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Parenteral versus oral iron therapy for adults and children with chronic kidney disease (Review)

Albaramki J, Hodson EM, Craig JC, Webster AC

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[Intervention Review]

Parenteral versus oral iron therapy for adults and children with chronic kidney disease

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ABSTRACT

Background

The anaemia seen in chronic kidney disease (CKD) may be exacerbated by iron deficiency. Iron can be provided through different routes, with advantages and drawbacks of each route. It remains unclear whether the potential harms and additional costs of intravenous (IV) compared with oral iron are justified.

Objectives

To determine the benefits and harms of IV iron supplementation compared with oral iron for anaemia in adults and children with CKD.

Search methods

In March 2010 we searched the Cochrane Renal Group's specialised register, the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE and EMBASE without language restriction.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs in which oral and IV routes of iron administration were compared in adults and children with CKD.

Data collection and analysis

Two authors independently assessed study eligibility, risk of bias, and extracted data. Results were reported as risk ratios (RR) or risk differences (RD) with 95% confidence intervals (CI) for dichotomous outcomes and for continuous outcomes the mean difference (MD) was used or standardised mean difference (SMD) if different scales had been used. Statistical analyses were performed using the random-effects model. Subgroup analysis and univariate meta-regression were performed to investigate between study differences.

Main results

Twenty eight studies (2098 participants) were included. Risk of bias attributes were poorly performed and/or reported with low risk of bias reported in 12 (43%) studies for sequence generation, incomplete outcome reporting and selective outcome reporting and in 6 (16%) studies for allocation concealment. No study was blinded for participants, investigators and outcome assessors but all were considered at low risk of bias because the primary outcome of haemoglobin was a laboratory outcome and unlikely to be influenced by lack of blinding. Haemoglobin (22 studies, 1862 patients: MD 0.90 g/dL, 95% CI 0.44 to 1.37); ferritin (24 studies, 1751 patients: MD 243.25 µg/L, 95% CI 188.74

to 297.75); and transferrin saturation (18 studies, 1457 patients: MD 10.20%, 95% CI 5.56 to 14.83) were significantly increased by IV iron compared with oral iron. There was a significant reduction in erythropoiesis-stimulating agent (ESA) dose in patients receiving dialysis who were treated with IV iron (9 studies, 487 patients: SMD -0.76, 95% CI -1.22 to -0.30). There was a high level of heterogeneity in all analyses. Mortality and cardiovascular morbidity did not differ significantly, but were reported in few studies. Gastrointestinal side effects were more common with oral iron, but hypotensive and allergic reactions were more common with IV iron.

Authors' conclusions

The included studies provide strong evidence for increased ferritin and transferrin saturation levels, together with a small increase in haemoglobin, in patients with CKD who were treated with IV iron compared with oral iron. From a limited body of evidence, we identified a significant reduction in ESA requirements in patients treated with IV iron, and found no significant difference in mortality. Adverse effects were reported in only 50% of included studies. We therefore suggest that further studies that focus on patient-centred outcomes are needed to determine if the use of IV iron is justified on the basis of reductions in ESA dose and cost, improvements in patient quality of life, and with few serious adverse effects.

PLAIN LANGUAGE SUMMARY

Iron treatment for adults and children with reduced kidney function

Anaemia often occurs in people who have kidney damage, especially those who need dialysis treatment. Anaemia can cause tiredness, reduce exercise tolerance and increase heart size. A common cause of anaemia is reduced production of a hormone, erythropoietin. Iron deficiency can make anaemia worse, and reduce response to drugs that stimulate erythropoietin production. Iron can be taken orally (by mouth) or injected intravenously (via a vein). Intravenous (IV) iron is given under supervision in hospitals. There is uncertainty about whether IV iron should be used rather than oral iron. In this review of 28 studies (2098 participants), IV iron resulted in higher levels of haemoglobin (a measure of anaemia) and blood iron levels compared with oral iron, and a reduction in the amount of erythropoietin required for people receiving dialysis. IV iron resulted in a small number of allergic reactions not seen with oral iron, but oral iron caused more vomiting, nausea, constipation and diarrhoea than IV iron. No differences were found in other outcomes (deaths from any cause, deaths due to heart disease, quality of life) but these were reported in few (9/28) studies. No studies investigated the impact on patients who did not need dialysis of coming to hospital to receive IV iron. Although the results confirm that IV iron is more effective in raising iron and haemoglobin levels compared with oral iron, we found insufficient data to determine if the benefits of IV iron are justified by improved quality of life (fewer gastric upsets) despite the small risk of potentially serious allergic effects in some patients given IV iron.

Summary of findings for the main comparison. Intravenous versus oral iron for adults and children with chronic kidney disease

Intravenous versus oral iron for adults and children with chronic kidney disease						
Patient or population: Adults and children with chronic kidney disease **Settings:** Tertiary centres **Intervention:** IV iron **Comparison:** Oral iron						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Oral iron	**Intravenous iron in CKD patients**				
Haemoglobin: Final or change in all patients g/dL Follow-up: 1.3 to 24 months		The mean Haemoglobin: Final or change - Haemoglobin in all patients in the intervention groups was **0.9 higher** (0.44 to 1.37 higher)		1862 (22 studies)	⊕⊕⊕⊖ **moderate**[1]	
Ferritin: Final or change in all patients Follow-up: 1.3 to 24 months		The mean Ferritin: Final or change - Ferritin in all patients in the intervention groups was **243.25 higher** (188.74 to 297.75 higher)		1751 (24 studies)	⊕⊕⊕⊖ **moderate**[1]	
Transferrin saturation: Final or change in all patients Follow-up: 1.3 to 24 months		The mean Transferrin saturation: Final or change - Transferrin saturation in all patients in the intervention groups was **10.2 higher** (5.56 to 14.83 higher)		1457 (18 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
Number achieving target haemoglobin or increase of 1 g/dL or more	**Study population**		**RR 1.7** (1.36 to 2.12)	1344 (10 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
	316 per 1000	**537 per 1000** (430 to 670)				
	Medium risk population					
	334 per 1000	**568 per 1000** (454 to 708)				

*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] Significant heterogeneity between studies
[2] Studies of variable quality but not sufficient to downgrade overall

Summary of findings 2. Intravenous versus oral iron in adults and children with chronic kidney disease: other outcomes

Intravenous versus oral iron in adults and children with chronic kidney disease: other outcomes

Patient or population: Adults and children with chronic kidney disease
Settings:
Intervention: IV iron versus oral iron

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	Intravenous versus oral iron in CKD patients: other outcomes				
End of treatment or change in ESA dose Follow-up: 1.5 to 24 months		The mean end of treatment or change in ESA dose in the intervention groups was **0.76 SDs lower** (1.22 to 0.3 lower)		487 (9 studies)	⊕⊕⊝⊝ **low**[1,2]	SMD -0.76 (-1.22 to -0.3)
All-cause mortality Follow-up: 1.3 to 24 months	**Study population**		**RR 1.16** (0.35 to 3.84)	435 (5 studies)	⊕⊕⊕⊝ **moderate**[3]	
	36 per 1000	**42 per 1000** (13 to 138)				
	Medium risk population					
	26 per 1000	**30 per 1000** (9 to 100)				

Cardiovascular mortality Follow-up: 6 to 24 months	**Study population**		**RR 3.2** (0.37 to 27.51)	70 (2 studies)	⊕⊕⊖⊖ **low**[4]
	0 per 1000	**0 per 1000** (0 to 0)			
	Medium risk population				
	0 per 1000	**0 per 1000** (0 to 0)			

*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] Only 9/28 studies provided this outcome
[2] Significant heterogeneity between studies
[3] only 5/28 studies provided this outcome
[4] only 2/28 studies reported this outcome

BACKGROUND

Description of the condition

Anaemia is a common comorbidity in patients with chronic kidney disease (CKD). The prevalence of anaemia escalates with increasing severity of kidney dysfunction.In people with CKD stages 3, 4 and 5D (who need dialysis) approximately 20%, 60% and 70%, respectively, are anaemic (McFarlane 2008). The primary cause of anaemia in CKD is erythropoietin deficiency, but iron deficiency can exacerbate the degree of anaemia and reduce response to erythropoietin-stimulating agents (ESAs). Iron deficiency may result from deficient dietary intake of the mineral, decreased gastrointestinal absorption, or frequent blood tests. In patients receiving haemodialysis (HD), blood losses from the gastrointestinal tract may reach 11 mL/m^2 daily; blood loss through HD filters average 8 mL/m^2/dialysis treatment (Muller-Wiefel 1977). The chronic inflammation seen in CKD can also reduce iron absorption from the gut and iron release from iron stores in macrophages.

Anaemia has a negative impact on exercise capacity, quality of life, and left ventricular function. Increasing levels of haemoglobin results in improved energy levels (Wolcott 1989), better cardiac performance and ejection fraction (Pappas 2008), and reversal of increased cardiac output and left ventricular mass index towards normal (Cannella 1990). Anaemia has been associated with higher rates of mortality and morbidity in people with CKD. An increase in haemoglobin concentration of 1 mg/L was associated with a 5% decrease in relative risk of mortality and a 4% decrease in risk of hospitalisation (Locatelli 2004). However, a recent systematic review of studies assessing the effects of targeting higher haemoglobin concentrations in patients with CKD by using higher doses of ESA showed a significantly higher risk of all-cause mortality (risk ratio (RR) 1.17) and arteriovenous access thrombosis (RR 1.34) in the higher haemoglobin target group compared with the lower haemoglobin group (Phrommintikul 2007). Recent national (CARI 2008) and international guidelines (Jacobs 2000; KDOQI 2007; Moist 2008) recommend target haemoglobin levels of 11 mg/L to 12 mg/L in patients with CKD.

Description of the intervention

Iron can be administered via oral or intravenous (IV) routes, but each has advantages and drawbacks. Oral iron causes gastrointestinal upset that affects patient compliance and limits total intake. IV forms of iron are associated with a variety of allergic reactions (Bailie 2005) and require administration under supervision. This need increases the costs of administration and is inconvenient for patients who are not receiving in-centre HD. Adverse reactions to IV iron preparations can be life threatening. Reporting rates for all adverse events associated with IV iron were 29.2, 10.5 and 4.2 reports per million 100 mg dosage equivalents for iron dextran, ferric gluconate and iron sucrose respectively, and fatal event reporting rates for the three iron preparations were 1.4, 0.6 and 0 per million (Bailie 2005). IV iron has been linked to an increased risk of infection, and some experimental data suggest that IV iron products may impair kidney function.

Evidence from a prospective cohort study (Gillespie 2004) and randomised controlled trial (RCT) data (Fishbane 1995) suggest that IV iron leads to significantly higher haemoglobin levels compared with oral iron in both HD and peritoneal dialysis (PD) patients (Johnson 2007). In non-dialysis CKD patients, controversy remains about the most effective and safe way to provide iron supplementation (Fishbane 2007). There is also debate about the most valuable measures to assess iron status, and setting optimum levels of these measures in patients with CKD to increase haemoglobin and optimise ESA response. Parameters used to monitor iron status include serum ferritin levels, transferrin saturation (TSAT), per cent of hypochromic red blood cells, and reticulocyte haemoglobin content. Reticulocyte haemoglobin content is considered to be a highly sensitive marker of functional iron deficiency (Mittman 1997), but is not routinely measured.

How the intervention might work

Iron deficiency anaemia is common in patients with CKD whether or not ESAs are administered. Iron deficiency is the most common cause of hyporesponsiveness to ESAs (Kwack 2006). ESAs accelerate erythropoiesis by increasing iron utilisation and depleting iron stores. Optimal efficacy of ESAs depends on availability of adequate iron stores to achieve and maintain target haemoglobin levels. Haemoglobin levels may increase in patients with CKD given iron therapy even when standard tests do not indicate iron deficiency. Patients with CKD stage 5D require higher targets for ferritin and TSAT levels compared with patients whose kidney function is normal to achieve increased haemoglobin levels. Two studies targeting ferritin levels of 400 ng/mL or 30% to 50% TSAT resulted in significant reductions in the ESA dose required to maintain haemoglobin levels compared with targeting a ferritin level of 200 ng/mL or TSAT levels of 20% to 30% (Besarab 2000; DeVita 2003). However, such high ferritin and TSAT levels increase the risk of iron overload and its associated complications. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (KDOQI 2007) and the Canadian (Madore 2008) and European guidelines (Jacobs 2000) recommend serum ferritin of > 200 ng/mL and TSAT > 20% in patients receiving HD. In other patients with CKD, serum ferritin levels > 100 ng/mL and TSAT > 20% are recommended.

Why it is important to do this review

At present, most HD patients routinely receive IV iron to maintain iron levels. Patients on PD, and those with CKD who do not require dialysis, receive oral iron. However, it remains unclear whether these are the correct indications for IV iron and if the potential hazards, additional costs, and inconvenience to patients of IV compared with oral iron are justified in terms of improved cardiac function, exercise tolerance and quality of life, increased iron stores and haemoglobin levels, and reduced requirements for ESAs. A recent systematic review identified seven small studies comparing IV and oral iron in HD patients (Rozen-Zvi 2008). Significant heterogeneity was found among studies; three showed no significant difference between IV and oral routes of iron administration. Meta-regression identified significant associations between haemoglobin response and lower baseline haemoglobin, and lower ESA and IV iron doses. Among patients with CKD on dialysis, a small benefit was noted with IV iron (0.31 g/dL), which is of uncertain clinical significance.

In this review, we aimed to explore all possible causes of heterogeneity of study results in detail by subgroup analysis and to further investigate the effects of IV iron in patients with CKD who were not on dialysis.

OBJECTIVES

Our objective was to determine the benefits and harms of IV iron supplementation compared with oral iron for anaemia in patients with CKD, treated with HD, PD, not receiving dialysis and post transplant. The review aimed to examine the effects of these interventions on iron parameters, achieving target levels of haemoglobin, reducing doses of ESA required, and on mortality, hospitalisation, cardiac function, quality of life, and to determine adverse effects of the therapies.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs and quasi-RCTs (studies in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which oral and IV routes of administration of iron were compared in patients with CKD.

Types of participants

Inclusion criteria

We included adult and paediatric patients with CKD (stages 3 to 5D; glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2). Studies in patients receiving HD, PD, or those not requiring dialysis, were included. Studies of kidney transplant patients were also included.

Exclusion criteria

Studies of iron administration in patients comparing different IV or oral iron preparations and different doses of the same IV or oral preparation were excluded. Studies in patients with acute kidney injury were excluded.

Types of interventions

- We examined different IV iron supplements (iron sucrose, dextran, ferric gluconate, ferumoxytol) and oral iron preparations, such as ferrous fumarate, and sulphate-including preparations that contain folic acid or vitamin C or both.
- We included studies using different doses and durations of IV iron compared with oral iron preparations provided that the control group received oral iron supplements only.

Types of outcome measures

Primary outcomes

- Haemoglobin
  - Per cent achieving target haemoglobin level
  - Time to achieve target haemoglobin
  - Mean change of haemoglobin from baseline
  - Increase in haemoglobin > 10 g/L or other target during study
- Iron
  - Per cent achieving target levels of iron (ferritin, TSAT, per cent of hypochromic red blood cells)

Secondary outcomes

- ESA
  - ESA dose
  - Numbers of patients needing to increase ESA dose or receive one or more blood transfusions
  - Reduction in required ESA dose
- All-cause mortality
- Cardiovascular mortality and morbidity
- Numbers of non-dialysis patients needing to commence dialysis
- Haematocrit (%)
- Reticulocyte haemoglobin concentration
- Any adverse events
  - Adverse effects of oral iron
  - Adverse effects of IV iron supplements including hypersensitivity reactions
  - Number of patients needing to cease oral or IV supplements because of adverse effects

Other outcomes

- Hospitalisation (other than for iron infusions and dialysis)
- Exercise tolerance
- Quality of life
- Left ventricular function
- Sexual function
- Nutritional status
- Malignancy
- Risk of infections
- Adherence to therapy
- Change in GFR in non-dialysis patients
- Time to achieve target iron levels
- Numbers and costs of hospitalisations/professional supervision required for IV iron supplements
- C-reactive protein (CRP), other inflammatory markers
- Iron overload (as defined by the triallists).

Search methods for identification of studies

Electronic searches

In March 2010 we searched the following electronic databases (Appendix 1).

1. The Cochrane Renal Group's specialised register and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*. CENTRAL contains the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity of the Cochrane Collaboration and is both retrospective and prospective (Master List 2009). Therefore, we did not specifically search conference proceedings. Please refer to The Cochrane Renal Group's Module in *The Cochrane Library* for the most up-to-date list of conference proceedings (Renal Group 2011).
2. MEDLINE (from 1966) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 2008) with a search strategy developed with input from the Cochrane Renal Group's Trials Search Co-ordinator.

3. EMBASE (from 1980) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 2008) with a search strategy developed with input from the Cochrane Renal Group's Trials Search Co-ordinator.

Searching other resources

1. Reference lists of nephrology textbooks, review articles and relevant studies
2. Letters to investigators seeking information about unpublished or incomplete studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that were potentially relevant to the review. The titles and abstracts were screened independently by JA and EH, who discarded studies that were not applicable. However, studies and reviews that might include relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts, and where necessary the full text, of these studies to determine which satisfied the inclusion criteria.

Data extraction and management

Data extraction and assessment of the risk of bias were performed independently by the same authors using standardised data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, only the publication with the most complete data was included. Where relevant outcomes were only published in earlier versions, these data were used. Any discrepancy between published versions was highlighted. Any further information required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review. Disagreements were resolved in consultation with a third author.

Assessment of risk of bias in included studies

The following items were assessed using the risk of bias assessment tool (Higgins 2008) (*see* Appendix 2).

- Was there adequate sequence generation?
- Was allocation adequately concealed?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (number reaching target haemoglobin, death) results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Risk differences (RD) with 95% CI were calculated for adverse effects. Where continuous scales of measurement were used to assess the effects of treatment (haemoglobin level, rise in haemoglobin, iron parameters) the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales had been used (end of study ESA dose). Either final levels or change in levels were included in meta-analyses of continuous scales of measurement. When both measures are provided in a study, final levels were included. Where standard deviations (SD) for changes in levels or initial or final levels were missing and not available from triallists, these were imputed (Higgins 2008).

Unit of analysis issues

Cross-over studies were thought likely to be inappropriate means of examining IV and oral iron because of carry over effects related to achieved haemoglobin levels and iron parameters. Therefore, only data from the first period of cross-over studies were included where these were reported separately, and included all or most patients who completed the first period, rather than only those who completed both treatment periods.

Dealing with missing data

Where necessary, we contacted triallists to request missing patient data due to loss to follow-up and exclusion from study analyses in an effort to conduct intention-to-treat analyses. Eight authors responded to our requests. Where missing dichotomous or continuous data were few, and unlikely to affect the overall results, we analysed available data.

Assessment of heterogeneity

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

Assessment of reporting biases

The search strategy included searching major databases, conference proceedings and prospective trial registers without language restriction in an attempt to reduce publication bias related to failure of authors to publish negative results or inability to publish negative results in journals indexed in major databases. When sufficient studies were available, attempts were made to assess for publication bias using funnel plots. Where multiple publications of the same study were identified, data were included from the most recent publication, and preferably, the definitive publication. However, all publications were reviewed to identify outcomes not reported in the index publication in an attempt to reduce outcome reporting bias.

Data synthesis

Data were pooled using the random-effects model for dichotomous and continuous data.

Subgroup analysis and investigation of heterogeneity

To explore clinical differences among studies that could influence the magnitude of the treatment effect for the primary outcomes of differences in ferritin, TSAT and haemoglobin, subgroup analyses and univariate meta-regression were performed using STATA software (StataCorp LP, Texas, USA) using restricted maximum-likelihood to estimate between study variance. The potential sources of variability were defined a priori and were related to study rationale (CKD stage, whether aiming to increase or maintain haemoglobin, concurrent use of erythropoietin co-intervention, timing of initiation of erythropoietin co-intervention),

dose delivered and duration of IV and oral iron therapy, and study sponsorship. Where subgroup analysis findings suggested that more than one factor could influence the magnitude of observed differences, we planned to conduct multivariate meta-regression.

Underlying cause of end-stage kidney disease (ESKD), baseline iron status, and previous iron therapy were not examined in subgroup analyses because most studies did not provide this information. All studies, except one paediatric study, included adults of similar ages so different age groups could not be examined in subgroup analyses. Only one study (Li 2008 PD) included solely PD patients so it was not possible to examine different types of renal replacement therapy in subgroup analyses.

Sensitivity analysis

Sensitivity analyses were performed to test decisions where inclusion of a study, with a much higher MD in haemoglobin, might have altered meta-analysis results.

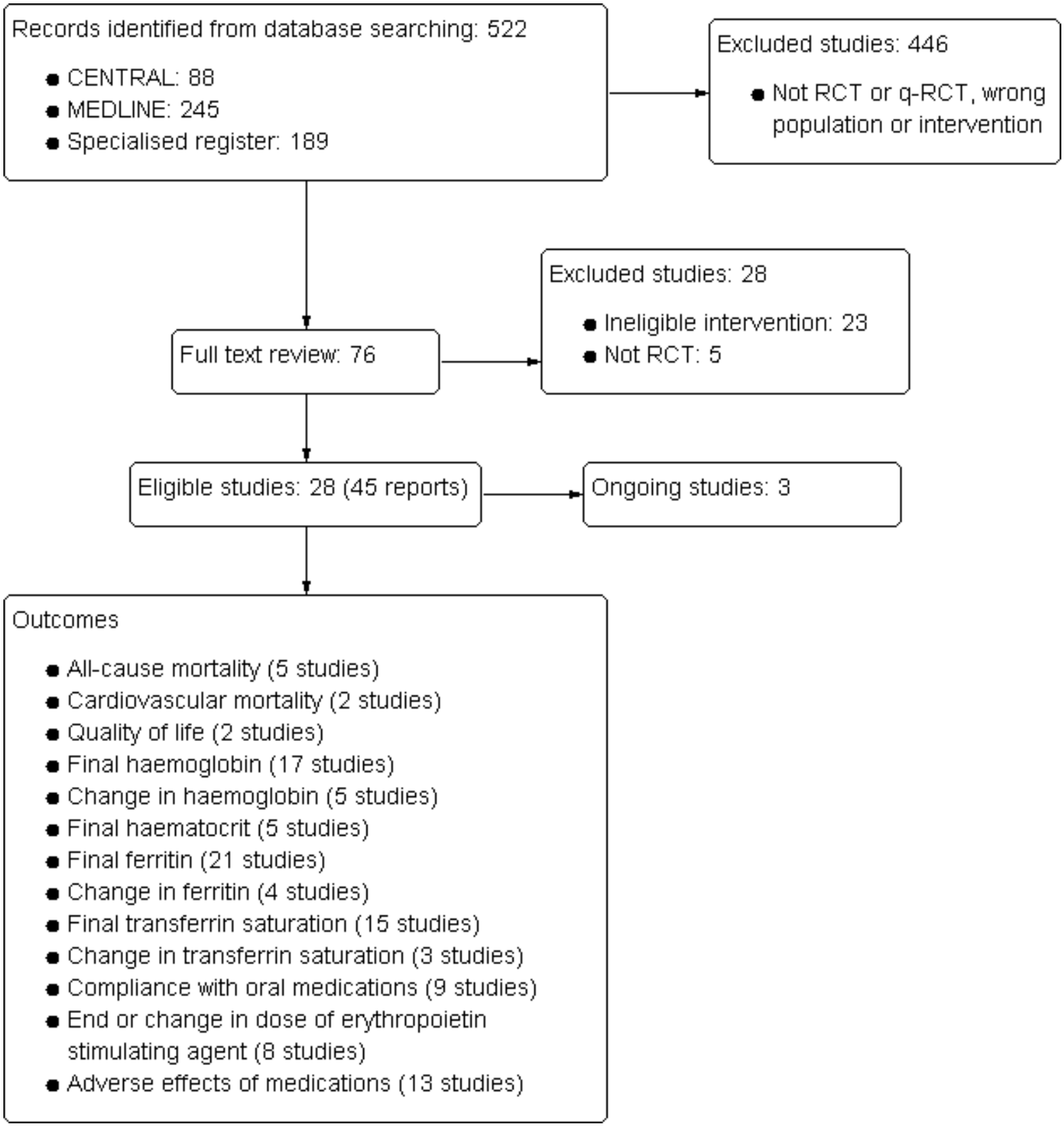
RESULTS

Description of studies

Results of the search

A total of 520 study reports were retrieved after searching the Cochrane Renal Group's specialised register to March 2010, CENTRAL (in *The Cochrane Library* Issue 1, 2010), MEDLINE (to October week 5 2008) and EMBASE (to week 45 2008). The Cochrane Renal Group's specialised register includes conference proceedings from nephrology meetings and is updated regularly, so searches of other databases after the initial search were not required. Search results are shown in Figure 1. Following full text review of 76 potentially eligible reports, 28 were excluded and 28 studies (45 reports) were identified as eligible for inclusion. Three additional studies were identified; two through trial registration databases (Agarwal 2008; Monofer 2010 CKD) and one from publication of the protocol (Mudge 2009 TX), but we did not identify any corresponding publication of results. Therefore, 28 studies (45 reports) were included in this review.

Figure 1. Flow diagram of studies included in the systematic review



Included studies

Of the 28 included studies, 27 (2078 participants) were parallel group studies, and one (20 patients) was a cross-over study (Strickland 1977 HD). With one exception, studies only included adult patients. Warady 2002 HD included only children on HD. Seventeen studies (Broumand 1998 HD; Erten 1998 HD; Fishbane 1995 HD; Fudin 1998 HD; Hussain 1998 HD; Kotaki 1997 HD; Li 2008 PD; Li 2008 HD; Lye 2000 HD; Macdougall 1999 HD,PD; Michael 2007 HD; Provenzano 2009 HD; Souza 1997 HD; Strickland 1977 HD; Svara 1996 HD; Wang 2003 HD; Warady 2002 HD) included patients on HD or PD. Li 2008 PD included only patients receiving PD. Ahsan 1997 TX (12 patients) included only patients who were in the early phase of post kidney transplantation. Results from this study were pooled with studies of dialysis patients. Nine studies (Agarwal 2006 CKD; Aggarwal 2003 CKD; Charytan 2005 CKD; Leehey 2005 CKD; McMahon 2009 CKD; Spinowitz 2008 CKD; Stoves 2001 CKD; Qunibi 2007 CKD; Van Wyck 2005 CKD) included non-dialysis patients (CKD stages 3 to 5) and Macdougall 1996 HD,PD,CKD (20 patients) included both dialysis and non-dialysis patients. Ten studies were available only as abstracts (Ahsan 1997 TX; Broumand 1998 HD; Erten 1998 HD; Leehey 2005 CKD; Lye 2000 HD; Macdougall 1999 HD,PD; Michael 2007 HD; Qunibi 2007 CKD; Souza 1997 HD; Wang 2003 HD). Nineteen studies were designed to increase haemoglobin levels and four studies were designed to maintain haemoglobin stability in iron replete patients and decrease ESA dose (Fishbane 1995 HD; Kotaki 1997 HD; Michael 2007 HD; Warady 2002 HD).

The duration of follow-up ranged from 35 days to 26 months.

Studies compared different oral and IV iron preparations. The oral iron agents investigated were ferrous sulphate (20 studies), ferrous fumarate (four studies), ferrous succinate (two studies), and unnamed agents in two studies. The IV iron agents investigated were iron sucrose (12 studies), iron dextran (six studies), ferumoxytol (two studies), sodium ferric gluconate complex (four studies), ferricarboxymaltose (one study), ferric citrate (one study) and ferric hydroxide polymaltose (one study). The IV iron agent was not reported in Kotaki 1997 HD. The calculated total dose of elemental iron ranged from 4347 to 63,000 mg in the oral iron groups and from 500 to 4800 mg in the IV iron groups. Erten 1998 HD included two IV iron treatment groups. Data from patients who received the higher total dose of IV iron were included in the meta-analyses.

Nineteen studies included patients on ESAs. ESA therapy was started at study commencement in six studies (Aggarwal 2003 CKD; Charytan 2005 CKD; Hussain 1998 HD; Lye 2000 HD; Macdougall 1996 HD,PD,CKD; Stoves 2001 CKD) and before study commencement in 12 studies (Broumand 1998 HD; Erten 1998 HD; Fishbane 1995 HD; Kotaki 1997 HD; Leehey 2005 CKD; Li 2008 PD; Li 2008 HD; Macdougall 1999 HD,PD; Michael 2007 HD; Provenzano 2009 HD; Svara 1996 HD; Warady 2002 HD). It was unclear when ESA treatment was commenced in Wang 2003 HD. Five studies reported that no included patients received ESA treatment (Agarwal 2006 CKD; Ahsan 1997 TX; Fudin 1998 HD; McMahon 2009 CKD; Strickland 1977 HD), but four studies indicated that varying proportions or patients received ESAs (Spinowitz 2008 CKD; Qunibi 2007 CKD; Souza 1997 HD; Van Wyck 2005 CKD).

The outcomes reported in studies are presented in Figure 1. Final haemoglobin, serum ferritin and TSAT levels were reported in 17, 21 and 15 studies respectively; some of these studies also reported on change in haemoglobin, ferritin or TSAT. Change in haemoglobin, serum ferritin and TSAT, but not final levels, were reported in five, four and three studies respectively. Four studies reported final haematocrit levels but not haemoglobin levels (Ahsan 1997 TX; Fishbane 1995 HD; Kotaki 1997 HD; Svara 1996 HD). Only five studies reported all-cause mortality (Fishbane 1995 HD; Fudin 1998 HD; McMahon 2009 CKD; Provenzano 2009 HD: Stoves 2001 CKD); two studies reported on cardiovascular mortality (Stoves 2001 CKD; Fudin 1998 HD); and two studies reported on quality of life assessment (Agarwal 2006 CKD; Van Wyck 2005 CKD). Thirteen studies reported on adverse events (Agarwal 2006 CKD; Aggarwal 2003 CKD; Charytan 2005 CKD; Fishbane 1995 HD; Hussain 1998 HD; Li 2008 PD; Li 2008 HD; Provenzano 2009 HD; Qunibi 2007 CKD; Spinowitz 2008 CKD; Stoves 2001 CKD; Strickland 1977 HD; Van Wyck 2005 CKD).

Funnel plots (data not shown) to examine for publication bias in reporting of haemoglobin, ferritin and TSAT levels suggested that some small studies which showed no significant benefit of IV compared with oral iron were not identified in the literature search.

Ten studies were available only as abstracts. Subgroup analyses that compared the change in haemoglobin or final haemoglobin in full text papers and in abstracts showed that the MD was slightly higher in studies reported as abstracts (MD 0.64 g/dL, 95% CI 0.35 to 1.78) compared with studies reported as full papers (MD 1.06 g/dL; 95% CI 0.35 to 1.78). This raises the possibility that studies remained unpublished because of the limited demonstrated benefit of IV iron compared with oral iron.

Excluded studies

Twenty eight reports were excluded after full text review. These included three reports for the study by Lye 1997 that compared intramuscular and oral preparations; the remainder compared different doses and preparations given IV. Three reports of two studies applied non-randomised sequential designs (Ahsan 2000; Johnson 2001); one study included non-randomised patients (Allegra 1991), and one study was a non-randomised comparator study of oral and IV iron (Jenq 2005).

Risk of bias in included studies

The assessment of risk of bias is shown in Figure 2 and Figure 3. Figure 2 shows relative proportional rankings of studies for each risk of bias indicator. Figure 3 shows the risk of bias items for individual studies.

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

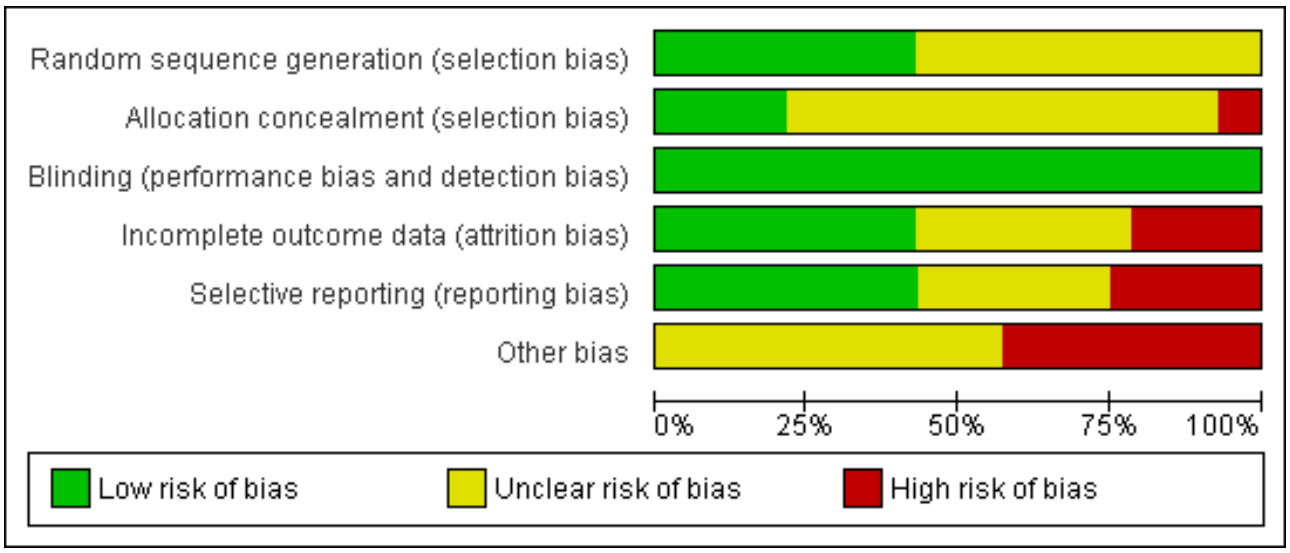


Figure 3. Risk of bias summary: Review authors' judgements about each risk of bias item for each included study

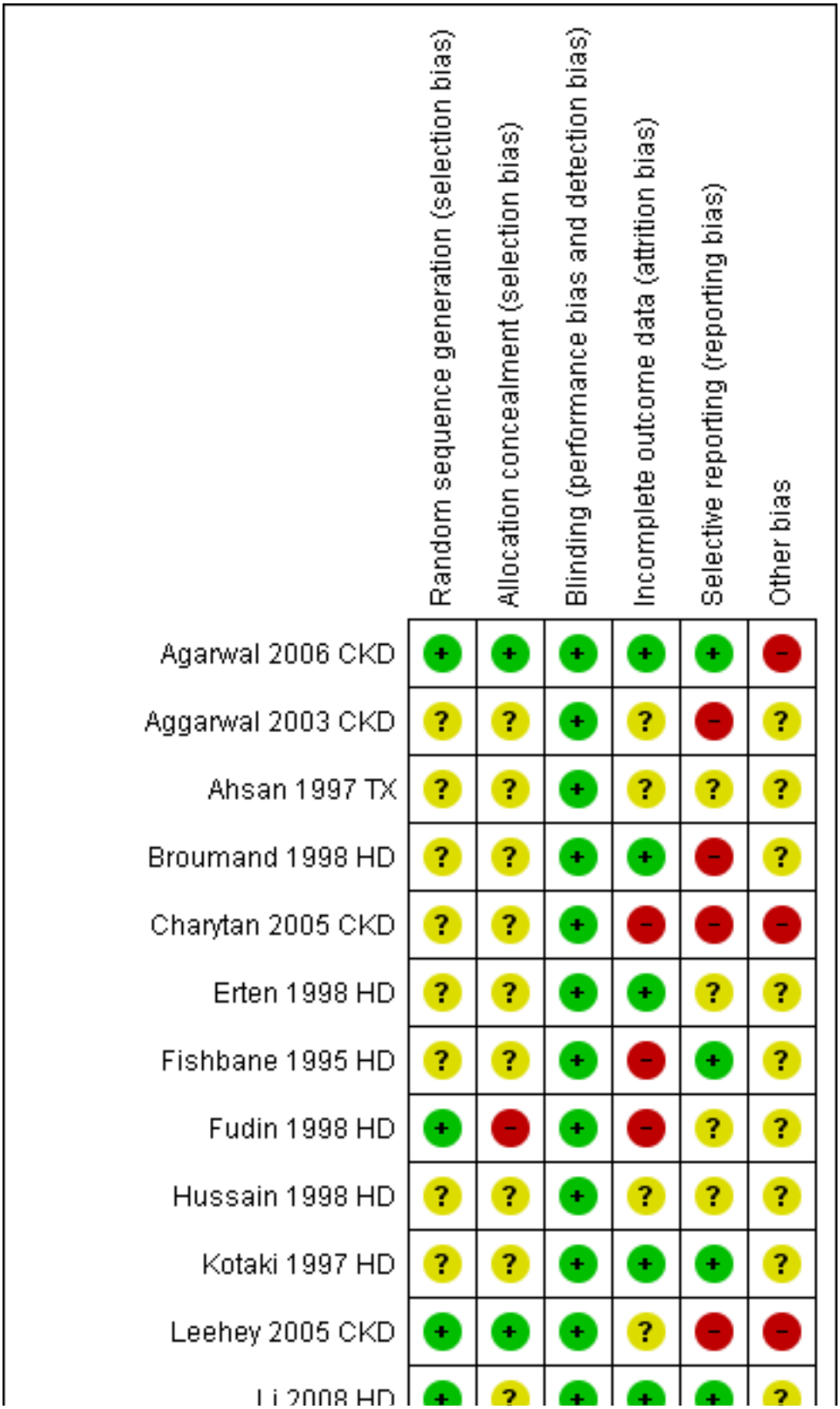


Figure 3. (Continued)

Allocation

Randomisation of sequence generation was reported adequately in 12 studies (Agarwal 2006 CKD: Fudin 1998 HD: Leehey 2005 CKD; Li 2008 PD: Li 2008 HD: Macdougall 1996 HD,PD,CKD; McMahon 2009 CKD; Spinowitz 2008 CKD; Stoves 2001 CKD; Strickland 1977 HD; Van Wyck 2005 CKD; Warady 2002 HD). Randomisation method was not reported in 16 studies. Six studies reported allocation concealment adequately (Agarwal 2006 CKD; Leehey 2005 CKD; Macdougall 1996 HD,PD,CKD; Provenzano 2009 HD; Spinowitz 2008 CKD; Van Wyck 2005 CKD), and for two studies this was inadequately reported (Fudin 1998 HD; Lye 2000 HD). Allocation concealment was unclear in 20 studies.

Blinding

Although none of the included studies reported methods of blinding for participants, investigators or outcomes assessors, all were considered to be at low risk of blinding bias. This was because most primary outcomes were laboratory measurements conducted independently from study investigators and unlikely to be influenced by blinding.

Incomplete outcome data

Outcomes data reporting was considered to be complete with a low risk of bias in 12 studies (Agarwal 2006 CKD; Broumand 1998 HD; Erten 1998 HD; Kotaki 1997 HD; Li 2008 PD; Li 2008 HD; Macdougall 1996 HD,PD,CKD; McMahon 2009 CKD; Provenzano 2009 HD; Spinowitz 2008 CKD; Van Wyck 2005 CKD; Warady 2002 HD). Six studies (Charytan 2005 CKD; Fishbane 1995 HD; Fudin 1998 HD; Strickland 1977 HD; Stoves 2001 CKD; Svara 1996 HD) reported that from 7% to 36% of patients were excluded from the analyses, so were considered to be at high risk of bias. The risk of bias was unclear in 10 studies because there was insufficient information provided to determine if data from all patients who entered the study were included in the analysis.

Selective reporting

We identified 12 studies (Agarwal 2006 CKD; Fishbane 1995 HD; Kotaki 1997 HD; Li 2008 PD; Li 2008 HD; Macdougall 1996 HD,PD,CKD; McMahon 2009 CKD; Provenzano 2009 HD; Spinowitz 2008 CKD; Svara 1996 HD; Van Wyck 2005 CKD; Warady 2002 HD) that were considered to have reported all outcomes based on the detailed protocols described in the trial methods. Seven studies (Aggarwal 2003 CKD; Broumand 1998 HD; Charytan 2005 CKD; Leehey 2005 CKD; Qunibi 2007 CKD; Stoves 2001 CKD; Strickland 1977 HD) reported outcomes incompletely so that they either could not be meta-analysed or included only with imputed SDs. It was unclear if outcomes were selectively reported in nine studies.

Other potential sources of bias

Twelve studies (Agarwal 2006 CKD; Charytan 2005 CKD; Leehey 2005 CKD; McMahon 2009 CKD; Michael 2007 HD; Provenzano 2009 HD; Qunibi 2007 CKD; Spinowitz 2008 CKD; Stoves 2001 CKD; Strickland 1977 HD; Van Wyck 2005 CKD; Warady 2002 HD) reported receiving monetary support from pharmaceutical companies; 16 studies did not report study funding.

Effects of interventions

See: **Summary of findings for the main comparison** Intravenous versus oral iron for adults and children with chronic kidney disease; **Summary of findings 2** Intravenous versus oral iron in adults and children with chronic kidney disease: other outcomes

In most studies, the primary outcome was final haemoglobin level or change in haemoglobin with final level. Changes in ferritin and TSAT were common secondary outcomes. End of treatment and change in values were combined in the meta-analyses of continuous variables. Where final results and changes in results were both reported, final levels were included in the meta-analyses. Changes in values in one or more of haemoglobin, ferritin and TSAT from six studies (Agarwal 2006 CKD; Charytan 2005 CKD; Leehey 2005 CKD; Michael 2007 HD; Qunibi 2007 CKD; Souza 1997 HD) were meta-analysed. Data from Strickland 1977 HD could not be meta-analysed because both arms of the cross-over study were combined. Data from Stoves 2001 CKD were reported as median with interquartile ranges so could not be included in meta-analyses of final haemoglobin, ferritin or final ESA dose. Where they were not reported by study authors (Broumand 1998 HD; Charytan 2005 CKD; Leehey 2005 CKD; Qunibi 2007 CKD), SDs were imputed using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) to enable meta-analysis (Broumand 1998 HD; Charytan 2005 CKD; Leehey 2005 CKD; Qunibi 2007 CKD). In subgroup analyses no significant differences in results were detected on testing for interaction among studies in which SDs were imputed and other studies (Table 1; Table 2; Table 3).

Effect on haemoglobin concentrations of IV iron compared with oral iron

Final haemoglobin level or change (g/dL) in haemoglobin were reported in 22 studies. Haemoglobin was significantly increased by IV iron compared with oral iron (Analysis 1.1 (22 studies, 1862 patients): MD 0.90 g/dL, 95% CI 0.44 to 1.37) in all patients, and in the subgroups of dialysis patients (13 studies, 828 patients: MD 1.16 g/dL, 95% CI 0.30 to 2.02), and non-dialysis patients (8 studies, 1020 patients: MD 0.45 g/dL, 95% CI 0.24 to 0.66) (Table 1). There were high levels of heterogeneity in all analyses (58% to 97%) which persisted when a fixed-effect model was used for analysis. Excluding a study of 26 months treatment and MD 4.92 g/dL (Fudin 1998 HD) did not reduce heterogeneity. Further analyses of heterogeneity are addressed in the following sections.

Number reaching target haemoglobin or increasing haemoglobin by 1 g/dL

The numbers of patients reaching target haemoglobin or increasing haemoglobin by at least 1 g/dL were each reported in 10 studies. Target haemoglobin or an increase in haemoglobin by 1 g/dL or more was achieved by significantly more patients receiving IV iron compared with oral iron (Analysis 1.2 (10 studies, 1344 patients): RR 1.70, 95% CI 1.36 to 2.12).

Effect on serum ferritin concentrations of IV iron compared with oral iron

Final ferritin level or change (µg/L) in serum ferritin levels were reported in 24 studies. Ferritin levels were significantly increased by IV iron compared with oral iron in all patients (Analysis 1.3 (24 studies, 1751 patients): MD 243.25 µg/L, 95% CI 188.74 to 297.75) and in the subgroups of dialysis (16 studies, 960 patients: MD 246.57 µg/L, 95% CI 162.21 to 330.92) and non-dialysis patients (7 studies, 771 patients: MD 229.01 µg/L, 95% CI 157.97 to 300.05) (Table 2). There was a high level of heterogeneity in all analyses (91% to 93%).

Effect on % TSAT levels of IV iron compared with oral iron

End of treatment or change in TSAT levels were reported in 18 studies. TSAT was significantly increased by IV iron compared with oral iron in all patients (Analysis 1.4 (18 studies, 1457 patients): MD 10.20%, 95% CI 5.56 to 14.83) and in the subgroups of dialysis (11 studies, 709 patients: MD 13.97%, 95% CI 6.00 to 21.34) and non-dialysis patients (6 studies, 729 patients): MD 6.89%, 95% CI 3.65 to 10.12) (Table 3). There was a high level of heterogeneity in all analyses (80% to 96%).

Effect on ESA administration of IV iron compared with oral iron

Nine studies reported final dose or change in ESA dose. There was a significant reduction in ESA dose in patients treated with IV iron compared with oral iron (Analysis 2.1 (9 studies, 487 patients): SMD -0.76, 95% CI -1.22 to -0.30), and a high level of heterogeneity (I^2 = 81%).

Two studies reported on the numbers of patients for whom an increase in ESA dose was required, but no significant difference was found (Analysis 2.2 (2 studies, 45 patients): RR 0.34, 95% CI 0.11 to

1.06). Four studies reported on numbers of patients in whom ESA dose could be reduced or ceased; no significant difference on this outcome was found between IV and oral iron therapy (Analysis 2.3 (4 studies, 150 patients): RR 2.02, 95% CI 0.69 to 5.91), although there was considerable heterogeneity (I^2 = 79%).

Effects of IV iron compared with oral iron on other outcomes

All-cause mortality was reported in five studies with no significant difference reported between IV and oral iron therapy (Analysis 2.4 (5 studies, 435 patients): RR 1.16, 95% CI 0.35 to 3.84).

Cardiovascular mortality was reported in two studies with no significant differenced detected between IV and oral therapy (Analysis 2.5 (2 studies, 70 patients): RR 3.20, 95% CI 0.37 to 27.51).

Three studies reported on the need for non-dialysis patients to commence dialysis and found no significant difference between IV and oral iron for this outcome (Analysis 2.6 (3 studies, 282 patients): RR 0.69, 95% CI 0.28 to 1.71).

Four studies reported results for haematocrit rather than haemoglobin. When combined, results from these four studies indicated that haematocrit levels did not differ significantly between IV and oral therapies (Analysis 2.7.1 (4 studies, 152 patients): MD 1.18%, 95% CI -2.17 to 4.52; I^2 = 96%). However exclusion of Kotaki 1997 HD, in which haematocrit levels were to be kept stable, reduced heterogeneity and resulted in a significant increase in haematocrit with IV iron (Analysis 2.7.2 (3 studies, 121 patients): MD 2.43%, 95% CI 0.42 to 4.44).

Four studies reported reticulocyte haemoglobin content (CHr) and found a significant increase between IV and oral iron therapies for this outcome (Analysis 2.8 (4 studies, 506 patients): MD 0.67, 95% CI 0.29 to 1.05).

In two studies, no significant differences were reported at study end in creatinine or GFR, so results could not be meta-analysed (Aggarwal 2003 CKD; McMahon 2009 CKD).

Two studies reported results of quality of life assessment. Agarwal 2006 CKD reported that the SF12 physical composite score improved by 4.8% in patients treated with IV iron, but there was no change in patients treated with oral iron. KDQOl items - improvement in the ability to do moderate activities and undertake work; and satisfaction with sex life - were reported to be significantly improved among patients treated with IV iron. Scores for a number of factors, including feelings of imposing a burden on family, were significantly lower in patients who received IV iron. In contrast, Van Wyck 2005 CKD found no significant differences when health concept categories in the SF36 instrument were applied.

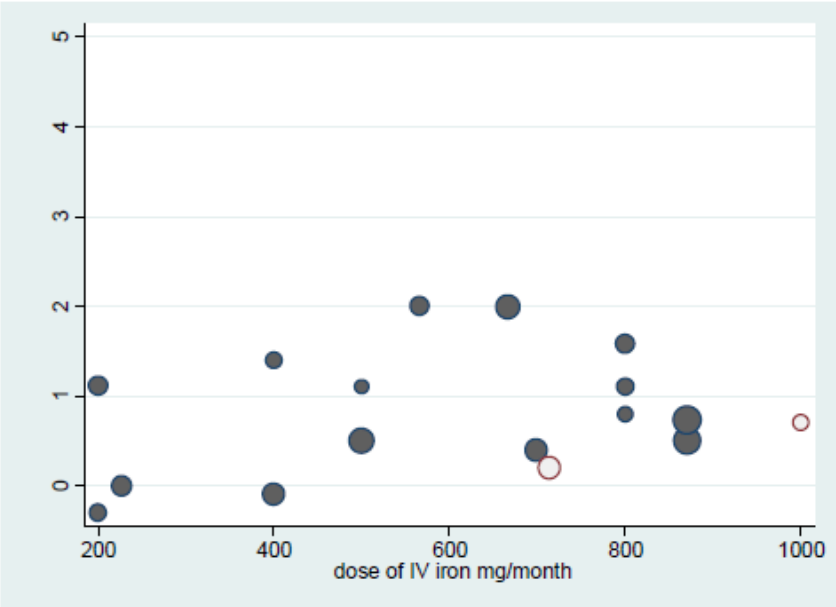
Although nine studies reported that patient adherence to oral iron was assessed, only two provided numerical data (Charytan 2005 CKD; Van Wyck 2005 CKD). Mean adherence rates for IV iron therapy were 95% and 97% respectively, and adherence to oral iron therapy was 85% and 88%.

Exploration of heterogeneity using subgroup analyses: Effect of different doses of IV or oral iron on haemoglobin, ferritin and TSAT

Subgroup analysis using testing for interaction was applied to investigate the effects of different total doses of IV iron (≤ 1000 mg, 1000 to 2000 mg, > 2000 mg), different doses/month of IV iron (≤ 400 mg/month, > 400 to 700 mg/month, > 700 mg/month), different total doses of oral iron (< 12,000 mg, 12,000 to 30,000 mg, > 30,000 mg) and different doses/month of oral iron (< 4000 mg/month, 4000 to <6000 mg/month, ≥ 6000 mg/month) on levels of haemoglobin, ferritin and TSAT. These values were chosen based on tertiles of doses investigated in the included studies. Results for the outcomes of haemoglobin, ferritin and TSAT are shown in Table 1; Table 2 and Table 3 respectively.

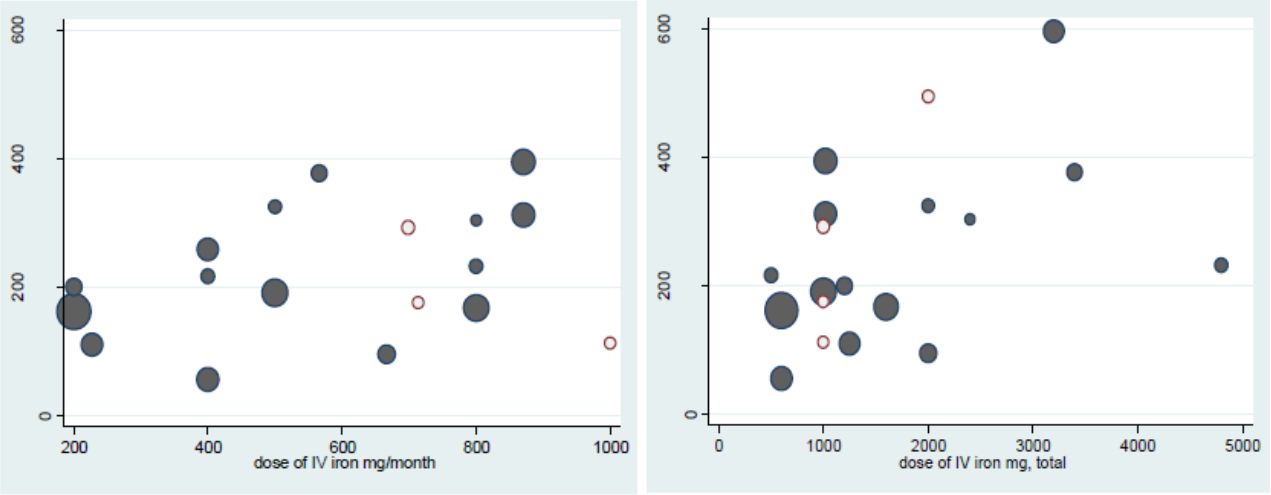
There were no significant differences in total dose administered of IV iron and of IV iron/month between subgroups for haemoglobin (Figure 4) and TSAT. The MD in ferritin levels increased significantly when total IV iron dose was increased, but not in relation to increased IV iron dose/month (Figure 5).

Figure 4. Metaregression of standard mean differences in haemoglobin for intravenous dose of iron/month



* Each circle represents a trial, with the area proportional to the inverse of the variance of the estimated mean difference (larger circles show trials given more weight in the meta-analysis). The shading of the circles represents whether mean difference calculated using mean end haemoglobin (dark circles) or mean change in haemoglobin (light circles)

Figure 5. Metaregression of standard mean differences of ferritin and dose of intravenous iron/month and total dose of intravenous iron

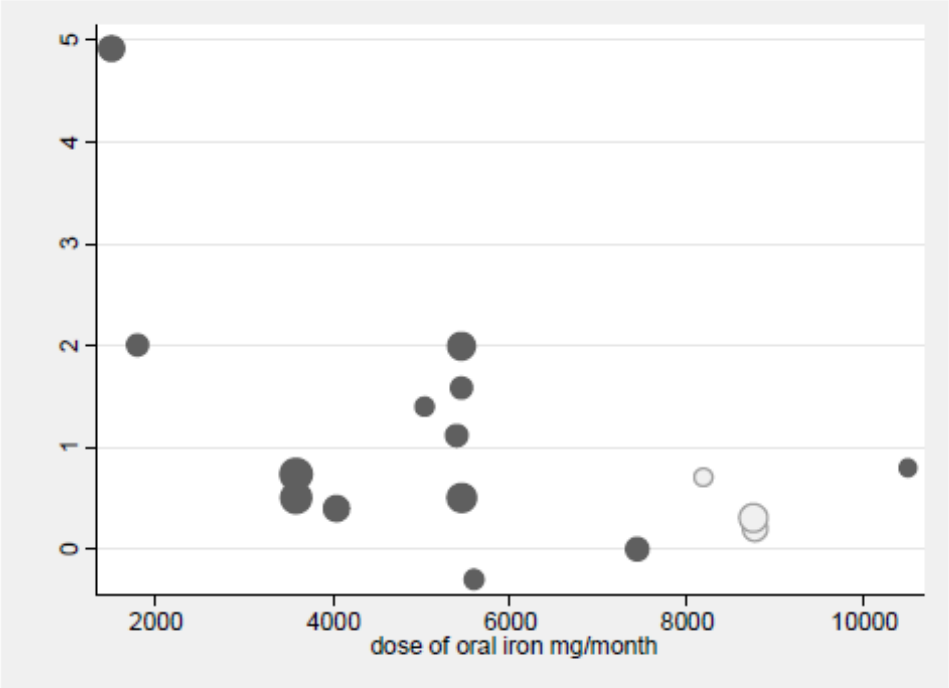


* Each circle represents a trial, with the area proportional to the inverse of the variance of the estimated mean difference (larger circles show trials given more weight in the meta-analysis). The shading of the circles represents whether mean difference calculated using mean end ferritin (dark circles) or mean change in ferritin (light circles)

There were no significant differences in total oral iron dose administered and oral iron dose/month between subgroups for ferritin or TSAT. The MD in haemoglobin escalated with increase in oral iron/month (Figure 6) but not for total oral iron dose. The

difference for oral iron/month was eliminated when one study with a very high MD (Fudin 1998 HD) was excluded from the analysis.

Figure 6. Metaregression of standard mean difference in haemoglobin for oral iron intake/months



* Each circle represents a trial, with the area proportional to the inverse of the variance of the estimated mean difference (larger circles show trials given more weight in the meta-analysis). The shade of the circles represents whether mean difference was calculated using mean end haemoglobin (dark circles) or mean change in haemoglobin (light circles)

Exploration of heterogeneity using subgroup analyses: Effects of erythrocyte-stimulating agents (ESAs) on the response to iron therapy

Subgroup analysis was used to investigate the differential response of haemoglobin, ferritin and TSAT levels in patients who did or did not receive ESAs during iron therapy, and in patients who began ESA therapy at study commencement compared with those already on ESA. No significant differences were found among subgroups (Table 1; Table 2; Table 3). Haemoglobin, ferritin and TSAT levels were increased by IV iron compared with oral iron in patients irrespective of if or when ESAs were administered.

Other subgroup analyses

Exclusion of two studies (Michael 2007 HD; Warady 2002 HD) that were designed to maintain stable haemoglobin levels from the haemoglobin meta-analysis, and four studies (Fishbane 1995 HD; Kotaki 1997 HD; Michael 2007 HD; Warady 2002 HD) designed to maintain stable haemoglobin levels from the ferritin and TSAT meta-analyses, did not alter heterogeneity (84% to 96%). No significant differences were found on testing for interaction (Table 1; Table 2; Table 3).

Subgroup analyses of study duration (≤ 2 months, ≥ 2 to 4 months, ≥ 4 months) showed no significant difference on testing for interaction (Table 1; Table 2; Table 3) for final levels or changes in levels in haemoglobin, ferritin or TSAT. There was significant heterogeneity.

Pharmaceutical company sponsorship of studies was associated with a significantly smaller increase in haemoglobin level compared with studies that did not report sponsorship status (Table 1). Exclusion of a study with a high MD (Fudin 1998 HD; MD 4.92) did not eliminate the difference. There were no significant differences for ferritin or TSAT levels (Table 2; Table 3).

Adverse effects

We identified 12 studies that provided some information on adverse effects of therapy. There were fewer patients who reported adverse effects with IV iron, but the result did not achieve significance. There was considerable heterogeneity of results (Analysis 3.1 (12 studies, 1488 patients: RD -0.09, 95% CI -0.19 to 0.00; I^2 = 85%).

Allergic reactions and hypotension were slightly but significantly increased with IV iron (Analysis 3.2.1 (8 studies, 1199 patients):

RD 0.02; 95% CI -0.00 to 0.04). All gastrointestinal adverse effects combined (Analysis 3.2.2 (8 studies, 925 patients): RD -0.17, 95% CI -0.27 to -0.06); and constipation, diarrhoea, and nausea or vomiting considered individually; were significantly more common with oral iron compared with IV iron (Analysis 3.2.3, Analysis 3.2.4, Analysis 3.2.5). There was significant heterogeneity in these results. Reports of taste disturbance (three studies), iron overload (two studies), and cessation of iron therapy due to adverse effects (one study) were analysed. No significant differences in heterogeneity were found in these analyses (Analysis 3.2.6, Analysis 3.2.7, Analysis 3.2.8).

Outcomes sought but not reported

No studies reported on cardiovascular morbidity, hospitalisation, exercise tolerance, left ventricular function, nutritional status, malignancy, risk of infection, cost of hospitalisation and professional supervision required for administration of IV iron supplement, or detailed information on CRP, or other inflammatory markers.

DISCUSSION

Summary of main results

We identified 28 studies that compared intravenous (IV) iron with oral iron therapy in patients with CKD. There was considerable variability among studies in dose and duration of IV and oral iron therapies prescribed. Durations of studies ranged from 1.3 to 24 months. The doses/month of IV iron and oral iron ranged from 200 mg to1000 mg (IV); and 2898 mg to 10,500 mg (oral). Use of ESAs also varied. Eight studies reported that ESAs were not administered. Of the studies that reported ESA use, some maintained ESA doses unchanged and others altered the dose to maintain haemoglobin within a target range.

Compared with oral iron, IV iron significantly increased levels of haemoglobin, serum ferritin and TSAT in all patients. The final weighted mean increase in haemoglobin was 0.90 g/dL in patients who received IV iron compared with those who received oral iron (22 studies; 1862 patients). The proportion of patients who reached the targeted haemoglobin or increased their haemoglobin by 1 g/dL was 70% higher among those treated with IV iron. The weighted mean increase in final ferritin levels (24 studies; 1751 patients) and TSAT levels (18 studies; 1457 patients) were 243 µg/L and 10% higher respectively in patients treated with IV iron compared with oral iron. The required ESA dose was significantly reduced in patients treated with IV iron compared with oral iron, but was reported in a smaller proportion of included studies (9 studies, 487 patients).

Examination of patient-centred outcomes including mortality (five studies), cardiovascular mortality (two studies) and quality of life (two studies) showed no significant differences between IV and oral iron treated groups.

Subgroup analyses of response to treatment revealed significant heterogeneity in haemoglobin, ferritin and transferrin levels. Although there was no difference in haemoglobin MD when IV iron dose/month was increased, haemoglobin MD increased significantly when oral iron dose/month was reduced. However, this significance was eliminated when a study with a high MD (4.92) was excluded from the sensitivity analysis (Fudin 1998 HD).

Studies that were sponsored by pharmaceutical companies were associated with a significantly greater increase in MD in haemoglobin compared with studies that did not report sponsorship. Ferritin levels increased significantly in terms of total IV iron dose, but this effect was not apparent with IV iron dose/month. Heterogeneity among studies therefore remains largely unexplained, but was likely to be related to the significant variation in the relative doses of IV and oral iron used in each study.

Adverse effects were reported in 13 studies. Overall, adverse effects were reported less often in relation to IV iron therapy. Gastrointestinal adverse effects were more common with oral iron, but allergic reactions and hypotension were seen only with IV iron.

Overall completeness and applicability of evidence

Most included studies reported on laboratory assessments of response to IV and oral iron treatment in patients with CKD stages 3 to 5 including those receiving dialysis. Our meta-analyses identified small but significant increases in laboratory parameters of haemoglobin, ferritin and transferrin in both dialysis and non-dialysis patients. Because key patient-centred outcomes were reported in only a few studies, we were unable to make definitive conclusions about the influence of IV iron therapy on all-cause mortality, cardiovascular mortality and morbidity, or quality of life. However, gastrointestinal disorders were found to be significantly more common in patients taking oral iron. In patients with gastrointestinal disturbances, the amount of oral iron that can be tolerated is limited, but we found no reports that any patients withdrew from studies because of oral iron intolerance. Although ESA dose was significantly lower in patients treated with IV iron, only a third of the included studies (all in dialysis patients) reported on ESA dosage at the end of the study.

The observed haemoglobin increase of 1.16 g/dL in dialysis patients, together with a significant reduction in ESA dose, provides some support for the current practice of administering IV iron to these patients, particularly among those unable to tolerate oral iron. Further data on these and other patient-centred outcomes are required to determine if the use of IV iron is justified.

The haemoglobin increase in non-dialysis patients was modest (0.45 g/dL), but this was not significantly different from the response in dialysis patients. None of the included studies assessed if the patient-centred benefits of achieving higher haemoglobin levels outweighed financial costs or disruption to patients not on dialysis as a result of additional or prolonged hospital visits. Only Agarwal 2006 CKD identified some improvement in quality of life in non-dialysis patients receiving IV iron, however the only other study that assessed quality of life did not report any differences (Van Wyck 2005 CKD). There were no data relating to non-dialysis patients to determine if ESA requirements were reduced. We were therefore unable to derive a definitive conclusion on the relative benefits and harms of IV iron for non-dialysis patients.

The applicability of the conclusions in children, PD patients and kidney transplant patients may be limited since only a single small study was identified for each of these patient groups. However the magnitude and direction of results in these studies did not differ from the overall results.

Quality of the evidence

Our review included 28 studies that involved 2098 participants, of whom about half were on dialysis. We included one paediatric study of 36 children on HD; one study of 46 adults on PD; and one study of 12 kidney transplant recipients. There was considerable variation among studies in dose and duration of IV and oral iron administration.

Of the 28 included studies, 10 were available only as abstracts; 12 reported adequate sequence generation; and six demonstrated adequate allocation concealment. Allocation concealment was therefore unclear or inadequate in most studies. Studies that lack adequate allocation concealment are considered to be at increased risk of bias (Moyer 1998; Schultz 1995). Blinding methodology was not reported in any study, but because key data were reported as laboratory measurements, studies were considered to be at low risk of bias for the primary outcomes. We found that 12 studies provided complete data reporting, and 13 reported all outcomes. The authors of 12 included studies indicated receiving some form of sponsorship from pharmaceutical companies. In this review, we observed a difference between studies that were sponsored by pharmaceutical companies and those that were not. A significantly smaller increase in haemoglobin level among patients who received IV iron, compared with oral iron, was observed in pharma-sponsored studies compared with the studies that did not report pharma sponsorship. Of the 12 pharma-sponsored studies, five demonstrated adequate allocation concealment, but only one of the 16 remaining non-pharma sponsored studies was able to meet this requirement. A possible explanation for this observation is that sponsorship enabled better study design and reporting standards to be incorporated.

Although administration of IV iron consistently resulted in an increase in haemoglobin or haematocrit, ferritin and TSAT, there was considerable heterogeneity among studies in the results of these laboratory outcomes. This effect could not be explained after examining for interactions related to participants, interventions and risk of bias items as reported.

The overall quality of included studies, and the heterogeneity in study results, decreased the quality of evidence to moderate for the outcomes of mean changes in haemoglobin, ferritin and TSAT and the number achieving target haemoglobin (Summary of findings for the main comparison). The quality of evidence for all-cause mortality, and cardiovascular mortality, were considered to be moderate and low respectively, because of small patient numbers included in the studies addressing this outcome (Summary of findings 2). The quality of evidence for end of treatment reduction in ESA dose was considered low because of significant heterogeneity between studies and the limited number of studies reporting this outcome (Summary of findings 2).

Potential biases in the review process

The relatively high proportion of included studies that were available only as abstracts (10/28) is a potential source of bias. To address reporting gaps in studies available only as abstracts, we contacted authors to seek additional information. Responses from nine study authors principally related to risk of bias attributes.

Since the protocol for this review was published, the literature search has been run several times (up to February 2010), to reduce the likelihood that studies published before that time that were eligible for inclusion were missed. Although the Cochrane Renal Group's trials register includes references of reports of studies identified by handsearching resources including conference proceedings, it is a possibility that relevant studies may have been added since our last search of the Register. Potentially relevant studies were also identified from other trials registries, but at the time of writing, data from these completed studies have yet to be published, including a completed study (NCT00255437 on ferumoxytol) which has been reported only in abstracts that present the combined data from several studies on this agent.

Some outcomes were reported in only a few studies which increased the risk of selection bias. In particular, the final or change in ESA dose was reported in nine studies (487 patients) so that the observed significant decrease in ESA dose with IV iron therapy compared with oral iron may not be generalisable to the dialysis population. Similarly, adverse effects were reported in only about half of the included studies.

Agreements and disagreements with other studies or reviews

A systematic review published in 2008 that included 13 studies applied a comprehensive literature review strategy that included searching some conference proceedings (American Society of Nephrology, European Renal Association - European Dialysis and Transplant Association) (Rozen-Zvi 2008). Our review included 12/13 studies included by Rozen-Zvi 2008, as well as two studies that had been published in the interim. We excluded one study that was included in the 2008 systematic review because it included both randomised and non-randomised data (Allegra 1991). Rozen-Zvi 2008 meta-analysed seven studies of dialysis patients and six of non-dialysis patients; we compared 12 and 8 studies in our respective meta-analyses. Both reviews reported increases in mean haemoglobin, ferritin, TSAT and reduction in ESA dose in patients treated with IV iron compared with oral iron. The meta-regression analysis conducted by Rozen-Zvi 2008 demonstrated a significant correlation between SMDs in haemoglobin and IV iron dose/month in dialysis patients, but this was not the case in non-dialysis patients. In this review we were unable to demonstrate an overall correlation, or a correlation n dialysis patients alone. Both reviews reported considerable heterogeneity for the outcomes of haemoglobin, ferritin and TSAT concentrations which could not be explained.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review identified evidence to indicate that compared with oral iron therapy, IV iron therapy contributed increased ferritin and TSAT levels, reduced ESA dose required, and provided a small but significant increase in haemoglobin. Limited patient-centred outcomes data (mortality, cardiovascular disease, quality of life) were reported in the included studies. These data support the current practice of administering IV iron to in-centre HD patients to increase iron stores, and probably, reduce both the ESA dose required, and its cost.

However, the included studies did not provide sufficient evidence on patient-centred outcomes, including adverse effects, to determine if benefits exceed harms for all patients with

CKD. Gastrointestinal adverse effects were common, and often debilitating, with oral iron. These effects must be balanced against the rare, but potentially life threatening adverse effects that are associated with IV iron. Further studies are required to determine if the benefits of IV iron for non-dialysis and PD patients outweigh the disadvantages of increased numbers and durations of hospital visits for treatment.

Implications for research

Further large randomised studies with longer follow-up periods are required. These need to assess patient-centred outcomes including all-cause mortality, cardiovascular mortality, cardiac morbidity using cardiac function tests, hospitalisations, kidney function and time to start dialysis, quality of life and patient inconvenience created by hospital or clinic visits for IV iron in non-dialysis or PD patients as well as common haematological parameters. The costs of all aspects of IV therapy must also be determined to assess overall value of IV iron, especially in non-dialysis and PD patients. These studies should be large enough to enable subgroup analyses to determine which patients would benefit from IV iron, particularly in non-dialysis patients. The doses of oral and IV iron should be standardised across studies in an effort to reduce the heterogeneity seen in this systematic review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Agarwal 2006 CKD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: 26 tertiary centres • Country: USA • Health status: GFR 10 to 59; Hb < 12 g/dL; ferritin <100 ng/mL; TSAT < 20%, no need for dialysis for ≥ 16 weeks, negative stool occult blood, pregnancy test • Number: IV iron 80 (44 analysed for safety; 36 analysed for efficacy); oral iron 84 (45 analysed for safety; 39 analysed for efficacy) • Mean age ± SD: IV iron 65.5 ± 12.9 years; oral iron 62.3 ± 15.2 years • Sex (M/F): IV iron 20/16; oral iron 15/24 Exclusion criteria • Receiving ESA or IV iron within previous 4 weeks; ferritin > 300 ng/mL; TSAT > 30%, albumin < 3 g/dL; allergy to SFGC; anaemia due to other causes than iron deficiency; systemic infection; uncontrolled hypertension; dialysis; kidney transplant; malignancy; clinical instability
Interventions	IV iron • Sodium ferric gluconate complex • Dose, duration, frequency: 250 mg, 4 times/week * Total dose of elemental iron: 1000 mg Oral iron • Ferrous sulphate

Agarwal 2006 CKD *(Continued)*

	• Dose, duration, frequency: 325 mg, 3 times/day for 6 weeks * Total dose of elemental iron: 12,285 mg Co-intervention • NS
Outcomes	• Change in Hb at day 43 • Change in TSAT at day 43 • Change in ferritin at day 43 • Change in CHr at day 43 • Change from baseline quality of life • Adverse effects
Notes	• Funding source: Watson Laboratories Inc • Follow-up period: 70 days • Loss to follow-up: 7 in IV group (16%), 8 in oral group (18%) • 8 (18%) excluded from analysis in IV group due to lack of pre-study evaluation • 6 (13%) excluded from analysis in oral group due to missing results • Exclusions post-randomisation but pre-intervention: NS • Stop or end point/s: None reported • Additional data requested from authors: Further information on methods and more detailed results were obtained from the sponsor, Watson Laboratories Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation of blocks of 4
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced in both groups, reason for missing data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	Study protocol available in paper and all of the pre-specified outcomes reported
Other bias	High risk	Watson Laboratories Inc

Aggarwal 2003 CKD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single tertiary centre

Aggarwal 2003 CKD *(Continued)*

- Country: India
- Health status: CKD on conservative treatment, Hb 5 to 8 g/dL, Hct 15% to 24%, negative stool occult blood, negative direct Coombs test
- Number: IV iron (20); oral iron (20)
- Age range: 21 to 66 years
- Sex (M/F): IV iron 13/7; oral iron 16/4

Exclusion criteria

- Age < 15 years; anaemia due to other causes; uncontrolled hypertension; CAD, chronic infections/inflammation; pregnancy; receiving androgen therapy during the previous month

Interventions	IV iron
	• Iron dextran
	• Dose, duration, frequency: 100 mg; twice/month for 3 months
	  * Total dose of elemental iron: 600 mg
	Oral iron
	• Ferrous sulphate
	• Dose, duration, frequency: 200 mg, 3 times/day for 3 months
	  * Total of dose of elemental iron: 16,200 mg
	Co-intervention
	• EPO 2000 IU twice/week for 3 months, stable dose

Outcomes	• Hb at end of study (3 months) • Ferritin at end of study (3 months) • TSAT at end of study (3 months) • PCV at end of study (3 months) • Reticulocyte % at end of study (3 months) • GFR at end of study (3 months) • Number with sensitivity reactions
Notes	• Funding source: NS • Follow-up period: 3 months • Loss to follow-up: NS • Exclusions post-randomisation but pre-intervention: None reported • Stop or end point/s: None reported • Additional data requested from authors: Method of randomisation and allocation concealment requested. No additional information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation NS
Allocation concealment (selection bias)	Unclear risk	Method of allocation NS
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding

Aggarwal 2003 CKD *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All reported patients included in follow up, but unclear whether any patients included were initially excluded from analysis
Selective reporting (reporting bias)	High risk	Some outcomes, such as symptoms of fatigue and shortness of breath, were reported incompletely and could not be included in the meta-analysis
Other bias	Unclear risk	Funding source NS

Ahsan 1997 TX

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single tertiary centre • Country: USA • Health status: Adult kidney transplant recipients; Hct < 35 %; TSAT < 25 % at day 5 post transplant • Number: IV iron (6); oral iron (6) • Age: IV iron 45.8± 4.7 years (SD); oral iron 46.6± 8.1 years (SD) • Sex (M/F): IV iron 5/1; oral iron 4/2 Exclusion criteria • Delayed graft function requiring dialysis, received blood transfusion, acute rejection

Interventions	IV iron
	• Iron dextran
	• Dose, duration, frequency: 1000 mg single dose
	  * Total dose of elemental iron: 1000 mg
	Oral iron
	• Ferrous sulphate
	• Dose, duration, frequency: 325 mg; 3 times/day for 3 months
	  * Total dose of elemental iron: 26,325 mg

Outcomes	• Hct at end of study • TSAT at end of study • Cr at end of study
Notes	• Abstract only • Funding source: NS • Follow-up period: 8 weeks • Loss to follow-up: None • Exclusions post randomisation but pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: We requested data on method of randomisation and allocation concealment, excluded patients before randomisation, and side effects. No additional information was obtained

Risk of bias

Ahsan 1997 TX *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation NS
Allocation concealment (selection bias)	Unclear risk	Method of allocation NS
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Scant data available from abstract
Selective reporting (reporting bias)	Unclear risk	Limited information to judge
Other bias	Unclear risk	Funding source NS

Broumand 1998 HD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Multicentre • Country: Iran • Health status: Patients on HD, EPO for 6 months • Number: IV iron (9); oral iron (8) • Age: NS • Sex: NS Exclusion criteria • Evidence of active and chronic infection

Interventions	IV iron
	• Iron sucrose
	• Dose, duration, frequency: 100 mg twice/week for 6 months
	  * Total dose of elemental iron: 4800 mg
	Oral iron
	• Ferrous formate
	• Dose, duration, frequency: 350 mg for 6 months
	  * Total oral elemental iron: 63,000 mg
	Co-intervention
	• EPO 2000 IU three times/week 6 months prior to study, stable dose

Outcomes	• Hb, Hct and ferritin at end of study (6 months)

Broumand 1998 HD *(Continued)*

Notes	• Abstract only • Funding source: NS • Randomisation method: NS • Follow-up period: 6 months • Loss to follow-up: NS, started with 20 patients, 3 excluded before randomisation due to HCV positivity, hypertension while on EPO • Exclusions post randomisation but pre-intervention: None reported • Stop or end points: None reported • Additional data requested from authors: We contacted authors seeking information on the method of randomisation and allocation concealment, type of oral iron, number of patients in both groups, whether SD or SE were reported, and data on ferritin. The authors provided data on type of oral iron, ferritin data, and patient numbers

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation NS
Allocation concealment (selection bias)	Unclear risk	Method of allocation NS
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were included in analysis
Selective reporting (reporting bias)	High risk	Limited information on methods. SDs imputed
Other bias	Unclear risk	Funding source NS

Charytan 2005 CKD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Multicentre • Country: USA • Health status: Adult > 18 years; not on dialysis;, CrCl < 40 mL/min; Hb < 10.5 g/dL; TSAT < 25 %; ferritin < 300 ng/mL; absence of other causes of anaemia; absence of infection, surgery and cancer; expected survival > 6 months • Number: IV iron (48; 39 analysed for efficacy and safety); oral iron (48; 44 analysed for efficacy and safety) • Mean age ± SD: IV iron 62 ± 14.4 years; oral iron 60 ± 14.4 years • Sex (M/F): IV iron 19/29; oral iron 14/34 Exclusion criteria

Charytan 2005 CKD *(Continued)*

	• IV iron or ESA within past month; blood transfusion within past month; gastrointestinal bleeding; albumin < 3 g/dL; pregnancy or lactation; HIV positivity; expected to commence dialysis or kidney transplant

Interventions	IV iron
	• Iron sucrose
	• Dose, duration, frequency: 200 mg weekly for 5 weeks
	  * Total dose of elemental iron: 1000 mg
	Oral iron
	• Ferrous sulphate (elemental iron 195 mg/d)
	• Dose, duration, frequency: 325 mg 3 times/day for 29 days
	  * Total dose of elemental iron: 5655 mg
	Co-intervention
	• EPO 2000 IU/week for 6 weeks, stable dose, started at day 1 of study

Outcomes	• Final Hb and change in Hb at day 43 • Change in TSAT at day 43 • Change in ferritin at day 43 • Number with adverse effects • Number reaching Hb > 11 g/dL
Notes	• Funding source: American Regent Inc • Follow-up period: 43 days • Loss to follow-up: NS. 39/48 in IV group completed. 44/48 in oral group completed • Exclusions post randomisation but pre-intervention: Unclear • Stop or end points: None reported • Additional data requested from authors: We contacted authors seeking information on method of randomisation and allocation concealment, SD for continuous variables, denominator for dichotomous outcomes as only percentages. No information was obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation NS
Allocation concealment (selection bias)	Unclear risk	Method of allocation NS
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for patients not completing the trial were not provided, patients with missing data were excluded from analysis (19% missing in IV, 8% missing in oral group). Data were provided as percentages with unclear denominators
Selective reporting (reporting bias)	High risk	Data were not provided with SD. SD imputed to enable entry in meta-analyses
Other bias	High risk	Funded by American Regent Inc

Erten 1998 HD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single centre • Country: Turkey • Health status: Hb < 10 g/dL; HD; hyporesponsiveness to ESA for at least 3 months; no other causes of ESA resistance • Number: IV iron group 1 (26), IV iron group 2 (21); oral iron (22) • Age: NS • Sex (M/F): NS Exclusion criteria • NS

Interventions	IV iron group 1
	
	• Iron sucrose
	• Dose, duration, frequency: 100 mg/session for 10 sessions then 100 mg/week for 6 months
	  * Total dose of elemental iron: 3400 mg
	• Data from this group used in meta-analyses
	
	IV iron group 2
	
	• Iron sucrose
	• Dose, duration, frequency: 100 mg for 10 sessions for 6 months
	  * Total dose of elemental iron: 1000 mg
	
	Oral iron
	
	• Ferrous sulphate
	• Dose, duration, frequency: 200 mg/day for 6 months
	  * Total dose of elemental iron: 10,800 mg
	
	Co-intervention
	
	• EPO 150 IU/kg 3 times/week for at least 3 months before study, dose varied during study

Outcomes	• Hb at end of study (6 months) • Ferritin at end of study (6 months) • Change in EPO dose
Notes	• Abstract only • Funding source: NS • Follow-up period: 6 months • Loss to follow-up: NS, 1 patient excluded from IV group due to side effects • Exclusions post randomisation but pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: We contacted authors seeking information concerning method of randomisation and allocation concealment requested. No additional data were obtained
Risk of bias	

Erten 1998 HD *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation NS
Allocation concealment (selection bias)	Unclear risk	Method of allocation NS
Blinding (performance bias and detection bias)	Low risk	Hematological outcomes not affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one patient excluded from analysis
Selective reporting (reporting bias)	Unclear risk	Limited information on methods
Other bias	Unclear risk	Funding source NS

Fishbane 1995 HD

Methods	Study design: parallel RCT Study duration/ time frame: NS
Participants	Inclusion criteria • Setting: Single centre • Country: USA • Health status: HD for at least 3 months; receiving ESA and oral iron for 3 months; no recent bleeding or transfusion; no haematologic disease other than anaemia; not treated with IV iron for at least 6 months; ferritin >100 ng/mL, TSAT> 15% • Number: IV group (20), oral group (32) • Mean age ± SD: IV group (48.7± 8.7 years); oral group (50.2 ± 9.9 years) • Sex (M/F):IV group (13/7); oral group (18/14) Exclusions • NS

Interventions	IV iron
	
	• Iron dextran
	• Dose, duration, frequency: 100 mg twice/week for 4 months
	  * Total dose of IV iron: 3200 mg
	
	Oral iron
	
	• Ferrous sulphate (21/32)
	  * Dose, duration: 325 mg three times/day for 4 months
	  * Total dose of elemental iron: 35,100 mg
	• Iron polysaccharide (11/32)
	  * Dose, duration, frequency: 150 mg twice/day for 4 months
	
	Co-intervention

Fishbane 1995 HD *(Continued)*

	• ESA started at least 3 months before study, dose adjusted to maintain Hct 30% to 34%
Outcomes	• Hct, Hb at end of study • TSAT at end of study • Ferritin at end of study • EPO dose at end of study • Number with reduction in ESA • Number with side effects
Notes	• Funding source: NS • Follow-up period: 4 months • Loss to follow-up: 5/25 discontinued treatment in IV group (one from diarrhoea, 2 from other illnesses, 2 from bleeding); 18/50 discontinued treatment in the oral group (4 failed treatment, others due to illness, bleeding, death) • Exclusions post randomisation but pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: We contacted authors to seek information concerning method of randomisation and allocation concealment. No additional data were obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation NS
Allocation concealment (selection bias)	Unclear risk	Method of allocation NS
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Large number excluded from analysis, 20% in oral group, 36% in IV group
Selective reporting (reporting bias)	Low risk	Study protocol available in paper and all of the pre-specified outcomes reported
Other bias	Unclear risk	Funding source NS

Fudin 1998 HD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single tertiary centre • Country: Israel • Health status: No blood transfusion or iron during previous year; commencing HD; no malignancy or chronic inflammation; no severe hyperparathyroidism; no other causes of anaemia • Number: IV iron (24); oral iron (12) • Mean age ± SD: IV iron (56.6 ± 15.1 years); oral iron (42.6 ± 17.03 years)

Fudin 1998 HD *(Continued)*

	• Sex (M/F): IV iron (12/8); oral iron (5/5) Exclusion criteria • NS

Interventions	IV iron
	
	• Iron sodium gluconate complex
	• Dose, duration, frequency: 62.5 mg/week until TSAT 35%, then 62.5 mg or 125 mg/month to maintain TSAT
	  * Total dose of elemental iron could be calculated
	
	Oral iron
	
	• Ferrous sulphate
	• Dose, duration, frequency: 150 mg ferrous sulphate equivalent to 50 mg/day of elemental iron
	  * Total dose of elemental iron: 39,000 mg
	
	Co-intervention
	
	• NS

Outcomes	• Hb at end of study (26 months) • Ferritin at end of study (26 months) • TSAT at end of study (26 months)
Notes	• Funding source: NS • Follow-up period: 26 months • Loss to follow-up: 4/24 (16%) in the IV group were excluded from analysis, 2/12 (16%) in the oral iron were excluded from analysis • Exclusions post randomisation but pre-intervention: NS • The authors included a third group of 9 patients who were not treated with iron supplements so not included in the analysis • Stop of end points: NS • Additional data requested from authors: We contacted authors to seek information concerning final Hb and TSAT. Data were provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of 1000 random digits generated by multiplicative congruent method
Allocation concealment (selection bias)	High risk	Open random allocation schedule
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	16% in both groups did not complete and were excluded from the analysis
Selective reporting (reporting bias)	Unclear risk	Limited information on methods

Fudin 1998 HD *(Continued)*

Other bias	Unclear risk	Funding source NS

Hussain 1998 HD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single tertiary centre • Country: Pakistan • Health status: Hb <8.5 g/dL; ferritin 200 to 800 ng/mL; TSAT> 30%, on HD; normal vitamin B_{12}, folate • Number: IV iron (10); oral iron (10) • Age: IV iron (58.4 years); oral iron (56 years) • Sex (M/F): IV iron (6/4); oral iron (5/5) Exclusion criteria • Uncontrolled hypertension; severe hyperparathyroidism; active peptic ulcer disease; hypersensitivity to IV iron

Interventions	IV iron
	• Iron sucrose
	• Dose, duration, frequency: 100 mg twice/week for 3 months
	  * Total dose of elemental iron: 2400 mg
	Oral iron
	• Ferrous sulphate
	• Dose, duration, frequency: 200 mg 3 times/day for 3 months
	  * Total dose of elemental iron: 16,200 mg
	Co-intervention
	• EPO 25 U/kg/week twice weekly, dose altered during study

Outcomes	• Hb at end of study (3 months) • Ferritin at end of study (3 months) • TSAT at end of study(3 months) • Mean EPO dose/week at end of study (3 months) • Number with change in EPO dose
Notes	• Funding source: NS • Follow-up period: 3 months • Lost to follow-up: NS • Exclusions post randomisation but pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: We contacted authors to seek information concerning method of randomisation and allocation concealment. No additional data were not obtained

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Hussain 1998 HD *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method of randomisation not mentioned
Allocation concealment (selection bias)	Unclear risk	Method of allocation not mentioned
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether results of all patients were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited information on methods
Other bias	Unclear risk	Funding source NS

Kotaki 1997 HD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single centre • Country: USA • Health status: HD > 6 months; no IV iron for 6 months; no recent bleeding or blood transfusion; on ESA > 3 months; Hct > 30%; ferritin > 100 ng/mL; TSAT> 20% • Number: IV iron (18, 15 analysed); oral iron (19, 16 analysed) • Age: NS • Sex (M/F): NS Exclusion criteria • Positive for HIV, other haematological disorders

Interventions	IV iron
	• Iron (preparation NS)
	• Dose, duration, frequency: 100 mg/week for 5 months
	  * Total dose of elemental iron: 2000 mg
	Oral iron
	• Ferrous sulphate
	• Dose, duration, frequency: 325 mg, 3 times/day for 5 months
	  * Total dose of elemental iron: 43,875 mg
	Co-intervention
	• ESA > 3 months before study, dose varied

Outcomes	• Hb at end of study (5 months) • Ferritin at end of study (5 months) • TSAT at end of study (5 months)

Kotaki 1997 HD *(Continued)*

	• Mean ESA dose at end of study (5 months)
Notes	• Funding source: NS • Follow-up period: 5 months • Lost to follow-up: 3/18 (17%) from IV group; 3/19 (16%) from oral group • Exclusion post randomisation but pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: We contacted authors to seek additional information concerning method of randomisation and allocation concealment. No additional data were obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not mentioned
Allocation concealment (selection bias)	Unclear risk	Method of allocation not mentioned
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Unclear risk	Funding source NS

Leehey 2005 CKD

Methods	Study design: parallel RCT Study duration/time frame:NS
Participants	Inclusion criteria • Setting: Multicentre • Country: USA • Health status: CKD stages 3 to 5 not on dialysis; Hb < 12 g/dL; ferritin < 100 ng/mL and/or TSAT < 20%; stable ESA dose for > 4 weeks before enrolment • Number: IV iron (26 safety arm, 24 efficacy arm); oral iron (24 safety arm, 24 efficacy arm) • Age: NS • Sex (M/F): NS Exclusion criteria • Dialysis patients; positive FOBT result
Interventions	IV iron • Sodium ferric gluconate complex

Leehey 2005 CKD *(Continued)*

	• Dose, duration, frequency: 250 mg/week for 4 weeks
	  * Total dose of elemental iron: 1000 mg
	
	Oral iron
	
	• Ferrous sulphate
	• Dose, duration, frequency: 325 mg, 3 times/day for 6 weeks
	  * Total dose of elemental iron: 12,285 mg
	
	Co-intervention
	
	• EPO: ≥ 4000 IU/week or ≥ 20 µg/week (darbepoetin), stable dose

Outcomes	• Hb at end of study (10 weeks) • Ferritin at end of study (10 weeks)
Notes	• Abstract only • Funding source: Watson Laboratories Inc • Follow-up period: 10 weeks • Lost to follow-up: Unclear • Exclusions post randomisation but pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: We contacted authors to seek additional information concerning SDs and numbers completing the study. The sponsor provided additional data on the study design, but no data on results

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Central randomisation in blocks of 4 at a 1:1 ratio. Investigators had no prior knowledge of allocation
Blinding (performance bias and detection bias)	Low risk	Laboratory based outcome unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only
Selective reporting (reporting bias)	High risk	Abstract only. Reported change in haemoglobin and ferritin. No SDs provided. SD imputed for inclusion in meta-analyses
Other bias	High risk	Funded by Watson Laboratories Inc

Li 2008 HD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single centre

Li 2008 HD *(Continued)*

	• Country: China • Health status: Stable on HD for 1 month, ferritin < 500 ng/mL, TSAT < 30%, Hb 60 to 90 g/dL, Hct 18 to 24%, all on oral iron and ESA pre-study • Number: IV iron (70); oral iron (66) • Mean age ± SE: IV iron (53.6 ± 13.8); oral iron (54.9 ± 12.6) • Sex (M/F): IV iron (31/39); oral iron (26/40) Exclusion criteria • Severe liver disease; hypersplenism; haemorrhage; blood transfusion in previous month; malignancy, sensitive to iron; high CRP > 20 mg/L; severe infection or inflammation

Interventions	IV iron
	
	• Iron sucrose
	• Dose, duration, frequency: 100 mg twice/week for 8 weeks, then once/week for 4 weeks
	  * Total dose of elemental iron: 2000 mg
	
	Oral iron
	
	• Ferrous succinate
	• Dose, duration, frequency, administration: 200 mg 3 times/day for 12 weeks
	  * Total dose of elemental iron: 16,800 mg
	
	Co-intervention
	
	• EPO 100 to 150 IU/kg/week started before study, dose varied; folic acid; vitamin B_{12}

Outcomes	• Final or change in Hb (12 weeks) • Final ferritin (12 weeks) • Final TSAT (12 weeks) • Mean ESA dose at end of study (12 weeks) • Number with adverse effects • Number with a specific rise in Hb
Notes	• Funding source: NS • Follow-up period: 12 weeks • Lost to follow-up: None • Exclusions post randomisation but pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: We contacted authors to seek additional information concerning method of randomisation and allocation concealment, and whether data were expressed as SD or SE. No additional data were obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random number list
Allocation concealment (selection bias)	Unclear risk	Method of allocation NS
Blinding (performance bias and detection bias)	Low risk	Haematological outcomes unlikely to be affected by lack of blinding

Li 2008 HD *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data. All participants completed the study and were included in the analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Unclear risk	Funding source NS

Li 2008 PD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single centre • Country: China • Health status: Stable on PD for 1 month; ferritin < 500 ng/mL; TSAT < 30%; Hb 60 to 90 g/L; Hct 18% to 27% • Number: IV iron (26); oral iron (20) • Mean age ± SE: IV iron (56.9 ± 14.8); oral iron (57.6 ± 15.6) • Sex (M/F): IV iron (12/14); oral iron (9/110 Exclusion criteria • Severe liver disease; hypersplenism; haemorrhage; active gastrointestinal ulcer; blood transfusion in previous month; malignancy; sensitive to iron; high CRP > 20 mg/L; severe infection or inflammation; malnourished

Interventions	IV iron
	
	• Iron sucrose
	• Dose, duration, frequency: 200 mg/week for 4 weeks, then every second week for 8 weeks
	  * Total dose of elemental iron: 1200 mg
	
	Oral iron
	
	• Ferrous succinate
	• Dose, duration, frequency: 200 mg, 3 times/day for 8 weeks
	  * Total dose of elemental iron: 11,200 mg
	
	Co-intervention
	
	• ESA 100 to 150 U/kg/week before study, dose varied during study

Outcomes	• Final or change in Hb (8 weeks) • Final or change in ferritin (8 weeks) • Final or change in TSAT (8 weeks) • Mean ESA dose at end of study (8 weeks) • Cr at end of study • Number with adverse effects • Number with specific rise in Hb
Notes	• Funding source: NS

Li 2008 PD *(Continued)*

- Follow-up period: 8 weeks
- Lost to follow-up: NS
- Exclusions post randomisation but pre-intervention: NS
- Stop or end points: NS
- Additional data requested from authors: We contacted authors to seek additional information concerning Method of randomisation and allocation concealment, and whether data were expressed as SE or SD. No additional data were obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random number list
Allocation concealment (selection bias)	Unclear risk	Method of allocation not mentioned
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Unclear risk	Funding source NS

Lye 2000 HD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single centre • Country: Singapore • Health status: Stable on HD ≥ 3 months; ferritin ≥ 100 ng/mL; TSAT ≥ 20%; no ESA for ≥ 1 month; adequate B_{12} and folate levels; no sepsis; no chronic inflammation; no active bleeding • Number: IV iron (30); oral iron (30) • Age: NS • Sex (M/F): NS Exclusion criteria • Bleeding, severe infection or inflammation
Interventions	IV iron • Ferric hydroxide polymaltose complex (Ferrum) • Dose, duration, frequency: 200 mg/month for 24 weeks * Total dose of elemental iron: 1200 mg

Lye 2000 HD *(Continued)*

	Oral iron • Ferrous fumarate • Dose, duration, frequency: 200 mg 3 times/day for 24 weeks * Total dose of elemental iron: 33,600 mg Co-intervention • EPO 4000 U/week started at study commencement. Dose stable through study
Outcomes	• Hb at end of study (24 weeks) • Ferritin at end of study (24 weeks)
Notes	• Abstract only • Funding source: NS • Follow-up period: 24 weeks • Lost to follow-up: Unclear • Exclusions at post randomisation: NS • Stop or end points: NS • Additional data requested from authors: The author provided information on numbers in each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only. No information provided
Allocation concealment (selection bias)	High risk	Inadequate allocation. Author reported that patients were allocated alternately to each group
Blinding (performance bias and detection bias)	Low risk	Abstract only. Outcome was laboratory based and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only. No information provided
Selective reporting (reporting bias)	Unclear risk	Abstract only. Reported end of study Hb and ferritin levels. Patient numbers provided by the author
Other bias	Unclear risk	Abstract only

Macdougall 1996 HD,PD,CKD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single tertiary centre • Country: UK • Health status: Stable on HD or CAPD > 3 months; CKD stage 5; Hb ≤ 8.5 g/dL on 3 occasions; normal folate and vitamin B_{12} levels; ferritin 100 to 800 µg/L; no other cause of anaemia; no malignancy; normal CRP; no infection; no surgery in last 3 months; no hyperparathyroidism

Macdougall 1996 HD,PD,CKD *(Continued)*

	• Number: IV iron (13, 1 discontinued due to anaphylactoid reaction; 12 were analysed); oral iron (13) • Mean age ± SD: IV iron (47 ± 15); oral iron (58 ± 16) • Sex (M/F): IV iron (6/6); oral iron (8/5) Exclusion criteria • Severe hyperparathyroidism (PTH > 100 pmol/L); uncontrolled hypertension; aluminium toxicity

Interventions	IV iron
	
	• Iron dextran
	• Dose, duration, frequency: 250 mg every 2 weeks for 16 weeks
	  * Total dose of elemental iron: 2000 mg
	
	Oral iron
	
	• Ferrous sulphate
	• Dose, duration, frequency: 200 mg three times/day for 16 weeks
	  * Total dose of elemental iron: 21,600 mg

Outcomes	• Hb at end of study (16 weeks) • Ferritin at end of study (16 weeks) • TSAT at end of study (16 weeks) • Mean ESA dose at end of study (16 weeks) • Number with a change in ESA dose
Notes	• Funding source: NS • Follow-up period: 16 weeks • Lost to follow-up: none • Exclusions post randomisation and pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: Further details concerning method of randomisation and allocation concealment were requested. Data were provided by the authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sealed envelopes containing random numbers
Allocation concealment (selection bias)	Low risk	Central, by pharmacy
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding source NS

Macdougall 1999 HD,PD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Country: UK • Setting: Multicentre • Health status: Stable on dialysis; receiving ESA; Hb 9 to 12 g/dL; ferritin 100 to 600 ng/mL • Number: IV iron (41); oral iron (35) • Age: NS • Sex (M/F): NS Exclusion criteria • NS
Interventions	IV iron • Iron sucrose • Dose, duration, frequency: 20 mg/dialysis session in HD patients and 200 mg/month in PD patients for 24 weeks * Total dose of elemental iron 1200 mg in PD and 1440 mg in HD (assuming dialysis 3 times/week) Oral iron • No information provided Co-intervention • Dose of ESA varied during study according to requirements
Outcomes	• Hb at end of study (24 weeks) • Ferritin at end of study (24 weeks) • ESA dose at end of study (24 weeks) • Per cent with rise in Hb > 1 g/dL (24 weeks)
Notes	• Abstract only • Funding source: NS - abstract only • Follow-up period: 24 weeks • Lost to follow-up: Unclear • Exclusions post randomisation but pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only
Allocation concealment (selection bias)	Unclear risk	Abstract only

Macdougall 1999 HD,PD *(Continued)*

Blinding (performance bias and detection bias)	Low risk	Abstract only. Outcome was laboratory based and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only. Unclear if all patients completed study
Selective reporting (reporting bias)	Unclear risk	Abstract only. Reported end of study Hb, ferritin and per cent of participants who had a rise in Hb
Other bias	Unclear risk	Abstract only

McMahon 2009 CKD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Multicentre • Country: Australia • Health status: CKD stages 3 to 5 (GFR ≤ 35 in non-diabetic participants, ≤ 50 in diabetic participants), non-dialysis; Hb > 11 g/dL; 36% diabetic; ESA naïve; aged 18 to 80 years, clinically significant fall in Hb and/or Cr in past 18 months • Number: IV iron (52, 43 completed at least 6 months, 39 completed 12 months); oral iron (48, 42 completed at least 6 months, 38 completed 12 months) • Median age, IQR: IV iron (70 years, 58 to 75); oral iron (68 years, 59 to 74) • Sex (M/F): IV iron (40/12); oral iron (33/15) Exclusion criteria • Receiving ESA; iron overload (ferritin > 300 µg/L, TSAT > 25%); severe iron deficiency (ferritin < 30, TSAT < 15); active malignancy, bleeding or haemolysis; chronic sepsis or inflammation (CRP > 25 mg/L); severe IHD or CHF; adult PCKD

Interventions	IV iron
	
	• Iron sucrose
	• Dose, duration, frequency: 100 to 200 mg every second month for 12 months to maintain ferritin 300 at 500 and/or TSAT 25% to 50%; 34 participants required monthly IV iron on one or more occasions.
	  * Dose of elemental iron could not be calculated
	
	Oral iron
	
	• Ferrous sulphate
	• Dose, duration, frequency: 325 mg (105 mg elemental iron) to maintain ferritin at 100 to 150 and/or TSAT 20% to 25%; 6 participants required no iron, 25 needed iron intermittently, 5 intolerant to iron and needed IV iron intermittently.
	  * Dose of elemental iron could not be calculated
	
	Co-intervention
	
	• ACEi administered to 51/52 IV group participants and 45/48 oral group participants

Outcomes	• Hb at end of study (at least 6 months) and 12 months • Ferritin at end of study (at least 6 months) and 12 months

McMahon 2009 CKD *(Continued)*

	• TSAT at end of study (at least 6 months) and 12 months • eGFR at end of study
Notes	• Funding source: Vifor • Follow-up period: 6 months or more; maximum 12 months • Lost to follow-up: IV group (9 died or discontinued, 14%); oral group (6 died or discontinued, 12.5%) • Exclusions post randomisation: NS • Stop or end points: None • Additional data requested from authors: We contacted authors to seek additional information concerning allocation concealment and data on missing patients. No data were obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple block randomisation from block randomisation lists generated with Graphpad Statmate
Allocation concealment (selection bias)	Unclear risk	Method of allocation not mentioned
Blinding (performance bias and detection bias)	Low risk	Open label study but outcomes based on laboratory results unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were accounted for. Patients not completing 6 months were excluded a priori
Selective reporting (reporting bias)	Low risk	Primary outcomes (end Hb, ferritin, TSAT) reported in either full publication or abstract
Other bias	High risk	Grant/research support from Vifor (NCT 000202345)

Michael 2007 HD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Tertiary centre • Country: USA • Health status: Adult HD patients; iron replete; stable ESA dose for 8 weeks; TSAT 20% to 50%; ferritin 100 to 800 ng/mL • Number: IV iron (33); oral iron (27) • Age: NS • Sex (M/F): NS Exclusion criteria • NS
Interventions	IV iron • Sodium ferric gluconate complex

Michael 2007 HD *(Continued)*

	• Dose, duration, frequency: 62.5 mg/week for 20 weeks
	  * Total dose of elemental iron: 1250 mg
	
	Oral iron
	
	• Ferrous sulphate
	• Dose, duration, frequency: 325 mg, 3 times/day for 20 weeks
	  * Total dose of elemental iron: 40,950 mg
	
	Co-intervention
	
	• ESA started before the study. Dose varied during study

Outcomes	• Change in Hb • Change in ferritin • Change in TSAT • Change in ESA dose
Notes	• Abstract only • Funding source: Watson Laboratories • Follow-up period: 22 weeks • Lost to follow-up: None • Exclusions post randomisation but pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: We sought method of randomisation and allocation concealment from authors. No data were obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not mentioned
Allocation concealment (selection bias)	Unclear risk	Method of allocation not mentioned
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all patients completed study
Selective reporting (reporting bias)	Unclear risk	No clear protocol
Other bias	High risk	Grant/Research support: Watson Laboratories

Provenzano 2009 HD

Methods	Study design: parallel RCT Study duration/time frame: October 2005 to April 2007
Participants	Inclusion criteria

Provenzano 2009 HD *(Continued)*

- Setting: Multicentre
- Country: USA
- Health status: Adults aged > 18 years; on HD for ≥ 90 days; Hb <11.5 g/dL; TSAT < 30%; ferritin < 600 ng/mL; stable ESA (dose ± 25 %) for ≥10 days before study commencement
- Number: IV iron (114; 110 started, 102 completed); oral iron (116; 114 started, 99 completed)
- Mean age ± SD: IV iron (59.5 ± 14.3); oral iron (60.8 ± 13)
- Sex (M/F): IV iron (57/57); oral iron (73/43)

Exclusion criteria

- Pregnancy or breastfeeding; other causes of anaemia; use of investigational drug within 30 days; iron treatment within 10 days; recent blood transfusion; active infection; allergy to iron or drug classes

Interventions	IV iron
	• Ferumoxytol
	• Dose, duration, frequency: 510 mg for 2 doses
	  * Total dose of elemental iron: 1020 mg
	Oral iron
	• Ferrous fumarate
	• Dose, duration, frequency: 200 mg/day for 21 days
	  * Total dose of elemental iron: 4200 mg
	Co-intervention
	• ESA maintained stable

Outcomes	• Final Hb and change in Hb (35 days) • Final ferritin and change in ferritin (35 days) • Final TSAT and change in TSAT (35 days) • Change TIBC, CHr at end (35 days) • Number with adverse events • Per cent who had a specific rise in Hb > 1 g/dL
Notes	• Funding source: AMAG Pharmaceuticals • Follow-up period: 35 days • Lost to follow-up: 8 withdrew from IV group, 4 due to adverse effects (7%), 15 withdrew from oral group, 9 due to adverse effects (13%) • Exclusions post randomisation but pre-intervention: IV group (4); oral group (2) • Stop or end points: NS • Additional data requested from authors: We sought additional information about method of randomisation and allocation concealment from authors. Some data were obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation NS
Allocation concealment (selection bias)	Low risk	Telephone-based system
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding

Provenzano 2009 HD *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients who were randomised were included in the analysis
Selective reporting (reporting bias)	Low risk	All outcomes defined in study registration reported
Other bias	High risk	Funded by AMAG Pharmaceuticals whose employees identified study sites, monitored the study and performed data analyses according to a predefined statistical analysis plan

Qunibi 2007 CKD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Multicentre • Country: USA • Health status: Non-dialysis patients GFR < 45 mL/min; Hb < 11g/dL; TSAT < 25%; ferritin < 300 ng/mL • Number: IV iron (147); oral iron (103) • Age: NS • Sex (M/F): NS Exclusion criteria • NS

Interventions	IV iron
	
	• Ferric carboxymaltose
	• Dose, duration, frequency: 1000 mg with up to 2 additional doses of 500 mg
	  * Total dose of elemental iron could not be calculated
	
	Oral iron
	
	• Ferrous sulphate
	• Dose, duration, frequency: 325 mg 3 times/day for 56 days
	  * Total dose of elemental iron: 16,380 mg
	
	Co-interventions
	
	• ESA in some patients, stable ESA dose before and during study

Outcomes	• Change in Hb • Number having a rise in Hb • Number with adverse reactions
Notes	• Abstract only • Funding source: American Reagent/Luipold Pharmaceuticals • Follow-up period: 56 days • Loss to follow-up: None • Exclusions post randomisation but pre-intervention: NS • Stop or end points: NS

Qunibi 2007 CKD *(Continued)*

- Additional data requested from authors: We sought information regarding method of randomisation and allocation concealment, number analysed, SD of change in Hb. No data were obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation NS
Allocation concealment (selection bias)	Unclear risk	Method of allocation NS
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of patients analysed in each group was unclear
Selective reporting (reporting bias)	High risk	No clear protocol available. SDs imputed for inclusion in meta-analyses
Other bias	High risk	Funding support from American Reagent/Luipold Pharmaceuticals

Souza 1997 HD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single tertiary centre • Country: Brazil • Health status: HD patients considered iron deficient based on Hb and ferritin levels • Number: IV iron (12); oral iron (12) • Age: NS • Sex (M/F): NS Exclusion criteria • NS

Interventions	IV iron
	
	• Iron sucrose
	• Dose, duration, frequency: Dose calculated based on iron status and body weight
	  * Total dose of elemental iron could not be calculated
	
	Oral iron
	
	• Ferrous sulphate
	• Dose, duration, frequency: Dose calculated based on iron status
	  * Total dose of elemental iron could not be calculated
	
	Co-intervention

Souza 1997 HD *(Continued)*

	• Some patients received ESA
Outcomes	• Change in Hb • Change in ferritin • Change in iron status
Notes	• Abstract only • Funding source: NS • Follow-up period: NS • Lost to follow-up: IV group: 4 (33%) did not complete; oral group: 1 (8%) did not complete • Exclusion post randomisation but pre-intervention: NS • Stop or end point: NS • Additional data requested from authors: We sought information regarding method of randomisation and allocation concealment, number of patients in each group, dose of oral iron, number of patients who were on ESA, variation in the dose of ESA during study, change in haemoglobin for those who were on ESA. No data were obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation NS
Allocation concealment (selection bias)	Unclear risk	Method of allocation NS
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all patients completed study
Selective reporting (reporting bias)	Unclear risk	No clear protocol
Other bias	Unclear risk	Funding source NS

Spinowitz 2008 CKD

Methods	Study design: parallel RCT Study duration/time frame: May 2004 to August 2006
Participants	Inclusion criteria • Setting: Multicentre • Country: USA • Health status: Adults on HD with CKD stages 1 to 5; Hb < 11 g/dL; TSAT < 30%; ferritin < 600 ng/mL; no change in ESA while in study; no parenteral or oral iron within 10 days of study start • Number: IV iron (228; 217 started, 207 completed); oral iron (76; 75 started, 63 completed) • Mean age ± SD: IV iron (65.1 ± 14.3); oral iron (63.7 ± 11.6) • Sex (M/F): IV iron (93/135); oral iron (24/52)

Spinowitz 2008 CKD *(Continued)*

	Exclusion criteria • Pregnancy or breastfeeding; other causes of anaemia; recent iron therapy; cancer; PTH > 1500 pg/mL; bleeding; surgery; recent blood transfusion; active infection; allergy to IV iron

Interventions	IV iron
	• Ferumoxytol
	• Dose, duration, frequency: 510 mg, 2 doses
	  * Total dose of elemental iron: 1020 mg
	Oral iron
	• Ferrous fumarate
	• Dose, duration, frequency: 100 mg elemental iron twice/day for 21 days
	  * Total dose of elemental iron: 4200 mg
	Co-intervention
	• ESA stable dose at < 35,000 IU/week or < 120 µg darbepoetin every 2 weeks or not started. 83/228 in IV group received ESA, 33/76 in oral group received ESA

Outcomes	• Final or change in Hb (35 days) • Final or change in ferritin (35 days) • Final or change in TSAT (35 days) • Number with adverse events • Per cent with rise in Hb > 1 g/dL
Notes	• Funding source: AMAG Pharmaceuticals • Follow-up period: 35 days • Lost to follow-up: IV group (10 patients did not complete study); oral group (12 patients did not complete study) • Exclusion post randomisation but pre-intervention: IV group (11); oral group (1) • Stop or end points: None stated • Additional data requested from authors: We sought information regarding method of randomisation and allocation concealment. Data were obtained from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	3:1 automated preprogrammed interactive voice response system
Allocation concealment (selection bias)	Low risk	Telephone based
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data of primary endpoint balanced between groups,10% IV,13% oral
Selective reporting (reporting bias)	Low risk	Study protocol available in paper and all of the prespecified outcomes reported

Spinowitz 2008 CKD *(Continued)*

Other bias	High risk	Funded by AMAG Pharmaceuticals whose employees identified study sites, monitored the study and performed data analyses according to a predefined statistical analysis plan

Stoves 2001 CKD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single tertiary centre • Country: UK • Health status: Progressive deterioration in renal function; Cr > 250 µmol/L; not on dialysis; worsening anaemia; Hb <11 g/dL; not on ESA • Number: IV iron (22, 15 completed); oral iron (23, 17 completed) • Mean age ± SD: IV iron (57.3 ±14); oral iron (59.9 ± 13.4) • Sex (M/F): IV iron (10/12); oral iron (15/8) Exclusion criteria • Treatment with IV iron for previous 6 months; malignancy; intolerance to oral iron; poor compliance; dialysis, on ESA; gastrointestinal bleeding

Interventions	IV iron
	
	• Iron sucrose
	• Dose, duration, frequency: 300 mg monthly according to ferritin levels
	  * Total dose of elemental iron: 1638 mg
	
	Oral iron
	
	• Ferrous sulphate
	• Dose, duration, frequency: 200 mg 3 times/day for 6 months
	  * Total dose of elemental iron: 32,400 mg
	
	Co-intervention
	
	• EPO 2000 IU twice weekly started at start of study, dose varied, ACEi 23% IV group, 52% oral group

Outcomes	• Hb at end of study • Ferritin at end of study • ESA dose at end of study • Number with adverse events • Number reaching target Hb • Number with change in ESA dose
Notes	• Funding source: Janssen Cilag and Syner-Med • Follow-up period: 6 months • Lost to follow-up: IV group: 7 (32%) discontinued; oral group 6 (26%) discontinued • Exclusion post randomisation but pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: We sought information regarding method of allocation concealment, Hb mean change and SD. No information was obtained

Stoves 2001 CKD *(Continued)*

- Email from Dr Richardson (8 Jan 2011) stated that the RCT registered in Current Clinical Trials is the report published by Stoves et al. No further information available as to why the RCT was published in 2001 but the trial registered in 2004

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer based
Allocation concealment (selection bias)	Unclear risk	Method of allocation not mentioned
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	29% did not complete the study; this large number could induce bias the results
Selective reporting (reporting bias)	High risk	Outcomes reported as median and IQR and could not be entered in meta-analyses
Other bias	High risk	Imbalance between ACEi treatment in each group Sponsored by Janssen Cilag and Syner-Med

Strickland 1977 HD

Methods	Study design: cross-over RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: University teaching hospital • Country: UK • Health status: HD for 3 months; no previous iron supplements • Number: IV iron 20 (19 completed 26 weeks and crossed over, 15 completed 52 weeks, 5 discontinued); oral iron (20) • Age: NS • Sex (M/F): NS Exclusion criteria • Blood transfusion in the previous 3 months; low vitamin B_{12}; folate; kidney transplant with rejection
Interventions	IV iron • Iron dextran • Dose, duration, frequency: 100 mg every 2 weeks * Total dose of elemental iron: 1300 mg Oral iron • Ferrous sulphate

Strickland 1977 HD *(Continued)*

	• Dose, duration, frequency: 100 mg daily for 26 weeks * Total dose of elemental iron: 18,200 mg Co-interventions • NS
Outcomes	• Hb change reported for all who received IV and oral iron • Number with adverse reactions
Notes	• Funding source: Abbott Laboratories Ltd and Fisons Pharmaceuticals Ltd • Follow-up period: 52 weeks • Loss to follow-up: None • Exclusions post randomisation but pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: Because of the date of the study (1977), authors were not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Balanced allocation within strata using a method similar to the minimisation procedure
Allocation concealment (selection bias)	Unclear risk	Method of allocation not mentioned
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	25% of participants were excluded from analysis
Selective reporting (reporting bias)	High risk	Data combined in crossover study and could not be incorporated in meta-analyses
Other bias	High risk	Funding support from Abbott Laboratories Ltd and Fisons Pharmaceuticals Ltd

Svara 1996 HD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single centre • Country: Czech Republic • Health status: HD patients; ferritin < 300 ng/mL; TSAT < 20 %; EPO 60 U/kg/week in both groups and were on a stable dose • Number: IV iron (30, 29 analysed); oral iron (32, 28 analysed) • Mean age: IV iron (61 years); oral iron (61 years) • Sex (M/F): NS

Svara 1996 HD *(Continued)*

	Exclusion criteria Non dialysis patients

Interventions	IV iron
	
	• Iron sucrose
	• Dose, duration, frequency: 100 mg/week for 6 weeks
	  * Total dose of elemental iron: 600 mg
	
	Oral iron
	
	• Ferrous sulphate
	• Dose, duration, frequency: 34.5 mg, 3 times/day (total dose 724.5 mg/week)
	  * Total dose of elemental iron: 4347 mg
	
	Co-intervention
	
	• EPO 60 IU/kg/week in both groups and were on a stable dose

Outcomes	• Hb at end of study (6 weeks) • Ferritin at end of study (6 weeks) • TSAT at end of study (6 weeks)
Notes	• Funding source: NS • Randomisation method: NS • Follow-up period: 6 weeks • Loss to follow-up: None; 4 patients excluded from analysis • Exclusion post randomisation but pre-intervention: IV iron: 1 excluded (chronic inflammatory process); oral iron: 3 excluded (gastrointestinal intolerance) • Stop or end points: NS • Additional data requested from authors: None requested

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation NS
Allocation concealment (selection bias)	Unclear risk	Method of allocation NS
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Three patients were excluded from oral, one from IV group
Selective reporting (reporting bias)	Low risk	All outcomes specified in methods were reported
Other bias	Unclear risk	Funding source NS

Van Wyck 2005 CKD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Multicentre • Country: USA • Health status: Non-dialysis patients; CKD stages 3 to 5; Hb <11 g/dL; TSAT < 25%; ferritin < 300 ng/mL; no ESA or no change in ESA for 8 weeks; no IV iron for 6 months • Number: IV iron (95, 91 started treatment); oral iron (93, 91 started treatment) • Age: IV iron (62.3 years); oral iron (63.9 years) • Sex (M/F): IV iron (26/53); oral iron (26/56) Exclusion criteria • Treatment with IV iron for previous 6 months; malignancy; allergy to oral or IV iron; infection; major surgery in the prior month; blood transfusion within 2 months; bleeding within 3 months; severe liver disease; pregnancy; lactation; asthma; haemochromatosis

Interventions	IV iron
	
	• Iron sucrose
	• Dose, duration, frequency: 1000 mg, divided doses over 14 days
	  * Total dose of elemental iron: 1000 mg
	
	Oral iron
	
	• Ferrous sulphate
	• Dose, duration, frequency: 325 mg, 3 times/day for 56 days
	  * Total dose of elemental iron: 10,920 mg
	
	Co-intervention
	
	• ESA use in some of patients, dose stable

Outcomes	• Change in Hb at end of study (56 days) • Change in ferritin at end of study (56 days) • Change in TSAT at end of the study (56 days) • Change in ESA dose • Number reaching target Hb or a specific rise • Number with adverse events
Notes	• Funding source: American Regent, Inc • Follow-up period: 56 days • Lost to follow-up: IV iron: 12 (13%) participants excluded from the analysis (discontinued treatment); oral iron: 9 (10%) excluded (discontinued treatment) due to unstable ESA dose prior to randomisation or lack of baseline data and 2 lost to follow-up • Exclusions post randomisation but pre-intervention: IV iron = 4; oral iron = 2 • Stop or end points: NS • Additional data requested from authors: We contacted author to seek method of allocation concealment and randomisation, numerical values for the change in Hb, TSAT, ferritin as mean and SD. Data were provided by authors

Risk of bias

Bias	Authors' judgement	Support for judgement

Van Wyck 2005 CKD *(Continued)*

Random sequence generation (selection bias)	Low risk	Sequential random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced between groups
Selective reporting (reporting bias)	Low risk	All of outcomes have been reported
Other bias	High risk	Supported by American Regent, Inc

Wang 2003 HD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Single tertiary centre • Country: China • Health status: Stable adult HD patients on ESA therapy • Number: IV iron (21); oral iron (22) • Age: NS • Sex (M/F): NS Exclsuion criteria • NS

Interventions	IV iron
	• Ferric citrate
	• Dose, duration, frequency: 50 mg twice/week for 5 weeks
	  * Total dose of elemental iron: 500 mg
	Oral iron
	• Ferrous sulphate
	• Dose, duration, frequency: 600 mg/day for 5 weeks
	  * Total dose of elemental iron: 6300 mg
	Co-interventions
	• EPO 6000 U/week. Unclear when started. Stable dose.

Outcomes	• Hb at end of study (5 weeks) • Ferritin at end of study (5 weeks)
Notes	• Abstract only

Wang 2003 HD *(Continued)*

- Funding source: NS - abstract only
- Follow-up period: 5 weeks
- Lost to follow-up: Unclear. Reported to have enrolled 45 patients, but 21 included in IV arm and 22 in oral arm
- Exclusions post randomisation but pre-intervention: NS
- Stop or end points: NS
- Additional data requested from authors: None requested

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only
Allocation concealment (selection bias)	Unclear risk	Abstract only
Blinding (performance bias and detection bias)	Low risk	Abstract only. Outcome is laboratory based and unlike to be altered by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only
Selective reporting (reporting bias)	Unclear risk	Abstract only. Reported end Hb and ferritin
Other bias	Unclear risk	Abstract only

Warady 2002 HD

Methods	Study design: parallel RCT Study duration/time frame: NS
Participants	Inclusion criteria • Setting: Multicentre • Country: USA • Health status: Patients aged > 1 year to < 20 years; HD > 2 months; TSAT > 20%; stable ESA > 4 weeks prior to study; urea reduction ratio > 60% • Number: IV iron (17); oral iron (18) • Mean age ± SD: IV iron (181.4 months ± 54.8); oral iron (175.9 months ± 41.9) • Sex (M/F): IV iron (7/10); oral iron (9/9) Exclusion criteria • Non-renal cause of anaemia; malignancy; serious reaction to IV iron; active infection or inflammation; HIV, iron overload (ferritin > 800 ng/mL); hyperparathyroidism (PTH > 1000 pg/mL); uncontrolled HTN
Interventions	IV iron • Iron dextran • Dose, duration, frequency: 12 doses weekly. Dose differed according to body weight * Total dose of elemental iron could not be calculated

Warady 2002 HD *(Continued)*

	Oral iron • Ferrous fumarate • Dose, duration, frequency: 5 mg/kg/day for 16 weeks * Total dose of oral iron: 560 mg/kg Co-intervention • ESA use, dose variable
Outcomes	• Final or change in Hb (16 weeks) • Final or change in ferritin (16 weeks) • Final or change in TSAT (16 weeks) • Final or change in mean ESA dose (16 weeks) • Final or change in CHr (16 weeks) • Number with change in ESA dose
Notes	• Funding source: Watson Laboratories • Follow-up period: 16 weeks • Lost to follow-up: None • Exclusions post randomisation but pre-intervention: NS • Stop or end points: NS • Additional data requested from authors: We contacted authors to seek method of allocation concealment, and to investigate if all patients were included in the analysis. Some data were obtained from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Method of allocation not mentioned
Blinding (performance bias and detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were included in the analysis (information from authors)
Selective reporting (reporting bias)	Low risk	All of outcomes have been reported
Other bias	High risk	Supported by a grant from Watson Laboratories

ACE: angiotensin-converting enzyme; ACEi: angiotensin-converting enzyme inhibitor; CAD: coronary artery disease; CAPD: continuous ambulatory peritoneal dialysis; CHF: congestive heart failure; CHr: reticulocyte haemoglobin content; CKD: chronic kidney disease; Cr: creatinine; CrCl: creatinine clearance; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; EPO: erythropoietin; ESA: erythrocyte-stimulating agent; FOBT: faecal occult blood test; GFR: glomerular filtration rate; Hb: haemoglobin; Hct: haematocrit; HCV: hepatitis C virus; HD: haemodialysis; HIV: human immunosuppressive virus; HTN: hypertension; IHD: ischaemic heart disease; IQR: interquartile range; IV: intravenous; NS - not stated; PCKD: polycystic kidney disease; PCV: packed cell volume; PD: peritoneal dialysis; PTH: parathyroid hormone; SFGC: sodium ferrigluconate complex; TIBC: total iron binding capacity; TSAT: transferrin saturation

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

Study	Reason for exclusion
Ahsan 2000	Sequential study, not RCT
Allegra 1991	Results included some non-randomised patients
Jenq 2005	Non-randomised comparator study, not RCT
Johnson 2001	Sequential study, not RCT
Lye 1997	RCT comparing intramuscular and oral routes

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

Agarwal 2008

Trial name or title	A clinical trial of oral versus IV iron in patients with chronic kidney disease
Methods	Phase IV randomised, controlled open-label trial comparing IV iron with oral iron
Participants	Non dialysis dependent CKD with GFR < 60 ml/min and renal anaemia
Interventions	IV iron compared with oral ferrous sulphate
Outcomes	Mean rate of decline in GFR in the two groups - oral and IV iron at 2 years Proteinuria at 2 years
Starting date	August 2008
Contact information	Jennifer E Bills, BS (jebills@iupui.edu)
Notes	

Monofer 2010 CKD

Trial name or title	Iron isomaltoside (Monofer) in non-dialysis dependent chronic kidney disease and with renal related anaemia
Methods	Phase III randomised comparative open-label study of IV iron (isomaltose 1000) administered by infusions or repeated bolus injections compared with oral iron sulphate
Participants	350 non-dialysis dependent CKD patients with renal related anaemia
Interventions	IV Isomaltoside or oral iron sulphate
Outcomes	Change in haemoglobin concentration from baseline to week 8
Starting date	April 2010
Contact information	Pharmacosmos A/S

Monofer 2010 CKD *(Continued)*

Notes	Estimated to be complete in September 2011

Mudge 2009 TX

Trial name or title	Intravenous versus oral iron supplementation for correction of post-transplant anaemia in renal transplant patients
Methods	Single centre prospective, open-label, randomised, controlled trial
Participants	100 renal transplant recipients
Interventions	Single dose of 500 mg iron polymaltose (within 5 days of transplant) or oral ferrous sulphate (2 slow release tablets daily)
Outcomes	Time to normalisation of haemoglobin post transplant
Starting date	2009
Contact information	Dr David Mudge (david_mudge@health.qld.gov.au)
Notes	Protocol published in BMC Nephrology

DATA AND ANALYSES

Comparison 1. Intravenous versus oral iron therapy: primary outcomes

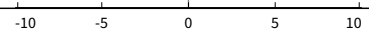
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Haemoglobin: Final or change (all patients)	22	1862	Mean Difference (IV, Random, 95% CI)	0.90 [0.44, 1.37]
2 Number achieving target haemoglobin or increase ≥1 g/dL	10	1344	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.36, 2.12]
3 Ferritin: Final or change (all patients)	24	1751	Mean Difference (IV, Random, 95% CI)	243.25 [188.74, 297.75]
4 Transferrin saturation: Final or change	18	1457	Mean Difference (IV, Random, 95% CI)	10.20 [5.56, 14.83]

Analysis 1.1. Comparison 1 Intravenous versus oral iron therapy: primary outcomes, Outcome 1 Haemoglobin: Final or change (all patients).

Study or subgroup	IV iron N	IV iron Mean(SD)	Oral iron N	Oral iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Lye 2000 HD	30	9.1 (1.4)	30	9.4 (1.5)		4.41%	-0.3[-1.03,0.43]
Warady 2002 HD	17	11.2 (1.3)	18	11.4 (0.8)		4.4%	-0.24[-0.98,0.5]
McMahon 2009 CKD	39	11.8 (1)	38	11.9 (1.2)		4.69%	-0.1[-0.59,0.39]
Michael 2007 HD	33	-0.2 (1.1)	27	-0.2 (1.1)		4.63%	0[-0.55,0.55]
Agarwal 2006 CKD	36	0.4 (0.8)	39	0.2 (0.9)		4.79%	0.2[-0.18,0.58]
Qunibi 2007 CKD	147	1 (0.8)	103	0.7 (0.9)		4.9%	0.3[0.08,0.52]
Charytan 2005 CKD	39	11.1 (1.1)	44	10.7 (1)		4.73%	0.4[-0.05,0.85]
Van Wyck 2005 CKD	72	10.9 (1)	71	10.4 (1.1)		4.81%	0.5[0.15,0.85]
Provenzano 2009 HD	114	11.7 (1.2)	116	11.2 (1.2)		4.84%	0.5[0.19,0.81]
Macdougall 1999 HD,PD	41	10.8 (1.4)	35	10.3 (1.1)		4.62%	0.5[-0.06,1.06]
Leehey 2005 CKD	24	1.5 (0.9)	24	0.8 (0.9)		4.67%	0.7[0.19,1.21]
Spinowitz 2008 CKD	228	10.9 (1.3)	76	10.2 (1)		4.86%	0.73[0.45,1.01]
Souza 1997 HD	8	1 (0.9)	11	0.2 (0.8)		4.37%	0.8[0.04,1.56]
Broumand 1998 HD	9	9.8 (1.1)	8	9 (1)		4.04%	0.8[-0.19,1.79]
Hussain 1998 HD	10	11.6 (0.6)	10	10.5 (1.1)		4.3%	1.1[0.29,1.91]
Macdougall 1996 HD,PD,CKD	9	11.7 (1.3)	11	10.6 (1.4)		3.75%	1.1[-0.09,2.29]
Aggarwal 2003 CKD	20	10.1 (0.9)	20	8.9 (1.2)		4.52%	1.11[0.46,1.76]
Wang 2003 HD	21	9.3 (1.8)	22	7.9 (1.4)		4.07%	1.4[0.43,2.37]
Li 2008 PD	26	12.2 (1.1)	20	10.6 (1)		4.56%	1.58[0.97,2.19]
Erten 1998 HD	26	11.8 (1.3)	22	9.9 (0.9)		4.54%	1.9[1.27,2.53]
Li 2008 HD	70	12 (1.3)	66	10 (1.1)		4.78%	1.99[1.6,2.38]
Fudin 1998 HD	20	11 (0.9)	12	6.1 (0.4)		4.73%	4.92[4.47,5.37]
Total ***	**1039**		**823**			**100%**	**0.9[0.44,1.37]**

Heterogeneity: Tau^2=1.14; Chi^2=449.44, df=21(P<0.0001); I^2=95.33%

Test for overall effect: Z=3.8(P=0)

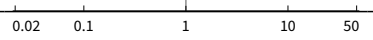


Analysis 1.2. Comparison 1 Intravenous versus oral iron therapy: primary outcomes, Outcome 2 Number achieving target haemoglobin or increase ≥1 g/dL.

Study or subgroup	IV iron n/N	Oral iron n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Stoves 2001 CKD	13/18	16/20		12.08%	0.9[0.63,1.29]
Van Wyck 2005 CKD	47/79	35/82		13.19%	1.39[1.02,1.9]
Li 2008 PD	23/26	11/20		10.84%	1.61[1.06,2.45]
Charytan 2005 CKD	21/39	14/44		8.96%	1.69[1.01,2.85]
Qunibi 2007 CKD	89/147	36/103		13.54%	1.73[1.29,2.32]
Hussain 1998 HD	9/10	5/10		6.98%	1.8[0.94,3.46]
Provenzano 2009 HD	56/114	29/116		11.96%	1.96[1.36,2.83]
Spinowitz 2008 CKD	89/228	14/76		9.32%	2.12[1.29,3.49]
Li 2008 HD	45/70	19/66		10.89%	2.23[1.47,3.39]
Macdougall 1999 HD,PD	19/41	2/35		2.23%	8.11[2.03,32.41]
Total (95% CI)	**772**	**572**		**100%**	**1.7[1.36,2.12]**

Total events: 411 (IV iron), 181 (Oral iron)

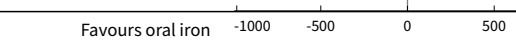
Heterogeneity: Tau^2=0.07; Chi^2=23.17, df=9(P=0.01); I^2=61.15%



Study or subgroup	IV iron n/N	Oral iron n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=4.69(P<0.0001)					

Analysis 1.3. Comparison 1 Intravenous versus oral iron therapy: primary outcomes, Outcome 3 Ferritin: Final or change (all patients).

Study or subgroup	IV iron N	IV iron Mean(SD)	Oral iron N	Oral iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Svara 1996 HD	29	166 (123)	28	109 (114)		4.59%	57[-4.54,118.54]
Li 2008 HD	70	495.7 (315.2)	66	400.3 (264.1)		4.22%	95.4[-2.13,192.93]
Michael 2007 HD	33	80 (147)	27	-31 (130)		4.51%	111[40.86,181.14]
Leehey 2005 CKD	24	132 (162)	24	19 (162)		4.29%	113[21.34,204.66]
Warady 2002 HD	17	259.1 (163.1)	18	122 (118.8)		4.25%	137.1[42.11,232.09]
Aggarwal 2003 CKD	20	267 (58.8)	20	104.4 (25.3)		4.82%	162.63[134.56,190.7]
Fudin 1998 HD	20	393.5 (249.3)	10	229.7 (113.6)		3.82%	163.8[33.82,293.78]
Li 2008 PD	26	466.7 (85.3)	20	299.4 (83.2)		4.69%	167.3[118.26,216.34]
Agarwal 2006 CKD	36	232 (160.8)	39	55.9 (236.2)		4.3%	176.1[85.25,266.95]
Van Wyck 2005 CKD	72	323 (178.5)	72	132 (90.3)		4.71%	191[144.79,237.21]
Lye 2000 HD	30	432 (288)	30	231 (204)		3.87%	201[74.71,327.29]
Wang 2003 HD	21	496 (306)	22	279 (206)		3.48%	217[60.35,373.65]
Broumand 1998 HD	9	779 (205)	8	546.5 (139)		3.37%	232.5[67.53,397.47]
Souza 1997 HD	8	245 (133)	11	2.3 (77.2)		4.16%	242.7[139.86,345.54]
McMahon 2009 CKD	39	412 (206)	38	153 (88)		4.51%	259[188.55,329.45]
Macdougall 1999 HD,PD	41	432 (202)	35	140 (91)		4.53%	292[223.21,360.79]
Charytan 2005 CKD	39	288 (150)	44	-5.1 (151)		4.56%	293.1[228.24,357.96]
Hussain 1998 HD	10	671 (388)	10	367 (238)		2.11%	304[21.88,586.12]
Provenzano 2009 HD	114	601.8 (283)	116	289.3 (165.8)		4.61%	312.49[252.43,372.55]
Macdougall 1996 HD,PD,CKD	9	490 (276)	11	165 (95)		3.08%	325[136.15,513.85]
Erten 1998 HD	26	573 (246.7)	22	247.4 (187.7)		3.91%	325.6[202.54,448.66]
Spinowitz 2008 CKD	228	555.7 (320)	76	160.8 (161)		4.65%	394.9[339.8,450]
Kotaki 1997 HD	15	750 (147)	16	255 (64)		4.41%	495[414.27,575.73]
Fishbane 1995 HD	20	753.9 (135)	32	157.3 (87)		4.55%	596.6[530.2,663]
Total ***	**956**		**795**			**100%**	**243.25[188.74,297.75]**
Heterogeneity: Tau^2=15848.34; Chi^2=303.54, df=23(P<0.0001); I^2=92.42%							
Test for overall effect: Z=8.75(P<0.0001)							

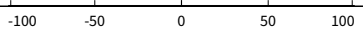


Analysis 1.4. Comparison 1 Intravenous versus oral iron therapy: primary outcomes, Outcome 4 Transferrin saturation: Final or change.

Study or subgroup	IV iron N	IV iron Mean(SD)	Oral iron N	Oral iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Macdougall 1996 HD,PD,CKD	12	23 (4)	13	31 (4)		5.95%	-8[-11.14,-4.86]
Michael 2007 HD	33	-0.6 (9.1)	27	-1.1 (8.4)		5.79%	0.5[-3.94,4.94]
Van Wyck 2005 CKD	72	25 (8.9)	72	22.2 (9.4)		5.96%	2.8[-0.2,5.8]
Charytan 2005 CKD	39	4.5 (8.3)	44	0.5 (8.5)		5.9%	4[0.38,7.62]
Svara 1996 HD	29	26.8 (11.1)	28	22.2 (9.6)		5.65%	4.6[-0.78,9.98]
Kotaki 1997 HD	15	35.7 (5.1)	16	30.6 (1.9)		5.99%	5.1[2.36,7.84]
Agarwal 2006 CKD	36	8.3 (7.5)	39	2.9 (8.8)		5.89%	5.4[1.71,9.09]
Provenzano 2009 HD	114	22.3 (13.3)	116	16.5 (9.7)		5.96%	5.85[2.83,8.87]
McMahon 2009 CKD	39	30 (9)	38	24 (11)		5.78%	6[1.5,10.5]
Spinowitz 2008 CKD	228	21 (10.1)	76	11.8 (6.7)		6.05%	9.2[7.2,11.2]
Li 2008 HD	70	39.6 (16.7)	66	28.6 (18.4)		5.56%	11[5.08,16.92]
Li 2008 PD	26	37.8 (16.1)	20	25.7 (17.5)		4.79%	12.1[2.25,21.95]
Warady 2002 HD	17	44.1 (14.1)	18	31.3 (15)		4.84%	12.73[3.11,22.35]
Fudin 1998 HD	20	33.2 (3.5)	10	19.9 (5.4)		5.89%	13.31[9.63,16.99]
Hussain 1998 HD	10	44.6 (19.8)	10	29 (11)		3.92%	15.61[1.57,29.65]
Ahsan 1997 TX	6	38 (8.2)	6	22 (3.4)		5.35%	16[8.9,23.1]
Aggarwal 2003 CKD	20	64.9 (11)	20	45.7 (14.1)		5.2%	19.23[11.39,27.07]
Fishbane 1995 HD	20	74.8 (13)	32	19.8 (5.7)		5.54%	55[48.98,61.02]
Total * **	**806**		**651**			**100%**	**10.2[5.56,14.83]**

Heterogeneity: Tau^2=91.51; Chi^2=391.08, df=17(P<0.0001); I^2=95.65%

Test for overall effect: Z=4.31(P<0.0001)



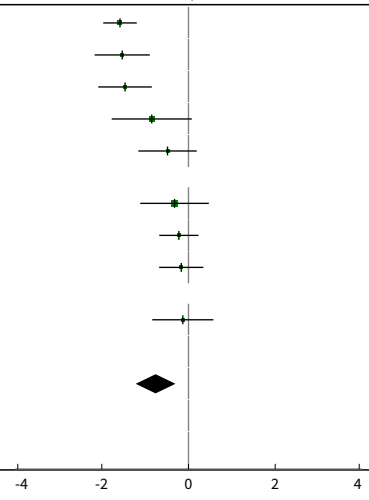
Comparison 2. Intravenous versus oral iron therapy: secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 End of treatment or change in ESA dose	9	487	Std. Mean Difference (IV, Random, 95% CI)	-0.76 [-1.22, -0.30]
2 Number requiring increase in ESA dose	2	45	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.11, 1.06]
3 Number requiring decrease or cessation of ESA	4	150	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.69, 5.91]
4 All-cause mortality	5	435	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.35, 3.84]
5 Cardiovascular mortality	2	70	Risk Ratio (M-H, Random, 95% CI)	3.20 [0.37, 27.51]
6 Numbers of non-dialysis patients needing to commence dialysis	3	282	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.28, 1.71]
7 Haematocrit	4		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 All studies	4	152	Mean Difference (IV, Random, 95% CI)	1.18 [-2.17, 4.52]
7.2 Excluding studies in which the aim was to maintain haematocrit unchanged	3	121	Mean Difference (IV, Random, 95% CI)	2.43 [0.42, 4.44]
8 Reticulocyte haemoglobin concentration (CHr)	4	506	Mean Difference (IV, Random, 95% CI)	0.67 [0.29, 1.05]

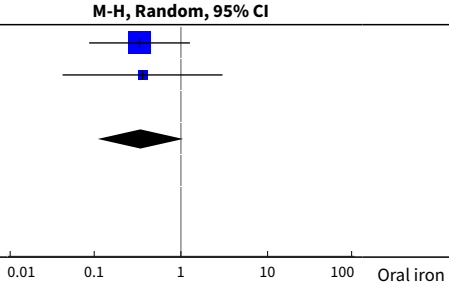
Analysis 2.1. Comparison 2 Intravenous versus oral iron therapy: secondary outcomes, Outcome 1 End of treatment or change in ESA dose.

Study or subgroup	IV iron N	IV iron Mean(SD)	Oral iron N	Oral iron Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Li 2008 HD	70	4500 (1049)	66	6140 (1014)		12.84%	-1.58[-1.97,-1.19]
Fishbane 1995 HD	20	4050 (2455)	32	7563 (2138)		11.1%	-1.53[-2.17,-0.89]
Li 2008 PD	26	6100 (1043)	26	7635 (1024)		11.25%	-1.46[-2.08,-0.85]
Hussain 1998 HD	10	3400 (1356)	10	4600 (1356)		8.98%	-0.85[-1.77,0.08]
Warady 2002 HD	17	-76.3 (104.7)	18	-30.9 (77.7)		10.83%	-0.48[-1.16,0.19]
Macdougall 1996 HD,PD,CKD	12	1202 (229)	13	1294 (314)		9.95%	-0.32[-1.11,0.47]
Macdougall 1999 HD,PD	41	74 (36)	35	84 (53)		12.42%	-0.22[-0.67,0.23]
Michael 2007 HD	33	-28.4 (103.6)	27	-12.6 (79.7)		12.03%	-0.17[-0.68,0.34]
Kotaki 1997 HD	15	3760 (1762)	16	4025 (2168)		10.59%	-0.13[-0.84,0.58]
Total * **	**244**		**243**			**100%**	**-0.76[-1.22,-0.3]**
Heterogeneity: Tau^2=0.39; Chi^2=42.96, df=8(P<0.0001); I^2=81.38%							
Test for overall effect: Z=3.25(P=0)							



Analysis 2.2. Comparison 2 Intravenous versus oral iron therapy: secondary outcomes, Outcome 2 Number requiring increase in ESA dose.

Study or subgroup	IV iron n/N	Oral iron n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hussain 1998 HD	2/10	6/10		71.54%	0.33[0.09,1.27]
Macdougall 1996 HD,PD,CKD	1/12	3/13		28.46%	0.36[0.04,3.02]
Total (95% CI)	**22**	**23**		**100%**	**0.34[0.11,1.06]**
Total events: 3 (IV iron), 9 (Oral iron)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%					
Test for overall effect: Z=1.86(P=0.06)					



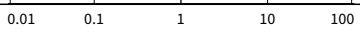
Analysis 2.3. Comparison 2 Intravenous versus oral iron therapy: secondary outcomes, Outcome 3 Number requiring decrease or cessation of ESA.

Study or subgroup	IV iron n/N	Oral iron n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Stoves 2001 CKD	7/18	10/20		29.33%	0.78[0.38,1.61]
Macdougall 1996 HD,PD,CKD	5/12	4/13		25.51%	1.35[0.47,3.89]
Warady 2002 HD	11/17	6/18		29.16%	1.94[0.92,4.08]
Fishbane 1995 HD	15/20	1/32		15.99%	24[3.43,167.95]
Total (95% CI)	**67**	**83**		**100%**	**2.02[0.69,5.91]**
Total events: 38 (IV iron), 21 (Oral iron)					
Heterogeneity: Tau^2=0.88; Chi^2=14.09, df=3(P=0); I^2=78.71%					
Test for overall effect: Z=1.29(P=0.2)					

IV iron — Oral iron

Analysis 2.4. Comparison 2 Intravenous versus oral iron therapy: secondary outcomes, Outcome 4 All-cause mortality.

Study or subgroup	IV iron n/N	Oral iron n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Fishbane 1995 HD	0/20	3/32		14.98%	0.22[0.01,4.13]
Provenzano 2009 HD	1/114	3/116		23.32%	0.34[0.04,3.21]
Fudin 1998 HD	2/20	1/12		22.61%	1.2[0.12,11.87]
Stoves 2001 CKD	1/18	0/20		13.1%	3.32[0.14,76.6]
McMahon 2009 CKD	5/41	1/42		25.99%	5.12[0.63,41.97]
Total (95% CI)	**213**	**222**		**100%**	**1.16[0.35,3.84]**
Total events: 9 (IV iron), 8 (Oral iron)					
Heterogeneity: Tau^2=0.29; Chi^2=4.72, df=4(P=0.32); I^2=15.19%					
Test for overall effect: Z=0.24(P=0.81)					



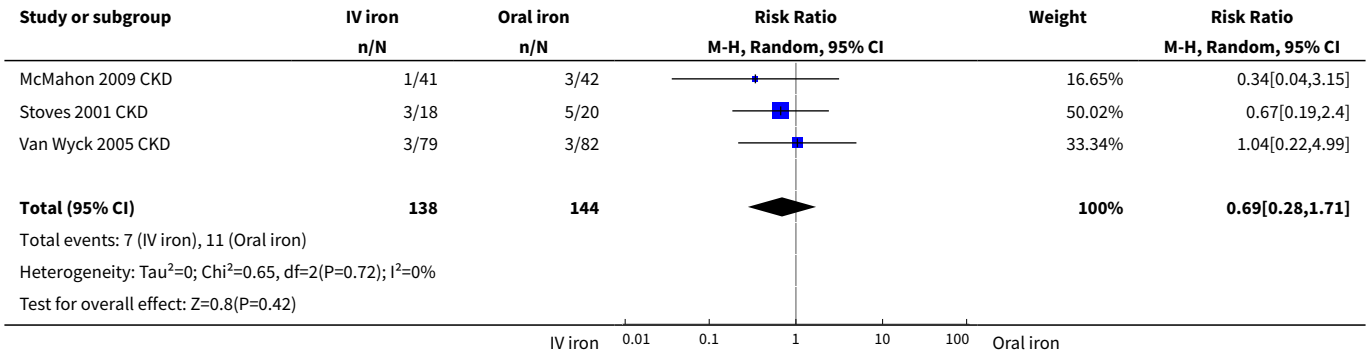
IV iron — Oral iron

Analysis 2.5. Comparison 2 Intravenous versus oral iron therapy: secondary outcomes, Outcome 5 Cardiovascular mortality.

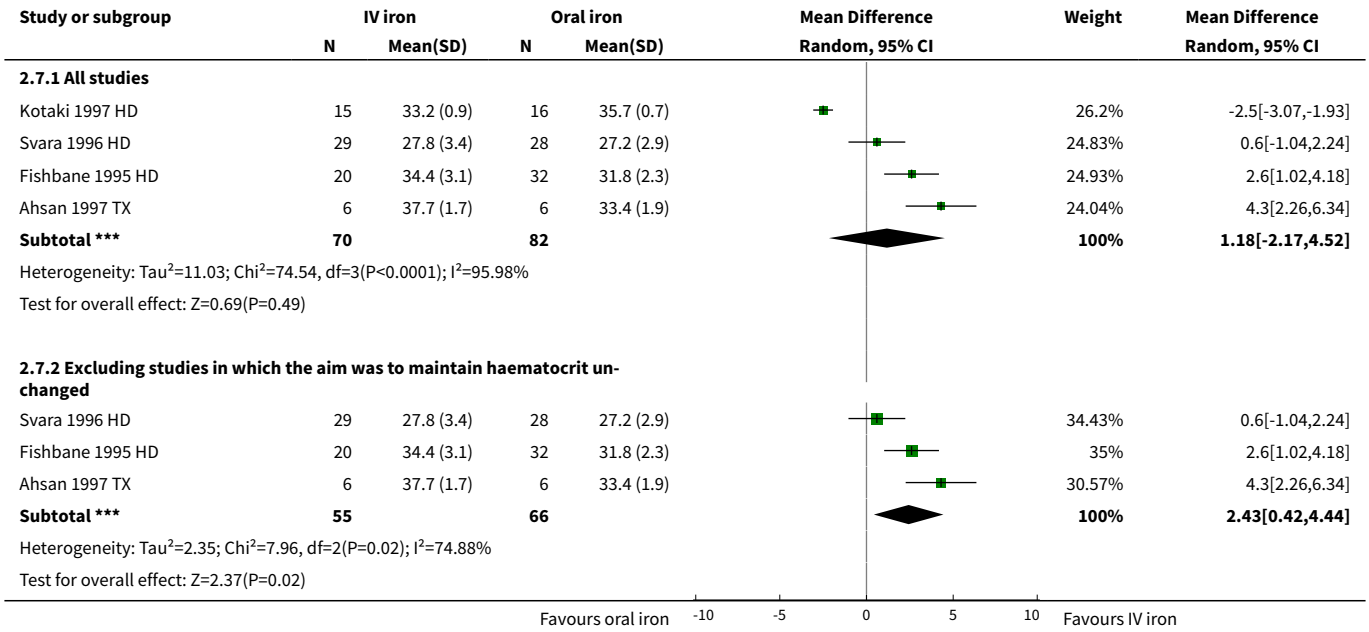
Study or subgroup	IV iron n/N	Oral iron n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Fudin 1998 HD	2/20	0/12		53%	3.1[0.16,59.52]
Stoves 2001 CKD	1/18	0/20		47%	3.32[0.14,76.6]
Total (95% CI)	**38**	**32**		**100%**	**3.2[0.37,27.51]**
Total events: 3 (IV iron), 0 (Oral iron)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%					
Test for overall effect: Z=1.06(P=0.29)					

Favours oral iron — Favours IV iron

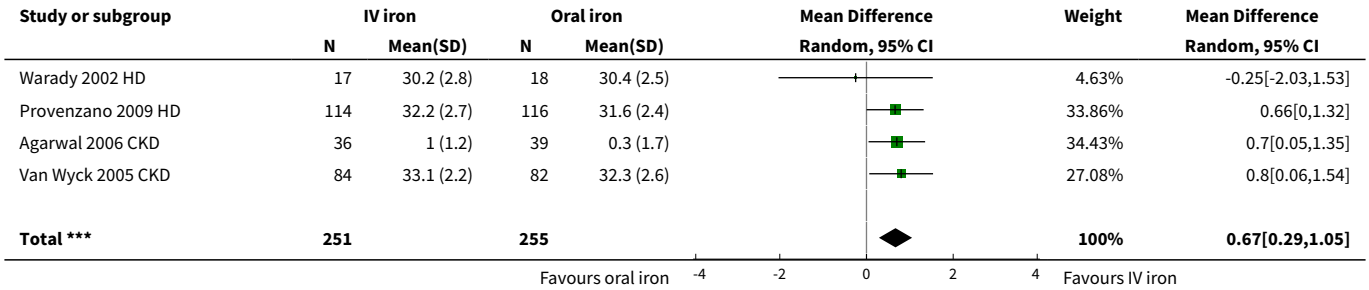
Analysis 2.6. Comparison 2 Intravenous versus oral iron therapy: secondary outcomes, Outcome 6 Numbers of non-dialysis patients needing to commence dialysis.



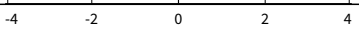
Analysis 2.7. Comparison 2 Intravenous versus oral iron therapy: secondary outcomes, Outcome 7 Haematocrit.



Analysis 2.8. Comparison 2 Intravenous versus oral iron therapy: secondary outcomes, Outcome 8 Reticulocyte haemoglobin concentration (CHr).



Study or subgroup	IV iron N	IV iron Mean(SD)	Oral iron N	Oral iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Tau²=0; Chi²=1.16, df=3(P=0.76); I²=0%							
Test for overall effect: Z=3.43(P=0)							

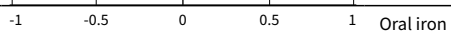


Comparison 3. Adverse effects

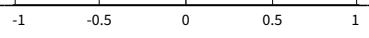
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse event	12	1458	Risk Difference (M-H, Random, 95% CI)	-0.09 [-0.19, 0.00]
2 Type of adverse event	12		Risk Difference (M-H, Random, 95% CI)	Subtotals only
2.1 Allergic reactions/hypotension	8	1199	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.00, 0.04]
2.2 All gastrointestinal adverse effects	8	925	Risk Difference (M-H, Random, 95% CI)	-0.17 [-0.27, -0.06]
2.3 Constipation	5	691	Risk Difference (M-H, Random, 95% CI)	-0.07 [-0.14, 0.00]
2.4 Diarrhoea	5	698	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.06, -0.00]
2.5 Nausea or vomiting	4	646	Risk Difference (M-H, Random, 95% CI)	-0.04 [-0.10, 0.02]
2.6 Taste disturbances	3	557	Risk Difference (M-H, Random, 95% CI)	0.04 [-0.02, 0.09]
2.7 Iron overload	2	55	Risk Difference (M-H, Random, 95% CI)	0.07 [-0.16, 0.30]
2.8 Number discontinuing treatment because of adverse effects	1	182	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.01, 0.07]

Analysis 3.1. Comparison 3 Adverse effects, Outcome 1 Any adverse event.

Study or subgroup	IV iron n/N	Oral iron n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Li 2008 PD	0/26	8/20		6.91%	-0.4[-0.62,-0.18]
Charytan 2005 CKD	10/39	28/44		7.31%	-0.38[-0.58,-0.18]
Li 2008 HD	0/70	22/66		9.1%	-0.33[-0.45,-0.22]
Qunibi 2007 CKD	4/147	27/103		9.57%	-0.23[-0.32,-0.15]
Spinowitz 2008 CKD	23/217	18/75		9.28%	-0.13[-0.24,-0.03]

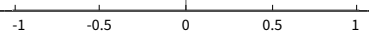


Study or subgroup	IV iron n/N	Oral iron n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Provenzano 2009 HD	54/110	64/113		8.77%	-0.08[-0.21,0.06]
Aggarwal 2003 CKD	0/20	0/20		9.52%	0[-0.09,0.09]
Van Wyck 2005 CKD	20/91	17/91		9.06%	0.03[-0.08,0.15]
Fishbane 1995 HD	1/20	0/32		9.04%	0.05[-0.07,0.17]
Stoves 2001 CKD	3/22	1/23		8.01%	0.09[-0.07,0.26]
Agarwal 2006 CKD	13/44	9/45		7.73%	0.1[-0.08,0.27]
Hussain 1998 HD	2/10	0/10		5.69%	0.2[-0.08,0.48]
Total (95% CI)	**816**	**642**		**100%**	**-0.09[-0.19,0]**
Total events: 130 (IV iron), 194 (Oral iron)					
Heterogeneity: Tau^2=0.02; Chi^2=72.22, df=11(P<0.0001); I^2=84.77%					
Test for overall effect: Z=1.87(P=0.06)					

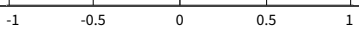


Analysis 3.2. Comparison 3 Adverse effects, Outcome 2 Type of adverse event.

Study or subgroup	IV iron n/N	Oral iron n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
3.2.1 Allergic reactions/hypotension					
Qunibi 2007 CKD	0/147	0/103		27.36%	0[-0.02,0.02]
Charytan 2005 CKD	0/39	0/44		11.27%	0[-0.05,0.05]
Provenzano 2009 HD	2/110	0/113		18.3%	0.02[-0.01,0.05]
Spinowitz 2008 CKD	4/217	0/75		20.66%	0.02[-0.01,0.04]
Van Wyck 2005 CKD	2/91	0/91		15.05%	0.02[-0.01,0.06]
Warady 2002 HD	1/17	0/18		1.58%	0.06[-0.09,0.21]
Agarwal 2006 CKD	3/44	0/45		4.42%	0.07[-0.02,0.15]
Stoves 2001 CKD	3/22	0/23		1.38%	0.14[-0.02,0.29]
Subtotal (95% CI)	**687**	**512**		**100%**	**0.02[-0,0.04]**
Total events: 15 (IV iron), 0 (Oral iron)					
Heterogeneity: Tau^2=0; Chi^2=12.63, df=7(P=0.08); I^2=44.58%					
Test for overall effect: Z=1.69(P=0.09)					
3.2.2 All gastrointestinal adverse effects					
Li 2008 PD	0/26	8/20		9.7%	-0.4[-0.62,-0.18]
Charytan 2005 CKD	10/39	28/44		10.36%	-0.38[-0.58,-0.18]
Li 2008 HD	0/70	22/66		13.44%	-0.33[-0.45,-0.22]
Spinowitz 2008 CKD	10/217	15/75		14.12%	-0.15[-0.25,-0.06]
Van Wyck 2005 CKD	8/91	16/91		14.03%	-0.09[-0.19,0.01]
Agarwal 2006 CKD	7/44	11/45		11.54%	-0.09[-0.25,0.08]
Stoves 2001 CKD	0/22	1/23		13.48%	-0.04[-0.16,0.07]
Fishbane 1995 HD	1/20	0/32		13.33%	0.05[-0.07,0.17]
Subtotal (95% CI)	**529**	**396**		**100%**	**-0.17[-0.27,-0.06]**
Total events: 36 (IV iron), 101 (Oral iron)					
Heterogeneity: Tau^2=0.02; Chi^2=39.73, df=7(P<0.0001); I^2=82.38%					
Test for overall effect: Z=3.01(P=0)					
3.2.3 Constipation					
Charytan 2005 CKD	5/39	16/44		10.39%	-0.24[-0.41,-0.06]
Van Wyck 2005 CKD	1/91	8/91		23.55%	-0.08[-0.14,-0.01]



Study or subgroup	IV iron n/N	Oral iron n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Spinowitz 2008 CKD	1/217	6/75		23.54%	-0.08[-0.14,-0.01]
Stoves 2001 CKD	0/22	1/23		16.57%	-0.04[-0.16,0.07]
Agarwal 2006 CKD	0/44	0/45		25.96%	0[-0.04,0.04]
Subtotal (95% CI)	**413**	**278**		**100%**	**-0.07[-0.14,0]**
Total events: 7 (IV iron), 31 (Oral iron)					
Heterogeneity: Tau^2=0; Chi^2=18.21, df=4(P=0); I^2=78.03%					
Test for overall effect: Z=1.86(P=0.06)					
3.2.4 Diarrhoea					
Charytan 2005 CKD	0/39	3/44		10.79%	-0.07[-0.15,0.02]
Spinowitz 2008 CKD	3/217	4/75		27.9%	-0.04[-0.09,0.01]
Van Wyck 2005 CKD	0/91	3/91		44.98%	-0.03[-0.07,0.01]
Agarwal 2006 CKD	2/44	2/45		10.64%	0[-0.09,0.09]
Fishbane 1995 HD	1/20	0/32		5.69%	0.05[-0.07,0.17]
Subtotal (95% CI)	**411**	**287**		**100%**	**-0.03[-0.06,-0]**
Total events: 6 (IV iron), 12 (Oral iron)					
Heterogeneity: Tau^2=0; Chi^2=3.19, df=4(P=0.53); I^2=0%					
Test for overall effect: Z=2.11(P=0.03)					
3.2.5 Nausea or vomiting					
Charytan 2005 CKD	2/39	9/44		13.63%	-0.15[-0.29,-0.02]
Spinowitz 2008 CKD	4/217	5/75		33.42%	-0.05[-0.11,0.01]
Van Wyck 2005 CKD	2/91	5/91		34.74%	-0.03[-0.09,0.02]
Agarwal 2006 CKD	5/44	2/45		18.21%	0.07[-0.04,0.18]
Subtotal (95% CI)	**391**	**255**		**100%**	**-0.04[-0.1,0.02]**
Total events: 13 (IV iron), 21 (Oral iron)					
Heterogeneity: Tau^2=0; Chi^2=6.43, df=3(P=0.09); I^2=53.31%					
Test for overall effect: Z=1.18(P=0.24)					
3.2.6 Taste disturbances					
Spinowitz 2008 CKD	2/217	0/75		45.23%	0.01[-0.01,0.03]
Van Wyck 2005 CKD	5/91	0/91		34.49%	0.05[0,0.11]
Charytan 2005 CKD	3/39	0/44		20.27%	0.08[-0.02,0.17]
Subtotal (95% CI)	**347**	**210**		**100%**	**0.04[-0.02,0.09]**
Total events: 10 (IV iron), 0 (Oral iron)					
Heterogeneity: Tau^2=0; Chi^2=7.03, df=2(P=0.03); I^2=71.56%					
Test for overall effect: Z=1.39(P=0.16)					
3.2.7 Iron overload					
Warady 2002 HD	0/17	0/18		64.03%	0[-0.1,0.1]
Hussain 1998 HD	2/10	0/10		35.97%	0.2[-0.08,0.48]
Subtotal (95% CI)	**27**	**28**		**100%**	**0.07[-0.16,0.3]**
Total events: 2 (IV iron), 0 (Oral iron)					
Heterogeneity: Tau^2=0.02; Chi^2=2.67, df=1(P=0.1); I^2=62.57%					
Test for overall effect: Z=0.61(P=0.54)					
3.2.8 Number discontinuing treatment because of adverse effects					
Van Wyck 2005 CKD	3/91	0/91		100%	0.03[-0.01,0.07]
Subtotal (95% CI)	**91**	**91**		**100%**	**0.03[-0.01,0.07]**
Total events: 3 (IV iron), 0 (Oral iron)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.54(P=0.12)					



ADDITIONAL TABLES

Table 1. Subgroup analysis and meta-regression to examine heterogeneity in haemoglobin meta-analyses

	Total studies (N)	Studies	MD (95% CI) (g/dL)	P
Dose IV iron/study month				
≥ 400 mg/month	9	4	0.51 (-0.25 to 1.28)	0.46
> 400 to 700 mg/month	5	5	1.17 (0.41 to 1.94)	
> 700 mg/month	8	7	0.73 (0.43, 1.03)	
Dose IV iron (mg total dose)				
≥ 1000 mg	8	6	0.59 (0.30 to 0.87)	0.21
1000 to 1999 mg	10	7	0.80 (0.25 to 1.37)	
> 2000 mg	4	3	1.34 (0.67 to 2.02)	
Oral dose iron/study month				
< 4000 mg/month	6	4	2.01 (0.74 to 3.88)	**0.04**
≥ 4000 and < 6000 mg/month	9	9	0.98 (0.47 to 1.50)	
≥ 6000 mg/month	7	5	0.32 (0.12 to 0.52)	
Dose oral iron (mg total dose)				
≥ 12,000 mg	7	7	0.91 (0.55 to 1.28)	0.66
1200 to 30,000 mg	10	7	0.91 (0.33 to 1.48)	
> 30,000 mg	7	4	1.36 (-1.54 to 4.26)	
Any ESA use				
No EPO	9	7	1.05 (-0.01 to 2.10)	0.30
EPO	19	15	1.02 (0.48 to 1.56)	
ESA timing of use				
Start of study	7	5	1.22 (-0.33 to 2.77)	0.61
Before study	12	8	0.88 (0.34 to 1.42)	
CKD stage				
1 to 5	9	8	0.45 (0.24 to 0.66)	0.27

Table 1. Subgroup analysis and meta-regression to examine heterogeneity in haemoglobin meta-analyses *(Continued)*

Dialysis (5D)	18	13	1.16 (0.30 to 2.02)	
Study duration				
≥ 2 months	10	9	0.60 (0.37 to 0.82)	0.44
> 2 to ≤ 4 months	7	5	1.03 (0.2 to 1.86)	
> 4 months	9	7	1.11 (-0.35 to 2.75)	
Intervention aim				
Increase Hb	24	20	1.00 (0.51 to 1.50)	0.18
Maintain Hb	4	2	-0.09 (-0.53 to 0.36)	
Pharmaceutical company sponsorship				
Unclear	16	12	1.42 (0.52 to 2.33)	**0.01**
Sponsored	12	10	0.36 (0.19 to 0.53)	
Imputed standard deviation				
Not imputed		18	0.38 (0.20 to 0.56)	0.48
imputed		4	0.98 (0.40 to 1.57)	

CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin

Table 2. Subgroup analysis and meta-regression to examine heterogeneity in ferritin meta-analyses

	Total studies (N)	Studies	MD (95% CI) (µg/L)	P
Dose IV iron/study month				
≥ 400 mg/month	9	7	263 (112 to 415)	0.12
> 400 to 700 mg/month	5	5	235 (155 to 315)	
>700 mg/month	8	7	240 (149 to 332)	
Dose IV iron (mg total dose)				
≥ 1000 mg	8	7	170 (118 to 223)	**0.01**
1000 to 1999 mg	10	8	262 (161 to 364)	
> 2000 mg	4	4	377 (171 to 582)	
Oral dose iron/study month				
<4000 mg/month	6	6	259 (147 to 371)	0.54

Table 2. Subgroup analysis and meta-regression to examine heterogeneity in ferritin meta-analyses *(Continued)*

≥ 4000 to < 6000 mg/month	9	8	171 (149 to 193)	
≥ 6000 mg/month	7	5	225 (67 to 193)	
Dose oral iron (mg total dose)				
≥ 12,000 mg	7	7	244 (163 to 324)	0.82
1200 to 30,000 mg	10	7	158 (117 to 199)	
> 30,000 mg	7	6	303 (111 to 495)	
Any ESA use				
No EPO	9	3	214 (150 to 276)	0.62
EPO	19	18	243 (189 to 298)	
ESA timing of use				
Start of study	7	5	237 (153 to 322)	0.89
Before study	12	12	245 (144 to 546)	
CKD stage				
1 to 5	9	7	229 (158 to 300)	0.73
Dialysis (5D)	18	16	247 (162 to 331)	
Study duration				
≥ 2 months	10	9	215 (142 to 289)	0.43
> 2 to ≤ 4 months	7	6	268 (84 to 452)	
> 4 months	9	8	262 (169 to 355)	
Intervention aim				
Increase Hb	24	20	336 (84 to 588)	0.12
Maintain Hb	4	4	282 (177 to 261)	
Pharmaceutical company sponsorship				
Unclear	16	15	257 (173 to 341)	0.52
Sponsored	12	9	224 (158 to 291)	
Imputed standard deviation				
Not imputed		21	247 (187 to 307)	0.68
imputed		3	214 (86 to 341)	

CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin

Table 3. Subgroup analysis and meta-regression to examine heterogeneity in transferrin saturation meta-analyses

	Total studies (N)	Studies	MD (95% CI) (µg/L)	P
Dose IV iron/study month				
≥ 400 mg/month	9	5	16.78 (-0.22 to 33.78)	0.96
>400 -700 mg/month	5	4	2.20 (-5.0 to 9.40)	
>700 mg/month	8	6	8.69 (5.83 to 11.55)	
Dose IV iron (mg total dose)				
≥ 1000 mg	8	6	7.60 (3.51 to 11.70)	0.10
1000 to 1999 mg	10	7	4.70 (-0.47 to 9.86)	
> 2000 mg	4	2	35.84 (-2.75 to 74.42)	
Oral dose iron/study month				
< 4000 mg/month	6	5	7.57 (4.49 to 10.66)	0.38
≥4000 to < 6000 mg/month	9	6	7.98 (-0.48 to 16.45)	
≥ 6000 mg/month	7	4	5.97 (1.62 to 10.32)	
Dose oral iron (mg total dose)				
≥ 12,000 mg	7	5	5.89 (3.21 to 8.57)	0.23
1200 to 30,000 mg	10	7	9.33 (-0.08 to 18.74)	
> 30,000 mg	7	4	18.32 (0.43 to 36.22)	
Any ESA use				
No EPO	9	4	9.77 (4.89 to 14.65)	0.89
EPO	19	12	11.22 (3.51 to 18.93)	
ESA timing of use				
Start of study	7	4	6.78 (-4.68 to 14.65)	0.62
Before study	12	8	13.26 (3.16 to 23.36)	
CKD stage				
1 to 5	9	6	6.89 (3.65 to 10.12)	0.35
Dialysis (5D)	18	11	13.69 (6.00 to 21.34)	

Table 3. Subgroup analysis and meta-regression to examine heterogeneity in transferrin saturation meta-analyses *(Continued)*

Study duration				
≥ 2 months	10	7	5.81 (3.53 to 8.09)	0.77
> 2 to ≤ 4 months	7	7	17.36 (-1.03 to 35.74)	
> 4 months	9	4	6.30 (1.31 to 11.29)	
Intervention aim				
Increase Hb	24	14	7.59 (4.07 to 17.11)	0.18
Maintain Hb	4	4	18.28 (-3.73 to 40.30)	
Pharmaceutical company sponsorship				
Unclear	16	10	14.28 (4.21 to 24.34)	0.17
Sponsored	12	8	5.38 (3.06 to 7.71)	
Imputed standard deviation				
Not imputed		17	4.00 (0.38 to 7.62)	0.62
imputed		1	10.61 (5.67 to 15.55)	

CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Ferric Compounds explode all trees 2. MeSH descriptor Ferrous Compounds explode all trees 3. MeSH descriptor Hematinics, this term only 4. MeSH descriptor Iron-Dextran Complex, this term only 5. MeSH descriptor Iron, this term only 6. MeSH descriptor Ferrosoferric Oxide, this term only 7. (iron and (gluconate* or fumarate* or dextran* or sucrose* or saccharate*)) in Clinical Trials 8. (iron and (supplement* or therap* or replacement)) in Clinical Trials 9. (ferric or ferrous) and gluconate* in Clinical Trials 10.(ferumoxytol or magnetite or "ferriferous oxide") in Clinical Trials 11.(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10) 12.MeSH descriptor Renal Replacement Therapy explode all trees 13.MeSH descriptor Renal Insufficiency, this term only 14.MeSH descriptor Kidney Failure, this term only 15.MeSH descriptor Renal Insufficiency, Chronic explode all trees 16.MeSH descriptor Kidney Diseases, this term only 17.MeSH descriptor Uremia, this term only

(Continued)

	18.(hemodialysis or haemodialysis) in Clinical Trials 19.(hemofiltration or haemofiltration) in Clinical Trials 20.(hemodiafiltration or haemodiafiltration) in Clinical Trials 21.(dialysis) in Clinical Trials 22.(PD or CAPD or CCPD or APD) in Clinical Trials 23.(end-stage renal or end-stage kidney or endstage renal or endstage kidney) in Clinical Trials 24.(ESRF or ESKF or ESRD or ESKD) in Clinical Trials 25.(chronic kidney or chronic renal) in Clinical Trials 26.(CKF or CKD or CRF or CRD) in Clinical Trials 27.(ur?emi*.) in Clinical Trials 28.(ur?emi*) in Clinical Trials 29.(12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28) 30.(11 AND 29)
MEDLINE	1. exp Ferric Compounds/ or exp Ferrous Compounds/ 2. Hematinics/ 3. Iron-Dextran Complex/ 4. Iron/ 5. Ferrosoferric Oxide/ 6. (iron and (gluconate$ or fumarate$ or dextran$ or sucrose$ or saccharate$)).tw. 7. (iron and (supplement$ or therap$ or replacement)).tw. 8. ((ferric or ferrous) and gluconate$).tw. 9. (ferumoxytol or magnetite or "ferriferous oxide").tw. 10.or/1-9 11.exp Renal Replacement Therapy/ 12.(hemodialysis or haemodialysis).tw. 13.(hemofiltration or haemofiltration).tw. 14.(hemodiafiltration or haemodiafiltration).tw. 15.dialysis.tw. 16.(PD or CAPD or CCPD or APD).tw. 17.Renal Insufficiency/ 18.Kidney Failure/ 19.exp Renal Insufficiency, Chronic/ 20.Kidney Diseases/ 21.Uremia/ 22.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 23.(ESRF or ESKF or ESRD or ESKD).tw. 24.(chronic kidney or chronic renal).tw. 25.(CKF or CKD or CRF or CRD).tw. 26.ur?emi$.tw. 27.or/11-26 28.and/10,27
EMBASE	1. Iron therapy/ 2. antianemic agent/ or ferric citrate/ or ferric gluconate/ or ferric hydroxide sucrose/ or ferric maltol/ or ferric pyrophosphate/ or ferrous ascorbate/ or ferrous aspartate/ or ferrous chloride/ or ferrous fumarate/ or ferrous gluconate/ or ferrous succinate/ or ferrous sulfate/ or ferrous sulfate plus folic acid/ or ferumoxytol/ or iron dextran/ or iron polymaltose/ or "iron poly(sorbitol gluconic acid) complex"/ or iron protein succinylate/ or iron saccharate/ or iron salt/ or iron sorbitex/ 3. Ferumoxytol/ 4. (iron and (gluconate$ or fumarate$ or dextran$ or sucrose$ or saccharate$)).tw.

(Continued)

5. (iron and (supplement$ or therap$ or replacement)).tw.
6. ((ferric or ferrous) and gluconate$).tw.
7. (ferumoxytol or magnetite or "ferriferous oxide").tw.
8. or/1-7
9. exp Renal Replacement Therapy/
10. (hemodialysis or haemodialysis).tw.
11. (hemofiltration or haemofiltration).tw.
12. (hemodiafiltration or haemodiafiltration).tw.
13. dialysis.tw.
14. (PD or CAPD or CCPD or APD).tw.
15. Kidney Disease/
16. Chronic Kidney Disease/
17. Kidney Failure/
18. Chronic Kidney Failure/
19. Uremia/
20. (chronic kidney or chronic renal).tw.
21. (CKF or CKD or CRF or CRD).tw.
22. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
23. (ESRF or ESKF or ESRD or ESKD).tw.
24. ur?emi$.tw.
25. or/9-24

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.

(Continued)

Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias 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.

(Continued)

	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anemia, Iron-Deficiency [blood] [*therapy]; Ferritins [blood]; Hemoglobin A [metabolism]; Injections, Intravenous; Iron Compounds [*administration & dosage]; Kidney Failure, Chronic [blood] [*complications]; Randomized Controlled Trials as Topic; Transferrin [metabolism]

MeSH check words

Adult; Child; Humans