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


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TABLE OF CONTENTS

HEADER ................................................................................................................................. 1
ABSTRACT ................................................................................................................................... 1
PLAIN LANGUAGE SUMMARY ............................................................................................... 2
SUMMARY OF FINDINGS ....................................................................................................... 4
BACKGROUND ....................................................................................................................... 7
OBJECTIVES ........................................................................................................................ 8
METHODS ............................................................................................................................. 8
RESULTS .................................................................................................................................. 10
Figure 1. .................................................................................................................................. 11
Figure 2. .................................................................................................................................. 12
Figure 3. .................................................................................................................................. 13
Figure 4. .................................................................................................................................. 15
Figure 5. .................................................................................................................................. 16
DISCUSSION ........................................................................................................................... 18
AUTHORS’ CONCLUSIONS ................................................................................................. 20
ACKNOWLEDGEMENTS ....................................................................................................... 20
REFERENCES ....................................................................................................................... 21
CHARACTERISTICS OF STUDIES ............................................................................................... 29
DATA AND ANALYSES ......................................................................................................... 80
 Analysis 1.1. Comparison 1 Patient centred outcomes, Outcome 1 Death (all causes). .................... 81
 Analysis 1.2. Comparison 1 Patient centred outcomes, Outcome 2 Cardiovascular death. .................... 82
 Analysis 1.3. Comparison 1 Patient centred outcomes, Outcome 3 Quality of life. ............................ 82
 Analysis 1.4. Comparison 1 Patient centred outcomes, Outcome 4 Number of non-dialysis patients needing to commence dialysis. ........................ 82
 Analysis 1.5. Comparison 1 Patient centred outcomes, Outcome 5 Number requiring transfusion. .................... 83
 Analysis 1.6. Comparison 1 Patient centred outcomes, Outcome 6 Type of adverse event. .................... 83
 Analysis 2.1. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 1 Number achieving target haemoglobin or increase ≥ 1 g/dL. .................... 86
 Analysis 2.2. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 2 Haemoglobin: final or change (all patients). .................... 86
 Analysis 2.3. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 3 Ferritin: final or change (all patients). .................... 87
 Analysis 2.4. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 4 Transferrin saturation: final or change. .................... 88
 Analysis 2.5. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 5 Haematocrit. .................... 89
 Analysis 2.6. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 6 End of treatment or change in ESA dose. .................... 89
 Analysis 2.7. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 7 eGFR end or change. .................... 90
ADDITIONAL TABLES ............................................................................................................ 90
APPENDICES ....................................................................................................................... 95
WHAT’S NEW ....................................................................................................................... 99
HISTORY ............................................................................................................................... 99
CONTRIBUTIONS OF AUTHORS ..................................................................................... 99
DECLARATIONS OF INTEREST .......................................................................................... 100
INDEX TERMS .................................................................................................................... 100
Parenteral versus oral iron therapy for adults and children with chronic kidney disease

Emma L O’Lone1, Elisabeth M Hodson2, Ionut Nistor3, Davide Bolignano4, Angela C Webster1,5, Jonathan C Craig2,6

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

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ABSTRACT

Background

The anaemia seen in chronic kidney disease (CKD) may be exacerbated by iron deficiency. Iron can be provided through different routes, with advantages and drawbacks of each route. It remains unclear whether the potential harms and additional costs of intravenous (IV) compared with oral iron are justified. 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 0.90 to 1.38) (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 to 1.61) or the number needing blood transfusions (5 studies, 774 participants: RR 0.86, 95% CI 0.53 to 1.34) (absolute effect: 87 per 1000 with IV iron versus 101 per 1000 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 1000 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) and 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 1.28) 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

#### Anticipated absolute effects (95% CI)

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

*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).*
### 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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Nº of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Number achieving target Hb or increase ≥1 g/dL | Risk with oral iron: 317 per 1,000 (453 to 646)  
Risk with IV iron: 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%. |
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Description</th>
<th>Mean Difference</th>
<th>N</th>
<th>Grade</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSAT: final or change (%)</td>
<td>The mean TSAT was 7.69% higher with IV iron compared to oral iron (5.1 to 10.28 higher)</td>
<td>-</td>
<td>3089  (27)</td>
<td>LOW 1 2</td>
<td>11/27 only are at low risk of bias and heterogeneity is 97%.</td>
</tr>
<tr>
<td>HCT (%)</td>
<td>The mean HCT was 1.18% higher with IV iron compared to oral iron (2.17 lower to 4.52 higher)</td>
<td>-</td>
<td>152  (4)</td>
<td>VERY LOW 1 2 3 4</td>
<td>Only 4 studies in this analysis, all with unknown risk of selection bias. Heterogeneity 96%.</td>
</tr>
<tr>
<td>ESA dose: final or change</td>
<td>The SMD for ESA dose was 0.72 lower with IV iron compared to oral iron (0.31 to 1.12 lower)</td>
<td>-</td>
<td>522  (11)</td>
<td>LOW 1 2</td>
<td>ROB downgraded as little information on RSG and Allocation concealment. Heterogeneity 77%</td>
</tr>
<tr>
<td>eGFR: final or change (mL/min)</td>
<td>the mean eGFR was 0.83 mL/min higher with IV iron compared to oral iron (0.79 lower to 2.44 higher)</td>
<td>-</td>
<td>1052 (8)</td>
<td>LOW 1 3</td>
<td>Half of the studies are at ROB for RSG &amp; allocation concealment.</td>
</tr>
</tbody>
</table>

*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; Vlachopoulos 2005; Weiner 2005) and decreased quality of life (Fukuharu 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 uremia 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 excisicated, 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 reticuloocyte 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 2006; 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 m²). 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 needed to increase ESA dose
  - Number needed to decrease ESA dose or cease ESA
- Infection
- Change in GFR in non-dialysis patients
- Number needed for 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 trialists)

**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

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 contactedtrialists 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 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).
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,C KD; Stoves 2001 CKD) and before study commencement in 15 studies (Broumand 1998 HD; Erten 1998 HD; Fishbane 1995 HD; Kotaki 1997 HD; Leehy 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 (Aggarwal 2006 CKD; Ahsan 1997 TX; Fishbane 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 (Aggarwal 2015 CKD; Charytan 2013); one study (HEMATOCRIT 2012) compared two oral iron preparations and one study (Adhikary 2011) included non-randomised patients.

The outcomes reported in 38 studies are presented in Figure 1. One study was terminated and did not provide any outcomes (NCT01155375 HD,PD,C KD). 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). 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; 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.

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

<table>
<thead>
<tr>
<th>Risk of Bias Item</th>
<th>Low risk of bias</th>
<th>Unclear risk of bias</th>
<th>High risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
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<td></td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
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<tr>
<td>Blinding of participants and personnel (performance bias)</td>
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<tr>
<td>Blinding of outcome assessment (detection bias)</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
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<tr>
<td>Other bias</td>
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</tbody>
</table>

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**Figure 2** is a diagram showing the relative risk of bias across all included studies. The diagram uses different colors to represent the risk of bias: green for low risk, yellow for unclear risk, and red for high risk.
### Figure 3. Risk of bias summary: Review authors' judgements about each risk of bias item for each included study

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal 2006 CKD</td>
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<tr>
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<tr>
<td>Li 2008 PD</td>
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<td>Lyu 2008 HD</td>
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<tr>
<td>MacDougall 1996 HD,PD,CKD</td>
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</table>
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; 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
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 make 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 1.17, 95% CI 1.43 to 2.04; I² = 60%). In all participants (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; I² = 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 283.82, I² = 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, I² = 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, I² = 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 (I² = 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 (I² = 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; I² = 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; I² = 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; I² = 63%), fewer participants with constipation (Analysis 1.6.4 (10 studies, 1618 participants: RR 0.32, 95% CI 0.18 to 0.57; I² = 19%) and possibly with diarrhoea (Analysis 1.6.5 (10 studies, 1625 participants: RR 0.70, 95% CI 0.47 to 1.05; I² = 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; I² = 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 (< 12000 mg, 12000 to 30000 mg, > 30000 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 erythropoietin-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 ($\leq 2$ months, $\geq 2$ to 4 months, $\geq 4$ 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, $225 \, \mu g/L$ 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 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 (Shepselovich 2016). Our updated review includes 22 of the 24 studies included by Shepselovich 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 (Allegro 1991; Adhikary 2011). Shepselovich 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 patients 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**

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

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References to studies included in this review

Agarwal 2006 CKD (published and unpublished data)


Agarwal 2015 CKD (published data only)

Aggarwal 2003 CKD (published data only)


Ahsan 1997 TX (published data only)

Brounand 1998 HD (published and unpublished data)

Charytan 2005 CKD (published data only)


Erten 1998 HD (published data only)


FIND-CKD 2014 CKD (published data only)


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


**Fishbane 1995 HD** *(published data only)*


**Fudin 1998 HD** *(published and unpublished data)*


**Hussain 1998 HD** *(published data only)*


**Kalra 2016 CKD** *(published data only)*


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* Lye WC. Ferric gluconate maltose 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.

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Parenteral versus oral iron therapy for adults and children with chronic kidney disease (Review)
**Souza 1997 HD** *(published data only)*


**Spinowitz 2008 CKD** *(published and unpublished data)*


**Stoves 2001 CKD** *(published data only)*


**Strickland 1977 HD** *(published data only)*


**Svara 1996 HD** *(published data only)*


**Tsuchida 2010 HD** *(published data only)*


**Van Wyck 2005 CKD** *(published and unpublished data)*


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

Wang 2003 HD *(published data only)*


Warady 2002 HD *(published and unpublished data)*


Winney 1977 HD *(published data only)*


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Lye 1997 *(published data only)*


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Besarab 2000


CARI 2008


Collister 2016


DeVita 2003

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

Fishbane 2007

Fishbane 2014

Fukuhara 2007

Gaweda 2015

GRADE 2008

GRADE 2011

Hedges 2007

Higgins 2003

Higgins 2011

Ishida 2014

Ishida 2015

KDIGO 2008

KDIGO 2012

KDOQI 2007

Kovesdy 2006

Kwack 2006

Levin 2006

Li 2004

Locatelli 2009

Locatelli 2010
Nephrol Dial Transplant 2010;25(9):2846-50. [MEDLINE: 20591813]

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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]

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Rozen-Zvi 2008

Sargent 2004

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Schünemann 2011a

Schünemann 2011b

Shah 2011

Shepshelevich 2016

Stauffer 2014

Susantitaphong 2014

Vlagopoulos 2005

Weiner 2005
References to other published versions of this review

Albaramki 2009

* Indicates the major publication for the study

**Characteristics of studies**

<table>
<thead>
<tr>
<th>Characteristics of included studies [ordered by study ID]</th>
</tr>
</thead>
</table>

**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

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer generated randomisation of blocks of 4</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Central randomisation</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No blinding. Lack of blinding could influence management</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Laboratory outcomes unlikely to be affected by lack of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Missing data balanced in both groups, reason for missing data unlikely to be related to true outcome</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Study protocol available in paper and all of the pre-specified outcomes reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Funded by Watson Laboratories Inc</td>
</tr>
</tbody>
</table>

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 meg-lumine (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
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

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Randomised in a 1:1 ratio using permuted blocks. The randomisation sequence was computer generated by a statistician</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Opaque and concealed envelopes</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Not blinded and lack of blinding could influence patient management</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Primary outcome is a laboratory outcome and unlikely to be influenced by lack of blinding. Adverse events adjudicated by blinded personnel.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>At 3 months &lt; 20% lost to follow-up (13/136). Trial stopped early</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>All prespecified outcomes reported but no standard deviations reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>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</td>
</tr>
</tbody>
</table>
### 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 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

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<th>Bias</th>
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<th>Support for judgement</th>
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Cochrane Database of Systematic Reviews

Parenteral versus oral iron therapy for adults and children with chronic kidney disease (Review)
Aggarwal 2003 CKD (Continued)

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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

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### 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

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### 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
• 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: 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

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<td>Laboratory outcomes unlikely to be affected by lack of blinding</td>
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</table>
Charytan 2005 CKD (Continued)

| Incomplete outcome data (attrition bias) | 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**

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**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 m² 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
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 µg/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**

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<tr>
<td>Allocation concealment (selection bias)</td>
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### FIND-CKD 2014 CKD (Continued)

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<td>Funding source bias: “This work was supported by Vifor Pharma”</td>
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### 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

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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
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

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<td>16% in both groups did not complete and were excluded from the analysis</td>
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</table>
### Hussain 1998 HD

#### Methods
- Study design: parallel RCT
- Study duration/lime 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 B₁₂, 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

<table>
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<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
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<td>Blinding of outcome assessment (detection bias)</td>
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<td>Laboratory outcomes unlikely to be affected by lack of blinding</td>
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### Hussain 1998 HD

(Continued)

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<th>Unclear risk</th>
<th>Unclear whether results of all patients were included in the analysis</th>
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<td>Other bias</td>
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### 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 < 11 g/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 monosaccharide 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**

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</table>

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**

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**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

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Leehey 2005 CKD (Continued)

Selective reporting (reporting bias)

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Other bias

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</table>

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 B₁₂

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

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### Li 2008 HD (Continued)

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<td>Blinding of outcome assessment</td>
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<tr>
<td>Other bias</td>
<td>Unclear</td>
<td>Funding source not reported</td>
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### 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**
- **Outcomes**
  - ESA 100 to 150 U/kg/week before study, dose varied during study
  - 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

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<td>Other bias</td>
<td>Unclear risk</td>
<td>Funding source not reported</td>
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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

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Lu 2010 CKD (Continued)

All outcomes

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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 B12 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 |
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Random sequence generation (selection bias) | Unclear risk | Abstract only. No information provided |
**Lye 2000 HD (Continued)**

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**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 B₁₂ 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
### Risk of bias

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<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No blinding. Lack of blinding could influence management</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Laboratory outcomes unlikely to be affected by lack of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>All patients were accounted for</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Primary outcomes reported in either full publication or abstract</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Funding source not reported</td>
</tr>
</tbody>
</table>

### 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)
### 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

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<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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<td>Abstract only. Outcome was laboratory based and unlikely to be influenced by blinding</td>
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<td>Other bias</td>
<td>Unclear risk</td>
<td>Abstract only</td>
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</table>

### 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

<table>
<thead>
<tr>
<th>Interventions</th>
<th>IV iron</th>
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<tr>
<td></td>
<td>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</td>
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<tr>
<td></td>
<td>* Dose of elemental iron could not be calculated</td>
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<table>
<thead>
<tr>
<th>Oral iron</th>
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<tbody>
<tr>
<td>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.</td>
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<tr>
<td>* Dose of elemental iron could not be calculated</td>
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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>ACEi administered to 51/52 IV group participants and 45/48 oral group participants</td>
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<table>
<thead>
<tr>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Hb at end of study (at least 6 months) and 12 months</td>
</tr>
<tr>
<td>Ferritin at end of study (at least 6 months) and 12 months</td>
</tr>
<tr>
<td>TSAT at end of study (at least 6 months) and 12 months</td>
</tr>
<tr>
<td>eGFR at end of study</td>
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<thead>
<tr>
<th>Notes</th>
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<tr>
<td>Funding source: Vifor</td>
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<tr>
<td>Lost to follow-up: IV group (9 died or discontinued, 14%); oral group (6 died or discontinued, 12.5%)</td>
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<tr>
<td>Exclusions post randomisation: not reported</td>
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<tr>
<td>Stop or end points: none</td>
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<tr>
<td>Additional data requested from authors: we contacted authors to seek additional information concerning allocation concealment and data on missing patients. No data were obtained</td>
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<tr>
<th>Risk of bias</th>
</tr>
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<tbody>
<tr>
<td>Bias</td>
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<td>Random sequence generation (selection bias)</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
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### McMahon 2009 CKD (Continued)

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<tr>
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<th>Support for judgement</th>
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<td>Incomplete outcome data (attrition bias) All outcomes</td>
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<td>All patients were accounted for. Patients not completing 6 months were excluded a priori</td>
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<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Primary outcomes (end Hb, ferritin, TSAT) reported in either full publication or abstract</td>
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<td>Other bias</td>
<td>High risk</td>
<td>Grant/research support from Vifor (NCT 000202345)</td>
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</table>

### 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
Michael 2007 HD (Continued)

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</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
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<td>Open label. Lack of blinding could influence management</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
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<td>Laboratory outcomes unlikely to be affected by lack of blinding</td>
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<td>Incomplete outcome data (attrition bias)</td>
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<td>High</td>
<td>Grant/Research support: Watson Laboratories</td>
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</table>

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

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated sequence with blocks of 10</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
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<td>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</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Open label. Lack of blinding could influence management</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Laboratory outcomes unlikely to be affected by lack of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All patients completed the study</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All prespecified outcomes were reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Funded by Princess Alexandra Hospital Research Foundation</td>
</tr>
</tbody>
</table>

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
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**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer generated sequence</td>
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<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Group allocation was stored in sealed opaque sequentially numbered envelopes</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Single blind (investigator) was blinded but no blinding of caregivers or patients. Lack of blinding could have influenced management</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Outcomes were laboratory based and unlikely to be influenced by lack of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>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</td>
</tr>
</tbody>
</table>
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 test

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
### Bias Authors' judgement Support for judgement

<table>
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<th>Support for judgement</th>
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<td>Selective reporting (reporting bias)</td>
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### 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 m², 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

<table>
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<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<td>outcomes were laboratory based and unlikely to be affected by lack of blinding</td>
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<td>Incomplete outcome data (attrition bias)</td>
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<td>99/109 patients analysed, only 6 lost to follow-up</td>
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</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
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</table>

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

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<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
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<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method of randomisation not reported</td>
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<td>Allocation concealment (selection bias)</td>
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<td>Telephone-based system</td>
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<td>Blinding of participants and personnel (performance bias)</td>
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<td>Blinding of outcome assessment (detection bias)</td>
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<td>Laboratory outcomes unlikely to be affected by lack of blinding</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
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<td>All patients who were randomised were included in the analysis</td>
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</table>
Provenzano 2009 HD (Continued)

<table>
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<tr>
<th>Selective reporting (reporting bias)</th>
<th>Low risk</th>
<th>All outcomes defined in study registration reported</th>
</tr>
</thead>
</table>

| 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 ≤ 11 g/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 ≥ 1 g/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

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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Parenteral versus oral iron therapy for adults and children with chronic kidney disease (Review) 65
Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Qunibi 2011 CKD (Continued)

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<td>Centralised interactive voice-response system</td>
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<td>Open label study. Lack of blinding could influence management</td>
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<td>Low risk</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
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<td>10/255 (4%) not included in analyses</td>
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<td>Data provided on expected outcomes including adverse effects</td>
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<td>Other bias</td>
<td>High risk</td>
<td>Funding support from American Reagent/Luipold Pharmaceuticals</td>
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</table>

### 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

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<td>Laboratory based outcome, unlikely to be affected by lack of blinding</td>
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<td>No prespecified outcomes and only medians reported with no IQR</td>
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<td>Unclear risk</td>
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</table>

### 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

<table>
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<td>Unclear risk</td>
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</tbody>
</table>

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

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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Laboratory outcomes unlikely to be affected by lack of blinding</td>
</tr>
</tbody>
</table>

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

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

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

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

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  * Total dose of elemental iron: 1638 mg

Oral iron

• Ferrous sulphate: 200 mg 3 times/day for 6 months
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• 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
### Risk of bias

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<th>Support for judgement</th>
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<td>Outcomes reported as median and IQR and could not be entered in meta-analyses</td>
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<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Imbalance between ACEi treatment in each group</td>
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</table>

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 B₁₂; folate; kidney transplant with rejection

**Interventions**

- **IV iron**
  - Iron dextran: 100 mg every 2 weeks
    - Total dose of elemental iron: 1300 mg
- Oral iron

---

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.
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

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<td>Laboratory outcomes unlikely to be affected by lack of blinding</td>
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<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Funding support from Abbott Laboratories Ltd and Fisons Pharmaceuticals Ltd</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
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<th>IV iron</th>
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<tbody>
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<td></td>
<td>Iron sucrose: 100 mg/week for 6 weeks</td>
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<td></td>
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<tbody>
<tr>
<td>Ferrous sulphate: 34.5 mg, 3 times/day (total dose 724.5 mg/week)</td>
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<tr>
<td>* Total dose of elemental iron: 4347 mg</td>
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<table>
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<th>Co-interventions</th>
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<td>EPO 60 IU/kg/week in both groups and were on a stable dose</td>
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<th>Outcomes</th>
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<td>Hb at end of study (6 weeks)</td>
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<tr>
<td>Ferritin at end of study (6 weeks)</td>
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<td>TSAT at end of study (6 weeks)</td>
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<td>Randomisation method: not reported</td>
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<td>Stop or end points: not reported</td>
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<td>Additional data requested from authors: none requested</td>
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**Risk of bias**

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<td>Method of randomisation not reported</td>
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<td>Allocation concealment (selection bias)</td>
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<tr>
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### 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**

- **Cideferon:** 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

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement</td>
</tr>
</tbody>
</table>

**Tsuchida 2010 HD**

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### Tsuchida 2010 HD (Continued)

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

### 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

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
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<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Central randomisation</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
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<td>No blinding. Lack of blinding could influence management</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Laboratory outcomes unlikely to be affected by lack of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Missing data balanced between groups</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All of outcomes have been reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Supported by American Regent, Inc</td>
</tr>
</tbody>
</table>

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

<table>
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<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tr>
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<td>Unclear risk</td>
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</tr>
<tr>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No blinding. Lack of blinding could influence management</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Outcome is laboratory based and unlike to be altered by blinding</td>
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<td>Selective reporting (reporting bias)</td>
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<td>Reported end Hb and ferritin</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement</td>
</tr>
</tbody>
</table>

### Warady 2002 HD

- Study design: parallel RCT
- Study duration/time frame: not reported

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

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<th>Support for judgement</th>
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</table>
### Warady 2002 HD

<table>
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<td>All of outcomes have been reported</td>
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<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Supported by a grant from Watson Laboratories</td>
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</table>

### 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

<table>
<thead>
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<th>Bias</th>
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<th>Support for judgement</th>
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<td>Random sequence generation (selection bias)</td>
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<td>Allocation concealment (selection bias)</td>
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<td>Insufficient information to permit judgement</td>
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</tbody>
</table>
### Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhikary 2011</td>
<td>Said to be RCT but included some non-randomised participants</td>
</tr>
<tr>
<td>Allegra 1991</td>
<td>Said to be RCT but results included some non-randomised patients</td>
</tr>
<tr>
<td>Charytan 2013</td>
<td>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</td>
</tr>
<tr>
<td>HEMATOCRIT 2012</td>
<td>Wrong intervention: Compares two oral iron preparations</td>
</tr>
<tr>
<td>Lye 1997</td>
<td>Wrong intervention: compares intramuscular and oral routes</td>
</tr>
</tbody>
</table>

**Abbreviations:** RCT - randomised controlled trial
### Comparison 1. Patient centred outcomes

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

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsuchida 2010 HD</td>
<td>0/12</td>
<td>0/11</td>
<td>Not estimable</td>
<td></td>
<td>3.12 [0.14, 76.6]</td>
</tr>
<tr>
<td>Stoves 2001 CKD</td>
<td>1/18</td>
<td>0/20</td>
<td>3.1%</td>
<td>3.24</td>
<td>3.51 [0.17, 72.43]</td>
</tr>
<tr>
<td>Qunibi 2011 CKD</td>
<td>2/147</td>
<td>0/103</td>
<td>3.34%</td>
<td>1.53</td>
<td>3.51 [0.17, 72.43]</td>
</tr>
<tr>
<td>Kalra 2016 CKD</td>
<td>3/228</td>
<td>0/117</td>
<td>3.5%</td>
<td>1.25</td>
<td>3.61 [0.19, 69.25]</td>
</tr>
<tr>
<td>Fishbane 1995 HD</td>
<td>0/20</td>
<td>3/32</td>
<td>3.6%</td>
<td>0.22</td>
<td>0.22 [0.01, 4.13]</td>
</tr>
<tr>
<td>Fudin 1998 HD</td>
<td>2/20</td>
<td>1/12</td>
<td>5.82%</td>
<td>1.23</td>
<td>1.23 [0.12, 11.87]</td>
</tr>
<tr>
<td>Provenzano 2009 HD</td>
<td>1/114</td>
<td>3/116</td>
<td>6.04%</td>
<td>0.34</td>
<td>0.34 [0.04, 3.21]</td>
</tr>
<tr>
<td>McMahon 2009 CKD</td>
<td>5/41</td>
<td>1/42</td>
<td>6.9%</td>
<td>5.12</td>
<td>5.12 [0.63, 141.97]</td>
</tr>
<tr>
<td>Lu 2010 CKD</td>
<td>4/225</td>
<td>3/77</td>
<td>14.05%</td>
<td>0.46</td>
<td>0.46 [0.1, 1.99]</td>
</tr>
<tr>
<td>Agarwal 2015 CKD</td>
<td>6/67</td>
<td>4/69</td>
<td>20.54%</td>
<td>1.54</td>
<td>1.54 [0.46, 5.23]</td>
</tr>
<tr>
<td>FIND-CKD 2014 CKD</td>
<td>6/153</td>
<td>12/308</td>
<td>33.11%</td>
<td>1.01</td>
<td>1.01 [0.39, 2.63]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1045</td>
<td>907</td>
<td>100%</td>
<td>1.12</td>
<td>[0.64, 1.94]</td>
</tr>
</tbody>
</table>

Less with IV iron | 0.01 | 0.1 | 1 | 10 | 100 | Less with oral iron
### Analysis 1.2. Comparison 1 Patient centred outcomes, Outcome 2 Cardiovascular death.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoves 2001 CKD</td>
<td>1/18</td>
<td>0/20</td>
<td></td>
<td>20.96%</td>
<td>3.32[0.14, 76.6]</td>
</tr>
<tr>
<td>Fudin 1998 HD</td>
<td>2/20</td>
<td>0/12</td>
<td></td>
<td>23.63%</td>
<td>3.1[0.16, 59.52]</td>
</tr>
<tr>
<td>Agarwal 2015 CKD</td>
<td>2/67</td>
<td>2/69</td>
<td></td>
<td>55.41%</td>
<td>1.03[0.15, 7.1]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>105</strong></td>
<td><strong>101</strong></td>
<td></td>
<td><strong>100%</strong></td>
<td><strong>1.71[0.41, 7.18]</strong></td>
</tr>
</tbody>
</table>

Total events: 5 (IV iron), 2 (Oral iron)
Heterogeneity: Tau²=0; Chi²=0.6, df=2(P=0.74); I²=0%
Test for overall effect: Z=0.73(P=0.47)

Less with IV iron 100
0.01 0.1 1 10 100
Less with oral iron

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron</th>
<th>Oral iron</th>
<th>Mean Difference Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalra 2016 CKD</td>
<td>204</td>
<td>7.6 (44.3)</td>
<td>6.1 (21.8)</td>
</tr>
</tbody>
</table>

Total (95% CI)

Mean Difference Random, 95% CI: 1.45[-5.89, 8.79]

Less with oral iron

Better with IV iron

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>McMahon 2009 CKD</td>
<td>1/41</td>
<td>3/42</td>
<td></td>
<td>9.58%</td>
<td>0.34[0.04, 3.15]</td>
</tr>
<tr>
<td>Van Wyck 2005 CKD</td>
<td>3/79</td>
<td>3/82</td>
<td></td>
<td>19.19%</td>
<td>1.04[0.22, 4.99]</td>
</tr>
<tr>
<td>Stoves 2001 CKD</td>
<td>3/18</td>
<td>5/20</td>
<td></td>
<td>28.79%</td>
<td>0.67[0.19, 2.4]</td>
</tr>
<tr>
<td>FIND-CKD 2014 CKD</td>
<td>5/153</td>
<td>10/308</td>
<td></td>
<td>42.44%</td>
<td>1.01[0.35, 2.89]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>291</strong></td>
<td><strong>452</strong></td>
<td></td>
<td><strong>100%</strong></td>
<td><strong>0.81[0.41, 1.61]</strong></td>
</tr>
</tbody>
</table>

Total events: 12 (IV iron), 21 (Oral iron)
Heterogeneity: Tau²=0; Chi²=0.93, df=3(P=0.82); I²=0%
Test for overall effect: Z=0.6(P=0.55)
## Analysis 1.5. Comparison 1 Patient centred outcomes, Outcome 5 Number requiring transfusion.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warady 2002 HD</td>
<td>0/17</td>
<td>0/18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nagaraju 2013 CKD</td>
<td>1/22</td>
<td>0/18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mudge 2009 TX</td>
<td>5/51</td>
<td>9/51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agarwal 2015 CKD</td>
<td>12/67</td>
<td>12/69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIND-CKD 2014 CKD</td>
<td>11/153</td>
<td>26/308</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>310</td>
<td>464</td>
<td>100%</td>
<td>0.86 [0.55, 1.34]</td>
<td></td>
</tr>
</tbody>
</table>

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)

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

### 1.6.1 Allergic reactions/hypotension

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charytan 2005 CKD</td>
<td>0/39</td>
<td>0/44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinibi 2011 CKD</td>
<td>0/147</td>
<td>0/103</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warady 2002 HD</td>
<td>1/17</td>
<td>0/18</td>
<td>4.13%</td>
<td>3.17 [0.14, 72.8]</td>
<td></td>
</tr>
<tr>
<td>Kahe 2016 CKD</td>
<td>2/228</td>
<td>0/117</td>
<td>4.43%</td>
<td>2.58 [0.12, 53.23]</td>
<td></td>
</tr>
<tr>
<td>Provenzano 2009 HD</td>
<td>2/110</td>
<td>0/113</td>
<td>4.44%</td>
<td>5.14 [0.25, 105.76]</td>
<td></td>
</tr>
<tr>
<td>Van Wyck 2005 CKD</td>
<td>2/91</td>
<td>0/91</td>
<td>4.45%</td>
<td>5.0 [0.24, 102.72]</td>
<td></td>
</tr>
<tr>
<td>Lu 2010 CKD</td>
<td>3/220</td>
<td>0/74</td>
<td>4.66%</td>
<td>2.38 [0.12, 45.46]</td>
<td></td>
</tr>
<tr>
<td>agarwal 2006 CKD</td>
<td>3/44</td>
<td>0/45</td>
<td>4.72%</td>
<td>7.16 [0.38, 134.62]</td>
<td></td>
</tr>
<tr>
<td>Spinowitz 2008 CKD</td>
<td>4/217</td>
<td>0/75</td>
<td>4.8%</td>
<td>3.14 [0.17, 57.6]</td>
<td></td>
</tr>
<tr>
<td>Stoves 2001 CKD</td>
<td>3/22</td>
<td>0/23</td>
<td>4.8%</td>
<td>7.3 [0.4, 133.75]</td>
<td></td>
</tr>
<tr>
<td>Pisani 2014 CKD</td>
<td>4/37</td>
<td>0/66</td>
<td>4.85%</td>
<td>15.87 [0.88, 286.81]</td>
<td></td>
</tr>
<tr>
<td>Ragab 2007 HD</td>
<td>4/12</td>
<td>0/12</td>
<td>5.11%</td>
<td>9 [0.54, 150.81]</td>
<td></td>
</tr>
<tr>
<td>Nagaraju 2013 CKD</td>
<td>4/22</td>
<td>1/18</td>
<td>9.2%</td>
<td>3.27 [0.4, 26.75]</td>
<td></td>
</tr>
<tr>
<td>Agarwal 2015 CKD</td>
<td>2/67</td>
<td>2/69</td>
<td>10.89%</td>
<td>1.03 [0.15, 7.1]</td>
<td></td>
</tr>
<tr>
<td>FIND-CKD 2014 CKD</td>
<td>8/154</td>
<td>5/312</td>
<td>33.53%</td>
<td>3.24 [1.08, 9.74]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1427</td>
<td>1180</td>
<td>100%</td>
<td>3.56 [1.88, 6.74]</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIND-CKD 2014 CKD</td>
<td>6/154</td>
<td>12/312</td>
<td>16.01%</td>
<td>1.01 [0.39, 2.65]</td>
<td></td>
</tr>
<tr>
<td>Quinibi 2011 CKD</td>
<td>20/147</td>
<td>8/103</td>
<td>24.15%</td>
<td>1.75 [0.8, 3.82]</td>
<td></td>
</tr>
<tr>
<td>Mudge 2009 TX</td>
<td>10/51</td>
<td>12/51</td>
<td>26.51%</td>
<td>0.83 [0.4, 1.75]</td>
<td></td>
</tr>
<tr>
<td>Agarwal 2015 CKD</td>
<td>19/67</td>
<td>11/69</td>
<td>33.34%</td>
<td>1.78 [0.92, 3.45]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>419</td>
<td>535</td>
<td>100%</td>
<td>1.32 [0.5, 1.95]</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIND-CKD 2014 CKD</td>
<td>6/154</td>
<td>12/312</td>
<td>16.01%</td>
<td>1.01 [0.39, 2.65]</td>
<td></td>
</tr>
<tr>
<td>Quinibi 2011 CKD</td>
<td>20/147</td>
<td>8/103</td>
<td>24.15%</td>
<td>1.75 [0.8, 3.82]</td>
<td></td>
</tr>
<tr>
<td>Mudge 2009 TX</td>
<td>10/51</td>
<td>12/51</td>
<td>26.51%</td>
<td>0.83 [0.4, 1.75]</td>
<td></td>
</tr>
<tr>
<td>Agarwal 2015 CKD</td>
<td>19/67</td>
<td>11/69</td>
<td>33.34%</td>
<td>1.78 [0.92, 3.45]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>419</td>
<td>535</td>
<td>100%</td>
<td>1.32 [0.5, 1.95]</td>
<td></td>
</tr>
</tbody>
</table>

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)
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fishbane 1995 HD</td>
<td>1/20</td>
<td>0/32</td>
<td></td>
<td>1.11%</td>
<td>4.71[0.2,110.4]</td>
</tr>
<tr>
<td>Stoves 2001 CKD</td>
<td>0/22</td>
<td>1/23</td>
<td></td>
<td>1.11%</td>
<td>0.35[0.01,8.11]</td>
</tr>
<tr>
<td>Li 2008 PD</td>
<td>0/26</td>
<td>8/20</td>
<td></td>
<td>1.39%</td>
<td>0.05[0.07,5]</td>
</tr>
<tr>
<td>Li 2008 HD</td>
<td>0/70</td>
<td>22/66</td>
<td></td>
<td>1.4%</td>
<td>0.02[0.03,0.34]</td>
</tr>
<tr>
<td>Tsuchida 2010 HD</td>
<td>1/12</td>
<td>3/11</td>
<td></td>
<td>2.29%</td>
<td>0.31[0.04,2.52]</td>
</tr>
<tr>
<td>Mudge 2009 TX</td>
<td>3/51</td>
<td>6/51</td>
<td></td>
<td>4.74%</td>
<td>0.53[0.13,1.89]</td>
</tr>
<tr>
<td>Agarwal 2006 CKD</td>
<td>7/44</td>
<td>11/45</td>
<td></td>
<td>8.15%</td>
<td>0.65[0.28,1.53]</td>
</tr>
<tr>
<td>Van Wyck 2005 CKD</td>
<td>9/91</td>
<td>16/91</td>
<td></td>
<td>8.68%</td>
<td>0.53[0.23,1.11]</td>
</tr>
<tr>
<td>Spinowitz 2008 CKD</td>
<td>10/217</td>
<td>15/75</td>
<td></td>
<td>9.11%</td>
<td>0.23[0.11,0.49]</td>
</tr>
<tr>
<td>Lu 2010 CKD</td>
<td>19/220</td>
<td>13/74</td>
<td></td>
<td>10.24%</td>
<td>0.49[0.26,0.95]</td>
</tr>
<tr>
<td>Charytan 2005 CKD</td>
<td>10/39</td>
<td>28/44</td>
<td></td>
<td>11.13%</td>
<td>0.40[0.23,0.72]</td>
</tr>
<tr>
<td>Agarwal 2015 CKD</td>
<td>14/67</td>
<td>28/69</td>
<td></td>
<td>11.53%</td>
<td>0.51[0.30,0.89]</td>
</tr>
<tr>
<td>FIND-CKD 2014 CKD</td>
<td>32/154</td>
<td>128/312</td>
<td></td>
<td>14.07%</td>
<td>0.51[0.36,0.71]</td>
</tr>
<tr>
<td>Nagaraju 2013 CKD</td>
<td>17/22</td>
<td>18/18</td>
<td></td>
<td>15.04%</td>
<td>0.78[0.61,0.99]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1055</strong></td>
<td><strong>931</strong></td>
<td></td>
<td><strong>100%</strong></td>
<td><strong>0.47[0.33,0.66]</strong></td>
</tr>
</tbody>
</table>

Total events: 35 (IV iron), 68 (Oral iron)

Heterogeneity: Tau²=0.19; Chi²=35.42, df=13(P=0); I²=63.29%

Test for overall effect: Z=4.34(P<0.0001)

### 1.6.4 Constipation

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal 2006 CKD</td>
<td>0/44</td>
<td>0/45</td>
<td></td>
<td>3.24%</td>
<td>0.35[0.01,8.11]</td>
</tr>
<tr>
<td>Stoves 2001 CKD</td>
<td>0/22</td>
<td>1/23</td>
<td></td>
<td>6.15%</td>
<td>0.59[0.06,5.51]</td>
</tr>
<tr>
<td>Pisani 2014 CKD</td>
<td>1/37</td>
<td>3/66</td>
<td></td>
<td>6.73%</td>
<td>0.33[0.04,2.77]</td>
</tr>
<tr>
<td>Ragab 2007 HD</td>
<td>1/12</td>
<td>3/12</td>
<td></td>
<td>6.82%</td>
<td>0.06[0.01,0.47]</td>
</tr>
<tr>
<td>Spinowitz 2008 CKD</td>
<td>1/217</td>
<td>6/75</td>
<td></td>
<td>7.07%</td>
<td>0.12[0.02,0.98]</td>
</tr>
<tr>
<td>Van Wyck 2005 CKD</td>
<td>1/91</td>
<td>8/91</td>
<td></td>
<td>13.28%</td>
<td>0.11[0.03,0.45]</td>
</tr>
<tr>
<td>FIND-CKD 2014 CKD</td>
<td>2/154</td>
<td>37/312</td>
<td></td>
<td>14.58%</td>
<td>0.78[0.21,2.96]</td>
</tr>
<tr>
<td>Lu 2010 CKD</td>
<td>7/220</td>
<td>3/74</td>
<td></td>
<td>17.77%</td>
<td>0.65[0.21,2.08]</td>
</tr>
<tr>
<td>Nagaraju 2013 CKD</td>
<td>4/22</td>
<td>5/18</td>
<td></td>
<td>24.36%</td>
<td>0.35[0.14,0.87]</td>
</tr>
<tr>
<td>Charytan 2005 CKD</td>
<td>5/39</td>
<td>16/44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>858</strong></td>
<td><strong>760</strong></td>
<td></td>
<td><strong>100%</strong></td>
<td><strong>0.32[0.18,0.57]</strong></td>
</tr>
</tbody>
</table>

Total events: 22 (IV iron), 82 (Oral iron)

Heterogeneity: Tau²=0.15; Chi²=9.9, df=8(P=0.27); I²=19.23%

Test for overall effect: Z=3.83(P=0)

### 1.6.5 Diarrhoea

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fishbane 1995 HD</td>
<td>1/20</td>
<td>0/32</td>
<td></td>
<td>1.64%</td>
<td>4.71[0.2,110.4]</td>
</tr>
<tr>
<td>Van Wyck 2005 CKD</td>
<td>0/91</td>
<td>3/91</td>
<td></td>
<td>1.87%</td>
<td>0.14[0.01,2.73]</td>
</tr>
<tr>
<td>Charytan 2005 CKD</td>
<td>0/39</td>
<td>3/44</td>
<td></td>
<td>1.89%</td>
<td>0.16[0.01,3.02]</td>
</tr>
<tr>
<td>Agarwal 2006 CKD</td>
<td>2/44</td>
<td>2/45</td>
<td></td>
<td>4.43%</td>
<td>1.02[0.15,6.94]</td>
</tr>
<tr>
<td>Nagaraju 2013 CKD</td>
<td>3/22</td>
<td>2/18</td>
<td></td>
<td>5.78%</td>
<td>1.23[0.23,6.57]</td>
</tr>
<tr>
<td>Pisani 2014 CKD</td>
<td>3/37</td>
<td>3/66</td>
<td></td>
<td>6.78%</td>
<td>1.78[0.38,8.39]</td>
</tr>
<tr>
<td>Spinowitz 2008 CKD</td>
<td>3/217</td>
<td>4/75</td>
<td></td>
<td>7.49%</td>
<td>0.26[0.06,1.13]</td>
</tr>
<tr>
<td>Lu 2010 CKD</td>
<td>5/220</td>
<td>3/74</td>
<td></td>
<td>8.21%</td>
<td>0.56[0.14,2.29]</td>
</tr>
<tr>
<td>Ragab 2007 HD</td>
<td>3/12</td>
<td>3/12</td>
<td></td>
<td>8.47%</td>
<td>1[0.25,4]</td>
</tr>
<tr>
<td>FIND-CKD 2014 CKD</td>
<td>15/154</td>
<td>45/312</td>
<td></td>
<td>53.45%</td>
<td>0.68[0.39,1.17]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>856</strong></td>
<td><strong>769</strong></td>
<td></td>
<td><strong>100%</strong></td>
<td><strong>0.7[0.47,1.05]</strong></td>
</tr>
</tbody>
</table>

Total events: 35 (IV iron), 68 (Oral iron)

Heterogeneity: Tau²=0; Chi²=7.61, df=9(P=0.57); I²=0%

Test for overall effect: Z=1.71(P=0.09)

### 1.6.6 Nausea and vomiting

<table>
<thead>
<tr>
<th>Less with IV iron</th>
<th>0.002</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
<th>500</th>
<th>Less with oral iron</th>
</tr>
</thead>
</table>

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

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<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pisani 2014 CKD</td>
<td>2/37</td>
<td>2/66</td>
<td>1.78 [0.26, 12.15]</td>
<td>6.83%</td>
<td></td>
</tr>
<tr>
<td>Nagaraju 2013 CKD</td>
<td>2/22</td>
<td>2/18</td>
<td>0.82 [0.13, 5.25]</td>
<td>7.23%</td>
<td></td>
</tr>
<tr>
<td>Ragab 2007 HD</td>
<td>2/12</td>
<td>2/12</td>
<td>1.017 [0.59, 1.81]</td>
<td>7.74%</td>
<td></td>
</tr>
<tr>
<td>Lu 2010 CKD</td>
<td>4/220</td>
<td>2/74</td>
<td>0.67 [0.43, 12.15]</td>
<td>8.67%</td>
<td></td>
</tr>
<tr>
<td>Van Wyck 2005 CKD</td>
<td>5/91</td>
<td>5/91</td>
<td>0.4 [0.08, 2.01]</td>
<td>9.26%</td>
<td></td>
</tr>
<tr>
<td>Agarwal 2006 CKD</td>
<td>6/44</td>
<td>2/45</td>
<td>0.5 [0.13, 2.12]</td>
<td>9.54%</td>
<td></td>
</tr>
<tr>
<td>Charytan 2005 CKD</td>
<td>6/94</td>
<td>9/44</td>
<td>0.25 [0.06, 0.91]</td>
<td>10.86%</td>
<td></td>
</tr>
<tr>
<td>Spinowitz 2008 CKD</td>
<td>8/217</td>
<td>5/75</td>
<td>0.28 [0.08, 0.81]</td>
<td>13.48%</td>
<td></td>
</tr>
<tr>
<td>FIND-CKD 2014 CKD</td>
<td>11/154</td>
<td>15/312</td>
<td>0.54 [0.45, 1.29]</td>
<td>26.38%</td>
<td></td>
</tr>
</tbody>
</table>

**Total events**: 32 (IV iron), 44 (Oral iron)

**Heterogeneity**: Tau²=0.11, Chi²=9.59, df=8 (P=0.3); I²=16.58%

**Test for overall effect**: Z=1.03 (P=0.31)

### 1.6.7 Taste disturbances

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pisani 2014 CKD</td>
<td>2/37</td>
<td>2/66</td>
<td>1.78 [0.26, 12.15]</td>
<td>6.83%</td>
<td></td>
</tr>
<tr>
<td>Nagaraju 2013 CKD</td>
<td>2/22</td>
<td>2/18</td>
<td>0.82 [0.13, 5.25]</td>
<td>7.23%</td>
<td></td>
</tr>
<tr>
<td>Ragab 2007 HD</td>
<td>2/12</td>
<td>2/12</td>
<td>1.017 [0.59, 1.81]</td>
<td>7.74%</td>
<td></td>
</tr>
<tr>
<td>Lu 2010 CKD</td>
<td>4/220</td>
<td>2/74</td>
<td>0.67 [0.43, 12.15]</td>
<td>8.67%</td>
<td></td>
</tr>
<tr>
<td>Van Wyck 2005 CKD</td>
<td>5/91</td>
<td>5/91</td>
<td>0.4 [0.08, 2.01]</td>
<td>9.26%</td>
<td></td>
</tr>
<tr>
<td>Agarwal 2006 CKD</td>
<td>6/44</td>
<td>2/45</td>
<td>0.5 [0.13, 2.12]</td>
<td>9.54%</td>
<td></td>
</tr>
<tr>
<td>Charytan 2005 CKD</td>
<td>6/94</td>
<td>9/44</td>
<td>0.25 [0.06, 0.91]</td>
<td>10.86%</td>
<td></td>
</tr>
<tr>
<td>Spinowitz 2008 CKD</td>
<td>8/217</td>
<td>5/75</td>
<td>0.28 [0.08, 0.81]</td>
<td>13.48%</td>
<td></td>
</tr>
<tr>
<td>FIND-CKD 2014 CKD</td>
<td>11/154</td>
<td>15/312</td>
<td>0.54 [0.45, 1.29]</td>
<td>26.38%</td>
<td></td>
</tr>
</tbody>
</table>

**Total events**: 11 (IV iron), 0 (Oral iron)

**Heterogeneity**: Tau²=0, Chi²=1.73, df=3 (P=0.63); I²=0%

**Test for overall effect**: Z=1.74 (P=0.08)

### 1.6.8 Iron overload

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pisani 2014 CKD</td>
<td>2/37</td>
<td>2/66</td>
<td>1.78 [0.26, 12.15]</td>
<td>6.83%</td>
<td></td>
</tr>
<tr>
<td>Nagaraju 2013 CKD</td>
<td>2/22</td>
<td>2/18</td>
<td>0.82 [0.13, 5.25]</td>
<td>7.23%</td>
<td></td>
</tr>
<tr>
<td>Hussain 1998 HD</td>
<td>2/10</td>
<td>0/10</td>
<td>5.0 [0.27, 92.62]</td>
<td>51.54%</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>64</td>
<td>94</td>
<td>6.58 [0.81, 53.51]</td>
<td>100%</td>
<td>3.78 [0.84, 16.97]</td>
</tr>
</tbody>
</table>

**Total events**: 4 (IV iron), 0 (Oral iron)

**Heterogeneity**: Tau²=0, Chi²=0.07, df=1 (P=0.79); I²=0%

**Test for overall effect**: Z=1.76 (P=0.08)
### Outcome or subgroup title

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

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron n/N</th>
<th>Oral iron n/N</th>
<th>Risk Ratio Weight</th>
<th>Risk Ratio Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macdougall 1999 HD, PD</td>
<td>19/41</td>
<td>2/35</td>
<td>1.46% 8.11[2.03,32.41]</td>
<td></td>
</tr>
<tr>
<td>Hussain 1998 HD</td>
<td>9/10</td>
<td>5/10</td>
<td>4.84% 1.8[0.94,3.46]</td>
<td></td>
</tr>
<tr>
<td>Charytan 2005 CKD</td>
<td>21/39</td>
<td>14/44</td>
<td>6.37% 1.69[1.01,2.85]</td>
<td></td>
</tr>
<tr>
<td>Spinowitz 2008 CKD</td>
<td>89/228</td>
<td>14/76</td>
<td>6.66% 2.12[1.29,3.49]</td>
<td></td>
</tr>
<tr>
<td>Lu 2010 CKD</td>
<td>117/225</td>
<td>15/77</td>
<td>7.09% 2.67[1.67,4.28]</td>
<td></td>
</tr>
<tr>
<td>Li 2008 PD</td>
<td>23/26</td>
<td>11/20</td>
<td>7.9% 1.61[1.06,2.45]</td>
<td></td>
</tr>
<tr>
<td>Li 2008 HD</td>
<td>45/70</td>
<td>19/66</td>
<td>7.94% 2.23[1.47,3.39]</td>
<td></td>
</tr>
<tr>
<td>Pisani 2014 CKD</td>
<td>18/33</td>
<td>19/66</td>
<td>8% 1.24[0.82,1.88]</td>
<td></td>
</tr>
<tr>
<td>Provenzano 2009 HD</td>
<td>56/114</td>
<td>29/116</td>
<td>8.84% 1.96[1.36,2.83]</td>
<td></td>
</tr>
<tr>
<td>Stoves 2001 CKD</td>
<td>13/18</td>
<td>16/20</td>
<td>8.95% 0.9[0.63,1.29]</td>
<td></td>
</tr>
<tr>
<td>Van Wyck 2005 CKD</td>
<td>47/79</td>
<td>35/82</td>
<td>9.91% 1.38[1.02,1.9]</td>
<td></td>
</tr>
<tr>
<td>Qunibi 2011 CKD</td>
<td>89/147</td>
<td>36/103</td>
<td>10.22% 1.73[1.28,2.32]</td>
<td></td>
</tr>
<tr>
<td>FIND-CKD 2014 CKD</td>
<td>87/153</td>
<td>99/308</td>
<td>11.81% 1.77[1.43,2.19]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1183</td>
<td>1023</td>
<td>100% 1.71[1.43,2.04]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 633 (IV iron), 324 (Oral iron)
Heterogeneity: Tau²=0.06; Chi²=29.67, df=12(P=0); I²=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).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron Mean(SD)</th>
<th>Oral iron Mean(SD)</th>
<th>Mean Difference Random, 95% CI</th>
<th>Weight</th>
<th>Mean Difference Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winney 1977 HD</td>
<td>7.5 (9.4)</td>
<td>8.4 (8.6)</td>
<td>0.23% -0.9[-7.56,5.76]</td>
<td>0.23% -0.9[-7.56,5.76]</td>
<td></td>
</tr>
<tr>
<td>Nagaraju 2013 CKD</td>
<td>11.3 (1.3)</td>
<td>11.8 (1.8)</td>
<td>2.8% -0.46[-1.45,0.53]</td>
<td>2.8% -0.46[-1.45,0.53]</td>
<td></td>
</tr>
<tr>
<td>Tsuchida 2010 HD</td>
<td>10.7 (1.1)</td>
<td>11.1 (0.6)</td>
<td>3.19% -0.36[-1.07,0.35]</td>
<td>3.19% -0.36[-1.07,0.35]</td>
<td></td>
</tr>
<tr>
<td>Lye 2000 HD</td>
<td>9.1 (1.4)</td>
<td>9.4 (1.5)</td>
<td>3.16% -0.3[-1.03,0.43]</td>
<td>3.16% -0.3[-1.03,0.43]</td>
<td></td>
</tr>
<tr>
<td>Warady 2002 HD</td>
<td>11.2 (1.3)</td>
<td>11.4 (0.8)</td>
<td>3.15% -0.24[-0.98,0.5]</td>
<td>3.15% -0.24[-0.98,0.5]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau²=0.0017; Chi²=12.71, df=7(P=0.04); I²=47.98%
Test for overall effect: Z=1.96(P=0.05)
### Analysis 2.3. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 3 Ferritin: final or change (all patients).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron</th>
<th>Oral iron</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td>Random, 95% CI</td>
<td></td>
<td>Random, 95% CI</td>
</tr>
<tr>
<td><strong>McMahon 2009 CKD</strong></td>
<td>39</td>
<td>11.8 (1)</td>
<td>38</td>
<td>11.9 (1.2)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Michael 2007 HD</strong></td>
<td>33</td>
<td>-0.2 (1.1)</td>
<td>27</td>
<td>-0.2 (1.1)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Agarwal 2015 CKD</strong></td>
<td>153</td>
<td>0.7 (1.2)</td>
<td>58</td>
<td>0.6 (1.2)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Agarwal 2006 CKD</strong></td>
<td>36</td>
<td>0.4 (0.8)</td>
<td>39</td>
<td>0.2 (0.9)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Pisani 2014 CKD</strong></td>
<td>33</td>
<td>11.7 (1)</td>
<td>66</td>
<td>11.4 (0.8)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Qunibi 2011 CKD</strong></td>
<td>147</td>
<td>1 (0.8)</td>
<td>103</td>
<td>0.7 (0.9)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Charytan 2005 CKD</strong></td>
<td>39</td>
<td>11.1 (1.1)</td>
<td>44</td>
<td>10.7 (1)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Kabra 2016 CKD</strong></td>
<td>210</td>
<td>0.9 (1.1)</td>
<td>112</td>
<td>0.5 (1.1)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Provenzano 2009 HD</strong></td>
<td>114</td>
<td>11.7 (1.2)</td>
<td>116</td>
<td>11.2 (1.2)</td>
<td>+</td>
</tr>
<tr>
<td><strong>FIND-CKD 2014 CKD</strong></td>
<td>153</td>
<td>12 (1.2)</td>
<td>308</td>
<td>11.5 (1.8)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Macduff 1999 HD,PD</strong></td>
<td>41</td>
<td>10.8 (1.4)</td>
<td>35</td>
<td>10.3 (1.1)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Van Wyk 2005 CKD</strong></td>
<td>72</td>
<td>10.9 (1)</td>
<td>71</td>
<td>10.4 (1.1)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Lu 2010 CKD</strong></td>
<td>226</td>
<td>11.2 (1.3)</td>
<td>77</td>
<td>10.6 (1.1)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Ragab 2007 HD</strong></td>
<td>24</td>
<td>1.5 (1.0)</td>
<td>24</td>
<td>0.8 (0.9)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Spinowitz 2008 CKD</strong></td>
<td>228</td>
<td>10.9 (1.3)</td>
<td>76</td>
<td>10.2 (1)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Souza 1997 HD</strong></td>
<td>8</td>
<td>1 (0.9)</td>
<td>11</td>
<td>0.2 (0.8)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Boumaend 1998 HD</strong></td>
<td>9</td>
<td>9.1 (1)</td>
<td>8</td>
<td>9 (1)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Hussain 1998 HD</strong></td>
<td>10</td>
<td>11.6 (0.6)</td>
<td>10</td>
<td>10.5 (1.1)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Macduff 1996 HD,PO,CKD</strong></td>
<td>9</td>
<td>11.7 (1.3)</td>
<td>11</td>
<td>10.6 (1.4)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Aggarwal 2003 CKD</strong></td>
<td>20</td>
<td>10.1 (0.9)</td>
<td>20</td>
<td>8.9 (1.2)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Wang 2003 HD</strong></td>
<td>21</td>
<td>9.3 (1.8)</td>
<td>22</td>
<td>7.9 (1.4)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Li 2008 PD</strong></td>
<td>26</td>
<td>12.1 (1.1)</td>
<td>20</td>
<td>10.6 (1)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Ertel 1998 HD</strong></td>
<td>26</td>
<td>11.8 (1.3)</td>
<td>22</td>
<td>9.9 (0.9)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Li 2008 HD</strong></td>
<td>70</td>
<td>12 (1.3)</td>
<td>66</td>
<td>10 (1.1)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Fudin 1998 HD</strong></td>
<td>20</td>
<td>11 (0.9)</td>
<td>12</td>
<td>6.1 (0.4)</td>
<td>+</td>
</tr>
</tbody>
</table>

**Total *** 1874 1499**

Heterogeneity: Tau²=0.76; Chi²=488.04, df=30(P<0.0001); I²=93.85%

Test for overall effect: Z=4.27(P<0.0001)

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

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<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron</th>
<th>Oral iron</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fudin 1998 HD</td>
<td>20</td>
<td>393.5(249.3)</td>
<td>10</td>
<td>229.7(113.5)</td>
<td>+</td>
</tr>
<tr>
<td>Li 2008 PD</td>
<td>26</td>
<td>466.7(85.3)</td>
<td>20</td>
<td>299.4(83.2)</td>
<td>+</td>
</tr>
<tr>
<td>Agarwal 2006 CKD</td>
<td>36</td>
<td>232(160.8)</td>
<td>39</td>
<td>55.9(236.2)</td>
<td>+</td>
</tr>
<tr>
<td>Van Wyck 2005 CKD</td>
<td>72</td>
<td>323(178.5)</td>
<td>72</td>
<td>132(90.3)</td>
<td>+</td>
</tr>
<tr>
<td>Lye 2000 HD</td>
<td>30</td>
<td>432(288)</td>
<td>30</td>
<td>231(204)</td>
<td>+</td>
</tr>
<tr>
<td>Wang 2003 HD</td>
<td>21</td>
<td>496(306)</td>
<td>22</td>
<td>279(206)</td>
<td>+</td>
</tr>
<tr>
<td>Broumand 1998 HD</td>
<td>9</td>
<td>779(205)</td>
<td>8</td>
<td>546.5(139)</td>
<td>+</td>
</tr>
<tr>
<td>Souza 1997 HD</td>
<td>8</td>
<td>245(133)</td>
<td>11</td>
<td>2.3(77.2)</td>
<td>+</td>
</tr>
<tr>
<td>McMahon 2009 CKD</td>
<td>39</td>
<td>412(206)</td>
<td>38</td>
<td>153(88)</td>
<td>+</td>
</tr>
<tr>
<td>Macdougall 1999 HD,PD</td>
<td>41</td>
<td>432(202)</td>
<td>35</td>
<td>140(91)</td>
<td>+</td>
</tr>
<tr>
<td>Lu 2010 CKD</td>
<td>225</td>
<td>443.8(282.4)</td>
<td>77</td>
<td>150.8(140.5)</td>
<td>+</td>
</tr>
<tr>
<td>Charytan 2005 CKD</td>
<td>39</td>
<td>288(150)</td>
<td>44</td>
<td>5.1(151)</td>
<td>+</td>
</tr>
<tr>
<td>Hussain 1998 HD</td>
<td>10</td>
<td>671(388)</td>
<td>10</td>
<td>367(238)</td>
<td>+</td>
</tr>
<tr>
<td>Prozenov 2009 HD</td>
<td>114</td>
<td>601.8(283)</td>
<td>116</td>
<td>289.3(165.8)</td>
<td>+</td>
</tr>
<tr>
<td>FIN-D 2014 CKD</td>
<td>153</td>
<td>503(136.1)</td>
<td>308</td>
<td>184(140.4)</td>
<td>+</td>
</tr>
<tr>
<td>Macdougall 1999 HD,PD,CKD</td>
<td>9</td>
<td>490(276)</td>
<td>11</td>
<td>165(95)</td>
<td>+</td>
</tr>
<tr>
<td>Erten 1998 HD</td>
<td>26</td>
<td>573(246.7)</td>
<td>22</td>
<td>247.4(187.7)</td>
<td>+</td>
</tr>
<tr>
<td>Qunibi 2011 CKD</td>
<td>147</td>
<td>358.8(178.4)</td>
<td>103</td>
<td>25.8(49.4)</td>
<td>+</td>
</tr>
<tr>
<td>Spineuwitz 2008 CKD</td>
<td>228</td>
<td>555.7(320)</td>
<td>76</td>
<td>160.8(161)</td>
<td>+</td>
</tr>
<tr>
<td>Kotaki 1997 HD</td>
<td>15</td>
<td>750(147)</td>
<td>16</td>
<td>255(64)</td>
<td>+</td>
</tr>
<tr>
<td>Fishbane 1995 HD</td>
<td>20</td>
<td>753.9(135)</td>
<td>32</td>
<td>157.3(87)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Total</strong>*</td>
<td>1830</td>
<td></td>
<td>1559</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2=27687.38; Chi^2=2866.96, df=32(P<0.0001); I^2=98.88%
Test for overall effect: Z=7.47(P=0.0001)

### Analysis 2.4. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 4 Transferrin saturation: final or change.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron</th>
<th>Oral iron</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macdougall 1996 HD,PD,CKD</td>
<td>12</td>
<td>23.4(4)</td>
<td>13</td>
<td>31.4(4)</td>
<td>+</td>
</tr>
<tr>
<td>Nagaraju 2013 CKD</td>
<td>22</td>
<td>21.8(10)</td>
<td>18</td>
<td>22.3(12)</td>
<td>+</td>
</tr>
<tr>
<td>Agarwal 2015 CKD</td>
<td>60</td>
<td>0.1(0.1)</td>
<td>57</td>
<td>0.1(0.1)</td>
<td>+</td>
</tr>
<tr>
<td>Michael 2007 HD</td>
<td>33</td>
<td>0.6(0.1)</td>
<td>27</td>
<td>-1.1(8.4)</td>
<td>+</td>
</tr>
<tr>
<td>Van Wyck 2005 CKD</td>
<td>72</td>
<td>25.8(8.9)</td>
<td>22</td>
<td>19.8(9.4)</td>
<td>+</td>
</tr>
<tr>
<td>Kala 2016 CKD</td>
<td>209</td>
<td>6.7(9.3)</td>
<td>112</td>
<td>3.5(9.3)</td>
<td>+</td>
</tr>
<tr>
<td>Pisani 2014 CKD</td>
<td>33</td>
<td>0.5(0.2)</td>
<td>66</td>
<td>18.3(4.3)</td>
<td>+</td>
</tr>
<tr>
<td>Ragab 2007 HD</td>
<td>12</td>
<td>21.5(5.2)</td>
<td>12</td>
<td>18.3(4.3)</td>
<td>+</td>
</tr>
<tr>
<td>Charytan 2005 CKD</td>
<td>39</td>
<td>4.5(8.3)</td>
<td>44</td>
<td>0.8(8.5)</td>
<td>+</td>
</tr>
<tr>
<td>Tsuchida 2010 HD</td>
<td>12</td>
<td>33.8(6.8)</td>
<td>11</td>
<td>29.7(7.2)</td>
<td>+</td>
</tr>
<tr>
<td>Svara 1996 HD</td>
<td>29</td>
<td>26.8(11.1)</td>
<td>28</td>
<td>22.9(9.6)</td>
<td>+</td>
</tr>
<tr>
<td>Qunibi 2011 CKD</td>
<td>144</td>
<td>12.1(8.8)</td>
<td>101</td>
<td>7(10.3)</td>
<td>+</td>
</tr>
<tr>
<td>Kotaki 1997 HD</td>
<td>15</td>
<td>35.7(5.1)</td>
<td>16</td>
<td>30.6(1.9)</td>
<td>+</td>
</tr>
<tr>
<td>Agarwal 2006 CKD</td>
<td>36</td>
<td>8.3(7.5)</td>
<td>39</td>
<td>2.9(8.8)</td>
<td>+</td>
</tr>
</tbody>
</table>
### Analysis 2.5. Comparison 2 Laboratory/pharmaceutical outcomes, Outcome 5 Haematocrit.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron</th>
<th>Oral iron</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>Random, 95% CI</td>
<td></td>
<td>Random, 95% CI</td>
</tr>
<tr>
<td>Ahsan 1997 TX</td>
<td>6 37.7 (1.7)</td>
<td>6 33.4 (1.9)</td>
<td></td>
<td>24.04%</td>
<td>4.3(2.26,6.34)</td>
</tr>
<tr>
<td>Svara 1996 HD</td>
<td>29 27.8 (3.4)</td>
<td>28 27.2 (2.3)</td>
<td></td>
<td>24.83%</td>
<td>0.61(0.24,1.22)</td>
</tr>
<tr>
<td>Fishbane 1995 HD</td>
<td>20 34.4 (3.1)</td>
<td>32 31.8 (2.3)</td>
<td></td>
<td>24.93%</td>
<td>2.6(1.02,4.48)</td>
</tr>
<tr>
<td>Kotaki 1997 HD</td>
<td>15 33.2 (0.9)</td>
<td>16 35.7 (0.7)</td>
<td></td>
<td>26.2%</td>
<td>-2.5(-3.07,1.93)</td>
</tr>
<tr>
<td>**Total *****</td>
<td>70 82</td>
<td></td>
<td></td>
<td>100%</td>
<td>1.18(-2.17,4.52)</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau²=11.03; Chi²=76.45, df=3(P<0.0001); I²=95.98%
Test for overall effect: Z=0.69(P=0.49)

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

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron</th>
<th>Oral iron</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>Random, 95% CI</td>
<td></td>
<td>Random, 95% CI</td>
</tr>
<tr>
<td>Nagaraju 2013 CKD</td>
<td>5 50 (28.3)</td>
<td>7 60 (28.3)</td>
<td></td>
<td>6.15%</td>
<td>-0.33(-1.48,0.83)</td>
</tr>
<tr>
<td>Hussain 1998 HD</td>
<td>10 3400 (1356)</td>
<td>10 4600 (1356)</td>
<td></td>
<td>7.54%</td>
<td>-0.85(-1.77,0.08)</td>
</tr>
<tr>
<td>Tsuchida 2010 HD</td>
<td>12 4735 (2473.7)</td>
<td>11 5589.9 (1513.6)</td>
<td></td>
<td>8.11%</td>
<td>-0.57(-1.4,0.27)</td>
</tr>
<tr>
<td>MacDowall 1996 HD,PD,CKD</td>
<td>12 1202 (229)</td>
<td>13 1294 (314)</td>
<td></td>
<td>8.43%</td>
<td>-0.32(-1.11,0.47)</td>
</tr>
<tr>
<td>Kotaki 1997 HD</td>
<td>15 3760 (1762)</td>
<td>16 4025 (2168)</td>
<td></td>
<td>9.03%</td>
<td>-0.13(-0.84,0.58)</td>
</tr>
<tr>
<td>Warady 2002 HD</td>
<td>17 -76.3 (104.7)</td>
<td>18 -30.9 (77.7)</td>
<td></td>
<td>9.25%</td>
<td>-0.48(-1.16,0.19)</td>
</tr>
<tr>
<td>Fishbane 1995 HD</td>
<td>20 4050 (2455)</td>
<td>32 7563 (2138)</td>
<td></td>
<td>9.51%</td>
<td>-1.53(-2.17,-0.89)</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IV iron</th>
<th>Oral iron</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li 2008 PD</td>
<td>N=26</td>
<td>N=26</td>
<td>-</td>
<td>9.65%</td>
<td>-1.46[-2.08,-0.85]</td>
</tr>
<tr>
<td>Michael 2007 HD</td>
<td>N=33</td>
<td>N=27</td>
<td>15.1</td>
<td>10.39%</td>
<td>-0.17[-0.68,0.34]</td>
</tr>
<tr>
<td>Macdougall 1999 HD,PD</td>
<td>N=41</td>
<td>N=35</td>
<td>12.8</td>
<td>10.77%</td>
<td>-0.22[-0.67,0.23]</td>
</tr>
<tr>
<td>Li 2008 HD</td>
<td>N=70</td>
<td>N=66</td>
<td>6.23</td>
<td>11.18%</td>
<td>-1.58[-1.97,1.19]</td>
</tr>
<tr>
<td><strong>Total</strong>*</td>
<td>N=261</td>
<td>N=261</td>
<td></td>
<td>100%</td>
<td>-0.72[-1.12,-0.31]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau²=0.34; Chi²=43.98, df=10(P=0.0001); I²=77.26%
Test for overall effect: Z=3.48(P=0)

### A D D I T I O N A L T A B L E S

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Population</th>
<th>Studies</th>
<th>Participants</th>
<th>MD</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>All studies</td>
<td>31</td>
<td>3373</td>
<td>0.72</td>
<td>-</td>
<td>0.39 to 1.05</td>
</tr>
<tr>
<td></td>
<td>Dialysis</td>
<td>17</td>
<td>917</td>
<td>1.01</td>
<td>-</td>
<td>0.26 to 1.77</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>14</td>
<td>2456</td>
<td>0.41</td>
<td>-</td>
<td>0.28 to 0.55</td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td>All studies</td>
<td>33</td>
<td>3389</td>
<td>224.8</td>
<td>-</td>
<td>165.8 to 283.8</td>
</tr>
<tr>
<td></td>
<td>Dialysis</td>
<td>19</td>
<td>1027</td>
<td>233.7</td>
<td>-</td>
<td>163.4 to 303.9</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>14</td>
<td>2362</td>
<td>213.1</td>
<td>-</td>
<td>123.7 to 302.6</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>All studies</td>
<td>27</td>
<td>3089</td>
<td>7.69</td>
<td>-</td>
<td>5.10 to 10.28</td>
</tr>
</tbody>
</table>
### Table 1. Laboratory outcomes in dialysis and chronic kidney disease participants (Continued)

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Studies (N)</th>
<th>Studies</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis</td>
<td>14</td>
<td>781</td>
<td>10.55</td>
<td>-</td>
</tr>
<tr>
<td>CKD</td>
<td>13</td>
<td>2308</td>
<td>5.32</td>
<td>-</td>
</tr>
<tr>
<td>Achieving target Hb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>13</td>
<td>2206</td>
<td>-</td>
<td>1.71</td>
</tr>
<tr>
<td>Dialysis</td>
<td>5</td>
<td>508</td>
<td>-</td>
<td>2.01</td>
</tr>
<tr>
<td>CKD</td>
<td>8</td>
<td>1698</td>
<td>-</td>
<td>1.59</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Studies (N)</th>
<th>Studies</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose IV iron/study month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 400 mg/month</td>
<td>12</td>
<td>8</td>
<td>0.17 (-0.18 to 0.52)</td>
<td>0.12</td>
</tr>
<tr>
<td>&gt; 400 to 700 mg/month</td>
<td>7</td>
<td>6</td>
<td>0.76 (0.29 to 1.24)</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 700 mg/month</td>
<td>9</td>
<td>8</td>
<td>0.74 (0.41 to 1.06)</td>
<td>-</td>
</tr>
<tr>
<td>Dose IV iron (mg total dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1000 mg</td>
<td>11</td>
<td>8</td>
<td>0.46 (0.25 to 0.66)</td>
<td>0.21</td>
</tr>
<tr>
<td>1000 to 1999 mg</td>
<td>12</td>
<td>10</td>
<td>0.48 (0.11 to 0.84)</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 2000 mg</td>
<td>5</td>
<td>4</td>
<td>0.89 (0.04 to 1.73)</td>
<td>-</td>
</tr>
<tr>
<td>Oral dose iron/study month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4000 mg/month</td>
<td>12</td>
<td>10</td>
<td>0.87 (0.37 to 1.38)</td>
<td>0.15</td>
</tr>
<tr>
<td>≥ 4000 and &lt; 6000 mg/month</td>
<td>12</td>
<td>11</td>
<td>0.46 (0.28 to 0.64)</td>
<td>-</td>
</tr>
<tr>
<td>≥ 6000 mg/month</td>
<td>7</td>
<td>5</td>
<td>0.37 (0.16 to 0.59)</td>
<td>-</td>
</tr>
<tr>
<td>Dose oral iron (mg total dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 12,000 mg</td>
<td>13</td>
<td>12</td>
<td>0.60 (0.38 to 0.82)</td>
<td>0.86</td>
</tr>
<tr>
<td>1200 to 30,000 mg</td>
<td>10</td>
<td>8</td>
<td>0.66 (0.29 to 1.03)</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 30,000 mg</td>
<td>18</td>
<td>11</td>
<td>0.45 (-0.05 to 0.94)</td>
<td>-</td>
</tr>
<tr>
<td>Any ESA use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No EPO</td>
<td>8</td>
<td>6</td>
<td>0.57 (0.05 to 1.08)</td>
<td>0.34</td>
</tr>
<tr>
<td>EPO</td>
<td>27</td>
<td>22</td>
<td>0.55 (0.32 to 0.78)</td>
<td>-</td>
</tr>
</tbody>
</table>
### Table 2. Subgroup analysis and meta-regression to examine heterogeneity in haemoglobin meta-analyses (Continued)

<table>
<thead>
<tr>
<th>ESA timing of use</th>
<th>Total studies (N)</th>
<th>Studies</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of study</td>
<td>8</td>
<td>7</td>
<td>0.40 (0.08 to 0.72)</td>
<td>0.90</td>
</tr>
<tr>
<td>Before study</td>
<td>19</td>
<td>15</td>
<td>0.57 (0.28 to 0.85)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>Total studies (N)</th>
<th>Studies</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 5</td>
<td>15</td>
<td>14</td>
<td>0.37 (0.26 to 0.50)</td>
<td>0.10</td>
</tr>
<tr>
<td>Dialysis (SD)</td>
<td>22</td>
<td>16</td>
<td>0.80 (0.37 to 1.24)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study duration</th>
<th>Total studies (N)</th>
<th>Studies</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 months</td>
<td>14</td>
<td>12</td>
<td>0.55 (0.35 to 0.75)</td>
<td>0.81</td>
</tr>
<tr>
<td>&gt;2 to ≤ 4 months</td>
<td>9</td>
<td>7</td>
<td>0.74 (0.28 to 1.19)</td>
<td>-</td>
</tr>
<tr>
<td>&gt;4 months</td>
<td>14</td>
<td>11</td>
<td>0.46 (0.002 to 0.91)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention aim</th>
<th>Total studies (N)</th>
<th>Studies</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase Hb</td>
<td>24</td>
<td>20</td>
<td>1.00 (0.51 to 1.50)</td>
<td>0.18</td>
</tr>
<tr>
<td>Maintain Hb</td>
<td>4</td>
<td>2</td>
<td>-0.09 (-0.53 to 0.36)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmaceutical company sponsorship</th>
<th>Total studies (N)</th>
<th>Studies</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclear</td>
<td>23</td>
<td>18</td>
<td>0.81 (0.40 to 1.23)</td>
<td>0.08</td>
</tr>
<tr>
<td>Sponsored</td>
<td>15</td>
<td>13</td>
<td>0.38 (0.28 to 0.48)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Imputed SD</th>
<th>Total studies (N)</th>
<th>Studies</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not imputed</td>
<td>-</td>
<td>5</td>
<td>0.42 (0.02 to 0.81)</td>
<td>0.52</td>
</tr>
<tr>
<td>Imputed</td>
<td>-</td>
<td>26</td>
<td>0.55 (0.35 to 0.76)</td>
<td>-</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Dose IV iron/study month</th>
<th>Total studies (N)</th>
<th>Studies</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 400 mg/month</td>
<td>12</td>
<td>8</td>
<td>1.59 (0.73 to 2.44)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;400 to 700 mg/month</td>
<td>7</td>
<td>6</td>
<td>1.62 (1.41 to 1.83)</td>
<td>-</td>
</tr>
<tr>
<td>&gt;700 mg/month</td>
<td>9</td>
<td>9</td>
<td>1.32 (0.85 to 1.78)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Dose IV iron (mg total dose)**

---

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

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<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>n</th>
<th>Estimate (CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1000 mg</td>
<td>11</td>
<td>9</td>
<td>1.67 (1.03 to 2.30)</td>
<td>0.08</td>
</tr>
<tr>
<td>1000 to 1999 mg</td>
<td>12</td>
<td>10</td>
<td>1.12 (0.83 to 1.42)</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 2000 mg</td>
<td>5</td>
<td>4</td>
<td>2.27 (0.55 to 3.99)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Oral dose iron/study month</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4000 mg/month</td>
<td>12</td>
<td>10</td>
<td>1.44 (0.77 to 2.11)</td>
<td>0.04</td>
</tr>
<tr>
<td>≥ 4000 to &lt; 6000 mg/month</td>
<td>12</td>
<td>11</td>
<td>1.43 (1.16 to 1.69)</td>
<td>-</td>
</tr>
<tr>
<td>≥ 6000 mg/month</td>
<td>7</td>
<td>7</td>
<td>2.16 (1.18 to 3.14)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Dose oral iron (mg total dose)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 12,000 mg</td>
<td>13</td>
<td>13</td>
<td>1.44 (1.05 to 1.83)</td>
<td>0.40</td>
</tr>
<tr>
<td>12000 to 30,000 mg</td>
<td>10</td>
<td>8</td>
<td>1.69 (1.05 to 2.34)</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 30,000 mg</td>
<td>18</td>
<td>12</td>
<td>1.79 (1.15 to 2.43)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Any ESA use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No EPO</td>
<td>8</td>
<td>5</td>
<td>1.27 (0.46 to 2.08)</td>
<td>0.91</td>
</tr>
<tr>
<td>EPO</td>
<td>27</td>
<td>25</td>
<td>1.62 (1.28 to 1.96)</td>
<td>-</td>
</tr>
<tr>
<td><strong>ESA timing of use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start of study</td>
<td>8</td>
<td>6</td>
<td>1.75 (0.88 to 2.62)</td>
<td>0.70</td>
</tr>
<tr>
<td>Before study</td>
<td>19</td>
<td>18</td>
<td>1.64 (1.22 to 2.06)</td>
<td>-</td>
</tr>
<tr>
<td><strong>CKD stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 5</td>
<td>15</td>
<td>14</td>
<td>1.70 (1.29 to 2.11)</td>
<td>0.66</td>
</tr>
<tr>
<td>Dialysis (5D)</td>
<td>22</td>
<td>18</td>
<td>1.50 (1.07 to 1.92)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Study duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2 months</td>
<td>10</td>
<td>13</td>
<td>1.18 (0.86 to 1.49)</td>
<td>0.54</td>
</tr>
<tr>
<td>&gt; 2 to ≤ 4 months</td>
<td>7</td>
<td>8</td>
<td>2.64 (1.45 to 3.82)</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 4 months</td>
<td>9</td>
<td>11</td>
<td>1.54 (1.05 to 2.04)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Intervention aim</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase Hb</td>
<td>24</td>
<td>20</td>
<td>336 (84 to 588)</td>
<td>0.12</td>
</tr>
<tr>
<td>Maintain Hb</td>
<td>4</td>
<td>4</td>
<td>282 (177 to 261)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pharmaceutical company sponsorship</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 3. Subgroup analysis and meta-regression to examine heterogeneity in ferritin meta-analyses (Continued)

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Total studies (N)</th>
<th>Studies (n)</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclear</td>
<td>23</td>
<td>20</td>
<td>1.84 (1.31 to 2.37)</td>
<td>0.63</td>
</tr>
<tr>
<td>Sponsored</td>
<td>15</td>
<td>13</td>
<td>1.36 (1.02 to 1.71)</td>
<td>-</td>
</tr>
<tr>
<td>Imputed SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not imputed</td>
<td>-</td>
<td>5</td>
<td>1.18 (0.51 to 1.86)</td>
<td>0.62</td>
</tr>
<tr>
<td>Imputed</td>
<td>-</td>
<td>26</td>
<td>1.63 (1.31 to 1.94)</td>
<td>-</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Dose IV iron/study month</th>
<th>Total studies (N)</th>
<th>Studies (n)</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 400 mg/month</td>
<td>12</td>
<td>7</td>
<td>0.69 (0.39 to 1.00)</td>
<td>0.20</td>
</tr>
<tr>
<td>&gt; 400 to 700 mg/month</td>
<td>7</td>
<td>5</td>
<td>0.46 (0.14 to 0.78)</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 700 mg/month</td>
<td>9</td>
<td>7</td>
<td>2.00 (0.55 to 3.45)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose IV iron (mg total dose)</th>
<th>Total studies (N)</th>
<th>Studies (n)</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1000 mg</td>
<td>11</td>
<td>8</td>
<td>0.62 (0.34 to 0.90)</td>
<td>0.06</td>
</tr>
<tr>
<td>1000 to 1999 mg</td>
<td>12</td>
<td>9</td>
<td>0.41 (0.07 to 0.74)</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 2000 mg</td>
<td>5</td>
<td>2</td>
<td>3.5 (-1.46 to 8.39)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral dose iron/study month</th>
<th>Total studies (N)</th>
<th>Studies (n)</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4000 mg/month</td>
<td>12</td>
<td>9</td>
<td>0.56 (0.25 to 0.86)</td>
<td>0.21</td>
</tr>
<tr>
<td>≥ 4000 to &lt; 6000 mg/month</td>
<td>12</td>
<td>9</td>
<td>0.54 (0.20 to 0.87)</td>
<td>-</td>
</tr>
<tr>
<td>≥ 6000 mg/month</td>
<td>7</td>
<td>6</td>
<td>1.64 (0.69 to 2.59)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose oral iron (mg total dose)</th>
<th>Total studies (N)</th>
<th>Studies (n)</th>
<th>SMD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 12,000 mg</td>
<td>13</td>
<td>11</td>
<td>0.56 (0.41 to 0.72)</td>
<td>0.15</td>
</tr>
<tr>
<td>1200 to 30,000 mg</td>
<td>10</td>
<td>8</td>
<td>0.56 (0.00 to 1.13)</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 30,000 mg</td>
<td>18</td>
<td>8</td>
<td>1.59 (0.55 to 2.63)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any ESA use</th>
<th>No EPO</th>
<th>EPO</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No EPO</td>
<td>8</td>
<td>6</td>
<td>0.83 (0.36 to 1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>EPO</td>
<td>27</td>
<td>19</td>
<td>0.73 (0.42 to 1.03)</td>
<td>-</td>
</tr>
</tbody>
</table>
### Table 4. Subgroup analysis and meta-regression to examine heterogeneity in transferrin saturation meta-analyses

<table>
<thead>
<tr>
<th>ESA timing of use</th>
<th>Start of study</th>
<th>Before study</th>
<th>CKD stage</th>
<th>Study duration</th>
<th>Intervention aim</th>
<th>Pharmaceutical company sponsorship</th>
<th>Imputed SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8</td>
<td>5</td>
<td>0.29 (-0.42 to 1.00)</td>
<td>0.57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>14</td>
<td>0.85 (0.51 to 1.20)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CKD stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 5</td>
<td>15</td>
<td>13</td>
<td>0.55 (0.35, 0.74)</td>
<td>0.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis (SD)</td>
<td>22</td>
<td>13</td>
<td>1.27 (0.75 to 1.80)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2 months</td>
<td>14</td>
<td>11</td>
<td>0.56 (0.41, 0.72)</td>
<td>0.93</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2 to ≤ 4 months</td>
<td>9</td>
<td>9</td>
<td>1.34 (0.32 to 2.35)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 4 months</td>
<td>14</td>
<td>7</td>
<td>0.67 (0.16 to 1.18)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intervention aim</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase Hb</td>
<td>24</td>
<td>14</td>
<td>7.59 (4.07 to 17.11)</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintain Hb</td>
<td>4</td>
<td>4</td>
<td>18.28 (-3.73 to 40.30)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pharmaceutical company sponsorship</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>23</td>
<td>15</td>
<td>1.07 (0.52 to 1.62)</td>
<td>0.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sponsored</td>
<td>15</td>
<td>12</td>
<td>0.52 (0.34 to 0.71)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Imputed SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not imputed</td>
<td>-</td>
<td>3</td>
<td>0.26 (-0.24 to 0.77)</td>
<td>0.45</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Imputed</td>
<td>-</td>
<td>21</td>
<td>0.72 (0.47 to 0.97)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

### APPENDICES

**Appendix 1. Electronic search strategies**

<table>
<thead>
<tr>
<th>Database</th>
<th>Search terms</th>
</tr>
</thead>
</table>
| 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 Ferrosferric Oxide, this term only |
7. (iron and (gluconate* or fumarate* or dextran* or sucrose* or saccharate*)) in Clinical Trials
8. (iron and (supplement* or therap* or replacement)) in Clinical Trials
9. (ferric or ferrous) and gluconate* in Clinical Trials
10. (ferumoxytol or magnetite or “ferriferous oxide”) in Clinical Trials
11. (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10)
12. MeSH descriptor Renal Replacement Therapy explode all trees
13. MeSH descriptor Renal Insufficiency, this term only
14. MeSH descriptor Kidney Failure, this term only
15. MeSH descriptor Renal Insufficiency, Chronic explode all trees
16. MeSH descriptor Kidney Diseases, this term only
17. MeSH descriptor Uremia, this term only
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.
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 end stage 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

<table>
<thead>
<tr>
<th>Potential source of bias</th>
<th>Assessment criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>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).</td>
</tr>
<tr>
<td>Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence</td>
<td>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.</td>
</tr>
</tbody>
</table>
### 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:** Insufficient information about the sequence generation process to permit judgement.

### Blinding of participants and personnel

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

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

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

- **Unclear:** Insufficient information to permit judgement

### Blinding of outcome assessment

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

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

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

- **Unclear:** Insufficient information to permit judgement

### Incomplete outcome data

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

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

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

- **Unclear:** Insufficient information to permit judgement

### Selective reporting

**Reporting bias due to selective outcome reporting**

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

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

Unclear: Insufficient information to permit judgement

Other bias

Bias due to problems not covered elsewhere in the table

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

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

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 February 2019</td>
<td>New search has been performed</td>
<td>New studies added (11)</td>
</tr>
<tr>
<td>20 February 2019</td>
<td>New citation required and conclusions have changed</td>
<td>GRADE used to assess the evidence</td>
</tr>
</tbody>
</table>

HISTORY

Review first published: Issue 1, 2012

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 March 2014</td>
<td>Amended</td>
<td>Search strategies updated</td>
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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