Cochrane Library

Cochrane Database of Systematic Reviews

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

O'Lone EL, Hodson EM, Nistor I, Bolignano D, Webster AC, Craig JC

O'Lone EL, Hodson EM, Nistor I, Bolignano D, Webster AC, Craig JC.
Parenteral versus oral iron therapy for adults and children with chronic kidney disease.
Cochrane Database of Systematic Reviews 2019, Issue 2. Art. No.: CD007857.
DOI: 10.1002/14651858.CD007857.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

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

Emma L O'Lone[1], Elisabeth M Hodson[2], Ionut Nistor[3], Davide Bolignano[4], Angela C Webster[1,5], Jonathan C Craig[2,6]

[1]Sydney School of Public Health, The University of Sydney, Sydney, Australia. [2]Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [3]Nephrology Department, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania. [4]Institute of Clinical Physiology, CNR - Italian National Council of Research, Reggio Calabria, Italy. [5]Centre for Transplant and Renal Research, Westmead Millennium Institute, The University of Sydney at Westmead, Westmead, Australia. [6]College of Medicine and Public Health, Flinders University, Adelaide, Australia

Contact address: Elisabeth M Hodson, Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW, 2145, Australia. elisabeth.hodson@health.nsw.gov.au.

Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 2, 2019.

Citation: O'Lone EL, Hodson EM, Nistor I, Bolignano D, Webster AC, Craig JC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database of Systematic Reviews* 2019, Issue 2. Art. No.: CD007857. DOI: 10.1002/14651858.CD007857.pub3.

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. This is an update of a review first published in 2012.

Objectives

To determine the benefits and harms of IV iron supplementation compared with oral iron for anaemia in adults and children with CKD, including participants on dialysis, with kidney transplants and CKD not requiring dialysis.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 7 December 2018 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal, and ClinicalTrials.gov.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs in which IV and oral 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) with 95% confidence intervals (CI) for dichotomous outcomes. 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. The certainty of the evidence was assessed using GRADE.

Main results

We included 39 studies (3852 participants), 11 of which were added in this update. A low risk of bias was attributed to 20 (51%) studies for sequence generation, 14 (36%) studies for allocation concealment, 22 (56%) studies for attrition bias and 20 (51%) for selective outcome reporting. All studies were at a high risk of performance bias. However, all studies were considered at low risk of detection bias because the primary outcome in all studies was laboratory-based and unlikely to be influenced by lack of blinding.

There is insufficient evidence to suggest that IV iron compared with oral iron makes any difference to death (all causes) (11 studies, 1952 participants: RR 1.12, 95% CI 0.64, 1.94) (absolute effect: 33 participants per 1000 with IV iron versus 31 per 1000 with oral iron), the number of participants needing to start dialysis (4 studies, 743 participants: RR 0.81, 95% CI 0.41, 1.61) or the number needing blood transfusions (5 studies, 774 participants: RR 0.86, 95% CI 0.55, 1.34) (absolute effect: 87 per 1,000 with IV iron versus 101 per 1,000 with oral iron). These analyses were assessed as having low certainty evidence. It is uncertain whether IV iron compared with oral iron reduces cardiovascular death because the certainty of this evidence was very low (3 studies, 206 participants: RR 1.71, 95% CI 0.41 to 7.18). Quality of life was reported in five studies with four reporting no difference between treatment groups and one reporting improvement in participants treated with IV iron.

IV iron compared with oral iron may increase the numbers of participants, who experience allergic reactions or hypotension (15 studies, 2607 participants: RR 3.56, 95% CI 1.88 to 6.74) (absolute harm: 24 per 1000 with IV iron versus 7 per 1000) but may reduce the number of participants with all gastrointestinal adverse effects (14 studies, 1986 participants: RR 0.47, 95% CI 0.33 to 0.66) (absolute benefit: 150 per 1000 with IV iron versus 319 per 1000). These analyses were assessed as having low certainty evidence.

IV iron compared with oral iron may increase the number of participants who achieve target haemoglobin (13 studies, 2206 participants: RR 1.71, 95% CI 1.43 to 2.04) (absolute benefit: 542 participants per 1,000 with IV iron versus 317 per 1000 with oral iron), increased haemoglobin (31 studies, 3373 participants: MD 0.72 g/dL, 95% CI 0.39 to 1.05); ferritin (33 studies, 3389 participants: MD 224.84 µg/L, 95% CI 165.85 to 283.83) and transferrin saturation (27 studies, 3089 participants: MD 7.69%, 95% CI 5.10 to 10.28), and may reduce the dose required of erythropoietin-stimulating agents (ESAs) (11 studies, 522 participants: SMD -0.72, 95% CI -1.12 to -0.31) while making little or no difference to glomerular filtration rate (8 studies, 1052 participants: 0.83 mL/min, 95% CI -0.79 to 2.44). All analyses were assessed as having low certainty evidence. There were moderate to high degrees of heterogeneity in these analyses but in meta-regression, definite reasons for this could not be determined.

Authors' conclusions

The included studies provide low certainty evidence that IV iron compared with oral iron increases haemoglobin, ferritin and transferrin levels in CKD participants, increases the number of participants who achieve target haemoglobin and reduces ESA requirements. However, there is insufficient evidence to determine whether IV iron compared with oral iron influences death (all causes), cardiovascular death and quality of life though most studies reported only short periods of follow-up. Adverse effects were reported in only 50% of included studies. We therefore suggest that further studies that focus on patient-centred outcomes with longer follow-up periods 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

What is the issue?

Anaemia (reduction in the number of circulating red blood cells) 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 the response to medications 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.

What did we do?

We reviewed 39 studies (3852 participants) which compared IV iron supplements with oral iron in participants with chronic kidney disease.

What did we find?

We found that IV iron may increase blood levels of haemoglobin and iron compared with oral iron. However, IV iron may increase the number of allergic reactions though it may reduce side effects such as constipation, diarrhoea, nausea and vomiting seen with oral iron. We did not find sufficient evidence to determine whether IV iron compared with oral iron improved quality of life, altered overall death rate or death due to heart disease.

Conclusions

Although the results suggest that IV iron compared with oral iron may be more effective in raising iron and haemoglobin levels, we found insufficient data to determine if the benefits of IV iron are justified by improved quality of life or mortality despite the small risk of potentially serious allergic effects in some patients given IV iron.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Patient-centred outcomes for oral versus IV iron in adults and children with chronic kidney disease

Patient-centred outcomes for oral versus IV iron in adults and children with CKD

Patient or population: adults and children with CKD
Setting: Nephrology departments
Intervention: IV iron
Comparison: oral iron

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with oral iron	Risk with IV iron				
Death (all causes)	30 per 1,000	33 per 1,000 (19 to 58)	RR 1.12 (0.64 to 1.94)	1952 (11)	⊕⊕⊖⊖ LOW [1 2]	Only 11/38 studies represented with only about 1/3 of patients.
Cardiovascular death	20 per 1,000	34 per 1,000 (8 to 142)	RR 1.71 (0.41 to 7.18)	206 (3)	⊕⊖⊖⊖ VERY LOW [1 2 4]	-
Type of adverse event: allergic reactions/hypotension	7 per 1,000	24 per 1,000 (13 to 46)	RR 3.56 (1.88 to 6.74)	2607 (15)	⊕⊕⊖⊖ LOW [1 2]	-
Type of adverse event: all gastrointestinal adverse effects	319 per 1,000	150 per 1,000 (105 to 211)	RR 0.47 (0.33 to 0.66)	1986 (14)	⊕⊕⊖⊖ LOW [2 3]	-
Type of adverse event: infection	80 per 1,000	106 per 1,000 (72 to 157)	RR 1.32 (0.90 to 1.95)	954 (4)	⊕⊕⊖⊖ LOW [1 2]	-
Numbers of non-dialysis patients needing to commence dialysis	46 per 1,000	38 per 1,000 (19 to 75)	RR 0.81 (0.41 to 1.61)	743 (4)	⊕⊕⊖⊖ LOW [1 2]	-
Number requiring transfusion	101 per 1,000	87 per 1,000 (56 to 136)	RR 0.86 (0.55 to 1.34)	774 (5)	⊕⊕⊖⊖ LOW [1 2]	-

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

CI: Confidence interval; **CKD:** chronic kidney disease; **IV:** intravenous; **RR:** Risk ratio

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

[1] Downgraded one level for imprecision
[2] Downgraded one level for likely publication bias
[3] Downgraded one level for high heterogeneity
[4] Downgraded one level for publication bias

Summary of findings 2. Laboratory and pharmaceutical outcomes for adults and children with chronic kidney disease

Laboratory and pharmaceutical outcomes for adults and children with CKD

Patient or population: adults and children with CKD
Setting: Nephrology departments
Intervention: IV iron
Comparison: oral iron

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with oral iron	Risk with IV iron				
Number achieving target Hb or increase ≥1 g/dL	317 per 1,000	542 per 1,000 (453 to 646)	RR 1.71 (1.43 to 2.04)	2206 (13)	⊕⊕⊖⊖ LOW [1,2]	Risk of bias (ROB) downgraded as little info on random sequence generation (RSG) and allocation concealment. Heterogeneity 60%
Hb: final or change (g/dL)	The mean Hb level was 0.72 g/dL higher with IV iron compared to oral iron (0.39 to 1.05 higher)		-	3373 (31)	⊕⊕⊖⊖ LOW [1,2]	21/31 are at ROB for RSG &/or allocation concealment. Heterogeneity 94%
Ferritin: final or change (µg/L)	The mean ferritin level was 224.84 µg/L higher with IV iron compared to oral iron (165.85 to 283.83 higher)		-	3389 (33)	⊕⊕⊖⊖ LOW [1,2]	8/13 are at ROB for RSG or allocation concealment. Heterogeneity 60%.

TSAT: final or change (%)	The mean TSAT was 7.69% higher with IV iron compared to oral iron (5.1 to 10.28 higher)	-	3089 (27)	⊕⊕⊖⊖ LOW [1] [2]	11/27 only are at low risk of bias and heterogeneity is 97%.
HCT (%)	The mean HCT was 1.18% higher with IV iron compared to oral iron (2.17 lower to 4.52 higher)	-	152 (4)	⊕⊖⊖⊖ VERY LOW [1] [2] [3] [4]	Only 4 studies in this analysis, all with unknown risk of selection bias. Heterogeneity 96%.
ESA dose: final or change	The SMD for ESA dose was 0.72 lower with IV iron compared to oral iron (0.31 to 1.12 lower)	-	522 (11)	⊕⊕⊖⊖ LOW [1] [2]	ROB downgraded as little information on RSG and Allocation concealment. Heterogeneity 77%
eGFR: final or change (mL/min)	the mean eGFR was 0.83 mL/min higher with IV iron compared to oral iron (0.79 lower to 2.44 higher)	-	1052 (8)	⊕⊕⊖⊖ LOW [1] [3]	Half of the studies are at ROB for RSG & allocation concealment.

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

CI: Confidence interval; **CKD:** chronic kidney disease; **eGFR:** estimated glomerular filtration rate; **ESA:** erythrocyte-stimulating agent; **Hb:** haemoglobin; **HCT:** haematocrit; **IV**: intravenous; **RR:** Risk ratio; **TSAT:** transferrin saturation

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

[1] Downgraded one level for risk of bias
[2] Downgraded one level for inconsistency
[3] Downgraded one level for imprecision
[4] Downgraded one level for likely publication bias

BACKGROUND

Description of the condition

A reduction in the number of circulating red blood cells is termed anaemia. The prevalence of anaemia in patients with chronic kidney disease (CKD) is twice that in the general population. As kidney function deteriorates, the prevalence of anaemia increases from 8.4% at CKD stage 1 to 53.4% at CKD stage 5 (Stauffer 2014). The cause of anaemia in CKD is multifactorial though largely driven by decreased kidney production of erythropoietin. Iron deficiency can exacerbate the degree of anaemia and reduce the response to erythropoietin-stimulating agents (ESAs). Anaemia has been found to contribute to a number of pathological processes. Observational studies have shown anaemia to be associated with increased mortality (at an haemoglobin level (Hb) < 11.0 g/dL) (Kovesdy 2006; Levin 2006), increased hospital stay (Li 2004), increased cardiovascular events (Li 2004; Vlagopoulos 2005; Weiner 2005) and decreased quality of life (Fukuhara 2007). Limited data have also shown that an increase in Hb can improve a number of these indices (Levin 2006; Moreno 2000). However, a systematic review of studies assessing the effects of targeting higher Hb concentrations in patients with CKD by using higher doses of ESA showed a significantly higher risk of death (all causes) (risk ratio (RR) 1.17) and arteriovenous access thrombosis (RR 1.34) in the higher Hb target group compared with the lower Hb group (Phrommintikul 2007). National (CARI 2008; Moist 2008; NICE 2015) and international guidelines (KDIGO 2008; Locatelli 2010) recommend target Hb levels of between 10 g/dL to 12 g/dL for patients with CKD. The most recent guidelines (KDIGO 2012) suggest that the Hb in adult CKD patients should not exceed 11.5 g/dL.

Iron is an essential mineral to maintain health. It is required in many intracellular processes including DNA synthesis, mitochondrial energy generation and enzymatic reactions. It is used in the production of myoglobin in muscles and Hb, the oxygen carrying component of the red blood cells. Determining iron deficiency in CKD can be challenging as it is often a functional deficiency caused by insufficient iron availability despite adequate body iron stores. The aetiology of iron deficiency in CKD is complex but includes reduced dietary intake and blood loss, particularly from the gastrointestinal tract, due to uraemia induced platelet dysfunction (Hedges 2007). These losses are compounded in patients on haemodialysis (HD) by the use of heparin, losses from clotted dialysis lines and blood sampling, which can lead to losses of 2 litres to 5 litres of blood per year (Sargent 2004). Lastly, chronic inflammation and uraemia result in an upregulation and reduced clearance of hepcidin, inhibiting the release of iron from macrophages and decreasing gastrointestinal iron absorption (Lopez 2015).

Description of the intervention

Therapeutic iron can be given orally. Four iron preparations are commonly used: ferrous sulphate, ferrous sulphate exsiccated, ferrous gluconate, and ferrous fumarate. It can be given intramuscularly in the form of iron dextran or it can be given intravenously. Six main forms of intravenous (IV) iron are currently available: iron sucrose, ferric gluconate, ferric carboxymaltose, iron isomaltoside-1000, ferumoxytol, and iron dextran (low-molecular-weight forms) (Lopez 2015).

Oral iron frequently causes gastrointestinal side effects including heartburn, nausea, vomiting, diarrhoea, and constipation (Lopez 2015). These events affect patient compliance and can limit total intake. Although serious adverse events related to IV forms of iron are rare, the effects can be life threatening and include pulmonary embolism, anaphylactic reaction, loss of consciousness, circulatory collapse, hypotension, dyspnoea, pruritus, hypersensitivity and urticaria (Bailie 2012; Lopez 2015). The cumulative rate for all adverse events, for all IV iron preparations, is 14.1 adverse events per million units sold though it appears to be higher in products such as ferumoxytol compared with iron sucrose (Bailie 2012). IV iron preparations require administration under supervision and this need increases the cost of administration and is inconvenient for patients who are not receiving in-centre HD. IV iron has also been linked to an increased risk of infection and cardiovascular disease; iron can act as a growth factor for some bacteria and free iron has been shown to impair neutrophil and T cell function as well as increase reactive oxygen species (Fishbane 2014; Ishida 2014). The majority of the literature to date supports these associations although the most recent cohort study of nearly 23,000 HD patients suggested no difference in length of stay, death or readmission for infection in those who received IV iron during admission and those who did not (Ishida 2015). Furthermore there is increasing evidence that free iron plays a role in direct injury to kidney tissue, which could result in more rapid deterioration in kidney function (Shah 2011).

Controversies remain about the most effective and safe way to provide iron supplementation in patients with CKD (Fishbane 2007; Macdougall 2016). Current parameters used to monitor iron status include serum ferritin levels, serum iron, transferrin saturation (TSAT), per cent of hypochromic red blood cells, and reticulocyte Hb content. There is debate about the most valuable measures to assess iron status, and the setting of optimum levels of these measures in patients with CKD to increase Hb and optimise ESA response. Novel markers being developed but not yet in routine use include hepcidin, soluble transferrin receptor one and non-transferrin bound iron (Gaweda 2015).

How the intervention might work

Iron deficiency is the most common cause of anaemia in CKD and of hypo-responsiveness to ESAs (Kwack 2006). ESAs accelerate erythropoiesis by increasing iron utilisation and depleting iron stores. Optimal efficacy of ESAs depends on the availability of iron to achieve and maintain target Hb levels. Patients with CKD stage 5D require higher targets for ferritin and TSAT levels to achieve increased Hb levels compared with patients whose kidney function is normal. 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 Hb 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), the Canadian (Madore 2008) and the European guidelines (Locatelli 2009) recommend serum ferritin of > 200 ng/mL and TSAT > 20% in patients receiving HD. KDIGO 2012 recommend that iron can be given until TSAT > 30% or serum ferritin > 500 ng/mL. In patients with less severe degrees of CKD, serum ferritin levels > 100 ng/mL and TSAT > 20% are recommended.

Why it is important to do this review

The original study published in 2012 found strong evidence for increased ferritin and TSAT levels and a small increase in Hb with IV iron compared with oral iron. There was limited evidence that this came with a reduction in ESA use. Only half of the studies reported on adverse events. There have been several studies done over the last six years which have looked at the adverse event rate of the many preparations of IV iron and also included hard end points including all cause and cardiovascular death. At present the majority of HD patients receive IV iron and the use of IV iron in the peritoneal dialysis (PD) and CKD populations is increasing. We felt it was important to update this review to ensure that patient focused adverse events were analysed as well as providing up to date evidence on the efficacy and safety of IV iron. 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 patient centred outcomes including death, requirements for transfusion, hospitalisation, cardiac function, quality of life and change in eGFR as well as iron parameters, achieving target levels of Hb, reducing doses of ESA required, and to determine adverse effects of the therapies.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (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 (including iron sucrose, dextran, ferric gluconate, ferric carboxymaltose, ferumoxytol) and oral iron preparations (including oral iron preparations which contain folic acid, 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

- Death (all causes)
- Cardiovascular death
- Quality of life

Secondary outcomes

- Hb
  - Number achieving target Hb level
  - Time to achieve target Hb
  - Final or change in Hb at end of study
  - Increase in Hb > 10 g/L or other target during study
- Iron
  - Number achieving target levels of iron (ferritin, TSAT, per cent of hypochromic red blood cells)
  - Final or change in ferritin levels at the end of study
  - Final or change in TSAT at end of study
  - Per cent of hypochromic red blood cells
- Erythrocyte stimulating agents (ESAs)
  - Reduction in required dose of ESA
  - Number needing to increase ESA dose
  - Number needing to decrease ESA dose or cease ESA
- Infection
- Change in GFR in non-dialysis patients
- Number needing transfusions
- Any adverse events of treatment
  - 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

- Haematocrit (HCT)
- Reticulocyte Hb concentration
- Numbers of non-dialysis patients needing to commence dialysis
- Hospitalisation (other than for iron infusions and dialysis)
- Exercise tolerance
- Left ventricular function
- Sexual function
- Nutritional status
- Adherence to therapy
- Numbers and costs of hospitalisations/professional supervision required for IV iron supplements
- Iron overload (as defined by the triallists)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 7 December 2018 through contact with the

Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources.

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

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

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

Searching other resources

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

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that were potentially relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable. However, studies and reviews that might 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, the publication with the most complete data was reviewed initially. 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 independently by two authors using the risk of bias assessment tool (Higgins 2011) (*see* Appendix 2).

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

Measures of treatment effect

For dichotomous outcomes (number reaching target Hb, death) results were expressed as RR with 95% confidence intervals (CI). RR with 95% CI were calculated for adverse effects. Where continuous scales of measurement were used to assess the effects of treatment (Hb level, 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.

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 Hb 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. Where possible we imputed missing standard deviations and standard errors if data was presented alternatively, using methods stated in the Cochrane handbook (Higgins 2011a).

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

Cochrane Kidney and Transplant's Specialised Register includes studies obtained from 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 their inability to publish negative results in journals indexed in major databases. When sufficient studies were available, we created funnel plots and calculated Eggers' test to assess publication bias. 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 outcomes of differences in ferritin, TSAT and Hb, 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 Hb, 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 two paediatric studies, 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 Hb, might have altered meta-analysis results.

'Summary of findings' tables

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

- Summary of findings for the main comparison
  - Death (all causes)
  - Cardiovascular death
  - Allergic reactions/hypotension
  - All gastrointestinal adverse effects
  - Infection
  - Numbers of non-dialysis patients needing to commence dialysis
  - Number requiring transfusion
- Summary of findings 2
  - Number achieving target Hb or increase ≥1 g/dL
  - Hb: final or change
  - Ferritin: final or change
  - TSAT: final or change
  - HCT
  - End of treatment or change in ESA dose
  - eGFR end or change

RESULTS

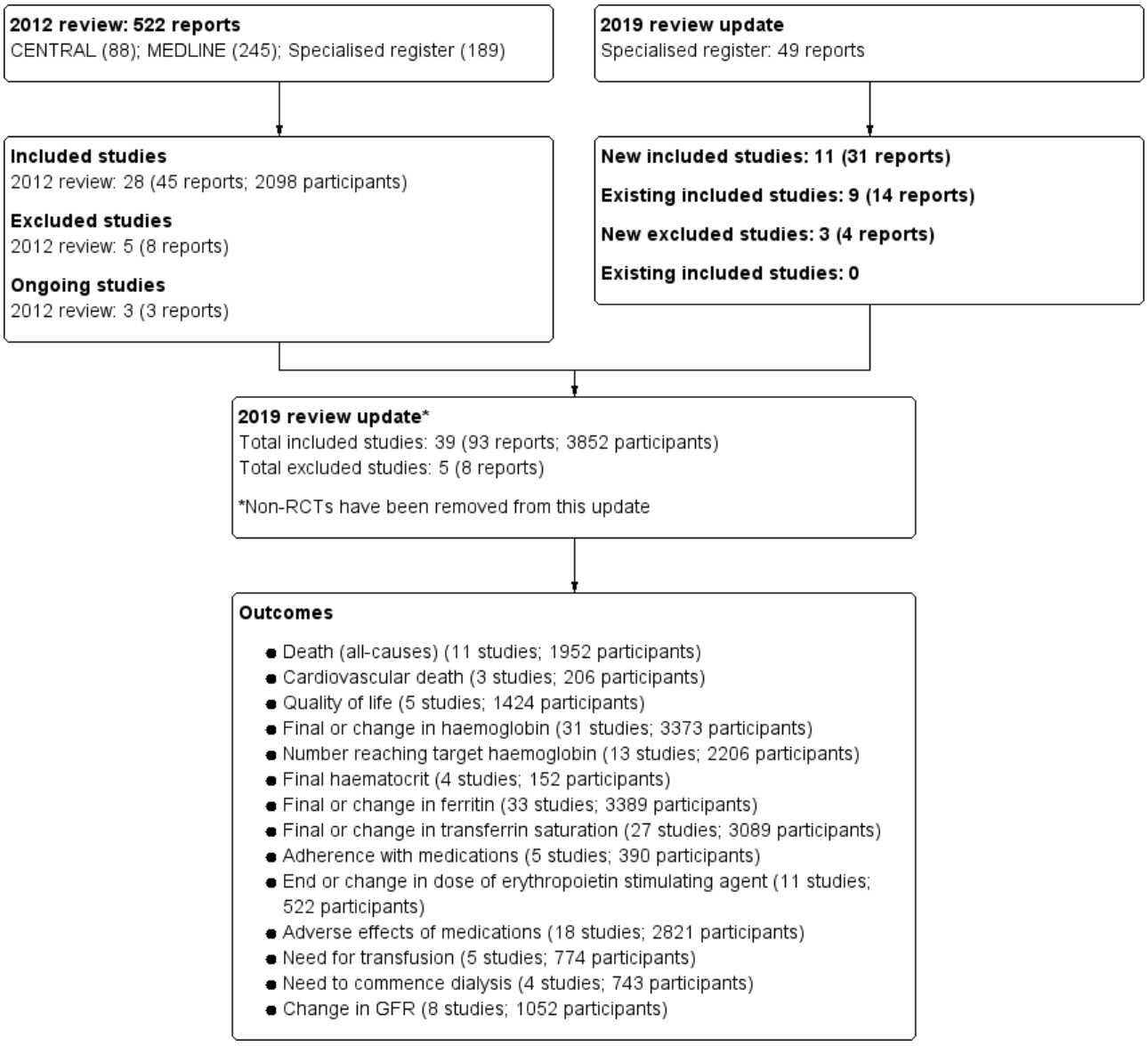
Description of studies

Results of the search

The initial study resulted in a total of 522 study reports from the Cochrane Kidney and Transplant 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). From these 522 reports, 28 studies (46 reports) were included in the systematic review while 28 studies were excluded; there were three ongoing studies.

For the 2019 update of this review, a search of the Cochrane Kidney and Transplant Specialised Register identified 49 new reports. From these we identified 11 new included studies (31 reports) (Agarwal 2015 CKD; FIND-CKD 2014 CKD; Kalra 2016 CKD; Lu 2010 CKD; Mudge 2009 TX; Nagaraju 2013 CKD; NCT01155375 HD,PD,CKD; Pisani 2014 CKD; Ragab 2007 HD; Tsuchida 2010 HD; Winney 1977 HD), three new excluded studies (4 reports) and 14 additional reports of previously included studies.. The additional reports included the full publication of Qunibi 2011 CKD. Of the 11 new included studies, four were publications of trials identified as ongoing trials in the 2010 review (Agarwal 2015 CKD; Kalra 2016 CKD; Mudge 2009 TX; NCT01155375 HD,PD,CKD). The paediatric study (NCT01155375 HD,PD,CKD) was terminated because of challenges with enrolment with minimal data reported. Search results are shown in Figure 1. One new report contained further information on two already included studies (Li 2008 HD; Li 2008 PD). Spinowitz 2008 CKD included all nine reports, which included data for one new included study (Lu 2010 CKD). This 2019 update contains 44 studies (101 reports).

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



Included studies

The 11 new included studies (31 reports) provided an additional 1754 participants bringing the total to 3852 participants. Of the new studies, seven included 1653 participants with CKD, three included 75 participants on HD and one included 102 transplant patients. One study included both dialysis and non-dialysis patients but did not specify how many patients were in each group.

Of the 39 included studies, 38 (3832 participants) were parallel group studies, and one (20 patients) was a cross-over study (Strickland 1977 HD). Only three studies involved paediatric patients (NCT01155375 HD,PD,CKD; Ragab 2007 HD; Warady 2002 HD). Nineteen studies included only HD patients. Li 2008 PD included only patients on PD while Macdougall 1999 HD,PD included both HD and PD patients. Two studies (Ahsan 1997 TX; Mudge 2009 TX) evaluated patients who were in the early phase of post-kidney transplantation. Results from these studies were pooled with studies of dialysis patients. Thirteen studies included non-dialysis patients (CKD stages 3 to 5) while two studies (Macdougall 1996 HD,PD,CKD; NCT01155375 HD,PD,CKD) included both dialysis and non-dialysis patients. Twelve studies were available only as abstracts or from ClinicalTrials.Gov (Ahsan 1997 TX; Broumand 1998 HD; Erten 1998 HD; Leehey 2005 CKD; Lu 2010 CKD; Lye 2000 HD; Macdougall 1999 HD,PD; Michael 2007 HD; NCT01155375 HD,PD,CKD; Souza 1997 HD; Wang 2003 HD; Winney 1977 HD). Thirty-two studies were designed to increase Hb levels and four studies were designed to maintain Hb stability in iron replete patients and decrease ESA dose (Fishbane 1995 HD; Kotaki 1997 HD; Michael 2007 HD; Warady 2002 HD). One study was designed to examine changes in GFR during (Agarwal 2015 CKD) while one study was designed to determine the time to the start of additional anaemia management other than iron (FIND-CKD 2014 CKD).

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 (25 studies), ferrous fumarate (7), ferrous succinate (2), iron gluconate (1), liposomal iron (1), heme iron polypeptide (1) and unnamed agents in two studies. The IV iron agents investigated were iron sucrose (15 studies), iron dextran (7), ferumoxytol (4), sodium ferric gluconate complex (5), ferric carboxymaltose (2), iron isomaltoside (1), ferric citrate (1), and ferric hydroxide polymaltose (3). The IV iron agent was not reported in Kotaki 1997 HD. The calculated total dose of elemental iron ranged from 2520 mg to 63,000 mg in the oral iron groups and from 500 to 10,920 mg in the IV iron groups. Three studies (Erten 1998 HD; FIND-CKD 2014 CKD; Kalra 2016 CKD) included two IV iron treatment groups. For these studies, data from patients who received the higher total dose of IV iron were included in the meta-analyses.

In twenty-two studies all participants were treated with an ESA. 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 15 studies (Broumand 1998 HD; Erten 1998 HD; Fishbane 1995 HD; Kotaki 1997 HD; Leehey 2005 CKD; Li 2008 HD; Li 2008 PD; Macdougall 1999 HD,PD; Michael 2007 HD; Mudge 2009 TX; Provenzano 2009 HD; Ragab 2007 HD; Svara 1996 HD; Tsuchida 2010 HD; Warady 2002 HD). It was unclear when ESA treatment was commenced in Wang 2003 HD. Seven studies reported that no included patients received ESA treatment (Agarwal 2006 CKD; Ahsan 1997 TX; Fudin 1998 HD; Kalra 2016 CKD; McMahon 2009 CKD; Strickland 1977 HD; Winney 1977 HD), but nine studies indicated that varying proportions of patients received an ESA (Agarwal 2015 CKD; FIND-CKD 2014 CKD; Nagaraju 2013 CKD; Lu 2010 CKD; Pisani 2014 CKD; Qunibi 2011 CKD; Spinowitz 2008 CKD; Souza 1997 HD; Van Wyck 2005 CKD).

The outcomes reported in 38 studies are presented in Figure 1. One study was terminated and did not provide any outcomes (NCT01155375 HD,PD,CKD). Final and/or change in Hb, serum ferritin and TSAT levels were reported in 31, 33 and 27 studies respectively. Four studies reported final HCT levels but not Hb levels (Ahsan 1997 TX; Fishbane 1995 HD; Kotaki 1997 HD; Svara 1996 HD). Only 11 studies reported death (all causes) (Agarwal 2015 CKD; FIND-CKD 2014 CKD; Fishbane 1995 HD; Fudin 1998 HD; Kalra 2016 CKD; McMahon 2009 CKD; Lu 2010 CKD; Provenzano 2009 HD; Qunibi 2011 CKD; Stoves 2001 CKD; Tsuchida 2010 HD) while three studies reported on cardiovascular events including death (Agarwal 2015 CKD; Fudin 1998 HD; Stoves 2001 CKD). Five studies reported on quality of life assessment (Agarwal 2006 CKD; Agarwal 2015 CKD; FIND-CKD 2014 CKD; Kalra 2016 CKD; Van Wyck 2005 CKD). Eighteen studies reported on adverse events (Agarwal 2006 CKD; Agarwal 2015 CKD; Charytan 2005 CKD; FIND-CKD 2014 CKD; Fishbane 1995 HD; Hussain 1998 HD; Kalra 2016 CKD; Li 2008 HD; Li 2008 PD; Nagaraju 2013 CKD; Lu 2010 CKD; Pisani 2014 CKD; Provenzano 2009 HD; Qunibi 2011 CKD; Spinowitz 2008 CKD; Strickland 1977 HD; Tsuchida 2010 HD; Van Wyck 2005 CKD).

Excluded studies

From the 2012 review, twenty-three reports were excluded based on titles and abstracts; one study was not an RCT and the remainder involved ineligible interventions. Five more studies (eight reports) were excluded after full text review because participants were not randomised or compared intramuscular with oral iron.

Three studies (four reports) identified in the search for the 2019 update were excluded. One study (Charytan 2013) involved an ineligible comparator (standard medical care which could be oral or IV iron), one study (HEMATOCRIT 2012) compared two oral iron preparations and one study (Adhikary 2011) included non-randomised patients.

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

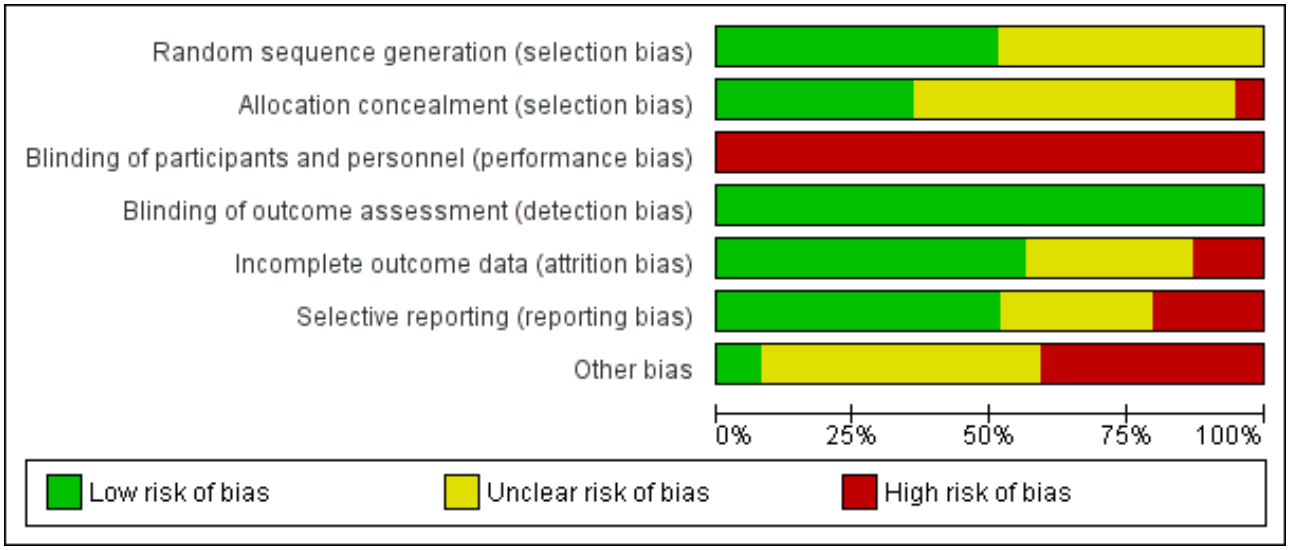


Figure 3. Risk of bias summary: Review authors' judgements about each risk of bias item for each included study

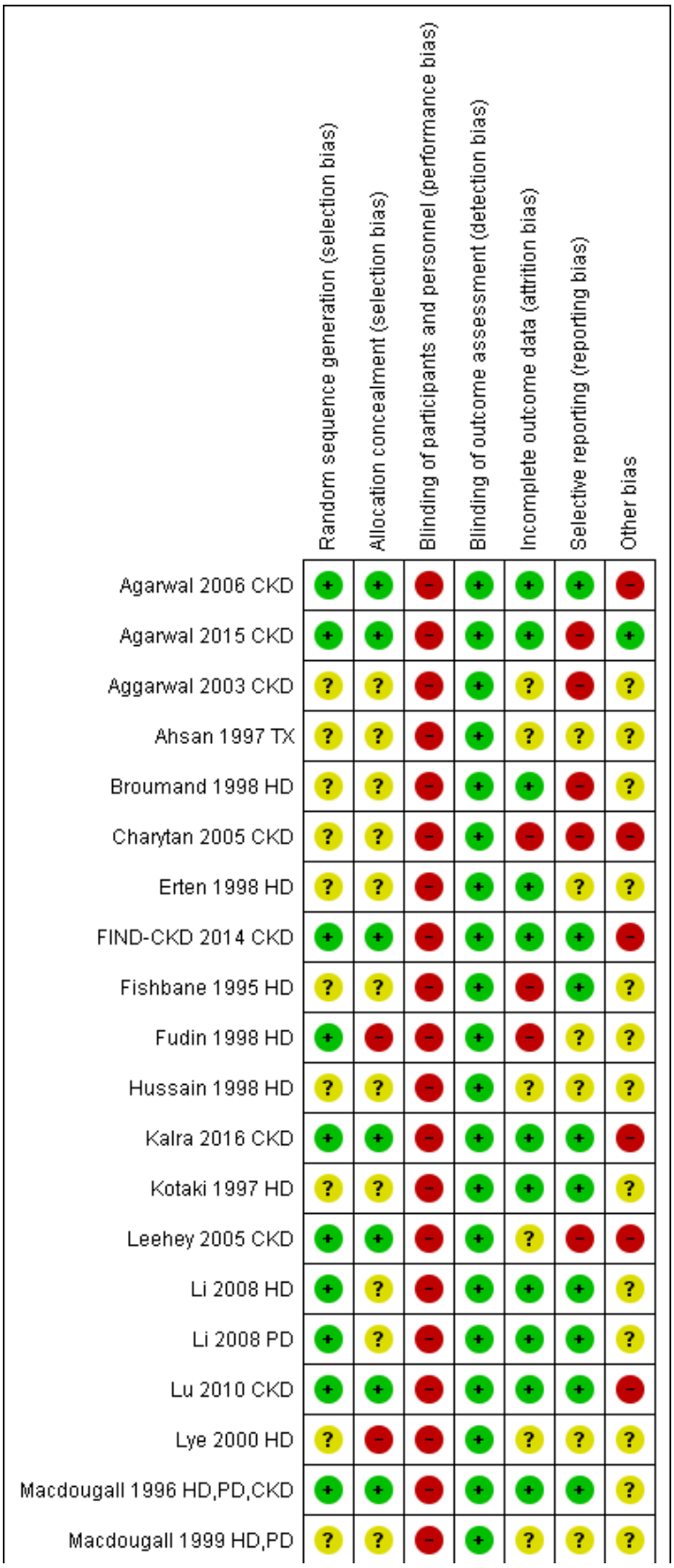
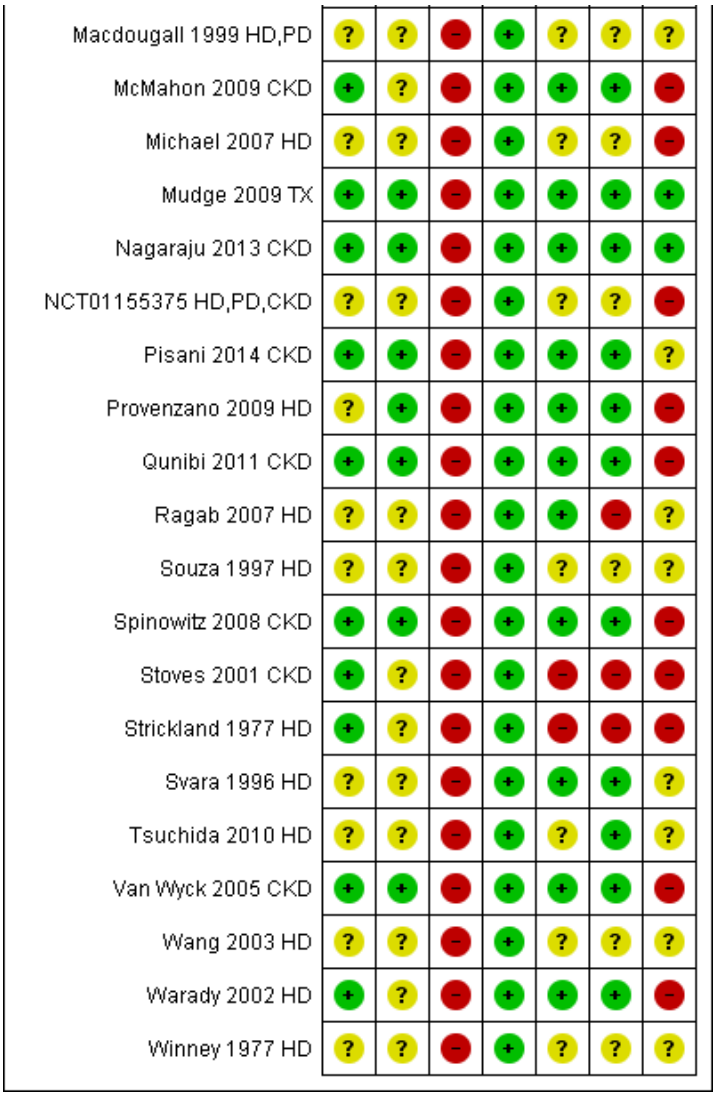


Figure 3. (Continued)



Allocation

Random sequence generation was at low risk of bias in 20 studies (Agarwal 2006 CKD; Agarwal 2015 CKD; FIND-CKD 2014 CKD; Fudin 1998 HD; Kalra 2016 CKD; Leehey 2005 CKD; Li 2008 HD; Li 2008 PD; Macdougall 1996 HD,PD,CKD; McMahon 2009 CKD; Mudge 2009 TX; Nagaraju 2013 CKD; Lu 2010 CKD; Pisani 2014 CKD; Qunibi 2011 CKD; Spinowitz 2008 CKD; Stoves 2001 CKD; Strickland 1977 HD; Van Wyck 2005 CKD; Warady 2002 HD). Random sequence generation was not reported in 18 studies.

Allocation concealment was at low risk of bias in 14 studies (Agarwal 2006 CKD; Agarwal 2015 CKD; FIND-CKD 2014 CKD; Kalra 2016 CKD; Leehey 2005 CKD; Macdougall 1996 HD,PD,CKD; Mudge 2009 TX; Nagaraju 2013 CKD; Lu 2010 CKD; Pisani 2014 CKD; Provenzano 2009 HD; Qunibi 2011 CKD; Spinowitz 2008 CKD; Van Wyck 2005 CKD); at high risk of bias in two studies (Fudin 1998 HD; Lye 2000 HD), and for the remaining 23 studies allocation concealment was unclear.

Blinding

No studies blinded either participants or personnel so were considered to be at high risk of bias. As all studies used laboratory data as primary outcomes, all studies were judged as having a low risk of bias for outcome assessment.

Incomplete outcome data

Outcomes data reporting was considered to be complete with a low risk of bias in 22 studies. Five studies (Charytan 2005 CKD; Fishbane 1995 HD; Fudin 1998 HD; Stoves 2001 CKD; Strickland 1977 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 12 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 20 studies that were considered to have reported all outcomes based on the detailed protocols described in the trial

methods. Eight studies (Agarwal 2015 CKD; Aggarwal 2003 CKD; Broumand 1998 HD; Charytan 2005 CKD; Leehey 2005 CKD; Ragab 2007 HD; Stoves 2001 CKD; Strickland 1977 HD) reported outcomes incompletely so that either outcomes could not be included in meta-analyses or included only with imputed standard deviations or as incidence rates. It was unclear if outcomes were selectively reported in 11 studies.

Other potential sources of bias

Sixteen studies reported receiving monetary support from pharmaceutical companies; three studies reported funding from non-pharmaceutical company sources and the remainder did not report on how their study was funded. In funnel plots, patient centred outcomes showed funnel plot symmetry (example provided in Figure 4), suggesting a low likelihood of publication and other biases. However, for biochemical outcomes, there was some funnel plot asymmetry (example provided in Figure 5) which suggests that the meta-analyses of these outcomes may be affected by some bias.

Figure 4. Funnel plot of comparison: 1 Patient-centred outcomes.Outcome: 1.1 Death (all causes) Eggers test P = 0.25

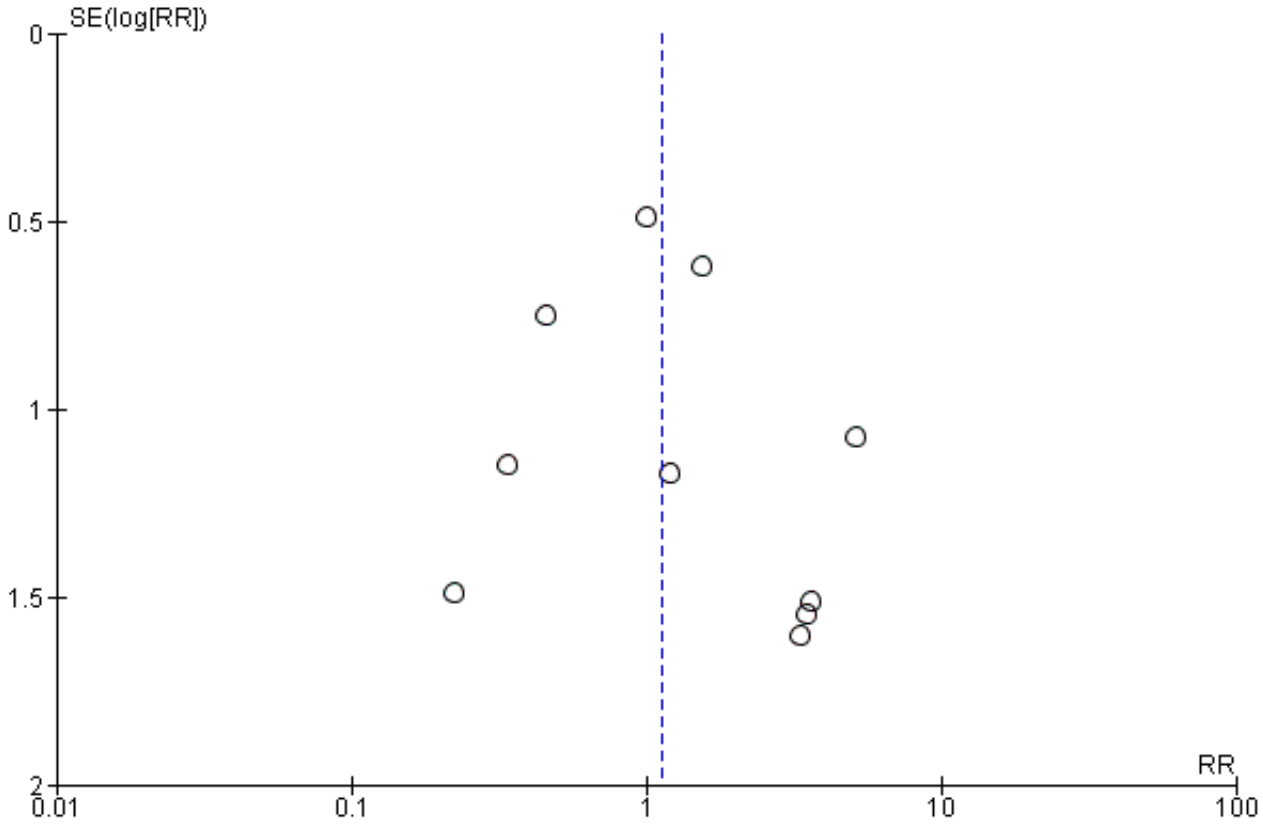
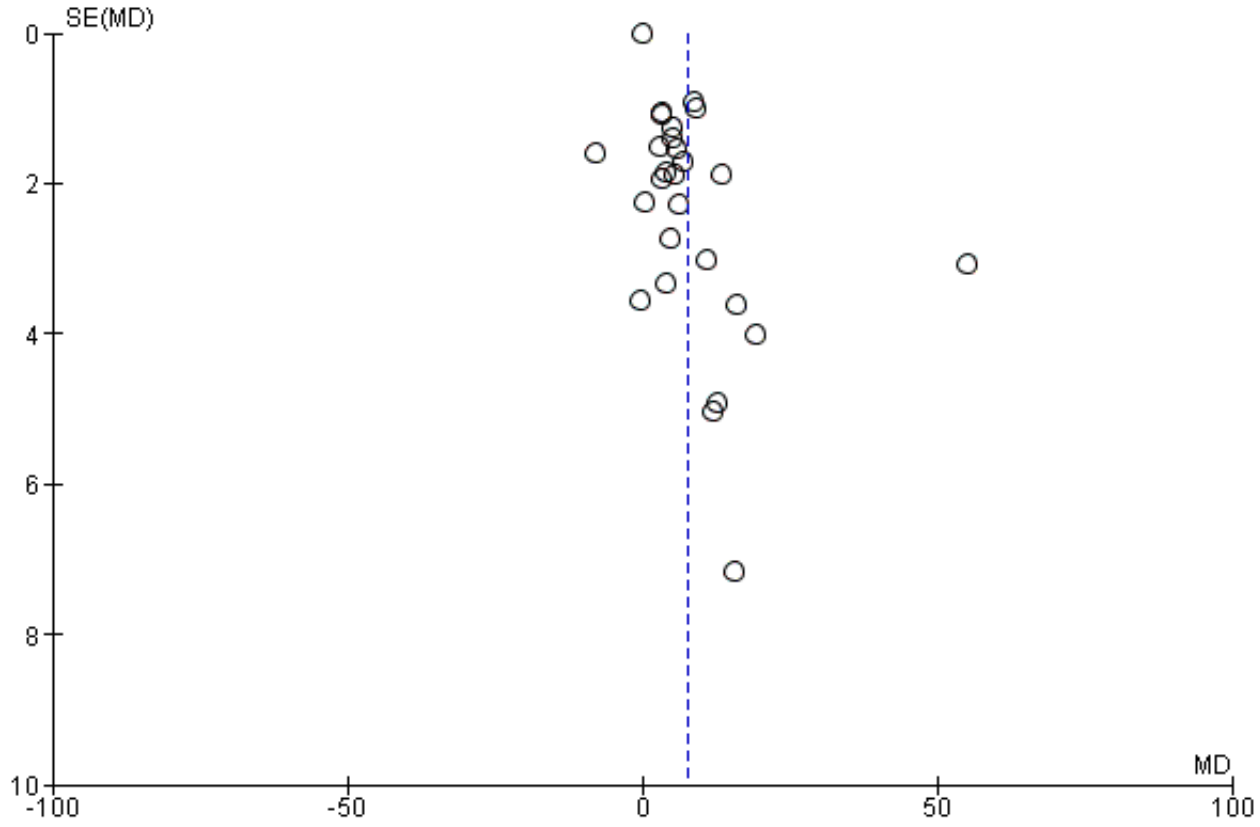


Figure 5. Funnel plot of comparison: 2 Laboratory/pharmaceutical outcomes, outcome: 2.4 Transferrin saturation: Final or change [%]. Eggers test P = 0.00



Effects of interventions

See: **Summary of findings for the main comparison** Patient-centred outcomes for oral versus IV iron in adults and children with chronic kidney disease; **Summary of findings 2** Laboratory and pharmaceutical outcomes for adults and children with chronic kidney disease

Effects of IV iron compared with oral iron on patient-centred outcomes

- Death (all causes) was only reported in 11 studies. There was insufficient evidence to determine whether IV iron compared with oral iron may makes any difference to death (low certainty evidence) (Analysis 1.1 (11 studies, 1952 participants): RR 1.12, 95% CI 0.64 to 1.94; I^2 = 0%). The absolute risk was 33 per 1000 with IV iron compared with 30 per 1000 with oral iron.
- Cardiovascular death was reported in only three studies. It is uncertain whether IV iron compared with oral iron reduces cardiovascular death because the certainty of this evidence was very low (Analysis 1.2 (3 studies, 206 participants): RR 1.71, 95% CI 0.41 to 7.18; I^2 = 0%).
- Quality of life was only reported in five studies (Agarwal 2006 CKD; Agarwal 2015 CKD; FIND-CKD 2014 CKD; Kalra 2016 CKD; Van Wyck 2005 CKD). 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. Kidney disease quality of life score (KDQOL) items - improvement in the ability to do moderate activities and undertake work; and satisfaction with sex life - were reported to be improved among patients treated with IV iron. Scores for a number of factors, including feelings of imposing a burden on family, were lower in patients who received IV iron. In contrast, Van Wyck 2005 CKD found no differences between treatment groups when health concept categories in the SF36 instrument were applied. Agarwal 2015 CKD reported no difference between groups or over time using the KDQOL. FIND-CKD 2014 CKD reported no difference between groups using the SF-36 tool. Using the Linear Analogue Scale Assessment score, Kalra 2016 CKD identified an improvement in quality of life from baseline to eight weeks in both treatment groups with no difference between groups (Analysis 1.3 (1 study, 312 participants): MD 1.45, 95% CI -5.89 to 8.79).
- IV iron compared with oral iron may make little or no difference to the number of participants needing to start dialysis (low certainty evidence) (Analysis 1.4 (4 studies, 743 participants): RR 0.81, 95% CI 0.41 to 1.61; I^2 = 0%). The absolute risk for starting dialysis was 38 per 1000 with IV iron and 46 per 1000 with oral iron.
- IV iron compared with oral iron may make little or no difference to the need for transfusion (low certainty evidence) (Analysis 1.5 (5 studies, 774 participants): RR 0.86, 95% CI 0.55 to 1.34; I^2 = 0%). The absolute risk for needing transfusion was 87 per 1000 with IV iron and 101 with oral iron.

- Although nine studies reported that patient adherence to oral iron was assessed, only three provided numerical data (Charytan 2005 CKD; Van Wyck 2005 CKD; Pisani 2014 CKD). Mean adherence rates for IV iron therapy were 95%, 97% and 96% respectively, and adherence to oral iron therapy was 85% and 88% and 95.8%.
- The certainty of the evidence was downgraded because of imprecision, heterogeneity between studies and publication bias.

See Summary of findings for the main comparison.

Effect of IV iron compared with oral iron on laboratory outcomes

- The numbers of patients reaching target Hb or increasing Hb by at least 1 g/dL were reported in 13 studies. Target Hb or an increase in Hb by 1 g/dL may be achieved by more participants receiving IV iron compared with oral iron (low certainty evidence) (Analysis 2.1 (13 studies, 2206 participants): RR 1.71, 95% CI 1.43 to 2.04; I^2 = 60%) in all patients (Summary of findings 2) and in the subgroups of dialysis participants and CKD participants (Table 1). There was low to moderate heterogeneity. The absolute benefit for reaching the target Hb was 542 per 1000 for IV iron and 317 per 1000 for oral iron.
- End of study or change (g/dL) in Hb were reported in 31 studies. IV iron compared with oral iron may increase Hb (low certainty evidence) (Analysis 2.2 (31 studies, 3373 participants): MD 0.72 g/dL, 95% CI 0.39 to 1.05); I^2 = 94%) in all participants and in subgroups of dialysis and CKD participants (Table 1). There was a high levels of heterogeneity, which persisted when a fixed-effect model was used for analyses. Excluding a study of 26 months treatment and MD 4.92 g/dL (Fudin 1998 HD) did not significantly reduce heterogeneity. Further analyses of heterogeneity are addressed in later sections.
- End of study or change (µg/L) in serum ferritin levels were reported in 33 studies. IV iron compared with oral iron may increase ferritin levels (low certainty evidence) in all participants (Analysis 2.3 (33 studies, 3389 participants): MD 224.84 µg/L, 95% CI 165.85 to 283.83, I^2 = 99%) and in subgroups of dialysis and CKD participants (Table 1). There was a high level of heterogeneity in these analyses.
- End of study or change (%) in TSAT levels were reported in 27 studies. IV iron compared with oral iron may increase TSAT levels (low certainty evidence) in all participants (Analysis 2.4 (27 studies, 3089 participants): MD 7.69 %, 95% CI 5.10 to 10.28, I^2 = 97%) and in subgroups of dialysis and CKD participants (Table 1). There was a high level of heterogeneity in these analyses.
- Five studies reported results for HCT rather than Hb. It is uncertain whether IV iron improves HCT because the certainty of this evidence was very low (Analysis 2.5.1 (5 studies, 180 participants): MD 1.09%, 95% CI -2.19 to 4.37, I^2 = 96%). There was a high level of heterogeneity in this analysis.
- Eleven studies reported end of study or change in ESA dose. IV iron probably leads to a reduction in ESA dose compared with oral iron (low certainty evidence) (Analysis 2.6 (11 studies, 522 participants): SMD -0.72, 95% CI -1.12 to -0.31) with a high level of heterogeneity (I^2 = 77%).
- IV iron compared with oral iron may make little or no difference to eGFR at the end of study (low certainty evidence) (Analysis 2.7 (8 studies,1052 participants): MD 0.83 mL/min, 95% CI -0.79 to 2.44). There was low to moderate heterogeneity (I^2 = 38%).
- The certainty of the evidence was downgraded because of high risk of bias, inconsistency, imprecision and possible publication bias.

See Summary of findings 2.

Adverse effects

18 studies provided some information on adverse effects of therapy.

- IV iron compared with oral iron may increase the numbers of participants, who experience allergic reactions or hypotension (low certainty evidence) (Analysis 1.6.1 (15 studies, 2607 participants): RR 3.56, 95% CI 1.88 to 6.74; I^2 = 0%). The absolute risk for allergic reactions/hypotension was 24 per 1000 with IV iron and 7 per 1000 with oral iron.
- Only four studies reported data on infection. The most commonly reported infections were respiratory and urinary tract infections. IV iron compared with oral iron may make little or no difference to the risk of infection (low certainty evidence) (Analysis 1.6.2 (4 studies, 954 participants): RR 1.32, 95% CI 0.90 to 1.95; I^2 = 2%).
- IV iron compared with oral iron may be associated with fewer participants with all gastrointestinal adverse effects (low certainty evidence) (Analysis 1.6.3 (14 studies, 1986 participants): RR 0.47, 95% CI 0.33 to 0.66; I^2 = 63%), fewer participants with constipation (Analysis 1.6.4 (10 studies, 1618 participants): RR 0.32, 95% CI 0.18 to 0.57; I^2 = 19%) and possibly with diarrhoea (Analysis 1.6.5 (10 studies, 1625 participants): RR 0.70, 95% CI 0.47 to 1.05; I^2 = 0%). The absolute risk of all gastrointestinal adverse effects was 150 per 1000 with IV iron and 319 per 1000 with oral iron.
- Only three studies reported data on iron overload. Each of these studies defined iron overload as ferritin levels > 800 ng/mL. IV iron compared with oral iron may make little or no difference to the risk of iron overload (low certainty evidence) (Analysis 1.6.8 (3 studies, 158 participants): RR 6.58, 95% CI 0.81 to 53.51; I^2 = 0%).

See Summary of findings for the main comparison.

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 Hb, ferritin and TSAT. These values were chosen based on tertiles of doses investigated in the included studies. Results for the outcomes of Hb, ferritin and TSAT are shown as SMD in Table 2; Table 3 and Table 4 respectively.

There were no significant differences in total dose administered of IV iron or of IV iron/month between subgroups for Hb or TSAT. There was a significant difference found in the SMD for ferritin in the doses

of IV iron per month, though the relationship did not appear to be linear (P = 0.02); there was no difference in ferritin levels with increasing total IV iron dose.

There were no significant differences in total oral iron dose or oral iron/month dose for Hb between subgroups for Hb or TSAT. There was a significant difference found in the SMD for ferritin in the dose of oral iron per month but not with total oral iron dose.

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 2; Table 3; Table 4).

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 Hb, ferritin and TSAT levels in patients who did or did not receive an ESA 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 2; Table 3; Table 4).

Other subgroup analyses

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

Pharmaceutical company sponsorship previously showed some association with a lower mean reported Hb. With additional data in this updated review, no significant association could be demonstrated (Table 2). There were no significant differences for ferritin or TSAT levels (Table 3; Table 4).

DISCUSSION

Summary of main results

This review included 39 studies which compared IV iron with oral iron therapy in patients with CKD. Eleven studies were added to the original review; one paediatric study was terminated and provided no outcome data. There was considerable variability among studies in the total dose and duration of IV and oral iron therapies prescribed. Durations of studies ranged from 35 days to 26 months with only 14 studies having durations greater than four months. The doses/month of iron ranged from 200 mg to 1000 mg for IV iron and 840 mg to 10,500 mg for oral iron. 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 Hb within a target range.

Patient-centred outcomes such as death (all causes) (11 studies), cardiovascular death (three studies), and quality of life (five studies) were rarely reported with studies concentrating on surrogate laboratory outcomes. While no differences overall in these outcomes were detected between treatment groups, the data available were limited and of low quality (GRADE) so we have low certainty evidence that IV iron compared with oral iron makes little or no difference to these outcomes.

Compared with oral iron, IV iron increased levels of Hb (31 studies), serum ferritin (33 studies) and TSAT (27 studies). The final weighted mean increase with IV iron compared with oral iron was 0.72 g/dL in Hb, 225 µg/L in ferritin and 8% in TSAT. The proportion of patients who reached the targeted Hb or increased their Hb by 1 g/dL was 71% higher among those treated with IV iron compared with oral iron. Increases in these outcomes were seen in dialysis and non-dialysis participants (Table 1). The required ESA dose was reduced in patients treated with IV iron compared with oral iron, but was reported in only 11 studies involving 522 participants. eGFR did not decline more rapidly with IV iron compared with oral iron. However, the quality of the evidence (GRADE) was considered low for all outcomes indicating that we have low certainty evidence to support the findings above.

Adverse effects were reported in 18 studies. Gastrointestinal adverse effects were more common with oral iron while allergic reactions and/or hypotension were more common with IV iron. However, the quality of the evidence (GRADE) was considered low indicating that we have low certainty evidence to support these findings.

There was considerable heterogeneity between studies so that subgroup analyses using meta-regression was carried out to investigate possible reasons for this heterogeneity. Subgroup analyses investigated the effect of different monthly and total doses of oral or IV iron, different uses of ESA, CKD stage, and different durations of treatment on Hb, ferritin and transferrin levels. Other than an increase in ferritin levels with increasing IV and oral iron per month, no differences were found in these analyses. Comparing the results of these subgroup analyses with those in the initial version of this systematic review, no increase in Hb SMD with increased oral iron dose/month could now be demonstrated. There was no longer a significant increase in ferritin levels with total IV or oral iron dose. The additional data from newly identified studies showed that studies sponsored by pharmaceutical companies were no longer associated with a significantly lower increase in MD in Hb compared with studies that did not report sponsorship. 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.

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 that there are probably small increases in laboratory parameters of Hb, ferritin and transferrin in both dialysis and non-dialysis patients though the certainty of the evidence was low. However, key patient-centred outcomes were reported in only a few studies so we were unable to make definitive conclusions about the influence of IV iron compared with oral iron therapy on death (all causes), cardiovascular death, morbidity, or on quality of life. This review confirmed that gastrointestinal disorders are found to be more common in patients taking oral iron while hypotension and allergic reactions are more common in patients receiving IV iron. Although ESA dose was probably lower in patients treated with IV iron, only 11 studies (522 participants) reported on ESA dosage at the end of the study and all studies providing these data were in dialysis patients.

The observed Hb increase of 1.01 g/dL in dialysis patients, together with a significant reduction in ESA dose, provides some support for

the practice of administering IV iron to these patients, particularly among those unable to tolerate oral iron. However, studies have identified that high Hb levels achieved with IV iron and ESA are associated with increased cardiovascular death and morbidity (Phrommintikul 2007).

The Hb increase in non-dialysis patients was modest (0.41 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 Hb levels outweighed financial costs or disruption to patients not on dialysis as a result of additional or prolonged hospital visits. While three further large studies (Agarwal 2015 CKD; FIND-CKD 2014 CKD; Kalra 2016 CKD) in CKD patients assessed quality of life, none identified improved quality of life with the higher Hb associated with IV iron therapy so that only one of five studies, which assessed quality of life, identified some improvement in quality of life in non-dialysis patients receiving IV iron (Agarwal 2006 CKD). A systematic review of RCTs identified no significant benefit on quality of life of higher Hb levels achieved with ESAs and iron supplements in CKD patients (Collister 2016).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 few studies were 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 39 studies, which involved 3852 participants. Twenty-one studies enrolled dialysis patients, two involved transplant patients, two enrolled dialysis and non-dialysis patients and the remainder enrolled CKD patients. There was considerable variation among studies in dose and duration of IV and oral iron administration.

Of the 39 included studies, 12 were available only as abstracts. Twenty studies reported adequate random sequence generation while only 14 studies demonstrated adequate allocation concealment. Studies that lack adequate allocation concealment are considered to be at increased risk of bias (Moyer 1998; Schultz 1995). Blinding of participants and personnel was not reported in any study. No study reported blinding of outcome assessment, but because primary outcomes were laboratory measurements and unlikely to be influenced by lack of blinding, all studies were considered to be at low risk of bias for blinding of outcome assessment. Twenty-two studies reported complete outcome data while 20 studies were at low risk of selective reporting. The authors of 15 included studies indicated receiving some form of sponsorship from pharmaceutical companies.

Although administration of IV iron consistently resulted in an increase in Hb or HCT, 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 certainty of the evidence for patient centred outcomes was considered low or very low because of small patient numbers included in these analyses and high risk or unclear risk of bias for allocation concealment in many studies (Summary of findings for the main comparison). Similarly the certainty of the evidence for laboratory and pharmaceutical outcomes was considered to be low or very low because of considerable heterogeneity in study results and the high or unclear risk for allocation concealment in many studies (Summary of findings 2).

Potential biases in the review process

The literature search has been run several times (up to December 2018) since the publication of the original review in 2012 to reduce the likelihood that additional studies eligible for inclusion were missed. Although the Cochrane Kidney and Transplant Specialised Register also includes references of reports of studies identified by handsearching resources including conference proceedings, it is a possibility that relevant studies may have been missed.

The relatively high proportion of included studies that were available only as abstracts (12/39; 31%) is a potential source of bias as abstracts may not contain complete results or provide detailed information on risk of bias attributes. To address reporting gaps in studies, we contacted authors to seek additional information. Responses from nine study authors were received but information received related principally to risk of bias attributes. In this update, we only identified the full publication of one study (Qunibi 2011 CKD) previously included as an abstract. A large completed RCT (Lu 2010 CKD) comparing IV ferumoxytol with oral iron enrolled 519 participants but has only been published in abstract form in combination with other similar studies.

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 only 11 studies (522 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 18 (46%) 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). This systematic review was updated to October 2015 and included 24 RCTs (Shepshelovich 2016). Our updated review includes 22 of the 24 studies included by Shepshelovich 2016. We excluded one study included in the 2008 systematic review and one included in the 2015 review because they included both randomised and non-randomised data (Allegra 1991; Adhikary 2011). Shepshelovich 2016 identified 13 studies involving CKD participants and 11 studies involving dialysis patients. Both reviews reported similar increases in mean Hb, ferritin, TSAT and the proportion of participants achieving an increase in Hb in patients treated with IV iron compared with oral iron. In their initial systematic review, Rozen-Zvi 2008 demonstrated a significant correlation between Hb and IV iron dose/month in dialysis patients but not non-dialysis patients. We were unable to demonstrate an overall correlation or a correlation

in dialysis patients alone in our 2012 review or in this update. Both reviews reported considerable heterogeneity for the outcomes of Hb, ferritin and TSAT concentrations which could not be explained. A systematic review of 103 RCTs has evaluated the safety of IV iron compared with oral iron, no iron, placebo or intramuscular iron (Avni 2015). The review found no increase in overall serious adverse effects with IV iron. As in this review, the authors found that serious infusion reactions were more common and gastrointestinal adverse reactions were less common with IV iron, while there was no increase in infections with IV iron. Another systematic review (Susantitaphong 2014) included 34 single-arm and RCTs evaluating IV iron in HD patients with relative or functional iron deficiency as defined by ferritin levels > 200 ± TSAT < 30%; studies of patients with absolute iron deficiency were excluded. Therefore only one study (Provenzano 2009 HD) included in our review was also included in that review. The review also concluded that IV iron resulted in increases in Hb, ferritin and TSAT and reductions in ESA dose though the changes were less evident in RCTs compared with single arm studies.

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 Hb. Limited patient-centred outcomes data (death, 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.

While this update identified a few more studies, which addressed patient-centred outcomes, including adverse effects, to determine if benefits exceed harms for all patients with CKD, only 11 studies reported on death (all causes), three reported on cardiovascular death and five reported on quality of life. However, because of small number of studies reporting these outcomes and low quality of evidence, the relative effects of different iron regimens on these patient-centred outcomes remain uncertain. More studies reported on allergic reactions/hypotension (14 studies) and gastrointestinal adverse effects (13 studies), While gastrointestinal adverse effects with oral iron are common with oral iron, these effects must be balanced against the rare, but potentially life threatening adverse effects seen with IV iron.

There are now additional large studies examining IV and oral iron in CKD participants with longer follow up periods. These confirm that IV iron compared with oral iron in CKD participants increases laboratory indices compared with oral iron, increases the number achieving target Hb without changing the rate of decline in kidney function. However, there are still no studies, which have assessed whether these benefits outweigh the disadvantages of increased numbers and durations of hospital visits for treatment.

Implications for research

Further large RCTs with longer durations of treatment and follow-up periods are still required. These need to assess patient-centred outcomes including death (all causes), cardiovascular death, cardiac morbidity using cardiac function tests, hospitalisations, 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. The doses of oral and IV iron should be standardised across studies in an effort to reduce the heterogeneity seen in this systematic review.

ACKNOWLEDGEMENTS

- We would like to thank the referees for their comments and feedback during the preparation of this review update.
- We would like to thank Drs Broumand, Fudin, Macdougall, Provenzano, Richardson, Spinowitz, Van Wyck and Warady, and Ms Dahl, for their responses to our queries about their studies.
- We would like to thank Dr Jumana Albaramki, who carried out all the steps in the original version of this review
- We would like to thank Dr Melani Mahendran for her help in obtaining the data for Figure 1

REFERENCES

References to studies included in this review

Agarwal 2006 CKD *{published and unpublished data}*

Agarwal R. Sodium ferric gluconate complex in sucrose (SFGC) injection improves energy level in chronic kidney disease (CKD) patients independent of increase in hemoglobin levels [abstract no: F-PO337]. *Journal of the American Society of Nephrology* 2004;**15**(Oct):140A. [CENTRAL: CN-01657325]

* Agarwal R, Rizkala AR, Bastani B, Kaskas MO, Leehey DJ, Besarab A. A randomized controlled trial of oral versus intravenous iron in chronic kidney disease. *American Journal of Nephrology* 2006;**26**(5):445-54. [MEDLINE: 17035697]

Agarwal 2015 CKD *{published data only}*

Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. *Kidney International* 2015;**88**(4):905-14. [DOI: 10.1038/ki.2015.163; MEDLINE: 26083656]

Aggarwal 2003 CKD *{published data only}*

Aggarwal HK, Kumar H, Singh S, Nand N. Iron therapy in patients of CRF receiving recombinant human EPO which route of iron? [abstract]. *Indian Journal of Nephrology* 2002;**12**(4):205. [CENTRAL: CN-00460253]

* Aggarwal HK, Nand N, Singh S, Singh M, Hemant, Kaushik G. Comparison of oral versus intravenous iron therapy in predialysis patients of chronic renal failure receiving recombinant human erythropoietin. *Journal of the Association of Physicians of India* 2003;**51**:170-4. [MEDLINE: 12725261]

Aggarwal SH, Hemant K, Singh S, Nand N, Sharma BD. Comparison of oral versus intravenous iron therapy in patients of chronic renal failure receiving recombined human erythropoietin (R-HUEPO) [abstract no: 56]. *Journal of the Association of Physicians of India* 2001;**50**(Oct). [CENTRAL: CN-00663209]

Ahsan 1997 TX *{published data only}*

* Ahsan N, Holman MJ, O'Brien B, Langhoff EG, Yang HC. Intravenous infusion of total is superior to oral iron in the treatment of post-kidney transplant functional anemia [abstract no: A3131]. *Journal of the American Society of Nephrology* 1997;**8**(Program & Abstracts):672A. [CENTRAL: CN-00676050]

Broumand 1998 HD *{published and unpublished data}*

Broumand B, Ghods A, Taheri FM, Hanjani MR. Intravenous versus oral iron supplementation in the management of anemia in end stage renal disease [abstract]. 35th Congress. European Renal Association. European Dialysis and Transplantation Association; 1998 Jun 6-9; Rimini, Italy. 1998:330. [CENTRAL: CN-00483339]

Charytan 2005 CKD *{published data only}*

* Charytan C, Qunibi W, Bailie GR, Venofer Clinical Studies Group. Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. *Nephron* 2005;**100**(3):c55-62. [MEDLINE: 15824508]

Charytan C, Qunibi W, Singh H, Schwenk M, Aronoff G, Besarab A. Safety of Venofer®, [iron sucrose injection] administered by rapid IV push (IVP) in predialysis CKD patients [abstract no: SU-PO260]. *Journal of the American Society of Nephrology* 2002;**13**(September, Program & Abstracts):521a. [CENTRAL: CN-00444759]

Erten 1998 HD *{published data only}*

* Erten Y, Ozdemir FN, Guz G, Sezer S, Haberal A, Kaya S, et al. Comparison of the effect of intravenous and oral iron therapies on hemodialysis patients [abstract no: M384]. *Journal of the American Society of Nephrology* 1998;**9**(Program & Abstracts):248A. [CENTRAL: CN-01657553]

Erten Y, Ozdemir FN, Guz G, Sezer S, Haberal A, Kaya S, et al. Comparison of the effect of intravenous and oral iron therapies on hemodialysis patients [abstract]. 35th Congress. European Renal Association. European Dialysis and Transplantation Association; 1998 Jun 6-9; Rimini, Italy. 1998:337. [CENTRAL: CN-00445251]

FIND-CKD 2014 CKD *{published data only}*

Gaillard CA, Bock AH, Carrera F, Eckardt K, Van Wyck DB, Bansal SS, et al. Hepcidin response to intravenous (IV) or oral iron in the randomized FIND-CKD trial of patients with non-dialysis CKD (ND-CKD) [abstract no: TH-OR040]. *Journal of the American Society of Nephrology* 2015;**26**(Abstract Suppl):11A.

Gaillard CA, Bock AH, Carrera F, Eckardt KU, Van Wyck DB, Bansal SS, et al. Hepcidin response to iron therapy in patients with non-dialysis dependent CKD: an analysis of the FIND-CKD trial. *PLoS ONE [Electronic Resource]* 2016;**11**(6):e0157063. [MEDLINE: 27276035]

Macdougall I, Bock AH, Carrera F, Eckardt KU, Gaillard CA, Van Wyck DB, et al. A model to predict haematopoietic non-response to oral iron in patients with non-dialysis dependent CKD (ND-CKD): an analysis from the FIND-CKD trial [abstract]. *Nephrology Dialysis Transplantation* 2016;**31**(Suppl 1):i193-4. [EMBASE: 72326413]

Macdougall IC, Bock A, Carrera F, Cushway T, Mori C, Roger S. Rationale and design of a new RCT of iron therapy in anemic non-dialysis CKD patients: FIND-CKD trial [abstract no: SA-PO2402]. *Journal of the American Society of Nephrology* 2009;**20**(Abstract Suppl):660A.

Macdougall IC, Bock A, Carrera F, Eckardt KU, Gaillard C, Van Wyck D, et al. The FIND-CKD study--a randomized controlled trial of intravenous iron versus oral iron in non-dialysis chronic kidney disease patients: background and rationale. *Nephrology Dialysis Transplantation* 2014;**29**(4):843-50. [MEDLINE: 24170814]

Macdougall IC, Bock A, Carrera F, Eckardt KU, Gaillard C, Van Wyck DB, et al. FIND-CKD: a 56-week randomized trial of intravenous ferric carboxymaltose versus oral iron in anemic patients with chronic kidney disease and iron deficiency [abstract no: SA-PO1079]. *Journal of the American Society of Nephrology* 2013;**24**(Abstracts):3B.

Macdougall IC, Bock A, Carrera F, Eckardt KU, Gaillard C, Van Wyck DB, et al. Intravenous ferric carboxymaltose vs oral iron in anaemic patients with non-dialysis dependent chronic kidney disease and iron deficiency: results of the randomised FIND-CKD study [abstract no: SO049]. *Nephrology Dialysis Transplantation* 2014;**27**(Suppl 3):ii21.

Macdougall IC, Bock AH, Carrera F, Eckardt K, Gaillard C, Van Wyck D, et al. Efficacy of oral iron for treating iron deficiency in anaemic patients with non-dialysis dependent CKD (ND-CKD) [abstract]. *Nephrology Dialysis Transplantation* 2017;**32**(Suppl 3):iii581. [EMBASE: 617290898]

Macdougall IC, Bock AH, Carrera F, Eckardt K, Gaillard CA, Van Wyck DB, et al. Iron administration to non-dialysis CKD patients for one year does not cause worsening of renal function: results from the FIND-CKD trial [abstract no: FR-PO809]. *Journal of the American Society of Nephrology* 2014;**25**(Abstract Suppl):555A.

Macdougall IC, Bock AH, Carrera F, Eckardt KU, Gaillard C, Van Wyck D, et al. Erythropoietic response to oral iron in patients with nondialysis-dependent chronic kidney disease in the FIND-CKD trial. *Clinical Nephrology* 2017;**88**(12):301-10. [MEDLINE: 29092739]

* Macdougall IC, Bock AH, Carrera F, Eckardt KU, Gaillard C, Van Wyck D, et al. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. *Nephrology Dialysis Transplantation* 2014;**29**(11):2075-84. [MEDLINE: 24891437]

Macdougall IC, Bock AH, Carrera F, Eckardt KU, Gaillard C, Van Wyck D, et al. Renal function in patients with non-dialysis chronic kidney disease receiving intravenous ferric carboxymaltose: an analysis of the randomized FIND-CKD trial. *BMC Nephrology* 2017;**18**(1):24. [MEDLINE: 28095881]

Macdougall IC, Bock AH, Carrera F, Eckardt KU, Gaillard CA, Van Wyck DB, et al. Hepcidin response to iron therapy in patients with non-dialysis CKD: an analysis of the FIND-CKD trial [abstract]. *Nephrology Dialysis Transplantation* 2015;**30**(Suppl 3):iii8-9. [EMBASE: 72206297]

Macdougall IC, Bock AH, Carrera F, Eckardt KU, Gaillard CA, Van Wyck DB, et al. Low rate of early response to oral iron in patients with non-dialysis dependent CKD (ND-CKD) [abstract no: TH-PO906]. *Journal of the American Society of Nephrology* 2016;**27**(Abstract Suppl):304A.

Roger S, Bock AH, Carrera F, Eckardt K, Gaillard CA, Van Wyck DB, et al. The safety of intravenous (IV) ferric carboxymaltose (FCM) in patients with non-dialysis dependent CKD (ND-CKD): 1-year results from the FIND-CKD trial [abstract]. *Nephrology Dialysis Transplantation* 2016;**31**(Suppl 1):i15-6. [EMBASE: 72325953]

Roger SD, Bock A, Carrera F, Eckardt KU, Gaillard C, Van Wyck DB, et al. IV ferric carboxymaltose (FCM) is a convenient and well-tolerated first-line therapy for the treatment of anaemia in patients with iron deficiency and non-dialysis dependent chronic kidney disease (ND-CKD): results of the randomised FIND-CKD study [abstract no: SO048]. *Nephrology Dialysis Transplantation* 2014;**27**(Suppl 3):ii21.

Roger SD, Bock AH, Carrera F, Eckardt KU, Gaillard CA, Van Wyck DB, et al. Intravenous (IV) ferric carboxymaltose (FCM) versus oral iron in the randomized FIND-CKD trial of patients with non-dialysis dependant CKD (ND-CKD): a safety analysis [abstract no: TH-PO652]. *Journal of the American Society of Nephrology* 2015;**26**(Abstract Suppl):238A.

Fishbane 1995 HD *{published data only}*

* Fishbane S, Frei GL, Maesaka J. Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. *American Journal of Kidney Diseases* 1995;**26**(1):41-6. [MEDLINE: 7611266]

Fudin 1998 HD *{published and unpublished data}*

* Fudin R, Jaichenko J, Shostak A, Bennett M, Gotloib L. Correction of uremic iron deficiency anemia in hemodialyzed patients: a prospective study. *Nephron* 1998;**79**(3):299-305. [MEDLINE: 9678430]

Hussain 1998 HD *{published data only}*

* Hussain R, Chishti SH, Naqvi S. Experience of iron saccharate supplementation in haemodialysis patients treated with erythropoietin. *Nephrology* 1998;**4**(1-2):105-8. [EMBASE: 1998205059]

Hussain R, Chishti SH, Naqvi SA. Experience of iron sucrose supplementation in haemodialysis patients treated with erythropoietin [abstract]. 3rd International Congress of Nephrology, Urology & Transplantation Society of SAARC Countries; 1999 Feb 18-21; Colombo, Sri Lanka. 1999:152. [CENTRAL: CN-00460975]

Kalra 2016 CKD *{published data only}*

Kalra PA, Bhandari S, Saxena S, Agarwal D, Wirtz G, Kletzmayr J, et al. A randomized trial of iron isomaltoside 1000 versus oral iron in non-dialysis-dependent chronic kidney disease patients with anaemia. *Nephrology Dialysis Transplantation* 2016;**31**(4):646-55. [MEDLINE: 26250435]

Kalra PA, Bhandari S, Thomsen LL. Iron isomaltoside 1000 (monofer) compared to oral iron sulphate in European patients with non-dialysis dependent chronic kidney disease (NDD-CKD) [abstract]. *Nephrology Dialysis Transplantation* 2015;**30**(Suppl 3):iii200. [EMBASE: 72206812]

Kalra PA, Bhandari S, Thomsen LL. Iron isomaltoside1000 (monofer) compared to oral iron sulphate in patients with non-dialysis dependent chronic kidney disease (NDD-CKD) [abstract no: SA-PO1106]. *Journal of the American Society of Nephrology* 2014;**25**(Abstract Suppl):B7.

Kotaki 1997 HD *{published data only}*

Kotaki M, Uday K, Henriquez M, Blum S, Dave M. Intravenous iron therapy in hemodialysis [abstract no: A1021]. *Journal of the American Society of Nephrology* 1996;**7**(9):1452. [CENTRAL: CN-01657494]

* Kotaki M, Uday K, Henriquez M, Blum S, Dave M. Maintenance therapy with intravenous iron in hemodialysis patients receiving erythropoietin. *Clinical Nephrology* 1997;**48**(1):63-4. [MEDLINE: 9247787]

Leehey 2005 CKD *{published and unpublished data}*

* Leehey DJ, Kaskas MO, Bastani B, Ferrlecit CKD Study Group. Sodium ferric gluconate complex (SFGC) in the treatment of chronic kidney disease (CKD) patients on stable erythropoietic therapy [abstract no: F-PO966]. *Journal of the American Society of Nephrology* 2005;**16**:547A. [CENTRAL: CN-00747316]

Li 2008 HD *{published data only}*

* Li H, Wang SX. Intravenous iron sucrose in Chinese hemodialysis patients with renal anemia. *Blood Purification* 2008;**26**(2):151-6. [MEDLINE: 18212498]

Li H, Wang SX. Intravenous iron sucrose in maintenance dialysis patients with renal anemia: a clinical study. *Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal]* 2009;**89**(7):457-62. [MEDLINE: 19567093]

Li 2008 PD *{published data only}*

Li H, Wang SX. Intravenous iron sucrose in maintenance dialysis patients with renal anemia: a clinical study. *Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal]* 2009;**89**(7):457-62. [MEDLINE: 19567093]

* Li H, Wang SX. Intravenous iron sucrose in peritoneal dialysis patients with renal anemia. *Peritoneal Dialysis International* 2008;**28**(2):149-54. [MEDLINE: 18332450]

Lu 2010 CKD *{published and unpublished data}*

Besarab A, Coyne D, Bolton WK, Sharma A, Foti A, Brenner L. Ferumoxytol as an intravenous iron replacement therapy: safety results from two phase III studies in subjects with chronic kidney disease (CKD) [abstract no: SU-PO0805]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):762A. [CENTRAL: CN-00747286]

Bolton WK, Besarab A, Germain M, Kovesdy CP, Hutchinson J, Krausz A. Ferumoxytol as an IV iron replacement therapy: efficacy results from two Phase III studies in subjects with chronic kidney disease (CKD) [abstract no: SU-PO798]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):761A. [CENTRAL: CN-00747287]

Bolton WK, Fishbane S, Li J, Milich L, Brenner R. Increases in hemoglobin and the effect of ESA use in CKD patients treated with IV ferumoxytol [abstract]. *American Journal of Kidney Diseases* 2009;**53**(4):A30. [EMBASE: 70141518]

Fishbane S, Bolton WK, Winkelmayer WC, Strauss W, Li Z, Pereira BJ. Factors affecting response and tolerability to ferumoxytol in nondialysis chronic kidney disease patients. *Clinical Nephrology* 2012;**78**(3):181-8. [MEDLINE: 22874106]

Germain M, Brenner L, Dioguardi J, Gilbertson D, Besarab A. Comparison of safety and efficacy of ferumoxytol in CKD subtypes: kidney transplant recipients, hemodialysis patients and non-hemodialysis patients [abstract no: SA-PO2530]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):678A. [CENTRAL: CN-00747289]

Lu M, Cohen MH, Rieves D, Pazdur R. FDA report: Ferumoxytol for intravenous iron therapy in adult patients with chronic kidney disease. *American Journal of Hematology* 2010;**85**(5):315-9. [MEDLINE: 20201089]

Spinowitz B, Besarab A, Bolton WK, Pereira BJ, Provenzano R, Rao M, et al. Ferumoxytol as intravenous iron replacement therapy in chronic kidney disease (CKD) patients not on dialysis - evaluation of safety and efficacy in two phase III studies [abstract no: F-PO026]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):342A. [CENTRAL: CN-00644267]

Spinowitz B, Kausz A, Miller P, Brenner L, Singh A. Achievement of target hemoglobin with ferumoxytol versus oral iron in anemic CKD patients [abstract no: SU-PO1031]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):814A. [CENTRAL: CN-00688845]

Spinowitz B, Krauz A, Dioguardi J, Kovesdy C. Evaluation of ferumoxytol safety and efficacy in all stages of chronic kidney disease (CKD) [abstract no: 249]. *American Journal of Kidney Diseases* 2008;**51**(4):A90. [CENTRAL: CN-00747323]

Lye 2000 HD *{published data only}*

* Lye WC. Ferric gluconate polymaltose complex (Ferrum) is safe and effective for intravenous use in hemodialysis (HD) patients [abstract no: A1489]. *Journal of the American Society of Nephrology* 2000;**11**(Sept):284A.

Macdougall 1996 HD,PD,CKD *{published and unpublished data}*

Macdougall IC, Tucker B, Thompson J, Baker IR, Raine AE. A randomised controlled study of iron supplementation in patients treated with erythropoietin [abstract]. *Journal of the American Society of Nephrology* 1993;**4**(Program & Abstracts):428. [CENTRAL: CN-00484929]

* Macdougall IC, Tucker B, Thompson J, Tomson CR, Baker LR, Raine AE. A randomized controlled study of iron supplementation in patients treated with erythropoietin. *Kidney International* 1996;**50**(5):1694-9. [MEDLINE: 8914038]

Macdougall IC, Tucker B, Thompson J, Tomson CR, Baker LR, Raine AE. Randomised controlled study of iron supplementation in patients treated with erythropoietin [abstract]. *Nephrology Dialysis Transplantation* 1993;**8**(12):1424. [CENTRAL: CN-00260914]

Macdougall IC, Tucker B, Thompson J, Tomson CRV, Baker LR, Raine AE. Randomised controlled study of iron supplementation in patients treated with erythropoietin [abstract]. *Nephrology Dialysis Transplantation* 1993;**8**(9):960. [CENTRAL: CN-01657602]

Macdougall 1999 HD,PD *{published data only}*

* Macdougall IC, UK Multicentre IV Iron Study Group. UK multicentre randomized controlled study of IV vs oral iron supplementation in dialysis patients receiving epoetin [abstract no: A1472]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):291A. [CENTRAL: CN-00747320]

McMahon 2009 CKD *{published data only}*

McMahon L, Kent AB, Roger S, Kerr P, Healy H, Irish A, et al. IV iron sucrose versus oral iron for the anaemia of chronic kidney disease (CKD) - a randomized controlled trial [abstract no: O82]. *Nephrology* 2008;**13**(Suppl 3):A120. [CENTRAL: CN-00747281]

* McMahon LP, Kent AB, Kerr PG, Healy H, Irish AB, Cooper B, et al. Maintenance of elevated versus physiological iron

indices in non-anaemic patients with chronic kidney disease: a randomized controlled trial. *Nephrology Dialysis Transplantation* 2010;**25**(3):920-6. [MEDLINE: 19906658]

McMahon LP, Kent AB, Roger SD, Kerr PG, Healy H, Irish AB, et al. IV iron sucrose versus oral iron for the anemia of chronic kidney disease (CKD) - a randomized controlled trial [abstract no: SU-PO1028]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):813A. [CENTRAL: CN-00690668]

Michael 2007 HD *{published data only}*

* Michael B, Trout JR, Hoel G, Volinn W, Jorgensen N, Dahl NV, et al. Effectiveness of continuous low-dose intravenous ferric gluconate therapy for maintaining Hgb and decreasing epoetin requirements in hemodialysis patients [abstract no: F-PO849]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):289A. [CENTRAL: CN-00689934]

Mudge 2009 TX *{published data only}*

Mudge DW, Tan K, Miles R, Johnson DW, Campbell SB, Hawley CM, et al. Intravenous versus oral iron for post-transplant anaemia: a randomised controlled trial [abstract no: 149]. *Transplantation* 2010;**90**(Suppl 1):679. [EMBASE: 71532404]

* Mudge DW, Tan KS, Miles R, Johnson DW, Badve SV, Campbell SB, et al. A randomized controlled trial of intravenous or oral iron for posttransplant anemia in kidney transplantation. *Transplantation* 2012;**93**(8):822-6. [MEDLINE: 22290270]

Mudge DW, Tan KS, Miles R, Johnson DW, Campbell SB, Hawley CM, et al. Intravenous versus oral iron supplementation for correction of post-transplant anaemia in renal transplant patients. *BMC Nephrology* 2009;**10**:14. [MEDLINE: 19500381]

Nagaraju 2013 CKD *{published data only}*

Nagaraju SP, Cohn A, Akbari A, Davis JL, Zimmerman DL. Heme iron polypeptide for the treatment of iron deficiency anemia in non-dialysis chronic kidney disease patients: a randomized controlled trial. *BMC Nephrology* 2013;**14**:64. [MEDLINE: 23514036]

NCT01155375 HD,PD,CKD *{published data only}*

Strauss MD. A randomized, open-label, active-controlled study of the safety, efficacy, and pharmacokinetics of ferumoxytol compared with oral iron for the treatment of iron deficiency anemia in pediatric subjects with chronic kidney disease. www.clinicaltrials.gov/ct2/show/NCT01155375 (first received 1 July 2010).

Pisani 2014 CKD *{published data only}*

* Pisani A, Riccio E, Sabbatini M, Andreucci M, Del Rio A, Visciano B. Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: a randomized trial. *Nephrology Dialysis Transplantation* 2014;**30**(4):645-52. [MEDLINE: 25395392]

Visciano B, Nazzaro P, Riccio E, Del Rio A, Mozzillo GR, Pisani A. Liposomial iron for the treatment of iron deficiency anemia in non dialysis chronic kidney disease patients: a randomized controlled trial [abstract]. *Nephrology Dialysis Transplantation* 2014;**29**(5 Suppl 3):iii141-2. [EMBASE: 71491842]

Visciano B, Nazzaro P, Tarantino G, Taddei A, Del Rio A, Mozzillo GR, et al. Liposomial iron: a new proposal for the treatment of anaemia in chronic kidney disease [Il ferro liposomiale: una nuova proposta per il trattamento dell'anemia nei pazienti affetti da insufficenza renale cronica]. *Giornale Italiano di Nefrologia* 2013;**30**(5). [MEDLINE: 24402627]

Provenzano 2009 HD *{published and unpublished data}*

Germain M, Brenner L, Dioguardi J, Gilbertson D, Besarab A. Comparison of safety and efficacy of ferumoxytol in CKD subtypes: kidney transplant recipients, hemodialysis patients and non-hemodialysis patients [abstract no: SA-PO2530]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):678A. [CENTRAL: CN-00747289]

Lu M, Cohen MH, Rieves D, Pazdur R. FDA report. Ferumoxytol for intravenous iron therapy in adult patients with chronic kidney disease. *American Journal of Hematology* 2010;**85**(5):315-9. [MEDLINE: 20201089]

* Provenzano R, Schiller B, Rao M, Coyne D, Brenner L, Pereira BJ. Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. *Clinical Journal of the American Society of Nephrology: CJASN* 2009;**4**(2):386-93. [MEDLINE: 19176796]

Spinowitz B, Krauz A, Dioguardi J, Kovesdy C. Evaluation of ferumoxytol safety and efficacy in all stages of chronic kidney disease (CKD) [abstract no: 249]. *American Journal of Kidney Diseases* 2008;**51**(4):A90. [CENTRAL: CN-00688845]

Qunibi 2011 CKD *{published data only}*

Benjamin J. A randomized controlled trial comparing IV ferric carboxymaltose (FCM) to oral iron in anemic nondialysis dependent CKD patients (with or without erythropoiesis stimulating agent use) [abstract no: M574]. World Congress of Nephrology; 2009 May 22-26; Milan, Italy. 2009. [CENTRAL: CN-01658222]

Benjamin J, Qunibi W. Comparison of intravenous (IV) ferric carboxymaltose (FCM) to oral iron in anemic non-dialysis dependent (NDD)-CKD patients with or without ESA therapy [abstract no: SA-PO2422]. *Journal of the American Society of Nephrology* 2009;**20**(Abstract Suppl):666A.

Qunibi W, Martinez C, Smith M, Benjamin J, Dinh Q. A randomized controlled trial comparing IV ferric carboxymaltose (FCM) to oral iron in anemic patients with non-dialysis-dependent CKD [abstract no: SU-PO1030]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):814A. [CENTRAL: CN-00689191]

* Qunibi WY, Martinez C, Smith M, Benjamin J, Mangione A, Roger SD. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anaemia of non-dialysis-dependent chronic kidney disease patients. *Nephrology Dialysis Transplantation* 2011;**26**(5):1599-607. [MEDLINE: 20929915]

Ragab 2007 HD *{published data only}*

* Ragab M, Mahmoud K, Ragab A. Maintenance intravenous iron sucrose therapy in children under regular hemodialysis. *Journal of Medical Sciences* 2007;**7**(7):1112-6. [EMBASE: 2007615596]

Souza 1997 HD *{published data only}*

* Souza RM, Defferrari R, Karohl C, Barros E, Thome F. Iron status evaluation and iron supplementation therapy in hemodialysis (HD) chronic renal failure (CRF) patients: a randomized clinical trial [abstract]. *Nephrology* 1997;**3**(Suppl 1):S307. [CENTRAL: CN-00461775]

Spinowitz 2008 CKD *{published and unpublished data}*

Besarab A, Coyne D, Bolton WK, Sharma A, Foti A, Brenner L. Ferumoxytol as an intravenous iron replacement therapy: safety results from two phase III studies in subjects with chronic kidney disease (CKD) [abstract no: SU-PO0805]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts issue):762A. [CENTRAL: CN-00747286]

Bolton WK, Besarab A, Germain M, Kovesdy CP, Hutchinson J, Krausz A. Ferumoxytol as an IV iron replacement therapy: efficacy results from two Phase III studies in subjects with chronic kidney disease (CKD) [abstract no: SU-PO798]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):761A. [CENTRAL: CN-00747287]

Bolton WK, Fishbane S, Li J, Milich L, Brenner R. Increases in hemoglobin and the effect of ESA use in CKD patients treated with IV ferumoxytol [abstract]. *American Journal of Kidney Diseases* 2009;**53**(4):A30. [EMBASE: 70141518]

Brenner L, Miller P, Rodriguez S, Parikh N, Coyne DW. Treatment of iron-deficiency anemia with IV ferumoxytol in CKD patients: efficacy compared with oral iron across different age groups [abstract]. *Blood* 2007;**110**(11). [CENTRAL: CN-00646734]

Fishbane S, Bolton WK, Winkelmayer WC, Strauss W, Li Z, Pereira BJ. Factors affecting response and tolerability to ferumoxytol in nondialysis chronic kidney disease patients. *Clinical Nephrology* 2012;**78**(3):181-8. [MEDLINE: 22874106]

Germain M, Brenner L, Dioguardi J, Gilbertson D, Besarab A. Comparison of safety and efficacy of ferumoxytol in CKD subtypes: kidney transplant recipients, hemodialysis patients and non-hemodialysis patients [abstract no: SA-PO2530]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):678A. [CENTRAL: CN-00747289]

Horl WH. Comparing the efficacy of intravenous iron and oral iron in nondialysis patients with chronic kidney disease. *Nature Clinical Practice Nephrology* 2008;**4**(10):530-1. [EMBASE: 2008457134]

Lu M, Cohen MH, Rieves D, Pazdur R. FDA report: Ferumoxytol for intravenous iron therapy in adult patients with chronic kidney disease. *American Journal of Hematology* 2010;**85**(5):315-9. [MEDLINE: 20201089]

Spinowitz B, Bernardo M, Noble S, Baptista J, Pereira B, Brenner L. Safety and efficacy of ferumoxytol as an intravenous iron replacement therapy: results from a phase III study of chronic kidney disease (CKD) patients not on dialysis [abstract no: 30]. *American Journal of Kidney Diseases* 2007;**49**(4):A32. [CENTRAL: CN-00644268]

Spinowitz B, Besarab A, Bolton WK, Pereira BJ, Provenzano R, Rao M, et al. Ferumoxytol as intravenous iron replacement therapy in chronic kidney disease (CKD) patients not on dialysis - evaluation of safety and efficacy in two phase III studies [abstract no: F-PO026]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):342A. [CENTRAL: CN-00644267]

Spinowitz B, Kausz A, Miller P, Brenner L, Singh A. Achievement of target hemoglobin with ferumoxytol versus oral iron in anemic CKD patients [abstract no: SU-PO1031]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):814A. [CENTRAL: CN-00688845]

Spinowitz B, Krauz A, Dioguardi J, Kovesdy C. Evaluation of ferumoxytol safety and efficacy in all stages of chronic kidney disease (CKD) [abstract no: 249]. *American Journal of Kidney Diseases* 2008;**51**(4):A90. [CENTRAL: CN-00747323]

* Spinowitz BS, Kausz AT, Baptista J, Noble SD, Sothinathan R, Bernardo MV, et al. Ferumoxytol for treating iron deficiency anemia in CKD. *Journal of the American Society of Nephrology* 2008;**19**(8):1599-605. [MEDLINE: 18525001]

Stoves 2001 CKD *{published data only}*

* Stoves J, Inglis H, Newstead CG. A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. *Nephrology Dialysis Transplantation* 2001;**16**(5):967-74. [MEDLINE: 11328902]

Strickland 1977 HD *{published data only}*

* Strickland ID, Chaput de Saintonge DM, Boulton FE, Francis B, Roubikova J, Waters JI. The therapeutic equivalence of oral and intravenous iron in renal dialysis patients. *Clinical Nephrology* 1977;**7**(2):55-7. [MEDLINE: 321170]

Svara 1996 HD *{published data only}*

* Svara F, Sulkova S, Kvasnicka J, Polakovic V. Iron supplementation during erythropoietin therapy in patients on hemodialysis [Doplnovani zeleza pri lecbe erytropoetinem u hemodialyzovanych pacientu]. *Vnitrni Lekarstvi* 1996;**42**(12):849-52. [MEDLINE: 9072885]

Tsuchida 2010 HD *{published data only}*

Tsuchida A, Paudyal B, Paudyal P, Ishii Y, Hiromura K, Nojima Y, et al. Effectiveness of oral iron to manage anemia in long-term hemodialysis patients with the use of ultrapure dialysate. *Experimental & Therapeutic Medicine* 2010;**1**(5):777-81. [EMBASE: 2010419867]

Van Wyck 2005 CKD *{published and unpublished data}*

* Van Wyck DB, Roppolo M, Martinez CO, Mazey RM, McMurray S, United States Iron Sucrose (Venofer) Clinical Trials Group. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney International* 2005;**68**(6):2846-56. [MEDLINE: 16316362]

Van Wyck DB, Roppolo M, Martinez CO, McMurray SD, Mazey R. A randomized controlled trial comparing IV iron sucrose to oral iron in anemic patients with non-dialysis-dependent CKD [abstract no: F-FC051]. *Journal of the American Society of Nephrology* 2005;**16**:49A. [CENTRAL: CN-01657327]

Wang 2003 HD *{published data only}*

* Wang L, Li G, Liao C, Wang F. The effects of oral vs venous iron supplement in treatment of iron deficiency of maintained patients with anemia [abstract no: PUB324]. *Journal of the American Society of Nephrology* 2003;**14**(Nov):842A. [CENTRAL: CN-00747318]

Warady 2002 HD *{published and unpublished data}*

* Warady BA, Kausz A, Lerner G, Brewer ED, Chadha V, Brugnara C, et al. Iron therapy in the pediatric hemodialysis population. *Pediatric Nephrology* 2004;**19**(6):655-61. [MEDLINE: 15064942]

Warady BA, Kausz AT, Lerner G, Brewer ED, Chadha V, Brugnara C, et al. A comparison of intravenous and oral iron therapy in children receiving hemodialysis [abstract no: F-PO789]. *Journal of the American Society of Nephrology* 2002;**13**(Program & Abstracts):221A. [CENTRAL: CN-01657600]

Winney 1977 HD *{published data only}*

Winney RJ, Swainson CP, Parker A, Bone JM, Robson JS. Iron therapy in hemodialysis patients: Oral or parenteral? [abstract]. *Kidney International* 1977;**12**(1):88. [CENTRAL: CN-00747346]

References to studies excluded from this review

Adhikary 2011 *{published data only}*

Adhikary L, Acharya S. Efficacy of IV iron compared to oral iron for increment of haemoglobin level in anemic chronic kidney disease patients on erythropoietin therapy. *Jnma, Journal of the Nepal Medical Association* 2011;**51**(183):133-6. [MEDLINE: 22922860]

Allegra 1991 *{published data only}*

Allegra V, Mengozzi G, Vasile A. Iron deficiency in maintenance hemodialysis patients: Assessment of diagnosis criteria and of three different iron treatments. *Nephron* 1991;**57**(2):175-82. [MEDLINE: 1902285]

Charytan 2013 *{published data only}*

Charytan C, Bernardo MV, Koch TA, Butcher A, Morris D, Bregman DB. Intravenous ferric carboxymaltose versus standard medical care in the treatment of iron deficiency anemia in patients with chronic kidney disease: a randomized, active-controlled, multi-center study. *Nephrology Dialysis Transplantation* 2013;**28**(4):953-64. [MEDLINE: 23222534]

HEMATOCRIT 2012 *{published data only}*

Barraclough KA, Brown F, Hawley CM, Leary D, Noble E, Campbell SB, et al. A randomized controlled trial of oral heme iron polypeptide versus oral iron supplementation for the treatment of anaemia in peritoneal dialysis patients: HEMATOCRIT trial. *Nephrology Dialysis Transplantation* 2012;**27**(11):4146-53. [MEDLINE: 22962411]

Barraclough KA, Noble E, Leary D, Brown B, Hawley CM, Campbell SB, et al. Rationale and design of the oral HEMe iron polypeptide Against Treatment with Oral Controlled Release Iron Tablets trial for the correction of anaemia in peritoneal dialysis patients (HEMATOCRIT trial). *BMC Nephrology* 2009;**10**:20. [MEDLINE: 19635169]

Lye 1997 *{published data only}*

Lye WC, Chin S, Lee WT, Fan KS, Tan SY. Prospective randomised comparison of three routes of iron supplementation during erythropoietin (rHuEPO) therapy in hemodialysis patients [abstract no: A1334]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):264A. [CENTRAL: CN-00677754]

Lye WC, Chin S, Wong KC, Fan KS. A prospective randomised comparison of three routes of iron administration during erythropoietin (RHEUPO) therapy in dialysis patients [abstract no: P949]. *Nephrology* 1997;**3**(Suppl 1):S311. [CENTRAL: CN-00520359]

Lye WC, Chin S, Wong KC, Fan KS. Prospective randomised comparison of three routes of iron administration during erythropoietin (rHuEPO) therapy in hemodialysis patients [abstract no: A1018]. *Journal of the American Society of Nephrology* 1997;**8**(Program & Abstracts):220A. [CENTRAL: CN-00446509]

Additional references

Avni 2015

Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. *Mayo Clinic Proceedings* 2015;**90**(1):12-23. [MEDLINE: 25572192]

Bailie 2012

Bailie GR. Adverse events associated with intravenous iron preparations: a comparison of reported rates. *Clinical Advances in Hematology & Oncology* 2012;**10**(9):600-2. [MEDLINE: 23073127]

Besarab 2000

Besarab A, Amin N, Ahsan M, Vogel SE, Zazuwa G, Frinak S, et al. Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. *Journal of the American Society of Nephrology* 2000;**11**(3):530-8. [MEDLINE: 10703677]

CARI 2008

McMahon L. Haemoglobin. *Nephrology* 2008;**13**(s2):S44-56. [DOI: 10.1111/j.1440-1797.2008.00997.x]

Collister 2016

Collister D, Komenda P, Hiebert B, Gunasekara R, Xu Y, Eng F, et al. The effect of erythropoietin-stimulating agents on health-related quality of life in anemia of chronic kidney disease: a systematic review and meta-analysis. *Annals of Internal Medicine* 2016;**164**(7):472-8. [MEDLINE: 26881842]

DeVita 2003

DeVita MV, Frumkin D, Mittal S, Kamran A, Fishbane S, Michelis MF. Targeting higher ferritin concentrations with intravenous iron dextran lowers erythropoietin requirement in hemodialysis patients. *Clinical Nephrology* 2003;**60**(5):335-40. [MEDLINE: 14640239]

Fishbane 2007

Fishbane S. Iron management in nondialysis-dependent CKD. *American Journal of Kidney Diseases* 2007;**49**(6):736-43. [MEDLINE: 17533016]

Fishbane 2014

Fishbane S, Mathew A, Vaziri ND. Iron toxicity: relevance for dialysis patients. *Nephrology Dialysis Transplantation* 2014;**29**(2):255-9. [MEDLINE: 24166458]

Fukuhara 2007

Fukuhara S, Yamazaki S, Marumo F, Akiba T, Akizawa T, Fujimi S, et al. Health-related quality of life of predialysis patients with chronic renal failure. *Nephron* 2007;**105**(1):c1-8. [MEDLINE: 17106210]

Gaweda 2015

Gaweda AE, Ginzburg YZ, Chait Y, Germain MJ, Aronoff GR, Rachmilewitz E. Iron dosing in kidney disease: inconsistency of evidence and clinical practice. *Nephrology Dialysis Transplantation* 2015;**30**(2):187-96. [MEDLINE: 24821751]

GRADE 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6. [MEDLINE: 18436948]

GRADE 2011

Guyatt G, Oxman A D, Akl E A, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**:383-94. [MEDLINE: 22818160]

Hedges 2007

Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ. Evidence-based treatment recommendations for uremic bleeding. *Nature Clinical Practice Nephrology* 2007;**3**(3):138-53. [MEDLINE: 17322926]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60. [MEDLINE: 12958120]

Higgins 2011

Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Ishida 2014

Ishida JH, Johansen KL. Iron and infection in hemodialysis patients. *Seminars in Dialysis* 2014;**27**(1):26-36. [MEDLINE: 24329610]

Ishida 2015

Ishida JH, Marafino BJ, McCulloch CE, Dalrymple LS, Dudley RA, Grimes BA, et al. Receipt of intravenous iron and clinical outcomes among hemodialysis patients hospitalized for infection. *Clinical Journal of The American Society of Nephrology: CJASN* 2015;**10**(10):1799-805. [MEDLINE: 26416943]

KDIGO 2008

Locatelli F, Nissenson AR, Barrett BJ, Walker RG, Wheeler DC, Eckardt KU, et al. Clinical practice guidelines for anemia in chronic kidney disease: problems and solutions. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney International* 2008;**74**(10):1237-40. [MEDLINE: 18596731]

KDIGO 2012

Kidney Disease: Improving Global Outcomes. Summary of recommendation statements. *Kidney International Supplements* 2012;**2**(4):283-7. [DOI: 10.1038/kisup.2012.41]

KDOQI 2007

Eckardt KU, van Wyck D. KDOQI 2007 update on hemoglobin target: recommendation and evidence base. www.kdigo.org/wp-content/uploads/2017/01/Eckardt-anemia-in-ckd-2007.pdf (accessed 11 February 2019).

Kovesdy 2006

Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE. Association of anemia with outcomes in men with moderate and severe chronic kidney disease.. *Kidney International* 2006;**69**(3):560-4. [MEDLINE: 16395253]

Kwack 2006

Kwack C, Balakrishnan VS. Managing erythropoietin hyporesponsiveness. *Seminars in Dialysis* 2006;**19**(2):146-51. [MEDLINE: 16551293]

Levin 2006

Levin A, Djurdjev O, Duncan J, Rosenbaum D, Werb R. Haemoglobin at time of referral prior to dialysis predicts survival: an association of haemoglobin with long-term outcomes. *Nephrology Dialysis Transplantation* 2006;**21**(2):370-7. [MEDLINE: 16249203]

Li 2004

Li S, Collins AJ. Association of hematocrit value with cardiovascular morbidity and mortality in incident hemodialysis patients. *Kidney International* 2004;**65**(2):626-33. [MEDLINE: 14717934]

Locatelli 2009

Locatelli F, Covic A, Eckardt K-U, Wiecek A, Vanholder R, ERA-EDTA ERBP Advisory Board. Anaemia management in patients with chronic kidney disease: a position statement by the Anaemia Working Group of European Renal Best Practice (ERBP). *Nephrology Dialysis Transplantation* 2009;**24**(2):348-54. [MEDLINE: 19037082]

Locatelli 2010

Locatelli F, Aljama P, Canaud B, Covic A, De Francisco A, Macdougall IA, et al. Target haemoglobin to aim for with erythropoiesis-stimulating agents: a position statement by ERBP following publication of the Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) Study.

Nephrology Dialysis Transplantation 2010;**25**(9):2846-50. [MEDLINE: 20591813]

Lopez 2015

Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet* 2016;**387**(10021):907-16. [MEDLINE: 26314490]

Macdougall 2016

Macdougall IC, Bircher AJ, Eckardt KU, Obrador GT, Pollock CA, Stenvinkel P, et al. Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney International* 2016;**89**(1):28-39. [MEDLINE: 26759045]

Madore 2008

Madore F, White CT, Foley RN, Barrett BJ, Moist LM, Klarenbach SW, et al. Clinical Practice Guidelines for assessment and management of iron deficiency. *Kidney International - Supplement* 2008, (110):S7-11. [MEDLINE: 18668119]

Moist 2008

Moist LM, Foley RN, Barrett BJ, Madore F, White CT, Klarenbach SW, et al. Clinical practice guidelines for evidence-based use of erythropoietic-stimulating agents. *Kidney International - Supplement* 2008, (110):S12-8. [MEDLINE: 18668116]

Moreno 2000

Moreno F, Sanz-Guajardo D, Lopez-Gomez JM, Jofre R, Valderrabano F. Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. Spanish Cooperative Renal Patients Quality of Life Study Group of the Spanish Society of Nephrology. *Journal of the American Society of Nephrology* 2000;**11**(2):335-42. [MEDLINE: 10665941]

Moyer 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**(9128):609-13. [MEDLINE: 9746022]

NICE 2015

National Institute of Health and Care Excellence. Chronic kidney disease: managing anaemia. *www.nice.org.uk/guidance/ng8* June 2015.

Phrommintikul 2007

Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. *Lancet* 2007;**369**(9559):381-8. [MEDLINE: 17276778]

Rozen-Zvi 2008

Rozen-Zvi B, Gafter-Gvilli A, Paul M, Leibovici L, Shpilberg O, Gafter U. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: systematic review and meta-analysis. *American Journal of Kidney Diseases* 2008;**52**(5):897-906. [MEDLINE: 18845368]

Sargent 2004

Sargent JA, Acchiardo SR. Iron requirements in hemodialysis. *Blood purification* 2004;**22**(1):112-23. [MEDLINE: 14732819]

Schultz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12. [MEDLINE: 7823387]

Schünemann 2011a

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Schünemann 2011b

Schünemann HJ, Oxman AD, Higgins JP, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Shah 2011

Shah SV, Rajapurkar MM, Baliga R. The role of catalytic iron in acute kidney injury. *Clinical Journal of The American Society of Nephrology: CJASN* 2011;**6**(10):2329-31. [MEDLINE: 21979910]

Shepshelovich 2016

Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. *American Journal of Kidney Diseases* 2016;**68**(5):677-90. [MEDLINE: 27321965]

Stauffer 2014

Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS ONE [Electronic Resource]* 2014;**9**(1):e84943. [MEDLINE: 24392162]

Susantitaphong 2014

Susantitaphong P, Alqahtani F, Jaber BL. Efficacy and safety of intravenous iron therapy for functional iron deficiency anemia in hemodialysis patients: a meta-analysis. *American Journal of Kidney Diseases* 2014;**39**(2):130-41. [MEDLINE: 24513913]

Vlagopoulos 2005

Vlagopoulos PT, Tighiouart H, Weiner DE, Griffith J, Pettitt D, Salem DN, et al. Anemia as a risk factor for cardiovascular disease and all-cause mortality in diabetes: the impact of chronic kidney disease. *Journal of the American Society of Nephrology* 2005;**16**(11):3403-10. [MEDLINE: 16162813]

Weiner 2005

Weiner DE, Tighiouart H, Vlagopoulos PT, Griffith JL, Salem DN, Levey AS, et al. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic

kidney disease. *Journal of the American Society of Nephrology* 2005;**16**(6):1803-10. [MEDLINE: 15857925]

References to other published versions of this review

Albaramki 2009

Albaramki J, Hodson EM, Craig JC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database of Systematic Reviews* 2009, Issue 7. [DOI: 10.1002/14651858.CD007857]

Albaramki 2012

Albaramki J, Hodson EM, Craig JC, Webster AC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database of Systematic Reviews* 2012, Issue 1. [DOI: 10.1002/14651858.CD007857.pub2]

* 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: not reported • Duration of follow-up: 70 days
Participants	• 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 (years): IV iron (65.5 ± 12.9); oral iron (62.3 ± 15.2) • 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: 250 mg weekly for 4 weeks
	  * Total dose of elemental iron: 1000 mg
	Oral iron
	• Ferrous sulphate: 325 mg, 3 times/day for 6 weeks
	  * Total dose of elemental iron: 12,285 mg
	Co-interventions
	• Not reported

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 • 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

Agarwal 2006 CKD *(Continued)*

- Exclusions post-randomisation but pre-intervention: not reported
- Stop or end point/s: not 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 of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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	Funded by Watson Laboratories Inc

Agarwal 2015 CKD

Methods	• Study design: Phase IV open-label RCT • Study duration: August 2008 to October 2014 • Duration of follow-up: 2 years
Participants	• Setting: "Single centre" 2 hospitals in Indianapolis, USA • Country: USA • Health status: >18 years, non-dialysis dependent, eGFR (MDRD) > 20 and ≤ 60 mL/min, Hb < 12 g/dL and ferritin < 100 ng/mL or serum TSAT of < 25% • Number: IV iron (67); oral iron (69) • Mean age ± SD (years): IV iron (63.2 ± 10.7); oral iron (67.8 ± 11.5) • Sex (M/F): IV iron (50/17); oral iron (54/15) • Exclusion criteria: pregnant or breast feeding; known hypersensitivity to any IV iron, iothalamate meglumine (Conray 60, Malinckrodt) or iodine; Hb < 8 g/dL or the potential need for imminent RBC transfusion (e.g., active bleeding); serum ferritin > 800 ng/mL or TSAT > 50%; AKI; IV iron use within the month prior to screening; anaemia not caused by iron deficiency (e.g., sickle cell anaemia); history of surgery or systemic or urinary tract infection within the past month; organ (any) transplant recipients or those who were currently being treated with immunosuppressive agents
Interventions	IV iron

Agarwal 2015 CKD *(Continued)*

	• Iron sucrose: 200 mg/week for 5 weeks
	  * Total dose of elemental iron 1000 mg
	
	Oral iron
	
	• Ferrous sulphate: 325 mg 3 times/day for 8 weeks
	  * Total dose of elemental iron 10,920 mg
	
	Co-interventions
	
	• 11 patients (8.1%) received ESA at the beginning of the study

Outcomes	• The difference between treatment groups in the slope of measured GFR from baseline to 2 years adjusted for the log of baseline urinary protein/creatinine ratio • Change in Hb • Change in ferritin • Change in TSAT • Quality of life • Adverse events
Notes	• "The trial was stopped early on the unanimous recommendation of the data and safety monitoring board based on an increase in the serious adverse event rate in participants assigned to IV iron treatment compared with oral iron therapy and little difference in mGFR between treatment groups. Given the persisting signal of safety, but little chance of finding the projected difference in measured GFR between groups, they unanimously recommended termination of the trial."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised in a 1:1 ratio using permuted blocks. The randomisation sequence was computer generated by a statistician
Allocation concealment (selection bias)	Low risk	Opaque and concealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome is a laboratory outcome and unlikely to be influenced by lack of blinding. Adverse events adjudicated by blinded personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	At 3 months < 20% lost to follow-up (13/136). Trial stopped early
Selective reporting (reporting bias)	High risk	All prespecified outcomes reported but no standard deviations reported
Other bias	Low risk	Supported in part by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (U01-DK71633) and Indiana Institute for Medical Research

Aggarwal 2003 CKD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: 3 months
Participants	• Setting: single tertiary centre • 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: 100 mg; twice/month for 3 months
	  * Total dose of elemental iron: 600 mg
	Oral iron
	• Ferrous sulphate: 200 mg, 3 times/day for 3 months
	  * Total of dose of elemental iron: 16,200 mg
	Co-interventions
	• 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: not reported • Follow-up period: 3 months • Loss to follow-up: not reported • 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 not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported

Aggarwal 2003 CKD *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
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 not reported

Ahsan 1997 TX

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: 8 weeks
Participants	• 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) • Mean age ± SD (years): IV iron (45.8 ± 4.7); oral iron (46.6 ± 8.1) • Sex (M/F): IV iron (5/1); oral iron (4/2) • Exclusion criteria: DGF requiring dialysis; received blood transfusion; acute rejection

Interventions	IV iron
	• Iron dextran: 1000 mg single dose
	  * Total dose of elemental iron: 1000 mg
	Oral iron
	• Ferrous sulphate: 325 mg; 3 times/day for 3 months
	  * Total dose of elemental iron: 26,325 mg
	Co-interventions
	• No reported

Outcomes	• HCT at end of study • TSAT at end of study • Cr at end of study
Notes	• Abstract-only publication • Funding source: not reported • Loss to follow-up: None • Exclusions post randomisation but pre-intervention: not reported • Stop or end points: not reported

Ahsan 1997 TX *(Continued)*

- 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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 not reported

Broumand 1998 HD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: 6 months
Participants	• Setting: multicentre • Country: Iran • Health status: patients on HD, EPO for 6 months • Number: IV iron (9); oral iron (8) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: evidence of active and chronic infection

Interventions	IV iron
	• Iron sucrose: 100 mg twice/week for 6 months
	  * Total dose of elemental iron: 4800 mg
	Oral iron
	• Ferrous formate: 350 mg for 6 months
	  * Total oral elemental iron: 63,000 mg

Broumand 1998 HD *(Continued)*

	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)
Notes	• Abstract-only publication • Funding source: not reported • Randomisation method: not reported • Loss to follow-up: not reported, 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 not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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 not reported

Charytan 2005 CKD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: 43 days
Participants	• Setting: multicentre (16 sites) • Country: USA

Charytan 2005 CKD *(Continued)*

- Health status: adults > 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 (years): IV iron (62 ± 14.4); oral iron (60 ± 14.4)
- Sex (M/F): IV iron (19/29); oral iron (14/34)
- Exclusion criteria: 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: 200 mg weekly for 5 weeks
	  * Total dose of elemental iron: 1000 mg
	Oral iron
	• Ferrous sulphate (elemental iron 195 mg/d): 325 mg 3 times/day for 29 days
	  * Total dose of elemental iron: 5655 mg
	Co-interventions
	• 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 • Loss to follow-up: not reported. 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: e 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 not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding

Charytan 2005 CKD *(Continued)*

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: not reported • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: Turkey • Health status: Hb < 10 g/dL; HD; hypo-responsiveness 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) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	IV iron group 1
	• Iron sucrose: 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: 100 mg for 10 sessions for 6 months
	  * Total dose of elemental iron: 1000 mg
	Oral iron
	• Ferrous sulphate: 200 mg/day for 6 months
	  * Total dose of elemental iron: 10,800 mg
	Co-interventions
	• 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 publication • Funding source: not reported • Loss to follow-up: not reported, 1 patient excluded from IV group due to side effects • Exclusions post randomisation but pre-intervention: not reported • Stop or end points: not reported • Additional data requested from authors: we contacted authors seeking information concerning method of randomisation and allocation concealment requested. No additional data were obtained

Erten 1998 HD *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory 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 not reported

FIND-CKD 2014 CKD

Methods	• Study design: parallel 3-arm RCT • Study duration: December 2009 to January 2012 • Duration of follow-up: 56 weeks
Participants	• Setting: multicentre (193 sites) • Country: 20 countries (Australia, Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, Switzerland, Turkey, UK and the USA) • Health status: adults ≥18 years; non-dialysis-dependent CKD with at least one Hb level between 9 and 11 g/dL or any ferritin level < 100 or < 200 µg/L with TSAT (TSAT) < 20%, within 4 weeks of randomisation; eGFR ≤ 60 mL/min/1.73 m^2 and no ESA had been administered within 4 months of randomisation. • Number: IV iron low-ferritin arm (154; 136 completed 56 weeks); IV iron high-ferritin arm (155; 133 completed 56 weeks); oral iron (317; 250 completed 56 weeks) • Mean age ± SD (years): IV iron low-ferritin arm (68.2 ± 13.3); IV iron high-ferritin arm (69.5 ±12.6); oral iron (69.3 ± 13.4) • Sex (M/F): IV iron low-ferritin arm (54/98); IV iron high-ferritin arm (62/91); oral iron (116/192) • Exclusion criteria: anaemia due to reasons other than iron deficiency; documented history of discontinuing oral iron products due to significant gastrointestinal distress; known active infection; CRP > 20 mg/L; overt bleeding; active malignancy; chronic liver disease and concomitant New York Heart Association Class IV heart failure
Interventions	IV iron low-ferritin arm • Ferric carboxymaltose (FCM): maximum single IV doses of 200 mg of iron targeting a ferritin level of 100 to 200 µg/L, after an initial screening period of up to 4 weeks. During weeks 4 to 48, FCM was

FIND-CKD 2014 CKD *(Continued)*

	administered every 4 weeks at a dose of 200 mg iron if ferritin was < 100 µg/L. Dosing was withheld if TSAT was > 40% or targeted ferritin level was 100 to 200 µg/L * Dose of elemental iron administered to reach target was 1040 ± 618 mg in the low ferritin group IV iron high-ferritin arm • Ferric carboxymaltose (FCM): maximum single IV doses of 1000 mg iron, after an initial screening period of up to 4 weeks. During weeks 4 to 48, FCM was administered every 4 weeks at a dose of 500 mg iron if ferritin was in the range 200 to < 400 µg/L, and at a dose of 1000 mg iron if ferritin was < 200 µg/L. Dosing was withheld if TSAT was > 40%. targeted ferritin level was 400 - 600 mcg/L. * Dose of elemental iron administered to reach target was 2685 ± 978 mg in the high ferritin group Oral iron • Ferrous sulphate: 100 mg iron twice daily to Week 52 * Calculated dose of elemental iron was 23,660 mg Co-interventions • During the first 8 weeks after randomisation, patients were not to receive ESA, blood transfusion or any anaemia therapy other than study drug unless there was an absolute requirement (e.g. severe or serious adverse reaction to study drug or otherwise unable to continue study drug, or rapid Hb drop requiring an ESA or transfusion, at the investigator's discretion). Subsequently, ESA and other therapies were permitted according to local practice if the Hb was < 10 g/dL. Alternative iron therapy in patients with Hb > 10 g/dL could be used but only when a patient was not able to comply with or tolerate the randomised treatment
Outcomes	• Time to initiation of other anaemia management, specified as ESA, blood transfusion, use of an alternative iron therapy (i.e. product, dosing schedule or total dose different from study drug) • Occurrence of an Hb trigger (two consecutive Hb values < 10 g/dL on or after week 8, without an increase of .0.5 g/dL between the two measurements) • Percentage of patients requiring a blood transfusion • Percentage of patients with an increase of Hb ≥ 1 g/dL • Change in haematologic and iron indices from baseline to end of study • Change in eGFR (MDRD-4) from baseline to end of study • Percentage of patients requiring dialysis • Percentage of patients discontinuing study drug due to intolerance • Change in health related quality of life using the SF-36 • Adverse events
Notes	• Funding source: Vifor Pharma, Glattbrugg, Switzerland • Lost to follow-up: IV high-ferritin group (22 died or discontinued, 14%); IV low-ferritin group (18 died or discontinued, 11.6%); oral group (67 died or discontinued, 21%) • Exclusions post randomisation: 2 in the IV high-ferritin group, 2 in the IV low-ferritin group and 9 in the oral iron group • Stop or end points: none • Additional data requested from authors: we contacted authors to seek additional information and data on missing patients. No response was received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Via a central interactive voice-response system in a 1:1:2 ratio, with randomisation blocks distributed by country
Allocation concealment (selection bias)	Low risk	Central interactive voice-response system

FIND-CKD 2014 CKD *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcomes unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were accounted for
Selective reporting (reporting bias)	Low risk	Review's prespecified primary outcomes reported in either full publication or abstract
Other bias	High risk	Funding source bias: "This work was supported by Vifor Pharma"

Fishbane 1995 HD

Methods	• Study design: parallel RCT • Study duration/ time frame: not reported • Duration of follow-up: 4 months
Participants	• 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 (years): IV iron (48.7 ± 8.7); oral iron (50.2 ± 9.9) • Sex (M/F): IV group (13/7); oral group (18/14) • Exclusions: not reported

Interventions	IV iron
	• Iron dextran: 100 mg twice/week for 4 months
	  * Total dose of IV iron: 3200 mg
	Oral iron
	• Ferrous sulphate (21/32): 325 mg, 3 times/day for 4 months
	  * Total dose of elemental iron: 35,100 mg
	• Iron polysaccharide (11/32): 150 mg twice/day for 4 months
	Co-interventions
	• 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

Fishbane 1995 HD *(Continued)*

Notes	• Funding source: not reported • 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: not reported • Stop or end points: not reported • 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 not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	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 not reported

Fudin 1998 HD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: 26 months
Participants	• 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 (years): IV iron (56.6 ± 15.1); oral iron (42.6 ± 17.03) • Sex (M/F): IV iron (12/8); oral iron (5/5) • Exclusion criteria: not reported
Interventions	IV iron

Fudin 1998 HD *(Continued)*

- Iron sodium gluconate complex: 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: 150 mg equivalent to 50 mg/day of elemental iron
  * Total dose of elemental iron: 39,000 mg

Co-interventions

- Not reported

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: not reported • 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: not reported • 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: not reported • 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 of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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
Other bias	Unclear risk	Funding source not reported

Hussain 1998 HD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: 3 months
Participants	• 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) • Mean 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: 100 mg twice/week for 3 months
	  * Total dose of elemental iron: 2400 mg
	Oral iron
	• Ferrous sulphate: 200 mg 3 times/day for 3 months
	  * Total dose of elemental iron: 16,200 mg
	Co-interventions
	• 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: not reported • Lost to follow-up: not reported • Exclusions post randomisation but pre-intervention: not reported • Stop or end points: not reported • 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
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not mentioned
Allocation concealment (selection bias)	Unclear risk	Method of allocation not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias)	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding

Hussain 1998 HD *(Continued)*

All outcomes		
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 not reported

Kalra 2016 CKD

Methods	• Study design: phase III open-label RCT • Study duration/timeframe: June 2010 to April 2014 • Duration of follow-up: 8 weeks
Participants	• Setting: multicentre (67 sites) • Country: India, Germany, UK, Austria, Russia, Poland, Denmark, Romania, USA, Sweden, Ireland • Health status: eGFR between 15 and 59 mL/min/1.73 m^2, · Hb < 11g/dL; either or both serum ferritin < 200 µg/L; TSAT < 20%; life expectancy > 12 months by PI's judgement • Number: IV iron (233); oral iron (118) • Mean age ± SD (years): IV iron (57.63 ± 15.54); oral iron (57.94 ± 16.34) • Sex (M/F): IV iron (92/141); oral iron (64/54) • Exclusion criteria: anaemia caused by factors other than renal impairment or iron deficiency (according to PI's judgment); iron overload or disturbances in utilization of iron (e.g. haemochromatosis and haemosiderosis); s-Ferritin > 500 µg/L; drug hypersensitivity (i.e. previous hypersensitivity to iron dextran or iron mono- or disaccharide complexes or iron sulphate or any excipients of the study drug); history of multiple allergies; decompensated liver cirrhosis or active hepatitis; active acute or chronic infections; active Rheumatoid arthritis; pregnancy or nursing; active bleeding necessitating blood transfusion; planned elective surgery during the study; participation in any other clinical study within 3 months prior to screening; untreated vitamin B12 or folate deficiency; IV or oral iron treatment or blood transfusion within 4 weeks prior to screening visit; ESA treatment within 8 weeks prior to screening visit; body weight < 30 kg

Interventions	IV Iron
	• Iron Isomaltoside 1000 administered to achieve cumulative dose mg from Ganzoni formula [BWkg x (13 g/dL - actual Hb g/dL)] x 2.4 + depot iron (set at 500 mg)
	  • Group A1: 116 patients received 1 dose of 1000 mg at week 0 and then 9 received second dose at week 1
	  • Group A2: 112 patients had 1 dose of 500 mg at week 0, 107 again at Week 1 and 16 patients again at Week 2
	Oral iron
	• Iron sulphate (65 mg elemental iron): 200 mg daily for 8 weeks (3640 mg elemental iron total)
	Co-interventions
	• No patient received an ESA

Outcomes	• Change in Hb from baseline to week 4 • Change in Hb at week 2 and 8 • Change in serum iron, ferritin, TSAT, TIBC at weeks 1, 2, 4 and 8 • Energy

Kalra 2016 CKD *(Continued)*

	• Activity • QOL
Notes	• Funding source: Pharmacosmos A/S

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An interactive web response system (IWRS) was used to randomise the patients
Allocation concealment (selection bias)	Low risk	Unique identifier number via IWRS
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded but primary outcome is laboratory measurement and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 (2%) lost to follow-up
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	High risk	Funded by Pharmacosmos A/S

Kotaki 1997 HD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: 5 months
Participants	• 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) • Mean age ± SD (years): not reported • Sex (M/F): not reported Exclusion criteria • Positive for HIV, other haematological disorders
Interventions	IV iron • Iron (preparation not reported): 100 mg/week for 5 months * Total dose of elemental iron: 2000 mg

Kotaki 1997 HD *(Continued)*

	Oral iron • Ferrous sulphate: 325 mg, 3 times/day for 5 months * Total dose of elemental iron: 43,875 mg Co-interventions • 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) • Mean ESA dose at end of study (5 months)
Notes	• Funding source: not reported • Lost to follow-up: 3/18 (17%) from IV group; 3/19 (16%) from oral group • Exclusion post randomisation but pre-intervention: not reported • Stop or end points: not reported • 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 of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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 not reported

Leehey 2005 CKD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: 10 weeks
Participants	• Setting: multicentre

Leehey 2005 CKD *(Continued)*

- 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)
- Mean age ± SD (years): not reported
- Sex (M/F): not reported
- Exclusion criteria: dialysis patients; positive FOBT result

Interventions	IV iron
	• Sodium ferric gluconate complex: 250 mg/week for 4 weeks
	  * Total dose of elemental iron: 1000 mg
	Oral iron
	• Ferrous sulphate: 325 mg, 3 times/day for 6 weeks
	  * Total dose of elemental iron: 12,285 mg
	Co-interventions
	• 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 publication • Funding source: Watson Laboratories Inc • Lost to follow-up: unclear • Exclusions post randomisation but pre-intervention: not reported • Stop or end points: not reported • 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 of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory based outcome unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only

Leehey 2005 CKD *(Continued)*

Selective reporting (reporting bias)	High risk	Abstract only. Reported change in Hb 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: not reported • Duration of follow-up: 12 weeks
Participants	• Setting: single centre • 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 (years): 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: 100 mg twice/week for 8 weeks, then once/week for 4 weeks
	  * Total dose of elemental iron: 2000 mg
	Oral iron
	• Ferrous succinate: 200 mg 3 times/day for 12 weeks
	  * Total dose of elemental iron: 16,800 mg
	Co-interventions
	• 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: not reported • Lost to follow-up: none • Exclusions post randomisation but pre-intervention: not reported • Stop or end points: not reported • 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

Li 2008 HD *(Continued)*

Random sequence generation (selection bias)	Low risk	Computerised random number list
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
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 not reported

Li 2008 PD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: 8 weeks
Participants	• 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 (years): 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: 200 mg/week for 4 weeks, then every second week for 8 weeks
	  * Total dose of elemental iron: 1200 mg
	Oral iron
	• Ferrous succinate: 200 mg, 3 times/day for 8 weeks
	  * Total dose of elemental iron: 11,200 mg
	Co-interventions
	• ESA 100 to 150 U/kg/week before study, dose varied during study

Outcomes	• Final or change in Hb (8 weeks)

Li 2008 PD *(Continued)*

- 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: not reported
- Lost to follow-up: not reported
- Exclusions post randomisation but pre-intervention: not reported
- Stop or end points: not reported
- 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 of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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 not reported

Lu 2010 CKD

Methods

- Study design: parallel RCT
- Study duration/time frame: June 2004 to November 2006
- Duration of follow-up: 35 days

Participants

- Setting: multicentre (31 sites)
- Country: USA
- Health status: adults > 18 years with CKD stages 1 to 5 (not on dialysis); 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

Lu 2010 CKD *(Continued)*

- Number: IV iron (227 (1 lost to follow up on entry; ITT population 226; 220 commenced medication; 215 completed; 7 withdrawn); oral iron (77; 74 commenced medication; 67 completed; 5 withdrawn)
- Mean age ± SD (years): IV iron (65.7 ± 14.1); oral iron (67.6 ± 12.9)
- Sex (M/F): IV iron (95/131); oral iron (29/48)
- 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; dialysis treatment; malignancy; uncontrolled hyperparathyroidism

Interventions	IV iron
	• Ferumoxytol: 510 mg, 2 doses
	  * Total dose of elemental iron: 1020 mg
	Oral iron
	• Ferrous fumarate: 100 mg elemental iron twice/day for 21 days
	  * Total dose of elemental iron: 4200 mg
	Co-interventions
	• ESA stable dose at < 35,000 IU/week or < 120 µg darbepoetin every 2 weeks or not started. 30% to 40% received ESA in stable dose. 95/226 in IV group received ESA, 34/77 in oral group received ESA

Outcomes	• Final or change in Hb (35 days) • Final or change in ferritin (35 days) • Number with adverse events: only provided as combined data with Spinowitz 2008 CKD • Number with rise in Hb > 1 g/dL
Notes	• Funding source: AMAG Pharmaceuticals • Lost to follow-up: IV group (1 lost to FU and 6 patients did not complete study); oral group (6 patients did not complete study) • Exclusion post randomisation but pre-intervention: IV group (5); oral group (3) • Additional information on this unpublished study obtained from AMAG Pharmaceuticals • Stop or end points: none stated • Additional data requested from authors: information provided by AMAG Pharmaceuticals about the study data on 4-3-2015 as no primary study reporting this study was identified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	3:1 automated pre-programmed interactive voice response system
Allocation concealment (selection bias)	Low risk	Telephone based
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding could have influenced management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open label but outcomes were laboratory based and unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias)	Low risk	Missing data of primary endpoint balanced between groups,5.3% IV,12% oral

Lu 2010 CKD *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Study protocol not available but identical to Spinowitz 2008. Information on outcomes provided by AMAG Pharmaceuticals
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

Lye 2000 HD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: 24 weeks
Participants	• 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) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: bleeding, severe infection or inflammation

Interventions	IV iron
	• Ferric hydroxide polymaltose complex (Ferrum): 200 mg/month for 24 weeks
	  * Total dose of elemental iron: 1200 mg
	Oral iron
	• Ferrous fumarate: 200 mg 3 times/day for 24 weeks
	  * Total dose of elemental iron: 33,600 mg
	Co-interventions
	• 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 publication • Funding source: not reported • Lost to follow-up: unclear • Exclusions at post randomisation: not reported • Stop or end points: not reported • 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

Lye 2000 HD *(Continued)*

Allocation concealment (selection bias)	High risk	Inadequate allocation. Author reported that patients were allocated alternately to each group
Blinding of participants and personnel (performance bias) All outcomes	High risk	Abstract only. No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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: not reported • Duration of follow-up: 16 weeks
Participants	• 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 • Number: IV iron (13, 1 discontinued due to anaphylactic reaction; 12 were analysed); oral iron (13) • Mean age ± SD (years): 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: 250 mg every 2 weeks for 16 weeks
	  * Total dose of elemental iron: 2000 mg
	Oral iron
	• Ferrous sulphate: 200 mg 3 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: not reported

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

- Lost to follow-up: none
- Exclusions post randomisation and pre-intervention: not reported
- Stop or end points: not reported
- 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 of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes reported in either full publication or abstract
Other bias	Unclear risk	Funding source not reported

Macdougall 1999 HD,PD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: 24 weeks
Participants	• 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) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	IV iron • Iron sucrose: 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

Macdougall 1999 HD,PD *(Continued)*

	• No information provided Co-interventions • 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 publication • Funding source: not reported • Lost to follow-up: unclear • Exclusions post randomisation but pre-intervention: not reported • Stop or end points: not reported • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only; not reported
Allocation concealment (selection bias)	Unclear risk	Abstract only; not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Abstract only. No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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: not reported • Duration of follow-up: 6 to 12 months
Participants	• Setting: multicentre (6 sites) • Country: Australia

McMahon 2009 CKD *(Continued)*

- 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 naive; 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: 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: 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-interventions • 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 • TSAT at end of study (at least 6 months) and 12 months • eGFR at end of study
Notes	• Funding source: Vifor • Lost to follow-up: IV group (9 died or discontinued, 14%); oral group (6 died or discontinued, 12.5%) • Exclusions post randomisation: not reported • 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 of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open label study but outcomes based on laboratory results unlikely to be influenced by lack of blinding

McMahon 2009 CKD *(Continued)*

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: not reported • Duration of follow-up: 22 weeks
Participants	• 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) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	IV iron
	• Sodium ferric gluconate complex: 62.5 mg/week for 20 weeks
	  * Total dose of elemental iron: 1250 mg
	Oral iron
	• Ferrous sulphate: 325 mg, 3 times/day for 20 weeks
	  * Total dose of elemental iron: 40,950 mg
	Co-interventions
	• 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 publication • Funding source: Watson Laboratories • Lost to follow-up: none • Exclusions post randomisation but pre-intervention: not reported • Stop or end points: not reported • 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

Michael 2007 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 of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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

Mudge 2009 TX

Methods	• Study design: open-label RCT • Study duration: December 2007 to March 2009 • Duration of follow-up: 90 days
Participants	• Setting: tertiary centre • Country: Australia • Health status: adult patients; undergoing living-donor or deceased donor kidney transplant surgery; • Number: IV iron (51); oral iron (51) • Mean age: 46 years • Sex (M/F): 74/28 • Exclusion criteria: iron overload (TSAT > 50% or ferritin > 800 g/L); women lactating, pregnant, or of child-bearing potential not using a reliable contraceptive method; patients with a history of psychological illness or condition thought to interfere with their ability to understand or comply with the requirements of the study; previous intolerance of IV or PO iron supplements

Interventions	IV iron
	• Iron polymaltose: single dose of 500 mg given on the fourth postoperative day
	  * Total dose of elemental iron: 500 mg
	Oral iron
	• Ferrous sulphate: 2 slow release tablets daily on the fifth postoperative day, and treatment was continued until the primary endpoint (Hb ≥ 11 g/dL) was reached
	  * Total dose of elemental iron: 210 mg elemental iron daily for median duration of 21 days (4410 mg)
	Co-interventions
	• ESA started before the study. Dose varied during study

Mudge 2009 TX *(Continued)*

Outcomes	• Time to normalisation of Hb post transplant (≥ 11 g/dL) • post-transplant Hb concentration • Gastrointestinal adverse effects defined as the onset of nausea, vomiting, abdominal cramping or diarrhoea • Infusion related reactions described as self-limiting flushing, sweating, chills, myalgias, arthralgias, bronchospasm and chest pain occurring at the time of the infusion • All infectious episodes
Notes	• Protocol published in BMC Nephrology • Funding source: P.A. Hospital Research Foundation funding the trial • Follow-up period: unclear; times to resolution of anaemia • Exclusions post randomisation but pre-intervention: 2 patients • Stop or end points: 2 patients discontinued the PO iron intervention • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence with blocks of 10
Allocation concealment (selection bias)	Low risk	Was performed by the use of sequentially numbered, sealed, opaque envelopes with stratification for calcineurin inhibitor type (cyclosporine or tacrolimus), in a one-to-one ratio
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	Funded by Princess Alexandra Hospital Research Foundation

Nagaraju 2013 CKD

Methods	• Study design: parallel RCT • Study duration/time frame: May 2007 to February 2011 • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: Canada • Health status: CKD stages 3 to 5 (GFR ≤ 60), non-dialysis; Hb 9 to 12 g/dL (females) and 9 to 13.5 g/dL (males); iron indices < 100 µg/L for ferritin or TSAT < 20%; aged > 18 years

Nagaraju 2013 CKD *(Continued)*

- Number: IV iron (22, 19 completed 6 months); oral iron (18, 14 completed 6 months)
- Median age, IQR (years): IV iron (66, 58 to 76); oral iron (76, 66 to 83)
- Sex (M/F): IV iron (12/10); oral iron (13/5)
- Exclusion criteria: receiving iron parenteral therapy or blood transfusion within the last 3 months; pregnant; major surgery; infection; active malignancy; bleeding or GI bleed or if serum folate or vitamin B12 levels below the normal limits (< 15 nmol/L, < 133 pmol/L)

Interventions	IV iron
	• Iron sucrose: 200 mg monthly for 12 months to maintain ferritin 100 - 500 µg/L and/or TSAT 20% to 50%;
	  * Dose of elemental iron: 1200 mg
	Oral iron
	• Heme Iron Polypeptide (HIP): 11 mg 3 times/day (33 mg/day) to maintain ferritin at 100 to 500 µg/L and/or TSAT 20% to 50%, 3 intolerant to iron due to new or worsening abdominal cramps
	  * Dose of elemental iron: 6006 mg
	Co-interventions
	• ESA administered to 6/22 IV group participants and 7/18 oral group participants at baseline. One in IV group ceased ESA and one in oral group commenced ESA. Dose altered according to Hb

Outcomes	• Hb at end of study (6 months) and changes from baseline • Ferritin at end of study (6 months) and changes from baseline • TSAT at end of study (6 months) and changes from baseline • Adverse events
Notes	• Funding source: Ottawa Hospital Research Institute • Lost to follow-up: IV group (3 died or discontinued, 13%); oral group (4 died or discontinued, 22.2%) • Exclusions post randomisation: not reported • Stop or end points: none • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence
Allocation concealment (selection bias)	Low risk	Group allocation was stored in sealed opaque sequentially numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single blind (investigator) was blinded but no blinding of care givers or patients. Lack of blinding could have influenced management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/40 (17.5%) dropped out but were included in analyses (last result carried forward). All randomised patients were followed until the end of the study, reasons for dropout provided

Nagaraju 2013 CKD *(Continued)*

Selective reporting (reporting bias)	Low risk	Outcomes were reported as median and IQR and could not be entered in meta-analyses; we have changed this to low risk as we have used the median as the mean and imputed standard deviations
Other bias	Low risk	Baseline age imbalance between the two groups but group ages were not significantly different. Funded by Ottawa Hospital Research Institute

NCT01155375 HD,PD,CKD

Methods	• Study design: parallel RCT • Study duration/time frame: enrolment July 2010 to November 2017 • Duration of study: 35 days
Participants	• Setting: multicentre (number not reported) • Country: USA • Health status: 14 dialysis (stable on HD or PD) and non-dialysis paediatric CKD patients; 6 months to < 18 years; CKD or stable on PD or HD; known to have iron deficiency anaemia defined as a) Hb ≤ 12.0 g/dL and b) with either TSAT level ≤ 40% or ferritin level < 100 ng/mL. • Number: IV iron (8); oral iron (6) • Mean age ± SD (years): IV iron (15.2 ± 1.65); oral iron (13.8 ± 4.52) • Sex (M/F): IV iron (3/5); oral iron (5/1) • Exclusion criteria: history of allergy to either oral or IV iron; Hb ≤ 7.0 g/dL; serum ferritin > 600 ng/mL; female participants who were pregnant or intended to become pregnant, or were breastfeeding, were within 3 months postpartum, or had a positive serum pregnancy

Interventions	IV ferumoxytol
	• Four IV injections of ferumoxytol 3.5 mg Fe/kg (maximum of 255 mg/dose) administered on non-consecutive days within a 14-day period as follows
	  * Day 1 (dose 1), Days 3* to 10 (dose 2), Days 5 to 12 (dose 3), and Days 7 to 14 (dose 4)
	  * *Participants participating in PK sampling received the second dose on Day 4 after the 72-hour PK sample was collected
	• Two IV injections of ferumoxytol 7.0 mg Fe/kg (maximum of 510 mg/dose), the first administered on Day 1 and the second on Days 3 through 9
	Oral ferrous fumarate
	• 2.5 mg Fe/kg twice daily (maximum of 100 mg/dose) on Days 1 through 35

Outcomes	• Mean change in Hb from baseline to week 5 • No outcomes provided when study terminated
Notes	• Study terminated because of significant challenges to recruitment. One adverse effect was recorded with ferumoxytol but type of reaction not recorded. No other results were reported. • Study AMAG-FER-CKD-251 (NCT01155375) was a study evaluating the efficacy and safety of IV ferumoxytol in paediatric participants with dialysis-dependent CKD. • Study AMAG-FER-CKD-252 (NCT01155388) was a study evaluating the efficacy and safety of IV ferumoxytol in paediatric participants with non-dialysis-dependent CKD • Study AMAG-FER-CKD-252 was combined with Study AMAG-FER-CKD-251 and enrolment continued under Study AMAG-FER-CKD-251. The enrolment number (n = 14) includes the number of participants for both AMAG-FER-CKD-251 and AMAG-FER-CKD-252 studies, combined
Risk of bias	

NCT01155375 HD,PD,CKD *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome laboratory based
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Study set up by AMAG Pharmaceuticals, Inc.

Pisani 2014 CKD

Methods	• Study design: parallel RCT • Study duration/time frame: October 2011 to September 2013 • Duration of follow-up: 3 months
Participants	• Setting: single centre • Country: Italy • Health status: aged > 18 years; eGFR (MDRD) ≤ 60 mL/min/1.73 m^2, Hb ≤ 12 g/dL, ferritin ≤ 100 ng/mL, TSAT≤ 25%, PTH between 30 and 300 pg/mL, and calcium and phosphate plasma levels within their normal values • Number: IV iron (37 started, 4 lost to FU, 33 analysed); oral iron (69 started, 3 lost to FU, 66 analysed) • Mean age ± SD (years): IV iron (47.6 ± 16); oral iron (53.1 ± 15) • Sex (M/F): IV iron (30%/70%); oral iron (27%/73%) • Exclusion criteria: CRP levels ≥ 5 mg/L; presence of inflammatory, infectious disease or surgical interventions in the last 3 months; haematological disorders, bleeding or blood transfusions in the last 6 months; malignancies or treatment with immunosuppressive drugs; severe malnutrition, concomitant severe liver or CV disease, chronic alcohol or drug abuse within the past 6 months; known hepatitis B or C infection; pregnant or lactating women
Interventions	IV iron • Iron gluconate: 125mg, weekly for 3 months * Elemental iron: 1000 mg Oral Iron • Sideral® Forte, PharmanutraSpa (30 mg of pyrophosphate liposomal iron and 70 mg of ascorbic acid):

Pisani 2014 CKD *(Continued)*

	• One capsule daily for 3 months * Elemental iron: 2520 mg Co-interventions • ESA: 9/99 patients received ESA
Outcomes	• Change in Hb values from baseline to end of treatment • Difference in the per cent of patients achieving an increase in Hb of ≥ 0.6 g/dL at any study point • Change in TSAT and ferritin from baseline to end of treatment • Treatment was suspended if ferritin exceeded 800 ng/mL or TSAT% exceeded 50%
Notes	• 93% completed study & were analysed • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list generated by computer
Allocation concealment (selection bias)	Low risk	numbered, sealed envelopes opened in sequence by staff personnel not involved in patient care
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	outcomes were laboratory based and unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	99/109 patients analysed, only 6 lost to follow-up
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Unclear risk	Funding not stated

Provenzano 2009 HD

Methods	• Study design: parallel RCT • Study duration/time frame: October 2005 to April 2007 • Duration of follow-up: 35 days
Participants	• Setting: multicentre (5 sites) • Country: USA • Health status: 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)

Provenzano 2009 HD *(Continued)*

- 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: 510 mg for 2 doses
	  * Total dose of elemental iron: 1020 mg
	Oral iron
	• Ferrous fumarate: 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 • 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: not reported • 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 not reported
Allocation concealment (selection bias)	Low risk	Telephone-based system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients who were randomised were included in the analysis

Provenzano 2009 HD *(Continued)*

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 2011 CKD

Methods	• Study design: parallel RCT • Study duration/time frame: May 2005 to February 2007 • Duration of follow-up: 56 days
Participants	• Setting: multicentre (47 centres) • Country: USA, Australia, Hong Kong • Health status: non-dialysis patients ≥ 12 years; GFR ≤ 45 mL/min; Hb ≤ 11g/dL; TSAT ≤ 25%; ferritin ≤ 300 ng/mL. Those on ESA had a fixed dose of ESA ≥ 8 weeks • Number: IV iron (152/147 received at least one dose); oral iron (103) • Mean age ± SD (years): IV iron (65.4 ± 12.6); oral iron (66.8 ± 13.5) • Sex (M/F): IV iron (53/94); oral iron (30/73) • Exclusion criteria: history of intolerance to oral iron; IV iron in previous 12 weeks; active infection; severe liver/heart disease; severe psychiatric disorders; drug abuse: pregnancy/lactation; hepatitis B/C; HIV: anticipated dialysis/transplant in 3 months

Interventions	IV iron
	• Ferric carboxymaltose: 1000 mg with up to 2 additional doses of 500 mg
	  * Total dose of elemental iron could not be calculated
	Oral iron
	• Ferrous sulphate: 325 mg 3 times/day for 56 days
	  * Total dose of elemental iron: 10,920 mg
	Co-interventions
	• ESA in some patients, stable ESA dose before and during study

Outcomes	• Mean change in Hb, ferritin, TSAT • Number having increase in Hb ≥ 1g/dL • Number with adverse reactions
Notes	• Funding source: American Reagent/Luipold Pharmaceuticals • Loss to follow-up: none • Exclusions post randomisation but pre-intervention: not reported • Stop or end points: not reported • 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 but additional information became available with full publication of study in 2011

Risk of bias

Bias	Authors' judgement	Support for judgement

Qunibi 2011 CKD *(Continued)*

Random sequence generation (selection bias)	Low risk	Centralised interactive voice-response system. Stratified by severity of CKD
Allocation concealment (selection bias)	Low risk	Centralised interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/255 (4%) not included in analyses
Selective reporting (reporting bias)	Low risk	Data provided on expected outcomes including adverse effects
Other bias	High risk	Funding support from American Reagent/Luipold Pharmaceuticals

Ragab 2007 HD

Methods	• Study design: quasi-RCT • Study duration/timeframe: December 2004 to March 2005 • Duration of follow-up: 3 months
Participants	• Setting: single centre • Country: Egypt • Health status: dialysis patients < 18 years; HD 3 times/week for ≥ 3.5 hours, Kt/V > 1.2, TSAT ≥ 20%, ferritin ≥ 100ng/mL, Hb < 11g/dL and/or HCT < 33%; no iron or transfusions; all on oral iron pre study • Number: IV iron (12); oral iron (12) • Median age: IV iron (12 years); oral iron (10 years) • Sex (M/F): IV iron (5/7); oral iron (8/4) • Exclusion criteria: TSAT ≤ 20% or ≥ 50% or ferritin ≤ 100g/dL or ≥ 800ng/dL; positive CRP

Interventions	IV Iron
	• Iron sucrose: 2 mg/kg, every 2 weeks, max 100 mg/dose, for 3 months
	  * Total dose could not be calculated.
	Oral Iron
	• Iron gluconate: 3 mg/kg daily for 3 months
	  * Total dose could not be calculated.
	Co-interventions
	• ESA: All participants received epoetin alpha

Outcomes	• Median serum iron at 3 months • Median TIBC at 3 months • Median TSAT at 3 months

Ragab 2007 HD *(Continued)*

	• Median Ferritin at 3 months • Median Hb at 3 months • Median HCT at 3 months
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were "randomly subdivided"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory based outcome, unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	High risk	No prespecified outcomes and only medians reported with no IQR
Other bias	Unclear risk	Funding not reported

Souza 1997 HD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: not reported
Participants	• 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) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	IV iron • Iron sucrose: dose calculated based on iron status and body weight * Total dose of elemental iron could not be calculated Oral iron

Souza 1997 HD *(Continued)*

	• Ferrous sulphate: dose calculated based on iron status * Total dose of elemental iron could not be calculated Co-intervention • Some patients received ESA
Outcomes	• Change in Hb • Change in ferritin • Change in iron status
Notes	• Abstract-only publication • Funding source: not reported • Lost to follow-up: IV group: 4 (33%) did not complete; oral group: 1 (8%) did not complete • Exclusion post randomisation but pre-intervention: not reported • Stop or end point: not reported • 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 Hb 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 not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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 not reported

Spinowitz 2008 CKD

Methods	• Study design: parallel RCT • Study duration/time frame: May 2004 to August 2006 • Duration of follow-up: 35 days

Spinowitz 2008 CKD *(Continued)*

Participants	• Setting: multicentre (number of sites not reported) • Country: USA • Health status: Adults 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) • 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: 510 mg, 2 doses
	  * Total dose of elemental iron: 1020 mg
	Oral iron
	• Ferrous fumarate: 100 mg elemental iron twice/day for 21 days
	  * Total dose of elemental iron: 4200 mg
	Co-interventions
	• 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 • 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 pre-programmed interactive voice response system
Allocation concealment (selection bias)	Low risk	Telephone based
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding

Spinowitz 2008 CKD *(Continued)*

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
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: not reported • Follow up: 6 months
Participants	• Setting: single tertiary centre • Country: UK • Health status: progressive deterioration in kidney 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 (years): 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: 300 mg monthly according to ferritin levels
	  * Total dose of elemental iron: 1638 mg
	Oral iron
	• Ferrous sulphate: 200 mg 3 times/day for 6 months
	  * Total dose of elemental iron: 32,400 mg
	Co-interventions
	• 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 • Lost to follow-up: IV group: 7 (32%) discontinued; oral group 6 (26%) discontinued • Exclusion post randomisation but pre-intervention: not reported • Stop or end points: not reported • 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 of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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: not reported • Duration of follow-up: 52 weeks
Participants	• 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) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: blood transfusion in the previous 3 months; low vitamin B_{12}; folate; kidney transplant with rejection
Interventions	IV iron • Iron dextran: 100 mg every 2 weeks * Total dose of elemental iron: 1300 mg Oral iron

Strickland 1977 HD *(Continued)*

	• Ferrous sulphate: 100 mg daily for 26 weeks * Total dose of elemental iron: 18,200 mg Co-interventions • Not reported
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 • Loss to follow-up: none • Exclusions post randomisation but pre-intervention: not reported • Stop or end points: not reported • 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 of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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: not reported • Duration of follow-up: 6 weeks
Participants	• 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

Svara 1996 HD *(Continued)*

- Number: IV iron (30, 29 analysed); oral iron (32, 28 analysed)
- Mean age ± SD (years): IV iron (61 years); oral iron (61 years)
- Sex (M/F): not reported
- Exclusion criteria: non-dialysis patients

Interventions	IV iron
	• Iron sucrose: 100 mg/week for 6 weeks
	  * Total dose of elemental iron: 600 mg
	Oral iron
	• Ferrous sulphate: 34.5 mg, 3 times/day (total dose 724.5 mg/week)
	  * Total dose of elemental iron: 4347 mg
	Co-interventions
	• 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: not reported • Randomisation method: not reported • 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: not reported • 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 not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low 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 not reported

Tsuchida 2010 HD

Methods	• Study design: parallel RCT • Study duration/time frame: March to September 2007 • duration of follow-up: 6 months
Participants	• Setting: single tertiary centre • Country: Japan • Health status: HD patients (> 6 months) using ultrapure dialysate; anaemia; tested negative for occult blood in stool • Number: IV iron (12, 12 completed); oral iron (11, 11 completed) • Mean age ± SD (years): IV iron (61 ±13.3); oral iron (59.5 ± 10.7) • Sex (M/F): IV iron (6/6); oral iron (5/6) • Exclusion criteria: uncontrolled hypertension; history of coronary artery disease; patients who changed treatment options from oral to IV or vice-versa; awaiting kidney transplantation; pregnant or lactating women; received a blood transfusion within 1 month prior to the study

Interventions	IV iron
	• Cideferron: 50 mg iron in 2 mL during HD once a week for 6 months
	  * Total dose of elemental iron: 1300 mg
	Oral iron
	• Ferrous fumarate: 305 mg once a day for 6 months
	  * Total dose of elemental iron: 18200 mg
	Co-interventions
	• rHuEPO: dose adjusted to maintain a target HCT of 33% to 38%.

Outcomes	• Hb and HCT at end of study • Ferritin at end of study • TSAT at end of study • ESA dose at end of study • Number with adverse events (gastrointestinal symptoms and gastrointestinal haemorrhage) • Changes in dry weight • Changes in cardiothoracic ratio • Changes in ESA dose
Notes	• Funding source: not reported • Lost to follow-up: IV group: 0 (0%) discontinued; oral group 0 (0%) discontinued • Exclusion post randomisation but pre-intervention: not reported • Stop or end points: not reported • Additional data requested from authors: We sought information regarding method of allocation concealment, Hb mean change and SD. No information was obtained

Risk of bias

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

Tsuchida 2010 HD *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcomes unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No flow chart provided, only data about included patients is provided
Selective reporting (reporting bias)	Low risk	Expected outcomes of haematological outcomes and adverse effects reported
Other bias	Unclear risk	Funding source not reported

Van Wyck 2005 CKD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Duration of follow-up: 56 days
Participants	• Setting: multicentre (35 sites) • 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) • Mean 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: 1000 mg, divided doses over 14 days
	  * Total dose of elemental iron: 1000 mg
	Oral iron
	• Ferrous sulphate: 325 mg, 3 times/day for 56 days
	  * Total dose of elemental iron: 10,920 mg
	Co-interventions
	• 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

Van Wyck 2005 CKD *(Continued)*

Notes	• Funding source: American Regent, Inc • 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: not reported • 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
Random sequence generation (selection bias)	Low risk	Sequential random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	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: not reported • Duration of follow-up: 5 weeks
Participants	• Setting: single tertiary centre • Country: China • Health status: stable adult HD patients on ESA therapy • Number: IV iron (21); oral iron (22) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	IV iron

Wang 2003 HD *(Continued)*

	• Ferric citrate: 50 mg twice/week for 5 weeks
	  * Total dose of elemental iron: 500 mg
	
	Oral iron
	
	• Ferrous sulphate: 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 publication • Funding source: not reported • 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: not reported • Stop or end points: not reported • Additional data requested from authors: none requested

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome is laboratory based and unlike to be altered by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Reported end Hb and ferritin
Other bias	Unclear risk	Insufficient information to permit judgement

Warady 2002 HD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported

Warady 2002 HD *(Continued)*

	• Duration of follow-up: 16 weeks
Participants	• Setting: multicentre (5 sites) • Country: USA • Health status: aged > 1 year to < 20 years; HD > 2 months; TSAT > 20%; stable ESA > 4 weeks prior to study; URR > 60% • Number: IV iron (17); oral iron (18) • Mean age ± SD (months): IV iron (181.4 ± 54.8); oral iron (175.9 ± 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: 12 doses weekly. Dose differed according to body weight
	  * Total dose of elemental iron could not be calculated
	Oral iron
	• Ferrous fumarate: 5 mg/kg/day for 16 weeks
	  * Total dose of oral iron: 560 mg/kg
	Co-interventions
	• 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 • Lost to follow-up: None • Exclusions post randomisation but pre-intervention: not reported • Stop or end points: not reported • 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 of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management

Warady 2002 HD *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	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

Winney 1977 HD

Methods	• Study design: parallel RCT • Study duration/time frame: not reported • Follow up: 12 months
Participants	• Setting: single centre • Country: UK • Health status: patients established on HD twice weekly • Number: 28 patients; umbers receiving IV iron or oral iron unclear • Mean age ± SD: not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	IV iron
	• Iron dextran: 50 mg IV weekly
	  * Total dose of elemental iron: 2600 mg
	Oral iron
	• Slow Fe: 320 mg daily for 12 months
	  * Total dose of oral iron: 36,400 mg
	Co-interventions
	• Not reported

Outcomes	• End Hb and HVT
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Winney 1977 HD *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding could influence results
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcomes unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Abstract only. Only information provided is for Hb/HCT
Other bias	Unclear risk	No information provided on funding

ACE - angiotensin-converting enzyme; ACEi - angiotensin-converting enzyme inhibitor; AKI - acute kidney injury; 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; DGF - delayed graft function; eGFR - estimated glomerular filtration rate; (rHu)EPO - (recombinant human) erythropoietin; ESA - erythrocyte-stimulating agent/s; 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; Kt/V - dialyser urea clearance adequacy; M/F - male/female; MDRD - Modified Diet in Renal Disease; PCKD - polycystic kidney disease; PCV - packed cell volume; PD - peritoneal dialysis; PTH - parathyroid hormone; RBC - red blood cell/s; SD - standard deviation; SE - standard error; SFGC - sodium ferric gluconate complex; TIBC - total iron binding capacity; TSAT - transferrin saturation; URR - urea reduction ratio

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

Study	Reason for exclusion
Adhikary 2011	Said to be RCT but included some non-randomised participants
Allegra 1991	Said to be RCT but results included some non-randomised patients
Charytan 2013	Wrong comparator: IV iron is compared to standard medical therapy, which could be oral or IV iron. No separate data available for patients receiving oral iron
HEMATOCRIT 2012	Wrong intervention: Compares two oral iron preparations
Lye 1997	Wrong intervention: compares intramuscular and oral routes

RCT - randomised controlled trial

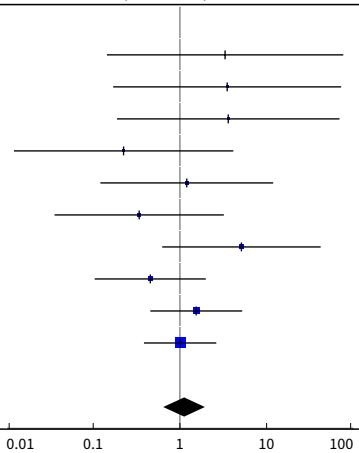
DATA AND ANALYSES

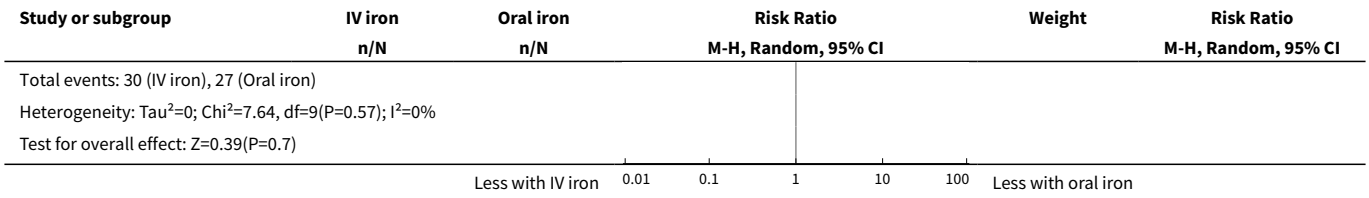
Comparison 1. Patient centred outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	11	1952	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.64, 1.94]
2 Cardiovascular death	3	206	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.41, 7.18]
3 Quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Number of non-dialysis patients needing to commence dialysis	4	743	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.41, 1.61]
5 Number requiring transfusion	5	774	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.55, 1.34]
6 Type of adverse event	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Allergic reactions/hypotension	15	2607	Risk Ratio (M-H, Random, 95% CI)	3.56 [1.88, 6.74]
6.2 Infection	4	954	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.90, 1.95]
6.3 All gastrointestinal adverse effects	14	1986	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.33, 0.66]
6.4 Constipation	10	1618	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.18, 0.57]
6.5 Diarrhoea	10	1625	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.47, 1.05]
6.6 Nausea and vomiting	9	1573	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.45, 1.29]
6.7 Taste disturbances	4	851	Risk Ratio (M-H, Random, 95% CI)	3.78 [0.84, 16.97]
6.8 Iron overload	3	158	Risk Ratio (M-H, Random, 95% CI)	6.58 [0.81, 53.51]

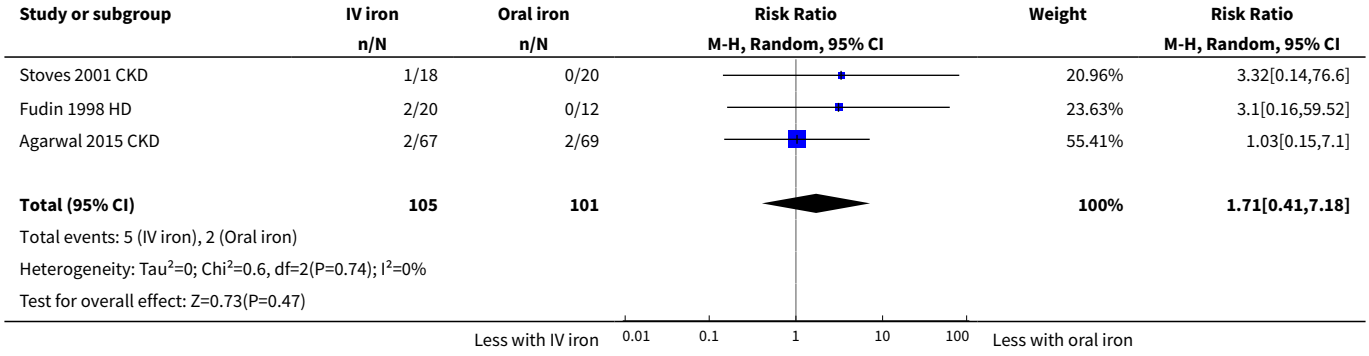
Analysis 1.1. Comparison 1 Patient centred outcomes, Outcome 1 Death (all causes).

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
Tsuchida 2010 HD	0/12	0/11			Not estimable
Stoves 2001 CKD	1/18	0/20		3.1%	3.32[0.14,76.6]
Qunibi 2011 CKD	2/147	0/103		3.34%	3.51[0.17,72.43]
Kalra 2016 CKD	3/228	0/117		3.5%	3.61[0.19,69.25]
Fishbane 1995 HD	0/20	3/32		3.6%	0.22[0.01,4.13]
Fudin 1998 HD	2/20	1/12		5.82%	1.2[0.12,11.87]
Provenzano 2009 HD	1/114	3/116		6.04%	0.34[0.04,3.21]
McMahon 2009 CKD	5/41	1/42		6.9%	5.12[0.63,41.97]
Lu 2010 CKD	4/225	3/77		14.05%	0.46[0.1,1.99]
Agarwal 2015 CKD	6/67	4/69		20.54%	1.54[0.46,5.23]
FIND-CKD 2014 CKD	6/153	12/308		33.11%	1.01[0.39,2.63]
Total (95% CI)	**1045**	**907**		**100%**	**1.12[0.64,1.94]**

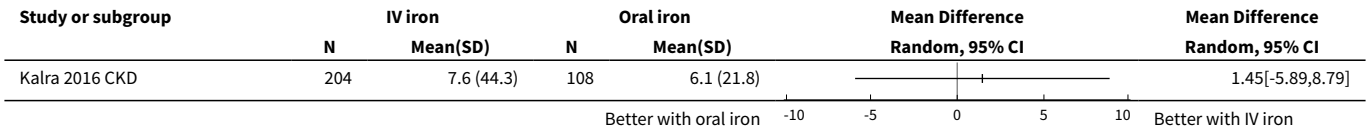




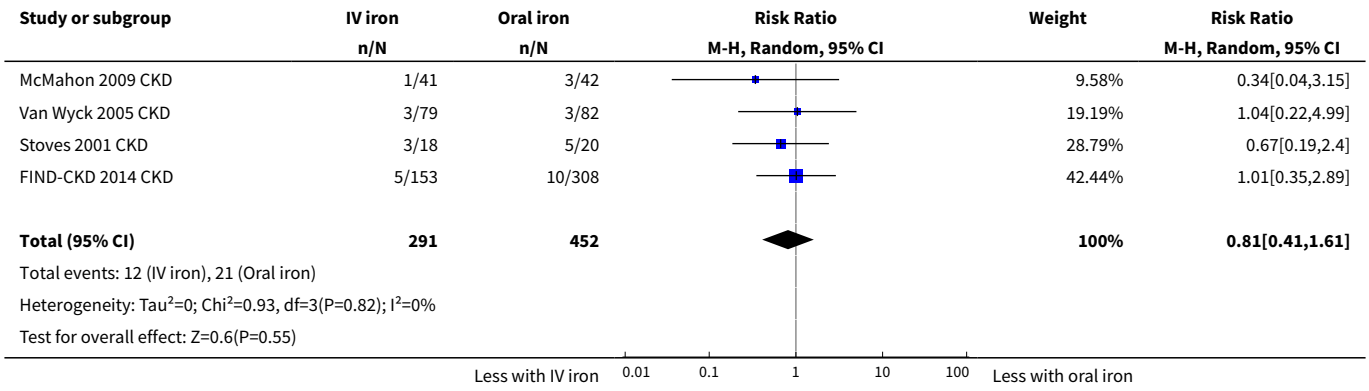
Analysis 1.2. Comparison 1 Patient centred outcomes, Outcome 2 Cardiovascular death.



Analysis 1.3. Comparison 1 Patient centred outcomes, Outcome 3 Quality of life.

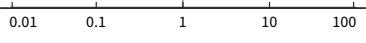


Analysis 1.4. Comparison 1 Patient centred outcomes, Outcome 4 Number of non-dialysis patients needing to commence dialysis.



Analysis 1.5. Comparison 1 Patient centred outcomes, Outcome 5 Number requiring transfusion.

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
Warady 2002 HD	0/17	0/18			Not estimable
Nagaraju 2013 CKD	1/22	0/18		1.97%	2.48[0.11,57.4]
Mudge 2009 TX	5/51	9/51		18.66%	0.56[0.2,1.54]
Agarwal 2015 CKD	12/67	12/69		36.96%	1.03[0.5,2.13]
FIND-CKD 2014 CKD	11/153	26/308		42.41%	0.85[0.43,1.68]
Total (95% CI)	**310**	**464**		**100%**	**0.86[0.55,1.34]**
Total events: 29 (IV iron), 47 (Oral iron)					
Heterogeneity: Tau²=0; Chi²=1.38, df=3(P=0.71); I²=0%					
Test for overall effect: Z=0.66(P=0.51)					



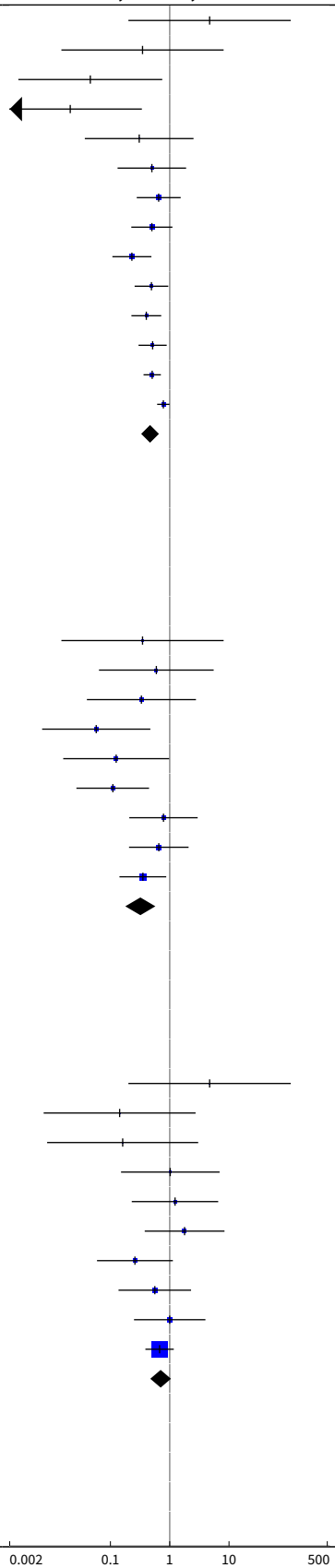
Less with IV iron — Less with 0ral iron

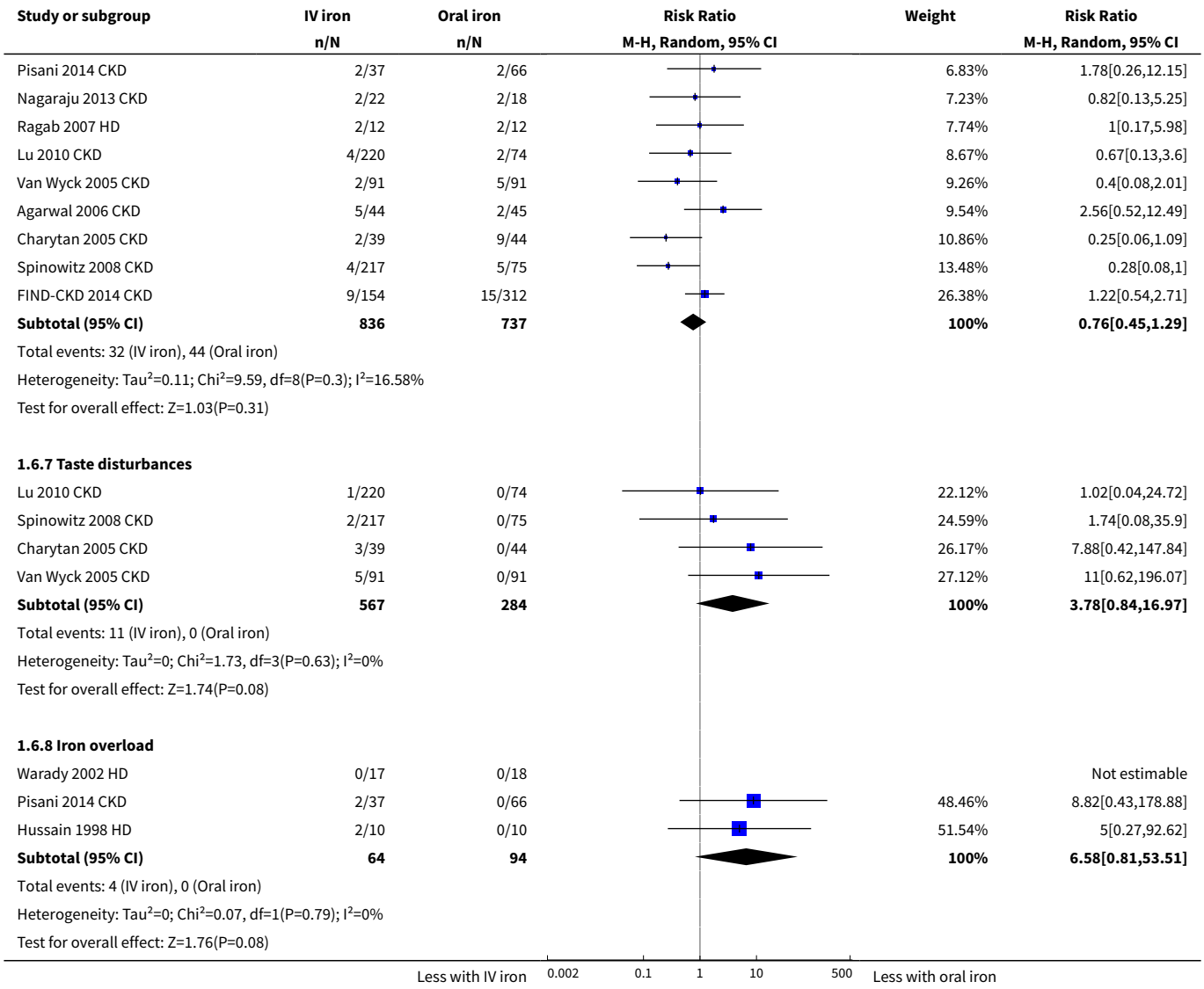
Analysis 1.6. Comparison 1 Patient centred outcomes, Outcome 6 Type of adverse event.

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
1.6.1 Allergic reactions/hypotension					
Charytan 2005 CKD	0/39	0/44			Not estimable
Qunibi 2011 CKD	0/147	0/103			Not estimable
Warady 2002 HD	1/17	0/18		4.13%	3.17[0.14,72.8]
Kalra 2016 CKD	2/228	0/117		4.43%	2.58[0.12,53.23]
Provenzano 2009 HD	2/110	0/113		4.44%	5.14[0.25,105.76]
Van Wyck 2005 CKD	2/91	0/91		4.45%	5[0.24,102.72]
Lu 2010 CKD	3/220	0/74		4.66%	2.38[0.12,45.46]
Agarwal 2006 CKD	3/44	0/45		4.72%	7.16[0.38,134.62]
Spinowitz 2008 CKD	4/217	0/75		4.8%	3.14[0.17,57.6]
Stoves 2001 CKD	3/22	0/23		4.8%	7.3[0.4,133.75]
Pisani 2014 CKD	4/37	0/66		4.85%	15.87[0.88,286.81]
Ragab 2007 HD	4/12	0/12		5.11%	9[0.54,150.81]
Nagaraju 2013 CKD	4/22	1/18		9.2%	3.27[0.4,26.75]
Agarwal 2015 CKD	2/67	2/69		10.89%	1.03[0.15,7.1]
FIND-CKD 2014 CKD	8/154	5/312		33.53%	3.24[1.08,9.74]
Subtotal (95% CI)	**1427**	**1180**		**100%**	**3.56[1.88,6.74]**
Total events: 42 (IV iron), 8 (Oral iron)					
Heterogeneity: Tau²=0; Chi²=3.82, df=12(P=0.99); I²=0%					
Test for overall effect: Z=3.91(P<0.0001)					
1.6.2 Infection					
FIND-CKD 2014 CKD	6/154	12/312		16.01%	1.01[0.39,2.65]
Qunibi 2011 CKD	20/147	8/103		24.15%	1.75[0.8,3.82]
Mudge 2009 TX	10/51	12/51		26.51%	0.83[0.4,1.75]
Agarwal 2015 CKD	19/67	11/69		33.34%	1.78[0.92,3.45]
Subtotal (95% CI)	**419**	**535**		**100%**	**1.32[0.9,1.95]**
Total events: 55 (IV iron), 43 (Oral iron)					
Heterogeneity: Tau²=0; Chi²=3.05, df=3(P=0.38); I²=1.54%					
Test for overall effect: Z=1.43(P=0.15)					
1.6.3 All gastrointestinal adverse effects					

Less with IV iron — Less with oral iron

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	1/20	0/32		1.11%	4.71[0.2,110.4]
Stoves 2001 CKD	0/22	1/23		1.11%	0.35[0.01,8.11]
Li 2008 PD	0/26	8/20		1.39%	0.05[0,0.75]
Li 2008 HD	0/70	22/66		1.4%	0.02[0,0.34]
Tsuchida 2010 HD	1/12	3/11		2.29%	0.31[0.04,2.52]
Mudge 2009 TX	3/51	6/51		4.74%	0.5[0.13,1.89]
Agarwal 2006 CKD	7/44	11/45		8.15%	0.65[0.28,1.53]
Van Wyck 2005 CKD	8/91	16/91		8.68%	0.5[0.23,1.11]
Spinowitz 2008 CKD	10/217	15/75		9.11%	0.23[0.11,0.49]
Lu 2010 CKD	19/220	13/74		10.24%	0.49[0.26,0.95]
Charytan 2005 CKD	10/39	28/44		11.13%	0.4[0.23,0.72]
Agarwal 2015 CKD	14/67	28/69		11.53%	0.51[0.3,0.89]
FIND-CKD 2014 CKD	32/154	128/312		14.07%	0.51[0.36,0.71]
Nagaraju 2013 CKD	17/22	18/18		15.04%	0.78[0.61,0.99]
Subtotal (95% CI)	**1055**	**931**		**100%**	**0.47[0.33,0.66]**
Total events: 122 (IV iron), 297 (Oral iron)					
Heterogeneity: Tau^2=0.19; Chi^2=35.42, df=13(P=0); I^2=63.29%					
Test for overall effect: Z=4.34(P<0.0001)					
1.6.4 Constipation					
Agarwal 2006 CKD	0/44	0/45			Not estimable
Stoves 2001 CKD	0/22	1/23		3.24%	0.35[0.01,8.11]
Pisani 2014 CKD	1/37	3/66		6.15%	0.59[0.06,5.51]
Ragab 2007 HD	1/12	3/12		6.73%	0.33[0.04,2.77]
Spinowitz 2008 CKD	1/217	6/75		6.82%	0.06[0.01,0.47]
Van Wyck 2005 CKD	1/91	8/91		7.07%	0.13[0.02,0.98]
FIND-CKD 2014 CKD	2/154	37/312		13.28%	0.11[0.03,0.45]
Lu 2010 CKD	7/220	3/74		14.58%	0.78[0.21,2.96]
Nagaraju 2013 CKD	4/22	5/18		17.77%	0.65[0.21,2.08]
Charytan 2005 CKD	5/39	16/44		24.36%	0.35[0.14,0.87]
Subtotal (95% CI)	**858**	**760**		**100%**	**0.32[0.18,0.57]**
Total events: 22 (IV iron), 82 (Oral iron)					
Heterogeneity: Tau^2=0.15; Chi^2=9.9, df=8(P=0.27); I^2=19.23%					
Test for overall effect: Z=3.83(P=0)					
1.6.5 Diarrhoea					
Fishbane 1995 HD	1/20	0/32		1.64%	4.71[0.2,110.4]
Van Wyck 2005 CKD	0/91	3/91		1.87%	0.14[0.01,2.73]
Charytan 2005 CKD	0/39	3/44		1.89%	0.16[0.01,3.02]
Agarwal 2006 CKD	2/44	2/45		4.43%	1.02[0.15,6.94]
Nagaraju 2013 CKD	3/22	2/18		5.78%	1.23[0.23,6.57]
Pisani 2014 CKD	3/37	3/66		6.78%	1.78[0.38,8.39]
Spinowitz 2008 CKD	3/217	4/75		7.49%	0.26[0.06,1.13]
Lu 2010 CKD	5/220	3/74		8.21%	0.56[0.14,2.29]
Ragab 2007 HD	3/12	3/12		8.47%	1[0.25,4]
FIND-CKD 2014 CKD	15/154	45/312		53.45%	0.68[0.39,1.17]
Subtotal (95% CI)	**856**	**769**		**100%**	**0.7[0.47,1.05]**
Total events: 35 (IV iron), 68 (Oral iron)					
Heterogeneity: Tau^2=0; Chi^2=7.61, df=9(P=0.57); I^2=0%					
Test for overall effect: Z=1.71(P=0.09)					
1.6.6 Nausea and vomiting					





Comparison 2. Laboratory/pharmaceutical outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number achieving target haemoglobin or increase ≥ 1 g/dL	13	2206	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.43, 2.04]
2 Haemoglobin: final or change (all patients)	31	3373	Mean Difference (IV, Random, 95% CI)	0.72 [0.39, 1.05]
3 Ferritin: final or change (all patients)	33	3389	Mean Difference (IV, Random, 95% CI)	224.84 [165.85, 283.83]

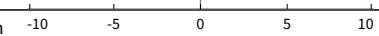
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Transferrin saturation: final or change	27	3089	Mean Difference (IV, Random, 95% CI)	7.69 [5.10, 10.28]
5 Haematocrit	4	152	Mean Difference (IV, Random, 95% CI)	1.18 [-2.17, 4.52]
6 End of treatment or change in ESA dose	11	522	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-1.12, -0.31]
7 eGFR end or change	8	1052	Mean Difference (IV, Random, 95% CI)	0.83 [-0.79, 2.44]

Analysis 2.1. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 1 Number achieving target haemoglobin or increase ≥ 1 g/dL.

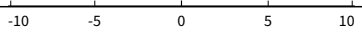
Study or subgroup	IV iron n/N	Oral iron n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Macdougall 1999 HD,PD	19/41	2/35		1.46%	8.11[2.03,32.41]
Hussain 1998 HD	9/10	5/10		4.84%	1.8[0.94,3.46]
Charytan 2005 CKD	21/39	14/44		6.37%	1.69[1.01,2.85]
Spinowitz 2008 CKD	89/228	14/76		6.66%	2.12[1.29,3.49]
Lu 2010 CKD	117/225	15/77		7.09%	2.67[1.67,4.28]
Li 2008 PD	23/26	11/20		7.9%	1.61[1.06,2.45]
Li 2008 HD	45/70	19/66		7.94%	2.23[1.47,3.39]
Pisani 2014 CKD	18/33	29/66		8%	1.24[0.82,1.88]
Provenzano 2009 HD	56/114	29/116		8.84%	1.96[1.36,2.83]
Stoves 2001 CKD	13/18	16/20		8.95%	0.9[0.63,1.29]
Van Wyck 2005 CKD	47/79	35/82		9.91%	1.39[1.02,1.9]
Qunibi 2011 CKD	89/147	36/103		10.22%	1.73[1.29,2.32]
FIND-CKD 2014 CKD	87/153	99/308		11.81%	1.77[1.43,2.19]
Total (95% CI)	**1183**	**1023**		**100%**	**1.71[1.43,2.04]**
Total events: 633 (IV iron), 324 (Oral iron)					
Heterogeneity: Tau^2=0.06; Chi^2=29.67, df=12(P=0); I^2=59.55%					
Test for overall effect: Z=5.96(P<0.0001)					

Analysis 2.2. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 2 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
Winney 1977 HD	14	7.5 (9.4)	14	8.4 (8.6)		0.23%	-0.9[-7.56,5.76]
Nagaraju 2013 CKD	22	11.3 (1.3)	18	11.8 (1.8)		2.8%	-0.46[-1.45,0.53]
Tsuchida 2010 HD	12	10.7 (1.1)	11	11.1 (0.6)		3.19%	-0.36[-1.07,0.35]
Lye 2000 HD	30	9.1 (1.4)	30	9.4 (1.5)		3.16%	-0.3[-1.03,0.43]
Warady 2002 HD	17	11.2 (1.3)	18	11.4 (0.8)		3.15%	-0.24[-0.98,0.5]

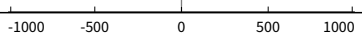


Study or subgroup	IV iron N	IV iron Mean(SD)	Oral iron N	Oral iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
McMahon 2009 CKD	39	11.8 (1)	38	11.9 (1.2)		3.45%	-0.1[-0.59,0.39]
Michael 2007 HD	33	-0.2 (1.1)	27	-0.2 (1.1)		3.38%	0[-0.55,0.55]
Agarwal 2015 CKD	153	0.7 (1.2)	58	0.6 (1.2)		3.58%	0.08[-0.28,0.44]
Agarwal 2006 CKD	36	0.4 (0.8)	39	0.2 (0.9)		3.56%	0.2[-0.18,0.58]
Pisani 2014 CKD	33	11.7 (1)	66	11.4 (0.8)		3.55%	0.3[-0.09,0.69]
Qunibi 2011 CKD	147	1 (0.8)	103	0.7 (0.9)		3.68%	0.3[0.08,0.52]
Charytan 2005 CKD	39	11.1 (1.1)	44	10.7 (1)		3.49%	0.4[-0.05,0.85]
Kalra 2016 CKD	210	0.9 (1.1)	112	0.5 (1.1)		3.66%	0.45[0.21,0.69]
Provenzano 2009 HD	114	11.7 (1.2)	116	11.2 (1.2)		3.61%	0.5[0.19,0.81]
FIND-CKD 2014 CKD	153	12 (1.2)	308	11.5 (1.8)		3.64%	0.5[0.22,0.78]
Macdougall 1999 HD,PD	41	10.8 (1.4)	35	10.3 (1.1)		3.37%	0.5[-0.06,1.06]
Van Wyck 2005 CKD	72	10.9 (1)	71	10.4 (1.1)		3.58%	0.5[0.15,0.85]
Lu 2010 CKD	226	11.2 (1.3)	77	10.6 (1.1)		3.62%	0.6[0.29,0.91]
Ragab 2007 HD	12	9.5 (1.1)	12	8.8 (1.1)		3%	0.7[-0.15,1.55]
Leehey 2005 CKD	24	1.5 (0.9)	24	0.8 (0.9)		3.43%	0.7[0.19,1.21]
Spinowitz 2008 CKD	228	10.9 (1.3)	76	10.2 (1)		3.64%	0.73[0.45,1.01]
Souza 1997 HD	8	1 (0.9)	11	0.2 (0.8)		3.12%	0.8[0.04,1.56]
Broumand 1998 HD	9	9.8 (1.1)	8	9 (1)		2.79%	0.8[-0.19,1.79]
Hussain 1998 HD	10	11.6 (0.6)	10	10.5 (1.1)		3.05%	1.1[0.29,1.91]
Macdougall 1996 HD,PD,CKD	9	11.7 (1.3)	11	10.6 (1.4)		2.53%	1.1[-0.09,2.29]
Aggarwal 2003 CKD	20	10.1 (0.9)	20	8.9 (1.2)		3.27%	1.11[0.46,1.76]
Wang 2003 HD	21	9.3 (1.8)	22	7.9 (1.4)		2.82%	1.4[0.43,2.37]
Li 2008 PD	26	12.2 (1.1)	20	10.6 (1)		3.32%	1.58[0.97,2.19]
Erten 1998 HD	26	11.8 (1.3)	22	9.9 (0.9)		3.3%	1.9[1.27,2.53]
Li 2008 HD	70	12 (1.3)	66	10 (1.1)		3.55%	1.99[1.6,2.38]
Fudin 1998 HD	20	11 (0.9)	12	6.1 (0.4)		3.49%	4.92[4.47,5.37]
Total ***	**1874**		**1499**			**100%**	**0.72[0.39,1.05]**
Heterogeneity: Tau^2=0.76; Chi^2=488.04, df=30(P<0.0001); I^2=93.85%							
Test for overall effect: Z=4.27(P<0.0001)							



Analysis 2.3. Comparison 2 Laboratory/pharmaceutical 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
Agarwal 2015 CKD	61	0.8 (0.6)	57	-0.2 (0.6)		3.27%	1.04[0.82,1.26]
Svara 1996 HD	29	166 (123)	28	109 (114)		3.16%	57[-4.54,118.54]
Tsuchida 2010 HD	12	183.5 (47.5)	11	115.4 (28.2)		3.24%	68.14[36.51,99.77]
Li 2008 HD	70	495.7 (315.2)	66	400.3 (264.1)		3%	95.4[-2.13,192.93]
Michael 2007 HD	33	80 (147)	27	-31 (130)		3.13%	111[40.86,181.14]
Leehey 2005 CKD	24	132 (162)	24	19 (162)		3.03%	113[21.34,204.66]
Nagaraju 2013 CKD	22	213 (227.2)	18	79.4 (60.1)		3%	133.6[34.71,232.49]
Warady 2002 HD	17	259.1 (163.1)	18	122 (118.8)		3.02%	137.1[42.11,232.09]
Pisani 2014 CKD	33	238.5 (49.7)	66	85.5 (31.3)		3.26%	153[134.44,171.56]
Ragab 2007 HD	12	238.5 (49.7)	12	85.5 (31.3)		3.24%	153[119.77,186.23]
Kalra 2016 CKD	209	222 (220)	112	66 (220)		3.2%	156[105.51,206.49]
Aggarwal 2003 CKD	20	267 (59)	20	104 (25)		3.25%	163[134.92,191.08]



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
Fudin 1998 HD	20	393.5 (249.3)	10	229.7 (113.6)		2.82%	163.8[33.82,293.78]
Li 2008 PD	26	466.7 (85.3)	20	299.4 (83.2)		3.2%	167.3[118.26,216.34]
Agarwal 2006 CKD	36	232 (160.8)	39	55.9 (236.2)		3.04%	176.1[85.25,266.95]
Van Wyck 2005 CKD	72	323 (178.5)	72	132 (90.3)		3.21%	191[144.79,237.21]
Lye 2000 HD	30	432 (288)	30	231 (204)		2.85%	201[74.71,327.29]
Wang 2003 HD	21	496 (306)	22	279 (206)		2.66%	217[60.35,373.65]
Broumand 1998 HD	9	779 (205)	8	546.5 (139)		2.61%	232.5[67.53,397.47]
Souza 1997 HD	8	245 (133)	11	2.3 (77.2)		2.98%	242.7[139.86,345.54]
McMahon 2009 CKD	39	412 (206)	38	153 (88)		3.13%	259[188.55,329.45]
Macdougall 1999 HD,PD	41	432 (202)	35	140 (91)		3.13%	292[223.21,360.79]
Lu 2010 CKD	225	443.8 (282.4)	77	150.8 (140.5)		3.2%	293[244.56,341.44]
Charytan 2005 CKD	39	288 (150)	44	-5.1 (151)		3.15%	293.1[228.24,357.96]
Hussain 1998 HD	10	671 (388)	10	367 (238)		1.87%	304[21.88,586.12]
Provenzano 2009 HD	114	601.8 (283)	116	289.3 (165.8)		3.16%	312.49[252.43,372.55]
FIND-CKD 2014 CKD	153	503 (136.1)	308	184 (140.4)		3.25%	319[292.34,345.66]
Macdougall 1996 HD,PD,CKD	9	490 (276)	11	165 (95)		2.45%	325[136.15,513.85]
Erten 1998 HD	26	573 (246.7)	22	247.4 (187.7)		2.86%	325.6[202.54,448.66]
Qunibi 2011 CKD	147	358.8 (178.4)	103	25.8 (49.4)		3.24%	333[302.62,363.38]
Spinowitz 2008 CKD	228	555.7 (320)	76	160.8 (161)		3.18%	394.9[339.8,450]
Kotaki 1997 HD	15	750 (147)	16	255 (64)		3.08%	495[414.27,575.73]
Fishbane 1995 HD	20	753.9 (135)	32	157.3 (87)		3.14%	596.6[530.2,663]
Total ***	**1830**		**1559**			**100%**	**224.84[165.85,283.83]**

Heterogeneity: Tau²=27687.38; Chi²=2866.96, df=32(P<0.0001); I²=98.88%

Test for overall effect: Z=7.47(P<0.0001)

Higher with oral iron -1000 -500 0 500 1000 Higher with IV iron

Analysis 2.4. Comparison 2 Laboratory/pharmaceutical 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)		4.05%	-8[-11.14,-4.86]
Nagaraju 2013 CKD	22	21.8 (10)	18	22.3 (12)		3.29%	-0.53[-7.47,6.41]
Agarwal 2015 CKD	60	0.1 (0.1)	57	0 (0.1)		4.31%	0.02[-0.01,0.05]
Michael 2007 HD	33	-0.6 (9.1)	27	-1.1 (8.4)		3.83%	0.5[-3.94,4.94]
Van Wyck 2005 CKD	72	25 (8.9)	72	22.2 (9.4)		4.07%	2.8[-0.2,5.8]
Kalra 2016 CKD	209	6.7 (9.3)	112	3.5 (9.3)		4.19%	3.19[1.05,5.33]
Pisani 2014 CKD	33	21.5 (5.2)	66	18.3 (4.3)		4.2%	3.2[1.14,5.26]
Ragab 2007 HD	12	21.5 (5.2)	12	18.3 (4.3)		3.94%	3.2[-0.62,7.02]
Charytan 2005 CKD	39	4.5 (8.3)	44	0.5 (8.5)		3.98%	4[0.38,7.62]
Tsuchida 2010 HD	12	33.8 (8.6)	11	29.7 (7.2)		3.39%	4.02[-2.48,10.52]
Svara 1996 HD	29	26.8 (11.1)	28	22.2 (9.6)		3.63%	4.6[-0.78,9.98]
Qunibi 2011 CKD	144	12.1 (8.8)	101	7 (10.3)		4.15%	5.1[2.63,7.57]
Kotaki 1997 HD	15	35.7 (5.1)	16	30.6 (1.9)		4.11%	5.1[2.36,7.84]
Agarwal 2006 CKD	36	8.3 (7.5)	39	2.9 (8.8)		3.96%	5.4[1.71,9.09]

Higher with oral iron -100 -50 0 50 100 Higher with IV iron

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
Provenzano 2009 HD	114	22.3 (13.3)	116	16.5 (9.7)		4.07%	5.85[2.83,8.87]
McMahon 2009 CKD	39	30 (9)	38	24 (11)		3.81%	6[1.5,10.5]
FIND-CKD 2014 CKD	153	35.3 (17.3)	308	28.6 (17.6)		4.02%	6.7[3.33,10.07]
Lu 2010 CKD	225	19.1 (10.4)	77	10.4 (5.2)		4.22%	8.7[6.91,10.49]
Spinowitz 2008 CKD	228	21 (10.1)	76	11.8 (6.7)		4.2%	9.2[7.2,11.2]
Li 2008 HD	70	39.6 (16.7)	66	28.6 (18.4)		3.52%	11[5.08,16.92]
Li 2008 PD	26	37.8 (16.1)	20	25.7 (17.5)		2.65%	12.1[2.25,21.95]
Warady 2002 HD	17	44.1 (14.1)	18	31.3 (15)		2.7%	12.73[3.11,22.35]
Fudin 1998 HD	20	33.2 (3.5)	10	19.9 (5.4)		3.96%	13.31[9.63,16.99]
Hussain 1998 HD	10	44.6 (19.8)	10	29 (11)		1.9%	15.61[1.57,29.65]
Ahsan 1997 TX	6	38 (8.2)	6	22 (3.4)		3.25%	16[8.9,23.1]
Aggarwal 2003 CKD	20	64.9 (11)	20	45.7 (14.1)		3.09%	19.23[11.39,27.07]
Fishbane 1995 HD	20	74.8 (13)	32	19.8 (5.7)		3.49%	55[48.98,61.02]
Total ***	**1676**		**1413**			**100%**	**7.69[5.1,10.28]**

Heterogeneity: Tau^2=40.48; Chi^2=745.19, df=26(P<0.0001); I^2=96.51%

Test for overall effect: Z=5.82(P<0.0001)

Higher with oral iron -100 -50 0 50 100 Higher with IV iron

Analysis 2.5. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 5 Haematocrit.

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
Ahsan 1997 TX	6	37.7 (1.7)	6	33.4 (1.9)		24.04%	4.3[2.26,6.34]
Svara 1996 HD	29	27.8 (3.4)	28	27.2 (2.9)		24.83%	0.6[-1.04,2.24]
Fishbane 1995 HD	20	34.4 (3.1)	32	31.8 (2.3)		24.93%	2.6[1.02,4.18]
Kotaki 1997 HD	15	33.2 (0.9)	16	35.7 (0.7)		26.2%	-2.5[-3.07,-1.93]
Total ***	**70**		**82**			**100%**	**1.18[-2.17,4.52]**

Heterogeneity: Tau^2=11.03; Chi^2=74.54, df=3(P<0.0001); I^2=95.98%

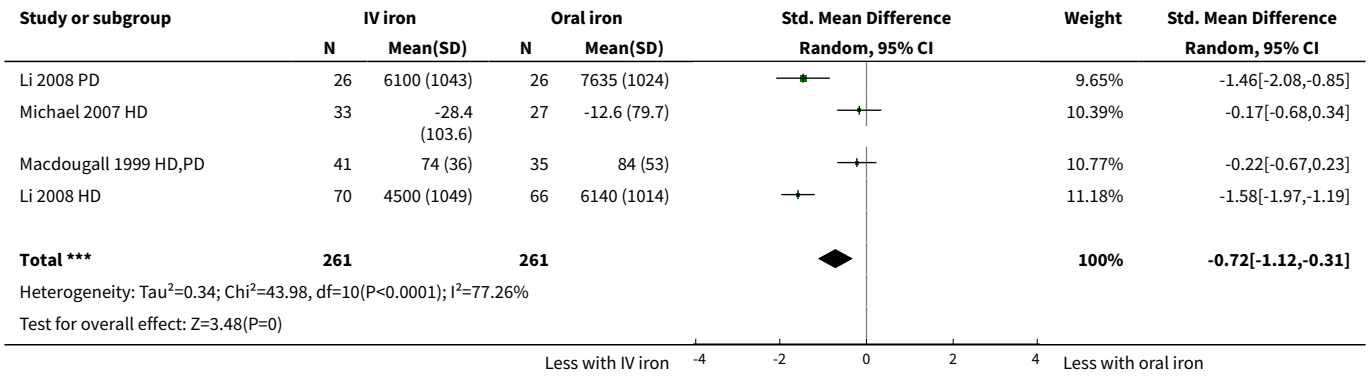
Test for overall effect: Z=0.69(P=0.49)

Higher with oral iron -10 -5 0 5 10 Higher with IV iron

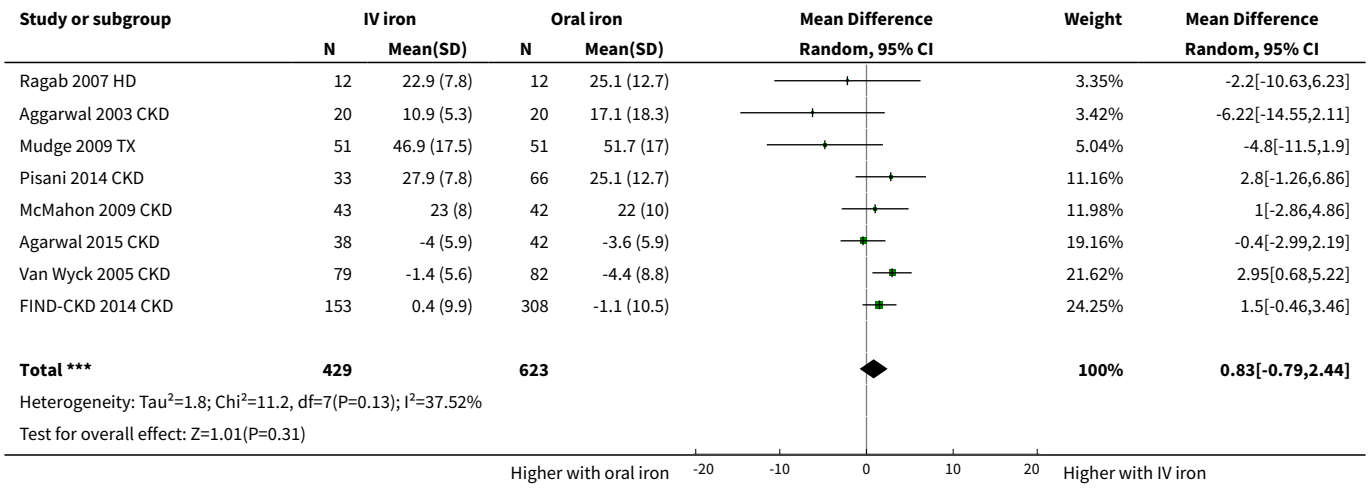
Analysis 2.6. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 6 End of treatment or change in ESA dose.

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
Nagaraju 2013 CKD	5	50 (28.3)	7	60 (28.3)		6.15%	-0.33[-1.48,0.83]
Hussain 1998 HD	10	3400 (1356)	10	4600 (1356)		7.54%	-0.85[-1.77,0.08]
Tsuchida 2010 HD	12	4375 (2473.7)	11	5590.9 (1513.6)		8.11%	-0.57[-1.4,0.27]
Macdougall 1996 HD,PD,CKD	12	1202 (229)	13	1294 (314)		8.43%	-0.32[-1.11,0.47]
Kotaki 1997 HD	15	3760 (1762)	16	4025 (2168)		9.03%	-0.13[-0.84,0.58]
Warady 2002 HD	17	-76.3 (104.7)	18	-30.9 (77.7)		9.25%	-0.48[-1.16,0.19]
Fishbane 1995 HD	20	4050 (2455)	32	7563 (2138)		9.51%	-1.53[-2.17,-0.89]

Less with IV iron -4 -2 0 2 4 Less with oral iron



Analysis 2.7. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 7 eGFR end or change.



ADDITIONAL TABLES

Table 1. Laboratory outcomes in dialysis and chronic kidney disease participants

Outcome	Population	Studies	Participants	MD	RR	95% CI
Hb (g/dL)	All studies	31	3373	0.72	-	0.39 to 1.05
	Dialysis	17	917	1.01	-	0.26 to 1.77
	CKD	14	2456	0.41	-	0.28 to 0.55
Ferritin (µg/L)	All studies	33	3389	224.8	-	165.8 to 283.8
	Dialysis	19	1027	233.7	-	163.4 to 303.9
	CKD	14	2362	213.1	-	123.7 to 302.6
TSAT (%)	All studies	27	3089	7.69	-	5.10 to 10.28

Table 1. Laboratory outcomes in dialysis and chronic kidney disease participants *(Continued)*

	Dialysis	14	781	10.55	-	3.89 to 17.22
	CKD	13	2308	5.32	-	2.67 to 7.97
Achieving target Hb	All studies	13	2206	-	1.71	1.43 to 2.04
	Dialysis	5	508	-	2.01	1.52 to 2.66
	CKD	8	1698	-	1.59	1.27 to 1.97

CKD - chronic kidney disease; Hb - haemoglobin; TSAT - transferrin saturation

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

	Total studies (N)	Studies	SMD (95% CI)	P
Dose IV iron/study month				
≥ 400 mg/month	12	8	0.17 (-0.18 to 0.52)	0.12
> 400 to 700 mg/month	7	6	0.76 (0.29 to 1.24)	-
> 700 mg/month	9	8	0.74 (0.41 to 1.06)	-
Dose IV iron (mg total dose)				
≤ 1000 mg	11	8	0.46 (0.25 to 0.66)	0.21
1000 to 1999 mg	12	10	0.48 (0.11 to 0.84)	-
> 2000 mg	5	4	0.89 (0.04 to 1.73)	-
Oral dose iron/study month				
< 4000 mg/month	12	10	0.87 (0.37 to 1.38)	0.15
≥ 4000 and < 6000 mg/month	12	11	0.46 (0.28 to 0.64)	-
≥ 6000 mg/month	7	5	0.37 (0.16 to 0.59)	-
Dose oral iron (mg total dose)				
≥ 12,000 mg	13	12	0.60 (0.38 to 0.82)	0.86
1200 to 30,000 mg	10	8	0.66 (0.29 to 1.03)	-
> 30,000 mg	18	11	0.45 (-0.05 to 0.94)	-
Any ESA use				
No EPO	8	6	0.57 (0.05 to 1.08)	0.34
EPO	27	22	0.55 (0.32 to 0.78)	-

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

ESA timing of use				
Start of study	8	7	0.40 (0.08 to 0.72)	0.90
Before study	19	15	0.57 (0.28 to 0.85)	-
CKD stage				
1 to 5	15	14	0.37 (0.26 to 0.50)	0.10
Dialysis (5D)	22	16	0.80 (0.37 to 1.24)	-
Study duration				
≥ 2 months	14	12	0.55 (0.35 to 0.75)	0.81
> 2 to ≤ 4 months	9	7	0.74 (0.28 to 1.19)	-
> 4 months	14	11	0.46 (0.002 to 0.91)	-
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	23	18	0.81 (0.40 to 1.23)	0.08
Sponsored	15	13	0.38 (0.28 to 0.48)	-
Imputed SD				
Not imputed	-	5	0.42 (0.02 to 0.81)	0.52
Imputed	-	26	0.55 (0.35 to 0.76)	-

CKD: chronic kidney disease; EPO - erythropoietin; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; SD: standard deviation

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

	Total studies (N)	Studies	SMD (95% CI)	P
Dose IV iron/study month				
≥ 400 mg/month	12	8	1.59 (0.73 to 2.44)	**0.02**
> 400 to 700 mg/month	7	6	1.62 (1.41 to 1.83)	-
>700 mg/month	9	9	1.32 (0.85 to 1.78)	-
Dose IV iron (mg total dose)				

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

≥ 1000 mg	11	9	1.67 (1.03 to 2.30)	0.08
1000 to 1999 mg	12	10	1.12 (0.83 to 1.42)	-
> 2000 mg	5	4	2.27 (0.55 to 3.99)	-
Oral dose iron/study month				
<4000 mg/month	12	10	1.44 (0.77 to 2.11)	**0.04**
≥ 4000 to < 6000 mg/month	12	11	1.43 (1.16 to 1.69)	-
≥ 6000 mg/month	7	7	2.16 (1.18 to 3.14)	-
Dose oral iron (mg total dose)				
≥ 12,000 mg	13	13	1.44 (1.05 to 1.83)	0.40
12000 to 30,000 mg	10	8	1.69 (1.05 to 2.34)	-
> 30,000 mg	18	12	1.79 (1.15 to 2.43)	-
Any ESA use				
No EPO	8	5	1.27 (0.46 to 2.08)	0.91
EPO	27	25	1.62 (1.28 to 1.96)	-
ESA timing of use				
Start of study	8	6	1.75 (0.88 to 2.62)	0.70
Before study	19	18	1.64 (1.22 to 2.06)	-
CKD stage				
1 to 5	15	14	1.70 (1.29 to 2.11)	0.66
Dialysis (5D)	22	18	1.50 (1.07 to 1.92)	-
Study duration				
≥ 2 months	10	13	1.18 (0.86 to 1.49)	0.54
> 2 to ≤ 4 months	7	8	2.64 (1.45 to 3.82)	-
> 4 months	9	11	1.54 (1.05 to 2.04)	-
Intervention aim				
Increase Hb	24	20	336 (84 to 588)	0.12
Maintain Hb	4	4	282 (177 to 261)	-
Pharmaceutical company sponsorship				

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

Unclear	23	20	1.84 (1.31 to 2.37)	0.63
Sponsored	15	13	1.36 (1.02 to 1.71)	-
Imputed SD				
Not imputed	-	5	1.18 (0.51 to 1.86)	0.62
Imputed	-	26	1.63 (1.31 to 1.94)	-

CKD: chronic kidney disease; EPO - erythropoietin; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; SD: standard deviation

Table 4. Subgroup analysis and meta-regression to examine heterogeneity in transferrin saturation meta-analyses

	Total studies (N)	Studies	SMD (95% CI)	P
Dose IV iron/study month				
≥ 400 mg/month	12	7	0.69 (0.39 to 1.00)	0.20
> 400 to 700 mg/month	7	5	0.46 (0.14 to 0.78)	-
> 700 mg/month	9	7	2.00 (0.55 to 3.45)	-
Dose IV iron (mg total dose)				
≥ 1000 mg	11	8	0.62 (0.34 to 0.90)	0.06
1000 to 1999 mg	12	9	0.41 (0.07 to 0.74)	-
> 2000 mg	5	2	3.5 (-1.46 to 8.39)	-
Oral dose iron/study month				
< 4000 mg/month	12	9	0.56 (0.25 to 0.86)	0.21
≥ 4000 to < 6000 mg/month	12	9	0.54 (0.20 to 0.87)	-
≥ 6000 mg/month	7	6	1.64 (0.69 to 2.59)	-
Dose oral iron (mg total dose)				
≥ 12,000 mg	13	11	0.56 (0.41 to 0.72)	0.15
1200 to 30,000 mg	10	8	0.56 (0.00 to 1.13)	-
> 30,000 mg	18	8	1.59 (0.55 to 2.63)	-
Any ESA use				
No EPO	8	6	0.83 (0.36 to 1.31)	0.83
EPO	27	19	0.73 (0.42 to 1.03)	-

Table 4. Subgroup analysis and meta-regression to examine heterogeneity in transferrin saturation meta-analyses *(Continued)*

ESA timing of use				
Start of study	8	5	0.29 (-0.42 to 1.00)	0.57
Before study	19	14	0.85 (0.51 to 1.20)	-
CKD stage				
1 to 5	15	13	0.55 (0.35, 0.74)	0.08
Dialysis (5D)	22	13	1.27 (0.75 to 1.80)	-
Study duration				
≥ 2 months	14	11	0.56 (0.41, 0.72)	0.93
> 2 to ≤ 4 months	9	9	1.34 (0.32 to 2.35)	-
> 4 months	14	7	0.67 (0.16 to 1.18)	-
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	23	15	1.07 (0.52 to 1.62)	0.26
Sponsored	15	12	0.52 (0.34 to 0.71)	-
Imputed SD				
Not imputed	-	3	0.26 (-0.24 to 0.77)	0.45
Imputed	-	21	0.72 (0.47 to 0.97)	-

CKD: chronic kidney disease; EPO - erythropoietin; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; SD: standard deviation

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

(Continued)

	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 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 administration, intravenous/ or exp administration, oral/ 12.(iv or intravenous or oral).tw. 13.or/11-12 14.Kidney Diseases/ 15.exp Renal Replacement Therapy/ 16.Renal Insufficiency/ 17.exp Renal Insufficiency, Chronic/ 18.dialysis.tw. 19.(hemodialysis or haemodialysis).tw. 20.(hemofiltration or haemofiltration).tw. 21.(hemodiafiltration or haemodiafiltration).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.(chronic kidney or chronic renal).tw. 25.(CKF or CKD or CRF or CRD).tw. 26.(CAPD or CCPD or APD).tw.

(Continued)

	27.(predialysis or pre-dialysis).tw. 28.or/14-27 29.10 and 13 and 28
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$)).tw. 5. (iron and (supplement$ 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.kidney disease/ 11.chronic kidney disease/ 12.kidney failure/ 13.kidney transplantation/ 14.chronic kidney failure/ 15.(hemodialysis or haemodialysis).tw. 16.(hemofiltration or haemofiltration).tw. 17.(hemodiafiltration or haemodiafiltration).tw. 18.dialysis.tw. 19.(CAPD or CCPD or APD).tw. 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.(predialysis or pre-dialysis).tw. 25.or/9-24 26.exp Injections, Intravenous/ 27.exp Administration, Oral/ 28.or/26-27 29.and/8,25,28

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.

(Continued)

	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or 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;

(Continued)

	the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
20 February 2019	New search has been performed	New studies added (11)
20 February 2019	New citation required and conclusions have changed	GRADE used to assess the evidence

HISTORY

Protocol first published: Issue 3, 2009
Review first published: Issue 1, 2012

Date	Event	Description
12 March 2014	Amended	Search strategies updated

CONTRIBUTIONS OF AUTHORS

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

9. Update the review: EO'L, EH, AW, DB, IN, JC

DECLARATIONS OF INTEREST

- Emma L O'Lone: none known
- Elisabeth M Hodson: none known
- Ionut Nistor: none known
- Davide Bolignano: none known
- Angela C Webster: none known
- Jonathan C Craig: none known

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anemia, Iron-Deficiency [blood] [*therapy]; Blood Transfusion [statistics & numerical data]; Cause of Death; Ferritins [blood]; Hemoglobin A [metabolism]; Injections, Intravenous; Iron Compounds [*administration & dosage] [adverse effects]; Kidney Failure, Chronic [blood] [*complications]; Randomized Controlled Trials as Topic; Transferrin [metabolism]

MeSH check words

Adult; Child; Humans