Erythropoietin therapy and left ventricular mass index in CKD and ESRD patients: a meta-analysis

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CRD summary
This review concluded that recombinant human erythropoietin was effective in reducing left ventricular mass index among severely anaemic chronic kidney disease and end-stage renal disease patients. High levels of variation coupled with unclear data quality and potential limitations in the search strategy suggest a need for a cautious interpretation of the authors' conclusions.

Authors' objectives
To evaluate the effectiveness of recombinant human erythropoietin (EPO) in reducing left ventricular mass index (LVMi) among anaemic chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients.

Searching
PubMed was searched between January 1990 and February 2007 for articles. A range of relevant search terms was used. Reference lists of publications were searched. Abstracts from American Society of Nephrology and European Dialysis and Transplant Association conference meetings were searched.

Study selection
All studies published in peer-reviewed journals that reported LVMi values before and after erythropoietin treatment for anaemia in chronic kidney disease or ESRD patients were eligible for inclusion.

Most participants were dialysis patients being treated for hypertension. There was considerable heterogeneity in the treatment period (range four months to 4.5 years, mean duration 16 months). There was variation in target level haemoglobin and mean baseline LVMi (only one study was in the normal LVMi range). The retrieved studies were cohorts. No studies compared outcomes of treated patients to randomly assigned untreated controls.

Two reviewers performed the study selection.

Assessment of study quality
Use of validated quality assessment instruments was not reported. The author's stated that data quality was assessed and mentioned randomisation of the cohorts, but they did not state whether quality assessment consisted of comparison of IPD (individual patient data) and aggregate data or testing the integrity of randomisation using IPD. It was unclear how the quality of individual studies was assessed and how this informed the analysis.

Two reviewers were involved in assessing data quality. A third reviewer was consulted in the event of discrepancies.

Data extraction
Mean LVMi and standard deviations were extracted from cohorts at baseline and final measurement.

Two independent reviewers performed the data extraction. Discrepancies were resolved by a third reviewer.

Methods of synthesis
Weighted mean differences (WMD) in LVMi were calculated and combined using an unspecified random-effects model, except where a statistical test (presumably $X^2$) resulted in rejection of a null hypothesis of heterogeneity amongst studies, in which case an unspecified fixed-effect model was used. Methods for weighting were unstated. Target level haemoglobin blood level (Hb), baseline Hb and stage of kidney disease (chronic kidney disease versus ESRD) were specified as hypothetical reasons for heterogeneity in results. Pooled point estimates and associated 95%
confidence intervals were calculated and displayed with trial effects in forest plots.

Results of the review
Fifteen studies were combined without distinction between their quality. Only five of the 15 studies assigned cohorts using a randomised design. The studies contained data on 23 cohorts that involved 1,731 chronic kidney disease and ESRD patients treated with erythropoietin. Patient cohort sample size ranged from seven to 300.

Overall, there was a significant reduction in LVMi (WMD -9.20, 95% CI -16.05 to -2.34). Effects were similar for chronic kidney disease and ESRD cohorts.

Nine cohorts with severe anaemia at baseline (≤10g/dL) showed significant reductions in LVMi (WMD -32.7g/m², 95% CI -49.4 to -16.1) when given erythropoietin using a lower target level (Hb≤12g/dL).

Cohorts with moderate anaemia at baseline showed no significant reduction in LVMi when given erythropoietin irrespective of Hb target level (Hb ≤12g/dL, WMD 5.3g/m², 95% CI -0.8 to -11.3; six studies and Hb>12g/dL, WMD -6.6, 95% CI -17.2 to 4.0; eight studies)

Authors’ conclusions
Erythropoietin therapy was effective for patients with severe anaemia where conventional haemoglobin targets were pursued. Where patients had moderate anaemia, erythropoietin therapy did not have a significant beneficial impact on LVMi irrespective of target haemoglobin.

CRD commentary
The authors addressed clear research questions supported by replicable inclusion criteria. The search appeared limited in scope and relevant studies may have been missed. Methods were used to reduce potential error and biases in all aspects of the review process. It was unclear which methods were used to assess data quality and how the results of this informed the analysis. Methods for pooling appeared robust, but there was no reported assessment of publication bias or consideration of how study results were affected by sample size. Interpretation of the analysis was complicated by the presentation of nine subgroup analyses that represented multiple non-independent comparisons and by large variations in baseline means. The authors’ conclusions that LVMi was reduced in severe anaemia, low-haemoglobin target patients and patients with moderate anaemia showed no benefit of erythropoietin on LVMi irrespective of target haemoglobin level reflected the evidence presented. High heterogeneity between studies and a lack of high-quality RCTs point to a need for a cautious interpretation of these conclusions.

Implications of the review for practice and research
Practice: The authors stated that the results of this study supported treatment of severe anaemia with erythropoietin.

Research: The authors did not state any implications for research

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