Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis
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CRD summary
The review concluded that intravenous iron therapy was associated with improved quality of life, reduced hospitalisations and increased walk distance in congestive heart failure patients with iron deficiency, without an increase in adverse events. The authors were suitably cautious in acknowledging the limitations of their results and their conclusions are likely to be reliable.

Authors' objectives
To assess the safety and efficacy of iron therapy in patients with congestive heart failure and iron deficiency, with or without anaemia.

Searching
MEDLINE (from January 1966 to June 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (up to 2011, issue 1), LILACS, KoreaMed and NLM Gateway were searched for relevant studies; limited search terms were reported. Conference proceedings of relevant cardiology and haematology associations (2004 to August 2011), clinical trials databases and reference lists of identified studies were searched. There were no language or date restrictions.

Study selection
Randomised controlled trials (RCTs) that compared iron with no iron for treatment of congestive heart failure and iron deficiency (regardless of anaemia status) were eligible for inclusion in the review. All symptomatic stages of congestive heart failure were included. Trials of patients under 18 years old, pregnant women and patients with active bleeding were excluded. The primary outcome was the effect of iron on quality of life parameters (such as the New York Heart Association class and the Minnesota Living with Heart Failure questionnaire). Secondary outcomes included all-cause mortality, mean ejection fraction, six-minute walk distance, hospitalisations due to any cause, iron indices, C-reactive protein levels and adverse events.

Mean age of participants in the included studies ranged from 62 to 76 years. Most participants were men. Most participants had chronic renal failure and all participants had symptomatic congestive heart failure (New York Heart Association classes II to IV). About half of the participants were anaemic (defined as Hb<12.5g/dL for men). Only intravenous iron therapy was used (iron sucrose or ferric carboxymaltose). Total iron dosages ranged from 1,000mg to 2,000mg. Half of the studies used saline as placebo controls and the other studies did not state what was used in the control arms. Patients were followed up for between 18 and 26 weeks.

The authors did not state how many reviewers selected studies for the review.

Assessment of study quality
Studies were assessed for quality according to the risk of bias tool specified by the Cochrane Collaboration; criteria included random sequence generation, allocation concealment, blinding, incomplete data reporting and selective outcome reporting. Each criterion was graded as low risk, unclear risk or high risk for bias.

Two reviewers independently assessed studies for quality, with disagreement resolved by consultation with a third reviewer, with the aim of achieving consensus.

Data extraction
Data were extracted on the outcomes to enable calculation of relative risks (RRs) for dichotomous data and mean differences for continuous data, together with 95% confidence intervals (CIs). When mean and standard deviations were not available, they were calculated from the data in figures or from other effect estimates or dispersion measures. Trial investigators were contacted for missing data, where necessary.
Two reviewers independently extracted data. Disagreements were resolved by consultation with a third reviewer with the aim of achieving consensus.

Methods of synthesis
The results of the included studies were pooled in meta-analyses and summary effect relative risks and weighted mean differences (WMDs) or standardised mean differences (SMDs), with 95% CIs, were calculated using a fixed-effect model (where no significant heterogeneity was identified) or a random-effects model (significant heterogeneity). Heterogeneity was assessed with the $X^2$ test and the $I^2$ value ($p<0.10$ and $I^2>40\%$ represented significant heterogeneity). Potential sources of heterogeneity were explored using meta-regression to assess the effect of anaemia occurrence on the effect estimates. Subgroup analyses were undertaken to compare results of anaemic patients with non-anaemic patients. Sensitivity analysis was undertaken to assess the effect of excluding the largest study on the results.

Results of the review
Four RCTs (594 participants, range 35 to 459) were included in the review. The largest trial had low risk of bias for all quality domains. One trial had no data for quality assessments. Random sequence generation and blinding were adequate in two trials and one trial had adequate allocation concealment. Follow-up losses ranged from 0% to 14% of patients.

Primary outcomes: Compared with control, there was a non significant trend towards better quality of life (as assessed by the Minnesota Living with Heart Failure and the Kansas City Cardiomyopathy Questionnaires) in patients who received intravenous iron (SMD $-2.66$, 95% CI $-5.40$ to $0.07$; $I^2=98\%$; three studies). Compared to control, there was a non-significant trend towards a better New York Heart Association class with intravenous iron (WMD $-0.68$, 95% CI $-1.45$ to $0.1$; $I^2=96\%$; three studies). There were insufficient data to assess the scores of other quality of life measures (Patient's Global Assessment of Change, European Quality of Life-5 Dimensions, Visual Analogue Scale and fatigue score).

Secondary outcomes: Compared with control, intravenous iron therapy was associated with significantly fewer hospitalisations due to any cause (WMD 0.51, 95% CI 0.30 to 0.87; $I^2=0\%$; three studies), improved exercise capacity as measured by six-minute walk difference (WMD 36.06 metres, 95% CI 34.17 to 37.95; $I^2=21\%$; two studies), increased ejection fraction (WMD 6.43%, 95% CI 4.23 to 8.63; $I^2=40\%$; two studies), reduced C-reactive protein levels (WMD $-4.04$ mg/L, 95% CI $-5.65$ to $-2.42$; $I^2=0\%$; two studies), increased ferritin levels (WMD 217.27, 95% CI 170.08 to 264.47; $I^2=99\%$; three studies), transferrin saturation levels (WMD 8.71, 95% CI 5.70 to 11.72; $I^2=99\%$; three studies) and fewer severe adverse events (RR 0.43, 95% CI 0.28 to 0.67; $I^2=0\%$; four studies). Compared with control, patients who received iron had significantly higher haemoglobin levels overall (SMD 0.87, 95% CI 0.18 to 1.67; $I^2=89\%$; two studies). There was no evidence of a difference between groups in the incidence of mortality (RR 0.73, 95% CI 0.23 to 2.30; $I^2=0\%$; three studies).

Supplementary material included with the publication contained a discrepancy in the graph labels for iron indices that suggested that the findings favoured control.

Authors' conclusions
Intravenous iron therapy was associated with improved quality of life parameters, reduction in hospitalisations and increased walk distance in congestive heart failure patients with iron deficiency. There was no increase in adverse events. The results were limited by the paucity of trials and the significant differences between them.

CRD commentary
The review addressed a clear research question supported by appropriate inclusion criteria. A wide range of relevant sources were searched for both published and unpublished studies without language restrictions, which minimised the chances of language and publication biases. The authors used appropriate methods to extract data and assess studies for quality but they did not state how many reviewers selected studies for the review so reviewer error and bias could not be ruled out.

A valid tool was used for quality assessment. Only one of the four included studies had a low risk of bias. This study dominated the results but excluding the study did not markedly change the results. Synthesis of the studies and assessment of heterogeneity were appropriate. Substantial heterogeneity for one of the quality of life assessments and
measures of iron indices limited the reliability of these findings. Follow-up was limited to six months, which hindered adequate assessment of some outcomes (such as mortality). The authors did not report the results of the meta-regression but provided analyses of subgroups according to anaemia status.

The authors were suitably cautious in acknowledging the limitations of their results and their conclusions are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that it was probably justified to screen congestive heart failure patients for iron deficiency and, if confirmed, consider treatment with intravenous iron.

**Research:** The authors stated that it may be worthwhile to conduct a well-designed large randomised controlled trial to compare intravenous iron, erythropoiesis-stimulating agents and both agents combined for patients with congestive heart failure and anaemia. Trials should have long term follow-up, pre-defined subgroups of anaemic patients and different iron deficiency levels, New York Heart Association class and ejection fraction.

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