignon 2000; Sohmiya 1998). Six studies (Amon 1992; Gertz 2012; Pergola 2009; Pergola 2010; PROMPT Study 2005; Spinowitz 2008) were assessed at low risk for selective reporting.

Other potential sources of bias

Only two studies were assessed at free of other potential bias sources (Frenken 1989; Sohmiya 1998). Eight studies were industry funded and determined as at high risk of bias (Gertz 2012; Haag-Weber 2012; Knebel 2008; Mignon 2000; Pergola 2009; Pergola 2010; PROMPT Study 2005; Spinowitz 2008). In the remaining four studies it was unclear whether the study was free of other potential sources of bias (Aggarwal 2002; Akiba 1992; Amon 1992; Kronborg 1994).

Effects of interventions

See: **Summary of findings for the main comparison** Epoetin alpha every 2 weeks versus to weekly for anaemia in CKD patients not receiving dialysis; **Summary of findings 2** Epoetin alfa every four weeks versus with every two weeks in CKD patients not receiving dialysis; **Summary of findings 3** Epoetin theta versus epoetin beta in CKD patients not receiving dialysis

Epoetin alpha administered at different frequencies using the same total dose

Six studies investigated this comparison (Amon 1992; Pergola 2009; Pergola 2010; PROMPT Study 2005; Sohmiya 1998; Spinowitz 2008).

Epoetin alpha weekly versus every two weeks using same total dose of epoetin

In meta-analyses of four non-inferiority studies (Pergola 2009; Pergola 2010; PROMPT Study 2005; Spinowitz 2008), final Hb levels (Analysis 1.1 (4 studies, 785 participants): MD -0.20 g/dL, 95% CI -0.33 to -0.07) and the number achieving target Hb were statistically significantly higher in patients receiving weekly doses compared with two weekly doses (Analysis 1.2 (4 studies, 798 participants): RR

0.96, 95% CI 0.93 to 0.99). The differences were not considered to be clinically significant. No significant heterogeneity was noted.

There were no significant difference in all-cause mortality (Analysis 1.3 (4 studies, 838 participants): RR 0.89, 95% CI 0.38 to 2.07), the number requiring transfusion (Analysis 1.4.1 (3 studies, 580 participants): RR 1.56, 95% CI 0.71 to 3.45), the number with hypertension (Analysis 1.4.2 (4 studies, 838 participants): RR 0.85, 95% CI 0.55 to 1.32), the number with thrombovascular complications Analysis 1.4.3 (4 studies, 838 participants): RR 1.41, 95% CI 0.67 to 3.00) or the number discontinuing therapy due to adverse effects (Analysis 1.4.4 (1 study, 258 participants): RR 0.98, 95% CI 0.20 to 4.79).

No neutralising antibodies were detected in study participants in Pergola 2009 and Pergola 2010. Most of the deaths were due to cardiovascular complications reflecting the underlying cardiovascular morbidity of the population studied. Only one study (PROMPT Study 2005) performed quality of life (QOL) assessments and reported no statistical differences in the final QOL scores between groups receiving epoetin once weekly or two weekly.

Epoetin alpha every two weeks versus every four weeks using same total dose of epoetin

In meta-analyses of three non-inferiority studies (Pergola 2010; PROMPT Study 2005; Spinowitz 2008), there were no significant differences in final Hb levels (Analysis 2.1 (3 studies, 671 participants): MD -0.16 g/dL, 95% CI -0.43 to 0.10; I^2 = 63%) or in the number reaching target Hb levels (Analysis 2.2 (3 studies, 687 participants): RR 0.95, 95% CI 0.84 to 1.07) with dosing every two weeks compared with every four weeks. There was unexplained marked heterogeneity between these studies.

There were no significant differences in all-cause mortality (Analysis 2.3 (3 studies, 724 participants): RR 0.95, 95% CI 0.33 to 2.75), the number requiring transfusions (Analysis 2.4.I (2 studies, 470 participants): RR 1.26, 95% CI 0.53 to 2.98); the number with hypertension (Analysis 2.4.2 (3 studies, 724 participants): RR 1.02, 95% CI 0.62 to 1.69); and the number with thrombovascular complications (Analysis 2.4.3 (3 studies, 724 participants): RR 1.02, 95% CI 0.39 to 2.68). PROMPT Study 2005 noted no difference in final QOL scores between participants who received epoetins at two weekly or four weekly intervals.

Other studies

Amon 1992 found that the time to reach a Hb level greater than 11.5 g/dL were significantly longer with weekly administration (15.6 weeks) compared with thrice weekly administration (9.3 weeks). Adverse effects were uncommon and did not differ between groups and there was no deterioration in glomerular filtration rate across the two groups. However there was no significant difference in mean dose/week to sustain Hb levels between different frequencies of administration.

Sohmiya 1998 in a cross-over study found that continuous subcutaneous infusion of epoetin beta resulted in a significantly greater increase in Hb levels compared with weekly subcutaneous injections (2.56 ± 0.77 g/dL versus 0.28 ± 0.62 g/dL, P < 0.05)

Epoetin alpha administered at same frequency using different total doses

Three studies reported on this comparison (Akiba 1992; Frenken 1989; Spinowitz 2008)

Epoetin alpha different doses given three times weekly

Frenken 1989 reported no statistical significance in the final Hb in groups which received 100 IU/kg/dose (Analysis 3.1.1 (1 study, 16 participants): MD 0.70 g/dL, 95% CI -0.78 to 2.18) or 150 IU/kg/dose (Analysis 3.1.2 (1 study, 16 participants): MD 1.00 g/dL, 95% CI -0.18 to 2.18) compared with 50 IU/kg/dose. Final mean arterial blood pressures and serum creatinine levels did not differ between subgroups (Analysis 3.2; Analysis 3.3). No anti-erythropoietin antibodies were detected in the study participants. The study reported overall improvement in well-being in all participants receiving epoetin.

Epoetin alpha different doses given every four weeks

Spinowitz 2008 reported no significant difference in the final Hb level (Analysis 4.1 (1 study, 144 participants): MD 0.17 g/dL 95% CI -0.19 to 0.53) and the number reaching target Hb (Analysis 4.2 (1 study, 144 participants): RR 1.07, 95% CI 0.92 to 1.24) when epoetin alpha was administered at 20,000 U compared with 40,000 U every four weeks. There was no significant difference in all-cause mortality (Analysis 4.3.1), the number with hypertension (Analysis 4.4.1), thrombovascular complications (Analysis 4.4.2) or number of patients requiring transfusions (Analysis 4.4.3).

Epoetin alpha different doses given every week

Akiba 1992 reported that 6000 IU and 12,000 IU given weekly increased HCT levels more than 3000 IU/week. No standard deviations were provided.

Epoetin alpha intravenous versus subcutaneous administration

Aggarwal 2002 reported no significant difference in final Hb at 12 weeks (Analysis 5.1 (20 participants): MD -0.99 g/dL, 95% CI -2.08 to 0.10) between intravenous and subcutaneous administration of epoetin alpha.

Epoetin alpha versus other epoetins or biosimilars

Five studies compared epoetin alpha with other epoetins or biosimilars.

Gertz 2012 found no significant differences in final Hb (Analysis 6.1 (288 participants): MD -0.02 g/dL, 95% CI -0.25 to 0.21) and weekly epoetin doses (Analysis 6.2 (288 participants) MD 0.40 U/kg, 95% CI -5.68 to 6.48) between epoetin theta and epoetin beta. No significant differences were noted in all-cause mortality (Analysis 6.3 (288 participants): RR 2.46, 95% CI 0.29 to 20.77), hypertension (Analysis 6.4.1 (288 participants): RR 0.35, 95% CI 0.11 to 1.08); transfusions (Analysis 6.4.2 (288 participants): RR 1.48, 95% CI 0.06 to 36.10) and discontinuation of therapy (Analysis 6.4.3 (288 participants): RR 1.77, 95% CI 0.68 to 4.63). No neutralising antibodies were noted in either intervention group. Most of the deaths were due to cardiovascular complications reflecting the population studied.

The quality of this single study was assessed as moderate for the surrogate outcome of final Hb but as low for mean weekly

epoetin dose because of imprecision (Summary of findings 3). The quality of evidence for patient-centred outcomes was assessed as low for all-cause mortality, need for blood transfusion and discontinuation of medications and moderate for hypertension because of imprecision due to small numbers of events

Haag-Weber 2012 (337 participants) compared the biosimilar HX575 epoetin alpha with epoetin alpha; both medications were administered subcutaneously. The study was ceased when two patients receiving HX575 developed antibodies to epoetin and pure red cell aplasia and HX575 epoetin alpha was withdrawn for subcutaneous administration. The change in Hb from baseline at 13 weeks did not differ between groups (HX575 2.2 ± 0.9 g/dL; epoetin alpha 2.2 ± 1.0 g/dL) but the data could not be included in meta-analyses since no denominators were provided and information could not be obtained from the authors.

Mignon 2000 (65 participants) found no significant differences in response between epoetin delta and epoetin alpha when both were given at the same dose (50 IU/kg/wk). Adverse events were similar between epoetin delta and epoetin alpha. No data were available from Knebel 2008 (60 participants). Since epoetin delta production was ceased for commercial reasons and no information could be obtained from the pharmaceutical company, no meta-analyses were performed.

Kronborg 1994 (29 participants) found that pain scores were higher in participants treated with subcutaneous epoetin alpha compared with epoetin beta. The results were provided as median with inter-quartile ranges so could not be included in a meta-analysis.

Other outcomes

From the available studies, we were not able to analyse the outcomes of causes of death, cardiovascular and cerebrovascular morbidity, kidney function, number of hospitalisations, additional requirement for IV iron, serious infections, or de novo malignancies.

DISCUSSION

Summary of main results

Fourteen studies (30 reports) with 2616 participants were included in this review, which evaluated the efficacy and safety of short-acting ESAs in CKD patients, not requiring dialysis.

Six studies (1613 enrolled participants) compared epoetin alpha or epoetin beta at different frequencies using the same total dose in each group, with two studies having insufficient data for inclusion in meta-analyses. Among four studies, no significant differences in end of study Hb, in the number of participants achieving target Hb, in all-cause mortality or in adverse effects were identified when dosing every two weeks was compared with weekly dosing or when four weekly dosing was compared with two weekly dosing. These data suggest that larger doses of short-acting epoetins given less frequently can be administered to CKD patients not requiring dialysis without a loss of efficacy or an increase in adverse effects. However this conclusion is based on low quality evidence (Summary of findings for the main comparison; Summary of findings 2). Three studies (including Spinowitz 2008, in which different frequencies were also evaluated) compared different total doses of epoetin alpha given at the same frequency though data from only two studies could be included in meta-analyses. Both studies found no significant difference in final Hb or adverse effects with different total doses.

The remaining five studies evaluated different interventions. One study (288 participants) compared epoetin theta with epoetin alpha and found no significant differences in efficacy or adverse effects. Two studies (125 participants) compared epoetin delta with epoetin alpha. However no results were available since the pharmaceutical company withdrew epoetin delta for commercial reasons. The fourth study was terminated before completion after two patients receiving the biosimilar epoetin, HX575 epoetin alpha, developed anti-epoetin antibodies and pure red cell aplasia. The fifth study found significantly higher pain scores with subcutaneous epoetin alpha compared with epoetin beta.

Overall completeness and applicability of evidence

For this review we were only able to identify 14 studies (2616 participants), which evaluated different frequencies, doses or routes of administration of the same epoetins or compared different epoetins in pre-dialysis patients. Only seven studies contributed data to meta-analyses with two of these studies enrolling only 20 and 24 patients respectively. Two studies evaluated children and neither had sufficient data for inclusion in meta-analyses. Two studies were terminated before completion without available data when the pharmaceutical company ceased production of epoetin delta for commercial reasons. One study was terminated when two patients developed antibody mediated pure red cell aplasia with HX575 epoetin alpha, a biosimilar epoetin. No studies in pre-dialysis patients were identified, which evaluated HX575 epoetin alpha, given intravenously, or of SB309 (epoetin zeta) given intravenously or subcutaneously. These biosimilar epoetins are approved for use by the European Medicines Agency. Preliminary information indicates that SB309 (epoetin zeta, Epoetin Hospira®) has not been approved for use in the USA (Big Molecule Watch Blog 2015).

Patient-centred outcomes were generally poorly reported. Only one study reported on a quality of life assessment with no differences identified in end of study quality of life scores between different frequencies of epoetin alpha administration (PROMPT Study 2005). Six studies reported on all-cause mortality. Data on hypertension and thrombovascular events, adverse effects known to be associated with epoetin administration, could be included in meta-analyses from only five studies. Data from four studies on the number of participants, requiring blood transfusions, could be included in meta-analyses. Anti-erythropoietin antibodies, which can cause pure red cell aplasia, were assessed In only five studies.

Quality of the evidence

Of the fourteen studies included in this review, four studies were available in abstract format only.

Only three of 14 studies demonstrated adequate random sequence generation, with only two studies assessed as showing low risk of bias for allocation concealment. Blinding of participants and personnel was at low risk of bias in one study only. Blinding of outcome assessment was judged at low risk in 13 studies as the outcome measures were laboratory based. Attrition and reporting bias were at low risk of bias in eight and seven studies respectively (Figure 3).

Only five of 14 studies could be included in the Summary of Findings tables as other comparisons included single small studies only or data which could not be included in the meta-analyses. Overall the quality of the studies (GRADE 2011a; GRADE 2011b) included in meta-analyses was assessed as low indicating that our confidence in the results is significantly reduced because of poor study quality and the use of surrogate outcomes as the primary outcomes of the included studies.

The quality of the studies included in meta-analyses comparing epoetin alpha every two weeks with weekly administration (Summary of findings for the main comparison) and in meta-analyses comparing epoetin alpha every four weeks with two weekly administration (Summary of findings 2) for the efficacy outcomes of change in Hb level and number reaching target Hb were assessed as low or very low. These were down-graded for indirectness on the GRADE profile, since these were surrogate outcomes and not patient-centred outcomes. In the comparison of epoetin alpha given every four weeks compared with every two weeks, the results were further downgraded because of marked unexplained heterogeneity. In addition the quality of the evidence for efficacy was downgraded because of poor study design and/or reporting particularly of sequence generation and allocation concealment and for imprecision, where small numbers of events resulted in wide confidence intervals. Outcomes for adverse effects were downgraded because of poor study design and imprecision.

The quality of the single study included in meta-analyses comparing epoetin theta with epoetin beta was assessed as moderate for the surrogate outcome of final Hb but as low for mean weekly epoetin dose because of imprecision (Summary of findings 3). The quality of evidence for patient-centred outcomes was assessed as low for all-cause mortality, need for blood transfusion and discontinuation of medications and moderate for hypertension because of imprecision due to small numbers of events.

Potential biases in the review process

For this review a comprehensive search of the Cochrane Kidney and Transplant's Specialised Register was performed, which reduced the likelihood that eligible published studies were omitted from the review. Eligible studies published after the last search date of 12 September 2016 or published in congress proceedings not routinely searched could have been missed. Four studies were only available in abstract form which provided limited information on study methods and results. Inclusion of these studies could be a source of bias.

The review was completed independently by at least three authors, who participated in all steps of the review. This limited the risk of errors in determining study eligibility, data extraction, risk of bias assessment and data synthesis.

Many of the earlier epoetin alpha studies were small with incomplete information on study methods and results. Further information could not be obtained about these studies from investigators or the literature.

Although six of the included studies were sponsored by pharmaceutical companies, these were multi-centre studies and so were able to attract larger patient numbers. In two of these studies per-protocol data were included in meta-analyses for the primary outcomes of final Hb or change in Hb, since ITT data were only presented graphically. In both studies the authors reported that sensitivity analyses using ITT populations were consistent with those from the per-protocol populations, thus increasing confidence in the findings.

Agreements and disagreements with other studies or reviews

No evidence was identified by the KDIGO working group to suggest that any given type of ESA was superior to another in terms of efficacy and safety (KDIGO 2012). The Working Group suggested ESA choice was dependent on patient and country specific issues including availability, cost and treatment setting. The NICE guidelines 2015 (NICE 2015) suggest the choice of ESA should be discussed with the patient with anaemia and CKD when initiating the patient on treatment, taking into consideration the route of administration and the local availability of ESA. There is no evidence to distinguish between ESAs in term of efficacy. The findings of this systematic review confirm these recommendations.

The findings of this review complement other Cochrane Kidney and Transplant reviews of ESA including an updated review comparing epoetin in pre-dialysis patients with placebo or no specific treatment (Cody 2016), a review evaluating the benefits and harms of different Hb or HCT targets in CKD patients receiving ESA treatment for anaemia (Strippoli 2006), a review evaluating darbepoetin (Palmer 2014b) and a network meta-analysis of studies of any ESA formulation (Palmer 2014a). While ESAs clearly reduce the need for blood transfusion, no systematic review to date has found clear evidence for the superiority of any ESA formulation over any other formulation based on available efficacy and safety data.

For consumers, clinicians and funders, considerations such as drug cost, availability and preferences for dosing frequency should be considered as the basis for individualising anaemia care due to lack of data for comparative differences in the clinical benefits and harms of different ESA preparations.

AUTHORS' CONCLUSIONS

Implications for practice

A previous review identified that epoetin alpha was effective compared with placebo or no treatment in raising Hb levels without a significant reduction in GFR in patients with CKD not on dialysis (Cody 2016). Our review extends these observations to show that epoetin alpha given at higher doses for extended intervals is non-inferior to more frequent dosing intervals. The benefits offered by the extended dosing intervals include convenience for the patients and healthcare providers and may also result in cost efficiency. This may be of benefit in countries with more limited resources and access to longer acting more costly ESAs. However the data are of low quality so that differences in efficacy and adverse effects cannot be completely excluded. We did not identify any studies which evaluated different frequencies of epoetin beta. In a single study, epoetin theta did not differ significantly from epoetin beta in haematological outcomes or adverse effects.

We only identified one study in predialysis patients comparing a biosimilar preparation of epoetin alpha (HX575 epoetin alpha, Binocrit®) in non-dialysis patients and this study was terminated because of the development of pure red cell aplasia with neutralising antibodies (Haag-Weber 2012). HX575 epoetin alpha

and a second biosimilar of epoetin alpha (epoetin zeta, Retacrit®) received marketing authorization throughout the European Union in 2007; HX575 epoetin alpha is limited to intravenous use. Because the safety record of these compounds is limited compared with epoetin alpha and epoetin beta, the ERBP Work Group recommends stringent pharmacovigilance for biosimilars of epoetin alpha (ERBP 2009). Two clinical studies evaluating the biosimilar HX575 epoetin alpha in the USA have been completed (NCT01693029a, NCT01576341a) but the results are not yet available. Of these one (NCT01576341a) evaluated subcutaneous administration of HX575 epoetin alpha in predialysis patients in a single arm study aiming to determine efficacy, adverse effects and the incidence of anti-epoetin antibodies. The uptake in the nephrology community of the biosimilar ESAs will ultimately depend on the balance between cost savings and residual concerns regarding safety (Mikhail 2013; Schellekens 2009).

Implications for research

As noted in earlier ESA reviews (Hahn 2014; Strippoli 2006) the reporting of treatment effects of ESAs on potentially important patient outcomes is heterogeneous and poor, thereby limiting a good understanding of how ESA therapy affects the way patients feel and function. Currently decisions regarding different agents in clinical practice are dictated by physician and patient preference, drug cost and availability since we have inconclusive evidence of the effects of different short-acting ESAs or of different frequencies of ESA administration on survival and quality of life. Data regarding effectiveness and safety when treating children with ESAs remains limited.

Therefore additional large, well designed, randomised studies are required in the following areas to compare larger doses of the shorter acting ESAs including new biosimilars of epoetin alpha administered less frequently with more frequent dosing in both children and adults with CKD not on dialysis. These studies should include patient-centred outcomes including all-cause mortality, cardiovascular mortality and morbidity, and quality of life assessment. Estimates of patient and carer satisfaction related to different frequencies of administration should be included. Studies of cost-effectiveness of different frequencies of administration should also be undertaken.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aggarwal 2002

Methods	• Study design: RCT • Study duration: not reported • Duration of follow-up: 3 months
Participants	• Country: India • Setting: Single centre, Nephrology outpatient clinic • Adults, pre-dialysis (SCr ≥ 2 mg/dL), anaemia (Hb 5 to 8 g/dL) • Number: 20 • Mean age ± SD (years): treatment group 1 (43.2 ± 16.1); treatment group 2 (47.32 ± 20.4) • Sex (M/F): 12/8 • Exclusion criteria: uncontrolled hypertension; coronary artery disease; chronic infections; chronic bleeding; androgen therapy
Interventions	Treatment group 1 • Epoetin alpha: 2000 IU SC in 1 mL pre-filled syringe 3 times/week for 4 weeks then twice weekly for 1 month then fortnightly for 1 month Treatment group 2 • Epoetin alpha: 2000 IU IV in 1 mL pre-filled syringe 3 times/week for 4 weeks then twice weekly for 1 month then fortnightly for 1 month Co-interventions • Ferrous sulphate: 200 mg twice daily • Folic acid: daily
Outcomes	• Hb level at 12 weeks
Notes	• Funding source: not reported

Aggarwal 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory based outcome and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in assessment
Selective reporting (reporting bias)	High risk	No information on adverse effects
Other bias	Unclear risk	Insufficient information to permit judgement

Akiba 1992

Methods	• Study design: RCT • Study duration: 8 weeks • Duration of follow-up: not reported
Participants	• Country: Japan • Setting: multicentre • Pre-dialysis, uraemic, adults • Number: 165 • Mean age (range): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	Treatment groups
	• Epoetin alpha dose given once weekly SC
	  * 3000 (L)
	  * 6000 (M)
	  * 12,000 (H)

Outcomes	• HCT at 8 weeks • Adverse effects: hypertension • Changes in BUN and SCr and slope
Notes	• Abstract only

Akiba 1992 *(Continued)*

- Aggravations in blood pressure noted in one case in L, two in M, and 3 in H
- Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Said to be double blind, though insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcome and blinding unlikely to influence
Incomplete outcome data (attrition bias) All outcomes	High risk	No patient denominators supplied
Selective reporting (reporting bias)	High risk	Insufficient information to permit judgement (abstract only), however no full text publication by December 2016
Other bias	Unclear risk	Insufficient information to permit judgement

Amon 1992

Methods	• Study design: RCT • Study duration: not reported • Duration of follow-up: not reported
Participants	• Country: Germany • Setting: multicentre • Children with CKD not on dialysis • Number: 22 (evaluated 18) • Mean age (range): 6.2 years (0.3 to 17 years) • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Epoetin alpha SC: 50 IU/kg 3 times/week Treatment group 2 • Epoetin alpha SC: 150 IU/kg once/week
Outcomes	• Response interval (time to increase in Hb of 2 g/dL) • Change in GFR

Amon 1992 *(Continued)*

Notes	• Abstract only • 4 excluded: transplantation, dialysis, compliance, non-response due to infection • Adverse effects equal across groups • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement - says study is "prospective randomized multi-centre study"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes of interest are laboratory based and unlikely to be affected by knowledge of allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol analysis was used, 18% of the children randomised to either treatment were excluded from analysis
Selective reporting (reporting bias)	High risk	All pre-specified outcomes reported; however no full-text publication by December 2016
Other bias	Unclear risk	Insufficient information to permit judgement

Frenken 1989

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 32 weeks (8 weeks correction phase, 24 weeks maintenance phase)
Participants	• Countries: Belgium, Netherlands • Setting: multicentre • Progressive kidney failure; SCr 375 to 1034 µmol/L; anaemic (Hb 5.3 to 10.2 g/dL and HCT 0.16 to 0.30 L/L) • Number: treatment group 1 (8); treatment group 2 (8); treatment group 3 (8) • Mean age (range): 23 to 68 years • Sex (M/F): 11/13 • Exclusion criteria: other attributable causes for anaemia; acute illness in last 7 days; blood transfusions within last 30 days
Interventions	Correction phase • Treatment group 1 * Epoetin alpha IVI: 50 U/kg 3 times/week for 8 weeks

Frenken 1989 *(Continued)*

	• Treatment group 2
	  * Epoetin alpha IVI: 100 U/kg 3 times/week for 8 weeks
	• Treatment group 3
	  * Epoetin alpha IVI: 150 U/kg 3 times/week for 8 weeks
	
	Maintenance phase (at end of 8 weeks; non-randomised)
	
	• Epoetin alfa IVI once/week commencing at 3 times the dose given during correction phase
	
	Co-interventions
	
	• Oral iron supplementation: up to 200 mg elemental iron/d
	• Folic acid: 2 weeks prior to inclusion and duration of study

Outcomes	• Final Hb • Adverse events: hypertension, mortality
Notes	• Two patients withdrawn at week 21 and 28; ESKD developed and dialysis therapy was started • One patient received a kidney transplant at week 30 • One patient died during the maintenance phase and was excluded from further evaluation • Funding source: medication provided by Ortho Pharmaceutical Corporation (Raritan, New Jersey, USA) and Cilag B.V. (Herentals, Belgium)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Low risk	Medication provided by Ortho Pharmaceutical Corporation (Raritan, New Jersey, USA) and Cilag B.V. (Herentals, Belgium)

Gertz 2012

Methods	• Study design: parallel RCT, randomised 2:1 • Study duration: August 2005 to May 2007

Gertz 2012 *(Continued)*

	• Duration of follow-up: 30 days post study
Participants	• Countries: Bosnia, Bulgaria, Croatia, Hungary, Israel, Poland, Romania, Russia, Serbia, Turkey • Setting: 47 centres • ≥ 18 years with CKD stage III or worse not on dialysis receiving maintenance treatment with epoetin beta for ≥ 3 months and Hb ≥ 9.5 < 12.0 g/dL and no evidence of iron deficiency within the last 4 weeks • Number: treatment group 1 (193); treatment group 2 (95) • Mean age ± SD (years): treatment group 1 (34.1 ± 13.1); treatment group 2 (61.7 ± 15.7) • Sex (M/F): treatment group 1 (92/101); treatment group 2 (59/36) • Exclusion criteria: active bleeding; RBC transfusion within the last 3 months; female patients of child-bearing potential; uncontrolled severe HTN; congestive heart failure (NYHA III or IV); severe metabolic acidosis; current systemic infection or inflammatory disease; current malignant disease; resistance to epoetin; known hypersensitivity to epoetin or excipients; known presence of antibodies to epoetin
Interventions	Treatment group 1 • Epoetin theta (2000 and 4000 IU/0.5 mL): weekly dose of 38.1 ± 26.8 IU/kg for 24 weeks Treatment group 2 • Epoetin beta (1000 or 4000 IU/0.3 mL): weekly dose of 37.7 ± 23.7 IU/Kg for 24 weeks • Dose adjusted to maintain Hb within a target interval defined as ± 1.0 g/dL of the baseline level and ≥ 9.5 to < 12.0 g/dL Type of epoetin • Epoetin beta: Recormin® • Epoetin theta: Eporatio®, Biopoin® Co-interventions • Iron administration
Outcomes	• Change in Hb level from baseline to end of treatment, non-inferiority of epoetin theta to epoetin beta • Mean weekly dose of EPO • Percentage of subjects with dose changes • Percentage of Hb levels per subjects within target interval • Time course of Hb level • Percentage of subjects with Hb level within target interval at each week • Blood transfusions • Adverse effects/other safety variables • Tolerability • Immunogenicity
Notes	• No anti-EPO antibodies detected • Funding source: "This clinical study and this article were sponsored by BioGeneriX AG, a member of the Teva Group"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation via an interactive voice response system
Allocation concealment (selection bias)	Low risk	"randomised to treatment by using central randomisation via IVRS"

Gertz 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Similar syringes of intervention EPO Administration of intervention medication by a person who was not part of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory-based outcome and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	89% were included of those randomised were included in the ITT population
Selective reporting (reporting bias)	Low risk	Studies pre-specified outcomes reported
Other bias	High risk	Study and paper writing assistance was sponsored by a Pharma

Haag-Weber 2012

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: planned for 52 weeks
Participants	• Country: Austria, Bulgaria, the Czech Republic, France, Germany, India, Poland, Romania, Russia and Slovakia • Setting: 89 centres • ≥ 18 years; CKD stage III-V, Hb level ≥ 7.5 and < 11.0 g/dL on at least two visits during the screening period; naïve to ESA treatment or with an ESA treatment-free period of ≥ 3 months before enrolment; adequate iron status (serum ferritin ≥ 100 mg/L or transferrin saturation ≥ 20%) • Number: treatment group 1 (174); treatment group 2 (163) • Mean age, range (years): treatment group 1 (64.1, 19 to 88); treatment group 2 (64.9, 20 to 90) • Sex (M/F): treatment group 1 (77/97); treatment group 2 (65/98) • Exclusion criteria: chronic dialysis within the prior 6 months; non-renal anaemia; acute deterioration of kidney function or blood transfusion during screening; suspicion of, or known, PRCA; any haematological disorder; thrombocytopenia or leucopenia; evidence of uncontrolled diabetes, uncontrolled hypertension, uncontrolled hyperparathyroidism or severe hepatic dysfunction; congestive heart failure and/or angina; myocardial infarction or stroke in the previous 6 months; acute or chronic infection; previous gastrointestinal bleeding (within 6 months) or haemolysis; evidence of active malignancy within the previous 5 years (except non-melanoma skin cancer); therapy with immunosuppressants (other than corticosteroids for chronic disease) within 3 months of screening; or known allergy to test products or hypersensitivity to mammalian-derived products.
Interventions	Treatment group A • HX575: 25 IU/kg 3 times/week or 75 IU/kg once/week SC Treatment group B • Epoetin alpha: 25 IU/kg 3 times/week or 75 IU/kg once/week Both groups • Dose adjusted after 5 weeks to maintain Hb levels between 10 to 12 g/dL
Outcomes	• Safety and immunogenicity

Haag-Weber 2012 *(Continued)*

- Mean change in Hb from baseline to end of 13 weeks
- Mean weekly EPO dose in week 11 to 13 weeks
- Adverse effects

Notes	• Change in Hb baseline to week 13: HX575 2.2 ± 0.9 g/dL; epoetin alpha 2.2 ± 1.0 g/dL • Study terminated due to 2 patients developing PRCA • Funding source: "This study was funded by Sandoz Biopharmaceuticals. Medical writing assistance in the preparation of this paper was provided by Tony Reardon of Spirit Medical Communications and funded by Sandoz Biopharmaceuticals"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"block randomisation, stratified by center"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory based outcome and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Analysis done per-protocol method. Study terminated & data in uncertain number of subjects only available to 13 weeks
Selective reporting (reporting bias)	High risk	Outcomes of interest for this review such as change in EPO dose, number reaching target Hb were presented in ways that could not be used in a meta-analysis
Other bias	High risk	Study and paper writing assistance was sponsored by a Pharma

Knebel 2008

Methods	• Study design: parallel, open-label RCT stratified by age and centre, 1:3 • Study duration: not reported • Duration of follow-up: 24 weeks
Participants	• Country: America, Argentina • Setting: multicentre • Children, 1 to 17 years with CKD and associated anaemia. IV or SC epoetin alfa or epoetin delta, with Hb 10-13g/dL • Number: treatment group 1 (13); treatment group 2 (47) • Mean age (range): 11.8 years (1 to 17) • Sex (M/F): 38/22 • Exclusion criteria: not reported

Knebel 2008 *(Continued)*

Interventions	Treatment group 1 • Epoetin alpha: SC 24 to 190 IU/kg; IV 36 to 88 IU/kg Treatment group 2 • Epoetin delta: SC 26 to 191 IU/kg; IV 54 to 769 IU/kg
Outcomes	• Pharmacokinetic study
Notes	• Funding source: analysis was funded by Shire Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Phase III randomised, multi-centre study. appropriate 3:1 ratio to epoetin delta or epoetin alfa
Allocation concealment (selection bias)	Unclear risk	No information provided other than that randomisation stratified by age and centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	No data on outcomes provided
Selective reporting (reporting bias)	High risk	No data on outcomes provided
Other bias	High risk	Pharmaceutical study Analysis funded by Shire Pharmaceuticals Study terminated for commercial reasons

Kronborg 1994

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: not reported
Participants	• Country: Norway • Setting: paediatric centres • Children with CKD not on dialysis • Number: 29 • Mean age (range): not reported • Sex (M/F): not reported

Kronborg 1994 *(Continued)*

	• Exclusion criteria: not reported
Interventions	• Treatment group 1 • Epoetin beta (Recormon): 2 doses SC Treatment group 2 • Epoetin alpha (Eprex): 2 doses SC Control group • Saline: frequency of injections not provided
Outcomes	• Pain score through VAS and VDS
Notes	• Abstract only available • Funding source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Comparative double-blind randomised placebo controlled study" but unclear how performed
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Said to double-blind but unclear how this was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who performed outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients received all injections and contributed to results
Selective reporting (reporting bias)	High risk	Insufficient information to permit judgement (abstract only), however no full text publication by December 2016
Other bias	Unclear risk	Insufficient information to permit judgement

Mignon 2000

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 12 weeks
Participants	• Country: Germany, France • Setting: multicentre • Adults with CKD & GFR < 45 mL/min not on dialysis with no prior use of ESA; Hb < 10.0 g/dL

Mignon 2000 *(Continued)*

- Number: treatment group 1 (23); treatment group 2 (15); treatment group 3 (13); treatment group 4 (14); control group (15)
- Mean age ± SD (years): not reported
- Sex (M/F): not reported
- Exclusion criteria: not reported except dialysis patients excluded

Interventions	Treatment group 1 • EPO delta (HMR4396) SC: 15 IU/kg twice weekly for 12 weeks Treatment group 2 • EPO delta (HMR4396) SC: 50 IU/kg twice weekly for 12 weeks Treatment group 3 • EPO delta (HMR4396) SC: 100 IU/kg twice weekly for 12 weeks Treatment group 4 • EPO delta (HMR4396) SC: 200 IU/kg twice weekly for 12 weeks Control group • Epoetin alpha SC: 50 IU/kg twice weekly for 12 weeks All groups • Correction targets were HB > 11.5 g/dL for 2 weeks or single level of HB > 13.0 g/dL • When target achieved, dose titrated to maintain HB ≥ 10.5 g/dL
Outcomes	• Total success: number with HB ≥ 11.5 g/dL for 2 consecutive weeks or > 13.0 g/dL on one visit and HB maintained ≥ 11.5 g/dL for remainder of 12 weeks • Change in HB • Number with PRCA • Adverse effects
Notes	• Data available only from three abstracts. EPO delta removed from sale by company for commercial reasons and the studies were not completed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"12 week multi-centre, randomised, double blind parallel group study" but not details provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Said to be double blind but no information provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and unlikely to be influenced by blinding

Mignon 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided. Abstracts only
Selective reporting (reporting bias)	High risk	Abstracts only, no full text publication by December 2016
Other bias	High risk	Aventis Pharma/Shire PLC

Pergola 2009

Methods	• Study design: parallel RCT • Study duration: August 2006 to February 2008 • Duration of follow-up: 48 weeks (22 weeks initiation and maintenance phase; 22 weeks safety phase; 4 weeks post-treatment phase)
Participants	• Country: USA • Setting: 77 centres • Adults with CKD stage 3 or 4 with: 1) no prior use of ESA & Hb < 10.5 g/dL; 2) no prior ESA & Hb < 11.0 g/dL with ≥ 1 g/dL Hb decrease in the past 12 months; or 3) no ESA within 2 months before screening resulting in a ≥ 1 g/dL Hb decrease since stopping ESA therapy and Hb <11 g/dL • Number (analysed/randomised): treatment group 1 (104/121); treatment group 2 (94/124); treatment group 3 (105/124) • Mean age ± SD (years): treatment group 1 (71.4 ± 12.88); treatment group 2 (68.8 ± 11.89); treatment group 3 (69.0 ± 13.04) • Sex (M/F): treatment group 1 (45/76); treatment group 2 (45/79); treatment group 3 (39/85) • Exclusion criteria: Iron deficiency, with serum ferritin concentration < 50 ng/mL and transferrin saturation < 20%; poorly controlled HTN; severe congestive heart failure or coronary artery disease; active infection or inflammation that could affect the response to epoetin alfa therapy; uncontrolled or new onset of seizures; deep venous thrombosis or pulmonary embolus within the prior 12 months; stroke, transient ischaemic attack, acute coronary syndrome, or other arterial thrombosis within the prior 6 months; and requiring dialysis or anticipated to require dialysis during the study
Interventions	Treatment group 1 • Epoetin alpha (Procrit®) SC: 50 IU/Kg 3 times/week. After 22 weeks the dose was adjusted to 10,000 IU weekly Treatment group 2 • Epoetin alpha (Procrit®) SC: 10,000 IU weekly Treatment group 3 • Epoetin alpha (Procrit®) SC: 20,000 IU every 2 weeks Both groups • Dose adjustment: epoetin withheld if Hb > 11.9 g/dL or if rise ≥ 1.5 g/dL in 2 weeks; 25% increase in dose if Hb ≤ 10.5 g/dL & rise < 0.5 g/dL in the prior 2 weeks; 25% decrease in dose if Hb rise was ≥ 1.0 but < 1.5 g/dL in the prior 2 weeks
Outcomes	• Change in Hb level from baseline to the average of Hb level over the last 8 weeks of the first 22 weeks of treatment with EPO • Proportions of subjects with ≥1.0 g/dL increase in Hb level from baseline by week 9 of treatment with EPO

Pergola 2009 *(Continued)*

Notes	• Funding source: "This work was supported by Johnson & Johnson Pharmaceutical Research & Development"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"subjects ... were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory based outcome and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounts for and modified ITT data used
Selective reporting (reporting bias)	Low risk	Stated and important outcomes of interest were reported
Other bias	High risk	The study and its authorship were supported by pharmaceutical firm

Pergola 2010

Methods	• Study design: parallel RCT • Study duration: June 2007 to March 2009 • Duration of follow-up: 40 weeks (36 weeks treatment, 4 weeks post-treatment phase)
Participants	• Country: USA • Setting: 53 centres • Adults with CKD stage 3 or 4 with Hb between 10.0 and 11.0 g/dL while on stable once weekly dose of EPO • Number (analysed/randomised): treatment group 1 (107/108); treatment group 2 (106/107); treatment group 3 (215/215) • Mean age ± SD (years): treatment group 1 (70.4 ± 13.04); treatment group 2 (71.7 ± 10.68); treatment group 3 (71.1 ± 12.48) • Sex (M/F): treatment group 1 (40/67); treatment group 2 (34/72); treatment group 3 (89/126) • Exclusion criteria: iron deficiency; poorly controlled hypertension; severe congestive heart failure or coronary artery disease; deep venous thrombosis or pulmonary embolus within the prior 12 months; stroke, transient ischaemic attack, acute coronary syndrome, or other arterial thrombosis within the prior 6 months; and dialysis or anticipated to require dialysis during the study
Interventions	Treatment group 1 • Epoetin alpha (Procrit®) SC: pre-randomisation dose

Pergola 2010 *(Continued)*

	Treatment group 2 • Epoetin alpha (Procrit®) SC: twice the pre-randomisation dose to a maximum of 20,000 IU Treatment group 3 • Epoetin alpha (Procrit®) SC: 4 times the pre-randomisation dose to a maximum of 40,000 IU Both groups • Dose was adjusted to reach the target Hb range of 11.0 to 11.9 g/dL Co-interventions • Oral iron supplements or parenteral iron
Outcomes	• Group 2 and 3 treatments with epoetin were non inferior to group 1, mean change in Hb level from baseline to the average of the Hb over the last 12 weeks of treatment • Proportions of weeks in which each subjects maintain Hb between 11.0 and 11.9 g/dL • Safety parameters related to Hb-related endpoints and clinical safety parameters
Notes	• Funding source: "This work was supported by Johnson & Johnson Pharmaceutical Research & Development LLC"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said that "subjects ... were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory-based outcome and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounts for and modified ITT data used
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes mentioned
Other bias	High risk	The study and its authorship were supported by pharmaceutical firm

PROMPT Study 2005

Methods	• Study design: parallel RCT • Study duration: June 2002 to September 2003 • Duration of follow-up: 16 weeks

PROMPT Study 2005 *(Continued)*

Participants	• Country: USA • Setting: 91 centres • Adults with CKD; stable Hb ≥ 11 g/dL and receiving epoetin alfa • Number (analysed/randomised): treatment group 1 (108/130); treatment group 2 (114/131); treatment group 3 (114/132); treatment group 4 (104/126) • Mean age ± SD (years): treatment group 1 (69.5 ± 11.4); treatment group 2 (66.7 ± 14.1); treatment group 3 (69.7 ± 14.6); treatment group 4 (68.8 ± 12.4) • Sex (M/F): treatment group 1 (67/63); treatment group 2 (68/63); treatment group 3 (62/70); treatment group 4 (67/59) • Exclusion criteria: uncontrolled HTN; known hypersensitivity to mammalian cell derived products or human albumin; receiving dialysis or scheduled to receive dialysis during the course of the study; iron deficiency despite intravenous iron therapy during the past six months; current diagnosis of anaemia due to B12 or folate deficiencies, haemolysis, or gastrointestinal bleeding; severe congestive heart failure (NYHA Class IV); and pregnancy, lactation or failure to use adequate contraception
Interventions	Treatment group 1 • Epoetin alpha (Procrit®) SC: 10,000 IU once weekly Treatment group 2 • Epoetin alpha (Procrit®) SC: 20,000 IU every 2 weeks Treatment group 3 • Epoetin alpha (Procrit®) SC 30,000 IU every 3 weeks Treatment group 4 • Epoetin alpha (Procrit®) SC: 40,000 IU every 4 weeks All groups • Dose reduction permitted only when Hb rose to > 13.0 g/dL or a rise of > 1.3 g/dL was attained in any 2-week period
Outcomes	• Mean final Hb • Mean final score for each Quality of Life score • Change in Hb level over time • Hb maintenance ≥ 11.0 g/dL • Treatment failure • GFR change over time
Notes	• Funding source: "This study was supported by a research grant from Ortho Biotech Clinical Affairs, LLC. Financial disclosure: R. Provenzano, MD, FACP, has a consulting agreement with Ortho Biotech Products, L.P., and is on the Speakers Bureau and Advisory Board. S. Bhaduri, MD, owns stock in Johnson & Johnson and is an employee of Ortho Biotech Clinical Affairs, LLC. A.K. Singh, MD, receives research support and is on the Speakers Bureau for Ortho Biotech Products, L.P."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

PROMPT Study 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory-based outcome and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	90% of the patients who received epoetin were included in efficacy analysis
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes mentioned
Other bias	High risk	The study and its authorship were supported by pharmaceutical firm

Sohmiya 1998

Methods	• Study design: cross-over RCT • Study duration: not reported • Duration of follow-up: 12 weeks (4 weeks first phase, 4-week wash-out; 4 weeks second phase)
Participants	• Country: Japan • Setting: Single centre • Adults with anaemia of pre-dialysis CKD, who had diabetes mellitus and were malnourished. not reported whether patients had received EPO before • Number: 5 • Mean age ± SD: 69.4 ± 9.04 years • sex (M/F): 3/2 • Exclusion criteria: not reported
Interventions	Treatment group 1 • Epoetin beta continuous SC infusion: 6000 IU/week at 36 IU/h for 4 weeks Treatment group 2 • Epoetin beta single weekly SC dose: 6000 IU/week or 4 weeks Cross-over study with 4-week washout period
Outcomes	• Change in Hb • Change in reticulocyte count
Notes	• Cross-over study and results not provided separately for first part of study • Funding source: "This work was supported in part by grants from the Ministry of Education and Culture, Japan, the Ministry of Health and Welfare, Japan, and the Foundation of Renal Disorders"

Risk of bias

Bias	Authors' judgement	Support for judgement

Sohmiya 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"The cross-over comparative study of two protocols was randomly performed for each patient with wash out period of 4 weeks"
Allocation concealment (selection bias)	Unclear risk	Unclear. No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding performed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	End points were laboratory-based
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported on all patients for each treatment
Selective reporting (reporting bias)	High risk	No report of adverse effects Data not provided in format that allowed results to be included in meta-analyses
Other bias	Low risk	Grants from Japanese Government and research organisations

Spinowitz 2008

Methods	• Study design: parallel RCT • Study duration: September 2005 to October 2006 • Duration of follow-up: 16 weeks
Participants	• Country: USA • Setting: 37 centres • Adults with anaemia of CKD, absence of iron deficiency and negative urine pregnancy test within 7 days of study • Number (analysed/randomised): treatment group 1 (39/39); treatment group 2 (76/77); treatment group 3 (72/73); treatment group 4 (72/73) • Mean age ± SD (years): treatment group 1 (65.2 ± 11.1); treatment group 2 (67.8 ± 13.6); treatment group 3 (67.8 ± 14.4); treatment group 4 (66.9 ± 13.6) • Sex (M/F): treatment group 1 (14/25); treatment group 2 (33/43); treatment group 3 (32/40); treatment group 4 (28/44) • Exclusion criteria: EPO in the prior 8 weeks; iron overload; breastfeeding mothers; poorly controlled HTN, serum albumin < 2.6 g/dL; history of cardiovascular disease or thrombovascular events; new-onset seizures within 3 months of study entry or uncontrolled seizures
Interventions	Treatment group 1 • Epoetin alpha (Procrit®) SC: 10,000 IU weekly Treatment group 2 • Epoetin alpha (Procrit®) SC: 20,000 IU every 2 weeks Treatment group 3

Spinowitz 2008 *(Continued)*

	• Epoetin alpha (Procrit®) SC: 20,000 IU every 4 weeks Treatment group 4 • Epoetin alpha (Procrit®) SC: 20,000 IU every 4 weeks All groups • Dose adjustment permitted after 4 weeks if Hb fell outside of 11 to 12 g/dL range or rate of rise of Hb fell outside the rate of rise of 0.5 to 1.0 g/dL in any 2 weeks Co-interventions • Oral elemental iron 200mg/d; parenteral iron at discretion of the site investigator
Outcomes	• Change of Hb from baseline to end of study • Hb increase of > 1.0 g/dL from baseline • Time to Hb response • Proportion with Hb > 11.0 g/dL and an increase of ≥ 1.0 g/dL from baseline • Change in Hb over time • Proportion who received packed red cell transfusion • Number of units of packed red cells received • Weekly EPO dose
Notes	• Funding source: Supported by Ortho Biotech Clinical Affairs, LLC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Centrally generated using an interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory-based outcome and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	The primary end points were presented for over 98% of the study population using modified ITT analysis
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes mentioned
Other bias	High risk	The study and its authorship were supported by a pharmaceutical firm

BUN - blood urea nitrogen; CKD - chronic kidney disease; EPO - erythropoietin; ESA - erythropoiesis-stimulating agent/s; GFR - glomerular filtration rate; Hb - haemoglobin; HCT - haematocrit; HTN - hypertension; ITT - intention-to-treat; IV - intravenous; IVI - IV infusion: M/F - male/female; PRCA - pure red cell aplasia; RBC - red blood cell/s; RCT - randomised controlled trial; SC - subcutaneous; SCr - serum creatinine; SD - standard deviation; VAS - visual analogue scale; VDS - verbal descriptive scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Brown 1988	Ineligible intervention; compares ESA with placebo
Clyne 1992	Ineligible intervention; compares ESA with no treatment
Duliege 2005	Phase 2 study of synthetic non-epoetin agent
Furukawa 1992	Pharmacokinetic study
Li 2004	Ineligible intervention; compares Bushen Jianpi Recipe + ESA with ESA
Meloni 2003	Ineligible intervention; compares short-acting ESA with no ESA
NCT00240734	Ineligible intervention; compares short-acting ESA with placebo Study terminated because of slow enrolment and no results posted
NCT00492427	Ineligible intervention; compares long acting ESA with short-acting ESA
NCT00563355	Ineligible intervention; compares short-acting ESA with no treatment
Patel 2012	Ineligible intervention; compares extended duration of short-acting ESA with standard care for institution
Schwartz 1989	Ineligible intervention; compares short-acting ESA with placebo
Shaheen 1983	Ineligible intervention; compares short-acting ESA with no treatment
Singh 1999	Ineligible intervention; compares short-acting ESA with no treatment
Teehan 1990	Ineligible intervention; compares short-acting ESA with placebo
Teplan 1995	Ineligible intervention; compares short-acting ESA to no treatment
Yamazaki 1993	Unclear whether this study is randomised
Zheng 1992	Unclear whether this study is randomised

ESA - erythropoiesis-stimulating agent/s

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT01576341

Methods	• Open-label RCT
Participants	Inclusion criteria • Adults ≥ 18 years with or without dialysis treatment • Stable IV or SC maintenance therapy with an EU-approved ESA treatment or ESA naïve • Adequate iron substitution Exclusion criteria

NCT01576341 *(Continued)*

	• History of PRCA)or anti-EPO antibodies • Contraindications for ESA therapy • Serum albumin < 3.0 g/dL • Immunocompromised patients (immunosuppressive treatment, chemotherapy) • Hepatitis C infection on an active treatment or hepatitis B or human immunodeficiency virus (HIV) infection • SLE • Symptomatic congestive heart failure, Unstable angina pectoris, or myocardial infarction within 6 months • History of malignancy of any organ system within the last 5 years • History of use of any non-EU approved ESA
Interventions	• Drug: HX575 epoetin alfa (Sandoz) Eligible patients are scheduled to receive HX575 (INN: Epoetin alfa) as a solution for injection in order to achieve or maintain the correction of renal anaemia. Other name: Binocrit®, Epoetin alfa HEXAL®, Novicrit®, Abseamed®
Outcomes	• Incidence of antibody formation against epoetin • Hb levels over time and change from baseline • Weekly epoetin dosage (IU and IU/kg) over time and change from baseline • Incidence and severity of AE, and of drug related AE
Notes	• Study completed; last updated 11 November 2015

NCT01693029

Methods	• Double-blind RCT
Participants	Inclusion criteria: • Patients with ESKD (stage CKD 5d), receiving stable SC maintenance therapy with Epogen® or Procrit® at least once per week • Mean Hb level between 9.0 to 11.5 g/dL during the screening period • Adequate iron substitution Exclusion criteria: • Contraindications for ESA therapy • History of PRCA, or anti-EPO antibodies • Known HIV or Hepatitis B infection • Hepatitis C infection on an active treatment • Symptomatic congestive heart failure (New York Heart Association [NYHA] class III and IV) • Unstable angina pectoris, or cardiac infarction during the last 6 months prior to randomization • Percutaneous coronary intervention, or coronary artery bypass grafting during the last 6 months prior to randomisation • History of malignancy of any organ system • SLE • Immunocompromised patients
Interventions	• Drug: HX575 epoetin alfa Solution for subcutaneous injection. The drug is administered subcutaneously at least once per week over 52 weeks. The dose will be individually titrated to maintain Hb levels between 10 to 11 g/dL. Other Names: Binocrit® (Europe) Epoetin alfa HEXAL® (Europe) Novicrit® (Europe) Abseamed® (Europe). • Comparator: epoetin alfa

NCT01693029 *(Continued)*

Outcomes	• Mean absolute change in Hb levels between the screening/baseline period (week -4 to day 1) and the evaluation period (week 21 to week 28) • Change from baseline in Hb levels over time • Change from baseline in the weekly epoetin dosage (International Unit [IU] and IU/kg) over time • Incidence and severity of adverse events, and of drug related adverse events • Incidence of antibody formation against Epoetin
Notes	• Study completed; last updated 1 June 2016

AE - adverse events; CKD - chronic kidney disease; EPO - erythropoietin; ESA - erythropoiesis-stimulating agent/s; ESKD - end-stage kidney disease; Hb - haemoglobin; HIV - human immunodeficiency virus; IV - intravenous; PRCA - pure red cell aplasia; RCT - randomised controlled trial; SC - subcutaneous; SLE - Systemic lupus erythematous

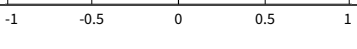
DATA AND ANALYSES

Comparison 1. Epoetin alpha every 2 weeks versus weekly

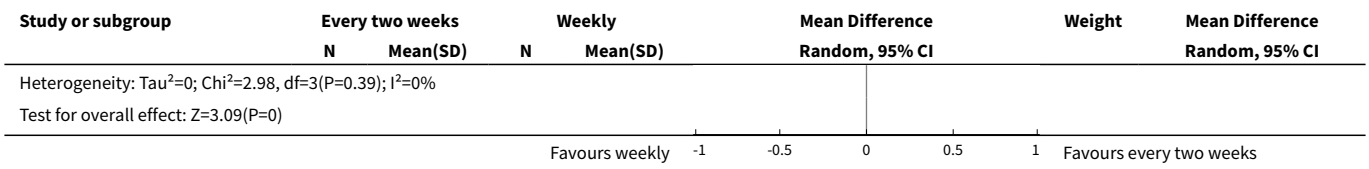
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in haemoglobin level	4	785	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.33, -0.07]
2 Number reaching target haemoglobin	4	798	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.93, 0.99]
3 Number of deaths	4	838	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.38, 2.07]
4 Adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 RBC transfusions	3	580	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.71, 3.45]
4.2 Hypertension	4	838	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.55, 1.32]
4.3 Thrombovascular events	4	838	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.67, 3.00]
4.4 Adverse events leading to discontinuation of therapy	1	258	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.20, 4.79]

Analysis 1.1. Comparison 1 Epoetin alpha every 2 weeks versus weekly, Outcome 1 Change in haemoglobin level.

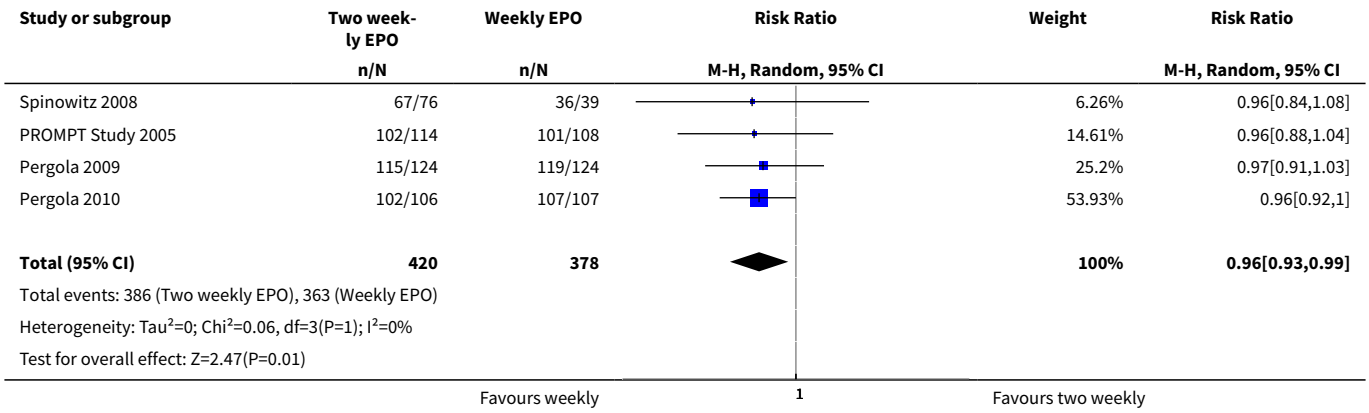
Study or subgroup	Every two weeks N	Every two weeks Mean(SD)	Weekly N	Weekly Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Spinowitz 2008	66	11.4 (0.9)	36	11.5 (0.9)		11.87%	-0.13[-0.5,0.24]
PROMPT Study 2005	114	11.9 (1.1)	108	12.2 (1.1)		20.33%	-0.3[-0.58,-0.02]
Pergola 2009	124	1.3 (0.9)	124	1.6 (1)		28.5%	-0.32[-0.56,-0.08]
Pergola 2010	106	-0.1 (0.8)	107	-0 (0.7)		39.3%	-0.08[-0.28,0.12]
Total ***	**410**		**375**			**100%**	**-0.2[-0.33,-0.07]**



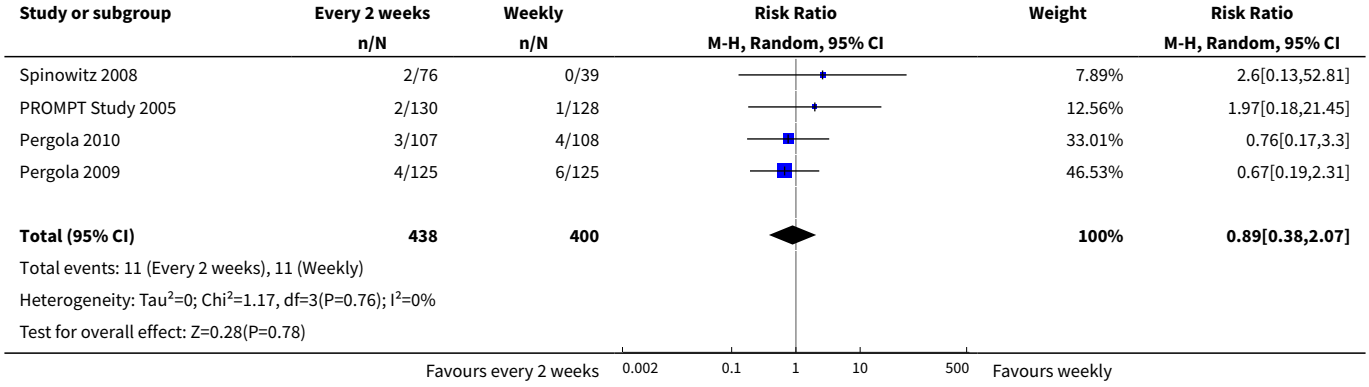
Favours weekly — Favours every two weeks



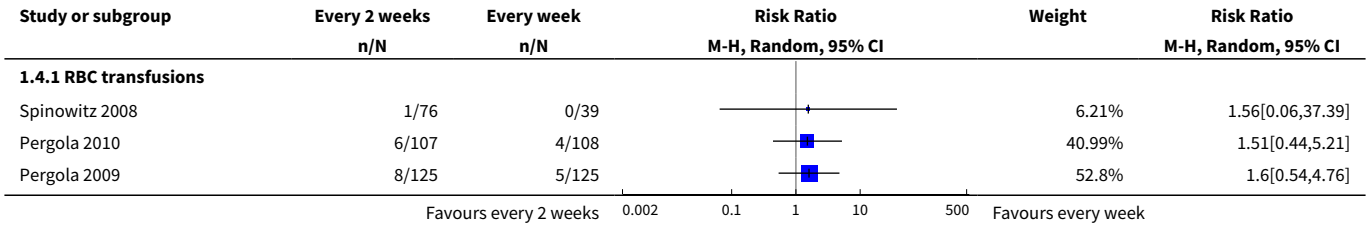
Analysis 1.2. Comparison 1 Epoetin alpha every 2 weeks versus weekly, Outcome 2 Number reaching target haemoglobin.

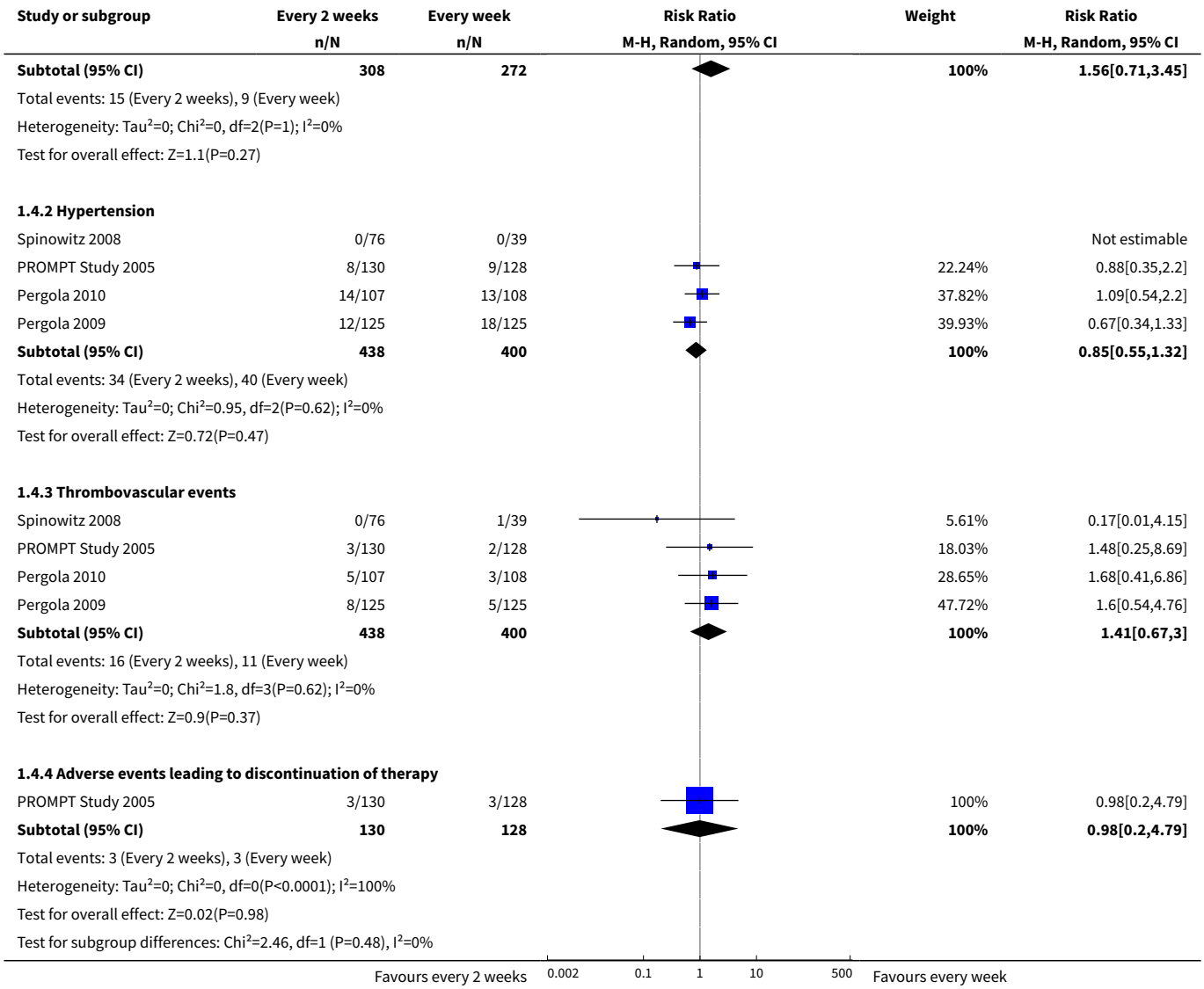


Analysis 1.3. Comparison 1 Epoetin alpha every 2 weeks versus weekly, Outcome 3 Number of deaths.



Analysis 1.4. Comparison 1 Epoetin alpha every 2 weeks versus weekly, Outcome 4 Adverse events.





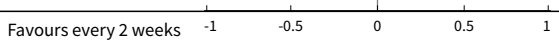
Comparison 2. Epoetin alpha every 4 weeks versus every 2 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in haemoglobin level	3	671	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.43, 0.10]
2 Number reaching target haemoglobin	3	687	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.07]
3 Number of deaths	3	724	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.33, 2.75]
4 Adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 RBC transfusions	2	470	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.53, 2.98]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.2 Hypertension	3	724	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.62, 1.69]
4.3 Arteriovenous complications	3	724	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.39, 2.68]

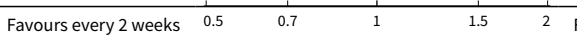
Analysis 2.1. Comparison 2 Epoetin alpha every 4 weeks versus every 2 weeks, Outcome 1 Change in haemoglobin level.

Study or subgroup	Every 4 weeks N	Every 4 weeks Mean(SD)	Every 2 weeks N	Every 2 weeks Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
PROMPT Study 2005	104	11.4 (1.5)	114	11.9 (1.1)		27.07%	-0.5[-0.86,-0.14]
Spinowitz 2008	65	11.4 (1)	66	11.4 (0.9)		29.98%	0.04[-0.28,0.36]
Pergola 2010	215	-0.2 (0.7)	107	-0.1 (0.8)		42.95%	-0.09[-0.27,0.09]
Total ***	**384**		**287**			**100%**	**-0.16[-0.43,0.1]**
Heterogeneity: Tau^2=0.03; Chi^2=5.43, df=2(P=0.07); I^2=63.19%							
Test for overall effect: Z=1.2(P=0.23)							



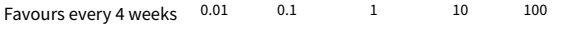
Analysis 2.2. Comparison 2 Epoetin alpha every 4 weeks versus every 2 weeks, Outcome 2 Number reaching target haemoglobin.

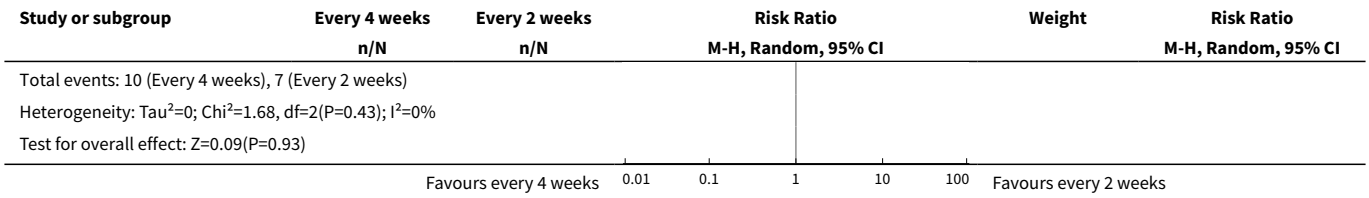
Study or subgroup	Every 4 weeks n/N	Every 2 weeks n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
PROMPT Study 2005	79/104	102/114		29.68%	0.85[0.75,0.96]
Spinowitz 2008	62/72	67/76		29.83%	0.98[0.86,1.11]
Pergola 2010	208/215	102/106		40.48%	1.01[0.96,1.05]
Total (95% CI)	**391**	**296**		**100%**	**0.95[0.84,1.07]**
Total events: 349 (Every 4 weeks), 271 (Every 2 weeks)					
Heterogeneity: Tau^2=0.01; Chi^2=9.72, df=2(P=0.01); I^2=79.42%					
Test for overall effect: Z=0.85(P=0.4)					



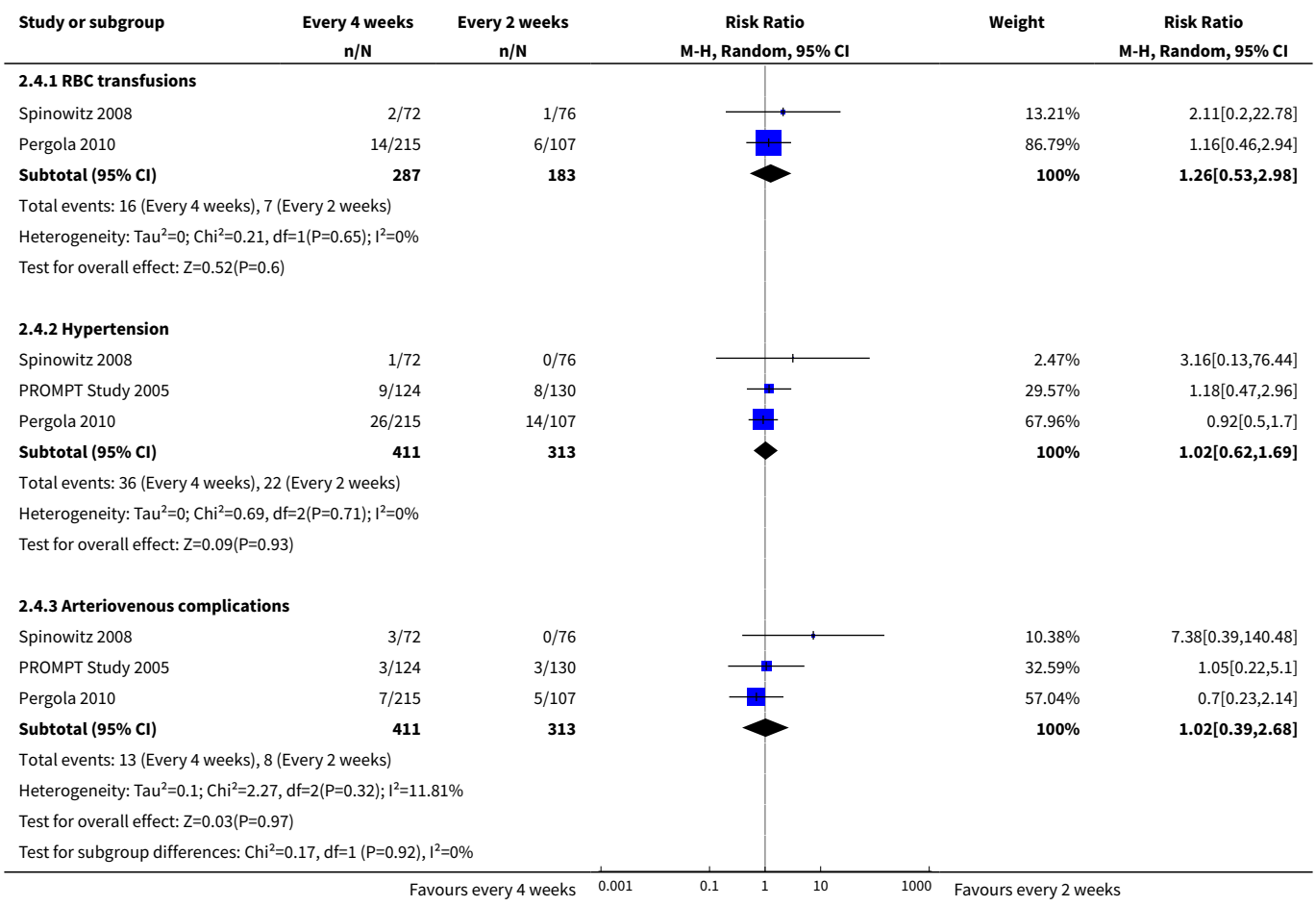
Analysis 2.3. Comparison 2 Epoetin alpha every 4 weeks versus every 2 weeks, Outcome 3 Number of deaths.

Study or subgroup	Every 4 weeks n/N	Every 2 weeks n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Spinowitz 2008	0/72	2/76		12.33%	0.21[0.01,4.32]
PROMPT Study 2005	1/124	2/130		19.71%	0.52[0.05,5.71]
Pergola 2010	9/215	3/107		67.96%	1.49[0.41,5.4]
Total (95% CI)	**411**	**313**		**100%**	**0.95[0.33,2.75]**





Analysis 2.4. Comparison 2 Epoetin alpha every 4 weeks versus every 2 weeks, Outcome 4 Adverse events.



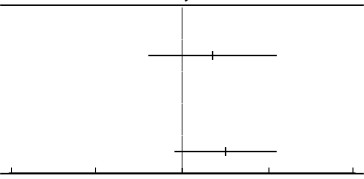
Comparison 3. Epoetin alpha different doses given three times weekly

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final haemoglobin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 100 U/kg versus 50 U/kg	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.2 150 U/kg versus 50 U/kg	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Mean arterial BP	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 100 IU/kg/wk versus 50 IU/kg/wk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 150 IU/kg/wk versus 50 IU/kg/wk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Final creatinine levels	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 100 IU/kg/wk versus 50 IU/kg/wk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 150 IU/kg/wk versus 50 IU/kg/wk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

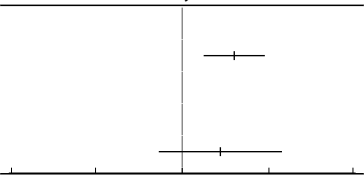
Analysis 3.1. Comparison 3 Epoetin alpha different doses given three times weekly, Outcome 1 Final haemoglobin.

Study or subgroup	100-150 U/kg/wk N	100-150 U/kg/wk Mean(SD)	50 U/kg/wk N	50 U/kg/wk Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
3.1.1 100 U/kg versus 50 U/kg						
Frenken 1989	8	11.8 (1.7)	8	11.1 (1.3)		0.7[-0.78,2.18]
3.1.2 150 U/kg versus 50 U/kg						
Frenken 1989	8	12.1 (1.1)	8	11.1 (1.3)		1[-0.18,2.18]



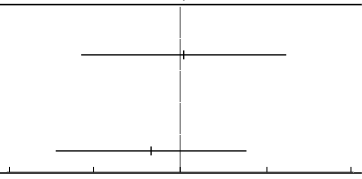
Analysis 3.2. Comparison 3 Epoetin alpha different doses given three times weekly, Outcome 2 Mean arterial BP.

Study or subgroup	100-150 U/kg/wk N	100-150 U/kg/wk Mean(SD)	50 U/kg/wk N	50 U/kg/wk Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
3.2.1 100 IU/kg/wk versus 50 IU/kg/wk						
Frenken 1989	8	113 (9)	8	98 (9)		15[6.18,23.82]
3.2.2 150 IU/kg/wk versus 50 IU/kg/wk						
Frenken 1989	8	109 (24)	8	98 (9)		11[-6.76,28.76]



Analysis 3.3. Comparison 3 Epoetin alpha different doses given three times weekly, Outcome 3 Final creatinine levels.

Study or subgroup	100-150 IU/kg/wk N	100-150 IU/kg/wk Mean(SD)	50 IU/kg/wk N	50 IU/kg/wk Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
3.3.1 100 IU/kg/wk versus 50 IU/kg/wk						
Frenken 1989	8	790 (244)	8	780 (350)		10[-285.65,305.65]
3.3.2 150 IU/kg/wk versus 50 IU/kg/wk						
Frenken 1989	8	696 (187)	8	780 (350)		-84[-358.98,190.98]

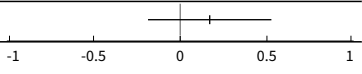


Comparison 4. Epoetin alpha different doses given every four weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final haemoglobin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Number reaching target haemoglobin	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Number of deaths	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Hypertension	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Thrombovascular events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 RBC transfusions	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

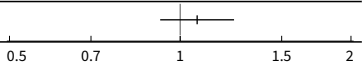
Analysis 4.1. Comparison 4 Epoetin alpha different doses given every four weeks, Outcome 1 Final haemoglobin.

Study or subgroup	40,000 IU every 4 weeks N	40,000 IU every 4 weeks Mean(SD)	20,000 IU every 4 weeks N	20,000 IU every 4 weeks Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Spinowitz 2008	65	11.4 (1)	62	11.2 (1.1)		0.17[-0.19,0.53]



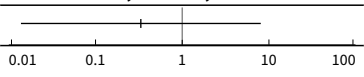
Analysis 4.2. Comparison 4 Epoetin alpha different doses given every four weeks, Outcome 2 Number reaching target haemoglobin.

Study or subgroup	40,000 IU every 4 weeks n/N	20,000 IU every 4 weeks n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Spinowitz 2008	62/72	58/72		1.07[0.92,1.24]



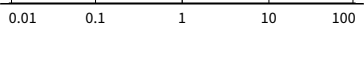
Analysis 4.3. Comparison 4 Epoetin alpha different doses given every four weeks, Outcome 3 Number of deaths.

Study or subgroup	40,000 IU every 4 weeks n/N	20,000 IU every 4 weeks n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Spinowitz 2008	0/72	1/72		0.33[0.01,8.05]



Analysis 4.4. Comparison 4 Epoetin alpha different doses given every four weeks, Outcome 4 Adverse events.

Study or subgroup	40,000 IU every 4 weeks n/N	20,000 IU every 4 weeks n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.4.1 Hypertension				
Spinowitz 2008	1/72	0/72		3[0.12,72.44]
4.4.2 Thrombovascular events				
Spinowitz 2008	3/72	1/72		3[0.32,28.17]
4.4.3 RBC transfusions				
Spinowitz 2008	2/72	2/72		1[0.14,6.91]

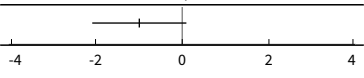


Comparison 5. Epoetin alpha IV versus subcutaneous administration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final haemoglobin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Epoetin alpha IV versus subcutaneous administration, Outcome 1 Final haemoglobin.

Study or subgroup	IV N	IV Mean(SD)	SC N	SC Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Aggarwal 2002	10	8.6 (1.1)	10	9.6 (1.3)		-0.99[-2.08,0.1]



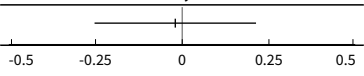
Comparison 6. Epoetin theta versus epoetin beta

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final Hb	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Mean weekly epoetin dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 Deaths	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Hypertension	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 RBC transfusions	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Discontinuation of therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

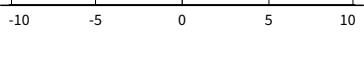
Analysis 6.1. Comparison 6 Epoetin theta versus epoetin beta, Outcome 1 Final Hb.

Study or subgroup	Epoetin theta		Epoetin beta		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Gertz 2012	193	11 (1)	95	11 (0.9)		-0.02[-0.25,0.21]



Analysis 6.2. Comparison 6 Epoetin theta versus epoetin beta, Outcome 2 Mean weekly epoetin dose.

Study or subgroup	Epoetin theta		Epoetin beta		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Gertz 2012	193	38.1 (26.8)	95	37.7 (23.7)		0.4[-5.68,6.48]

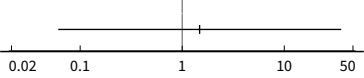


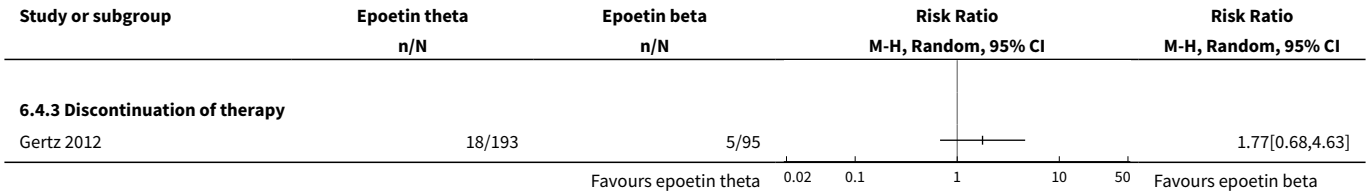
Analysis 6.3. Comparison 6 Epoetin theta versus epoetin beta, Outcome 3 Deaths.

Study or subgroup	Epoetin theta	Epoetin beta	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Gertz 2012	5/193	1/95		2.46[0.29,20.77]

Analysis 6.4. Comparison 6 Epoetin theta versus epoetin beta, Outcome 4 Adverse events.

Study or subgroup	Epoetin theta	Epoetin beta	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
6.4.1 Hypertension				
Gertz 2012	5/193	7/95		0.35[0.11,1.08]
6.4.2 RBC transfusions				
Gertz 2012	1/193	0/95		1.48[0.06,36.1]





APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Renal Insufficiency] this term only 2. MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees 3. MeSH descriptor: [Kidney Diseases] this term only 4. "chronic kidney" or "chronic renal":ti,ab,kw (Word variations have been searched) 5. CKF or CKD or CRF or CRD:ti,ab,kw (Word variations have been searched) 6. pre-dialy* or predialy*:ti,ab,kw (Word variations have been searched) 7. MeSH descriptor: [Uremia] explode all trees 8. uremi* or uraemi*:ti,ab,kw (Word variations have been searched) 9. {or #1-#8} 10.MeSH descriptor: [Anemia] explode all trees 11.anemi* or anaemi*:ti,ab,kw (Word variations have been searched) 12.{or #10-#11} 13.MeSH descriptor: [Erythropoietin] this term only 14.erythropoietin:ti,ab,kw (Word variations have been searched) 15.epoetin:ti,ab,kw (Word variations have been searched) 16.rhuepo:ti,ab,kw (Word variations have been searched) 17.EPO:ti,ab,kw (Word variations have been searched) 18.{or #13-#17} 19.{and #9, #12, #18}
MEDLINE	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. uremi.tw. 9. or/1-8 10.exp Anemia/ 11.(anemia or anaemia).tw. 12.or/10-11 13.Erythropoietin/ 14.erythropoietin.tw. 15.EPO.tw.

(Continued)

	16.rHuepo.tw. 17.epoetin.tw. 18.or/13-17 19.and/9,12,18
EMBASE	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.erythropoietin.tw. 15.EPO.tw. 16.rHuepo.tw. 17.epoetin.tw. 18.or/13-17 19.and/9,12,18

Appendix 2. Risk of bias assessment tool

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

(Continued)

	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 standardized 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.
	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. subscales) 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	*Low risk of bias:* The study appears to be free of other sources of bias.

(Continued)

Bias due to problems not covered elsewhere in the table	*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.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: DH, EH
2. Study selection: DH, EH, NE
3. Extract data from studies: DH, EH, CE, NE
4. Enter data into RevMan: DH, CE, EH
5. Carry out the analysis: DH, EH, CE
6. Interpret the analysis: DH, EH
7. Draft the final review: DH, EH
8. Disagreement resolution: AW
9. Update the review: DH, EH

DECLARATIONS OF INTEREST

- Deirdre Hahn: none known
- Elisabeth M Hodson: none known
- Angela C Webster: none known
- Noha Elserafy: none known
- Christopher Esezobor: none known

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Removal of the comparison of short-acting ESAs in evaluating the benefits and harms of different Hb or HCT targets in CKD patients receiving ESA treatment for anaemia as this is included in another systematic review (Strippoli 2006).

INDEX TERMS

Medical Subject Headings (MeSH)

*Renal Dialysis; Anemia [blood] [*drug therapy]; Epoetin Alfa [*administration & dosage]; Erythropoietin [*administration & dosage]; Hematinics [*administration & dosage]; Hemoglobin A; Injections, Intravenous; Randomized Controlled Trials as Topic; Recombinant Proteins [administration & dosage]; Renal Insufficiency, Chronic [*blood]

MeSH check words

Adult; Child; Humans