Use of iron in chronic kidney disease patients

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Guidelines

For:
All chronic kidney disease (CKD) patients (CKD Stage 3-5; CKD Stage 5D [both peritoneal dialysis (PD) and haemodialysis (HD)]).

We recommend:
a. That therapeutic iron be used to correct diagnosed iron deficiency.(1D)
b. Parenteral iron (intravenous) is administered in preference to oral iron to correct iron deficiency. (As it is more likely to: achieve target haemoglobin (Hb) levels (1B), maintain ferritin and transferrin saturation (%TSAT) at target ranges (1C), reduce erythropoiesis stimulating agent (ESA) dose requirements (1C) and have fewer adverse reactions (1C).)

We suggest:
c. That to achieve target haemoglobin levels in patients with CKD (2C), HD (2B) and PD (2D) the following iron indices should be targeted by increasing or decreasing iron therapy.:

<table>
<thead>
<tr>
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<th>Prior to ESA</th>
<th>During ESA</th>
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<tbody>
<tr>
<td>Serum ferritin</td>
<td>&gt;100 μg/L</td>
<td>200-500 μg/L</td>
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<tr>
<td>Transferrin saturation (TSAT %)</td>
<td>&gt;20%</td>
<td>20 to 30%</td>
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d. That when ferritin levels are >500 μg/L, that iron dosage be reduced (2C), although, ferritin levels <=1200 μg/L have shown no sign of toxicity in short term studies (<6months) (2C).
e. Delivery of iron can be given intravenously as a smaller weekly bolus (50mg to 100mg) or large bolus (1000mg) as both achieve responses in iron indices and haemoglobin targets. (2C)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

• Regular monitoring helps to predict iron overload and the overshoot of target Hb. (Ungraded)

Suggested Frequency of Testing iron Indices (Ungraded)

<table>
<thead>
<tr>
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<th>CKD Stage 1-2</th>
<th>CKD Stage 3-5</th>
<th>PD</th>
<th>HD</th>
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<tbody>
<tr>
<td>As clinically indicated</td>
<td>~ 3 monthly</td>
<td>~ 3 monthly</td>
<td>~ 1-3 monthly</td>
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• For CKD (Stages 3-5; not on dialysis) patients with anaemia, there is benefit from IV iron in achieving target iron indices and less ESA use but no benefit in the maintenance of target Hb levels
• Mortality data would suggest that not exceeding 1000 mg every 6 months as total maximum dose per patient per period is desirable. (Ungraded)
• IV iron can usually be given as a bolus rapid infusion (<1hr) with minimal toxicity. (Ungraded)
• Vitamin C administration has been shown to be associated with mild improvement in iron indices in the short term when given in conjunction with standard care for supplementary iron but not in the achievement of target Hb levels in HD patients. (Ungraded)
IMPLEMENTATION AND AUDIT

1. Identify the proportion of patients with serum ferritin levels in the target range of 200-500 μg/L.
2. Identify the number/proportion of patients with transferrin saturation of >= 30-40%.
3. Identify the number/proportion of patients on ESA with Hb in target ranges (usually 100-115 g/L). (See Appendix)

BACKGROUND

In recent years, since the publication of adjusted Hb targets (refer to KHA-CARI guideline "Haemoglobin Levels in Patients using ESAs") and the demonstration that higher dosing of ESA’s to achieve Hb targets is associated with an excess of cardiovascular events [1], more emphasis has been placed on reasons for renal anaemia and the subsequent ESA resistance that may occur. The use of iron as a means of treating renal anaemia has assumed greater importance and particularly in people who have a higher demand for iron when on ESA’s.

Ten per cent of patients receiving ESA’s are unresponsive [2]. Pro-inflammatory cytokines antagonise the action of ESA’s by exerting an inhibitory effect on erythroid progenitor cells and disrupting iron metabolism (a process where hepcidin has a central role). Iron deficiency is also common in predialysis CKD. In the NHANES III study less than one-third of the CKD non-dialysis patients had TSAT% >20% and ferritin >100 μg/L [3], suggesting that iron homeostasis disruption begins relatively early in CKD progression. In many patients with CKD, as with patients with other chronic inflammatory diseases, poor absorption of dietary iron and the inability to utilise iron stores contribute to the anaemia [4]. Detection is also complicated by the lack of sensitivity of peripheral indices [5]. Caution also exists around the fear of toxicity both in minor adverse effects (gastro-intestinal intolerance, constipation, diarrhoea, nausea and vomiting) and major morbidity (allergy, hypotension). The potential for iron overload (liver haemosiderosis) and cardiac arrhythmias are also a concern.

This guideline has been re-written to address both this clinical effect and to provide a practical guide to iron usage by physicians, nephrologists and renal nursing teams.

SEARCH STRATEGY

**Databases searched:** MeSH terms and text words for iron and iron compounds/complexes were combined with MeSH terms and text words for dialysis and chronic kidney disease. These were then combined with search filters for randomised controlled trials, cohort studies and case-control studies. The search was carried out in Medline (1946 – November Week 3, 2011) and not restricted to the year of publication. The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of searches:** 15 September 2012.

WHAT IS THE EVIDENCE?

**Intravenous versus oral iron**

The Cochrane meta-analysis has reviewed 28 randomised controlled trials (RCTs; 2098 individuals) comparing the use of intravenous iron and oral iron in both adults and children with CKD (including those on dialysis) [6]. The parameters of, increasing towards target of Hb, ferritin and transferrin saturation were significantly increased by IV iron compared with oral iron. With the use of IV iron compared to oral iron, there was also a more significant reduction in ESA use in patients from the dialysis populations (9 studies; 487 patients), not seen in the CKD studies. In addition, many small single and multicentre studies in CKD patients (including dialysis patients) receiving ESAs have demonstrated achievement of adequate iron parameters with IV iron irrespective of achieving target Hb levels. [7-10].

**Dosage**
No formal recommendation exists as to whether IV iron should be administered as a single large bolus dose or regular (e.g. weekly) smaller doses since the lower doses have never been compared to single higher dose in more than small cohort studies. Any associated toxicity of this comparison was not revealed in the Cochrane meta-analysis [6]. In most studies of low dose IV iron with the comparator is oral iron [11].

**TARGETS**

Although there is confusion as to what is the most appropriate gold standard for an iron replete individual, all studies show that current peripheral markers of iron indices (TSAT and ferritin levels) generally predict the true iron status poorly [5, 12].

Unfortunately, there is a lack of true treat to target studies. There has only been a series of small open label single centre studies, where IV iron was used in different doses randomly to achieve target Hb [13, 14]. These were not aimed at detecting whether iron indices lead to better HB’s but rather that different amounts of iron lead to better Hb. Of course, the group treated with the greatest dose of iron has the corresponding higher indices. Thus since none of these studies were randomised to peripheral iron indices, there is very little evidence to base any recommendation on. More importantly, excessive IV iron dosing has been shown to be an independent predictor for exceeding Hb targets in HD patients. [15]

The suggested targets for iron indices (with or without ESA therapy) come from both smaller retrospective cohorts [16] and larger database cohort studies examining reasons for hypo-responsiveness to ESAs. For example, from a large database of 38,000 patients [4], ferritin <200 ng/mL, TSAT <20% and elevated PTH and alkaline phosphatase predicted ESA hypo-responsiveness. Smaller studies suggested TSAT 30-50%, and ferritin 200-500 µg/L would lead to a better response as judged by less ESA usage [13, 16, 17].

Recently there has been a suggestion that there is minimal short term toxicity from a higher upper limit to ferritin. In the DRIVE study the ceiling for ferritin was <= 1200. This small 6 week observational study considered a patient population on ESA with TSAT <25%. By pursuing ferritins >500 µg/L, there was significantly less ESA usage and improved attainment of target [18-20] and no worsening of iron overload in the treated groups (not clearly defined in the study). As discussed below, the inflammatory state of the patient is both a better predictor of response to ESA and a more likely explanation for anaemia in a patient with high ferritin levels and low TSAT. [21].

**Resistance**

When considering individuals with apparent ESA resistance (or who are seemingly ESA resistant), multivariate analysis suggests that inflammation or inflection will lead to a state where the elevated CRP is coupled with both elevated ferritin and low TSAT. This state excludes any useful interpretation of iron indices beyond that the patient has an inflammatory state. In such an inflammatory state it is considered not ideal to give IV iron based on the studies suggesting worse outcomes for the infection [21].

**Monitoring**

Monitoring is generally used to reach and maintain Hb within a target range, to prevent toxicity associated with iron, overload and to minimise ESA dose. The current practise of maintaining adequate iron stores is based on the use of TSAT% and ferritin levels derived from small cohorts randomly assigned to increased iron supplementation and thus higher targets. Comparison between measures has been difficult with many contradictory single centre small cohorts suggesting preference of one index over another. For instance in a small case control study, % hypochromic RBCs [22] and TSAT were better than reticulocyte Hb [23] at predicting iron status. In an open trial in which 157 haemodialysis patients were randomised to iron management on the basis of TSAT% and ferritin levels, or reticulocyte haemoglobin levels and followed for 6 months…… the same outcomes with respect to ESA dose and mean haematocrit were achieved. However the TSAT% and ferritin monitored group, received significantly higher IV iron supplementation possibly associated with the higher variability of TSAT% and ferritin measurement [7]. The results of reticulocyte Hb content is not commonly routinely available though some cohort studies suggest it provides greater predictive ability for iron status and its unavailability precludes recommendation in an Australian and New Zealand context. Similarly the use of hepcidin, as a measure of iron homeostasis is not yet established. The receiver operating curve ROC
characteristics as a sensitive index of iron status, suggests that at the moment at least it [22] would remain outside of clinical utility.

The supposed “gold standard” of reduced bone marrow iron stores, taken from specimens collected by bone biopsy, has now had contradictory cohort studies making reproducibility an issue [12]. Liver iron stores (as estimated by MRI) in a small cohort also need further exploring to determine its validity but it may represent a very late marker of excessive iron usage. The cost alone would virtually preclude its usage as a regular test [24].

In reality many recent studies suggest that the response to IV iron, as assessed by rise in Hb would be the most accurate predictor of iron status but form a practical perspective, this cannot be used as a screening index of low iron stores but more a response measure where exceeding target Hb is now a prime concern in anaemia management [16].

Delivery

The time taken (particularly in CKD and PD patients) has resulted in only a few cohort studies on whether there is safety in rapid infusions. The rapid push trial (200mg in 2mins) [25] and the high dose, rapid infusion trial 1.5g in 1 hr (after 15min test dose) [26] both showed safety but experimental analysis does not exist in the literature to date and there is a concern that the maximum dose over 6 months may be exceeded readily by this method, unless there is active bleeding.

Adverse Reactions to iron.

The large Cochrane meta-analysis of both IV and oral iron usage (with more reactions seen in the oral iron group) failed to demonstrate significant toxicity in CKD patients (whether on dialysis or not) however, there was significant unexplained heterogeneity limiting the conclusions that could be made [6]. The literature has numerous studies suggesting iron toxicity in small cohort groups when looking at subclinical [27] or biochemical parameters. These include measures of oxidative stress [28-30], in vitro increased growth of infectious organisms [31] increased proteinuria in CKD patients [32] and cardiac toxicity via increases in QT dispersion with higher iron stores [33]. None of this toxicity was seen in the Cochrane review however, none of the RCTs included in the review were compared to placebo, rather a comparison of different iron formulations.

The only mortality study of a large database suggests a maximum dose for every 6 month period (which is not covered by the Cochrane review) where iron doses >1000-1800 over 6 months in a large data base study from US (Fresenius Data Base) [34] showed a significant increase in mortality. This again is not compared to placebo and large iron versus placebo studies are wanting.

Vitamin C

Multiple small studies of short duration were reviewed in the meta-analysis by Deved et al [35] and suggested reduction in ESA usage, improved TSAT% with a trend to Hb reaching target and minimal toxicity in the short term assessment of multiple studies. This may be related to plasma vitamin C levels [36] but longer duration studies would be necessary to provide evidence to recommend this beyond the short term application.

Newer iron compounds

Early small cohort studies of newer low molecular weight iron compounds are now appearing [37] showing safety, tolerance and target achievement but at this stage they are neither tested in paired analysis nor yet available in Australia.

SUMMARY OF THE EVIDENCE

Overall the Cochrane review has both confirmed that IV iron is appropriate and useful in achieving Hb and iron targets and significantly better than oral iron with minimal clinical toxicity.

The monitoring of iron and mode of delivery is still based on small cohort studies of the apparent effective targets whether in dialysis or just CKD alone patients and with or without the use of an ESA.
Both the resistance to iron and the use of adjuncts like Vitamin C or different iron compounds is not at this stage with sufficient clinical evidence to recommend them in standard care in the long term.

**WHAT DO THE OTHER GUIDELINES SAY?**

**Kidney Disease Outcomes Quality Initiative:**
(a) For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients a 1-3 month trial of oral iron therapy) if (2C)
(b) An increase in Hb concentration without starting ESA treatment is desired* and TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 μg/l)
(c) For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients a 1-3 month trial of oral iron therapy) if (2C)
(d) An increase in Hb concentration† or a decrease in ESA dose is desired and TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 μg/l).
(e) Guide subsequent iron administration in CKD patients based on Hb responses to recent iron therapy, as well as iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status. (Not Graded)
(f) Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to continue iron therapy in patients receiving iron. Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted. (Not Graded)
(g) Avoid administering IV iron to patients with active systemic infections. (Not Graded)

**UK Renal Association:**
(a) A definition of adequate iron status is a serum ferritin
- 200-500 ng/mL in HD patients,
- 100-500 ng/mL in non-HD patients and
- Either <6% hypochromic red cells (HRC), or TSAT>20%
(b) We recommend that ESA therapy should not be initiated in the presence of absolute iron deficiency (ferritin <100ng/ml). In patients with functional iron deficiency iron supplements should be given prior to or when initiating ESA therapy. (1A)
(c) Treatment of anaemia with iron therapy - Route of Administration We suggest that oral iron will, in general, be sufficient to attain and maintain the Hb above targets in ESA treated CKD patients not yet requiring dialysis and in those on peritoneal dialysis (PD). (2B) In contrast most HD patients will require intravenous iron. (2A)
(d) We recommend that serum ferritin should not exceed 800ng/ml in patients treated with iron, and to achieve this iron management should be reviewed when the ferritin is > 500ng/ml. (1B)
(e) We recommend that Hb concentration should be monitored every 2-4 weeks in the correction phase and every 1-3 months for stable patients in the maintenance phase. More frequent monitoring will depend on clinical circumstances. (1B)
(f) We recommend regular monitoring of iron status (1-3 monthly) during treatment to avoid toxicity (1B): a serum ferritin consistently greater than 800 ng/ml is suggestive of iron overload. (1B)

**Canadian Society of Nephrology:**
(a) iron should be administered to maintain the following iron indices in patients with a haemoglobin 110 g/l (Grade D):
- ferritin 100 ng/ml
- transferrin-iron saturation percentage 420%
(b) iron should be administered to maintain the following iron indices (Grade D):
- ferritin 4100 ng/ml
- TSAT 420%
(c) Use oral iron as the preferred first-line therapy (Opinion).
(d) In patients who do not meet serum ferritin or transferrin saturation targets on oral iron, or in whom oral iron is not tolerated, use intravenous iron (Opinion).
Kidney Disease Improving Global Outcomes  
Chapter 2: Use of iron to treat anemia in CKD

Treatment with iron agents

2.1.1: When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g. anaphylactoid and other acute reactions, unknown long-term risks). (Not Graded)

2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):
   - an increase in Hb concentration without starting ESA treatment is desired* and
   - TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 µg/l)

2.1.3: For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):
   - an increase in Hb concentration** or a decrease in ESA dose is desired*** and
   - TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 µg/l)

2.1.4: For CKD ND patients who require iron supplementation, select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost. (Not Graded)

2.1.5: Guide subsequent iron administration in CKD patients based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter, and the patient’s clinical status. (Not Graded)

2.1.6: For all pediatric CKD patients with anemia not on iron or ESA therapy, we recommend oral iron (or IV iron in CKD HD patients) administration when TSAT is ≤20% and ferritin is ≤100 ng/ml (≤100 µg/l). (1D)

2.1.7: For all pediatric CKD patients on ESA therapy who are not receiving iron supplementation, we recommend oral iron (or IV iron in CKD HD patients) administration to maintain TSAT >20% and ferritin >100 ng/ml (>100 µg/l). (1D)

*Based on patient symptoms and overall clinical goals, including avoidance of transfusion, improvement in anemia-related symptoms, and after exclusion of active infection.
**Consistent with Recommendations #3.4.2 and 3.4.3.
***Based on patient symptoms and overall clinical goals including avoidance of transfusion and improvement in anemia-related symptoms, and after exclusion of active infection and other causes of ESA hyporesponsiveness.

Iron status evaluation

2.2.1: Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy. (Not Graded)

2.2.2: Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted. (Not Graded)

Cautions regarding iron therapy

2.3: When the initial dose of IV iron dextran is administered, we recommend (1B) and when the initial dose of IV nondextran iron is administered, we suggest (2C) that patients be monitored for 60 minutes after the infusion, and that resuscitative facilities (including medications) and personnel trained to evaluate and treat serious adverse reactions be available.

Iron during infection

2.4: Avoid administering IV iron to patients with active systemic infections. (Not Graded)
SUGGESTIONS FOR FUTURE RESEARCH

1. RCTs on the use of newer measures suggested in cohort studies (like reticulocyte Hb) in predicting iron stores in order to have widespread acceptance of it as a more accurate measure.
2. Experimental studies of iron versus placebo to detect if iron in any formulation increases mortality

CONFLICT OF INTEREST

Rob MacGinley, Rowan Walker and Michelle Irving have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement as set down by CARI.

REFERENCES

## Appendix
### Table 1. Characteristics of key studies

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<th>Study ID</th>
<th>N</th>
<th>Study design</th>
<th>Description - Participants and Interventions</th>
<th>Follow up</th>
<th>Comments and results</th>
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| Albaramiki et al 2012 (Cochrane review) [6] | 28 RCT’s; 2098 participants. | Systematic review and meta-analysis of randomised and quasi randomised controlled trials. Search date March 2010. | Participants: Adult and paediatric CKD patients (stages 3 to 5D) treated with HD, PD, not receiving dialysis and post-transplant patients.  
Interventions: Different IV iron supplements and oral iron preparations. Different doses and durations of IV iron compared with oral iron preparations where the control group received only oral iron supplements.  
Primary outcomes: Haemoglobin (Hb); iron.  
Secondary outcomes: ESA dose, all-cause mortality; CVD mortality and morbidity, commencement of dialysis’ haematocrit, adverse events.  
Exclusions included studies comparing different IV or oral iron preparations and different doses of the same IV or oral preparation. Studies in patients with acute kidney injury. | 1.3 to 24 months | IV iron versus oral iron:  
• All-cause mortality (5 studies):  
  o RR: 1.16 (95%CI 0.35, 3.84); control risk 2.6%.  
  o CVD mortality (2 studies):  
    o RR: 3.2 (95%CI 0.37, 27.51); control risk 0%.  
  • End of ESA treatment or change in ESA dose (9 studies):  
    o SMD: -0.76 (95%CI -1.22, -0.30).  
  • Commencement of dialysis (3 studies):  
    o RR: 0.69 (95%CI 0.28, 1.71); control risk 7.6%.  
• Any adverse events (12 studies):  
  o RD: -0.09 (95%CI -0.19, 0.00).  
• Final or change in Hb (22 studies):  
  o MD: 0.9 g/dL (95%CI 0.44, 1.37).  
• Ferritin final or change (24 studies)  
  o MD: 243.25 µg/L (95%CI 188.74, 297.75).  
• Transferrin saturation final or change (18 studies)  
  o MD: 10.2 % (95%CI 5.56, 14.83).  
• Number achieving target Hb or increase of 1g/dL or more (10 studies):  
  o RR: 1.7 (95%CI 1.36, 2.12); control rate 32%.  
Limitations: Considerable variation in dose and duration of IV and oral iron therapies. Only a small number of studies included patient-centred outcomes. Significant heterogeneity in Hb, ferritin and transferrin that remains largely unexplained. Significant heterogeneity in adverse events. Insufficient evidence on patient-centred outcomes and adverse effects to determine if benefits exceed harms for all CKD patients for IV versus oral iron. |
Data censored for: death, discontinuation of dialysis, transfer from unit.  
Outcome: Effect modification of Hb sensitivity to EPO by serum ferritin, transferrin saturation, Kt/V, intact PTH, serum albumin. | 13- 69 months   | Maximum Hb sensitivity to EPO:  
• Serum ferritin: 350 to 500 ng/mL  
• Transferrin saturation: >30%  
• Kt/V >1.4  
• Serum albumin >3.8 g/dL.  
Limitations: Limited to CKD treated with HD. Modelled estimates of indicator ranges. Retrospective analysis. |
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<tr>
<th>Study ID</th>
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| deVita et al  | 36  | Randomised controlled trial.               | HD patients on rHuEPO >5,000 U/Rx and serum ferritin ≥ 70 ng/ml and ≤400 ng/ml; HCT ≤33%. Low (200 ng/ml) vs. High (400 ng/ml) ferritin target, iron dose using iv iron dextran. rHuEPO dose adjusted to achieve HCT between 32.5 and 36%. Primary outcome not defined. | 5 months (average) | Final ferritin concentrations:  
- Low target group: 298.6 sd93.7 ng/ml  
- High target group: 469.4 sd 210.4 ng/ml (P>0.05)  
Total iron:  
- Low target group: 906.7 sd 953.1 g  
- High target group: 1,650 sd 981.2 g (P0.04)  
Mean difference in rHuEPO dose at end of trial low vs. high target group:  
- -60.10 (95%CI -139.97, 19.77) U/kg bw/wk  
Reduction in rHuEPO dose from baseline to end of study:  
- Low target group 31 U/kg bw/wk (12% decline) P>0.05  
- High target group 154 U/kg bw/wk (53% decline) P<0.001  
Limitations: No detail provided on treatment allocation or blinding. Primary outcome not defined. Small numbers. rHuEPO dose at end of study not significantly different between low and high target groups. Large confidence intervals for all parameters at baseline and end of study. Ferritin concentrations between low and high target ferritin groups not significantly different. |
| Kalantar-Zadeh et al | 38,328 | Retrospective cohort. National database records. | Long term HD patients treated over a 12 month period on dialysis at least 3 months prior and receiving ESA at least once monthly for 9 consecutive months during 3 consecutive calendar quarters. Outcome measure: ESA responsiveness over time (slope of ESA dose versus Hb). | 12 months | After dividing serum ferritin into 5 groups (<200, 200 to 500, 500 to 800, 800 to 1,200 and ≥1,200 ng/mL), logistic regression indicated:  
- Highest ESA responsiveness in the 500 to 1,200 ng/mL group (OR not provided)  
- Lowest ESA responsiveness in the <200 ng/mL group (adj. OR 0.77; 95%CI 0.70 to 0.86)  
Limitations: Retrospective review of medical records which included missing variables. Comparison of averaged ESA dose with and quarterly Hb values within the same calendar month without accounting for delay between ESA exposure and Hb. Provides only short term association between ESA dose and Hb with no long term patient relevant outcomes. |
| Besarab et al  | 42  | Open label randomised controlled trial.    | Adult HD patients with cell volume >80 fl, TSAT 19 to 30%, ferritin 150 to 600 ng/mL, Hb ≥9.5 g/dL, stable rEPO dose (>700 U IV 3 x per week) over prior 3 months. High TSAT target >30% vs. low TSAT target 20 to 30% - after 16 to 20 week run in to achieve steady state Hb. Primary outcome: Change in EPO dose (powered to detect 40% difference). | 6 months | Dose reduction of EPO in high TSAT group was approximately 40% at months 4,5 and 6. EPO reduction >20% (considered to be clinically significant) in the study group compared to the control group:  
- RR 2.48 (95%CI 0.95, 6.44)  
Hb levels were the same between the low20 to 30% TSAT group and the >30% TSAT group.  
Limitations: Open label. No detail of randomisation or assessor blinding. Small size and single centre. Groups did not achieve statistically significant differences in TSAT (27.6 % vs. 32.6%, P>0.05). Large confidence intervals. Not powered to detect clinically meaningful difference in EPO reduction. |
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| Feldman et al (2004) [34] | 32,566 | Retrospective cohort. National database medical records. Multi-centre US | HD patients - more than 1 year of HD and survived for more than 6 months from recruitment due to use of 6 month iron exposure period for baseline. Outcome: Mortality hazard ratio estimated using a time-dependent model and the prior 6 month total Fe dose. | 24 months | Time dependent model results for adjusted HRs for mortality 12 to 18 months:  
  - Total iron dose over previous 6 months:  
    - 0 TO 700 mg: 0.83 (95%CI 0.67, 1.04)  
    - >700 TO 1000 mg: 0.99 (95%CI 0.80, 1.23)  
    - >1000 TO 1800 mg: 0.96 (95%CI 0.79, 1.18)  
    - >1800 mg: 1.16 (95%CI: 0.94, 1.44)  
  Limitations: Retrospective cohort. No data available for other important outcomes such as infections or cardiovascular morbidity and mortality. Generalisability to current iron dosing practices. Excluded patients who died on dialysis within 1.5 years thus may have omitted patients with greater morbidity and selected a healthier cohort. |