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Frequency of administration of erythropoiesis-stimulating agents for the anaemia of end-stage kidney disease in dialysis patients (Review)

Hahn D, Cody JD, Hodson EM

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Frequency of administration of erythropoiesis-stimulating agents for the anaemia of end-stage kidney disease in dialysis patients.
Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD003895.
DOI: 10.1002/14651858.CD003895.pub3.

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[Intervention Review]

Frequency of administration of erythropoiesis-stimulating agents for the anaemia of end-stage kidney disease in dialysis patients

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Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: Edited (no change to conclusions), published in Issue 11, 2014.

Citation: Hahn D, Cody JD, Hodson EM. Frequency of administration of erythropoiesis-stimulating agents for the anaemia of end-stage kidney disease in dialysis patients. *Cochrane Database of Systematic Reviews* 2014, Issue 5. Art. No.: CD003895. DOI: 10.1002/14651858.CD003895.pub3.

ABSTRACT

Background

The benefits of erythropoiesis-stimulating agents (ESA) for dialysis patients have been demonstrated. However, it remains unclear whether the efficacy and safety of new, longer-acting ESA given less frequently is equivalent to recombinant human erythropoietin (rHuEPO) preparations. This is an update of a review first published in 2002 and last updated in 2005.

Objectives

This review aimed to establish the optimal frequency of ESA administration in terms of effectiveness (correction of anaemia, and freedom from adverse events) and efficiency (optimal resource use) of different ESA dose regimens.

Search methods

We searched the Cochrane Renal Group's Specialised Register to 21 March 2013 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

We included randomised control trials (RCTs) comparing different frequencies of ESA administration in dialysis patients.

Data collection and analysis

Two authors independently assessed study eligibility, 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) or standardised mean difference (SMD) with 95% confidence intervals (CI) was used. Statistical analyses were performed using the random-effects model.

Main results

This review included 33 studies (5526 participants), 22 of which were added for this update. Risk of bias was generally high; only nine studies were assessed at low risk of bias for sequence generation and 14 studies for allocation concealment. Although only four studies were placebo-controlled, all were considered to be at low risk of performance or detection bias because the primary outcome of haemoglobin level was a laboratory-derived assessment and unlikely to be influenced by lack of blinding. We found that 16 studies were at low risk of attrition bias and five were at low risk of selection bias; only one study reporting sources of support was not funded by a pharmaceutical company.

We compared four different interventions: Continuous erythropoietin receptor agonists (CERA) versus other ESA (darbepoetin or rHuEPO); different frequencies of darbepoetin administration; darbepoetin versus rHuEPO; and different frequencies of rHuEPO administration.

There were no significant differences in maintaining final haemoglobin between CERA administered at two weekly intervals (4 studies, 1762 participants: MD 0.08 g/dL, 95% CI -0.04 to 0.21) or four weekly intervals (two studies, 1245 participants: MD -0.03 g/dL, 95% CI -0.17 to 0.12) compared with rHuEPO administered at two to three weekly intervals. In one study comparing CERA administered every two weeks with darbepoetin administered once/week, there was no significant difference in final haemoglobin (313 participants: MD 0.30 g/dL, 95% CI 0.05 to 0.55). In comparisons of once/week with once every two weeks darbepoetin (two studies, 356 participants: MD 0.04 g/dL, 95% CI -0.45 to 0.52) and once every two weeks with monthly darbepoetin (one study, 64 participants: MD 0.40 g/dL, 95% CI -0.37 to 1.17) there were no significant differences in final haemoglobin levels. There was marked heterogeneity among studies comparing weekly darbepoetin with once every two weeks and was possibly related to different administration protocols. Eight studies compared weekly darbepoetin with rHuEPO given two to three times/week; no statistical difference in final haemoglobin was demonstrated (6 studies, 1638 participants: MD 0.02 g/dL, 95% CI -0.09 to 0.12). Fourteen studies compared different frequencies of rHuEPO. No statistical difference was demonstrated in final haemoglobin (7 studies, 393 participants: SMD -0.17 g/dL, 95% CI -0.39 to 0.05). Adverse events did not differ significantly within comparisons; however, mortality and quality of life were poorly reported, particularly in earlier publications.

Authors' conclusions

Longer-acting ESA (darbepoetin and CERA) administered at one to four week intervals are non-inferior to rHuEPO given one to three times/week in terms of achieving haemoglobin targets without any significant differences in adverse events in haemodialysis patients. Additional RCTs are required to evaluate different frequencies of ESA in peritoneal and paediatric dialysis patients and to compare different longer-acting ESA (such as darbepoetin compared with CERA).

PLAIN LANGUAGE SUMMARY

Frequency of administration of erythropoiesis-stimulating agents for the anaemia of end-stage kidney disease in dialysis patients

Anaemia (having too few red blood cells) is a major cause of tiredness and other problems often experienced by people on dialysis. Dialysis is treatment for kidney disease using an artificial kidney machine (haemodialysis) or by exchanging fluid through a tube in the abdomen (peritoneal dialysis).

Manufactured erythropoietin (a hormone that increases red blood cell production) improves anaemia and is often prescribed for people on dialysis. Several different forms of manufactured erythropoietin that can be given less often are now available.

We looked at evidence from 33 studies that involved over 5500 people that were published before March 2013 to find out if how often erythropoietin agents are given to people who are receiving dialysis can help to improve anaemia.

We found that the newer erythropoietin agents given less often (weekly to every four weeks) resulted in similar correction of anaemia compared with older agents (given two to three times per week) for people on haemodialysis. We did not find any significant differences in side effects between the newer and older agents, but not all studies reported information on side effects.

There was not enough information about use of these agents for children or people on peritoneal dialysis to determine if less frequent administration was effective for these groups of people.

This review updates information previously published in 2002 and 2005.

Summary of findings for the main comparison. CERA versus other ESA for the anaemia of end-stage kidney disease in dialysis patients

CERA versus other ESA for the anaemia of end-stage kidney disease in dialysis patients						
Patient or population: patients with the anaemia of end-stage kidney disease undergoing dialysis **Settings:** tertiary centres **Intervention:** CERA versus other ESA						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**CERAversus other ESA**				
Final Hb g/dL: CERA every 2 weeks versus rHuEPO		Mean final Hb g/dL: CERA every 2 weeks versus rHuEPO in the intervention groups was **0.08 higher** (0.04 lower to 0.21 higher)		1126 (4)	⊕⊕⊕⊕ **high**	
Final Hb g/dL: CERA every 4 week versus rHuEPO		Mean final Hb g/dL: CERA every 4 weeks versus rHuEPO in the intervention groups was **0.03 lower** (0.17 lower to 0.12 higher)		672 (2)	⊕⊕⊕⊕ **high**	
Final Hb g/dL: CERA every 2 week versus darbepoetin		Mean final Hb g/dL: CERA every 2 weeks versus darbepoetin in the intervention groups was **0.3 higher** (0.05 to 0.55 higher)		249 (1)	⊕⊕⊕⊖ **moderate**[1]	
All-cause mortality: CERA every 2 weeks versus rHuEPO	**Study population**		**RR 1.03** (0.67 to 1.57)	1341 (4)	⊕⊕⊕⊖ **moderate**[2]	
	62 per 1000	**64 per 1000** (41 to 97)				
	Moderate					
	61 per 1000	**63 per 1000** (41 to 96)				
Transfusions: CERA every 2 weeks versus rHuEPO	**Study population**		**RR 0.92** (0.64 to 1.32)	1341 (4)	⊕⊕⊕⊖ **moderate**[2]	
	90 per 1000	**83 per 1000** (58 to 119)				
	Moderate					
	88 per 1000	**81 per 1000** (56 to 116)				

Numbers of adverse events due to hypertension: CERA every 2 weeks versus rHuEPO	**Study population**		**RR 0.93** (0.69 to 1.26)	1341 (4)	⊕⊕⊕⊕ **high**
	151 per 1000	**140 per 1000** (104 to 190)			
	Moderate				
	149 per 1000	**139 per 1000** (103 to 188)			
Numbers of adverse events due to access thrombosis: CERA every 2 weeks versus rHuEPO	**Study population**		**RR 0.96** (0.56 to 1.65)	1341 (4)	⊕⊕⊕⊖ **moderate**[3]
	92 per 1000	**88 per 1000** (52 to 152)			
	Moderate				
	85 per 1000	**82 per 1000** (48 to 140)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[1] One study, 249 participants
[2] Small numbers of events
[3] Heterogeneity among studies

Summary of findings 2. Different frequencies of CERA for the anaemia of end-stage kidney disease in dialysis patients

Different frequencies of CERA for the anaemia of end-stage kidney disease in dialysis patients

Patient or population: patients with the anaemia of end-stage kidney disease undergoing dialysis
Settings: tertiary
Intervention: different frequencies of CERA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

	Control	Different frequencies of CERA			
Final Hb (g/dL)		Mean final Hb in the intervention groups was **0.11 lower** (0.35 lower to 0.14 higher)		675 (2)	⊕⊕⊕⊖ **moderate**[1]
All-cause mortality	**Study population**		**RR 1.03** (0.6 to 1.78)	822 (2)	⊕⊕⊕⊕ **high**
	78 per 1000	**80 per 1000** (47 to 139)			
	Moderate				
	77 per 1000	**79 per 1000** (46 to 137)			
Transfusion	**Study population**		**RR 1.11** (0.52 to 2.37)	822 (2)	⊕⊕⊕⊖ **moderate**[1]
	80 per 1000	**89 per 1000** (42 to 190)			
	Moderate				
	79 per 1000	**88 per 1000** (41 to 187)			
Numbers of adverse effects due to hypertension	**Study population**		**RR 1.18** (0.83 to 1.67)	822 (2)	⊕⊕⊕⊕ **high**
	122 per 1000	**144 per 1000** (101 to 203)			
	Moderate				
	123 per 1000	**145 per 1000** (102 to 205)			
Numbers of adverse events due to access thrombosis	**Study population**		**RR 0.96** (0.64 to 1.43)	822 (2)	⊕⊕⊕⊕ **high**
	105 per 1000	**100 per 1000** (67 to 150)			
	Moderate				
	104 per 1000	**100 per 1000** (67 to 149)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[1] Heterogeneity among studies

Summary of findings 3. Darbepoetin versus rHuEPO for the anaemia of end-stage kidney disease in dialysis patients

Darbepoetin versus rHuEPO for the anaemia of end-stage kidney disease in dialysis patients

Patient or population: patients with the anaemia of end-stage kidney disease in dialysis patients
Settings: tertiary
Intervention: darbepoetin versus rHuEPO

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Darbepoetin versusrHuEPO				
Final/change in Hb (g/dL)		Mean final/change in Hb in the intervention groups was **0.02 higher** (0.09 lower to 0.12 higher)		1245 (6)	⊕⊕⊕⊖ **moderate**[1]	
Final/change in ESA dose		Mean final/change in ESA dose in the intervention groups was **12.27 lower** (21.72 to 2.82 lower)		757 (3)	⊕⊕⊖⊖ **low**[1],[2]	
All-cause mortality	**Study population**		**RR 1.29** (0.82 to 2.02)	1596 (5)	⊕⊕⊕⊖ **moderate**[1]	
	55 per 1000	**71 per 1000** (45 to 112)				
	Moderate					
	64 per 1000	**83 per 1000** (52 to 129)				
Total treatment-related adverse events	**Study population**		See comment	570 (3)		Risks were calculated from pooled risk differences
	84 per 1000	**91 per 1000** (54 to 134)				
	Moderate					
	17 per 1000	**18 per 1000** (11 to 27)				

Hypertension	**Study population**		See comment	1475 (4)	⊕⊕⊝⊝ **low**[1],[2]	Risks were calculated from pooled risk differences
	144 per 1000	**137 per 1000** (84 to 194)				
	Moderate					
	70 per 1000	**67 per 1000** (41 to 95)				
Access thrombosis/vascular complication	**Study population**		See comment	1475 (4)	⊕⊕⊕⊝ **moderate**[1]	Risks were calculated from pooled risk differences
	95 per 1000	**81 per 1000** (65 to 95)				
	Moderate					
	29 per 1000	**25 per 1000** (20 to 29)				
Transfusion	**Study population**		See comment	1069 (3)	⊕⊕⊕⊝ **moderate**[1]	Risks were calculated from pooled risk differences
	53 per 1000	**29 per 1000** (3 to 53)				
	Moderate					
	50 per 1000	**28 per 1000** (3 to 50)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[1] High risk of bias for several domains in each study
[2] Significant heterogeneity between studies

Summary of findings 4. rHuEPO once/week versus rHuEPO 2 to 3 times/week for the anaemia of end-stage kidney disease in dialysis patients

rHuEPO once/week versus with rHuEPO 2 to 3 times/week for the anaemia of end-stage kidney disease in dialysis patients
Patient or population: patients with the anaemia of end-stage kidney disease undergoing dialysis

Settings: tertiary
Intervention: rHuEPO once/week
Comparison: rHuEPO 2 to 3 times/week

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	RHuEPO 2 to 3 times/week	RHuEPO once/week				
Final/change in Hb		Mean final/change in Hb in the intervention groups was **0.17 SD lower** (0.39 lower to 0.05 higher)		363 (7)	⊕⊕⊖⊖ **low**[1,2]	SMD -0.17 (-0.39 to 0.05)
Final/change in EPO dose		Mean final/change in EPO dose in the intervention groups was **8.47 higher** (1.01 lower to 17.95 higher)		217 (5)	⊕⊕⊖⊖ **low**[1,2]	
Adverse effects: transfusions	**Study population**		See comment	173 (1)	See comment	Risks were calculated from pooled risk differences
	90 per 1000	**71 per 1000** (-10 to 150)				
	Moderate					
	90 per 1000	**71 per 1000** (-10 to 150)				
Adverse effects: hypertension	**Study population**		See comment	175 (4)	⊕⊕⊖⊖ **low**[1,2]	Risks were calculated from pooled risk differences
	265 per 1000	**260 per 1000** (146 to 374)				
	Moderate					
	240 per 1000	**235 per 1000** (132 to 338)				
Adverse effects: access problems	**Study population**		See comment	173 (1)	See comment	Risks were calculated from pooled risk differences
	34 per 1000	**24 per 1000** (-26 to 74)				
	Moderate					
	34 per 1000	**24 per 1000** (-27 to 74)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

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[1] Significant risk of bias in several domains in all studies
[2] Small patient numbers

BACKGROUND

Description of the condition

Anaemia is a condition very often encountered among people with chronic kidney disease (CKD). There is a direct relationship between anaemia severity and decline in kidney function (Koch 1991). Anaemia results in significant morbidity causing symptoms including lack of energy, breathlessness, dizziness, angina, poor appetite and decreased exercise tolerance (Canadian EPO 1990a; Lundin 1989). Decreased production of erythropoietin, a naturally occurring hormone mainly produced by the kidney, is the major cause of anaemia among people with CKD (Jensen 1994). Improvement in energy levels (Wolcott 1989), increased cardiac performance and ejection fraction (Pappas 2008), and normalisation of increased cardiac output and left ventricular mass (Cannella 1990) occurred with increasing haemoglobin levels. Before recombinant human erythropoietin (rHuEPO) became available, anaemia was treated by blood transfusion together with iron and folate supplements. Blood transfusions were used sparingly because they have associated risks of infection transmission and inducing cytotoxic antibodies that could jeopardise future kidney transplantation (Ward 1990). Cloning of the human gene for erythropoietin was achieved in 1983 (Lin 1985), and production of rHuEPO followed. The efficacy of rHuEPO treatment in dialysis patients was demonstrated by 1986 (Winearls 1986). National (CARI 2011) and international guidelines (KDIGO 2012) currently recommend target haemoglobin levels of 110 mg/L to 120 mg/L in people with CKD.

Description of the intervention

Administration of erythropoiesis-stimulating agents (ESA) aims to replace endogenous erythropoietin production, which is reduced in CKD, and to raise haemoglobin levels to alleviate signs and symptoms of anaemia.

ESA products, such as epoetin-α and epoetin-β, have proven efficacy in treating anaemia in people with CKD (Eschbach 1987). However, because of the relatively short half-life of these agents (six to eight hours when administered intravenously, and 19 to 24 hours when administered subcutaneously), they require administration at two to three weekly intervals in most people, although some stable haemodialysis patients with low dose requirements may require weekly administration only (Locatelli 2011). Such frequent administration may be inconvenient for both patients and healthcare workers. Following red cell aplasia, a complication predominantly associated with subcutaneous administration of epoetin-α, intravenous administration was recommended (Ortho Biotech Jansen Cilag 2001).

There has been a general trend towards less frequent dosing regimens using new long-acting ESA preparations that offer greater patient comfort and convenience. Darbepoetin was the first ESA with a prolonged half-life to enter the market. It has five N-linked carbohydrate chains, whereas rHuEPO has only three. Because of its increased sialic acid-containing carbohydrate content, darbepoetin has a threefold longer terminal half-life (25 hours intravenous and 48 hours subcutaneous) compared with rHuEPO. This enables once a week or once every two weeks administration in people with CKD (Macdougall 1999). More recently, the continuous erythropoietin receptor activator (CERA), methoxy polyethylene glycol-epoetin-β has been developed to ensure stable maintenance and correction of haemoglobin levels at less frequent administration in people with CKD. CERA differs from rHuEPO through the formation of a chemical bond between either the N-terminal amino group or the ε-amino group of any lysine present in erythropoietin and methoxy polyethylene glycol-butanoic acid (Macdougall 2005). Despite lower receptor affinity, CERA induces a more prolonged response than epoetin-α or epoetin-β.

How the intervention might work

The primary cause of anaemia in CKD is the relative insufficiency of erythropoietin production associated with CKD. ESA accelerate erythropoiesis, increase iron utilisation and raise haemoglobin levels with clinical improvement in signs and symptoms of anaemia. ESA requirements are difficult to predict in individual patients, and may be increased in people with associated comorbidities including cardiovascular disease, diabetes and chronic inflammation. ESA requirements are generally lower in patients not receiving dialysis. ESA therapy aims to increase haemoglobin levels slowly at a rate of < 1 g/dL to 2 g/dL per month during the correction phase. This is done to avoid major side effects including hypertension, vascular access thrombosis and cardiovascular events, and then maintain stable haemoglobin.

A major issue in ESA use relates to the haemoglobin target to be achieved. Recent systematic reviews have suggested that aiming for haemoglobin levels similar to those seen in healthy adults is associated with a significantly higher risk of all-cause mortality (Palmer 2010).

Why it is important to do this review

ESA are effective in correcting anaemia associated with kidney disease and increasing haemoglobin levels but choice of agent should include the drug's pharmacodynamics, pharmacokinetics, route and frequency of administration, adverse effects, availability and economic issues. The 2002 review (Cody 2002) and subsequent 2005 update (Cody 2005a) assessed different frequencies of rHuEPO. This update (2013) evaluated the benefits and adverse effects of the newer ESA, which are administered at less frequent intervals than rHuEPO.

This review assessed different frequencies of ESA in patients on dialysis. A review by (Cody 2005b), which assessed rHuEPO frequencies in non-dialysis patients, is being updated to include longer-acting ESA.

OBJECTIVES

This review aimed to establish optimal frequency of ESA administration in terms of:

1. effectiveness (correction of anaemia, and freedom from adverse events); and
2. efficiency (optimal resource use) of different ESA dose regimens.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) or quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use

of alternate medical records, date of birth or other predictable methods) comparing different frequencies of ESA administration in patients dialysed for end-stage kidney disease (ESKD) were eligible for inclusion.

Types of participants

Haemodialysis or peritoneal dialysis patients (adults and children) with the anaemia of ESKD.

Types of interventions

Different frequencies and administration of ESA: rHuEPO, darbepoetin and continuous erythropoietin receptor agonists (CERA)

1. CERA versus other ESA (darbepoetin or rHuEPO)
2. Different frequencies of darbepoetin administration
3. Darbepoetin versus rHuEPO
4. Different frequencies of rHuEPO administration.

Types of outcome measures

1. Measures of correction of anaemia: values of haemoglobin/haematocrit or change in haemoglobin/haematocrit at the end of the study
2. Change in ESA requirements
3. All-cause mortality; cardiovascular mortality
4. Measures of hypertension: systolic and diastolic blood pressure, numbers with hypertension
5. Other adverse events: numbers of blood transfusions; numbers discontinued due to adverse events (e.g. access problems)
6. Quality of life.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register to 21 March 2013 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

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

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

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

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

For search strategies used in the previous reviews please refer to Cody 2002 and Cody 2005a.

Data collection and analysis

Selection of studies

In the previous versions of this review (2002 and 2005) all electronically-derived abstracts and study titles were assessed by a single author for subject relevance and methodological quality. All possible RCTs or quasi-RCTs which were relevant were assigned specific topic keywords in Reference Manager, and the full published paper was obtained for full assessment.

In the current review (2014), study titles and abstracts were reviewed by two authors (DH, EH). Full text articles of studies considered relevant were obtained and reviewed for eligibility by both authors.

Data extraction and management

A data abstraction form was devised to record details of data elements such as outcome measures, participants and intervention from each included study for the 2002 and 2005 reviews. Only comparisons and outcomes which were prespecified in the protocol were included. For these reviews, data were abstracted by a single assessor and a sample was double checked.

For the current review, data extraction and assessment of risk of bias was performed by two authors (DH, EH) using standardised data extraction forms. Disagreements not resolved by discussion between authors could be referred to a third person. Studies reported in languages other than English were to be translated before data extraction, but no foreign language reports were identified. Where more than one report of a study was identified, data were extracted from all reports. Where there were discrepancies between reports, data from the primary source were used. Study authors were contacted for additional information about studies; however, no additional information was obtained.

Assessment of risk of bias in included studies

Hard copies of studies were independently assessed for methodological quality by two assessors for the 2002 and 2005 reviews. Quality assessments were made for allocation concealment, blinding, description of withdrawals and drop-outs, numbers lost to follow-up, and whether intention-to-treat (ITT) analysis was possible.

In this review, the following items were assessed 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 (detection bias)?
  - Participants and personnel

- Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (all-cause mortality, adverse effects), relative risk (RR) with 95% confidence intervals (CI) were calculated. For continuous outcomes (final haemoglobin or change in haemoglobin), mean difference (MD) with 95% CI were calculated. Either final haemoglobin or changes in haemoglobin were included in meta-analyses. When both measures were provided, final haemoglobin was included in meta-analyses. Standard mean difference (SMD) with 95% CI was used to combine different units of measurement which measured the same underlying concept (e.g. haematocrit and haemoglobin).

Unit of analysis issues

Data from cross-over studies were to be included in meta-analyses if separate data for the first study phase were available. However, no such data were available.

Dealing with missing data

We aimed to analyse available data in meta-analyses using ITT data. However, where ITT data were only available graphically or not provided and additional information could not be obtained from the study authors, per-protocol (PP) data were used in analyses.

Assessment of heterogeneity

Heterogeneity was analysed using Chi^2 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 of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity respectively.

Assessment of reporting biases

The search strategy applied aimed to reduce publication bias caused by lack of publication of studies with negative results. We had planned to investigate for publication bias using funnel plots but there were too few studies on each comparison. Where there were multiple publications of the same study, all reports were reviewed to ensure that all details of methods and results were included.

Data synthesis

Data were combined using a random-effects model for dichotomous and continuous data.

Subgroup analysis and investigation of heterogeneity

Included studies were divided into four groups based on the ESA comparisons. Subgroup analysis was planned based on dialysis modality (haemodialysis versus peritoneal dialysis), patient age (paediatric versus adult) and route of ESA administration (intravenous versus subcutaneous). However, there were few data on peritoneal dialysis patients, no data on paediatric patients and insufficient studies to evaluate route of administration.

Sensitivity analysis

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

RESULTS

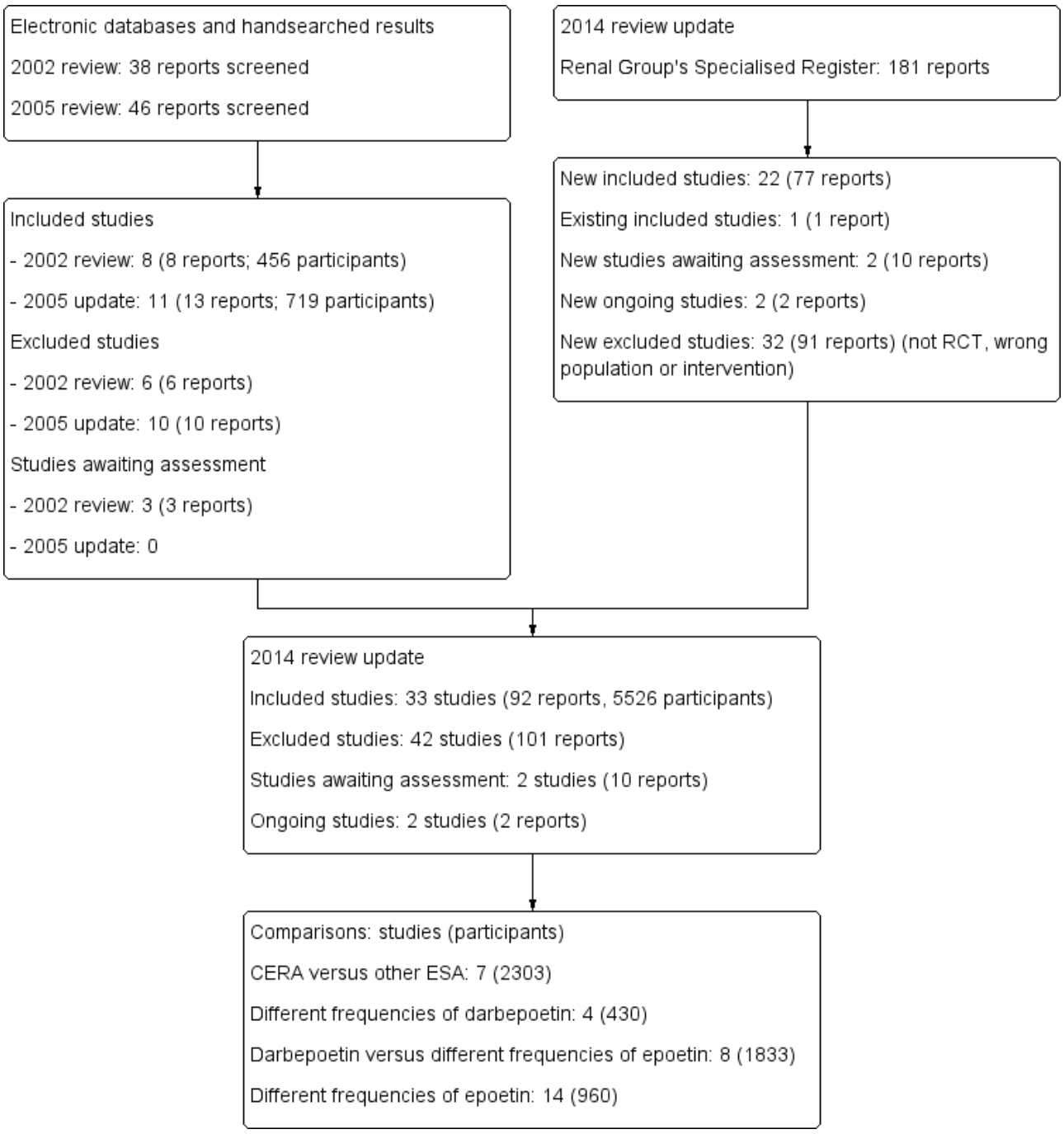
Description of studies

Results of the search

In the first version of this review (Cody 2002), there were 38 studies identified and assessed for relevance. Of these, eight studies met the inclusion criteria (Canaud 1995; Frifelt 1996; Lago 1996; Lui 1991; Lui 1992; Miranda 1990; Paganini 1991; Weiss 2000). For the first update (Cody 2005a) of this review, three new studies were added (Brahm 1999; Leung 1995; Locatelli 2002) to provide a total of 11 studies that involved 719 participants.

For the 2014 update, 181 potentially relevant articles were identified. Of these, 22 studies satisfied the inclusion criteria (AMICUS Study 2007; BA16285 Study 2007; BA16286 Study 2007; Carrera 2003; Coyne 2000; Coyne 2006a; Hori 2004; Nagaya 2010; Kwan 2005; Lee 2008; Locatelli 2004; MAXIMA Study 2007; Mircescu 2006; Muirhead 1989; Murtagh 2000; Nissenson 2002; PROTOS Study 2007; RUBRA Study 2008; STRIATA Study 2008; Tessitore 2008; Vanrenterghem 2002; Yoon 2004). Two studies were identified from study registration databases with no results to date. We excluded 32 studies. In this update, 33 studies (92 reports) involving 5526 participants were included for analysis (Figure 1).

Figure 1. Flow diagram for study selection CERA - continuous erythropoietin receptor agonists; ESA - erythropoiesis-stimulating agents



Following external review, the literature search was updated to March 2013. Two additional studies (EMERALD 1 Study 2013; EMERALD 2 Study 2013) were identified that assessed peginesatide in patients with anaemia undergoing dialysis. These studies are listed in Studies awaiting classification and will be assessed for inclusion during the next update of this review.

Included studies

The 33 included studies were divided into four groups according to ESA comparisons. There were 20 studies available as full papers and 13 in abstract form only. Data from 10 studies could not be included in any meta-analyses.

CERA versus other ESA

Seven studies (2303 participants) compared CERA to another ESA (AMICUS Study 2007; BA16285 Study 2007; BA16286 Study 2007; MAXIMA Study 2007; PROTOS Study 2007; RUBRA Study 2008; STRIATA Study 2008). Six studies (AMICUS Study 2007; BA16285 Study 2007; BA16286 Study 2007; MAXIMA Study 2007; PROTOS Study 2007; RUBRA Study 2008) compared CERA given

two weekly with rHuEPO, with evaluation of efficacy at 24 to 36 weeks and assessment of safety up to 52 weeks. Two studies (MAXIMA Study 2007; PROTOS Study 2007) had third arms that compared CERA given four weekly with rHuEPO. Four studies (AMICUS Study 2007; MAXIMA Study 2007; PROTOS Study 2007; RUBRA Study 2008) recorded dosages of CERA and rHuEPO as median and interquartile range (IQR), and therefore, final ESA dosages could not be meta-analysed. The STRIATA Study 2008 compared CERA given two weekly with darbepoetin given once weekly or once every two weeks. Since more than 80% of participants received darbepoetin weekly, and the results were not separated according to the frequency of darbepoetin use, data for darbepoetin-treated patients included in the meta-analyses included all darbepoetin-treated patients. Three of these studies exclusively used intravenous administration, with one study using a combination of subcutaneous and intravenous administration, and one study using only subcutaneous administration

Two studies (BA16285 Study 2007; BA16286 Study 2007) provided the results of the ITT population graphically only so data could not be included in meta-analyses. CERA and rHuEPO dosages were not recorded at the end of the evaluation period. In the STRIATA Study 2008 dosages of CERA and darbepoetin were recorded as medians with IQR and could not be meta-analysed. Only 70 participants in these studies received peritoneal dialysis, and they were not analysed separately, so a distinct analysis could not be made.

Different frequencies of darbepoetin administration

Four studies (430 participants) compared differing frequencies of darbepoetin administration (Nagaya 2010; Kwan 2005; Locatelli 2004; Murtagh 2000). Murtagh 2000 reported results for all patients together so could not be meta-analysed.

Darbepoetin once/week versus rHuEPO two to three times/week

Eight studies (1833 participants) compared darbepoetin with rHuEPO (Carrera 2003; Coyne 2000; Coyne 2006a; Hori 2004; Nissenson 2002; Tessitore 2008, Vanrenterghem 2002; Yoon 2004). Participant numbers in each group were not provided by Yoon 2004 so data from this study could not be meta-analysed.

Different frequencies of rHuEPO administration

The remaining 14 studies (960 participants) evaluated different frequencies of rHuEPO administration.

- Ten studies compared weekly dosing of rHuEPO with administration two to three times/week (Canaud 1995; Frifelt 1996; Lago 1996; Lee 2008; Locatelli 2002; Lui 1991; Lui 1992; Muirhead 1989; Paganini 1991; Weiss 2000)
- Canaud 1995 included a third arm comparing rHuEPO daily versus weekly
- Mircescu 2006 compared weekly dosing with doses given every second week
- Leung 1995 compared twice weekly dosing with dosing three times weekly
- Brahm 1999 compared four different frequencies (weekly, twice weekly, three times/week, and daily)
- Miranda 1990 compared daily, twice weekly and three times weekly dosing.

Data from six studies could not be included in the meta-analyses. Brahm 1999, Miranda 1990 and Muirhead 1989 were cross-over studies and provided combined data for all patients. Frifelt 1996 provided data only as medians and IQR; Leung 1995 did not provide standard deviations; and Locatelli 2002 provided data as graphical presentations only.

Excluded studies

We excluded 42 studies (101 reports); these included 32 studies (91 reports) that were identified for the 2014 update.

Although 28 studies were RCTs, they investigated interventions that were not eligible for inclusion for this review (BA16260 Study 2006; Besarab 1998; Bhuiyan 2004; Brandt 1999; Brown 1988; Canadian EPO Study 1990; Chazot 2009; Dougherty 2004; Ifudu 1998; Kawanishi 2005; Kim 2009a; Macdougall 2003; Macdougall 2007a; Martin 2007; Moiz 2000; Muirhead 1992; Parfrey 2005; PATRONUS Study 2009; Pawlak 2007; Smith 2007; Provenzano 2006; Schmitt 2006; Smyth 2006; Spaia 1995; Spinowitz 2006; Stockenhuber 1990; Tolman 2005; Yalcinkaya 1997). Four were chiefly pharmacokinetic or safety studies (Allon 2002; Knebel 2008; Macdougall 2006; Raftery 2000); two included participants who were not on dialysis (Bennett 1991; Hirakata 2010); and five were not randomised studies (Castro 1994; Fan 1992; Ifudu 1998; Raftery 2000; Wang 2000). The frequency of administration of the intervention in the control group was unclear in Locatelli 2008.

Risk of bias in included studies

Figure 2; Figure 3

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

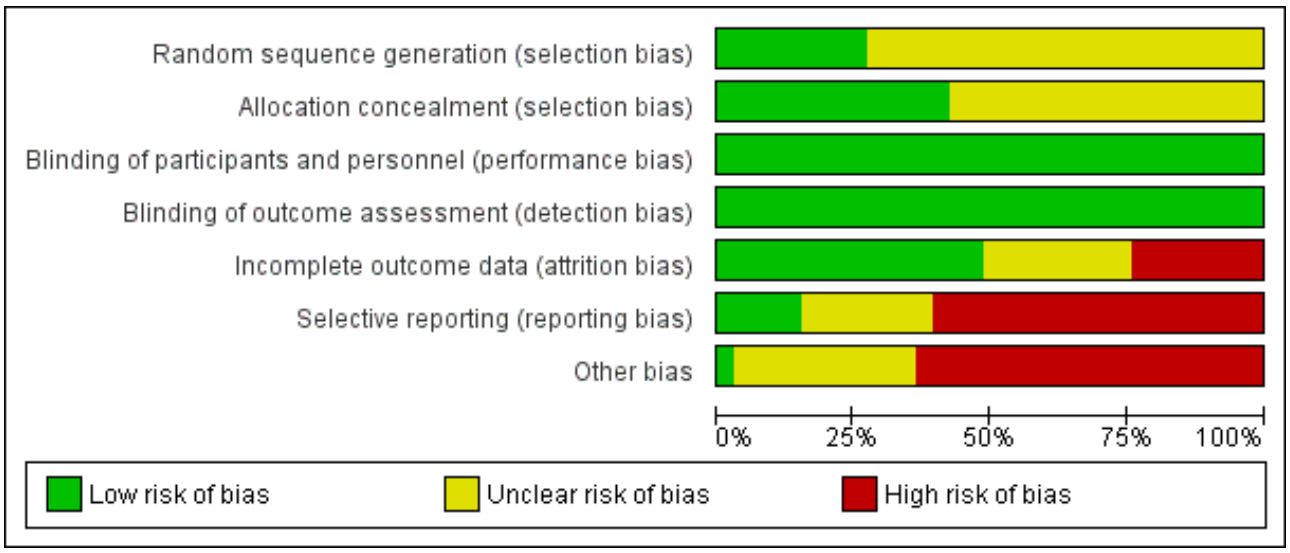


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

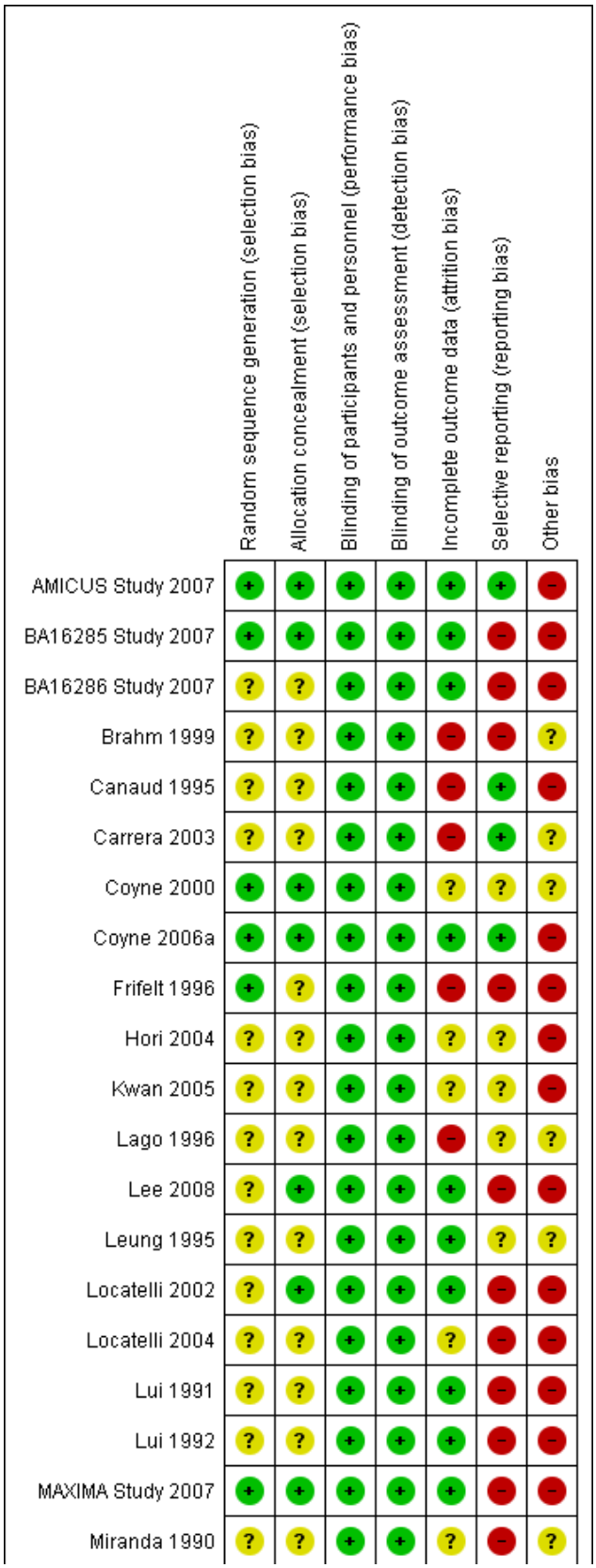
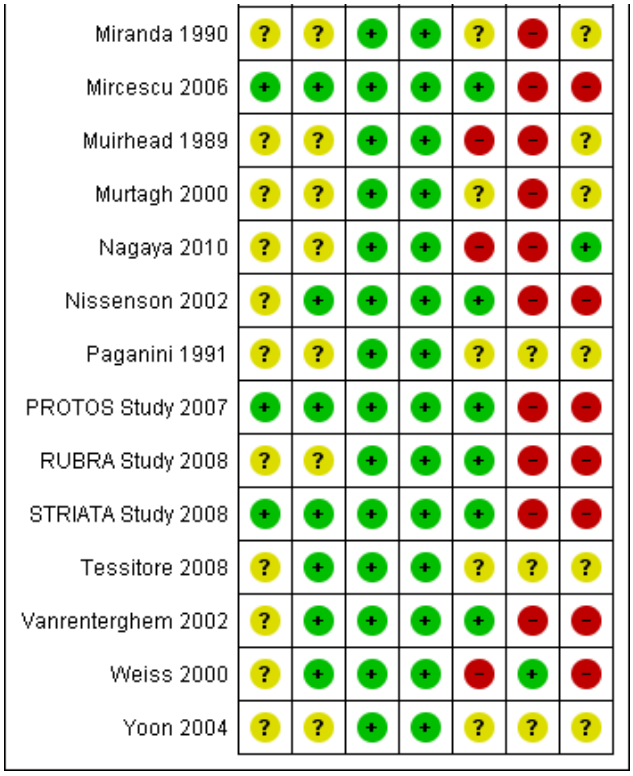


Figure 3. (Continued)



Allocation

Nine studies reported sequence generation at low risk of bias (AMICUS Study 2007; BA16285 Study 2007; Coyne 2000; Coyne 2006a; Frifelt 1996; MAXIMA Study 2007; Mircescu 2006; PROTOS Study 2007; STRIATA Study 2008). Sequence generation methodology was unclear in all other included studies.

There were 14 studies that reported central randomisation methods at low risk of bias (AMICUS Study 2007; BA16285 Study 2007; Coyne 2000; Coyne 2006a; Lee 2008; Locatelli 2002; MAXIMA Study 2007; Mircescu 2006; Nissenson 2002; PROTOS Study 2007; STRIATA Study 2008; Tessitore 2008; Vanrenterghem 2002; Weiss 2000). Allocation concealment methodology was unclear in all other included studies.

Blinding

Four studies (Coyne 2006a; Hori 2004; Locatelli 2004; Nissenson 2002) were placebo-controlled, and eight studies (AMICUS Study 2007; Canaud 1995; Lee 2008; Locatelli 2002; RUBRA Study 2008; STRIATA Study 2008; Vanrenterghem 2002; Weiss 2000) were described as open-label. However, because the primary outcome (haemoglobin, haematocrit) in all studies was based on laboratory-based assessment, and unlikely to be influenced by blinding, all included studies were considered to be at low risk of performance and detection biases.

Incomplete outcome data

Sixteen studies were considered to be at low risk of attrition bias (AMICUS Study 2007; BA16285 Study 2007; BA16286 Study 2007; Coyne 2006a; Lee 2008; Leung 1995; Locatelli 2002; Lui 1991; Lui 1992; MAXIMA Study 2007; Mircescu 2006; Nissenson 2002; PROTOS Study 2007; RUBRA Study 2008; STRIATA Study 2008; Vanrenterghem 2002). Eight studies were considered to be at high risk of attrition bias because between 19% and 41% of participants were lost to follow-up or excluded from analysis (Brahm 1999; Canaud 1995; Carrera 2003; Frifelt 1996; Nagaya 2010; Lago 1996; Muirhead 1989; Weiss 2000). Nine studies were considered to be at unclear risk of attrition bias.

Selective reporting

Studies were considered to be at high risk of reporting bias if they did not provide data on final or change in haemoglobin or haematocrit levels, final ESA requirement, all-cause mortality, and adverse effects (transfusions, hypertension, problems with haemodialysis access). Studies were also considered to be at high risk of bias if they provided results of ITT analyses in formats that could not be meta-analysed or provided combined data for all periods in cross-over studies.

Five studies (AMICUS Study 2007; Canaud 1995; Carrera 2003; Coyne 2006a; Weiss 2000) were considered to be at low risk of reporting bias. We assessed eight studies as unclear risk of bias (Coyne 2000; Hori 2004; Kwan 2005; Lago 1996; Leung 1995; Paganini 1991; Tessitore 2008; Yoon 2004), and 20 studies were considered to be at high risk of reporting bias.

Other potential sources of bias

Studies reporting any funding from pharmaceutical companies were considered to be at high risk of bias. There were 21 funded studies (AMICUS Study 2007; BA16285 Study 2007; BA16286 Study 2007; Canaud 1995; Coyne 2006a; Frifelt 1996; Hori 2004; Kwan 2005; Lee 2008; Locatelli 2002; Locatelli 2004; Lui 1991; Lui 1992; MAXIMA Study 2007; Mircescu 2006; Nissenson 2002; PROTOS Study

2007; RUBRA Study 2008; STRIATA Study 2008; Vanrenterghem 2002; Weiss 2000). Nagaya 2010 was considered to be at low risk of bias because it was funded by the Japan Dialysis Outcome Research Group. Risk of bias was unclear in the remaining 11 studies because no information on funding sources was provided.

Effects of interventions

See: **Summary of findings for the main comparison** CERA versus other ESA for the anaemia of end-stage kidney disease in dialysis patients; **Summary of findings 2** Different frequencies of CERA for the anaemia of end-stage kidney disease in dialysis patients; **Summary of findings 3** Darbepoetin versus rHuEPO for the anaemia of end-stage kidney disease in dialysis patients; **Summary of findings 4** rHuEPO once/week versus rHuEPO 2 to 3 times/week for the anaemia of end-stage kidney disease in dialysis patients

Outcomes assessed included final or change in haemoglobin/haematocrit, final ESA dose, and adverse events including all-cause mortality, hypertension, transfusion requirements and vascular access complications.

CERA every two or four weeks versus rHuEPO or darbepoetin

Meta-analysis of four studies (AMICUS Study 2007; MAXIMA Study 2007; PROTOS Study 2007; RUBRA Study 2008) showed no significant difference in final haemoglobin between CERA given every two weeks and rHuEPO given two to three times/week (Analysis 1.1.1 (4 studies, 1126 participants) MD 0.08 g/dL, 95% CI -0.04 to 0.21; I^2 = 0%). No significant heterogeneity was demonstrated.

In two studies (MAXIMA Study 2007; PROTOS Study 2007) a third group treated monthly with CERA was compared with rHuEPO given two to three times/week. There was no significant difference in final haemoglobin (Analysis 1.1.2 (2 studies, 672 participants): MD -0.03 g/dL, 95% CI -0.17 to 0.12; I^2 = 0%).

STRIATA Study 2008 compared CERA given every two weeks with weekly darbepoetin. This study reported haemoglobin was statistically significantly higher among participants who received CERA compared with those on darbepoetin, although this difference was unlikely to be of clinical significance (Analysis 1.1.3 (1 study, 249 participants): MD 0.30 g/dL, 95% CI 0.05 to 0.55).

Among the four studies that compared CERA given every two weeks with rHuEPO, and two studies comparing CERA given every four weeks with rHuEPO, there were no significant differences in all-cause mortality (Analysis 1.2.1 (4 studies, 1341 participants): RR 1.03, 95% CI 0.67 to 1.57; I^2 = 0%); (Analysis 1.2.2 (2 studies, 827 participants): RR 1.15, 95% CI 0.70 to 1.89; I^2 = 5%), numbers of adverse events due to hypertension (Analysis 1.3.1 (4 studies, 1341 participants): RR 0.93, 95% CI 0.69 to 1.26; I^2 = 24%); (Analysis 1.3.2 (2 studies, 827 participants): RR 1.00, 95% CI 0.71 to 1.40; I^2 = 3%), numbers of patients requiring transfusions (Analysis 1.4.1 (4 studies, 1341 participants): RR 0.92, 95% CI 0.64 to 1.32; I^2 = 0%; Analysis 1.4.2 (2 studies, 827 participants): RR 1.01 95% CI 0.65 to 1.57; I^2 = 0%). Furthermore, there were no significant differences in or haemodialysis access thrombosis (Analysis 1.5.1 (4 studies, 1341 participants): RR 0.96 95% CI 0.56 to 1.65; I^2 = 50%; Analysis 1.5.2 (2 studies, 827 participants) RR 1.16, 95% CI 0.53 to 2.54; I^2 = 63%). For the outcomes of haemodialysis access thrombosis, there was significant heterogeneity in the analyses which was eliminated by removal of one study (PROTOS Study 2007), which had significantly fewer access events in the rHuEPO-treated group compared with either CERA treated groups.

One study comparing CERA with darbepoetin reported no significant differences in all-cause mortality (Analysis 1.2.3 (1 study, 313 participants): RR 0.93, 95% CI 0.44 to 1.97), numbers of adverse events due to hypertension (Analysis 1.3.3 (1 study, 309 participants): RR 0.91, 95% CI 0.43 to 1.92), numbers of patients requiring transfusions (Analysis 1.4.3 (1 study, 313 participants): RR 0.79, 95% CI 0.42 to 1.51) or haemodialysis access thrombosis (Analysis 1.5.3 (1 study, 309 participants): RR 0.51, 95% CI 0.05 to 5.56). Only AMICUS Study 2007, an open-label study, reported any quality of life assessment findings: CERA produced clinically significant improvements in 7/8 subscales of quality of life at the end of the assessment period compared with 2/8 subscales with rHuEPO. No studies reported specifically on cardiovascular mortality.

Different frequencies of CERA

In two studies with three arms, CERA given every four weeks could be compared with CERA given every two weeks. There was no significant difference in final haemoglobin (Analysis 2.1 (2 studies, 675 participants): MD -0.11 g/dL, 95% CI -0.35 to 0.14; I^2 = 62%), all-cause mortality (Analysis 2.2 (2 studies, 822 participants): RR 1.03, 95% CI 0.60 to 1.78; I^2 = 24%), numbers of adverse events due to hypertension (Analysis 2.3 (2 studies, 822 participants): RR 1.18, 95% CI 0.83 to 1.67; I^2 = 0%), numbers of participants requiring transfusions (Analysis 2.4 (2 studies, 822 participants): RR 1.11, 95% CI 0.52 to 2.37; I^2 = 63%), or numbers of adverse events due to access thrombosis (Analysis 2.5 (2 studies, 822 participants): RR 0.96, 95% CI 0.64 to 1.43; I^2 = 0%). Although the I^2 analyses for final haemoglobin and transfusions were 62% and 63% respectively, the 95% CI overlapped and Chi^2 analyses did not indicate significant heterogeneity.

Assessment or evaluation dosages of CERA, darbepoetin or rHuEPO were expressed as medians with IQR in four studies (AMICUS Study 2007; MAXIMA Study 2007; PROTOS Study 2007; RUBRA Study 2008) and therefore could not be meta-analysed.

Only 70 of the included participants received peritoneal dialysis and these data were not presented separately from haemodialysis patients' data in study results. Likewise, different routes of administration were not separated in the study results.

Different frequencies of darbepoetin

Two studies (Locatelli 2004; Nagaya 2010) compared once/week with every two weeks dosing of darbepoetin. There were no significant differences in haemoglobin (Analysis 3.1 (2 studies, 252 participants): MD 0.04 g/dL, 95% CI -0.45 to 0.52; I^2 = 69%) or darbepoetin dose (Analysis 3.2 (2 studies, 252 participants): MD -8.03 µg/wk, 95% CI -21.64 to 5.59; I^2 = 77%) between treatment groups at the end of the evaluation period. However, there was significant heterogeneity in both analyses which could be related to different protocols used to determine the initial darbepoetin dose in patients who converted from once/week to every two weeks.

Locatelli 2004 reported no significant differences in all-cause mortality (Analysis 3.3 (1 study, 306 participants) RR 1.11, 95% CI 0.46, 2.66), total treatment related adverse events (Analysis 3.4.1 (1 study, 306 participants): RR 3.50, 95% CI 0.74 to 16.58) and numbers who required transfusions (Analysis 3.4.2 (1 study, 206

participants): RR 0.60, 95% CI 0.22 to 1.61). Nagaya 2010 did not provide information on all-cause mortality or transfusions, and neither study provided comparative information on hypertension and access thrombosis.

Kwan 2005 reported no significant difference in final haemoglobin between darbepoetin once/month compared with every two weeks (Analysis 4.1 (1 study, 64 participants): MD 0.40 g/dL, 95% CI -0.37 to 1.17). The only adverse outcome reported was transfusion requirement; there was no significant difference reported between the two groups (Analysis 4.2.1 (1 study, 64 participants): RR 0.33, 95% CI 0.10 to 1.14).

Murtagh 2000 compared weekly with three times/week darbepoetin, and combined the results for both groups. It was reported that all patients achieved target haemoglobin. Murtagh 2000 reported that one graft thrombosis occurred, but did not specify the participant's treatment group.

Darbepoetin versus rHuEPO two to three times/week

Seven (Carrera 2003; Coyne 2000; Coyne 2006a; Hori 2004; Nissenson 2002; Tessitore 2008; Vanrenterghem 2002) of the eight studies that evaluated this comparison contributed data to one or more meta-analyses.

There was no significant difference between final haemoglobin or change in haemoglobin at end of the evaluation period (Analysis 5.1 (6 studies, 1245 participants): MD 0.02 g/dL, 95% CI -0.09 to 0.12; I^2 = 0%). Hori 2004 reported the mean change in haemoglobin concentration from baseline only between groups and found no significant difference (0.07 g/dL, 95% CI -0.25 to 0.39).

Three studies (Coyne 2006a; Nissenson 2002; Tessitore 2008) reported ESA dose at evaluation. To enable dose comparisons, rHuEPO doses were converted from units to µg using the formula: 200 U rHuEPO = 1 µg darbepoetin (Nissenson 2002). Compared with rHuEPO-treated participants, people on darbepoetin received significantly lower weekly ESA doses (Analysis 5.2 (3 studies, 757 participants): MD -12.27 µg/wk, 95% CI -21.72 to -2.82; I^2 = 52%). All studies favoured darbepoetin although there was a moderate degree of heterogeneity in this analysis, which was eliminated by exclusion of Tessitore 2008 (I^2 = 0%).

There were no significant differences in all-cause mortality (Analysis 5.3 (5 studies, 1596 participants): RR 1.29, 95% CI 0.82 to 2.02; I^2 = 10%), hypertension (Analysis 5.4 (4 studies, 1475 participants): RR -0.01, 95% CI -0.06 to 0.05; I^2 = 68%), total treatment-related adverse events (Analysis 5.6 (3 studies, 570 participants): RR -0.01, 95% CI -0.03 to 0.05; I^2 = 0%), or vascular access complications (Analysis 5.7 (4 studies, 1477 participants) RR -0.01, 95% CI-0.03 to 0.00; I^2 = 0%). There was significant heterogeneity in the analysis of hypertension, which was eliminated in sensitivity analyses by excluding study data from Vanrenterghem 2002, which reported a significantly higher risk of hypertension among rHuEPO-treated patients. Transfusion requirements were significantly increased among rHuEPO-treated patients (Analysis 5.5 (3 studies, 1069 participants): RD -0.02, 95% CI -0.05 to -0.00; I^2 = 0%).

Data from Yoon 2004 could not be included in meta-analyses because numbers of participants in each treatment group were not provided. The reported difference in haemoglobin between treatments was -0.30 g/dL (95% CI -0.84 to 0.23), which was not significantly different.

Different frequencies of rHuEPO

Among the included studies, 14 compared different frequencies of rHuEPO administration.

Once/week versus two to three times/week

Of 10 studies that evaluated rHuEPO given weekly with rHuEPO given two to three times/week, seven could be included in meta-analyses (Canaud 1995; Lago 1996; Lee 2008; Lui 1991; Lui 1992; Paganini 1991; Weiss 2000). There was no significant difference between final haemoglobin and haematocrit at the end of the evaluation period (Analysis 6.1 (7 studies, 363 participants): SMD -0.17, 95% CI -0.39 to 0.05; I^2 = 0%). Three studies reported no significant differences among frequencies but results could not be meta-analysed because: results were provided as medians with IQR (Frifelt 1996), graphically (Locatelli 2002), or as combined data in a cross-over study (Muirhead 1989).

Five studies reported final or change in EPO dose (Canaud 1995; Lee 2008; Lui 1991; Lui 1992; Paganini 1991). There was no significant difference between weekly and two to three times/week (Analysis 6.2 (5 studies, 504 participants): MD 8.47 U/kg/wk, 95% CI -1.01 to 17.95; I^2 = 0%). There were no significant differences in hypertension (Analysis 6.3.1 (4 studies, 175 participants): RR -0.00, 95% CI -0.12 to 0.11: I^2 = 0%), transfusion requirements (Analysis 6.3.2 (1 study, 173 participants): RR -0.02, 95% CI -.010 to 0.06)) and haemodialysis access thrombosis (Analysis 6.3.3 (1 study, 173 participants): RR -0.01 95% CI -0.06 to 0.04).

Once/week versus every two weeks

One study compared once weekly rHuEPO with rHuEPO given every two weeks (Mircescu 2006). This study reported no significant differences in haemoglobin (Analysis 7.1 (1 study, 203 participants): MD -0.03 g/dL, 95% CI -0.27 to 0.21) or final rHuEPO dose (Analysis 7.2 (1 study, 203 participants): MD 4.0 IU/kg/wk, 95% CI -2.05 to 10.05). Systolic blood pressure was significantly lower among patients treated with rHuEPO weekly compared with two weekly (Analysis 7.3 (1 study, 203 participants): MD - 8.7 mm Hg, 95% CI -13.08 to -4.32), but there was no significant difference in diastolic blood pressure (Analysis 7.4 (1 study, 203 participants): MD 0.40 mm Hg, 95% CI -2.73 to 3.53). No vascular access complications were reported.

Daily versus weekly

Canaud 1995 enrolled a third group comparing daily rHuEPO with once weekly dosing. This study reported no significant differences in mean haemoglobin (Analysis 8.1 (1 study, 42 participants): MD -0.20 g/dL, 95% CI -0.65 to 0.25) or final rHuEPO dose (Analysis 8.2 (1 study, 42 participants) MD 34.60 U/kg/wk, 95% CI -6.34 to 75.54) at the end of the study.

Other results

Brahm 1999 compared multiple different rHuEPO frequencies; Leung 1995 compared rHuEPO twice/week with three times/week; and Miranda 1990 reported on rHuEPO daily compared with twice/week. Brahm 1999 (a cross-over study) and Miranda 1990 reported data for combined treatment groups only. Leung 1995 did not provide standard deviations. Brahm 1999 maintained

stable haemoglobin levels and found no difference in numbers of rHuEPO injections required/week to achieve this outcome. All-cause mortality and adverse effects were not reported. Leung 1995 reported that there were no significant differences in haemoglobin change, rHuEPO dose or numbers of antihypertensive drugs required between the twice and three times/week dosing regimen. Miranda 1990 reported satisfactory rises in haemoglobin in patients and no differences in required rHuEPO doses between treatment groups.

DISCUSSION

Summary of main results

Previous versions of this review presented analyses based on 11 studies that assessed different frequencies of rHuEPO - epoetin-α or epoetin-β. An additional 22 studies were included in this update, most of which evaluated the longer-acting ESA darbepoetin and CERA. For ease of comparison, we divided the included studies into four groups.

CERA versus other ESA

Our findings demonstrated that CERA administered at reduced frequencies compared with rHuEPO provides comparable degrees of anaemia correction without new or increased numbers of adverse effects or increase in all-cause mortality. In addition, no significant differences in efficacy or adverse effects were demonstrated using different frequencies of CERA. Two studies investigated intravenous ESA administration, one used subcutaneous administration and another used both routes. Interpretation of the meta-analyses revealed no obvious variation in results according to route of administration, but this could not be formally tested in subgroup analyses.

Only AMICUS Study 2007, an open-label study, reported on quality of life with improvement and determined greater improvement with CERA compared with rHuEPO.

MAXIMA Study 2007 and PROTOS Study 2007 compared administration of CERA at two weekly and four weekly intervals. No significant differences were found in final haemoglobin or reports of adverse events.

CERA administered intravenously every two weeks showed no significant difference in maintaining haemoglobin compared with darbepoetin administered at once/week. There were no significant differences between groups for all-cause mortality and adverse events including hypertension, vascular access complications and transfusion requirements.

Different frequencies of darbepoetin

Two studies compared darbepoetin administered once weekly with every two weeks. There were no significant differences in final haemoglobin, all-cause mortality and other reported adverse events between frequencies. There was significant heterogeneity between studies for the outcomes of haemoglobin and darbepoetin dosage, which may have resulted from different dosing schedules.

Darbepoetin versus rHuEPO

Six studies compared once/week darbepoetin with two to three times/week administration of rHuEPO, with no significant differences in final haemoglobin or change in haemoglobin, all-cause mortality and adverse effects. ESA dose was significantly lower in darbepoetin-treated patients but this outcome was only reported in three studies (757 participants).

Different frequencies of rHuEPO

No significant differences in final haemoglobin, haematocrit or rHuEPO dose were identified in 10 studies that compared rHuEPO once/week with two to three times/week. No studies reported all-cause mortality, and there were limited data on other adverse effects. The other included studies assessed different frequencies of rHuEPO administration and identified no significant differences in final haemoglobin or rHuEPO dose with limited data on other outcomes.

Overall completeness and applicability of evidence

This review included only studies that evaluated ESA for people on dialysis. However, most participants were on haemodialysis. Lui 1991 only included peritoneal dialysis patients and evaluated rHuEPO. Other studies included few participants on peritoneal dialysis but did not separate data according to mode of dialysis. Furthermore, we did not identify any studies in children on dialysis. An open-label, non-inferiority study that compared darbepoetin-α and rHuEPO in 124 children with CKD not on dialysis found no significant difference in maintaining haemoglobin (Warady 2006).

There were limited data available that compared long-acting ESA. We identified one study in dialysis patients which compared darbepoetin and CERA and included 313 participants (STRIATA Study 2008). This study identified a small (0.3 g/dL) statistically significant, but not clinically significant, benefit from CERA over darbepoetin with no differences in adverse event profiles. However, further studies comparing different frequencies are required to determine if these drugs provide similar clinical benefits. PATRONUS Study 2009, which did not match our inclusion criteria for this review, found that CERA was superior to darbepoetin when both drugs were given at four weekly intervals.

Patient-centred outcomes were generally poorly reported. We found that 13/33 studies recorded all-cause mortality; only four reported cardiovascular mortality data; and none reported on cardiovascular morbidity. AMICUS Study 2007, which compared CERA with rHuEPO, provided limited quality of life data. Six older studies (Lee 2008; Leung 1995; Lui 1991; Lui 1992; Paganini 1991; Weiss 2000) that evaluated different frequencies of rHuEPO were less likely to report adverse effects data, and none reported on all-cause mortality.

Although hypertension and vascular access complications are known to be associated with ESA administration, these were reported in only 14 and 11 studies respectively. It is widely accepted that ESA therapy reduces transfusion requirements, however, 22 studies failed to report on transfusion events.

ESA doses in the CERA studies could not be meta-analysed because data were reported as medians and IQR. Furthermore, ESA doses in other studies could not be meta-analysed because of different reporting methods. Nagaya 2010 and Locatelli 2004 compared different frequencies of darbepoetin administration, but there was marked heterogeneity in the analyses for haemoglobin (Analysis 3.1) and darbepoetin dose (Analysis 3.2). Reasons for heterogeneity were unclear, but may be related to different schedules used to alter darbepoetin dose in these studies.

Quality of the evidence

We included 33 studies that involved 5526 participants in this review. Of these, 13 were available only in abstract form.

We found that nine (27%) studies demonstrated adequate random sequence generation, and 14 (42%) were assessed as showing allocation procedures at low risk of bias. These parameters were found to be less commonly reported in earlier studies that compared erythropoietin administration frequencies. Blinding was reported in only a few studies, but because outcome measures were reported as laboratory results, this was considered to confer a low risk of bias. Attrition bias (incomplete outcome data) was identified in 50% of the included studies, and reporting bias (selective reporting) was identified or unclear in fewer than 15% of studies (Figure 2).

Quality of studies comparing CERA and rHuEPO was considered high for the outcome of final haemoglobin (Summary of findings for the main comparison), but a small sample size meant that quality was moderate in the study that compared CERA and darbepoetin. Small numbers of events meant that study quality was assessed as moderate for all-cause mortality. The quality of studies reporting on adverse events was considered to be moderate for all outcomes, except hypertension, where quality was high. These studies were all well-funded, large multicentre studies, with potentially better study design and reporting.

Overall, quality of studies comparing different durations of CERA administration was considered to be high or moderate for all outcomes (Summary of findings 2).

In the studies comparing darbepoetin and rHuEPO for outcomes of final haemoglobin and all-cause mortality, overall quality was assessed as moderate (Summary of findings 3). In relation to adverse effects, overall quality was assessed as moderate or low because of heterogeneity and high risk of bias in individual studies.

In studies that compared different frequencies of rHuEPO administration, quality of evidence was considered to be low for all outcomes (Summary of findings 4). Many of these studies were available only in abstract form. Among these earlier studies participant numbers were low, important outcomes such as mortality were not reported, and components of study design were poorly reported or at high risk of bias.

Only 17/33 studies could be included in Summary of findings tables because other comparisons involved single studies only or data could not be included in meta-analyses.

Potential biases in the review process

A comprehensive search of the Cochrane Renal Group's Specialised Register was undertaken; the last search was completed in March 2013. This decreased the likelihood that published eligible studies were omitted from our review. However, more recently published eligible studies and eligible studies in congress proceedings not searched could have been missed. We found that 40% of included studies were available only in the abstract form that provided limited information on study methods and results; inclusion of these data could be a source of bias. Two potentially eligible studies in progress were identified from study registries.

This was an extensive review completed independently by two authors who both 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 rHuEPO 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.

Among the more recent studies of longer-acting ESA per-protocol data were meta-analysed for the primary outcome of haemoglobin level in three (MAXIMA Study 2007; PROTOS Study 2007; RUBRA Study 2008) of the four studies; ITT data were either not provided or were presented in graphical form only. We did not receive responses from authors we contacted with requests for ITT data. Sensitivity analysis that excluded the study that provided ITT data (AMICUS Study 2007) did not alter the MD and 95% CI. This suggested that use of per-protocol data did not bias the results.

Agreements and disagreements with other studies or reviews

Carrera 2007 published a narrative review that assessed different frequencies of darbepoetin or comparisons of darbepoetin with rHuEPO in dialysis patients and patients not yet on dialysis. Among dialysis patients, the review included 13 studies of which seven were RCTs. We included six of those RCTs in our review; the other study compared different routes of administration, and therefore was not eligible for inclusion in this review.

A narrative review by Foley 2010 included 10 studies that evaluated darbepoetin or CERA. Of those, seven involved dialysis patients and were included in this review.

Our review results concur with these earlier reviews that longer-acting ESA administered at less frequent intervals are non-inferior in RCTs to rHuEPO without differences in adverse events.

The Anaemia Working Group of the European Renal Best Practice (Locatelli 2009) recommended that CERA be administered every two weeks for anaemia correction, and then every four weeks. The Group considered that the safety and tolerability of CERA was similar to other ESA.

The KDIGO Working Group identified no evidence that any given type of ESA was superior to another in terms of efficacy and safety (KDIGO 2012). The KDIGO Working Group concluded that differences in efficacy among ESA were unlikely and made no recommendations about specific types of ESA. The Working Group further suggested that ESA choice would depend on patient and country-specific issues such as availability and cost.

AUTHORS' CONCLUSIONS

Implications for practice

Longer-acting ESA are now standard practice for management of anaemia among people with CKD. This review identified evidence to demonstrate that darbepoetin and CERA administered at one to four weekly intervals are non-inferior to rHuEPO given one to three times/week in terms of achieving haemoglobin targets without any significant differences in adverse events.

As well as greater convenience offered by extended dosing intervals for both patients and healthcare providers, longer-acting ESA use may also result in improved cost efficiency. A recent audit of 82 patients (Summers 2005) demonstrated that switching from a more frequent rHuEPO dose regimen to once or every two weeks, darbepoetin significantly decreased ESA acquisition costs. The MERCURIUS project assessed costs in 21 haemodialysis centres in eight European countries. Administration of ESA at two weekly intervals resulted in significant reductions in pharmacy and dialysis unit staff and equipment costs (Burnier 2009). In many countries, costs of newer longer-acting but more costly ESA would have to be balanced against costs associated with more frequent rHuEPO administration because agents provide similar degrees of efficacy and safety. Less frequent administration could also reduce needle stick injuries potentially further reducing costs. A possible downside of less frequent administration of ESA could be that doses are missed, although there are no data to support or refute this possibility.

Implications for research

Additional large, well designed, RCTs are required in the following areas:

- Comparisons of different longer-acting ESA (e.g. darbepoetin compared with CERA)
- Comparisons of different frequencies of ESA administration among peritoneal dialysis and paediatric dialysis patients.

Studies should include patient-centred outcomes including all-cause mortality, cardiovascular mortality and morbidity, and quality of life assessment. They should also include an estimate of patient and carer satisfaction related to different frequencies of administration.

Additional studies of cost-effectiveness of different frequencies of administration should be undertaken, particularly in the developing world.

ACKNOWLEDGEMENTS

- We are grateful to Conal Day, Marion Campbell, Cam Donaldson, Adrian Grant, Luke Vale, Sheila Wallace and Alison MacLeod who were authors on the original and first update of this review (Cody 2002; Cody 2005a), contributing to the design, quality assessment, data collection, entry, analysis and interpretation, and writing.
- We wish to thank the referees for their comments and feedback during the preparation of these reviews.
- The initial review (Cody 2002) was supported by a grant from the Chief Scientist's Office, Scottish Office Department of Health.
- We would like to thank Dr Daniel Coyne, Dr Marian Klinger, Dr Agnieszka Zolkiewicz, and Dr Anatole Besarab who provided additional information on their studies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

AMICUS Study 2007

Methods	• Study design: parallel group, phase III RCT • Time frame: March 2004 to December 2005 • Duration of follow-up: 24 weeks
Participants	• Countries: international • Setting: 42 tertiary centres • Age ≥18 years; No ESA for ≥ 12 weeks; CKD on PD/HD ≥ 2 weeks before screening; baseline Hb 8 to 11 g/dL; adequate iron status: serum ferritin ≥100 ng/mL or TSAT ≥ 20%. HD: Kt/v ≥1.2 or URR ≥ 65% • Number: treatment group 1 (135); treatment group 2 (46) • Mean age ± SD (years): treatment group 1 (54.7 ± 14.43); treatment group 2 (53.4 ± 15.19) • Sex (M/F): treatment group 1 (82/55); treatment group 2 (32/14) • Exclusion criteria: ESA therapy ≤ 12 weeks previously; non-renal cause of anaemia; CRP ≥ 30 mg/L; poorly controlled hypertension; presence of severe disease (e.g. MI, stroke); overt GI bleeding requiring blood transfusion < 8 weeks before screening; life expectancy ≤ 12 months
Interventions	Treatment group 1 • CERA IV

AMICUS Study 2007 *(Continued)*

	○ Starting dose: 0.40 µg/kg every 2 weeks, for 24 weeks ○ Adjustments performed according to a predefined protocol, but no more frequently than once every 4 weeks ○ Doses titrated to achieve individual increases ≥ 1.0 g/dL versus baseline and single Hb levels ≥ 11 g/dL Treatment group 2 • EPO ○ Dose: 3 times/wk IV with dosing based on approved recommendations, continued for 24 weeks ○ Doses titrated to achieve individual increases ≥ 1.0 g/dL versus baseline and single Hb levels ≥ 11 g/dL Co-interventions • participants received IV iron to maintain adequate iron status
Outcomes	• Change in Hb during correction period • Number reaching target Hb • Change in ESA dose • Quality of life • Adverse effects: total, serious, leading to withdrawal of therapy, hypertension, AV fistula thrombosis, mortality
Notes	• Loss to follow-up/excluded: withdrawals from ITT population; kidney transplant, refusal of treatment, dialysis no longer required, transfusion, insufficient Hb results, missing administration of study medication. • Additional data requested from authors: information on randomisation procedures and ITT data were requested from the authors: response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation, computer generated
Allocation concealment (selection bias)	Low risk	Central allocation with IVRS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open label study but primary outcome was laboratory based and unlikely to be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open label study but primary outcome was laboratory based and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy data and safety data available for all patients
Selective reporting (reporting bias)	Low risk	Study protocol not available but published results include all expected outcomes
Other bias	High risk	Roche sponsored

BA16285 Study 2007

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 19 weeks, with 12 month extension

Participants	• Country: USA
	• Setting: 14 centres
	• Age ≥18 years; HD ≥ 3 months; Kt/V ≥ 1.2; URR > 65%; IV EPO > 3 months; baseline Hb 10 to12 g/dL; adequate iron status; ferritin > 100 ng/mL; TSAT > 20%
	• Number
	  ○ Treatment group A: 30; weekly dosing (15); two weekly dosing (15)
	  ○ Treatment group B: 30; weekly dosing (15); two weekly dosing (15)
	  ○ Treatment group C: 31; weekly dosing (16); two weekly dosing (15)
	• Mean age SD (years)
	  ○ Treatment group A: weekly dosing (50.2 ± 9.9); two weekly dosing (58.6 ± 12.6)
	  ○ Treatment group B: weekly dosing (53.8 ± 12.7); two weekly dosing (62.8 ± 15.8)
	  ○ Treatment group C: weekly dosing (60.1 ± 11.9); two weekly dosing (62.5 ± 10.8)
	• Sex (M/F)
	  ○ Treatment group A: weekly dosing (13/2); two weekly dosing (7/8)
	  ○ Treatment group B: weekly dosing (9/6); two weekly dosing (9/6)
	  ○ Treatment group C: weekly dosing (10/6); two weekly dosing (12/3)
	• Exclusion criteria: non-renal cause of anaemia; B_{12} or folate deficiency; conditions with inadequate response to ESA (Infection/inflammation, hyperparathyroidism); blood transfusions 3 months previously; MI/coronary artery disease

Interventions	Treatment group A • CERA: 0.25 µg • EPO: 150 U • Dose: once/wk or once every 2 weeks for 19 weeks Treatment group B • CERA: 0.4 µg • EPO: 150 U • Dose: once/wk or once every 2 weeks for 19 weeks Treatment group C • CERA: 0.6 µg • EPO: 150 U • Dose: once/wk or once every 2 weeks for 19 weeks Other information • Dose adjustments permitted in all groups after 6 weeks to maintain within ± 1.5 g/dL of baseline Co-interventions • NS
Outcomes	• Change in Hb from baseline • Change in HCT from baseline • Mortality • Adverse events

BA16285 Study 2007 *(Continued)*

Notes	• Additional data on sequence generation and allocation concealment and ITT data requested from authors: response received from author regarding randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation, computer generated
Allocation concealment (selection bias)	Low risk	Central randomisation, computer generated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/91 did not complete core period but all patients included in ITT analysis. Reasons for withdrawal: adverse events, treatment refusal, inadvertent coadministration of EPO, insufficient therapeutic response, transplant, anaemia not related to CKD
Selective reporting (reporting bias)	High risk	Published results did not include ESA dosage. Results of ITT analysis only available graphically and cannot be entered in meta-analysis.
Other bias	High risk	Funded F. Hoffman La Roche Ltd

BA16286 Study 2007

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 19 weeks with 12 month extension

Participants	• Countries: Italy, USA, Spain, Germany
	• Setting: multicentre
	• Age ≥ 18 years; CKD; anaemia; dialysis, HD/PD ≥ 3 months; Kt/v ≥1.2 HD, Kt/v ≥ 1.8 PD; SC EPO ≥ 3/12; stable Hb 10 to 12 g/dL; adequate iron stores, ferritin ≥ 100 ng/mL
	• Number
	  ○ Treatment group A: 46; weekly dosing (15); three weekly dosing (15); four weekly dosing (15)
	  ○ Treatment group B: 44; weekly dosing (16); three weekly dosing (16); four weekly dosing (12)
	  ○ Treatment group C: 47; weekly dosing (16); three weekly dosing (15); four weekly dosing (16)
	• Mean age SD (years)
	  ○ Treatment group A: weekly dosing (67 ± 13.0); three weekly dosing (65.6 ± 11.3); four weekly dosing (64.8 ± 10.3)
	  ○ Treatment group B: weekly dosing (61.8 ± 13.5); three weekly dosing (64.1 ± 12.8); four weekly dosing (67.3 ± 13.3)
	  ○ Treatment group C: weekly dosing (62.7 ± 13.7); three weekly dosing (58.9 ± 13.1); four weekly dosing (64.1 ± 13.3)
	• Sex (M/F)

BA16286 Study 2007 *(Continued)*

- Treatment group A: weekly dosing (11/5); three weekly dosing (7/8); four weekly dosing (10/5)
- Treatment group B: weekly dosing (10/6); three weekly dosing (11/5); four weekly dosing (5/7)
- Treatment group C: weekly dosing (12/4); three weekly dosing (10/5); four weekly dosing (9/6)

- Exclusion criteria: life expectancy < 6 months; severe disease e.g. MI, unstable CAD; poorly controlled BP; blood transfusions in last 3 months; non-renal causes of anaemia; infection; inflammation (RA/SLE); GI bleeding; B_{12} or folate deficiency; severe hyperparathyroidism

Interventions	Treatment group A • CERA: 0.4 µg • EPO: 150 U • Dose: once/wk; once every 3 weeks, once/mo for 19 weeks Treatment group B • CERA: 0.8 µg • EPO: 150 U EPO • Dose: once/wk, once every 3 weeks, once/mo for 19 weeks Treatment group C • CERA: 1.2 µg • EPO: 150 U • Dose: once/wk, once every 3 weeks, once/mo for 19 weeks Other information • Dose adjustments were allowed in all groups after 6 weeks to maintain Hb within ± 1.5 g/dL of baseline Co-interventions • NS
Outcomes	• Change in Hb level • Change in HCT • Mortality • Adverse effects
Notes	• Additional information randomisation and allocation concealment and ITT data requested from authors: no response obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided: "phase II, randomised, open label"
Allocation concealment (selection bias)	Unclear risk	No information provided: "assignment in sequential fashion"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding

BA16286 Study 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	11/137 withdrawn; 2 died, 2 withdrew because of adverse events, 3 insufficient therapeutic response, 1 transplant, 1 failure to return, 1 holiday, 1 hospitalisation; all patients included in ITT analysis
Selective reporting (reporting bias)	High risk	No outcome data provided on ESA dosage. Data on ITT analysis only available graphically and could not be included in meta-analysis
Other bias	High risk	Funded by F. Hoffmann La Roche Ltd

Brahm 1999

Methods	• Study design: cross-over RCT • Study duration: NS • Duration of follow-up: 8 to 20 week run-in/correction period; 24 week treatment duration
Participants	• Country: Denmark • Setting: single centre • Stable patients on CAPD for at least 6 months; Hb ≤ 6.0 mmol/L or requiring blood transfusions; patients with stable target Hb within ± 0.2 mmol/L for at least 4 weeks entered study; CAPD • Number: 30 consecutively recruited to correction period, 22 randomised to once, twice, or three times weekly or daily • Mean age (range): 51 years (21 to 64) • Sex (M/F): 10/12 • Exclusion criteria: NS

Interventions	EPO (SC)
	• Once, twice, or three times/wk or daily
	• Dose
	  ◦ Correction period initial dose 50 U/kg twice/wk, dose adjusted in two-week intervals to reach target Hb during 8 to 20 weeks. Increase in HCT aimed at 1%/wk
	• Duration of study
	  ◦ Correction period 8 to 20 weeks (median 12 weeks).
	  ◦ RCT period: four periods of 8 to16 weeks (median 12 weeks)
	• Type of EPO: NS

Outcomes	• Change in dose of EPO with different frequency regimens to maintain HCT 35% • Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomised
Allocation concealment (selection bias)	Unclear risk	NS
Blinding of participants and personnel (performance bias)	Low risk	Primary outcome was laboratory based and not likely to be influenced by blinding

Brahm 1999 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and not likely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	27% not analysed and of 22, only 13 completed all 4 cross-over periods; loss to follow-up: 8/30 (27%) dropped out during correction period 13/22 (59%) completed all four frequency regimens
Selective reporting (reporting bias)	High risk	Cross-over study; data reported for correction periods and not patients so data cannot be included in meta-analysis
Other bias	Unclear risk	Funding: NS

Canaud 1995

Methods	• Study design: open-label, parallel RCT • Study duration: NS • Duration of follow-up: 16 weeks
Participants	• Countries: Europe • Setting: 10 dialysis centres • ESKD on regular HD; anaemia corrected for ≥12 months x 3 weekly IV • Number: treatment group 1 (18); treatment group 2 (20); treatment group 3 (16); treatment group 4 (22) • Mean age ± SD (years): NS • Sex (M/F): 56/60 • Exclusion criteria: iron deficiency; uncorrected folate and/or Vitamin B_{12} deficiency; corticotherapy; uncontrolled hypertension; acute illness; surgery; secondary hyperparathyroidism; aluminium intoxication
Interventions	Treatment group 1 • EPO: IV, 3 times/wk Treatment group 2 • EPO: SC, once/wk Treatment group 3 • EPO: SC, 3 times/wk Treatment group 4 • EPO: SC, daily SC Other information • Dose: Initial dose as for previous control period • Dose adjustments at 4 weekly intervals to maintain Hb level between 9 and 12 g/dL • Type of EPO: Alpha Co-interventions • Iron supplement, IV and oral

Canaud 1995 *(Continued)*

Outcomes	• Number failing to achieve target Hb/HCT • Mean Hb achieved at end of maintenance phase • Mean EPO dose given during maintenance phase • Numbers commencing or increasing antihypertensive therapy
Notes	• Only data from SC groups included in meta-analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised but no other information provided: "open, randomised, multicentre study"
Allocation concealment (selection bias)	Unclear risk	NS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-labelled study. Primary outcome was laboratory based and not likely to be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open-labelled study. Primary outcome was laboratory based and not likely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	40 (34%) of 116 patients withdrawn from final analysis and this loss could influence the results: transplantation (7), death (1), lost to follow-up (3), unable to self-inject (1), final Hb at week 16 higher than target Hb > 12 g/dL (11)
Selective reporting (reporting bias)	Low risk	Specified essential outcomes included
Other bias	High risk	Study overseen by Cilag laboratories

Carrera 2003

Methods	• Study design: parallel RCT • Time frame: NS • Duration of follow-up: 10 months
Participants	• Country: Portugal • Setting: single centre • Age: ≥18 years; HD; 6 months on IV rHuEPO; Hb stable 11.0 to 12.5 g/dL • Number (completed/evaluated): treatment group 1 (18/24); treatment group 2 (13/20) • Mean age ± SD (years): treatment group 1 (57.7 ± 11.78); treatment group 2 (61.5 ± 22.6) • Sex (M/F): treatment group 1 (16/2); treatment group 2 (7/6) • Exclusion criteria: no active bleeding, infection or inflammation
Interventions	Treatment group 1 • DA: IV weekly for 10 months • Dose calculated according to previous dose when 200 IU EPO = 1 µg DA • Dose at baseline: 35.70 µg/wk (95% CI 26.90 to 47.40)

Carrera 2003 *(Continued)*

	Treatment group 2 • rHuEPO: IV 3 times/wk for 10 months • Continued previous dose • Dose at baseline: 5837 IU/wk (95% CI 3670 to 9281 IU/wk) • Doses of EPO and DA were titrated to maintain Hb in the range 11.0 to 12.5 g/dL Co-interventions • Iron supplements as necessary
Outcomes	• Hb at end of study • Change in Hb • ESA dose at end of study • Iron parameters at end of study • Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study stated to be randomised but no other information provided: "randomised study"
Allocation concealment (selection bias)	Unclear risk	Study stated to be randomised but no other information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Primary outcome was laboratory based and not likely to be influenced by blinding. Study participants and personnel not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and not likely to be influenced by blinding. Study participants and personnel not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Data only reported on patients, who completed study. 13 (29.5%) did not complete the study; DA group: died (2), transplants (2), surgery (2); rHuEPO group: died (3), transplant (1), surgery (3)
Selective reporting (reporting bias)	Low risk	Study protocol not available but published results include all expected outcomes
Other bias	Unclear risk	Funding: NS

Coyne 2000

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 20 weeks
Participants	• Country: USA • Setting: multicentre

Coyne 2000 *(Continued)*

- Dialysis patients; no rHuEPO in previous 12 weeks; baseline Hb ≤ 10.0 g/dL
- Number: treatment group 1 (90); treatment group 2 (31)
- Mean age ± SD (years): NS
- M/F: NS
- Exclusion criteria: NS

Interventions	Treatment group 1 • DA: 0.45 µg/kg IV or SC once/wk, continued for 20 weeks Treatment group 2 • rHuEPO: 50 U/kg 3 times/wk (150 U/kg/wk), continued for 20 weeks Other information • Dose adjustments made as necessary to achieve target Hb Co-interventions • NS
Outcomes	• % achieving target Hb • Adverse events
Notes	• Loss to follow-up: no information about any losses to follow-up or patients excluded from analyses • Additional data requested from author and information on randomisation was obtained • Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was centrally performed using an IVRS system" (information from author)
Allocation concealment (selection bias)	Low risk	"Randomization was centrally performed using an IVRS system" (information from author)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Primary outcome was laboratory based and not likely to be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and not likely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR; data provided as % and unclear whether all patients completed study
Selective reporting (reporting bias)	Unclear risk	Abstract only, not all results available
Other bias	Unclear risk	NS

Coyne 2006a

Methods	• Study design: parallel, RCT • Time frame: 29 May 2002 to 23 June 2004 • Duration of follow-up: 28 weeks
Participants	• Country: USA • Setting: multicentre • Undergoing HD; Hb 9.5 to 12.5 g/dL; TSAT ≥ 20%; stable doses of IV rHuEPO • Number: treatment group 1 (200); treatment group 2 (206) • Mean age ± SD: 57.6 ± 13 years • Sex (M/F): 211/196 • Exclusion criteria: NS
Interventions	Treatment group 1 • DA: IV once/wk • Placebo: twice/wk • Dose based on previous EPO dose; continued for 28 weeks Treatment group 2 • rHuEPO: IV 3 times/wk • Continued previous dose; continued for 28 weeks Other information • Dose in both groups titrated to maintain Hb 10 to 12 g/dL Co-interventions • NS
Outcomes	• Change in Hb • Hb at end of study • ESA dose at end of study • Adverse effects: total due to ESA; serious due to ESA; AV fistula, thrombosis; hypertension
Notes	• Additional information obtained from www.amgentrials.com • End point analysed: all subjects who received one dose and had at least one Hb measurement during evaluation period • Additional data requested from author and information on randomisation was obtained • Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was centrally performed using an IVRS system" (information from author)
Allocation concealment (selection bias)	Low risk	"Randomization was centrally performed using an IVRS system" (information from author)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	DA group received placebo IV twice weekly

Coyne 2006a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	DA group received placebo IV twice weekly
Incomplete outcome data (attrition bias) All outcomes	Low risk	406/407 included in safety analysis. 363, who had at least one evaluation Hb, were included in efficacy analysis
Selective reporting (reporting bias)	Low risk	Includes expected outcomes
Other bias	High risk	Grant/research support: Amgen

Frifelt 1996

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: NS
Participants	• Country: Denmark • Setting: single centre • Hb < 9.7 g/dL; CAPD ≥ 3 months; age ≥ 18 years; rHuEPO started and adjusted before randomisation to reach target Hb 10.5 to 12.0 g/dL • Number: treatment group 1 (16); treatment group 2 (17) • Mean age ± SD (years): NS • Sex (M/F): NS • Exclusion criteria: immunosuppressive therapy; moderate or severe hypertension; anaemia due to other causes
Interventions	Treatment group 1 • rHuEPO: SC once/wk for 3 months starting at 60 U/kg/wk • Doses adjusted to maintain target Hb Treatment group 2 • rHuEPO: SC 3 times/wk for 3 months starting at 60 U/kg/wk • Doses adjusted to maintain target Hb Other information • Type of EPO: recormon beta Co-interventions • IV and oral iron supplementation
Outcomes	• Hb levels at end of study • rHuEPO doses end of study
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Frifelt 1996 *(Continued)*

Random sequence generation (selection bias)	Low risk	"randomised, prospective study"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Primary outcome was laboratory based and not likely to be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and not likely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	15% (6/39) excluded and missing data could have influenced final result; peritonitis (4); cerebral ischaemia (1); death due to AMI (1)
Selective reporting (reporting bias)	High risk	No reports on mortality and incomplete reporting of adverse effects. Results available only as median and IQR and cannot be entered in meta-analyses
Other bias	High risk	Funded study by Ercopharm, Kvistgaard, Denmark

Hori 2004

Methods	• Study design: RCT • Study duration: NS • Duration of follow-up: 28 weeks
Participants	• Country: Japan • Setting: multicentre • HD; rHuEPO 2 to 3 times/wk • Number: treatment group 1 (61); treatment group 2 (59) • Mean age ± SD (years): NS • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group 1 • DA: once/wk for 28 weeks • Initial dose: NS • Study drug dose adjusted to maintain Hb within ± 1.0 g/dL of baseline Hb and between 9 and12 g/dL Treatment group 2 • rHuEPO: 2 to 3 times/wk; continued previous dose for 28 weeks • Study drug dose adjusted to maintain Hb within ± 1.0 g/dL of baseline Hb and between 9 and 12 g/dL Co-interventions • NS
Outcomes	• Hb difference between groups at end of study • Adverse events: total due to ESA, serious due to ESA

Hori 2004 *(Continued)*

Notes	• Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study stated to be randomised but no further information given
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Primary outcome was laboratory based and unlikely to be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on completeness of follow-up
Selective reporting (reporting bias)	Unclear risk	Abstract only
Other bias	High risk	Funding Kirin Brewery Company

Kwan 2005

Methods	• Study design: open-label RCT • Study duration: NS • Duration of follow-up: 24 weeks
Participants	• Country: Hong Kong • Setting: single centre • PD; weekly SC EPO • Number: treatment group 1 (30); treatment group 2 (34) • Mean age ± SD: 51.2 ± 13.3 years • Sex (M/F): 26/64 • Exclusion criteria: NS
Interventions	Treatment group 1 • DA: SC every 4 weeks • Dose calculated from previous EPO dose Treatment group 2 • DA: SC every 2 weeks • Dose calculated from previous EPO dose Other information

Kwan 2005 *(Continued)*

	• Duration of study: 24 weeks • Dose was kept stable in both groups during duration of study Co-interventions • Oral and IV iron administered according to unit policy
Outcomes	• Final Hb at 24 weeks (evaluation) • Number requiring transfusion • Number requiring iron supplements
Notes	• Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded but primary outcome is laboratory based and unlikely to be subject to bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment, and outcome unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement; 9 (14%) excluded from evaluation but group and reasons not stated
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Grant/research support (Kirin). Drug supplied by Kirin

Lago 1996

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 12 months
Participants	• Country: Spain • Setting: single centre • Stable HD patients • Number: treatment group 1 (21); treatment group 2 (9) • Mean age ± SD (years): treatment group 1 (55.2 ± 15.9); treatment group 2 (63 ± 16.2) • Sex (M/F) treatment group 1 (9/12); treatment group 2 (4/5) • Exclusion criteria: NS

Lago 1996 *(Continued)*

Interventions	Treatment group 1 • EPO: SC once/wk for 12 months Treatment group 2 • EPO: SC 3 times/wk for 12 months Other information • Dose: NS • Target Hb: 10.5 mg/dL • Type of EPO: NS Co-interventions • NS
Outcomes	• Hb and HCT at study end
Notes	• Letter

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Study stated to be randomised but no further information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome, but unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	6/21 in experimental group and 2/9 in control group did not complete study
Selective reporting (reporting bias)	Unclear risk	Letter only. Only Hb levels reported
Other bias	Unclear risk	No mention of funding source

Lee 2008

Methods	• Study design: open-label, parallel RCT • Study duration: July 2004 to April 2005 • Duration of follow-up: 12 weeks
Participants	• Country: Korea

Lee 2008 *(Continued)*

- Setting: multicentre
- Regular HD ≥ 3 months; age ≥18 years; stable EPO dose 3000 to 12,000 U/wk. Hb 9 to 12 g/dL; stable iron stores
- Number: treatment group 1 (44); treatment group 2 (39)
- Mean age ± SD (years): treatment group 1 (55.7 ± 10.1); treatment group 2 (53.3 ± 12.9)
- Sex (M/F): treatment group 1 (24/20); treatment group 2 (23/16)
- Exclusion criteria: uncontrolled HT; DBP ≥110 mm Hg; hyperparathyroidism ≥ 800 pg/mL; acute infection/inflammation; severe CCF; GI bleed; pregnancy; immunosuppressive or androgen therapy; malignancy; epilepsy; transfused ≤ 2 months previous; sensitivity to EPO

Interventions	Treatment group 1 • EPO: SC once/wk for 12 weeks • Starting dose previous total weekly dose Treatment group 2 • EPO: SC 2 to 3 times/wk for 12 weeks • Continue previous dose Other information • Type of ESA: EPO alfa • Dose adjusted in both groups to maintain Hb level at 9 to 12.0 g/dL Co-interventions • All received IV iron therapy
Outcomes	• Final Hb at 12 weeks • Mean EPO dose at week 10 • Proportion of patients keeping a stable Hb level • Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation process to permit judgement
Allocation concealment (selection bias)	Low risk	Randomised by central randomisation. Stratified for EPO dose
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study but primary outcome was laboratory measure and unlikely to be subject to bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open-label study but primary outcome was laboratory measure and unlikely to be subject to bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported ITT and PP data. Loss to follow-up/withdrawal post randomisation: 4 in each group (protocol violation; dose change in study period; Hb ≥ 12 at randomisation). Loss to follow-up unlikely to influence results

Lee 2008 *(Continued)*

Selective reporting (reporting bias)	High risk	No information on mortality and incomplete information on adverse effects
Other bias	High risk	Supported/funded by LG Life Sciences Co Ltd

Leung 1995

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: NS
Participants	• Country: Hong Kong • Setting: single centre • Stable CAPD • Number: treatment group 1 (20); treatment group 2 (20) • Mean age ± SD (years): NS • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group 1 • EPO: SC twice/wk for 16 weeks Treatment group 2 • EPO: SC 3 times/wk for 16 weeks Other information • Dose in both groups: initial 100 U/kg/wk then adjusted to increase Hb by 1 g/dL/mo with a target Hb of 10 to 12 g/dL • Type of EPO: NS Co-interventions • Anti-hypertensive
Outcomes	• Hb at end of study • Average weekly dose of EPO • Weekly EPO dose at end of study • Number of antihypertensive drugs
Notes	• Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available

Leung 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Primary outcome was laboratory measure and unlikely to be subject to bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory measure and unlikely to be subject to bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data unlikely to influence results; 2/20 in each group, no reasons given. 10% participants excluded from analysis
Selective reporting (reporting bias)	Unclear risk	No information provided on mortality and incomplete information on adverse effects. All data provided without standard deviations so cannot be included in meta-analyses
Other bias	Unclear risk	Funding sources not mentioned

Locatelli 2002

Methods	• Study design: RCT • Study duration: NS • Duration of follow-up: 24 weeks
Participants	• Countries: Italy, Germany, France, Spain • Setting 19 dialysis centres • Stable HD for the last 3 months; age ≥ 18 years; delivered dialysis dose ≥ 1.2; SC epoetin-ß 3 times/wk over the last 3 months; mean dose 30 to 240 IU/kg in the last 2 weeks before start of study Stable HCT 28 to 38%; adequate iron status, ferritin level 100 ng/mL and transferrin saturation > 20% • Number: treatment group 1 (69); treatment group 2 (63) • Mean age ± SD (years): treatment group 1 (63.6 ± 14.8); treatment group 2 (62.0 ± 12.4) • Sex (M/F): treatment group 1 (38/31); treatment group 2 (32/31) • Exclusion criteria: haemoglobinopathy; haemolysis or GI bleeding; hypertension requiring interruption of epoetin treatment in last 6 months; acute infection or systemic inflammatory disease; malignancy; epilepsy; severe hyperparathyroidism; serum aluminium level > 50 ng/mL; vitamin B_{12} > 200 pg/mL; folic acid > 2 ng/mL; thrombocyte count < 500,000/µL; pregnancy or lactation; no blood transfusion within last 3 months; no history of hypersensitivity to epoetin B
Interventions	Treatment group 1 • EPO: SC once/wk for 24 weeks • First 12 weeks excluded from analysis to avoid carry over effect of epoetin treatment prior to randomisation • Dose: after randomisation, weekly dose corresponded to individual mean weekly doses in the pre-study period Treatment group 2 • EPO: SC 3 times/wk for 24 weeks Other information • Adjustments in both groups were indicated if HCT differed from baseline by ± 3% Co-interventions

Locatelli 2002 *(Continued)*

	• Iron supplementation as required
Outcomes	• Difference between groups in mean time-adjusted AUC for HCT for PP and ITT populations • Median change in weekly epoetin-ß dose/kg of body weight • Number needing transfusion • Adverse events: hypertension, AV fistula thromboses
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified by centre, but no further information provided
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study but primary outcome was laboratory measure and unlikely to be subject to bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open-label study but primary outcome was laboratory measure and unlikely to be subject to bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	16% (27/173) lost to follow-up or withdrawn but reasons for missing data unlikely to be related to true outcome: death (6), adverse events (5), protocol violations (4), improvement in anaemia (2), refusal of treatment (2), administrative reasons (7), loss to follow-up (1)
Selective reporting (reporting bias)	High risk	Reported outcomes consistent with expected but data not provided in format that can be entered in meta-analysis
Other bias	High risk	Supported in part by Hoffmann-La Roche Ltd, Switzerland

Locatelli 2004

Methods	• Study design: parallel RCT • Study duration/time frame: 25 August 2002 to 29 September 2003 • Duration of follow-up: 30 weeks
Participants	• Countries: UK, Europe • Setting: multicentre • Age: ≥ 18 years; HD ≥ 6 months; on stable IV rHuEPO 1 to 3 times/wk; baseline Hb 10.0 to 13.0 g/dL • Number: treatment group 1 (154); treatment group 2 (154) • Mean age ± SD (years): NS • Sex (M/F): NS • Exclusion criteria: seizures ≤ 6 months; CHF; uncontrolled hypertension; current malignancy; surgery within 3 months; systemic haematological disease; RBC transfusion 12 weeks before screening
Interventions	Treatment group 1

Locatelli 2004 *(Continued)*

	• DA: IV every two weeks for 30 weeks • Starting dose was previous weekly EPO dose in units divided by 200 multiplied by 2 Treatment group 2 • DA: IV every week for 30 weeks • Starting dose was previous weekly EPO dose in units divided by 200. Other information • Dose was titrated for each patient throughout the study to maintain Hb within -1.0 to + 1.5 g/dL of baseline and between 10.0 and 13.0 g/dL Co-interventions • NS
Outcomes	• Final Hb • Instability of Hb concentrations • DA alfa dosing requirements • RBC transfusions • Adverse events
Notes	• Multiple abstracts • Additional information from www.amgentrials.com • Data sought from authors: randomisation process

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not stated. Stratified by centre according to EPO dose "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding maintained by placebo injections weekly in patients on 2 weekly regimen. Unclear whether both participants and personnel blinded. Primary outcome is laboratory measurement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding maintained by placebo injections weekly in patients on 2 weekly regimen
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear. Abstracts only; 213/307 (69%) were included in primary analysis; deaths (19), adverse events (5)
Selective reporting (reporting bias)	High risk	Important outcomes provided but data for primary outcome only provided for PP population
Other bias	High risk	Funding Amgen Inc, Thousand Oaks, CA

Lui 1991

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 16 weeks
Participants	• Country: Hong Kong • Setting: single centre • CAPD at least 6 months. Hb levels < 8 g/dL • Number: treatment group 1 (10); treatment group 2 (10) • Mean age ± SD (years): treatment group 1 (49 ± 11); treatment group 2 (40 ± 12) • Sex (M/F): treatment group 1 (3/7); treatment group 2 (3/7) • Exclusion criteria: anaemia due to other causes; uncontrolled hypertension
Interventions	Treatment group 1 • EPO: IV once/wk for 16 weeks Treatment group 1 • EPO: IV twice/wk for 16 weeks Other information • Dose for each group: starting dose 100 U/kg week with adjustments for target Hb of 10 g/dL • Type of EPO: alpha Co-interventions • Iron supplements given to all patients unless iron overload
Outcomes	• Mean Hb or HCT at end of maintenance phase • Average EPO dose during the study • Number of patients with an increase or introduction of antihypertensive treatment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomised. No other information provided
Allocation concealment (selection bias)	Unclear risk	Said to be randomised. No other information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Laboratory outcome, blinding unlikely to influence outcome
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcome, blinding unlikely to influence outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing data unlikely to be related to true outcome; loss to follow-up/withdrawal: 3/20 (15%) excluded; peritonitis (2), failure to respond to therapy (1)

Lui 1991 *(Continued)*

Selective reporting (reporting bias)	High risk	No report of mortality and incomplete reporting of adverse events
Other bias	High risk	Epoetin supplied by Jansen Cilag. Supported by Cilag Research

Lui 1992

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 12 weeks
Participants	• Country: Hong Kong • Setting: single centre • HD for at least 6 months of dialysis; pre-treatment Hb < 8 g/dL • Number: treatment group (10); treatment group (10) • Mean age ± SD (years): treatment group 1 (41 ± 8); treatment group 2 (38 ± 6) • Sex (M/F): treatment group 1 (6/4); treatment group (7/3) • Exclusion criteria: uncontrolled hypertension
Interventions	Treatment group 1 • EPO: starting dose SC 100 U/kg body weight once/wk for 12 weeks • Adjusted to maintain target Hb 10 g/dL Treatment group 2 • EPO: starting dose 100 U/kg body weight twice/wk for 12 weeks • Adjusted to maintain target Hb 10 g/dL Other information • Type of EPO: alpha Co-interventions • Iron administered unless evidence of gross degree of iron overload; antihypertensives, metoprolol and nifedipine
Outcomes	• Number who failed to achieve/maintain target Hb or HCT during correction/maintenance phase • Mean Hb or HCT at end of correction phase • Change in Hb • Average EPO dose used during study • Number with increase/introduction of antihypertensive treatment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients said to be randomised. No other information provided
Allocation concealment (selection bias)	Unclear risk	Patients said to be randomised. No other information provided

Lui 1992 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Laboratory outcome, blinding unlikely to influence outcome
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcome, blinding unlikely to influence outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawals stated and unlikely to affect results
Selective reporting (reporting bias)	High risk	No information on mortality and limited information on adverse effects
Other bias	High risk	Supported by Cilag Research

MAXIMA Study 2007

Methods	• Study design: parallel RCT • Study duration: recruitment April 2004 to August 2004; completed August 2005 • Duration of follow-up: 52 weeks
Participants	• Countries: USA, Canada, Europe • Setting. 96 centres • CKD 5D; HD ≥ 12 weeks; stable Hb (10.5 to 13.0 g/L); rHuEPO 8 weeks before screening; adequate iron status; PD patients included theoretically, but none participated as not receiving IV ESA • Number: treatment group 1 (233); treatment group 2 (224); treatment group 3 (226) • Mean age ± SD (years): treatment group 1 (55 ± 15.2); treatment group 2 (59 ± 15); treatment group 3 (58.6 ± 15.1) 5 years (SD) • Sex (M/F): treatment group 1 (133/90); treatment group 2 (126/98); treatment group 3 (134/92) • Exclusion criteria: overt bleeding requiring transfusion ≤ 8 weeks before study; CRP ≥ 30 mg/L; life expectancy ≤ 12 months; likelihood of early withdrawal

Interventions	Treatment group 1
	• CERA: twice/mo for 52 weeks
	• Route of administration: IV and SC
	• Dosage
	  ○ 60 µg CERA if previous dose < 8000 U rHuEPO
	  ○ 100 µg CERA if previous dose 8000 to 16,000 U rHuEPO
	  ○ 180 µg if previous dose > 16,000 U rHuEPO
	Treatment group 2
	• CERA: once/mo for 52 weeks
	• Route of administration: IV and SC
	• Dosage
	  ○ 120 µg CERA if previous dose < 8000 U rHuEPO
	  ○ 200 µg CERA if previous dose 8000 to16000 U rHuEPO
	  ○ 360 µg CERA if previous dose > 16,000U rHuEPO
	Treatment group 3

MAXIMA Study 2007 *(Continued)*

	• rHuEPO: 3 times/wk for 52 weeks • Route of administration: IV and SC Other information • Assessment period weeks 28 to 36. Follow up to 52 weeks • Dosages of CERA were adjusted according to protocol and not more often than every 4 weeks. Dosages of rHuEPO were adjusted according to their labels Co-interventions • Iron supplementation
Outcomes	• Change in Hb • Adverse events: AV thrombus, hypertension, seizures, SAE due to ESA • Mortality • ESA dose
Notes	• Information requested from authors regarding ITT data: none received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random computer numbers generated by computer at coordinating centre
Allocation concealment (selection bias)	Low risk	Randomisation at coordinating centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Laboratory endpoint, therefore unlikely to be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory endpoint, therefore unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted; loss to follow-up/excluded: adverse events (8), deaths (26), insufficient therapy (1), refused treatment (12), other (36), failure to return for follow-up (2)
Selective reporting (reporting bias)	High risk	Expected outcomes reported but ITT data only shown in graph. PP data in text and tables
Other bias	High risk	Industry funded, Hoffman La Roche

Miranda 1990

Methods	• Study design: parallel RCT • Study duration: NS • Duration of study: 9 months
Participants	• Country: Spain • Setting: single centre

Miranda 1990 *(Continued)*

- CAPD; Hb < 8 g/dL
- Number: treatment group 1 (8); treatment group 2 (7)
- Mean age ± SD (years): treatment group 1 (44 ± 12); treatment group 2 (56 ± 17): years (SD)
- Sex (M/F): NS
- Exclusion criteria: NS

Interventions	Treatment group 1 • rHuEPO: SC 20 U/kg/d for 9 months Treatment group 2 • rHuEPO: SC 2000 U twice/wk for 9 months Co-interventions • Iron administered; target Hb 10.5 g/dL
Outcomes	• Hb levels at the end of the study • EPO doses at the end of the study • Adverse effects
Notes	• Third group given intraperitoneal rHuEPO daily not included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Laboratory outcome, unlikely to be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcome, unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether all patients completed study
Selective reporting (reporting bias)	High risk	Information provided graphically or for combined groups of patients so could not be included in meta-analyses
Other bias	Unclear risk	Funding sources NS

Mircescu 2006

Methods	• Study design: parallel RCT • Duration of study: 1 March 2004 to 31 January 2005

Mircescu 2006 *(Continued)*

	• Duration of follow-up: 24 weeks
Participants	• Country: Romania • Setting: multicentre • HD 6 months (Kt/v 1.2); Hb > 10 g/dL; adequate iron stores; ferritin 100 to 88 ng/mL; TSAT 20 to 50%; once weekly SC EPO for 2 months before enrolment ≥ 18 years • Number: treatment group 1 (104); treatment group 2 (103) • Mean age ± SD (years): treatment group 1 (49.6 ± 13.3); treatment group 2 (48.0 ± 12.9) • Sex (M/F): treatment group 1 (57/47); treatment group 2 (62/41) • Exclusion criteria: CHF; hepatic disease; CRP > 12 mg/L; severe hyperparathyroidism (PTH > 800 ng/mL); serum B_{12} or folate deficiency; poor BP control; malnutrition; albumin < 40 g/L; blood transfusions in last 2 months
Interventions	Treatment group 1 • rHuEPO: SC every 2 weeks, same cumulative dose administered every other week for 24 weeks Treatment group 2 • rHuEPO SC once/wk, continued the previous once weekly schedule Other information • Dose adjustments were made to maintain Hb levels in both groups Co-interventions • Iron therapy was continued according to Romanian Best Practice Guidelines
Outcomes	• Final or change in Hb • Number reaching target HB • Change in median EPO dose • Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Renal Registry Romania. Numbered containers
Allocation concealment (selection bias)	Low risk	Central randomisation. Renal Registry Romania
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/207 excluded from analyses (4 withdrew after randomisation (2 from each group)), unlikely to influence results

Mircescu 2006 *(Continued)*

Selective reporting (reporting bias)	High risk	No information on mortality
Other bias	High risk	Funding for laboratory tests from F. Hoffman la Roche Ltd

Muirhead 1989

Methods	• Study design: cross-over RCT • Study duration: NS • Duration of follow-up: NS
Participants	• Country: Canada • Setting: single centre • HD patients; 12 weeks rHuEPO; stable Hb 10.5 to 12.5 g/dL • Number: 19 • Mean age ± SD (years): NS • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group 1 • rHuEPO: IV once/wk ○ Received total weekly dose as a weekly injection. Continued for 12 weeks, then crossed-over • Matched placebo: twice/wk Treatment group 2 • rHuEPO: IV 3 times/wk for 12 weeks then crossed-over • Dose adjustment was made according to Hb and total weekly rHuEPO dose Co-interventions • NS
Outcomes	• Change in Hb • Adverse events
Notes	• Abstract only • Only data for the whole group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo given to weekly rHuEPO group. Patients and staff did not know frequency

Muirhead 1989 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unclear if outcome assessors blinded but outcome of Hb unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	31% did not complete the study
Selective reporting (reporting bias)	High risk	Data only available for combined groups
Other bias	Unclear risk	NS

Murtagh 2000

Methods	• Study design: RCT • Study duration: NS • Duration of follow-up: 16 weeks
Participants	• Country: Ireland • Setting: single centre • HD patients; Hb < 10 g/dL; no rHuEPO in previous 3 months • Number: 10 • Mean age ± SD (years): NS • Sex (M/F): 8/2 • Exclusion criteria: NS
Interventions	Treatment group 1 • DA: IV 3 times/wk • Total dose: 0.75 µg/kg/wk in divided doses for 16 weeks Treatment group 2 • DA: IC once/wk • Dose: 0.75 µg/kg/wk for 16 weeks Co-interventions • NS
Outcomes	• Final Hb • Adverse events
Notes	• Abstract only • Results for intervention groups not provided separately for each treatment regimen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NS

Murtagh 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	NS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All 10 patients completed the initial 16 weeks
Selective reporting (reporting bias)	High risk	Data only provided for combined groups
Other bias	Unclear risk	Funding source: NS

Nagaya 2010

Methods	• Study design: prospective RCT • Study duration: NS • Duration of follow-up: 24 weeks
Participants	• Country: Japan • Setting: single centre • HD; age ≥18 years • Number (randomised/evaluated): treatment group 1 (24/20); treatment group 2 (24/19) • Mean age ± SD (years): treatment group 1 (66.9 ± 9.3); treatment group 2 (68.8 ± 9.9) • Sex (M/F): treatment group 1 (12/8); treatment group 2 (11/8) • Exclusion criteria: underlying malignancy; haemorrhagic disease; CHF; uncontrolled hypertension; transfusion; surgery post-screening
Interventions	Treatment group 1 • DA: IV at 2 weekly intervals; dose double of previous weekly dose; continued for 24 weeks • Weekly dose: 0.43 ± 0.19 µg/kg/wk • DA adjusted to maintain Hb level 10.5 to 11.5 g/dL Treatment group 2 • DA: IV once/wk for 24 weeks; continued dose used prior to randomisation • Weekly dose: 0.49 ± 0.22 µg/kg/wk • DA doses titrated according to international guidelines • DA adjusted to maintain Hb level 10.5 to 11.5 g/dL Co-interventions • IV iron supplementation
Outcomes	• Weekly dose of DA at week 24 • Final Hb at 24 weeks

Nagaya 2010 *(Continued)*

- Adverse events

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation process to permit judgement "prospective and randomised"
Allocation concealment (selection bias)	Unclear risk	Study stated to be randomised but further information not given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but outcome is unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment, but outcome assessment unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Patients excluded: 48 randomised, PP 39 (loss to follow-up/withdrawal: 9/48 (18.8%); surgery (4), transfer to another institution (2), death (10), haematologic disease (1), nasal bleeding (1); missing data may have influenced outcome
Selective reporting (reporting bias)	High risk	Insufficient information on adverse effects
Other bias	Low risk	Grant from Japan Dialysis outcome Research Group

Nissenson 2002

Methods

- Design: parallel group, non-inferiority RCT
- Study duration: NS
- Duration of follow-up: 28 weeks

Participants

- Countries: Canada, USA
- Setting: multicentre, Canada (5); USA (35)
- Aged ≥18 years; HD ≥ 12 weeks; IV EPO-α for 8 weeks; stable Hb concentration 9.5 to 12.5 g/dL; stable iron stores
- Number: treatment group 1 (169); treatment group 2 (338)
- Mean age, range (years): treatment group 1 (58.0, 20 to 86); treatment group 2 (57.8, 21 to 90)
- Sex (M/F): treatment group 1 (94/75); treatment group 2 (191/147)
- Exclusion criteria: haematologic, inflammatory or infectious conditions; transfusion in previous 8 weeks

Interventions

Treatment group 1

- DA: based on total weekly dose of EPO at time of randomisation (200 U EPO = 1 µg DA); IV once/wk
- Placebo: IV twice/wk for 28 weeks

Treatment group 2

- rHuEPO: continued previous dose given IV 3 times/wk for 28 weeks

Nissenson 2002 *(Continued)*

	Other information • Dose adjustments made in each treatment group to maintain individual patient's Hb within -1.0 to + 1.5 g/dL of baseline value and within range of 9.0 to 13.0 g/dL throughout 28 week study period Co-interventions • Iron supplementation administered according to individual unit policy
Outcomes	• To assess that DA at reduced dose frequency is effective and as well tolerated as epoetin • Hb within target range
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified by centre. No information provided on sequence generation
Allocation concealment (selection bias)	Low risk	Central computer allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	DA group received placebo twice per week
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo-controlled. Primary outcome was laboratory-based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/507 excluded from ITT analysis and unlikely to influence results; loss to follow-up/withdrawal: 81/507. Protocol violation (1), intolerable AE (24), withdrawal requested (11), death (28), kidney transplant (15), administration decision (2), change in dialysis modality (1)
Selective reporting (reporting bias)	High risk	Information provided on all expected outcomes but ITT data available from figures and could not be included in meta-analyses
Other bias	High risk	Supported by Amgen

Paganini 1991

Methods	• Study design: RCT • Study duration: NS • Duration of follow-up: 27 to 38 weeks
Participants	• Country: USA • Setting: 6 centres • Stable HD patients; IV EPO > 3 years • Number: treatment group 1 (25); treatment group 2 (33) • Mean age ± SD (years): NS • Sex (M/F): NS

Paganini 1991 *(Continued)*

	• Exclusion criteria: NS
Interventions	Treatment group 1 • EPO: SC once/wk • Mean weekly dose at baseline: 254 ± 198 U/kg Treatment group 2 • EPO: 3 times/wk Co-interventions • Iron and folic acid
Outcomes	• HCT at the end of the study • EPO dose at end of study
Notes	• Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all patients completed the study
Selective reporting (reporting bias)	Unclear risk	No report of mortality or adverse effects
Other bias	Unclear risk	No information

PROTOS Study 2007

Methods	• Study design: open-label, parallel group, comparator controlled, phase III RCT • Study duration: March 2004 to September 2005 • Duration of follow-up: 1 year
Participants	• Countries: international • Setting: 92 centres

PROTOS Study 2007 *(Continued)*

- Aged ≥18 years; PD or HD ≥ 12 weeks; Kt/V≥ 1.2 or URR ≥ 65% for HD; weekly Kt/V ≥1.8 for PD patients; Hb concentration 10.5 to 13.0 g/dL; SC rHuEPO maintenance therapy; ferritin ≥ 100 ng/mL or TSAT ≥ 20%
- Number: treatment group 1 (190); treatment group 2 (191); treatment group 3 (191)
- Mean age ± SD (years): treatment group 1 (62.3 ± 15.4); treatment group 2 (60.59 ± 15.4); treatment group 3 (60.4 ± 14.7)
- Sex (M/F): treatment group 1 (117/74); treatment group 2 (108/82); treatment group 3 (110/81)
- Exclusion criteria: GI bleeding or bleeding requiring transfusion < 8 weeks before screening; non-renal causes of anaemia; uncontrolled or symptomatic inflammatory disease, e.g. SLE, RA; CRP > 30 mg/L; platelets > 500 x 10^9/L; PRCA; CHF; poorly controlled hypertension; high likelihood of withdrawal/interruption of the study (MI, stroke); Life expectancy < 12 months

Interventions	Treatment group 1 • CERA: every 2 weeks • Starting dose: SC 60 µg/2 wk Treatment group 2 • CERA: every 4 weeks • Starting dose: SC 120 µg/4 wk Treatment group 3 • rHuEPO: given one to three/wk with dose based on approved recommendations to maintain Hb as above Other information • During titration and evaluation periods CERA dose was adjusted to maintain Hb within ± 1.0 g/dL of baseline and 10.0 to 13.5 g/dL. CERA dose adjustments were performed according to a predefined protocol and no more frequently than once every 4 weeks Co-interventions • Iron supplementations were performed according to each centre's practice and adjusted to maintain adequate stores
Outcomes	• Mean change in Hb • Adverse effects: hypertension, AV fistula thrombosis, AE leading to withdrawal and death
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation with geographic stratification
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study but laboratory endpoint unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias)	Low risk	Open-label study but laboratory endpoint unlikely to be influenced by lack of blinding

PROTOS Study 2007 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted
Selective reporting (reporting bias)	High risk	Data provided for PP not ITT population. ITT data only available graphically so PP data only included in meta-analyses (98 excluded from ITT population). Withdrawal/loss to follow-up: 111/572. Death (41), kidney transplantation (39), treatment refusal (13), AEs (2), insufficient therapeutic response (2), other (13)
Other bias	High risk	Funding F. Hoffman La Roche Ltd

RUBRA Study 2008

Methods	• Study design: parallel group, open-label RCT • Time frame: NS • Duration of study: 36 weeks; evaluation 29 to 36 weeks
Participants	• Country: international • Setting: multicentre • Aged ≥ 18 years; HD or PD ≥ 12 weeks; stable on EPO ≥ 8 weeks; baseline Hb 10.5 to 13.0 g/dL; adequate iron stores, serum ferritin ≥100 ng/mL or TSAT ≥ 20% • Number: treatment group 1 (104); treatment group 2 (168) • Mean age ± SD (years): treatment group 1 (59.8 ± 14.4); treatment group 2 (60.1 ± 13.9) • Sex (M/F): treatment group 1 (104/64); treatment group 2 (113/55) • Exclusion criteria: blood transfusions < 8 weeks; GI bleeding; non-renal causes of anaemia; CAD; liver disease; uncontrolled hypertension
Interventions	Treatment group 1 • CERA: SC or IV every two weeks • Initial dose based on EPO dose received during week preceding randomisation. Patients receiving weekly EPO > 8000, 8000 to 16,000 or > 16,000 IU were administered a starting CERA twice weekly dose of 60, 100 or 180 µg respectively Treatment group 2 • EPO: continued, once/wk or 3 times/wk SC/IV Other information • Dose adjustments were permitted for safety at any point during the study to maintain individual's Hb within 1g/dL of baseline value and within 10.0 to 13.5 g/dL. For CERA dose adjustment was not permitted more frequently than once every 4 weeks Co-interventions • Iron supplementation was performed according to individual centre practice
Outcomes	• Final Hb • Number reaching target Hb • Median dose of ESA • Adverse events

RUBRA Study 2008 *(Continued)*

Notes	• Information on sequence generation and allocation concealment requested from authors: no information received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	Stratified by geographical region and route of administration
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted; 54/282 (19%) withdrew due to AEs (4), death (16), transplantation (16), insufficient therapeutic response (1), refusal of treatment (1), failure to return (1), other (12)
Selective reporting (reporting bias)	High risk	All important outcomes provided. ITT data only available graphically and PP data entered in meta-analyses
Other bias	High risk	Funded by Roche

STRIATA Study 2008

Methods	• Study design: open-label, parallel RCT • Study duration: NS • Duration of follow-up: 52 weeks
Participants	• Countries: Europe (12 countries), Australia, Canada • Setting: multicentre (48 centres) • Aged ≥18 years; chronic anaemia receiving HD; Kt/V ≥ 1.2 or urea reduction ≥ 65%; PD weekly Kt/V ≥ 1.8 for ≥ 12 weeks; IV DA therapy weekly or 2 weekly ≥ 8 weeks • Number (randomised/evaluated): treatment group 1 (157/123); treatment group 2 (156/126) • Mean age ± SD (years): treatment group 1 (62.49 ± 16.17); treatment group 2 (61.8 ± 14.74) • Sex (M/F): treatment group 1 (100/57); treatment group 2 (81/75) • Exclusion criteria: non-renal causes of anaemia; CRP > 30 mg/L; life expectancy < 12 months
Interventions	Treatment group 1 • CERA: IV 2 weekly • Starting CERA dose calculated according to DA dose before randomisation. 60 µg to 180 µg/2 weeks Treatment group 2 • DA: IV weekly or 2 weekly according to previous dose

STRIATA Study 2008 *(Continued)*

	• During dose titration and evaluation, doses in both groups were adjusted to maintain Hb within 1.0 g/dL of baseline or Hb values between 10 and 13.5 g/dL Other information • Dose adjustments for CERA were performed not more frequently than once every 4 weeks Co-interventions • IV iron supplements as required in both treatment groups
Outcomes	• Mean Hb change between baseline and evaluation (29 to 36 weeks) • Proportion patients maintaining Hb ± 1 g/dL of baseline during evaluation. • Incidence of RBC transfusions • Adverse effects
Notes	• Request for ITT data (only available graphically in report) made to authors: no information obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization numbers "allocated sequentially for each study centre"
Allocation concealment (selection bias)	Low risk	"Central randomization centre"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for. Loss to follow-up/withdrawals: death (22), transplantation (20), refusal of treatment (7), adverse events (2), failure to return (2), patient vacation, patient decision, patient instability, protocol violation, discontinuation of dialysis (11)
Selective reporting (reporting bias)	High risk	ITT data only provided graphically and PP data entered in meta-analyses
Other bias	High risk	Funded by F.Hoffman- La Roche Ltd. Basel Switzerland; data analyses conducted by sponsor

Tessitore 2008

Methods	• Study design: pilot cross-over RCT • Study duration: NS • Duration of follow-up: 54 weeks
Participants	• Country: Italy • Setting: single centre

Tessitore 2008 *(Continued)*

- Stable HD patients on IV EPO and IV iron
- Number: treatment group 1 (18); treatment group 2 (18)
- Mean age ± SD (years): NS
- Sex (M/F): NS
- Exclusion criteria: NS

Interventions	Treatment group 1 • DA: 20 or 50 µg doses IV for 39 weeks; converted from EPO according to 200 U rHuEPO equivalent to 1 µg DA Treatment group 2 • rHuEPO: 2000, 4000, 10,000 U for 39 weeks according to previous dose Other information • Dose adjustments: NS • 15 week titration and 39 week evaluation Co-interventions • IV NaFe gluconate
Outcomes	• Final Hb • Final rHuEPO dose
Notes	• Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Low risk	Coin toss
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all patients included in analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Information not provided

Vanrenterghem 2002

Methods	• Study design: parallel RCT • Study duration: November 1997 to July 1998 • Duration of follow-up: 52 weeks
Participants	• Countries: Europe, Australia • Setting: multicentre • HD/PD; age ≥18 years; stable rHuEPO for 3 months; stable Hb 9.5 to 12.5 g/dL; adequate iron stores serum ferritin > 100 µg/L • Number (randomised/evaluated): treatment group 1 (347/224); treatment group 2 (175/112) • Mean age, range (years): treatment group 1 (60.1,18 to 88); treatment group 2 (60.9, 22 to 87) • Sex (M/F): treatment group 1 (188/159); treatment group 2 (100/75) • Exclusion criteria: haematological, inflammatory or infectious conditions; blood transfusion < 1 month before enrolment
Interventions	Treatment group 1 • DA: patients on rHuEPO once/wk converted to DA once every 2 weeks for 52 weeks • Patients on EPO 2 to 3 times/wk converted to DA once/wk for 52 weeks • Dose adjusted to maintain individual's Hb within -1.0 to + 1.5 g/dL of baseline and between 9 and 13 g/dL Treatment group 2 • EPO: IV/SC once, twice or 3 times/wk for 52 weeks • Dose adjusted to maintain Hb within -1.0 to + 1.5 g/dL of baseline, and 9 to 13 g/dL • Evaluation at weeks 25 to 32 Co-interventions • IV iron therapy as required
Outcomes	• Change in Hb • ESA dosage • Mortality • Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Low risk	Central randomisation. Stratified by centre and EPO dose at study entry
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding

Vanrenterghem 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted; loss to follow-up/withdrawals: 133 did not complete 52 weeks of study. Main reason was death (52), transplant and withdrawal requested; rates were similar between groups during evaluation period
Selective reporting (reporting bias)	High risk	Results provided for per protocol population with all results only provided graphically
Other bias	High risk	Amgen Inc funded study

Weiss 2000

Methods	• Study design: open-label, parallel group RCT • Study duration: NS • Duration of follow-up: 24 weeks
Participants	• Country: Sweden • Setting: multicentre • HD patients aged 18 to 80 years; Hb 10 to 12.5 g/dL; serum ferritin > 200 µg/L and/or TSAT > 20%; Kt/V > 1 • Number (randomised/evaluated): treatment group 1 (118/88); treatment group 2 (40/30) • Mean age ± SD (years): treatment group 1 (66 ± 12); treatment group 2 (65 ± 13) • Sex (M/F): treatment group 1 (75/43); treatment group 2 (27/13) • Exclusion criteria: uncontrolled hypertension; serum aluminium > 100 µg/L; B_{12} or folic acid deficiency; ongoing infection; known epilepsy; known hyperparathyroidism; pregnancy or lactation
Interventions	Treatment group 1 • rHuEPO (epoetin-ß): SC weekly for 24 weeks • Dose/wk equivalent to previous total weekly dose Treatment group 2 • rHuEPO: SC twice or 3 times/wk as pre-trial for 24 weeks • Same rHuEPO dose and frequency continued as pre trial Co-interventions • Iron when necessary
Outcomes	• % maintaining stable Hb without requiring increase in total weekly dose of EPO • Hb at the end of study • Weekly EPO dose at end of study • Mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NS

Weiss 2000 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central randomisation 3:1 ratio. Stratified by sex and age
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	25% withdrew from each group before evaluation; withdrawals 30 and 10 patients respectively in once weekly and control groups withdrew prior to week 16
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Funded by Amgen

Yoon 2004

Methods	• Study design: RCT • Study duration: NS • Duration of follow-up: NS
Participants	• Country: Korea • Setting: multicentre • HD patients, SC or IV rHuEPO • Number: 74 • Mean age ± SD (years): NS • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group 1 • rHuEPO once/wk received DA every 2 weeks SC/IV for 20 weeks • rHuEPO 2 to 3 times/wk received DA once/wk SC/IV for 20 weeks Treatment group 2 • rHuEPO continued SC/IV for 20 weeks Other information • rHuEPO and DA doses titrated to maintain Hb concentrations within range 8.0 to 13.0 g/dL or within -1.0 to +1.5 g/dL of patient's baseline values Co-interventions • Iron therapy: NS
Outcomes	• Change in Hb from baseline to evaluation
Notes	• Abstract only

Yoon 2004 *(Continued)*

- DA analysed as one group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcome of Hb unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data to enable assessment
Selective reporting (reporting bias)	Unclear risk	Insufficient data to enable assessment
Other bias	Unclear risk	Funding: NS

AE, adverse event; AMI - acute myocardial infarction; AUC - area under the curve; AV - arteriovenous; BP - blood pressure; CAD - coronary artery disease; CAPD - continuous ambulatory peritoneal dialysis; CCF - chronic coronary failure; CKD - chronic kidney disease; CHF - coronary heart failure; CRP - C-reactive protein; DA - darbepoetin; DBP - diastolic blood pressure; ESA - erythropoietin-stimulating agent; ESKD - end-stage kidney disease; GI - gastrointestinal; Hb - haemoglobin; HCT - haematocrit; HD - haemodialysis; ITT - intention-to-treat analysis; IV - intravenous; IVI - intravenous injection; IVRS - interactive voice response system; MI - myocardial infarction; NS - not stated; PD - peritoneal dialysis; PP - per protocol analysis; PRCA - pure red cell aplasia; RA - rheumatoid arthritis; RBC - red blood cell; SAE - serious adverse event; SC - subcutaneous; SLE - systemic lupus erythematosus; TSAT - transferrin saturation; URR -urea reduction ratio

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

Study	Reason for exclusion
Allon 2002	Pharmacokinetic study
BA16260 Study 2006	Dose finding study
Bennett 1991	Participants not on dialysis
Besarab 1998	Haematocrit target study
Bhuiyan 2004	Dose varied, not frequency
Brandt 1999	Dose varied, not frequency
Brown 1988	Haematocrit target study

Study	Reason for exclusion
Canadian EPO Study 1990	Injection frequency was not randomised; participants were randomised to placebo (Group 1) and two groups maintaining Hb from 95 to 110 g/L (Group 2) or 115 to 130 g/L (Group 3)
Castro 1994	Unclear how patients were allocated to groups; no reply from study author
Chazot 2009	Dose study
Dougherty 2004	Dose dependent study not on dialysis
Fan 1992	Unclear how patients were allocated to groups, wrote to authors, no response
Hirakata 2010	Participants not on dialysis
Icardi 1990	Different routes of administration (not frequency)
Ifudu 1998	No control group, no change in frequency
Iwasaki 2008	Examined conversion ratios for EPO to darbepoetin
Kawanishi 2005	Dose escalation study
Kim 2009a	Compared different routes of administration
Knebel 2008	Pharmacokinetic study
Locatelli 2008	Control group received either weekly darbepoetin or rHuEPO 2 to 3 times weekly; numbers receiving each control intervention could not be separated.
Macdougall 2003	Dose escalation study
Macdougall 2006	Participants not on dialysis
Macdougall 2007a	Study terminated by sponsor for commercial reasons. No results available
Martin 2007	Dose only varied, not frequency
Moiz 2000	Only varied dosage, not frequency
Muirhead 1992	Injection frequency was not randomised; participants randomised to placebo (Group 1) and two groups maintaining Hb from 95 to 110 g/L (Group 2) or 115 to 130 g/L (Group 3)
Nissenson 1995	Safety and efficacy study of EPO vs. placebo
Parfrey 2005	Hb target study
PATRONUS Study 2009	Compared CERA and darbepoetin at same dose intervals
Pawlak 2007	Study of metalloproteinases with ESA
Provenzano 2006	Described two phase-2 studies. Dialysis and non-dialysis patients not separated
Raftery 2000	Not RCT
Schmitt 2006	Not relevant. Focus on pain

Study	Reason for exclusion
Smith 2007	Pharmacokinetic study
Smyth 2006	Not a frequency study
Spaia 1995	No mention of randomisation. Changed both dose and frequency
Spinowitz 2006	Dosage, no change in frequency
Stockenhuber 1990	Study of EPO effect on stem cells
Tan 1990a	Not a frequency study
Tolman 2005	Computer-assisted anaemia management
Wang 2000	Not clear how patients were allocated to treatment. Cross-over study, wrote to authors to establish if patients were randomised - no reply
Yalcinkaya 1997	Primary randomisation was to two different doses of rHuEPO

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

EMERALD 1 Study 2013

Methods	• Study design: open-label, parallel RCT • Start date: September 2007
Participants	Inclusion criteria • Participants with CKD on HD for ≥ 3 months prior to randomisation • On IV epoetin alfa maintenance therapy continuously prescribed for a minimum of 8 weeks prior to randomisation • Four consecutive Hb values with a mean ≥ 10.0 and ≤ 12.0 g/dL during the screening period Exclusion criteria • Females who are pregnant or breast-feeding; known intolerance to any ESA or pegylated molecule or to all parenteral iron supplementation products • Known bleeding or coagulation disorder • Known hematologic disease or cause of anaemia other than kidney disease • Poorly controlled hypertension • Evidence of active malignancy within one year prior to randomisation • Temporary (untunneled) dialysis access catheter • A scheduled kidney transplant • A scheduled surgery that may be expected to lead to significant blood loss
Interventions	Peginesatide • IV injection once every 4 weeks. The starting dose was based on the participant's total weekly epoetin alfa dose during the last week of the screening period; the first dose was administered one week after the last epoetin alfa dose. The dose was adjusted to maintain haemoglobin levels in a target range of 10.0 to 12.0 g/dL and ± 1.5 g/dL from baseline during the titration and evaluation periods, and 10.0 to 12.0 g/dL during the long-term safety and efficacy period Epoetin alfa

EMERALD 1 Study 2013 *(Continued)*

	• Continued to receive commercially available epoetin alfa by intravenous injection, at the same starting dose and frequency as received during the last week of the screening period, with the first study dose of epoetin alfa administered after randomisation at Week 0. The dose was adjusted to maintain haemoglobin levels in a target range of 10.0 to 12.0 g/dL and ± 1.5 g/dL from baseline during the titration and evaluation periods, and 10.0 to 12.0 g/dL during the long-term safety and efficacy period
Outcomes	• Mean change in Hb between baseline and the evaluation period (baseline and Weeks 29-36) • Proportion of participants who receive RBC transfusions during the titration and evaluation periods • Proportion of participants whose mean Hb level during the evaluation period is within the target range of 10.0 to 12.0 g/dL
Notes	

EMERALD 2 Study 2013

Methods	• Study design: open-label, parallel RCT • Start date: October 2007
Participants	Inclusion criteria 1. Participants with CKD on HD for ≥ 3 months prior to randomisation 2. On IV epoetin alfa or beta maintenance therapy continuously prescribed for a minimum of 8 weeks prior to randomisation 3. Four consecutive Hb values with a mean ≥ 10.0 and ≤ 12.0 g/dL during the screening period Exclusion criteria 1. Females who are pregnant or breast-feeding 2. Known intolerance to any ESA or pegylated molecule or to all parenteral iron supplementation products 3. Known bleeding or coagulation disorder 4. Known hematologic disease or cause of anaemia other than kidney disease 5. Poorly controlled hypertension. 6. Evidence of active malignancy within one year prior to randomisation 7. Temporary (untunneled) dialysis access catheter 8. A scheduled kidney transplant 9. A scheduled surgery that may be expected to lead to significant blood loss
Interventions	Peginesatide • IV or SC injection once every 4 weeks. The starting dose was based on the participant's total weekly epoetin alfa or beta dose during the last week of the screening period; the first dose was administered one week after the last epoetin alfa or beta dose. The dose was adjusted to maintain haemoglobin levels in a target range of 10.0 to 12.0 g/dL and ± 1.5 g/dL from baseline during the titration and evaluation periods, and 10.0 to 12.0 g/dL during the long-term safety and efficacy period Epoetin alfa or beta • Continued to receive commercially available epoetin alfa by IV or SC injection, at the same starting dose and frequency as received during the last week of the screening period, with the first study dose of epoetin alfa administered after randomisation at Week 0. The dose was adjusted to maintain haemoglobin levels in a target range of 10.0 to 12.0 g/dL and ± 1.5 g/dL from baseline

EMERALD 2 Study 2013 *(Continued)*	
	during the titration and evaluation periods, and 10.0 to 12.0 g/dL during the long-term safety and efficacy period
Outcomes	• Mean change in Hb between baseline and the evaluation period (baseline and weeks 29 to 36) • Proportion of participants who receive RBC transfusions during the titration and evaluation periods • Proportion of participants whose mean Hb level during the evaluation period is within the target range of 10.0 to 12.0 g/dL
Notes	

CKD - chronic kidney disease; ESA - erythropoiesis stimulating agent; Hb - haemoglobin; HD - haemodialysis; IV - intravenous; RBC - red blood cell; RCT - randomised controlled trial; SC - subcutaneous

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

NCT00436748

Trial name or title	A multi-center, double-blind, randomized study evaluating de novo weekly and once every two week darbepoetin alfa dosing for the correction of anemia in pediatric subjects with chronic kidney disease receiving and not receiving dialysis
Methods	• Parallel RCT
Participants	Countries: USA, Belgium, Latvia, Lithuania, Mexico, Poland, Puerto Rico, Russian Federation, Slovakia, UK Inclusion criteria • Current diagnosis of CKD, either receiving or not receiving dialysis • Anaemic, with two consecutive screening Hb values drawn at least 7 days apart < 11.0 g/dL • TSAT ≥ 20% Exclusion criteria • Any ESA use within 12 weeks prior to randomisation • other hematologic disorders • upper or lower GI bleeding within 6 months prior to randomisation • uncontrolled hypertension • prior history (within 12 weeks prior to randomisation) of acute myocardial ischaemic, hospitalisation for congestive heart failure, myocardial infarction, stroke or transient ischaemic attack • prior history (within 6 months prior to randomisation) of thromboembolism
Interventions	Treatment group 1 • Darbepoetin alfa: once/wk; 10, 20, 30, 40, 50, 60, 80, 100, 150, 200, or 300 µg IV or SC Treatment group 2 • Darbepoetin alfa: once every 2 weeks; 10, 20, 30, 40, 50, 60, 80, 100, 150, 200, or 300 µg IV or SC
Outcomes	Primary outcome measures • Proportion of subjects achieving a Hb value ≥ 10.0 g/dL at any time point after the first dose during the study is > 0.8 when administered de novo darbepoetin alfa Secondary outcome measures

NCT00436748 *(Continued)*

	• To assess the health-related quality of life in paediatric CKD subjects ≥ 2 years over the duration of the study • To obtain pharmacokinetic data in subjects < 6 years of age • To assess the safety and tolerability of darbepoetin alfa administered once/wk and once every 2 weeks • To estimate Hb values over the duration of the study in the both arms • To estimate doses over the duration of the study in both arms
Starting date	August 2008
Contact information	Amgen Call Centre
Notes	

NCT00717821

Trial name or title	A randomized, controlled, open label, french multicenter parallel group study to compare the hemoglobin maintenance with once monthly administration of mircera versus epoetin beta or darbepoetin alfa in patients with chronic kidney disease on hemodialysis
Methods	• Open-label, parallel RCT
Participants	Inclusion criteria • Adult patients,≥18 years • regular long term HD with same schedule for ≥ 12 weeks • continuous IV or SC maintenance epoetin beta or darbepoetin alfa therapy, with the same dosing interval during the previous month, and no change in total weekly dose Exclusion criteria • transfusion of red blood cells during previous 2 months • significant acute or chronic bleeding • poorly controlled hypertension requiring hospitalisation or interruption of epoetin beta/darbepoetin alfa treatment in previous 6 months • weekly dose of epoetin beta >16000 UI, or weekly dose of darbepoetin alfa >80 µg during previous month
Interventions	Treatment group 1 • Methoxy polyethylene glycol-epoetin beta (Mircera): 120 µg or 200 µg IV or SC (starting dose) Treatment group 2 • Epoetin beta or darbepoetin alfa: as prescribed
Outcomes	Primary outcome measures • Percentage of patients maintaining average Hb concentration within target range (10 to 12 g/dL) during evaluation period Secondary outcome measures • Mean change in Hb concentration between reference and evaluation period, and mean time spent in Hb range of 10 to 12g/dL during evaluation period • Dose adjustments, RBC transfusions, adverse events

NCT00717821 *(Continued)*

Starting date	October 2008
Contact information	Hoffmann-La Roche
Notes	

CKD - chronic kidney disease; ESA - erythropoiesis stimulating agent; GI - gastrointestinal; IV - intravenous; RCT - randomised controlled trial; SC - subcutaneous; TSAT - transferrin saturation

DATA AND ANALYSES

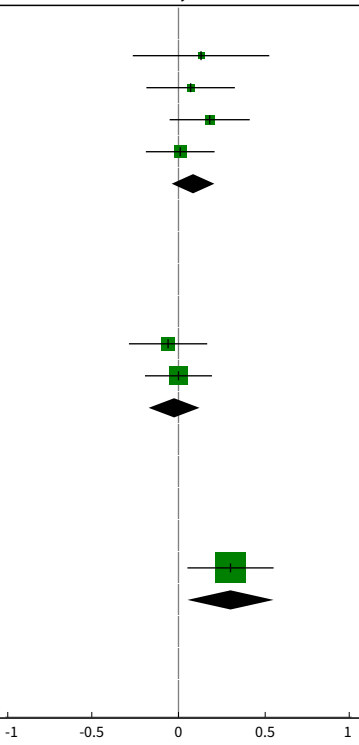
Comparison 1. CERA versus other ESA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final Hb	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 CERA every 2 weeks versus rHuEPO	4	1126	Mean Difference (IV, Random, 95% CI)	0.08 [-0.04, 0.21]
1.2 CERA every 4 weeks versus rHuEPO	2	672	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.17, 0.12]
1.3 CERA every 2 weeks versus darbepoetin	1	249	Mean Difference (IV, Random, 95% CI)	0.30 [0.05, 0.55]
2 All-cause mortality	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1 CERA every 2 weeks versus rHuEPO	4	1341	Risk Ratio (IV, Random, 95% CI)	1.03 [0.67, 1.57]
2.2 CERA every 4 weeks versus rHuEPO	2	827	Risk Ratio (IV, Random, 95% CI)	1.15 [0.70, 1.89]
2.3 CERA every 2 weeks versus darbepoetin	1	313	Risk Ratio (IV, Random, 95% CI)	0.93 [0.44, 1.97]
3 Number of adverse events due to hypertension	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1 CERA every 2 weeks versus rHuEPO	4	1341	Risk Ratio (IV, Random, 95% CI)	0.93 [0.69, 1.26]
3.2 CERA every 4 weeks versus rHuEPO	2	827	Risk Ratio (IV, Random, 95% CI)	1.00 [0.71, 1.40]
3.3 CERA every 2 weeks versus darbepoetin	1	309	Risk Ratio (IV, Random, 95% CI)	0.91 [0.43, 1.92]
4 Transfusions	5	2481	Risk Ratio (IV, Random, 95% CI)	0.93 [0.72, 1.20]

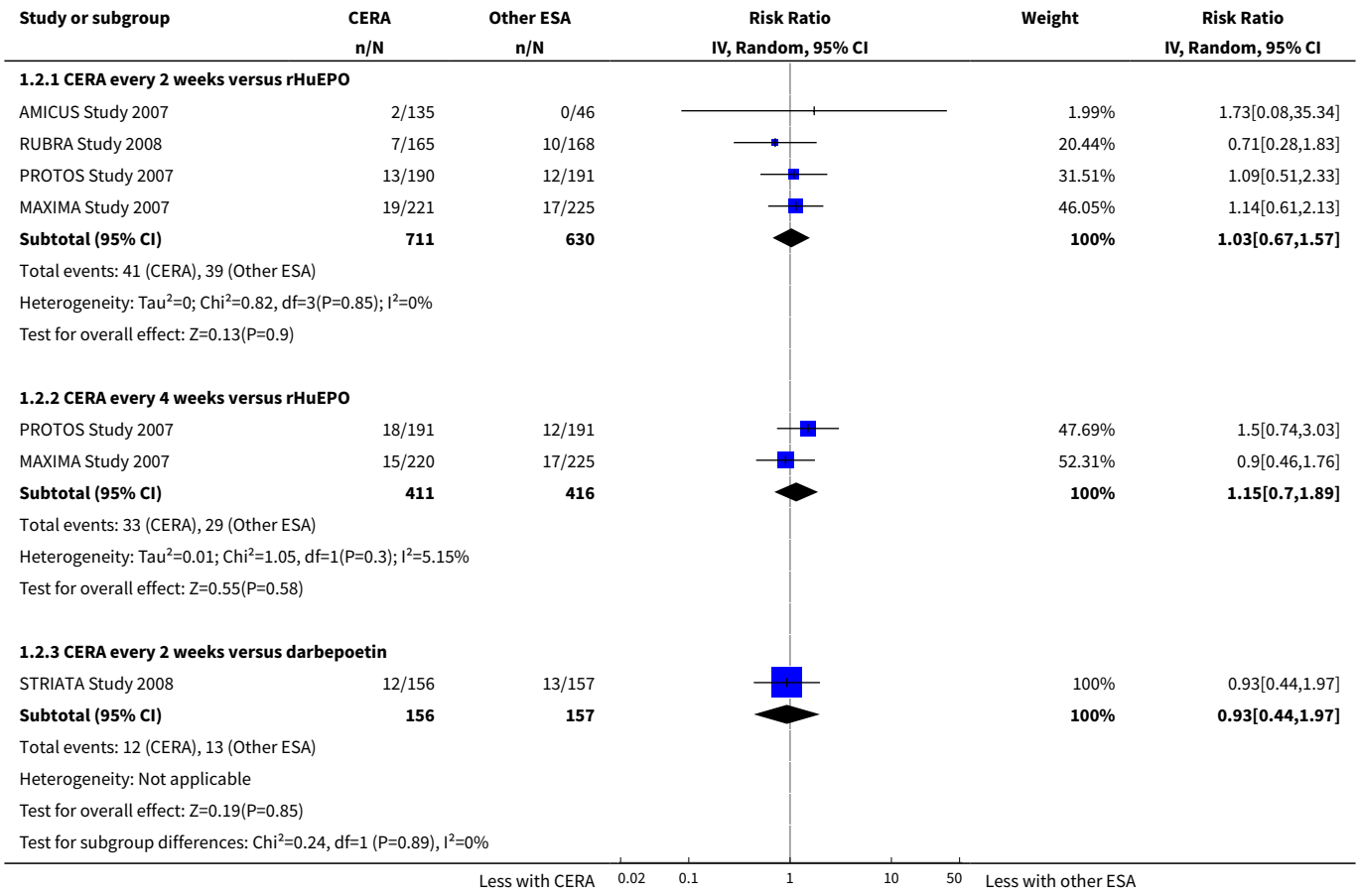
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 CERA every 2 weeks versus rHuEPO	4	1341	Risk Ratio (IV, Random, 95% CI)	0.92 [0.64, 1.32]
4.2 CERA every 4 weeks versus rHuEPO	2	827	Risk Ratio (IV, Random, 95% CI)	1.01 [0.65, 1.57]
4.3 CERA every 2 weeks versus darbepoetin	1	313	Risk Ratio (IV, Random, 95% CI)	0.79 [0.42, 1.51]
5 Number of adverse events due to access thrombosis	5	2477	Risk Ratio (IV, Random, 95% CI)	0.99 [0.69, 1.42]
5.1 CERA every 2 weeks versus rHuEPO	4	1341	Risk Ratio (IV, Random, 95% CI)	0.96 [0.56, 1.65]
5.2 CERA every 4 weeks versus rHuEPO	2	827	Risk Ratio (IV, Random, 95% CI)	1.16 [0.53, 2.54]
5.3 CERA every 2 weeks versus darbepoetin	1	309	Risk Ratio (IV, Random, 95% CI)	0.51 [0.05, 5.56]

Analysis 1.1. Comparison 1 CERA versus other ESA, Outcome 1 Final Hb.

Study or subgroup	CERA N	CERA Mean(SD)	Other ESA N	Other ESA Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.1.1 CERA every 2 weeks versus rHuEPO							
AMICUS Study 2007	135	12.1 (1.4)	46	12 (1.1)		9.78%	0.13[-0.26,0.52]
RUBRA Study 2008	123	11.9 (1.1)	133	11.9 (1)		23.26%	0.07[-0.19,0.33]
PROTOS Study 2007	154	11.7 (1)	167	11.5 (1.1)		28.39%	0.18[-0.05,0.41]
MAXIMA Study 2007	188	11.9 (1.1)	180	11.9 (0.9)		38.56%	0.01[-0.19,0.21]
Subtotal ***	**600**		**526**			**100%**	**0.08[-0.04,0.21]**
Heterogeneity: Tau^2=0; Chi^2=1.26, df=3(P=0.74); I^2=0%							
Test for overall effect: Z=1.34(P=0.18)							
1.1.2 CERA every 4 weeks versus rHuEPO							
PROTOS Study 2007	153	11.5 (1)	167	11.5 (1.1)		42.28%	-0.06[-0.29,0.17]
MAXIMA Study 2007	172	11.9 (1)	180	11.9 (0.9)		57.72%	0[-0.19,0.19]
Subtotal ***	**325**		**347**			**100%**	**-0.03[-0.17,0.12]**
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.69); I^2=0%							
Test for overall effect: Z=0.34(P=0.73)							
1.1.3 CERA every 2 weeks versus darbepoetin							
STRIATA Study 2008	123	12.1 (1)	126	11.8 (1)		100%	0.3[0.05,0.55]
Subtotal ***	**123**		**126**			**100%**	**0.3[0.05,0.55]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.37(P=0.02)							
Test for subgroup differences: Chi^2=4.96, df=1 (P=0.08), I^2=59.7%							

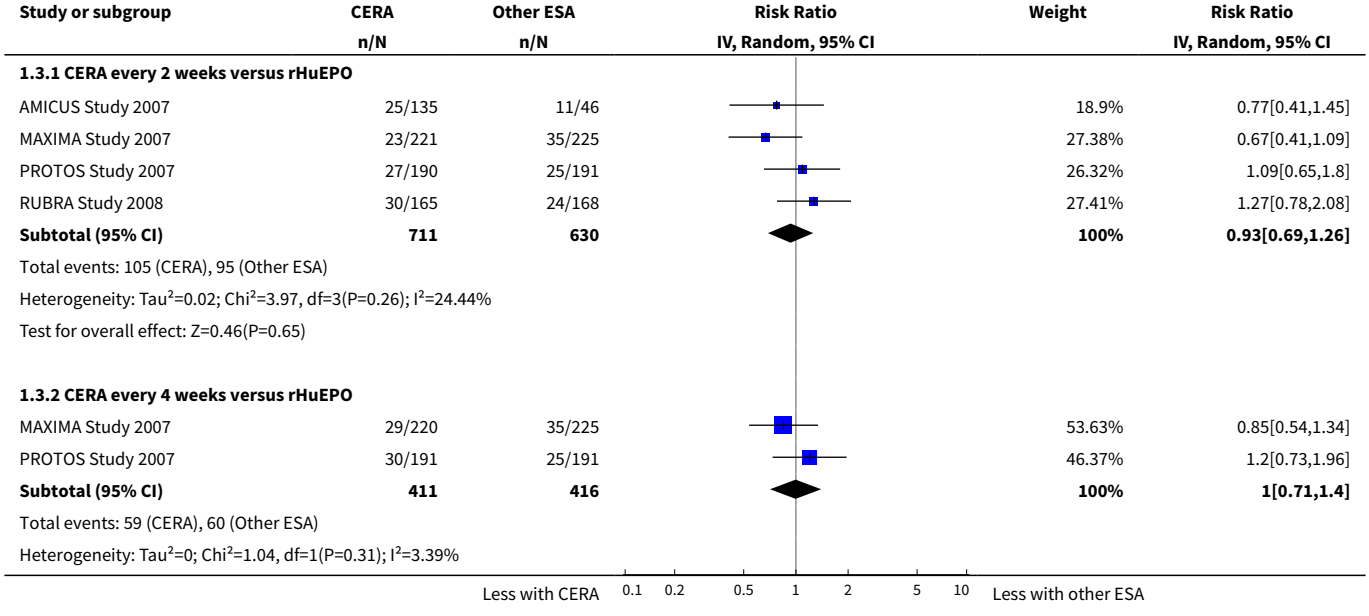


Analysis 1.2. Comparison 1 CERA versus other ESA, Outcome 2 All-cause mortality.



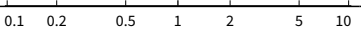
Study or subgroup	CERA n/N	Other ESA n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 CERA every 2 weeks versus rHuEPO					
AMICUS Study 2007	2/135	0/46		1.99%	1.73[0.08,35.34]
RUBRA Study 2008	7/165	10/168		20.44%	0.71[0.28,1.83]
PROTOS Study 2007	13/190	12/191		31.51%	1.09[0.51,2.33]
MAXIMA Study 2007	19/221	17/225		46.05%	1.14[0.61,2.13]
Subtotal (95% CI)	**711**	**630**		**100%**	**1.03[0.67,1.57]**
Total events: 41 (CERA), 39 (Other ESA)					
Heterogeneity: Tau²=0; Chi²=0.82, df=3(P=0.85); I²=0%					
Test for overall effect: Z=0.13(P=0.9)					
1.2.2 CERA every 4 weeks versus rHuEPO					
PROTOS Study 2007	18/191	12/191		47.69%	1.5[0.74,3.03]
MAXIMA Study 2007	15/220	17/225		52.31%	0.9[0.46,1.76]
Subtotal (95% CI)	**411**	**416**		**100%**	**1.15[0.7,1.89]**
Total events: 33 (CERA), 29 (Other ESA)					
Heterogeneity: Tau²=0.01; Chi²=1.05, df=1(P=0.3); I²=5.15%					
Test for overall effect: Z=0.55(P=0.58)					
1.2.3 CERA every 2 weeks versus darbepoetin					
STRIATA Study 2008	12/156	13/157		100%	0.93[0.44,1.97]
Subtotal (95% CI)	**156**	**157**		**100%**	**0.93[0.44,1.97]**
Total events: 12 (CERA), 13 (Other ESA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.19(P=0.85)					
Test for subgroup differences: Chi²=0.24, df=1 (P=0.89), I²=0%					

Analysis 1.3. Comparison 1 CERA versus other ESA, Outcome 3 Number of adverse events due to hypertension.



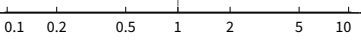
Study or subgroup	CERA n/N	Other ESA n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 CERA every 2 weeks versus rHuEPO					
AMICUS Study 2007	25/135	11/46		18.9%	0.77[0.41,1.45]
MAXIMA Study 2007	23/221	35/225		27.38%	0.67[0.41,1.09]
PROTOS Study 2007	27/190	25/191		26.32%	1.09[0.65,1.8]
RUBRA Study 2008	30/165	24/168		27.41%	1.27[0.78,2.08]
Subtotal (95% CI)	**711**	**630**		**100%**	**0.93[0.69,1.26]**
Total events: 105 (CERA), 95 (Other ESA)					
Heterogeneity: Tau²=0.02; Chi²=3.97, df=3(P=0.26); I²=24.44%					
Test for overall effect: Z=0.46(P=0.65)					
1.3.2 CERA every 4 weeks versus rHuEPO					
MAXIMA Study 2007	29/220	35/225		53.63%	0.85[0.54,1.34]
PROTOS Study 2007	30/191	25/191		46.37%	1.2[0.73,1.96]
Subtotal (95% CI)	**411**	**416**		**100%**	**1[0.71,1.4]**
Total events: 59 (CERA), 60 (Other ESA)					
Heterogeneity: Tau²=0; Chi²=1.04, df=1(P=0.31); I²=3.39%					

Study or subgroup	CERA n/N	Other ESA n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Test for overall effect: Z=0.02(P=0.98)					
1.3.3 CERA every 2 weeks versus darbepoetin					
STRIATA Study 2008	12/156	13/153		100%	0.91[0.43,1.92]
Subtotal (95% CI)	**156**	**153**		**100%**	**0.91[0.43,1.92]**
Total events: 12 (CERA), 13 (Other ESA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.26(P=0.8)					
Test for subgroup differences: Chi^2=0.1, df=1 (P=0.95), I^2=0%					

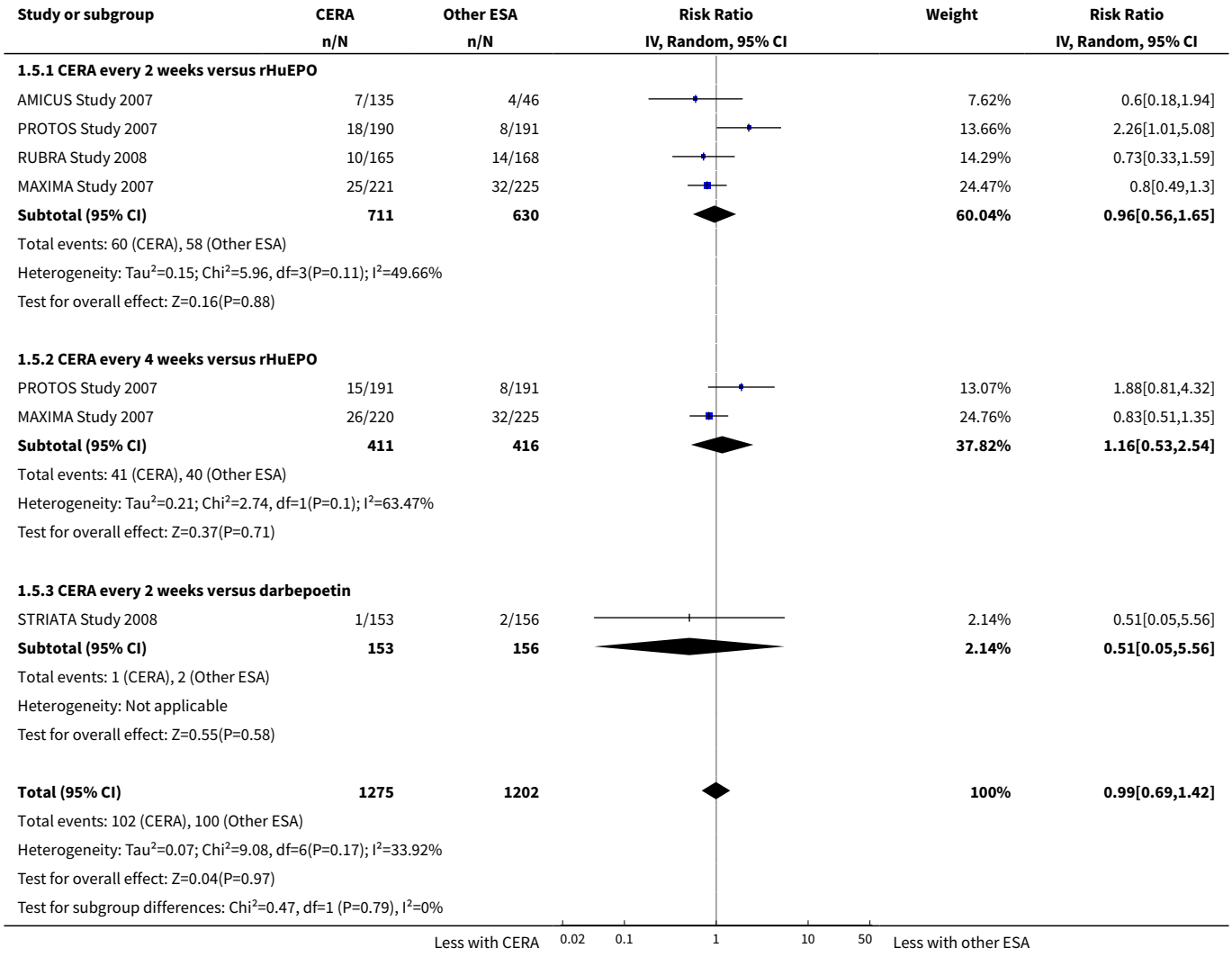


Analysis 1.4. Comparison 1 CERA versus other ESA, Outcome 4 Transfusions.

Study or subgroup	CERA n/N	Other ESA n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.4.1 CERA every 2 weeks versus rHuEPO					
AMICUS Study 2007	7/135	2/46		2.78%	1.19[0.26,5.54]
MAXIMA Study 2007	21/221	17/225		17.48%	1.26[0.68,2.32]
PROTOS Study 2007	12/190	19/191		13.58%	0.63[0.32,1.27]
RUBRA Study 2008	16/165	19/168		16.52%	0.86[0.46,1.61]
Subtotal (95% CI)	**711**	**630**		**50.35%**	**0.92[0.64,1.32]**
Total events: 56 (CERA), 57 (Other ESA)					
Heterogeneity: Tau^2=0; Chi^2=2.26, df=3(P=0.52); I^2=0%					
Test for overall effect: Z=0.46(P=0.65)					
1.4.2 CERA every 4 weeks versus rHuEPO					
MAXIMA Study 2007	16/220	17/225		15.17%	0.96[0.5,1.86]
PROTOS Study 2007	20/191	19/191		18.49%	1.05[0.58,1.91]
Subtotal (95% CI)	**411**	**416**		**33.65%**	**1.01[0.65,1.57]**
Total events: 36 (CERA), 36 (Other ESA)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.84); I^2=0%					
Test for overall effect: Z=0.05(P=0.96)					
1.4.3 CERA every 2 weeks versus darbepoetin					
STRIATA Study 2008	15/156	19/157		15.99%	0.79[0.42,1.51]
Subtotal (95% CI)	**156**	**157**		**15.99%**	**0.79[0.42,1.51]**
Total events: 15 (CERA), 19 (Other ESA)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.7(P=0.48)					
Total (95% CI)	**1278**	**1203**		**100%**	**0.93[0.72,1.2]**
Total events: 107 (CERA), 112 (Other ESA)					
Heterogeneity: Tau^2=0; Chi^2=2.67, df=6(P=0.85); I^2=0%					
Test for overall effect: Z=0.58(P=0.56)					
Test for subgroup differences: Chi^2=0.37, df=1 (P=0.83), I^2=0%					



Analysis 1.5. Comparison 1 CERA versus other ESA, Outcome 5 Number of adverse events due to access thrombosis.



Comparison 2. CERA frequencies

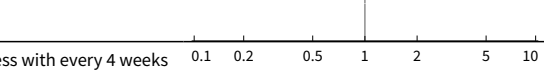
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final haemoglobin	2	675	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.35, 0.14]
2 All-cause mortality	2	822	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.60, 1.78]
3 Number of adverse effects due to hypertension	2	822	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.83, 1.67]
4 Transfusion	2	822	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.52, 2.37]
5 Number of adverse events due to access thrombosis	2	822	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.64, 1.43]

Analysis 2.1. Comparison 2 CERA frequencies, Outcome 1 Final haemoglobin.

Study or subgroup	CERA (every 4 weeks) N	CERA (every 4 weeks) Mean(SD)	CERA (every 2 weeks) N	CERA (every 2 weeks) Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
PROTOS Study 2007	153	11.5 (1)	154	11.7 (1)		47.43%	-0.24[-0.47,-0.01]
MAXIMA Study 2007	188	11.9 (1.1)	180	11.9 (0.9)		52.57%	0.01[-0.19,0.21]
Total ***	**341**		**334**			**100%**	**-0.11[-0.35,0.14]**
Heterogeneity: Tau²=0.02; Chi²=2.64, df=1(P=0.1); I²=62.16%							
Test for overall effect: Z=0.87(P=0.38)							

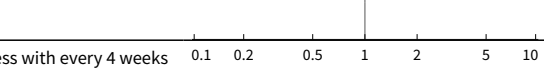
Analysis 2.2. Comparison 2 CERA frequencies, Outcome 2 All-cause mortality.

Study or subgroup	CERA (every 4 weeks) n/N	CERA (every 2 weeks) n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
PROTOS Study 2007	18/191	13/190		48.07%	1.38[0.69,2.73]
MAXIMA Study 2007	15/220	19/221		51.93%	0.79[0.41,1.52]
Total (95% CI)	**411**	**411**		**100%**	**1.03[0.6,1.78]**
Total events: 33 (CERA (every 4 weeks)), 32 (CERA (every 2 weeks))					
Heterogeneity: Tau²=0.04; Chi²=1.31, df=1(P=0.25); I²=23.8%					
Test for overall effect: Z=0.12(P=0.9)					



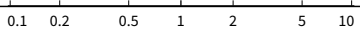
Analysis 2.3. Comparison 2 CERA frequencies, Outcome 3 Number of adverse effects due to hypertension.

Study or subgroup	CERA (every 4 weeks) n/N	CERA (every 2 weeks) n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
MAXIMA Study 2007	29/220	23/221		46.5%	1.27[0.76,2.12]
PROTOS Study 2007	30/191	27/190		53.5%	1.11[0.68,1.79]
Total (95% CI)	**411**	**411**		**100%**	**1.18[0.83,1.67]**
Total events: 59 (CERA (every 4 weeks)), 50 (CERA (every 2 weeks))					
Heterogeneity: Tau²=0; Chi²=0.14, df=1(P=0.7); I²=0%					
Test for overall effect: Z=0.91(P=0.36)					



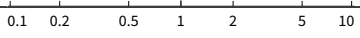
Analysis 2.4. Comparison 2 CERA frequencies, Outcome 4 Transfusion.

Study or subgroup	CERA (every 4 weeks) n/N	CERA (every 2 weeks) n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
PROTOS Study 2007	20/191	12/190		48.18%	1.66[0.83,3.3]
MAXIMA Study 2007	16/220	21/221		51.82%	0.77[0.41,1.43]
Total (95% CI)	**411**	**411**		**100%**	**1.11[0.52,2.37]**
Total events: 36 (CERA (every 4 weeks)), 33 (CERA (every 2 weeks))					
Heterogeneity: Tau^2=0.19; Chi^2=2.67, df=1(P=0.1); I^2=62.54%					
Test for overall effect: Z=0.27(P=0.79)					



Analysis 2.5. Comparison 2 CERA frequencies, Outcome 5 Number of adverse events due to access thrombosis.

Study or subgroup	CERA (every 4 weeks) n/N	CERA (every 2 weeks) n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
PROTOS Study 2007	15/191	18/190		38.31%	0.83[0.43,1.6]
MAXIMA Study 2007	26/220	25/221		61.69%	1.04[0.62,1.75]
Total (95% CI)	**411**	**411**		**100%**	**0.96[0.64,1.43]**
Total events: 41 (CERA (every 4 weeks)), 43 (CERA (every 2 weeks))					
Heterogeneity: Tau^2=0; Chi^2=0.3, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					

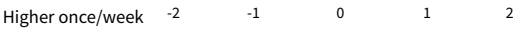


Comparison 3. Darbepoetin every 2 weeks versus once/week

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final/change in Hb	2	252	Mean Difference (IV, Random, 95% CI)	0.04 [-0.45, 0.52]
2 Final ESA/change in dose	2	252	Mean Difference (IV, Random, 95% CI)	-8.03 [-21.64, 5.59]
3 All-cause-mortality	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 Total treatment-related adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Transfusions	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

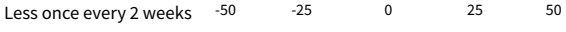
Analysis 3.1. Comparison 3 Darbepoetin every 2 weeks versus once/week, Outcome 1 Final/change in Hb.

Study or subgroup	Every 2 weeks N	Every 2 weeks Mean(SD)	Once/week N	Once/week Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Locatelli 2004	115	0.3 (0.1)	98	0.1 (0.2)		65.31%	0.22[0.19,0.25]
Nagaya 2010	19	10.9 (0.9)	20	11.2 (0.9)		34.69%	-0.3[-0.87,0.27]
Total ***	**134**		**118**			**100%**	**0.04[-0.45,0.52]**
Heterogeneity: Tau^2=0.09; Chi^2=3.24, df=1(P=0.07); I^2=69.14%							
Test for overall effect: Z=0.16(P=0.87)							



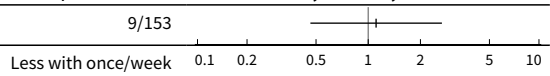
Analysis 3.2. Comparison 3 Darbepoetin every 2 weeks versus once/week, Outcome 2 Final ESA/change in dose.

Study or subgroup	Every 2 weeks N	Every 2 weeks Mean(SD)	Once/week N	Once/week Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Locatelli 2004	115	33.7 (22.2)	98	35.6 (24)		56.24%	-1.9[-8.15,4.35]
Nagaya 2010	19	23.9 (12.1)	20	39.8 (23.2)		43.76%	-15.9[-27.43,-4.37]
Total ***	**134**		**118**			**100%**	**-8.03[-21.64,5.59]**
Heterogeneity: Tau^2=75.61; Chi^2=4.38, df=1(P=0.04); I^2=77.15%							
Test for overall effect: Z=1.16(P=0.25)							



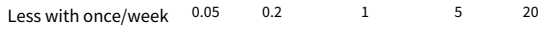
Analysis 3.3. Comparison 3 Darbepoetin every 2 weeks versus once/week, Outcome 3 All-cause-mortality.

Study or subgroup	Every 2 weeks n/N	Once/week n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Locatelli 2004	10/153	9/153		1.11[0.46,2.66]



Analysis 3.4. Comparison 3 Darbepoetin every 2 weeks versus once/week, Outcome 4 Adverse events.

Study or subgroup	Every 2 weeks n/N	Once/week n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.4.1 Total treatment-related adverse events				
Locatelli 2004	7/153	2/153		3.5[0.74,16.58]
3.4.2 Transfusions				
Locatelli 2004	6/153	10/153		0.6[0.22,1.61]

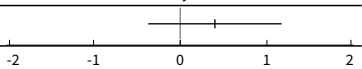


Comparison 4. Darbepoetin every 2 weeks versus once/month

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final/change in HB	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Transfusions	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Darbepoetin every 2 weeks versus once/month, Outcome 1 Final/change in HB.

Study or subgroup	Every 2 weeks N	Every 2 weeks Mean(SD)	Once/month N	Once/month Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Kwan 2005	34	8.8 (1.4)	30	8.4 (1.7)		0.4[-0.37,1.17]



Analysis 4.2. Comparison 4 Darbepoetin every 2 weeks versus once/month, Outcome 2 Adverse events.

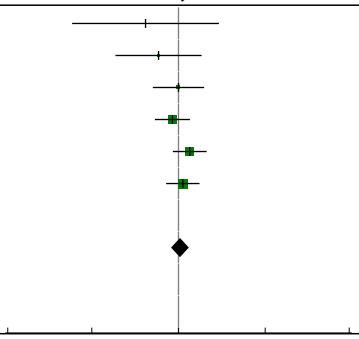
Study or subgroup	Every 2 weeks n/N	Once/month n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.2.1 Transfusions				
Kwan 2005	3/34	8/30		0.33[0.1,1.14]

Comparison 5. Darbepoetin versus rHuEPO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final/change in Hb	6	1245	Mean Difference (IV, Random, 95% CI)	0.02 [-0.09, 0.12]
2 Final/change in ESA dose	3	757	Mean Difference (IV, Random, 95% CI)	-12.27 [-21.72, -2.82]
3 All-cause mortality	5	1596	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.82, 2.02]
4 Hypertension	4	1475	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.06, 0.05]
5 Transfusion	3	1069	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.05, -0.00]
6 Total treatment-related adverse events	3	570	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.03, 0.05]
7 Access thrombosis/vascular complication	4	1475	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.03, 0.00]

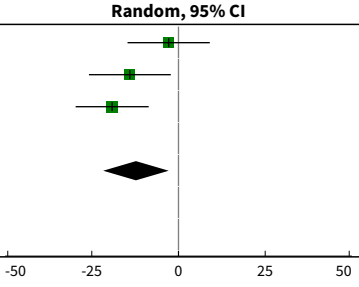
Analysis 5.1. Comparison 5 Darbepoetin versus rHuEPO, Outcome 1 Final/change in Hb.

Study or subgroup	Darbepoetin N	Darbepoetin Mean(SD)	rHuEPO N	rHuEPO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Carrera 2003	18	12 (1)	13	12.4 (1.3)		1.47%	-0.38[-1.23,0.47]
Coyne 2000	90	1.1 (1.3)	31	1.3 (1.2)		4.27%	-0.23[-0.73,0.27]
Tessitore 2008	18	11.6 (0.4)	18	11.6 (0.5)		12.05%	0[-0.3,0.3]
Coyne 2006a	176	11 (1)	187	11.1 (1)		25.94%	-0.07[-0.27,0.13]
Nissenson 2002	118	0.2 (1.1)	240	0.1 (0.1)		27.73%	0.13[-0.07,0.33]
Vanrenterghem 2002	224	0.1 (0.8)	112	0 (0.9)		28.55%	0.05[-0.14,0.24]
Total ***	**644**		**601**			**100%**	**0.02[-0.09,0.12]**
Heterogeneity: Tau²=0; Chi²=3.92, df=5(P=0.56); I²=0%							
Test for overall effect: Z=0.32(P=0.75)							



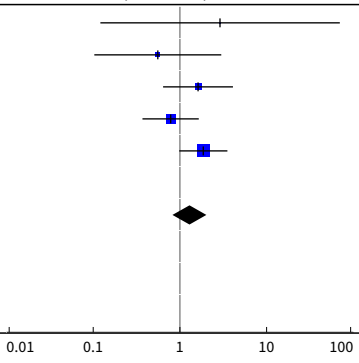
Analysis 5.2. Comparison 5 Darbepoetin versus rHuEPO, Outcome 2 Final/change in ESA dose.

Study or subgroup	Darbepoetin N	Darbepoetin Mean(SD)	rHuEPO N	rHuEPO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Tessitore 2008	18	31.6 (20)	18	34.4 (16.1)		32%	-2.83[-14.69,9.03]
Nissenson 2002	118	54.2 (47.6)	240	68.2 (64)		32.17%	-14.02[-25.82,-2.22]
Coyne 2006a	176	45.5 (41)	187	64.6 (60.1)		35.83%	-19.13[-29.66,-8.6]
Total ***	**312**		**445**			**100%**	**-12.27[-21.72,-2.82]**
Heterogeneity: Tau²=36.08; Chi²=4.14, df=2(P=0.13); I²=51.69%							
Test for overall effect: Z=2.54(P=0.01)							



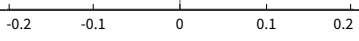
Analysis 5.3. Comparison 5 Darbepoetin versus rHuEPO, Outcome 3 All-cause mortality.

Study or subgroup	Darbepoetin n/N	rHuEPO n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hori 2004	1/61	0/59		1.99%	2.9[0.12,69.87]
Carrera 2003	2/24	3/20		6.88%	0.56[0.1,3]
Coyne 2006a	11/200	7/206		21.06%	1.62[0.64,4.09]
Nissenson 2002	9/169	23/338		30.58%	0.78[0.37,1.65]
Vanrenterghem 2002	41/346	11/173		39.49%	1.86[0.98,3.53]
Total (95% CI)	**800**	**796**		**100%**	**1.29[0.82,2.02]**
Total events: 64 (Darbepoetin), 44 (rHuEPO)					
Heterogeneity: Tau²=0.03; Chi²=4.42, df=4(P=0.35); I²=9.57%					
Test for overall effect: Z=1.1(P=0.27)					



Analysis 5.4. Comparison 5 Darbepoetin versus rHuEPO, Outcome 4 Hypertension.

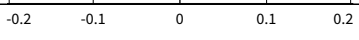
Study or subgroup	Darbepoetin n/N	rHuEPO n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Carrera 2003	0/24	0/20		19.41%	0[-0.09,0.09]
Nissenson 2002	48/169	80/335		20.17%	0.05[-0.04,0.13]
Vanrenterghem 2002	8/346	16/175		30%	-0.07[-0.11,-0.02]
Coyne 2006a	12/200	10/206		30.42%	0.01[-0.03,0.06]
Total (95% CI)	**739**	**736**		**100%**	**-0.01[-0.06,0.05]**
Total events: 68 (Darbepoetin), 106 (rHuEPO)					
Heterogeneity: Tau^2=0; Chi^2=9.42, df=3(P=0.02); I^2=68.14%					
Test for overall effect: Z=0.29(P=0.77)					



Less with darbepoetin — Less with rHuEPO

Analysis 5.5. Comparison 5 Darbepoetin versus rHuEPO, Outcome 5 Transfusion.

Study or subgroup	Darbepoetin n/N	rHuEPO n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Carrera 2003	1/24	1/20		3.37%	-0.01[-0.13,0.12]
Nissenson 2002	7/169	21/335		33.13%	-0.02[-0.06,0.02]
Vanrenterghem 2002	3/346	6/175		63.51%	-0.03[-0.05,0]
Total (95% CI)	**539**	**530**		**100%**	**-0.02[-0.05,-0]**
Total events: 11 (Darbepoetin), 28 (rHuEPO)					
Heterogeneity: Tau^2=0; Chi^2=0.09, df=2(P=0.95); I^2=0%					
Test for overall effect: Z=2.02(P=0.04)					



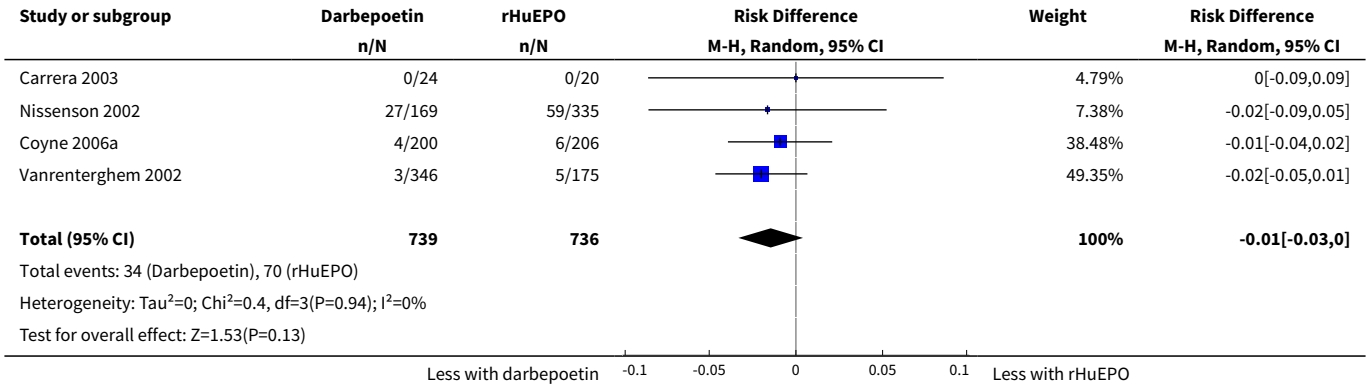
Less with darbepoetin — Less with rHuEPO

Analysis 5.6. Comparison 5 Darbepoetin versus rHuEPO, Outcome 6 Total treatment-related adverse events.

Study or subgroup	Darbepoetin n/N	rHuEPO n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Carrera 2003	0/24	0/20		20.69%	0[-0.09,0.09]
Hori 2004	3/61	1/59		37.3%	0.03[-0.03,0.1]
Coyne 2006a	20/200	23/206		42.01%	-0.01[-0.07,0.05]
Total (95% CI)	**285**	**285**		**100%**	**0.01[-0.03,0.05]**
Total events: 23 (Darbepoetin), 24 (rHuEPO)					
Heterogeneity: Tau^2=0; Chi^2=1.2, df=2(P=0.55); I^2=0%					
Test for overall effect: Z=0.36(P=0.72)					

Less with darbepoetin — Less with rHuEPO

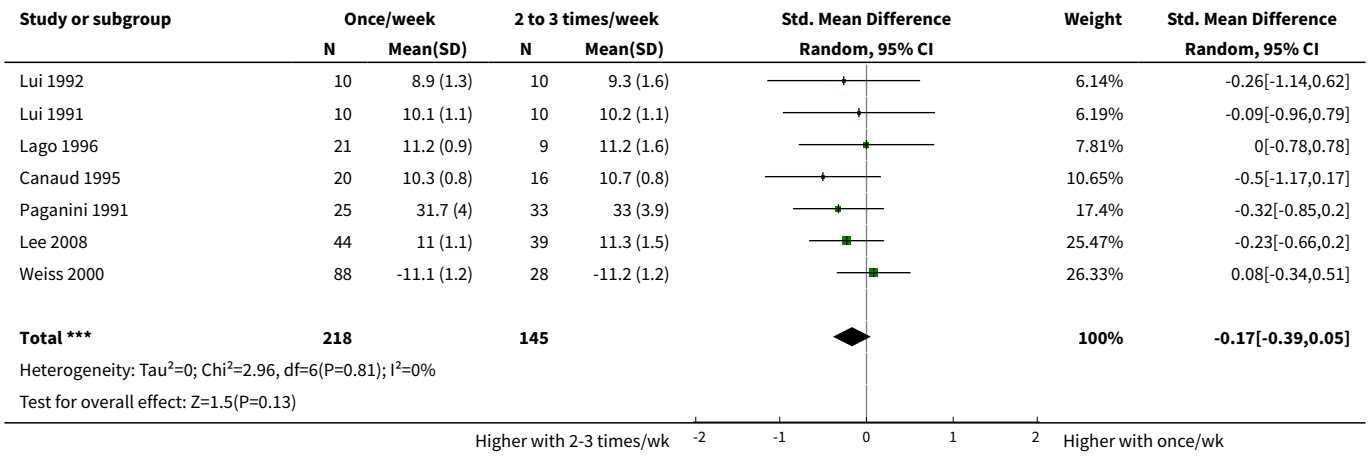
Analysis 5.7. Comparison 5 Darbepoetin versus rHuEPO, Outcome 7 Access thrombosis/vascular complication.



Comparison 6. rHuEPO once/week versus 2 to 3 times/week

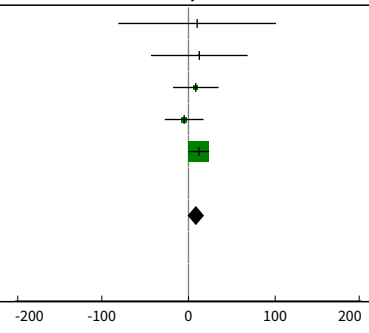
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final/change in Hb or HCT	7	363	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.39, 0.05]
2 Final/change in EPO dose	5	217	Mean Difference (IV, Random, 95% CI)	8.47 [-1.01, 17.95]
3 Adverse effects	5		Risk Difference (IV, Random, 95% CI)	Subtotals only
3.1 Hypertension	4	175	Risk Difference (IV, Random, 95% CI)	-0.00 [-0.12, 0.11]
3.2 Transfusions	1	173	Risk Difference (IV, Random, 95% CI)	-0.02 [-0.10, 0.06]
3.3 Access problems	1	173	Risk Difference (IV, Random, 95% CI)	-0.01 [-0.06, 0.04]

Analysis 6.1. Comparison 6 rHuEPO once/week versus 2 to 3 times/week, Outcome 1 Final/change in Hb or HCT.



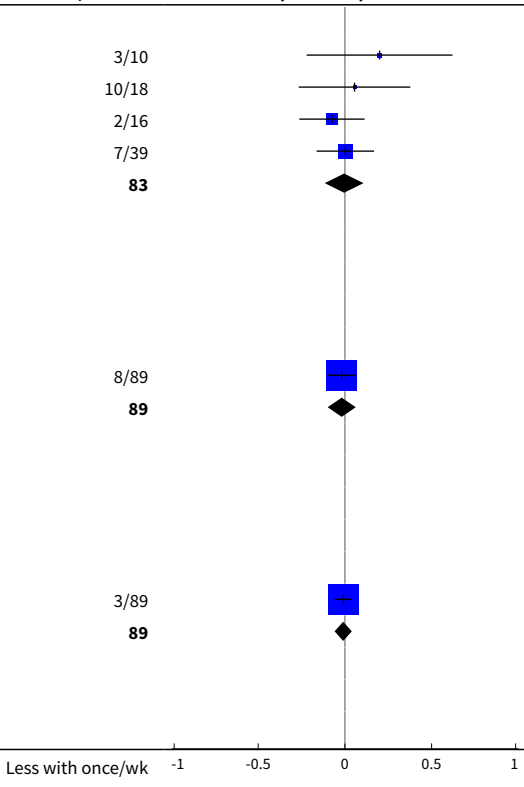
Analysis 6.2. Comparison 6 rHuEPO once/week versus 2 to 3 times/week, Outcome 2 Final/change in EPO dose.

Study or subgroup	Once/week N	Once/week Mean(SD)	2 to 3 times/week N	2 to 3 times/week Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Paganini 1991	25	223 (177)	33	213 (172)		1.09%	10[-80.87,100.87]
Canaud 1995	20	123.2 (75.9)	16	110.7 (91.2)		2.9%	12.5[-43.21,68.21]
Lee 2008	44	104.5 (69.6)	39	96.1 (52)		13.04%	8.4[-17.85,34.65]
Lui 1991	10	81 (26)	10	86 (25)		17.98%	-5[-27.36,17.36]
Lui 1992	10	127 (6)	10	115 (18)		64.99%	12[0.24,23.76]
Total * **	**109**		**108**			**100%**	**8.47[-1.01,17.95]**
Heterogeneity: Tau²=0; Chi²=1.76, df=4(P=0.78); I²=0%							
Test for overall effect: Z=1.75(P=0.08)							



Analysis 6.3. Comparison 6 rHuEPO once/week versus 2 to 3 times/week, Outcome 3 Adverse effects.

Study or subgroup	Once/week n/N	2 to 3 times/week n/N	Risk Difference IV, Random, 95% CI	Weight	Risk Difference IV, Random, 95% CI
6.3.1 Hypertension					
Lui 1992	5/10	3/10		7.08%	0.2[-0.22,0.62]
Leung 1995	11/18	10/18		12.09%	0.06[-0.27,0.38]
Canaud 1995	1/20	2/16		35.34%	-0.07[-0.26,0.11]
Lee 2008	8/44	7/39		45.49%	0[-0.16,0.17]
Subtotal (95% CI)	**92**	**83**		**100%**	**-0[-0.12,0.11]**
Total events: 25 (Once/week), 22 (2 to 3 times/week)					
Heterogeneity: Tau²=0; Chi²=1.59, df=3(P=0.66); I²=0%					
Test for overall effect: Z=0.08(P=0.94)					
6.3.2 Transfusions					
Locatelli 2002	6/84	8/89		100%	-0.02[-0.1,0.06]
Subtotal (95% CI)	**84**	**89**		**100%**	**-0.02[-0.1,0.06]**
Total events: 6 (Once/week), 8 (2 to 3 times/week)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.45(P=0.66)					
6.3.3 Access problems					
Locatelli 2002	2/84	3/89		100%	-0.01[-0.06,0.04]
Subtotal (95% CI)	**84**	**89**		**100%**	**-0.01[-0.06,0.04]**
Total events: 2 (Once/week), 3 (2 to 3 times/week)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.7)					

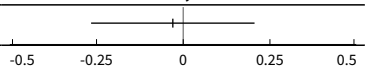


Comparison 7. rHuEPO once/week versus every 2 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final/change in Hb	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Final rHuEPO dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Systolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Diastolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7 rHuEPO once/week versus every 2 weeks, Outcome 1 Final/change in Hb.

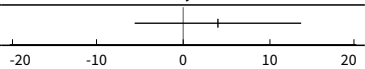
Study or subgroup	Once/week		Once every 2 weeks		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Mircescu 2006	102	11.4 (0.8)	101	11.4 (0.9)		-0.03[-0.27,0.21]



Higher with 2 weekly — Higher with once/week

Analysis 7.2. Comparison 7 rHuEPO once/week versus every 2 weeks, Outcome 2 Final rHuEPO dose.

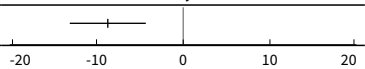
Study or subgroup	Once/week		Once every 2 weeks		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Mircescu 2006	101	71.8 (30.8)	102	67.8 (38.6)		4[-5.6,13.6]



Less with once/week — Less with every 2 weeks

Analysis 7.3. Comparison 7 rHuEPO once/week versus every 2 weeks, Outcome 3 Systolic blood pressure.

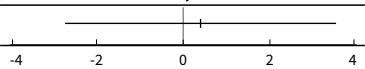
Study or subgroup	Once/week		Once every 2 weeks		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Mircescu 2006	101	121.1 (16.9)	102	129.8 (14.9)		-8.7[-13.08,-4.32]



Lower with once/week — Lower with every 2 weeks

Analysis 7.4. Comparison 7 rHuEPO once/week versus every 2 weeks, Outcome 4 Diastolic blood pressure.

Study or subgroup	Once/week		Once every 2 weeks		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Mircescu 2006	101	70.9 (12.4)	102	70.5 (10.2)		0.4[-2.73,3.53]



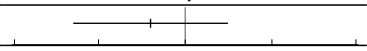
Lower with once/week — Lower with every 2 weeks

Comparison 8. rHuEPO daily versus weekly

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 Final/change in EPO dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

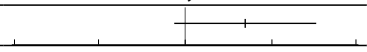
Analysis 8.1. Comparison 8 rHuEPO daily versus weekly, Outcome 1 Final Hb.

Study or subgroup	Weekly N	Weekly Mean(SD)	Daily N	Daily Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Canaud 1995	20	10.3 (0.8)	22	10.5 (0.7)		-0.2[-0.65,0.25]



Analysis 8.2. Comparison 8 rHuEPO daily versus weekly, Outcome 2 Final/change in EPO dose.

Study or subgroup	Weekly N	Weekly Mean(SD)	Daily N	Daily Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Canaud 1995	20	123.2 (75.9)	22	88.6 (57.1)		34.6[-6.34,75.54]



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Erythropoietin explode all trees 2. (erythropoietin):ti,ab,kw in Clinical Trials 3. (epo* or epoetin or epoietin):ti,ab,kw in Clinical Trials 4. (epogen):ti,ab,kw in Clinical Trials 5. (eprex or recormon or repotin*):ti,ab,kw in Clinical Trials 6. (procit* or marogen):ti,ab,kw in Clinical Trials 7. (darbepoetin or mircera or "Methoxy polyethylene glycol-epoetin beta"):ti,ab,kw in Clinical Trials 8. (r-huepo or rhepo or rh-epo or rhuepo):ti,ab,kw in Clinical Trials 9. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) 10. MeSH descriptor Renal Dialysis explode all trees 11. MeSH descriptor Hemofiltration explode all trees 12. MeSH descriptor Kidney Failure, Chronic, this term only 13. (dialysis or hemodialysis or haemodialysis):ti,ab,kw in Clinical Trials 14. (hemofiltration or haemofiltration):ti,ab,kw in Clinical Trials 15. (hemodiafiltration or haemodiafiltration):ti,ab,kw in Clinical Trials

(Continued)

	16.(CAPD or CCPD or APD):ti,ab,kw in Clinical Trials 17.(end-stage kidney or end-stage renal or endstage kidney or endstage renal):ti,ab,kw in Clinical Trials 18.(ESKD or ESKF or ESRD or ESRF):ti,ab,kw in Clinical Trials 19.(#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) 20.#20(#9 AND #19)
MEDLINE	1. exp Erythropoietin/ 2. erythropoietin$.tw. 3. (epo or epoetin or epoietin).tw. 4. epogen.tw. 5. 11096 26 7.rn. 6. eprex.tw. 7. recormon.tw. 8. (r-huepo or rhepo or rhuepo).tw. 9. repotin$.tw. 10.procit$.tw. 11.marogen.tw. 12.darbepoetin$.tw. 13.mircera.tw. 14.Methoxy polyethylene glycol-epoetin beta.tw. 15.or/1-14 16.exp Renal Dialysis/ 17.exp Hemofiltration/ 18.Kidney Failure, Chronic/ 19.dialysis.tw. 20.(hemodialysis or haemodialysis).tw. 21.(hemofiltration or haemofiltration).tw. 22.(hemodiafiltration or haemodiafiltration).tw. 23.(CAPD or CCPD or APD).tw. 24.(end-stage kidney or end-stage renal or endstage kidney or endstage renal).tw. 25.(ESKD or ESKF or ESRD or ESRF).tw. 26.or/16-25 27.and/15,26
EMBASE	1. exp recombinant erythropoietin/ 2. erythropoietin.tw. 3. epo.tw. 4. (epo or epoetin or epoietin).tw. 5. (r-huepo or rhepo or rhuepo).tw. 6. Methoxy polyethylene glycol-epoetin beta.tw. 7. mircera.tw. 8. darbepoetin$.tw. 9. or/1-8 10.exp Renal Replacement Therapy/ 11.(hemodialysis or haemodialysis).tw. 12.(hemofiltration or haemofiltration).tw. 13.(hemodiafiltration or haemodiafiltration).tw. 14.dialysis.tw. 15.(CAPD or CCPD or APD).tw. 16.Chronic Kidney Disease/ 17.Kidney Failure/

(Continued)

18.Chronic Kidney Failure/
19.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
20.(ESRF or ESKF or ESRD or ESKD).tw.
21.or/10-20
22.and/9,21

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.
	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

(Continued)

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 Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
12 November 2014	Amended	Minor edit to study numbers in "Quality of the evidence" section

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 4, 2002

Date	Event	Description
2 June 2014	Amended	Minor copy edit made to search strategies and study name
16 May 2014	New search has been performed	Methods updated, new search performed, title changed to reflect current terminology and the new scope of the review
16 May 2014	New citation required and conclusions have changed	New studies and interventions included
30 September 2008	Amended	Converted to new review format.
25 May 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Two reviewers (JC, CD) independently undertook study quality assessment For the initial review and first update. Data extraction was performed by the lead author (JC) and a sample was double-checked by another author (CD). Sheila Wallace performed extensive literature searched. The lead author entered data and wrote the text of the review. Marion Campbell and Adrian Grant provided statistical and methodological advice. Alison MacLeod, Conal Daly and Izhar Khan provided clinical perspectives. Cam Donaldson and Luke Vale provided health economics perspectives. All authors commented on the review.

For this 2013 update two authors (DH, EH) undertook all stages of the review and wrote the text of the review.

DECLARATIONS OF INTEREST

This systematic review was initially one of six funded (in 1996) by Janssen Cilag who manufacture of Eprex (erythropoietin-α) a recombinant human erythropoietin. Our contract stated that the University of Aberdeen owned the intellectual property rights and we had the right to publish the results without restriction.

No industry funding was sought for the updates of this review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Newer agents have been added to the 2014 review update; methods updated; title changed to reflect new focus of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia [*drug therapy] [etiology]; Drug Administration Schedule; Erythropoietin [*administration & dosage]; Hematinics [*administration & dosage]; Kidney Failure, Chronic [*therapy]; Randomized Controlled Trials as Topic; Recombinant Proteins [administration & dosage]; Renal Dialysis [*adverse effects]

MeSH check words

Humans